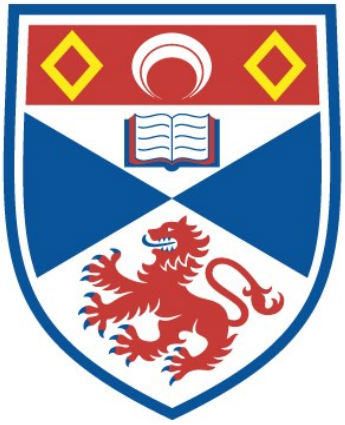
FREE RADICAL REARRANGEMENTS OF CYCLOHEXA - 2.5 - DIENE DERIVATIVES AND STRAINED POLYCYCLIC COMPOUNDS

Gavin Binmore

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews

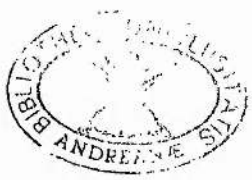


1995

Free Radical Rearrangements of Cyclohexa-2,5-diene Derivatives and Strained Polycyclic Compounds.

A thesis presented by Gavin Binmore, B.Sc., to the University of St. Andrews in application for the degree of Doctor of Philosophy.

April 1995.



Declarations

I, Gavin Thomas Binmore, hereby certify that this thesis has been composed by myself, that it is a record of my own work and that it has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

Signed _____ Date 18th April 1995

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on the 1st of October 1991 and as a candidate for the degree of Ph.D. on the 1st of October 1992.

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Contents

Chapter 3

9-Homocubyl and 9-Basketyl Radicals.

Chapter 4

The Norcubylcarbinyl Radical.

Part Three: Bicyclo[1.1.1]pent-1-yl & Bicyclo[2.2.2]oct-1-yl Radicals.

Chapter 5

The Chemistry of 3-Substituted Bicyclo[1.1.1]pent-1-yl Radicals.

Chapter 6

The Chemistry of 4-Substituted Bicyclo[2.2.2]oct-1-yl Radicals.

Acknowledgements

Sincerest gratitude goes first and foremost to Dr. John C. Walton whose undisputed enthusiasm and expert knowledge of Chemistry has made my Ph.D. at St. Andrews both interesting and productive.

Thanks are due to Dr. Ernest W. Della and Dr. William Adcock, Flinders University, South Australia, who along with their co-workers have synthesised the many compounds that have yielded such interesting results. Warm thanks also go to the R.S. Lumsden bequest for a maintenance grant which made this research possible. The technical staff at the Chemistry Department in St. Andrews, especially Jim 'Mac' Bews. To all the friends I have made in the laboratory over the last three years, especially John Park and Ahmed Iraqi. Also to those I am indebted to who believed I was capable of this work, you know who you are.

Away from chemistry I would like to sincerely thank my parents, Jason my 'bro', Jane my 'sis' and Max and Sam, I should also like to thank Ian Gregory, Mary and Teddy (the poodle) for the roof over my head. Last but not least, to Jennifer for her support through troubled times. Thank you.

List of Abbreviations

AIBN	Azo-bisisobutyronitrile
AM	Austin Method
δ	Relative To Tetramethylsilane
BOOB	Di-*tert*-Butyl Peroxide
COSY	Correlated Spectroscopy
DCC	Dicyclohexylcarbodiimide
EIMS	Electron Impact Mass Spectrometry
EPR	Electron Paramagnetic Resonance
ESR	Electron Spin Resonance
GC	Gas Chromatography
GC/MS	Gas Chromatographic Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
hfs	Hyperfine Splittings
IR	Infra Red
MINDO	Modified Intermediate Neglect of Differential Overlap
NBS	*N*-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
SE	Strain Energy
SOMO	Semi-Occupied Molecular Orbital
TMS	Tetramethylsilane
THF	Tetrahydrofuran
UV	Ultra Violet

Abstract

Esters of cyclohexa-2,5-diene-1-carboxylic acid were investigated to study the transfer of the labile bisallylic hydrogens (C-4) to give the cyclohexadienyl radical and then the subsequent decarboxylative stage to give R•, the driving force being the rearomatisation of the benzene ring. The undesirable reaction, whereby hydrogen is abstracted from C-1, was prevented by the introduction of a methyl group into this position.

The cyclohexa-2,5-diene-1-carboxylic acids are readily prepared by a Birch type reduction of benzoic acid. All the esters derived from cyclohexa-2,5-diene-1-carboxylic acid, were examined by EPR spectroscopy and showed the cyclohexadienyl radical. No decarboxylation was evident by this technique. Also investigated, by EPR spectroscopy, were the acids with different substituents at C-1, showing that for acids with highly stabilised alkyl substituents, decomposition occurs. Esters reacted with *N*-bromosuccinimide showed some of the desired bromides, formed after CO_2 loss from the cyclohexadienyl radical. Esters forming non-stabilised radicals on decarboxylation have given the intended products in lower yields. The esters have also been examined in reactions with acrylonitrile, addition being observed to varying degrees.

The radicals generated from 9-hydroxy- and 9-bromo-pentacyclo-[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (homocubane) and for the same derivatives of pentacyclo-[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]decane (basketane) were observed by EPR spectroscopy. In spite of their very large strain energies both radicals rearranged extremely slowly and unrearranged products were obtained from homolytic reactions in solution at temperatures below 150°C. At higher temperatures the 9-basketyl radical rearranged by a cascade of three β-scissions, the ultimate product being 1-(4-cyclobut-2-enyl)cyclohexa-2,4-diene. The 9-homocubyl radical did not rearrange even at 220°C. Several reasons why these cage radicals rearrange at least six orders of magnitude more slowly than the related cubylcarbinyl radical are discussed. Photobromination of basketane yielded a mixture of four tetrabromides which were formed by bimolecular homolytic substitution at every bridgehead.

Norcubylcarbinyl radicals, that were generated by bromine abstraction from norcubylcarbinyl bromide, rearranged so rapidly that only the product of β-scission, 6-methylenebicyclo[3.1.1]hept-3-yl, could be observed by EPR spectroscopy. The rate constant for β-scission was estimated from the EPR experiments, and from reductions of norcubylcarbinyl bromide with tributyltin hydride, to be $> 5x10^9\ s^{-1}$ at 298K.

A series of 3-substituted bicyclo[1.1.1]pent-1-yl radicals, including the 3-fluoro-derivative, was generated by bromine atom abstraction from 1-bromo-3-substituted-bicyclo[1.1.1]pentanes and examined by EPR spectroscopy. The exceptionally large hyperfine splittings obtained from magnetic nuclei of the 3-substituents indicated that cross-cage electronic interactions were substantial in these species. Bromine atom abstraction by triethylsilyl radicals from 1-bromo-3-fluorobicyclo[1.1.1]pentane was found to take place more rapidly than bromine abstraction from the unsubstituted parent, i. e. the fluorine substituent mediated a significant polar effect. Evidence was found of a novel disproportionation process in which the γ-fluorine atom was transferred from the 3-fluoro-radical to a triethylsilyl or to a second bicyclo[1.1.1]pent-1-yl radical; an analogous chlorine atom transfer process was found for the 3-chloro-radical.

4-Substituted bicyclo[2.2.2]oct-1-yl radicals were generated by bromine atom abstraction from the corresponding 1-bromobicyclo[2.2.2]octanes and observed in solution by EPR spectroscopy. The EPR data indicated that 4-substituents exercised a significant effect at the radical centre, mainly by a through bond mechanism. 10-Substituted triptycyl radicals were generated in a similar way but showed no hfs from magnetic nuclei of the substituents. Bicyclo[2.2.2]oct-1-yl radicals were added to benzene, *tert*-butylbenzene and 1,3-di-*tert*-butylbenzene to give cyclohexadienyl radicals which were characterised by EPR spectroscopy. The bicyclo[2.2.2]oct-1-yl radical generated in *tert*-butylbenzene showed exclusive *meta* addition with formation of the corresponding 1-polycyclo-3-*tert*-butylcyclohexadienyl radical.

To Mum and Dad

"The meeting of two personalities is like the contact of two chemical substances: if there is any reaction, both are transformed."

- Carl Gustav Jung,
Modern Man in Search of a Soul (1933).

Part One:

Derivatives of

Cyclohexa-1,4-diene

As Radical Sources

Chapter 1

Derivatives of Cyclohexa-1,4-diene As Radical Sources

1.0 Background

Free radicals are reactive intermediates of considerable importance in the development of organic chemistry. However, despite a detailed understanding of the reactivity of organic radicals, the synthetic application of free radical reactions has lagged behind.

Instead of attempting to provide comprehensive coverage of every utilisation of free radical chain reactions, this introduction is an overview of reactions that involve the production of carbon dioxide as a side product, i.e., free radical reactions involving decarboxylative processes. "Clean" methods for generating free radicals $R^{\bullet}$, are required for various synthetic procedures. Few reactions are known whereby decarboxylation occurs via a free radical pathway.

Highlighted in this introduction are five known methods for conducting decarboxylative radical reactions, along with their benefits and drawbacks: the Kolbe synthesis, the Hunsdiecker reaction, the peroxy decarboxylation, the thiohydroxamic acid ester (Barton) method and the chain reaction involving *S*-alkoxycarbonyl dithiocarbonates. Each method has unique characteristics allowing the preparation of compounds previously difficult to synthesise (the Barton method being the basis for the preparation of a number of compounds used in the work described in this dissertation; Chapter 5, Section 5.1) and others which were pioneering reactions in the history of organic chemistry. As will be seen the main difficulties associated with these reactions are either the toxicity of the reagents, or the formation of undesirable side products.

In recent years interest in the use of radicals in organic synthesis has expanded and currently there is a period of rapid growth in the application of radical chemistry.[1] The purpose of this work is to develop a versatile alternative synthetic method based on the decarboxylative chain reaction of cyclohexa-2,5-diene-1-carboxylic acid and its esters. Further, to use these pathways for new cyclisation and addition reactions.

1.0.1 Kolbe Synthesis[2]

The first process by which alkyl radicals were formed, via a decarboxylative process, was in fact the first general hydrocarbon synthesis ever discovered. Prior to the Kekulé structure theory, Liebig regarded ether as the oxide of the ethyl radical and ethyl alcohol as the hydrate of this oxide. The ethyl radical, then, should bear the same relationship to its oxide as a metal (Na) does to its oxide (Na_20). Since sodium and other metals were known as such, isolation of ethyl radicals seemed an objective worth researching.

In 1849, the German chemist Kolbe[3] found that electrolysis of an aqueous solution of a salt of the acid C_4H_9COOH gave a hydrocarbon assumed to have the formula C_4H_9 and to be the butyl radical. Kolbe's "butyl radical" was surprisingly inert, had a perturbingly high boiling point and molecular weight determinations which were twice that expected. In 1850, Sir Benjamin Brodie resolved the issue, concluding that if a butyl radical had formed, it had combined with a second radical to form a stable molecule of twice the size (C_4H_9-C_4H_9).

$$2\,C_4H_9COO^-Na^+ \;+\; 2\,H_2O \xrightarrow{\text{Electrolysis}} \underbrace{C_8H_{18} \;+\; 2\,CO_2}_{\text{Anode}} \;+\; \underbrace{2\,NaOH \;+\; H_2}_{\text{Cathode}}$$

Figure 1.0

The Kolbe Reaction.

Under the influence of the electric current, sodium ions migrate to the cathode, pick up electrons from the inflowing stream and yield sodium hydroxide and hydrogen. The butylcarboxylate anion gives up its charge at the anode to form a transient acyloxyl free radical, and quickly loses carbon dioxide to form a butyl radical, which achieves stabilisation by coupling with a second butyl radical to form octane. The drawback of this method is the obvious inability of the reaction to form, uniquely, unsymetrical

hydrocarbons. For example, electrolysis of a mixture of the acid salts, $RCOO^-K^+$ and $R'COO^-K^+$ yields both the unsymetrical product R-R' and the two symmetrical hydrocarbons R-R and R'-R'.

1.0.2 Hunsdiecker Reaction

The degradation of a silver salt of a carboxylic acid in anhydrous medium, in the presence of a halogen, to an alkyl halide of one carbon atom less than the original acid[4] can be expressed by the equation in Figure 1.1. This wide scope reaction is

Figure 1.1

The Hunsdiecker Reaction.

called the Hunsdiecker reaction[5] and gives good results for R being alkyl or aryl. The reaction has also been titled the "silver salt reaction" or "silver salt-halogen reaction" and some[6] have named it the Borodine reaction in recognition of its discovery by Borodine[7] in 1861. The extensive reach of the reaction also allows functional groups

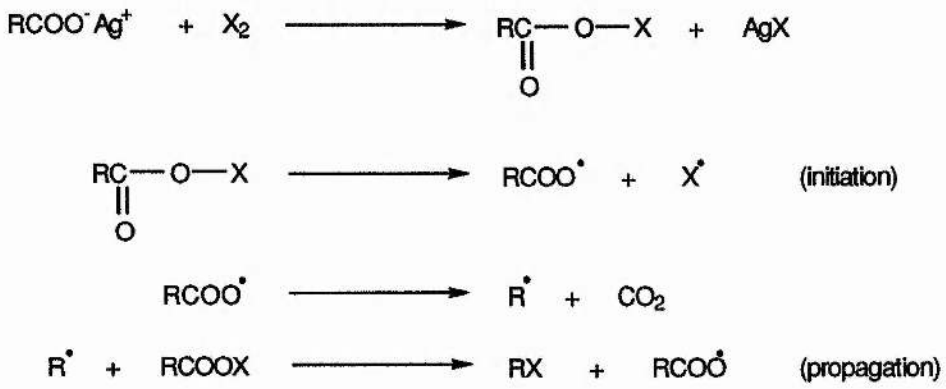


Figure 1.2

Mechanism of the Hunsdiecker Reaction.

to be present in R as long as they are not α-substituted, however, if R contains unsaturation the reaction does not give good results.

Normally the ratio between the reactants is 1:1. However a 2:1 ratio of salt to iodine gives the ester RCOOR and is called the Simonini reaction. The mechanism of the Hunsdiecker reaction[8] is shown in Figure 1.2. The first step is not a free radical process, and its actual mechanism is not known. An acyl halite is presumed to be formed as an intermediate although it has never been isolated.

Figure 1.3

The Cristol-Firth Reaction.

A more convenient way to perform the Hunsdiecker reaction is by use of a mixture of the acid and mercuric oxide instead of the salt. This process, known as the Cristol-Firth reaction[9] overcomes the difficulty of preparing the very pure and dry silver salts needed in the Hunsdiecker reaction.

1.0.3 Peroxy Decarboxylation[10]

At 100 - 180°C pyrolysis of dialkyl peroxides is the most convenient and reliable source of free radicals for initiating chain and other homolytic reactions. The most common being *tert*-butyl peroxide. The alkoxy radical may also be formed

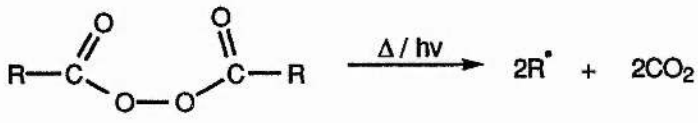


Figure 1.4

Decarboxylation of Diacyl Peroxides.

photolytically and *tert*-butyl peroxide has again been examined in several photolytic studies.[11]

The direct photolytic and pyrolytic method is also applicable to the decomposition of diacyl peroxides (Figure 1.4), this method being an excellent way of forming primary alkyl radicals. Further to this point photolysis of peroxy esters also leads to decomposition via decarboxylation.[12] Photolysis of *tert*-butyl peroxyacetate yielding observable methyl radicals in solution.

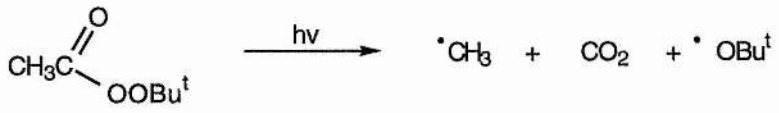


Figure 1.5

Decarboxylation of *tert*-Butyl Peroxyacetate.

The limitations involved with using peroxides, as a class of compounds, is their exceptional sensitivity to violent decomposition induced by mechanical shock or heating. The peroxide bond, -O-O-, is weak, leading to a tendency for spontaneous change toward more stable products. Coupled with this is their exceptional lability to catalysts and promoters that accelerate decomposition.

1.0.4 Barton Thiohydroxamate Ester Method

Barton and co-workers[13,14] have recently developed a successful free radical transformation involving the chemistry of thiohydroxamic acid esters (**1**), the ester usually being formed by the reaction of an acid chloride with the sodium salt of *N*-hydroxypyridine-2-thione. The simple experimental procedure and the wide variety of transformations of intermediate radicals has meant the method has been increasingly adopted for synthetic applications.

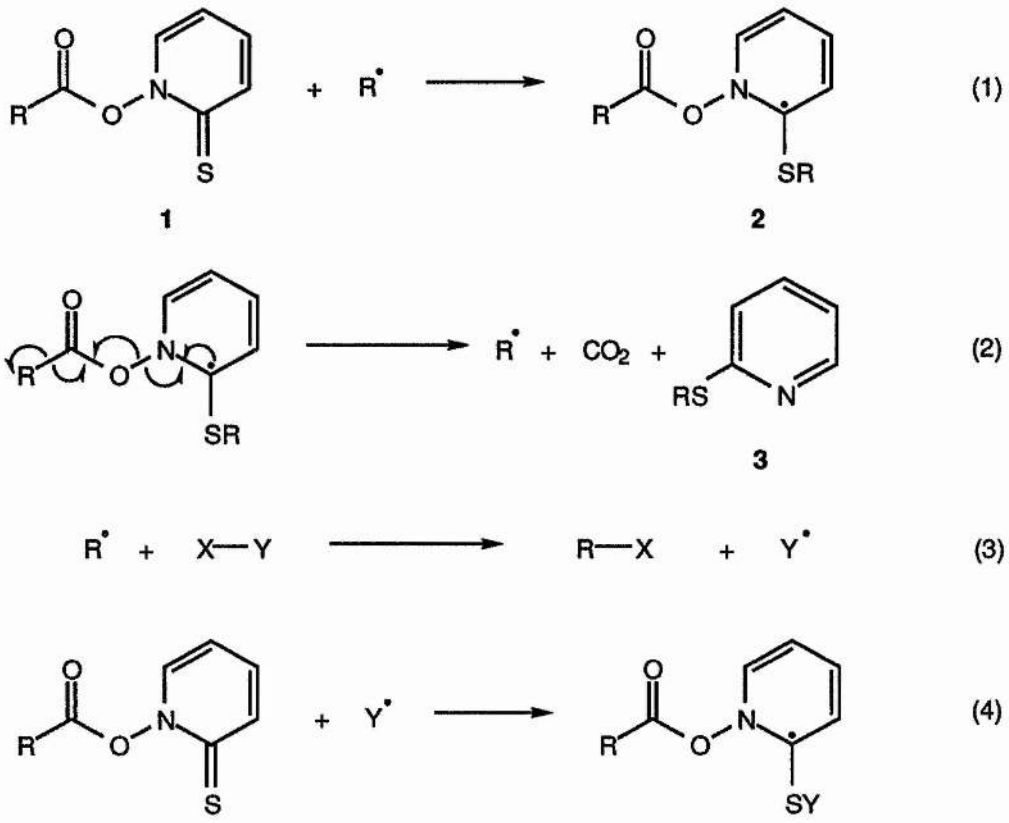


Figure 1.6

Mechanism for the Barton Ester Decarboxylation.

Mechanistic studies by Barton have provided good evidence for the propagation sequence in Figure 1.6. Addition of the alkyl radical R• to the thiohydroxamate **1** produces the radical **2** (step 1). Fragmentation of **2** (step 2) may be concerted or stepwise, involving an intermediate carboxyl radical. It is important to recognise that a

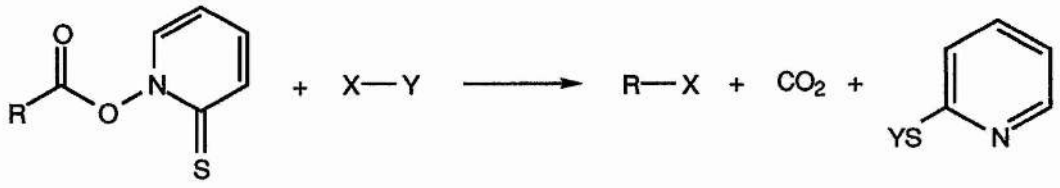


Figure 1.7

Reaction of the Barton Ester With a Molecule X-Y.

carbon is lost from the chain in the Barton method.

Although the decarboxylative transformations of acids to pyridyl sulphides is useful, the real power of the Barton method is in the ability of the intermediate radicals R• to be intercepted by a variety of other molecules, X-Y (Figure 1.7). Requirements for successful formation of R-X are outlined in steps 3 and 4 of Figure 1.6. The rate of abstraction of an atom or group (X) from X-Y (step 3) by the alkyl radical must be more rapid than direct addition to the starting hydroxamate (step 1). A wide variety of groups X can be introduced by this general approach (Figure 1.8).[15,16,17-24] The halogenation process is noteworthy as it would appear to offer substantial advantages over the traditional Hunsdiecker reaction, most notably that of cost.

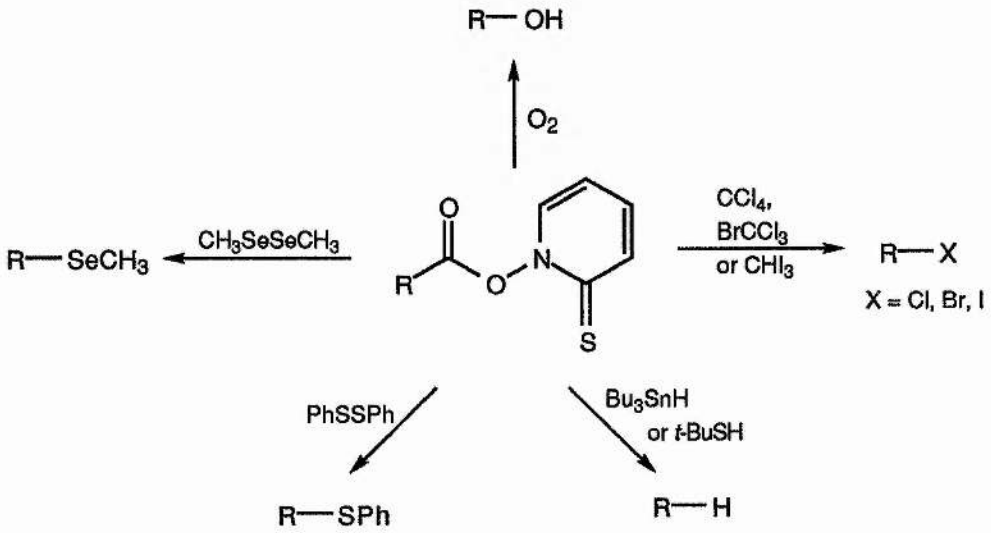


Figure 1.8

The Variety of Transformations of Thiohydroxamic Esters.

1.0.5 *S*-Alkoxycarbonyl Dithiocarbonates[25]

The methods shown above all involve processes in which a carboxyl radical is/may be formed. In this process the generation of alkyl radicals is through decarboxylation of the corresponding alkoxycarbonyl radical, derived from *S*-alkoxycarbonyl dithiocarbonates. Only recently has this novel procedure come to light

and follows an investigation by S.Z. Zard and co-workers into the radical chemistry of dithiocarbonates and xanthates.[26]

Alkoxycarbonyl radicals (ROCO•) have seldom found use as precursors of the corresponding alkyl radicals (R•), mainly because release of carbon dioxide from these species is relatively slow in comparison with other possible competing reactions.[27-29] If ROCO• radicals are to be used as useful precursors of the corresponding alkyl radicals they must be generated in such a way as to give sufficient lifetime to allow them to extrude CO_2.

The system based on **4** fulfils this crucial condition. As outlined in Figure 1.9, the alkoxycarbonyl radical formed on irradiation of *S*-alkoxycarbonyl xanthates can react in two ways. It can react with its precursor (path A) in which case **5** can only collapse back to the same alkoxycarbonyl radical and its precursor. Therefore, this reaction does not compete with the expulsion of CO_2 (path B), in sharp contrast to processes based on the chemistry of thiohydroxamate esters,[28] where competition restricts their synthetic utility to examples involving an especially rapid decarboxylation step, as is the case when a relatively stabilised alkyl radical is produced.

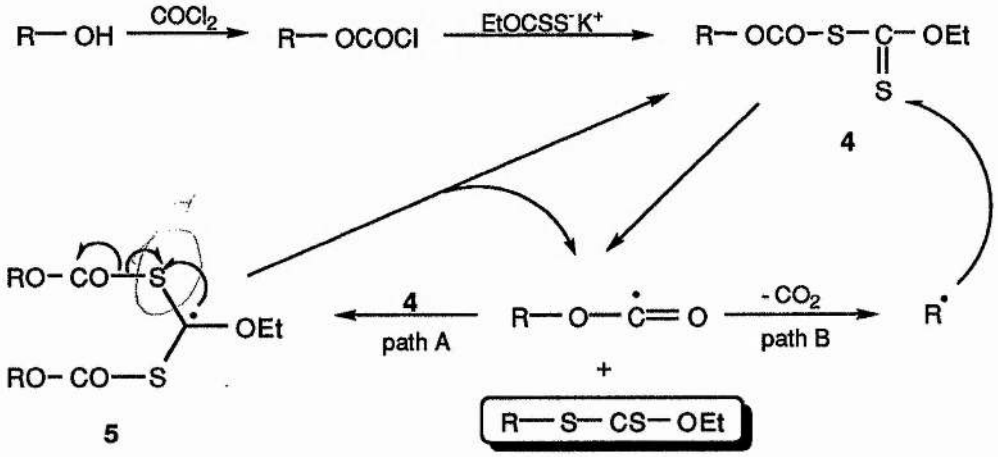
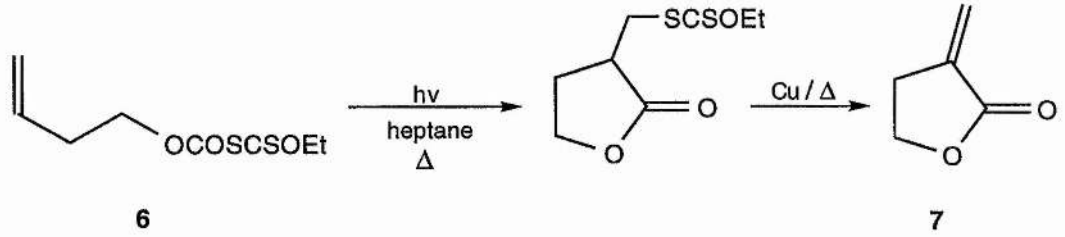


Figure 1.9

Decarboxylation of *S*-Alkoxycarbonyl Dithiocarbonates.

The simplest process whereby an alcohol is converted into the corresponding *S*–xanthate through a radical chain mechanism (the overall result being the replacement of a C-O with a C-S bond), was studied in detail by Zard and Forbes for a number of alkyl groups. One especially interesting reaction (Figure 1.10) is the conversion of **6** derived from 3-buten-1-ol into the lactone and subsequent elimination of the xanthate group by heating with copper powder[30] to form tulipalin A (**7**).



6 **7**

Figure 1.10

Formation of Tulipalin A.

This experiment shows not only unarguable evidence as to the radical nature of the mechanism but also the flexibility of the reaction.

Clearly both the Barton thiohydroxamate ester method and the *S*-alkoxycarbonyl dithiocarbonate method are high yielding and, more importantly, versatile. The drawback is in their use of reactants, and related reagents, which are either toxic, or form undesirable side products. The sulphur containing reactants are not only pungent smelling but also form side products that are sometimes difficult to separate.

1.1 Introduction

The primary aim of the project was to develop a synthesis of an ester that could rearrange via a homolytic pathway to give a specific free radical, carbon dioxide and a volatile, non toxic by-product.

It was decided to concentrate on esters that contained allylic, or bisallylic, hydrogens which are highly labile towards transfer by carbon-centred radicals, so that intermediate delocalised radicals would be formed with high selectivity. Antecedent projects involved using a 5-bromo derivative of pent-3-enoic acid esters, to study whether they would decarboxylate (Figure 1.11).

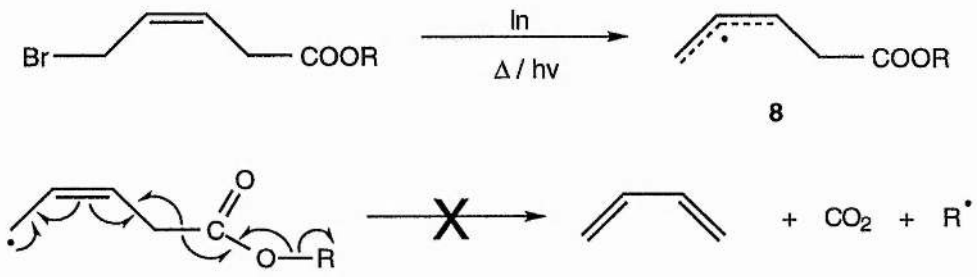
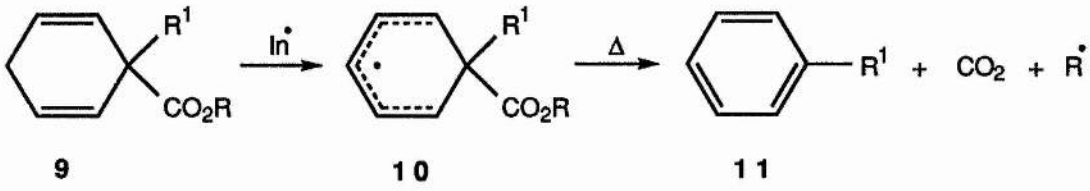


Figure 1.11

Reaction of 5-Bromopent-3-enoic Acid Ester.

The intermediate **8**, was observed by EPR spectroscopy, but decarboxylation was neither detected by EPR nor by chemical reaction. The concept of this project was to investigate the esters of various 1-substituted cyclohexa-2,5-diene-1-carboxylic acids (**9**) and to study the transfer of the labile bisallylic hydrogens at C-4 to give the cyclohexadienyl radical (**10**) (Figure 1.12) and then the subsequent decarboxylative stage to give R•. Formation of the aromatic product will provide the driving force for decarboxylation. The alkyl radical R• produced in this step is then able to take part in intra- or inter-molecular reactions before continuing the chain by reacting with another molecule of **9**.

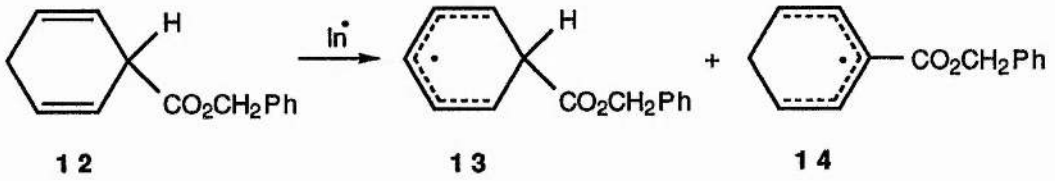


9 10 11

Figure 1.12

The Proposed Mechanism for Decarboxylation of **9**.

The introduction of an alkyl substituent into C-1 of **9** is essential if the reaction is to work efficiently. Initially, the simplest esters (R^1 = H, R = $PhCH_2$, **12**) were investigated.[29] Reaction showed some of the intended products, i.e., the expected chain sequence took place, but they were in low yields and additional side products were encountered. Examination of the intermediate radicals by EPR spectroscopy allowed us to understand why such poor yields were obtained. On photolysis of **12** the spectrum showed the presence of two cyclohexadienyl radicals (**13** and **14**), in comparable amounts, i.e. hydrogen abstraction had occured with little or no selectivity. The problem arises from the inability of **14** to decarboxylate, and hence leads to a convoluted reaction.



12 13 14

Figure 1.13

Formation of the Undesirable Radical **14**.

To circumvent this problem it was decided to prepare esters with alkyl substituents of low molecular weight at the C-1 position, hence blocking the possibility of forming the undesirable intermediate **14**. The attractive feature of such a substitution is that in each case the aromatic by-product (**11**) is easily removed because

of its volatility and it would be comparitively benign. Moreover a large substituent at C-1 could sterically hinder the reaction of the acid with the alcohol, and lead to an aromatic with a higher boiling point, thereby hindering separation of the aromatic and the radical product. It was therefore decided to initially form esters containing a methyl substituent at the C-1 position.

1.2 Preparation of 1-Alkylcyclohexa-2,5-diene-1-carboxylic Acids (Birch Reduction)

When aromatic rings are reduced by alkali metals (Li, Na and K) in liquid ammonia, usually with an alcohol, 1,4-addition of hydrogen takes place. This type of reduction is known as a 'dissolving metal reduction' or a Birch reduction.

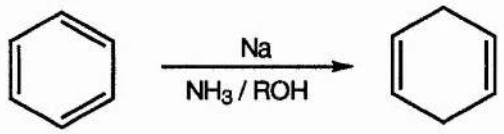


Figure 1.14

1,4-Dihydro-addition.

When substituted aromatics are subjected to Birch reduction the product obtained is controlled by the nature of the substituent. Hence if it is an electron-donating group, such as alkyl or alkoxyl, the reaction rate is decreased and the substituent is generally found on the *non reduced* positions of the product. On the other hand, an increased reaction rate is produced if electron withdrawing groups such as COOH and $CONH_2$ are present and they are found on the *reduced* positions of the product.

The mechanism (Figure 1.15) involves direct transfer of electrons from the metal, to the solvent, to the aromatic ring. The lithium becomes oxidised to Li^+ and a

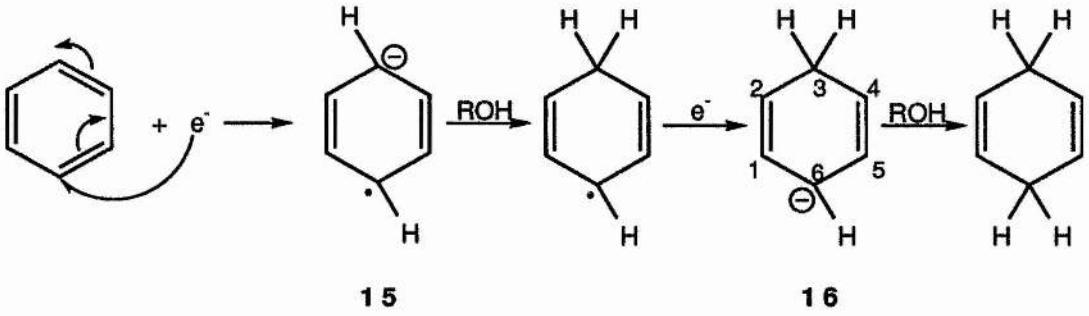


Figure 1.15

Mechanism for Birch Reduction.

radical anion, **15**, is created. This then accepts a proton from the alcohol to form a radical, which is in turn reduced to a carbanion (**16**) by another lithium atom. Finally, **16** accepts another proton to give the product.

The intermediate **16** is a resonance hybrid and can be written in three ways. It therefore poses the question of why the 1,4-diene is produced and not the 1,3-isomer? An explanation was provided by Hine who suggested that this was an example of the "principle of least motion".[31] This states that "those elementary reactions will be favoured that involve the least change in atomic position and electronic configuration". The principle can be applied to this case in the following way: The valence bond orders for the 6 C-C bonds (on the assumption that each of the 3 forms contributes equally) are (going around the ring) $1^2/_3$, 1,1, $1^2/_3$, $1^1/_3$ and $1^1/_3$. When the carbanion is converted to the diene, these bond orders change. The two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there *is* a change. If the 1,4-diene is formed, the change is $1^1/_3$, while formation of the 1,3-diene requires a change of 2 (Figure 1.16). Since a greater change is required to form the 1,3-diene, the principle of least motion predicts the formation of the 1,4-diene. Also, ^{13}C NMR of **16** shows that the 6-position has a somewhat greater electron density than the 2-position, thus making the former seemingly more attractive to a proton.[32]

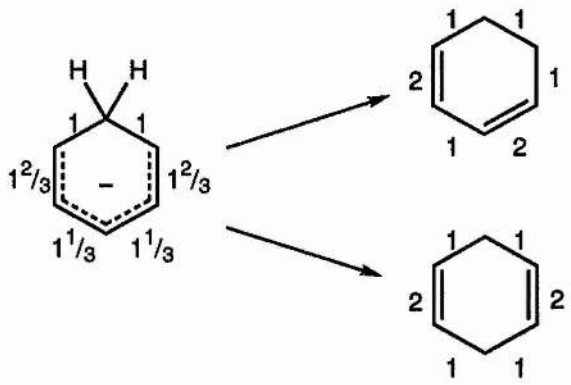


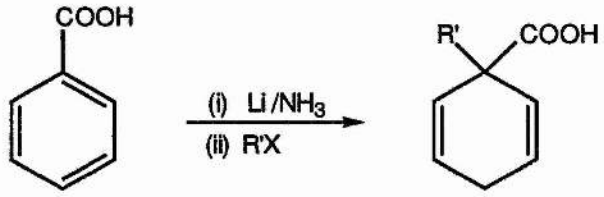
Figure 1.16

The change in Valence Bond Order For **16**.

As alkyl-substituted, reduced acids (**17**) are not commercially available it was necessary to prepare **17** by the method described below. It was known that cyclohexa-2,5-diene-1-carboxylic acid is readily prepared by Birch type reduction of benzoic acid, using sodium metal.[33,34] The usual method of preparation is to add a proton donor, ammonium chloride, to introduce a hydrogen at the 1-position. However the formation of **17a** using methyl iodide instead of ammonium chloride proved ineffective, the product obtained being the unmethylated cyclohexa-2,5-diene-1-carboxylic acid.

After a further study of the literature,[35] it was decided to take a different approach. This involved the addition of lithium to a suspension of the benzoic acid in liquid ammonia (Figure 1.17), in the absence of any other proton donor i.e. ethanol or water. The reaction is technicoloured, the solution turning yellow, orange and green, lithium addition only being stopped when a permanent navy blue colour was obtained (usually 2.5-3.5 molar equivalents of lithium were needed). Subsequently, addition of a large excess of methyl iodide was found to introduce the methyl group selectively and exclusively into the C-1 position. The reaction is efficient and high yielding, as long as there is a plentiful excess of solvent ammonia (at least 40ml per g of benzoic acid).

If however the reaction is done on a large scale and the quantity of ammonia is not subsequently increased (12ml per g of benzoic acid) the reaction mixture becomes slurry like, and the exothermicity produced, by the addition of the alkyl iodide, brings about a strong uncontrollable effervescence leading to loss of product from the reaction vessel.



X = Br, I

		R'
17	a	CH_3
	b	$CH(CH_3)_2$
	c	$C(CH_3)_3$
	[d	C_6H_5]

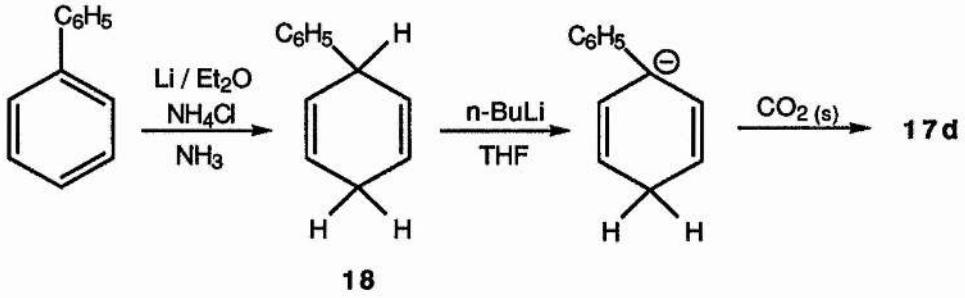
Figure 1.17

Preparation of 1-Alkylcyclohexa-2,5-diene-1-carboxylic Acids (**17**).

Both **17b** and **17c** were prepared by the procedure described for **17a**, using isopropyl bromide and *tert*-butyl iodide as the alkylating agents. However the yields were not as high, 62% and 32% for **17b** and **17c** respectively. This may well be due to the increasingly bulky nature of the substituent hindering attack at the C-1 position of the carboxylate analogue of the carbanion **16**.

The phenyl substituted acid (**17d**) was understandably, unable to be prepared by the method described above; presumably the iodobenzene was reduced on addition to the reaction mixture. This theory is supported by the persistence of a strong red colour after addition of the iodobenzene, showing that destruction of the radical intermediate was not complete. In the case of **17a-c** addition of the corresponding alkyl halide returned the solution to a yellow-white colour.

A literature search revealed a preliminary communication that described a synthesis of **17d** as a two step reaction (Figure 1.18).[36] Firstly, biphenyl was



18

Figure 1.18

Preparation of **17d**.

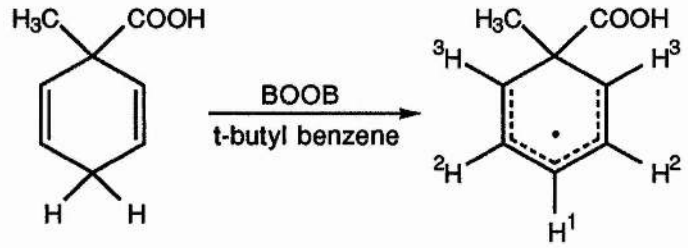
selectively reduced by a Birch reduction of one aromatic ring,[37] the reaction being quenched by the addition of a large excess of ammonium chloride. Biphenyl was initially dissolved in THF. However, this led to the need to remove the THF before work up of the reduced product (**18**). The reaction was found to work equally well with sodium dry ether bypassing this complication. Further reduction was avoided by partition between brine and ether, separating the dihydrobiphenyl product (**18**) from the ammonia solution. The previous practice of allowing the ammonia to evaporate before isolation of the product tended to lead to isomerisation and other secondary processes.

Carboxylation was undertaken by quenching, with carbon dioxide, the anion which results from the treatment of **18** with n-butyl lithium. The carbon dioxide was bubbled through the solution by means of evaporating cardice. This process formed a very small amount of a strong smelling, viscous liquid which was shown by proton NMR to contain some acidification (-COOH at 9.5ppm) but mainly a complex mixture of organic residues including **18**. This mixture was unable to be separated by crystallisation or distillation.[38]

1.3 Study of the Acids by EPR Spectroscopy

The acids formed, and isolated, i.e. **17a,b** and **c** were investigated by EPR to ensure hydrogen abstraction would occur exclusively at the C-4 position and to study the ease at which this abstraction would take place. The reaction was initiated by *tert*-

butoxyl radicals derived from di-*tert*-butyl peroxide (BOOB) and was carried out in *tert*-butylbenzene. Photolysis of the methyl substituted acid (**17a**) gave rise to a clean spectrum under EPR conditions [$g = 2.003 \pm 0.001$, $a(1H^1) = 13.20$, $a(2H^3) = 9.20$, $a(2H^2) = 2.65$ G at 220K, see Figure 1.23 for identical spectrum] of the single cyclohexadienyl radical (**19**, Figure 1.19). Radical **19** persisted up to *ca.* 400K, which indicated no decomposition was occuring. The analysis of the spectrum was verified by computer simulation.

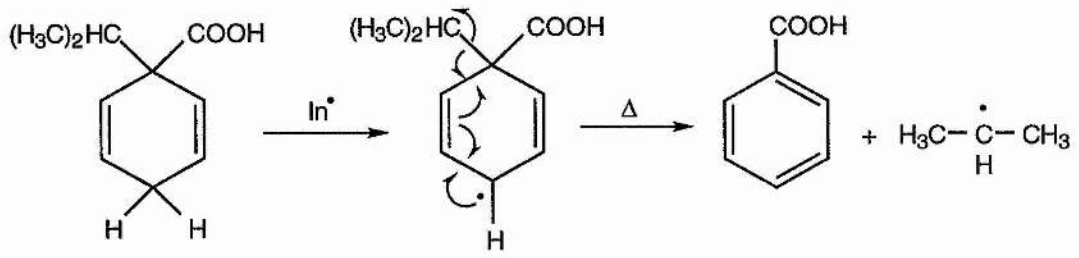


19

Figure 1.19

Study of **17a** by EPR Spectroscopy.

The isopropyl acid (**17b**) also showed the cyclohexadienyl radical (**20**, see Figure 1.23 for similar spectrum) in studies undertaken at low temperatures (*ca.* 220K), with almost identical splittings to **19** [$g = 2.003 \pm 0.001$, $a(1H^1) = 13.30$, $a(2H^3) = 9.20$, $a(2H^2) = 2.80$ G at 220K], although the spectrum was of larger line width. As the temperature was increased the spectrum became broader and less intense, until at 300K a different spectrum was observed. The radical, detected at the higher temperature, was identified from the literature as being the isopropyl radical [$g = 2.003 \pm 0.001$, $a(1H) = 21.9$, $a(6H) = 24.8$ G 300K].[39] The isopropyl radical is derived from the decomposition of **20** (Figure 1.20) and was clearly dependent on the temperature. An increase in the temperature, leads to an increased rate of decomposition of **20**, over possible termination processes such as dimerisation. Hence there is a decrease in the stationary state concentration of **20** and an increase in



20

Figure 1.20

The Thermal, Radical Decomposition of **20**.

the concentration of the isopropyl radical, leading to the observation of the latter. This theory was justified by the observance of the radical **20** on returning to the lower temperature.

In theory, the *tert*-butyl substituted cyclohexadienyl radical should decompose more readily than both **19** and **20**, as the *tert*-butyl radical is thermodynamically more stablised than either the primary methyl or secondary isopropyl radical. This was found to be the case with the *tert*-butyl radical [$g = 2.003 \pm 0.001$, a(9H) = 22.75 G at 230K][39] being the only species observed at temperatures as low as 105K, in propane solvent.

The decomposition of **19** and **20**, to give the secondary and tertiary radicals respectively, is clearly a reaction worthy of further investigation, as a source of alkyl radicals. However, in the context of decarboxylation studies, the use of esters with secondary and tertiary groups at the C-1 position would not lead to decomposition of the esters via the decarboxylative pathway. In the case of **19** and **20**, the benzoate formed upon decomposition of the ester would be unable to decarboxylate by a radical reaction. It would obviously be desirable to utilise thermally stable acids, i.e. substituents at C-1 that would form high energy radicals on decomposition, and it was therefore decided to study esters derived from the 1-methyl substituted acid (**17a**).

1.4 Preparation of 1-methyl-2,5-cyclohexadienoates

The first step involved the formation of the acid chloride (**21**) using oxalyl chloride in dry ether (Figure 1.21), in an overnight reaction.[40] Compound **21** was isolated by distillation on a Kugelrohr and purification was verified by IR spectroscopy. The IR spectrum showed no broad -OH stretch but a carbonyl band at 1800 cm^{-1}, indicative of an acid chloride.

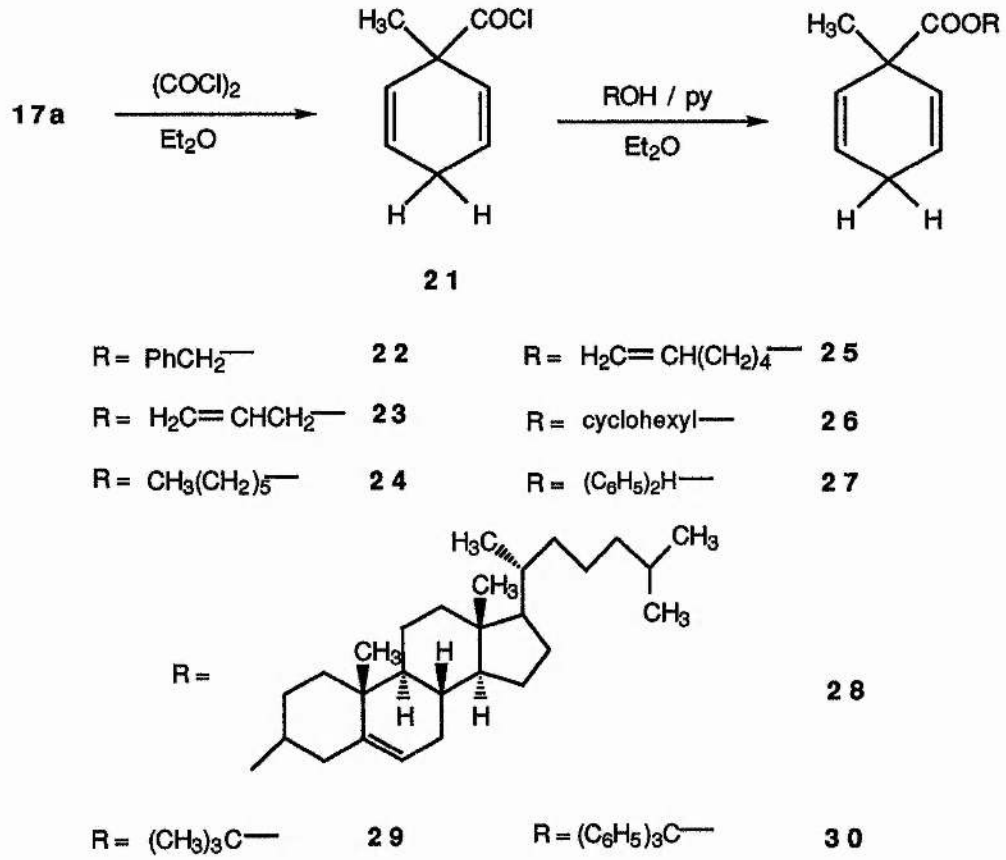


Figure 1.21

Preparation of Various 1-Methylcyclohexa-2,5-dienoates.

The isolated acid chloride was then reacted with various alcohol/pyridine 1:1 mixtures in dry ether.[41] Preparation of esters **22-28** proved to be straightforward with varying yields obtained (Table 1.0), optimisation being achieved only for the

benzyl ester (see Experimental Section). The cholesteryl ester (**28**) was found to be more difficult to purify due to a small percentage of cholesterol in the final product. The solubilities of both cholesterol and **28** were similar, in a range of solvents, and so

Table 1.0 Yields of Esters **22-30**.

Starting Alcohol (R-OH)	Yield (%)
benzyl → (**22**)	90[a]
allyl → (**23**)	45
hexyl → (**24**)	76
hexenyl → (**25**)	60
cyclohexyl → (**26**)	61
diphenylmethyl → (**27**)	27
cholesteryl → (**28**)	55[b]
tert-butyl → (**29**)	79
triphenylmethyl → (**30**)	0[c]

[a] Optimised Yield. [b] Yield after five recrystallisations, yield after column chromatography not available. [c] No reaction (see text).

separation by recrystallisation proved a time consuming and unproductive method. Eventually the ester was separated by column chromatography using a neutral alumina packing, the ester coming through on the solvent front.

It was found that the tertiary alcohols corresponding to **29** and **30** would not react with **21** giving as the products, the initial starting material **17a**. Such alcohols that can form stable carbocations, are precluded from substantial ester formation by the by-product in acid chloride-ester reactions, hydrogen chloride, although pyridine is present to overcome this problem. In the case of **29**, the ester was synthesised via the lithium alkoxide salt of the alcohol, bypassing this difficulty.[42] The salt was prepared by treatment of the alcohol with n-butyl lithium, followed by addition of an equivalent

of the acid chloride (**21**), and a reflux for one hour (Figure 1.22). Although this reaction proved to be adequate for *tert*-butyl alcohol, forming **29** in good yields (79%), it was an ineffective method for the trityl alcohol. No product was isolated or observed for the reaction of either the trityl alcohol with the acid chloride (Figure 1.21) or the

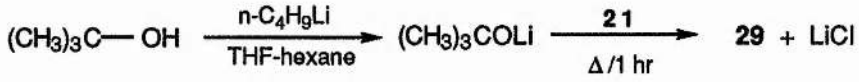


Figure 1.22

The Preparation of the *tert*-Butyl Ester.

acid chloride with the lithium triphenylmethoxide salt (Figure 1.22). It was therefore concluded that the non reaction of triphenylmethanol must be due to some other restricting factor, most likely steric hinderance due to the bulky triphenylmethyl group. This may well be the reason for the low yields obtained, in the formation of the diphenylmethyl ester (**27**), from the substantial biphenylmethyl group. All the esters prepared, that were liquids at room temperature (**22-26, 29**), were found to decompose slowly at room temperature and in sunlight and so were redistilled before further use.

Finally it should be noted that attempts to obtain accurate microanalyses for any of the esters proved a fruitless task, except for **22**, which had to be distilled six times, and analysed immediately, before a close result was achieved. A problem was also encountered when the esters were investigated by EIMS, with no molecular ion observed, due to loss of the ester moiety during analysis.

1.5 Study of 1-Methyl-2,5-cyclohexadienoates by EPR Spectroscopy

The aim of this study was to see if the esters **22-29** would decarboxylate in the confines of the EPR cavity. As was the case for the acids, the reaction was initiated by *tert*-butoxyl radicals and was carried out in *tert*-butylbenzene. At low temperatures

(215-240K) the radical observed, for all compounds analysed, was the cyclohexadienyl radical (Figure 1.19), the analyses of the spectra were verified by computer simulation. (Figure 1.23 and 1.24). By increasing the temperature up to 390K, it was hoped decarboxylation would take place causing a change in the spectrum. However this was not to be the case and no change was evident for even the esters with highly stabilised groups (R = benzyl, allyl and *tert*-butyl). Indeed this was the reasoning behind forming the ester with the very highly stabilised radical, diphenylmethyl (**27**). However it should be noted, that for **27**, the spectrum weakened in intensity, more dramatically than for the others, as the temperature was raised. This may well be an indication that a small degree of decarboxylation was taking place. Following is a table of the hyperfine splittings observed for the esters examined (Table 1.1). The table shows that the ester function had only marginal effects on the hyperfine splittings of the cyclohexadienyl radicals.

Table 1.1. Hfs for the Cyclohexadienyl Radicals Derived From Esters **22-29**.[a]

Compound	Temp (K)	$a(2H^2)$ (G)	$a(2H^3)$ (G)	$a(H^1)$ (G)
17a[b]	220	2.65	9.20	13.20
22	220	2.70	9.20	13.25
23	220	2.65	9.20	13.35
24	215	2.75	9.30	13.35
26	215	2.75	9.30	13.40
27	220	2.70	9.25	13.40
28	240	2.75	9.25	13.30
29	220	2.70	9.25	13.40

[a] Hexenyl ester (**25**) was not studied by EPR and is presumed to have the same hfs.

[b] The hfs for the acid are included for completeness.

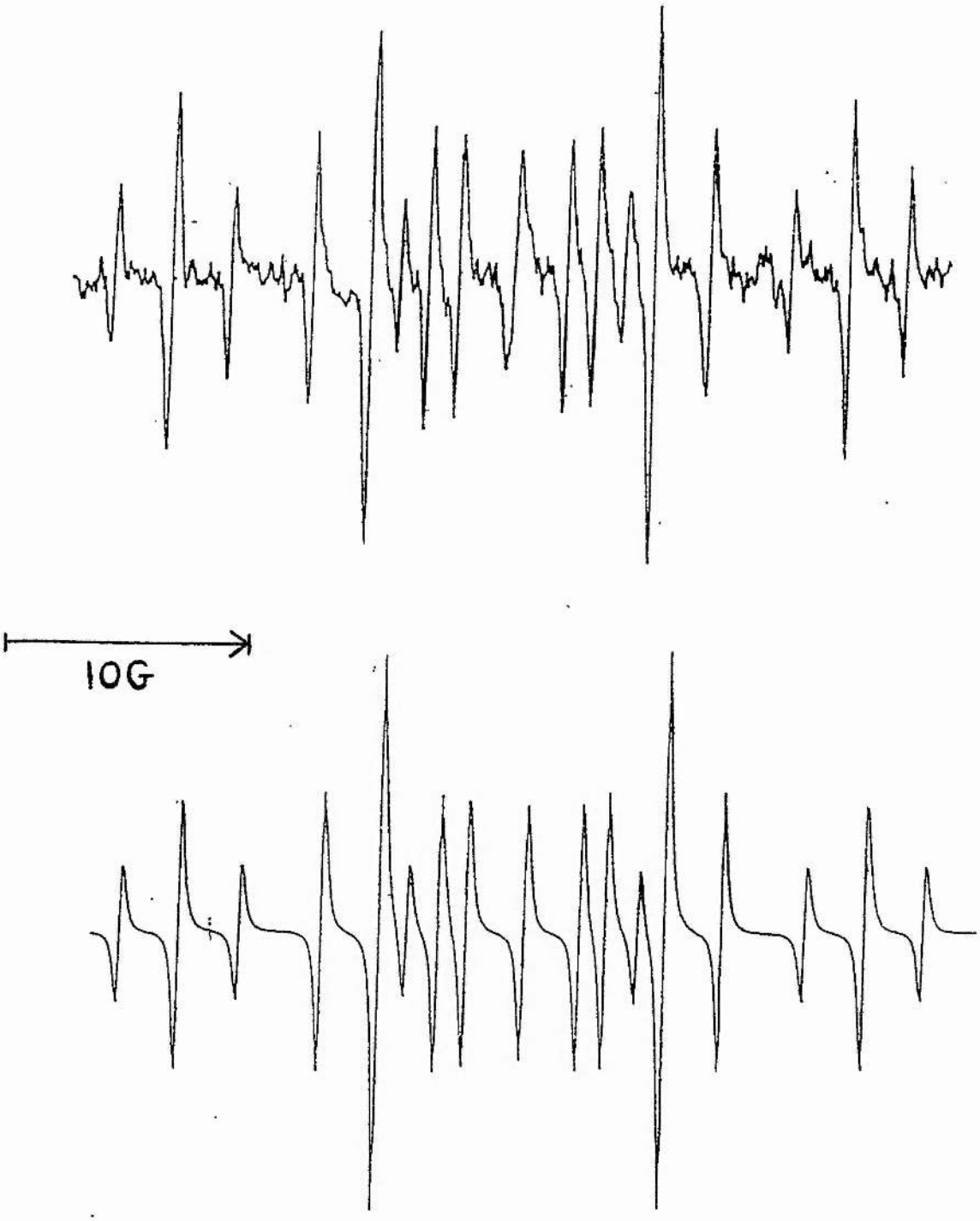


Figure 1.23 and 1.24

Upper: 9.3 GHz EPR spectrum obtained by hydrogen abstraction from **27**, in *tert*-butylbenzene at 220K.

Lower: Computer simulation of the same radical using hfs from Table 1.1.

1.6 Product Analysis

The following section describes an examination of several inter- and intra-molecular chain reactions of **10** (R' = CH_3). They were studied to observe the degree to which the esters would decarboxylate.

1.6.1 *N*-Bromosuccinimide

Refluxing the esters with one molar equivalent of *N*-bromosuccinimide (NBS) in a non polar solvent (carbon tetrachloride) should, with the correct conditions, bring about decarboxylation and give the corresponding alkyl bromide, RBr. The progress of the reaction could be followed by the fact that at first the dense NBS is at the bottom of the reaction vessel and is gradually replaced by succinimide, which rises to the surface (Figure 1.25). The reaction was complete when all the crystals were floating at the surface (detected by stopping the boiling momentarily). Under the initial conditions, whereby the ester was added dropwise to a refluxing mixture of NBS, two main problems were encountered. Firstly, a large peak was observed in the GC chromatograph, corresponding to the starting ester, showing difficulty in ensuring complete consumption of the reactants. This problem was particularly prevalent with the esters of primary and secondary alcohols that were studied (**24** and **26** respectively), in which decarboxylation occurred to only a minor extent, when one equivalent of NBS was employed. The second obstacle to decarboxylation was the observation, by product analysis, of a large amount of aromatisation of the cyclohexadiene ring, due to the loss of the methyl group from the C-1 position. This was also prevalent when the NBS was added, spatula wise, to a refluxing solution of the ester in carbon tetrachloride (see experimental). 1,3-Dibromo-5,5-dimethylhydantoin, a reagent similar in reaction to NBS, was also employed in an attempt to increase the yields of the alkyl bromide. However no improvement was

observed. This was also found to be the case when chlorobenzene was used as the solvent, in order to increase the temperature of the reaction (*ca.* 138°C).

The reaction was refined, to some extent, as follows. The ester was dropped over a period of two hours onto a refluxing solution of NBS (no excess). After a

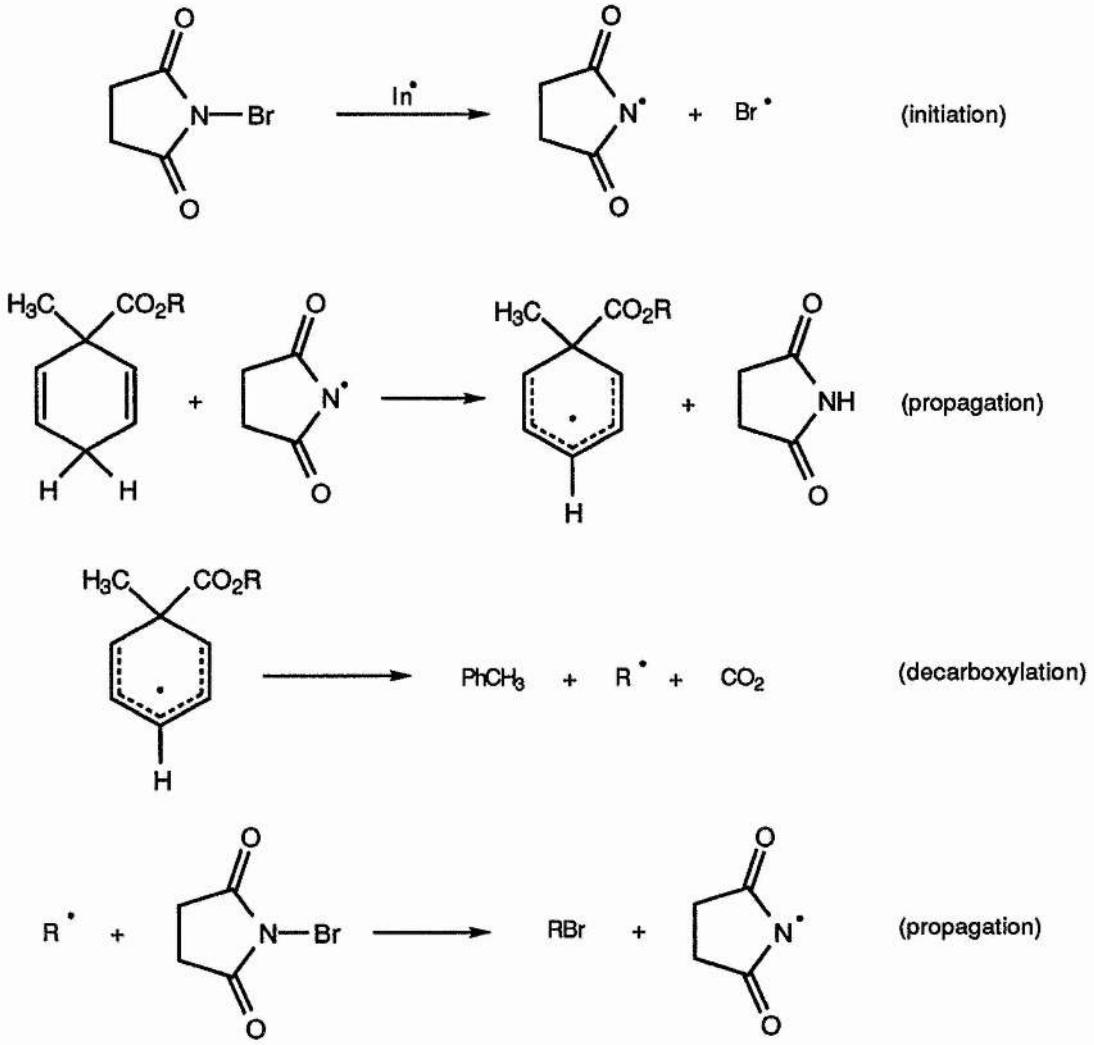


Figure 1.25

Mechanism for Reaction with *N*-Bromosuccinimide.

further two hours refluxing, another equimolar amount of NBS was added and allowed to reflux for yet another two hours. The addition of NBS was repeated once more and the mixture left to reflux for three hours. This method, proved to give good

conversion for secondary (**26**), tertiary (**29**) and benzylic (**22**) esters. Apart from **22**, which was reacted on a large scale and an isolated yield obtained, the yields shown in Table 1.2 were calculated from the GC chromatograph using n-heptane as standard. Bromide formation was best for **22**, although **29** showed a large amount of polybrominated material, indicating a high degree of decarboxylation. The second problem with the reaction of the esters was the interesting and unexpected formation of the analogous benzoate esters. This is evidently formed by rearomatisation of the ring

Table 1.2. Yields from Reaction with *N*-Bromosuccinimide

Compound	Products (%)	
	$PhCH_3$	RBr
24[a] (primary)	7	1[b]
26[a] (secondary)	-[c]	20
29[a] (tertiary)	47	40
22 (benzylic)	-	63[d]

[a] Incomplete consumption of ester. [b] Also noticeable quantities of other monobrominated hexanes observed. [c] Toluene lost on solvent evaporation. [d] Isolated yield by product distillation.

via the loss of a methyl radical from the intermediate **10** (R' = CH_3). This was unforeseen due to the instability of the methyl radical which would not have been expected to form in preference to decarboxylation, especially when the esters contained groups that formed stabilised radicals on decarboxylation i.e. **22** and **29**.

Clearly the NBS reaction yielded better results when comparatively stabilised radicals were ejected and so decarboxylation of the cyclohexadienyl radical **10** was more prevalent for **22** and **29**. However, it was decided to concentrate on a different method for the utilisation of the esters, intermolecular chain addition to alkenes, because the problems associated with the chain reaction of NBS remained significant.

1.6.2 Alkene Addition

All the esters prepared, were examined for intermolecular addition reactions with acrylonitrile, thermally initiated at 140°C with BOOB. A standard, n-heptane, was added for product analysis and the reaction carried out in *tert*-butylbenzene. The sealed tube experiment was allowed to react in an oven for eighteen hours.

After reaction, the product mixture was analysed by GC/MS and the product yields determined. More accurate yields were attained by using sensitivity factor

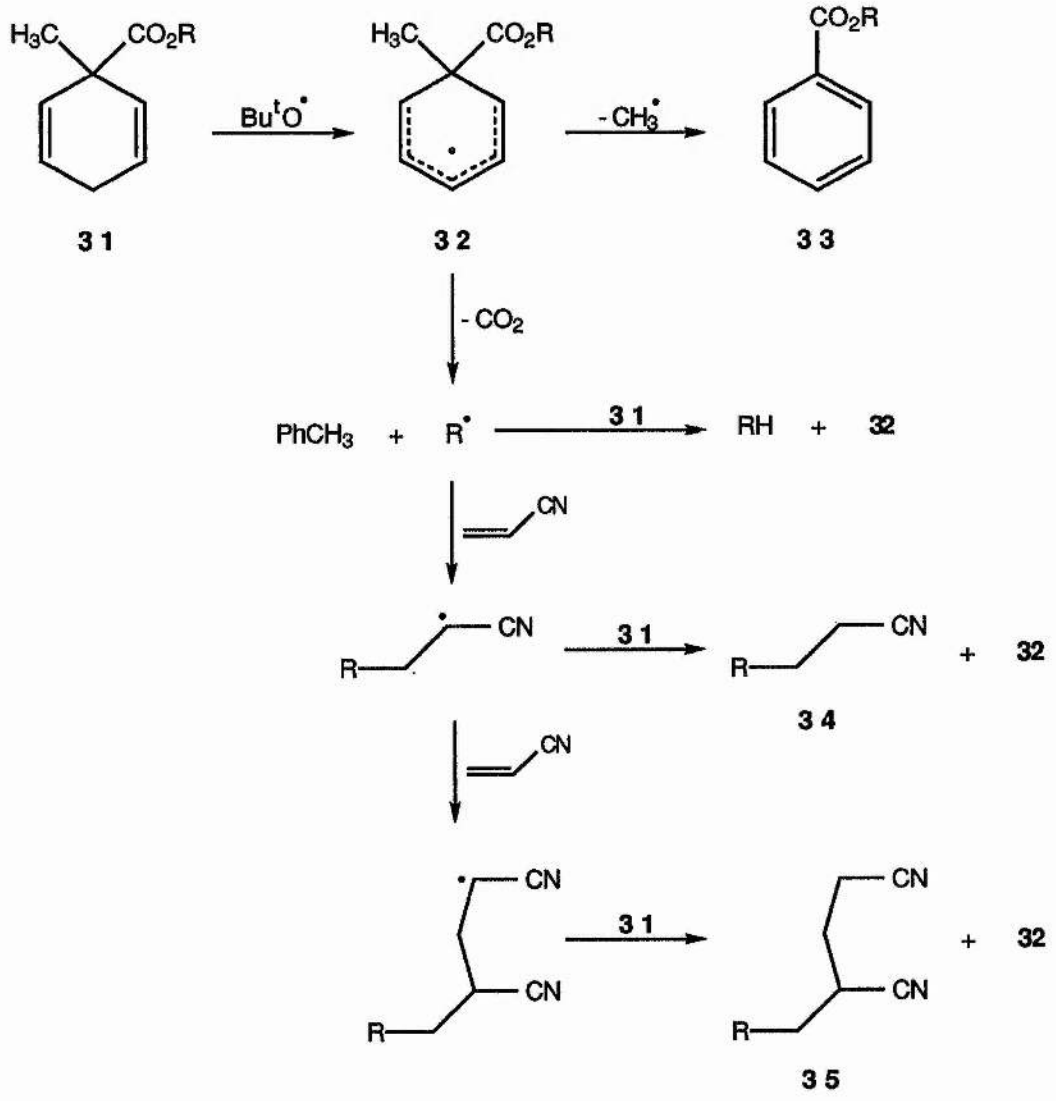


Figure 1.26

The Products of Intermolecular Addition to Acrylonitrile.

calculations for toluene, heptane, methyl benzoate and undecane nitrile. The product range included the expected monoadduct (**34**), together with increasingly minor amounts of the di- and triadducts respectively; further oligomeric adducts may have been present but they were not detected in the GC spectra. Sizeable amounts of the reduction product (RH) were also detected as well as significant amounts of benzoate esters (**33**). The relatively large amounts of RH formed showed that the alkyl radicals $R^{\bullet}$ abstracted hydrogen from **31** almost as readily as they added to the alkene; the proportion of adduct could obviously be increased by using more alkene, although this was found to promote oligomerisation to a significant amount. The appreciable quantities of benzoic acid esters (**33**), again indicated the competing radical rearrangements of **32** to either decarboxylate, via the intended pathway, or to undergo methyl radical loss, a result obviously more prevalent at higher temperatures. Table 1.3 gives the results obtained directly from the GC spectra.

Table 1.3. The Product Yields from Addition of the Various Esters to Acrylonitrile.[a]

	Product Yield (%)						
Ester	RH	PhMe	**34**	**35**	Triadduct	**33**[b]	**31**
22	-	21	9.5	-[c]	-	19	14
23	2[e]	11	1.1	0.7	-	9	-
24	34	21	8	4.5	3	21	22
25	7[f]	19	4	-	-	22	2
26	13	21	10	5.5[g]	2	24	9
28[d]	-	42	-	-	-	-	-
29	14	18	13	8	2	15	18

[a] Yields calculated from G.C. sensitivity factors for toluene, n-heptane, methyl benzoate, undecane nitrile and benzoic acid. [b] Broader peak in comparison to **31** and so may have been of greater yield. [c] Not visible. [d] No visible sign of any cholesteryl containing products. [e] Combination product of two allyl radicals. [f] Only rearranged methylcyclopentane detected. [g] Isolated yield of diadduct 37% rel. to initial ester.

1.6.3 Other Attempted Chain Reactions

Reaction of the esters with Bromoform. The reaction is similar in method to the NBS process, the intended mechanism forming the alkyl bromide and dibromomethane on reaction. The reaction between bromoform and the cyclohexyl ester (**26**) was initiated by azobisisobutyronitrile (AIBN) and was carried out on a small scale in a sealed NMR tube.

From analysis by GC/MS, ester **26** was found to have reacted poorly, with **26** remaining by far the the largest peak (apart from the solvent *tert*-butylbenzene and unreacted bromoform) in the product chromatogram. Of the small amount that did react, only two products were detected. Toluene was evident, but any corresponding

Figure 1.27

Intermolecular Decarboxylation with Bromoform.

cyclohexyl products were not detected (neither the cyclohexyl bromide obtained by bromine abstraction from bromoform nor cyclohexane by hydrogen abstraction from **26**). Also evident and by far the largest product obtained (ca. 30% rel to inital ester) was the product of methyl loss from **26**, cyclohexyl benzoate.

Reaction of the esters with *tert*-butyl hypochlorite. *tert*-Butyl hypochlorite readily forms a chlorine atom when exposed to sunlight. This can therefore be used as an alternative source of halogen in the decarboxylative process. Because the reagent is

so reactive, it was prepared immediately before its use.[43] One advantage of this reaction is that an initiator is not required to commence the reaction.

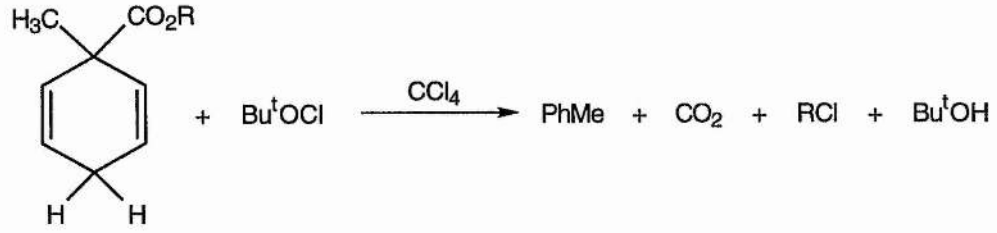


Figure 1.28

Decarboxylation With *tert*- Butyl Hypochlorite.

The results obtained where not encouraging, as only small amounts of the desired product, cyclohexyl chloride, or its corresponding byproduct toluene were detected by GC/MS. The major compounds observed were yet again the unreacted ester **26** and, to a larger extent than the previous reaction with bromoform, the undesired ester cyclohexyl benzoate.

Reaction of the esters with Carbon Tetrachloride. Using BOOB as the initiator for the reaction, carbon tetrachloride may also be used as a chlorine atom generating species. The experiment however proved to be ineffective at producing decarboxylation of the cyclohexadiene ester, **26**. Analysis of the product mixture showed no reaction had occured.

Reaction of the esters with *N*-Bromobis(trimethylsilyl)amine. The intended halogenation of the alkyl radical can be studied by product analysis techniques using *N*-bromobis(trimethylsilyl)amine.[44] The reaction takes place by a free radical chain mechanism which involves propagation similar to that of the NBS reaction. The reaction can be initiated by either thermal decomposition (in darkness) of azobisisobutyronitrile, AIBN, or by photochemical decomposition by irradiation from a

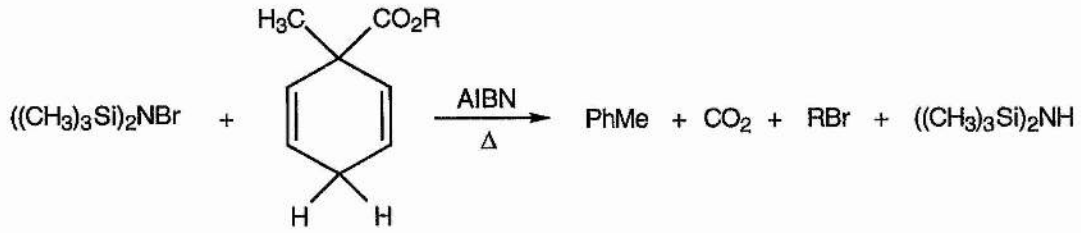


Figure 1.29

Decarboxylation with *N*-Bromobis(trimethylsilyl)amine.

125W medium pressure mercury lamp. The method used in this reaction is the former, i.e. by thermolysis.

The halogenation of the bis(trimethylsilyl)amine is a documented procedure[45] and was a relatively simple preparation involving the reaction of NBS with the amine, at 0°C, in darkness. The freshly prepared halogenated amine was then combined with the ester in a suitable solvent and refluxed. The GC/MS of the product mixture showed similar results to the bromoform experiment although *N*-bromobis(trimethylsilyl)amine proved to be a much more reactive reagent, with evidence for the formation of brominated toluene and polybrominated cyclohexanes.

1.6.4 Intramolecular Addition of Hex-5-enyl Esters

The hex-5-enyl ester (**25**) was prepared to study the rate of hydrogen abstraction of the bisallylic hydrogens at C-4. The ester **25** decomposed over 25hr at 140°C in *tert*-butylbenzene solvent with BOOB as the initiator. GC analysis showed the products of the reaction to be toluene, the product of intra-molecular addition i.e. methylcyclopentane, the product of methyl loss at C-1 of the ester to form hex-5-enyl benzoate, together with minor amounts of hex-1-ene and cyclohexane. The high ratio

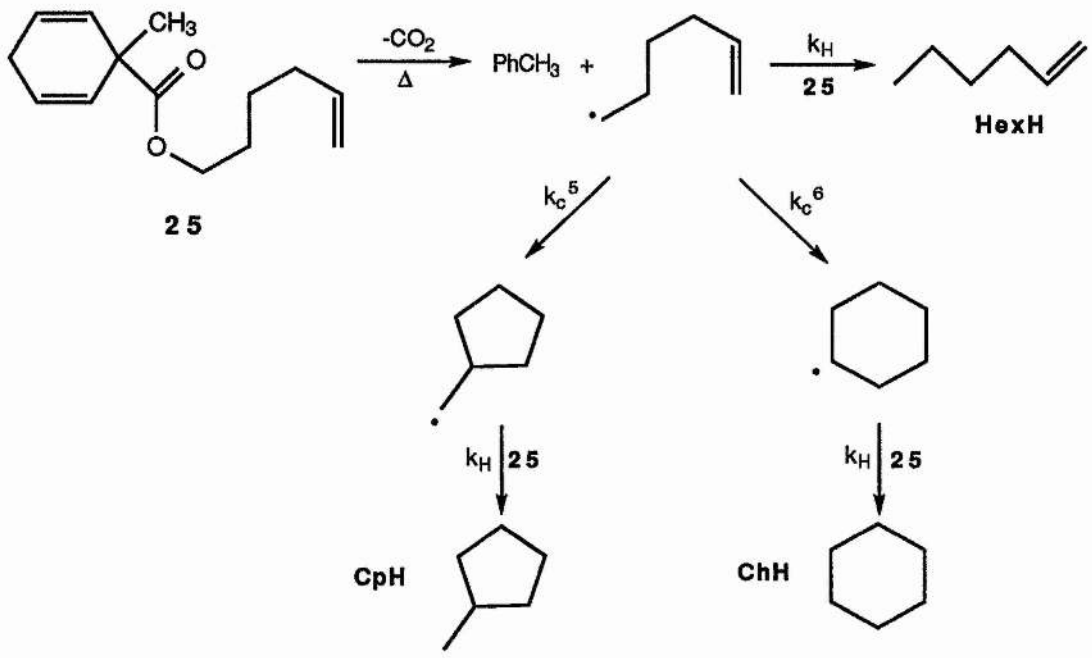


Figure 1.30

Decarboxylation of **25** Showing Intra-molecular Addition.

of products in favour of methylcyclopentane illustrates the expected preference of an unsubstituted hex-5-enyl radical to undergo exo-1,5-cyclisation to form the kinetically favoured 5-membered ring as opposed to endo-1,6-cyclisation to form the thermodynamically more stable 6-membered ring. The small amount of hex-1-ene produced also indicates that hydrogen abstraction from the cyclohexadiene ring is relatively slow compared to rapid hydrogen transfer methods, such as tin hydride reactions.

By performing a steady state analysis on this reaction, it was possible to derive equations that would allow us to estimate the rate of hydrogen abstraction from C-4 of ester **25**.

$$\frac{d[\mathbf{HexH}]}{d[\mathbf{CpH}]} = \frac{k_H[\mathbf{25}]}{k_c^5} \qquad (1)$$

$$\frac{d[\mathbf{HexH}]}{d[\mathbf{ChH}]} = \frac{k_H[\mathbf{25}]}{k_c^6} \qquad (2)$$

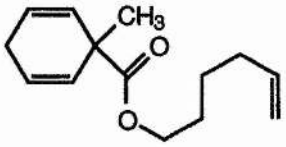
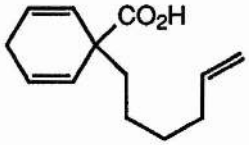
Concentrating on equation (1) first, from the known ratio of methylcyclopentane to hex-1-ene and the concentration of **25**, the ratio of the rate constants for exo-1,5-cyclisation (k_c^5) to hydrogen abstraction from **25** (k_H) was determined to be: $k_H / k_c^5 = 1.3 \times 10^{-2}$ dm^3 mol^{-1}. Using the known value for k_c^5 at 142°C[46-48] we find $k_H(142°C) = 0.82 \times 10^5$ dm^3 mol^{-1} s^{-1}. Equation (2), involves the endo-1,6-cyclisation rate constant (k_c^6) which has been less extensively studied.[49] It may be assumed therefore that the value obtained for k_c^6 at 142°C maybe less accurate. However from the ratio k_H / k_c^6, the rate of hydrogen abstraction, by the cyclohexyl radical from **25**, was determined, as before, to be $k_H(142°C) = 0.75 \times 10^5$ dm^3 mol^{-1} s^{-1}. The difference in the two values may not only be due to the potential error in k_c^6 but also due to a reading error in the estimations of **[HexH]**, **[CpH]** and **[ChH]** from the GLC trace.

Using the rate constant obtained from equation (1) it can be seen that this value is lower than previous estimates of k_H for abstraction from cyclohexa-1,4-diene by primary alkyl radicals (1×10^5 and 2.3×10^5 dm^3 mol^{-1} s^{-1} at 50°C).[50,51] However there are four abstractable hydrogen atoms in cyclohexa-1,4-diene compared with only two in **25** so statistical correction brings the value obtained in this work to within the combined experimental errors.

Table 1.2 shows that the rate of hydrogen abstraction from **25** by primary alkyl radicals is about one order of magnitude slower than that for tributyltin hydride and about one order of magnitude greater than the rate of chlorine abstraction (k_{Cl}) from tetrachloromethane by carbon centred radicals.

The slow hydrogen donation of the cyclohexa-2,5-dienyl esters may be advantageous, in synthetic procedures, in comparison to organotin hydrides, because the rapid hydrogen transfer by organotin reagents is inconvenient in many applications.

Table 1.2. Rates of Atom Transfer Reactions by Primary Alkyl Radicals from Common Chain Partners (Y-X)

Y–X	k_X (37°C Unless Stated)	Ref.
Bu_3Sn—H	2.9×10^6	47
PhS—H	1.5×10^8	52
PhSe—H	2.0×10^9	53
	0.82×10^5 (142°C)	54
	2.0×10^4 (148°C)	(unpublished work)[a]
CCl_3—Cl	1.8×10^4	55
CCl_3—Br	2.0×10^4	56

[a] Work done by A. Milne in undergraduate project.

1.7 Conclusion and Future Work

The results obtained from the *N*-bromosuccinimide and acrylonitrile reactions show the esters examined to function effectively as radical sources for chain reactions. In general the product yields varied considerably, depending on the nature of the alkyl radical to be produced on decarboxylation (the lower the energy of the alkyl radical to be formed, the greater the degree of decarboxylation observed). However, two obstacles were encountered, that hindered the formation of high product yields; (i) the lack of total reaction of the esters under a range of forcing conditions and (ii) the rearomatisation of the cyclohexadiene ring by loss of the alkyl moiety at C-1.

The first point has proved to be an insurmountable obstacle for *all* the esters examined. From the results obtained by EPR measurements the problem was not in the initiation of the cyclohexadienyl radical (Figure 1.24), as this species was observed over a wide range of temperatures. The barrier to decarboxylation is in the high

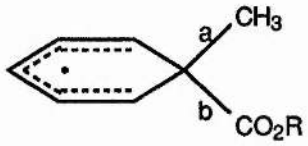


Figure 1.24

strength of bond (b), hindering homolytic cleavage. The alkoxycarbonyl radical that does form from bond (b) breaking, decarboxylates with ease, as no termination products derived from this intermediate radical have been observed. Figure 1.24 also gives a reason for the observation of the benzoate esters. The bond energies of (a) and (b), and their angle relative to the cyclohexadienyl radical, are too similar to favour the breaking of bond (b) exclusively, hence the formation of significant amounts of benzoate esters.

For synthetic purposes it would be of great advantage if decarboxylation could occur under milder conditions without competition from methyl loss. This final point is indeed the reasoning behind the attempted formation of the phenyl substituted acid. The phenyl radical being of higher energy than the methyl radical and hence less inclined to form over the competing decarboxylative pathway.

The facile formation of the isopropyl and *tert*-butyl radicals from acids **17b** and **17c** respectively has proved, accidently, to be an area of research worthy of investigation. Preliminary studies of reactions with acrylonitrile have shown promising results, although clearly the byproduct of such a reaction, benzoic acid, is not as easy to separate as the byproduct of the decarboxylation of the esters, toluene.

1.8 Experimental Section

Routine ^{1}H NMR spectra (200MHz) were obtained on a Varian Gemini 200 spectrometer. ^{13}C (75MHz) and some ^{1}H NMR (300MHz) data were collected on a Bruker AM300 instrument. NMR measurements were made in $CDCl_3$ solution unless otherwise stated, and chemical shifts relative to TMS are reported in ppm (δ). Mass spectra and high resolution mass spectra (HRMS) were recorded on a Kratos M25RF spectrometer. EPR spectra were recorded with a Bruker ER 200D spectrometer operating at 9.3GHz with 100-kHz modulation. Samples were photolysed in the cavity by light from a 500-W super pressure Hg lamp. GC/MS analyses were run on a Finnigan Incos 50 Quadrupole Mass Spectrometer using a Hewlett Packard HP5890 Gas Chromatograph, filled with capillary column HP17 (50% phenyl methyl silicone, 25m).

EPR Spectra. All samples (*ca.* 40mg) analysed by EPR spectroscopy were prepared in Spectrosil tubes with di-*tert*-butyl peroxide (*ca.* 30μL) and *tert*-butylbenzene. The tubes were then degassed before analysis. For the low temperature studies, the *tert*-butyl substituted acid (**17c**) (*ca.* 40mg) was dissolved in di-*tert*-butyl peroxide . This solution was placed in a quartz EPR tube and degassed on a vacuum line by a series of freeze-pump-thaw cycles. The solvent, propane, was distilled in and the tube was flame sealed.

Attempted preparation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid. To a stirred solution of benzoic acid (10g; 82mmol) in dried ethanol (50ml) and ammonia (600ml) was added, in small pieces, an excess of sodium metal (4.71g; 0.205 mol; 2.5mol eq). The reaction mixture effervesced strongly on each addition. Following addition of the sodium, methyl iodide (11.64g; 82mmol) was added dropwise to the reaction vessel. Stirring was continued for 30mins and the ammonia left to evaporate. The residue was treated with a water-ice mixture, acidified with 50%

H_2SO_4 and the organic matter extracted with ether (3 x 100ml). The combined ether layers were dried ($MgSO_4$), and the crude product distilled on a Kugelrohr apparatus (1.8mmHg, 194°C). It was an oily, slightly yellow, solid (5.26g, 46.4%) with a melting point slightly above room temperature. It had a sickly pungent smell that was readily absorbed into the skin and was difficult to remove. NMR analysis showed the product to be dihydrobenzoic acid, with spectroscopic data in accordance with the literature.[31]

1-Methylcyclohexa-2,5-diene-1-carboxylic acid (17a). Benzoic acid (15g; 123mmol) was dissolved in liquid ammonia (900ml) in a 2l, three necked, round-bottom flask. Lithium (2.2g; 314mmol; 2.55mol eq) was added in small portions until a permanent deep blue colour appeared. Following this, an excess of methyl iodide (25ml; 400mmol) was added slowly dropwise, which returned the mixture to a colourless solution, containing an insoluble white solid. After addition the ammonia was left to evaporate. The residue was treated with a water-ice mixture, acidified with 50% H_2SO_4 and the organic matter extracted with ether (4 x 100ml). The combined ether layers were washed with thiosulphate solution (100ml), then with water (100ml) and dried ($MgSO_4$). After evaporation to dryness, the orange-yellow crude product was distilled, on a Kugelrohr apparatus (0.4 mmHg, 85°C), to yield a yellow, oily crystalline solid (17.07g, 95%, m.p. 36°C) identified as **17a**. ^1H NMR δ 1.4 (s, 3H), 2.6 (m, 2H), 5.8 (m, 4H), 12.3 (bs, 1H); ^{13}C NMR δ 26.6 (CH_3), 27.7 (CH_2), 44.1 (quaternary), 125.4 (CH), 128.5 (CH), 182.6 (CO_2H); EIMS *m/z* (relative intensity) 138 (M^+, 2), 123 (1), 93 (100), 91 (80), 77 (90), 65 (26), 51 (31), 45 (16), 39 (49), 27 (23).

Attempted preparation of 17a on a large scale. Benzoic acid (50g; 410mmol) was dissolved in liquid ammonia (600ml) in a 2l, three necked, round-bottom flask. Lithium (5.3g; 757mmol; 1.84mol eq) was added in small portions until a permanent deep blue colour appeared. As before methyl iodide was added in excess (60ml).

However, on each dropwise addition the solution became a yellow slurry that effervesced uncontrollably raising the level of the reaction mixture out of the reaction vessel. Extra ammonia was added to aid the flow. The work up was as before (the only fraction boiling at 96°C at 1.4mmHg), however the yield of **17a** was drastically reduced (18.3g, 32%).

1-Isopropylcyclohexa-2,5-diene-1-carboxylic acid (17b). Benzoic acid (10g; 82mmol) was dissolved in liquid ammonia (900ml). As for **17a**, lithium (1.9g; 271mmol; 3.3mol eq) was added in small portions until a permanent deep blue colour just appeared. Addition of an excess of isopropyl bromide (12.5g; 101mmol), dropwise, returned the mixture to a yellow solution. This colour may well be due to the presence of a small amount of bromine. After addition the ammonia was left to evaporate. The resulting solid was acidified with 2M H_2SO_4 at 0°C and the organic matter extracted with ether (3 x 100ml). The combined ether layers were washed with water (100ml), dried ($MgSO_4$) and evaporated. Recrystallisation from petroleum ether (40-60°C) yielded the pure product, **17b**, as large transparent crystals (8.96g, 66%, m.p. 79-81°C). ^{1}H NMR δ 0.87 (d, *J*=7Hz, 6H), 2.1 (spt, *J*=7Hz, 1H), 2.65 (s, 2H), 5.85 (m, 4H), 11.4 (bs, 1H); ^{13}C NMR δ 17.8 (CH_3), 27.0 (CH), 36.2 (CH_2), 52.3 (quaternary), 125.7 (CH), 127.4 (CH), 182.2 (CO_2H); EIMS *m/z* (relative intensity) 166 (M^+, 1), 124 (56), 123 (67), 105 (23), 79 (100), 77 (61), 51 (28), 43 (97), 41 (50), 39 (35), 27 (48), 18 (36).

1-*tert*-Butylcyclohexa-2,5-diene-1-carboxylic acid (17c). Benzoic acid (10g; 82mmol) was dissolved in liquid ammonia (800ml). As for **17a**, lithium (2.0g; 285mmol; 3.5mol eq) was added in small portions until a permanent deep blue colour just appeared. Addition of an excess of 2-iodo-2-methylpropane (20ml; 166mmol), dropwise, returned the mixture to a colourless solution. After addition the ammonia was left to evaporate. The residue was treated with a water-ice mixture, acidified with 50% H_2SO_4 and the organic matter extracted with ether (3 x 100ml). The combined

ether layers were washed with thiosulphate solution (100ml), then with water (100ml), dried ($MgSO_4$) and evaporated. Recrystallisation from petroleum ether (40-60°C) yielded the pure product, **17c**, as a white thin crystalline solid (4.4g, 32%, m.p. 99-101°C). ^1H NMR δ 0.98 (s, 9H), 2.60 (m, 2H), 5.99 (m, 4H); ^{13}C NMR δ 25.9 (CH_3), 26.20 (quaternary), 38.6 (CH_2), 52.8 (quaternary), 125.5 (CH), 126.2 (CH), 181.0 (CO_2H); EIMS *m/z* (relative intensity) 124 (56), 123 (69), 105 (14), 79 (50), 77 (41), 57 (100), 51 (24), 41 (73), 39 (38), 29 (59), 28 (24), 27 (23).

Attempted preparation of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid (17d). Benzoic acid (10g; 82mmol) was dissolved in liquid ammonia (600ml). Lithium (1.8g; 257mmol; 3.1mol eq) was added in small portions until a permanent deep blue colour just appeared. Addition of an excess of redistilled iodobenzene (23.4g; 40% excess), dropwise, immediately turned the mixture a deep red colour, and the red colour remained throughout addition. After addition the ammonia was left to evaporate. The workup was identical to **17b.** Recrystallisation from petroleum ether (40-60°C) yielded 5.1g of a cream coloured crystalline solid which was identified by NMR as being benzoic acid.

1,4-Dihydrobiphenyl (18). Biphenyl (10g; 65mmol) was dissolved in ether (300ml) and ammonia (800ml). The lithium metal (1.8g; 3.6 mol eq) was added in small portions until the colour of the solution had gone orange-black. It was found that after $^2/_3$ addition of lithium, the rate that the lithium would dissolve in the ammonia solution, significantly slowed. This was overcome by addition of a further amount of ether (*ca.* 250ml) and ammonia (*ca.* 200ml). Ammonium chloride (100g) was added as quickly as possible followed by the addition of water and ether to separate the product from further reaction and isomerisation. The ammonia was then left to evaporate. The product was extracted with ether (3 x 100ml), washed with water (100ml) and dried ($MgSO_4$). The crude product, a cloudy viscous liquid, was purified by oil pump distillation (0.2mmHg, 98°C) forming a colourless viscous liquid (9.3g,

92%).^{1}H NMR δ 2.75 (m, 2H), 4.0 (m, 1H), 5.8 (m, 4H), 7.3 (m, 5H); ^{13}C NMR δ 26.5 (CH_2), 42.7 (CH), 124.3 (olefinic CH), 126.9 (phenylic C_p) 128.6 (olefinic CH), 129.1 (phenylic C_o or C_m), 129.2 (phenylic C_m or C_o) 145.8 (quaternary phenylic).The NMR indicated that the product contained a very small amount of unreacted biphenyl as an impurity.

Attempted preparation of 1-phenylcyclohexa-2,5-diene-1-carboxylic acid (17d). n-Butyl lithium was added dropwise to 1,4-dihydrobiphenyl (4.2g; 27mmol) in dry THF (50ml) at -70°C. After 1hr of stirring CO_2 was allowed to bubble through the solution, by means of evaporating cardice, at -70°C for 0.5hr and then at room temperature for 3hr. The THF was evaporated off and the remaining product acidified by the addition of 1M HCl (100ml) turning the solution milky white in colour. The organic product was then extracted from the aqueous layer by methylene chloride (3 x 50ml) and dried ($MgSO_4$). Evaporation of the solvent yielded an orange brown liquid. ^{1}H NMR showed the viscous liquid to contain a small amount of carboxylation; ^{1}H NMR δ 2.7 (bisallylic protons), 5.7-6.4 (olefinic protons), 10.5 (COOH). However separation of the acid has so far proved ineffective.

1-Methylcyclohexa-2,5-diene-1-carbonyl chloride (21). To a stirred solution of the acid (4g; 29mmol) in dry ether (30ml), was added dropwise, a solution of oxalyl chloride (4.42g; 20% excess) also in dry ether (25ml) at room temperature. On addition the reaction mixture effervesced slightly. The reactants were left to stir overnight and further refluxed for 2hr in the morning. The solvent and any residual oxalyl chloride were evaporated off on the Buchi at room temperature. The crude product, a clear yellow liquid was distilled on a Kugelrohr (62°C, 0.2 mmHg) yielding a colourless liquid (3.9g, 86%). The product was identified, as being **21**, from the IR spectrum which showed a strong, acid chloride, carbonyl band at 1800 cm^{-1} and no hydroxyl stretch. From these data it was decided the acid chloride was of sufficient purity to form the esters.

Benzyl 1-methyl-2,5-cyclohexadienoate (22). Freshly prepared **21** (1.15g; 7mmol) in dry ether (25ml) was added dropwise to equimolar amounts of pyridine (0.58g; 7mmol) and benzyl alcohol (0.79g; 7mmol) in dry ether (25ml) at room temperature. A white precipitate of pyridinium hydrochloride formed immediately. The reaction mixture was then left to stir for a further 2 hours. The product was filtered, washed with 0.25M HCl, then with water, dried ($MgSO_4$) and the remaining ether evaporated on the Buchi . The pure product, **22**, was distilled over on the oil pump (0.1mmHg, 108°C) as a colourless liquid (1.5g, 90%). ^{1}H NMR δ 1.4 (s, 3H), 2.6 (bs, 2H), 5.1 (s, 2H), 5.8 (m, 4H), 7.3 (m, 5H); ^{13}C NMR δ 26.4 (bisallylic CH_2), 27.9 (CH_3), 44.5 (quaternary), 66.9 (OCH_2), 125.1 (olefinic CH's), 128.2 (olefinic CH's), 128.5 (phenylic CH), 129.0 (phenylic CH), 129.1 (phenylic CH), 136.7 (quaternary phenylic), 175.4 (C=O); EIMS *m/z* (relative intensity) 93 (89), 91 (100), 77 (78), 65 (50), 51 (29), 41 (20), 39 (49), 27 (12). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06%. Found: C, 78.97; H, 7.37%.

2-Propenyl 1-methyl-2,5-cyclohexadienoate (23). Freshly prepared **21** (2.97g; 19mmol) in ether (25ml) was added, as in the previous synthesis, to equimolar quantities of allyl alcohol (1.1g; 19mmol) and pyridine (1.5g; 19mmol) in dried ether (30ml). The product was worked up as before and distilled on a Kugelrohr (0.4 mmHg, 88°C), yielding **23**, the pure product as a yellow liquid (0.96g, 45%). ^{1}H NMR δ 1.35 (s, 3H), 2.64 (m, 2H), 4.58 (dt, J_{vic}=5.5, $J_{allylic}$=1.4Hz, 2H), 5.21 (ddt, J_{cis}=10.5, J_{gem}=1.5, $J_{allylic}$=1.4Hz, 1H), 5.30 (ddt, J_{trans}=17.2, J_{gem}=1.5, $J_{allylic}$=1.4Hz, 1H), 5.80 (m, 4H), 5.89 (ddt, J_{trans}=17.2, J_{cis}=10.5, J_{vic}=5.5Hz, 1H); ^{13}C NMR δ 25.91 (bisallylic CH_2), 27.37 (CH_3), 43.92 (quaternary), 65.28 (OCH_2), 117.69 (olefinic CH_2), 124.48 (olefinic CH's), 128.67 (olefinic CH's), 132.22 (olefinic CH), 174.76 (C=O); EIMS *m/z* (relative intensity) 93 (100), 92 (30), 91 (54), 77 (51), 65 (10), 51 (10), 41 (36), 39 (30), 27 (12).

Hexyl 1-methyl-2,5-cyclohexadienoate (24). Preparation for this ester was the same as for the benzyl ester. Freshly prepared **21** (6.26g; 40mmol), in dry ether (30ml), was added to equimolar amounts of n-hexanol (4.11g; 40mmol) and pyridine (4,11g; 40mmol) in dry ether. The product was worked up as before and distilled on a Kugelrohr (0.1mmHg, 76°C) yielding a colourless liquid, **24**, (6.75g, 76%). ^{1}H NMR δ 0.85 (t, 3H), 1.3 (m, 9H), 1.6 (m, 2H), 2.6 (bs, 2H), 4.05 (t, 2H), 5.8 (m, 4H); ^{13}C NMR δ 14.4 (CH_3), 22.9 (CH_2), 25.9 (bisallylic CH_2), 26.3 (CH_3), 27.7 (CH_2), 28.9 (CH_2), 31.7 (CH_2), 44.2 (quaternary), 65.3 (OCH_2), 124.5 (olefinic CH's), 129.2 (olefinic CH's), 175.5 (C=O); EIMS *m/z* (relative intensity) 220 (M^+-2, 2), 137 (16), 136 (40), 119 (50), 118 (79), 91 (70), 65 (44), 43 (100), 41 (65), 39 (40), 29 (41), 27 (35).

5-Hexenyl 1-methyl-2,5-cyclohexadienoate (25). The acid chloride, **21**, (4.78g; 31mmol) in ether (30ml) was added, as for the synthesis of **22**, to equimolar quantities of hexenyl alcohol (2.45g; 31mmol) and pyridine (3.06g; 31mmol) in dry ether (30ml). The product was worked up as before and distilled on a Kugelrohr (0.1mmHg, 82°C) yielding **25**, the pure product, as a yellow liquid (4.6g, 60%). ^{1}H NMR δ 1.33 (s, 3H), 1.45 (m, 2H), 1.65 (m, 2H), 2.07 (m, 2H), 2.65 (bs, 2H), 4.08 (t, J=6.5Hz, 2H), 4.95 (dm, J_{cis}=10Hz, 1H), 5.0 (ddt, J_{trans}=17, J_{gem}=1.6, $J_{allylic}$= 1.7Hz, 1H), 5.78 (m, 4H), 5.80 (m, 1H); ^{13}C NMR δ 25.18 (CH_2), 25.93 (bisallylic CH_2), 27.37 (CH_3), 28.02 (CH_2), 33.24 (CH_2), 43.91 (quaternary), 64.71 (OCH_2), 114.80 (olefinic CH_2), 124.31 (olefinic CH's), 128.83 (olefinic CH's), 138.31 (olefinic CH), 175.14 (C=O).

Cyclohexyl 1-methyl-2,5-cyclohexadienoate (26). Although a secondary alcohol was used, the conditions for formation of the ester were identical to the primary alcohols. The acid chloride (3.2g; 20mmol) in ether (30ml) was added, as before, to equimolar quantities of cyclohexyl alcohol (2.10g; 20mmol) and pyridine (1.63g; 20mmol) in dried ether (30ml). The product was worked up as before and distilled on

a Kugelrohr (0.8mmHg, 98°C), yielding **26**, as a yellow liquid (3.93g, 61%). ^{1}H NMR δ 1.32 (s, 3H), 1.42 (m, 6H), 1.74 (m, 4H), 2.63 (s, 2H), 4.76 (m, 1H), 5.78 (m, 4H); ^{13}C NMR δ 23.37 (cyclohexyl $CH_2\underline{C}H_2CH_2\underline{C}H_2CH_2$), 25.52 (cyclohexyl $CH_2CH_2\underline{C}H_2CH_2CH_2$), 25.98 (bisallylic CH_2), 27.42 (CH_3), 31.07 (cyclohexyl $\underline{C}H_2CH_2CH_2CH_2\underline{C}H_2$), 43.94 (quaternary), 72.41 (OCH), 124.17 (olefinic CH's), 129.01 (olefinic CH's), 174.51 (C=O); EIMS *m/z* (relative intensity) 138 (3), 93 (100), 92 (32), 91 (41), 83 (60), 77 (33), 55 (78), 41 (42), 39 (21), 27 (13).

Diphenylmethyl 1-methyl-2,5-cyclohexadienoate (27). As before equimolar quantities of diphenylmethanol (5.34g; 29mmol) and pyridine (2.29g; 29mmol) were reacted with the acid chloride, **21**, (4.53g; 29mmol) and were left to stir at room temperature for 24 hours. The crude product obtained, a greeny yellow solid, was recrystallised from 40-60°C petroleum ether. The pure product, **27**, (2.43g, 27%) was a white solid with small needle like crystals. m.p. 99-100°C. ^{1}H NMR δ 1.4 (s, 3H), 2.7 (bs, 2H), 5.85 (m, 4H), 6.8 (s, 1H), 7.3 (m, 10H); ^{13}C NMR (tentative assignments) δ 21.6 (CH_3), 22.7 (CH_2), 39.95 (OCH), 120.3 (olefinic CH's), 122.5 (phenylic C_o or C_m), 123.4 (olefinic CH's), 124.1 (phenylic C_o or C_m), 136.2 (quaternary phenylic), 169.9 (C=O), (phenylic C_p not observed either due to obscuring by background noise or to overlapping); EIMS *m/z* (relative intensity) 167 (65), 165 (38), 152 (23), 139 (10), 115 (13), 89 (16), 83 (100), 82 (70), 76 (20), 70 (26), 63 (51), 51 (47), 50 (31), 39 (53).

Attempted preparation of cholesteryl 1-methyl-2,5-cyclohexadienoate (28). The acid chloride (4.54g; 29mmol) was added dropwise to a solution of 5-cholesten-3β-ol (11.22g; 29mmol) and pyridine (2.85g; 29mmol) in dry ether (250ml). The addition of the acid chloride immediately formed a thick yellow precipitate. The reactants were dissolved in a further 200ml of dry ether in a 1l flask and stirred overnight. The product was filtered and the ether evaporated. The product was dissolved in toluene and dried ($MgSO_4$). After this had been filtered off, the toluene

was evaporated and the solid crystallised out of petroleum ether 40-60°C at -20°C. This was filtered, washed with a small amount of petroleum ether, also at -20°C and dried under vacuum. The product was a white crystalline material (8.1g, 55%; m.p. 137-140°C). (Due to the size of the integral of the cholesteryl group, the ratio of the hydrogens is estimated) ^{1}H NMR δ 0.7 (s, 3H), 0.85 (s, 6H,), 0.9 (s, 3H), 1.05 (s, 3H), 1.3 (s, 3H), 2.65 (s, 2H), 4.6 (qt, 1H), 5.35 (d, 1H), 5.8 (s, 4H), all other hydrogens in chemical shift of between 1.0 and 2.05. Anal. Calcd for $C_{35}H_{54}O_2$: C, 83.0; H 10.7%. Found C 80.7; H 10.9%. The low reading shows signs of unreacted cholesterol in the final product. Selective recrystallisation of the product proved unproductive in separating the **28** from 5-cholesten-3β-ol.

Cholesteryl 1-methyl-2,5-cyclohexadienoate (28). To overcome the problems encountered in the initial preparation of **28**, certain changes were introduced into the experimental procedure. To ensure complete reaction of cholesterol, a 20% excess of **21** (3.75g; 24mmol) was used. This was added dropwise to a solution of 5-cholesten-3β-ol (7.43g, 19.2mmol) and pyridine (1.52g, 19.2mmol) in dry THF (150ml). THF was used as it dissolved cholesterol more easily, and pyridinium hydrocloride was found to precipitate out almost as readily as in diethyl ether. After 5hr of stirring, the product was filtered and the THF evaporated. The crude product was then redissolved in ether (300ml), washed with 0.1M HCl (100ml) followed by water (2x100ml) and finally dried ($MgSO_4$). To purify the ester from the cholesterol, the impure product was passed down a neutral alumina column (2cm x 50cm), the elutant being a mixture of cyclohexane and ethyl acetate (7%). The pure product, **28**, came through on the solvent front. m.p. 147-151°C. The proton NMR data is as before. ^{13}C NMR δ 11.86 (CH_3), 18.72 (CH_3), 19.37 (CH_3), 21.04 (CH_2), 22.57 (CH_3), 22.83 (CH_3), 23.84 (CH_2), 24.29 (CH_2), 25.94 (bisallylic CH_2), 27.49 (CH_3), 27.61 (CH_2), 28.02 (CH), 28.24 (CH_2), 31.86 (CH), 31.92 (CH_2), 35.80 (CH), 36.18 (CH_2), 36.60 (quaternary), 36.97 (CH_2), 37.94 (CH_2), 39.52 (CH_2), 39.73 (CH_2), 42.31 (quaternary), 43.80 (quaternary), 50.00 (CH), 56.13

(CH), 56.69 (CH), 74.19 (CH), 122.57 (olefinic CH_2), 124.22 (olefinic CH's), 128.90 (olefinic CH's), 139.69 (olefinic CH), 174.61 (C=O).

Attempted preparation of *tert*-butyl 1-methyl-2,5-cyclohexadienoate. *Tert*-butyl alcohol (2.65g, 29mmol) and pyridine (2.85g, 29mmol) were reacted with the acid chloride (4.54g; 29mmol) in dry ether (50ml). The reactants turned a red-brown colour immediately, with the usual appearance of the precipitate of pyridinium hydrochloride. The reactants were then left to stir at room temperature for 10 hours. After working up the crude product in the usual way, it was found reaction had not proceeded.

***tert*-Butyl 1-methyl-2,5-cyclohexadienoate (29).** To the *tert*-butyl alcohol (1.41g; 19mmol) in dry THF (40ml) was added, under nitrogen during several minutes, 15ml of n-butyl lithium (1.6M) solution in hexane. After 30 minutes the resulting solution was treated during 5 minutes by the dropwise addition of a solution of **21** (3.0g; 19mmol) in THF (40ml). The resulting solution was brought to reflux for 1hr, cooled to 0°C by an ice bath, and hydrolysed by the addition of water (100ml). The aqueous phase was extracted with ether (4x100ml). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by oil pump distillation on a Kugelrohr apparatus (0.8mmHg, 82°C). The pure product, **29**, was a colourless liquid (2.7g, 79%). ^1H NMR δ 1.25 (s, 3H), 1.4 (s, 9H), 2.6 (bs, 2H), 5.75 (m, 4H); ^{13}C NMR δ 21.6 (CH_3), 23.1 (bisallylic CH_2), 23.6 (CH_3), 40.1 (quaternary), 76.1 (quaternary), 119.65 (olefinic CH's), 124.85 (olefinic CH's), 170.0 (C=O); EIMS *m/z* (relative intensity) 138 (1), 93 (63), 91 (28), 77 (26), 57 (100), 41 (33), 39 (15), 29 (22).

Attempted preparation of triphenylmethyl 1-methyl-2,5-cyclohexadienoate. To triphenylmethanol (9.1g; 35mmol) in dry THF (50ml), was added under nitrogen during several minutes, 20ml of n-butyl lithium (1.6M)

solution in hexane. After 30 minutes the resulting solution was treated during 5 minutes by the dropwise addition of a solution of the acid chloride (6.1g; 39mmol) in THF (40ml). The resulting solution was brought to reflux for 1 hour, cooled to 0°C by an ice bath, and hydrolysed by the addition of water (100ml). The aqueous phase was extracted with ether (4x100ml). The combined organic layers were dried ($MgSO_4$) and concentrated. A crystalline solid was separated and found to be triphenylmethanol by NMR analysis. The mass of this solid was such, that it could be deduced, that no reaction had occured between the lithium triphenylmethoxide salt, and **21**, probably due to the bulky nature of the triphenylmethyl moiety.

Initial attempted reaction of cyclohexyl ester with *N*-bromosuccinimide (NBS). The cyclohexyl ester, **26**, (0.8g; 3.6mmol) in CCl_4 (20ml), was added to a refluxing solution of NBS (0.7g; 3.9mmol) and the initiator, lauroyl peroxide (20mg), in CCl_4 (30ml). The addition was over 10 min and the solution was further refluxed for 10 hr. The CCl_4 was then 75% evaporated on the Buchi at room temperature. Clean GC/MS obtained with no other products apart from those obtained below.

Conditions: 50°C for 5min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
110	145	toluene	92 (M^+, 33), 91 (100), 65 (22), 63 (18), 51 (19), 39 (39).
299	44	cyclohexyl bromide	164, 162 (M^+, 1), 83 (91), 55 (100), 41 (77), 39 (48), 27 (37).
881	57	ester (**26**)	138 (3), 93 (100), 91 (42), 83 (68), 77 (43), 55 (98), 41 (61), 39 (30), 29 (18), 27 (22).
915	24	cyclohexyl benzoate	204 (M^+, 1), 123 (69), 105 (100), 82 (29), 77 (65), 67 (42), 55 (23), 51 (24), 41 (30), 27 (19).

975	62	unidentified byprod	218 (3), 136 (84), 119 (100), 118 71), 91 (88), 67 (50), 65 (52), 55 (83), 41 (82), 39 (55), 29 (28).

Further attempted reaction of cyclohexyl ester with NBS. The cyclohexyl ester (**26**) (0.8g; 3.6mmol) was brought to reflux in CCl_4 (50ml) and the NBS (0.7g; 3.9mmol) was added to the refluxing mixture by spatula. The reaction was refluxed for a further 3 hr. The CCl_4 was 75% evaporated at room temperature on the Buchi. The GC/MS with the known products are listed below.

Conditions: 50°C for 5min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z (%)*
150	159	toluene	as before
450	103	cyclohexyl bromide	as before
997	10	ester (**26**)	as before
1061	100	cyclohexyl benzoate	as before
1118	112	unidentified byprod	as before
1257	52	cyclohexyl tribromide	83 (89), 55 (100), 41 (44), 39 (17), 27 (13).

Attempted reaction of cyclohexyl ester with NBS in chlorobenzene. As previous experiment except for the use of chlorobenzene (40ml) as the solvent, instead of carbon tetrachloride.

Conditions: 50°C for 5min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z (%)*
149	22	toluene	as before
450	42	cyclohexyl bromide	as before
763	18	cyclohexyl dibromide	242 (M^+, 1) [peaks at 240 and 244 too weak], 163 (5), 161 (6), 81 (100), 53 (18), 39 (29), 27 (28).

996	70	ester (**26**)	as before
1060	22	cyclohexyl benzoate	as before
1111	59	unidentified byprod	as before

Large scale reaction of benzyl cyclohexa-2,5-dienoate with NBS (improved method). NBS (1.0g; 5.6mmol) was brought to reflux in carbon tetrachloride (30ml). Lauroyl peroxide (*ca.* 20mg) was added followed by the dropwise addition of benzyl cyclohexa-2,5-dienoate, **22**, (1.3g; 5.6mmol) over a period of 2hr. After addition the reactants were left to reflux for 2hr. Another equimolar amount of NBS was then added and refluxed for a further 2hr. This addition was further repeated with the addition of more initiator (*ca.* 20mg). After a final reflux for 3hr the solvent was 70% evaporated. GC/MS of the product mixture showed the major product to be benzyl bromide; EIMS *m/z* (rel intensity) 172,170 (M^+, 3), 91 (100), 65 (36), 50 (18), 39 (37), 27 (4). The crude product was distilled on a Kugelrohr under water pump pressure (15mmHg, 81°C), to give the pure product (0.61g; 63%). ^1H and ^{13}C NMR as given in the literature.

Reaction of cyclohexyl cyclohexa-2,5-dienoate with NBS (improved method). Reaction carried out as for previous reaction with **22** but using **26** (1g; 4.5mmol) as the starting ester along with dodecane as a standard (100µl). Both the chromatograph and the MS obtained by GC/MS of the final mixture were very weak and so only a tentative yield could be calculated for cyclohexyl bromide (20% relative to initial ester); EIMS *m/z* (rel intensity) [M^+ peak to weak to be observed], 84 (8), 83 (74), 67 (23), 55 (100), 41 (61), 39 (54), 27 (31).

Reaction of *tert*-butyl cyclohex-2,5-dienoate with NBS (improved method). Reaction carried out as for reaction with **22** but using **29** (1g; 4.5mmol) as the starting ester along with dodecane as a standard (100µl). GC/MS of the final mixture showed that a large percentage of **29** had not reacted, but on comparison to the

internal standard, the yields of toluene and *tert*-butyl bromide were 47 and 40% respectively relative to the starting ester. Toluene MS as before; *tert*-butyl bromide; EIMS *m/z* (rel intensity) 123 ([M-CH_3]$^+$, 2), 81 (3), 57 (97), 41 (100), 39 (46), 29 (84), 27 (31), 15 (7).

Reaction of n-hexyl ester with NBS (improved method). Reaction carried out as for reaction with **22** but using **24** (1.3g; 5.9mmol) as the starting ester along with dodecane as a standard (100µl). GC/MS of the final mixture showed that a very large percentage of **24** had not reacted, leading to low yields for the intended products, however a tentative yield could be calculated for both n-hexyl bromide (1.2%) and toluene (7%). MS for toluene as before, n-hexyl bromide; EIMS *m/z* (rel intensity) 137 (9), 135 (10), 86 (4), 69 (8), 56 (26), 55 (46), 43 (100), 41 (73), 29 (30), 27 (50), 18 (30).

Benzyl ester with acrylonitrile. The ester **22** (0.1g; 0.44mmol), acrylonitrile (50µl), BOOB (as initiator), n-heptane (10µl) and *tert*-butylbenzene (400µl) were placed in a long glass tube. The reaction mixture was degassed by a series of 'freeze-pump-thaw' cycles, under vacuum. The tube was then flame sealed and heated at 144°C for 20hr. The tip was then broken off and a GC/MS immediately obtained on the mixture.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
121	124	n-heptane	100 (M$^+$, 8), 71 (31), 70 (17), 57 (36), 56 (24), 43 (100), 42 (30), 41 (73), 39 (20), 29 (50), 27 (38), 15 (3).
166	73	toluene	92 (M$^+$, 46), 91 (100), 77 (2), 65 (15), 63 (9), 51 (10), 45 (6), 39 (20), 27 (5).
787	>63	t-butylbenzene	134 (M$^+$, 46), 119 (100), 91 (90), 77 (20), 51 (17), 41 (38), 39 (22).

1073	34	monoadduct (**34**)	145 (M^+, 13), 104 (19), 91 (100), 77 (8), 65 (14), 51 (11), 39 (14), 27 (10).
1337	39	ester (**22**)	as for preparation
1386	49	benzoate (**33**)	212 (M^+, 13), 105 (100), 91 (56), 77 (48), 65 (18), 51 (26), 39 (11), 27 (4).

Allyl ester with acrylonitrile. Conditions identical to the benzyl ester, with 0.1g of allyl ester (**23**) used.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
96	42	hexa-1,5-diene	64 (2), 52 (4), 41 (100), 29 (58), 27 (32), 15 (3).
124	223	n-heptane	as before
165	106	toluene	as before
271	42	monoadduct (**34**)	95 (M^+, 4), 80 (50), 67 (8), 55 (100), 41 (74), 39 (40), 32 (6), 29 (24), 27 (32), 18 (14).
1010	59	ester (**23**)	as for preparation
1028	54	benzoate (**33**)	162 (M^+, 3), 105 (100), 77 (50), 51 (25), 41 (11), 39 (14), 27 (7), 15 (2).

Hexyl ester with acrylonitrile. Conditions identical to the benzyl ester, with 0.1g of cyclohexyl ester (**24**) used.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
83	126	n-hexane	86 (M^+, 7), 71 (3), 57 (71), 56 (32), 43 (73), 42 (43), 41 (100), 39 (26), 29 (70), 27 (50), 15 (5).
122	144	n-heptane	as before

162	86	toluene	as before
954	33	monoadduct (**34**)	139 (M^+, 1), 124 (4), 110 (20), 96 (40), 82 (53), 69 (45), 57 (28), 55 (40), 54 (50), 43 (50), 41 (100), 39 (33), 29 (52), 27 (52), 15 (4).
1237	67	ester (**24**)	as for preparation
1275	65	benzoate (**33**)	206 (M^+, 1), 123 (66), 105 (100), 84 (16), 77 (68), 69 (16), 56 (40), 51 (27), 41 (31), 29 (22), 27 (23).
1296	19	diadduct (**35**)	178 ($[M-14]^+$, 1), 163 (5), 153 (13), 135 (10), 122 (6), 107 (11), 97 (20), 82 (33), 69 (27), 54 (62), 41 (100), 29 (58), 27 (55), 18 (8).
1564	10	triadduct	162 (10), 153 (5), 135 (10), 122 (8), 105 (16), 97 (20), 93 (36), 82 (22), 77 (19), 70 (30), 54 (61), 43 (79), 41 (100), 39 (28), 29 (58), 27 (50), 18 (14)

Hexenyl ester with acrylonitrile. Conditions identical to the benzyl ester, with 0.1g of hexenyl ester (**25**) used.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
80	53	methylcyclopentane	84 (M^+, 8), 69 (30), 56 (100), 55 (30), 42 (30), 41 (70), 39 (28), 27 (21), 15 (4).
111	117	n-heptane	as before
153	67	toluene	as before

977	15	monoadduct (**34**)	137 (M^+, 2), 123 (1), 109 (7), 96 (40), 80 (9), 69 (40), 55 (28), 41 (100), 39 (34), 27 (25), 18 (9).
1216	5	ester (**25**)	as for preparation
1250	54	benzoate (**33**)	175 (1), 124 (9), 105 (100), 82 (52), 77 (64), 67 (50), 54 (80), 51 (28), 41 (31), 39 (23), 27 (18), 15 (2).

Cyclohexyl ester with acrylonitrile. Conditions identical to the benzyl ester, with 0.1g of cyclohexyl ester (**26**) used.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
100	88	cyclohexane	84 (M^+, 57), 69 (29), 56 (100), 55 (45), 42 (35), 41 (80), 39 (35), 27 (23), 15 (4).
122	102	n-heptane	as before
166	64	toluene	as before
982	29	monoadduct (**34**)	136 ($[M-1]^+$, 7), 122 (3), 108 (13), 95 (11), 83 (43), 82 (90), 67 (12), 55 (100), 54 (26), 41 (73), 39 (40), 27 (32)
1254	20	ester (**25**)	as for preparation
1301	52	benzoate (**33**)	204 (M^+, 1), 123 (62), 105 (100), 99 (7), 82 (28), 77 (60), 67 (41), 55 (22), 51 (24), 41 (30), 39 (18), 27 (18).
1317	17	diadduct (**35**)	190 (M^+, 5), 176 (2), 162 (5), 151 (9), 136 (20), 122 (5), 108 (13), 95 (10), 83 (32), 67 (22), 55 (98), 41 (100), 39 (41), 27 (36), 18 (12).

1604	8	triadduct	204 (5), 196 (5), 190 (7), 150 (14), 143 (10), 138 (25), 123 (12), 108 (18), 95 (16), 83 (42), 67 (22), 55 (100), 41 (85), 39 (34), 28 (42), 18 (38).

Cholesteryl ester with acrylonitrile. Conditions identical to the benzyl ester, with 0.1g of cholesteryl ester (**28**) used.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
115	112	n-heptane	as before
155	61	toluene	as before

***tert*-Butyl ester with acrylonitrile.** Conditions identical to the benzyl ester, with 0.1g of *tert*-butyl ester (**29**) used.

Conditions: 30°C for 10min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
67	160	2-methylpropane	58 (M^+, 23), 43 (100), 42 (14), 27 (10), 15 (31).
122	152	n-heptane	as before
166	91	toluene	as before
378	65	monoadduct[57](**34**)	96 (60), 69 (28), 57 (100), 55 (51), 41 (79), 39 (26), 29 (38), 27 (39), 18 (22).
979	67	ester (**29**)	as for preparation
1301	52	benzoate (**33**)	178 (M^+, 1), 123 (45), 105 (70), 77 (41), 57 (100), 56 (63), 51 (29), 41 (55), 29 (31), 15 (5).
1080	39	diadduct (**35**)	150 (7), 136 (18), 118 (20), 108 (6), 91 (16), 81 (7), 65 (12), 57 (100), 41 (47), 39 (25), 29 (31), 15 (6).

1375	10	triadduct	203 (6), 175 (5), 159 (1), 149 (2), 135 (2), 121 (3), 108 (6), 95 (5), 81 (6) 68 (5), 57 (100), 54 (13), 41 (34), 29 (21), 18 (12).

Product analysis using Bromoform. Cyclohexyl ester, **26**, (200mg, 0.91mmol), bromoform (230mg, 0.91mmol) and AIBN (10mg), the initiator, were combined in a sealed NMR tube, 2/3 full with *tert*- butylbenzene. This was then heated at 100°C for 60 hours. The GC/MS obtained showed that little of **26** had reacted. The main product was not however the intended cyclohexyl bromide. It was the undesired product obtained after methyl loss from **26**, cyclohexyl benzoate.

Conditions: 50°C for 5min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
107	53	toluene	as before
882	162	ester (**26**)	as for preparation
913	76	cyclohexyl benzoate	as before

Preparation of *tert*-butyl hypochlorite.[43] Sodium hypochlorite (500ml) was stirred in a round bottomed flask at a temperature of <10°C. At this point the lights in the vicinity of the apparatus were turned off. A solution of *tert*-butyl alcohol (37ml; 400mmol) and glacial acetic acid (24ml; 420mmol) were added in a single portion to the rapidly stirred bleach and stirring was continued for about 3 minutes. The reaction mixture was transferred to a separating funnel and the lower aqueous layer discarded. The oily yellow organic layer was washed with 10% aq. Na_2CO_3 (50ml) and then water (50ml). The product was dried over 1g of calcium chloride and filtered (31.9g, 73.5%). The product was stored in the refrigerator over calcium chloride in an amber glass bottle. ^1H NMR δ 1.3 (s, 9H).

Product analysis using *tert*-butyl hypochlorite. To a refluxing solution of cyclohexyl ester, **26**, (0.8g; 3.6mmol) in CCl_4 (40ml) was added dropwise, over a period of 10min, *tert*-butyl hypochlorite (0.55g; 5.0mmol) in CCl_4 (20ml). The reactants were left to reflux for 5hr under a light source. The solvent was then 75% evaporated, at room temperature. The GC/MS obtained is listed below.

Conditions: 50°C for 5min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
150	55	toluene	as before
310	12	cyclohexyl chloride	118 (M^+, 2), 82 (40), 67 (100), 55 (43), 41 (60), 39 (43), 28 (51), 18 (33).
1003	113	ester (**26**)	as for preparation
1063	93	cyclohexyl benzoate	as before
1114	64	unidentified byprod	220 (1), 136 (87), 119 (100), 91 (99), 65 (58), 55 (77), 41 (77), 27 (33).

Product analysis using carbon tetrachloride. Cyclohexyl ester (100mg; 4.5mmol) and carbon tetrachloride (20% excess) were combined in a NMR tube with a trace of lauroyl peroxide. The NMR tube was sealed and left to react for 48 hr at 70°C. GC/MS showed no reaction had occurred.

Preparation of *N*-bromobis(trimethylsilyl)amine.[45] Bis(trimethylsilyl)amine (12.47g; 77mmol) was treated with *N*-bromosuccinimide (13.7g; 77mmol) at -10°C in CCl_4 (40ml) in the dark for 4 hr. At the end the succinimide formed was filtered off. Distillation of the product (20mmHg, 80°C) yielded an orange liquid (10.75g, 58 %) as the pure product.

Product analysis using *N*-bromobis(trimethylsilyl)amine. To the cyclohexyl ester (0.6g; 2.7mmol) in CCl_4 (40ml), was added norbornylene (5mol%)

and AIBN (5mol%). To this was added dropwise, *N*-bromobis(trimethylsilyl)amine (0.5g; 3mmol), in CCl_4 (20ml). The reactants were then refluxed for 2 hr, and the resulting solution analysed by GC/MS.

Conditions: 50°C for 5min then 10°C/min to 200°C.

Scan No.	Peak Ht. (mm)	Compound	*m/z* (%)
151	11	toluene	as before
444	62	cyclohexyl bromide	as before
566	30	bromotoluene	172 (M^+, 2), 93 (100), 91 (70), 77 (73), 65 (30), 51 (20), 39 (69), 27 (36), 18 (19).
1001	123	ester (**26**)	as for preparation
1062	92	cyclohexyl benzoate	as before
1112	80	unidentified byprod	218 (1), 136 (50), 119 (70), 91 (86), 65 (61), 55 (88), 41 (100), 27 (40).
1197	43	cyclohexyl polybromide	83 (60), 77 (13), 55 (100), 41 (50), 39 (18), 29 (14), 27 (21), 18 (8).
1254	42	cyclohexyl polybromide	83 (82), 67 (11), 55 (100), 41 (52), 39 (18), 29 (18), 27 (15), 18 (9).

Kinetic Reaction of hexenyl ester. The ester, **25**, (0.1g; 0.45 mmol), BOOB as initiator (15µl), n-heptane (10µl) and *tert*-butylbenzene (400µl) were combined in a long glass tube. The reaction mixture was degassed by a series of 'freeze-pump-thaw' cycles, under vacuum. The tube was then flame sealed and heated at 140°C for 25hr. The tip was then broken off and a GC immediately obtained on the mixture. Yields: hex-1-ene (0.1%), cyclopentane (9.95%), cyclohexane (0.29%). Although low, the yields are in similar proportion to the addition experiments with acrylonitrile.

GLC Packed Column: Conditions: 3µl injection.

Column Temperature =61°C, Detector = 200°C, Injection =200°C.

Chart Speed = 5mm min^{-1}.

Retention Time (mm)	Peak Height (mm)	Area (Rt x Pht)	Sensitivity	Compound	Ratio (%)
36	17	612	16×10^2	hex-1-ene	9.6
50.5	70	3535	256×10^2	methylcyclopentane	55.6
67	33	2211	16×10^2	cyclohexane	34.8
90	60	5400	256×10^2	n-heptane	

The identities of these peaks were confirmed by retention time comparisons with authentic samples under identical conditions.

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Part Two:

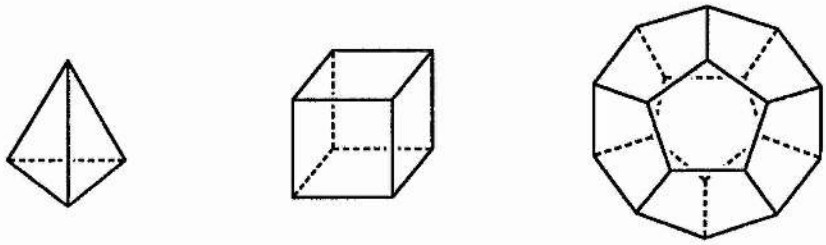
Cubane and Related Polycyclic Cage Molecules

Chapter 2

Introduction to the Chemistry of Cubane and Related Polycycles

2.0 Cubane

The cube is one of the five convex Platonic solids[1], i.e. it is made up of identical regular polygonal faces, with each vertex being congruent with every other vertex. Of the five, only three carbocyclic $(CH)_n$ analogues have been synthesised, those being 'tetrahedrane'[2,3] (n=4), 'cubane'[4] (n=8) and 'dodecahedrane'[5] (n=20), and/or derivatives thereof.



(a) (b) (c)

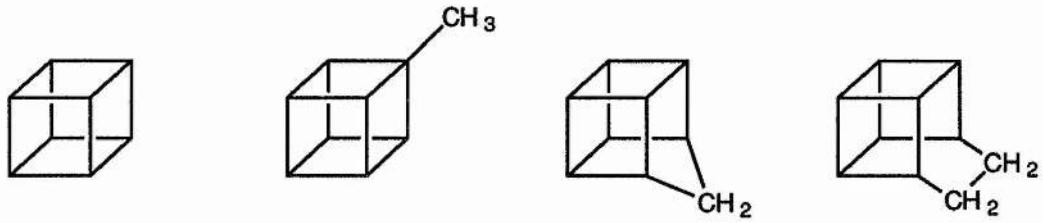
Figure 2.0

Three of the Platonic Solids. The (a) Tetrahedron, (b) Cube and (c) Dodecahedron.

Tetrahedrane, the simplest platonic hydrocarbon is unknown. The system, being highly strained, readily decomposes and the molecule fails to survive for any length of time.[6] However tetrasubstituted derivatives, such as tetra-*tert*-butyltetrahedrane[2] and tetralitiotetrahedrane have been isolated, probably due to greater stability from being fully substituted.

Dodecahedrane is much less strained (SE < 100 kcal mol^{-1}). However the total synthesis is some twenty three[5a,b] steps and it is obtained, understandably, in low yields.

The first of the "Platonic hydrocarbons" to be prepared from a rational synthesis was pentacyclo[4.2.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]octane, or cubane. Its synthesis was solved by Eaton and Cole,[4] in 1964. Since then many derivatives of cubane have been isolated



(a) (b) (c) (d)

Figure 2.1

(a) Cubane, (b) Methylcubane, (c) Homocubane and (d) Basketane.

and their behaviour studied extensively. In this chapter the discussion is going to be concentrated on cubane and three variations of the cubane structure; methylcubane, pentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]nonane or 'homocubane' and finally pentacyclo[4.4.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]decane, otherwise known as '1,1-bishomocubane' or as it shall be referred to here, 'basketane'.

2.1 Preparation of Cage Molecules

There are two apparent routes to the cage system. These are (i) the cycloaddition of functionalised noncage precursors, and (ii) the ring contraction of functionalised cage precursors.

Intramolecular [2+2] photocyclisations of appropriately constructed dienes would appear to be a most attractive technique with which to access the cage structure. However, with cubane, photocyclisation generally does not occur. Reasons put forward for this include the effect of strain in the product relative to the effects in the reactants and the large non bonded distance (*ca.* 3.05Å) separating the two carbon-carbon double bonds in the starting diene, syn-tricyclo[4.2.0.$0^{2,5}$]octa-3,7-diene.[7]

The homocubane and basketane cages were able to be constructed by cycloaddition reactions and their ability to ring contract was invaluable in the first successful synthesis of the cubane skeleton.

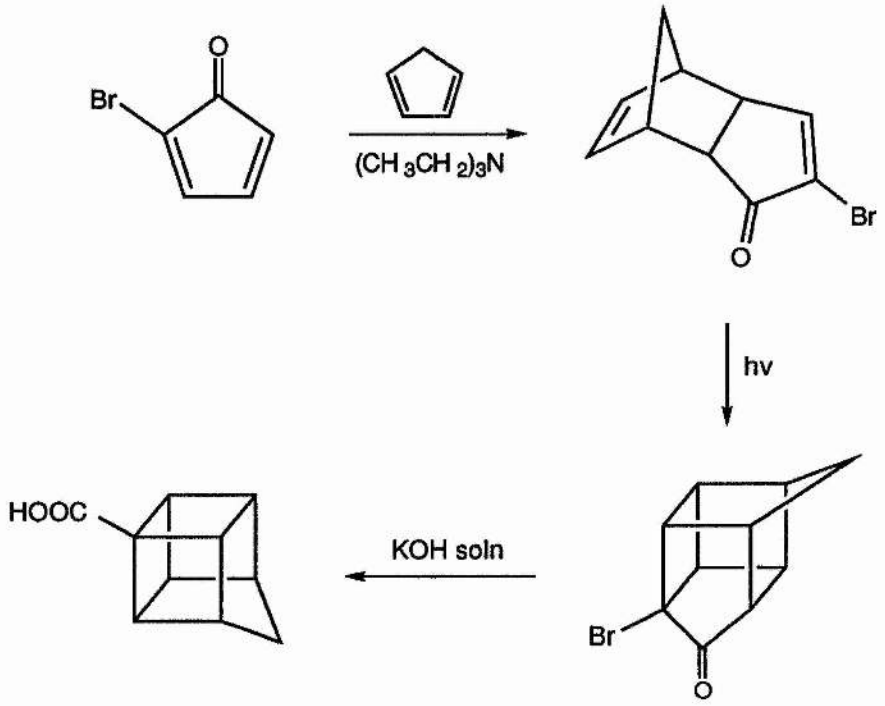


Figure 2.2

Synthesis of Homocubanes.

The homocubane skeleton was originally prepared by Eaton and Cole[4] and by Scherer.[8] Dipasquo and co-workers[9] further refined the synthesis of homocubanes containing a single functional group as in Figure 2.2. The final step utilises the base promoted Favorski-type ring contraction of α-halo ketones to generate the homocubane skeleton. Many cubane preparations followed, including the synthesis of

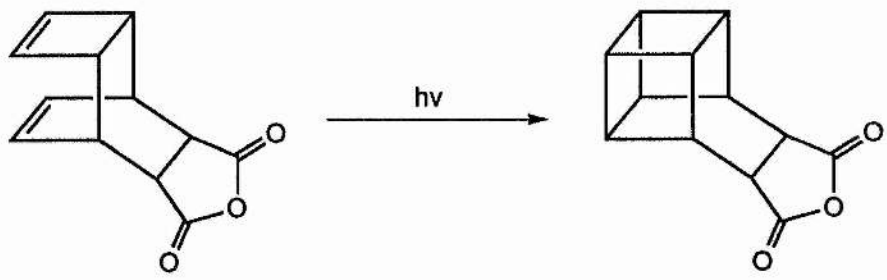


Figure 2.3

Original Preparation of The Basketane Cage.

methylcubane, based on the Eaton and Cole method, and it is still deemed the most efficient route to polycyclic cage-like systems.

Basketane was originally prepared[10] from the product derived from the photolysis of cyclooctatetraene and maleic anhydride (Figure 2.3).[11]

2.2 Strain in Polycycles

The synthesis and chemistry of novel, strained, saturated polycarbocyclic cage molecules are continually proving to be a source of fascination to organic chemists. They possess rigid, highly compact structures with carbon-carbon bond angles and bond lengths frequently deviating from the "normal" values associated with sp^3 hybridised carbon atoms. These deviations provide a measure of strain energy that is contained within the system.

It would be thought therefore that high levels of molecular strain in such systems would confer upon them corresponding levels of thermodynamic instability. However despite the considerable strain introduced into a molecule by the bond deformations of eight, nine and ten sp^3-hybridised carbons in cubane, homocubane and basketane respectively (see Table 2.0 for strain energies of cage molecules), they all display unusual thermal stability. In 1966, Dauben and Whalen noticed that the IR spectrum of homocubane remained unchanged after heating it at 513K for 5 minutes. It is also known[6] that cubane survives unchanged at temperatures of up to *ca.* 473K and basketane, in control experiments undertaken in the following chapter, remained unaltered after photolysis at 473K for 2 hours.

The calculations for the strain energies of the five bishomocubane hydrocarbons, $(CH)_8(CH_2)_2$, by the MM2 method show an increasing trend in the order 1,4 < 1,3 < 1,3' < 1,2 < 1,1, indicating basketane to be the most strained system. This is as expected because this bishomocubane is the only one with four four-membered rings fused to each other and four membered rings are significantly more strained than five- or six- membered rings. All five of these isomers are also

lower in strain energy than that of homocubane and cubane, mainly because of smaller deviations from the "normal" tetrahedral bond angles for the bishomocubanes.

Table 2.0. MM2 Calculations of Strain Energy in Caged Polycycles

Compound	Strain Energy[a] kcal mol^{-1}	ΔH_f[a] kcal mol^{-1}
cubane	166.12	148.85
homocubane	118.13	95.11
1,1-bishomocubane (basketane)	112.57	83.78
1,2-bishomocubane	93.12	65.12
1,3'-bishomocubane	90.14	61.35
1,3-bishomocubane	76.63	47.85
1,4-bishomocubane	73.34	44.55

[a] ref 17.

2.3 Reactions of Polycycles

Substituted polycycles can react in many ways. To simplify this they are summarised into four reaction groups. (i) Fragmentation and (ii) ring expansion of the cage, (iii) rearrangements promoted by transition metals and (iv) functionalisation of the cage structure itself.

Cage opening reactions derive some of their driving force from the release of strain on cleaving a carbon-carbon σ-bond in the cage system. Stober and Musso[18] investigated the hydrogenolysis of cubane and found that up to three carbon-carbon bonds will undergo hydrogenolysis in a sequential manner under the correct conditions. Basketane has also been shown[19] to undergo a similar type of expansion. In both cases hydrogenolysis occurs at the most highly strained carbon-carbon bond leading to a product with the lowest strain energy.[18,19] Thus in the basketane case the two

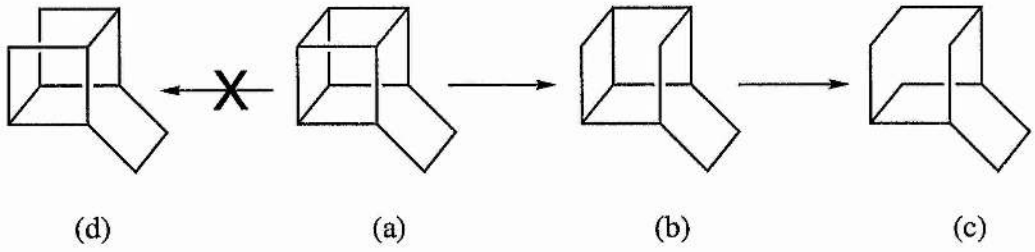


Figure 2.4

The Sequential Hydrogenolysis of Basketane.

concurrent products were the unsymmetrical dihydrobasketane (b) structure followed by a further reduction to twistane (c). No sign of hydrogenolysis of the symmetrical bond (d) was apparent as was earlier postulated by Masamune.[10] Other types of ring opening reactions have been investigated by Klunder and Zwanenburg who have studied base promoted reactions such as homoketonisation[19] and homoallylic rearrangements, which lead to ring opening.

Transition metal ions (such as Ag^+ and Rh^+) at high concentrations, induce very rapid ring opening and/or rearrangement reactions.[21-30] Figure 2.5 shows an example of metal ion induced rearrangement of homocubane to norsnoutane. Similarly basketane rearranges to snoutane and cubane to cuneane.

Derivatives of cubane and the other cage systems are usually prepared by direct substitution on the cage. Initially, functionalisation centred around the manipulation of

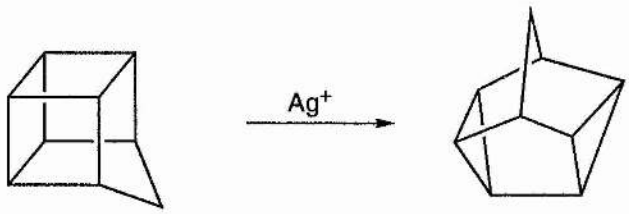


Figure 2.5

Metal Induced Rearrangement Of Homocubane to Norsnoutane.

the carboxylic acid groups by standard techniques (the acid and diacid were the first substituted polycycles isolated). For example bis decarboxylation of the 9,10-trans-diacid of basketane gives basket-9-ene which can be subsequently hydroborated to basketan-9-ol.[13] Increased functionality has come about through the ability to directly metalate the cage skeleton. This process was first discovered by Eaton[14] and has subsequently increased the interest in such strained systems as a potentially important new class of energetic materials.[15]

In recent years attention has been focused upon applications of cage molecules that take advantage of their strain energy. Potential military applications are at the forefront with efforts to use the strain energy content of the cages, released on combustion, as a new class of solid and liquid fuels. Incorporation of nitro groups into energetic molecules is known to confer upon these molecules desirable explosive properties.[15] Eaton and co-workers,[31] together with the United States Air Force, are currently working on the addition to cubanes of increasing numbers of NO_2 groups. Up to now only the 1,3,5,7-tetranitrocubane has been synthesised but increasing this number up to the fully functionalised octanitrocubane is under study. Polynitropolycyclic cage compounds may also be readily reduced to polyamines. This may well prove beneficial if the cage amines show any anti viral properties similar to 1-aminoadamantane.

2.4 Cubyl and Cubylcarbinyl Radicals

The following two chapters study the basketyl, homocubyl and norcubylcarbinyl radicals in some depth, therefore it would be superfluous to our needs to describe in full detail the cubyl radical as this differs from the others in being the only bridgehead radical species. The cubyl radical, unlike other three- or four-membered ring compounds, does not readily undergo β-scission under normal conditions. This is somewhat surprising when it is considered that the cubyl radical contains *ca.* 15 kcal mol^{-1} more strain energy per carbon-carbon bond, than for the cyclobutyl radical, and it

takes part in reactions at temperatures greater than 373K without rearrangement. The explanation for this is that β-scission of the cubyl radical would result in the formation of a high-energy bridgehead alkene.

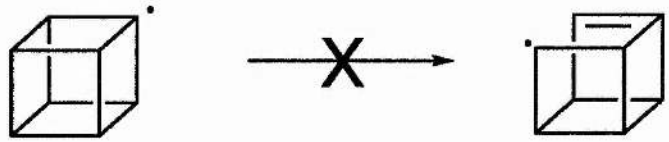


Figure 2.6

A close relation to the cubyl system is the cubylcarbinyl radical. The cubylcarbinyl cation is very unstable and undergoes a Wagner-Meerwein 1,2-bond shift exceptionally quickly. Rearrangement into the homocubyl system is driven by a concomitant release of strain.[32,33]

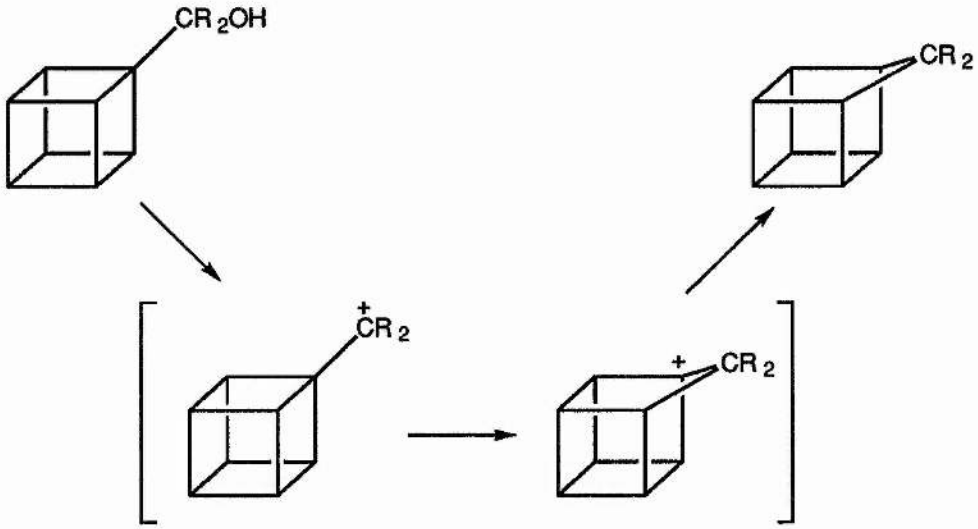


Figure 2.7

The Rearrangement of the Cubylcarbinyl Cation.

The cubylcarbinyl radical however does not rearrange in this manner.[34] Eaton and Yip proposed the rearrangement to be a sequence of β-scissons of the cage system,

the first being a rupture of the strained cubane bond, familiar from the cleavage of the cyclobutylcarbinyl radical to the pent-4-enyl radical.[35] The following bond cleavages are helped by the thermodynamic stability of the allylic radicals subsequently formed. The arguement for this mechanism was further strengthened by the observation of some of the intermediate radicals by EPR spectroscopy.[15(b)]

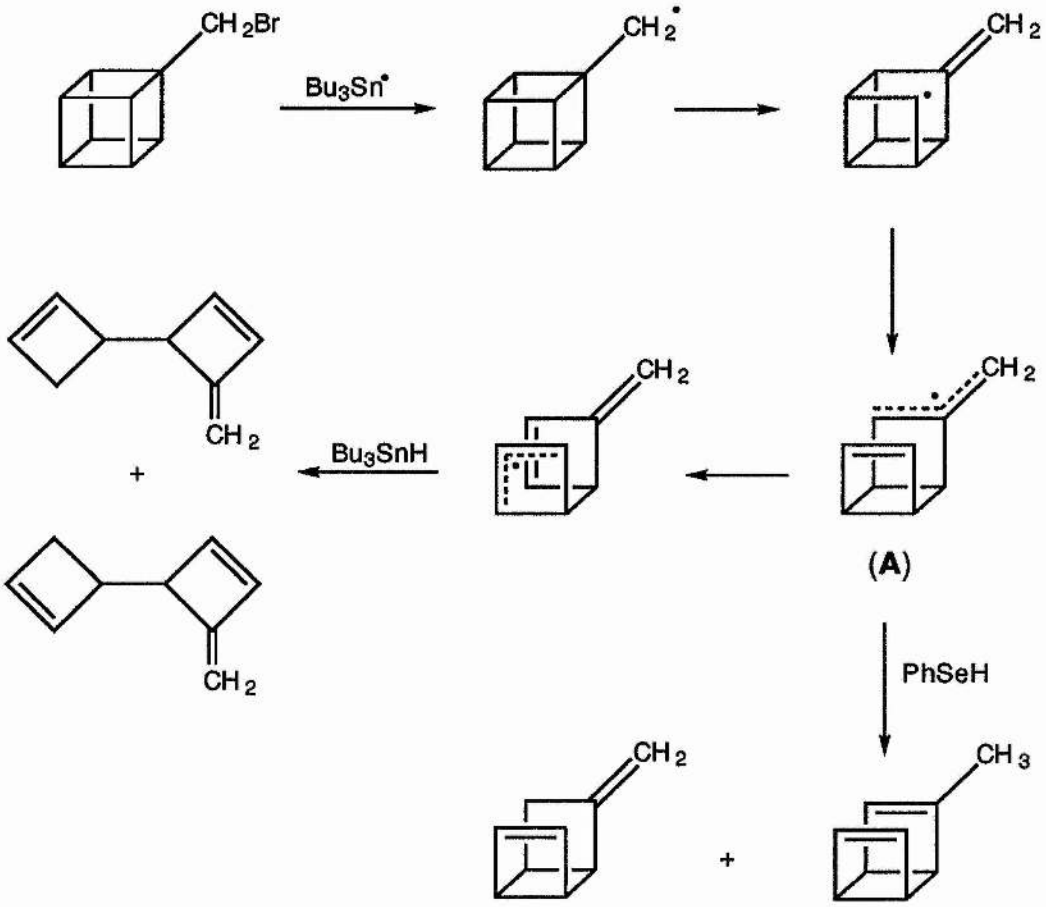


Figure 2.8

Rearrangement of the Cubylcarbinyl Radical.

Radical A is trapped when selenophenol is employed at high concentrations.

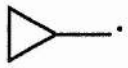
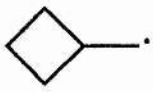
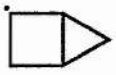
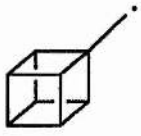
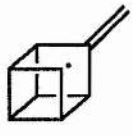
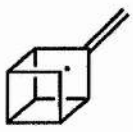
The rate of rearrangement of the cubylcarbinyl radical is extremely rapid and selenophenol was used to attempt to trap the radicals formed.[36] Selenophenol is known to be an efficient hydrogen donor[37] and was able to trap the radical marked **A**.

The rate constant for conversion of the cubylcarbinyl radical to the radical **A** was *ca.* 2 x 10^{10} s^{-1} at 293K, making the initial cleavage reaction one of the fastest known radical reactions involving bond breakage. Knowing the rate constants introduces possibilities of using the unimolecular rearrangement of the cubylcarbinyl radical as a radical clock and/or a mechanistic probe.

2.5 Radical Rearrangements as Radical Clocks and Mechanistic Probes

In a radical clock application,[38] a known rate constant for a rearrangement and

Table 2.1. Rates of Ring Opening of Various Radicals

Initial Radical	Rearranged Radical	k_r[a] (s^{-1})	ref.
		1.2 x 10^8 (310K)	39
		4.7 x 10^3	40
		3.0 x 10^{11}	41
		2.1 x 10^9	39
		2.9 x 10^{10}	36
		>1.5 x 10^{11}	36

[a] Rearrangement carried out at 298K unless stated.

the distribution of products formed when the rearrangement competes with another reaction can be used to determine the kinetics of the competition reaction. As a mechanistic probe, the production of rearranged products implies a radical intermediate in a reaction pathway. An exceptionally fast radical rearrangement is desirable so that competing reactions will not intercept the first formed radical intermediate before rearrangement. Table 2.1 shows various radical clocks and their rates of rearrangement. The accuracy of calibration varies for each.

There are many reactions, both enzymic and non-enzymic, where these types of radical rearrangements have been employed.[41] An example of such a reaction which has been recently studied to some depth is the hydroxylation of alkanes by Cytochrome P-450, an enzyme containing an iron photoporphyrin as the oxygenation catalyst.[39,43] The catalytic cycle is depicted below.

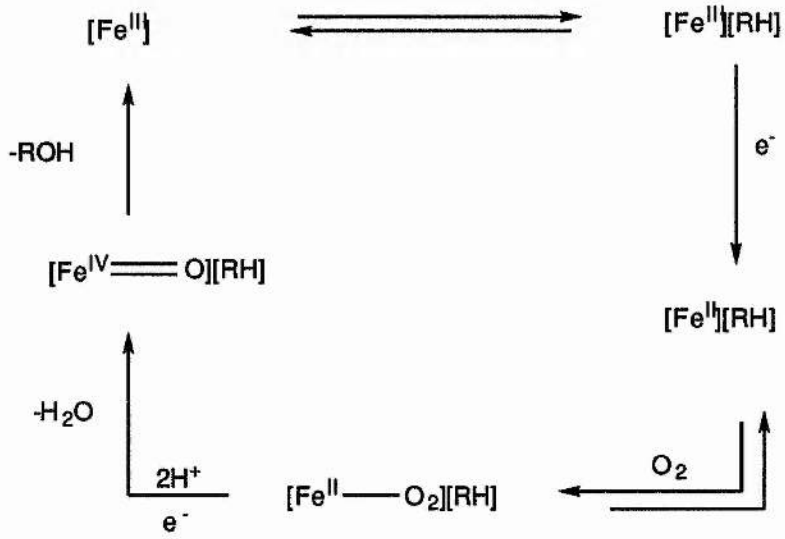


Figure 2.9

Catalytic Hydroxylation by P-450.

The precise mechanism of oxygen insertion into the carbon-hydrogen bond has been proposed to be a so called 'oxygen rebound' mechanism whereby hydrogen

abstraction from the carbon-hydrogen bond is followed by a transfer of a hydroxyl radical to the resulting alkyl radical.

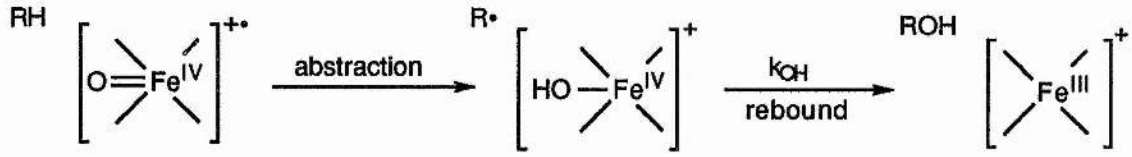


Figure 2.10

Oxygen Rebound Mechanism Proposed For P-450.

By using bicyclo[2.1.0]pentane as the radical clock, the ratio of unrearranged and rearranged products enabled the rate constant of oxygen rebound to be determined, $k_{OH} = 2.2 \times 10^{10}\ s^{-1}$ at 310K.

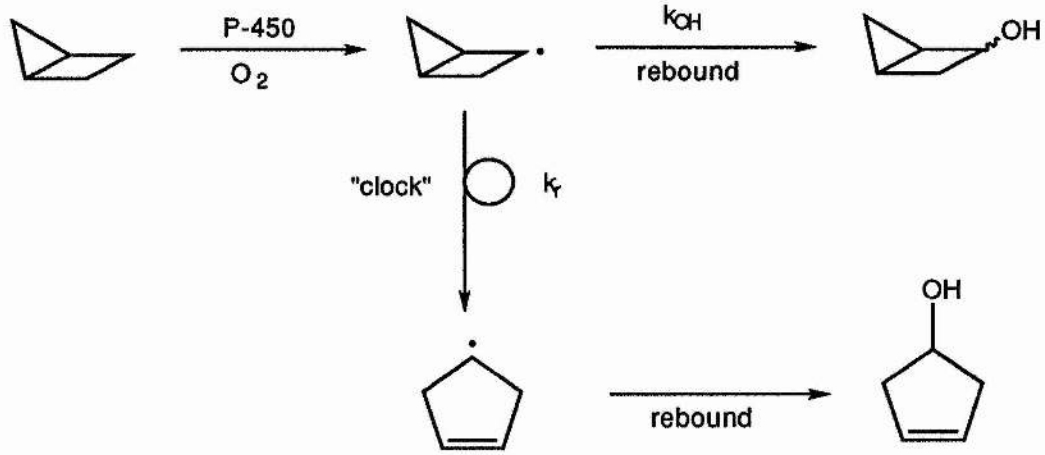


Figure 2.11

Use of Bicyclo[2.1.0]pentane as a Radical Clock.

2.6 Basketyl and Homocubyl Radicals

The contrast in unimolecular reactivity between the cubyl and cubylcarbinyl radicals was so novel that it provoked us to examine the homolytic rearrangements of several free radicals with structures incorporating some of the features of both types of radical. It was anticipated that the kinetic parameters of their rearrangements, and the EPR spectral data of the radicals, would disclose essential details of the factors controlling the β-scissions.

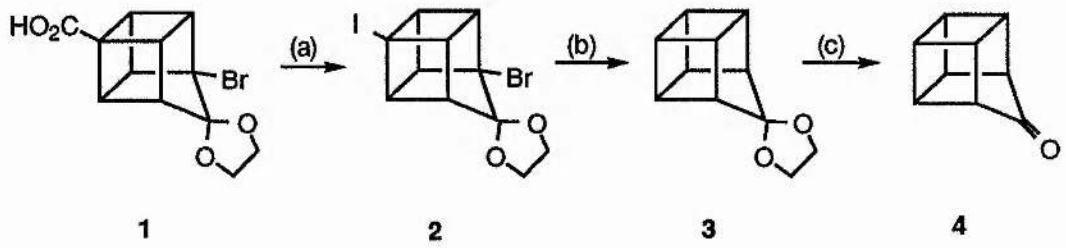
The rates of ring-opening reactions generally increase with the amount of strain released in the process. The skeleton of the 9-homocubyl radical contains *ca.* 118 kcal mol^{-1} of strain and has four equivalent C_β-C_γ bonds capable of undergoing β-scission to give non-bridgehead alkenes. On this basis, the 9-homocubyl radical seemed therefore to be a good candidate for rapid unimolecular rearrangement, as did the 9-basketyl radical which has *ca.* 113 kcal mol^{-1} of strain. On the other hand, both the 9-homocubyl and 9-basketyl radicals are highly constrained analogs of the cubylcarbinyl radical. An important property of the latter is that the radical centre is freely able to rotate, and this allows the transition state for ring-opening of the cubylcarbinyl radical to adopt the conformation which most facilitates the β-scission; the optimal dihedral angle between the SOMO and the C_β-$C\gamma$ bond in this arrangement is 0°. The 9-homocubyl and 9-basketyl radicals, however, are much more rigid species in which the dihedral angle between the SOMO and C_β-$C\gamma$ is fixed and significantly larger than 0° in each case. Accordingly, it was deemed of interest to examine the effects of such restriction on the capacity of the 9-homocubyl and 9-basketyl radicals to rearrange.

Chapter 3

9-Homocubyl and 9-Basketyl Radicals

3.0 Preparation of 9-Hydroxy and 9-Bromo Derivatives of Homocubane and Basketane

All of the structures examined in this study were synthesised by Ernest W. Della, Gordon M. Elsey and Nick J. Head, from Flinders University in South Australia, our co-workers on this polycyclic rearrangement project. The radical precursors were prepared from a common intermediate, homocubanone (**4**).[45] For this work, homocubanone was prepared from the bromoacid **1** by a route based on that described by Mehta and his associates[45a] but involving the mixed halide **2**. Dehalogenation of **2** with tributyltin hydride gave the ketal **3**.

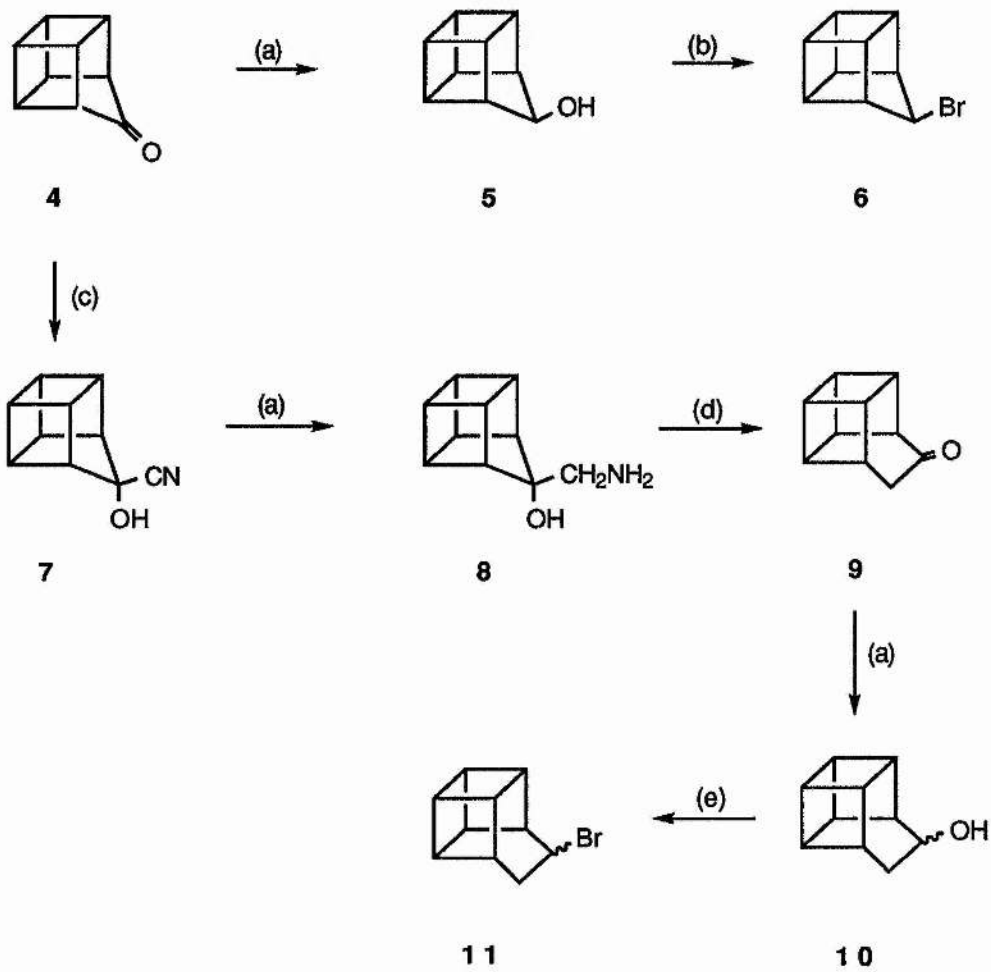


(a) $Pb(OAc)_4$ / I_2; (b) Bu_3SnH; (c) H^+

Figure 3.0

Reduction of **4** with lithium aluminum hydride gave the alcohol **5**; however, conversion of this to the corresponding bromide **6** proved unsuccessful with concentrated HBr on the one hand, or triphenylphosphine dibromide in CH_2Cl_2 or DMF on the other. Both PBr_3 and PBr_5 gave better conversion, but the most effective route to **6** involved treatment of **5** with thionyl bromide; this gave a product (71%) which could be purified readily. Conversion of **4** into basketone (**9**) was achieved as shown in Figure 3.1. Although ring-expansions of bromohomocubanones have been successfully performed by the use of diazomethane,[46] ketone **4** did not respond favorably to these conditions. Cage homologation in this case was effected *via* the

following procedure.[47] Reduction of the derived cyanohydrin **7** by lithium aluminum hydride produced the aminoalcohol **8**, deamination of which proceeded with



(a) $LiAlH_4$; (b) $SOBr_2$; (c) HCN; (d) NO_2^- / H^+; (e) Ph_3PBr_2

Figure 3.1

ring expansion to give the ketone **9** in good yield. The latter was reduced to **10** with lithium aluminum hydride. Unlike its lower homolog **6**, 9-basketanol (**10**) was found to be far more prone to rearrangement during attempts to convert it to the corresponding bromide. Only when the very mild brominating reagent, triphenylphosphine dibromide, was employed was 9-bromobasketane (**11**) obtained free from

contaminants. The compounds thus prepared were >99% pure and fully characterised by ^{1}H and ^{13}C NMR, mass spectra and elemental analysis data.[48]

9-Bromobasketane was found to be somewhat more labile than 9-bromohomocubane and had to be handled more carefully. Attempts to purify it by chromatography for example led to complex mixtures of degradation products. GC/MS also showed signs of degrading the starting material all be it to a smaller extent.

3.1 EPR Spectra of 9-Homocubyl and 9-Basketyl Radicals

As was mentioned in Chapter 2 the basketyl[34] and homocubyl[49] radicals contain ca. 113 and 118 kcal mol^{-1} of strain respectively but, just as importantly, are highly constrained at the radical centre. It was therefore deemed of interest to examine the radicals by EPR spectroscopy to study whether the structural integrity was maintained under a range of conditions.

The generation of substituted cubyl radicals from their corresponding bromides

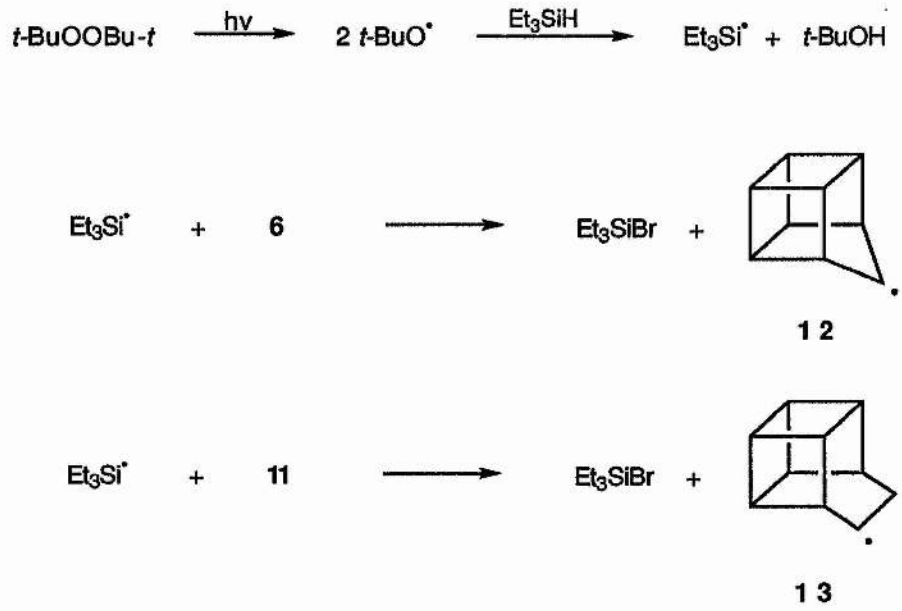


Figure 3.2

has already been reported.[50] Both photochemically produced trimethyltin and triethylsilyl radicals were used, but the former produced no EPR signals which could be attributed to the cubyl system. As a result of this we favoured the use of triethylsilyl radicals to abstract bromine atoms from the compounds examined. A cyclopropane solution containing 9-bromohomocubane, triethylsilane and di-*tert*-butylperoxide was photolysed in the cavity of an EPR spectrometer at low temperatures. The $Et_3Si^{\bullet}$ radical generated in this system should abstract bromine from the substrate leaving the polycyclic radical and/or its rearrangement products as the main EPR active species. A good spectrum of a radical with a large doublet, and some additional much smaller hyperfine splittings (hfs) was observed (Figure 3.3). The doublet hfs can be assigned to H_α of the 9-homocubyl radical, **12**. The magnitude of $a(H_\alpha)$ is consistent with **12** being a planar π-radical, unlike the strongly pyramidal σ-cubyl radical.[12(b)] The two β-hydrogens of **12** are at bridgehead sites, essentially in the nodal plane of the p-orbital at C-9 containing the unpaired electron (SOMO). Small $a(H_\beta)$ are therefore expected for **12**, in agreement with the spectroscopic

Table 3.0. EPR Data for 9-Homocubyl and 9-Basketyl Radicals[a]

radical	T (K)	$a(H_\alpha)$	$a(2H_\beta)$	$a(4H_\gamma)$	*a*(other)
12	160	20.70	0.98	0.98	
14a	170		2.04	0.55	1.60 (OH)
14b	170		2.04	0.55	[b]

radical	T (K)	$a(H_\alpha)$	$a(1H_\beta)$	$a(2H_\beta)$	*a*(other)
13	170	22.0	1.8	39.8	
15a	170		2.3	31.3	<1.5 (OH)
15b	170		2.2	31.3	[b]

[a] All g-factors 2.003 ± 0.001, hfs in Gauss, all checked by simulation. [b] *a*(OD) unresolved.

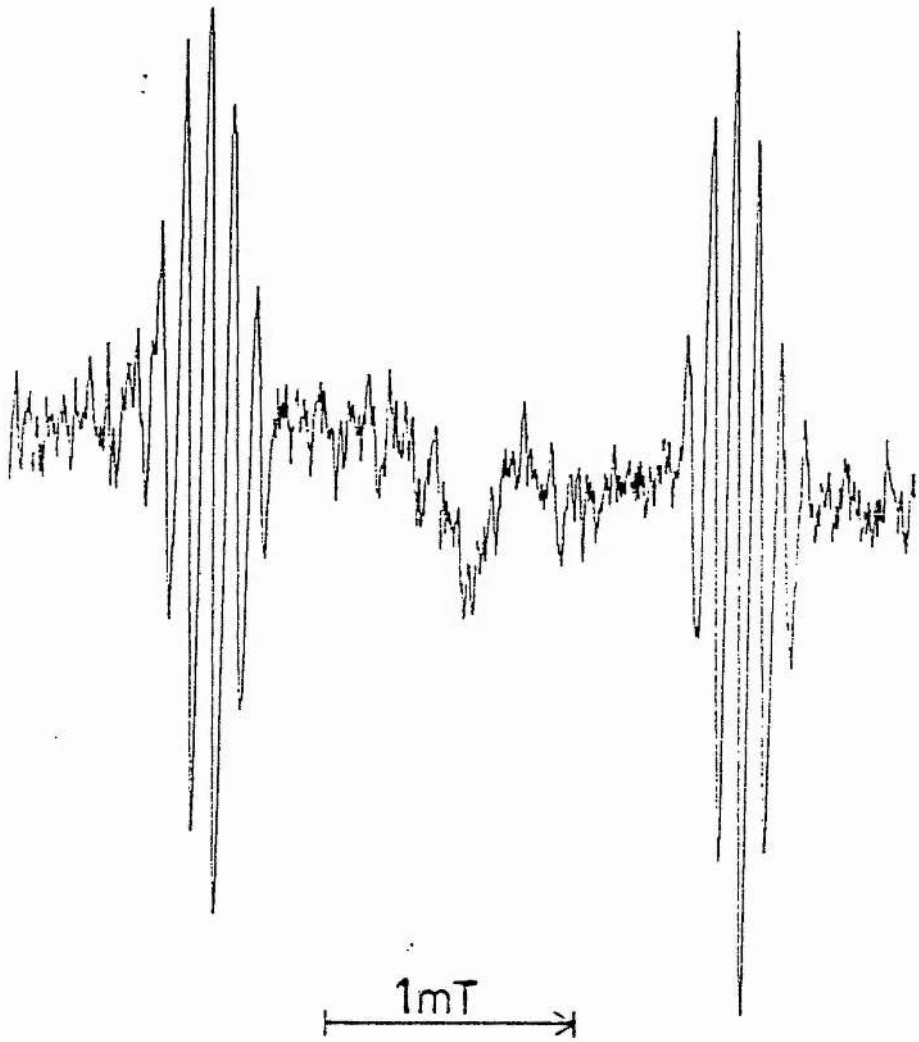


Figure 3.3

9.3 GHz EPR spectrum obtained by bromine abstraction from 9-bromohomocubane in cyclopropane at 160K.

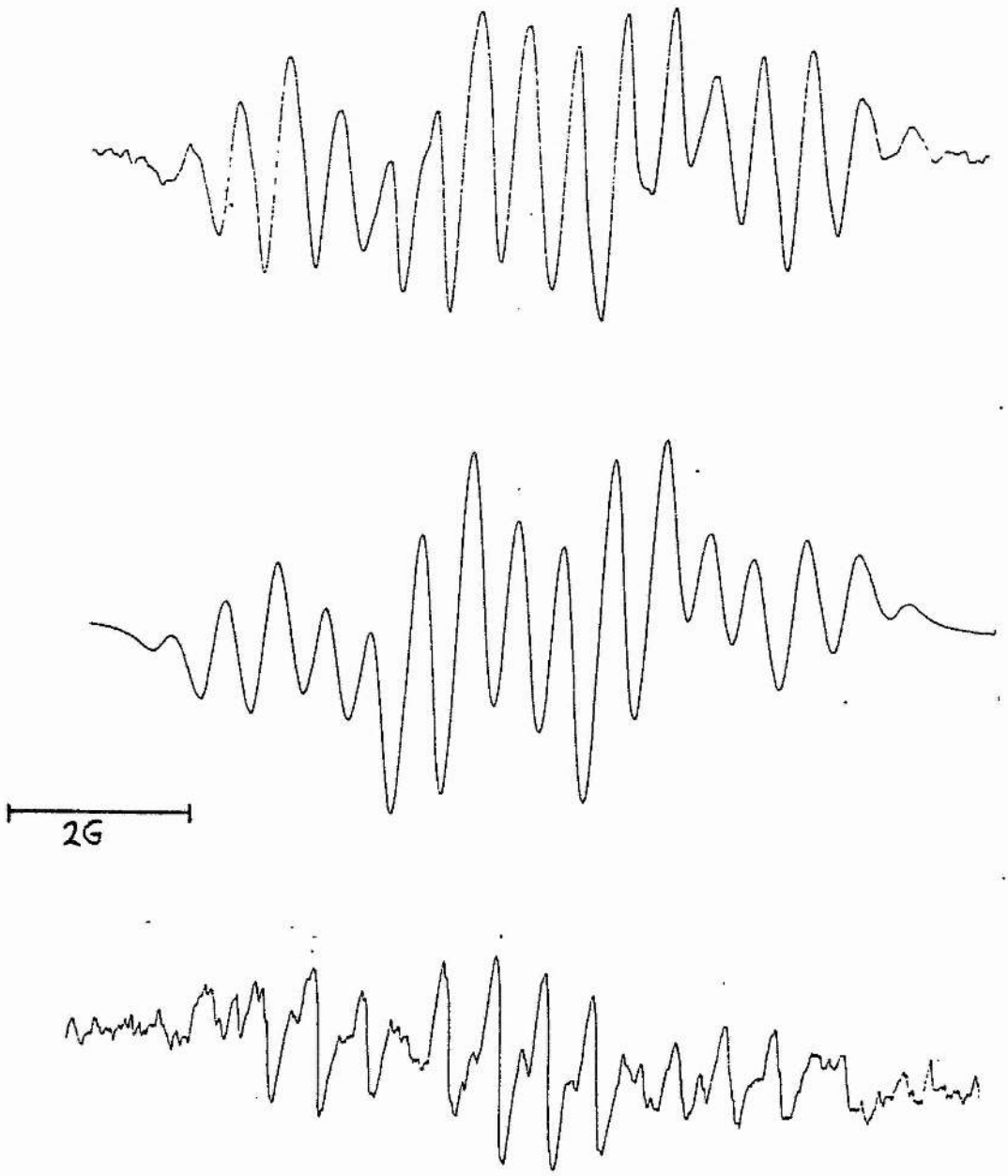


Figure 3.4

Upper: 9.3 GHz EPR spectrum obtained by hydrogen abstraction from α-hydroxy-9-homocubane at 170K. Middle: Computer simulation of the α-hydroxy-9-homocubyl radical using the hfs in Table 3.0. Bottom: 9.3 GHz EPR spectrum obtained by deuterium abstraction from α-deuteroxy-9-homocubane at 170K.

observations. The radical shows additional long range splitting from four equivalent γ-hydrogens (Table 3.0). The spectrum remained visible in the temperature range 153 to 203K, which indicated that **12** rearranged much more slowly than the cubylcarbinyl radical. The α-hydroxy- (**14a**) and α-deuteroxy-9-homocubyl radicals (**14b**) were also spectroscopically observed on hydrogen abstraction from **5** with photochemically generated *t*-BuO• radicals (Figure 3.5). The unrearranged radicals could be observed at temperatures up to 243K; above this no signals were detectable. The hydroxy substituent caused minor changes in the spin density distribution, but the hfs (Table 3.0, Figure 3.4) were entirely consistent with the detected species being substituted homocubyl radicals.

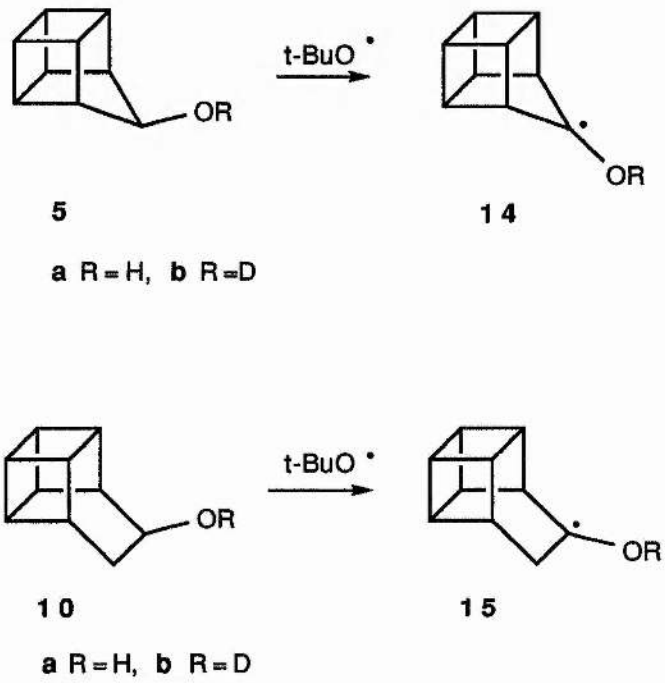


Figure 3.5

The EPR spectrum of the 9-basketyl radical (**13**) was obtained in a similar way using **11** as the substrate. The hfs from H_α was normal for a planar radical centre (Table 3.0); in addition, the spectrum showed large hfs from two equivalent H_β and a small doublet splitting from a single β-hydrogen. This latter hfs can be assigned to the bridgehead hydrogen which is essentially in the nodal plane of the SOMO. No long

range hfs were resolved, but the linewidth (1.5 G) was considerably larger than that of **12** and probably masked γ-hydrogen hfs. The analogous 9-hydroxy- (**15a**) and 9-deuteroxy-radicals (**15b**) were generated by hydrogen abstraction from the corresponding alcohols **10** (Figure 3.2) and their EPR parameters are in Table 3.0. The parent radical **13** was spectroscopically observable up to 203K and **15a,b** were detectable at 243K; above these temperatures no signals appeared, *i.e.*, rearranged radicals were not detected. For both **6** and **11** EPR samples with hexamethylditin in place of triethylsilane were examined but no well defined spectra were obtained. The spectra of **12** and **13** correspond to some of the most highly strained cage radicals ever observed spectroscopically, and demonstrate the remarkable stability of the homocubyl and basketyl cage structures, even after the removal of one hydrogen atom.

3.2 Tin Hydride Reductions of 9-Bromobasketane and 9-Bromohomocubane

It was evident from the EPR experiments in Section 3.1 that both the homocubyl (**12**) and the basketyl (**13**) radicals rearranged too slowly for this process to be studied within the constraints of EPR spectroscopy. Alternatively the bromides may be reacted with tributyltin hydride (Bu_3SnH). Bu_3SnH readily forms tributyltin radicals on photolysis which then abstract bromine forming the cage radicals **12** and **13**. The cage radicals may then complete the chain reaction by abstracting hydrogen from Bu_3SnH to give the hydrocarbon products or alternatively may rearrange before abstracting hydrogen.

At 343K, reduction of **11** with Bu_3SnH yielded the unrearranged product basketane (**16**) as the only product, on analysis by GC/MS. The reaction was clean with few side products apart from various, long retention time, tin products. However, when the reaction was carried out at higher temperatures (i.e., above 413K), a mixture containing both **16** and two rearranged hydrocarbons was observed. On increasing the temperature up to 485K (the highest possible temperature attainable

under the experimental conditions) an increasing proportion of the two rearranged products was obtained. Although the mixture was not separable by preparative TLC, 300 and 500MHz NMR analysis were sufficient to enable us to identify the products as

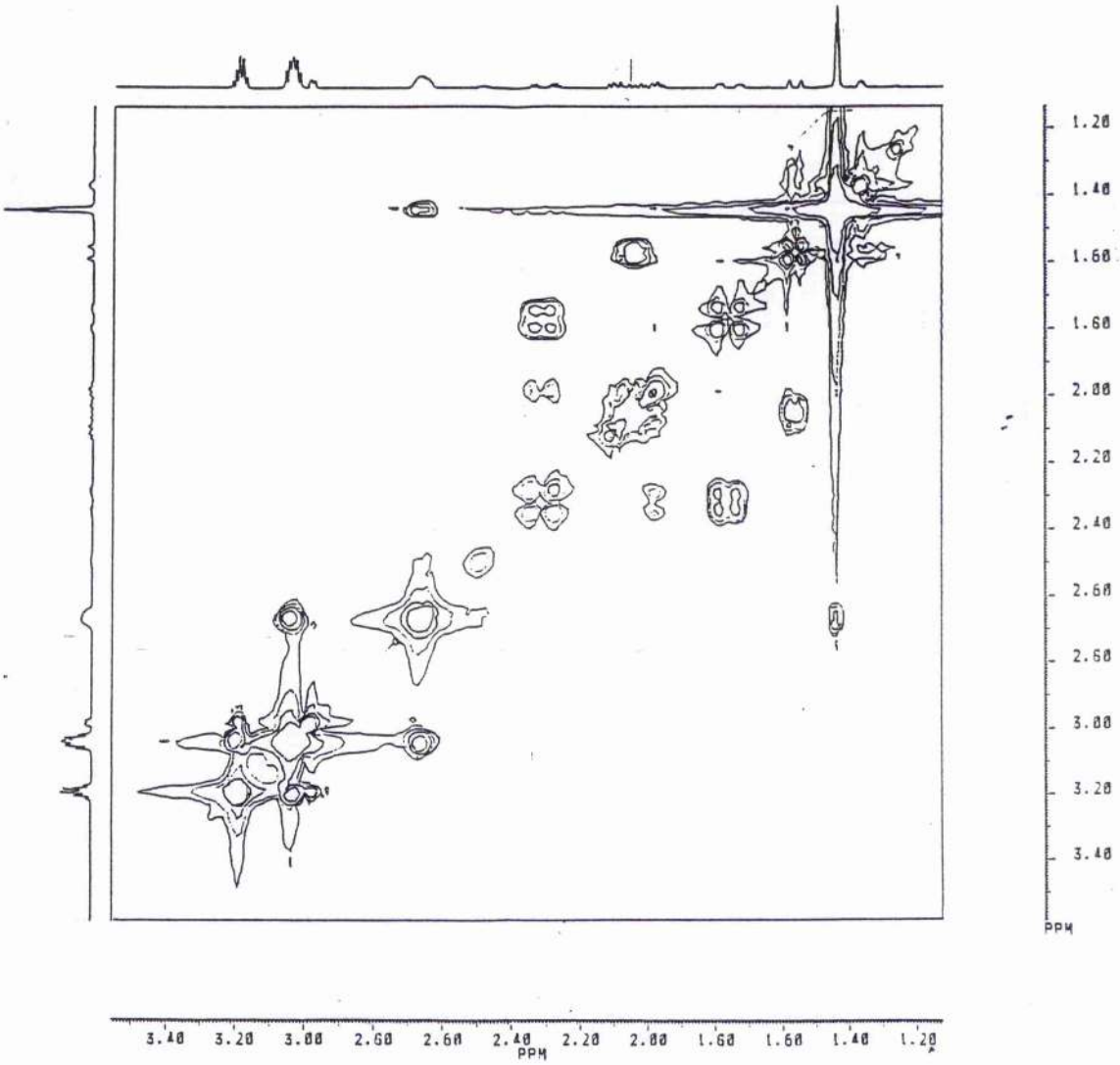
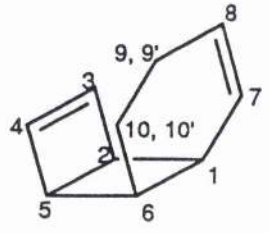


Figure 3.6

Expansion of the 2D COSY NMR Contour Plot of Tricyclo[4.4.0.0^{2,5}]deca-3,7-diene (below), Tricyclo[4.4.0.0^{2,5}]deca-3,8-diene and Basketane.



tricyclo[4.4.0.0^{2,5}]deca-3,7-diene (**19**) and tricyclo[4.4.0.0^{2,5}]deca-3,8-diene (**20**).

Although the experiment was undertaken on a small scale the sample was of sufficient concentration for a 2D COSY NMR (300MHz) spectrum to be obtained. The COSY spectrum contour plot was unable to show the coupling between hydrogens in the minor product **20**, but was of adequate strength to show cross coupling in **19** (the spectrum also contains a large amount of basketane: ^{1}H NMR δ 3.19, 3.04, 2.67, 1.44). The 2D COSY NMR spectrum can be explained as follows. The doublet at 6.00ppm (1H) couples strongly to the doublet at 5.895ppm (1H) as these are the alkene hydrogens at H^3 and H^4. The multiplet at 5.85ppm (H^7) also couples strongly with its corresponding alkene hydrogen multiplet at 5.33ppm (H^8). In the aliphatic region the couplings become complex, however peak assignments were made possible by the following couplings. H^{10} and H$^{10'}$ (2.03 and 1.98ppm), couple with their neighbouring hydrogen H^6 (1.57ppm). The large doublet signal at 2.32ppm couples strongly with an equally large doublet at 1.77ppm as these are the two hydrogens H^9 and H$^{9'}$. There is also coupling between H$^{9 \text{ or } 9'}$ (2.32ppm) and H$^{10 \text{ or } 10'}$ (1.98ppm). Other pairings are produced between the alkene and aliphatic regions. For instance H^7 (5.85ppm) couples with H^1 (2.11ppm) and H^8 (5.33ppm) couples with H$^{9 \text{ or } 9'}$ (2.11ppm). However some expected couplings were not observed, probably due to the cage nature of the molecule, hindering interaction between two hydrogen centres. The anticipated route to these products is shown in Figure 3.7.

Radical **13**, with the correct conditions, undergoes β-scission to give **17**, which may then undergo a further β-scission by several routes. The course of this β-scission is under stereoelectronic control, like other cyclobutylcarbinyl-type rearrangements.[35] Therefore the second β-scission would take place between the p-orbital containing the unpaired electron and either of the β-C-C bonds parallel to the orbital, marked a and b. Scission of b is favoured as this leads to formation of a resonance-stabilised allyl-type radical **18**. This rearrangement can be expected to be rapid as there is a large relief of cage strain and, thermodynamically, **18** is of lower energy relative to its radical predecessor **17**. The product analysis showed that radical

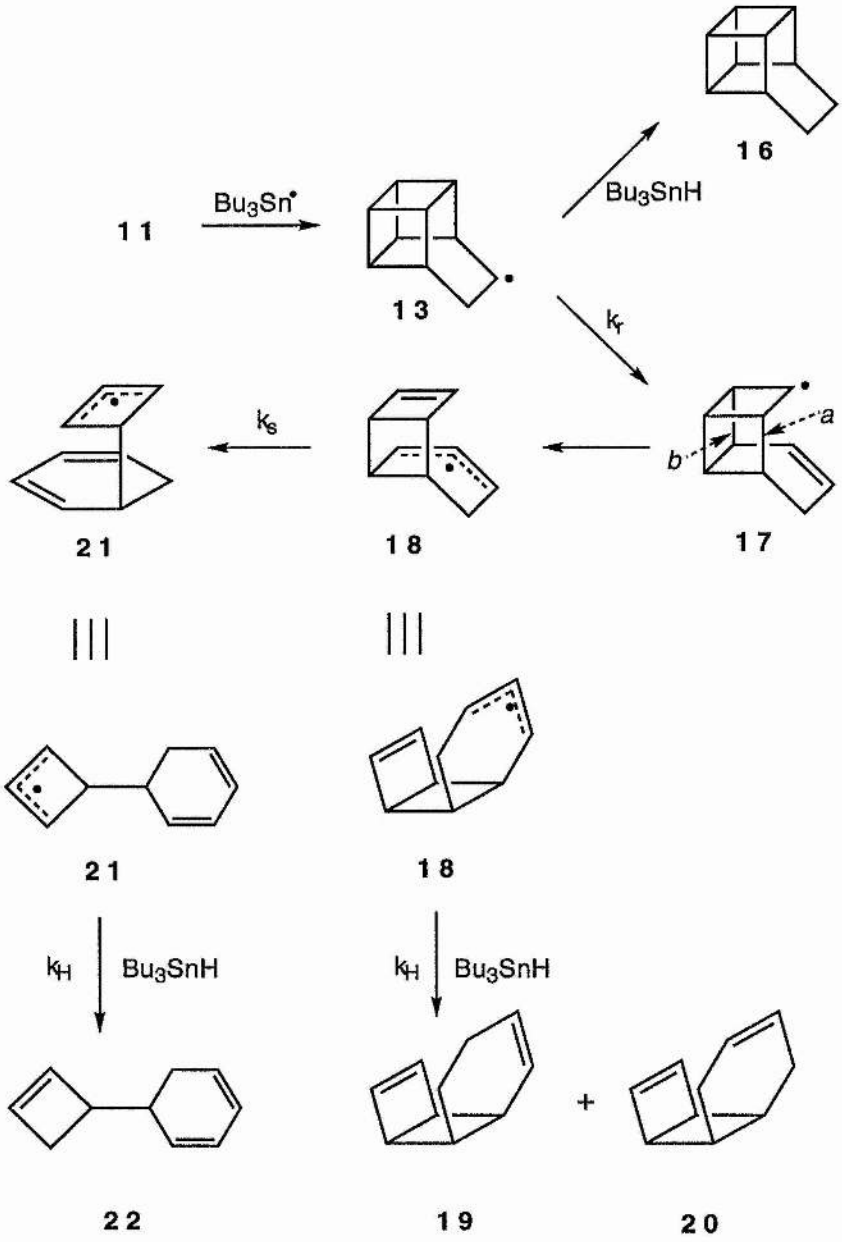


Figure 3.7

18 did not undergo another β-scission to form radical **21**. Instead, under the experimental conditions, hydrogen abstraction was preferred at either end of the allyl system of **18** to give the observed products **19** and **20**. If hydrogen abstraction were solely dependent on statistical theory, **19** and **20** should have been observed in a 1:1 ratio. However, the experimentally obtained ratio of **19**:**20** was 4:1 at 485K. It is therefore likely that the hydrogen abstraction of **18** from Bu_3SnH is controlled by

subtle steric effects.

In the analogous case of the cubylcarbinyl radical, three β-scissions were shown to rapidly occur to give the completely rearranged radical, **26** (Figure 3.8). The basketyl radical did not undergo an analogous third β-scission to give **21** in the presence of tributyltin hydride at high temperatures.

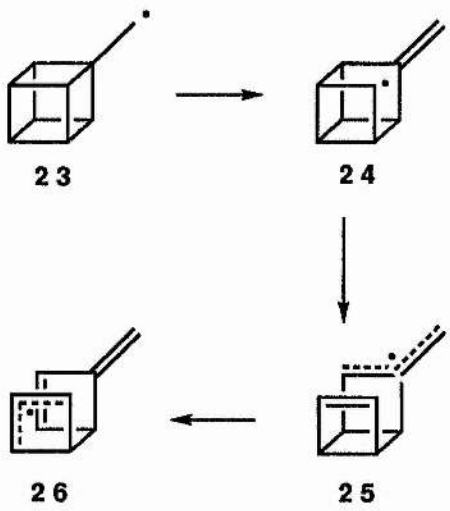


Figure 3.8

Two factors are involved, stopping any further rearrangement of **18**. First, **18** contains less strain than its analogous radical in the cubylcarbinyl rearrangement, **25** (two four-membered rings and one six-membered ring compared to three four-membered rings). Second, β-scission of **18** is in competition with hydrogen abstraction from Bu_3SnH. At the very high temperatures of the basketyl rearrangement experiments (485K), hydrogen abstraction will be much faster than in the case of the cubylcarbinyl experiments (351K),[34] and hence β-scission of **18** will compete less effectively. To test this hypothesis and to confirm the product structures, the reduction of 9-bromobasketane was examined with Bu_3SnD (see Section 3.5).

The reduction of 9-bromohomocubane (**6**) with Bu_3SnH was examined at several temperatures. Amazingly, even at the highest practicable temperature obtainable with the experimental equipment (491K), the reaction produced only a

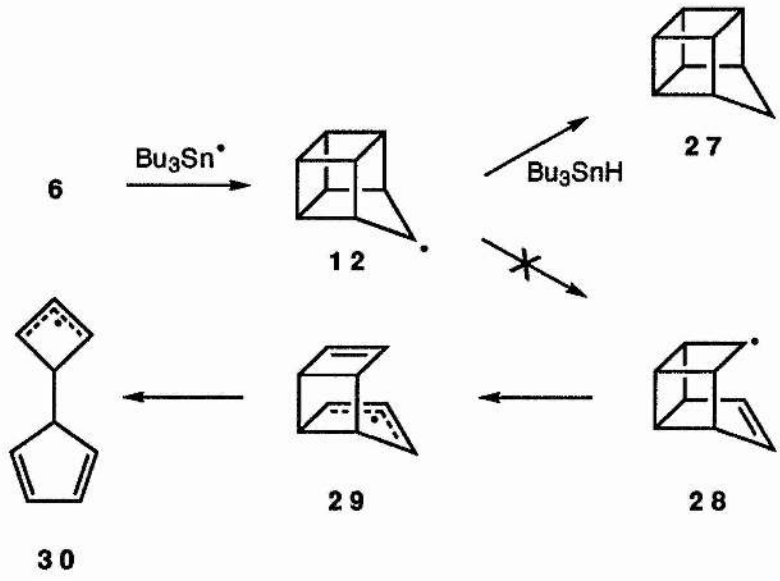


Figure 3.9

single product the hydrocarbon homocubane (**27**). Consequently, the parent radical **12** failed to rearrange under any of the reaction conditions (Figure 3.9). Only estimations were therefore possible for the Arrhenius parameters of rearrangement (Section 3.4.2).

3.3 Control Experiments to Verify Product Formation via Free Radical Reactions

Tin hydride reductions are normally carried out at much lower temperatures, and therefore two control experiments were performed to check the stability of the reactants and products. At temperatures greater than 423K, the reductions of the 9-bromobasketane will have been completed within a few minutes. Therefore a sample of 9-bromobasketane was irradiated at 463K, under a 400W UV light, for 10 minutes. No Bu_3SnH was added. The bromide darkened considerably, but GC/MS and NMR analysis of the product mixture showed none of the reduction products, basketane, bicyclo[4.4.0.$0^{2,5}$]deca-3,8-diene or bicyclo[4.4.0.$0^{2,5}$]deca-3,7-diene had formed.

GC/MS showed that 9-bromobasketane was still the main component.

Second, a sample of basketane was formed in a reduction of the bromide with Bu_3SnH at 358K. This basketane was then reacted with fresh Bu_3SnH and showed no decomposition after a further 2 hours of irradiation at 473K.

3.4.1 Kinetics of the Rearrangement Reaction of 9-Bromobasketane

The products of the reaction between 9-bromobasketane and tributyltin hydride were shown (Section 3.2) to be the unrearranged product basketane (**16**), and the two rearranged products tricyclo[4.4.0.$0^{2,5}$]deca-3,8-diene and tricyclo[4.4.0.$0^{2,5}$]deca-3,7-diene (**19+20**). From the ratio of the two products in the gas chromatogram, the kinetics for the rearrangement can be studied and a value for the activation energy for rearrangement of the basketyl radical can be obtained.

Table 3.1. Ratio of **16** and (**19+20**) at the various experimental temperatures

T (K)	10^3 / T (K^{-1})	**16**[a] (%)	**19+20**[b] (%)	**19+20 / 16**	[Bu_3SnH] (M)
413	2.421	87.1	12.9	0.148	2.94
428	2.336	88.6	11.4	0.129	2.94
453	2.208	79.1	21.0	0.265	2.94
477	2.096	62.1	37.9	0.610	2.99[c]
493	2.028	56.9	43.1	0.757	2.94

[a] **16** as a percentage of the total product. [b] **19+20** as a percentage of the total product. [c] Only 40µl used.

The volume of Bu_3SnH was known, as was the volume of 9-bromobasketane, hence the concentration of the Bu_3SnH in the above table could be calculated to be 2.94M. At 477K the volumes used are different (40µl of Bu_3SnH and 15µl of 9-bromobasketane) and hence the concentration of the Bu_3SnH was calculated to be 2.99M.

The ratio of k_r / k_H can be expressed as a simple equation involving the concentrations of the unrearranged and rearranged products:

$$k_r / k_H = [Bu_3SnH][\mathbf{19+20}] / [\mathbf{16}] \qquad \text{(Equation 1)}$$

Table 3.2. Kinetics of the Reduction of 9-Bromobasketane with Bu_3SnH[a] derived from the equation above.

T (K)	k_r / k_H (M^{-1})	k_H ($M^{-1}s^{-1}$)	$10^7 k_r$[b] (s^{-1})	log [k_r (s^{-1})]
413	0.435	1.31×10^7	0.570	6.75
428	0.380	1.52×10^7	0.578	6.76
453	0.790	1.94×10^7	1.530	7.19
477	1.820	2.38×10^7	4.330	7.64
493	2.230	2.71×10^7	6.030	7.78

[a] [Bu_3SnH] = 2.98M, [9-Bromobasketane] = 1.96M, except at 477K, when it was 1.87M. [b] Derived by use of log k_H = 9.07 - 3.69 / θ (ref. 51).

The rate constant for hydrogen abstraction from Bu_3SnH, k_H, does not depend strongly on the structure of the carbon-centred radical and use of the Arrhenius parameters determined by C. Chatgilialoglu *et al.*[51] is usually quite accurate (see Table 3.2).

Further refinement of the values of k_r may be undertaken (assuming that all the bromide had reacted), by correcting the figures using an integrated equation,[35] which corrects for the consumption of tin hydride during the reaction. The values of k_r obtained in Table 3.3, by using the integrated equation, are consistently smaller in comparison with the values obtained by using equation 1 (Table 3.2). A result that should be expected in view of the fact that equation 1 assumes the concentration of Bu_3SnH to be constant and therefore expects the ratio of k_r/k_H to be consistently higher throughout the course of the reaction.

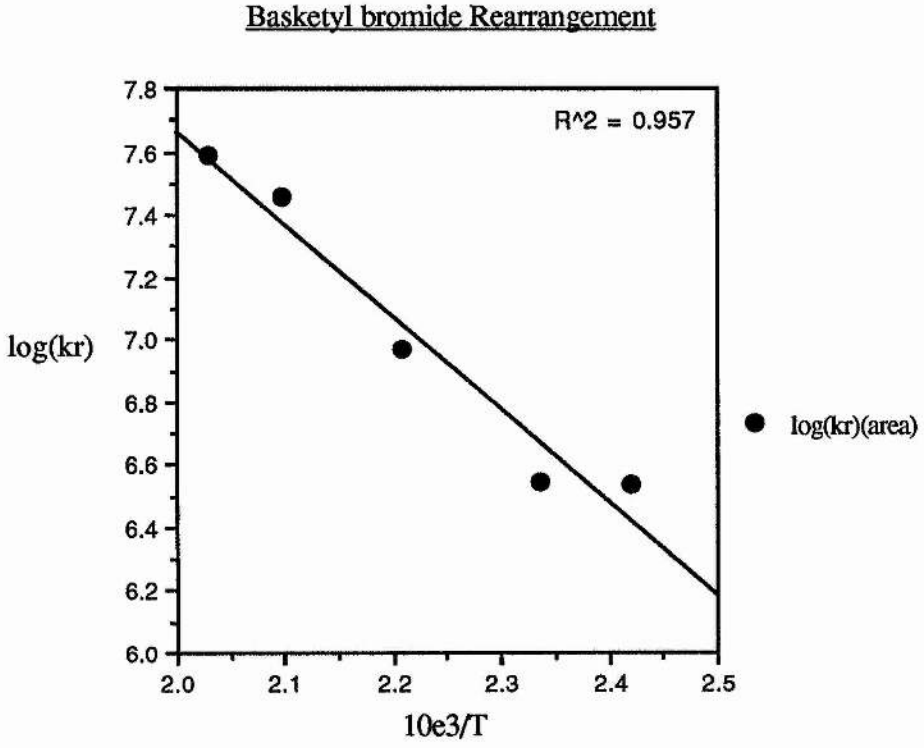
A graph may be constructed of log k_r against $10^3/T$, the gradient of which

gives the Arrhenius activation energy E_a, and the intercept, the pre-exponential A-factor, i.e.

Table 3.3. Kinetics of the Reduction of 9-Bromobasketane with Bu_3SnH[a] using an Iterative Procedure

10^3 / T (K^{-1})	**16** (M)	**19+20** (M)	k_r/k_H[b] (M^{-1})	10^7 k_r[c] (s^{-1})	log [k_r (s^{-1})]
2.421	1.71	0.252	0.267	0.347	6.540
2.336	1.74	0.223	0.231	0.351	6.545
2.208	1.55	0.412	0.484	0.939	6.973
2.096	1.16	0.709	1.195	2.840	7.454
2.028	1.11	0.845	1.421	3.850	7.586

[a] [Bu_3SnH] = 2.98M, [9-Bromobasketane] = 1.96M, except at 477K, when it was 1.87M. [b] Obtained by an iterative procedure. [c] Derived by use of log k_H = 9.07 - 3.69 /θ (ref. 51).



$$\log [k_r / s^{-1}] = (13.57 \pm 0.80) - (2.95 \pm 0.36) / \theta$$

3.4.2 Kinetics of the Reduction of 9-Bromohomocubane with Bu_3SnH

As was the case for the reduction of 9-bromobasketane, 9-bromohomocubane was reduced at various temperatures to observe whether at high temperatures the strained structure would rearrange. As indicated in section 3.2 no rearrangement was detected even at the highest practicable temperature (218°C), the reaction yielding a single product, homocubane. Consequently, the intermediate radical **12** failed to rearrange even at this elevated temperature and so an exact value for the rate of rearrangement at the top temperature is not possible. However a lower limit for the activation energy can be calculated by using the peak height of the homocubane formed compared to the baseline offset, which represents the maximum amount of rearranged product, obtained by GC analysis of the product mixture. Therefore [homocubane] / [rearranged] $\geq$ 32 / 1. Using the equation;

$$k_r / k_H = [n\text{-}Bu_3SnH][\text{rearranged}] / [\text{unrearranged}]$$

It follows that $k_r(491K) < 1 \times 10^8\ s^{-1}$ (knowing that $[Bu_3SnH] = 2.83M$ and $k_H(491K) = 2.66 \times 10^7\ M^{-1}s^{-1}$ (ref. 51)). For most unimolecular rearrangements of this type the Arrhenius pre-exponential factor is close to $10^{13}\ s^{-1}$ and if we assume this holds true then $E_a \geq 62.4\ kJ\ mol^{-1}$ and $k_r(298K) \leq 1.1 \times 10^2\ s^{-1}$ (see Table 3.5).

3.5 Tin Deuteride Reduction of 9-Bromobasketane

In Section 3.2 it was shown that the reaction between Bu_3SnH with 9-bromobasketane yielded basketane (**16**), tricyclo[4.4.0.0^{2,5}]deca-3,7-diene (**19**) and tricyclo[4.4.0.0^{2,5}]deca-3,8-diene (**20**) as the three products with none of the totally rearranged product **22** being observed. The hypothesis cited was that at 485K further rearrangement was competing less effectively than the rapid hydrogen abstraction from Bu_3SnH. Therefore the reaction of 9-bromobasketane with tributyltin deuteride

(Bu_3SnD) was carried out as the deuterium abstraction step is known to be slower in accord with the kinetic isotope effect (k_D/k_H). At 212°C the reduction products were 9-deuterobasketane (49.4%) (**16-D**), 9-deuterotricyclo[4.4.0.$0^{2,5}$]deca-3,7-diene (**19-D**) (46.8%) and a minor amount (3.9%) of 1-(4-deuterocyclobut-2-enyl)-cyclohexa-

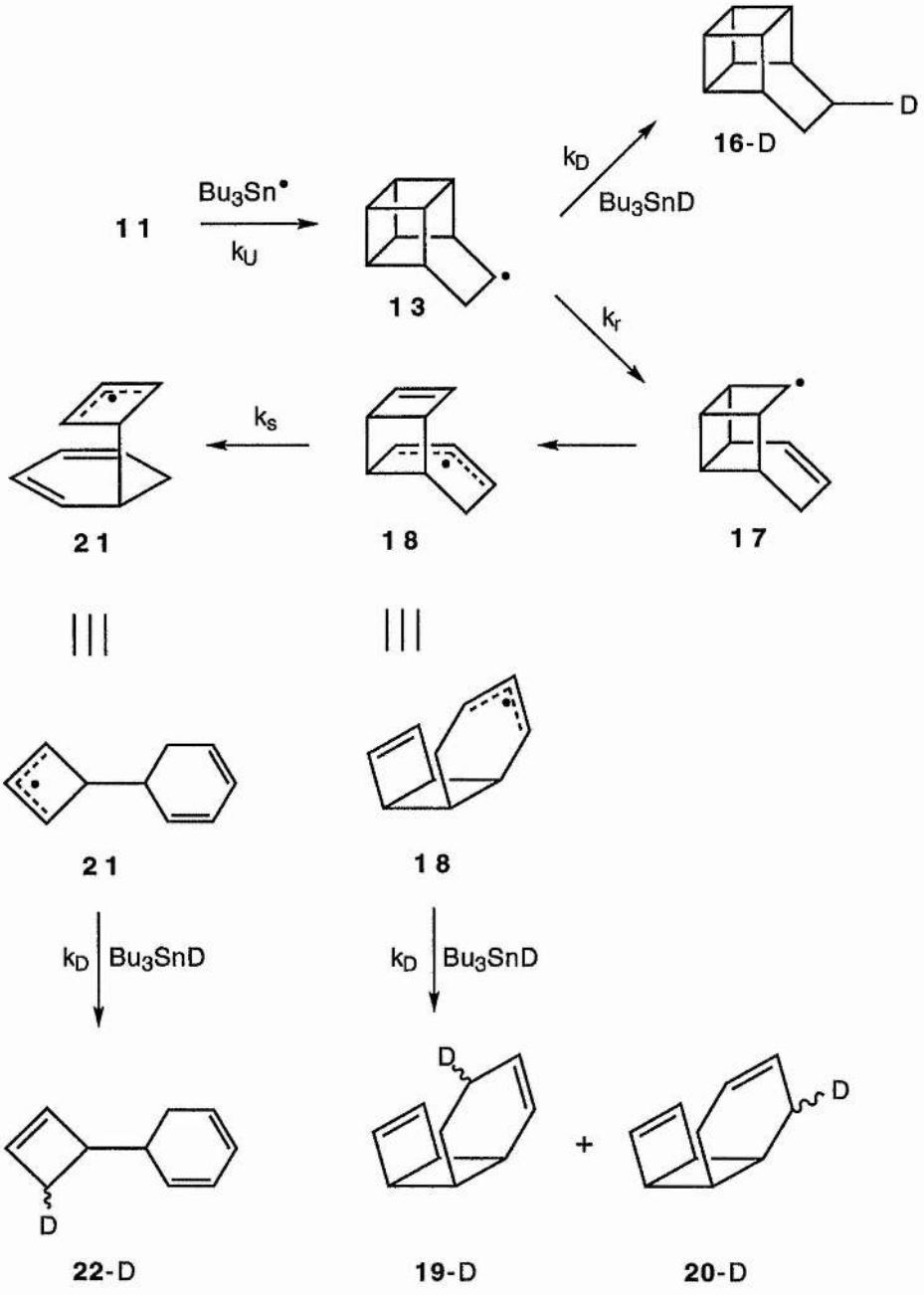


Figure 3.10

2,4-diene (**22-D**) as the three products (Figure 3.10), the last of these being the totally rearranged product. The isomer **20**-D was formed in only trace amounts (<1%).

Thus, the reaction with Bu_3SnD was successful in showing the cascade of three β-scissions and showed that the rearrangement pathway of 9-bromobasketane was entirely analogous to that of the cubylcarbinyl radical, even though the rate was, in comparison, extremely slow.

3.6 Kinetics of the Reduction of 9-Bromobasketane Promoted by Bu_3SnD

The following chemical equations, show the pathways of the reaction and may be used to derive equations that will allow values of k_r and k_S to be obtained. Also by using data obtained from the kinetics of the tin hydride reduction in section 3.4.1 a value for the deuterium isotope effect may be calculated.

$$Bu_3Sn\bullet + \mathbf{11} \xrightarrow{k_U} \mathbf{13} + Bu_3SnBr$$

$$\mathbf{13} + Bu_3SnD \xrightarrow{k_D} \mathbf{16}\text{-D} + Bu_3Sn\bullet$$

$$\mathbf{13} \xrightarrow{k_r} \mathbf{18}$$

$$\mathbf{18} + Bu_3SnD \xrightarrow{k_D} \mathbf{19}\text{-D} + \mathbf{20}\text{-D} + Bu_3Sn\bullet$$

$$\mathbf{18} \xrightarrow{k_S} \mathbf{21}$$

$$\mathbf{21} + Bu_3SnD \xrightarrow{k_D} \mathbf{22}\text{-D} + Bu_3Sn\bullet$$

$$d[\mathbf{16}\text{-D}] / dt = k_D [\mathbf{13}][Bu_3SnD] \quad (1)$$

$$d[\mathbf{19}\text{-D} + \mathbf{20}\text{-D}] / dt = k_D [\mathbf{18}][Bu_3SnD] \quad (2)$$

$$d[\mathbf{22}\text{-D}] / dt = k_D [\mathbf{21}][Bu_3SnD] \quad (3)$$

From the steady state approximation it follows that

$$d[\mathbf{13}] / dt = k_U [Bu_3Sn\bullet][\mathbf{11}] - k_D [\mathbf{13}][Bu_3SnD] - k_r [\mathbf{13}] = 0 \quad (4)$$

$$d[\mathbf{18}] / dt = k_r [\mathbf{13}] - k_D[\mathbf{18}][Bu_3SnD] - k_S[\mathbf{18}] = 0 \quad (5)$$

$$d[\mathbf{21}] / dt = k_S[\mathbf{18}] - k_D[\mathbf{21}][Bu_3SnD] = 0 \quad (6)$$

From (3) and (6) $$d[\mathbf{22}\text{-D}] / dt = k_S [\mathbf{18}] \quad (7)$$

Therefore from (2) and (7) $$d[\mathbf{22}\text{-D}] / d[\mathbf{19}\text{-D} + \mathbf{20}\text{-D}] = k_S / (k_D [Bu_3SnD]) \quad (8)$$

From (5) $$[\mathbf{18}] = k_r [\mathbf{13}] / (k_D [Bu_3SnD] + k_S) \quad (9)$$

Therefore from (1), (2) and (9)

$$d[\mathbf{16}\text{-D}] / d[\mathbf{19}\text{-D} + \mathbf{20}\text{-D}] = (k_D[Bu_3SnD] + k_S) / k_r \quad (10)$$

The equations (8) and (10), derived above, can be used to obtain the rate constants of both the first and the second rearrangements of the reaction of Bu_3SnD with 9-bromobasketane (**11**) along with the rate of reaction. The initial concentrations of Bu_3SnD and **11** were 2.94 M and 1.96M respectively and the reaction was carried out at 485K.

Table 3.4 The ratio of the products obtained from the ^2H NMR.

	16-D / **19**-D + **20**-D	**22**-D / **19**-D + **20**-D
From Peak Heights	1.06	0.083
From Intensities	1.03	-*

* data not obtained by NMR

The rate of deuterium abstraction from Bu_3SnD by carbon-centred radicals, as is the case with Bu_3SnH, is not sensitive to the radical structure, and therefore k_D values were calculated from the equation derived by Chatgilialoglu *et al.*:[51]

$$\log k_D = 8.63 - 3480 / 2.3RT$$

Hence k_D (485K) = 1.15×10^7 M^{-1} s^{-1}. Neglecting corrections to equation (8) due to integration and substituting the experimental **22**-D / (**19**-D + **20**-D) ratio and the above literature value of k_D at 485K, gives $k_s(485K) = 2.8 \times 10^6$ s^{-1}. The Arrhenius pre-exponential factors of rearrangements of this general type are normally *ca.* 10^{13} s^{-1}. Assuming this to hold for the rearrangement of **18** leads to an estimate of 60.8 kJ mol^{-1} for the activation energy and hence $k_s(298K) = 2.2 \times 10^2$ s^{-1}. Thus, rearrangement of **18** is slower than the rearrangement of the archetypal cyclobutylcarbinyl radical (Table 3.5). This is probably because **18** is thermodynamically stabilised by the resonance delocalisation of the unpaired electron.

Substitution of the k_s value from equation (8) together with the literature value of k_D into (10) gives a figure of k_r (485K) = 3.45×10^7 s^{-1}. This figure is in excellent agreement with the data derived in 3.4.1 where k_r (485K) = 3.02×10^7 s^{-1} and gives confidence in the internal consistency of the kinetic results.

Equation (10) can be applied to derive the kinetic isotope effect on hydrogen abstraction from Bu_3SnD by carbon-centred radicals. Thus, insertion of the derived k_s and k_r values leads to k_H / k_D (485K) = 2.5, which, in view of the temperature difference, is in very satisfactory agreement with previously reported values of 2.7 and 2.8 at 298K for cyclohexyl and *tert*-butyl radicals, respectively.[52]

3.7 Why Are These Radicals so Resistant to Rearrangement ?

The data in table 3.5 show that the 9-basketyl radical rearranges nearly seven orders of magnitude more slowly than the cubylcarbinyl radical at 498K and that for the homocubyl radical the difference is even greater. Most of the reduction in rate is due to the much greater Arrhenius activation energies for **13** and probably for **12**. On studying the structure of both **12** and **13** and comparing them to the cubylcarbinyl radical this result would seem, initially, to be unexpected on two basic accounts. The structures of both radicals **12** and **13**, are similar in regard to the position of the radical centre with respect to the β-bond. Second, the bonds of both **12** and **13** are in a

Table 3.5. Kinetic Data for the Rearrangements of 9-Basketyl (**13**), 9-Homocubyl (**12**) and Related Radicals.

radical	k_r(298K) (s^{-1})	$\log[A_r/s^{-1}]$	E_r (kJ mol^{-1})	ref
cyclobutylcarbinyl	4.7×10^3	12.6	51.2	53
cubylcarbinyl (**23**)	2.9×10^{10}	13.2	15.5	37
9-basketyl (**13**)	4.5×10^3	13.6	56.6	c
9-homocubyl (**12**)	$<1.0 \times 10^2$ [b]	[13.0][a]	>62.4[b]	c
tricyclo[4.4.0.$0^{2,5}$]deca-3,7-dienyl (**18**)	2.2×10^2	[13.0][a]	60.8[b]	c

[a] Assumed value. [b] Estimated values; see text. [c] This work.

highly strained sp^3 configuration and therefore breaking of these bonds would lead to a species of lower energy, releasing most of the original cage strain. In the case of **13**, the first step of the rearrangement gives **17** and subsequently (with enough energy) to **21** (Figure 3.7). Similarly, β-scission of **12** would initially produce **28**, and ultimately **30** (Figure 3.9), i.e., a plausible, downhill pathway exists which is analogous to the rearrangement of the cubylcarbinyl radical. Clearly, there are other more subtle reasons for the apparent resistance of both **12** and **13** to rearrange.

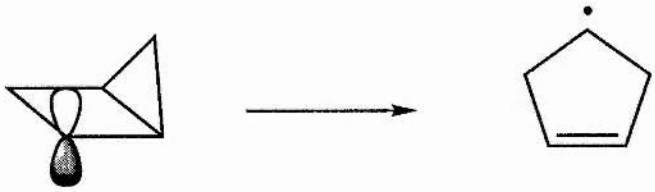
Kinetically, **12** and **13** are similar to the cubyl radical (**31**) which rearranges extremely slowly, if at all. In the case of **31** this can be easily understood because the first β-scission would produce the highly strained bridgehead alkenyl radical **32**, a radical of extremely high energy. As was mentioned in the previous paragraph this is not the case for both **12** and **13**. The slow rearrangement of **12** and **13** in comparison with the cubylcarbinyl radical could partly be accounted for by the fact that there will be less cage strain relief on undergoing β-scission. For example, strain relief for **13** to **21** is *ca.* 327 kJ mol^{-1} and for **12** to **30** is *ca.* 344 kJ mol^{-1} in comparison with 444 kJ mol^{-1} for cubylcarbinyl (**23**) to fully rearrange to **26**. However, the overall relief of strain is so large for both **12** and **13** that it does not seem justifiable to accept that this

is the reason for such extreme reductions in the rates of rearrangement. This caveat is supported by the fact that there is only *ca.* 109 kJ mol^{-1} of ring strain relief in the β-scission of the cyclobutylcarbinyl radical, and yet it rearranges more rapidly[41] than either **12** or **13** (Table 3.5).

Other factors which affect the rates of β-scission need, therefore, to be investigated to explain this resistance of both the 9-homocubyl (**12**) and the 9-basketyl (**13**) radicals to rearrange. One such significant factor is the degree of overlap between the SOMO and the σ*-orbital of the bond undergoing scission.[54] Optimum overlap and therefore ease of β-scission is achieved when the dihedral angle between the SOMO and the C_β -C_γ bond is 0°. This alignment can be readily achieved, in the case of the cubylcarbinyl radical, because of the unrestricted rotation of the SOMO. 3-dimensional models of both the ground states of **12** and **13** indicate that the SOMO is constrained by the cage structures at approximately 40° and 30°, respectively, thus precluding optimum overlap. The extent of overlap of the SOMO with the C_β -C_γ bond increases in the order **12** to **13** to **23**, which correlates with the rate constants for β-scission. However, optimum overlap is not mandatory for β-scission to occur. For example, the spiro[2.3]hex-2-yl (**33**) radical and homologous radicals rearrange rapidly even though the SOMO and the C_β-C_γ bond are staggered (Figure 3.11).[55] In the case of the bicyclo[2.1.0]pent-2-yl (**34**) radical the angle in question is 90°, i.e., the bond is in the nodal plane of the SOMO.[53,56] The nonallignment of both **12** and **13** is therefore inadequate to account for their slow, even non-existent, β-scissions.

To see a possible explanation to the comparative ease of **13** to rearrange more readily than **12**, attention should be drawn to the unique structure of the product of the first β-scission of **12**, i.e., radical **28**. The frontier orbital arrangement is shown in **28a** (Figure 3.12). In this structure the SOMO is held by the symmetrical cage structure directly above the centre of the π-orbital of the newly formed double bond. The rigid structure ensures that the distance separating the SOMO and either of the carbon atoms of this double bond will not be much greater than a "normal" C-C bond length. Thus all three p-orbitals will still significantly overlap in a triangular array in

33

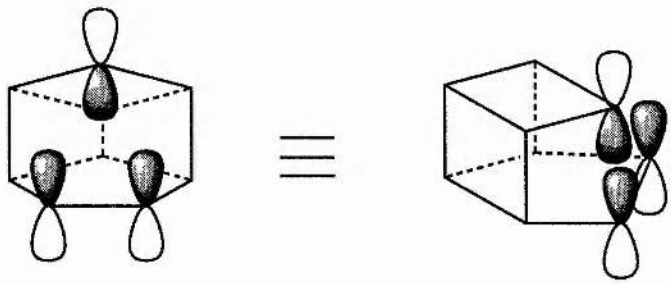


34

Figure 3.11

The Rearrangements of Spiro[2.3]hex-2-yl (**33**) and Bicyclo[2.1.0]pent-2-yl (**34**) Radicals.

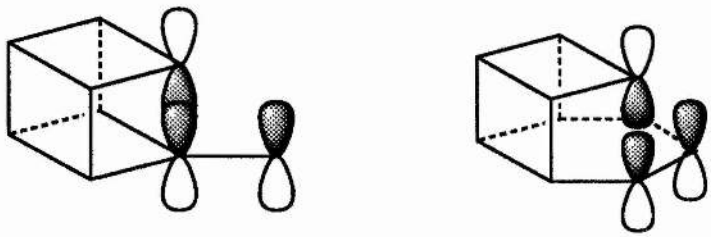
the ground state of **28**. Simple frontier orbital treatments of this situation indicate that this type of interaction produces one bonding and two degenerate antibonding MOs, so that one of the three electrons must occupy a high energy antibonding orbital.[57] This will greatly increase the energy of radical **28** and may explain why the activation energy



28a 28a

Figure 3.12

The Frontier Orbital Arrangement of **28**.



24a **17a**

Figure 3.13

The Frontier Orbital Arrangement of **24** and **17**.

for β-scission of **12** is so high.[58] In the radical **24**, formed by the first β-scission of the cubylcarbinyl radical (**23**), the SOMO is also held close to the newly formed π-bond, but in this case overlap is at one end of the double bond, **24a**. The frontier MOs in this situation consist of one bonding, one non-bonding and one antibonding orbital. The three electrons can occupy the bonding and non-bonding MOs so that the energy of **24** is comparatively low. Radical **17** formed in the first β-scission of **13** will be an unsymmetrical homologue, i.e., **17a**, where the distance of the SOMO from the double bond is greater and its placement is not so central as in **28a**. Thus, the energy of **17** will not be so high and this may explain why the rearrangement of **13** though sluggish is faster than that of **12**.

3.8 Theoretical Study of Strained Cyclobutylcarbinyl Radical Ring-Opening

An examination of the potential energy surfaces for the rearrangement of the intermediate radicals **12** and **13** was undertaken in this department[48] in an attempt to establish a fuller understanding of the effects operating in these strained systems and to provide an explanation for their reluctance to ring-open. It was felt that MINDO/3 would yield the most reliable data for the ring-openings **12**→**28** and **13**→**17** because experience[59] has been that this method consistently outperformed both AM1 and

MNDO when applied to highly strained systems of this kind.

Calculated activation energies for ring-opening, together with the heats of reaction for ring-opening of radicals **12** and **13** and, for comparison, the corresponding data on the reaction profiles for ring-opening of the related strained radicals, cubylcarbinyl, cubyl, 6-norcubylcarbinyl, 1-bicyclo[1.1.1]pentylcarbinyl, and 1-bicyclo[2.1.1]hexylcarbinyl radicals (**23, 31** and **35-37**) are displayed in Table 3.6. Also included is the data for the parent species, the cyclobutylcarbinyl radical (**38**), together with that of its derivative the 3-methylenecyclobutylcarbinyl radical (**39**). Inspection of the calculated enthalpies of reaction in Table 3.6 reveals that, apart from

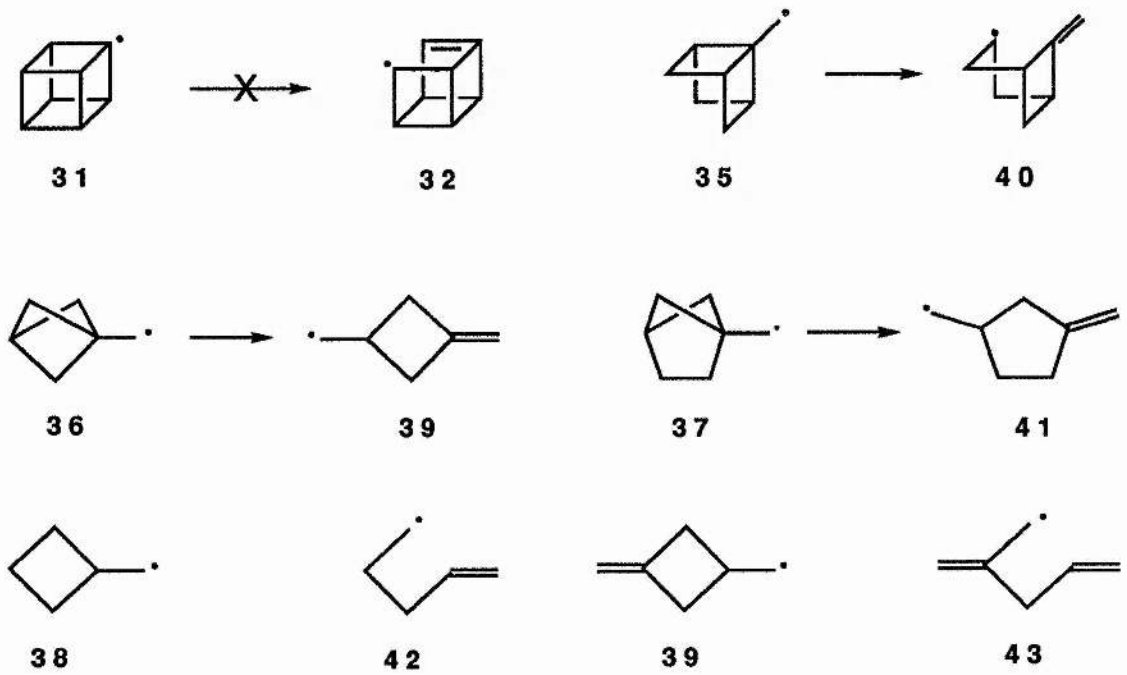


Figure 3.14

Ring-Opening Reactions of Some Cyclobutylcarbinyl Radicals.

the cubyl radical (**31**) the rearrangement of which is highly endothermic and has a very high activation barrier, the remaining strained systems undergo ring-opening accompanied by considerable relief of strain. For the strained substrates, **12, 13, 23, 31** and **35-37** the calculated and experimental values of E_T are in very good agreement

with each other. Thus, the experimental observation that the cubyl radical (**31**) does not ring-open readily is supported by the theoretical predictions. It is noteworthy that the 9-homocubyl and 9-basketyl radicals (**12, 13**) are predicted to rearrange with considerably lower exothermicities than the remaining strained radicals, which is

Table 3.6. Experimental and Calculated Energy Barriers to Ring-Opening of some Cyclobutylcarbinyl Radicals

	ΔH (calcd)[a]	E_r (kJ mol^{-1})	
radical rearrangement	(kJ mol^{-1})	exptl	calcd[b]
cubyl (**31**) → **32**	+42.0	na[c]	118.2
cubylcarbinyl (**23**) → **24**	-72.9	15.5[d]	25.6
9-homocubyl (**12**) → **28**	-43.2	>62.4[e]	67.5
9-basketyl (**13**) → **17**	-52.0	56.6[e]	70.0
6-norcubylcarbinyl (**35**) → **40**	-96.4	< 18.9[f]	24.7
1-bicyclo[1.1.1]pentylcarbinyl (**36**) → **39**	-163.4	29.8[g]	38.1[h]
1-bicyclo[2.1.1]hexylcarbinyl (**37**) → **41**	-182.3	39.0[g]	49.4
cyclobutylcarbinyl (**38**) → **42**	+21.8	51.1[i]	98.0
3-methylenecyclobutylcarbinyl (**39**) → **43**	+5.0	48.2[i]	100.0

[a] MINDO/3-estimated enthalpy of reaction. [b] MINDO/3-estimated. [c] Not available; rate too slow to be determined. [d] Ref. 37. [e] This work. [f] Upper limit (unpublished data, Della and Walton). [g] Ref. 60. [h] *Ab initio* estimates (ref. 60) are 32.7 (3-21G) and 46.9 (6-31*G). [i] Ref. 53.

consistent with the observed sluggish nature of **12** and **13** towards ring-opening.

An examination of the calculated structures of **17** and **28** was undertaken with the aim of determining whether the explanation presented in Section 3.7 for the slow

rate of ring-opening of **12** compared to **13** as embodied in the forms **17a**, **24a**, and **28a** could be corroborated. Unfortunately, the data obtained was not sufficiently discriminating to allow a firm conclusion to be drawn. Since, therefore, the results do not support the expectation based on frontier orbital theory, an *ab initio* study is obviously desirable.

3.9 Bridgehead Homolytic Substitution Reactions

A concept whereby substitution reactions can take place by means of electrically neutral radicals was postulated by D.H. Hey[61] in 1934. These reactions, classified as homolytic substitution reactions, distinguish themselves from heterolytic reactions, where electrophilic and nucleophilic species are involved.[62]

Figure 3.15

The S_H2 Reaction.

Homolytic substitution involves the addition of a neutral radical to a multivalent centre M. The intermediate, or transition state, thus formed then eliminates an electrically neutral species (Figure 3.15).

Bimolecular homolytic substitution (S_H2) reactions are not common when M is a carbon atom[62] and are mainly confined to halogenations of compounds containing three membered rings.[63] Cyclopropane for instance undergoes halogenation by initially an S_H2 type reaction, with release of strain within the three-membered ring (Figure 3.16). Most cyclobutane derivatives are both chlorinated and brominated[64] by straightforward hydrogen abstraction to give unrearranged products,[65] although the ring strain of cyclobutane (110 kJ mol^{-1}) is only 5 kJ mol^{-1} less than that of cyclopropane.[66] A few exceptions to this have been discovered comprising of

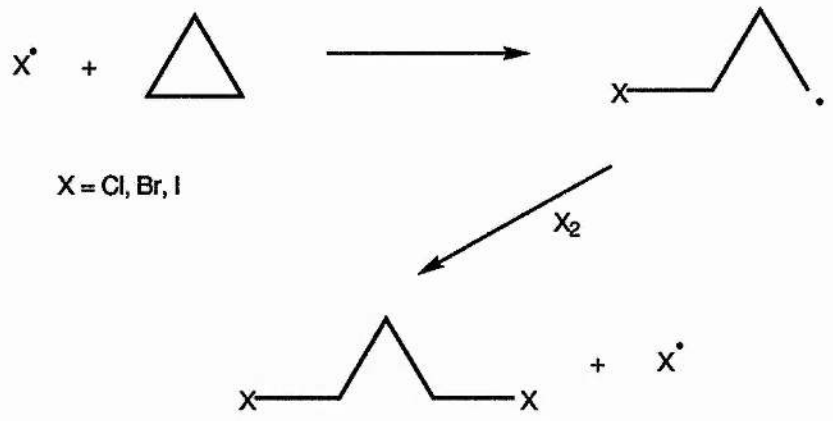


Figure 3.16

Homolytic Substitution Resulting in Addition to Cyclopropane.

bromine attack at bridgehead carbon atoms in bi- or polycyclic molecules containing four membered rings. In each case however the cyclobutane rings are fused. Bicyclo[2.2.0]hexane may be readily photobrominated to produce two major S_H2

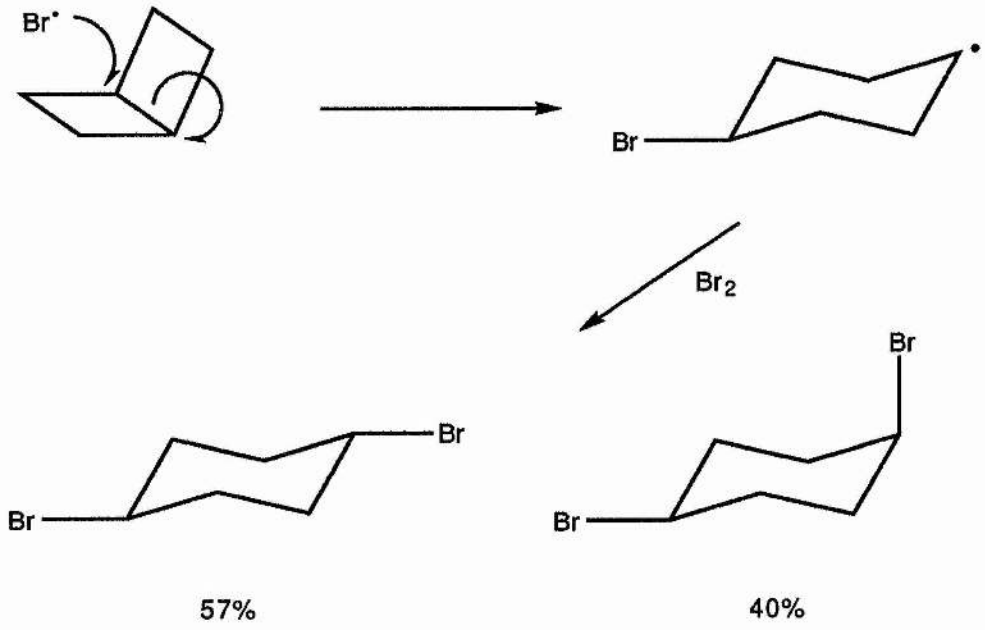


Figure 3.17

Photobromination of *cis*-Bicyclo[2.2.0]hexane Showing the Major Products.

products (*trans*-1,4-dibromocyclohexane and *cis*-1,4-dibromocyclohexane) (Figure 3.17).[67] Although there is a minor amount of electrophilic bromination and some mono-brominated products are also formed, they account for less than 3% of the total yield. Other S_H2 type reactions have been discovered. [n.2.2] Propellanes, where n = 2, 3 and 4 (ref. 68,69 and 69 respectively), undergo halogenation across the central carbon-carbon bonds. [1.1.1] Propellanes have been observed to undergo S_H2 reactions forming dimers and even oligomers.[70]

However, more importantly to this work, cubane has recently been examined[12(b)] to see if it also undergoes halogenation via an S_H2 reaction. Comparison of cubane to *cis*-bicyclo[2.2.0]hexane would seem to indicate similarities that would favour S_H2 type reaction. The bridgehead carbon atoms are at a juncture of three four-membered rings and cubane contains a high degree of ring strain (approximately 15 kJ mol^{-1} more per C-C bond than cyclobutane). The results obtained may be seen in Scheme 11.

The tetrabromo-*syn*-tricyclooctane is potentially able to undergo a further S_H2 reaction to form the hexabromo compound, but none of this was observed. This could well have been due to poor solubility of the tetrabromo compound and the crowded nature of the hexabromo compound making the step too slow to observe.

3.10 Bimolecular Homolytic Substitution of Basketane with Bromine

It was of interest to see if the meagre list of S_H2 reactions, within molecules containing cyclobutane rings, could be extended to include other cage systems. Sufficient basketane (but not homocubane) was obtained for a few trial experiments.

When bromine (1.1 equivalents), dissolved in degassed CCl_4, was added to basketane (**16**) in CCl_4 at 298K and photolysed, over 24 hours with a tungsten lamp, the bromine colour faded. A white solid was observed to crystallise out on addition of a small amount of light petroleum. Examination by NMR and GC/MS of the supernatant liquid, after filtration, showed that it contained unreacted **16** but no other

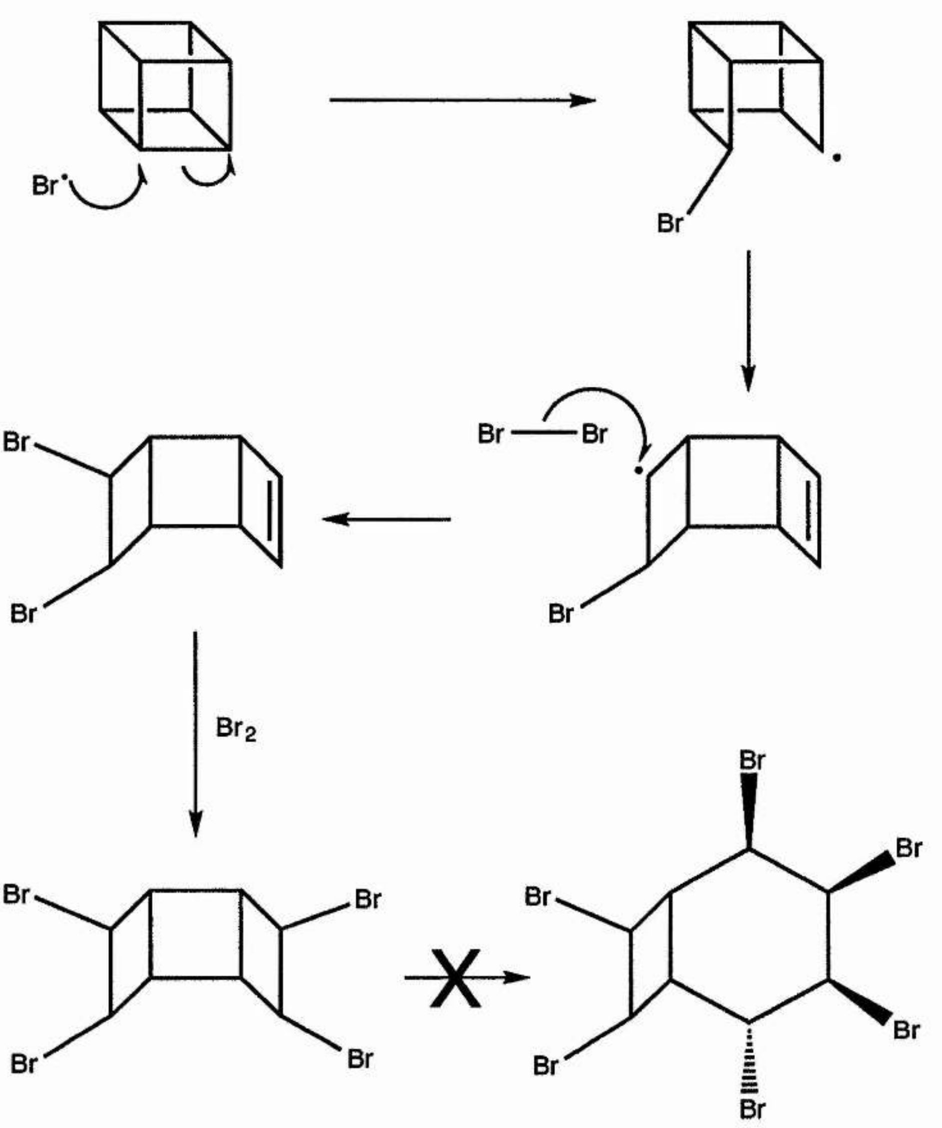


Figure 3.18

significant products. GC/MS analysis of the solid showed it to be a mixture of four long retention time (t_r) components all with formula $C_{10}H_{12}Br_x$ together with minor amounts of additional products. Comparison of the t_r values with, for example, the corresponding values for the tetrabromide formed in the photobromination of cubane[12(b)], strongly suggested that the four components were tetrabromides. The NMR spectra of the mixture showed that 9-bromobasketane (**11**) had not formed, and that alkene resonances were absent. These observations indicated that the main process was substitution and not hydrogen abstraction.

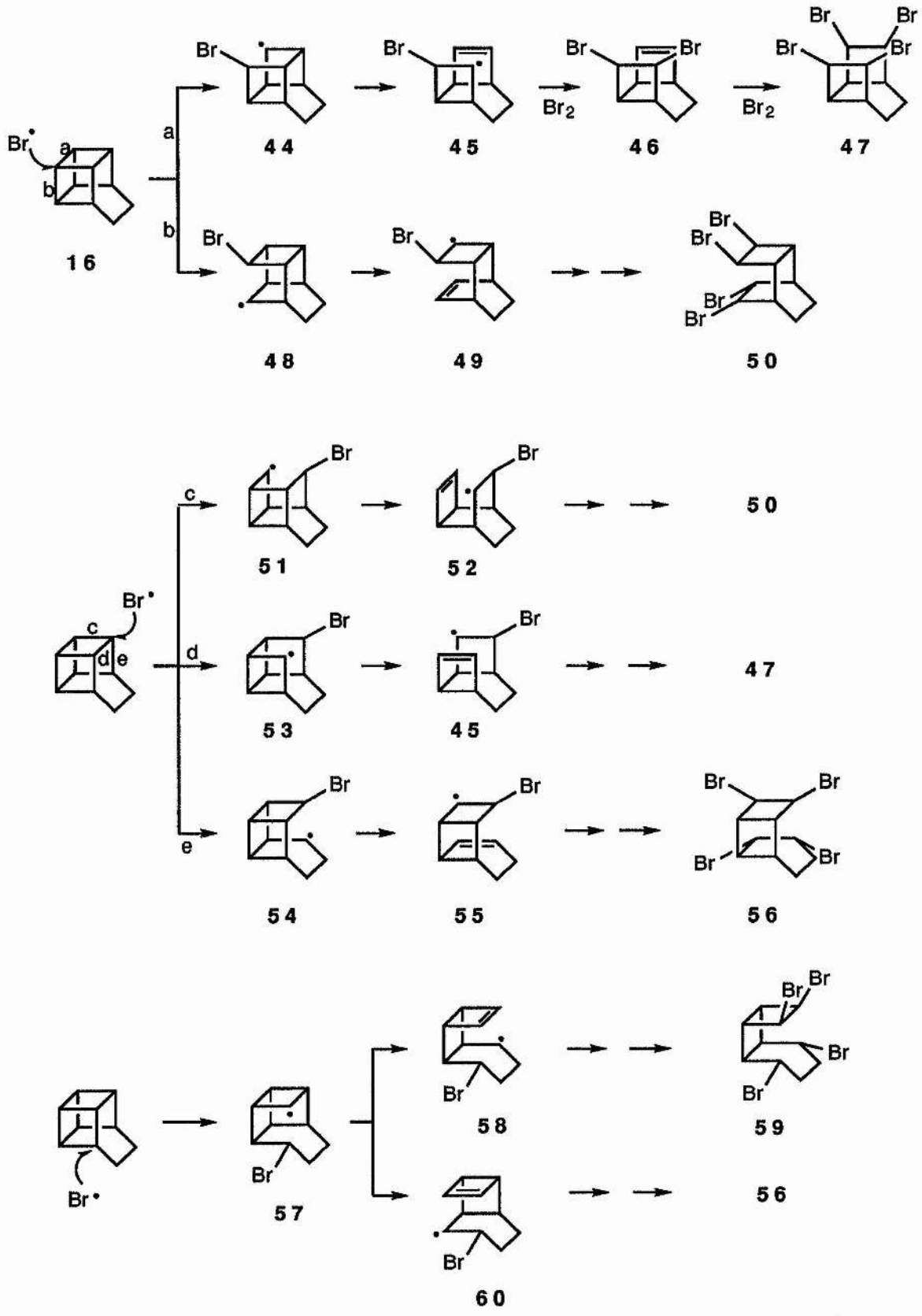


Figure 3.19

There are three bridgehead methine sites in **16** where bromine atom attack could occur (Figure 3.19). Attack at the methine furthest from the bismethylene bridge would be accompanied by scission of one or other of two non-equivalent C_β-C_γ bonds to give **44** or **48**. In radical **44** β-scission will give **45** which can abstract a bromine atom from molecular bromine to give **46**. Because the 'inside' of the cage structure of **45** is screened by the proximity of the *cis*-cyclobutene ring, **46** will be formed with its bromine atoms *cis* to each other. Similarly, the final addition of a second bromine molecule will also occur in the *cis* mode to give the tetrabromide **47** stereospecifically as a single isomer. This specificity is analogous to the formation of a single, all-*cis* tetrabromide from cubane.[12(b)] In radical **48** there are two C_β-C_γ bonds aligned parallel to the SOMO. However, formation of **49** will be accompanied by greatest relief of ring strain and hence this is the most likely β-scission.[71]

Figure 3.19 indicates that bromine atom substitution at the four equivalent methines can occur with β-scission of each of the three non-equivalent bonds to give eventually **47**, **50**, and **56**. Similarly, attack at the remaining bridgehead sites, adjacent to the bismethylene bridge, will lead to the formation of **56** and **59**. In every case the cage structures dictate that the bromine atoms enter with *cis* stereochemistry. Thus the mechanism predicts the formation of only four tetrabromides, in agreement with the experimental finding. The tetrabromide mixture was separated by preparative TLC into two bands. The slower eluting band was a single compound which had one CH_2 and four CH resonances in its ^{13}C NMR spectrum. This, and the ^1H NMR data, suggested compound **50**, but **47** could not be ruled out. The faster running band contained the three remaining components and the NMR data was consistent with this being a mixture of **47** (or **50**), **56** and **59**.

3.11 Conclusions

9-Homocubyl (**12**) and 9-basketyl (**13**) radicals are highly strained but they rearrange extremely slowly by β-scission reactions. Consequently, the EPR spectra of

both unrearranged radicals could be observed, and unrearranged products were obtained in homolytic reactions in solution at T < 423K. Above this temperature **13** rearranged by a cascade of three β-scissions which was analogous to the rearrangement of the cubylcarbinyl radical. The work done in this chapter has shown that radicals **12** and **13** retain their structural integrity under moderate conditions (in the case of **12** under extreme conditions) and so have the possibility of being used as useful intermediates in further reactions. From the photobromination of basketane it was established that S_H2 reactions occurred at each of the three bridgehead sites to give a mixture of four tetrabromides. These are further examples of S_H2 reactions involving four-membered rings.

3.12 Experimental Section

EPR Spectra. The bromohomocubane or bromobasketane (ca. 40mg) was dissolved in di-*tert*-butyl peroxide (ca. 30μl) and triethylsilane (ca. 20 μl). This solution was placed in a quartz EPR tube and degassed on a vacuum line by a series of freeze-pump-thaw cycles. The solvent, cyclopropane, was distilled in and the tube was sealed. Experiments were also carried out with hexamethylditin in place of triethylsilane, but no well-defined spectra were observed. In the hydrogen abstraction experiments samples were prepared in a similar way but without Et_3SiH or $Me_3SnSnMe_3$.

Reduction of 9-bromohomocubane using Bu_3SnH. A 5mm NMR tube containing 9-bromohomocubane (29.0mg, 0.15mmol) was submerged in an oil bath, at 70°C, for 10s. Bu_3SnH (54.1mg, 0.21mmol) was injected into the NMR tube which was then sealed and left in the oil bath, under a 400W UV light, for 1hr. The GC/MS obtained from the resultant mixture showed the reaction had yielded a single product. The mixture contained residual tin products which could not be satisfactorily separated by TLC. The following NMR spectrum was therefore of both homocubane and of the unwanted side products. The unwanted peaks have been ignored. ^1H NMR δ 3.27 (m, 2H), 3.22 (m, 4H), 3.11 (qn, J = 8.50 Hz, 2H), this spectrum was essentially identical to that reported,[34] except for the peak at 1.65 ppm (s, 2H), which was obscured by organotin residues; ^{13}C NMR δ 45.40 (CH_2), 44.21 (CH), 44.02 (CH), 41.71 (CH). EIMS *m/z* (relative intensity) 118 (M^+, 9), 117 (100), 115 (48), 103 (12), 91 (60), 77 (20), 65 (29), 52 (43), 39 (96), 27 (14). The spectroscopic data are fully consistent with the reported values.[72] The experiment was repeated at 220°C, with identical results.

Reduction of 9-bromobasketane (large scale). A 10mm NMR tube containing 9-bromobasketane (0.50g, 2.4mmol), was submerged in an oil bath, at 212°C, for 10s.

Immediately, Bu_3SnH (0.97g, 3.9mmol) was injected into the heated NMR tube. The tube was then sealed and left in the oil bath, at 212°C, under a 400W UV light, for 35mins. The product was decanted into a small scale distillation apparatus, leaving a grey metallic tin residue. Distillation on a vacuum line at ca. 0.01 Torr was carried out in two stages to give an overall yield of 181mg (57%). In the first stage two fractions were obtained. A sublimed, sugary white, crystalline solid (74.8mg, 23.6%), which was shown by NMR to be the unrearranged product, i.e. basketane m.p. 102-104°C (see small scale reduction for spectroscopic data), and a second fraction which was a colourless liquid (74.3mg, 23.4%). GC showed this liquid to be a mixture of basketane (**16**) and the two rearranged compounds tricyclo[4.4.0.$0^{2,5}$]dec-3,8-diene (**20**) and tricyclo[4.4.0.$0^{2,5}$]dec-3,7-diene (**19**). The assignment of the peaks in the following NMR spectra was made possible with the aid of data obtained from a 2D COSY spectrum. The minor product **20** (20 rel %): ^{1}H NMR δ 5.96 (dd, J = 3.25, 4.84 Hz, $H^{8,9}$), 5.86 (s, $H^{3,4}$), 2.65 (m, $H^{2,5}$) [this peak was only resolved from basketane resonances on a 500-MHz spectrum], 2.50 (m, $H^{1,6}$), 2.06 (t, J = 4.57 Hz, $H^{7',10'}$), 1.37 (m, $H^{7,10}$); ^{13}C NMR δ 138.28 ($C^{3,4}$), 129.97 ($C^{8,9}$), 46.20 ($C^{2,5}$), 34.36 ($C^{1,6}$), 23.99 ($C^{7,10}$); EIMS *m/z* (relative intensity) 131 (10), 117 (81), 103 (11), 91 (100), 79 (32), 78 (100), 77 (71), 65 (30), 54 (56), 51 (47), 39 (84), 27 (51). The major product **19** (80 rel %): ^{1}H NMR δ 6.00 (d, J = 2.76 Hz, H^{3or4}), 5.90 (d, J = 2.76 Hz, H^{4or3}), 5.85 (m, H^7), 5.33 (dddd, J = 1.30, 2.69, 3.96, 9.56 Hz, H^8), 3.19 (m, H^{5or2}) [this peak was only resolved from basketane resonances on a 500-MHz spectrum], 2.98 (d, J = 3.13 Hz, H^{2or5}), 2.32 (ddt, J = 17.82, 4.94, 2.54 Hz, $H^{9or9'}$), 2.11 (dd, J = 6.45, 3.98 Hz, H^1), 2.03 (t, J = 4.88 Hz, $H^{10or10'}$), 1.98 (t, J = 4.88 Hz, $H^{10'or10}$), 1.77 (dm, J = 17.81 Hz, $H^{9'or9}$), 1.57 (d, J = 10.74 Hz, H^6); ^{13}C NMR δ 139.09 (C^{3or4}), 137.96 (C^{4or3}), 133.54 (C^{8or7}), 124.45 (C^{7or8}), 57.89 (C^{2or5}), 54.94 (C^{5or2}), 33.98 (C^9), 33.49 (C^1), 31.84 (C^6), 29.12 (C^{10}); MS *m/z* (relative intensity) 131 (12), 117 (64), 104 (22), 91 (83), 79 (44), 78 (78), 77 (52), 65 (32), 54 (43), 51 (49), 39 (100), 27 (68). A second stage of distillation gave an additional 31.6mg (10.0%).

Kinetics of the Reduction of 9-bromobasketane The reaction was carried out as for the 9-bromohomocubane reduction (see above) except for the use of 9-bromobasketane (29mg, 0.14mmol), instead of the 9-bromohomocubane. At 70°C, one product was observed by GC/MS. ^{1}H NMR δ 3.19 (qn, J = 3.01 Hz, 2H), 3.04 (m, 4H), 2.67 (m, 2H), 1.44 (t, J = 1.59 Hz, 2H); ^{13}C NMR δ 44.00 (CH), 40.16 (CH), 32.96 (CH),17.16 (CH_2). EIMS *m/z* (relative intensity) 131 (11), 117 (37), 104 (31), 91 (83), 78 (96), 65 (30), 51 (51), 39 (100), 27 (63). The spectroscopic data was consistent with literature values for basketane.[73] When the experiment was repeated at 220°C, two product peaks were observed by GC/MS. One was the unrearranged basketane peak, while on closer examination the other was actually found to be two overlapping peaks (NOT of equal intensity), of two rearranged products.(see large scale reduction for spectroscopic data). Therefore the reaction was carried out at a range of temperatures (140, 150, 180, 204 and 220°C) on the same scale, to determine the kinetic parameters of the rearrangement. The k_r/k_H values were obtained at each temperature from the final product concentrations and the initial Bu_3SnH concentration by means of an integrated rate equation.[35] Best values of the rate constant ratios were located with an iterative computer program based on NAG routine CO5 AXF.

Control experiments for reduction of basketane with Bu_3SnH.(a) A 5-mm NMR tube containing 9-bromobasketane (29mg, 0.14mmol) was submerged in an oil bath, at 85°C, for 10s. Bu_3SnH (54.1mg, 0.21mmol) was injected into the NMR tube which was then sealed and left in the oil bath, under a 400W UV light, for 40mins. GC/MS and NMR obtained from the resultant mixture showed the reaction had yielded a single product, basketane (**16**). The oil bath was then heated to 200°C and the mixture returned to the oil bath for a further 2hrs of irradiation. GC/MS analysis of the mixture showed no further reaction of the basketane formed. (b) A 5-mm NMR tube containing 9-bromobasketane (29mg, 0.14mmol) was submerged in an oil bath, at 190°C, under a 400W UV light, for 10mins. No Bu_3SnH was added. The

GC/MS of the product mixture showed none of the reduction products, **16**, **19** or **20**, observed with the presence of Bu_3SnH. The ^1H NMR showed the starting material, 9-bromobasketane to be the main component along with other undeterminable side products.

Reduction of 9-bromobasketane using Bu_3SnD. A 5-mm NMR tube containing 9-bromobasketane (**11**) (29.0mg, 0.15mmol) was submerged in an oil bath, at 210°C, for 10s. Bu_3SnD (54.1mg, 0.36mmol) was injected into the NMR tube which was then sealed and left in the oil bath, under a 400W UV light, for 45 mins. The GC/MS obtained from the resultant mixture showed the reaction had yielded two main products, 9-deuterobasketane and 9-deuterotricyclo[4.4.0.$0^{2,5}$]dec-3,7-diene. The resultant mixture contained residual tin products which could not be separated. The following NMR was therefore of both 9-deuterobasketane, 9-deuterotricyclo[4.4.0.$0^{2,5}$]dec-3,7-diene and of the unwanted tin residues. The peaks of the organotin components have been ignored. 9-Deuterobasketane (49.4%): ^1H NMR δ 3.19 (qn, J = 3.01 Hz, 2H), 3.04 (m, 4H), 2.67 (m, 2H), 1.44 (obscured by butyl group from organotin); ^2H NMR δ 1.44 (s, D^9); ^{13}C NMR δ 43.54 (CH) 39.70 (CH), 32.43 (CH), 16.56 (CHD,CH_2); EIMS *m/z* (relative intensity) 132 (27), 118 (58), 104 (39), 91 (65), 78 (100), 65 (24), 52 (48), 39 (58), 27 (27). 9-deuterotricyclo[4.4.0.$0^{2,5}$]dec-3,7-diene (46.8%): ^1H NMR δ 6.00 (d, J = 2.80 Hz, H^{3or4}), 5.90 (d, J = 2.80 Hz, H^{4or3}), 5.85 (m, H^7), 5.33 (ddd, J = 1.30, 3.96, 9.56 Hz, H^8), 3.19 (unresolved), 2.98 (d, J = 3.13 Hz, H^{2or5}), 2.11 (dd, J = 6.45, 4.00 Hz, H^1), 2.03 (t, J = 4.88 Hz, $H^{10or10'}$), 1.98 (d, J = 4.88 Hz, $H^{10'or10}$), 1.77 (dm, J = 17.81 Hz, $H^{9'or9}$), 1.57 (obscured by butyl group from organotin); ^2H NMR δ 2.32 (s, D^9); ^{13}C NMR δ 139.07 (C^{3or4}), 137.95 (C^{4or3}), 133.61 (C^{8or7}), 124.39 (C^{7or8}), 57.83 (C^{2or5}), 54.87 (C^{5or2}), 33.82 (C^9), 33.44 (C^1), 31.69 (C^6), 29.10 (C^{10}); EIMS *m/z* (relative intensity) 132(25), 118(100), 105(28), 91(77), 78(81), 65(28), 51(35), 39(53), 27(27). In the product mixture, little 7-deuterotricyclo[4.4.0.$0^{2,5}$]dec-3,8-diene was observed. Instead the ^1H NMR spectrum showed additional peaks in the

alkene region, which we assign to 1-(4-deuterocyclobut-2-enyl)-cyclohexa-2,4-diene (**22**-D): ^{1}H NMR δ 6.41 (dd, J = 4.32, 2.98 Hz), 6.10 (s, poss. 2H), 6.04 (dd, J = 3.32, 4.44 Hz), 5.29 (s), 3.66 (m), 3.54 (m), 3.43 (m), 3.08 (m), 2.84 (m); ^{2}H NMR δ 1.8 (s); ^{13}C NMR δ 139.80 (CH), 134.44 (CH), 130.37 (CH), 44.84 (CH), 42.09 (CH), 41.10 (CH), (other ^{13}C data obscured by organotin residues); EIMS *m/z* (relative intensity) 133 (11), 129 (50), 115 (17), 102 (12), 74 (12), 62 (12), 52 (100), 39 (21), 26 (11).

Photobromination of Basketane (20). Bromine (24mg, 0.150mmol) was added to a solution of (**20**) (18mg, 0.136mg) in degassed CCl_4 (2ml) in an NMR tube. The tube was sealed and left in daylight for 24 h. Addition of light petroleum b.p. 40-60°C (~4ml) caused crystallisation of a small amount of white solid (28.3mg, 46%) which was shown by GC/MS to be a mixture of four main compounds, $C_{10}H_{12}Br_x$, with some additional minor products. ^{1}H and ^{13}C NMR analysis of the supernatant liquid showed it to contain basketane but no other significant products. The white solid was subjected to preparative TLC (eluant: 9:1 pentane/chloroform) in an attempt to purify and separate the products. Two distinct bands were observed. The top band gave a brown solid (16mg, 26%) mp 163-165°C(dec.), which was shown by GC analysis to be a mixture of three of the rearranged tetrabromides. The impurities, common to both bands, were subtracted from the following NMR data. ^{1}H NMR δ 5.78 (t, J = 6.82 Hz), 5.35 (bd, J = 9.08 Hz), 4.94-4.76 (m), 4.55 (t, J = 7.23 Hz), 4.30 (d, 7.30 Hz), 3.12-2.93 (m), 2.44-2.00 (m); ^{13}C NMR δ 57.18, 55.59, 52.73, 49.95, 49.15, 48.80, 48.70, 48.05, 47.02, 45.93, 42.84, 37.98, 36.78, 35.76, 34.46 (CH's); 26.37, 20.71, 18.29, 18.15 (CH_2's): GC/MS *m/z* (relative intensity); a) t_r 19:37mins, 211 (3), 131 (78), 91 (100), 79 (31), 77 (31), 65 (40), 51 (35), 39 (48), 27 (26); b) t_r 19:52mins, 211 (4), 131 (66), 91 (100), 77 (35), 6 5(35), 51 (35), 39 (47), 27 (26); c) t_r 20:31mins, 211 (5), 131 (17), 103 (20), 91 (25), 79 (100), 65 (15), 51 (28), 39 (28), 27 (16). These data are consistent with a mixture of **47** (or possibly **50**), **56** and **59**. The other band also yielded a brown solid (8.8mg, 13%).mp. 175-

178°C(dec). GC analysis of this band showed it to be the fourth tetrabromide. ^{1}H NMR δ 4.86 (s, 1H), 4.81 (d, J = 3.84 Hz, 1H), 3.05 (dt, J = 2.31, 3.69 Hz, 1H), 2.33 (bs, 1H), 2.23 (bd, J = 8.47 Hz, 1H), 1.28 (1H, m); 2D COSY NMR, δ 4.87 interacts with 2.23, 4.80 with 3.05, 3.05 with 2.33, 2.23 strongly with 1.28; ^{13}C NMR δ 50.61, 48.20, 47.23, 36.00 (CHs), 18.88 (CH_2): GC/MS m/z (relative intensity), t_r 20.13mins, 211 (3), 131 (18), 103 (21), 91 (28), 79 (100), 78 (55), 65 (18), 51 (28), 39 (28), 27 (16). These data are consistent with structure **50** but could possibly indicate **47**. The brown coloration of the two layers may well be due to partial decomposition of the original polybromides during TLC.

Chapter 4

The Norcubylcarbinyl Radical

4.0 Introduction

As was discussed in Chapter 2, highly strained polycyclic radicals containing three- and/or four-membered rings normally rearrange rapidly by β-scission processes. Consequently, only a few such intermediates have been spectroscopically observed and their chemistry has only been explored to a limited extent. Strained polycycloalkylcarbinyl radicals can relieve much of their ring strain, immediately they come into existence, by means of one or more β-scissions. Thus, as has been shown previously (see Chapter 3, Section 3.2, Scheme 6), rearrangement of the cubylcarbinyl radical (**23**), which is accompanied by huge relief of strain, is one of the fastest known radical rearrangements[12(b),50] to date. In the case of **23** the initial β–scission is followed rapidly by two further β-scissions of **24** and **25** to give an isomeric pair of reactive trienes[34] derived from radical **26**. The mechanistic complexity of the rearrangement detracts from the usefulness of what would otherwise be a very valuable "free radical clock".

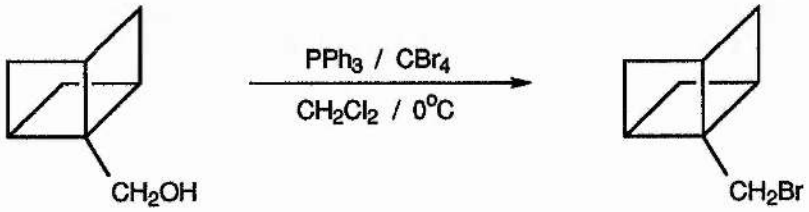
The 6-tricyclo[3.1.1.$0^{3,6}$]heptylmethyl or norcubylcarbinyl radical (**65**) is structurally similar to the cubylcarbinyl radical (the structure of methylnorcubane being essentially that of methylcubane less one carbon atom, i.e., one corner of the cube missing). Obviously the geometry will not be identical as the missing carbon atom will "relax" the framework making the structure less strained. Due to this similarity in structure the norcubylcarbinyl radical should behave in an equivalent way to the cubylcarbinyl radical and rapidly rearrange. However , far more importantly, it has the potential to relieve its ring strain by way of a single β-scission. Clearly, this comparatively simple rearrangement, would make the norcubylcarbinyl radical a potentially extremely useful and quick free radical clock.

The following study of the norcubylcarbinyl radical by EPR spectroscopy and by product analysis was undertaken to assess the viability of this rearrangement and to make an approach at calibrating the free radical clock. The results also show a comparison between the 6-norcubylcarbinyl (**35**) and the 6-norcubyl (**72**) radicals. All

the work and the results of **72** were obtained by Philip Mallon during his Ph.D. study at the University of St. Andrews.

4.1 Preparation of the 6-Bromomethylnorcubane (61)

Preparation of norcubane-6-methanol was carried out by Ernest Della and co-workers at Flinders University, near Adelaide, in South Australia. Norcubane-6-methanol being prepared as described in the literature.[74] The bromide was found to be very labile and rearranged with ease in common with other related derivatives,[74] and as also observed with bromomethylcubane,[12(b),34] and thus it was freshly prepared prior to being utilised in the radical experiments (Figure 4.1). Preparation of **61** was therefore accomplished by treatment of norcubane-6-methanol with triphenylphosphine



61

Figure 4.1

Preparation of 6-Bromomethylnorcubane From Norcubane-6-methanol.

and carbon tetrabromide[75,76] under similar conditions to those employed for the preparation of bromomethylcubane.[12(b),34]

4.2 Rearrangement of the Norcubylcarbinyl Radical

Triethylsilyl radicals were used to abstract the bromine atoms from norcubylcarbinyl bromide **61** (Figure 4.2). A very weak spectrum was observed which was satisfactorily analysed with the following hfs: a(1H) = 22.0, a(2H) = 32.6,

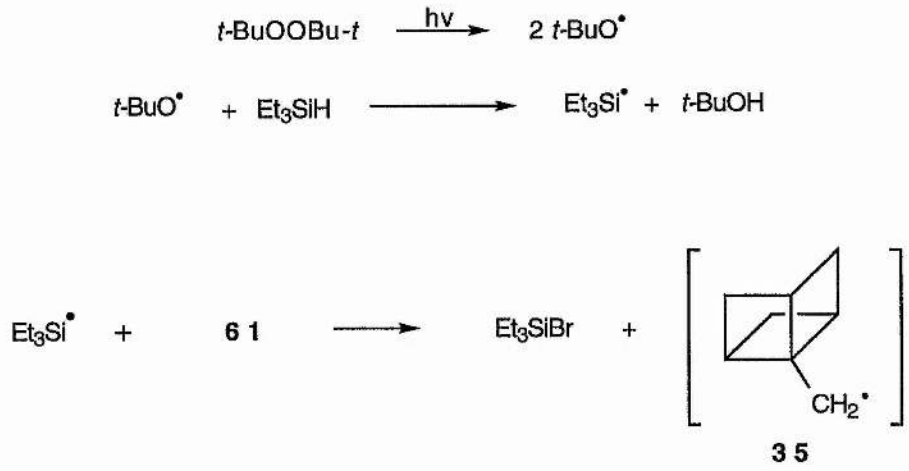


Figure 4.2

Generation of Norcubylcarbinyl Radicals.

a(2H) = 34.5 G at 150K. This and only this spectrum was visible in the whole of the accessible temperature range down to 100K in propane solvent. The spectrum obtained was assigned to the product formed after β-scission had taken place i.e. the

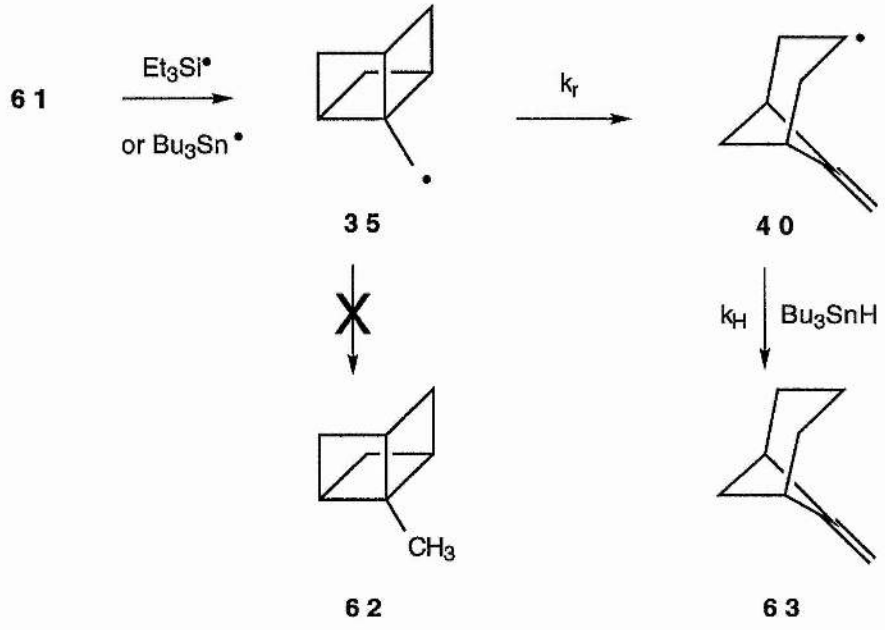
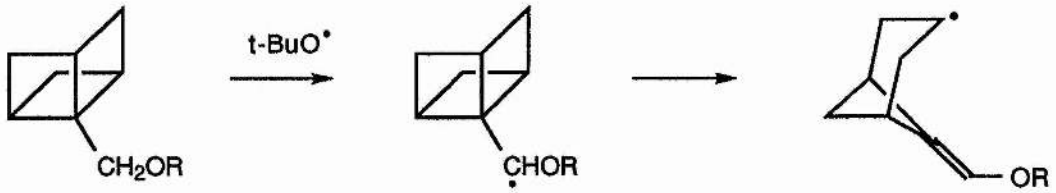


Figure 4.3

Rearrangement of the Norcubylcarbinyl Radical.

cyclohexyl type radical **40** (Figure 4.3). Essentially identical spectra were obtained at 145K on hydrogen abstraction from norcubylmethanol, **64a**, and the deuterated analogue, **64b** (Figure 4.4). The splittings from these spectra were assigned to the cyclohexyl type radicals **66a** and **66b**. In these rearranged radicals the substituents are too far away from the unpaired electron to interact significantly and hence the spectra of **40**, **66a** and **66b** all have the same appearance. The EPR hfs differ somewhat from those of the archetype cyclohexyl radical [a(1H) = 21.0, a(2H) = 39.4, a(2H) = 5.3 G at 193 K].[77] However, the methylene bridge in **40** puts serious restraints on the conformation of the six-membered ring i.e. a boat conformation must be present. Because of the resulting "prow to prow" steric interactions there will be flattening of the ring and hence the β-hydrogens will be more alike than true axial and equatorial hydrogens. This explains why the two a(Hβ) values are much closer to one another than in the cyclohexyl radical.



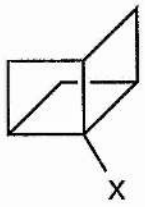
64 **65** **66**

a, R = H; **b**, R = D

Figure 4.4

Rearrangement of the Radical Derived From Norcubylmethanol

The EPR results show that norcubylcarbinyl radicals rearrange extremely rapidly under EPR conditions. The parent **35** was fully rearranged even at 100K. Rapid rearrangement is also a feature of the norcubylcarbinyl derivatives **67** and **68** which undergo ring expansion either via the corresponding cation or by a concerted process.[74] For instance conversion of tricyclo[3.1.1.$0^{3,6}$]heptane-6-methanol (**64a**)



67 = $CH_2OH_2^+$

68 = CH_2OTs

69 = CH_2COOH

into the corresponding tosylate (**68**) leads instead to a rearranged isomer tricyclo[3.2.1.$0^{3,6}$]oct-6-yl tosylate (Figure 4.5).

Section 4.4 discusses the similarity in reaction between the norcubyl radical and the cubyl radical . The similarity is also evident in the case of norcubylcarbinyl (**35**), with the extremely fast β-scission being similar to that of the cubylcarbinyl radical (**23**). Introduction of oxygen functionality at the radical centre often decreases the rate

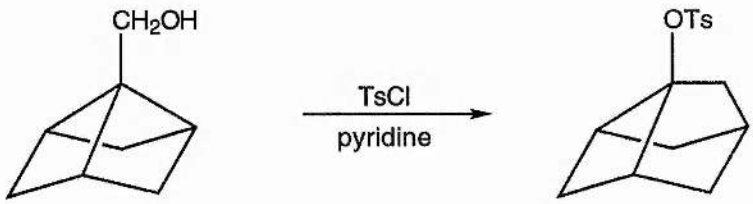


Figure 4.5

Rearrangement of Norcubylmethanol

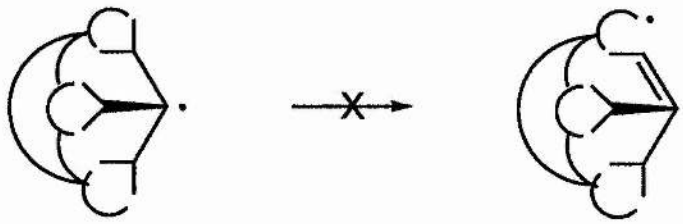
of β-scission of cycloalkylcarbinyl radicals.[12(b),78] For example, α–hydroxycubylcarbinyl radicals rearranged approximately three orders of magnitude more slowly than cubylcarbinyl radicals and were spectroscopically detectable[12(b)] at 160K. Because **65a,b** could not be detected at 145K, but only the rearranged **66a,b**, it is evident that β-scission of these hydroxy-substituted norcubylcarbinyl radicals is faster than for the analogous cubylcarbinyl radical. It is likely therefore that β-scission of the norcubylcarbinyl radical is at least as quick as, but most likely faster than the cubylcarbinyl radical.

4.3 Kinetics of the Rearrangement of the Norcubylcarbinyl Radical

To confirm these results the rearrangement was examined by reduction of 9-bromomethylnorcubane (**61**) with tributyltin hydride. At 343K, the reaction of **61** yielded only one detectable product, on analysis by GC/MS. Small scale distillation of the reacted mixture gave a clear liquid that was identified by proton NMR. The alkene protons at 4.6ppm, the two bridgehead hydrogens at 2.8ppm and the remaining aliphatic proton signals led to the conclusion that the only product formed was the rearranged product 6-methylenebicyclo[3.1.1]heptane (**63**) (Figure 4.3). The photochemical reaction at 277K was incomplete after 3h, but the only reduction product was again the rearranged compound **63**. From the amount of **63** formed and the limit for detection of methylnorcubane (**62**) we found that [**63**]/[**62**] > 28 at 277K. This ratio is given by;[35(c),(d)] $k_r/k_H[Bu_3SnH]$, where k_r is the rate constant for β-scission of **35**. It follows that $k_r(277K) > 1x10^8\ s^{-1}$. For most unimolecular rearrangements of this type the Arrhenius pre-exponential factor is close to $10^{13}\ s^{-1}$ and if we assume this holds true then $E_r < 26\ kJ\ mol^{-1}$. The EPR observations suggest that E_r is considerably below this limit. From the appearance of **35** as low as 100K it is possible to estimate[79] that $E_r < 19\ kJ\ mol^{-1}$ and hence $k_r(298K) > 5x10^9\ s^{-1}$. It is evident therefore that β-scission of **35** is one of the fastest radical rearrangements known. In a mechanistic sense, it is much simpler than cubylcarbinyl because it proceeds in one step to give a single product without intermediates that are potentially able to be trapped. This reaction is therefore extremely promising as an ultra fast radical clock for use in timing enzyme reactions. Obviously the clock needs calibrating more accurately, but a different radical precursor, e.g. the Barton ester of **69**, will be needed with a faster hydrogen donor than tributyltin hydride, possibly selenophenol.[37]

4.4 Comparison of Norcubyl/Cubyl and Norcubylcarbinyl/ Cubylcarbinyl Radicals

In polycyclic radicals, where the radical centre, and all three carbon atoms attached to the radical centre, are bridgehead atoms as in **70** (or where the three β-carbon atoms are sp^2 hybridised) β-scission is forbidden because this would produce a highly strained, bridgehead alkene **71** (Figure 4.5). The only two examples of this



70 **71**

Figure 4.5

"Forbidden" β-Scission to Form an Anti-Bredt, Bridgehead Alkene.

type of radical studied to date are the cubyl[12(b),34,37] and norcubyl[80] (**72**) radicals which, in spite of having an exceptionally high strain energy, retain their structural integrity under a variety of conditions. For example the cubyl radical does not undergo rearrangement in solution even at 420K in spite of ca. 690 kJ mol^{-1} of ring strain. This property is of considerable value because it enables functional group manipulations at the bridgehead to be carried out successfully via free radical intermediates.

The norcubyl radical is intrinsically similar in structure to its analogue the cubyl radical. It, too, does not undergo β-scission because the product radical **73** would be highly strained. For the same reason, hyperconjugative stabilisation of **72** to structures such as **72'** is likely to be negligible (Figure 4.6).

Table 4.0 shows the hyperfine splittings of both the cubyl and the analogous norcubyl radicals to be of comparable magnitude. This is hardly surprising as, similar

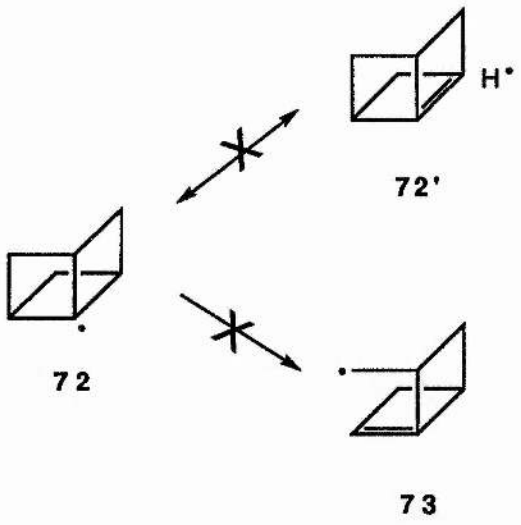


Figure 4.6

Structural Integrity of the Norcubyl Radical.

to the case of methylcubane and the 6-methylnorcubane, the structure of norcubane is essentially that of cubane less one carbon atom.

In the case of the norcubyl radical, the EPR spectrum was a complex set of signals produced by couplings to three groups of three hydrogen atoms $3H^{\beta}$, $3H^{\gamma}$(anti) and $3H^{\gamma}$(syn). On comparison of the hyperfine splittings of the norcubyl radical with the cubyl radical[12(b),50] the similarity in the hfs confirmed the norcubyl radical retained its structural integrity under the spectroscopic conditions and shows the apparent similarity, in resistance to rearrange, between the norcubyl and cubyl radicals.

Table 1. The Norcubyl Radical in Comparison With the Cubyl Radical hfs.

Hydrogen Atoms	Hyperfine Splittings (G)	
	Norcubyl Radical[a]	Cubyl Radical
H^{β}	10.60	12.40
H^{γ} (anti)	8.25	8.20
H^{γ} (syn)	0.80	--

[a] Tentative assignments for H^{β} and H^{γ} (anti).

In stark contrast to the inability of both the cubyl and norcubyl radicals to rearrange, the cubylcarbinyl (**23**) and norcubylcarbinyl (**35**) radicals undergo rapid ring opening reactions via β-scission. The rate of rearrangement of **23** to **24** has been determined to be 2.9×10^{10} s^{-1}, at 298K, and in this work it has been shown that the rearrangement of **35** is greater than 5×10^{9} s^{-1} at the same temperature. The important property of the cubylcarbinyl radical is that the radical centre is freely able to rotate, and this allows the transition state for ring-opening to adopt the conformation which most facilitates the β-scission (a dihedral angle between the SOMO and the C_β-C_γ bond of 0°). Again due to the essentially similar structures of **23** and **35**, it can be safely assumed that this is the reason for the ease of β-scission of **35** as well. It has therefore been shown that **35** behaves in the same way as **23** and so adds further strength to the proposed mechanism by which **23** rearranges.

4.5 Experimental Section

EPR Spectra. See experimental section 3.12 for preparation of EPR samples.

6-Bromomethyltricyclo[3.1.1.0^{3,6}]heptane (61). A stirred solution of tricyclo[3.1.1.0^{3,6}]heptane-6-methanol (0.36g, 2.93mmol) and triphenylphosphine (1.54g, 5.86mmol) in dichloromethane (5mL, passed through basic alumina and stored over sodium carbonate) was cooled to 0°C with an ice-water bath. A solution of carbon tetrabromide (1.08g, 3.25mmol) in dry dichloromethane (4ml) was added dropwise via a pipette. After ca.70% of the tetrabromide was added the solution turned an orange-brown colour. The mixture was stirred for 5h at room temperature. The whole reaction was poured into pentane (ca. 150ml) at -10°C, and the cold mixture was filtered through celite. The filtrate was concentrated, and the residue was triturated with pentane (2 x 50ml). The pentane solution was dried with magnesium sulphate and evaporated to give a colourless liquid. The crude product was vacuum transferred (0.1 Torr, 65°C) to give colourless 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane (0.29g, 53%): ^{1}H NMR δ 3.69 (s, 2H), 2.74 (m, 6H), 2.11 (bd, J = 9.1 Hz, 3H); ^{13}C NMR δ 59.40 (quatenary), 37.56 (CH), 34.96 (CH_2), 34.38 (CH_2); EIMS *m/z* (relative intensity) 188, 186 (M^+, 3), 146 (97), 144 (100), 107 (12), 91 (18), 79 (34), 77 (31), 66 (43), 65 (91), 51 (22), 39 (50), 27 (29): along with a small amount of unidentified side product: EIMS *m/z* (relative intensity) 144 (4), 107 (26), 91 (60), 79 (100), 77 (50), 65 (58), 53 (33), 39 (58), 27 (32).

Reduction of 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane using Bu_3SnH (low temperature study). A 5mm NMR tube containing 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane (29.0mg, 0.16mmol) was submerged in an ice bath, at 4°C, for 10s. Bu_3SnH (54.1mg, 0.21mmol) was injected into the NMR tube which was then sealed and left in the ice bath, under a 400W UV light, for 3h. The GC/MS obtained from the resultant mixture showed the reaction had yielded only

one product along with some of the unreacted bromide and its associated side product. The mixture contained residual tin products which could not be satisfactorily separated by TLC. The reaction was therefore repeated at a higher temperature to ensure that all the bromide had reacted (see following experiment for spectroscopic data).

Reduction of 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane with Bu_3SnH hydride (large scale). Bu_3SnH (0.54g, 1.86mmol) was injected into an NMR tube containing 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane (0.145g, 0.78mmol) at 28°C. The tube was then sealed and photolysed with a 400W UV light at 28°C for 2h. The product was decanted into a small scale distillation apparatus. Distillation on a vacuum line at ca. 0.01 Torr was carried out to yield 0.092g of clear liquid. The NMR spectrum of the distillate showed the product to be 6-methylenebicyclo[3.1.1]heptane. ^1H NMR δ 4.60 (s, 2H), 2.80 (bs, 2H), 1.97 (bt, J = 6.5 Hz, 5H), 1.71 (spt, J = 7.3 Hz, 2H), 1.37 (d, J = 7.5 Hz, 1H); ^{13}C NMR δ 157.86 (quaternary), 97.26 (=CH_2), 44.56 (CH), 32.64 (CH_2), 31.97 (CH_2), 17.10 (CH_2) [contaminated with a minor amount of unreacted norcubylcarbinyl bromide]. EIMS *m/z* (relative intensity) 108 (M^+, 10), 93 (98), 91 (50), 79 (100), 77 (56), 67 (27), 53 (21), 41 (42), 39 (68), 27 (38). The GC/MS confirmed that the product contained ca. 20% of unreacted 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane.

Reduction of 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane using Bu_3SnH (high temperature study). In a reduction at 70°C with the same quantities as the low temperature study, 6-methylenebicyclo[3.1.1]heptane was the only detectable reduction product, i.e., all the 6-bromomethyltricyclo[3.1.1.0^{3,6}]heptane had reacted and had undergone 100% rearrangement.

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Part Three:

Bicyclo[1.1.1]pent-1-yl

&

Bicyclo[2.2.2]oct-1-yl

Radicals

Chapter 5

The Chemistry of 3-Substituted Bicyclo[1.1.1]pent-1-yl Radicals

5.0 Introduction

The bicyclo[1.1.1]pentane skeleton (Figure 5.0) presents interesting features of strained, fused four membered ring systems. The dihedral angle for the cyclobutane rings is restricted to 120° by molecular symmetry but what is of exceptional interest is the short 1,3-distance between the bridgeheads. Experiment[1] and *ab initio* calculations[2] indicate that this distance is one of the shortest non bonded carbon-carbon

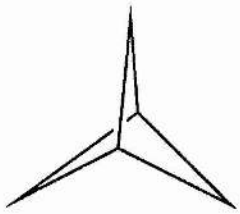


Figure 5.0

Bicyclo[1.1.1]pentane.

distances on record at only ca. 1.85 Å. Hence the non-bonded carbon-carbon interactions are strong in this molecule and large cross cage couplings can be expected, i.e. a substituent at C^3 is expected to have a very powerful influence on the detailed structure and reactivity at C^1. In 1966, Wiberg and Connor[3] studied the long range coupling constant between the bridgehead hydrogens of bicyclo[1.1.1]pentane and found it to be remarkably large, 18 Hz. Subsequently, other large coupling constants between atoms attached to the bridgehead carbons have been observed: 71 Hz for hydrogen-fluorine,[4] 30-60 Hz for hydrogen-phosphorus[5,6] and 156-180 Hz for hydrogen-tin.[5]

Prior to this work, only the parent radical **1** (X = H) had been characterised by EPR spectroscopy. Maillard and Walton[7] showed the parent radical to be unsusceptable to rearrangement, in the confines of the EPR cavity, at temperatures of up to 310K; an experimental observation that supported unequivocally the prediction

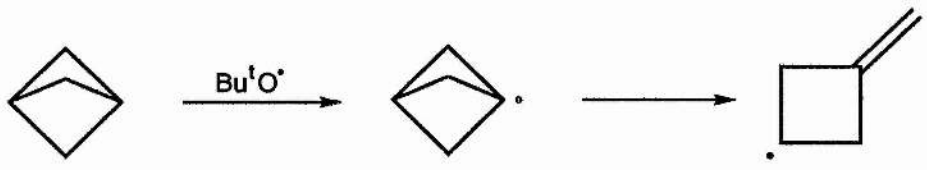


Figure 5.1

The Possible Bicyclo[1.1.1]pentyl Rearrangement.

that the rearrangement to the methylenecyclobutane radical (Figure 5.1) was kinetically disfavoured.[5] Their work also showed the radical to have an exceptionally large electron-nuclear hyperfine splitting (hfs) of 69.6 G from the bridgehead hydrogen; a result that displays the immense effect the C^3 position has on the chemistry of the carbon at the radical centre. Such interactions (which can lead to substantial hyperfine coupling) have even been observed with the 1-norbornyl and 1-bicyclo[2.2.2]octyl radicals (see Chapter 6), in which the cross-ring distances are much larger.[8] Cross

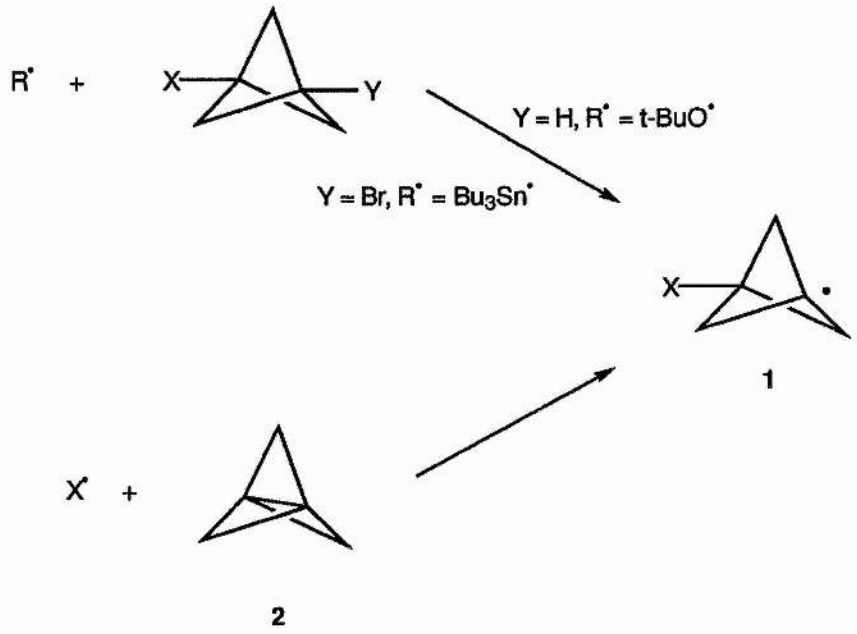


Figure 5.2

Two Way Formation of Bicyclo[1.1.1]pentyl Radicals.

cage interactions should be manifested particularly readily in 3-substituted bicyclo[1.1.1]pent-1-yl radicals (**1**) which should be amenable to study by EPR spectroscopy and for which reaction modes can be established by well understood homolytic methods. Radicals of type **1** are easily made by hydrogen or halogen abstraction from bridgehead substituted bicyclo[1.1.1]pentanes (Figure 5.2) or by addition of radicals to [1.1.1]propellane (**2**).

The chemistry of **2** has undergone a remarkable evolution over a relatively short period and the technique of radical addition to **2** has been studied by several groups. [1.1.1]Propellane was originally predicted to be incapable of existence.[9] Theoretical predictions then showed it to be relatively stable and the first successful preparation followed in 1982, from a 1,3-disubstituted bicyclo[1.1.1]pentane. The dibromide was prepared using a Cristol-Firth reaction, followed by a debromination with methyllithium.[10]

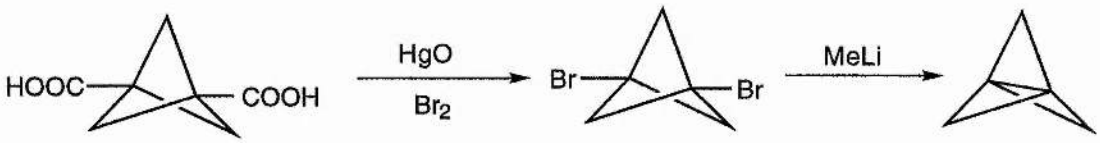


Figure 5.3

Wiberg's Original Preparation of **2**.

Szeimies *et al.* followed this with an even simpler preparation[11] and it now is one of the most easily obtained of small ring compounds.

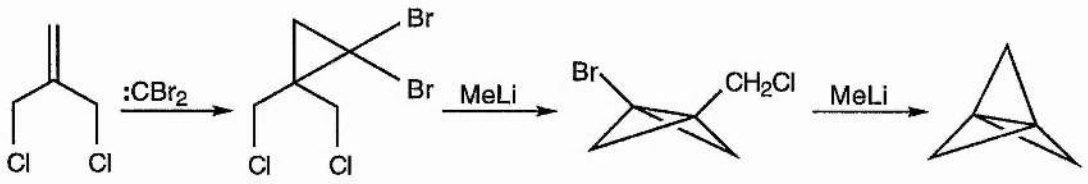


Figure 5.4

Szeimies's Preparation of **2**.

Several research groups have studied the addition of radicals to **2**, to investigate the ease at which C^1-C^3 bond scission occurs upon radical attack. The results have shown that the 3-substituted bicyclopent-1-yl radicals function effectively as propagating intermediates in many chain sequences.[12]

[1.1.1]propellane is one of the most thermally stable of all small ring propellanes, probably because it has the highest bond energy for the central carbon-carbon bonds. However, facile free radical additions occur almost instantaneously with iodine, bromotrichloromethane, thiophenol,[13] diphenyl disulphide[14] and a range of other reactants including acetaldehyde.[12] All these reactions presumably involve free radical processes. It should be noted that reagents such as iodine, which do not normally react with unstrained alkenes, react rapidly with [1.1.1]propellane due to the driving force of ring-strain relief.

2 also undergoes numerous reactions forming oligomers and even polymers. These [n]staffanes[15] (n=1-5) as they are called are functionalised at both ends and can be used as "building blocks" for the development of a molecular size civil engineering construction set analogous to childrens' toy construction kits.[16]

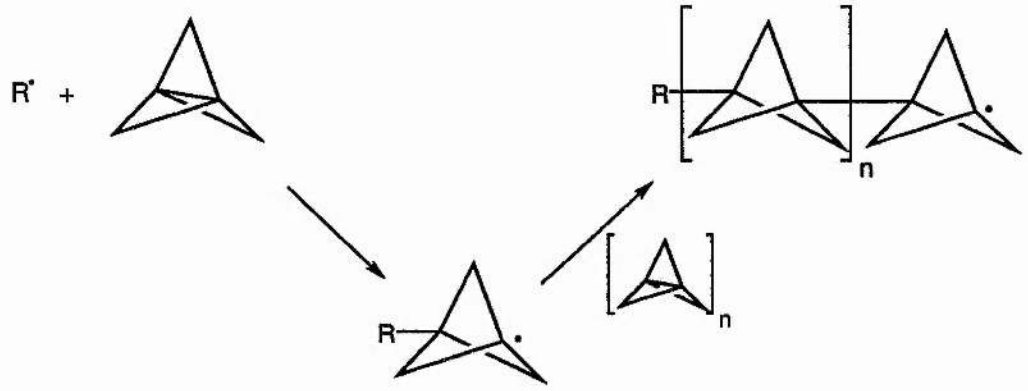


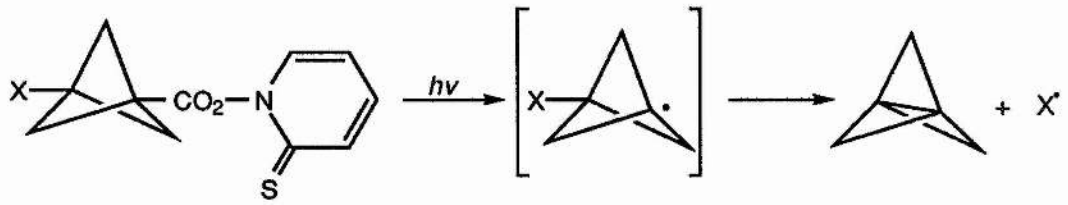
Figure 5.5

The Formation of [n]Staffanes.

One further, and important reaction of **2** in context with this work, is the reaction with thiophenol, followed by reduction with the lithium radical anion from

4,4'-di-*tert*-butylbiphenyl, to give 1-lithiobicyclo[1.1.1]pentane.[12] This compound has been shown to be an exceptionally useful reagent in the preparation of 1-substituted bicyclo[1.1.1]pentanes, previously difficult compounds to prepare.

Several theoretical assessments of the parent radical have appeared.[2,17-19] Although the cage possesses *ca.* 285 kJ mol^{-1} of strain energy[20] the activation energy for ring scission was calculated to be very high. This agrees with experimental evidence[21,22] of the reluctance of **1** to undergo β-scission to methylenecyclobutyl derivatives (Figure 5.1). A particularly significant theoretical result in context to this work was obtained by Feller and Davidson.[19] They found the first bridgehead carbon-hydrogen bond dissociation energy of bicyclo[1.1.1]pentane to be 444 kJ mol^{-1} and the second, i.e. in the bicyclo[1.1.1]pent-1-yl radical, to be 193 kJ mol^{-1}. This implies that comparatively little expenditure of energy was entailed in the loss of the second bridgehead hydrogen of **1** (X = H) (i.e. forming **2**), leading to a bridgehead-bridgehead bond energy of 277 kJ mol^{-1} in [1.1.1]propellane. This agrees with bond energy estimates achieved in other ways.[23] The second bridgehead hydrogen atom has no significant stabilisation energy and hence implies that a 3-substituted bicyclo[1.1.1]pent-1-yl radical might convert quite readily to **2** by loss of a radical with a greater stabilisation energy. Experimental evidence on this point is rather meagre. When X in **1** is carbon-centred the resulting bicyclo-radicals are stable in solution at moderate temperatures, with the probable exception of the benzyl and allyl species which could not be made by addition of benzyl or allyl halides to **2**.[24,25] The 3-iodobicyclo[1.1.1]pent-1-yl radical was found to readily lose an iodine atom[24] and loss of a bromine atom from radical **1** (X = Br) has also been noted.[26] An experiment was also undertaken by Della and Taylor[26] to study the Barton bromodecarboxylation of 3-substituted bicyclo[1.1.1]pentyl thiohydroxamic esters in 1-bromo-1-chloro-2,2,2-trifluoroethane. Irradiation of the esters did not even yield a trace of the respective bromide (Figure 5.6). In the case of the selenyl ester, for example, the hydrocarbon moiety was lost as [1.1.1]propellane, and diphenyl diselenide was isolated in



X = Me_3Si, Me_3Sn, PhSe

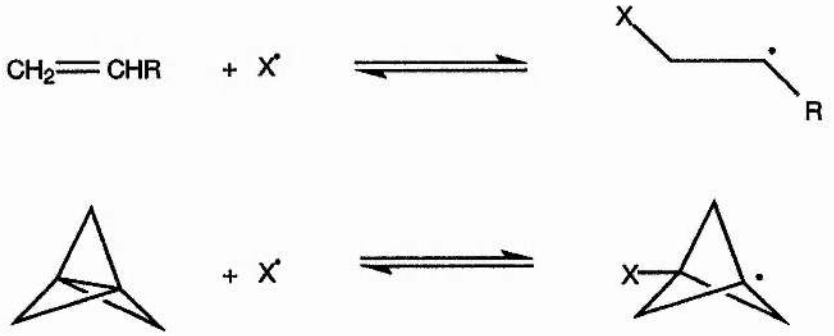
Figure 5.6

The Barton Decarboxylation of

3-Substituted Bicyclo[1.1.1]pentyl Thiohydroxamic Esters.

quantitative yields. This evidence is supported by the reversibility shown on addition of thiyl radicals to **2**.[27] The comparable situation may be considered of iodine atom and thiyl radical additions to alkenes. These are also reversible, as is the addition to alkenes of tin centred radicals, however carbon-centred radical addition is not at moderate temperatures so, broadly speaking, the γ-fragmentations of **1** resemble β-fragmentations of 2-substituted alkyl radicals (Figure 5.7).

The research reported in this chapter was undertaken to examine the influence of



X = I, Br, RS, R_3Sn

Figure 5.7

The Similarity Between γ-Fragmentations of **1** and β-Fragmentation's

of 2-Substituted Alkyl Radicals.

3-substituents on the structure and reactivity of **1**. In spite of their high strain energies and high reactivities, we successfully observed a short series of such radicals by EPR spectroscopy at low temperatures. This spectroscopic technique revealed unprecedentedly large hyperfine interactions from the magnetic nuclei of the 3-substituents. Bromine atom abstraction from 3-fluorobicyclo[1.1.1]pentyl bromide was found to be subject to a dramatic kinetic polar effect originating from the γ-fluorine atom. Fluorine atom abstractions are extremely rare in homolytic processes, but evidence was found for a novel type of disproportionation reaction in which a fluorine atom was transferred from a 3-fluorobicyclo[1.1.1]pent-1-yl radical to another radical. John Wilkie of St. Andrews University undertook a feasibility study of fluorine atom, and methyl group, loss from radicals of type **1** by *ab initio* MO theory. The results, which are discussed briefly in Section 5.3, indicted that γ-scission (i.e. loss of X) to give **2** would be comparatively easy.

5.1 Preparation of 3-Substituted 1-Bromobicyclo[1.1.1]pentanes

Until recently, the only viable synthetic entry into bridgehead-disubstituted

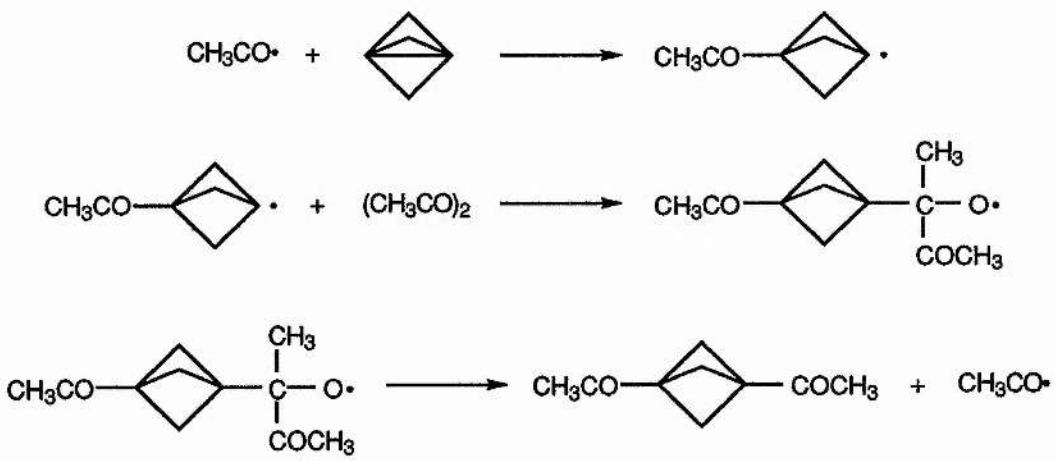
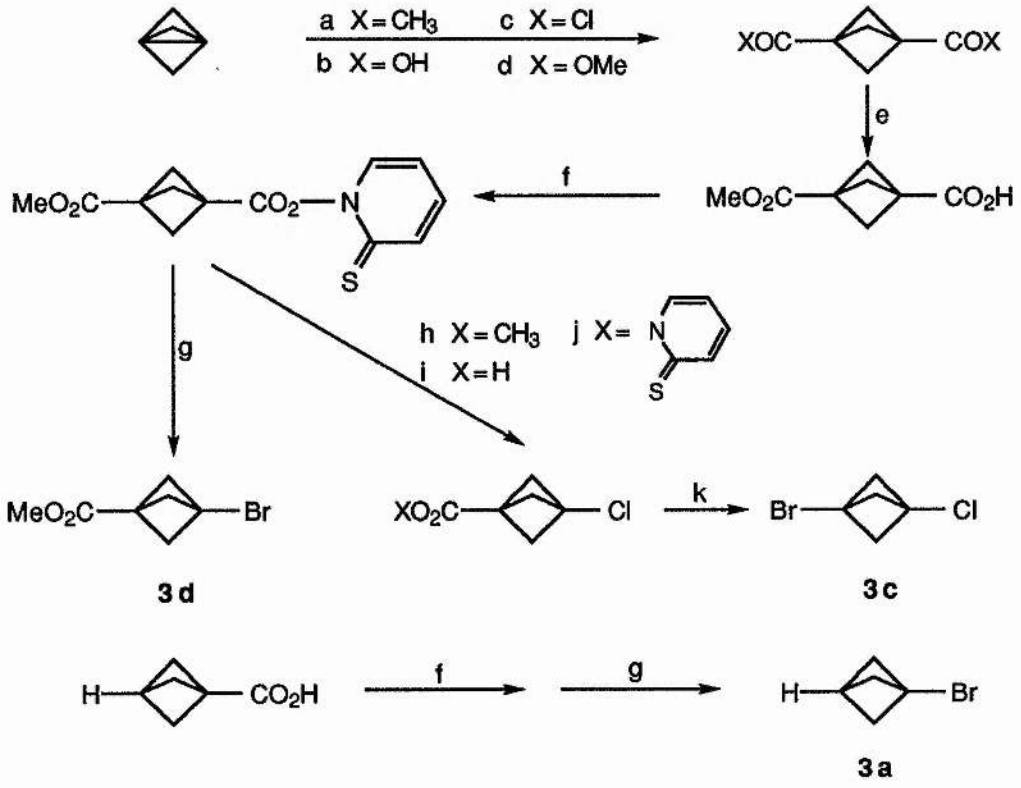


Figure 5.8

Mechanism for Photo Addition of Biacetyl.

bicyclo[1.1.1]pentanes was that reported 12 years ago by Applequist and co-workers.[28] However this route suffered from the disadvantage of being low-yielding and labour-intensive. It has now been replaced by a procedure developed principally by Michl[24] and his colleagues and also by Wiberg and co-workers.[13] The more recent method, which is efficient and rapid, is based on the discovery[13,24] that under photochemical irradiation, a variety of reagents can be induced to add to [1.1.1]propellane **2**. The formation of the bromides is made even easier by the fact that 1-bicyclo[1.1.1]pentyl radicals are kinetically stable intermediates.[29] With this



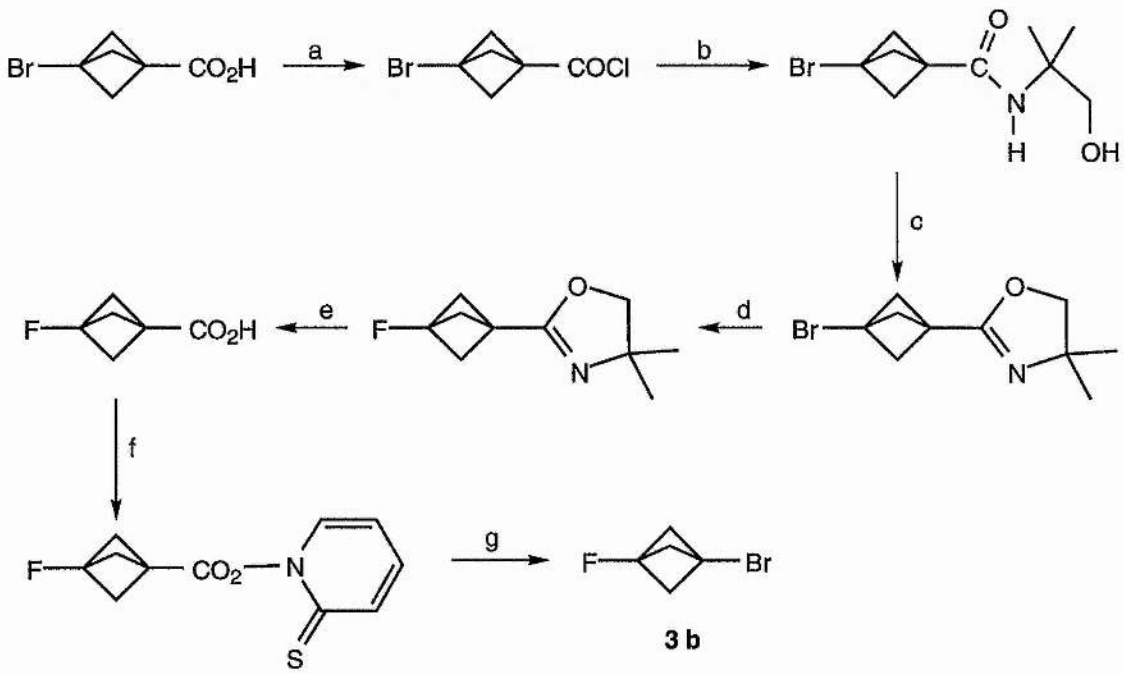
(a) $(CH_3CO)_2$, hv; (b) NaOBr; (c) $SOCl_2$; (d) MeOH; (e) NaOH, MeOH; (f) *N*-hydroxypyridine-2-thione, DCC; (g) $CF_3CHClBr$, cat. DMAT, hv; (h) $CFCl_3$; (i) aqueous NaOH; (j) *N*-hydroxypyridine-2-thione, DCC; (k) $CF_3CHClBr$, hv.

Figure 5.9

Preparation of **3a**, **3c** and **3d**.

fact in mind, insertion of bromine can be accomplished with minimal formation of side products by bromodecarboxylation of the Barton ester.

Our co-workers W. Adcock and A. R. Krstic from Flinders University in Adelaide prepared the four different 3-substituted bicyclo[1.1.1]pentyl bromides (**3**). 1-Bromobicyclo[1.1.1]pentane (**3a**), 1-bromo-3-chlorobicyclo[1.1.1]pentane (**3c**) and methyl 3-bromobicyclo[1.1.1]pentane-1-carboxylate (**3d**) were all prepared by literature procedures (Figure 5.9).[26] All three can be made relatively easily from [1.1.1]propellane (**2**), which is obtained via the Szeimies procedure (Figure 5.4) and is then reacted with biacetyl[24(a)] in a photoaddition reaction where the key step is a β-



(a) $SOCl_2$; (b) $(CH_3)_2C(NH_2)CH_2OH$; (c) (i) $SOCl_2$; (ii) aqueous NaOH; (d) (i) Bu^tLi; (ii) *N*-fluoro-3,3-dimethyl-2,3-dihydro-1,2-benzothiazol-1,1-dioxide (*N*-fluorosultam); (e) aqueous HCl; (f) *N*-hydroxypyridine-2-thione, DCC; (g) $CF_3CHClBr$, hv.

Figure 5.10

Synthesis of 1-Bromo-3-fluorobicyclo[1.1.1]pentane.

fragmentation of an alkoxy radical (Figure 5.8). The addition was followed by a hypobromite oxidation of the resulting diketone, yielding the desired diacid.

This diacid may then be di-esterified via the acid chloride, followed by conversion into the half ester using conditions similar to that for selective hydrolysis of cubane 1,4-diester devised by Eaton.[30] The ester may then be converted to the Barton ester, followed by reaction to form either **3a, 3c** or **3d.**

It was discovered by Della and co-workers[26] that 1-bromo-3-fluorobicyclo[1.1.1]pentane (**3b**) may not be prepared via the Barton ester method, by the route shown in Figure 5.9. Instead Adcock used a known fluorinating agent, *N*-fluorosultam[31] to displace the bromine atom (Figure 5.10). To avoid unnecessary side reactions, the acid group was protected by forming the bromo-oxazoline compound.

5.2 EPR Spectra of 3-Substituted Bicyclo[1.1.1]pent-1-yl Radicals

As was the case in Chapter 3, radicals **1a-d** were generated from the bromides in cyclopropane solution at low temperatures by bromine atom abstraction with photochemically generated triethylsilyl radicals and observed by EPR spectroscopy. The methodology used was the same as that employed to generate the parent radical (**1a**).[32] When **3a** was irradiated the spectrum obtained was not the expected **1a**

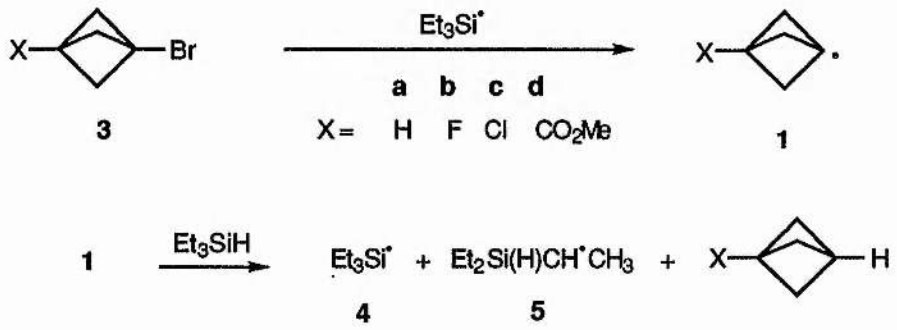


Figure 5.11

Generation of 3-Substituted Bicyclo[1.1.1]pentyl Radicals.

radical, but instead a weak spectrum of the dichloromethyl radical, corresponding to literature parameters.[33] Spectra from the other bicyclo[1.1.1]pent-1-yl radicals were successfully observed but degraded rather rapidly, except for that of **1d**, and in each case a second spectrum due to the silylethyl radical (**5**), with EPR parameters the same as those given in the literature,[34,35] was observed. This species is formed, along with triethylsilyl radicals, only when highly reactive σ-radicals like **1** abstract hydrogen from the ethyl groups of triethylsilane. The proportion of this silylethyl radical could be reduced to spectroscopically acceptable levels by working with lower than normal amounts of triethylsilane.

For the generation of the 3-fluoro radical **1b**, a 2:1 mixture of **3b** and **3a** was used. In addition to **5**, the EPR spectrum at 155K showed a weak and extremely wide doublet [a(F) = 167 G] (Figure 5.12). The components of this doublet were not resolvable so that the coupling from the six bridge hydrogen atoms of **1b** was less than the peak to peak line width (ΔH_{pp} = 1G). Surprisingly, none of the unsubstituted radical **1a** was observed. This suggested that triethylsilyl radicals abstracted bromine atoms from the 3-fluoro bromide *in preference* to the unsubstituted bromide, i.e. that the 3-fluorine atom exerted a favourable substituent effect. The spectrum obtained on bromine abstraction from **1c** (Figure 5.13) showed two sets of four lines with corresponding components having an intensity ratio of ca. 3 as expected from the natural abundances of ^{35}Cl and ^{37}Cl (I = 3/2 for both isotopes). The measured ^{35}Cl and ^{37}Cl hfs of **1c** are probably the largest known for carbon-centred radicals, being greater than the α-Cl hfs and β-Cl hfs of chloroalkyl radicals.[36] The ratio of the hfs of the two isotopes (1.21) was equal to the ratio of their magnetic moments (1.201) to within the experimental error. The decrease in the apparent intensities of the individual component lines towards higher field (Figure 5.13) was reproducible. Similar intensity variation within chlorine multiplets has been observed before and attributed to the modulation by Brownian diffusion of the anisotropic g and hyperfine tensor.[37] Hyperfine interaction from the six bridge hydrogen atoms could not be resolved; as was found for **1b**. The spectrum of **1d** (Figure 5.14) consisted of a single narrowly

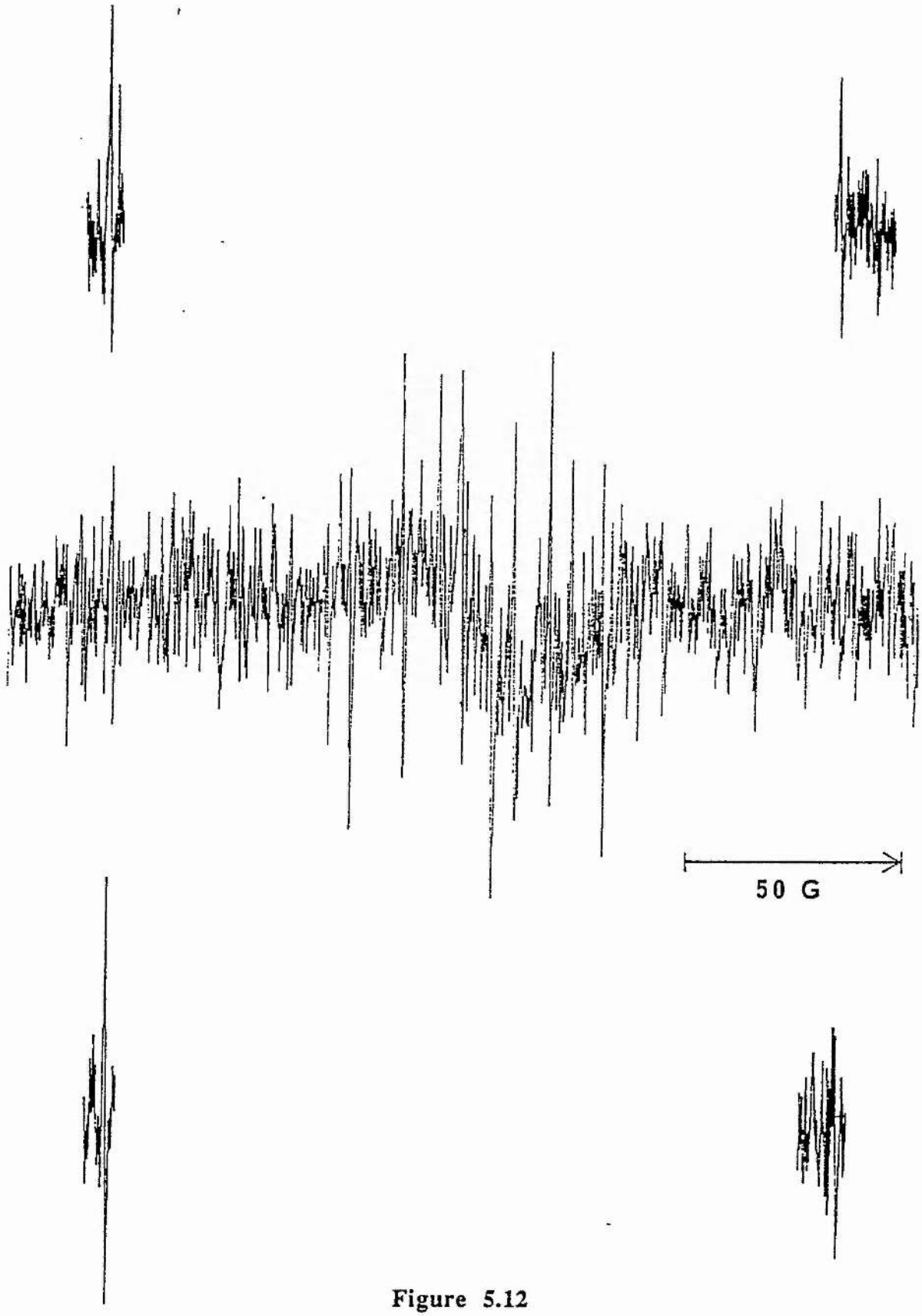


Figure 5.12

9.3 GHz EPR spectrum obtained by bromine abstraction from **3b**, in cyclopropane, at 155K. Spectrum in centre due to the diethylsilylethyl radical.

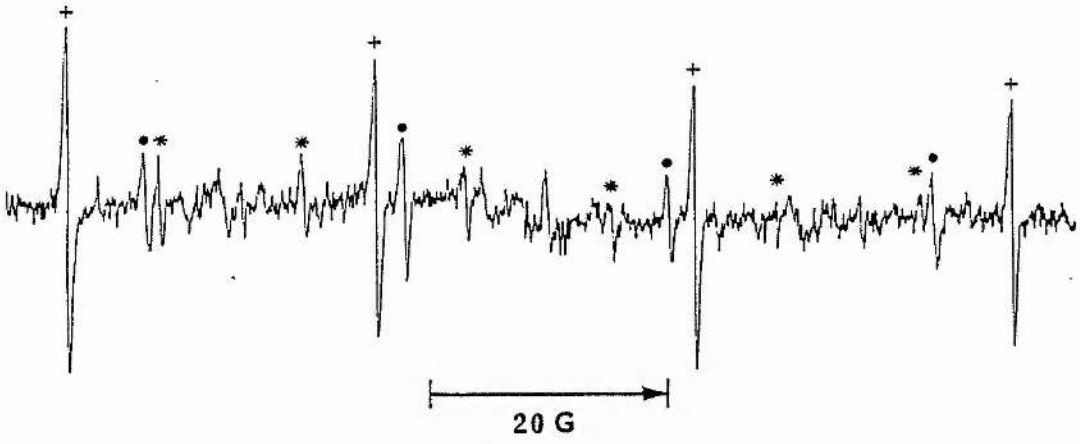


Figure 5.13

9.3 GHz EPR spectrum obtained by bromine abstraction from **3c**, in cyclopropane, at 155K.The four lines of the ^{35}Cl containing radical are indicated with + and the four lines of the ^{37}Cl containing analogue are indicated with • Some of the main resonance lines of $Et_2Si(H)CH^{\bullet}CH_3$ are distinguished by a *.

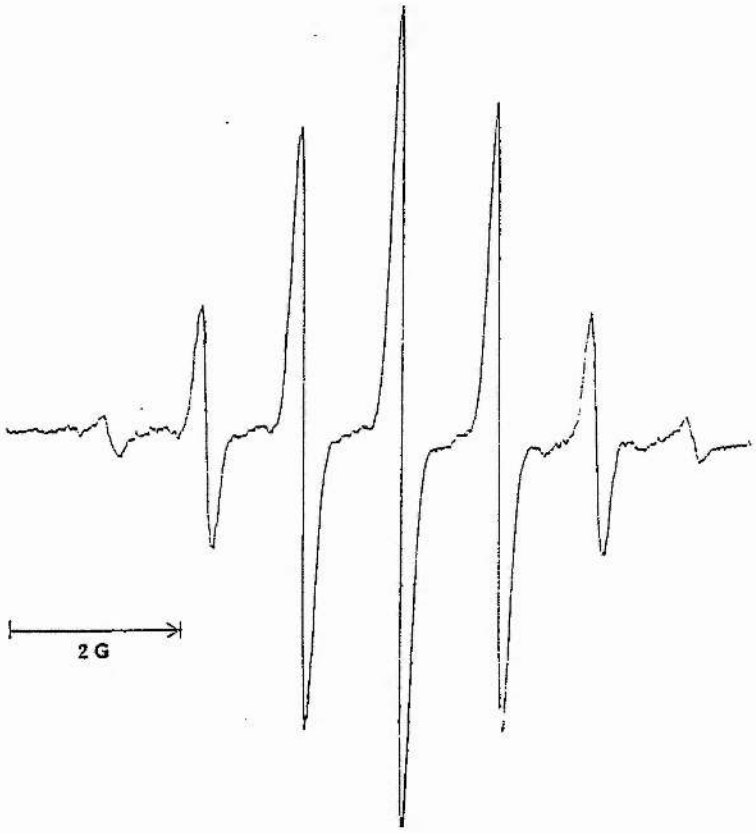


Figure 5.14

9.3 GHz EPR spectrum obtained by bromine abstraction from methyl 3-bromobicyclo[1.1.1]pentane-1-carboxylate, in cyclopropane, at 155K.

Table 5.0. EPR Parameters of 3-Substituted Bicyclo[1.1.1]pentyl Radicals (**1**) at 155K in Cyclopropane.[a]

Radical	X	*a*(6H)	*a*(X)
1a[b]	H	1.2	69.6(H)
1b	F	≤0.5	167.0(F)
1c	^{35}Cl	≤0.2	26.2(^{35}Cl)
1c	^{37}Cl	≤0.2	21.7(^{37}Cl)
1d	CH_3O_2C	1.12	≤0.07(CH_3)

[a] Hfs in gauss, all g-factors 2.003 ± 0.001. [b]Data from ref. 8.

spaced septet which was more intense and longer lasting than the spectra of **1b-c**. The EPR parameters for the series of radicals are collected in Table 5.0.

The exceptionally large magnitudes of the hyperfine couplings from the radical centre to the substituents at C^3 confirm the basic fact of strong cross cage electronic interactions. It is interesting to compare the hfs of the cross cage bridgehead atoms of **1** with analogous bridgehead hydrogens in bicyclo[2.2.2]oct-1-yl radicals **6** and cubyl radicals **7**. In these latter two radicals the cross cage bridgehead C-H bonds are in similar orientations with respect to the radical SOMO i.e. at 180° to the σ-orbital containing the unpaired electron and exactly in line, but at greater distances of ca. 2.44 and 2.67 Å respectively.[38] The experimental EPR hfs of H^4 in **6** and **7** are 2.7 G[39] and 6.3 G[35] respectively. Thus, the hfs are not linearly related to the distance

6

7

Figure 5.15

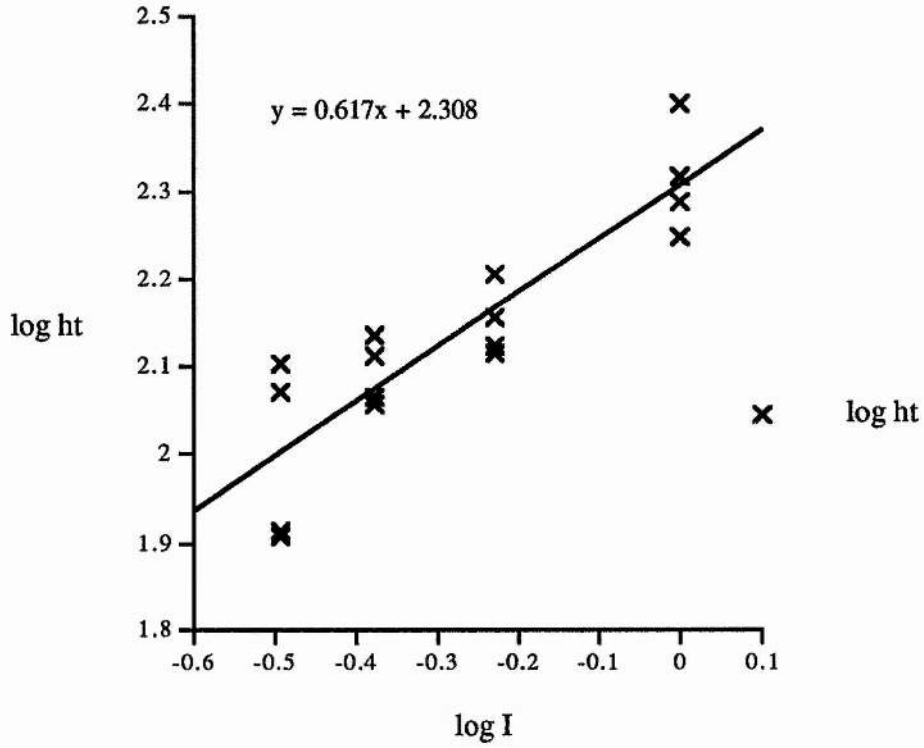
The Bicyclo[2.2.2]oct-1-yl Radical and Cubyl Radical.

separating the radical centre from the hydrogen nucleus. This is not surprising and is in accord with expectations that through bond as well as through space interactions will play important roles in such cage molecules.[40] Through bond transmission of spin density is at a maximum when every bond separating the nucleus from the unpaired electron is *trans* with respect to flanking bonds.[41] This structural situation is present in **1** but not in **6** or **7** and therefore the huge magnitudes of the hfs from substituents at C^3 in **1** result from mutual reinforcement of the short through space distance and the *all trans* through bond orbital overlap. The $a(H^3)$ hfs in **1a** is 11.0 times $a(H^4)$ in **6** whereas the analogous ratios for $a(F)$ and $a(^{35}Cl)$ are 5.7 and 6.1; these differences are a good indication that the strength of the cross cage interaction is substantially modified by the nature of the substituent. A further indication of this comes from the magnitude of the hfs of the six bridge hydrogens in **1** which was strongly reduced by electron withdrawing substituents (Table 5.0). For all four radicals the magnitude of the hfs from these six bridge atoms was very small for β-hydrogens. This is not at all surprising because the C—H_β bonds are orthogonal to the SOMO. The analogous NMR coupling constants between bridgehead hydrogen and the bridge methylenes are also unresolvably small in the corresponding mono-substituted bicyclo[1.1.1]pentanes.[42]

The EPR signals from **1b** were only detectable up to *ca.* 160K but the spectrum from **1c** was observed up to 200K and that from **1d** up to 240K. On shuttering the light beam the spectra of all bicyclo[1.1.1]pent-1-yl radicals decayed instantly, within the spectrometer response time, that is the radical lifetimes were less than about 10^{-3} seconds. Thus, as expected, all the radicals were transient. No spectroscopic evidence of any rearranged species was obtained at higher temperatures. It is probable therefore that radicals **1** take part exclusively in intermolecular processes in the temperature range covered. The spectra from **1b-c** were too weak and short-lived for accurate intensity measurements, but for **1d** the dependence of the radical concentration on incident light intensity was determined by measuring the change in signal height on attenuating the light beam with calibrated gauzes. The signal height and light intensity

Table 5.1. EPR Peak Height Data at Various Light Intensities for Radical **1d**.

$\log_{10}$ (peak height) / mm				Light Intensity	$\log_{10}$
Run 1	Run 2	Run 3	Run 4	I	I
2.401	2.290	2.318	2.248	1.00	0.000
2.124	2.114	2.204	2.155	0.59	-0.229
2.057	2.064	2.111	2.134	0.42	-0.337
1.908	1.914	2.104	2.072	0.32	-0.495

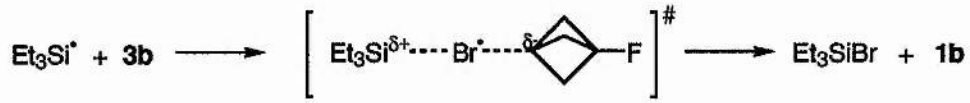


Graph 5.1. Plot of log ht for peak height of the methyl 3-bromobicyclo[1.1.1]pentyl-carboxylate (**3d**) radical against log I for the intensity of the light source, changed by placing calibrated gauzes in the photolysis beam (see experimental section). All four runs were included and the best line fit was calculated by a computational procedure.

data with their corresponding logarithms are displayed in Table 5.1 and in Graph 5.0. The accuracy was limited due to the degradation of the spectra, but a value was obtained of 0.62 ± 0.17 for the exponent of the light intensity, which is not greater than the theoretical value for bimolecular termination (0.5) by more than the experimental error i.e. the main termination(s) of **1d** occurred by radical-radical reactions, but a minor amount of decay by process(es) first order in radical concentration could not be ruled out.

The photochemical reaction of each bridgehead bromide (**3**) with triethylsilane was examined in solution at 200K and products were characterised by NMR and mass spectral analysis. For the 2.4:1 mixture of **3b** and **3a** the products were 1-fluorobicyclo[1.1.1]pentane, fluorotriethylsilane, 2-bromo-2-methylpropane and the silane oxidation product, hexaethyldisiloxane ($Et_3SiOSiEt_3$). The product chromatogram was quite "clean" and all peaks were identified, apart from a minor compound C_5H_7Br, which was probably 3-bromo(methylene)cyclobutane (see Experimental Section) and some minor, long retention time, siloxanes. Thus, neither [1.1.1]propellane **2** nor bicyclo[1.1.1]pentane were present, nor were any dimers of **3b** or cross combination products. Propellane **2** readily polymerises (Section 5.0) and is volatile and therefore might easily have eluded detection. Bicyclo[1.1.1]pentane is volatile but, had significant quantities been formed, it should have been detected (as it is no more volatile than 1-fluorobicyclo[1.1.1]pentane and less so than cyclopropane and both these molecules were readily detected). The proportion of unreacted **3b** in the product mixture was lower than in the starting mixture, i.e. final ratio of **3b** to **3a** was 1.2:1 and this, together with the absence of bicyclo[1.1.1]pentane, indicated that the triethylsilyl radicals *selectively* abstracted bromine from the fluoro-bromide **3b**; this agrees with the absence of the EPR spectrum of **1a**. Thus, our experiments clearly show that the fluoro-radical is formed much more easily than the parent radical. We attribute this to a dramatic kinetic polar effect. There is much evidence of extensive charge transfer in the transition state (TS) for halogen abstraction by the triethylsilyl radical (Figure 5.16).[43] In the case of radical **1b** such a polar TS, i.e. **8**, would be

markedly stabilised by an electrostatic field effect and by through space electron delocalisation (homohyperconjugation, see canonical form **9**).



8

9

Figure 5.16

Charge Transfer in the Transition State (TS)

for Halogen Abstraction by the Triethylsilyl Radical.

The really unprecedented aspect of the reaction was the discovery of fluorotriethylsilane, with possible traces of 1,3-difluorobicyclo[1.1.1]pentane (**11b**). Entirely analogous products, i.e. chlorotriethylsilane and 1,3-dichlorobicyclo[1.1.1]pentane (**11c**), were identified in the reaction of the chloro-bromide **3c**. The main process is the expected chain reduction of the halo-bromides **3b,c** to the corresponding monohalides **10b,c** [reactions (1) and (2), Figure 5.17]. Abstraction of a fluorine atom from the parent bromide **3b** by triethylsilyl radicals is most unlikely on thermodynamic grounds and such a reaction has no precedent. We attribute therefore the formation of the halotriethylsilanes to an unusual termination step in which the triethylsilyl radical abstracts a fluorine (or chlorine) atom from **1b,c** [reaction (3)][44]. Fluorine atom abstractions are rare, but in this case the fluorine atom transfer will be favoured because of the propensity of radical **1b** (and **1c**) to convert to [1.1.1]propellane (see *ab initio* calculations below). Similarly, disproportionation of two halobicyclo[1.1.1]pent-1-yl radicals will give **2** together with the 1,3-dihalides **11b** and **11c** [reaction (4)]. The absence of radical dimers and cross-coupled products

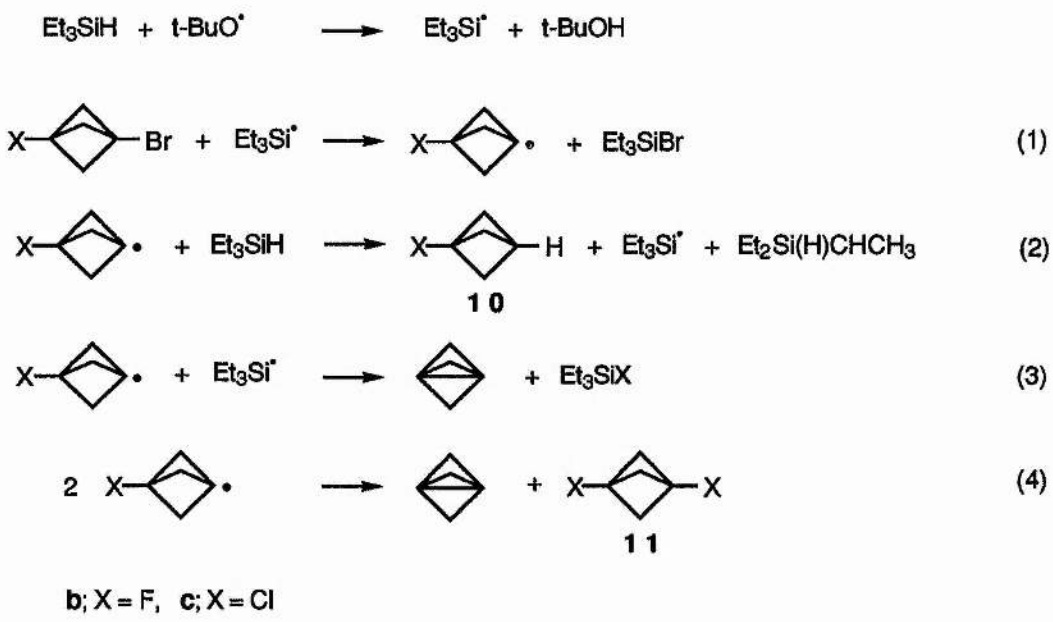


Figure 5.17

suggests that steps (3) and (4) are the main chain terminations under the present experimental conditions. Alternative routes to fluorotriethylsilane such as the production of hydrogen fluoride and its subsequent reaction with triethylsilane [reactions (5) and (6)] are implausible; evidence for hydrogen fluoride formation, such as etching of the quartz tubes, was completely absent.

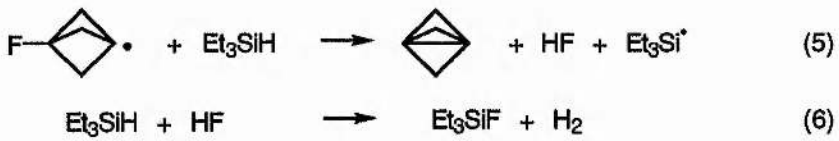


Figure 5.18

The mechanism outlined in Figure 5.17 requires the formation of *tert*-butanol and bromotriethylsilane, whereas 2-bromo-2-methylpropane and hexaethyldisiloxane were detected. It is probable, however, that the former are the initial products which convert to 2-bromo-2-methylpropane and triethylsilanol after admission of air and $CDCl_3$ during analysis. The silanol readily transforms to hexaethyldisiloxane in the presence

of peroxides.[45] The formation of 2-bromo-2-methylpropane and hexaethyldisiloxane in reductions of organobromides with triethylsilane has been observed previously.[46] The bromo-ester reaction products were largely as expected (see Experimental Section).

5.3 *Ab initio* Calculations on Bicyclo[1.1.1]pent-1-yl Radicals and Related Species

The unsubstituted radical **1a** was previously studied by the semi-empirical MINDO/3 method[17] and by several groups using *ab initio* methods.[2,19] With a 6-31G* basis set at the MP2 level, Feller and Davidson found that removal of the first bridgehead hydrogen from bicyclo[1.1.1]pentane cost 444 kJ mol^{-1} but, most interestingly, that loss of the second hydrogen to give [1.1.1]propellane cost only 193 kJ mol^{-1}. Wiberg *et al.*[2] took calculations for **1a** to the MP4 level and found 436 kJ mol^{-1} for removal of the first hydrogen with 1.797 Å as the 1-3 non-bonded, cross cage, distance.

John Wilkie of the University of St. Andrews carried out a number of *ab initio* molecular orbital calculations on 3-substituted bicyclo[1.1.1]pent-1-yl radicals, and related molecules, using the GAUSSIAN 92 series of programs.[47] The computed structure of bicyclo[1.1.1]pentane was the same as that of Wiberg. One important feature was observed on removal of the first bridgehead hydrogens to form the neutral radicals, that being a small trend towards flattening at the radical centres. Thus, in forming bridgehead radicals, the cage structures moved towards that of [1.1.1]propellane, which would be formed on loss of the second bridgehead substituent.

The isotropic hyperfine splittings at the hydrogen nuclei of the bicyclo series along with some other associated radicals were also calculated by J. Wilkie, and as can be seen in Table 5.2, are comparable with experimental hfs. However, comparison with the experimental data indicates that the agreement for ^{19}F and ^{13}C

Table 5.2. Comparison of Computed hfs With Experimental EPR hfs.

Radical	Nucleus	hfs MP2	hfs MP4	hfs exptl/G
H•	H	475	475	507
CH_3•	H	-48.3	-48.3	-23.0
CH_3•	^{13}C	79.7	79.7	38.3
1a	H^3	64.4	60.1	69.6
1a	$^{13}C^1$	106	137	223
1a	H^2	-1.3	-1.5	(±)1.2
1b	F	125	123	167
1b	$^{13}C^1$	138	169	--
1b	H^2	-0.3	0.5	<0.5

computed data is qualitative at best, but that rather better predictions are obtained for hydrogen hfs.

5.4 Conclusions

Substituents at C^3 in bicyclo[1.1.1]pentanes are only a short distance in space from C^1 and can exert a profound influence by a combination of through space and through bond mechanisms. EPR spectra showed that an unprecedentedly large amount of spin density from an unpaired electron produced at C^1 reaches substituents at C^3. Competitive experiments of several types with 1-bromo-3-fluorobicyclo[1.1.1]pentane showed that the fluorine substituent exerted a powerful activating kinetic polar effect on bromine atom abstraction. It is probable that analogous polar effects will operate in homolytic reactions of 3-substituted bicyclo[1.1.1]pent-1-yl radicals. *Ab initio* MO theory predicted that 3-methyl and 3-fluoro substituted bicyclo[1.1.1]pent-1-yl radicals

would easily undergo γ-scission to [1.1.1]propellane with loss of the substituent. Experimental evidence was forthcoming for the easy loss of the 3-fluorine atom in a novel disproportionation process.

5.5 Experimental Section

EPR spectra were recorded with a Bruker ER 200D spectrometer operating at 9.3 GHz with 100 kHz modulation. Solution phase samples were prepared in Spectrosil tubes, degassed, and photolysed in the microwave cavity by light from a 500-W super pressure Hg lamp. The incident light intensity was varied by placing calibrated gauzes in the photolysis beam. The amplitude of a single resonance line from the 3-carbomethoxybicyclo[1.1.1]pent-1-yl radical was rapidly recorded as a function of incident light intensity. The normal slow reduction in signal amplitude with time of photolysis was compensated for by averaging sets of experiments carried out with increasing and decreasing light intensity. Only the spectra of 3-carbomethoxybicyclo[1.1.1]pent-1-yl were sufficiently strong and long lasting for successful application of this procedure. Radical *g* factors were measured relative to the known values for the cyclopropyl and $Et_2Si(H)CH^{\bullet}CH_3$ radicals.

Photochemical reaction of 1-bromo-3-fluorobicyclo[1.1.1]pentane (3b) with triethylsilane. A mixture containing 1-bromo-3-fluorobicyclo[1.1.1]pentane and 1-bromobicyclo[1.1.1]pentane (40 µl mol. ratio 2.4:1) and ca. 5% 1-bromo-1-chloro-2,2,2-trifluoroethane was combined with triethylsilane (20µl) and di-*tert*-butylperoxide (30µl) and passed through a short plug of neutral alumina into a quartz tube (dia. 4 mm). Cyclopropane (*ca.* 500µl) was distilled in and the solution was degassed by a series of freeze-pump thaw cycles before flame sealing. The mixture was photolysed with unfiltered light from a 500-W super pressure Hg arc for 90 min at -73°C. The reaction was monitored by EPR spectroscopy at -118°C during the first 10 min, which showed the 3-fluoro radical but none of the unsubstituted radical derived from the minor amount of unsubstituted bromide. The tube was cooled, opened, and suspended in a Dewar just above liquid nitrogen so that the cyclopropane slowly evaporated over ca. 3h. $CDCl_3$ (1 mL) containing TMS and CCl_3F was added and the product mixture was examined by NMR spectroscopy and GC/MS. The spectra

showed all the solvents and reference standards together with unreacted 1-bromo-3-fluorobicyclo[1.1.1]pentane and 1-bromobicyclo[1.1.1]pentane in a mol ratio (estimated from the ^{1}H NMR spectrum) of 1.2:1; i.e. *selective* consumption of the fluoro-derivative was indicated. The products, listed in order of GC elution, were as follows. 1-Fluorobicyclo[1.1.1]pentane, ^{19}F NMR δ_F -133.4(dspt, J = 70.2, 3.0 Hz), ^{1}H NMR δ_H 2.04(d, 6H, J = 3.0 Hz), 2.42(d, 1H, J = 70 Hz) lit.[42,48] EIMS *m/z* (rel intensity) 86 (M^+, 6), 85 (59), 71 (16), 66 (18), 65 (28), 60 (25), 59 (100), 57 (19), 53 (24), 41 (43), 40 (41), 39 (79). 2-Bromo-2-methylpropane; ^{1}H NMR and MS essentially identical to the literature. Fluorotriethylsilane, ^{19}F NMR δ_F -176.4 (sep, J = 6.1 Hz) lit.,[49] EIMS *m/z* (rel intensity) 134 (M^+, 8), 105 (74), 77 (100), 49 (24), 47 (30), 43 (30), 41 (12). The ^{1}H and ^{13}C NMR spectra were very weak and/or overlapped by signals from ethyl groups of triethylsilane and other products. A minor unidentified component with a MS similar to that of 1-bromobicyclo[1.1.1]pentane; possibly 3-bromo-methylenecyclobutane. Hexaethyldisiloxane, with ^{1}H, ^{13}C NMR and MS spectra in accord with the literature. The GC/MS showed no other products, apart from some minor, long retention time Si-containing compounds. The ^{19}F NMR spectrum showed an additional, very weak, signal at -217 ppm which we attribute to 1,3-difluorobicyclo[1.1.1]pentane. This compound was not observed on the GC/MS but could have been obscured by the large solvent and reactant peaks.

Photochemical reaction of 1-bromo-3-chlorobicyclo[1.1.1]pentane (3c) with triethylsilane. The reaction was carried out as described above for the 3-fluoro compound. The chromatogram showed all the solvents and reactants including 1-bromo-3-chlorobicyclo[1.1.1]pentane. The products, listed in order of GC elution, were as follows. 2-Bromo-2-methylpropane; ^{1}H NMR essentially identical to the literature (this compound was not observed on the GC/MS because it was obscured by the large $CDCl_3$ peak). 1-Chlorobicyclo[1.1.1]pentane, ^{1}H NMR δ_H 2.79 (s, 1H), 2.18 (s, 6H), ^{13}C NMR δ_C 49.58 (CCl), 56.81 (CH_2), 24.69 (CH), EIMS *m/z* (rel intensity) 103 (M^+, 1), 67 (100), 66 (31), 65 (53), 53 (10), 41 (70), 40 (29), 39 (82),

27 (27). A minor unidentified component with a MS similar to that of 1-chlorobicyclo[1.1.1]pentane; possibly 3-chloromethylenecyclobutane. A minor peak with *m/z* (rel intensity) 103, 101 ([M-Cl]$^+$, 9, 27), 75 (8), 65 (100), 61 (17), 49 (11), 40 (15), 39 (51), 38 (17) which we identify as 1,3-dichlorobicyclo[1.1.1]pentane. 1-Bromobicyclo[1.1.1]pentane, *m/z* (rel intensity) 148, 146 (M$^+$, 4, 5), 67 (100), 65 (18), 41 (38), 40 (33), 39 (51), 27 (16). Chlorotriethylsilane, *m/z* (rel intensity) 150 (M$^+$, 7), 123 (40), 121 (94), 95 (30), 93 (100), 92 (16), 65 (44), 63 (28), 28 (17); the ^{1}H and ^{13}C NMR spectra were very weak and/or overlapped by signals from ethyl groups of triethylsilane and other products. Hexaethyldisiloxane, with ^{1}H, ^{13}C NMR and MS spectra in accord with the literature was again a major side product of the reaction. Longer t_R components included a series of minor siloxanes but no dimers or cross-coupled products were observed.

Photochemical reaction of methyl 3-bromobicyclo[1.1.1]pentane-1-carboxylate (3d) with triethylsilane. The reaction was carried out as described above for the 3-fluoro compound. The spectra showed all the solvents and the reference standard together with the reduction product methyl bicyclo[1.1.1]pentane-1-carboxylate, ^{1}H NMR δ_H 3.67 (s, 3H), 2.43 (s, 1H), 2.11 (s, 6H), ^{13}C NMR δ_C 42.40 (C1), 51.59 (C2), 27.65 (C3), 51.28 (CH_3), 169.90 (CO), EIMS *m/z* (rel intensity) 125 ([M-1]$^+$, 2), 111 (9), 95 (13), 83 (13), 67 (100), 66 (49), 65 (42), 41 (83), 39 (70). The NMR spectral properties of this ester were identical to those of an authentic sample.[48] The conversion was high in this case and the only other products which could be identified with certainty were 2-bromo-2-methylpropane and hexaethyldisiloxane. A minor unidentified bicyclo[1.1.1]pentyl derivative, possibly the dimer was also detected.

Chapter 6

The Chemistry of 4-Substituted Bicyclo[2.2.2]oct-1-yl Radicals

6.0 Bridgehead Radicals

Bridgehead radicals possess rigid molecular frameworks, with bond angles and dihedral angles which are fixed. These well defined structures are often unusual with abnormal bond lengths and angles, especially when the molecule is highly strained, as was the case shown in the previous chapter. Further to this work it was decided to study species with structures similar to the bicyclo[1.1.1]pentyl radical. The bridgehead radicals discussed in this chapter are the bicyclo[2.2.2]oct-1-yl radicals and the triptycyl radicals. These are two of the three different limiting types of bridgehead radicals.[50] The bicyclo[2.2.2]oct-1-yl radical is in the same distinguishing group as the bicyclo[1.1.1]pent-1-yl radical, discussed in the previous chapter, that being the β-methylene type in which the radical centre is directly bonded to three methylene groups. The triptycyl radical is a β-quarternary type of bridgehead radical, that is the radical bridgehead is flanked by quarternary carbon atoms. These bridgehead radicals are different to other tertiary radicals in many ways.

Spectroscopic and theoretical studies have shown that the simple alkyl radicals are not strictly planar, and that the *tert*-butyl radical has a degree of pyramidal character.[51-54] However, the difference in energy between the planar and pyramidal forms of simple carbon free radicals is actually quite small,[54] so that for all intents and purposes the *tert*-butyl radical can be assumed to be planar. In contrast, bridgehead radicals are permanently pyramidal, and can neither undergo inversion nor become planar. Consequently, they are expected to be less stable than the corresponding acyclic tertiary radicals. In bridgehead radicals the β-carbons of the bridgehead are "held back", leaving the radical centre sterically uncongested and vulnerable, increasing their reactivity. Another important factor which sets bridgehead radicals aside from acyclic tertiary radicals is the inability of the former to undergo hyperconjugation. In the bicyclo[2.2.2]oct-1-yl case, the hyperconjugative structure would contain an alkene with a single bridgehead (Figure 6.0 (b)), while the triptycyl radical would be incapable of hyperconjugation. However the increased stability of the *tert*-butyl radical over

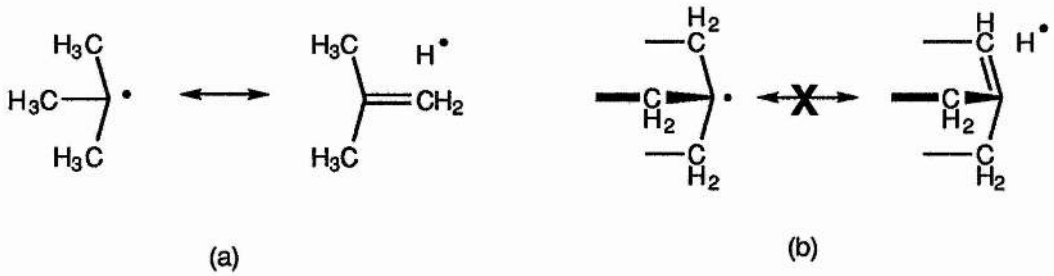


Figure 6.0

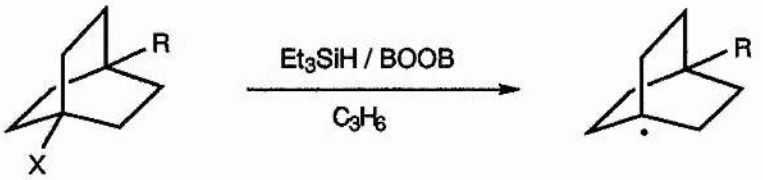
Hyperconjugation of the *tert*-Butyl Radical (a) and the High Energy Bridgehead Alkene Formed on Hyperconjugation of B–Methylene Type Bridgehead Radical (b).

primary aliphatic radicals is generally attributed to hyperconjugative effects (Figure 6.0(a)).

6.1 EPR Spectra of 4-Substituted Bicyclo[2.2.2]oct-1-yl Radicals

All of the 4-substituted bromobicyclo[2.2.2]octanes were synthesised by Bill Adcock and co-workers at Flinders University in Australia and were prepared according to known literature procedures. The primary aim was to study the bridgehead radical of the tricyclic system, and to analyse the effect the 4-substituent has on the resulting spectrum. As has been discussed in previous chapters, the generation of the radicals, by bromine atom abstraction, is a well used procedure with photochemically produced trimethyltin and triethylsilyl radicals being used. In the case of the compounds examined here triethylsilyl radicals were used (produced by hydrogen abstraction from triethylsilane with photochemically generated *tert*-butoxyl radicals) to abstract the bromine atoms. To obtain a clean spectrum of the bridgehead radical, a solvent was needed that would be unreactive towards the resulting radical. Again cyclopropane was the solvent used for these studies as it has the advantage of having a low freezing point and thus behaves well in the temperature range at which these radicals are observed. A difficulty encountered with most of the bromides was their low solubility in hydrocarbon solvents at 150K which meant they crystallised out

of solution during the course of the experiment. In several cases ca. 10% benzene was added to the mixture to improve solubility, but even then the spectra lasted for only a short period of time (<5 min) and rapid spectral accumulation was necessary. The amount of added triethylsilane had to be kept to a minimum as otherwise the signals of the diethylsilylethyl radical [$Et_2Si(H)CH^{\bullet}CH_3$] dominated the spectrum.



R = H, Me, CMe_3, $CH{=}CH_2$, C≡CH, Ph, CN, CO_2Me,
OMe, NMe_2, NO_2, F, Cl, Br, $SnMe_3$, $GeMe_3$, $SiMe_3$

Figure 6.1

Generation of 4-Substituted Bicyclo[2.2.2]octyl Radicals.

The 4-substituted bromobicyclo[2.2.2]octanes examined and discussed in this section, are shown in Figure 6.1, with the EPR spectra of some of the corresponding radicals being displayed in Figures 6.2 to 6.5. With the exception of the 4-carbomethoxybicyclo[2.2.2]octyl radical, all of the EPR spectra degraded quite quickly. Also investigated was 1-iodobicyclo[2.2.2]octane which showed no spectrum on photolysis with the same reagents.

The hfs for the 4-substituted bicyclo[2.2.2]octyl radicals are displayed in Table 6.0. As can be seen, the variations in magnitude of the hfs of the β-hydrogens and γ-hydrogens are small as the substituent at the 4-position is changed, and there is no discernible trend to these hfs changes. Also, neither the β-hydrogen nor the γ-hydrogen hfs correlate with the Hammett σ_p or σ_I parameters of their corresponding 4-substituents (this result is consistent with the work done on the 4-substituted cubyl radicals).[55] In general the radicals formed, produced strong, well-defined spectra with

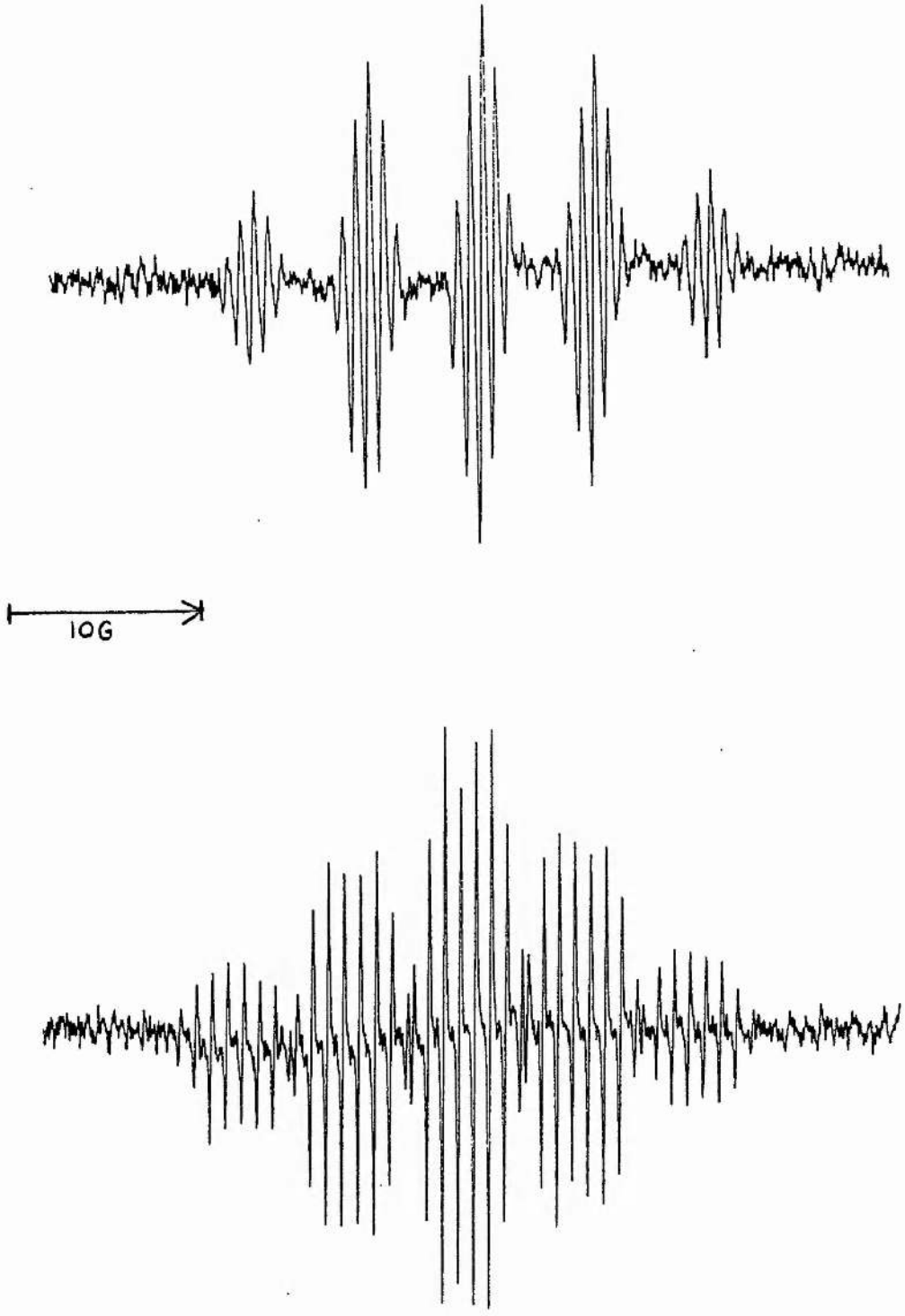


Figure 6.2 and 6.3

Top: 9.3 GHz EPR spectrum obtained by bromine abstraction from 1-bromo-4-methylbicyclo[2.2.2]octane, in cyclopropane, at 170K.

Bottom: 9.3 GHz spectrum obtained from 1-bromobicyclo[2.2.2]octane.

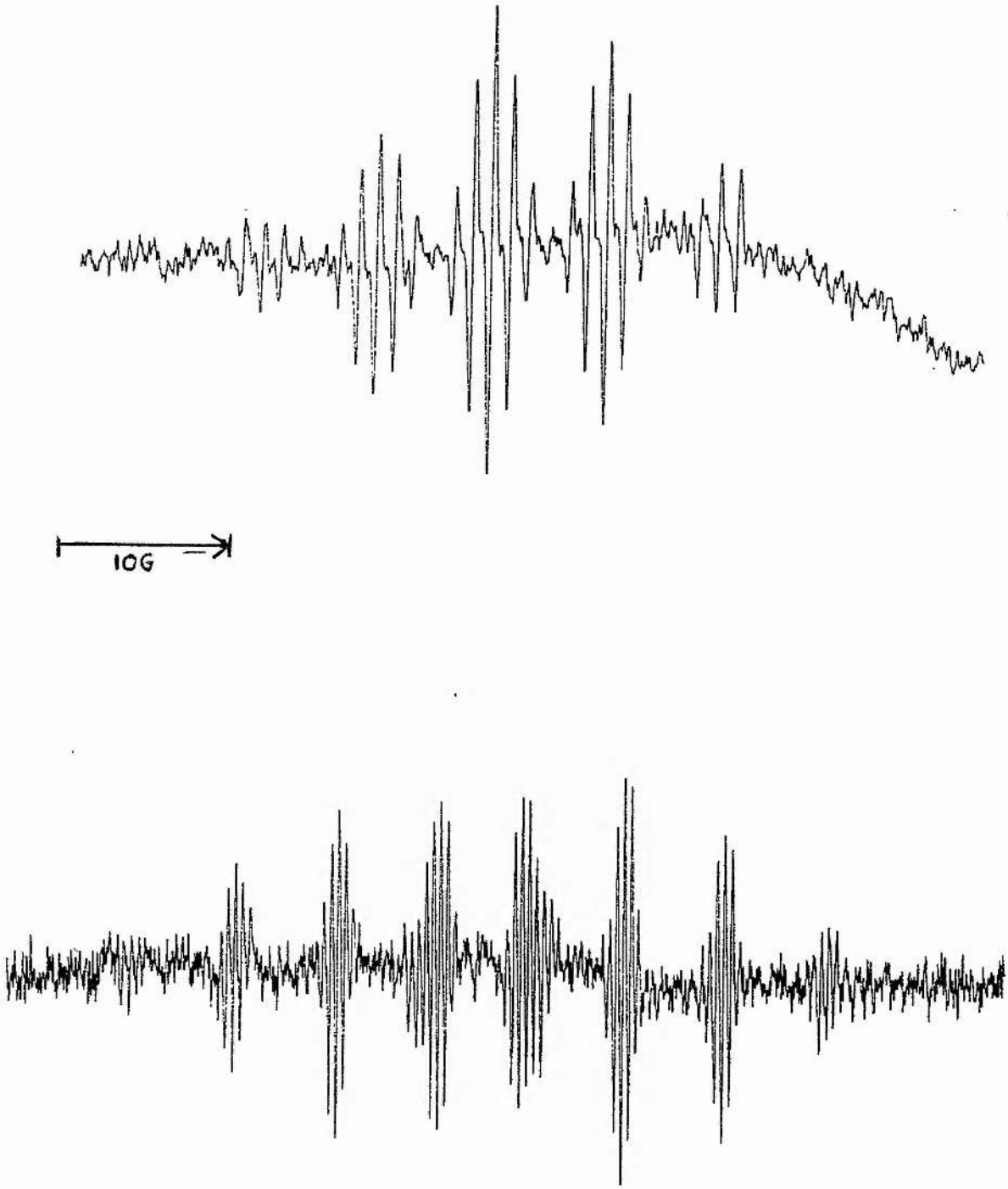


Figure 6.4 and 6.5

Top: 9.3 GHz EPR spectrum obtained by bromine abstraction from 1-bromo-4-trimethyltinbicyclo[2.2.2]octane, in cyclopropane, at 170K.

Bottom: 9.3 GHz spectrum obtained from 4-fluoro-1-bromobicyclo[2.2.2]octane.

hfs being observed not only for the β-hydrogens and γ-hydrogens but also, in some instances, for atoms in positions even further from the radical centre. For example a doublet splitting was clearly visible for the δ-hydrogen of the unsubstituted radical (a(1H) = 2.55G) , as shown in Figure 6.3, and for the δ-fluorine of the fluoro-

Table 6.0. Hfs of Various 4-substituted Bicyclo[2.2.2]octyl Radicals.

4-substituent (-R)	$a(6H_\beta)$/ Gauss	$a(6H_\gamma)$/ Gauss	a(R)/ Gauss
-H	6.70	0.85	a(1H)=2.55
-Me	6.50	0.70	a(3H)≤0.1
$-CMe_3$	6.70	0.72	-
$-CH=CH_2$	6.60	[0.85][a]	b
-C≡CH	6.60	[0.80][a]	[a(1H)≈0.2][a]
-Ph	6.49	0.73	-
-CN	6.70	0.70	-
$-CO_2Me$	6.60	0.72	-
-OMe	6.20	0.53	-
$-NMe_2$	[6.70][a]	[<0.50][a]	[a(N)=3.0][a]
$-NO_2$	c		
-F	6.20	0.44	a(F)=17.20
-Cl	d		
-Br	6.60	0.71	-
$-SnMe_3$	6.85	1.10	-
$-GeMe_3$	6.86	0.97	-
$-SiMe_3$	6.81	0.91	-

[a] Tentative assignments. [b] Complex of unresolved long range hfs. [c] Two nitroxide radicals apparently formed (major a(N)=28.4G; minor a(N)=9.8G). The major nitroxide is probably the silyloxy-*tert*alkyl nitroxide, $Et_3SiON(O^\bullet)CR_3$. [d] Complex spectrum too weak for assignment of hfs.

substituted radical (a(F) = 17.20G), shown in Figure 6.5. In the case of the latter, the hfs obtained can be seen to be of a similar magnitude to the value acquired on investigation of the 4-fluorocubyl radical (a(F) = 29.1G),[56] also a δ-substituent. It can also be perceived to be significantly smaller than the massive splitting of the γ-fluorine in the case of the 3-fluorobicyclo[1.1.1]pentyl radical (a(F) = 167G). Unfortunately, further to this point, the 4-chloro substituted bromide was found to be too insoluble in cyclopropane for a spectrum to be obtained and so no hfs from the δ-chlorine could be observed and compared to the 3-chlorobicyclo[1.1.1]pentyl radical or the 4-chlorocubyl radical. In the case of the ethynyl substituted radical a complex set of hfs was observed with a small splitting due to the ζ-hydrogen (a(H) ≈ 0.2G). In the vinyl substituted radical the long range coupling was even more apparent with the single ε-hydrogen and the two ζ-hydrogens, all in different environments, producing an EPR spectrum that was of exceptional complexity.

1-Bromo-4-nitrobicyclo[2.2.2]octane did not give the intended bridgehead radical on photolysis in the EPR cavity; instead two nitroxide radicals were observed. The nitroxide with a small weak signal (a(N) = 9.8G) was not identified. The nitroxide with the stronger signal had a much larger nitrogen hfs (a(N) = 28.4G). From the literature[57] it was known that t-butoxy phenyl nitroxide has a splitting of about 14.7G and is approximately of equal size to the splitting obtained from phenyl triethylsilyloxy nitroxide (a(N) = 14.76G)[58] i.e. the silyl moiety has little effect on the EPR spectra.

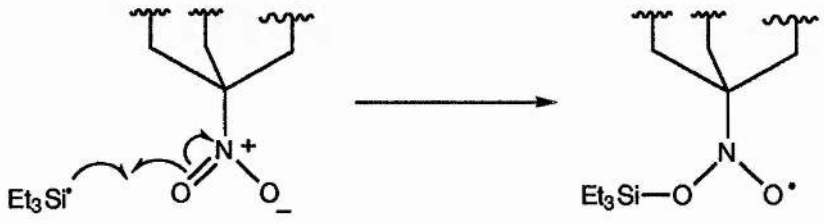


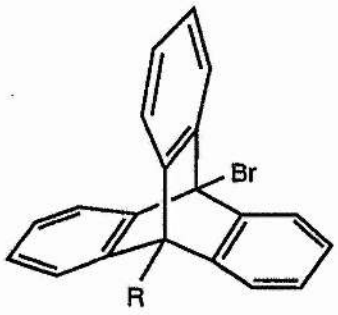
Figure 6.6

Formation of the Nitroxide.

Therefore if it is known[59] that the splitting from *tert*-butyl *tert*-butoxy nitroxide is 28.3G it can be reasonally assumed that the splitting for a silyloxy-*tert*-alkyl nitroxide would be of similar size, i.e. 28.4G. From this reasoning it was deduced that the major radical present was the 4-bromobicyclo[2.2.2]octyl triethylsilyloxy nitroxide The formation of this nitroxide can be accounted for by the reaction of the triethylsilyl radical with the nitro group of 4-nitrobromobicyclo[2.2.2]octane (Figure 6.6).

6.2 9-Triptycyl Radicals

In addition to the investigation of bicyclo[2.2.2]oct-1-yl radicals and the effects the C4 substituent has on the radical centre it was deemed of interest to examine bromine abstraction from compounds with structures relating to bicyclo[2.2.2]octane. Therefore a series of 10-substituted 9-triptycyl radicals was generated by bromine atom abstraction from the appropriate 9-substituted bromides.[60] The triptycyl compounds



R = H, Me, F, $SnMe_3$

Figure 6.7

10-Substituted 9-Bromotriptycene.

are structurally similar to bicyclo[2.2.2]octane and are thus included in this chapter for comparison with the bicyclo[2.2.2]oct-1-yl radicals.

Triethylsilyl radicals in cyclopropane were again used to abstract the bromine atoms. Although all the triptycyl compounds were very insoluble in cyclopropane solution enough was dissolved for a spectrum to be observed. However, as was

noticed in the case of the bicyclo[2.2.2]oct-1-yl radicals, the bicyclic bridgehead radicals produced initially degraded rather quickly. All four compounds, apart from the methyl substituted bromotriptycene, gave a simple spectrum containing two singlets of differing line width, indicating that two radicals were present in the EPR cavity (Table 6.1). However one of the singlets had a g value equal to 2.005±0.001 that indicated it was not a carbon based radical. The broader singlet was centred about the expected value and was presumed to be the 10-substituted 9-triptycyl radical. The methyl substituted

Table 6.1. Position of Singlets Observed by EPR on Photolysis of the Triptycene Compounds.

10-Substituent	Broad Singlet		Sharp Singlet	
	g value	ΔH_{pp} (G)	g value	ΔH_{pp}
H[a]	2.003±0.001	0.7	2.0048	0.3
Me[a,b]	2.003±0.001	0.7	-	-
F[c]	2.003±0.001	0.7	2.005±0.001	0.3
$SnMe_3$	2.003±0.001	0.6	2.005±0.001	0.2

[a] Observed 7 line spectrum (a(6H)=5.6G) with EPR parameters identical to triethylsilyl radical. [b] Another radical observed g = 2.003±0.001, a(1H)=22.2G and a(4H)=25.0G probably due to $RCH_2CH^{\bullet}CH_2R$. [c] Sharper than other narrow singlets at g = 2.005.

triptycene showed the 10-methyl 9-triptycyl radical but not the non-carbon based radical.

The observation in each case of a singlet at g = 2.003 indicated that no splitting was evident for the substituent at C4, for any of the triptycyl radicals investigated. This result does not correlate with the hfs obtained for the bicyclo[2.2.2]octyl radicals, especially in the case of the fluorine substituted radical. Therefore, it must be concluded that the triptycyl radicals transmit spin density from the SOMO at C1 much less effectively, via the aromatic nuclei, to the various substituents at C4, than do the

analogous bicyclo[2.2.2]octyl radicals via their bis methylene bridges.

6.3 Homolytic Substitution Reactions

The remainder of this chapter is an EPR investigation of the addition of 4-substituted bicyclo[2.2.2]octyl radicals to a variety of aromatics.

6.3.1 Introduction

From early studies,[61] it was known that the nucleophilicity of secondary alkyl radicals was more pronounced than in primary radicals. It was found that tertiary radicals were difficult to investigate due to their tendency to disproportionate rather than to undergo substitution reactions. Further studies[62] on the alkylation of protonated heteroaromatic bases showed that tertiary radicals do effect aromatic substitution and are more nucleophilic than secondary radicals.

Marcello Tiecco investigated the reactivity of tertiary radicals, concentrating on the radical generated at the bridgehead position of tricyclic systems. Two points in particular made tertiary bridgehead radicals interesting. Firstly their structure would be of higher energy than an aliphatic tertiary radical; secondly and more importantly the rigidity of the system will block disproportionation. Tiecco's initial work[63] on aromatic nucleophilic substitution looked at three bridgehead radical systems (1-bicyclo[2.2.1]heptyl, 1-bicyclo[2.2.2]octyl and 1-adamantyl, Figure 6.8) and investigated their relative reactivity with *p*-difluorobenzene.

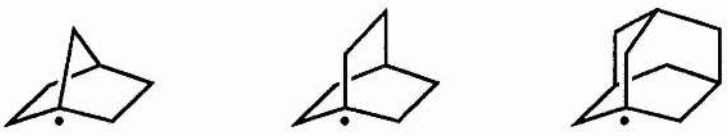


Figure 6.8

The 1-Bicyclo[2.2.1]heptyl, 1-Bicyclo[2.2.2]octyl and 1-Adamantyl Radicals.

It was noted that the reaction yielded mainly the homolytic hydrogen substituted product, although an ipso substitution reaction, whereby one of the halogen atoms of p-difluorobenzene was replaced, occured to a very small extent. Tiecco's later work on ipso substition concentrated particularly on the reactions of the 1-adamantyl radical.[64-69]

6.3.2 Ipso Attack and Substitution

The term 'ipso' originates from that used by Perrin and Skinner[70] to denote a substituted position in an aromatic ring but it is now commonly used to describe a displacement of a group other than hydrogen. Ipso attack has mostly been studied for nitration of monosubstituted benzenes,[71] the result of the ipso attack is displacement of a substituent by an incoming radical. Certain factors govern the fate of the ipso intermediate directing it towards the ipso substitution product, the return of the starting materials, or other products, depending largely on the substituent in the aromatic ring.

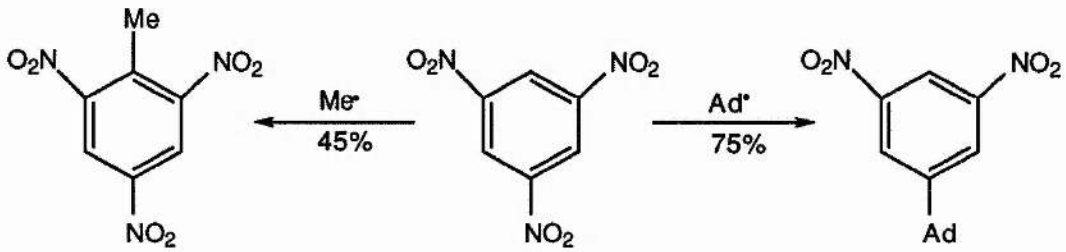


Figure 6.9

Ipso and Hydrogen Substitution by Different Radicals.

Ipso substitution is the mechanism occuring in not only nucleophilic aromatic substitutions but also in electrophilic substitutions.[72] Radical ipso substitution was studied in great depth by Tiecco and co-workers,[73] and interesting results were obtained. For example, 1,3,5-trinitrobenzene would form the expected 2,4,6-trinitrotoluene when allowed to react with methyl radicals; however when reacted with the bridgehead adamantyl radical (Ad•), the ipso substitution product, 1-(1-adamantyl)-

75% yields.[68]

X = NO_2, CN, SO_2R, CO_2Me, COMe, CHO

Figure 6.10

Ipso Substitution of 1-Adamantyl Radicals.

1-Adamantyl radicals also effect alkyldenitration in nitrobenzenes, provided that the aromatic ring is rendered sufficiently electron deficient by the presence of an electron-withdrawing substituent, usually situated in the *para* position.

6.3.3 Hydrogen Substitution of Bridgehead Radicals to Aromatics

Bicyclo[2.2.2]oct-1-yl radicals abstract hydrogen readily and comparatively unselectively. Evidence for this comes from the observation of the $Et_2Si(H)CH^{\bullet}CH_3$ radical, derived from the bridgehead radical abstracting hydrogen from the ethyl groups in competition with abstraction of the silyl hydrogen.

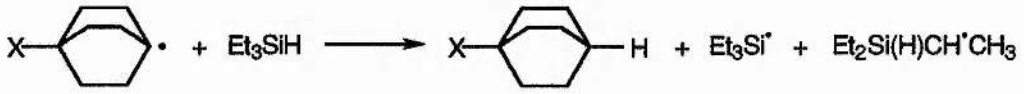


Figure 6.11

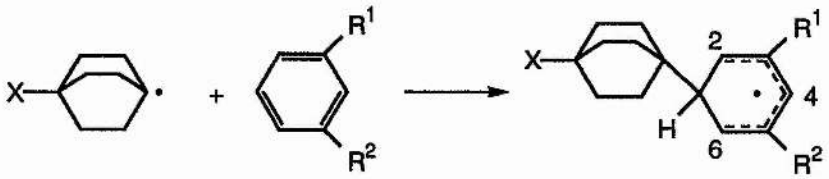
Formation of the Diethylsilylethyl Radical.

Other bridgehead radicals including cubyl,[74] norcubyl[75] and bicyclo[1.1.1]pent-1-yl[76] also produce this radical.

When a bicyclo[2.2.2]octyl bromide together with triethylsilane and peroxide

was photolysed in t-butylbenzene solvent, the main species detected by EPR spectroscopy was found to be a cyclohexadienyl radical. Similar spectra showing one large and four smaller doublet hfs were obtained with fluorine, hydrogen and tin as the 4-substituent. These spectra were obviously due to addition of some radical *meta* to the t-butyl substituent of the solvent to give the corresponding cyclohexadienyl radical **A**. Similar spectra were obtained when hexamethylditin was used in place of Et_3SiH/peroxide, so the radical which adds is not $Et_3Si^{\bullet}$ but is almost certainly the bicyclo[2.2.2]octyl radical. Cyclohexadienyl radicals were also observed with 1,3-di-t-butylbenzene as solvent and a very weak spectrum was obtained in benzene itself. The EPR parameters from these radicals are listed in Table 6.2. The EPR spectrum of 1-(trimethylsilyl)-3,5-di-t-butylcyclohexadienyl has been reported[77] and its EPR

Table 6.2. EPR parameters of cyclohexadienyl radicals formed by addition of bridgehead radicals (bR$^{\bullet}$) to aromatics[a]



A

X = ·	R^1	R^2	H^1	H^2	H^3	H^4	H^5	H^6
F	H	H	30.9	8.9	2.7	13.2	2.7	8.9
F	t-Bu	H	42.1	8.1	-	13.1	2.8	9.2
H	t-Bu	H	42.6	8.1	-	13.1	2.8	9.0
H[b]	t-Bu	t-Bu	40.7	8.6	-	13.0	-	8.6
Sn[c]	t-Bu	H	42.8	8.4	-	13.1	2.8	9.1

[a] Hfs (in G) essentially independent of temperature in the range 220-300K, all g-factors 2.003±0.001. [b] Figure 6.12. [c] Figure 6.13.

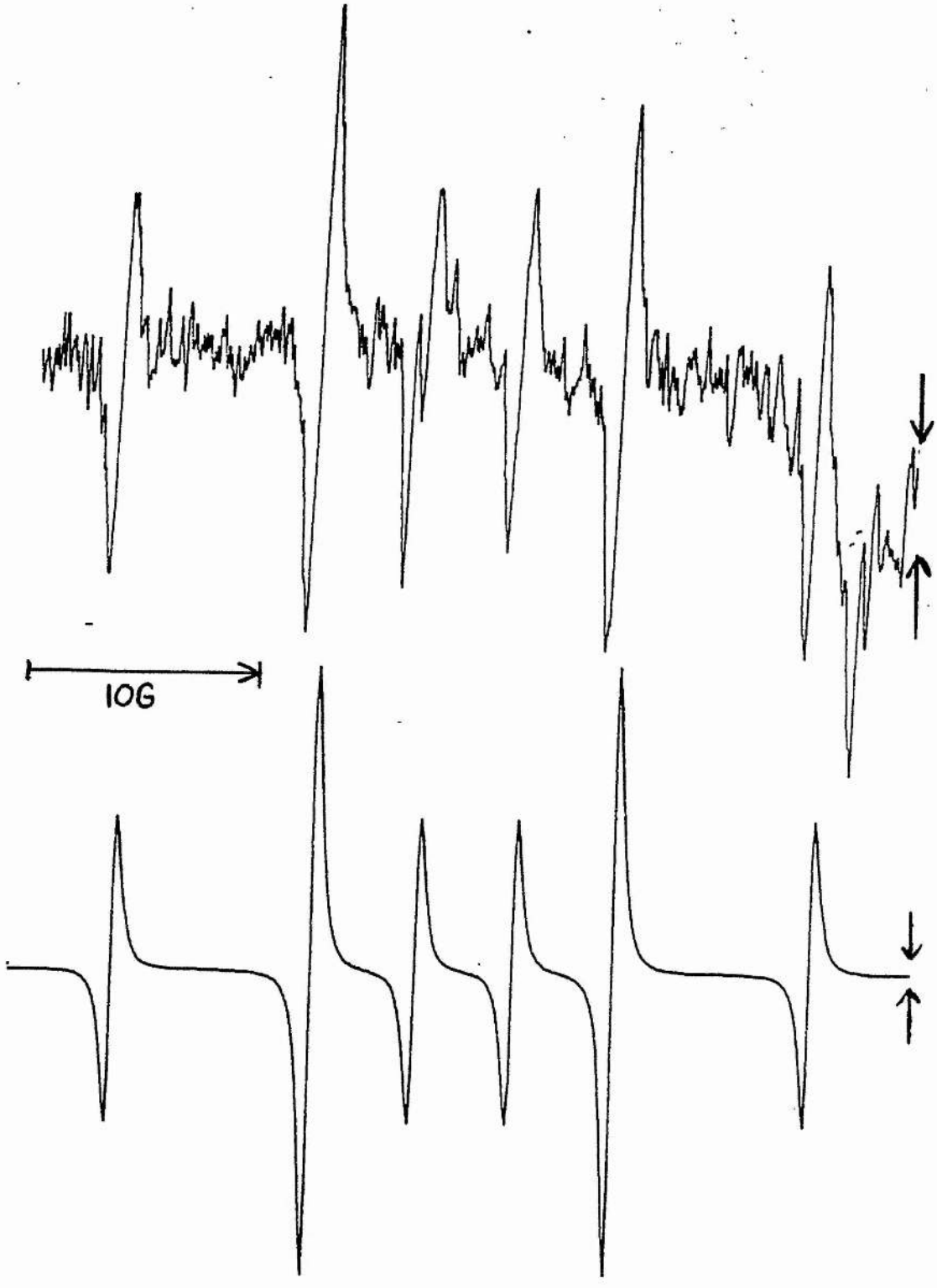


Figure 6.12

Top: Low field half of the 9.3 GHz EPR spectrum obtained by the addition of the bicyclo[2.2.2]oct-1-yl radical to 1,3-di-*tert*-butylbenzene. Arrows indicate the centre of the spectrum. Bottom: Computer simulation of the same radical (see Table 6.2).

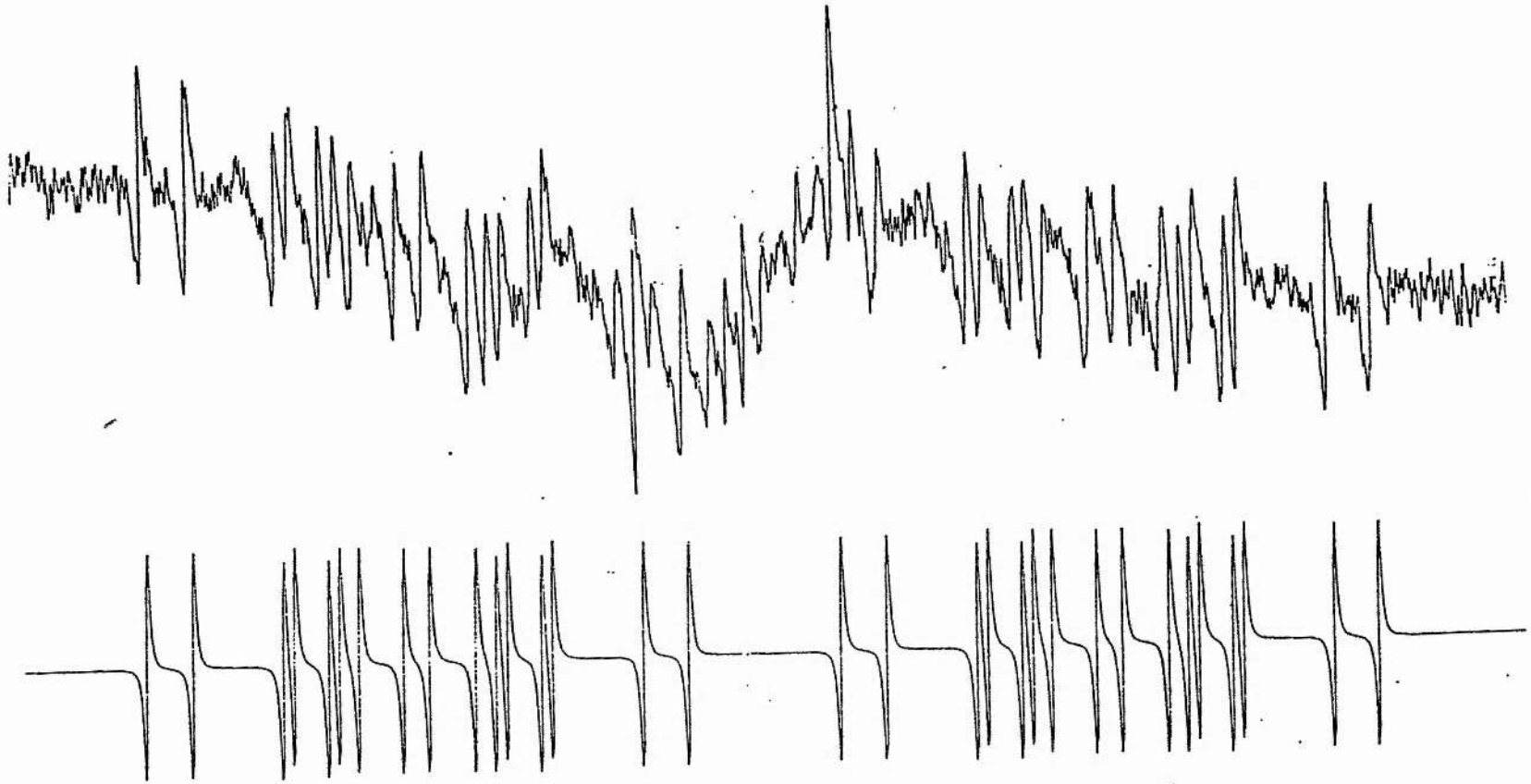


Figure 6.13

Top: 9.3 GHz EPR spectrum obtained by the addition of the 4-(trimethylstannyl)-bicyclo[2.2.2]oct-1-yl radical to *tert*-butylbenzene.

Below: Computer simulation of the same radical using the hfs in Table 6.2.

parameters are significantly different from analogous spectra in Table 6.2 which confirms that these spectra are not due to adducts of $Et_3Si^{\bullet}$ radicals. When toluene was used as solvent only the benzyl radical was detected and similarly, with *meta*-xylene as solvent, a good spectrum of the 3-methylbenzyl radical was obtained with hfs identical to those reported.[78] For these benzyl substrates hydrogen abstraction predominates over addition. Experiments were carried out in other aromatic solvents including anisole, diphenylether, methyl benzoate and fluorobenzene, but no well defined spectra were obtained.

Also investigated was the reaction of triptycyl bromide with 1,3-di-t-butylbenzene and t-butylbenzene. However no signals were observed, probably due to the much more sterically congested triptycyl radicals slowing up the addition step.

A noteworthy feature of these results was that only the radical formed by addition *meta* to the *tert*-butyl substituent of the aromatic solvents was detected. Addition *ortho* to a t-butyl substituent will be strongly disfavoured by steric hindrance and hence the formation of a single cyclohexadienyl radical from 1,3-di-*tert*-butylbenzene is easily understood. However, some *para* addition might have been expected for *tert*-butylbenzene.

In previous studies of the decomposition of ditriptoyl peroxide, and other triptycyl radical precursors, in benzene, no addition products were isolated.[79,80] The failure to detect cyclohexadienyl radicals on photolysis of triptycyl bromide in an aromatic solvent, in the EPR cavity, is entirely consistent with this.

6.4 Experimental

EPR spectra. Solution phase samples were prepared in Spectrosil tubes, degassed by several freeze-pump-thaw cycles on a vacuum line and flame sealed or, for samples in aromatic solvents, by bubbling nitrogen for ca. 20 min., and photolysed in the microwave cavity by light from a 500-W super pressure Hg lamp. Radical *g*-factors were measured relative to the known values for the cyclopropyl and $Et_2Si(H)CH^{\bullet}CH_3$ radicals.

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