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THE STUDY OF CHEMICAL EXCHANGE KINETICS
BY NUCLEAR MAGNETIC RESONANCE

Abstract

A study of the rates of hindered internal rotation about the C-N bond in N,N-dimethyltrifluoroacetamide and N,N-dimethyldeuteroformamide has been made using the nuclear magnetic resonance spin echo method. A 40 Mc/sec spin echo spectrometer, which enables measurements to be made of the transverse relaxation time (T_2) from a Carr-Purcell sequence of radio-frequency pulses, is described and its performance illustrated. The precision of T_2 values obtained is estimated to be of the order of +5%.

Equations derived from a theory developed by Bloom, Reeves and Wells for the dependence of T_2 measured in a Carr-Purcell experiment, on pulse intervals in the presence of a suitable exchange process have been used to extract the kinetic data for the two molecules. The chemical shift, rate constant and natural relaxation time (T_{20}) have been calculated from the data by curve fitting procedures using computer techniques, and the experimental verification of the theory has been noted.

The accuracy of the rate constants and activation parameters derived is discussed in the light of previous steady state nuclear magnetic resonance studies. The relative merits of the spin echo and steady state methods are examined and the possibility of the occurrence of systematic errors in such studies is investigated.

Steady state studies of the proton exchange between methanol and two phenols (meta-cresol and ortho-hydroxyacetophenone) and of the ring inversion of N,N-dimethylpiperazine are also presented and the relative merits of the kinetic parameters discussed.

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2. Correlation of Nuclear Spin-Spin Coupling Constants with Atomic Number V. Deviation Parameters for Substituted Methanes and Silanes. P. T. Inglefield and L. W. Reeves. J. Chem. Phys. 40, 2424 (1964).
3. The Description and Use of a "Spin Echo" Spectrometer to Study Chemical Exchange. K. H. Abramson, P. T. Inglefield, E. Krakower and L. W. Reeves. Can. J. Chem. 44, 1685 (1966).

THE STUDY OF CHEMICAL EXCHANGE KINETICS BY
NUCLEAR MAGNETIC RESONANCE

by

PAUL T. INGLEFIELD, B. Sc.

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
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DOCTOR OF PHILOSOPHY

in the Department
of
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A study of the rates of hindered internal rotation about the C—N bond in N,N-dimethyltrifluoroacetamide and N,N-dimethyldeuteroformamide has been made using the nuclear magnetic resonance spin echo method. A 40 Mc/sec. spin echo spectrometer, which enables measurements to be made of the transverse relaxation time (T_2) from a Carr Purcell sequence of radio-frequency pulses, is described and its performance illustrated. The precision of T_2 values obtained is estimated to be of the order of $\pm 5\%$.

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and the possibility of the occurrence of systematic errors in such studies is investigated.

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INTRODUCTION

The purpose of the thesis is the study of chemical exchange kinetics by use of nuclear magnetic resonance. The various methods used will be discussed and their relative merits evaluated. Firstly, a brief description of the basic concepts used in nuclear magnetic resonance theory and relevant to this problem will be given with references if further details are required.

Simple Resonance Theory.

An isolated nucleus in a magnetic field H_0 has a Larmor precession frequency given by $\omega_0 = \gamma H_0$. The absorption of radiation at a radiofrequency ω_0 (the H_1 field) causes transitions between the nuclear energy levels (1). The dissipation of this absorbed nuclear spin energy is accomplished by means of relaxation processes. These relaxation processes are of two types. In one the absorbed spin energy is dissipated to the lattice (i.e. the electrons and other nuclei of the sample). This is called Spin Lattice Relaxation and is designated by the time T_1 . The other relaxation process is one in which the absorbed energy is dissipated within the spin system itself by dephasing of the individual spin vectors. This process is called Spin-Spin Relaxation and is designated by the time T_2 (2).

The N.M.R. experiment and the relaxation times are usefully described by the phenomenological equations of Bloch (3). In this a first order decay law is incorporated to describe the magnetization under the influence of the relaxation processes. The nuclear magnetization vector \underline{M} per unit volume satisfies the equation,

$$\frac{d\underline{M}}{dt} = \gamma (\underline{M} \times \underline{H}) \quad \text{_____} \quad (1)$$

This may now be split into its three components and the relaxation terms added giving,

$$\frac{dM_z}{dt} = - \frac{M_z - M_0}{T_1} \quad \text{_____} \quad (2a)$$

$$\frac{dM_x}{dt} = \omega_0 M_y - \frac{M_x}{T_2} \quad \text{_____} \quad (2b)$$

$$\frac{dM_y}{dt} = - \omega_0 M_x - \frac{M_y}{T_2} \quad \text{_____} \quad (2c)$$

The effect of an irradiating field \underline{H}_1 perpendicular to \underline{H}_0 and rotating with an angular frequency - with components $(H_1)_x = H_1 \cos \omega t$ (3a)

$$(H_1)_y = -H_1 \sin \omega t \quad (3b)$$

is added to equations (2) to give the complete Bloch equations. It is convenient to remove the time dependence of

\underline{H}_1 from these equations by using a rotating co-ordinate system (4) rotating with an angular velocity $-\omega$ about the Z axis. We then define u and v as the components of \underline{M} along and perpendicular to \underline{H}_1 and the final Bloch equations become in the rotating frame

$$\frac{du}{dt} + \frac{u}{T_2} + (\omega_0 - \omega)v = 0 \quad (4a)$$

$$\frac{dv}{dt} + \frac{v}{T_2} - (\omega_0 - \omega)u + \gamma H_1 M_Z = 0 \quad (4b)$$

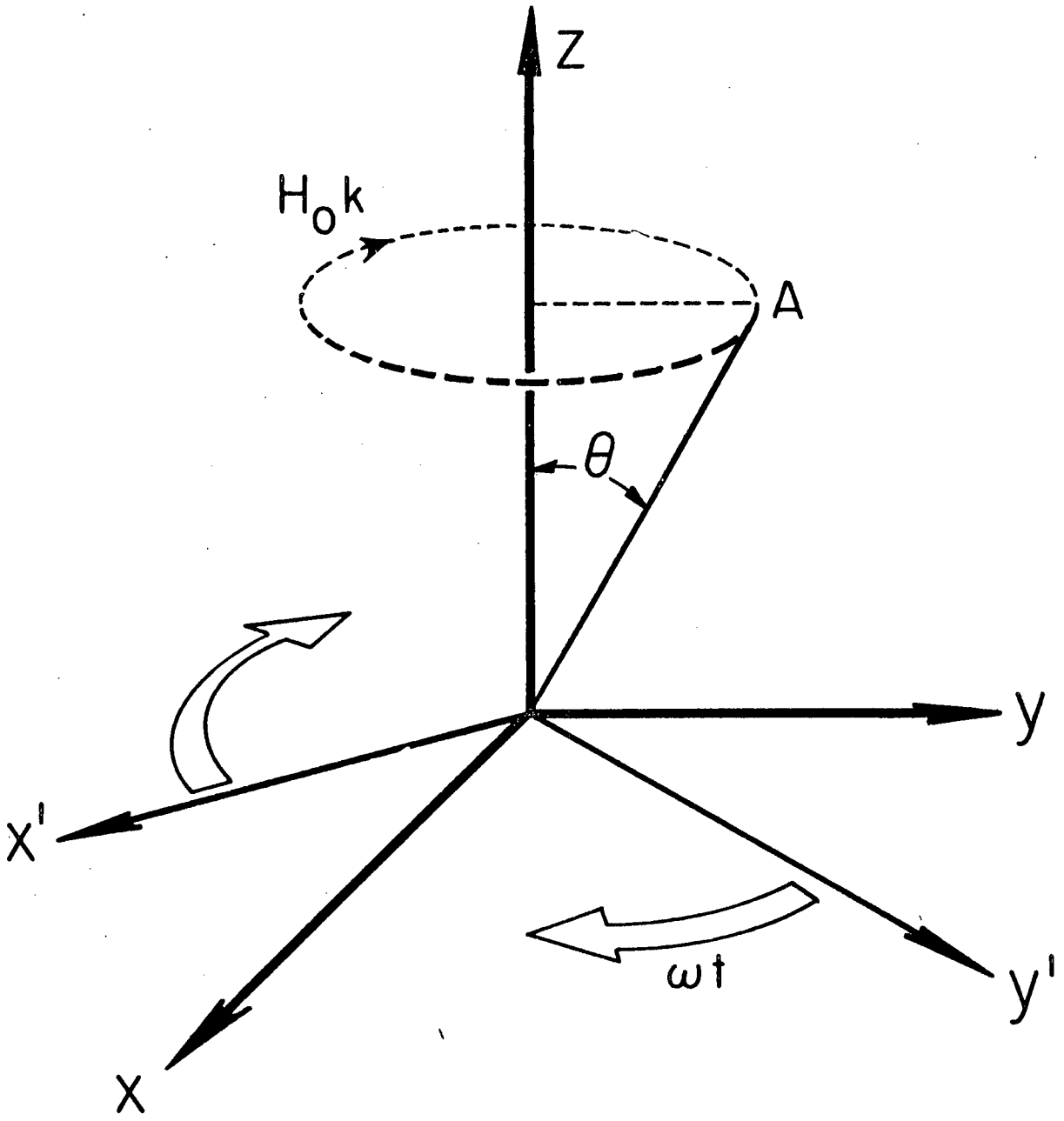
$$\frac{dM_Z}{dt} + \frac{M_Z - M_0}{T_1} - \gamma H_1 v = 0 \quad (4c)$$

The equilibrium magnetizations remain constant in the rotating frame and so their time derivatives can be equated to zero and a steady state solution of them obtained.

The components of the magnetization discussed are shown in fig. (1).

Chemical exchange is the flipping of a nucleus between two or more sites of different environment i. e., of different Larmor frequencies. The lifetime in a given site is the inverse of the rate constant k when the exchange is unimolecular and of first order which is true for the cases studied in this work. The relation of the lifetime to conventional rate constants for more complex systems is discussed by Loewenstein and Connor (5).

The study of exchange kinetics by N.M.R. is divided into



two main sections:* Steady State methods and Spin Echo methods. In the most common steady state methods the Bloch equations have been modified to allow for exchange by introducing the lifetime parameter in the form of an additional relaxation term. (6) (7). The steady state spectrum is then analysed on the basis of the resulting equations to obtain the lifetime and hence the rate constant. Also quantum mechanical treatments have been made of exchange modified lines (8, 9) and used experimentally (10).

In the spin echo methods there are two main theories, giving essentially the same result, which describe the decay of echo amplitudes in a Carr-Purcell sequence of pulses (11) in the presence of exchange. In the Bloom, Reeves, Wells treatment (12) (used extensively in this work) probability theory is used to calculate phase angle distribution in the $x'y'$ plane and a matrix operator technique to generate amplitudes of alternate echoes. The Allerhand and Gutowsky treatment (13, 14) obtains the same result from the Bloch equations.

These techniques will be discussed in greater detail and the relative advantages of each for the range and accur-

*This is not strictly true in that a pulsed double resonance technique exists (a mixture of steady state and pulse methods) and will be mentioned later.

acy of determination of rate constants will be given.

In this thesis a study of chemical exchange by the spin echo method is carried out for the hindered rotation about the C --- N bond in N;N dimethyltrifluoroacetamide and N;N dimethyldeuteroformamide. The accuracy obtained is discussed and the advantages over previous steady state studies (15, 16) suggested. Steady state studies of the kinetics of conformational isomerization in N;N dimethylpiperazine and the proton exchange between methanol and two phenols (meta-cresol and ortho-hydroxyacetophenone) are given in appendices I and II and their relative shortcomings discussed.

The Steady State Methods.

The modification of the Bloch equations to include the effect of exchange was first made by Gutowsky, McCall and Slichter (6) and later presented in a simpler, more general form by McConnell (7). The following treatment is based on their work.

We will consider a simple two site case where the nuclei are flipping between sites A and B. The time spent between sites is considered negligible compared to the lifetime in a particular site, τ_A and τ_B . If we assume H_1 is small then M_Z will not be altered from its equilibrium value M_0 .

We define a complex resultant moment of magnetization

$$G = u + iv \quad (5)$$

and from the Bloch equations obtain

$$\frac{dG}{dt} + \left[\frac{1}{T_2} - i(\omega_0 - \omega) \right] G = -i \gamma H_1 M_0 \quad (6)$$

The two equations of this type for site A and site B can now be modified for exchange by use of the lifetime parameter τ_A (and τ_B):

$$\tau_A^{-1} = \text{probability per unit time of nucleus flipping from A} \longrightarrow \text{B}$$

$$\therefore \tau_A^{-1} G_A = \text{rate of decrease of } G_A \text{ due to transfer A} \longrightarrow \text{B.}$$

Therefore we have, replacing $\left[\frac{1}{T_2} - i(\omega_0 - \omega) \right]$

by α , that in the presence of exchange

$$\frac{dG_A}{dt} + \alpha_A G_A = -i \gamma H_1 M_{0A} + \tau_B^{-1} G_B - \tau_A^{-1} G_A \quad (7a)$$

$$\text{and } \frac{dG_B}{dt} + \alpha_B G_B = -i \gamma H_1 M_{0B} + \tau_A^{-1} G_A - \tau_B^{-1} G_B \quad (7b)$$

The time derivatives can be equated to zero and the equations solved as in the case of the normal Bloch equations; (noting that $M_{0A} = P_A M_0$ and $M_{0B} = P_B M_0$ where P_A and P_B are the fractional populations of the sites) giving

$$G = G_A + G_B = -i \gamma H_1 M_0 \frac{\tau_A + \tau_B + \tau_A \tau_B (\alpha_A P_B + \alpha_B P_A)}{(1 + \alpha_A \tau_A)(1 + \alpha_B \tau_B) - 1} \quad (8)$$

Since the v component is proportional to the absorption intensity, this is given by the imaginary part of equation (8) for the exchange modified signal. Equation (8) can be simplified to study the regions of slow and fast exchange. We shall use a simplification suggested by Piette and Anderson (17) to examine these regions. We define a new relaxation time

$$T_2' \text{ by } \frac{1}{T_2'} = \frac{1}{T_2} + \frac{1}{\tau} \quad \text{_____ (9)}$$

The slow exchange is defined by

$$|\omega_A - \omega_B| T_{2A,B}' \gg 1 \quad (\text{i.e., } k < \delta\omega)$$

If $\omega \sim \omega_A$ then $\omega_A - \omega_B = \omega - \omega_B$

and we can neglect terms involving

$$\frac{1}{|\omega_B - \omega| T_{2A}'}$$

in the determination of the imaginary part of G giving us

$$v = -\gamma H_1 M_0 \frac{P_A T_{2A}'}{1 + (T_{2A}')^2 (\omega_A - \omega)^2} \quad \text{_____ (10)}$$

which is analogous to the normal solution for v obtained from the Bloch equations and hence describes a signal centred at ω_A with width defined by $\frac{1}{T_{2A}'}$. Similarly, if

$\omega \sim \omega_B$ we will have a signal at ω_B with width $\frac{1}{T_{2B}'}$.

Hence if T_2 can be estimated the lifetimes can be obtained.

The fast exchange region is defined by

$$|\omega_A - \omega_B| T_{2A,B}' \ll 1$$

and τ is usually less than T_2 . Therefore using

$|\omega_A - \omega_B| \tau \ll 1$ in the determination of v we get

$$v = -\gamma H_1 M_0 \frac{T_2'}{1 + T_2' (P_A \omega_A + P_B \omega_B - \omega)^2} \quad (11)$$

This describes a signal centred on $P_A \omega_A + P_B \omega_B$ with

width $\frac{P_A}{T_{2A}} + \frac{P_B}{T_{2B}}$. This is in the limit of fast ex-

change and a more correct form can be obtained by substi-

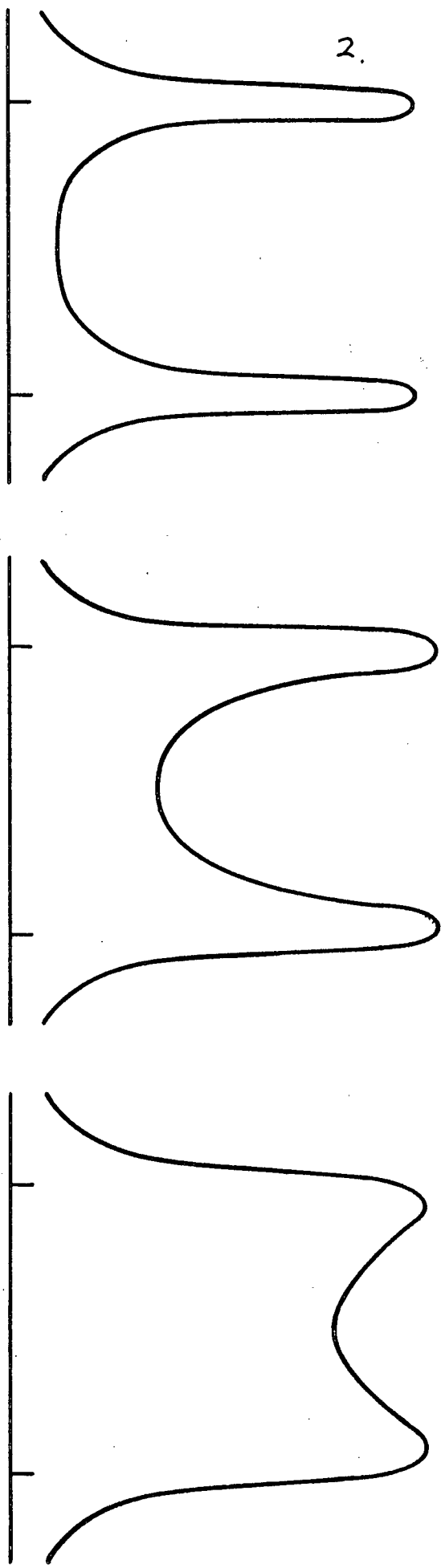
tuting $\omega = P_A \omega_A + P_B \omega_B$ in equation (8) giving

$$\frac{1}{T_2'} = \frac{P_A}{T_{2A}} + \frac{P_B}{T_{2B}} + P_A^2 P_B^2 (\omega_A - \omega_B)^2 (\tau_A + \tau_B) \quad (12)$$

from which the lifetimes can be obtained.

In the case of intermediate exchange, where the rate constant is of the order of the frequency difference between the sites, and no approximations can be made, the imaginary part of G can be calculated (16) and used to compute a line shape which can be compared with experiment to determine the lifetimes. In figure (2) the line shape for increasing exchange rates is shown for the simplified case of two sites with equal populations and lifetimes and large values of T_2 such that $\frac{1}{T_{2A}} = \frac{1}{T_{2B}} = 0$.

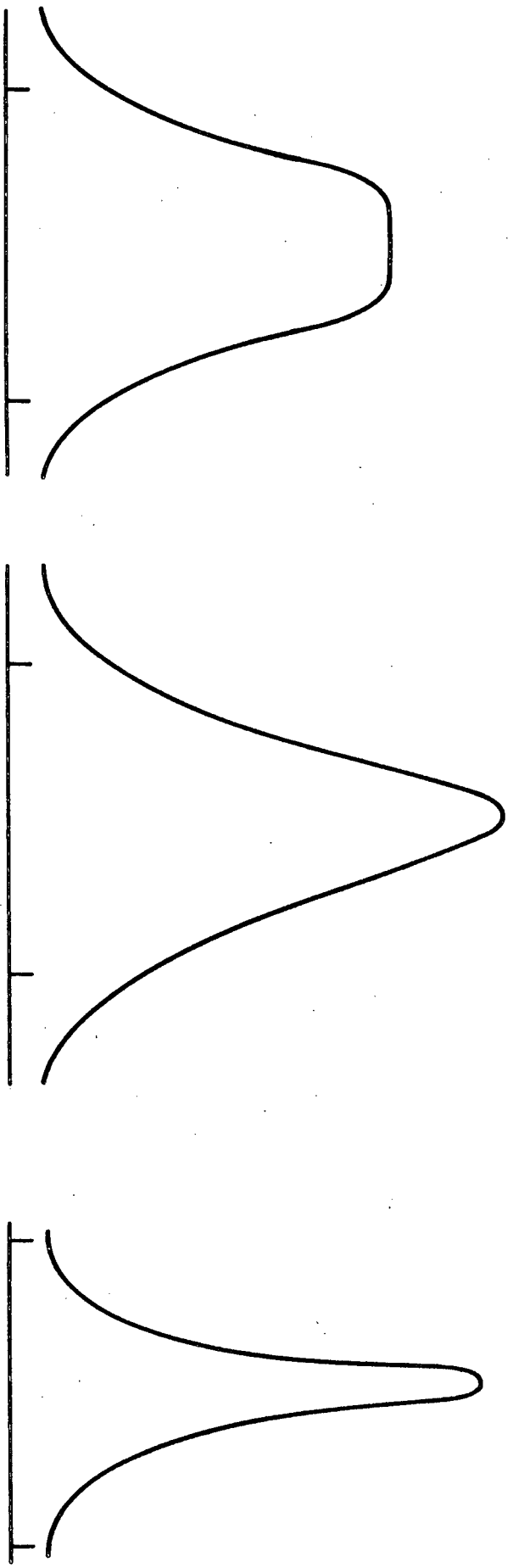
2.



$$\tau(\omega_A - \omega_B) = 10$$

$$\tau(\omega_A - \omega_B) = 4$$

$$\tau(\omega_A - \omega_B) = 2$$



$$\tau(\omega_A - \omega_B) = 10$$

$$\tau(\omega_A - \omega_B) = 4$$

$$\tau(\omega_A - \omega_B) = 2$$

The v component for this case is given by

$$v = -\frac{1}{4} \gamma H_1 M_0 \frac{\tau (\omega_A - \omega_B)^2}{[\frac{1}{2}(\omega_A + \omega_B) - \omega]^2 + \tau^2 (\omega_A - \omega)^2 (\omega_B - \omega)^2} \quad (13)$$

Another simplification suggested by Loewenstein and Meiboom (18) and since used by Rogers and Woodbrey (15) relates the ratio of the maximum to the minimum intensities of a coalescing doublet in the intermediate exchange region to the mean lifetime. The equation used to study several N,N-dimethylamides (15) was

$$\tau (\omega_A - \omega_B) = \pm \frac{1}{\pi \sqrt{2}} \sqrt{r \pm (r^2 - r)^{\frac{1}{2}}} \quad (14)$$

where r is the above ratio and the equation is valid if

$\pi \sqrt{2} \tau (\omega_A - \omega_B) > 1$; that is if the overlap of the components of the doublet is negligible and also implying that $\frac{1}{T_{2A}} \ll \omega_A - \omega_B \ll \frac{1}{T_{2B}}$. When the natural line widths and chemical shift are such that overlap is not negligible in the absence of exchange, r can be calculated from the more detailed line shape function of Gutowsky and Holm (16) as a function of τ for given values of T_{2A} and T_{2B} and the results compared with experiment to determine the lifetimes. (15).

The most accurate of the above methods is the use of the complete classical line shape function (16) to fit the experimental spectra over all the exchange regions (slow,

fast, and intermediate). All of the other methods mentioned above are approximations or simplifications of the complete solution (16) and as such suffer in accuracy. The effect of spin-spin coupling in the spectrum has not been mentioned so far. If this exists in first order spectra it can easily be accommodated but in second order spectra if it is ignored considerable error must result in the lifetime determinations. The problem of coupling may be avoided by deuteration of the sites giving rise to it and then applying a strong R. F. field H_2 at the deuterium frequency while observing the proton spectrum. If selective deuteration is not feasible the problem can be solved, even when strong coupling exists, by the quantum mechanical treatment of the problem. (10).

Insofar as chemical exchange is merely a special case of general relaxation theories (2,8) it can be comprehensively treated by quantum mechanical methods (8,9,10). Alexander (10) using density matrix techniques (19) has derived a complete solution for the line shape of the steady state spectrum. An equation is derived to determine the time dependence of the nuclear spin density matrix (ρ) under the influence of chemical exchange

$$\frac{d\rho}{dt} = \left\{ (P\rho P - \rho) / \tau \right\} + \left\{ (\rho_0 - \rho) / T_1 \right\} - (\rho_{od} / T_2) + i [\rho \mathcal{H}] \quad (15)$$

where (1) P is the unitary exchange operator i.e.,

$$\psi(t) \rightarrow P \psi(t) \text{ under exchange}$$

$$\text{and } \rho(t) \rightarrow P \rho(t) P \text{ under exchange}$$

(2) τ is the correlation time for the exchange

(3) \mathcal{H} is the nuclear spin Hamiltonian for the system

(4) ρ_0 is $\exp(-\mathcal{H}/kT) / \text{Tr} \{ \exp(-\mathcal{H}/kT) \}$

(5) ρ_{od} includes all off diagonal elements of ρ

in a suitable representation.

(6) $\frac{1}{T_2'} = \frac{1}{T_2} - \frac{1}{T_1}$ describes all T_2 processes occurring.

This equation (15) is then transferred into the rotating reference frame (4) for ρ^ω (the density matrix in the rotating frame)

$$\text{where } \rho^\omega = \exp(i \omega \sum_j I_z^j) \rho \exp(-i \omega \sum_j I_z^j) \quad (4)$$

and the steady state (slow passage) solutions obtained, by setting $d\rho/dt = 0$, for the matrix elements of ρ^ω .

The expectation value of the transverse component of the total magnetisation, which is the quantity measured in the N.M.R. experiment, is now given by

$$\begin{aligned} \left\langle \sum_j (I_x^j + i I_y^j) \right\rangle &= \text{Tr} \left\{ \rho^\omega \sum_j (I_x^j + i I_y^j) \right\} \\ &= \sum_{kl} \rho_{kl}^\omega \sum_j (I_x^j + i I_y^j)_{lk} \end{aligned} \quad (16)$$

As a function of ω this gives a complete description of the steady state spectrum, the real and imaginary parts of (16) describing the dispersion and absorption modes

respectively. A line shape function so derived can be made completely general for the cases of both strong and weak coupling ($J/\delta\omega > 1$ and $J/\delta\omega < 0.1$ resp.)

Taking into account all the above there is still a severe limitation imposed on the range of exchange rates measurable by the steady state methods. The limit in the regions of slow and fast exchange, where the spectral lines are narrow, is imposed by the instrumental broadening of the line denoted by $\frac{1}{T_2}$ inhomogeneity. Defining an observed line width as $\frac{1}{T_2}$ obs. we have

$$\frac{1}{T_2} \text{ obs.} = \frac{1}{T_{20}} + \frac{1}{T_2} \text{ inhom.} + \frac{1}{T_2} \text{ exchange} = \frac{1}{T_2^{**}} + \frac{1}{T_2} \text{ exch.} \quad (17)$$

This relaxation process (T_2^{inhom}) will be present in all steady state spectra and will be obviously worse in true slow passage experiments due to instrumental instabilities during the period of the experiment. The contribution to T_2^{inhom} due to instabilities can be reduced by rapid passage techniques (17, 20, 21), which also increase the accuracy with which $T_2^{\text{obs.}}$ can be measured, so extending slightly the range of exchange rates measurable. This has been done successfully for both the slow and fast exchange regions in the d_{11} cyclohexane ring inversion (22).

In theory $\frac{1}{T_2}$ inhom. can be removed by spin echo tech-

niques as the experimenter has another parameter at his disposal, the pulse repetition frequency. The spin echo method and its application to the study of chemical exchange will now be introduced.

The Spin Echo Methods.

The spin echo as such was first developed by Hahn in 1950. The essential differences from steady state N.M.R are that the radio frequency is applied in the form of a short intense pulse of length t_w which tilts the magnetisation vectors from their equilibrium position in the rotating frame (along the z axis) by angle θ given by

$\theta = \gamma H_1 t_w$. After the end of the pulse the individual magnetisation vectors (called spin isochromats by Hahn) decay back to their equilibrium position along the z axis by T_1 and T_2 relaxation mechanisms. If t_w is adjusted such that $\theta = \pi/2$ the pulse is called a $\pi/2$ pulse and the vectors will be rotated into the $x'y'$ plane. At the end of the pulse the vectors in the $x'y'$ plane will dephase and fan out because some nuclei will precess faster or slower than the mean Larmor frequency (i.e., that of the rotating reference frame) as they experience slightly different fields (H_0). The instrument detects the vector sum of these spin isochromats and hence a decay of the signal is observed. This is called a free induction decay and has a time constant

given by $\frac{1}{T_2^*} = \frac{1}{T_{20}} + \frac{1}{T_2}$ inhom. The free induction decay contains all the information of the steady state absorption spectrum and is a Fourier transform of it (24), the line shape in the steady state spectrum $g(\Delta \omega)$ being given by

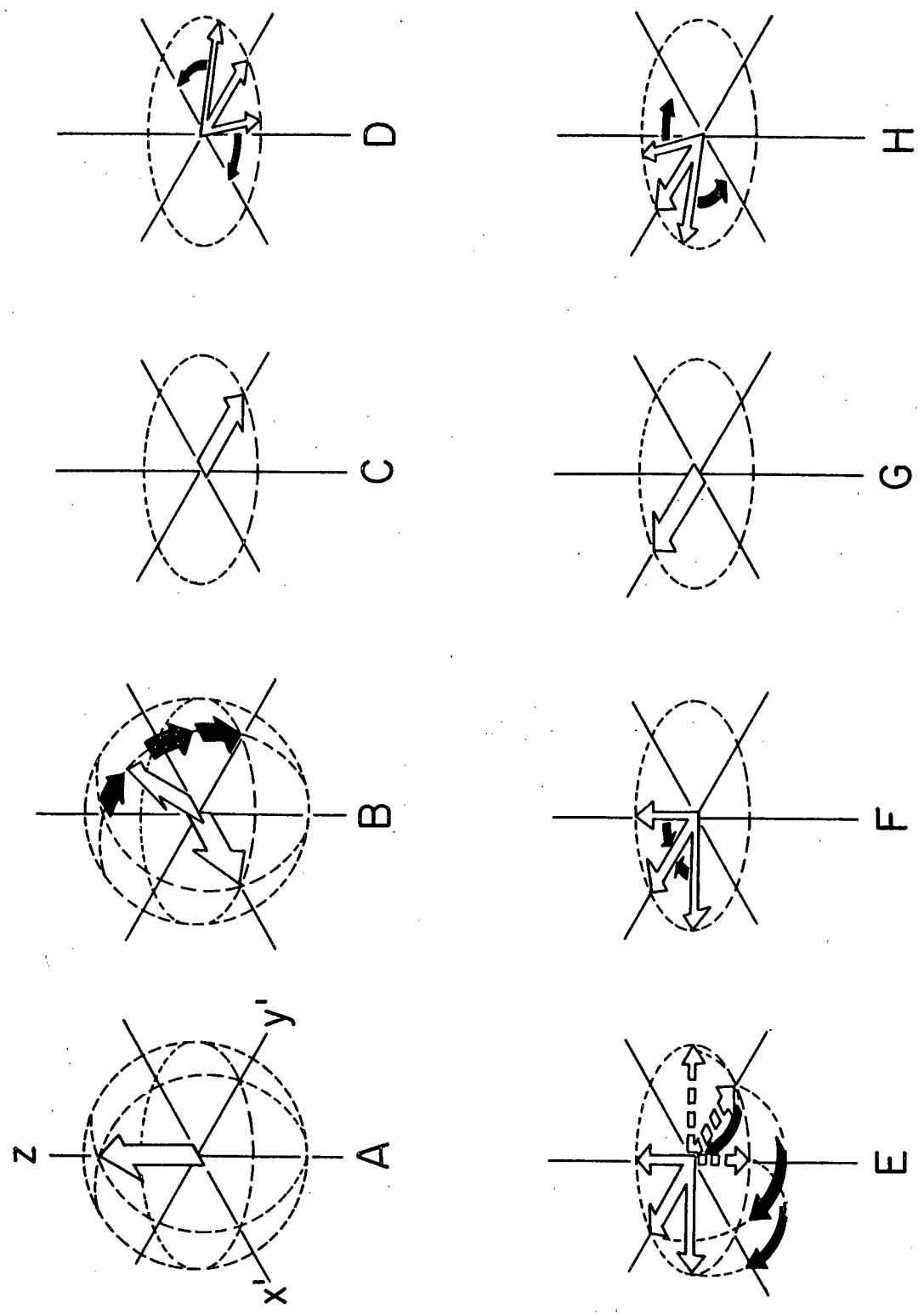
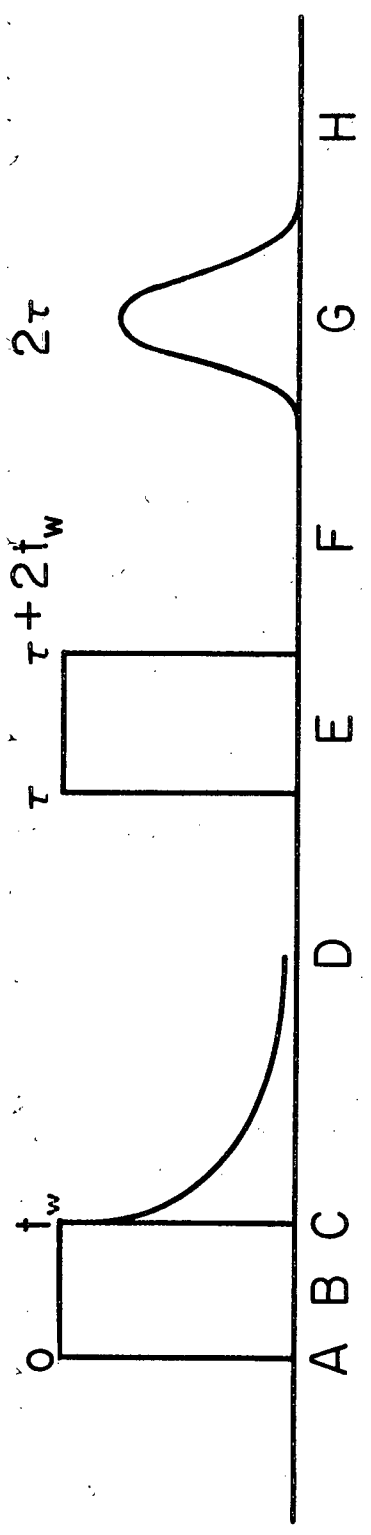
$$g(\Delta \omega) = (2\pi)^{-\frac{1}{2}} T_2^* \exp\left\{\frac{-(\Delta \omega T_2^*)^2}{2}\right\} \quad (18)$$

in the case of a single resonance line. (gaussian)

If a π pulse is now applied at time τ after the $\pi/2$ pulse, with the condition that $t_w \ll \tau \ll T_1$ or T_2 , the individual vectors are still in the x'y' plane but have been flipped through 180° and hence the dephasing process becomes reversed and the vectors refocus at time 2τ to give a spin echo (fig. 3). The amplitude of the echo is less than that of the induction decay because of the relaxation processes and would theoretically be proportional to $\exp(-2\tau/T_2)$ if T_2 was the only relaxation process. However, in liquids diffusion exists especially in an inhomogeneous field and contributes to the relaxation process giving us that (23):

$$\text{Echo amplitude} \propto \exp\left\{-\frac{2\tau}{T_2} - k \frac{(2\tau)^3}{3}\right\} \quad (19)$$

where $k = \frac{1}{4} \gamma^2 G^2 D$ and D is the diffusion constant and G is the mean value of the magnetic field gradient $\left(\frac{dH_0}{dl}\right)_{\text{avr}}$. (11). Carr and Purcell (11) suggested a



sequence of pulses which could be used to eliminate the diffusion effect. Their sequence was a $\pi/2$ pulse followed at time τ by a train of π pulses separated by 2τ with echoes appearing as before between the π pulses. (i.e., π pulses at times $(2n+1)\tau$ after an initial $\pi/2$ with echoes at times $2n\tau$). With this sequence τ can be made small and hence the diffusion term in equation (19) becomes negligible, and in the limit of fast pulsing the echo amplitudes will decay with a time constant T_2 . Chemical exchange leads to random dephasing of spins somewhat analogous to a diffusion process and can similarly be affected by changing the pulse repetition rate (2τ). It is reasonable to suppose therefore that $(\frac{1}{T_2})$ exchange can be investigated by the Carr Purcell experiment in a homogeneous field preferably (to minimise diffusion effects especially when pulsing slowly).

Theoretical treatments of the effect of exchange on the spin echo experiment have been few in number compared with the corresponding problem by steady state methods. Woessner (25) emphasised that the exchange process is analogous to diffusion in liquids, and as such its effect can be reduced by a rapid pulse repetition rate in the Carr Purcell experiment. He deduced the effect of two site exchange on the free induction decay using the Bloch equations and his results were verified experimentally by Reeves and

Wells (26). He also calculated the amplitude of echoes following a $\pi/2, \pi$ sequence of pulses neglecting diffusion effects and incorporating exchange; no method for obtaining the rate constant k was derived however.

Luz and Meiboom (27) more recently derived an approximate analytical expression describing the decay of echo amplitudes down a Carr Purcell train of pulses for the two site, fast exchange case from the McConnell equations (7).

$$\frac{1}{T_2(g)} - \frac{1}{T_{20}} = PaPb(\delta\omega)^2\tau [1 - 2\tau g \tanh(2\tau g)^{-1}] \quad (20)$$

where (1) $T_2(g)$ is the observed echo decay at pulse repetition rate g

- (2) T_{20} is natural relaxation time
- (3) τ is the mean lifetime between exchanges
- (4) Pa and Pb are the populations of the sites
- (5) $(\delta\omega)$ is the chemical shift.

This expression, which could be used beyond the region available to the steady state method, has been tested numerically by Allerhand and Gutowsky (13) and found to be quite accurate over a wide experimental range.

Allerhand and Gutowsky have since derived closed form expressions (14) for the echo envelope in a Carr Purcell sequence of pulses by modifying the Hahn-Maxwell-McConnell equations (28,7) for the time dependence of site magnetizations. This treatment gives a similar result to that of

Bloom, Reeves and Wells (12), which is used in the main in this thesis and will now be described.

The Bloom, Reeves, Wells treatment shows, using simple probability theory, that the alternate echo amplitudes in a Carr Purcell sequence are in general expressed by a sum of two exponentials for two site exchange with no spin coupling. The magnetization is given by:

$$M(4n \tau) = A_1 \exp(-r_1 4n \tau) + A_2 \exp(-r_2 4n \tau) \quad (21)$$

where n is the number of pulses, 2τ is the π pulse interval, r_1 and r_2 are the decay constants and A_1 and A_2 are dependent on the initial experimental conditions.

The usual experimental conditions imply that $A_2 \ll A_1$ and so the decay is exponential with time constant r_1 .

This treatment using only the assumptions of first order rate theory computes the phase angle distribution function $P(\phi, t)$ of nuclear spins in a plane perpendicular to H_0 ($x'y'$ plane) allowing any number of site transfers (ie any rate) and any number of pulses (ie any τ) in time t . Knowing $P(\phi, t)$ the nuclear magnetization can be calculated (29) as outlined below.

We have two sites A and B with populations P_a and P_b and Larmor frequencies ω_a and ω_b with reference to the central angular frequency ω_0 of the radiofrequency magnetic field $H_1(\cos \omega_0 t \underline{i} + \sin \omega_0 t \underline{j})$ that is

$\omega_a - \omega_0 = \omega_b - \omega_0$. The first order rate constants for transfer out of the sites are k_a and k_b secs^{-1} . At equilibrium the magnetization of nuclei in the A sites is $p_a k$ and in the B sites $p_b k$ in units of the equilibrium magnetization M_0 . Now after a $\pi/2$ pulse the magnetization is swung into the x'y' plane and in units of M_0 would be $\underline{M}(t) = [(P_a \cos \omega_a t + P_b \cos \omega_b t) \underline{i} +$

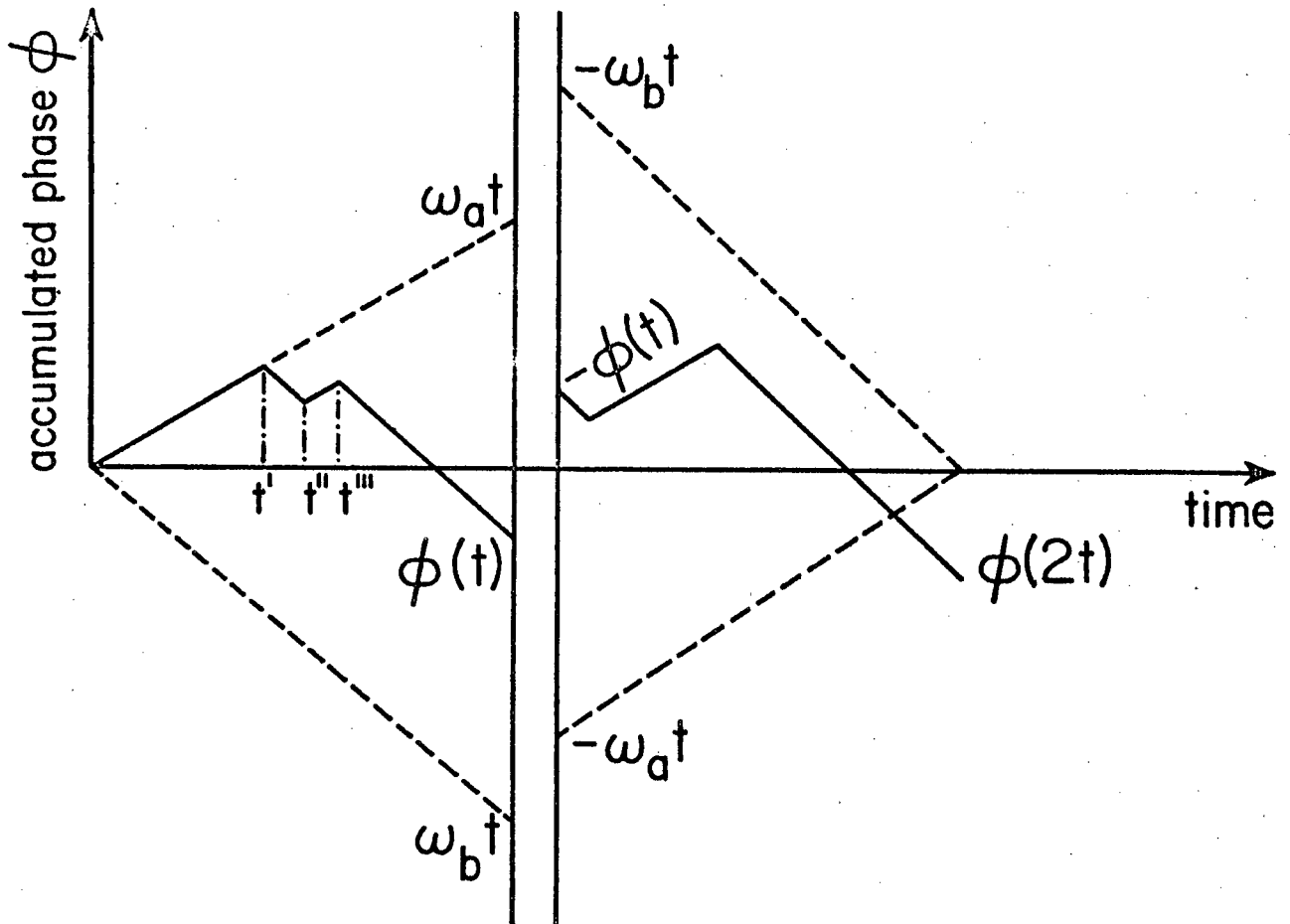
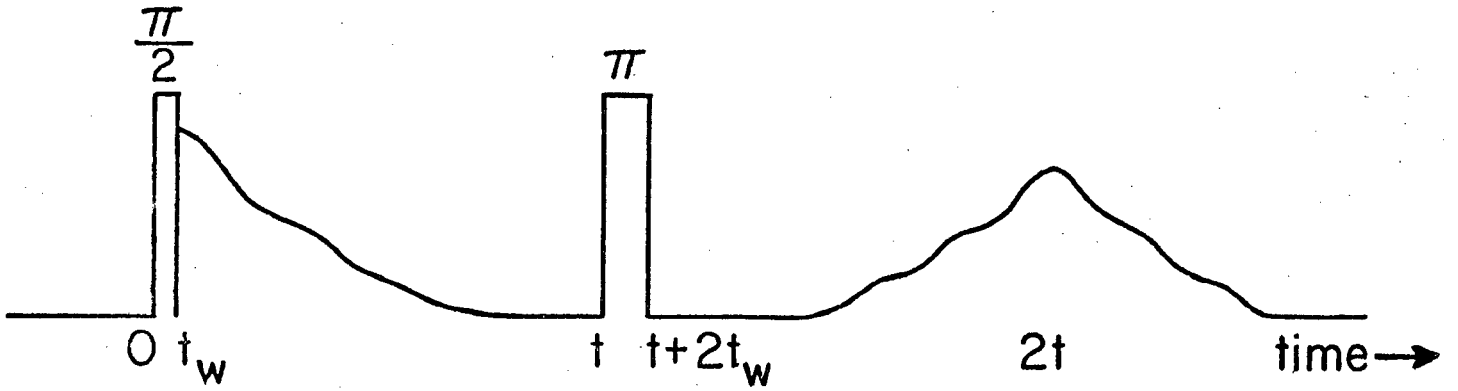
$$(p_a \sin \omega_a t + p_b \sin \omega_b t) \underline{j}] G(t) \quad (22)$$

where $G(t)$ is a relaxation function which can be ignored.

If $A \rightleftharpoons B$ then the precession frequency of an individual nucleus becomes time dependent $\omega(t)$ and the accumulated phase is given by $\phi(t) = \int_0^t \omega(t') dt'$ and not $\omega_a t$ or $\omega_b t$ as in (22). $\underline{M}(t)$ is now calculated by averaging $\cos \phi(t)$ and $\sin \phi(t)$ over all $\phi(t)$. (Figure 4 shows the accumulated phase of a spin as a function of time in a $\pi/2, \pi$ pulse sequence).

The calculation is accomplished using probability theory for the transfer $A \rightleftharpoons B$ knowing the respective lifetimes of A and B are $\frac{1}{k_a}$ and $\frac{1}{k_b}$. Four phase angle distribution functions are obtained:

$p^{aa}(\phi, t)$ for a nucleus in A at time $t=0$ and in A at time $t=t$
 $p^{bb}(\phi, t)$ " " " " B " " " " " B " " " "
 $p^{ab}(\phi, t)$ " " " " A " " " " " B " " " "
 $p^{ba}(\phi, t)$ " " " " B " " " " " A " " " "



Using these, average values for phase can be calculated from

$$\langle \exp [i \phi (t)] \rangle_{ij} = \int_{-1}^{+1} \exp [i \phi (x, t)] p^{ij}(x, t) dx. \quad (23)$$

where x is merely a transformation used to simplify the mathematics, $x = (2 \phi - \omega_a t - \omega_b t) / (\omega_a - \omega_b)$ and i and j are any of the sites. Thus four average phases are obtained as functions of k and ω for the four possible events above (where $\omega = \frac{1}{2}(\omega_a - \omega_b)$).

$$\langle e^{i \phi} \rangle_{aa}; \quad \langle e^{i \phi} \rangle_{bb}; \quad \langle e^{i \phi} \rangle_{ab} = \langle e^{i \phi} \rangle_{ba} \frac{k_a}{k_b}$$

Hence the magnetization is calculated, first for the free induction decay after a $\pi/2$ pulse then for an echo following a $\pi/2, \pi$ sequence and finally for the echo envelope of a Carr Purcell sequence by the introduction of an echo operator $\underline{\underline{E}}$ with element

$$E_{ij} = \sum_k \langle e^{-i \phi(\tau)} \rangle_{ik} \langle e^{i \phi(\tau)} \rangle_{kj} \quad (24)$$

For the first echo:

$$\underline{\underline{M}}(2\tau) = \underline{\underline{E}} \underline{\underline{M}}^*(0) \quad (25)$$

and thence for a Carr Purcell sequence:

$$\begin{aligned} \underline{\underline{M}}(4n\tau) &= \underline{\underline{E}} \underline{\underline{M}}^*[(4n-2)\tau] = (\underline{\underline{E}}\underline{\underline{E}}^*) \underline{\underline{M}}[(4n-4)\tau] \\ &= (\underline{\underline{E}} \underline{\underline{E}}^*)^n \underline{\underline{M}}(0), \quad n \text{ even} \end{aligned} \quad (26)$$

Two eigenvalues are found and a general formula for r_1 in equation (21) for the symmetric case (equal populations

and equal lifetimes) is computed.

$$r_1 = k - \frac{1}{2\tau} \sinh^{-1} F \quad (27)$$

where $\frac{1}{r_1} = \frac{1}{T_{2cp}} - \frac{1}{T_{2o}}$, T_{2cp} is the experimentally observed decay time (28)

$$\text{and } F = \left[k / (\omega^2 - k^2)^{\frac{1}{2}} \right] \sin 2(\omega^2 - k^2)^{\frac{1}{2}} \tau \text{ for } \omega > k \quad (29a)$$

$$\text{and } F = \left[k / (k^2 - \omega^2)^{\frac{1}{2}} \right] \sinh 2(k^2 - \omega^2)^{\frac{1}{2}} \tau \text{ for } \omega < k \quad (29b)$$

$$\text{and } F = 2k\tau \text{ for } \omega = k \quad (29c)$$

Some limiting cases of interest experimentally are easily derived from the above general formulae

(1) In the short τ limit ($k\tau \ll 1$, $\omega\tau \ll 1$ and valid for $\omega \geq k$ and $\omega \leq k$) we have that

$$r_1 = \frac{2}{3} k (\omega\tau)^2 \quad (30)$$

(2) In the long τ limit (slow pulsing \sinh $(k^2 - \omega^2)^{\frac{1}{2}} \tau \gg 1$)

we have (a) for slow exchange $r_1 = k$ (31a)

(b) for very fast exchange ($\omega \ll k$)

$$r_1 = \omega^2 / 2k \quad (31b)$$

(c) for fast exchange $\omega < k$

$$r_1 = k - (k^2 - \omega^2)^{\frac{1}{2}} \quad (31c)$$

Also in the short τ region we have that as $\tau \rightarrow 0$

$\frac{1}{T_{2cp}} \rightarrow \frac{1}{T_{2o}}$. Here we are pulsing fast enough to remove

the exchange contribution to the relaxation process.

The theory also predicts (as noted in Gutowsky's treatment (14) that in the long τ limit for slow exchange $\frac{1}{T_{2cp}}$ has a damped periodic amplitude when plotted against $\frac{1}{2\tau}$ logarithmically. It can be shown that the first maximum occurs when

$$2\tau (\omega^2 - k^2)^{\frac{1}{2}} = \frac{3\pi}{2} \quad \text{_____ (32a)}$$

and the frequency of the damped modulation in cycles is given by

$$\nu = 2\tau (\omega^2 - k^2)^{\frac{1}{2}} / 2\pi \quad \text{_____ (32b)}$$

The range of kinetic rates accessible to the spin echo method is increased from that accessible to steady state methods in both the limits of slow and fast exchange because of the increased accuracy in the T_2 measurement; the effect of $T_2^{\text{inhom.}}$ is no longer a critical factor because of the ability to pulse rapidly. T_{20} can also be extracted easily from the experimental results. The chemical shift also comes out of the data, k and ω being the unknown parameters extracted by fitting the experimental data to equation (27).

Another advantage is that heteronuclear coupling has no effect on the echo decay (28, 30) provided it is time independent or the amount that fluctuates with the exchange is small (31). The effect of homonuclear coupling

cannot be ignored however except for certain cases when it is small compared with k (31). A detailed theory has been developed to include the effects of homonuclear coupling by Gutowsky, Vold and Wells (32) but its practical application to the determination of rates is cumbersome.

The following work is an attempt to illustrate with what accuracy and range the spin echo method can be used to study chemical exchange. Much doubt exists concerning the precision of the rate constant determinations in the compounds studied in this work by other methods (16, 15, 33). This doubt is exemplified by the poor values obtained for the entropy of activation in previous work implying a low precision on the rate constant determination.

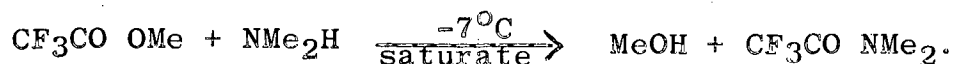
The study of chemical exchange as suggested so far has been divided between the steady state and the spin echo methods. There does however exist a technique which is a combination of both steady state and pulsed N.M.R. which may be used to study relaxation processes in a constant magnetic field. In that chemical exchange may be incorporated as a relaxation mechanism into the basic relaxation theories (2,8, 41) it is amenable to study by frequency sweep double resonance experiments (42). In general a density matrix treatment must be used to extract the relaxation information (42). The relaxation analysis may be simplified by observing single resonance line in-

tensities after the second field is turned off. This immediately suggests study when the second R.F. field is pulsed. Such a pulsed double resonance technique for the study of relaxation processes has been developed by Baldeschwieler (43). Though this technique has not as yet been used to derive kinetic data for chemical exchange the obvious application exists.

EXPERIMENTAL

1. Treatment of Compounds.

N,N-dimethyl trifluoroacetamide was prepared by the reaction of methyl trifluoroacetate and dimethylamine gas at -7°C . The solution was left at room temperature for twelve hours and the product N,N-dimethyl trifluoroacetamide (b. pt. 134 to 136°C) distilled out to 81% yield, the reaction being as follows,



Thanks are due to Dr. T.M. Connor, National Physical Laboratories, Teddington, England, for the gift of the compound N,N-dimethyl deuterioformamide previously synthesised by Merke, Sharpe and Dome.

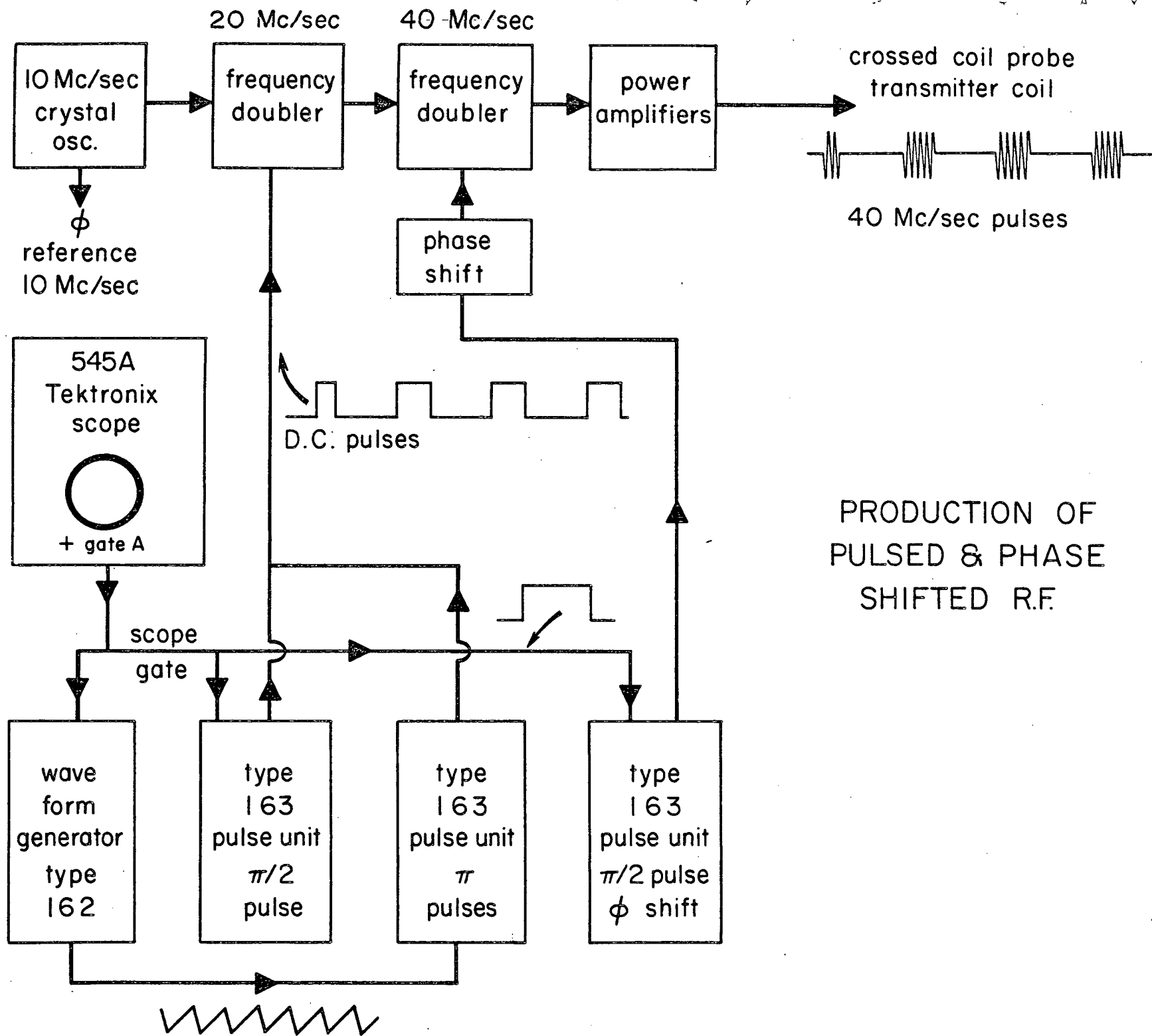
Experimental and literature values for physical constants agreed for the compounds. Each sample was thoroughly degassed and sealed in vacuo in N.M.R. tubes of 5mm o.d. after purification by distillation. The degassing procedure removes the paramagnetic oxygen dissolved in the liquids which would greatly shorten the T_2 value measured in the Carr Purcell experiment.

2. The Spin Echo Apparatus.

A spin echo spectrometer operating at 40 Mc/s. was con-

structed in our laboratories,* and will now be described. In fig. (5) the generation of the Carr Purcell pulse sequence (11) is illustrated. The radiofrequency generator consisted of a highly stable 10Mc/s crystal oscillator, a pulse modulator stage, two frequency doublers, a 40Mc/s. driver stage and a push-pull final amplifier stage. Careful interstage shielding was used to eliminate 40Mc/s. leakage during the "pulse off" period. Phase coherent 40Mc/s. R.F. pulses were obtained by allowing the 10Mc/s. oscillator to run continuously while pulse modulating the first doubler stage. A 90° R.F. phase shift during the $\pi/2$ pulse was accomplished in the second doubler grid circuit by means of the Meiboom, Gill method (35). In this method a pulse identical to the $\pi/2$ modulation pulse, switches a back-biased semiconductor diode into its conductive state; this procedure effectively places a phase-changing capacitor across the tuned circuit for the duration of the $\pi/2$ pulse. The 90° R.F. phase shift during the $\pi/2$ pulse served to minimise the effect of accumulative error which might occur in the width of the π pulses. (35). If H_1 for the π pulses is phase shifted by 90° from that for the $\pi/2$ pulse it is easy to see from fig. (3) that successive echoes will refocus at the same point and not 180° out of phase with each other and alternate π pulses will correct for any slight error

*Thanks are due at this point to Mr. K.A. Abramson and Mr. E. Fisher for valuable assistance in the construction and maintenance of the spin echo spectrometer.



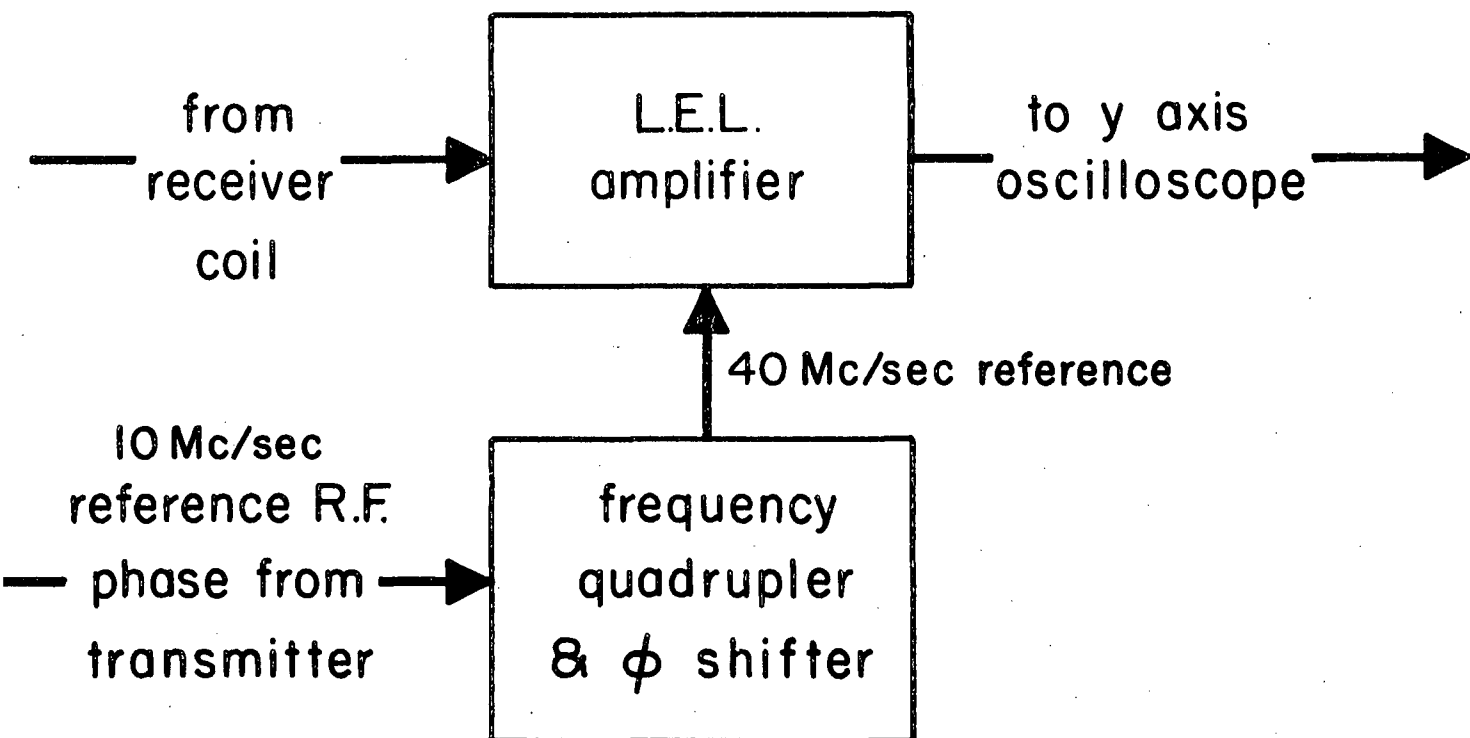
in their width.

The modulated pulse train was synthesized by the combined use of a Tetronix 545A oscilloscope, a Tetronix Type 162 waveform generator and three Type 163 pulse generators. A positive gate voltage was fed from the "+ Gate A" terminal of the oscilloscope to the trigger inputs of two Type 163 pulse generators (modified to give pulse amplitudes of + 90 volts peak). These two generators produced the single $\pi/2$ modulating pulse and the 90° R.F. phase shifting pulse. The $\pi/2$ and R.F. phase shift pulses were thus synchronized with the beginning of the oscilloscope sweep. In order to produce the modulating train of π pulses at times τ , 3τ , 5τ , etc., the same "+ Gate A" was used to gate a Type 162 waveform generator, producing a negative sawtooth train of variable frequency. This negative sawtooth train was used to trigger the remaining Type 163 pulse generator ("negative trigger" mode), producing the train of π modulating pulses. The train of π pulses could be delayed from the $\pi/2$ pulse simply by adjusting the "output pulse delay" control. The π pulse repetition period was adjusted by means of the "Pulse Interval" control on the waveform generator (Type 162).

A Varian cross coil probe was used and modified by appropriate changes of capacitors in the transmitter coil circuit to facilitate impedance matching. The probe can be used both for high resolution and spin echo operation.

The Varian probe, although quite inefficient in coupling R.F. energy from the transmitter coil to the sample, did give a homogeneous H_1 field as indicated by the complete disappearance of the induction tail after a π pulse in a $\pi/2, \pi$ sequence. Receiver coil orthogonality and leakage paddles used normally for high resolution N.M.R. experiments could be adjusted to obtain excellent isolation between the transmitting and receiving coils. This optimal isolation condition facilitated quick receiver recovery time (about three microseconds), and avoided inducing into the receiver coil large "ringing currents" which could distort the overall H_1 from the transmitter coils, thus causing H_1 to be inhomogeneous.

The receiver was a modified L.E.L. - I.F. amplifier which was used as a 40Mc/s broadband receiver. The receiver must have a bandpass much greater than $\omega_a - \omega_b(12)$. A block diagram of the receiver is shown in fig. (6). The preamplifier section used cascaded 5842 stages. Manual control of the receiver gain was provided by varying the grid bias of the third and fourth stages. Two means of detection were provided: ordinary diode detection and phase detection. In the phase detection mode, the receiver was supplied with a 10Mc/s. signal from the crystal oscillator of the transmitter. This signal was fed to two frequency doubler stages which produced a 40Mc/s. phase reference signal. The incoming N.M.R. signal from the

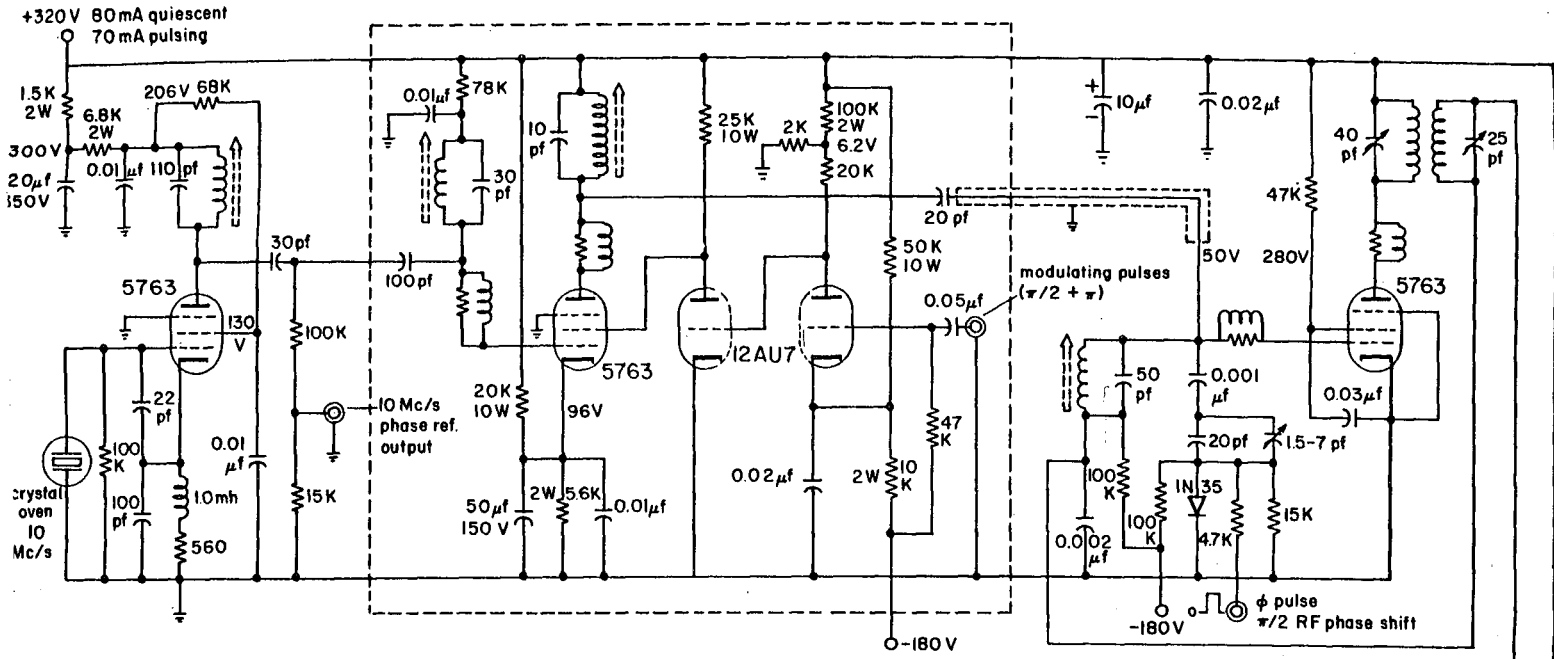


RECEIVER CIRCUITS

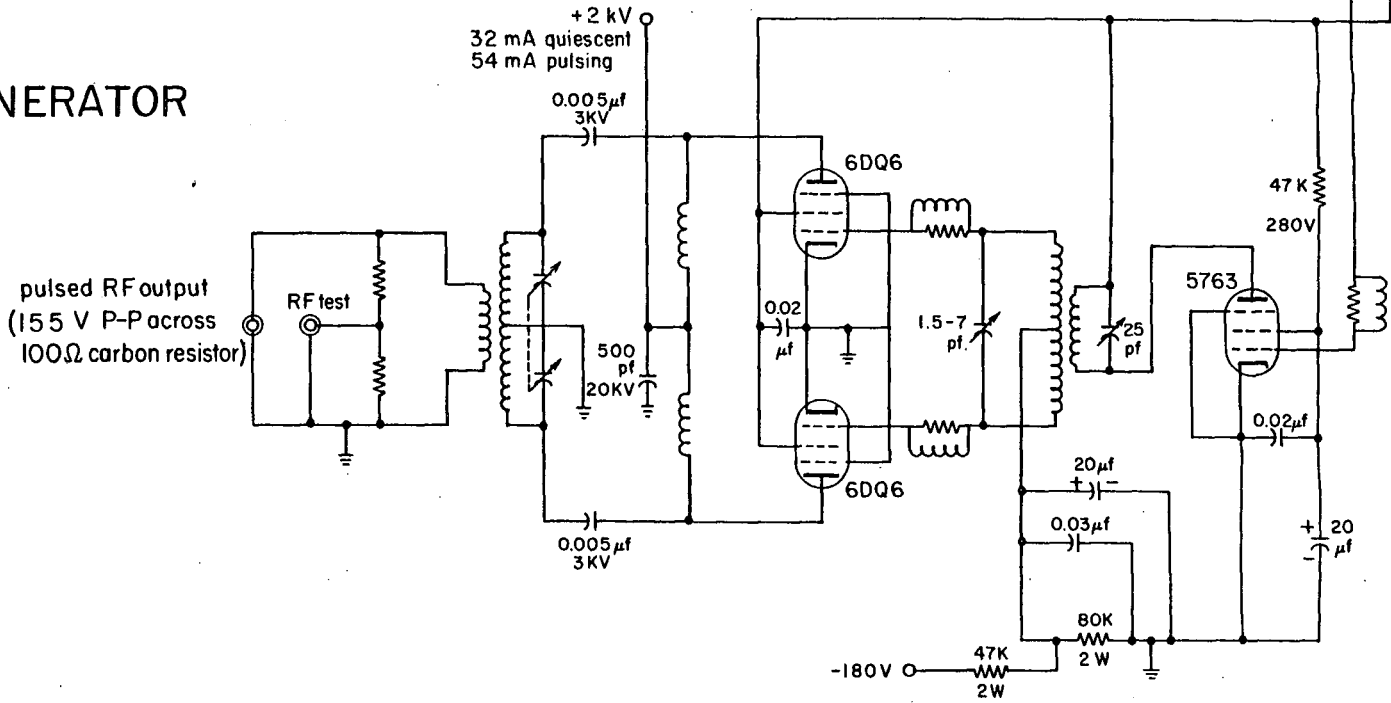
probe was then mixed with this 40Mc/s. phase reference signal in the input transformer of the receiver to produce a phase detected signal. Diode detection was used to study the Carr Purcell trains in this work and the phase detector used only to determine the resonance condition as will be described. Detailed circuit diagrams of the transmitter and receiver are shown in figs. (7) and (8) respectively.

A brief summary will now be given of the spin echo spectrometer:

- (a) Power Requirements: 120 Volts \pm 10%; 60c/s;
1500 Watts; 13 Amps.
- (b) Output Frequency: 40Mc/s.
- (c) Oscillator Frequency: 10Mc/s. crystal controlled.
The oscillator runs continuously for phase coherent R.F. pulses. Stability is approximately 1 part in 10^7 .
- (d) Power Output: 250 Watts peak power into a resistive load of 100 ohms. A $\pi/2$ pulse width of 15 microseconds is obtained with the cross coil probe indicating an H_1 of approximately 3.5 gauss.
- (e) Signal Presentation: 5" Tetrax 545A oscilloscope.
- (f) Signal Detection: Phase coherent diode or phase sensitive
- (g) π Pulse Repetition Periods (2τ in Carr Purcell sequence)
1.0 to 10.0 milliseconds in 11 steps with multiplier ranges of 10, 100 and 1000 (giving an overall range of 1 millisecond to 10 seconds).
- (h) Receiver: M.D.S. (minimum discernible signal) =
0.7 μ volts. Gain is variable from 0 to 200,000. Recovery time is 3 microseconds minimum.



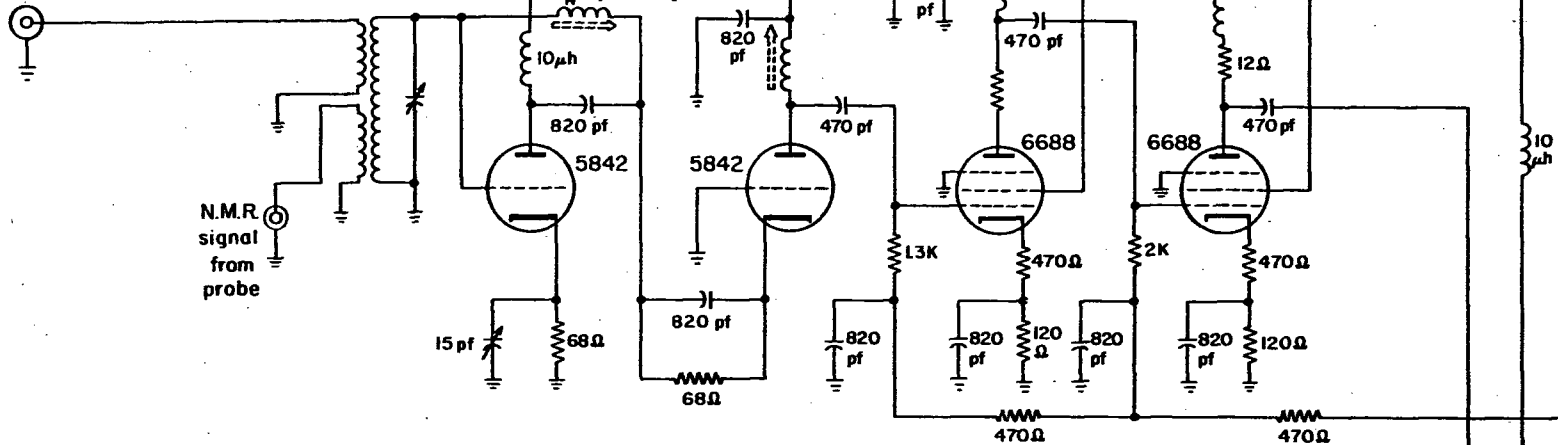
RF GENERATOR



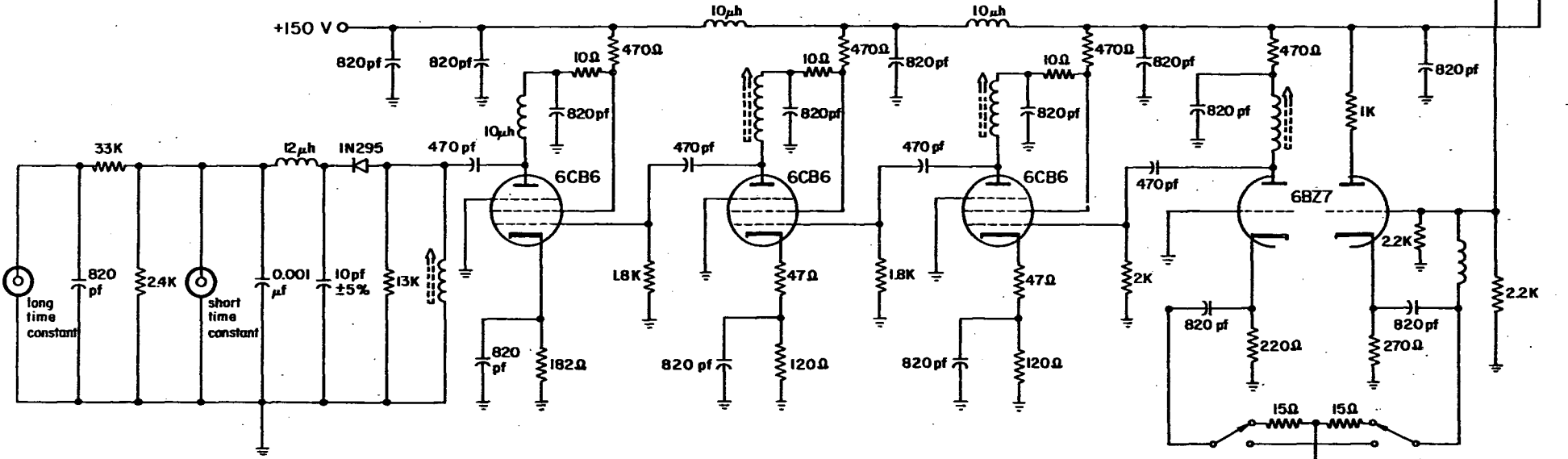
Input from Reference Amplifier / Multiplier



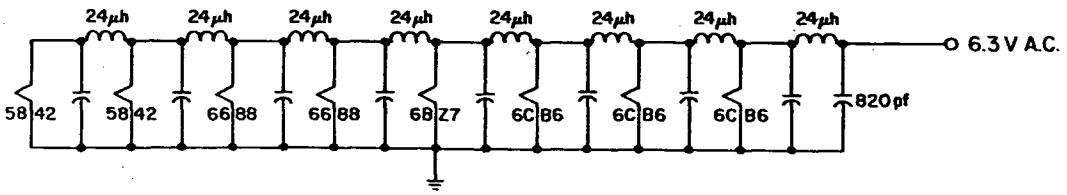
N.M.R. signal from probe



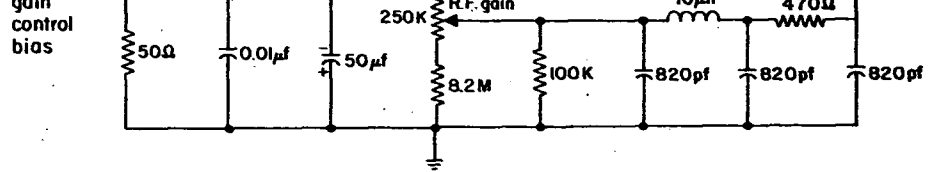
+150 V O



FILAMENT STRING



-5 V O



The magnetic field was provided by a Varian 12" magnet shimmed for high resolution experiments and with additional homogeneity trimming provided by a Varian V-4365 field homogeneity control unit. The magnet operated at a field of approximately 10 Kilogauss and gave a T_2^* (measured from the free induction decay of a non spinning sample) of 150 milliseconds under optimum homogeneity conditions.

The echo amplitudes were photographed with a Polaroid Oscilloscope Camera on 3000 A.S.A. film, and then measured. The π pulse interval (2τ) was timed on a Hewlett Packard 522B electronic counter.

The magnetic field could be swept by using a Varian Slow Sweep Unit (V3507) incorporated with a Super Stabilizer (V3506) which was also used to hold the field constant and minimise drift off resonance.

3. Temperature Control.

Variable temperature N.M.R. measurements present numerous problems to the experimenter. The restricted width of the magnet gap presents an immediate problem in size of the temperature equipment and usually necessitates a flow system for heat transfer to the sample. Also heat transfer to the magnet pole faces leads to homogeneity problems and so heat lagged, vacuum-jacketed or dewared instrumentation must be used. If the receiver coil is heated or cooled then base line stabilization becomes a problem in steady state

work though in spin echo experiments this is not a problem.

In this work a vacuum-jacketed receiver coil insert was used and a constant flow of air, the temperature of which was accurately controlled by means of a 600 Watt heater. The air was carried into and out of the probe by lagged leads, to limit the heat transfer to the pole faces and the corresponding deterioration of homogeneity at high temperatures. The temperature of the sample could be controlled to $\pm 0.5^{\circ}\text{C}$. at the high temperatures, and was measured by a copper-constantan thermocouple in the air inlet stream about an inch above the sample. This thermocouple was calibrated, for the differential between its temperature and that of the sample, against another thermocouple immersed in a sample in its normal position in the probe.

4. Experimental Technique.

Great care was taken with the experimental conditions in order to get as accurate a measurement as possible of T_2 by the Carr Purcell method. The usual precision obtained is $\pm 10\%$ in the T_2 value. Since accuracy in the rate constant determination is the main object of this work many more precautions were taken in making the T_2 measurement and it is felt that the precision in T_2 is $\pm 5\%$, at least.

A homogeneous H_0 field was used for all the measurements in order to eliminate the effect of diffusion espe-

cially when pulsing slowly. In a homogeneous field overlap of successive echoes occurred (24) and it was found that these homogeneity conditions were easily attained by first setting up a high resolution experiment in the magnet before switching over to the pulse experiment. It was found that the homogeneity so obtained was well above that required to shorten a given T_2 measurement.

Meticulous balancing of the probe is required in order to:

(a) facilitate quick receiver recovery time and thus provide good receiver sensitivity

(b) avoid inducing "ringing" currents in the receiver coil causing inhomogeneities in H_1 leading to short T_2 determinations. This balance was achieved by adjusting the probe paddles to reduce the central portion of a pulse into the noise level leaving only the high frequency components (the leading and tailing edges) of the pulse visible.

The tuning of the probe was quite critical in order to obtain the lowest possible pulse widths ($\pi/2$ of 15 μ secs). Therefore for tuning the spectrometer a sample with a T_2 of approximately 40 milliseconds was used (ordinary pump oil) so that it was not necessary to wait long between adjustments for the nuclei to relax.

The inclusion of the 90° phase shift (35) eliminated the effect of cumulative error in the π pulse width but since this phase shift causes the magnetisation to be refocused in the same direction, the coherent Carr Purcell

experiment may be as sensitive to radiation damping effects as the rapid passage "wobble beat" method of determining T_2^* (37). However, in the absence of any exchange the T_2 value obtained by the Carr Purcell method was found to be independent of homogeneity between $T_2^* = 1$ millisecc. and $T_2^* = 150$ milliseccs. The experiment in an inhomogeneous field gives sharp echoes (24) and therefore there is no continuous emission of coherent radiation and radiation damping is minimised.

The T_2 measurement is also very sensitive to the resonance condition (38). This is quite difficult to maintain in a field of relatively good homogeneity (i.e., where the resonance line is narrow.). The resonance condition was defined by mixing the free induction decay following a single $\pi/2$ pulse with the 40Mc/s. phase reference signal and sweeping the field to give a "zero beat" condition. This "zero beat" was observed for a fairly long period while adjusting the drift. Slight field drifts away from resonance can cause T_2 values greater than 5 seconds to be appreciably shortened. These slight field drifts over a period of time when measuring long T_2 's are the most difficult to eliminate, and the ideal solution to the problem would be a field-frequency locked spectrometer system.

5. Computation of Results.

An iterative FORTRAN computer program designated BESFIT was used to calculate the results from the experimental

data. The program was designed for use on an I.B.M. 7040 computer. The program uses a mathematical technique described by Margenau and Murphy (36).

Experimental values of $T_{2C.P.}$, T_{20} and τ are read in with trial values for k , the rate constant and ω , the chemical shift parameter. The best fit to equation (27) is computed and the sum of the squares of the errors printed out. The trial values of k and ω are changed by computed increments obtained by differentiating equation (27) with respect to k and ω . The process is repeated with the new trial k and ω and the best fit printed out on the basis of the minimum of the sum of squares of the errors. This was repeated for usually twenty iterations or until values of k and ω were converged upon to ± 0.5 .

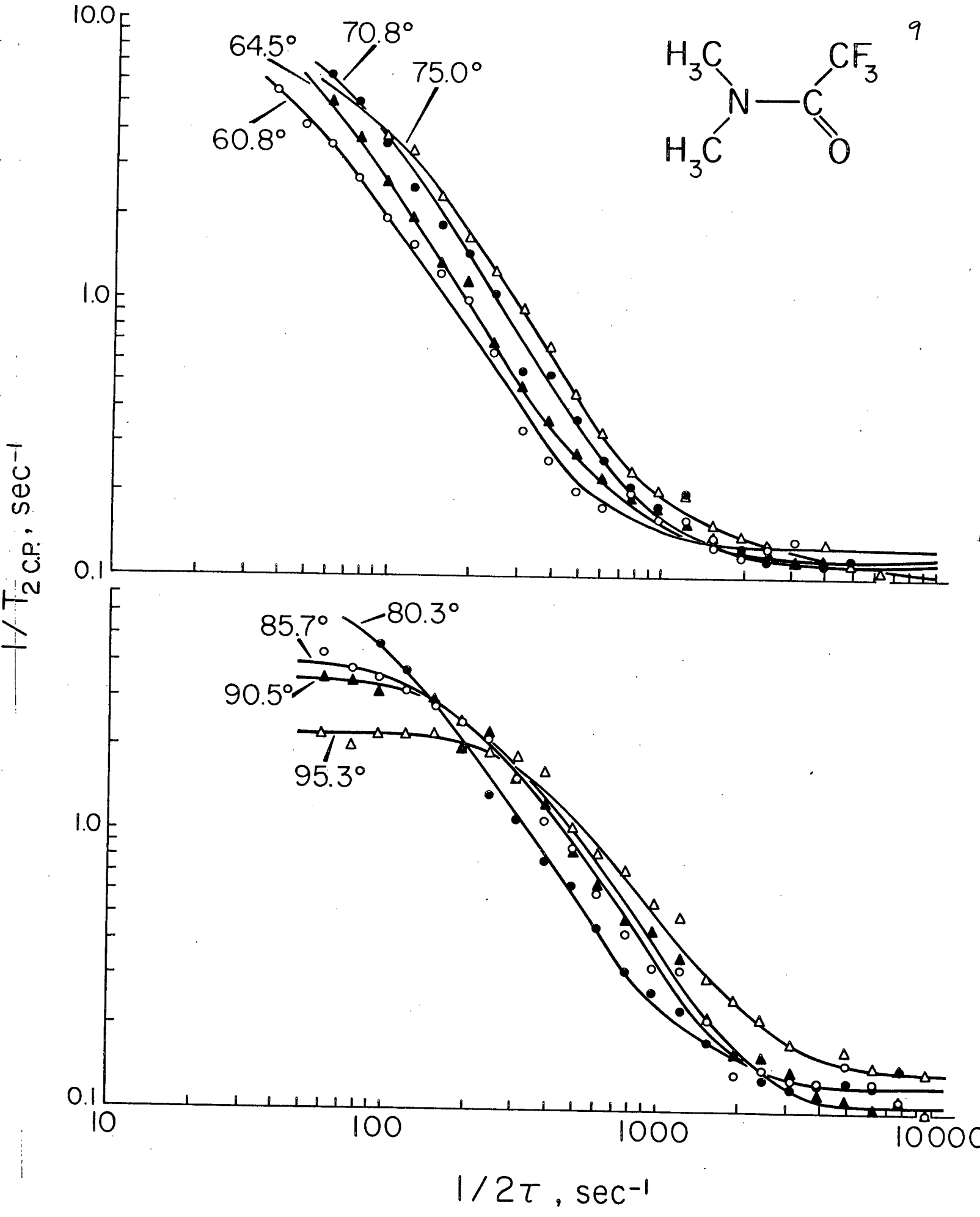
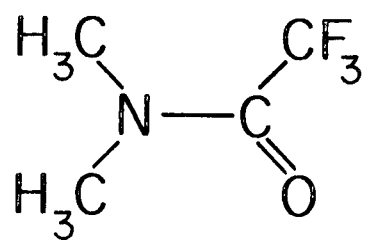
When a fit to equation (27) was not required and some of the limiting expressions were used, such as the short τ limit expression (30) a simple least squares program for fitting data to a straight line was used to calculate the results. This program was also used to obtain the activation energy and other kinetic parameters for the exchange.

RESULTS

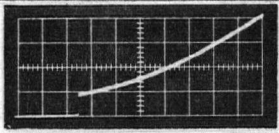
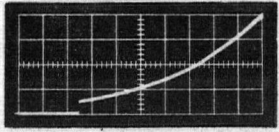
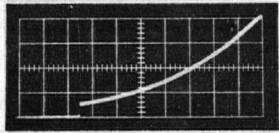
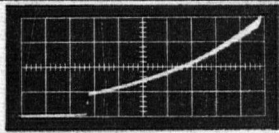
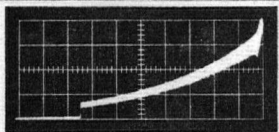
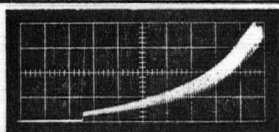
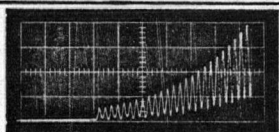
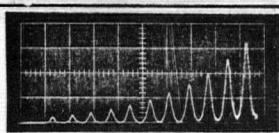
1. N,N, dimethyltrifluoroacetamide.

The proton T_{2cp} values observed for N,N-dimethyltrifluoroacetamide (as a pure liquid) are given in fig. (9) as log-log plots of $1/T_{2cp}$ versus $1/2 \tau$. T_{2cp} values covered a range from approximately 10 secs. to 0.1 secs. for a corresponding range of τ pulse interval (2τ) from 1 millisecc. to 0.25 secs. The performance of the apparatus, while using the Meiboom and Gill (35) phase shift, is illustrated in the form of some experimental Carr-Purcell trains obtained. The trains are given with their corresponding values of pulse interval (2τ), computed T_2 value (T_{2cp}) and time calibration, in fig. (10). The decays are all accurately exponential and with the larger pulse spacings the individual echoes can be resolved.

The results were fitted to equation (27), using the computer program previously described, to obtain k , the rate constant, and ω , the chemical shift parameter over the temperature range studied (60° to 95°C.). The values for the natural relaxation time (T_{20}) were determined from the limiting values of T_{2cp} in the fast pulsing limit (as 2τ tends to zero) in fig. (9) and from another technique which will be described later. The values obtained for the chemical shift parameter were found to be insensitive over



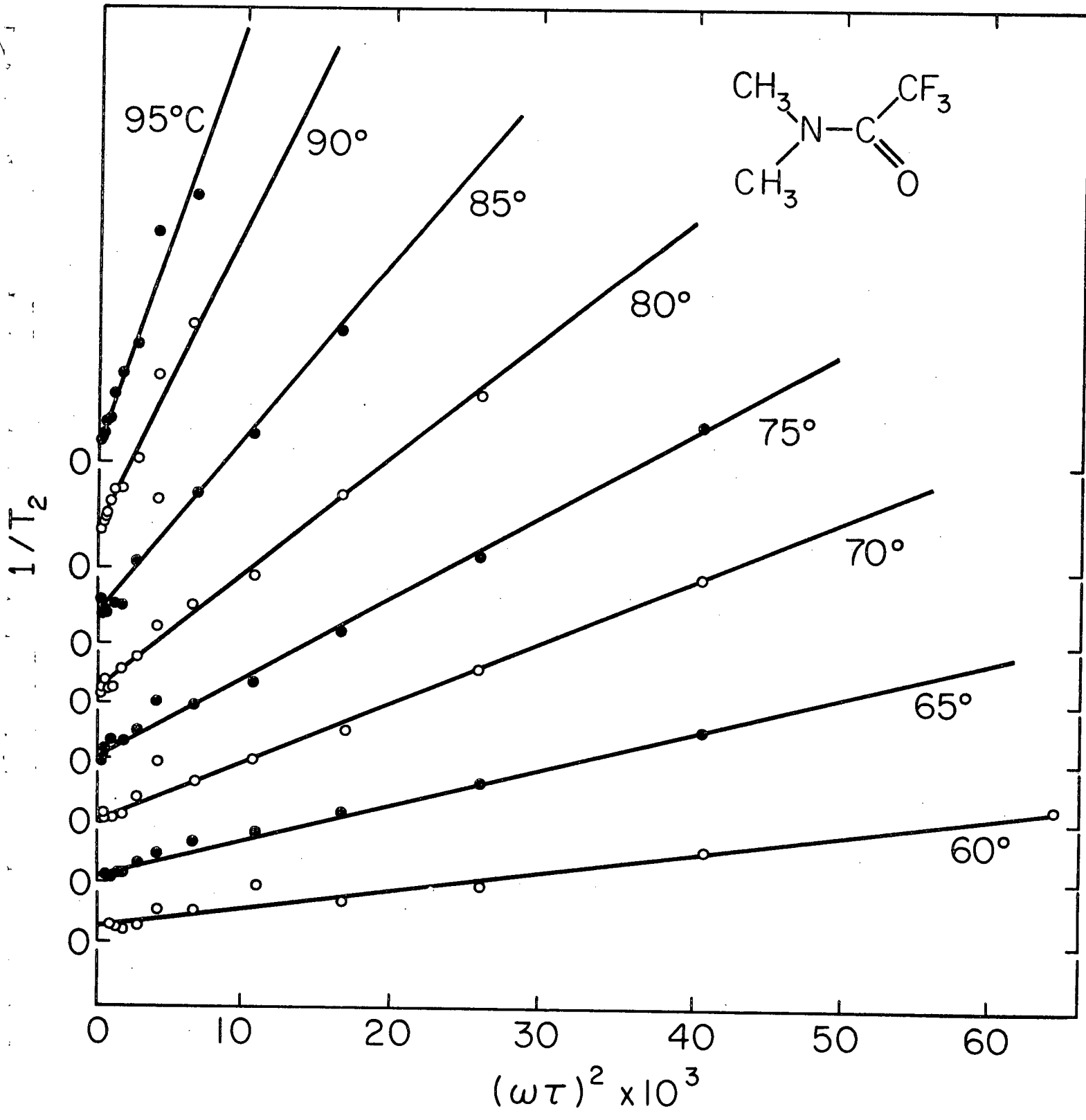
N,N-DIMETHYLTRIFLUOROACETAMIDE
CARR-PURCELL TRAINS AT 75° C

Pulse Interval (2τ), msec	Echo Decay	Time Scale sec/cm	T, sec
1.63		2.0	9.70
3.23		2.0	7.40
5.13		2.0	7.30
8.11		1.0	4.88
13.02		1.0	4.23
25.76		.5	1.50
51.35		.2	0.60
81.15		.1	0.30

the entire region studied and remained, within the limits of experimental error, equal to the steady state high resolution value of 15.7 radians/sec. at 40Mc/sec. This value was obtained from a low temperature, high resolution measurement made in this laboratory and agreed with that quoted in a previous study (15).

The rate constants were also obtained by using equation (30) in the fast pulsing limit. Within the validity of equation (30) the value of $1/T_{2cp}$ was plotted against $(\omega \tau)^2$ and a straight line of slope $\frac{2k}{3}$ obtained for each temperature. The results are given in fig. (11) and to avoid overcrowding, the values of $1/T_{2cp}$ are plotted without a scale and each temperature is vertically displaced on the diagram. The value of $1/T_{2cp}$ when $(\omega \tau)^2 = 0$ gives T_{20} , which may be used in the complete fit of the data to equation (27). The value of ω used was that obtained previously (15.7 rads/sec.). The rate constants obtained in this limit could be used as trial values in the computer program for the complete fit.

Although there was very little change observed in the region studied it was noted that T_{20} tended to increase slightly with temperature as expected since we are obviously below the critical correlation time for the random motions in the liquid, corresponding to the T_1 minimum (2). We are assuming here that $T_1 = T_{20}$, which is probably true for a low viscosity liquid such as the ones studied in this work.



The values of the rate constants, for the temperatures studied, obtained from the two above methods are given in Table I along with those obtained from a previous steady state study (15) for comparison. The mean values of T_{20} obtained are also listed for the temperatures studied. The relative merits of these values will be discussed in detail later.

The region studied is that in the neighbourhood of coalescence, the coalescence temperature being approximately 90°C . at 40Mc/sec. In this region the theory predicts the maximum change in T_2 as a function of pulse repetition rate, making it the most desirable region experimentally. The nature of the log-log plots of $\frac{1}{T_{2cp}}$ versus $1/2 \tau$ has been calculated from the basic theoretical equation (27) by Allerhand and Gutowsky (14) and the experimental curves in fig. (9) follow their predictions. In the limit as $1/2 \tau$ tends to infinity then $\frac{1}{T_{2cp}}$ tends to $\frac{1}{T_{20}}$ giving us the natural relaxation time as described above. In the slow pulsing limit of fast exchange (i.e. as $1/2 \tau \longrightarrow 0$) the value of $\frac{1}{T_{2cp}}$ approaches the line width of the steady state spectrum. In the limit of fast exchange this region is described by equation (31b) and it can be seen immediately that this equation is identical to that describing the steady state line width in the region of fast exchange (12). The values of k derived by use of equation (31b), and also (31c), which is slightly more accurate, from the limiting

TABLE IN,N-dimethyltrifluoroacetamide.

Temp. °C.	k(1) secs ⁻¹	k(2) secs ⁻¹	k(3) secs ⁻¹	T ₂₀ secs
60.0	4.20	4.72	4.98	7.52
64.5	9.10	9.00	-	8.33
70.0	12.90	14.54	6.53	8.85
75.0	17.30	19.80	8.04	8.62
80.3	18.40	28.82	9.46	7.94
85.7	35.70	44.72	12.60	8.83
90.5	47.00	81.39	14.40	10.64
95.3	88.70	103.11	-	7.19

- (1) Computer calculated fit to equation (27)
- (2) Least square analysis of equation (30)
- (3) Steady state study of Woodbrey and Rogers (15)

TABLE IIN,N-dimethyltrifluoroacetamide

(rate constants for fast exchange limit).

Temp. °C.	k (equation 31b) secs ⁻¹	k (equation 31c) secs ⁻¹
90.5	37.4	39.0
95.3	59.6	60.7

values of $\frac{1}{T_{2cp}}$ in this region are given in Table II for the two highest temperatures. The measurement of $\frac{1}{T_{2cp}}$ in the limit of slow pulsing suffers from the same inaccuracies as a steady state line width measurement and these rate constants, which are seen to be considerably lower than those determined from completely fitting the data to equation (27), must be considered approximate. However the experimental observation that as k increases the limiting value of $\frac{1}{T_{2cp}}$ for slow pulsing decreases, as in fig. (9), agrees with theory.

The results for the hindered rotation in *N,N*-dimethyltrifluoroacetamide are given as Arrhenius plots in fig. (12). The activation parameters were obtained by a method of least squares, used to obtain the slopes and intercepts of the Arrhenius plots, and are given in Table III along with those obtained by Woodbrey and Rogers (15) for comparison. The Arrhenius equation is:

$$k = A \exp(-E_a/RT) \quad (33a)$$

being used in form

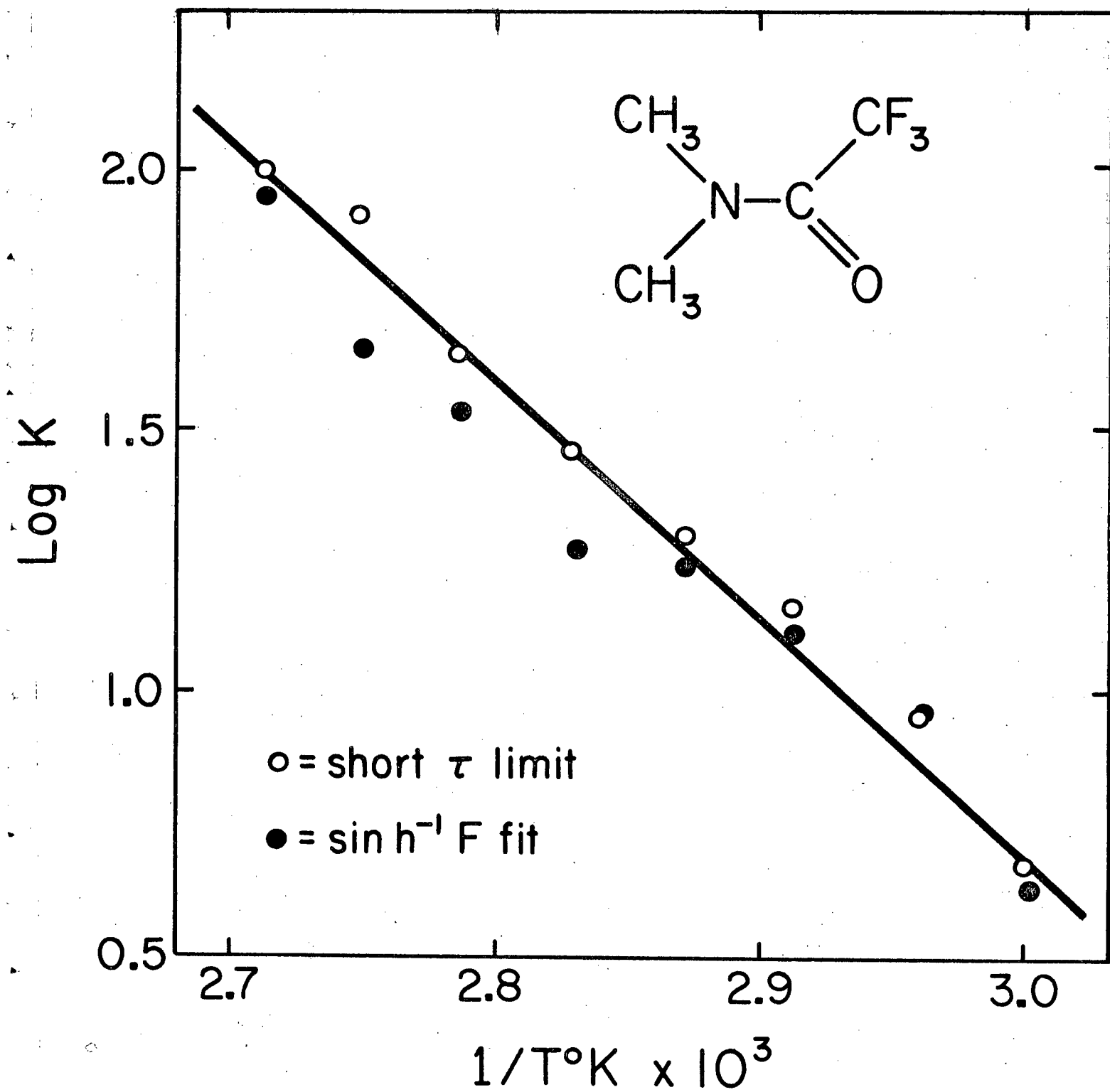
$$\log k = \log A - E_a/2.303RT \quad (33b)$$

To obtain the entropy (S) we have from kinetic theory that:

$$\text{for a unimolecular reaction } E_a = \Delta H + RT \quad (34)$$

where ΔH is the enthalpy in kcal/mole

$$\text{and } k = \left(\frac{kT}{h} \right) e^{\frac{S}{R}} e^{-\frac{\Delta H}{RT}} = \left(\frac{kT}{h} \right) e^{\frac{S}{R}} e^{-E_a/RT} \quad (35)$$



giving us that

$$\log A = 0.4335 + \log \frac{kT}{h} + S/2.303R \quad (36)$$

where k is the Boltzman constant = 1.381×10^{-16}

and h is Plank's constant = 6.624×10^{-27}

χ is the transmission coefficient which is assumed to be unity.

It is obvious from this last equation that, to obtain a reasonable entropy, which for a hindered rotation of this type must be a small number, the intercept of the Arrhenius plot ($\log A$) should be of the order of 13. Hence, this intercept, which is very sensitive to any systematic errors in k , gives a very good indication of the validity of the kinetic determination.

TABLE III

Activation parameters for N,N-dimethyltrifluoroacetamide.

	Sinh ⁻¹ fit (equation 27)	Fast pulsing Limit (equation 30)	Steady State (ref. 15)
Ea	18.5 ± 2.7	20.6 ± 1.4	9.3 ± 0.6
log A	12.84	14.26	6.8
S (at coalescence)	-2.33	4.22	-29.0

Ea = Activation energy (kcal/mole)

A = Frequency factor (secs⁻¹)

S = Entropy of activation (e.U.)

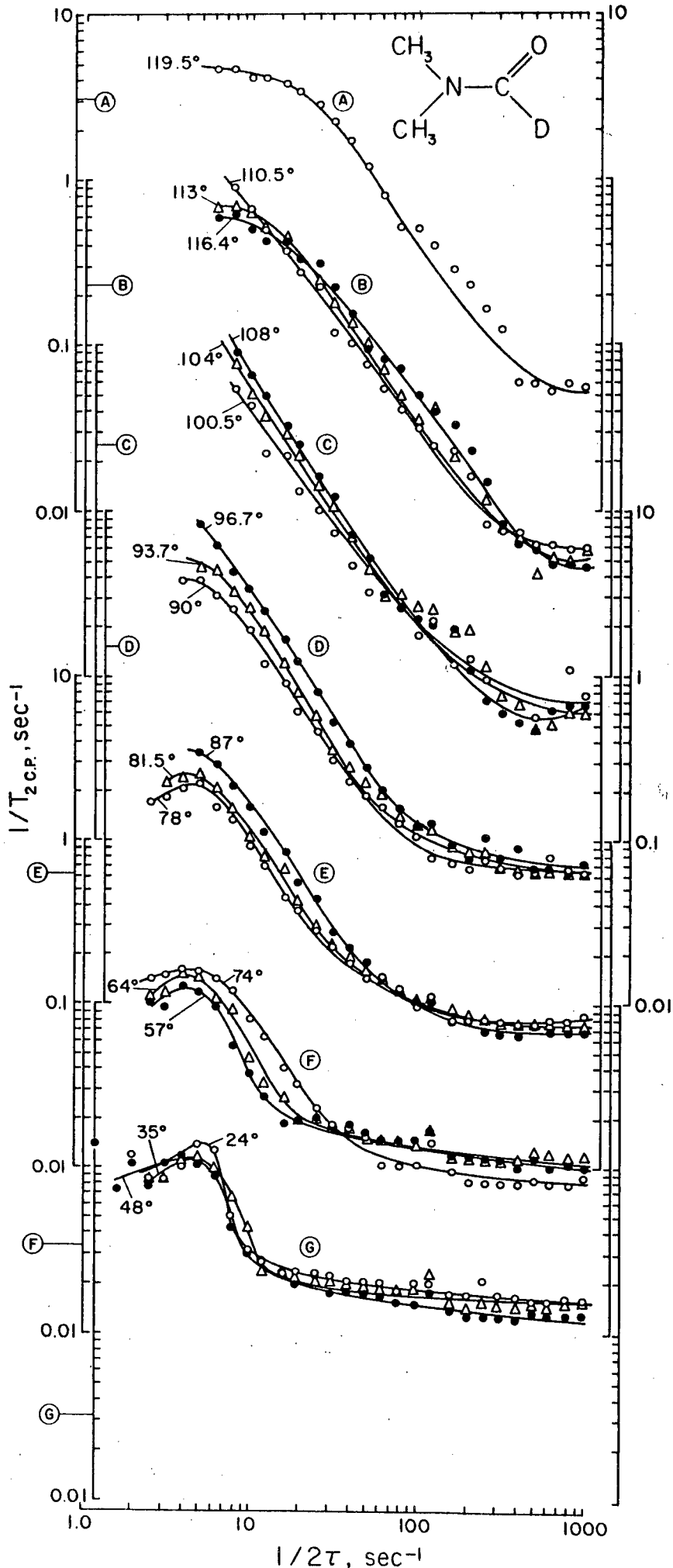
The random errors of the individual experimental parameters is estimated to be as follows:

- (1) T_{2cp} estimated at $\pm 5\%$ and probably slightly less in the region of slow pulsing.
- (2) T_{20} estimated at $\pm 10\%$
- (3) 2τ (τ pulse interval) estimated at better than $\pm 1\%$
- (4) k estimated at between 15 and 20%
- (5) ω estimated at $\pm 5\%$

The precision of the determinations is probably the same over the whole temperature region studied since it is near coalescence and a large change in T_{2cp} as a function of pulse interval was observed for all the temperatures studied. The values and errors given for E_a include the limits of 90% confidence, where the confidence limits and converts the standard error to the confidence limit desired.

2. N,N-dimethyldeuteroformamide.

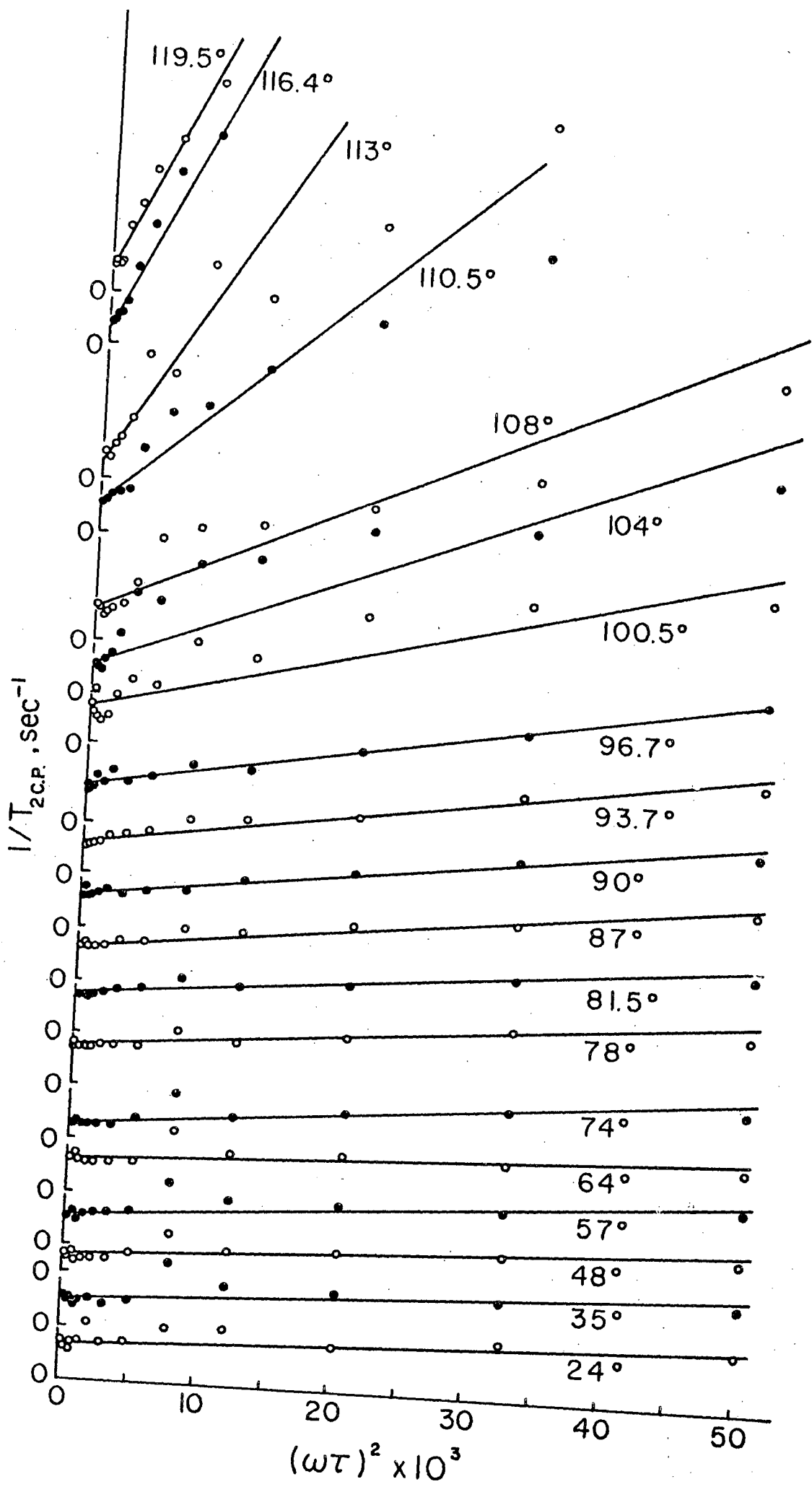
The rates of hindered internal rotation in N,N-dimethyldeuteroformamide were investigated in a similar manner but over a much wider range of the exchange rate than the previous molecule. The proton T_{2cp} values observed for the molecule as a pure liquid are given as log-log plots (as in the previous study) in fig. (13). The T_{2cp} values covered a range from approximately 20 secs. to 0.1 secs. for a corresponding range of τ pulse interval from 1 millisecc. to 0.5 secs. The kinetics were investigated over a range in



temperature from 24°C. (the very slow exchange region $k \ll \omega$) to 120°C. (the coalescence temp. being approximately 400°K at 40Mc/sec.). The Carr Purcell trains were accurately exponential except in the fast pulsing region at the higher temperatures ($> 100^\circ\text{C}$) where T_{2cp} is long (> 15 secs) and vigorous boiling of the sample interfered with the refocussing of the individual spin isochromats during the period of the trace. This rapid boiling of the sample prevented the investigation from being continued well into the region of fast exchange beyond coalescence.

The results were fitted to equation (27) as before to obtain k and ω for all the temperatures studied. In order to fit the data in the fast exchange region ($k > \omega$) the limits of convergence had to be increased. The difficulties encountered in fitting experimental data to the theory in this region will be discussed at length later. The values obtained for the chemical shift parameter (ω) were again found to be insensitive over the entire temperature range and remained, within the limits of experimental error, equal to the steady state high resolution value of 21.99 radians/sec. at 40Mc/sec., measured in this laboratory.

The T_{2cp} values obtained in the fast pulsing limit were used in equation (30) to determine the rate constants. The plots of $\frac{1}{T_{2cp}}$ versus $(\omega \tau)^2$ are given in fig. (14) as before. The correlation in these fast pulsing limit plots



is in general poorer than those obtained for N,N-dimethyl-trifluoroacetamide. This is probably due to the increased error in the measurement of longer T_{2cp} values (> 15 secs). The accuracy in the rate constants obtained from these plots is obviously poor, as will be exemplified by the entropy of activation they yield. However, they can be used as trial values in the computer program for the complete fit.

The values of T_{20} were obtained as before from the limiting value of T_{2cp} in the fast pulsing region and from the intercepts in the short τ limit plots of $\frac{1}{T_{2cp}}$ versus $(\omega \tau)^2$. Some measurements of T_1 , the spin lattice relaxation time, were made as a check on the T_{20} values. The technique used was one suggested by Carr and Purcell (11). Multiple exposure pictures were taken of the free induction decay following a π , $\pi/2$ pulse sequence as a function of pulse separation. The T_{20} values obtained are listed in Table IV.

The T_{20} values show a marked temperature dependence and this dependence is plotted in fig. (15) as $\log \left(\frac{1}{T_{20}} \right)$ against $1/\text{Temp}$ ($^{\circ}\text{K}$). The normal behaviour is observed as explained before and the slope of the line in fig. (15) gives the activation energy corresponding to the correlation time for the random motions in the liquid. The value obtained for this was 3.5kcal. which is of the order of Van der Waals forces as expected.

The T_{20} values used in fitting the data to equation (27) were those obtained from the limiting value of T_{2cp} in the region of fast pulsing. These were assumed to be more reliable than those obtained from the $(\omega\tau)^2$ plots because of the poor correlation in these plots as mentioned previously. The T_1 values measured are seen to be less than the corresponding T_{20} values. This is contrary to what one would expect if the T_{20} values obtained from the spin echo data were in error because of inability to pulse fast enough to remove the exchange contribution to the relaxation. Therefore the possibility of some systematic error in the T_1 measurement exists and the values are probably good to only 20%. The general tendency of T_1 to increase with temperature is however identical to that of T_{20} as seen in fig. (15).

The values of the rate constants obtained from the two above methods are given in Table V for all the temperatures studied.

The determinations at the low temperatures where k is less than unity are the most critical because of the limited change in the value of T_{2cp} in the region of very slow exchange ($k \ll \omega$). These determinations are probably the most inaccurate with the possible exception of the determination at 104°C. which is obviously in error. The relative merit of these rate constants in light of previous work will be discussed later.

TABLE IV

T₂₀ values for N,N-dimethyldeuteroformamide

Temperature °C.	T ₂₀ (1) secs.	T ₂₀ (2) secs.	T ₁ secs.
24.0	6.06	5.99	5.26
35.0	6.25	6.67	
48.0	7.41	7.69	
57.0	9.61	9.09	7.41
64.0	8.93	8.70	
74.0	11.90	12.50	
78.0	12.80	12.50	
81.5	13.70	13.30	
87.0	15.20	15.40	
90.0	15.60	15.60	
93.7	16.70	15.40	10.42
96.7	15.20	13.30	
100.5	15.60	16.70	
104.0	18.90	20.00	
108.0	17.90	20.00	
110.5	17.00	18.20	
113.0	20.00	28.60	
116.4	21.30	28.60	
119.5	22.20	22.20	

T₂₀(1): from limiting value of T_{2cp} in fast pulsing region

T₂₀(2): from $\frac{1}{T_{2cp}}$ vs. $(\omega\tau)^2$ plots.

TABLE V

Rate constants derived for the hindered rotation in
N,N-dimethyldeuteroformamide

Temp °C.	k(1) secs ⁻¹	k(2) secs ⁻¹
24.0	0.78	1.15
35.0	0.75	1.31
48.0	0.79	1.42
57.0	0.86	1.98
64.0	1.02	1.05
74.0	1.29	2.34
78.0	1.62	2.27
81.5	1.90	2.59
87.0	2.54	3.46
90.0	2.89	3.93
93.7	3.71	4.97
96.7	5.91	6.08
100.5	6.36	11.60
104.0	20.67	21.65
108.0	11.30	17.80
110.5	21.60	28.05
113.0	32.03	46.80
116.4	39.67	62.20
119.5	49.98	72.10

k(1) obtained by complete fit to equation (27)

k(2) obtained by least squares analysis of equation (30).

The nature of the log-log plots of $\frac{1}{T_{2cp}}$ versus $\frac{1}{2\tau}$ in fig. (13) follows the theoretical predictions over all the exchange regions. In the slow pulsing limit of fast exchange the value of $\frac{1}{T_{2cp}}$ approaches the line width of the steady state spectrum and the rate constants derived from this limiting value by use of equations (31b) and (31c) are given in Table VI.

TABLE VI

N,N-dimethyldeuteroformamide
(rate constants for fast exchange limit)

Temp. °C.	k (equation 31b) secs ⁻¹	k (equation 31c) secs ⁻¹
113.0	34.6	38.1
116.4	40.3	43.3
119.5	55.0	57.2

It should be noted that although these rate constants are approximately the mean of those determined by the other two methods (given in Table V) they must still be considered approximate for the reasons given previously. They can however be used as trial values in the computer program for the complete fit of the data to equation (27). In the case of the two highest temperatures this was done since the trial values from the short τ limit plots (k(2) in Table V) were too much in error to allow convergence in this critical region.

Similarly in the slow exchange limit ($k \ll \omega$)

the value of $\frac{1}{T_{2cp}}$ approaches that of the steady state line width and hence $r_1 = k$ as in equation (31a). The values of r_1 in this region were all approximately unity. No accurate rate constants could be extracted though the order of magnitude is correct and r_1 tends to increase slightly with temperature in this region as can be seen in fig. (13).

The most interesting feature of the log-log plots in the slow exchange region is observation of the modulation in amplitude of $\frac{1}{T_{2cp}}$ as a function of pulse interval in the slow pulsing limit. This is the first experimental verification of this theoretically predicted modulation described by equations (32). The rate constants derived from the value of the pulse interval at which the first maximum occurs using equation (32a) are given in Table VII.

TABLE VII

Rate constants derived from the $\frac{1}{T_{2cp}}$ modulation in the slow exchange region for N,N-dimethyldeuteroformamide

Temp °C.	k (equation 32a) secs	$(\frac{1}{2\tau})$ maximum (first modulation max.) secs ⁻¹
24.0	~0	5.3
35.0	~0	4.6
48.0	8.3	4.1
57.0	8.3	4.1
64.0	9.1	4.0

The rate constants derived are seen to be extremely sensitive to the value of the pulse interval at which the first maximum occurs. This is an extremely difficult quantity to

measure and hence the rate constants serve only to illustrate the expected behaviour with temperature. The rate constants derived from the frequency of the modulations using equation (32b) are even more critical though the general tendency of $\Delta 2 \tau$, the change in pulse interval for one modulation, to increase with temperature can be easily seen.

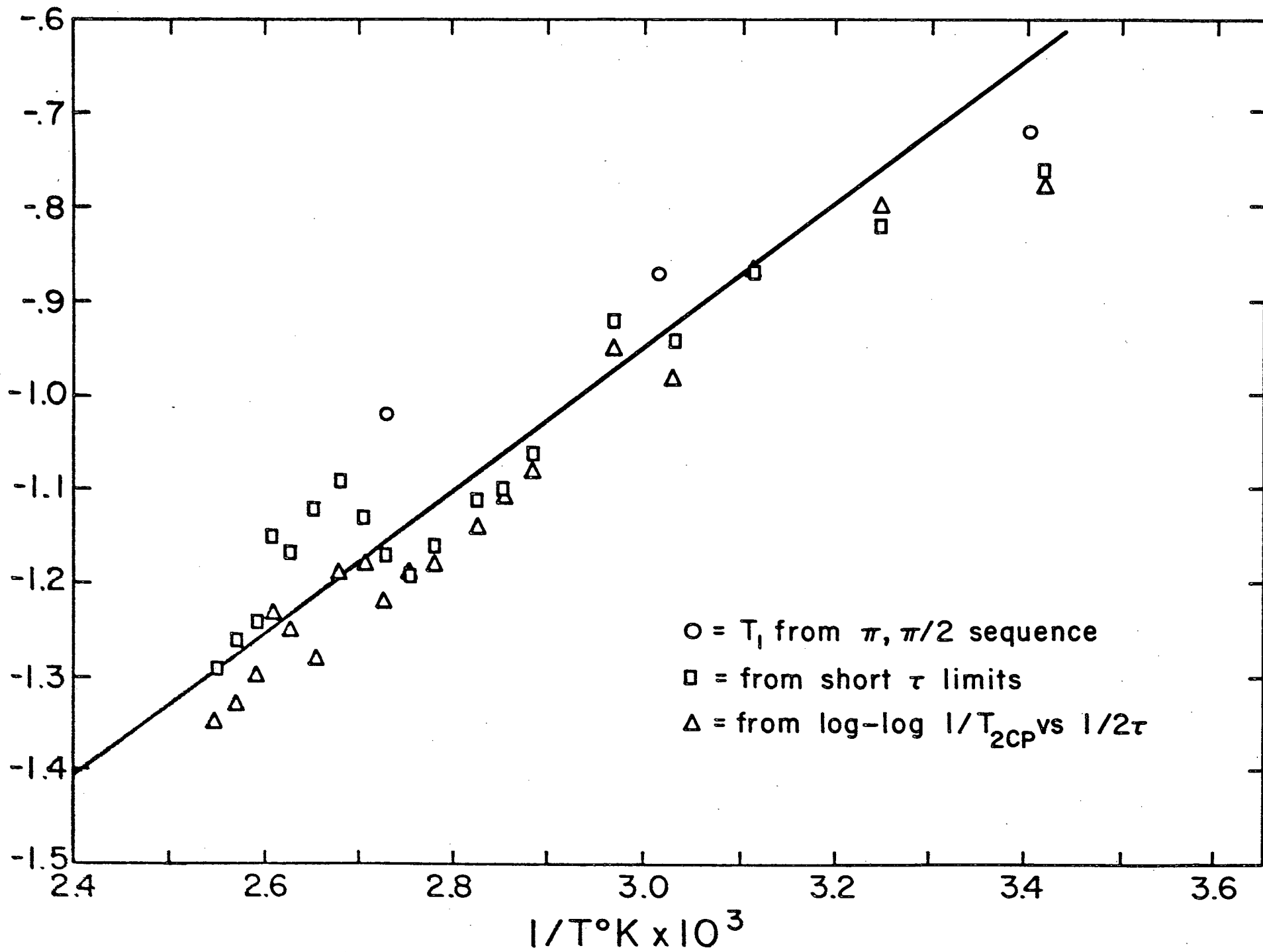
The results for N,N-dimethyldeuterioformamide are summarized in the Arrhenius plots in fig. (16). The activation parameters were obtained by the method of least squares as before and are given in Table VIII along with those obtained from a steady state study on the undeuterated molecule by Woodbrey and Rogers (15) for comparison.

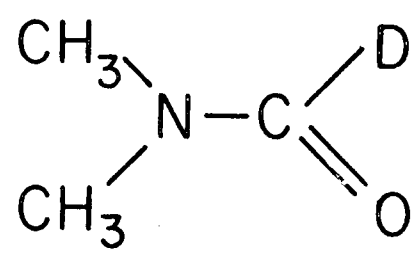
TABLE VIII

Activation parameters for N,N-dimethyldeuteroformamide

	\sinh^{-1} fit (equation 27)	Fast Pulsing Limit (equation 30)	Steady State ref. (15) (undeuterated)
E_a kcal/mole	21.65 \pm 2.7	24.3 \pm 3	18.3 \pm 0.7
log A	13.62	15.33	10.8
S (at coalescence)	1.2	9.0	-11.0

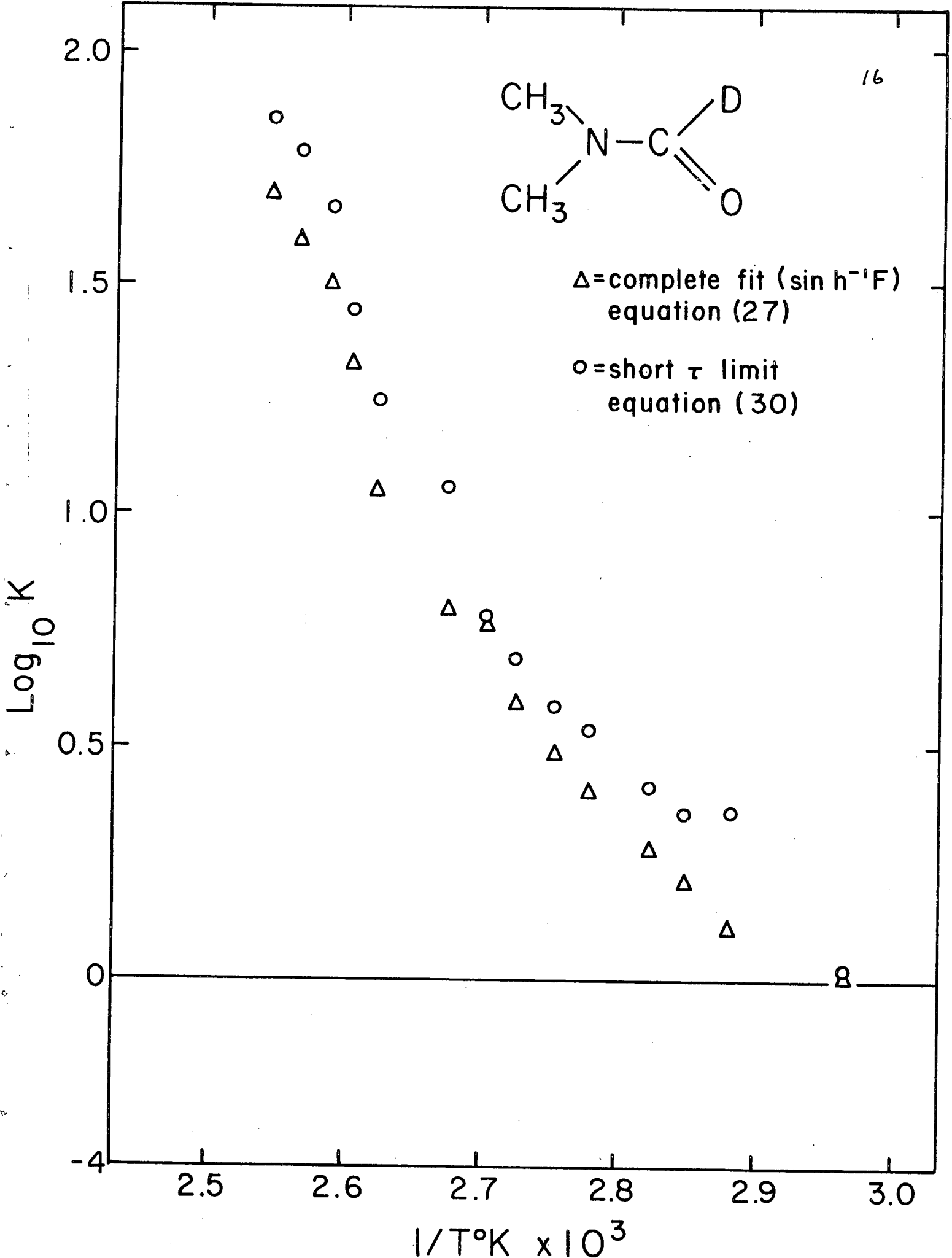
The relative validity of these determinations will be discussed later in detail, though it is obvious that, for the spin echo determination, the most reliable rate constants are only obtained by a complete fit of the data to equation (27) without any approximations being used.





Δ = complete fit (sinh⁻¹F) equation (27)

○ = short τ limit equation (30)



The random error of the individual determinations is estimated to be as before

- (1) T_{2cp} to $\pm 5\%$
- (2) T_{2o} to $\pm 10\%$
- (3) 2τ to less than $\pm 1\%$
- (4) k to between 15 and 25%
- (5) ω to $\pm 5\%$

The accuracy most definitely varies considerably over the range studied. It is probably best in the intermediate slow exchange region (k slightly less than ω) and worst at either end. A detailed account of the errors both systematic and random and their sources will be given in the discussion.

DISCUSSION

We shall now examine the results of the above studies in the light of previous work in an attempt to establish the relative merits of the N.M.R. methods in general, and the spin echo method in particular, for the accurate elucidation of the kinetic parameters for chemical exchange.

Hindered internal rotation in molecules of the type studied in this work: $(\text{CH}_3)_2\text{N-CO-R}$, has been investigated extensively by steady state, high resolution methods (16, 15, 33, 46). In many cases the results are inconsistent and some yield surprisingly low frequency factors. In the case of N,N-dimethylformamide several determinations yield values for the activation energy ranging from 7 to 24kcal/mole. The quoted errors on these values are approximately ± 1 kcal/mole, which is much less than the differences between individual determinations. The quoted error takes into account only random errors and the effect of systematic errors may be very serious, especially since in most steady state work the range in temperature of the study is generally small. Systematic errors can result from experimental sources, the temperature dependence of the activation energy itself or invalid theoretical assumptions in the treatment of data.

A small systematic error in the activation energy will lead to a much larger error in the "more sensitive" entropy

of activation. It can be shown by simple substitution in the basic kinetic relations for activation parameters (31) that if a systematic error adds a quantity (E) to the activation energy (E_a) then a quantity E/T_0 is added to the entropy of activation (S), where T_0 is the temperature at which the apparent, measured rate constant is equal to the true rate constant (usually assumed to be around the coalescence temperature). Hence the entropy, which is most probably around zero for a hindered internal rotation of the type studied, since the difference in the degree of randomness between the activated complex and the initial state is obviously negligible, gives a good indication of the presence of any systematic error in our determination. Also, it is apparent that a systematic error will pivot the Arrhenius plot about the coalescence temperature.

The factors contributing to systematic errors in steady state studies will now be enumerated.

(1) Saturation broadening: In steady state analyses it is assumed that H_1 , T_1 and T_{20} are small enough such that saturation effects to the lineshape will be negligible (1). It is difficult to determine experimentally whether H_1 is small enough not to be causing saturation broadening. Also for a fixed H_1 saturation broadening depends on T_1 and T_{20} , which are of course temperature dependent. Thus saturation will vary throughout the temperature range of the investigation.

(2) Inhomogeneity broadening: The line width in the steady state spectrum is broadened by the inhomogeneity of the magnetic field, as described by equation (17), and it is difficult to allow for the variance of this with temperature. It is usual to use the T_2^* of the line in the absence of exchange as an effective T_{20} for use in line width calculations (equations (9) to (12)). The fact that T_{20} has temperature dependence could also introduce systematic errors at this point.

(3) Chemical shift uncertainty: The determination of the chemical shift in steady state is made at low temperature, in the absence of exchange. No allowance is made for the variation of the shift with temperature except in a complete fit to the theoretical line shape. The spin echo studies in this work indicate however that the variation of the chemical shift is negligible with temperature and it remains within experimental error at the low temperature steady state value. Hence it is considered that this is not a contributing factor to systematic errors in steady state studies.

(4) Theoretical errors: Care must be taken that no invalid assumptions are made in the calculation of kinetic parameters. The effect of spin-spin coupling if significant must not be neglected, and care must be taken that if the assumption that $T_{2A} = T_{2B}$ is made it is valid.

If care is taken to eliminate the theoretical errors, by the use of a complete, general line shape function if necessary we are left with those from experimental sources ((1) and (2) above). These two sources of error will tend to broaden the line with the following results in line width studies.

(1) Slow exchange region: $\frac{1}{T_2}$ will be too large and hence k will be too large (equation 9).

(2) Fast exchange region: $\frac{1}{T_2}$ will be too large and hence k will be too small (equation 12).

The Arrhenius plot hence pivots about the intermediate region ($\omega = k$) at approximately the coalescence temperature. Some examples of the inconsistent values obtained in the case of N,N-dimethylformamide as a result of these systematic errors are shown in Table IX, along with the result obtained in this work.

It is interesting to note the value obtained by Phillips (46) in 1957 for the activation energy as it is in fair agreement with the value obtained in this work. His value was obtained by assuming an entropy of activation of zero (i.e., a frequency factor of $\sim 10^{13}$ at coalescence) and a transmission coefficient of 1 and calculating the value of k , the rate constant, at the coalescence temperature from the formula (46):

$$k = \frac{\pi \Delta \nu}{\sqrt{2}} \quad \text{at coalescence} \quad \text{-----} \quad (37)$$

where $\Delta \nu$ is the chemical shift in cps.

TABLE IX

Activation Parameters obtained for N,N-dimethylformamide*
by steady state methods.

Ea (kcal/mole)	log A (A sec ⁻¹)	S e.U.	Reference
7 ± 3	3 to 7	~ -50	(16)
18.3 ± 0.7	10.8	-11	(15)
9.6 ± 1.5	6.53	-31	(33)
24	13	0 (Assumed)	(46)
6.2 ± .3	~ 4	-54	(47)
21.6 ± 2.7	13.6	+1.2	This work.

*It is relevant to point out here that we are comparing the kinetics of hindered rotation of N,N-dimethylformamide and N,N-dimethyldeuteroformamide. We have assumed that the difference in the kinetics between these two is negligible since the moment of inertia about the N-~~S~~C bond will be practically unaltered by the substitution.

Using this k , a low temperature chemical shift and a coalescence temperature of 180°C ., (in light of subsequent work this would appear to be too high), he determined the activation energy by substitution in the Arrhenius equation. It would appear from this that for a hindered rotor, where the assumptions of zero entropy and unit transmission coefficient are most probably valid, this method gives us an approximate value for the correct activation energy, the limitation being the determination of the coalescence temperature, a difficult quantity to measure precisely. The activation energies derived for the compounds studied in this work using our own values for the chemical shifts and the coalescence temperature are given in Table X, along with two other hindered rotors of interest.

TABLE X

Activation energies derived from coalescence temperatures

Molecule	Ea from coalescence (kcal/mole)	Ea other work (kcal/mole)
N,N-dimethyldeuteroformamide	21.3	21.6 (this work)
N,N-dimethyltrifluoroacetamide	19.8	18.5 (this work)
N,N-dimethylacetamide	19.1	10.6 (ref. 15)
Methyl nitrite	11.6	9.0 (ref. 17)

It would appear from the numbers in Tables IX and X that the systematic errors in the steady state determinations make the activation energies too low and hence lead to high nega-

tive entropies. As we mentioned previously, the errors in the slow and fast exchange regions pivot the Arrhenius plot downwards (anti-clockwise) about the coalescence point thus leading to low activation energies and high negative entropies as observed. Hence we may say that, if systematic errors of the "line broadening" type are occurring, the activation energy determination will be low in a steady state study in either the slow or fast exchange region.

It is instructive to digress at this point and apply the coalescence determination to the controversial case of cyclohexane. Assuming an entropy of 4.9 from symmetry grounds (48) and a transmission coefficient of 0.5 by use of equation (37) we can derive an activation energy of 11.5 kcal/mole. This would tend to support Anet's value of 10.85 kcal/mole (22) over that of Gutowsky's, 9.5 kcal/mole (31) by spin echo methods. A more recent 100Mc/sec study by Reeves (49) gives an activation energy of 12.1 kcal/mole and an entropy of 4.4, which tends to confirm this. Anet's study extended the normal 60Mc/s range by fast passage techniques and the direct advantages of the 100Mc/sec. study incorporating the stability advantages of a field-frequency locked system in extending the range are obvious. It would appear that in this case the usual systematic errors are minimal in the steady state study.

In conclusion we may say that in using the steady state

methods great care has to be taken in order to minimise the systematic errors which in general broaden the line yielding low activation energies and high negative entropies.

The relative merits of the spin echo method will now be considered in light of the results obtained and the experimental difficulties encountered in this study. The critical factor in the spin echo method is the measurement of T_{2cp} , the time constant of the echo decay measured by the Carr Purcell method (11) with the Meiboom-Gill phase shift modification (35). The precision of the T_2 measurement is in general low and the optimum achieved in this work is estimated to be around $\pm 5\%$. The random errors could be minimised by the use of logarithmic amplifiers and recorders and the use of digital averaging techniques instead of the simple measurement of the exponential decay along the linear time base of an oscilloscope.

However the T_2 measurement is also subject to systematic errors (50) and it is imperative to minimise these if one is to obtain meaningful kinetic parameters for chemical exchange. The experimental sources of these systematic errors will now be discussed. It is felt that these have been minimised as far as possible with the equipment used in its present form, however some suggestions are discussed for further experimental improvements.

Great care must be taken in setting up the correct $\pi/2$

and π pulse widths the most critical one being the π pulse width. Even with the Meiboom-Gill phase shift, an error of 5% in the π pulse width makes the exact determination of T_2 unfeasible. The reason for this is that after two incorrect π pulses not all the spin isochromats are in the x'y' plane. The results of an incorrect π pulse are observed as deviations from exponentiality and a shortening in the measured time constant for the decay. It should be noted here that the deviations from exponentiality are much less pronounced if a linear time base is used rather than an exponential one, thus suggesting an obvious improvement to the system used. Also it should be mentioned that any deviations from exponential behaviour are more pronounced if phase sensitive detection is used in place of diode detection.

Homogeneity of H_1 is a critical factor in achieving an accurate measurement of T_2 . However, for the reasons given in the experimental section it is felt that any inhomogeneity in H_1 is negligible in this work. A suggestion which could be used if this became a problem is the use of spherical samples placed at the centre of the H_1 coils limiting the effects due to any variation in H_1 over the length of the sample.

The effects of field drifts off resonance was a problem which was difficult to eliminate in this work. It was diffi-

cult to detect and compensate for small changes in H_0 during the period of a trace. A method for the minimisation of the effects due to a linear drift in H_0 using phase sensitive detection has been suggested by Mehlkopf and Smidt (50) though the obvious solution to this, where the drift cannot be assumed to be linear, is the use of a field-frequency locked spectrometer system.

The elimination of diffusion effects by the use of a homogeneous field has been mentioned previously and it is considered that any shortening of the measured T_2 value due to diffusion effects is minimal except possibly in the region of slow pulsing at the higher temperatures where the homogeneity of the magnetic field tends to deteriorate slightly.

The choice of the correct base-line is important when calculating the time constant of an observed echo train. If the base-line chosen is too low, which is the general tendency if the echoes do not decay to the zero level (in the absence of R.F. pulses), then the calculated T_2 value will be too long. If the position of the base-line is uncertain a method of calculating the time constant without knowledge of the base-line could be used (51). This well known method, due to Guggenheim, eliminates the systematic errors but gives a large random error.

In general these effects mentioned so far will tend

to make the value of T_{2cp} measured in the experiment too short. If this is the case the value of r_1 in equation (27) will be too large, neglecting any systematic error in T_{2o} , which will only be significant when (T_2) exchange $\approx T_{2o}$. In the short τ limit (equation 30) we can see that if r_1 is too large the value of the rate constant will be too high. This is supported by the fact that the rate constants derived from equation (30) in Tables I and V tend to be higher than those derived from the complete fit to equation (27) and the resulting activation energy is higher than that determined from the coalescence point. In the long τ fast exchange limit it can be seen from equation (31b) that if r_1 is too long k as determined by equation (31b) will be too short. This is borne out by the results in Tables II and VI. The results of the long τ slow exchange limit (equation 31a) also bear out these trends.

It is more difficult to predict the effect of a given systematic error in T_{2cp} on the value of k obtained by the complete fit to equation (27). At the region where 2τ is of the order of the rate constant k , (i.e., the point most sensitive to k in the total dependence of T_{2cp} on 2τ) it can be shown by simple substitution that a given error in r_1 will lead to a corresponding error similar in magnitude and in the same direction in k . However, the dir-

ection and magnitude of the effect on k of a given systematic error in r_1 is dependent on 2τ , the pulse interval used in the measurement. Hence it is difficult to make any generalisations concerning the effect of a given systematic error on a rate constant (k) derived from fitting measurements of r_1 made at over twenty pulse intervals (2τ) to equation (27).

Up to now no mention has been made of the effect of systematic errors on ω and T_{20} . It was found that these were not critical parameters in curve fitting process so the effect of any error in them was neglected. There is also merit in neglecting any systematic error in T_{20} , as it will probably have the same source as that in T_{2cp} and the value of r_1 thus obtained may be free of any systematic error.

The major advantage of the spin echo method over that of the steady state in minimising systematic errors, is the extended range over which it can be used. This, and the fact that at a given k numerous measurements are made of T_{2cp} as a function of 2τ , will tend to average out any systematic errors to a greater extent than in a steady state study. The range available to the spin echo method is limited by the condition that we can detect a measurable change between the value of $\frac{1}{T_{2cp}}$ and that of $\frac{1}{T_{20}}$ (i.e., a measurable r_1) over the range of 2τ used. Thus, it can be seen from fast exchange long τ limit (equation 31b)

that the upper limit of the range which can be investigated is proportional to the magnitude of both the chemical shift and T_{2_0} and the advantages of studying a molecule with a long T_1 and a large chemical shift are obvious.

In the compounds investigated in this work it is felt that the activation energies derived are valid since they yield entropies of approximately zero. In both compounds the random errors are higher than those generally quoted for steady state studies but this is to be expected from the low precision of the T_2 measurement. The values derived from the fast pulsing limit (equation 30) tend to be higher than those from the complete fit (equation 27) and as mentioned this would result from a systematic error making r_1 too long (T_2 too short or T_{2_0} too long). In the case of N,N-dimethyldeuteroformamide it can be seen from fig. (16) that the rate constants above and below coalescence bend away from linearity indicating the presence of a systematic error rather than a random one. The activation energy of 21.6 kcal/mole is one derived by a least square analysis of all the k's. The region below coalescence yields an activation energy of 18 kcal/mole with an entropy of approximately -10 e.U. and that above yields an activation energy of 24 kcal/mole with an entropy of approximately + 9 e.U. (similar to that obtained for the fast pulsing limit). It is felt that, though these two numbers contain systematic errors, the true acti-

vation energy is higher than that determined by Woodbrey and Rogers (15) of 18.3 kcal/mole and closer to that predicted by the coalescence point determination of 21.3 kcal/mole.

The precision of the rate constants obtained by the spin echo method is given previously, it is best around the coalescence temperature and worst at either limit of the exchange where a small change in T_{2cp} is observed for the entire pulse repetition range used. In the fast exchange region F in equation (27) is much more sensitive numerically and hence it is more difficult to fit the data in this region. Once a good convergence has been achieved however (a sum of squares of errors of approximately zero), the precision of the rate constant is similar to that of the other regions.

In conclusion we may say that both the spin echo method and the steady state methods suffer from systematic errors. In which of these methods we can eliminate the systematic error by experimental modifications is still in doubt. It would appear that this is more feasible in the spin echo method and therein may lie the success of this method. (Trappeniers (52) (53) has suggested that by taking extreme experimental care it is possible to measure T_1 and T_2 accurate to + 1.0% by the spin echo technique). However with the present equipment one has to get agreement between the spin echo

method and the steady state method (preferably a complete fit to the line shape) where the systematic errors will give different effects, in order to place any degree of validity on the kinetic determinations.

The conclusions reached here agree in the most part with those obtained by E. Krakower (54) for the hindered rotation barrier in N,N-dimethylnitrosamine and N,N-dimethylcarbonyl chloride by the spin echo method. His reported value of -10 for the entropy of activation in N,N-dimethylcarbonyl chloride was attributed to the presence of systematic errors in the spin echo determination.

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APPENDIX I

A steady state N.M.R. study of proton exchange between methanol and two phenols.

Introduction.

The two phenols used in this study were orthohydroxyacetophenone (having an internal hydrogen bond) and meta-cresol (with no intramolecular hydrogen bond). Reeves has reported (39) proton exchange rates measured by N.M.R. methods between methanol and orthochlorophenol. In such a system the presence of traces of acid, base or water will affect both proton transfer rates and the mechanism by which exchange occurs. In this study rigorous methods have been used to exclude the above trace impurities, which would catalyse the exchange. The energetics of the exchange process are shown to be dependent on the presence of an intra-molecular hydrogen bond. In addition the aging effect on solutions left in a vacuum sealed N.M.R. tube served to illustrate both the sensitivity of such proton exchange systems to impurities and the reason for the low apparent activation energies previously measured (39).

The spectra studied were appropriate to the "slow exchange" region, explained previously, and showed two exchange broadened resonances: the one corresponding to the phenol OH and the other to the methanol OH . They are des-

cribed by the relationships of Piette and Anderson given previously as equations (9, 10).

Experimental

A vacuum system was prepared with a succession of traps containing 8 mesh Calcium Sulphate. Two separate trains of three traps were connected separately at one end to a bulb containing phenol and a bulb containing methanol. These drying trains were joined outside isolating stopcocks with a single N.M.R. sample tube (pyrex 5mm. o.d.) glass blown onto the system. Methanol, m-cresol and o-hydroxyacetophenone (A.R. Karl Fischer) were fractionally distilled and pre-dried over calcium sulphate which had been baked out. Pre-dried samples of methanol and either m-cresol or o-hydroxyacetophenone were loaded into the storage bulbs on the vacuum line with minimum air exposure. The samples were then frozen, pumped down and degassed and isolated. A series of heaters were then used to bake out the traps containing CaSO_4 at 200°C . in a hard vacuum (10^{-6} mm. Hg) over a 24 hour period. The stored samples were then allowed to distil onto the cooled CaSO_4 . Successive distillations finally allow a mixture of methanol and phenol to be transferred to the N.M.R. sample tube and sealed off. The calibration of the mole fraction of each component in the final sample is first achieved by volume than checked by integration of the proton resonance signals appropriate to

(iii)

each molecule. At room temperature all samples showed separate resonances for the methanol OH and the phenol OH. Below room temperature resolution of the methanol OH quartet was achieved and used as an indication of sample purity.

Proton resonance spectra were taken on a Varian A60 spectrometer fitted with a variable temperature attachment V6057. The temperatures at the sample were calibrated by using the known temperature dependence of the chemical shift in a sample of pure methanol inserted in place of the phenol solution. The samples prepared were duplicated and contained $50 \pm 2\%$ of the total OH intensity in each OH resonance peak.

Results and Discussion.

These mixtures of phenols and methanol were first taken to lower temperatures and the line widths of both OH peaks monitored at a series of temperatures. The first order rate constants out of a given site were taken to be $(\pi \Delta \nu \frac{-1}{T_2})$ as given by Piette and Anderson (17) and described previously (where $\Delta \nu$ is the line width). The rate constants for exchange of magnetizations out of the phenol and methanol OH sites are quite different and not simply related as found before (39) to the population weighted rate constant between two sites. Rate constants for exchange out of the methanol site are consistently higher. Care was taken to avoid the region of temperature where the line width of the

methanol-OH resonance was beginning to show multiplicity due to spin-spin coupling. The implication of these observations is that the exchange process out of the methanol site is influenced by at least two processes as suggested by Luz, Gill and Meiboom (40) namely phenol-methanol and methanol-methanol exchange in the present case. In this work we are only concerned with the phenol-methanol exchange so that the specific rate constant of interest is that observed by measuring line widths of the phenol-OH proton resonance. The line width of the methanol OH signal was also measured since it serves as a comparison with the previous work (39). The energetics of the phenol-phenol exchange process is especially unfavourable with an intramolecular hydrogen bond present.

Two specific effects were noticed which indicated the introduction of irreversible exchange catalysts even in evacuated sealed tubes. After a tube had been exposed to temperatures about 50°C. the activation energies associated with exchange out of the phenol site decreased markedly and finally tended to a value of 5kcal equal to that for the methanol site. If a tube were stored for a period of three months at room temperature and reinvestigated the activation energy obtained also decreased to 5kcal. These effects seemed to be independent of the presence of drying agent (CaSO₄) sealed in the N.M.R. sample tube.

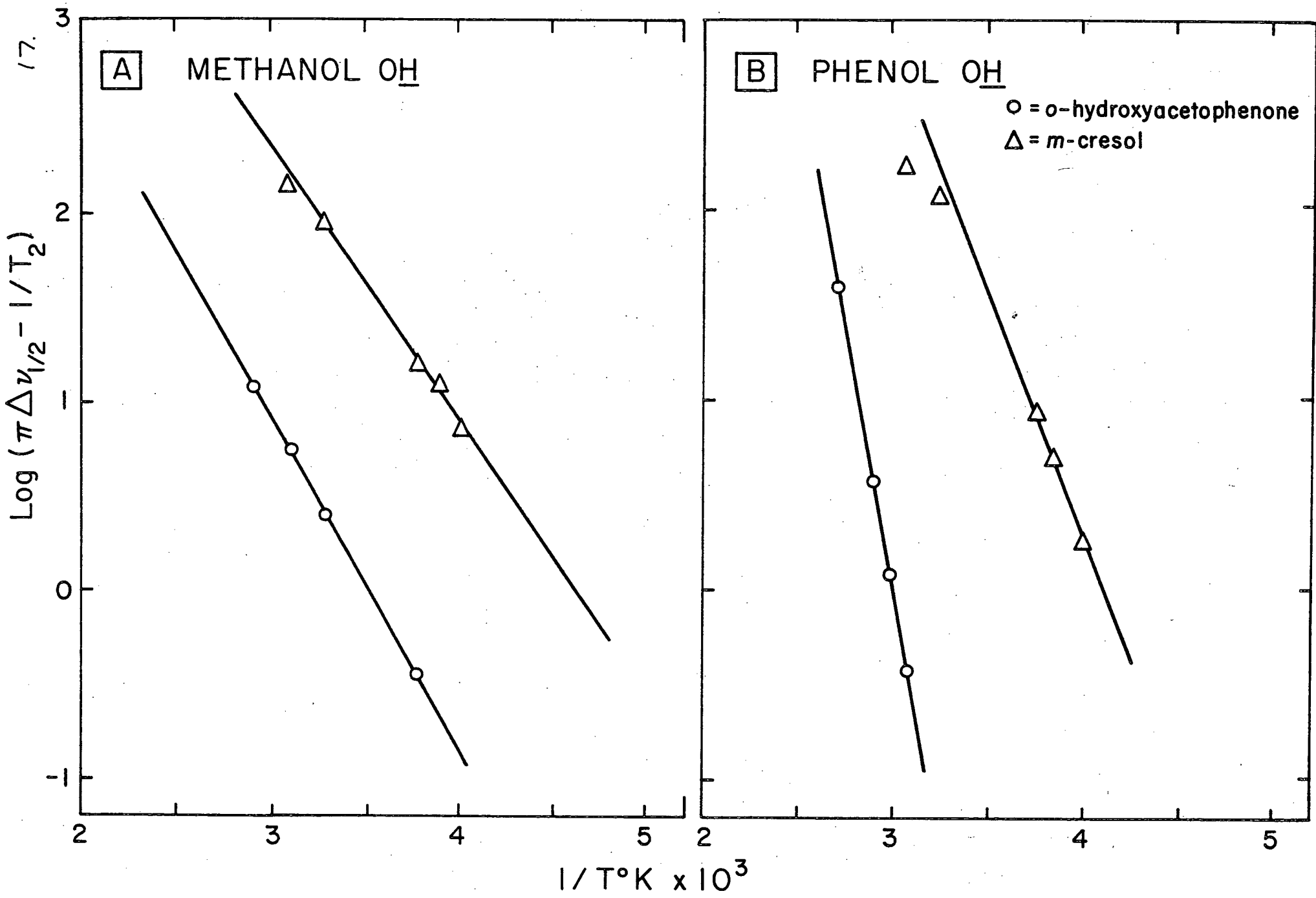
The specific rate constants obtained are only meaningful on freshly prepared samples and the logarithm of specific rate constants for exchange out of methanol sites is plotted against the reciprocal of absolute temperature in fig. (17a). Corresponding graphs are reproduced for the phenol sites in fig. (17b).

Energies and Entropies of activation for these specific rates are listed in the table below.

Exchange Site	Solution	Ea kcal.s.	S e.U.	Remarks
Phenol OH	o-hydroxyacetophenone/methanol.	24.5	-10	Freshly prepared
Phenol OH	m-cresol/methanol.	10.3	-19	Freshly prepared
Methanol OH	o-hydroxyacetophenone/methanol.	7.9	-32	Freshly prepared
Methanol OH	m-cresol/methanol.	6.2	-32	Freshly prepared
Phenol OH	o-hydroxyacetophenone/methanol.	5.5	-30	Aged three months
Methanol OH	o-chlorophenol/methanol	4.6	-32	Contaminated Ref. (39)
Methanol OH	o-hydroxyacetophenone/methanol	5.7	-30	Aged three months.
Phenol OH	o-chlorophenol/methanol	4.6	-32	Contaminated Ref. (39)

The results indicate that intrusion of a proton exchange catalyst results in a single phenol/methanol exchange process

via the catalyst, causing the activation parameters from both sites to tend towards 5kcal. activation energy and -30 e.U. for activation entropy. The extrusion of water or a trace of base from the glass tube is the probable cause. The results are also successful in showing that the phenol-methanol exchange has a much higher activation energy and low negative entropy with the strong intramolecular hydrogen bond as in *o*-hydroxy acetophenone.



APPENDIX 2

A steady state N.M.R. study of ring inversion in N,N-dimethylpiperazine.

Introduction

It has been shown previously that the six membered alicyclic ring compound N,N-dimethylpiperazine, which is not locked in one conformation, is resolved into two chair conformations at low temperatures (below -40°C) (44). The ring proton resonance spectra below -40°C . are typical of an A_2B_2 case (34). The axial equatorial chemical shift (δ_{AB}) has been obtained from an analysis of the low temperature spectrum and was found to be 0.63 p.p.m. (45). At room temperature the spectra of these conformers are rapidly averaged, the coalescence temperature (T_c) being about -10°C . at 60Mc/sec.

The ring inversion was studied in the fast exchange region (-10°C . to $+30^{\circ}\text{C}$.) and an activation energy for the ring inversion derived from line width observations in this region. The line width in this region is described by equation (12) given previously and used in the form:

$$\left(\pi \Delta \nu - \frac{1}{T_2} \right) = 1/8(\omega_A - \omega_B)^2/k \quad \text{_____} \quad (12a)$$

where $\Delta \nu$ is the line width at half amplitude.

Experimental.

N,N-dimethylpiperazine available commercially was distilled and showed no impurity peaks in the proton resonance spectrum and was therefore used without further purification. The physical constants for the compound agreed with those quoted in the literature. A 30 mole percent solution in dichloromethane was degassed and sealed under vacuum in a 5m.m. o.d. N.M.R. tube.

The spectra were taken on a Varian A-60 N.M.R. spectrometer using the variable temperature attachment V6057. The temperatures were calibrated using the temperature dependence of the chemical shift in a standard methanol sample, and the stability was estimated at better than $\pm 0.5^{\circ}\text{C}$. over the range investigated. A natural line width of approximately 0.3cps was realised for all but the lower temperatures (below 0°C).

Results and Discussion.

The results of the line width measurements are given in fig. (19) as an Arrhenius plot of $\log(\pi \Delta \nu - \frac{1}{T_2})$ versus $\frac{1}{T^{\circ}\text{K}}$. The activation parameters, derived from a method of least squares and use of equation (12a), are given below.

N,N-dimethylpiperazine (Activation parameters for the ring inversion).

E_a (Activation energy kcal/mole)	=	13.05 ± 0.35
$\log A$ (A is frequency factor secs^{-1})	=	12.97
S (entropy of Activation e.U.)	=	-0.9 at 250°K .

(iii)

The result for the activation energy agrees with a recent 100Mc/sec. study (45) published after this work though the authors do not quote a frequency factor or entropy. The reasonable values obtained here for the entropy and the frequency factor must be regarded as fortuitous in view of the small range in temperature over which the kinetics was studied (40°C) and the fact that the resonance line may be broadened by scalar coupling to a quadrupolar nucleus.

The above study serves to give us a reliable value for the activation energy of the ring inversion but the accuracy of any rate constants determined from the data would have to be in doubt. A complete steady state study would entail a lineshape fit over the complete range of collapse of the A_2B_2 while decoupling the nitrogen.

