DNMR STUDY OF THE THERMODYNAMIC AND KINETIC

PARAMETERS ASSOCIATED WITH THE RING

REVERSAL OF A SPIRO SYSTEM CON-

TAINING AN α-METHYLENE-γ-

BUTYROLACTONE RING

By

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CHAPTER I

HISTORICAL

Structure and Activity of Selected Natural
Products Containing an α-Methylene-γ-
butyrolactone Ring

More than 500 different sesquiterpene lactones have been isolated
over the last two decades and many have shown a wide range in degree
and type of biological activity.[79] From a variety of systems uncovered
the highest level of biological activity has been displayed by those
with the α-methylene butyrolactone unit. While most of these units
have been part of a large carbocyclic skeleton, the simplest α-methylene
lactone structure isolated from a plant source was tulipalin A (1a).[5,88]
This compound and the hydroxy homolog tulipalin B (1b) may have as
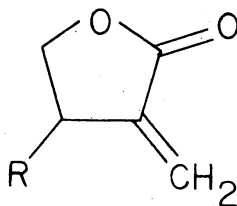
$$\underset{\sim}{1a} \; R = H; \quad \underset{\sim}{1b} \; R = OH$$

precursors in the tissue of young tulips the glucosides tuliposide A
(2a) and tuliposide B (2b) which degrade to the lactones.[5] Lactones 1a
and 1b have been shown to be a fungitoxic component from the skin of
the young tulip, which may be a factor in the prevention of fungal
infections.[5]

$$\underset{\sim}{2a} \ R = H; \quad \underset{\sim}{2b} \ R = OH$$
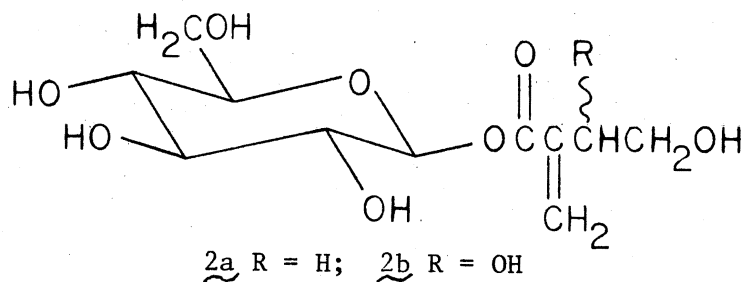
In 1959, S. M. Kupchan and co-workers began to screen the crude extracts of a variety of plants available in the vicinity of the University of Wisconsin at Madison and from cooperative sources outside the United States with the expectation that a few active components might have potential use as antitumor agents.[59] This "modest" beginning led to the isolation and identification of over sixty active compounds. Included in these compounds were several sequiterpene α-methylene lactones which displayed a considerable degree of cytotoxicity against certain KB cell lines. Two sesquiterpene dilactones, elephantin (3) and elephantopin (4), were isolated from the plant <u>Elephantopus</u> <u>elatus</u> Bertol, family <u>Compositae</u>, and were shown to be very active against

$$\underset{\sim}{3} \ R = \ \overset{O}{\overset{\|}{-C}}-CH=C(CH_3)_2; \quad \underset{\sim}{4} \ R = \ \overset{O}{\overset{\|}{-C}}\overset{CH_2}{\overset{\|}{-C}}-CH_3$$
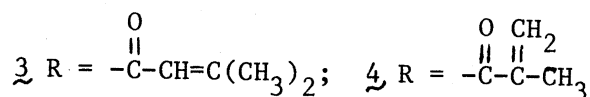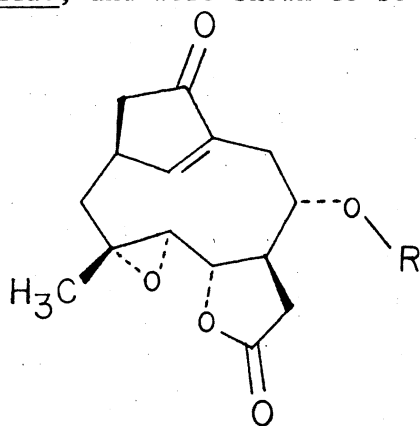
Walker intramuscular carcinosarcoma 256.

Three novel, halogen-containing sesquiterpene lactones (the first

halogen sesquiterpenes ever isolated) were extracted along with five

other active lactones from the plant Eupatorium rotundifolium L., also

of the family Compositae.[62] While all eight lactones showed cytotox-

icity against a KB cell line, only euparotin acetate (5) and eupachlorin

acetate (6) were tested in vivo and were shown to be active [T/C = 23

for 75 mg/kg and 42 for 400 mg/kg, respectively; where T/C = weight of

the tumor in the test animal/weight of the tumor in the control] against

Walker 256.[62] All eight of the isolated lactones contained the same

basic guaianolide 7 carbocyclic backbone with the α-methylene-γ-

butyrolactone unit present in each molecule.

5

6

7
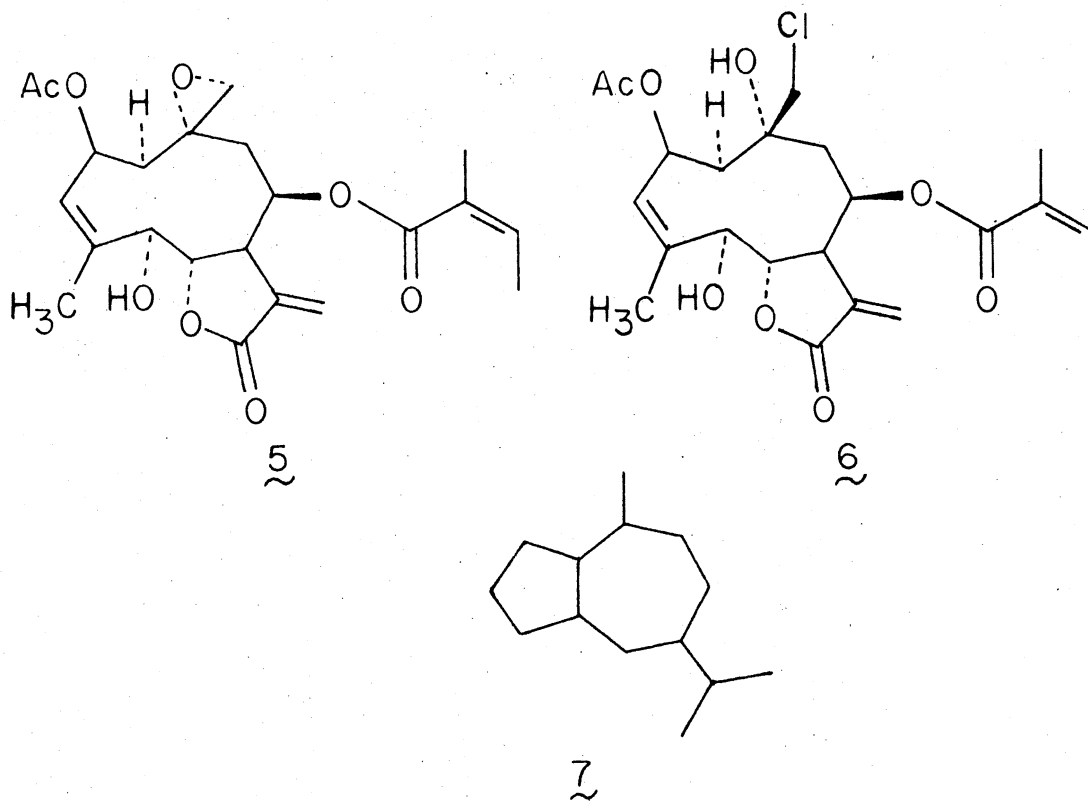
The dilactones vernolepin (8) and veromenin (9) were isolated from

the plant Veronia hymenolepus A. Rich. and differ only in the position
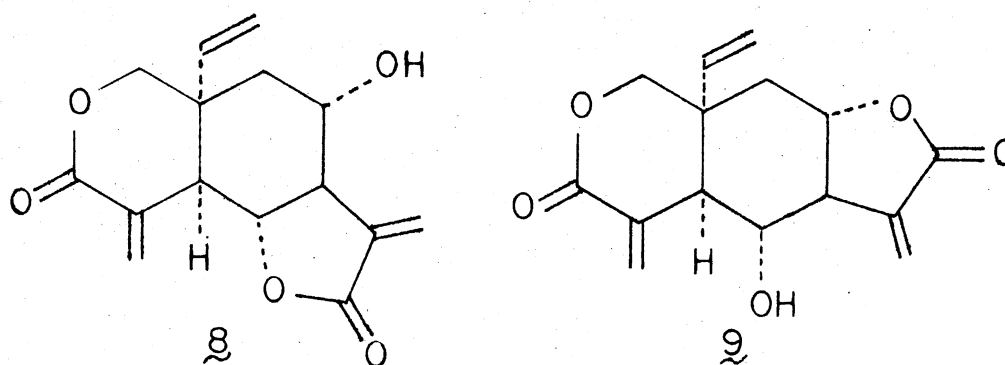
of the γ-lactone ring.[61] These compounds are novel in that they con-

tain both a γ- and δ-lactone unit with an α-methylene group. Later

studies of the reactivity of 8 with model biological nucleophiles

revealed the α-methylene-γ-butyrolactone probably was the reactive

moiety.[59] For example, the reactivity of 8 with amino acid cysteine

was facile but in contrast, lysine or guanine were very slow to

react.[59,82] Nevertheless, the action of the lactone _in vivo_ could

involve a cysteine unit as a coreactant.

Of all the many sesquiterpene lactones isolated to date, the

majority have come from the extracts from the species of the family

Compositae. Structural relationships between compounds isolated from

two different plants within a tribe have been suggested as a means to

screen certain classifications.[29] The similarity in structure of ses-

quiterpene lactones found within a plant tribe has thus been linked to

a human allergenic response to the members in the tribe, and, in each

case, an α-methylene lactone was indicated as the active unit.[79]

Current research directed primarily toward investigating possible

chemotaxonomic classification of species has resulted in the isolation

of several new α-methylene lactones.[9] This strongly suggests that

attempted isolation of these compounds as potential antitumor agents

should be concentrated within a certain species. This is especially true when compounds obtained from members of a species show specific antitumor activity since the basic carbocyclic structure (eg. 7) appears to remain essentially unchanged for compounds isolated from a particular species. Functional groups attached to the periphery of the basic structure may change (eg. 5 and 6) and could alter the activity in a very positive manner, as exemplified by the different activities of compounds 5 and 6.[62] A recent study suggested that synthetic modifications of certain natural products may be a viable way of producing quantities of less available lactone-containing chemicals.[69]

It is also intriguing to note that α-methylene-γ-aminobutyric acid (10), the decarboxylation produce of α-methyleneglutamic acid (11), has
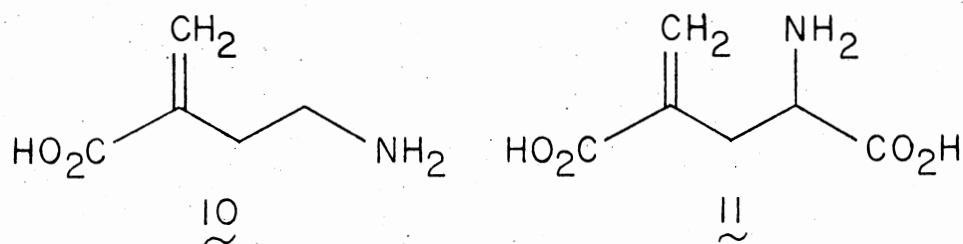
been isolated from plant sources.[23,38] These compounds were also reported to have been isolated from tulips.[23] One can easily envision the closure of α-methylene-γ-aminobutyric acid to the five-membered lactam (12), the nitrogen analog of compound 1a. Since 1a is stored
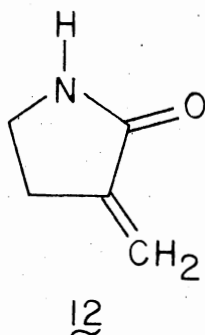
in the tulip as the glucoside, it is not unreasonable that $\underset{\sim}{12}$ might
also exist as the glucoside. The fact that this glucoside has not been
isolated may not be surprising considering the reported ease by which
the glucoside bond is broken in the case of $\underset{\sim}{2a}$.[5,88] Amazingly, no
large scale attempts have been made to isolate or synthesize α-methyl-
ene-γ-butyrolactams with the intent to examine cytotoxicity in spite
of the obvious similarity to the α-methylene-γ-butyrolactones.

<div align="center">

Synthesis of Selected Compounds Containing

an α-Methylene-γ-butryolactone Ring

</div>

The biological activity of the many natural products in which the
active unit is an α-methylene-γ-butyrolactone ring has prompted an
intense effort to synthesize a wide range of compounds with this group
as a major unit.[27,31] While it is beyond the scope of this discussion
to present a review of the literature in this area, a few of the many
synthetic techniques will be presented as examples of the variety of
approaches applied to the problem.

One general method of synthesizing the α-methylene-γ-butyrolactone
unit has involved the formation of the α-methylene group on a preformed
butyrolactone synthon. A recent synthesis of tulipalin A (α-methylene-
γ-butyrolactone, $\underset{\sim}{1a}$) clearly demonstrated this approach.[43] The simple
lactone $\underset{\sim}{13}$ was converted to $\underset{\sim}{14}$ via standard techniques. The sodium
salt $\underset{\sim}{14}$ was then reductively aminated with sodium cyanoborohydride to
give $\underset{\sim}{15}$, which was then quaternized with methyl iodide. Treatment of
the quaternary ammonium salt with aqueous $NaHCO_3$ effected an elimina-
tion of trimethylamine to give $\underset{\sim}{1a}$ (70%).
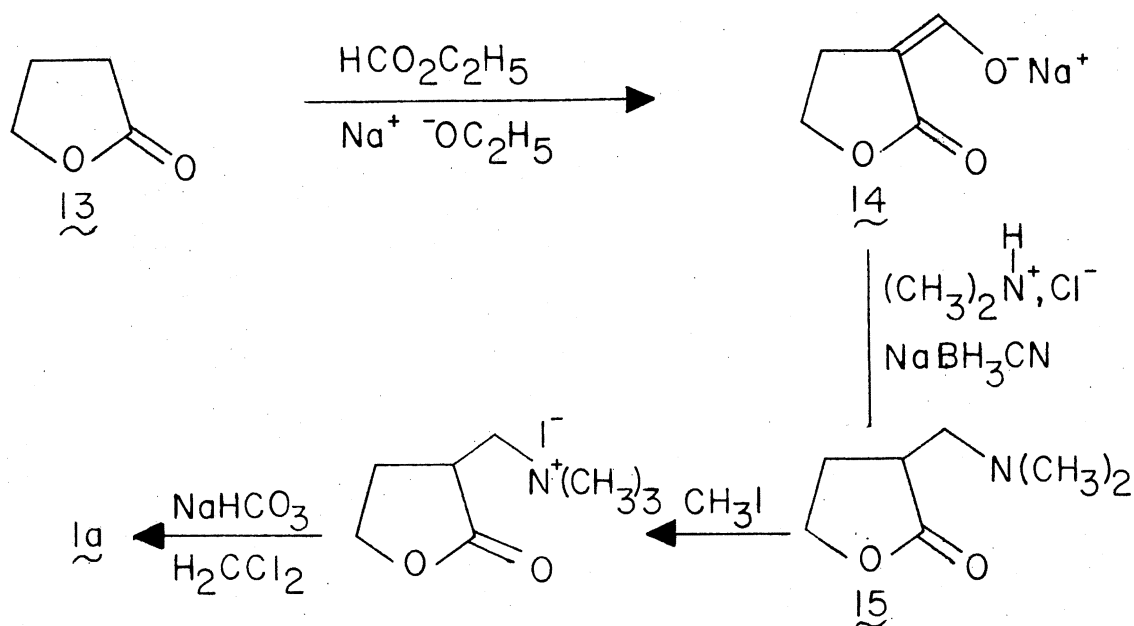
Because of the high reactivity of the α-methylene-γ-butyrolactone unit, the creation of the α-methylene group is often left to the latter part of a synthesis, especially if it is lengthy. Grieco and coworkers in the elegant synthesis of (±)-vernolepin (8)[33] employed a bis-α-hydroxymethylation procedure which was ultimately followed by mesylation of the tetrahydropyranyl (THP) ether 16 in pyridine at 5°C. The resulting bismesylation product 17 was added to a benzene solution of diazabicyclo[5.4.0]undec-5-ene (DBU) which promoted elimination. Hydrolysis of the THP ether yielded (±)-vernolepin (8).

In the synthesis of (+)-costunolide (21), Grieco and Nishizawa[32] formed the methylene group using selenenylation of lactone 18 to give seleneylated lactone 19. This product underwent oxidative elimination to 20, which suffered thermolysis in a GLC column to yield (+)-costunolide (21).

16

H₃COSO₂Cl
Pyridine/14 h/5°C

17

8

1. DBU/Benzene/RT
2. 60% HOAc/45°C
3 h

18

LDA/PhSeSePh
HMPA/THF/-78°C

19

30% H₂O₂
THF

21

200°C

20
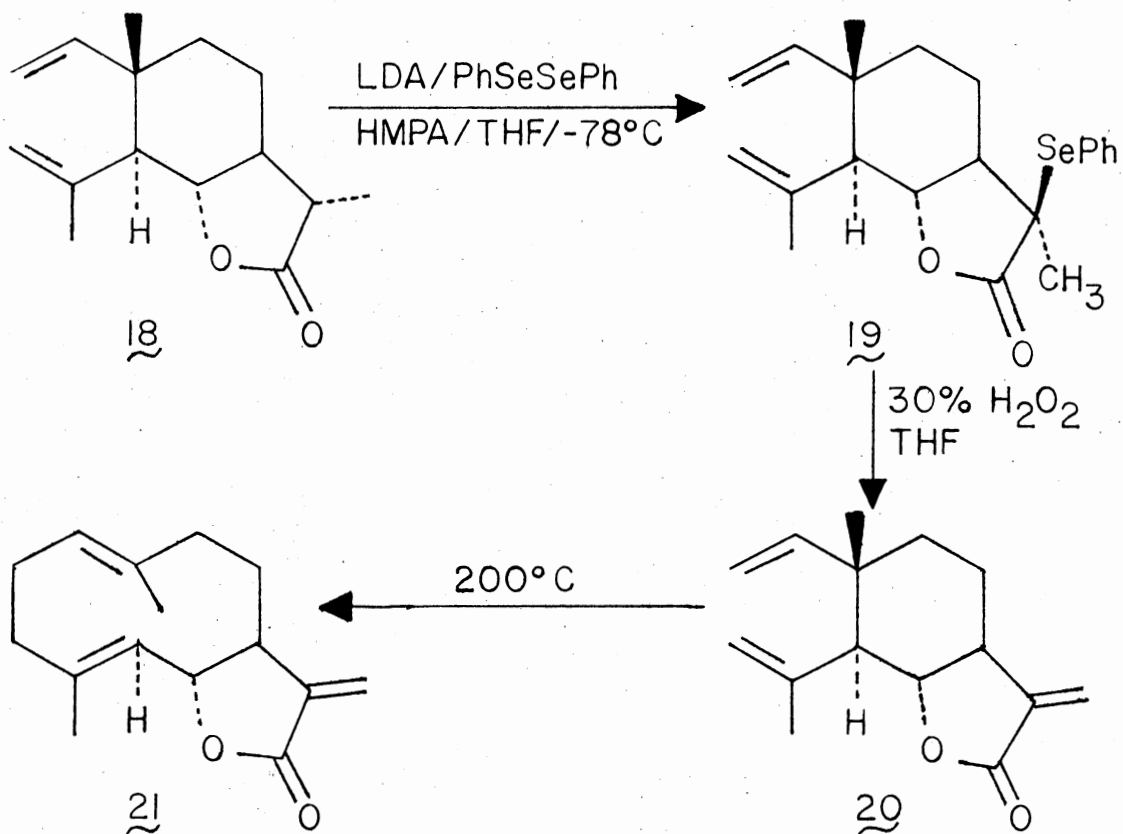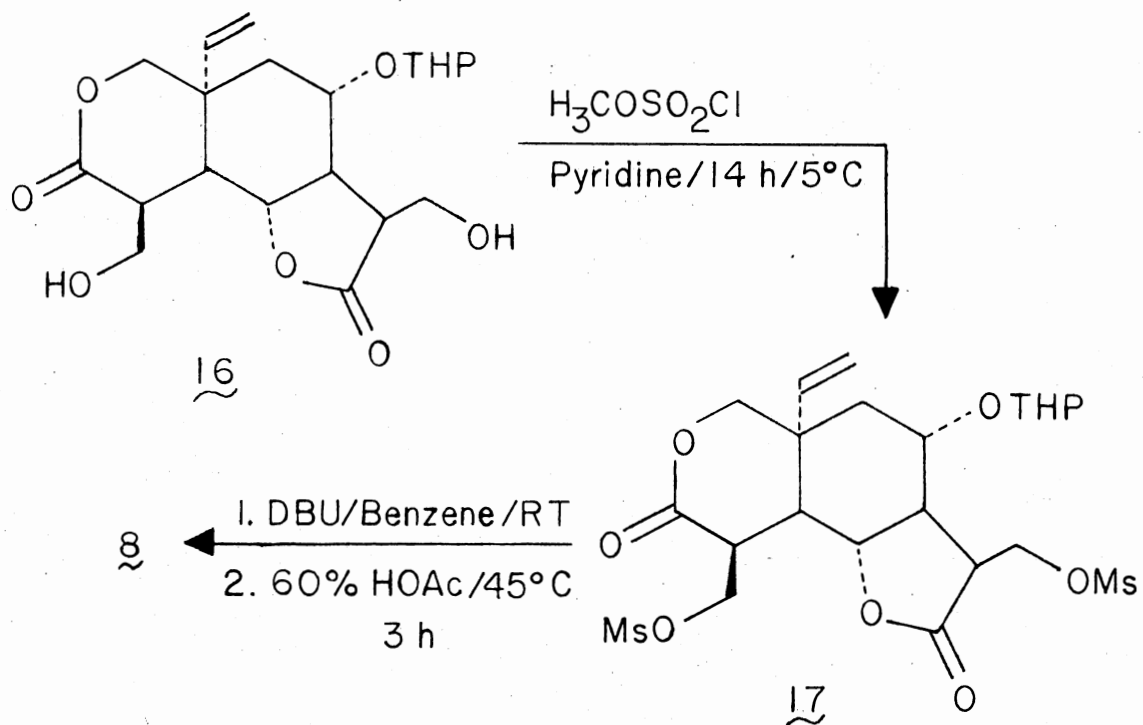
These methods for α-methylenation, as well as several specific modifications thereof, have been successfully used in the synthesis of other natural products.[34,35] A clever and efficient technique was recently reported[85] for effecting α-methylenation using diethyl oxalate and sodium hydride to generate the α-glyoxylate ester (eg. 22). Subsequent reaction of 22 with a solution of diethylamine and aqueous

22

23
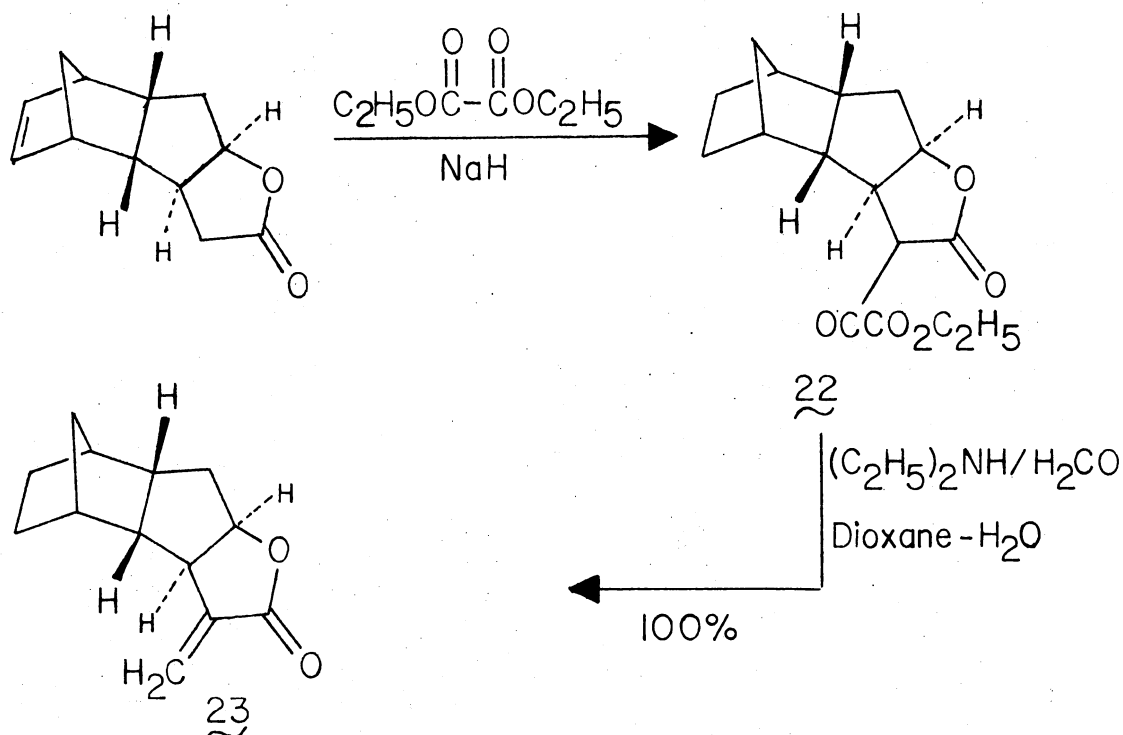
formaldehyde gave the appropriate substituted α-methylene-γ-butyrolactone 23 in quantitative yield.

The α-methylene group may also be incorporated prior to lactonization, but care must be exercised in the eventual lactonization step to avoid polymerization of this highly reactive functional group.[82] Perhaps the method of widest utility in this regard involves the Reformatsky reaction involving a key precursor ethyl α-(bromomethyl)-acrylate (24) which, however, is somewhat difficult to prepare and

polymerizes readily.[21] Öhler and co-workers synthesized a variety of

substituted α-methylene-γ-butyrolactones via this procedure.[75] As

an example, benzaldehyde was allowed to react with 24 and Zn in THF
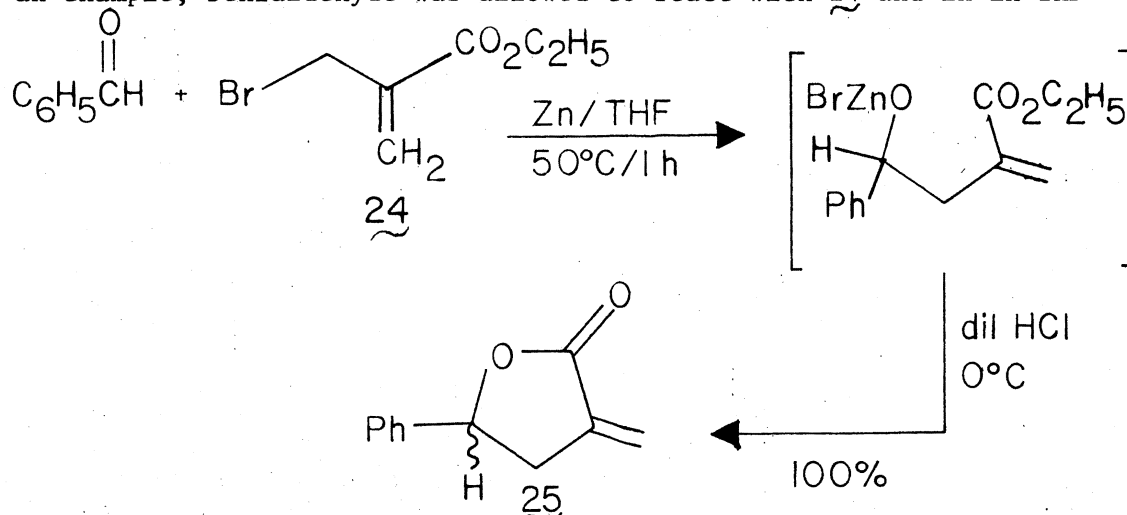
for 1 hour at 50°C. The reaction mixture was cooled, then poured into

dilute ice-cold HCl; the product 25 was isolated in near quantitative

yield. Rosowsky and co-workers[82] also used this synthesis to obtain

a variety of spiro α-methylene-γ-butyrolactones. However, the yields

were poor, primarily due to the heating conditions used for the

lactonization step. In most cases, the product polymerized either

upon boiling in concentrated HCl or during the subsequent distillation.

Ramalingam and Berlin[80] circumvented this problem and reported high

yields of several spiro lactones using ice-cold 5% H_2SO_4 as the

lactonizing agent in the final step. Several substituted heterocyclic

ketones were allowed to react with 24 to give lactones containing

heteroatoms in the carbon skeleton (eg. 26). Recently Lee and co-

workers[66] reported the synthesis of several uracil and thymine

α-methylene-γ-butyrolactones using 24 in a very similar fashion.

Lactone 27 was synthesized in this manner (90%), for example. These

26

27
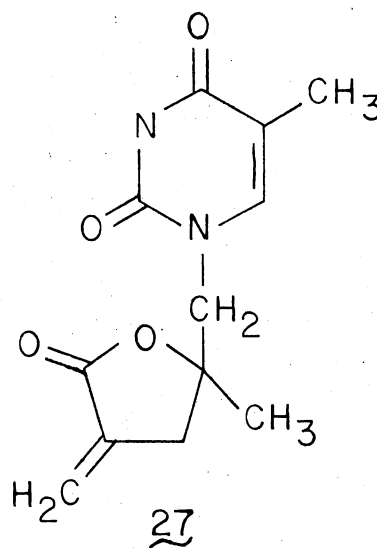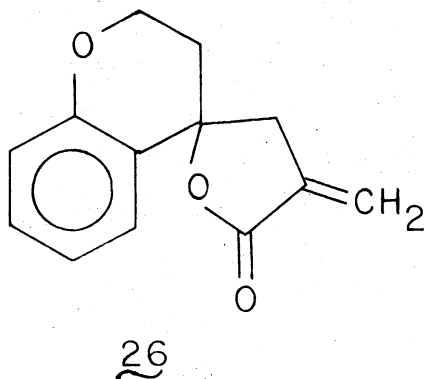
compounds, as well as certain previously synthesized steroidal α-methyl-ene-γ-butyrolactones,[65] showed significant cytotoxicity against Walker 256 carcinosarcoma.

There are also several syntheses which involve organometallic complexes or intermediates which may be used to synthesize α-methylene lactones. Among these are procedures which involve allyl nickle complexes,[39] substituted propenyl cuprates and corresponding lithio compounds[70] as well as certain palladium complex intermediates.[73] While these synthetic methods have proven useful in certain reactions, they have not been widely adopted.

Several specific compounds have also been prepared recently which bear a striking resemblance to the butyrolactone system. A series of α-methylenelactams were recorded in 1974,[64] but surprisingly no other studies have appeared with this heterocyclic system. The natural occurring α-methylene ketone (±)-methylenomycin A. (28) a known antibiotic, was recently synthesized.[83] The strong resemblance to sarkomy-cin (29), a known antitumor agent,[90] suggested that the α-methylene

28   29
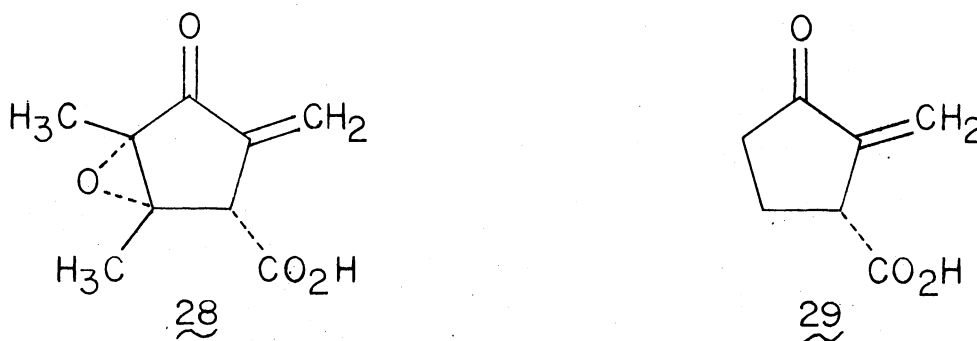
ketone function may be a viable alternative unit to the α-methylene

lactone as an antitumor active group. Indeed, among the many cytotoxic

α-methylene lactones listed in a recent review were several natural

products containing both the α-methylene lactone and the α-methylene

ketone functions.[79]

DNMR Studies of Selected Systems

Thermodynamic Studies

The use of dynamic nuclear magnetic resonance (DNMR) spectroscopy

for analysis of physical properties of dynamic organic systems was

first proposed in 1953 by Gutowsky and co-workers.[37] Little was done

at that time to test this proposal, primarily because of the primative

state of the art in instrumentation. Only four years later Nair and

Roberts[74] demonstrated for the first time that NMR spectroscopy could

be used in conformational analysis of certain geminal difluoro compounds

(eg. 30). Lemieux and co-workers[67] suggested that the method might be

30
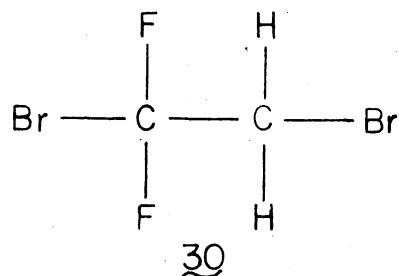
applicable to the study of six-membered ring compounds in carbohydrate chemistry. The first attempt at a semi-quantitative analysis of the thermodynamic properties of a two-site exchange process was Eliel's examination of the ring reversal in bromocyclohexane ($31 \rightleftarrows 32$) in 1959.[16] The methine proton of the cyclohexyl system appeared as a lone
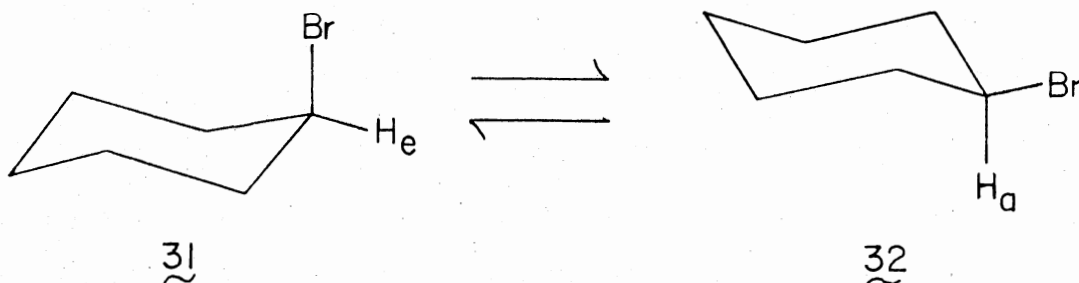
signal at room temperature, even though the earlier work by Lemieux and co-workers[67] had clearly demonstrated that protons in an axial conformation (H_a in 32) were magnetically different from protons in an equatorial conformation (H_e in 31) and therefore should give rise to separate signals in the NMR spectrum. Using Gutowsky and Saika's[37] earlier theory, Eliel derived the following equation:

$$K_{eq} = (\delta_a - \delta)/(\delta - \delta_e)$$

K_{eq} = the equilibrium constant for the reversal

δ_a = chemical shift of pure axial proton (H_a in 32)

δ_e = chemical shift of pure equatorial proton (H_e in 31)

δ = chemical shift of the equilibrating system.

At room temperature, the chemical shifts for the axial and equatorial protons were not obtainable for bromocyclohexane and thus the shifts of the appropriate protons in the conformationally "locked" and

isomeric 1-bromo-4-t-butylcyclohexanes, 33 and 34, were used. Inter-

estingly, Eliel attempted to cool bromocyclohexane to a point at which

signals for individual conformers could be observed in the spectrum.

He stated, however, that ". . . even at low temperatures the signal
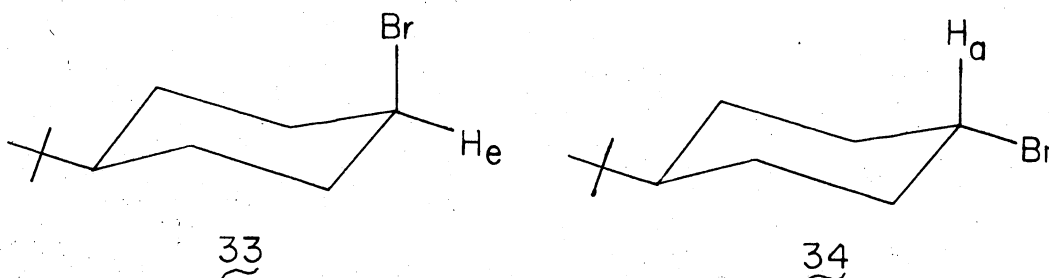
for the tertiary hydrogen was not split and thus the position for

the signals corresponding to the pure conformations could not be

observed."[16] Only a year later, Berlin and Jensen[6] achieved tempera-

tures low enough to detect separate signals in the NMR spectra for the

methine proton in several mono-substituted cyclohexanes. The chemical

shift method outlined above was then used to calculate the equilibrium

constant using the actual chemical shifts of the individual conformers

at low temperatures. More important, the actual relative concentra-

tions of the two conformers could be measured directly from the low

temperature spectra using the integrated areas under the respective

peaks, thus providing a second method of analysis. The equilibrium

constant could then be calculated by:

$$K_{eq} = [A] / [B]$$

K_{eq} = the equilibrium constant for the reversal process

[A] = the integrated area for the signal corresponding

to the axial conformer

[B] = the integrated area for the signal corresponding to the

equatorial conformer.

This represented the more theoretically satisfying approach for determination of the equilibrium constant for the reversal process since actual parameters for the equilibrating system were used and not those of model compounds. Unfortunately, values could be obtained only at very low temperatures (< - 80°C) which were experimentally difficult to achieve and maintain. In spite of the theoretical and experimental difficulties associated with these methods, both have been extensively used to evaluate the thermodynamic character of a large number of ring-reversal processes particularly in cyclohexanes.[25,40] Although several other NMR methods have been employed,[25] these two have been the most popular.

Criticism of the chemical shift method focuses around the use of proton signals in model biased compounds such as 33 and 34 for comparison with the chemical shifts of the corresponding protons for the pure axial and pure equatorial conformers in the equilibrating system.[42,48] Jensen and Beck[47] compared the chemical shifts of the methine protons for several mono-substituted cyclohexanes with that corresponding signal in the 4-t-butyl analogues at very low temperatures to distinguish signals for both conformers in the equilibrating system (eg. 31 ⇄ 32). Comparison of the H(1) proton signals for the axial and equatorial conformers in the equilibrating system with the corresponding signals for the axial and equatorial isomers in the spectra of the analogous biased systems (eg. 33 and 34) showed that distinct shift differences existed. Therefore, the authors considered the

simple method _invalid_. Eliel,[18] in an article published at about the

same time, used a series of gem-substituted compounds (eg. 35 ⇄ 36)

and their 4-_t_-butyl analogues to defend the method. The chemical

shifts of the methoxy groups in the equilibrating systems were shown

to lie exactly midway between the signals corresponding to the axial
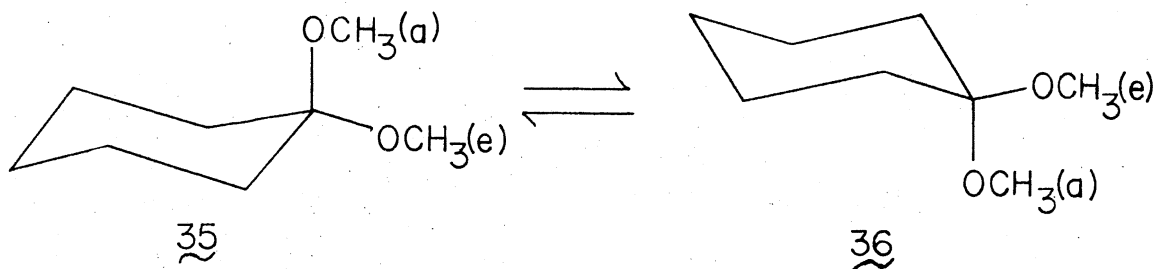
and equatorial methoxy groups in the 4-_t_-butyl system 37. The

combined results of these studies suggested that, while the method may be
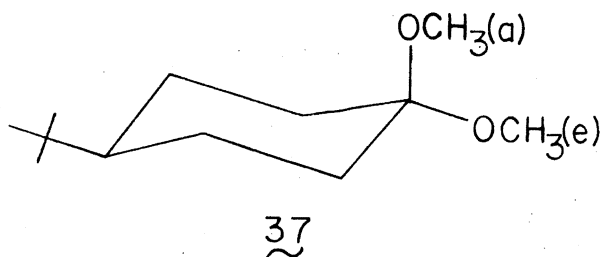
of doubtful validity for the compounds studied by Jensen and Beck[47]

under the specific conditions employed, insulation of the object pro-

tons in systems such as 35 ⇄ 36 may effectively cancel the influence

of the _t_-butyl group. A later study by Ford and Allinger strongly

supported this observation.[22] Jensen and Beck[47] then applied a correc-

tion to the method for the mono-substituted systems. It was observed

that the temperature dependence of the chemical shifts for protons

in the biased systems paralleled the dependence shown by the equili-

brating systems at very low temperatures. This parallel relationship

was assumed to be true at higher temperatures, and thus the chemical

shifts of protons in the actual axial and equatorial substituted con-

formers in the unbiased system were extrapolated to the higher (ca.

25°C) temperatures. For example, in the case of bromocyclohexane

(31 ⇌ 32) and cis- and trans-4-t-butylbromocyclohexane (33 and 34),

δ 3.821 (− 102°C)
δ 3.204 (24°C)

δ 4.560 (− 102°C)
δ 4.529 (24°C)
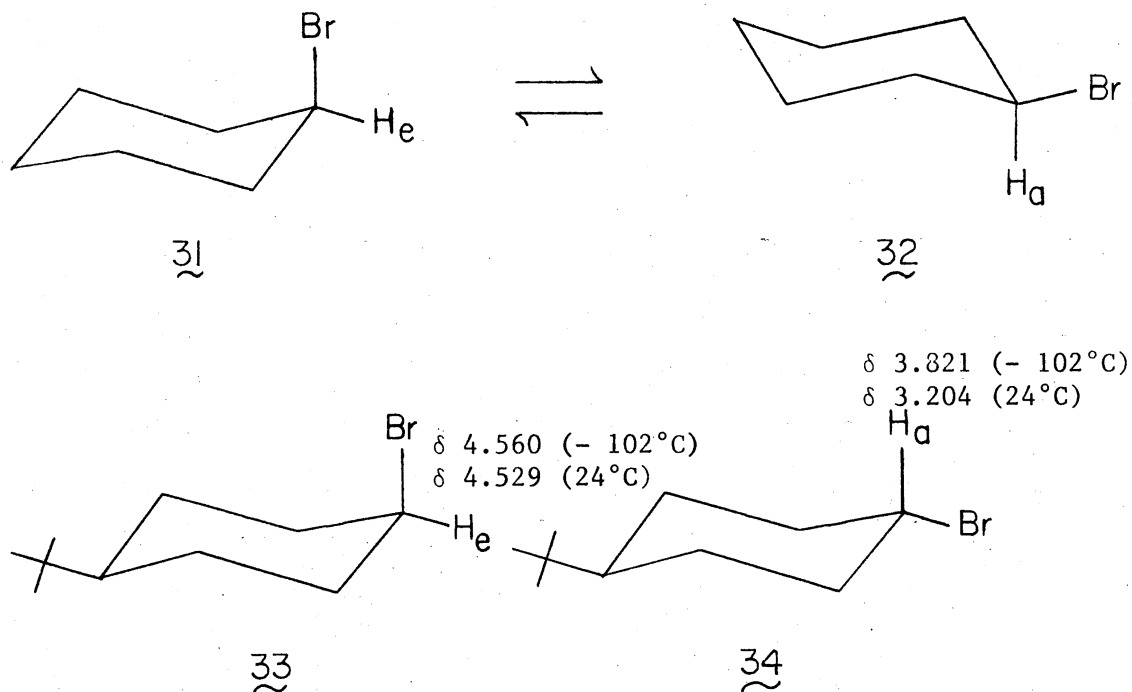
the chemical shifts of the axial methine protons (H_a) for 32 and 34

were shown to differ by a constant 4 Hz for temperatures from -84 to

-102°C. A similar difference (5.5 Hz) was shown to exist for the

equatorial signals (H_e) in 31 and 33. The chemical shifts of the

corresponding protons in the t-butyl isomers 33 and 34 at -102°C

were 456.0 and 382.1 Hz (relative to internal TMS), respectively.

At $+24^{o}$C, the shifts were 452.9 and 380.4 Hz, respectively. To com-

pensate for this obvious temperature dependence, the differences

observed at the very low temperatures between 31 and 33 and between

32 and 34 were applied at the higher temperature. The chemical shift

method was then used with these "corrected" values. The ΔG^O value

obtained in this manner (0.55 kcal/mol) compared favorably with the

value obtained at -82^OC using integrated areas (0.49 kcal/mol). The

value for ΔG^O obtained by using the "uncorrected" chemical shifts for

33 and 34 was given as 0.35 kcal/mol. The corrected method assumes

the parallel shift relationships (observed over an 18° temperature

range for the systems 31 ⇄ 32, 33 and 34) extends over a temperature

range of 128°. At the present time, insufficient data exist to make

an assessment of the validity of this correction on a general basis.

Furthermore, recent studies[78,89] (see below) suggest that the original

shift method may be valid in specific cases; hence the need exists

to evaluate each case on its own merit.

Several spiro systems have been investigated by NMR methods in

which both conformers have a non-hydrogen, axial substituent (38 ⇄ 39).

where X ≠ Y
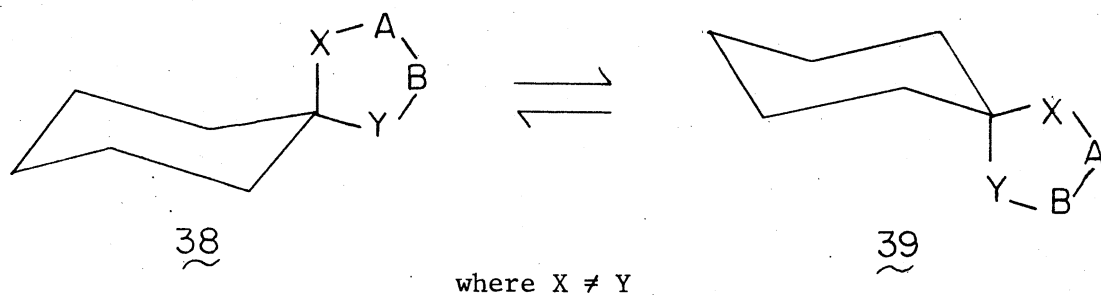
In 1971, Jones and co-workers[50,52] examined a series of spiro-

substituted 1-t-butylpiperidines (40 ⇄ 41) in which the authors have

assumed that atomic inversion about the nitrogen atom occurs simul-

taneously and that this inversion is facile compared to the ring

reversal. It was anticipated that the use of spiro compounds of this

type would eliminate some of the difficulties involved in comparison of the conformational analysis of 1,1-disubstituted compounds. The spiro compounds proposed could eliminate rotational isomeric contributions, provide accessible signals for investigation, and isolate the object protons from the six-membered ring.[51] The method of
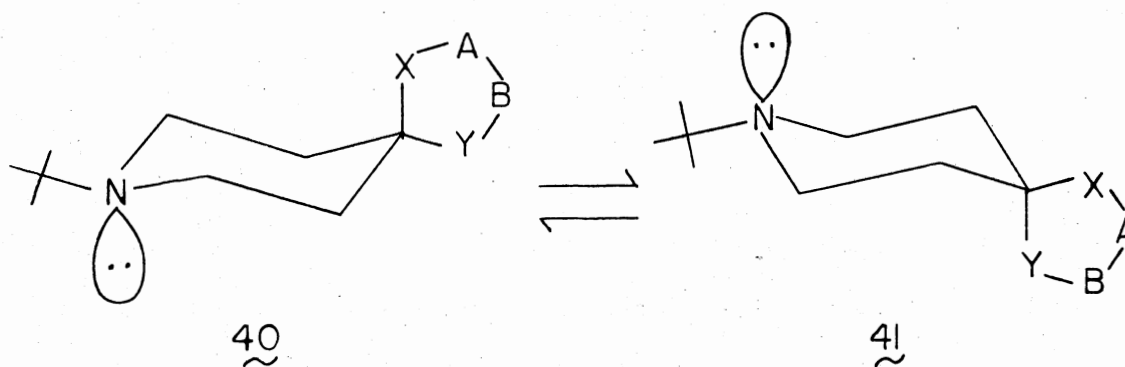
integrated areas at low temperature was used, and K_{eq} = 1.29 was calculated for the equilibrium 40 $\rightleftharpoons$ 41 at 30°C where X-A-B-Y was $-CH_2-NH-C(CH_3)_2-O-$.[50] This corresponded to a ΔG^o of 0.12 kcal/mol in favor of the conformer with the C-O <u>axial</u> bond. In contrast, a value for K_{eq} of 0.81 was calculated for the case where X-A-B-Y was $-CH_2-O-C(CH_3)_2-NH-$, corresponding to a ΔG^o of 0.12 kcal/mol in favor of the isomer with the C-N bond (Y = N in 41) in the <u>equatorial</u> position.

Uebel and co-workers[89] investigated the conformational equilibrium of several 1-oxaspiro 4.5 decanes (42a-c $\rightleftharpoons$ 43a-c). The analysis of both 42a $\rightleftharpoons$ 43a and 42c $\rightleftharpoons$ 43c at low temperatures (< -80°C) showed that the conformer with the axial C-O band (42a and 43c) was favored in each case. Analysis of 42b $\rightleftharpoons$ 43b showed a startling reversal of this trend. In this case, conformer 43b was favored by -0.13 kcal/mol at

42   43

a. Z = CH$_2$
b. Z = C(CH$_3$)$_2$
c. Z = C=O
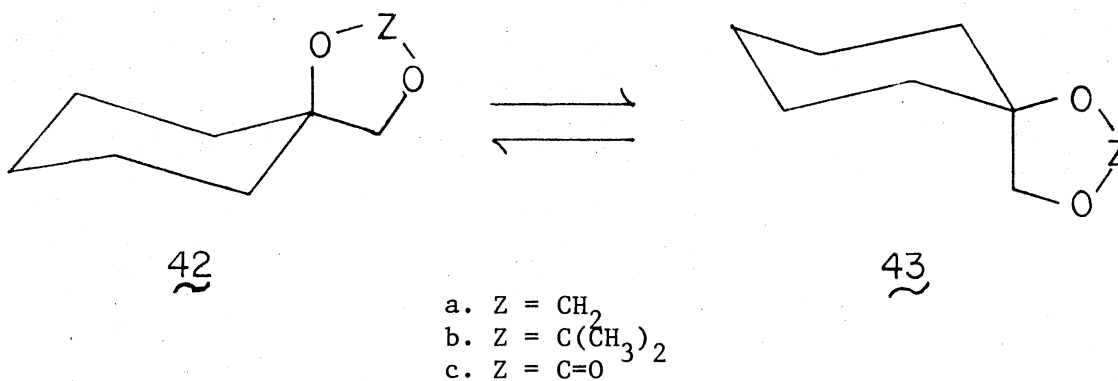
-80°C (by integrated areas) and by -0.28 kcal/mol at 35°C (by uncor-
rected chemical shifts). This suggests that substituents alpha to the
groups which occupy the axial-equatorial positions in the equilibrating
system may sterically influence the equilibrium.

Picard and Moulines[78] have investigated the conformational equi-
librium of spiro-substituted cyclohexanes (44a,b $\rightleftarrows$ 45a,b). Using bands

44   45

a. Z = CH$_2$, R = H
b. Z = C=O, R = t-bu
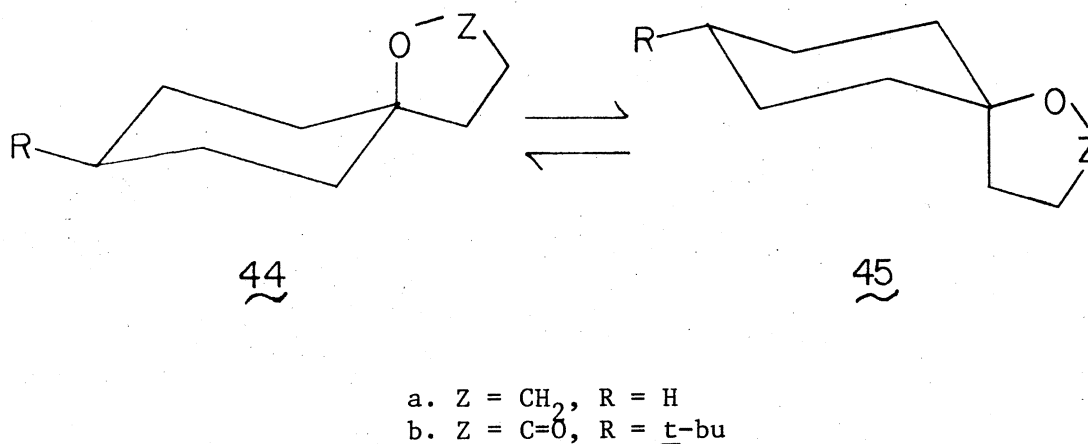
in the IR spectrum, the equilibrium 44a $\rightleftarrows$ 45a was shown to favor 44a
by 0.46 kcal/mol at 35°C. The two t-butyl spiro lactones 44b and 45b

were examined by equilibration of the isomers in 50% H_2SO_4. Isomer 44b

was favored by 0.278 kcal/mol at 55°C.

The equilibrium of the unsaturated lactone 46 ⇄ 47 was also

investigated by Picard and Moulines[78] by the uncorrected chemical

46   47
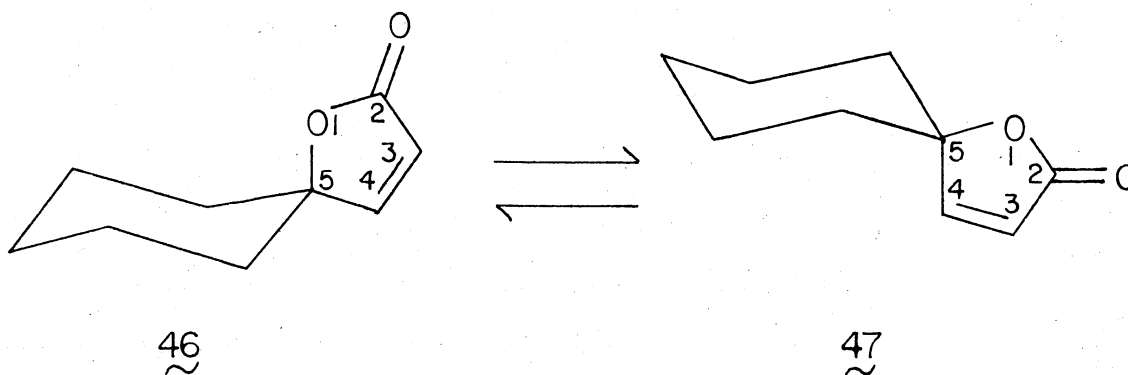
shift method using the cis- and trans-8-t-butyl-substituted analogues

to establish the chemical shifts of the axial and equatorial signals

for H(4). A conformational preference of 0.47 kcal/mol was shown for

conformer 46 at 38°C, in excellent agreement with the value of 0.50

kcal/mol favoring 46 at -95°C found by Uebel and co-workers[89] by

integrated areas.

Kinetic Studies

Gutowsky and Saika[37] apparently were the first to propose that

kinetic parameters, such as the activation free energy, ΔG^*, could be

determined by the line-shape analysis of the NMR spectra of dynamic

systems. In 1956, the first successful quantitative analysis was made

of the internal rotational barriers for N,N-dimethylformamide via DNMR

line shape analysis.[36] From this initial study, the field has expanded

to include a large variety of exchange processes. It is beyond the

scope of this work to describe all the theoretical aspects and

applications of DNMR in the analysis of kinetic parameters associated with exchange processes. The reader is instead referred to the excellent reviews of the area[55,87] as well as the recently published reference[46] which surveys the entire subject. Specific examples of ring reversal in substituted cyclohexyl systems follow as well as a discussion of the factors which may contribute to the height of the barrier to the reversal process.

The ring reversal for cyclohexane and cyclohexane-d_{11} has been extensively investigated[4] (the deuterated compound has a less complex spectrum, especially with deuterium decoupling, and therefore was somewhat easier to analyze). Best values for the kinetic parameters were reported[4] from a compilation of these many studies. The free energy barrier to ring reversal (ΔG^*) was given as 10.5 kcal/mol and the enthalpy of activation (ΔH^*) as 10.8 kcal/mol for cyclohexane.

The kinetic parameters for a variety of substituted cyclohexanes have also been determined.[26] The value for ΔG^* for 1,1-dimethylcyclohexane (10.6 kcal/mol) differed only very slightly from that of cyclohexane (10.5 kcal/mol). Interestingly, a slightly higher value (10.8 kcal/mol) was determined for 1,1-dimethoxycyclohexane. When the ^{1}H spectra of tetra-substituted compounds 48 were analyzed very carefully, a series of effects became apparent. The magnitude of the activation free energy showed a decrease for 1,1,3,3-tetramethylcyclohexane 48a (9.6 kcal/mol), suggesting that the 1,3-interactions of the axial methyl groups destabilize the two chair conformers relative to the boat or twist boat intermediate 49a. This would effectively lower the reversal barrier, resulting in the lower ΔG^* value.
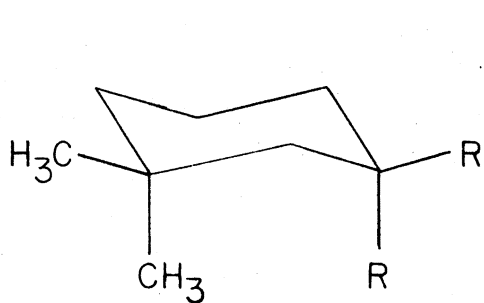
48
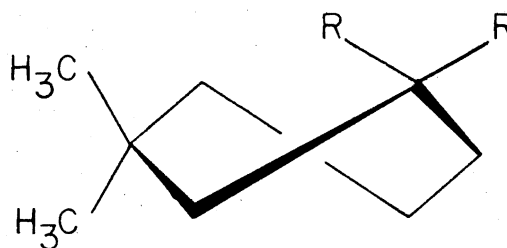
49

a. R = CH$_3$
b. R = O-CH$_3$

As a means of comparing the steric requirements of different

groups, the 1,1-dimethoxy-3,3-dimethylcyclohexane system 48b was also

analyzed by Friebolin and co-workers.[26] The value obtained for ΔG^*

(10.4 kcal/mol) suggested that the 1,3-interaction of the non-bonded

pairs on oxygen with the methyl groups was less than that of the

1,3-methyl-methyl interactions. Not surprising, however, was the

value of 9.5 kcal/mol for the ΔG^o of the bis-ethylene ketal of cyclo-

hexan-1,3-dione (50) which suggested that the non-bonded electronic
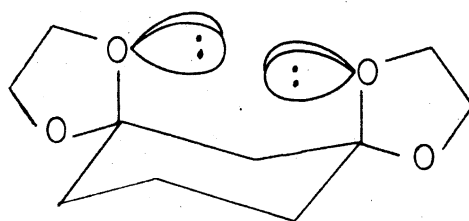
50

repulsions of the syn-axial oxygens shown are of the same order as

1,3-methyl-methyl interactions. Rather surprising was the observa-

tion that separate signals for the axial and equatorial groups in 51

were <u>not</u> detected even at temperatures as low as -95°C.[26] This implies

51
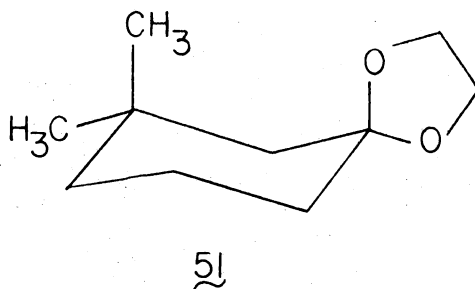
that the activation free energy for the reversal is affected by the

rotational freedom of the substituents.

The hexa-substituted cyclohexanes 52 and 53 investigated by

Friebolin and co-workers[26] apparently have low ΔG^* values. Both com-

pounds 52 and 53 failed to display separate signals for axial and

equatorial conformers at temperatures as low as $-100°C$. This is

apparently due to an effective lowering of the barrier so that equi-

libration is still rapid even at the low temperature.

52

53
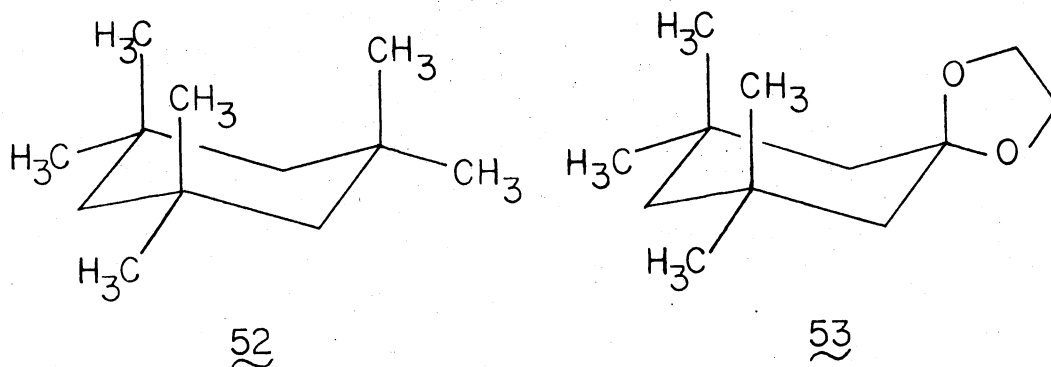
The interesting compound 54 which showed anomolous behavior was

determined to have a free energy barrier to reversal of $\Delta G^* = 12.0$

kcal/mol.[26] Such behavior was believed due to the destabilizing

affect that 1,2- and 1,4-interactions had on the possible intermediates

for the reversal. Specifically, eclipsing in the boat or twist boat

54
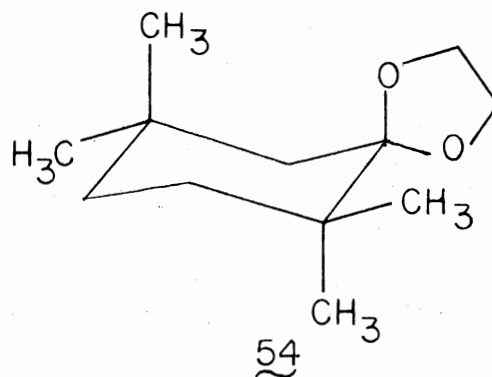
form of 54 (eg. 55) could raise the energy of the intermediate relative to the chair form. Analysis of these compounds using theoretical models

55
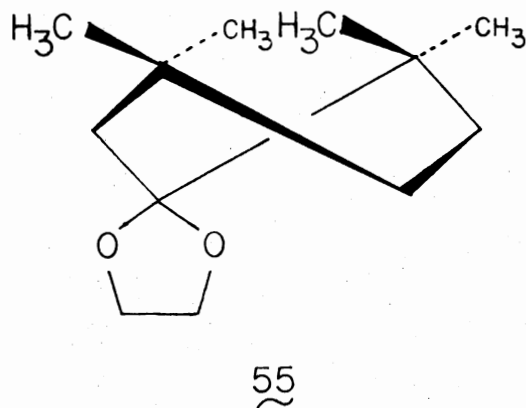
and semi-empirical calculations to derive relative conformational energies provided some support for this hypothesis.[84]

Error Analysis

The linearized, relative error equation for ΔG^O can be derived from Eq. (1):

$$\Delta G^O = -RT \ln K_{eq} \qquad \text{Eq. (1)}$$

ΔG^O = standard free energy

R = gas constant [1.987 (10^{-3}) kcal/mol·deg]

T = temperature in $^{\circ}K$

K_{eq} = equilibrium constant

It can be shown that Eq. (2) can be derived from Eq. (1)

$$(\sigma_{\Delta G^{\circ}}/\Delta G^{\circ}) \simeq \{(\sigma_T/T)^2 + (\ln K_{eq})^{-2} (\sigma K_{eq}/K_{eq})^2\}^{\frac{1}{2}} \qquad \text{Eq. (2)}$$

$\sigma_{\Delta}G^{\circ}$ = uncertainty in ΔG°

σ_T = uncertainty in T

$\sigma_{K_{eq}}$ = uncertainty in K_{eq}

where ΔG°, T and K_{eq} have the same meaning as above [see page 96 for the derivation Eq. (2)]. Thus, an error in T of 0.5% (at T $\simeq$ 180 K) would be expected to result in a relative error of the same order of magnitude in ΔG°. An error of ~ 5% in K_{eq} (K_{eq} $\simeq$ 0.8) would be expected to result in an error of 22% in ΔG°. The combined error is about 23%. Therefore, it is important to measure as accurately as possible either the integrated areas or the chemical shifts but preferably both. To this end, multiple runs should be employed to help eliminate random errors and, if possible, several methods of measuring the dependent variables should be used. Temperature control is especially critical but is difficult at extremely low temperatures; hence the need exists to monitor the temperature constantly. The use of emperically derived equations which allow one to calibrate chemical shift differences of protons in known compounds (i.e. methanol or ehtylene glycol) with temperatures has proven most useful also.[95]

The linearized relative error equation for ΔH° is given by Eq. (3):

$$(\sigma_{\Delta H}o/\Delta H^O) \simeq \{\ 2T^2/(\Delta T)^2\ (\sigma_T/T)^2 + 2[\Delta(\ln K_{eq})]^{-2}(\sigma_{K_{eq}}/K_{eq})^2\}^{\frac{1}{2}}\quad \text{Eq. (3)}$$

where ΔH^O = the standard enthalpy of the equilibrium, ΔT = the range

of temperatures, $\Delta(\ln K_{eq})$ = the range of $\ln K_{eq}$ and the other

symbols have the same meaning as above [see page 97 for a derivation

of Eq. (3)]. Thus a temperature range of 10° and an uncertainty in T

of 0.5% introduces an uncertainty of 14% in ΔH^O. An uncertainty of

5% in the values of K_{eq} (for values of K_{eq} ranging from 0.8 to 0.7)

results in an uncertainty in ΔH^O of 53%; the combined uncertainty is

about 55%. If the temperature range is 230 to 280° (Kelvin), the

range of K_{eq} values is 0.7 to 0.6 and the uncertainties remain the

same. The uncertainty values are 2.8%, 46% and 46%, respectively.

The overall error is primarily due to the small change in the value

of K_{eq} over the temperature range studied and the fact that ΔH^O is

dependent upon the difference in the logarithms.

Although the instrumental problems, such as temperature control,

also affect the determinations of the kinetic parameters, the typically

wider range of values for the absolute rate constant for temperature

ranges of 30 to 40° reduces the overall relative error. One can derive

the linearized, relative error equation for ΔG^* from the Eyring

Equation (4):

$$k = \kappa(k_B T/h)\ \exp(-\Delta G^*/RT) \qquad \text{Eq. (4)}$$

k = absolute rate constant

κ = frequency factor

k_B = Boltzman constant $[3.2996(10^{-27})\text{kcal/mol}]$

T = temperature in K

G^* = activation free energy

R = gas constant $[1.987(10^{-3})kcal/mol \cdot deg]$

h = Planck's constant $[1.5836(10^{-37})kcal \cdot sec]$

The relative error can be shown to be:[8]

$$(\sigma_{\Delta G^*}/\Delta G^*) \simeq \{|\ln(k_B T/hk)|^{-2} (\sigma_k/k)^2 + (\sigma_T/T)^2\}^{\frac{1}{2}} \qquad Eq.\ (5)$$

where the symbols have their usual meanings. For the typical case where T = 300 K (k = 100 s^{-1}), an error of 100% in k produces an error of only 4% in ΔG^*, and an error of 6°K in the temperature introduces only 2% error in ΔG^*.

The Arrhenius equation (6) may be used to calculate a value

$$k = A \exp(-E_a/RT) \qquad Eq.\ (6)$$

k = reaction rate constant

A = pre-exponential factor

E_a = Arrhenius activation energy

R and T have their usual meaning

of E_a from a plot of ln k vs 1/T. It can be shown that the relative error in E_a is given by Eq. (7):[8]

$$(\sigma_{E_a}/E_a \simeq \{[2T^2/(\Delta T)^2](\sigma_T/T)^2 + 2[\Delta(\ln k)]^{-2}(\sigma_k/k)^2\}^{\frac{1}{2}} \qquad Eq.\ (7)$$

where the symbols have their usual meanings. Since Equation (8) is valid for a unimolecular process,

$$E_a \simeq \Delta H^* \qquad Eq.\ (8)$$

an error introduced in k and T into the calculation of ΔH^* will

result in an error in ΔH^* of the same order of magnitude as that

associated with E_a, i.e.:

$$\sigma_{E_a}/E_a \simeq \sigma_{\Delta H^*}/\Delta H^* \qquad \text{Eq. (9)}$$

From Eq. (7), the error in E_a introduced by a relative error in T of

1%, for a 20° (Kelvin) temperature range centered around 200°K is

approximately 14%. If the temperature range, ΔT, is extended to cover

30°K, the error in E_a is reduced to 9%. For an uncertainty of 25%

in the values of k for a range of k values of 2.0 to 60 s^{-1}, the error

in E_a is approximately 10%. The total error in E_a for $\Delta T = 30°K$ and

a range in k of 2 to 60 s^{-1} is approximately 21%. This is a sig-

nificant error in E_a (and subsequently ΔH^*) and graphically demon-

strates the reason why so many of the values in the literature for

ΔH^* (and ΔS^*) for dynamic organic systems differ markedly.[4]

The total error in E_a (and ΔH^*) may be reduced somewhat by exten-

sion of the temperature range, as can be seen from the calculations

above. More important, however, is the accurate measurement of the

reaction rate constant k. To insure the best possible analysis, it

is therefore imperative that the line-shape remain sensitive to tem-

perature changes over the entire temperature range. To enhance this

sensitivity, Kleier and co-workers[57] suggested that moderately complex

spin-systems may be better candidates for DNMR studies since there

are usually present several temperature dependent spectral parameters.

For example, there would be several signals and/or coupling constants

for visual comparison. Thus, the probability that more than one set

of variables would produce the same spectrum would expectedly be

reduced. Since visual comparison of simulated and experimental spectra

appears to be the method of choice[8] for the determination of the rate

constant, this may significantly reduce the uncertainty in the rate

constant k.

CHAPTER II

RESULTS AND DISCUSSION

The large amount of research activity concerning the isolation[79]

and synthesis[27,31] of α-methylene-γ-butyrolactones as possible anti-

tumor agents prompted our investigation of the dynamic characteristics

of the spiro-α-methylene-γ-butyrolactone system 56a $\rightleftarrows$ 57a. Reported
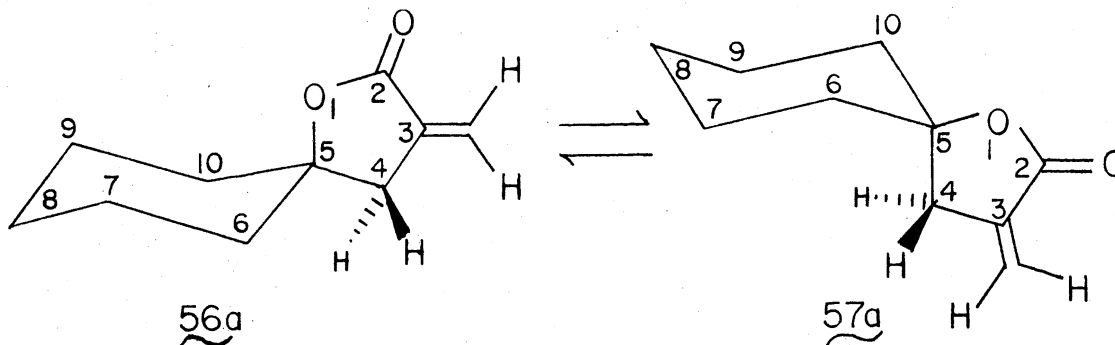
herein are the first thermodynamic ($\Delta G^O_{-88^OC}$ = + 0.10 kcal/mol;

$\Delta H^O \simeq$ -0.13 kcal/mol; $\Delta S^O \simeq$ - 1.2 eu) and kinetic ($\Delta G^*_{-55^OC}$ = + 10.9

kcal/mol; $\Delta H^* = + 9.6$ kcal/mol; $\Delta S^* \simeq - 5.9$ eu) parameters associated

with ring reversal of such a system although there is known antitumor

activity associated with such a spiro lactone.[82] Also reported are

the syntheses, NMR (^{1}H and ^{13}C), IR and physical characteristics for

a series of analogous substituted compounds. In addition, an analysis

of possible solvent effects displayed in the NMR spectra of several of

these compounds is presented. A single crystal X-ray analysis of

compound 56b is also reported; this allowed unequivocal assignment of

the stereochemistry for this solid isomer and aided in the assignment

of resonances in the NMR spectra of these compounds.

31

Although a variety of techniques are available for the synthesis of α-methylene-γ-butyrolactones,[27,31] the method outlined below[80] was chosen for its simplicity and adaptability to the synthesis of the compounds 56a-56e and 57a-57e necessary for subsequent DNMR studies. In all cases, the Reformatsky reaction was employed under identical conditions for reaction with an appropriate cyclohexanone. Addition of each reaction mixture to H_2SO_4 at $0°C$ yielded either an oil or a crystalline product which was extracted with ether. However, careful recovery of the crude product, followed by purification either by distillation or recrystallization, gave, upon cooling, a crystalline material for each compound except 56e ⇄ 57e. The physical and synthetic data are reported in Table I for the various compounds synthesized.

Spectral data from the ^{1}H NMR (Plates I-XIII) and IR (Plates XIV-XVIII) for each of the compounds 56a-56e and 57a-57e are given in Table II. Although the synthesis of compound 56a ⇄ 57a was previously reported,[75,82] only an oil was obtained which was undoubtedly due to the attempted purification via distillation which resulted in partial decomposition.[82] It is also highly probable that some polymerization occurred in the distillation as well. In our hands, only 56e ⇄ 57e has not as yet yielded a crystalline product upon cooling a solution of the oil in commercial hexanes (bp $67°-71°C$). Distillation of 56e ⇄ 57e yielded a contaminated product which partially polymerized even in the dark and when refrigerated.

Ethyl α-(bromomethyl)acrylate (24) was initially synthesized via a published method.[21] However, it was later shown that careful control of the reaction conditions can greatly improve the yield while eliminating a step.[81]
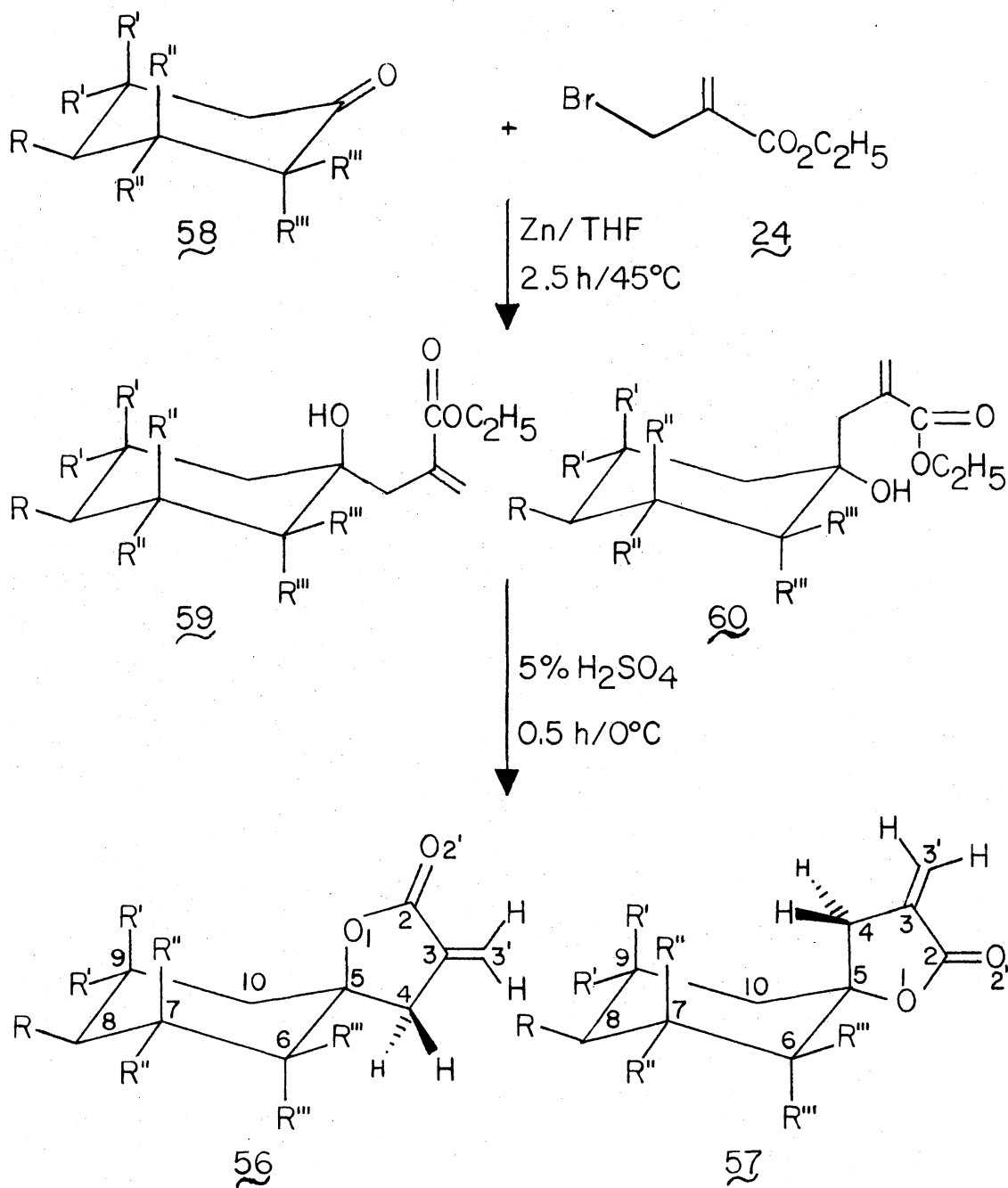
a. R = R' = R'' = R''' = H

b. R = $(CH_3)_3C$; R' = R'' = R''' = H

c. R'' = CH_3; R = R' = R''' = H

d. R' = R'' = CH_3; R = R''' = H

e. R''' = CH_3; R = R' = R'' = H

TABLE I

SYNTHETIC AND PHYSICAL DATA FOR COMPOUNDS 56a-56e AND 57a-57e

Cpd	R	R'	R''	R'''	mp °C	bp °C	yield
56a ⇄ 57a	H	H	H	H	26-27.5	76-77 (0.05 mm)	86%
56b	t-bu	H	H	H	84-85	---------	48%[a]
57b	t-bu	H	H	H	83-84	---------	1.0%[a]
56c ⇄ 57c	H	H	CH$_3$	H	38.5-39.5	100-102 (0.25 mm)	75%
56d ⇄ 57d	H	CH$_3$	CH$_3$	H	102-103	---------	73%
56e ⇄ 57e	H	H	H	CH$_3$	---------	57-59 (0.05 mm)	~40%[b]

[a] Isolated yields from a mixture of 56b and 57b. Total yield was 65%.

[b] Compound 56e ⇄ 57e failed to crystallize, and partial polymerization occurred in the distillation step.

TABLE II

^{1}H NMR AND IR SPECTRAL DATA FOR 56a-56e AND 57a-57e

Cpd	R	R'	R''	R'''	^{1}H NMR Data (ppm from TMS in acetone-d_6	IR (cm^{-1})	
56a $\rightleftarrows$ 57a	H	H	H	H	1.2–1.9 (m) 10 H; 2.78, 2 H;[a] 5.62, 1 H;[b] 6.05, 1 H.[b]	$\nu_{c=o}$ 1761 $\nu_{c=c}$ 1664 (film)	
56b	t-bu	H	H	H	0.88 (s) 9 H; 1.0–2.0 (m) 9 H; 2.74, 2 H;[a] 5.62, 1 H;[b] 6.05, 1 H.[b]	$\nu_{c=o}$ 1748 $\nu_{c=c}$ 1653 (KBr)	
57b	t-bu	H	H	H	0.89 (s) 9 H; 1.0–2.0 (m) 9 H; 2.85, 2 H;[a] 5.64, 1 H;[b] 6.05, 1 H.[b]	$\nu_{c=o}$ 1751 $\nu_{c=c}$ 1653 (KBr)	
56c $\rightleftarrows$ 57c	H	H	CH$_3$	H	0.94 (s) 3 H; 1.04 (s) 3 H; 1.1–1.95 (m) 8 H; 2.78, 2 H;[c] 5.62, 1 H;[b] 6.04 1 H.[b]	$\nu_{c=o}$ 1757 $\nu_{c=c}$ 1664 (film)	
56d $\rightleftarrows$ 57d	H	CH$_3$	CH$_3$	H	0.95 (s) 6 H; 1.18 (s) 6 H; 1.0–1.9 (m) 6 H; 2.77, 2 H;[a] 5.68, 1 H;[b] 6.08, 1 H.[b]	$\nu_{c=o}$ 1754 $\nu_{c=c}$ 1658 (KBr)	

TABLE II (Continued)

Cpd	R	R'	R''	R'''	^{1}H NMR Data (ppm from TMS in acetone-$\underline{d}_6$)	IR (cm^{-1})
56e $\rightleftharpoons$ 57e	H	H	H	CH$_3$	0.90 (s) 3 H; 0.96 (s) 3 H; 1.1-1.9 (m) 8 H; 2.44, 2.62, 3.02, 3.20 (q ot t) 2 H; 5.64 (d of t) 1 H; 6.06 (d of t) 1 H.	$\nu_{c=o}$ $\nu_{c=c}$ (d)

[a]Three line pattern resulting from X$_2$ of AMX$_2$ where $J_{AX} \sim J_{MX}$.

[b]A or M portion of AMX$_2$ pattern where $J_{AM} < J_{AX} \sim J_{MX}$.

[c]Four line portion of AMXY pattern.

[d]Spectrum showed gross impurities.

Compound 58c was synthesized from diketone 61 using a modified procedure of Frank and Hall[24] as outlined below (see Experimental). The overall yield of 3,3-dimethylcyclohexanone (58c) was 17%.
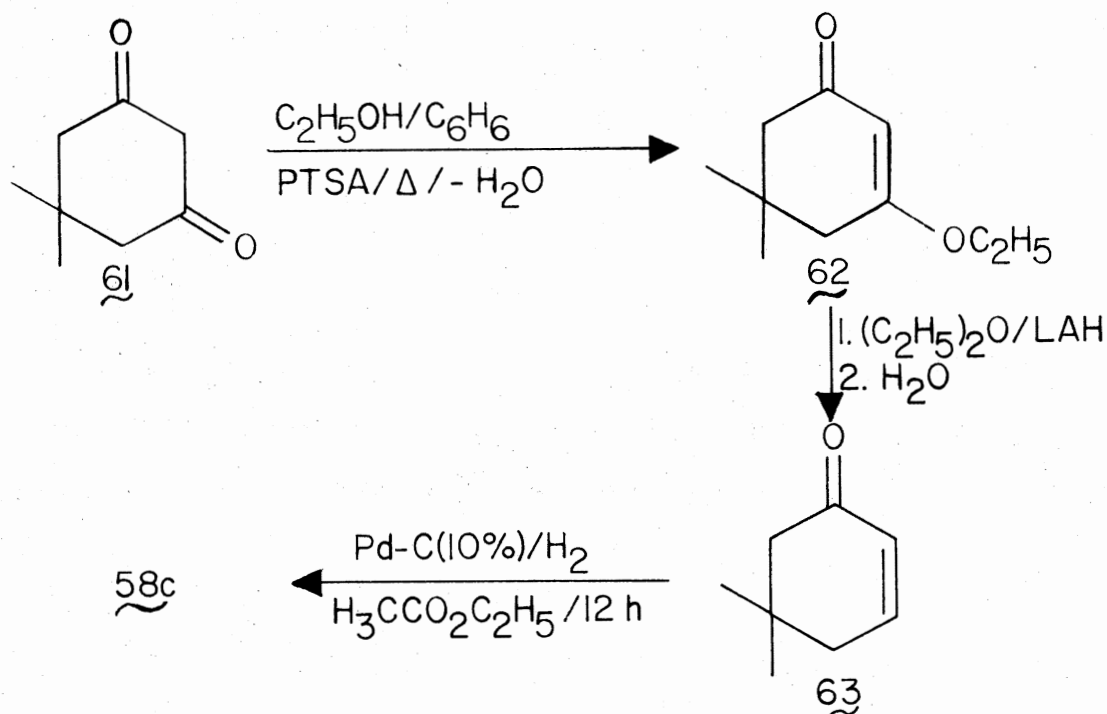
Compound 58e was synthesized by a minor modification of the method of Coates and Sowerby[11] from cyclohexanone (58a) as outlined below (see Experimental). The overall yield of 2,2-dimethylcyclo-hexanone (58e) was 14%.

Compounds 56a and 57a are interconvertable conformers. At temperatures below 198°K (-75°C), the frequency of interconversion between these two conformers is sufficiently slow that signals for each conformer are distinguishable in the low temperature ^{1}H NMR spectra, i.e., [55,87]

$$k_r \ll \pi[\nu_a - \nu_e]/\sqrt{2}$$

k_r = reaction rate constant

ν_a = the chemical shift of H(4) in 56a

ν_e = the chemical shift of H(4) in 57a
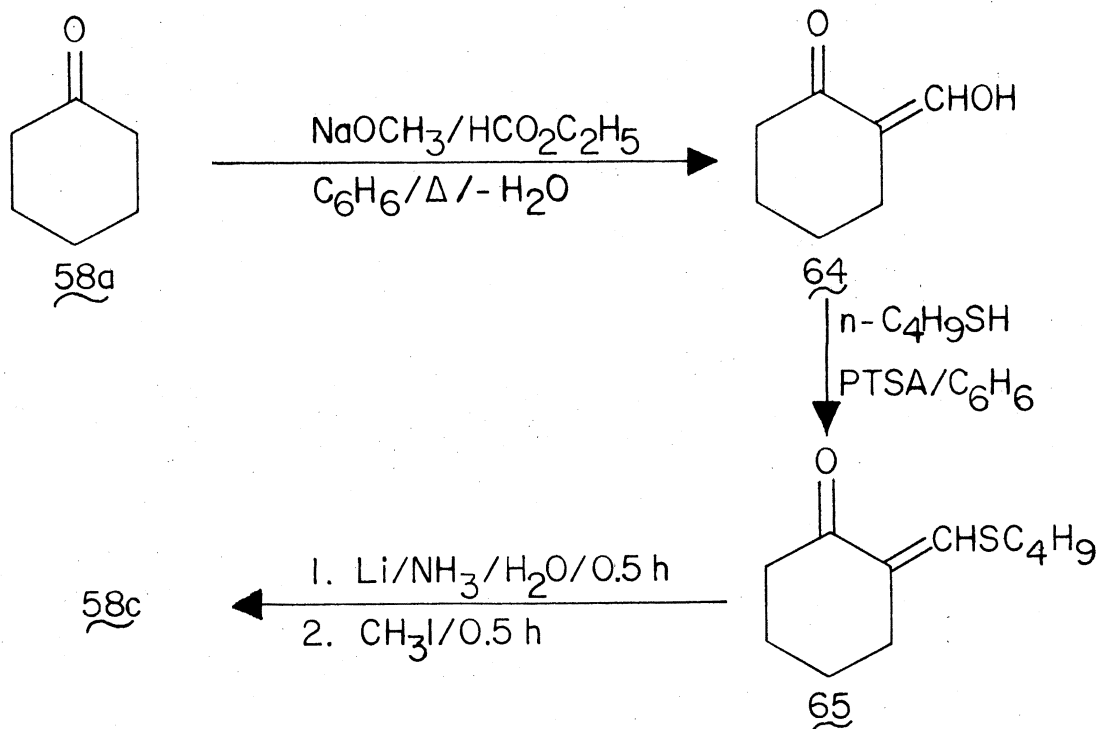
Under these conditions, both conformers are easily detected, and the relative peak areas can be measured by integration. In this particular case, 56a and 57a gave rise to two separate, three-line spin patterns (X_2 of an AMX_2 pattern) between $177^\circ K$ and $185^\circ K$ which was below the compound's coalesence temperature (T_c) of $209^\circ K$ ($-64^\circ C$). The two concentrations used were 0.024 M and 0.036 M solutions in acetone-d_6. A representative partial spectrum of a solution (0.036 M) of 56a $\rightleftharpoons$ 57a is shown in Figure 1. The equilibrium constant for the ring reversal can be determined from the relative areas and, using these values, calculation of ΔG° follows:
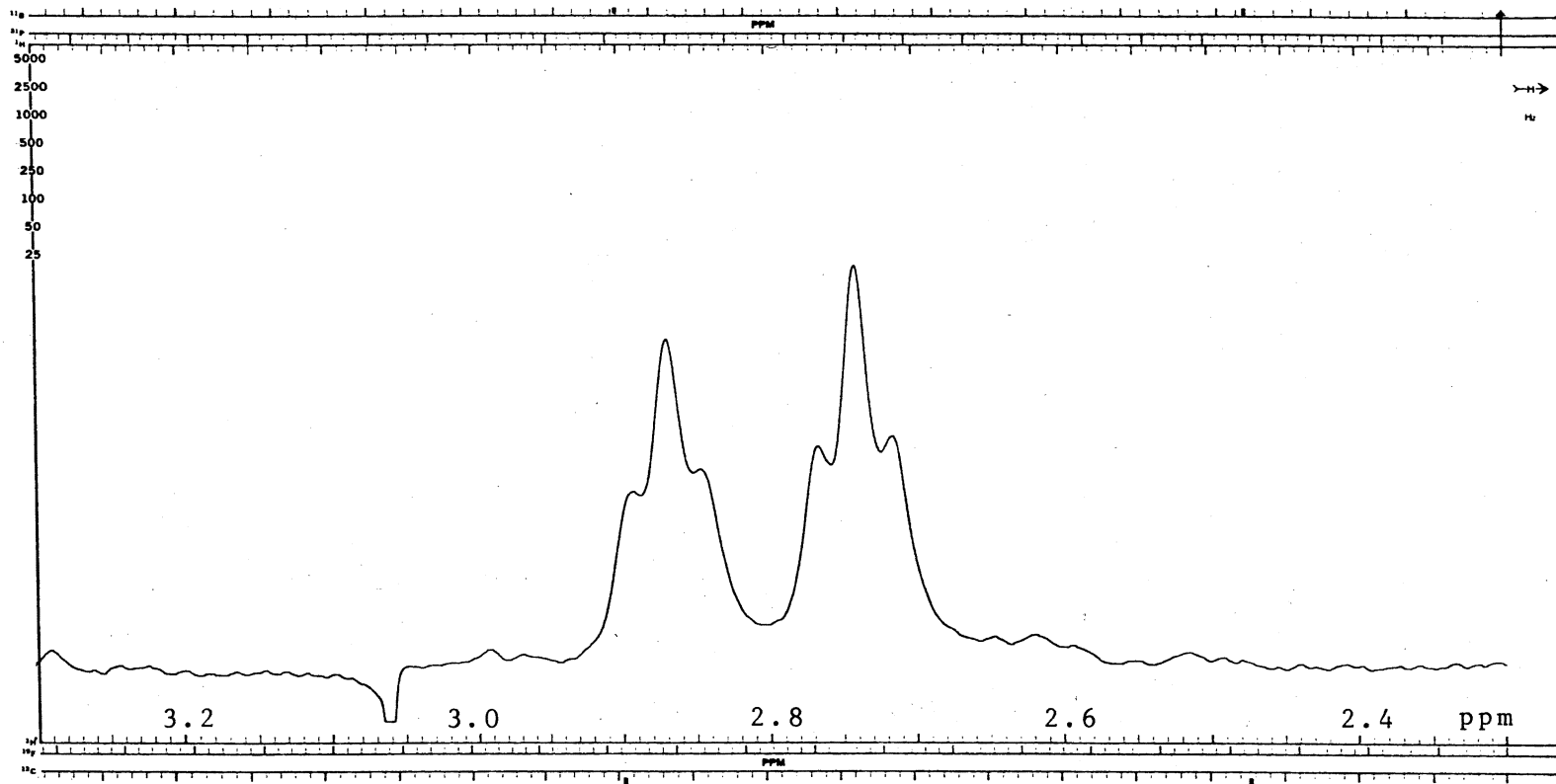
Figure 1.   Spectrum of $\underset{\sim}{56a} \overset{\rightarrow}{\leftarrow} \underset{\sim}{57a}$, 177^OK, 0.036 M in Acetone-d_6.
Sweep Width = 100 Hz, Offset = 230 Hz (PFT)

$$\Delta G^O = -RT \ln([57a]/[56a])$$

[56a] = area under peak corresponding to conformer 56a.

[57a] = area under peak corresponding to conformer 57a.

Values for ΔG^O at various temperatures for the two different concentrations are given in Table III. Qualitative values for ΔH^O are also given. However, the very narrow temperature range accessible, because of solubility limitations in the determination of K_{eq} (as well as the very small change in K_{eq} over this temperature range) does not permit extremely acurate ΔH^O values to be obtained (see Error Analysis in the Historical). The values of ΔH^O at the different concentrations were calculated to permit relative comparisons between this method of evaluating ΔG^O and the chemical shift method[16] also used in this study. Calculations of ΔH^O were done by a least-squares analysis of the plot of ln K_{eq} vs 1/T using a programmable, hand calculator (Hewlett-Packard model 25) (see Figure 5, page 100). The values for ΔG^O in Table III clearly show that the conformer corresponding to the upfield signal in the low temperature NMR spectra of this equilibrating system is favored thermodynamically by a modest amount.

Previous work recorded in the literature[50] suggested that steric compression due to typical 1,3-interactions with protons on the cyclohexyl ring would cause proton signals to be shifted to lower field for axially situated methylene groups. Based on these observations, we initially concluded that structure 56a represented the predominant conformer in our system. In order to establish unequivocally the

TABLE III

CALCULATION OF THERMODYNAMIC PARAMETERS BY INTEGRATED AREAS[a] FOR 56a $\rightleftarrows$ 57a
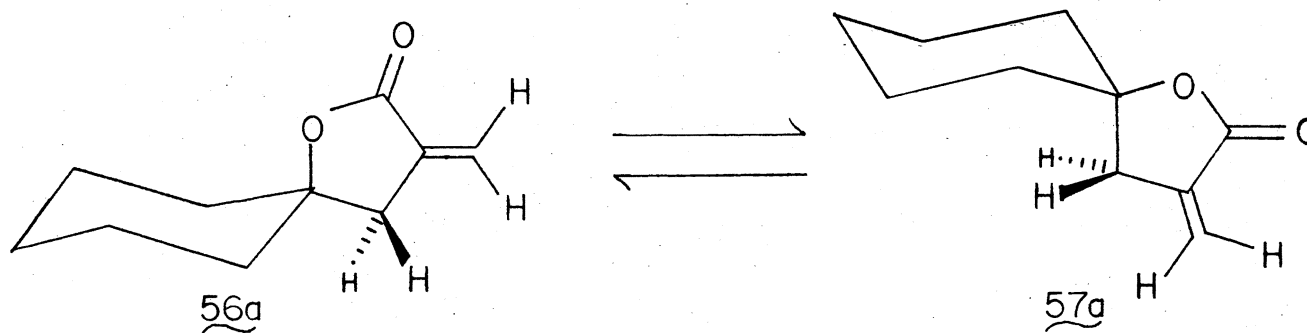
Conc.	T °K	K_{eq} ([57a]/[56a])	ΔG^o (kcal/mol)	ΔH^o (kcal/mol)[b]
0.036 M	185	0.754 ± 0.009	+ 0.105 ± 0.005	
	181	0.779 ± 0.023	+ 0.090 ± 0.011	−0.563 (r^2 = 0.99)
	177	0.808 ± 0.006	+ 0.075 ± 0.003	
0.024 M	185	0.763 ± 0.005	+ 0.099 ± 0.002	
	181	0.776 ± 0.020	+ 0.091 ± 0.009	−0.480 (r^2 = 0.94)

TABLE III (Continued)

Conc.	T $^\circ$K	K_{eq} ([57a]/[56a])	ΔG° (kcal/mol)	ΔH° (kcal/mol)[b]
	177	0.811 ± 0.019	$+ 0.074 \pm 0.008$	

[a] Samples were prepared in acetone-$\underline{d}_6$ with TMS as an internal standard.

[b] ΔH° was calculated by a least-squares fit of ln K_{eq} $\underline{vs}$ $1/T$ using average values of K_{eq}.

conformer in predominance, compounds 56b and 57b were synthesized and isolated as shown above. Separation of the two isomers was achieved by column chromatography over Florisil. The compound isolated in predominance was submitted for X-ray analysis and was determined to be 56b. Independent NMR analysis of both isomers in solution showed distinctly that protons of the methylene group at C(4) in 56b resonate at higher field (δ 2.74) than the analogous protons in 57b (δ 2.85) (see page 35).

Although the low temperature method of integrated areas is the most theoretically satisfying technique for determining the equilibrium constant and for subsequent calculation of ΔG^o, it suffers from several limitations in this case. It was difficult to maintain constant probe temperatures below the coalesence temperature T_c for extended periods of time. The range of temperature in which determinations could be made was governed by the coalesence process and by the freezing point of the solvent. The compound 56a $\rightleftarrows$ 57a proved to be insoluble at low temperatures in CS_2, H_2CCl_2, $HOCH_3$ and cyclohexane. No other solvents were tried. While the values obtained for ΔG^o for 56a $\rightleftarrows$ 57a are of good accuracy, one cannot assume that they represent the equilibrium at higher temperatures, especially in view of the rather high value estimated for ΔH^o.

The chemical shift method of determining the equilibrium constant[16] was used to obtain values for ΔG^o at temperatures above T_c for which k_r (reaction rate constant) has the following relationship to ν_a and ν_e:

$$k_r \ll \pi[\nu_a \ \nu_e]/\sqrt{2}$$

Under these conditions of frequent exchange, a mobil system will give
rise to only one signal in the NMR spectrum for protons previously
affected by the reversal process under conditions of "slow" or infre-
quent exchange. The chemical shift of this signal will result from a
time averaging of the independent signals for the individual conformers,
weighted by the mean lifetime of the mobil system in each conformational
orientation.[8] The equilibrium constant can therefore be calculated by:

$$K_{eq} = (\delta_a - \delta) / (\delta - \delta_e)$$

δ_a = shift of $H_a(4)$ for pure conformer 57a

δ_e = shift of $H_e(4)$ for pure conformer 56a

δ = time average shift of 56a $\vec{\leftarrow}$ 57a.

Since δ_a and δ_e were not available above T_c in mobile systems, these
values were evaluated from the shift of the conformationally locked
t-butyl-substituted compounds 56b and 57b. Average shifts obtained at
each temperature are given in Table IV. The results of this method of
determining K_{eq} as well as ΔG^O (and ΔH^O-see Figure 6, page 101) are
shown in Table V. Again, the positive values of ΔG^O indicate the
conformational preference of 56a over 57a. The magnitudes of the
values for ΔG^O are greater from this method of calculation by a factor
of three than those values obtained by the low temperature area method.
However, values for ΔG^O for the lower temperatures may be calculated
from the higher temperature shift data using the thermodynamic
relationship shown;

$$\Delta G^O = \Delta H^O - T\Delta S^O$$

one can, of course, also calculate ΔH^O and ΔS^O. Comparison of the

TABLE IV

AVERAGE CHEMICAL SHIFTS[a] FOR H(4) PROTONS FOR $56a \overset{\rightarrow}{\leftarrow} 57a$, $56b$ AND $57b$
AT THE TEMPERATURES INVESTIGATED

Cpd	232.6°K	251.9°K	274.3°K	286.5°K
$56a \overset{\rightarrow}{\leftarrow} 57a$	282.896 (0.045)	281.816 (0.016)	280.580 (0.050)	279.895 (0.003)
$56b$	278.491 (0.017)	277.356 (0.010)	276.220 (0.050)	275.395 (0.052)
$57b$	288.881 (0.056)	288.011 (0.048)	286.956 (0.004)	286.499 (0.021)

[a]Average chemical shifts (and standard deviations in Hz from internal TMS for a minimum of 4 trials.

TABLE V

CALCULATION OF THERMODYNAMIC PARAMETERS BY CHEMICAL SHIFTS FOR $\underset{\sim}{56a} \overset{\rightarrow}{\underset{\leftarrow}{}} \underset{\sim}{57a}$[a]

T °K	K_{eq}	ΔG^o (kcal/mol)	ΔS^o (eu)[b]	ΔH^o (kcal/mol)[c]
286.5	0.681 ± 0.011	$+ 0.218 \pm 0.010$		
274.3	0.684 ± 0.022	$+ 0.208 \pm 0.009$	-1.5	-0.209
				$(r^2 = 0.96)$
251.9	0.720 ± 0.012	$+ 0.164 \pm 0.009$		
232.6	0.736 ± 0.023	$+ 0.142 \pm 0.015$		
185.0		$+ 0.099 \pm 0.002$[d]		
		$(+0.070)$[e]		
181.0		$+ 0.091 \pm 0.009$[d]		
		$(+ 0.064)$[e]		
177.0		$+ 0.074 \pm 0.008$[d]		
		$(+ 0.058)$[e]		

[a]Samples were prepared as 0.024 M solutions in acetone-$\underline{d}_6$ with TMS as an internal standard.

[b]Calculated from: $\Delta S^o = (\Delta H^o - \Delta G^o)/T$.

[c]ΔH^o caclulated by least-squares fit of ln K_{eq} $\underline{vs}$ 1/T using average values of K_{eq}.

[d]Values calculated from integrated areas (Table III).

[e]Values extrapolated from chemical shift data.

extrapolated values with actual values calculated at low temperatures
by the use of integrated areas (Table V) shows good agreement. A plot
of ln K_{eq} vs 1/T (see Figure 8, page 103) of the combined integrated
area and chemical shift data gave a "best" value for ΔH^o of $-0.133 \pm$
0.04 kcal/mol and a "best" value of ΔS^o of ca. -1.2 eu.

To investigate the kinetics of the ring reversal, a study of the
NMR spectra of the mobil system 56a $\rightleftarrows$ 57a was undertaken using complete
line-shape analysis (L.S.A.).[8] The 56a $\rightleftarrows$ 57a system was particularly
suited to this type of evaluation because the spiro ring junction effec-
tively isolates the five-membered ring of the lactone from the six-
membered ring. This reduces the spectral pattern of the protons in the
lactone ring to a first-order AMX_2 pattern which can be simulated by a
DNMR3 program.[56] Because of the extensive H-H coupling in the spectrum,
as well as the need to evaluate the rate constant over a range of tem-
peratures, the approximate equations[58] which were derived from line-
shape theory were not deemed feasible.

The chemical shifts and coupling constants used in the analysis
were extrapolated to higher temperatures assuming a linear relation-
ship. Values for the transverse relaxation time (T_2) were estimated
by measuring the width at half height of the TMS internal standard.
The values used as the input parameters for the line-shape analysis
are given for each temperature in Table VI.

Visual comparison of the simulated spectra with the experimental
spectra was used to assess the closeness of the fit. Estimates of
the deviations in the rate constant were also done in this fashion.
The results of the simulations are shown in Figure 2 and in Plates
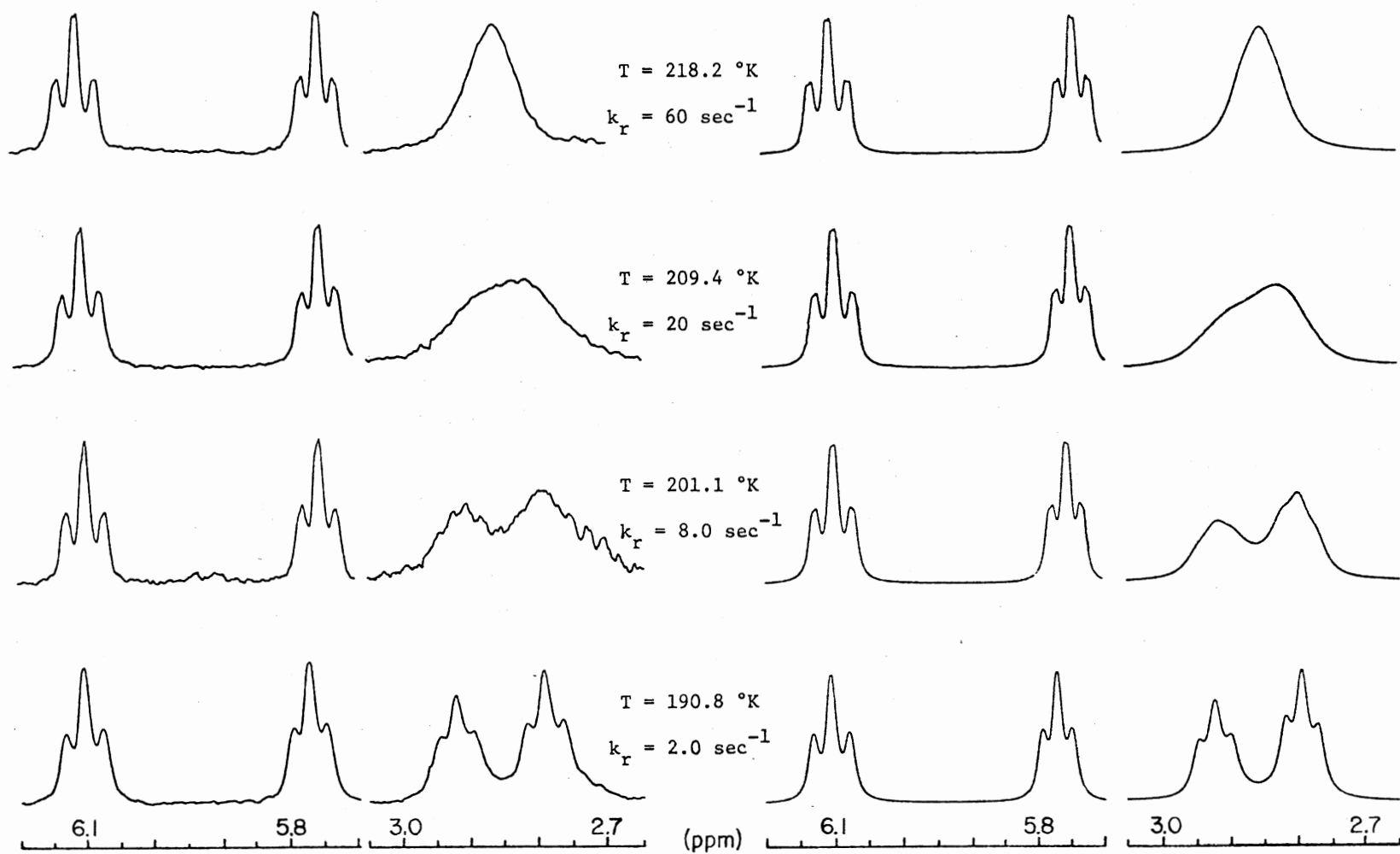
Figure 2. Experimental (Left) and Simulated (Right) $AMX_2 \rightleftharpoons AMX'_2$ DNMR Spectrum of 56a $\rightleftharpoons$ 57a. Samples Were Prepared as 0.024 M Solutions in Acetone-$\underline{d}_6$ with TMS as an Internal Standard

TABLE VI

SPECIAL PARAMETERS USED IN THE LINE SHAPE ANALYSIS OF 56a $\rightleftarrows$ 57a
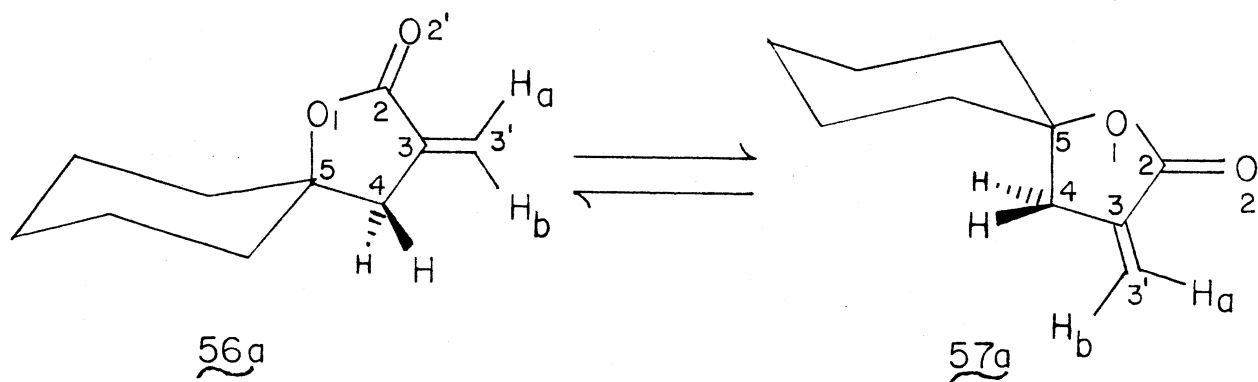
T(^{O}K)	Chemical Shifts (Hz from TMS)				Coupling Constants (Hz)			K_{eq}	T_2(s)	k(s^{-1})
	56a $\rightleftarrows$ 57a		57a	56a	56a $\rightleftarrows$ 57a					
	H_a(3')	H_b(3')	H(4)	H(4)	$J_{H_a-H_b}$	$J_{H_a-H_c}$	$J_{H_b-H_c}$			
190.8	609.320	576.192	279.477	292.338	0.545	2.667	2.278	0.802	0.220	2.00
201.1	608.800	574.600	279.477	292.338	0.759	2.768	2.400	0.757	0.260	8.00
209.4	608.600	574.000	279.477	292.338	0.759	2.768	2.400	0.750	0.260	20.00
218.2	608.939	573.198	279.477	292.338	0.759	2.768	2.400	0.748	0.300	60.00

XIX-XXVI and the calculated activation parameters are tabulated in Table VII.

Side bands resulting from a large solvent peak (upfield) is noticeable in the experimental spectrum obtained at $201^{\circ}K$ as shown in Figure 2. Repeated attempts failed to remove this interference at this temperature. However, the side bands were minor or did not exist at the other temperatures used in this investigation.

It is interesting that values from the literature[26,84] for ΔG^* in simple and 1,1-disubstituted cyclohexyl systems are in close agreement with our values for the various temperatures investigated. A comparison of published values for ΔS^* and ΔH^* for the simple systems with those found for $\underset{\sim}{56a} \rightleftarrows \underset{\sim}{57a}$ is difficult since there appears to be large discrepancies in the magnitudes of these parameters even in simple systems. For example, values for ΔS^* ranging from + 4.9 to 5.8 eu have been recorded for cyclohexane itself.[4] In regard, it is known that errors in ΔH^* and ΔS^* are coupled (due to the methods used to calculate them) so that high ΔH^* values correspond to low ΔS^* values and vice versa.[8] While it has been suggested that extension of the temperature range would reduce the error in ΔH^* and ΔS^*, the spectra must remain reasonably sensitive to changes in the rate constant at the extremes of this range.[8] We did not detect any significant change in the spectrum for our system above $235^{\circ}K$ ($- 38^{\circ}C$).

It was found that the five-membered lactone ring is puckered in the solid state. Indeed, even though the molecule $\underset{\sim}{56b}$ does not possess an asymmetric carbon, it crystallizes in the non-centrosymmetric space group $P2_12_12_1$ due to selective crystallization of the puckered forms.

TABLE VII

ACTIVATION PARAMETERS CALCULATED FROM LINE-SHAPE
ANALYSIS FOR 56a $\rightleftharpoons$ 57a[a]

T (^{O}K)	k_r (by L.S.A.)	ΔG^* (kcal/mol)
218.2	60 $\pm$ 5	10.9 $\pm$ 0.11
209.4	20 $\pm$ 2	10.9 $\pm$ 0.11
201.1	8 $\pm$ 1	10.9 $\pm$ 0.13
190.8	2 $\pm$ 0.2	10.7 $\pm$ 0.10

ΔH^* (kcal/mol)[b]	ΔS^* (eu)[b]
+ 9.60 $\pm$ 1.3	- 5.9 $\pm$ 6.3

[a]Samples were prepared as 0.024 M solutions in acetone-d_6 with TMS as
as an internal standard.

[b]ΔH^* and ΔS^* were calculated from a least squares fit of $\ln(k_r/T)$ vs
$1/T$, $r^2 = 0.998$ (see Figure 7, page 102).

Although the mirror image of this form would be expected to be of equal energy, the space requirements of a disordered lactone would be too great to allow both conformers of the puckered ring to exist together in a disordered crystal structure.

In solution, the barrier to interconversion of the five-membered ring between two conformers must be very small. One can see from the NMR data in Table II for the 7,7-dimethyl analogue $\underset{\sim}{56c} \xrightarrow{\leftarrow} \underset{\sim}{57c}$ that this interconversion may be biased indirectly by destruction of the symmetry of the system owing to increased 1,3-interactions experienced by the five membered ring. This results in nonequivalence of the H(4) protons. This symmetry of interaction is restored in the 7,7,9,9-tetramethyl substituted analogue $\underset{\sim}{56d} \xrightarrow{\leftarrow} \underset{\sim}{57d}$ resulting in the familiar AMX_2 pattern for the lactone ring protons (see Plates X and XI). The interconversion (or "breathing motion") of the five-membered ring must occur in solution simultaneously with the six-membered reversal process. Although not strictly analogous, the barrier for the pseudorotation between puckered forms of cyclopentanone has been determined to be between 2.1 and 3.7 kcal/mol.[12] This corresponds to a rate of reversal (assuming small ΔS^*) at $190^{\circ}K$ of 2.2×10^8 to 1.5×10^{10} s^{-1}. Thus, it would seem to be much too rapid to be detectable via NMR methods. However, if the NMR spectrum is sensitive to changes induced by this process, the possibility of the breathing motion affecting the magnetic field around certain nuclei in the spectrum cannot be eliminated and may be a source of error, especially at the lower temperatures. However, this process would not be expected to interfere with evaluation
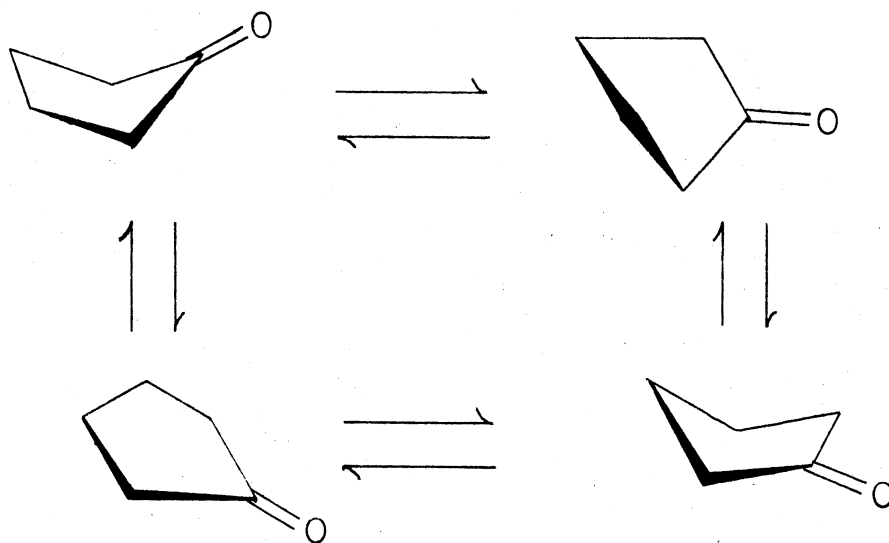
of the thermodynamic parameters, assuming that this motion in the five-

membered ring does not impart any dissymmetric operation preferentially

on either of the six-membered conformers.

As mentioned previously, several studies in the past have cast

doubt on the validity of the chemical shift method in the evaluation

of an equilibrium constant.[6,47,48] Jensen and Beck [47] showed evidence

suggesting that the chemical shift method, as originally applied by

Eliel,[16] was invalid. Free energy values (reported as $A = -\Delta G^{\circ}$ for an

equilibrium defined as axial $\overrightarrow{\leftarrow}$ equatorial) for several mono-substituted

cyclohexanes obtained by the shift method at ~25°C were compared directly

with A values obtained at very low temperatures (< - 80°C) from inte-

grated areas. As mentioned previously (see Historical), a correction

was applied to the chemical shift method based on the shift difference

observed at low temperatures; the values thus derived at ~25°C were

also compared to the values calculated by integrated areas. It was

noted by Jensen and Beck that the "corrected" values in all cases were

much closer to the values obtained by integrated areas than those obtained by the "uncorrected" method. However, this inherently assumes that the ΔS^o for the equilibrium over a temperature range > 100°C is ca. 0.0 eu. As will be demonstrated later, this is not necessarily the case. Jensen and Beck[47] report only one complete set of chemical shifts at a temperature other than ~25°C. The complete set of values for bromocyclohexane ($\underset{\sim}{31} \overset{\rightarrow}{\leftarrow} \underset{\sim}{32}$) are reproduced in Table VIII. For a temperature of + 24°C the "corrected" value of ΔG^o (- 0.55 kcal/mol) compared well with the value obtained by integrated areas at - 84°C (- 0.49 kcal/mol) if one assumed a negligible change for ΔS^o. The "uncorrected" value for ΔG^o at 25°C was given as - 0.35 kcal/mol.[47] At ~- 48°C, we obtain a completely different result. The "corrected" value, calculated from the data given by Jensen and Beck[47] using the method which they outlined, was - 0.76 kcal/mol and the "uncorrected" value (calculated directly from the data) was - 0.55 kcal/mol. Clearly, if the "corrected" method is valid, one should be able to calculate intermediate values of ΔG^o which also compare favorably with those obtained by the integrated area method at very low temperatures. In this case, the value of ΔG^o (- 0.76 kcal/mol at - 48°C) calculated for an intermediate temperature does not correlated well with the integrated area value. This fact, coupled with the comparative improvement in the ΔG^o value (- 0.55 kcal/mol at - 48°C) calculated by the "uncorrected" method (same temperature), suggests that many careful variable temperature studies are needed before either method can be accepted unequivocally.

A comparison of the "corrected" and "uncorrected" chemical shift methods for $\underset{\sim}{56a} \overset{\rightarrow}{\leftarrow} \underset{\sim}{57a}$ is shown in Table IX. The correction values were

TABLE VIII

THE EFFECT OF TEMPERATURE ON THE CHEMICAL SHIFTS[a] OF METHINE RESONANCES IN
BROMOCYCLOHEXANE, AND CIS- AND TRANS-1-BROMO-4-t-BUTYLCYCLOHEXANE[47]
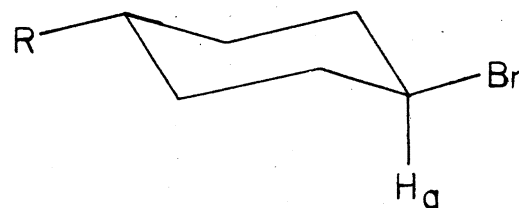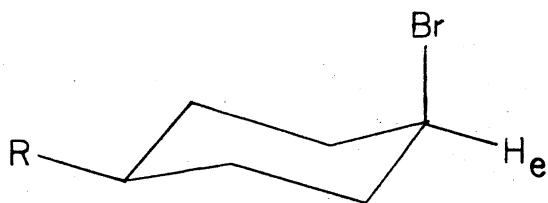
T $^{\circ}$C	31 $\rightleftarrows$ 32 (R = H)		T $^{\circ}$C	33 and 34 (R = t-bu)		-ΔG$^{\circ}$ (kcal/mol)[b]	
	31 (H$_e$)	32 (H$_a$)		33 (H$_e$)	34 (H$_a$)	"corrected"	"uncorrected"
+ 24		406.2	+ 24	452.9	380.4	0.55	0.35
- 47		397.6	- 49	454.2	380.9	0.76[c]	0.55[c]
- 84	459.0	387.2	- 84	455.3	381.7	0.55[d]	
- 91	459.7	387.4	- 92	455.7	381.9	----[e]	----[e]

TABLE VIII (Continued)

T $^{\circ}$C	31 32 (R = H		T $^{\circ}$C	33 and 34 (R = $\underline{t}$-bu)		$-\Delta G^{\circ}$ (kcal/mol)[b]	
	31 (H$_e$)	32 (H$_a$)		33 (H$_e$)	34 (H$_a$)	"corrected"	"uncorrected"
- 102	460.0	387.8	- 100	456.0	382.1	----[e]	----[e]

[a] Shifts in H$_z$ from TMS for 0.50 $\pm$ 0.01 M solutions in CS$_2$.

[b] $-\Delta G^{\circ}$ given as A values in Ref. 47.

[c] Calculated from values reported in Ref. 47

[d] From integrated areas (Ref. 47)

[e] Shift method cannot be applied.

TABLE IX

COMPARISON OF "CORRECTED" AND "UNCORRECTED" CHEMICAL SHIFT METHODS FOR 56a $\rightleftarrows$ 57a

T (°K)	Chemical Shifts[a]				$\Delta G°$ (kcal/mol)	
	56a[H(4)]	57a[H(4)]	56b[H(4)]	57b[H(4)]	"corrected"[c]	"uncorrected"[d]
286.5	279.895[b]		275.395	286.499	0.081	0.218
274.3	280.580[b]		276.220	286.956	0.072	0.208
251.9	281.816[b]		277.356	288.011	0.046	0.164
232.6	282.896[b]		278.441	288.881	0.032	0.146
185.0	279.522	292.426	281.491	291.470	----[e]	----[e]
177.0	280.067	292.932	281.973	292.258	----[e]	----[e]

[a]Shifts in Hz from TMS for 0.024 M solutions in acetone-d_6.

[b]Time averaged shifts for equilibrium 56a $\rightleftarrows$ 57a.

[c]Calculated by method given in Ref. 47.

[d]Calculated by method given in Ref. 16.

[e]Shift methods are not applicable.

determined at the low temperature ($< - 190^{\circ}K$) and applied to the shift values as given in Table IV. It is evident that if one considers only one temperature, e.g. $286.5^{\circ}K$ ($13^{\circ}C$), the "corrected" values calculated by the method of Jensen and Beck[47] would compare favorably with those values obtained at low temperatures (Table III). However, if one considers the temperature dependence of the equilibrium constant (and ultimately the value of ΔS°), the method of Jensen and Beck shows a progressively larger deviation at lower temperatures from the integrated area values, whereas the original chemical shift method proposed by Eliel[16] shows a progressively smaller deviation. Also, as seen in Table V, values obtained by extrapolation to lower temperatures for the method of Eliel gives values in very good agreement with those obtained at low temperature. It should be emphasized that in bromocyclohexane the data is very meager and no attempt is made here to discredit either method. On the contrary, it is our opinion that each case must be judged on its individual characteristics, and that all methods must be compared carefully over an extended temperature range.

The H(4) protons for $\underset{\sim}{56a} \overset{\rightarrow}{\leftarrow} \underset{\sim}{57a}$, $\underset{\sim}{56b}$, and $\underset{\sim}{57b}$ are insulated from the six-membered ring by a carbon atom. It has been observed[18,22] that this insulation could reduce the influence of distortion in the six-membered ring due to the t-butyl group in the determination of ΔG°. In addition, the X-ray analysis of $\underset{\sim}{56b}$ shows that distortion in the cyclohexyl system due to the spiro ring junction is greater than the distortions due to the t-butyl group. This can best be seen by comparison of the tortion angles listed in Table X. Angles C(9)-C(10)-C(5)-C(6) and C(10)-C(5)-C(6)-C(7) clearly show a deviation at the spiro end from the normal value of 57° for cyclohexane [28,63] by

TABLE X

TORSION ANGLES FROM X-RAY ANALYSIS OF CIS-8-t-BUTYL-3-METHYLENE-
1-OXASPIRO[4.5]DECAN-2-ONE (56b)

56b
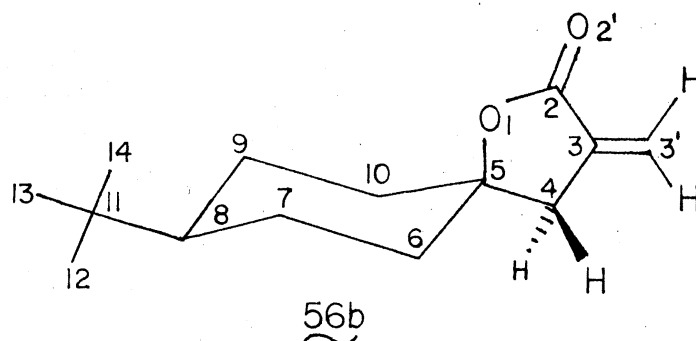
Five-membered Ring		Six-membered Ring	
O(1)-C(2)-C(3)-C(4)	6.7°	C(5)-C(6)-C(7)-C(8)	-55.1°
C(2)-C(3)-C(4)-C(5)	-18.6°	C(6)-C(7)-C(8)-C(9)	59.4°
C(3)-C(4)-C(5)-O(1)	23.1°	C(7)-C(8)-C(9)-C(10)	-60.4°
C(4)-C(5)-O(1)-C(2)	-20.5°	C(8)-C(9)-C(10)-C(5)	56.5°
C(5)-O(1)-C(2)-C(3)	8.9°	C(9)-C(10)-C(5)-C(6)	-49.5°
		C(10)-C(5)-C(6)-C(7)	48.8°

7.6° and 8.2°, respectively. Angles C(6)-C(7)-C(8)-C(9)-C(10) show a

deviation at the t-butyl end of 2.4° and 3.4°, respectively. These

value, of course, cannot be extrapolated directly to a solution of 56b.

However, studies of a few simple and substituted cyclohexanes as well

as a variety of pentamethylene heterocycles in solution[63] have shown

agreement with X-ray data of such parameters within $\pm$ 2°. This sug-

gests that structural changes for such systems upon dissolution are

small. Hence, it would be expected that chemical shift differences

between biased and unbiased systems in solution due to the t-butyl

group would be small relative to the effects at the spiro part of

the molecule. The agreement of the extrapolated values in Table V

with those values obtained by integrated areas clearly supports this

contention.

As stated previously, the thermodynamic parameter ΔG° calculated

displays a small but distinct conformational preference for the con-

former 56a (C-O bond axial). Values in the literature for similar

spiro dioxolane systems[89] have yielded comparable results for ΔG° at

low temperatures. The ΔG° values obtained at higher temperatures are

consistent with those obtained at low temperatures, if one assumes

a value of - 1.5 eu to be representative for ΔS°. This value is

not unreasonable when compared to published values obtained for the

entropy change favoring, for example, the less assqciated OH group

in the axial conformer of 3,3,5-trimethylcyclohexanol in strongly

associating solvents.[17] It has also been shown that aprotic, polar

solvents can strongly influence the position of an equilibrium when

there exists a possible preferential solvation effect for one of the

isomers.[22]

In order to qualitatively assess the affects of solvation in the equilibrium, each of the spiro lactones in this study was subjected to ^{1}H NMR analysis in acetone-$\underline{d}_6$ and CCl_4 (or $DCCl_3$ when FT-NMR was necessary due to limited quantities of the compound). The results of these comparative studies are given in Table XI.

Careful inspection of Table XI reveals some extremely interesting features. Comparison of the chemical shift of the $\underset{\sim}{56}$ [H(4)] $\rightleftarrows$ $\underset{\sim}{57}$ [H(4)] for the $\underset{\sim}{56a}$ $\rightleftarrows$ 57a system with those in $\underset{\sim}{56b}$ [H(4)] and $\underset{\sim}{57b}$ [H(4)] systems

$\underset{\sim}{56}$ $\underset{\sim}{57}$
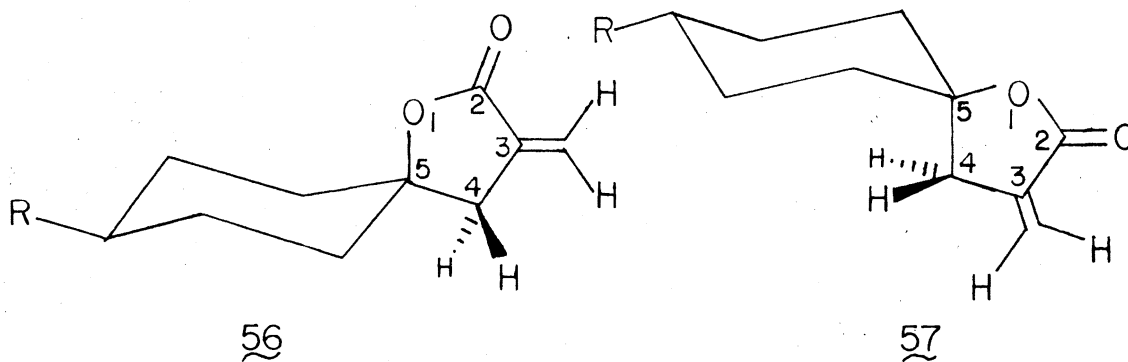
in $DCCl_3$ shows that the shift in $\underset{\sim}{56a}$ $\rightleftarrows$ $\underset{\sim}{57a}$ (δ 2.71) is closer to the shift for $\underset{\sim}{57b}$ (δ 2.74) than for $\underset{\sim}{56b}$ (δ 2.65). This suggests that in $DCCl_3$ the position of the equilibrium is <u>reversed</u> from that observed in acetone-$\underline{d}_6$. That is to say, in $DCCl_3$ conformer $\underset{\sim}{57a}$ is favored ($\Delta G^o \simeq -0.4$ kcal/mol), while in acetone-$\underline{d}_6$ $\underset{\sim}{56a}$ is favored ($\Delta G^o \simeq 0.2$ kcal/mol). Low temperature measurements of the equilibrium constant by integrated areas, which support the chemical shift findings in acetone-$\underline{d}_6$, unfortunately could not be done in $DCCl_3$ because of the high melting point of this solvent (- 63°C) and the very low solubility of $\underset{\sim}{56a}$ $\rightleftarrows$ $\underset{\sim}{57a}$.

This same type of startling reversal was also observed by Uebel and co-workers[89] for 2,2-dimethyl-1,3-dioxaspiro[4.5]decane

TABLE XI

SELECTED SOLVENT INDUCED CHEMICAL SHIFTS[a] FOR SPIRO LACTONES 56a-56e, 57a-57e

56

57

Cpd	Plate	Solvent	Chemical Shifts[a]			Coupling Constants[b]			R[g]	R, Chemical Shift[g]
			$H(3'a)^c$	$H(3'b)^c$	$H(4)^c$	J_{a-b}	J_{a-c}	J_{b-c}		
56a $\overset{\rightarrow}{\leftarrow}$ 57a	I	CCl_4	6.10	5.50	2.64	0.0	2.5	2.5		1.2-2.0
	II	$DCCl_3$	6.23	5.60	2.71	0.0	2.8	2.6	H	1.1-2.0
	III	$(D_3C)_2C=O$	6.07	5.62	2.78	0.8	2.8	2.5		1.2-1.9
56b	IV	$DCCl_3$	6.20	5.56	2.65	0.0	2.8	2.6	R(c)	0.86 (c)
	V	$(D_3C)_2C=O$	6.05	5.62	2.74	0.8	2.9	2.6		0.88 (c)

62

TABLE XI (Continued)

Cpd	Plate	Solvent	Chemical Shifts[a]			Coupling Constants[b]			R[g]	R, Chemical Shift[g]
			$H(3'a)^c$	$H(3'b)^c$	$H(4)^c$	J_{a-b}	J_{a-c}	J_{b-c}		
$\underset{\sim}{57b}$	VI	$DCCl_3$	6.22	5.59	2.74	0.0	2.8	2.6	$R(\underline{t})$	0.87 ($\underline{t}$)
	VII	$(D_3C)_2C{=}O$	6.05	5.63	2.85	0.7	2.8	2.5		0.89 ($\underline{t}$)
$\underset{\sim}{56c} \overset{\rightarrow}{\leftarrow} \underset{\sim}{57c}$	VIII	CCl_4	6.10	5.46	2.60	0.0	2.8	2.6	R''	1.10 (c), 0.93 (t)[d]
	IX	$(D_3C)_2C{=}O$	6.05	5.63	2.78^e	0.8	3.0	2.6	($\underline{c}$ & $\underline{t}$)	1.04 (c), 0.93 (t)[d]
$\underset{\sim}{56d} \overset{\rightarrow}{\leftarrow} \underset{\sim}{57d}$	X	CCl_4	6.10	5.47	2.60	0.0	2.8	2.6	R', R''	1.22 ($\underline{c}$), 0.93 ($\underline{t}$)[d]
	XI	$(D_3C)_2C{=}O$	6.08	5.68	2.80	0.8	2.8	2.6	(c & t)	1.18 ($\underline{c}$), 0.95 ($\underline{t}$)[d]
$\underset{\sim}{56e} \overset{\rightarrow}{\leftarrow} \underset{\sim}{57e}$	XII	CCl_4	6.08	5.46	2.64^f	0.75	2.8	2.75	R''	0.93 (c & t)
	XIII	$(D_3C)_2C{=}O$	6.06	5.64	2.82^f	0.8	2.8	2.6	($\underline{c}$ & $\underline{t}$)	0.96 ($\underline{c}$), 0.90 ($\underline{t}$)[d]

[a] Chemical Shifts in ppm from TMS.
[b] Coupling constants in Hz.
[c] Time averaged value for equilibrating systems, center of triplet.
[d] Assignment uncertain.
[e] Center of doublet of doublets.
[f] Center of quartet of triplets.
[g] $\underline{c}$ = cis; $\underline{t}$ = trans.
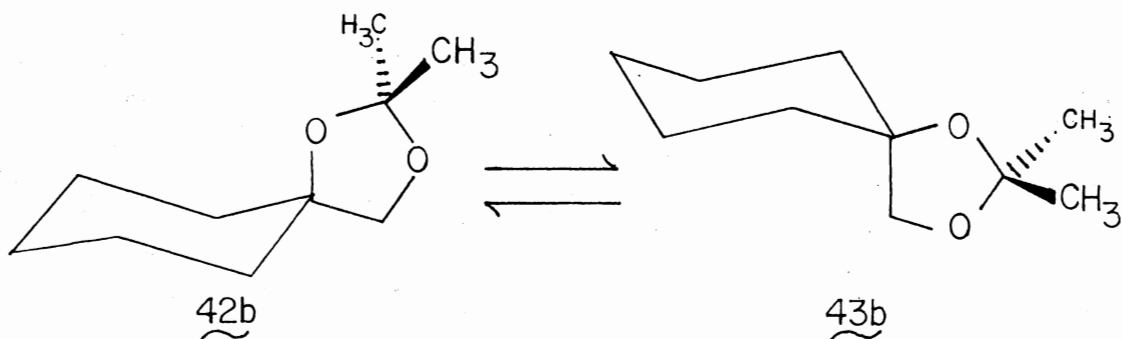
42b $\rightleftarrows$ 43b. Several other similar 1,3-dioxaspiro[4.5]decanes were also examined in this work.[89] Of all the systems studied, only 42b $\rightleftarrows$ 43b showed by the chemical shift method (ΔG^O = - 0.28 kcal/mol) and integrated area (ΔG^O = 0 0.13 kcal/mol) analysis a conformational preference for the conformer with the C-O bond in the equatorial posi-tion(43b). The investigation of 42b $\rightleftarrows$ 43b was done in a 1:9 mixture of $D_3COD:DCCl_3$ for the chemical shift measurements and in a 1:1 mix-ture of $D_3COD:DCCl_3$ for the integrated area method. All of the other experiments reported by Uebel and co-workers[89] on the other similar spiro dioxolanes were done in acetone-d_6.

Some type of differential solvent effect must be present in the 56a $\rightleftarrows$ 57a equilibrium. Ford and Allinger,[22] in a study of solvent effects of the carbethoxycyclohexane system (66 $\rightleftarrows$ 67), postulated that
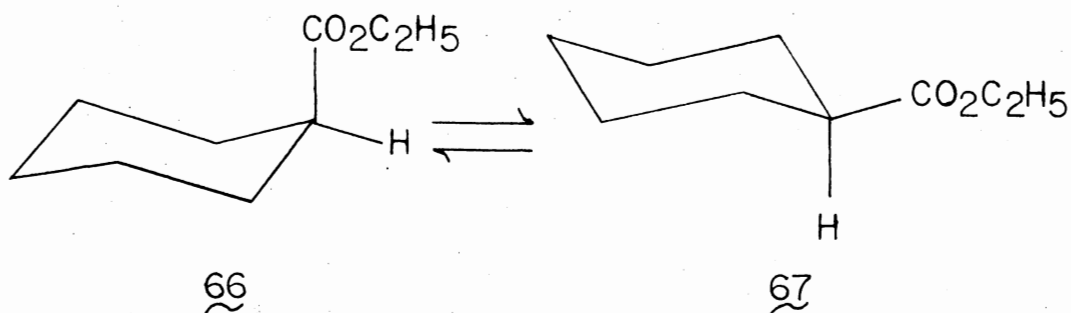
the axial conformer 66 would occupy a smaller molar volume than 67 and

therefore would be favored due to the exertion of internal solvent

pressure.[76] The latter would be greater in polar solvents than in non-

polar solvents. It is difficult to predict which conformer in the

56a ⇌ 57a system would have a larger molar volume and even more diffi-

cult to rationalize by this argument alone the apparent complete rever-

sal of the conformational preference. Eliel and Gilbert[17] have shown

that the magnitudes of ΔH^o and ΔS^o for the equilibrium of cis and

trans-butylcyclohexanol are very dependent upon the association proper-

ties of the solvent. However, no drastic changes in conformational

preferences were observed. While there is evidence in the litera-

ture[20,41,42,53] that chloroform can associate to some extent with many

proton acceptors (e.g. acetone[20,41,42] and diethyl ether[20,41]) it would

be very difficult to determine how this interaction could result in a

reversal of the conformational preference in the 56a ⇌ 57a system.

It is clear from the shift differences between CCl_4 and $DCCl_3$ for

protons 56a [H(4)]⇌57a [H(4)] that $DCCl_3$ in some manner solvates the

system different from that in acetone-d_6. Hydrogen bonding of the

deuterium with either or both of the oxygens seems very probable.

Indeed, evidence from both IR[20] and NMR[20,41,42,53] analysis strongly

suggests that hydrogen bonding between $HCCl_3$ and acetone exists to a

considerable extent. The deshielding of protons H(3'a), H(3'b) and

H(4) in the 56a ⇌ 57a system (as evidence by the down field shifts

for these proton signals in $DCCl_3$ compared to CCl_4) could result from

a net increase in the polarization of the lactone ring due to this

hydrogen bonding.[77] This assumes the dipole is directed parallel to
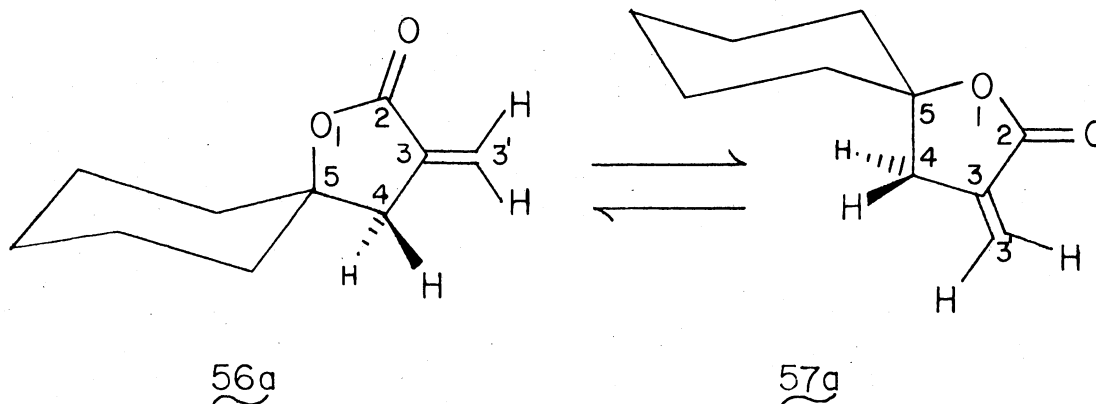
56a   57a

Shift Differences (DCCl$_3$ - CCl$_4$)

			$\Delta\delta$
56a [H(3'a)]	$\overset{\rightarrow}{\leftarrow}$	57a [H(3'a]	+ 13 Hz
56a [H(3'b)]	$\overset{\rightarrow}{\leftarrow}$	57a [H(3'b)]	+ 10 Hz
56a [H(4)]	$\overset{\rightarrow}{\leftarrow}$	57a [H(4)]	+ 7 Hz

the carbonyl bond and hydrogen bonding (with DCCl$_3$) could reduce the charge density of the lactone ring. If differential solvation of one of the conformers occurs in the 56a $\overset{\rightarrow}{\leftarrow}$ 57a system, one might expect that solvation effects would be dissymmetric with respect to the plane of the six-membered ring. In order to investigate this possibility, the spectra of the gem-substituted homologs 56c $\overset{\rightarrow}{\leftarrow}$ 57c and 56e $\overset{\rightarrow}{\leftarrow}$ 57e were examined. Conceivably the 7,7-dimethyl proton signal of 56c $\overset{\rightarrow}{\leftarrow}$ 57c might be used to evaluate this hypothesis. It is immediately evident as shown below that only one of the methyl groups in 56c $\overset{\rightarrow}{\leftarrow}$ 57c displays a solvent shift ($\Delta\delta$) in acetone-d$_6$ compared to the situation in CCl$_4$. The 6,6-dimethyl proton signals in 56e $\overset{\rightarrow}{\leftarrow}$ 57e whow a somewhat different behavior. Again, one of the proton signals for one methyl group is shifted upfield (- 4 Hz), but the proton signal for the other geminal group is shifted downfield (+ 2 Hz). This would seem to indicate that
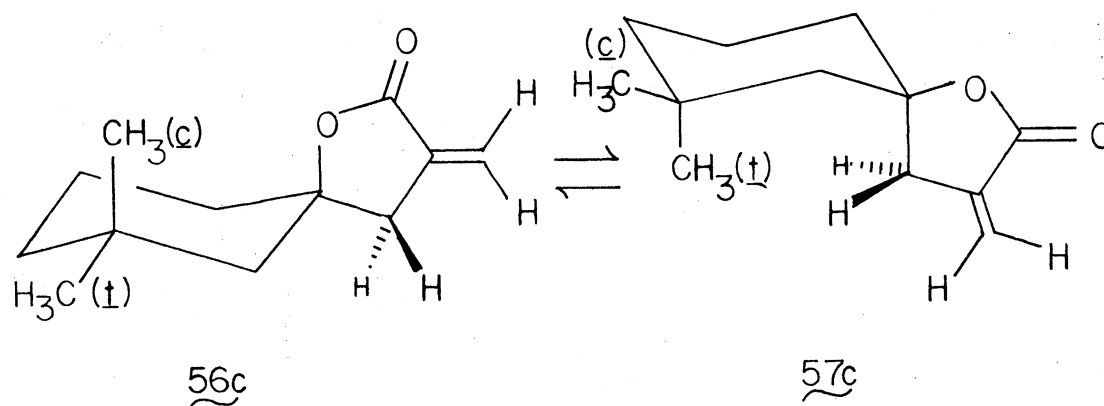
56c ⇌ 57c

	δCCl₄	δ(D₃C)₂C=O	Δδ
-CH₃(c)*	1.10	1.04	0.06
-CH₃(t)	0.93	0.9	~ 0.00

*tentative assignment of cis-, (c) and trans-, (t)

one of the methyl groups in the 56c ⇌ 57c equilibrium is within the anisotropic influence of the solvating acetone-d₆. The lack of a large shift difference for the other methyl group (¹H signals) suggests that this methyl lies outside the anisotropic influence of the acetone-d₆ which may be aligned with the dipole of the lactone ring. Results similar to this are also observed for the 56d ⇌ 57d system; however, the nature of the strong 1,3,5-interactions in this case makes the use of this compound as a model of somewhat dubious value. Nevertheless, some general conclusions can be drawn from these results. Solvation is acetone-d₆ most probably occurs in a dissymmetric fashion across the plane of the six-membered ring (note 56c ⇌ 57c; see above) and these solvation effects in acetone-d₆ can be detected for methyl protons situated in a cis or trans arrangement to the C-O bond in the
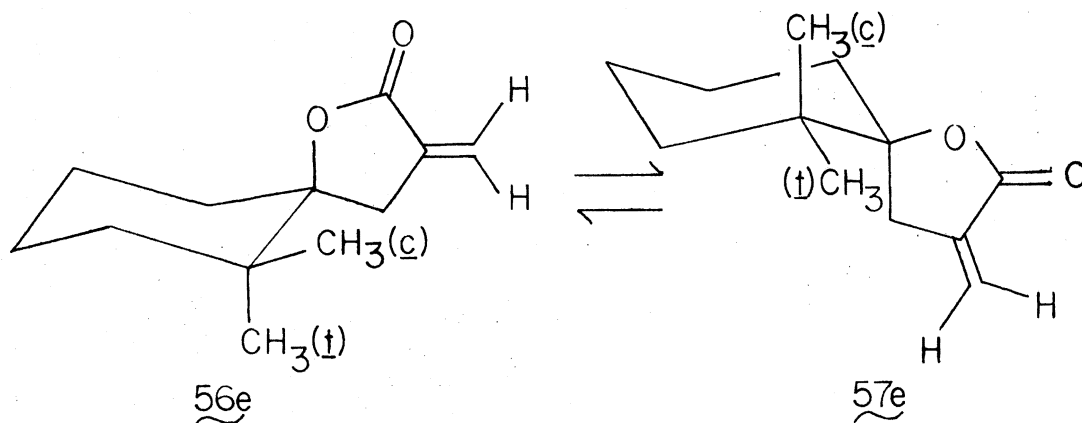
56e   ⇌   57e

δCCl_4	$\delta (D_3C)_2 C=O$	$\Delta \delta$
$-CH_3(\underline{c})^*$	1.18	~ $- 0.04$
$-CH_3(\underline{t})^*$	0.95	~ $+ 0.02$

five-membered ring (note 56e ⇌ 57e). Proposed solvent orientations for

the two different solvents are given below based upon parallel

(68 ⇌ 69, 70 ⇌ 71 and 72 ⇌ 73) and anti-parallel (74 ⇌ 75) alignment

of the solute-solvent dipoles. Of the four proposed interactions

suggested, the 74 ⇌ 75 antiparallel interaction seems unlikely. In

our opinion, the relatively high dielectric constant (ϵ = 20.5)[71] of

acetone would disfavor this type of alignment.[72] Both 68 ⇌ 69 and

70 ⇌ 71 could be expected to be favored in this type of polar medium,

and neither situation can be ruled out. The steric bulk of the methyl

groups in acetone-d_6 might be situated such that an increase in the

1,3-type interactions for conformer 69 could be manifested as shown.

This could lead to a favoring of conformer 68 in acetone-d_6 as

observed. However, if one assumes that the steric requirements of the

nonbonding electron pairs on O(1) are less than that of C(4) (see

page 69), then the relative lack of steric interference evident in

68 ⇌ 69

70 ⇌ 71

72 ⇌ 73

$\underset{\sim}{74}$ $\qquad$ $\underset{\sim}{75}$
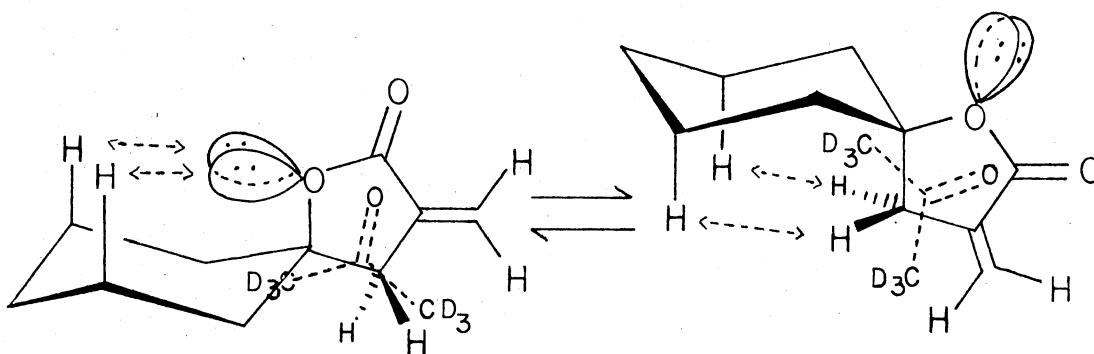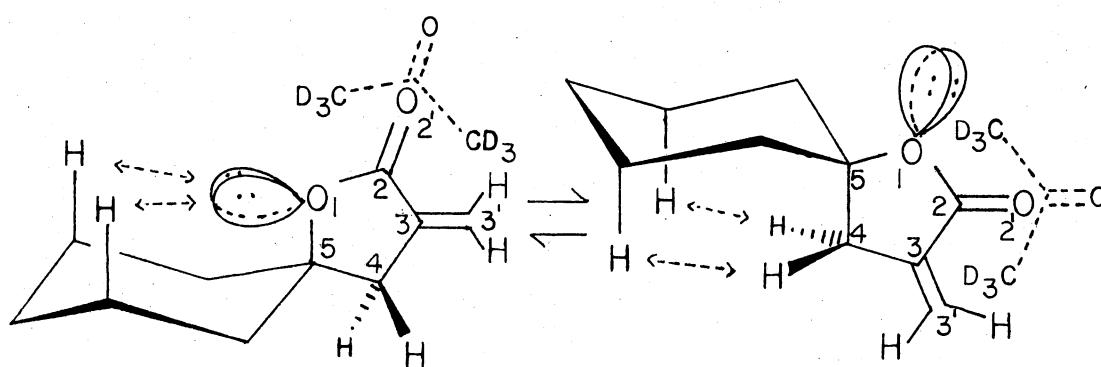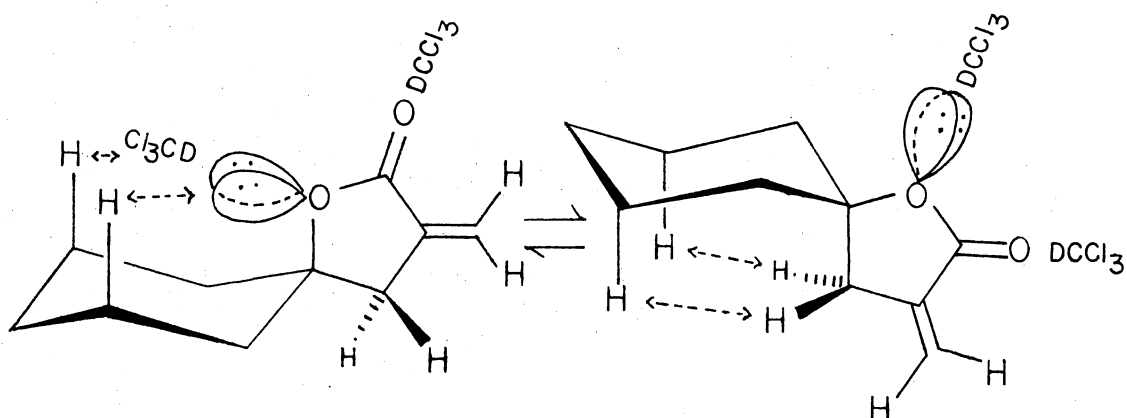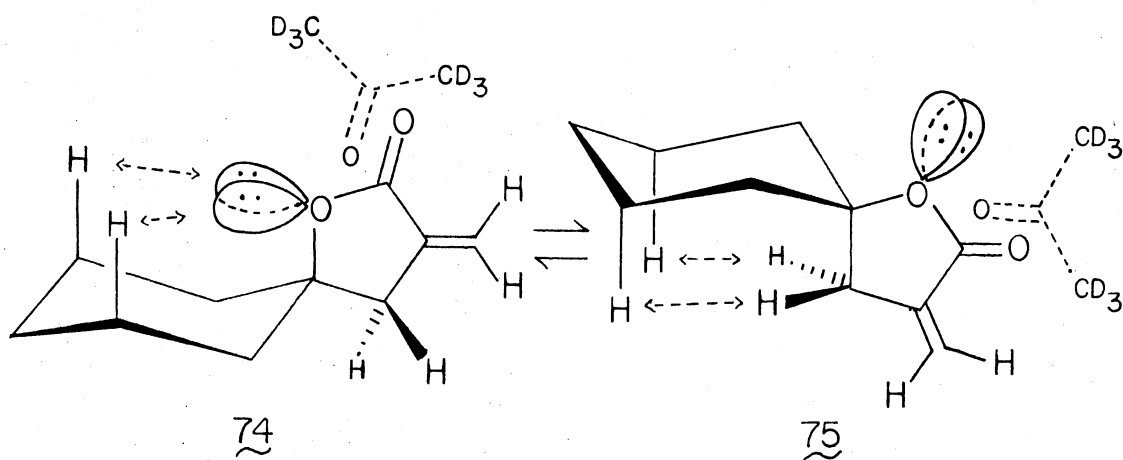
$\underset{\sim}{70} \overset{\rightarrow}{\leftarrow} \underset{\sim}{71}$ could also explain the observed preference for the conformer

with the C-O bond in the axial position.

A possible hydrogen-bond type of interaction of $DCCl_3$ with the

lactone could result in associations shown in $\underset{\sim}{72} \overset{\rightarrow}{\leftarrow} \underset{\sim}{73}$. Although the

carbonyl oxygen is probably the site of primary solvation, interactions

with the nonbonding electron pairs on O(1) must also be considered

(as shown in $\underset{\sim}{72} \overset{\rightarrow}{\leftarrow} \underset{\sim}{73}$). Such interactions could lead to a conforma-

tion preference for the more easily solvated conformer $\underset{\sim}{73}$ in which

O(1) is equatorially situated.

INDO calculations based upon the positional parameters obtained

from a single-crystal X-ray analysis of $\underset{\sim}{56b}$ predicts a dipole moment

of 4.8 D. The resultant vector is most probably directed across the

lactone ring towards the carbonyl oxygen ($\underset{\sim}{76}$). This approximation is

in good agreement with the observed dipole moment of 3.82 D for

γ-butyrolactone.[68] The direction and position of the dipole vector

as shown in $\underset{\sim}{76}$ was deduced by assuming the vector of the dipole

passes through the center of the negative and positive charges for

the lactone ring. These centers were calculated from the partial

$$\underset{\sim}{76}$$
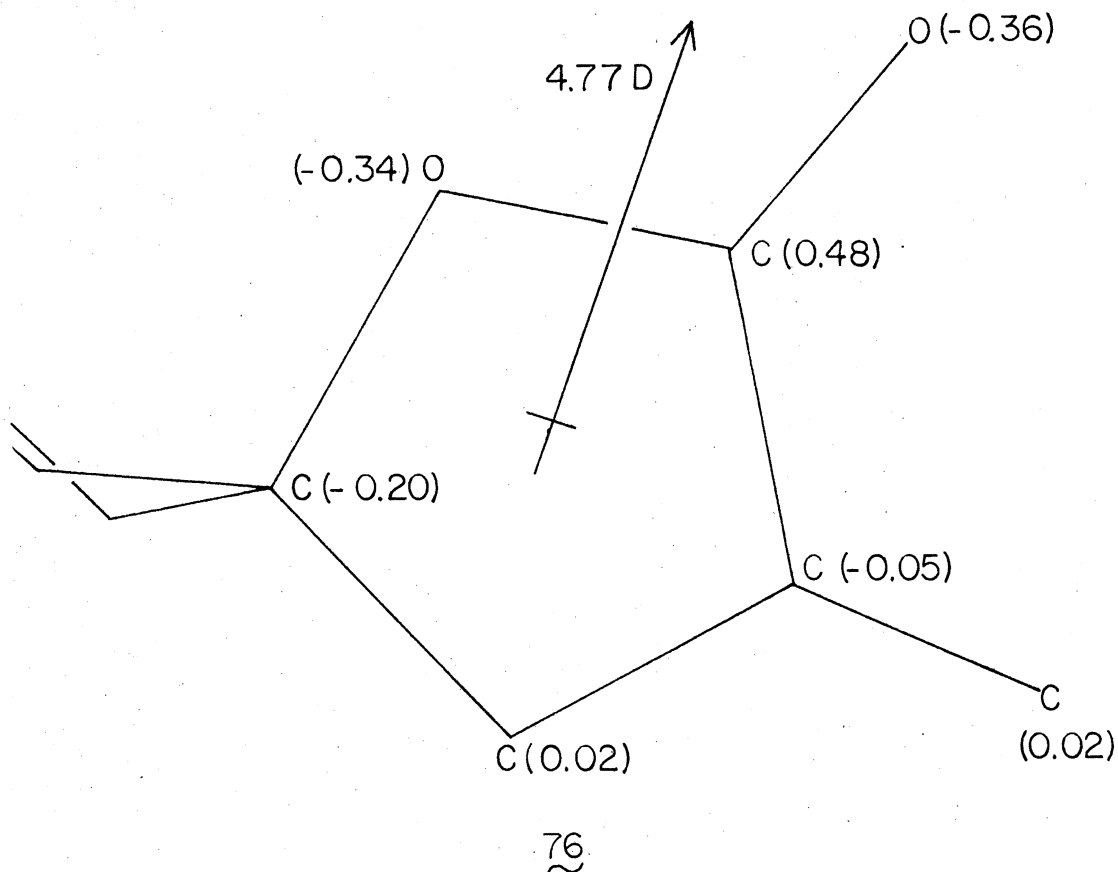
charges shown in $\underset{\sim}{76}$, also obtained from the INDO calculations. This strong dipole moment supports the possibility of both dipole-dipole and hydrogen bond-like interactions as postulated above.

The ^{13}C NMR of compounds ($\underset{\sim}{56a}$-$\underset{\sim}{56d}$ and $\underset{\sim}{57a}$-$\underset{\sim}{57d}$) were recorded in $DCCl_3$ and the shifts have been given in Table XII. Assignments of shifts were made on the basis of selected model compounds and off-resonance ^1H decoupled spectra. Since substitution of the six-membered ring results in shift differences for the ring carbons, little information can be gleaned from these shift values. Hence, these shifts are not discussed below, but are given in Table XII. The carbon

TABLE XII

^{13}C CHEMICAL SHIFTS OF CARBONS IN 56a-56d, 57a-57d
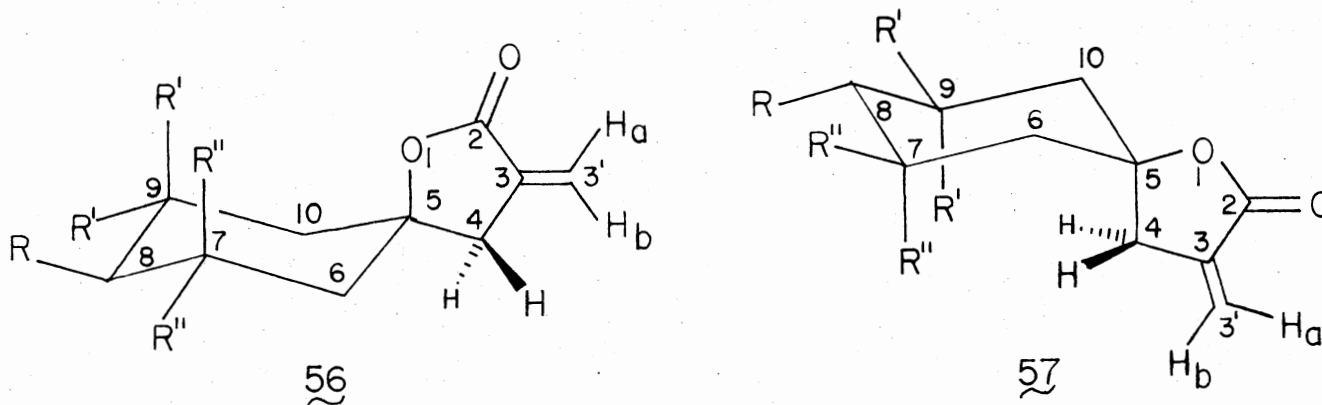
a. R = R' = R'' = H
b. R = t-bu; R' = R'' = H
c. R = R' = H; R'' = CH$_3$
d. R = H; R' = R'' = CH$_3$

Cpa[a]	^{13}C Chemical Shifts (Hz from TMS)[b]						Plate
	C(2)	C(3)	C(4)	C(5)	C(3')	C(6-10) and R Groups	
56a $\overset{\rightarrow}{\leftarrow}$ 57a	4272	3415	996	2097	3070	C(6)-C(10), 943; C(7)-C(9), 567; C(8), 624.	XXVII
56b	4275	3414	1024	2075	3067	C(6)-C(10), 960; C(7)-C(9), 578; C(8), 1184; R(t-bu), 815, 693.	XXVIII
57b	4192	3414	940[c]	2116	3072	C(4)-C(6)-C(10), 943[c]; C(7)-C(9), 606; C(8), 1175; R(t-bu), 811, 693[c].	XXIX

TABLE XII (Continued)

Cpa[a]	^{13}C Chemical Shifts (Hz from TMS)[b]						Plate
	C(2)	C(3)	C(4)	C(5)	C(3')	C(6-10) and R Groups	
56c ⇄ 57c	4272	3414	1043	2104	3061	C(6), 1246; C(7), 789; C(8), 962; C(9), 477; C(10), 943; R'', 711, 799[c].	XXX
56d ⇄ 57d	4272	3405	1078	2119	3053	C(6)-C(10), 1237; C(7)-C(9), 795; C(8), 1288; R''-R', 886, 722[c].	XXXI

[a]Samples were 0.3 g/3 mL solutions in $DCCl_3$, except 57b which was a saturated 0.05 mL micro solution.

[b]Assignment based upon off-resonance decoupled spectra and selected model compounds; spectrometer base frequency = 25.2 MHz.

[c]Assignment uncertain.

signals for the lactone ring, however, would be expected to be influ-
enced by the substitution of the six-membered ring perhaps in a subtle
and indirect fashion. As can be seen from Table XII, the chemical
shift of C(3) remains fairly constant in the series. A similar con-
sistency is present in the shifts of C(3'). The shift variation ($\Delta \nu$)
observed for C(2) is no greater than 3 Hz over the entire series except
for 57b. For example, the shift of C(2) in 57b (4192 Hz from TMS) is
$\Delta \nu$ = - 80 Hz from the shift for C(2) in 56a $\overset{\rightarrow}{\leftarrow}$ 57a (4272 Hz from TMS),
while C(2) in 56b (4275 Hz from TMS) differs from the 56a $\overset{\rightarrow}{\leftarrow}$ 57a C(2)
signal by $\Delta \nu$ = + 3 Hz. If the chemical shift method is applied to
these signals, a value of 0.0375 is calculated for K_{eq}, suggesting
56a is heavily favored. When the method is applied to the C(4)
signals in the 56a $\overset{\rightarrow}{\leftarrow}$ 57a, 56b and 57b systems, a value of 0.5 is
calculated for K_{eq}, again suggesting that 56a is favored. Clearly,
the shift method as applied to ^{13}C shifts must be treated with caution
and cannot be as yet universally accepted.

Single Crystal Analysis of 56b

The numbering scheme and bond distances are shown in Figure 3,
and bond angles in Figure 4. The structure consists of a six-membered
ring in the chair conformation, a spiro-fused, α,β-unsaturated γ-lactone
and an anchoring t-butyl group. The chair conformation of the six-
membered ring is significantly flattened near the spiro carbon atom as
can be seen from the torsion angles reported in Table X. This is most
likely due to a 1,3,5-interaction involving the axial C-O bond attached
to the spiro carbon atom since all other axial positions are occupied
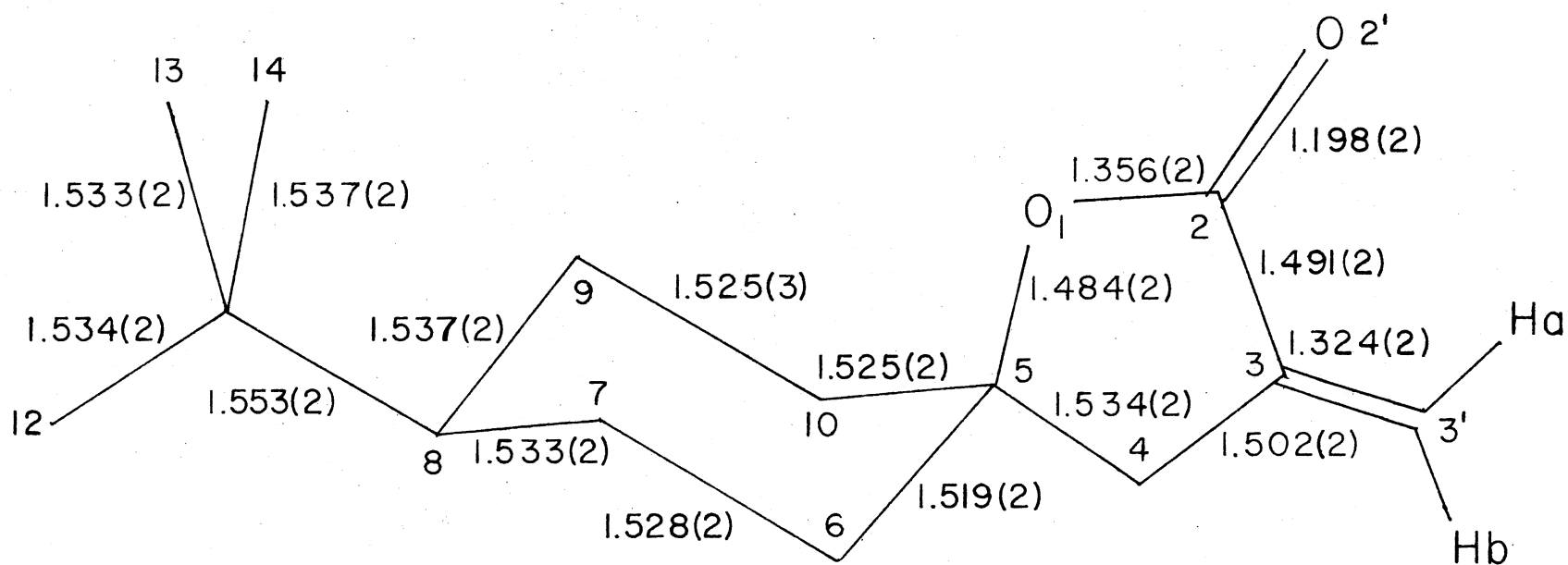
Figure 3. Bond Distances and Numbering Scheme for 56b. Estimated Standard
Deviations are Given in Parentheses
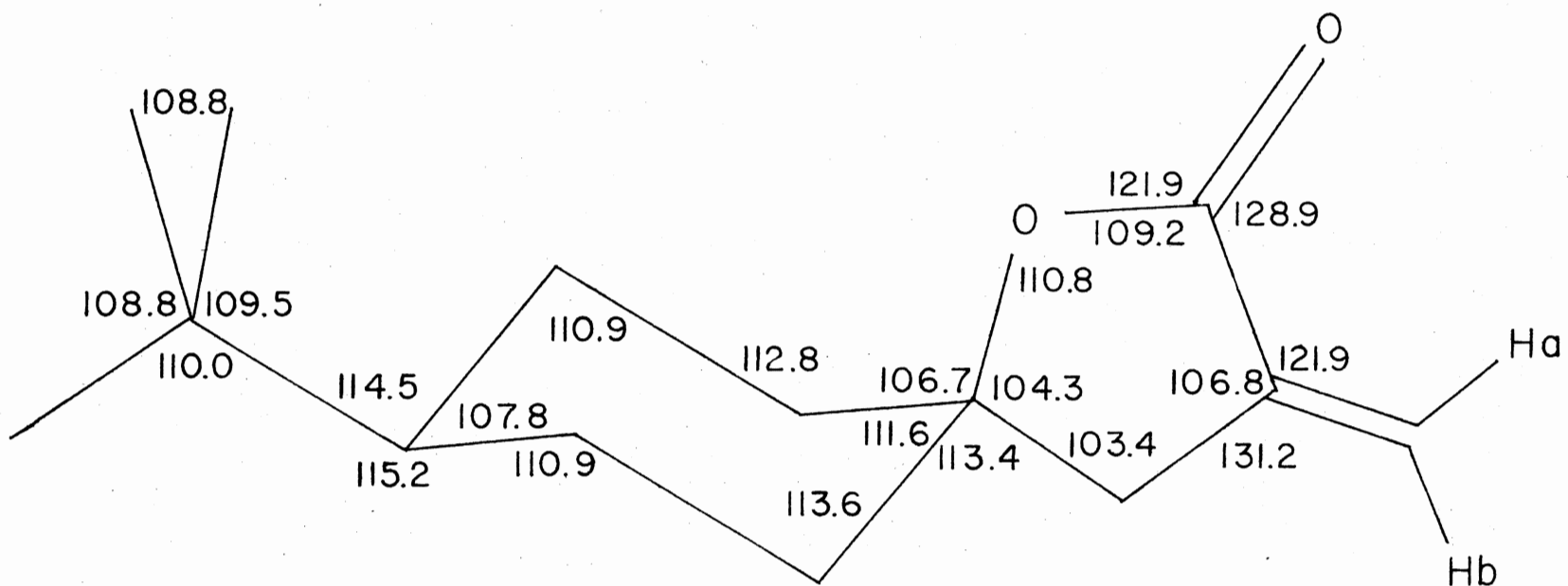
Figure 4. Bond Angles for $\underline{56b}$. The Standard Deviations are Between 0.11 and 0.16°. Additional Bond Angles are $O(1)-C(5)-C(6) = 107.2^{\circ}$, $C(4)-C(5)-C(6) = 113.0^{\circ}$, $C(8)-C(11)-C(13) = 112.^{\circ}$ and $C(12)-C(11)-C(6) = 107.6^{\circ}$.

by H atoms. The lactone ring is in a flattened twist (C_2) conformation as can be seen from the values of the internal torsion angles in Table X. The approximate two-fold axis passes through atom C(2) and bisects the C(4)-C(5) bond. The α,β-unsaturated γ-lactone in a group of natural products[10,15,54,91,92,94] show a wide range of conformations for the five-membered ring. Both the envelope (C_s) and twist (C_2) conformations have been observed with varying degrees of flatness.[15,54,92] The factors affecting the conformation in the present compound may include an attempt to minimize contacts with O(1) and the axial hydrogen atom or atoms C(7) and C(9) and at the same time minimize contacts between the hydrogen atoms on atom C(4) and the axial hydrogen atoms of atoms C(6) and C(10). In addition, crystal packing forces may also affect the conformation. It is interesting to point out that since many compounds possessing an α,β-unsaturated γ-lactone show biological activity which is attributed to this functional group that a structure activity relationship might exist which involves the conformation of the lactone ring. At this time, however, sufficient data is not available to test this hypothesis. The t-butyl group which anchors the conformation by occupying the equatorial position on C(8) is staggered with respect to the ring. The values of two representative torsion angles are C(7)-C(8)-C(11)-C(14) = 174.8° and C(9)-C(8)-C(11)-C(12) = 182.6°. One of the primary reasons for using X-ray diffraction to determine this structure was to ascertain whether the O atom or $\diagdown$CH$_2$ group occupies the axial position of the spiro C atom. All data including electron densities, bond lengths, least-squares refinement and location of H atoms show conclusively that the O atom occupies the axial position with no evidence for a disordered structure.

The bond lengths in the lactone compare well with the values reported for several natural products.[10,15,54,91,92,94] The weighted averages compiled from the literature are $O(1)-C(2) = 1.356$, $C(2)-C(3) = 1.486$, $C(3)-C(4) = 1.506$, $C(4)-C(5) = 1.542$, $C(5)-O(1) = 1.461$, $C(2)-O(2') = 1.205$ and $C(3)-C(3') = 1.324$ Å. The largest difference $(0.023$ Å$)$ is for the $C(5)-O(1)$ distance; all other differences are less than 0.01 Å. The $C(8)-C(11)$ bond length is slightly lengthened which is not unexpected for a bond to a bulky substituent. Inspection of bond angles indicate that the surroundings of atoms $C(2)$ and $C(3)$ are planar having the sum of bond angles equal to 360.0 and $359.9°$, respectively. The bond angles in the lactone ring show the same trends as those observed for the natural products.

The molecule could contain a mirror plane passing through atoms $C(5)$, $C(8)$, $C(11)$ and the midpoints between $C(7)-C(9)$ and $C(6)-C(10)$. However, if one calculates a least-squares plane through these points one finds that the entire lactone group is significantly out of the plane. The distances from this plane are as follows: $O(1) - 0.019$, $C(2) - 0.477$, $C(3) - 0.601$, $C(4) - 0.010$, $C(5) - 0.003$, $O(2') - 0.711$ and $C(3') - 1.146$ Å. One could also construct a stereoisomer of the molecule in the present structure by taking the mirror image through the least-squares plane thus flipping the lactone group to the opposite side. This molecule would have exactly the same energy and most likely occurs in both solution and the solid state. Although one conformer is selectively crystallized in the present structure, no attempt was made to determine which conformer precipitates although the question

could be resolved using the anomalous scattering of the oxygen atoms.[19]

It is not possible for both to exist in a disordered crystal structure

because the space requirements of a disordered lactone would be too

great. Experimentally no evidence for disorder was found as the refine-

ment of thermal parameters for all C, O and H atoms of the lactone

group was normal and no residual electron density was found in this

area of the final difference Fourier map. A calculation of intermo-

lecular distances revealed an unusually short contact between O(2')

and H(3'a) of 2.41 $\overset{o}{A}$ [H(3') transformed by (x, y, z-1)] which is about

0.2 $\overset{o}{A}$ shorter than the sum of the van der Waal radii.

To summarize, the thermodynamic parameters reported herein show

a slight predominance ($\Delta G^{o}_{-88^{o}C}$ = 0.10 kcal/mol) for conformer 56a

(C-O bond axial) in the equilibrium 56a $\rightleftarrows$ 57a in acetone-$\underline{d}_6$. This was

demonstrated conclusively by the determination of the integrated areas

56a   57a
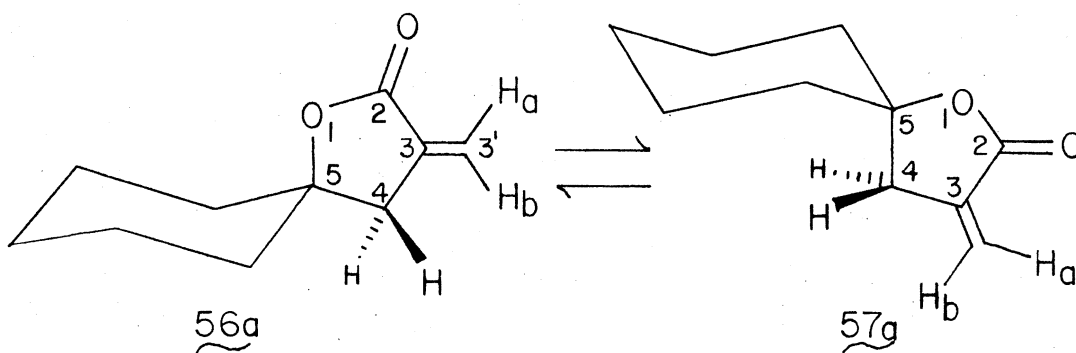
at very low temperatures and supported strongly by values (e.g.

$\Delta G^{o}_{13^{o}C}$ = 0.22 kcal/mol) calculated by the chemical shift method

at higher temperatures. It was also noted that while it is the O(1)-

C(5) bond and the C(4)-C(5) bonds which alternate between the axial

and equatorial positions in the equilibrating six-membered ring, the

substituents on the adjacent carbons may also play an important role in directing the equilibrium, especially in regards to their ability to interact with the solvent. This was graphically illustrated in the apparent reversal of the conformational preference of $\underset{\sim}{56a} \xrightarrow{\leftarrow} \underset{\sim}{57a}$ in $DCCl_3$ ($\Delta G^o_{37^oC}$ = - 0.4 kcal/mol favoring $\underset{\sim}{57a}$). A study involving determination of ΔG^o at one temperature for a series of substituted spiro dioxolanes[89] has also indicated that these types of interactions can markedly influence the equilibrium process so that predictions of values for the thermodynamic parameters, based on analogous systems in which substituents in the five-membered ring are different, must be done with care.

Variable temperature studies of the equilibrium constant given herein demonstrate the need for careful evaluation of general experimental techniques for the determination of thermodynamic parameters as applied to specific systems. Whereas both the "corrected"[47] and "uncorrected"[16] chemical shift methods can give values at specific temperatures which are in close agreement to those obtained by integrated areas, it is necessary to evaluate the temperature dependence of the conformational equilibrium to establish which method is best for a particular system.

Interestingly, the ΔG^* values (10.9 kcal/mol) determined for $\underset{\sim}{56a} \xrightarrow{\leftarrow} \underset{\sim}{57a}$ are similar to those reported for several 1,1-disubstituted cyclohexanes (e.g. 1,1-dimethoxycyclohexane, ΔG^* = 10.8 kcal/mol).[26] Comparison with the values of ΔG^* determined for cyclohexane (10.5 kcal/mol)[4] suggest that the spiro substitution actually stabilizes the ground state conformers relative to the transition state by a modest amount. Additional substitution on the six-membered ring,

which might increase the energy of the two conformers relative to the transition state _via_ steric 1,3-interactions, might be expected to lower the ring reversal energy barrier. Studies of 1,1,3,3-tetra- and 1,1,3,3,5,5-hexa-substituted cyclohexanes support this conclusion.[26] Hence it is not surprising that the coalesence phenomenon is not observed for either 56c $\overset{\rightarrow}{\leftarrow}$ 57c or 56d $\overset{\rightarrow}{\leftarrow}$ 57d for temperatures as low as 177°K (- 96°C).

The X-ray analysis conclusively identified _cis_-8-_t_-butyl-3-methylene-1-oxaspiro[4.5]decan-2-one as structure 56b. Several novel features of this molecule were notable. The significant flattening of the six-membered ring at the spiro end implied that a distinct interaction exists between the axial oxygen and the axial H atoms on C(7) and C(9). It was also evident from the X-ray analysis that two forms of the twisted lactone ring could exist, and that these forms probably would rapidly interconvert in solution. However, it was concluded that any such interconversion would be much too fast to be detectable on the NMR time scale.

Suggestions for Future Work

In view of the work presented herein, a more detailed analysis of solvent effects upon the conformational equilibria of 56a $\overset{\rightarrow}{\leftarrow}$ 57a would be of intrinsic value in perhaps determining the nature of the solvent-solute complex. This would necessitate use of PFT-NMR techniques since the solubility characteristics of 56a $\overset{\rightarrow}{\leftarrow}$ 57a are very limited in most organic solvents examined to date. Possible candidates for appropriate solvent systems include the freons, mixtures of methanol

and higher molecular weight branched alcohols, and possibly chloroform-
methanol mixes as were used by Uebel and co-workers.[89]   The use of
such a solvent group(s) with wide polarity properties should be
instructive with respect to shifts in the equilibrium by hydrogen
bonding or highly polar solvent-solute interactions.

Selective deuteration of the six-membered ring in cis-8-t-butyl-
3-methylene-1-oxaspiro[4.5]decan-2-one (56b) could allow one to de-
termine axial and equatorial coupling constants between the H(7) and
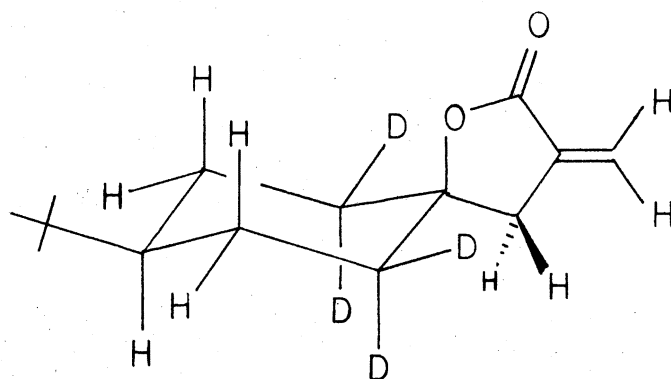
H(9) protons. This could permit the calculation of an R value[63] for
this molecule in solution, and hence permit an assessment of a possible
deformation in the cyclohexane ring due to the t-butyl group (or
lactone). Comparisons could then be made of the molecular configura-
tion in the crystalline state from the X-ray data and in solution and
with model systems.

CHAPTER III

EXPERIMENTAL

Melting points for compounds 56b, 57b and 56d (or 57d) were

obtained on a Thomas-Hoover melting point apparatus. Melting points of

56a (or 57a) and 56c (or 57c) were obtained on a Fisher-Johns melting

point apparatus by first cooling the block with ice and then placing

the crystal on the block to allow the block to warm slowly. All

melting and boiling points were uncorrected. Cyclohexanone (58a)

[bp 56-57° (20 mm)], 4-t-butylcyclohexanone (58b) (mp 47-49°C) and

3,3,5,5-tetramethylcyclohexanone (58d) [bp 92-94°C (20 mm)] were ob-

tained commercially and purified by vacuum distillation. Tetrahydro-

furan was dried by distillation first from NaH and then from LiAlH$_4$.

All other solvents were distilled and then dried over Na when appro-

priate. The IR spectra were recorded on a Beckman IR-5A spectrometer

and were calibrated with the 1602 cm^{-1} band of polystyrene. The mass

spectral data, when obtainable, are presented as per cent of and

normalized to the most intense ion. All spectral data, with the excep-

tion of mass spectral data, are reported in Table II in Results and

Discussion. Elemental analyses were performed by Galbraith Labora-

tories, Knoxville, Tennessee.

NMR and DNMR Spectroscopic Studies

The ^{1}H NMR spectra were recorded on a Varian XL-100(15) NMR

spectrometer equipped with a Nicolet TT-100 PFT accessory, operating

at 100.1 MHz with $(CH_3)_4Si$ as an internal reference. All controlled

temperature spectra were recorded in acetone-d_6 in the FT mode with

the solvent providing the necessary deuterium lock. A pulse width

(P2) of 5.7 µsec was used with a 4-6 sec delay (D5) between pulses.

Temperature control was provided by a Varian temperature controller.

A capillary of CH_3OH with a trace of HCl present was placed in a

5 mm NMR tube containing 0.5 mL acetone-d_6 and was used to calibrate

the temperature according to the method of Van Geet.[9] Calibrations

were done before and after each spectrum, and those spectra whose

temperature calibrations differed by more than $1^{\circ}C$ were discarded

and the shifts were reexamined at that temperature. Integrations were

done electronically on the computer of the TT-100 and cross-checked

using hand planimetry on the plotted spectra.

The ^{13}C NMR spectra were recorded with the unit operating at

25.2 MHz in the FT mode with the solvent providing the deuterium lock.

A pulse width of 15.5 µ was used with a 12 sec delay between pulses

with $(CH_3)_4Si$ as an internal standard.

Preparation of Ethyl α-Bromomethylacrylate (24)

Ester 24 was synthesized from 288g (1.8 mol) of diethyl malonate,

bp $98^{\circ}C$ (18 mm), using the method of Ramarajan and co-workers.[81]

This multi-step procedure gave 82.3 g (0.426 mol 23%) of ester 24.

bp $56^{\circ}C$ (2.0 mm) [lit.[21] bp $44-45^{\circ}C$ (1.7 mm)].

Preparation of 3,3-Dimethylcyclohexanone (58c)[24]

In a 1000 mL, round-bottom flask, equipped with a condenser and a

continuous water extractor (Dean–Stark trap) were placed 50 g (0.357 mol) of 5,5-dimethyl-1,3-cyclohexadione (61) (mp 147-150°C, 51 g (65 mL, 1.12 mol) of absolute ethanol (distilled from CaO and then from Mg) and 2 g (0.012 mole) of p-CH₃C₆H₄SO₃H (mp 104-106°C) in 300 mL of benzene (dried over Na). The reaction mixture was allowed to reflux until water ceased to be collected in the trap. The mixture was then stripped of solvent on a roto-evaporator, and then fractionally distilled under reduced pressure to give 50.3 g (0.299 mol -84%) of 5,5-dimethyl-3-ethoxy-2-cyclohexenone (62); bp 125°C (3.0 mm) [lit.[24] bp 93°C (1 mm)].

To solution of 50 g (0.297 mol) of 5,5-dimethyl-3-ethoxy-2-cyclo-hexenone (62) in 280 mL of ether (dried over Na) in a 500 mL, 3-necked, round-bottom flask equipped with stirrer, condenser, and N₂ inlet and packed in ice was added with care 2.8 g (0.073 mol) of LiAlH₄. The mixture came to a gentle boil upon each addition of LiAlH₄ and was allowed to cool between additions. The ice was removed and the reaction mixture was stirred for 1 h at room temperature. The solution was then poured with extreme caution into 550 mL of ice-cold H₂O and a gas (H₂) evolved. The solution was made acidic with dilute (6 M) H₂SO₄ and the ether layer was separated from the aqueous layer. The aqueous layer was then washed with an additional 100 mL of ether; the ether portions were combined and dried (MgSO₄). Roto-evaporation of the solvent, followed by fractional distillation under reduced pressure afforded 12.5 g (0.101 mol - 34%) of 5,5-dimethyl-2-cyclo-hexenone (63); bp 82-85°C (25 mm) [lit[24] bp 75°C (15 mm)]. This ketone 63 (31.7 g, 0.255 mol) was reduced over a 12-h period by the action of

H_2 (1 atm) over Pd-C (10%) in a Parr unit with $CH_3CO_2C_2H_5$ as the solvent. Distillation afforded 18.9 g (0.150 mol-60%) of 3,3-dimethyl-cyclohexanone (58c); bp 49°C (3.2 mm) [lit[13] bp 174-175°C (757 mm)].

Preparation of 2,2-Dimethylcyclohexanone (58e)[3]

To an ice-cold solution of 27 g (0.50 mol) of $NaOCH_3$, 37 g (0.50 mol) of ethyl formate in 190 mL of benzene (dried over Na) in a 100 mL, 3-necked, round-bottom flask equipped with a mechanical stirrer, condenser, N_2 gas inlet and addition funnel was added 24.5 g (0.25 mol) of cyclohexanone (58a) in 100 mL of benzene. An additional 100 mL of benzene was added, and the mixture was stirred overnight. After addition of 200 mL of ice-cold H_2O, the layers were separated, and the organic layer was washed with 100 mL of 5% NaOH. The combined aqueous layers were acidified with dilute (6 M) HCl, saturated with NaCl and extracted (200 mL of ether). The ether layers were dried (Na_2SO_4) and then concentrated. Distillation afforded 19.1 g (0.151 mol-60.5%) of 2-(hydroxymethylene)cyclohexanone (64); bp 70°C (5 mm) [lit[3] bp 70-72°C (5 mm)].

Ketone 64 (19 g, 0.151 mol) was allowed to react with 15 g (0.174 mol) of n-butylmercaptan (undistilled) and 0.03 g (0.00015 mol) of p-$CH_3C_6H_4SO_3H$ in 115 mL of benzene in a 250 mL, round-bottom flask equipped with a continuous water extractor (Dean-Stark), condenser and N_2 inlet. After 2.75 mL of H_2O had been collected (8 h), the reaction was cooled and then washed with 10% $NaHCO_3$. Drying (Na_2SO_4) of the organic layer overnight, followed by distillation, afforded 17 g (0.086 mol-56%) of 2-n-butylthiomethylene cyclohexanone (65); bp 85-88°C (0.05 mm) [lit.[7] bp 120-130°C (0.5 mm)].

An ether solution (180 mL) of ketone, 65, (7 g, 0.035 mL) and

1.25 mL (0.07 mole) of H_2O was added over a 30-min period to 1.47 g

(0.21 g at) of Li in 700 mL of liquid NH_3 in a 2-ℓ, 3-necked, round-

bottom flask equipped with stirrer (polypropylene bar), a 500 mL

addition funnel and a dry ice-acetone condenser. After an additional

30 min, 360 mL of dry ether was added followed by a solution of CH_3I

(60.2 g, 0.42 mol) in 180 mL of ether. The reaction was stirred for

30 min, and then the NH_3 was allowed to evaporate slowly. The result-

ing oily residue was extracted with either and the resulting extract was

dried ($MgSO_4$) and vacuum distilled to yield 1.9 g (0.015 mol-43%) of

2,2-dimethylcyclohexanone (58e); bp 47°C (4 mm) [lit.[45] bp 170-172°C

(750 mm)].

General Procedure for Synthesis of the

α-Methylene Spiro Lactones (56a-56e,

57a-57e) from the Ketones 58a-58e

A solution of 5.3 g (0.0275 mol) of ester 24 in 15 mL of dry THF

was added slowly with stirring to a suspension of 1.7 g (0.027 g at)

of Zn (20 mesh) dispersed in a solution of 0.025 mol of the appropriate

ketone 58a-58e in 8 mL of dry THF in a 100 mL, 3-necked, round-bottom

flask equipped with magnetic stirrer, condenser, thermometer and N_2

inlet. The temperature was allowed to rise during the addition to 45°C

and was maintained at 50°C by gentle heating for two additional hours.

After cooling to room temperature, the reaction mixture was poured

directly into 200 mL of ice-cold, 5% H_2SO_4 with vigorous stirring.

Stirring of the mixture at a reduced speed was continued for 0.5 hr

after the addition, the product separating during this time either as

an oil or as a crystalline solid. This product was taken up with

ether and the extract was washed with NaHCO$_3$ followed by H$_2$O and was

dried (MgSO$_4$) overnight.

Synthesis and Purification of 3-Methylene-1-
oxaspiro[4.5]decan-2-one (56a or 57a)

Cyclohexanone (3.6 g, 0.037 mol) was allowed to react in 35 mL

of dry THF with Zn (2.63 g, 0.40 g-at) and ester 24 (7.95 g, 0.041 mol)

as described above. The crude produce 56a $\rightleftharpoons$ 57a was isolated as an oil

from the ether by roto-evaporation and was taken up in a minimum

(50 mL) of hot commercial hexanes and the resulting solution was

filtered. The solution was chilled slowly to -78°C. A crystalline

product formed and was filtered off at -78°C using a jacketed funnel.

Vacuum drying of the crystals at room temperature (20°C) gave 5.2 g

(86%) of 56a (or 57a); mp 26-27.5°C; bp 76-77°C/(0.05 mm) [lit.[7] bp

80-85°C/(1.0 mm)].

Anal. Calcd. for C$_{10}$H$_{14}$O$_2$: C, 72.26; H, 8.49.

Found: C, 72.05; H, 8.29.

Synthesis and Purification of cis- and trans-
8-t-Butyl-3-methylene-1-oxaspiro[4.5]decan-
2-one (56b and 57b)

The reaction of 4-t-butylcyclohexanone (58b) (3.86 g, 0.025 mol)

with ester 24 (5.3 g, 0.2075 mol) and Zn (1.76 g, 0.027 g-at) in

23 mL of THF as described above afforded 3.6 g (65%) of a mixture of

56b and 57b, mp 63-71°C. NMR analysis (in CCl$_4$) of this crude product

revealed a ratio of 4:1 for 56b:57b. Careful fractional crystalli-

zation (CH$_3$OH) initially afforded colorless crystals of 56b, mp 83-84°C,

in which the trans-isomer 57b was no longer detectable via NMR analysis.

Subsequent fractions showed evidence of both isomers. These latter

fractions of isomers were chromatographed on a column of Florisil

(Research Specialties Co.) in a ratio of 30:1 adsorbant:substrate,

using 150 mL of hexane, followed by 100 mL of 50:50 benzene:hexane

and then 100 mL of benzene. Those fractions containing the trans-isomer

57b identified via NMR analysis were combined and rechromatographed

as described above. The trans-isomer 57b (50 mg) was isolated from

the benzene fractions, mp 84-85°C. The total yield of product was

3.6 g (65%) and was composed of 2.65 g (48%) of cis-isomer 56b and

50 mg (1.0%) of trans- 57b along with 0.91 g (16.4%) of a mixture of

the two. Analysis of the two separate isomers gave the following

results:

Anal. Calcd. for C$_{14}$H$_{22}$O$_2$: C, 75.63; H, 9.97.

Found: C, 75.73; H, 10.00 (cis);

Synthesis and Purification of 7,7-Dimethyl-3-

methylene-1-oxaspiro[4.5]decan-2-one

(56c or 57c)

The reaction of 3,3-dimethylcyclohexanone (58c) (3.15 g, 0.025 mol)

with ester 24 (5.3 g, 0.0275 mol) and Zn (1.76 g, 0.027 g-at) in 23 mL

of THF as described above afforded (upon recrystallization of the

crude product from hot hexanes) 3.64 g (75%) of 56c (or 57c); mp

38.5-39.5°C bp 100-102°C (0.25 mm).

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.

Found: C, 74.51; H, 9.28.

Mass spectral data for 56c (or 57c) follows; m/e (% of 151 mass):
194(72.5) M^+; 180(21.4); 179(53.3); 165(41.7); 151(100); 148(62.6);
137(41.2); 123(46.2); 121(22.0); 114(23.6); 105(26.4); 95(31.9);
91(33.0); 77(34.0); 68(45.0); 55(27.5); 44(76.9); 43(40.1); 41(46.7);
40(29.7); 39(28.6); 29(45.0); 28(87.9); 27(34.1); 18(53.8).

<div align="center">

Synthesis and Purification of 7,7,9,9-Tetra-

methyl-3-methylene-1-oxaspiro[4.5]decan-

2-one (56d or 57d)

</div>

The reaction of 3,3,5,5-tetramethylcyclohexanone (58d) (3.86 g,
0.025 mol) with ester 24 (5.3 g, 0.0275 mol) and Zn (1.76 g, 0.027 g-at)
in 23 mL of THF in the manner previously described yielded (upon re-
crystallization from hexanes) 4.06 g (73%) of 56d (or 57d), mp
101.5-103°C.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97.

Found: C, 75.86; H, 9.98.

The mass spectral data for 56d (or 57d) follows; m/e (% of 151 mass):
222(19.8) M^+; 207(41.2); 161(23.5); 151(100); 137(16.8); 121(29.4);
97(22.0); 95(23.5); 69(36.8); 57(23.5); 55(61.0); 41(52.9); 40(48.5).

<div align="center">

Synthesis and Attempted Purification of

6,6-Dimethyl-3-methylene-1-

oxaspiro[4.5]decan-2-one

(56e or 57e)

</div>

The reaction of 2,2-dimethylcyclohexanone (58e) (1.9 g, 0.015 mol)

with ester 24 (2.12 g, 0.011 mol) and Zn (0.72 g, 0.011 g-at) in 15 mL
THF was performed as described above. The product was isolated from
the either extract as an oil. Attempts to crystallize the cryde pro-
duct either from a solution of hexanes or neat gave a glassy,
amorphous solid. Distillation of this product was accomplished under
reduced pressure [bp 57-59°C (0.05 mm)] in a spinning band micro dis-
tillation apparatus, 1.16 g (40%). The NMR of the resulting distillate
showed the presence of several trace contaminates (Plate XII). Sur-
prisingly, the product polymerized rapidly in the dark even under
refrigeration.

Elemental analysis confirmed the presence of contaminants, but the
^{1}H NMR spectrum (Plate XIII) had the correct signals for the expected
compound at δ 0.90 (s) 3 H; 0.96 (s) 3 H; 1.1-1.9 (m) 8 H; 2.44, 2.62,
3.02, 3.20 (q of t) 2 H; 5.64 (d of t) 1 H; 6.06 (d of t) 1 H.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34.

Found: C, 73.30; H, 8.98.

X-Ray Analysis and Structure Refinement

Crystals suitable for X-ray intensity measurement were obtained
by cooling a solution prepared by dissolving a small amount of 56b in
hot methanol. Initial diffraction experiments showed the crystals to
be orthorhombic. The crystal data are: $C_{14}H_{22}O_2$, M = 222.32, space
group $P2_12_12_1$, a = 11.455(2), b - 18.356(2), c = 6.100(1) Å,
V = 1282.6 Å^3 (at -135°C) Z= 4, F(000) = 488, Ni filtered CuKα
radiation: λ(CuKα) = 1.54051 Å for determination of cell constants and
λ(CuK$\bar{\alpha}$) = 1.54178 Å for intensity data. The unit cell parameters were

determined by least-squares to the +2θ and -2θ values of 44 reflections distributed throughout all regions of reciprocal space.

A total of 1551 intensities representing all unique reflections with 2θ $\leq$ 150 were measured using a Nonius CAD-4 automatic diffracto-meter and -2θ scan techniques. The scan with (Δθ) was adjusted for dispersion and calculated as Δθ = (1.0 + 0.1 tan θ)^{o} for each refelc-tion. A receiving aperture with variable width calculated as (4.0 + 0.86 tan θ) mm and constant height of 6.00 mm was located 173 mm from the sample. A maximum of 60 s was spent on each intensity with 2/3 of the time spent scanning the peak and 1/6 of the time spent scanning each the left and right background. Less than 60 s was used if 40,000 counts could be obtained with a faster scan speed. The total time was divided into two scans and if the results of those two scans varied by more than 3σ up to three additional scans were made. A monitor reflection was measured after every 25 observations and did not show a systematic variation during data collection. Three additional reflections were re-centered after every 100 measurements and a new orientation matrix was automatically calculated if any angle changed by more than 0.1^{o} from its original value. A total of 122 intensities could not be distinguished from the background on the basis that the intensity (I) was less than 2σ (I). These reflections were assigned an intensity of 0.95 times the square root of the total count for the purpose of further data analysis. The value of 0.95 was chosen such that the sum of the observed magnitudes of the structure factor was equal to the sum of the calculated magnitudes for this class of data.

The observed intensities were corrected for Lorentz and polariza-tion effects and structure factor magnitudes derived. Absorption

corrections were not applied as the calculated linear absorption coeffi-
cient had a value of only 6.44 cm^{-1}. Throughout the data analysis an
experimental weight, based on counting statistics, was assigned to
each structure factor.[93]

The structure was solved using direct methods and the computer
program MULTAN.[30] An E-map based on the magnitudes of the 160 largest
normalized structure factors, $|E|$'s, and the MULTAN phase set having
the largest absolute figure of merit and lowest residual revealed the
positions of the 16 non-hydrogen atoms. An initial structure factors
calculation gave an R value ($\Sigma||kF_o|-|F_c||/\Sigma|kF_o|$) equal to 24.2%
where $|F_o|$ is the observed structure factor magnitude, F_c is the cal-
culated structure factor and k is a scale factor which places the
observed data on an absolute scale. After the block-diagonal least-
square refinement of the isotropic model had converged (R = 10.3%)
a difference Fourier map was claculated from which the position of
all hydrogen atoms were located. After several more cycles of re-
finement all non-hydrogen atoms were given anisotropic thermal
parameters. The refinement using anisotropic thermal parameters
for C and O atoms and isotropic thermal parameters for H atoms was
terminated when all shifts were samll fractions of the corresponding
estimated standard deviation. The R value based on the final parame-
ters (Table XIII and XIV) was 3.8%. The standard error in an obser-
vation of unit weight, $[\Sigma\omega\Delta F^2/(m - n)]^{1/2}$, is 1.18 e, where ω is the
experimental weight, ΔF, is the difference between the observed and
calculated structure factor magnitudes, m is the number of observa-
tions and n is the number of parameters in the refinement.

TABLE XIII

POSITIONAL PARAMETERS ($x \times 10^5$; $y \times 10^5$; $z \times 10^4$) AND ANISOTROPIC THERMAL PARAMETERS ($\times 10^4$) FOR C AND O ATOMS. CALCULATED STANDARD DEVIATIONS ARE GIVEN IN PARENTHESES. THERMAL PARAMETERS ARE OF THE FORM: $EXP[-2\pi^2(U_{11}h^2a^{*2} + U_{22}K^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$ (for 56b)

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	80159(10)	89504(6)	1329(2)	186(5)	283(5)	184(5)	1(4)	−10(5)	−7(5)
C(2)	68770(13)	87874(8)	1681(3)	195(7)	191(7)	228(7)	28(6)	−9(7)	−8(6)
C(3)	66369(14)	88026(8)	4082(3)	213(7)	198(7)	205(7)	14(6)	−24(6)	−3(7)
C(4)	77227(15)	90829(10)	5175(3)	206(8)	336(9)	229(8)	−42(7)	4(7)	−55(7)
C(5)	86695(14)	89721(8)	3429(3)	195(7)	249(7)	170(7)	1(6)	−25(6)	−23(6)
C(6)	95273(14)	96016(9)	3284(3)	199(7)	207(7)	274(8)	−7(6)	11(7)	−34(7)
C(7)	104999(14)	94809(8)	1609(3)	204(7)	183(7)	263(8)	−7(6)	11(7)	8(7)
C(8)	111495(13)	87665(8)	2064(3)	186(7)	189(7)	193(7)	−3(6)	−12(6)	6(6)
C(9)	102573(15)	81427(8)	1939(3)	226(7)	172(7)	339(9)	−7(6)	−3(8)	−7(7)
C(10)	92960(14)	82423(9)	3642(3)	219(7)	218(7)	284(9)	−50(6)	−13(8)	61(7)
O(2')	62185(10)	86630(7)	201(2)	239(6)	347(7)	237(6)	17(5)	−60(5)	−23(6)
C(3')	56196(15)	85962(10)	4903(3)	245(8)	319(9)	242(8)	−37(7)	−10(7)	4(8)
C(11)	122686(14)	86437(9)	676(3)	197(7)	217(7)	215(7)	10(6)	−22(6)	−17(7)
C(12)	131188(15)	92805(9)	1002(3)	213(7)	248(9)	338(9)	−13(6)	39(8)	3(7)
C(13)	119937(16)	85710(9)	−1774(3)	316(9)	439(10)	205(8)	41(8)	2(8)	−27(8)
C(14)	128855(15)	79460(9)	1451(3)	231(7)	237(7)	317(9)	38(6)	−6(8)	−28(7)

TABLE XIV

POSITIONAL PARAMETERS (x 10^3) AND ISOTROPIC THERMAL PARAMETERS FOR H
ATOMS. STANDARD DEVIATIONS FOR THE LAST DIGIT ARE
GIVEN IN PARENTHESE (for 56b)

	x	y	z	$B(\overset{\circ}{A}{}^2)$
H(4)A	791(2)	881(1)	649(3)	2.9(5)
H(4)B	762(2)	962(1)	549(4)	3.1(5)
H(6)A	914(2)	1005(1)	303(4)	2.5(4)
H(6)B	986(2)	966(1)	475(3)	1.8(4)
H(7)A	1018(2)	948(1)	13(3)	1.8(4)
H(7)B	1103(2)	991(1)	170(3)	2.0(4)
H(8)	1139(2)	881(1)	358(3)	2.2(4)
H(9)A	990(2)	816(1)	38(4)	3.3(5)
H(9)B	1069(2)	765(1)	231(3)	2.1(4)
H(10)A	873(2)	785(1)	363(3)	2.5(4)
H(10)B	965(2)	822(1)	514(3)	1.6(4)
H(3')A	549(2)	862(1)	650(4)	3.1(5)
H(3')B	504(2)	847(1)	393(3)	3.0(5)
H(12)A	1323(2)	937(1)	261(4)	3.3(5)
H(12)B	1391(2)	916(1)	21(4)	3.3(5)
H(12)C	1282(2)	974(1)	31(4)	3.0(5)
H(13)A	1150(2)	813(1)	-202(3)	2.2(4)
H(13)B	1158(2)	899(1)	-230(4)	3.7(5)
H(13)C	1270(2)	852(1)	-261(4)	5.2(6)
H(14)A	1305(2)	797(1)	302(4)	2.6(4)
H(14)B	1367(2)	790(1)	68(4)	2.6(4)
H(14)C	1244(2)	751(1)	106(3)	2.7(4)

All structure refinement was carried out using the block-diagonal least-squares program of Ahmed[2] in which the quantity $\Sigma(wF_o - F_c)^2$ was minimized. All Fourier maps were calculated using Ahmed's Fourier transform program.[1] Scattering factors for C and O atoms were taken from the International Tables for X-ray Crystallography, Vol. III[44] while those for H atoms were taken from Stewart, Davidson and Simpson.[86] A final difference Fourier map contained no peaks greater than 0.16 e $\overset{\circ}{A}^{-3}$. A final structure factor analysis showed that $\Sigma w\Delta F^2$ did not vary with either $\sin \theta/\lambda$ or $|F_o|$ thus validating the weighting scheme used. The positional parameters and anisotropic thermal parameters for non-hydrogen atoms are given in Table XIII. The positional parameters and isotropic thermal parameters for H atoms are given in Table XIV.

Mathematical Manipulations Used in Error Analysis - Derivations of Equations (2) and (3)

The approximate relative error in ΔG^O resulting from errors in K_{eq} and T is given by the general expression:

$$(\sigma_{\Delta G^O})/(\Delta G^O) \simeq \{[\partial(\Delta G^O)/\partial(K_{eq})]^2(\sigma_{K_{eq}}/\Delta G^O)^2$$

$$+ [\partial(\Delta G^O)/\partial T]^2(\sigma_T/\Delta G^O)^2\}^{\frac{1}{2}}$$

Eq. (10)

From Eq. (1) (page 25) the appropriate partial derivatives are:

$$\partial(\Delta G^O)/\partial(K_{eq}) = -RT/K_{eq}$$

$$\partial(\Delta G^O)/\partial T = -R \ln K_{eq}$$

Substituting these expressions into Eq. (10) above, one obtains:

$$(\sigma_{\Delta G^o})/(\Delta G^o) \simeq \{(-RT/K_{eq})^2[\sigma_{K_{eq}}/(-RT \ln K_{eq})]^2$$

$$+ (-R \ln K_{eq})^2[\sigma_T/(-RT \ln K_{eq})]^2\}^{\frac{1}{2}} .$$

Combining like terms, one obtains Eq. (2), i.e.:

$$(\sigma_{\Delta G^o}/\Delta G^o) \simeq \{(\sigma_T/T)^2 + (\ln K_{eq})^{-2} (\sigma_{K_{eq}}/K_{eq})^2\}^{\frac{1}{2}} .$$

The expression below was used to calculate ΔH^o.

$$\Delta H^o = -R \, d(\ln K_{eq})/d(1/T).$$

For two specific measurements of K_{eq}, K_1 and K_2, at temperatures T_1 and T_2, respectively, the above expression becomes:

$$\Delta H^o = -R \, (\ln K_2 - \ln K_1)/(1/T_2 - 1/T_1) \qquad \text{Eq. (11)}$$

The approximate relative error in ΔH^o resulting from errors in K_1, K_2, T_1 and T_2 is given by the general expression:

$$(\sigma_{\Delta H^o})/(\Delta H^o) \simeq \{[\partial(\Delta H^o)/\partial K_2]^2(\sigma_{K_2}/\Delta H^o)^2 + [\partial(\Delta H^o)/\partial K_1]^2(\sigma_{K_1}/\Delta H^o)^2$$

$$+ [\partial(\Delta H^o)/\partial T_2]^2(\sigma_{T_2}/\Delta H^o)^2 + [\partial(\Delta H^o)/\partial T_1]^2(\sigma_{T_1}/\Delta H^o)^2\}^{\frac{1}{2}} \qquad \text{Eq. (12)}$$

where σ_{K_2}, σ_{K_1}, σ_{T_2} and σ_{T_1} are the errors associated with K_2, K_1, T_2 and T_1, respectively. The appropriate partial derivatives are:

$$\partial(\Delta H^o)/\partial K_2 = -R/(1/T_2 - 1/T_1) \; (1/K_2)$$

$$\partial(\Delta H^o)/\partial K_1 = R/(1/T_2 - 1/T_1) \; (1/K_1)$$

$$\partial(\Delta H^o)/\partial T_2 = -R(\ln K_2 - \ln K_1) \left[1/(T/T_2 - 1/T_1)^2 (1/T_2)^2 \right]$$

$$\partial(\Delta H^o)/\partial T_1 = R(\ln K_2 - \ln K_1) \left[1/(1/T_2 - 1/T_1)^2 (1/T_1)^2 \right].$$

If the range of temperatures is small, so that $T_1 \simeq T_2$ and $K_1 \simeq K_2$, then:

$$\partial(\Delta H^o)/\partial K_2 \simeq \partial(\Delta H^o)/\partial K_1 \simeq \left[R/(1/T_2 - 1/T_1) \right] (1/K).$$

Moreover, one can write the following expression:

$$\partial(\Delta H^o)/\partial T \simeq \partial(\Delta H^o)/\partial T_1$$

$$\simeq R(\ln K_2 - \ln K_1)/(1/T_2 - 1/T_1) \left[1/(1/T_2 - 1/T_1)(1/T)^2 \right]$$

In this case, K is the value of K_{eq} at the center of the temperature range T. Dividing each of these new expressions by ΔH^o [i.e. $-R(\ln K_2 - \ln K_1)/(1/T_2 - 1/T_1)$], one obtains the two equations below:

$$\partial(\Delta H^o)/\partial K(\Delta H^o) = \left[1/(\ln K_2 - \ln K_1) \right](1/K)$$

$$\partial(\Delta H^o)/\partial T(\Delta H^o) = \left[1/(1/T_2 - 1/T_1) \right](1/T)^2$$

However, the following expression also is valid:

$$(1/T_2 - 1/T_1) \simeq \Delta T/T^2$$

where $\Delta T = T_2 - T_1$. Substituting these expressions into Eq. (12), and defining $\Delta(\ln K) = \ln K_2 - \ln K_1$ one obtains Eq. (3) (page 27);

$$\sigma_{\Delta H^O}/\Delta H^O \simeq \{2\Delta(\ln K)^{-2}(\sigma_K/K)^2 + 2(T/\Delta T)^2(\sigma_T/T)^2\}^{\frac{1}{2}} \qquad \text{Eq. (3)}$$

One can see a similarity between Eq. (3) and the equation given by Binsch[8] (see below) for the approximate error associated with E_a, Eq. (7):

$$\sigma_{E_a}/E_a \simeq \{[2T^2/(\Delta T)^2](\sigma_T/T)^2 + 2[\Delta(\ln k)]^{-2}(\sigma k/k)^2\}^{\frac{1}{2}}$$

This is not surprising since the mathematical expressions for ΔH^O and E_a are of the same form.

A graphical representation of the error associated with the calculation of ΔH^O and ΔH^* by a least-squares analysis of the appropriate plots can be seen in the scatter of points along the least-squares line in Figures 5, 6, 7 and 8.
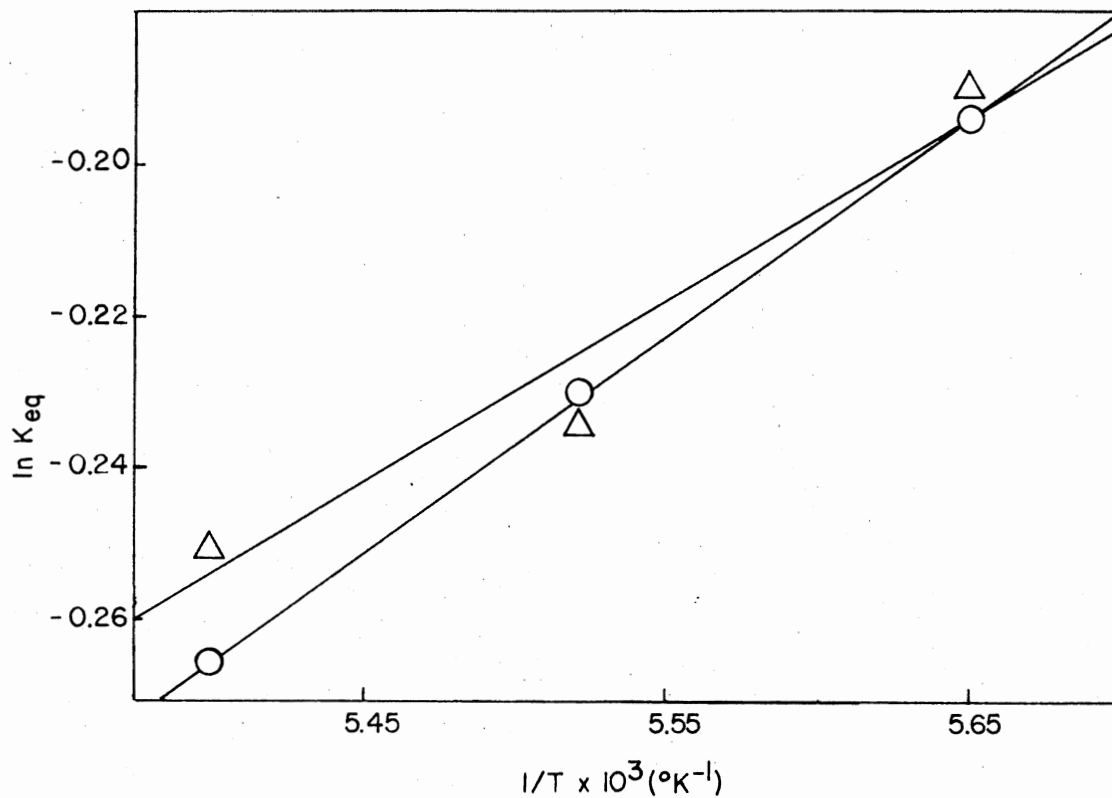
Figure 5. Plot of ln K_{eq} vs 1/T for 56a $\rightleftarrows$ 57a, Integrated
Area Method: 0.024 M (△); 0.036 M (◯).
Solvent, $(D_3C)_2C=O$ (Symbols Do Not Represent
Errors)
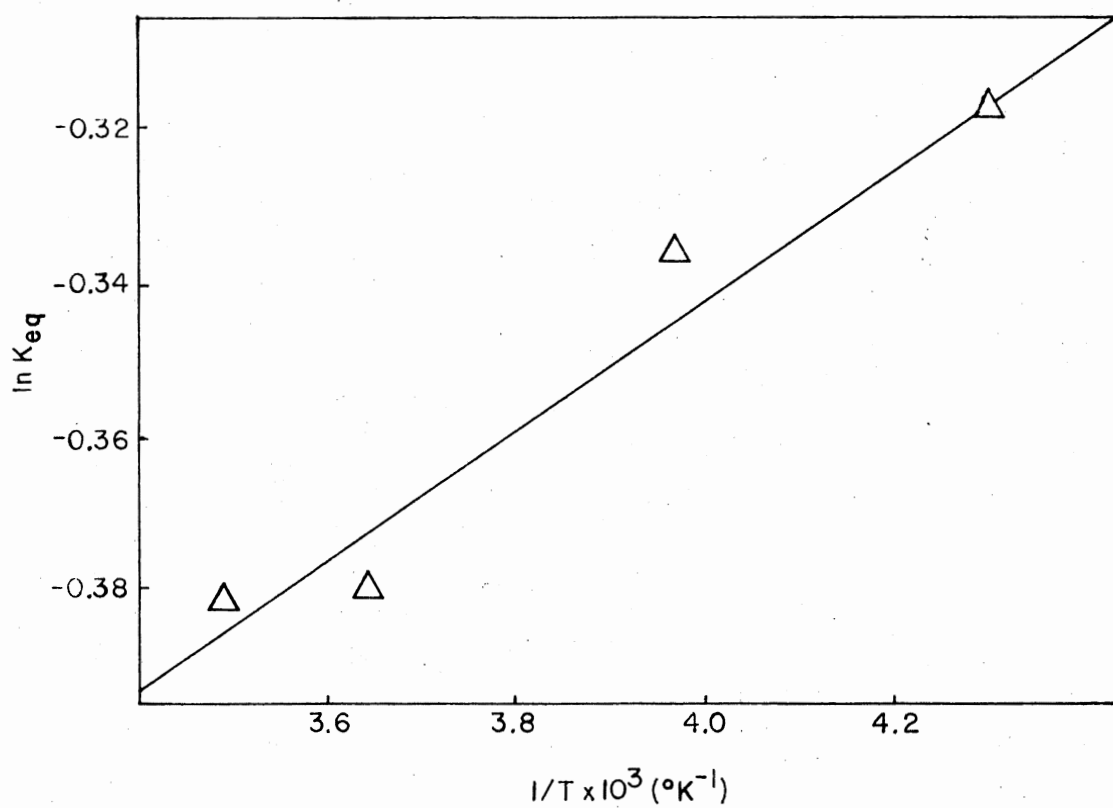
Figure 6. Plot of ln K_{eq} vs 1/T for 56a $\overset{\rightarrow}{\leftarrow}$ 57a, Chemical Shift Method: 0.024 M in $(D_3C)_2C=0$ (Symbols Do Not Represent Error)

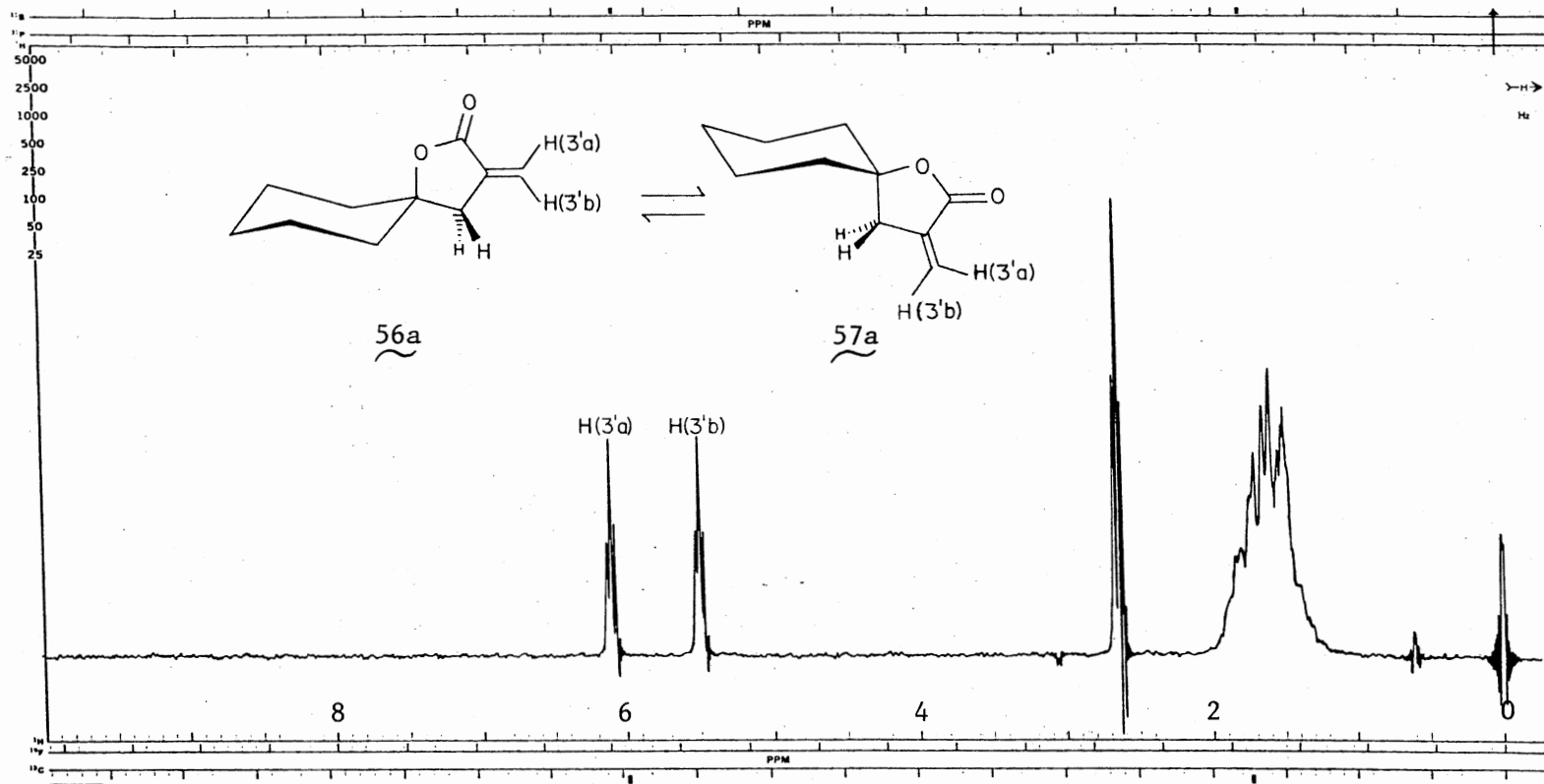Figure 7. Plot of ln k_r/T vs 1/T for 56a $\rightleftarrows$ 57a from L. S. A.: 0.024 M in $(D_3C)_2C=0$ (Symbols Do Not Represent Errors).

Figure 8. Plot of ln K_{eq} vs 1/T for 56a $\overset{\rightarrow}{\leftarrow}$ 57a. Combined
Plot of Chemical Shift and Integrated Area
Methods: 0.024 M in $(D_3C)_2C=O$ (Symbols
Do Not Represent Errors)

PLATE I

^{1}H NMR Spectrum of 3-Methylene-1-oxaspiro[4.5]decan-2-one (56a $\rightleftharpoons$ 57a)

Solvent. . . . CCl$_4$ S.F. . . . 100.1 MHz F.B. . . . 2 H   R.F. . . . 46 dB

S.W. . . . 1000 Hz   S.T. . . . 250 s   S.O. . . . 83701 Hz S.A. . . . 1.6   Lock. . . . ^{1}H
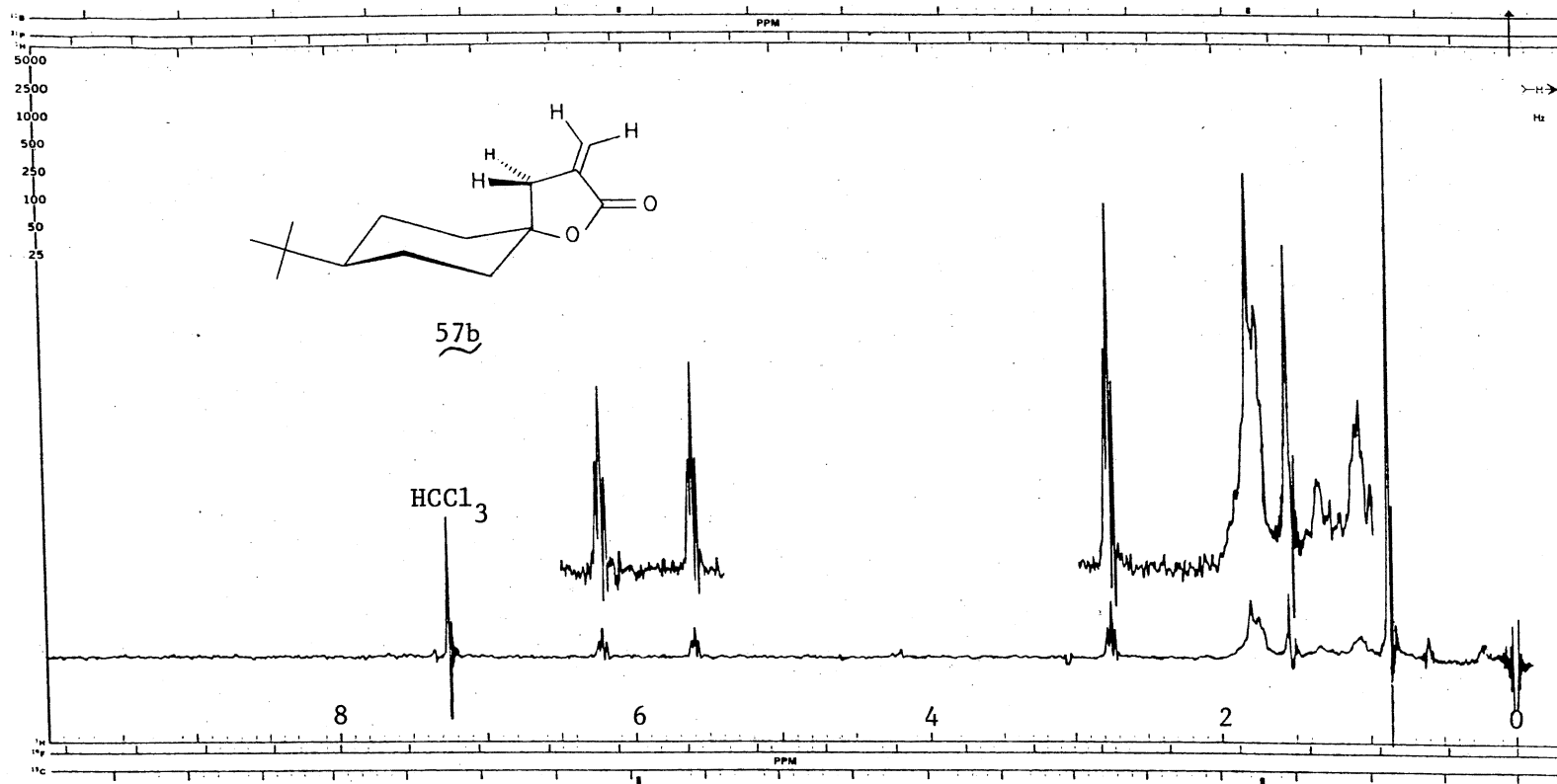
PLATE II
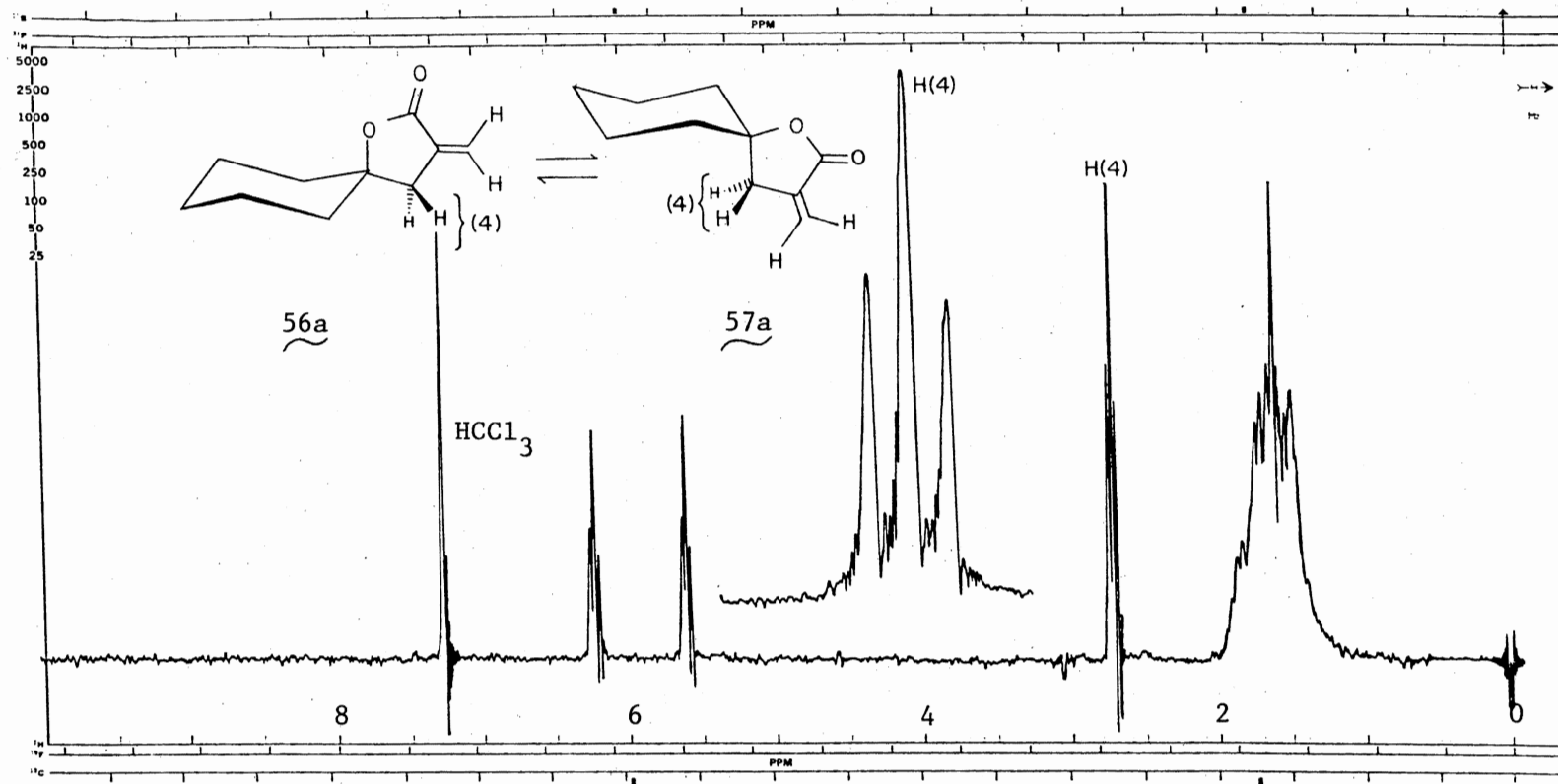
^{1}H NMR Spectrum of 56a $\overset{\rightarrow}{\leftarrow}$ 57a

Solvent. . . .   DCCl$_3$ S.F. . . . .   100.1 MHz   F.B. . . . .   2 Hz   R.F. . . . .   72 dB

S.W. . . .   1000 Hz   S.T. . . . .   250 s   S.O.   83701   S.A. . . . .   3.2   Lock. . . .^{1}H

PLATE III
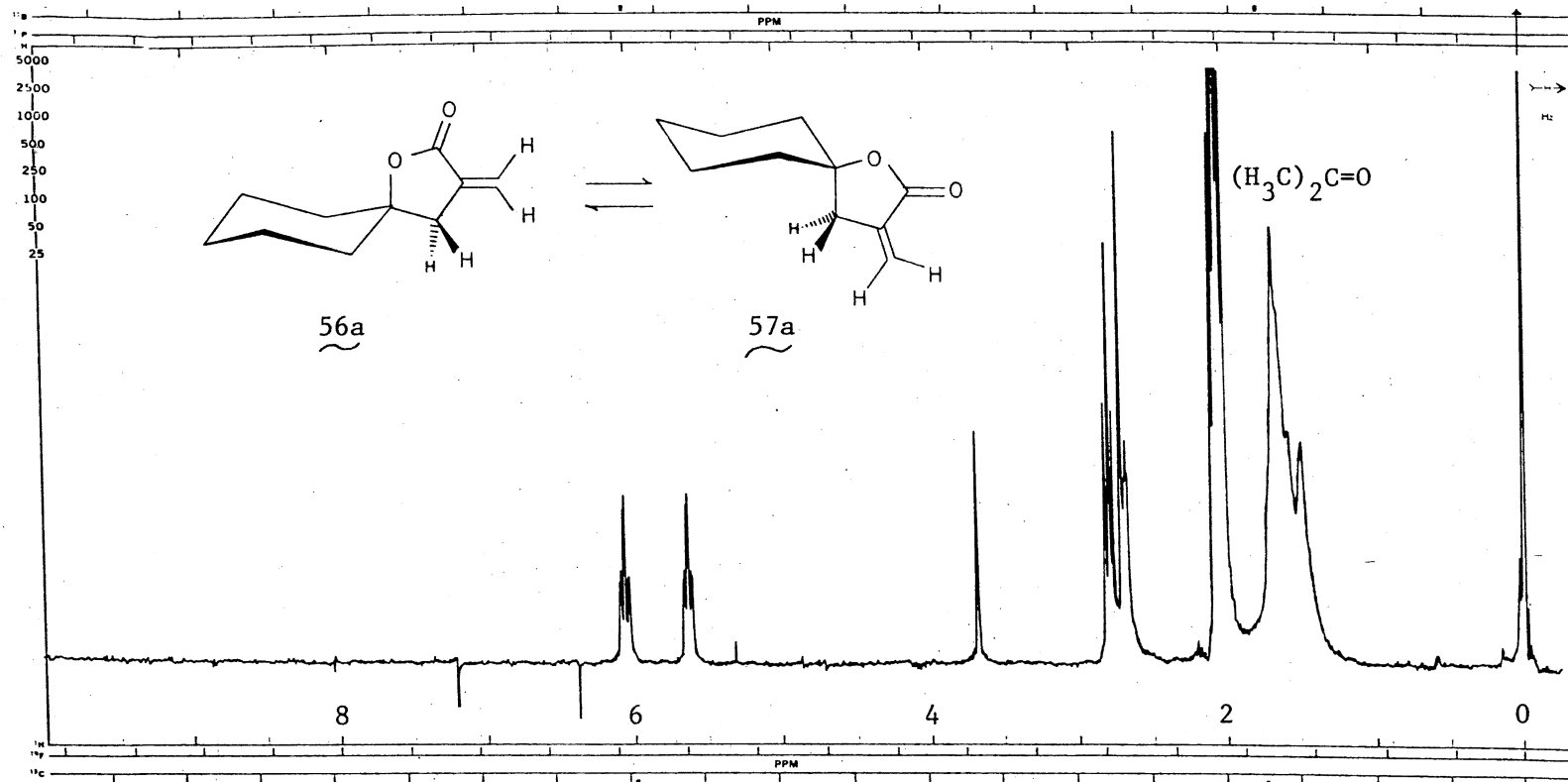
PFT ^{1}H NMR Spectrum of 56a $\rightleftarrows$ 57a

Solvent. . . . $(D_3C)_2C{=}O$ S.F. . . . 100.1 MHz   P.W. . . . 1000 Hz   S.W. . . . 1200 Hz   Acq. 28

Size. . . . 8k pts   P2 . . . . . 5.7 µs   D5 . . . . . 4.0 s   S.O. . . . . 45801 Hz   Lock . . . .^{2}H
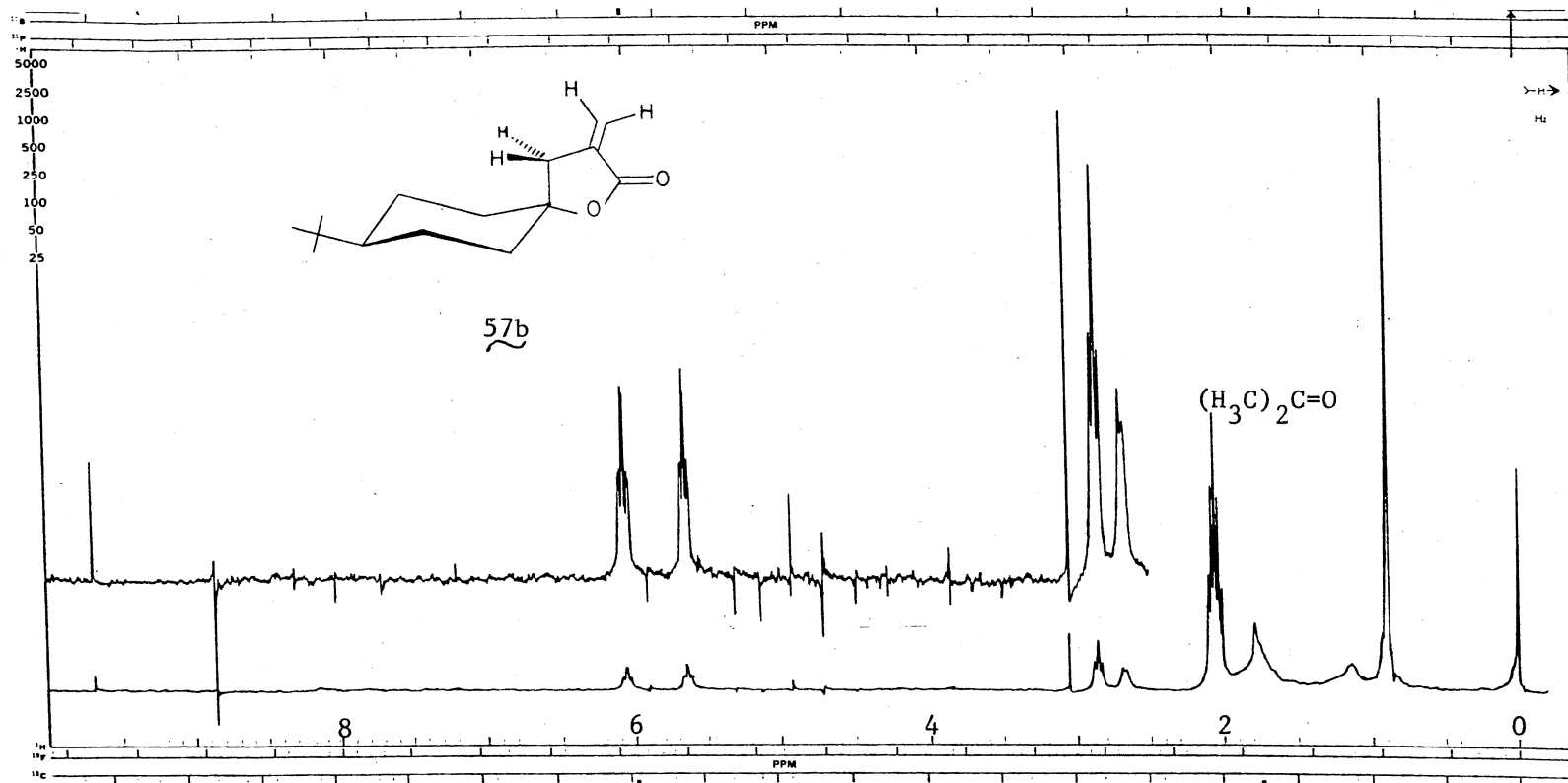
PLATE IV
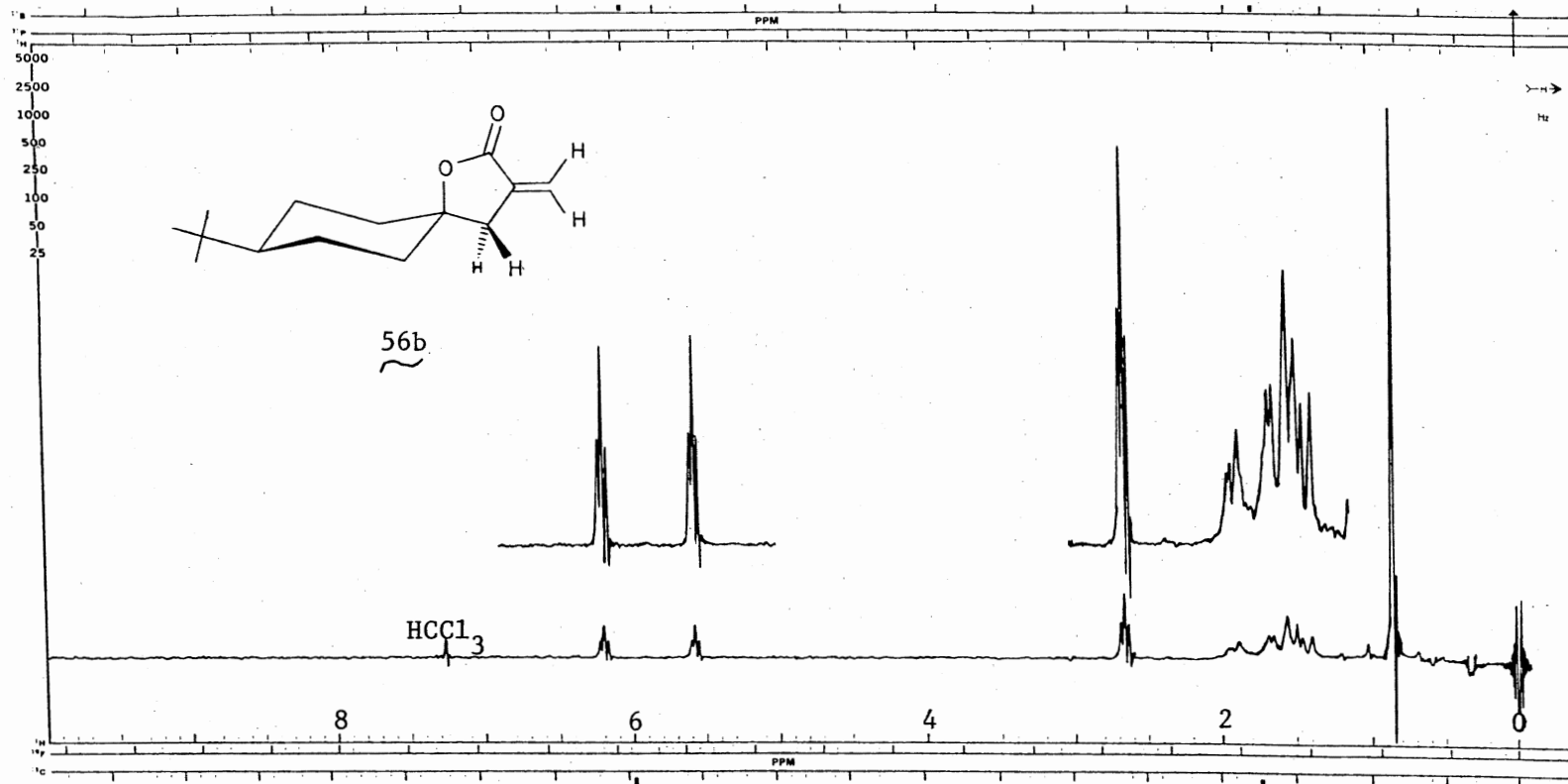
^{1}H NMR Spectrum of <u>cis</u>-8-<u>t</u>-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56b)

Solvent. . . .   DCCl$_3$ S.F. . . . 100.1 MHz F.B. . . . 2 Hz   R.F. . . . . 63 dB

  S.W. . . .   1000 Hz S.T. . . . 250 s   S.O. . . . 83701 Hz S.A. . . . 1.0   Lock. . . .^{1}H
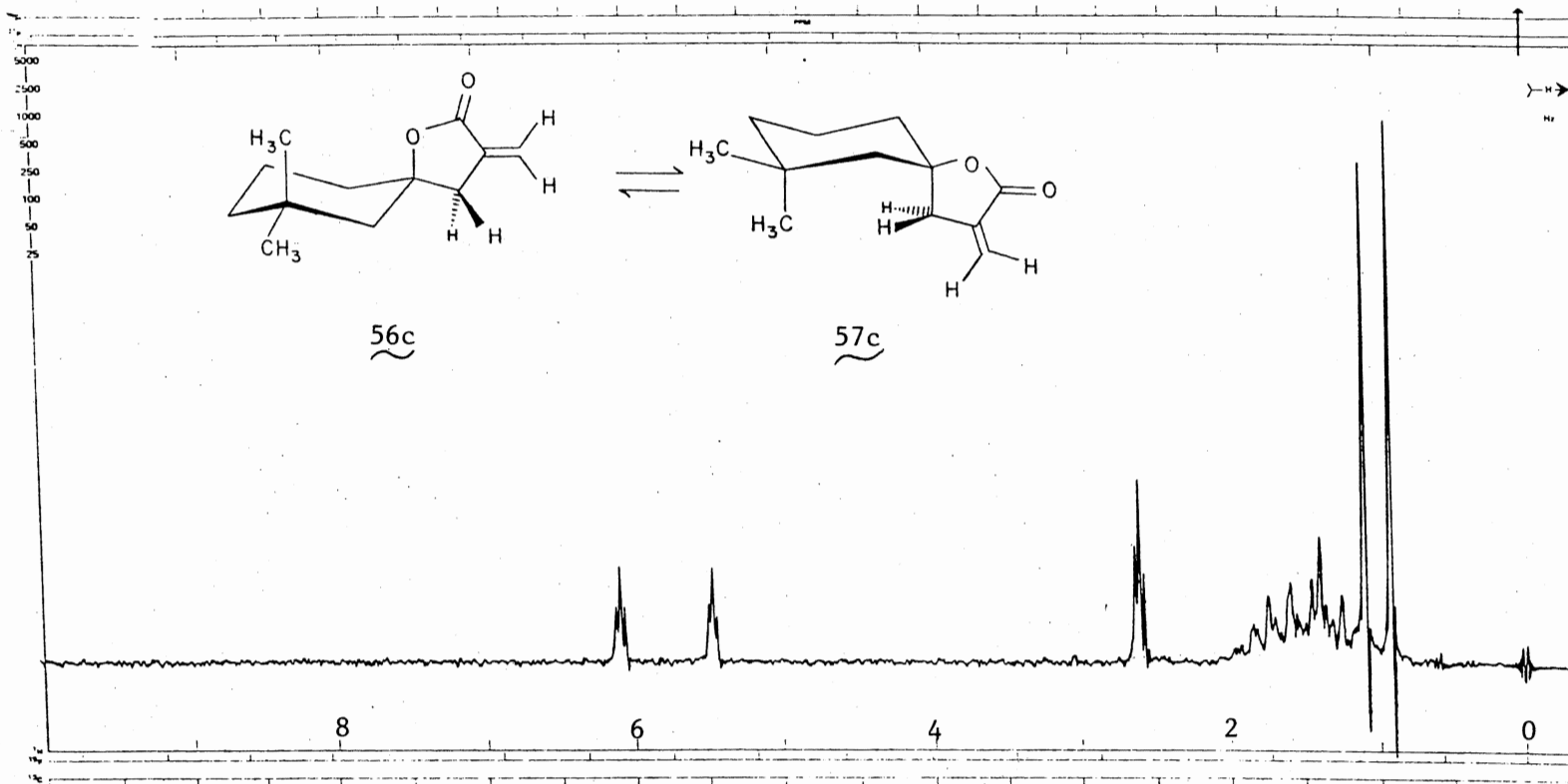
PLATE V

PFT ^{1}H NMR Spectrum of 56b

PLATE VI

^{1}H NMR Spectrum of <u>trans</u>-8-<u>t</u>-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (57b)

Solvent. . . . DCCl$_3$ S.F. . . . 100.1 MHz   F.B. . . . 2 Hz   R.F. . . . 53 dB

S.W. . . . 1000 Hz   S.T. . . . 250 s   S.O. . . . 83701 Hz S.A. . . . 3.2   Lock. . . . ^{1}H

PLATE VII

PFT ^{1}H NMR Spectrum of 57b

Solvent. . . . $(D_3C)_2C=O$ S.F. . . . 100.1 MHz   P.W. . . . 1000 Hz   S.W. . . . , 1200 Hz   Acq. . . . 40

Size. . . . 8k pts   P2. . . . 5.7 μs   D5. . . . 6.0 s   S.O. . . . 45801 Hz   Lock. . . .^{2}H
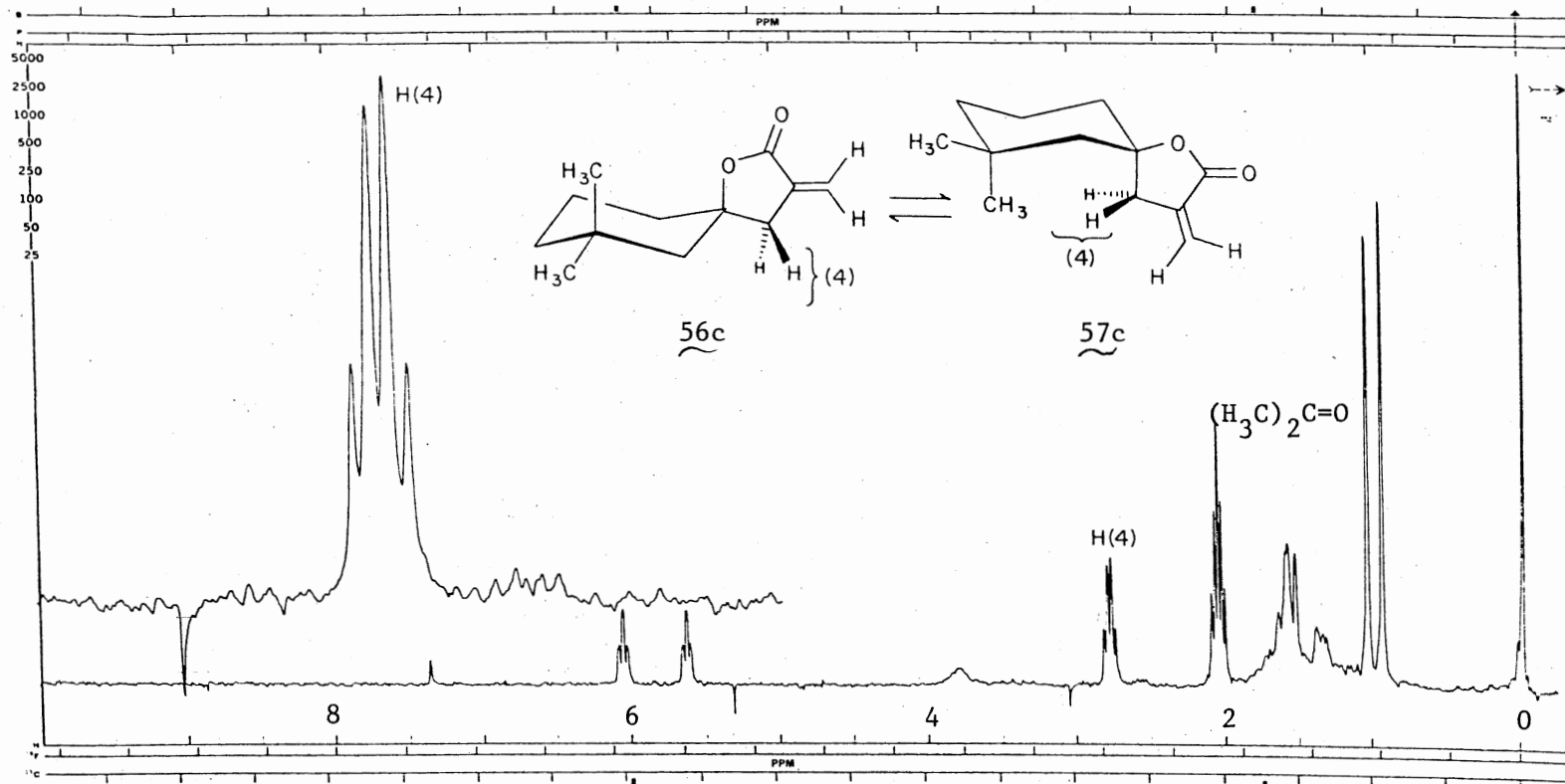
PLATE VIII

¹H NMR Spectrum of 7,7-Dimethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56c ⇄ 57c)

Solvent. . . . CCl$_4$ S.F. . . . 100.1 MHz   F.B. . . . 2 Hz   R.F. . . . 71 dB

S.W. . . . 1000 Hz   S.T. . . . 250 s   S.O. . . . 83701 Hz S.A. . . . 2.0   Lock. . . .¹H
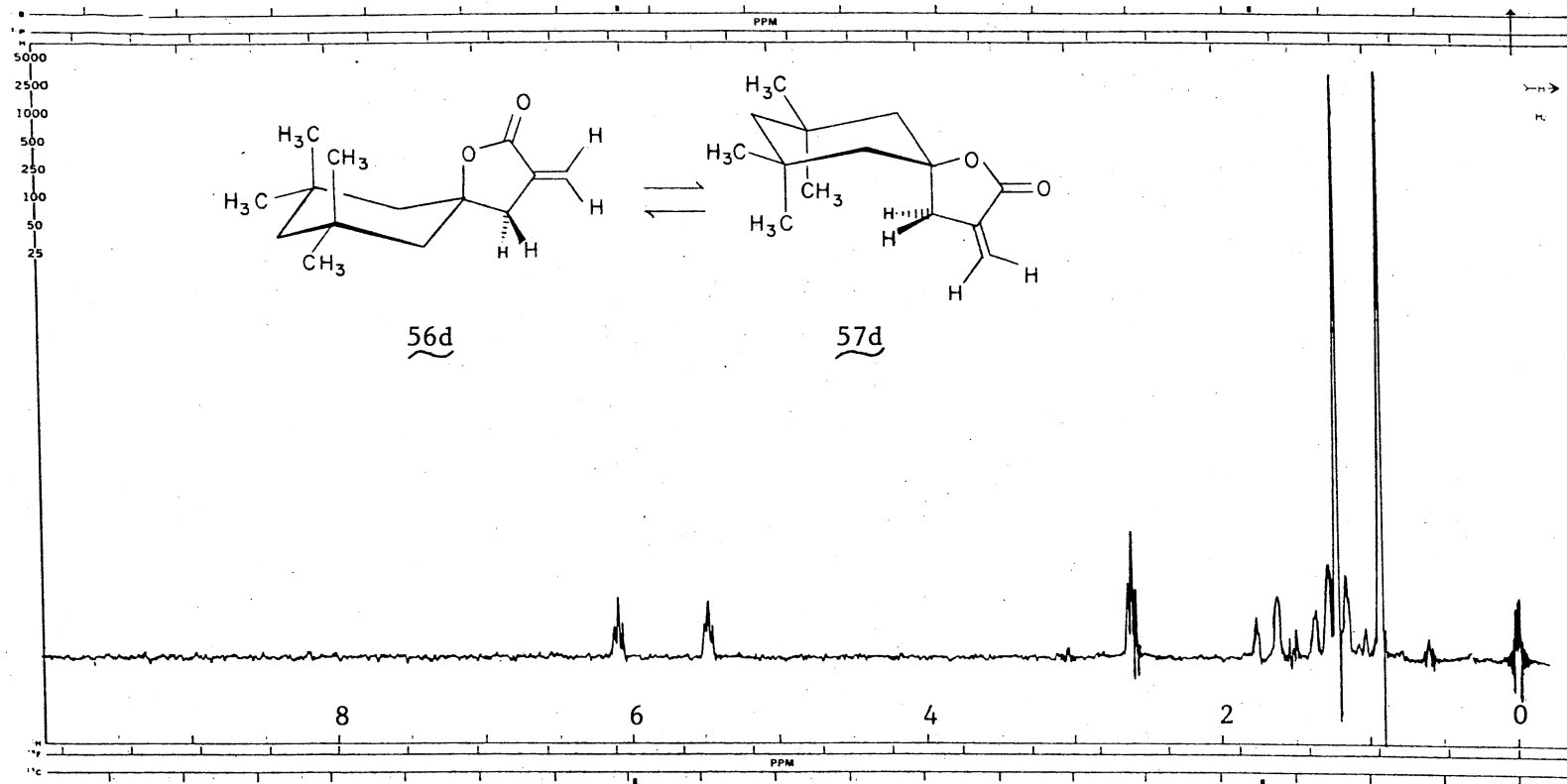
PLATE IX

PFT ^{1}H NMR Spectrum of 56c $\rightleftharpoons$ 57c

Solvent. . . . $(D_3C)_2C=O$ S.F. . . . 100.1 MHz   P.W. . . . 100 Hz   S.W. . . . 1200 Hz   Acq. 20

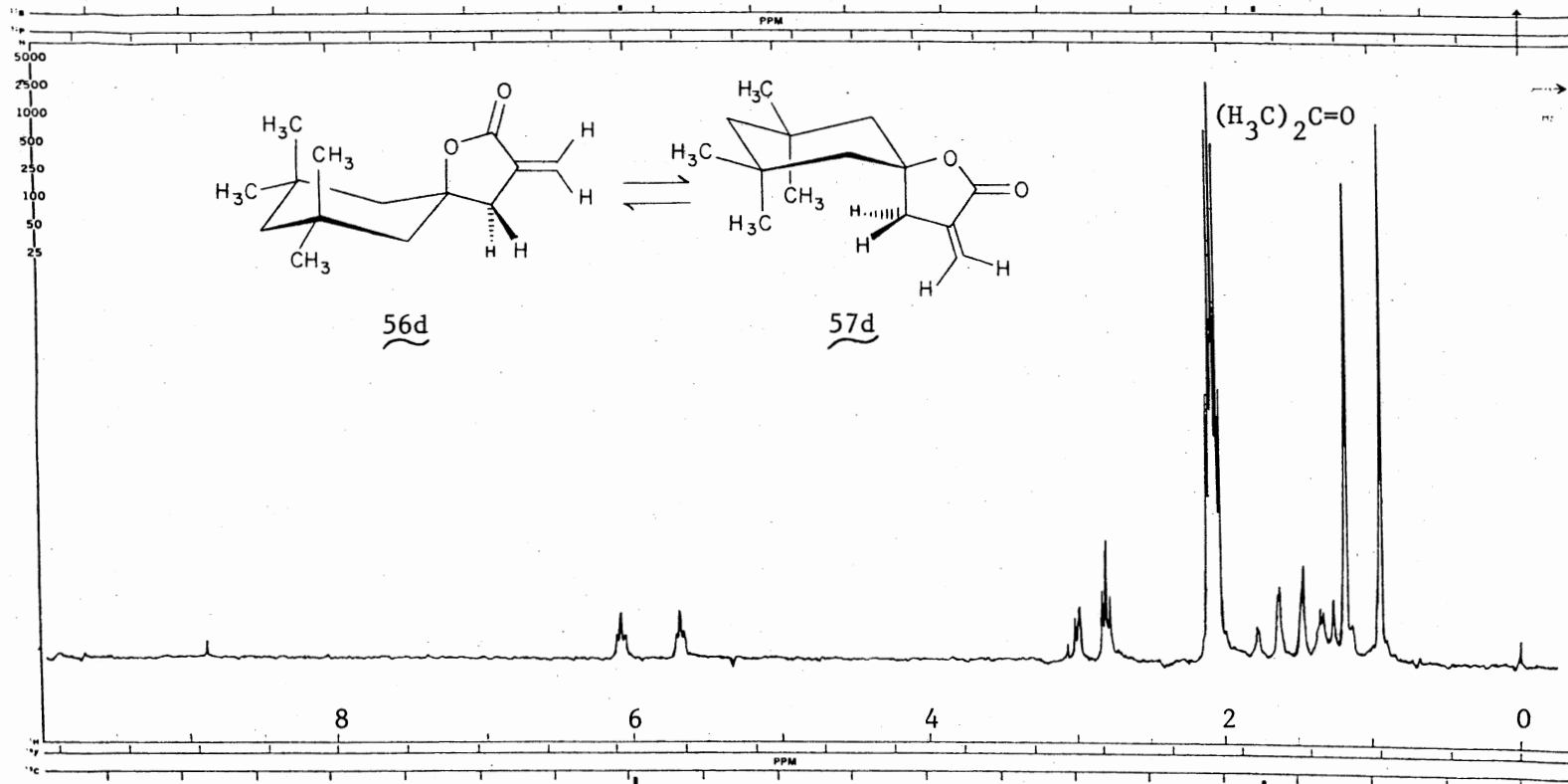Size. . . . 8k pts   P2. . . . 5.7 μs   D5. . . . 6.0 s   S.L. . . . 45801   Lock . . . ^{2}H

PLATE X

^{1}H NMR Spectrum of 7,7,9,9-Tetramethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56d $\rightleftarrows$ 57d)

Solvent. . . . CCl$_4$ S.F. . . . 100.1 MHz   F.B. . . . 2 Hz   R.F. . . . 60 dB

S.W. . . . 1000 Hz   S.T. . . . 250 s   S.O. . . . 83701 Hz   S.A. . . . 2.0   Lock. . . . ^{1}H
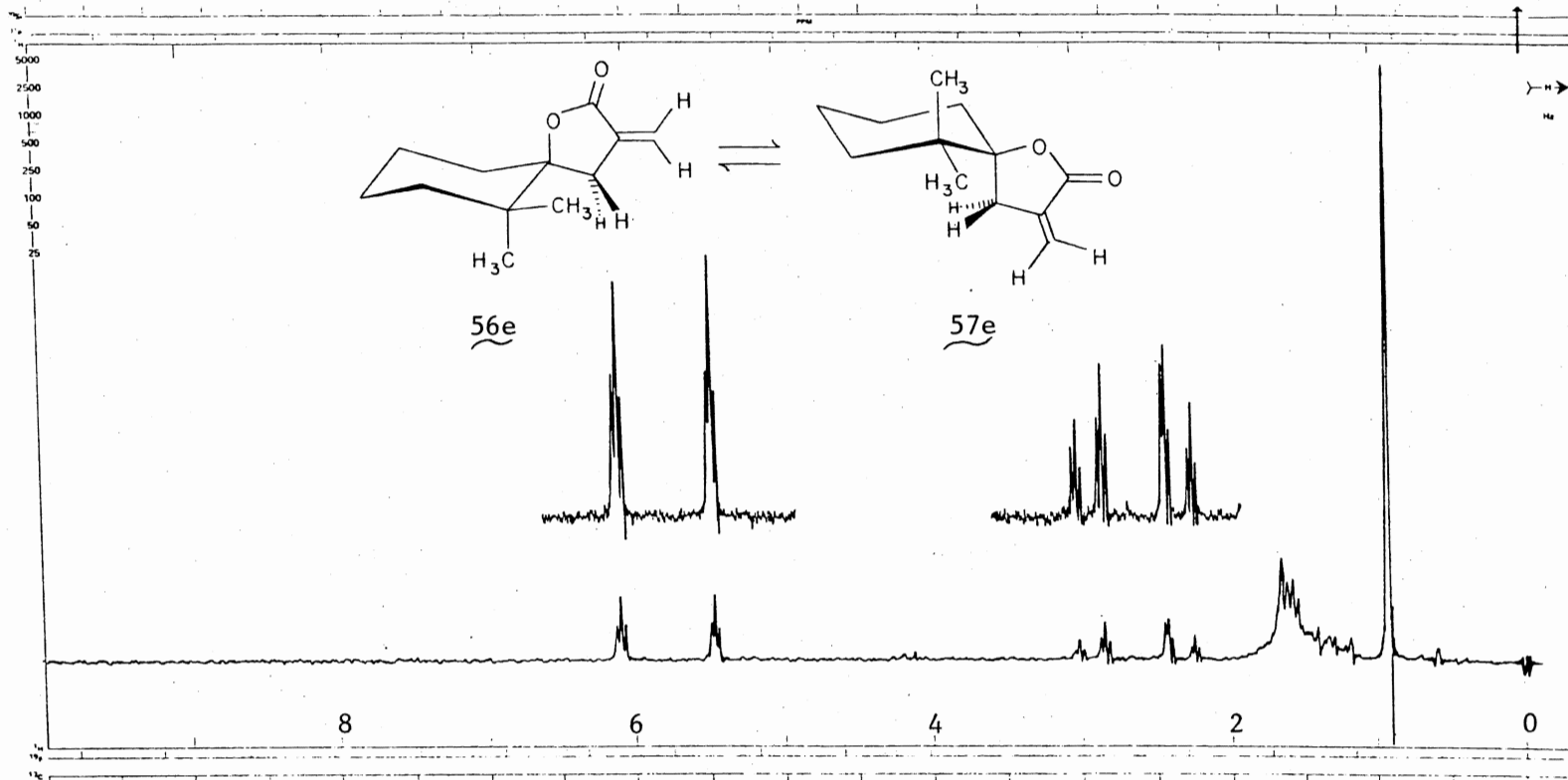
PLATE XI

PFT ^{1}H NMR Spectrum of 56d $\overset{\rightarrow}{\leftarrow}$ 57d

Solvent. . . . $(D_3C)_2C=O$ S.F. . . . . 100.1 MHz   P.W. . . . 1000 Hz   S.W. . . . 1200 Hz   Acq. 16

Size. . . . . 8k pts   P2. . . . 5.7 μs   D5. . . . 6.0 s   S.O. . . 45801 Hz   Lock. . . . ^{2}H
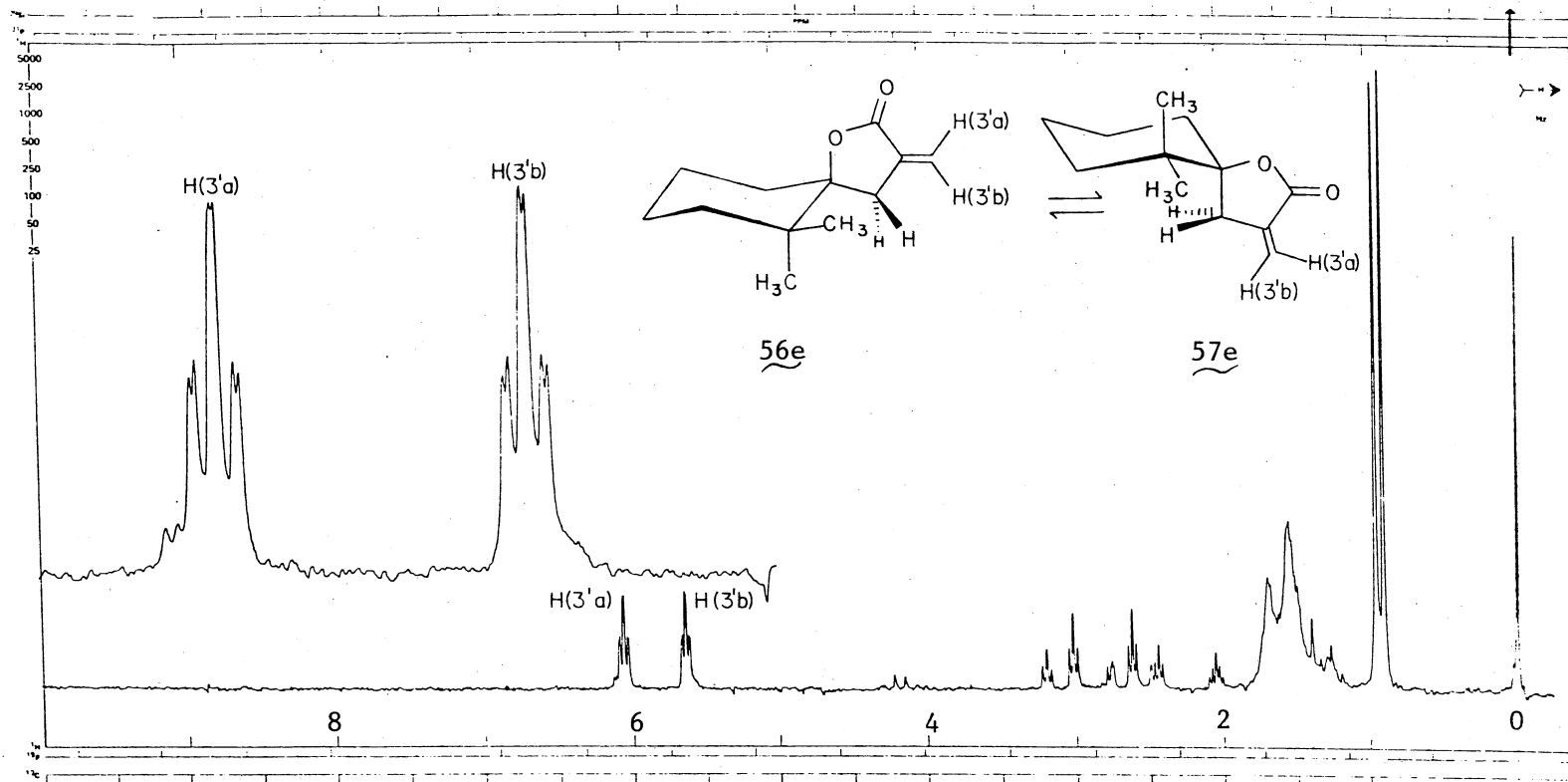
PLATE XII

^{1}H NMR Spectrum of 6,6-Dimethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56e $\rightleftarrows$ 57e)

Solvent. . . .   CCl$_4$ S.F. . . .   100.1   5.B. . . .   2 Hz   R.F. . . .   65 dB

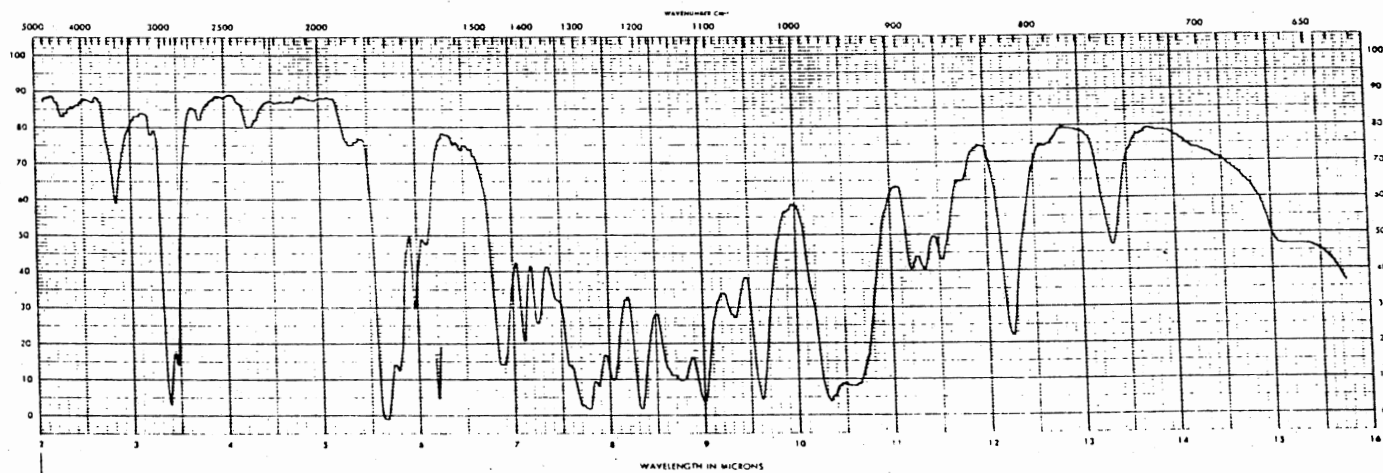S.W. . . .   1000 Hz   S.T. . . .   250 s   S.O. . . .   83701 Hz   S.A. . . .   1.25   Lock. . . .^{1}H

PLATE XIII

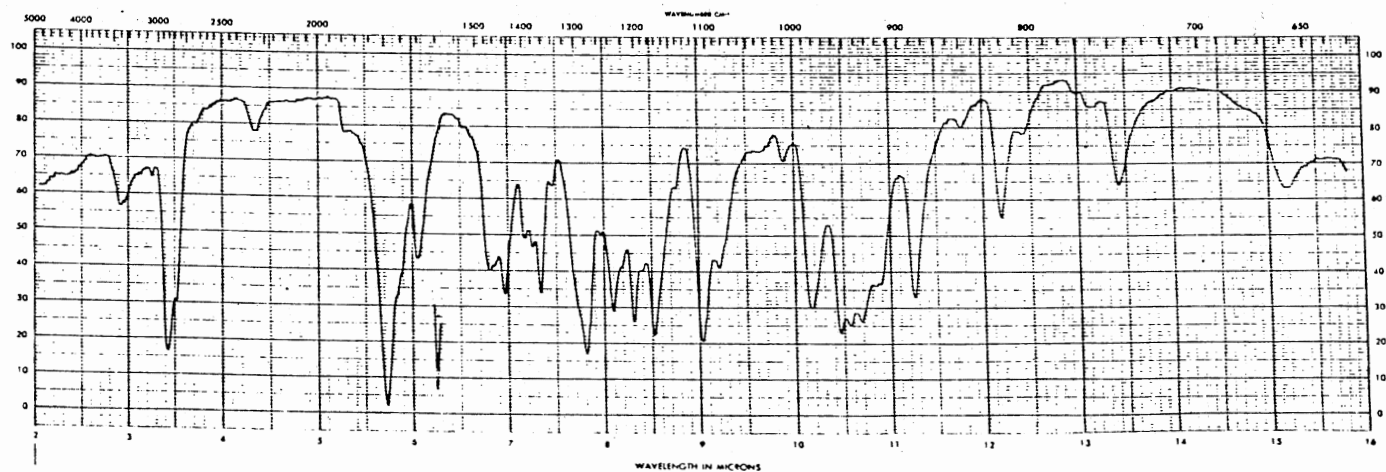PFT ^{1}H NMR Spectrum of 56e $\rightleftarrows$ 57e

Solvent. . . . $(D_3C)_2C=O$ S.F. . . . 100.1   P.W. . . . 1000 Hz   S.W. . . . 1200 Hz   Acq. . . . 20

Size. . . .   8k pts   P2. . . . 5.7 μs   D5. . . . 6.0 s   S.O. . . . 45801 Hz   Lock . . . ^{2}H
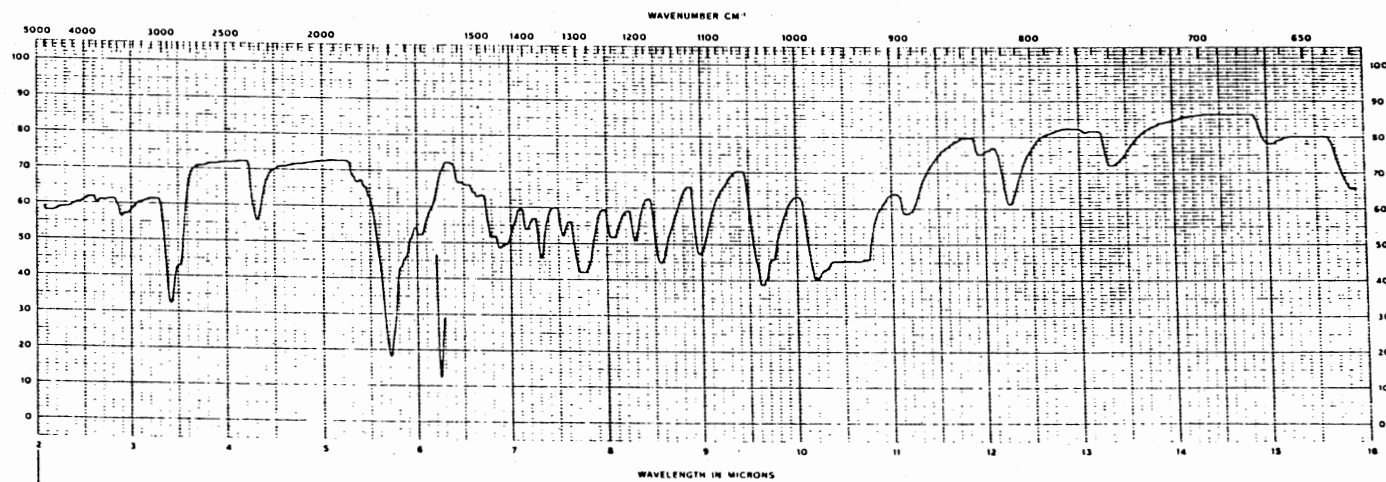
PLATE XIV

IR Spectrum of 3-Methylene-1-oxaspiro[4.5]decan-2-one (56a ⇄ 57a), Thin Film

PLATE XV

IR Spectrum of <u>cis</u>-8-<u>t</u>-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56b), KBr Pellet
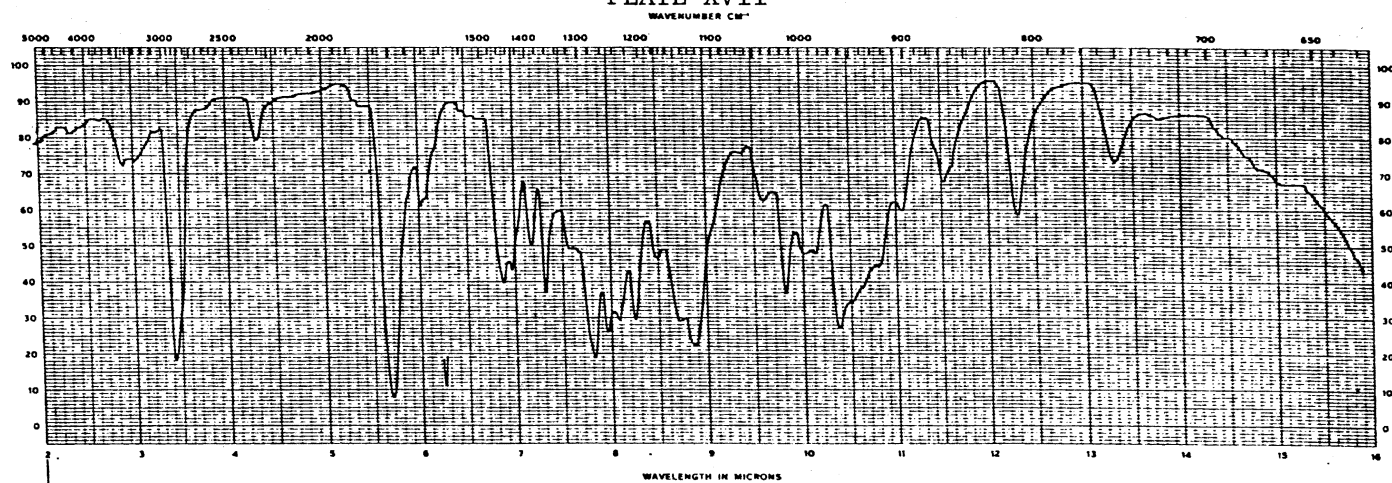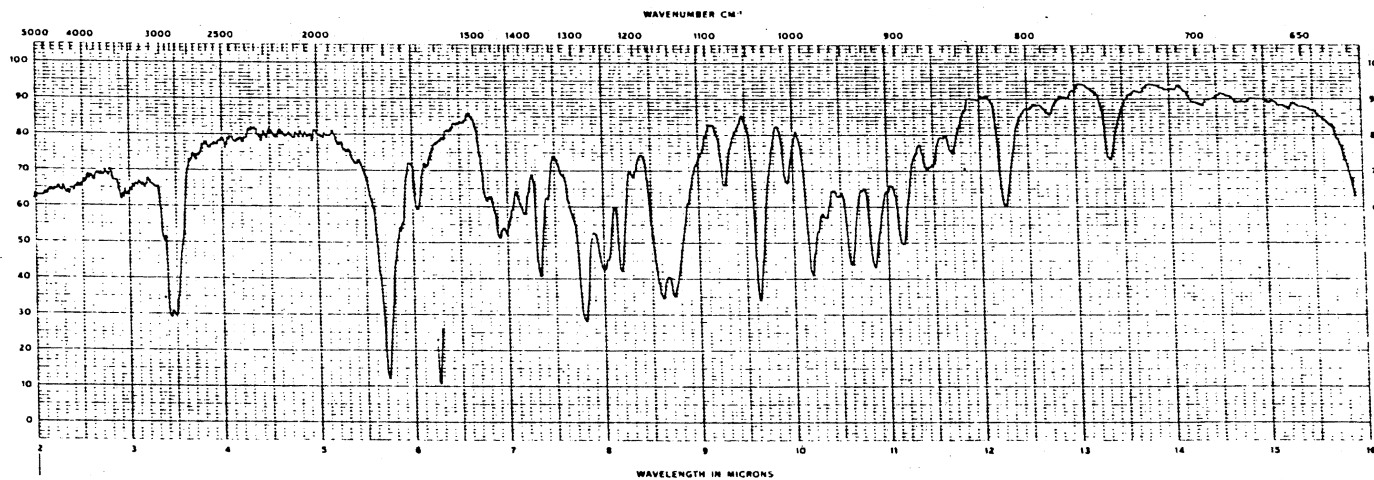
PLATE XVI

IR Spectrum of trans-8-t-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (57b), KBr Pellet

PLATE XVII

IR Spectrum of 7,7-Dimethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56c ⇄ 57c), Thin Film

PLATE XVIII

WAVENUMBER CM⁻¹

WAVELENGTH IN MICRONS

IR Spectrum of 7,7,9,9-Tetramethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56d or 57d), KBr Pellet

PLATE XIX
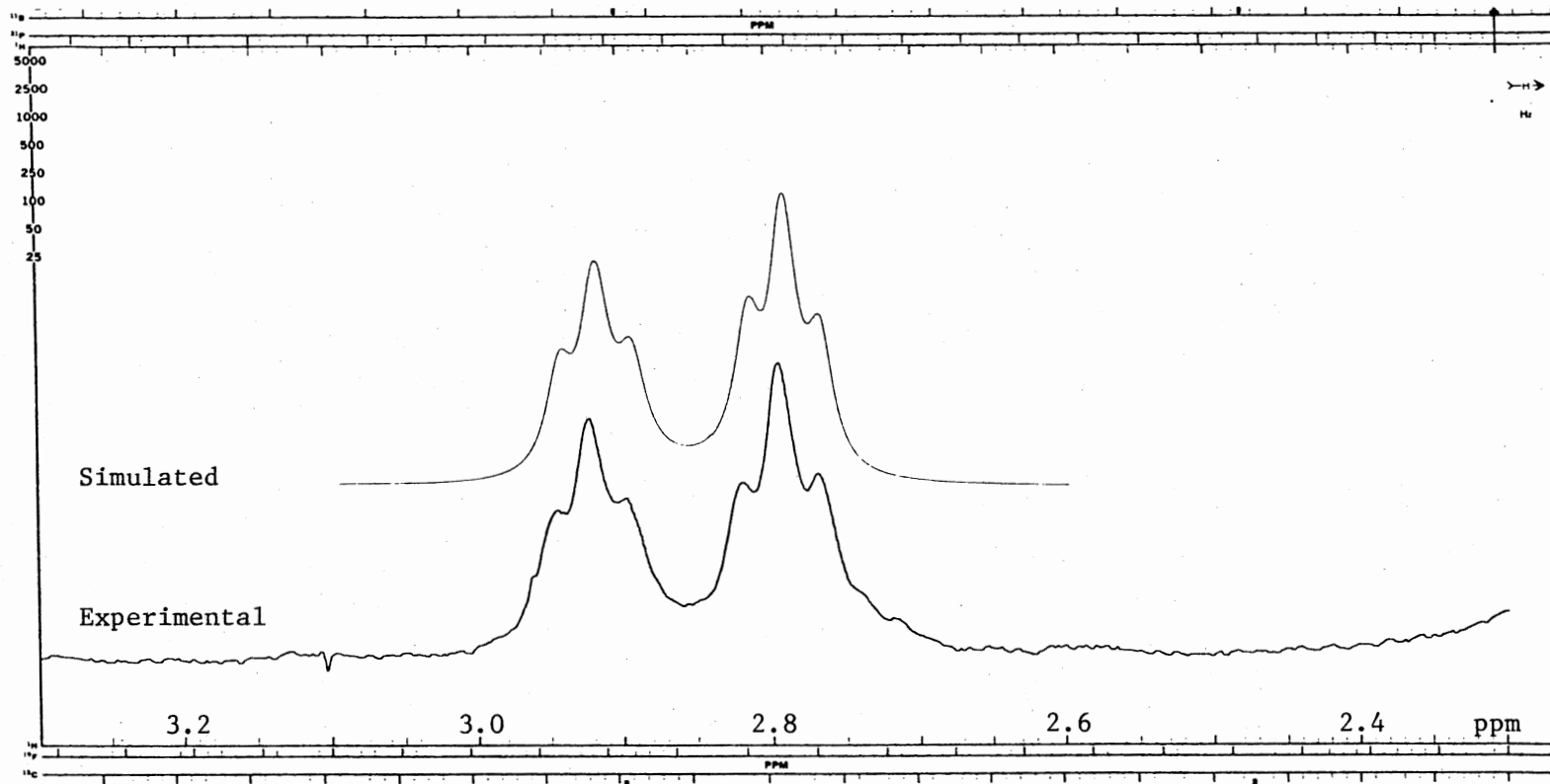
Simulated and Experimental PFT ^{1}H NMR Spectra of 3-Methylene-1-oxaspiro[4.5]decan-2-one (56a $\overset{\rightarrow}{\underset{\leftarrow}{}}$ 57a)

Temperature. . . . 190.8°K

Simulated	k. . . . 2.00 s^{-1}		T$_2$. . . . 0.220 s		K$_{eq}$. . . . 0.802
Experimental	S.W. . . . 100 Hz		Off. . . . 230 Hz		Solvent. . . . (D$_3$C)$_2$C=O

PLATE XX

Simulated and Experimental PFT ^{1}H NMR Spectra of 56a $\rightleftharpoons$ 57a (Downfield Portion)

Temperature. . . . 190.8 K

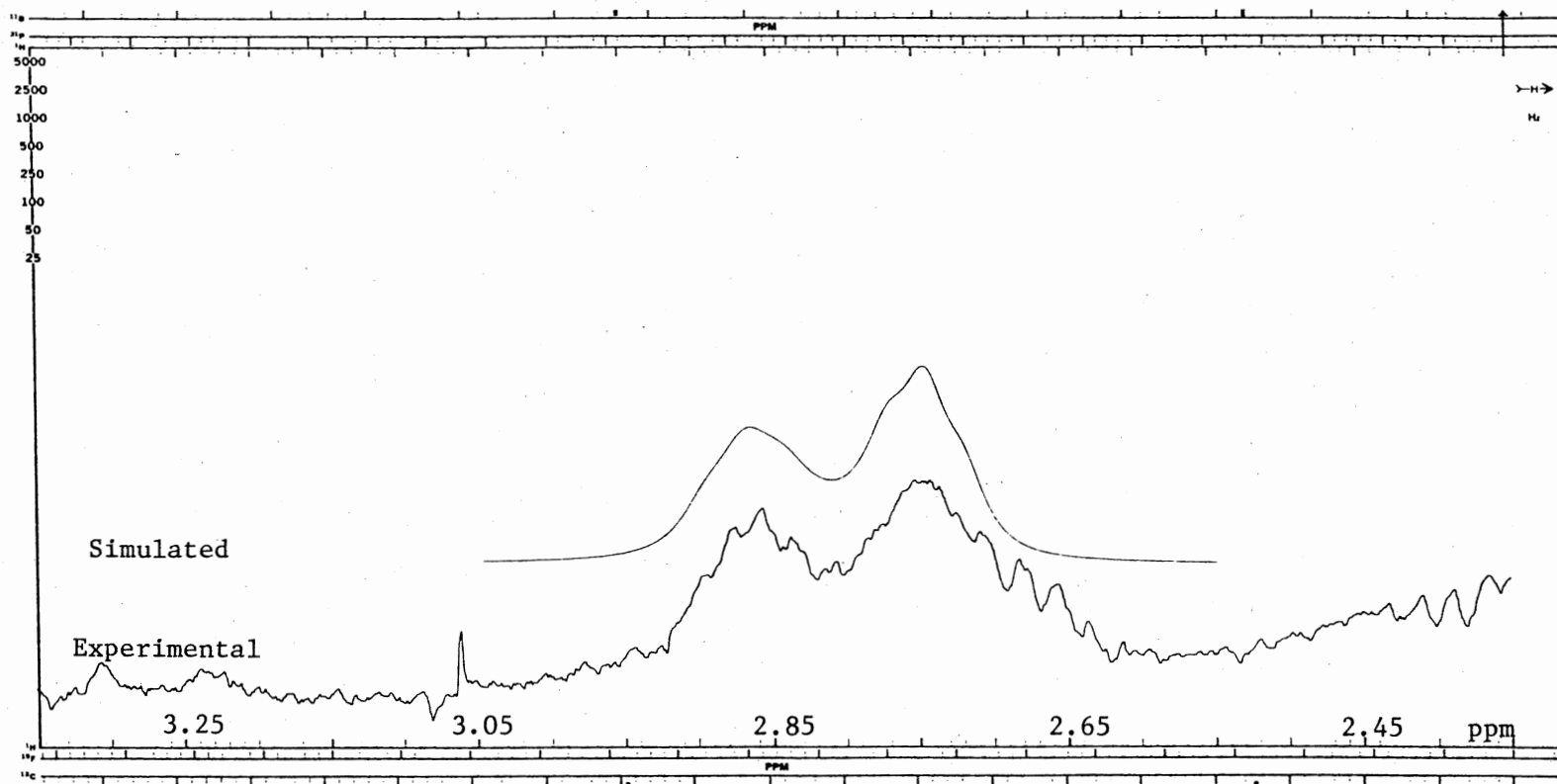|						
Simulated	k. . . .	2.00 s^{-1}	T$_2$. . . .	0.220 s	K$_{eq}$. . . .	0.802
Experimental	S.W. . . .	100 Hz	Off. . . .	550 Hz	Solvent. . . .	$(D_3C)_2C=O$

PLATE XXI

Simulated and Experimental PFT ^{1}H NMR Spectra of $\underline{56a} \rightleftarrows \underline{57a}$
Temperature. . . . 201.1°K

Simulated	k. . . .	8.00 s^{-1}	T_2. . . .	0.260 s	K_{eq}. . . .	0.757
Experimental	S.W. . . .	100 Hz	Off. . . .	235 Hz	Solvent. . . .	$(D_3C)_2C=O$
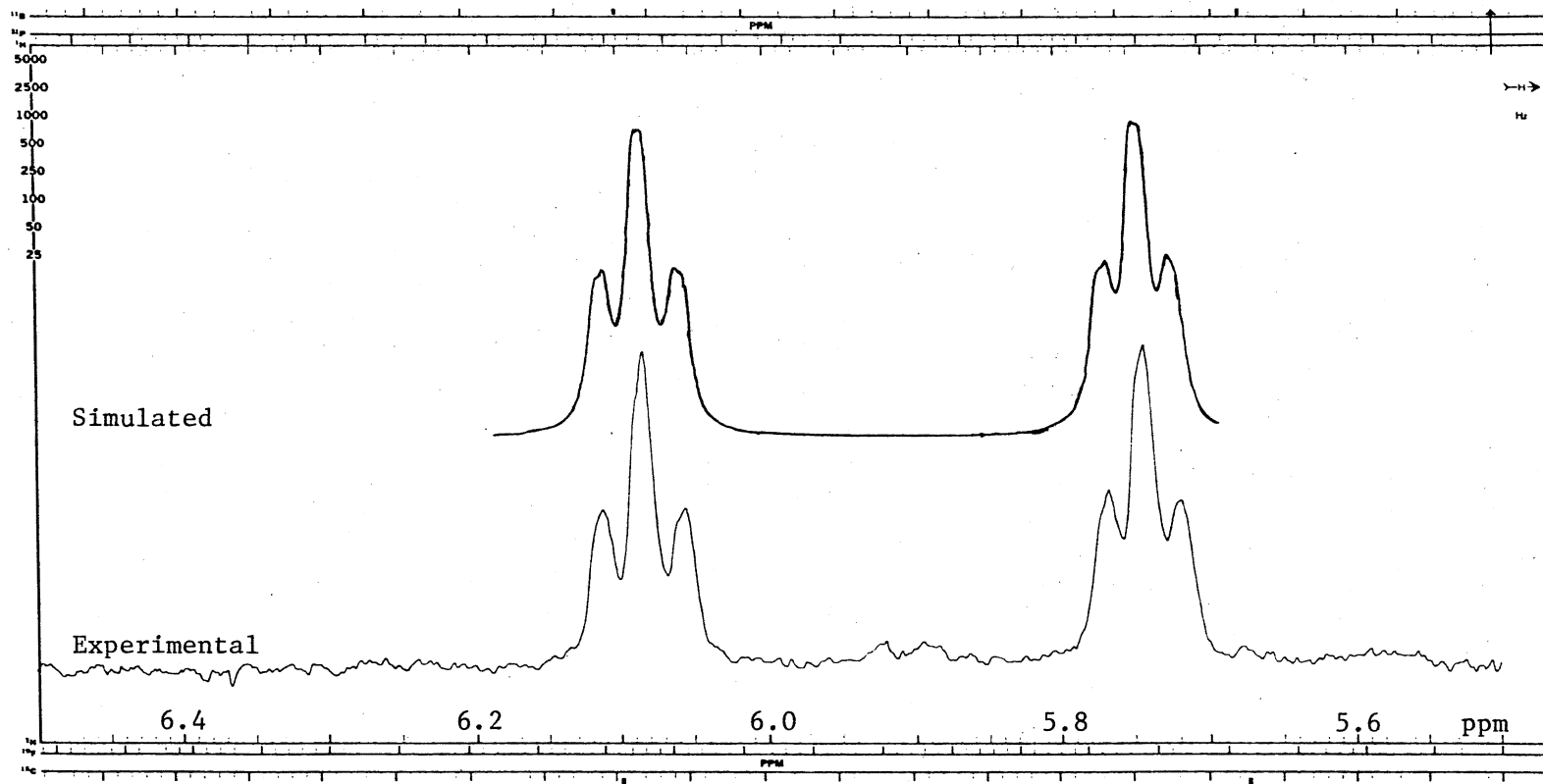
PLATE XXII

Simulated and Experimental PFT ^{1}H NMR Spectra of 56a $\rightleftharpoons$ 57a (Downfield Portion)
Temperature. . . . 201.1°K

| Simulated | k. . . . | 8.00 s^{-1} | T$_2$. . . . | 0.260 x | K$_{eq}$. . . . | 0.757 |
| Experimental | S.W. . . . | 100 Hz | Off. . . . | 550 Hz | Solvent. . . . | (D$_3$C)$_2$C=O |

PLATE XXIII

Simulated and Experimantal PFT ^{1}H NMR Spectra of 56a $\rightleftharpoons$ 57a
Temperature. . . . 209.4^{o}K

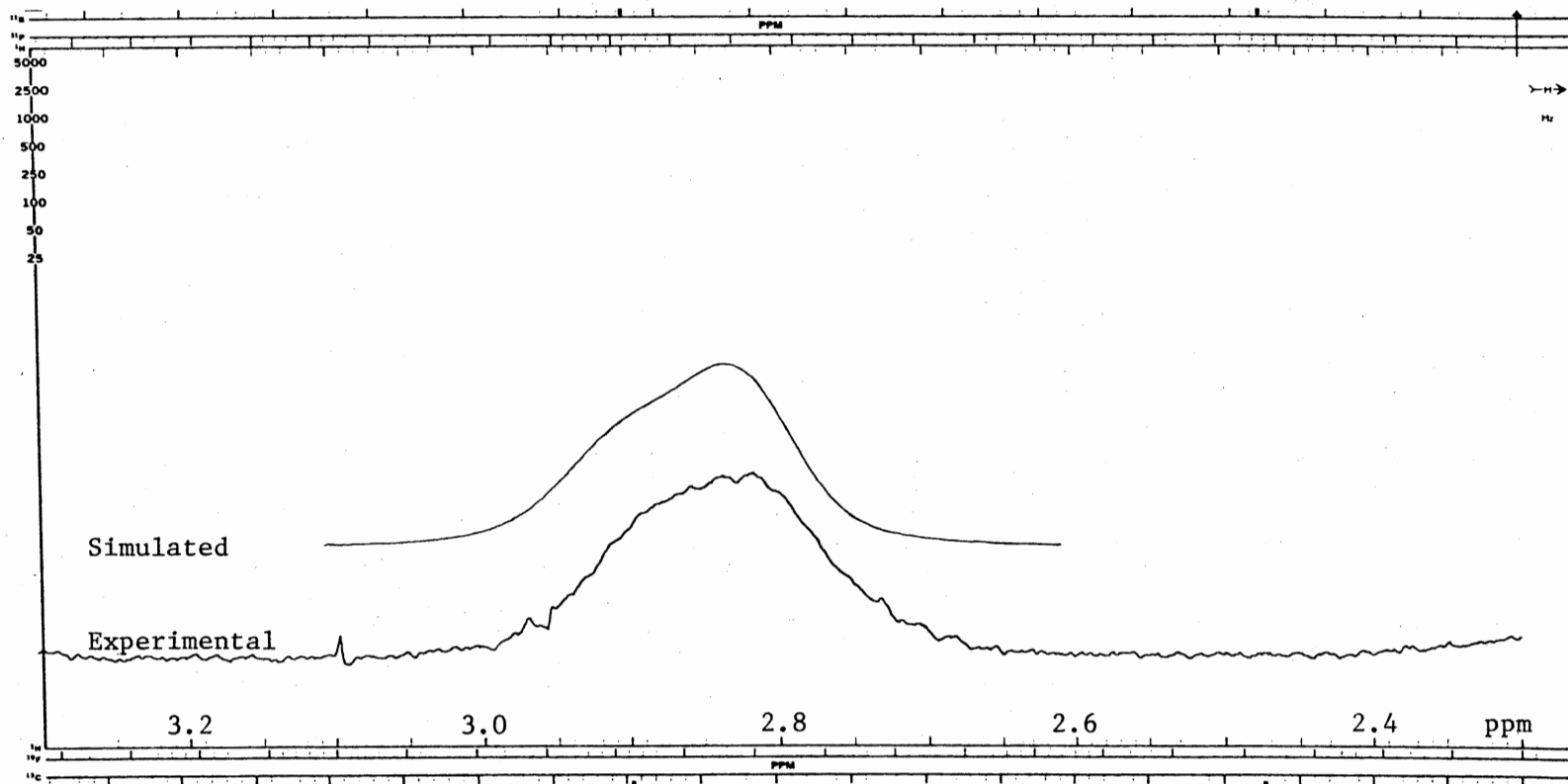|			
Simulated	k. . . . 20.00 s^{-1}	T$_2$ . . . . 0.260 s	K$_{eq}$ 0.750
Experimental	S.W. . . . 100 Hz	Off. . . . 230 Hz	Solvent. . . . $(D_3C)_2C{=}O$

PLATE XXIV
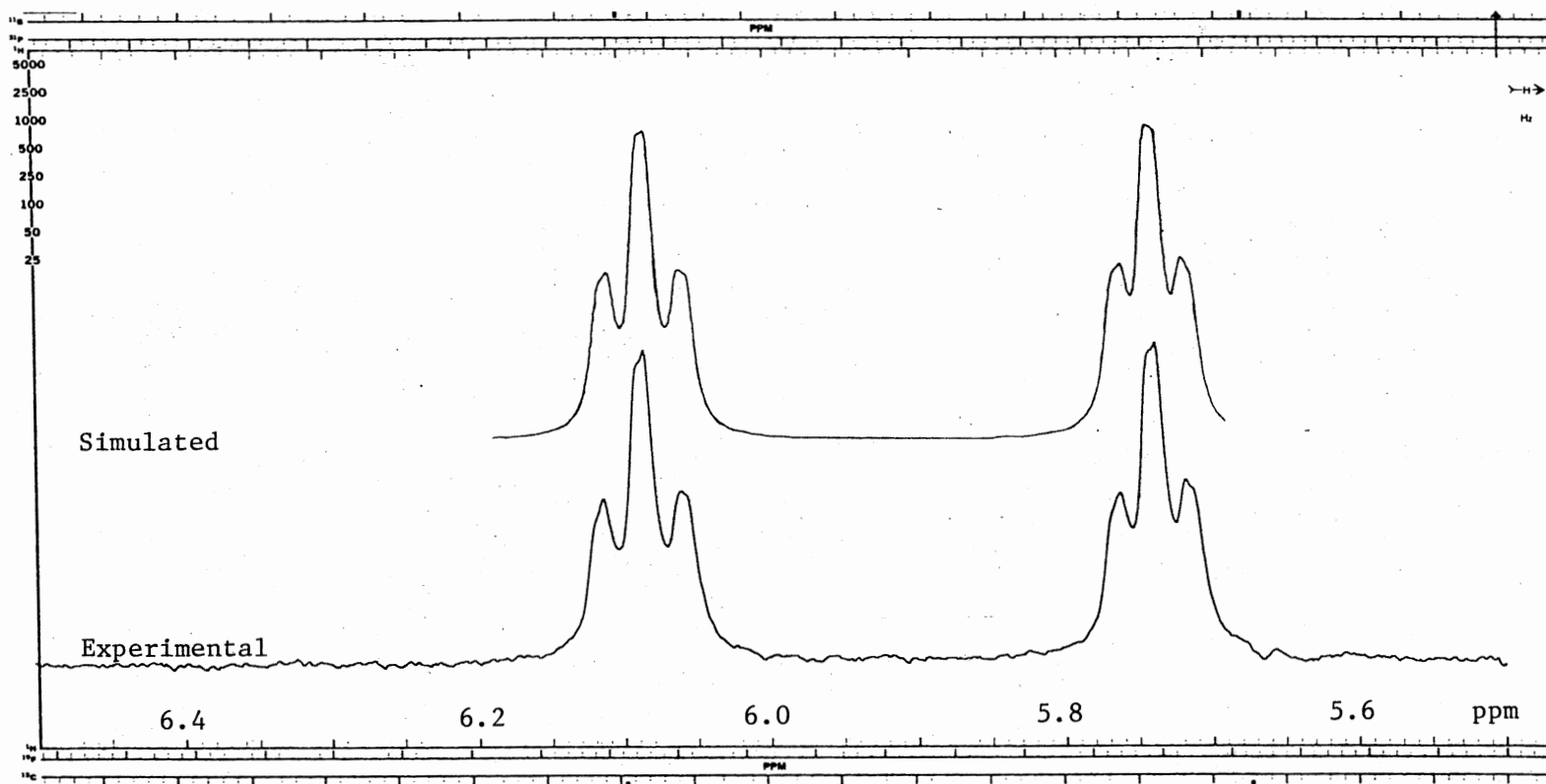
Simulated and Experimental PFT ^{1}H NMR Spectra of 56a $\rightleftharpoons$ 57a (Downfield Portion)

Temperature. . . . 209.4^{o}K

Simulated	k. . . .	20.00 s^{-1}	T$_2$. . . .	0.260 s	K$_{eq}$. . . .	0.750
Experimental	S.W. . . .	100 Hz	Off. . . .	550 Hz	Solvent. . . .	$(D_3C)_2C=O$

PLATE XXV

Simulated and Experimental PFT ^{1}H NMR Spectra of $\underset{\sim}{56a} \overset{\rightarrow}{\underset{\leftarrow}{}} \underset{\sim}{57a}$
Temperature. . . . 218.2°K

Simulated   k. . . . 60.00 s^{-1} T$_2$. . . . 0.300 s   K$_{eq}$. . . . 0.748

Experimental   S.W. . . . 100 Hz   Off. . . . 230 Hz   Solvent. . . . $(D_3C)_2C{=}0$

PLATE XXVI

Simulated and Experimental PFT ^{1}H NMR Spectra of 56a $\rightleftharpoons$ 57a (Downfield Portion)
Temperature. . . . 218.2 K

Simulated	k. . . . 60.00 s^{-1}	T$_2$. . . . 0.300 s	K$_{eq}$. . . . 0.748
Experimental	S.W. . . . 100 Hz	Off. . . . 545 Hz	Solvent. . . . $(D_3C)_2C=O$

PLATE XXVII

PFT ^{13}C NMR Spectrum of 3-Methylene-1-oxaspiro[4.5]decan-2-one (56a $\rightleftarrows$ 57a)

Solvent. . . .	DCCl$_3$	S.F. . . .	25.2 MHz	P.W. . . .	5000 Hz	S.W. . . .	6024 Hz	Acq. . . . 260
Size. . . .	8k pts	P2. . . .	15.5 µs	D5. . . .	12.0 s	S.O. . . .	35101 Hz	Lock . . . ^{2}H

PLATE XXVIII
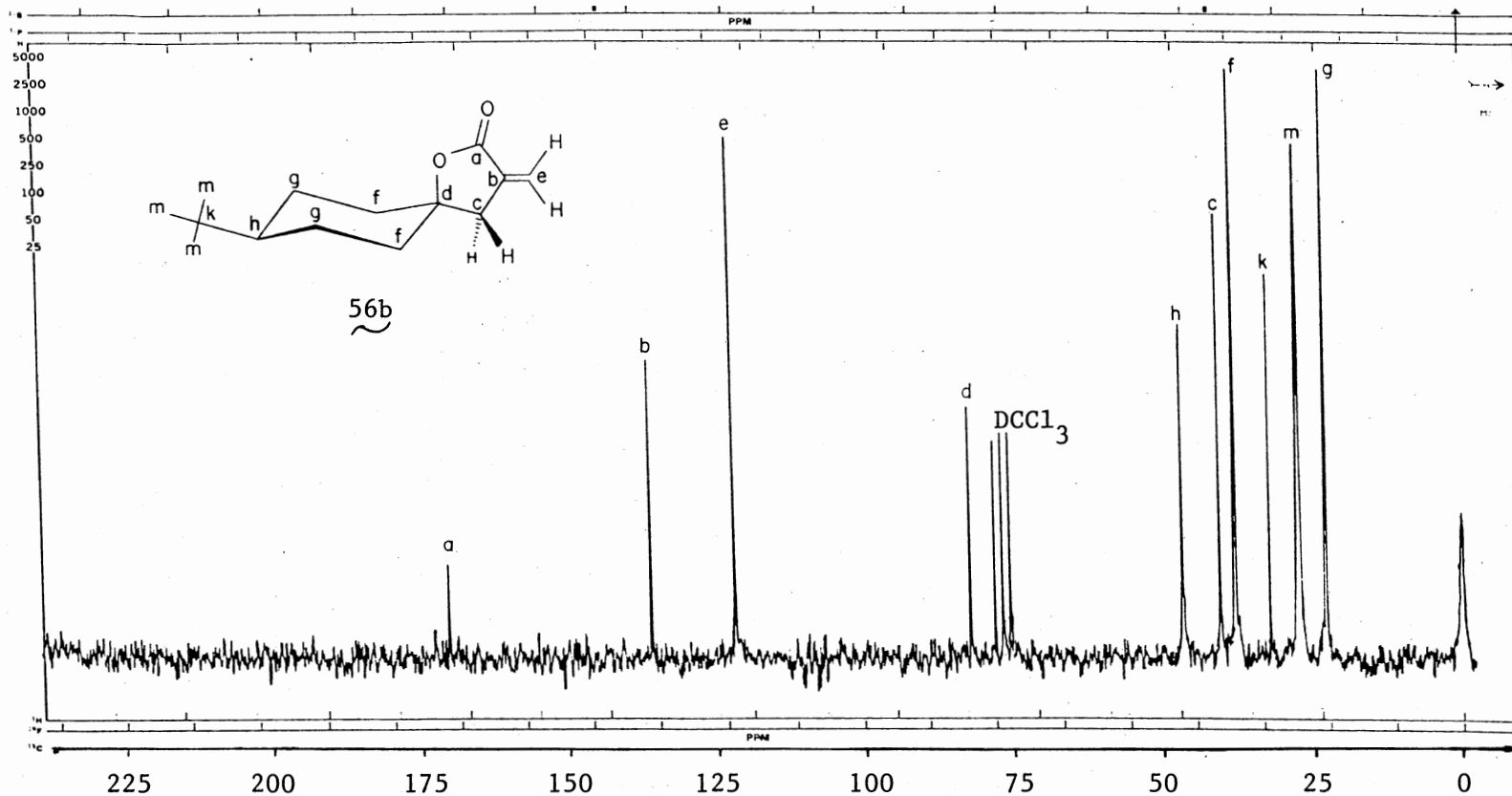
PFT ^{13}C NMR Spectrum of cis-8-t-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56b)

Solvent. . . . DCCl$_3$ S.F. . . . 25.2 MHz   P.W. . . . 6000 Hz   S.W. . . . 6024 Hz   Acq. . . . 200

Size. . . . 8k pts   P2. . . . 15.5 μs   D5. . . . 12.0 s   S.O. . . . 35101 Hz   Lock . . ^{2}H

PLATE XXIX
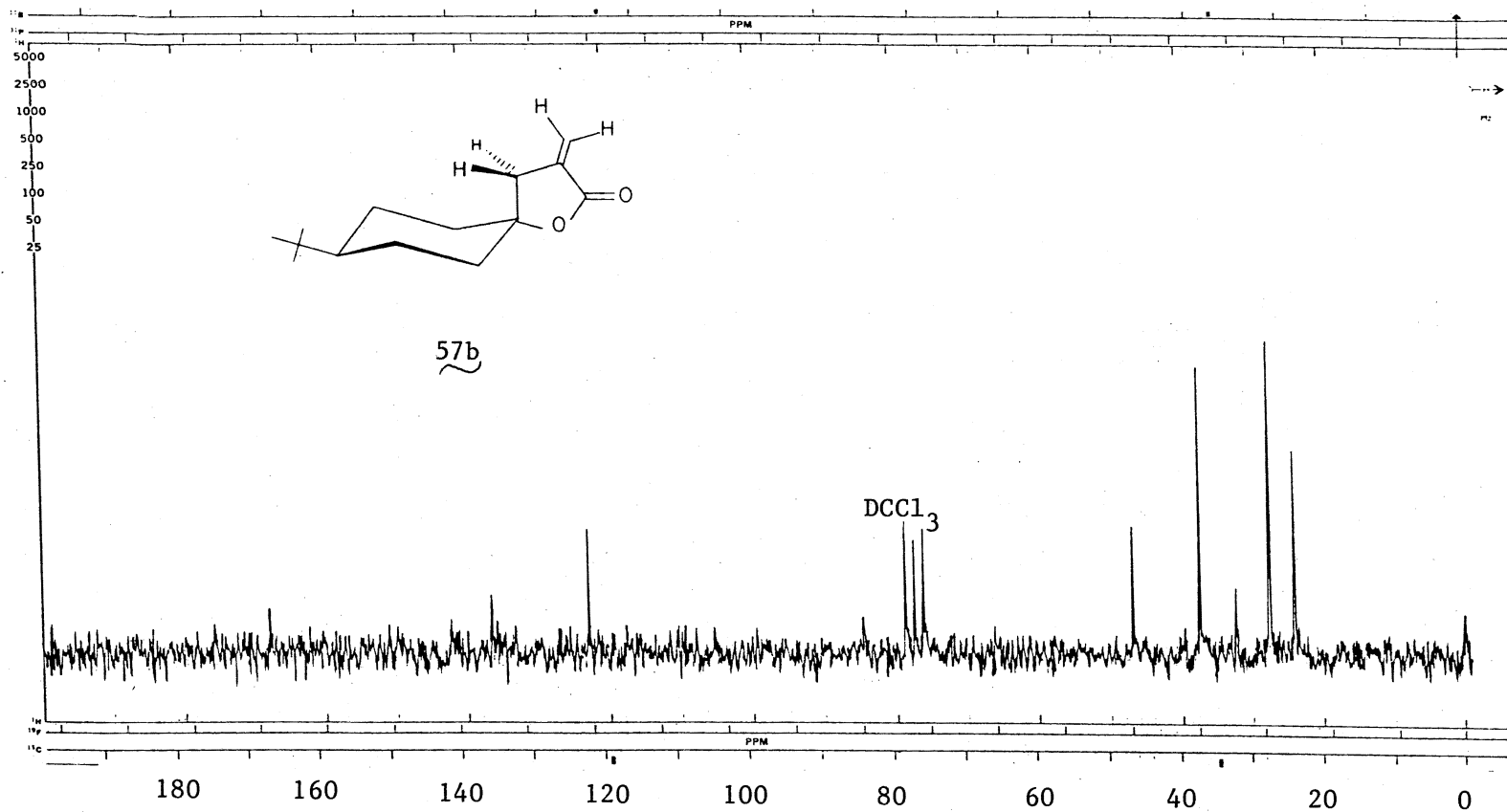
PFT ^{13}C NMR Spectrum of trans-8-t-Butyl-3-methylene-1-oxaspiro[4.5]decan-2-one (57b)

Solvent. . . . DCCl$_3$ S.F. . . . 25.2 MHz   P.W. . . . 5000 Hz   S.W. . . . 6024 Hz   Acq. . . 5500

Size. . . . 8k pts   P2. . . . 10.0 μs   D5. . . . 6.0 s   S.O. . . . 35101 Hz   Lock . . ^{2}H
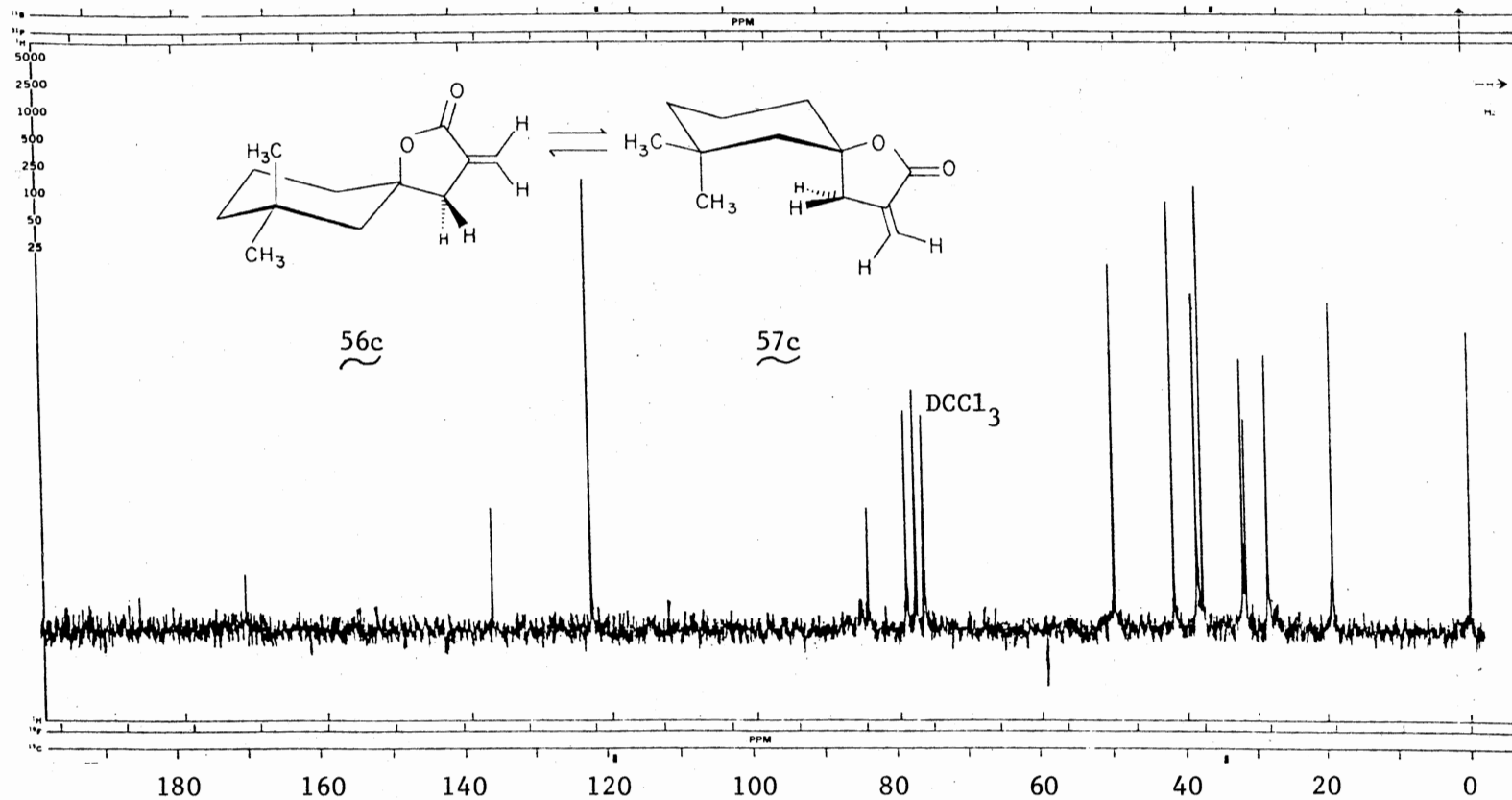
PLATE XXX

PFT ^{13}C NMR Spectrum of 7,7-Dimethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56c $\rightleftarrows$ 57c)

Solvent. . . . DCCl$_3$ S.F. . . . 25.2 MHz   P.W. . . . 5000 Hz   S.W. . . . 6024 Hz   Acq. . . 260

Size. . . . 8k pts   P2. . . . 15.5 μs   D5. . . . 12.0 s   S.O. . . . 35101 Hz   Lock . . ^{2}H

PLATE XXXI
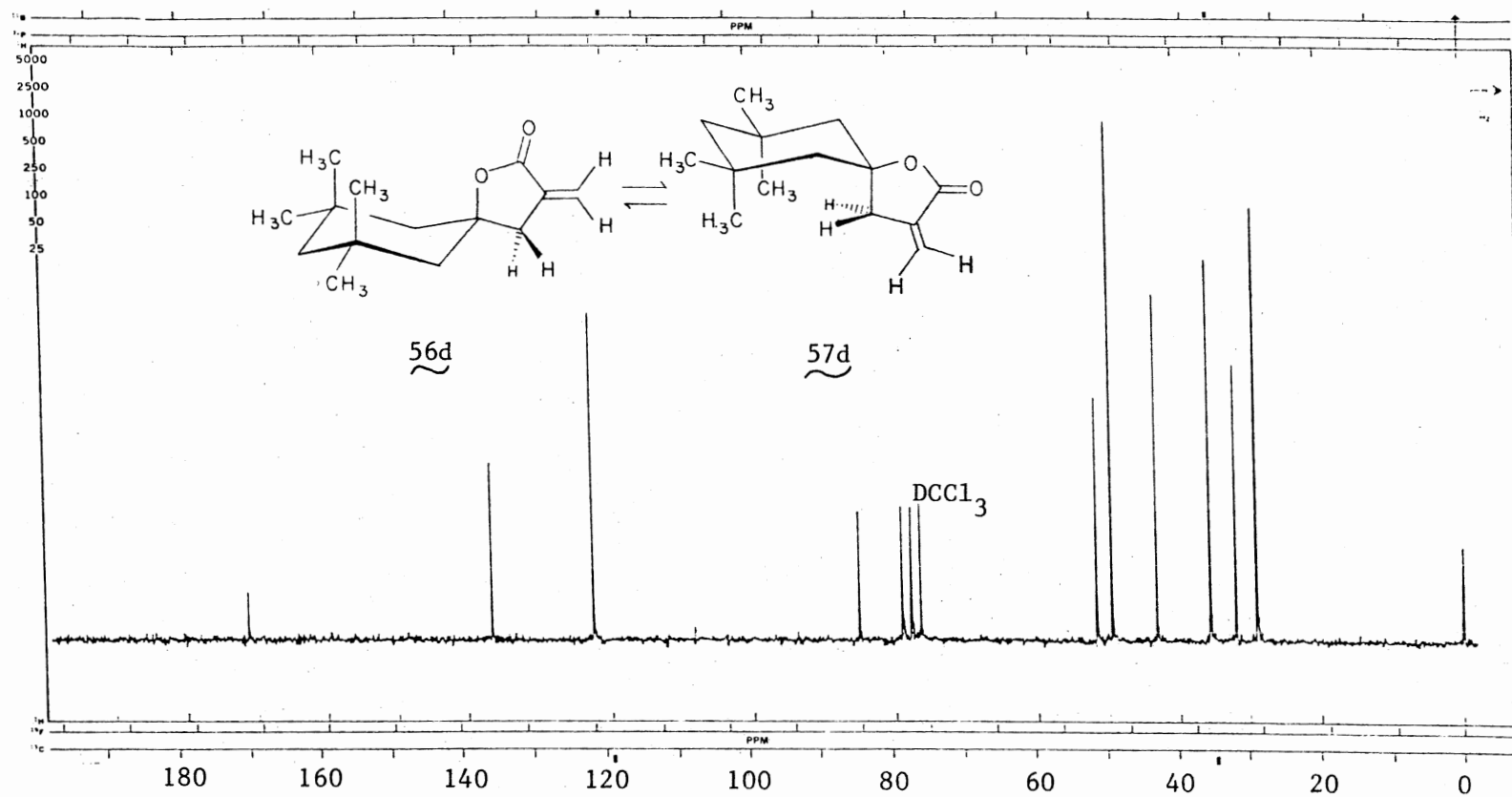
PFT ^{13}C NMR Spectrum of 7,7,9,9-Tetramethyl-3-methylene-1-oxaspiro[4.5]decan-2-one (56d $\overset{\rightarrow}{\underset{\leftarrow}{}}$ 57d)

Solvent. . . . DCCl$_3$ S.F. . . . 25.2 MHz   P.W. . . . 5000 Hz   S.W. . . . 6024 Hz   Acq. . . 260

Size. . . . 8k pts   P2. . . . 15.5 μs   D5. . . . 12 s   S.O. . . . 35101 Hz   Lock . . ^{2}H

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VITA

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