Stereoelectronic Effects in Homolytic Reactions

A Thesis

Presented for the Degree of

Doctor of Philosophy

in

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by

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"Oft expectation fails, and most oft there
where most it promises; and oft it hits
where hope is coldest and despair most fits."

Source: "All's Well That Ends Well,"
by William Shakespeare
(1602-3).

CONTENTS

SUMMARY

An investigation of stereoelectronic effects in homolytic reactions is described and discussed in this thesis.

The work described in Chapter II involved a study of the thermolysis of several peroxides; the yields of the products obtained are discussed in relation to reactions of substituted cyclohexyl radical intermediates. This work clearly demonstrates that C — H bond homolysis adjacent to a semioccupied p orbital is stereoelectronically controlled.

An EPR technique involving measurement of stationary radical concentrations and a GLC technique involving measurement of rates of consumption of substrates have been used to determine the relative rates of hydrogen atom abstraction from a series of substituted 1,3-dioxanes. The GLC technique has also been used to determine the relative rates of chlorine atom abstraction from some substituted 1,4-dioxanes. This work, which is described in Chapter III, shows that homolysis of C — H and C — Cl bonds adjacent to a filled non-bonding orbital is also stereoelectronically controlled.

A product study of the copper-catalysed reactions of a series of substituted methylenecyclohexanes with tert-butyl perbenzoate, and a kinetic study of these reactions and of reactions of the methylenecyclohexanes with di-tert-butyl peroxide, are presented and discussed in Chapter IV. These studies demonstrate that C — H bond homolysis adjacent to a filled π orbital is also stereoelectronically controlled.

STATEMENT

This thesis contains no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

C. J. Easton

ACKNOWLEDGEMENTS

I would sincerely like to thank my supervisor, Professor A.L.J. Beckwith, for his guidance, encouragement and enthusiasm during the course of this work. I also wish to thank Dr G.E. Gream for his supervision during 1979, and for his assistance at other times.

I am also indebted to Drs K.U. Ingold and A.K. Serelis, and to the many members of the Organic Chemistry Department who have helped me during my course of study.

Finally, I would like to thank my parents and my wife for their understanding and support.

PUBLICATION

Part of the work described in this thesis has been reported in the publication:

"A Stereoelectronic Effect in Hydrogen Atom Abstraction from a Substituted Cyclohexyl Radical," A.L.J. Beckwith and C. Easton, J. Am. Chem. Soc., 100, 2913 (1978).

CHAPTER I

INTRODUCTION

The stereoelectronic factor in chemical reactions, first proposed by Corey and Sneen,[1] is that which acts because of conformational restrictions placed on the geometry of the transition state by the requirement of maximum electron delocalization in the transition state. If the stereoelectronic factor governs the course of reaction then the reaction is said to be stereoelectronically controlled, and results of reactions which can be attributed to the stereoelectronic factor are called stereoelectronic effects. These have been observed in reactions of many organic molecules.[2,3]

The proposed transition state for addition of radicals to olefins is one formed by initial coplanar interaction of the semioccupied p orbital with the π^* antibonding orbital[4-8] because this allows maximum delocalization of the three electrons involved in the redistribution process.[4] These reactions might therefore be expected to be influenced by the stereoelectronic factor. The transition state proposed for the reverse process, bond homolysis adjacent to a radical centre, is one formed by initial coplanar interaction of the semioccupied p orbital with the σ^* antibonding orbital of the bond undergoing fission.[4,8,9] Therefore these reactions might also be influenced by the stereoelectronic factor.

Intramolecular addition reactions of alkenyl radicals have been rationalized using this model of the transition state.[4,6-9] These reactions indicate that ring closure affording the least substituted radical is kinetically favoured over the alternative cyclization.[4,6-9] This can be attributed to the stereoelectronic factor because the proposed transition state[4-8] is readily accommodated in pathways leading to exocyclic radicals, but not in those leading to endocyclic radicals.[4,6-9] The strain energy associated with the transition state leading to endocyclic radicals outweighs the normal thermodynamic preference. Thus hex-5-enyl and some related radicals undergo regioselective intramolecular addition to give predominantly the thermodynamically less stable product.[7,10-13] Cycliza-

tion of hept-6-enyl and related radicals proceeds predominantly by 1,6-intramolecular addition,[13,14] but relatively more 1,7-addition occurs in this system as compared to 1,6-addition in the hex-5-enyl system[13] because the strain energy associated with the transition state leading to endocyclic products is lower in this system.[8] The proposed transition state[4-8] also accords satisfactorily with the kinetic data for radical cyclizations in the hex-5-enyl system.[6,8,13,15,16]

Addition of thiyl radicals to cyclohexenes is also subject to stereoelectronic control.[17-21] The preferred axial radical incorporation observed in thiyl radical addition to conformationally rigid cyclohexenes[17-22] can be rationalized by considering the stereoelectronic factor.[17-21] Considering the example of methanethiyl radical addition to 4-tert-butylcyclohexene (1),[20] energetically favourable perpendicular attack can occur at either end of the double bond and from either above or below the double bond (Fig.I.1). The requirement of maximum delocalization of

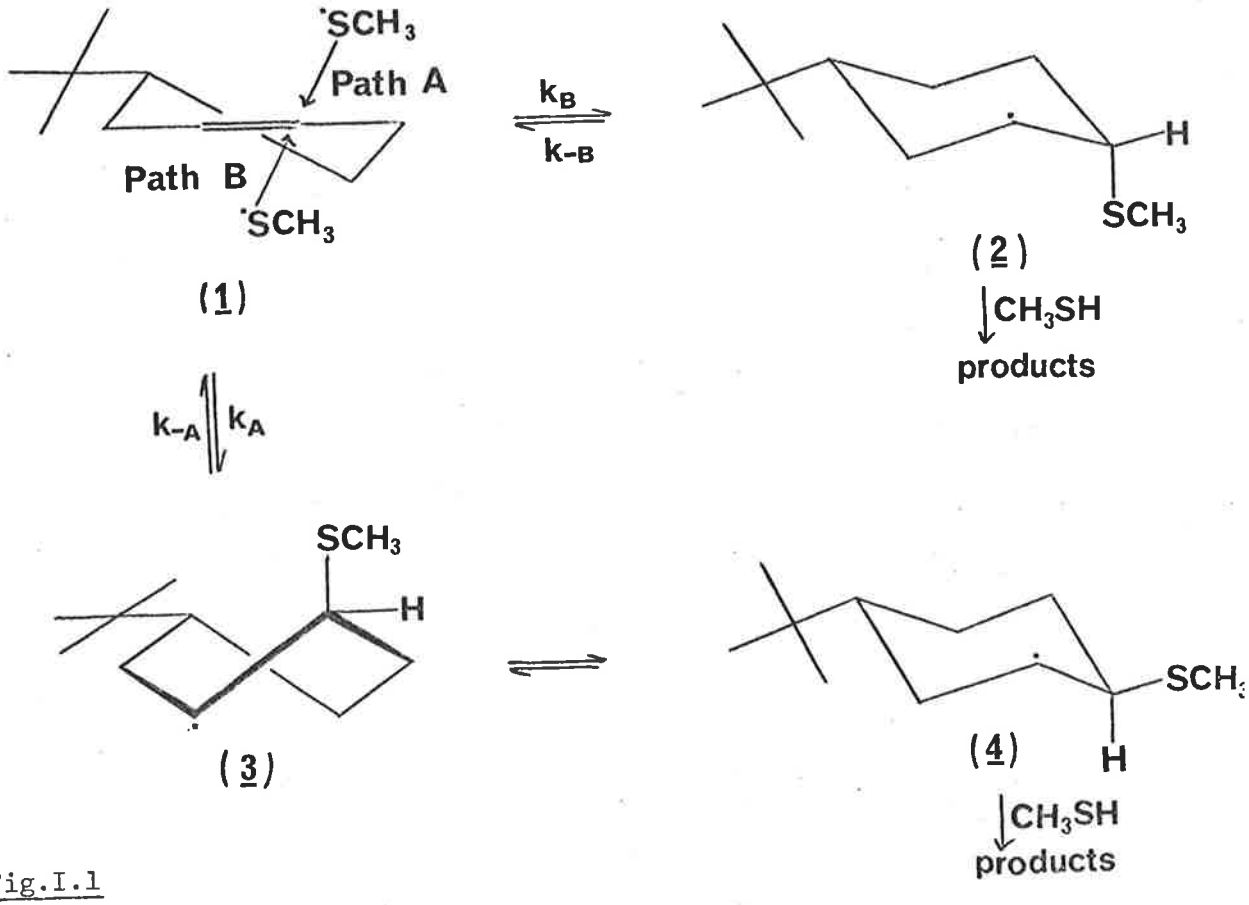


Fig.I.1

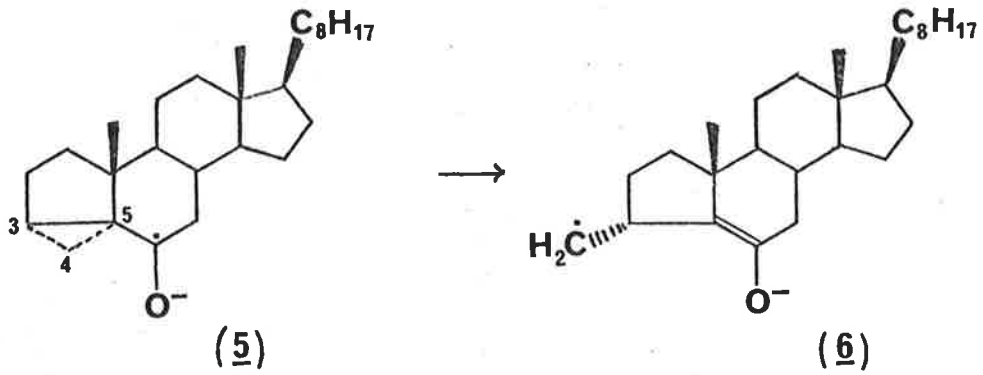
the three electrons involved in the redistribution process is satisfied by maximum coplanarity of the orbitals involved in the reaction. Therefore attack at C-1 from below the double bond (Path B) will lead directly to the axially substituted cyclohexyl radical (2) having the chair conformation, while attack at C-1 from above the double bond (Path A) will initially give the twist-boat radical intermediate (3) which could undergo conformational change to the equatorially substituted chair form (4). The difference in energy between the chair and twist-boat forms of cyclohexane has been calculated to be 1.3 kJ mol^{-1}.[23,53] Assuming that there is a similar energy difference between the radical intermediates (2) and (3), the rate of formation of (2) should be faster than that of (3). Therefore, since the activation energy difference between chain transfer from the intermediates (2) and (4) is probably small, a preference for axial addition of methanethiyl radical should result. A similar argument for radical attack at C-2 also indicates that axial incorporation should be favoured.

Free-radical addition of hydrogen bromide to conformationally rigid cyclohexenes affords predominantly products arising from axial bromine incorporation.[21,24] These results can also be rationalized by a similar consideration of the stereoelectronic factor.

With clear indications that the addition of radicals to olefins is stereoelectronically controlled, it is not unexpected that the reverse process, bond homolysis adjacent to a radical centre, is also influenced by the stereoelectronic factor. The extent of reversibility observed with thiyl radical additions to conformationally rigid cyclohexenes has been rationalized by considering the effect of this factor in C — S bond homolysis adjacent to a radical centre.[21]

It has also been established that scission of a C — C bond adjacent to a radical centre is subject to stereoelectronic control. Many examples of C — C bond homolysis occurring by the thermodynamically

less favourable reaction pathway have been reported. For example, the radical anion (5) undergoes rearrangement by specific $C_4 - C_5$ bond fission to give (6) (Fig.I.2),[25] β-scission of the radical (7) gives, almost exclusively, a final product derived from the radical (8) (Fig.I.3),[26] and specific rearrangement of the radical (9) occurs to give (10) (Fig.I.4).[27] Other examples have also been reported.[28-33] In all of

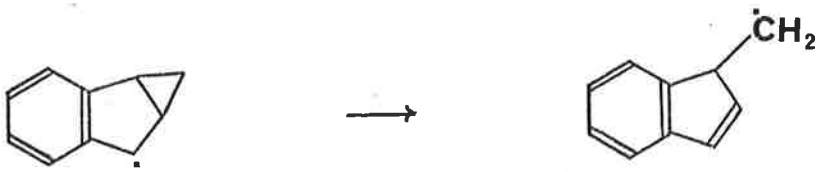


(5) (6)

Fig.I.2

(7) (8)

Fig.I.3



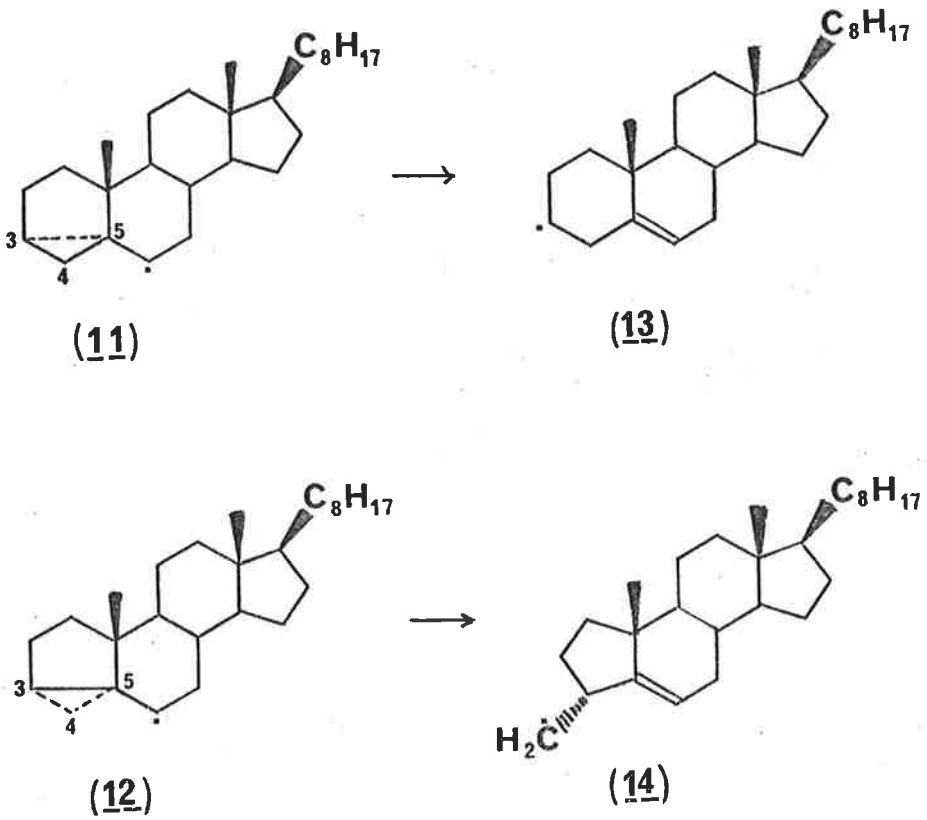
(9) (10)

Fig.I.4

these the most stable conformation of the parent radical is that in which the semioccupied p orbital and the β,γ-bond which prefentially undergoes fission are almost coplanar. However, the possibility of anionic fragmentation of the radical anion (5) cannot be precluded, and in all of the

other cases cited[26-33] the parent radical could react via a conformation other than the most stable one. Therefore none of these results unambiguously shows that C — C bond homolysis adjacent to a radical centre is stereoelectronically controlled.

However, β-scission reactions of the 3α,5— and 3β,5— cyclocholestanyl radicals (11) and (12)[9,34,35] are clearly governed by the stereoelectronic factor.[9,35] The rigid structures of these radicals ensures a fixed spatial relationship of the semioccupied p orbital and the bonds of the cyclopropyl ring. There is maximum coplanarity of the $C_3 - C_5$ bond with the semioccupied p orbital in the radical (11), while there is maximum coplanarity of the $C_4 - C_5$ bond with the semioccupied p orbital in the radical (12). The 3α,5-cyclocholestanyl radical (11) undergoes specific fission of the $C_3 - C_5$ bond to give the cholesteryl radical (13) (Fig.I.5),[34] and the 3β,5-cyclocholestanyl radical (12) undergoes specific fission of the $C_4 - C_5$ bond to give the thermodynamically less stable radical (14) (Fig.I.5).[9,35] These rearrangements provide



(11) (13)

(12) (14)

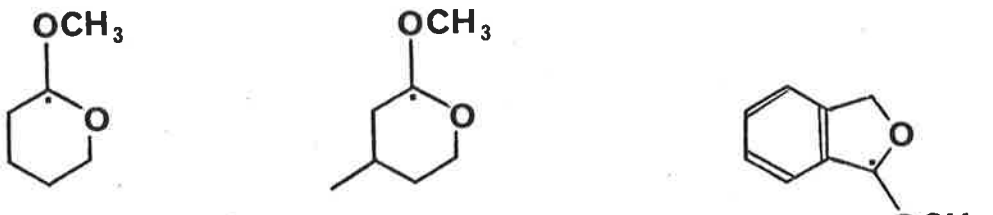
Fig.I.5

compelling evidence that in homolytic cleavage of a C — C bond adjacent to a radical centre the bond preferentially broken is the one which can attain the maximum degree of coplanarity with the semioccupied p orbital.[9,35] It is with this bond that the primary interaction involved in forming the transition state is stereoelectronically favoured.[4,8,9] *

The possibility that C — O bond homolysis adjacent to a semi-occupied p orbital is also stereoelectronically controlled has been used[36] to explain the preferred exocyclic fission of the radical (15) to form the lactone (16) (Fig.I.6),[37] by the thermodynamically less favourable reaction pathway.[36] The preferential exocyclic C — O bond fission of the radicals (17),[38] (18),[39] and (19)[40] has been similarly rationalized.[40]

(15) (16)

Fig.I.6



(17) (18) (19)

By analogy with the general transition state proposed for bond homolysis adjacent to a radical centre,[4,8,9] C — O bond homolysis should involve an

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* A more recent study has also indicated that C — C bond homolysis adjacent to a semioccupied p orbital is stereoelectronically controlled.[181]

initial coplanar interaction of the semioccupied p orbital and the σ* antibonding orbital of the C — O bond.[36,40] This can only occur if the bond is exocyclic to the ring.[36,40]

Since homolysis of C — S, C — C, and C — O bonds adjacent to a radical centre is subject to stereoelectronic control, the same might reasonably be expected for C — H bond homolysis. Two contradictory results relating to this issue have been reported.[41,42]

Agosta and Wolff[41] have reported preferential reactivity of axial β-hydrogens in cyclohexyl radicals generated as intermediates in the photochemical isomerization of the bicyclo [3.2.1] octan-6-ones (20). This isomerization is thought to involve initial α-cleavage to the biradical (21), inversion to equatorially substituted (22), and finally intramolecular hydrogen atom transfer to (23) (Fig.I.7).[43,44] The degree

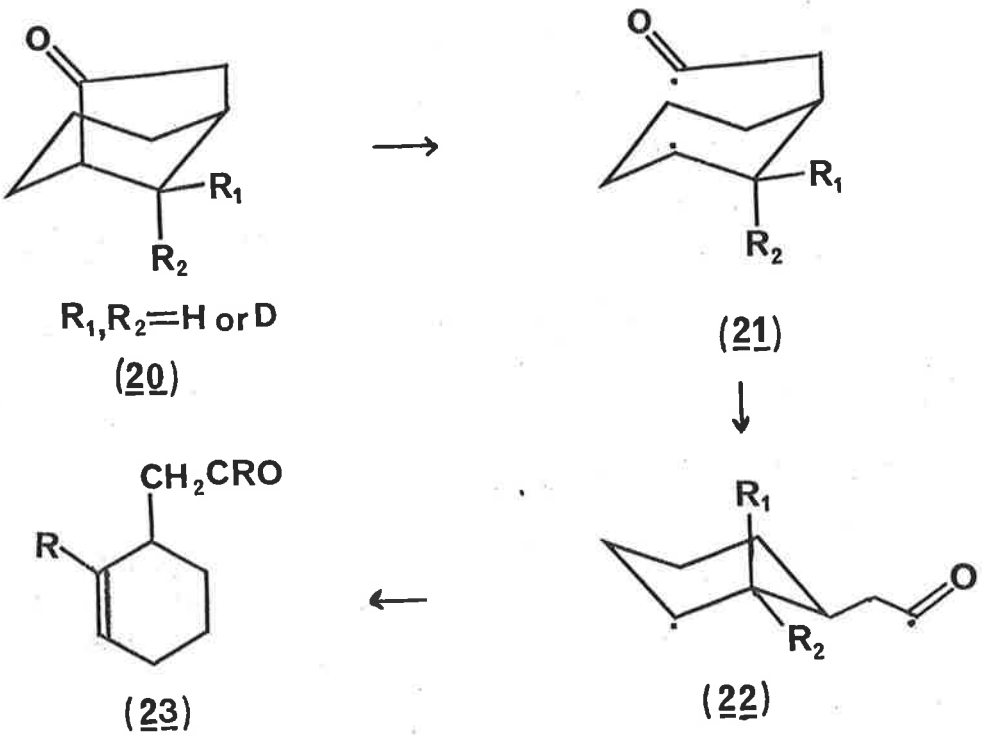

Fig.I.7

of stereoselectivity was determined by photochemical isomerization of the deuterium labelled bicyclo [3.2.1] octan-6-ones (20).[41] Results indicated that the axial hydrogen (R_1) was transferred preferentially from (22).[41]

This stereospecificity would be expected for a stereoelectronically controlled reaction as there is optimal coplanarity of the axial C — H bond with the adjacent semioccupied p orbital.[41]

Livant and Lawler[42] have reported exactly the opposite mode of selectivity. They recorded the CIDNP spectrum of the olefinic protons of cyclohexene in the ^1H NMR spectrum of a tetrahydrofuran solution of cyclohexyl bromide reacting with magnesium metal.[42] Their spectra were consistent with preferential transfer of the equatorial hydrogen atom in the disproportionation of cyclohexyl radical.[42]

Several explanations of this conflicting evidence have been proposed.[42] The steric bulk of a cyclohexyl radical might favour its abstraction of the less hindered equatorial hydrogen atom from the partner radical, or the disproportionation reaction might take place *via* a severely distorted conformation of the six-membered ring in which the normal equatorial hydrogen occupies a position relative to the semi-occupied p orbital which resembles that of the axial hydrogen in the chair conformation.[42] The stereoselectivity observed by Agosta and Wolff[41] may also have been steric in origin.[42] Although the acyl radical can approach the axial and equatorial hydrogens equally closely, there may be small energy differences in the favourable geometry for each transfer.[42]

In the present work it was decided to investigate the stereochemical course of β-C — H bond scission of radicals in more conventional chemical systems in an attempt to evaluate further the nature of the stereoelectronic factor and resolve the discrepancy of the previous reports.[41,42]

Alkyl *tert*-butylperoxyglyoxalates[45-49] and diacyl peroxides[50] decompose thermally by homolytic mechanisms to the corresponding alkyl radicals. Disproportionation reactions of suitably substituted cyclohexyl radicals should illustrate the effect of the stereoelectronic factor

in C — H bond scission adjacent to a radical centre. Therefore the thermolysis of the alkyl tert-butylperoxyglyoxalates (24c)-(30c), synthesized from 4-tert-butylcyclohexanol (24a), c-4-tert-butyl-c-2, c-6-dimethylcyclohexan-r-1-ol (25a), t-4-tert-butyl-c-2, t-6-dimethylcyclohexan-r-1-ol (26a), c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a), t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a), c-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (29a), and t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a), and of the diacyl peroxides (31c)-(34c), synthesized from t-4-tert-butylcyclohexane-r-1-carboxylic acid (31a), t-4-tert-butyl-t-2-methylcyclohexane-r-1-carboxylic acid (32a), c-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (33a), and t-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (34a), was investigated.

In these systems the tert-butyl group is assumed to act as a remote and effective conformational lock.[51,52] The energy associated with the preference of the tert-butyl group for the equatorial position in cyclohexanes has been found to be 1.3 kJ mol^{-1}.[53] The radicals expected from thermolysis of the peroxides (24c)-(34c) may therefore be regarded as being conformationally homogeneous.* In the previous reports[41,42] a fixed conformation of the radical involved in the hydrogen atom transfer step was not unequivocally confirmed.

As the previous reports[41,42] indicated, the two hydrogens adjacent to the semioccupied p orbital in a conformationally-fixed cyclohexyl

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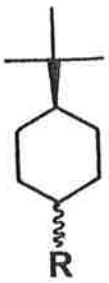
* The recent suggestion[54] that the tert-butyl group may distort the ground state geometry of a cyclohexane ring and exclude certain transition state geometries by increasing the steric strain will be discussed in the appropriate place in the text.



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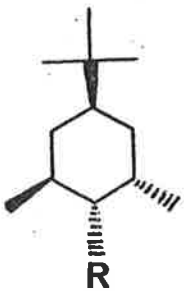

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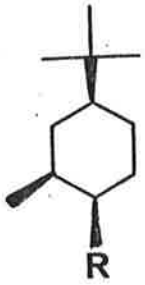

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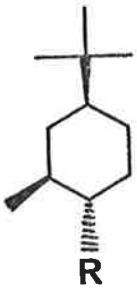

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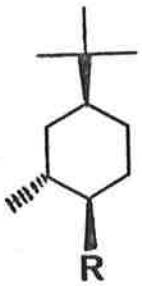

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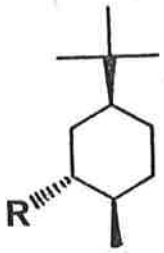
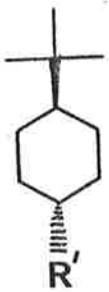


(30)

a) R=OH
b) R=OCOCOCl
c) R=OCOCOOOC$(CH_3)_3$



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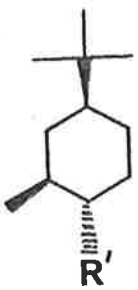

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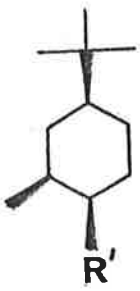

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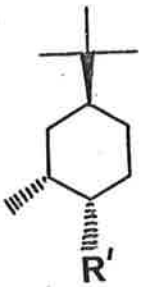


(34)

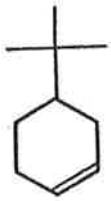
a) R'=COOH
b) R'=COCl
c) R'=COO$\frac{+}{2}$

radical are stereochemically non-equivalent. This has been established by extensive studies of the EPR spectrum of cyclohexyl radical[55-64] which exhibits splittings from two pairs of equivalent β-protons of 39.4 and 5.3G.[57] The splitting of 39.4G indicates that the angle θ between the axis of the semioccupied p orbital and that of the relevant C — H bond is 22°, while the splitting of 5.3G indicates that θ is 82°.[57] Since the EPR spectrum can be attributed to the chair conformation of cyclohexyl radical[55,57] these splittings can be attributed to the axial and equatorial β-protons respectively. Stereoelectronic control would result in preferential abstraction of axial hydrogens since there is a greater degree of coplanarity of the axial β-C — H bonds with the semioccupied p orbital (θ=22°) than of the equatorial β-C — H bonds (θ=82°).

Incorporation of methyl substituents enables distinction to be made between axial and equatorial hydrogen atom abstraction. The energy associated with the preference of the methyl group for the equatorial position in cyclohexanes has been calculated as 0.4 kJ mol $^{-1}$.[53] In the present system the methyl substituents should not affect conformation as this is much less than the energetic preference of the tert-butyl group[53] and the preference of the cyclohexane ring to exist in a chair conformation.[23,53] Evidence supporting this assumption will be provided later in the text.

The results of a product study of the thermolysis of the peroxides (24c)-(34c) are presented and discussed in Chapter II.A of this thesis. The synthesis of these peroxides (24c)-(34c) *via* the cyclohexanols (24a)-(30a) and the cyclohexanecarboxylic acids (31a)-(34a) is discussed in Chapter II.B. Attempts to synthesize stereospecifically α-deuterated 4-tert-butylcyclohexyl derivatives are also discussed in Chapter II.B.

To aid in the unambiguous identification of the products and the accurate determination of the yields of these products expected from thermolysis of the peroxides (24c)-(34c), the cyclohexenes (1) and (35)-



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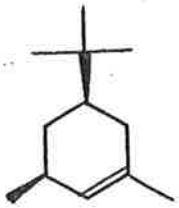

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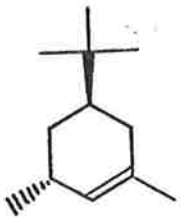

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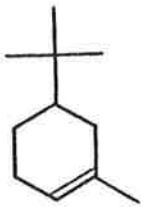

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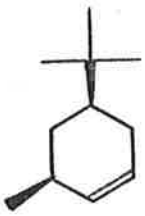

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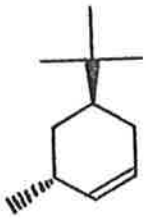

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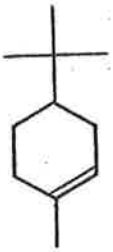

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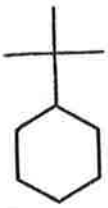

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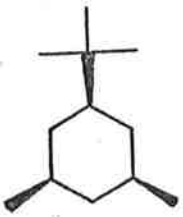

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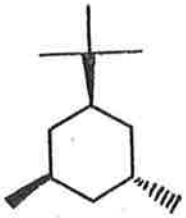

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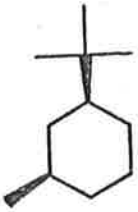

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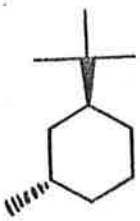
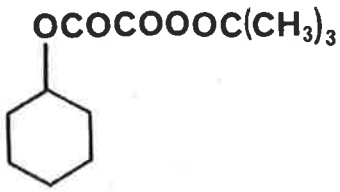


(46)

(47)

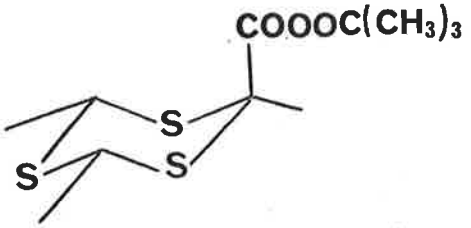
(41), and the cyclohexanes (42)-(47) were synthesized. This work is discussed in Chapter II.C.

The CIDNP spectra of solutions of decomposing 4-tert-butylcyclohexyl and cyclohexyl tert-butylperoxyglyoxalate, (24c) and (48), are presented in Chapter IV.D. These spectra are discussed in relation to the work of Livant and Lawler.[42]

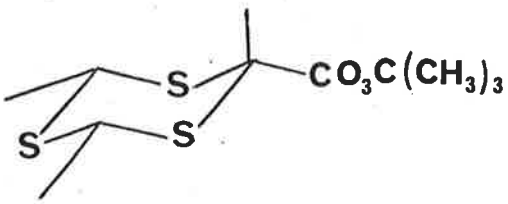


(48)

The possibility that bond homolysis adjacent to a filled nonbonding orbital is subject to stereoelectronic control has also been discussed. The greater rate of thermolysis of the axial perester (49) as compared with the equatorial epimer (50) has been attributed to the influence of the stereoelectronic factor in C — C bond homolysis adjacent to a lone pair of electrons on sulphur.[65] Decomposition of each of the epimers (49) and (50) in toluene afforded similar mixtures of the products (51)-(54), the formation of which was attributed to reactions of the common intermediate radical (55) with toluene and benzyl radical.[65] The high yields of (51) and (53), as compared to their respective epimers (52) and (54), were attributed to stereoelectronic control of C — C and C — H bond formation adjacent to a lone pair of electrons on sulphur.[65] Bond homolysis is the reverse of bond formation and, since in any system the forward and reverse processes must proceed through the same transition state and follow the same free energy profile, these results indicate that C — C and C — H bond homolysis adjacent to a lone pair of electrons on sulphur is also stereoelectronically controlled.



(49)



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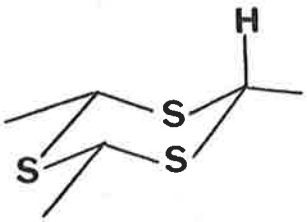
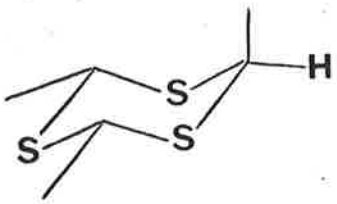


(51)



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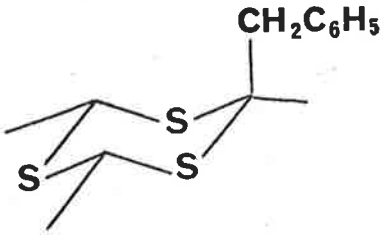

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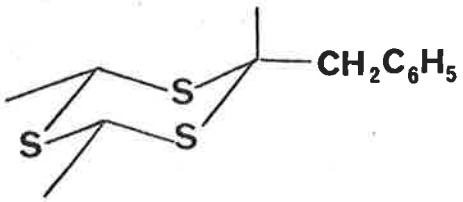

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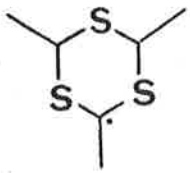


(55)

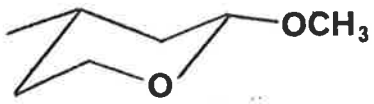
The same stereoelectronic control might reasonably be expected for C — H bond homolysis adjacent to a lone pair of electrons on oxygen. Photoelectron spectroscopy indicates that the two non-bonding orbitals on oxygen are not equivalent.[66-68] One is an essentially pure p-type orbital and the other is an s-type orbital.[66-68] It has been suggested that radical reactions of oxygen containing six-membered ring compounds might be expected to proceed under stereoelectronic control because there could be considerable overlap of the developing orbital with the adjacent oxygen's p-type orbital.[69]

Results of several recent studies can be attributed to stereoelectronic control of C — H bond homolysis adjacent to a lone pair of electrons on oxygen.[38,70] The axial hydrogen at C-2 in r-2-methoxy-c-4-methyltetrahydropyran (56) is abstracted by triplet benzophenone approximately 8 times faster than the equatorial hydrogen at C-2 in its epimer (57).[38] A product study[38] and an EPR spectral study[71] have both verified that the initial reaction involves homolysis of the C — H bonds at C-2. r-2,c-6-Dimethoxytetrahydropyran (58) which has two axial hydrogens attached to carbons adjacent to the oxygen of the ring reacts by hydrogen atom loss approximately twice as fast as its trans-epimer (59) which has only one.[70] The relative reactivities of (56) and (57),[38] and of (58) and (59),[70] can be attributed to preferential reactivity of the axial C — H bonds adjacent to oxygen, due to favourable interactions of these bonds with the filled non-bonding orbitals on oxygen.[38,70] *

However, neither of these results can be attributed unambiguously to the stereoelectronic factor. Because of the anomeric effect[72-77] r-2-methoxy-c-4-methyltetrahydropyran (56) is less stable than its

---

* In both of these cases an sp^3 hybridization of ethereal oxygen was assumed.[38,70] Although this is probably incorrect[66-68] it will lead to the same conclusions as those derived by considering the lone pairs of electrons to be non-equivalent.



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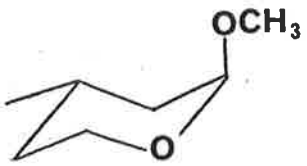

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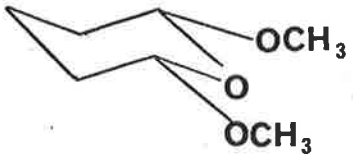
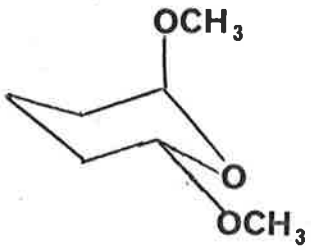


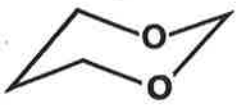
(58)



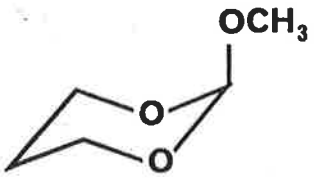
(59)

trans-epimer by 0.17 kJ mol^{-1},[72] and r-2,c-6-dimethoxytetrahydropyran (58) is less stable than its trans-epimer (59) by 0.18 kJ mol^{-1}.[77] The preferential reactivity of (56)[38] and (58)[70] may therefore merely reflect the relative stabilities of the substrates. If the relative reactivities of (56) and (57),[38] and of (58) and (59),[70] are due to the stereoelectronic factor, it is still not possible to determine the extent of its affect. Since the methoxy substituents in (56)-(59) are not held rigidly in any particular orientation with respect to the reaction centre, they may adopt conformations in which the stereoelectronic interactions between the bond undergoing fission and the non-bonding orbitals on the substituent oxygen are more or less favourable in (56) than in (57), and in (58) than in (59). Also, there may be a contribution to the reaction from the conformers of (56)-(59) other than the most stable ones.

In an attempt to define more accurately the nature of the stereoelectronic effect in C — H bond homolysis adjacent to a filled non-bonding orbital on oxygen it was decided to investigate reactions involving C — H bond scission in 1,3-dioxane (60), 2-methoxy-1,3-dioxane (61), 2-methyl-1,3-dioxane (62), r-4,c-6-dimethyl-1,3-dioxane (63), r-2-methoxy-c-4,c-6-



(60)



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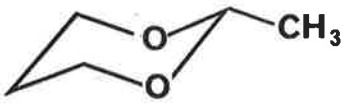

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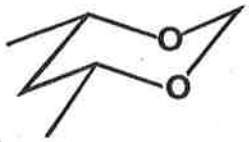

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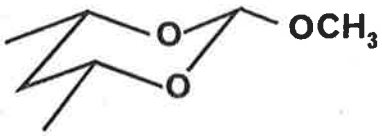

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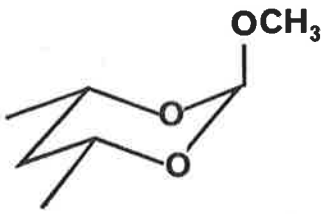

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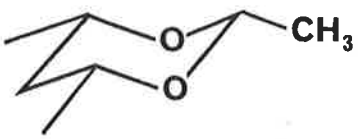

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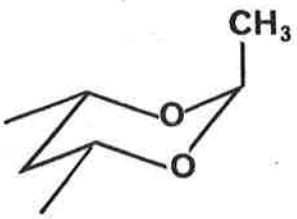


(67)

dimethyl-1,3-dioxane (64), r-2-methoxy-t-4,t-6-dimethyl-1,3-dioxane (65), r-2,c-4,c-6-trimethyl-1,3-dioxane (66), and r-2,t-4,t-6-trimethyl-1,3-dioxane (67).

The preferred conformation of each of these dioxanes (60)-(67) has been previously determined.[78-80] Each exists in a chair conformation.[78-80] The methyl substituents at C-4 and C-6 in the dioxanes (63)-(67) are equatorially oriented and act as conformational locks.[78] In these fixed-chair conformations the axial and equatorial C — H bonds at C-2 are stereochemically non-equivalent. Stereoelectronic control in hydrogen atom abstraction from these systems would result in preferential loss of the axial hydrogen since there is greater overlap of the axial C — H bond with the p-type non-bonding orbitals of the adjacent ring oxygens. Incorporation of methyl and methoxy substituents at C-2 serves to distinguish between axial and equatorial hydrogen atom abstraction. These substituents do not appreciably alter the conformation of the rest of the molecule.[78-80]

The relative rates of hydrogen atom abstraction from C-2 in the dioxanes (60)-(67) can therefore be used to investigate the nature of the stereoelectronic effect in C — H bond homolysis adjacent to a lone pair of electrons on oxygen. Previous studies in similar systems[38,70,71] show that if discriminating hydrogen atom abstractors are used, reaction will occur preferentially at C-2. The relative rates of suitable reactions of the dioxanes (60)-(67) should therefore reflect the relative reactivities of their C — H bonds at C-2.

The relative rates of reaction of the dioxanes (60)-(67) can be determined by various competitive methods. The relative reactivities of two or more substrates can be determined by reacting mixtures of those substrates with a common reactant and measuring the relative rates of consumption of each substrate:

81,82a

$$\frac{k_1}{k_2} = \frac{\text{Ln} \dfrac{[R_1H]_t}{[R_1H]_o}}{\text{Ln} \dfrac{[R_2H]_t}{[R_2H]_o}} \qquad 1)$$

where k_1 and k_2 are the rate constants for reaction of R_1H and R_2H respectively.

This method is only valid if the initial reaction of each substrate is irreversible and none of the substrates are produced or consumed in subsequent reaction steps. These limitations will be considered in the text where appropriate.

If the relative reactivities of the substrates are being measured by reaction with tert-butoxy radical, then another competitive method is available. tert-Butoxy radical can either abstract hydrogen or undergo β-cleavage:

$$(CH_3)_3CO^{\cdot} + RH \xrightarrow{k_H} (CH_3)_3COH + R^{\cdot} \qquad 2)$$

$$(CH_3)_3CO^{\cdot} \xrightarrow{k_\beta} CH_3COCH_3 + {}^{\cdot}CH_3 \qquad 3)$$

For any substrate RH, k_H/k_β can be determined from a measurement of the tert-butanol-acetone ratio:

82b

$$k_H/k_\beta = \frac{[\text{tBuOH}]}{[\text{Acetone}]} \times \frac{[1]}{[RH_o]} \qquad 4)$$

The rate of β-cleavage of tert-butoxy radical may therefore be used as a standard if constant media and temperature conditions are maintained.

EPR spectroscopy can also be used to investigate the kinetics of irreversible radical reactions in studies which require the determination of relative radical concentrations. The integrated absorption intensity of an EPR spectrum is directly proportional to the number of radicals in the

sample. Therefore, provided certain precautions are taken,[83] relative radical concentrations can be obtained by comparing the integrated absorption intensities of the samples under consideration.[83]

When mixtures of substrates and di-tert-butyl peroxide are photolyzed the reaction scheme can be represented by:

$$(CH_3)_3COOC(CH_3)_3 \xrightarrow{h\nu} 2(CH_3)_3CO^{\cdot} \qquad 5)$$

$$(CH_3)_3CO^{\cdot} + AH \xrightarrow{k_{AH}} A^{\cdot} + (CH_3)_3COH \qquad 6)$$

$$(CH_3)_3CO^{\cdot} + BH \xrightarrow{k_{BH}} B^{\cdot} + (CH_3)_3COH \qquad 7)$$

$$A^{\cdot} + A^{\cdot} \xrightarrow{k_{AA}} \text{Inactive products} \qquad 8)$$

$$B^{\cdot} + B^{\cdot} \xrightarrow{k_{BB}} \text{Inactive products} \qquad 9)$$

$$A^{\cdot} + B^{\cdot} \xrightarrow{k_{AB}} \text{Inactive products} \qquad 10)$$

Under steady state conditions:

$$k_{AH}[(CH_3)_3CO^{\cdot}][AH] = 2k_{AA}[A^{\cdot}] + 2k_{AB}[A^{\cdot}][B^{\cdot}] \qquad 11)$$

$$k_{BH}[(CH_3)_3CO^{\cdot}][BH] = 2k_{BB}[B^{\cdot}] + 2k_{AB}[A^{\cdot}][B^{\cdot}] \qquad 12)$$

On the assumption that all radical decay reactions occur at the diffusion-controlled limit:*

$$k_{AA} \simeq k_{AB} \simeq k_{BB}$$

and therefore:

$$\frac{k_{AH}}{k_{BH}} = \frac{[A^{\cdot}]}{[B^{\cdot}]}\,\frac{[BH]}{[AH]} \qquad 13)$$

---

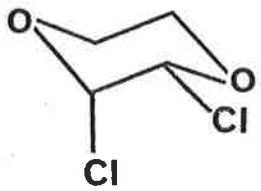
* The limitations of this assumption in the present work will be discussed later in the text.

The relative rates of hydrogen atom abstraction from AH and BH can thus be determined by measuring the relative stationary concentrations of radicals $A^{\cdot}$ and $B^{\cdot}$.

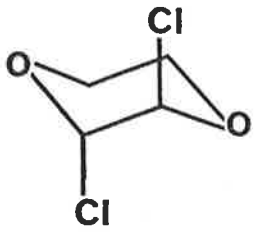
The relative rates of hydrogen atom abstraction from the dioxanes (60)-(67) were determined by a variety of the methods described and the results are presented and discussed in Chapter III.A of this thesis. The synthesis associated with this work is described in Chapter III.C.

In an attempt to further investigate the effect of the stereoelectronic factor in bond homolysis adjacent to a lone pair of electrons on oxygen the stereospecificity of chlorine atom abstraction adjacent to oxygen was also investigated. Again there could be considerable interaction of the C — Cl bond undergoing fission and the non-bonding orbitals on oxygen. Therefore these reactions might be expected to be subject to stereoelectronic control.

To investigate the stereochemical course of C-Cl bond scission adjacent to oxygen it was decided to measure the relative rates of chlorine atom abstraction from r-2,c-3-dichloro-1,4-dioxane (68) and r-2,t-3-dichloro-1,4-dioxane (69). The dioxane (68) exists in the chair



(68)



(69)

conformation in which one chlorine is in an axial position and the other is in an equatorial position.[84,85] The dioxane (69) also exists in a chair conformation, but in this case both chlorine substituents are axially oriented.[86,87] This preference of chlorine substituents for axial positions is due to the anomeric effect.[87,88]

In the chair conformations of (68) and (69) the axial and equator-

ial C — Cl bonds are stereochemically non-equivalent. By analogy with the discussion of C — H bond fission adjacent to oxygen (page 18), stereoelectronic control in chlorine atom abstraction from these compounds would result in preferential loss of axial chlorine.

The relative rates of chlorine atom abstraction from (68) and (69) can be measured by determining the relative rates of consumption of each substrate from mixtures of the two (page 19). Previous work[6,8,9,13,16,89-94] has demonstrated that the reduction of an alkyl halide with a trialkyl or triaryl-stannane is a simple and convenient procedure for halogen atom abstraction under controlled conditions (Scheme I.1).

Initiation

initiator → $R^{\cdot}$ 14)

Propagation

$R^{\cdot} + R^1_3SnH \rightarrow RH + R^1_3Sn^{\cdot}$ 15)

$R^1_3Sn^{\cdot} + RX \rightarrow R^1_3SnX + R^{\cdot}$ 16)

Termination

$R^{\cdot} + R^{\cdot} \rightarrow$ 17)

$R^{\cdot} + R^1_3Sn^{\cdot} \rightarrow$ } Inactive products 18)

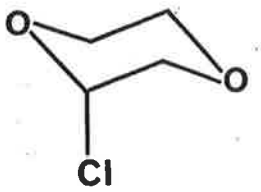
$R^1_3Sn^{\cdot} + R^1_3Sn^{\cdot} \rightarrow$ 19)

Scheme I.1

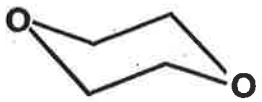
The validity of the free radical chain mechanism has been established.[93] Reaction with tri-n-butyltin hydride was therefore the method chosen for measuring the relative rates of chlorine atom abstraction from the dioxanes (68) and (69). This study is described and discussed in Chapter III.B.

The major products expected from these reactions of the dioxanes

(68) and (69) are 2-chloro-1,4-dioxane (70) and 1,4-dioxane (71).



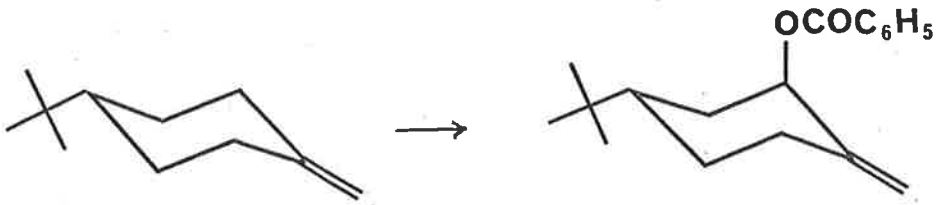
(70)



(71)

A discussion of the formation of these compounds is included in Chapter III.B. The mono-chloro dioxane (70) exists in the chair conformation in which the chlorine substituent is axially oriented[88,95] due to the favourable anomeric interactions in this conformation.[87,88] The subsequent reduction of this compound expected under the reaction conditions used should also be important and is discussed in Chapter III.B. The synthesis of the dioxanes (68) - (70) is described in Chapter III.C.

It has been suggested that homolytic reactions adjacent to a π orbital are also influenced by the stereoelectronic factor.[96-98] For example, the copper catalysed reaction of 4-tert-butylmethylenecyclohexane (72) with tert-butyl perbenzoate affords mainly t-5-tert-butyl-2-methylenecyclohex-r-1-yl benzoate (73) (Fig.I.8),[96] and it has been suggested

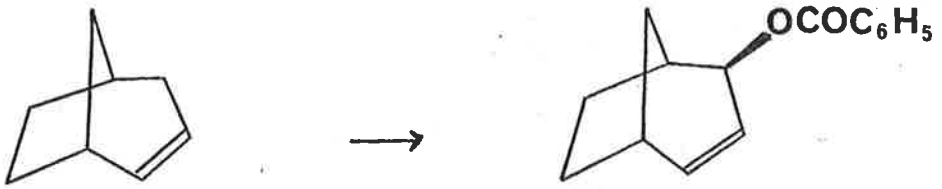


(72) (73)

Fig.I.8

that the mechanism of this reaction involved preferential loss of the axial hydrogen atom, the removal of which is facilitated by favourable overlap of the olefinic π orbital with the developing semioccupied p orbital.[96] Conversely, axial approach of the cupric carboxylate to the intermediate allylic radical should be similarly favoured.[96] It has been

postulated that the same stereoelectronic factor is partly responsible for the stereospecific formation of exo-bicyclo [3.2.1] oct-3-en-2-yl benzoate (75) from bicyclo [3.2.1] oct-2-ene (74) (Fig.I.9).[99]

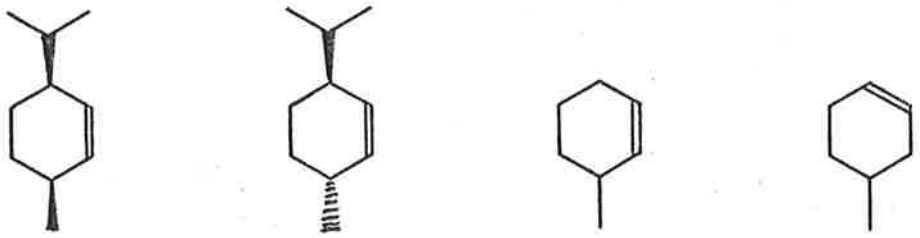


(74) (75)

Fig.I.9

However, in neither of these cases is it possible to determine clearly the stereochemical consequences of the hydrogen atom transfer step for in each of the substrates (72) and (74) the same allylic radical is produced by abstraction of either an axial or equatorial allylic hydrogen atom.

Stereospecificity of hydrogen atom abstraction adjacent to a π orbital has been directly observed by Beckwith and Phillipou.[97,98] In their investigation of the copper catalysed reactions of cis and trans-p-menth-2-ene, (76) and (77), and 3- and 4-methylcyclohexene, (78) and (79),



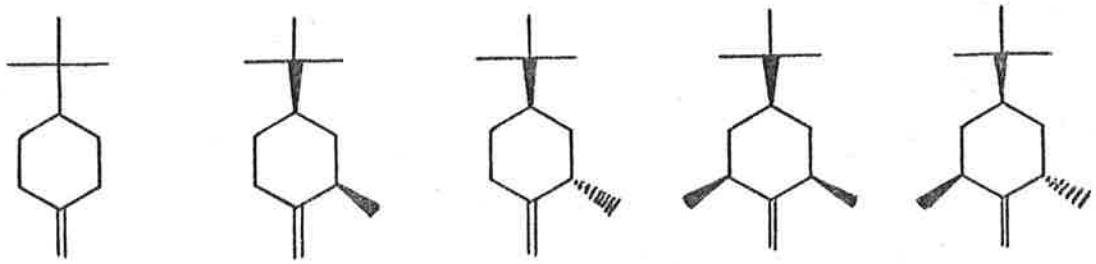
(76) (77) (78) (79)

with tert-butyl perbenzoate, the relative yields of the products obtained were attributed to the influence of the stereoelectronic factor in C — H bond homolysis adjacent to a π orbital.[97,98] The results of experiments with trans-p-menth-2-ene (77) in which the two allylic hydrogens are stereochemically equivalent, each being pseudoaxial in the more stable conformation, show that the position bearing the methyl substituent is more reactive than that bearing isopropyl, probably due to the greater ability of the methyl substituent to stabilize the product allylic radical

by hyperconjugation.[97,98] Unlike its trans-isomer (77), cis-p-menth-2-ene (76) does not undergo preferential attack by tert-butoxy radical at the 1-position.[97,98] These results are explicable in terms of the hypothesis that the preferred transition state for hydrogen atom abstraction at an allylic position is that which allows maximum overlap between the π system and the developing p orbital.[97,98] The reactivities of the allylic hydrogens in the menthenes (76) and (77) have been rationalized by considering the energies involved in attaining the conformations required for hydrogen atom abstraction to proceed under stereoelectronic control.[97,98] Results consistent with this rationalization were obtained from reactions of the cyclohexenes (78) and (79).[97,98]

Although it seems reasonable to conclude that homolytic reactions adjacent to a π orbital are subject to stereoelectronic control, it has not been proven that copper-olefin complexes do not participate in the hydrogen atom transfer step. This possibility has been a source of much conjecture in the past.[96,98,100-104] Furthermore the extent of the influence of the stereoelectronic factor in controlling the stereospecificity of these reactions has not been clearly determined.

In the present work it was decided to investigate the copper catalysed reactions of 4-tert-butylmethylenecyclohexane (72), c-4-tert-butyl-r-2-methylmethylenecyclohexane (80), t-4-tert-butyl-r-2-methylmethylenecyclohexane (81), c-4-tert-butyl-r-2,c-6-dimethylmethylenecyclohexane (82), and c-4-tert-butyl-r-2,t-6-dimethylmethylenecyclohexane (83), with tert-butyl perbenzoate, in an attempt to more clearly define the nature of the stereoelectronic effect in C — H bond homolysis adjacent to a π orbital.



(72) (80) (81) (82) (83)

A kinetic and product study of these reactions was conducted to examine the extent of the influence of the stereoelectronic factor. It was also decided to measure the relative rates of reaction of the olefins (72) and (80)-(83) with tert-butoxy radical generated in the absence of a copper catalyst, in an attempt to determine the extent of the participation of copper-olefin complexes in the hydrogen atom transfer step.

tert-Butoxy radical is known to show a strong preference for allylic attack.[96-99,105] Thus the rates of reaction and the products obtained from these reactions of the olefins (72) and (80)-(83) should reflect the susceptibility of their respective allylic hydrogens towards attack by tert-butoxy radical.

In the olefins (72) and (80)-(83) the tert-butyl group is again assumed to act as a remote and effective conformational lock (page 9). Each compound would be expected to exist in the chair conformation with the tert-butyl group equatorially oriented.* In such conformations axial and equatorial C — H bonds adjacent to the π bond are stereochemically non-equivalent. Stereoelectronic control in hydrogen atom abstraction from these systems would result in preferential reactivity of axial C — H bonds since these are more coplanar with the orbitals of the π system. Incorporation of methyl substituents serves to distinguish between axial and equatorial hydrogen atom abstraction.

The results of a kinetic and product study of the copper catalysed reactions of the olefins (72) and (80)-(83) with tert-butyl perbenzoate, and of a kinetic study of their reactions with di-tert-butyl peroxide are presented and discussed in Chapter IV.A of this thesis. The synthesis of the olefins (72) and (80)-(83) is discussed in Chapter IV.B.

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* The preferred conformations of the olefins (72) and (80)-(83) are discussed in Chapter IV.B.

Following Chapter IV an afterword is included in which the general relationships between the work described in Chapters II-IV are discussed.

To assist in the reading of this thesis the structures of the key compounds mentioned in Chapters II-IV are shown on lift-outs in the pocket on the back cover.

CHAPTER II

Results and Discussion

Stereoelectronic Effects in Hydrogen Atom Abstraction from Substituted Cyclohexyl Radicals.

CHAPTER II.A A Product Study.

The yields of the cyclohexenes (1) and (35)-(41), and the cyclohexanes (42)-(47), obtained by heating dilute cyclohexane solutions of the peroxides (24c)-(34c) (c. 0.5 M), are shown in Table II.1. They are given as percentages based on the amounts of the alkyl chloroglyoxalates (24b)-(30b) and the acid chlorides (31b)-(34b) used in the synthesis of the peroxides (24c)-(34c). They were calculated using internal standards and were corrected for molar response factors. For each of the peroxides (24c)-(34c) the yields shown are the highest obtained from at least two experiments. Although the total yield of products varied considerably, the ratios of products obtained from experiments with any particular substrate were constant to within a factor of ± 1.2. The reaction products (1) and (35)-(47) were identified by comparison of their GLC properties with those of authentic samples, and by comparison of the physical and NMR properties of these samples with those of individual components separated from the reaction mixtures by chromatography on silver nitrate impregnated silica.[152]

Several experiments were conducted to investigate the mechanisms of decomposition of the peroxides (24c)-(34c). Whereas decomposition of the peroxide (26c) afforded more of the trans-cyclohexene (36) than its cis-isomer (35), solvolysis of t-4-tert-butyl-c-2,t-6-dimethylcyclohexyl-1-yl toluene-p-sulphonate (84) gave the cis-cyclohexene (35) and rearranged olefins, but none of the trans-cyclohexene (36). Also, no rearranged olefins were observed in reactions of the peroxides (24c)-(30c), although ionic reactions of cyclohexyl derivatives have been reported to give rearrangement products.[106] It was therefore concluded that decomposition of the alkyl tert-butylperoxyglyoxalates (24c)-(30c) does not involve cationic intermediates. Since decomposition of the diacyl peroxides (31c)-(34c) gave products without rearrangement it is also unlikely that these

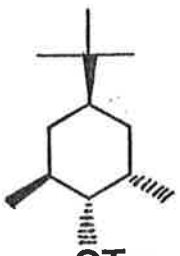
Table II.1

Products of thermolysis of the peroxides (24c)-(34c).

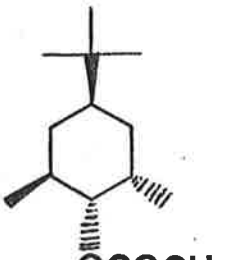
Substrate	Yields of products, %				
	Cyclohexanes		Cyclohexenes		
	(42)		(1)		
(24c)	70		14		
(31c)	55		16		
	(43)	(44)	(35)	(36)	
(25c)	69	-	22	-	
(26c)	1†	72	1.7	14	
	(45)	(46)	(38)	(39)	(37)
(27c)	68	-	9.5	-	7.0
(28c)	67	-	8.5	-	7.5
(29c)	-	71	-	14	2.5
(32c)	59	-	8	-	7
(33c)	56	-	8	-	6.5
(34c)	-	52	-	13	3
	(47)		(41)	(40)	
(30c)	64		10	3.5	

† Formed from the isomeric impurity in the peroxide (26c).

reactions involve cationic intermediates.



(84)



(85)

t-4-tert-Butyl-c-2,t-6-dimethylcyclohex-r-1-yl acetate (85) and the alkyl chloroglyoxalate (26b) were found to be stable to the reaction conditions used in the thermolysis of the peroxides (24c)-(34c). It therefore seems unlikely that decomposition of these peroxides proceeds by intramolecular concerted elimination (Fig.II.1).

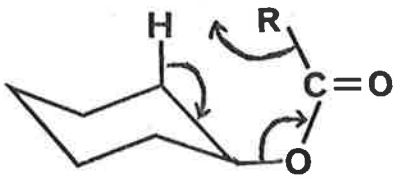


Fig.II.1

Cyclohexene (> 0.6 mol/mol peroxide) and tert-butanol were formed in the reactions of the alkyl tert-butylperoxyglyoxalates (24c)-(30c). Cyclohexene (> 0.2 mol/mol peroxide) was also formed in the reactions of the diacyl peroxides (31c)-(34c). Formation of this amount of cyclohexene in the decomposition of the peroxyglyoxalates (24c)-(30c) indicates that direct abstraction of a β-hydrogen by tert-butoxy radical (Fig.II.2) is unlikely to be a significant reaction pathway.

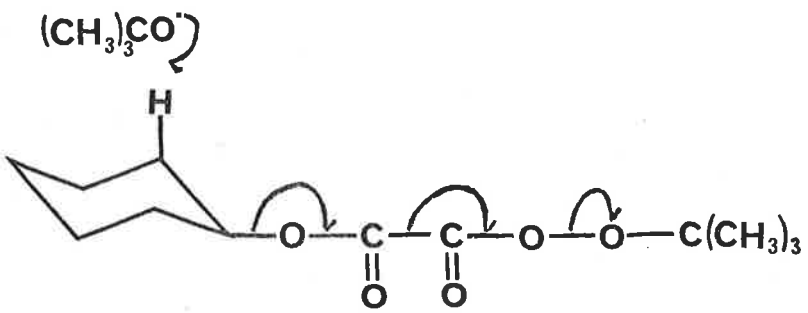
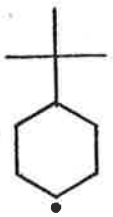
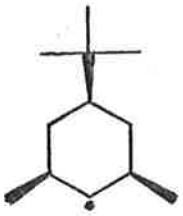


Fig.II.2

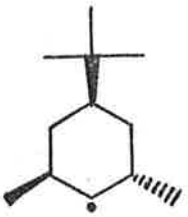
It therefore seems likely that decomposition of the peroxyglyoxalates (24c)-(30c) involves homolysis to the substituted cyclohexyl radicals (86)-(91).[45-49]



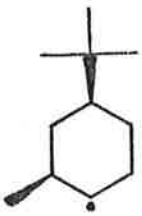
(86)



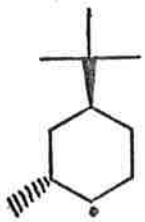
(87)



(88)



(89)



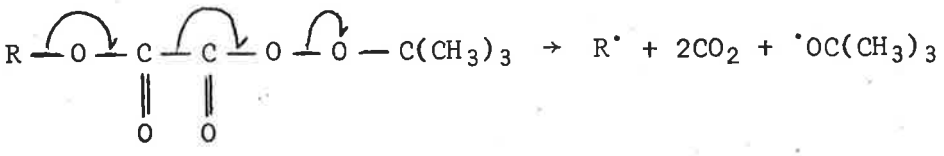
(90)

(91)

The similarity in the ratios of products derived from the peroxides (27c), (28c), (32c), and (33c), indicates that common intermediates are formed, and thus that the diacyl peroxides (31c)-(34c) also undergo homolysis to give the cyclohexyl radicals (86), (89), and (90).[50] The overall yields from the diacyl peroxides (31c)-(34c) are somewhat lower than those from the peroxyglyoxalates (24c)-(30c), probably due to some induced decomposition in the former case. A comparison of the ratios of products obtained from the peroxides (24c) and (31c), and (29c) and (34c), also indicates that common intermediates are involved.

The products obtained from decomposition of the peroxides (24c)-(34c) are consistent with homolytic reaction mechanisms and the formation of the intermediate cyclohexyl radicals (86)-(91). Homolysis of the peroxyglyoxalates (24c)-(30c) should afford the cyclohexyl radicals (86)-

(91), carbon dioxide, and tert-butoxy radical:

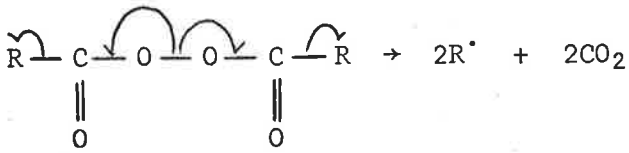


20)

The tert-butoxy radical would be rapidly consumed by reaction with cyclohexane solvent:

$$(CH_3)_3CO^{\cdot} + C_6H_{12} \rightarrow (CH_3)_3COH + C_6H_{11}^{\cdot} \qquad 21)$$

Homolysis of the diacyl peroxides (31c)-(34c) should afford the cyclohexyl radicals (86), (89), and (90), and carbon dioxide:



22)

When the thermolysis of each of the peroxides (24c)-(34c) was conducted in an open system a rapid evolution of gas was observed.

Of the products formed from the intermediate radicals (86)-(91), the cyclohexenes (1) and (35)-(41) would be formed by disproportionation reactions with another identical radical, with cyclohexyl radical, and with tert-butoxy radical:

$$2R^{\cdot} \rightarrow R(-H) + R\text{-}H \qquad 23)$$

$$R^{\cdot} + C_6H_{11}^{\cdot} \rightarrow R(-H) + C_6H_{12} \qquad 24)$$

$$R^{\cdot} + (CH_3)_3CO^{\cdot} \rightarrow R(-H) + (CH_3)_3COH \qquad 25)$$

The contribution from the latter reaction would only be expected to be minor as the concentration of tert-butoxy radical in the reaction mixtures would be low (equation 21). The cyclohexanes (42)-(47) would be formed by disproportionation reactions with another identical radical (equation 23) and with cyclohexyl radical:

$$R^{\cdot} + C_6H_{11}^{\cdot} \rightarrow R\text{-}H + C_6H_{10} \qquad 26)$$

The amounts of cyclohexene produced in the reactions suggests that cyclohexyl radical also reacts by disproportionation with another cyclohexyl radical and with tert-butoxy radical:

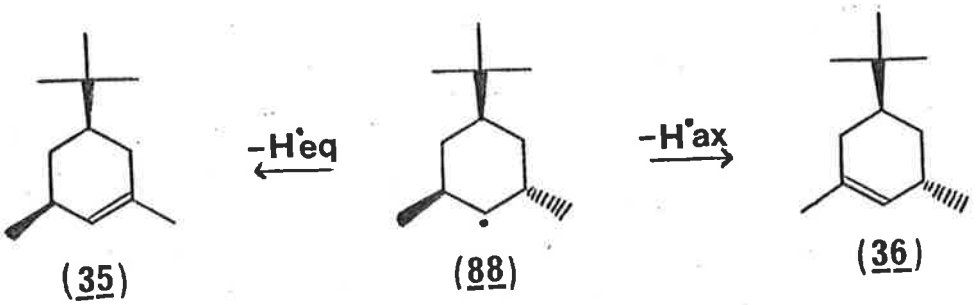
$$2\ C_6H_{11}^{\cdot} \rightarrow C_6H_{12} + C\ H \qquad 27)$$

$$(CH_3)_3CO^{\cdot} + C_6H_{11}^{\cdot} \rightarrow (CH_3)_3COH + C_6H_{10} \qquad 28)$$

Again the contribution from the latter reaction would only be expected to be minor. Radical coupling is clearly unimportant as a high yield of monomeric products was obtained.

These reactions of the radicals (86)-(91) are assumed to involve their chair conformations in which the tert-butyl group is equatorially oriented. The ESR spectrum of cyclohexyl radical has been attributed to the chair conformation (page 11),[55,57] and the energy associated with the conformational preferences of an equatorial tert-butyl substituent and the methyl substituents would not be expected to deform this conformation. Also, ^{1}H and ^{13}C NMR spectral data of similar systems (Chapter II, B and C) indicates that the chair conformation is preferred. It seems unlikely that steric strain involved in forming the transition state would change the conformation.

The relative yields of the cyclohexenes (1) and (35)-(41) obtained from thermolysis of the peroxides (24c)-(34c)(Table II.1) clearly show that axial hydrogens are preferentially transferred in reactions of the intermediate cyclohexyl radicals (86)-(91). Disproportionation of c-4-tert-butyl-r-2,t-6-dimethylcyclohexyl radical (88) affords c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) by loss of the equatorial β-hydrogen, and t-5-tert-butyl-1,r-3-dimethylcyclohexene (36) by loss of the axial β-hydrogen (Fig.II.3). Of these two competing processes loss of the equatorial hydrogen should be favoured on steric and thermodynamic grounds. There would be less steric hindrance to abstraction of the equatorial hydrogen and nonbonded interactions are less severe in the cis-cyclohexene (35) than in its stereoisomer (36). However, the results shown in Table II.1

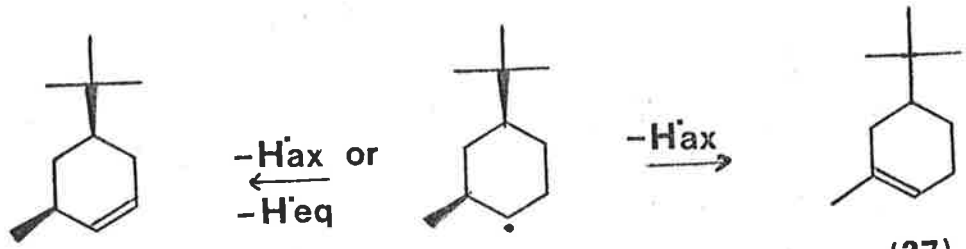


(35) (88) (36)

Fig.II.3

clearly show that the axial β-hydrogen is transferred approximately 8 times more readily than the equatorial β-hydrogen. This mode of selectivity might have been expected from a consideration of the stereoelectronic factor as the β-C — H bond which preferentially undergoes fission is that which can attain the maximum degree of coplanarity with the adjacent semioccupied p orbital.

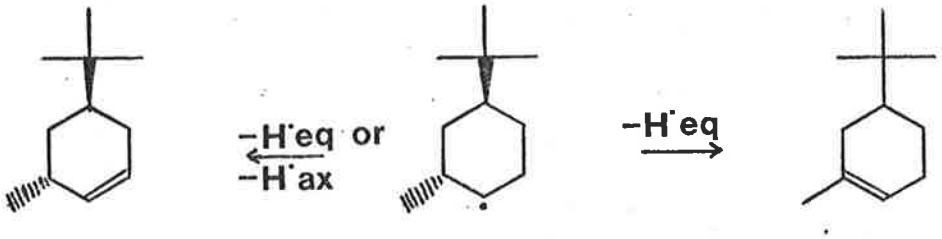
The yields of the cyclohexenes (37)-(39) obtained from disproportionation of c-4-tert-butyl-r-2-methylcyclohexyl radical (89) and its trans-isomer (90) also indicate that there is a preferential reactivity of axial β-C — H bonds. Loss of an axial β-hydrogen from the cis-radical (89) can produce either c-5-tert-butyl-r-3-methylcyclohexene (38) or 5-tert-butyl-1-methylcyclohexene (37), while loss of an equatorial β-hydrogen can produce only the disubstituted cyclohexene (38) (Fig.II.4).



(38) (89) (37)

Fig.II.4

Similarly, loss of an equatorial hydrogen from the trans-radical (90) can produce either t-5-tert-butyl-r-3-methylcyclohexene (39) or the tri-substituted cyclohexene (37), whereas loss of an axial β-hydrogen can produce only the trans-cyclohexene (39) (Fig.II.5).

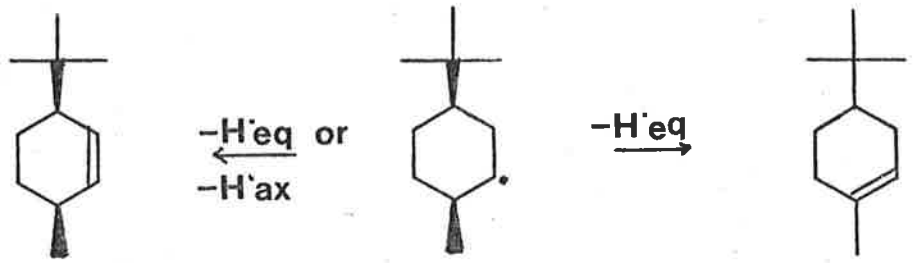


(39) (90) (37)

Fig.II.5

Disproportionation of the cis-radical (89) afforded approximately equal amounts of the cyclohexenes (37) and (38) (Table II.1). However, disproportionation of the trans-radical (90) gave approximately five times more of the trans-cyclohexene (39) than of the cyclohexene (37) (Table II.1). While neither of these results can be individually interpreted as a stereoelectronic effect, a consideration of both results clearly demonstrates that hydrogen atom transfer from the intermediate cyclohexyl radicals (89) and (90) is stereoelectronically controlled. The statistical factor is the same for disproportionation of both of the radicals (89) and (90). The different ratios of yields of the cyclohexenes (37) and (38), and (37) and (39), obtained from the respective radicals (89) and (90), can not be due to steric or thermodynamic factors. Steric interactions would favour abstraction of equatorial β-hydrogens from radicals (89) and (90). These interactions would be particularly important in the case of abstraction of the axial hydrogen from C-6 of the radical (90) because of the proximity to the reaction centre of the axially oriented methyl group at C-2. Nonbonded interactions are less severe in the cis-cyclohexene (38) than in the trans-isomer (39). Therefore both the steric and thermodynamic factors should favour formation of (37) in the disproportionation of the radical (89), relative to its formation in the disproportionation of the radical (90). However, the opposite was observed. The results can be attributed to preferential reactivity of axial β-hydrogens due to the influence of the stereoelectronic factor.

The yields of the cyclohexenes (40) and (41) obtained from disproportionation of c-5-tert-butyl-r-2-methylcyclohexyl radical (91) also indicate that the hydrogen atom transfer is stereoelectronically controlled. Loss of an equatorial β-hydrogen from the radical (91) can produce either 4-tert-butyl-1-methylcyclohexene (40) or c-6-tert-butyl-r-3-methylcyclohexene (41), while loss of an axial β-hydrogen can produce only the cis-cyclohexene (41) (Fig.II.6).



(41) (91) (40)

Fig.II.6

The preferential formation of the cis-cyclohexene (41) (Table II.1) can be attributed to preferential transfer of the axial β-hydrogen due to the influence of the stereoelectronic factor in the disproportionation reaction. However, in this case the result is not unambiguous as the effects of the steric and thermodynamic factors cannot be determined.

In view of the high yields of the cyclohexanes (42)-(47) relative to those of the cyclohexenes (1) and (35)-(41), it seems likely that in the disproportionation reactions of the substituted cyclohexyl radicals (86)-(91) with cyclohexyl radical (equations 24 and 26) hydrogen atom transfer from cyclohexyl radical (equation 26) is favoured. Although the extent of this study is insufficient to clearly delineate the reasons for this, it is worth noting that all four hydrogens adjacent to the semi-occupied p orbital in cyclohexyl radical may be abstracted from chair conformations of that radical in a reaction proceeding through a transition state formed by an initial coplanar interaction of the C — H bond undergoing fission and the adjacent semioccupied p orbital, whereas this is only true for the axial β-C — H bonds in the conformationally-fixed

cyclohexyl radicals (86)-(91). In light of this it is interesting that the yield of the cyclohexene (35) obtained from disproportionation of the radical (87), which has two axial β-C — H bonds, is considerably greater than the combined yields of the cyclohexenes (35) and (36) obtained from disproportionation of the radical (88), which has only one axial β-C — H bond. However, a similar result was not observed with the radicals (89) and (90) where the same effect might have been expected.

An alternative explanation for the high yields of the cyclohexanes (42)-(47) is that the cyclohexyl radicals (86)-(91) also react by hydrogen atom abstraction from solvent:

$$R^{\bullet} + C_6H_{12} \rightarrow R\text{-}H + C_6H_{11}^{\bullet} \qquad 29)$$

However, this seems unlikely as there is no apparent driving force for the reaction.

In summary, the results of this work clearly show that homolysis of a C — H bond adjacent to a radical centre is stereoelectronically controlled, proceeding more readily when the C — H bond undergoing fission and adjacent semioccupied p orbital are coplanar. Under these circumstances the transition state can be readily formed by coplanar interaction of the semioccupied p orbital and the σ* antibonding orbital of the bond undergoing fission.[4,8,9] These results agree with those previously reported by Agosta and Wolff,[41] and they also conform to the general pattern for C — S,[21] C — C,[9,25-27,35,181] and C — O[36,40] bond homolysis adjacent to a radical centre. However, no explanation is evident for the contradictory result of Livant and Lawler.[42]

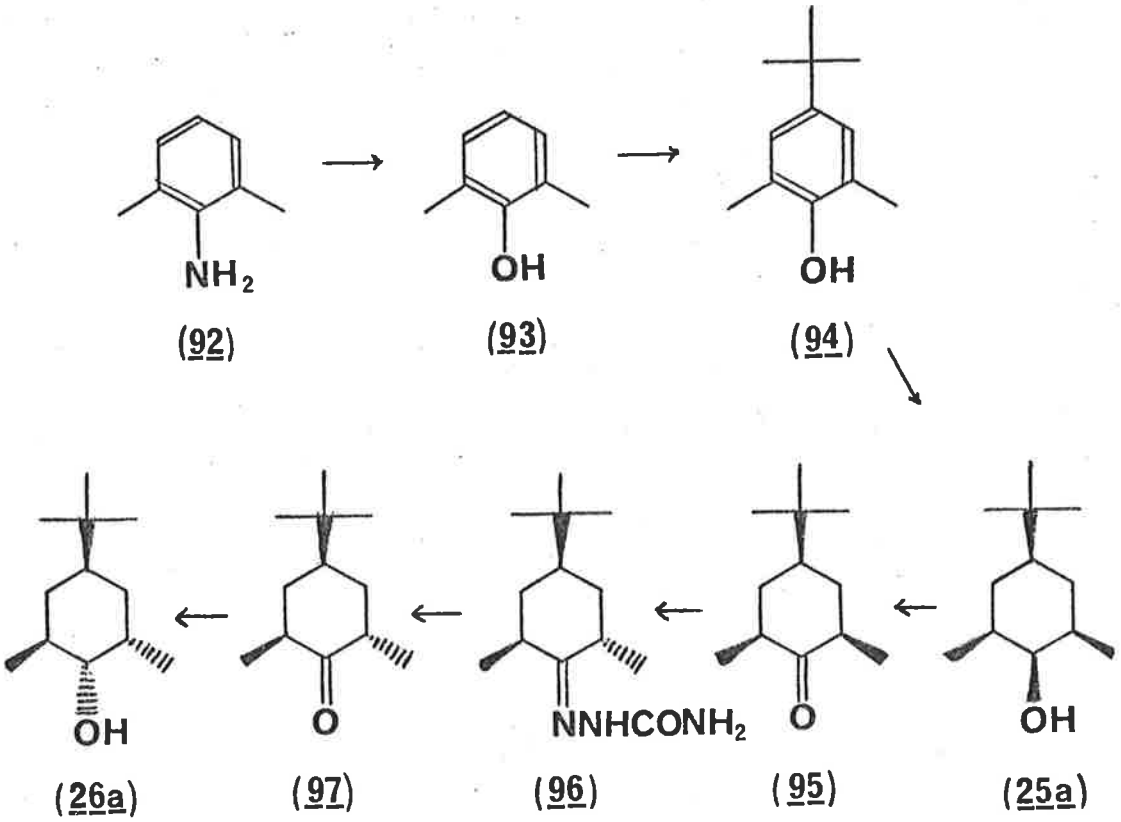
CHAPTER II.B Synthesis of Substrates.

The route by which c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) and t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a) were synthesized is outlined in Scheme II.1. The initial problem involved synthesis of a c-4-tert-butyl-r-2,t-6-dimethylcyclohexyl derivative suitable for preparation of the cyclohexanol (26a). Fortunately the cyclohexanol (25a) was obtained in the same reaction sequence.

Previously reported syntheses of c-4-tert-butyl-r-2,c-6-dimethylcyclohexanone (95) and c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) have been lengthy and have involved tedious preparative GLC separations of the final products.[107-109] These syntheses did not give pure (97) as some isomerization always occurred during preparative GLC purification.[109] These methods[107-109] were therefore considered unsuitable for the present synthesis. The use of a sample of the cyclohexanone (95) prepared from 4-tert-butyl-2,6-dimethylphenol (94) has been mentioned.[109] No details of this synthesis were given,[109] but the concept was used as the basis of the present work. A very useful general preparation of trans-2,3-dialkylcyclohexanones from a mixture of isomers, via formation of the intermediate semicarbazone, has been reported,[110] and this method has been used previously to prepare the cyclohexanone (97).[109] The approach outlined in Scheme II.1 therefore appeared to be a suitable method for obtaining the required cyclohexanol (26a).

Reaction of 2,6-dimethylaniline (92) with sodium nitrite in acid medium[111] gave the diazonium salt, which was decomposed by slow addition to refluxing dilute sulphuric acid[111] to give 2,6-dimethylphenol (93). Treatment of a tert-butanol solution of the phenol (93), with sulphuric acid gave 4-tert-butyl-2,6-dimethylphenol (94).[112]

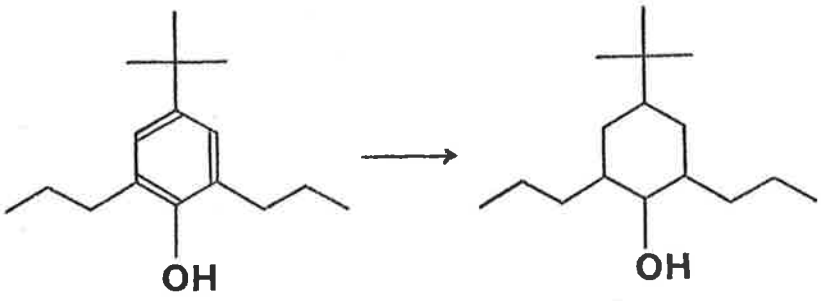
Reduction of the phenol (94) proved unexpectedly difficult. Catalytic hydrogenation of 4-tert-butyl-2,6-di-n-propylphenol (98) with



(92) (93) (94) (25a) (95) (96) (97) (26a)

Scheme II.1

platinum oxide in acetic acid has been found to give 4-tert-butyl-2,6-di-n-propylcyclohexanol (99) (Fig.II.7).[113]



(98) (99)

Fig II.7

However, hydrogenation of the phenol (94) by this method only once gave c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a), and then only in 15% yield. Other attempts gave only starting material. Attempted

catalytic hydrogenations with Raney nickel[114] in ethanol and in acetic acid, with hydrogen pressures ranging from 700-1800 psi, were also unsuccessful.

If the reaction conditions are sufficiently vigorous, Birch reduction of some phenols can occur.[115] However, the phenol (94) was stable to the reported reduction conditions.[115] This is probably due to the fact that the alkyl substituents retard reduction because they increase the high potential energy barrier for electron addition to the phenolate anion, needed to form the dianion radical intermediate.[116]

Reduction of the phenol (94) to the cyclohexanol (25a) was finally accomplished by catalytic hydrogenation with 5% rhodium on alumina in 95% aqueous ethanol, at 2500 psi and 100°, for 72h. At lower temperatures and pressures hydrogenation did not occur, and at higher temperatures the catalyst was deactivated. The reduction product was found to be homogeneous by GLC. Although the stereochemistry of this product was not critical to the overall synthetic scheme, it was determined by ^{13}C and ^{1}H NMR spectroscopy. The ^{13}C NMR spectrum was assigned to the chair conformation of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) by comparison of the observed chemical shifts with predicted values (Table II.2). The magnitude of the differences between the predicted and observed chemical shifts is small enough to indicate that the assigned stereochemistry and conformation of the cyclohexanol (25a) are correct. The ^{1}H NMR spectrum of (25a) is also consistent with the assigned structure. The narrow width of the resonance attributable to the equatorial proton at C-1 (δ3.43 ppm, multiplet)[119] is consistent with the assigned stereochemistry.[120]

Oxidation of the cyclohexanol (25a) by treatment with Jones' reagent[121] gave c-4-tert-butyl-r-2,c-6-dimethylcyclohexanone (95). The oxidation product was shown to be homogeneous by GLC. As with the cyclohexanol (25a), the stereochemistry of this product was not critical to the

Table II.2

^{13}C Chemical Shifts in the Cyclohexanols (25a) and (26a).[A]

Assignment	(25a)		(26a)	
	Predicted	Observed	Predicted	Observed
C-1	-	74.6[B]	-	78.8[B]
C-2	38.9[C]	37.4	36.8[D]	35.3
C-3	29.4[C]	28.5	30.6[D]	32.1
C-4	48.2[C]	47.7	41.9	40.1
C-5	29.4[C]	28.5	34.5[D]	33.1
C-6	38.9[C]	37.4	35.9[D]	34.6
Quaternary C	32.4[E]	32.4	32.1[E]	31.9
tert-Butyl $1^{o}C$	27.4[E]	27.6	27.5[E]	27.5
Methyl C at C-2	-	18.8[F]	19.1[G]	19.1
Methyl C at C-6	-	18.8[F]	-	12.2[H]

A. δc, ppm from TMS.

B. Chemical shifts of carbinyl carbons can not be predicted accurately. However, an axial hydroxyl tends to shield the carbinyl carbon more than an equatorial hydroxyl by approximately 5 ppm.[117a]

C. Calculations based on the reported chemical shifts of c-4-tert-butylcyclohexan-r-1-ol (100)[118] and the additivity parameters for methyl substitution of cyclohexanes.[117b]

D. Calculations based on the reported chemical shifts of t-4-tert-butylcyclohexan-r-1-ol (101)[118] and the additivity parameters for methyl substitution of cyclohexanes.[117b]

E. Chemical shifts of the relevant carbons in the cyclohexanols (100)

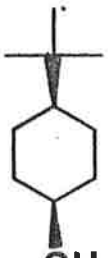
Table II.2 continued.

and (101).[118]

F. Typical ^{13}C chemical shift for an equatorial methyl carbon at C-2 in cyclohexanol.[117c]

G. Chemical shift of the methyl carbon in t-2-methylcyclohexan-r-1-ol (102).[117c]

H. Axial methyl carbons tend to be shielded more than equatorial methyl carbons in substituted cyclohexanols[117c] and cyclohexanes.[117d]



(100)

(101)

(102)

overall synthetic scheme, but it was determined by ^{13}C and ^{1}H NMR spectroscopy. The observed ^{13}C NMR chemical shifts correlate well with those predicted for the chair conformation of the cyclohexanone (95) (Table II.3). The small differences between the predicted and observed chemical shifts indicates that there is no appreciable deformation of the chair conformation. The ^{1}H NMR spectrum of the oxidation product is the same as that previously reported for the ketone (95).[107-109]

The homogeneity of the oxidation product is surprising as the equilibrium ratio of c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) to the cyclohexanone (95) has been reported as 1:9[109] and alternatively as 1:5.6,[107] and acid catalysed equilbration would have been expected under the reaction conditions. However, the previous synthesis of (95) from the phenol (94) also gave only the single stereoisomer.[109]

Conversion of the cyclohexanone (95) to its stereoisomer (97) was accomplished by reaction of (95) with semicarbazide hydrochloride and potassium acetate in methanol[110] to give the semicarbazone (96), which was treated with sodium nitrite in aqueous acetic acid[110] to give (97). The stereochemistry of the ketone (97) was determined on the basis of its ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum is identical to that previously reported for the cyclohexanone (97),[107-109] and the ^{13}C NMR spectrum is very similar to that expected for the chair conformation of this compound (Table II.3).

The stereochemistry of (97) is consistent with its mode of synthesis.[110] GLC analysis showed that (97) was contaminated with 1-2% of the cyclohexanone (95). This impurity may have resulted from a stereoisomeric impurity in the semicarbazone (96), or from isomerization during the reaction of the semicarbazone (96).

Reduction of the ketone (97) by treatment with lithium aluminium hydride gave t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a), which was shown by GLC to be contaminated with 1-2% of the cyclohexanol

Table II.3

^{13}C Chemical Shifts in the Cyclohexanones (95) and (97).[A]

Assignment	(95)		(97)	
	Predicted	Observed	Predicted	Observed
C-1	-	215.2[B]	-	218.5[B]
C-2	44.5[C]	44.3	38.4[C]	40.6
C-3	37.6[C]	38.2	36.2[C]	36.3
C-4	47.1[C]	47.0	41.0[C]	41.3
C-5	37.6[C]	38.2	34.5[C]	34.1
C-6	44.5[C]	44.3	44.7[C]	43.4
Quaternary C	32.4[D]	32.4	32.4[D]	32.2
tert-Butyl 1°C	27.6[D]	27.7	27.6[D]	27.5
Methyl C at C-2	14.6[E]	14.8	14.6[E]	15.1
Methyl C at C-6	14.6[E]	14.8	17.4[F]	17.5

A. δc, ppm from TMS.

B. Chemical shifts of carbonyl carbons vary considerably. However, an equatorial β-methyl substituent tends to shield the carbonyl carbon more than an axial β-methyl substituent by approximately 2.4 ppm.[122,123]

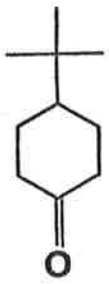
C. Calculations based on the reported chemical shifts of 4-tert-butylcyclohexanone (103)[122] and the additivity parameters for methyl substitution of cyclohexanones.[122,123]

D. Chemical shifts of the relevant carbons in 4-tert-butylcyclohexanone (103).[122]

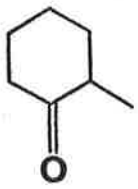
Table II.3 continued.

E. Predicted chemical shift for an equatorial methyl carbon at C-2 in 2-methylcyclohexanone (104).[123]

F. Predicted chemical shift for an axial methyl carbon at C-2 in 2-methylcyclohexanone (104).[123]



(103)



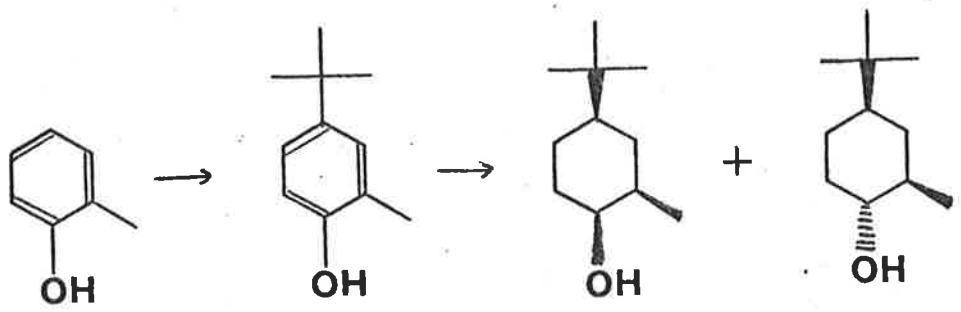
(104)

(25a), but was otherwise free of impurities. The stereochemistry of the alcohol (26a) was determined by analysis of its ^{1}H and ^{13}C NMR spectra. There is a good correlation between the observed ^{13}C NMR chemical shifts and those predicted for the chair conformation of the cyclohexanol (26a) (Table II.2). The ^{1}H NMR spectrum is consistent with the assigned stereochemistry in that it shows a clearly defined doublet of doublets centred at δ3.20 ppm which can be attributed to the proton at C-1 in the cyclohexanol (26a).[119] This represents a shift to lower field compared with the stereoisomer (25a), as expected,[119] and the doublet of doublets would be expected from coupling of the proton at C-1 with the protons at C-2 and C-6.

The stereochemistry of the cyclohexanol (26a) might have been expected. Because of the conformational preference of hydroxyl substituents,[124] reduction to give the hydroxyl group equatorially oriented would be the thermodynamically favoured reaction pathway. This mode of reduction would also be favoured by the steric factor as it involves approach of the reducing agent to the less hindered side of the double bond. Presumably the 1-2% impurity of the cyclohexanol (25a) arises from reduction of the traces of the cyclohexanone (95) present in the cyclohexanone (97). Formation of the cyclohexanol (25a) in this case may be due to steric hindrance to the alternative mode of reduction.

GLC retention times of the cyclohexanols (25a) and (26a) were consistent with their assigned structures as the cyclohexanol (25a), in which the hydroxyl substituent is equatorially oriented, had a shorter retention time than the cyclohexanol (26a), in which the hydroxyl substituent is axially oriented.[125]

The method used in the synthesis of c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a) is outlined in Scheme II.2.

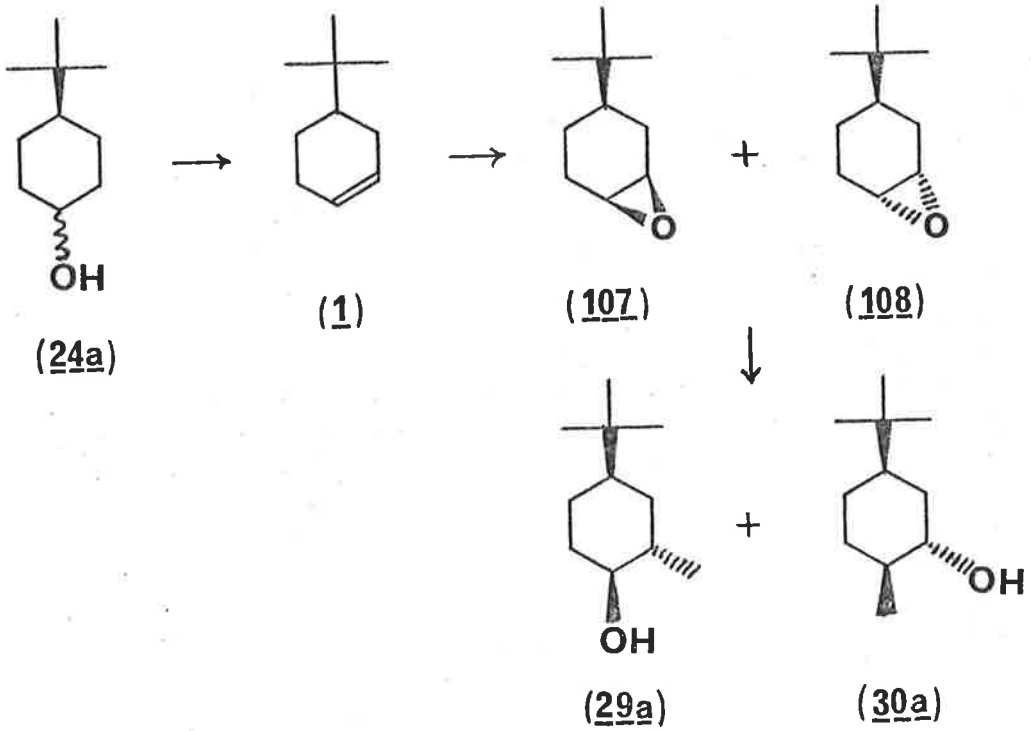


(105) (106) (27a) (28a)

Scheme II.2

Both reactions have previously been reported.[126,127] Treatment of a solution of 2-methylphenol (105) in phosphoric acid, with tert-butanol gave 4-tert-butyl-2-methylphenol (106).[126] Hydrogenation of a solution of (106) in acetic acid, using platinum oxide catalyst, gave a mixture of the cyclohexanols (27a) and (28a),[127] which were separated by chromatography on alumina.[127]

The route chosen for the synthesis of c-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (29a) and t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a) is outlined in Scheme II.3.



(24a) (1) (107) (108) (29a) (30a)

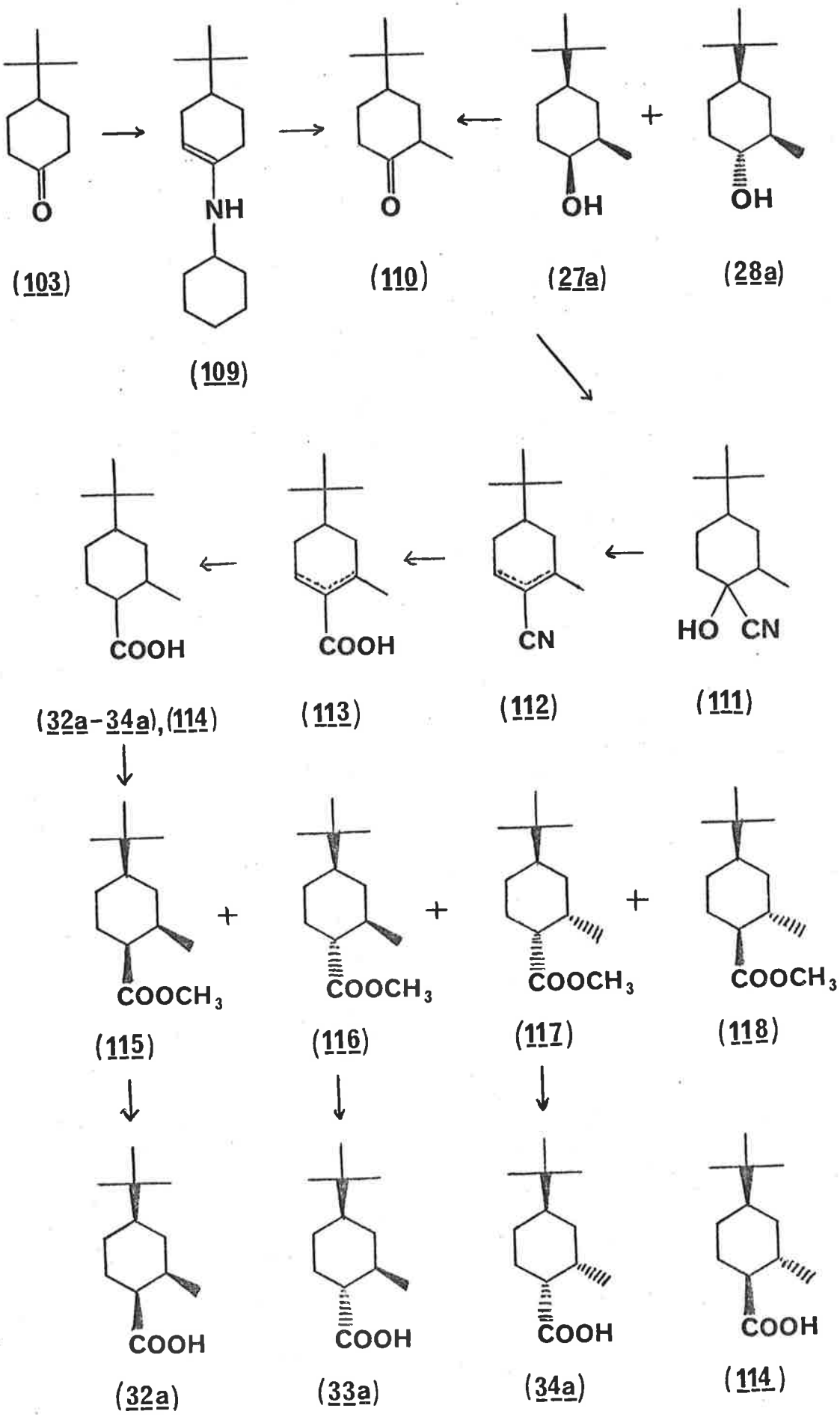
Scheme II.3

Reaction of 4-tert-butylcyclohexanol (24a) with methane sulphonyl chloride in pyridine gave 4-tert-butylcyclohexene (1).[128] Treatment of the cyclohexene (1) with m-chloroperbenzoic acid in ether gave a mixture of the cyclohexene oxides (107) and (108).[129] Reaction of the cyclohexene oxides (107)[130] and (108)[131] with dimethyl magnesium has been reported to give the cyclohexanols (29a)[130] and (30a),[131] respectively. In the present work a mixture of the cyclohexene oxides (107) and (108) was treated with dimethyl magnesium[130,131] to give a mixture of the cyclohexanols (29a) and (30a), which were separated by HPLC.

A synthesis of c-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (32a), t-4-tert-butyl-t-2-methylcyclohexane-r-1-carboxylic acid (33a), and t-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (34a), has been reported.[132] A slightly modified version of this method was used in the present work which is outlined in Scheme II.4.

4-tert-Butyl-2-methylcyclohexanone (110) required for this synthesis was obtained by two methods. One involved Jones' oxidation[121] of a mixture of the cyclohexanols (27a) and (28a). The other involved alkylation of the enamine (109).[108] The alkylation product also contained small amounts of (95) and (97). These were not separated as 4-tert-butyl-2-methylcyclohexanone (110) was converted to the cyanohydrin (111) by treatment of the bisulphite adduct of (110) with sodium cyanide,[132] and the cyclohexanones (95) and (97) do not form bisulphite adducts. Reaction of the cyanohydrin (111) with phosphorus oxychloride in pyridine afforded a mixture of isomers of the unsaturated nitrile (112).[132] Base hydrolysis of (112) gave a mixture of the unsaturated acids (113),[132] which was hydrogenated with platinum oxide in acetic acid to give a mixture of the carboxylic acids (32a)-(34a) and (114).[132]

The mixture of the carboxylic acids (32a)-(34a) and (114) was esterified to enable easier separation of the components. Carboxylic acids can be quantitatively converted to the corresponding methyl esters by reaction

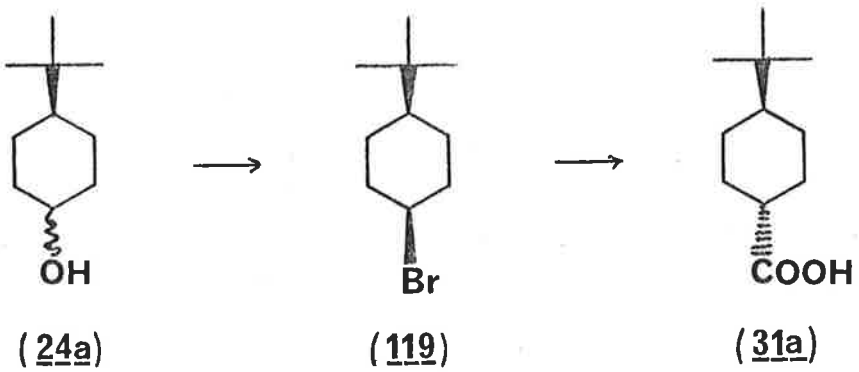

O
NH
O
OH
OH
(103)
(109)
(110)
(27a)
(28a)
COOH
COOH
CN
HO CN
(32a-34a),(114)
(113)
(112)
(111)
COOCH3
COOCH3
COOCH3
COOCH3
(115)
(116)
(117)
(118)
COOH
COOH
COOH
COOH
(32a)
(33a)
(34a)
(114)

Scheme II.4

of their sodium salts with methyl iodide in hexamethylphosphoramide at room temperature.[134] This method was used to esterify the mixture of the carboxylic acids (32a)-(34a) and (114), in preference to the reported reaction using diazomethane.[132] HPLC of the product mixture enabled separation of each of the esters (115)-(117). The ester (118) was not separated. It was only present to the extent of 5% in the crude ester mixture, and it could not be easily separated by HPLC as it was not cleanly separated from the ester (116). Also, no extra information would be obtained from the carboxylic acid (114) in the study described in Chapter II.A.

The esters (116) and (117) in which the substituent at C-1 is equatorially oriented, were hydrolysed to the corresponding carboxylic acids (33a) and (34a) by treatment with sodium hydroxide. The ester (115) in which the substituent at C-1 is axially oriented, was inert to these conditions. This might have been expected as similar results have been observed previously with related systems.[132,135] The ester (115) was hydrolysed to the carboxylic acid (32a) by treatment with hydrochloric acid.

The method used in the synthesis of t-4-tert-butylcyclohexane-r-1-carboxylic acid (31a) is outlined in Scheme II.5.



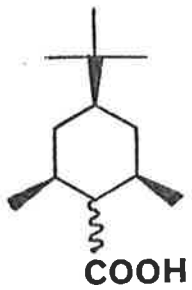
(24a) (119) (31a)

Scheme II.5

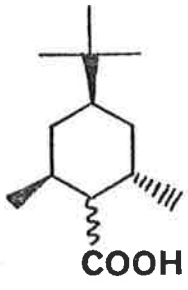
4-tert-Butylcyclohexanol (24a) was treated with phosphorus tribromide and pyridine in benzene, to give c-4-tert-butylcyclohex-r-1-yl bromide (119).

The Grignard reagent prepared from the bromide (119), reacted with carbon dioxide to give t-4-tert-butylcyclohexane-r-1-carboxylic acid (31a).

Attempted syntheses of the carboxylic acids (120) and (121) were unsuccessful. As previously stated the cyclohexanones (95) and (97) would

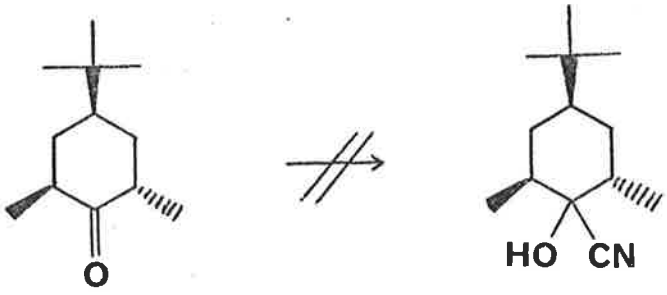


(120)



(121)

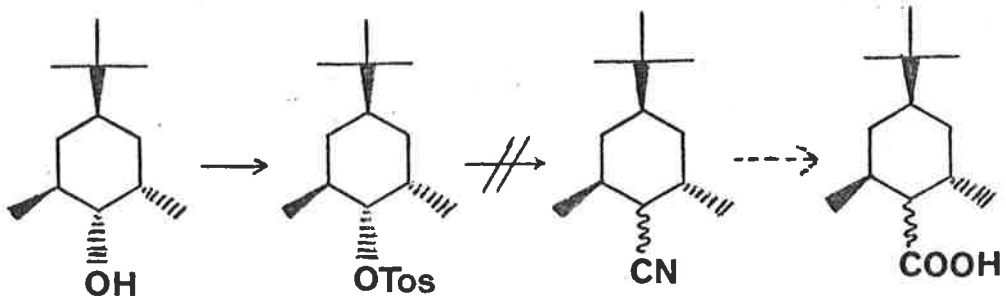
not form bisulphite adducts, and therefore a synthesis of the carboxylic acids (120) and (121) analogous to that outlined in Scheme II.4 was not feasible. Also, the cyclohexanone (97) did not react with acetonecyanohydrin,[136] and so the cyanohydrin (122) could not be prepared by this method (Fig.II.8).



(97) (122)

Fig.II.8

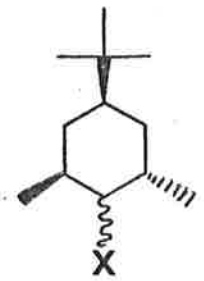
In another attempt to synthesize the carboxylic acid (121), the cyclohexyl toluene-p-sulphonate (84), prepared by reaction of the cyclohexanol (26a) with toluene-p-sulphonyl chloride,[137] was treated with sodium cyanide[138] in an attempt to form the nitrile (123), which might then be hydrolysed to the carboxylic acid (121) (Fig.II.9). However, elimination reactions occurred instead of the required substitution, and none of the required nitrile (123) was obtained.



(26a) (84) (123) (121)

Fig II.9

Attempts were also made to synthesize the cyclohexyl halide (124). It was hoped that (124) could be used as a precursor to the carboxylic acid (121) in a synthesis analogous to that outlined in Scheme II.5.



X=Cl or Br

(124)

Previous attempts to synthesize cyclohexyl halides of this type have been unsuccessful.[139,140] The rigidity and steric hindrance associated with this pseudoneopentyl system makes it prone to hydride shifts, alkyl rearrangements, and elimination reactions, rather than nucleophilic substitution reactions.[139,140] In the present study no successful synthesis of the cyclohexyl halide (124) was found, although a variety of methods were investigated which have been previously found to be suitable for the synthesis of alkyl halides from the corresponding alcohols in rearrangement prone systems.[141-143] In all cases investigated only olefinic products and starting material were recovered.

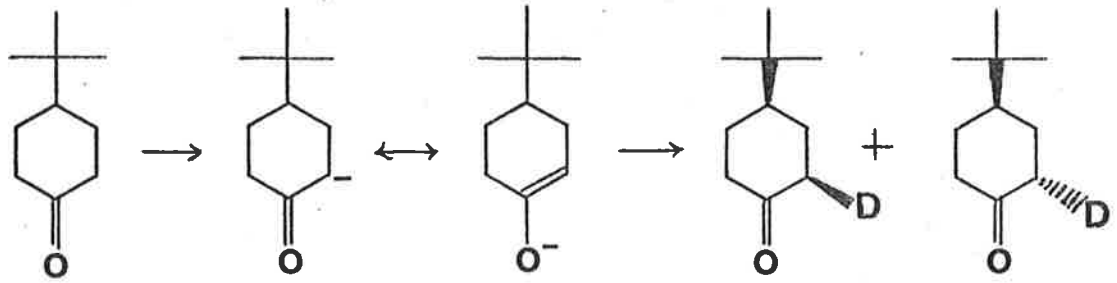
The reaction of alkyl radicals, generated by thermal decomposition of alkyl tert-butylperoxyglyoxalates, with halogenated solvents has been used to synthesize alkyl halides in rearrangement prone systems.[49] However, no attempt was made to synthesize the cyclohexyl halide (124) by this method as the yields reported in the previous work were often low, and the products were difficult to separate.[49] Also, in view of the difficulties experienced in other attempted syntheses of (124), subsequent reactions of the cyclohexyl halide (124) would be expected to give only rearrangement products and none of the desired carboxylic acid (121). The synthesis of the carboxylic acids (120) and (121) was not pursued further.

Reaction of the cyclohexanols (24a)-(30a) with oxalyl chloride[49] gave the corresponding cyclohexyl chloroglyoxalates (24b)-(30b), which reacted with tert-butyl hydroperoxide[49] to give the corresponding cyclohexyl tert-butylperoxyglyoxalates (24c)-(30c). Reaction of the cyclohexanecarboxylic acids (31a)-(34a) with thionyl chloride[144] gave the corresponding acid chlorides (31b)-(34b), which reacted with sodium peroxide[144] to give the corresponding diacyl peroxides (31c)-(34c). Owing to the potential explosion hazard none of the peroxides (24c)-(34c) were isolated. They were all prepared and reacted in dilute solutions.

The stereochemistry of the alkyl chloroglyoxalates (24b)-(30b), the acid chlorides (31b)-(34b), and the peroxides (24c)-(34c), was not determined. However, since formation of all of these involved reactions remote to the cyclohexyl ring, isomerization is not likely. The stereochemistry of the peroxides (24c)-(34c) is therefore assumed to be the same as that of the cyclohexanols (24a)-(30a) and the carboxylic acids (31a)-(34a) from which they were derived.

Attempts were also made to synthesize 4-tert-butylcyclohexyl derivatives labelled regiospecifically and stereospecifically with deuterium at the 2-position. Several methods directed towards the stereospecific α-deuteration of 4-tert-butylcyclohexanone (103) were investigated. The axial α-hydrogens of 4-tert-butylcyclohexanone (103) undergo base

catalysed hydrogen-deuterium exchange at a faster rate than the equatorial α-hydrogens (Fig.II.10).[105]



(103) (125) (126) (127) (128)

Fig.II.10 *

This is thought to be a stereoelectronic effect resulting from a preferred direction of deuteron capture by the 4-tert-butylcyclohexanone enolate anion (125).[145] This approach therefore appeared to be a suitable method for stereospecific axial α-deuteration of the cyclohexanone (103).

Treatment of 4-tert-butylcyclohexanone (103) with sodium deuteroxide in a deuterium oxide-dioxane mixture resulted in α-deuteration.[145] The extent and stereospecificity of these deuterations is shown in Table II.4. The stereospecificity was determined by integration of the ^1H NMR spectra of the products, which were recorded in the presence of $Eu(THD)_3$ so that the resonances of the axial and equatorial α-protons were completely separated.[146] The extent of reaction was calculated by integration of the ^1H NMR spectra, using the integration of the tert-butyl substituent as a standard. These results were consistent with those obtained by mass spectroscopy.

It can be seen from Table II.4 that the ratio of axial to equatorial deuterium incorporation was at most 2.35:1. Since this was considered

---

* Since the cyclohexanones (127) and (128) may react further, Fig.II.10 only indicates the initial reaction, and not the exact nature of the isolated products.

Table II.4

Results of Base Catalysed Deuterations of 4-tert-Butylcyclohexanone (103) in Deuterium Oxide-Dioxane at 20°C.

Experiment	[⁻OD] (mol lit^{-1})	Reaction Time (minutes)	Axial Deuterium Incorporation	Equatorial Deuterium Incorporation	% Exchange	Axial/Equatorial Deuterium Incorporation
1.	0.042	30	1.48	0.66	54	2.24
2.	0.040	30	1.25	0.60	46	2.08
3.	0.037	5	0.40	0.17	14	2.35
4.	0.037	15	0.87	0.42	32	2.07
5.	0.037	30	1.15	0.50	41	2.30

to be insufficient for an investigation of stereoelectronic effects, the results of modifying the experimental conditions were studied. The deuteration was investigated over a range of temperatures in a solvent mixture of deuterium oxide and 1,2-dimethoxyethane, and the results are shown in Table II.5. This solvent mixture has a low freezing point, thus enabling a study of the reaction at low temperatures.

From an examination of Table II.5 it is clear that the degree of stereospecificity decreases as the extent of reaction increases. This is not surprising as, for example, subsequent reactions of the monodeuterated cyclohexanones (127) and (128) would be expected to result in a decrease in the stereospecificity of the label. The stereospecificity of this reaction does not alter appreciably with changes in the reaction temperature and, as expected, the concentration of base affects only the

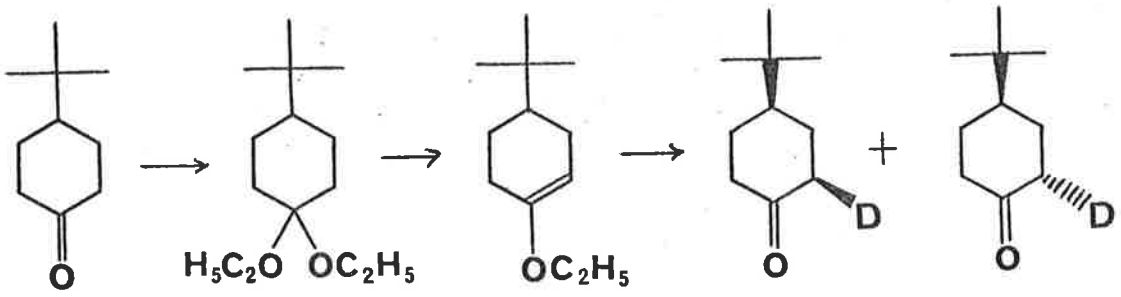
Table II.5

Results of Base Catalysed Deuterations of 4-tert-Butylcyclohexanone (103) in Deuterium Oxide-1,2-Dimethoxyethane.

Experiment	Temperature (°C)	[⁻OD] (mol lit^{-1})	Reaction Time (minutes)	Axial Deuterium Incorporation	Equatorial Deuterium Incorporation	% Exchange	Axial/Equatorial Deuterium Incorporation
6.	30	0.042	15	1.50	0.75	56	2.00
7.	30	0.042	30	1.88	1.45	83	1.30
8.	30	0.023	30	1.71	1.04	69	1.64
9.	30	0.023	60	1.86	1.48	84	1.26
10.	0	0.023	30	1.04	0.57	40	1.82
11.	0	0.023	65	1.50	0.95	61	1.58
12.	-30	0.023	15	0.39	0.17	14	2.29
13.	-30	0.023	30	0.71	0.43	29	1.65
14.	-30	0.023	60	0.88	0.52	35	1.69

rate of reaction and not the stereospecificity.

An alternative method for α-deuteration of 4-tert-butylcyclohexanone (103) was therefore investigated. A method has been reported for the synthesis of a mixture of the mono-α-deuterated 4-tert-butylcyclohexanones (127) and (128) in which the ratio of (127) to (128) is less than 1:9 (Fig.II.11).[133] Following this method, treatment of 4-tert-butylcyclohexanone (103) with ethyl formate in ethanol, in the presence of p-toluenesulphonic acid, gave 1,1-diethoxy-4-tert-butylcyclohexane (129).[133] Heating (129) with ammonium dihydrogen phosphate resulted in

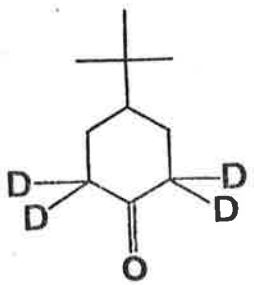


(103) (129) (130) (127) (128)

Fig.II.11

elimination of ethanol to give 1-ethoxy-4-tert-butycyclohexene (130),[133] which was treated with a mixture of deuteroacetic acid and deuterium oxide in 1,2-dimethoxyethane.[133] Analysis of the product mixture by ^{1}H and ^{2}H NMR spectroscopy and mass spectroscopy showed that it consisted of 4-tert-butylcyclohexanone (103) (14%), r-2-deutero-c-4-tert-butylcyclohexanone (127) (c. 39%), r-2-deutero-t-4-tert-butylcyclohexanone (128) (c. 45%), and several dideuterated 4-tert-butylcyclohexanones (2%). Therefore the deuteration was almost nonstereospecific. Although the reaction was repeated several times, no greater degree of stereospecificity was observed.

Acid catalysed hydrogen-deuterium exchange does occur under the conditions used in the reaction of (130) (complete deuterium loss was observed when 2,2,6,6-tetradeutero-4-tert-butylcyclohexanone (131) was heated on a steam bath with a large excess of 50% aqueous acetic acid for 6h).



(131)

However, mass spectra of the products of these deuterations indicate that the low degree of stereospecificity was not due to acid catalysed rearrangement of the deuterium label. The mass spectrum of a typical product mixture showed that it consisted of (103) (14%), the monodeuterated cyclohexanones (127) and (128) (84%), and several dideuterated cyclohexanones (2%). Acid catalysed reactions would be expected to yield more of the dideuterated ketones at the expense of the monodeuterated species (127) and (128).

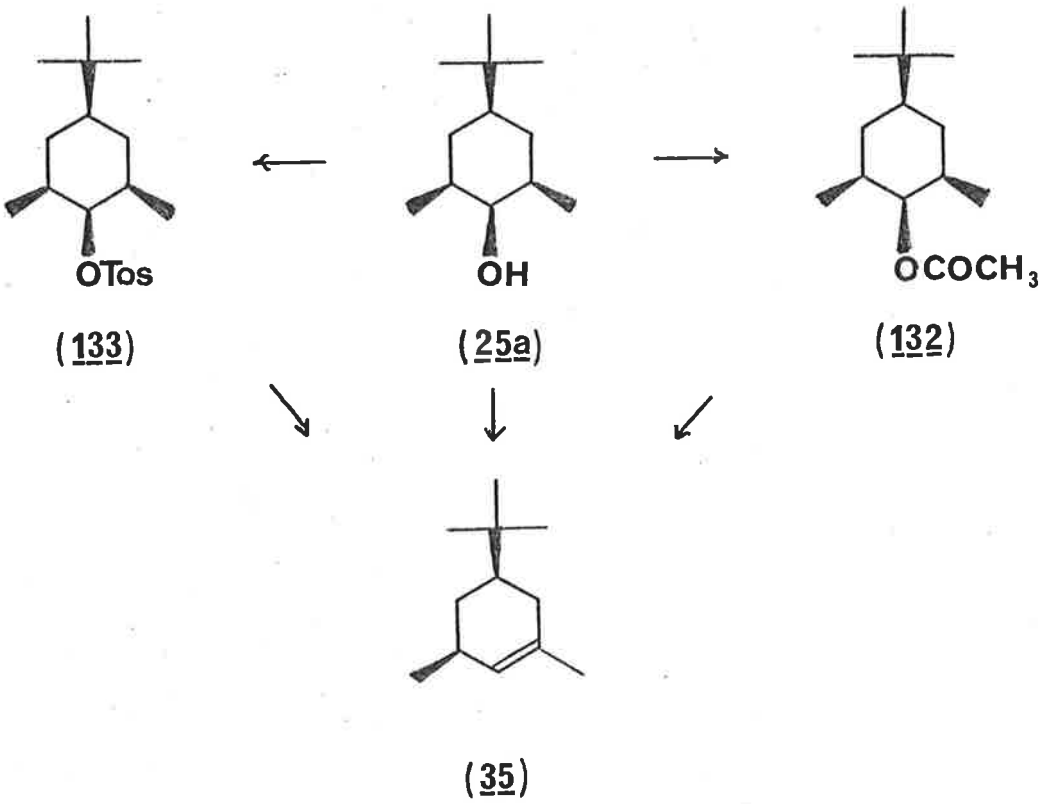
Although other methods have been reported for the synthesis of 4-tert-butylcyclohexyl derivatives containing a moderately stereospecific deuterium label at the 2-position,[147,148] these were not investigated as a sufficient number of 4-tert-butylcyclohexyl derivatives, labelled at C-2 and C-6 with axial and equatorial methyl substituents, had already been obtained for the study described in Chapter II.A.

CHAPTER II.C Synthesis of Products.

The methods used in the synthesis of c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) and t-5-tert-butyl-1,r-3-dimethylcyclohexene (36) are outlined in Scheme II.6. Reaction of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) with thionyl chloride in pyridine[149] gave the cis-cyclohexene (35). Also, treatment of the cyclohexanol (25a) with acetic anhydride and pyridine[137] gave c-4-tert-butyl-c-2,c-6-dimethylcyclohex-r-1-yl acetate (132), which was subjected to flash vacuum pyrolysis[127] to give the cis-cyclohexene (35). Finally, reaction of the cyclohexanol (25a) with toluene-p-sulphonyl chloride[137] gave c-4-tert-butyl-c-2,c-6-dimethylcyclohex-r-1-yl toluene-p-sulphonate (133), which reacted with potassium tert-butoxide in a mixture of benzene and dimethyl sulphoxide[150] to give the cis-cyclohexene (35).

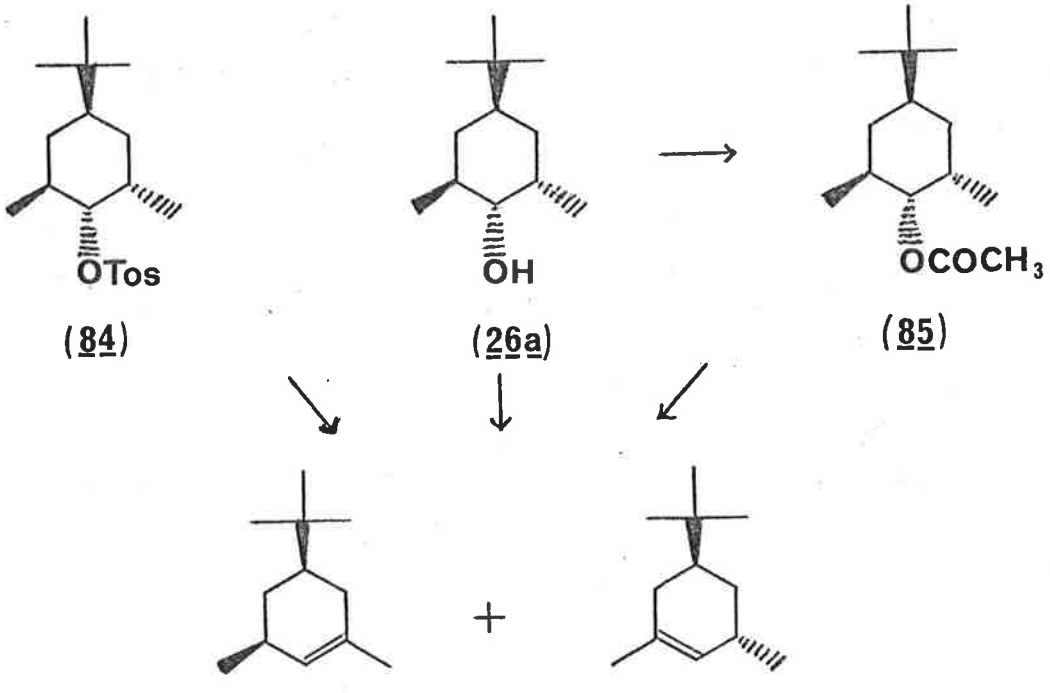
Reaction of t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a) with thionyl chloride in pyridine[149] gave a mixture of the cis-cyclohexene (35) (93%) and t-5-tert-butyl-1,r-3-dimethylcyclohexene (36) (7%). Flash vacuum pyrolysis[127] of t-4-tert-butyl-c-2,t-6-dimethylcyclohex-r-1-yl acetate (85), obtained by treatment of the cyclohexanol (26a) with acetic anhydride and pyridine,[149] gave a mixture of the trans-cyclohexene (36) (93%) and the cis-cyclohexene (35) (7%). These relative yields of (35) and (36) show that the acetate (85) reacts predominantly by cis-elimination, as expected.[151] Reaction of t-4-tert-butyl-c-2,t-6-dimethylcyclohex-r-1-yl toluene-p-sulphonate (84) with potassium tert-butoxide in a mixture of benzene and dimethyl sulphoxide[150] gave a mixture of the cis-cyclohexene (35) (91%) and the trans-cyclohexene (36) (9%). This reaction is consistent with previous reports[137,150] in that the toluene-p-sulphonate (84) reacts predominantly by trans-elimination.

The stereochemistry of the cyclohexenes (35) and (36) was determined by ^{13}C NMR spectroscopy. The excellent correlation between the



(133) (25a) (132)

(35)



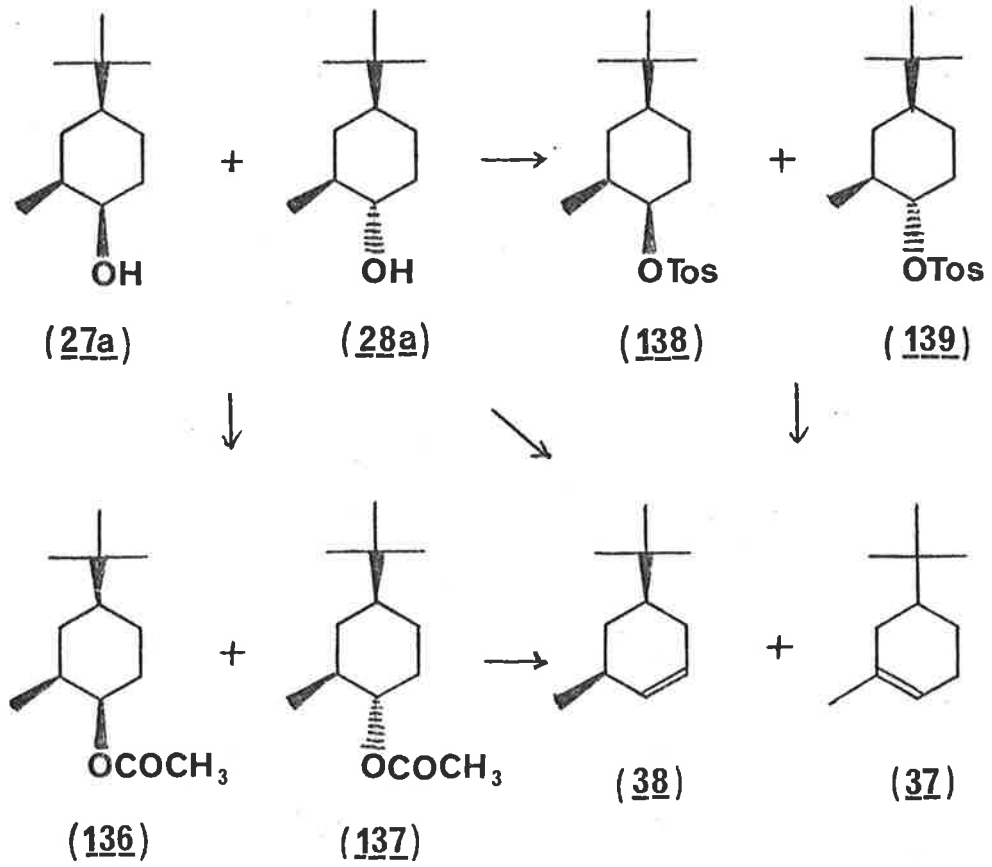
(84) (26a) (85)

(35) (36)

Scheme II.6

observed and predicted ^{13}C chemical shifts in these compounds (Table II.6) indicates that the assigned stereochemistry is correct in both cases.

The routes by which c-5-tert-butyl-r-3-methylcyclohexene (38) and 5-tert-butyl-1-methylcyclohexene (37) were synthesized are outlined in Scheme II.7.



Scheme II.7

Dehydration of a mixture of c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a) (64%) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a) (36%) by treatment with thionyl chloride in pyridine[149] gave a mixture of the disubstituted cyclohexene (38) (8%) and the trisubstituted cyclohexene (37) (92%). Treatment of a mixture of the cyclohexanols (27a) (64%) and (28a) (36%) with acetic anhydride and pyridine[149] gave a mixture of c-4-tert-butyl-c-2-methylcyclohex-r-1-yl acetate (136) (64%) and t-4-tert-butyl-t-2-methylcyclohex-r-1-yl acetate (137) (36%). When this mixture of the acetates (136) and (137) was subjected to flash vacuum pyrolysis[127]

Table II.6

^{13}C Chemical Shifts in the Cyclohexenes (35) and (36).[A]

Assignment	(35)		(36)	
	Predicted	Observed	Predicted	Observed
C-1	-	133.7[B]	-	133.5[B]
C-2	-	127.9[B]	-	126.9[B]
C-3	32.3[C]	32.4	27.8[C]	30.4[D]
C-4	33.7[C]	33.6	30.0[C]	30.0
C-5	45.5[C]	44.8	40.1[C]	39.1
C-6	31.6[C]	31.8	31.8[C]	32.2
Quaternary C	32.7[E]	32.4	32.7[E]	32.2
tert-Butyl 1°C	27.7[E]	27.3	27.7[E]	27.4
Methyl C at C-1	23.8[F]	23.7	23.8[F]	24.0
Methyl C at C-3	22.4[G]	22.2	-	21.0[H]

A. δc, ppm from TMS.

B. Assignments based on chemical shifts in 1-alkylcyclohexenes.[117e]

C. Calculations based on the reported chemical shifts in 1-methylcyclohexene (134)[117e, 117f] and the additivity parameters for methyl substitution of cyclohexanes,[117b] allowing for the effect of the tert-butyl substituent by considering the chemical shifts in tert-butylcyclohexane (42).[117g]

D. This variance from the predicted value is consistent with the axial methyl substituent at C-3 tending towards a pseudoequatorial orientation, caused by deformation of the chair conformation of the

Table II.6 continued.

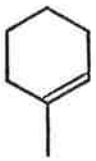
six-membered ring by the double bond.

E. Chemical shifts of the relevant carbons in tert-butycyclohexane (42).[117g]

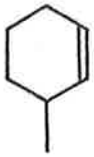
F. Chemical shift of the methyl carbon in 1-methylcyclohexene (134).[117f]

G. Chemical shift of the methyl carbon in 3-methylcyclohexene (135).[117f]

H. Axial methyl carbons tend to be shielded more than equatorial methyl carbons in substituted cyclohexanes.[117d]



(134)

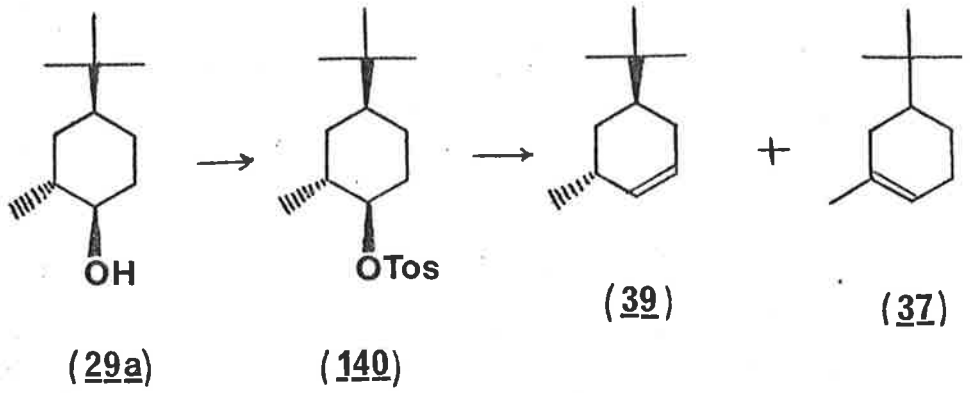


(135)

a mixture of the disubstituted cyclohexene (38) (32%) and the trisubstituted cyclohexene (37) (68%) was obtained. It is interesting to note that this yield of the cyclohexene (37) is too high for reaction to have occurred solely by cis-elimination from the acetates (136) and (137). Presumably trans-elimination can occur from distorted chair conformations of the acetates (136) and (137), to give the thermodynamically more stable cyclohexene (37).

Reaction of a mixture of the cyclohexanols (27a) (64%) and (28a) (36%) with toluene-p-sulphonyl chloride in pyridine[149] gave a mixture of c-4-tert-butyl-c-2-methylcyclohex-r-1-yl toluene-p-sulphonate (138) (64%) and t-4-tert-butyl-t-2-methylcyclohex-r-1-yl toluene-p-sulphonate (139) (36%). Treatment of this mixture of the toluene-p-sulphonates (138) and (139) with potassium tert-butoxide in a mixture of benzene and dimethyl sulphoxide[150] gave a mixture of the cyclohexenes (38) (12%) and (37) (88%). The relative yields of the cyclohexenes (38) and (37) obtained from this reaction are consistent with those reported for reactions of the individual toluene-p-sulphonates (138) and (139).[137] The yield of the cyclohexene (37) is too high for reaction to have occurred solely by trans-elimination from the toluene-p-sulphonates (138) and (139). However, it has previously been suggested that some cis-elimination occurs from boat conformations of the toluene-p-sulphonates (138) and (139), to give the thermodynamically more stable cyclohexene (37).[137,150] Each of the cyclohexenes (37) and (38) was separated from the mixtures by chromatography on silver nitrate impregnated silica.[152]

The method used in the synthesis of t-5-tert-butyl-r-3-methylcyclohexene (39) is outlined in Scheme II.8. This method was chosen since the preference for trans-elimination from cyclohexyl toluene-p-sulphonates[137,150] favours formation of the thermodynamically less stable cyclohexene (39) in the reaction of c-4-tert-butyl-t-2-methylcyclohex-r-1-yl toluene-p-sulphonate (140).

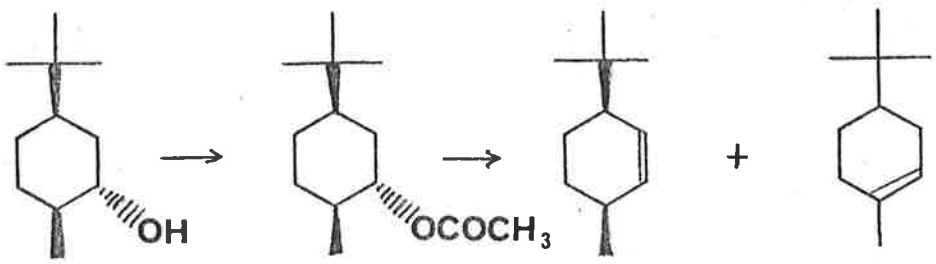


(29a) (140) (39) (37)

Scheme II.8

Treatment of the product obtained from the reaction of c-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (29a) with toluene-p-sulphonyl chloride in pyridine,[137] with potassium tert-butoxide in a mixture of benzene and dimethyl sulphoxide[150] gave mixture of the cyclohexene (39) (33%) and the trisubstituted cyclohexene (37) (67%). The cyclohexene (39) was separated from the mixture by chromatography on silver nitrate impregnated silica.[152] The relative yields of the cyclohexenes (39) and (37) obtained from this reaction indicate that some cis-elimination from the toluene-p-sulphonate (140) occurs, to give the thermodynamically more stable cyclohexene (37).

The method used to synthesize r-3-tert-butyl-c-6-methylcyclohexene (41) and 4-tert-butyl-1-methylcyclohexene (40) is outlined in Scheme II.9. This method was chosen because of the reported preference of cyclohexyl acetates to react by cis-elimination.[151] This favours formation of the thermodynamically less stable cyclohexene (41) in the reaction of t-5-tert-butyl-t-2-methylcyclohex-r-1-yl acetate (141).

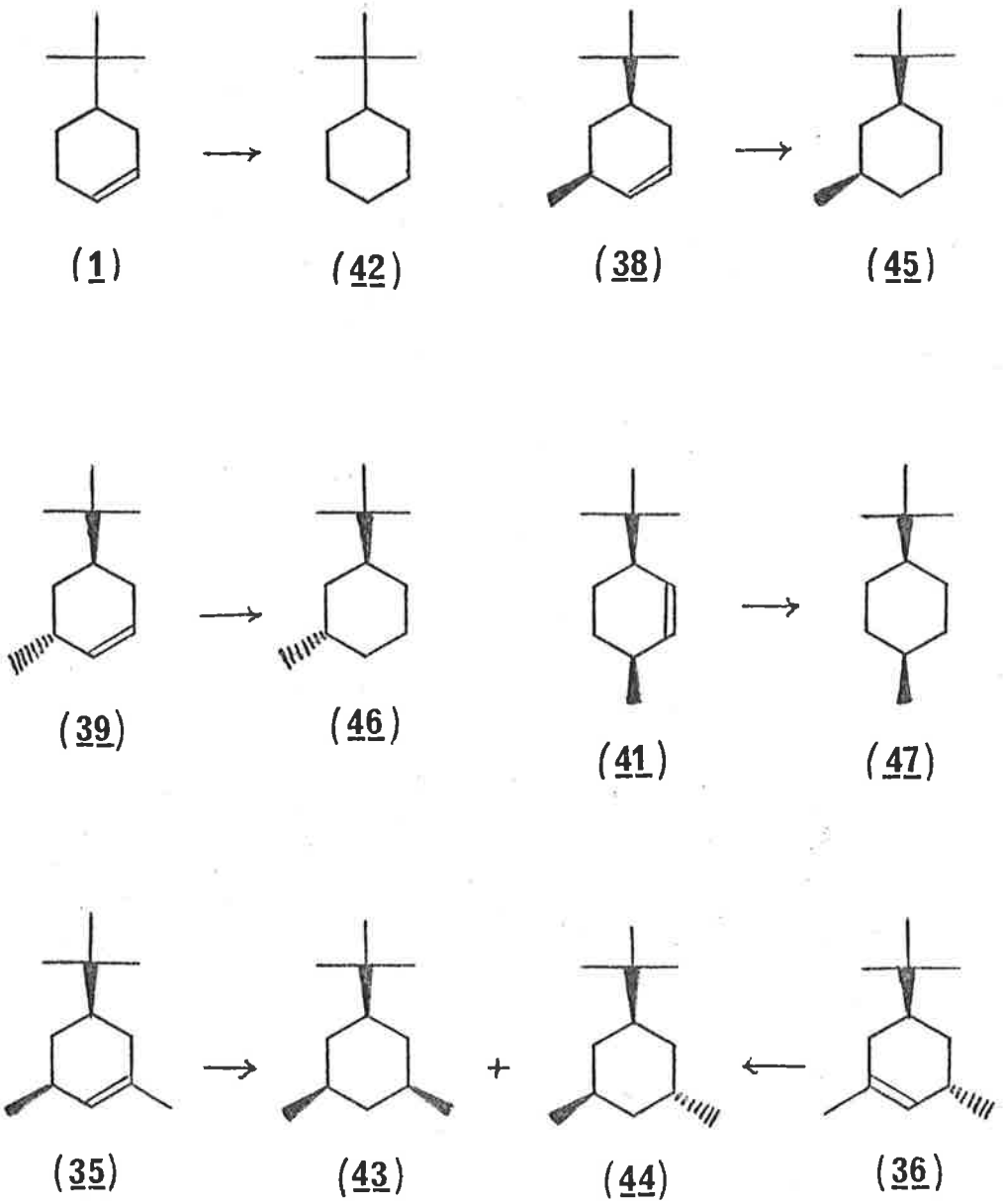


(30a) (141) (41) (40)

Scheme II.9

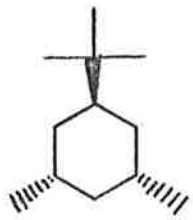
Flash vacuum pyrolysis[149] of the product obtained from the reaction of t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a) with acetic anhydride in pyridine,[149] gave a mixture of the cyclohexenes (40) (58%) and (41) (42%). The cyclohexenes (40) and (41) were separated by chromatography of this mixture on silver nitrate impregnated silica.[152] The relative yields of the cyclohexenes (40) and (41) indicate that all of the reaction does not occur by cis-elimination from the acetate (141).

The synthesis of the cyclohexanes (42)-(47) is outlined in Scheme II.10.



Scheme II.10

Catalytic hydrogenation of 4-tert-butylcyclohexene (1), c-5-tert-butyl-r-3-methylcyclohexene (38), t-5-tert-butyl-r-3-methylcyclohexene (39), and r-3-tert-butyl-c-6-methylcyclohexene (41), with platinum oxide in acetic acid gave 4-tert-butycyclohexane (42), r-1-tert-butyl-c-3-methylcyclohexane (45), r-1-tert-butyl-t-3-methylcyclohexane (46), and r-1-tert-butyl-c-4-methylcyclohexane (47), respectively. A similar reaction of c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) gave a mixture of two compounds in the ratio 89:11. In view of the yields of the cyclohexanes (45) and (46) obtained from hydrogenation of the cyclohexene (37),[21] these compounds were assigned the structures r-1-tert-butyl-c-3,c-5-dimethylcyclohexane (43) and r-1-tert-butyl-c-3,t-5-dimethylcyclohexane (44), respectively. Catalytic hydrogenation of a mixture of the cyclohexenes (35) (15%) and (36) (85%) afforded a mixture of the cyclohexanes (43) (12%) and (44) (88%). No third component was detected by GLC which suggests that hydrogenation of (36) to r-1-tert-butyl-t-3,t-5-dimethylcyclohexane (142) does not occur.



(142)

CHAPTER II.D A CIDNP Study.

When 4-tert-butylcyclohexyl tert-butylperoxyglyoxalate (24c) was dissolved in 1,4-dioxane (71) a spontaneous gaseous evolution was observed. This can be attributed to carbon dioxide formed by free radical decomposition of the peroxide (24c). The ^1H NMR spectrum of such a mixture showed a decaying emission triplet at δ7.1 ppm (Fig.II.12) which was considered to be a CIDNP signal. The nature of the compound responsible for this signal is not clear. However, no signal was observed which could be attributed to the CIDNP spectrum of the olefinic protons of 4-tert-butylcyclohexene (1).

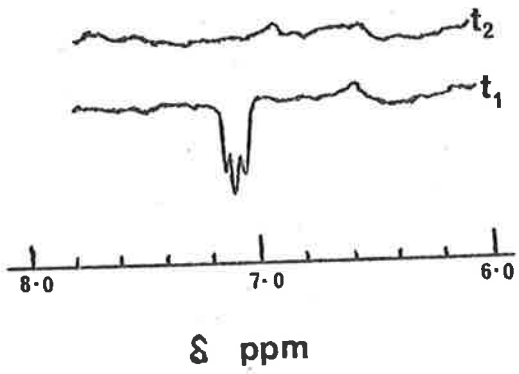


Fig.II.12 ^1H NMR spectrum of a solution of (24c) in 1,4-dioxane (71).

When the solvent was changed to carbon tetrachloride no spontaneous decomposition of the peroxide (24c) occurred, but the ^1H NMR spectrum of a warmed carbon tetrachloride solution of the peroxide (24c) showed a decaying emission singlet at δ7.3 ppm. (Fig.II.13). This CIDNP signal can be attributed to chloroform produced by hydrogen atom abstraction by trichloromethyl radical, itself produced by chlorine atom transfer from carbon tetrachloride. Again no signal was observed which could be attributed to the CIDNP spectrum of the olefinic protons of

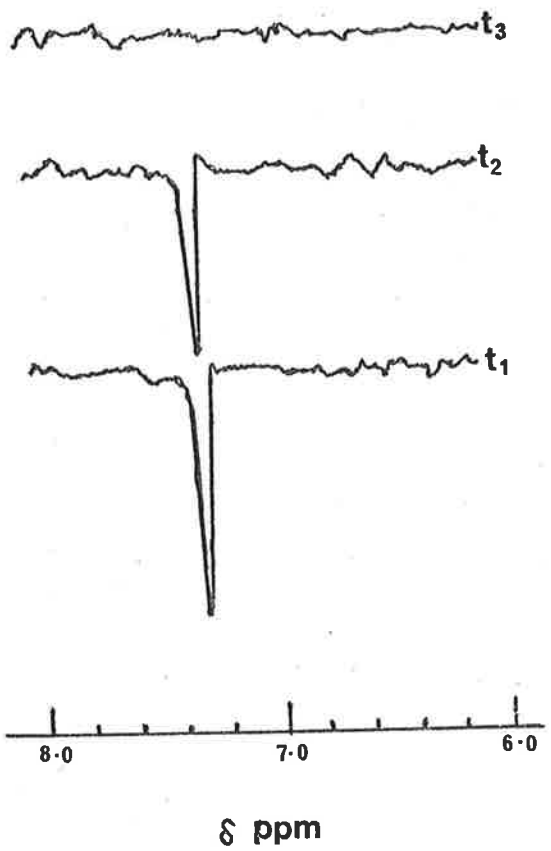


Fig.II.13 ^{1}H NMR spectrum of a warmed solution of (24c) in carbon tetrachloride.

4-tert-butylcyclohexene (1).

The ^{1}H NMR spectrum of a warmed cyclohexane solution of the peroxide (24c) showed a decaying absorption at δ5.6 ppm which might possibly be the CIDNP spectrum of the olefinic protons of 4-tert-butyl-cyclohexene (1) (Fig.II.14). Similarly, the ^{1}H NMR spectrum of a warmed cyclohexane solution of cyclohexyl tert-butylperoxyglyoxalate (48) showed a decaying complex absorption at δ5.6 ppm which may be attributed to the CIDNP spectrum of the olefinic protons of cyclohexene (Fig.II.15). In neither of these cases is it possible to determine the exact nature of the CIDNP signal as they are poorly resolved and coincide with the normal ^{1}H NMR signals of the products. However, the signal recorded in the latter case is clearly different to that observed by Livant and Lawler.[42]

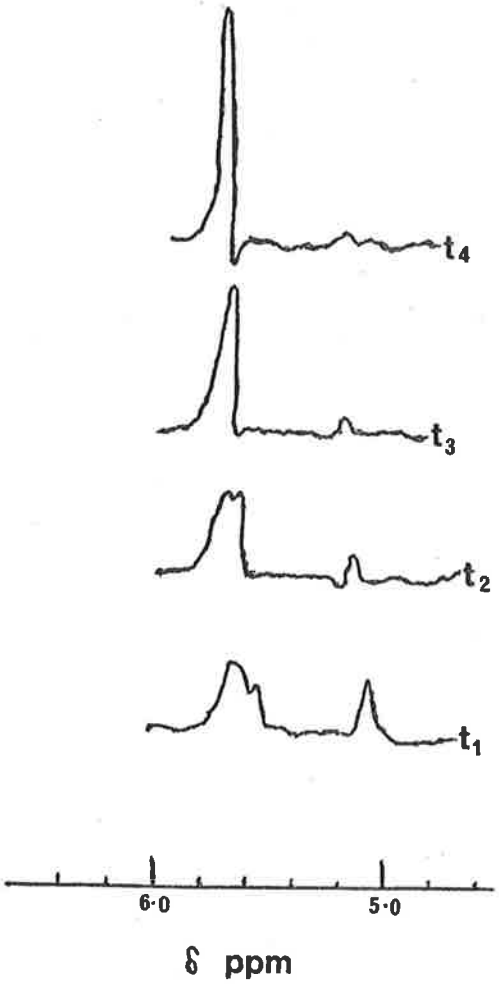


Fig.II.14 ^{1}H NMR spectrum of a warmed solution of (24c) in cyclohexane.

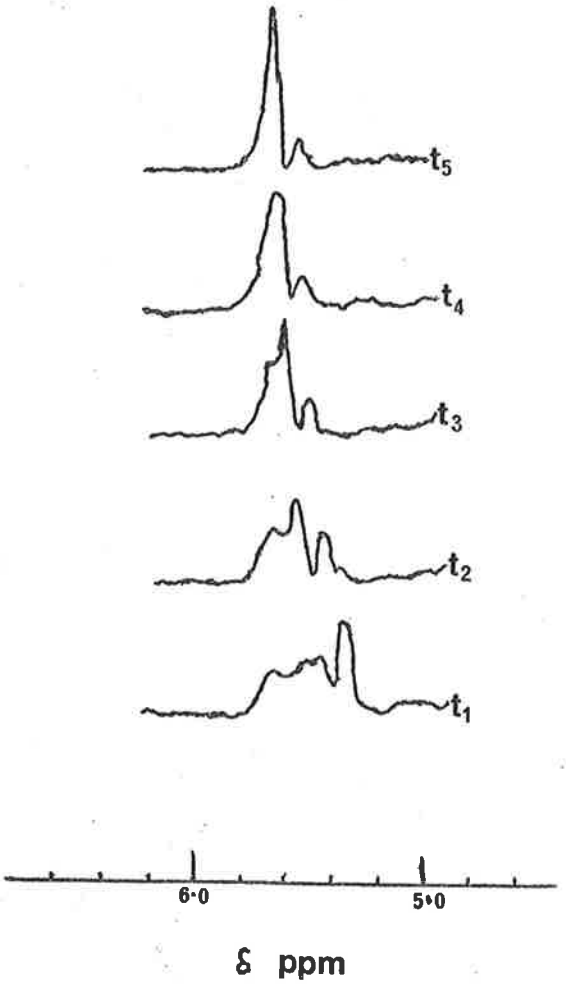


Fig.II.15 ^{1}H NMR spectrum of a warmed solution of (48) in cyclohexane.

CHAPTER III

Results and Discussion

Stereoelectronic Effects in Hydrogen Atom Abstraction from Substituted 1,3-Dioxanes and in Chlorine Atom Abstraction from Substituted 1,4-Dioxanes.

CHAPTER III.A A Kinetic Study of Some Reactions of Substituted 1,3-Dioxanes.

The relative rates of hydrogen atom abstraction from the dioxanes (60)-(67) were determined by measuring the relative rates of consumption of the substrates from mixtures. Many of the methods normally used to measure rates of hydrogen atom abstraction were found to be unsuitable in the present work because rapid epimerization of the dioxanes (64), (65), and (67), occurred. No epimerization of the dioxane (66) was detected, presumably because it has a much lower ground state energy than its epimer (67).[78]

During the copper-catalysed reaction of each dioxane (64), (65), and (67), with tert-butyl perbenzoate in refluxing benzene, rapid epimerization of the substrate was observed. This was probably catalysed by traces of benzoic acid produced in the reactions. Epimerization of (64), (65), and (67), was also observed when benzene solutions of benzophenone and each substrate were irradiated. In this system it is not likely that the epimerization is acid catalysed. The rate of epimerization was unchanged when pyridine was added to the reaction mixtures and when the reactions were conducted in the presence of potassium carbonate. Since epimerization only occurred while the reaction mixtures were being irradiated, it is probable that the isomerization is a photochemical process. An investigation of the nature of this epimerization will be discussed later in the text.

Attempts to determine the relative rates of hydrogen atom transfer from the dioxanes (60)-(67) by measuring the relative rates of consumption of each component from mixtures of the substrates reacting with di-tert-butylperoxyoxalate (143) were also unsuccessful. When solutions of the peroxide (143) (1.0M) and substrate (0.2-1.0M) were heated acetone was observed as the major reaction product and little reaction of the substrates occurred. Heating of the concentrated solutions of di-tert-

butylperoxyoxalate (143) which would be required for reaction of appreciable amounts of the dioxanes (60)-(67) was not attempted due to the possibility of explosion.[47]

Reactions of (143) with large excesses of the dioxanes (60)-(67) afforded considerable amounts of tert-butanol. Experiments conducted with the dioxane (61) showed that the inverse relationship between the ratio acetone/tert-butanol and the initial concentration of substrate was not strictly first order. The acetone/tert-butanol ratio did not increase as much as predicted (equation 4) when the initial concentration of (61) was decreased. This may be attributed to tert-butanol being formed by reactions of tert-butoxy radical other than hydrogen atom abstraction from (61), or to secondary reactions of acetone.

The relative yields of acetone and tert-butanol were determined for reaction of each of the 2-methoxy substituted dioxanes (64) and (65) with (143). To minimise the degree of error the same concentrations of peroxide (143) and of substrate (64) or (65) were used in each experiment. The acetone/tert-butanol ratios determined for these reactions indicate (equation 4) that the dioxane (64) reacts by hydrogen atom loss almost 5 times faster than its epimer (65). This measurement of the relative reactivities of (64) and (65) will be discussed later in the text.

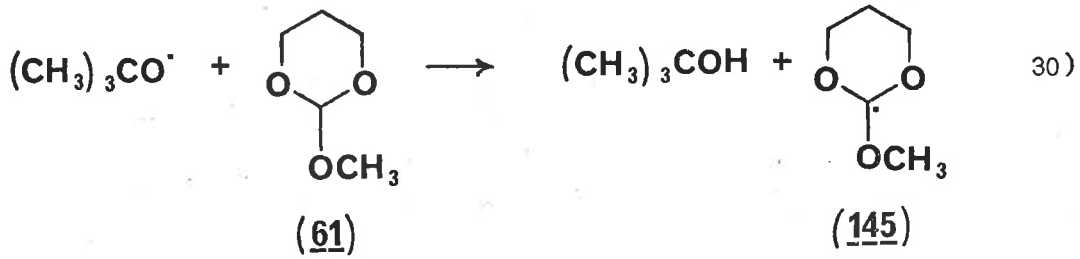
It was considered desirable to use a more direct method to measure the relative rates of hydrogen atom abstraction from the dioxanes (60)-(67). Irradiation of benzene solutions of mixtures of these substrates and di-tert-butyl peroxide was found to be unsuitable because epimerization of the dioxanes (64), (65), and (67), also occurred under these conditions. This was not prevented by the addition of pyridine to the reaction mixtures or by conducting the reactions in the presence of potassium carbonate, and it only occurred while the reaction mixtures were being irradiated. Thus it seems that this epimerization is more likely a photochemical process than an acid catalysed one.

In an attempt to prevent epimerization of the dioxanes (64), (65), and (67), the solvent used in these reactions was changed from benzene to carbon tetrachloride. Carbon tetrachloride should be a suitable solvent for these reactions as it has often been used as a solvent in reactions of compounds with tert-butylhypochlorite,[102,105,153-158] and in reactions designed to determine the relative rates of reaction of a variety of compounds with tert-butoxy radical.[105,153] However, carbon tetrachloride would be expected to be relatively more reactive than benzene towards reaction intermediates. Therefore, in reactions of the dioxanes (60)-(67), regeneration of the initial substrate and epimerization of (64), (65), and (67), might be prevented.

Di-tert-butyl peroxide photosensitizes the decomposition of carbon tetrachloride into trichloromethyl radicals and chlorine atoms.[159] The chlorine atoms may abstract hydrogen atoms to produce hydrogen chloride.[159] Production of hydrogen chloride in the photoinitiated reactions of the dioxanes (60)-(67) with di-tert-butyl peroxide in carbon tetrachloride would be expected to cause acid catalysed epimerization of the dioxanes (64), (65), and (67). Therefore pyridine was added to the reaction mixtures to remove any acid produced.

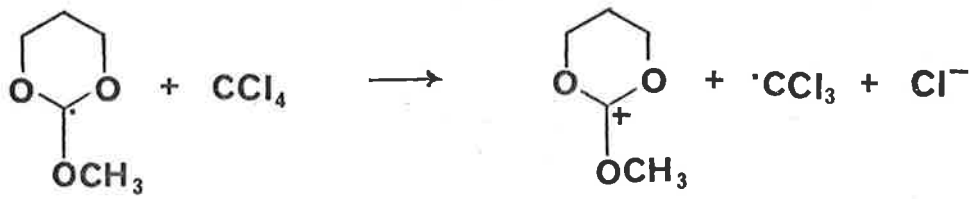
Solutions of di-tert-butyl peroxide and two or more of the dioxanes (60)-(67) in a mixture of carbon tetrachloride (90%) and pyridine (10%), were irradiated. The extent of reaction was determined by GLC analysis of aliquots taken from the reaction mixtures using a variety of standards as references. Using equation 1 the relative reactivities per equivalent hydrogen (ρ) of the dioxanes (60)-(67) were determined by this method (Method A). These values are shown in Table III.1. They were determined from repeated experiments and the experimental variation in each value was always less than ±5%. Separate experiments showed that under the conditions used in this study no epimerization of the dioxanes (64), (65), and (67), occurred.

Unfortunately it has not been possible to identify enough products from these reactions of the dioxanes (60)-(67) to clearly establish the reaction mechanism. Reaction of 2-methoxy-1,3-dioxane (61) afforded an off-white precipitate which was isolated and identified as N-methylpyridinium chloride (144) by comparison of its ^{1}H NMR spectrum with that of an authentic sample. Under the reaction conditions used, tert-butoxy radical or other radical species should abstract a hydrogen atom from C-2 in the dioxane (61):



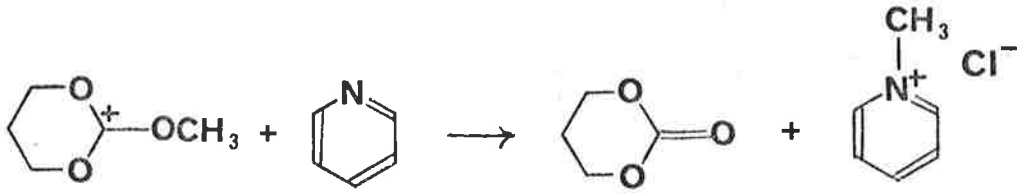
(61) (145) (30)

As radicals similar to the dioxan-2-yl radical (145) are good electron donors,[159,160] (145) would be expected to undergo a rapid election transfer reaction with carbon tetrachloride:



(145) (146) (31)

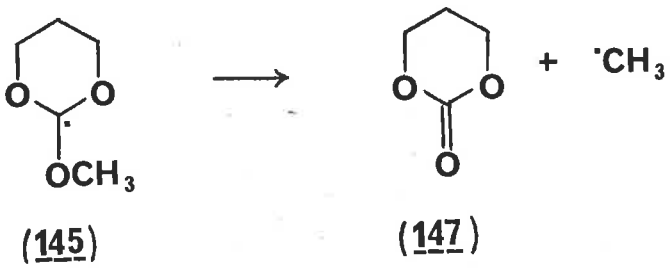
A similar reaction of hydroxymethyl radical with carbon tetrachloride has been reported previously.[160] The pyridinium salt (144) may have formed by reaction of the dioxonium ion (146) with pyridine:



(146) (147) (144) (32)

1,3-Dioxan-2-one (147) was not present in the product mixture, but an authentic sample of (147) was found to be unstable to the reaction conditions. Allyl alcohol was detected in the product mixture and decomposition of (147) to allyl alcohol has been previously reported.[161]

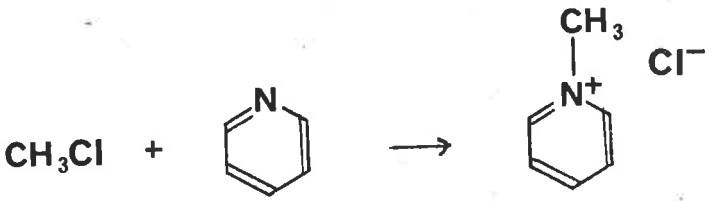
There are several alternative mechanisms which may account for the formation of the pyridinium salt (144). The dioxan-2-yl radical (145) might be expected[36-40] to undergo a β-scission reaction to give (147) and methyl radical:



(145) (147) 33)

Methyl radical may react by chlorine atom abstraction from carbon tetrachloride to give chloromethane, which may in turn react with pyridine to give the pyridinium salt (144):

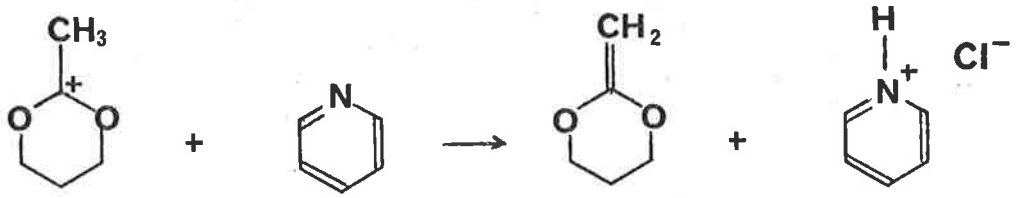
$$\cdot CH_3 + CCl_4 \longrightarrow CH_3Cl + \cdot CCl_3 \qquad 34)$$



(144) 35)

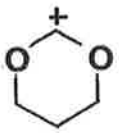
Methyl radical produced by intramolecular β-cleavage of tert-butoxy radical (equation 3) probably reacts in the same way. However, it is not likely that this latter process is entirely responsible for the formation of (144). Although (144) was still produced in reactions conducted in the absence of the dioxane (61), its rate of formation was much slower.

Reaction of 2-methyl-1,3-dioxane (62) gave an off-white precipitate which was identified as a mixture of the pyridinium salt (144) and pyridine hydrochloride (150) by analysis of its ^{1}H NMR spectrum. In this reaction (144) is probably produced by subsequent reactions of methyl radical formed by intramolecular β-cleavage of tert-butoxy radical (equations 3, 34, and 35). Pyridine hydrochloride (150) is probably produced by reaction of the dioxonium ion (148) with pyridine:



(148) (149) (150) 36)

In the reaction of 1,3-dioxane (60) an oily precipitate slowly formed. After isolation it was shown that this precipitate was only partially soluble in deuterium oxide. The soluble fraction was identified as the pyridinium salt (144) by analysis of its ^{1}H NMR spectrum. It was probably produced by reactions similar to those responsible for its production in the reaction of the dioxane (62) (equations 3, 34, and 35). The deuterium oxide insoluble fraction was not identified. However, it may arise from reactions of the dioxonium ion (151) since this cannot undergo the facile exocyclic β-scission reactions expected of the ions (146) and (148).



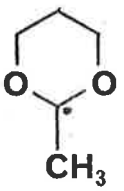
(151)

The products isolated from these reactions of the dioxanes (60)-

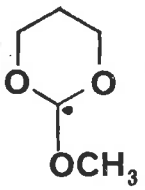
(62) are therefore compatible with a mechanism involving initial reaction of the substrates by hydrogen atom transfer from C-2. The relative rates of reaction of the dioxanes (60)-(67) determined in this way are therefore considered to indicate the relative reactivities of their C — H bonds at C-2. However, contributions from non-radical reactions, and from reactions involving radical attack at positions other than C-2, are possible sources of error in this study.

The relative rates of hydrogen atom abstraction from the dioxanes (60)-(67) were also determined by recording the EPR spectra of mixtures of these compounds and di-tert-butyl peroxide being irradiated in the cavity of an EPR spectrometer. The relative stationary concentrations of the radicals (145) and (152)-(156), derived from the dioxanes (60)-(67), were determined by integration of the EPR spectra and used to investigate the relative reactivities of the C — H bonds at C-2 in these compounds.

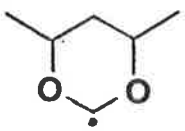
(152)



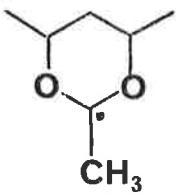
(153)



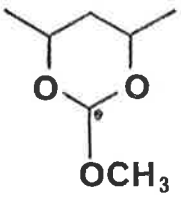
(145)



(154)



(155)



(156)

Under the conditions used to record the EPR spectra long range hyperfine splittings were not resolved. The 2-methoxy substituted radicals (145) and (156) derived from the dioxanes (61), (64), and (65), and the radicals (152) and (154) derived from the dioxanes (60) and (63), therefore showed only a broad singlet with g = 2.0028. The 2-methyl substituted radicals (153) and (155) derived from the dioxanes (62), (66), and (67), showed only a 1 : 3 : 3 : 1 quartet with g = 2.0029 and a splitting due to the β-protons of approximately 14.2G. These results accord well with previously reported spectral data for similar radicals.[69,71,162-164]

In some cases other signals were also observed in the EPR spectra. These could be attributed to radicals derived from the dioxanes (60)-(67) by hydrogen atom abstraction from positions other than C-2. However, their intensities were too small to allow spectral parameters to be determined. The intensities of these signals indicates that hydrogen atom transfer from the dioxanes (60)-(67) occurs predominantly by regiospecific transfer from the 2-position.

Experiments with 1,3-dioxane (60) showed that the best EPR spectrum of 1,3-dioxan-2-yl radical (152) was obtained with a 2 : 1 ($^{w}/_{w}$) peroxide to substrate ratio. With lower peroxide concentrations the signal was less intense, and at higher concentrations signals were observed in the EPR spectra which could not be attributed to radicals arising from the dioxane (60). Separate experiments with mixtures of the dioxanes (60) and (62), and (61) and (62), showed that the ratios of the EPR signals arising from the respective radicals were independent of the concentration of di-tert-butyl peroxide. However, the ratios of signals were directly proportional to the ratio of the substrates used, and repeated experiments gave ratios which deviated by less than ±10%.

To determine the relative rates of hydrogen atom abstraction from the dioxanes (60)-(67) the EPR spectra were recorded of mixtures of di-tert-butyl peroxide, 1,3-dioxane (60), and each of the 2-methyl substituted

dioxanes (62), (66), and (67), as well as of mixtures of di-tert-butyl peroxide, 2-methyl-1,3-dioxane (62), and each of the dioxanes (60), (61), and (63)-(65), being irradiated directly in the cavity of the spectrometer. These choices of substrates avoided the problem of overlapping EPR spectra. The relative reactivities per equivalent hydrogen (ρ) of the dioxanes (60)-(67) as determined by this method (Method B) are shown in Table III.1.

These values of ρ are only accurate if all of the radicals (145) and (152)-(156) decay at the same rate (page 20). Minor variations in their decay rates may be a source of error in this study. Preferential reaction of the more reactive substrate from a mixture would decrease its relative concentration with respect to the other substrate. Since a non-flow technique was used in these experiments, the relative concentrations of the substrates at the time the spectra were recorded might therefore be expected to be slightly different from the initial values. This affect should result in the range of values of ρ determined by this method being somewhat lower than the true value.

Separate experiments showed that no detectable epimerization of the dioxanes (64), (65), and (67), occurred under the conditions used to record the spectra.

The values of ρ determined by the two methods are very similar (Table III.1). The correlation between the two sets of results is certainly sufficient to indicate that the proposed mechanistic schemes are correct. Therefore major differences in the reaction rates of the dioxanes (60)-(67) may be considered to indicate differences in the relative reactivities of the C — H bonds at C-2 in these compounds. The minor variations between the two sets of results probably arise from the sources of error already discussed, but the accuracy of these results is insufficient for a detailed analysis.

In view of the relative reactivities of the 2-methoxy substituted

Table III.1

Relative Reactivities per Equivalent Hydrogen (ρ) to Hydrogen Atom Abstraction from C-2 in the Dioxanes (60)-(67).

Substrate	ρ	
	Method A	Method B
(60)	1.0	1.0
(61)	0.6	0.4
(62)	1.5	2.4
(63)[A]	2.6	1.6
(64)	3.4	1.4
(65)	0.3	0.16
(66)	2.8	2.1
(67)	0.25	0.3[B]

A. The dioxane (63) has only one equivalent hydrogen at C-2.

B. This value has been corrected for the epimeric impurity in the sample of (67) used.

dioxanes (64) and (65), and the 2-methyl substituted dioxanes (66) and (67), it is clear that the C — H bonds at C-2 in the dioxanes (64) and (66) are much more reactive than those in their respective epimers (65) and (67). This conclusion could also have been drawn for the dioxanes (64) and (65) from the investigation of the reaction of each of these compounds with di-tert-butylperoxyoxalate (143) described above (page 72). Since the preferred conformations of the dioxanes (64) and (66) are those in which the substituent at C-2 is equatorially oriented,[78-80] while those of the dioxanes (65) and (67) have the substituent at C-2 axially oriented[78-80] (page 18), these results clearly demonstrate that the axial C — H bonds at C-2 in the dioxanes (64) and (66) are more reactive than the equatorial C — H bonds at C-2 in the dioxanes (65) and (67).

The greater reactivity of the dioxanes (64) and (66) as compared to their respective epimers (65) and (67), cannot be associated with the differences between the ground state energies of these compounds. Although the less stable 2-methoxy substituted dioxane (64)[79] reacts preferentially, so does the more stable 2-methyl substituted dioxane (66).[78] Since the ratio of the reactivities of the 2-methyl substituted dioxanes, ρ (66)/ρ (67), is similar to that of the 2-methoxy substituted dioxanes, ρ (64)/ρ (65), it is unlikely that the latter can be associated with conformational change about the exocyclic C — O bond. It therefore seems likely that the enhanced reactivity of the axial C — H bonds at C-2 in the dioxanes (64) and (66), and of the axial C — H bonds adjacent to oxygen in the systems previously studied,[38,70] is a direct consequence of the stereoelectronic factor which arises because of favourable interactions between the bond being broken and the filled non-bonding orbitals on adjacent oxygen atoms.

If it is assumed that the two lone pairs of electrons on oxygen are nonequivalent,[66-68] then in the 1,3-dioxane system the axial C — H bond at C-2 has a much greater degree of coplanarity with the adjacent oxygens' p-type non-bonding orbitals than does the equatorial C — H bond.

The enhanced reactivity of the axial C — H bond at C-2 in the dioxanes (64) and (66) may therefore be attributed to stabilization of the transition state by overlap of the σ* antibonding orbital of the bond undergoing fission and the p-type orbital on each adjacent ring oxygen.

The results can be similarly rationalized by considering ethereal oxygens to be sp^3 hybridized.[38,70,165,166] In the 1,3-dioxane system each oxygen would then have one non-bonding orbital disposed in an antiperiplanar orientation with respect to the axial C — H bond at C-2, but there would be no such relationship between the equatorial C — H bond at C-2 and the oxygens' non-bonding orbitals. Using this model the enhanced reactivity of the axial C — H bond at C-2 in the dioxanes (64) and (66) can be attributed to stabilization of the transition state by favourable overlap of the σ* antibonding orbital of the bond undergoing fission and one of the non-bonding orbitals on each adjacent ring oxygen.

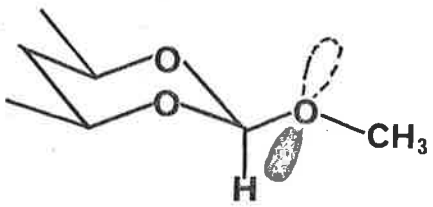
Since the relative reactivities of the 2-methoxy substituted dioxanes (64) and (65), and of the 2-methyl substituted dioxanes (66) and (67), can be attributed to preferential reactivity of the axial C — H bond at C-2 in the 1,3-dioxane system, the reactivity of r-4,c-6-dimethyl-1,3-dioxane (63) may be attributed predominantly to fission of its axial C — H bond at C-2. The similarity between the ρ value of this compound and those of the 2-methyl substituted dioxanes (62) and (66), in which the methyl substituents are equatorially oriented in the preferred conformations,[78] indicates that the introduction of an equatorial methyl substituent at C-2 in a 1,3-dioxane has little effect on the reactivity of the axial C — H bond at that position.

The similarity of the ratio of reactivities of the 2-methyl substituted dioxanes, ρ (66)/ρ (67), to that of the 2-methoxy substituted dioxanes, ρ(64)/ρ (65), indicates that axial and equatorial methoxy substituents affect the rate of hydrogen atom abstraction at C-2 to approximately the same extent as axial and equatorial methyl substituents.

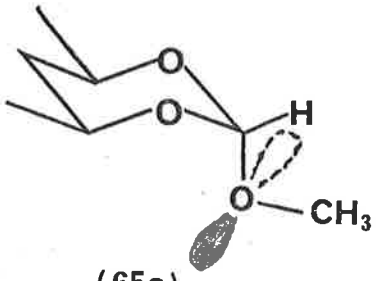
The low reactivity of 2-methoxy-1,3-dioxane (61) relative to the unsubstituted dioxane (60) and the 2-methyl substituted dioxane (62) may be attributed to the fact that the preferred conformation of (61) has the methoxy substituent axially oriented.[79]

The fact that neither axial nor equatorial methoxy substituents at C-2 in 1,3-dioxanes dramatically affect the reactivity of the remaining C — H bond at that position, implies that in compounds such as (64) and (65) the methoxy substituent adopts conformations in which the stereoelectronic interactions between the C — H bond and the lone pairs of electrons on substituent oxygen are at a minimum. This may be rationalized by considering the anomeric interactions involved.

If the lone pairs on oxygen are not equivalent,[66-68] then the dioxanes (64) and (65) would be expected to adopt the conformations (64a) and (65a) respectively, in which there are two favourable anomeric interactions between the substituent oxygen's p-type orbital and the β,γ-C — O bonds of the ring. Presumably these two anomeric interactions are of sufficient magnitude to outweigh any unfavourable steric interactions between the O — CH_3 and C — H bonds.

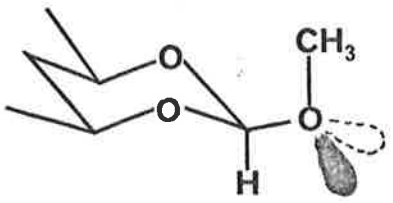


(64a)

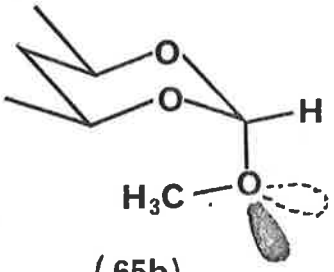


(65a)

If, on the other hand, the non-bonding orbitals on oxygen are sp^3 hybridized,[38,70,73,165] then the dioxanes (64) and (65) would be expected to adopt the conformations (64b) and (65b) respectively, in which the two non-bonding orbitals on substituent oxygen are both almost antiperiplanar to C — O bonds of the ring. This model is somewhat less attractive



(64b)

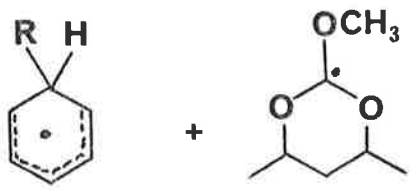


(65b)

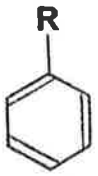
as in (65b) there is a strong non-bonded interaction between the o-methyl group and the axial protons at C-4 and C-6.

However, regardless of which model more accurately describes the hybridization of the non-bonding orbitals on oxygen, in the conformations of (64) and (65) in which there are the most favourable anomeric interactions, there is no favourable stereoelectronic interaction between the lone pairs of electrons on substituent oxygen and the C — H bonds at C-2.

It was stated above that irradiation of benzene solutions of the dioxanes (60)-(67) and benzophenone resulted in epimerization of (64), (65), and (67) (page 71). Two possible mechanisms of this epimerization were investigated. When benzene has been used as a solvent for free-radical transformations, products arising from aromatic substitution reactions have sometimes been formed.[39,81,166] These reactions proceed *via* intermediate substituted cyclohexadienyl radicals, which in the system used here might be expected to react by hydrogen atom transfer[39,81,166] to the dioxanyl radical (156), resulting in the formation of (64) and (65):

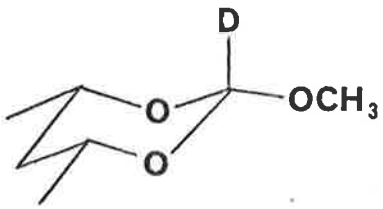


(156)

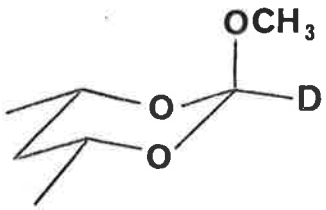


+ (64) + (65) 37)

To investigate this possibility a solution of the dioxane (64) and benzophenone in perdeuterobenzene, was photolyzed. Although rapid epimerization of (64) occurred, neither of the deuterated species (157) nor (158) was formed. This precludes the participation of solvent in the reaction.

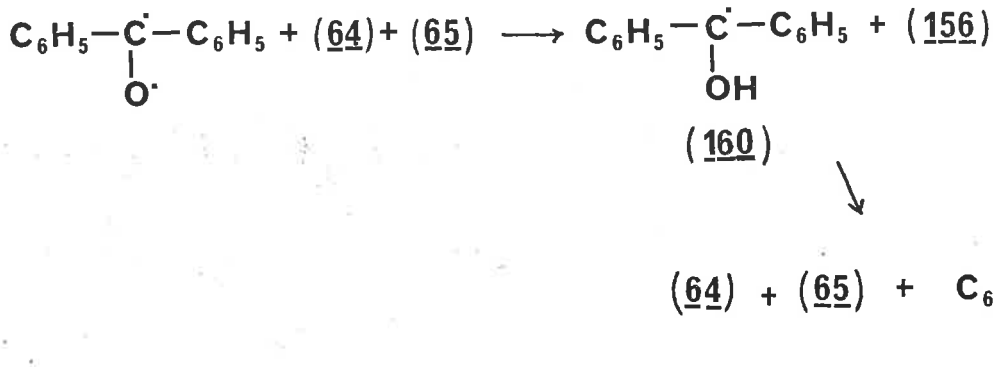


(157)



(158)

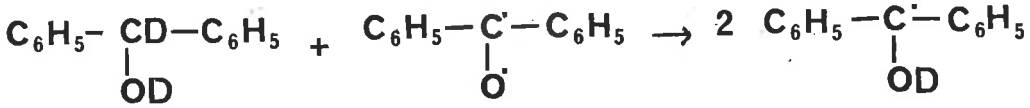
The alternative mechanism considered for the epimerization is hydrogen atom abstraction from the dioxanes (64), (65), and (67), by triplet benzophenone, followed by hydrogen atom transfer from the radical (160) to the intermediate dioxanyl radical (155) or (156):



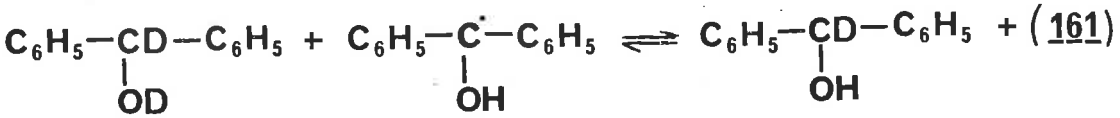
38)

This mechanism seemed feasible in view of the previously reported intramolecular hydrogen atom transfer reactions of triplet ketones.[167-170]

To test the validity of this mechanism it was decided to add the deuterated benzhydrol (159) to the reaction mixtures. Deuterium atom transfer from (159) to triplet benzophenone, and proton-deuteron exchange between (159) and (160), would produce the deuterated radical (161):

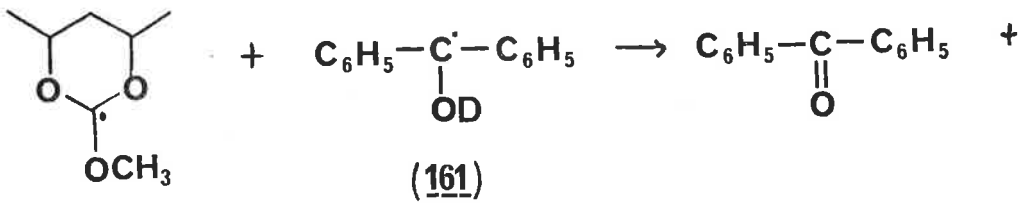


(159) (161) 39)



(159) (160) 40)

Reaction of (161) with the dioxanyl radical (156) would then be expected to produce the deuterated dioxanes (157) and (158):



(156) (161) (157) + (158) 41)

When a mixture of the dioxane (65), benzophenone, and the deuterated benzhydrol (159), in benzene was photolyzed, epimerization of (65) occurred. An ^{2}H NMR spectrum of the product mixture showed that the deuterated dioxanes (157) and (158) were formed in the ratio 2:1 in favour of the less stable epimer (157). It therefore seems that hydrogen atom transfer from (161) to the dioxanyl radical (156) does occur.

The ratio of the deuterated species (157) and (158) produced in this reaction is interesting. It confirms that the epimerization of (65) is not acid catalysed as this would have produced predominantly the more stable dioxane (158). The preferential axial deuterium incorporation to

form the less stable deuterated species (157) indicates that deuterium atom transfer to the intermediate radical (156) is stereoelectronically controlled. The ratio of (157) to (158) in the product mixture is probably much less than the stereospecificity of deuterium atom transfer to (156) as subsequent reaction of (157) and (158) would be expected to decrease the stereospecificity of the deuterium label.

It is interesting to note that epimerization of (65) occurred much more readily than formation of (157) and (158). One explanation of this is that the concentration of the deuterated radical (161) in the reaction mixture is much lower than the concentration of the undeuterated species (160). This implies that the reaction of triplet benzophenone with the deuterated benzhydrol (159) (equation 39) is slow and that other reactions of (160) occur much faster than proton-deuteron exchange between (159) and (160) (equation 40). The alternative explanation is that hydrogen atom transfer from (160) to (156) occurs in the solvent cage. If this is the case then intersystem crossing in the geminate triplet pair must be very rapid, and the radical (156) either undergoes very rapid inversion or is planar at the radical centre. From previous work in similar systems[69,71,162-164] it seems unlikely that (156) is planar at the radical centre.

To summarize this discussion, the work described here clearly shows that C — H bond homolysis adjacent to oxygen is stereoelectronically controlled, proceeding with optimal coplanarity of the bond undergoing fission and the filled non-bonding orbitals on oxygen. Results also indicate that C — D bond formation adjacent to oxygen is stereoelectronically controlled. This study clarifies the reasons for the stereospecificity previously observed by Bernasconi and Descotes,[70] and by Hayday and McKelvey.[38] The results are in complete agreement with a similar study recently conducted by Malatesta and Ingold.[171] They also conform to the general pattern for C — C bond homolysis, and C — H and C — C bond forma-

tion adjacent to filled non-bonding orbitals on sulphur.[65]

CHAPTER III.B A Kinetic Study of Some Reactions of Substituted 1,4-Dioxanes.

The relative rates of reaction of the dioxanes (68) and (69) with tri-n-butyltin hydride were determined by measuring their relative rates of consumption from several mixtures of the two (page 19). In these experiments the trans-dioxane (69) reacted approximately 1.9 times faster than the cis-dioxane (68). This value was calculated by analysis of aliquots taken from the reaction mixtures. The experimental deviation from this value was always less than ±5%.

^{1}H NMR spectra and GLC analysis of aliquots taken from the reaction mixtures confirmed that 2-chloro-1,3-dioxane (70) and 1,4-dioxane (71) were produced in these reactions. The yields of (70) and (71) depended on the extent of reaction, but their combined yields always represented greater than 80% of the theoretical yield of products. GLC analysis showed that 2-chloro-1,4-dioxane (70) slowly decomposed in the reaction mixtures, but not to 1,4-dioxane (71). This is reasonable in view of the previously reported spontaneous decomposition of (70).[172] Some decomposition of the cis-dioxane (68) was also observed when the reaction mixtures were let stand for extended periods. However, the trans-dioxane (69) was observed to be stable. To minimise the decomposition the reaction mixtures were stored over potassium carbonate.

Reaction of each of the dioxanes (68) and (69) with tri-n-butyltin hydride under identical conditions gave different relative yields of (70) and (71). These results are summarized in Table III.2. Since reaction of the mono-chlorodioxane (70) to give (71) may be considered as a standard in these reactions, these results also indicate that the trans-dioxane (69) reacts faster than the cis-dioxane (68), as relatively more (71) is formed in the latter case. Unfortunately it is not possible to determine by this method the relative rate of reaction of (70) with respect to the dichlorodioxanes (68) and (69), as such a determination would require

Table III.2

Products of Reactions of (68) and (69) with Tri-n-butyltin Hydride

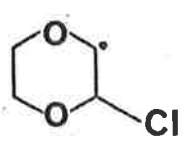
Substrate	% of Substrate reacted	Yield of (70)[A]	Yield of (71)[A]
(68)	28	68	14
(68)	46	70	18
(68)	65	63	21
(69)	36	81	6
(69)	68	77	9
(69)	73	74	8

A. Given as percentages based on the amount of substrate reacted.

that (70) and (71) were the sole products formed in these reactions, or that the other products were identifiable.

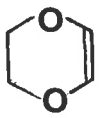
The formation of (70) and (71) in these reactions is consistent with an homolytic C — Cl bond cleavage mechanism. Chlorine atom abstraction from either (68) or (69) by tri-n-butyltin radical would produce 3-chloro-1,4-dioxan-2-yl radical (162), which could react by hydrogen atom abstraction from tri-n-butyltin hydride to give (70). Subsequent reaction of (70) with tri-n-butyltin radical would be expected to produce 1,4-dioxan-2-yl radical (163), which could in turn react with tri-n-butyltin hydride to produce (71). No signals were observed in the ^{1}H NMR spectra of the product mixtures which could be attributed to 1,4-diox-2-ene

(164).[173] This indicates that loss of a chlorine atom from (162) does not occur to any significant extent, a result which might have been expected since this process would be competing with the reaction of tri-n-butyltin hydride and (162), and the latter would be favoured by the high concentrations of the hydride used in these studies.



(162)

(163)



(164)

The relative reactivities of the dioxanes (68) and (69) clearly show that axial chlorines are preferentially abstracted from these compounds because the trans-dioxane (69) which has two axial chlorine substituents reacts almost twice as fast as the cis-dioxane (68) which has one axial and one equatorial chlorine substituent. The preferential abstraction of axial chlorine substituents can not be attributed to steric interactions as these would be less severe for abstraction of the less hindered equatorial chlorine. Nor can it be due to the thermodynamic factor as a chlorine substituent occupying an axial position in a 1,4-dioxane is energetically preferred over one occupying an equatorial position, due to anomeric interactions.[87,88]

However, the preferential transfer of axial chlorine substituents may be attributed to stereoelectronic control since there is greater overlap of an axial C — Cl bond than of an equatorial C — Cl bond with the adjacent oxygen's filled non-bonding orbitals. The rationalization of this is analogous to that described previously for C — H bond homolysis adjacent to oxygen (page 81).

These results therefore conform to the general pattern for C – C[65] and C – H[38,65,70,171] (Chapter III.A) bond homolysis adjacent to a filled non-bonding orbital.

CHAPTER III.C Synthesis.

The dioxanes (60)-(67) were all prepared by literature methods. 1,3-Dioxane (60) was prepared by the acid catalysed reaction of propan-1,3-diol with paraformaldehyde.[174] The reaction of propan-1,3-diol with trimethyl orthoformate afforded 2-methoxy-1,3-dioxane (61).[79] 2-Methyl-1,3-dioxane (62) was obtained from the reaction of acetaldehyde with propan-1,3-diol.[175]

Reduction of acetylacetone with sodium borohydride in the presence of sodium hydroxide gave a mixture of 2,4-pentanediols.[176] The cyclic sulphites of this mixture were fractionally distilled, and saponification of the low boiling fraction gave meso-2,4-pentanediol.[176] Reaction of this compound with trimethyl orthoformate afforded a mixture of the diastereoisomeric orthoformates (64) and (65) in the ratio 1:2 in favour of the more stable epimer (65).[79] Fractional distillation of this mixture enabled separation of (64) and (65).[79]

Treatment of an equilibrium mixture of (64) and (65) with lithium aluminium hydride gave r-4,c-6-dimethyl-1,3-dioxane (63).[80] r-2,c-4,c-6-Trimethyl-1,3-dioxane (66) was obtained from the reaction of meso-2,4-pentanediol with acetaldehyde.[78] It was contaminated with approximately 0.5% of the less stable epimer (67).[78] Reaction of the 2-methoxy substituted dioxane (65) with methylmagnesium iodide afforded a mixture of r-2,t-4,t-6-trimethyl-1,3-dioxane (67) (92%) and its epimer (66) (8%).[79] The dioxanes (66) and (67) were not separated from the epimeric impurities, but allowances were made for these in the work described in Chapter III.A.

Spectral and physical properties of the dioxanes (60)-(67) were consistent with those previously reported.[78-80,174,175] The ^{13}C NMR spectra of the dioxanes (60)-(67) were consistent with the previous assignments of the preferred conformations of these compounds[78-80] (page 18). The ^{13}C chemical shifts in the dioxanes (60) and (62)-(64)

correlated well with the previously reported chemical shifts for these compounds,[177,178] which were taken to indicate that the dioxanes (60) and (62)-(64) exist in the chair conformations.[178] The correlation between the observed and predicted ^{13}C chemical shifts in the dioxane (67) (Table III.3) indicates that this compound also exists in the chair conformation, as previously determined.[78-80]

The ^{13}C NMR spectra of the 2-methoxy substituted dioxanes (61), (64), and (65), were assigned with the aid of off-resonance decoupled spectra, and the assignments are shown in Table III.4. No additivity parameters have been determined for incorporation of a methoxy substituent at C-2 in 1,3-dioxanes. However, since a comparison of the chemical shifts in (64) and (65) (Table III.4) with those in (66) and (67) (Table III.3) indicates that the differences between the chemical shifts of the respective carbons in (64) and (65) are very similar to those between the chemical shifts of the respective carbons in (66) and (67), it seems reasonable to conclude that the dioxanes (64) and (65) also exist in the chair conformations previously assigned.[78-80]

The chlorodioxanes (68)-(70) were also prepared by literature methods. Reaction of 1,4-dioxane (71) with chlorine in carbon tetrachloride afforded a mixture of r-2,c-3-dichloro-1,4-dioxane (68) and r-2,t-3-dichloro-1,4-dioxane (69).[179] The cis-dioxane (68) was separated from the mixture by repeated fractional crystallization.[179] Reaction of a mixture of (68) and (69) with aluminium chloride in benzene afforded the trans-dioxane (69).[179] 2-Chloro-1,4-dioxane (70) was prepared by the photoinitiated reaction of 1,4-dioxane (71) with p-bromoiodosobenzene-dichloride.[180]

Table III.3

^{13}C Chemical Shifts in the Dioxanes (66) and (67). [A]

Assignment	(66)	(67)	
	Observed	Predicted	Observed
C-2	98.5	91.6[C]	93.9
C-4, C-6	72.4	64.7[C]	64.4
C-5	40.3	41.9[C]	40.6
Methyl C at C-2	21.3	-	17.0
Methyl C at C-4, C-6	21.6	-	22.0[B]

A. δc, ppm from TMS.

B. Typical ^{13}C chemical shift for an equatorial methyl carbon at C-4 or C-6 in a 1,3-dioxane.[177]

C. Calculations based on the reported chemical shifts of r-4,c-6-dimethyl-1,3-dioxane (64)[177,178] and the additivity parameters for introduction of an axial methyl substituent at C-2 in 1,3-dioxanes.[178]

Table III.4

Observed ^{13}C Chemical Shifts in the Dioxanes (61), (64) and (65).[A]

Assignment	(61)	(64)	(65)
C-2	109.6	112.1	109.4
C-4, C-6	61.2	71.1	64.1
C-5	24.4	39.4	40.1
Methyl C	-	21.1	21.4
Methoxy C	52.0	52.9	52.8

A. δc, ppm from TMS.

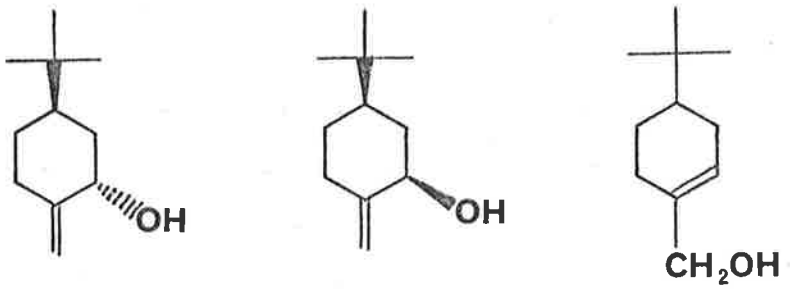
CHAPTER IV

Results and Discussion

Stereoelectronic Effects in Hydrogen Atom Abstraction from Substituted Methylenecyclohexanes.

CHAPTER IV.A A Kinetic and Product Study.

The copper catalysed reaction of 4-tert-butylmethylenecyclohexane (72) with tert-butyl perbenzoate afforded a mixture of benzoates which was reduced with lithium aluminium hydride. When the mixture of alcohols obtained by this procedure was chromatographed on alumina, three allylic alcohols were separated and identified as t-5-tert-butyl-2-methylene-cyclohexan-r-1-ol (165), the cis-isomer (166), and 4-tert-butylcyclohex-1-enyl methanol (167), by comparison of their spectral and physical properties with literature values.[96,182-184]



(165) (166) (167)

The ^{13}C NMR spectra of (165) and (166) were assigned to the chair conformations of these compounds in which the tert-butyl substituent is equatorially oriented (Table IV.1). From these assignments substituent effects of the hydroxyl group in these compounds were calculated. These are shown in Table IV.2. The ^{1}H NMR spectra of (165) and (166) are consistent with the stereochemical assignments. The signal arising from the equatorial proton at C-1 in (165) (δ4.30 ppm) is much narrower[120] and at higher field[119] than that arising from the axial proton at C-1 in (166) (δ4.00 ppm).

When the copper catalysed reaction of c-4-tert-butyl-r-2,c-6-dimethylmethylenecyclohexane (82) with tert-butyl perbenzoate was investigated, two allylic alcohols were separated by chromatography of the mix-

Table IV.1

^{13}C Chemical Shifts in the Allylic Alcohols (165) and (166).[A]

Assignment	(165)		(166)	
	Predicted[B]	Observed	Predicted[B]	Observed
C-1	75.0	73.1	74.6	72.9
C-2	153.6	150.6	154.5	152.2
C-3	28.1	28.7	34.3	34.0
C-4	29.6	30.4	29.5	28.7
C-5	40.8	40.7	45.8	47.1
C-6	34.7	35.3	38.0	38.7
$>=CH_2$	107.3	109.6	103.8	103.2
tert-Butyl $1^{o}C$	-	27.6[C]	-	27.7[C]
tert-Butyl $4^{o}C$	-	32.0[C]	-	32.4[C]

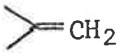
A. δc, ppm from TMS.

B. Calculations based on the chemical shifts of 4-tert-butylmethylene-cyclohexane (72) (Chapter IV.B) and additivity parameters determined by combining the additivity parameters for methyl substitution at C-2 in methylenecyclohexanes[123] with the correlation between methyl and hydroxyl substituent effects.[118]

C. Typical chemical shifts of the appropriate carbons in tert-butyl substituted cyclohexyl derivatives (Tables II. 2,3, and 6.)

Table IV.2

Substituent Effects of the Hydroxyl Group in (165) and (166).[A]

Assignment	(165)	(166)
C-1	+37.6	+37.4
C-2	+ 0.2	+ 1.8
C-3	- 5.1	- 1.5
C-4	- 0.5	- 0.5
C-5	- 7.4	- 1.0
C-6	+ 6.1	+ 9.5
	+ 3.3	- 3.1
tert-Butyl 1°C	- 0.1	0.0
tert-Butyl 4°C	- 0.4	0.0

A. $\Delta\delta = (\delta c^{(165)} \text{ or } (166) - \delta c^{(72)})$ in ppm for corresponding carbons relative to the hydroxyl group. The chemical shifts of (72) are taken from Chapter IV.B.

ture of reduction products. The ^{1}H NMR spectrum of each of these was consistent with the structure 5-tert-butyl-1,3-dimethyl-2-methylenecyclohexanol. On the basis of the correlation between the observed ^{13}C chemical shifts and those predicted for the various stereoisomers of this structure, the stereochemistry of the two products was assigned as t-5-tert-butyl-1,t-3-dimethyl-2-methylenecyclohexan-r-1-ol (168) and c-5-tert-butyl-1,c-3-dimethyl-2-methylenecyclohexan-r-1-ol (169) (Table IV.3).

Table IV.3

^{13}C Chemical Shifts in the Allylic Alcohols (168) and (169).[A]

Assignment	(168)		(169)	
	Predicted[B]	Observed	Predicted[B]	Observed
C-1	76.2	72.3	76.5	74.5
C-2	158.8	157.6	160.4	159.3
C-3	33.5	33.2	30.8	34.6[F]
C-4	37.6	38.0	37.9	38.0
C-5	40.6	42.3[C]	40.9	44.4[C,F]
C-6	44.2	42.5[C]	44.5	44.9[C]
Methyl C at C-1	-	28.7[D]	-	27.9[D]
Methyl C at C-3	-	18.8[D]	-	18.8[D]
$>=CH_2$	104.2	104.2	100.6	101.8
tert-Butyl $1^{o}C$	27.7	27.6	27.6	27.6
tert-Butyl $4^{o}C$	32.0	32.0	32.2	32.2

A. δc, ppm from TMS.

B. Calculations based on the chemical shifts of c-4-tert-butyl-r-2,c-6-dimethylmethylenecyclohexane (82) (Chapter IV.B) and the substituent effects of the hydroxyl group in t-5-tert-butyl-2-methylenecyclohexan-r-1-ol (165) (Table IV.2).

C. Assignments C-5 and C-6 may be reversed.

D. Typical chemical shifts of the appropriate carbons in methyl substituted cyclohexyl derivatives.[117d]

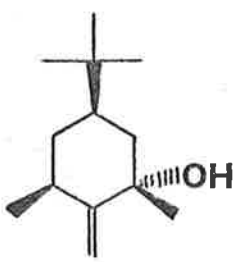
E. Calculations based on the chemical shifts of c-4-tert-butyl-r-2,t-6-

Table IV.3 continued

dimethylmethylenecyclohexane (83) (Chapter IV.B) and the substituent effects of the hydroxyl group in c-5-tert-butyl-2-methylenecyclohexan-r-1-ol (166) (Table IV.2).

F. The variation between this value and the predicted value may reflect some deformation of the chair conformation of the cyclohexane ring.

The reaction of (82) was repeated, only this time the benzoyloxylation reaction mixture was refluxed for 72h more than the 8h required for decomposition of the tert-butyl perbenzoate. In this case another compound was separated from the mixture of reduction products. On the basis of its spectral and physical properties it was identified as r-4-tert-butyl-2,c-6-dimethylcyclohex-1-enyl methanol (170). Subsequent GLC analysis showed that it was also present as a minor component in the mixture of products obtained from the earlier reaction of (82).



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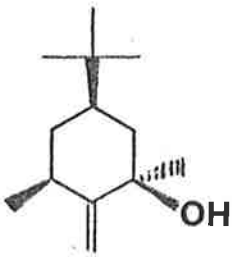

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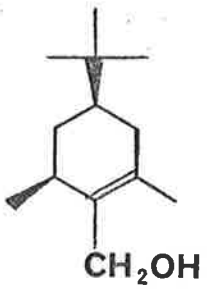
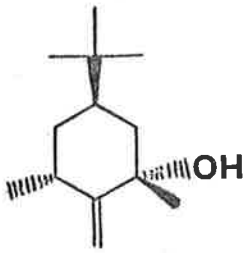


(170)

Three allylic alcohols were separated by chromatography of the reduced products obtained from the copper catalysed reaction of c-4-tert-butyl-r-2,t-6-dimethylmethylenecyclohexane (83) with tert-butyl perbenzoate. Two of these were identified as (168) and (169) by comparison of their spectral and physical properties with those of samples obtained from the reaction of (82). The ^{1}H NMR spectrum of the third alcohol

indicated that it had a similar structure to the other two. On the basis of the correlation between the observed ^{13}C chemical shifts and predicted values the stereochemistry of this product was assigned as t-5-tert-butyl-1,c-3-dimethyl-2-methylenecyclohexan-r-1-ol (171)(Table IV.4).



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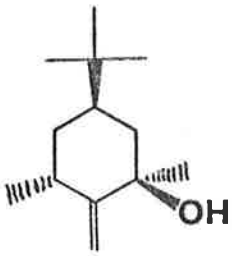

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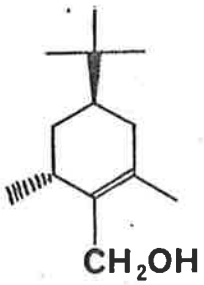
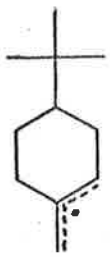


(173)

The reactions of the olefins (72), (82), and (83), were repeated several times. The yields of the allylic alcohols (165)-(171) obtained were determined, and these are shown in Table IV.5. The experimental deviation in these values was less than ±10% of the values shown.

Formation of the alcohols (165)-(167) in the reaction of (72), and of (168)-(170) in the reaction of (82), is consistent with the reactions proceeding via the respective intermediate allylic radicals (174) and (175). In the reaction of (83) loss of the equatorial allylic



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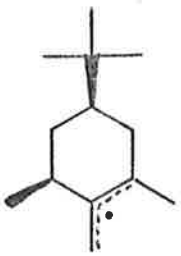
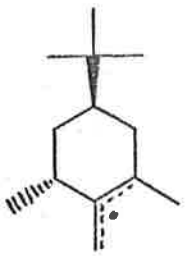


(175)



(176)

hydrogen would also produce the radical (175) and this would be expected to react to give (168) and (169). In view of the relative amounts of (168) and (170) formed in the reaction of (82), the amount of (170) formed

Table IV.4

^{13}C Chemical Shifts in the Allylic Alcohol (171).[A]

Assignment	Predicted[B]	Observed
C-1	69.9	73.7
C-2	158.8	160.2
C-3	34.0	38.4[C,D]
C-4	34.5	34.7[C]
C-5	34.5	35.6[C]
C-6	44.5	41.0[D]
Methyl C at C-1	-	30.1[E]
Methyl C at C-3	-	20.8[E]
	107.0	107.6
tert-Butyl 1°C	27.5	27.4
tert-Butyl 4°C	31.8	32.0

A. δc, ppm from TMS.

B. Calculations based on the chemical shifts of c-4-tert-butyl-r-2,t-6-dimethylmethylenecyclohexane (83) (Chapter IV.B) and the substituent effects of the hydroxyl group in t-5-tert-butyl-2-methylenecyclohexan-r-1-ol (165) (Table IV.2).

C. Assignments C-3 - C-5 may be incorrect.

D. The variation between this value and the predicted value probably reflects deformation of the chair conformation of the cyclohexane ring, caused by steric interactions between the hydroxyl substituent at C-1 and the methyl substituent at C-3.

E. Typical chemical shifts of the appropriate carbons in methyl substituted cyclohexyl derivatives.[117d]

Table IV.5

Products of Reduction of the Benzoate Mixtures Obtained from the Copper Catalysed Reactions of (72), (82) and (83), with tert-Butyl Perbenzoate.

Substrate	Yields of Products,% [A]					
	(165)	(166)			(167)	
(72)	46	13			23	
	(168)	(169)	(171)	(172)	(170)	(173)
(82)	54	21	-	-	2	-
(83)	8	3	4	N.D.[B]	N.D.[B]	N.D.[B]

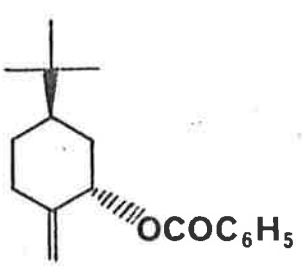
A. Based on the amount of substrate consumed.

B. N.D. = Not determined.

in the reaction of (83) was probably too small to be detected. Reaction of (83) by loss of the axial allylic hydrogen atom would produce (176) and this would be expected to react to give (171). The alcohols (172) and (173) which might also be expected from reaction of (176) were probably formed in amounts too small to be separated.

Separate experiments showed that some rearrangement of the intermediate benzoates occurred under the reaction conditions used. When the mixture of benzoates obtained from the reaction of (82) was refluxed for 72h prior to reduction, the yields of the alcohols (168)-(170) were respectively 37, 13, and 18%. In a similar experiment with (72) the yields of the alcohols (165)-(167) were respectively 37, 9, and 28%. A comparison of these yields with those shown in Table IV.5 indicates that the yields of the alcohols (167) and (170) containing the more substituted double bond were increased by the extended reaction time. Formation of (170) in the reaction of (82) may be attributed to benzoate rearrangement. However, since the standard reaction time was only 8h, benzoate rearrangement can only be partly responsible for the formation of (167) in the reaction of (72).

HPLC of the mixture of benzoates obtained from the reaction of (72) enabled isolation of a mixture of two components which were identified as t-5-tert-butyl-2-methylenecyclohex-r-1-yl benzoate (177) and c-5-tert-butyl-2-methylenecyclohex-r-1-yl benzoate (178) on the basis of the ^{1}H NMR spectrum of the mixture and the reduction of the mixture to give a mixture of (165) and (166). Another component was also isolated in this manner, and it was identified as 4-tert-butylcyclohex-1-enylmethyl benzoate (179) on the basis of its ^{1}H NMR spectrum and its reduction to give (167). GLC analysis of the crude benzoate mixture showed that the relative yields of the benzoates (177)-(179) were 55, 16, and 29%, respectively. Since these are very similar to those of the



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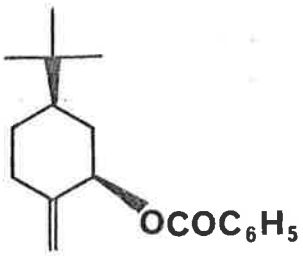

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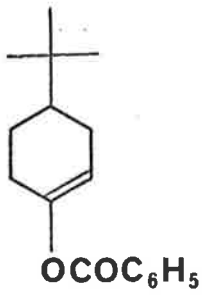


(179)

corresponding alcohols (165)-(167) (Table IV.5) it seems that each of the benzoates (177)-(179) is reduced without rearrangement. Unfortunately a similar examination of the benzoate mixtures obtained from the reactions of (82) and (83) could not be conducted as the mixtures could not be analysed by GLC. However, it seems reasonable to conclude that little rearrangement occurred as this would have resulted in the formation of (170) and (173). It is therefore assumed that the yields of the alcohols (165)-(171) shown in Table IV.5 accurately reflect the yields of the benzoates obtained from the copper catalysed reactions of the olefins (72), (82), and (83), with tert-butyl perbenzoate.

The relative rates of reaction of the olefins (72) and (80)-(83) with tert-butyl perbenzoate in refluxing benzene, in the presence of a copper catalyst, (Method A) are shown in Table IV.6. Their relative rates of reaction with di-tert-butyl peroxide at 145^{o} (Method B) are also shown in Table IV.6. These rates were calculated by measuring the relative rates of consumption of the olefins (72) and (80)-(83) from mixtures containing two or more of them. The extent of reaction was determined by GLC analysis of aliquots of the reaction mixtures. Using equation 1 the relative rates of reaction of the olefins (72) and (80)-(83) were determined. These values were calculated from repeated experiments and the experimental variation in these values was always less than ±5%. Separate experiments showed that no isomerization of the olefins

(72) and (80)-(83) occurred under the reaction conditions used in either method and therefore it is concluded that the initial reaction of the substrates is irreversible. These rates are therefore considered to reflect the rates of abstraction of allylic hydrogen atoms from these compounds.

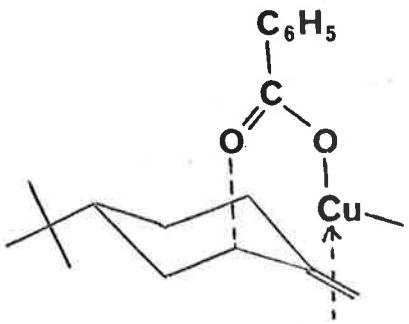
The yields of the alcohols (165)-(171) shown in Table IV.5 clearly indicate that there is a preference for products containing the less substituted double bond, and for axial benzoate incorporation. These observations are compatible with a mechanism[97,98,185,186] involving reaction of the allylic radicals (174)-(176) through a cyclic transition state involving ligand transfer and the formation of a Cu^{I}-olefin complex. The stability of a Cu^{I}-olefin complex is greater for a less substituted double bond.[187] Therefore the intermediate (180) would be expected to be more stable than (181), and (182) even more stable than (183). The stereospecificity is readily accounted for by the stereoelectronic requirement of approach of the benzoate in the plane of the developing π orbital.[96-98] Formation of the equatorially substituted methylene-cyclohexanes (166) and (169) would then require the reaction to proceed *via* a high energy non-chair intermediate.

Since the conditions used in the reactions of both olefins (82) and (83) were identical, the 75% combined yield of the alcohols (168) and (169) obtained from the reaction of (82), presumably *via* the intermediate radical (175), suggests that the 11% combined yield of (168) and (169) obtained from the reaction of (83) may be attributed to formation of the same intermediate (175) to the extent of approximately 15%. It therefore seems reasonable to assume that (83) reacts predominantly *via* formation of the alternative intermediate radical (176). The low yield of (171) and the failure to isolate (172) and (173) may be rationalized by considering the possible reaction intermediates. Both (184) and (185) would be

Table IV.6

Relative Rates of Reaction of the Olefins (72) and (80)-(83).

Substrate	Rates of Reaction	
	Method A	Method B
(72)	1.00	1.00
(80)	1.22	1.17
(81)	0.62	0.82
(82)	1.28	1.27
(83)	0.50	0.87



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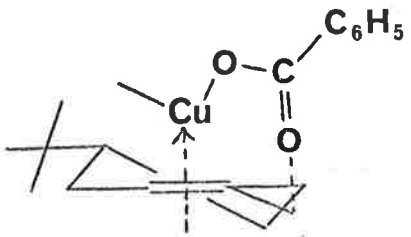

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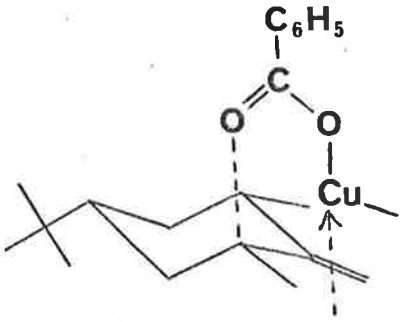

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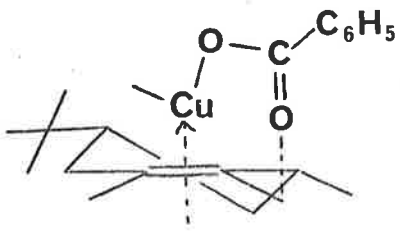
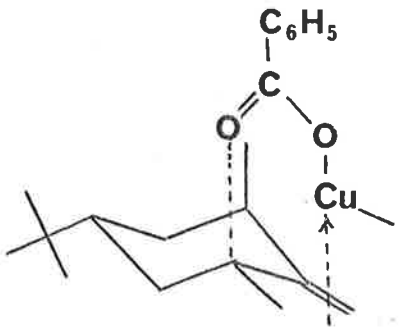


(183)

highly destabilized by steric interactions between the axial methyl substituent and the incoming benzoate. Also, steric interactions between the axial methyl substituents at C-1 and C-3 in (172) would be expected to destabilize intermediates leading to this compound. Therefore the trans-radical (176) probably reacts by other more favourable reaction pathways. This conclusion is consistent with the observation that in the reaction of (83) several unidentified products with long GLC retention times were formed, whereas similar products were not detected in the reactions of (72) and (82).



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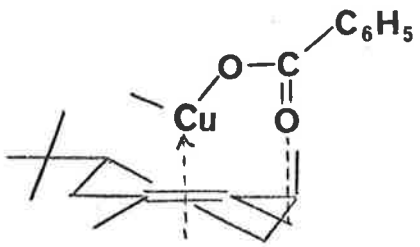

(185)

On this basis it seems reasonable to conclude that (83) reacts by loss of the axial allylic hydrogen atom to give (176) approximately 6 times faster than it reacts by loss of the equatorial allylic hydrogen atom to give (175). This is one example of the generally greater reactivity of axial allylic hydrogens, over equatorial allylic hydrogens, to abstraction from this system. Other examples of this are reflected in

the rates of reaction of the olefins (72) and (80)-(83) with tert-butyl perbenzoate in refluxing benzene, in the presence of a copper catalyst (Table IV.6).

It is clear from the relative rates of reaction of (72), (80), and (82), that incorporation of an equatorial allylic methyl substituent increases the rate of hydrogen atom abstraction.* As previous studies have shown that 3° allylic hydrogens are more reactive than 2° allylic hydrogens towards attack by tert-butoxy radical[105] this result might have been expected. Clearly a quantitative analysis cannot be given as the effect of a second equatorial methyl substituent is similar but the magnitude is not as great.

Incorporation of an axial allylic methyl substituent decreases the rate of hydrogen atom abstraction. As non-bonded interactions are more severe in axially substituted cyclohexanes than in equatorially substituted cyclohexanes this result cannot be a thermodynamic effect. It may be partly due to steric interactions as abstraction of an axial hydrogen from C-6 may be hindered by incorporation of an axial methyl substituent at C-2. This is probably one of the reasons why (83) reacts more slowly than (81). If steric interactions inhibit abstraction of the axial allylic hydrogen in (83) and (81) then the rate enhancement by incorporation of an equatorial methyl substituent might be outweighed by the decrease in the number of allylic hydrogens.

However, the steric effect would only be expected to be minor as similar steric interactions in the radical (88) (Chapter II.A) did not control its reactions. Also, the products obtained from reaction of (83) (Table IV.5) are not consistent with the reaction being controlled

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* The exception noted for the relative rates of reaction of (81) and (83) will be discussed later in the text.

by these steric interactions as much higher yields of the alcohols (168) and (169) would have been expected. It therefore seems that the decrease in the reaction rate by incorporation of an axial allylic methyl substituent must be due to preferential reactivity of axial allylic hydrogens. As previously discussed (page 109) the products obtained from the reaction of (83) (Table IV.5) are consistent with this.

The relative rates of reaction of the olefins (72) and (80)-(83) with di-tert-butyl peroxide at 145° (Method B) are very similar to those determined by Method A (Table IV.6). The differences between the values determined by the two methods probably result from the different temperatures at which the reactions were conducted. The similarity between the two sets of values indicates that Cu^{I}-olefin complexes do not participate in the hydrogen atom transfer step. Therefore this cannot be the reason for the preferential reactivity of the axial allylic hydrogens.

The observed stereospecificity is consistent with these reactions proceeding under stereoelectronic control. An examination of models indicates that the angle between the axis of the π orbital and that of the axial allylic C — H bonds in the methylenecyclohexane system is approximately 20°, whereas the angle between the axis of the π orbital and that of the equatorial allylic C — H bonds is approximately 85°. Therefore axial C — H bond fission would be facilitated by favourable overlap of the bond undergoing fission and the orbitals of the π system. Axial C — H bond fission can proceed by a coplanar interaction of the π orbital and the σ* antibonding orbital of the bond undergoing fission.

Thus the results described and discussed here indicate that C — H bond homolysis adjacent to a π orbital is stereoelectronically controlled. The results therefore conform to the proposal of Cross and Whitham,[96] and the conclusions of Beckwith and Phillipou.[97,98]

CHAPTER IV.B Synthesis of Substrates.

Treatment of the ketones (103), (110), and (95) with methylenetriphenylphosphorane, generated from methyltriphenylphosphonium bromide and potassium tert-butoxide, afforded 4-tert-butylmethylenecyclohexane (72), c-4-tert-butyl-r-2-methylmethylenecyclohexane (80), and c-4-tert-butyl-r-2,c-6-dimethylmethylenecyclohexane (82), respectively. Each of the olefins (72), (80), and (82), was identified by its spectral and physical properties. The ^{13}C NMR spectra of the products can be assigned to the chair conformations of these compounds in which the tert-butyl substituent is equatorially oriented (Tables IV.7 and 8).

Although the ketone (110) is a mixture of isomers, the olefin (80) obtained by this method contained no isomeric impurity. A similar reaction of the ketone (97) afforded only the olefin (82). The isomerization observed in these reactions is not unusual. Similar observations have previously been reported[125,188,189] and Wittig reactions of α-deuterated ketones have resulted in positional scrambling and loss of the deuterium label.[190-194]

A mixture of the olefins (80) and (81) was prepared by treatment of the ketone (110) with methylenetriphenylphosphorane, generated from methyltriphenylphosphonium bromide and sodium hydride in dimethyl sulphoxide.[195] The trans-olefin (81) comprised 5% of the product mixture. A small amount of (81) was separated from the mixture by preparative GLC and identified by its spectral and physical properties. Its ^{13}C NMR spectrum can be attributed to the chair conformation in which the tert-butyl substituent is equatorially oriented (Table IV.8).

When the ketone (97) was treated with methylenetriphenylphosphorane, generated from methyltriphenylphosphonium bromide and sodium hydride in dimethyl sulphoxide, the olefin (82) was produced exclusively. Therefore this method was not suitable for preparing the olefin (83).

Table IV.7

^{13}C Chemical Shifts in the Olefin (72).[A]

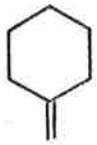
Assignment	Predicted	Observed
C-1	149.6[B]	150.4
C-2	35.7[B]	35.5
C-3	29.0[B]	29.2
C-4	47.8[B]	48.1
C-5	29.0[B]	29.2
C-6	35.7[B]	35.5
$>=CH_2$	106.6[C]	106.3
tert-Butyl $1^{o}C$	-	27.7[D]
tert-Butyl $4^{o}C$	-	32.4[D]

A. δc, ppm from TMS.

B. Calculations based on the reported chemical shifts of methylenecyclohexane (186)[123] and substituent effects of the tert-butyl group in tert-butylcyclohexane (42).[118]

C. Chemical shift of the appropriate carbon in the olefin (186).[123]

D. Typical chemical shifts of the appropriate carbons in tert-butyl substituted cyclohexyl derivatives (Tables II.2,3, and 6).



(186)

Table IV.8

^{13}C Chemical Shifts in the Olefins (80)-(83).[A]

Assignment	(80)		(81)		(82)		(83)	
	Pred.[B]	Obs.	Pred.[B]	Obs.	Pred.[B]	Obs.	Pred.[B]	Obs.
C-1	154.0	154.5	153.1	154.3	157.6	158.6	156.7	158.6
C-2	37.6	38.1[C]	38.0	37.6	38.1	38.6[C]	31.9	32.3
C-3	37.5	37.3[C]	35.2	34.7	37.8	38.1[C]	37.9	38.4
C-4	47.5	48.5	42.5	41.3	46.9	48.0	41.9	41.9
C-5	29.5	29.5	29.6	29.3	37.8	38.1[C]	35.5	35.0
C-6	36.0	36.8	29.8	29.3	38.1	38.6[C]	38.5	39.1
$>=CH_2$	103.8	103.7	107.3	105.9	101.3	100.9	104.8	103.7
tert-Butyl 1°C	-	27.7[D]	-	27.7[D]	-	27.8[D]	-	27.6[D]
tert-Butyl 4°C	-	32.4[D]	-	32.4[D]	-	32.4[D]	-	32.2[D]
Methyl C at C-2	18.6[E]	18.6	-	19.9[F]	18.6[E]	18.8	18.6[E]	18.9
Methyl C at C-6	-	-	-	-	18.6[E]	18.8	-	20.3[F]

A. δc, ppm from TMS.

B. Calculations based on the chemical shifts of 4-tert-butylmethylenecyclohexane (72) (Table IV.7) and additivity parameters determined for methyl substitution in methylenecyclohexanes.[123]

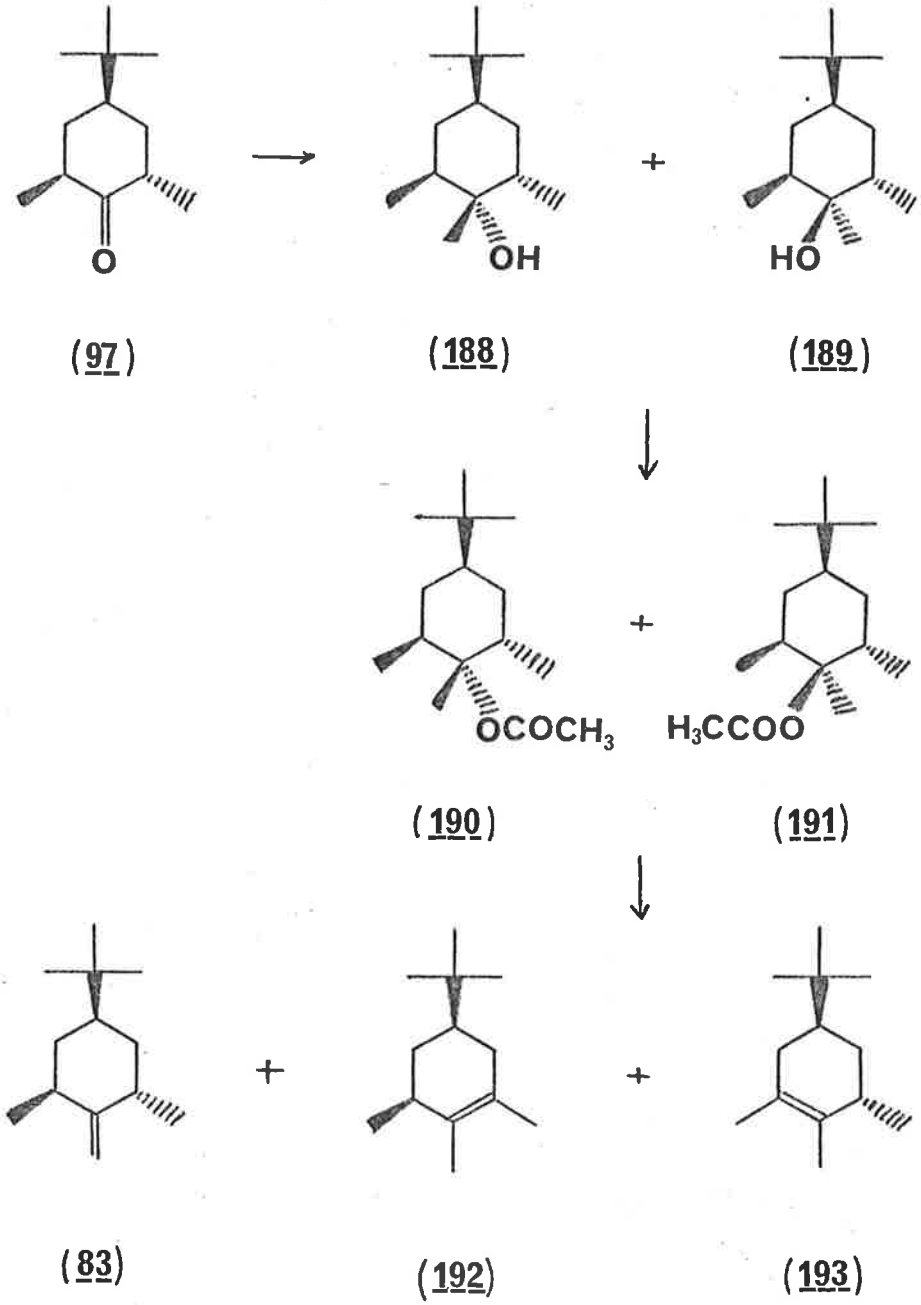
C. Assignments may be incorrect.

D. Typical chemical shifts of the appropriate carbons in tert-butyl substituted cyclohexyl derivatives (Tables II.2,3, and 6).

E. Chemical shift of the methyl carbon in the olefin (187).[123]

F. Axial methyl carbons at C-2 in methylenecyclohexanes tend to be deshielded relative to their equatorial counterparts.[123]

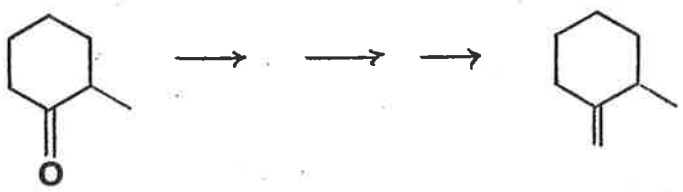
One of the reaction sequences used to prepare (83) is outlined in Scheme IV.1.



(97) (188) (189) (190) (191) (83) (192) (193)

Scheme IV.1

The synthesis of a mixture of olefins containing 2-methylmethylenecyclohexane (187), from 2-methylcyclohexanone (104), has previously been reported[196] and therefore this method seemed viable.



(104) (187)

Reaction of the ketone (97) with methylmagnesium iodide gave a mixture of two components in the ratio 9:16 as determined by GLC. Although the ^{13}C NMR spectrum of the mixture was too complicated to be interpreted completely, the peaks at 74.6 and 73.5 ppm from TMS, which were in the respective ratio of approximately 2:1, were attributed to the carbinyl carbons of t-4-tert-butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (188) and c-4-tert-butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (189) respectively, on the basis of the carbinyl chemical shifts of c-4-tert-butyl-1-methylcyclohexan-r-1-ol (194) and t-4-tert-butyl-1-methylcyclohexan-r-1-ol (195).[117h] The ^{1}H NMR spectrum of the mixture

(194) (195)

was consistent with these assignments. The predominance of the alcohol (188) in the mixture might have been expected as it is formed by approach of the Grignard reagent to the ketone (97) from the less hindered side.

Reaction of the mixture of (188) and (189) with acetyl chloride in N,N-dimethylaniline[196] gave a mixture of two components in the ratio

9:16 as determined by GLC. It was therefore concluded that both of the cyclohexanols (188) and (189) were converted to the corresponding acetates (190) and (191) without isomerization.

GLC analysis of the mixture of olefins obtained by pyrolysis[196] of the mixture of acetates (190) and (191) showed the presence of three components in the relative yields 54, 30, and 16%. By chromatography of the mixture of olefins on silver nitrate impregnated silica[152] a mixture of the two minor components and a pure sample of the major component were obtained. The major component was identified as the methylene-cyclohexane (83) on the basis of its spectral and physical properties. Its ^{13}C NMR spectrum can be assigned to the chair conformation of (83) in which the tert-butyl substituent is equatorially oriented (Table IV.8). The sample of (83) obtained by this method was contaminated with approximately 1% of (82). This was probably formed by reaction of (95) present in the sample of (97) used.

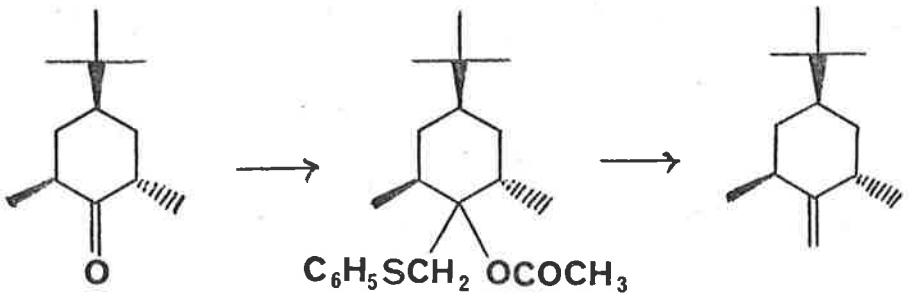
The two minor components of the pyrolysate were identified as c-5-tert-butyl-1,2,r-3-trimethylcyclohexene (192) and t-5-tert-butyl-1,2,-r-3-trimethylcyclohexene (193). The ^{13}C NMR spectrum of the mixture of (192) and (193) was not interpreted, but the peaks at 19.4 and 20.6 ppm from TMS, which were in the respective ratio of approximately 2:1, were attributed to the methyl carbons at C-3 in (192) and (193) respectively, on the basis of the chemical shifts of the methyl carbons at C-3 in (35) and (36) (Table II.6). The ^{1}H NMR spectrum of the mixture of (192) and (193) was consistent with these assignments.

The order of elution of the olefins (83), (192), and (193), from the silver nitrate impregnated silica column provided physical evidence that the assigned structures were correct as the disubstituted olefin (83) eluted after the tetrasubstituted olefins (192) and (193).

If it is assumed that the reaction of each of the acetates (190)

and (191) proceeds with the same degree of endocyclic elimination, then the relative yields of the olefins (192) and (193) indicate that reaction proceeds by cis-elimination.

The alternative method used to prepare (83) is outlined in Scheme IV.2.



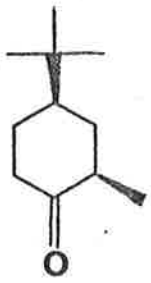
(97) (196) (83)

Scheme IV.2

This method utilizes the procedure developed by Sowerby and Coates[197] for ketone methylenation without isomerization. Thus treatment of the ketone (97) with phenylthiomethyl lithium and then with acetic anhydride[197] afforded the phenylthiomethylcarbinyl acetate (196). Reductive elimination of (196) by treatment with lithium in ammonia gave the olefin (83). Again the sample of (83) obtained was contaminated with approximately 1% of (82).

A mixture of the olefins (80) and (81) was prepared by a method analogous to that shown in Scheme IV.2 for the preparation of (83). To maximise the proportion of (81) in the product mixture the ketone (110) was isomerized by formation of the pyrrolidine enamine followed by ketone regeneration.[109] This afforded a mixture of t-4-tert-butyl-r-2-methylcyclohexanone (110a) and c-4-tert-butyl-r-2-methylcyclohexanone (110b) in the ratio 71:29. Reduction with lithium in ammonia[197] of the mixture obtained by treatment of this mixture of ketones (110a) and (110b) with phenylthiomethyl lithium and then with acetic anhydride,[197]

(110a)



(110b)

gave a mixture of the olefins (80) and (81) in the ratio 31:69. A small sample of (81) was separated from this mixture by preparative GLC.

AFTERWORD

The work described in this thesis clearly shows that radical fragmentation processes are often stereoelectronically controlled. Homolytic bond cleavage is facilitated by a coplanar interaction of the bond concerned with an adjacent semioccupied p orbital or filled non-bonding or π orbital. This has been shown to apply to homolysis of C — S,[21] C — C,[9,25-27,35,181] C — O,[36,40] and C — H[41] (Chapter II) bonds adjacent to a semioccupied p orbital, C — C,[65] C — H,[38,65,70,171] (Chapter III) and C — Cl (Chapter III) bonds adjacent to a filled non-bonding orbital, and a C — H[96-98] (Chapter IV) bond adjacent to a filled π orbital. It is therefore reasonable to expect that the rates and pathways of radical fragmentation processes might be influenced by the stereochemistry of the parent compound.

Two avenues for the continuation of this work would appear to be warranted. It would be a valuable exercise to investigate other systems where homolytic reactions might be expected to be stereoelectronically controlled. This avenue could be used to elaborate on the guidelines discussed above. Another logical continuation is to use the results already obtained to develop syntheses of useful compounds by stereo-electronically controlled homolytic reaction pathways.

EXPERIMENTAL

GENERAL

Melting points were measured using a Kofler hot-stage melting point apparatus under a Reichert microscope and are uncorrected.

Microanalyses were performed by the Australian Microanalytical Service, Melbourne.

Infrared spectra were recorded on either a Jasco IRA-1 or a Unicam SP200 grating infrared spectrophotometer. They were determined as liquid films, unless otherwise stated, using the 1603 cm^{-1} band of polystyrene as a reference. The characteristics of the infrared bands are expressed in the text as follows: s, strong; m, medium; w, weak; b, broad.

Mass spectra were recorded on either an Hitachi Perkin-Elmer RMU-7D double focusing mass spectrometer operating at 70eV or an AEI MS-30 mass spectrometer operating at 70eV. Only the major fragments are quoted with their relative abundances shown in parentheses.

^{1}H nuclear magnetic resonance (NMR) spectra were recorded on either a Varian T60 spectrometer operating at 60MHz or a Jeol JNM-PMX 60 spectrometer operating at 60 MHz. They were determined in carbon tetrachloride, unless otherwise stated, using tetramethylsilane as an internal reference. The characteristics of the spectra are expressed in the text as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br.s, broad singlet; d of d, doublet of doublets; exch., signal disappears when D_2O is added to the sample.

^{13}C NMR spectra were recorded on either a Bruker HX-90E spectrometer operating at 22.625 MHz or a Bruker WP-80 spectrometer operating at 22.1 MHz. They were determined in deuterochloroform using tetramethylsilane as an internal reference.

^{2}H NMR spectra were recorded at the National NMR Centre, Canberra, on a Bruker HX-270 spectrometer operating at 41.443 MHz.

Electron paramagnetic resonance (EPR) spectra were recorded on a Varian E9 spectrometer. Samples were photolyzed in the cavity of the spectrometer using an Oriel 1000W high pressure mercury lamp.

Photolytic reactions were conducted in a Rayonet photochemical reactor equipped with 16 RPR 3500 lamps.

Gas-liquid chromatographic (GLC) analyses were carried out on either a Perkin-Elmer 800, 881, or 990, or a Pye 104 gas chromatograph. The Perkin-Elmer 881 gas chromatograph is fitted with a Perkin-Elmer 194B printing integrator. The Perkin-Elmer 990 gas chromatograph is fitted with an Hitachi Perkin-Elmer 159 recorder equipped with a disc integrator. All chromatographs were equipped with flame ionization detectors and nitrogen was used as the carrier gas. The following columns were used:

A. 0.75% FFAP on Chromosorb W (100/120), 6.0m x 3.0mm, stainless steel.

B. 5% Carbowax 20M on Gaschrom P (80/100), 3.0m x 3.0mm, stainless steel.

C. 5% FFAP on Chromosorb W (80/100) (base washed), 3.0m x 3.0mm, glass.

D. 20% FFAP on Chromosorb W (80/100), 2.6m x 4.0mm, glass.

E. SCOT Carbowax 20M, 58m x 0.5mm, glass.

F. 15% SE30 on Chromosorb W (60/80), 2.0m x 6.0mm, glass.

G. SCOT Carbowax 20M, 68.6m x 0.5mm, glass.

H. SCOT SP1000, 34m x 0.5mm, glass.

The carrier gas flow rate was 25mL min^{-1} for the analytical columns A-D, 3.0mL min^{-1} for the capillary columns E, G, and H, and 50mL min^{-1} for the preparative column F.

High performance liquid chromatographic (HPLC) separations were carried out on a Spectra-Physics 3500B chromatograph equipped with a Spectra-Physics 230 detector and a Pye-Unicam LCM2 detector. Two

Lichrosorb Si.60 (10μ, 50cm x 1cm) columns were used in series.

Silver nitrate impregnated silica was prepared by the method of Serelis.[152] Column chromatography was carried out on Spence neutral alumina, sorbsil, or silver nitrate impregnated silica. Only redistilled solvents were used.

All solvents were purified by standard procedures. Light petroleum refers to the fraction of B.P. 55-65°.

WORK DESCRIBED IN CHAPTER II.A.

General procedure for the preparation and thermolysis of the alkyl tert-butylperoxyglyoxalates (24c)-(30c):

The alkyl tert-butylperoxyglyoxalates (24c)-(30c) were prepared by a procedure based on the method of Jensen and Moder.[49] The cyclohexanols (24a)-(30a) were first converted to the corresponding alkyl chloroglyoxalates (24b)-(30b). The alcohol (1 mmol) was added in small portions over approximately 10 minutes into excess oxalyl chloride (2 mmol), under nitrogen, at 0°. When addition was complete, the reaction mixture was allowed to warm to room temperature and the excess oxalyl chloride was removed under reduced pressure. The residue was distilled to give a colourless oil which was stored in the dark.

The alkyl chloroglyoxalates (24b)-(30b) were then converted to the corresponding alkyl tert-butylperoxyglyoxalates (24c)-(30c), which were thermolysed. Because of their liability to explosion the peroxides (24c)-(30c) were not isolated, but were prepared and reacted in dilute solution. A solution of tert-butyl hydroperoxide (5×10^{-4}mol) and pyridine (5×10^{-4}mol) in cyclohexane (1mL), was kept below 0° during the dropwise addition of a solution of the alkyl chloroglyoxalate (5×10^{-4}mol) in cyclohexane (1mL). Pyridine hydrochloride began precipitating immediately. When addition was complete, the solution was allowed to warm to room temperature and was then filtered. The solid was washed with cyclohexane (1mL), and the combined cyclohexane solutions were placed in an ampoule, flushed with nitrogen, then sealed under a nitrogen atmosphere and heated at 100° for 2h. The ampoule was then cooled in ice, opened, and an accurately weighed sample of an internal standard (one of the cyclohexanes (42)-(47)) was added. The mixtures were analysed as follows:

(a) Qualitative analysis: The products were initially identified by comparing the GLC retention times of the components with those of authentic samples, and by peak enhancement. Columns B(75°), E(100°), and G(100°) were used for this purpose.

The products were also identified by comparison of physical and NMR spectral properties of components, separated from the product mixtures by chromatography on silver nitrate impregnated silica,[152] with those of authentic samples. In each case the product mixture was concentrated and chromatographed. Elution with light petroleum gave one of the cyclohexanes (42)-(47). Continued elution gave the appropriate cyclohexene/s. When more than one cyclohexene was produced, the one with the most substituted double bond eluted first.

(b) Quantitative analysis: In order to calculate the yields of the products, the response ratios of the authentic samples with respect to tert-butylcyclohexane (42) were determined. The response ratios, retention times, and the columns used to determine these, are shown in Table V.1. Determination of the peak areas by integration when the product mixtures were analysed on the same columns, and allowing for the response ratios, enabled the yields of the products to be determined. These are shown in Table II.1 as percentages based on the amounts of the alkyl chloroglyoxalates (24b)-(30b) used. Each experiment was conducted in duplicate and each analysis was performed in triplicate.

General procedure for the preparation and thermolysis of the diacyl peroxides (31c)-(34c):

The diacyl peroxides (31c)-(34c) were prepared by a procedure based on the method of Hart and Cipriani.[144] The carboxylic acids (31a)-(34a) were first converted to the corresponding acid chlorides (31b)-(34b). The carboxylic acid (5 mmol) and thionyl chloride (15 mmol) were refluxed

Table V.1

Response Ratios and GLC Retention Times of the Products of Thermolysis of the Peroxides (24c)-(34c):

Product	Retention Time [C] (minutes).		Relative Response Ratio [D]
	Column E (100°)	Column G (100°)	
(1)	22.5		1.00
(35)	31.3		1.07
(36)	32.2		1.07[A]
(37)		32.4	1.04
(38)		28.0	1.04[A]
(39)		28.9	1.04
(40)		33.5	1.04
(41)		29.7	1.04[A]
(42)	18.6		1.00
(43)	23.5		1.07[B]
(44)	25.3		1.07[B]
(45)		23.0	1.04
(46)		25.3	1.04[A]
(47)		26.0	1.04

A. Assumed value based on the relative response ratio of isomers.

B. Value calculated for mixture of isomers (see text).

C. Typical values whose absolute magnitudes may vary slightly.

D. Accurate to ±2%.

for ½h. Then the excess thionyl chloride was removed under reduced pressure and the residue was distilled to give a colourless oil.

The acid chlorides (31b)-(34b) were then converted to the corresponding diacyl peroxides (31c)-(34c), which were thermolysed. To a suspension of sodium peroxide (0.1g, 0.0013 mol) in anhydrous ether (3mL), a solution of the acid chloride (0.002 mol) in ether (1mL) was added. The reaction was initiated by adding a drop of water. Reaction was assumed to be complete when the yellow colour of the peroxide had disappeared and the addition of a drop of water no longer caused the temperature to rise. Cold water (5mL) was then added to dissolve the sodium chloride, the layers were separated, and the ether layer was washed with 10% aqueous sodium carbonate (2x5mL), dried (magnesium sulphate), and concentrated under reduced pressure. No heat was applied. Cyclohexane (2mL) was then added to the residue, and the resultant solution was placed in an ampoule, flushed with nitrogen, sealed under a nitrogen atmosphere and heated at 100° for 2h. The ampoule was then cooled in ice, opened, and an accurately weighed sample of an internal standard (one of the cyclohexanes (42)-(47)) was added. The mixtures were analysed by the method used to analyse the product mixtures obtained from thermolysis of the alkyl tert-butylperoxyglyoxalates (24c)-(30c).

Solvolysis of t-4-tert-butyl-c-2,t-6-dimethylcyclohex-r-1-yl toluene-p-sulphonate (84):

After a solution of t-4-tert-butyl-c-2,t-6-dimethylcyclohex-r-yl toluene-p-sulphonate (84) (0.5g, 1.5 mmol) and anhydrous sodium acetate (0.25g, 3.0 mmol) in anhydrous acetic acid (15mL) had been heated in a sealed ampoule under nitrogen at 75° for 8h, it was cooled, diluted with water (40mL) and extracted with light petroleum (3x20mL). The combined extracts were washed with water (3x30mL), 5% aqueous sodium bicarbonate

(3x30mL), again with water (3x30mL), dried (magnesium sulphate), and concentrated. GLC analysis of the residue showed that the mixture consisted of c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) (47%) and two other components which were not identified (E, 100°, 27.7 min (36%), 29.6 min (17%), and 31.3 min (47%)).

WORK DESCRIBED IN CHAPTER II.B.

4-tert-Butylcyclohexanol (24a):

Commercial grade (Koch-Light Laboratories) 4-tert-butylcyclohexanol (24a) was recrystallized from light petroleum. GLC analysis showed that the sample was a mixture of two compounds (A, 150°, 5.4 min (30%) and 6.1 min (70%)) which were considered to be the two isomers of 4-tert-butylcyclohexanol (24a).

M.P. 61-5° (lit.[51] 61.8-75.9°);

^{1}H NMR : δ0.86 (s,9H,-C(CH_3)$_3$), 1.00-2.20 (broad absorption, 9H), 1.75 (br.s,1H,-OH,exch.), 3.42 (m,0.7H,>CH_{axial}-OH), and 3.95 (m,0.3H, >$CH_{equatorial}$-OH).

2,6-Dimethylphenol (93):

To a solution of 2,6-dimethylaniline (92) (30.0g, 0.25 mol) in acetic acid (100mL), 40% sulphuric acid (100mL) was added dropwise while the temperature was kept below 20°. The resultant mixture was cooled to 0° and maintained below 5° during the dropwise addition of a solution of sodium nitrite (20.7g, 0.3 mol) in water (150mL). The mixture was stirred at 0-5° for ½h. Then ice-cooled water (150mL) was added, followed by urea (10g) in small portions, and the mixture was filtered into an ice-cooled flask. The filtrate was added to a refluxing solution of 10% sulphuric acid (400mL) at such a rate that reflux was not interrupted. After an additional ½h at reflux, the reaction mixture was cooled to room temperature and extracted with ether (3x250mL). The combined ether extracts were washed with water (3x200mL), 5% aqueous sodium bicarbonate (3x200mL), again with water (3x200mL), dried (magnesium sulphate), and concentrated . Distillation of the residual oil gave a colourless liquid which solidified on cooling, and was recrystallized

from light petroleum to give 2,6-dimethylphenol (93) as white needles.

Yield 24.7g, 81%;

B.P. 78-80° / 18mm Hg (lit.[198] 197-202° / 760mm Hg);

M.P. 48-9° (lit.[199] 49°).

4-tert-Butyl-2,6-dimethylphenol (94):

4-tert-Butyl-2,6-dimethylphenol (94) was prepared in 54% yield by the method of Hultzch.[112]

B.P. 135-6° / 20mm Hg (lit.[112] 131° / 15mm Hg);

M.P. 80-2° (lit.[112] 81-2°).

c-4-tert-Butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a):

A solution of 4-tert-butyl-2,6-dimethylphenol (94) (10.0g, 0.06 mol) in 95% aqueous ethanol (40mL) with 5% rhodium on alumina (1.0g) was hydrogenated at 2500 psi and 100° for 72h. The mixture was then filtered through celite (2g) and concentrated to give an oil which was distilled. The distillate crystallized from light petroleum as white needles of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) which were shown to be homogeneous by GLC (A,150°, 5.45 min).

Yield 7.5g, 68%;

B.P. 88-90° / 4mm Hg;

M.P. 62-3°;

^{1}H NMR : δ0.86 (s,9H,-C(CH_3)$_3$), 0.92 (d,J=6Hz,6H,>CH-CH_3), 1.00 - 2.20 (broad absorption, 7H), 2.35 (br.s,1H,-OH,exch.), and 3.43 (m,1H,>CH-O-);

Mass Spectrum : $^{m}/_{e}$ 184 (M^{+})(27), 167 (14), and 109 (100);

ν_{max} (nujol) : 961(s), 1363(s), and 3446cm^{-1}(m,b);

Found : C,78.5; H,12.9. C_{12} H_{24} O requires C,78.2; H,13.1%.

c-4-tert-Butyl-r-2,c-6-dimethylcyclohexanone (95):

To a solution of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) (5.5g, 0.03 mol) in acetone (50mL), 8N Jones' reagent[121] was added dropwise until the orange-brown colour persisted. The mixture was then poured onto water (150mL) and extracted with ether (3x100mL). The combined ether extracts were washed with water (2x100mL), 5% aqueous sodium bicarbonate (3x100mL), again with water (3x100mL), dried (magnesium sulphate), and concentrated. Distillation of the residual oil gave c-4-tert-butyl-r-2,c-6-dimethylcyclohexanone (95) as a colourless liquid which was shown to be homogeneous by GLC (F, 150°, 4.20 min).

Yield 5.1g, 93%;

B.P. 95-8° / 10mm Hg;

^{1}H NMR : δ0.95 (s,9H,-C(CH_3)$_3$), 0.98 (d,J=7.5Hz,6H,>CH-CH_3), and 1.00 - 2.60 (broad absorption,7H);

Mass Spectrum: $^{m}/_{e}$ 182 (M^{+})(11), 126(56), 57(100), and 41(27);

ν_{max} : 1365(s) and 1718cm^{-1}(s);

Found : C,78.8; H,12.1. C_{12} H_{22} O requires C,79.1; H,12.1%.

These spectral data are consistent with those previously reported for the cyclohexanone (95).[107-109]

c-4-tert-Butyl-r-2,t-6-dimethylcyclohexanone (97):

A solution of c-4-tert-butyl-r-2,c-6-dimethylcyclohexanone (95) (4.8g, 0.026 mol), semicarbazide hydrochloride (5.6g, 0.05 mol), and potassium acetate (5.0g, 0.05 mol), in methanol (90mL), was refluxed for 18h. The mixture obtained by concentration of this solution was diluted with water (100mL), and the precipitate was separated by filtration, washed with water (200mL), and dried. Two recrystallizations from methanol gave white needles of the semicarbazone (96).

Yield 5.2g, 86%;

M.P. 173-4°;

^{1}H NMR ($CDCl_3$) : δ9.90 (s,9H,-C(CH_3)$_3$), 1.10 (d,J=7.5Hz,6H,>CH-CH_3), 1.40 - 3.60 (broad absorption,7H), 6.00 (br.s,2H,-NH_2), and 8.86 (br.s, 1H,>NH);

Found : C,64.9; H,10.5. $C_{13}H_{25}N_3O$ requires C,65.2; H,10.5%.

A solution of the semicarbazone (96) (5.0g, 0.021 mol) in acetic acid (30mL) was maintained below 5° while a solution of sodium nitrite (4.2g, 0.06 mol) in water (30mL) was added over ½h. The mixture was then extracted with ether (3x20mL), and the combined ether extracts were washed with water (3x30mL), 5% aqueous sodium bicarbonate (3x30mL), again with water (3x30mL), dried (magnesium sulphate), and concentrated. The residual oil was distilled to give c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) as a colourless liquid which was shown by GLC to be contaminated with 1-2% of the cyclohexanone (95) (F,150°, 4.20 min (<2%) and 4.55 min (>98%).

Yield 3.4g, 89%;

B.P. 104-5° / 10mm Hg;

^{1}H NMR : δ0.86 (s,9H,-C(C$\underline{H}_3$)$_3$), 0.95 (d,J=7.5Hz,3H,>CH-C$\underline{H}_3$ equatorial), 1.12 (d,J=7.5Hz,3H,>CH-C$\underline{H}_3$ axial), and 1.30 - 2.80 (broad absorption,7H);

ν_{max} : 1373(s) and 1716cm^{-1}(s) ;

Mass Spectrum : $^m/_e$ 182 (M^+)(16), 126(77), 57(91), and 41(100).

Found : C,79.4; H,12.0. C_{12} H_{22} O requires C,79.1; H,12.1%.

These spectral data are consistent with those previously reported for the cyclohexanone (97).[107-109]

t-4-tert-Butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a):

A solution of c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) (3.1g, 0.017 mol) in dry ether (10mL) was added to a suspension of lithium aluminium hydride (1.0g, 0.025 mol) in dry ether (50mL), and the mixture was refluxed for 3h, then cooled. Water (1mL), 10% aqueous sodium hydroxide (1mL), and water (4mL), were added, and the mixture was stirred for ½h. The precipitate was separated by filtration and washed with ether (2x25mL). The combined ether solutions were washed with water (2x25mL), dried (magnesium sulphate), concentrated, and the residual oil was distilled. The distillate was recrystallized from light petroleum to give t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a) as white needles which were shown by GLC to be contaminated with 1-2% of the cyclohexanol (25a) (A,150°, 5.45 min (<2%) and 6.50 min (>98%)).

Yield 2.1g, 69%;

B.P. 106-8° / 15mm Hg;

M.P. 56-8°;

^{1}H NMR : δ0.86 (s,9H,-C(C$\underline{H}_3$)$_3$), 0.92 (d,J=6Hz,6H,>CH-C$\underline{H}_3$), 1.10 - 2.50 (broad absorption,7H), 2.20 (br.s,1H,-O$\underline{H}$,exch.) and 3.20 (d of d, $\Delta\nu_{1,2}$

= 5Hz , $\Delta\nu_{1,3}$=10Hz,1H,>C<u>H</u>-OH);

ν_{max} (nujol) : 1043(s), 1363(s) and 3432cm^{-1}(m,b);

Mass Spectrum : $^{m}/_{e}$ 184 (M^{+})(14), 167(8), and 109(100);

Found : C,78.5; H,13.1. $C_{12}H_{24}O$ requires C,78.2; H,13.1%.

<u>4-tert-Butyl-2-methylphenol (106)</u>:

4-<u>tert</u>-Butyl-2-methylphenol (<u>106</u>) was prepared in 71% yield by the method of Hart and Haglund.[126]

B.P. 108-9° / 10mm Hg (lit.[126] 235-237° / 740mm Hg).

<u>c-4-tert-Butyl-c-2-methylcyclohexan-r-1-ol (27a) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a)</u>:

A mixture of <u>c</u>-4-<u>tert</u>-butyl-<u>c</u>-2-methylcyclohexan-<u>r</u>-1-ol (<u>27a</u>) (64%) and <u>t</u>-4-<u>tert</u>-butyl-<u>t</u>-2-methylcyclohexan-<u>r</u>-1-ol (<u>28a</u>) (36%) was prepared in 82% yield by the method of Pasto and Gontarz.[127] The ratio of the cyclohexanols (<u>27a</u>) and (<u>28a</u>) was determined by GLC analysis (C,150°, 6.5 min (64%) and 7.8 min (35%)). Chromatography of this mixture on alumina by the reported procedure[127] enabled separation of <u>c</u>-4-<u>tert</u>-butyl-<u>c</u>-2-methylcyclohexan-<u>r</u>-1-ol (<u>27a</u>) in 43% yield.

M.P. 79-81° (lit.[127] 78-9°).

Continued elution of the column gave <u>t</u>-4-<u>tert</u>-butyl-<u>t</u>-2-methylcyclohexan-<u>r</u>-1-ol (<u>28a</u>) in 17% yield.

B.P. 132-4° / 15mm Hg (lit.[127] 54° / 0.1mm Hg);

M.P. 69-70° (lit.[127] 72-3°).

4-tert-Butylcyclohexene (1):

4-tert-Butylcyclohexene (1) was prepared in 65% yield by the method of Sicher, Sipos, and Tichy.[128]

B.P. 57-8° / 15mm Hg (lit.[128] 54-5° / 10mm Hg).

c-4-tert-Butyl-r-1,c-2-oxidocyclohexane (107) and
t-4-tert-butyl-r-1,c-2-oxidocyclohexane (108):

A mixture of c-4-tert-butyl-r-1,c-2-oxidocyclohexane (107) and t-4-tert-butyl-r-1,c-2-oxidocyclohexane (108) was prepared in 76% yield by the method of Rickborn and Quartucci.[129]

B.P. 85-8° / 20mm Hg (lit.[129] 68-9° / 4mm Hg).

c-4-tert-Butyl-t-2-methylcyclohexan-r-1-ol (29a) and
t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a):

A mixture of c-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (29a) and t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a) was prepared in 57% yield by the method used by Sipos, Krupicka, Tichy, and Sicher,[130] and by Sicher and Tichy,[131] to prepare the individual compounds. The crude product was shown by GLC analysis to be a mixture of two components (C, 150°, 6.5 min (68%) and 6.9 min (32%)), which were separated by HPLC (ethyl acetate : light petroleum (1 : 10), 16mL min^{-1}, 12.5 min (68%) and 13.2 min (32%)). The first was distilled to give an oil which crystallized from light petroleum to give white needles of c-4-tert-t-2-methylcyclohexan-r-1-ol (29a).

Yield 2.3g, 32%;

B.P. 108-9° / 15mm Hg (lit.[130] 102-3° / 9mm Hg);

M.P. 70-2° (lit.[130] 70-1°).

The second crystallized from light petroleum to give white needles of t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a).

Yield 0.9g, 13%;

M.P. 74-6° (lit.[131] 75-6°).

4-tert-Butyl-2-methylcyclohexanone (110):

(i) 4-tert-Butyl-2-methylcyclohexanone (110) was prepared in 76% yield from a mixture of c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a) (64%) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a) (36%), by the method used to prepare c-4-tert-butyl-r-2,c-6-dimethylcyclohexanone (95) from c-4-tert-butyl-c-2 ,c-6-dimethylcyclohexan-r-1-ol (25a).

B.P. 122-5° / 1.5mm Hg (lit.[108] 130° / 0.7mm Hg).

(ii) 4-tert-Butyl-2-methylcyclohexanone (110) was also prepared by the method of Harding and Tseng,[108] in 57% yield.

B.P. 110-112° / 18mm Hg.

t-4-tert-Butyl-t-2-methylcyclohexane-r-1-carboxylic acid (32a), c-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (33a), and t-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (34a):

A mixture of stereoisomers of 4-tert-butyl-2-methylcyclohexane-carboxylic acid was prepared in 44% yield from 4-tert-butyl-2-methylcyclohexanone (110)by the method of Sicher, Tichy, and Sipos.[132] To a solution of this mixture (13.5g, 0.068 mol) in hexamethylphosphoramide (150mL), a solution sodium hydroxide (4.0g, 0.1 mol) in water (12mL) was added, and the resultant mixture was stirred at room temperature for 1h. Methyl

iodide (15.0g, 0.106 mol) was then added and the mixture was again stirred at room temperature for 1h. The solution was then poured onto 5% hydrochloric acid (200mL), extracted with ether (3x150mL), and the combined extracts were washed with water (6x150mL), dried (magnesium sulphate), and concentrated. The residue distilled as a clear oil. GLC analysis of this oil showed that it consisted of four components (D,100°, 8.5 min (18%), 10.5 min (65%), 10.8 min (5%), and 12.0 min (12%)) which were assigned the structures methyl c-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylate (115), methyl t-4-tert-butyl-t-2-methylcyclohexane-r-1-carboxylate (116), methyl c-4-tert-butyl-t-2-methylcyclohexane-r-1-carboxylate (118), and methyl t-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylate (117), respectively, on the basis of an alternative synthesis.[132]

Yield 13.2g, 91%;

B.P. 112-7° / 2mm Hg (lit.[132] 80-100° / 0.4mm Hg).

HPLC of the mixture (ethyl acetate : light petroleum (1 : 20), 10mL min^{-1}, 12.0 min (18%), 14.5 min (65%), 14.8 min (5%), and 16.0 min (12%)) enabled separation of the esters (115), (116), and (117).

The ester (117) was hydrolysed to t-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (34a) by the method of Sicher, Tichy, and Sipos.[132]

M.P. 182-4° (lit.[132] 185-185.5°).

The ester (116) was hydrolysed to t-4-tert-butyl-t-2-methylcyclohexane-r-1-carboxylic acid (33a) by the method used to prepare the acid (34a) from the ester (117).

M.P. 131-2° (lit.[132] 131.5-132°).

When the ester (115) was subjected to the conditions used to hydrolyse the esters (116) and (117), only starting material was recovered.

Therefore the ester (115) (0.45g, 2.1mmol) was refluxed for ½h in a mixture of 10% hydrochloric acid (2.5mL) and ethanol (2.5mL). The mixture was cooled, diluted with water (5mL), and extracted with ether (3x10mL). The ether extracts were washed with water (4x15mL), dried (magnesium sulphate), and concentrated. The residual solid was recrystallized from ethanol to give c-4-tert-butyl-c-2-methylcyclohexane-r-1-carboxylic acid (32a) as white needles.

Yield 0.36g, 86%;

M.P. 100-2° (lit.[132] 102.5-103.5°).

c-4-tert-Butylcyclohex-r-1-yl bromide (119):

A mixture of 4-tert-butylcyclohexanol (24a) (3.0g, 0.019 mol), phosphorus tribromide (5.4g, 0.020 mol), and five drops of pyridine in dry benzene (30mL), were stirred and heated at 55° for 12h. The reaction mixture was then poured onto ice (30g) and the organic and aqueous layers were separated. The aqueous layer was extracted with benzene (2x30mL) and the combined organic solutions were washed with water (2x50mL), 15% aqueous sodium carbonate (2x50mL), again with water (3x50mL), dried (magnesium sulphate), and concentrated. The residual oil was distilled to give c-4-tert-butylcyclohex-r-1-yl bromide (119) as a colourless liquid.

Yield 3.5g, 84%;

B.P. 112-4° / 19mm Hg (lit.[200] 104-10° / 14mm Hg).

t-4-tert-Butylcyclohexane-r-1-carboxylic acid (31a):

The Grignard solution prepared from c-4-tert-butylcyclohex-r-1-yl bromide (119) (2.2g, 0.01 mol), magnesium (0.48g, 0.02 mol), and dry ether

(50mL), was poured onto solid carbon dioxide (12g). Ether (25mL) and 10% sulphuric acid (25mL) were added, the organic layer was separated, and the aqueous layer was extracted with ether (2x25mL). The combined ether solutions were washed with water (3x50mL), then extracted with saturated aqueous sodium bicarbonate (3x50mL). The basic extracts were washed with ether (2x50mL), then neutralized with 10% hydrochloric acid. The precipitate which formed was separated by suction filtration, washed with cold water (20mL), and recrystallized from ethanol to give white flakes of t-4-tert-butylcyclohexane-r-1-carboxylic acid (131a).

Yield 0.95g, 52%;

M.P. 176-8° (lit.[201] 174-5°).

α-Deuteration of 4-tert-butylcyclohexanone (103):

The general method used for the α-deuteration of 4-tert-butylcyclohexanone (103) by base catalysed hydrogen-deuterium exchange is the same as that reported by Trimitsis and Van Dam.[145]

For recording ^1H NMR spectra in the presence of $Eu(THD)_3$, samples were prepared by dissolving the ketone (0.05g) and $Eu(THD)_3$ (0.10g) in carbon tetrachloride (0.5mL).

Mass spectra of the products were recorded and used to calculate the extent of deuterium incorporation by comparison with the mass spectrum of 4-tert-butylcyclohexanone (103), recorded under the same conditions.

The results of these experiments are shown in Tables II. 4 and 5.

1,1-Diethoxy-4-tert-butylcyclohexane (129):

1,1-Diethoxy-4-tert-butylcyclohexane (129) was prepared in 55% yield by the method of House, Tefertiller, and Olmstead.[133]

B.P. 78-82° / 1.5mm Hg (lit.[133] 67-70° / 0.1mm Hg).

1-Ethoxy-4-tert-butylcyclohexene (130):

1-Ethoxy-4-tert-butylcyclohexene (130) was prepared in 82% yield by the method of House, Tefertiller, and Olmstead.[133]

B.P. 112-6° / 18mm Hg (lit.[133] 114-7° / 11mm Hg).

Deuterolysis of 1-ethoxy-4-tert-butylcyclohexene (130):

Deuterolysis of 1-ethoxy-4-tert-butylcyclohexene (130) by the method of House, Tefertiller, and Olmstead,[133] gave a mixture of α-deuterated 4-tert-butylcyclohexanones in 82% yield.

B.P. 118-20° / 20mm Hg;

M.P. 46-7° (lit.[133] 46-48.5°);

Mass Spectrum : d^0,14.0; d^1,84.0; d^2,2.0%;

^1H NMR (in the presence of $Eu(THD)_3$) : δ0.10 (s,9H,-C(CH_3)$_3$), 2.45 (m,5H, protons at C-3, C-4, and C-5), 6.75 (m,1.52H, axial protons at C-2 and C-6), and 7.60 (m,1.57H, equatorial protons at C-2 and C-6).

WORK DESCRIBED IN CHAPTER II.C.

c-5-tert-Butyl-1,r-3-dimethylcyclohexene (35):

(i) A solution of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) (1.0g, 0.0054 mol) in pyridine (20mL) was treated dropwise with thionyl chloride (4mL) while the temperature was kept below -5°. After an additional 4h at -5°, the reaction mixture was poured onto ice (50g), extracted with ether (3x50mL), and the ether extracts were washed with water (2x100mL), 10% hydrochloric acid (3x100mL), again with water (3x 100mL), dried (potassium carbonate), and concentrated. The residual oil was chromatographed on alumina. Elution with light petroleum gave an oil which was distilled to give c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) as a colourless liquid. The product was shown to be homogeneous by GLC analysis (E,100°, 31.3 min).

Yield 0.54g, 60%;

B.P. 45-7° (block) / 15mm Hg;

^{1}H NMR : δ0.90 (s,9H,-C(CH_3)$_3$), 0.94 (d,J=8.5Hz,3H,>CH-CH_3), 1.70 (m,3H, =C-CH_3), 1.20-2.60 (broad absorption,6H), and 5.20 (m,1H,=CH-);

ν_{max} : 1363cm^{-1}(s);

Mass Spectrum : $^m/_e$ 165 (M^+-1)(100) and 57(42);

Found : C,86.5; H,13.4. $C_{12}H_{22}$ requires C,86.7; H,13.3%.

(ii) A solution of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) (3.9g, 0.02 mol) in dry pyridine (50mL) was cooled to 0° and treated with toluene-p-sulphonyl chloride (7.2g, 0.04 mol). After solution was complete, the reaction mixture was kept at 3° for 30h, during which time the reaction mixture turned a light brown and crystals of pyridine hydro-

chloride precipitated. The reaction mixture was then poured onto ice-cooled water (250mL). The resultant mixture was extracted with ether (3x100mL), and the ether extracts were washed with water (3x150mL), 10% hydrochloric acid (3x150mL), again with water (3x150mL), dried (potassium carbonate), and concentrated. The residual oil crystallized from light petroleum at -78° (dry ice - acetone) to give c-4-tert-butyl-c-2,c-6-dimethylcyclohex-r-1-yl toluene-p-sulphonate (133) as white needles.

Yield 1.7g, 63%;

M.P. 117-8°;

^{1}H NMR ($CDCl_3$) : δ0.87 (s,9H,-C(CH_3)$_3$), 0.98 (d,J=7Hz,6H,>CH-CH_3), 1.10-2.30 (broad absorption,7H), 2.50 (s,3H, Ar-CH_3), 4.90 (m,1H,>CH-O-), and 7.30-8.10 (m,4H,Ar-H).

A solution of c-4-tert-butyl-c-2,c-6-dimethylcyclohex-r-yl toluene-p-sulphonate (133) (0.65g, 0.0019 mol) in a mixture of dimethyl sulphoxide (2mL) and benzene (10mL) was added dropwise, with stirring, to a suspension of potassium tert-butoxide (0.5g, 0.0068 mol) in dimethyl sulphoxide (8mL). The mixture was stirred for 16h at ambient temperature, then poured into ice-cooled water (20mL), and extracted with pentane (3x20mL). The pentane extracts were washed with water (5x30mL), dried (magnesium sulphate), and concentrated. The residue was distilled to give c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) as a colourless liquid, which was identical to the sample of (35) already obtained.

Yield 0.13g, 41%;

B.P. 60-5° (block) / 20mm Hg.

(iii) A mixture of c-4-tert-butyl-c-2,c-6-dimethylcyclohexan-r-1-ol (25a) (6.2g, 0.034 mol), acetic anhydride (15mL), and pyridine (15mL), was stirred at 50° for 6h. The mixture was then poured onto ice (40g)

and extracted with ether (3x25mL). The combined ether extracts were washed with water (3x30mL), 10% hydrochloric acid (3x30mL), water (3x30mL), 5% aqueous sodium bicarbonate (3x30mL), again with water (3x30mL), dried (magnesium sulphate), and concentrated. The residue was distilled to give c-4-tert-butyl-c-2,c-6-dimethylcyclohex-r-1-yl acetate (132) as a pale yellow oil which was shown to be homogeneous by GLC analysis (D,100°, 3.30 min).

Yield 4.7g, 61%;

B.P. 141-4° / 18mm Hg;

^{1}H NMR : δ0.87 (s,9H,-C(CH_3)$_3$), 0.93 (d,J=6.5Hz,6H,>CH-CH_3), 1.10-2.60 (broad absorption,7H), 2.10 (s,3H, -OCOCH_3), and 4.90 (m,1H,>CH-O-).

c-4-tert-Butyl-c-2,c-6-dimethylcyclohex-r-1-yl acetate (132) (2.0g, 0.0088 mol) was slowly distilled under reduced pressure (15mm Hg) through a Vycor tube (50cm x 2.5cm) packed with silica beads and heated at 475°. The pyrolysate was collected in a trap cooled to -78° (dry ice - acetone). When the distillation was complete, water (10mL) was added to the pyrolysate and the mixture was extracted with light petroleum (3x10mL). The combined extracts were washed with 5% aqueous sodium bicarbonate (2x15mL) and water (2x15mL), dried (magnesium sulphate), and concentrated. The residual oil was chromatographed on alumina. Elution with light petroleum gave an oil which was distilled to give c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) as a colourless liquid. This sample was identical to the samples of (35) already obtained.

Yield 0.68g, 47%;

B.P. 56-62° (block) / 18mm Hg.

t-5-tert-Butyl-1,r-3-dimethylcyclohexene (36):

t-5-tert-Butyl-1,r-3-dimethylcyclohexene (36) was prepared from t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a) by the method used to prepare the cyclohexene (35) from the cyclohexanol (25a) via the acetate (132). The intermediate, t-4-tert-butyl-c-2,t-6-dimethylcyclohex-r-1-yl acetate (85), was obtained as a pale yellow oil which was shown by GLC analysis to be contaminated with 1-2% of the acetate (132) (D,100°, 3.30 min (<2%) and 3.75 min (>98%)).

Yield 1.15g, 68%;

B.P. 130-5° / 15mm Hg;

^{1}H NMR : δ0.88 (s,9H,-C(CH_3)$_3$), 0.90 (d,J=8Hz,3H,>CH-CH_3 equatorial), 0.93 (d,J=8Hz,3H,>CH-CH_3 axial), 1.00-2.50 (broad absorption,7H), 2.00 (s,3H,-OCOCH_3), and 4.42 (d of d,$\Delta\nu_{1,2}$=4.5Hz,$\Delta\nu_{1,3}$=11Hz,1H,>CH-OCOCH_3).

The final product, t-5-tert-butyl-1,r-3-dimethylcyclohexene (36), was obtained as a colourless liquid which was shown by GLC analysis to be contaminated with 7% of the cyclohexene (35) (E,100°, 31.3 min (7%) and 32.2 min (93%)).

Yield 0.37g, 51%;

B.P. 47-8° (block) / 20mm Hg;

^{1}H NMR : δ0.89 (s,9H,-C(CH_3)$_3$), 0.95 (d,J=9Hz,3H,>CH-CH_3), 1.68 (m,3H, =C(-CH_3)), 1.10-2.60 (broad absorption,6H), and 5.35 (m,1H,=CH-);

Mass Spectrum : $^m/_e$ 165 (M^+-1)(52) and 57(100);

Found : C,86.3; H,13.2. $C_{12}H_{22}$ requires C,86.7; H,13.3%

c-5-tert-Butyl-1,r-3-dimethylcyclohexene (35) and
t-5-tert-butyl-1,r-3-dimethylcyclohexene (36):

(i) Dehydration of t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a) by the method used to prepare the cyclohexene (35) by dehydration of the cyclohexanol (25a), gave a colourless oil which was shown to be a mixture of the cis-cyclohexene (35) (93%) and the trans-cyclohexene (36) (7%) by GLC analysis (E,100°, 31.3 min (93%) and 32.2 min (7%)).

Yield 0.24g, 47%;

B.P. 109-112° (block) / 13mm Hg.

(ii) A mixture of c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) (91%) and t-5-tert-butyl-1,r-3-dimethylcyclohexene (36) (9%) was prepared from t-4-tert-butyl-c-2,t-6-dimethylcyclohexan-r-1-ol (26a) by the method used to prepare the cyclohexene (35) from the cyclohexanol (25a) via the toluene-p-sulphonate (133). The intermediate, t-4-tert-butyl-c-2,t-6-dimethylcyclohex-r-1-yl toluene-p-sulphonate (84), was obtained as a white solid.

Yield 1.65g, 24%;

M.P. 103-4° decomp.;

^{1}H NMR ($CDCl_3$) : δ0.90 (s,9H,-C(CH_3)$_3$), 1.04 (d,J=7.5Hz,6H,>CH-CH_3), 1.10-2.30 (broad absorption,7H), 2.54 (s,3H,Ar-CH_3), 4.35 (d of d, $\Delta\nu_{1,2}$=5.5Hz, $\Delta\nu_{1,3}$=11Hz,1H,>CH-O-), and 7.30-8.10 (m,4H,Ar-H).

The final product was obtained as a colourless oil. The ratio of (35) to (36) in this product was determined by GLC analysis (E,100°, 31.3 min (91%) and 32.2 min (9%)).

Yield 0.17g, 34%;

B.P. 50-55° (block) / 18mm Hg.

c-5-tert-Butyl-r-3-methylcyclohexene (38) and

5-tert-butyl-1-methylcyclohexene (37):

(i) Dehydration of a mixture of c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a) (64%) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a) (36%) by the method used to prepare the cyclohexene (35) by dehydration of the cyclohexanol (25a), gave a colourless oil which was shown by GLC analysis to be a mixture of two components (G,100°, 28.0 min (8%) and 32.4 min (92%)). The oil was chromatographed on silver nitrate impregnated silica.[152] Elution with light petroleum gave an oil which was distilled to give 5-tert-butyl-1-methylcyclohexene (37) as a colourless liquid. This was shown by GLC analysis to be the major component of the crude product mixture (G,100°, 32.4 min).

Yield 1.7g, 54%;

B.P. 59-62° / 20mm Hg (lit.[21] 82-82.5° / 18mm Hg).

Continued elution of the chromatography column with light petroleum gave an oil which was distilled to give c-5-tert-butyl-r-3-methylcyclohexene (38) as a colourless liquid. This was shown by GLC analysis to be the minor component of the crude product mixture (G,100°, 28.0 min).

Yield 0.13g, 4%;

B.P. 60-2° (block) / 20mm Hg (lit.[137] 85-7° / 35mm Hg).

(ii) A mixture of c-5-tert-butyl-r-3-methylcyclohexene (38) (12%) and 5-tert-butyl-1-methylcyclohexene (37) (88%) was prepared from a mixture of c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a) (64%) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a) (36%) by the method used to prepare the cyclohexene (35) from the cyclohexanol (25a) via the toluene-p-sulphonate (133). The intermediate, a mixture of c-4-tert-butyl-c-2-methylcyclohex-r-1-yl toluene-p-sulphonate (138) (64%) and t-4-tert-

butyl-t-2-methylcyclohex-r-1-yl toluene-p-sulphonate (139) (36%), was obtained as a white solid.

Yield 1.46g, 35%;

M.P. 52-9° decomp.;

^{1}H NMR ($CDCl_3$) : δ0.88 (s,9H,-C(CH_3)$_3$, 1.02 (d,J=7Hz,3H,>CH-CH_3), 1.00-2.10 (broad absorption,8H) 2.53 (s,3H,Ar-CH_3), 4.40 (m,c.0.35H,>CH axial -O-), 4.85 (m,c.0.65H,>CH equatorial-O-), and 7.30-8.10 (m,4H,Ar-H).

The final product was obtained as a colourless oil. The ratio of (38) to (37) in this product was determined by GLC analysis (G,100°, 28.0 min (12%) and 32.4 min (88%)).

Yield 0.24g, 52%;

B.P. 43-9° (block) / 12mm Hg.

Again the cyclohexenes (37) and (38) were separated by chromatography of the product mixture on silver nitrate impregnated silica.[152]

(iii) A mixture of c-5-tert-butyl-r-3-methylcyclohexene (38) (32%) and 5-tert-butyl-1-methylcyclohexene (37) (68%) was prepared from a mixture of c-4-tert-butyl-c-2-methylcyclohexan-r-1-ol (27a) (64%) and t-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (28a) (36%) by the method used to prepare the cyclohexene (35) from the cyclohexanol (25a) via the acetate (132). The intermediate was obtained as a pale yellow oil which was shown by GLC analysis to be a mixture of two components (D,100°, 3.1 min (64%) and 3.6 min (36%)). These were assigned the structures c-4-tert-butyl-c-2-methylcyclohex-r-1-yl acetate (136) and t-4-tert-butyl-t-2-methyl-cyclohex-r-1-yl acetate (137), respectively.

Yield 3.7g, 73%;

B.P. 126-9° / 19mm Hg.

The final product was obtained as a colourless oil. The ratio of

(38) to (37) in this product was determined by GLC analysis (G,100°, 28.0 min (32%) and 32.4 min (88%)).

Yield 1.3g, 72%;

B.P. 51-5° / 16mm Hg.

Again the cyclohexenes (37) and (38) were separated by chromatography of the product mixture on silver nitrate impregnated silica.[152]

t-5-tert-Butyl-r-3-methylcyclohexene (39) and
5-tert-butyl-1-methylcyclohexene (37):

Reaction of c-4-tert-butyl-t-2-methylcyclohexan-r-1-ol (29a) by the method used to prepare the cyclohexene (35) from the cyclohexanol (25a) via the toluene-p-sulphonate (133), gave a colourless oil which was shown by GLC analysis to be a mixture of two components (G,100°, 28.9 min (33%) and 32.4 min (67%)). This oil was chromatographed on silver nitrate impregnated silica.[152] Elution with light petroleum gave an oil which was distilled to give 5-tert-butyl-1-methylcyclohexene (37) as a colourless liquid. This was shown by GLC analysis to be the major component of the crude product mixture (G,100°, 32.4 min).

Yield 0.53g, 17%;

B.P. 63-7° (block) / 18mm Hg. (lit.[21] 82-82.5° / 18mm Hg).

Continued elution of the chromatography column with light petroleum gave an oil which was distilled to give t-5-tert-butyl-r-3-methylcyclohexene (39) as a colourless liquid. This was shown by GLC analysis to be the minor component of the crude product mixture (G,100°, 28.9 min).

Yield 0.19g, 6%;

B.P. 51-7° (block) / 16mm Hg (lit.[137] 63° / 10mm Hg).

r-3-tert-butyl-c-6-methylcyclohexene (41) and
4-tert-butyl-1-methylcyclohexene (40):

Reaction of t-5-tert-butyl-t-2-methylcyclohexan-r-1-ol (30a) by the method used to prepare the cyclohexene (35) from the cyclohexanol (25a) via the acetate (132), gave a colourless oil which was shown by GLC analysis to be a mixture of two components (G,100°, 29.7 min (42%) and 33.5 min (58%)). This oil was chromatographed on silver nitrate impregnated silica.[152] Elution with light petroleum gave an oil which was distilled to give 4-tert-butyl-1-methylcyclohexene (40) as a colourless liquid. This was shown by GLC analysis to be the major component of the crude product mixture (G,100°, 33.5 min).

Yield 0.43g, 24%;

B.P. 50-7° (block) / 17mm Hg (lit.[40] 180-182° / 752mm Hg).

Continued elution of the chromatography column with light petroleum gave an oil which was distilled to give r-3-tert-butyl-c-6-methylcyclohexene (41) as a colourless liquid. This was shown by GLC analysis to be the minor component of the crude product mixture (G,100°, 29.7 min).

Yield 0.34g, 19%;

B.P. 62-4° (block) / 25mm Hg.

The spectral properties of this compound were identical with those previously reported[202,203] for the cyclohexene (41).

tert-Butylcyclohexane (42):

4-tert-Butylcyclohexene (1) (1.0g, 0.0072 mol) was hydrogenated in acetic acid (15mL) over platinum oxide (0.3g) at 50 psi for 12h. The catalyst was removed by filtration of the solution through celite, and the

filtrate was diluted with water (40mL) and extracted with light petroleum (3x25mL). The combined extracts were washed with water (3x30mL), 5% aqueous sodium bicarbonate (3x30mL), again with water (3x30mL), dried (magnesium sulphate), and concentrated. The residue was distilled to give tert-butylcyclohexane (42) as a colourless liquid which was shown to be homogeneous by GLC analysis (E,100°, 18.6 min).

Yield 0.68g, 67%;

B.P. 69-72° / 15mm Hg (lit.[204] 171.7-171.8° / 760mm Hg).

r-1-tert-Butyl-c-3-methylcyclohexane (45):

r-1-tert-Butyl-c-3-methylcyclohexane (45) was prepared in 54% yield from c-5-tert-butyl-r-3-methylcyclohexene (38) by the method used to prepare the cyclohexane (42) from the cyclohexene (1). The product was shown to be homogeneous by GLC analysis (G,100°, 23.0 min).

B.P. 77-80° (block) / 17mm Hg (lit.[21] 75° / 20mm Hg).

r-1-tert-Butyl-t-3-methylcyclohexane (46):

r-1-tert-Butyl-t-3-methylcyclohexane (46) was prepared in 68% yield from t-5-tert-butyl-r-3-methylcyclohexene (39) by the method used to prepare the cyclohexane (42) from the cyclohexene (1). The product was shown to be homogeneous by GLC analysis (G,100°, 25.3 min).

B.P. 70-5° (block) / 15mm Hg (lit.[109] 163-175°).

r-1-tert-Butyl-c-4-methylcyclohexane (47):

r-1-tert-Butyl-c-4-methylcyclohexane (47) was prepared in 60% yield from r-3-tert-butyl-c-6-methylcyclohexene (41) by the method used

to prepare the cyclohexane (42) from the cyclohexene (1). The product was shown to be homogeneous by GLC analysis (G,100°, 26.0 min).

B.P. 76-82° (block) / 14mm Hg (lit.[205] 188.8°C / 760mm Hg).

r-1-tert-Butyl-c-3,c-5-dimethylcyclohexane (43) and
r-1-tert-butyl-c-3,t-5-dimethylcyclohexane (44):

(i) Hydrogenation of c-5-tert-butyl-1,r-3-dimethylcyclohexene (35) by the method used to prepare the cyclohexane (42) from the cyclohexene (1), gave a colourless oil which was shown by GLC analysis to be a mixture of two components (E,100°, 23.5 min (89%) and 25.3 min (11%)). These were assigned the structures r-1-tert-butyl-c-3,c-5-dimethylcyclohexane (43) (89%) and r-1-tert-butyl-c-3,t-5-dimethylcyclohexane (44) (11%) on the basis of the relative yields of the cyclohexanes (45) and (46) reported for hydrogenation of the cyclohexene (37).[21]

Yield 0.23g, 76%;

B.P. 78-80° (block) / 20mm Hg;

^{1}H NMR : δ0.87 (s,9H,-C(CH_3)$_3$), 0.90 (d,J=7Hz,6H,>CH-CH_3), and 0.95-2.40 (broad absorption,9H);

Found : C,85.7; H,14.5. C_{12} H_{24} requires C,85.6; H,14.4%.

(ii) Hydrogenation of t-5-tert-butyl-1,r-3-dimethylcyclohexene (36) by the method used to prepare the cyclohexane (42) from the cyclohexene (1), gave a colourless oil which was shown by GLC analysis to be a mixture of r-1-tert-butyl-c-3,c-5-dimethylcyclohexane (43) (12%) and r-1-tert-butyl-c-3,t-5-dimethylcyclohexane (44) (88%) (E,100°, 23.5 min (12%) and 25.3 min (88%)).

Yield 0.15g, 79%;

B.P. 75-8° (block) / 14mm Hg;

^{1}H NMR : δ0.86 (s,9H,-C($\underline{CH_3}$)$_3$), 0.88 (d,J=6Hz,6H,>CH-$\underline{CH_3}$), and 1.00-2.40 (broad absorption,9H);

Found: C,85.3; H,14.5. C_{12} H_{24} requires C,85.6; H,14.4%.

WORK DESCRIBED IN CHAPTER III.A.

Because of the sensitivity of the dioxanes (60)-(67) to traces of acid (Chapter III.A), they were freshly distilled from potassium carbonate prior to use, as was carbon tetrachloride. Di-tert-butyl peroxide was purified by passage through alumina.[210]

Kinetic study:

The relative rates of reaction of the dioxanes (60)-(67) with di-tert-butyl peroxide were determined by measuring their relative rates of consumption from a variety of mixtures of them (Method A). The mixtures investigated included: (60), (61), and (62); (61), (64), and (65); (62), (66), and (67); (60) and (63); and (63), (64), and (66).

Solutions of mixtures of the dioxanes (60)-(67) (c.0.01M total dioxane concentration) and di-tert-butyl peroxide (c.0.1M) in a mixture of pyridine (10%) and carbon tetrachloride (90%) were flushed with nitrogen and irradiated. After the appropriate time intervals, aliquots (2.0mL) were taken from the reaction mixture and an accurately weighed sample of a standard (one of the dioxanes (60)-(67) not involved in the study) was added. The solutions were then analysed by GLC to determine the amounts of the dioxanes (60)-(67) remaining. The GLC retention times of the dioxanes (60)-(67) are shown in Table V.2.

The relative amounts of the dioxanes (60)-(67) consumed in several typical experiments are shown in Table V.3. From values such as these the relative rates of reaction of the dioxanes (60)-(67) were determined using equation 1.

Table V.2

GLC Retention Times of the Dioxanes (60)-(67) (E,70°).

Dioxanes	Retention Time (minutes) [A]
(60)	19.0
(61)	17.5
(62)	60.0
(63)	19.7
(64)	79.0
(65)	42.0
(66)	16.7
(67)	23.2

A. Typical values whose absolute magnitudes may vary slightly.

Table V.3

Results of Competitive Reactions of the Dioxanes (60)-(67) with Di-tert-butyl Peroxide.

Reaction Time (h)	% Substrate Remaining		
	(60)	(61)	(62)
4	78	93	83
7	63	87	70
10	46	80	54
24	15	57	26
	(60)	(63)	
4	82	78	
7	69	61	
10	55	46	
24	30	21	
	(61)	(64)	(65)
3.5	94	74	97
6	91	56	95
8	86	44	93
18	78	25	88
	(62)	(66)	(67)
2	86	74	97
5	78	63	96
7.5	61	41	91
19	49	25	89

EPR study:

The relative rates of reaction of the dioxanes (60)-(67) with di-tert-butyl peroxide were determined by measuring the relative stationary concentrations of the radicals (145) and (152)-(156) produced upon irradiation of mixtures of the dioxanes (60)-(67) and di-tert-butyl peroxide (Method B).

Mixtures of the dioxanes (60)-(67) and di-tert-butyl peroxide, in which the peroxide to total substrate ratio was approximately 2:1 ($^{w}/_{w}$), were flushed with nitrogen and irradiated directly in the cavity of the EPR spectrometer. By integration of the signals arising from the radicals (145) and (152)-(158), the reactivities of the dioxanes (60)-(67) were determined using equation 13.

Diphenylmethan-1-d-ol-d (159):

A solution of benzophenone (2.0g, 1.1×10^{-2} mol) in dry ether (25mL) was added dropwise with stirring to a suspension of lithium aluminium deuteride (0.25g, 6×10^{-3} mol) in dry ether (25mL). The resultant mixture was refluxed for 2h, then cooled. Deuterium oxide (0.25mL), 10% sodium deuteroxide in deuterium oxide (0.25mL), and deuterium oxide (0.75mL), were added, and the mixture was stirred for ¼h, then filtered. The filtrate was concentrated to give a white solid which was recrystallized from dried light petroleum to give white flakes of diphenylmethan-1-d-ol-d (159).

Yield 1.45g, 72%;

M.P. 69-70°;

Mass Spectrum : d^0,2%; d^1,4%; d^2,94%.

Reaction of r-2-methoxy-c-4,c-6-dimethyl-1,3-dioxane (64) with benzophenone in perdeuterobenzene:

A solution of r-2-methoxy-c-4,c-6-dimethyl-1,3-dioxane (64) (0.25g, 1.7mmol) and benzophenone (0.31g, 1.7mmol) in perdeuterobenzene (30mL) was flushed with nitrogen and then irradiated. GLC analysis of an aliquot (c.1.0mL) taken from the reaction mixture after 1h indicated the presence of the dioxanes (64) (39%) and (65) (61%) (A,100°, 6.10 min (61%) and 7.50 min (39%)).

After the reaction mixture had been irradiated for 12h it was concentrated to c.2.0mL and analysed by ^{2}H NMR spectroscopy. Only one signal was observed and this was attributed to perdeuterobenzene.

Reaction of r-2-methoxy-t-4,t-6-dimethyl-1,3-dioxane (65) with benzophenone and diphenylmethan-1-d-ol-d (159) in benzene:

A solution of r-2-methoxy-t-4,t-6-dimethyl-1,3-dioxane (65) (0.25g, 1.7mmol), benzophenone (0.52g, 2.8mmol), and diphenylmethan-1-d-ol-d (159) (0.79g, 4.2mmol), in benzene (30mL), was flushed with nitrogen and then irradiated. GLC analysis of an aliquot (c.1.0mL) taken from the reaction mixture after 1h indicated the presence of the dioxanes (64) (34%) and (65) (66%) (A,100°, 6.10 min (66%) and 7.50 min (34%)).

After the reaction mixture had been irradiated for 12h it was concentrated. The residue was dissolved in chloroform (3.0mL) (freshly distilled from potassium carbonate) and filtered. The filtrate was analysed by ^{2}H NMR spectroscopy. The signals at 2.4 and 2.7 ppm downfield from perdeuterobenzene, which were in the approximate ratio 1:2, were attributed to the dioxanes (158) and (157) respectively.

Reaction of the 2-methoxy substituted dioxanes (61), (64), and (65), with di-tert-butylperoxyoxalate (143):

The relative rates of reaction of the dioxanes (61), (64), and (65), with di-tert-butylperoxyoxalate (143) were determined by comparing the relative amounts of acetone and tert-butanol formed in the reaction of each substrate with the peroxide (143).

Solutions of each of the dioxanes (61), (64), and (65), (0.05-1.0M) and di-tert-butylperoxyoxalate[47] (0.001-0.01M) in benzene were flushed with nitrogen, sealed in ampoules, and heated at 80° for ½h. The mixtures were then cooled, opened, and analysed by GLC (B,70°). Under these conditions the GLC retention times of acetone and tert-butanol were 4.9 min and 5.6 min respectively, and the response ratio of tert-butanol was 1.55 times that of acetone. The results of some typical experiments are shown in Table V.4.

Table V.4

Results of Competitive Reactions of the Dioxanes (61), (64), and (65), with Di-tert-butylperoxyoxalate (143)[A]:

Substrate	Substrate Concentration (M)	Ratio Acetone/ tert-Butanol
(61)	0.05	2.55
(61)	0.10	1.38
(61)	0.20	0.76
(64)	0.50	0.19
(65)	0.50	0.92

A. $[(143)] \simeq 1 \times 10^{-3}$M.

WORK DESCRIBED IN CHAPTER III.B.

Kinetic study:

The relative rates of reaction of r-2,c-3-dichloro-1,4-dioxane (68) and r-2,t-3-dichloro-1,4-dioxane (69) with tri-n-butyltin hydride were determined by measuring their relative rates of consumption from several mixtures of the two.

In a typical experiment aliquots (1.5mL) of a solution of r-2, c-3-dichloro-1,4-dioxane (68) (0.32g, 2.0mmol), r-2,t-3-dichloro-1,4-dioxane (69) (0.48g, 3.0mmol), and tri-n-butyltin hydride (2.9g, 9.7mmol), in benzene (8mL),* were placed in ampoules containing azoisobutyronitrile (c.10mg), flushed with nitrogen, sealed under a nitrogen atmosphere, and heated at 80°. After the appropriate time intervals the ampoules were cooled to 0° to quench the reaction, opened, and an accurately weighed sample of 4-tert-butylmethylenecyclohexane (72) was added. The solutions were then analysed by GLC and ^{1}H NMR spectroscopy. The ratios of the dioxanes (68)-(71) were determined by integration of the following resonances in the ^{1}H NMR spectra of the reaction mixtures:

δ5.96, s ((70), $\underset{-O}{\overset{-C}{>}}$CH-Cl, 1H),
δ5.78, s ((69), $\underset{-O}{\overset{-C}{>}}$CH-Cl, 2H),
δ5.31, s ((68), $\underset{-O}{\overset{-C}{>}}$CH-Cl, 2H), and
δ3.54, s ((71), $\underset{-O}{\overset{-C}{>}}CH_2$, 8H).

The amounts of the dioxanes (68)-(71) present in the mixtures were determined by GLC analysis. Qualitative identifications were made by comparing the GLC retention times of the components with those of authentic samples, and then by peak enhancement. Column C (150°) was used for

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* Because of the sensitivity of the dioxanes (68) and (69) to traces of acid[172,179] each of the reagents used in this reaction was freshly distilled from potassium carbonate prior to use.

this purpose. The amounts of the dioxanes (68)-(71) present in the mixtures were determined by comparison of the appropriate peak areas with that of the standard. On the basis of the observation that the ratios of the dioxanes (68)-(71) as determined by this method were the same as those determined by ^{1}H NMR spectral analysis, it was assumed that the dioxanes (70) and (71) had the same detector response ratios as (68) and (69). Any error introduced by this assumption has no affect on the determination of the relative rates of reaction of the dioxanes (68) and (69).

The amounts of the dioxanes (68) and (69) consumed in the described reaction are shown in Table V.5, Using values such as these the relative rates of reaction of the dioxanes (68) and (69) were determined using equation 1.

Table V.5

Results of A Competitive Reaction of the Dioxanes (68) and (69) with tri-n-Butyltin Hydride:

Reaction Time (h)	% Substrate Remaining	
	(68)	(69)
2	75	58
4	66	45
6	45	22
8	30	9

WORK DESCRIBED IN CHAPTER III.C.

1,3-Dioxane (60):

1,3-Dioxane (60) was prepared in 74% yield by the method of Clarke.[174] The product was shown to be homogeneous by GLC analysis (E,70°, 19.0 min).

B.P. 107-8° (lit.[174] 105° / 755mm Hg).

2-Methoxy-1,3-dioxane (61):

2-Methoxy-1,3-dioxane (61) was prepared in 65% yield by the method of Eliel and Giza.[73] The product was shown to be homogeneous by GLC analysis (E,70°, 60.0 min).

B.P. 47-9° / 18mm Hg (lit.[73] 142-4° / 745mm Hg).

2-Methyl-1,3-dioxane (62):

2-Methyl-1,3-dioxane (62) was prepared in 41% yield by the method of Rondestvedt.[175] The product was shown to be homogeneous by GLC analysis (E,70°, 17.5 min).

B.P. 108-110° (lit.[175] 109-110° / 760mm Hg).

r-2-Methoxy-c-4,c-6-dimethyl-1,3-dioxane (64) and
r-2-methoxy-t-4,t-6-dimethyl-1,3-dioxane (65):

A mixture of r-2-methoxy-c-4,c-6-dimethyl-1,3-dioxane (64) (33%) and r-2-methoxy-t-4,t-6-dimethyl-1,3-dioxane (65) (67%) was prepared in 84% yield by the method of Eliel and Nader.[79] The ratio of the dioxanes (64) and (65) was determined by GLC analysis (E,70°, 42.0 min (67%) and 79.0 min (33%)).

Spinning-band distillation[79] of this mixture gave a 34% yield of r-2-methoxy-t-4,t-6-dimethyl-1,3-dioxane (65) as the low boiling fraction.

B.P. 52-4° / 21mm Hg (lit.[79] 57-8° / 18mm Hg).

Recrystallization from light petroleum of the high boiling fraction gave a 15% yield of r-2-methoxy-c-4,t-6-dimethyl-1,3-dioxane (64) as white needles.

B.P. 72-5° / 21mm Hg (lit.[79] 72-3° / 18mm Hg);

M.P. 38-40° (lit.[79] 38-9°).

r-2,c-4,c-6-Trimethyl-1,3-dioxane (66):

r-2,c-4-c-6-Trimethyl-1,3-dioxane (66) was prepared in 65% yield by the method of Eliel and Knoeber.[78] The product was shown to be contaminated with 0.5% of the dioxane (67) by GLC analysis (E,70°, 16.7 min (99.5%) and 23.2 min (0.5%)).

B.P. 56-7° / 43mm Hg (lit.[78] 122-3°).

r-2,t-4,t-6-Trimethyl-1,3-dioxane (67):

r-2,t-4,t-6-Trimethyl-1,3-dioxane (67) was prepared in 35% yield by the method of Eliel and Nader.[79] The product was shown to be contaminated with 8% of the dioxane (66) by GLC analysis (E,70°, 16.7 min (8%) and 23.2 min (92%)).

B.P. 61-5° / 52mm Hg (lit.[79] 135-6° / 745mm Hg).

r-4,c-6-Dimethyl-1,3-dioxane (63):

r-4,c-6-Dimethyl-1,3-dioxane (63) was prepared in 54% yield by the method of Eliel and Nader.[80] The product was shown to be homogeneous by

GLC analysis (E,70°, 19.7 min).

B.P. 63-6° / 108mm Hg (lit.[80] 28° / 15mm Hg).

r-2,c-3-Dichloro-1,4-dioxane (68) and
r-2,t-3-dichloro-1,4-dioxane (69):

A mixture of r-2,c-3-dichloro-1,4-dioxane (68) (81%) and r-2,t-3-dichloro-1,4-dioxane (69) (19%) was prepared in 69% yield by the method of Summerbell and Lunk.[179] The ratio of the dioxanes (68) and (69) was determined by GLC analysis (C,150°, 21.8 min (81%) and 23.3 min (19%)).

r-2,c-3-Dichloro-1,4-dioxane (68) was separated from the mixture in 17% yield by repeated fractional crystallization.

M.P. 50-2° (lit.[179] 53°).

Reaction of a mixture of the dioxanes (68) (69%) and (69) (31%) with aluminium chloride in benzene by the method of Summerbell and Lunk[179] gave r-2,t-3-dichloro-1,4-dioxane (69) in 86% yield.

M.P. 27-31° (lit.[179] 28-30°).

2-Chloro-1,4-dioxane (70):

2-Chloro-1,4-dioxane (70) was prepared in 52% yield by the method of Vilsmaier.[180] The product was shown to be homogeneous by GLC analysis (C,150°, 19.6 min).

B.P. 64-7° / 18mm Hg (lit.[172] 62-3° / 14mm Hg).

WORK DESCRIBED IN CHAPTER IV.A.

General procedure for determination of yields of the products obtained from reactions of the olefins (72), (82), and (83), with tert-butyl perbenzoate in the presence of copper octanoate:

Copper octanoate (c.10mg) was added to a solution of the olefin (2mmol) and tert-butyl perbenzoate (0.23g,1mmol) in dry benzene under a nitrogen atmosphere. The mixture was refluxed for 8h, cooled, and carefully concentrated. The residual oil was dissolved in dry ether (3mL) and added dropwise to a suspension of lithium aluminium hydride (0.1g, 2.5mmol) in dry ether (2mL). The resultant mixture was refluxed for 3h, cooled, water (0.1mL), 10% aqueous sodium hydroxide (0.1mL), and water (0.4mL) were added, and the mixture was stirred for ½h. The precipitate was separated by filtration and washed with ether (2x3mL). The combined ether solutions were washed with water (2x3mL), dried (magnesium sulphate), and concentrated. The residual oil was dissolved in light petroleum (2.0mL) and an accurately weighed sample of an internal standard ((168) for reactions of the olefin (72), and (165) for reactions of the olefins (82) and (83)) was added. The mixture was then analysed as follows:

(a) Qualitative analysis: The products were initially identified by comparing the GLC retention times of the components with those of authentic samples, and by peak enhancement. Columns A (150°) and H (160°) were used for this purpose.

(b) Quantitative analysis: In calculating the yields of the products the response ratios of the alcohols (165)-(167) were assumed to be the same, as were those of the alcohols (168)-(171). The response ratio of (168) was determined to be 1.13 times that of (165). Using these values, determination of the peak areas by integration when the product mixtures were analysed by GLC (H,160°), enabled the yields of the products to be

determined. These are shown in Table IV.5 as percentages based on the amounts of the olefins (72), (82), and (83), consumed. Each experiment was conducted in triplicate and each analysis was performed in triplicate. The GLC retention times of the alcohols (165)-(171) are shown in Table V.6.

Table V.6

GLC Retention Times of the Alcohols (165)-(171).

Alcohol	Retention Time (minutes).[A]	
	Column A (150°)	Column H (160°)
(165)	11.0	7.5
(166)	13.5	10.2
(167)	16.2	15.4
(168)	8.9	6.1
(169)	8.9	8.0
(170)	15.4	14.6
(171)	8.9	7.6

A. Typical values whose absolute magnitudes may vary slightly.

The yields of the products obtained from reactions of the olefins (72) and (82) under the extended reaction times (page 101) were determined in the same way. Benzyl alcohol was produced in all of these reactions, but the yields were not determined.

Authentic samples of the allylic alcohols (165)-(171):

Authentic samples of the allylic alcohols (165)-(171) were obtained by chromatography on alumina of the crude product mixtures obtained from reactions of the olefins (72), (82), and (83), as described above.

When the crude product mixture obtained from the reaction of the olefin (72) was chromatographed on alumina, elution with light petroleum gave the starting olefin (72) (0.8g). Subsequent elution with light petroleum-ether (70:30) gave an oil which was distilled to give a colourless liquid that solidified on cooling. Recrystallization of the solid from light petroleum gave t-5-tert-butyl-2-methylenecyclohexan-r-1-ol (165) as white flakes.

Yield 0.29g, 17%;

B.P. 120-5° (block) / 15mm Hg (lit.[96] 116-118° / 12mm Hg);

M.P. 46-7° (lit.[182] 49°).

Continued elution of the column with light petroleum-ether (70:30) gave an oil which was distilled to give c-5-tert-butyl-2-methylenecyclohexan-r-1-ol (166) as a colourless liquid.

Yield 0.08g, 5%;

B.P. 132-6° (block) / 18mm Hg (lit.[96] 74° / 0.4mm Hg).

Elution of the column with light petroleum-ether (50:50) gave an oil which was distilled to give 4-tert-butylcyclohex-1-enylmethanol (167) as a colourless liquid.

Yield 0.11g, 6%;

B.P. 130-5° (block) / 17mm Hg (lit.[184] 99-100° / 0.5mm Hg).

When the crude product mixture obtained from the reaction of the olefin (82) was chromatographed on alumina, elution with light petroleum gave the starting olefin (82) (1.2g). Subsequent elution with light petroleum-ether (70:30) gave an oil which was distilled to give a colourless liquid that solidified on cooling. Recrystallization of the solid from light petroleum gave t-5-tert-butyl-1,t-3-dimethyl-2-methylenecyclohexan-r-1-ol (168) as white needles.

Yield 0.47g, 32%;

B.P. 124-6° (block) / 15mm Hg;

M.P. 39-42°;

^{1}H NMR ($CDCl_3$) : δ0.85 (s,9H,$-C(CH_3)_3$), 1.05 (d,J=6Hz,3H,>CH-CH_3), 1.40 (s,3H,$\overset{|}{C}-CH_3$), 1.00-2.90 (broad absorption,6H), 1.50 (m,1H,-OH,exch.), and 4.65 and 4.88 (m and m,2H,$>C=CH_2$);

ν_{max}(nujol) : 905(s), 1114(s), 1368(s), 1646(s), 3056(m), and 3375cm^{-1} (m,b);

Mass Spectrum : $^m/_e$ 196 ($M^{\cdot+}$)(11), 181(7), 178(4), 163(11), 139(46), and 57(100);

Found : C,79.5; H,12.1. $C_{13}H_{24}O$ requires C,79.5; H,12.3%.

Continued elution of the column with light petroleum-ether (70:30) gave an oil which was distilled to give c-5-tert-butyl-1,c-3-dimethyl-2-methylenecyclohexan-r-1-ol (169) as a colourless liquid.

Yield 0.20g, 14%;

B.P. 135-7° (block) / 12mm Hg;

^{1}H NMR ($CDCl_3$) : δ0.84 (s,9H,$-C(CH_3)_3$), 1.07 (d,J=6Hz,3H,>CH-CH_3), 1.32 (s,3H,$\overset{|}{C}-CH_3$), 1.00-2.50 (broad absorption,6H), 1.55 (m,1H,-OH,exch.),

and 4.60 and 4.98 (m and m,2H,>C=C$\underline{H}_2$);

ν_{max} : 898(s), 1110(s), 1365(s), 1643(s), 3053(m), and 3320cm^{-1}(m,b);

Mass Spectrum : $^{m}/_{e}$ 196 ($M^{\dagger}$)(8), 181(23), 178(20), 163(18), 139(61), 57(100), and 43(47);

Found : C,79.7; H,12.6. $C_{13}H_{24}O$ requires C,79.5; H,12.3%.

The reaction of c-4-tert-butyl-r-2,c-6-dimethylmethylenecyclohexane (82) was repeated, only this time the benzoylation reaction mixture was refluxed for an extra 72h prior to reduction. Again the crude product mixture was chromatographed on alumina. Elution with light petroleum gave the olefin (82) (0.9g). Subsequent elution with light petroleum-ether (70:30) gave the allylic alcohol (168) (0.17g, 12%), and later the allylic alcohol (169) (0.06g, 4%). Both (168) and (169) were identified by comparison of their spectral and physical properties with samples previously obtained.

Continued elution of the column with light petroleum-ether (70:30) gave an oil which was distilled to give r-4-tert-butyl-2,c-6-dimethylcyclohex-1-enylmethanol (170) as a colourless liquid.

Yield 0.19g, 13%;

B.P. 120-6° (block) / 15mm Hg;

^{1}H NMR ($CDCl_3$) : δ0.85 (s,9H,-C($C\underline{H}_3$)$_3$), 1.08 (d,J=6Hz,3H,>CH-$C\underline{H}_3$), 1.70 (s,3H, =C-$C\underline{H}_3$), 1.50 (m,1H,-O$\underline{H}$,exch.), 1.00-2.60 (broad absorption,6H), and 4.12 (s,2H,-$C\underline{H}_2$-OH);

ν_{max} : 1364(s) and 3303cm^{-1}(m,b);

Mass Spectrum : $^{m}/_{e}$ 196 ($M^{\dagger}$)(11), 179(12), 165(43), 139(18), and 57(100);

Found : C,79.5; H,12.3. $C_{13}H_{24}O$ requires C,79.5; H,12.3%.

When the crude product mixture obtained from the reaction of the olefin (83) was chromatographed on alumina, elution with light petroleum gave the starting olefin (83) (4.2g). Subsequent elution with light petroleum-ether (70:30) gave the allylic alcohol (168) (0.29g, 5%) which was identified by comparison of its spectral and physical properties with samples previously obtained.

Continued elution of the column with light petroleum-ether (70:30) gave an oil which was distilled to give t-5-tert-butyl-1,c-3-dimethyl-2-methylenecyclohexan-r-1-ol (171) as a colourless liquid.

Yield 0.12g, 2%;

B.P. 120-4° (block) / 15mm Hg;

^{1}H NMR ($CDCl_3$) : δ0.83 (s,9H,-C(CH_3)$_3$), 1.17 (d,J=7Hz,3H,>CH-CH_3), 1.33 (s,3H >C-CH_3), 0.90-2.50 (broad absorption,6H), 1.50 (m,1H,-OH,exch.), and 4.76 and 5.00 (m and m,2H, >C=CH_2);

ν_{max} : 904(s), 1365(s), 1645(s), 3043(m), and 3400cm^{-1}(m,b);

Mass Spectrum : $^m/_e$ 196 ($M^{\cdot+}$)(4), 181(11), 178(9), 163(13), 139(41), and 57(100);

Found : C,79.6; H,12.1. $C_{13}H_{24}O$ requires C,79.5; H,12.3%.

Further elution of the column with light petroleum-ether (70:30) gave the allylic alcohol (169) (0.14g, 2%) which was identified by comparison of its spectral and physical properties with samples previously obtained.

Analysis of the mixture of benzoates obtained as intermediates in the reaction of 4-tert-butylmethylenecyclohexane (72):

The crude product mixture obtained from reaction of the olefin (72)

(1.5g, 10mmol) with tert-butyl perbenzoate (1.0g, 5.2mmol) in the presence of copper octanoate (c.50mg), by the procedure described above, was chromatographed on silica. Elution with light petroleum gave 4-tert-butylmethylenecyclohexane (72) (0.54g). Subsequent elution with light petroleum-ether (90:10) gave an oil (0.67g) which was shown to be a mixture of three compounds by GLC analysis (A,210°, 14.6 min (55%), 19.0 min (16%), and 28.3 min (29%)). Two fractions were separated from the mixture by HPLC (ethyl acetate-light petroleum (1:20), 10mL min^{-1}, 12.2 min and 12.5 min). The first fraction was shown to be a mixture of two components by GLC analysis (A,210°, 14.6 min (73%) and 19.0 min (27%)) and was identified by its ^1H NMR spectrum as a mixture of t-5-tert-butyl-2-methylenecyclohex-r-1-yl benzoate (177) (73%) and c-5-tert-butyl-2-methylenecyclohex-r-1-yl benzoate (178) (27%).

^1H NMR ($CDCl_3$) : δ0.93 (s,9H,$-C(CH_3)_3$), 1.10-2.60 (broad m,7H), 4.80 (t,J=3Hz,0.27H,>CH axial-OCOPh), 5.00 and 5.20 (m and m,2H,$>C=CH_2$), 5.68 (t,J=3Hz,0.73,>CH equatorial-OCOPh), and 7.20-8.30 (m,5H,Ar-H).

The second fraction was shown to be homogeneous by GLC analysis (A,210°, 28.3 min) and was identified by its ^1H NMR spectrum as 4-tert-butylcyclohex-1-enylmethyl benzoate (179).

^1H NMR ($CDCl_3$) : δ0.96 (s,9H,$-C(CH_3)_3$), 1.00-2.50 (broad m,7H), 4.70 (s,2H,$-CH_2-O-$), 5.80 (m,1H,-CH=), and 7.20-8.40 (m,5H,Ar-H).

Reduction of a mixture of the benzoates (177) (73%) and (178) (27%) by the method used to reduce the intermediates in the reactions of the olefins (72), (82), and (83), gave a mixture of t-5-tert-butyl-2-methylene-cyclohexan-r-1-ol (165) (73%) and c-5-tert-butyl-2-methylenecyclohexan-r-1-ol (166) (27%) in 56% yield. The ratio of the alcohols (165) and (166) was determined by GLC analysis (A,150°, 11.0 min (73%) and 13.5 min (27%)).

A similar reduction of the benzoate (179) gave 4-tert-butylcyclohex-1-enylmethanol (167) in 39% yield. The product was shown to be homogeneous by GLC analysis (A,150°, 16.2 min).

Kinetic Study:

The relative rates of reaction of the olefins (72) and (80)-(83) with tert-butyl perbenzoate at 80°, in the presence of copper octanoate, were determined by measuring their relative rates of comsumption from a variety of mixtures of them (Method A). The mixtures investigated included: (72), (80), and (81); (72), (82), and (83); (72), (80), and (82); and (72) and (80)-(83).

Solutions of mixtures of the olefins (72) and (80)-(83) (c.0.1M total olefin concentration), tert-butyl perbenzoate (c.0.1M), and copper octanoate (c.0.001M), in benzene, were flushed with nitrogen and heated under reflux. After the appropriate time intervals aliquots (2.0mL) were taken from the reaction mixture and an accurately weighed sample of an internal standard (undecane, dodecane, or tert-butylbenzene) was added. The solutions were then analysed by GLC to determine the amounts of the olefins (72) and (80)-(83) remaining. The GLC retention times of the olefins (72) and (80)-(83), and of the compounds used as standards, are shown in Table V.7. The relative amounts of the olefins (72) and (80)-(83) consumed in a typical experiment are shown in Table V.8. From values such as these the relative rates of reaction of the olefins (72) and (80)-(83) were determined using equation 1.

The relative rates of reaction of the olefins (72) and (80)-(83) with di-tert-butyl peroxide at 145° were determined by measuring their relative rates consumption from a variety of mixtures of them (Method B).

Table V.7

GLC Retention Times of Compounds used in the Measurement of the Rates of Reaction of the Olefins (72) and (80)-(83) by Methods A and B.

Compound	Retention Time (minutes) [A]
(72)	16.9
(80)	22.3
(81)	18.8
(82)	31.1
(83)	24.5
Undecane	12.7
Dodecane	18.8
tert-Butylbenzene	22.3

A. Typical values whose absolute magnitudes may vary slightly.

Table V.8

Results of a Competitive Reaction of the Olefins (72) and (80)-(83) with tert-Butyl Perbenzoate in the Presence of Copper Octanoate, at 80°.

Reaction Time (h)	% Substrate Remaining				
	(72)	(80)	(81)	(82)	(83)
2	60	53	72	52	77
4	25	19	41	18	51
6	16	11	32	9	41

Table V.9

Results of a Competitive Reaction of the Olefins (72) and (80)-(83) with Di-tert-butyl Peroxide at 145°.

Reaction time (h)	% Substrate Remaining				
	(72)	(80)	(81)	(82)	(83)
0.5	72	66	76	64	76
1	57	51	62	50	61
2	29	24	38	20	33

The mixtures investigated included: (72), (80), and (81); (72), (82), and (83); (72), (80), and (82); and (72) and (80)-(83).

Aliquots (2.0mL) of a solution of mixtures of the olefins (72) and (80)-(83) (c.0.1M total olefin concentration) and di-tert-butyl peroxide (c.0.2M) in benzene, were placed in ampoules, flushed with nitrogen, sealed under a nitrogen atmosphere, and heated at 145°. After the appropriate time intervals the ampoules were cooled, opened, and an accurately weighed sample of an internal standard (undecane, dodecane, or tert-butylbenzene) was added. The solutions were then analysed by the procedure used to analyse the mixtures obtained by Method A. The relative amounts of the olefins (72) and (80)-(83) consumed in a typical experiment are shown in Table V.9. From values such as these the relative rates of reaction of the olefins (72) and (80)-(83) were determined using equation 1.

WORK DESCRIBED IN CHAPTER IV.B.

4-tert-Butylmethylenecyclohexane (72):

Methyltriphenylphosphonium bromide[206] (36.3g, 0.106 mol) was added to dry ether (100mL) under a nitrogen atmosphere and the resultant slurry was cooled to 0°. Potassium tert-butoxide (11.0g, 0.098 mol) was then added. After the slurry had been stirred for ½h at 0°, a solution of 4-tert-butylcyclohexanone (103) (14.0g, 0.091 mol) in dry ether (100mL) was added slowly over a period of 2h while the temperature was maintained at 0°. The reaction mixture was then stirred at room temperature for 4h, washed with water (3x500mL), diluted with hexane (300mL), washed again with water (2x400mL), dried (magnesium sulphate), and concentrated. The residual oil was distilled to give 4-tert-butylmethylenecyclohexane (72) as a colourless liquid which was shown to be homogeneous by GLC analysis (E,80°, 16.9 min).

Yield 7.9g, 57%;

B.P. 89-92° / 15mm Hg (lit.[207] 90° / 25mm Hg).

c-4-tert-Butyl-r-2-methylmethylenecyclohexane (80):

c-4-tert-Butyl-r-2-methylmethylenecyclohexane (80) was prepared in 79% yield from 4-tert-butyl-2-methylcyclohexanone (110) by the method used to prepare the olefin (72). The product was shown to be homogeneous by GLC analysis (E,80°, 22.3 min).

B.P. 78-80° / 14mm Hg (lit.[208] 78% / 20mm Hg).

t-4-tert-Butyl-r-2-methylmethylenecyclohexane (81):

A mixture of t-4-tert-butyl-r-2-methylmethylenecyclohexane (81) (5%) and c-4-tert-butyl-r-2-methylmethylenecyclohexane (80) (95%) was

prepared in 67% yield by the method of Senda, Kamiyama, and Imaizumi.[195] The ratio of the olefins (80) and (81) was determined by GLC analysis (E,80°, 18.8 min (5%) and 22.3 min (95%)).

B.P. 75-80° / 12mm Hg (lit.[195] 86-7° / 30mm Hg).

A sample of t-4-tert-butyl-r-2-methylmethylenecyclohexane (81) was separated from the mixture by preparative GLC (F,90°).[195]

c-4-tert-Butyl-r-2,c-6-dimethylmethylenecyclohexane (82):

(i) c-4-tert-Butyl-r-2,c-6-dimethylmethylenecyclohexane (82) was prepared in 82% yield from c-4-tert-butyl-r-2,c-6-dimethylcyclohexanone (95) by the method used to prepare the olefin (72). The product was shown to be homogeneous by GLC analysis (E,80°, 31.1 min).

B.P. 78-9° / 12mm Hg;

^{1}H NMR : δ0.85 (s,9H,-C(CH_3)$_3$), 1.03 (d,J=6Hz,6H,>CH-CH_3), 1.00-2.40 (broad absorption,7H), and 4.47 (m,2H,>C=CH_2);

ν_{max} : 885(s), 1366(s), 1644(s), and 3057cm^{-1}(m);

Mass Spectrum : $^m/_e$ 180 (M^+)(11), 165(10), and 57(100);

Found : C,86.9; H,13.1. $C_{13}H_{24}$ requires C,86.6; H.13.4%.

(ii) c-4-tert-Butyl-r-2,c-6-dimethylmethylenecyclohexane (82) was prepared in 75% yield from c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) by the method used to prepare the olefin (72). The product was shown to be homogeneous by GLC analysis (E,80°, 31.1 min) and was identical to the sample of (82) already obtained.

B.P. 76-8° / 18mm Hg.

(iii) c-4-tert-Butyl-r-2,c-6-dimethylmethylenecyclohexane (82) was

prepared in 60% yield from c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) by the method used to prepare the mixture of olefins (81) (5%) and (80) (95%). The product was shown to be homogeneous by GLC analysis (E,80°, 31.1 min) and was identical to the samples of (82) already obtained.

B.P. 76-9° / 15mm Hg.

c-4-tert-Butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (189) and t-4-tert-butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (188):

To the Grignard solution prepared from methyl iodide (5.0g, 0.035 mol), magnesium (0.8g, 0.033 mol), and dry ether (50mL), a solution of c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) (5.5g, 0.030 mol) in dry ether (25mL) was added dropwise over a period of 1h. The resultant solution was refluxed for 4h, cooled in ice, then treated dropwise with water (50mL) and 10% sulphuric acid (100mL). The organic and aqueous layers were separated and the aqueous layer was extracted with ether (2x100mL). The combined organic solutions were washed with water (2x150mL), 5% aqueous sodium bicarbonate (2x150mL), again with water (3x150mL), dried (magnesium sulphate), and concentrated. The residual oil was distilled to give a mixture of c-4-tert-butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (189) (36%) and t-4-tert-butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (188) (64%) as a colourless liquid. The ratio of the cyclohexanols (188) and (189) was determined by GLC analysis (A,120°, 9.3 min (36%) and 9.9 min (64%)).

Yield 4.9g, 82%;

B.P. 135-7° / 12mm Hg;

^{1}H NMR : δ0.83 (s,9H,-C(CH_3)$_3$), 0.86 (m,6H,>CH-CH_3), 1.06 (s,3H,-O-C-CH_3), 1.42 (m,1H,-OH,exch.), and 1.00-2.10 (broad absorption,7H);

ν_{max} : 1364(s), and 3400cm^{-1}(m,b);

Mass Spectrum : $^{m}/_{e}$ 198 ($M^{\cdot+}$)(26), 183(6), 165(12), 141(11), 123(46), 57(67), and 43(100);

Found : C,78.4; H,13.2. $C_{13}H_{26}O$ requires C,78.7; H,13.2%.

c-4-tert-Butyl-r-2,t-6-dimethylmethylenecyclohexane (83):

To an ice-cooled solution of a mixture of c-4-tert-butyl-1,c-2,-t-6-trimethylcyclohexan-r-1-ol (189) (36%) and t-4-tert-butyl-1,c-2,t-6-trimethylcyclohexan-r-1-ol (188) (64%) (4.9g, 0.025 mol) in N,N-dimethylaniline (30mL), acetyl chloride (4.7g, 0.050 mol) was added dropwise over ½h. The mixture was then warmed slowly to 80° and maintained at 80° for 3h. It was then cooled and poured onto 20% hydrochloric acid (100mL). The resultant mixture was extracted with light petroleum (3x80mL), and the combined extracts were washed with water (3x100mL), 5% aqueous sodium bicarbonate (3x100mL), again with water (3x100mL), dried (magnesium sulphate), and concentrated. Distillation of the residual oil gave a mixture of c-4-tert-butyl-1,c-2,t-6-trimethylcyclohex-r-1-yl acetate (191) (36%) and t-4-tert-butyl-1,c-2,t-6-trimethylcyclohex-r-1-yl acetate (190) (64%) as a colourless liquid. The ratio of the acetates (190) and (191) was determined by GLC analysis (A,90°, 8.8 min (36%) and 9.6 min (64%)).

Yield 3.6g, 60%;

B.P. 70-2° / 0.3mm Hg;

^{1}H NMR : δ0.83 (s,9H,-C(CH_3)$_3$), 0.95 (m,6H,>CH-CH_3), 1.42 (s,3H,-O-$\overset{\diagdown}{C}$-CH_3), 1.92 (s,3H,-OCOCH_3), and 1.00-1.90 (broad absorption,7H);

ν_{max} : 1369(s), and 1730cm^{-1}(s);

Mass Spectrum : $^{m}/_{e}$ 180 ($M^{\cdot+}$-60)(17), 166(16), 165(20), 123(59), 109(55),

57(100), and 43(77).

A mixture of c-4-tert-butyl-1,c-2,t-6-trimethylcyclohex-r-1-yl acetate (191) (36%) and t-4-tert-butyl-1,c-2,t-6-trimethylcyclohex-r-1-yl acetate (190) (64%) (2.0g, 0.08 mol) was slowly distilled under reduced pressure (18mm Hg) through a Vycor tube (50cm x 2.5cm) packed with silica beads and heated at 450°. The pyrolysate was collected in a trap cooled to -78° (dry ice - acetone). When the distillation was complete, water (5mL) was added to the pyrolysate and the mixture was extracted with light petroleum (3x5mL). The combined extracts were washed with water (2x10mL), 5% aqueous sodium bicarbonate (2x10mL), again with water (2x10mL), dried (magnesium sulphate), and concentrated. The residual oil was distilled to give a colourless liquid which was shown to be a mixture of three components by GLC analysis (E,80°, 24.5 min (54%), 30.6 min (30%), and 31.9 min (16%)). The mixture was chromatographed on silver nitrate impregnated silica.[152] Elution with light petroleum gave an oil which was distilled to give a mixture of c-5-tert-butyl-1,2,r-3-trimethylcyclohexene (192) (64%) and t-5-tert-butyl-1,2,r-3-trimethylcyclohexene (193) (36%) as a colourless liquid. These compounds were shown to be the two minor components of the crude product mixture by GLC analysis (E,80°, 30.6 min (64%) and 31.9 min (36%)).

Yield 0.35g, 24%;

B.P. 110-112° (block) / 15mm Hg;

^{1}H NMR : δ0.84 (s,9H,-C(CH_3)$_3$), 0.95 (d,J=6Hz,3H,>CH-CH_3), 1.55 (s,6H =C-CH_3), and 0.90-2.40 (broad absorption,6H);

ν_{max} : 1364cm^{-1} (s);

Mass Spectrum : $^m/_e$ 180 (M^+)(6), 165(9), 123(22), and 57(100);

Found : C,86.6; H,13.3. $C_{13}H_{24}$ requires C,86.6; H,13.4%.

Continued elution with light petroleum gave an oil which was distilled to give c-4-tert-butyl-r-2,t-6-dimethylmethylenecyclohexane (83) as a colourless liquid. This compound was shown to be the major component of the crude product mixture and to be contaminated with <1% of the olefin (82) by GLC analysis (E,80°, 24.5 min (>99%) and 31.1 min (<1%)).

Yield 0.45g, 31%;

B.P. 120-5° (block) / 15mm Hg;

^{1}H NMR : δ0.82 (s,9H,-C(CH_3)$_3$), 1.00 (d,J=6Hz,3H,>CH-CH_3 equatorial), 1.06 (d,J=6Hz,3H,>CH-CH_3 axial), 1.00-2.80 (broad absorption,7H), and 4.40 and 4.57 (m and m,2H,>C=CH_2);

ν_{max} : 887(s), 1366(s), 1646(s), and 3038cm^{-1}(m);

Mass Spectrum : $^m/_e$ 180 ($M^{\cdot+}$)(6), 165(8), 123(26), 57(44), and 43(100);

Found : C,86.6; H,13.5. $C_{13}H_{24}$ requires C,86.6; H,13.4%.

(ii) A solution of c-4-tert-butyl-r-2,t-6-dimethylcyclohexanone (97) (2.6g, 0.014 mol) in tetrahydrofuran (20mL) was added dropwise over ½h to a solution of phenylthiomethyl lithium in tetrahydrofuran-hexane (1.0M,20mL)[209] at 0°. The resultant mixture was stirred at room temperature for 3h, cooled to 0°, and a solution of acetic anhydride (4.0g, 0.040 mol) in tetrahydrofuran (20mL) was added dropwise. The mixture was stirred for 1h at room temperature, diluted with light petroleum (50mL), filtered, and the filtrate was concentrated. The residual oil was dissolved in ether (50mL) and added dropwise over ½h to a solution of lithium (1.4g, 0.2 mol) in ammonia (200mL). After an additional ½h, light petroleum (60mL) and ammonium chloride (6g) were added. The ammonia was allowed to evaporate over 12h, then water (50mL) and light petroleum (50mL) were added. The organic and aqueous layers were separated and the aqueous layer was extracted with light petroleum

(2x25mL). The combined organic solutions were washed with water (2x50mL), 10% aqueous sodium hydroxide (2x50mL), again with water (2x50mL), dried (magnesium sulphate), and concentrated. The residual oil was chromatographed on alumina. Elution with light petroleum gave an oil which was distilled to give c-4-tert-butyl-r-2,t-6-dimethylmethylenecyclohexane (83) as a colourless liquid. This compound was shown to be contaminated with <1% of the olefin (82) by GLC analysis (E,80°, 24.5 min (>99%) and 31.1 min (<1%)) and was identical to the sample of (83) already obtained.

Yield 1.7g, 67%;

B.P. 86-9° / 20mm Hg.

c-4-tert-Butyl-r-2-methylmethylenecyclohexane (80) and
t-4-tert-butyl-r-2-methylmethylenecyclohexane (81):

A mixture of t-4-tert-butyl-r-2-methylcyclohexanone (110a) (71%) and c-4-tert-butyl-r-2-methylcyclohexanone (110b) (29%), prepared by the method of Johnson, Duquette, Whitehead, and Dorman,[109] was treated according to the procedure used to prepare the olefin (83) from the cyclohexanone (97). The crude product was distilled to give a 56% yield of a mixture of c-4-tert-butyl-r-2-methylmethylenecyclohexane (80) (31%) and t-4-tert-butyl-r-2-methylmethylenecyclohexane (81) (69%) as a colourless liquid. The olefins (80) and (81) were identified by GLC analysis (E,80°, 18.8 min (69%) and 22.3 min (31%)) and by comparison of the spectral properties of the mixture with those of samples of (80) and (81) already obtained.

B.P. 78-83° / 27mm Hg.

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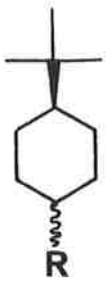

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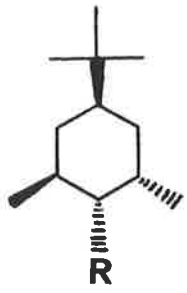

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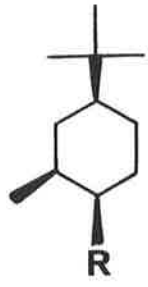

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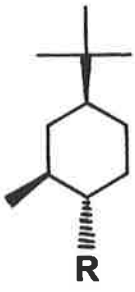

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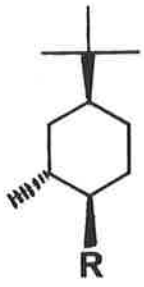

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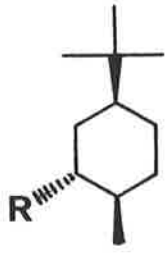
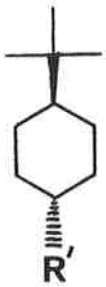


(30)

a) R=OH

b) R=OCOCOCl

c) R=OCOCOOOC$(CH_3)_3$



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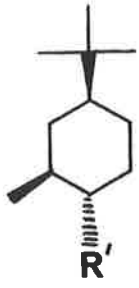

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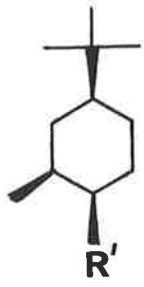

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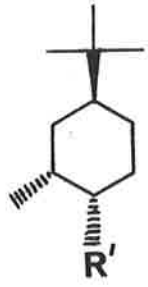
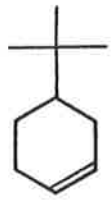


(34)

a) R′=COOH

b) R′=COCl

c) R′=$COO\frac{+}{2}$



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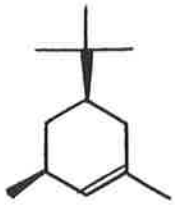

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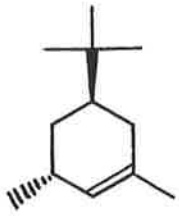

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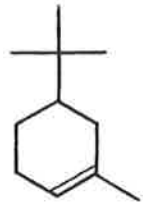

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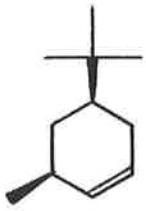

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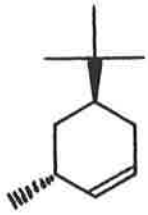

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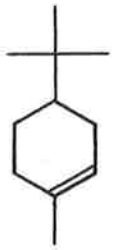

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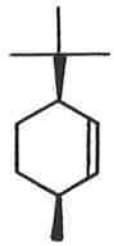

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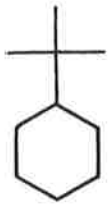

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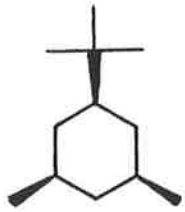

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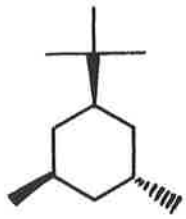

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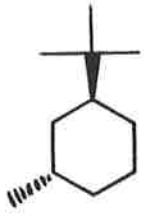

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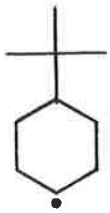

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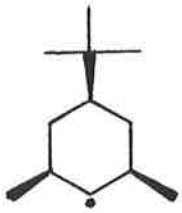

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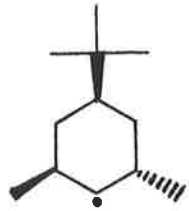

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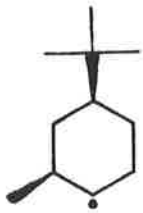

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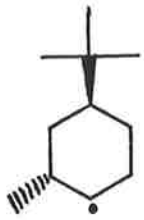

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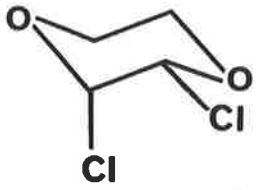

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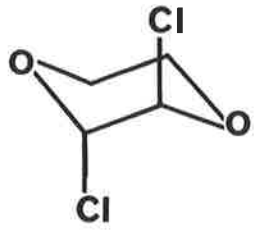

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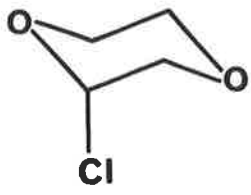

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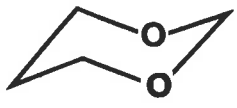

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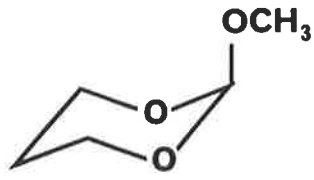

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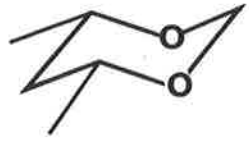

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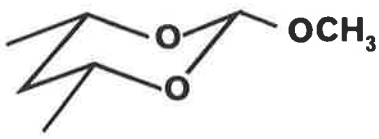

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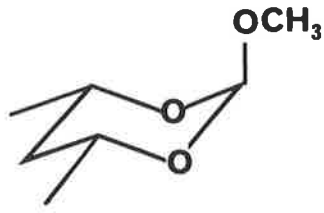

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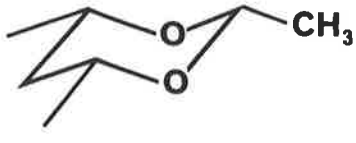

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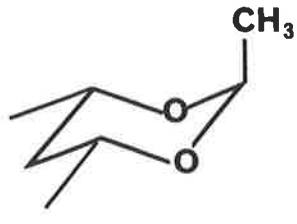

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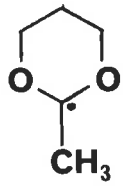

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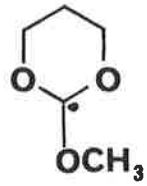

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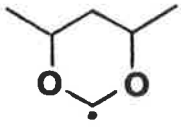

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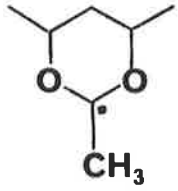

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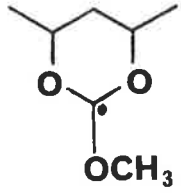

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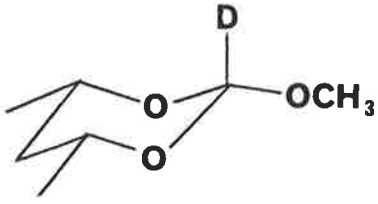

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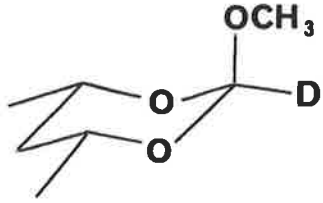

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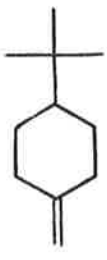

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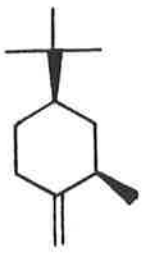

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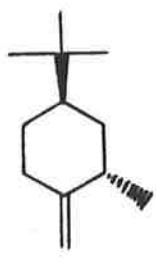

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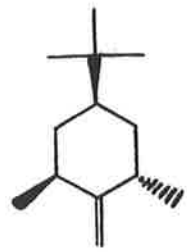

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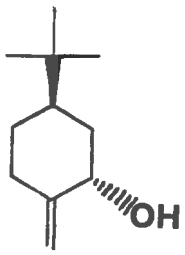

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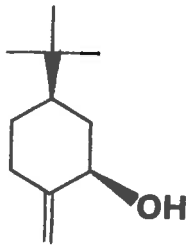

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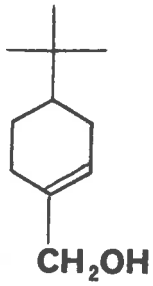

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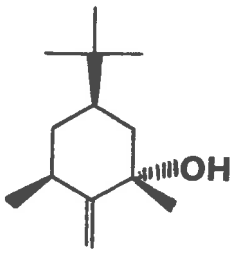

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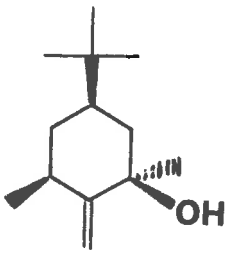

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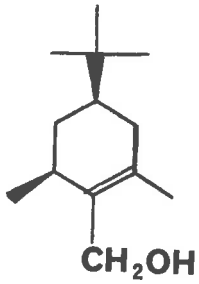

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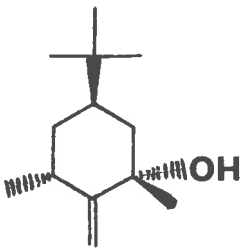

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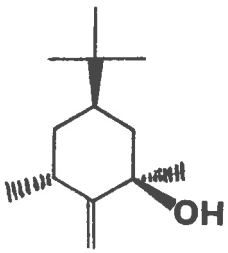

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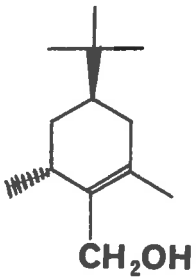

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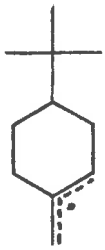

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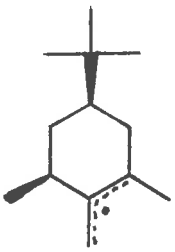

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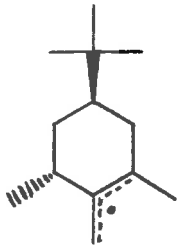

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