STEREOCHEMICAL STUDIES IN THE 1,3-DIOXAN SERIES

A thesis submitted to the
University of Stirling
for the degree of
Doctor of Philosophy

George M. Kellie

Department of Chemistry
February 1972

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The studies described in this thesis are principally concerned with an examination of the chair-boat equilibrium in 1,3-dioxans and the nature of the boat (or twist) conformations.

Chapter 1 reviews the basic features of conformational analysis, with special reference to 1,3-dioxans, and also describes some of the physical techniques (especially n.m.r. spectroscopy) which were widely used in this work.

The ^{13}C n.m.r. spectra of a number of methyl, gem-diethyl, and phenyl 1,3-dioxans are reported. Using a least squares method substituent chemical shift parameters are evaluated for compounds known to exist in chair conformations. When these parameters are used to calculate chemical shifts for compounds which would have a 2,4 or 4,6-syn-diaxial interaction in their chair conformations, large differences are noted between the observed and calculated chemical shifts for the compounds with a 2,4 interaction, but smaller differences are found for the compounds with a 4,6 interaction. These deviations are considered to demonstrate that the former compounds prefer *non*-chair conformations whereas compounds with a 4,6 interaction exist with appreciable amounts of chair and twist forms. The conformational equilibria in some 5-methyl-1,3-dioxans are estimated using the methyl group chemical shifts.

The ^{1}H n.m.r. spectra of some *non*-chair 1,3-dioxans are recorded. An analytical scheme is proposed which enables selection of the most stable twist conformation for each molecule. In many cases the vicinal coupling constants are found to be independent of temperature and this, and other features of the spectra, are interpreted as being indicative of conformationally biased twist conformations.

A microcalorimetric method for the determination of conformational enthalpies is described. The conformational free energy difference between the *cis* and *trans*-2,5-dimethyl-1,3-dioxans is found to be 4.02 ± 0.04 kJ mol^{-1}. The chair-boat enthalpy difference for 1,3-dioxan is estimated to be 36.5 kJ mol^{-1} on the basis of assumptions concerning the nature of the twist conformations.

The crystal structure of r-2-4,4-*c*-6-tetramethyl-2-(4'-bromophenyl)-1,3-dioxan is determined and refined to R = 0.12. The 1,3-dioxan ring exists in a severely distorted chair conformation with the phenyl group axial. The conformation, in solution, of this molecule and some related compounds, is discussed.

An empirical scheme for the analysis of the boiling points and molar volumes of a homologous series of compounds is described. This method is used to demonstrate the presence of *non*-chair conformations in some 1,3-dioxans.

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CHAPTER 1

INTRODUCTION

CHAPTER 1

1.1 Introduction

This thesis is concerned with some stereochemical studies on substituted 1,3-dioxans. In order to provide an introduction to the topics examined in this work, this chapter is devoted to a discussion of the theory and methods of conformational analysis, particularly with respect to the 1,3-dioxans. As physical techniques, notably nuclear magnetic resonance (n.m.r.) spectroscopy and X-ray diffraction, were widely utilised in this study, their application to conformational problems is also discussed.

1.2 Conformational Analysis

Conformational analysis may be considered to have originated in the work of Sachse[1] who, in 1890, postulated that cyclohexane was capable of existing in two puckered forms (now termed the chair and boat conformations) rather than as a flat ring (as proposed by Baeyer[2]). He also recognised the difference between what are now referred to as the axial and equatorial positions on the cyclohexane ring. In spite of a period of rejection of Sachse's ideas, the work of Mohr[3] and Hückel[4] on the *cis* and *trans* decalins, and the later diffraction studies of Hassel[5], led to a general acceptance of these principles. However it was not until the appearance of Barton's famous paper[6] pointing out the relationship between conformation and chemical and physical properties, that conformational analysis took its place as a distinct branch of organic stereochemistry.

Booth[7] has defined conformation as follows: "The conformations of a molecule are the non-superimposable arrangements in space of the atoms of a molecule, these arrangements being interconvertible by rotation about single bonds". However this statement means that many molecules have an infinite number of conformations available to them. As a result this definition is normally qualified so that it is only applicable to those arrangements which correspond to potential energy minima. In the context of this thesis, the definition of Dauben and Pitzer[8], which includes this qualification, will be applied. This states, "By conformation is meant any arrangement in space of the atoms of a molecule that can arise by rotation about a single bond and is capable of finite existence." The study of such conformations is termed conformational analysis.

1.3 The Conformations of Acyclic and Alicyclic Molecules

In order to gain an insight into the operation of conformational effects in cyclic systems, it is important to study the conformations of acyclic molecules. Indeed it was Pitzer's suggestion[9], that there exists a barrier to rotation about the carbon-carbon bond of ethane, that led to

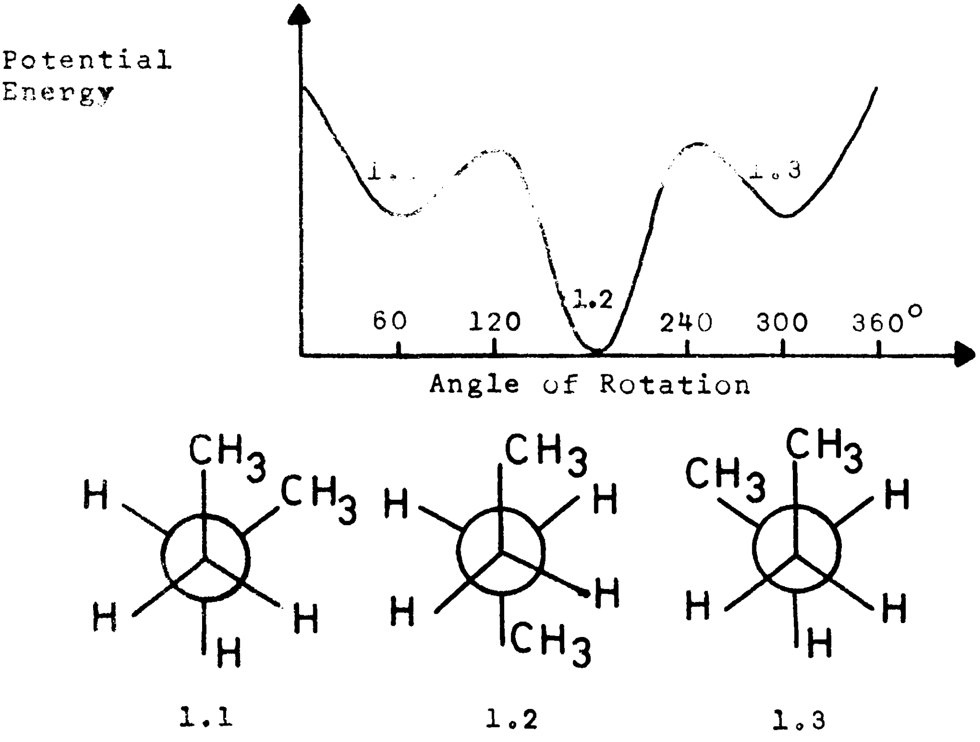


Figure 1.1. The Potential Energy Diagram for n-Butane

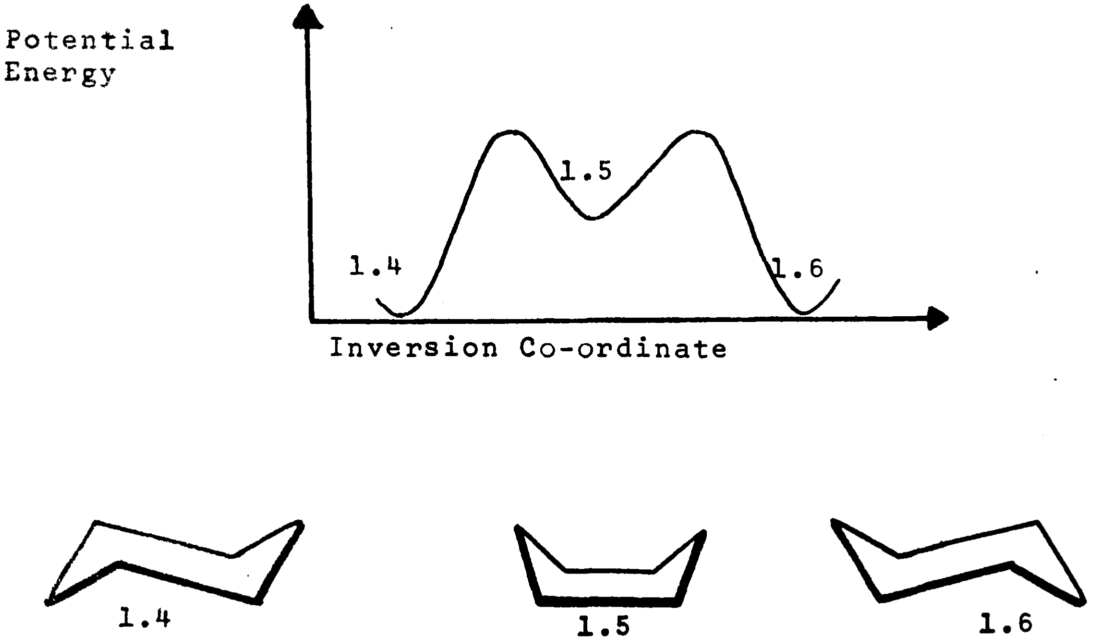


Figure 1.2. The Potential Energy Diagram for Cyclohexane Ring Inversion

much of present-day theory. If the potential energy function for rotation about the carbon-carbon bond of n-butane is plotted (Figure 1.1), three energy minima and three maxima are generated by a 360° rotation. The lowest minimum corresponds to the staggered (or antiperiplanar) conformation (1.2) in which the methyl groups are spatially as far apart as possible. In the enantiomeric gauche or <u>syn</u>-clinal conformations (1.1 and 1.3) the two methyl groups are close enough to have some mutual repulsions. This so-called gauche-butane interaction occupies an important place in conformational theory. The maxima correspond to arrangements in which the groups are eclipsed (<u>syn</u>-periplanar arrangements). If hetero-atoms are present in the molecule then the barriers for rotation about carbon-hetero-atom, or the hetero-atom - hetero-atom bonds can show marked differences from the barrier in ethane (Table 1.1). The origin of these potential or torsional barriers is, at present, not fully understood.[10]

A similar approach can be used to describe the conformations of cyclohexane. Rotation about the carbon-carbon bonds results in the potential function displayed in Figure 1.2. The two energy minima, 1.4 and 1.6, correspond to the so-called chair conformations, and the higher minimum, 1.5, to the boat form. The process of passing from 1.4 to 1.6, termed ring inversion, is analogous to a 120° rotation about the carbon-carbon

TABLE 1.1

Rotational Barriers for some Alicyclic Compounds[10]

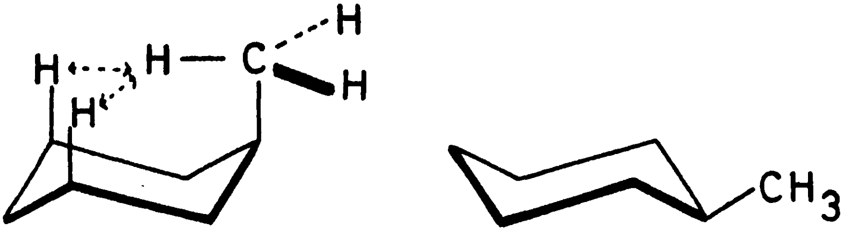
Compound	Bond[A]	Rotational Barrier (kJ mol^{-1})
$CH_3.CH_3$	C-C	12.1
$CH_3.OH$	C-O	4.6
$CH_3.O.CH_3$	C-O	11.3
$CH_3.NH_2$	C-N	8.4
$(CH_3)_2.NH$	C-N	15.1
$(CH_3)_3.N$	C-N	18.4
$CH_3.SH$	C-S	5.4
$CH_3.SeH$	C-Se	4.2
$CH_3.PH_2$	C-P	8.4
$CH_3.SiH_3$	C-Si	7.1
$(CH_3)_2.SiH_2$	C-Si	7.1
$(CH_3)_4.Si$	C-Si	7.5
$HO.OH$	O-O	31.4
$NH_2.NH_2$	N-N	48.1

A. The bond about which rotation takes place.

bond of ethane. Detailed examination of these conformations reveals that the boat form has two bonds along which the groups are eclipsed, whereas all the bonds are staggered in the chair conformation. Hence the chair form is the more stable conformation, and the chair-boat enthalpy difference (ΔH_{CB}) is approximately 20 kJ mol^{-1}. This conclusion has been confirmed by Raman spectroscopy[11] and electron diffraction[5].

As all the bonds in an ideal chair conformation are in perfectly staggered arrangements early workers considered that this conformation was essentially strain free. However recent evidence[12] suggests that as a result of repulsions between the *syn*-axial hydrogens and interactions between the carbon atoms across the ring, the cyclohexane chair conformation possesses ca. 5.6 kJ mol^{-1} strain energy. The presence of this strain is shown by the ring adopting a flattened chair conformation, in which the interactions described above are relieved at the expense of an increase in angle strain. This effect has been studied by Hassel,[13] who interpreted the electron diffraction pattern of cyclohexane in terms of a flattened chair conformation.

If methyl cyclohexane is examined it is observed that the methyl group may occupy one of two possible positions in the cyclohexane chair conformation viz. the axial position as



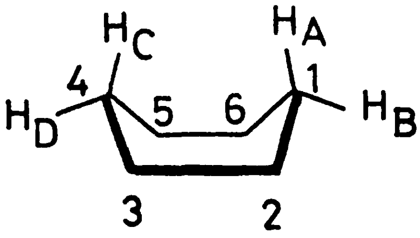
1.7 1.8

Figure 1.3. The Axial and Equatorial Conformations of Methylcyclohexane.

in 1.7, and the equatorial position as in 1.8. These conformations are interconvertible by a ring inversion process, but are not of equal energy. The axial conformer is the least stable due to strain, principally in the form of non-bonded repulsions between the axial methyl group and the syn-axial protons at C(3) and C(5), as shown in Figure 1.3. This interaction is analogous to the gauche butane effect and is termed a 1,3-diaxial interaction. In addition, various angle and torsional strains are present in the axial conformer which do not take place in 1.8. The free energy difference between 1.7 and 1.8 is approximately 7.1 kJ mol^{-1}, and this is termed the conformational free energy of a methyl group in cyclohexane. The greater stability of the equatorially orientated conformer has been verified by electron diffraction[14] and infra-red spectroscopy.[15]

1.4 Boat Conformations

Although cyclohexane predominantly exists in the chair conformation under most circumstances, there is always a small percentage of molecules in the boat conformation (ca. 1%). Originally the form assigned to the boat was the classical boat conformation (1.9). The principal sources of strain in this structure are the torsional interactions along the eclipsed bonds and the non-bonded repulsions between the hydrogens H_A and H_C (flagpole positions). If positions 1 and 4 are



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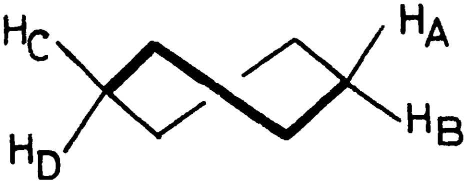

1.10

Figure 1.4. The Classical Boat and Twist Conformations of Cyclohexane.

rotated in opposite directions the molecular potential energy decreases and a minimum energy conformation is reached, in which the bowsprit (H_B and H_D) and flagpole hydrogens are equivalent* (1.10). In this form the flagpole repulsions are reduced and the torsional interactions are minimised. This is the conformation described by Johnson[16] as the twist or twisted form (also referred to as the skew or twist boat) and is clearly distinguished from the classical boat by possession of a two-fold axis of symmetry, in contrast to two mirror planes. In order to obtain a clear distinction between these conformations, the term twist form (or conformation) will be applied to the minimum energy structures, e.g. 1.10, and the designation boat conformation will be used to describe the family of <u>non</u>-chair conformations generated by this rotation process. On continuation of rotation of the end positions the molecule passes through another classical boat form to a second equivalent twist conformation. This process is called pseudo-rotation.

Hendrickson[17] has carried out several detailed analyses

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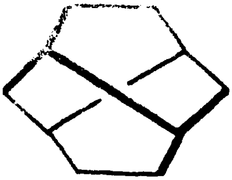
* These have also been termed stem and stern positions.



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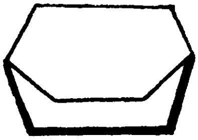

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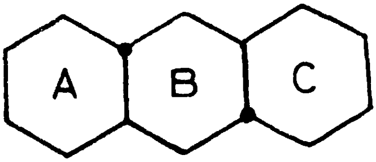

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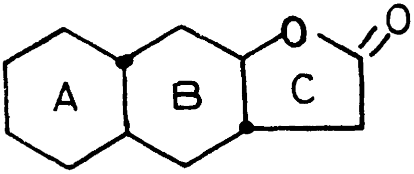

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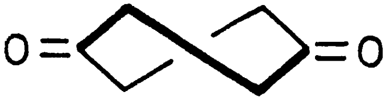

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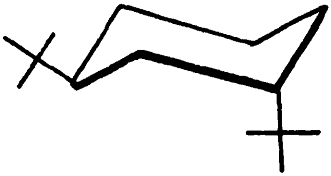

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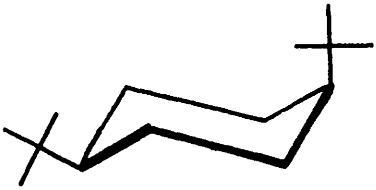


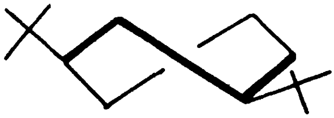
1.17

Figure 1.5. Some Compounds which may exist in Twist Conformations.

of these processes from a theoretical standpoint, by evaluating the variation in the total strain energy (angle strain, torsional strain, non-bonded interactions etc.) during ring inversion. His results suggest that the twist conformation is approximately 3.4 kJ mol^{-1} more stable than the classical boat form.

For certain molecules the twist conformation may become the most stable form. Compounds in which this occurs may be classified into three groups. This first class consists of compounds which are forced by their structure to adopt boat forms. Well known examples of this are twistane[18] (1.11), bicyclo[2,2,2]octane (1.12), and ring B of _trans_-_anti_-_trans_-perhydroanthracene[19] (1.13) and the lactone[16] (1.14). In all these molecules at least one six-membered ring is constrained into a twist conformation, ring inversion being excluded by the molecular structure (an analogous molecule with a locked chair structure is adamantane).

For some compounds it appears that the twist conformation is inherently the most stable. Cyclohexane-1,4-dione is an example of this class, X-ray diffraction[20] and dipole moment[21] studies having demonstrated that the twist conformation (1.15) predominates for this molecule. However, this is a rare occurrence, as it appears that most six-membered ring systems prefer the chair conformation for their parent compounds.



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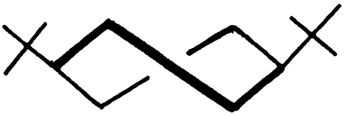

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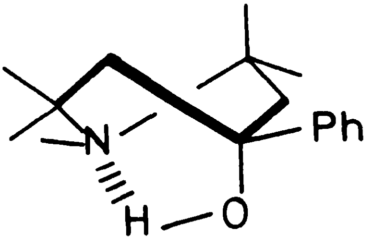

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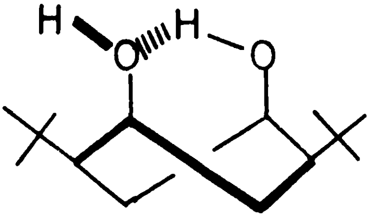

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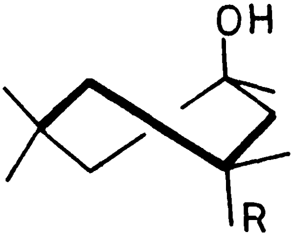

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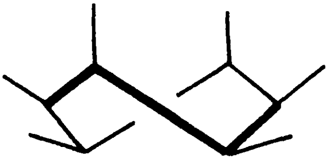

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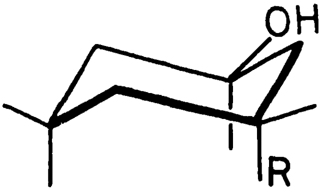

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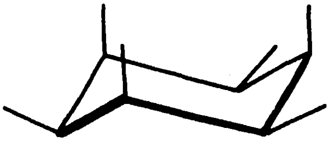
R=1-Naphthyl



1.25

Figure 1.5. (continued)

The third category, and most important with respect to this work, consists of molecules which reject the chair conformation due to the severity of the interactions (steric electronic etc.) which take place in that form. Trans-1,3 and cis-1,4-di-t-butyl-cyclohexanes[22] (1.16 and 1.17) are classic examples in which these effects are considered to occur. In the chair conformations severe steric repulsions take place as one of the bulky t-butyl groups must occupy an axial position. However these interactions appear to be largely relieved in some of the twist conformations that can be envisaged, (e.g. 1.18 and 1.19) hence these may be the preferred conformations.* For certain molecules not only can the strains in the chair forms be relieved, but certain stabilising effects may take place only in the twist conformations e.g. 1,2,2,5,5-pentamethyl-4-phenyl-piperidinol[23] (1.20) and cis-1,4-di-t-butyl-cyclohexane-cis-2,5-diol[24] (1.21), in which hydrogen bonds can form.

It is important to note that compounds in this third class can only exist in twist forms if there is available a conformation in which some or all of the strains present in the chairs are substantially relieved. Although this may be valid for some of the molecules described above, it does

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* Direct evidence in favour of the twist conformations is scant however, and recent n.m.r. studies[29] indicate that substantial proportions of chair conformations may be present for these molecules.

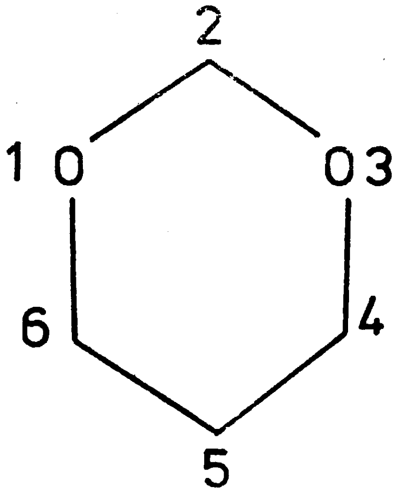


Figure 1.6. The 1,3-Dioxan Ring System.

not appear so likely for r-1-3,3-t-5-tetramethyl-1-hydroxy-c-5-(1'-naphthyl)-cyclohexane[25] and r-1-c-2,3,4,5,6-hexamethyl-cyclohexane[26]. For neither compound can a twist conformation be constructed which does not possess two axial (or more correctly, pseudo-axial) substituents e.g. 1.22 and 1.23. As a result, in spite of the strain due to non-bonded repulsions in the chair[27] being greater than 30 kJ mol^{-1} (i.e. > ΔH_{CB} for cyclohexane itself), they both appear to prefer these chair conformations (1.24 and 1.25). These conclusions are supported by the semi-empirical calculations of Hendrickson[17] and Allinger[28], which indicate that pseudo-axial methyl groups in twist conformations experience steric repulsions of similar magnitude to those found in chair conformations.

The chair-boat enthalpy difference for cyclohexane has been determined by Allinger (24.7 kJ mol^{-1})[22] and Johnson (23.0 and 20.1 kJ mol^{-1})[16,19], and calculated by Allinger (20.5 kJ mol^{-1})[28] and Hendrickson[17] (23.4 kJ mol^{-1}).

1.5 The Conformational Analysis of the 1,3-Dioxans

Next to the cyclohexanes the most studied six-membered ring system, from a conformational viewpoint, is the 1,3-dioxan system[30] (Figure 1.6). This is partly attributable to their ease of synthesis with a wide range of substituents at the 2,4,5 and 6 positions on the ring. In addition, their structures

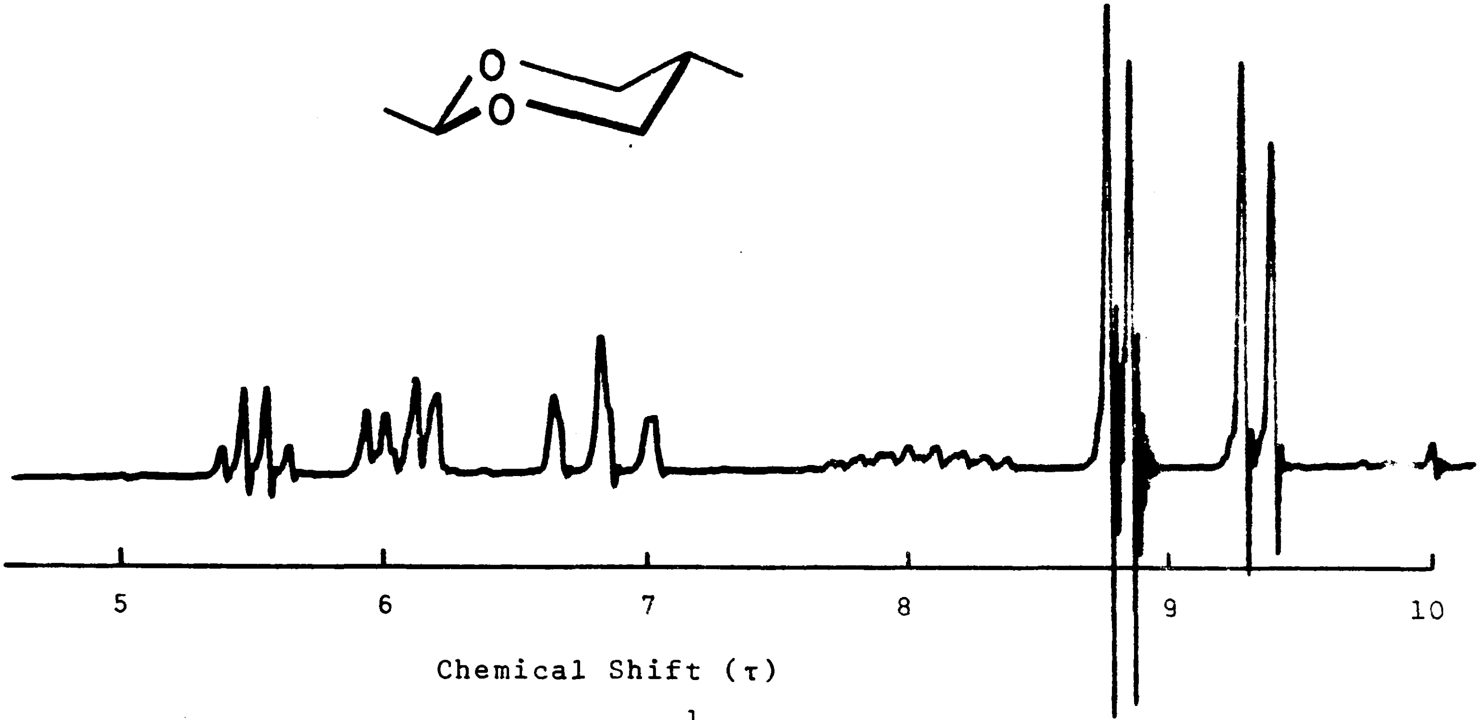


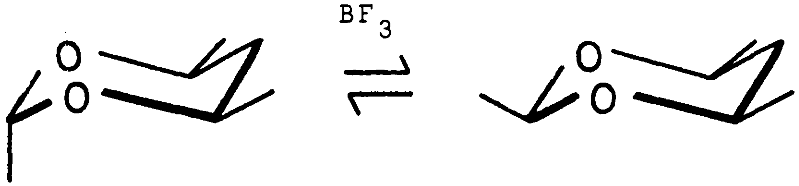
Figure 1.7. The Room Temperature ^{1}H N.M.R. Spectrum of
<u>Trans</u>-2,5-Dimethyl-1,3-Dioxan.

can be conveniently assigned using ^1H n.m.r. spectroscopy, the protons at each ring position resonating in different spectral regions, often with first order splitting patterns e.g. trans-2,5-dimethyl-1,3-dioxan gives rise to the readily interpretable spectrum shown in Figure 1.7. Conformational energies can also be conveniently determined, as stereoisomers may be equilibrated using Lewis acids which catalyse a reversible ring opening reaction e.g. the conformational free energy of a 2-methyl group can be evaluated by observing the equilibration of r-2-c and t-4,6-trimethyl-1,3-dioxans using g.l.c. techniques (Figure 1.8) ΔG $(t \rightarrow c)$ can be determined from the following equations:

$$K = \frac{[c]}{[t]} \qquad 1.1$$

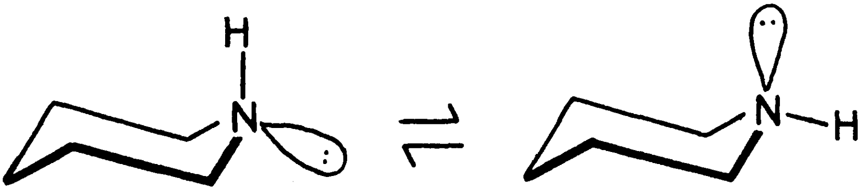
$$-\Delta G = RT \ln K \qquad 1.2$$

The presence of the two oxygen atoms in the ring results in this system having markedly different properties compared with the cyclohexanes. The fact that the carbon-oxygen bond length (1.43 Å) is less than the carbon-carbon bond length (1.54 Å) suggests that the ring will have an unsymmetrical puckering. Also each oxygen atom has two lone pairs of electrons (conventionally considered to be directed axially and equatorially) in place of the carbon-hydrogen bonds in cyclohexane. The nature and influence of these lone pairs are



t c

Figure 1.8. Equilibration of two epimeric 1,3-Dioxans.



1.26 1.27

Figure 1.9. The Conformational Equilibrium in Piperidine (only Nitrogen Inversion is shown).

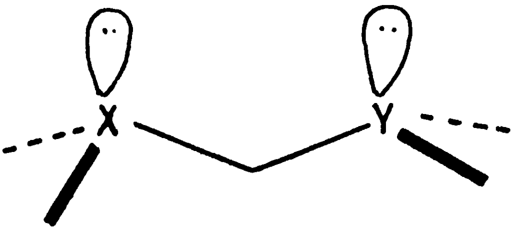


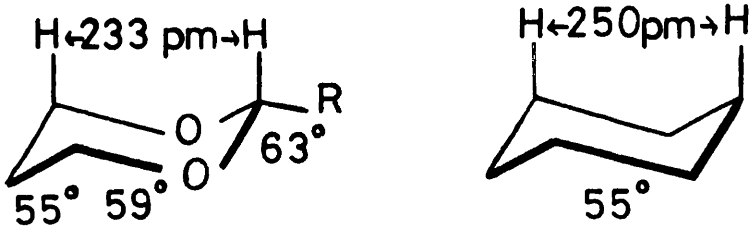
Figure 1.10. The "Rabbit-Ear" Effect (X and Y are hetero-atoms).

important in heterocyclic conformational analysis,[31] it having been proposed that the size of a lone pair of electrons is less than that of a proton. This implies, that in the conformational equilibrium in piperidine, the conformation with an axial lone pair on nitrogen (1.27) will be the favoured one. Recent evidence[32] supports this hypothesis, indicating that the free energy difference between 1.27 and 1.26 is 1.7 kJ mol^{-1} in favour of conformation 1.27.

Eliel has proposed that electrostatic dipolar interactions may be responsible for the preferred conformation of 2-methoxy-1,3-dioxan being the sterically crowded axial conformation.[33] When two lone pairs are orientated as in Figure 1.10, Eliel considers that an unfavourable interaction (the "rabbit-ear" effect) takes place. This is akin to the anomeric effect first observed by Lemieux for glycosides.[34]

The electronegative oxygen atoms can also participate in hydrogen bonding interactions, as in 5-hydroxy-1,3-dioxan, and polar interactions, as in 5-fluoro-1,3-dioxan, both of which exist with the 5-substituent predominantly in an axial orientation.[35]

The structure of the 1,3-dioxan ring has been established by an X-ray diffraction study of 2-(4'-chlorophenyl)-1,3-dioxan[36] (Figure 1.11). Like cyclohexane the



R = 4-Chlorophenyl

Figure 1.11. The Structure of the 1,3-Dioxan and Cyclohexane Chair Conformations. (Ring Torsion Angles are displayed beside the appropriate bonds).

chair conformation is preferred,* but due to the introduction of the oxygen atoms, the molecule is puckered in the O(1)-C(2)-O(3) region and flattened C(4)-C(5)-C(6) portion of the ring. This puckering results in positions 2,4 and 6 being in closer proximity than the equivalent cyclohexane positions.

The consequences of this structure on the conformational behaviour of the 1,3-dioxans can be seen by examining the conformational free energies for various substituents at each ring position (Table 1.2). The result of "pinching" the 2 and 4 positions together is to increase the steric repulsions experienced by an axial group at these positions. Hence the conformational energy of a non-polar group at C(2) and C(4) will be higher than for the same group in cyclohexane. Consequently it is normally necessary to employ only a methyl group at C(2) ($\Delta G = 16.7$ kJ mol^{-1}), as a conformational locking group. This avoids the use of the t-butyl group, used for cyclohexanes,[42] which has been considered to cause ring flattening effects.[43]

The lower conformational energies for groups at position 5 may reflect the weaker nature of the interaction between an

---

* This structure applies only to the solid state, but ^{1}H n.m.r. and other data are best interpreted assuming a chair conformation in solution as well.

TABLE 1.2

Conformational Free Energies for Groups in the 1,3-Dioxan and Cyclohexane rings

Group	Conformational Free Energy (kJ mol^{-1})[A]			
	1,3-Dioxan[37,38]			Cyclohexane[41]
	C(2)	C(4,6)	C(5)	
Methyl	16.7(17.2)[39]	12.1(12.1)[39]	4.2(3.4,3.8)[39,40]	7.1
Ethyl	16.7	-	2.9(3.4)[40]	7.5
i-Propyl	17.6	-	4.2(4.6)[40]	8.8
t-Butyl	-	-	5.8(7.1)[40]	>18.4
Phenyl	13.0	-	-	13.0

A. In every case the equatorial conformation is the more stable.

axial methyl group and syn-axial lone pairs (compared with syn-axial protons), and also that the axial 5 position leans out from the ring to a certain extent. Riddell and Robinson's proposal,[40] subsequently verified by Eliel,[38] that cis-2,5-di-t-butyl-1,3-dioxan exists in a chair conformation with an axial 5-t-butyl group, as opposed to the twist form of the analogous cyclohexane,[22] is further evidence of the weaker nature of the interactions of axial groups at C(5).

1.6 Boat Conformations of the 1,3-Dioxans

The boat conformations of the 1,3-dioxans, and the magnitude of the chair boat enthalpy difference, (ΔH_{CB}), have been the subject of much speculation and experiment in recent years. An early attempt to calculate ΔH_{CB} was made by Eliel,[41] who estimated a value of 9.2 kJ mol^{-1}. Subsequent estimates of greater than 12.6 kJ mol^{-1} (Anderson, Robinson and Riddell[44]), 23.9, 30.1, 34.7 and 35.6 kJ mol^{-1} (Pihlaja[45,39,46,47]), 25.9 kJ mol^{-1} (Anteunis[48]) and > 34.7 kJ mol^{-1} (Eliel[37]), have been put forward. This multitude of values stems partly from a lack of concrete evidence as to which substituted 1,3-dioxans exist in twist conformations.

Delmau[49] suggested that 4-t-butyl-4-methyl-1,3-dioxan

TABLE 1.3

Vicinal Coupling Constants for Trans-4,6-Dialkyl-1,3-Dioxans[50]

Alkyl Group	Sum of Vicinal Coupling Constants Hz[A]
Methyl	10.82
Ethyl	10.74
n-Propyl	10.45
i-Propyl	10.92
i-Butyl	10.62
sec-Butyl	11.06
t-Butyl	15.55

A. Between the ring protons at the 4, 5 and 6 positions.

was forced to adopt a twist form due to the presence of an axial 4-methyl group. However ^1H n.m.r. evidence proved that this molecule existed predominantly in a chair conformation.[44,50] Eliel[37] and Pihlaja[51] have proposed that molecules which possess two syn-diaxial methyl groups might prefer twist conformations. ^1H n.m.r. solvent shifts[51] and coupling constants[37,51], thermochemical[39] and molecular rotation[52] studies, tended to support this argument.

Anteunis has tackled this problem by preparing model compounds which would be forced to have an axial t-butyl group in their chair conformations[50] e.g. trans-4,6-di-t-butyl-1,3-dioxan. He examined the sum of the vicinal coupling constants for a series of trans-4,6-dialkyl-1,3-dioxans. For the chair conformations he anticipated that the sum of the vicinal couplings between the 4,5 and 6 protons would be ca. 11 Hz, whereas for a twist conformation a value of ca. 15 Hz would be more likely. Examination of the results in Table 1.3 indicates that only for trans-4,6-di-t-butyl-1,3-dioxan is the latter criterion satisfied. Hence Anteunis assigned a twist conformation to this molecule.

1.7 Nuclear Magnetic Resonance Spectroscopy in Conformational Analysis

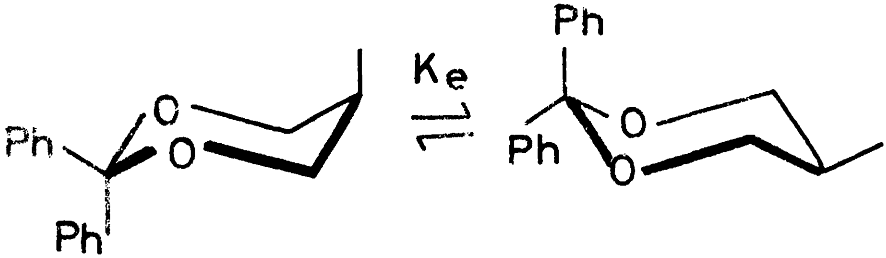
The impact of n.m.r. methods in the field of conformational analysis has been great, with almost every new development in technique and instrumentation being applied to conformational problems. Several reviews exclusively devoted to such applications of the n.m.r. technique have appeared,[53,54] the most recent being that of Booth[7]. In the course of this work ^{1}H and ^{13}C n.m.r. were extensively employed, therefore some discussion of their use in conformational analysis is warranted.

^{1}H N.M.R. Spectroscopy

In spite of its rather limited range of chemical shifts (ca. 10 p.p.m. for most organic compounds) the proton is the nucleus most studied by magnetic resonance. Both of the readily available n.m.r. parameters, viz. the chemical shift (τ), and the coupling constant (J), are influenced by stereochemical forces. This technique may be applied to conformational problems of several different types.

Ring inversion barriers[53] may be determined by n.m.r. provided the barrier falls in the range 20-85 kJ mol^{-1}, as the rate of interconversion of two species across such a barrier is of the same order of magnitude as the transitions involved in n.m.r. spectroscopy. The Franck-Condon principle predicts that under these conditions the spectrum observed will be dependent on the relative rates of the two processes. If d_{11}-cyclohexane[55] is examined at room temperature only a single resonance is observed as ring inversion is the more

τ(5 Me) = 8.75 p.p.m. τ(5 Me) = 9.42 p.p.m.



τ(5 Me) = 9.28 p.p.m.

$$Ke = \frac{\tau_e - \tau_{cis}}{\tau_{trans} - \tau_e}$$

$$= 3.8$$

$$-\Delta G = RT \ln Ke$$

$$= 3.3 \text{ kJ mol}^{-1}$$

Figure 1.12. The Conformational Equilibrium in 2,2-Diphenyl-5-Methyl-1,3-Dioxan (all values measured at 306.5K).

rapid process and the spectrometer is unable to distinguish between the shift of the proton in the axial and the equatorial conformations. If the temperature is reduced to ca. -70°, ring inversion becomes slow, relative to the nuclear transitions, and two resonances are observed. By examining the change in line shape as the temperature is lowered[53] it is possible to evaluate the barrier to ring inversion, ΔG^{*}.

The chemical shifts can also be used to study conformational equilibria. A good example of this can be seen for 2,2-diphenyl-5-methyl-1,3-dioxan examined in this work. This compound exists at room temperature as an equilibrium mixture of the conformer with the 5-methyl group axial, and that with the 5-methyl equatorial. If the shifts of the 5-methyl protons in two conformationally biased compounds, <u>cis</u>-2-phenyl-5-methyl-1,3-dioxan (axial 5-methyl), and <u>trans</u>-2-phenyl-5-methyl-1,3-dioxan (equatorial 5-methyl), are measured, it is observed that they differ appreciably. By measuring the shift of the 5-methyl protons in 2,2-diphenyl-5-methyl-1,3-dioxan, the equilibrium constant, and the conformational free energy of the 5-methyl group may be estimated as shown in Figure 1.12.

Perhaps the most widely applied n.m.r. parameter in conformational analysis, is the vicinal coupling constant

$^3J_{H,H}$. Karplus[56], in a series of pioneering papers, proposed that this coupling constant in ethane was dependent on a number of factors, the principal one of which was the dihedral angle, ϕ, between the coupled protons. This principle was embodied in the so-called Karplus Equations, which can be written:

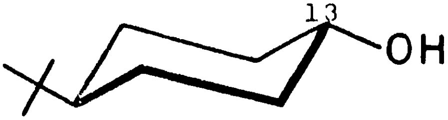
$$^3J_{H,H} = \begin{cases} 8.5\cos^2\phi - 0.28\ \text{Hz} & 0^\circ \leqslant \phi \leqslant 90 \\ 9.5\cos^2\phi - 0.28\ \text{Hz} & 90^\circ \leqslant \phi \leqslant 180^\circ \end{cases} \qquad 1.3$$

This equation cannot be applied quantitatively for heterocyclic molecules and is conveniently used in an empirical fashion. In general it may be said that large values of $^3J_{H,H}$ (greater than 10 Hz) are indicative of large dihedral angles (or angles of 0°) i.e. trans or diaxial arrangements, smaller values (1-6 Hz) result from gauche arrangements (ca. 60° angles), and values near zero are due to ca. 90° angles. Used in this manner the vicinal coupling constants are an invaluable aid to assigning stereochemistry. The geminal coupling constants, $^2J_{H,H}$ are also influenced by stereochemical factors and have been applied to conformational problems notably by Crabb[57] and Anteunis[48].

Carbon-13 (^{13}C) N.M.R. Spectroscopy

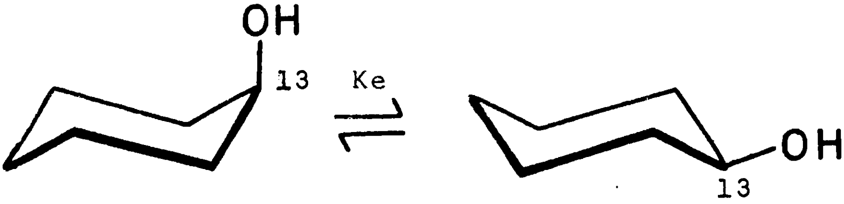
In contrast to ^{1}H n.m.r., ^{13}C n.m.r. has been slow to be applied as a tool in conformational studies, due to instrumental problems. ^{13}C has a low natural abundance (ca. 1%) and a small magnetic moment, resulting in a sensitivity of only 10^{-4} of that for protons under comparable conditions. Early workers employed high values of radio frequency power, rapid scanning, large sample volumes and computer accumulation of spectra (C.A.T.), to enhance the poor signal to noise ratios normally obtained.[58] Due to high cost ^{13}C enrichment of compounds has not been commonly employed. The advent of sophisticated decoupling techniques has led to important improvements in sensitivity. Broad band (or noise) decoupling[59], conveniently performed using a random noise generator, can decouple all the protons in a molecule simultaneously. In addition to the intensity enhancements expected from collapsing multiplets to singlets, nuclear Overhauser effects lead to still greater peak intensities. Roberts[60] has developed an off-resonance decoupling procedure which incompletely decouples the protons, leaving the splitting patterns intact with reduced splittings, thus aiding spectral assignments.

One of the most important advances in spectrometer design has been the use of Fourier Transform n.m.r.[61,62].



<u>cis</u> <u>trans</u>

δcis = 126.4 p.p.m. δtrans = 121.5



δe = 122.8 p.p.m.

$$K_e = \frac{\delta cis - \delta e}{\delta e - \delta trans}$$

$$= 2.77$$

$$-\Delta G = 2.5 \text{ kJ mol}^{-1}$$

Figure 1.13. The Conformational Equilibrium in Cyclohexanol.

In this experiment the radio frequency field is applied as a pulse of ca. 1 millisecond length, instead of being steadily swept as in the conventional n.m.r. experiment. All the spectral lines are simultaneously excited, and the pulse decays to negligible intensity in a time which depends on magnetic field inhomogeneity and relaxation effects. This decay pattern is the Fourier Transform of the conventional absorption mode spectrum. Therefore a series of pulses can be accumulated and transformed to obtain a certain signal to noise ratio, in a much shorter time than is possible with the conventional C.A.T. technique.

The first observation of conformational effects by ^{13}C n.m.r. was by Stothers[63], who examined the shift of the carbinol carbon atoms in a series of conformationally biased 4-t-butyl-cyclohexanols (Figure 1.13). He noted that for the isomer with an axial hydroxyl group the carbinol carbon resonated ca. 5 p.p.m. to higher field of that in the isomer with an equatorial hydroxyl group.

Using these observations he was able to estimate the conformational equilibrium in cyclohexanol itself by measuring the carbinol carbon shift and applying a method similar to that described for proton shifts.

Ring inversion barriers can also be studied using variable temperature ^{13}C n.m.r. spectroscopy. Grant[64] and

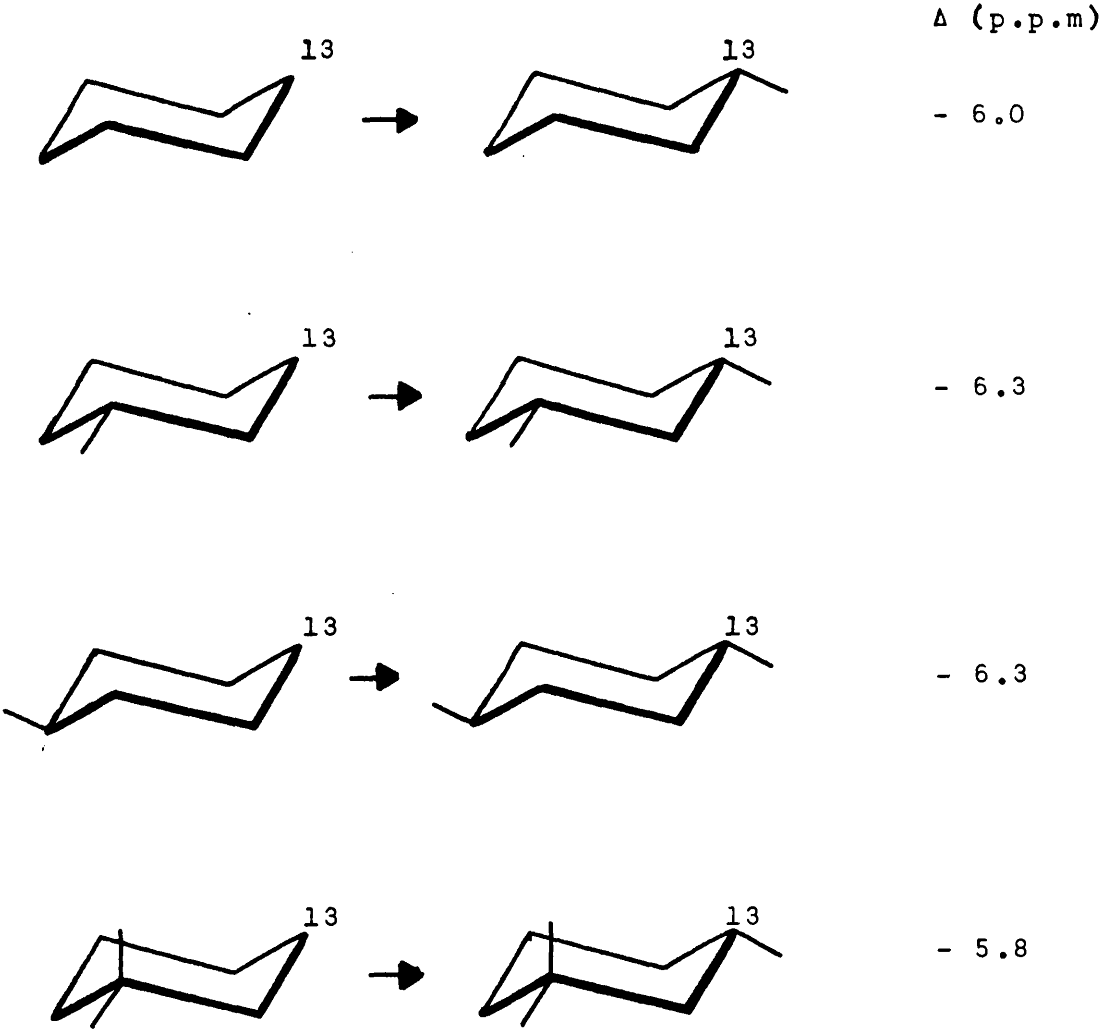


Figure 1.14. The Effect, on the Chemical Shift of the Substituted Carbon Atom, of introducing an Equatorial Methyl Group into the Cyclohexane Ring.

Schneider[65] have examined some dimethyl cyclohexanes using a line shape analysis. However, as both workers employed complete proton decoupling, it is possible that differential nuclear Overhauser effects could have influenced the line shapes as well as the intensities. Until some analysis of these effects is undertaken, inversion barriers determined by such a method must be open to criticism.

The ^{13}C shifts of many organic compounds have been rationalised by the use of so-called substituent parameters[66]. It has been found that these shifts are dependent on the type and orientation of each substituent in the molecule. Grant[67] applied this method to the methyl cyclohexanes. He observed that introducing (say) an equatorial methyl group into the cyclohexane ring produced a consistent effect on the shifts of the other carbon atoms, (Figure 1.14), regardless of what other substituents were present (unless they were in close proximity). Having evaluated "best-fit" values for these parameters by a least squares method, he could use these figures to calculate the shifts of the ring carbon atoms with great accuracy. However for 1,1,2-trimethyl-cyclohexane, which was not included in the least squares analysis, he was unable to calculate the ring carbon shifts with any accuracy. As a result he suggested that this compound adopts a twist conformation rather than any of the possible chair forms.

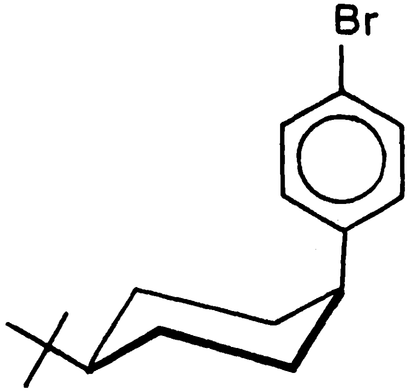


Figure 1.15 The Structure of <u>cis</u> - 1 -(4' - bromophenyl) - 4 - t - butyl - cyclohexane

However this explanation seems unlikely, as the interactions present in both chair conformations would not be expected to force this molecule into a twist conformation. It is more likely that this arrangement of three methyl groups requires an additional substituent parameter to account for the observed chemical shifts.

1.8 X-ray Diffraction

This technique, in spite of the pioneering work of Hassel[5], has been slow to be applied to conformational problems. At present no systematic study of the effects of different substituents on the conformations of a cyclic system has been undertaken, although Altona and his co-workers[68] have examined a series of heterocyclic ring systems. In fact only recently has the structure of cis-1-(4'-bromophenyl)-4-t-butylcyclohexane[69] (Figure 1.15) been determined, in spite of considerable discussion of its possible structure extending over a period. In view of the power of the technique the lack of applications in conformational analysis is at first sight surprising, but may in fact be due to the widespread use of n.m.r. spectroscopy which is convenient, and enables the study of molecular conformations in solution. In contrast X-ray diffraction is time consuming and is normally only applied to solids.

However this situation is now changing with the greater availability of diffractometers and the use of direct methods[70] for solving structures that do not require the molecule to possess heavy atoms[68]. Therefore it is likely that x-ray diffraction will play an increasing role in conformational studies in the future.

1.9 Conclusions

This chapter has highlighted some of the more important unresolved questions in the conformational analysis of the 1,3-dioxans. When the work described in this thesis was commenced the principal questions remaining to be settled concerned the chair-boat equilibrium for 1,3-dioxan. Accordingly this study was undertaken with three principal objectives:

(1) To develop a simple unambiguous method for deciding which 1,3-dioxans exist principally in non-chair forms.

(2) To determine the details of the stereochemistry of these non-chair conformations.

(3) To settle the question of the chair-boat energy difference in this system.

The methods employed and the results obtained are presented in the subsequent chapters.

CHAPTER 2

THE ^{13}C N.M.R. SPECTRA OF SOME 1,3-DIOXANS

CHAPTER 2

2.1 Introduction

A principal aim of this work, as outlined in Chapter 1, was to establish a simple and unambiguous method by which 1,3-dioxans, which exist in twist conformations, might be identified. Some of the techniques employed by previous workers for this purpose have been discussed in Chapter 1. However, none of these approaches was without some limitations, and a more reliable technique was sought.

Carbon-13 n.m.r. spectroscopy appeared to be a more viable proposition. Stothers[63,71], Grant[64,67], and Roberts,[60,72,73,74,75,76,77] had established ^{13}C n.m.r. as a tool for conformational studies, and Grant had assigned a twist conformation to 1,1,2-trimethylcyclohexane using this technique.[67] Further, it was anticipated that the 1,3-dioxans would give rise to simple, readily interpretable spectra, due to the large differences in the magnetic environments of the carbon atoms at position 2 (acetal like), positions 4 and 6 (ether like), and position 5 (hydrocarbon like).

Prior to this study the ^{13}C n.m.r. spectrum of 1,3-dioxan itself had been recorded by Maciel and Savitsky[78], and Riddell[79] had examined some simple methyl substituted 1,3-dioxans. However, Riddell's values were somewhat inaccurate due to non-linearity of his spectrometer's sweep, and it was necessary to correct his results to take account of this factor. Following publication[80] of this work, Eliel and his co-workers[81] reported some ^{13}C results for similar 1,3-dioxans. Although some of the compounds were recorded in solvents not used in this work, there is considerable agreement between Eliel's data and the results to be presented in this chapter.

2.2 Experimental Method

All of the compounds examined in this study were synthesised by standard methods (see Chapter 7), or were obtained as gifts. The ^{13}C n.m.r. spectra were recorded either for neat liquids at 15.1 MHz using the undecoupled computer accumulation technique, or were measured in $CDCl_3$ solution, using a Fourier Transform method, at 22.63 MHz. Full details of these procedures are to be found in Chapter 7.

2.3 Assignment of Resonances

The assignment of the resonances was carried out initially for the undecoupled spectra, and these conclusions applied to the noise decoupled spectra. The principal peaks observed for each compound were analysed by two different

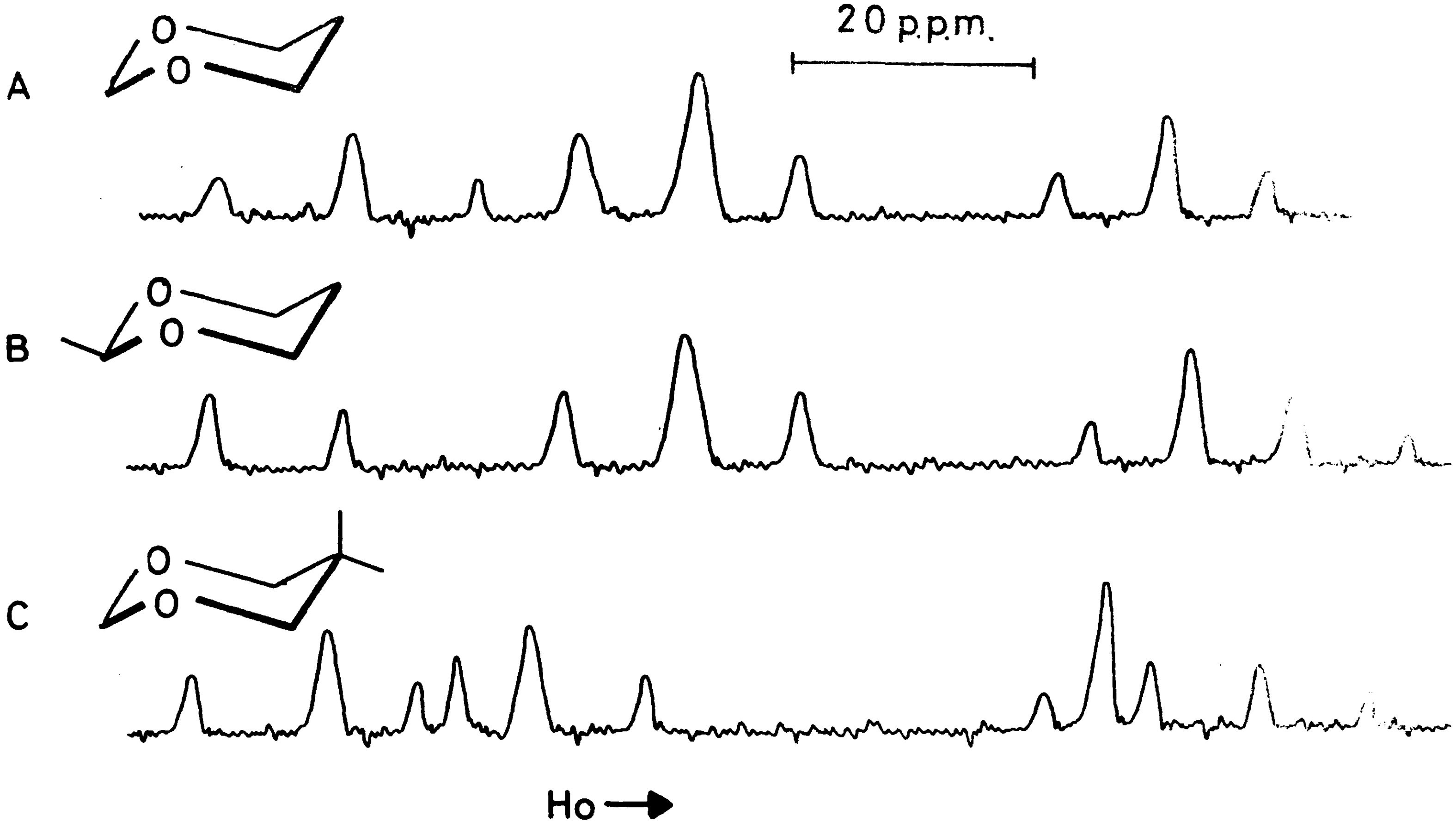
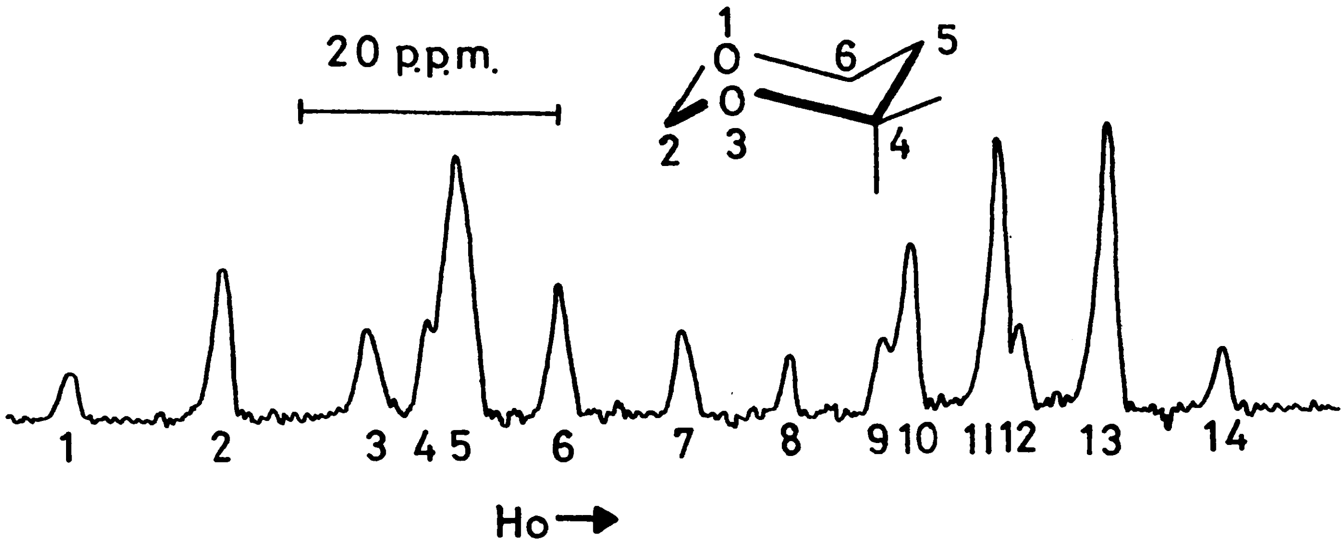


Figure 2.1. The ^{13}C n.m.r. spectra of three 1,3-dioxans.

approaches. The first method employed the proton-carbon directly bound coupling constants, $J_{^{13}C,H}$, which were readily obtained from the proton spectra. These showed a wide variation in magnitude between the different positions on the 1,3-dioxan ring (Table 2.1). In spite of the large error involved in measuring these couplings from the ^{13}C spectra ($\pm$ 7.5 Hz), the variation in the couplings for different ring positions was detectable. This method failed when a carbon atom had no directly attached protons, and only indicated in which spectral region each type of carbon atom resonated.

A complementary approach was to consider a series of compounds of known structure (Figure 2.1), and to examine the multiplicities of the resonances. Spectrum (a), of 1,3-dioxan, comprised three triplets of relative area 1:2:1 and shifts of 99.7, 126.6, and 165.9 p.p.m. respectively (shifts were measured in p.p.m. upfield from $^{13}CS_2$ reference). Coupling constant measurements indicated that $J_{^{13}C,H}$ decreased progressively proceeding from the low field to the high field resonances. The intensities suggested that the absorption of largest area was attributable to the equivalent 4 and 6 positions and the couplings led to the conclusion that the low field signals were due to C(2). Examination of spectrum (b),



C(2) : peaks 1, 2, 3

C(4) : peak 5

C(5) : peaks 8, 10, 12

C(6) : peaks 4, 6, 7

Methyls : peaks 9, 11, 13, 14

Figure 2.2. The ^{13}C n.m.r. spectrum of 4,4-dimethyl-1,3-dioxan.

of 2-methyl-1,3-dioxan, confirmed this, as the low field resonance was the doublet anticipated for C(2). For 5,5-dimethyl-1,3-dioxan, spectrum (c), the C(5) signal was a singlet at high field in agreement with the previous deductions. It was also important to note that compounds (b) and (c) had their methyl quartets at high field.

Use of both criteria enabled convenient assignment of the resonances for most of the 1,3-dioxans examined, e.g., all the lines of the spectrum of 4,4-dimethyl-1,3-dioxan were assigned by this method (Figure 2.2).

2.4 Analysis of the Chemical Shift Results

In order to use the chemical shifts to demonstrate the presence of non-chair conformations for some 1,3-dioxans, the following approach was adopted. Substituent parameters, of the type successfully employed by Grant[66,67] and Roberts[72,73,76], were evaluated for 1,3-dioxans known to exist predominantly in chair conformations, with a view to calculating the shifts of compounds suspected of preferring non-chair forms. As the calculated values would only apply to chair conformations any deviation between the observed and calculated shifts might reflect the presence of non-chair conformations.

In choosing compounds to form the basic set for substituent parameter analysis, it was important to consider the possibility of conformational equilibria in some of the 1,3-dioxans. In Chapter 1 it was noted that the free energy difference between equatorial and axial methyl groups at positions 2, 4 and 6 is greater than 12.0 kJ mol^{-1}, therefore compounds such as 2-methyl-1,3-dioxan will exist almost exclusively with the methyl group equatorial. In all similar cases, the possibility of the methyl group occupying an axial orientation was excluded from the analysis. However, for a methyl group at C(5) the free energy difference between the axial and equatorial positions is small, i.e., ca. 3.7 kJ mol^{-1}, resulting in compounds, such as 5-methyl-1,3-dioxan, having about 20% of the conformer with the 5-methyl group axial. These compounds were not included in the analysis, but it was anticipated that some measure of their conformational equilibrium constants might be made from the ^{13}C shift data.

1,3-dioxans possessing single axial methyl groups, e.g., 2,2-dimethyl-1,3-dioxan, had been adequately demonstrated to prefer chair forms by ^{1}H n.m.r. spectroscopy[44,50], and were included in the analytical set of compounds. As various workers[37,51] had proposed that molecules with two syn-diaxial methyl groups were forced into twist conformations, 1,3-dioxans possessing such a grouping were not included in the analysis.

In order to evaluate the substituent parameters the following scheme was used. The chemical shift of the Xth carbon atom in the Nth compound, ΔC_{XN}, was expressed in the following equation.

$$\Delta C_{XN} = \Delta C_{XP} + \Sigma a_{iN} . E_{iX} \qquad 2.1$$

ΔC_{XP} was the shift of the Xth carbon atom in the parent compound (1,3-dioxan); E_{iX} was the ith substituent effect on the chemical shift of the Xth carbon atom and a_{iN} the number of times a given effect had to be taken into account. A set of N simultaneous equations with unknowns E_{X1}, E_{X2}, etc. was obtained. Using a least squares analysis "best fit" values of the substituent parameters were calculated.

2.5 Substituent Parameters

Prior to carrying out the analytical procedure described above, it was necessary to consider which parameters should be used in the equation. Initially single parameters relating to ring positions were employed, e.g., a 2-equatorial methyl effect, but in order to improve the fit between the observed shifts, and those calculated using the substituent parameters, additional "combination" effects were introduced, e.g., a 2-geminal dimethyl effect. These parameters were worthy of consideration as it is reasonable to suppose that the effect of a geminal group, say, on the electronic

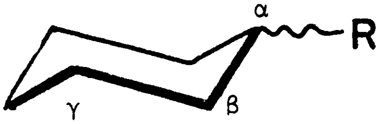


Figure 2.3. Nomenclature of the ^{13}C n.m.r. Substituent Effects.

distribution and geometry of the ring, will not be identical to the sum of an equatorial and an axial group effects. It is also important to note, that, due to the nature of the least squares treatment, as the number of parameters introduced increases, the regression coefficient approaches unity. In order to minimise the number of parameters consistent with a reasonable regression coefficient, all effects, apart from those in the initial set, with values less than 1.0 p.p.m., were excluded, and those in excess of this figure retained in the analysis.

The final group of parameters chosen is displayed in Table 2.2. The fit between the observed and calculated shifts of the compounds in the analytical set was extremely good with regression coefficients of ca. 0.99 being obtained.

As substituent parameters have been topics of considerable interest in ^{13}C n.m.r. spectroscopy,[66,67,72,73,76] it is important to examine them in some detail. Figure 2.3 shows the accepted notation for describing these effects. The carbon atom at which substitution is made is termed α, the nomenclature of the subsequent atoms following logically from this.

Substitution of an Equatorial Methyl Group

Introduction of a 2 or 4 equatorial methyl group causes

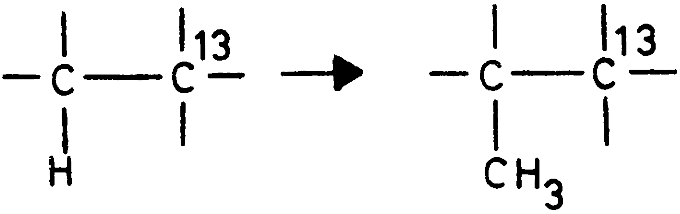


Figure 2.4. The β-Effect.

a downfield shift of the α-carbon atom of similar magnitude to that observed for the methyl cyclohexanes[67]. A 5-methyl group also produces a downfield shift but of somewhat smaller size. Jackman[82] has proposed that this type of shift indicates that a methyl group has an electron withdrawing rather than electron releasing, inductive effect. As unhindered α-methyl groups cause downfield shifts for a wide range of compounds, and in general electronegative groups cause shifts in a similar direction[83], Jackman's hypothesis would seem to have some validity.

The downfield shift of the adjacent β-carbon (the β-effect, Figure 2.4) is consistent with such effects in cyclohexanes[67], cyclohexanols[72] and cyclohexanones[73]. This parameter has been the subject of some controversy[72,84], and still remains to be satisfactorily accounted for.

Substitution of an Axial Methyl Group

In the series of compounds examined no example was present which had a 2-axial methyl group as the sole C(2) substituent; hence no parameter for its effect at C(2) was evaluated. However, assuming that a 2-geminal dimethyl effect is of the same magnitude as the 4-geminal dimethyl parameter, then a 2-axial methyl group creates an α-effect of ca. -1.5 p.p.m. at C(2). The difference between the

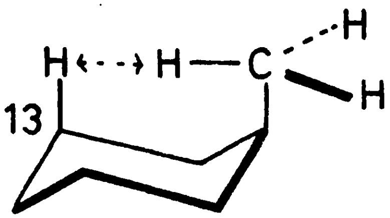


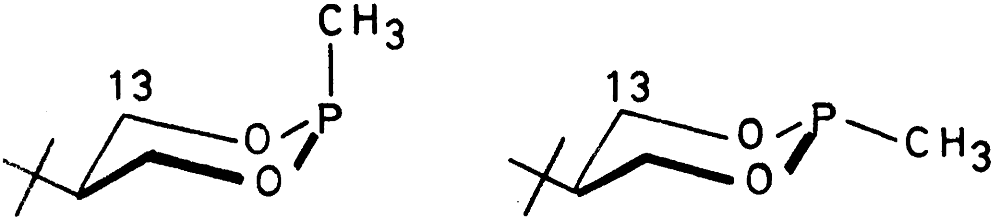
Figure 2.5. The γ-Axial Methyl Effect.

equatorial and axial α-effects possibly results from the severe steric interactions encountered by the axial methyl group causing changes in the electron density at the α-carbon atom. It is the large difference in the chemical shift effects caused by substitution of an axial group and substitution of an equatorial group which renders ^{13}C n.m.r. so valuable in conformational analysis.

The α-effect of an axial 5-methyl group is identical to that of a 5-equatorial group, reflecting the less hindered environment of this axial position (cf. 2 and 4 axial positions).

The γ-effects of the axial methyl groups at positions 2, 4 and 6, which create large upfield shifts of the γ-carbon atom, are very important. Grant[85], in a valence bond description of this phenomenon, has ascribed this effect to charge polarisation along the H-^{13}C bond due to the interaction shown in Figure 2.5. He has proposed an equation relating this shift to various factors, the most important being the distance between the interacting protons. Although this approach is open to criticism it does predict that the closer the interacting protons are, the larger is the γ-effect.

The results for the 1,3-dioxans are at least in qualitative agreement with this. The effect of a 2-axial methyl



cis *trans*

δ*cis* - δ*trans* = + 3.43 p.p.m.

Figure 2.6. The *cis* and *trans*-2-methyl 5-t-butyl-1,3,2-Dioxaphosphorinans.

on C(4) (or vice versa) is ca. + 8.0 p.p.m., whereas the analogous parameter for the methyl cyclohexanes is + 5.4 p.p.m. This is precisely what is anticipated, as the 2 and 4 positions in 1,3-dioxan are closer than the equivalent 1,3 positions in cyclohexane.* It is also known that the 4 and 6 carbons are further apart than the 2 and 4 carbons; hence the effect of a 4-axial methyl group on C(6) is less than on C(2) (5.3 p.p.m. compared with 9.0 p.p.m.).

Combination Effects

In justifying the use of combination terms in the least squares analysis it was necessary to demonstrate that not only did they improve the fit between the calculated and observed chemical shifts, but also that they could be related to some stereochemical or electronic effect. The gem-dimethyl parameter has already been discussed and the other terms may be considered in a similar fashion. The vicinal dimethyl effects, e.g., the 4-5 diequatorial dimethyl

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* Further evidence for this general relationship is provided by the ^{13}C n.m.r. shifts of the 2-methyl-5-t-butyl-1,3,2-dioxaphosphorinans[86] (Figure 2.6), in which the distance between C(4) and the 2-methyl group is greater than the equivalent cyclohexane distance. The γ-effect at C(4) is + 3.43 p.p.m. i.e. less than cyclohexane.

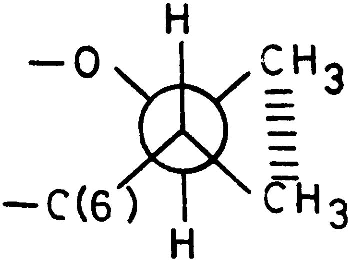


Figure 2.7. Possible Origin of the 4 eq. - 5 eq. dimethyl effects.

parameter, may originate from a gauche torsional interaction as shown in Figure 2.7. Pihlaja's suggestion that ring flattening occurs in 1,3-dioxans with a 4,4,5 or 4,5,5-trimethyl grouping[87], supports this argument. The 4,6-diequatorial and equatorial-axial parameters may reflect the so-called "buttressing" effect noted by Eliel[88] and Allinger[89] in 1,3-disubstituted cyclohexanes.

2.6 Non-Chair Conformations

Having evaluated the parameters described, these were then used to calculate the chemical shifts of the ring carbon atoms of those 1,3-dioxans which were considered to adopt non-chair conformations. Such 1,3-dioxans can be divided into two categories; those with two axial methyl groups at the 2 and 4 positions in their chair forms, and those with the two groups at the 4 and 6 positions. Romer's X-ray diffraction study of the 1,3-dioxan ring[36], and an examination of models, indicated that the repulsions between the two groups situated at the 2 and 4 positions should be the more severe.

These conclusions were supported by an examination of the observed and calculated shifts for these molecules (Table 2.4 and Figure 2.8). Compounds with a 2,4 interaction (26,27,28,29 and 30) showed substantial differences between the observed and calculated figures, whereas compounds 31 and 32,

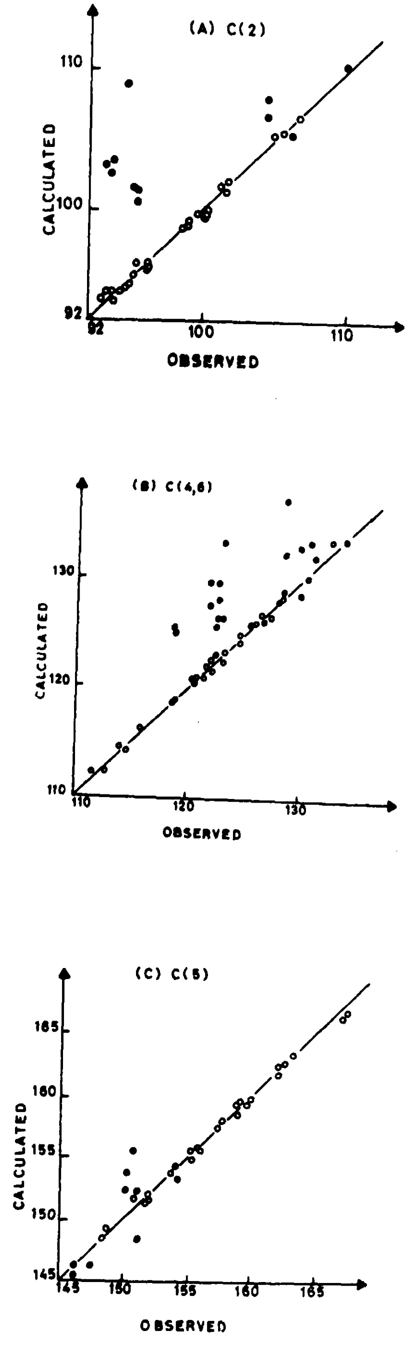


Figure 2.8 Plots of the Observed and Calculated ^{13}C Chemical Shifts (relative to $^{13}CS_2$) for some of the 1,3-Dioxans studied.

○ Compound in the reference series.

● Compound suspected of existing in a non-chair conformation.

whose chair conformations have a 4,6 interaction, displayed smaller differences. This may indicate that the latter 1,3-dioxans exist with appreciable amounts of chair and twist forms, a conclusion supported by an analysis of the ultrasonic relaxation in these compounds[90]. For trans-2,4,4,6-tetramethyl-1,3-dioxan (cpd 33), Eliel suggested[37] that chair and twist forms were present in a 5:1 ratio at room temperature. However, the magnitudes of the deviations found are indicative of a substantial proportion of a twist conformation (the conformational analysis of this molecule is more fully discussed in Chapter 3).

In spite of the success of this method in pointing out stereochemically anomalous compounds, the results cannot be taken to demonstrate unequivocally the presence of twist, as opposed to deformed chair, conformations. However, in view of the weight of evidence supporting the existence of twist conformations for many of these molecules[51,52,91], it is more likely that these 1,3-dioxans do adopt twist forms.

2.7 Methyl Group Shifts

The methyl group chemical shifts could not be interpreted as readily as the ring carbon shifts, due to certain problems.

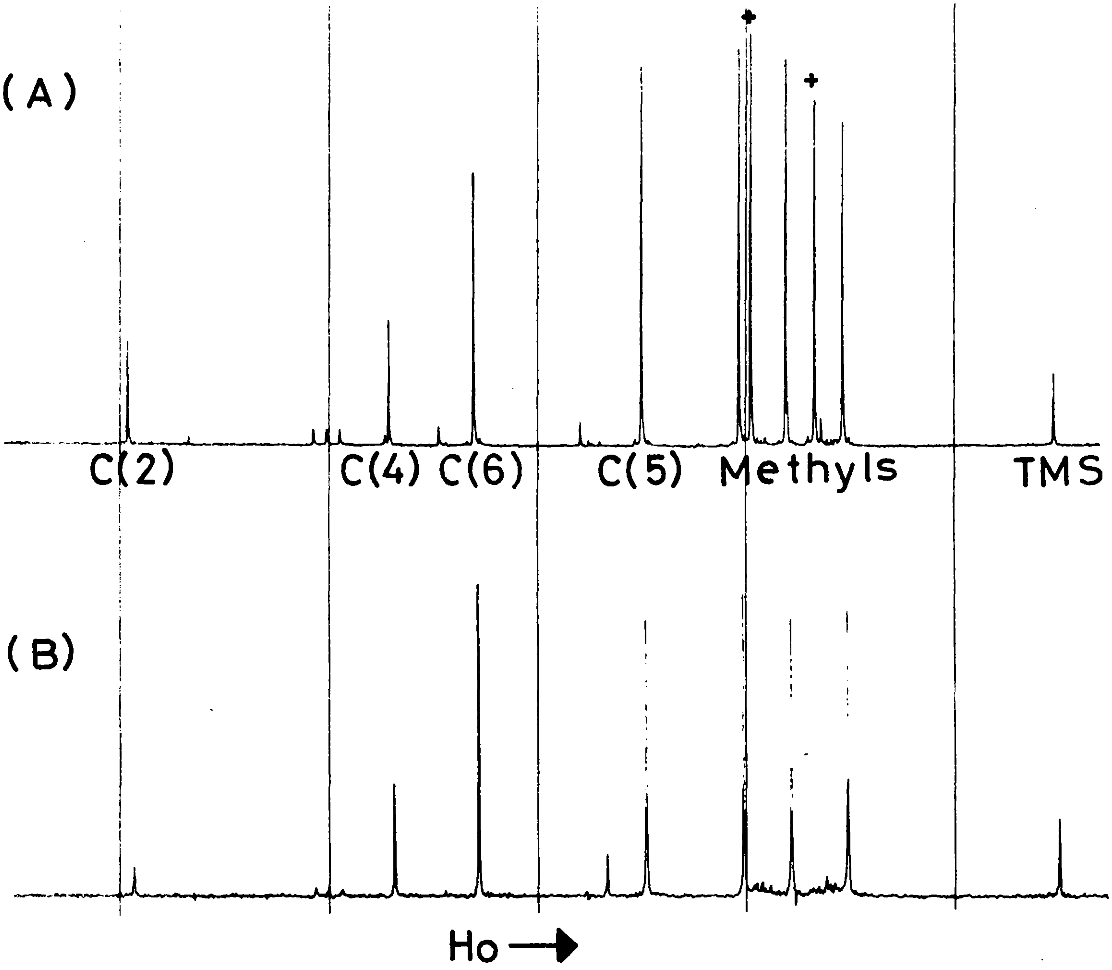


Figure 2.9 The Fourier Transform ^{13}C n.m.r. spectra of (a) 2,2,4,4,6-pentamethyl-1,3-dioxan and (b) 2,2-bis(trideuteriomethyl)-4,4,6-trimethyl-1,3-dioxan.

+ : Resonances due to the 2-methyl groups.

In the undecoupled spectra difficulty was encountered in identifying individual resonances as all the methyl groups tended to absorb in similar spectral regions. In addition the signals could not be assigned to specific methyl groups except in the simplest cases. Similar difficulties were encountered by Grant[67] and Eliel[81], although the latter was able to assign some resonances by selective decoupling experiments.

After careful examination of the spectra (undecoupled and decoupled), methyl group assignments were made for certain compounds, and these results are shown in Table 2.5. In general the assignments agree with those noted by Eliel[81]. The most reliable method of assigning such shifts is to prepare selectively deuteriated derivatives in which the deuteriated carbons will be readily saturated and thus not observed. Although this tedious procedure was not carried out in this work, in connection with another problem the 2,2-bis(trideuteriomethyl) derivative of 2,2,4,4,6-pentamethyl-1,3-dioxan was synthesised. Figure 2.9 shows the effect of this deuteriation as the 2-methyl groups are not observed in spectrum (b) which is otherwise almost identical to spectrum (a). These spectra also effectively demonstrate the excellent resolution to be obtained from the Fourier Transform method.

The shifts recorded in Table 2.5 reveal certain interesting trends. At positions 2, 4 and 6 the axial methyl groups resonate at higher field than the equatorial groups. These differences may result from the steric interactions experienced by the axial groups which were discussed in connection with the γ-axial effect. In contrast the axial methyl groups at position 5 absorb at lower field than the equatorial groups, due perhaps to the influence of the ring oxygen atoms.

2.8 Conformational Equilibria at C(5)

The possibility of obtaining estimates of the equilibrium constants for conformationally mobile 1,3-dioxans (substituted at position 5) was discussed earlier. The first attempt made to evaluate these parameters involved calculation of the ring carbon atom shifts for each of the possible conformations using data from Table 2.2. By comparing the observed shifts with the limit values it was hoped that the equilibrium constants might be determined. However, for most of the compounds examined the chemical shift difference between the ring carbon atoms in each of the conformations was small and this approach could not be used (Table 2.6).

Examination of the shifts of the methyl carbon atoms revealed a more favourable situation. The difference in shift between the axial and equatorial groups was large (ca. 4.0 p.p.m.) and the equilibrium constants could be obtained from the following equation.

$$K = \frac{\delta_e - \delta_{ax.}}{\delta_{eq.} - \delta_e} \qquad 2.2$$

δ_e was the chemical shift of the 5-methyl group in the conformationally mobile compound. δ_{ax} was the average of the 5-methyl shifts in cis-2,5-dimethyl, cis-2-phenyl-5-methyl and cis-2-t-butyl-5-methyl-1,3-dioxans. δ_{eq} was the average of the 5-methyl shifts in trans-2,5-dimethyl, trans-2-phenyl-5-methyl, and trans-2-t-butyl-5-methyl-1,3-dioxans. The equilibrium constants and conformational free energies are shown in Table 2.7.

Although the results obtained by this method have large errors they are in reasonable agreement with more accurately determined values of the conformational free energy of a 5-methyl group (see Chapter 4). The importance of this method is that it permits estimation of the equilibrium constants for compounds which cannot be readily studied by other methods.

TABLE 2.1

The $^{13}C-^{1}H$ Directly Bound Coupling Constants for 1,3-Dioxans

Ring Carbon Atom	$J_{^{13}C,H}$ (Hz ± 0.2 Hz)
C(2)	162.0
C(4,6)	141.6
C(5)	126.0

TABLE 2.2

Substituent Effects on the ^{13}C Chemical Shifts of 1,3-Dioxans^{A,B}

<table>
<tr><th>Substituent Effect</th><th>on C(2)</th><th>on C(4)</th><th>on C(6)</th><th>on C(5)</th><th>No. of occurrences</th></tr>
<tr><td>C(2) eq. Me</td><td>-5.3</td><td colspan="2">-0.1</td><td>0.8</td><td>16</td></tr>
<tr><td>C(2) ax. Me</td><td>+1.7^{C}</td><td colspan="2">+7.3</td><td>-0.1</td><td>5</td></tr>
<tr><td>C(4) eq. Me</td><td>-0.8</td><td>-5.7</td><td>+0.1</td><td>-7.3</td><td>19</td></tr>
<tr><td>C(4) ax. Me</td><td>+9.0</td><td>-0.6</td><td>+5.3</td><td>-3.7</td><td>6</td></tr>
<tr><td>C(5) eq. Me</td><td>+0.2</td><td colspan="2">-5.8</td><td>-3.1</td><td>7</td></tr>
<tr><td>C(5) ax. Me</td><td>-0.4</td><td colspan="2">-4.5</td><td>-3.1</td><td>6</td></tr>
<tr><td>C(6) eq. Me</td><td>-0.8</td><td>+0.1</td><td>-5.7</td><td>-7.3</td><td>19</td></tr>
<tr><td>C(6) ax. Me</td><td>+9.0</td><td>+5.3</td><td>-0.6</td><td>-3.7</td><td>6</td></tr>
<tr><td>C(4) gem di Me</td><td>-2.3</td><td>+2.0</td><td>-1.5</td><td>+0.8</td><td>3</td></tr>
<tr><td>C(6) gem di Me</td><td>-2.3</td><td>-1.5</td><td>+2.0</td><td>+0.8</td><td>3</td></tr>
<tr><td>C(5) gem di Me</td><td>-</td><td colspan="2">-</td><td>+2.3</td><td>5</td></tr>
<tr><td>C(5) gem di Et</td><td>-0.3</td><td colspan="2">-7.7</td><td>-8.5</td><td>3</td></tr>
<tr><td>C(4,6) eq. di Me</td><td>+1.6</td><td colspan="2">-</td><td>-</td><td>5</td></tr>
<tr><td>C(4) eq. C(6) ax. di Me</td><td>-1.1</td><td colspan="2">-</td><td>-</td><td>5</td></tr>
<tr><td>C(4) eq. C(5) eq. di Me</td><td>-</td><td>+1.9</td><td>-1.8</td><td>+4.5</td><td>3</td></tr>
<tr><td>C(5) eq. C(6) eq. di Me</td><td>-</td><td>-1.8</td><td>+1.9</td><td>+4.5</td><td>3</td></tr>
<tr><td>C(4) ax. C(5) eq. di Me</td><td>-</td><td>-</td><td>-1.4</td><td>-3.2</td><td>1</td></tr>
<tr><td>C(5) eq. C(6) ax. di Me</td><td>-</td><td>-1.4</td><td>-</td><td>-3.2</td><td>1</td></tr>
</table>

A. In p.p.m. A positive sign represents an upfield shift and a negative sign a downfield shift.

B. Certain terms appear twice in this table as they are related by the symmetry of positions 4 and 6.

C. As no 1,3-dioxan with a single axial methyl group at C(2) was examined, this term is a combination of a 2 gem di Me and 2 ax. Me effects. See the text for a discussion of this point.

TABLE 2.3

Observed and Calculated Chemical Shifts[A] for the 1,3-Dioxans used in the Least Squares Analysis

Cpd	Substituents	C(2)		C(4,6)[B]		C(5)	
		obs.	calc.[C]	obs.	calc.[D]	obs.	calc.[E]
1	-	99.7	99.7	126.6	126.6	165.9	165.9
2	2-Me	94.7	94.4	127.2	126.5	167.6	166.7
3	2,2-di Me	96.2	96.1	134.0	133.8	167.0	166.4
4	4-Me	98.9	98.9	120.4 126.7	120.9 120.7	158.8	158.6
5	4,4-di Me	105.7	105.8	123.2 130.7	122.3 130.5	156.1	155.7
6	5,5-di Me	100.2	99.5	116.6	116.3	162.1	162.0
7	*cis*-2,4-di Me	94.0	93.6	120.6 126.7	120.8 126.6	159.2	159.4
8	2,5,5-tri Me	93.4	94.2	116.0	116.2	162.7	162.8
9	r-2-*c*-4,6-tri Me	94.6	94.5	120.9	120.9	152.0	152.1
10	*cis*-4,6-di Me	100.4	99.8	121.7	121.0	151.9	151.3
11	*trans*-4,6-diMe	106.9	106.9	126.6	126.1	155.2	154.9
12	2,2,4-tri Me	95.3	95.3	128.2 132.9	128.1 133.9	159.0	159.3
13	2,2-*cis*-4,6-tetra Me	95.5	96.2	128.2	128.2	151.9	152.0
14	4,4,6-tri Me	105.3	105.5	122.2 124.7	122.4 124.8	148.6	148.5
15	2,2,5,5-tetra Me	96.2	95.9	123.4	123.5	162.7	162.7
16	r-2-*c*-4-*t*-5-*c*-6-tetra Me	101.7	101.8	120.7 120.7	120.7 120.7	153.9	153.9
17	5,5-di Et	99.3	99.4	119.1	118.9	157.5	157.4
18	2,2-diMe-5,5-diEt	96.2	95.8	126.0	126.2	157.9	158.1
19	r-2-*c*-4-*t*-6-tri Me	101.7	101.6	125.8 125.8	126.0 126.0	155.5	155.7
20	*cis*-2,4,4,6-tetra Me	100.4	100.2	121.6 124.5	122.3 124.6	148.8	149.3
21	*cis*-2,4,5,5-tetra Me	93.2	93.5	112.9 114.8	112.3 114.4	160.2	160.0

TABLE 2.3 (continued)

Cpd	Substituents	C(2)		C(4,6)^B		C(5)	
		obs.	calc.^{C}	obs.	calc.^{D}	obs.	calc.^{E}
22	4,5,5-tri Me	98.8	98.8	111.8 114.2	112.3 114.5	159.9	159.2
23	*cis*-2,5-di Me	94.2	94.0	121.9	122.0	163.6	163.6
24	*trans*-2,5-di Me	94.9	94.6	120.6	120.7	163.6	163.6
25	2-Me-5,5-di Et	93.8	94.1	118.8	118.8	158.2	158.2

A. In p.p.m. upfield from $^{13}CS_2$. Recorded at 15.1 MHz for neat liquids.

B. In cases where two shifts are reported the upper value refers to C(4) and the lower to C(6).

C. Regression coefficient = 0.996; standard deviation = 0.3 p.p.m.

D. Regression coefficient = 0.997; standard deviation = 0.4 p.p.m.

E. Regression coefficient = 0.998; standard deviation = 0.3 p.p.m.

TABLE 2.4

Observed and Calculated Chemical Shifts^{A} for 1,3-Dioxans suspected of existing in Non-Chair Conformations

Cpd	Substituents	C(2)		C(4,6)^{B}		C(5)	
		obs.	calc.	obs.	calc.	obs.	calc.
26	2,2,4,4,6-penta Me	95.3	101.7	122.7	129.6	149.2	149.2
				131.1	132.0		
27	2,2-r-4-_c_-5-_t_-6-penta Me	93.6	103.4^{C}	122.6^{I}	128.1^{G}	150.4	153.8^{C}
			102.8^{D}	122.6^{I}	125.7^{G}		152.5^{C}
				128.6^{I}	128.8^{H}		
				128.6^{I}	128.9^{H}		
28	2,2,4,4,5-penta Me	95.6	102.3^{C}	119.0	125.6^{C}	154.3	154.6^{C}
			101.7^{D}	119.0	125.0^{D}		153.3^{D}
				130.0	128.7^{C}		
				130.0	133.2^{D}		
29	2,2,4,4,6,6-hexa Me	94.6	109.2	123.0	133.4	147.8	146.2
30	2,2-_trans_-4,6-tetra Me	93.4	103.3	130.7	133.4	150.8	155.6
31	4,4,6,6-tetra Me	110.1	110.9	123.0	126.2	146.2	145.5
32	2,4,4,6,6-penta Me	106.1	105.6	122.6	126.1	146.6	146.3
33	_Trans_-2,4,4,6-tetra Me	104.6	108.3^{E}	122.0	127.5^{E}	151.2	152.8^{E}
			107.0^{F}	128.5	132.1^{E}		
				122.0	129.8^{F}	151.2	148.4^{F}
				128.5	137.2^{F}		

TABLE 2.4 (continued)

A. In p.p.m. upfield from $^{13}CS_2$. Recorded at 15.1 MHz for neat liquids.

B. Where two values are presented the upper value refers to C(4) and the lower to C(6).

C. 5-Me equatorial.

D. 5-Me axial.

E. 2-Me equatorial.

F. 2-Me axial.

G. 4-Me equatorial - 5-Me axial.

H. 4-Me axial - 5-Me axial.

I. Two resonances are observed but are not readily ascribed to either carbon (4) or (6).

TABLE 2.5

^{13}C Chemical Shifts of Methyl Groups in certain 1,3-Dioxans[A,B]

Compound	2eq.	2ax.	4eq.	4ax.	5eq.	5ax.
2-Me	171.7	-	-	-	-	-
4-Me	-	-	171.0	-	-	-
5-Me[C]	-	-	-	-	179.8	
2,2-diMe	170.8	170.8	-	-	-	-
4,4-diMe	-	-	166.7	166.7	-	-
5,5-diMe	-	-	-	-	170.5	170.5
cis-2,4-diMe	171.1	-	171.1	-	-	-
cis-2,5-diMe[C]	171.7	-	-	-	-	176.9
trans-2,5-diMe[C]	172.1	-	-	-	180.7	-
cis-4,6-diMe	-	-	171.5[E]	-	-	-
trans-4,6-diMe	-	-	173.7[E]		-	-
r-2-*c*-4,6-triMe	171.1	-	171.1[E]	-	-	-
r-2-*c*-4-*t*-6-triMe	170.9	-	170.9	175.0[F]	-	-
2,2,5,5-tetraMe	171.3	171.3	-	-	170.3	170.3
cis-2-Ph-4-Me[C]	-	-	170.8	-	-	-
2,2-diPh-4-Me[C]	-	-	171.1	-	-	-
2-Ph-5,5-diMe[C]	-	-	-	-	171.4	170.0
2,2-diPh-5,5-diMe[C]	-	-	-	-	170.3	170.3
cis-2Ph-5-Me[C]	-	-	-	-	-	177.1
trans-2-Ph-5-Me[C]	-	-	-	-	180.9	-
2,2-diPh-5-Me[C]	-	-	-	-	179.6	
2,2,5-triMe[C]	165.3	172.5	-	-	179.9	
cis-2-t-Bu-5-Me[D]	-	-	-	-	-	177.2
trans-2-t-Bu-5-Me[D]	-	-	-	-	180.7	-

A. In p.p.m. relative to $^{13}CS_2$.

B. Recorded for neat liquids at 15.1 MH_z unless otherwise noted.

C. Recorded at 22.63 MH_z in $CDCl_3$ solution.

D. Values from reference 81.

E. This value applies to the 6-methyl group as well.

F. 6-axial methyl group shift.

TABLE 2.6

Observed and Calculated Chemical Shifts for 1,3-Dioxans with a C(5) Axial-Equatorial Equilibrium[A]

Cpd	Substituent	C(2) obs.	C(2) calc.eq.	C(2) calc.ax.	C(4,6)[B] obs.	C(4,6)[B] calc.eq.	C(4,6)[B] calc.ax.	C(5) obs.	C(5) calc.eq.	C(5) calc.ax
34	5-Me	99.8	99.9	99.3	120.7	120.8	122.1	163.6	162.8	162.8
35	2,2,5-tri Me	96.2	96.3	95.7	126.8	128.0	129.3	164.0	163.5	163.5
36	4,4,5-tri Me	105.0	105.9	105.3	118.5 120.4	118.4 121.5	117.8 126.0	153.4	153.9	152.6
37	r-4-*c*-5-*t*-6-tri Me	106.6	107.1	106.5	122.2[C] 120.4[C]	120.9 118.5	121.6 121.7	153.4	153.1	151.8

A. In p.p.m. upfield from $^{13}CS_2$. Recorded at 15.1 MHz for neat liquids.

B. In cases where two values are presented C(4) is given above C(6).

C. This assignment of resonances fits the predictions best.

TABLE 2.7

Equilibrium constants and conformational Free Energies for some 5-Methyl-1,3-Dioxans.[A]

Compound	K	$-\Delta G$(kJ mol^{-1})[B,C]
5-Me	2.7	2.5 ± 0.8
2,2,5-triMe	3.1	2.9 ± 0.9
2,2-diPh-5-Me	2.1	1.9 ± 0.6

A. Evaluated using equation 2.2.

B. All measurements were carried out at 306.5K.

C. The errors quoted are estimated values.

CHAPTER 3

THE ^{1}H N.M.R. SPECTRA OF SOME *NON*-CHAIR 1,3-DIOXANS

CHAPTER 3

3.1 Introduction

In the previous chapter evidence was presented to support the contention that certain 1,3-dioxans, which would exist with *syn*-diaxial methyl groups in their chair conformations, tended to prefer twist forms. Such a view was substantiated by a number of other studies involving different techniques.[51,52,91] For some of the compounds to be examined, ^{1}H n.m.r. data had already been published[51,92], but the coupling constants recorded were first order splittings and, as such, open to criticism. In view of the wealth of structural information potentially available from the proton spectra, a detailed ^{1}H n.m.r. study of some of the 1,3-dioxans considered to prefer twist conformations seemed warranted.

Although the Karplus equations[56] cannot be applied in a quantitative fashion to the 1,3-dioxans, for reasons discussed in Chapter 1, examination of the data in Table 3.1 indicates that there is a certain interdependence between $^{3}J_{H,H}$ and the dihedral angle. On the basis of such results, and data from other sources[7], the following generalisations can be made. Large values of $^{3}J_{H,H}$ ($>$ 10 H_z) correspond to large dihedral angles (or angles near 0°) and smaller values (1 - 6 H_z) result from ca. 60° angles.

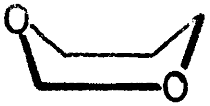
Whenever first order vicinal coupling constants are employed in a spectral analysis, care must be taken to see that these splittings do indeed represent the actual coupling constants. If the ratio of the chemical shift difference to the coupling constant ($\Delta\nu_{A,B}/J_{A,B}$) for two protons is small (say < 2.0) then the first order approximation is not valid and the spectrum must be analysed by a more rigorous method. For many 1,3-dioxans the first order conditions are satisfied and the couplings are often conveniently measured from the well defined H(4,6) region. However this can still involve some errors, e.g. Pihlaja's first order values[51] do not coincide with Eliel's figures[93] for 2-methyl-1,3-dioxan (Table 3.2). Computer programs are readily available[94] which permit evaluation of the coupling constants regardless of the magnitude of $\Delta\nu_{A,B}/J_{A,B}$. In this study the program LAOCN3 of Bothner-By and Castellano[95], was employed. For a given set of chemical shifts and coupling constants, this program calculates the frequencies and intensities of the nuclear transitions. By assigning calculated transitions to observed lines, an iterative procedure can be set in motion which evaluates the coupling constants and chemical shifts which give the best fit between the observed and calculated spectra.

3.2 Analysis of the Spectra

For many of the compounds examined the first order approximation was not valid, and in these cases the spectral analyses were carried out using LAOCN3. Following Bernstein's notation[96] the spectra may be considered to be of types AB, AMX, ABX and AA'XX' (with additional couplings to some of the protons from methyl groups). In order to obtain more readily interpretable spectra some of the 1,3-dioxans were examined at 220 MHz as well as 60 MHz. The principal advantage of the higher magnetic field in this context is that $\Delta\nu_{A,B}/J_{A,B}$ is increased (ν is field dependent, J is not) hence the spectrum tends to approach the first order state. Lanthanide contact shift reagents, $Eu(dpm)_3$[97] and $Eu(fod)_3$[98], which have proved useful in rendering complex spectra amenable to analysis by first-order methods were also employed, but only relatively small shifts were observed. This may be attributed to the weakly basic nature of the ring oxygen atoms, which will not form strong complexes with the rare-earth atom. The coupling constants and chemical shifts of the compounds studied are presented in Tables 3.3 and 3.4.

3.3 Twist Conformations of the 1,3-Dioxans

In order to interpret the data obtained for these compounds an empirical scheme was developed, which allowed



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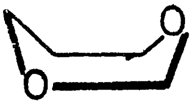

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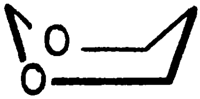

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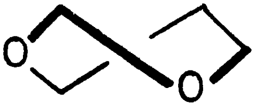

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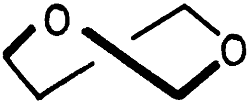

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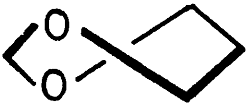

3.6

Figure 3.1. The Classical Boat and Twist Conformations of 1,3-Dioxan.

assignment of preferred twist conformations to 1,3-dioxans depending on their substitution pattern. This scheme did not directly arise from any theoretical approach, rather it was arrived at by a consideration of the results obtained and a detailed examination of accurate molecular models. Its greatest virtue is that it largely explains many of the features of the n.m.r. spectra in a consistent manner.

If the possible boat and twist conformations available to 1,3-dioxan are constructed using models, three classical boat and three twist forms can be envisaged* (Figure 3.1). The three classical boats (3.1, 3.2 and 3.3) appear to be less stable than any of the twists on the grounds of larger steric and torsional interactions (as for the cyclohexane classical boat and twist forms). Closer examination of the twist forms reveals that 3.4 and 3.5 are identical, leaving only two possible twists which shall be termed the 1,4-twist (3.4 and 3.5) and the 2,5-twist (3.6), the designations referring to the stem and stern positions. It is not possible, merely by examining models, to determine which, if any, of these unsubstituted twists should be the more stable. An analysis, of the type used by Hendrickson[17] and Allinger[28], would be required if the potential energies of each twist conformation were to be evaluated.

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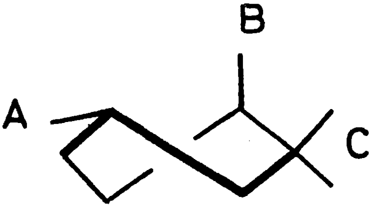
* For each conformation another pseudorotated enantiomeric form can be constructed.



Substituent Positions

A: Pseudo-equatorial (ψE)

B: Pseudo-axial (ψA)

C: Stem and Stern (S.S.)

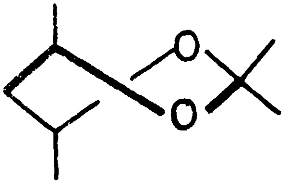
Figure 3.2. Non-equivalent positions on a Twist Conformation.

In contrast to the chair conformation which has two positions available for substitution (axial and equatorial positions), both twists have three positions. These are the pseudo-equatorial (ψ_E), stem and stern (S.S.) and the pseudo-axial (ψ_A) positions (Figure 3.2). Inspection of models reveals that the ψ_E and S.S. positions are less hindered than the ψ_A position, hence a solitary methyl group will prefer the two former situations to the ψ_A orientation. On similar grounds it can be seen that a gem-dimethyl grouping will occupy the stem and stern positions in preference to a ψ_E and ψ_A combination. These conclusions are supported by calculations made by Hendrickson[17] for substituted cyclohexane twist forms.

If the 1,3-dioxan has a 2,2,4,4-tetramethyl substitution pattern both of the two possible twist forms must possess a pseudo-axial methyl group. These conformations have a large number of non-bonded and torsional strains present and, as in the case of the unsubstituted twists, it is not possible to decide which should be the more stable on purely qualitative grounds.

3.4 Discussion

The scheme can now be applied to some of the 1,3-dioxans considered to adopt twist conformations.



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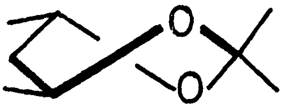

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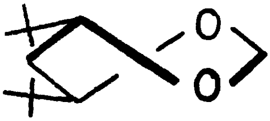

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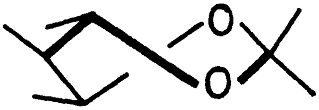
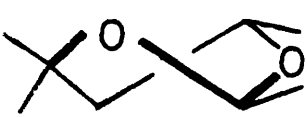


3.10

Figure 3.3. 2,5-Twist Conformations of some 1,3-Dioxans.

2,2-trans-4,6-tetramethyl-1,3-dioxan(I), by virtue of possessing a gem dimethyl grouping at C(2) would be expected to have a 2,5-twist structure with the 4,6 methyls in pseudo-axial (3.7) or pseudo-equatorial (3.8) orientations. On the basis of the previous discussion, the latter is obviously the more stable. The ring protons of this compound form an AA'XX' system and therefore the ^1H n.m.r. spectrum would be expected to display a complex pattern. However a deceptively simple triplet is observed for the C(5) protons, a pattern which is only possible if $J_{A,X}$ is approximately equal to $J_{A,X'}$. Examination of the 2,5-twist conformation proposed for this molecule reveals that the dihedral angles are ca. 30° and 150°. Assuming that a Karplus-type relationship holds for the 1,3-dioxans it can be seen that these angles should result in similar couplings. This is partly substantiated as the spectrum can be generated using LAOCN3 with couplings of 8.0 and 6.8 Hz. Anteunis[50] proposed a similar twist form for trans-4,6-di-t-butyl-1,3-dioxan (3.9) on the grounds that the sum of the vicinal coupling constants (15.6 Hz) best fitted that conformation (for a chair he anticipated $\Sigma^3J_{H,H}$ = ca. 11 Hz). The sum of the vicinal couplings for I is 14.8 Hz, in good agreement with Anteunis's values.



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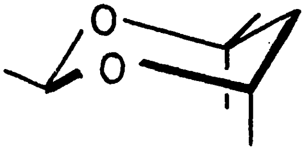


3.12

Figure 3.4. Preferred Chair and Twist Conformations of Trans-2,4,4,6-Tetramethyl-1,3-Dioxan.

Similar arguments can be used to assign the twist conformation of 2,2-r-4-c-5-t-6-pentamethyl-1,3-dioxan(II). The most stable twist would be expected to be analogous to the 2,5-twist of I, with an additional S.S. methyl group at C(5) (3.10). The vicinal coupling constants, 7.8 and 5.3 Hz, are consistent with this structure and resemble the values used to calculate the spectrum of 2,2-trans-4,6-tetramethyl-1,3-dioxan. It is of interest to note that the observed splittings for both I and II are essentially temperature independent. Such an invariance of a property with temperature is good evidence for the lack of a conformational equilibrium in these compounds.

Support for this conclusion can be obtained by examining the energy difference between cis and trans-2,2,4,6-tetramethyl-1,3-dioxan. Eliel[99] obtained a value for the free energy difference between these isomers of 13.4 kJ mol^{-1} and Pihlaja[39] determined the enthalpy difference to be 13.0 kJ mol^{-1}. Therefore the entropy difference between the isomers is approximately zero. This is the result expected if the trans-isomer(I) exists predominantly in one twist conformation.

Trans-2,4,4,6-tetramethyl-1,3-dioxan(III) provides further evidence for the usefulness of this approach. The

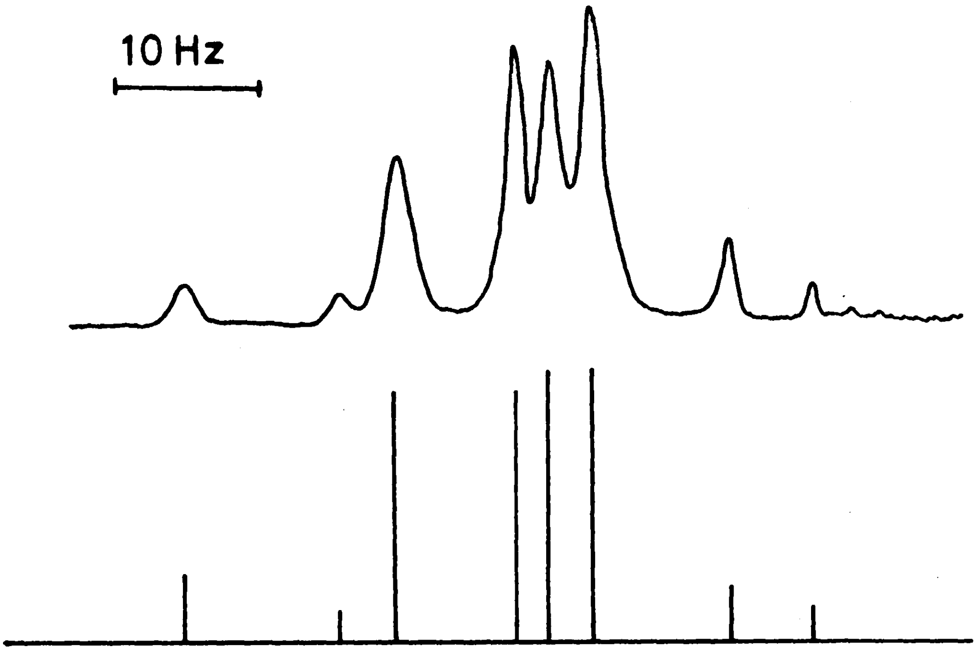


Figure 3.5.

The Observed and Calculated (LAOCN3) 220 MHz ^{1}H N.M.R. spectra of the C(5) Protons of Trans-2,4,4,6-Tetramethyl-1,3-Dioxan.

3.13 3.14

Figure 3.6.

The 1,4-Twist Conformations of 2,2,4,4,6- and 2,2,4,4,5-Pentamethyl-1,3-Dioxans.

most stable twist conformation which emerges from the scheme previously described, is a 1,4-twist with the methyl groups at C(2) and C(6) in pseudo-equatorial positions (3.11). The vicinal coupling constants for the ring protons have values of 11.8 and 4.4 Hz in agreement with this structure which has dihedral angles of approximately 60° and 180°. The observed and calculated spectra for the H(5) protons is shown in Figure 3.5. The LAOCN3 analysis of the spectrum shows that the chemical shift difference between the C(5) protons is only 3.6 Hz at 60 MHz ($\Delta\nu_{A,B}/J_{A,B} = 0.3$) therefore the first order splittings measured for this compound by Eliel[37], do not correspond to the actual couplings. The variation of these splittings with temperature is accounted for by assuming that small changes in the magnitude of $\Delta\nu_{A,B}$ over the temperature range alters the first order splitting pattern. It is worth noting that the chair conformation (3.12), which should be the more stable chair form, would give rise to two small gauche couplings. This is clearly incompatible with the observed figures.

2,2,4,4,6- and 2,2,4,4,5-pentamethyl-1,3-dioxans(IV and V) can conveniently be considered together. In the case of IV co-incidence of some of the C(5) protons resonances, and certain alkyl peaks necessitated the synthesis of a 2,2-bis (trideuteriomethyl) derivative for which most of the peaks for the C(5) protons were visible. On analysis both compounds were found to have one large and one small vicinal coupling constant, an observation best rationalised by considering that the 1,4-twist conformations, 3.13 and 3.14, predominate. The couplings observed for V are essentially invariant with temperature, suggesting that its 1,4-twist form is not involved in a conformational equilibrium. For 2,2,4,4,6-pentamethyl-1,3-dioxan variations in the 1st order splittings with temperature are observed. These changes may well reflect alterations in the chemical shift difference between the C(5) protons.

1,4 and 2,5-twist conformations can be constructed for the diastereoisomeric cis and trans 2,2,4,4,5,6-hexamethyl-1,3-dioxans, (VI and VII), which would give rise to couplings similar to those observed. Hence it is not possible to assign a twist conformation to these molecules although the couplings do differ from those expected for chair conformations.

A significant conclusion which may be drawn from this work is that many of the molecules examined largely exist in only one of the possible twist conformations. This is important as the twist form has often been termed the flexible conformation[41] i.e. it is assumed that pseudo-rotation is facile between a number of twist conformations. Although this may be valid for cyclohexane (and 1,3-dioxan itself), as the number of substituents on the ring increases so the number of favourable conformations decreases. The recent suggestion[43] that trans,trans-2,5-di-t-butyl-cyclohexanol is restricted to a small part of its pseudo-rotation circuit indicates that this is a general phenomenon, and is not restricted to the 1,3-dioxans. It is likely therefore, that the scheme for choosing the most stable twist forms, described in the chapter, is applicable to other systems.

TABLE 3.1

Dihedral Angles and Vicinal Coupling Constants for 2-(4'-chlorophenyl)-1,3-Dioxan

Protons	Dihedral Angle ($^{\circ}$)[A]	$^{3}J_{H,H}$(Hz)[B]
4-axial,5-axial	175.2	12.3
4-axial, 5-equatorial	54.6	2.6
4-equatorial, 5-axial	55.1	4.9
4-equatorial, 5-equatorial	65.5	1.3

A. Obtained from an X-ray diffraction study.[36]

B. Evaluated using LAOCN3.[93]

TABLE 3.2

Vicinal Coupling Constants for 2-Methyl-1,3-Dioxan

Protons	$^{3}J_{H,H}$(Hz)^{A}	$^{3}J_{H,H}$(Hz)^{B}
4-axial,5-axial	11.1	12.4
4-axial,5-equatorial	2.7	2.6
4-equatorial,5-axial	5.2	5.0
4-equatorial, 5-equatorial	1.5	1.3

A. 1st order splittings measured by Pihlaja.[51]

B. Evaluated by Eliel[93] using LAOCN3.

TABLE 3.3

Chemical Shifts of the Ring Hydrogens of some of the 1,3-Dioxans examined.[A],[B]

Compound	2-H	4,6-H	5-H
I	-	6.13	8.51
II	-	6.02 6.69	C
III	4.99	5.98	8.38 8.44
IV[D]	-	6.04	8.64 8.73
V	-	6.47 6.53	8.25
VI	-	6.26	E
VII	-	5.74	E

A. In τ units (p.p.m.)

B. All shifts were recorded at 33.5°C for 10% w/v CCl_4 solutions.

C. Resonance obscured by alkyl peaks.

D. 2,2-bis(trideuteriomethyl)derivative.

E. Mixture of stereoisomers. Only H(6) resonances unambiguously assigned.

TABLE 3.4

Coupling Constants for some 1,3-Dioxans

Cpd.	$T(^\circ C)^A$	Solvent	$J_{5,5}^{B,C}$	$J_{6,6}^{B,C}$	$J_{5,6(1)}^{B,C}$	$J_{5,6(2)}^{B,C}$	$J_{5,Me}^{B,C}$	$J_{6,Me}^{B,C}$
I	+33.5	CCl_4^G	-13.0^F	-	8.0^F (7.4)	6.8^F (7.4)	-	6.3^F (6.3)
	-50.0	CH_2Cl_2	-	-	7.5	7.5	-	-
	-20.0	CH_2Cl_2	-	-	7.5	7.5	-	-
	+33.5	CH_2Cl_2	-	-	7.5	7.5	-	-
	+70.0	CH_2Cl_2	-	-	7.5	7.5	-	-
II	+33.5	CCl_4^G	-	-	7.8	5.3	6.4	6.5,6.3
	-55.0	CH_2Cl_2	-	-	7.9	5.3	6.4	6.5,6.3
	-35.0	CH_2Cl_2	-	-	7.9	5.3	6.4	6.5,6.3
	0.0	CH_2Cl_2	-	-	7.9	5.3	6.4	6.5,6.3
	+33.5	CH_2Cl_2	-	-	7.9	5.3	6.4	6.5,6.3
	+70.0	CH_2Cl_2	-	-	7.9	5.3	6.4	6.5,6.3
	+33.2	Benzene^I	-	-	7.7	5.3	-	-
	+51.8	Benzene^I	-	-	7.6	5.3	-	-
	+71.6	Benzene^I	-	-	7.9	5.4	-	-
	+91.5	Benzene^I	-	-	7.8	5.3	-	-
III	+33.5	CCl_4^G	-14.1^D	-	11.8^D	4.4^D	-	6.3^D
IV^H	+33.5	CCl_4^G	-12.9^D	-	10.9^D (8.4)	2.5^D (5.6)	-	6.0^D

Cpd.	T(°C)[A]	Solvent	$J_{5,5}$[B,C]	$J_{6,6}$[B,C]	$J_{5,6(1)}$[B,C]	$J_{5,6(2)}$[B,C]	$J_{5,Me}$[B,C]	$J_{6,Me}$[B,C]
IV	+33.2	Benzene[I]	-	-	9.0	5.0	-	6.0
	+51.8	Benzene[I]	-	-	8.4	5.6	-	6.0
	+71.6	Benzene[I]	-	-	8.0	6.2	-	6.0
	+91.5	Benzene[I]	-	-	7.7	6.4	-	6.0
	+33.2	Nitrobenzene[I]	-	-	9.3	4.8	-	-
	+91.5	Nitrobenzene[I]	-	-	9.3	4.8	-	-
	+121.0	Nitrobenzene[I]	-	-	9.3	4.8	-	-
	+151.0	Nitrobenzene[I]	-	-	9.2	4.8	-	-
	+180.0	Nitrobenzene[I]	-	-	9.3	4.8	-	-
V	+33.5	CCl_4	-	-11.8[D]	10.3[D]	4.9[D]	6.0	-
	+33.2	Benzene[I]	-	-11.9[D]	10.1[D]	5.0[D]	-	-
	+51.8	Benzene[I]	-	-12.0[D]	10.0[D]	5.3[D]	-	-
	+71.6	Benzene[I]	-	-12.1[D]	9.9[D]	5.4[D]	-	-
	+91.5	Benzene[I]	-	-11.8[D]	9.9[D]	5.3[D]	-	-
	-60.0	Toluene	-	-11.8[D]	10.2[D]	5.0[D]	6.1	-
	-10.0	Toluene	-	-11.8[D]	10.0[D]	5.2[D]	6.1	-
	+20.0	Toluene	-	-11.8[D]	9.9[D]	5.3[D]	6.1	-
	+60.0	Toluene	-	-11.8[D]	10.1[D]	5.1[D]	6.1	-
	+100.0	Toluene	-	-11.8[D]	10.0[D]	5.2[D]	6.1	-
	+ 33.5	Pyridine	-	-11.8[D]	10.1[D]	5.1[D]	-	-

Cpd.	T(°C)[A]	Solvent	$J_{5,5}$ [B,C]	$J_{6,6}$ [B,C]	$J_{5,6(1)}$ [B,C]	$J_{5,6(2)}$ [B,C]	$J_{5,Me}$ [B,C]	$J_{6,Me}$ [B,C]
VI	+33.5	CCl_4	-	-	2.4	-	E	6.4
	0.0	CH_2Cl_2	-	-	2.4	-	E	6.4
	+60.0	CH_2Cl_2	-	-	2.5	-	E	6.4
	+80.0	CH_2Cl_2	-	-	2.5	-	E	6.4
VII	+33.5	CCl_4	-	-	-	9.7	E	6.1
	0.0	CH_2Cl_2	-	-	-	9.7	E	6.1
	+60.0	CH_2Cl_2	-	-	-	9.8	E	6.1
	+80.0	CH_2Cl_2	-	-	-	9.7	E	6.1

A ± 1.0°C.

B Values in Hertz ± 0.2 Hz.

C All couplings are first order values unless otherwise stated.

D Values from a LAOCN3 analysis.

E Mixture of stereoisomers. Only H(6) resonances unambiguously assigned.

F Values found to give a good approximation to the experimental spectrum.

G Values from 220 MH_z spectrum.

H 2,2-bis(trideuteriomethyl) derivative.

I Figures independently obtained by K. Pihlaja,[100] and confirmed in many cases in this work.

CHAPTER 4

THE DETERMINATION OF CONFORMATIONAL ENTHALPIES BY MICROCALORIMETRY

CHAPTER 4

4.1 Introduction

Calorimetric techniques offer, in theory, the most direct methods for determining conformational enthalpies. However little application of these methods to conformational problems has taken place, largely due to the tedious nature of the work, and the requirement of relatively large quantities (ca. 0.1 mole) of pure materials.[101] Bomb calorimetry has been used by Philaja[39] to study some methyl 1,3-dioxans, but this method requires exceedingly pure samples and a very precise experimental technique, in order to measure conformational energy differences of around 4 kJ mol^{-1} from a total heat of combustion 1000 times as large. The errors quoted for this method would appear to be rather optimistic and conformational energies for 1,3-dioxans have been commonly determined by other methods e.g. gas-liquid chromatography.[37,38,40]

However commercial microcalorimeters are now becoming widely available. These instruments require smaller quantities of samples (millimoles) and can measure heat changes extremely accurately. As stereoisomeric 1,3-dioxans may be easily equilibrated, this system appeared ideally suited to examination by microcalorimetry, and studies were therefore commenced.

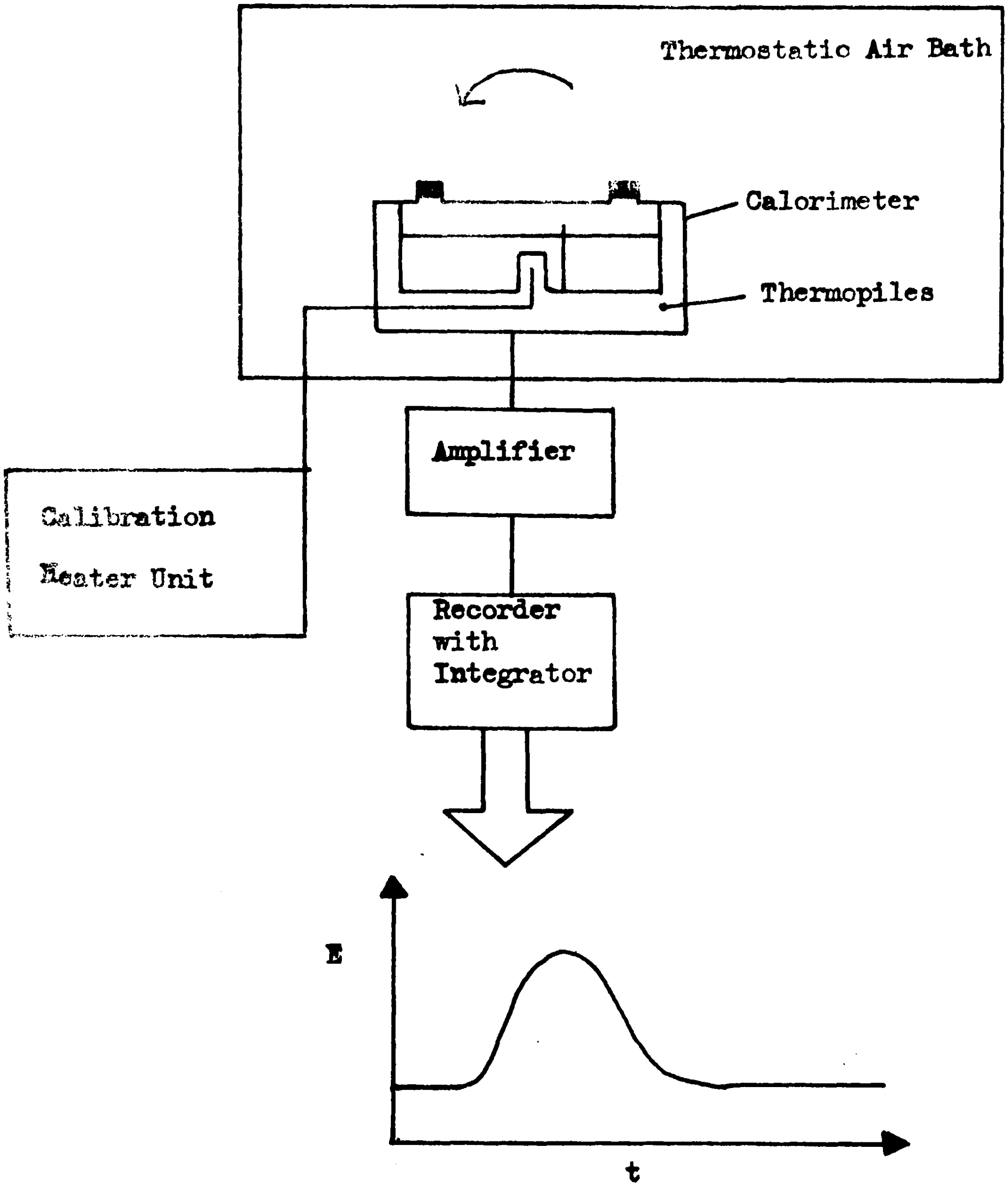


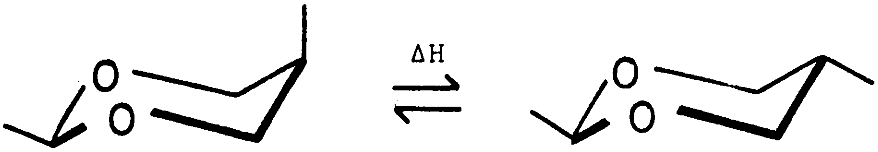
Figure 4.1. A Diagram of the Microcalorimeter.

4.2 Experimental Method

A diagram of the instrument used is displayed in Figure 4.1. It consists of a partitioned rotatable calorimeter suspended in a thermostated air bath. On rotation of the calorimeter the two solutions are thoroughly mixed and thermopiles located around the cell measure the heat of the reaction as a voltage. This voltage is presented on a recorder as the heat absorbed or liberated per unit time. By applying an accurately known amount of electrical energy to the cell a calibration curve is generated, enabling precise measurement of the heat of the reaction.

4.3 The Conformational Enthalpy of a 5-Methyl Group

As a test of the accuracy and usefulness of the microcalorimetric technique, it was first used to examine the epimeric 2,5-dimethyl-1,3-dioxans (4.1 and 4.2). In one half of the calorimeter was placed a solution of the 1,3-dioxan in 1,4-dioxan, and in the other half a solution of boron trifluoride (Lewis Acid) also in 1,4-dioxan. Using the method described above the heat change on converting each isomer to the equilibrium mixture was recorded. Small corrections were applied to compensate for the heat of dilution of each solution. From Figure 4.2 it can be seen that this method not only allows evaluation of the enthalpy



cis
4.1

trans
4.2

ΔH_1 = *cis* → equilibrium mixture
$= -\ 3.20 \pm 0.03$ kJ mol^{-1}

ΔH_2 = equilibrium mixture → *trans*
$= -\ 0.630 \pm 0.006$ kJ mol^{-1}

ΔH = *cis* → *trans* $= \Delta H_1 + \Delta H_2$
$= -\ 3.83 \pm 0.04$ kJ mol^{-1}

$$K = \frac{\Delta H_1}{\Delta H_2} = 5.08$$

$\Delta G = -\ RT \ln K$
$= -\ 4.02 \pm 0.04$ kJ mol^{-1}

$\Delta S = +\ 0.650 \pm 0.007$ J deg^{-1}

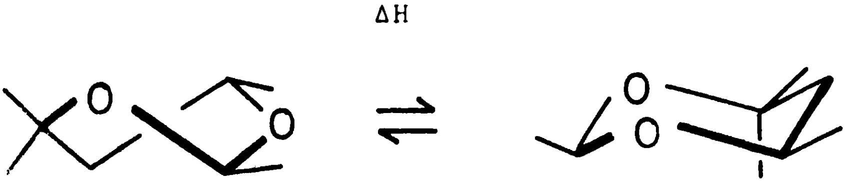
Figure 4.2. The Equilibration of *cis* and *trans*-2,5-dimethyl-1,3-dioxans.

difference between the isomers but also the equilibrium constant, K, and hence the free energy and entropy changes.

The values obtained are a measure of the conformational energies of a 5-methyl group and may be compared with data measured by other techniques (see Chapter 1, Table 1.2). Examination of these results shows that the microcalorimetric figures are in good agreement with previous determinations but are more accurate. Thus microcalorimetry offers a convenient and accurate method of evaluating conformational energies and should find wide applicability for conformational studies in many systems.

4.4 The Chair-Boat Enthalpy Difference for 1,3-Dioxan

In view of the success encountered in applying the microcalorimetric method to the 5-methyl-1,3-dioxans it seemed likely that it could be used to estimate ΔH_{CB} for 1,3-dioxan. As trans-2,4,4,6-tetramethyl-1,3-dioxan (4.3) had been shown by ^{1}H and ^{13}C n.m.r. spectroscopy to exist in a twist conformation, and the cis-isomer (4.4) was known to prefer the chair form[44], their equilibrium was examined. Eliel had attempted to measure the free energy difference between these isomers by g.l.c.[37], but was unsuccessful as he could not detect any of the trans-isomer in the equilibrium mixture. This also limited the microcalorimetric



trans
4.3

cis
4.4

Figure 4.3. The *cis* and *trans*-2,4,4,6-tetramethyl-1,3-Dioxans.

method as it was found that the heat change proceeding from the cis-isomer to the equilibrium mixture was negligible, and hence the free energy difference could not be measured. However the enthalpy difference was easily obtained, as it essentially corresponded to the heat change proceeding from the trans-isomer to the equilibrium mixture. As the trans-isomer was extremely unstable in the presence of acids, great care was taken when carrying out the calorimetric measurements.

The enthalpy difference between trans and cis-2,4,4,6-tetramethyl-1,3-dioxans was found to be 24.4 ± 0.2 kJ mol^{-1}. The cis-isomer, by virtue of possessing an axial 4-methyl group, has 12.1 kJ mol^{-1} of strain energy*, hence ΔH_{CB} for 1,3-dioxan is 24.4 + 12.1 = 36.5 kJ mol^{-1}. This estimate is made using the assumption that the stem and stern, and pseudo-equatorial methyl groups in 4.3, and the equatorial methyls in 4.4, give rise to no strain in each of these molecules. Although this is supported to a certain extent by the calculations of Hendrickson[17], the value of 36.5 kJ mol^{-1} is probably an upper limit figure. Pihlaja[47] has recently measured the gas phase enthalpy difference to be 35.5 ± 2.0 kJ mol^{-1} by the use of appearance potentials in the mass spectrum, and this value is in excellent agreement

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* This is a free energy value, but it is likely to be very similar to the strain enthalpy.

with the figure given above.

It has been shown (Chapter 3) that the trans-isomer exists predominantly in a single twist conformation. As a result the entropy difference between 4.3 and 4.4 will be near zero, and the free energy and enthalpy differences will be similar. However as 1,3-dioxan itself has six possible twist conformations, and only two possible chairs, ΔS_{CB} will not be zero and ΔG_{CB} will not be equal to 36.5 kJ mol^{-1}. If all the twists are of the same energy then $\Delta G_{CB} = 36.5 - RT\ln 3 = 33.8$ kJ mol^{-1}. If any of the twist forms predominates then ΔS will be somewhat smaller. On this basis it is likely that ΔG_{CB} lies between 34 and 36 kJ mol^{-1}.

CHAPTER 5

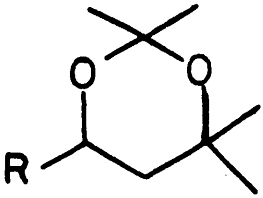
THE CRYSTAL AND MOLECULAR STRUCTURE OF r-2-4,4-*c*-6-TETRAMETHYL-2-(4'-BROMOPHENYL)-1,3-DIOXAN

CHAPTER 5

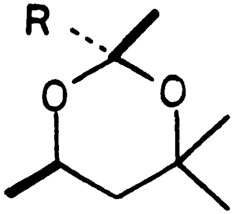
5.1 Introduction

In Chapters 2 and 3 the ^{13}C and ^{1}H n.m.r. spectra of certain 1,3-dioxans, thought to exist in non-chair conformations, were examined. Important conclusions regarding the presence of certain twist conformations were drawn, and an empirical scheme was presented to enable selection of the most stable twist form for any substituted 1,3-dioxan. Although the structure of the chair conformation of 1,3-dioxan had been established by an X-ray diffraction study of 2-(4'-chlorophenyl)-1,3-dioxan[36], the twist conformations had not been examined by this technique. In view of this situation, and in order to obtain some evidence regarding the conclusions discussed above, it seemed appropriate to synthesise model 1,3-dioxans, which might exist in non-chair forms, for study by X-ray diffraction.

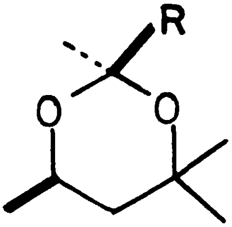
The first such compound considered was 2,2,4,4-tetramethyl-6-(4'-bromophenyl)-1,3-dioxan (5.1), which would have a severe 2,4-diaxial dimethyl interaction in its more stable chair conformation. However it proved to be extremely labile, decomposing readily in the presence of traces of water or acids, and also great difficulty was encountered in obtaining crystals suitable for an X-ray



5.1



5.2



5.3

R = 4-Bromophenyl

Figure 5.1 Some Compounds considered for an X-ray Analysis.

diffraction study. Alternative molecules which appeared to merit consideration were the diastereoisomeric 2,4,4,6-tetramethyl-2-(4'-bromophenyl)-1,3-dioxans (5.2 and 5.3). For both compounds strong repulsions, either between two axial methyl groups, or an axial phenyl and an axial methyl group, take place in their chair conformations. An examination of these compounds was also of interest as only a few studies of the conformational preferences of 2-methyl-2-phenyl 1,3-dioxans had been carried out.[99,102,103]

Reaction of 2-methyl-pentane-2,4-diol with the diethyl ketal of 4-bromoacetophenone yielded a crystalline product which g.l.c., ^{1}H and ^{13}C n.m.r. indicated was a single isomer. The method of preparation was such as to suggest that this product should be the thermodynamically more stable isomer. However, the n.m.r. parameters did not permit unequivocal assignment of the structure. As a result an X-ray diffraction study of this compound was undertaken with the objectives of elucidating firstly its stereochemistry, and secondly, its conformation. In addition ^{13}C and ^{1}H n.m.r. spectra were recorded for this molecule and some model compounds in order to obtain some information about its conformation in solution.

5.2 Crystallographic Measurements*

The unit cell dimensions and space group were determined from oscillation and Weissenberg photographs taken with CuKα(λ = 154.18 pm) radiation. The crystal data is shown in Table 5.1. Although the crystals were apparently satisfactory when examined optically, the photographs obtained were often poor, having streaked spots with a mosaic spread of several degrees. The compound was thoroughly re-examined by g.l.c. and n.m.r. and was found to contain no detectable impurities. This suggested that the photographic defects arose from poor crystallinity. Several recrystallisations from methanol were performed under varied conditions in order to improve the quality of the photographs. However no significant improvement was obtained.

In a preliminary examination 11 crystals were photographed and the least unsatisfactory used for data collection. This crystal (0.3 x 0.3 x 0.4 mm) was exposed to MoKα(λ = 71.07 pm) radiation on a Hilger-Watts linear diffractometer. 688 reflections from levels hk0 to hk6 and 587 reflections from levels h0l to h4l were collected with a large ω scan of around 5° (necessitated by the nature of the reflections), which thus reduced the intensity of the reflections. As a result of the high proportion of low

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* All photographic measurements and the diffractometer data collection were performed by Dr. P. Murray-Rust.

intensity reflections, only reflections with intensity less than 2.5 e.s.d. were rejected. Layer scale factors for the data from each axis were then calculated and applied to the sets of data. The agreement between the data from each axis was satisfactory, with a discrepancy factor $\frac{|F_1 - F_2|}{\frac{1}{2}|F_1+F_2|}$ of 0.15, where F_1 and F_2 are the values of F on each axis after scaling. A unique set of 635 reflections was obtained. This is a low figure (ca. 10 observations for each variable parameter) but was considered to be sufficient for the solution of a structure containing a heavy atom.

5.3 Structure Determination[104]

Three dimensional Patterson syntheses, unsharpened and sharpened (with a modifying function of exp $\frac{2B\sin^2\theta}{\lambda^2}$ with $B = 4.0$) were calculated. The latter proved to be the best resolved of the two syntheses. The co-ordinates of the bromine atom ($x = 0.0000$, $y = 0.0396$, $z = 0.2525$) were determined from the Harker sections. Structure factors were calculated (F_{calc}) on the basis of these co-ordinates, and a Fourier synthesis was carried out ($R = 0.67$).* Due to the x co-ordinate being zero and the z co-ordinate having a value extremely close to 0.25, the Fourier map possessed

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* $R = \Sigma|\Delta F|/\Sigma|F_{obs.}|$ where $\Delta F = F_{obs.} - F_{calc.}$

two planes of false mirror symmetry passing through the bromine atom. This resulted in a rather complex electron density map which was not readily interpretable. As the bromine atom must be attached to the benzene ring, the electron density close to this atom was drawn out on perspex sheets and it was possible to assign certain regions to five carbons of a benzene ring, although the atomic positions were not well resolved. The C(14) atom appeared to lie in a negative area of electron density, but as this was at the distance (ca. 200 pm) from the bromine that a diffraction ripple would be expected, it was included in the next structure factor calculations. Similar reasoning led to the discovery of C(2) and three atoms arranged in tetrahedral positions around it (C(21), O(1) and O(3)). At this stage it was not possible to say which of these peaks were oxygen and which carbon atoms, and they were considered in the subsequent Fourier synthesis as carbon atoms. Using the co-ordinates of these ten atoms as well as the bromine a second structure factor and electron density calculation was carried out (R = 0.43). From this improved map, in which the planes of false mirror symmetry were completely destroyed, C(4), C(41), and C(42) were found and the oxygen atoms identified. A third Fourier synthesis (R = 0.42) resulted in the discovery of the remaining atoms of the molecule. As several small spurious peaks remained on this map a ΔF synthesis was carried out. This served to confirm the structure previously found as no extra regions of high electron density were observed. The structure was further supported by ^{1}H and ^{13}C n.m.r. data (see section 5.7).

5.4 Structure Refinement

The structure was refined by a full matrix least squares method. Unit weights for all reflections were employed throughout, as no other weighting scheme gave a significant improvement. Introduction of anisotropic temperature factors after cycle 5 ($R = 0.16$) reduced R to 0.12, although it is unlikely that these have much physical significance in view of the poor quality of the intensity measurements. As a result the e.s.d.'s of the light atoms were high. Hydrogen atoms were not included at any stage of the analysis. The observed and calculated structure factors are listed in Appendix A. The computer programs used in solving the structure were developed from the series of programs "Crystal 69" (by A. Griffith and M.T.G. Powell) by Dr. P. Murray-Rust.

5.5 Molecular Structure

The final atomic co-ordinates, isotropic temperature factors, bond lengths and angles, and torsion angles are presented in Tables 5.2, 5.3, 5.4 and 5.5. In spite of the

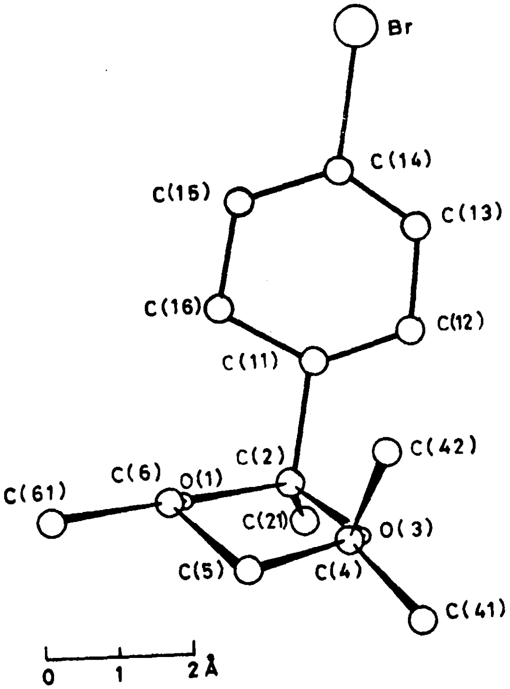


Figure 5.2 A view of the molecule, projected onto the benzene ring, showing the atomic numbering scheme.

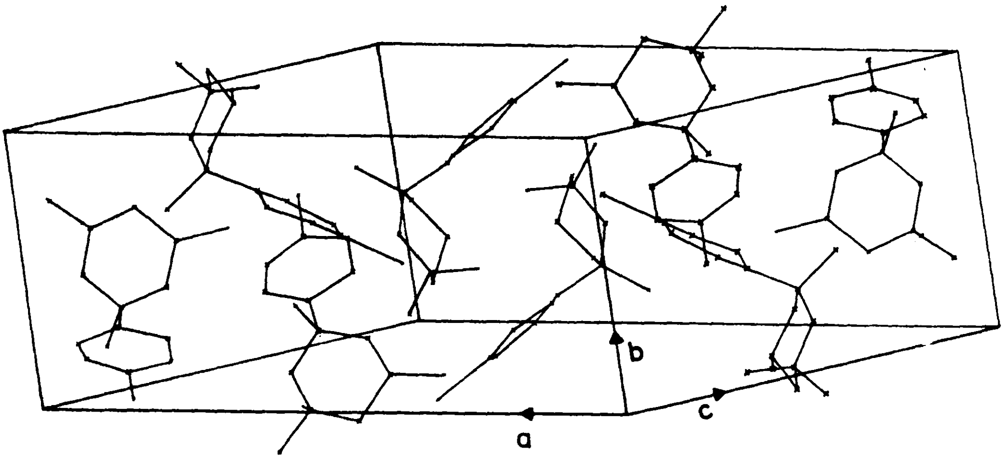
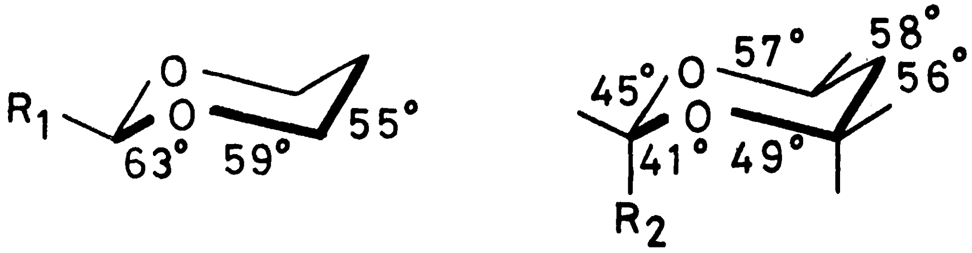


Figure 5.3 A view of the Unit Cell.

poor quality of the data, which introduces large errors into the calculated parameters, the structure of the compound can be clearly seen (Figures 5.2 and 5.3). The 1,3-dioxan ring exists in a deformed chair conformation with the 2 and 6 methyl groups in cis equatorial positions, and the phenyl group in an axial orientation, i.e. the isomer formed is compound 5.2. The severity of the 1,3-diaxial repulsion between the phenyl group and the axial 4-methyl group, C(42) (contact distance 320 pm), is not of sufficient magnitude to force the ring into a twist conformation, but it does severely distort the chair. Both the phenyl ring and the axial 4-methyl group are displaced outwards so that the axial bonds (parallel in a perfect chair) intersect at an angle of ca. 30°. Further, the C(2) end of the molecule is considerably flattened compared with the undistorted chair form of 2-(4'-chlorophenyl)-1,3-dioxan[36] (5.4). This can be clearly seen by examination of the ring torsion angles for both molecules (Figure 5.4). The C(2)-O(3)-C(4)-C(5) side of the ring, along which the principal non-bonded interactions take place, is flatter than the C(2)-O(1)-C(6)-C(5) side.

As a result of a study of some 1,3-dioxans with axial aryl substituents at C(2), Eliel[37] suggested that these axial groups might be able to bend outward from the ring, and hence



5.4 5.2

R_1 = 4-Chlorophenyl R_2 = 4-Bromophenyl

Figure 5.4 Ring Torsion Angles for two 1,3-Dioxans (The angles are listed beside the appropriate bonds).

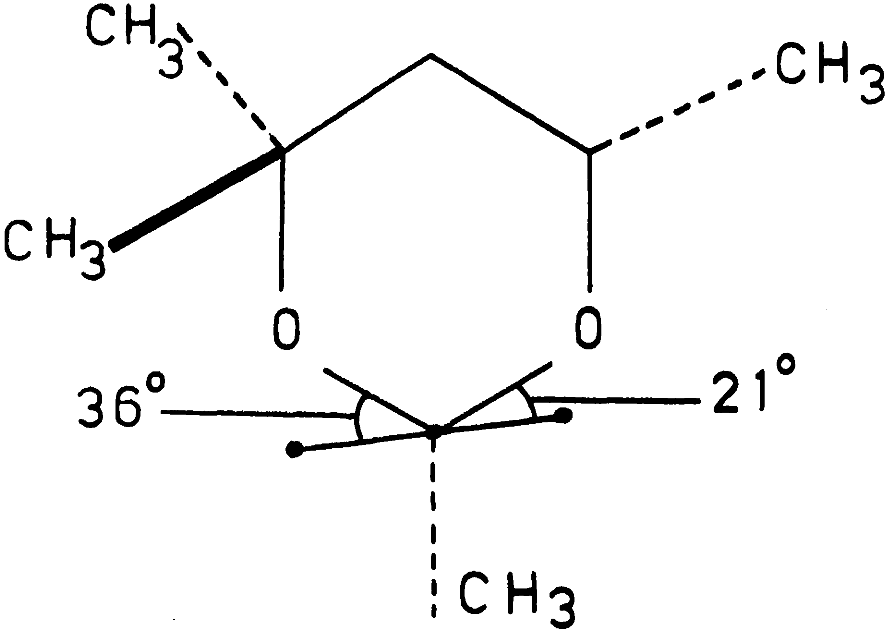


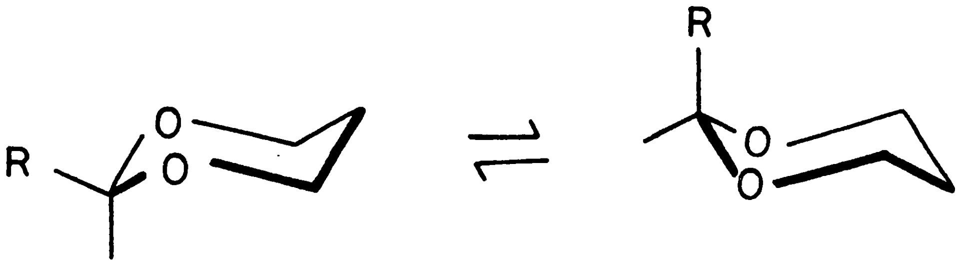
Figure 5.5 The Conformation of the Phenyl Group.

reduce their non-bonded interactions with the *syn*-axial protons at C(4) and C(6). For axial alkyl groups he considered that such deformations would be less likely. Eliel's conclusions are partly supported by the structure of 5.2 in which much of the non-bonded strain in the molecule is relieved by the phenyl group leaning out from the ring. In contrast 2,2,4,4,6-pentamethyl-1,3-dioxan appears to prefer a twist conformation.

As a further means of reducing the 1,3-diaxial strain, the phenyl group in compound 5.2 rotates slightly so that it presents a broadside appearance to the axial methyl group (Figure 5.5). Although this involves an increase in the repulsions between the ortho and the 6-axial protons, these considerations are outweighed by the consequent reduction in the interactions between the phenyl ring and the axial methyl group. Such rotomers are often adopted by phenyl groups in the solid state and have been considered by Ermer and Dunitz[105] to be due to packing forces in the crystal. However for this molecule it is more likely that the preferred orientation of the phenyl ring is controlled by intramolecular forces.

5.6 2-Methyl-2-Phenyl-1,3-Dioxans

The structure of compound 5.2 leads to some important conclusions regarding the preferred conformations of 2-methyl-2-



5.5 5.6

R = Phenyl

Figure 5.6 The Conformational Equilibrium in 2-Methyl-2-Phenyl-1,3-Dioxan.

phenyl-1,3-dioxans. On the basis of a dipole moment study of such molecules Havinga[103] concluded that the more stable conformation of 2-methyl-2-phenyl-1,3-dioxan was that with the phenyl group axial (5.6) and the free energy difference* between 5.5 and 5.6 was ca. 3.4 kJ mol^{-1}. Examination of the ^{1}H n.m.r. coupling constants for 2-methyl-2-phenyl and 2-methyl-2-(4'-nitrophenyl)-1,3-dioxans (Table 5.6) confirmed that they each exist predominantly in a single conformation but did not permit estimation of the free energy difference between the conformers. When compound 5.2 was treated with acid under conditions known to epimerise 1,3-dioxans no peaks were observed in the g.l.c. or the n.m.r. spectra which could be assigned to the other isomer. This indicates that compound 5.2 is more stable than 5.3 by greater than 9.0 kJ mol^{-1}.

An explanation of the differences between the energies discussed above may be found in the semi-empirical calculations made by Allinger[106] of the energies of similarly substituted cyclohexanes. His results indicate that the more stable conformation of 1-methyl-1-phenyl-cyclohexane is that with the phenyl group axial and the free energy difference between the conformers is 3.8 kJ mol^{-1}. Further for 1,3,3-trimethyl-1-phenyl-cyclohexane, which is analogous to compound 5.2, a

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* This energy difference was determined for 2-methyl-2-phenyl-1,3-dithiane but Havinga noted that 2-methyl-2-phenyl-1,3-dioxan had a similar equilibrium and energy difference.

larger free energy difference ($\Delta G = 15.3$ kJ mol^{-1}) was found in favour of the conformation with an axial phenyl group. Hence it is likely that the arguments put forward by Allinger are applicable to the 1,3-dioxans.

5.7 The Preferred Conformation of Compound 5.2 in Solution

A detailed analysis of the ^{1}H n.m.r. data for compound 5.2 and some model compounds (Table 5.7) suggests that the distorted chair is the preferred conformation in solution as well as in the solid state. One of the 4-methyl groups absorbs ca. 0.4 p.p.m. to high field of similar groups in 2,2,4,4,6-pentamethyl-1,3-dioxan (twist model) and cis-2,4,4,6-tetramethyl-1,3-dioxan (chair model). An estimation of the shielding that would result from the deformed chair conformation can be made by determining the methyl proton-phenyl ring distance (for C(42)) from the crystal structure. Using Bovey's tables[107], a shielding of ca. 0.5 p.p.m., in good agreement with the observed value, can be calculated for this intramolecular distance. The coupling constants observed for 5.2 could have resulted from a 1,4-twist conformation, but almost no shielding of the 4-methyl-protons would occur for such a structure (the phenyl ring occupies a pseudo-equatorial position).

The ^{13}C n.m.r. spectra of a number of phenyl, gem-diphenyl and 2-methyl-2-phenyl-1,3-dioxans, known to prefer chair conformations, were also measured. Using the method described in Chapter 2 substituent parameters were calculated for the carbon atoms at positions 4 and 6. These were then used to calculate the shifts of the same carbons in r-2-4,4-c-6-tetramethyl-2-phenyl-1,3-dioxan (the non-brominated derivative of compound 5.2) and 2,2-diphenyl-4,4,6-trimethyl-1,3-dioxan. From the results shown in Table 5.8 it can be seen that C(6) can be calculated with reasonable accuracy, but in both cases a large difference of ca. 7.6 p.p.m., between the observed and calculated shifts for C(4), is found. This fits well with the crystal structure as C(4) is rather more deformed than C(6).

In Chapter 2 it was noted that differences between the observed and calculated chemical shifts could not unequivocally be taken to indicate the presence of twist conformations as opposed to severely distorted chairs. The result of the work described in this chapter is to show that in order to assign a non-chair conformation to a compound evidence must be obtained by several different techniques as was done for many of the compounds discussed in Chapters 2 and 3.

TABLE 5.1

Crystal Data

$C_{14}H_{19}BrO_2$, M = 299, Orthorhombic,

a = 2765(3), b = 795(1), c = 1316(1) pm,

Dm = 1.385 g cm^{-3} (by floatation in aqueous potassium carbonate), z = 8, Dc = 1.373 g cm^{-3}, F(000) = 1232. Space Group Pbca (D^{15}_{2h}, No61).

Linear absorption coefficient for MoKα radiation (λ = 71.07 pm) μ = 41.2 cm^{-1}.

TABLE 5.2

Fractional Co-ordinates*

	x/a	y/b	z/c
Br	0.0020(2)	0.5392(5)	0.2679(3)
C(11)	0.1160(12)	0.2187(36)	0.4482(25)
C(12)	0.1304(9)	0.2891(30)	0.3486(22)
C(13)	0.0943(11)	0.3888(40)	0.2937(24)
C(14)	0.0490(11)	0.4137(37)	0.3425(33)
C(15)	0.0379(10)	0.3387(28)	0.4297(30)
C(16)	0.0713(10)	0.2650(28)	0.4944(25)
C(21)	0.1806(15)	0.2445(66)	0.5838(36)
C(41)	0.1224(12)	-0.2844(48)	0.5915(29)
C(42)	0.0803(13)	-0.1564(40)	0.4570(26)
C(61)	0.2307(11)	-0.1006(48)	0.3014(29)
C(2)	0.1595(15)	0.1288(56)	0.5020(34)
C(4)	0.1287(12)	-0.1600(40)	0.5044(29)
C(5)	0.1704(11)	-0.2117(37)	0.4451(25)
C(6)	0.1832(10)	-0.0726(37)	0.3674(26)
O(1)	0.1953(7)	0.0774(25)	0.4315(18)
O(3)	0.1393(7)	-0.0047(25)	0.5572(17)

* Estimated standard deviations are shown in parenthesis

TABLE 5.3

Isotropic Temperature Factors x 10^{-4} (pm^2)*

Br	6.0(2)	C(42)	4.0(11)
C(11)	3.7(10)	C(61)	5.0(12)
C(12)	2.3(8)	C(2)	2.9(9)
C(13)	3.6(10)	C(4)	3.3(10)
C(14)	3.8(10)	C(5)	4.2(11)
C(15)	2.8(9)	C(6)	3.2(9)
C(16)	3.1(9)	O(1)	4.0(6)
C(21)	4.6(12)	O(3)	4.5(7)
C(41)	4.6(11)		

* Estimated standard deviations are shown in parenthesis

TABLE 5.4

Interatomic Distances and Angles

(a) Bonded Distances (pm)*

Br-C(14)	194(3)	C(2)-O(1)	145(4)
C(13)-C(14)	136(5)	C(2)-O(3)	139(4)
C(13)-C(12)	152(5)	C(61)-C(6)	159(5)
C(14)-C(15)	133(5)	C(6)-C(5)	157(5)
C(12)-C(11)	146(5)	C(6)-O(1)	147(4)
C(11)-C(16)	137(5)	C(5)-C(4)	145(5)
C(11)-C(2)	162(5)	C(42)-C(4)	144(5)
C(16)-C(15)	134(5)	C(4)-C(41)	154(5)
C(2)-C(21)	153(5)	C(4)-O(3)	146(4)

* Estimated standard deviations are shown in parenthesis.

(b) Interbond Angles (°)*

Br-C(14)-C(13)	115	C(2)-O(3)-C(4)	115
Br-C(14)-C(15)	119	C(21)-C(2)-O(3)	105
C(13)-C(12)-C(11)	115	C(21)-C(2)-O(1)	112
C(13)-C(14)-C(15)	126	C(61)-C(6)-O(1)	103
C(14)-C(15)-C(16)	122	C(61)-C(6)-C(5)	116
C(14)-C(13)-C(12)	114	C(6)-C(5)-C(4)	104
C(12)-C(11)-C(16)	122	C(5)-C(6)-O(1)	108
C(12)-C(11)-C(2)	109	C(5)-C(4)-C(42)	121
C(11)-C(16)-C(15)	118	C(5)-C(4)-C(41)	108
C(11)-C(2)-C(21)	108	C(5)-C(4)-O(3)	112
C(11)-C(2)-O(1)	110	C(42)-C(4)-C(41)	99
C(11)-C(2)-O(3)	107	C(42)-C(4)-O(3)	115
C(16)-C(11)-C(2)	127	C(41)-C(4)-O(3)	98
C(2)-O(1)-C(6)	114	O(1)-C(2)-O(3)	115

* Estimated standard deviations of all angles are 2°.

(c) Intermolecular Distances (pm)

C(13)-O(3)	344(10)

The co-ordinates of the oxygen atom are $-1+x$, $\frac{1}{2}-y$, $-\frac{1}{2}+z$.

TABLE 5.5

Torsion Angles (°)*

The convention used, is that a torsion angle A-B-C-D is positive if, when viewed in projection along bond B → C, the sense of rotation from BA to CD is clockwise.

C(6) - O(1) - C(2) - O(3)	+ 45
C(1) - C(2) - O(3) - C(4)	- 41
C(2) - O(3) - C(4) - C(5)	+ 49
O(3) - C(4) - C(5) - C(6)	- 56
C(4) - C(5) - C(6) - O(1)	+ 58
C(5) - C(6) - O(1) - C(2)	- 57

* Estimated standard deviations on all angles are 2°.

TABLE 5.6

^{1}H n.m.r. Coupling Constants for some 1,3-Dioxans

	Coupling Constants (Hz)	
Coupling Protons[A]	2-Methyl-2-Phenyl-1,3-Dioxan[B]	2-Methyl-2(4'-nitrophenyl)-1,3-Dioxan[C]
4A, 4E	- 11.8	- 12.0
5A, 5E	- 13.0	- 13.3
4A, 5A	12.0	12.0
4A, 5E	2.2	2.9
4E, 5A	5.0	5.0
4E, 5E	1.6	2.2

A. A = Axial, E = Equatorial.

B. Values ± 0.3 Hz obtained from the 220 MHz spectrum of a 10% (w/v) solution of the 1,3-dioxan and Eu(fod)$_3$ in CCl$_4$.

C. Values ± 0.2 Hz from a LAOCN3 analysis of the 220 MHz spectrum of a 10% (w/v) solution of the 1,3-dioxan in CCl$_4$.

TABLE 5.7

^{1}H n.m.r. parameters for some 1,3-Dioxans

(a) Chemical Shifts (τ, p.p.m.)^A

Compound	2 Me	4 Me	6 Me
cis-2,4,4,6-tetra Me	8.72	8.83 8.85	8.88
2,2,4,4,6-penta Me	8.51 8.51	8.83 8.89	8.83
r-2-4,4-*c*-6-tetra Me -2-(4'-bromo Ph)	8.49	8.76 9.29	8.85

A. In benzene solution.

(b) Coupling Constants (Hz)

Compound	$^3J_{5,6(1)}$	$^3J_{5,6(2)}$	$^2J_{5,5}$	$^3J_{6,Me}$
cis-2,4,4,6-tetra Me	11.0	2.5	-	6.2^{A,C}
2,2,4,4,6-penta Me	10.9	2.5	-12.9	6.0^{B,D}
r-2-4,4-*c*-6-tetra Me -2-(4'-bromo Ph)	11.6	2.2	-13.0	6.6^{A,D}

A. In benzene solution.

B. In CCl_4 solution.

C. 1st order splittings. (± 0.3 Hz)

D. LAOCN3 calculated values (± 0.2 Hz)

TABLE 5.8

^{13}C n.m.r. Chemical Shifts for some 1,3-Dioxans^{A,B}

Substituents	C(4)		C(6)	
	obs.	calc.^{C,D}	obs.	calc.^{C,D}
-	125.9	125.9	125.9	125.9
2-Ph	125.8	125.6	125.8	125.6
cis-2-Ph-4-Me	119.3	120.0	125.7	125.7
2-Ph-5,5-diMe	115.5	115.2	115.5	115.2
r-2-Ph-*c*-4,6-diMe^{E}	120.3	120.1	120.3	120.1
2,2-diPh	131.5	131.3	131.5	131.3
2,2-diPh-4-Me	125.9	125.7	131.2	131.3
2,2-diPh-5,5-diMe	120.6	120.8	120.6	120.8
r-2-*c*-4,6-triMe-2-Ph	126.5	126.3	126.5	126.3
r-2-*c*-4-diMe-2-Ph	126.3	126.2	131.6	131.9
2,5,5-triMe-2-Ph	121.3	121.4	121.3	121.4
r-2-4,4-*c*-6-tetraMe-2-Ph^{F}	120.7	128.4	129.6	130.8
2,2-diPh-4,4,6-triMe^{F}	120.2	127.8	129.2	130.2

A. In p.p.m. upfield from $^{13}CS_2$

B. Recorded at 22.63 MHz in $CDCl_3$ solution.

C. Calculated using the following parameters:
2 eq. Ph = -0.3, 2 ax. Ph = 5.7, 2 eq. Me = 0.3,
4 eq. Me = -5.6, 6 eq. Me = 0.0, 5,5-diMe = -10.5 p.p.m.

D. Regression coefficient = 0.999, standard deviation = 0.3 p.p.m.

E. Value from reference 81.

F. Not included in the analysis. Calculated using data from Chapter 2 and the substituent parameters given above.

CHAPTER 6

AN EMPIRICAL APPROACH TO THE ANALYSIS OF BOILING POINTS

CHAPTER 6

6.1 Introduction

Over the past fifty years many chemists have felt that there might exist a simple relationship between the structure of an organic compound and its bulk physical properties e.g. boiling point, density, refractive index, etc. As these properties are, in general, readily measurable, it was felt that by applying such a relationship the structure of a compound might be conveniently determined. The first attempt to formulate a rule of this type was made by Von Auwers[108] in a study of some dimethyl cyclohexanes. Since then a large number of rules have been proposed, a typical example being that put forward by Allinger[109], which states: "With respect to cis and trans isomers in cyclic systems, that isomer which has the highest boiling point, highest index of refraction, and highest density, is the isomer which possesses the least stable configuration."

Van Bekkum[110] and his co-workers examined many of these rules in detail and concluded that none of them was without some distinct limitations. Since the demise of these rules little work has been carried out on this subject, largely due to the widespread application of physical techniques (e.g. n.m.r.) to stereochemical problems.

However, in the course of the work described in this thesis, a large body of physical data (particularly boiling points) was accumulated for compounds of known stereochemistry, and thus an attempt to rationalise this information in an empirical manner was carried out.

6.2 An Analytical Scheme for Boiling Points

As an initial approach it is useful to examine the thermodynamic properties of a liquid boiling under equilibrium conditions. The free energy difference between the liquid and vapour phases must be zero, hence the following relationship results:-

$$\Delta H_{VAP} = T\Delta S_{VAP} \qquad 6.1$$

ΔH_{VAP} is the enthalpy, and ΔS_{VAP} the entropy of vaporisation. Trouton's Rule[111] states that the entropy of vaporisation is constant for a series of <u>non</u>-polar liquids. If the assumption is made that ΔH_{VAP} is a linear function of the type and orientation of the substituents present in each compound in a homologous series, then it follows that the boiling points of these molecules will be influenced in a similar fashion by these factors.

In the light of these considerations the following equation was proposed to apply to the boiling points of a homologous series of <u>non</u>-polar compounds.

$$B_X = B_p + \Sigma a_N \Delta T_N \qquad 6.2$$

B_X was the boiling point of the Xth compound; B_p the boiling point of the parent (unsubstituted) compound; ΔT_N was the Nth substituent effect on the boiling point, and the a_N factor the number of times this effect was taken into account. Using the least squares treatment discussed previously (Chapter 2), "best fit" values of the incremental factors could be found. Hence the validity of this approach could be tested by comparing the observed boiling points with those calculated using the "best fit" parameters.

6.3 Boiling Point Correlations

The first series of compounds analysed in this fashion was the methyl benzenes. Using only two factors, a methyl group incremental parameter (+ 29.1°) and an ortho group incremental parameter (+ 1.8°), an excellent fit was obtained between the observed and calculated boiling points (regression coefficient = 0.998; standard deviation = 2.6°). These results are shown in Table 6.1.

In view of this success, the method was next applied to a homologous series of methyl cyclohexanes known to exist predominantly in chair conformations. Once more a good correlation was noted between the observed and calculated boiling points using the parameters presented in Table 6.2

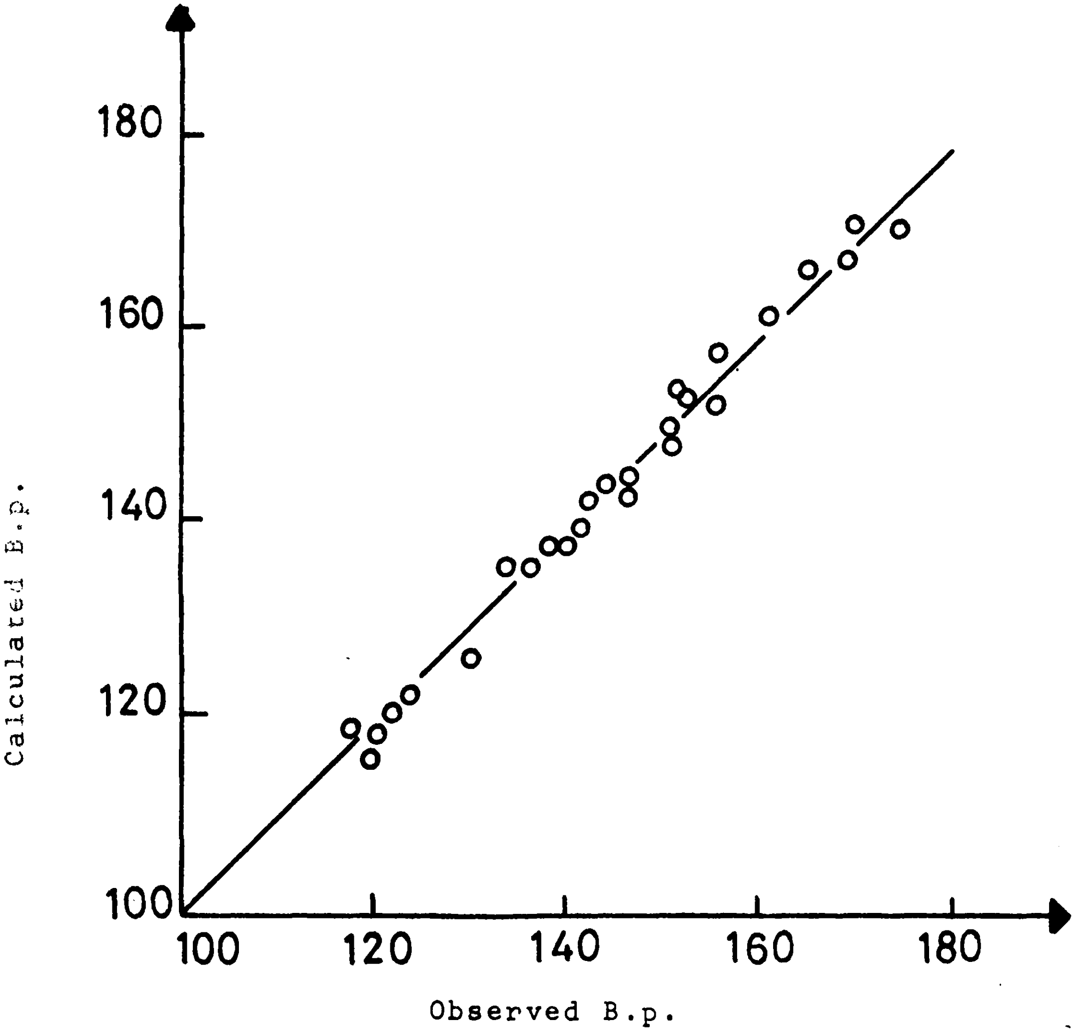

Figure 6.1. Plot of Observed and Calculated Boiling Points* for the Methyl Cyclohexanes.

* In °C at 760 mm.

(regression coefficient = 0.997, standard deviation = 2.0°). These results are shown in Table 6.3 and Figure 6.1. A significant point, which is seen from the factors employed, is that an axial group increases the boiling point to a greater extent than an equatorial group. This indicates that the boiling points are sensitive to molecular stereochemistry as previously suspected[108,109]. In addition these results demonstrate that a linear relationship does exist between ΔH_{VAP} (and hence the boiling point) and the substituents. Before applying this method further it is important to consider the origin of this relationship.

6.4 Factors influencing the Enthalpy of Vaporisation

When deriving equation 6.1 it was assumed that the enthalpy of vaporisation is a linear function of substituents. In order to justify this assumption the forces influencing ΔH_{VAP} must be examined. The major attractive forces to be overcome when a liquid boils are the dispersion forces which depend on how closely molecules can pack together and hence depend on the molar volume. For a compound with an axial methyl group overlapping of the methyl protons with the 1,3-*syn* diaxial protons will result in a smaller molar volume than that for an identical molecule with an equatorial methyl group. The former isomer will, as a result, have the higher boiling point due to larger intermolecular forces. As the molar volumes of a homologous series of compounds will be affected in a regular manner by the type and orientation of each substituent present, it is likely that ΔH_{VAP} will be subject to similar forces.

This theory is supported by the observation that the molar volumes of the methyl benzenes and cyclohexanes can be analysed in the same way as their boiling points. The results of these analyses are shown in Tables 6.4 and 6.5. The calculated and observed molar volumes are in close agreement (regression coefficients = 0.999 (Benzenes) and 0.998 (cyclohexanes); standard deviations = 0.5 $cm^3\ mol^{-1}$ (benzenes) and 0.7 $cm^3\ mol^{-1}$ (cyclohexanes)). The magnitude of the parameters used are as expected, e.g., an axial methyl group has a smaller molar volume effect (16.0 $cm^3\ mol^{-1}$) than an equatorial methyl group (19.2 $cm^3\ mol^{-1}$). In consequence, as this analysis succeeds for the molar volumes, it should also apply to the boiling points. This influence of molar volume on the boiling point of a compound has also been recognised by Allinger[112].

Extension of this method to include polar molecules creates some difficulties. Previous rules always excluded polar systems, although Van Arkel[113] had formulated his "dipole rule", according to which the isomer of highest dipole moment has the largest boiling point.

Trouton's Rule will not apply to a homologous series of polar compounds. This is because the molecules will adopt preferred orientations in the liquid phase due to dipolar interactions and hence ΔS_{VAP} will no longer be a constant for this series. However, if ΔS_{VAP} varies in a predictable manner then the previous approach might still be successful if the parameters chosen can account for the dipolar effects. In order to test this hypothesis a series of chlorobenzenes was examined using parameters that reflected not only molar volume increments but dipolar interactions as well. The satisfactory correlation found between the observed and calculated boiling points (Table 6.6) indicates that polar molecules can indeed be analysed using the scheme outlined.

6.5 Discussion of Results

Examination of the boiling point correlations obtained for a series of methyl substituted cycloalkanes (Tables 6.7, 6.8 and 6.9) reveals certain interesting features. In all cases, save the cyclohexanes, only one parameter was required for the introduction of a methyl group, reflecting, perhaps, the similarity of the environments of pseudo-equatorial and pseudo-axial groups in these series. The magnitude of this parameter decreases progressively on passing from the cyclopropanes to the cycloheptanes, since the methyl group

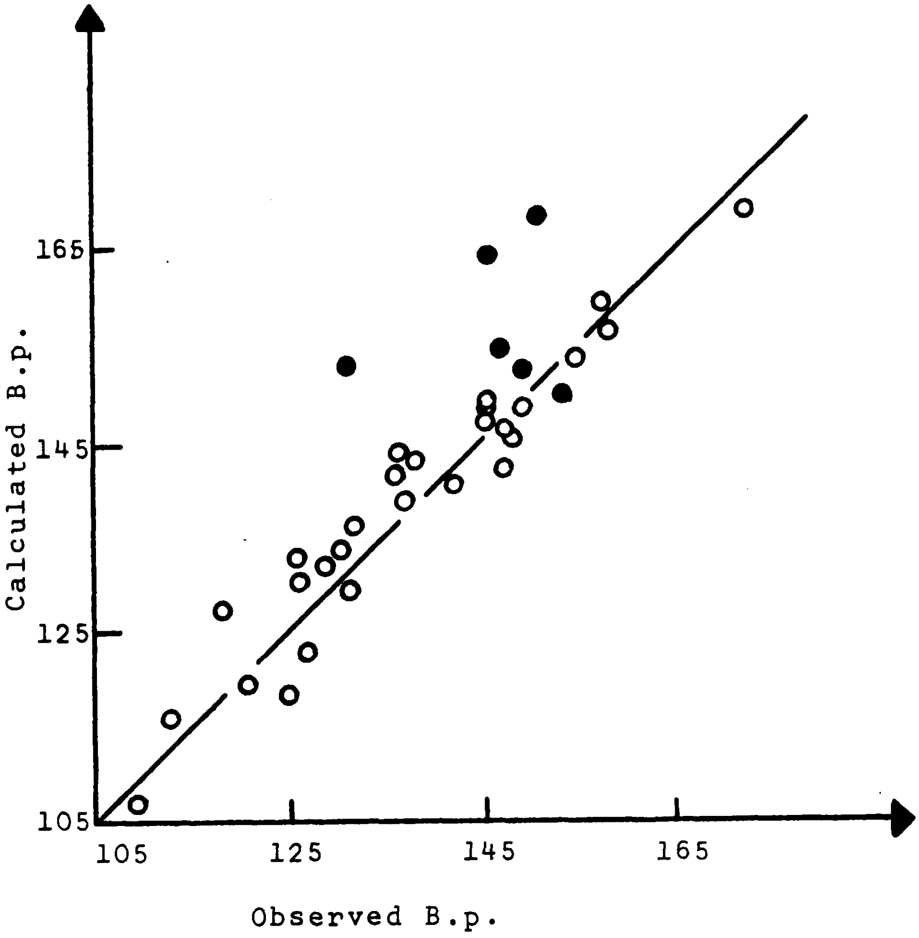

Figure 6.2. Plot of Observed and Calculated Boiling Points* for the Methyl 1,3-Dioxans.

* In °C at 760 mm.

○ Compounds in the reference series.

● Compounds suspected of existing in <u>non</u>-chair conformations.

will cause a lower percentage molar volume increase as the ring volume increases. For some compounds vicinal dimethyl parameters were used and these may reflect the proximity of the methyl groups.

The method was next used to examine some methyl 1,3-dioxans known to prefer chair conformations. Although the 1,3-dioxan ring must have a sizeable dipole moment, it was anticipated that this would be effectively constant for these compounds due to the similarity of their conformations. Hence the parameters used reflected only molar volume effects not dipolar interactions. A reasonable agreement was noted between the observed and calculated boiling points (regression coefficient = 0.97; standard deviation = 4^{o}). However, this correlation was not as good as that found for the cyclohexanes. This may be due to certain groups hindering orientations in the liquid phase more than other groups, hence altering ΔS_{VAP}. The results are shown in Table 6.10 and Figure 6.2.

When the boiling points of certain non-chair 1,3-dioxans were calculated (Table 6.11), large discrepancies were noted between the observed and calculated figures for some compounds. On applying an analysis to the molar volumes of these compounds an excellent correlation was found for the chair 1,3-dioxans, but a large difference was observed for 2,2-trans-4,6-tetramethyl-1,3-dioxan (Table 6.12).

These results can be considered to demonstrate that certain 1,3-dioxans prefer twist conformations. As these twists will have larger molar volumes than the chair conformations of these molecules (some axial groups occupy ψ_E positions in the twists) their observed boiling points should be lower than the calculated figures. The data in Table 6.11 tend to bear this out and the molar volume deviation observed for 2,2-*trans*-4,6-tetramethyl-1,3-dioxan is in the correct sense (i.e. the observed molar volume is larger than the calculated figure). The boiling point deviations might also have arisen from dipolar effects, but it is more likely that molar volume effects predominate.

Therefore, this method of using boiling point and molar volume data to examine the stereochemistry of compounds in a homologous series, seems to have some applicability. It is best applied in an empirical manner, and its greatest virtue is its ability to point out unusual stereochemistries. An extension of this approach would be to apply it to gas chromatographic retention times. By suitable choice of a liquid phase it should be possible to obtain retention times which are linearly related to boiling points. As retention times can be accurately determined this may provide another convenient method for examining molecular stereochemistries.

In connection with the similarity of this analysis to that applied to the ^{13}C n.m.r. shifts in Chapter 2, it is interesting to note that Perlin[114] has recently considered that ^{13}C shifts resemble bulk physical properties and may be accommodated in a Von Auwers type rule.

TABLE 6.1

METHYL BENZENE BOILING POINTS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B]
0	80.1	80.1
1	110.6	109.2
1,2	144.4	140.2
1,3	139.1	138.4
1,4	138.3	138.4
1,3,5	164.7	167.5
1,2,4	169.4	169.4
1,2,3	176.1	171.2
1,2,3,4	205.0	202.2
1,2,3,5	198.0	200.4
1,2,4,5	196.8	200.4
1,2,3,4,5	231.8	233.2
1,2,3,4,5,6	265.0	266.0

A Values at 760 mm from reference 115.

B Calculated using parameters given in Chapter 6.

TABLE 6.2

SUBSTITUENT PARAMETERS* USED IN THE ANALYSIS OF THE METHYL CYCLOHEXANE BOILING POINTS

Substituents	Δ B.p. (^{o}C)
Equatorial Me	19.1
Axial Me	23.0
Gem di Me	-5.7
Equatorial-Axial Vicinal di Me	4.2
Equatorial-Equatorial Vicinal di Me	3.1

* Obtained from the least squares analysis.

TABLE 6.3

METHYL CYCLOHEXANE BOILING POINTS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B]
0	81	81
1	101	100
1,1	120	117
cis-1,2	130	127
trans-1,2	123	122
cis-1,3	120	119
trans-1,3	124	123
cis-1,4	124	123
trans-1,4	119	119
1,1,3	136	136
1,1,4	135	136
r-1-*c*-3,5	139	138
r-1-*c*-3-*t*-5	142	142
r-1-*c*-2,3	151	150
r-1-*c*-2-*t*-3	151	149
r-1-*t*-2-*c*-3	146	144
r-1-*c*-2,4	146	146
r-1-*c*-2-*t*-4	146	146
r-1-*t*-2-*c*-4	145	145
r-1-*t*-2,4	142	141
1,1,3,3	155	153
1,1,4,4	153	153
1,1-*cis*-3,5	152	155
1,1-*trans*-3,5	156	159
r-1-*c*-2,3,5	169	169
r-1-*t*-2,4-*c*-5	161	163
r-1-*t*-2-*c*-4,5	165	168
r-1-*c*-2-*t*-4,5	170	173
r-1-*c*-2,4,5	170	173

A Values at 760 mm from references 116 and 117.

B Calculated using parameters given in Chapter 6.

TABLE 6.4

METHYL BENZENE MOLAR VOLUMES

Substituents	Observed Vm[A]	Calculated Vm[B]
0	88.7	88.7
1	106.3	105.9
1,2	120.6	119.9
1,3	122.9	122.8
1,4	123.3	122.8
1,3,5	138.9	139.8
1,2,3	134.4	134.4
1,2,4	137.2	136.9
1,2,3,4	148.3	148.1
1,2,3,5	150.8	151.0
1,2,4,5	151.2	151.0
1,2,3,4,5	161.7	162.2

A Values in cm^3 mol^{-1} from reference 115.

B Calculated using a methyl group incremental factor (17.0 cm^3 mol^{-1}) and an ortho group incremental factor (-2.9 cm^3 mol^{-1}).

TABLE 6.5

METHYL CYCLOHEXANE MOLAR VOLUMES

Substituents	Observed Vm[A]	Calculated Vm[B]
0	107.9	107.9
1	127.6	127.1
1,1	143.7	143.1
cis-1,2	140.9	140.9
trans-1,2	144.6	144.1
cis-1,3	146.5	146.3
trans-1,3	143.0	143.1
cis-1,4	143.3	143.1
trans-1,4	147.2	146.3
1,1,3	162.1	162.4
1,1,4	163.5	162.4
r-1-c-2,3	158.2	157.8
r-1-t-2,3	156.4	157.9
r-1-t-2-c-3	161.6	161.2
r-1-c-2,4	160.4	160.1
r-1-c-2-t-4	160.4	160.1
r-1-t-2-c-4	160.2	160.2
r-1-t-2,4	161.2	162.3
r-1-c-3,5	164.0	165.5
r-1-c-3-t-5	163.5	163.4

A Values in cm^3 mol^{-1} from reference 118.

B Calculated using the following incremental factors:

Equatorial Me = 19.2; Axial Me = 16.0;
Equatorial-Axial Vicinal di Me = -2.3;
Equatorial-Equatorial Vicinal di Me = -2.2 cm^3 mol^{-1}.

TABLE 6.6

CHLORO BENZENE BOILING POINTS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B,C]
0	80	80
1	131	131
1,2	179	180
1,3	173	173
1,4	173	173
1,3,5	208	207
1,2,3	218	219
1,2,4	213	213
1,2,3,4	254	250
1,2,3,5	246	253
1,2,4,5	245	244
1,2,3,4,5	277	280

A Values at 760 mm from reference 115.

B Calculated using the following incremental factors:

Chloro parameter (51°), ortho parameter (-3°), meta parameter (-9°) and para parameter (-9°).

C Regression coefficient = 0.997; Standard deviation = 3°.

TABLE 6.7

METHYL CYCLOPROPANE BOILING POINTS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B,C]
0	-33	-33
1	5	1
1,1	21	23
cis-1,2	37	35
trans-1,2	29	31
1,1,3	56	53
r-1-*c*-2,3	66	68
r-1-*c*-2-*t*-3	60	60

A Values at 760 mm from references 115 and 119.

B Calculated using the following incremental factors: methyl group (34°), gem-dimethyl (-11°) and *trans*-1,2-vicinal dimethyl (-4°).

C Regression coefficient = 0.994; Standard deviation = 3°.

TABLE 6.8

METHYL CYCLOPENTANE BOILING POINTS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B,C]
0	49	49
1	72	70
1,1	88	86
cis-1,2	100	96
trans-1,2	92	91
cis-1,3	92	91
trans-1,3	91	91
1,1,2	114	112
1,1,3	105	107
r-1-*t*-2-*c*-3	110	112
r-1-*t*-2-*c*-4	109	112
r-1-*c*-2-*t*-3	118	117
r-1-*c*-2-*t*-4	117	117
r-1-*c*-2,4	118	117
1,1-*cis*-3,4	133	133
1,1-*trans*-3,4	122	122
1,1,3,3	118	117
r-1-*c*-2,3,4	147	148
r-1-*t*-2,3-*c*-4	134	133
1,1-*c*-2,3	136	138

A Values at 760 mm from references 115 and 119.

B Calculated using the following incremental factors: methyl group (21°), gem dimethyl (-5°), *cis* vicinal dimethyl (5°) and 1,3-*syn* pseudo-axial dimethyl (-6°).

C Regression coefficient = 0.997; Standard deviation = 2°.

TABLE 6.9

METHYL CYCLOHEPTANE BOILING POINTS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B,C]
0	118	118
1	136	136
1,1	152	153
cis-1,2	161	161
trans-1,2	157	157
cis-1,3	153	153
trans-1,3	153	153
cis-1,4	154	153
trans-1,4	154	153

A Values at 760 mm from reference 120.

B Calculated using the following incremental factors: methyl group (18°), *cis*-1,2-vicinal dimethyl (8°) and *trans*-1,2-vicinal dimethyl (4°).

C Regression coefficient = 0.996; Standard deviation = 1°.

TABLE 6.10

METHYL-1,3-DIOXAN BOILING POINTS

Substituents	Observed B.p. (°C)^{A}	Calculated B.p. (°C)^{B}
0	105	105
2	110	108
4	114	115
5	118	121^{C} 118^{D}
5,5	127	134
cis-4,6	126	130
trans-4,6	137	139
cis-2,4	119	118
cis-2,5	121	120
trans-2,5	127	124
2,2	125	119
4,4	133	135
4,4,6	143	140
r-2-*c*-4,6	129	132
r-2-*c*-4-*t*-6	138	142
r-4-*c*-5-*t*-6	157	155^{C} 152^{D}
r-4-*c*-5,6	148	146
r-4-*t*-5-*c*-6	148	143
2,5,5	132	136
2,2,4	132	129
cis-2,4,4,6	139	142
r-2-*c*-4-*t*-5,6	159	158
cis-2,4,5,5	147	147
2,2-*cis*-4,6	138	144
2,2,5,5	145	148
r-2-*c*-4,5,6	149	148
r-2-*c*-4,6-*t*-5	149	145
trans-4,5,5,6	173	168
cis-4,5,5,6	159	159
cis-2,4,4,5	156	153
2,2,5	137	135^{C} 132^{D}

(continued)

Table 6.10 (continued)

A Values at 760 mm determined in this work or an average of published figures.[37,38,40,45,46,51,87,100,121]

B Calculated using the following incremental factors:
2-equatorial Me (3°), 2-axial Me (11°),
4-equatorial Me (10°), 4-axial Me (33°), 5-equatorial Me (16°),
5-axial Me (13°), 4-gem di Me (-14°),
4,6-diequatorial di Me (4°) and 4-equatorial-6-axial
di Me (-9°).

C Calculated for 5-equatorial methyl.

D Calculated for 5-axial methyl.

TABLE 6.11

OBSERVED AND CALCULATED BOILING POINTS FOR 1,3-DIOXANS SUSPECTED OF EXISTING IN NON-CHAIR CONFORMATIONS

Substituents	Observed B.p. (°C)[A]	Calculated B.p. (°C)[B]
2,2-*trans*-4,6	132	153
2,2,4,4,6	147	155
2,2-*r*-4-*c*-5-*t*-6	152	169[C]
2,4,4,6,6	150	152
4,4,6,6	154	150
2,2,4,4,5[D]	147	165[C]

A Values at 760 mm determined in this work.

B Calculated for chair conformations.

C Calculated for 5-methyl equatorial.

D Value at 760 mm from reference 100.

TABLE 6.12

METHYL-1,3-DIOXAN MOLAR VOLUMES

Substituents	Observed Vm[A]	Calculated Vm[B,C]
0	85.4	85.4
4	104.6	104.6
5,5	121.4	122.1
cis-4,6	124.4	123.7
trans-4,6	120.9	121.0
4,4,6	140.1	140.1
2	105.5	105.0
cis-2,4	124.0	124.1
2,5,5	142.2	141.7
r-2-*c*-4,6	142.5	143.2
r-2-*c*-4-*t*-6	140.5	140.5
cis-2,4,4,6	159.7	159.6
2,2	121.0	121.2
2,2,4	140.1	140.3
2,2,5,5	158.1	157.9
2,2-*cis*-4,6	159.8	159.5
2,4,4,6,6[D]	176.0	176.0
4,4,6,6[D]	155.7	156.5
2,2-*trans*-4,6[D]	161.1	156.7

A Values in cm^3 mol^{-1} from reference 121.

B Calculated using the following incremental factors: 2-equatorial methyl (19.5), 2-axial methyl (16.2), 4-equatorial methyl (19.1), 4-axial methyl (16.4), 5-gem dimethyl (36.7 cm^3 mol^{-1}).

C Regression coefficient = 0.999, standard deviation = 0.4 cm^3 mol^{-1}.

D Compounds suspected of existing in *non*-chair conformations. These were not included in the analysis.

CHAPTER 7

EXPERIMENTAL

CHAPTER 7

7.1 Nuclear Magnetic Resonance Spectra

^{1}H N.M.R. Spectra

The 60 MHz spectra were recorded using a Perkin-Elmer R.10 instrument operating at 33.5°C. For the variable temperature spectra the same instrument was employed with the addition of a variable temperature probe and ancillary equipment. In all cases the measurements were made on 10% (w/v) solutions. The 220 MHz spectra were recorded on a Varian HR 220 Spectrometer at Runcorn (S.R.C. n.m.r. service).

^{13}C N.M.R. Spectra

The spectra of the methyl and gem-diethyl 1,3-dioxans were measured using the Perkin-Elmer R.10 operating at 15.1 MHz. In all cases the compounds were examined as neat liquids in stationary 8.5 mm o.d. tubes at 33.5°C. A sample of ^{13}C enriched carbon disulphide or methyl iodide (both approximately 60% enriched) sealed in a 2.8 mm o.d. capillary tube, served as a reference and trigger for the computer. A Digiac computer (C.A.T.) on line to the spectrometer was used for spectral accumulations. Depending on the complexity of the spectrum, between 64 and 256 spectra were accumulated into 1500 channels. $^{13}CS_2$ was used as reference for all the reported shifts; when methyl iodide was employed the shifts were corrected to $^{13}CS_2$ using the relationship[122]:

$$\delta_{(\text{rel. to } ^{13}CS_2)} = 213.1 - \delta_{(\text{rel. to } ^{13}CH_3I)} \text{ p.p.m.} \qquad 7.1$$

As the spectrometer sweep was found to be <u>non</u>-linear corrections were applied to the chemical shifts (0 - 1 p.p.m.). The shifts recorded in this work were estimated to be accurate to ± 0.5 p.p.m. (± 7.5 Hz).

The spectra of the phenyl substituted 1,3-dioxans and some of the methyl 1,3-dioxans were recorded at 22.63 MHz using a Fourier Transform method. The spectrometers used were a Bruker HFX13 (S.R.C. N.M.R. Service) and a Bruker HX72, both equipped with a Fabritek Fast Fourier Transform system. The 1,3-dioxans were measured as ca. 50% (w/v) solutions in $CDCl_3$ with C_6F_6 added to provide the heteronuclear lock (^{19}F), and T.M.S. as internal reference. All spectra were recorded under conditions of complete proton decoupling. Chemical Shifts recorded in this manner were estimated to be accurate to ± 0.2 p.p.m. (± 4.5 Hz). In order to convert these shifts to $^{13}CS_2$ standard the following relationship was employed[123].

$$\delta_{(\text{rel. to } ^{13}CS_2)} = 193.1 - \delta_{(\text{rel. to } ^{13}TMS)} \text{ p.p.m.} \qquad 7.2$$

7.2 Gas-Liquid Chromatography

Gas-liquid chromatographs were obtained using a Perkin-Elmer F11 instrument with nitrogen as the carrier gas. Excellent separations of 1,3-dioxans were found using a 2 metre 1½% fluorosilicon oil on A.W. D.M.C.S. chromosorb W column (efficiency = 500 theoretical plates), and a 2 metre 15% silicon grease on chromosorb W column (efficiency = 800 theoretical plates).

7.3 Spinning Band Distillations

Mixtures of isomeric 1,3-dioxans were conveniently separated using a 2 foot Nester-Faust annular spinning band column with manual reflux ratio adjustment. Separation of compounds with boiling points as little as 2° apart was possible. Continuous monitoring of fractions by g.l.c. and n.m.r. assisted in obtaining pure samples.

7.4 Microcalorimetry

An L.K.B. batch microcalorimeter, of the type described in Chapter 4, was used for determination of the thermochemical data. A Phillips chart recorder equipped with a Disc integrator enabled measurement of the peak areas with a maximum error of ± 1%. In the case of the 2,5-dimethyl-1,3-dioxans, 0.15 molar solutions of the 1,3-dioxans in 1,4-dioxan, and a 0.12 molar solution of BF_3 in 1,4-dioxan, were used. As <u>trans</u>-2,4,4,6-tetramethyl-1,3-dioxan gave out more heat per mole than the 5-methyl-1,3-dioxans, only a 0.01 molar solution of this 1,3-dioxan, and a 0.02 molar solution of BF_3 were required.

For each determination ca. 1 ml of the 1,3-dioxan solution and a similar quantity of the BF_3 solution were used, and up to eight determinations were carried out for each compound. On completion of each experiment the cell was washed once with a 10% solution of pyridine in chloroform, twice with dry chloroform and finally twice with dry ether. Compressed air was then passed into the cell to ensure removal of all traces of solvents and reactants. All of the calorimetric measurements were carried out at 298K.

7.5 The Preparations of the 1,3-Dioxans

The 1,3-dioxans examined in this thesis were prepared directly or indirectly by the reactions of 1,3-diols with aldehydes or ketones in the presence of acid. The preparations of the precursors is first described, then the syntheses of the 1,3-dioxans themselves are presented.

Aldehydes and ketones

All were commercially available compounds. Liquid samples were distilled immediately prior to their use.

1,3-Diols

Propane-1,3-diol, 2,2-dimethyl-propane-1,3-diol, 2,2-diethyl-propane-1,3-diol, 2-methyl-pentane-2,4-diol, and a mixture of the isomeric 3-methyl-pentane-2,4-diols, were all commercially available. They were all redistilled prior to their use.

Pentane-2,4-diol

A 50:50 mixture of the d, ℓ and meso-forms was prepared by a Raney nickel reduction of acetylacetone as described by Pritchard and Vollmer[124].

2,3-Dimethyl-pentane-2,4-diol

This compound was synthesised according to the method of Pihlaja[121], by the Grignard reaction of methyl magnesium iodide and ethyl-2-methyl-3-hydroxy-butyrate.

2,4-Dimethyl-pentane-2,4-diol

The reaction of methyl magnesium iodide and *iso*-propenylacetate described by Zwahlen et al.[125] yielded this diol.

2-Methyl-propane-1,3-diol

A lithium aluminium hydride reduction of methyl diethyl malonate was carried out in the manner of Riddell and Robinson[40].

1-(4'-bromophenyl)-3-methyl-butane-1,3-diol

The preparation of one of the precursors of this diol, ethyl-3-(4'-bromophenyl)-3-hydroxypropionate, is first described.

Ethyl-3-(4'-bromophenyl)-3-hydroxy-propionate

A 500 ml. flask was equipped with a mechanical stirrer, condenser with a drying tube, and a dropping funnel. 0.12 mole of zinc dust, previously dried at 100°C in vacuo, was placed in the flask and 10 ml. of a mixture of 0.1 mole ethyl bromoacetate and 0.1 mole 4-bromobenzaldehyde in 50 ml. sodium dried benzene was added. The mixture was stirred and gently heated until the reaction commenced. The heating was then stopped and the rest of the mixture added at such a rate so as to maintain gentle reflux of the benzene. When addition was complete the solution was refluxed for one hour and then allowed to cool to room temperature. 40 ml. of 1 molar sulphuric acid solution was added slowly to the stirred mixture and the organic layer separated and shaken, first with 5% sulphuric acid solution, then 20% sodium carbonate solution, and finally with water. The solution was dried over anhydrous sodium sulphate. The crude product was obtained after filtration and removal of the solvent. No attempt was made to purify this compound as β-hydroxy esters tend to dehydrate on distillation. However the product was left in ether solution over anhydrous sodium sulphate for 2 days to ensure complete removal of residual water. Yield (of crude material) = 50%.

1-(4'-bromophenyl)-3-methyl-butane-1,3-diol

0.05 mole of the crude ethyl-3-(4'-bromophenyl)-3-hydroxy-propionate in 50 ml. of anhydrous ether, was slowly added to 0.12 mole of previously prepared methyl magnesium iodide in 50 ml. of anhydrous ether. After addition was complete the mixture was refluxed for 2 hours, cooled, and then poured onto an ice cold 20% ammonium chloride solution.

The ether layer was separated off and the aqueous layer extracted twice with ether. The combined ether extracts and the original ether layer were dried over anhydrous sodium sulphate, filtered and the solvent distilled off. The diol was recrystallised from petroleum spirit (boiling point 80-100°C). Yield = 80%, m.p. = 102-103°. Microanalysis, found C, 50.91, H, 5.89; $C_{11}H_{15}BrO_2$ requires C, 50.97; H, 5.79%.
Physical data on the 1,3-diols is shown in Table 7.1.

Preparations of the 1,3-Dioxans

Three general methods were employed.

Method A.

A 1:1 molar mixture of the carbonyl compound and the 1,3-diol in benzene was refluxed in the presence of acid in a Dean and Stark apparatus, as described by Rondestvedt[126].

Method B.

The aldehyde and diol were refluxed in methylene chloride with paratoluene sulphonic acid and anhydrous copper sulphate, in the manner of Riddell and Robinson[40].

Method C.

A 1:1 molar mixture of 2,2-dimethoxypropane and the 1,3-diol was heated in the presence of para toluene sulphonic acid. The methanol formed was slowly removed by distillation from a Vigreux column. When ca. 80% of the theoretical amount of methanol was collected, the heating was stopped and the acid neutralised by the addition of sodium carbonate. The 1,3-dioxans formed by this method were then purified by filtration and distillation or recrystallisation. Yield = 70 - 80%.

2,2-bis(trideuteriomethyl)-4,4,6-trimethyl-1,3-dioxan

This compound was prepared by method C starting from the dimethyl ketal of hexadeuterioacetone.

Trans-2,4,4,6-tetramethyl-1,3-dioxan

The method of Eliel and Nader[127] was employed to synthesise this 1,3-dioxan.

2,2-diphenyl-4,4,6-trimethyl-1,3-dioxan

An equimolar mixture of the dimethyl ketal of benzophenone and 2-methyl-pentane-2,4-diol was heated in cyclohexane in the presence of a catalytic amount of paratoluene sulphonic acid. The methanol formed in the reaction was distilled off as an azeotrope with cyclohexane. When the boiling point of this azeotrope reached 80° the heating was stopped and the reaction mixture cooled to room temperature. Anhydrous sodium carbonate was added and the mixture was stirred for one hour. The crude 1,3-dioxan, obtained by filtration and distillation, was purified by sublimation. Yield = 80%.

r-2-4,4-c-6-tetramethyl-2-(4'-bromophenyl)-1,3-dioxan

The diethyl ketal of 4-bromoacetophenone and freshly distilled 2-methyl-pentane-2,4-diol were mixed in a 1:1 molar ratio and warmed for one minute. A crystal of paratoluene sulphonic acid was added and the mixture left, in a sealed flask, at room temperature for three days. The precipitated product was filtered off and dissolved in dry ether to which a small quantity of anhydrous sodium carbonate was added to neutralise any excess acid. After filtration and removal of the solvent, the product was recrystallised five times from methanol. Yield = 80%.

r-2-4,4-c-6-tetramethyl-2-phenyl-1,3-dioxan

A similar procedure to the above was used to prepare this 1,3-dioxan. Yield = 80%.

All of the compounds prepared in this work were characterised by i.r. and n.m.r. spectroscopy and, in certain cases, by mass spectrometry and microanalysis. Physical data on the 1,3-dioxans is shown in Tables 7.2 and 7.3.

TABLE 7.1

Physical Properties of the 1,3-Diols

1,3-Diol	B.p.[A](M.p.)[B]	Lit.Value	Reference
Propane-1,3-diol	210	214	128
2-Methyl-propane-1,3-diol	115/10 mm	118-120/14 mm	129
2,2-Dimethyl-propane-1,3-diol	97/10 mm	206	128
2,2-Diethyl-propane-1,3-diol	120/10 mm	240	128
Butane-1,3-diol	202	204	128
1-(4'-bromophenyl)-3-methyl-butane-1,3-diol	(102)	-	-
Pentane-2,4-diol	196	194-197	124
2-Methyl-pentane-2,4-diol	110/12 mm	190-194	128
3-Methyl-pentane-2,4-diol	220	221-222	128
2,3-Dimethyl-pentane-2,4-diol	100/6 mm	108-112/7 mm	121
2,4-Dimethyl-pentane-2,4-diol	95/10 mm	100/17 mm	125

A. In °C at 760 mm unless otherwise noted.

B. In °C.

TABLE 7.2

Physical Data on the 1,3-Dioxans

Substituents	B.p.[A](M.p.)[B]	Lit.Value	Reference
-	105	102-106	121
4-Me	114	113-115	121
5-Me	118	119-121	121
5,5-diMe	127	127	126
5,5-diEt	183	76/20 mm	130
4,4,6-triMe	143	143	121
r-4-*c*-5-*t*-6-triMe	157	157	121
r-4-*c*-5,6-triMe[C]	148	148	121
r-4-*t*-5-*c*-6-triMe[C]	148	148	121
4,4,6,6-tetra Me	154	154-155	121
2-Me	110	109-110	126
cis-2,4-diMe	119	118-120	121
cis-2,5-diMe	121	-	-
trans-2,5-diMe	127	-	-
r-2-*c*-4,6-triMe	129	129	121
r-2-*c*-4-*t*-6-triMe	138	139	121
2,5,5-triMe	132	130-131	126
2-Me-5,5-diEt	187	70/5 mm	131
cis-2,4,4,6-tetra Me	139	140	121
trans-2,4,4,6-tetra Me	82/95 mm	51/30 mm	127
r-2-*c*-4-*t*-5,6-tetra Me	159	160	121
r-2-*c*-4,5,6-tetra Me[C]	149	149	121
r-2-*c*-4,6-*t*-5-tetra Me[C]	149	149	121
2,4,4,6,6-penta Me	150	151	121
2,2-diMe	125	124-125	38
2,2,4-triMe	132	133	121
2,2,5-triMe	137	-	-
2,2,5,5-tetra Me	145	144-145	126
2,2-diMe-5,5-diEt	199	198	131

TABLE 7.2 (continued)

Substituents	B.p.[A](M.p.)[B]	Lit.Value	Reference
2,2-*cis*-4,6-tetra Me	138	138	121
2,2-*trans*-4,6-tetra Me	132	132-133	121
2,2,4,4,6-penta Me	147	-	-
2,2-r-4-*c*-5-*t*-6-penta Me	152	152	121
2,2,4,4-*cis*-5,6-hexa Me[C]	48/5 mm	-	-
2,2,4,4-*trans*-5,6-hexa Me[C]	48/5 mm	-	-
2,2,4,4,6,6-hexa Me	62/42 mm	-	-
2-Ph	(45)	(46-47)	103
2-Ph-*cis*-4-Me	102/8 mm	135-136/14 mm	129
2-Ph-*cis*-5-Me[C]	119/10 mm	134-136/14 mm	129
2-Ph-*trans*-5-Me[C]	119/10 mm	134-136/14 mm	129
2-Ph-5,5-diMe	(37)	(35)	129
2,2-diPh	(97-98)	(98-99)	103
2,2-diPh-4-Me	(72)	(72-73)	133
2,2-diPh-5-Me	(67-68)	-	-
2,2-diPh-5,5-diMe	(81)	(81-82)	132
2,2-diPh-4,4,6-triMe	(68-69)	-	-
2-Me-2-Ph	(43)	(43-44)	103
2-Me-2-(4'-nitroPh)	(72)	-	-
r-2-*c*-4-diMe-2-Ph	(49)	-	-
r-2-*t*-5-diMe-2-Ph	(73)	-	-
r-2-*c*-4,6-triMe-2-Ph	(43-44)	-	-
2,5,5-triMe-2-Ph	240-241	-	-
r-2-4,4-*c*-6-tetraMe-2-Ph	(50-51)	-	-
r-2-4,4-*c*-6-tetraMe-2-(4'-bromo Ph)	(80)	-	-
2,2,4,4-tetraMe-6-(4'-bromo Ph)	(68-69)	-	-

A. In °C at 760mm unless otherwise noted.

B. In °C.

C. Not separated from its stereoisomer.

TABLE 7.3

Microanalytical Data for some 1,3-Dioxans

1,3-Dioxan	Found		Required	
	% C	% H	% C	% H
2,2,4,4,6-penta Me	68.49	11.50	68.36	11.39
2,2,4,4-tetraMe-6-(4'-bromo Ph)[A]	56.27	6.50	56.19	6.35
r-2-4,4-*c*-6-tetraMe-2-(4'-bromo Ph)	56.35	6.47	56.19	6.35
r-2,4,4-*c*-6-tetraMe-2-Ph	76.52	9.13	76.36	9.09
2-Me-2-(4'-nitro Ph)[B]	59.34	5.70	59.19	5.83
2,2-diPh-5-Me	80.55	7.02	80.31	7.09
2,2-diPh-4,4,6-triMe	80.48	7.80	80.82	7.85
r-2-*t*-5-diMe-2-Ph	74.74	8.21	75.00	8.33
r-2-*c*-4,6-triMe-2-Ph	75.48	8.81	75.73	8.74

A. Found Br, 26.38; Required Br, 26.78%.

B. Found N, 6.19; Required N, 6.28%.

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APPENDIX A

STRUCTURE FACTORS FOR r-2-4,4-*c*-6-TETRAMETHYL-2-(4'-BROMOPHENYL)-1,3-DIOXAN

Values given are h, k, l, $F_{obs.}$ and $F_{calc.}$

Appendix A

H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
0	0	4	227.5	210.7	1	3	8	28.0	25.0
0	0	6	145.2	-128.8	1	3	9	43.1	46.6
0	0	8	37.5	5.9	1	3	10	27.4	-36.2
0	0	10	39.7	-36.1	1	4	2	43.2	-47.3
0	2	0	70.7	91.6	1	4	3	36.2	37.8
0	2	1	61.3	31.2	1	4	6	32.7	-18.0
0	2	2	308.8	-290.7	1	5	2	24.8	-23.7
0	2	3	107.4	97.8	1	5	4	50.9	40.4
0	2	4	140.9	124.4	1	5	6	39.0	-39.6
0	2	5	90.7	-85.9	1	7	4	34.9	34.9
0	2	6	87.9	-90.5	1	7	6	31.1	-28.6
0	2	7	53.2	52.5	2	0	4	215.4	198.2
0	4	0	92.3	83.9	2	0	6	75.3	-80.2
0	4	1	124.4	-129.4	2	0	8	60.8	73.8
0	4	2	50.3	-37.6	2	1	1	17.7	31.8
0	4	3	48.8	42.2	2	1	3	44.8	-32.2
0	4	4	38.3	35.8	2	1	4	12.7	5.0
0	4	5	123.6	-110.8	2	1	5	14.1	11.2
0	4	6	76.2	-78.1	2	1	6	25.8	-23.7
0	4	7	39.9	39.8	2	2	0	162.0	159.7
0	6	1	82.3	-85.3	2	2	1	91.1	-88.3
0	6	3	80.9	81.5	2	2	2	222.4	-212.0
0	6	4	33.4	30.5	2	2	3	150.0	139.2
0	6	5	79.1	-80.2	2	2	4	127.0	119.4
0	8	1	52.0	-56.8	2	2	6	89.0	-94.0
0	8	3	45.9	50.3	2	2	7	43.8	46.0
1	0	4	60.0	-35.8	2	2	8	37.0	41.5
1	0	6	48.4	38.3	2	3	2	17.5	9.3
1	0	8	25.5	28.3	2	3	3	62.3	52.6
1	1	2	63.9	69.9	2	3	5	67.8	68.5
1	1	3	172.0	-159.7	2	3	7	22.9	7.8
1	1	4	16.4	17.5	2	3	8	36.0	19.2
1	1	7	58.3	-74.3	2	4	0	56.3	65.1
1	1	8	24.0	21.7	2	4	1	115.6	-120.7
1	2	1	27.5	-23.5	2	4	2	75.4	-81.7
1	2	2	26.0	11.0	2	4	3	115.9	111.5
1	2	3	78.2	65.1	2	4	4	78.2	80.4
1	2	4	28.9	-21.6	2	4	5	68.3	-69.7
1	2	5	38.9	-37.7	2	4	6	22.1	-17.5
1	2	6	39.9	-35.4	2	4	7	34.9	46.8
1	3	2	21.9	-17.8	2	4	8	36.0	44.6
1	3	4	28.5	27.1	2	5	0	17.7	-27.3
1	3	5	84.9	76.0	2	5	2	28.3	-29.9
1	3	6	33.9	-31.8	2	5	3	18.0	14.6
1	3	7	24.0	-29.7	2	5	4	20.5	-5.9

Appendix A

H	K	L	FOBS	FCALC
2	6	1	91.5	-94.9
2	6	3	65.9	62.2
2	6	5	60.0	-59.6
2	6	6	24.2	-31.2
2	7	0	27.1	32.4
2	7	3	30.7	28.7
2	7	5	35.9	35.0
2	8	1	41.2	-35.3
2	8	3	37.8	54.2
2	10	0	24.6	-27.9
3	0	2	35.1	41.5
3	0	6	35.9	22.9
3	0	8	30.2	30.8
3	1	2	13.4	8.6
3	1	3	37.0	-26.9
3	1	4	55.4	45.9
3	1	5	80.2	75.1
3	1	6	15.5	-14.9
3	1	7	83.7	-87.3
3	2	1	80.1	-88.4
3	2	2	65.3	-57.5
3	2	3	14.8	-14.2
3	2	4	62.6	-49.9
3	2	6	50.5	-39.4
3	3	3	98.3	-85.6
3	3	4	23.6	-17.8
3	3	5	26.9	27.4
3	3	6	82.7	-82.4
3	3	7	52.6	-56.1
3	3	8	51.7	60.7
3	3	11	32.6	-34.8
3	4	1	40.8	10.8
3	4	4	26.6	-2.7
3	4	5	38.7	15.4
3	4	7	27.0	23.4
3	5	2	26.5	-24.0
3	5	3	18.2	22.0
3	5	4	21.6	26.6
3	5	6	51.0	-46.1
3	7	4	26.4	24.8
3	7	6	26.9	-27.9
4	0	2	416.8	-391.6
4	0	4	159.5	136.9
4	0	6	106.9	-112.1
4	0	8	56.2	61.5
4	1	0	38.5	-54.5
4	1	1	117.4	113.9
4	1	2	25.6	11.5
4	1	3	13.7	17.9
4	1	4	10.8	-12.2
4	1	6	28.4	-33.0
4	2	0	254.8	283.5
4	2	1	105.7	-107.6
4	2	2	165.0	-149.7
4	2	3	80.3	76.7
4	2	4	116.1	115.9
4	2	5	51.3	-49.9
4	2	6	64.9	-70.0
4	2	7	31.5	35.4
4	2	8	42.0	51.4
4	3	2	89.9	84.0
4	3	3	19.7	-16.7
4	3	4	70.5	71.1
4	3	5	17.7	-5.5
4	4	0	19.9	23.6
4	4	1	102.7	-98.7
4	4	2	101.1	-92.8
4	4	3	99.5	99.7
4	4	4	99.5	91.2
4	4	5	96.7	-96.3
4	4	8	50.2	45.3
4	5	1	34.0	-37.8
4	5	6	46.5	-42.9
4	6	1	85.9	-95.9
4	6	3	65.7	64.6
4	6	5	39.0	-34.5
4	8	1	29.1	-30.0
4	8	3	40.1	45.4
5	0	2	98.4	81.7
5	0	4	60.6	51.0
5	0	6	44.3	46.1
5	1	1	12.8	-14.1
5	1	2	117.7	-105.3
5	1	4	16.7	14.7
5	1	5	81.5	77.1
5	1	6	36.7	-31.1
5	1	7	52.8	-61.0
5	1	9	39.7	44.7
5	2	1	67.1	-67.5
5	2	2	23.1	25.6

Appendix A

H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
5	2	5	21.3	-18.1	6	3	0	30.3	-13.1
5	2	6	18.4	20.9	6	3	2	37.2	-32.6
5	2	12	24.8	-28.5	6	3	3	76.5	-72.7
5	3	2	28.7	24.1	6	3	4	26.7	28.2
5	3	3	79.9	-71.7	6	3	5	46.3	-41.6
5	3	4	145.7	139.9	6	3	6	21.1	-14.3
5	3	5	46.5	46.6	6	3	8	33.6	20.7
5	3	6	24.3	-26.0	6	4	0	92.3	106.0
5	3	7	45.9	-45.6	6	4	1	127.7	-131.1
5	3	8	40.3	41.1	6	4	2	101.0	-95.0
5	3	9	32.0	40.2	6	4	3	91.7	90.4
5	3	10	38.7	-53.5	6	4	4	33.3	32.5
5	4	2	33.3	-19.1	6	4	5	83.0	-82.3
5	4	3	42.2	26.6	6	4	6	59.0	-63.7
5	4	5	40.4	-29.8	6	4	7	34.6	36.2
5	4	6	35.6	-7.8	6	5	0	17.1	17.1
5	5	1	25.0	27.3	6	5	5	20.8	27.0
5	5	2	49.1	-51.7	6	6	1	61.7	-61.1
5	5	4	22.9	6.3	6	6	3	79.2	75.3
5	5	5	29.2	24.6	6	6	4	23.9	25.4
5	5	6	45.8	-45.0	6	6	5	47.0	-46.6
5	6	1	17.1	19.9	6	8	1	31.9	-38.1
5	6	4	32.3	38.9	6	8	3	29.2	19.3
5	7	1	23.3	33.5	6	8	5	32.1	-29.2
5	7	4	24.7	32.3	7	0	2	53.0	53.6
6	0	0	233.4	271.9	7	0	4	77.0	73.2
6	0	2	114.3	-122.0	7	0	6	31.2	-35.0
6	0	4	110.8	106.9	7	1	2	37.9	20.8
6	0	6	128.7	-134.2	7	1	3	94.0	-93.8
6	0	8	46.1	57.9	7	1	4	28.5	18.4
6	0	10	27.7	-30.9	7	1	5	47.1	50.5
6	1	0	41.2	-49.9	7	1	6	19.3	-19.8
6	1	1	32.6	-25.9	7	1	7	69.5	-78.1
6	1	2	88.1	-87.1	7	1	9	40.0	46.6
6	1	3	52.6	-49.7	7	2	2	37.4	38.5
6	1	5	24.8	-22.1	7	2	3	19.6	25.2
6	1	6	22.2	26.2	7	2	4	31.6	23.6
6	2	0	166.0	196.3	7	2	5	50.1	55.9
6	2	1	136.0	-135.4	7	3	2	59.8	-58.7
6	2	2	121.4	-114.1	7	3	4	38.3	34.0
6	2	3	87.4	90.8	7	3	5	75.1	70.0
6	2	4	144.9	140.8	7	3	6	41.0	-37.0
6	2	5	75.7	-77.1	7	3	8	31.6	33.4
6	2	6	60.7	-63.5	7	3	9	40.8	62.8
6	2	8	41.6	53.5	7	4	0	25.3	-0.0

Appendix A

H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
7	4	1	23.4	21.9	8	6	0	44.7	55.2
7	4	2	26.1	-24.6	8	6	1	66.0	-66.7
7	4	3	46.7	31.4	8	6	3	61.6	61.1
7	4	4	23.4	-22.8	8	6	5	58.3	-61.9
7	4	6	30.8	11.8	8	7	3	21.7	23.0
7	4	7	41.3	-50.7	8	8	1	33.6	-36.8
7	5	1	18.0	-17.5	8	8	5	32.7	-22.4
7	5	2	22.9	-24.4	9	0	2	59.5	-60.7
7	5	3	37.4	-39.3	9	0	4	58.1	-68.0
7	5	4	27.7	24.6	9	0	6	56.8	-60.6
7	5	5	21.0	21.5	9	1	1	27.1	22.3
7	5	6	49.9	-53.4	9	1	2	51.9	44.5
7	6	1	19.2	-20.1	9	1	3	30.4	-37.6
8	0	0	144.2	164.4	9	1	4	79.2	72.4
8	0	2	227.9	-221.6	9	1	5	65.6	60.1
8	0	4	155.1	156.6	9	1	7	48.1	-54.1
8	0	6	68.8	-77.5	9	1	9	51.3	61.3
8	0	8	51.8	45.1	9	2	1	23.8	-20.9
8	1	0	16.5	-21.4	9	2	2	79.5	-70.4
8	1	1	47.1	51.1	9	2	4	36.7	-26.4
8	1	2	14.9	-8.7	9	2	6	28.5	-11.4
8	1	3	42.5	34.2	9	3	2	69.6	-72.0
8	1	4	16.8	24.3	9	3	3	40.8	-25.7
8	1	5	55.6	53.0	9	3	4	23.7	13.7
8	1	6	14.5	-14.7	9	3	5	38.1	37.9
8	2	0	132.7	144.1	9	3	6	51.8	-47.4
8	2	1	79.1	-87.6	9	3	7	40.2	-46.3
8	2	2	112.6	-110.0	9	3	8	26.1	36.1
8	2	3	58.4	50.4	9	4	1	18.8	-14.3
8	2	4	164.4	160.6	9	4	2	18.0	6.2
8	2	5	42.8	-46.5	9	4	3	18.3	-22.4
8	2	6	87.3	-82.2	9	5	3	27.1	-34.2
8	3	2	49.0	-44.5	9	5	4	56.4	61.1
8	3	6	37.3	-35.2	9	5	6	38.3	-37.3
8	4	0	87.2	96.2	9	6	3	19.6	21.0
8	4	1	111.9	-114.0	10	0	0	133.5	149.6
8	4	2	64.7	-61.6	10	0	2	176.6	-185.2
8	4	3	105.4	103.7	10	0	4	114.3	110.7
8	4	4	33.7	19.1	10	0	6	122.2	-122.2
8	4	6	53.9	-52.3	10	0	8	20.7	22.8
8	4	7	43.3	50.5	10	1	1	31.4	32.6
8	5	0	40.5	48.7	10	1	3	50.0	42.3
8	5	2	21.4	26.2	10	1	4	58.5	45.6
8	5	4	25.4	32.1	10	1	5	43.6	41.1
8	5	6	20.9	-20.0	10	1	7	22.0	-13.1

Appendix A

H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
10	1	8	29.2	33.6	11	3	4	52.1	44.4
10	1	9	24.0	30.4	11	3	7	61.4	-59.4
10	2	0	113.4	130.6	11	5	2	27.8	-27.9
10	2	1	79.1	-89.2	11	5	4	45.0	46.4
10	2	2	135.4	-135.4	12	0	0	97.1	107.5
10	2	3	18.5	19.8	12	0	2	144.2	-151.1
10	2	4	96.2	96.5	12	0	4	141.1	152.6
10	2	5	46.9	-54.6	12	0	6	53.9	-52.0
10	2	6	59.1	-52.5	12	0	8	50.4	52.8
10	2	8	45.8	53.4	12	1	3	93.7	-90.8
10	3	0	20.1	28.9	12	1	6	28.0	29.8
10	3	2	34.7	-33.0	12	1	8	33.5	41.2
10	3	3	15.4	-12.9	12	2	0	101.4	110.1
10	3	4	32.8	36.0	12	2	1	54.7	-59.3
10	3	7	22.8	-23.7	12	2	2	136.3	-136.3
10	4	0	54.0	58.8	12	2	3	64.2	56.0
10	4	1	92.7	-92.0	12	2	4	76.1	62.1
10	4	2	50.4	-45.9	12	2	6	49.0	-53.4
10	4	3	71.7	71.7	12	2	8	31.2	41.8
10	4	4	47.0	51.3	12	3	3	29.3	-24.2
10	4	5	55.5	-52.6	12	3	6	24.9	-15.8
10	4	6	20.1	-25.1	12	4	0	47.2	54.3
10	4	9	27.9	-14.8	12	4	1	62.4	-61.2
10	5	0	24.0	25.6	12	4	2	55.1	-43.0
10	5	6	30.3	-36.9	12	4	3	70.0	73.7
10	6	1	68.0	-73.5	12	4	4	48.8	39.6
10	6	2	22.0	-34.3	12	4	5	53.4	-59.1
10	6	3	60.8	57.1	12	6	1	63.0	-63.0
10	6	5	47.9	-41.4	12	6	2	27.0	-18.3
10	8	1	26.2	-27.2	12	6	3	55.6	56.9
10	8	3	35.5	26.4	13	0	2	40.3	8.1
11	0	2	38.7	7.2	13	0	4	41.9	46.9
11	0	4	26.3	26.5	13	1	2	64.0	-63.1
11	1	2	80.5	-81.9	13	1	3	40.4	-39.0
11	1	3	20.0	-23.4	13	1	5	29.6	32.3
11	1	4	39.2	-38.6	13	1	6	31.2	-36.3
11	1	5	107.1	100.8	13	1	7	55.2	-48.7
11	1	7	80.3	-79.8	13	1	9	31.9	41.9
11	1	9	47.5	54.6	13	2	7	30.0	36.2
11	1	11	29.6	-28.7	13	3	1	34.6	36.0
11	2	4	46.5	35.4	13	3	2	24.6	-24.9
11	2	5	39.6	-30.8	13	3	3	25.5	-24.8
11	2	7	30.6	-34.9	13	3	5	33.6	26.8
11	3	1	42.4	52.8	13	3	6	51.3	-51.7
11	3	3	33.2	-21.8	13	5	4	30.9	34.6

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H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
13	5	5	33.7	31.3	15	3	5	30.3	28.5
13	5	6	29.2	-21.4	15	3	6	34.0	-20.6
13	6	4	35.7	17.8	15	3	7	33.2	-23.9
14	0	0	106.9	110.4	15	3	9	35.1	37.1
14	0	2	89.0	-97.6	15	5	4	37.6	37.8
14	0	4	131.8	133.1	15	6	1	22.2	-17.4
14	0	6	26.1	-23.6	16	0	0	131.0	149.8
14	0	8	36.0	45.1	16	0	2	52.0	-63.9
14	1	0	41.7	35.8	16	0	4	44.6	41.4
14	1	4	22.7	-15.5	16	0	6	55.9	-50.1
14	1	5	38.2	34.7	16	0	10	31.8	-25.6
14	1	6	30.8	-25.1	16	1	1	21.4	26.2
14	1	7	33.7	-35.4	16	1	3	22.9	-26.1
14	1	8	32.3	-28.8	16	1	5	33.7	30.0
14	1	10	30.8	-44.1	16	2	0	60.0	68.9
14	2	0	100.8	117.2	16	2	1	51.0	-49.5
14	2	1	59.6	-68.2	16	2	2	84.5	-80.7
14	2	2	69.8	-66.3	16	2	3	35.0	33.5
14	2	3	30.1	27.9	16	2	4	52.3	53.6
14	2	4	67.0	62.9	16	2	5	55.4	-59.6
14	2	6	87.4	-97.3	16	2	6	41.4	-43.5
14	2	10	31.8	-24.1	16	3	0	26.7	22.6
14	3	2	21.1	-26.3	16	3	4	24.0	18.0
14	3	6	27.2	-32.4	16	3	5	27.0	24.7
14	4	0	57.8	61.3	16	4	0	68.8	72.9
14	4	1	75.3	-76.0	16	4	1	58.4	-58.1
14	4	2	42.5	-39.7	16	4	2	30.3	-24.5
14	4	3	59.9	61.4	16	4	3	52.4	52.0
14	4	4	44.3	37.1	16	4	4	41.2	38.5
14	5	0	33.6	37.3	16	4	5	32.4	-31.0
14	5	4	25.7	25.9	16	5	2	26.7	-34.9
14	6	1	49.6	-47.8	16	6	1	34.5	-26.3
14	6	3	32.3	40.0	16	6	3	38.3	39.8
14	6	5	36.8	-31.0	16	6	5	45.1	-35.2
15	0	2	41.5	-40.8	17	0	4	22.1	-3.5
15	1	1	20.3	-22.7	17	0	6	27.2	-36.4
15	1	3	52.5	-54.0	17	1	1	22.9	20.4
15	1	4	27.5	20.5	17	1	3	22.6	-11.8
15	1	5	68.3	59.6	17	1	4	24.1	17.8
15	1	7	27.8	-18.8	17	1	5	28.7	23.5
15	1	9	51.6	48.9	17	1	7	34.7	-38.8
15	2	2	27.0	-36.3	17	2	4	22.5	27.1
15	2	7	34.6	36.6	17	2	7	36.5	-41.6
15	3	3	28.6	-19.0	17	3	1	21.6	17.7
15	3	4	29.3	29.6	17	3	2	26.5	-30.8

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H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
17	3	6	34.3	-34.8	20	2	4	42.8	39.4
17	3	7	43.8	-38.9	20	2	6	36.1	-27.2
18	0	0	62.1	55.7	20	3	4	28.8	29.6
18	0	2	102.3	-97.4	20	4	1	27.5	-28.9
18	0	4	62.9	60.2	20	4	2	32.7	-30.6
18	0	6	26.3	-30.1	20	4	3	23.5	26.6
18	1	3	25.1	-23.8	20	4	5	33.1	-33.3
18	1	5	27.2	22.9	20	6	1	34.8	-36.2
18	2	0	41.8	41.5	21	0	2	31.5	-14.6
18	2	1	25.6	-25.3	21	0	4	29.4	26.5
18	2	2	84.4	-84.7	21	1	3	22.9	-19.1
18	2	3	29.8	35.4	21	1	5	42.9	41.5
18	2	4	56.1	50.3	21	2	1	34.3	40.3
18	2	5	25.8	-17.0	21	3	3	32.2	-22.6
18	2	8	38.4	39.6	21	3	4	26.5	27.1
18	3	0	61.4	68.9	22	0	0	70.2	81.1
18	3	5	27.7	29.1	22	0	2	70.8	-72.0
18	4	0	24.9	29.3	22	0	6	29.8	-29.2
18	4	1	36.9	-31.2	22	1	3	24.2	-18.7
18	4	2	37.9	-25.9	22	2	0	54.5	60.5
18	4	3	50.0	50.8	22	2	2	34.0	-28.9
18	4	6	34.6	-37.7	22	2	4	39.9	34.8
18	4	7	34.2	24.6	22	2	6	29.6	-22.8
18	5	2	47.0	-41.7	22	2	7	30.0	10.4
18	6	1	31.6	-35.4	22	4	1	28.9	-20.0
18	6	3	36.4	37.9	22	4	3	25.8	21.3
19	0	2	33.4	-20.1	22	4	4	33.1	15.6
19	0	8	27.4	24.4	22	4	5	28.8	-21.1
19	1	1	31.8	31.6	23	0	2	29.8	5.6
19	1	3	38.0	-40.1	23	0	4	28.7	-32.0
19	1	5	31.0	28.5	23	0	6	29.4	-17.9
19	1	7	41.0	-38.2	24	0	0	52.4	47.6
19	2	2	27.0	2.0	24	0	4	30.6	32.1
19	3	3	24.5	-17.0	24	1	1	25.3	27.3
19	3	6	29.6	-32.4	24	2	1	24.9	-15.1
19	4	4	27.3	25.7	24	2	2	45.7	-35.6
19	7	6	38.1	-17.7	24	2	3	27.4	29.8
20	0	0	48.6	43.9	24	2	4	29.7	31.7
20	0	2	78.1	-75.6	24	3	6	30.4	-21.2
20	0	4	51.2	42.6	24	4	1	30.8	-34.1
20	0	6	35.4	-38.4	24	4	2	32.6	-32.0
20	1	3	26.2	-23.5	25	4	2	35.4	4.8
20	2	0	90.8	90.9	26	0	0	43.6	42.4
20	2	1	34.3	-33.6	26	0	2	26.4	-13.0
20	2	2	25.1	-28.0	26	0	4	27.7	27.6

Appendix A

H	K	L	FOBS	FCALC	H	K	L	FOBS	FCALC
26	0	6	32.2	-19.0	26	2	0	29.7	18.1
26	1	4	29.0	11.2	26	2	2	37.9	-30.2