PART I. SYNTHESIS AND DNMR STUDIES OF CERTAIN

DERIVATIVES OF 9-METHYLENE-7-OXA-1-THIA-

SPIRO[4.5]DECAN-8-ONE

PART II. AN INVESTIGATION OF THE SPIN-LATTICE

RELAXATION PHENOMENA ($\underline{T}_1$ VALUES) OF THE

^{31}P NUCLEUS IN CERTAIN CLASSES OF

ORGANOPHOSPHORUS COMPOUNDS

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MAY, 1980

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ACKNOWLEDGMENTS

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INTRODUCTION

Owing to the difference in the primary objective of the two investigations recorded herein, this dissertation has been divided into two parts. Each is complete and independent of the other, containing its own Historical section, Results and Discussion, Experimental section and Bibliography.

PART I.   SYNTHESIS AND DNMR STUDIES OF CERTAIN

DERIVATIVES OF 9-METHYLENE-7-OXA-1-THIA-

SPIRO[4.5]DECAN-8-ONE

CHAPTER I

HISTORICAL

Occurrence of the α-Methylene-γ-butyrolactone
Ring System in Natural Products and the Phy-
siological Activity of Such Compounds Con-
taining α-Methylene-γ-butyrolactone Units

The isolation and structural elucidation of several
sesquiterpene lactones[29,31,32,52,56,60-64,91] having an α-
methylene-γ-butyrolactone unit is not uncommon in nature.
A number of these sesquiterpene lactones have been shown to
possess high levels of cytotoxicity against tumor cells in
vitro.[32,40,41,56,57,60-64,68,69,90] These substances have
stimulated considerable synthetic and biological interest
in these and other similar ring systems.

In a search for tumor inhibitors from plant sources,
Kupchan and co-workers isolated two novel sesquiterpene di-
lactones of the germacrane type, elephantin (1) and elephan-
topin (2), from alcoholic extracts of dried Elephantopus
elatus Bertol (Compositae).[56] The alcoholic extract showed
significant inhibitory activity in vitro against cells deri-
ved from human carcinoma of the nasopharynx (KB).[56] There
followed the isolation from Eupatorium rotundifolium L.

3

(Compositae) of euparotin acetate (3) and euparotin (4),[60] and from <u>Vernomia</u> <u>hymenolepis</u> <u>A.Rich</u> (Compositae) of vernolepin (5) and vernomenin (6), all being active <u>in</u> <u>vitro</u> against cells derived from human carcinoma of the naso-pharynx (KB).[60,62] For all cultures, the dose of compound that inhibits growth to 50% of the control growth is usually the criteria for activity. Eupachlorin acetate (7), eupa-chlorin (8) and eupachloroxin (9), isolated by Kupchan and co-workers from the same source for euparotin acetate (3) and euparotin (4), appear to be the first recognized natural occurring chloro-sesquiterpenes.[64]
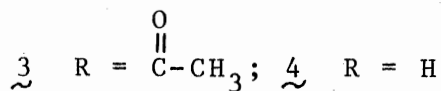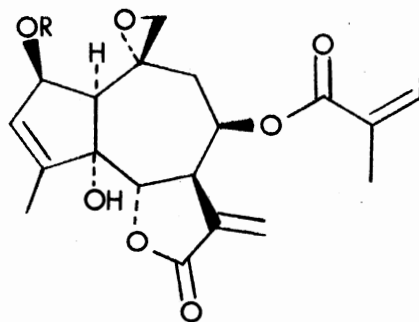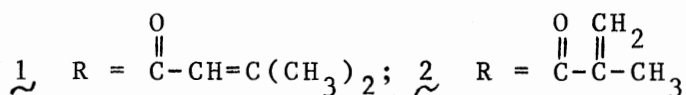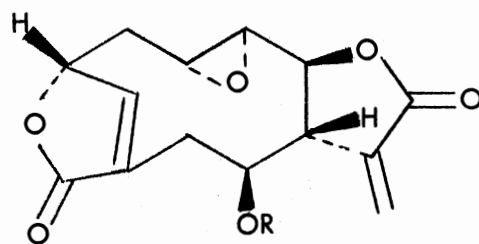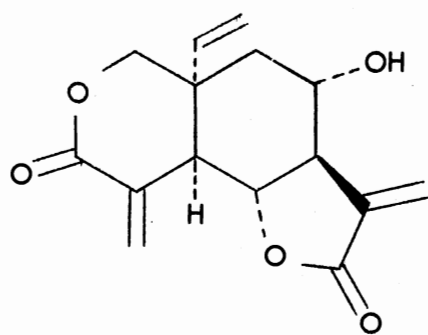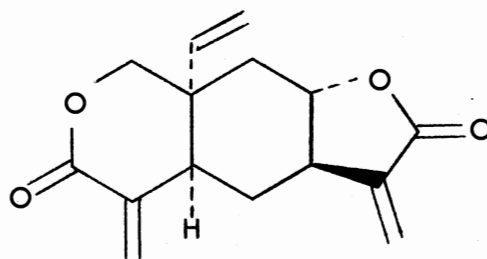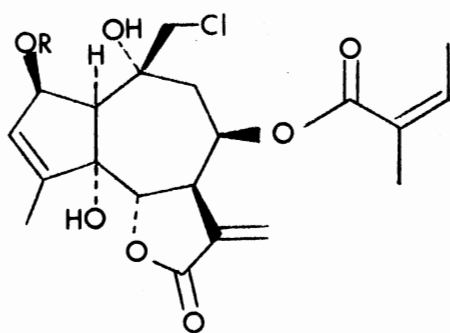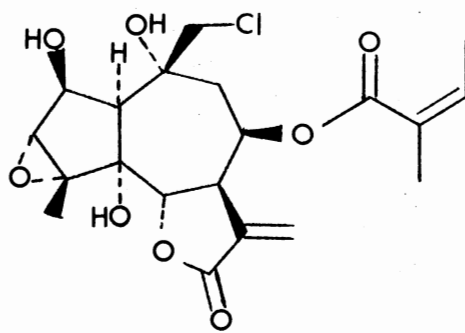
1 R = C-CH=C(CH$_3$)$_2$; 2 R = C-C-CH$_3$

3 R = C-CH$_3$; 4 R = H

5

6

7   R = C-CH₃; 8   R = H
         ‖
         O

9
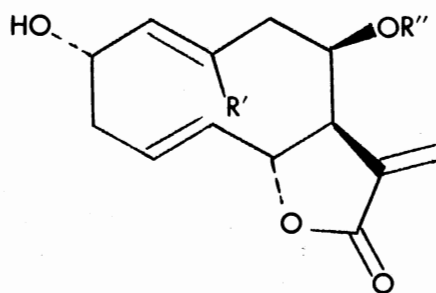
10   R' = CH₂OH, R" = C-C=CH-CH₃
                        ‖ |
                        O CH₃

11   R' = CH₂OH, R" = C-C-CH₃
                        ‖ ‖
                        O CH₂

The potent cytotoxic action of these sesquiterpenes, with the ability to inactivate selected enzymes in vitro, has been attributed to the presence of an α-methylene-γ-butyrolactone unit.[27,54] The extreme ease with which this functionality reacts witn thiols (such as with cysteine)[54,90] and other biological nucleophiles is well documented.[36,58,59] However, studies made by Kupchan and co-workers[55,57] have suggested that an important requirement for biological activity is the simultaneous presence of more than one chemically reactive group in the molecule. The groups necessary for in vivo activity were found to be a side chain composed of an α,β-unsaturated ester adjacent to the γ-lactone unit and either a primary or secondary allylic alcohol function or both. Thus, eriofertin (10), eriofertopin (11) and de-acetyleupaserrin (12) have shown significant in vivo acti-vity[55] against P-388 lymphocytic leukemia in the mouse. The unsaturated ester function adjacent to the α-methylene-γ-butyrolactone unit has been shown to increase the rate of cysteine addition to the butyrolactone ring.[57] The primary
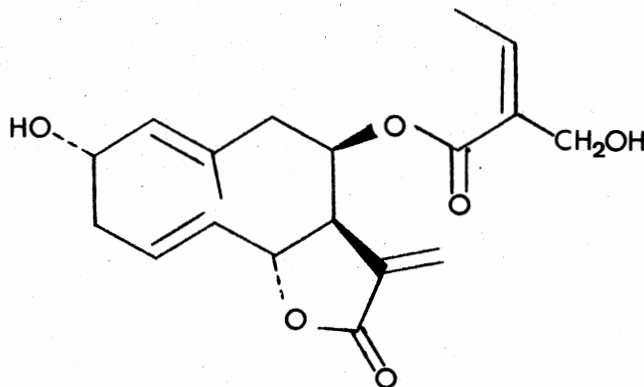
12

and secondary allylic alcohol functions may serve as potential alkylation sites by a nucleophilic center on a biological macromolecule.

DNMR Spectroscopy as a Tool in the Study of Conformational Equilibria and Intramolecular Rate Processes

In the past three decades high resolution nuclear magnetic resonance (NMR) spectroscopy has developed from an ancillary technique of the nuclear physicist into one of the chemist's most valuable and immensely efficient tool for probing the structure and stereochemistry of molecules. Analysis of NMR spectra recorded at various temperatures can provide information regarding the existence of more than one conformation, the nature and relative weight of different conformations and the energetics for the interconversion of certain conformers.

Study of Conformational Equilibria

Nuclear magnetic resonance spectroscopy was used to assess conformational equilibria in acylic systems for the first time by Nair and Roberts in 1957.[74] A year later Lemieux and co-workers pointed out the differences in chemical shifts and spin-spin coupling between equatorial and axial protons in cyclohexyl systems. Determination of the equilibrium constant by Eliel[15] for the equilibrium 13a $\rightleftharpoons$ 13b, based on the difference in chemical shift bet-

ween the axial and equatorial protons, represents the first

quantitative application of NMR spectroscopy to the study of

a conformational equilibrium in a cyclic system. At that

time, it was reported that the ^{1}H NMR spectrum of bromo-

cyclohexane showed no sign of splitting for the α-proton

signal at the temperatures used. However, later workers[76]

observed a difference of 0.78 ppm between the axial and

equatorial protons at -75°C. Therefore instead of bromo-

cyclohexane itself, the conformationally biased[16] cis- (14)

and trans-4-tert-butylbromocyclohexane (15) were used to

determine the chemical shifts of each α-proton in the indi-

vidual conformers. The conformational equilibrium constant

was calculated using Eq. (1). The assumption here is that

the 4-tert-butyl group does not in any significant way

affect the chemical shift of H(1) at C(1).[15,18,19,21] This

13a   13b

14   15
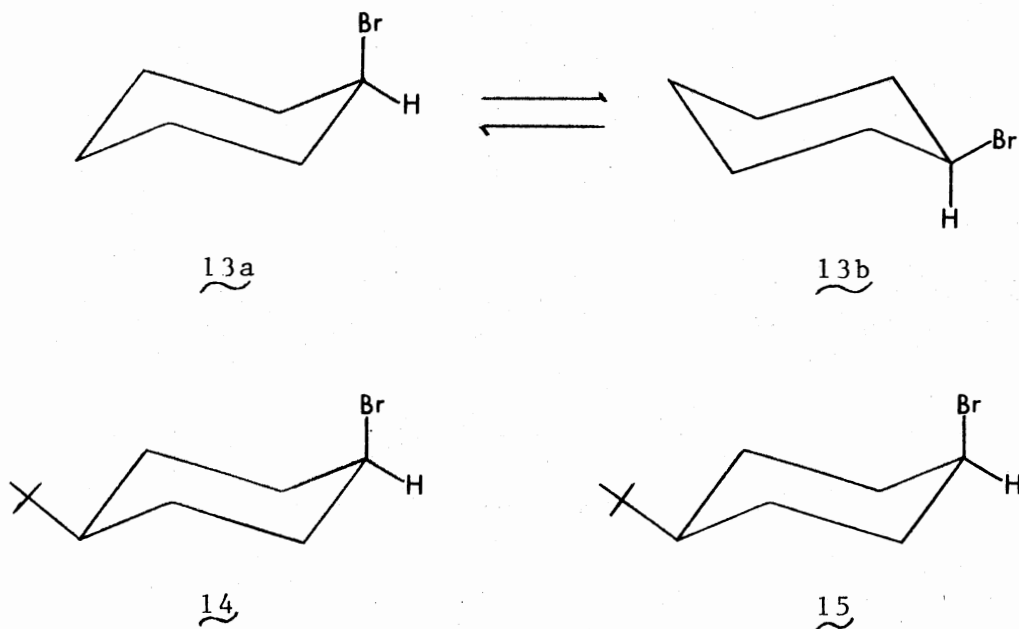
assumption was later disputed by other workers.[4,44,73] In

$$K = N_e/N_a = \frac{\delta_a - \delta_H}{\delta_H - \delta_e} \qquad\qquad \text{Eq. (1)}$$

K = the equilibrium constant for the ring reversal

process

N_e = mole fraction of the conformation with equa-

torial bromide 13b

N_a = mole fraction of the conformation with axial

bromide 13a

δ_a = chemical shift for the α-hydrogen in 14

δ_e = chemical shift for the α-hydrogen in 15

δ_H = chemical shift for BrC-H signal in bromocyclo-

hexane under rapidly equilibrating conditions

an attempt to test the validity of this assumption, Jensen

and Beck carried out a systematic study[43] on bromo-, chloro-,

acetoxy-, trifluoroacetoxy-, and cyanocyclohexane and the

corresponding cis- and trans-4-tert-butylcyclohexanes. At

low temperatures (between -80° and -105°C), significant

differences were observed in all cases between the axial

and equatorial methine proton resonances of the cyclohexyl

derivatives and those of the corresponding 4-tert-butylcyclo-

hexyl derivatives. However, plots of the chemical shifts

against temperatures of the axial and equatorial H(1) reso-

nances in the cyclohexyl derivatives paralleled those for

the corresponding H(1) resonances in the 4-tert-butyl deri-

vatives within the uncertainty of the experiment.[43] Thus,

the chemical shift of the axial and equatorial H(1) reso-
nances for the cyclohexyl derivatives (above the coales-
cence temperature) could be approximated by correcting the
observed individual low temperature resonances in the mono-
substituted cyclohexanes by the change observed between low
temperature and the desired temperature for the correspond-
ing resonances of the 4-tert-butylcyclohexyl compounds.
The equilibrium constant values calculated from these
corrected chemical shifts compare favorably with those cal-
culated by the theoretically sound, peak-area measurement
method[6] at about -80°C. However, the values determined by
the original uncorrected chemical shift method of Eliel and
co-workers[15] were significantly lower than the values
obtained by either of the above methods. As was mentioned
above, the peak area measurement is the most theoretically
sound method as it involves no assumptions except, of course,
that the activity coefficients for the conformers are taken
as equal to unity. The areas under the signals for axial
and equatorial methine protons are directly proportional to
the concentrations of conformers present. The equilibrium
constant could be calculated from Eq. (2):

$$K = [A]/[E] \qquad \text{Eq. (2)}$$

    K = the equilibrium constant for the confor-
        mational equilibrium

   [E] = the integrated area under the equatorial
        proton signal

[A] = the integrated area under the axial
proton signal

Nevertheless, this method is experimentally difficult
for two reasons: accurate peak areas at a definite tempera-
ture much below room temperature are not easily obtained
(because of difficulty in measuring the temperature required,
because of viscosity broadening of the signals and fre-
quently because of solubility problems), and the confor-
mational equilibria at these low temperatures need not, and,
in fact, often do not necessarily reflect the conformational
equilibria at room temperature. The literature abounds with
examples where one conformer is preferred at low temperature
and another at room temperature. Thus for P-methyl-,
P-ethyl- and P-phenylphosphorinanes (compounds shown to
exist in the chair conformation[71] like cyclohexanes), the
equatorial conformer was found to predominate at -110°C and
the axial conformer was shown to predominate at room tempe-
rature.[23,24] This is not surprising since the equilibrium
constant is governed by both ΔH^o and ΔS^o by Eq. (3). If

$$-RT \ln K = \Delta G^o = \Delta H^o - T\Delta S^o \qquad \text{Eq. (3)}$$

T = temperature in degrees kelvin

K = equilibrium constant

ΔG^o = standard free energy difference
between the two conformers

ΔH^o = standard enthalpy difference
between the two conformers

ΔS^O = standard entropy difference

between the two conformers

both ΔH^O and ΔS^O terms carry the same sign, both negative

for example, then at low temperature ΔG^O also may be nega-

tive as the magnitude of the $T \Delta S^O$ term may not exceed that

of ΔH^O term at this temperature. However, as the tempera-

ture increases, the magnitude of the $T \Delta S^O$ term changes at a

much faster rate than that of the ΔH^O term and may eventu-

ally exceed the latter and thus ΔG^O can be positive. Conse-

quently, both the chemical shift method as well as the peak

area method have merits and demerits.

In an attempt to evaluate the criticism voiced against

his chemical shift method, Eliel and co-workers investigated

a number of cyclohexane and 1,3-dioxane derivatives.[20]

While the time average chemical shift of the proton signal

for the methyl ($C\underline{H}_3O$) protons in cyclohexanone dimethyl

ketal (which exists as an equilibrium mixture of equal parts

of two indistinguishable conformers 16 and 17) appears mid-

way between the clearly resolved chemical shifts of the ^1H

$\nu = -183.9$ Hz
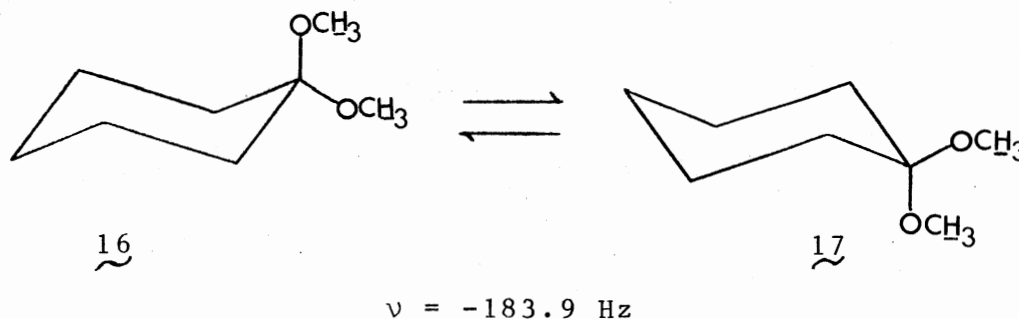
signal for the axial and equatorial methyl ($C\underline{H}_3O$) protons of

4-<u>tert</u>-butylcyclohexanone dimethyl ketal (18), the same is
not true for the 3-<u>tert</u>-butylcyclohexanone dimethyl ketal
(19). Consequently, it appears that while a 4-<u>tert</u>-butyl
group does not affect the chemical shift of the proton sig-
nal for the methyl (C<u>H</u>$_3$O) protons, the 3-<u>tert</u>-butyl group
does.[20] In the following diagrams the chemical shifts are
referenced to TMS standard and taken at 60 MHz. However,

OC<u>H</u>$_3$

OC<u>H</u>$_3$

OC<u>H</u>$_3$

OC<u>H</u>$_3$

18

19
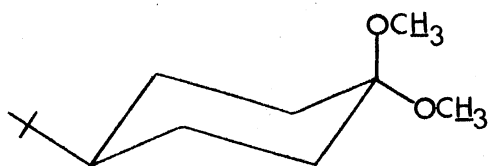
ν_a = -182.9 Hz

ν_a = -181.9 Hz

ν_e = -184.9 Hz
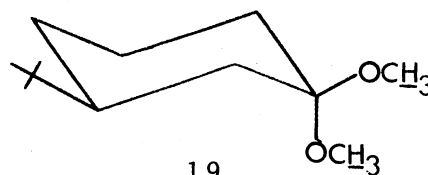
ν_e = -185.6 Hz

the situation in 1,3-dioxane is exactly the opposite as is
evident from the chemical shift data shown for 20 ⇌ 21, 22,
23, 24 ⇌ 25, 26 and 27.[20] While there could be several rea-
sons for the differing effects of substituents (such as the
bond distance; C-O distance of 1.42 Å in lieu of a C-C dis-

H

H

O

O

O

O

H

H

20

21
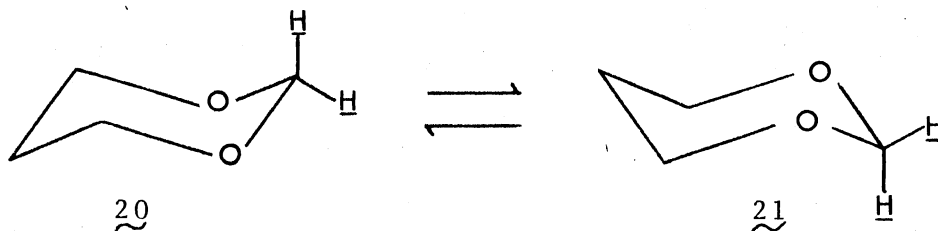
ν = -282.6 Hz

tance of 1.53 Å in cyclohexane and a small difference in
shape of the 1,3-dioxane system), it was apparent that an
extrapolation of the method used with cyclohexyl systems to

heteracyclohexanes may not be valid. The assignments for
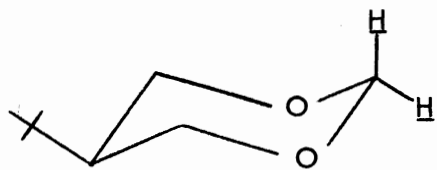
22

$$\nu_a = -264.4 \text{ Hz}$$

$$\nu_e = -289.2 \text{ Hz}$$

Average ν = -276.6 Hz
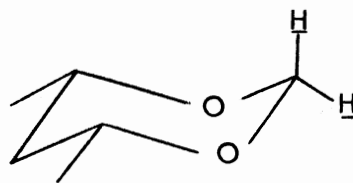
23

$$\nu_a = -271.7 \text{ Hz}$$

$$\nu_e = -292.0 \text{ Hz}$$

Average ν = -281.9 Hz

ν_a and ν_e in 26 and 27 are still open to question since protons in axial methyl groups usually appear at higher field than equatorial methyl protons. In our work, a
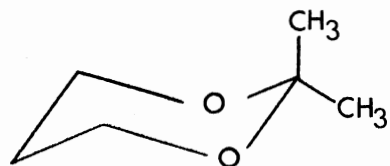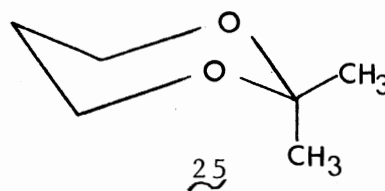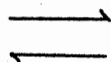
24 ⇌ 25

$$\nu = -78.0 \text{ Hz}$$
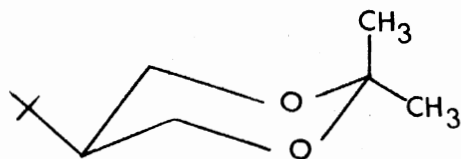
26

$$\nu_a = -78.0 \text{ Hz}$$

$$\nu_e = -74.1 \text{ Hz}$$

Average ν = -76.0 Hz
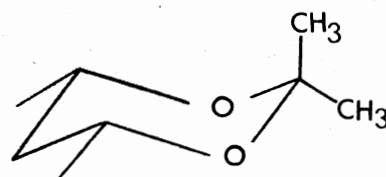
27

$$\nu_a = -80.6 \text{ Hz}$$

$$\nu_e = -75.6 \text{ Hz}$$

Average ν = -78.1 Hz

possible analogy with model systems 28 and 29, which were

used in the study of the equilibrium 30a ⇌ 30b,[79] was sought

28

29

30a

30b
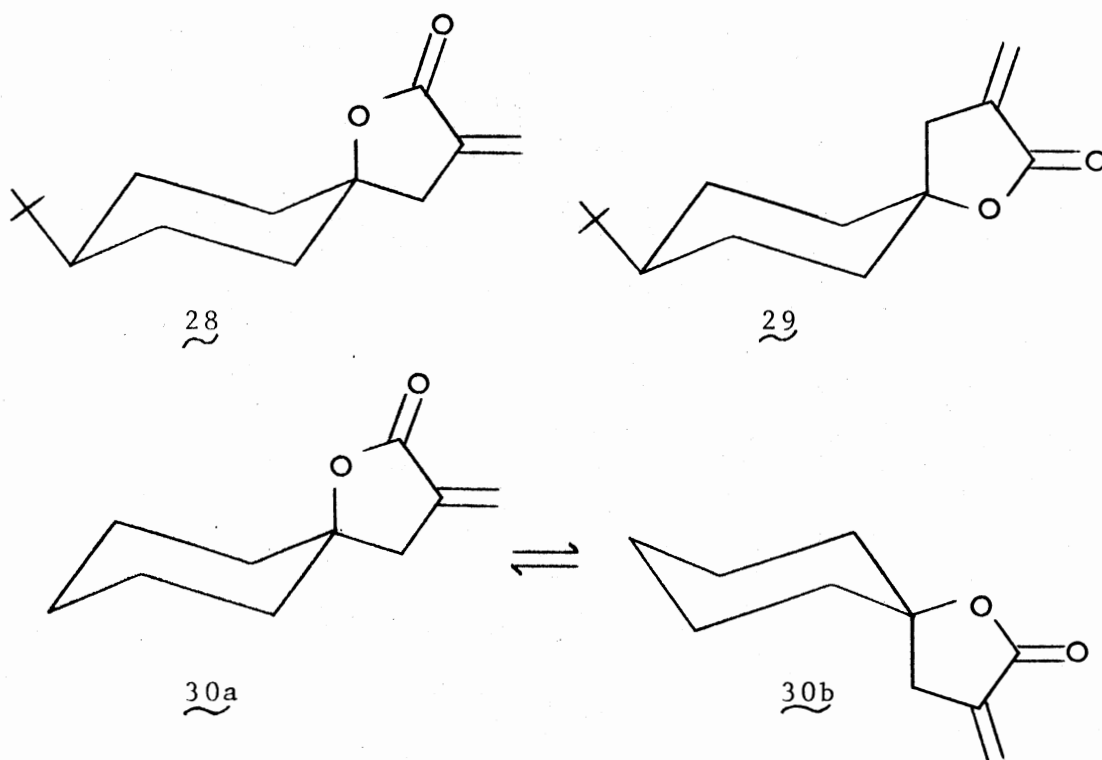
with which to compare the ^{1}H NMR spectra for the 31a ⇌ 31b

system to be investigated. The 2,6-diphenyl-substituted

analogs 32a and 32b were considered reasonable since the

phenyl groups were syn oriented and the long C-S bond would

likely minimize non-bonded, axial 1,3,5-interactions.

31a

31b

32a   32b
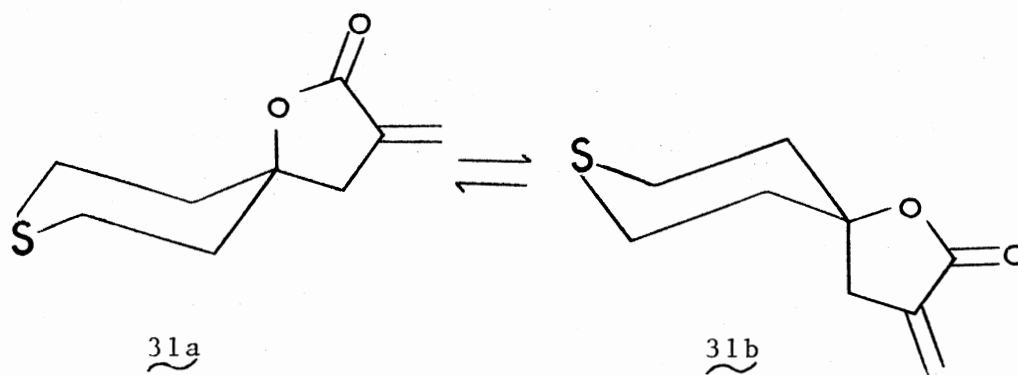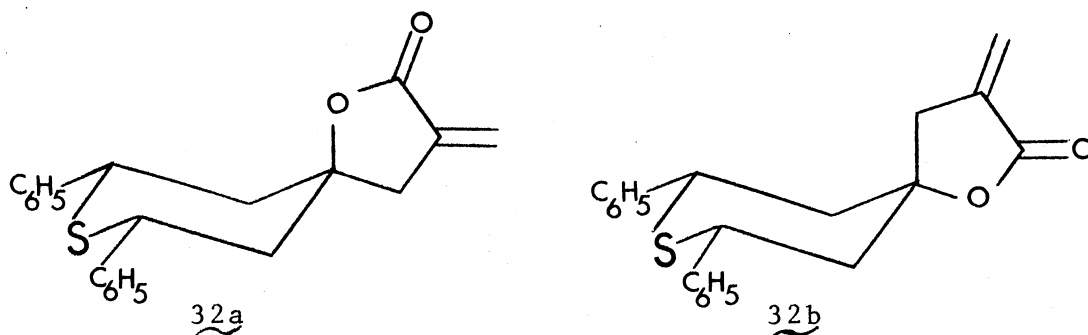
Six-membered sulfur heterocyclics have been reported to exist mostly in the chair conformation.[10,13,38,39,48,72,92] Recent ^{1}H NMR and ^{13}C NMR spectral investigations and single crystal X-ray diffraction studies of a few substituted 4-thianones and 4-thianols[85,86] further confirm the assignment of chair conformation for six-membered sulfur heterocyclics. Thus, the NMR spectral investigation of the conformational equilibrium for our system 31a ⇌ 31b could provide insight as to the effect the sulfur atom might have on the equilibrium compared to the carbocyclic analogous system 30a ⇌ 30b.

The conformational equilibria in a few spiro systems have been investigated in the past decade. In an attempt to evaluate the steric requirements of both the formally sp^3-hybridized NH and NCH$_3$ atoms and the oxygen atom (in comparison with a methylene group), Jones and co-workers[46] examined the systems 33a ⇌ 33b and 34a ⇌ 34b. It was observed that at low temperatures the ^{1}H signal for the methylene group in the oxazolidine ring was split into two singlets of unequal area. Equilibrium constants were calculated by the peak area method.[46] The results of the investigation

showed that in the equilibrium 33a $\rightleftharpoons$ 33b, 33a is favored, a

33a   33b

a   b

34   R' = H; R'' = CH_3

35   R' = CH_3; R'' = H
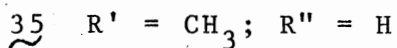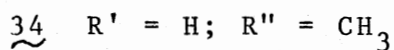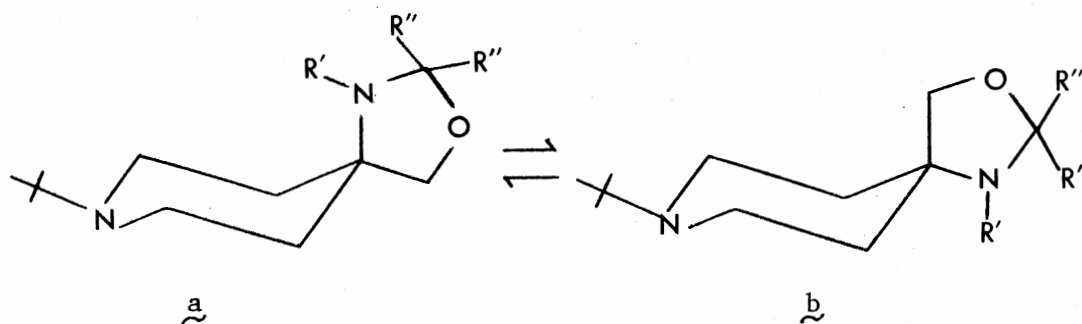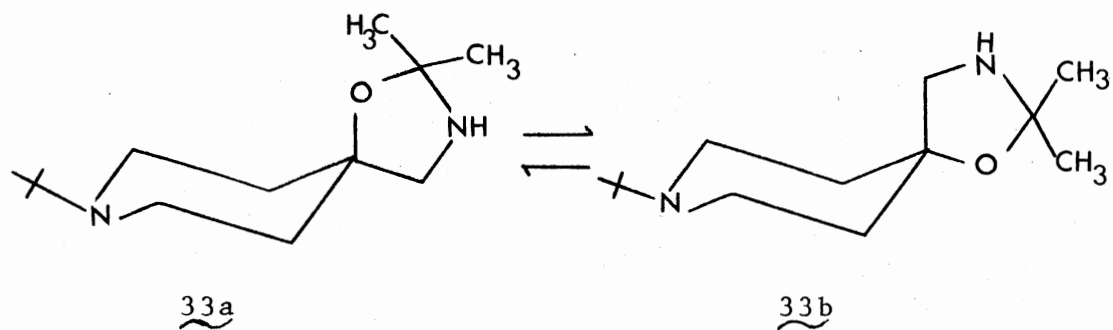
situation similar to that for the corresponding[47] dioxolane

equilibrium 36a $\rightleftharpoons$ 36b. Thus evidence was provided for a

smaller steric requirements of an sp^3-hybridized lone pair

on oxyzen as compared with a CH_2 group. However, the situa-

tion was reversed in the systems 34a $\rightleftharpoons$ 34b and 35a $\rightleftharpoons$ 35b.

Conformers 34b and 35b were favored over 34a and 35a, respec-

36a   36b
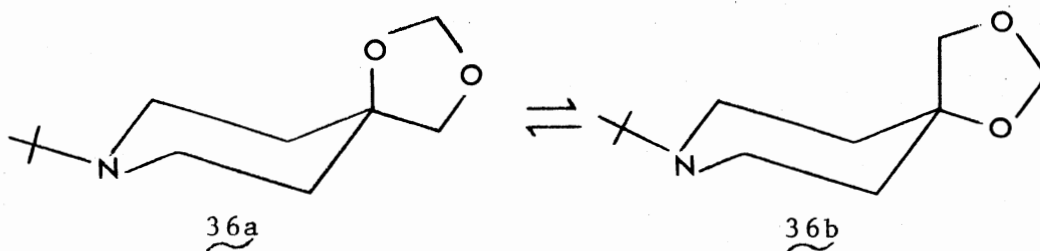
tively.

Similar investigations by Uebel and co-workers[96] on
37a ⇌ 37b and 38a ⇌ 38b at low temperatures (less than
-80°C) by the peak area method and by Picard and Moulines[81]
on 39a ⇌ 39b at 38°C by the uncorrected chemical shift
method favored conformers with axial C-O bond.

37 G = CH$_2$; 38 G = C=O

39a   39b
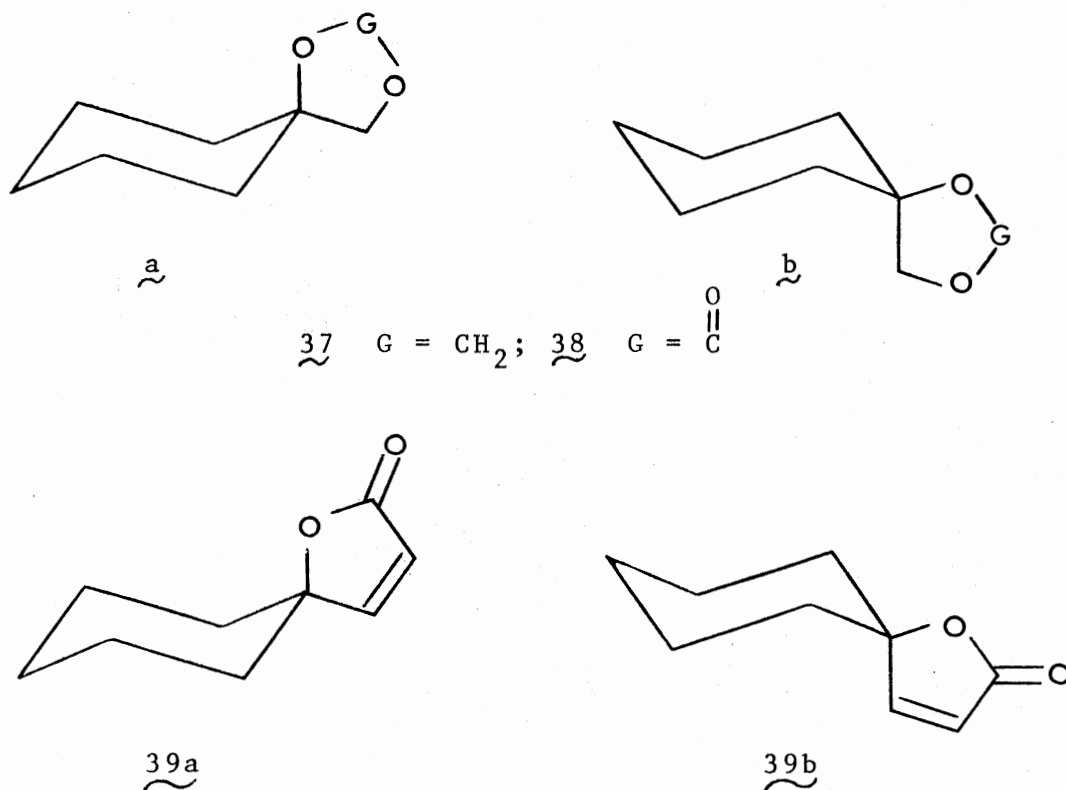
Very recently O'Donnell and co-workers[79] reported an
investigation of the thermodynamic and kinetic aspects of
the equilibrium 30a ⇌ 30b. Working at low temperatures
(less than 185°K), it was determined from peak area measure-
ments that conformer 30a was favored over 30b to the extend
of about 0.09 kcal/mole difference in standard free
energy.[79] This finding was corroborated by a second inves-

tigation employing the corrected chemical shift method.[79]

Moreover a single crystal analysis by X-ray diffraction of

the isomer formed in preponderance (from reaction between

4-tert-butylcyclohexanone and the Reformatsky reagent of

ethyl α-bromomethylacrylate) confirmed its structure to be

cis-8-tert-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one

(28) with an axial C-O bond.[79]

Study of Intramolecular Rate Processes

DNMR spectroscopy provides the chemist a powerful tool

for studying intramolecular movements (like ring reversals,

atomic inversions etc.) with activation energies of 5 to 40

kcal/mole.[2,8,89] Processes of this type are frequently so

fast that the resulting isomers cannot be separated at room

temperature and, hence, are not amenable to conventional

kinetic methods of investigation. On the other hand, they

are too slow for investigation by IR and Raman spectroscopy.

The theoretical aspects governing rate measurements by

NMR data from the line shape function have been developed

for a two-site exhange by Gutowsky and Holm.[33] When two

NMR active nuclei A and B reside in regions with different

magnetic environments, there can be observed different

resonance frequencies ν_A and ν_B. If the nuclei exhange

sites by an intra- or intermolecular process, the NMR spect-

rum is a function of the difference in resonance frequency,

$|\nu_A - \nu_B| = \Delta\nu$, and of the rate of exchange. Thus, in N,N-di-

methylbenzamide, the equilibrium 40a ⇌ 40b was one of the

earliest examples studied. The exchange of methyl groups A and B is a first order degenerate process, the rate of which is determined by the temperature. At low temperature, when the exhange is slow and the rate coefficient k << $\Delta\nu$, the spectrum consists of two sharp singlets at ν_A and ν_B. At high temperatures (k >> $\Delta\nu$) only one sharp signal is observed. In the intermediate region, when k increased from the lower to higher limit, the spectrum changed via a broadening of the two lines[28,98] which coalesced[49,50] and gave a single line with gradually decreasing line-width
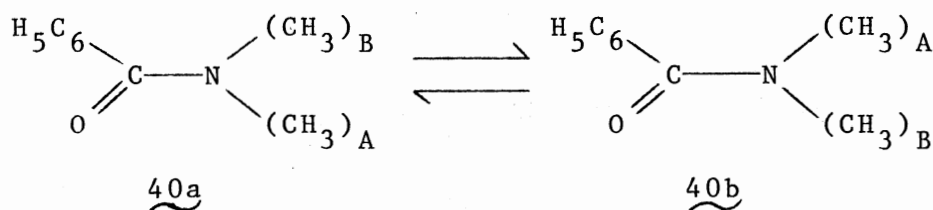
with increasing temperature.[7] The line shape, v,[3,8,42] of the NMR absorption can be written as Eq. (4) where ν is the

$$v = f(\nu, \ k, \ \Delta\nu, \ T_2) \qquad \text{Eq. (4)}$$

frequency and T_2 is the transverse relaxation time (related to the line width at half intensity, $W_{\frac{1}{2}}$) in the absence of exhange by Eq. (5). By making a computer comparison between

$$T_2 = 1/\pi W_{\frac{1}{2}} \qquad \text{Eq. (5)}$$

the total experimental and theoretical line shapes, via variation of the parameters k, $\Delta\nu$ and T_2, until a minimum value is achieved for the expression $\Sigma|v_{theor} - v_{exp}|^2$ for

a number of selected frequencies, the rate coefficients can be calculated. From the rate coefficients and the Eyring equation, Eq. (6), the free energy of activation can be calculated. From a plot of $\ln(k/T)$ vs $1/T$, the thermodynamic

$$k = \kappa \; \frac{k_B \, T}{h} \; \exp(-\Delta G^*/RT) \qquad \text{Eq. (6)}$$

where κ = transmission coefficient (usually

assumed as equal to 1)

k_B = Boltzmann constant

h = Planck's constant

T = temperature in degrees Kelvin

ΔG^* = free energy of activation

R = gas constant

parameters ΔH^* (activation enthalpy) and ΔS^* (activation entropy) can be obtained.

$$\ln(k/T) = \ln(\kappa \; \frac{k_B}{h}) + \Delta S^*/R - \Delta H^*/RT \qquad \text{Eq. (7)}$$

Rate coefficients at the coalescence temperature T_c can be also determined by means of approximate expressions, such as Eq. (8), for the coalescence of singlets associated with uncoupled, diastereotopic atoms or groups.[83] Eq. (9) is for systems in which the coalescence of the coupled AB spin system occurs as a singlet.[65] Rate coefficients calculated by these approximate expressions have been compared

$$k_c = \frac{\pi \; \Delta\nu}{\sqrt{2}} \qquad \text{Eq. (8)}$$

with those obtained by complete line shape analysis[67] and

$$k_c = \frac{\pi}{\sqrt{2}} (\Delta\nu^2 + 6J^2)^{\frac{1}{2}} \qquad \text{Eq. (9)}$$

have been found to give reliable estimates of free energies
of activation. Use of Eq. (8) in conjunction with the
Eyring equation (6) leads to Eq. (10) for $\Delta G_{T_c}^*$. This ex-
pression is the one most commonly used for determination of

$$\Delta G_{T_c}^* = 0.004573 \ T_c[9.97 + \log(T_c/\Delta\nu)] \qquad \text{Eq. (10)}$$

approximate free energy barriers.[42]

CHAPTER II

RESULTS AND DISCUSSION

During the past two decades a large number of natural products containing the α-methylene-γ-butyrolactone unit have been isolated by several workers.[29,31,32,52,56,60-64] However, most of the research activity has centered around the physiological activity of these compounds.[40,41,57,68,69] O'Donnell and co-workers were the first group who made a DNMR study of a system containing the α-methylene-γ-butyro-lactone unit.[79] In part this investigation prompted the present study of the thermodynamic and kinetic parameters of the ring reversal process in the hetero system 31a ⇌ 31b.
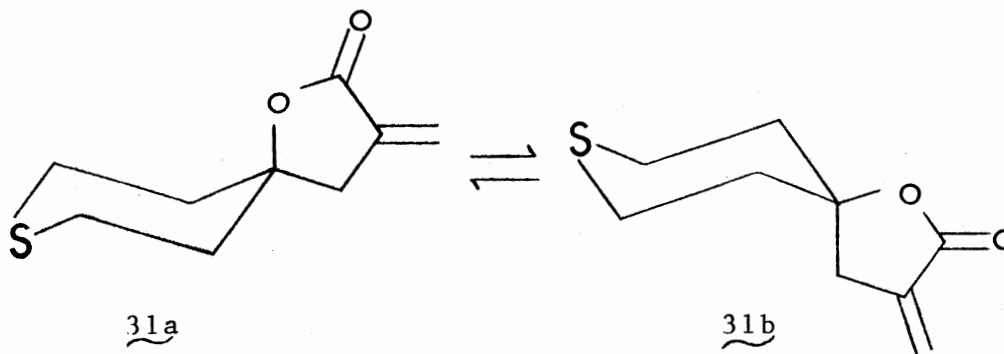
31a ⇌ 31b

Presented herein are the synthesis and physical and spectral characteristics of 9-methylene-7-oxa-1-thiaspiro-[4.5]decan-8-ones. Also included is an estimate for the upper limit for the barrier to ring reversal, ΔG^*, for the

system 31a ⇌ 31b, which is approximately 8 kcal/mole.   In

addition, results of a single crystal analysis by X-ray

diffraction of 2,2,6,6-tetramethyl-9-methylene-7-oxa-1-thia-

spiro[4.5]decan-8-one is also reported.

Although there is no dearth of synthetic techniques

available for the synthesis of α-methylene-γ-butyrolactones,

none of them[26,30-32,51,84] were found suitable for the syn-

thesis of the required 9-methylene-7-oxa-1-thiaspiro[4.5]-

decan-8-ones.   Since the techniques employed for the syn-

thesis of these compounds bear a partial resemblance to the

one developed by O'Donnell[79] for the synthesis of 30a ⇌ 30b,

a brief description of our modification[87] is presented.

A solution of ethyl α-bromomethylacrylate (42) in dry

THF is added slowly to a suspension of Zn in a solution of

cyclohexanone (41) in dry THF.   The mixture is stirred

for 3 hr.   After cooling to room temperature, the mixture

is added to 5% ice-cold H_2SO_4.   The lactone formed can be

41

CH_2Br
$H_2C=C-CO_2C_2H_5$

42

Zn/THF
$45-50°C/3\ hr$

$CO_2C_2H_5$
HO

43a

$CO_2C_2H_5$
OH

43b

5% H_2SO_4

0.5 hr/0°C

30a   30b
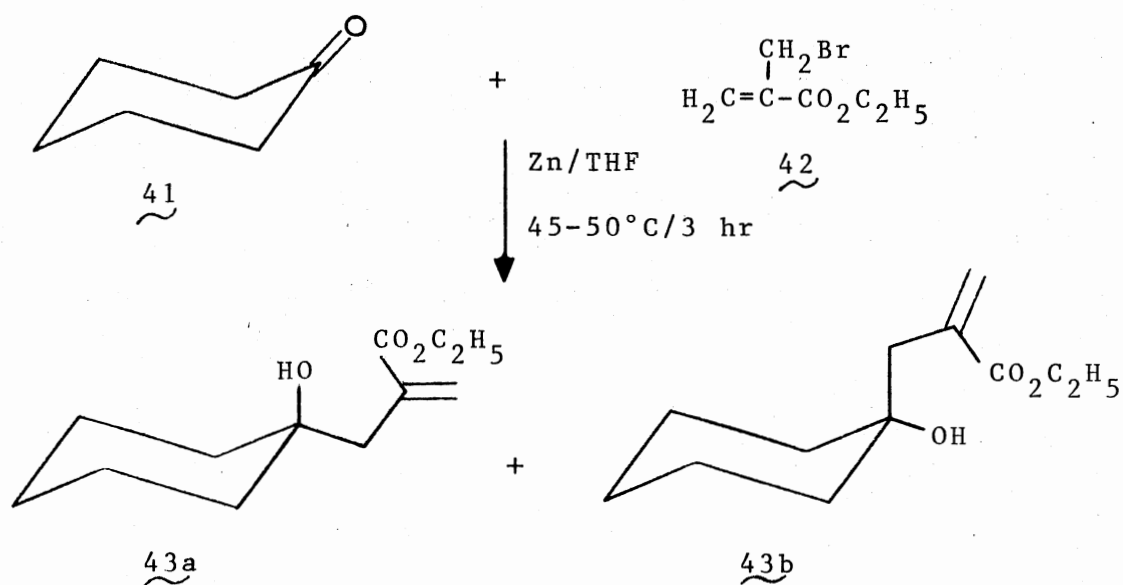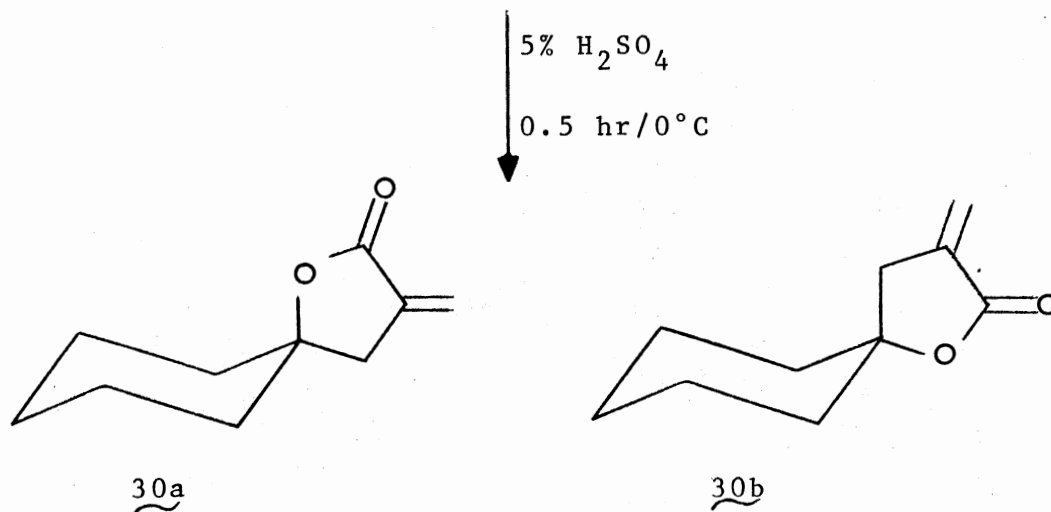
isolated by extraction with ether.[79] Surprisingly, a simi-
lar technique when used with thian-4-ones resulted in the
formation of only sulfonium salts. Hence, the following
modified procedure was adopted.[87] In all cases, the
Reformatsky reagent was formed initially by treating the
ester 42 (in dry THF) with a suspension of Zn in dry THF.
This was followed by the addition of the appropriate thian-
one 45. Stirring the solution at 45-50°C under N_2 for 3 hr
and addition of the resulting solution to 5% ice-cold H_2SO_4
resulted in formation of the lactone which usually separa-
ted as an oil. Extraction with ether and careful recovery
from the ether extract (see chapter III for details) gave
crystalline lactone in all the cases.[87]

$$H_2C=C-CO_2C_2H_5 \quad + \quad Zn \quad \xrightarrow[45-50°C]{Dry\ THF} \quad H_2C=C-CO_2C_2H_5$$
$$\quad\ \ |\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad\ \ |$$
$$\quad CH_2Br \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2ZnBr$$

42   44
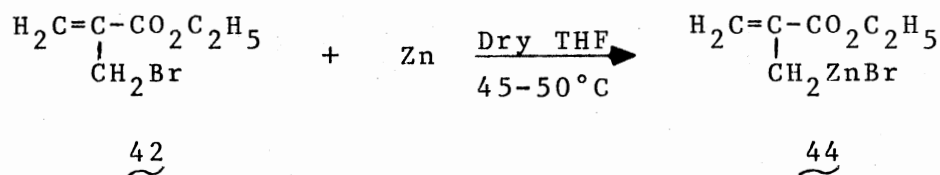
Although a published procedure is available for the

$$\underset{\sim}{45} \quad + \quad \underset{\sim}{44}$$

$\underset{\sim}{a} \quad R' = R'' = R''' = R'''' = H$

$\underset{\sim}{b} \quad R' = R'' = D; \quad R''' = R'''' = H$

$\underset{\sim}{c} \quad R' = R'' = H; \quad R''' = R'''' = CH_3$

$\underset{\sim}{d} \quad R' = R'' = R''' = H; \quad R'''' = C_6H_5$

Dry THF

45-50°C/3 hr

$\underset{\sim}{a} \qquad \underset{\sim}{b}$

$\underset{\sim}{46} \quad R' = R'' = R''' = R'''' = H$

$\underset{\sim}{47} \quad R' = R'' = D; \quad R''' = R'''' = H$

$\underset{\sim}{48} \quad R' = R'' = H; \quad R''' = R'''' = CH_3$

$\underset{\sim}{49} \quad R' = R'' = R''' = H; \quad R'''' = C_6H_5$

5% H_2SO_4

0.5 hr/0°C

a   +   b

$\underline{50}$ R' = R" = D; R"' = R"" = H

$\underline{31}$ R' = R" = R"' = R"" = H

$\underline{51}$ R' = R" = H; R"' = R"" = CH$_3$

$\underline{32}$ R' = R" = R"' = H; R"" = C$_6$H$_5$
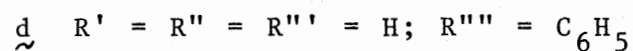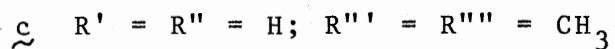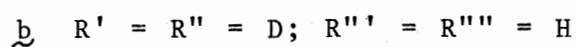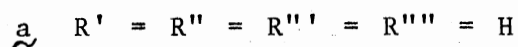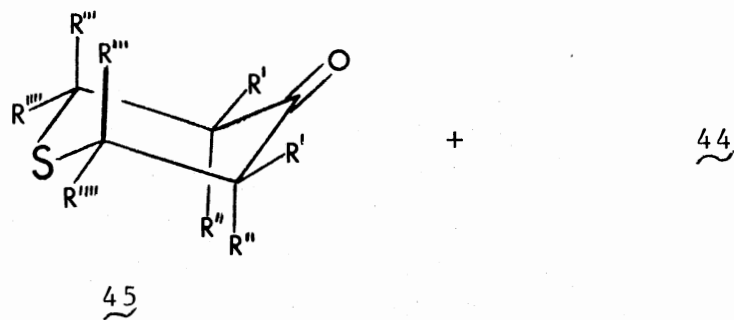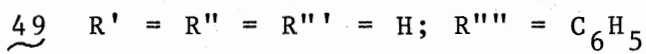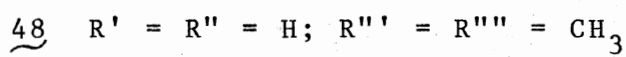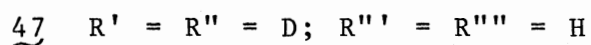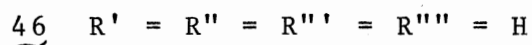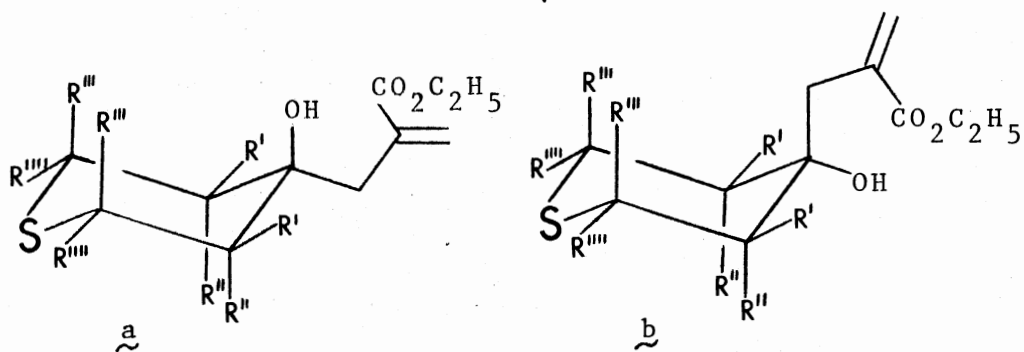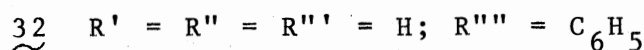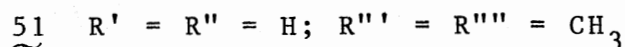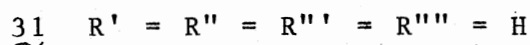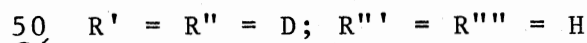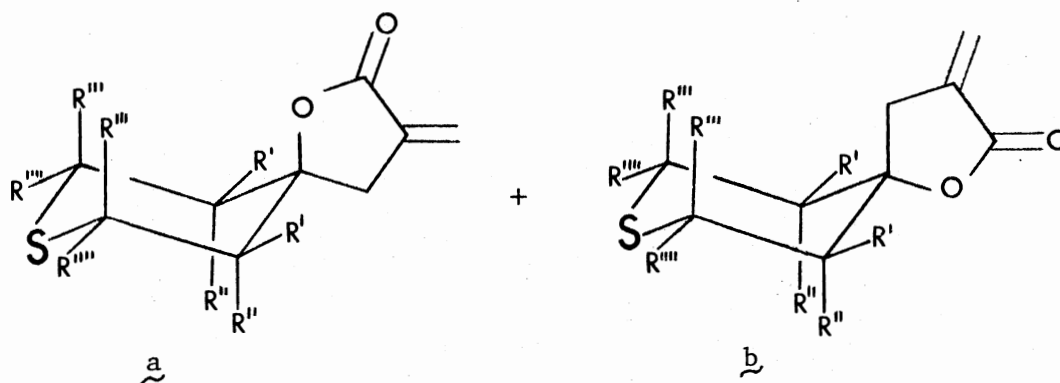
synthesis of ethyl α-bromomethylacrylate,[25] we have shown[88] that by careful control of conditions one can eliminate one step with the added advantage of improved yield. The procedure adopted is outlined below.

$$(HOH_2C)_2C(CO_2C_2H_5)_2 \ + \ 48\% \ HBr \ \xrightarrow[\text{12 hr}]{\text{85-90°C}} \ \underset{\underset{CH_2Br}{|}}{H_2C{=}C{-}CO_2H}$$

$\underline{52}$ $\underline{53}$

$$\underline{53} \ + \ C_2H_5OH \ \xrightarrow[\text{36 hr}]{\text{H}_2\text{SO}_4/\text{boil}} \ \underset{\underset{CH_2Br}{|}}{H_2C{=}C{-}CO_2C_2H_5}$$

$\underline{42}$
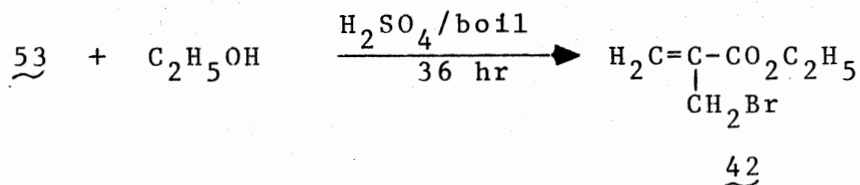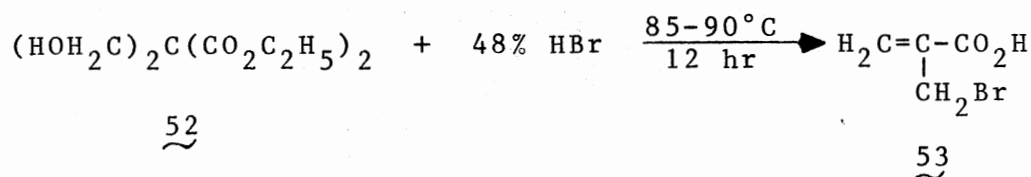
The physical and synthetic data for the various lactones synthesized are reported in Table I. Compounds $\underline{31a}$, $\underline{50a}$ and $\underline{51a}$ are conformationally related to compounds $\underline{31b}$, $\underline{50b}$ and $\underline{51b}$ by a ring reversal process. Although in sol-

TABLE I

SYNTHETIC AND PHYSICAL DATA FOR COMPOUNDS 31a

(or 31b), 32a (or 32b), 50a (or 50b) and 51a
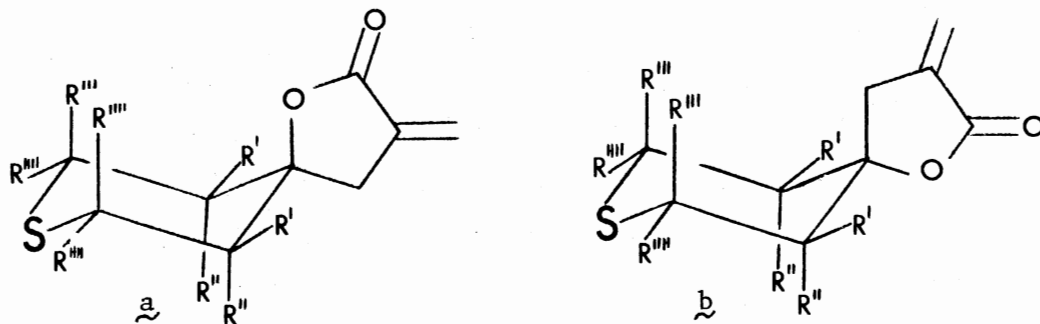
Cpd.[a]	R'	R"	R"'	R""	mp (°C)	yield (%)
50a (or 50b)	D	D	H	H	94-96	15.2
31a (or 31b)	H	H	H	H	94-95	14.2
51a	H	H	CH_3	CH_3	109-111	34
32a (or 32b)	H	H	H	C_6H_5	148.5-150	10

[a]Compounds 50a (or 50b) and 31a (or 31b) were re-crystallized from CH_3OH, compound 51a from CH_3OH and petroleum ether and compound 32a (or 32b) from 1:1 CH_3OH and petroleum ether containing a little benzene.

ution (at room temperature) these conformers are in rapid
reversible equilibrium, isolation of a solid in each case
with a sharp melting point by the aforesaid synthetic tech-
nique suggests that the solid, at least, is only one confor-
mational isomer.[87]   A single crystal analysis by X-ray di-
ffraction of 2,2,6,6-tetramethyl-9-methylene-7-oxa-1-thia-
spiro[4.5]decan-8-one shows that the C(4)-O(7) bond is
axial.   A similar finding was reported previously[79] for
cis-8-tert-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one
(54).
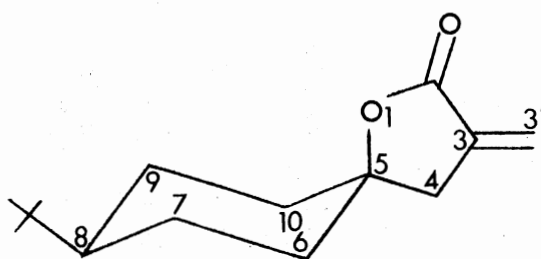
54

In an attempt to evaluate the steric requirements of
the formally sp^3-hybridized oxygen atom in comparison with
a methylene group, Jones and co-workers[46] examined the sys-
tem 33a ⇌ 33b at low temperatures by the peak area method.
The results of the investigation showed that conformer 33a
(with axial C-O bond) is preferred over 33b (with axial
$C-CH_2$ bond) to the extent of 0.12 kcal/mole in standard
free energy difference.[46]   This shows that most likely an
sp^3-hybridized lone pair on oxygen has a smaller steric
requirement as compared to a CH_2 group.   Similar findings

were reported for the dioxolane equilibrium $\underline{36a} \rightleftharpoons \underline{36b}$[47] and

spirolactone equilibrium $\underline{30a} \rightleftharpoons \underline{30b}$.[79] It may be presumed

that a similar situation (namely axial preferrence for C-O

bond) exists in our system $\underline{31a} \rightleftharpoons \underline{31b}$, and this results in

preferrential crystallization of the conformer with C-O

bond axial as evidenced by the X-ray diffraction analysis

of 2,2,6,6-tetramethyl-9-methylene-7-oxa-1-thiaspiro[4.5]-

decan-8-one ($\underline{51a}$). Although the other three spirolactones

$\underline{31b}$ (or $\underline{31b}$), $\underline{50a}$ (or $\underline{50b}$) and $\underline{32a}$ (or $\underline{32b}$) were not analy-

zed by X-ray diffraction, an evaluation, based on spectral

analysis, suggests an axial orientation for the C(4)-O(7)

bond. Compounds $\underline{32a}$ and $\underline{32b}$ are configurational isomers

and are not interconvertible by ring reversal process.

Again, isolation of a solid with a sharp melting point sug-

gests that the solid contains only one isomer, presumably

$\underline{32a}$ with the C(4)-O(7) bond in the axial position.[87]

The proton NMR spectral data are reported in Table II.

The signal at δ 4.54 (dd, J = 11 and 4 Hz) for compound $\underline{32a}$

(or $\underline{32b}$) suggests that this compound has the two phenyl

groups at C(2) and C(6) in equatorial positions. The coup-

ling constants for $^3J_{H(2a),H(3a)}$ or $^3J_{H(6a),H(5a)}$ = 11 Hz

and for $^3J_{H(2a),H(3e)}$ or $^3J_{H(6a),H(5e)}$ =4 Hz observed for

this compound are typical values expected for vicinal coup-

ling constants $^3J_{trans}$ and $^3J_{cis}$ in the chair conformation

for a cyclohexane system.[42] Indeed, this indicates that the

C(2)-H and C(6)-H bonds are axial. The signals due to the

H(3) and H(5) protons in $\underline{32a}$ (or $\underline{32b}$) at δ 2.04-2.41 (m,

TABLE II

^{1}H NMR DATA FOR 31a ⇌ 31b, 32a (or 32b),

50a ⇌ 50b and 51a ⇌ 51b
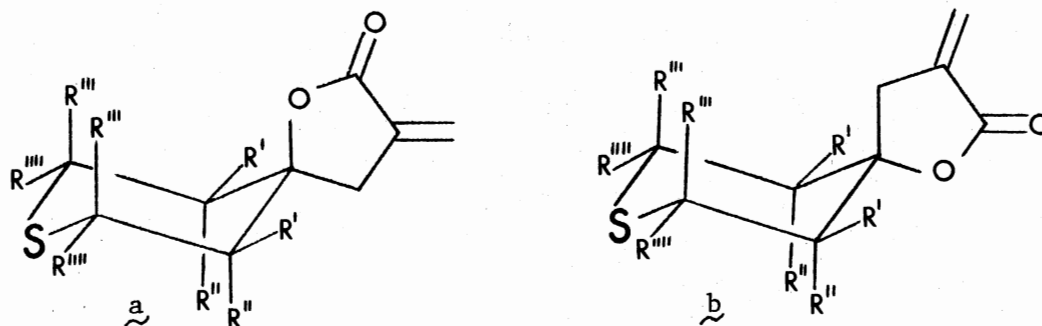
50   R' = R" = D; R"' = R"" = H

31   R' = R" = R"' = R"" = H

51   R' = R" = H; R"' = R"" = CH$_3$

32   R' = R" = R"' = H; R"" = C$_6$H$_5$

Cpd.	^{1}H NMR Chemical Shift Data in ppm from TMS (DCC1$_3$)			
	H(10)[a]	H$_b$(9')[b]	H$_a$(9')[c]	other
50a ⇌ 50b	2.70(m, 2 H)	5.66(m, 1 H)	6.27(m, 1 H)	2.42-3.07 (m, 4 H[d])
31a ⇌ 31b	2.70(m, 2 H)	5.66(m, 1 H)	6.27(m, 1 H)	1.76-3.18 (m, 8 H)
51a ⇌ 51b	2.72(m, 2 H)	5.64(m, 1 H)	6.26(m, 1 H)	1.27(m, 6 H) 1.61(s, 6 H) 1.59-2.09 (m, 4 H[e])
32a (or 32b)	2.84(m, 2 H)	5.68(m, 1 H)	6.30(m, 1 H)	2.04-2.41 (m, 4 H) 4.54(m, 2 H[f]) 7.20-7.50 (m, 10 H)

TABLE II (Continued)

---

[a]Three line pattern resulting from X_2 of AMX_2 where $J_{AX} \simeq J_{MX} \simeq 2.5$ Hz. The center of the triplet is taken as the chemical shift.

[b]M portion of AMX_2 pattern where $J_{AM} < J_{AX} \simeq J_{MX} \simeq 2.5$ Hz. The center of the triplet is taken as the peak position.

[c]A portion of AMX_2 pattern where $J_{AM} < J_{AX} \simeq J_{MX} \simeq 2.5$ Hz. The center of the triplet is taken as the peak position.

[d]AB quartet with $J_{AB} = 14.2$ Hz.

[e]AB quartet with $J_{AB} = 14.0$ Hz.

[f]Doublet of a doublet with $^3J_{H(2a),H(3a)}$ (or $^3J_{H(6a),H(5a)}$) = 11 Hz and $^3J_{H(2a),H(3e)}$ (or $^3J_{H(6a),H(5e)}$) = 4 Hz. The center of the multiplet is taken as the peak position.

4 H) are considerably downfield than the signals due to similar protons in 51a ⇌ 51b at δ 1.59-2.09, suggests that the H(3) and H(5) protons in 32a (or 32b) are situated towards an edge of the arene ring. The cause for the deshielding effect experienced by these protons can be traced to the presence of phenyl groups at C(2) and C(6). The diamagnetic anisotropy of the electron cloud in the benzene ring is long known to shield any proton situated over the benzene ring (signal shifted to higher field than otherwise expected) and deshield any proton situated in the region of the periphery of the benzene ring (signal shifted to lower field than otherwise expected).[35] A molecular model of 32a (or 32b) shows that the H(3) and H(5) protons are indeed on the periphery of the benzene ring. The ^{1}H NMR spectrum of 32a (or 32b) also shows that the diamagnetic anisotropy effect of the benzene ring may be felt, although to a lesser extent, even by the distant H(10) protons (δ 2.84) in comparison to δ ≃ 2.70 found for similar protons in the other three lactones (31, 50 and 51). The assignment of signals at δ ≃ 5.66 and δ ≃ 6.27 for the H_b(9') and H_a(9') protons, respectively, was made on the basis of the empirical correlation Eq. (11) developed by Tobey[94] and Pascual, Meir and Simon[84] for the chemical shift of a proton on a double bond:

$$\delta = 5.28 + Z_{gem} + Z_{cis} + Z_{trans} \qquad \text{Eq. (11)}$$

where Z_{gem}, Z_{cis} and Z_{trans} are the substituent constants

for the other groups on the double bond that are added to the chemical shift of protons in ethylene (for ethylene δ 5.28). The molecular fragment of interest can be represented as $\underset{\sim}{55}$. The calculation of chemical shifts for $H_a(9')$ and $H_b(9')$ follows.[80,94] As can be seen from Table II

$$\underset{\sim}{55}$$
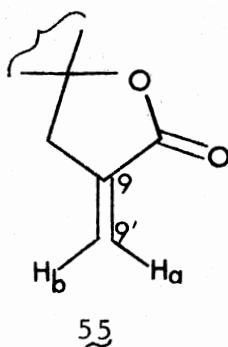
$$\delta_{H_a(9')} = 5.28 + Z_{gem} + Z_{cis} + Z_{trans}$$

$$Z_{gem} \text{ for } -H = 0.0$$

$$Z_{cis} \text{ for } -CO_2R = 1.15$$

$$Z_{trans} \text{ for } -Alkyl = -0.29$$

Thus, $\delta_{H_a(9')} = 5.28 + 0.0 + 1.15 - 0.29 = 6.14$

$$\delta_{H_b(9')} = 5.28 + Z_{gem} + Z_{cis} + Z_{trans}$$

$$Z_{gem} \text{ for } -H = 0.0$$

$$Z_{cis} \text{ for } -Alkyl = -0.26$$

$$Z_{trans} \text{ for } -CO_2R = 0.56$$

Thus, $\delta_{H_b(9')} = 5.28 + 0.0 - 0.26 + 0.56 = 5.58$

these values compare very favorably with experimental values.

The ^{13}C NMR spectral data are reported in Table III.

TABLE III

^{13}C NMR DATA FOR 31a⇌31b, 32a (or 32b), 50a⇌50b and 51a
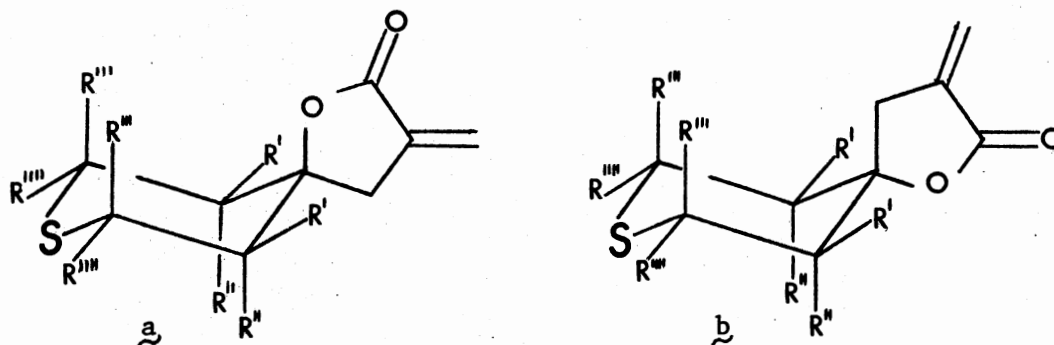
50	R' = R" = D;	R'" = R"" = H
31	R' = R" = R'" = R"" = H	
51	R' = R" = H;	R'" = R"" = CH$_3$
32	R' = R" = R'" = H;	R"" = C$_6$H$_5$

Cpd.	^{13}C Chemical Shifts (in Hz from TMS in DCCl$_3$)[a]						
	C(2), C(6)	C(3), C(5)	C(4)	C(8)	C(9)	C(9')	C(10)
50a⇌50b	615.4	77.8	2099	4258	3386	3098	1019
31a⇌31b	620.0	970	2040	4260	3386	3098	1023
51a⇌51b[b]	1052	1272	2102	4261	3381	3079	1089
32a (or 32b)	1141	1108	2080	4257	3375	3108	1046

[a]Assigment based upon off-resonance decoupled spectra, signals for selected model compounds and peak intensities.

[b]Assignment uncertain. R'" = R"" = CH$_3$ and occur at 858 and 796 Hz.

Comparison of the chemical shift for C(2)-C(6) in 31a ⇌ 31b

and 51a ⇌ 51b with those for C(7)-C(9) in 30a ⇌ 30b and

56a ⇌ 56b gives information regarding the electrostatic

effect due to the presence of the sulfur atom.[78] Besides,

the presence of the more electronegative sulfur atom in

both lactone 31a ⇌ 31b or 51a ⇌ 51b changes the electron

density at C(2)-C(6) as reflected in the down field shift

of these α-carbon ^{13}C signals compared with the shift for

C(7)-C(9) in 30a ⇌ 30b and 56a ⇌ 56b[78] as shown in Table IV.

As reported by Ramalingam and co-workers[86] for a number of

2,6-disubstituted 1-thia-4-cyclohexanones, an upfield

γ-shift was observed for the resonance of C(4) in 31a ⇌ 31b

and 51a ⇌ 51b. As suggested by Jones and Hassan[45] and

Dutch[14] for simple systems, the upfield γ-shift probably

arises from a field effect. Eliel and co-workers have pro-

posed a hyperconjugative-type interaction of an electron

pair on a heteroatom through the C_α-C_β bond (in certain

heterocyclohexanes), consequently affecting the shift of

the antiperiplanar γ-carbon atom.[17] The signal due to C(3)

C(5) in 50a ⇌ 50b and 31a ⇌ 31b shows an upfield shift in

30 R' = R" = H; 56 R' = R" = CH_3

TABLE IV

^{13}C CHEMICAL SHIFTS OF SELECTED CARBONS IN 31a ⇌ 31b

30a ⇌ 30b, 51a ⇌ 51b AND 56a ⇌ 56b
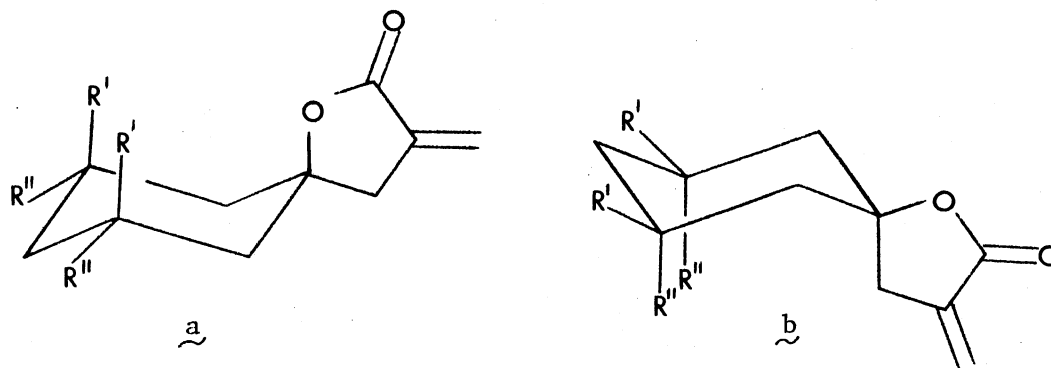
30 R' = R'' = H

56 R' = R'' = CH$_3$

Cpd.	^{13}C Chemical Shifts (in Hz from TMS)[a]			
31a ⇌ 31b	C(2),C(6)	620	C(4)	2040
30a ⇌ 30b	C(7),C(9)	567	C(5)	2097
51a ⇌ 51b	C(2),C(6)	1052	C(4)	2102
56a ⇌ 56b	C(7),C(9)	795	C(5)	2119

[a]In DCCl$_3$ solvent.

the deutero-substituted compounds. Similar isotope-induced upfield shifts have been reported[95] for long-chain, aliphatic compounds.

The IR and mass spectral data are reported in Table V. The mass spectral data, besides confirming the molecular weight (mass of the parent ion peak corresponds to the molecular mass), also confirms the molecular formula through the ratio of intensities of the isotope peaks.[93] A model calculation for obtaining the isotope peak intensities follows:

Compound 31a (or 31b): Molecular formula $C_9H_{12}O_2S$

Calculation of isotope peak intensities:

$$\%(M + 1) = 100 \frac{(M + 1)}{M}$$

$$\simeq 1.1 \text{ x number of carbon atoms } +$$

$$0.78 \text{ x number of sulfur atoms}$$

$$= 1.1 \text{ x } 9 + 0.78 = 10.68$$

$$\%(M + 2) = 100 \frac{(M + 2)}{M}$$

$$\simeq \frac{(1.1 \text{ x number of carbon atoms})^2}{200} +$$

$$0.20 \text{ x number of oxygen atoms } +$$

$$4.4 \text{ x number of sulfur atoms}$$

$$= \frac{(1.1 \text{ x } 9)^2}{200} + 0.20 \text{ x } 2 + 4.4$$

$$= 5.29$$

In an attempt to obtain the thermodynamic and kinetic parameters for the ring reversal equilibrium 31a $\rightleftharpoons$ 31b, the ^{1}H NMR spectra of a solution of 9-methylene-7-oxa-1-thia-

TABLE V

IR AND MASS SPECTRAL DATA FOR 31a (or 31b)

32a (or 32b), 50a or 50b and 51a

a   b
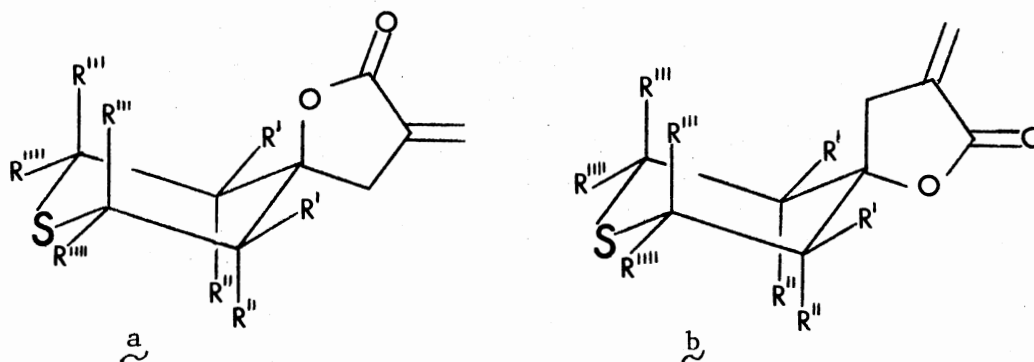
Cpd.	R'	R"	R'''	R''''	IR(cm^{-1})^a	Mass Spec. Data m/e	%
50a (or 50b)	D	D	H	H	C=O(1748)	188(M)	100
					C=C(1653)	189(M+1)	12.5
						190(M+2)	6.9
31a (or 31b)	H	H	H	H	C=O(1748)	184(M)	100
					C=C(1653)	185(M+1)	10.8
						186(M+2)	5.2
51a	H	H	CH$_3$	CH$_3$	C=O(1754)	240(M)	100
					C=C(1656)	241(M+1)	18.4
						242(M+2)	6.6
32a (or 32b)	H	H	H	C$_6$H$_5$	C=O(1754)	336(M)	100
					C=C(1664)	337(M+1)	20.5
						338(M+2)	7.3

^{a}Spectrum taken in KBr pellet.

spiro[4.5]decan-8-one-3,3,5,5-$\underline{d}_4$ in acetone-$\underline{d}_6$ were record-
ed at several temperatures. Measurement of chemical shift
differences between the signals for the methyl and hydroxyl
protons of methanol and the use of an empirical correlation
relating chemical shift differences to temperature[97] permit-
ted the determination of temperatures at which these spectra
were recorded. As the environment of the H(10) protons
differ in the two conformers, the C(4)-C(10) bond being
equatorial in one conformer and axial in the other, the
chemical shifts for these protons are expected to be
different. However, at temperatures at which
$k_r \gg \pi|\nu_a - \nu_e|/\sqrt{2}$, the frequency of interconversion bet-
ween the two conformers is fast enough to give only one
single time-averaged signal.[9,66] In our case the signal
appeared as a three-line pattern (X_2 of an AMX_2 pattern).
Lowering the temperature lowers the frequency of intercon-
version and, at temperatures at which $k_r \ll \pi|\nu_a - \nu_e|/\sqrt{2}$,
a splitting[9,66] of this single, three-line pattern into two
separate three-line patterns should be observed. However,
even cooling to as low as -100°C did not, unfortunately,
result in a splitting of the signal due to the H(10) pro-
tons. As acetone-$\underline{d}_6$ freezes at -96°C (a temperature of
-100°C was obtainable with this solvent because of the low-
er freezing point of the solution as compared to that of
the solvent), a 1:1 mixture of Freon-21 and acetone-$\underline{d}_6$ was
tried as the solvent system. Unfortunately, no splitting
was observed for H(10) protons even down to about -110°C.

This probably fixes an upper limit for the coalescence temperature since there appeared to be the initial stages of peak splitting in the spectrum. The actual coalescence temperature is, of course, less than -110°C. Obviously, the barrier for ring reversal, ΔG^*, in our system 31a $\rightleftharpoons$ 31b is lower than that observed for the system 30a $\rightleftharpoons$ 30b.[79] A barrier of 10.9 kcal/mole and coalescence temperature of about -65°C were observed for the latter system.[79]

Reported in Table VI are the torsional angles from X-ray analysis of single crystal of 51a. Although it may appear presumptuous to extrapolate these solid data to a solution of 51a, several workers in the past have demonstrated agreement within ± 2° for these angles between X-ray data and the solution data for a number of simple and substituted cyclohexanes as well as for mono and dihetera-cyclohexanes.[66] We suggest that structural changes which accompany dissolution, if any, may well be rather small in our case. The X-ray analysis of 51a, besides confirming the chair configuration for the six-membered ring, also shows that the six-membered ring is flattened on all sides. All the internal torsional angles in 51a are lower than that observed in cyclohexane.[9] For cyclohexane, the internal torsional angle is about 56° all around the ring.[9] Not only the torsional angle found in 51a are lower than this figure but the values of -48.4° and 47.0° measured for the C(5)-C(6)---S(1)-C(2) and C(6)-S(1)---C(2)-C(3) internal angles respectively, in 51a are significantly lower than

TABLE VI

TORSIONAL ANGLES FROM X-RAY ANALYSIS OF 2,2,6,6-

TETRAMETHYL-9-METHYLENE-7-OXA-1-THIA-

SPIRO[4.5]DECAN-8-ONE (51a)
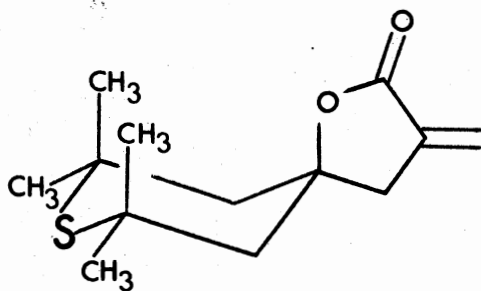
51a

Bonds Involved	Torsional Angle (°)
S(1)-C(2)---C(3)-C(4)	-53.9
C(2)-C(3)---C(4)-C(5)	54.3
C(3)-C(4)---C(5)-C(6)	-52.6
C(4)-C(5)---C(6)-S(1)	53.4
C(5)-C(6)---S(1)-C(2)	-48.4
C(6)-S(1)---C(2)-C(3)	47.0
C(2)-C(3)---C(4)-O(7)	-68.1
C(6)-C(5)---C(4)-O(7)	68.1
C(2)-C(3)---C(4)-C(10)	177.6
C(6)-C(5)---C(4)-C(10)	182.1

those found around the ostensibly sp^2-hybridized carbonyl carbon in the thianones 57 and 58. Table VII reports the relevant torsional angles found in the thianones 57 and 58.[85]

57   R = CH$_3$

58   R = C$_2$H$_5$
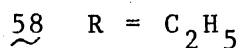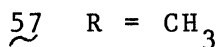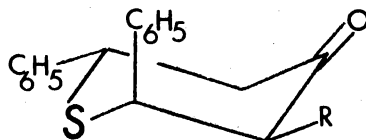
The significantly lower torsional angles found in 51a (-48.4°, 47.0° compared to -52°, 51° and -54°, 52° in 57 and 58, respectively)[85] suggests extensive flattening around sulfur. Such flattening around sulfur is likely the major explanation for the low barrier of 8 kcal/mole for the ring reverlal and a coalescence temperature below -110°C in 51a. There is presented on page 45 an energy diagram for the conversion of one chair form of cyclohexane to another.[82] Of course this assessment, which is supported by theoretical calculations,[1,22] assumes that the transition state more closely resembles a half-chair. It is not unreasonable to expect a similar geometry for the transition state in the ring reversal process of heteracyclohexane and its derivatives. However, there are three possible half-chair forms, namely 59-61, for the latter system.[67] Allinger and co-workers[1] have shown that the major cause for the increase in energy in going from the ground-state chair to the transition state in cyclohexane is due to the increase

TABLE VII

SELECTED TORSIONAL ANGLES IN 57 AND 58

Fragment	Torsional Angle (°)	
	57	58
C(2)-C(3)---C(4)-C(5)	51	52
C(3)-C(4)---C(5)-C(6)	-52	-54

Half-twist

Half-twist

10.8 kcal/mol

5.5 kcal/mol

Energy

Reaction Coordinate
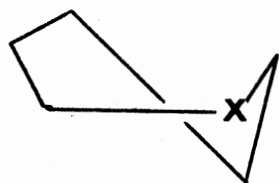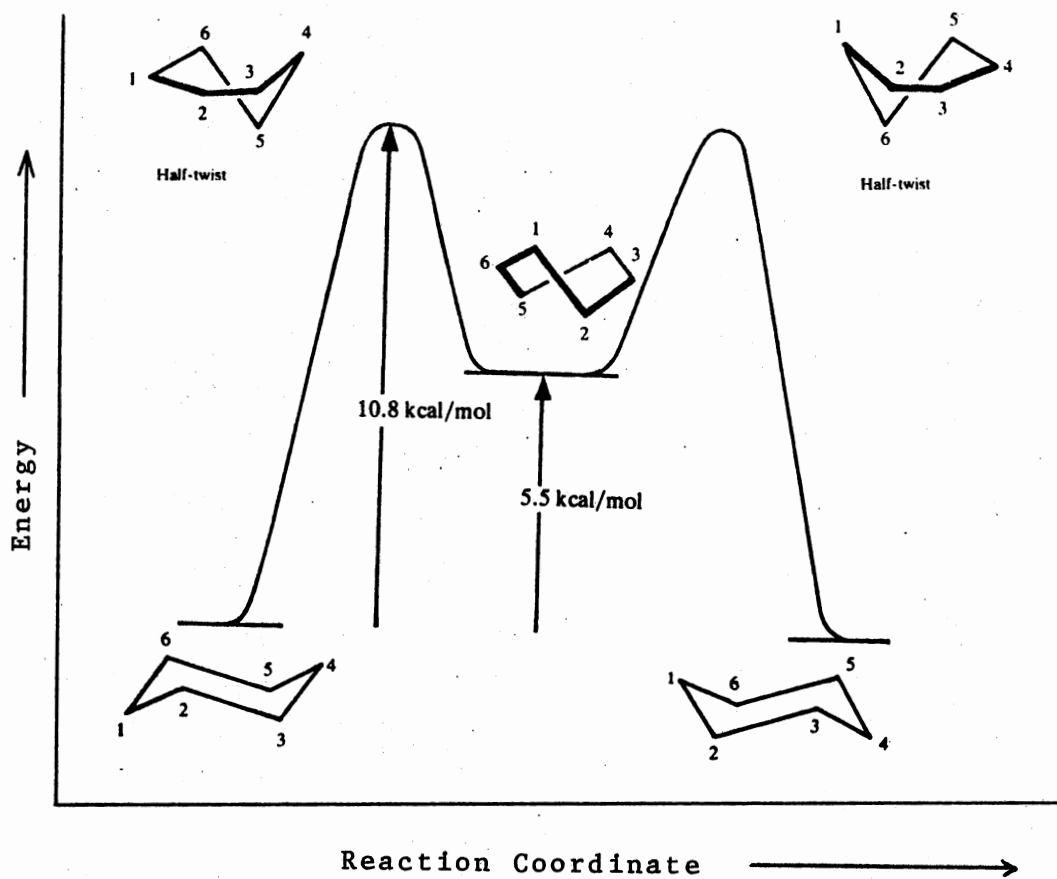
59
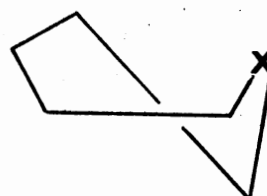
60
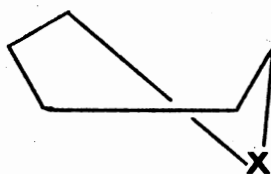
61

in torsional strain. Contributions from van der Waals strain, and especially angle bending strain, are thought to be much smaller.[1,37] In fact, Allinger[1] calculates that bending strain makes a contribution of only 2 out of 12 kcal/mole to the barrier. Of the three possible forms $\underset{\sim}{59}$-$\underset{\sim}{61}$,[67] the least energetic one will be the most preferred. An estimate can be made of the torsional interactions in these three forms from the barrier to CH_3-X- rotation (where X = O, S, NH etc.) in molecules of the type CH_3-X-CH_3. If the C-X torsional barrier is lower than that of the C-C bond, form $\underset{\sim}{59}$ (in which the heteroatom relieves the greatest amount of eclipsing strain) will be preferred, and indeed this is found.[67]

Lambert and co-workers[67] show a parallel between the ring reversal barrier in a number of 1-heteracyclohexanes and the C-X torsional energy. The torsional energy in molecules of the type CH_3-X-CH_3 decreases in the order: C-C > C-O > C-S > C-Se > C-Te.[67] Reported in Table VIII are the ring reversal barriers for a few 1-heteracyclohexanes.[67] This suggests that a lower barrier should be expected for the sulfur containing system $\underset{\sim}{31a} \rightleftharpoons \underset{\sim}{31b}$ than for the carbocyclic system $\underset{\sim}{30a} \rightleftharpoons \underset{\sim}{30b}$ (a value of 10.9 kcal/mole was found[79] for the latter system). Moreover, the extensive flattening around sulfur (found from X-ray analysis of $\underset{\sim}{51a}$) leads to a ground state configuration that is energetically close to the transition state configura-

TABLE VIII

FREE ENERGY BARRIER TO RING REVERSAL IN A

FEW SELECTED 1-HETERACYCLOHEXANES
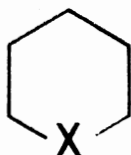
62 X = O

63 X = S

64 X = Se

65 X = Te

Cpd.	ΔG^* (kcal/mole)
62	10.3
63	9.4
64	8.2
65	7.3

tion (a situation that should be reflected in a lower barrier for the equilibrium 31a ⇌ 31b).

At the other end of the six-membered ring, namely around C(4), the ring is relatively puckered in 51a (see Table VI), thus creating another strain factor that probably contributes to the easy attainment of the initial transition state in the ring reversal process. To summarize, lower C-S torsional energy, extensive flattening around sulfur and relative puckering around C(4) are all consistent with a lower ring reversal barrier for our system 31a ⇌ 31b compared to that for the system 30a ⇌ 30b. Assuming the separation, $\Delta\nu$, between the H(10) proton signals in 31a and 31b (at temperatures well below the coalescence temperature) to be between 5 to 15 Hz (which seems reasonable from the results of the system 30a ⇌ 30b)[78] and using Eq. (10),[86] the free energy of activation for 31a ⇌ 31b can be calculated. Results of the calculation for three different coalescence temperatures are shown in Table IX. The signal due to H(10) protons did begin to broaden at -110°C but did not split into separate signals. It can be tentatively concluded that T_c is probably not much below -110°C. Inspection of Table IX clearly shows that small changes in

$$\Delta G^* = 0.004573 \ T_c [9.97 + \log(T_c/\Delta\nu)] \qquad \text{Eq. (10)}$$

T_c cause large deviations in the calculated value of ΔG^*. The same conclusion is supported by error analysis (see error analysi below). Consequently, it can be reasonably

TABLE IX

CALCULATED ΔG^* VALUES FOR $\underset{\sim}{31a} \rightleftharpoons \underset{\sim}{31b}$ FROM

VARIATIONS OF $\Delta \nu$ AND T_c

$\Delta \nu$ (Hz)	T_c (°C)	ΔG^* (kcal/mole)
5	-110	8.6
10	-110	8.3
15	-110	8.2
5	-120	8.0
10	-120	7.7
15	-120	7.7
5	-130	7.5
10	-130	7.3
15	-130	7.2

concluded that the ΔG^* value for the equilibrium $\underset{\sim}{31a} \rightleftharpoons \underset{\sim}{31b}$ lies somewhere between 7-8.5 kcal/mole.

Single Crystal Analysis by X-ray Diffraction

Results of a single crystal analysis by X-ray diffraction of $\underset{\sim}{51a}$ are shown in Figure 1 (numbering scheme and bond distance) and Figure 2 (bond angles). The torsional angles are given in Table VI. As can be seen from the torsional angles, the six-membered ring exists in the chair conformation. Also evident from the torsional angles is the fact that the six-membered ring is significantly flattened around sulfur and relatively puckered (but still flatter than cyclohexane) around C(4).[9] The dihedral angles C(2)-C(3)---C(4)-O(7) = 68.1° and C(6)-C(3)---C(4)-O(7) = -68.1° confirm that the C(4)-O(7) bond is axial. As a corrolary, the dihedral angles C(2)-C(3)---C(4)-C(10) = 182.1° and C(6)-C(3)---C(4)-C(10) = 177.6° confirm that the C(4)-C(10) bond is equatorial. The 1,3,5-interaction between the two axial C-CH$_3$ bonds and the C-O bond could probably be the cause for the overall flattening of the six-membered ring. The large 1,3-interaction between the two axial C-CH$_3$ bonds is reflected in the increased torsional angles C(13)-C(6)---C(5)-C(4) = 74.0° and C(11)-C(2)---C(3)-C(4) = -72.8° as illustrated on page 53. The lactone ring is in a flattened twist conformation with the appropriate two-fold symmetry axis passing through atom C(8) and bisecting the C(10)-C(4) bond.
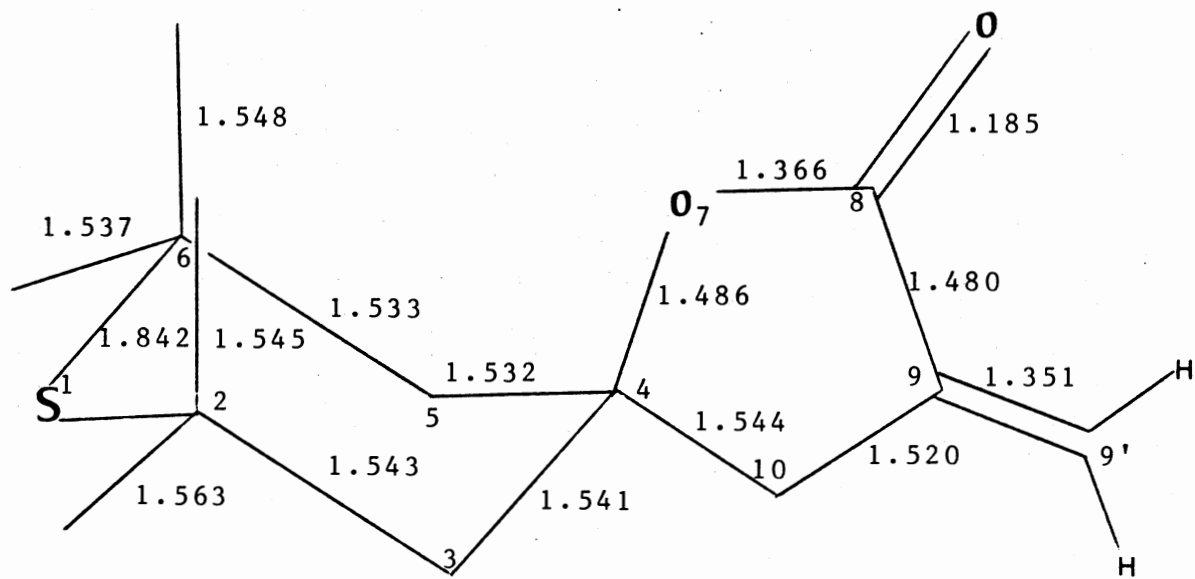
Figure 2.   Bond angles for 51a (in °).
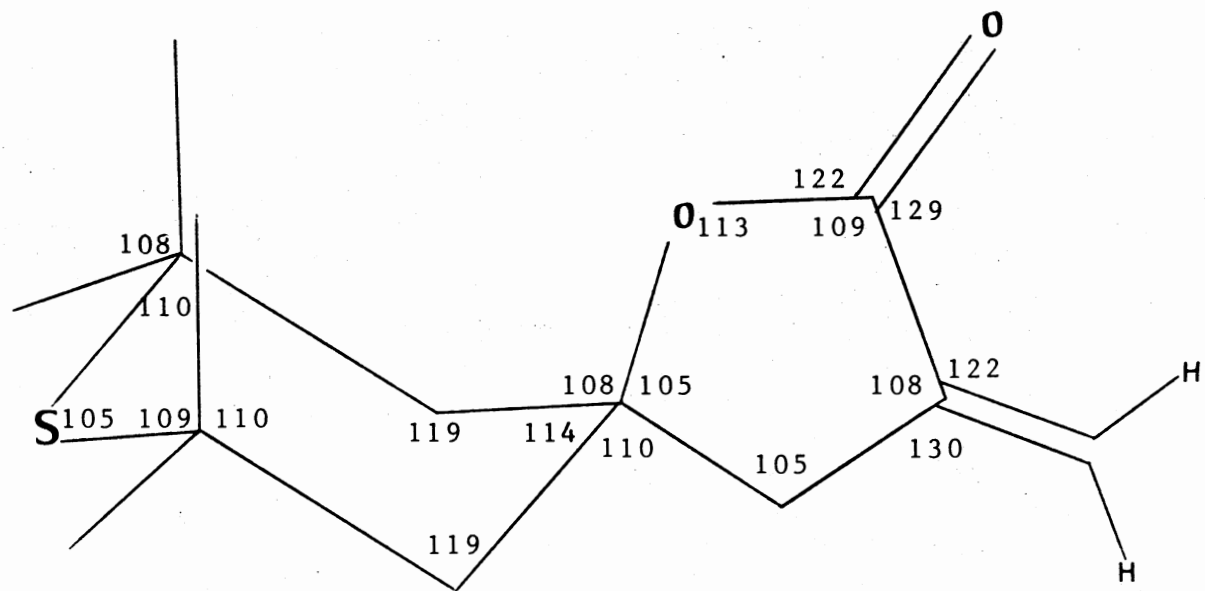
Figure 1.   Numbering scheme and bond distance (in Å) for 51a.

74.0°   -72.8°

CH₃   CH₃

CH₃   S   CH₃
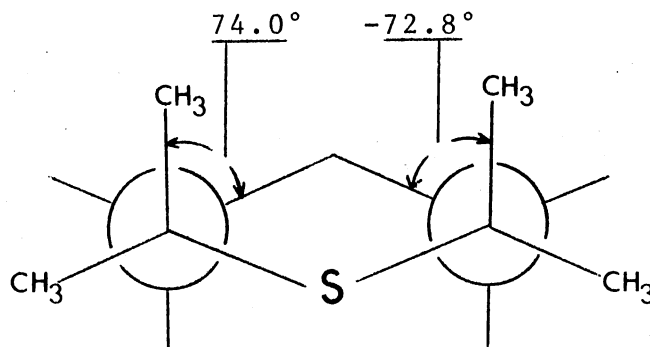
Suggestions for Future Work

As reported above, the coalescence temperature T_c for the system 31a ⇌ 31b is very probably not much below -110°C. Hence it will be interesting to extend the DNMR study to temperatures below -110°C with selected Freons as the solvents.

It has been observed that for the 1-heteracyclohexanes 62-65, the ring reversal barriers and the coalescence temperatures decrease with an increase in the atomic weight (and size) of the heteroatom.[67] It is not unreasonable to expect a similar trend for the spirolactones 31 and 66-68. It would be interesting to study these compounds and test the prediction.
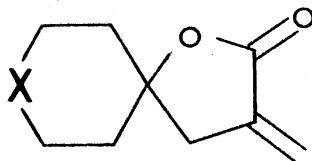
66   X = O; 31   X = S

67   X = Se; 68   X = Te

Error Analysis

The rate coefficient at the coalescence temperature, and hence the free energy of activation at that temperature, are calculated using Eq. (8), and the Eyring's equation Eq. (6). The symbols have the usual meanings cited previously.

$$k_c = \pi \, \Delta\nu/\sqrt{2} \qquad \text{Eq. (8)}$$

$$k_c = \kappa k_B T_c/h \, \{\exp(-\Delta G^*/RT)\} \qquad \text{Eq. (6)}$$

Eq. (6) yields the following formula for the error in ΔG^*, where σ_{T_c} and σ_{k_c} are the errors associated with T_c and k_c respectively.

$$(\sigma_{\Delta G}^*)^2 \simeq \{\partial(\Delta G^*)/\partial T_c\}^2 \, (\sigma_{T_c})^2 +$$
$$\{\partial(\Delta G^*)/\partial k_c\}^2 \, (\sigma_{k_c})^2 \qquad \text{Eq. (12)}$$

Dividing both sides of Eq. (12) by $(\Delta G^*)^2$, yields the expression, Eq. (13) for the relative statistical error in ΔG^*.

$$(\sigma_{\Delta G}^*/\Delta G^*)^2 = \{\partial(\Delta G^*)/\partial T_c\}^2 \, (\sigma_{T_c}/\Delta G^*)^2 +$$
$$\{\partial(\Delta G^*)/\partial k_c\}^2 \, (\sigma_{k_c}/\Delta G^*)^2 \qquad \text{Eq. (13)}$$

Multiplying both sides of equation (6) by $h/k_B T_c$, we get equation (14) after assuming that $\kappa = 1$.

$$k_c h/k_B T_c = \exp(-\Delta G^*/RT_c) \qquad \text{Eq. (14)}$$

Taking logarithm of equation (14) results in equation (15).

$$\ln (k_c h / k_B T_c) = -(\Delta G^*/RT_c) \qquad \text{Eq. (15)}$$

or

$$\Delta G^* = RT_c \ln (k_B T_c / k_c h) \qquad \text{Eq. (16)}$$

Equations (17) and (18) are the partial derivatives of ΔG^* with respect to T_c and k_c respectively.

$$\partial (\Delta G^*/\partial T_c) = R \ln (k_B T_c / k_c h) + R \qquad \text{Eq. (17)}$$

$$\partial (\Delta G^*/\partial k_c) = -RT_c / k_c \qquad \text{Eq. (18)}$$

Substitution of equations (17) and (18) in equation (13) results in equation (19).

$$(\sigma_{\Delta G}*/\Delta G^*)^2 = \{R \ln (k_B T_c / k_c h) + R\}^2 (\sigma_{T_c}/\Delta G^*)^2$$

$$+ (-RT_c / k_c)^2 (\sigma_{k_c}/\Delta G^*)^2 \qquad \text{Eq. (19)}$$

Substituting for ΔG^* from equation (16) and simplifying, we get equation (20).

$$(\sigma_{\Delta G}*/\Delta G^*)^2 = [1 + \{\ln (k_B T_c / k_c h)\}^{-1}]^2 (\sigma_{T_c}/T_c)^2$$

$$+ \{\ln (k_B T_c / k_c h)\}^{-2} (\sigma_{k_c}/k_c)^2 \qquad \text{Eq. (20)}$$

The above equation may be approximated to Eq. (21):

$$(\sigma_{\Delta G}*/\Delta G^*)^2 = (\sigma_{T_c}/T_c)^2 + \{\ln (k_B T_c / k_c h)\}^{-2} (\sigma_{k_c}/k_c)^2$$

For a case with $T_c \simeq 160$ K, a reasonable value for our system, and $k_c \simeq 30$ sec^{-1} (reasoned from observations made on the system $\underline{30a} \rightleftharpoons \underline{30b}$ by O'Donnell and co-workers), a relative error of 100% in the rate coefficient introduces a relative error of only 4% in ΔG^*. A temperature error of about 10 K introduces a relative error of 7% in ΔG^*. This amounts to a total relative error of 8% or for a typical value of $\Delta G^* = 8$ kcal/mole, the limits of error would be $\pm$ 0.69 kcal/mole.

CHAPTER III

EXPERIMENTAL

General Information

Melting points were obtained on a Thomas-Hoover melt-ing point apparatus and are uncorrected. The ^{1}H NMR spectra and broad-band proton decoupled ^{13}C NMR spectra were obtained on a Varian XL-100(15) NMR spectrometer equip-ped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for ^{1}H observation and at 25.2 MHz for ^{13}C signals with tetramethylsilane (TMS) as the internal standard. All low temperature spectra were recorded in acetone-$\underline{d}_6$ in the FT mode with the solvent providing the necessary deuterium lock. Temperature regulation was made possible with a Varian temperature regulator. A sealed capillary filled with CH_3OH and a trace of HCl placed in a 5 mm NMR tube containing 0.5 mL acetone-$\underline{d}_6$ was used as a check to measure the temperature according to the method of Van Geet.[97] IR spectra were recorded on a Beckmann IR-5A unit. Mass spectral data were collected on a CEC model 21-110B HR mass spectrometer. Elemental analysis were performed by Galbraith Laboratories, Knoxville, Tennessee. Solvents used were reagent grade. Tetrahydrofuran (THF) was dried

via an initial distillation over NaH and then over LiAlH$_4$.
All other solvents were distilled and then dried over Na
where required.

<div align="center">

Preparation of Diethyl Bis(hydroxy-
methyl)malonate (52)[25]

</div>

Into a 2-liter, Erlenmeyer flask fitted with a magnet-
ic stirrer, thermometer and dropping funnel were placed
200.0 g (1.25 mole) of diethylmalonate and 360.0 g (4.44
mole) of 37% formalin solution. A few drops of BDH Univer-
sal Indicator was added. This was followed by the addition
of 10% NaOH (15-20 mL) slowly and dropwise. Reaction began
at a pH of about 7.5 (room temperature) and became rapid at
pH 8.5 as indicated by a rapid rise (nearly a 30° rise to
55°C) in temperature. The addition of NaOH was continued
over a period of 48 hr. During this period, the temperature
was maintained below 50°C and the pH below 8.5. The react-
ion mixture was diluted with twice the volume of water (ca
1000 mL) and was then saturated with NaCl. The ester was
extracted with 3 x 150-mL portions of ether. The ether
extracts were combined and dried (Na$_2$SO$_4$) for 3 hr.
Removal of the ether was effected in a rotary evaporator.
Residual traces of ether were removed by keeping the crude
ester at 50°C under vacuum (2 mm) for 2 hr to yield 243.0 g
(88%) of the diester 52.[25] This crude ester was used as
such. No attempt was made to solidify the ester. It has
been reported[25] that the crude ester solidifies after some

months, mp 55-56°C.

Preparation of α-Bromomethyl-
acrylic acid (53)[88]

A 1000 mL, two-necked, round-bottom flask was equipped
with a magnetic stirrer, a fraction collector, a cold-
finger condenser and two thermometers. Into the flask were
placed 55.0 g (0.25 mole) of diethyl bis(hydroxymethyl)-
malonate (52) and 142 mL (1.25 mole) of 47-49% HBr. The
mixture was then heated and the temperature of the liquid
was maintained between 85-90°C. A mixture of ethyl bromide
and water distilled over for about 1.5 to 2 hr. The mixture
was then boiled for 10 hr, maintaining the temperature bet-
ween 85-90°C. At the end of this period, the mixture was
concentrated on a rotary evaporator at 65-70°C. About 100
mL of water were removed. The residue was cooled in the
refrigerator overnight. Crystals of α-bromomethylacrylic
acid were filtered in the cold to give, after drying in the
air for 3 days, 13.0 g (33%) of acid. Recrystallization
was effected from Skelly B (bp 60-80°C); an analytical
sample of 53 required sublimation at 60°C (1.5 mm).

Anal. Calcd. for $C_4H_5BrO_2$: C, 29.12; H, 3.05.

Found: C, 29.07; H, 3.10.

^{1}H NMR (in $DCCl_3$): Chemical shift in ppm from TMS
internal standard (multiplicity, number of protons, iden-
tity of proton): 4.18 (s, 2 H, C$\underline{H}_2$); 6.09 (s, 1 H, vinylic
proton trans to CO_2H); 6.49 (s, 1 H, vinylic proton cis to

CO_2H).

IR (KBr): Absorption frequency in cm^{-1} (functional group): 1689 (C=O); 1626 ($C=CH_2$).

Preparation of Ethyl α-Bromo-methylacrylate (42)[88]

In a nitrogen flushed, 1000 mL, round-bottom flask equipped with a magnetic stirrer, a Dean-Stark trap, and a condenser were placed 42.0 g (0.25 mole) of α-bromomethyl-acrylic acid and 300 mL of benzene. Approximately 50 mL of a binary azeotrope of benzene and water were distilled out. The Dean-Stark trap was removed and 100 mL of absolute alcohol and 1 mL of concentrated H_2SO_4 were added slowly. The contents of the flask were boiled (N_2) for 36 hr, the condensate being passed through 100 g of molecular sieve (Linde 3A) before being returned to the flask. About 125 mL of a mixture of benzene and ethanol were removed from the reaction mixture by distillation (at 67°C). Then, 100 mL of benzene was added, and another 125 mL of a benzene-ethanol mixture was distilled (between 67-75°C). The residue was poured into 200 mL of water, which was neutralized with solid $NaHCO_3$ (ca 10-15 g) until CO_2 evolution ceased. The relulting solution was extracted with 3 x 75-mL portions of ether, and the combined extracts were dried (Na_2SO_4) for 3 hr. The ether was removed by rotary evaporation and the crude ester was distilled to give a fraction boiling at 43-45°C (1.7 mm) which weighed 36.0 g (75%).

^{1}H NMR (in DCCl$_3$): Chemical shift in ppm from TMS internal standard (multiplicity, number of protons, identity of proton): 1.26-1.40 (m, 3 H, C$\underline{H}_3$); 4.16-4.38 (m, 2 H, C$\underline{H}_2$-CH$_3$); 4.19 (s, 2 H, C$\underline{H}_2$Br); 5.96 (s, 1 H, vinylic proton trans to CO$_2$C$_2$H$_5$); 6.32 (s, 1 H, vinylic proton cis to CO$_2$C$_2$H$_5$).

IR (KBr): Absorption frequency in cm^{-1} (functional group): 1695 (C=O); 1610 (C=CH$_2$).

<div align="center">

Preparation of 2,2,6,6-Tetramethyl-

4-thianone (69)[75]

</div>

Exactly 100 g (0.725 mole) of phorone and 2 g (0.0357 mole) of KOH dissolved in 200 mL of 95% ethanol were placed in a 500 mL, three-necked round-bottom flask, equipped with a condenser, magnetic stirrer and gas inlet. The solution was heated to a boil, and a steady stream of H$_2$S was passed through this hot solution for 7 hr. It was then diluted with 200 mL of water and extracted with 3 x 200-mL portions of ether. The combined ether extracts were dried (Na$_2$SO$_4$) and filtered. Removal of ether was effected in a rotary evaporator. The crude product was distilled under aspirator pressure and the liquid that boiled between 123-133°C (27 mm) was collected; the yield of ketone 69 was 99.4 g (79.7%). Further purification was effected in the following way.

Semicarbazide hydrochloride (97 g, 0.87 mole) and sodium acetate trihydrate (120 g, 0.87 mole) dissolved in

400 mL of 50% alcohol were placed in a 1000 mL beaker. To the solution was added, slowly, with stirring at room temperature, ketone 69 (99.4 g, 0.58 mole). The semicarbazone formed was set aside for 4 hr and was then filtered and dried. The dry semicarbazone and 1000 mL of concentrated HCl were placed in a 2000 mL, round-bottom flask equipped with a condenser and magnetic stirrer. The reaction mixture was gently boiled for 4 hr and was then allowed to cool to room temperature. To the cold mixture was added 500 mL of water. The reaction mixture was then extracted with 3 x 250-mL portions of ether. The combined ether extracts were first washed with 3 x 100-mL portions of 10% aqueous $NaHCO_3$ and then with water. Drying (Na_2SO_4), filtration, ether removal by rotary evaporation and distillation of the residue afforded 64.5 g (0.375 mole, 52%) of ketone 69, bp 73°C (2 mm) [lit.[75] bp 92°C (13 mm)] .

^1H NMR (in $DCCl_3$): Chemical shift in ppm from TMS internal standard (multiplicity, number of protons, identity of proton): 1.4 (s, 12 H, $C\underline{H}_3$); 2.56 (s, 4 H, $C\underline{H}_2$).

IR (neat): Absorption frequency in cm^{-1} (functional group): 1695 (C=O).

<div align="center">

Preparation of 4-Thianone-

3,3,5,5-$\underline{d}_4$ (70)

</div>

4-Thianone (1.16 g, 0.01 mole, mp 59-61°C, Aldrich Chemical Company, Inc.) (71) and anhydrous Na_2CO_3 (1.5 g, 0.0142 mole) dissolved in 50 g (2.5 mole) of D_2O were placed

in a 200 mL, two-necked, round-bottom flask equipped with a condenser, magnetic stirrer, N_2 inlet and an anhydrous $CaCl_2$ tube. The reaction mixture was boiled gently for 24 hr. After cooling to room temperature, the reaction mixture was extracted with 3 x 50-mL portions of ether. Drying (Na_2SO_4) of the combined ether extracts and removal of ether by rotary evaporation afforded 0.7 g (0.0058 mole, 58%) of ketone 70. The colorless solid was recrystallized from pet-roleum ether to give pure 70, mp 60-61°C.

^{1}H NMR (in $DCCl_3$): Chemical shift in ppm from TMS internal standard (multiplicity, number of protons, iden-tity of proton): 2.89 (s, 4 H, $C\underline{H}_2$).

IR (KBr): Absorption frequency in cm^{-1} (functional group): 1681 (C=O).

<div align="center">

Preparation of Dibenzal-

acetone (72)[12]

</div>

Dibenzalacetone (72) was synthesized from 106 g (1 mole) of benzaldehyde, bp 178-179°C (760 mm), following the literature procedure.[12] This gave 90 g (0.77 mole, 77%) of pure 72, mp 111-112°C [lit.[12] mp 111-112°C].

<div align="center">

Preparation of cis-2,6-Diphenyl-

4-thianone (73)[5]

</div>

Ketone 73 was synthesized from 50 g (0.214 mole) of di-benzal acetone according to literature procedure[5] to give 20 g (0.0746 mole, 34.9%) of 73, mp 112°C [lit.[5] mp 112°C].

General Procedure for the Synthesis of the
9-Methylene-7-oxa-1-thiaspiro[4.5]decan-
8-ones 31, 32, 50 and 51

The spirolactones were synthesized by using a Refor-
matsky reagent. The appropriate thianone was allowed to
react with the Reformatsky reagent prepared from activated
Zn (20 mesh, Baker Analyzed) and ethyl α-bromomethylacry-
late in dry THF solvent. Since the usual method of carry-
ing out this reaction[77,84] (namely, addition of ethyl α-
bromomethylacrylate in dry THF to a mixture of Zn and
hianone in dry THF) resulted in the formation of sulfonium
salts, the following modified procedure was adopted.[87]
Separate solutions of ethyl α-bromomethylacrylate (42) and
the appropriate thianone were first prepared by dissolving
0.01 mole of each reagent in 10 mL of dry THF. Activated
Zn (20 mesh, 0.72 g, 0.011 g at) was placed in a 50 mL dry
three-necked, round-bottom flask equipped with a magnetic
stirrer, condenser, two pressure-equalizing addition
funnels (25 mL) and a N_2 inlet. Ten mL each of the solut-
ion of ester 42 and thianone (in dry THF) were then placed
separately in the two pressure-equalizing addition funnels.
Twenty five drops of a solution of ester 42 were first
added to the activated Zn, keeping the temperature at 45-
50°C. After 3 min, during which time the Reformatsky rea-
gent formed, twenty five drops of the solution of thianone
were added. This was followed by the addition, after 3
min, of twenty five drops of the solution of ester. After

these alternate additions were completed (ca 2 hr, the temperature being maintained at 45-50°C during the entire period), the reaction mixture was stirred for an additional period of 3 hr at 45-50°C. The reaction mixture was then allowed to cool to room temperature and was then added to 100 mL of ice-cold 5% H_2SO_4. This usually yielded an oily product. Extraction with 3 x 50-mL portions of ether, drying the combined ether extracts (Na_2SO_4), and removal of ether by rotary evaporation resulted in the formation of crystalline products which were recrystallized from suitable solvents.[87] The relevant data are found in Table I.

Synthesis of 9-Methylene-7-oxa-1-thiaspiro-
[4.5]decan-8-one (31a or 31b)[87]

4-Thianone (1.16 g, 0.01 mole, Aldrich Chemical Company Inc.) (70) in dry THF (10 mL) was allowed to react with Zn (0.72 g, 0.011 g at) and ethyl α-bromomethylacrylate (1.93 g, 0.01 mole) (49) in dry THF (10 mL) as described above at 45-50°C. The reaction mixture was cooled to room temperature and poured into 100 mL of ice-cold 5% H_2SO_4. The oily product that resulted was extracted with 3 x 50-mL portions of ether. The combined ether extracts were dried (Na_2SO_4), and the ether was removed by rotary evaporation. To the thick viscous oily residue was added 2 mL of absolute methanol and the solution was cooled to -78°C (dry ice-acetone mixture). A solid formed was quickly filtered and recrystallized from absolute methanol to afford 0.26 g

(0.0014 mole, 14.2%) of spirolactone $\underset{\sim}{31a}$ (or $\underset{\sim}{31b}$), mp 94–95°C.

Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.65; H, 6.58; S, 17.41.

Found: C, 58.59; H, 6.63; S, 17.45.

Mass spectral data for $\underset{\sim}{31a}$ (or $\underset{\sim}{31b}$) are as follows:

m/e (% of 184 mass): 184 (100) M^+; 185 (10.8); 186 (5.3).

^1H NMR (in $DCCl_3$): Chemical shift in ppm from TMS internal standard (multiplicity, number of protons, identity of proton): 2.70 (m, 2 H, $C\underline{H}_2$ in lactone ring); 5.66 (m, 1 H, exocyclic $=C\underline{H}_2$); 6.27 (m, 1 H, exocyclic $=C\underline{H}_2$); 1.76–3.18 (m, 8 H, thiane ring $C\underline{H}_2$).

IR (KBr): Absorption frequency in cm^{-1} (functional group): 1748 (C=O); 1653 ($C=CH_2$).

Synthesis of 9-Methylene-7-oxa-1-thiaspiro-[4.5]decan-8-one-3,3,5,5-$\underline{d}_4$ ($\underset{\sim}{50a}$ or $\underset{\sim}{50b}$)[87]

The reaction of 4-thianone-3,3,5,5-$\underline{d}_4$ (1.20 g, 0.01 mole) ($\underset{\sim}{70}$) with Zn (0.72 g, 0.011 g at) and ethyl α-bromomethylacrylate (1.93 g, 0.01 mole) in a manner described for the undeuterated thianone ($\underset{\sim}{71}$), yielded, after recrystallization (absolute methanol), 0.286 g (0.00152 mole, 15.2%) of spirolactone $\underset{\sim}{50a}$ (or $\underset{\sim}{50b}$), mp 94–96°C.

Mass spectral data for $\underset{\sim}{50a}$ (or $\underset{\sim}{50b}$) are as follows:

m/e (% of 188 mass): 188 (100) M^+; 189 (12.5); 190 (6.9).

^1H NMR (in $DCCl_3$): Chemical shift in ppm from TMS internal standard (multiplicity, number of protons, identity of proton): 2.70 (m, 2 H, $C\underline{H}_2$ in lactone ring); 5.66

(m, 1 H, exocyclic =C$\underline{H}_2$); 6.27 (m, 1 H, exocyclic =C$\underline{H}_2$); 2.42-3.07 (m, 4 H, thiane ring C$\underline{H}_2$).

IR (KBr): Absorption frequency in cm^{-1} (functional group): 1748 (C=O); 1653 (C=CH$_2$).

Synthesis of 2,2,6,6-Tetramethyl-9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-one (51a)[87]

2,2,6,6-Tetramethyl-4-thianone (1.72 g, 0.01 mole) (69) dissolved in 100 mL of dry THF was allowed to react with the Reformatsky reagent prepared from Zn (0.72 g, 0.011 g at) and ethyl α-bromomethylacrylate (1.93 g, 0.01 mole) taken in 10 mL of dry THF in a manner analogous to the preparation of lactones 31 and 50. Recrystallization from 1:1 methanol:petroleum ether (bp 60-80°C) afforded 0.817 g (0.0034 mole, 34%) of lactone 51a, mp 109-111°C.

Anal. Calcd. for C$_{13}$H$_{20}$O$_2$S: C, 64.95; H, 8.39; S, 13.34.

Found: C, 64.88; H, 8.41; S, 13.27.

^{1}H NMR (in DCCl$_3$): Chemical shift in ppm from TMS internal standard (multiplicity, number of protons, identity of proton): 2.72 (m, 2 H, C$\underline{H}_2$ in lactone ring); 5.64 (m, 1 H, exocyclic =C$\underline{H}_2$); 6.26 (m, 1 H, exocyclic =C$\underline{H}_2$); 1.27 (s, 6 H, C$\underline{H}_3$); 1.59-2.09 (m, 4 H, thiane ring C$\underline{H}_2$).

IR (KBr): Absorption frequency in cm^{-1} (functional group): 1754 (C=O); 1656 (C=CH$_2$).

Mass spectral data for 51a are as follows: m/e (% of 240 mass): 240 (100) M$^+$; 241 (18.4); 242 (6.6).

Synthesis of 2,6-Diphenyl-9-methylene-7-oxa-
1-thiaspiro[4.5]decan-8-one (32a or 32b)[87]

2,6-Diphenyl-4-thianone (73) (2.68 g, 0.01 mole) dis-
solved in 10 mL of dry THF was allowed to react with the
Reformatsky reagent prepared from Zn (0.72 g, 0.011 g at)
and ethyl α-bromomethylacrylate (42) taken in 10 mL of dry
THF in a manner analogous to the preparation of the pre-
vious lactones. The crude product obtained was recrystal-
lized twice with 1:1 methanol:petroleum ether mixture (20
mL) containing a little (0.5 mL) benzene to yield 0.336 g
(0.001 mole, 10%) of lactone 32a (or 32b), mp 148.5-149.5°C.

Anal. Calcd. for $C_{21}H_{20}O_2S$: C, 75.00; H, 5.95; S, 9.54.

Found: C, 75.08; H, 6.03; S, 9.72.

Mass spectral data for 32a (or 32b) are as follows:
m/e (% of 336 mass): 336 (100) M^+; 337 (10.8); 338 (5.3).

^1H NMR (in $DCCl_3$): Chemical shift in ppm from TMS
internal standard (multiplicity, number of protons, iden-
tity of proton): 2.84 (m, 2 H, $C\underline{H}_2$ in lactone ring); 5.68
(m, 1 H, exocyclic $=C\underline{H}_2$); 6.30 (m, 1 H, exocyclic $=C\underline{H}_2$);
2.04-2.41 (m, 4 H, thiane ring $C\underline{H}_2$); 4.54 (m, 2 H, $C\underline{H}$ in
the thiane ring); 7.20-7.50 (m, 10 H, Ar-$\underline{H}$).

IR (KBr): Absorption frequency in cm^{-1} (functional
group): 1754 (C=O); 1664 (C=CH_2).

Synthesis of 1-Methylthianium-9-methylene-7-
oxaspiro[4.5]decan-8-one Iodide (74)

Into a 25 mL, round-bottom flask equipped with a condenser,

magnetic stirrer and N_2 inlet, were placed spirolactone 32a
(or 32b) (0.310 g, 0.00169 mole) and methyl iodide (2.28 g,
0.0161 mole) dissolved in 3 mL of absolute methanol. The
mixture was stirred at room temperature for 24 hr. The
reaction mixture was then triturated with 5 mL of dry ether,
and the mixture was refrigerated overnight and then filter-
ed. The dry salt was dissolved in the minimum amount of
absolute ethanol. Dry ether was then added dropwise to
this solution until a cloudiness appeared. The mixture was
again refrigerated overnight and the solid formed was
filtered and dried over P_2O_5 in vacuum (56°C, 2 mm) to
yield 0.360 g (0.0011 mole, 65%) of salt 74, mp 135.5-137°C.

Anal. Calcd. for $C_{10}H_{15}IO_2S$: C, 36.82; H, 4.64; S, 9.81.

Found: C, 36.67; H, 4.49; S, 9.89.

IR (KBr): Absorption frequency in cm^{-1} (functional
group): 1754 (C=O); 1653 (C=CH_2).

^{1}H NMR (in $DCCl_3$): Chemical shift in ppm from TMS
internal standard (multiplicity, number of protons, iden-
tity of proton): 5.91 (m, 1 H, exocyclic =CH_2); 6.30 (m,
1 H, exocyclic =CH_2); 3.02 (s, 3 H, CH_3); 2.96 (m, 2 H, CH_2
in lactone ring); 2.12-2.70 (m, 4 H, CH_2 in the thiane
ring); 3.20-4.00 (m, 4 H, CH_2 in the thiane ring).

PLATE I
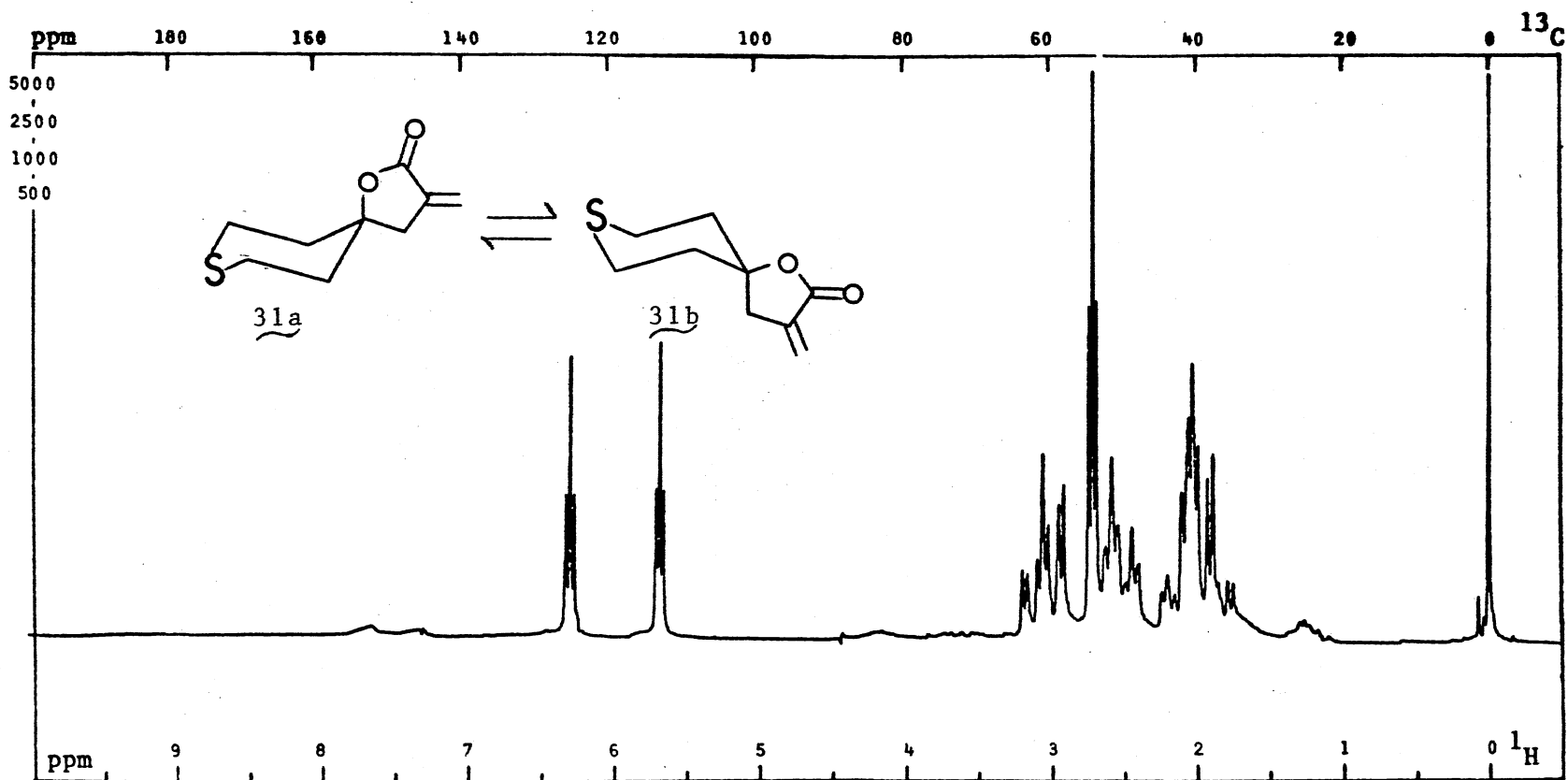
^{1}H NMR Spectrum of 31a ⇌ 31b

PFT.   X;   Solvent DCCl$_3$;   SO.   45251 Hz;   PW.   1000 Hz;   T.   30°C;   Acq. 100;

Size   8K; P2   5 μs;   SF. 100.1 MHz;   FB.   700 Hz;   Lock ^{2}H;   D5   2 s.
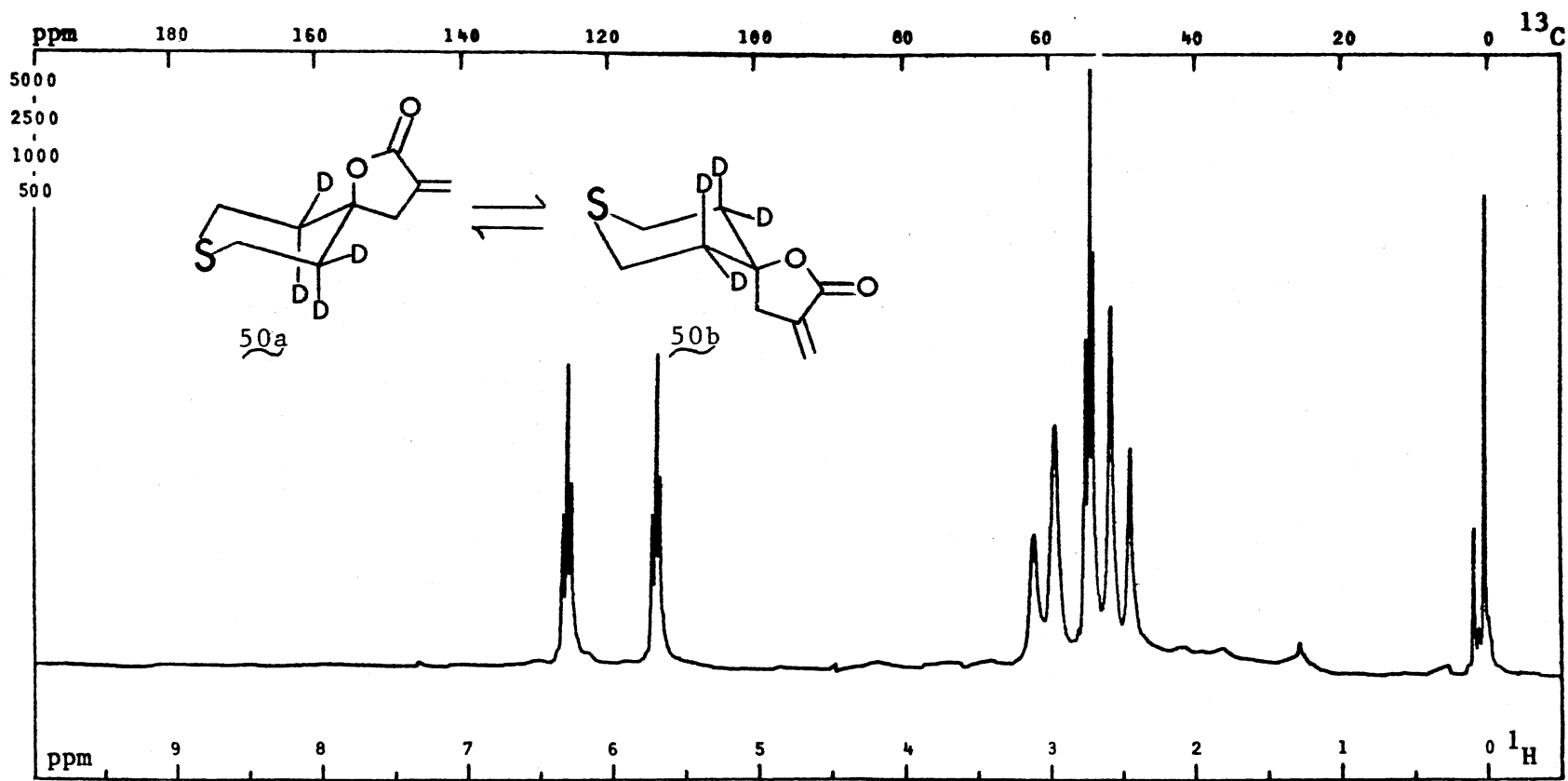
PLATE II

^{1}H NMR Spectrum of 9-Methylene-7-oxa-1-thiaspiro[4.5]decan-8-one-3,3,5,5-$\underline{d}_4$ (50a⇌50b)

PFT.   X;   Solvent   DCCl$_3$;   SO.   45251 Hz;   PW. 1000 Hz;   T.   30°C;   Acq.   100;

Size 8K;   P2   5 μs ;   SF.   100.1 MHz;   FB.   700 Hz;   Lock ^{2}H ;   D5   2 s.

PLATE III
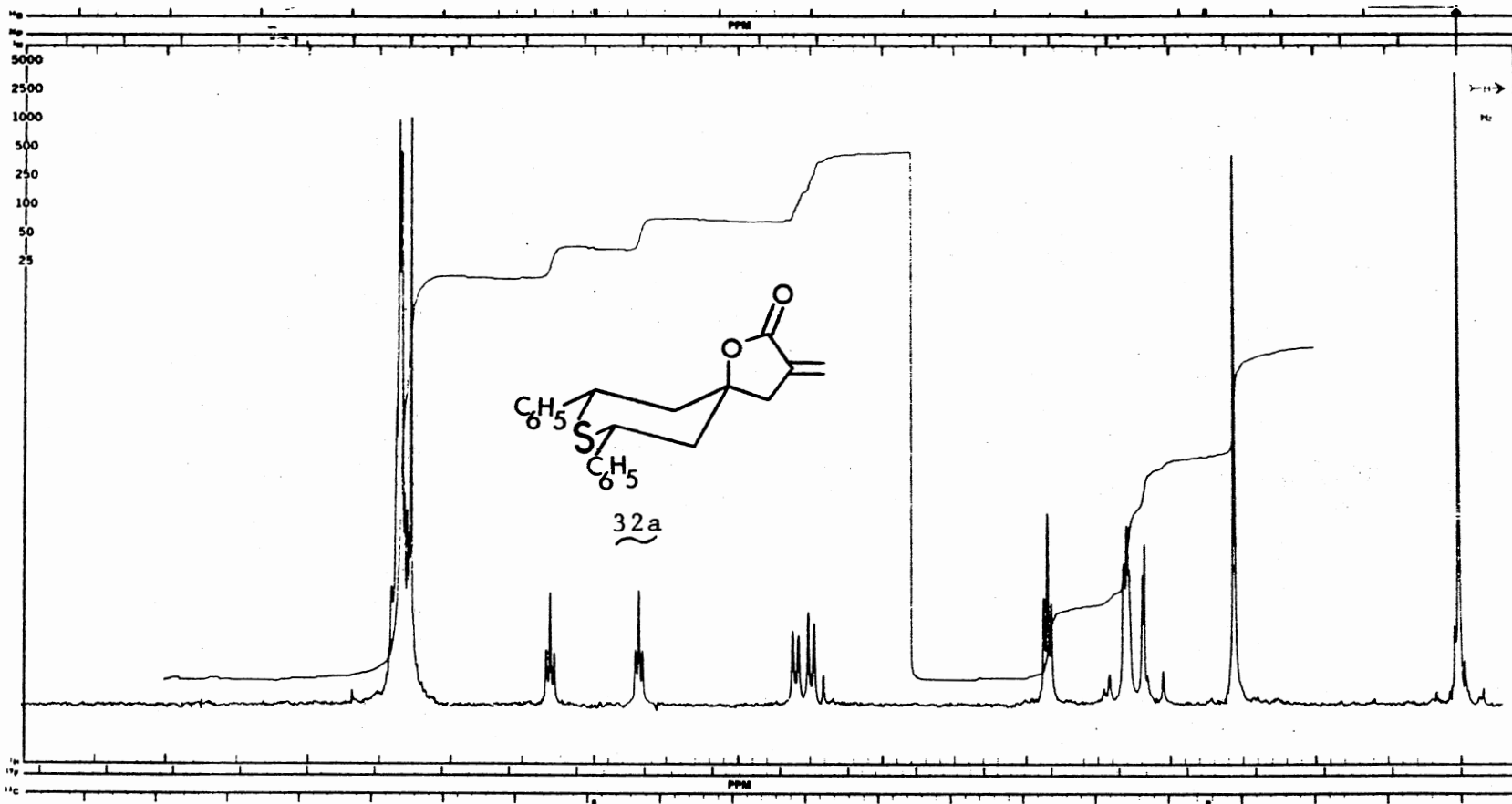
^{1}H NMR Spectrum of <u>cis</u>-2,6-Diphenyl-9-methylene-7-oxa-1-thiaspiro[4.5]decan-8-one

PFT.   X;   Solvent   DCCl$_3$;   SO.   45251 Hz;   PW. 1000 Hz;   T.   30°C;   Acq.   160;

Size. 8K   P2   5 μs;   SF.   100.1 MHz;   FB. 700 Hz;   Lock ^{2}H ;   D5   2 s.

PLATE IV
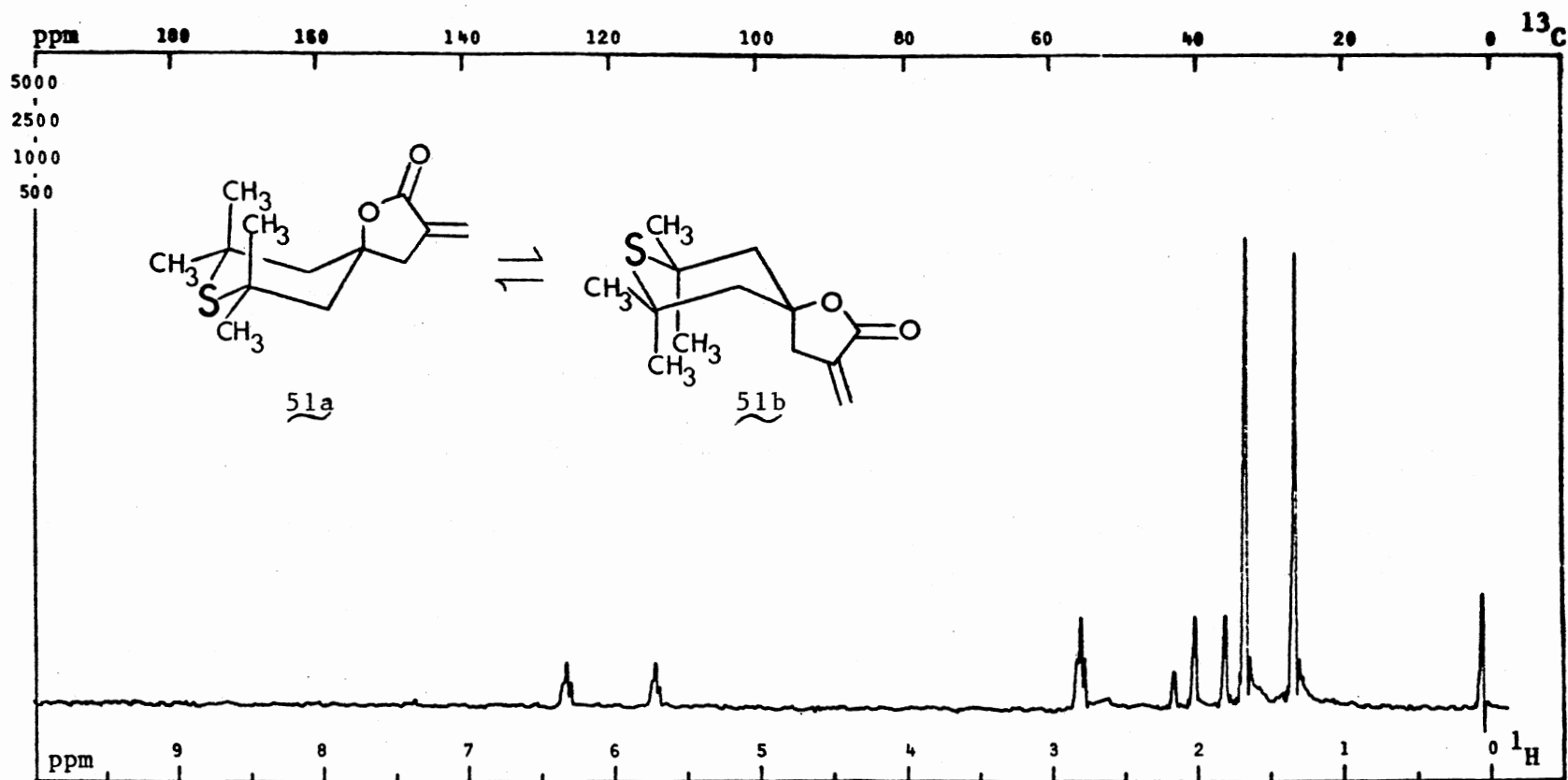
^{1}H NMR Spectrum of 51a ⇌ 51b

CW.   X;   Solvent   DCCl$_3$;   SO.   85771 Hz;   PW.   1000 Hz;   T.   30°C;   SA. 1.0;

RF. 51 dB;   SF.   100.1 MHz;   FB.   2 Hz;   Lock ^{2}H;   ST.   250 s.
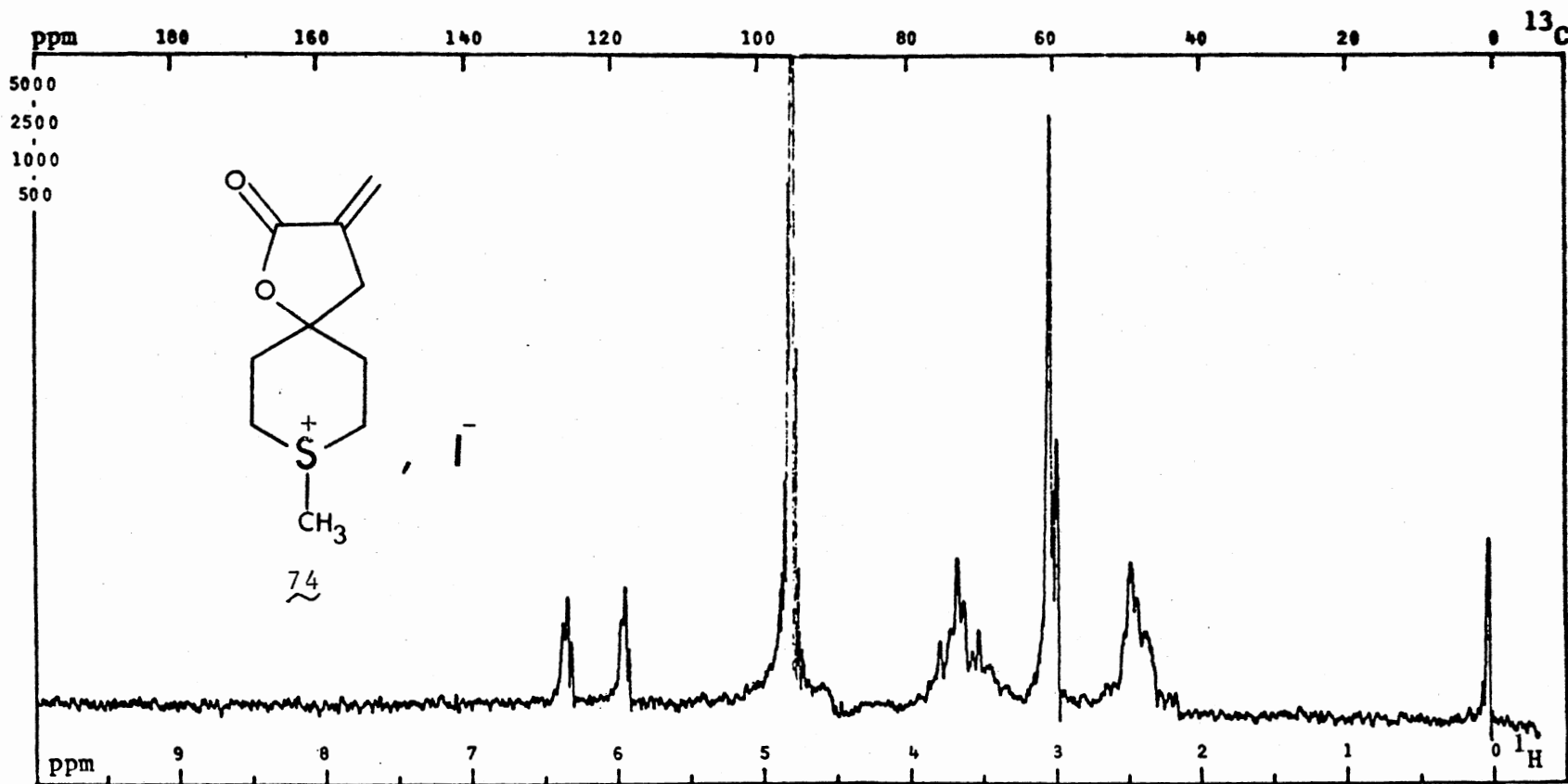
PLATE V

^{1}H NMR Spectrum of $\underset{\sim}{74}$

CW.   X;   Solvent D_2O;   SO.   86103 Hz;   PW.   1000 Hz;   T.   30°C;   SA. 1.0;

RF. 53 dB;   SF. 100.1 MHz;   FB.   2 Hz;   Lock ^{2}H;   ST.   250 s.

PLATE VI
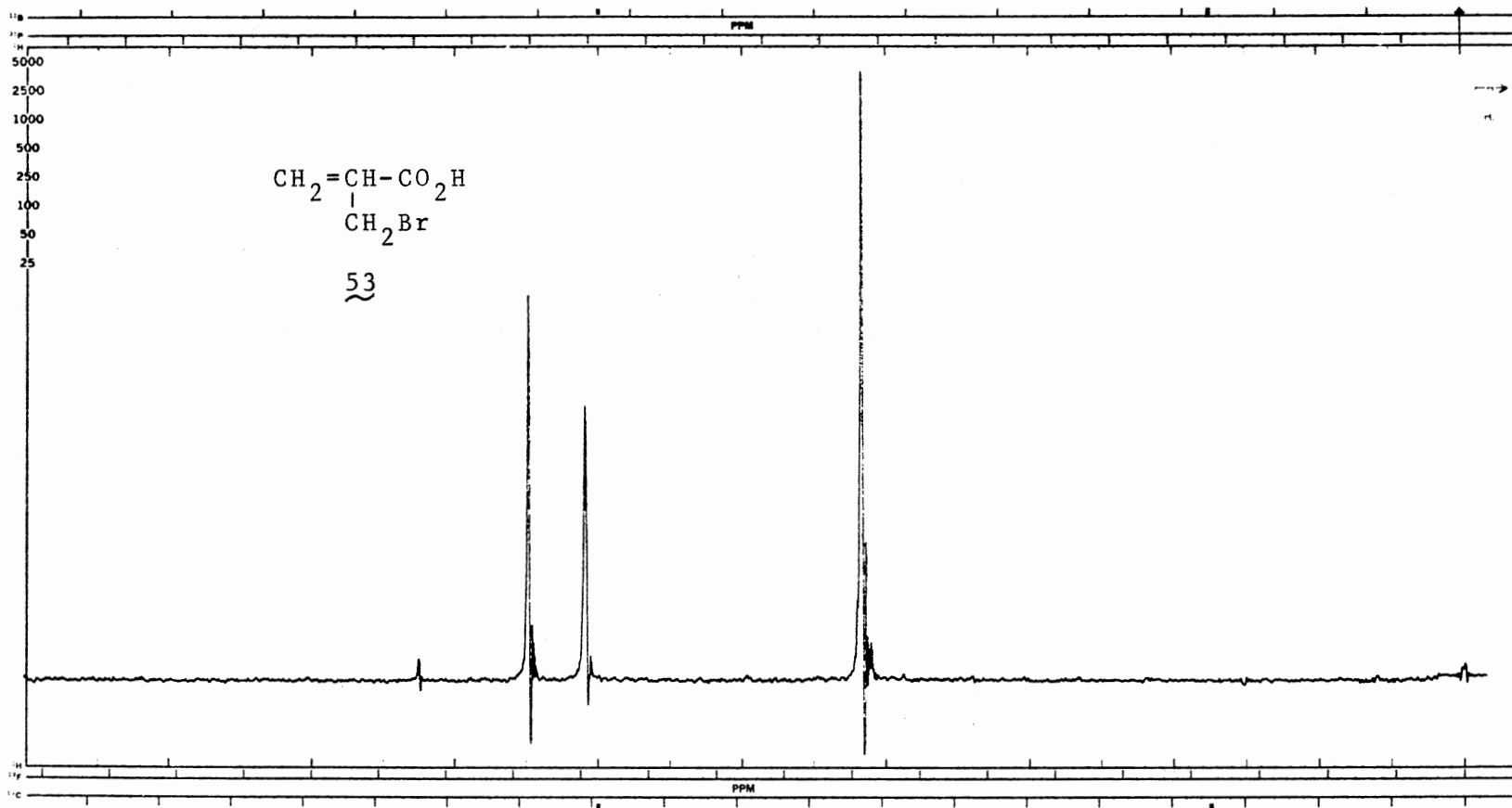
^{1}H NMR Spectrum of $\underline{53}$

CW.   X;   Solvent DCCl$_3$;   SO.   83701 Hz;   PW.   1000 Hz;   T.   30°C;   SA. 1.0;

RF.   57 dB;   SF.   100.1 MHz;   FB.   2 Hz;   Lock ^{1}H;   ST.   250 s.
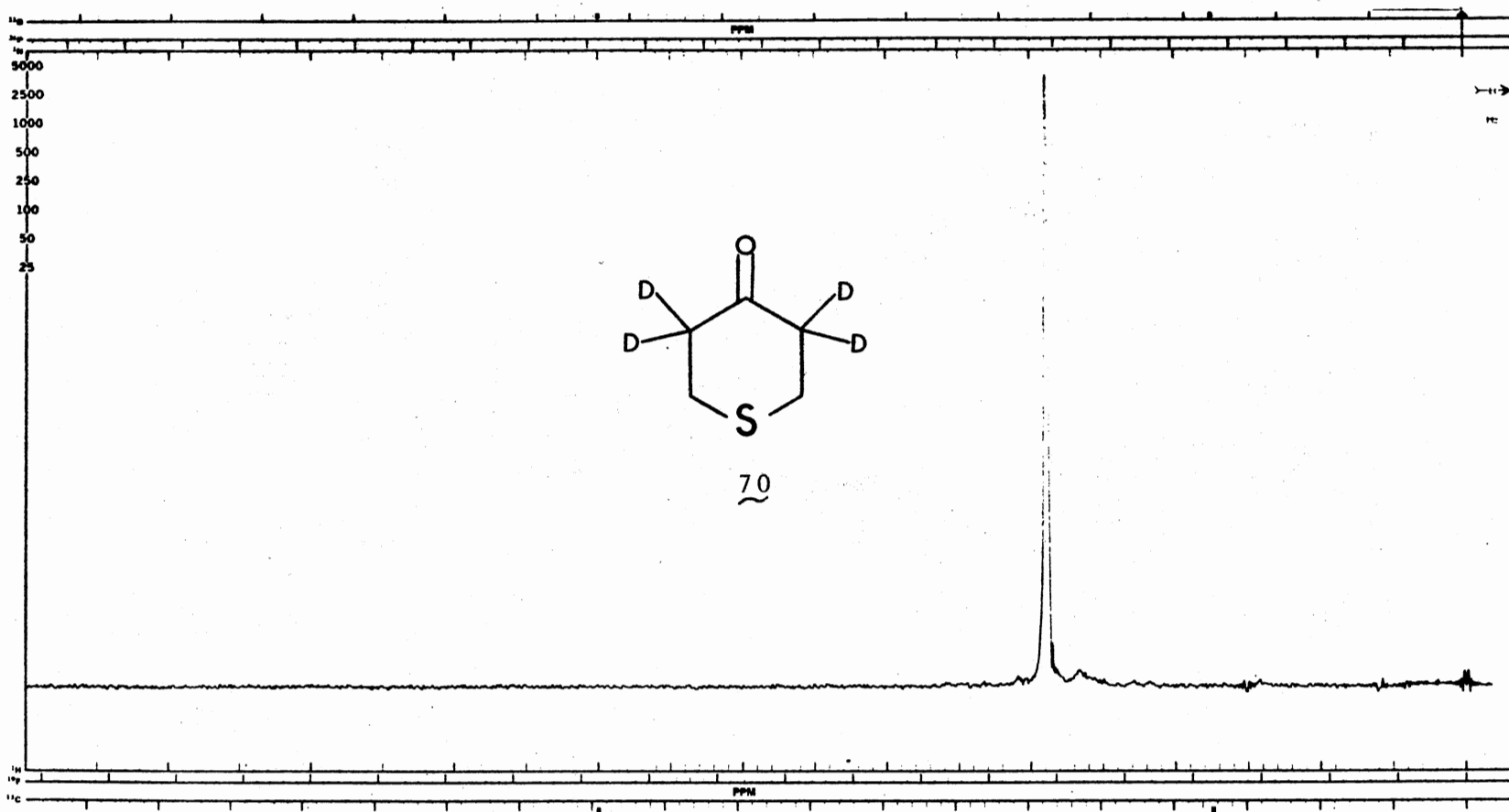
PLATE VII

^{1}H NMR Spectrum of 70

CW.   X;   Solvent   CCl$_4$;   SO.   83701 Hz;   PW.   1000 Hz;   T.   30°C;   SA. 1.0;

RF.   62 dB;   SF.   100.1 MHz;   FB..   2 Hz;   Lock ^{1}H;   ST.   250 s.

PLATE VIII
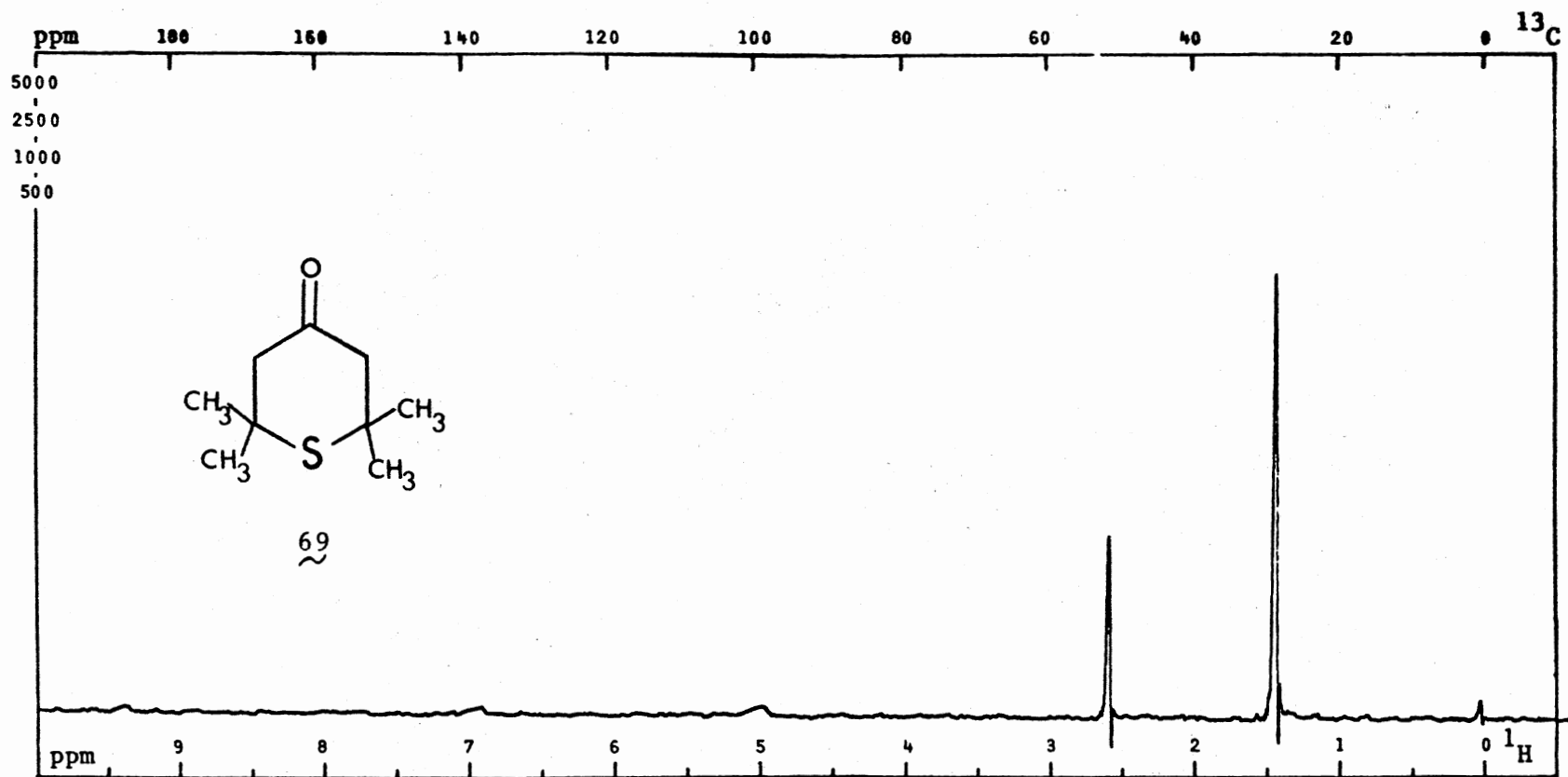
^{1}H NMR Spectrum of 69

CW.   X;   Solvent   DCCl$_3$;   SO.85771 Hz;   PW.   1000 Hz;   T.   30°C;   SA. 1.0;

RF.   57 dB;   SF.   100.1 MHz;   FB.   2 Hz;   Lock ^{2}H;   ST.   250 s.

PLATE IX
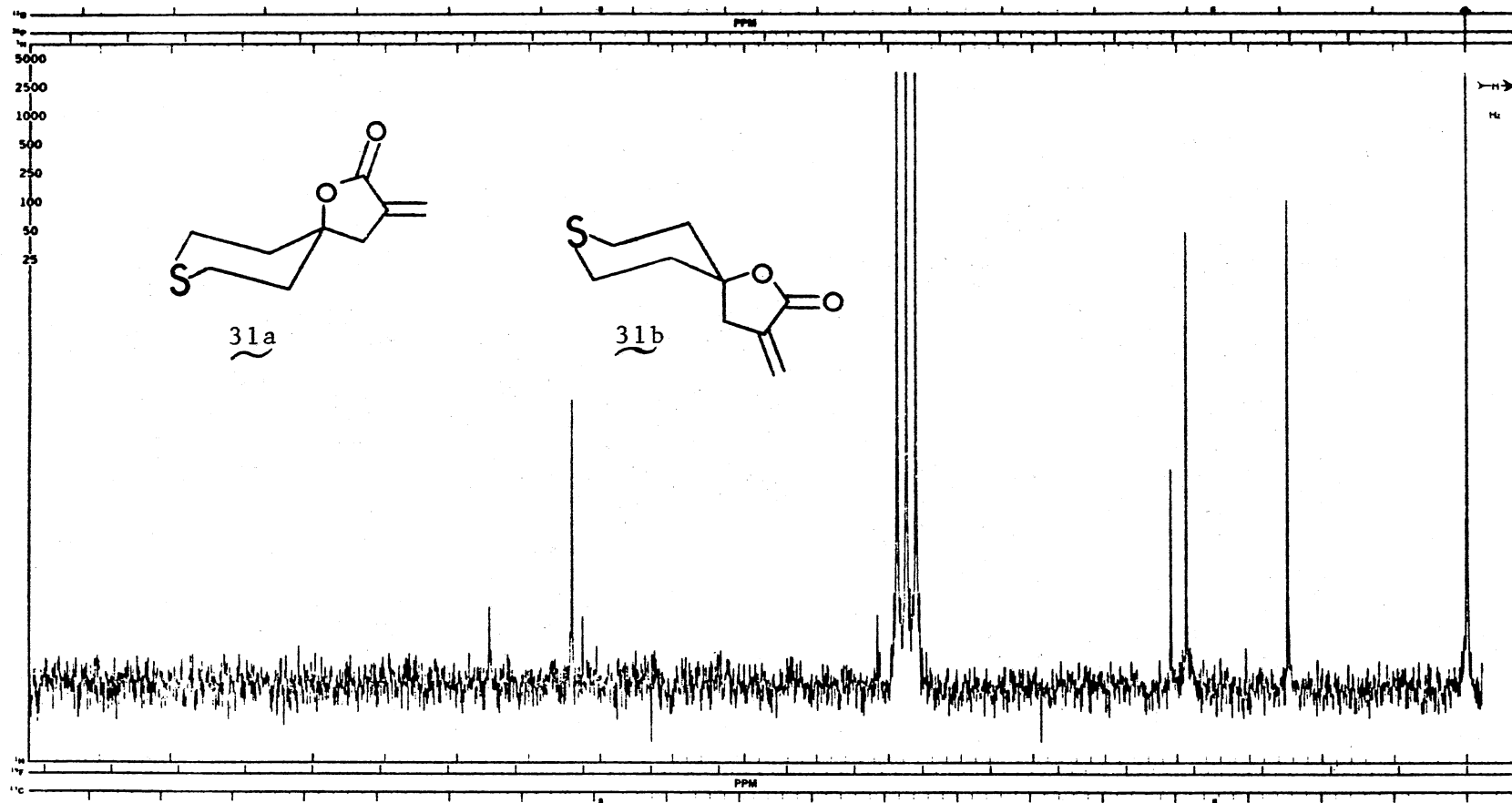
^{13}C NMR Spectrum of 9-Methylene-7-oxa-1-thiaspiro[4.5]decan-8-one (31a ⇌ 31b)

PFT. X;   Solvent $DCCl_3$;   SO. 35101 Hz;   PW. 5000 Hz;   T. 30°C;   Acq.6000;   Size   8K;

P2 15.5μs;   SF.   25.2 MHz;   FB.   3 KHz;   Lock. ^2H;   D5. 8 s.
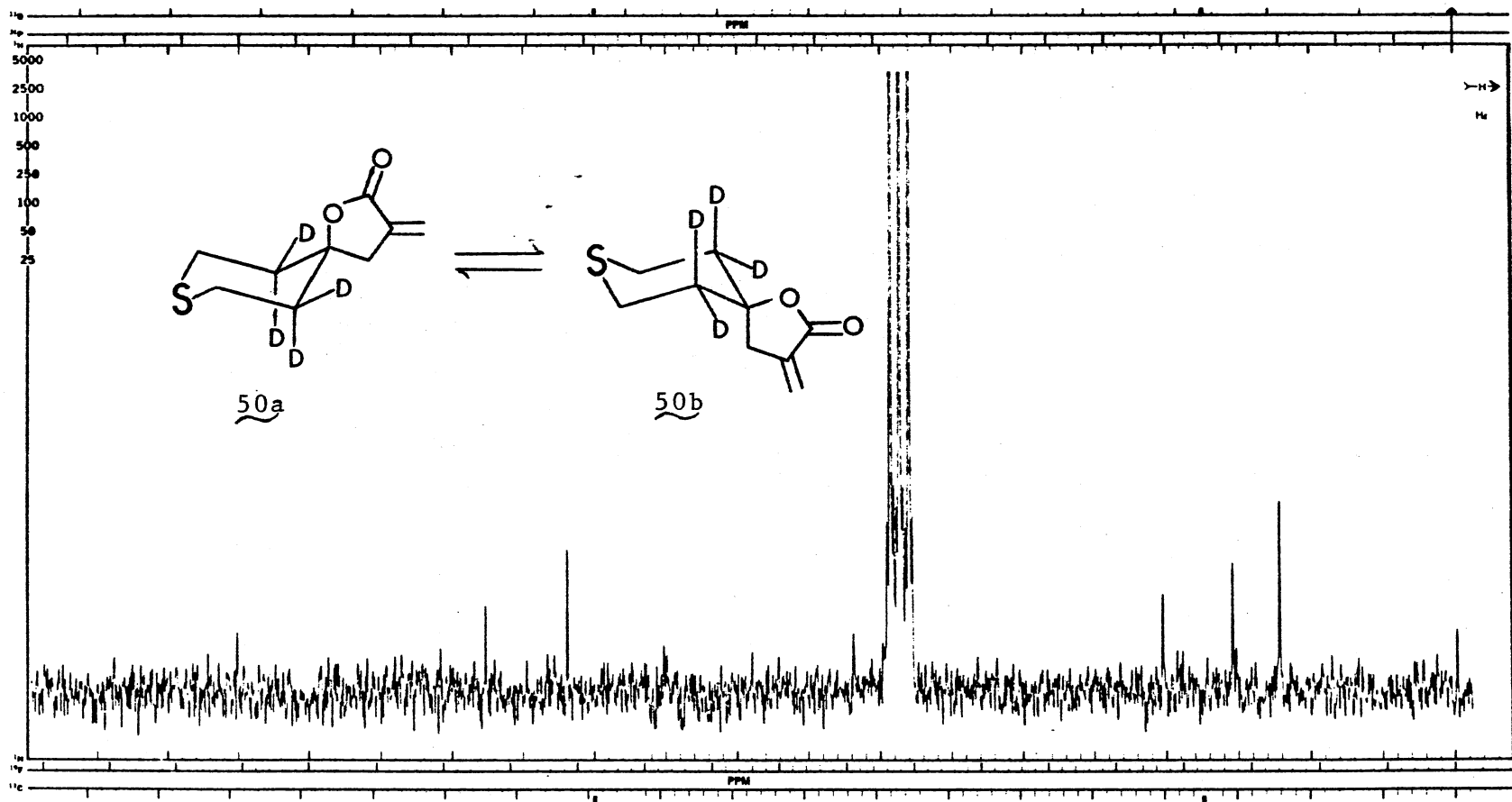
PLATE X

^{13}C NMR Spectrum of 50a ⇌ 50b

PFT.   X;   Solvent. DCCl$_3$;   SO.   35101 Hz;   PW.   5000 Hz;   T.   30°C;   Acq. 6200;

Size   8K;   P2   15.5 s;   SF.   25.2 MHz;   FB.   3 KHz;   Lock ^{2}H;   D5   7 s.

PLATE XI
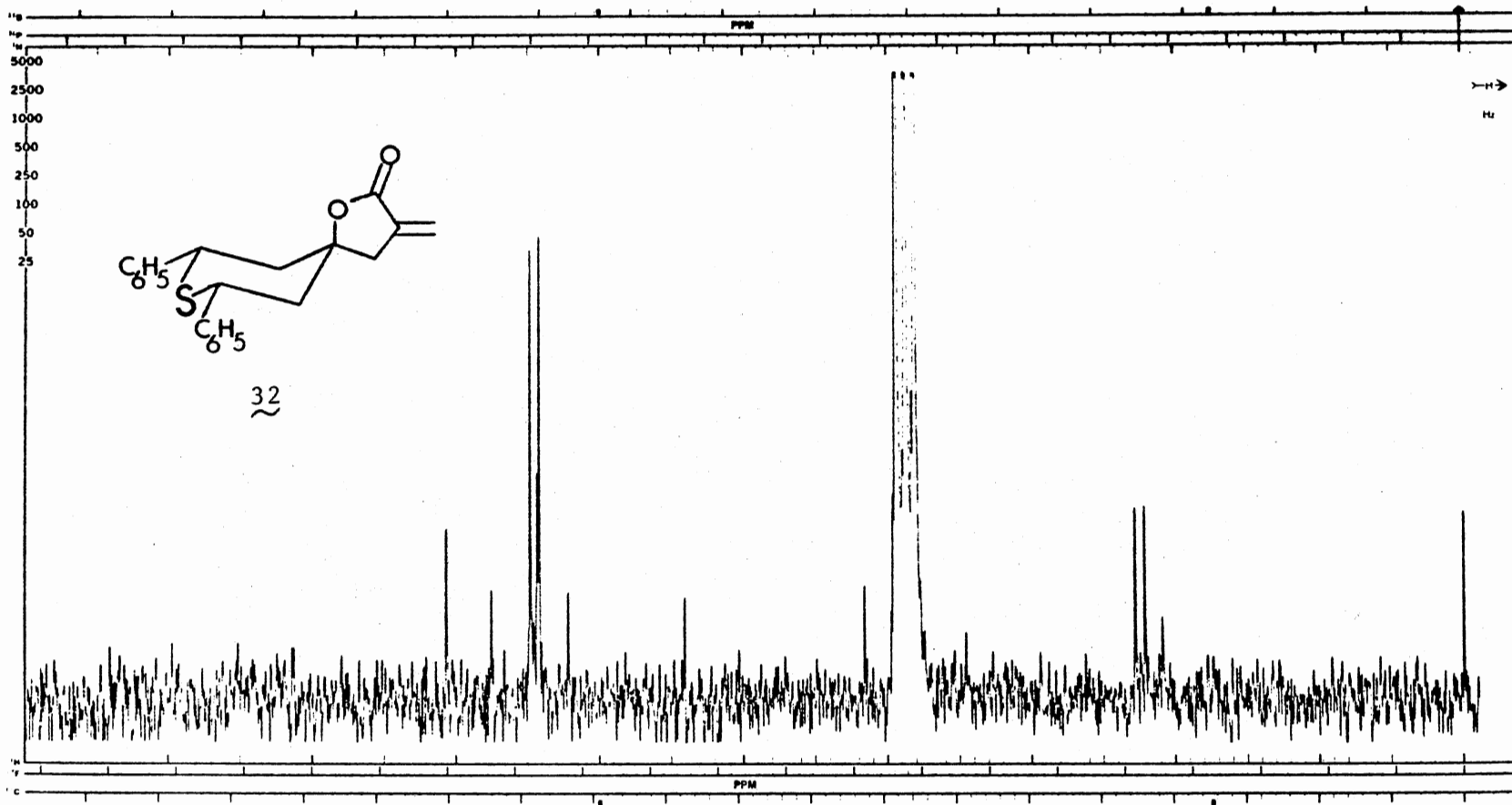
^{13}C NMR Spectrum of 32

PFT.   X;   Solvent DCCl$_3$;   SO.   35101 Hz;   PW.   5000 Hz;   T.   30°C;   Acq. 6000;

Size   8K;   P2   15.5 s;   SF.   25.2 MHz;   FB.   3 KHz;   Lock ^{2}H;   D5   8 s.

PLATE XII
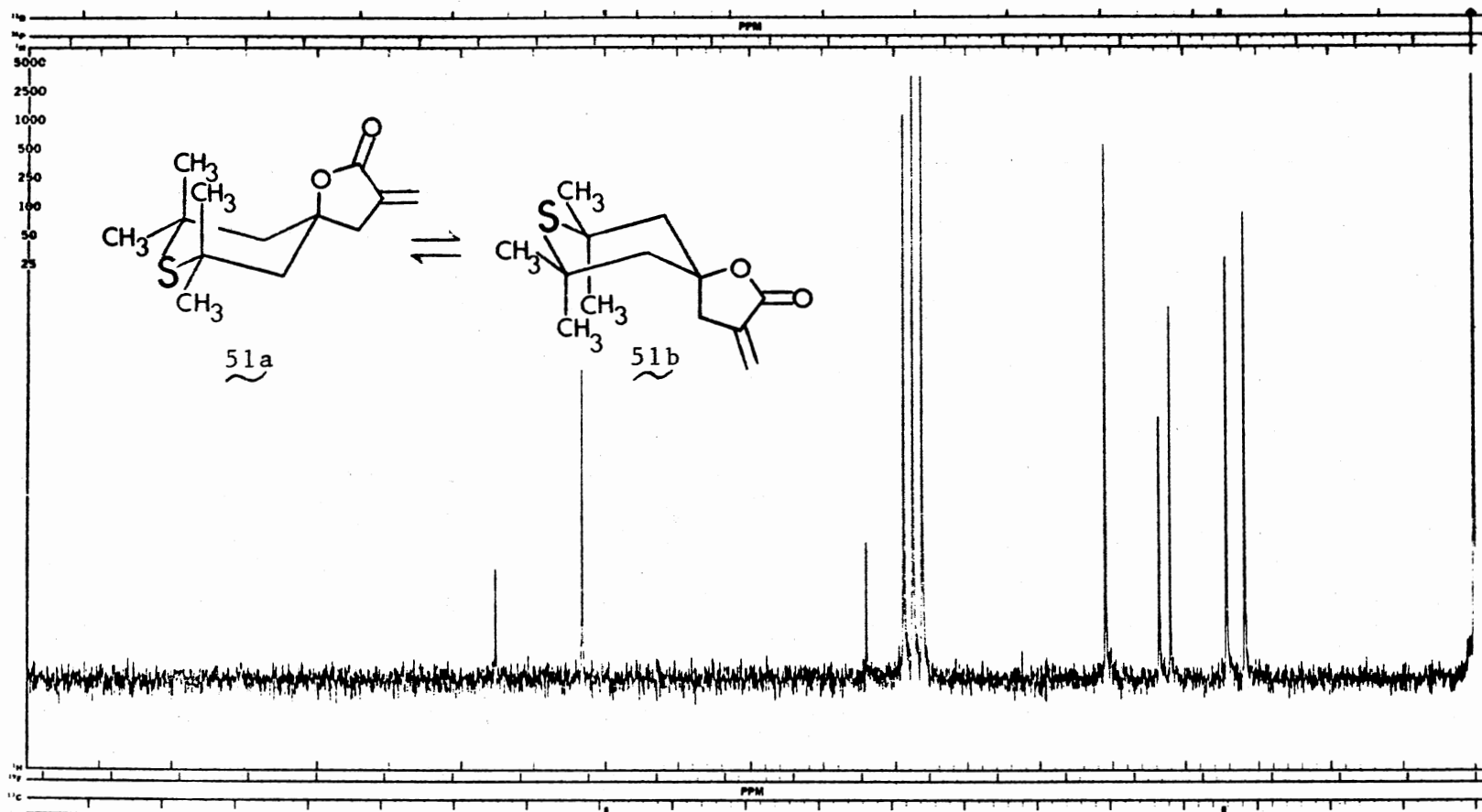
^{13}C NMR Spectrum of 51a $\rightleftharpoons$ 51b

PFT.   X;   Solvent DCCl$_3$;   SO.   35101 Hz;   PW.   5000 Hz;   T. 30°C;   Acq. 6700;

Size   8K;   SF.   100.1 MHz;   FB.   3 KHz;   Lock ^{2}H;   P2 15.5 μs;   D5   9 s.
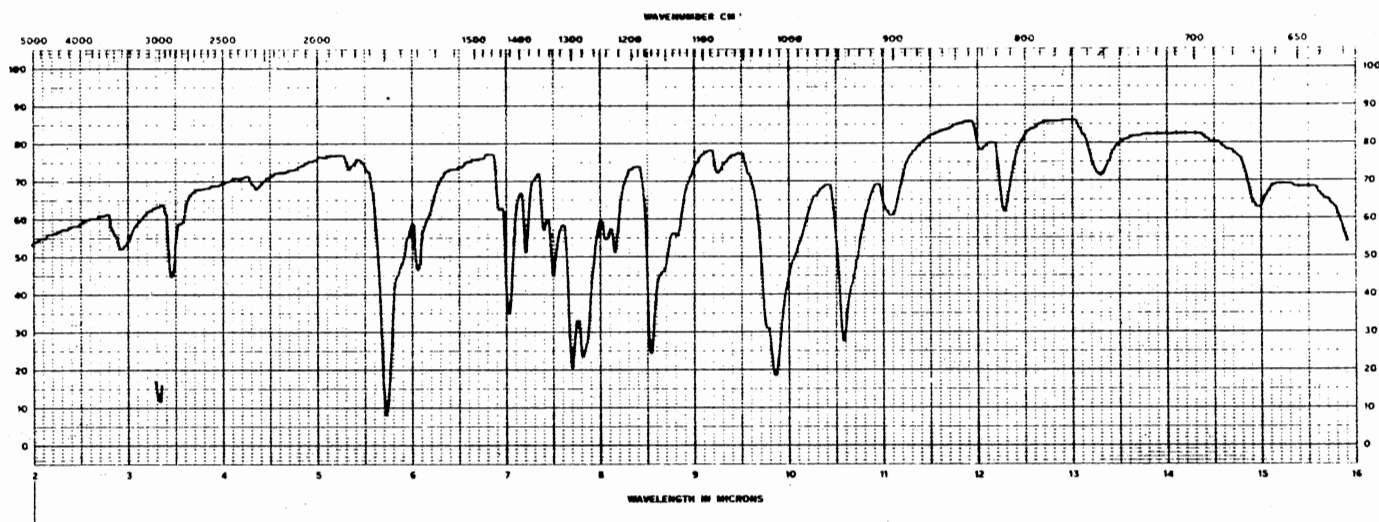
PLATE XIII

IR Spectrum of 9-Methylene-7-oxa-1-thiaspiro[4.5]-

decan-8-one (31a or 31b), KBr Pellet

PLATE XIV
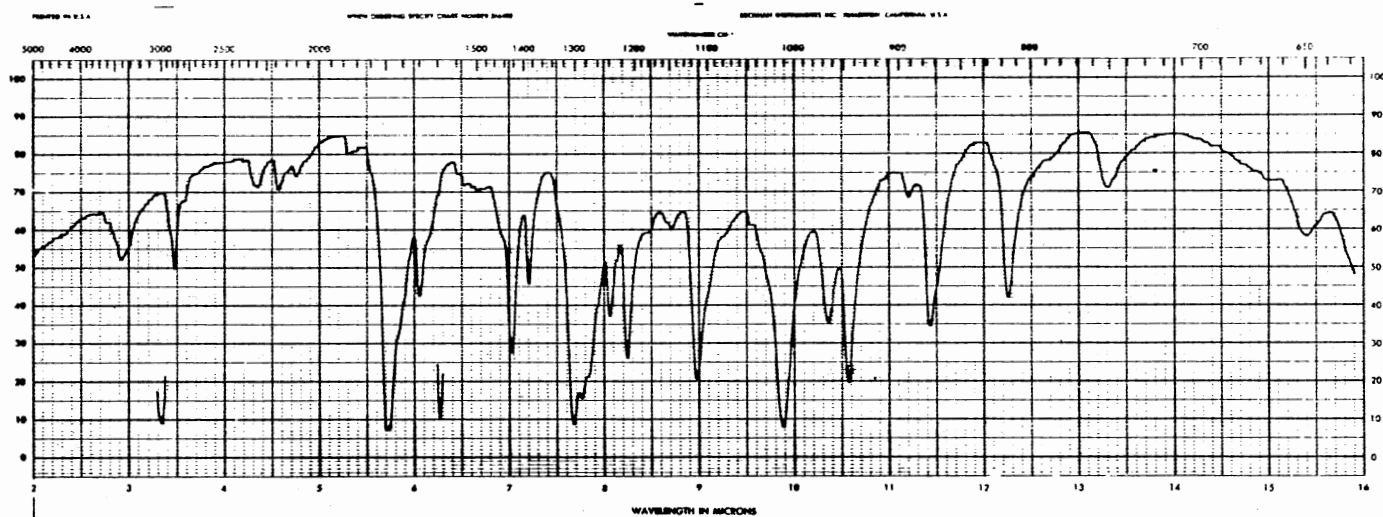
IR Spectrum of 9-Methylene-7-oxa-1-thiaspiro[4.5]-

decan-8-one-3,3,5,5-$\underline{d}_4$ (50a or 50b) KBr Pellet

PLATE XV
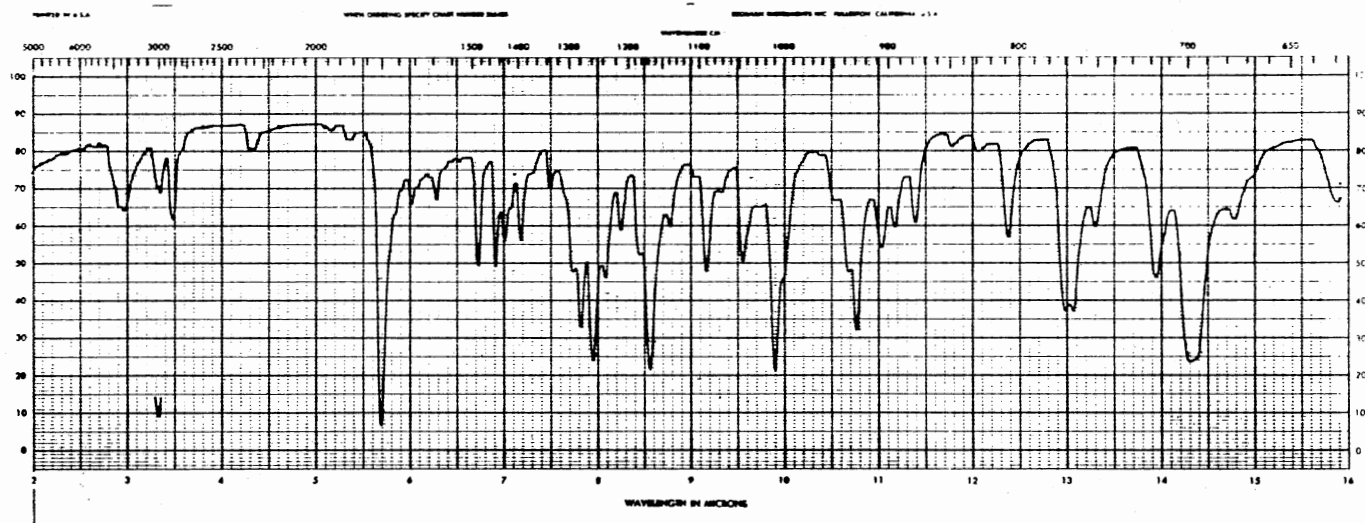
IR Spectrum of <u>cis</u>-2,6-Diphenyl-9-methylene-7-oxa-1-
thiaspiro[4.5]decan-8-one (<u>32a</u> or <u>32b</u>) KBr Pellet

PLATE XVI
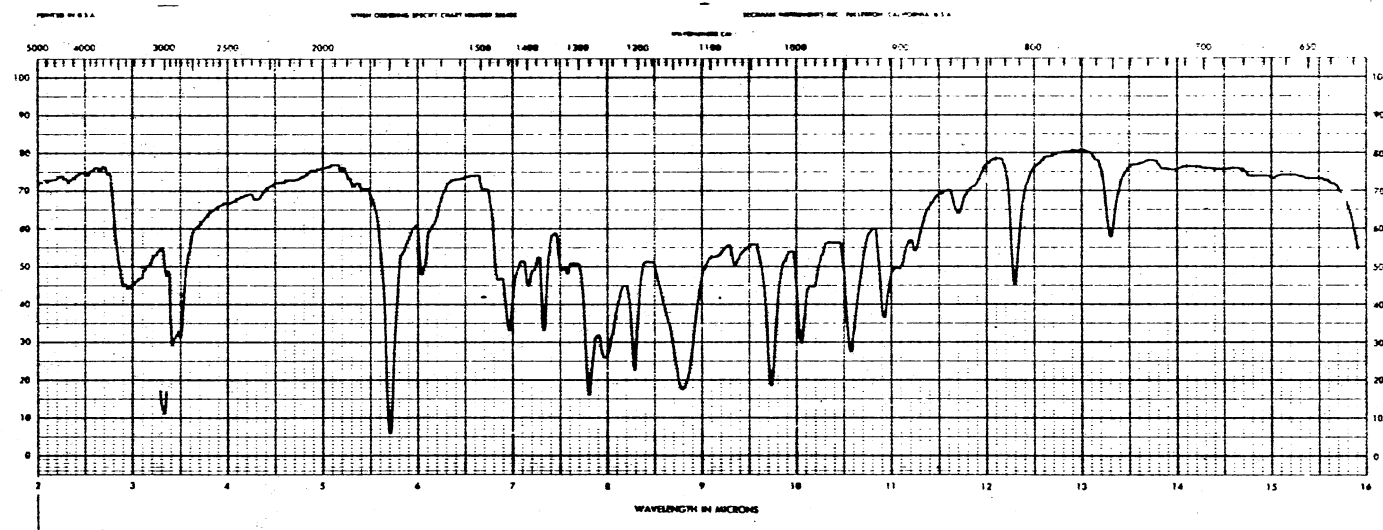
IR Spectrum of 2,2,6,6-Tetramethyl-9-methylene-7-oxa-1-

thiaspiro[4.5]decan-8-one (51a), KBr Pellet

PLATE XVII
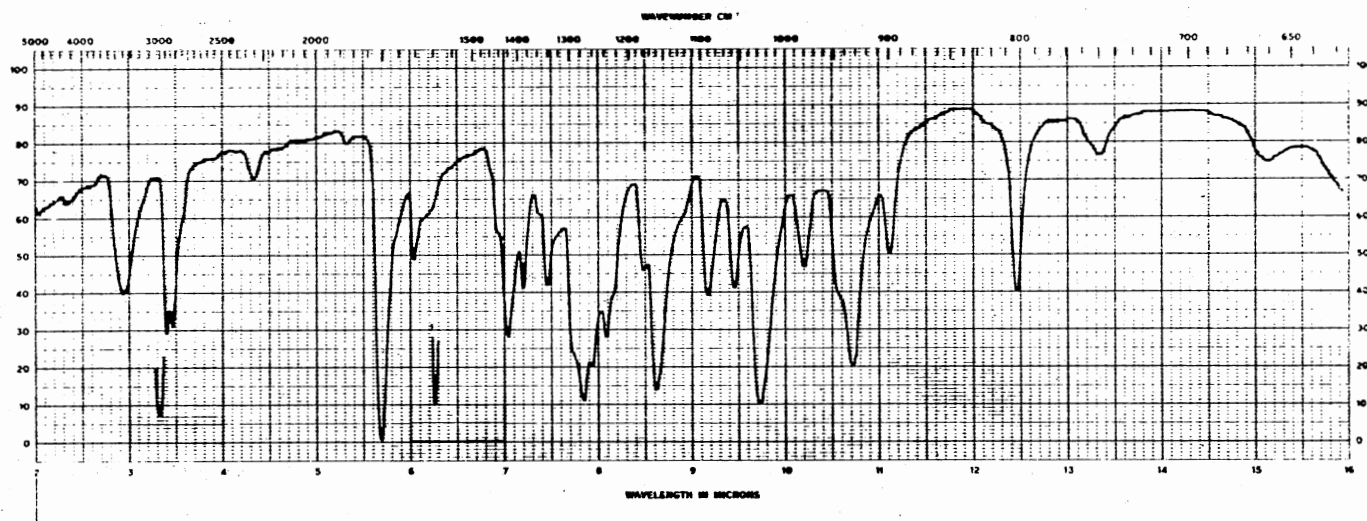
IR Spectrum of the Methyl Iodide of 9-Methylene-7-oxa-1-
thiaspiro[4.5]decan-8-one (74), KBr Pellet

PLATE XVIII
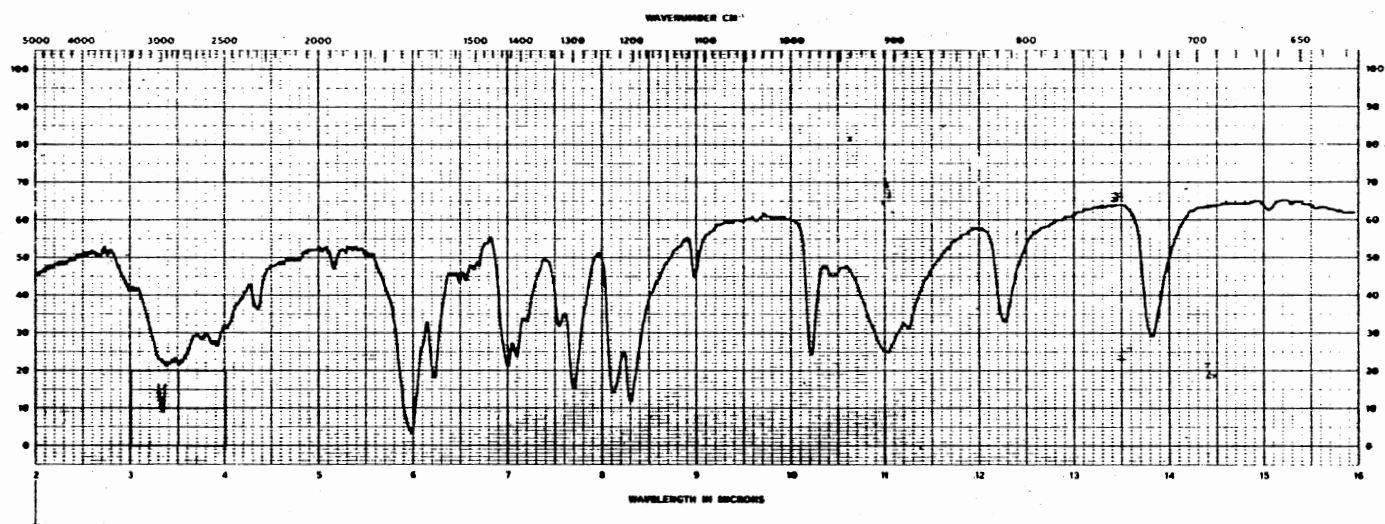
IR Spectrum of α-(Bromomethyl)acrylic Acid (53), KBr Pellet

PLATE XIX
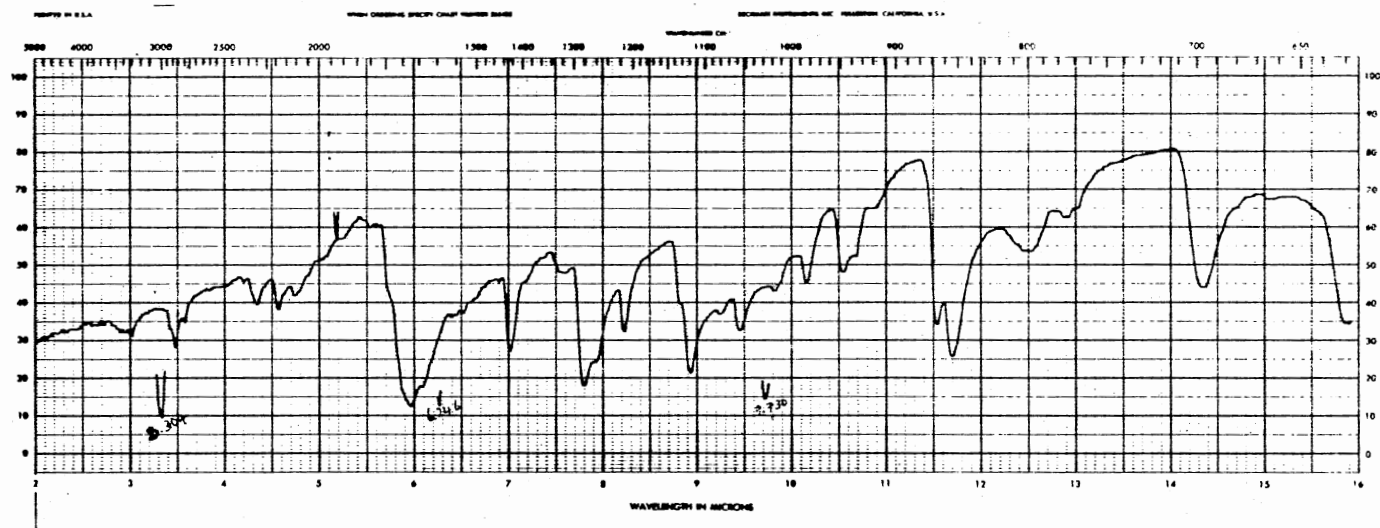
IR Spectrum of 4-Thianone-3,3,5,5-$\underline{d}_4$ ($\underset{\sim}{70}$), KBr Pellet

PLATE XX
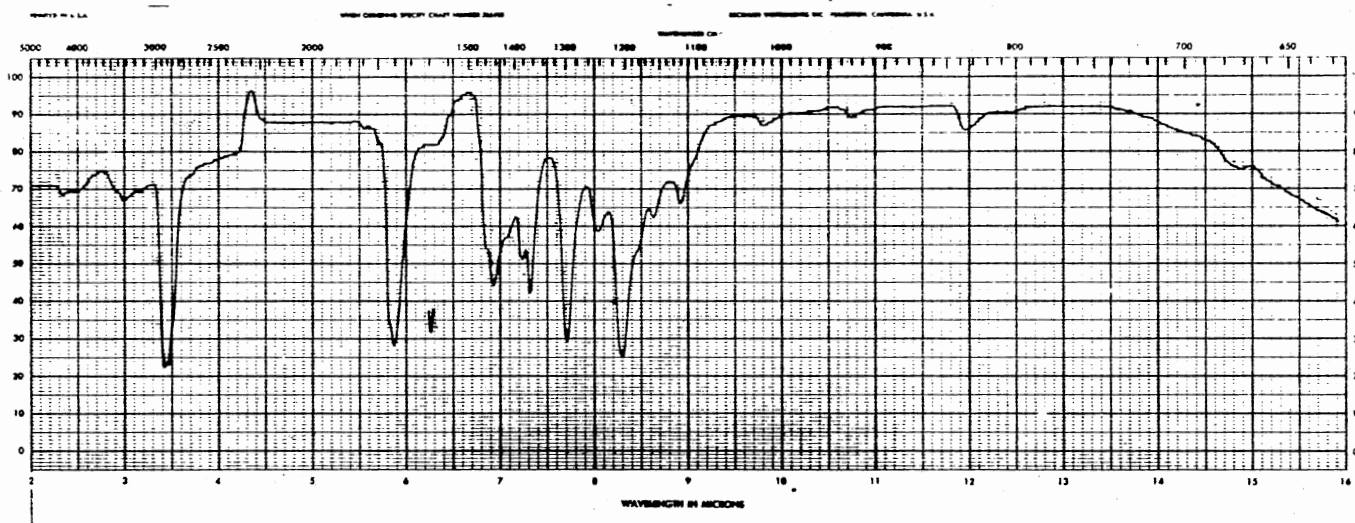
IR Spectrum of 2,2,6,6-Tetramethyl-4-thianone (69), KBr Pellet

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PART II.   AN INVESTIGATION OF THE SPIN-LATTICE

RELAXATION PHENOMENA (T_1 VALUES) OF THE

^{31}P NUCLEUS IN CERTAIN CLASSES OF

ORGANOPHOSPHORUS COMPOUNDS

CHAPTER I

HISTORICAL

INTRODUCTION

The advent of Fourier transform NMR[51] has added one more tool, namely, spin-lattice relaxation time, to the arsenal of organic chemist in attacking structural problems. Along with the nuclear Overhauser effect[42] (NOE) arising out of the broad-band proton decoupling of ^{31}P NMR spectra, the T_1 values of ^{31}P nuclei in a molecule may be expected to provide useful conclusions regarding the relaxation mechanisms, the mobility of a molecule in solution and the steric hindrance to internal motion of the groups containing the nuclei of interest in a molecule.[34] Most of the work in the past has been centered around the T_1 and NOE of ^{13}C nuclei.[7] Except for a few isolated studies, studies,[6,10,22,27,31,54] no systematic investigation of the T_1 values of ^{31}P in organophosphorus compounds has been attempted and this has prompted the present endeavor.

Spin-lattice Relaxation

All nuclei are charged particles and some, in addition, have the property of spin angular momentum. The angular

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momentum imparts a magnetic moment, $\mu = \gamma P$, to these nuc-
lei. The ratio between the magnetic moment (μ) and the
mechanical angular momentum (P) is called the gyromagnetic
constant (γ), a constant characteristic of the nucleus. In
the presence of an external magnetic field, H_o (or B_o),
nuclei with spin quantum number I = 1/2, for example ^{1}H,
^{13}C and ^{31}P, distribute themselves between the two possible
energy levels in accordance with the Boltzmann distribution
law. Nuclei in the lower energy levels have their magnetic
vectors aligned with the field and those in the upper level
have the opposite orientation for their magnetic vectors as
shown in the diagram below. The difference in energy, ΔE,
between the two energy levels depends on the strength of the
external magnetic field and the gyromagnetic constant of the
nucleus, according to Eq. (1):

$$\Delta E = (h/2\pi)\gamma H_o \qquad\qquad Eq. \ (1)$$
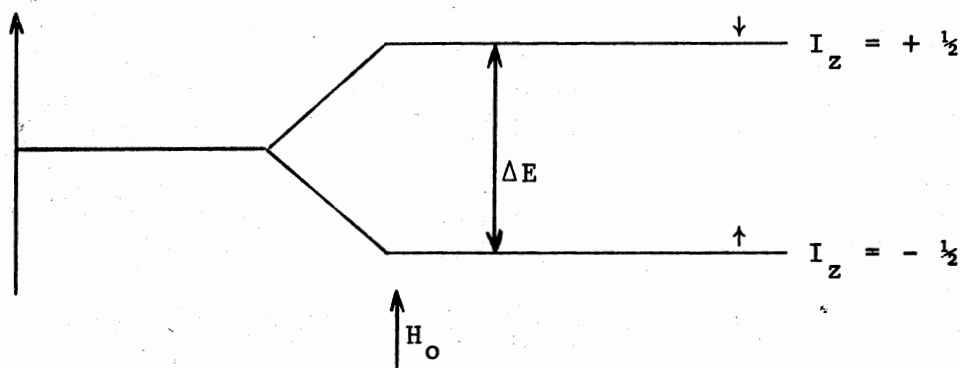
The I_z is the z component of spin quantum number which for
^{1}H, ^{13}C and ^{31}P is $\pm \frac{1}{2}$.

Radiation (continuous or pulsed) in the radio frequency range (with energy corresponding to the difference between the two energy levels) can induce transition between the two nuclear magnetic energy levels (the NMR phenomenon) and this ultimately results in equal population in these two levels. At this stage nuclear magnetic absorption ceases unless there exists some mechanism by which the Boltzmann excess of nuclei in the lower level is restored. This restoration of equilibrium distribution by the return of the excited nuclear spins to the ground levlel is called the spin-lattice relaxation. The energy liberated during this process is transferred to the environment (neighboring or solvating solvent molecules called the "lattice") of the nuclei. Consequently, the spin-lattice relaxation time, T_1, is a measure of the time T_1 required for this process to occur.

Another way of looking at the phenomenon of spin-lattice relaxation (a way which is more convenient from the point of view of understanding the methods of measurement) is to examine the whole phenomenon from the point of view of classical mechanics.[4,5,16] According to this view point, in the presence of an external magnetic field, nuclei having $I = \frac{1}{2}$ adopt two possible modes of precession, i.e. precession about the direction of the field vector (by convention in the z direction) and precession in the opposite direction with a precessional frequency $\nu_o = \gamma H_o/2\pi$ as shown in the diagram that follows. At equilibrium, there is a net

excess of nuclei precessing about the direction of the
field vector and this excess gives rise to the equilibrium
magnetization M_o along the z direction. Radiation with
radiofrequency radiation (with a frequency corresponding to
the Larmor frequency) in the x direction flips the resultant
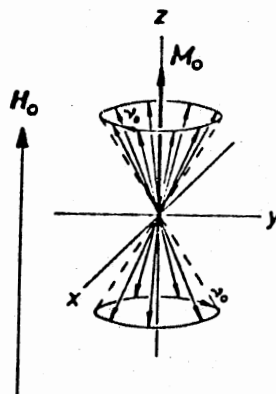
magnetization towards the y direction. In a coordinate
system rotating at the Larmor frequency about the z axis
(x', y', z coordinate system),[4,5,16] the radiofrequency
vector H_1 rotates with the x' axis, causes a deflection of
the M_o vector towards y', builds up the transverse magnet-
ization $M_{y'}$ and induces a signal in the receiver proportio-
nal to $M_{y'}$. The angle of deflection Θ of M_o (twist, flip
or pulse angle) depends upon the duration of the radio-
frequency irradiation in pulsed nuclear magnetic resonance
according to $\Theta = \gamma H_1 t_p$, where t_p is the duration of the
pulse (called pulse width). Immediately after a 90° pulse,
$M_{y'} = M_o$ and $M_z = 0$. Following the 90° pulse, the nuclear
spin system returns to the normal equilibrium situation,
and the magnetization along the z axis approaches its equi-
librium value M_o. Spin-lattice relaxation is assumed to

be a continuous increase in the longitudinal magnetization M_z to the equilibrium value with a time constant T_1, the spin-lattice relaxation time. The process is diagrammed below.[4,5.16] T_1 is the time after which M_z has risen to 1/e of the equilibrium value M_o.
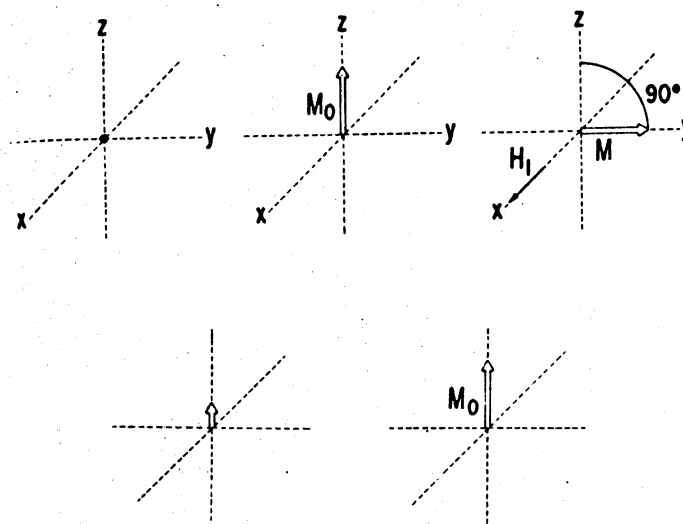
$$dM_z/dt = -(M_z - M_o)/T_1 \qquad \text{Eq. (2)}$$

where M_z = the z component of magnetization
     at any time

M_o = the z component of magnetization
     at equilibrium

T_1 = the spin-lattice relaxation time

Method of Measurement

The advent of Fourier transform NMR analysis[51] made possible, in general, the simultaneous determination of

spin-lattice relaxation times (T_1 values) for each NMR active nuclei in a complex molecule. The approach most commonly used for the measurement of T_1 is the inversion recovery method combined with Fourier transform IRFT).[1,2,17,21,32,51] This method is based on the pulse sequence: $\{180°-\tau-90°(FID)-T\}$. T is the time set to $5(T_1)_{max}$ value, where $(T_1)_{max}$ is the longest spin-lattice relaxation time to be measured. The 180° pulse inverts the ^{31}P energy level populations, thus producing a Boltzmann excess of nuclei in the higher energy level. Following the 180° pulse, the nuclei immediately begin to relax to re-establish the normal Boltzmann distribution, namely with excess nuclei in the lower energy state. The 90° pulse is applied after a waiting period τ, which is varied in the successive experiments. The free induction decays (FID's) that follow the 90° pulse are digitized, stored and then Fourier transformed. This leads to a spectrum of partially relaxed (for a time τ) nuclei. The relaxation of the nuclei from the inverted Boltzmann distribution (following the 180° pulse) to the normal Boltzmann distribution follows the first order rate law as given by Eq. (2). Integration of Eq. (2) between $M_z = -M_o$ at $t = 0$ and $M_z = M_\tau$ at $t = \tau$ leads to Eq. (4). As the intensity of a line in a partially

$$\int_{M_o}^{M_\tau} dM_z / (M_z - M_o) = - \int_0^\tau (1/T_1) \, dt \qquad \text{Eq. (3)}$$

$$\ln (M_o - M_z)/2M_o = - \tau/T_1 \qquad \text{Eq. (4)}$$

relaxed (for a time τ) Fourier transform NMR spectrum is proportional to the z component of magnetization at that time, M_τ, Eq. (4) can be rewritten as Eq. (5):

$$\ln (M_o - M_\tau) = \ln (2M_o) - \tau/T_1 \qquad \text{Eq. (5)}$$

where M_o = the intensity of the signal at

equilibrium

M_τ = the intensity of the signal at τ

Thus the spin-lattice relaxation time, T_1, is obtained as the negative of the reciprocal slope of the semilogarithmic plot of $(M_o - M_\tau)$ vs τ.

In addition to the inversion recovery Fourier transform method, other methods in vogue for T_1 measurements are the saturation recovery Fourier transform method (SRFT)[36,38] and the progressive saturation Fourier transform method (PSFT)[18,19] The IRFT method suffers from the drawbacks such as the $(T_1)_{max}$ is usually not known beforehand (thus necessitating a trial run which is eventually discarded), and it is excessively time consuming due to the long waiting time, about $5(T_1)_{max}$, between the pulse sequences.[29] However, Levy and Peat, who made a critical examination of these three methods,[35] conclude that although the SRFT and PSFT methods are faster and somewhat more convenient than the IRFT method, the pulsing requirements in the PSFT method are most stringent. Mis-set pulse lengths (pulse angles) and variable spectral offsets are shown[35] to introduce errors to the extent of 25% or more on the T_1 values measured by the

PSFT method, while IRFT and SRFT methods lead to errors under 10-15%. This relative insensitivity to the instrumental and other experimental deficiences[35] makes the SRFT and IRFT methods the most preferred. The advantage that SRFT has {compared to IRFT in speed (SRFT is approximately twice as fast as IRFT)} is more than offset by a loss of dynamic range (or sensitivity) of 50% in SRFT with respect to IRFT.[18,19] This is evident from Eq. (6) and Eq. (7) used in IRFT and SRFT experiments, respectively. Eq. (6) follows from Eq. (5). Canet and co-workers have shown[9] that inversion recovery with an arbitrary short waiting time much less than $5(T_1)_{max}$ is comparable to the SRFT and PSFT methods in speed, and that such a sequence gives optimum dynamic range

$$M_\tau = M_o \{1 - 2 \exp(-\tau/T_1)\} \qquad \text{Eq. (6)}$$

$$M_\tau = M_o \{1 - \exp(-\tau/T_1)\} \qquad \text{Eq. (7)}$$

(usually approaching that of IRFT). This method is called the fast inversion recovery Fourier transform method (FIRFT) by contrast to standard inversion recovery Fourier transform (IRFT).[9] The FIRFT method utilizes a waiting time T much smaller than $5(T_1)_{max}$ and the successive FID's have amplitudes equal to:[9] $M_o \{1 - 2 \exp(-\tau/T_1)\}$; $M_o \{1 - (2 - E_1) \exp(-\tau/T_1)\}$; ....; $M_o \{1 - (2 - E_1) \exp(-\tau/T_1)\}$, where $E_1 = \exp(-T/T_1)$. Hence the accumulated signal intensity M_τ is given by Eq. (8):

$$M_\tau = M_o \{1 - \alpha \exp(-\tau/T_1)\} \qquad \text{Eq. (8)}$$

where $\alpha = 2 - E_1 (n - 1)/n$

If n (the number of acquisitions) is large or if the first FID is not added, M_τ reduces to:

$$M_\tau = M_o \{1 - (2 - E_1)\exp(-\tau/T_1)\} \qquad \text{Eq. (9)}$$

The usual semilogarithmic plot of $(M_o - M_\tau)$ vs τ will lead to the determination of T_1, the τ values being chosen as in conventional IRFT. The measurement of M_o, however, requires that one spectrum be obtained where $\tau = 5(T_1)_{max}$. A comparison of the results from IRFT and FIRFT methods are given in Table I.[9] As can be seen, the two sets of results do not differ by more than the experimental error.

Comparison of Eq. (6) and Eq. (9) reveals that instead of a dynamic range of 2 found in the standard IRFT method, the FIRFT method has a dynamic range of $(2 - E_1)$ where E_1 is much less than 1. The actual value of E_1 depends upon the waiting time T and the relaxation time T_1. For values of T comparable to T_1 (for all our measurements $T \simeq 2T_1$), E_1 is very small. Thus, FIRFT compares with SRFT and PSFT in speed and at the same time does not suffer a loss in dynamic range (or sensitivity) by more than a very small fraction.[9] Canet and co-workers[9] have also examined the effects of mis-set pulse angles and variation in spectral offset on the T_1 values determined by the FIRFT method. It is found[9] that the FIRFT method is reasonably insensitive to pulse characteristics and spectral offsets

It has been pointed out recently[12,29] that a further

TABLE I

COMPARISON OF IRFT AND FIRFT EXPERIMENTS

$80\%(w/v)$ PHENOL IN D_2O[9]

Carbon	T_1 (sec)	
	FIRFT[a]	IRFT[b]
C-1	29.5	28.8
C-2	4.2	4.2
C-3	4.1	4.1
C-4	3.1	3.0

[a] $T = 5$ sec

[b] $T = 160$ sec

time saving in the determination of T_1 by the FIRFT method
can be effected by omitting the time consuming measurement
of the equilibrium magnetization corresponding to $\tau =$
$5(T_1)_{max}$ in the $(180°-\tau-90°)_n$ sequence. However, in order
to achieve this additional time saving, it is necessary[12,29]
to replace the usual semilogarithmic plot method of data
reduction by a non-linear, least-squares fitting procedure
using the two-parameter expression, Eq. (10):

$$M_\tau = M_o[1 - \{2 - \exp(-W/T_1)\}\exp(-\tau/T_1)] \qquad \text{Eq. (10)}$$

where W is the waiting time between the $180°-\tau-90°$ sequences.
But the above two-parameter expression has the disadvantage
of being highly sensitive to systematic errors such as from
misadjusted pulse angles and improper settings of the fre-
quency offset between the carrier frequency and the reso-
nance line positions.[29] Sass and Ziessow[45] have recently
suggested that a more flexible expression, to which the mea-
sured signal intensities can be fitted, should contain three
adjustable parameters as shown in Eq. (11):

$$M_\tau = A + B \exp(-\tau/T_1) \qquad \text{Eq. (11)}$$

where A, B and T_1 are the adjustable parameters. Sass and
Ziessow[45] have demonstrated that the non-linear, three-
parameter-fit procedure is capable of producing reliable
data in cases of misadjusted pulses and for large frequency
offsets. The question still remains regarding the minimal
acceptable value for the longest τ $(\tau)_{max}$. This was

addressed in an empirical manner by Kowalewski and co-
workers[29] by determining T_1 for different τ_{max} using the
same number of experimental points. On the basis of their
experimental findings,[29] it appears necessary to use τ
values covering a range upto at least 1.5 to 2 T_1 for accu-
rate determination of T_1 values. Moreover, inclusion of
such τ values provides an optimum dynamic range and better
signal to noise ratio, since the peak intensities may be
rather attenuated for short τ values in the FIRFT experi-
ment.

Mechanism of Spin-lattice Relaxation[34]

During spin-lattice relaxation, the excited nuclei
transfer their excitation energy to their environment (the
lattice) via interaction of their magnetic vectors with
fluctuating local fields of sufficient strength, proper
phase and a fluctuation frequency on the order of the Larmor
frequency of the nuclei of interest. Depending on the nature
of the environment of the relaxing nuclei, four possible
mechanisms contribute to spin-lattice relaxation.[16,32,34]

Chemical Shift Anisotropy (CSA mechanism): The magnetic
shielding of a nucleus arising from the surrounding electron
cloud may be anisotropic. Thus, the ^{13}C nucleus in carbon
disulfide, for example, experiences a different local field
when the axis of the molecule is parallel with the field
direction compared to when it is orthogonal to the field.
Therefore as the molecule tumbles in solution, the local

field experienced by the nucleus fluctuates. Frequency components of this fluctuating field corresponding to the Larmor frequency of the ^{13}C nucleus can induce spin-lattice relaxation. A contribution, of the CSA mechanism will be evident from a proportionality of the T_1 values measured to the square of the magnetic field strength H_o (or B_o) applied. This contribution is usually found to be negligible for the ^{13}C nuclei of organic molecules.[7] However, a substantial contribution from the CSA mechanism has been noticed in organophosphorus compounds containing the P=O bond, such as triphenylphosphine oxide, certain phosphoryl compounds and in phosphate groups in biochemical compounds.[26,39,41]

Scalar Coupling Mechanism (SC): Quadrupolar nuclei having $I > 1/2$, i.e. nuclei whose charge distribution is not spherically symmetrical, relax so fast that they accelerate the relaxation of neighboring coupled nuclei. The contribution of the scalar coupling mechanism, becomes particularly large when the coupling nuclei precess with similar Larmor frequencies, as can be seen by comparing the ^{13}C relaxation in $HCCl_3$ (T_1 = 32.4 sec) and $HCBr_3$ (T_1 = 1.65 sec).[34] Bromine and carbon precess with similar Larmor frequencies. In the absence of quadrupolar nuclei in the molecules, as is the case in the present investigation, there cannot be any contribution from the scalar coupling mechanism.

Spin Rotation Mechanism (SR): When a molecule or part of a molecule rotates, the magnetic vectors of the bonding

electron spins also rotate. This creates fluctuating magnetic fields in the immediate vicinity, thereby inducing spin-lattice relaxation. In situations where the spin rotation mechanism makes a significant contribution to spin-lattice relaxation, as in small symmetrical molecules which do not have a proton directly attached to the relaxing nuclei, T_1 values have been found to decrease significantly with an increase in temperature.[34] Reported in Table II are the T_1 values for ^{31}P nuclei in $(C_2H_5)_3P$ and $(C_6H_5)_3P$ determined as a function of temperature.[27] It is clear that for these two compounds the spin rotation mechanism makes a significant contribution to the relaxation process. Dale and Hobbs[10] investigated a number of trialkyl phosphites and trialkyl-phosphates. By means of relaxation times determined at two magnetic field strengths and by the different dependence of the spin rotation and dipolar interactions on the viscosity and temperature, they were able to effect a reasonably quantitative separation of the contributing mechanisms. The results of their investigation show that for PBr_3, $O=P(OCH_3)_3$, $S=P(OCH_3)_3$ and the cyclic phosphoryl compound 1,3-dimethyl-3-phospholene 1-oxide, the spin rotation (SR) mechanism clearly dominates.[10]

Internuclear Dipole-Dipole Interaction Mechanism (DD): Each nucleus with a spin quantum number $I > 0$ generates a local magnetic field. If two such nuclei, for example ^{31}P and ^1H or ^{13}C and ^1H, are linked by a bond, then each of the nuclei will experience not only the constant external field

TABLE II

SPIN-LATTICE RELAXATION TIME AS A

FUNCTION OF TEMPERATURE

Cpd.	Conc. (moles/liter)[a]	Temp. ($^{\circ}$C)	T_1 (sec)
$(C_2H_5)_3P$	0.7	-19	15.3
	0.7	29	10.4
	0.7	58	3.4
$(C_6H_5)_3P$	0.7	29	30.8
	0.7	50	25.8

[a] In $DCCl_3$.

H_o (or B_o) but also the local field due to the other nuclear spin. This is the internuclear dipole-dipole interaction. The strength and direction of this interaction depends on the magnetic moments of the interacting nuclei, the inter-nuclear separation and the relative internal orientations of these nuclei with respect to H_o (or B_o). In solution, due to rapid molecular motions, the relative orientations of the two nuclei with respect to H_o (or B_o) are constantly changing, and this generates fluctuating local fields which contribute to the relaxation of the nuclei. Only those molecular motions whose "frequencies" lie in the region of the ^{31}P Larmor preceesion frequency lead to rapid dipolar relaxation. The ^{31}P nuclei are known to precess with a frequency of $\nu_o = 4.05 \times 10^7$ Hz or $\omega_o = 2\pi\nu_o = 2.55 \times 10^8$ rad/s at a field strength of $H_o = 23.5$ KG. The present investigation was carried out at 23.5 KG. Most efficient dipole-dipole relaxation, therefore, requires molecular motions having effective correlation times, τ_c (i.e. the average time required for a molecule to rotate through 1 radian)[14,16,23,53] of:

$$\tau_c = (1/2.55) \times 10^8 = 3.92 \times 10^{-9} \text{ sec}$$

Thus a plot of T_1 as a function of τ shows a minimum which corresponds to a correlation time comparable to the Larmor precession[34] as shown in the diagram that follows. Both slow and rapid molecular motions lead to an increase in T_1. Except for highly restricted polymer systems, the correlation

time, for most molecules, falls on the left side of the minimum with correlation times of the order of $10^{-11} - 10^{-13}$ sec. If the dipole dipole interaction is the major contributing mechanism, then any factor that shortens τ_c will
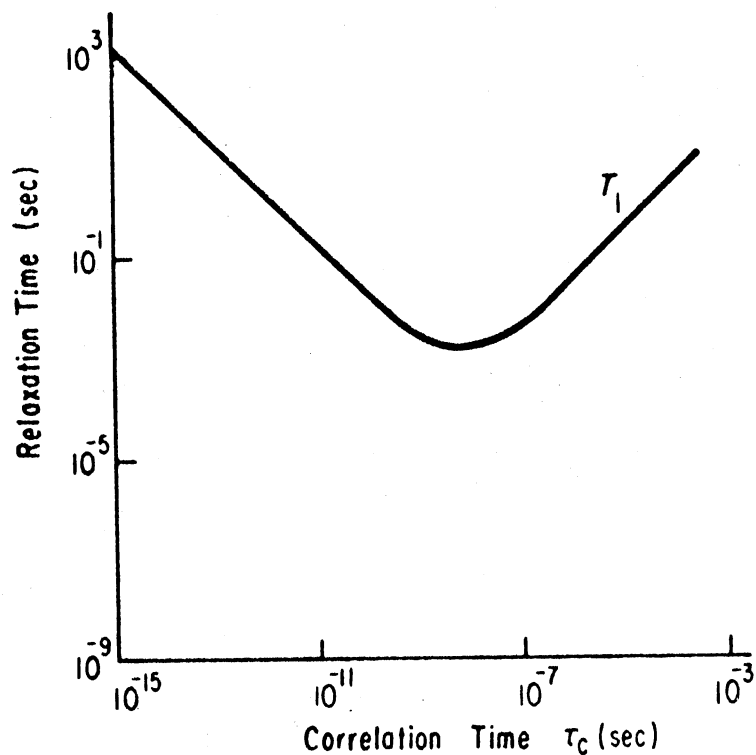
result in a lengthening of T_1. For example, lowering solution viscosity and raising the temperature should both shorten τ_c. Thus for tetraethylphosphonium iodide, values of 9.0 sec and 11.0 sec have been observed[27] for a 0.7 M solution in $DCCl_3$ at 29°C and 58°C, respectively.

By measuring the NOE factors[42] it is frequently possible to separate the contribution of dipole-dipole interaction mechanism from the other mechanisms. During the broad-band proton decoupling of the ^{31}P NMR spectra, the protons transfer their excitation energy to the "lattice" primarily by

internuclear dipole-dipole interaction with ^{31}P (and ^{13}C) and this forces the relaxation of ^{31}P (and ^{13}C) nuclei. As a consequence, the population of the energetically more favorable ^{31}P spin states increases and the ^{31}P signal intensities are enhanced on proton decoupling more than would be expected from the multiplet intensities in the un-decoupled spectra.[42] This enhancement is the nuclear Overhauser enhancement (NOE).[42] If ^{31}P relaxation proceeds exclusively by the dipolar (DD) interaction mechanism, the NOE factor will be given by the ratio of the gyromagnetic constant of the proton to twice the gyromagnetic constant of the ^{31}P nucleus. NOE factors less than 1.235 indicates

$$\eta = \gamma_H/2\gamma_P = 1.235$$

participation of other mechanisms besides dipolar interact-ion. The percentage contribution of dipolar interaction mechanism can be evaluated from the measured NOE factor according to the relation:

% DD contribution = $(\eta/1.235)$ x 100

The time constant $T_{1(DD)}$ of the DD mechanism is, therefore, given by:

$$T_{1(DD)} = T_1 (1.235/\eta)$$

Since the total relaxation rate is the sum of the contri-butions from the various mechanisms according to:

$$1/T_1 = 1/T_{1(DD)} + 1/T_{1(SR)} + 1/T_{1(CSA)} + 1/T_1(SC)$$

the NOE parameter helps to factor out the DD contribution from other contributions. Thus:

$$1/T_1 = 1/T_{1(DD)} + 1/T_{1(other)}$$

As expected, $T_{1(DD)}$ increases with an increase in temperature.[10,27] The temperature dependence of dipole-dipole relaxation is that of the correlation time τ_c. An Arrhenius type of equation can be written for the correlation time:

$$\tau_c = \tau_{c_o} \; x \; exp(\Delta E/RT) \qquad \text{Eq. (12)}$$

Thus a semilogarithmic plot of $T_{1(DD)}$ versus reciprocal temperature should provide ΔE, the activation energy for molecular reorientation which is usually of the order of 2-4 kcal/mole.[24]

When DD is the major relaxation mechanism, as is the case with protonated phosphorus (or carbon), and the overall tumbling of the molecule is relatively isotropic (non-directional, i.e. no preferrence for any particular rotational mode), the T_1 value for each protonated carbon is inversely proportional to the number of directly attached protons. The values for isooctane are given below to illustrate with carbon.[34] Although a similar trend should be

$$9.3 \qquad 12.8 \quad 23 \quad 9.8$$
$$(CH_3)_3C-CH_2-CH(CH_3)_2$$
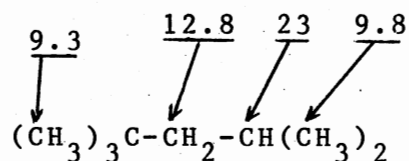
expected for the T_1 values of protonated phosphorus, no

attempt has been made to prove this hypothesis. Some of the results of our investigation suggest this trend.

In situations where part of the molecule is anchored and hence tumbles slowly (with a frequency matching the Larmor frequency of the relaxing nuclei), the T_1 values for the nuclei located at the anchored site are smaller than the values for the nuclei situated at the rapidly "wiggling" end. This "segmental motion" is observed in the case of n-decanol[33] where the hydroxyl end is anchored by H-bonding. Although it is difficult to create an exactly analogous situation for phosphorus, it would be interesting to examine the T_1 values for phosphorus in a diphosphorus compound where one phosphorus is situated at the slowly tumbling end and the other at the rapidly "wiggling" end. No such data exist in the literature to date.

CHAPTER II

RESULTS AND DISCUSSION

In recent years a relatively large amount of work has been done on the relaxation behavior of carbon nuclei.[7] However, except for a few isolated studies,[6,10,22,27,31,54] no systematic investigation of the relaxation behavior of ^{31}P nuclei has been undertaken. Nevertheless relaxation measurements on ^{31}P nuclei should provide useful information regarding the relaxation mechanisms and the ease with which such molecules tumble in solution.[34] Reported in the following pages are the results of the investigation on the spin-lattice relaxation behavior of ^{31}P nuclei as a function of temperature and concentration in systems 1-5.

$$(C_6H_5)_3X \qquad\qquad (C_6H_5)_2XCH_2X(C_6H_5)_2$$

$$\underset{\sim}{1} \qquad\qquad\qquad \underset{\sim}{2}$$

$$(C_6H_5)_2XCH_2CH_2X(C_6H_5)_2$$

$$\underset{\sim}{3}$$

$$\overset{+}{(C_6H_5)_3PCH_3} \ I^-$$

$$\underset{\sim}{5}$$

$$\underset{\sim}{4}$$

$$\underset{\sim}{a}. \quad X = P; \quad \underset{\sim}{b}. \quad X = P(O); \quad \underset{\sim}{c}. \quad X = P(S)$$

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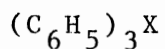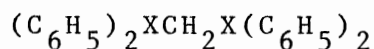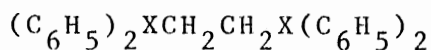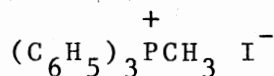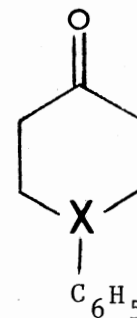
In general, the phosphine sulfides seem to relax predominantly by the dipole-dipole (DD) interaction mechanism. The activation energies for molecular rotational reorientation for these sulfides lie in the predictable range of 1-3 kcal/mole. Activation energies for rotational reorientation have also been computed for compounds 3a, 3b and 4a. Relaxation via spin-rotation (SR) appears to dominate in triphenylphosphine (1a) and 1-phenyl-4-phosphorinanone (4a). The results of our investigation point towards the chemical shift anisotropy (CSA) mechanism as the major contributing factor in the relaxation of the phosphine oxides 1b, 2b, 3b and 4b. For most of the systems examined, the T_1 values were found to <u>increase</u> with <u>decrease</u> in concentration.

For reasons outlined in chapter I, the fast inversion recovery Fourier transform (FIRFT)[9] method has been used for all our T_1 measurements. The T_1 values are computed by fitting the signal intensities (by a non-linear, least-squares fitting procedure) to the expression of Eq. (11):[45]

$$M_\tau = A + B \exp(-\tau/T_1) \qquad \text{Eq. (11)}$$

With a view to confirm that a shorter waiting time ($\simeq 2 \ T_1$) between the pulse sequences (as in FIRFT) did not lead to the T_1 values significantly different from those obtained with a longer time delay ($\simeq 5 \ T_1$ as in IRFT), the relaxation times of ^{31}P nuclei in a few selected compounds were determined by both the IRFT and FIRFT methods. The results are reported in Table I. A similar investigation on

TABLE III

COMPARISON OF IRFT WITH FIRFT

Cpd.	Conc. (moles/liter)[a]	Temp. ($^\circ$C)[b]	T_1 values (sec)[c]	
			IRFT	FIRFT
1b	0.2	35	$19.1 \pm 0.6(100)$	$18.4 \pm 0.8(40)$
1c	0.2	35	$31.6 \pm 0.7(150)$	$32.4 \pm 0.1(60)$
			$31.8 \pm 0.8(150)$	$32.6 \pm 0.2(60)$
		15	$27.7 \pm 0.3(150)$	$27.7 \pm 0.5(60)$
			$28.1 \pm 0.2(150)$	$27.4 \pm 0.2(40)$
2c	0.2	35	$11.8 \pm 0.1(150)$	$11.9 \pm 0.1(25)$
		15	$8.35 \pm 0.14(75)$	$8.50 \pm 0.14(20)$
3c	0.2	35	$8.93 \pm 0.08(100)$	$9.23 \pm 0.11(18)$
			$8.77 \pm 0.28(100)$	$9.05 \pm 0.14(20)$
			$9.01 \pm 0.11(50)$	$9.14 \pm 0.09(20)$
		15	$6.60 \pm 0.06(40)$	$6.63 \pm 0.08(15)$
			$6.15 \pm 0.05(40)$	$6.60 \pm 0.08(15)$

[a] In $DCCl_3$. All solutions were degassed.

[b] Temperature accurate to $\pm 2^\circ$C.

[c] Waiting time, in sec, between the pulse sequences are given in the parenthesis.

the T_1 values of ^{13}C nuclei in phenol by Canet and co-workers workers[9] reveal that the two sets of results do not differ by more than the experimental error.

Canet and co-workers[9] have also found from their investigation of the relaxation behavior of ^{13}C in benzene that the FIRFT method is relatively insensitive to pulse characteristics. Reported in Table II are the T_1 values measured for two different sets of pulse angles. As the data indicate, small changes in pulse characteristics do not significantly affect the T_1 values.

Reported in Table III and Table IV are the T_1 values for the compounds investigated. Relaxation data for the phosphines were collected in acetone-$\underline{d}_6$. $DCCl_3$ was used as the solvent for all other compounds. Although T_1 values of ^{31}P in phosphines have been reported previously in $DCCl_3$ solvent,[27] we have observed that the use of $DCCl_3$ for phosphines resulted in T_1 values that were not reproducible and decreased with time. Although $HCBr_3$ and triphenylphosphine (1a) are reported to react at 150°C,[8] to our knowledge no systematic analysis of the reaction mixture has been reported. Whether or not $HCCl_3$ reacts with phosphines to a small extent on extended exposure is still apparently an unanswered question and could be the cause of the lack of consistency in the T_1 values found in our studies. The benzene-$\underline{d}_6$ solvent also gave T_1 values for the phosphines that were not reproducible and decreased with time.

Three mechanisms, namely, dipole-dipole (DD) interaction,

TABLE IV

EFFECT OF PULSE ANGLES ON T_1 VALUES

Cpd.	T_1 (sec)[a]	
	$(180°-\tau-90°)$	$(172°-\tau-86°)$
2c	$11.9 \pm 0.1(35)$	$11.9 \pm 0.1(35)$
	$8.69 \pm 0.08(15)$	$8.50 \pm 0.14(15)$
3c	$9.05 \pm 0.14(35)$	$9.14 \pm 0.09(35)$
	$6.65 \pm 0.05(15)$	$6.60 \pm 0.08(15)$

[a]Temperature values in °C are given in the parenthesis.
Pulse angles were adjusted by controlling the duration
of the pulse width.

TABLE V

RELAXATION DATA FOR SYSTEMS $\underset{\sim}{1}-\underset{\sim}{5}$

Cpd.	Conc. (moles/liter)	T_1 (sec)		
		15°C	25°C	35°C
$\underset{\sim}{1a}$	0.05	23.2 ± 0.4	20.2 ± 0.3	17.3 ± 0.2
$\underset{\sim}{2a}$	0.05	20.6 ± 0.7	21.3 ± 0.3	22.7 ± 0.2
$\underset{\sim}{3a}$	0.05	16.5 ± 0.4	19.1 ± 0.1	21.1 ± 0.2
$\underset{\sim}{4a}$	0.05	16.0 ± 0.2	16.0 ± 0.2	14.9 ± 0.1
$\underset{\sim}{1b}$	0.2	14.4 ± 0.2	15.6 ± 0.6	18.7 ± 1.2
$\underset{\sim}{2b}$	0.2	6.4 ± 0.07	7.07 ± 0.23	8.37 ± 0.14
$\underset{\sim}{3b}$	0.2	3.78 ± 0.02		6.28 ± 0.47
$\underset{\sim}{4b}$	0.2	8.79 ± 0.04	9.85 ± 0.07	11.3 ± 0.3
$\underset{\sim}{1c}$	0.2	27.5 ± 0.3	29.7 ± 0.2	32.5 ± 0.1
$\underset{\sim}{2c}$	0.2	8.60 ± 0.1	9.90 ± 0.2	11.9 ± 0.1
$\underset{\sim}{3c}$	0.2	6.61 ± 0.07	7.98 ± 0.16	9.14 ± 0.1
$\underset{\sim}{4c}$	0.2	13.2 ± 0.0	14.7 ± 0.3	16.0 ± 0.1
$\underset{\sim}{5}$	0.2	9.78 ± 0.05	10.8 ± 0.2	12.6 ± 0.2

TABLE VI

RELAXATION DATA FOR SYSTEMS $\underset{\sim}{1}-\underset{\sim}{4}$

Cpd.	Conc. (moles/liter)	15°C	T_1 (sec) 25°C	35°C
$\underset{\sim}{1a}$	0.03	27.8 ± 0.4	23.1 ± 0.3	21.1 ± 0.5
$\underset{\sim}{2a}$	0.03	20.2 ± 0.7	23.3 ± 0.2	25.2 ± 0.7
$\underset{\sim}{3a}$	0.03	17.5 ± 0.5	18.8 ± 0.3	20.1 ± 0.4
$\underset{\sim}{4a}$	0.03	15.4 ± 0.2	14.4 ± 0.1	14.0 ± 0.2
$\underset{\sim}{1b}$	0.1	18.9 ± 0.2	19.9 ± 0.6	24.3 ± 1.2
$\underset{\sim}{2b}$	0.1	6.45 ± 0.1	7.45 ± 0.14	9.94 ± 0.45
$\underset{\sim}{3b}$	0.1	5.42 ± 0.05	6.25 ± 0.11	7.03 ± 0.25
$\underset{\sim}{4b}$	0.1	10.4 ± 0.3	11.1 ± 0.3	12.1 ± 0.3
$\underset{\sim}{1c}$	0.1	27.4 ± 0.2	29.7 ± 0.3	32.9 ± 0.2
$\underset{\sim}{2c}$	0.1	9.48 ± 0.06	10.7 ± 0.1	12.2 ± 0.2
$\underset{\sim}{3c}$	0.1	7.15 ± 0.04	8.30 ± 0.08	9.75 ± 0.12
$\underset{\sim}{4c}$	0.1	13.3 ± 0.1	15.7 ± 0.5	16.6 ± 0.3

spin-rotation interaction (SR) and chemical shift anisotropy (CSA) could contribute to the relaxation of the ^{31}P nucleus in the systems investigated.[34] Since none of the molecules examined has a spin quantum number I > 1/2, scalar coupling (SC) mechanism cannot make any contribution to the relaxation phenomena.[7,34] In general, for most of the compounds (under the conditions examined) the relaxation value increased with an increase of temperature. However, for both triphenyl-phosphine (1a) and 1-phenyl-4-phosphorinanone (4a), the relaxation times were found to decrease with increasing temperature, a trend that should be expected if spin-rotation (SR) interaction was the predominant relaxation mechanism.[34] A similar trend was observed by Kooli and co-workers with triethylphosphine and triphenylphosphine in DCCl$_3$ solvent.[27] Usually the SR mechanism plays an important role in small symmetrical molecules (such as in the ^{13}C relaxation process for methane, cyclopropane, etc.) or in small segments of larger molecules (such as in the ^{13}C relaxation in CH$_3$ groups).[34] Hence, it was somewhat surprising that the SR process was the predominant relaxation mechanism for a mole-cule of the size of triphenylphosphine (1a). In the absence of geminal or vicinal protons, the DD interaction cannot be the dominant relaxation mechanism. This consideration and the fact that the molecule possesses an axis of symmetry (passing through the lone pair and phosphorus) may perhaps account for the dominance of the SR mechanism. This result is also in keeping with a similar observation made by Dale

and Hobbs[10] on trimethyl phosphite, a compound with similar symmetry properties as that of triphenylphosphine.

Although the change in T_1 with temperature for 1-phenyl-4-phosphorinanone (4a) was in the same direction as in triphenylphosphine (1a), it was not as significant as in the latter. The presence of neighboring protons H-2 and H-6 may permit the DD mechanism to compete favorably with the SR mechanism in 4a. Also changes in the molecular symmetry in 4a may have diminished the contribution of the SR mechanism. It is quite possible that the combined motion of ring reversal and molecular rotation reduces the tumbling rate of the molecule, with the consequent increase in effective correlation time τ_c. This lengthening of the τ_c value in the region of motional narrowing may account for the improved efficiency of the DD mechanism.[34] While T_1 values decrease with increase in temperature when SR is the predominant mechanism, the opposite behavior is often the result when DD is the dominant mechanism.[34] Since the temperature dependence of these two mechanisms are in the opposite directions, it is conceivable that the decrease in T_1 with increase in temperature (due to SR) is moderated by the opposing trend (due to DD) with a predominance of the SR mechanism as the net result.

Attempts to measure the nuclear Overhauser enhancement (NOE) factor by Eq. (13) often resulted in η values higher than the theoretical maximum of 1.235. The theoretical maximum is related to the gyromagnetic constants of the ^1H

and ^{31}P nuclei according to Eq. (14):

$$\eta = (S_\infty/S_o) - 1 \qquad \text{Eq. (13)}$$

S_∞ = the intensity of the signal with the heteronuclear decoupler turned on during the entire measurement period.

S_o = the signal intensity with the decoupler gated off during a suitable delay period prior to the analytical 90° pulse and gated on during the pulse and the acquisition.

$$\eta = \gamma_H/2\gamma_P = 1.235 \qquad \text{Eq. (14)}$$

The programme GENLSS,[13] which computes η values from Eq. (15) could not be used because this programme is not compatible with the Nicolet TT-100 computer system coupled to a Varian XL-100(15) spectrometer. Hardware is also lacking on this unit to perform an NOE and a non NOE experiment in a rapid alternating manner.

In the absence of NOE measurements, it is not possible to gauge precisely the extent of DD interaction to the over-all relaxation time. As discussed in chapter I, the effectiveness of dipolar relaxation depends in the effective correlation time τ_c $\{T_1 = f(\tau_c)\}$.[34] The temperature dependence of the latter can be written in the form of an Arrhenius type Eq. (16):

$$\tau_c = \tau_{c_o} \exp(\Delta E/RT) \qquad \text{Eq. (16)}$$

where τ_{c_o} = a constant

ΔE = activation energy for molecular

rotational reorientation

The temperature dependence of dipole-dipole relaxation is that of the correlation time. Hence, if DD interaction is the predominant relaxation mechanism, the temperature dependence of relaxation time should also follow an Arrhenius type Eq. (17):

$$T_1 = K \exp(-\Delta E/RT) \qquad Eq. \ (17)$$

where K = a constant

A semilogrithmic plot of relaxation time versus the reciprocal temperature should give a straight line and from the slope of which the activation energy for molecular reorientation can be evaluated. Shown in Figures 1-4 are the plots of the logarithm of the relaxation time versus the reciprocal temperature for those systems where a linear relationship is observed. This suggests that for these systems under the conditions specified, DD is the predominant relaxation mechanism.

Reported in Table V are the activation energies, obtained from the slope of these straight line plots. The ΔE values, for molecules of the size examined, lie in the predictable range of 1-3 kcal/mole.[7] The activation energies seem to correlate reasonably well with the size and shape of the molecules. The relatively small and symmetrical molecule, such as triphenylphosphine sulfide (1c), has a lower
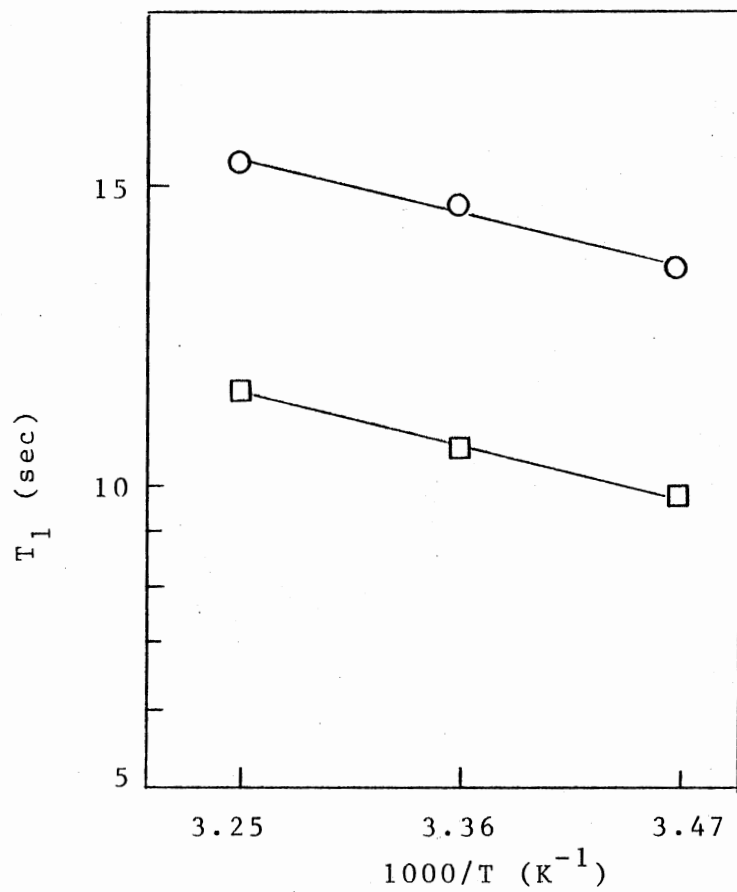
Figure 1. Temperature dependence
of spin-lattice relaxa-
times in 3a and 5.
○ represents 0.05 M 3a;
□ represents 0.2 M 5.
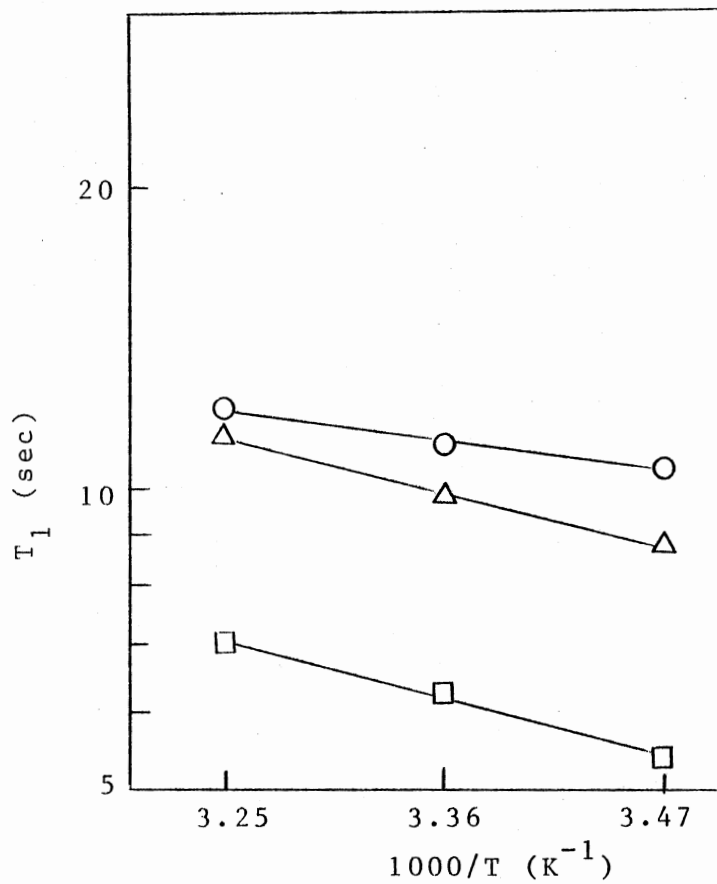
Figure 2. Temperature dependence of
spin-lattice relaxation
times in 3b and 4b.
○ represents 0.1 M 4b;
△ represents 0.2 M 4b;
□ represents 0.1 M 3b.
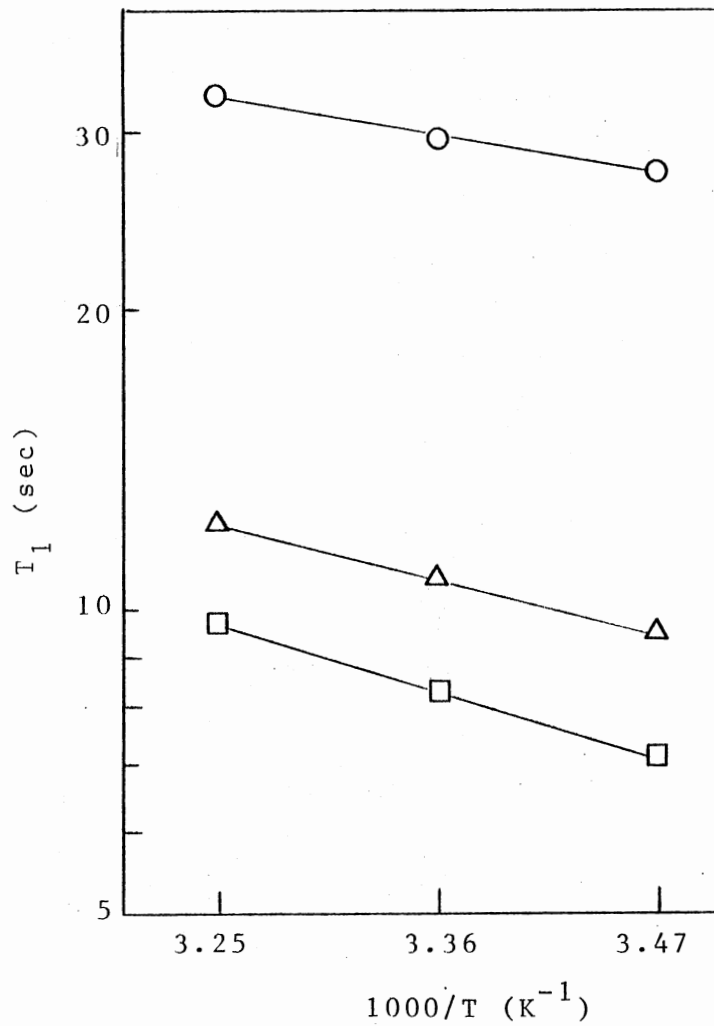
Figure 3.   Temperature dependence of
spin-lattice relaxation
times in 1c, 2c and 3c.
O represents 0.1 M 1c;
△ represents 0.1 M 2c;
□ represents 0.1 M 3c.
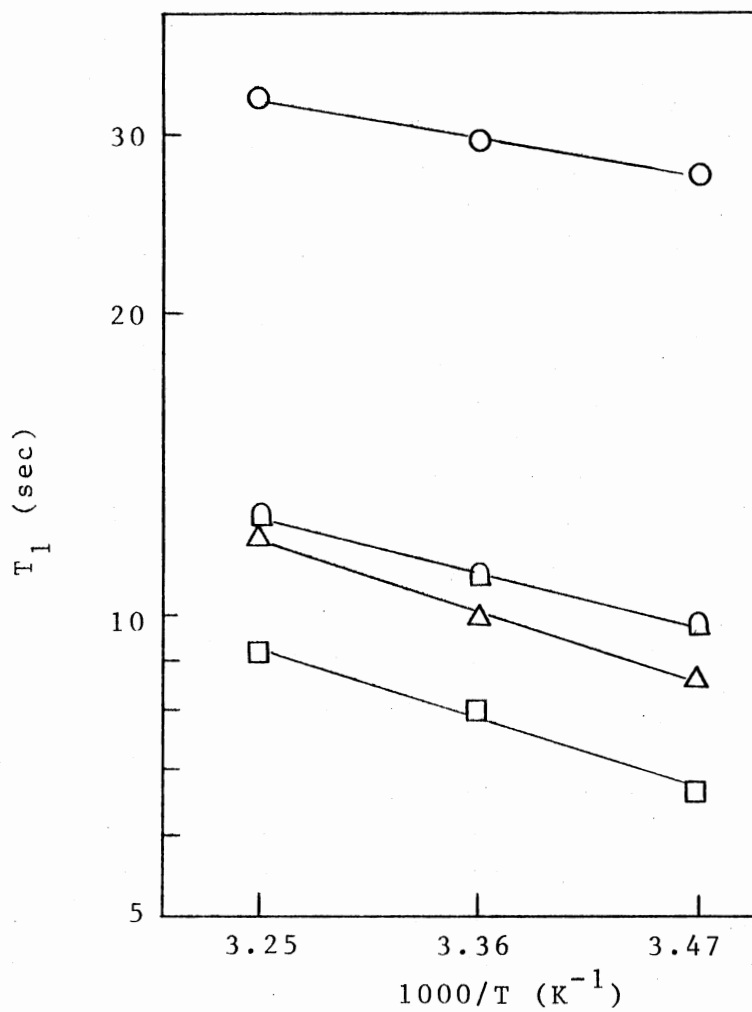
Figure 4. Temperature dependence of
spin-lattice relaxation
times in 1c, 2c, 3c and
4c. O represents 0.2 M
1c. △ represents 0.2 M
2c. □ represents 0.2 M
3c. ⌂ represents 0.2 M
4c.

TABLE VII

ACTIVATION ENERGIES FOR MOLECULAR

ROTATIONAL REORIENTATION

Cpd.	Conc. (moles/liter)[a]	Coefficient of Determination[b]	ΔE (kcal/mole)[c]
3a	0.05	0.988	2.2
3b	0.1	0.997	2.3
4b	0.1	0.994	1.4
1c	0.2	0.998	1.5
2c	0.2	0.994	2.9
3c	0.2	0.991	2.9
4c	0.2	0.995	1.7
1c	0.1	0.995	1.6
2c	0.1	0.999	2.3
3c	0.1	1.000	2.8

[a] Compound 3a is in acetone-d_6 solvent and all other compounds are in $DCCl_3$.

[b] The coefficient of determination corresponds to the plot of $\log T_1$ vs $1/T_1$.

[c] The error limits for the activation energies are $\pm 1\%$ or about 0.02 kcal/mole.

activation energy. This implies that the molecule tumbles rather easily in solution. However, for the less symmetrical and relatively large molecules such as $\underset{\sim}{2c}$, $\underset{\sim}{3a}$, $\underset{\sim}{3b}$ and $\underset{\sim}{3c}$, the activation energies are found to be higher. The rotational reorientation of these larger molecules in solution probably requires a major reorganization of the solvent molecules in the solvent cage. In comparison with the molecules just cited, phosphorinanones $\underset{\sim}{4b}$ and $\underset{\sim}{4c}$ are smaller and more compact, and this is reflected in the lower activation energies for these molecules. Comparing the oxides $\underset{\sim}{3b}$ and $\underset{\sim}{4b}$ with the corresponding sulfides $\underset{\sim}{3c}$ and $\underset{\sim}{4c}$, the lower molecular weight oxides have lower activation energies as is reasonable. The T_1 values for phosphorinanones $\underset{\sim}{4}$ are the first ever recorded for the family.

Illustrated in Figures 5-10 is the influence of structure and temperature on the T_1 values of phosphines $\underset{\sim}{1a}$-$\underset{\sim}{3a}$, phosphine oxides $\underset{\sim}{1b}$-$\underset{\sim}{3b}$ and phosphine sulfides $\underset{\sim}{1c}$-$\underset{\sim}{3c}$, each system being examined at two different concentrations and three different temperatures. For both the sulfides and oxides, the change in structure from $(C_6H_5)_3X$ to $(C_6H_5)_2XCH_2X(C_6H_5)_2$ resulted in a large decrese in the T_1 values at all the temperatures and concentrations investigated. This is in keeping with our previous conclusion regarding the relaxation mechanism in sulfides. It may be recalled that sulfides relax predominantly by the DD mechanism. The presence of geminal protons has been shown[34] to improve the efficiency of DD interaction in ^{13}C relaxation.
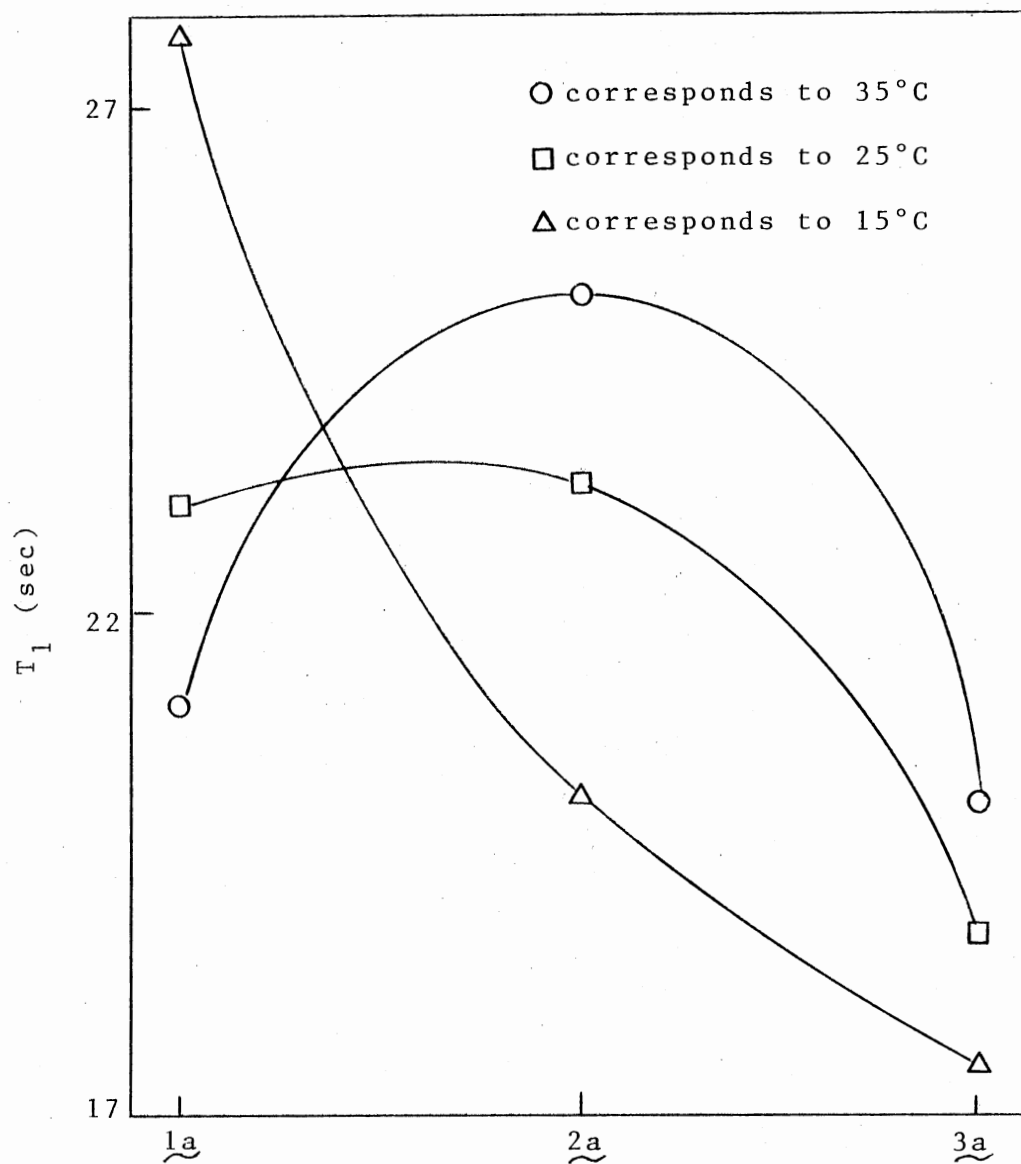
Figure 5. T_1 vs Structure for the phosphines 1a, 2a and 3a at 0.03 M.
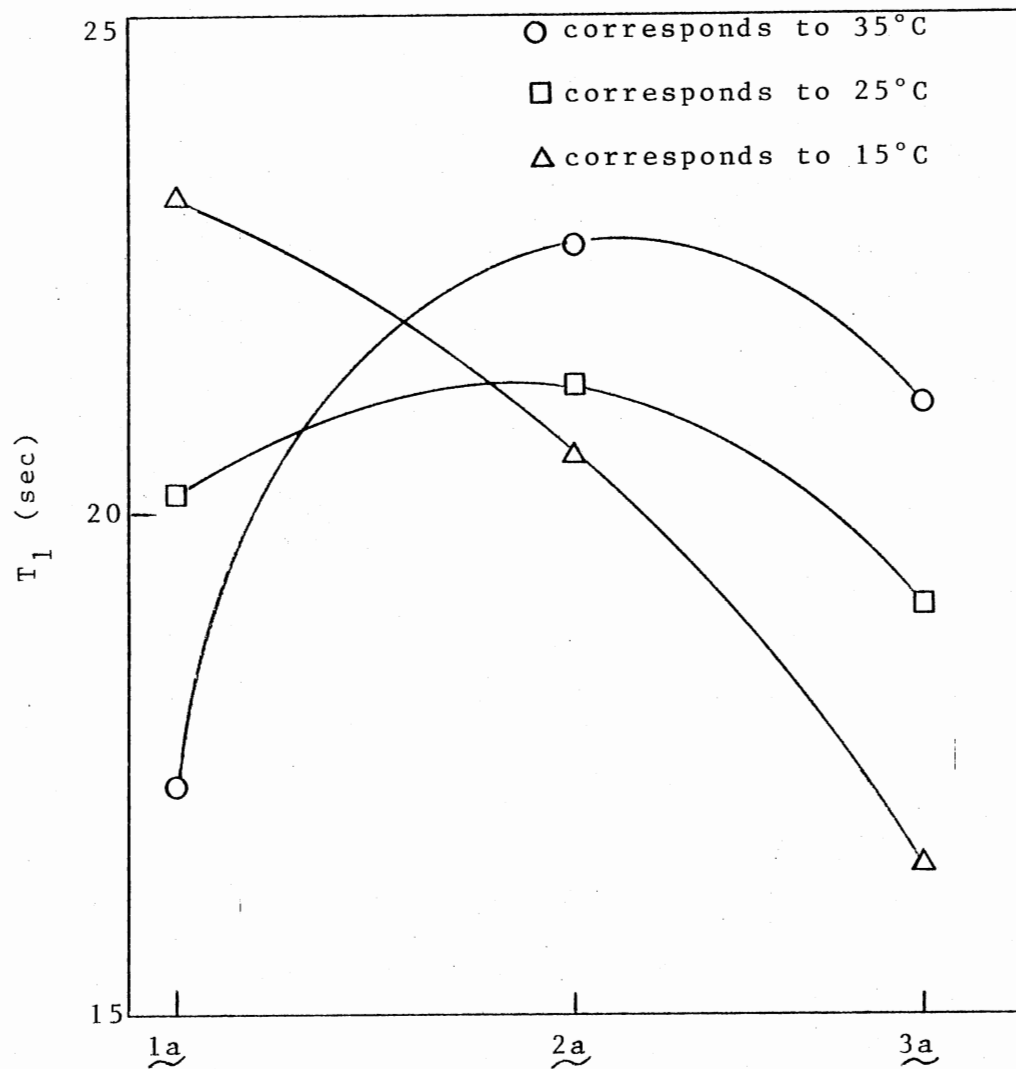
Figure 6. T_1 vs Structure for the phosphines 1a, 2a and 3a at 0.05 M.
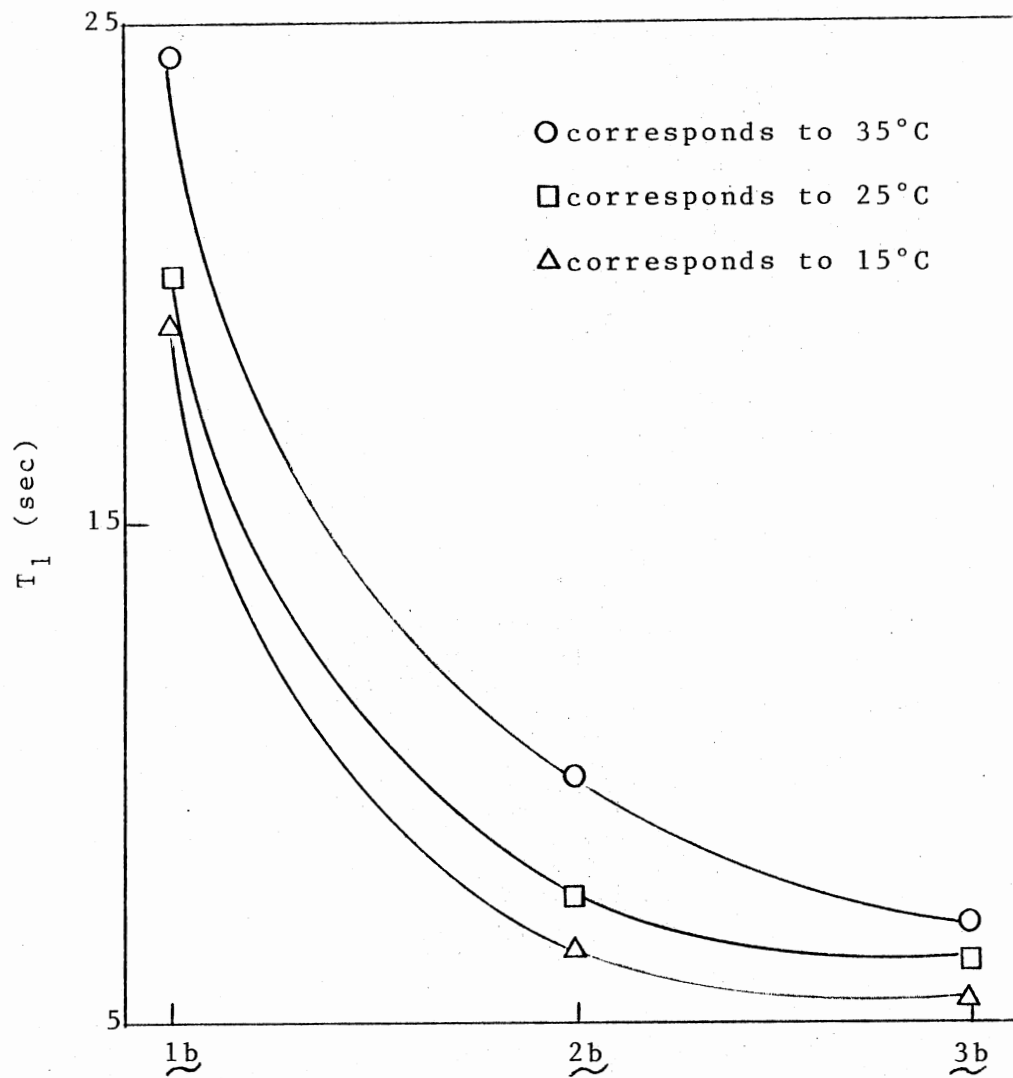
Figure 7. T_1 vs Structure for the phosphine oxides 1b, 2b and 3b at 0.1 M.
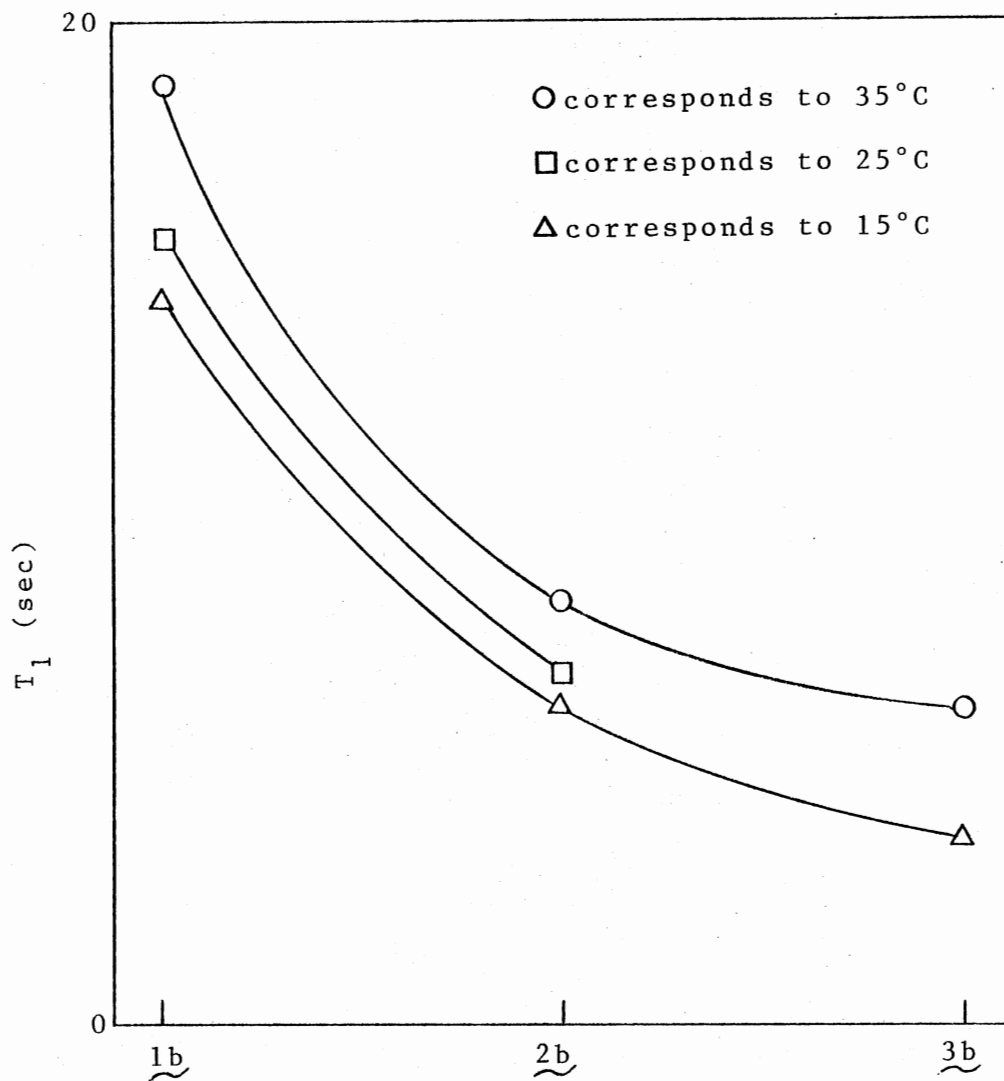
Figure 8. T_1 vs Structure for the phosphine oxides
1b, 2b and 3b at 0.2 M.
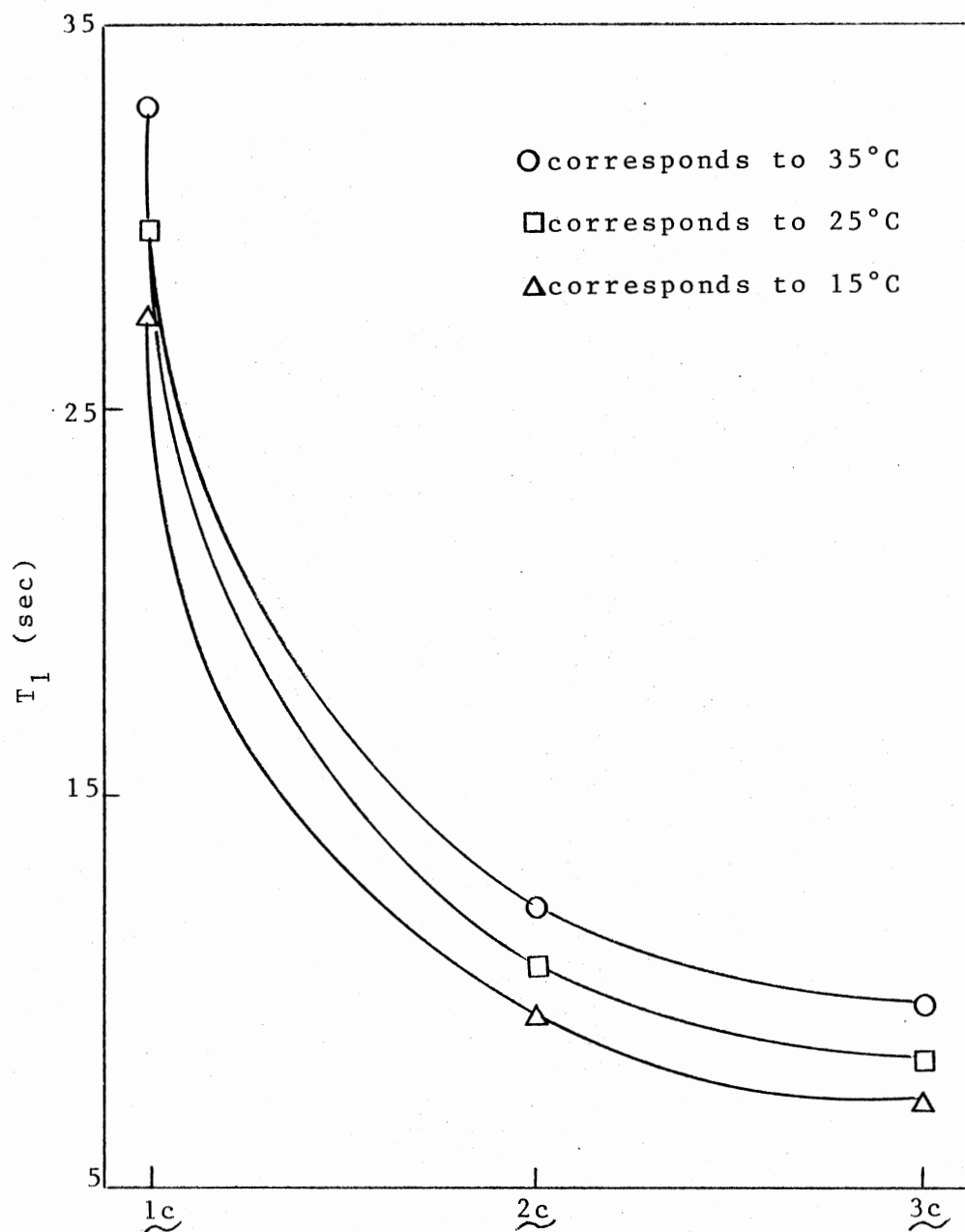
Figure 9. T_1 vs Structure for the phosphine sulfides 1c, 2c and 3c at 0.1 M.
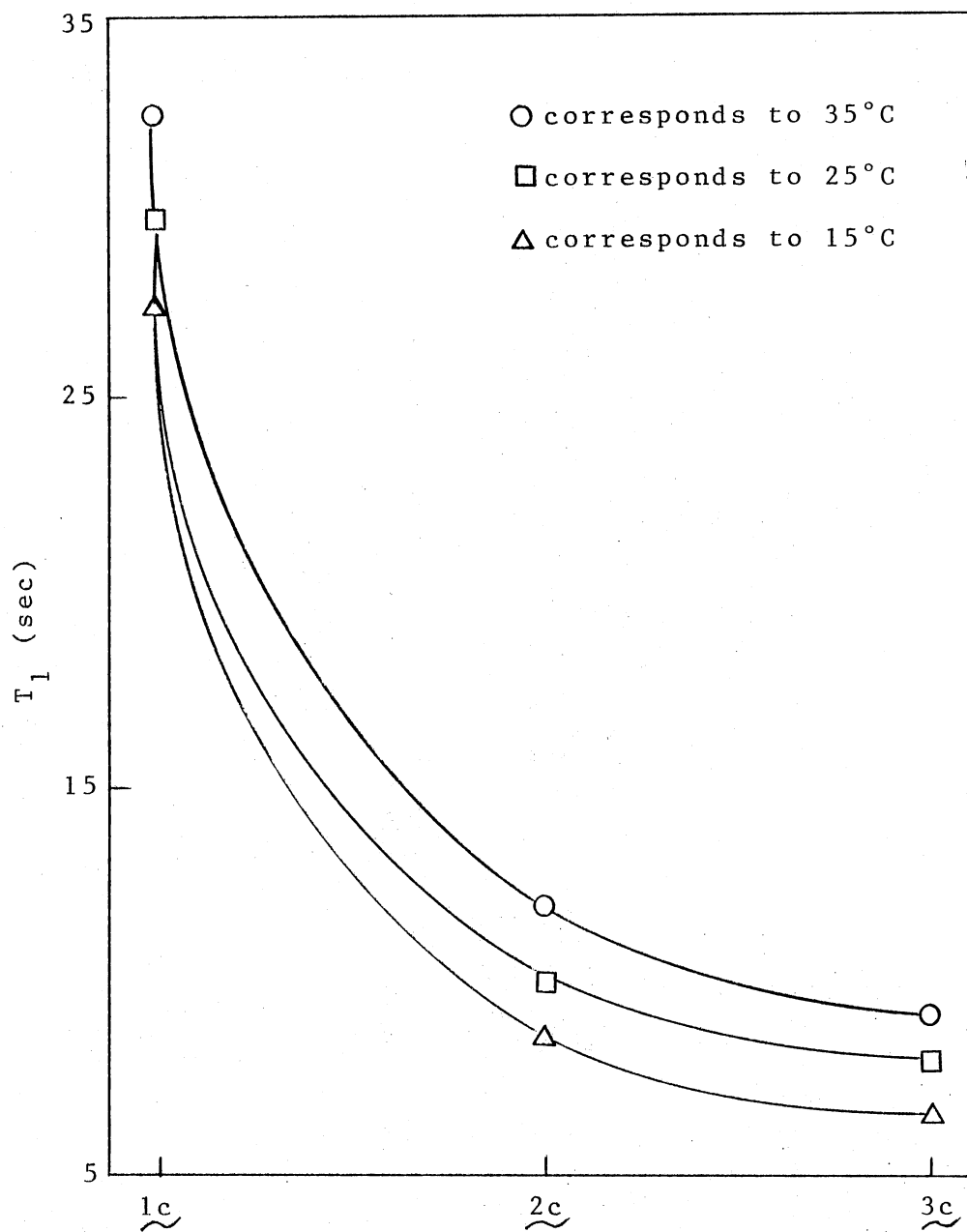
Figure 10. T_1 vs Structure for the phosphine sulfides 1c, 2c and 3c at 0.2 M.

A similar effect may be expected for the ^{31}P relaxation process. In the absence of geminal protons, the vicinal protons could offer substantial assistance for the relaxation process via a DD interaction. This probably explains the considerable decrease in T_1 values for the sulfides in going from 1c to 2c. A similar large decrease in the T_1 values for the corresponding oxides indicates a significant contribution from DD for the relaxation of these molecules. Introduction of a second CH_2 group, as in going from $(C_6H_5)_2XCH_2X(C_6H_5)_2$ to $(C_6H_5)_2XCH_2CH_2X(C_6H_5)_2$, resulted in a further decrease in T_1 values under all the conditions examined. This observation again suggests a predominant (for sulfides) or significant (for oxides) contribution of DD in the relaxation process.

For the phosphines, however, a change from $(C_6H_5)_3P$ (1a) to $(C_6H_5)_2PCH_2P(C_6H_5)_2$ (2a) relulted in an increase in T_1 at both 35°C and 25°C for the two concentrations investigated. It has already been cited that triphenylphosphine relaxed predominantly by the SR mechanism. It is possible that in the system, bisdiphenylphosphinomethane (2a) both SR and DD interactions make substantial contributions to the relaxation process. However, since the T_1 values in the latter system were observed to increase with increase in temperature, it is probable that the influence of the SR process is outweighed by that of DD. Since SR may not be as efficient in the less symmetric bisdiphenylphosphinomethane (2a) compared to the more symmetric triphenylphosphine, the above mentioned

results for 2a are observed. In comparing 2a with 3a, a decrease in T_1 was observed for all the three temperatures and the two concentrations examined. This suggested a large DD contribution. At 15°C, however, there was a monotonous decrease in T_1 in going from 1a to 3a for both the concentrations. At this lower temperature, the molecules apparently tumbled rather slowly in solution. The slower tumbling probably increased the effective rotational correlation time and thereby improved the efficiency of DD interaction.

At every temperature and concentration examined, the phosphine oxides were found to have lower T_1 values compared to those of the sulfides. If the oxides and sulfides relaxed by the same mechanism, the relatively heavier sulfides, tumbling rather slowly in solution (as is evident from the activation energies for rotational reorientation) should be more efficiently relaxed. However, the contrary was observed. The lower T_1 values for the oxides suggested that a different mechanism was operating in the case of the oxides. Kooli and co-workers[27] concluded that in the case of triphenylphosphine oxide (1b) the results of their investigation were consistent with the operation of a CSA mechanism. The presence of a CSA mechanism has also been noted in some phosphoryl compounds[10] containing P=O bond. It is probable this mechanism was dominant in all the oxides examined in our work. Presumably, the P=O bond disturbed the isotropic electron distribution around the ^{31}P nucleus, resulting in substantial values for the anisotropy tensor.

Lowering the concentration resulted in an increase in T_1 values for both the sulfides and the oxides at all the three temperatures studied. It is probable that lowering the concentration reduced constraints on molecular tumbling and increased tumbling rate. This would result in a lower value for the effective rotational correlation time and consequently would reduce the efficiency of DD contribution. The effect of concentration on the relaxation times of phosphines was found to be irregular.

Compared to triphenylphosphine sulfide (1a) and triphenylphosphine oxide (1b), the salt methyltriphenylphosphonium iodide (5) had a lower T_1 value at each of the three temperatures examined. This may partly be due to the presence of nearby protons in the CH_3 group. However, a more important consideration may be the formation of ion-pairs in solution.[27] As a result of ion-pair formation the tumbling rate of the phosphonium ion could be restricted and consequently the effective correlation time should increase. This increase in τ_c in the region of motional narrowing could account for the improved efficiency of the DD mechanism.

Thus, the T_1 values of ^{31}P in four classes of phosphorus compounds show a pattern of behavior similar to the T_1 values of ^{13}C nuclei. The presence of geminal or vicinal protons assists in the relaxation process. A decrease in viscosity or an increase in temperature, in general, increases the T_1 values. Any modification in the size and geometry

of the molecule that increaes τ_c resulted in a more efficient relaxation process and smaller T_1 values.

Error Analysis

The activation energies were evaluated using Eq. (17):

$$T_1 = K \exp(-\Delta E/RT) \qquad \text{Eq. (17)}$$

Eq. (17) yields the following formula for the relative error in ΔE, where σ_T and σ_{T_1} are the errors associated with T and T_1 respectively.

$$(\sigma_{\Delta E}/\Delta E)^2 \simeq \{\partial(\Delta E)/\partial T\}^2 \, (\sigma_T/\Delta E)^2 + \{\partial(\Delta E)/\partial T\}^2 \, (\sigma_{T_1}/\Delta E)^2$$

Substituting for the partial derivatives of ΔE with respect to T and T_1 and simplifying, we get Eq. (19):

$$(\sigma_{\Delta E}/\Delta E)^2 \simeq (\sigma_T/T)^2 + 1/\{\ln(k/T_1)\}^2 \, (\sigma_{T_1}/T_1)^2 \qquad \text{Eq. (19)}$$

At the temperatures at which the T_1 measurements are made, an error of 3°C introduces an error of only 1% in ΔE.

PLATE 1

τ (sec)
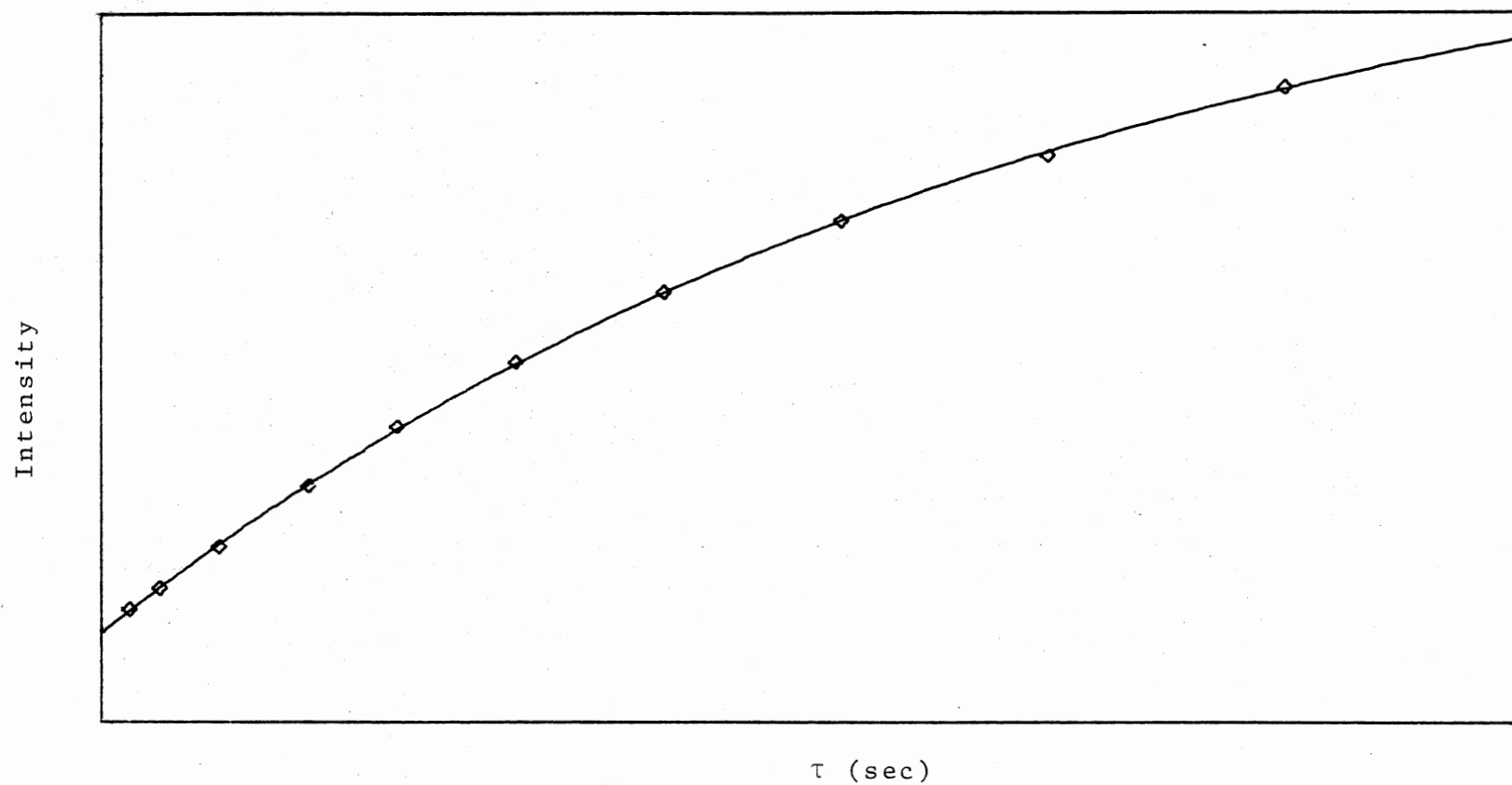
Signal intensity vs τ for the relaxation of ^{31}P nucleus in 0.2 M triphenyl-
phosphine sulfide (1c), at 35°C.

PLATE II

τ (sec)
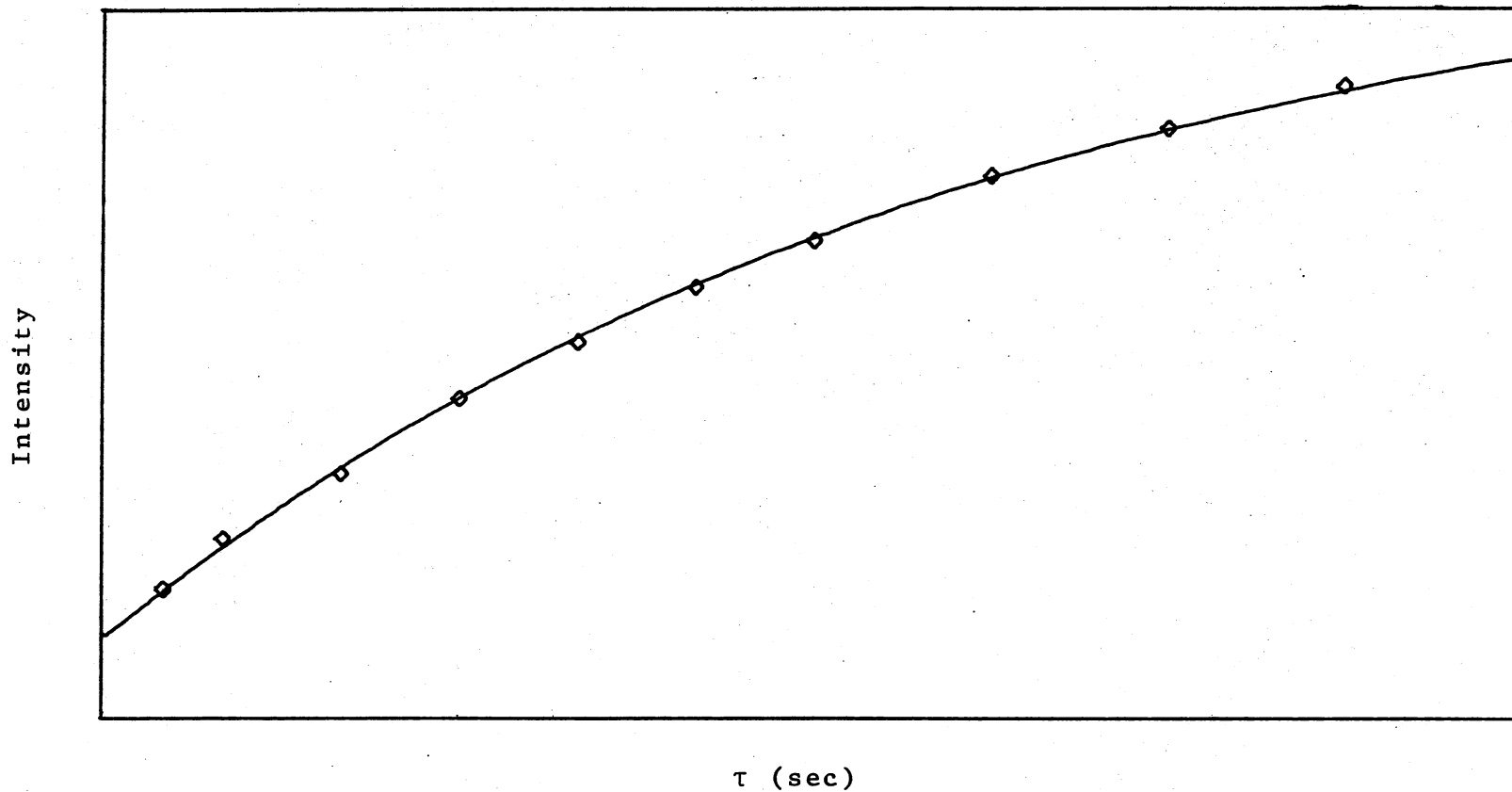
Signal intensity vs τ for the relaxation of ^{31}P nucleus in 0.1 M triphenyl-
phosphine sulfide (1c), at 25°C.

CHAPTER III

EXPERIMENTAL

GENERAL INFORMATION

All T_1 measurements were made on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 40.5 MHz for ^{31}P observation. The spectra were recorded in an FT mode with the solvent (DCCl$_3$ or acetone-$\underline{d}_6$) providing the necessary deuterium lock. The solvent DCCl$_3$ (99.8 atom% D) and acetone-$\underline{d}_6$ (99+ atom% D) were obtained from Aldrich Chemical Company. All solutions were flushed with dry, oxygen-free nitrogen for 5 minutes. The samples were then degassed by repeated (at least 5 times) freezing, evacuation and thawing. The tubes were finally sealed under vacuum with a hand torch. A Varian temperature regulator was used for temperature control during the NMR experiments. A sealed capillary filled with methanol and a trace of HCl placed in a 5 mm NMR tube containing 0.5 mL acetone-$\underline{d}_6$ was used as a check to measure the temperature according to the method of Van Geet.[49] The fast inversion recovery Fourier transform method recommended by Canet and co-workers[9] was used for all the T_1 measurements. A waiting period ranging from 1 sec upto 1.5 to 2 T_1, as suggested by Kowalewski and

co-workers,[29] was allowed between the 180° and 90° pulses.
A minimum of nine experimental points were used for each
measurement.   A trial run at 35° ± 1°C preceded the regular
measurement of T_1 values for all the sample.   At least two
and upto four separate measurements were made for each con-
centration at each of the three different temperatures.
The temperature chosen for this investigation being 35°C,
25°C and 15°C.   The 180° and 90° pulses were obtained with
pulse widths of 24μs and 12μs, respectively.   A waiting
period of 200μs was allowed after the 90° pulse before the
data acquisition commenced.   A non-linear, three-parameter
expression, Eq. (10) was used to evaluate T_1 values from the
experimental points.[43]

   Triphenylphosphine (1) was obtained commercially from
Eastman Organic Chemicals and purified by recrystallization
from pentane containing a minimum amount of benzene,
mp 80-81°C {lit.[48] mp 79°C}.

   Bis(diphenylphosphino)methane (2) was obtained from
Pressure Chemical Company and was used as such.   The compound
melted at 119-120°C and gave only one signal (23.1 ppm with
respect to 85% H_3PO_4) in the ^{31}P NMR spectrum {lit.[25]
mp 122°C}.

   Ethylenebis(diphenyl)phosphine (3) was obtained commer-
cially from Arapahoe Chemicals and melted at 138-139°C
{lit.[25] mp 159-161°C}.

   Triphenylphosphine sulfide (4) was obtained from
Aldrich Chemical Company and was used as such.   The compound

melted at 162-164°C {lit.[43] mp 163°C}. The ^{31}P NMR spectrum of the compound gave a single signal at -39.9 ppm.

Triphenylphosphine oxide (5) was obtained from Aldrich Chemical Company and was purified by recrystallization from petroleum ether containing a minimum amount of benzene, mp 156-157°C {lit.[47] mp 154-155°C}. The ^{31}P NMR spectrum gave a signal at -23.0 ppm.

Preparation of 1-Phenyl-4-phosphorinanone (6)

1-Phenyl-4-phosphorinanone (6) was made following the literature procedure.[45] Recrystallization (cyclohexane:n-hexane, in 3:1) and subsequent drying over P_2O_5 to constant weight gave pure 1-phenyl-4-phosphorinanone (6), mp 43°C {lit.[37,40,52] mp 42.5-43.5°C}.

Preparation of Methylenebis(diphenyl)-phosphine Oxide (7)

Bis(diphenylphosphino)methane (2a) (3.0 g, 0.0078 mole) dissolved in 75 mL of benzene was placed in a 250 mL, Erlenmeyer flask equipped with a magnetic stirrer. The solution was cooled to 0°C. To the cooled solution was added dropwise, with stirring, a solution of m-ClC$_6$H$_4$CO$_3$H (4.0 g, 0.023 mole) in 20 mL of ether, maintaining the temperature at 0°C. After the addition, the reaction mixture was stirred for 30 min at 0°C and 15 hr at room temperature. The reaction mixture was then washed with 3 x 50-mL portions

of 10% NaHCO$_3$ solution, dried (MgSO$_4$), and filtered; the solvent was removed by rotary evaporation. The crude solid was recrystallized from 1:1 acetone and benzene mixture to yield 1.0 g (31%) of 7, mp 181-183°C {lit.[44] mp 181-182°C}.

<div align="center">

Preparation of 1,2-Ethanediylbis-

(diphenyl)phosphine Oxide (8)

</div>

Ethylenebis(diphenylphosphine) (3a) (4.0 g, 0.01 mole) dissolved in 75 mL of benzene was placed in a 250 mL, Erlenmeyer flask equipped with a magnetic stirrer. The solution was cooled to 0°C. To the cooled solution was added, dropwise, with stirring, a solution of m-ClC$_6$H$_4$CO$_3$H (4.5 g, 0.026 mole) in 20 mL of ether, maintaining the temperature at 0°C. After the addition, the reaction mixture was stirred for 30 min at 0°C and 15 hr at room temperature. The rest of the procedure was the same as for the preparation of 7. The crude solid was recrystallized (acetone:benzene, in 1:1) to yield 1.2 g (28%) of 8, mp 265-266°C {lit.[28] mp 276-278°C}.

<div align="center">

Preparation of 1-Phenyl-4-phosphorinanone

1-Oxide (9)

</div>

1-Phenyl-4-phosphorinanone 1-oxide (9) was prepared following the literature procedure,[49] mp 164-165°C {lit.[50] mp 164-165°C}.

Preparation of Methylenebis(diphenyl)-

phosphine Sulfide (10)

Bis(diphenylphosphino)methane (3a) (4.0 g, 0.0104 mole)
dissolved in 100 mL of reagent grade toluene was placed in a
250-mL, round-bottom flask equipped with a condenser, a
nitrogen inlet and a magnetic stireer. To this solution was
added 1.0 g (0.0313 g at) of sulfur, and the mixture was
boiled for 15 hr. At the end of this period, the mixture
was cooled and filtered and the solvent was removed (rotary
evaporation). The crude yellowish residue was recrystallized
(metahnol and benzene, in 1:1). A second recrystallization
from acetonitrile and subsequent drying over P_2O_5 gave 3.0 g
(64%) of a pure colorless crystalline 10, mp 174-176°C
{lit.[11] mp 175-176°C}.

Preparation of 1,2-Ethanediylbis(diphenyl)-

phosphine Sulfide (11)

Ethylenebis(diphenyl)phosphine (3a) (4.0 g, 0.01 mole)
dissolved in 100 mL of reagent grade toluene was placed in
a 250-mL, round-bottom flask equipped with a condenser,
nitrogen inlet and a magnetic stirrer. To this was added
1.0 g (0.0313 g at) of sulfur and the mixture was boiled for
15 hr. The remaining steps were identical to those used for
10. Recrystallization (methanol:chloroform, in 3:1) of the
crude yellow solid and drying the resulting sample over P_2O_5
at 110°C for 5 hr gave 2.1 g (45%) of pure, colorless 11,

mp 228-229°C {lit.[25] mp 196-198°C}.

Preparation of 1-Phenyl-4-phosphorinanone
1-Sulfide (12)

1-Phenyl-4-phosphorinanone 1-sulfide was made following the literature procedure,[50] mp 144-145°C {lit.[50] mp 144-145°C}.

Preparation of Methyltriphenyl-
phosphonium Iodide (13)

Triphenylphosphine (1a) (2.62 g, 0.01 mole) and methyl iodide (2.84 g, 0.02 mole) were dissolved in 5 mL of reagent grade benzene. The mixture was stirred at room temperature for 15 hr. The solid formed was recrystallized by dissolving in a minimum amount of reagent grade methanol and adding dry ether to give 3.2 g (80%) of 13, mp 185-186°C {lit.[3] mp 186°C}.

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                      THIASPIRO[4.5]DECAN-8-ONE

           Part II.   AN INVESTIGATION OF THE SPIN-LATTICE
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