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Conformational analysis of 1,3,2-dioxathiane. Conformational analysis of 4-chlorothiane-1,1-dioxide.

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PART I

CONFORMATIONAL ANALYSIS OF 1,3,2-DIOXATHIANE

PART II

CONFORMATIONAL ANALYSIS OF 4-CHLOROTHIANE-1,1-DIOXIDE

BY

BRIAN E. ADLAM

A Thesis
Submitted to the Faculty of Graduate Studies through the
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of the Requirements for the Degree of
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University of Windsor

Windsor, Ontario
1973

To my parents

ABSTRACT

PART I

The determination of the energy barrier, $\Delta G^{\ddagger}$, for ring reversal of 1,3,2-dioxathiane is carried out by an analysis of the low temperature proton magnetic resonance spectra of 1,3,2-dioxathiane-4,4,6,6-d_4. From an analysis of the AB spin system, the rate of chair-chair interconversion at the coalescence temperature was determined as $k_c = 126.65\ \text{sec}^{-1}$, and the energy barrier for ring inversion, $\Delta G^{\ddagger} = 11.2$ kcal/mole. The 1,3,2-dioxathiane system is suggested as a model for trimethylene sulfites and hence the results are interpreted and correlated with existing evidence to give a more coherent picture of trimethylene sulfites.

PART II

The conformational analysis of 4-chlorothiane-1,1-dioxide was attempted through low temperature nuclear magnetic resonance studies. The analysis qualitatively shows an overwhelming preference for the conformer with axial chlorine over the equatorial one. The large deviation from additivity is consistent with a 1,4-dipolar interaction.

ACKNOWLEDGEMENTS

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Part 1

Conformational Analysis of 1,3,2-Dioxathiane

Chapter 1

INTRODUCTION

Conformational analysis may be described as the interpretation of the reactions and properties of compounds in terms of their conformations. Barton and Cookson[1] suggest the fundamental principle of conformational analysis is that the chemical and physical properties of organic molecules depend not only on their gross structure and stereochemistry but also on the conformations they adopt. The availability of such powerful tools as gas liquid chromatography (glc) and nuclear magnetic resonance (nmr) has led to a reasonable understanding of the behaviour of alicyclic systems.

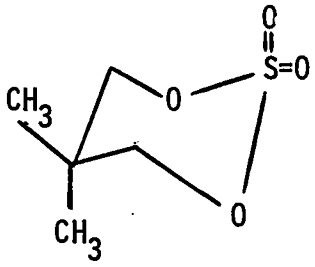
In recent years, attention has been directed more towards the conformational studies of heterocyclic systems[2] which have provided interesting features. The ^1H n.m.r. technique, especially the variable temperature method, provided invaluable information regarding the conformation and the energy barrier associated with these molecules.

Low temperature n.m.r. spectrometry is conveniently applied in the studies of six-membered heterocyclic compounds. In general, these compounds, like cyclohexane and its derivatives, prefer chair conformations, and when in solution undergo rapid chair-chair interconversion at room temperature. Hence at room temperature there are two conformational isomers in equilibrium and the observed spectrum is really a single spectrum representing an average environment of the protons. The reason for this is that the equilibration of the two chair forms is very fast compared to the rate of nuclear transition being examined. Thus one does not observe separate peaks due to the two conformers, but rather a spectrum corresponding to an average conformation. Now as the temperature is lowered, the rate of conformational interconversion will begin to decrease, until a point is reached where the rate has been sufficiently retarded to enable the n.m.r. to record the separate spectra of the two conformations superimposed. Data regarding coalescence, chemical shifts, and coupling constants may be extracted from these spectra and used to determine the kinetic parameters for the chair-chair interconversion.

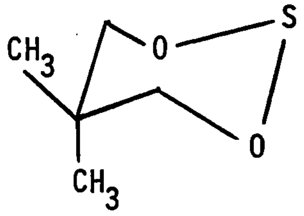
It has been experimently established that two or more adjacent hetero atoms in a ring raise the barrier to chair-chair interconversion, (ring reversal), significantly.[3,4,5] This is in agreement with the theoretical predictions of Wolfe and co-workers[6] which state that electron pair - electron pair, electron pair - polar bond, or polar bond - polar bond interactions cause a significant increase in rotation - inversion barriers.

Efforts to observe the conformational isomers of various trimethylene sulfites[7] and 1,2-oxathiane-2-oxide[8] by variable temperature n.m.r. spectrometry have been unsuccessful. These results rule out conformational equilibria across a barrier of magnitude comparable to that anticipated for chair-chair ring reversal. Although the possibility of a chair-chair barrier too high for n.m.r. detection was considered likely at one time, the favoured interpretation in this laboratory at the present depends on the strong preference of the exocyclic S=O for the axial position. In the absence of large steric effects, trimethylene sulfites are anancomeric, i.e. they possess a single conformation. Introduction of steric interactions has so far failed to produce a system in which the chair forms can be demonstrated to be in equilibrium. Thus, the barrier for interconversion is probably comparable to that for structurally similar molecules, but not amenable to n.m.r. measurement because the sulfite ring system is strongly biased toward one chair form. An explanation for the axial preference of the exocyclic S=O bond in these systems has been given.[7]

Wood and co-workers[9] reported that the barrier to chair-chair interconversion in 5,5-dimethyltrimethylene sulfate (1a) was 8.1 - 8.4 kcal/mole. This value is approximately 2.0 kcal/mole less than that of cyclohexane[10] but apparently higher than a cyclic sulfate barrier measured by ultrasonic absorption and attributed to ring reversal.[11] This n.m.r. result presumably arises from a balancing of several factors, including electron pair - polar bond interactions across the S-O bonds and reduced rotational barriers about the C-O bonds.



(1a)

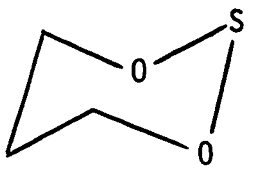


(2a)

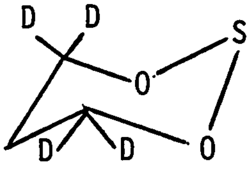
In an attempt to gain more information about the influence of vicinal electron pair interactions on the barrier height, Wood and Srivastava examined 5,5-dimethyl-1,3,2-dioxathiane (2a). The barrier, ($\Delta G^{\ddagger}$), to chair-chair reversal in (2a) has been found to be 12.6 ± 0.2 kcal/mole based on the coalescence of the methyl signals and 12.3 ± 0.2 kcal/mole obtained from the coalescence of the methylene quartet.[12]

An investigation of the parent 1,3,2-dioxathiane (2b) showed that the barrier in this system is slightly lower. The ^{1}H n.m.r. spectrum of (2b) at room temperature consisted of a triplet at $\delta = 4.38$ and a quintet at $\delta = 1.98$. Upon lowering the temperature, the quintet (C-5 protons) at $\delta = 1.98$ broadened and at -70° gave two separate proton signals; one at $\delta = 3.0 - 2.0$ (multiplet), and the other at $\delta = 1.6$ (broad doublet). The former and the latter are due to axial and equatorial protons. On raising the temperature, the two signals broadened and moved towards each other. Due to the very broad nature of the separate proton signals, the coalescence temperature, (the temperature at which the two separate proton signals coalesce), could only be approximated.

For the triplet (C-4 and C-6 protons) at $\delta = 4.38$, it appeared difficult to observe good separation of axial and equatorial protons since the chemical shifts of these two were quite close, and hence even a rough estimate of the coalescence temperature could not be obtained. The barrier to chair-chair ring reversal in (2b) was calculated to be 11.31 kcal/mole based on the coalescence temperature of the C-5 protons.[13] In order to



(2b)



(2c)

obtain a more accurate value of the coalescence temperature, it was suggested that the compound (2b) be labelled with deuterium (2c). Deuterium (^2H or D) is introduced into a molecule usually to detect a group or to simplify a spectrum. ^2H has a spin number of 1, a small coupling constant with protons and a small electrical quadruple moment. In this case it is used to eliminate unwanted couplings between the C_4 - C_5 and C_5 - C_6 protons. The elimination of these couplings yields a spectrum more amenable to exact analysis. The simplification of an n.m.r. spectrum by the elimination of long range or unwanted couplings through the use of deuterium substitution is a generally useful technique.[14] Deuterium labelling in compound (2b) should give a room temperature spectrum consisting only of a single peak in the vicinity of $\delta = 2.0$ comparable to the quintet ($\delta = 1.98$) in the parent compound. Upon lowering the temperature the single peak should broaden and eventually split into a non first-order AB quartet.

STATEMENT OF PROBLEM

The objective of this work was to:

1. Synthesize 1,3,2-dioxathiane-4,4,6,6-d_4.
2. Determine the ring reversal barrier.

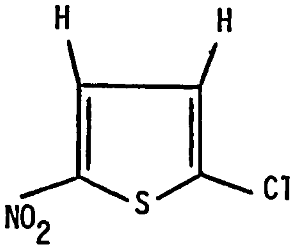
3. The symmetry of 1,3,2-dioxathianes makes it ideal for n.m.r. study and its close structural resemblance to trimethylene sulfite confers on it some value as a model for the latter. Hence the results are to be interpretated and correlated with existing evidence to give a more coherent picture of trimethylene sulfites.

THE TWO-SPIN SYSTEM

The simplest system of interacting nuclei in which the effects of chemical shift and spin coupling are intermingled is the two-spin system. For two nuclei A and B of a two-spin system, the spectral parameters are the two chemical shifts ν_A and ν_B and the spin coupling constant J_{AB}. The limiting case of coincident chemical shifts is denoted "A_2", the proton resonance of methylene dichloride, CH_2Cl_2, being an example of this kind. At the other extreme, the "first order" limit is denoted "AX" and here $|J_{AB}| <<< |\nu_A - \nu_B|$. When in a two-spin system, the magnitude of the chemical shift $|\nu_A - \nu_B|$ between the nuclei becomes similar to or smaller than J, (i.e. $|\nu_A - \nu_B|/J < 10$), the spectrum is designated as an AB system.

First Order Spectra:

Consider the spectrum of 2-chloro-5-nitro-thiophen (3). It has two protons in the molecule, on adjacent carbon atoms, each in a different chemical environment. One may expect, therefore, two signals in the spectrum. In fact, four lines, in two pairs, are observed as indicated in Fig. 1 [15]



(3)

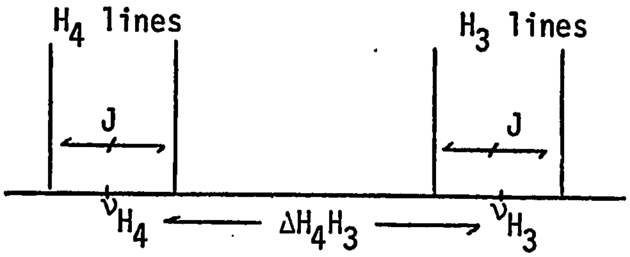
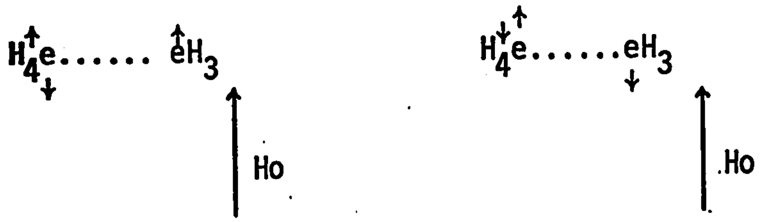


Fig. 1

There is a low field pair of lines from H_4 and a higher field of lines from H_3 with each pair separated by an equal spacing.

This separation is a direct measure of the effectiveness of the electron coupled spin-spin interaction and is known as the coupling J. J is independent of field strength and its magnitude is dependent on the gyromagnetic ratio of the nuclei and on the structural relationships of the groups involved. For example, the coupling J can have a range of values because the electron correlation of nuclear spins will be more or less efficient, depending on the number of intervening bonds (i.e. electrons), the bond angles (i.e. degree of overlap of electron orbitals), and the nature of the orbitals involved.

An explanation of the spectra is understood if one considers that a proton in its particular spin state produces a small magnetic polarization on the adjacent electrons, so that the spins tend to become antiparallel: H ↑ e ↓ e ↑. This effect really results from there being a small probability of the electron being at the nucleus itself: of necessity, spins would then have to be paired. This correlation effect is transmitted through further bonding electrons to neighbouring protons. Any two electrons in one bonding orbital have their spins antiparallel by the Pauli exclusion principle. Therefore in Fig. 2a for the spin H_4↑, the effective field at nucleus H_3 would be increased to (Ho↑ + ↑e), since the applied field Ho at proton H_3 is increased by a contribution from the spin of the adjacent electron.



2a 2b

Fig. 2

Equally probable would be the situation in which nucleus H_4 had the opposite spin. The electron spins would then tend to correlate in the opposite since, as in Fig. 2b and the effective field at nucleus H_3 would be diminished to (Ho↑ + ↓e). It follows that nucleus H_3 experiences two modifications of the applied field, one on each side of the value which would be required for the unperturbed nucleus. The effect is mutual of course, so that two coupled protons perturb each other, and each gives rise to a doublet signal.

The two spin states are equally probable so the four spectral lines are of equal intensity. The mid-point of the components of each doublet is called the origin position of the respective proton and gives the chemical shift of the respective proton.

The spectrum of 2-chloro-5-nitro-thiophen is an example of a first order AX two-spin system; i.e. their chemical shift $\delta = |\nu_A - \nu_B|$ in Hz between the coupled protons is large compared to the coupling constant J in Hz such that $\delta/J \geqq 10$. Simple first order spectra exhibit the following rules.[16]

1. The nuclei of an equivalent group do not interact with

each other in such a way as to cause observable multiplicity.

2. The number of lines in a multiplet is $(2nI + I)$ where n is the number of adjacent nuclei of spin I.
3. The intensities of a multiplet are symmetrical about the mid-point of the band, and the relative intensities are given by the coefficients of the terms in the expansion of $(r + 1)^n$.

The failure of equivalent nuclei to produce mutual splitting is not because they do not interact, in actual fact there is coupling, but it happens that the quantum mechanical selection rules forbid any observable effect from the spin-spin coupling of equivalent nuclei.

Non First Order Spectra:

When the chemical shift is not much greater than J, say $\delta/J = 2$ to 5, then the component lines in each multiplet no longer have the ideal intensities. There is a distortion within each multiplet such that the innermost lines increase in intensity at the expense of the outermost lines, and the splitting patterns are no longer "first order". The number of lines observed may be increased and either or both the parameters δ and J are no longer directly extractable from the multiplet patterns as in the AX case where the coupling J and the origin positions of the nuclei were directly obtainable from the spectrum.

As stated previously, in a two-spin system, when the magnitude of the chemical shift, δ , between the nuclei becomes similar to or smaller than J, the spectrum is designated as an AB system. Two pairs of lines are again observed, each separated by J_{AB} Hz, but the origin positions are no longer the mid-points of the doublets, and the lines have distorted intensities as shown in Fig. 3.[17] If m is the distance between

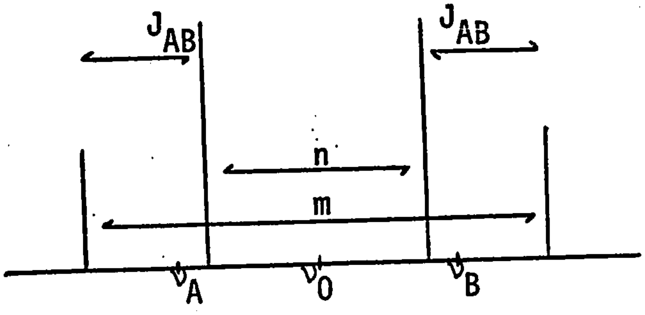


Fig. 3

the outer lines and n that between the inner lines, then the chemical shift between nuclei A and B is given by:

$$\delta = |\nu_A - \nu_B| = \sqrt{mn}$$

If the mid-point of the quartet of lines is ν_o Hz (from TMS) then the origin positions of nucleus A and B is given by:

$$\nu_A = \nu_o + 1/2 \sqrt{mn} \text{ Hz} \qquad \nu_B = \nu_o - 1/2 \sqrt{mn} \text{ Hz}$$

If m and n are not readily obtainable from the spectrum, the chemical shift δ, may be calculated from the equation:[18]

$$c = 1/2 \sqrt{J_{AB}^{2} + \delta^{2}}$$

$$\delta = \sqrt{(2c)^2 - J_{AB}^2}$$

where 2c is the distance shown in Fig. 4

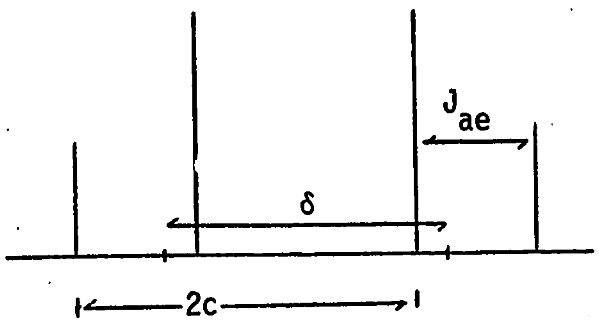


Fig. 4

In the limit, in a two spin system, the chemical shift between the nuclei is zero. This is designated as an "A_2" group and the spectrum consists of a single line. The inner two lines of the AB quartet increase in intensity to finally merge together as the outermost lines dwindle to zero, as $\delta_{AB} \longrightarrow 0$.

At the other extreme limit, the AX case in which J = 0, the spectrum will consist only of two absorption lines corresponding to two different spin transition energies, one for nucleus A at ν_A and one from nucleus X at ν_X.

EVALUATION OF RATE CONSTANTS

N.M.R. spectroscopy is one of the most powerful tools for the evaluation of rate constants for conformational changes with energies of activation in the range ca. 6 - 25 kcal/mole. Rate constants at the coalescence point (k_c) are usually evaluated using approximate equations: (a) $k_c = (\pi / \sqrt{2})\ \Delta\nu$, for the coalescence of singlets associated with uncoupled diastereotopic atoms or groups[19], and (b) $k_c = (\pi / \sqrt{2}) \sqrt{(\Delta\nu^2 + 6J^2)}$, for the coalescence of the coupled AB spin system to a singlet.[20]

In order to determine the general validity of the approximate equations, Raban and co-workers[21], carried out a systematic comparison of the rate constants obtained using equations (a) and (b) with those obtained by complete line shape analysis. In making comparisons between rates obtained using equations (a) and (b) and complete line shape analysis, it is important to realize that errors of 10, 25, and 100% in rate constants produce errors in $\Delta G^{\ddagger}$ of only 0.06, 0.1, and 0.4 kcal/mole respectively, at 300°K. An experimental error of ± 2° corresponds to an error of ca. 1% in $\Delta G^{\ddagger}$, (if T_c is near 300°K) or ca. 0.1 - 0.2 kcal/mole.

Considering the particular case relevant to this work, it was found that when coalescing nuclei are spin coupled to one another, approximate equation (a) ceases to be accurate. For the coalescing AB quartet Fig. 5, equation (b) was in acceptable agreement with the results of line shape analysis for $\Delta\nu > J$.

Equation (a) was within an acceptable range only when $\Delta\nu/J > 3$, as the two functions began to converge.

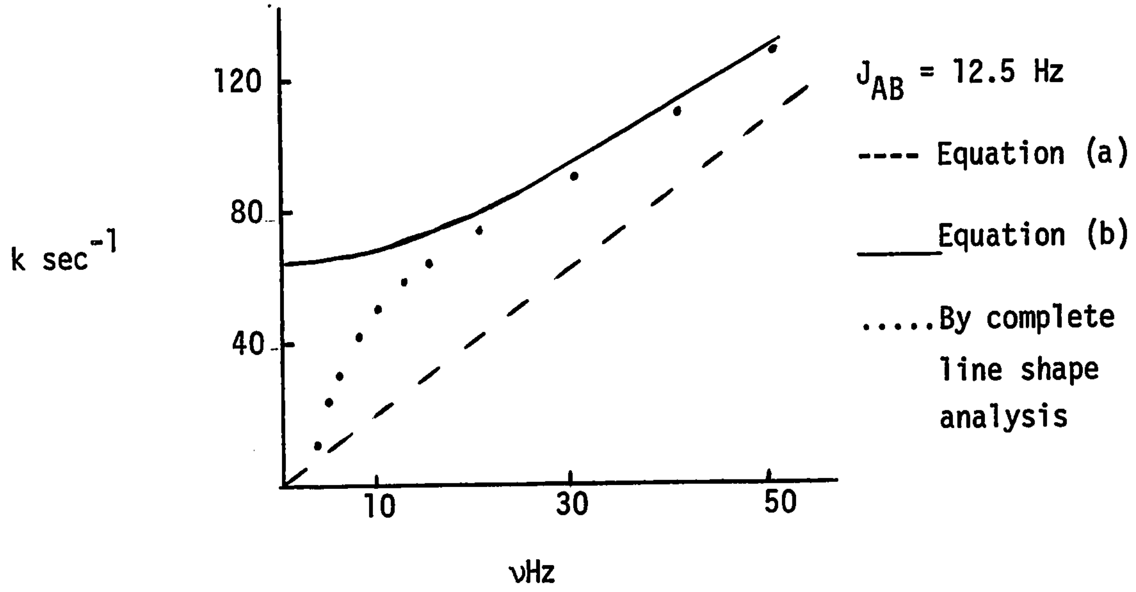


Fig. 5

At lower values of the chemical shift difference, the complete line shape rate constants began to deviate considerably and approached zero while equation (b) approaches a lower limit of $k_c = (\pi \sqrt{3}) J$.

In general, equation (a) yields reliable estimates of rates of coalescence, in most cases, when nuclei are not spin coupled; and the coalescence rate constant of spin coupled nuclei (AB spin system) can be approximated using equation (b), but only if the chemical shift difference exceeds the coupling constant.

Chapter 2

RESULTS AND DISCUSSION

Previously in this laboratory, the synthesis of substituted 1,3,2-dioxathianes was carried out according to the method of Thompson.[22] This involved the direct combination of the substituted alcohol with sulphur dichloride to get the desired product and also some trimethylene sulfite. However as the substitution of the alcohol was decreased, the per cent yield of total product decreased. The per cent of total product was less than 5% for the reaction of 1,3-propanediol and sulphur dichloride.

An alternative method of preparing di-1-imidazolyl sulphide as an intermediate was chosen to increase the yield.[23] Here the per cent yield of total product was increased to over 37%; however, the ratio of dioxathiane to trimethylene sulfite decreased. Several experiments had to be carried out to find the best conditions to increase the ratio of dioxathiane to trimethylene sulfite.

SYNTHETIC ROUTE

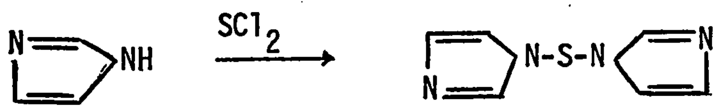
A)

$$CH_2(\overset{O}{\overset{\|}{C}}-OMe)_2 \xrightarrow{LiAlD_4} CH_2(CD_2OH)_2$$

57.9%

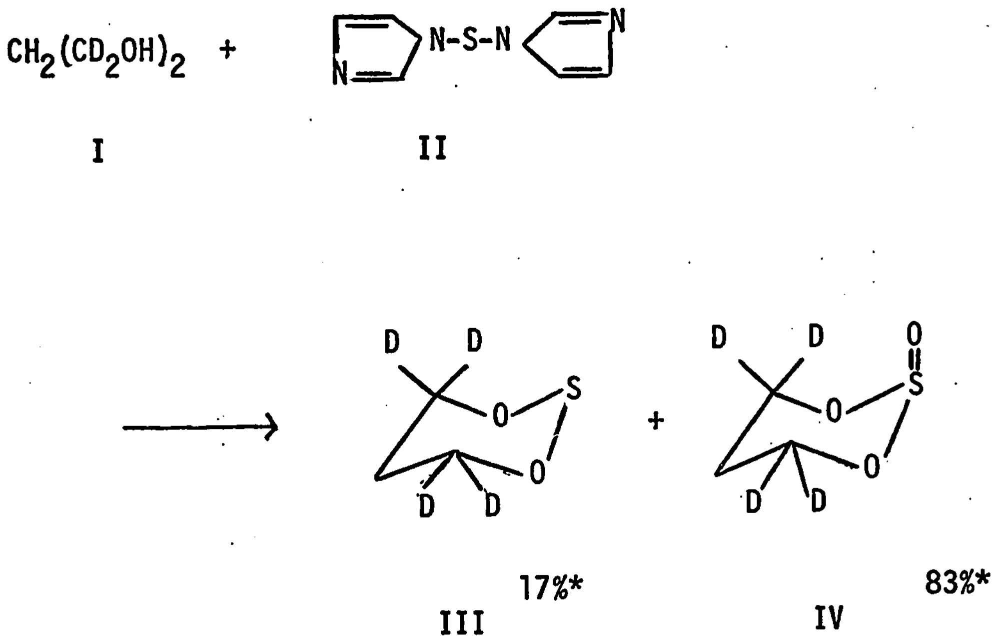
I

B)



74.5%

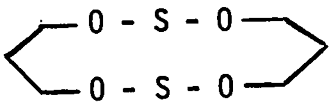
C)



* of total product

The compound III was synthesized from 1,1,3,3-tetradeutero-1,3-propanediol and di-1-imidazolyl sulfide. Here as in the case of (2a) and (2b), the isolated liquid showed two peaks on the gas-liquid chromatogram. These could be separated readily by preparative g.l.c. The one with the lower retention time was found to be III and the other, the corresponding sulfite, IV. The ^1H n.m.r. spectrum of III, at room temperature reveals a single sharp peak at $\delta = 2.0$.

In the investigation of the parent 1,3,2-dioxathiane, (2b), the question of macrocyclic structure such as (4) came up since the same n.m.r. spectrum would have been observed. In order to clarify this suspicion, the mass spectrum of (2b) was taken and ruled out the presence of any impurity of high molecular weight, including (4).



(4)

The single sharp peak, representing the average environment of the two protons, progressively broadens as the temperature is lowered. At a temperature of -40°, the broadening of the peak is quite noticeable. At -48°, the separation of the individual resonances for the axial and equatorial protons is clearly evident. In an addition, the broad nature of the peaks clearly indicates additional splittings which are incompletely resolved. This is further substantiated at lower temperatures where the spectra (at -55° and -58°) indicate the partial formation of an AB spectrum. At -60°, the spectrum reveals the complete formation of the AB spectrum with two separate doublets, one at $\delta = 1.58$ and the other at $\delta = 2.50$ due to the axial and equatorial protons respectively. At -61°, the separation of the individual resonances for the axial and equatorial protons is quite sharp and remains unchanged down to -70°.

Considering the changes in the spectrum more closely, one notes that the transition from a single time average signal to separation of the resonances of the individual protons occurs over a relatively small temperature interval. From this interval a coalescence temperature may be determined; i.e. - a temperature at which the AB spectrum coalesces into one band. As stated previously, this temperature is related to the rate constant for interconversion by one of the equations given in the introduction. From the rate constant, the value of $\Delta G^{\ddagger}$, the energy barrier for ring inversion was readily obtained using Eyring's equation:[24]

$$k_c = [(Kk_BT)/h]\,e^{-\Delta G^{\ddagger}/RT}$$

where: K = the transmission coefficient (assumed to be = 1)

k_B= Boltzmann's constant 1.381 x 10^{-16} erg/deg

T = Temperature in °K

h = Plank's constant 6.6256 x 10^{-27} erg.sec.

R = Gas constant 1.987 cal/°K mole.

This equation may be simplified to yield the expression:

$$\Delta G^{\ddagger} = -4.57\ T \log_{10}(4.8 \times 10^{-11}\ k_c/T)$$

TABLE 1

THE CHEMICAL SHIFT, δ, AND THE COUPLING CONSTANT, J_{ae}

Temperature oC	n cps	m cps	$\delta = \sqrt{nm}$ cps	J_{ae} cps
-60	40.50	68.00	52.48	15.5
-62	40.50	69.00	52.86	15.5
-64	40.50	69.50	53.05	15.5
-65	40.50	69.75	53.15	15.5
-67	41.00	69.75	53.48	15.5
-69	40.00	69.75	52.82	15.5
-69.8	41.25	69.50	53.54	15.5
		Avg.	53.05	

RATE CONSTANT

Since this study reveals a simple AB spin system, the equation best approximating the rate constant at coalescence is:

$$k_c = (\pi/\sqrt{2})\sqrt{(\delta)^2 + 6J_{ae}^2}$$

$$k_c = 3.14/1.414\sqrt{(53.05)^2 + 6\ (15.5)^2}$$

$$= 126.65\ \text{sec}^{-1}$$

BARRIER TO RING REVERSAL

From an analysis of the spectra, the coalescence temperature was estimated to occur at -42°C with a possible error of ± 1. Therefore:

$$\Delta G^{\ddagger} = -4.57T \log_{10}(4.8 \times 10^{-11} k_c/T)$$

$$\Delta G^{\ddagger} = -4.57 (231) \log_{10}(4.8 \times 10^{-11} \times 126.65/231)$$

$$= 11.17 \text{ kcal/mole}$$

Since $\Delta v/J = 3.4$, an answer within acceptable range could also be determined from the equation:

$$k_c = (\pi/\sqrt{2})\, \Delta v$$

which gives a value of 117.81 sec^{-1} for the rate constant and a value of 11.20 kcal/mole for the barrier to ring reversal.

Interpretation of n.m.r. results and comparison with related systems.

The determined ring reversal barrier of 11.2 kcal/mole for 1,3,2-dioxathiane is similar to other six membered ring systems with two or more adjacent heteroatoms in the ring, in that it is generally higher than the comparable cyclohexane or 1,3-dioxane structure. This result is usually attributed to the presence of vicinal electron pairs which appear to increase the barrier to rotation about the connecting bond. Removal of vicinal electron pair interaction in 1,3,2-dioxathiane by conversion to trimethylene sulfate lowers the barrier to a value comparable to the similarly substituted 2,2,5,5-tetramethyl-1,3-dioxane.

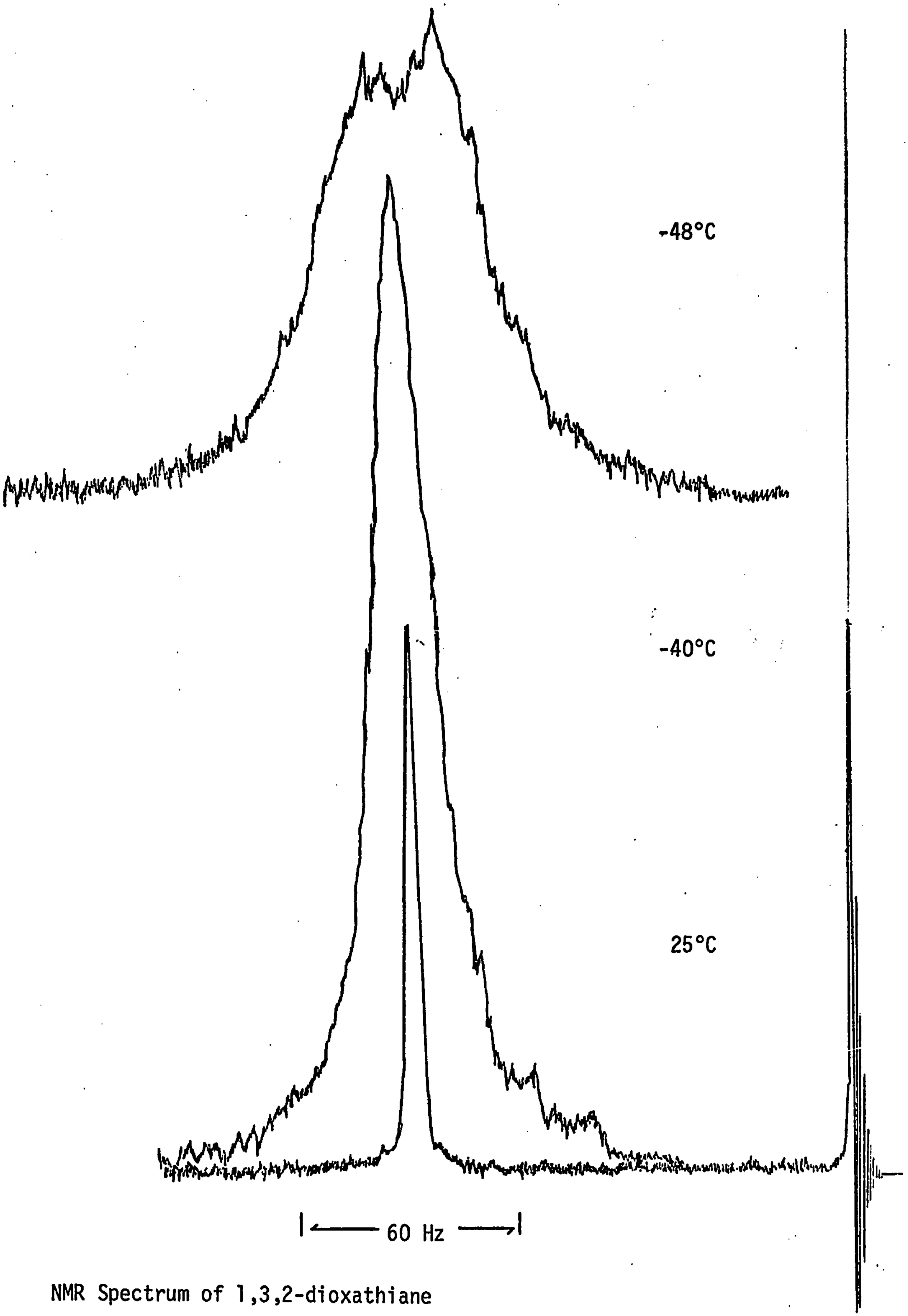
Trimethylene sulfite differs from 1,3,2-dioxathiane only in the possession of one exocyclic oxygen. Since the trimethylene sulfites were not amenable to direct n.m.r. measurement, it was proposed that an analysis of the 1,3,2-dioxathianes could further substantiate the existing data for a more coherent description of the conformational properties of these molecules.

Some understanding as to the effect of the exocyclic oxygen is obtained from a comparison (values of nmr shifts) of its interaction with the axial substituents on C-4 and C-6 positions in trimethylene sulfites and the corresponding 1,3,2-dioxathianes which lack the exocyclic oxygen. When allowance is made for the averaging of n.m.r. signals caused by conformational interconversion in the 1,3,2-dioxathianes, most of the shifts observed for these compounds are within 0.1 ppm of the value for the corresponding trimethylene sulfite.[25] This would seem to indicate that the presence of the exocyclic oxygen has no extraordinary influence. If the analysis of the 1,3,2-dioxathiane system has any relevance for the case of trimethylene sulfite barriers, then these compounds should have ring reversal barriers near those for the 1,3,2-dioxathianes and certainly higher than the trimethylene sulfates.

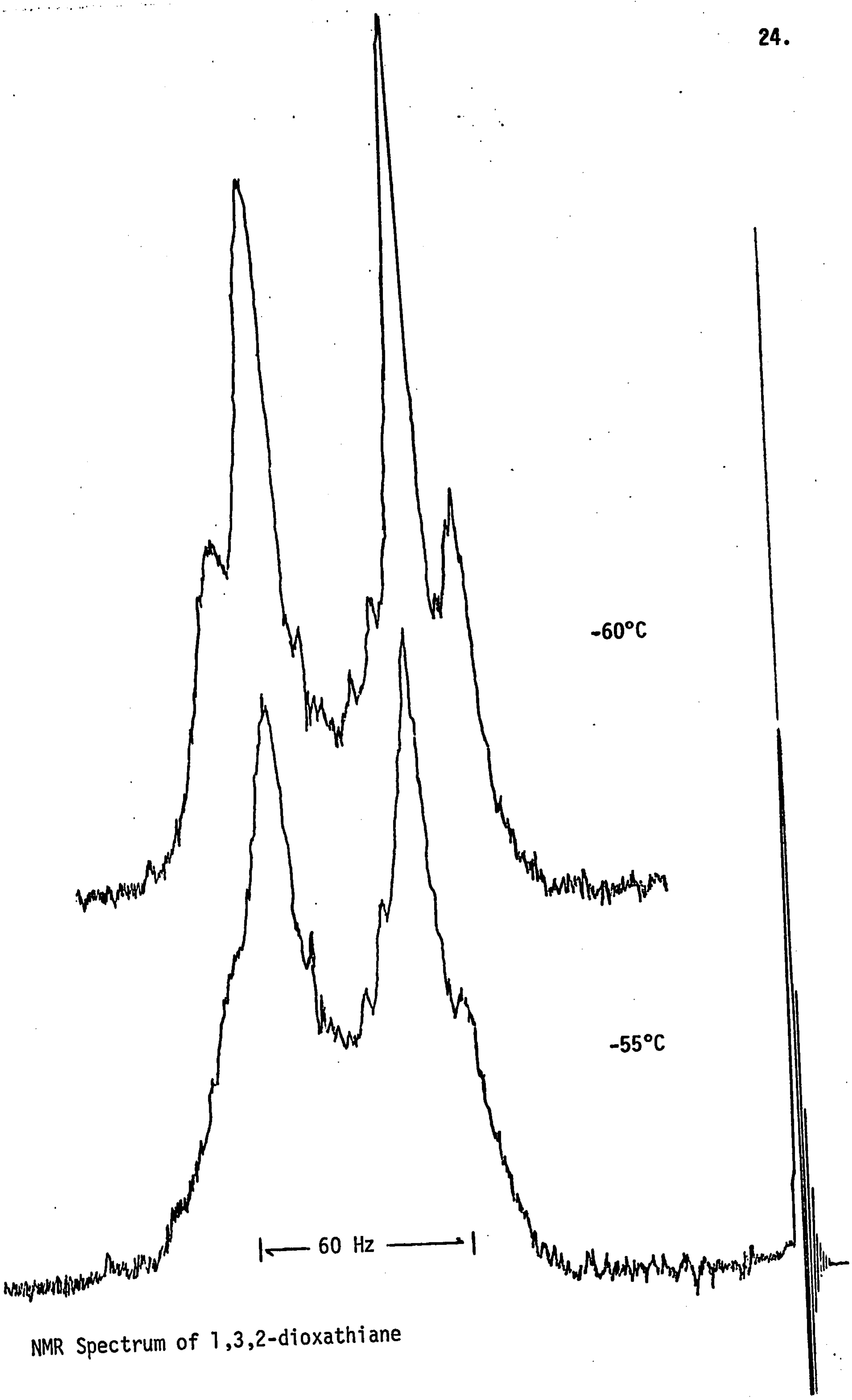
SUMMARY AND CONCLUSIONS

The synthesis of 1,3,2-dioxathiane was facilitated to a certain extent with di-1-imidazolyl sulphide as an intermediate. From low temperature n.m.r. analysis of the AB spin system, the energy barrier for ring inversion was determined as $\Delta G^{\ddagger} = 11.2$ kcal/mole. This value is in agreement with previous findings for systems of this general type, in that ring reversal barriers are found to be higher than for similar compounds lacking vicinal election pairs. The results support the general conclusion that electron pairs on adjacent atoms in a ring increase the barrier to rotation about the bond joining them, and in this way increase the barrier to ring reversal.

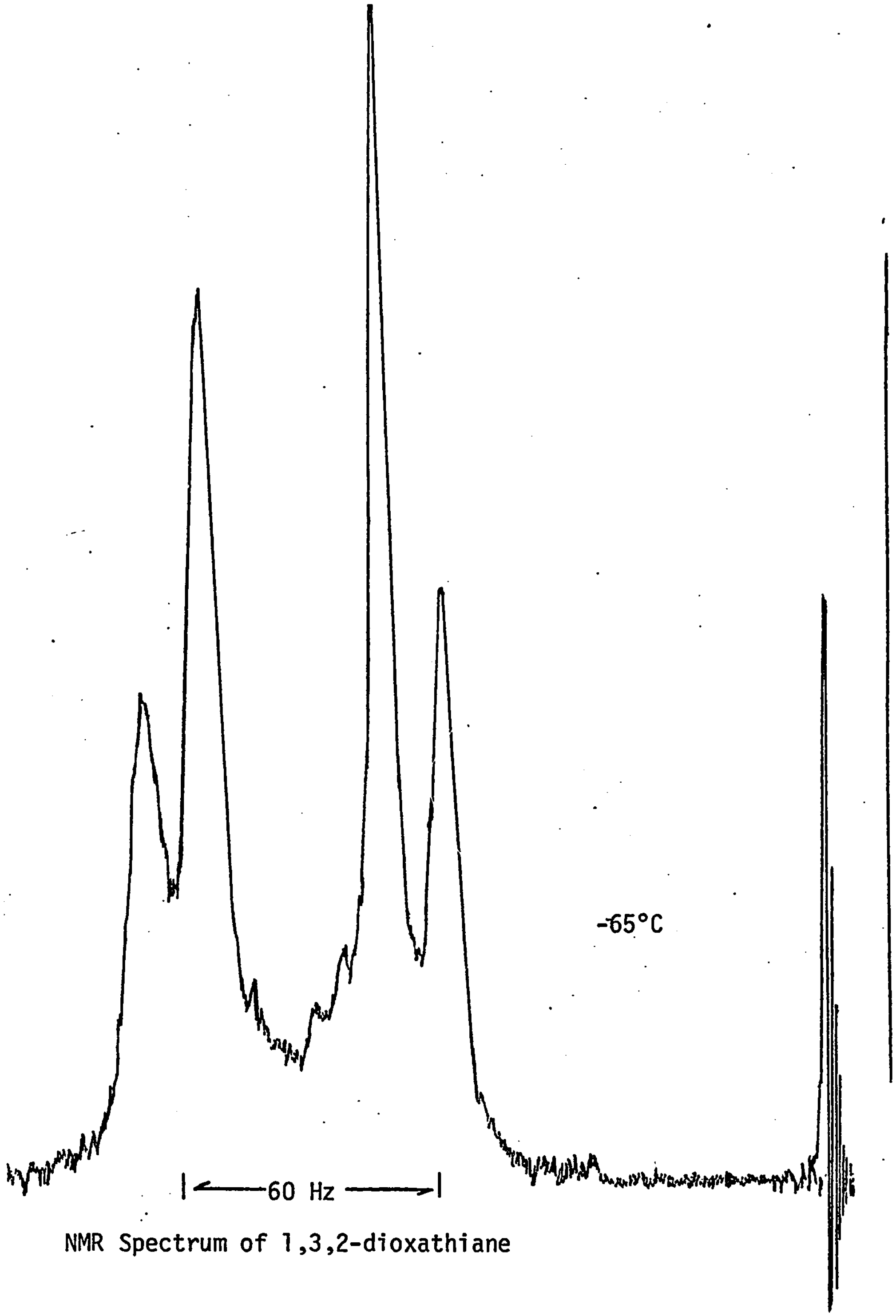
Furthermore, the analysis of the 1,3,2-dioxathiane system reinforces the proposed model mentioned in the introduction, that of an anomalous type of molecule having a barrier which is comparable to that for structurally similar molecules, but which is not amenable to n.m.r. measurement because the sulfate ring system is strongly biased toward one chair form.



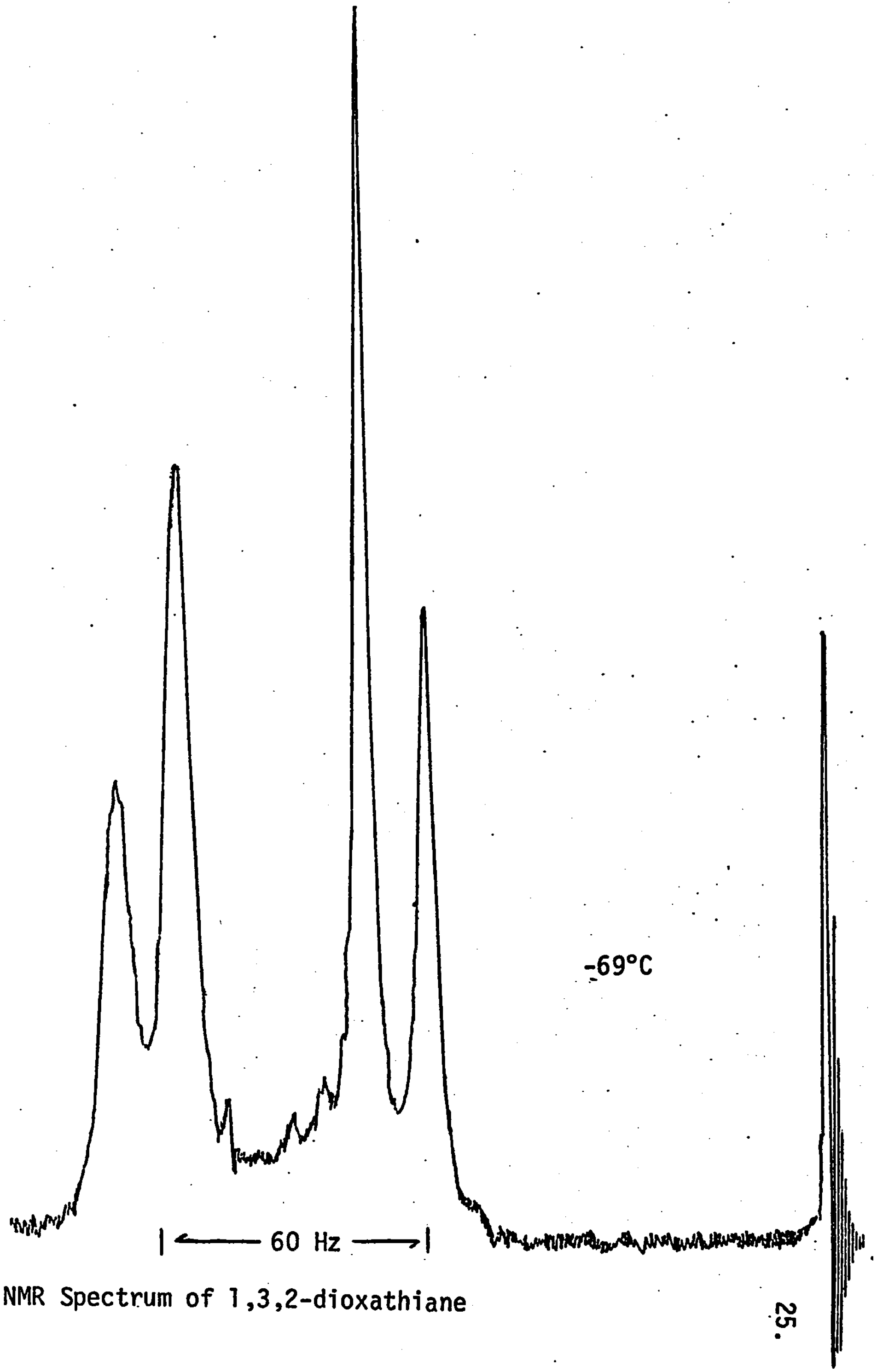
NMR Spectrum of 1,3,2-dioxathiane



NMR Spectrum of 1,3,2-dioxathiane



NMR Spectrum of 1,3,2-dioxathiane



NMR Spectrum of 1,3,2-dioxathiane

Chapter 3

EXPERIMENTAL

Proton n.m.r. spectra were measured on a JEOL C60HL spectrometer using TMS as internal reference.

Gas-liquid chromatographic analyses were made with an F & M Model 720 instrument using columns packed with 10% diethyleneglycol succinate (LAC728) on chromosorb W and at a flow rate of carrier gas (helium) of 60 ml/min. Analytical work was done on a 1/4" x 5 1/2' column (70 - 90°) and collections on a 3/4" x 8' column (135°).

1,1,3,3-tetradeutero-1,3-propanediol[26]

A solution of 5.0 g of $LiAlD_4$ in 200 ml of anhydrous tetrahydrofuran was placed under a nitrogen atmosphere in a 500 ml three-necked flask equipped with a reflux condenser, dropping funnel, and magnetic stirrer. Dimethyl malonate (13.2 g) diluted to 25 ml with anhydrous tetrahydrofuran was introduced with stirring at a rate sufficient to maintain gentle reflux. The mixture was then heated and stirred under reflux for 20 hr. Decomposition was accomplished by the careful addition of water (5.0 ml), 15% NaOH (5.0 ml), and water (15.0 ml). The mixture was filtered and the precipitate washed with 6 50 ml portions of boiling tetrahydrofuran. Evaporation of solvent from the dried ($MgSO_4$) filtrate and washings yielded 4.4 g of a clear, light yellow oil.

Ir analysis showed the usual hydroxyl absorption as well as C-D stretching at 2100 and 2200 cm^{-1}. A singlet at 1.7 ppm in the nmr spectra was assigned to C-2 protons and the hydroxyl protons appeared at 3.89 ppm.

Di-1-imidazolyl sulfide

Following the procedure of Walter and Radke[27], 36.0 g of imidazole was reacted with sulphur dichloride (13.5 g) to yield 16.2 g of product, mp 78 - 83°. Literature[27] mp 80 - 85°.

4,4,6,6-tetradeutero-1,3,2-dioxathiane

Under a nitrogen atmosphere 8.58 g of di-1-imidazolyl sulfide was dissolved in 250 ml of anhydrous tetrahydrofuran in 500 ml three-necked flask equipped with an addition funnel and a magnetic stirrer. 1,1,3,3-tetradeutero-1,3-propanediol (3.45 g diluted to 15 ml with anhydrous tetrahydrofuran) was introduced rapidly with stirring. After 15 min. of stirring, the tetrahydrofuran was removed on the rotary evaporator and the residue vacuum distilled. The product was contained in a fraction (2.24 g) with bp 29 - 33°/0.25 mm.

The peak of lower retention time on preparative glc (17% of total) was found to be the desired product III. The other major peak (83%) had a retention time corresponding to trimethylene sulfite, IV.

PART I

CONFORMATIONAL ANALYSIS OF 1,3,2-DIOXATHIANE

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PART II

CONFORMATIONAL ANALYSIS OF 4-CHLOROTHIANE-1,1-DIOXIDE

Part II

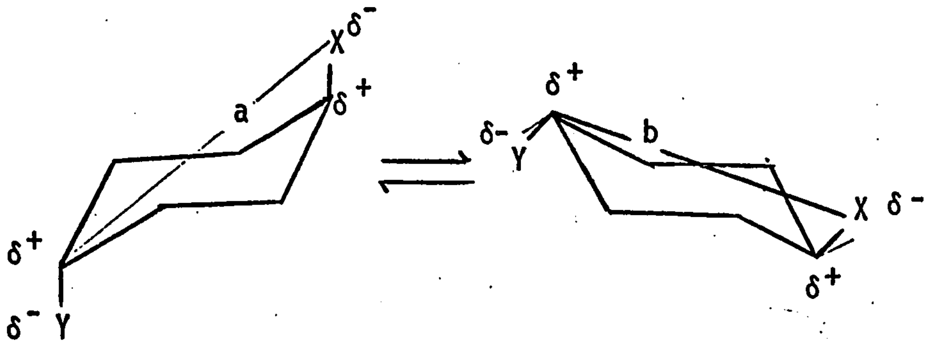
Conformational Analysis of 4-Chlorothiane-1,1-dioxide

Chapter 1

INTRODUCTION

In the past six years numerous conformational studies on six-membered ring compounds have suggested that 1,4-interactions of polar substituents are important.[1,2,3] Studies were carried out to elucidate the influence of substituents on conformational preferences with regard to additivity. Generally, when one of the substituents is an alkyl group, it is assumed that additivity holds.[4] However, Wood and co-workers have shown that if two polar groups are trans to each other, marked deviations from additivity are observed.[5,6] For example, the relative proportion of the two conformers of cis-1,4-bromochlorocyclohexane present at low temperature was shown to be nearly as equal as expected from additivity of conformational energies. However, the conformational composition of a series of trans-1,4-dihalocyclohexanes was shown to differ considerably from the predicted values.

Indeed, it is clear that dipole-dipole interactions are a significant factor in conformational preferences. A rationalization for the observed trends has been reported[7,8] and can be understood with the aid of structures (1) and (2) in Fig. 1. Illustrated in Fig. 1 is the case in which the C-X and C-Y bond moments are oriented in the same direction. It is



(1) (2)

Fig. 1

evident in structure (2) that the negative monopole, (δ^-), associated with a given dipole is at a maximum distance from the positive monopole, ($\delta+$), of the other dipole. By converting to the structure (1) the postive monopoles are not moved with respect to one another, but the negative monopoles are moved significantly closer to the positive monopoles of the other dipoles, i.e., $a < b$. The net result is a more effective charge neutralization and tendency to stabilize the diaxial conformer (1).

Wood and Barker used this concept of a 1,4-electrostatic effect in their analysis of heterocyclic compounds of 4-chlorothiane-1-oxides. The 4-chlorothiane-1-oxides were of particular interest because of the unusual preference of the S=O for the axial position.[9]

Experimental results for the cis compound indicated an equilibrium mixture, (3:1), of the two conformers, the predominant conformer with the S=O in the axial position and chlorine in the equatorial position; and the other in which S=O is equatorial and chlorine axial. The experimental result of 0.4 kcal/mole for the conformational energy, (-ΔG°), agrees reasonably well with additivity of conformational free energies, i.e. 0.6 kcal/mole.

N.m.r. control experiments established a minimum value for the conformational ratio at 96:4 for the trans compound and a corresponding minimum conformational energy of 1.2 kcal/mole.[10] In the absence of an electrostatic effect, the trans compound would be expected to have virtually no preference for one conformation over the other, since here the individual conformational free energy values must be subtracted to give the additivity result of 0.2 kcal/mole. This additivity result, indicating a slight preference for the diequatorial form, presents a sharp contrast to the experimental result showing a strong preference (1.2 kcal/mole) for the diaxial form. Wood and Barker attribute the discrepancy (1.4 kcal/mole) to the 1,4-dipolar interaction.

Oxidation of 4-chlorothiane 1-oxide to the corresponding sulfone presents an interesting system for conformational analysis, Fig. 2. In a similar system, R. D. Stolow and T. Groom, studying the transannular substituent effects in cyclohexanols proposed that the functional group O_2S would cause the equilibrium to favour the conformer with the axial hydroxyl group.[11] Thus in this system, Fig. 2, one would expect the equilibrium to lie to the left, structure (3a), in favour of the axial chlorine. Since this compound lacks the axial S=O preference present in

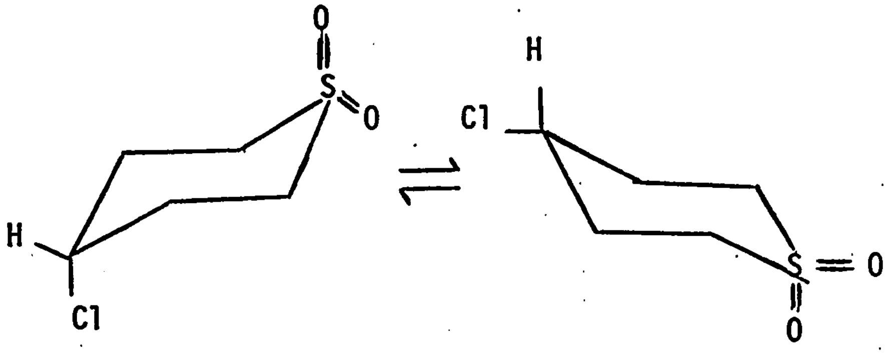


Fig. 2

4-chlorothiane-1-oxide, the ratio of the conformers in the equilibrium mixture may not be as high as that for trans-4-chlorothiane-1-oxide.

Determination of Conformational Energy

When two conformational isomers are in equilibrium the difference between the free energies of the two isomers is known as the "conformational energy", $(- \Delta G°)$. It will denote the free energy of a conformation above that of the conformation of minimum energy. $-\Delta G = RT\ln K$, where K is the equilibrium constant of the two isomers.

In order to calculate K, the position of the equilibrium must be known, and K expressed as a ratio of the population of the isomers in equilibrium. For cyclohexane derivatives, the interconversion and equilibration of conformational isomers are rapid at room temperature. As a result, physical methods (eg. ir, nmr) are best suited to determine the magnitude of the properties of the individual isomers, and from these values, K can be calculated.

Determination of conformational equilibrium by n.m.r. proves to be more direct than i.r. and less dependent on assumptions. The use of n.m.r. for conformational analysis of cyclohexane derivatives has been reviewed by Franklin and Feltkamp.[12]

It has been found that axial and equatorial protons, with the same chemical environment have different chemical shifts. The equatorial proton is usually detected at a lower frequency than the axial in cyclohexanes. The equatorial proton has a small coupling constant both with equatorial and axial protons. Consequently, the half width of an equatorial proton signal (ca. 7 cps) is less than that of an axial proton signal (ca. 22 cps) which has a large axial-axial coupling in it.[13] The ratio of the areas of the axial and equatorial signals is a direct measure of the relative amounts of the two conformers in the equilibrium mixture.

In cyclohexane and derivatives of cyclohexanes, the methine proton (CHX) is the most suitable for conformational analysis. The methine proton has a lower diamagnetic shielding than the methylene proton (CH_2) on the ring, and generally appears at a lower field. If the substituent X in (CHX) is more electronegative than the methylene group, the diamagnetic shielding is decreased and the methine proton will appear at an even lower field.

At room temperature, rapid interconversion of the conformers make the results into average values for the chemical shift, the bandwidth, and coupling constant of axial and equatorial protons. It is then necessary to obtain these values for the separate conformers and this can be accomplished by reducing the temperature below the coalescence point; below this temperature the axial and equatorial protons appear as separate signals.

STATEMENT OF PROBLEM

The objectives of this work were:

1. To synthesize 4-chlorothiane-1,1-dioxide.
2. Examine the conformational equilibrium at low temperatures in solution.

At sufficiently low temperatures, one should observe in the n.m.r. spectrum, two separate methine signals, provided a significant amount of the two conformers exist. Identification of these signals can be based on the peak width at half-height and on the chemical shift of the methine proton.

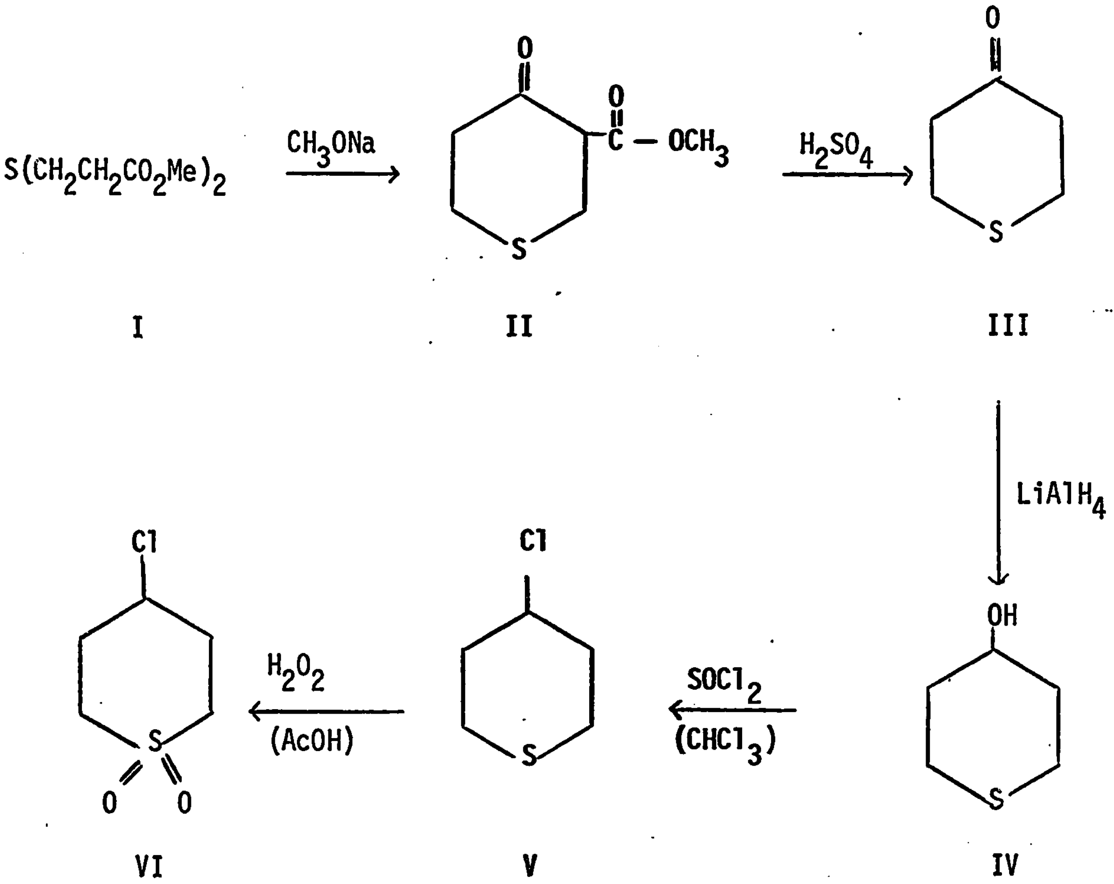
Since the area under a signal is proportional to the number of protons producing it, and if there is no overlap of the two signals of the methine protons,the ratio of the areas of the signals should be the ratio of the conformers in the equilibrium.

Chapter II

RESULTS AND DISCUSSION

The synthesis of 4-chlorothiane-1,1-dioxide follows the same synthetic route for the preparation of 4-chlorothiane-1-oxide[14] with the exception of the last step. Oxidation of the sulfide V, 4-chlorothiopyrane, was carried out with hydrogen peroxide in glacial acetic acid to get the corresponding sulfone, VI.

Synthetic Route



I	Dimethyl-3,3-thiodipropionate
II	3-carbomethoxy-4-oxothiocyclohexane
III	4-Ketothiopyrane
IV	4H-thiopyran-4-ol
V	4-chlorothipyrane
VI	4-chlorothiane-1,1-dioxide

The nmr spectrum of 6% 4-chlorothiane-1,1-dioxide in CD_2Cl_2/C_2D_5Br, (4:1), at room temperature reveals a quintet at $\delta = 4.43$, characteristic of the methine proton, CHCl. As the temperature is lowered, below -80°, the quintet becomes obscured into one band due to a loss in resolution. At -100°, a fairly narrow band of $W_{1/2}$ of 7.5 Hz is present. There is no further change in the signal down to -120°. No separation of the methine proton (CHCl) at low temperatures was observed. This would seem to indicate that the equilibrium is strongly biased toward one chair form. Careful consideration of the interacting dipoles present would tend to support this. For the equilibrium, Fig. 3:

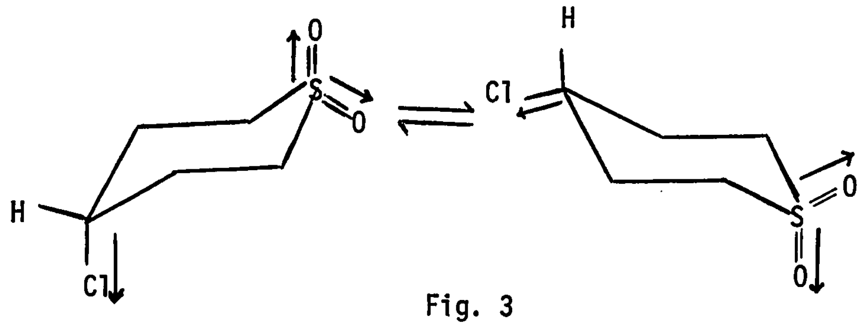


Fig. 3

the following dipoles are present.

$$(ax_{Cl} \rightleftharpoons ax_{S=0}) + (ax_{Cl} \rightleftharpoons eq_{S=0}) \xrightleftharpoons{vs} (eq_{Cl} \rightleftharpoons eq_{S=0}) + (eq_{Cl} \rightleftharpoons ax_{S=0})$$

If one assumes that the dipole-dipole interactions of $(ax_{Cl} \rightleftharpoons eq_{S=0})$ and $(eq_{Cl} \rightleftharpoons ax_{S=0})$ to be equal then one has left to consider;

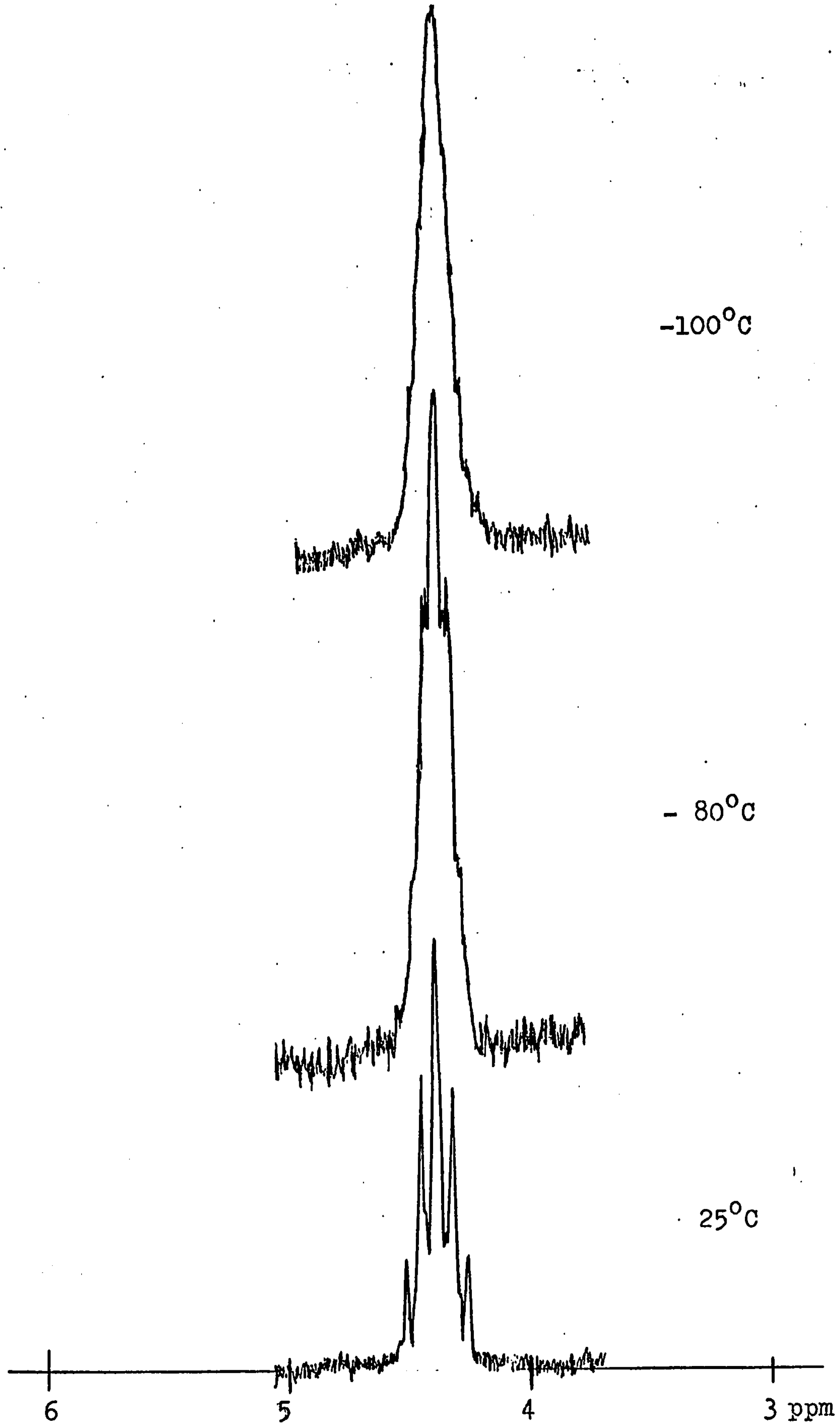
$$(ax_{Cl} \rightleftharpoons ax_{S=0}) \quad vs \quad (eq_{Cl} \rightleftharpoons eq_{S=0})$$

and from previous work on 1,4-dipolar effects, the diaxial chair form has overwhelming preference over the diequatorial form for electrostatic reasons. Thus the diaxial chair form with axial chlorine and equatorial hydrogen would be preferred. From the nmr spectrum the peak width at half-height of 7.5 Hz is assigned as an equatorial hydrogen implying an axial chlorine. This is in agreement with the 1,4-dipolar effect.

In the absence of an electrostatic effect, a theoretical result, from additivities, might be expected to reflect fairly accurately the conformational preference. Using the "best values"[15] for chlorine and the n.m.r. determined value for thiane oxide, additivity would give, (the individual conformational free energy values must be substracted), $\Delta G° = 0.6 - 0.2 = 0.4$ kcal/mole in favour of the diequatorial form. However, since the experimental results qualitatively show that the equilibrium favours the diaxial conformer, it appears that the 1,4-dipolar interaction is present. Failure to detect a signal corresponding to axial hydrogen places the equilibrium constant for the conformational interconversion of 4-chlorothiane-1,1-dioxide at a value comparable to that for trans-4-chlorothiane-1-oxide. As stated previously, for trans-4-chlorothiane-1-oxide, control experiments established a minimum value for the conformational ratio at 96:4.

CONCLUSION

It was unfortunate that the analysis of 4-chlorothiane-1,1-dioxide was not quantitative, however, the analysis does qualitatively show the overwhelming preference for the conformer with axial chlorine over the equatorial one. This is in agreement with the results of Wood and Barker's study of the 4-chlorothiane-1-oxide system and adds to the growing number of instances, which support the hypothesis that highly electronegative groups in the 1,4-positions of a six membered ring favour the diaxial form, and results in deviations from additivity of accepted substituent values. This interaction between polar groups across a six-membered ring thus seems to be a general phenomenon which frequently determines the position of conformational equilibrium.



NMR Spectra of 4-chlorothiane-1,1-dioxide

Chapter 3

EXPERIMENTAL

Elemental analyses were obtained from Microanalysis Laboratories Limited, Toronto, Ontario.

Proton nmr spectra were measured on a JEOL C60HL spectrometer using T.M.S. as internal reference.

Gas-liquid chromatographic analyses were made with an F & M Model 720 instrument. Analytical work was done on a 6' x 1/4" silicone gum rubber column (GE XE-60), at a flow rate of carrier gas (helium) of 60 ml/min.

Except for the last reaction in the synthetic route, the synthesis of the intermediates follows Barker's work on 4-chlorothiane-1-oxide.[16]

II 3-Carbomethoxy-4-oxothiacyclohexane

Cyclization of dimethyl-3,3-thiodipropionate, I, followed the procedure of Onesta and Castelfranchi.[17]

V 4-Chlorothiopyrane

The three-step procedure of Adlerova and Protiva[18] was used to convert the cyclization product to 4-chlorothiopyrane.

VI 4-Chlorothiane-1,1-dioxide

To a solution of 1.1g (0.008 mole) of 4-chlorothiopyrane, V, in 10 ml of glacial acetic acid was added 14.42 g (0.127 mole) of 30% H_2O_2

in 10 ml of glacial acetic acid at such a rate to keep the reaction temperature near 50°. The reaction mixture was stirred for 24 hours at room temperature. Following the stirring period, the reaction mixture was diluted with 10 ml of water, neutralized with Na_2CO_3, and extracted with three 50 ml portions of CH_2Cl_2. The dried extract ($MgSO_4$) was evaporated affording 1.46 gm of a white finely divided crystalline solid. The product was recrystallized from petroleum ether.

Anal. Calcd. for

$C_5H_9ClO_2S$: C, 35.6; H, 5.4; Cl, 21.1; S, 19.0

Found: C, 35.7; H, 5.6; Cl, 21.0; S, 19.0

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