"KINETIC STUDIES"

A Thesis

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Preface.

This thesis divides into two parts which are independent of each other, the first a kinetic study by nmr, the second a solvolysis study. References are numbered from 1 upwards in the nmr study, and from 101 upwards in the solvolysis section, and are found together at the end of the thesis.

Tables and Figures are numbered from 1 upwards in each section while molecular diagrams are numbered D1, D2,.... again in each part to obviate figures like LXXXVIII which occur if Roman numerals are used.

Where complex molecules have been referred to several times in the text, molecular diagrams have often been repeated and renumbered to maintain the numerical sequence.

CONTENTS

CHAPTER ONE

RING INVERSION - THEORY AND INTRODUCTION

1.1 The nucleus of a hydrogen atom has spin quantum number $\frac{1}{2}$ so that, when a magnetic field H_o is applied, there are two allowed orientations of the nucleus in that field, these orientations having energies + and - μH_o where μ is the component of the nuclear magnetic moment in the direction of the applied field. An equilibrium is reached when there is a Boltzmann distribution of nuclei between the two orientations, and as a result, an excess of nuclei in the lower $-\mu H_o$ level. The difference in energy between the two orientations, $2\mu H_o$ is so small that this excess population

is slight. A second consequence of applying the field H_o is that a nucleus in either orientation undergoes precessional motion about the direction of H_o.

For a transition between the levels, absorption or emission of energy $2\mu H_o$ is necessary; this corresponds to absorption or emission of radiation of frequency ν_o such that

$$h\nu_o = 2\mu H_o$$

Thus if we irradiate a sample at equilibrium between the two energy levels in a magnetic field H_o with a range of frequencies around ν_o, absorption of radiation will take place when the frequency is precisely ν_o.

Alternatively, we can irradiate the sample at a fixed frequency ν_o, and vary the field by a few gauss on either side of H_o; absorption will then take place when the field is precisely H_o.

1.2 Now, when a molecule is placed in a magnetic field, the field induces orbital motions of the electrons which that molecule comprises, and these motions produce secondary fields within the molecule. These secondary fields are small compared with the applied field H_o, being of the order $10^{-6}xH_o$, but they affect the above-mentioned energy absorption in an interesting way. This can be understood if we consider a molecule containing two chemically different kinds of hydrogen atoms, for example propynal $H-C\equiv C-C\overset{H}{\underset{O}{<}}$

The environments of the two hydrogen atoms in the molecule are different, so that they will be affected by the various secondary fields to different extents and thus, the nett field observed by each atom, that is the correct combination of H_o and the secondary fields, will be different. As a result, when we irradiate a sample of propynal around the frequency ν_o, there will be two separate absorptions corresponding to the two different kinds of hydrogen atoms. The separation of the two absorption signals is called the chemical shift between them. This can be extended, so that the number of different absorptions in a spectrum indicates the number of different kinds of protons in the molecule studied. Thus we obtain a spectrum of absorptions, a nuclear magnetic resonance, nmr, spectrum.

1.3 Another phenomenon which affects the appearance of an nmr spectrum should be pointed out. There are small magnetic fields intrinsically associated with nuclear spins. Two such fields suitably close to each other in a molecule interact by means of the bonding electrons in the molecule. The size and nature of the effect depends on the electronic state of the molecule, and the sign of the spins which are interacting. Except in certain cases, the interactions are too small to observe if the nuclei are separated by more than three bonds.

The effect of the sign of the spins can be

illustrated by an example, acetaldehyde CH_3—CHO. There are two signals, one three times the intensity of the other. There are two possible spin states of the aldehydic proton, so that the CH_3-signal will be split in two, one absorption corresponding to CH_3-protons in a molecule where the aldehydic proton has spin $+\frac{1}{2}$, and the other where the spin is $-\frac{1}{2}$. The aldehydic proton signal will be a quartet of absorptions of relative magnitude 1:3:3:1, corresponding to the various combinations of possible spin states of the CH_3-protons. If the magnitude of the spin coupling effect between two kinds of protons is of the same order as the chemical shift of the protons, the relative intensities of the components of the spin-coupled signals will not be as expected from the probabilities of the various combinations of spins (1). This is the case in some spectra discussed later.

These then are the two effects which determine the appearance of an nmr spectrum. The first, the chemical shift effect is due to the different local magnetic fields in the molecule. The second, spin-spin coupling, arises from interactions of neighbouring nuclei.

1.4 From what has been said so far one would expect an nmr spectrum to consist of a series of infinitely narrow absorption lines. The lines observed have in fact a measureable line width. Several factors contribute

to this line width (2); two of these are of particular importance.

The first factor is called spin-lattice relaxation. A nucleus has a finite lifetime in either of the two spin states before a transition takes place, this time being known as the spin-lattice relaxation time, T_1. From the uncertainty principle $\Delta E.\Delta T \sim h/2\pi$ so that $h\Delta\nu \sim h/2\pi\Delta T$. Thus the uncertainty in the frequency of absorption is $1/2\pi\Delta T$. The line width will then be of the order $1/T_1$.

The second factor is signal broadening due to inhomogeneity of the magnetic field. Limitations of technique obviate the achievement of a homogeneous field throughout the sample so that instead of a sharp absorption at frequency ν_0 corresponding to an applied field H_0, a broadened signal is obtained around ν_0.

Throughout the present work, with the equipment used, it is found that in the absence of exchange, it is inhomogeneity rather than relaxation times which determines ordinary signal widths.

1.5 An idealised nmr experiment consists of applying a voltage oscillating with frequency around ν_0 orthogonal to the magnetic field H_0. We define a set of axes with the z-direction along H_0, the x-axis along the direction of the applied voltage, and the y-axis orthogonal to these both.

Associated with the fluctuating voltage along

the x-direction will be a fluctuating field H_1. This linearly fluctuating field can be considered as the resultant of two circularly polarised fields. One of these will be rotating in the same sense as the precessional motion of nuclei about the direction of H_o, and the classical picture of the resonance situation is that, as the frequency of the applied voltage increases the rotational frequency will increase until it is the same as the precessional frequency, and it is at this point that resonance takes place. The other circularly polarised field in the opposite sense to the precessional motion will have no net effect.

1.6 Bloch (3) has derived equations to describe the behaviour of a nuclear magnetic moment in variable magnetic fields. These equations were introduced as postulates, but they are useful, as their solution leads to results in agreement with experimental observations.

The Bloch equations in the form of differential equations express the variation of the x, y, and z-components of the nuclear magnetic moment in the rotating field with time. Bloch introduced a second relaxation time T', the transverse relaxation time, which characterises the natural decay of the x and y components.

The resonance condition, that is the point at which the rotating field has the same frequency as the Larmor precession, is the steady-state solution

obtained by putting all derivatives in the Bloch equations equal to zero.

From these solutions it is possible to calculate a line-shape function for the absorption signal. This should be a Lorentzian curve with peak height $2KT'$ where K is a function of the chemical concentration of protons, and peak width at half height $1/\pi T'$. As was pointed out in Section 1.4 however, the peak height and width are determined by the inhomogeneity of the magnetic field so that we can define a new relaxation time T_2 such that the observed peak width at half height is $1/\pi T_2$ and the peak height is $2KT_2$ Since the peak height depends on the concentration of protons and on electronic amplification of course, as well as on the relaxation time T_2, it is not usually convenient to measure T_2 from peak heights, though it has been done in some kinetic work (4). It is much simpler to calculate T_2 from the width of the peak, $\delta\nu$, at half-height for, $T_2^{-1} = \pi\delta\nu$.

This relationship holds only if the signal is recorded at a slow sweep rate. Otherwise extraneous effects distort the signal (5). T_2 then, can be obtained from line shapes provided the signal is scanned through slowly. Even then, line shapes may very occasionally not be Lorentzian: this is a limitation derived from Bloch's original postulates.

1.7 In N,N-dimethylacetamide (D1), due to the mesomerism shown in Figure 1, there is hindered rotation

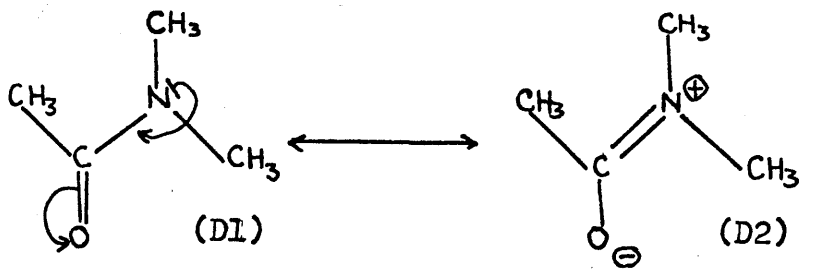


Figure 1

about the carbon-nitrogen bond so that there are two locations for an N—CH_3-group, either cis or trans to the carbonyl group. If the exchange between cis and trans positions is very slow, that is rotation about the partial double bond does not take place readily, the nmr spectrum should show two signals one for cis-N—CH_3, and one for the trans-form. If rotation about the double bond is very rapid, we will see only a time-averaged signal. Thus as we go from slow rotation to fast rotation, the appearance of the signal changes as shown in Figure 2.

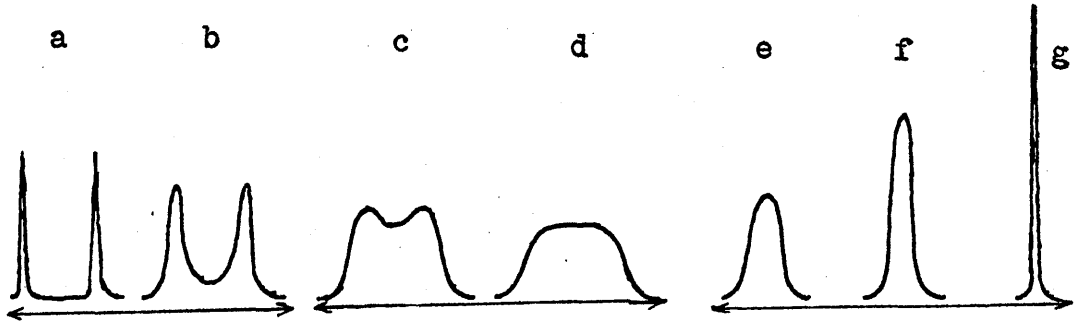


Figure 2

The criterion for the change from a doublet to a singlet is that at the point of collapse, the mean

lifetime τ spent by a proton in either location is of the order of the inverse of the frequency separation $\delta\nu_o$ (in cycles per second), of the two members of the doublet. The exact relation is that at the point of collapse (Figure 2.d), $\tau = \sqrt{2}/\pi\delta\nu_o$.

A reaction such as the one discussed has first order kinetics so that the rate is independent of the concentration. Variation in the rate constant is brought about by altering the temperature. Thus the $N—CH_3$ spectrum of dimethylacetamide shows two completely distinct lines up to about 293°K, and one line above 325°K (6), see Figure 3.

If we can derive some way of relating the variation of line shape (Figure 2, a→g) to the rate constant for rotation, we can determine the kinetics of the reaction. Since at the coalescence point, the rate constant $k = 1/\tau$ is equal to $\pi/\sqrt{2}$ times the chemical shift which can vary from 1cps to 100cps say, rate constants will vary from 2.2/sec to 220/sec. Thus, nmr can be used to study the rate of reactions very much faster than can be studied by classical methods.

Rotation about partial double bonds is only one of a class of reactions which can be studied by nmr. Hindered rotation about single bonds, ring inversion of cyclic compounds, and proton exchange between alcohols and water or more generally, exchange

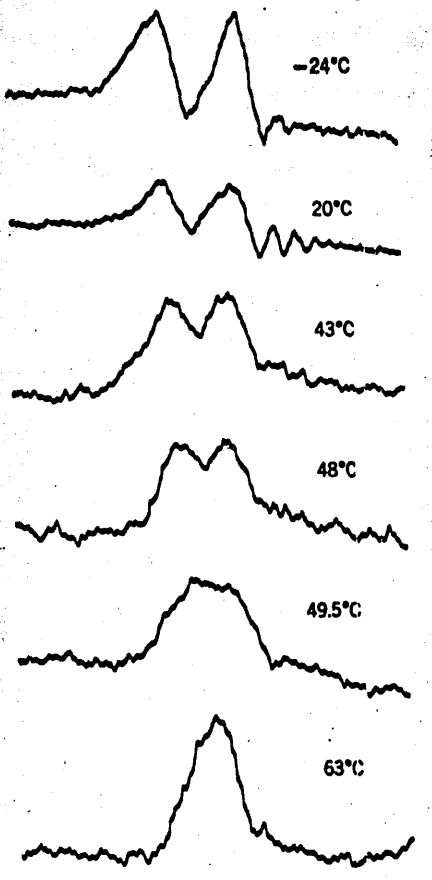


Figure 3 Variation of the N—CH_3 signal of dimethylacetamide with temperature. Taken from reference (6).

of activated protons with bases, are other examples. A recent review of the subject is given by Leffler and Grunwald (7).

1.8 A general theoretical treatment considers protons exchanging between two environments A and B, the average lifetime of a proton at each environment being τ_A and τ_B respectively, and the fractional population of each site being p_A and p_B (such that $p_A + p_B = 1$). At equilibrium,

$$p_A/\tau_A = p_B/\tau_B$$

In many cases such as the dimethylacetamide case (6) and the ring inversions discussed in this thesis, $p_A = p_B = \frac{1}{2}$, and $\tau_A = \tau_B$.

McConnell (8) assumed that a proton occupies one site until it is instantaneously transferred to the other. He then modified the Bloch equations for each nucleus A and B by introducing a term to allow for the contribution of B to the magnetic moment of A resulting from exchange, and vice versa. From his modified equations he derived a line-shape function as in the original case.

Just as, in the line shape function in the absence of exchange there is a characteristic relaxation time T_2, such that the peak width at half-height is $1/\pi T_2$, McConnell's theory derives an expression for

a new characteristic time T_2' in terms of T_2, τ_A, and τ_B, such that the width at half-height of the signal of the exchanging proton is $1/T_2'\pi$. The half-width of this peak can be measured, so that if we can also measure T_2, we can obtain the reaction parameters τ_A and τ_B from McConnell's theory.

Since line widths in the absence of exchange are found to be determined by the inhomogeneity of the magnetic field, T_2 can be obtained from an other convenient non-exchanging proton signal in the sample.

An earlier and more complex approach along the same lines by Gutowsky, McCall and Slichter (9) leads to the same results. McConnell's equations will now be presented in a form suitable for the problem being studied, the ring inversion of 1,3-dioxanes. Here $p_A = p_B$, and so $\tau_A = \tau_B$.

1.9 Slow Exchange The region of slow exchange is defined to be that region in which the two collapsing signals are discrete that is, there is no overlap of the signals. In this situation the observed relaxation time T_2' of proton A is related to the relaxation time in the absence of exchange T_2 by the equation

$$1/T_2' = 1/T_2 + 1/\tau_A$$

Thus the rate constant for the inversion k is given by

$$k = 1/\tau_A = 1/T_2' - 1/T_2 = \Delta, \text{ say} \qquad \ldots\ldots(1)$$

Similar results are obtained for proton B.

There are no difficulties with AB type or even more complicated spectra provided the various signals are discrete, so that equation (1) can be applied in these cases as well.

1.10 Fast Exchange The region of fast exchange is that in which the two signals of the exchanging protons have merged into one. In this region, the relationship used has been derived by Piette and Anderson (10) from McConnell's treatment. They define a quantity τ such that

$$1/\tau = 1/\tau_A + 1/\tau_B \qquad \ldots\ldots(2)$$

Then, the relationship is given in the form

$$1/T_2' = 1/T_2 + \nabla\tau T_2/(\tau + T_2) \qquad \ldots\ldots(3)$$

where

$$\nabla = \sum_A^B p_A(\omega_A - \langle\omega\rangle)^2 \qquad \ldots\ldots(4)$$

ω_A and ω_B being the frequency of the proton signals A and B in radians per second and $\langle\omega\rangle$ being given by

$$\langle\omega\rangle = \sum_A^B p_A\omega_A \qquad \ldots\ldots(5)$$

Thus in this case, where $p_A = p_B = \frac{1}{2}$,

$$\nabla = \tfrac{1}{2}(\omega_A - \tfrac{1}{2}\omega_A - \tfrac{1}{2}\omega_B)^2 + \tfrac{1}{2}(\omega_B - \tfrac{1}{2}\omega_A - \tfrac{1}{2}\omega_B)^2 \ldots$$

$$= \tfrac{1}{2}\left[\tfrac{1}{4}(\omega_A - \omega_B)^2 + \tfrac{1}{4}(\omega_B - \omega_A)^2\right]$$

$$= 1/8(\omega_A - \omega_B)^2 \cdot 2 \quad = \frac{(\omega_A - \omega_B)^2}{4}$$

converting to cycles per second, that is replacing

$(\omega_A - \omega_B)$ by $2\pi\delta\nu_o$ we get

$$\nabla = (2\pi\delta\nu_o)^2/4$$
$$= \pi^2\delta\nu_o^2$$

where $\delta\nu_o$ is the chemical shift between protons A and B.

Equation (3) can usually be used in a simplified form. If τ is very much smaller than T_2, $\tau + T_2 \sim T_2$ so that equation 3 becomes

$$1/T_2' = 1/T_2 + \nabla\tau \qquad \text{.....(6)}$$

The requirement that $\tau \ll T_2$ is very readily met for the values of T_2 we normally obtain experimentally. The only situation in which the requirement will not be met is one where the chemical shift of the collapsing signals is very small (that is only two or three cycles per second), and thus τ which is inversely proportional to the chemical shift is relatively large.

Using the expression derived for ∇, and putting $\Delta = 1/T_2' - 1/T_2$, as before,

$$\tau = \Delta/\nabla$$
$$= \Delta/(\pi^2\delta\nu_o^2)$$

and thus since $k = 1/\tau_A = 1/2\tau$ from equation (2) with $\tau_A = \tau_B$,

$$k = \pi^2\delta\nu_o^2/2\Delta \qquad \text{.....(7)}$$

In the case where the spectrum below the temperature of coalescence is an AB quartet, rather than

a doublet, the expression for ∇ becomes a summation of four terms. It can easily be shown that in this case ∇ is again equal to $\pi^2(\delta\nu_0)^2$ where $\delta\nu_0$ is the true chemical shift between the two protons. Thus equation (7) can be used both in the case of a doublet or an AB quartet.

1.11 Intermediate Rates of Exchange This is the region from where the signals just begin to overlap through to the point of collapse, Figure 4, (D3)→(D5).

(D3) (D4) (D5)

Figure 4

The use of peak widths at half-heights is not suitable in this case. Other parameters derived from the line-shape function have been used. Meiboom (11) has used the ratio of peak height to trough height with considerable success, using a computer to calculate values of this ratio for various values of T_2 and τ (12). Since, as the signals broaden and merge, the separation of the peaks decreases, this parameter has also been used (6, 13) to give values of τ.

In this second case the expression for τ is

independent of T_2 provided T_2 is large. With this assumption the following equation is obtained from the line-shape function for the ratio of the observed peak separation ($\delta\nu$) to the peak separation in the absence of exchange ($\delta\nu_0$)

$$\delta\nu/\delta\nu_0 = \left[1 - 1/(2\pi^2\tau^2\delta\nu_0^2)\right]^{\frac{1}{2}} \qquad \ldots\ldots(8)$$

from which

$$1/2\pi^2\tau^2\delta\nu_0^2 = 1 - \delta\nu^2/\delta\nu_0^2$$

that is

$$2\pi^2\tau^2\delta\nu_0^2 = (\delta\nu_0)^2/(\delta\nu_0^2 - \delta\nu^2)$$

thus

$$\tau^2 = 1/2\pi^2(\delta\nu_0^2 - \delta\nu^2)$$

and so

$$k = 1/2\tau = \sqrt{2\pi^2(\delta\nu_0^2 - \delta\nu^2)}/2 \qquad \ldots\ldots(9)$$

The temperature of coalescence is that at which $\delta\nu = 0$, thus at this temperature

$$\begin{aligned} k &= \sqrt{2\pi^2\delta\nu_0^2}/2 \\ &= \sqrt{2}\pi\delta\nu_0/2 \\ &= 2.221\delta\nu_0 \end{aligned} \qquad \ldots\ldots(10)$$

In the case of an AB quartet, the validity of the intermediate exchange equations may appear questionable. Their use, however has been shown to produce results in agreement with those found when the theoretical equations are rigorously applicable. Thus Jensen et al. (13), using the intermediate exchange equations only, on the complex low temperature spectrum

of cyclohexane found $\Delta G^{\#}$ for ring inversion to be 10.1 kcal/mole, while recent work by Bovey (14) and Anet (15) on the simple spectrum of undecadeutero-cyclohexane gives the value as 10.3 kcal/mole.

When it has been necessary to treat an AB quartet then, in measuring the value of k at the temperature of coalescence, the true chemical shift has been used. In using equation (9) the separation of the two strong peaks of the quartet has been measured, and compared with the splitting of these peaks observed for large values of τ.

1.12 Equations (1), (7), (9), and (10) summarised below, are the equations which will be used throughout this work.

Slow Exchange

$$k = \Delta \qquad \ldots\ldots(1)$$

Fast Exchange

$$k = \pi^2 \delta\nu_0^2/2 \qquad \ldots\ldots(7)$$

Intermediate Exchange

$$k = \sqrt{2\pi^2(\delta\nu_0^2 - \delta\nu^2)}/2 \qquad \ldots\ldots(9)$$

$$k = 2.221\,\delta\nu_0 \quad \text{at coalescence} \qquad \ldots\ldots(10)$$

The Eyring equation (11) can then be used to

$$k = \frac{kTf}{h} \cdot \exp\left(\frac{\Delta S^{\#}}{R}\right) \cdot \exp\left(\frac{-\Delta H^{\#}}{RT}\right) \qquad \ldots\ldots(11)$$

calculate values of $\Delta H^{\#}$, $\Delta S^{\#}$, and $\Delta G^{\#}$.

Thus from equation (11) in which k = Boltzmann's

Constant, h = Planck's Constant, and f = transmission coefficient,

$$\log(k/T) = \log(K/h) + \log f + \Delta S^{\#}/2.3R - \Delta H^{\#}/2.3RT$$

Thus a plot of $\log(k/T)$ against $1/T$ has slope $-\Delta H^{\#}/2.3R$ and intercept on the y-axis

$$\log(K/h) + \log f + \Delta S^{\#}/2.3R$$

so that

$$\Delta H^{\#} = -2.3R \times (\text{slope})$$

and

$$\Delta S^{\#} = 2.3R(\text{intercept} - \log K/h - \log f)$$

$\Delta G^{\#}$ is given by the equation

$$\Delta G^{\#} = \Delta H^{\#} - T\Delta S^{\#}$$

so that $\Delta G^{\#}$ can be calculated at any temperature. In other reported work it has been usual to quote $\Delta G^{\#}$ at the temperature of coalescence. In this present work there are sometimes three temperatures of coalescence for the same compound. As a result, all values of $\Delta G^{\#}$ are quoted at 200°K, a temperature intermediate among the various coalescence temperatures.

In the work reported in this thesis the value of the transmission coefficient has been taken as $\frac{1}{2}$. The reasons for this will be considered in chapter 3 when discussing the mechanism of ring inversion.

There are many examples among earlier work where spectra because of multiple spin-spin couplings are not convenient for treating by the slow exchange

or fast exchange equations. In these and in other cases where workers have had only a passing interest in energy barriers, an approximate value of $\Delta G^{\#}$ has been obtained by observing the temperature of coalescence. Using equation (10) a value of k is obtained, and by assuming the transmission coefficient is 1, a value of $\Delta G^{\#}$ is obtained.

This is unsatisfactory for the transmission coefficient should often be more correctly taken as $\frac{1}{2}$, and, there is inherent in the use of equation (10), the requirement that T_2 should be large. These and the obvious difficulty of deciding when precisely a complex multiplet has just collapsed lead to inaccuracies in the values of $\Delta G^{\#}$ given.

1.13 Apart from studies of complex formation and electron transfer in inorganic systems (16), there are two kinds of fast reactions which have proved outstandingly amenable to study by nmr. These are proton exchange reactions and hindered rotation studies. There are some small differences between the two.

The principal difference is mechanistic. Proton exchange requires a base to transfer the proton, so that these reactions are bimolecular or of molecularity higher than two. As a result, in proton exchange, the rate constant for the reaction

$$A + X^- \xrightarrow{k_2} \text{Products}$$

is given by

$$k_2 = 1/\tau_A[X^-]$$

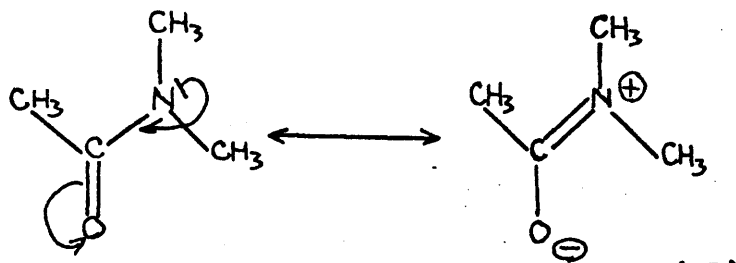
It often happens, too, that the population of the two sites between which the proton is exchanging are different, and allowance has to be made for this. A full review of the work on proton exchange has been given by Loewenstein and Connor (16). The kinetics of hindered rotation are always satisfactorily first order.

Studies of hindered internal rotation by nmr can be divided into three classes, 1) Rotation about single bonds 2) Rotation about partial double bonds 3) Ring inversion in cyclic compounds, which is a special case of 1).

1.14 The barrier to rotation about single bonds is small and has been shown to be of the order one to three kcal/mole (17). Substituted ethanes have been studied by nmr (the topic has been reviewed by Gutowsky, 18), and while energy differences between conformations have been readily obtained, the potential energy of activation for rotation is too low to be suitable for measurement by nmr in the present state of the technique.

1.15. There are many examples of hindered internal rotation due to partial double bond character, and this is the field which has been most fully studied by nmr.

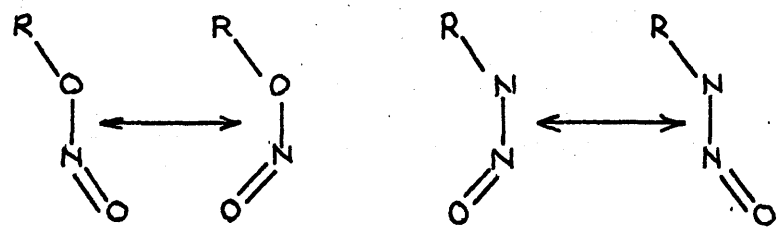
The classical hindered rotation study by nmr is that of amides (Figure 5), first indicated by Phillips (19)



(D6) (D7)

Figure 5

in 1955, and studied by Gutowsky and Holm (6) in 1956, see Figure 3, and more fully by Rogers (20) and Piette and Schneider (21). The analogous thionamides have been studied by Loewenstein (22). Alkyl nitrites (D8), (10, 23) and the similar nitrosamines (D9), (24) are

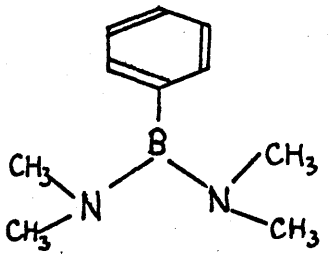


(D8) (D9)

Figure 6

other compounds which have proved suitable for investigation. Partial double-bond character of phenyl-carbon bonds in benzaldehydes has been examined by Anet (25) while Brand and MacNicol (26) have looked at the similar effect in phenyl-nitroso bonds. Hindered rotation in biphenyls has been studied (27), while there has also been work on amidinium compounds (28)

and on rotation about the B—N bond in the compound



(D10)

(D10), (29).

These systems have generally proved very suitable for study by having simple spectra. In many cases, too, the temperature of coalescence has been within thirty or forty degrees centigrade of room temperature, which has allowed a complete analysis to be carried out readily.

1.16 There have been over forty ring compounds whose inversion has been studied by nmr. In fewer than ten of these compounds have the reaction parameters, energy of activation $\Delta H^{\#}$, entropy of activation $\Delta S^{\#}$, and free energy of activation $\Delta G^{\#}$ been determined. There are several reasons for this. Firstly, it is possible to obtain a reasonably accurate value of $\Delta G^{\#}$ from the temperature of coalescence of a spectrum, and this is fairly easily to measure. Considerably more work is necessary to obtain values of $\Delta S^{\#}$ and $\Delta H^{\#}$ so that, when there has only been passing interest in ring inversion, workers have often been content to determine the more easily accessible $\Delta G^{\#}$. Secondly, the spectrum of a ring compound below the temperature of coalescence

is often very complex, due to multiple spin-spin coupling - Bovey (14) has considered that cyclohexane should be treated as a twelve-spin system with many thousands of overlapping lines - and as a result the equations derived in Section 1.12 may not apply. A third point is that almost invariably the temperature of coalescence, which is normally in the middle of the range of temperatures over which measurements are made, is much below 0°C, and there are some problems in attaining these low temperatures.

As a result, when a survey is made of presently published results, one is impressed by the large assortment of ring types which has been studied, often with only one example of each type, which has proved particularly suitable for nmr treatment. A survey of these results is useful, and at the present time, not too tedious, and, in fact served to indicate the problem which is reported in this thesis.

There are three headings for this survey, 1) Rings other than six-membered rings, 2) Cyclohexane and its derivatives, 3) Six-membered heterocyclic rings.

1.17 Rings other than Six-membered Rings (see Table 1). In this class there are only four examples which have been fully investigated. Anet (30) found a value of

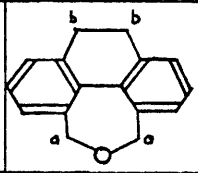
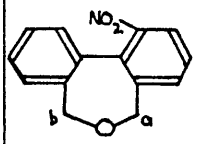
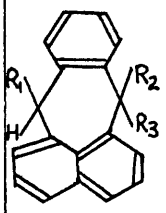
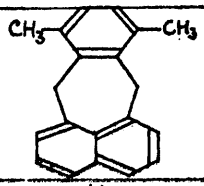
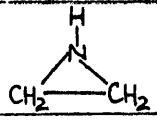
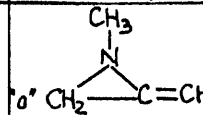
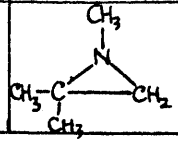
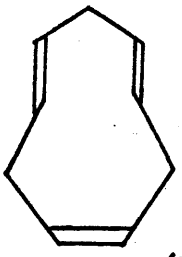
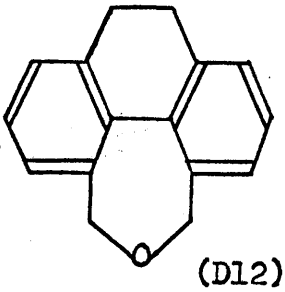
Diagram Number.	COMPOUND	$\Delta G^{\#}$ kcal/mole	$\Delta H^{\#}$ kcal/mole	$\Delta S^{\#}$ e.u.	Temperature of Coalescence. (°C)	Reference
	Cycloöctane	7.7	7.0	-4.4	-111.5	30
D11	Cyclononatriene	14.6	9.8	-16.0	-25	31
D12	 Ring "a"	11.2		logA = 12.9	-55	32
D13		15.5		logA = 12.0	"a" +56 "b" +48	32
	Cycloöctatetraene	13.7			-10	33
D14	 R_1 R_2 R_3 All H H D D OCH_3 H OCH_3 $OCOCH_3$ H $OCOCH_3$	13.5 13.5 15.2 14.3			+8 +8 +23 +7	34
D14		15.4			+40	34
D15		19.0		logA = 11.0		35
	 pure liquid.	6.4			"a" -70 "b" -25	36
	 pure liquid 25% v/w in MeOH 25% v/w in CCl_4	10.0 6.8 7.8				36

TABLE 1 Reaction parameters for the inversion of rings other than six-membered rings.

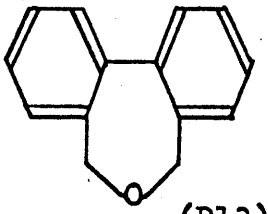
7.7 kcal/mole for $\Delta G^{\#}$ in cyclooctane, while Untch (31) has investigated cyclononatriene (D11). In Japan, Oki



(D11)



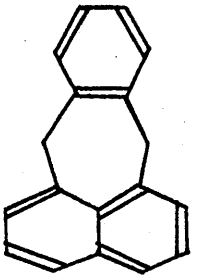
(D12)



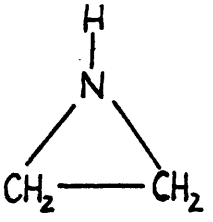
(D13)

(32) has examined compounds of rather esoteric interest, a pair of dihydrodibenzoxepins (D12 and D13).

Examples where the free energy of activation alone has been reported, usually from coalescence temperature results are cyclooctatetraene (33), and recent work on derivatives of dihydropleiadene (D14)



(D14)



(D15)

by Lansbury and Bieron (34). Some of the earliest work on ring inversion was carried out by Gutowsky (35) and by Loewenstein (36) on derivatives of the three-membered ring aziridine (D15).

1.18 Cyclohexane and its Derivatives (see Table 2). Because of its importance in conformational analysis, the barrier to inversion of cyclohexane has been sought after diligently by nmr spectroscopists (13, 14, 15, 37,

38, 39). The investigation is rendered more difficult by the complex spectrum of cyclohexane below its coalescence temperature as indicated above (Section 1.16), and only by recent very elegant work by Anet (15) and by Bovey (14), independently, has the problem been elucidated. These workers prepared undecadeuterocyclohexane, whose single proton spectrum at low temperatures is simpler than that of cyclohexane, but still shows hydrogen-deuterium coupling. By irradiating the sample at the deuterium frequency, this coupling was removed, and the spectrum reduced to a doublet corresponding to axial and equatorial protons, which was treated by the usual methods. Thus Anet (14) and Bovey (15) found that for the inversion of cyclohexane, $\Delta G^{\#}$ = 10.3 kcal/mole, $\Delta H^{\#}$ = 10.7 kcal/mole, $\Delta S^{\#}$ = +2.1 e.u.

The same problem of spin-spin coupling arises in simple substituted cyclohexanes, and as a result the majority of reported results are of free energies of activation only; these are shown in Table 2.

It will be noted that apart from the hexaacetates (42), there are two other derivatives of which a full study has been made. Both of these are fluorocompounds, perfluorocyclohexane (40) and cyclohexyl fluoride (41). In both cases results have been obtained by looking at the F^{19} spectrum. In cyclohexyl fluoride $C_6H_{11}F$, which is exactly analogous to his earlier study of

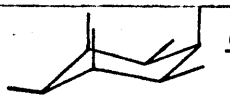
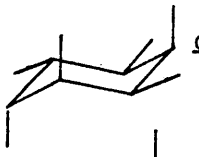
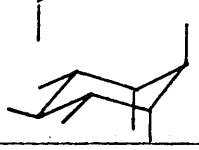
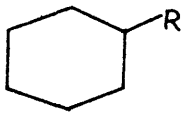
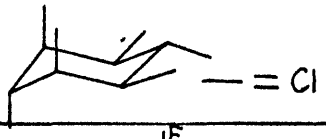
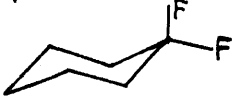
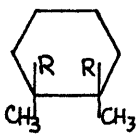
Diagram Number	COMPOUND	$\Delta G^{\#}$ kcal/mole	$\Delta H^{\#}$ kcal/mole	$\Delta S^{\#}$ e.u.	(°C) Coalescence Temperature	Reference.
	Cyclohexane	10.3	10.9	+2.9	-66.7	15
		10.2	10.5	+1.4		14
		10.3	10.3	-0.2		39,15
		10.1	11.1	+4.9		13
	Perfluorocyclohexane	10.9	7.5	-10.7	-66.5	40
	Cyclohexyl Fluoride	10.0	9.6	-0.6	-33	41
D16	 cis	13.6	6.6	-27.8	Ring H +40 Acetate +20	
D17	 allo —=OCOCH$_3$	12.3	5.5	-27.1	Ring H -23 Acetate -33	42
D18	 muco	11.6	4.7	-27.4	Both -65	
	 R = Cl, Br	10.9		(40Mcs - -55)		43
	R = Cl, Br, OH, I	11.7		(60Mcs - -65)		44
	trans-1,2-dihalogeno-cyclohexanes	11.9		(40Mcs - -45)		45
		9.9		(60Mcs - -79)		46
	 —=Cl	13.0			-15	47
		12.0				48
	 R = OCOCH$_3$	10.5			-70 for CH$_3$ signal	49

TABLE 2 Reaction parameters for the inversion of cyclohexane and its derivatives.

undecadeuterocyclohexane $C_6D_{11}H$ (14), Bovey (41) spin-decoupled the eleven hydrogen atoms in this case, to obtain simple low-temperature spectra. There was an additional complication in this case, for the populations of the axial and equatorial positions are different, but making simple allowances for this, Bovey was able to obtain values for the reaction parameters.

The perfluorocyclohexane molecule on which Tiers worked (40) is analogous to cyclohexane, but is more tractable since F^{19}—F^{19} coupling constants are larger and as a result, there is less overlap in the low temperature spectrum.

Another series of compounds, again of more esoteric interest, has been studied by Brownstein (42), namely cis- allo- and muco-inositol hexaacetates (D16 to D18 in Figure 7)

(D16), cis (D17), allo (D18), muco

Figure 7

It can be seen then, that there has been no systematic study of cyclohexane derivatives by nmr and that, what results have been obtained usually require an indirect approach using sophisticated equipment. The numerous reports which give only values

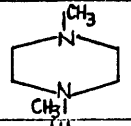
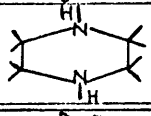
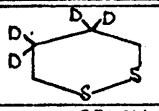
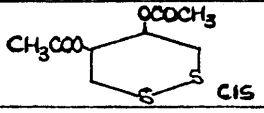
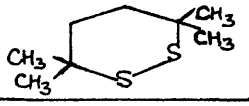
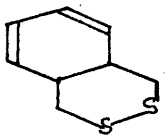
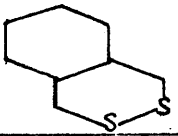
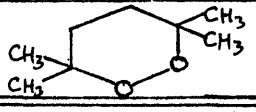
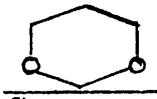
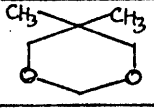
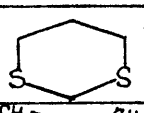
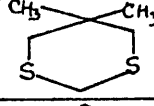
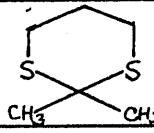
Diagram Number	COMPOUND	$\Delta G^{\#}$ kcal/mole	$\Delta H^{\#}$ kcal/mole	$\Delta S^{\#}$ e.u	Coalescence Temperature	Reference
		13.3			-25	50
		6.1				51
		11.6 11.7	 11.5	 ~-1.0	-42 -48	54 53
D22		13.9	12.0	~-7.0	-8	53
D21		13.8	16.1	+6.7	-2	55
		8.5			-80	53
		15.5			~0	53
D19		11.7 14.6	 18.5	 +14.5	-20 +12	52 55
		9.7		"a" -82		49
		11.2	~12.8	~+7.0	"a","c"~-50 "b" -61	49
		~9.4		"a"-80±10		49
		10.3		"a","b"~-65 "c" -77±3		49
		9.8	11.2	~+7.0	"a","b"~-80	49

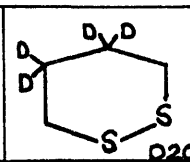
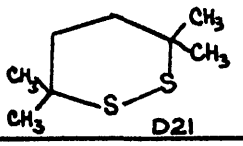
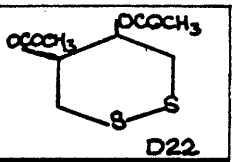
TABLE 3 Reaction parameters for the inversion of heterocyclic six-membered ring compounds.

of $\Delta G^{\#}$ are of little value in comparisons; the two investigations of trans-1,2-dihalogenocyclohexanes (45, 46) which give values of 11.9 and 9.9 kcal/mole for $\Delta G^{\#}$, are an indication of the reliability of these results.

1.19 Heterocyclic six-membered rings There are three series of compounds which fall under this heading which have been studied, 1,2-dioxanes and 1,2-dithianes, 1,3-dioxanes and 1,3-dithianes, and piperazine derivatives, see Table 3. Reeves (50, 51) has studied these last, but only free energies of activation have been determined.

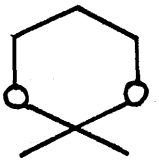
The 1,2-dioxanes and dithianes have been studied by Friebolin and Maier (52, 53) and by Claeson, Androes and Calvin (54, 55). Only half the compounds in this class have been fully investigated; there is an unfortnate disagreement in the results reported by the two groups (52, 55) for 3,3,6,6-tetramethyl-1,2-dioxane (D19). Taking the three compounds (D20, D21, D22) together,

TABLE 4

	 D20	 D21	 D22
$\Delta G^{\#}$	11.7	13.8	13.9
$\Delta H^{\#}$	11.5	16.1	12.0
$\Delta S^{\#}$	-1.0	+6.7	-9.0
Coalescence Temperature	-45	-2	-8
Reference	53, 54	55	53

see Table 4, one can conclude that the increased degree of substitution has raised the barrier to internal rotation by 2 kcal/mole.

The German group of Friebolin and Maier have examined (49) a series of 1,3-dioxanes and 1,3-dithianes, see Table 3. They determined only coalescence temperatures for the various signals, and since some of the compounds gave two or more signals which split on cooling, they were able to calculate values for $\Delta H^{\#}$ and $\Delta S^{\#}$. This method of obtaining $\Delta H^{\#}$ and $\Delta S^{\#}$ is open to large errors, for they are in effect measuring the slope and intercept of a straight line graph drawn through only two points the precision of which is ±10% at an optimistic estimate. They also examined 2,2-dimethyl-1,3-dioxane (D23), but were unable to detect spitting



(D23)

at -88°C. From this they concluded that $\Delta G^{\#}$ for this compound is less than 8.0 kcal/mole. This is a questionable conclusion, for using the Eyring equation as they do, taking the highest likely coalescence temperature as -90°C, and the smallest likely value of the chemical shift of the axial and equatorial methyl groups as 8.5cps - the value for this shift in

5,5-dimethyl-1,3-dithiane - the most one can say is that the barrier will be less than 9.6 kcal/mole. These authors were able to draw some conclusions from their results; these will be considered in the discussion in Chapter 3.

1.20 The present position is then that while the barrier to ring-inversion of six-membered rings, and the effect of substituents on this barrier is of considerable interest, there has been little systematic work on this problem, principally because results can not usually be obtained in a straightforward manner.

One solution to the problem, namely the use of exhaustive deuteration and deuterium decoupling, has been indicated above; two others indicate themselves from the above survey.

The first is the use of geminal dimethyl compounds. The coupling constant between the protons of a methyl group attached to one carbon atom and a proton on an adjacent carbon atom, that is a—b in (D24) in Figure 8, is so small as to be undetectable (56),

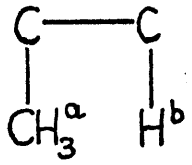


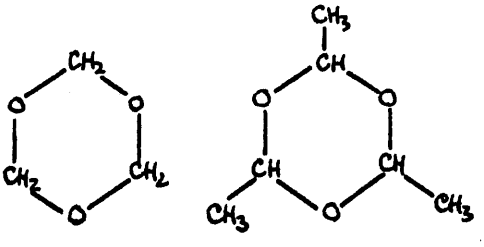
Figure 8 (D24)

so that in a gem-dimethyl group one would expect no coupling either between the two methyl groups themselves,

or between either of the methyl groups and other protons in the molecule. The use of geminal dimethyl compounds thus recommends itself. It is of interest that Sheppard (39) was thus led to study 1,1-dimethylcyclohexane, but found that the methyl signal was unsplit even at -120°C.

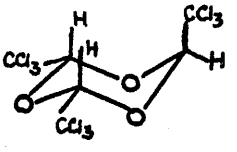
The second solution is the use of 1,3-dioxanes. In these compounds one $-CH_2-$group is isolated from the remainder of the molecule by two oxygen atoms, and as a result there will be no coupling with other protons in the molecule. There will be coupling between the methylenedioxy-protons themselves at low temperatures, but the resultant spectrum, an AB quartet, is still suitably simple for treatment.

1.21 With this last factor in mind, it was decided to study the ring inversion of trioxane (D25), the trimer of formaldehyde, and to look at the effects of

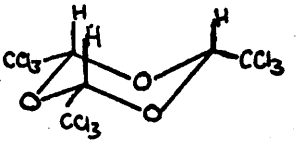


(D25)

(D26)



(D27)



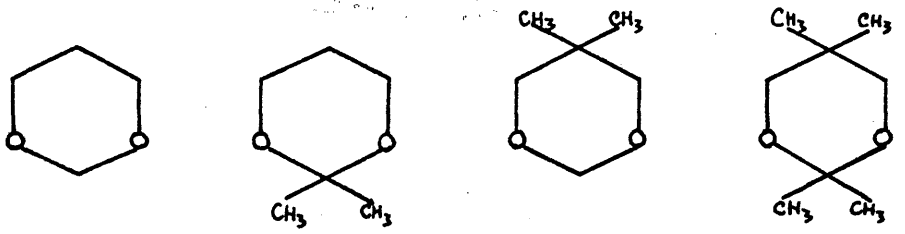
(D28)

substituents on energy barriers in 1,3-dioxanes using all the techniques outlined in Section 1.12.

The only substituted trioxanes known are acetaldehyde trimer, paraldehyde (D26) and the α (D27) and β (D28) forms (57) of chloral trimer. It appears

that in each of these compounds there is a preferred conformation, and that there is no rapid ring inversion (57). There is therefore no scope for investigating substituent effects on ring inversion in this series.

1,3-Dioxane (D28) and three of its geminally-substituted methyl derivatives, 2,2-dimethyl-1,3-dioxane (D29), 5,5-dimethyl-1,3-dioxane (D30), and



(D29) (D30) (D31) (D32)

2,2,5,5-tetramethyl-1,3-dioxane (D31) have been prepared.

The nmr spectrum of trioxane and of each of these dioxanes has been examined over a wide range of temperatures, and from the various changes in certain suitable absorption lines in each spectrum, the free energy of activation, the entropy of activation and the energy of activation for the ring inversion of each compound have been calculated.

From these results it has been possible to draw conclusions on the factors which affect the value of these parameters.

CHAPTER TWO

RING INVERSION — EXPERIMENTAL

2.1 The trioxane used was supplied by British Drug Houses Ltd.; its nmr spectrum showed only the absorption line for trioxane, so it was used without further purification.

1,3-Dioxane and its methyl-substituted derivatives were prepared by condensation of the appropriately-substituted propan-1,3-diol with formaldehyde in the form of paraformaldehyde or acetone, see Figure 9.

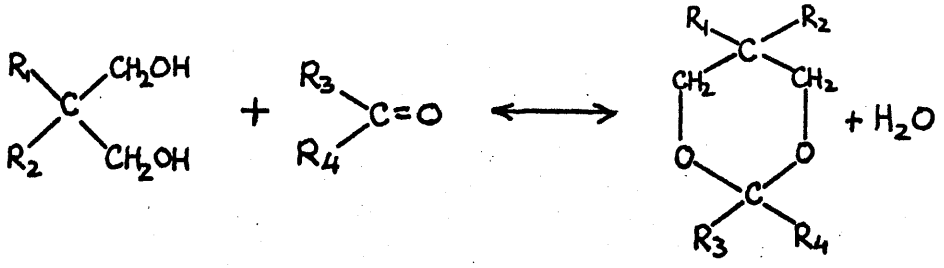


Figure 9

For 1,3-dioxane, $R_1 = R_2 = R_3 = R_4 = H$; for 2,2-dimethyl-1,3-dioxane, $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$; for the 5,5-dimethyl compound $R_1 = R_2 = CH_3$, $R_3 = R_4 = H$; for tetramethyl dioxane, $R_1 = R_2 = R_3 = R_4 = CH_3$.

The condensation is reversible. When paraformaldehyde was the carbonyl compound, the equilibrium favoured the dioxane. With acetone however, the equilibrium favoured the alcohol. The method used to prepare 1,3-dioxane and 5,5-dimethyl-1,3-dioxane was then, basically that of Boeseken and Hermans (58) and illustrated in the synthesis of 1,3-dioxane.

1,3-Dioxane 30.4g, 0.4mole of propane-1,3-diol and paraformaldehyde (13g, 0.425moles) were refluxed with 0.1g toluene-p-sulphonic acid for 8 hours. The reaction mixture was thendistilled and the fraction boiling from 95°C to 120°C was retained. This fraction was extracted with ether and dried with "Drierite". The liquid which remained after removing the ether was chromatographed on grade 2 neutral alumina. The product was a clear liquid (B.p. 105°C, $n_D^{20} = 1.41650$)

2,2-dimethyl-1,3-dioxane and 2,2,5,5-tetramethyl-1,3-dioxane were prepared by an azeotropic method similar to that of Conrad (59). Apart from using a Dean and Stark head during reflux which in the case of the dimethyl compound lasted 175 hours, the method of preparation is very similar to that used for 1,3-dioxane itself.

All the dioxanes are clear liquids; physical constants obtained are compared with literature values in Table 5. In all cases the satifactory purity of the

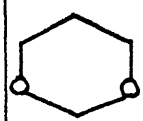
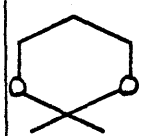
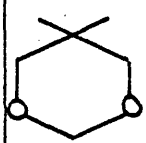
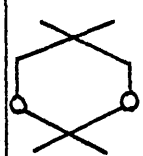
COMPOUND	Observed Values		Literature Values		
	B.Pt. °C.	n_D^{16}	B.Pt. °C.	n_D	Ref.
 1,3-Dioxane	105	-	105	n_D^{20} 1.4165	60
 2,2-Dimethyl 1,3-Dioxane	26 (44mm)	-	124-6	n_D^{20} 1.4190	61
 5,5-Dimethyl 1,3-Dioxane	123-5	1.4190	126.5	n_D^{25} 1.4191	62
 2,2,5,5-Tetra-methyl-1,3-Dioxane.	143-6	1.4188	144.5	n_D^{25} 1.4178	62

TABLE 5 Physical Constants for the Dioxanes.

dioxane was confirmed by the absence of extraneous lines in the nmr spectrum.

2.2 There were three factors governing the choice of solvent for the present internal rotation studies. The first is solubility. While normally the signal of a proton present in a concentration of 0.2 molar is readily observed, this may become difficult when the signal is broadened by exchange. A solution 0.6 molar

in the proton being examined is about the minimum one can conveniently use, and since the temperature of observation is often around -100°C, the solvent chosen must be one in which the dioxane is soluble to that extent at that temperature.

The second consideration is the freezing point of the solvent. It occasionally happened that, although as the sample was cooled the dioxane remained soluble, the whole solution froze at temperatures higher than those at which some observations were required.

The third factor is the nmr spectrum of the solvent. The acetone-diethylether solvent used for trioxane is unsuitable for the dioxanes, for the ether spectrum overlaps and obscures all the dioxane signals except the O—CH_2—O protons.

For trioxane, the solvent used was a mixture of acetone and diethylether, 1/3 v/v. For both 1,3-dioxane and 5,5-dimethyl-1,3-dioxane, acetone was used. For 2,2,5,5-tetramethyl-1,3-dioxane, acetone was again used except that, to prevent freezing of solutions examined below the coalescence temperatures that is below -110°C, mixtures of acetone with carbon disulphide or methanol were used at these temperatures.

2,2-Dimethyl-1,3-dioxane where the coalescence temperature is -126°C was prepared for examination in dichlorodifluoromethane, Arcton 12 supplied by Imperial Chemical Industries Ltd. The sample was in a sealed

tube with a little acetone as a reference compound. This proved an ideal solvent system, and spectra were obtained at temperatures as low as -150°C.

Samples were examined in thin-walled Pyrex tubes of outside diameter 5mm, supplied by Messrs Jencons Ltd.

2.3 The instrument used was an RS2 model high-resolution nmr spectrometer manufactured by Associated Electrical Industries Ltd., with operating frequency 60 megacycles per second. Spectra were recorded on a Hellige recorder with variable chart speed, and were calibrated by the usual sideband technique (63).

A modified sample probe was provided by A.E.I. for variable temperature work. In this, the probe was made with double walls, and the space between the walls was evacuated. Built into the probe was a copper-constantan thermocouple located at the inner surface of the evacuated system. The thermocouple was connected to a voltmeter calibrated to give a direct but approximate reading of temperature.

The A.E.I. equipment was intended for high temperature work only so that a cooling system had to be devised. A feed system of vacuum-jacketed tubes was constructed to fit the variable temperature probe, and the sample was cooled by a stream of dry nitrogen which had passed through a copper coil heat exchanger

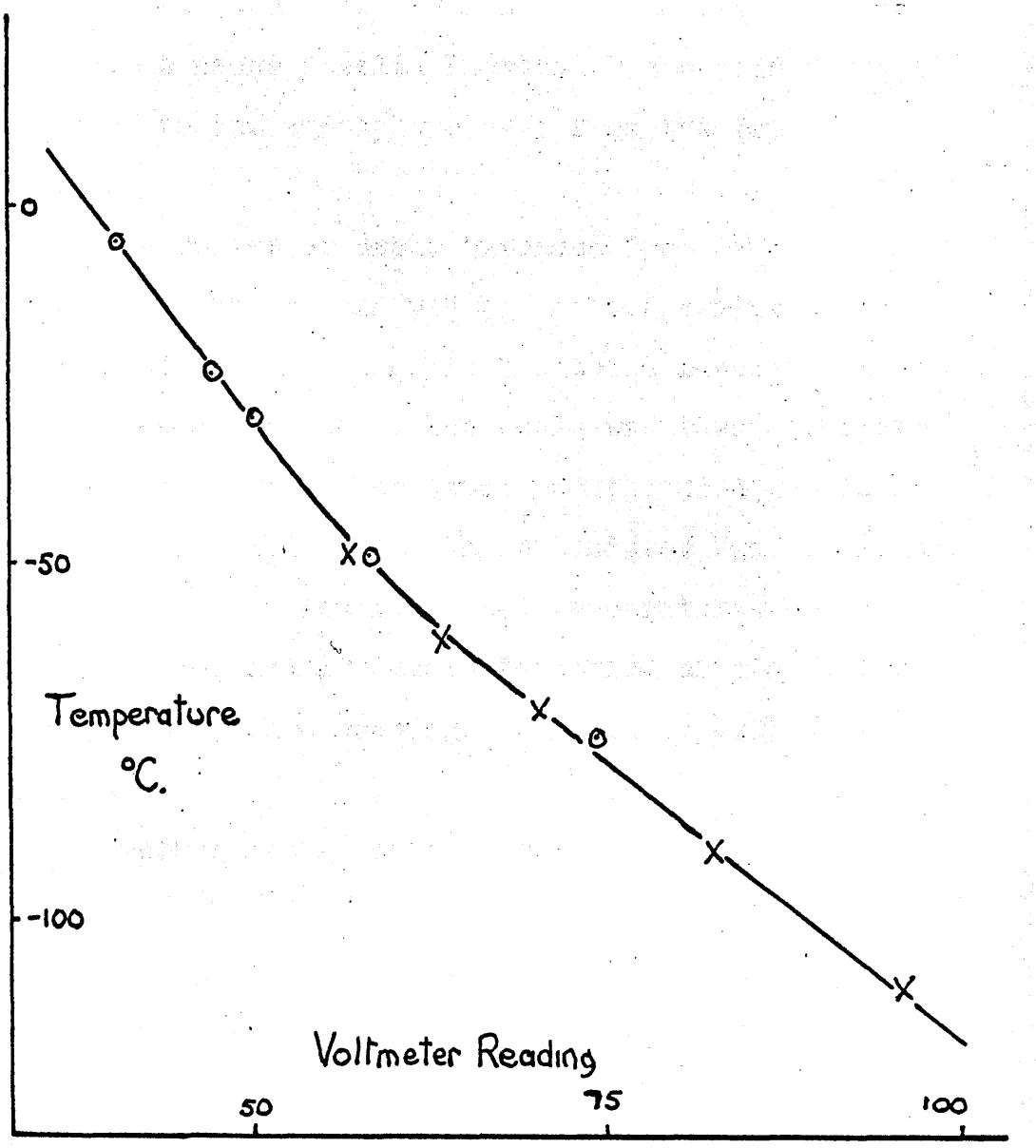


Figure 10 Calibration of Voltmeter by Thermistor and by "Methanol Thermometer" (64).

immersed in liquid nitrogen, and then through the feed tubes to the probe itself. Thereafter the cold nitrogen was vented to the atmosphere away from the faces of the magnet.

The voltmeter scale extended from 0°C upwards so that, when the sample was at low temperatures, the terminals of the thermocouple had to be reversed to give an on-scale reading. The scale was then calibrated against an F22 model thermistor manufactured by Standard Telephones and Cables Ltd. The thermistor had previously been calibrated at several fixed temperatures between 0°C and -126°C, and its characteristics obtained. In this way temperature readings accurate to ±2C° were obtained.

Another method of temperature calibration is by using a methanol thermometer (64). The chemical shift between the CH_3 and the OH signals of a sample of pure methanol increases as the temperature is lowered, a plot of chemical shift against temperature being linear. Varian Associates (64) have prepared a calibration graph, and this can be used to measure temperatures from room temperature to -60°C. Such a thermometer has been used to calibrate the built-in thermocouple in the present apparatus; the resultant graph agreed well with that from the thermistor calibration, see Figure 10.

2.4 The other parameters which have to be measured are the relaxation time in the absence of exchange (T_2), and the experimental relaxation time (T_2') of the exchange broadened signal. T_2 was measured from the acetone signal in the samples. When T_2 is large, that is, greater than about 0.3 seconds, the wiggles method of measurement (5) was found to be satisfactory. When T_2 was less than 0.3 seconds as was sometimes the case at particularly low temperatures, the acetone signal was recorded at a slow sweep rate, and the line-width $\delta\nu$ of the signal was measured. $T_2 = 1/\pi\delta\nu$ was then calculated.

T_2' was obtained using this latter method, from dioxane spectra recorded at slow sweep rates.

The use of "slow sweep rates" in the measurement of relaxation times from line-widths can be more precisely defined. If the signal is scanned too quickly, wiggles will begin to appear, see Figure 11, and this

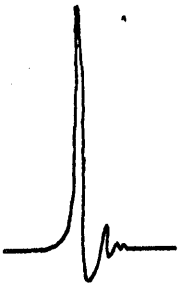


Figure 11

vitiates line-width measurements. Jacobsohn and Wangsness (5) have shown that wiggles will not appear if the sweep rate S in cycles per second per second is

less than or equal to $1/8\pi T_2^2$. Since the wiggle method is suitable for $T_2 > 0.3$seconds, then, when $T_2 < 0.3$, a "slow sweep rate" is one less than $1/8\pi(0.3)^2$ cps/sec, that is ~ 0.5 cps/sec.

In the small region of values of T_2 where it is possible to calculate this value from both wiggles and line-widths, the two methods have been found to give the same results.

2.5 For 1,3-dioxane, only the signal of the methylenedioxy protons O—CH_2—O, is suitable for treatment, spin-spin couplings affecting the other signals. The position is the same in 2,2-dimethyl-1,3-dioxane, where only the methyl signal can be used.

In 5,5-dimethyl-1,3-dioxane, the spectrum at room temperature consists of three sharp lines of relative intensity 1:2:3 corresponding to O—CH_2—O, O—CH_2—C, and C—$C(CH_3)_2$—C protons. The first two split to AB quartets at low temperatures while the third is an AX doublet. All of these are suitable for treatment.

The spectrum of 2,2,5,5-tetramethyl-1,3-dioxane comprises three lines of relative intensities 2:3:3 at room temperature. The first signal due to the O—CH_2—C protons splits to an AB quartet at low temperatures, when the second and third signals are AX doublets.

Thus in the case of 5,5-dimethyl-1,3-dioxane

and 2,2,5,5-tetramethyl-1,3-dioxane it was usually possible to obtain two or three values of the rate constant for inversion at any temperature. The mean of the values obtained was used

The trioxane spectrum is a single peak at room temperature. At low temperatures the signal should become an AB quartet and thus be suitable for treatment.

2.6 Temperatures in any series are accurate to ±2C°. The deviation in values of log(k/T) depends in addition, in the accuracy of measurement of values of T_2 and T_2', which is different in every case. Thus in plots of log(k/T) against 1/T from the equations in Section 1.12, points, and the calculated deviations are represented in each case. The average deviation in values of k can be estimated by examination to be about 20%.

When the points had been plotted, lines of maximum and minimum slope as wellas a line of best fit were drawn. From the slope and intercept on the log(k/T) axis of the 'best-fit' line, values of $\Delta H^{\#}$ and $\Delta S^{\#}$ were calculated as outlined in Section 1.12. The deviation in $\Delta H^{\#}$ and $\Delta S^{\#}$ was taken as half the difference between the values of these constants obtained from the lines of maximum and minimum slope.

Values of $\Delta G^{\#}$ were calculated at the temperature 200°C using equation 12. The deviation in values of

the temperature is 2C°, and in values of k is 20%. From this it can be calculated that the deviation in values of $\Delta G^{\#}$ is .2kcal/mole.

The natural line width that is $1/\pi T_2$ at low temperatures is usually quite substantial and may be as much as 1cps. As a result incipient splitting of a signal may be obscured by this poor homogeneity. For this reason, values of the rate constant at temperatures of coalescence are not used in plotting the graph, but have been inserted afterwards for comparison.

CHAPTER THREE

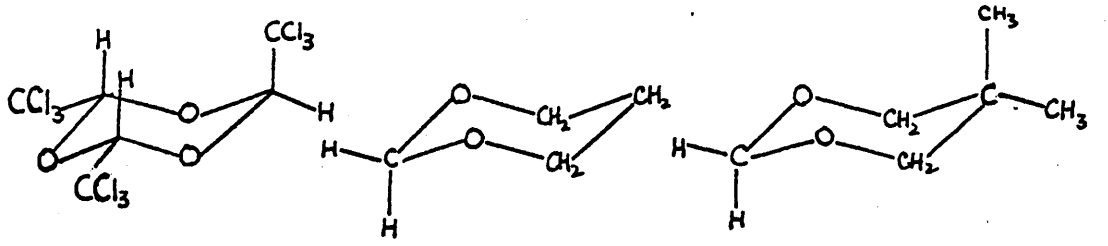
RING INVERSION — RESULTS AND DISCUSSION

3.1 Trioxane At room temperature the spectrum of trioxane consists of a single sharp absorption at 5.00ppm downfield from tetramethylsilane. On cooling to about -70°C the signal begins to broaden; on further cooling the broadening increases, but at -140°C the signal is still not split. This has been confirmed by Anet (65). Difficulties in maintaining a homogeneous field below -140°C prevented further cooling of the sample.

Measurements are confined then to the region of fast exchange. To calculate values of k, the rate constant for inversion using equation 7 of Section 1.12 it is necessary to know the chemical shift of

axial and equatorial protons, and since this has not been observed, any rate constants calculated from the broadened signal depend on an assumed value for this shift.

The only available analogies from which one might draw a value for the chemical shift are α-parachloral (D33) where the shift between axial and equatorial protons is 25.5cps (57), and 1,3-dioxane (D34) and



5,5-dimethyl-1,3-dioxane (D35) reported in this thesis, where the shift has a value 19.3cps and 30.4cps respectively. None of these compounds is a suitable model. In α-parachloral, the different location of axial and equatorial protons with respect to the various trichloromethyl groups must affect the chemical shift. 1,3-Dioxane might appear suitable, but the very fact that there is a marked difference in chemical shift, between this compound and the 5,5-disubstituted compound shows that the nature of the substitution at position 5 does affect the shift at position 2, and therefore in the case of trioxane where there is an oxygen atom at position 5, there is no reason to expect that the

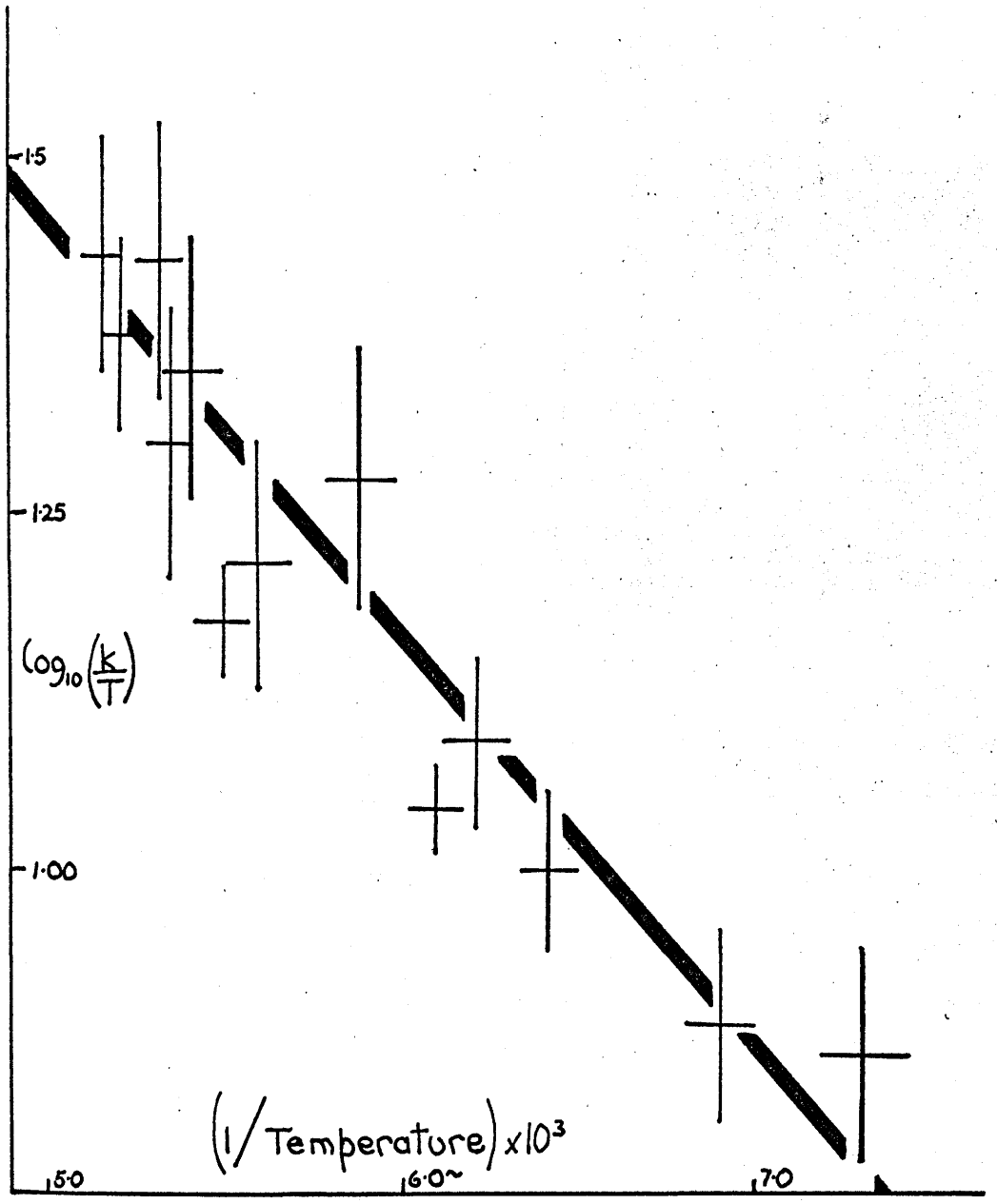


FIGURE 12 Graphical plot of the trioxane results assuming $\delta\nu_o$ = 30cps.

TEMPERATURE °K.	RATE CONSTANT k_1, (sec^{-1})
194	5230 ± 1070
192	4580 ± 780
188	5050 ± 1220
187	3730 ± 900
185	4150 ± 960
182	2730 ± 250
179	2940 ± 630
170	3220 ± 740
164	1810 ± 120
161	1992 ± 280
156	1564 ± 210
145	1130 ± 190
137	1016 ± 195

TABLE 6 Rate Constants for the Ring-Inversion of Trioxane assuming $\delta\nu_o$ = 30cps.

chemical shift will be similar to that of either dioxane.

The expression for the rate constant under conditions of fast exchange is from Section 1.12

$$k = (\kappa^2 \delta\nu_o^2)/2\Delta$$

Thus a plot of log(k/T) against 1/T has slope independent of $\delta\nu_o$ though the intercept on the log(k/T) axis is a function of $\delta\nu_o$. Consequently we may obtain $\Delta H^{\#}$ but not $\Delta S^{\#}$ from measurements of the line broadening.

Values of 30cps, 20cps, and 10cps have been assumed for $\delta\nu_o$, and plots of log(k/T) against 1/T have been drawn in each case. $\Delta H^{\#}$ as expected was the same in each graph, but $\Delta S^{\#}$ was found to decrease as the assumed value of $\delta\nu_o$ increased. Table 6 and Figure 12 show the values of k, and the plot of log(k/T) against 1/T based on the assumption that $\delta\nu_o$ = 30cps.

Table 7 shows the value of $\Delta H^{\#}$ obtained, and the variation of $\Delta S^{\#}$ with $\delta\nu_o$. For reasons mentioned later it seems unlikely that the results in Table 7 are valid.

value of $\delta\nu_o$ chosen (cps)	$\Delta H^{\#}$ kcal/mole	$\Delta S^{\#}$ (e.u.)
10	1.27 ± .45	-33.1 ± 2.6
20	1.27 ± .45	-34.7 ± 2.6
30	1.27 ± .45	-37.5 ± 2.6

TABLE 7 $\Delta H^{\#}$, and the variation of $\Delta S^{\#}$ for the ring-inversion of trioxane as the value assumed for $\delta\nu_o$ varies.

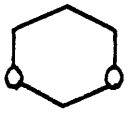
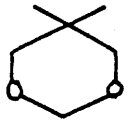
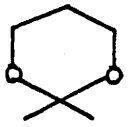
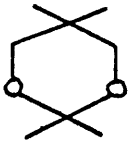
COMPOUND	$\Delta H^{\#}$ kcal/mole	$\Delta S^{\#}$ (e.u.)	$\Delta G^{\#}$ kcal/mole
 1,3-Dioxane	10.2 ± 1.0	+6.2 ± 5.2	9.0 ± 0.2
 2,2-Dimethyl-1,3-Dioxane	12.4 ± 0.8	+9.5 ± 3.5	10.5 ± 0.2
 5,5-Dimethyl-1,3-Dioxane	5.6 ± 0.6	-12.4 ± 3.5	8.1 ± 0.2
 2,2,5,5-Tetramethyl-1,3-Dioxane	9.1 ± 0.9	+3.8 ± 0.8	8.3 ± 0.2

TABLE 8 Thermodynamic Constants for the Ring-Inversion of Substituted 1,3-Dioxanes.

3.2 The results obtained for $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ for the ring inversion of the various 1,3-dioxanes are shown in Table 8. Each of the four dioxanes is considered individually in the next four sections (3.3 to 3.6).

In the tables of rate constants given in these four sections "a" indicates that the fast-exchange equation (equation 7 of Section 1.12) was used, "b", the intermediate exchange equation (1.12, equation 9), "c", the temperature of coalescence equation (1.12, equation 10), "d", the slow exchange equation (1.12, equation 1).

3.3 1,3-Dioxane. The spectrum of 1,3-dioxane at room temperature comprises a single sharp line at 4.72ppm downfield from tetramethylsilane, 5.28τ, corresponding to the O—CH_2—O protons, a 1:2:1 triplet at 6.19τ, corresponding to the O—CH_2—C protons and a 1:4:6:4:1 quintuplet at 8.32τ arising from the C—CH_2—C protons, the coupling constant between the O—CH_2—C and C—CH_2—C protons being 5.3±.1cps.

Thus only the O—CH_2—O proton signal is suitable for treatment. On cooling below -55°C, the signal begins to broaden; at -85°C the broad signal begins to split, and at -100°C the signal is a well-defined quartet still centred at 5.28τ, and with $\delta\nu_o$ = 19.3±0.5cps and J_{a-e} = 6.3±0.2cps.

It has been shown (57, 66) that when a signal for both axial and equatorial protons is observed, the

upfield signal can be assigned to the axial protons.

In the spectrum at -100°C, the axial and equatorial proton signals have different line widths, the appearance of the spectrum being as in Figure 13. This

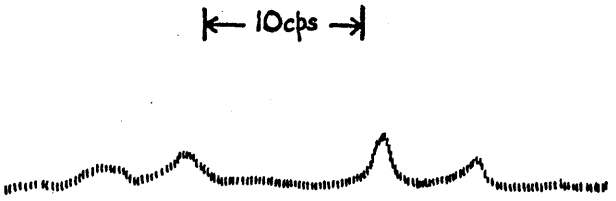


Figure 13 O—CH_2—O spectrum of 1,3-dioxane at -100°C.

suggests that there may be coupling between the equatorial O—CH_2—O proton and the O—CH_2—C protons. One would expect the coupling constant to be very small, so small in fact as to be unresolvable, and observed as broadening of the signal only. Because of the unequal line widths, the slow-exchange equation was not applied to the resolved quartet.

Rate constants calculated at various temperatures are shown in Table 9. A plot of log(k/T) against 1/T

Temperature (°K.)	Rate Constant k_1 (sec^{-1})		Temperature (°K.)	Rate Constant k_1 (sec^{-1})	
212.2	1460 ± 260	a	188.7	60.5 ± 9.4	a
209.7	1240 ± 390	a	188.2	42.9 ± 1.1	c
201.7	456 ± 119	a	181.9	18.3 ± 4.0	b
196.2	294 ± 60	a	180.2	16.0 ± 1.1	b
194.2	293 ± 29	a	177.7	12.8 ± 6.9	b

TABLE 9 Rate Constants for the ring inversion of 1,3-dioxane. Letters indicate treatment used, see p52.

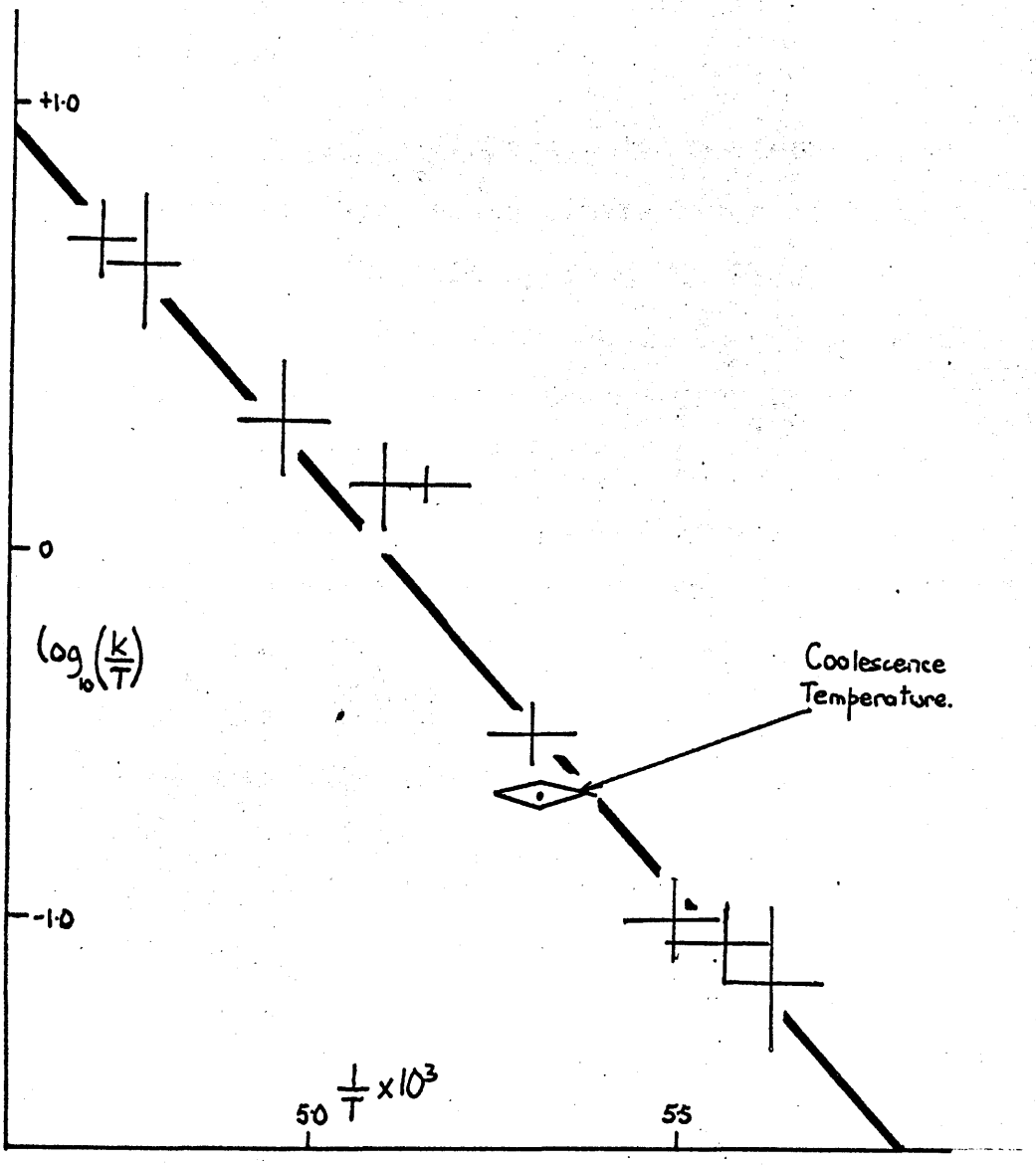


Figure 14 Graphical plot of the results for the ring-inversion of 1,3-dioxane.

derived from figures in Table 9 is shown in Figure 14. From this plot the following parameters were obtained. $\Delta H^{\#}$ = 10.2±1.0kcal/mole; $\Delta S^{\#}$ = +6.2±5.2e.u.; $\Delta G^{\#}$ = 9.0±0.2kcal/mole.

3.4 5,5-Dimethyl-1,3-dioxane. The room-temperature spectrum comprises three sharp single lines of relative heights 1:2:3, at 5.30τ, arising from the O—CH_2—O protons, at 6.59τ, arising from the O—CH_2—C protons, and at 9.10τ, corresponding to the C—$C(CH_3)_2$—C protons. On cooling below -30°C, the signals begin to broaden, and each in turn splits, the O—CH_2—O and C—$C(CH_3)_2$—C signals at about -58°C, and the O—CH_2—C signal at about -62°C. At -96°C each signal is well resolved, and the spectrum at this temperature is shown diagrammatically in Figure 15. The axial-equatorial

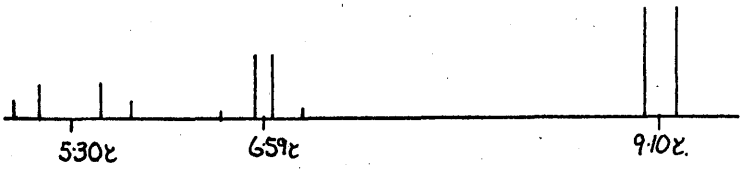


Figure 15
Diagram of the Spectrum of 5,5-Dimethyl-1,3-dioxane at -90°C

coupling constants are shown along with the chemical shifts in Table 10.

Signal	O—CH_2—O	O—CH_2—C	C—$C(CH_3)_2$—C
$\delta\nu_0$(a-e) . (cps)	30.4 ± 0.4	10.3 ± 0.8	27.1 ± 0.9
J(a-e) . . .(cps)	6.0 ± 0.1	10.4 ± 0.7	—

Table 10 NMR data for 5,5-dimethyl-1,3-dioxane.

In this case all three signals can be treated to give rate constants, but there are small temperature ranges where particular signals are not suitable.

At the higher temperatures, for example where the broadening of the O—CH_2—O and C—$C(CH_3)_2$—C signals is being measured, the O—CH_2—C signal has not begun to broaden. At intermediate temperatures some of the signals are so broad that instrument noise prevents accurate measurements being made. As in the case of 1,3-dioxane, the equatorial O—CH_2—O signal shows signs of long-range coupling, and in this case it is possible to confirm this coupling from the spectrum of the O—CH_2—C protons (with which the coupling would be expected to take place) where the signals again have slightly different breadths, see figure 16.

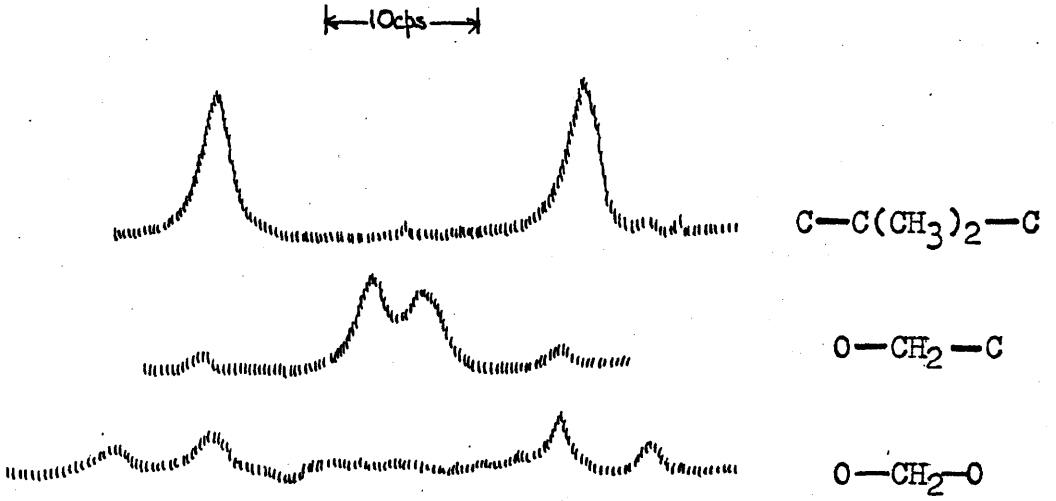


Figure 16 The various proton signals in the spectrum of 5,5-dimethyl-1,3-dioxane at -96°C.

The slow exchange equation can be used on the O—CH_2—O

Temperature (°K)	Signal Observed		Rate Constant k_1 (sec^{-1})	Value of k_1 used for graph.
207.4	O—CH_2—O	d	24.2 ± 4.4	22.6 ± 5.7
207.4	C—$C(CH_3)_2$—C	d	18.2 ± 1.3	
207.4	C—$C(CH_3)_2$—C	b	26.2 ± 5.6	
209.5	C—$C(CH_3)_2$—C	d	22.1 ± 1.8	22.1 ± 1.8
211.2	C—$C(CH_3)_2$—C	d	24.2 ± 1.6	27.7 ± 6.1
211.2	C—$C(CH_3)_2$—C	b	31.2 ± 7.3	
212.0	O—CH_2—C	c	22.9 ± 1.8	22.9 ± 1.8
215.5	C—$C(CH_3)_2$—C	c	60.2 ± 2.0	63.8 ± 2.6
215.5	O—CH_2—O	c	67.5 ± 0.9	
216.4	C—$C(CH_3)_2$—C	a	90.2 ± 12.0	96.3 ± 19.5
216.4	O—CH_2—C	a	102 ± 16.9	
223.2	O—CH_2—O	a	231 ± 56.3	199 ± 77
223.2	O—CH_2—C	a	189 ± 98.9	
223.2	C—$C(CH_3)_2$—C	a	178 ± 26.0	
227.2	O—CH_2—C	a	298 ± 103	330 ± 97
227.2	C—$C(CH_3)_2$—C	a	308 ± 42.0	
227.2	O—CH_2—O	a	383 ± 54.0	
230.2	C—$C(CH_3)_2$—C	a	469 ± 106	472 ± 100
230.2	O—CH_2—C	a	476 ± 168	
234.2	O—CH_2—O	a	816 ± 86.0	806 ± 155
234.2	C—$C(CH_3)_2$—C	a	796 ± 131	

Table 11 Rate Constants for the Ring-inversion of 5,5-Dimethyl-1,3-dioxane. Column three shows the method of treating data, see page 52.

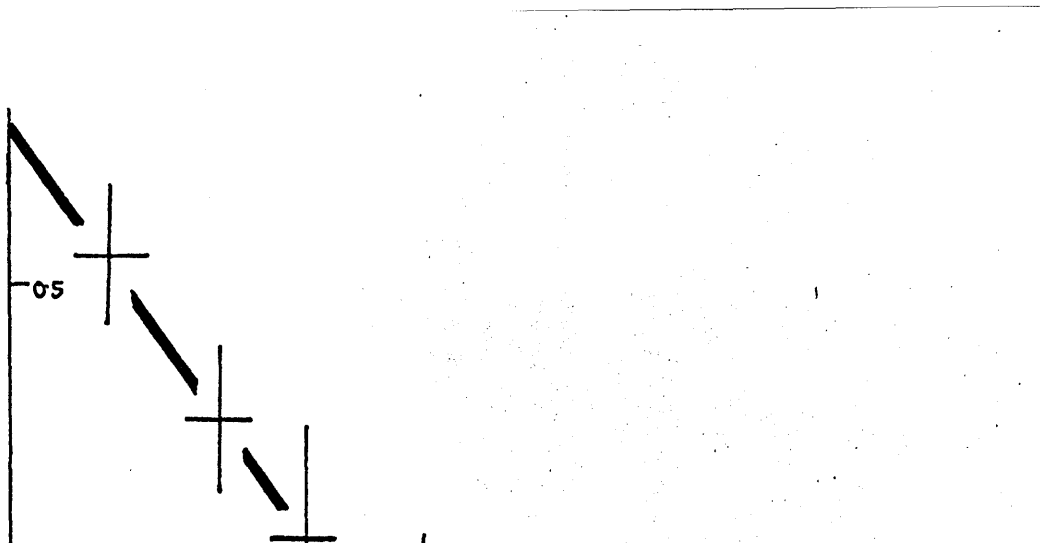


Figure 17 Graphical plot of the results for 5,5-Dimethyl-1,3-dioxane.

signals immediately below the coalescence temperature for the small broadening due to weak coupling is relaxed out by ring inversion. At low temperatures the two strong peaks of the O—CH_2—C AB quartet, whose separation is only 4cps, are not discrete and so are not treated using the slow-exchange equation.

Rate constants determined at various temperatures are shown in Table 11. A plot of log(k/T) against 1/T based on Table 11 is shown in Figure 17. From this graph the parameters for the ring inversion of 5,5-dimethyl-1,3-dioxane are $\Delta H^{\#}$ = 12.4±0.8kcal/mole; $\Delta S^{\#}$ = +9.5±3.5 e.u.; $\Delta G^{\#}$ = 10.5±0.2kcal/mole

3.5 2,2-dimethyl-1,3-dioxane. The spectrum of this compound at room temperature comprises three signals. At 6.19τ there is a 1:2:1 triplet (J = 5.7cps) which is assigned to the O—CH_2—C protons. At 8.26τ there is a 1:4:6:4:1 quintuplet (J = 5.7cps) corresponding to the C—CH_2—C protons. At 8.69τ there is a strong single line assigned to the O—$C(CH_3)_2$—O protons.

Thus, only the signal of the gem-dimethyl group is suitable for treatment. On cooling to -90°C, the signal begins to broaden, and at -126°C the broadened signal resolves into a doublet which at -150°C has a chemical shift of 10.8±0.3cps, see Figure 18. The signal is suitable for treatment by all four equations of Section 1.12 in turn. The values of the rate constant

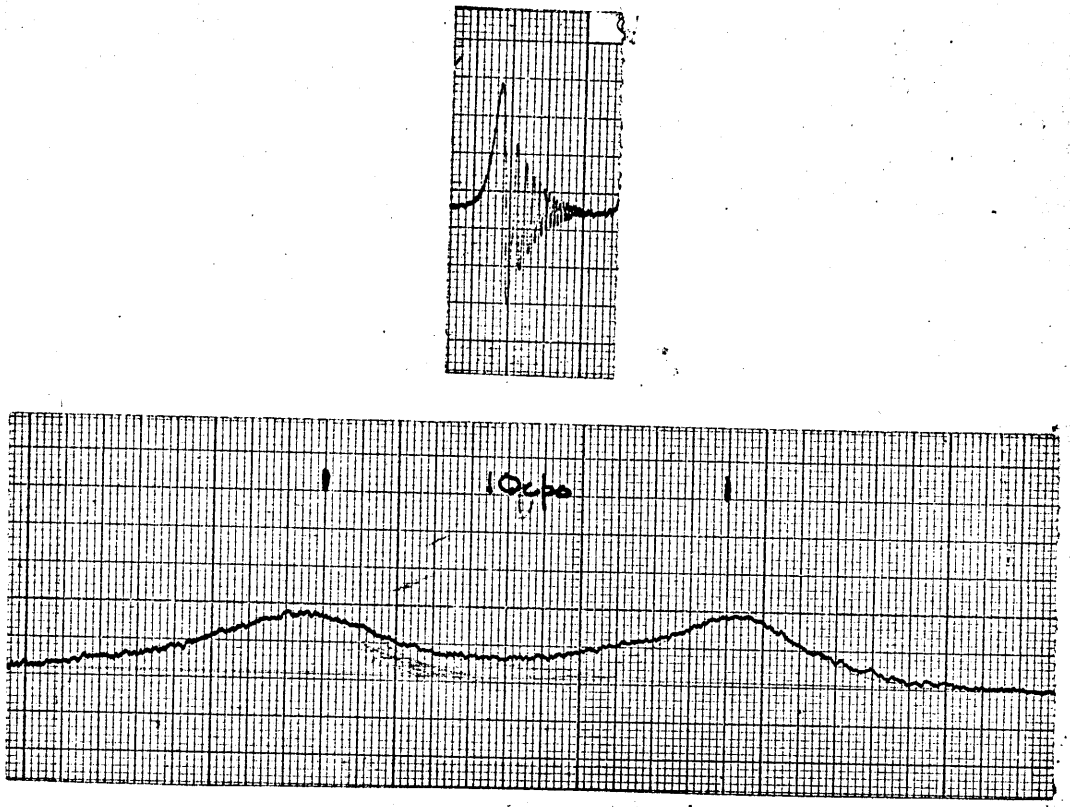


FIGURE 18 The Methyl Proton Spectrum of 2,2-Dimethyl-1,3-dioxane and, above, the reference acetone signal recorded at -150°C.

Temperature (°K.)	Rate Constant k_1 (sec^{-1})	
134.1	6.60 ± 0.94	d
139.1	11.4 ± 2.4	b
144.9	15.4 ± 1.5	b
147.0	24.0 ± 0.7	c
150.0	50.3 ± 2.2	a
151.9	74.8 ± 4.5	a
156.0	92.5 ± 8.8	a
164.7	247 ± 29	a
169.4	417 ± 96	a
179.4	1404 ± 253	a

Table 12 Rate constants for the ring inversion of 2,2-Dimethyl-1,3-dioxane. Column three indicates the method used, see page 52.

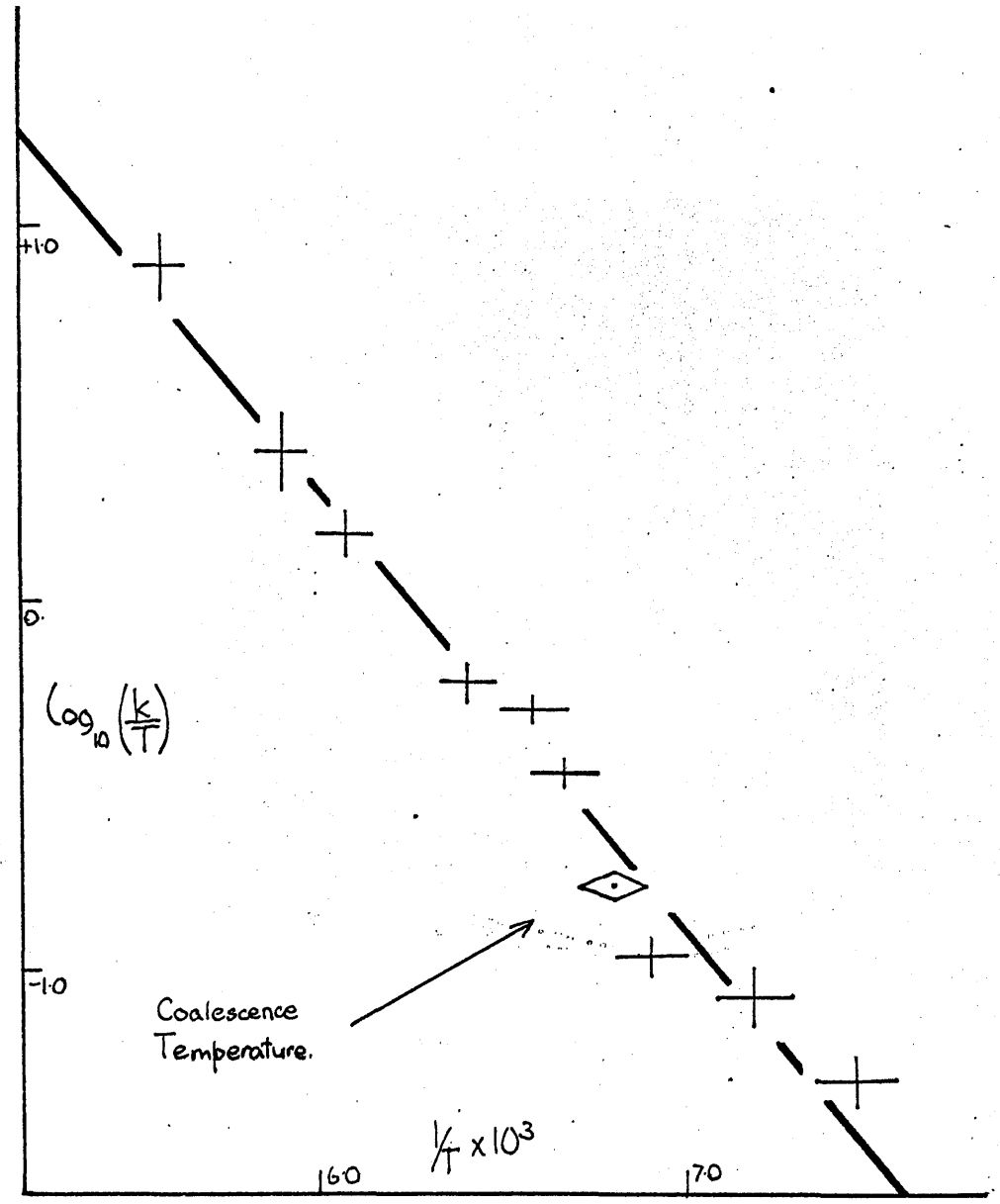


Figure 19 Graphical Plot of the results for the ring inversion of 2,2-Dimethyl-1,3-dioxane.

k obtained at various temperatures is shown in Table 12, while Figure 19 shows the plot of log(k/T) against 1/T based on this table. From the graph, the values obtained for the kinetic constants are $\Delta H^{\#} = 5.6 \pm 0.6$ kcal/mole; $\Delta S^{\#} = -12.4 \pm 3.5$ e.u.; $\Delta G^{\#} = 8.1 \pm 0.2$ kcal/mole.

3.6 2,2,5,5-Tetramethyl-1,3-dioxane. The spectrum of this compound at room temperature comprises three lines of relative intensities 2:3:3. The line at lowest field assigned to the O—CH_2—C protons is at 6.60τ; the signal corresponding to the O—$C(CH_3)_2$—O protons is at 8.69τ, while the C—$C(CH_3)_2$—C signal appears at 9.11τ.

All signals should be suitable for treatment. On cooling below -70°C the O—CH_2—C and C—$C(CH_3)_2$—C signals begin to broaden; they split into an AB quartet and a doublet respectively at about -100°C. The O—$C(CH_3)_2$—O signal begins to broaden only a little above its coalescence temperature of -108°C. Figure 20 shows the three signals in the spectrum at -130°C., while Table 13 shows the chemical shifts and coupling constants of the low-temperature spectrum.

Proton Signal.	O-CH_2—C	C—$C(CH_3)_2$—C	O—$C(CH_3)_2$—O
Chemical Shift	6.60τ	8.69τ	9.11τ
$\delta\nu_{a(a-e)}$ (cps)	24.0 ± .5	24.2 ± 0.2	3.3 ± 0.1
$J_{(a-e)}$ (cps)	11.6 ± .2	——	——

Table 13 NMR data for tetramethyl-1,3-dioxane at -130°C.

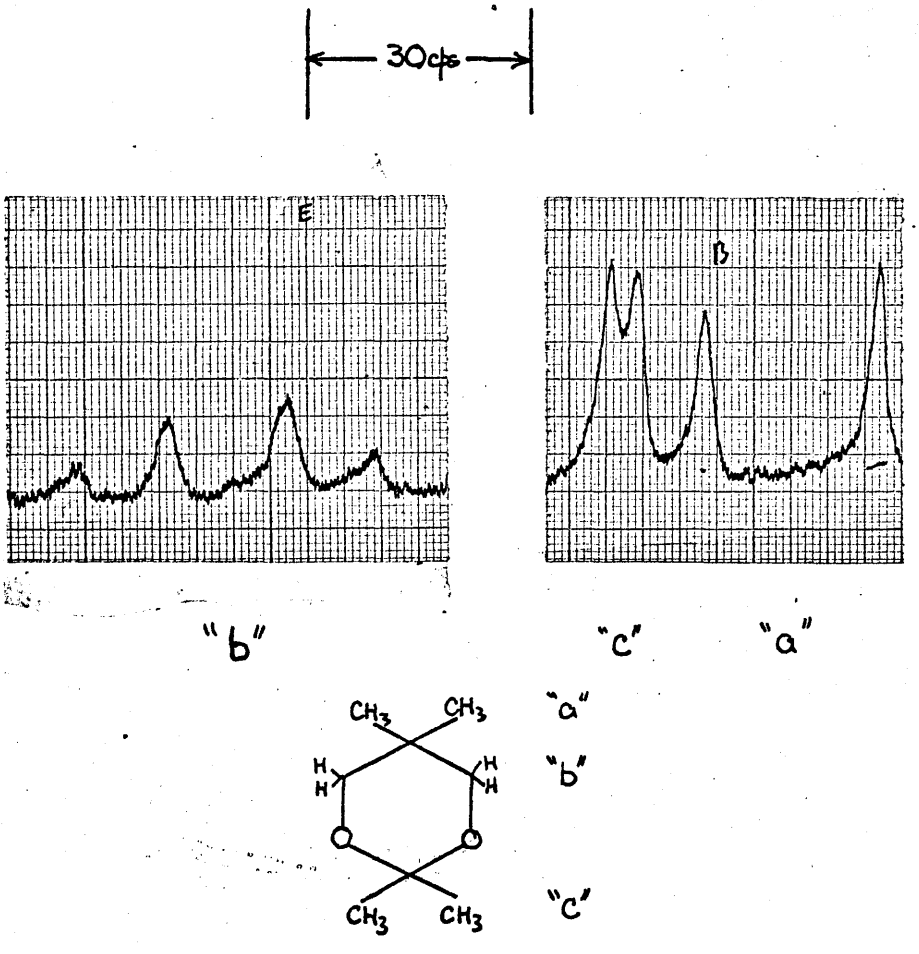


Figure 20 Spectrum of 2,2,5,5-tetramethyl-1,3-dioxane at -130°C.

Temperature (°K)	Signal Examined.		Rate Constant k_1, (sec^{-1})	Value of k_1 used for graph
196.4	O—CH_2—C	a	1136 ± 216	1122 ± 288
196.4	C—$C(CH_3)_2$—C	a	1108 ± 191	
189.2	O—CH_2—C	a	545 ± 75	611 ± 138
189.2	C—$C(CH_3)_2$—C	a	677 ± 116	
187.7	O—CH_2—C	a	334 ± 37	334 ± 37
182.3	O—CH_2—C	a	281 ± 46	365 ± 94
182.3	C—$C(CH_3)_2$—C	a	449 ± 82	
181.8	O—CH_2—C	a	195 ± 20	173 ± 43
181.8	C—$C(CH_3)_2$—C	a	152 ± 38	
175.8	O—CH_2—C	a	81.6 ± 22	97.3 ± 23
175.8	C—$C(CH_3)_2$—C	a	113 ± 7.0	
174.9	O—CH_2—C	c	53.3 ± 1.1	53.5 ± 1.2
174.9	C—$C(CH_3)_2$—C	c	53.7 ± 0.4	
174.0	O—CH_2—C	b	28.1 ± 1.2	36.3 ± 8.1
174.0	C—$C(CH_3)_2$—C	b	44.5 ± 3.1	
166.1	O—CH_2—C	d	10.7 ± 1.9	14.0 ± 3.3
166.1	C—$C(CH_3)_2$—C	d	17.3 ± 1.6	
165.8	O—$C(CH_3)_2$—O	c	7.8 ± 0.2	7.8 ± 0.2
165.5	C—$C(CH_3)_2$—C	d	8.23 ± 1.4	8.2 ± 1.4
164.7	C—$C(CH_3)_2$—C	d	8.4 ± 1.2	8.4 ± 1.2
163.1	C—$C(CH_3)_2$—C	d	6.7 ± 1.2	6.7 ± 1.2

Table 14 Rate Constants for the ring inversion of 2,2,5,5-tetramethyl-1,3-dioxane. Column three indicates the method of analysis used, see page 52.

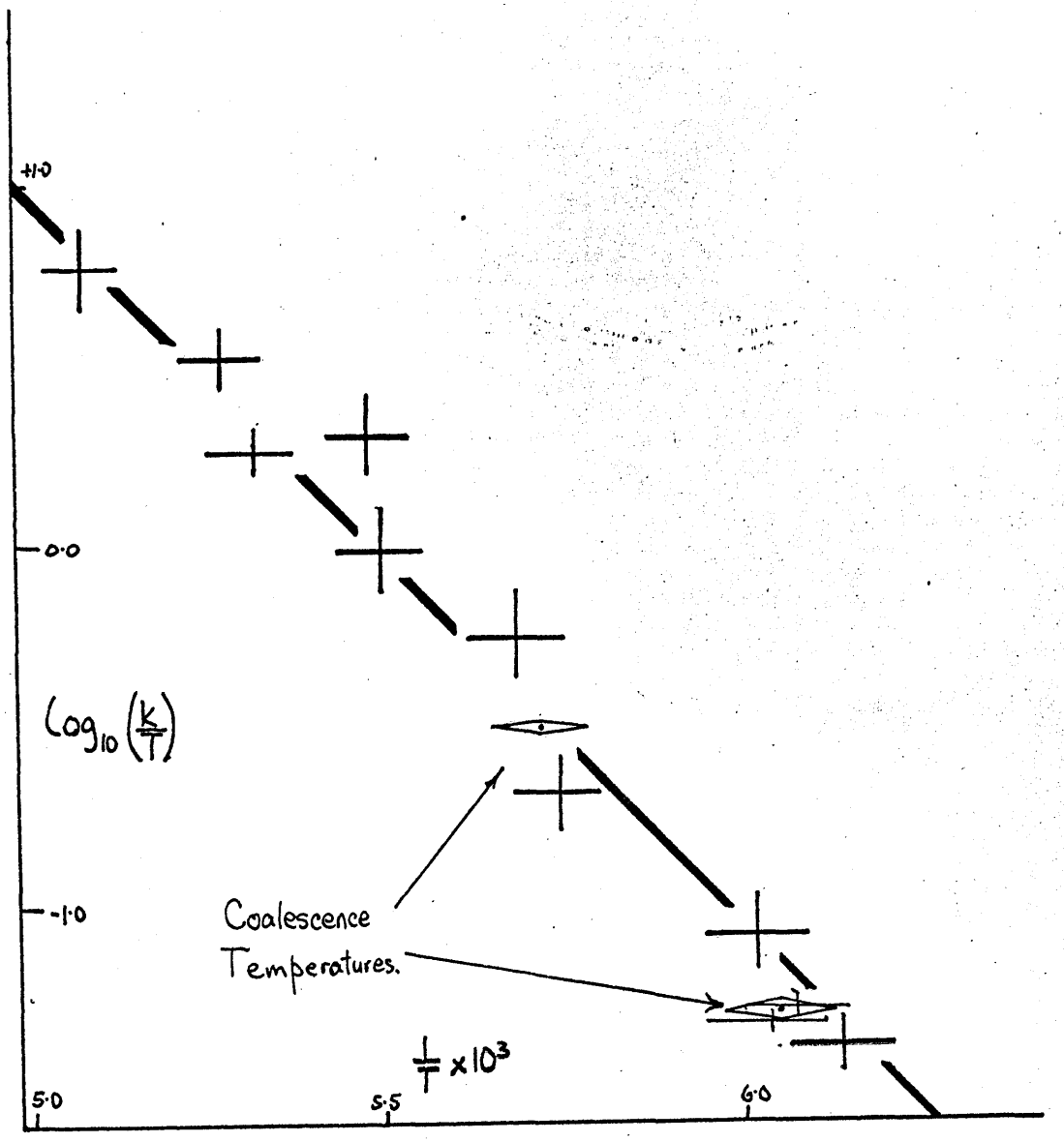


Figure 21 Graphical plot of the results for the ring inversion of 2,2,5,5-tetramethyl-1,3-dioxane

It was found that the $O—C(CH_3)_2—O$ spectrum was unsuitable for treatment by any equation other than that for the temperature of coalescence. The fast exchange equation (Equation 7, 1.12) requires that γshould be small compared with T_2; because of the low value of $\delta\nu_o$ this is not the case for this signal. The slow exchange equation (Equation 1, 1.12) cannot be applied for the signals always overlap slightly. The intermediate exchange equation applies over only a small range of temperature, and is subject to large errors since only small differences are being measured.

Thus, apart from the temperature of coalescence, results are derived from the $O—CH_2—C$ and $C—C(CH_3)_2—C$ signals only. Values of the rate constant k obtained are shown in Table 14. The graphical plot based on these results is shown in Figure 21 and gives the following values for the parameters of the ring-inversion reaction - $\Delta H^{\#} = 9.1 \pm 0.9$kcal/mole; $\Delta S^{\#} = +3.8 \pm 4.8$e.u.; $\Delta G^{\#} = 8.3 \pm 0.2$kcal/mole.

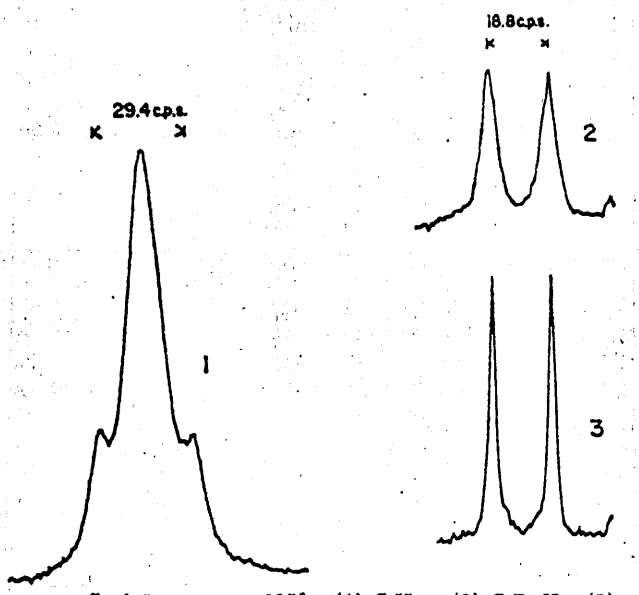
3.7 There are three additional facts of relevance to a discussion of the trioxane results. Firstly, Busetti et al. (67) have shown that in the crystal trioxane adopts a cyclohexane-like chair form with all bond angles very nearly tetrahedral. This suggests that in solution the structure is likewise that of a chair.

Secondly, the effect on ring inversion of a six-membered ring of replacing carbon atoms by oxygen atoms in the ring skeleton has been shown in other work in this thesis. Thus $\Delta G^{\#}$ for cyclohexane is 10.3 kcal/mole (14, 15); for 1,3-dioxane, $\Delta G^{\#}$ is 9.0 kcal/mole. An extrapolation of these results would suggest a value of about 8.0kcal/mole for $\Delta G^{\#}$ for trioxane.

The third and most significant fact is the history of investigations into the ring inversion of cyclooctane. Harris and Sheppard (39) first investigated this and reported in 1961 that the single-line spectrum begins to broaden below -85°C, but is still not split at -113°C. Using a treatment similar to the one used in Section 3.1 for trioxane, they found $\Delta H^{\#} = 2.6 \pm 0.9$kcal/mole, and assuming a chemical shift similar to that in cyclohexane they found $\Delta S^{\#} \sim -30$e.u. In 1963, Anet and Hartman (30) prepared quindecadeuterocyclooctane, and by a method similar to that they used for cyclohexane (15, see Section 1.18), they found the following unequivocal values for the kinetic parameters - $\Delta H^{\#} = 7.7 \pm 0.3$kcal/mole; $\Delta S^{\#} = -4.4$e.u.; temperature of coalescence = -111.5°C.

It appears that because of complex spin-spin couplings, encountered previously in cyclohexane, the low-temperature spectrum of cyclooctane at no time resolves into a doublet. Anet has shown (30) that even

at -135°C, well below the coalescence temperature for the deuterocycloöctane, the spectrum of cycloöctane itself shows no sign of such a doublet, see Figure 22.



Cycloöctane at −135°: (1) C_8H_{16}; (2) $C_8D_{15}H$; (3) $C_8D_{15}H$, D decoupled.

Figure 22 Cycloöctane spectra at -135°C; recorded by Anet (30).

This explains why what appear to be reasonable assumptions have led Harris and Sheppard to results which are incorrect.

There are some likenesses between Harris and Sheppard's work and the present report on trioxane. If these results are valid the barrier is remarkably low, while the entropy of activation is much more negative than any value found in accurate work on other ring compounds, though much the same as that found for cycloöctane by Harris and Sheppard. Likewise the assumptions made in both cases are similar.

The explanation proposed in Harris and Sheppard's case will not apply directly in the trioxane case, for the low temperature spectrum should be a simple AB quartet. If however the coupling constant between axial and equatorial protons is large compared with the chemical shift between them, say $J_{a-e} = 2\delta\nu_{a-e}$, which is not inconceivable, the calculated low-temperature is as shown in Figure 23 (68). In a case such as trioxane, this would mean that the separation between the two inner lines would be less than 1cps

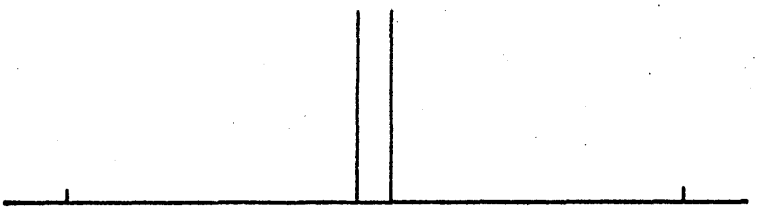
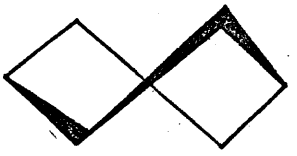


Figure 23 Calculated AB spectrum, $J_{ab} = 2\delta\nu_{ab}$.

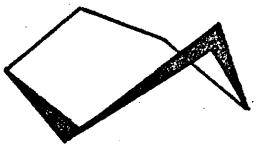
and so, because of the limitation on field homogeneity at temperatures below -100°C, no splitting would be observed. The two outer lines would be so weak as to be masked by instrumental noise. This is offered as a possible explanation for the lack of success in the examination of trioxane.

The work on trioxane is then, inconclusive. This has been the experience of Anet (65) with the same compound.

3.8 It is now recognised (69, 70) that the most likely path for a ring inversion in cyclohexane and similar molecules passes through a boat-form. Hendrickson (69) has shown that the skew boat conformation (D36) is slightly more stable than that of the

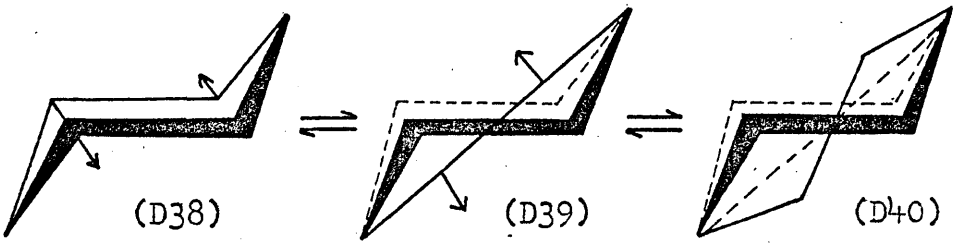


(D36)



(D37)

conventional boat (D37), and has suggested a direct route from the chair form to the skew-boat form involving rotation about two bonds, see Figure 24.



(D38) chair (D39) cyclohexene-like (D40) skew-boat

Figure 24 Proposed route for cyclohexane inversion (69).

The cyclohexene-like structure (D39) is postulated as the transition state on this route. Hendrickson then assumed that the inversion process is completed by a rapid isomerisation among the various possible skew-boat forms (each such isomerisation involving a transition state of the true-boat structure), followed eventually by a reversal of the process shown in Figure 24 to give another chair form.

The resultant potential diagram is shown in Figure 25.

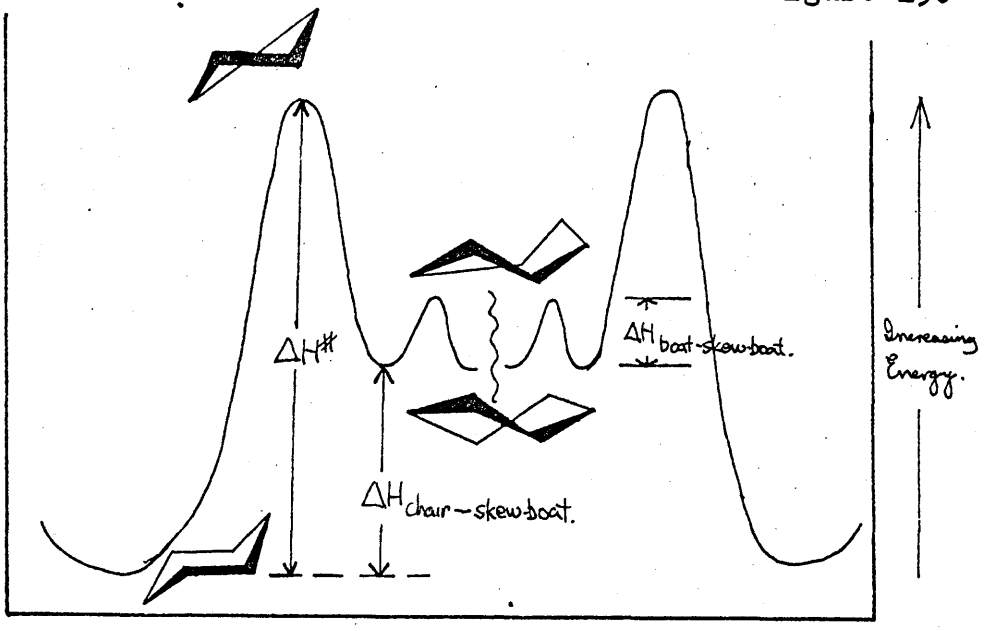


Figure 25 Potential Diagram for the ring-inversion of cyclohexane (Ref. 69).

Hendrickson (69) then considered in turn each of the four structures, chair, cyclohexene-like, skew-boat and true-boat, and calculated the energy of each, assuming that strain could arise from three sources, and taking as his zero of energy a hypothetical structure in which all these strains are absent. The three sources of strain are bond-angle strain, interactions between hydrogen atoms on adjacent carbon atoms, 1,2-interactions, and interactions between axial hydrogen atoms on alternate carbon atoms, 1,3-interactions.

From his calculations Hendrickson was able to predict values for certain of the parameters for the ring inversion, and these are shown along with recent

experimentally observed values in Table 15. (Added in Proofs - Table 15 also shows values of the inversion parameters calculated by Simmons and Williams (78, September, 1964) based on the same sources of strain but calculating their magnitude in a different way).

Parameter	Calculated Value		Observed Value	
	Ref. 69	Ref. 78		
$\Delta H^{\ddagger}$	12.7	11.7	10.9 10.5	Ref. 15 Ref. 14
$\Delta H_{chair-skew\text{-}boat}$	5.3	5.6	5.9 5.5	Ref. 71 Ref. 72

Table 15 Calculated and observed values for cyclohexane ring inversion parameters. Values in kcal/mole.

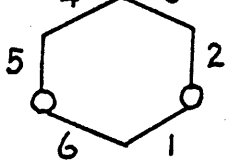
The agreement between calculated and observed values is very satisfactory, and suggests that the proposed mechanism for inversion is reasonably correct.

The shape of the potential diagram indicates the choice of $\frac{1}{2}$ as the value of the transmission coefficient. Every molecule that crosses the energy barrier $\Delta H^{\ddagger}$ from the chair form then enters the slough of the various boat and skew-boat forms. There is an equal possibility that when the molecule leaves the slough it will either return to its original chair form, or complete the inversion. This equal possibility is allowed for in the choice of $\frac{1}{2}$ as the

transmission coefficient.

In the light of this mechanism, a discussion on the relative values of reaction parameters in the dioxanes now follows. This will be in terms of $\Delta G^{\#}$. Discussion on the relative values of $\Delta S^{\#}$ will be carried out separately in Section 3.11

3.9 The free energy of activation for the inversion process in 1,3-dioxane has been found to be 9.0kcal/mole compared with 10.2kcal/mole for cyclohexane (14, 15). From the diagram (Figure 24) of the mechanism for ring inversion, it can be seen that rotation about two alternate bonds is sufficient to bring about the inversion. In 1,3-dioxane all the bonds are not of the same type, there being carbon-carbon bonds and carbon-oxygen bonds in the proportion two to four (D41), so that



(D41)

if the two alternate bonds whose rotation is necessary for inversion are chosen at random, there is a statistical probability that the two bonds will be $1\frac{1}{3}$ carbon-oxygen and $\frac{2}{3}$ carbon-carbon.

Now Pitzer (73) has determined the barrier to rotation in propane $CH_3CH_2CH_3$ as 3.4kcal/mole, while

Kasai and Myers (74) have found the barrier in dimethyl-ether CH_3OCH_3 to be 2.7kcal/mole, 0.7kcal/mole less. Thus if the statistical probability in the choice of bonds rotating is followed, one might expect a reduction in the energy of activation for the inversion of $1\frac{1}{3} \times 0.7 = 0.9$kcal/mole.

This explanation of the lower barrier in 1,3-dioxane is over-simplified of course, but it does show that the change one would expect to result from replacing two CH_2-groups by two oxygen atoms is of the magnitude of that observed.

3.10 It does emerge from the results reported for the various substituted dioxanes that the free energy of activation for the inversion of 5,5-dimethyl-1,3-dioxane is higher than that of 1,3-dioxane, while the 2,2-dimethyl isomer has a lower value than 1,3-dioxane, see Table 16.

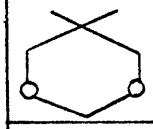
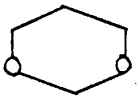
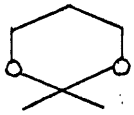
Compound	$\Delta G^{\#}$ (kcal/mole)
 5,5-dimethyl-1,3-dioxane	10.5
 1,3-dioxane	9.0
 2,2-dimethyl-1,3-dioxane	8.1

Table 16 Free energy of activation for the ring inversion of 1,3-dioxanes.

The difference between the 5,5-dimethyl compound and dioxane itself can readily attributed to the greater 1,2-interactions during rotation between the methyl groups and hydrogen atoms on the adjacent carbon atoms.

In 2,2-dimethyl-1,3-dioxane, the methyl groups are located between two oxygen atoms so that there will be no 1,2-hydrogen-methyl interactions on rotation. There will be interactions between the methyl groups and the lone pairs of electrons on the oxygen atoms, but it has now been fairly conclusively shown (75, 76) that the volume requirements of a lone pair are less than those of a bonded hydrogen atom. On this basis one would expect that the barrier to rotation in the 2,2-dimethyl compound would be greater than that of dioxane itself but smaller than that of the 2,2-dimethyl compound, which is not the position found experimentally.

Since the activation energy for inversion is the difference in energy between the cyclohexene-like transition state and the chair-form ground state, the particularly low value for 2,2-dimethyl-1,3-dioxane may be the result of a lower than normal energy of the transition state or a higher than normal energy of the ground state. Friebolin et al. (49), on the basis of their rather rough work using temperatures of coalescence have indicated what appears to be the correct

explanation.

A carbon-oxygen covalent bond is normally about 1.43Å long which is 0.11Å shorter than the normal carbon-carbon bond. This brings about a reduction in the size of the ring in 1,3-dioxanes compared with cyclohexane, and particularly it reduces the separation of the axial proton on carbon atom 2 and axial protons on carbon atoms 4 and 6. An examination of molecular models suggests that in dioxane itself, this separation is ~2.4Å compared with ~2.56Å in cyclohexane. The value of 2.4Å is still not less than the combined van der Waal's radii of the two hydrogen atoms which is itself about 2.4Å (77). The axial proton at the 5-position is not affected to such a large extent, the bond shortening being at the other end of the ring and in addition, the corresponding 1,3-interaction in this case is between the axial proton and two lone pairs whose steric requirements are smaller (75, 76, see above).

Leaving the unsubstituted dioxane and comparing 2,2-dimethyl-1,3-dioxane and 5,5-dimethyl-1,3-dioxane, the difference between the 2- and the 5-positions with reference to 1,3-interactions becomes clear. The protons of the axial methyl group in the 2,2-dimethyl compound are very much nearer the axial protons on carbon atoms 4 and 6 than their combined van der Waal's radii. As a result there will be considerable energy of interaction

in the ground state chair form arising from the distortion necessary to accomodate these interactions. Thus the ground state of 2,2-dimethyl-1,3-dioxane is of relatively high energy, and since the 1,3-interactions are not present in the cyclohexene-like transition state, the result is that the energy of activation for ring inversion is low in this compound.

In the 5,5-dimethyl compound, the axial methyl group and the axial lone pairs are not as near to each other as the proton and the methyl group in the 2,2-dimethyl isomer. In addition it has been shown that a lone pair is "smaller" than a bonded hydrogen atom. Thus, the energy of interaction present in the 2,2-dimethyl compound, and the cause of its low barrier to inversion, is absent in the 5,5-dimethyl isomer, and as a result the barrier is higher.

The effect of 1,3-interactions of raising the energy of the ground state and thus lowering the activation energy for ring inversion explains why Harris and Sheppard (39) were unable to bring about splitting of the methyl-proton spectrum of 1,1-dimethyl-cyclohexane even at -120°C.

In the tetramethyl compound the two factors operating in the dimethyldioxanes balance out to some extent. Thus, because of the presence of four methyl groups, the interactions between these groups and

hydrogen atoms or lone pairs on adjacent atoms, which take place during rotation, are greater and the barrier is increased. There are however 1,3-interactions between the axial methyl group in the 2-position and protons on carbon atoms 4 and 6, and since these raise the energy of the ground state chair form, they lower the barrier to inversion. Thus, the activation energy of ring inversion in tetramethyl dioxane is between that of 2,2-dimethyl-1,3-dioxane and that of 5,5-dimethyl-1,3-dioxane.

3.11 In so far as a ground state chair form is much more rigid than a transition state skew-boat or cyclohexene-like form, one would expect the entropy of activation for a ring inversion to be positive. Further, using calculations based on changes of symmetry between the ground state and the transition state, Jensen (13) and Bovey (41) have calculated values for this entropy of activation for cyclohexane of +4.9e.u. and +7.1e.u, respectively.

On these two bases, the entropies of activation for the inversion of 1,3-dioxane, 5,5-dimethyl-1,3-dioxane and 2,2,5,5-tetramethyl-1,3-dioxane would appear to be of reasonable magnitude and sign (see Table 17, over). Bovey (41) has pointed out however

that symmetry considerations alone are inadequate for

Dioxane	$\Delta S^{\#}$ (e.u.)
1,3-dioxane	+6.2 5.2
5,5-dimethyl-1,3-dioxane	+9.5 3.5
2,2-dimethyl-1,3-dioxane	-12.4 3.5
2,2,5,5-tetramethyl-1,3-dioxane	+3.8 4.8

Table 17 Entropy of activation for the ring inversion of 1,3-dioxanes.

predicting entropies of activation.

The most remarkable of the values in Table 17 is the high negative value for 2,2-dimethyl-1,3-dioxane. Symmetry considerations and the variations of rigidity mentioned above would suggest that the value of $\Delta S^{\#}$ in this case should be no different from that of 5,5-dimethyl-1,3-dioxane. Bovey's caution is well-justified.

We have postulated above that the low free energy of activation in the 2,2-dimethyl case arises from steric strain in the ground state due to 1,3-interactions. An examination of the six-membered ring compounds in Tables 2 and 3 of Chapter One shows that there are three other cases where the entropy of activation for ring inversion is large and negative, see Table 18, over, and it is significant that in each

case there appear to be strong interactions. In perfluorocyclohexane, Tiers (40) specifically suggests

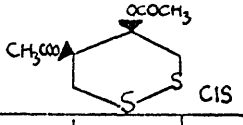
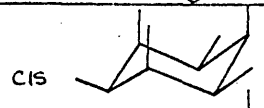
Diagram	Compound	$\Delta S^{\#}$ (e.u.)	Ref.
——	Perfluorocyclohexane	-10.7	40
D22		~-7	53
D16		-27.8+	42
D17		-27.1+	42
D18		-27.4+	42

Table 18 Compounds with a high negative entropy of activation for ring inversion (+ indicates values calculated from reported frequency factors).

that there are large fluorine-fluorine 1,3-interactions in an attempt to explain other effects. In (D22), the two acetate groups are cis to each other in a gauche conformation, and thus there must be large interactions in the ground state. Finally, in the inositol hexa-acetates of Brownstein's study, (42), no matter what chair conformation is adopted, there are always two axial acetate groups which will interact strongly.

It appears that while there is no apparent explanation for a highly negative entropy of activation, such a value may be diagnostic of steric strain in the ground state chair form of a six-

membered ring.

There is some support for this hypothesis in Bovey's observation that the entropy of activation for the ring inversion of cyclohexyl fluoride (F equatorial) where there are no F—H 1,3-interactions is greater than that of cyclohexyl fluoride (F axial) where there are F—H interactions, by 1.1e.u.

3.12 It is now possible to summarise the conclusions drawn.

1,3-Dioxane in the chair-form ground state has a slightly lower energy content than cyclohexane, since 1,3-interactions will be slightly smaller. The energy of dioxane's transition state is markedly lower because 1,2-interactions are lower.

5,5-Dimethyl-1,3-dioxane in the ground state has a higher energy content than 1,3-dioxane since 1,3-interactions involving an axial methyl group will be greater than the corresponding interactions in dioxane. 1,2-Interactions in the transition state make the barrier to inversion noticeably larger than in 1,3-dioxane.

2,2-Dimethyl-1,3-dioxane will have a ground-state energy considerably larger than 1,3-dioxane because of well defined 1,3-interactions. Its energy content in the transition state will be a little

less than that of 5,5-dimethyl-1,3-dioxane, so that overall the barrier to inversion will be less even, than in 1,3-dioxane.

In the ground-state chair form, tetramethyl dioxane will have a higher energy content than the 2,2-dimethyl compound because of greater 1,2-interactions arising from the additional methyl groups. This same effect will be more pronounced in the transition state so that the barrier to inversion will be greater than in 2,2-dimethyl-1,3-dioxane.

The entropies of activation are of the magnitude and sign expected except for that of 2,2-dimethyl-1,3-dioxane. The low value in this case may be a diagnostic test for steric strain in the ground state.

CHAPTER FOUR

INTRODUCTION TO THE SOLVOLYSIS STUDIES

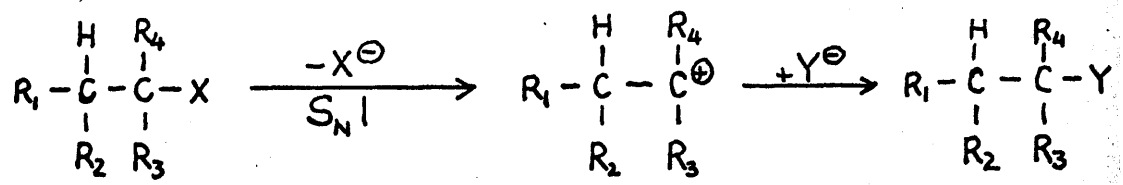
4.1 By the end of the decade 1920 to 1930, two alternate mechanisms for nucleophilic substitutions at a saturated carbon atom had been suggested.

Le Bel (101) had proposed that the introduction of the replacing group and the expulsion of the leaving group were two stages of a synchronous process; Lewis (102) in 1923 stated this theory in an electronic form. In 1925, Lowry (103) suggested that the compound substituted might first dissociate to give a carbonium ion which could then combine with the nucleophilic substituting group.

Following work carried out from 1927 to 1933, Hughes and Ingold (104) proposed a theory of nucleophilic substitution which suggested that in normal circumstances, substitution is achieved by one of two mechanisms. These mechanisms are similar to those pro-

posed earlier but are more precisely stated in a form which fits with experimental and particularly kinetic observations. These are the two well-known mechanisms S_N1 and S_N2. Since that time Hughes and Ingold have elaborated this theory (104) to show the effect of structure and reaction condition variations on the mechanism, in all cases verifying theoretical conclusions with experimental results.

4.2 Very much at the same time Hughes and Ingold developed an equivalent set of mechanisms for elimination reactions, designated E1 (105) and E2 (106). The rate-determining steps in E1 and S_N1 are identical as is shown in Figure 1.



Rate-determining step

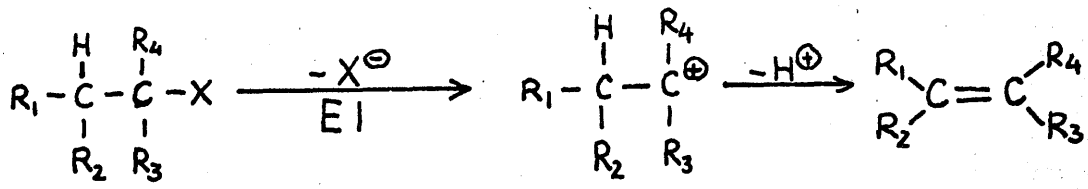


Figure 1

Thus when a study is being made of unimolecular nucleophilic substitution, unimolecular elimination will be a competing reaction, so that if one follows

the kinetics of reaction by observing the rate of disappearance of $R_1R_2CHC(R_3R_4)X$ or the rate of appearance of X^- ions, the observed rate will be that for a combination of substitution and elimination. Since both these processes have the same rate-determining step, the observed rate will be that of formation of the carbonium ion, so that when studying unimolecular substitution reaction kinetics, one should not worry if some of the product results from an elimination reaction.

4.3 Since 1935 numerous special cases have arisen which have required extensions of the Hughes-Ingold theory of substitution reactions. One example is optically active 1-phenylethyl alcohol (D1) which on

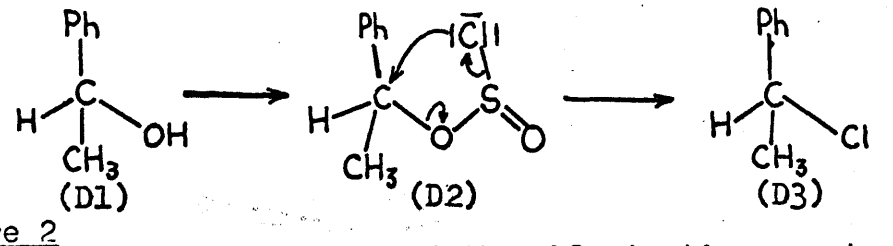


Figure 2

solvolysis in the presence of the chlorinating agent thionyl chloride gives 1-phenylethyl chloride (D3) of the same configuration (107). If the substitution follows an S_N2 mechanism the configuratuon should be reversed, while an S_N1 mechanism should bring about racemisation (108). Hughes and Ingold suggested that first of all hydrogen chloride is eliminated between the alcohol and thionyl chloride to give the compound (D2), which rearranges internally as shown to give the

chloride (D3) of the same configuration (109). They called this mechanism internal nucleophilic substitution S_Ni.

4.4 From about this time on and during the Second War, Winstein in California was investigating (110) participation in solvolyses by substituents adjacent to the reaction centre, so-called neighbouring group participation.

He showed for example (111) that the unimolecular solvolysis by silver acetate in acetic acid of meso-2,3-dibromobutane (D4=D5) goes with retention of configuration.

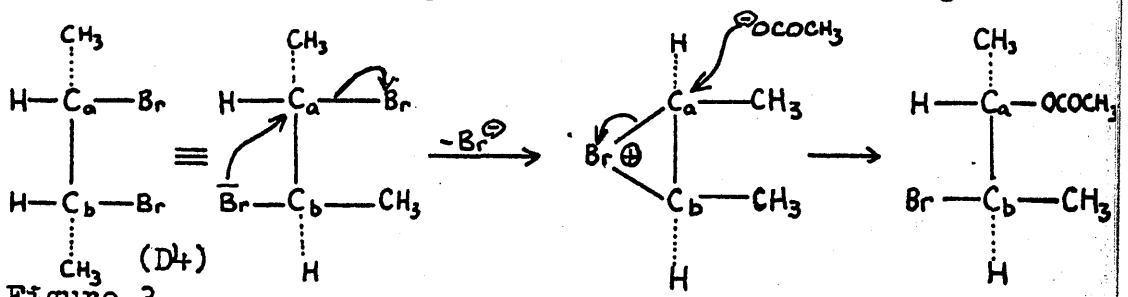


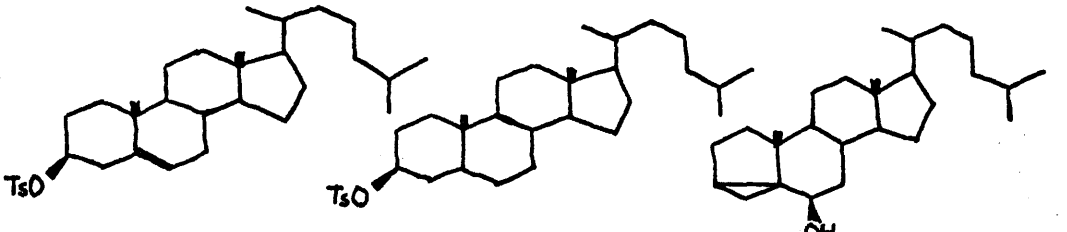
Figure 3

He considered that simultaneously with or immediately following the ionisation, an intermediate of the type (D6) is formed. This intermediate which has inverted configuration at carbon a., is broken down by the substituting acetate ion, again with inversion to give the bromo-acetate (D7), with the same configuration as the original dibromide (D5). He thus postulates retention of configuration by double inversion. By considering loss of the bromide ion as the rate-determining step, the mechanism is still unimolecular. Retention of configuration is such a striking phenomenon that its observation

in a unimolecular solvolysis is taken as a primary indication of neighbouring group participation.

4.5 Bridged ions of the type (D5) which are the origin from which non-classical carbonium ions developed, were first suggested in 1937 by Roberts and Kimball (112). Even as early as 1939, such ions were postulated in discussions of Wagner-Meerwein rearrangements of monoterpenes (113, and see later, section 4.8). An account of the development of the concept is given by Bethel and Gold (114)

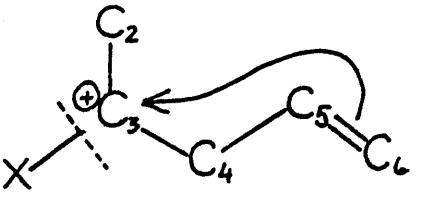
4.6 At the same time that Ingold and Hughes were developing their S_Ni theory (109), Stoll (115) reported that β-cholesterol toluene-p-sulphonate (tosylate), (D8)



(D8) (D9) (D10)

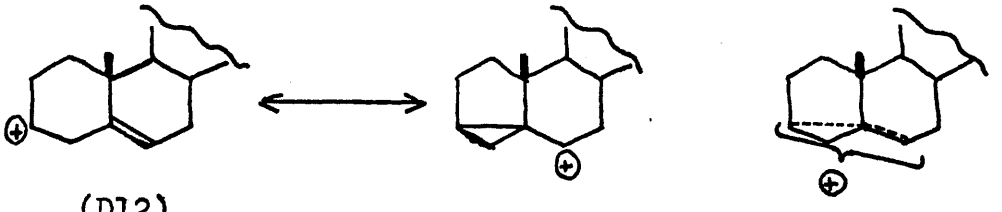
undergoes unimolecular solvolysis in boiling ethanol forty times faster than the corresponding saturated β-cholestanol ester (D9). Stoll merely reported this fact although the existence and structure of i-cholesterol (D10) were known at that time (116). It was not until 1946 that Shoppee (117) suggested that as a tosylate group separates to leave a carbonium ion, the electrons of the double bond are 'polarised', and interact with the carbonium ion to prevent its becoming planar and

thus racemising, and he gave the picture (D11).



(D11)

Immediately on the appearance of this paper, Winstein (118) published results on the kinetic aspects of the same problem, re-reporting and extending Stoll's work of 1937. He took the increased rate to indicate another example of neighbouring group participation, the participant here being an ethylenic double bond. He suggested that the intermediate carbonium ion is a mesomeric equilibrium of the forms (D12) and (D13),



(D12) (D13) (D14)

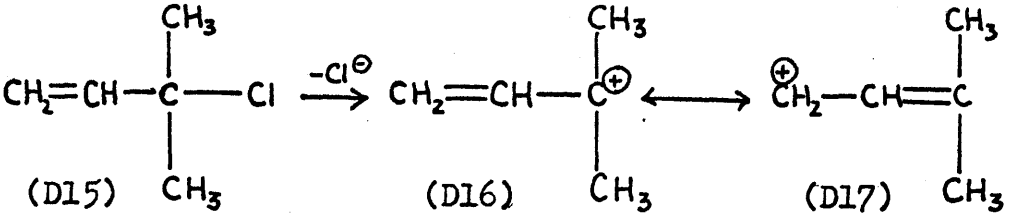
Figure 4.

which he represented by the structure (D14), and that the stabilisation of the reaction intermediate due to this mesomerism explained the increased rate of reaction.

Since that time many other examples of neighbouring group participation in substitutions have been reported (119). Some of these, relevant to the work described in this thesis are now discussed.

4.7 Another example of ethylenic double bond participation is the allylic system shown in Figure 5,

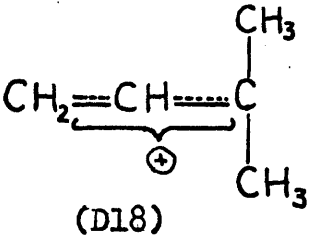
1,1-dimethylallyl chloride (D15), which when solvolysed



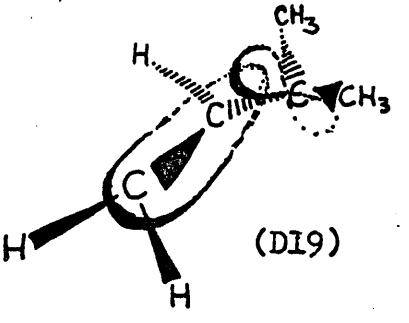
(D15) (D16) (D17)

Figure 5.

in 75% ethanol at 25°C. has a unimolecular rate constant $k_1 = 3.8 \times 10^{-3}$/sec. (120), while t-butyl chloride where the ethylene group has been replaced by a saturated methyl group has $k_1 = 2.1 \times 10^{-5}$/sec. (121), 180 times slower. This acceleration in the allyl chloride case has been explained (120), again as resulting from stabilisation of the intermediate carbonium ion. It is considered that when the ion (D16) forms, mesomerism between this and structure (D17) takes place; this can be represented by (D18).



(D18)



(D19)

A more realistic picture of this mesomerism is gained by noting that the vacant orbital of the carbonium ion overlaps (D19) the filled π-orbital of the double bond to give an orbital spread over three centres containing two electrons.

One can generally consider these neighbouring group effects in terms of overlap of filled orbitals

of the neighbouring group with the vacant carbonium ion orbital in a way similar to that illustrated above.

De la Mare and Vernon (120), were able to confirm that an intermediate of the type (D18) was formed by examining the reaction products. They found that in the ethanolysis of 3,3-dimethylallyl chloride (D20), the product was 60% 1,1-dimethylallyl ethyl ether (D21), and 40% of the 3,3-dimethyl isomer (D22), while ethanolysis of 1,1-dimethylallyl chloride (D15) gives

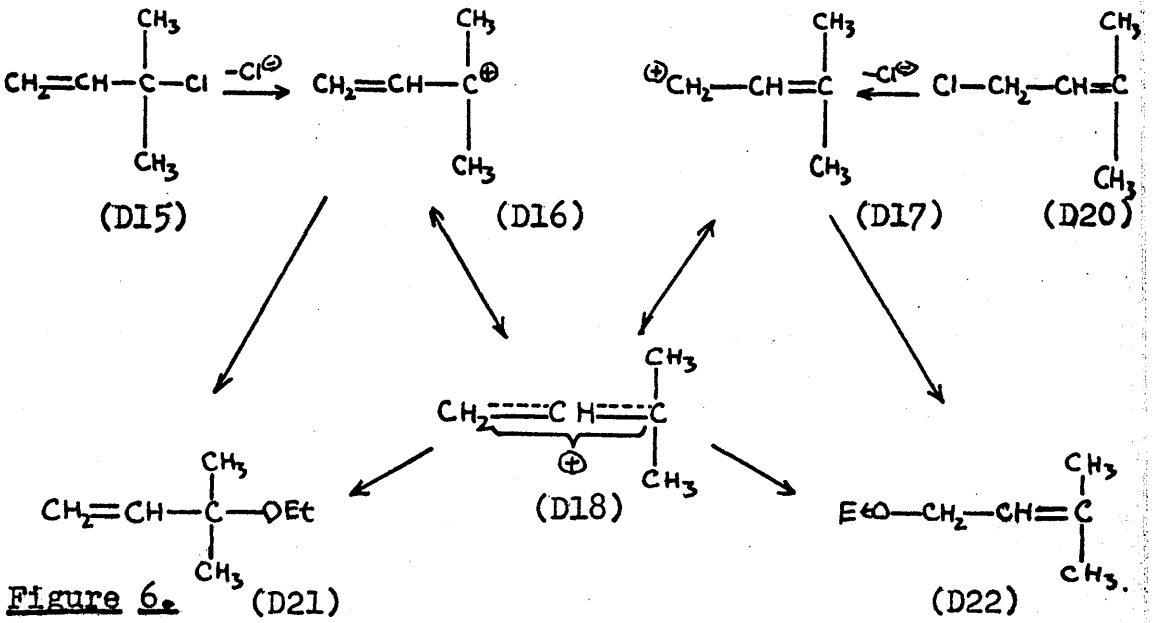
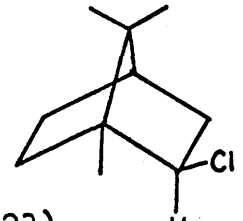


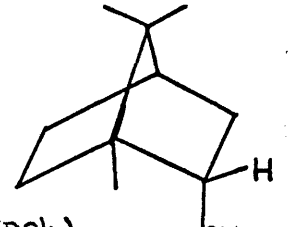
Figure 6.

figures of 70% and 30% respectively. This shows that there is mesomerism of the reaction intermediate so that the solvolysis of the two chlorides can be represented in one system as shown in Figure 6. It can be seen then, that in discussing neighbouring group effects, analysis of reaction products should serve to verify postulated mechanisms.

4.8 Another interesting effect is seen in Wagner-Meerwein rearrangements of monoterpenes. In 80% ethanol at 25°C., isobornyl chloride (D23) is solvolysed . . 2.5×10^5 times faster than bornyl chloride (D24)(122).

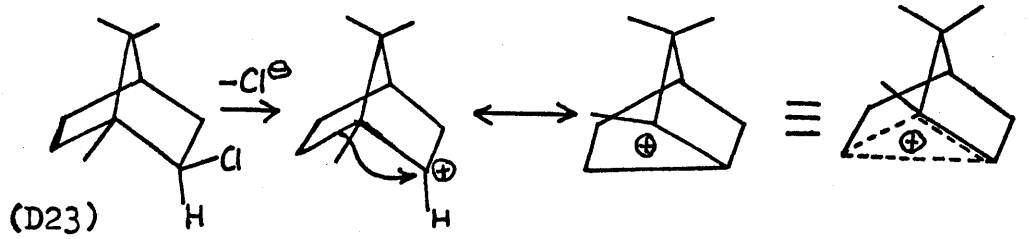


(D23)



(D24)

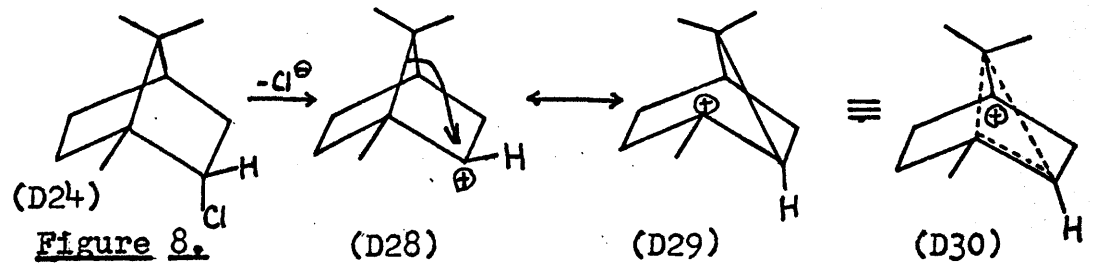
Winstein's explanation (122) of this much faster reaction is of interest. The carbon-carbon bond participates in the reaction as shown in Figure 7 to give the two forms (D25) and (D26), which may be written as a three-centred



(D23) (D25) (D26) (D27)

Figure 7.

carbonium ion (D27). A similar postulation for bornyl chloride would give the structures (D28), (D29), and (D30). In this latter case the mesomeric form (D29)



(D24) (D28) (D29) (D30)

Figure 8.

has a four-membered ring which is unstable for steric reasons. This difference in stability between the

intermediate ions is the explanation of the difference in reactivity.

In fact, the product of solvolysis in both cases is camphene (122). The interpretation in the case of isobornyl chloride is that the carbonium ion form (D26)

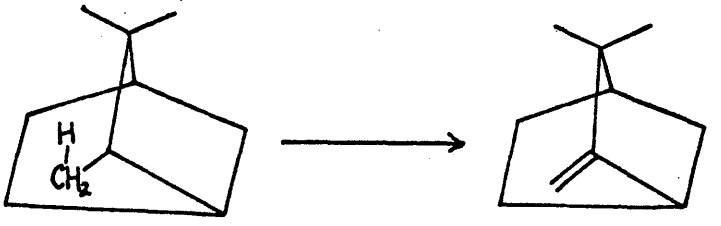
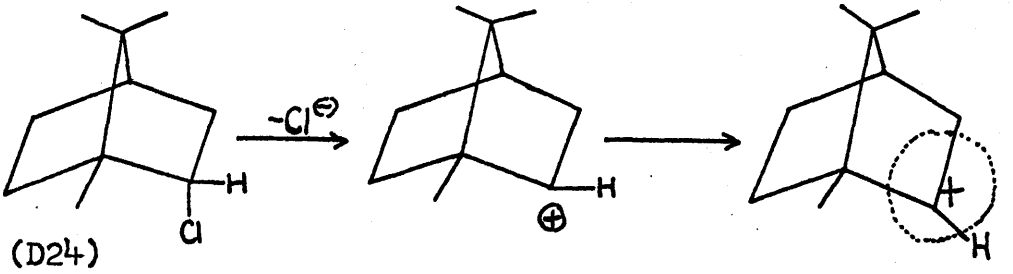


Figure 9. (D26) (D31)

loses a proton to give camphene (D31) directly. In bornyl chloride the migration (D28) ⟶ (D29) is so unfavorable that it does not take place to any extent, that is, the non-classical carbonium ion (D30) is unstable. It is considered that the carbonium ion centre in (D28) becomes planar subsequent to the ionisation, and that



(D24) (D28) (D32)

Figure 10.

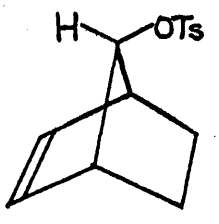
participation of a methylene group then takes place as in isobornyl chloride to give (D26) and then camphene (D31), see Figure 10. The methylene participation must be subsequent to the ionisation and so can have no effect on the rate of reaction.

Once more, a consideration of the orbitals

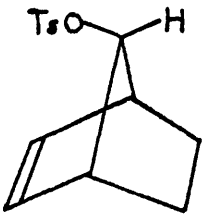
involved gives a better conception of the ion (D27). The relevant orbitals are the molecular orbital of the carbon-carbon bond trans to the C—Cl bond, and the vacant orbital of the ion. In the isobornyl case an examination of molecular models shows some overlap of these orbitals. This allows the formation of a three-centred bond, and it is this bond which stabilises the carbonium ion intermediate, and which we represent as the non-classical ion (D28).

In the case of bornyl chloride there appears to be little overlap of orbitals, and thus no stabilisation of the intermediate ion.

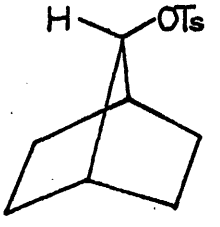
4.9 In two papers (123, 124) in 1955 and 1957, Winstein et al. described the solvolyses of a series of compounds the mechanisms of which combined aspects of the cholesterol, allyl alcohol and isobornyl chloride cases. They measured the rate of acetolysis of anti- and syn-7-norbornenyl tosylates (D33 and D34), and the



(D33)



(D34)



(D35)

corresponding saturated compound, 7-norbornyl tosylate (D35), and found that the relative rates of solvolysis are $10^{11} : 10^{4} : 1$ for (D33) : (D34) : (D35).

Winstein was able to explain these relative

rates (123,124) in terms of the three examples described above. Participation of the anti- carbon-carbon bond in the syn-compound (D34) and the saturated compound (D35) would lead, via (D36) and (D40) respectively, to

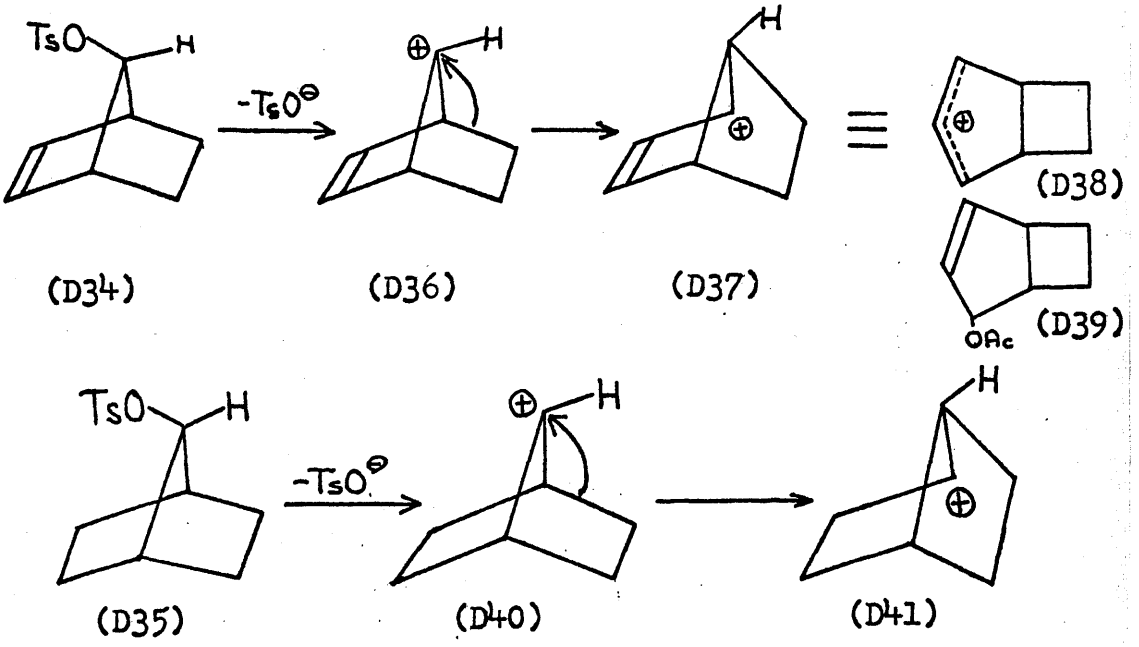
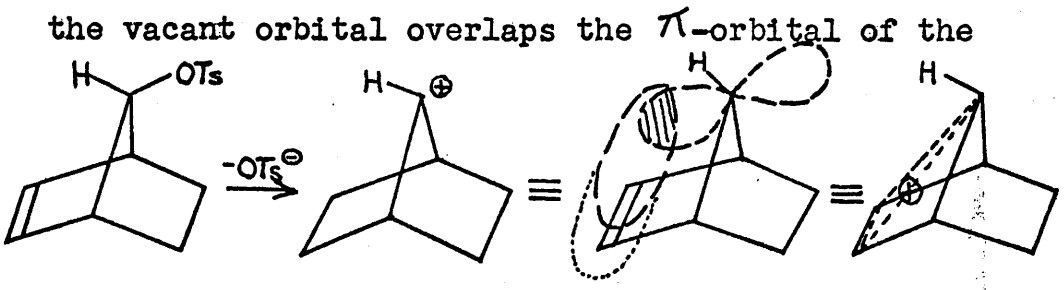


Figure 11.

the ions (D37) and (D41), both of which have sterically unfavourable four-membered rings. (D37) however is analogous to the allyl ion, and a three-centred bond can be formed as shown in (D38). The product of solvolysis of the syn-compound is about 90% (D39), (124) derived from (D38) which confirms the existence of the stabilised carbonium ion (D38) in this case, and thus explains why the syn-isomer reacts 4,100 times faster than the saturated compound.

Winstein then showed that in the rate-determining step of the acetolysis of the anti-isomer (D33), an ion

of structure (D42) is formed, and that in this case, the vacant orbital overlaps the π-orbital of the

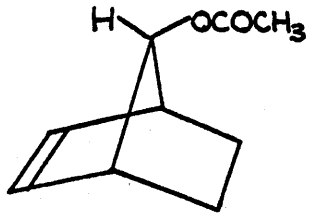


(D33) (D42) (D43) (D44)

Figure 12.

double bond as in (D43), to give once more a three-centred bond (D44).

The readiness with which the three-centred bond is formed after the ionisation step, and the stability of the resulting intermediate explain why the solvolysis of the anti-mesylate takes place 10^7 times faster than that of the syn-isomer, and 10^{11} times faster than that of the saturated compound. The product of the acetolysis of the anti-tosylate is the acetate (D45),



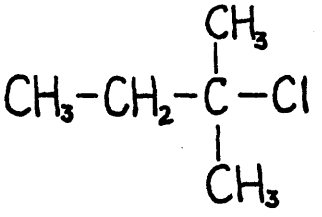
(D45)

with complete retention of configuration, which is a confirmation of the proposed intermediate (D44).

4.10 The enhancement of rates of solvolysis produced by these three-centred bonds is called anchimeric assistance to solvolysis(125). The cholesterol case

and the norbornenyl case are particularly interesting since the three centres are not adjacent; consideration of molecular models does show however that the orbitals concerned overlap.

4.11 To detect and measure anchimeric assistance it is necessary to know what the rate of reaction would be in the absence of participation by neighbouring groups. This is readily found in the allyl chloride case, see section 4.7, where the difference in reaction rates under identical conditions between the allyl chloride and t-butyl chloride or better still t-pentyl



(D 46)

chloride (D46), can be attributed directly to participation by the ethylenic double bond.

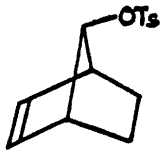
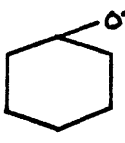
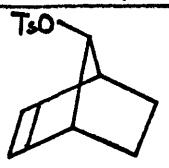
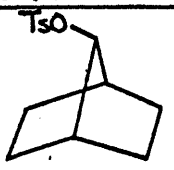
The problem is more difficult in the norbornenyl tosylate case (123,124). In the anti-isomer there is anchimeric assistance due to direct double bond participation, so one might expect that since such double bond participation cannot take place in the syn-isomer, this isomer would give the required comparison for the estimation of anchimeric assistance. In the syn-isomer however, there is less marked anchimeric assistance due to participation by the anti-

carbon-carbon single bond followed by allylic double bond participation as was shown in section 4.9. In the saturated norbornyl compound there is some anti- carbon-carbon single bond participation, so even this compound is not a wholly suitable reference.

4.12. The corresponding cyclohexanol ester is often used as a reference compound in such bridged-ring studies. These esters are useful since there is not usually any participation by neighbouring groups, but there is the drawback that cyclohexane is a relatively flexible system whereas bridged-ring compounds are rigid and therefore, do not readily undergo the changes in bond angles necessary to reach the transition state. Also, access to the reaction centre may be hindered by the bridging ring.

The relative rates of solvolysis of Winstein's norbornyl compounds, section 4.9, are compared with cyclohexane in table 1 (123,124). The syn-ester and

Table 1 Relative rates of solvolysis of norbornyl and cyclohexyl tosylates (123, 124).

			
"anti"	"cyclohexyl"	"syn"	"saturated"
10^4	1	10^{-3}	10^{-7}

the saturatedcompound are solvolysed very much more slowly than the cyclohexyl ester, yet from analysis

of reaction products there is known to be neighbouring group participation in both these reactions. Thus, the comparison with the corresponding cyclohexane ester may be of doubtful use.

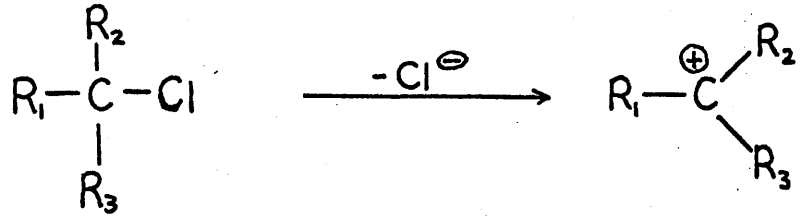
4.13 Winstein (126) has suggested that when a suitable reference in which there is no neighbouring group participation is available, the decrease in the free energy of activation of the solvolysis brought about by participation should be taken as an estimate of the anchimeric assistance. This has not been followed up by recent workers. Such a procedure gives an absolute measurement of anchimeric effects rather than the relative measurements which are popular with organic chemists. Its usefulness will be illustrated in the Discussion section of this thesis.

In general, if the rates at which two similar compounds undergo the same reaction are measured, and if there is in one, neighbouring the reaction centre, a group likely to participate in the reaction, then, if the rates are markedly different, such participation is probably taking place.

4.14 There is a more indirect kind of neighbouring group participation which can cause enhanced rates of reaction. This is steric compression. Because of interactions across space of some of the atoms which it comprises, a molecule may have a high energy content.

If these interactions are relieved in going to the transition state, the energy of activation will be low, and the reaction rate will be relatively great.

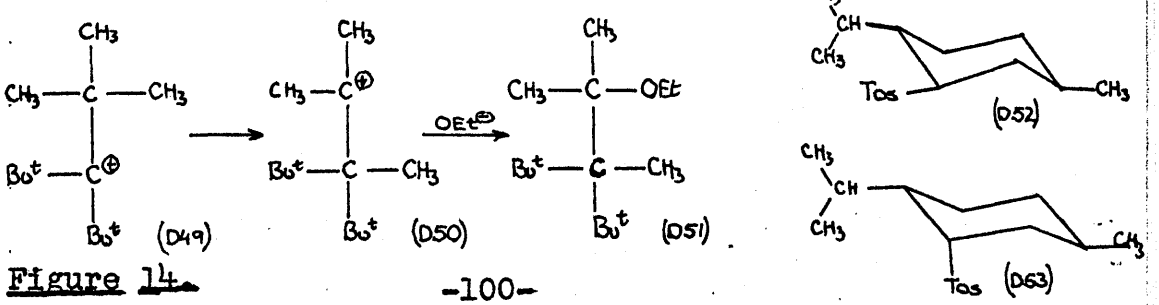
In the unimolecular solvolysis of trialkylmethyl chlorides (D47), the transition state is the carbonium



(D47) (D48)

Figure 13.

ion (D48). If the groups R_1, R_2, and R_3 are bulky and interfere with each other, the steric strain of interaction will be relieved in going from the tetrahedral chloride (D47) to the trigonal carbonium ion (D48), and the reaction will be faster. Thus in 80% ethanol at 35°C, tri-t-butylmethyl chloride, (D47, $R_1=R_2=R_3$=t-Bu) reacts 590 times faster (127,128) than t-butyl chloride, (D47, R =R =R =Me). Part of this factor, perhaps two or three times may be attributed to the -I effect of the highly substituted t-butyl groups, and there is known to be a neighbouring group effect due to methyl migration as shown in Figure 14, but the greatest part



(D49) (D50) (D51) (D52) (D53)

Figure 14.

of the enhanced rate is ascribed to the relief of steric compression.

Another example is the acetolysis of menthyl (D52) and neomenthyl (D53) tosylates, derived from the equatorial and axial forms of p-menthan-2-ol. The neomenthyl compound reacts 170 times faster (122). This is partly explained by the steric compression due to interaction in the neomenthyl case between the tosylate group and the axial hydrogens H_a and H_b shown, interaction which is not present in the carbonium ion. The other part of the explanation is that in the neomenthyl case there is a hydrogen atom trans-anti-parallel to the tosylate group, so that elimination is facilitated. In fact olefin forms the greater part of the reaction product so that the second part-explanation is more important.

Both these examples illustrate what is meant by steric compression; they are also illustrations, perhaps more effective, of how difficult it is to observe pure steric acceleration and pure anchimeric effects in solvolyses.

4.15 It should be pointed out that there is a minority school of thought, led by Professor Brown of Purdue University which considers that while neighbouring group participation is a well-defined phenomenon, the invocation of the non-classical carbonium ion concept is not always necessary.(129).

So attractive and, one might almost say, so fashionable is this concept that, rather than discuss each new example briefly and perhaps inconclusively, Brown has preferred to examine a few classical examples in detail. He bases his arguments on two premises. The first is that relief of steric strain may be the driving force producing enhanced rates (rather than the stable transition state carbonium ion). The second is that when there does appear to be a particularly stable carbonium ion, it should be considered not as having a non-classical structure, but rather as being a rapidly equilibrating set of classical carbonium ions.

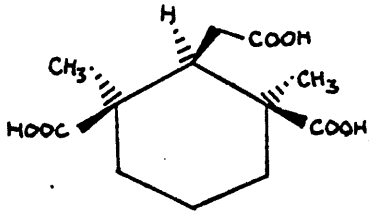
To comment on Brown's views would be unfair without outlining his case more fully. In this work, possible steric effects will be carefully discussed, and any neighbouring group participation will be reported. No attempt will be made to distinguish between two essentially qualitative pictures of the intermediate carbonium ion.

4.16 When more detailed information is required about the nature of the intermediate carbonium ion, the usefulness of isotopically substituted molecules has been shown by Roberts and his co-workers. A review of this work which shows the scope of such an approach is given in an article by Bethell and Gold (130).

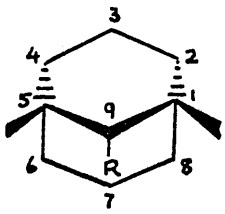
4.17 To sum up, there are two similar effects which

bring about large increases in reaction rates, steric compression and participation by neighbouring groups. When one cannot predict which of these is the more likely explanation of an enhanced rate, it may be possible to obtain an answer by analysis of the reaction products. A choice of suitable reference compounds should allow an estimate of the size of these effects to be made, and if applicable, a separation of these effects into several parts.

4.18 While investigating approaches to trans,meso-2,6-dimethyl-2,6-dicarboxycyclohexylacetic acid (D54),



(D54)



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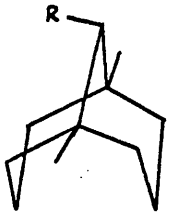
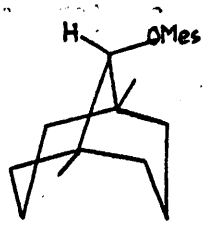
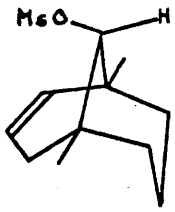


(D56)

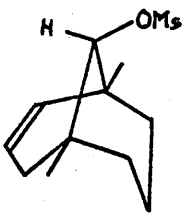
a primary degradation product of abietic acid, Martin, Parker, and Raphael (131) prepared compounds with carbon skeleton as shown (D55 or D56) and in particular the three compounds 9-methanesulphoxy-1,5-dimethylbicyclo-[3,3,1]nonane (D57), and the syn- and anti- forms (D58



(D57)



(D58)



(D59)

and D59) of 9-methanesulphoxy-1,5-dimethylbicyclo-[3,3,1]non-2-ene. (Where syn- and anti- show the relation of the ester group to the double bond).

These are methanesulphonic acid esters, mesylates, of alcohols of type (D56, R=OH), and are analogues of Winstein's norbornyl and norbornenyl compounds (D33, D34, and D35), but with six- instead of five-membered rings, and with two angular methyl groups not present in Winstein's compounds. Another difference is that the present compounds are mesylates instead of tosylates. Martin was unable to obtain the tosylates for reasons which he outlines (131).

The second part of this thesis describes the solvolysis of these bicyclononane-type compound, and interprets the relative rates of solvolysis in terms of their structure.

CHAPTER FIVE

SOLVOLYSIS SECTION - EXPERIMENTAL

5.1 1,5-Dimethylbicyclo[3,3,1] nonan-9-ol, and the syn- and anti- forms of 1,5-dimethylbicyclo[3,3,1]-non-2-en-9-ol were prepared by Martin (131). A flow sheet for the syntheses is shown in Figure 15. Attempts to form the toluene-p-sulphonic acid esters, tosylates, of these alcohols were unsuccessful, probably because of the bulky nature of the tosylate group and the steric congestion in the alcohol. When the much smaller molecule methanesulphonic acid was used, esters, mesylates, were obtained and characterised quite readily (132).

5.2 Cyclohexyl mesylate. Cyclohexanol (10g. in 20c.c. pyridine) and methanesulphonyl chloride (15g.

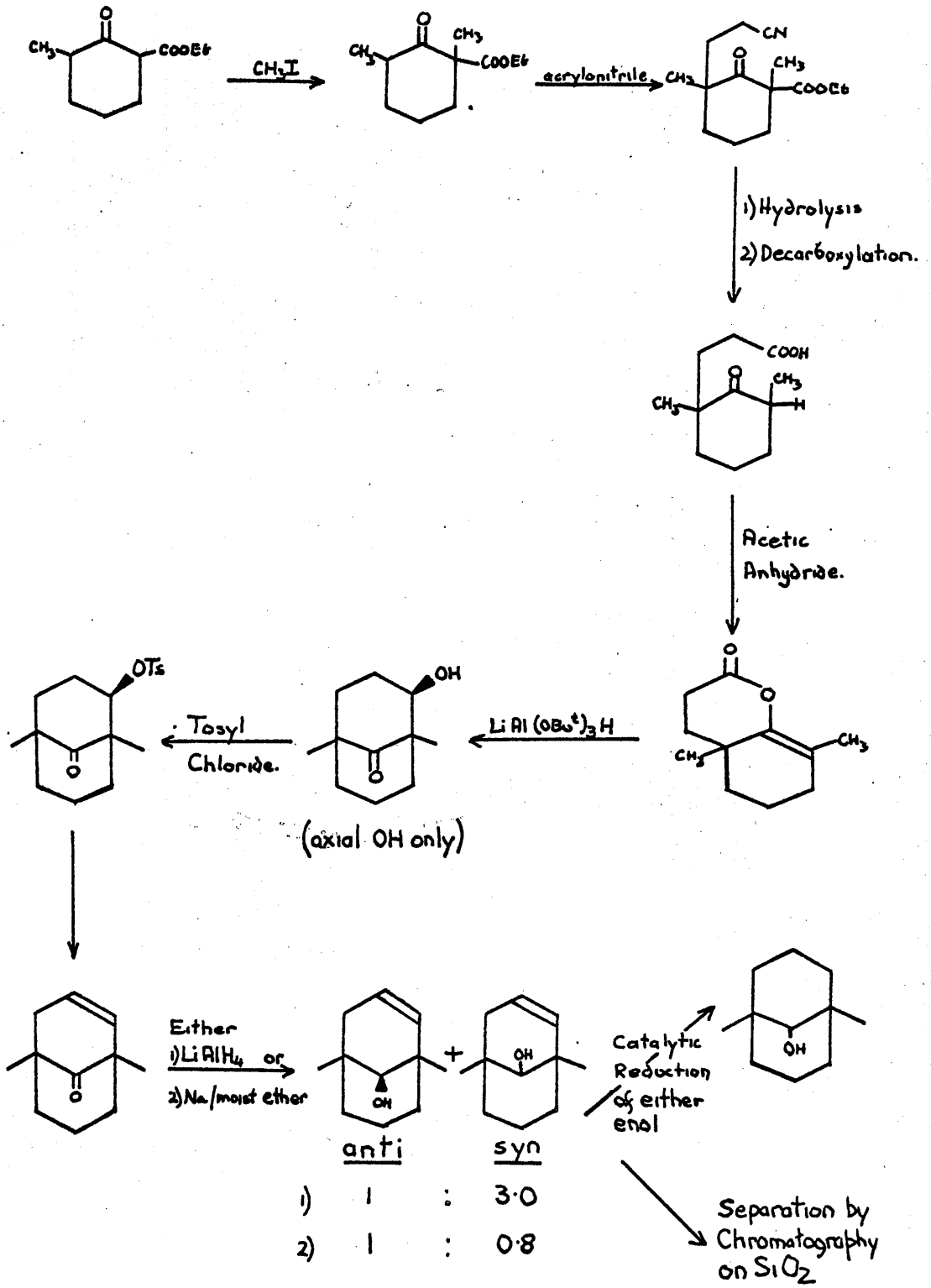


Figure 15 Flow sheet for the synthesis of bicyclo [3,3,1] nonane structures, (Martin, 131).

in 20c.c. pyridine) were cooled, mixed, and left overnight in an icebath. Pyridine hydrochloride was removed with water, and the residue was extracted with ether. The ether extract was washed with hydrochloric acid, sodium bicarbonate solution, and water, then finally dried with magnesium sulphate. The solvent was removed and the resultant oil was vacuum distilled to give a clear liquid (b.p. 138.5°C/19.5m.m., $n_D^{18} = 1.4342$).

5.3 The solvolyses were carried out in a medium four parts by volume ethanol to one part water, the acid liberated being measured potentiometrically. This method was chosen so that studies could be carried out with very small samples of esters. The minimum size of cell is then one which can contain the two electrodes, so that a sample solution of 5c.c. would be easily sufficient. Solutions 10^{-3}M are suitable for potentiometric estimation so that for any of the mesylates studied, a solvolysis study could be carried out on less than two milligrams of ester.

As it happened, relatively large quantities of the esters became available so that miniaturisation was unnecessary.

For potentiometric measurements at low concentrations, a medium of acetic acid, which has often been used, for example by Winstein in much of his work (122-126), is unsuitable. Another common medium four parts by volume ethanol to one part water was used.

5.4 The potentiometer used was a Cambridge bench pH meter, with the usual glass and calomel electrodes, which can be used either as a pH meter or a potentiometer. Before an experiment the instrument has to be standardised against a known potential or, which is the same thing, against a solution of known pH. This can be achieved by dissolving a fixed amount of a suitable buffer system usually prepared in the form of a tablet, in a known volume of distilled water at a known temperature. For experiments in slightly acid solutions, Burroughs Wellcome and Co. have prepared tablets of acid salts of phosphoric acid which give a solution of pH 4.01 when dissolved in 100c.c. water at 25°C.

There is the difficulty that while this defines a hydrogen ion concentration scale in aqueous solutions, this scale cannot be directly transferred to solutions in ethanol/water media.

One of two alternatives was adopted. In the first method, the meter was standardised in aqueous solution as outlined above; solutions of the experimental ethanol/water medium were then prepared containing known amounts of the strong acid, hydrochloric acid. By allowing the electrodes to equilibrate in each solution in turn, a series of nominal pH readings was obtained, and a plot of these readings against the corresponding known acid concentration was made. Thus pH readings during a solvolysis experiment could be related to

the amount of acid liberated.

An alternative method of calibration was to standardise the meter in buffer solution of pH 4.01 as before, then to carry out the experimental run, taking readings from the standardised but uncalibrated pH meter. The reading at $t = \infty$ was noted and the solution at this point was titrated with base to obtain the actual acid present. This gave one point on the graph of $-\log[H^+]$ against pH, and by assuming that the graph is a straight line of slope 1 passing through this point, a calibration curve was obtained. This assumption was confirmed to be true by examining a typical calibration made by the first method.

In practice the second method is much more convenient. Both methods were used on various occasions, and when both were applied to the same calibration, it was found that the results were in very good agreement.

During the solvolysis runs the electrodes were usually introduced into the reaction vessel through a stopper thus producing a system sealed throughout the experiment. When reaction rates were very low the electrodes were introduced to the reaction vessel at the time of taking readings; at other times the vessel was kept sealed.

In a trial run on the solvolysis of t-butyl bromide in four parts by volume ethanol to one part water, a first order rate constant of 3.48×10^{-4} /sec.

at 25°C was found. Hughes and Ingold (133) report a value of 3.60×10^{-4}/sec. This was taken as a satisfactory test of the potentiometric method of measurement.

5.5 The bridged-ring esters are analogues of di-t-butylcarbinyl compounds which are well-known to undergo unimolecular solvolysis and, quite significantly, to rearrange very readily (134). The esters all gave the expected first order kinetics.

In each case a plot of the logarithm of the concentration of the mesylate remaining against reaction time was drawn, and the slope of the resultant line was measured. The unimolecular rate constant is -2.303x this slope. A typical experimental run is illustrated in Table 2. Figure 16 shows the graphical plot of these results.

TABLE 2 Data and results for a typical experimental run.

Run 20 Solvolysis of anti-9-methanesulphoxy-1,5-dimethyl-bicyclo[3,3,1] non-2-ene in 80% v/v ethanol, 20% water at 45.6°C. Initial concentration of mesylate = 298.7×10^{-5}M.

Time (secs.)	1560	4080	7680	10560	16620	25860	48180	82380	172800
pH reading	4·08	3·59	3·328	3·20	3·052	2·93	2·82	2·787	2·778
$[H^+]$ ($\times 10^5$)	14·8	45·6	83·3	111·9	157·3	206·9	268·4	289·6	295·7
[Mesylate] ($\times 10^5$)	280·9	250·1	212·4	183·8	138·4	88·8	27·3	6·1	—
log[Mesylate]	-2·5514	-2·6019	-2·6729	-2·7357	-2·8588	-3·0516	-3·5638	-4·2417	—

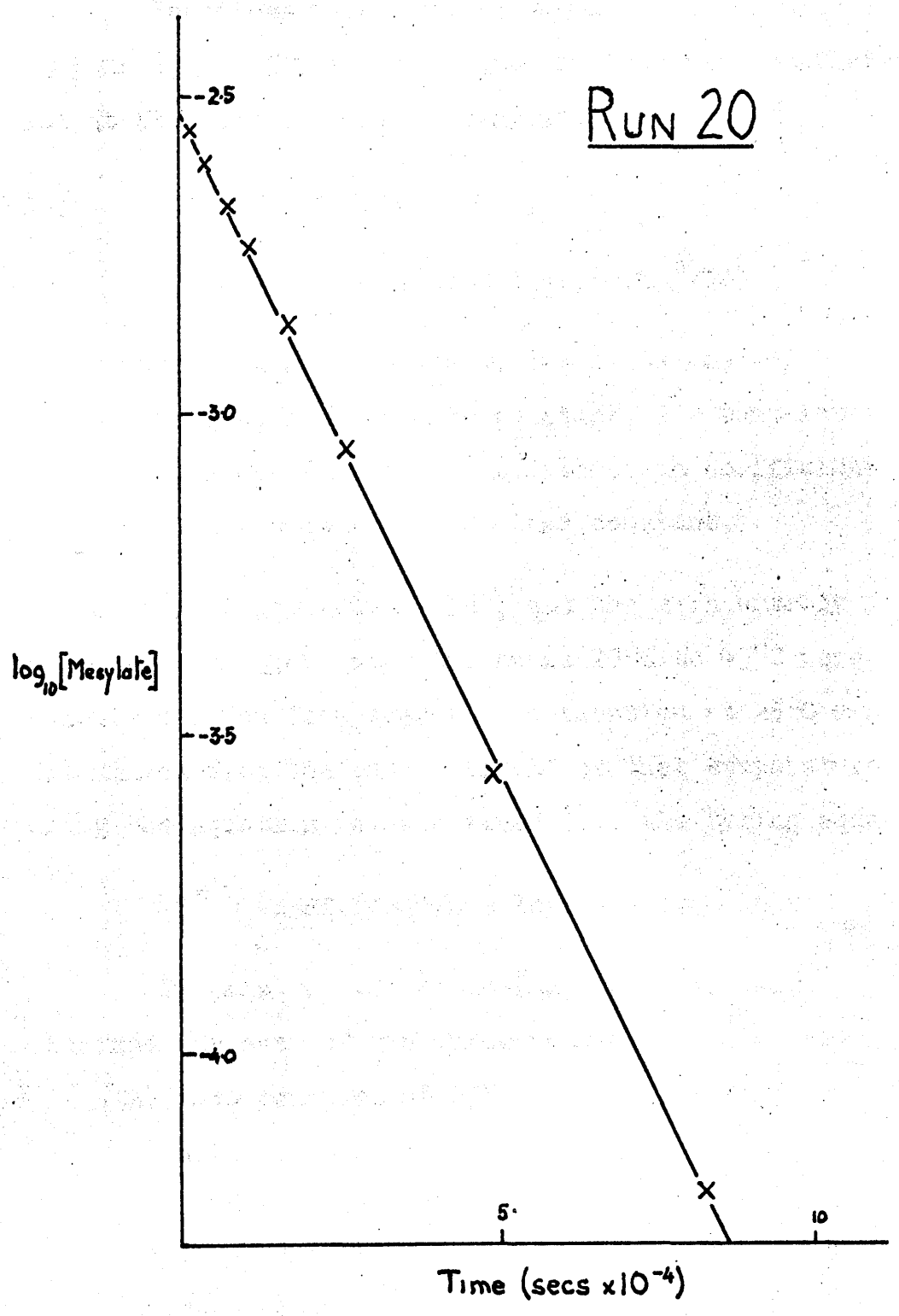


Figure 16 Graphical plot of results of a typical run.

Reactions were carried out at 25°C for all compounds, at 45°C for the three bridged-ring mesylates, and at 55°C for cyclohexyl mesylate.

5.6 Using Eyring's equation,

$$k = \frac{kTf}{h} \cdot \exp(\Delta S^{\#}/R) \cdot \exp(-\Delta H^{\#}/RT)$$

where k = rate constant, k = Boltzmann's constant, h = Planck's constant, T = temperature, in degrees Kelvin, f = transmission coefficient here taken as 1, and R = gas constant.

the energy of activation $\Delta H^{\#}$, and the mean entropy of activation $\Delta S^{\#}$, over the range 25°C to 45°C were calculated. The free energy of activation at 25°C was calculated from the rate constant at that temperature using the equation below derived from the Eyring equation.

$$\Delta G^{\#} = 2.3RT.(\log k/h + \log T + \log f - \log k)$$

In this way the following constants were obtained for each of the three mesylates

a) Rate constant at 25°C.

b) Rate constant at 45°C.

c) Rate relative to cyclohexyl mesylate at 25°C.

d) Energy of activation.

e) Entropy of activation.

f) Free energy of activation.

5.7 Cyclohexyl mesylate reacted so slowly that the

rate given is the initial rate of reaction over the first thirty per cent reaction.

For each plot lines of maximum and minimun slope through the points were drawn. The mean of the values obtained from these two lines was taken as the rate constant, and the deviation was taken as half the difference between the two values. For the solvolyses of the bridged-ring esters at 45°C, the deviation in every case was close to 3%, while for experiments at 25°C it was 7%. Deviations in $\Delta H^{\#}$ and $\Delta S^{\#}$ were calculated from these values of the error using the equations of Schaleger and Long (135). The deviation in $\Delta G^{\#}$ was calculated from the deviation of the rate constant at 25°C. For cyclohexyl mesylates where the precision of the results was somewhat worse, deviations were calculated in a similar way.

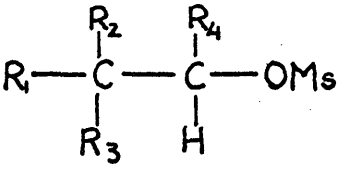
Temperatures were constant throughout each experiment to within 0.1°C of the temperature given.

CHAPTER SIX

SOLVOLYSIS SECTION - RESULTS AND DISCUSSION

6.1 Results of the solvolyses are shown in Table 3.

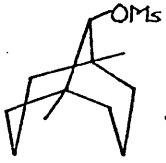
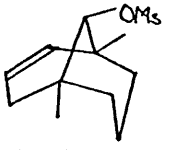
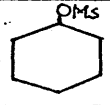
6.2 The mesylates being studied are very highly substituted, having the neopentyl structure twice over (D60),



(D60)

and as a result they rearrange very readily (136). This has made the analysis of reaction products very complicated, for these products are themselves highly substituted and they undergo further rearrangements on work up. In particular, alcohols are dehydrated by

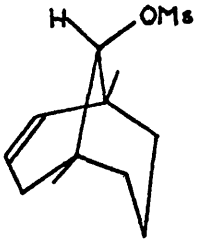
Table 3 Bicyclononane derivatives — Rate constants for the hydrolysis of mesylates in aqueous ethanol.

COMPOUND.	Structural Formula.	k_1 at 25°C $(sec^{-1})\times10^7$	k_1 at 45°C $(sec^{-1})\times10^7$	k_1 at 55°C $(sec^{-1})\times10^7$	$\Delta H^{\#}$ (kcal/mole)	$\Delta S^{\#}$ (e.u)	$\Delta F^{\#}$ (kcal/mole)	Relative Rates at 25°
1,5-dimethyl bicyclo[3,3,1]-nonan-9-ol mesylate. "saturated compound"		214	2750 (a)	—	23·2 ±0·7	-2·5 ±2·0	23·9 ±0·9	$1{\cdot}1\times10^2$
1,5-dimethyl bicyclo[3,3,1]-non-3-en-9-ol mesylate. "anti-isomer"		25·4	485 (b)	—	26·7 ±0·7	+4·9 ±2·0	25·2 ±0·9	$1{\cdot}3\times10^1$
1,5-dimethyl bicyclo[3,3,1]-non-3-en-9-ol mesylate "syn-isomer"		24·0	496 (c)	—	27·8 ±0·7.	+8·4 ±2·0	25·1 ±0·9	$1{\cdot}2\times10^1$
cyclohexanol mesylate.		1·93	—	71·6 (d)	23·3 ±1·3	-11·7 ±6·1	26·8 ±2·2.	1

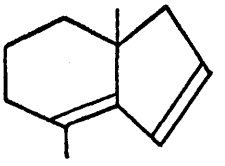
a) 45·35°C
b) 45·50°C
c) 45·25°C
d) 54·60°C.

liquid-phase chromatography (137). There is some information on reaction products; this and other useful observations are now outlined.

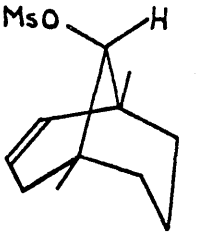
Hydrolysis of the anti- isomer of 1,5-dimethylbicyclo[3,3,1]non-3-en-9-ol mesylate (D61) gives five



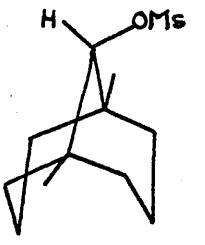
(D61)



(D62)



(D63)



(D64)

principal products (137). There is a very small amount of the direct hydrolysis product, the anti-alcohol, formed, and considerably more of the isomeric syn-alcohol. There are several hydrocarbon dienes formed one of which appears from its ultra-violet spectrum to be the compound (D62). Quantitative estimates of the products are vitiated by dehydration of alcohols which takes place during work-up as mentioned above.

The reaction product in the hydrolysis of the syn-isomer (D63) has been shown (137) to be a mixture of at least four compounds some of which are hydrocarbons. There appears to be no syn-alcohol formed.

6.3 There has been no product analysis on the solvolysis of the mesylate of the saturated alcohol 1,5-dimethylbicyclo[3,3,1]nonan-9-ol (D64). On heating above its melting point, this mesylate decomposes into

a mixture of hydrocarbons. Martin (132) has studied these products which are produced by a series of rearrangements and eliminations.

Vapour-phase chromatography suggested that there are three compounds in the pyrolysis product. It was postulated that the series of reactions shown in Figure 17 is taking place. Ultra-violet and infra-

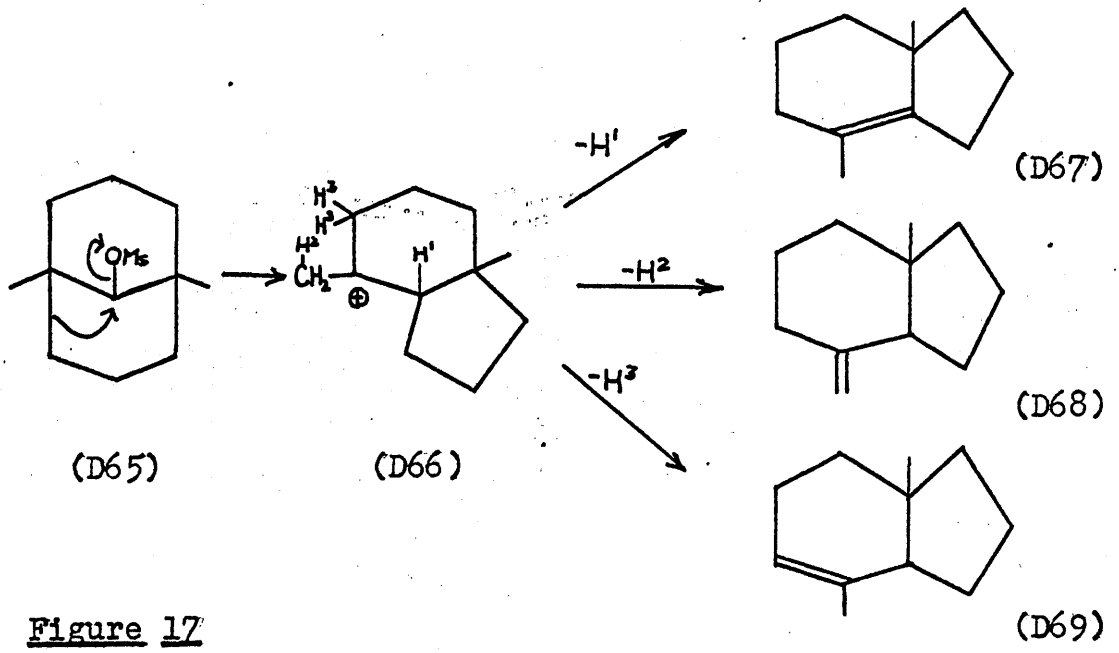
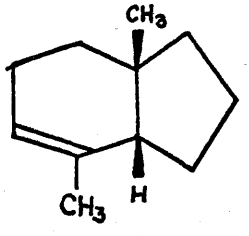
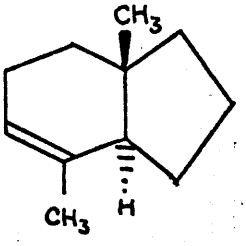


Figure 17

red spectroscopy showed that (D68) is not present so it was concluded that the three products are (D67) and the cis- and trans-fused-ring forms (D70 and D71)



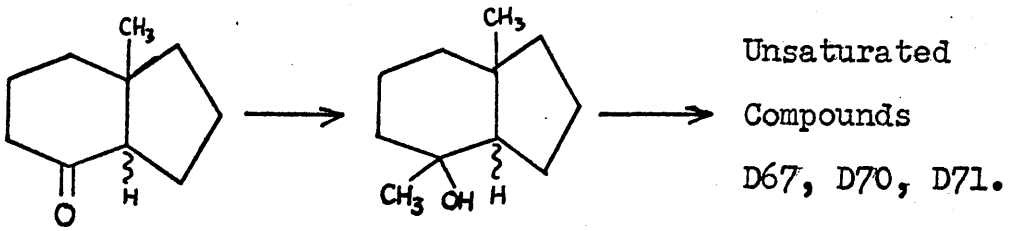
(D70)



(D71)

of (D69).

That this is in fact the case was shown (132) by taking the known compound (D72), a mixture of cis- and trans-fused-ring forms and treating it with methyl



(D72) (D73)

Figure 18

magnesium bromide then hydrolysing the product. The expected tertiary alcohol (D73) is labile and is readily dehydrated to give a mixture of three hydrocarbons, identical with those resulting from the pyrolysis.

Since there are no hydrogen atoms on the carbon atom adjacent to the reaction centre, the pyrolysis cannot proceed by direct elimination of methanesulphonic acid. It would seem that in this case pyrolytic elimination must begin either by the separation of a mesylate ion, followed by a rearrangement, or by a process in which the separation and rearrangement occur more or less simultaneously.

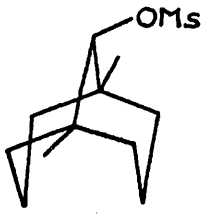
No matter which of the two routes is followed, the mechanism is similar to that which one would postulate for unimolecular elimination of the same mesylate in solution. Thus in the case of the saturated compound (D64) we have within limitations, an indication of what the reaction products are.

The unsaturated mesylates (D61 and D63), on pyrolysis give polymeric products. A scheme similar to Figure 17 would indicate a mixture of dienes which would be expected to polymerise readily.

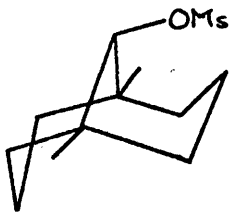
6.4 Two facts are particularly striking in the results reported in Table 3. Firstly, the syn- and anti-isomers have rate constants and other reaction parameters almost identical. Secondly, the saturated mesylate is solvolysed nine times faster than either of the unsaturated esters.

The first observation suggests that the mechanistic route for the solvolysis of the two unsaturated mesylates is similar and in particular, that there is no participation by the double bond of the type found by Winstein (123), see Section 4.9, peculiar to the anti-isomer.

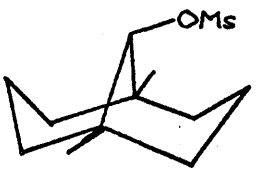
The second observation can be explained in terms of the structure of bicyclo [3,3,1] nonane systems. There are three possible combinations of ring confirmations for the two rings, the chair-chair form (D74), the chair-boat (D75), and the boat-boat



(D74)



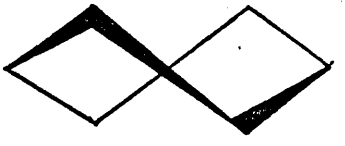
(D75)



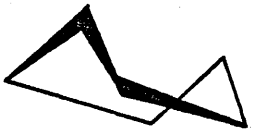
(D76)

(D76). When the term boat-form is used, it is realised

that of the conformations of the boat-type, the skew-boat or crown-form (D77) is more stable than the true-boat form (D78). This has been discussed in Section 3.8.

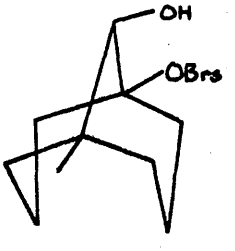


(D77)

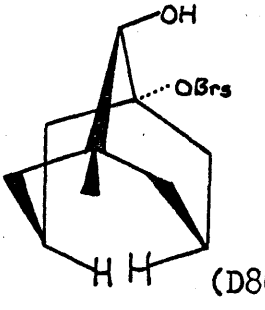


(D78)

Classical arguments would favour the chair-chair form (D74), because of low 1,2 interactions and lack of 1,4 interactions. X-ray crystallographic studies by Brown et al. (138) have shown that the crystal structure of the bromobenzene-p-sulphonate ester, brosylate, (D79) of the analogous diol is in fact the



(D79)



(D80)

chair-chair form, but with considerable flattening of the rings. This flattening has been attributed to steric interaction of the axial hydrogen atoms on carbon atoms 3 and 7 as illustrated in the diagram (D80).

In the saturated mesylate (D64) a similar situation will obtain, and there will be considerable steric strain in the molecule. Pyrolysis results have shown the readiness with which the ring-methylene

group anti- to the mesylate participates in that reaction. In the saturated mesylate such participation in the solvolysis would remove the interaction, see Figure

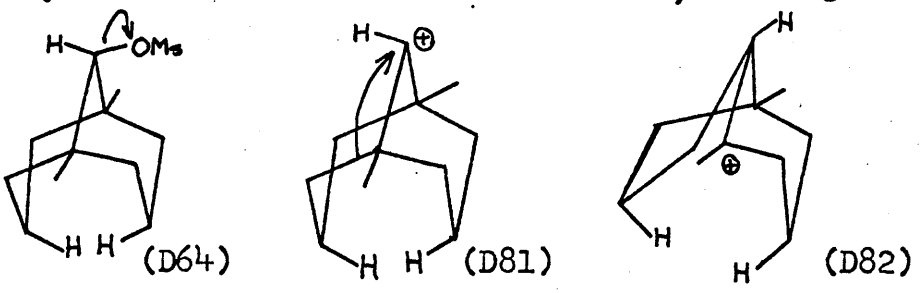


Figure 19

19, so that the large rate relative to the unsaturated compounds (D61 and D63) can be attributed to the relief of steric strain.

6.5 These then are the results and the immediate conclusions drawn from them. The results were briefly reported in July, 1963 (139). Since that time two papers have appeared reporting the solvolyses of further bridged-ring compounds (140, 141). It is proposed to record these results and the conclusions drawn by the authors and then to group together Winstein's results (123,124) and other relevant early work, the results reported in this thesis and these recent results, and to discuss generally, neighbouring-group effects in the solvolysis of bridged-ring compounds.

6.6 Le Bel and Spurlock (140) examined the acetolysis of the tosylates of the syn- and anti- forms (D83 and D84 respectively) of bicyclo [3,2,1] -

Table 4 Rate constants for the solvolysis of unsaturated bicyclooctane derivatives in acetic acid (140).

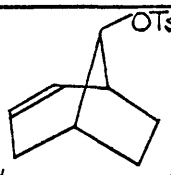
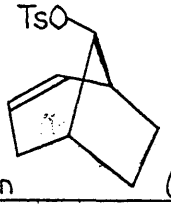
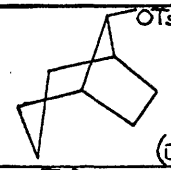
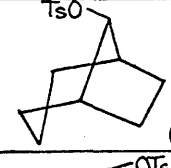
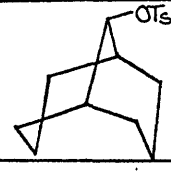
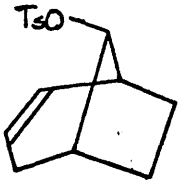
COMPOUND	k_1 at 25°C (sec^{-1})	Relative Rate	Product Analysis at 125°C. Unrearranged Skeleton with the Configuration		Methylene Participation by the ring	
			Retained	Inverted	anti to the tosylate	syn to the tosylate
 anti (D84)	3.6×10^{-8}	7.4×10^{-1}	21%	0	48%	25%
 syn (D83)	1.4×10^{-13}	2.9×10^{-6}	11%	30%	23%	33%
Cyclohexyl Tosylate	4.9×10^{-8}	1.	-	-	-	-

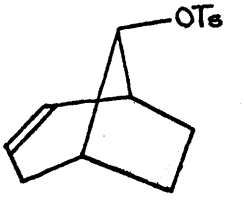
Table 5 Rate constants for the solvolysis of saturated bicyclooctane and bicyclononane derivatives in acetic acid (Ref. 141)

COMPOUND	k_1 at 25°C (sec^{-1})	Relative Rate.	Product Analysis. Unrearranged Products with Configuration		Participation by the six-membered ring followed by elimination or acetate formation
			Retained	Inverted	
 exo (D85)	4.2×10^{-8}	8.6×10^{-1}	7%	~0	92%
 endo (D86)	5.2×10^{-12}	1.1×10^{-4}	2%	51%	47%
 (D87)	2.0×10^{-7}	4.1×10^{0}	5%		87%
Cyclohexyl Tosylate.	4.9×10^{-8}	1	-	-	-

oct-2-en-8-ol. The rate constants and product analyses



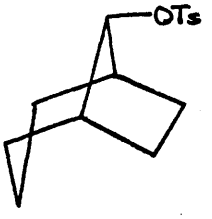
(D83)



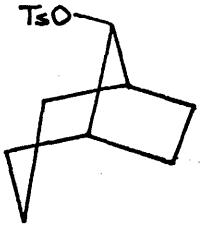
(D84)

obtained are shown in Table 4.

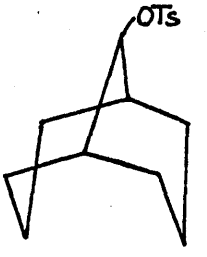
6.7 Foote and Woodward examined the tosylates of three compounds, the exo- (D85) and endo- (D86) forms



(D85)



(D86)



(D87)

of bicyclo [3,2,1] octan-8-ol, where exo- and endo- refer the tosylate group to the six-membered ring, and bicyclo [3,3,1] nonan-9-ol (D87). Table 5 shows the results obtained.

6.8 Although Le Bel's paper preceded that of Woodward, he knew of Woodward's results for the saturated bicyclooctane esters, and in the light of these results, his interpretation is somewhat surprising. The relative rates under consideration are shown in Table 6.

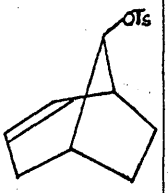
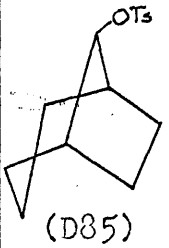
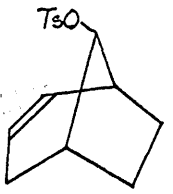
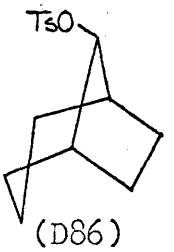
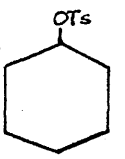
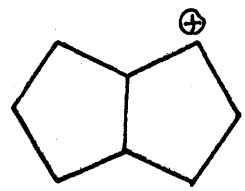
Compound	 (D84)	 (D85)	 (D83)	 (D86)	
Rate Constant	0.74	0.86	2.9×10^{-6}	110×10^{-6}	1

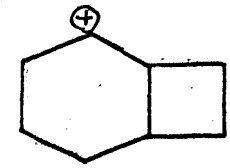
Table 6

Le Bel suggests that (D83) derives no anchimeric assistance through participation by the double bond directly or by a methylene group and that the rate relative to cyclohexyl tosylate and the product analysis bear out this conclusion. He implies the same conclusion for the same reasons in the corresponding saturated compound (D86) and suggests that it reacts 40 times faster than (D83) because of the inductive effect of the double bond.

He then concludes, and it seems very reasonable, that the saturated exo-compound (D85) reacts 8000 times faster than the endo-compound because a six-membered ring anti- to the leaving group is more ready than a five-membered ring to take part in the reaction by methylene participation. This can be understood since the ion resulting from six-membered ring participation is (D88) whereas a five-membered ring gives rise to the strained form (D89).



(D88)

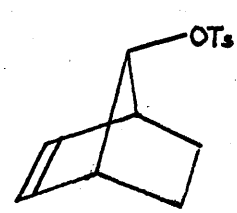


(D89)

Le Bel then rejects this explanation when he considers why the anti-unsaturated compound (D84) is more reactive than the syn-isomer by a factor of 260,000. He attributes this factor to direct double bond participation in the anti-isomer of a type similar to that proposed by Winstein (123,124) in the norbornane series.

It does seem however that of this factor of 260,000, part of the order 8,000 should be attributed to the fact that there is a six-membered ring anti- to the leaving group rather than a five-membered ring. There remains now a factor of 33, (260,000/8,000) which can be attributed to other effects, perhaps direct double-bond participation.

There is a second point that, whereas the solvolysis of anti-7-norbornenyl tosylate (D90), the



(D90)

classical example of direct double-bond participation,

occurs with complete retention of configuration (123), the compound (D84) gives only 20% unrearranged product which is all however, of the same configuration as the starting material (140).

On the other hand, in the exo-saturated compound (D85) where there is definite anti-methylene participation, all the unrearranged product is again of the same configuration as the starting material (141) which suggests that retention of configuration in (D84) can be attributed to methylene participation and that direct double-bond participation need not be invoked.

Thus, if one is to be hypercritical, the only evidence to suggest that there is double-bond participation in the anti-isomer (D84), is a possibly unexplained factor of about thirty in reaction rates; analysis of reaction products offers no support.

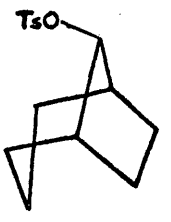
The conclusion to be drawn from Le Bel and Spurlock's work then is that part of the enhanced rate of the anti-compound (D84) compared with the syn-compound (D83) may be attributed to double-bond participation, but that much more important is participation by an anti-six-membered-ring methylene.

6.9 The conclusion which Woodward draws from his results (141), supported quite clearly by the relative rates of reaction and by analysis of products is that there is methylene participation in all cases but that, when the methylene is in a five-membered ring, the

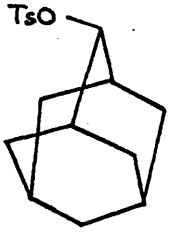
participation takes place much less readily, since the resultant product is a strained four-membered ring compound.

Woodward also brings out another point, first made by Schleyer and Nicholas (142). The classical carbonium ion will prefer to have trigonal geometry at the reaction centre, and thus a bond angle of 120°. The bond angle at the bridging carbon atom in the ester itself is determined by the amount of strain involved in the bridged-ring system; in norbornyl tosylate this angle is known to be about 96° (143). Now, the greater the difference between the bond-angle in the ester and 120°, the more the carbon skeleton of the ester will oppose the process of ionisation for, achieving the ideal trigonal angle of 120° of the carbonium ion requires a distortion away from the ideal bond angle of the carbon skeleton. Thus norbornyl tosylate is observed to react 10^7 times slower than cyclohexane, (123), in keeping with this theory.

The endo-compound (D86) of Foote and Woodward



(D86)



(D91)

(141) has a six-membered and a five-membered ring so that the bridge angle should be between the 96° value

of norbornyl tosylate and the 109.5° of adamantyl tosylate (D91, 142). There will be little participation by the five-membered ring anti to the tosylate group, so that the increased rate of reaction in (D86) compared with norbornyl tosylate can be attributed to the fact that the bridging angle is rather nearer to the ideal angle of the carbonium ion.

6.10 Before entering a general discussion it would perhaps be useful to enumerate all the factors which have been shown to affect reaction rates in bridged ring compounds.

1) Strained bond angles at the reaction centre (Section 6.9).
2) Size of the ring anti to the leaving group and its suitability for methylene participation (Section 4.9).
3) Homo-allylic double bond participation (Section 4.7).
4) Steric interaction effects (Sections 4.14, 6.4).
5) Direct double bond participation (Section 4.9).

In the discussion which now follows, an attempt will be made to show to what extent each of these factors is involved in the solvolysis of a range of bridged-ring esters. Some of the conclusions reached have already been suggested in discussions of particular examples in Table 7. When this is so, acknowledgement will be made. It is intended however, to extend these conclusions

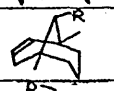
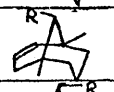
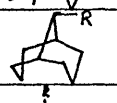
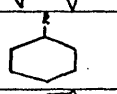
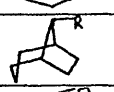
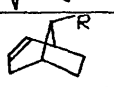
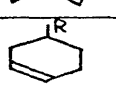
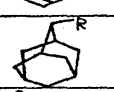
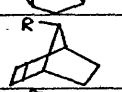
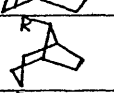
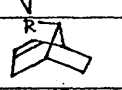
	COMPOUND "R" indicates the ester group.	RATIO of RATES at 25°C	acetolysis k_1 at 25°C (sec^{-1})	ethanolysis k_1 at 25°C (sec^{-1})	$\Delta H^{\#}$ (kcal/mole)	$\Delta S^{\#}$ (e.u.)	$\Delta G^{\#}$ (kcal/mole)	PRODUCT ANALYSIS (percentages) A	B	C	D	Reference
T1		1.8×10^{4}	90×10^{-4}	–	23.3	+5.7	21.6	100	0	–	–	123
T2		1.1×10^{2}	–	2.14×10^{-5}	23.2	-2.5	23.9	–	–	100**	–	†
T3		1.3×10^{1}	–	2.54×10^{-6}	26.7	+4.9	25.2	✓	✓	✓	–	†
T4		1.2×10^{1}	–	2.40×10^{-6}	27.8	+8.4	25.1	0	✓	✓	–	†
T5		4.1×10^{0}	2.0×10^{-7}	—	27.2	+2.0	26.6	5 §		87	–	141
T6		1	4.9×10^{-8}	1.93×10^{-7}	*	*	~27.0*	–	–	–	–	123
T7		8.6×10^{-1}	4.2×10^{-8}	—	26.8	-2.6	27.6	7	0	92	–	141
T8		7.4×10^{-1}	3.6×10^{-8}	—	29.0	+3.0	28.1	20	0	50	25	140
T9		7.4×10^{-1}	–	–	–	—	—	–	–	–	–	141
T10		6.7×10^{-2}	3.25×10^{-9}	—	30.0	+3.2	29.0	100 §		–	–	142
T11		5.3×10^{-4}	2.6×10^{-11}	—	31.8	-1.0	32.1	–	–	90	–	124
T12		1.1×10^{-4}	5.2×10^{-12}	—	31.9	-3.5	32.9	2	51	–	47	141
T13		2.9×10^{-6}	1.4×10^{-13}	—	35.8	+2.0	35.2	11	30	25	30	140
T14		1.3×10^{-7}	6.36×10^{-15}	—	35.7	-3.5	36.7	91 §		9	—	123

Table 7 Kinetic data for the solvolysis of some bicyclic esters.

NOTES

Product Analysis. A — Corresponding acetate or ethyl ether with retention of configuration.

B — Corresponding acetate or ethyl ether with inversion of configuration

C — Methylene participation by the ring anti to the leaving group.

D — Methylene participation by the ring syn to the leaving group.

* — The values of $\Delta H^{\#}$, $\Delta S^{\#}$, and $\Delta G^{\#}$ for cyclohexane vary with the solvolysis; they are 27.0, -1.1, and 27.3 respectively for acetolysis, and 23.3, -11.7, and 26.8 respectively for ethanolysis.

§ — Because of the symmetry of the molecule, retention and inversion of configuration cannot be distinguished.

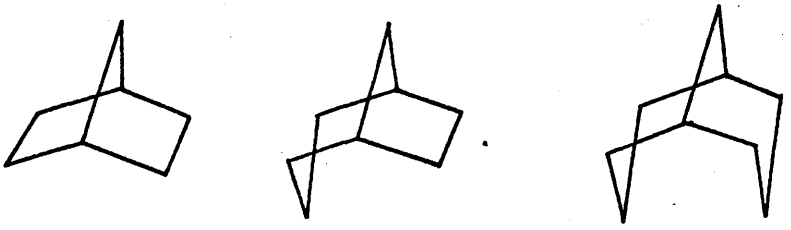
† — This work.

** — Indication from pyrolysis work, see Section 6.3.

✓ — Indicates products observed to be present from a qualitative examination. See Section 6.2

to cover the whole series.

6.11 Table 7 shows kinetic results for a series of bicyclo compounds containing a one-carbon bridge on which there is an ester group. There are three main carbon skeletons, the bicyclo [2,2,1] heptane or norbornane structure (D92), and those of bicyclo [3.2.1] - octane (D93), and bicyclo [3,3,1] nonane (D94).



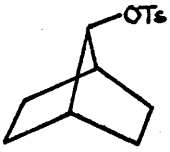
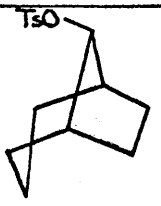
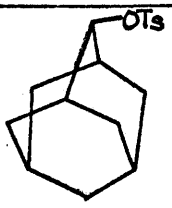
(D92) (D93) (D94)

In table 7, the compounds are arranged in order of decreasing relative rates, cyclohexyl tosylate = 1 being the reference. This reference allows acetolysis and ethanolysis results to be incorporated in one table. This arrangement is of course one of increasing free energies of activation, which allow discussion of different esters on an absolute rather than a relative scale. For ease of reference, the compounds are re-numbered T1 to T14 from their positions in the table.

6.12 Bond angle strain at the reaction centre. It is known (143) that the bond angle in norbornyl tosylate (T14), is about 96°. The corresponding angle is taken to be about 109.5° in adamantyl tosylate (T10, 142). In endo- and exo-bicyclo [3,2,1] octyl tosylates (T12, T7)

where there are a six-membered ring and a five-membered ring, the angle should be about the mean of these values of 96° and 109.5°, and it has been calculated to be so (144).

Since there is expected to be methylene participation in the solvolysis of (T7), we will omit it from this discussion. In the other three cases (T14, T12, and T10), product analysis shows there is very little (less than 10% in all cases) methylene participation, so that a direct comparison of energies of activation in terms of bond angles is valid, and these are shown in Table 8.

COMPOUND		BOND ANGLE	$\Delta G^{\#}$ (kcal/mole)
T14		96°	36.7
T12		Between 96° and 109.5°.	32.9
T10		109.5°	29.0
T6	Cyclohexyl tosylate	109.5°	27.0

The effect of the bond angle at the reaction centre is clearly illustrated. The difference of 2 kcal./mole between adamantyl tosylate and cyclohexyl tosylate cannot be due to bond-angle effects, since the angle is the same in the two cases (142), but must be due to the increased rigidity of the molecule arising from the bridged ring. When discussing the effect of the bond angle at the reaction centre in other bridged-ring systems, adamantyl rather than cyclohexyl tosylate will be taken as the reference compound.

The effect of bond angles has been commented on previously (141, 142), but following X-ray crystallographic work by Brown (138), it is possible to extend the discussion to the bicyclo [3,3,1] nonane system. Brown has shown (145) that the bond angle at the reaction centre in this system is about 111°. This should produce a reduction, scarcely sensible within the limits of experimental error, in the free energy of activation of bicyclo [3,3,1] nonyl esters compared with the corresponding adamantyl ester.

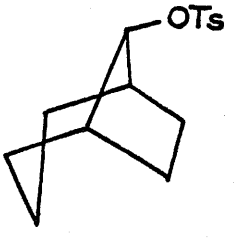
Another consequence should be seen in the unsaturated esters. The introduction of a double bond into a ring tends to flatten it and thus to bring bond angles nearer to 120°. This should produce a reduction in the free energy of activation, but again it is anticipated that this will be small.

It can be seen then that bond-angle strain will

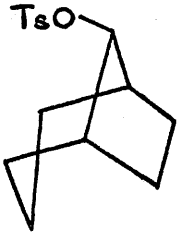
be of less importance in the three esters studied in this thesis, than in any other class of compounds in Table 7.

6.13 Size of the ring anti- to the leaving group and its suitability for methylene participation. Before opening the discussion under this heading, one must point out an overlap of this effect with the bond-angle effect discussed above. If one replaces a six-membered ring anti to a leaving group in a bridged-ring system by a five-membered ring, the bond angle at the reaction centre must change. In comparing effects of ring size, one must bear this in mind.

This competing effect is eliminated by discussing the two compounds exo- and endo-bicyclo-[3,2,1]octan-8-ol tosylates (T7 and T12)(141). The



(T7)

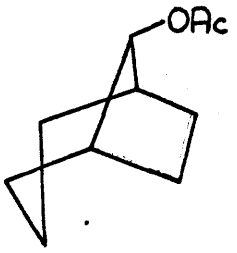


(T12)

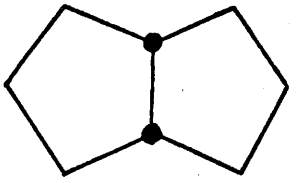
ring anti to the ester group is six-membered and five-membered respectively in the two compounds, yet the bond angle remains the same. In the exo-case (T7), product analysis indicates that the mechanism involves participation by the anti-located ring which is six-membered to 100%. In the endo-case there is no indication of any participation by the anti-located

five-membered ring. Thus the difference in rates between (T7) and (T12) can be attributed directly to the effect of ring size.

A closer examination of the products in the endo-compound suggests an interesting conclusion which Foote and Woodward (141) seem to have missed. Half the product is the corresponding acetate with inverted configuration (D95), while the other half has a carbon skeleton (D96) which indicates participation by the



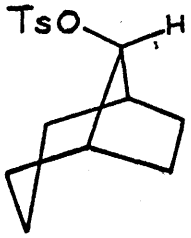
(D95)



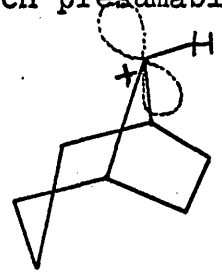
(D96)

syn-located six-membered ring.

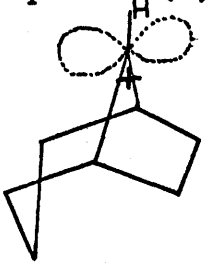
The conclusion to be drawn is that the endo-compound (T12) ionises in a classical manner to give the ion (D97) which presumably becomes planar (D98).



(T12)



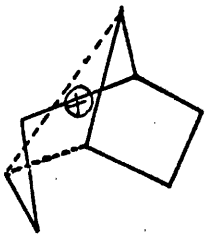
(D97)



(D98)

The distinction between syn- and anti-location of the six-membered ring has now disappeared, and this ring can now participate in the reaction to give a non-classical carbonium ion (D99). This ion ensures

inversion of configuration if the corresponding acetate is to be formed, or a carbon skeleton of type



(D99)

(D96) if rearrangement is to take place. This would appear to be the only way of explaining the products.

This one example shows then, that a six-membered ring anti to a leaving group is much more ready to take part in a reaction by methylene participation, than a five-membered ring, and that such participation has lowered the free energy of activation by 5.3 kcal./mole.

If we consider now other compounds in Table 7, there are three with five-membered rings anti to the ester group, namely (T11, T13, and T14). In T11 and (T13) there is considerable participation by the five-membered ring as established from product analysis. In these two cases however, the ion resulting from this participation is stabilised by homo-allylic participation by the double bond.

This complicating feature is not present in the norbornyl case (T14) and there, the five-membered ring participates to a small extent only. Thus, when five-membered ring participation can be separated

from other effects, it is found to be small, and as a result, the free energies of activation of the solvolysis of compounds with five-membered rings anti to the leaving group tend to be high.

There are three esters (apart from the adamantyl compound (T10) which has an extra bridge) which have a six-membered ring anti to the leaving group, and whose products of solvolysis are known, (T5), (T7), and (T8). Of these, (T8) is excluded because of complications resulting from a double bond. The extent to which participation is involved in the remaining two solvolyses can be judged from the carbon skeleton of any rearranged product and from the retention of configuration of unrearranged product. This is shown in Table 9 below.

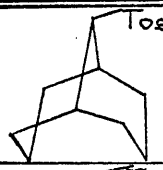
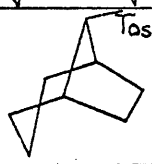
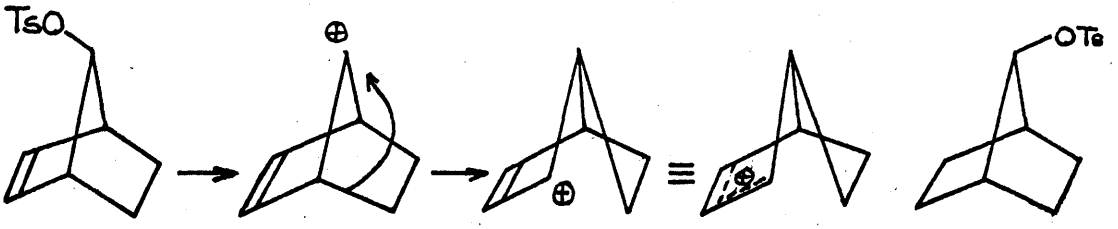
Compound		$\Delta G^{\#}$ (kcal/mole)	Product Analysis		
			A	C	A + C
T5		26.6	5+	87	92
T7		27.6	7	92	99

TABLE 9 A — Corresponding acetate with retention of configuration. B — Methylene participation by the anti six-membered ring. + — Since the molecule is symmetrical this cannot definitely be claimed as retention of configuration.

(T5) and (T8) indicate quite clearly that when there is a six-membered ring anti to the leaving group, the reaction path involves methylene participation almost completely, and there is a corresponding reduction in free energies of activation.

These conclusions extend those reached by Foote and Woodward (141).

6.14 Homo-allylic participation. The presence of a homo-allylic system stabilises a carbonium ion. This has been used by Winstein (124) to explain why the syn unsaturated compound (T11) reacts faster than the norbornyl compound (T14). This is shown diagrammatically in Figure 21, and has been discussed above (Section 4.9).



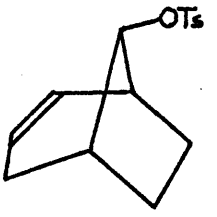
(T11) (T14)

Figure 21

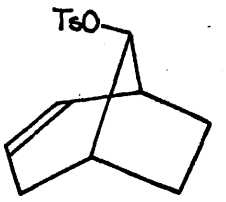
Thus, though it has been shown in section 6.13 that five-membered-ring participation does not take place readily, when such participation leads to a homo-allylic carbonium ion, it does take place.

There are two other esters in Table 7 to whose solvolyses a discussion of homo-allylic participation is pertinent, (T8) and (T13). In both cases homo-allylic participation must follow participation by

the five-membered ring and the ions would be of the

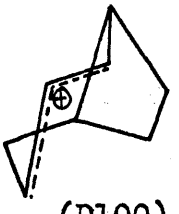


(T8)

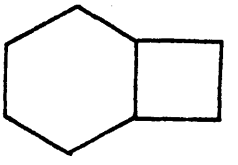


(T13)

form (D100). In the case of (T8), this ion could not be achieved by direct participation of the five-membered ring since it is <u>syn</u> to the leaving group, but would require formation of a classical planar carbonium ion first of all. The product from the ion (D100) would have carbon skeleton (D101). (T8) and



(D100)



(D101)

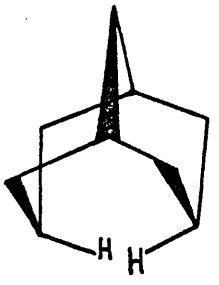
(T13) have solvolysis products of this skeletal form to 25% and 30% respectively, which shows that in both these cases homo-allylic stabilisation plays a part.

In analysing the various factors affecting the solvolysis of the compounds in Table 7, the ester (T13) presents a problem. It reacts only 22 times faster than the norbornyl compound (T14), the difference in free energies of activation being only 1.5 kcal./mole, and yet, two of the rate-enhancing factors we have discussed would appear to operate. The C-C-C bond angle at the reaction centre is known to be considerably

larger than in the norbornyl case, and there has been shown above to be some stabilisation of the intermediate carbonium ion by homo-allylic participation. In this case the result of these factors is not as well marked as one might have expected.

It does seem however, that homo-allylic participation plays a not unimportant rôle in these solvolyses, and that allowance must be made for this when considering mechanisms for the reactions reported in this thesis.

6.15 Steric strain. It has been pointed out in Section 6.4 that there is considerable strain in the bicyclo [3,3,1] nonane system because of 1,4 hydrogen interactions (D102). This would appear to be a



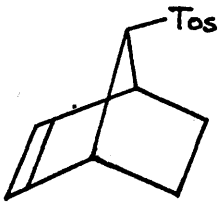
(D102)

significant factor in the solvolysis of (T2) and (T5), a point of which Foote and Woodward seem to have been unaware. Since both these esters solvolyse with ring-methylene participation, which removes the strain, this steric factor should cause an increase in rates of reaction and a reduction in free energies of activation of (T2) and (T5).

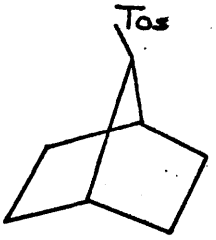
It would appear that this factor does not apply

not apply to any othercompounds in the table 7.

6.16 Direct double-bond participation. This last is the explanation for the most dramatic example yet known of anchimeric assistance.(123). Anti-7-norbornenyl tosylate (T1) is acetolysed 10^{11} times faster than norbornyl tosylate, and the free energy of activation is 15.1 kcal./mole less. It would appear that the



(T1)



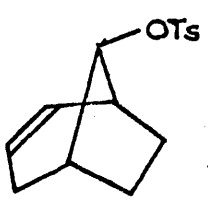
(T14)

bond angle at the two reaction centres is about the same. Product analysis indicates that there is no anti-methylene or homo-allylic participation which could produce the rate enhancement of (T1) compared with (T14), and yet there is this enhancement, far greater even on its own than any produced by the three factors mentioned. Winstein (123) attributes this as explained in Section 4.9 to direct participation of the double bond, the π-orbitals of which overlap the vacant orbital of the carbonium ion and stabilise it.

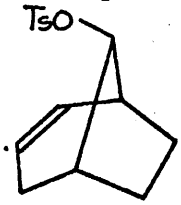
Can a similar postulate be the explanation for any other results given in Table 7? For this to be so, we require first of all a very large rate enhancement or correspondingly, a large fall in the

free energy of activation, and secondly, a product completely unrearranged and of the same configuration as the starting material, for these are the outstanding features of the solvolysis of anti-7-norbornenyl tosylate.

Leaving aside the compounds reported in this thesis, the only compound in Table 7 in which we might expect such participation is the compound (T8) which



(T8)



(T13)

solvolyses 260,000 times faster than the corresponding compound of opposite configuration (T13). (140). These compounds have been discussed above, Section 6.8, but the argument will be followed through briefly in the light of the headings used above.

In the two compounds, the bond angle at the reaction centre will be the same, and in addition product analysis indicates similar amounts of five-membered-ring participation to produce a homo-allylic ion. There are no steric effects peculiar to either compound so that the reduction in free energy in (T8) must be attributed either to the fact that it has a six-membered ring anti to the leaving group whereas (T13) has a five-membered ring, or to direct double

bond participation.

It has been shown in Section 6.13 that having a six-membered ring as opposed to a five-membered ring *anti* to the ester group in one case reduced the free energy of activation by 5.3 kcal./mole. This is of the same order as the reduction found in this case, 7.1 kcal./mole. This effect must then form a greater part of the explanation we are looking for, and may be the complete explanation.

A large part of the difference in free energies of activation is now explained; what remains, 1.8 kcal./mole is very small compared with the 15.1 kcal./mole of the norbornenyl case. In addition, as explained in Section 6.8, product analysis does not support the suggestion of direct double-bond participation.

Thus, it seems that while direct double-bond participation is definitely established in the norbornenyl case, it seems unlikely in the bicyclo [3,2,1] octane case. Since the participation has been explained in terms of orbital overlap (123), this suggests that there is less overlap in the bicyclo-octane case. This is borne out by an examination of molecular models.

6.17 The results of the ethanolysis of the three compounds reported in this thesis will now be discussed in the light of the five factors outlined above. The

values of reaction parameters obtained are shown in Table 10, those on product analyses being qualitative

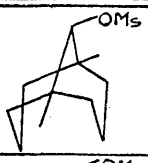
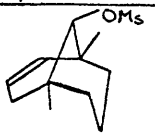
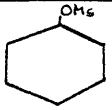
Compound		Relative Rates at 25°C.	$\Delta G^{\#}$ (kcal /mole)	Product Analysis		
				A	B	C
T2		110	23.9	-	-	100+
T3		13	25.2	✓	✓	✓
T4		12	25.1	-	✓	✓
T6		1	26.8	-	-	-

Table 10 A,B — Corresponding ethyl ether with retentionand inversion of configuration respectively. C — Participation by the anti six-membered ring + — Pyrolysis result.

only.

The three esters are second, third and fourth in Table 7, or in other words, compared with other bridged ring compounds of a similar type, they react very quickly, and have low free energies of activation. This is readily understood in the light of the first two factors discussed above.

Firstly, the bond angle at the reaction centre is about 111° (147), so that to achieve the ideal transition state, only a small change in bond angle would be necessary. There is thus no great energy barrier to reaction arising from this consideration.

Secondly, in all three cases the ring anti to the leaving group is six-membered, so that methylene participation would be expected to take place readily, and such participation would again lower the free energy of activation, Such participation is supported by the available product analyses.

Thus, the high position in Table 7 of the three esters is simply explained. It remains to explain their reaction constants relative to each other and to one or two other particularly relevant comparisons in Table 7.

6.18 The saturated compound (T2) has a lower energy of activation than the unsaturated compounds (T3 and T4), even although in these latter two compounds there may be direct double-bond participation or homo-allylic participation, both of which would lower the energy of activation. This marked reduction in the saturated compound is attributed to steric strain as outlined in Section 6.15.

The two unsaturated compounds have nearly equal energies of activation. This suggests that there is

no particular participation peculiar to either isomer. The factors contributing to the relatively low energy of activation in these two compounds are the favourable bond angle at the reaction centre, the possibility of homo-allylic participation by the double bond, and probably most importantly, the fact that there is in both, anti to the leaving group, a six-membered ring which can stabilise the transition state by methylene participation.

Thus it appears that the reaction parameters of these three compounds are consistent with each other. It would seem that there should be one direct comparison with another compound in Table 7 for each of these three esters. (T2) is compared with (T5), (T3) with (T8), and (T4) with (T13).

6.19 In (T2) and (T5), the bond angle, the steric

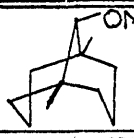
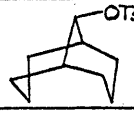
Ester		Relative Rates at 25°C.	$\Delta G^{\#}$ (kcal /mole)
T2		110	23.9
T5		4.1	26.6
T6	cyclohexyl	1	27.0

Table 11

factor and ring sizes are the same yet there is a difference of 2.7 kcal./mole in the free energy of

activation. The only structural difference is the increased degree of substitution in (T2). These substituents certainly stabilise any carbonium ion formed, and encourage any rearrangement that may be likely to take place. They also introduce further steric crowding which is relieved in the transition state where the relatively bulky mesylate group is absent. Thus another cause of the low energy of activation of (T2) arises from the angular methyl groups; this factor should also operate in the unsaturated compounds (T3) and (T4).

6.20 (T3) has a lower activation energy than

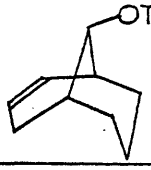
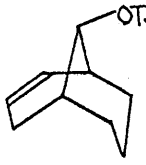
Ester		Relative Rates at 25°C.	$\Delta G^{\#}$ (kcal /mole)
T3		13	25.9
T8		0.74	28.1
T6	cyclohexyl	1	27.0

Table 12

(T8) because two of the factors outlined above operate in (T3) but not in (T8). Firstly, there are angular methyl groups present in (T3), and secondly the angle at the reaction centre is nearer 120° in

(T3) than in (T8). Other factors no doubt operate, but will be the same in both cases.

6.21 The lower activation energy of (T4) compared with (T13) can be explained in the same way as the

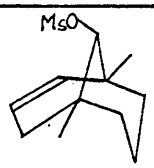
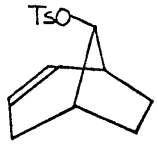
Ester		Relative Rates at 25°C.	G (kcal /mole)
T4		12	25.1
T13		2.9x10	35.2
T6	cyclohexyl	1	27.0

Table 13

(T3)—(T8) comparison. In addition, in (T4) the ring anti to the ester group is six-membered while it is five-membered in (T13).

6.22 Thus, a careful examination of Table 7 has made clear the factors which affect the rate of solvolysis and free energy of activation of solvolysis of bicyclo compounds with an ester group on the one-carbon bridge. Application of these considerations to the three esters whose solvolyses are reported in this thesis shows that the present results are compatible with this theory.

6.23 It is now possible to draw up diagrams, one each for the bicyclo[2,2,1]heptane, bicyclo[3,2,1]-octane, and bicyclo[3,3,1]nonane series, showing the various factors contributing to the free energy of activation, see Figures 22 to 24. Using the comparisons made in this discussion, the diagrams are set on a semiquantitative scale.

In the diagrams are summarised the conclusions drawn in the second part of this thesis.

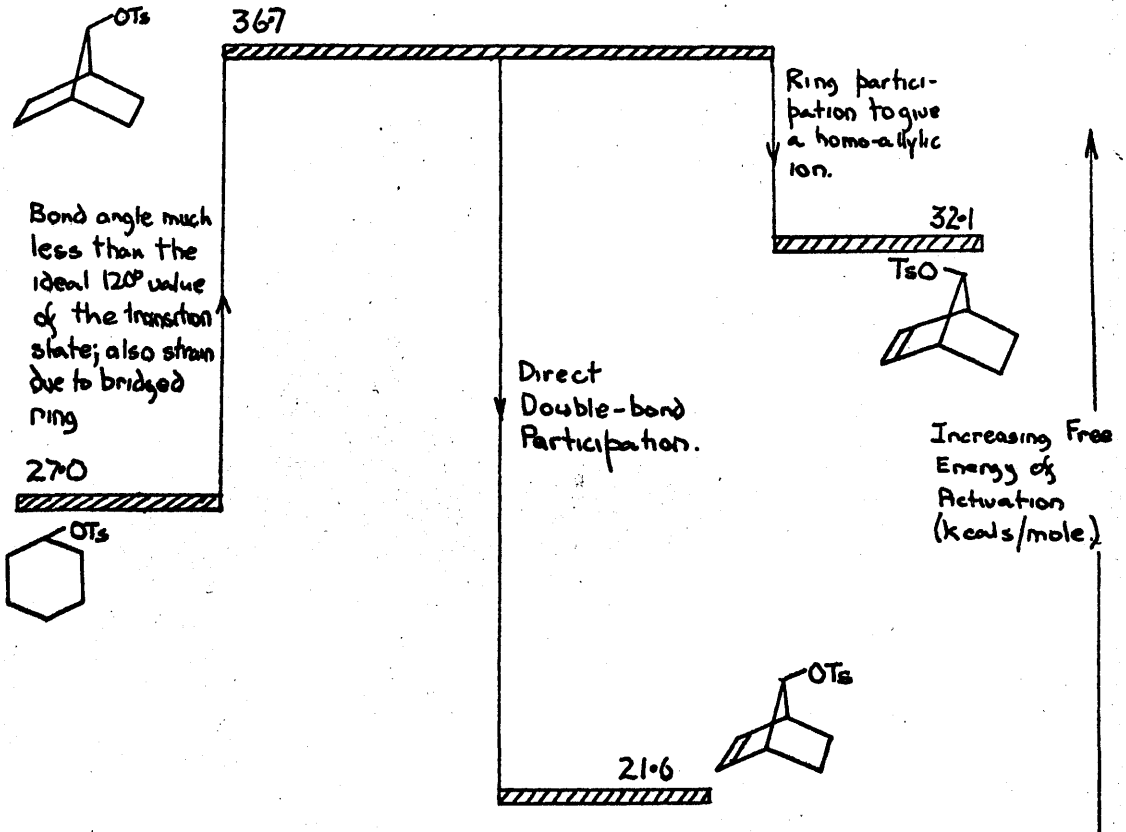


Figure 22 Diagram of the factors affecting the solvolysis of bicyclo[2,2,1]heptane compounds.

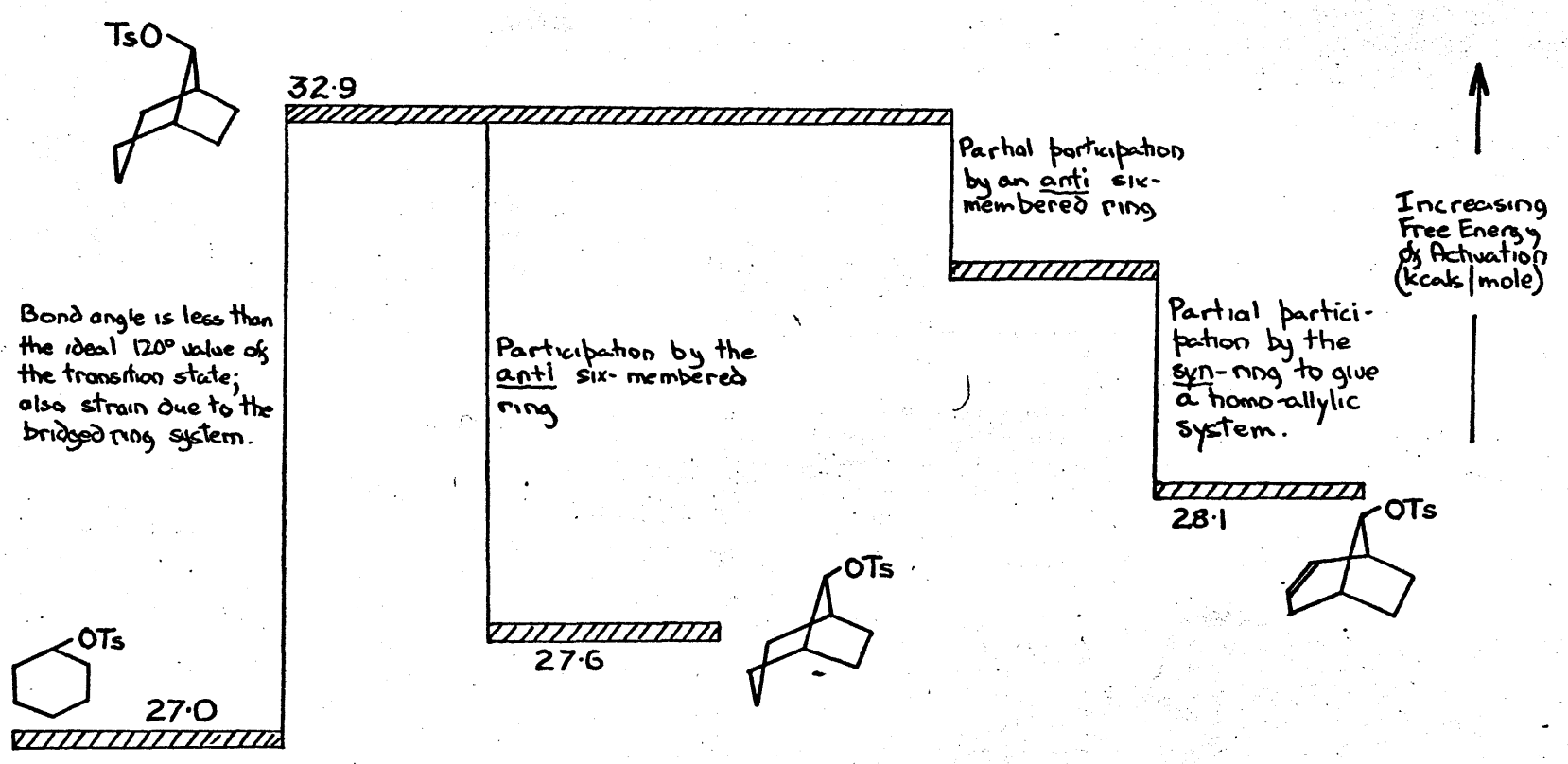


Figure 23 Schematic Diagram of the Factors affecting the solvolysis of bicyclo-[3,2,1]octane compounds.

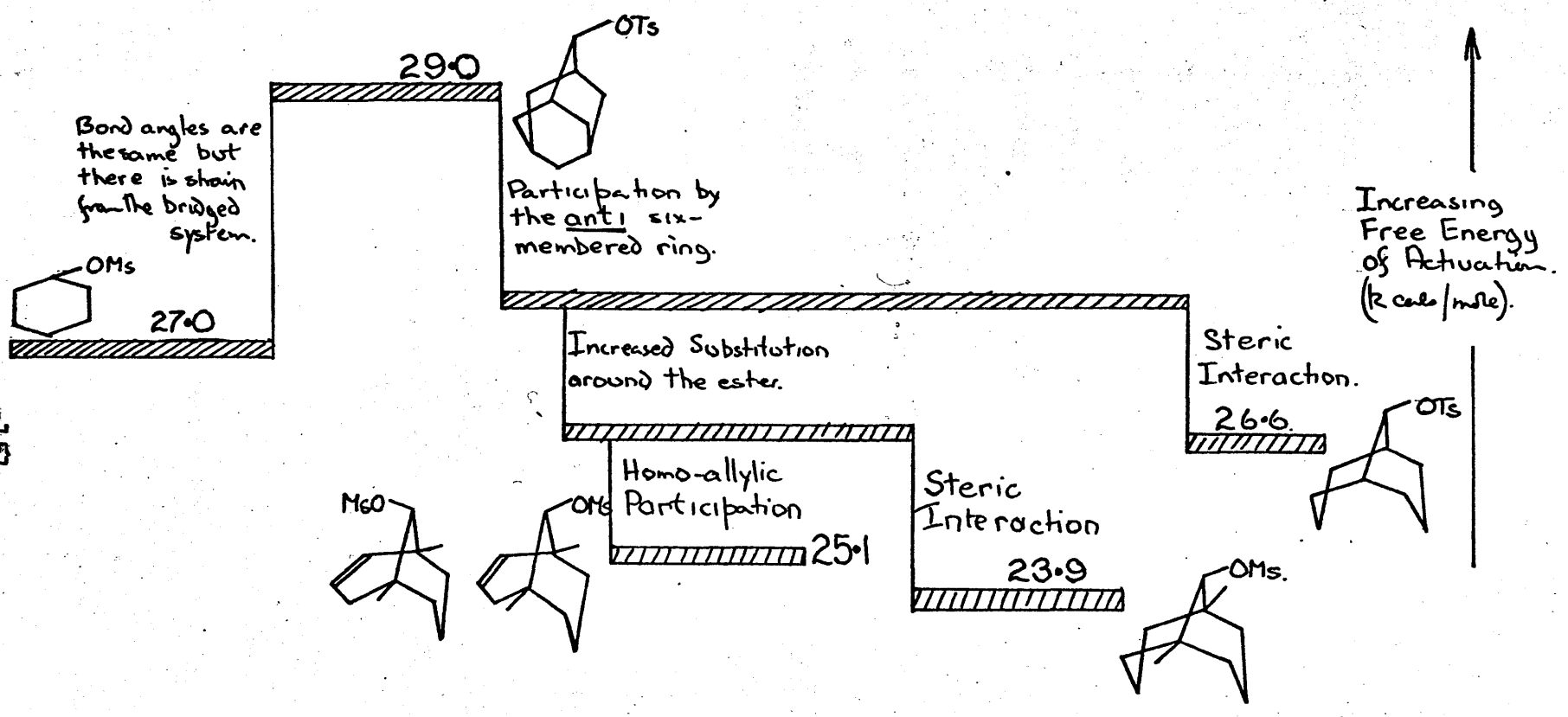


Figure 24 Schematic diagram of the factors affecting the solvolysis of bicyclo-[3,3,1]nonane compounds.

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