23

TUTORIAL CHEMISTRY TEXTS

RS•C

Mechanisms in Organic Reactions

by RICHARD A. JACKSON

TUTORIAL CHEMISTRY TEXTS

23

Mechanisms in Organic Reactions

RICHARD A. JACKSON
University of Sussex

RS•C
ROYAL SOCIETY OF CHEMISTRY

Cover images © Murray Robertson/visual elements 1998–99, taken from the 109 Visual Elements Periodic Table, available at www.chemsoc.org/viselements

ISBN 0-85404-642-9

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry, Thomas Graham House, Science Park,
Milton Road, Cambridge CB4 0WF, UK
Registered Charity No. 207890
For further information see our web site at www.rsc.org

Typeset in Great Britain by Alden Bookset, Northampton
Printed and bound by Italy by Rotolito Lombarda

TUTORIAL CHEMISTRY TEXTS

This series of books consists of short, single-topic or modular texts, concentrating on the fundamental areas of chemistry taught in undergraduate science courses. Each book provides a concise account of the basic principles underlying a given subject, embodying an independent-learning philosophy and including worked examples. The one topic, one book approach ensures that the series is adaptable to chemistry courses across a variety of institutions.

TITLES IN THE SERIES

Stereochemistry *D G Morris*
Reactions and Characterization of Solids *S E Dann*
Main Group Chemistry *W Henderson*
d- and f-Block Chemistry *C J Jones*
Structure and Bonding *J Barrett*
Functional Group Chemistry *J R Hanson*
Organotransition Metal Chemistry *A F Hill*
Heterocyclic Chemistry *M Sainsbury*
Atomic Structure and Periodicity *J Barrett*
Thermodynamics and Statistical Mechanics *J M Seddon and J D Gale*
Basic Atomic and Molecular Spectroscopy *J M Hollas*
Organic Synthetic Methods *J R Hanson*
Aromatic Chemistry *J D Hepworth, D R Waring and M J Waring*
Quantum Mechanics for Chemists *D O Hayward*
Peptides and Proteins *S Doonan*
Biophysical Chemistry *A Cooper*
Natural Products: The Secondary Metabolites *J R Hanson*
Maths for Chemists, Volume I, Numbers, Functions and Calculus *M Cockett and G Doggett*
Maths for Chemists, Volume II, Power Series, Complex Numbers and Linear Algebra *M Cockett and G Doggett*
Nucleic Acids *S Doonan*

TITLES IN THE SERIES

Inorganic Chemistry in Aqueous Solution *J Barrett*
Organic Spectroscopic Analysis *R J Anderson, D J Bendell and P W Groundwater*
Mechanisms in Organic Reactions *R A Jackson*

Further information about this series is available at www.rsc.org/tct

Order and enquiries should be sent to:
Sales and Customer Care, Royal Society of Chemistry, Thomas Graham House,
Science Park, Milton Road, Cambridge CB4 0WF, UK

Tel: +44 1223 432360; Fax: +44 1223 426017; Email: sales@rsc.org

Preface

The wonderful complexity of organic chemistry involves thousands of different reactions which allow the synthesis and interconversions of millions of compounds, some of great complexity. The key to understanding this vital branch of chemistry is the concept of the reaction mechanism.

This book starts with a discussion of how covalent bonds break and form, and how these bond-breaking and bond-forming processes provide the basis of reaction mechanisms. The principles governing how to make sensible suggestions about possible mechanisms are set out, and the distinction is made between elementary reactions, which involve just one step, and stepwise reactions which have more than one step and involve the production of intermediates that react further.

Chapter 2 covers kinetics, which provides useful information about reaction mechanisms, and allows us to distinguish between possible mechanisms in many cases. Elementary reactions do not involve intermediates, but go through a transition state. Although this transition state cannot be isolated, it can be studied in various ways which provide insights into the reaction mechanism, and this forms the subject matter of Chapter 3. This is followed by three chapters on the most important intermediates in organic chemistry: anions, radicals and cations. A final chapter on molecular reactions concerns thermal and photochemical processes. The concepts of frontier orbitals and the aromatic transition state allow us to predict which reactions are "allowed" and which are "forbidden", and provide insights into why most reactions of practical interest involve multi-step processes.

Where common names are used for organic compounds, the systematic name is given as well at the first mention. Common names are widely used in the chemical literature, in industry and commerce, and there is a great divergence in the use of systematic as opposed to non-systematic nomenclature in the English-speaking world.

I thank many colleagues for helpful comments and advice, particularly Mr Martyn Berry and Professor Alwyn Davies FRS who have read the entire manuscript and whose suggestions for changes have improved the text in numerous places. I would also like to thank my wife Pat for her support and forbearance over the past three years. Enjoy the book!

Richard A. Jackson
University of Sussex

Contents

1

What Is a Mechanism?

The chemical structure of most organic compounds is well established. Spectroscopic methods and X-ray crystallography show that individual atoms in a molecule are connected, usually by covalent bonds. Bond lengths are often known to within about ±1 pm (0.01 Å) and bond angles to within ±1°. Molecular models and graphics programs give a good picture of the overall shape of the molecule, including possible interactions between atoms that are not covalently bonded to each other. These structures correspond to energy minima.

Molecules can acquire extra energy by collisions, and this energy may cause distortions of bond lengths or angles by small amounts. However, the bond lengths and angles will tend to return to the equilibrium values.

However, if the distortions become too great, one or more covalent bonds may break, and new bonds may be formed, either within the molecule or with a new molecule with which the first has collided. A chemical reaction has occurred, and when equilibrium is reached, one or more new molecules will be produced, which may be stable or may undergo further reactions.

The energy required to break covalent bonds may be provided thermally by molecular collisions, which give a range of molecular energies, providing some molecules with enough energy to react. At higher temperatures, more molecules will have sufficient energy to react, so the reaction will be faster. Alternatively, the energy can be provided in other ways, especially by visible or UV light. Absorption of a photon by a molecule causes electronic excitation, and the excited state of the molecule may then undergo reactions which cannot be carried out thermally.

Aims

This chapter describes the main features of organic reaction mechanisms and how "reasonable" mechanisms can be written. Having worked through this chapter you should be able to:

- Explain the importance of reaction mechanisms in organic chemistry
- Understand the difference between elementary and stepwise reactions, and the role played by transition states and intermediates
- Know the main types of bond-breaking and bond-making processes
- Identify the bonds made and broken in a reaction, given the starting materials and products, thereby allowing a number of possible reaction mechanisms to be written
- Cut down the number of possible mechanisms by using the concepts of energy and molecularity requirements

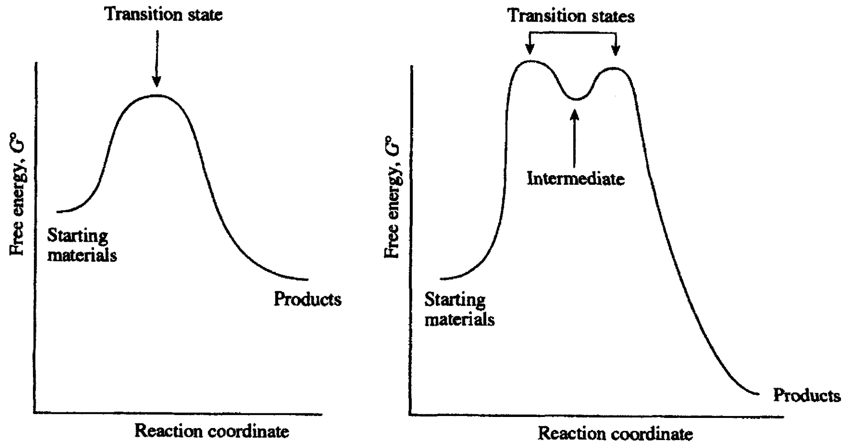
1.1 Elementary and Stepwise Reactions

Reactions are of two types. In **elementary reactions** the reacting molecule or molecules are transformed into products directly, without the formation of intermediates. In a **stepwise reaction**, one or more intermediate species are produced, which react further to give the products. A stepwise reaction can be split up into two or more elementary reactions.

As an elementary reaction proceeds, the Gibbs free energy increases up to a maximum value and then goes down to a value corresponding to that of the products. The position of highest energy is called the **transition state**, and is a key feature of the reaction; most of the experimental information about chemical reactions relates to the transition state and will be discussed in the next two chapters.

In a stepwise reaction, at least one of the products of the first elementary reaction reacts further in a second elementary reaction. This may be followed by further elementary reactions until the reaction is complete. Any molecules produced in the course of a stepwise reaction which react further and are not present at the end of the reaction are known as **intermediates**. Intermediates are discussed in more detail in Chapters 4, 5 and 6.

Figure 1.1 shows free energy diagrams for an elementary reaction (1.1a) and for a stepwise reaction with two steps (1.1b).



(1.1a) Elementary reaction
e.g. $HO^- + CH_3{-}Br \longrightarrow HO{-}CH_3 + Br^-$

(1.1b) Stepwise reaction
e.g. $Me_3C{-}Br \longrightarrow Me_3C^+ + Br^-$
$Me_3C^+ + {}^-OH \longrightarrow Me_3C{-}OH$

Figure 1.1 Free energy diagrams for elementary and stepwise reactions

An example of an elementary reaction (1.1a) is the S_N2 displacement of a bromide ion from bromomethane by the hydroxide anion. The reaction is thermodynamically favourable (negative ΔG°) and takes place when a hydroxide ion collides with a bromomethane molecule. A bond starts to form between the oxygen atom and the carbon atom at the same time as the carbon-bromine bond breaks. Because of electron repulsion, in the early stages of the reaction the energy released by the formation of the new bond is not quite as much as the energy required to break the C–Br bond, so the free energy increases and eventually reaches a maximum at the transition state, before decreasing to the value appropriate to the products. No intermediate is involved; the reaction proceeds smoothly from reagents through the transition state directly to products.

In contrast, the hydrolysis of *tert*-butyl bromide (2-bromo-2-methylpropane) occurs in a stepwise manner (reaction 1.1b). In the first slow step, the C–Br bond breaks, with the bromine atom taking both electrons from the bond and leaving as a negatively charged bromide ion. The remainder of the molecule is the positively charged *tert*-butyl cation (2-methylprop-2-yl cation). This is a highly reactive intermediate, which reacts rapidly with the hydroxide ion to form the corresponding alcohol.

Box 1.1 Elementary and Stepwise Reactions

In an elementary reaction, reacting molecules are transformed into products without going through intermediates. A stepwise reaction involves consecutive elementary reactions where the intermediate(s) produced in the first elementary reaction react further in subsequent elementary reactions.

Mechanisms cannot be established just by looking at the structures of reactants and products.

These two examples raise an important point about mechanisms. The two reactions are similar from the point of view of reagents and products, yet are known to have different mechanisms. Thus we cannot determine mechanisms merely by knowing the starting materials and products; we need further information. The remainder of this chapter is devoted to writing sensible possible mechanisms for a new reaction, and the remainder of the book concerns the methods that we can use to distinguish between the various mechanistic possibilities.

1.2 Bond Making and Bond Breaking

Inspection of the structure of the reagents and products tells us which covalent bonds have been broken and formed during the reaction.

1.2.1 Bond Breaking

Covalent bonds, which involve two electrons, can be broken in two ways, **homolytically** (homo = same), when one electron is retained by each fragment, or **heterolytically** (hetero = different), when both electrons go to one of the fragments. Heterolysis is more likely if the two atoms in the bond have different electronegativities, and in polar solvents which stabilize charges. Electronegativity is a measure of the power of an atom or a group of atoms to attract electrons from other parts of the same molecule: fluorine is the most electronegative element; cesium is the most electropositive. A covalent bond between two different elements is polarized in the direction $^{\delta+}X{-}Y^{\delta-}$, where Y is the more electronegative element. In a heterolysis, the bond will almost always break in the direction which will leave both bonding electrons on the more electronegative atom. If the original molecule has no net charge, this will give an anion centred on the more electronegative element and the cation centred on the less electronegative element. The electronegativities of elements commonly found in organic compounds are listed in Table 1.1.

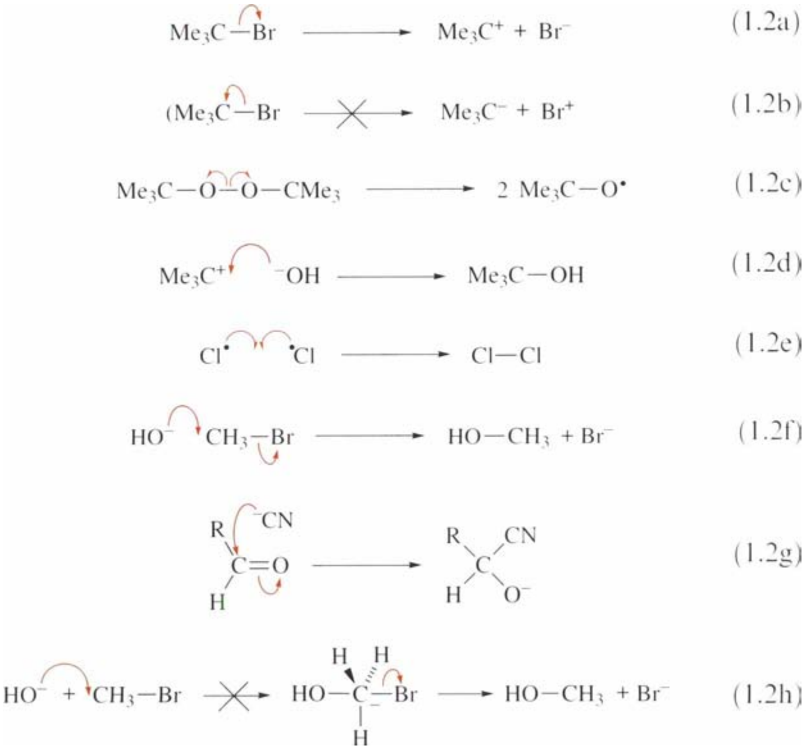
Table 1.1 Electronegativities of elements commonly found in organic compounds[a]

H						
2.1						
Li	Be	B	C	N	O	F
1.0	1.5	2.0	2.6	3.0	3.4	4.0
Na	Mg	Al	Si	P	S	Cl
0.9	1.3	1.6	1.9	2.2	2.6	3.2
K						Br
0.8						3.0
						I
						2.7

[a] Low numbers = electropositive; high numbers = electronegative

The first stage of the S_N1 reaction in reaction (1.1b) is a heterolysis involving a neutral molecule dissociating into a cation and an anion. Heterolysis will take place exclusively in the direction indicated in reaction (1.2a), with no contribution from (1.2b). For the heterolysis shown in (1.2a), the electrons originate in the covalent bond; both move to the bromine atom during the reaction.

We show the movement of an **electron pair** in a reaction by a **curved arrow**: ⌒. The tail of the arrow shows the origin of the electrons that move, the head shows where they end up; thus the arrow gives a good representation of the movement of an electron pair during a reaction.



Half-headed curved arrows (fish-hooks), ⌒, may be used to show the movement of **single electrons** during a free radical reaction. Because they are more awkward to draw and give a cluttered look to the reaction scheme, curved arrows are less commonly used in homolytic than in heterolytic processes.

Homolysis is more likely for weak covalent bonds and for bonds containing atoms with similar electronegativities. Heating di-*tert*-butyl peroxide affords an example of homolysis (equation 1.2c). The central O–O bond breaks homolytically to give two *tert*-butoxyl radicals. Since one electron from the two shared electrons in the covalent bond goes to each atom, no charge is created during an homolysis.

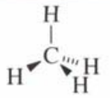
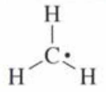
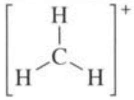
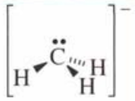
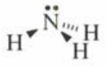
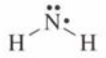
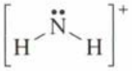
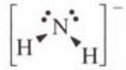
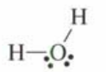
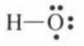
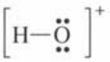
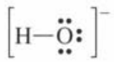
1.2.2 Bond Formation

This is the reverse of bond breaking. The electrons involved in the new bond may both come from one of the reagents; this is the reverse of heterolysis. An example is the second step of reaction (1.1b), redrawn in (1.2d) to show the movement of an electron pair from an unshared pair on the oxygen atom (arrow-tail) to a position between the oxygen and the carbon atom where the covalent bond will form (arrow-head). Since an unshared electron pair becomes shared during bond formation, the oxygen effectively loses one electron and the formal negative charge on the oxygen atom is reduced from –1 to zero. Likewise, the positively charged carbon atom acquires a half-share of two electrons and its formal charge changes from + 1 to zero.

If one electron comes from each of the atoms forming the new bond (the reverse of homolysis), there will be no change in formal charge (half of two shared electrons is equivalent to one attached to an individual atom). The combination of two chlorine atoms to form a chlorine molecule is shown in reaction (1.2e); the curved half-arrows show the movement of the electron from the chlorine atom (tail) to the position where the bond will be (head).

Box 1.2 Formal Charge

A carbon atom is electrically neutral if it has four electrons in its valence shell. It is also formally neutral in methane: though surrounded by eight electrons, these are all shared, and are equally involved in balancing the charge on the carbon and the four hydrogen atoms. For each electron pair, one can be formally considered as neutralizing the positive charge on a hydrogen atom; the other will contribute to neutralizing the charge on the carbon atom. Thus the carbon atom will formally have $8/2 = 4$ electrons in its valence shell and will be electrically neutral. In a carbanion such as CH_3^- (see below) there are six shared electrons (counting $6/2 = 3$) and two unshared electrons (belonging exclusively to the carbon atom). This gives five electrons, one more than the number needed for a neutral carbon atom, so the carbon atom has a formal negative charge. Formal charges for some carbon, nitrogen and oxygen species are shown below.

					
Valence shell electrons	4	$8/2 = 4$	$(6/2) + 1 = 4$	$6/2 = 3$	$(6/2) + 2 = 5$
Charge	neutral	neutral	neutral	+1	-1
					
Valence shell electrons	5	$(6/2) + 2 = 5$	$(4/2) + 3 = 5$	$(4/2) + 2 = 4$	$(4/2) + 4 = 6$
Charge	neutral	neutral	neutral	+1	-1
					
Valence shell electrons	6	$(4/2) + 4 = 6$	$(2/2) + 5 = 6$	$(2/2) + 4 = 5$	$(2/2) + 6 = 7$
Charge	neutral	neutral	neutral	+1	-1

These formal charges at specified atoms do not depend on the type of atom at the other end of the bond, so for example the oxygen atom in the methoxide ion $:\ddot{\underset{\cdot\cdot}{O}}-CH_3$ will have the same formal negative charge as the oxygen atom in ^{-}OH.

1.2.3 Timing of Electron Movements

The hydrolysis of halogenoalkanes involves the breaking of a carbon–halogen bond and the formation of a carbon–oxygen bond. If the reaction is heterolytic, there are three mechanistic possibilities. The first is that bond breakage takes place first, followed by bond formation, as in reaction (1.1b). The difficulty with processes of this type is that they often have a high activation energy.

Alternatively, both bond-breaking and -making take place at the same time. For example, in reaction (1.1a), as the carbon–halogen bond breaks, the new carbon–oxygen bond is forming. The energy required for bond breakage is partially provided by the energy given out as the new bond forms. Processes of this type, with simultaneous bond-breaking and -making, are termed **concerted**. We show the movement of electrons as two (or more) curved arrows, as in reaction (1.2f). Since electrons are flowing both towards and away from the central carbon atom, little or no charge is built up there during the reaction. Concerted reactions may also involve attack by a reagent at an unsaturated centre. Here the bond

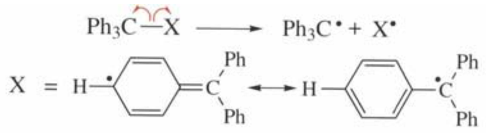
Concerted processes usually involve less activation energy than stepwise processes where a bond has to be broken before a new bond is formed. Almost all biological reactions, which are constrained by the need to take place at relatively low temperatures, are concerted.

broken is the double bond, leaving a charge or a radical centre at the other end of the bond. An example is shown in reaction (1.2g). Note the movement of an electron pair from the π bond to the oxygen atom.

The third possibility, that bond formation precedes bond breakage, is not feasible at saturated carbon centres. Atoms of first-period elements cannot expand their octet, and carbon atoms cannot form more than four covalent bonds, so that mechanisms such as that shown in reaction (1.2h) can be ruled out.

Free radical reactions show the same timing possibilities as heterolytic processes. Reactions (1.3a–c) illustrate a non-concerted and two types of concerted reaction. More detailed consideration of homolytic processes will be given in Chapter 6.

Ph = phenyl = C_6H_5

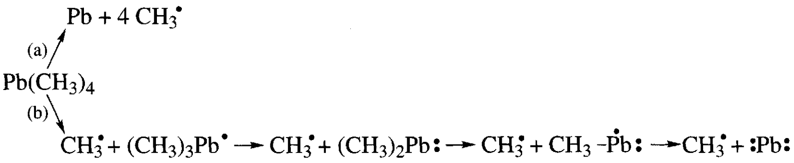


(1.3a)

(1.3b)

(1.3c)

When postulating mechanisms, concerted possibilities should be considered first, then processes that require one bond to be broken at the start of the reaction process. Steps in which more than one bond is broken before any new bonds are formed can normally be ruled out as requiring too much energy. Thus the homolysis of tetramethyllead to give lead and four methyl radicals is more likely to proceed by the sequential homolysis of the four carbon–lead bonds (reaction 1.4b) rather than by simultaneous rupture of all four bonds (reaction 1.4a).

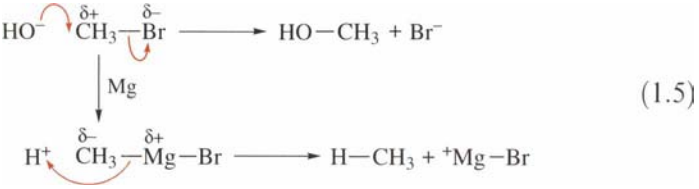


$$\mathrm{Pb(CH_3)_4} \xrightarrow{(a)} \mathrm{Pb} + 4\,\mathrm{CH_3^{\bullet}}$$

$$\mathrm{Pb(CH_3)_4} \xrightarrow{(b)} \mathrm{CH_3^{\bullet}} + \mathrm{(CH_3)_3Pb^{\bullet}} \longrightarrow \mathrm{CH_3^{\bullet}} + \mathrm{(CH_3)_2Pb{:}} \longrightarrow \mathrm{CH_3^{\bullet}} + \mathrm{CH_3{-}\dot{P}b{:}} \longrightarrow \mathrm{CH_3^{\bullet}} + \mathrm{{:}Pb{:}}$$

(1.4)

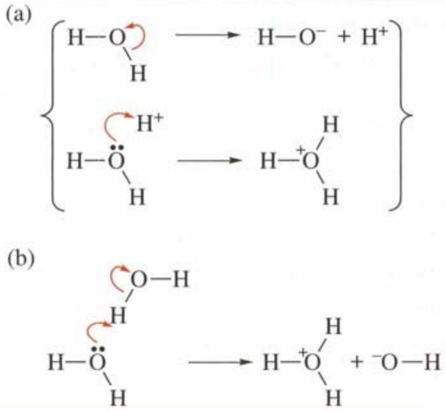
For heterolytic reactions, consideration of polarity is important in predicting possible reaction paths: positive reagents tend to react with the negatively polarized atom of a covalent bond and *vice versa*. Thus bromomethane, with $^{\delta+}$C, reacts with $^{-}$OH to give methanol, but not with a proton to give methane (reaction 1.5). If the bromomethane is allowed to react with magnesium to form methylmagnesium bromide, the polarity is reversed, giving $^{\delta-}$C, which reacts with acids to give methane and not with bases to give methanol. Polar reactions are considered in more detail in Chapters 4 and 5.



(1.5)

Worked Problem 1.1

Q In liquid water, small concentrations of hydroxonium ions, H_3O^+, and hydroxide ions, ^-OH, are present. Two possible mechanisms for this dissociation are shown below. Which process is the more likely?



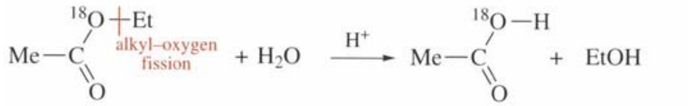
A In (a), the first step involves breakage of a strong covalent bond, which will require a large amount of energy and an activation energy of at least this amount. In (b), a bond is formed simultaneously with bond breakage, so the reaction is much less endothermic and the activation energy is likely to be considerably lower.

1.2.4 Labelling

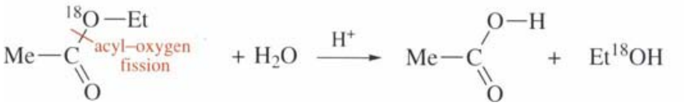
It may often be obvious which bonds are broken and formed in a reaction. However, in some cases it is not so obvious. In the acid-catalysed hydrolysis of esters (reaction 1.6), it is not obvious whether the alkyl–oxygen bond is broken (1.6a) or the acyl–oxygen bond (1.6b). This question can be resolved by use of an ^{18}O isotopic label in the ester.

Route (1.6a) predicts that the ^{18}O label will end up in the carboxylic acid, whereas route (1.6b) predicts labelling of the alcohol. By mass spectrometry, it is established that the ^{18}O label ends up in the alcohol, thus showing that acyl–oxygen fission takes place (reaction 1.6b). Note that neither (1.6a) nor (1.6b) represents complete mechanisms: the timing of the bond breaking and bond formation is not established, nor is the role of the acid catalyst. However, all the possibilities represented by (1.6a) are eliminated, simplifying the mechanistic search.

Et = ethyl = C_2H_5
Me = methyl = CH_3

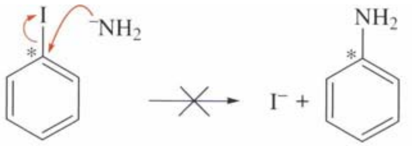


(1.6a)

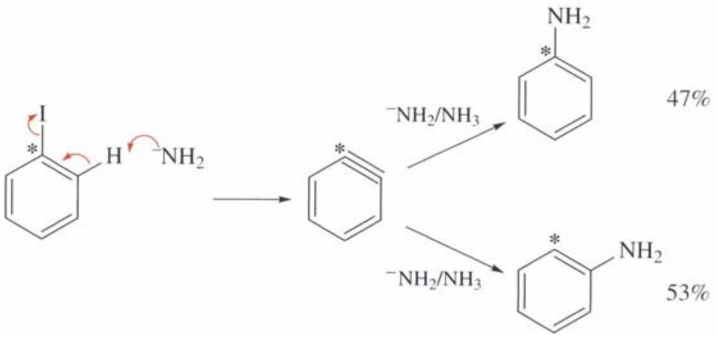


(1.6b)

Sometimes a reaction is more complicated than appears at first sight. The halide hydrolysis reactions in Figure 1.1 result in formation of the new C–O bond at the same carbon atom from which the bromide ion is detached. However, in the apparently analogous reaction in which iodobenzene reacts with the amide ion to give aniline (phenylamine), the reaction does not go by route (1.7a). Carbon labelling of the atom to which the iodine atom is attached shows that in the aniline product about half the label is on the carbon attached to the NH_2 group, whereas the other half is located on the adjacent carbon atoms. Significantly, none of the label is located further away. This shows that an intermediate must be formed in which two carbon atoms have become equivalent, leading to the proposal of the extraordinary benzyne intermediate in route (1.7b), an intermediate whose existence was later demonstrated by trapping experiments.



(1.7a)



(1.7b)

Labelling can sometimes be carried out by introduction of an inert substituent group in the molecule, rather than by isotopic substitution. For example, 4-iodotoluene (4-iodomethylbenzene) can be used to detect the change of position of the substituent group in reaction (1.7). The products are a mixture of 3- and 4-aminotoluenes, but not the 2-isomer, again pointing to the benzyne intermediate, rather than to complete freedom of attack for the incoming amide ion.

1.3 Molecularity

We conclude this chapter by considering the **molecularity** of elementary reactions, that is the number of molecules that are involved in the transition state. This number is almost always one or two. Such reactions are termed **unimolecular** and **bimolecular**.

1.3.1 Unimolecular Reactions

Unimolecular reactions may be concerted, involving simultaneous bond formation and cleavage, as in reaction (1.8), or may involve the breakage of one bond, either heterolytically, as in the first stage of (1.1b), or homolytically, as in (1.4b). The energy required for reaction may be acquired by random collisions, which occasionally give a molecule the energy required for reaction. Photolysis, in which a photon of visible or UV light is absorbed by a molecule, may also cause reaction, often by homolysis of a covalent bond, for example the photolysis of a chlorine molecule to give two chlorine atoms (equation 1.9).

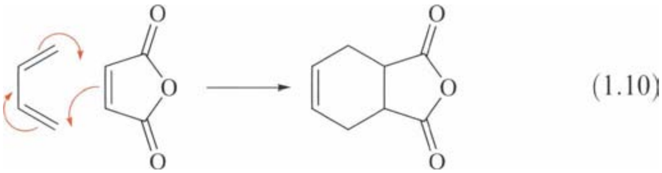
(1.8)

$$\mathrm{Cl{-}Cl} \xrightarrow{h\nu} 2\ \mathrm{Cl}^{\bullet} \qquad (1.9)$$

1.3.2 Bimolecular Reactions

Bimolecular reactions involve a collision between two molecules, with enough energy to overcome the activation barrier. These processes are usually concerted, with bond formation and breaking taking place simultaneously. The relative orientation is important, so that the new bonds can be formed between atoms that are near enough to each other. Reactions (1.1a) and the first step of (1.7b) are examples of bimolecular reactions. Reaction (1.10) is an example of a bimolecular reaction that does not involve ions. Three covalent bonds are broken and formed synchronously, and **Diels–Alder reactions** of this type are very useful synthetically, particularly in forming compounds with new six-membered rings.

In reaction (1.10), the electron pairs are shown flowing in the clockwise direction. They could equally well have been shown as flowing in the anticlockwise direction or as single electron movements. See Problem 1.4.



(1.10)

1.3.3 Termolecular Reactions

Termolecular reactions, involving three molecules in the transition state, are very rarely encountered. Bimolecular reactions have to take place in the very brief time that two molecules collide, before they bounce apart again. The chance that a third molecule will collide at exactly the same time, in a suitable orientation for reaction, is extremely improbable. Termolecular reactions only occur under very unusual conditions, where special circumstances apply. For example, the reaction of two hydrogen atoms in the gas phase to form a hydrogen molecule (reaction 1.11) cannot take place as a bimolecular reaction because the energy liberated by the formation of the H–H covalent bond can only go into vibrational and rotational energy of the new molecule, and this energy is sufficient to cause the almost immediate reversal of the reaction to give back the two hydrogen atoms. However, if a third molecule is available to absorb the energy, reaction (1.11) can take place.

$$H^{\bullet} + H^{\bullet} + M \longrightarrow H{-}H + M \qquad (1.11)$$

Almost all reactions take place in steps that are either unimolecular or bimolecular.

Reactions involving more than three molecules are virtually impossible.

1.3.4 Microscopic Reversibility

In principle, all elementary reactions are reversible, although if they are very exothermic the reverse reaction may be immeasurably slow. The reverse reaction must follow the same route (in reverse) as the forward reaction and go *via* the same transition state. This is known as the **Principle of Microscopic Reversibility**. The main practical application of this principle is in ruling out, as elementary processes, reactions which would give more than three molecules. The reverse of any such reaction would have a molecularity greater than three, which we have established above would be virtually impossible. Mechanism (1.4a) can be ruled out on these grounds, and another example will be found in the problems at the end of the chapter.

1.4 Formulating Mechanisms

We have seen above in reaction (1.1) that there are at least two possible mechanisms for the hydrolysis of halogenoalkanes. How do we formulate possible mechanisms?

First, inspect the bonding in the reagents and products, to find what bonds have been broken and formed. Then, use this information to create possible mechanistic paths based on the different ways in which these bond-breaking and -making processes can be achieved, trying different possibilities involving bond breakage first, bond formation first, or simultaneous breakage and formation of two or more bonds. Remember that bonds can break homolytically or heterolytically.

Rule out steps involving more than one net bond-breaking process taking place at the same time, and bond-forming reactions that would expand the octets of first-row elements on energetic grounds. Rule out steps that involve more than two reactant or three product molecules on "probability of collision grounds" (see Section 1.3). Look for concerted reactions where possible; reactions where bond breakage and formation take place at the same time will usually have lower activation energies than reaction steps involving bond breakage.

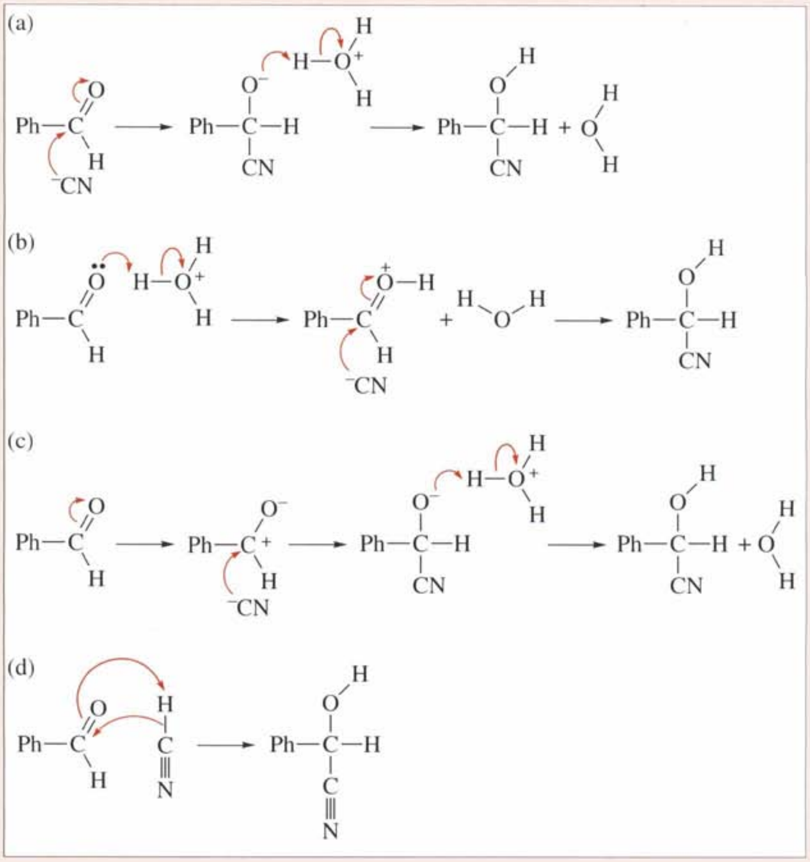
If a catalyst is required for the reaction, ensure that it figures in your mechanistic scheme. A bond will need to be established between the catalyst and one of the reacting molecules, usually in the first step of the reaction. In a later step, this bond will be broken again to regenerate the catalyst.

Heterolytic processes are favoured in polar solvents where the ions formed are stabilized, but are uncommon in non-polar solvents and virtually unknown in the gas phase. Homolytic and molecular processes are much less affected by solvents, and are therefore the favoured possibilities for reactions taking place in the gas phase or in non-polar solvents.

Worked Problem 1.2

Q Aromatic aldehydes such as benzaldehyde (phenylmethanal), PhCH=O, react with HCN in water to give the cyanohydrin PhCH(OH)CN. Suggest possible mechanisms for this reaction. *Hint*: HCN is partially dissociated in water, with the formation of H_3O^+ and ^-CN ions.

A The C=O π bond is broken and C–CN and O–H bonds are formed. In route (a), the first step involves nucleophilic addition of the ^-CN ion to the carbonyl carbon, with the simultaneous breakage of the C=O π bond to give the intermediate anion, which in a second step acquires a proton from a hydroxonium ion (or a water molecule) to give the cyanohydrin.



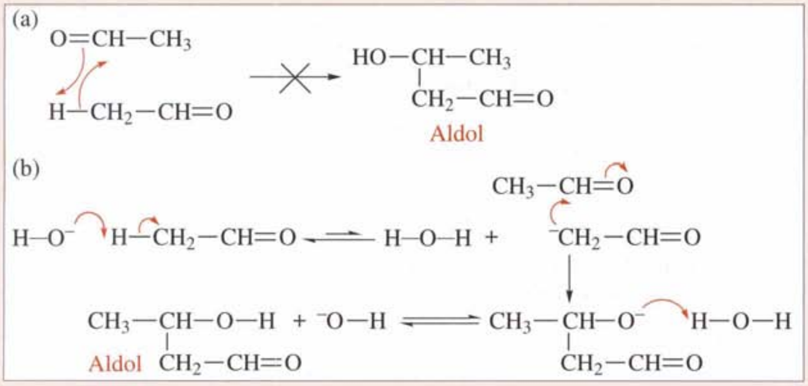
Alternatively, in route (b) the O–H bond may be formed first, followed by attack of $^{-}$CN at the carbonyl carbon atom. In both these routes, in each of the two steps, a concerted process takes place with the simultaneous formation and breakage of a covalent bond, making these routes likely candidates.

Route (c) involves the unimolecular breakage of the C=O π bond in the first step. This will require energy, which is not offset, as in (a) and (b), by simultaneous formation of a new covalent bond, making (c) less likely. The molecular reaction shown in (d) looks plausible, as two bonds are simultaneously broken and formed. A reason why a mechanism of this type is unlikely is given in Chapter 7.

Worked Problem 1.3

Q Acetaldehyde (ethanal) reacts in aqueous solution, in the presence of sodium hydroxide, to form 3-hydroxybutanal (aldol), $CH_3CH(OH)CH_2CHO$. The reaction does not take place in the absence of the base. Formulate a possible mechanism or mechanisms.

A Two molecules of acetaldehyde are needed to give the product. In one molecule a C–H bond is broken, and in the other the π bond of the carbonyl group is broken. Bonds formed are an O–H bond and a C–C bond between the two carbon fragments. The reaction takes place in aqueous solution and the catalyst, sodium hydroxide, is ionic, so an ionic mechanism is likely.



Mechanism (a) does not show the involvement of the hydroxide ion and must therefore be ruled out. Mechanism (b) invokes the removal of a proton from the methyl group of an acetaldehyde molecule by a hydroxide ion to give an unstable carbanion intermediate. This reacts with a second acetaldehyde molecule by nucleophilic addition to the carbonyl group. The resultant anion picks up a proton from a water molecule to give the 3-hydroxybutanal product, and regenerates the hydroxide anion catalyst. All three steps are concerted and involve the simultaneous breakage and formation of covalent bonds. Multi-step concerted reactions of this type are common in biological systems.

1.5 Why Study Mechanisms?

There are a number of reasons, not mutually exclusive, which may be listed by the type of person most affected:

Students. Mechanisms form a framework on which the factual detail of organic chemistry, necessary for a good understanding, can be hung. It would be possible to learn all the individual reagents which add to carbonyl groups, but the classification of many of these as nucleophiles, together with an understanding of why these reagents add to the carbon centre, makes the information more memorable.

Chemists Involved in Synthesis. Mechanistic knowledge allows intelligent variation of reaction conditions, temperatures and proportions of reagents to maximize yields of pure products.

Industrial Chemists. Mechanistic knowledge allows the prediction of new reagents and reaction conditions which may affect desired transformations. It also allows optimization of yields, cutting down on raw materials costs and waste material which may be expensive to dispose of. For example, Augmentin is a broad-spectrum antibiotic, marketed by GlaxoSmithKline, with sales of over $2 billion in 2001. If, say, 5% of the costs are in raw materials, a 1% improvement in reaction yield would save GSK at least a million dollars per annum.

Biochemists, and Those Involved in Medical Research. The reactions involved in metabolism in living organisms are organic, and many are understood in some detail. The establishment of mechanism is of vital importance in understanding how diseases affect metabolism, how drug molecules can assist or prevent particular biochemical reactions, and in the development of new drugs.

Chemists Giving Advice on Environmental Issues. Organic molecules in the environment can have beneficial or harmful effects (or both). An understanding of the mechanistic chemistry involved in the degradation of chemicals in the environment can lead to improvements in the environment. For example, chlorofluorocarbons (CFCs), used as refrigerants, escape into the atmosphere and diffuse to the stratosphere where they damage the ozone layer. Knowledge of the reaction mechanisms involved has led to replacement of these chemicals for some purposes by hydrochlorofluorocarbons (HCFCs). These degrade before they reach the stratosphere and do much less harm to the ozone layer.

Summary of Key Points

1. *Elementary and Stepwise Reactions*

In an elementary reaction, there are no intermediates. Reagents are converted into products via a transition state in a single step.

A stepwise reaction involves more than one elementary reaction. Intermediates are produced which react further to give products, often involving many steps.

2. *Molecularity*

Elementary steps are normally either unimolecular or bimolecular. In either case, no more than three product molecules are formed.

3. *Formulating Mechanisms*

Note which bonds are made and broken in going from reagents to products, and use these to formulate several possible mechanisms. If a catalyst is needed, it must be involved in the mechanism. Avoid steps which would:

(a) have a molecularity greater than two, or which give more than three product molecules;
(b) produce intermediates with expanded octets of first-period elements;
(c) involve overall breakage (bonds broken *minus* bonds formed) of more than one bond;
(d) require bonds to be formed between atoms that cannot approach each other closely in the transition state;
(e) require the formation of ions in the gas phase or in non-polar solvents.

4. *Determination of Mechanism*

Having formulated several possible mechanisms, try to rule out all but one by focusing on experiments which provide information about transition states (Chapters 2 and 3) or on intermediates (the rest of the book). A mechanism cannot be "proved", but becomes accepted if it is the only one that fits all known experimental facts. A currently accepted mechanism must be modified if new conflicting experimental evidence comes to light.

Further Reading

J. McMurry, *Organic Chemistry*, Brooks/Cole, Pacific Grove, California, USA, 1996, Chapter 5.

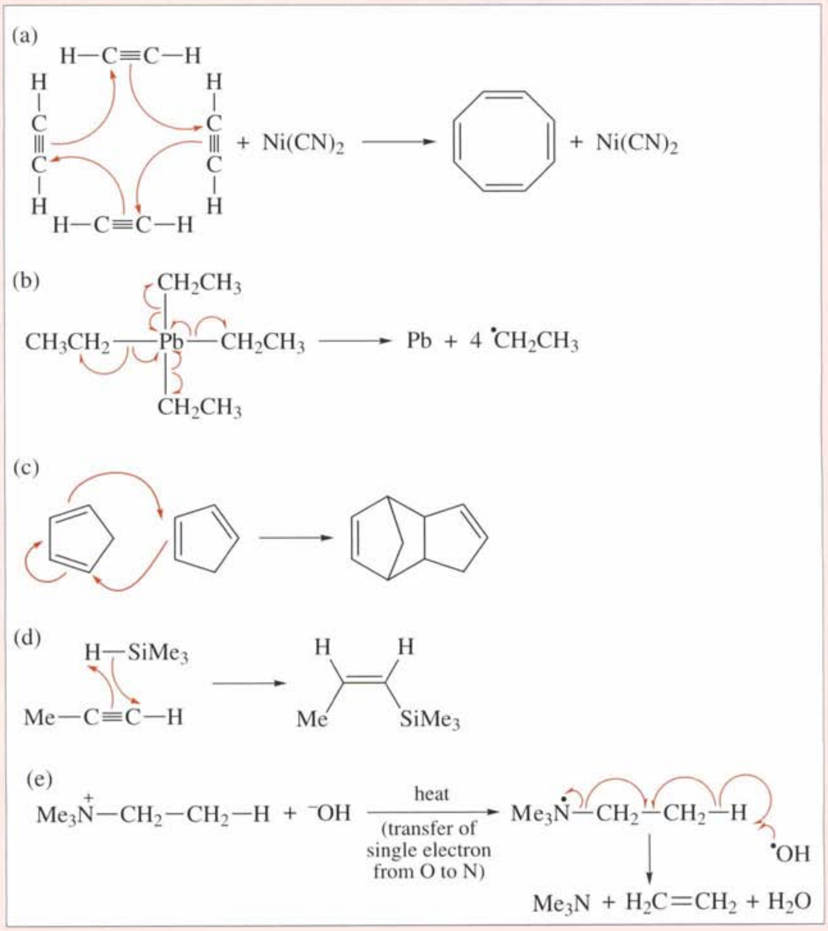
R. B. Grossman, *The Art of Writing Reasonable Organic Reaction Mechanisms*, Springer, New York, 1999.

Problems

1.1. Dibenzylmercury, $(PhCH_2)_2Hg$, decomposes in octane at 140 °C to give 1,2-diphenylethane ($PhCH_2CH_2Ph$) and mercury. Suggest at least two plausible mechanisms for this reaction.

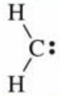
1.2. Bromine reacts with benzene in the presence of aluminium tribromide to give bromobenzene and hydrogen bromide. Suggest at least two plausible mechanisms for this reaction. *Hint*: Aluminium tribromide and bromine form a complex which can be regarded as $[Br]^+[AlBr_4]^-$.

1.3. Comment on the following reaction schemes. Each of the processes indicated by an arrow should be considered as a possible elementary reaction.



1.4. Reaction (1.10) shows a concerted reaction with three pairs of electrons flowing in a clockwise direction. Show alternative formulations where (a) the electron pairs are shown flowing in the anticlockwise direction, and (b) six single electrons are moving, three clockwise and three anticlockwise.

1.5. Carbene, CH_2, whose electronic structure is shown below, is a reactive intermediate formed in some reactions. Assign a formal charge to the central carbon atom, showing your reasoning.



2

Kinetics

In Chapter 1, we established some ground rules for writing plausible mechanisms (normally several) for particular reactions, based on the identification of bonds formed and broken in the reaction. In this chapter, we show how **kinetics** the study of how concentrations of reagents or products vary with time, enable us to rule out some potential mechanisms and provide insight into elementary and stepwise reactions.

Aims

This chapter describes the use of kinetics in supporting or disproving potential mechanisms for a reaction. By the end of this chapter you should be able to:

- Establish zero-, first- and second-order behaviour for particular reaction components from concentration/time data
- Use information about order to support or rule out suggested mechanisms
- Interpret mixed and fractional order kinetic behaviour
- Make inferences from observed Arrhenius parameters in simple cases
- Make inferences from primary kinetic isotope effects

2.1 Rates and Rate Constants

2.1.1 First-order Reactions

When we study the rate of a reaction, we normally actually measure concentrations of reagents or products at different times as the reaction proceeds. To see how this is connected to mechanism, let us look first at elementary unimolecular and bimolecular reactions.

Kinetic theory tells us that reactions take place because random collisions between molecules produce a small number of molecules with an energy greater than the minimum (the activation energy) for reaction to occur. For unimolecular reactions at a particular temperature, this number (and thus the rate of reaction) will be proportional to the number of molecules present in a particular space (volume), *i.e.* the concentration. Thus for a reaction

$$\mathrm{A} \rightarrow \mathrm{B} \tag{2.1}$$

$$\text{Rate of reaction} = \mathrm{d[B]}/\mathrm{d}t = -\mathrm{d[A]}/\mathrm{d}t = k_1[\mathrm{A}] \tag{2.2}$$

The constant k_1 is known as the **first-order rate constant** and has the units of 1/time, normally expressed as s^{-1}.

For a reaction of this type, the reaction will slow down as the reaction proceeds, so that when half the starting compound has been used up, the rate will have fallen to half of the original value. After three-quarters has been used up (and only a quarter remains), the rate will have fallen to a quarter of the original rate, and so on. The time taken for the concentration to drop to a half of the original value in a first-order reaction is a constant, the **half-life**; this does not depend on the original concentration.

It is easier to measure concentration than rate; a plot of concentration against time is shown in Figure 2.1(a). This type of process is known as exponential decay. In principle, reactions of this type are never complete. However, 99.9% completion corresponds to about 10 half-lives, and 99.9999% to 20 half-lives, at which point for all practical purposes the reaction is complete.

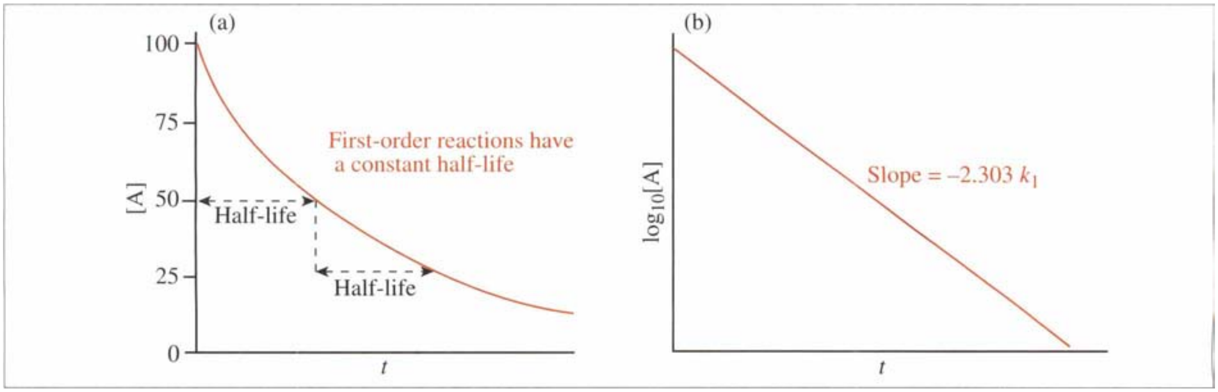


Figure 2.1 First-order reactions

To find out if the reaction is first order, you can make a plot of the type shown in Figure 2.1(a) and check that the half-life is constant, *i.e.* that the time taken for the concentration to fall from 100% to 50% is the same as that for 50% to 25% and 25% to 12.5%. In practice, it is often difficult to be sure of half-lives, particularly if there is significant scatter, and it may be impractical to measure the rate over several half-lives.

An alternative is to use calculus to transform equation (2.2) by integration. This gives equations (2.3) and (2.4):

$$\ln\{[\mathrm{A}]_0/[\mathrm{A}]_t\} = k_1 t \tag{2.3}$$

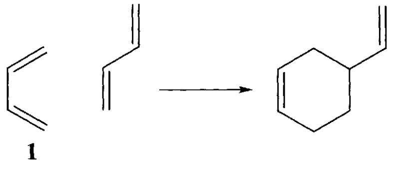
$$\log_{10}[\mathrm{A}] = -2.303k_1 t + \log_{10}[\mathrm{A}]_0 \tag{2.4}$$

Thus a plot of $\log_{10}[\mathrm{A}]$ against time should give a straight line of slope $-2.303k_1$. The straightness of the plot is evidence for first-order behaviour, and the slope allows the first-order rate constant k_1 to be determined (Figure 2.1b).

From a practical point of view, it is often easier to monitor the concentration of product rather than reagent. Provided that the reaction is quantitative, the final concentration of B, $[\mathrm{B}]_\infty$, will equal $[\mathrm{A}]_0$, so a plot of $[\mathrm{B}]_\infty - [\mathrm{B}]_t$ against t will be equivalent to a plot of $[\mathrm{A}]_t$ against t.

2.1.2 Second-order Reactions

For an elementary bimolecular reaction, the two molecules involved may be the same or different. The number of product molecules is almost always one or two. We have already come across reactions of this type: the S_N2 hydrolysis of halogenoalkanes involves reaction between two different molecules; reaction (2.5) involves two molecules of the same compound, buta-1,3-diene (**1**):



(2.5)

Since two molecules are involved in the reaction, and the rate of reaction depends on the frequency of collisions, the rate of reaction will depend on both [A] and [B] (different reagents), or on $[\mathrm{A}]^2$ if there is only one reagent:

$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{C} + \mathrm{D} \tag{2.6}$$

$$\text{Rate of reaction} = d[C]/dt = d[D]/dt = -d[A]/dt = -d[B]/dt = k_2[A][B] \quad (2.7)$$

$$A + A \longrightarrow C \quad (2.8)$$

$$\text{Rate of reaction} = -d[A]/dt = k_2[A]^2 \quad (2.9)$$

For reactions involving a single component A, a plot of [A] against time will give a curve of the type shown in Figure 2.2(a). Because the rate of reaction depends on the square of the concentration of the reagents, the rate will fall off more rapidly with time than for a first-order reaction, and the half-life will increase as the reaction proceeds. As with first-order reactions, it is useful to integrate the rate equation to give an expression involving concentration directly; the result of integrating equation (2.9) is equation (2.10), from which it can be seen that a plot of 1/[A] against time should be a straight line, with a slope of k_2. This is shown in Figure 2.2(b).

$$1/[A] - 1/[A]_0 = k_2t \quad (2.10)$$

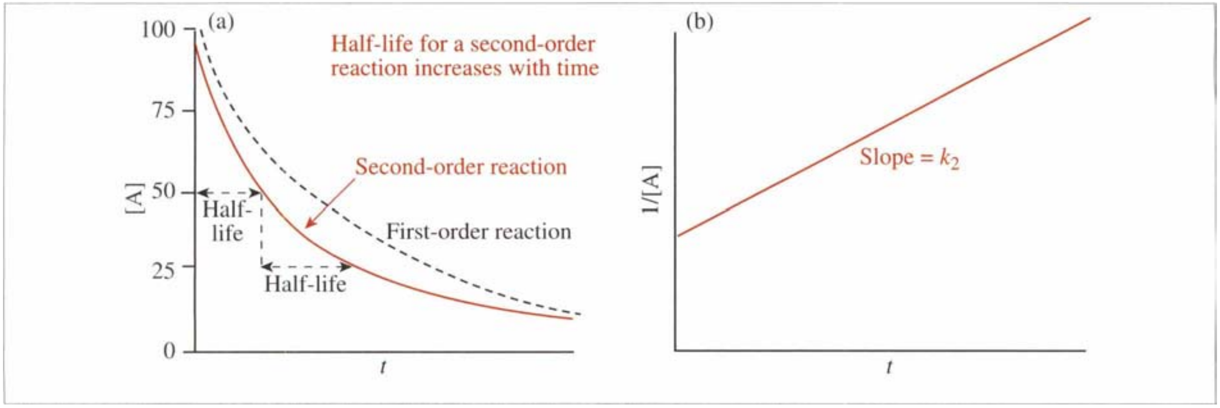


Figure 2.2 Second-order reactions

Similar expressions can be derived for reactions of different orders.

For reactions with two components, it is better to determine the order with respect to each component separately, as described in the next section.

2.1.3 Order of Reaction and Connection between Reaction Order and Reaction Mechanism

In more complicated reactions with several reagents, the reaction rate depends on the concentrations of some or all of the components, and for a reaction of type (2.11), an expression of the type (2.12) can often be written:

$$A + B + C \ldots \longrightarrow \text{Products} \tag{2.11}$$

$$\text{Rate} = -\mathrm{d}[A]/\mathrm{d}t = -\mathrm{d}[B]/\mathrm{d}t = -\mathrm{d}[C]/\mathrm{d}t = k[A]^l[B]^m[C]^n \ldots \tag{2.12}$$

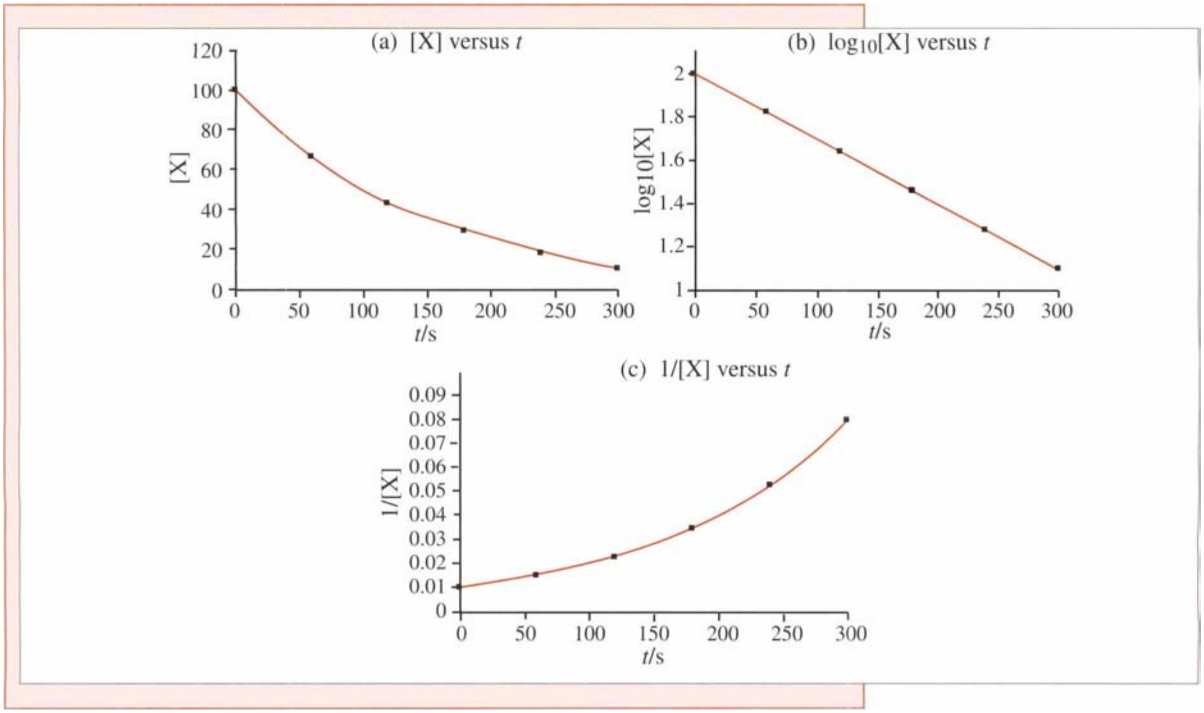
The reaction is then said to be of l-th order with respect to A, m-th order with respect to B, n-th order with respect to C, and so on, with a total order of $l+m+n$. The orders with respect to each component are usually but not always integers. Experimentally, orders with respect to individual reagents are usually obtained by carrying out the reaction with all other components except the one being investigated (say A) being in a large (10- to 20-fold) excess. Under these conditions, the concentrations of B, C, *etc.*, will not change appreciably during the reaction, and the rate will effectively depend only on [A] as the only reagent being depleted. We talk of pseudo-first-order, pseudo-second-order, *etc.*, behaviour in these cases.

Worked Problem 2.1

Q The following data were obtained for the disappearance of a reagent X in a reaction in which all other components are present in a 20-fold excess. Use appropriate plots to determine, if possible, if the reaction is zero, first, or second order with respect to the reagent concerned.

t/s	*0*	*60*	*120*	*180*	*240*	*300*
[X]/M	1.0	0.66	0.43	0.29	0.18	0.10

A Plots of [X], $\log_{10}$[X] and 1/[X] against time are conveniently obtained using a spreadsheet and are shown below. As outlined in Section 2.1, these plots should produce straight lines for zero-, first- or second-order dependence respectively of the rate with respect to component X. Inspection of the plot shows that curve (b) corresponding to first-order behaviour is straight, whereas the other two plots are curved. These plots provide convincing evidence of first-order behaviour with respect to X, provided that the order is an integer.



2.2 Conclusions about Mechanism that can be Drawn from Kinetic Order

2.2.1 First- and Second-order Reactions

Elementary uni- and bimolecular reactions will necessarily show first- and second-order kinetic behaviour, but the reverse is not necessarily true: a first-order reaction *may* not be unimolecular and a second-order reaction *may* not be bimolecular. For example, we considered the decomposition of dibenzylmercury in Chapter 1, in which the mechanism could either be elementary, giving a mercury atom and a 1,2-diphenylethane molecule directly (reaction 2.13a), or the reaction could be complex, with a slow initial homolysis of a carbon–mercury bond, followed by rapid further reactions to give the products (reaction 2.13b). Similarly for the Cope rearrangement of diene **2** to diene **4**, the reaction could be elementary, with a concerted cyclic movement of electrons (reaction 2.14a), or might involve a di-radical intermediate **3** which rapidly reacted further to give the observed product **4** (reaction 2.14b). Both these mechanisms would lead to first-order kinetics, so the establishment of first-order kinetic behaviour for both these reaction schemes does not establish the

Elementary uni- and bimolecular reactions must show first- and second-order kinetics, respectively; however, reactions showing first- and second-order kinetics are not necessarily elementary.

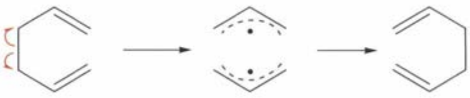
mechanism. In fact, based on other evidence, reaction (2.13) is believed to involve the complex mechanism (2.13b) whereas the Cope rearrangement is believed to be an elementary unimolecular reaction (2.14a). The same is true for reactions between two different species to give products: second-order rate dependence (first order with respect to both components) is consistent with a bimolecular reaction but does not prove it.

$$\mathrm{PhCH_2{-}Hg{-}CH_2Ph} \longrightarrow \mathrm{PhCH_2{-}CH_2Ph} + \mathrm{Hg} \tag{2.13a}$$

$$\begin{tikzcd}
\mathrm{(PhCH_2)_2Hg} \arrow[r, "k_\mathrm{d}"] & \mathrm{PhCH_2{-}Hg^\bullet} + {}^\bullet\mathrm{CH_2Ph} \arrow[d] \\
\mathrm{PhCH_2CH_2Ph} & \mathrm{PhCH_2^\bullet} + \mathrm{Hg} \arrow[l, "\mathrm{PhCH_2^\bullet}"']
\end{tikzcd} \tag{2.13b}$$

2 4

(2.14a)



2 3 4

(2.14b)

2.2.2 Rate-determining Step

If a reaction has a rate-determining step, only species that are involved in steps up to and including the rate-determining step can affect the rate of reaction.

Why does the mechanism shown in reaction (2.13b) lead to simple first-order kinetics, not involving rate constants for the reactions subsequent to the first step? The answer is that the first step is *slow*; subsequent reactions are much faster. The only reaction by which dibenzylmercury is destroyed is the first step, which is a unimolecular reaction that is first order. The overall rate of loss of dibenzylmercury will therefore show first-order kinetics, with the measured rate constant corresponding to k_d. Reactions of this type with a "bottleneck" are said to have a **rate-determining** (or **rate-limiting**) **step**. Reactions subsequent to the rate-determining step, which need not be the first step, can have no effect on the kinetics. We have already come across another reaction involving a rate-determining step, the $\mathrm{S_N1}$ hydrolysis of a halogenoalkane by a base. Although reaction (2.15) involves both a *t*-butyl bromide (2-bromo-2-methylpropane) molecule **5** and a hydroxide ion, experimentally the rate shows a first-order dependence on **5** and zero-order (*i.e.* no) dependence on the hydroxide ion, in accordance with equation (2.15). *Reactions which show a zero-order dependence on one of the components cannot be elementary reactions.*

$$\underset{\mathbf{5}}{\mathrm{Me_3C{-}Br}} \xrightarrow{\text{slow}} \mathrm{Br^- + Me_3C^+} \xrightarrow[\text{fast}]{^-\mathrm{OH}} \mathrm{Me_3C{-}OH} \tag{2.15}$$

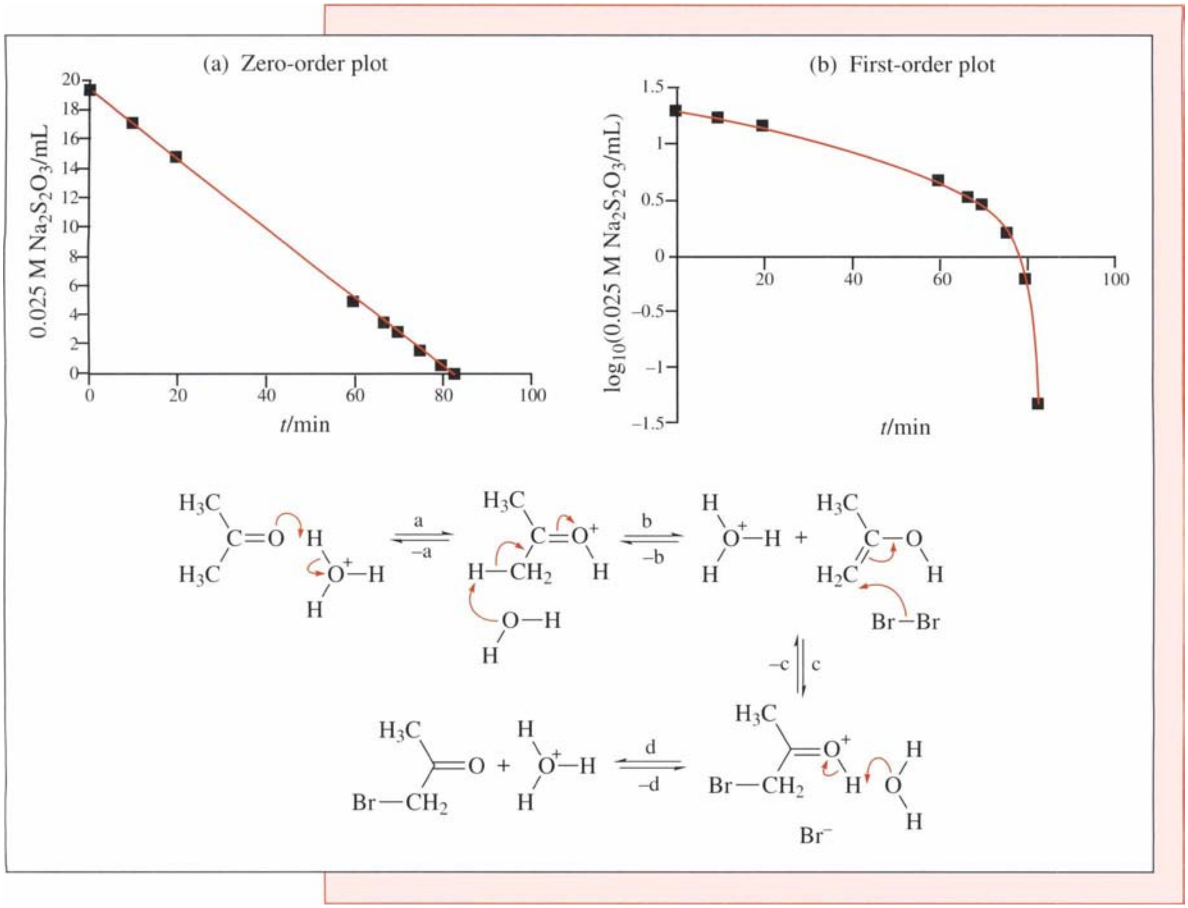
Worked Problem 2.2

Q In the acid-catalysed bromination of acetone (propanone) in water, the reaction was followed by measuring the disappearance of bromine by taking aliquots at intervals, adding excess potassium iodide (which converts the remaining bromine into iodine) and titrating the iodine liberated against 0.025 M sodium thiosulfate ($Na_2S_2O_3$) solution. The data shown below were obtained (the $Na_2S_2O_3$ titre is proportional to the residual bromine concentration). What conclusions about the reaction can be drawn?

$$\mathrm{CH_3COCH_3 + Br_2 \xrightarrow{H^+} CH_3COCH_2Br + HBr}$$

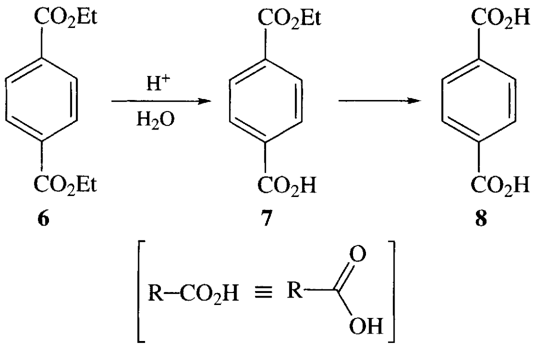
t/min	*0*	*10*	*20*	*60*	*67*	*70*	*75*	*80*	*83*
0.025 M $Na_2S_2O_3$ solution/mL	19.25	17.05	14.8	5.0	3.5	3.0	1.6	0.65	0.05

A The plot of the $Na_2S_2O_3$ titre, which is proportional to $[Br_2]$, against time shown below in (a) is linear, whereas a logarithmic plot (b) is curved. This shows that the rate of the bromination reaction does not depend on $[Br_2]$. Thus a bromine molecule is not involved in the rate-determining step, so the initial reaction must involve the other components. A possible scheme, consistent with this evidence, is shown below. There will be a zero-order dependence on $[Br_2]$ provided that the rate of reaction c (the only step which involves a bromine molecule) is considerably faster than −b. This mechanism would need to be tested further by other experiments, the first of which would be to confirm the kinetic dependence on the other two components.



2.2.3 Rate of Formation of Products

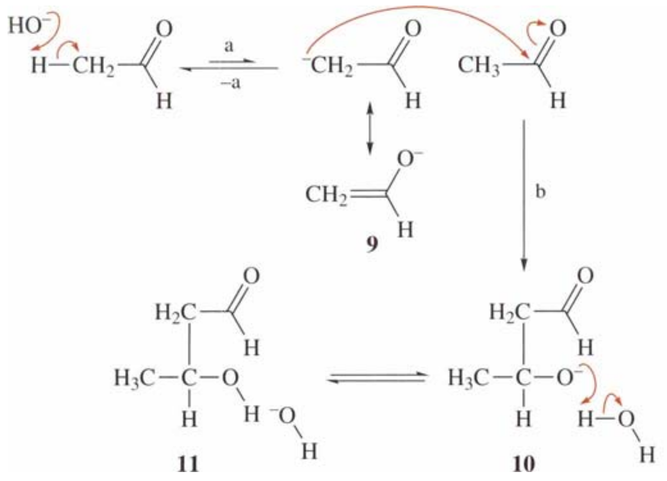
Incidentally, if we tried to measure the rates of reactions (2.13) or (2.15) by measuring the rate of appearance of the products, we would find that the rates would almost exactly match those of the disappearance of the starting materials. Even though intermediates are involved, they are so unstable as not to build up any measurable concentration during the reaction. However, in the acid-catalysed hydrolysis of the diester **6** (reaction 2.16), the initial rate of disappearance of **6** will be greater than the rate of formation of **8** because the intermediate **7** will have a similar reactivity to the initial diester **6**, so it will build up in concentration initially, and until an appreciable amount of the intermediate is formed, the rate of production of the diacid product will be negligible. *Reactions where the rate of formation of the products is initially slower than the rate of disappearance of starting materials cannot be elementary.*



(2.16)

2.2.4 Reactions of Order Higher than Second

These cannot be elementary, since termolecular organic reactions are virtually non-existent. The most common reason for third-order kinetics is for two reagents to react with each other rapidly and reversibly to give an intermediate, which then undergoes a slow rate-determining reaction to give a product. An example is the base-catalysed dimerization of two acetaldehyde (ethanal) molecules to give 3-hydroxypropanal (aldol, **11**). The rate is proportional to $[\mathrm{CH_3CHO}]^2[\mathrm{OH^-}]$. Proton abstraction by the hydroxide ion from the acetaldehyde molecule gives rise to a small concentration of the intermediate anion **9**. The reverse reaction is rapid, an equilibrium is set up and the concentration of this intermediate, [**9**], will be $k_{2.17\mathrm{a}}[\mathrm{CH_3CHO}][\mathrm{OH^-}]/k_{-2.17\mathrm{a}}[\mathrm{H_2O}]$. The rate-determining step is equation (2.17b), a second-order reaction involving addition of **9** to a $\mathrm{CH_3CHO}$ molecule to give the anion **10**. The rate of formation of product will therefore be the rate of this reaction, $k_{2.17\mathrm{b}}[\mathrm{CH_3CHO}] \times [\mathrm{^-CH_2CHO}] = k_{2.17\mathrm{a}}k_{2.17\mathrm{b}}[\mathrm{CH_3CHO}]^2[\mathrm{OH^-}]/k_{-2.17\mathrm{a}}[\mathrm{H_2O}]$, accounting for the third-order behaviour.



(2.17)

2.2.5 Reactions with Fractional Order: Radical Chain Reactions

These cannot be elementary. The fractions are usually 1/2 or 3/2 and indicate a **radical chain reaction**. An example is the bromination of trichloromethane (chloroform; reaction 2.18); the kinetic expression is given by equation (2.19).

$$\mathrm{Br_2 + CHCl_3 \longrightarrow BrCCl_3 + HBr} \qquad (2.18)$$

$$\frac{-\mathrm{d}[\mathrm{Br_2}]}{\mathrm{d}t} = k_{\mathrm{obs}}[\mathrm{CHCl_3}][\mathrm{Br_2}]^{0.5} \qquad (2.19)$$

Radical reactions will be discussed in more detail in Chapter 6. Radicals are molecules or atoms with an unpaired electron, usually formed by thermolysis (*e.g.* reaction 2.20) or by photolysis of compounds containing a weak covalent linkage. In reaction (2.18), the Br–Br bond is the weakest bond present in the two molecules, and the homolysis (2.20) takes place at an appreciable rate at temperatures above 150°C. Processes that produce radicals in this way are termed **initiation reactions**. Since the radicals are formed in very small quantities, and since they are very reactive species, the bromine atom will react predominantly with trichloromethane (reaction 2.21) to give hydrogen bromide and the trichloromethyl radical. This in turn reacts with a bromine molecule (usually not a bromine atom – there are very few of these around) to give the bromotrichloromethane product and regenerating a bromine atom (reaction 2.22). The pair of reactions (2.21) and (2.22) are called **propagation reactions**. These are the reactions that turn reagents into products: up to several thousand molecules for each bromine atom produced. The bromine atom used up in (2.21) is regenerated in (2.22). Finally, the combination reactions (2.23), (2.24) and (2.25) destroy the radicals (**termination**). These bimolecular reactions have very large rate constants, so the radical concentrations can only reach a very low level.

$$\mathrm{Br_2 \longrightarrow 2\ Br^{\bullet}} \qquad \text{Initiation} \qquad (2.20)$$

$$\left.\begin{array}{l} \mathrm{Br^{\bullet} + H{-}CCl_3 \longrightarrow Br{-}H + {}^{\bullet}CCl_3} \quad (2.21) \\ \mathrm{Br{-}Br + {}^{\bullet}CCl_3 \longrightarrow Br^{\bullet} + Br{-}CCl_3} \quad (2.22) \end{array}\right\} \text{Propagation}$$

$$\left.\begin{array}{l} \mathrm{Br^{\bullet} + Br^{\bullet} \longrightarrow Br_2} \quad (2.23) \\ \mathrm{Br^{\bullet} + {}^{\bullet}CCl_3 \longrightarrow Br{-}CCl_3} \quad (2.24) \\ \mathrm{2\ {}^{\bullet}CCl_3 \longrightarrow Cl_3C{-}CCl_3} \quad (2.25) \end{array}\right\} \text{Termination}$$

For this reaction, it turns out that the propagation step (2.21) is much slower than (2.22), so that when a bromine atom is lost in reaction (2.21), it is quickly regenerated by (2.22); therefore most of the radicals present in the system at any one time are bromine atoms. Since the instantaneous concentration ($\sim 10^{-8}$ M) of bromine atoms is much smaller than the throughput of the atoms and its absolute value falls only very slowly as the reaction proceeds, the rates of formation ($= 2k_{20}[Br_2]$) and destruction ($= 2k_{23}[Br^\bullet]$) of these reactive atoms are approximately equal, so we can equate these rates in equation (2.26) and derive an expression for the concentration of the bromine atoms in equation (2.27). This is the **steady-state approximation**. Because $[Br^\bullet] >> [^\bullet CCl_3]$, termination steps (2.24) and (2.25) can be ignored. Throughput to products depends on the propagation steps, and since (2.21) is rate determining, the overall rate of reaction is given by equation (2.28), and the reaction has an overall order of 1.5: first order with respect to the trichloromethane and 0.5 order with respect to the bromine.

Fractional orders, particularly if half powers are involved, suggest a free radical reaction.

$$\frac{d[Br^\bullet]}{dt} = 2k_{2.20}[Br_2] - 2k_{2.23}[Br^\bullet]^2 \approx 0 \tag{2.26}$$

$$[Br^\bullet] = (k_{2.20}/k_{2.23})^{0.5}[Br_2]^{0.5} \tag{2.27}$$

$$\begin{aligned}\frac{d[BrCCl_3]}{dt} = \frac{-d[CHCl_3]}{dt} &= k_{2.21}[CHCl_3][Br^\bullet] \\ &= k_{2.21}\left(\frac{k_{2.20}}{k_{2.23}}\right)^{0.5}[CHCl_3][Br_2]^{0.5}\end{aligned} \tag{2.28}$$

2.2.6 Reactions with Mixed Order: Competing Reactions

In many reactions, two or more processes may contribute to the disappearance of a reactant. These processes may have different kinetic dependence on the reagent concentrations. For example, when 2-bromopropane is hydrolysed to propan-2-ol by sodium hydroxide in aqueous ethanol, both S_N1 and S_N2 processes take place at the same time, and each contributes to the loss of the 2-bromopropane, as shown in reactions (2.29) and (2.30). Both processes involve $[Me_2CH{-}Br]$, but the S_N2 process also depends on $[OH^-]$ whereas the S_N1 process does not. The overall rate of loss of 2-bromopropane is given by expression (2.31), showing a mixed kinetic dependence of zero and first order with respect to the hydroxide ion.

$$Me_2CH{-}Br \xrightarrow{\text{slow}} Br^- + Me_2CH^+ \xrightarrow{^-OH} Me_2CH{-}OH \tag{2.29}$$

$$Me_2CH{-}Br + {}^-OH \longrightarrow Me_2CH{-}OH + Br^- \tag{2.30}$$

$$\text{Rate} = \frac{-\mathrm{d}[\mathrm{Me_2CHBr}]}{\mathrm{d}t} = k_{2.29}[\mathrm{Me_2CHBr}] + k_{2.30}[\mathrm{Me_2CHBr}][\mathrm{OH^-}] \qquad (2.31)$$

This kinetic behaviour is difficult to distinguish from the fractional order dependence discussed in the previous section. However, if several experiments are carried out with different [OH^-] concentrations, and a plot of {initial rate of reaction/[Me_2CH–Br]} against [OH^-] is made, the result will be a straight line of slope k_2 and an intercept of k_1, as shown in Figure 2.3. For this reaction, $k_1 = k_{2.29}$ and $k_2 = k_{2.30}$.

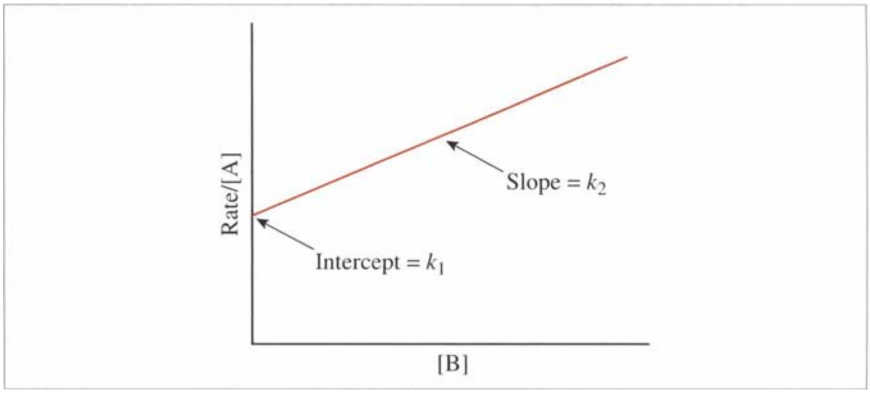
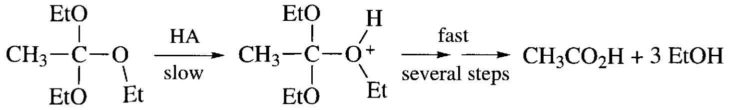


Figure 2.3 Mixed first- and second-order kinetics. A plot of rate/[A] against [B] for a reaction which follows the rate expression: rate = k_1[A]+k_2[A][B]

Mixed order kinetics indicate that two or more reactions are taking place in parallel.

Many acid- and base-catalysed reactions show mixed-order kinetics. For example, 1,1,1-triethoxyethane (ethyl orthoacetate, **12**) is hydrolysed to ethanol and acetic acid (ethanoic acid) in aqueous buffers of *m*-nitrophenol (a weak acid) and its sodium salt (reaction 2.32). The kinetic dependence is shown in equation (2.33). It appears that three separate processes contribute to the loss of **12** from the reaction mixture. The second term in rate expression (2.33) suggests a reaction with a rate-determining step involving transfer of a proton from H_3O^+ with a rate constant k_h. This would correspond to the first step of (2.32), with $HA = H_3O^+$. The third term suggests a similar process, but with the transfer of the proton from the undissociated *m*-nitrophenol (first step in 2.32, but with $HA = HOC_6H_4NO_2$, rate constant k_a). The first term probably relates to the transfer of a proton to **12** from a water molecule (first step in 2.32, but with $HA = H_2O$). The k_u term should involve the water concentration, but this cannot be varied significantly in aqueous solution. The mixed order kinetic expression for reaction (2.32) provides strong evidence that the reaction can be catalysed by any acid present (H_3O^+, $HOC_6H_4NO_2$ or H_2O). Any acid can provide the proton in the rate-determining step, though with different rate constants, and the reaction is therefore subject to general acid catalysis.



12

$$CH_3C(OEt)_2OEt \xrightarrow[\text{slow}]{HA} CH_3C(OEt)_2O^+(H)Et \xrightarrow[\text{several steps}]{\text{fast}} \longrightarrow CH_3CO_2H + 3\,EtOH \qquad (2.32)$$

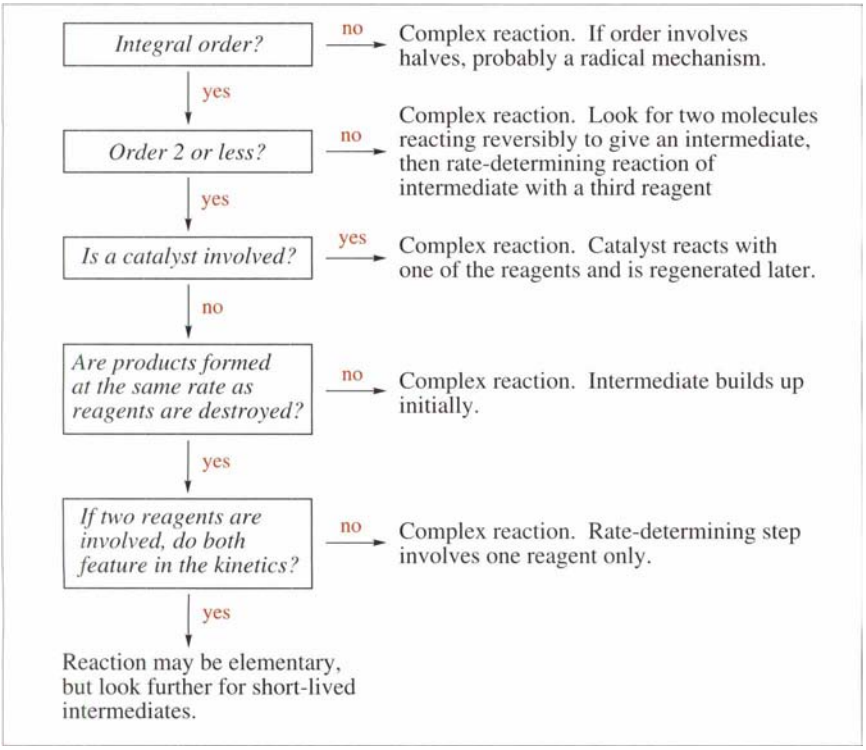
$$\frac{-\mathrm{d}[\mathbf{12}]}{\mathrm{d}t} = k_u[\mathbf{12}] + k_h[\mathbf{12}][H_3O^+] + k_a[\mathbf{12}][HOC_6H_4NO_2] \qquad (2.33)$$

2.2.7 More Complex Kinetic Behaviour

Not all reactions show a kinetic behaviour based on a simple order dependence. The most common reason for this is that the reaction is reversible, so the rate will fall as product accumulates, and its concentration will enter the kinetic rate expression. The simplest solution if this happens is to measure initial rates and confine the kinetic study to the first few percent of the reaction.

2.2.8 Summary

A flow chart showing how information about kinetic order gives useful information about mechanisms is shown in Figure 2.4. It must be emphasized that kinetic information can rule out possible mechanisms



Complex reaction. If order involves halves, probably a radical mechanism.

Complex reaction. Look for two molecules reacting reversibly to give an intermediate, then rate-determining reaction of intermediate with a third reagent

Complex reaction. Catalyst reacts with one of the reagents and is regenerated later.

Complex reaction. Intermediate builds up initially.

Complex reaction. Rate-determining step involves one reagent only.

Reaction may be elementary, but look further for short-lived intermediates.

Figure 2.4 Information about reaction mechanisms from kinetics studies but can never prove a particular mechanism. If more than one mechanistic possibility remains that is consistent with the observed kinetics, then other methods need to be employed, as discussed in the next four chapters.

2.3 The Dependence of Rate of Reaction on Temperature: Arrhenius Parameters

Most reactions go faster at higher temperatures, and for the majority of reactions the variation with temperature can be expressed in the form of equation (2.34). If we take logarithms of both sides of this equation, we obtain equation (2.35), from which we see that a plot of $\log_{10}k$ against $1/T$ (in Kelvin) should be a straight line of slope $E/2.303R$ and intercept $\log_{10}A$. Equation (2.34) is known as the **Arrhenius equation**. A is known as the **Arrhenius A** or **pre-exponential factor** and E is the **activation energy**, which can be identified for elementary reactions as the energy required for the molecules to reach the transition state and therefore be able to react. These parameters provide useful information, particularly for radical or molecular reactions; for ionic reactions, solvent effects make it difficult to extract useful information.

$$k = Ae^{-E/RT} \tag{2.34}$$

$$\log_{10}k = \log_{10}A - E/2.303RT \tag{2.35}$$

2.3.1 Information from Activation Energies

Although it is difficult to predict activation energies, it is easier to measure or predict heats (enthalpies) of formation and hence heats of reaction. For an endothermic reaction, the activation energy must be at least as great as the endothermicity ΔH (Figure 2.5), so if the measured activation energy of reaction is less than the endothermicity of a proposed elementary reaction or an initial rate-determining step, that proposal can be ruled out.

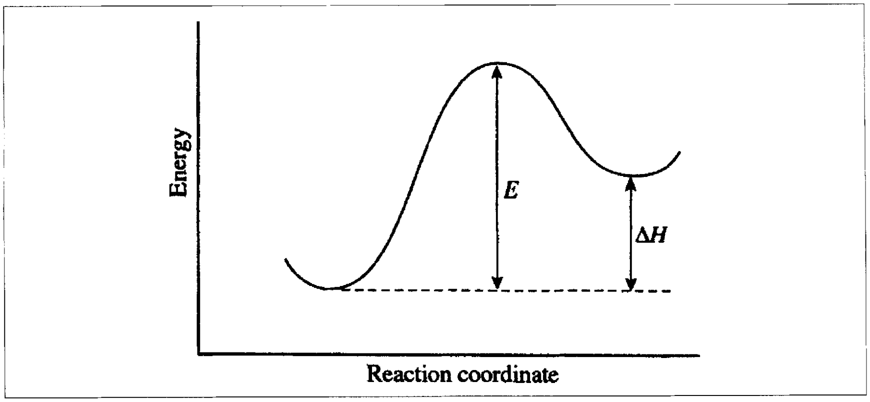


Figure 2.5 Endothermic reactions

For example, tetraethyllead decomposes on heating to give lead, ethane, ethene and butane. Two possible mechanisms are equations (2.36) and (2.37). Mechanism (2.36) involves simultaneous rupture of all four Pb–C bonds to give a lead atom and four ethyl radicals. From the known heats of formation of tetraethyllead, lead and the ethyl radical, the heat of reaction of (2.36) can be estimated as +515 kJ mol^{-1}. This is massively greater than the observed activation energy of 155 kJ mol^{-1}, so it must be concluded that (2.36) cannot be correct, which suggests that the stepwise breakage of successive Pb–C bonds as shown in (2.37) is favoured. Since the simple homolysis of one bond in an organic molecule normally takes place without an extra activation energy over and above that required by its endothermicity, the figure of 155 kJ mol^{-1} can be equated with ΔH for the first step of (2.37), allowing the heat of formation of the triethyllead radical to be determined. A large number of heats of formation of organic radicals have been determined in this way.

$$\mathrm{Pb(C_2H_5)_4} \longrightarrow \mathrm{Pb} + 4\,\mathrm{C_2H_5^{\bullet}} \qquad \Delta H = +515\ \mathrm{kJ\ mol^{-1}} \tag{2.36}$$

$$\begin{tikzcd}
\mathrm{Pb(C_2H_5)_4} \arrow[r] & \mathrm{(C_2H_5)_3\dot{P}b^{\bullet} + C_2H_5^{\bullet}} \arrow[r, "-\mathrm{C_2H_5^{\bullet}}"] & \mathrm{(C_2H_5)_2Pb\!:} \arrow[r, "-\mathrm{C_2H_5^{\bullet}}"] & \mathrm{C_2H_5{-}\dot{P}b\!:} \arrow[d, "-\mathrm{C_2H_5^{\bullet}}"'] \\
 & & & \mathrm{Pb}
\end{tikzcd} \tag{2.37}$$

Cyclohexene decomposes on heating to give butadiene and ethene. Two mechanistic possibilities are equations (2.38) and (2.39). Mechanism (2.38) involves breakage of a single C–C bond, a process which should require an energy input of about 343 kJ mol^{-1}, lessened by say 38 kJ mol^{-1} to about 305 kJ mol^{-1} to take account of the allylic stabilization expected in the intermediate diradical **13**. The observed activation energy is 279 kJ mol^{-1}, significantly less than this value, which suggests that the alternative concerted reaction (2.39), where three bonds are made concurrently with three bonds being broken, is more likely.

13

(2.38)

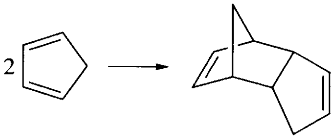
(2.39)

2.3.2 Arrhenius *A* factors

Low Arrhenius *A* factors suggest a "tight" transition state, with loss of entropy compared with reagents. High *A* factors suggest a "loose" transition state, with a gain of entropy compared with reagents.

Simple kinetic theory for bimolecular reactions equates the activation energy of the reaction to the minimum energy for the reaction to take place, which is brought to the reacting system by the energy of collision of the two reagent molecules. The *A* factor is seen as the product *PZ* of the rate of collisions *Z* multiplied by a probability factor *P*, which depends on the likelihood of a particular collision having the correct geometry for the reaction to take place. Transition state theory relates the *A* factor to the difference in entropy $\Delta S^{\ddagger}$ between the reagent molecule(s) and the transition state. The more entropy that is lost (*e.g.* by molecules associating, forming new bonds that restrict rotation), the lower the *A* factor. This is known as a "tight" transition state. Conversely, if the molecule is dissociating into fragments with a gain in entropy, this corresponds to a "loose" transition state and a high *A* factor. For unimolecular reactions, homolyses of molecules into radicals form excellent examples of a loose transition state, which is close to the two incipient free radicals. These have $\log_{10}A$ in the region of 15–17 s^{-1}. On the other hand, molecular eliminations such as the elimination of HBr from CH_3CH_2Br, which involves a four-membered transition state with some bonding between the H and Br atoms and a restriction of rotation round the C–C bond, have $\log_{10}A$ in the region of 12.5–14 s^{-1}. For bimolecular reactions, the loosest transition states are found in combination reactions of radicals, where (as for the reverse homolysis) the transition state corresponds to very loose association between the two radicals, with most of the rotational entropy conserved. These give $\log_{10}A$ values in the range of 9–10.5 $M^{-1}\ s^{-1}$. Radical addition to double bonds and transfer reactions show some loss in entropy in the transition state, and have $\log_{10}A$ values in the region of 7–9 $M^{-1}\ s^{-1}$. Cycloadditions such as the Diels–Alder reaction, in which bonds are formed simultaneously between both ends of the reagent molecules, lose even more entropy, with $\log_{10}A$ values in the region of 5–7 $M^{-1}\ s^{-1}$. These results are summarized in Table 2.1. It should be emphasized that these generalizations apply only to molecular and radical reactions. For polar reactions, solvation effects are often very large, making generalization difficult.

Table 2.1 Ranges of Arrhenius pre-exponential factors for different reaction types

Molecularity	*Type of reaction*	*Example*	*log$_{10}$A* (s^{-1} or M^{-1} s^{-1})
1	Homolysis	$C_2H_6 \longrightarrow 2\,CH_3^\bullet$	15–17
1	Four-centre process	$C_2H_5Br \longrightarrow CH_2{=}CH_2 + HBr$	12.5–14
2	Pericyclic reactions		5–7
2	Radical combination	$2\,CH_3^\bullet \longrightarrow C_2H_6$	9–10.5
2	Radical transfer or addition to a double bond (reagent an organic radical)	$CH_3^\bullet + CH_2{=}CH_2 \longrightarrow CH_3{-}CH_2{-}CH_2^\bullet$ $CH_3^\bullet + C_2H_6 \longrightarrow CH_4 + C_2H_5^\bullet$	7–9
2	As above, but with a univalent atom as reagent	$Cl^\bullet + CH_4 \longrightarrow HCl + CH_3^\bullet$	10–11

2.4 Primary Kinetic Isotope Effects

Isotopes (particularly deuterium) are often used as labels to show where a reaction has occurred in a particular molecule. A specialized use of kinetics applied to isotopically substituted molecules provides information about the mechanism that is often not available from other sources.

The energy of a C–H bond in an organic molecule as a function of bond length is shown in Figure 2.6a. If we compress the bond below its equilibrium value, the energy rises steeply because of electron–electron and nuclear–nuclear repulsion. If we stretch the bond, the energy rises more gradually due to decreased orbital overlap and bonding. At an infinite separation we have the free organic radical R$^\bullet$ and a hydrogen atom. The forces involved are electrostatic, and will not be affected if we replace the hydrogen by deuterium, since this merely involves adding an uncharged neutron to the proton in the hydrogen nucleus. However, the deuteron is approximately twice as heavy as the proton, so even though the force constant of the bond is unchanged, the vibration frequency will

Deuterium ($^2H \equiv D$) is a heavy isotope of hydrogen, with a natural abundance 0.02% compared with 99.98% for ^1H. Tritium ($^3H \equiv T$) is a radioactive isotope, obtained from nuclear reactions.

be dramatically reduced because the same force is having to move a particle with twice the mass. At room temperature, most molecules are in their lowest vibrational state, but because of the zero-point energy, this is just above the minimum on the energy curve. This zero-point energy will be slightly smaller for the C–D than the C–H bond, so the deuteriated compound will have a slightly greater bond dissociation energy than the protiated compound, as shown in Figure 2.6a.

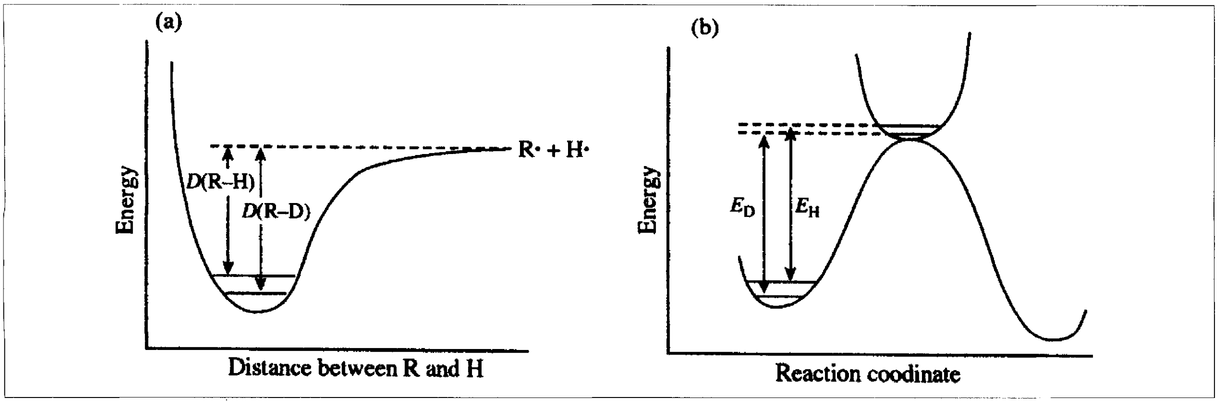
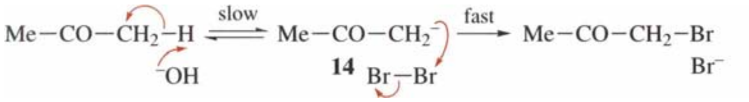


Figure 2.6 The primary deuterium isotope effect. (a) The homolytic dissociation of an alkane, showing the differences between the bond dissociation energies *D*(R–H) and *D*(R–D) due to zero-point energy differences (exaggerated). (b) A reaction in which some zero-point energy is retained in the transition state. $E_D - E_H$ is less than *D*(R–D) − *D*(R–H)

If the rate-determining step of the reaction involves breakage of the isotopically substituted bond, in the transition state the zero-point energy of that bond will have been lost. Accordingly, there will be a slightly higher activation energy for breakage of the stronger C–D bond than the weaker C–H bond. This is known as the **primary kinetic isotope effect**k_H/k_D has a maximum value of about 7 at 25°C and k_H/k_T cannot be greater than about 17 for reactions in which a hydrogen atom is transferred from one species to another. For heavier atoms, the isotope effects are much smaller. The smaller relative difference in isotopic mass ($C_{13}/C_{12} = 1.08$, $D/H = 2$) will give a much smaller difference in zero-point energies, and the maximum value of a C_{13}/C_{12} isotope effect at room temperature will be in the region of 1.04. The nearer the observed isotope effect is to the theoretical maximum, the more completely the bond in question must be broken in the transition state.

The greater availability and cheapness of deuterium compounds, coupled with the large isotope effects, has until recently made this isotope the most widely used in mechanistic studies. However, recent work using nuclear magnetic resonance or mass spectrometry has allowed the determination of heavy atom isotope effects in natural abundance, by carrying out reactions to a high level of completion and comparing the isotopic composition of the initial reagent with recovered reagent. This technique magnifies small differences in isotope effects into larger differences in ratios of species left after reaction. As an illustration, let us consider two isotopically substituted species A and B present initially in the same concentrations, showing a kinetic isotope effect k_A/k_B of 2. After three half-lives of reaction of the slower species B, its concentration would have fallen to 12.5% of its original value, but the faster species A would have fallen to 1.56%, and the ratio of the two concentrations [B]/[A] in the recovered starting material would be 12.5/1.56 = 8.

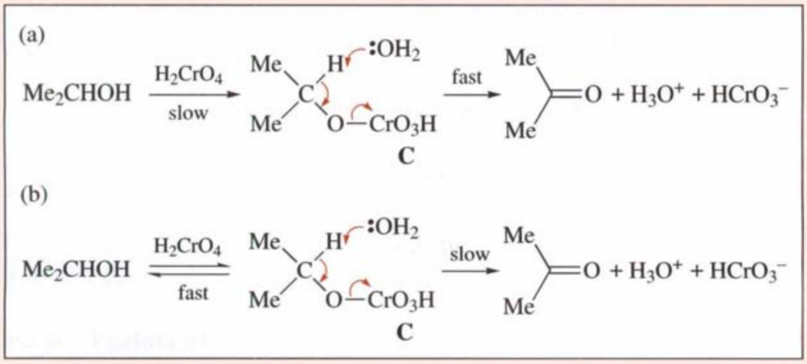
An example of a reaction showing a primary deuterium isotope effect is reaction (2.40), in which acetone (propanone) reacts with bromine in the presence of base to give bromoacetone (bromopropanone). Under similar conditions, the fully deuteriated compound CD_3COCD_3 reacts about seven times more slowly. This is consistent with the mechanism shown; the rate-determining step is the production of the anion **14** in the first step. The C–H bond is partially broken in the transition state, so the deuteriated compound will react more slowly.



(2.40)

Worked Problem 2.3

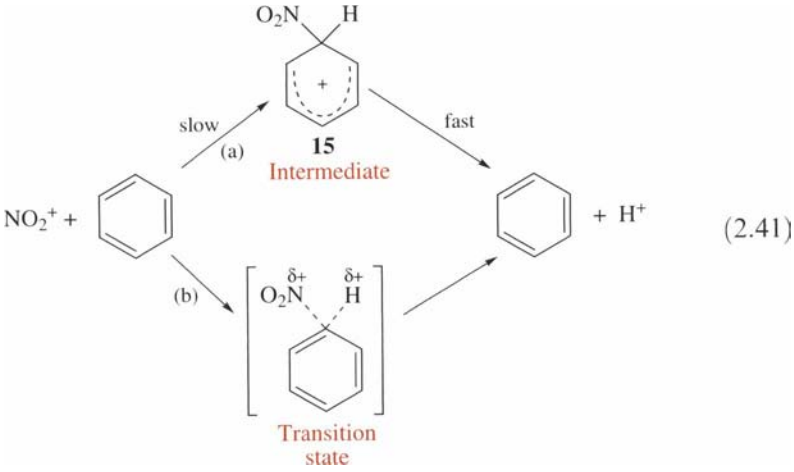
Q Propan-2-ol, Me_2CHOH, is oxidized to acetone (propanone) by chromium(VI) in dilute acid solution by the $HCrO_4^-$ anion at a rate proportional to $[Me_2CHOH][HCrO_4^-][H^+]$. The rate of reaction is reduced by a factor of about 7 if the deuteriated compound Me_2CDOH is used instead. Which of the following mechanisms is consistent with this evidence?



A Mechanism (a) involves a slow, rate-determining step producing the intermediate ester **C**, followed by a fast oxidation step. Since the C–H bond is not broken until after the rate-determining step, there should be no rate change if the propan-2-ol is replaced by Me_2CDOH. Thus mechanism (a) can be ruled out.

Mechanism (b) would involve a rapid equilibrium to be set up between the propan-2-ol and its chromate ester **C**. The second step in which the secondary C–H bond is partially broken in the transition state is rate determining, so a substantial isotope effect should be observed. Thus, of the two schemes shown, the substantial isotope effect observed supports (b).

The absence of a primary kinetic isotope effect throws important light on the mechanism of electrophilic aromatic substitution. Nitration of benzene labelled with very small amounts of the radioactive hydrogen isotope tritium was carried out to a partial extent. The radioactivity in the unreacted benzene recovered was virtually identical to that of the initial benzene, showing that there was no significant isotope effect. This suggests that there is no significant breakage of the C–H (or C–T) bond in the transition state, and that equation (2.41b) can be ruled out in favour of (2.41a) where the rate-determining step involves addition of the nitronium ion to give the stabilized intermediate **15**, followed by a rapid loss of a proton (or T^+).

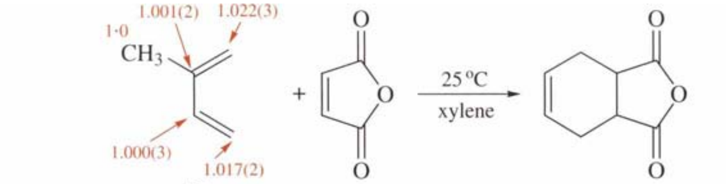


(2.41)

The presence of a significant ^{13}C isotope effect at both ends of the diene system (but not for the central carbon atoms) in **16** in the Diels–Alder

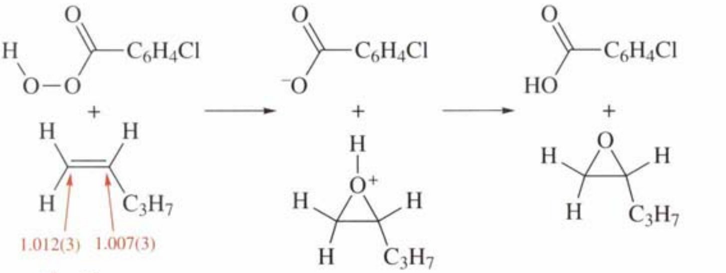
The primary kinetic isotope effect provides information about bonds broken in steps up to and including the rate-determining step.

reaction (2.42) provides strong evidence that both the terminal carbon atoms are changing their bonding in the transition state, supporting the concerted mechanism shown. Likewise, there is a significant ^{13}C isotope effect at both ends of the C=C double bond in the epoxidation reaction (2.43), indicating that both atoms are involved in the transition state, favouring the concerted mechanism shown.



16

(2.42)



(2.43)

$^{12}C/^{13}C$ kinetic isotope effects at indicated positions; figures in parentheses are standard deviations in the third place of decimals

Summary of Key Points

1. Kinetic evidence can cut down the number of mechanistic possibilities for organic reactions, but cannot "prove" a particular mechanism, since more than one mechanism may give the same kinetic order.

2. First- and second-order reactions may be either elementary or stepwise. Third- and higher-order reactions are almost always stepwise.

3. Fractional orders suggest a radical mechanism.

4. Mixed orders suggest two or more competing mechanisms for loss of reagents.

5. In reactions with a rate-determining step, species that only react *after* the rate-determining step cannot affect the kinetics.

6. The primary kinetic isotope effect is particularly valuable in showing whether or not a particular bond is involved in the rate-determining step.

Further Reading

B. G. Cox, *Modern Liquid Phase Kinetics*, Oxford University Press, Oxford, 1994.

B. K. Carpenter, *Determination of Organic Reaction Mechanisms*, Wiley, New York, 1984.

N. S. Isaacs, *Physical Organic Chemistry*, Longman, Harlow, 1995, Chapters 2 and 7.

L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley, New York, 1980.

Problems

2.1. (a) The following data were obtained for the disappearance of a reagent **A**, in a reaction in which all other components are present in a 20-fold excess. Use plots of [**A**], $\log_{10}$[**A**] and 1/[**A**] against time to determine, if possible, if the reaction is zero, first or second order with respect to **A**.

Time/s	*0*	*20*	*40*	*60*	*80*	*100*
Concentration/M	0.99	0.87	0.75	0.67	0.56	0.51

(b) The same reaction was followed for a further period of time and the following additional data were obtained. Extend your graphs to cover this additional data. Can you refine your conclusions about the order of reaction with respect to **A**?

Time/s	*120*	*140*	*160*	*180*	*200*
Concentration/M	0.44	0.39	0.32	0.28	0.22

2.2. Write at least two possible mechanisms which are consistent with each of the following observations:

(a) Bromoethane decomposes in the gas phase to ethene and hydrogen bromide, showing first-order kinetics.

(b) Solutions of bis(trimethylsilyl)mercury, $(Me_3Si)_2Hg$, in inert solvents decompose to give mercury and hexamethyldisilane, $Me_3Si–SiMe_3$, showing second-order kinetics.

2.3. The rate of nitration of benzene in a mixture of nitric acid and sulfuric acid does not depend on the benzene concentration. What can be deduced from this?

2.4. A simplified reaction scheme for the autoxidation of hydrocarbons by oxygen is shown below:

$$\text{Initiator} \xrightarrow{k_i} 2\,R^\bullet$$

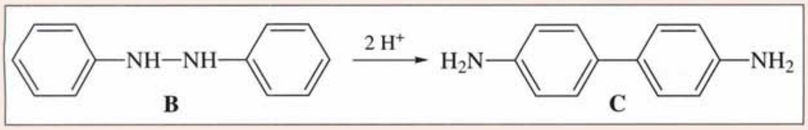
$$R^\bullet + O{=}O \xrightarrow[\text{fast}]{k_{p1}} R{-}O{-}O^\bullet$$

$$R{-}O{-}O^\bullet + H{-}R \xrightarrow[\text{slow}]{k_{p2}} R{-}O{-}O{-}H + R^\bullet$$

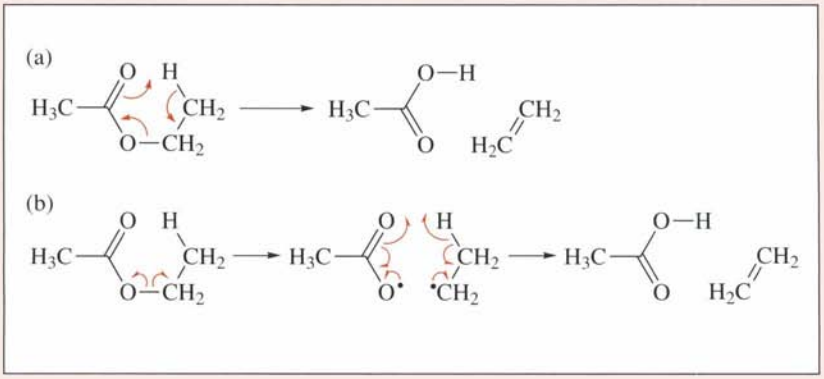
$$2\,R{-}O{-}O^\bullet \xrightarrow{k_t} R{-}O{-}O{-}R + O{=}O$$

Oxygen may be presumed to be present in excess. Apply the steady-state treatment to work out the expected kinetics for the reaction. Why is the termination step k_t, which involves two $R–O–O^\bullet$ radicals, likely to be much more significant than alternative termination reactions?

2.5. Suggest a mechanism for the benzidine rearrangement (**B** ⟶ **C**) which is consistent with the following information: (1) the reaction is first order with respect to **B** and second order with respect to $[H^+]$; (2) the reaction is strictly intramolecular; and (3) there is no isotope effect if the *para*-H atoms are replaced by D.

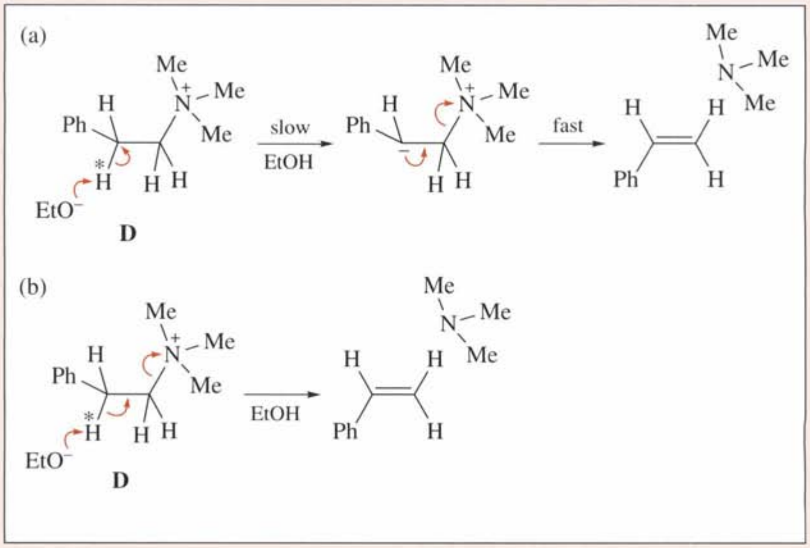


2.6. The Arrhenius *A* factor for the first-order gas-phase pyrolysis of ethyl acetate is $10^{12.5}$. Which of the two postulated mechanisms shown below does this favour?



2.7. In the Diels–Alder reaction shown in equation (2.42), rationalize the observation that there is no appreciable ^{13}C isotope effect at the 2- and 3-positions of 2-methylbuta-1,3-diene (**16**).

2.8. In the elimination reaction of the (2-phenylethyl)trimethylammonium ion **D** with the ethoxide ion, there is a $^{14}N/^{15}N$ nitrogen isotope effect $k_{^{14}N}/k_{^{15}N}$ of 1.0133 ± 0.0002 and a deuterium isotope effect at the position shown (*) k_H/k_D of 3.2. Which of the following mechanisms does this evidence support?



3

The Transition State

We cannot isolate the transition state of a chemical reaction, nor can we study it by spectroscopic methods which rely on the presence of appreciable concentrations of species with particular energy and geometry. However, the transition state does have a geometry and energy; what we can do is to investigate how changes in the reagents and solvents can influence the difference in energy between reagents and the transition state. If these influences make the transition state more stable compared with the reagents, the reaction will be faster; if the transition state is made less stable relative to the reagents, the reaction will be slower. We shall consider the effects of substituents, solvents, steric crowding and stereochemistry. We focus on elementary reactions or rate-determining steps of stepwise reactions.

Aims

By the end of this chapter you should:

- Know how solvents, substituents, steric crowding and stereochemistry can affect the rates of elementary reactions
- Use evidence from these sources to distinguish between or support particular mechanisms
- In the case of substituent effects, be able to identify whether positive or negative charge is being built up in the transition state, and whether the charge is conjugated with the substituent

3.1 Early and Late Transition States

Figure 3.1(a) represents a reaction coordinate reaction for a thermoneutral reaction, for example the abstraction of a hydrogen atom by a methyl radical from a methane molecule (reaction 3.1). Since the products are identical with the reactants, the reaction is exactly thermoneutral, with a transition state involving the transferred hydrogen being equidistant from both methyl carbon atoms. The activation energy of 61 kJ $\mathrm{mol^{-1}}$ reflects the fact that because of electron repulsion, each of the partial C–H bonds has less than half the strength of the C–H bond in methane. If we now consider the very similar reaction (3.2), this reaction is exothermic by 25 kJ $\mathrm{mol^{-1}}$, attributed to the stabilization of the ethyl radical compared with the methyl radical. Since the reaction is approximately symmetrical, we may expect the transition state to have approximately half the bonding of the breaking $\mathrm{H{-}CH_2CH_3}$ bond and half that of the forming $\mathrm{CH_3{-}H}$ bond. Thus we can expect the activation energy to be lowered by about half the change in exothermicity. The observed activation energy of 49 kJ $\mathrm{mol^{-1}}$ is in accord with this, and in general we should expect that, for similar approximately thermoneutral reactions, if we change the exothermicity by 2 kJ $\mathrm{mol^{-1}}$ we will expect an activation energy change of about 1 kJ $\mathrm{mol^{-1}}$. This is illustrated in Figure 3.1(a).

$$\mathrm{CH_3^{\bullet} + H{-}CH_3 \longrightarrow CH_3{-}H + {}^{\bullet}CH_3} \tag{3.1}$$

$$\mathrm{CH_3^{\bullet} + H{-}CH_2CH_3 \longrightarrow CH_3{-}H + {}^{\bullet}CH_2CH_3} \tag{3.2}$$

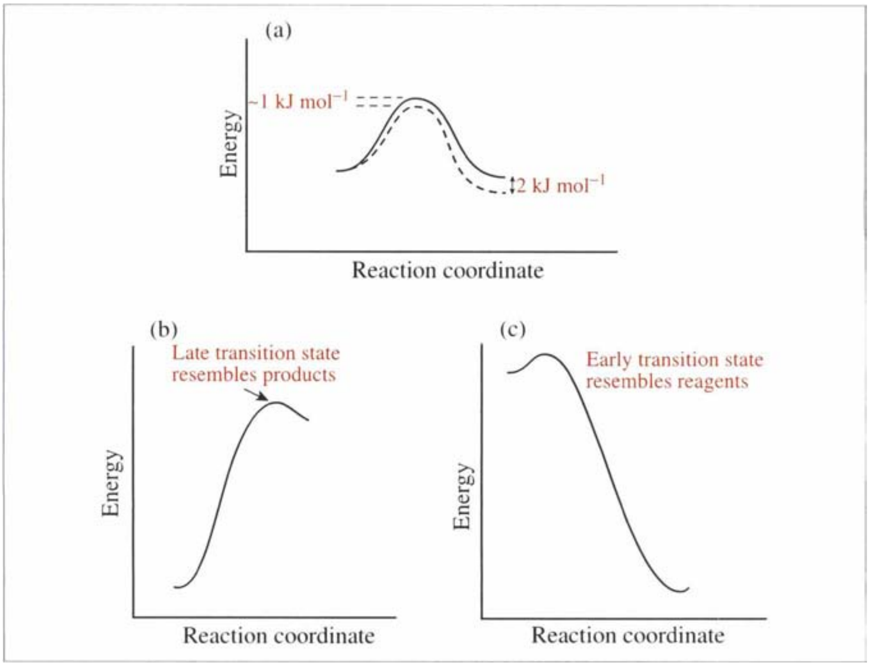


Figure 3.1 The Hammett postulate. (a) Approximately thermoneutral reaction. (b) Very endothermic reaction. (c) Very exothermic reaction

Figure 3.1(b) and (c) show reaction coordinates for very endothermic and exothermic reactions, respectively. The **Hammond postulate** states that for very endothermic reactions the transition state resembles the products almost completely, with a late transition state (Figure 3.1b), whereas for very exothermic reactions the transition state is very like the reagents, *i.e.* an early transition state (Figure 3.1c). There is much experimental evidence to support this view.

For endothermic reactions, since the transition state resembles the products, if a small change is made in the endothermicity of the reaction, almost the whole of the difference will have been developed in the transition state. This will make the rates of reactions of this type very much affected by small changes in endothermicity, often giving rise to strong selectivity between different sites in a molecule for a particular reagent. The reaction that determines the position of bromination of alkanes under free radical conditions is the abstraction of hydrogen by a bromine atom from a C–H bond. This is 44 kJ mol^{-1} endothermic for the reaction with propane to give the prop-1-yl radical (reaction 3.3a), reduced to 29 kJ mol^{-1} for attack at the 2-position (reaction 3.3b). Since these reactions are significantly endothermic, with a late transition state, this will result in a large difference in activation energies for attack at the 1- and 2-positions, giving an increased rate at the 2-position, and hence selectivity in attack there.

$$\mathrm{Br}^{\bullet} + \mathrm{C_3H_8} \longrightarrow \mathrm{Br{-}H} + {}^{\bullet}\mathrm{CH_2CH_2CH_3} \qquad \Delta H = +44\ \mathrm{kJ\ mol^{-1}} \qquad (3.3a)$$

$$\longrightarrow \mathrm{Br{-}H} + \mathrm{CH_3\dot{C}H_2CH_3} \qquad \Delta H = +29\ \mathrm{kJ\ mol^{-1}} \qquad (3.3b)$$

Conversely, for very exothermic reactions, changes in enthalpy of reaction will have little effect on the activation energy, giving unselective reactions. The corresponding fluorination of propane (reaction 3.4) is highly exothermic: $\Delta H = -159$ kJ mol^{-1} at the 1-position and -173 kJ mol^{-1} at the 2-position. However, with an early transition state and a very small activation energy for both reactions, there is little difference in rate for attack at the two positions and the reaction is very unselective.

Very exothermic reactions have an early transition state and show little positional selectivity. Very endothermic reactions have a late transition state and show high positional selectivity.

$$\mathrm{F}^{\bullet} + \mathrm{C_3H_8} \longrightarrow \mathrm{F{-}H} + {}^{\bullet}\mathrm{CH_2CH_2CH_3} \qquad \Delta H = -159\ \mathrm{kJ\ mol^{-1}} \qquad (3.4a)$$

$$\longrightarrow \mathrm{F{-}H} + \mathrm{CH_3\dot{C}H_2CH_3} \qquad \Delta H = -173\ \mathrm{kJ\ mol^{-1}} \qquad (3.4b)$$

3.2 Solvent Effects

Ions are stabilized by polar solvents. Hydrogen chloride dissolves in benzene as covalent molecules, but in water it is completely dissociated to give solvated $\mathrm{H_3O^+}$ and $\mathrm{Cl^-}$ ions. The high dielectric constant of water decreases the energy of the ions. This principle can be applied to reactions: if charge is being built up in the transition state of a reaction, the transition state will be more stabilized compared with the reagents if the reaction is carried out in a more polar solvent, resulting in an increase in rate. This is shown in Figure 3.2(a). Conversely, if charge is being dispersed or destroyed, the reagents will be more stabilized in more polar solvents, compared with the transition state, resulting in a decrease in reaction rate (Figure 3.2b).

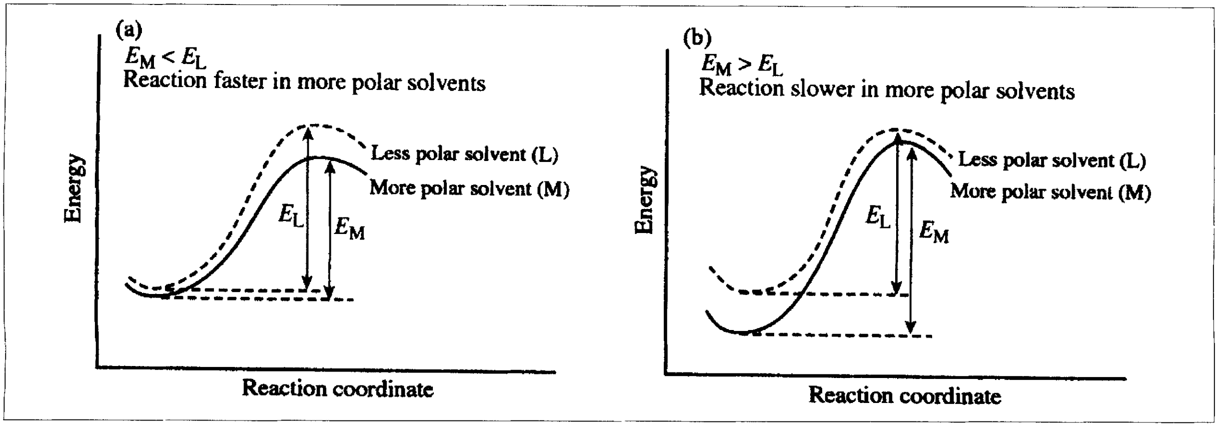


Figure 3.2 Effect of solvent polarity on reaction rate. (a) Charge built up in the transition state. (b) Charge destroyed or dispersed in the transition state

Solvent effects show whether charge is created or destroyed/dispersed in the transition state, but do not indicate the sign of the charge generated at a particular position.

Table 3.1 shows the effect of solvent polarity on four different nucleophilic substitution reactions. Creation or destruction of charge gives the biggest effects; spreading or dispersal of charge as in the second and third examples in the table gives smaller effects. Molecular and radical reactions do not involve charge build-up in the transition state, and are little affected by solvents; thus a check for the presence or absence of a solvent effect often allows a distinction to be made between radical or molecular mechanisms, on the one hand, and polar reaction mechanisms, on the other. Care should be taken in applying a solvent effect test. The change in solvent should be small, such as a 10% increase in water in aqueous ethanol; more dramatic changes in solvent polarity risk changing the mechanism.

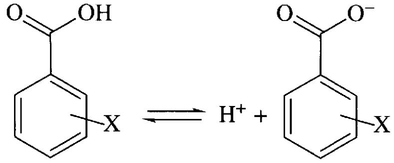
Table 3.1 Examples of solvent effects on reaction rates

Reagents		*Transition state*		*Products*	*Type*	*Effect on rate of increasing solvent polarity*
Me_3C-Br	→	$Me_3C^+\ Br^-(+H_2O)$	→	$Me_3C-OH_2^+ + Br^-$	Charge created	Large increase
$HO^- + CH_3-Br$	→	$HO^{\delta-}\cdots CH_3\cdots Br^{\delta-}$	→	$HO-CH_3 + Br^-$	Charge spread	Small decrease
$H_2O + {}^+SEt_3$	→	$H_2O^{\delta+}\cdots Et\cdots {}^{\delta+}SEt_2$	→	$H_2O^+-Et + SEt_2$	Charge spread	Small decrease
$HO^- + {}^+SEt_3$	→	$HO^{\delta-}\cdots Et\cdots {}^{\delta+}SEt_2$	→	$HO-Et + SEt_2$	Charge destroyed	Large decrease

3.3 Electronic Effects of Substituents in Polar Reactions

Solvent effects are useful in differentiating polar from non-polar reactions, but give no direct information about the location or polarity of the charges being produced or destroyed. The effect of substituent groups near to a reaction site provides more detailed insight.

A convenient system for studying substituent effects is the equilibrium between *meta*- and *para*-substituted benzoic acids and their corresponding anions (reaction 3.5). The acids are straightforward to synthesize, and the acidities in water at 25 °C are readily determined: the pH of a solution containing equal molar quantities of the acid and its fully ionized sodium salt will be equal to $-\log K_A$, where K_A is the dissociation constant of the acid. *Ortho* substituents are not considered because of complications caused by steric effects.



(3.5)

$$K_A = \frac{[H^+][XC_6H_4CO_2^-]}{[XC_6H_4CO_2H]} \tag{3.6}$$

$$\log_{10}\left(\frac{K_A}{K_H}\right) = \sigma \tag{3.7}$$

We define a **substituent constant** σ (Greek sigma = s for *s*ubstituent) for any particular *meta* or *para* substituent as log (K_A/K_H), where K_A is the dissociation constant for the substituted benzoic acid and K_H is the dissociation constant for benzoic acid itself (equation 3.7). σ values for some common substituents are given in Table 3.2.

Table 3.2 Some values of Hammett substituent constants[a]

Substituent	*meta*	*para*		
	σ	σ	σ^+	σ^-
NMe_2	−0.10	−0.32	−1.70	–
Me	−0.06	−0.14	−0.31	–
OMe	0.10	−0.28	−0.78	–
F	0.34	0.15	−0.07	–
Cl	0.37	0.24	0.11	–
Br	0.37	0.26	0.15	–
I	0.34	0.28	0.13	–
CO_2R	0.35	0.44	–	0.74
CF_3	0.46	0.53	–	–
CN	0.62	0.70	–	0.88
NO_2	0.71	0.81	–	1.26

[a] For further values, see for example N. B. Chapman and J. Shorter, *Correlation Analysis in Chemistry*, Plenum, New York, 1978

Looking at reaction (3.5), the undissociated acid is uncharged, whereas the anion has a negative charge. We might therefore expect that electronegative substituents would withdraw electrons from the anion, therefore spreading the negative charge, stabilizing the anion, and thus making the compound more acidic. In accordance with this, the halogens all have positive σ values at the *meta* positions. However, there are anomalies: for example, σ_{para} for the very electronegative fluorine is only just positive, and the methoxy substituent appears to be electron withdrawing at the *meta* position but electron releasing if it is at the *para* position.

3.3.1 Inductive and Resonance Effects

To make sense of the σ values in Table 3.2, we need to look in more detail at how substituents can stabilize a developing positive or negative charge. Two factors are involved. The more obvious is the effect of the electronegativity of the substituent. Carbon and hydrogen have similar electronegativities, so C–H and C–C bonds in neutral saturated organic molecules are non-polar. Carbon becomes more electronegative in CH_3^+ as it changes its hybridization and acquires a positive charge. If one hydrogen is replaced by a fluorine atom, the electronegative fluorine atom will polarize the sigma bond so that, relative to the C–H bond, the electron density will be centred closer to the fluorine, and away from the C^+. This will build up the positive charge on the carbon and destabilize the ion. Conversely, groups such as alkyl groups can (relative to hydrogen) release electrons and stabilize a carbocation. This effect is called the **inductive effect**. Most of the common groups found in organic compounds are centred on elements which are more electronegative than carbon, and therefore tend to withdraw electrons inductively. The effect falls off sharply with distance.

The second and often more powerful influence is the **resonance** or **delocalization effect**. For any molecule for which more than one electron-pair bond "structure" can be written, the true structure will be intermediate between these "structures" and the molecule will be more stable than expected. Well-known examples include benzene (Figure 3.3a) and charged structures such as the allyl cation (Figure 3.3b). A carbocation can be stabilized either by an adjacent lone pair, which can be donated to form a double bond (Figure 3.3c) or by donation of electrons from an adjacent multiple bond (Figure 3.3b). Anions can be stabilized by donation of the lone pair to an adjacent multiply bonded atom (Figure 3.3d).

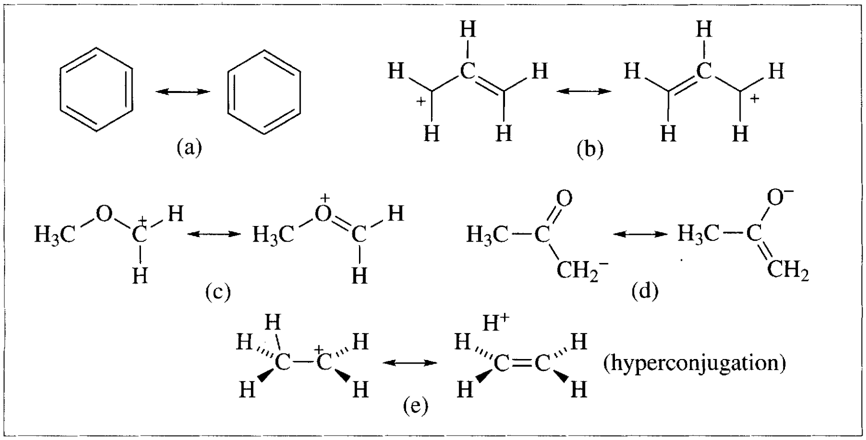


Figure 3.3 Delocalization

Resonance effects are frequently opposed to the inductive effect. The methoxy group is a striking example. The oxygen atom will withdraw electrons inductively but release them from its lone pair by resonance. The inductive effect predominates at the *meta* position, but the resonance effect predominates at the *para* position. Why is this?

The inductive effect falls off with distance, so we should expect that the inductive withdrawal of electrons by the methoxy group should be somewhat less at the *para* position (though still in the same direction). The resonance effect, on the other hand, will release electrons and produce negative charges at three locations on the benzene ring, as shown in Figure 3.4. For the *meta* substituents, none of these positions is adjacent to the carboxylate anion group, but for the *para* substituent, one of the negative charge positions is adjacent to the carboxylate anion as shown: this will destabilize the anion and outweigh the inductive withdrawal of electrons, giving a net negative σ value.

Inductive effects arise from the differing electronegativities of different atoms in the molecule. They operate through bonds or space and fall off rapidly with distance. Resonance effects, arising from interactions between non-bonding orbitals or π-bonds with a π-system, can be transmitted over long distances.

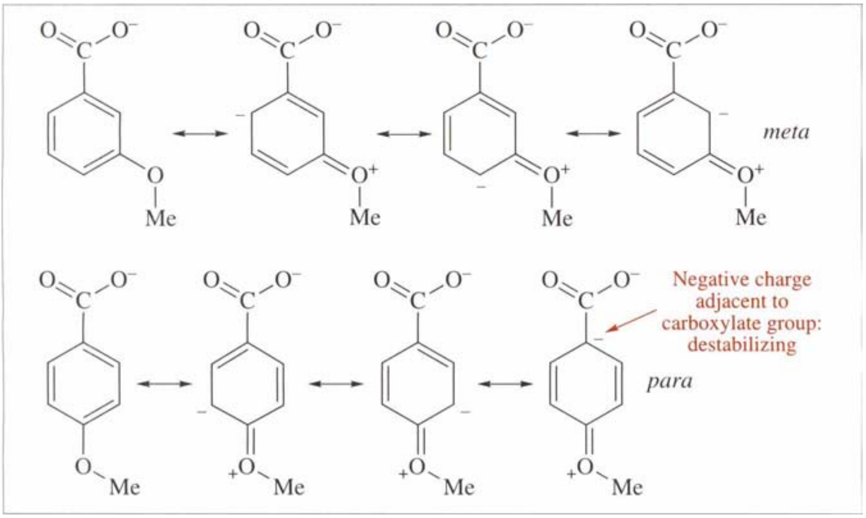


Figure 3.4 Resonance effects of *meta* and *para* substituents

The halogens also show inductive withdrawal of electrons and conjugative release. The release is greatest for fluorine in spite of its electronegativity. Being a first-row element, its size is similar to that of carbon, and overlap between its lone pair orbital and the neighbouring carbon p orbital is therefore greater than for chlorine. However, unlike the methoxy group, the resonance effect at the *para* position does not quite outweigh the inductive effect. The dimethylamino group shows the greatest difference between σ_{para} and σ_{meta}. Nitrogen, being more electropositive than oxygen, more readily accommodates a positive charge, so resonance from structures analogous to those shown in Figure 3.3(c) will be more effective. The CO_2Et, CN and NO_2 groups all have resonance effects in the same direction as the inductive effect; accordingly, the positive σ values at the *meta* positions are enhanced at the *para* position by the extra resonance contribution.

Finally, we consider the methyl substituent. The very slightly negative σ value at the *meta* position indicates that, relative to hydrogen, the methyl group releases electrons inductively to a neighbouring carbon atom. The more negative value at the *para* position indicates a conjugative release as well; this is surprising because the group is saturated and there is no lone pair to donate electrons. The effect is explained in terms of **hyperconjugation**. The alternative structure shown in Figure 3.3(e) is thought to contribute to the overall structure of a methyl group attached to a sp^2 hybridized carbon atom.

Thus from the experimentally obtained acidities of benzoic acids with a particular substituent at the *meta* and *para* positions, we obtain insight into the inductive and resonance effects for that substituent.

Worked Problem 3.1

Q Hammett σ constants for the NMe_3^+ substituent at the *meta* and *para* positions are 0.99 and 0.96, respectively. What can be inferred about the electronic effects of this substituent?

A σ_m reflects particularly the inductive effect of the substituent. The formal positive charge on the nitrogen makes this group strongly electron withdrawing, much more so than fluorine for example. The fact that σ_p is slightly smaller indicates that, unlike the NMe_2 group, NMe_3^+ has no lone pair to contribute electrons to the ring by the resonance effect, so the resonance contribution is virtually absent.

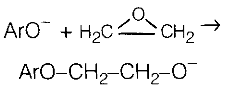
3.3.2 Hammett Reaction Constants: ρ (rho) Values

The Hammett σ substituent constants would be of little value if they only applied to the dissociation of substituted benzoic acids. Fortunately, this is not the case. For a very wide variety of reactions or equilibria involving a substituted phenyl group, if a plot is made of log k or log K against the Hammett σ substituent constant, a straight line is obtained, showing that a relationship of type (3.8) holds:

$$\log_{10}\left(\frac{k_A}{k_H}\right) = \rho\sigma \qquad (3.8)$$

This is the **Hammett equation**. The slope of the plot is denoted by ρ (Greek rho = r for reaction), and is characteristic of the reaction being studied. If negative charge is being built up in the transition state (or positive charge is being destroyed), ρ will be positive. If the reaction centre is further away from the benzene ring, as in the ionization of phenylacetic (phenylethanoic) acids (Table 3.3c), the ρ value will be smaller. If the reaction takes place even nearer the substituent on the benzene ring itself, as in electrophilic aromatic substitution, the value can be substantially higher than unity (Table 3.3i). Substituents have a greater effect in non-polar solvents or in the gas phase, where there is no solvent to stabilize developing charges (Table 3.3l).

Table 3.3 Hammett ρ values

Reaction	*Medium*	ρ
(a) $ArCO_2H \rightleftharpoons ArCO_2^- + H^+$	Water	1.00
(b) $ArCO_2H \rightleftharpoons ArCO_2^- + H^+$	Ethanol	1.96
(c) $ArCH_2CO_2H \rightleftharpoons ArCH_2CO_2^- + H^+$	Water	0.49
(d) $ArNH_3^+ \rightleftharpoons ArNH_2 + H^+$	Water	2.77
(e) $Ar_3CCl \rightleftharpoons Ar_3C^+ + H^+$	Liquid SO_2	−3.97
(f) $ArCMe_2Cl + H_2O \rightarrow ArCMe_2OH + HCl$	Acetone/water	−4.54
(g) $ArH + HNO_3 \rightarrow ArNO_2 + H_2O$	Acetic anhydride	−7.29
(h) $ArH + HOBr \rightarrow ArBr + H_2O$	$HClO_4$/dioxane/water	−6.2
(i) $ArH + Br_2 \rightarrow ArBr + HBr$	Acetic acid/water	−12.1
(j) $ArCl$[a]$+MeO^- \rightarrow ArOMe + HCl$	Methanol	3.9
(k)  $ArO^- + H_2C\overset{O}{—}CH_2 \rightarrow ArO{-}CH_2{-}CH_2{-}O^-$	Ethanol	−1.12
(l) $ArCH_2^\bullet \rightarrow ArCH_2^+ + e^-$	Gas	−20
(m) $ArCH(Cl)CH_3 \rightarrow ArCHCH_2 + HCl$	Gas	−1.36
(n) $ArCH_3 + Cl^\bullet \rightarrow ArCH_2^\bullet + HCl$	CCl_4	−0.66
(o) $ArCOCl + Bu_3Sn^\bullet \rightarrow ArCO^\bullet + Bu_3SnCl$	m-Xylene	+2.6

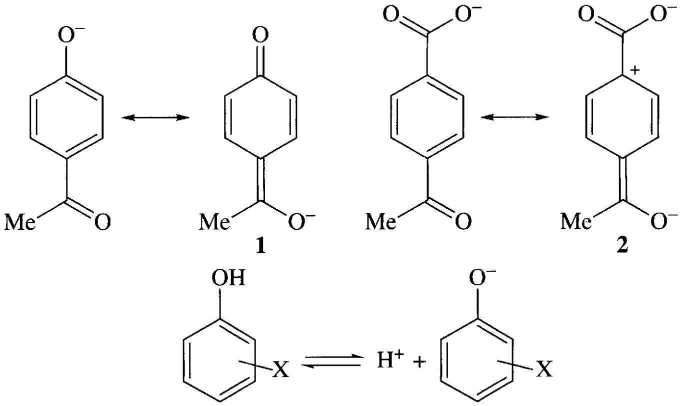
[a] $ArCl = 1\text{-}Cl\text{-}2\text{-}NO_2\text{-}4\text{-}X\text{-}C_6H_3$

For reactions in which positive charge is being built up (or negative charge destroyed), the effect of substituents will be reversed, and substituents that release electrons will favour reaction. Thus in reactions of this sort, the slope of the Hammett plot will be negative, and negative values of ρ will result.

σ^+ and σ^-

Hammett plots should follow σ if the charge build-up or destruction is at a site not conjugated with the substituent. If conjugated, σ^+ is followed by *para* substituents which can stabilize a positive charge, σ^- by *para* substituents which can stabilize a negative charge.

The defining reaction for Hammett σ constants is the ionization of substituted benzoic acids. Although a full negative charge is produced in the anion, which is delocalized between the two oxygen atoms of the carboxylate anion group, the charge cannot be spread by delocalization onto the benzene ring or further onto substituents (reaction 3.9a). Substituents such as CH_3CO stabilize the anion by an electron-withdrawing resonance contribution which builds up a partial positive charge on the carbon atom adjacent to the CO_2^-, but there is no through conjugation of the type that is possible for the substituted phenoxide ion. For this ion, structure **1**, in which the negative charge is moved to the carbonyl group with no net loss of covalent bonds or charge creation, will contribute more than structure **2** does to the stabilization of the *para*-acetylbenzoate ion, which would involve charge creation and net breakage of a covalent bond.

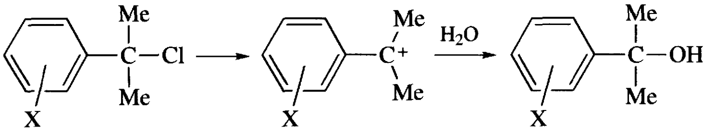


(3.9)

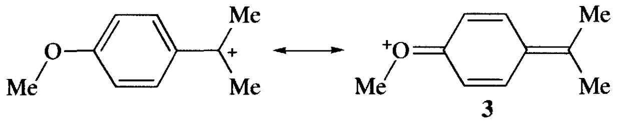
This means that substituents that can withdraw electrons conjugatively will have a greater effect on the acidity of phenols (reaction 3.9) than on the acidity of benzoic acids. The difference will only be appreciable at the *para* position; for the *meta* position, no through resonance is possible. If we make a plot of $\log K_A$ for the acidities of *meta*-substituted phenols against Hammett σ constants, we find that the points lie on a straight line, the slope of which gives the ρ value for the reaction as +2.23

(see Figure 3.5a). For *para* substituents such as p-NO_2, which stabilize the anion significantly by through conjugation, the acidities are much greater than expected on the basis of their σ values. For each substituent, a new σ^- value can be defined, to ensure that the point will fall on the graph. These σ^- values will apply for reactions in which a product anion can be stabilized by through-bond conjugation.

In an analogous manner, through conjugation from *para* substituents can stabilize a positive ion. The *para*-methoxy substituent shows this type of stabilization for the cumyl (2-phenylprop-2-yl) cation **3**. Rates of hydrolysis of substituted cumyl chlorides (reaction 3.10) in aqueous acetone were plotted against σ. The *meta*-substituted points fell on the line; substituents such as methoxy and methyl were faster than expected, and these values were used to derive σ^+ values for *para* substituents of this type (Figure 3.5b).



(3.10)



3

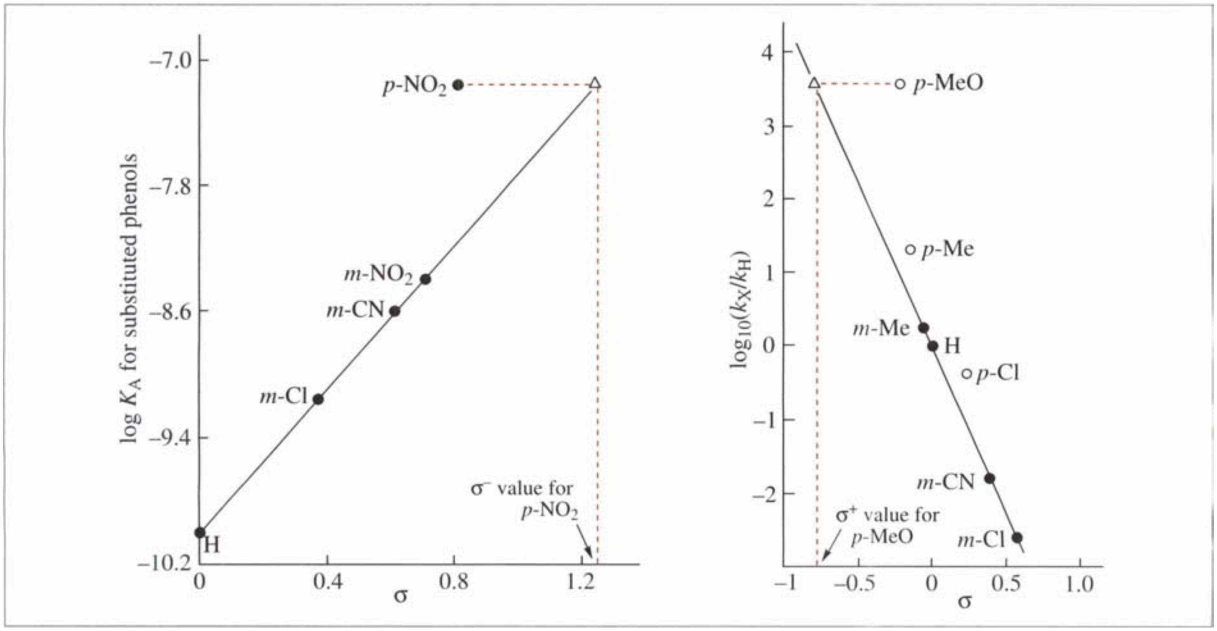


Figure 3.5 (a) Hammett plot for acidity of phenols. (b) Hammett plot for reaction (3.10)

3.3.3 Deductions about Mechanism from Substituent Studies

Ideally, we determine the Hammett ρ factor for a reaction by studying the rates of reaction with a number of *meta* substituents, plotting log k against Hammett σ substituent constants. A positive ρ factor means that negative charge is being built up (or positive charge is being destroyed). The magnitude of ρ often provides information about how close to the benzene ring is the position where charge is being built up.

We now look at the rates for a number of *para* substituents, choosing ones which have different σ, σ^+ and σ^- values. We check how well the experimental log k values for these *para*-substituted compounds lie on the line defined by the *meta* substituents when we use (a) σ, (b) σ^+ or (c) σ^- values for the *para* substituents. If σ^- is followed, this provides strong evidence that a negative charge is being built up at a position in the molecule which is conjugated with the *para* substituent, if ρ is positive. If ρ is negative, a negatively charged site of this type must be being destroyed during the reaction. If σ^+, is followed, with a negative ρ value, a positive charge is being built up during the reaction at a position conjugated with the *para* substituent; if ρ is positive, this positive charge, present in the reactant, must be destroyed in the reaction. If σ is followed, the positive or negative charge being built up or destroyed during the reaction is not conjugated with the reaction centre. The various possibilities are listed in Table 3.4, with examples.

Table 3.4 Deductions made from the sign of ρ, and which of σ, σ^+ or σ^- gives the best fit in the Hammett equation[a]

	ρ positive	*ρ negative*
σ^-	Reaction centre[b] conjugated with Ar group; negative charge builds up in the transition state. Example: reaction (3.9)	Reagent stabilized by conjugative electron release of electrons to Ar group; this conjugation is less important in the transition state. Example: reaction (*k*) in Table 3.3
σ	Reaction centre not conjugated with Ar group; transition state has less demand for electrons than reactant. Example: hydrolysis of aromatic esters by bases	Reaction centre not conjugated with Ar group; transition state has a greater demand than reactant for electrons. Example: hydrolysis of arylmethyl acetates, $ArCH_2OCOMe$, by acids
σ^+	Reaction centre conjugated with Ar group and stabilized by electron-releasing substituents; conjugation less important in transition state. Examples: rare	Reaction centre conjugated with Ar group; transition state has greater demand than reactant for electrons. Example: reaction (i) in Table 3.3

[a] σ values are used where a special σ^+ or σ^- value has not been derived

[b] The reaction centre for the purpose of this table is the position at which charge is built up or destroyed during the reaction

The following worked problems show how useful information about reaction mechanisms is derived from the sign and magnitude of the Hammett ρ factor, and whether σ, σ^+ or σ^- is followed for *para* substituents.

Worked Problem 3.2

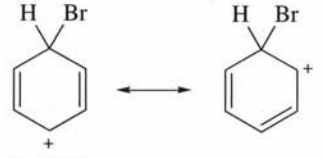
Q The ionization constants for $ArCH_2CH_2CO_2H$ in water show a Hammett ρ value of 0.24 and follow σ rather than σ^+ or σ^-. Comment on these observations in relation to other data in Table 3.3.

A Entries (a) and (c) in Table 3.3 show Hammett ρ values for $ArCO_2H$ and $ArCH_2CO_2H$ of 1.0 and 0.49, respectively, showing that the insulating effect of the CH_2 group reduces ρ by a factor of about 2. $ArCH_2CH_2CO_2H$, with a further CH_2 group, shows a further fall by a factor of 2, showing a similar insulating effect of the second CH_2 group. The σ dependence is expected for substituents that are not conjugated with the negative charge of the carboxylate anion.

Worked Problem 3.3

Q The bromination of substituted benzenes in acetic acid/water mixtures shows a ρ value of –12.1 and a dependence on σ^+ rather than σ or σ^-. What conclusions can be drawn?

A The very large negative ρ value indicates a large build up of positive charge close to the substituent in the transition state. The dependence on σ^+ shows that the position at which the charge is being formed is conjugated with substituents at the *para* position. This supports (but does not prove) the formation of a charged intermediate of the type shown below.

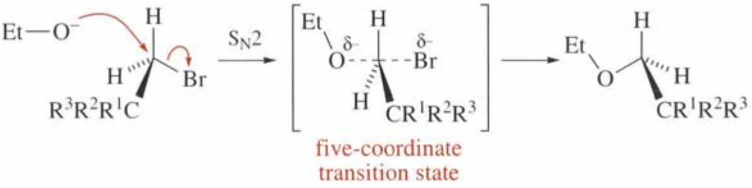


3.4 Steric Effects

The previous section has focused on the electronic effects of substituents. The size of substituents can also affect reaction rates. Bulky substituents destabilize molecules or ions, and the greater the number of groups attached to a reaction centre, the greater the destabilization.

Many reactions involve a change in coordination round the reaction centre. If the coordination number increases on going from the starting molecule to the transition state, replacement of an atom or group at the reaction centre by a bulkier group will cause a reduction in rate. If there is a reduction in coordination number, introduction of a bulkier group will cause an increase in rate. These two effects are termed **steric retardation** and **steric acceleration**, respectively.

A good example of steric retardation is shown by S_N2 reactions, in which an incoming nucleophile displaces a leaving group (reactions 1.1a and 3.11). In the transition state, the new bond is partially formed whilst the breaking bond is still partially bonded. Thus the original four coordination round the carbon reaction centre is increased in the transition state to five coordination. Hence if we increase the bulk of the substituents, the crowding will be worse in the transition state, so the reaction will be slower. For the reaction of sodium ethoxide with primary bromoalkanes $(R^1R^2R^3C)CH_2Br$ in ethanol at 55 °C (reaction 3.11), the effects on the relative rates of reaction for increasing numbers of substituent methyl groups are given in Table 3.5.



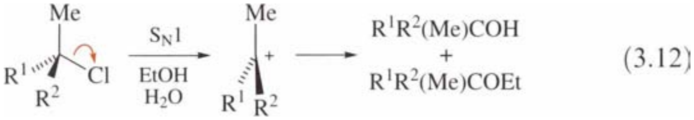
(3.11)

Table 3.5 Relative effects of successive substitutions

	Reaction (3.11) (S_N2)	*Reaction (3.12) (S_N1)*	*Acid strength of substituted acetic acids*
Substituent change	H → Me	Me → *t*-Bu	H → Cl
Effect of first substitution	÷3.6	×1.2	×80
Effect of second substitution	÷9.4	×15.2	×24
Effect of third substitution	÷7022	–	×6
Increasing or decreasing?	Increasing	Increasing	Decreasing
Steric or electronic?	Steric	Steric	Electronic

The effect of introducing a methyl group at the β-position is to decrease the rate by a factor of 4. The second methyl produces a more pronounced reduction by a factor of 9 as the transition state becomes more crowded. The third methyl group produces a massive rate decrease by a factor of 7000; this last methyl effectively blocks access to the ethoxide ion as it approaches the reaction centre.

In a S_N1 reaction (1.1b or 3.12), the reaction centre in the halogenoalkane is four coordinated. The transition state is close to the intermediate carbocation in structure, which is three coordinated (and planar). Crowding is therefore less severe in the transition state than in the initial molecule, so substitution of bulky groups at the reaction centre gives rise to steric acceleration. In reaction (3.12), the solvolysis of R^1R^2MeCCl in 50% ethanol at 25 °C, relative rates for Me_3CCl, *t*-$BuMe_2CCl$ and *t*-Bu_2MeCCl are 1:1.21:18.4. There is a very small increase in rate as the first *t*-butyl group is introduced, but a much larger effect is caused by the second *t*-butyl group. This is seriously crowded by the first *t*-butyl group in the original molecule, but the crowding is relieved as the bond angles at the central carbon atom spread out from about 109½° to 120°.



(3.12)

This increase in effect on rates as further similar substituents are introduced is typical of steric effects, where each further substituent causes an increase in the amount of crowding. This is to be contrasted with polar effects, where a second substituent usually causes a smaller relative increase or decrease than the first. For example, if the substituent stabilizes a positive charge by releasing electrons, the charge is diminished and a further substituent will be releasing electrons to a centre where there is less demand, so the stabilizing effect will be less. In the series acetic (ethanoic) acid, chloroacetic acid, dichloroacetic acid and trichloroacetic acid, the acid dissociation constant values (K_A) in water are 1.76×10^{-5}, 1.40×10^{-3}, 3.32×10^{-2} and 2×10^{-1}, respectively. The first chlorine strengthens the acid by a factor of 80, the second only produces an increase of a factor of 24, and the third produces less than a factor of 10. This suggests that the effect of the chlorine substitution is electronic rather than steric. These steric and electronic substituent effects are summarized in Table 3.5.

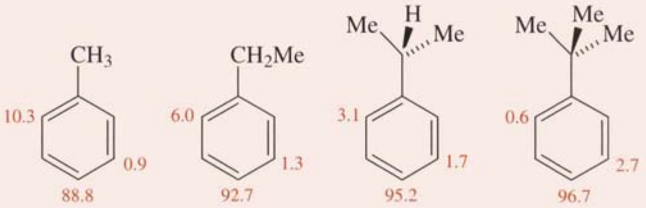
When substituents are added successively at or near to a reaction centre, if the effect of adding successive identical substituents causes increasing changes in the rate, the effect is probably steric. If the effect diminishes, the origin of the effect is probably electronic.

Worked Problem 3.4

Q The Friedel-Crafts acylation of alkylated benzenes by $[PhCO^+][SbF_6^-]$ (reaction 3.13) shows the following percentage distributions of isomers. As the number of methyl substituents on the α-carbon atom is increased, the proportion of *ortho* isomer decreases. Is this likely to be an electronic or a steric effect?

$$C_6H_5R + PhCO^+SbF_6^- \longrightarrow PhCOC_6H_4R + HSbF_6 \qquad (3.13)$$

$R = CH_3, CH_2Me, CHMe_2, CMe_3$:



A As we introduce the first extra methyl group into the toluene molecule, the *ortho* percentage drops by a factor of 1.7(=10.3/6.0). The second group produces a decrease of a factor of 1.9, but the third produces a much larger decrease, by a factor of 5.2. The greater effect of the second and especially the third substituent methyl group supports a steric explanation, consistent with the three-coordinate *ortho* carbon atom becoming four coordinated in the transition state as the new group starts to bond.

3.5 Stereochemistry

The stereochemistry of products relative to starting materials can give important clues to the structure of the transition state. The stereochemistry of molecules gives rise to two types of isomerism: **optical isomerism (enantiomerism)** and **geometrical isomerism**.

3.5.1 Enantiomerism (Optical Isomerism)

If four different groups surround a central carbon atom, two (and only two) different stereoisomers are possible, as illustrated in Figure 3.6. These are known as enantiomers (or optical isomers). These two isomers are different because rotation about any of the bond axes of the molecule cannot bring all four groups of the *R*-isomer into coincidence with the *S*-isomer. There are not more than two: any other arrangement of groups round the central carbon atom can always be rotated around a bond axis to bring the ethyl group to the top, and if the hydrogen atom is not at the back, rotation round the C–ethyl bond to bring the hydrogen to the back will lead to one or the other of the two isomers shown in Figure 3.6.

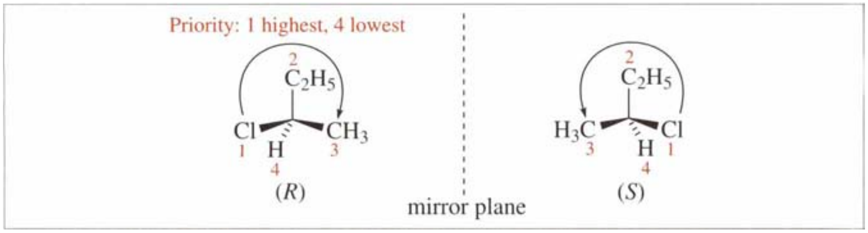


Figure 3.6 Enantiomers

To enable the enantiomers to be identified without the need for a drawing, the following convention has been established. The four groups are assigned a priority from 1 (highest) to 4 (lowest) on the basis of the atomic numbers of the atom directly connected to the central carbon atom. This establishes the chlorine atom as the group with highest priority (1) and hydrogen as the lowest (4), but both methyl and ethyl both have a carbon atom attached to the central carbon atom, with the same atomic number. Ties are broken by considering the atoms attached to the first (carbon) atom in the group. Ethyl has a carbon and two hydrogens (C,H,H); methyl has three hydrogens (H,H,H). Since carbon has a higher atomic number than hydrogen, the ethyl group has the higher priority (2) and methyl the lower (3). A single atom of higher priority takes precedence over any number of atoms of lower priority, *e.g.* (N,H,H) beats (C,C,C). If the tie is not broken at the atoms two removed from the central atom, we go one further out and so on until the tie is resolved. A double bond is counted as having a normal bond to the atom at the other end, plus a further bond to a fictitious atom of the same type which does not have any further connections. Thus isopropyl [$-CH(CH_3)_2$] (C,C,H) and vinyl [$-CH{=}CH_2$] (C,(C),H) both beat ethyl [$-CH_2CH_3$] (C,H,H). Isopropyl [$-CH(C\mathit{H}_3)_2$] beats vinyl [$-CH{=}C\mathit{H}_2$] by having six hydrogens at the next position out, whereas vinyl has only two. These slightly arcane rules are to ensure compatibility with the older D,L stereochemical convention used for sugars and α-amino-acids.

Once priorities have been assigned, the molecule is viewed from a position where the group of lowest priority (4) is at the back. The remaining groups are viewed in decreasing order of priority: (1) to (2) to (3). If this is clockwise, the configuration is (*R*) (*rectus*, right-handed). If anticlockwise, the configuration is (*S*) (*sinister*, left-handed).

Enantiomers have very similar properties. Since each has the same groups attached to the same atoms, with identical bond lengths and angles, properties such as melting point, solubility, reaction rate with particular reagents, *etc.*, will be identical. The two enantiomers are related as an object and its mirror image as shown in Figure 3.6, and can only be distinguished under circumstances in which this "handedness" or chirality is important. For present purposes, the most important difference is that solutions of the enantiomers will rotate the plane of polarized light in opposite directions by an exactly equal amount. The rotation of a 1 g mL^{-1} solution in a 10 cm cell, measured for yellow sodium D-line light, is called the specific rotation and is denoted as $[\alpha]_D^{20}$. The superscript number refers to the temperature used in °C. Positive values for $[\alpha]_D^{20}$ correspond to a clockwise rotation, negative values to anti-clockwise rotation.

For mechanistic studies, we are mostly interested in relative configuration. We would like to know, for example in an S_N2 reaction, whether the incoming group replaces the outgoing group without changing stereochemistry at the reaction centre (retention), or if the reaction involves inversion at the reaction centre to give the opposite configuration. Unfortunately, the sign of rotation is not a reliable guide to absolute or relative configuration. Of 19 common optically active α-amino acids, $RCH(NH_2)CO_2H$, involved in proteins which all have the same configuration (Figure 3.7), 11 have negative specific rotations but 8 have positive rotations.

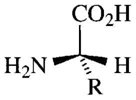
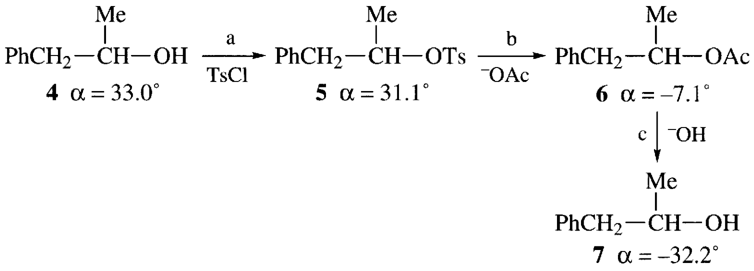


Figure 3.7 Configuration of naturally occurring α-amino acids

Absolute configurations can now be obtained by X-ray crystallography. Determination of the absolute stereochemistry of both reagent and product molecules will in principle allow us to determine if a particular reaction involves retention or inversion. Historically, an alternative, which does not require knowledge of absolute stereochemistry, involves carrying out a set of reactions in which an optically active reagent molecule is converted in several steps via a number of intermediates back into the same molecule, but with the opposite configuration. All but one of the reaction steps do not take place at the optically active centre, and in these steps it is assumed that no change in configuration can take place. This leaves one step only where reaction takes place at the optically active centre. If the final molecule has the same rotation as the initial molecule, the reaction must take place with retention of configuration; if the sign of rotation is reversed, the reaction must involve inversion of configuration to the other enantiomer.

This type of logic is illustrated by reaction sequence (3.14), in which the positively rotating form of the alcohol **4** is converted in two stages through **5** and **6** into its negatively rotating enantiomer **7**. At the time these experiments were carried out, no absolute stereochemistries were known, but since the overall process gave inversion of configuration, either one or all three of the individual steps must involve inversion of configuration. Step (a) involves attack of the hydroxyl oxygen on the *p*-toluenesulfonyl chloride, and should not affect the C–O bond, and step (c) involves ester hydrolysis, which again is thought to leave the C–O bond intact. This leaves step (b), in which an acetate ion attacks the chiral carbon atom, displacing the *p*-toluenesulfonate anion, and so this reaction is where the inversion of stereochemistry must occur.

Ts = *p* – $MeC_6H_4SO_2$–; Ac = MeCO – .

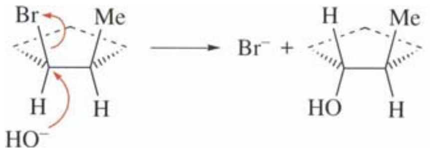


$$\underset{\mathbf{4}\ \alpha = 33.0^\circ}{PhCH_2-\overset{Me}{\overset{|}{C}H}-OH} \xrightarrow[TsCl]{a} \underset{\mathbf{5}\ \alpha = 31.1^\circ}{PhCH_2-\overset{Me}{\overset{|}{C}H}-OTs} \xrightarrow[^-OAc]{b} \underset{\mathbf{6}\ \alpha = -7.1^\circ}{PhCH_2-\overset{Me}{\overset{|}{C}H}-OAc}$$

$$c \Big\downarrow {}^-OH \qquad (3.14)$$

$$\underset{\mathbf{7}\ \alpha = -32.2^\circ}{PhCH_2-\overset{Me}{\overset{|}{C}H}-OH}$$

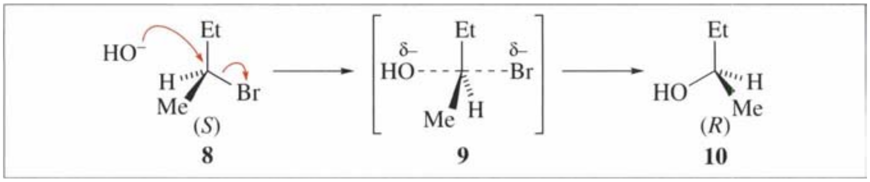
A simple way of determining the stereochemical course of S_N2 reactions is to study reactions of disubstituted cyclopentane and cyclohexane rings, where retention or inversion can be established by finding out if the product has the same geometric form (*cis* or *trans*, see next section) as the starting molecule, which proves retention of configuration at the reaction centre, or has the opposite geometrical form, which proves inversion. Reaction (3.15) shows that inversion of configuration takes place for this S_N2 reaction.



(3.15)

Transition State for S_N2 Reactions

The simplest way to account for the inversion of configuration which always accompanies S_N2 reactions is that the incoming nucleophile approaches the molecule from the side opposite to the leaving group (Figure 3.8). As the nucleophile approaches, the bond to the leaving group lengthens and the hybridization of the central carbon atom moves towards sp^2, so that the unchanged groups take up a trigonal configuration with 120° bond angles. In the transition state **9**, the remaining p orbital allows a partial bond to both the incoming and the leaving group, at a 180° angle to each other. As the reaction goes beyond the transition state, the hybridization reverts to sp^3, but the bond to the incoming nucleophile is on the opposite side of the molecule to where the leaving group was situated. The movement of the three unchanged groups round the central carbon atom is like an umbrella blowing inside out in the wind, and is called inversion. The product **10** has the opposite configuration to that of the starting molecule **8**. This mechanistic insight into the S_N2 reaction can *only* be obtained from stereochemical studies.



8 **9** **10**

Figure 3.8 Inversion in S_N2 reactions

Stereochemistry of S_N1 Reactions

In contrast to S_N2 reactions, S_N1 reactions of molecules with a chiral centre proceed with racemization, that is the product comprises a mixture of equal numbers of molecules with the same and opposite configurations compared with the starting molecule. Each individual reaction must of course involve either retention or inversion of configuration, but the processes which lead to these two products must proceed at the same rate. This accords with the mechanism proposed in Chapter 1. The rate-determining step involves the heterolytic breakage of the bond to the leaving group, leaving a carbocation which from this and other evidence has a planar trigonal structure with sp^2 hybridization. Since the carbocation is planar, the incoming nucleophile can approach from either face equally readily, as shown in Figure 3.9, giving rise to an equal mixture of (*R*) and (*S*) molecules, whose rotations will cancel out. A mixture of this type is known as a **racemic mixture**, and racemization is the characteristic stereochemical feature of S_N1 reactions.

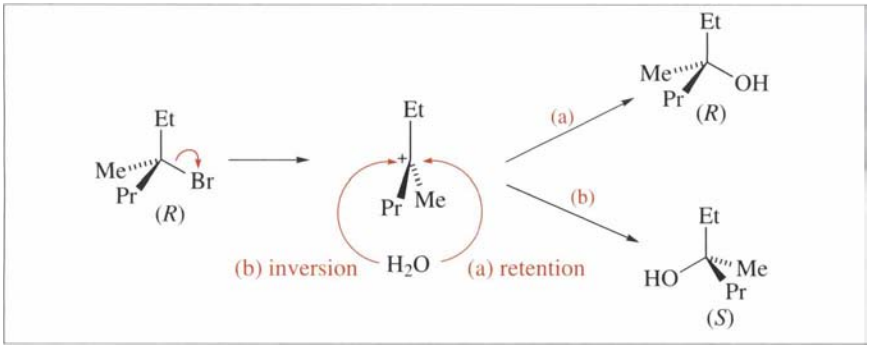


Figure 3.9 Stereochemistry of S_N1 reactions

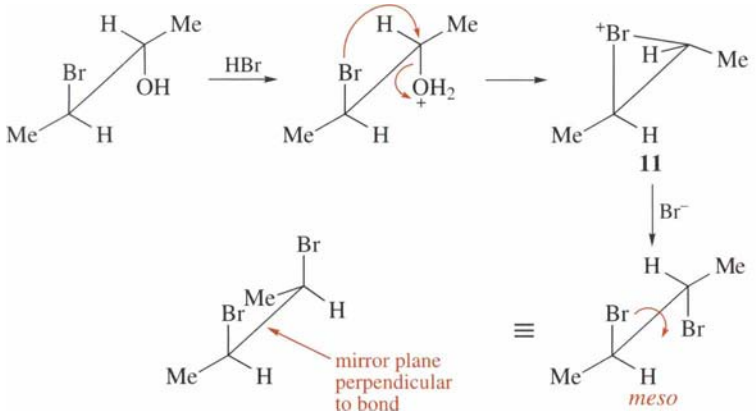
In contrast to S_N2 reactions, where the stereochemical outcome is always complete inversion, the racemization of S_N1 reactions is sometimes only partial. This can arise because the leaving group, though free from the carbocation intermediate, still blocks that side of the molecule, so that attack from the opposite face is easier, giving a product in which the inverted molecules predominate over those with retention of stereochemistry.

Neighbouring Group Assistance

A vast number of S_N2 reactions at carbon centres has been studied. In every case, it is found that inversion of configuration occurs. This certainty now allows us to use inversion of configuration as a diagnostic test: if inversion does not take place, the reaction cannot have a simple S_N2 mechanism. S_N1 reactions show partial or complete racemization, depending on how "free" the intermediate carbocation becomes.

A small number of nucleophilic substitutions show retention of configuration, *i.e.* the new group comes in on the same side as the leaving group departs, in spite of the unfavourable steric interactions that would occur between the two groups. Reactions of this type tend to be faster than expected by comparison with similar compounds. The reactions are kinetically of first order, depending only on concentration of the halogen compound, and not on that of the attacking nucleophile. These reactions are characterized by the presence of a neighbouring substituent group (*e.g.* Br, OH) which has a lone pair that makes the group nucleophilic. This group can carry out an intramolecular substitution, as shown in reaction (3.16), forming a cyclic intermediate **11**, with the expulsion of the leaving group and inversion of configuration at the reacting centre. The incoming nucleophile attacks the intermediate by an S_N2 reaction, opening the ring, restoring the internal substituent group and inverting the configuration again at the reaction centre. The overall reaction involves two inversions of configuration, thereby giving overall retention of configuration.

S_N2 reactions always involve inversion of configuration. S_N1 reactions are associated with racemization, although this may not be complete. Retention in nucleophilic substitutions suggests assistance from a neighbouring group.



(3.16)

In these "sawhorse" representations of stereochemistry, the part of the molecule on the lower left is in front of the part on the upper right.

3.5.2 Geometrical Isomerism

A second form of stereoisomerism is associated with restriction of rotation round a bond joining two atoms in a molecule. The restriction can be caused by a double bond, or by a ring structure, and gives rise to two **geometrical isomers**. For a 1,2-disubstituted ethene, the substituents can be on the same side of the double bond (*cis*) or on opposite sides (*trans*). The two geometrical isomers will have different reactivity and physical properties. For example, the two geometrical isomers of 1,2-dichloroethene (Figure 3.10a and b) differ by 11 °C in boiling points, attributable to the presence of a dipole moment in the *cis* isomer, whereas the *trans* isomer has no overall dipole. The *cis*/*trans* nomenclature can be extended to tri- or tetrasubstituted ethenes, provided that there is a pair of identical substituents on each end of the double bond, for example **13** in equation (3.18) below. For more complex situations, where the double bond has three or four different substituents, the isomers are distinguished by assigning priorities as for the *R*,*S* convention to the substituents at each end of the double bond. If the substituents of higher priority at each end of the double bond are on the same side, the molecule is *Z* (*zusammen*, German, together); if they are on opposite sides, the isomer is *E* (*entgegen*, German, opposite) (Figure 3.10c and d). For double bonds with identical substituents on each end, $Z \equiv$ *cis* and $E \equiv$ *trans*.

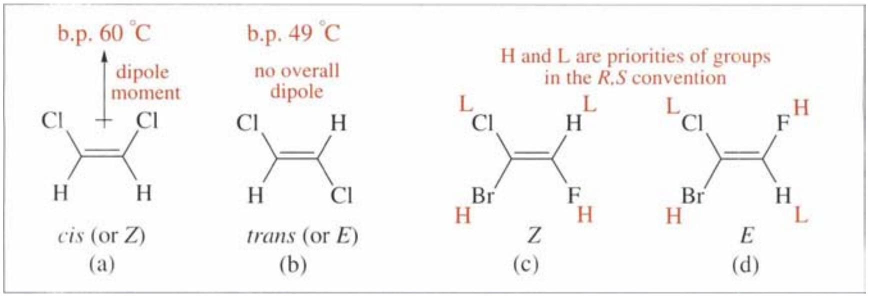
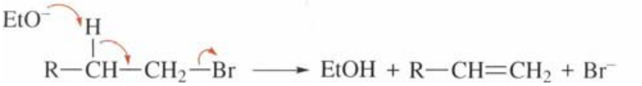


Figure 3.10 Geometrical isomerism

Geometrical isomerism is a useful tool in investigating the stereochemical course of addition and elimination reactions.

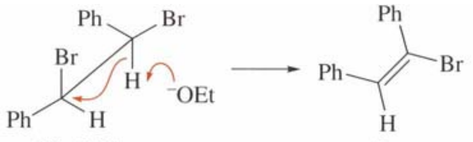
Stereochemistry of E2 Elimination Reactions

For S_N2 reactions, there is almost always a competing reaction in which the nucleophile removes a proton from the β-carbon atom. This is accompanied by loss of the leaving group and formation of a C=C double bond, as shown in reaction (3.17). The reaction is usually elementary, and is termed **E2** or **bimolecular elimination**. In an E2 reaction, there is no intermediate. Can we determine anything about the transition state, in particular, the direction of approach of the incoming nucleophile (base) from the stereochemical course of the reaction?

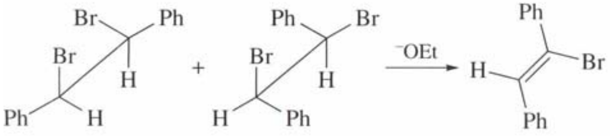


$$EtO^- + R{-}CH(H){-}CH_2{-}Br \longrightarrow EtOH + R{-}CH{=}CH_2 + Br^- \qquad (3.17)$$

Compounds such as PhCHBr–CHBrPh have two asymmetric centres, each of which can have the *R* or the *S* configuration. There will be three stereoisomers (reactions 3.18 and 3.19), which can be designated *S,S* (**14**), *R,R* (**15**), and *R,S* (**12**) (*S,R* will be the same as *R,S* because of the symmetry of the molecule). The *R,R* and *S,S* forms will be optically active and rotate polarized light in opposite directions by an equal amount. Synthesis will normally give a 50/50 mixture of the two isomers, the **racemic** or (±) mixture. The *R,S* or ***meso*** isomer will be optically inactive since it is identical with its mirror image (the mirror plane in **12** can be seen in the eclipsed conformation obtained by rotation of the front of the molecule clockwise by 60° round the central C–C bond).



12 (*R,S*) *meso* **13** *cis* (3.18)



14 (*S,S*) **15** (*R,R*) **16** *trans* (3.19)

Experimentally, it is found that PhCHBr–CHBrPh reacts with sodium ethoxide by elimination of hydrogen bromide to give 1-bromo-1,2-diphenylethene. The *meso* compound **12** gives the *cis*-alkene **13** (reaction 3.18), whereas the (*S,S* and *R,R*) racemic mixture **14** and **15** gives the *trans*-alkene **16** (reaction 3.19). The disposition of the substituent groups in the alkene product suggests that the molecule reacts in the conformation shown in Figure 3.11 and the incoming base attacks *anti* to the departing halide anion (180° dihedral angle). In this conformation the carbon atoms which are rehybridizing from sp^3 to sp^2 can begin to form the π bond as the reaction proceeds, as shown in Figure 3.11. Since two new bonds are being formed at the same time as two are being broken, the reaction is concerted and can take place with a relatively low activation energy.

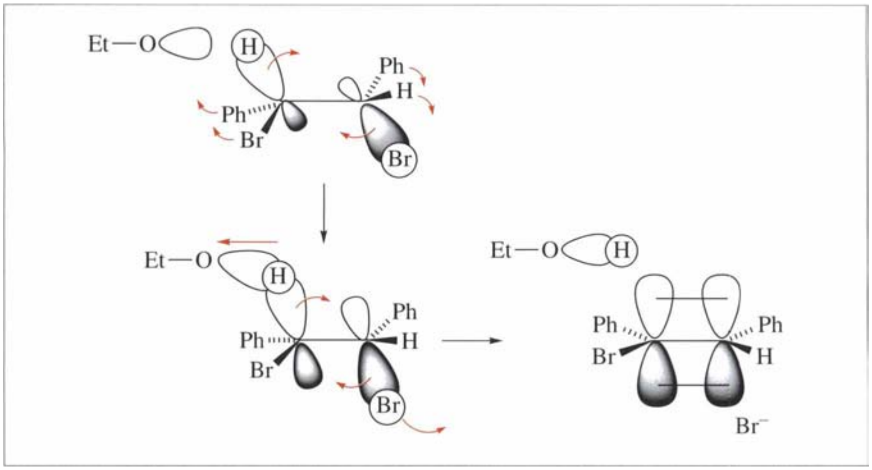
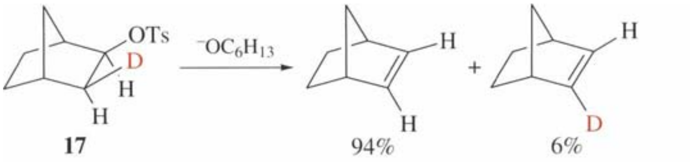


Figure 3.11 *Anti* elimination in E2 reactions

The geometrical isomerism of the products of elimination reactions shows that, in E2 reactions, reaction is fastest if the leaving groups are *anti* to each other. If an *anti* arrangement is impossible, *syn* elimination takes place.

For rigid strained molecules such as the norbornane derivative **17**, it is impossible for the leaving proton and toluenesulfonate anion to adopt the *anti* conformation, since the molecule is locked in an eclipsed conformation where the only possible dihedral angles are 0° (*syn*) or 120°. Under these circumstances, *syn* elimination in reaction (3.20) allows the reaction to take place in a concerted manner, and is the preferred route. It must be emphasized that for compounds in which free rotation is possible, *anti* elimination takes place almost exclusively, even though both *syn* and *anti* orientations would allow concerted reaction. The *anti* orientation has the advantage of having the attacking base on the opposite side of the molecule to the leaving halide, and the staggered conformation involved would be an energy minimum, compared with the energy maximum for the eclipsed conformation required for *syn* elimination.



(3.20)

Summary of Key Points

1. Solvent effects provide information about the relative polarity of the transition state compared with the reactants, and may be used to cut down mechanistic possibilities.

2. The electronic effects of substituents (electron-withdrawing or -releasing) give more precise information: Hammett ρ values show whether positive or negative charge is being built up (or destroyed) at the reaction centre, and the dependence of $\log_{10} k$ or $\log_{10} K$ on σ, σ^+ or σ^- tells us whether or not this charge build up is in a position conjugated with the substituent.

3. The two types of electronic effects of substituents are inductive and resonance; these can operate in the same or opposite directions.

4. The steric effect of introducing substituents at the reaction centre is to increase the rate if the transition state is less crowded than the reactant, and to decrease the rate if the transition state is more crowded.

5. Optical and geometrical isomerism throw light on the stereochemistry of reactions. S_N2 reactions always involve inversion of configuration; S_N1 reactions are associated with racemization, though this may not be complete; retention in nucleophilic substitutions suggests assistance from a neighbouring group.

6. In E2 reactions, reaction is fastest if the leaving groups are *anti* to each other. If an *anti* arrangement is impossible, *syn* elimination takes place.

Further Reading

C. Reichardt, *Solvent Effects in Organic Chemistry*, Verlag Chemie, Weinheim, 1979.

C. D. Johnson, *The Hammett Equation*, Cambridge University Press, Cambridge, 1973.

E. L. Eliel, S. H. Wilen and L. N. Mander *Stereochemistry of Carbon Compounds*, Wiley, New York, 1994 (long).

M. J. T. Robinson, *Organic Stereochemistry*, Oxford University Press, Oxford, 2000 (short).

O. B. Ramsay, *Stereochemistry*, Heyden, London, 1981 (historic).

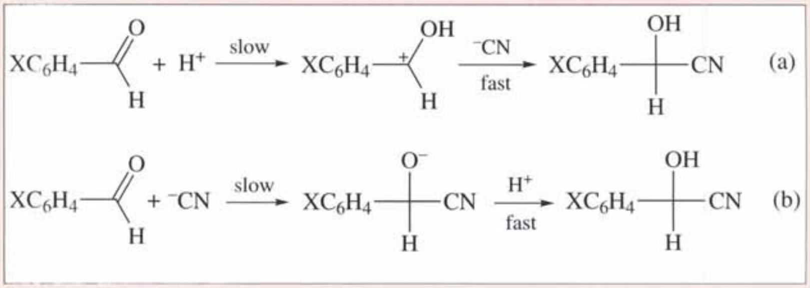
Problems

3.1. For the bimolecular hydrolysis of 2-bromopropane with OH^- in aqueous ethanol, the rate constant decreased by a factor of 1.6 when the proportion of water was raised from 20% to 40%. When a corresponding change in solvent was made for the bimolecular hydrolysis of 2-bromopropane with water, the rate increased by a factor of 2.8. Explain these differences.

3.2. Hammett σ_m values for the OMe and O–CO–Me groups are 0.10 and 0.26, respectively. Comment on this difference.

3.3. Suggest a number of substituents for which (a) σ^+ will be significantly different from σ and (b) σ^- will be significantly different from σ.

3.4. Aldehydes XC_6H_4CHO undergo addition of hydrogen cyanide across the C=O double bond in the presence of aqueous sodium cyanide, Na^+CN^-. Two possible mechanisms are shown below. For each of the two routes, predict the sign of the Hammett ρ factor and whether the Hammett plot will follow σ, σ^+ or σ^-.



3.5. 1-Arylethyl acetates, $MeCO_2CH(Me)C_6H_4X$, decompose on heating in the gas phase in a first-order reaction to give acetic acid and the arylethene. For substituents on the aromatic ring, a Hammett correlation with σ^+ is observed, with $\rho = -0.7$. What light does this throw on the mechanism of the decomposition?

3.6. Suggest reactions other than those discussed in this chapter which should show (a) positive and (b) negative ρ values and for which correlations would be best (1) with σ, (2) with σ^+ or (3) with σ^-, *i.e.* six categories in all. It may be difficult to find examples of some of these categories.

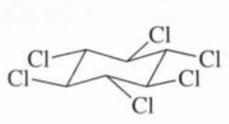
3.7. For the S_N1 solvolysis of the tertiary chloroalkanes R–Cl in 50% ethanol at 25 °C, relative rates for three different halides are 1:1.2:18.4 for R = Me_3C, *t*-$BuMe_2C$, and *t*-Bu_2MeC, respectively. Are these differences likely to be due to electronic or to steric effects?

3.8. The acid dissociation constants of CH_3CO_2H, $PhCH_2CO_2H$, and Ph_2CHCO_2H in water are 1.76×10^{-5}, 5.2×10^{-5} and 1.15×10^{-4}, respectively. Is the effect of the phenyl group primarily steric or primarily electronic?

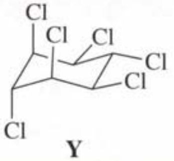
3.9. Using the rules to establish the priority of substituents, confirm that the compounds in Figure 3.8 have been assigned their correct stereochemical configurations.

3.10. All 19 common optically active α-amino acids involved in proteins have the same configuration shown in Figure 3.7, and were given the designation L in the D,L convention, applicable to sugars and α-amino acids. Typical side chains are R = $PhCH_2$ for phenylalanine and $HO_2CCH_2CH_2$ for glutamic acid. All but one of the α-amino acids have the (*S*) configuration. Cysteine, with R = $HSCH_2$, has the same configuration shown in Figure 3.6, but is designated (*R*). Why is this?

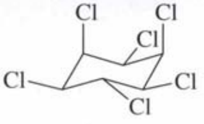
3.11. Three of the stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane, **X**, **Y** and **Z**, undergo elimination of HCl in 76% aqueous ethanol with second-order rate constants of 2.1×10^{-4}, 0.15 and 0.5 M^{-1} s^{-1}, respectively. Suggest a reason for the differences in rates.



X



Y



Z

4

Anions and Nucleophilic Reactions

Chapter 3 considered elementary reactions and the information about their transition states that can be obtained by a variety of techniques. The next three chapters deal with complex reactions, in which intermediates are produced. These may be short lived, but they have an independent existence, show spectroscopic properties and can sometimes be trapped out of the reaction mixture.

This chapter considers reactions in which anionic intermediates are involved. **Anions** are species that carry a negative charge. Also important here are:

Bases:: species (often anions) that can remove a proton from another molecule.

Nucleophiles:: species with a lone pair of electrons that can be donated to an electron-deficient centre, normally a carbon atom, to form a covalent bond.

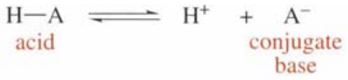
Aims

After reading this chapter you should be able to:

- Define and distinguish between bases and nucleophiles
- Assess the likely points of attack by nucleophiles and bases on molecules
- Suggest plausible reaction steps for condensation reactions
- Understand the catalytic role of bases in base-catalysed reactions
- Rationalize the steps involved in substitution reactions of carboxylic acid derivatives
- Predict whether a particular carbanion will undergo elimination to give a carbene

4.1 Acids and Bases

Bases are molecules or ions that abstract protons. **Acids** can donate protons to a base. The base formed when an acid loses a proton is called the **conjugate base** of the acid and *vice versa* (reaction 4.1). The strength of an acid corresponds to its ability to donate protons; that of a base depends on its ability to accept protons. It follows that if an acid is strong (readily donates protons to a different base), its conjugate base is weak (cannot readily abstract protons from the conjugate acid of the different base). A strong acid will react with a strong base to give a weak acid and a weak base, as shown in reaction (4.2), with an example shown in reaction (4.3) where hydrogen chloride, which is a stronger acid than phenol, donates a proton to the sodium salt of phenol to give phenol and the chloride ion. In practical terms, this reaction goes entirely to completion.



$$\underset{\text{acid}}{\text{H—A}} \rightleftharpoons \text{H}^+ + \underset{\text{conjugate base}}{\text{A}^-} \qquad (4.1)$$

$$\underset{\substack{\text{strong}\\\text{acid}}}{\text{H—A}} + \underset{\substack{\text{strong}\\\text{base}}}{\text{A}'^-} \rightleftharpoons \underset{\substack{\text{weak}\\\text{acid}}}{\text{H—A}'} + \underset{\substack{\text{weak}\\\text{base}}}{\text{A}^-} \qquad (4.2)$$

$$\text{H—Cl} + \underset{\substack{\text{(sodium)}\\\text{phenoxide}}}{{}^-\text{O—Ph}} \rightleftharpoons \underset{\text{phenol}}{\text{H—O—Ph}} + \text{Cl}^- \qquad (4.3)$$

Table 4.1 shows the acidities of a number of acids, arranged in order from strongest to weakest. A number of factors contribute to acid strength. These include the electronegativity of the atom which bears the negative charge in the anion formed on loss of the proton, the strength of the bond to the proton, and delocalization. Other things being equal, electronegative atoms, in particular the halogens and oxygen, will be more stable carrying a negative charge, and these elements comprise the central atom of the conjugate bases of the strongest acids. Electronegativity will not account for the strengths of the hydrogen halides: hydrogen fluoride is the weakest of these acids, even though fluorine is the most electronegative element. However, the hydrogen–fluorine bond is one of the strongest known, whereas the hydrogen–iodine bond is extremely weak, and this factor counterbalances the electronegativity effect.

Table 4.1 Acidity, basicity and nucleophilicity

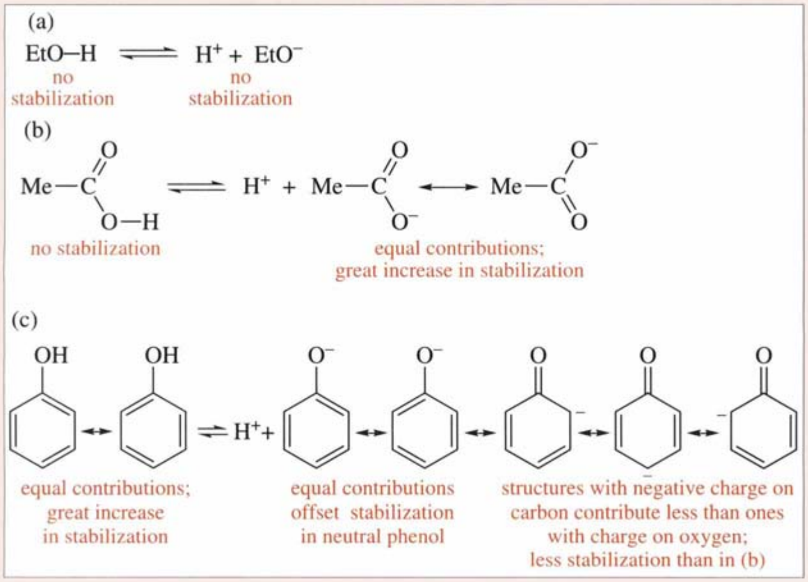
Acid (strongest at top, weakest at bottom)	*Conjugate base (weakest at top, strongest at bottom)*	*pK_A of acid*[a] *(most negative = most acidic)*	*Nucleophilicity, n, of base*[b] *(high = most nucleophilic) (bold = oxygen-centred nucleophile)*
$HClO_4$	ClO_4^-	−11	
HI	I^-	−10	5
H_2SO_4	HSO_4^-	−10	
HBr	Br^-	−9	3.5
HCl	Cl^-	−7	2.7
H_3O^+	H_2O	−1.7	**0**
HF	F^-	3.2	2.0
$MeCO_2H$	$MeCO_2^-$	4.8	**2.7**
H_2S	HS^-	7.0	5.1
PhOH	PhO^-	9.9	**3.5**
$MeCOCH_2COMe$	$MeCOCH^-COMe$	9	
HCN	CN^-	9.2	5.1
RNH_3^+	RNH_2	10–11	4.5
$MeCOCH_2CO_2R$	$MeCOCH^-CO_2R$	11	
$EtOCOCH_2CO_2Et$	$EtOCOCH^-CO_2Et$	13	
$HCCl_3$	CCl_3^-	13.6	
H_2O	OH^-	15.7	**4.2**
EtOH	EtO^-	16	
cyclo-C_5H_6	cyclo-$C_5H_5^-$	16	
$RCOCH_2R$	$RCOCHR^-$	19–20	
$ROCOCH_2R$	$ROCOCHR^-$	24.5	
$H\text{-}C{\equiv}C\text{-}H$	$H\text{-}C{\equiv}C^-$	25	
$PhNH_2$	$PhNH^-$	30.6	
NH_3	NH_2^-	38	
$PhCH_3$	$PhCH_2^-$	40	
$CH_2{=}CH\text{-}CH_3$	$CH_2{=}CH\text{-}CH_2^-$	43	
C_6H_6	$C_6H_5^-$	43	
$CH_2{=}CH_2$	$CH_2{=}CH^-$	44	
CH_4	CH_3^-	48	

[a] $pK_A = -\log_{10}K_A = -\log_{10}\{[H^+][A^-]/[HA]\}$. For strong, highly dissociated, acids, the equilibrium value of $[H^+]$ is high, giving high K_A values, and thus low or negative pK_A values

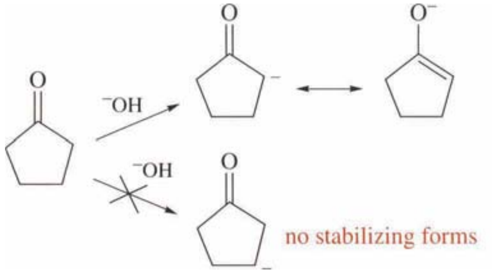
[b] Nucleophilicity, *n*, is defined by the expression $\log_{10}(k_n/k_0) = sn$, where (k_n/k_0) is the relative rate of attack by the nucleophile on a substrate compared with attack by water on the same substrate, *s* is the sensitivity of the substrate to nucleophilic attack, and n_{H_2O} is defined as zero

For acids where a hydrogen–oxygen bond is to be broken, we might expect similar acidities, and indeed this is true for compounds such as water and ethanol where there are no structural stabilizing features in either the acid or the corresponding conjugate base. However, for acetic (ethanoic) acid, the acetate ion has two equally contributing resonance structures (see Chapter 3). The negative charge will therefore be spread equally over the two oxygen atoms, so the ion will be more stable than expected. Thus the equilibrium shown in Box 4.1(b) will lie (relative to the ethanol equilibrium shown in Box 4.1a) more to the right, and acetic acid will be more acidic than ethanol. This is confirmed by the data in Table 4.1. Phenol (Box 4.1c) is intermediate in acidity. The phenolate (phenoxide) anion is stabilized by delocalization of the charge onto three ring carbon atoms. However, since these contributing structures have the negative charge on carbon rather than oxygen, they would have a higher energy and contribute less; so the stabilization, though significant, is not so great as in the acetate ion.

Box 4.1 Acidities



Carbon–hydrogen bonds are much less acidic than oxygen–hydrogen bonds. For simple alkanes, there is effectively no dissociation and the values given in Table 4.1 have been estimated by indirect methods. A carbonyl group adjacent to a C–H bond increases the acidity of that bond significantly. Although there will be no measurable dissociation in water, a very small equilibrium concentration of the anion will be formed, and this anion, being reactive, may react with other reagents. As it does so, more of the carbonyl compound will dissociate, so that complete reaction may occur. This dissociation occurs because of delocalization of the charge onto the carbonyl group. It should be noted that this effect only applies to C–H bonds adjacent to a carbonyl group. If the carbonyl group is further away, the anion will not be stabilized and there will be no appreciable acidity of these bonds. This is illustrated in reaction (4.4) for cyclopentanone.



(4.4a)

(4.4b)

By the definition given above, the strongest bases will be those at the bottom of the second column of Table 4.1 and the weakest will be those at the top. Thus the metal salts of hydrocarbons will be the strongest bases, bases such as hydroxide and ethoxide will be intermediate in strength and molecules such as water are relatively weak bases. Bases lower in Table 4.1 will be able to abstract protons from acids higher in the table. For example, the ethoxide ion will abstract a proton from pentane-2,4-dione almost quantitatively (reaction 4.5).

$$\mathrm{MeCOCH_2COMe} + {}^{-}\mathrm{OEt} \rightleftharpoons \mathrm{MeCO\overset{-}{C}HCOMe} + \mathrm{HOEt} \qquad (4.5)$$

Worked Problem 4.1

Q A solution of the sodium salt of diphenylmethane, $Ph_2CH^-Na^+$, in diethyl ether is orange, due to absorption of light in the blue region by the delocalized diphenylmethide ion. When colourless triphenylmethane is added, the colour gradually changes to red, the colour of the triphenylmethide ion, Ph_3C^-. Explain this result. Would you expect the addition of diphenylmethane to the sodium salt of triphenylmethane, $Ph_3C^-Na^+$, in diethyl ether to result in a change of colour from red to orange?

A The colour change observed means that the orange Ph_2CH^- anion must abstract a proton from a triphenylmethane molecule to give diphenylmethane and the Ph_3C^- anion:

Triphenylmethane will be a stronger acid than diphenylmethane because the conjugate base Ph_3C^- is more stabilized, compared to Ph_2CH^-, by delocalization of the negative charge over the extra phenyl ring. Thus stabilization is gained when the reaction goes in the forward direction, and the equilibrium will lie to the right. The gradual change in colour means that the reaction rate is relatively slow. Since the equilibrium lies to the right, the addition of diphenylmethane to $Ph_3C^-Na^+$ will not cause significant reversal of the reaction, and the colour will remain red.

4.2 Bases and Nucleophiles

Bases always contain a lone pair of electrons which can form a bond to a proton. Most, but not all, bases have a negative charge. We have seen an example of a reaction of bases with halogenoalkanes to give alkenes in the last chapter, and others will follow in this chapter.

Bases can also react to form bonds to other elements, especially carbon, and when reacting in this way they are termed nucleophiles. We have already come across nucleophilic reactions in the S_N1 and S_N2 reactions of nucleophiles with halogenoalkanes. The scale of nucleophilicity used in Table 4.1 is based on S_N2 reactions, but it is not possible to define a single scale of nucleophilicity that will apply to all nucleophilic processes. In general, strong bases tend to be strong nucleophiles, and this trend is followed most closely when the central element is the same. The values for oxygen-centred nucleophiles in Table 4.1 (bold type) fall from 4.2 for OH^- to zero for H_2O, in line with base strengths, but nucleophiles such as I^- and Br^- are strongly nucleophilic even though they are very weak bases. A likely explanation is that small ions such as OH^- and F^- are highly solvated in water, whereas bigger ions such as I^- and Br^- are less solvated. The solvation energy is partially lost as the covalent bond forms in the transition state for the S_N2 reaction, which retards the rate more for the small nucleophiles.

Bases abstract protons (from acids). Nucleophiles react with electron-deficient centres (especially carbon atoms) by displacement of a leaving group, addition to a multiple bond or addition to a carbocation.

4.3 Carbanions

Carbanions have a formal negative charge on a carbon atom. They are important nucleophiles and bases.

4.3.1 Formation of Carbanions

There are four important methods.

(a) Abstraction of a proton by a base from a C–H bond.

This can only be done by strong bases, and is made easier if the carbanion to be formed is stabilized, for example by conjugation with an adjacent C=O group. In such cases (*e.g.* reaction 4.4a), the equilibrium concentration of the carbanion produced is often very small, but since carbanions of this type are very reactive, as the carbanion is removed it will be replaced by further hydrogen abstraction by the base, and nearly 100% reaction can often be achieved.

(b) Reaction of a metal with an organic halide.

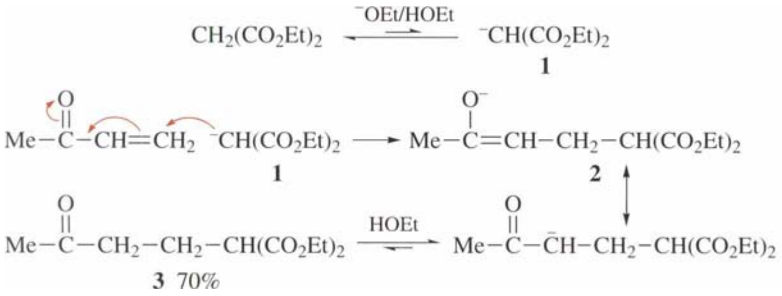
Reaction of organic halides with metals gives organometallic compounds. The carbon–metal bond can vary in character from being essentially covalent, as in organomercury compounds, to mainly ionic, as in the alkali metal compounds, especially where the potential carbanion is resonance stabilized, as in the cyclopentadienyl anion, $C_5H_5^-$, or the triphenylmethyl anion, Ph_3C^- (reaction 4.6). Organomagnesium compounds or Grignard reagentsare particularly useful in synthesis. They are made by the reaction of the halide with magnesium in the presence of a coordinating solvent such as diethyl ether (reaction 4.7). Grignard reagents have a complex structure, but the magnesium-carbon bonds are covalent and the compounds react as though they had the structure R–Mg–X, with polarization of the carbon–magnesium bond $^{\delta-}C\text{–}Mg^{\delta+}$. As a consequence, Grignard reagents are strongly nucleophilic, and can bring the organic group with the electrons from the covalent bond to a reaction site as a carbanion equivalent.

$$Ph_3C\text{—}Cl \xrightarrow{2\,Na} Ph_3C^-\,Na^+ + NaCl \qquad (4.6)$$

$$R\text{—}Br \xrightarrow[\text{ether}]{Mg} R\text{—}Mg\text{—}Br \qquad (4.7)$$

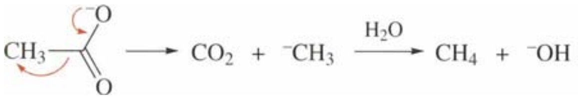
(c) Addition of a nucleophile to a C=C double bond.

The π bond in alkenes gives a region of high electron density in the region that a nucleophile would need to approach to form a bond to one of the sp^2 carbon atoms, and electron repulsion therefore prevents such attack. However, if the C=C bond is conjugated with a C=O group, the electron-withdrawing nature of the carbonyl group polarizes the C=C bond so that nucleophilic attack can take place at the C=C carbon atom remote from the carbonyl group. This is the basis of the Michael addition reaction (4.8). The ethoxide ion abstracts a proton from diethyl malonate (propane-1,3-dioate) to give the malonate anion **1** which can attack the butenone molecule to give the stabilized anion **2**, which in turn abstracts a proton from an ethanol molecule to give the adduct molecule **3**.


(4.8)

(d) Fragmentation of anions.

Elimination of a stable molecule, often CO_2 or a carbonyl compound, can give an anion which usually reacts further. Examples include elimination of carbon dioxide from acetates (reaction 4.9). The reaction of iodine with acetone (propanone) in the presence of base also involves a step of this type (reaction 4.17), as does the reverse of the Claisen condensation (reaction 4.34).


(4.9)

4.3.2 Structure of Carbanions

The methide anion (CH_3^-) has been shown to be pyramidal in the gas phase, and other saturated carbanions are also pyramidal. Hybridization is essentially sp^3, with the lone pair electrons occupying one of the tetrahedral positions.

Conjugated carbanions, for example those with an adjacent carbonyl group, are essentially planar. Hybridization is sp^2 with π overlap to the carbonyl group, and the majority of the negative charge resides on the oxygen atom. ^{13}C NMR spectra of anions show upfield shifts compared with the corresponding hydrocarbons, consistent with the increased shielding caused by the electron pair on the carbon atom which bears the charge. The ^{13}C NMR spectrum of conjugated anions such as penta-2,4-dienide (Figure 4.1) shows that the charge is mainly spread on the odd-numbered carbon atoms, in accordance with resonance or molecular orbital theory, with the even-numbered atoms having shifts in the range

Carbanions have a formal negative charge on a carbon atom. They are strongly basic and nucleophilic.

shown by alkenes, showing that little of the negative charge is associated with these atoms.

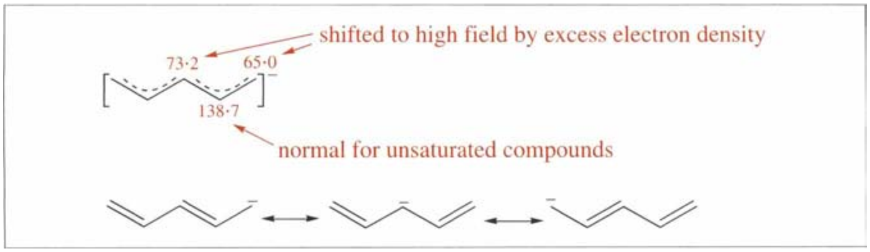


Figure 4.1 Chemical shifts in the ^{13}C NMR spectrum of the penta-2,4-dienide anion

4.3.3 Reactions of Carbanions (and Nucleophiles)

Carbanions, being strong bases and nucleophiles, react readily with acids and undergo the S_N2 reactions considered in Chapter 1 and the bimolecular E2 eliminations considered in Chapter 3. Other important reactions of carbanions (and nucleophiles) include addition to unsaturated compounds, especially those containing carbonyl groups, fragmentation (the reverse of addition) and elimination to give carbenes.

Reaction with Acids

This has been discussed earlier in the chapter. Carbanions will abstract a proton from acids (including carbon acids) provided that the acid is stronger than the conjugate acid of the carbanion (see Table 4.1). Since water is acidic, most organometallic compounds will react with water to give the hydrocarbon and the hydroxide ion, so water must be rigorously excluded from most organometallic preparations and reactions. The reaction of water with organometallic compounds does however provide a route to organic compounds deuteriated (or tritiated) in particular positions, for example reaction (4.10).

$$\mathrm{D{-}\overset{\delta-}{O}{-}\overset{\delta+}{D}\quad \overset{\delta-}{R}{-}\overset{\delta+}{Mg}{-}Br \longrightarrow DO^- + D{-}R + {}^{+}Mg{-}Br} \qquad (4.10)$$

Although the reaction of hydroxide or alkoxide ions with carbonyl compounds to abstract a proton from a carbon atom adjacent to the carbonyl group is thermodynamically unfavourable, and the equilibria in reactions such as (4.11) and (4.12) lie well over to the left, the high reactivity of the carbanion intermediates formed makes reactions of this type of vital importance in a number of cases, especially in halogenation (reaction 4.14) and in some carbonyl addition reactions, *e.g.* reactions (4.20) and (4.30).

$$\mathrm{H{-}O^- + H{-}CH_2CHO \rightleftharpoons H{-}O{-}H + {}^{-}CH_2CHO} \qquad (4.11)$$

$$\mathrm{Et{-}O^- + H{-}CH_2CO_2Et \rightleftharpoons Et{-}O{-}H + {}^{-}CH_2CO_2Et} \qquad (4.12)$$

Nucleophilic Substitution

Carbanions are strong nucleophiles. The S_N2 reaction with halogenoalkanes gives a new carbon–carbon bond, allowing long or complex hydrocarbon groups to be introduced into organic molecules (reaction 4.13). Carbanions will react with halogens to give the halogenoalkane and halide ion (4.14).

(4.13)

(4.14)

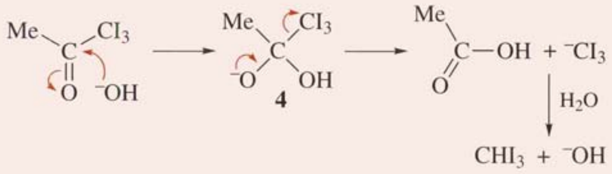
Worked Problem 4.2

Q When acetone is allowed to react with iodine in the presence of sodium hydroxide, the final major products are triiodomethane and the acetate anion. How do you account for this?

A The first step is clearly the formation of iodoacetone (reaction 4.15, a specific example of reaction 4.14). In iodoacetone, there are still five replaceable hydrogen atoms, so the base can attack to give either CH_3COCHI^- or $^-CH_2COCH_2I$. Since iodine is more electronegative than hydrogen, the former anion will be more stabilized, because the negative charge is partly located on the carbon with the iodine and thus can be stabilized by inductive electron withdrawal. Therefore further iodination will preferentially give 1,1,1-triiodoacetone (reaction 4.16). The hydroxide ion adds to the C=O carbon atom to give the intermediate anion **4**, which eliminates a $^-CI_3$ anion, a strong base which will abstract a proton from a water molecule to give CHI_3 (reaction 4.17). The elimination of $^-CI_3$ is possible because the electronegative iodine atoms inductively withdraw negative charge from the carbon, thus stabilizing the carbanion.

$$CH_3COCH_3 \underset{H_2O}{\overset{^-OH}{\rightleftharpoons}} CH_3COCH_2^- \xrightarrow{I_2} CH_3COCH_2I + I^- \quad (4.15)$$

$$CH_3COCH_2I \longrightarrow \longrightarrow CH_3COCI_3 \quad (4.16)$$



(4.17)

E2 Eliminations

Alkyl sodium and potassium compounds, R^-Na^+ and R^-K^+, are strong enough bases to react with ethers, such as diethyl ether (ethoxyethane), to give ethene and the ethoxide ion (reaction 4.18). This means that ethers are unsuitable solvents for the preparation of these reactive compounds.

(4.18)

Worked Problem 4.3

Q Although alkylsodium compounds react with diethyl ether, organomagnesium halides (Grignard reagents) do not. Why is this?

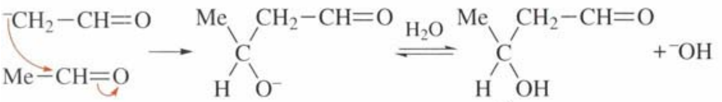
A Alkylsodium compounds are almost completely ionic and the alkyl anions are very strong bases, capable of abstracting a proton from ethers to cause an E2 elimination, as in reaction (4.18). Alkylmagnesium halides have polarized C–Mg bonds; although there is considerable ionic character in the bond, it is less ionic than in the alkylsodium compounds. Accordingly, the organomagnesium halides are less basic than alkylsodium compounds, and although they will react with water to give the alkane (reaction 4.10), they are not basic enough to remove a proton from diethyl ether.

Addition to the Carbonyl Group

The carbonyl group is strongly polarized in the direction $^{\delta+}C{=}O^{\delta-}$, so it is not surprising that a carbanion (or any other nucleophile) will bring its electron pair to the $^{\delta+}C$ atom to form a bond, displacing the π bond electron pair onto the oxygen atom which can readily accommodate them, as shown in reaction (4.19). This type of reaction is important synthetically and biologically. An important example is the aldol condensation, the simplest example of which is shown in reaction (4.20). The hydroxide ion reversibly removes the weakly acidic proton from an acetaldehyde (ethanal) molecule to give the stabilized carbanion **5**. Although present only in a tiny concentration at equilibrium, this carbanion is highly nucleophilic and adds to the carbonyl carbon atom of a second acetaldehyde molecule to give an adduct that reversibly reacts with water to give aldol (3-hydroxybutanal, **6**). The mechanism shown in reaction (4.20) is supported by the observed kinetics: first order with respect to $[OH^-]$, second order with respect to $[CH_3CHO]$. A rapid equilibrium is set up between the acetaldehye and its anion **5** (equation 4.20a), giving a small concentration of $^-CH_2CHO$, which is proportional to $[CH_3CHO][OH^-]$. The product is formed by a second-order reaction of the anion **5** with a further acetaldehyde molecule (equation 4.20b), thereby accounting for the overall kinetics.

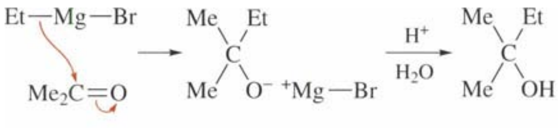

(4.19)

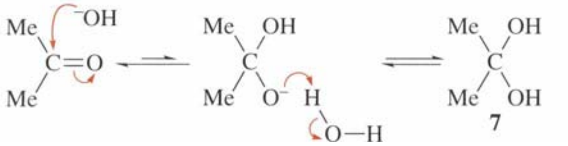
$$HO^- + CH_3{-}CHO \overset{\text{water}}{\rightleftharpoons} H_2O + \underset{\mathbf{5}}{{}^-CH_2{-}CH{=}O} \longleftrightarrow CH_2{=}CH{-}O^- \qquad (4.20a)$$


6

(4.20b)

Neutral nucleophiles, such as Grignard reagents (R–Mg–Br), also react readily with carbonyl compounds, as shown in reaction (4.21). The hydroxide ion will also react as a nucleophile (reaction 4.22), but here the overall equilibrium lies well to the left so that only a few percent of the diol **7** is present in an aqueous solution of acetone.


(4.21)


7

(4.22)

Reaction with Esters

Nucleophiles react with esters by substitution rather than addition, as shown in ester hydrolysis (4.23) or conversion to an amide by ammonia (4.24). Why the difference from aldehydes and ketones, and what is the mechanism?

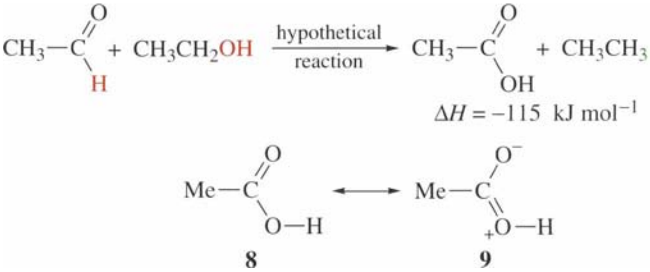
$$MeCO_2Et + {}^-OH \longrightarrow MeCO_2{}^- + EtOH \qquad (4.23)$$

$$MeCO_2Et + NH_3 \longrightarrow MeCONH_2 + EtOH \qquad (4.24)$$

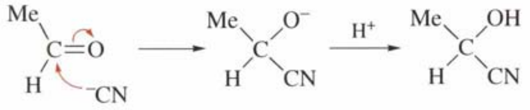
The key difference is thermodynamic. By placing a carbonyl group and a hydroxyl group on the same carbon atom, we have created a new functional group, the carboxylic acid group. This has different chemical properties and, in particular, is more thermodynamically stable than would be expected from a compound containing separate C=O and

Carboxylic acids and their derivatives (*e.g.* esters and amides) possess thermodynamic stabilization. They tend to react by substitution to retain this stabilization, rather than by addition, which would destroy it.

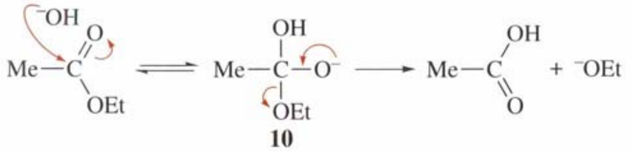
OH groups. The magnitude of this stabilization can be estimated by considering the hypothetical reaction (4.25) in which the hydroxyl group in ethanol and the aldehyde hydrogen in ethanal are notionally exchanged to give acetic acid and ethane. If there were no interaction between the C=O and the OH group in acetic acid, the reaction would be expected to be thermoneutral. In fact, based on experimental heats of formation, the reaction is 115.5 kJ mol^{-1} exothermic. This shows that there is a strong stabilizing interaction between the C=O and the OH groups. A lone pair on the oxygen atom of the OH group can interact with the π bond of the C=O group, or, to use resonance language, there are two possible resonance contributions to the structure. Structure **9**, which has the same number of covalent bonds as **8**, but has charge separation, will not contribute as much as **8** to the overall structure, but the infrared carbonyl stretching frequency ranges of aldehydes and ketones, on the one hand, and carboxylic acids and derivatives, on the other, demonstrate less double-bond character in carboxylic acids and derivatives, showing a significant contribution of **9** to the structure. Stabilization of this type is also important for other related functional groups, in particular esters ($-CO_2R$) and amides ($-CONH_2$).


$$CH_3CHO + CH_3CH_2OH \xrightarrow[\text{reaction}]{\text{hypothetical}} CH_3COOH + CH_3CH_3 \quad (4.25)$$
$$\Delta H = -115\ \text{kJ mol}^{-1}$$

Aldehydes and ketones tend to react with nucleophiles by addition of the nucleophile at the carbonyl carbon, and this is often followed by addition of an electrophile at the carbonyl oxygen, giving a stable adduct. Reaction (4.26), involving an aldehyde and the cyanide ion, is a good example. The first step of reaction of the hydroxide ion with ethyl acetate (reaction 4.27a) likewise involves addition of the hydroxide ion to the ester carbonyl group to give the tetrahedral intermediate **10**. This destroys the carboxylic stabilization energy which would not be recovered if this intermediate were to add a proton. Instead, the lone pair electrons on the negatively charged oxygen come in to re-form the carbonyl double bond, and the ethoxide ion is expelled. This restores the carboxylic stabilization energy. In subsequent steps, the ethoxide ion reacts with a water molecule to give ethanol and the hydroxide ion (reaction 4.27b), which in turn removes a proton from the acetic acid to give the even more stabilized acetate anion, where the negative charge is delocalized equally onto its two oxygen atoms (reaction 4.27c).

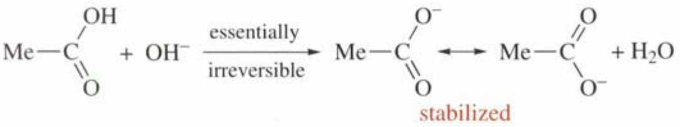


(4.26)



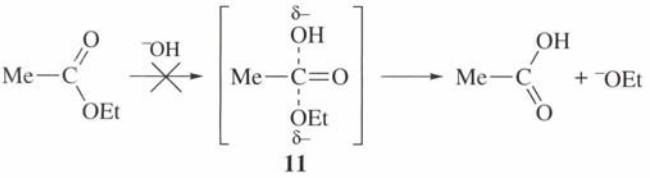
(4.27a)

$$H_2O + {}^-OEt \rightleftharpoons HO^- + HOEt \qquad (4.27b)$$

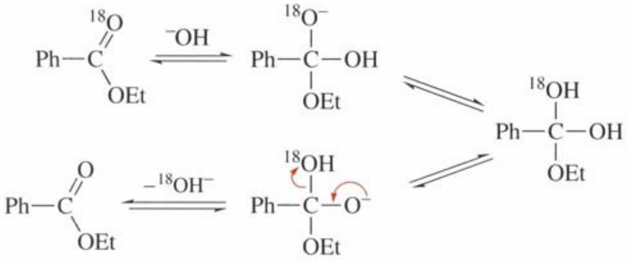


(4.27c)

Why not postulate the direct substitution reaction analogous to the S_N2 reaction, with a transition state **11** as shown in reaction (4.28), with no intermediate? The best evidence for the formation of a tetrahedral intermediate comes from studies of hydrolysis, in ordinary water ($H_2{}^{16}O$), of benzoate esters which have been labelled at the carbonyl oxygen with ^{18}O. If the reaction was not carried out to completion, and the unchanged ester was isolated, it was found that some of the ^{18}O had been lost from the carbonyl group. Quantitative analysis for ethyl benzoate showed that the ratio of the rate constant for exchange of oxygen to that for hydrolysis, k_{ex}/k_{hyd}, was 4.8, implying that an adduct is formed initially, but after a movement of a proton, the addition is reversed with loss of $^{18}OH^-$, as in reaction (4.29).



(4.28)

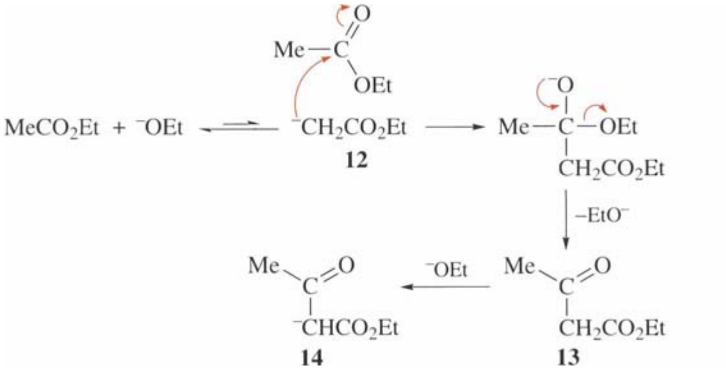


(4.29)

The Claisen Condensation

Claisen and aldol condensations are important in biological systems, with protein catalysts that enable reactions to take place in aqueous solution at temperatures close to ambient.

An important reaction of esters is the **Claisen condensation**, illustrated in reaction (4.30), in which two molecules of an ester react, in the presence of base, to give a β-keto ester. The initial steps of the reaction are similar to the aldol condensation already considered, but because of the lesser acidity of the ester compared with an aldehyde or ketone, a strong base has to be used, and the reaction cannot be carried out in water.



(4.30)

The first step involves the abstraction of a proton by the base from the α-carbon atom of the ester. The equilibrium for this reaction lies overwhelmingly in favour of starting materials, but the carbanion **12** produced is very reactive, and adds to the carbonyl group of an ester molecule. The tetrahedral intermediate loses an ethoxide ion to give the β-keto ester product **13**. This molecule is much more acidic than the original ester, and readily loses a proton to form the highly stabilized anion **14**. In practical terms, the reaction is carried out by adding sodium to the neat ester. A trace of alcohol is always present in the ester, which reacts with sodium to form the base sodium ethoxide. The ethanol produced in the reaction reacts with sodium as it is formed to provide further ethoxide ions, driving the reaction to the right, giving as the final product the sodium salt of the β-keto ester **14**, from which the β-keto ester is recovered at the end of the reaction by acidification.

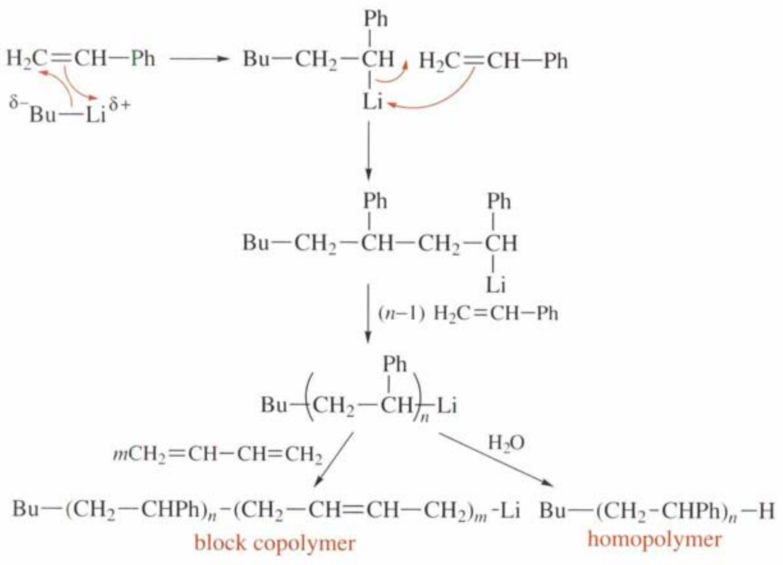
Although this reaction cannot be carried out in aqueous solution in the laboratory, an enzymic version of the Claisen condensation is responsible in living cells for the conversion of acetic acid derivatives to fatty acids.

Base-catalysed Reactions

A number of reactions of carbonyl compounds require the presence of a base, but the base is not used up in the reaction and is therefore acting as a catalyst. The aldol condensation considered earlier (reaction 4.20) is an example, and another is the base-catalysed exchange of ^{18}O between water and esters (reaction 4.29) which accompanies hydrolysis. The base reacts with the carbonyl compound in the first stage of the reaction, either by abstraction of a proton (4.20) or by addition at the carbonyl carbon atom (4.29). In both cases, the base is regenerated in the final step of the reaction. Other reactions which similarly involve a base include ester hydrolysis (reaction 4.27) and the Claisen condensation (reaction 4.30). However, in these reactions, a mole of base is used up in the final step to convert the carboxylic acid to its anion in ester hydrolysis and the β-keto ester to its anion in the Claisen condensation. Since base is used up, these reactions are better described as **base-promoted**.

Reaction with Alkenes

Although carbanions and nucleophiles add readily to the highly polarized C=O group, addition to the C=C bond is difficult because of the high electron density in the π bond, which makes approach of nucleophiles difficult. We have already seen in reaction (4.8) that attack is possible if electron density is pulled away from one end of the C=C double bond by a carbonyl group. Organometallic compounds with a high degree of ionic character in the carbon–metal bond, such as butyllithium, will react with conjugated alkenes such as buta-1,3-diene or styrene (phenylethene) to give adducts which in the absence of moisture or oxygen can add further alkene molecules to give polymers; these continue to grow until all the alkene is used up. At this point, the **living polymer** is still reactive: if a further supply of the same or a different conjugated alkene is added, polymerization continues, giving in the latter case a **block copolymer** where blocks of different monomer units can be assembled (reaction 4.31). The process is finished by adding water or air, which quenches the organometallic compound by donation of a proton to give the alkane (reaction 4.32), or addition to a dioxygen molecule to give in turn the peroxide anion and then the alkoxide anion (reaction 4.33).



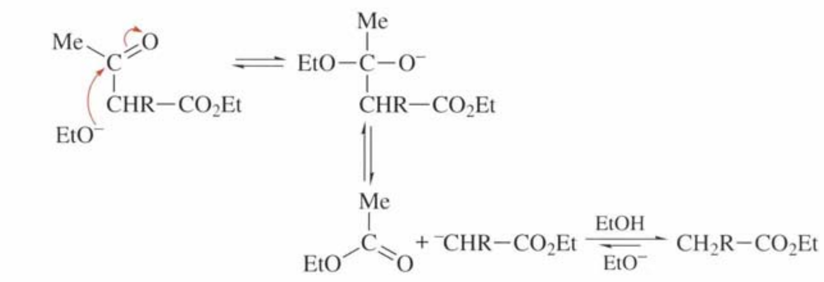
(4.31)

$$\text{R—Li} \xrightarrow{H_2O} \text{R—H} + \text{Li}^+ + {}^-\text{OH} \quad (4.32)$$

$$\text{R—Li} \xrightarrow{O{=}O} \text{R—O—O}^-\ \text{Li}^+ \xrightarrow{\text{R—Li}} 2\,\text{R—O}^- + 2\,\text{Li}^+ \quad (4.33)$$

Fragmentation

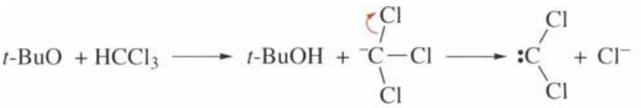
Carbanions (and other anions) can undergo fragmentation reactions to produce a carbanion and a smaller molecule, usually carbon dioxide or a molecule containing a carbonyl group. Examples include the loss of carbon dioxide from the acetate anion (reaction 4.9), considered above. Other important examples include reactions of type (4.34), which are the reverse of addition reactions such as (4.20) and (4.30).



(4.34)

Elimination to give Carbenes

Carbanions with a good leaving group, such as a halogen atom, attached to the carbanion centre may react in a unimolecular elimination process to give a **carbene**, a different type of reactive intermediate with only six electrons in the valence shell. Dichlorocarbene may be conveniently made by the reaction of potassium *t*-butoxide with trichloromethane (chloroform; reaction 4.35). Abstraction of the proton is made easier by the presence of the three chlorine atoms which stabilize the charge on the intermediate carbanion **15**, and the subsequent elimination of the chloride ion transfers the negative charge from carbon to the much more electronegative chlorine.

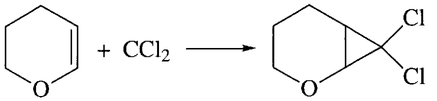


$$t\text{-BuO} + \text{HCCl}_3 \longrightarrow t\text{-BuOH} + {}^-\text{CCl}_3 \longrightarrow :\text{CCl}_2 + \text{Cl}^- \quad (4.35)$$

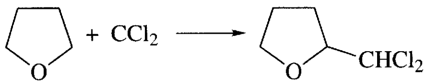
15

Carbenes are very reactive: since they contain divalent carbon, they have the capacity to react to form two new bonds. Two important ways in which this happens are by addition to both ends of a double bond synchronously to give a cyclopropane ring (reaction 4.36) or by insertion into a single bond (reaction 4.37). The former reaction has synthetic utility, since few reactions exist to produce cyclopropane rings in good yields.

Carbenes are neutral reactive species that can form two bonds, either by insertion into a single covalent bond, or by addition to both ends of a double bond to give a cyclopropane ring.



(4.36)

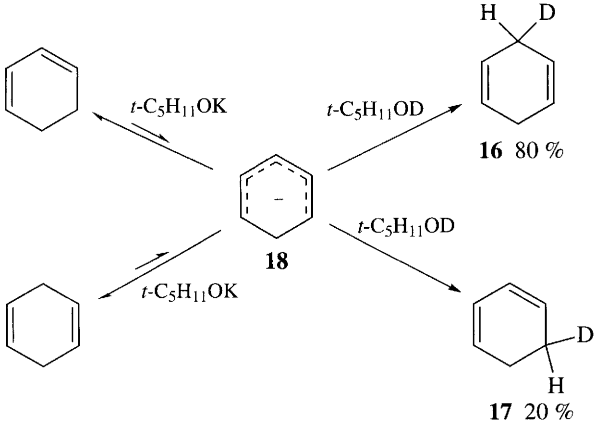


(4.37)

4.3.4 Detection of Carbanions and Indications for Anionic Intermediates

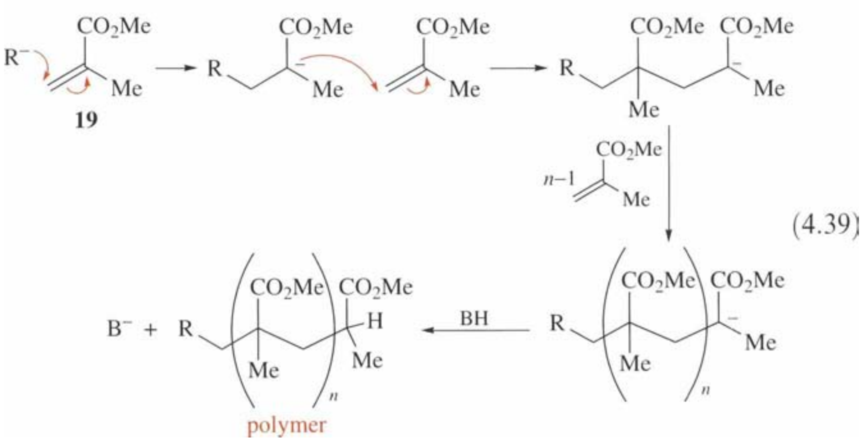
In some cases, carbanion intermediates can be detected, for example by NMR spectroscopy. More frequently, they are inferred as being the most likely intermediate, or characterized by trapping with reagents known to react with anions. Reactions taking place in basic solutions are likely to involve anionic intermediates, formed either by abstraction of a proton or by addition to a multiple bond (usually containing a heteroatom). Reactions in acidic media virtually never involve reactive anionic intermediates; any anions present merely balance the positive charges. Stepwise reactions in basic media usually involve alternating sequences of neutral and negatively charged species. Do not suggest steps involving positively charged species including protons: any protons needed to complete a reaction will come from solvent molecules.

For example, both cyclohexa-1,3-diene and its isomer cyclohexa-1,4-diene, when heated separately with *t*-$C_5H_{11}OK$ and *t*-$C_5H_{11}OD$ at 95 °C [*t*-$C_5H_{11} = (C_2H_5)(CH_3)_2C$–] give the same mixture of monodeuteriated compounds **16** and **17** (reaction 4.38). This is not the equilibrium mixture, which suggests that the mixture of products arises from an intermediate which is the same for both reactions. The only likely intermediate is the stabilized anion **18**, arising from proton abstraction from the cyclohexadiene molecules by the base, followed by abstraction of a deuteron from the solvent by the common intermediate anion.



(4.38)

Trapping of anions can be achieved by adding methyl methacrylate (methyl 2-methylpropenoate, **19**) to a reaction mixture. The formation of a polymer, precipitated out of the reaction mixture by adding methanol, indicates an anion intermediate (reaction 4.39). Addition of a mixture of methyl methacrylate and styrene is even more specific for reactive anions. If an anion initiates the polymerization, the polymer contains only methyl methacrylate units. If a radical is involved, a copolymer of styrene and methyl methacrylate will be formed, whereas cations will give a styrene polymer. The three possible polymer outcomes, and thus the nature of the initiator, can readily be distinguished by combustion analysis: the weight percentages of carbon and hydrogen in the three types of polymers are markedly different (see Table 4.2).



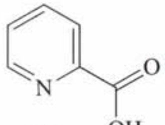
(4.39)

Table 4.2 Copolymerization of methyl methacrylate in the presence of various initiators

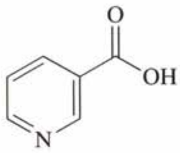
Polymer composition	*Carbon* (%)	*Hydrogen* (%)	*Initiator*
Polystyrene	92.3	7.7	Cation
Poly(methyl methacrylate)	60.0	8.1	Anion
Copolymer of styrene and methyl methacrylate (1:1)	76.4	7.9	Radical

Worked Problem 4.4

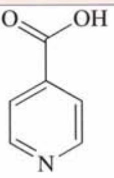
Q Pyridine-2-carboxylic acid (**20**) decarboxylates on heating, to give pyridine and carbon dioxide. The reaction is more rapid for **20** than for its isomers **21** and **22**. Suggest a mechanism for this reaction and an experiment to support it.



20

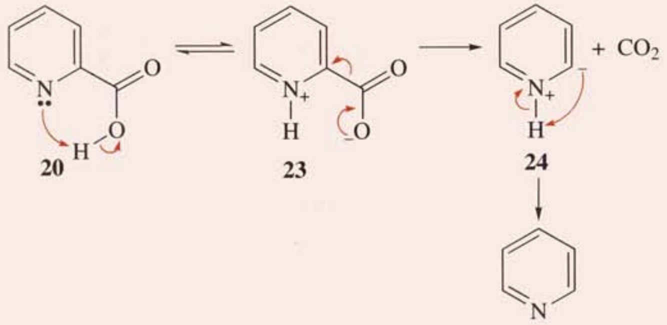


21



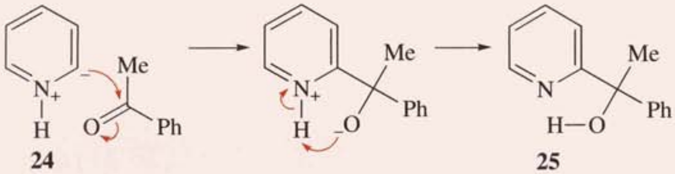
22

A The fact that **20** reacts faster than **21** or **22** suggests that the first step may be the abstraction of a proton from the carboxylic acid group by the nitrogen atom to give the zwitterion **23** (reaction 4.40). This could be followed by loss of carbon dioxide from the carboxylate group to give **24**, which would rapidly be converted into pyridine by a proton shift.



(4.40)

The presence of **24** as an intermediate is supported by carrying the reaction out in the presence of acetophenone (phenylethanone), when the adduct **25** is isolated (reaction 4.41). A carbanion intermediate such as **24** would be expected to add to the carbon atom of a carbonyl group, giving the adduct **25**.



(4.41)

Summary of Key Points

1. Bases are species that can donate a lone pair of electrons to a proton, forming a covalent bond, to give its conjugate acid. If the conjugate acid is a weak acid, the base will be a strong base. Bases are usually negatively charged or neutral.

2. Nucleophiles can donate a lone pair of electrons to form a bond to an atom (usually carbon), by displacing a leaving group (nucleophilic substitution), by breaking a multiple bond (nucleophilic addition) or by adding to a carbocation (second step of an S_N1 reaction).

3. Carbanions can exist as metal salts, and are also important intermediates in reactions carried out under basic conditions. They react as strong bases and nucleophiles, undergoing hydrogen abstraction reactions, nucleophilic substitution and addition, fragmentation, and loss of halide ions to give carbenes. They can be identified spectroscopically or by trapping.

4. Carbanions (and other reactive anions) are not formed under acidic conditions.

5. In base-catalysed reactions, the base starts the reaction sequence by abstraction of a proton or addition to a multiple bond (often C=O) to give an intermediate anion which is chemically reactive. In the last step of the reaction, the base is re-formed, usually by abstraction of a proton from a solvent molecule by the final anionic intermediate.

Further Reading

M. B. Smith and J. March, *March's Advanced Organic Chemistry*, Wiley, New York, 2001, Chapter 5.

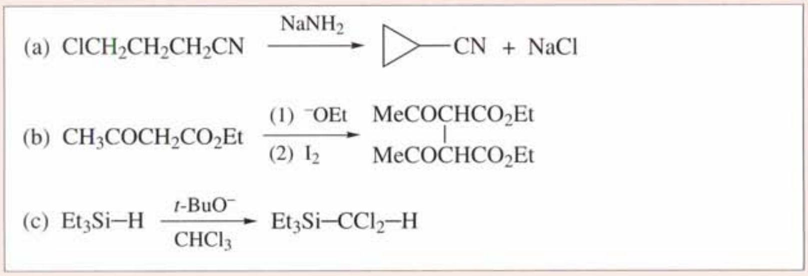
Problems

4.1. Define the terms base, nucleophile, carbanion and carbene. List the common reactions of carbanions and carbenes.

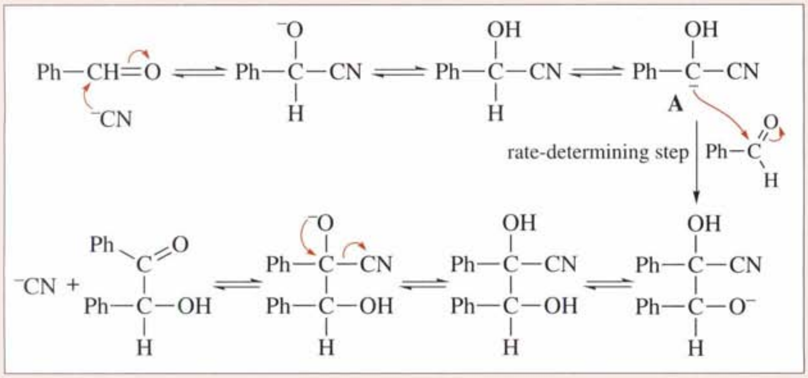
4.2. In Worked Problem 4.1 it was asserted that the Ph_3C^- anion is more stable than the Ph_2CH^- anion because of the extra stabilization caused by delocalization of the charge over the extra benzene ring. Draw and count the resonance structures for the two anions, with the charge on different carbon atoms, to confirm this.

4.3. The pK_a values for CH_3CH_3, $CH_3CO_2C_2H_5$ and CH_3COCH_3 are 48, 26 and 20, respectively. Account for the differences.

4.4. Suggest plausible mechanisms for the following reactions, and comment on the reaction steps you suggest:



4.5. The benzoin condensation of benzaldehyde in the presence of the cyanide ion in aqueous solution is believed to have the following mechanism:



(a) What kinetics would be expected?

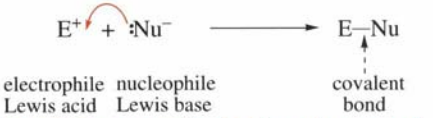
(b) By considering the stability of the carbanion **A**, provide an explanation for the fact that the reaction is not catalysed by the hydroxide ion, OH^-.

4.6. The keto alcohol $Me_2C(OH)CH_2COMe$ in aqueous sodium hydroxide is converted into acetone (propanone), MeCOMe. Suggest a plausible mechanism, and the kinetics expected.

5

Cations and Electrophiles

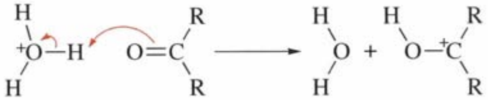
Many reactions in polar solvents involve the production of cations as intermediates. This chapter focuses on **electrophiles**. These are electron-deficient species that form a covalent bond with a reaction partner (the nucleophile) by accepting both electrons for the bond from the nucleophile (reaction 5.1). The terms **Lewis acid** and **Lewis base** are also used to describe electrophiles and nucleophiles, especially in the context of inorganic chemistry. Electrophiles can be positively charged or neutral. If positively charged, they are **cations**. Cations centred on carbon are **carbocations**. All proton acids are electrophiles; other electrophiles include the nitronium ion NO_2^+ and the bromine molecule. Some examples of reactions of electrophiles with nucleophiles (which can be negatively charged or neutral) are shown in reactions (5.2)–(5.5). Reactions (5.2) and (5.3) involve positively charged electrophiles, whereas the electrophiles in (5.4) and (5.5) are neutral.



(5.1)

Electrophiles are positively charged or neutral
Nucleophiles are negatively charged or neutral

(5.2)


(5.3)

(5.4)

(5.5)

The *tert*-butyl (2-methylprop-2-yl) cation, which is the electrophile in reaction (5.2), has a vacant orbital which can accept the electron pair from the nucleophile without the need for any further movement of electrons. However, in many reactions a further electron pair movement is needed. The electrophilic proton in H_3O^+, HBr or H_2O (reactions 5.3–5.5) can only support one covalent bond, so as the nucleophile attacks with its electron pair, the bond from the proton to the oxygen or bromine atom has to break, with the electrons from that bond forming a lone pair on the oxygen or bromine atom.

Aims

By the end of this chapter, you should:

- Understand the meaning of the terms electrophile, cation, carbocation
- Know how cations are detected as reaction intermediates
- Know the principal reactions of carbocations
- Understand the importance of acid-catalysed reactions
- Be aware of the types of reactions that may involve cationic intermediates, and be able to postulate plausible reaction mechanisms involving cations

5.1 Formation of Carbocations

Carbocations can be formed in a number of ways, including heterolysis of a covalent bond and addition of an electrophile to a multiple bond.

5.1.1 Heterolysis of a Covalent Bond

Organic compounds with covalent bonds to electronegative elements may dissociate to form carbocations, especially if the cation is stabilized by the inductive effect, as in the *t*-butyl cation, or by resonance, as in the cumyl (2-phenylprop-2-yl) cation. This can happen slowly in polar solvents such as water. The S_N1 reaction of *t*-butyl halides is an example (reaction 5.6). The slow and rate-determining heterolysis of the halide is followed by a rapid reaction of the *t*-butyl cation with water to give the alcohol product.

$$\mathrm{Me_3C}\overset{\curvearrowleft}{-}\mathrm{Cl} \xrightarrow[\text{slow}]{-\mathrm{Cl}^-} \mathrm{Me_3C^+} \xrightarrow[\text{fast}]{\mathrm{H_2O}} \mathrm{Me_3C{-}OH} \qquad (5.6)$$

Loss of halide can be assisted by the presence of a Lewis acid such as antimony(V) fluoride (reaction 5.7). In this or other polar aprotic solvents the carbocation formed has no nucleophile to react with except for the

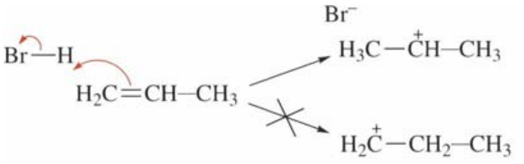
SbF_5Cl^- anion, which regenerates the original halide. In these solutions, concentrations of cations can be achieved which are high enough to allow study by NMR spectroscopy.

$$Me_2CH{-}Cl \quad SbF_5 \longrightarrow Me_2CH^+ + SbF_3Cl^- \tag{5.7}$$

5.1.2 Addition of an Electrophile to a Multiple Bond

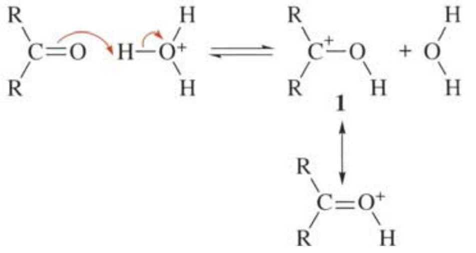
The proton and other electrophiles can readily add to one end of a C=C or C≡C double or triple bond, and to the more electronegative atom in C=N, C≡N or C=O bonds. In addition to a C=C or C≡C bond, the direction of addition is to give the most stabilized cation. Alkyl groups stabilize a cation by their inductive and hyperconjugative effects (see Chapter 3); unsaturated and aromatic groups stabilize a cation by delocalization of the positive charge onto remote atoms. Propene reacts with HBr in the first step to give the secondary prop-2-yl cation (reaction 5.8), rather than the less stable primary prop-1-yl cation (reaction 5.9). Protonation of a carbonyl group (reaction 5.10) gives a delocalized cation **1**, with the charge spread between the carbon and the oxygen atoms. This reaction is reversible and forms the first step of many acid-catalysed reactions.

Electrophiles normally add to the end of a multiple bond which gives the more stable cation intermediate.



(5.8)

(5.9)



1

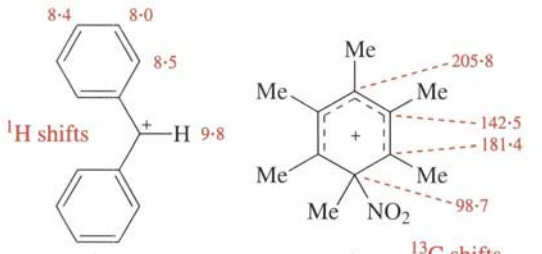
(5.10)

Addition of a proton or other electrophile is often rapidly followed by addition of a nucleophile at the other terminus of the multiple bond.

5.2 Evidence for Cations

5.2.1 NMR Spectroscopy

Reactions such as S_N1 reactions in water are believed to involve cationic intermediates, but do not give sufficient concentrations of the cations for them to be identified spectroscopically. However, cations can be observed conveniently in solutions in aprotic polar solvents such as SbF_5. The strong deshielding, resulting in high values of chemical shift for both ^{13}C and ^{1}H NMR spectra, is good evidence for cationic character. For example, the ^{1}H NMR spectrum of the prop-2-yl cation $(CH_3)_2CH^+$ shows a one-proton resonance at $\delta = 13.5$ ppm, split into septets by the six methyl protons. The methyl protons appear at 5.1 ppm. The very high value for the CH proton is consistent with its attachment to a carbon bearing a positive charge; the high value for the methyl protons suggests that the charge on the neighbouring carbon is causing deshielding by inductively and hyperconjugatively withdrawing electrons. The diphenylmethyl cation **2** (Figure 5.1) shows a high-field proton at 9.8 ppm; the ring protons are more deshielded at the *ortho* and *para* positions, corresponding to greater positive charge density at these positions compared with the *meta* protons, in accord with resonance and molecular orbital theory.



2

3

Larger chemical shifts for ^{1}H or ^{13}C atoms of a particular type correspond to greater deshielding, caused by more positive charge at these positions

Figure 5.1 ^{1}H and ^{13}C NMR chemical shifts (δ)

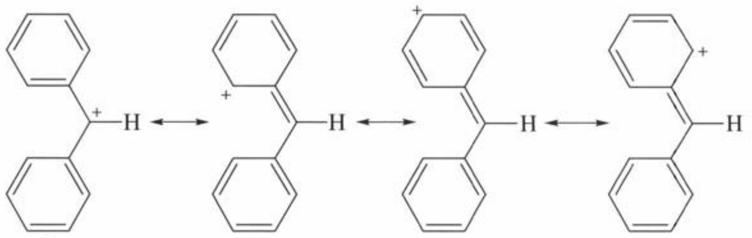
The nitronium ion NO_2^+ attacks hexamethylbenzene to give an adduct **3** of the type thought to be involved in electrophilic aromatic substitution; the ^{13}C chemical shifts for the ring carbon atoms are shown in Figure 5.1. The δ value of 98.7 ppm is very high for a sp^3 carbon atom and is attributed to the positive charge build-up on the adjacent carbon atoms. Again the *ortho* and *para* carbon chemical shifts are higher than those of the *meta* carbon atoms, in line with resonance and molecular orbital theory.

Carbocations show characteristic ^{1}H and ^{13}C NMR spectra with chemical shifts for the charged centres downfield of all neutral centres, due to the deshielding effect of the positive charge.

Worked Problem 5.1

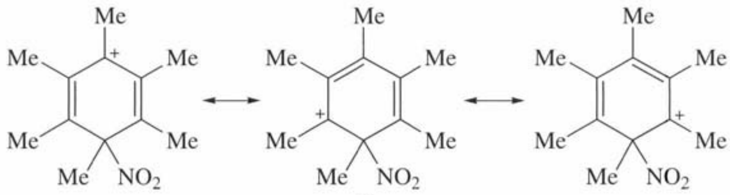
Q Draw resonance structures for **2** and **3** to show the positions at which positive charge build-up is expected.

A



2

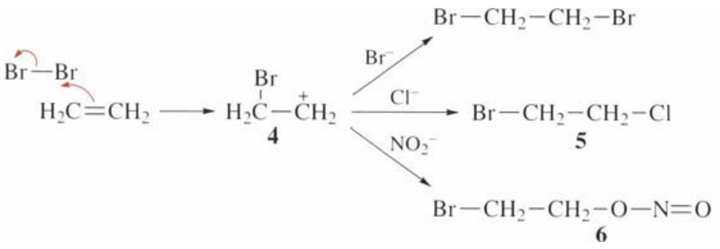
(and similar structures with the charge on the other ring)



3

5.2.2 Trapping

Cations react rapidly and indiscriminately with nucleophiles. Thus if a reaction which is suspected to go *via* a cationic intermediate is carried out in the presence of an added nucleophile, and an adduct containing the new nucleophile is obtained, this provides evidence for a cationic intermediate which is trapped by the added nucleophile. For example, the addition of bromine to alkenes is thought to go *via* a cationic intermediate **4** (reaction 5.11). If chloride or nitrite ions are added to the reaction mixture, the chloride or nitrite adducts **5** and **6** are obtained, even though the chloride and nitrite ions do not react with ethene (or 1,2-dibromoethane) directly at a rate that would account for the amount of these products in the reaction mixture. This provides strong evidence for the intermediate bromoethyl cation **4**, which will be trapped by the added chloride or nitrite ions (reactions 5.12 and 5.13). The structure of bromoalkyl cations is discussed further in the section on electrophilic addition.

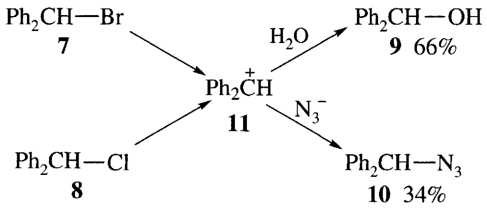


(5.11)

(5.12)

(5.13)

If a carbocation will react with two nucleophiles to give the corresponding adducts, we would expect the adducts to be formed in the same ratios however the carbocation is formed. Although the decomposition of benzhydryl bromide (bromodiphenylmethane, **7**) in 90% aqueous acetone at 50 °C in the presence of 0.1 M sodium azide is 335 times faster than the decomposition of the corresponding chloride **8**, the proportion of alcohol **9** to azide **10** remains constant, pointing to a common intermediate, the carbocation **11**, in both solvolyses (reactions 5.14).



(5.14)

5.2.3 Rearrangements

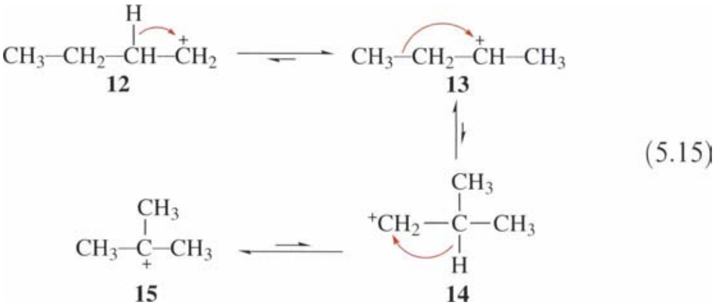
Rearrangement of the carbon skeleton in a chemical reaction is a strong indication that carbocations are involved. Examples and the mechanism are discussed in the next section. Carbanions and carbon-centred free radicals rarely rearrange.

5.3 Reactions of Carbocations

There are three important reactions of carbocations: rearrangements, addition of a nucleophile, and elimination, usually of a proton. Since rearrangements involve conversion of one carbocation into another, these reactions will need to be completed to give an uncharged product by addition of a nucleophile or by elimination.

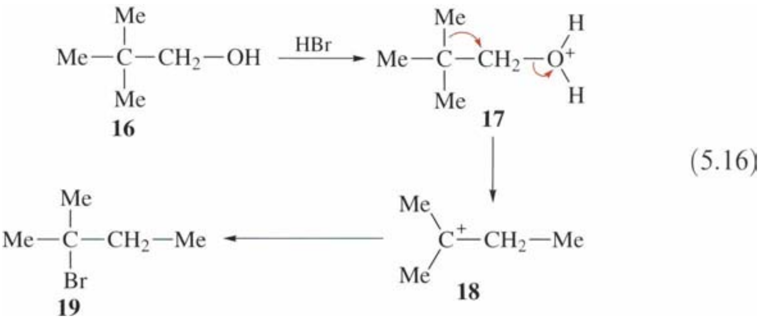
5.3.1 Rearrangements

Intramolecular rearrangements are the most characteristic reaction of carbocations; whenever a free carbocation can undergo rearrangement to give a more stable cation, it will do so provided there is a possible reaction pathway. Thus both 1- and 2-fluoropropane in SbF_5 give the prop-2-yl cation, and all four isomers of C_4H_9F give the *t*-butyl cation. This also provides strong evidence that the stability order is tertiary > secondary > primary. The mechanism is thought to involve a succession of 1,2-hydrogen or alkyl shifts, shown for the rearrangement of the *n*-butyl cation **12** to the *t*-butyl cation **15** in reaction (5.15). The second step involving the rearrangement of the but-2-yl cation **13** to the isobutyl cation **14** (*i.e.* secondary to primary) is endothermic, but overall, reaction (5.15) is strongly exothermic and the equilibrium overwhelmingly favours the *t*-butyl cation **15**.



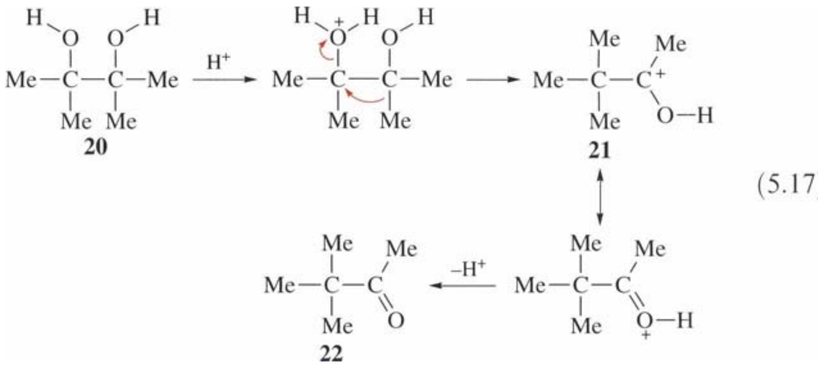
(5.15)

The primary alcohol **16** reacts with HBr to give the rearranged bromide **19** (reaction 5.16). Protonation will give the oxonium ion **17**; as the water molecule leaves in the second step, the methyl group migrates so that the tertiary carbocation **18** is formed, which adds a bromide ion to give the final product.



(5.16)

The diol **20** (pinacol) rearranges to pinacolone **22** in the presence of acid; in the second step the methyl group migrates with its bonding electrons to give the stabilized cation **21**, which loses a proton to give the final ketone **22** (reaction 5.17).



(5.17)

Box 5.1 Carbocation, Radical and Carbanion Rearrangements

In a carbocation arrangement, the transition state is a delocalized three-orbital system with two electrons from the R–C covalent bond. The number 2 is a Hückel number ($4n+2$, $n=0$), so the transition state will be stabilized and the activation energy will be lowered. The corresponding radical will involve three electrons, and the carbanion will involve four electrons. These extra electrons will have to go into higher-energy orbitals in the transition state, which will therefore be less stabilized. Thus radicals and carbanions rearrange less readily than carbocations.

5.3.2 Addition of a Nucleophile

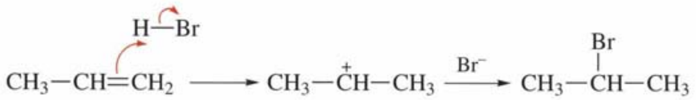
Carbocations, however formed, are very electrophilic. They react readily with nucleophiles, as shown in reaction (5.18). These reactions are important as steps in electrophilic addition to double bonds and unimolecular nucleophilic substitution (S_N1) reactions.

$$\mathrm{R}^{+}\curvearrowleft\mathrm{Nu} \longrightarrow \mathrm{R{-}Nu} \qquad (5.18)$$

Electrophilic Addition to Multiple Bonds

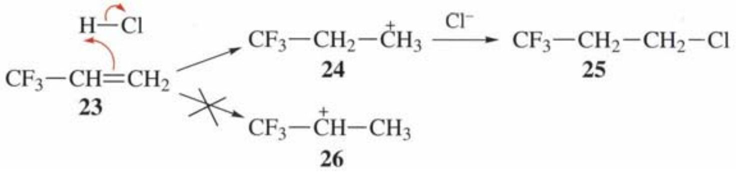
Molecules such as hydrogen bromide add to alkenes to form bromoalkanes. Trapping experiments (see above) support the intermediate formation of a carbocation; the direction of addition is determined by the stability of the intermediate cation. Thus propene gives 2-bromopropane via the prop-2-yl cation (reaction 5.19); this direction of addition is termed **Markovnikov** addition, to distinguish it from the radical-catalysed addition considered in the next chapter which gives the **anti-Markovnikov** product 1-bromopropane. However, 3,3,3-trifluoropropene (**23**) adds HCl in the opposite direction to give **25**, in which the proton has added to the central rather than the terminal carbon atom (reaction 5.20). The secondary ion **26** is destabilized by the electron-withdrawing fluorine atoms; as a result, the reaction goes through the primary cation **24**.

The electrophile adds first to give the more stable cation intermediate.



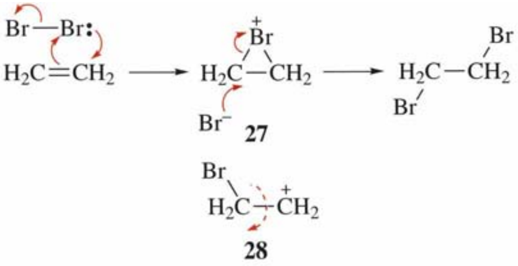
$$CH_3-CH=CH_2 \longrightarrow CH_3-\overset{+}{C}H-CH_3 \xrightarrow{Br^-} CH_3-\overset{Br}{C}H-CH_3$$

(5.19)

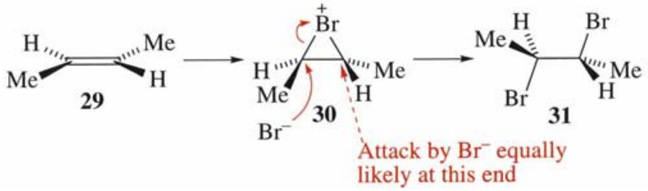


(5.20)

The electrophile does not need to be a proton. Bromine adds to double bonds to give the 1,2-dibromo compound (reaction 5.21). The intermediate bromonium cation here is believed to have the cyclic structure **27** rather than the open structure **28** because of the stereochemistry of the products. *trans*-But-2-ene (**29**) reacts with bromine to give the optically inactive *meso* dibromide **31** as a single compound (reaction 5.22) [*cis*-but-2-ene gives an equimolar mixture of the two enantiomers (*R,R*)- and (*S,S*)-2,3-dibromobutane, which is also optically inactive].



(5.21)



Attack by Br⁻ equally likely at this end

(5.22)

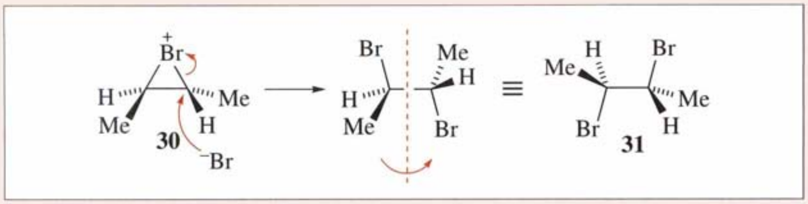
The *anti* addition of the two bromine atoms of a bromine molecule across a C=C bond shows that the bonds cannot be formed in a concerted manner and supports the formation of a bromonium ion intermediate.

This shows that the two bromine atoms add to the opposite sides of the double bond, which rules out a molecular mechanism for this reaction in which both new bonds are formed simultaneously. This suggests that the bridged bromonium ion **30** is formed as an intermediate; the bridging will prevent free rotation round the C–C bond which would allow a mixture of diastereoisomers to be formed. The second step is effectively an S_N2 reaction, in which we expect attack by the incoming nucleophile on the opposite side to the leaving group.

Worked Problem 5.2

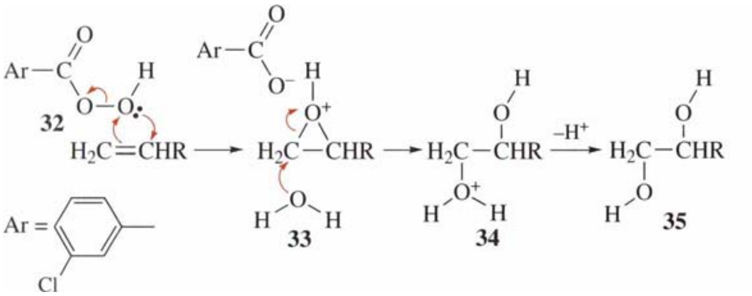
Q Show that attack by Br^- at the 3-position of **30** would give the same product.

A



Epoxidation by Peroxy Acids

The O–O bond in peroxycarboxylic acids **32** can be regarded as polarized in the direction Ar–CO–$O^{\delta-}$–$O^{\delta+}$H, so **32** reacts by electrophilic addition of the $O^{\delta+}$H group to a double bond (reaction 5.23). However, a lone pair of electrons on the oxygen atom immediately coordinates with the other carbon which would otherwise have developed the positive charge, to give the bridged intermediate hydroxonium ion **33**. The benzoate anion escapes and takes no further part in the reaction; the stabilization of the benzoate anion provides a driving force for the reaction. The oxonium ion **33** is attacked from the opposite side by a water molecule in an S_N2 reaction to form the cation **34**. This loses a proton to give the diol **35**, in which the two hydroxyl groups have been added to the original C=C bond in the *anti* (opposite sides) orientation.



(5.23)

S_N1 Reactions

S_N1 reactions (5.24), discussed in Chapter 1, involve a slow rate-determining step in which a leaving group departs, taking the electrons from the covalent bond, and leaving a reactive carbocation intermediate.

This reacts rapidly by addition to any nucleophile present, especially with the solvent, to form a stable product. A final proton loss may be necessary. Since carbocations are planar, it might be expected that optically active starting materials should give racemic products: if a completely free carbocation is formed, the incoming nucleophile would be expected to be able to attack equally readily from both sides of the cation (Figure 5.2a). In practice, a mixture of racemization and inversion is observed, suggesting that the leaving group is still in the vicinity, either free or as an ion pair, which inhibits attack from the same side as the departing group and therefore favours attack from the opposite side, giving rise to a greater amount of inversion than retention (Figure 5.2b).

$$\mathrm{R{-}Hal} \xrightarrow{\text{slow}} \mathrm{Hal^- + R^+} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}\overset{+}{O}H_2} \xrightarrow{\mathrm{H_2O}} \mathrm{R{-}OH + H_3O^+} \qquad (5.24)$$

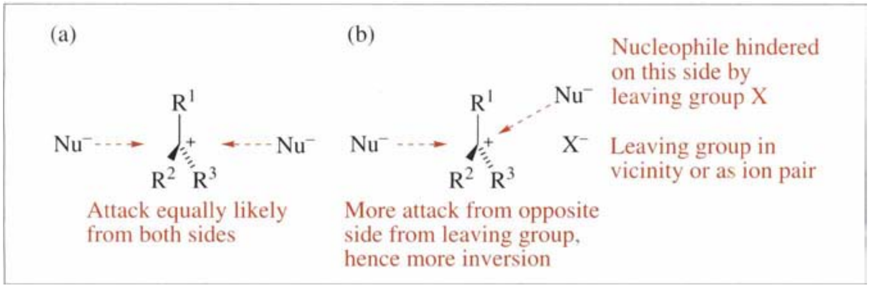


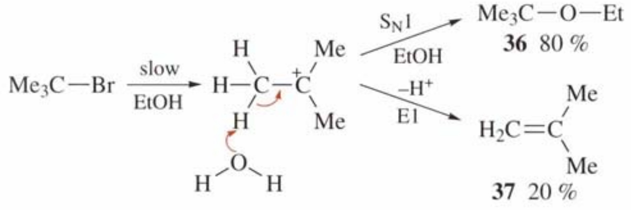
Figure 5.2 Stereochemistry of S_N1 reactions

5.3.3 Elimination

The alternative way in which a carbocation can be converted into a neutral product is by elimination of a cation, almost always a proton. Two important reactions involve elimination as the final step.

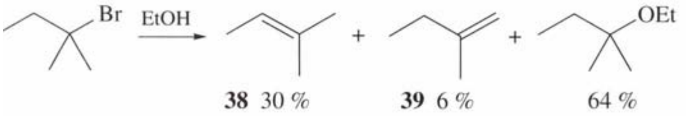
Unimolecular Elimination (E1) Reactions

When a carbocation is formed by loss of a nucleophile, as in the S_N1 reaction, elimination of a proton will always compete with substitution, provided that there is a β-C–H bond in the cation. These eliminations are described as **unimolecular eliminations (E1)** because, as with the competing S_N1 reaction, the rate-determining step is the unimolecular reaction of the original halide to give the carbocation. For example, *t*-butyl chloride in ethanol gives the *t*-butyl cation, which can either react with a solvent molecule to give the ethyl ether **36** (S_N1, **solvolysis**, reaction 5.25) or a proton can be removed by a solvent molecule to give 2-methylpropene **37** (E1, reaction 5.26). If more than one type of β-C–H bond is available, a mixture of products will be formed. The proportion of products is mainly determined by the stability of the alkene produced. For unhindered monoalkenes, this will favour the alkene product which has most substituents on the C=C, since this alkene will be the most stable. For example, $Me_2C{=}CHMe$ ($\Delta H_f = -42.1$ kJ mol^{-1}, three substituents) is more stable than $Me(Et)C{=}CH_2$ ($\Delta H_f = -35.6$ kJ mol^{-1}, two substituents), which in turn is more stable than $Me_2CH{-}CH{=}CH_2$ ($\Delta H_f = -27.4$ kJ mol^{-1}, one substituent). This stabilization is probably due to the greater strength of the $C_{sp2}{-}C_{sp3}$ bond than the $C_{sp3}{-}C_{sp3}$ single bond, due to better overlap. There are more of these bonds in more substituted alkenes. However, bulky groups such as the *t*-butyl group cause steric destabilization, especially when *cis* to another group at the other end of the double bond. Examples of these effects are shown in reactions (5.27) and (5.28). In (5.27), the trisubstituted alkene **38** predominates over the disubstituted alkene **39**; in (5.28), the predominant product is the disubstituted isomer **40** where the *t*-butyl and methyl groups are *trans* to each other, followed by the monosubstituted **41**, with a very small amount of the *cis* product **42**, which, although disubstituted, has significant steric hindrance between the two groups *cis* to each other. The proportions follow the measured heats of formation of the three isomers.

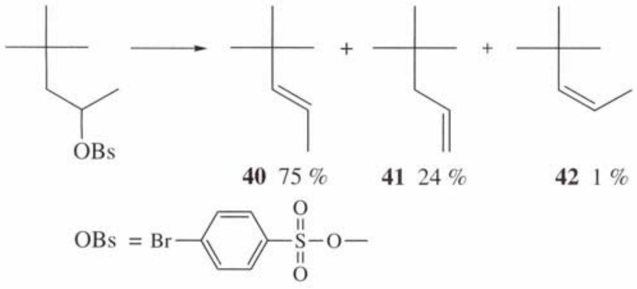


(5.25)

(5.26)



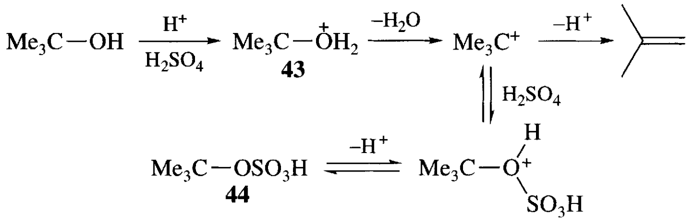
(5.27)



(5.28)

Elimination of a proton from a carbocation gives predominantly the most stable alkene.

Elimination from halides almost always gives a mixture of elimination and solvolysis products. The acid-catalysed elimination of water from alcohols provides a preparative alternative (reaction 5.29). The protonated alcohol **43** loses a water molecule to give the carbocation, which can eliminate a proton to form the alkene. Even if some of the carbocation is trapped as the sulfate ester **44**, this reaction is reversible, and the alkene can be distilled out of the reaction mixture to bring the reaction to completion.

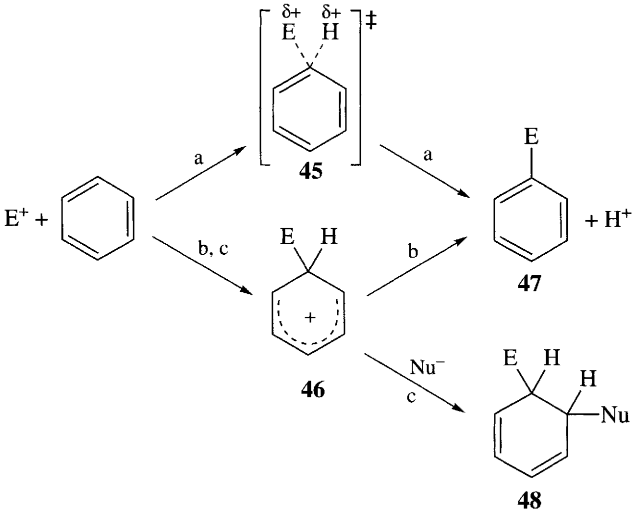


(5.29)

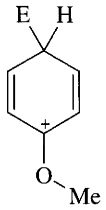
Electrophilic Aromatic Substitution

In these important reactions, one electrophile replaces another (usually a proton) on an aromatic ring. In a classical example, benzene is converted into nitrobenzene by a mixture of nitric and sulfuric acids (reaction 5.30). The reagent that attacks the benzene ring is believed to be the nitronium ion, NO_2^+, for which there is spectroscopic and other evidence. Two possible mechanisms are shown in reactions (5.31, $E^+ = NO_2^+$). The first (route a) would involve simultaneous bond making and bond breaking, going through a transition state **45** to the substituted product **47**. Evidence against this route is the absence of a hydrogen isotope effect, which shows that the C–H bond is not significantly broken in the transition state, and the effect of substituents on the benzene ring. The rate of reaction is speeded up by electron-releasing substituents such as methyl, supporting the presence of a positively charged intermediate or transition state. Additionally, the effect of substituents at the *para* position on the rate shows that the effect correlates with σ^+ rather than σ (see Chapter 3), which shows that the charge is conjugated with the *para* substituent, allowing extra stabilization as indicated in structures **49** and **50**. The involvement of an intermediate **46** (a **Wheland intermediate**) and thus route (b) is supported by NMR evidence (see the section on structure of carbocations above), which shows that structures of this type can be identified for highly substituted benzenes. Salts of cations of type **46** have recently been isolated as crystals whose structures have been determined by X-ray crystallography.

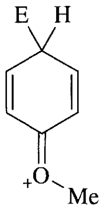
$$HNO_3 + H_2SO_4 \longrightarrow NO_2^+ \xrightarrow{C_6H_6} C_6H_5NO_2 + H^+ \qquad (5.30)$$



(5.31)



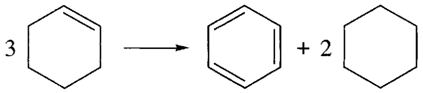
49



50

Why do the adduct carbocations **46** not react with a nucleophile to give an adduct of type **48**, as happens in electrophilic addition to double bonds? The main reason is probably thermodynamic. The hypothetical reaction (5.32) is very exothermic, based on experimental heats of formation. If we attribute this exothermicity to the stabilization of the benzene nucleus, we obtain a value of 150 kJ mol^{-1} for this stabilization. This stabilization would be lost in reaction (5.31) if the adduct **48** were formed, but is regained if the substituted product **47** is produced. This stabilization does not apply to reaction with alkenes, so addition can take place if the reaction is favourable energetically.

Electrophiles add to both alkenes and aromatic compounds to give an intermediate adduct cation. For alkenes, this cation normally reacts with a nucleophile to give an adduct, rather than eliminating another electrophile. For aromatic compounds, elimination of an electrophile regains the original aromatic stabilization energy, so this is the preferred route.



$\Delta H = -150$ kJ mol^{-1} (5.32)

5.4 Electrophilic Rearrangements involving Migration of C to O or N

Rearrangements of carbocations by migration of a carbon-centred group from an adjacent atom as in reaction (5.33) are common, and this is indeed a characteristic reaction, as discussed in Section 5.3.1. We might expect that similar reactions might be observed for positively charged nitrogen and oxygen species with six electrons in their valence shell, as in reactions (5.34) and (5.35). However, the greater electronegativity of nitrogen and oxygen makes species such as **51** and **53** so unstable that it is almost impossible to create them in solution. Thus in reaction (5.36) the first stage involves the protonation of the oxygen atom in the oxime **55** to give **56** in which the OH_2 fragment would be a good leaving group, but its loss with a pair of electrons to leave the positively charged nitrogen-centred intermediate **57** is too endothermic to take place. Instead, the production of **57** can be forestalled by the simultaneous migration of the group R^1 to the nitrogen atom to give the carbocation **58**, which in turn is attacked by a water molecule to give **59**, and after three subsequent protonation and deprotonation steps gives the amide **60** in good yield. Evidence that the reaction is concerted and does not involve **57** as an intermediate is provided by the observation that the isomeric oxime **61** reacts to give the amide **62** in which R^2, the other group, has migrated. If the symmetrical intermediate **57** were involved, a mixture of amides **60** and **62** would be expected from the rearrangement of either of the oximes **55** or **61**. This rearrangement is useful synthetically and is known as the **Beckmann rearrangement**.

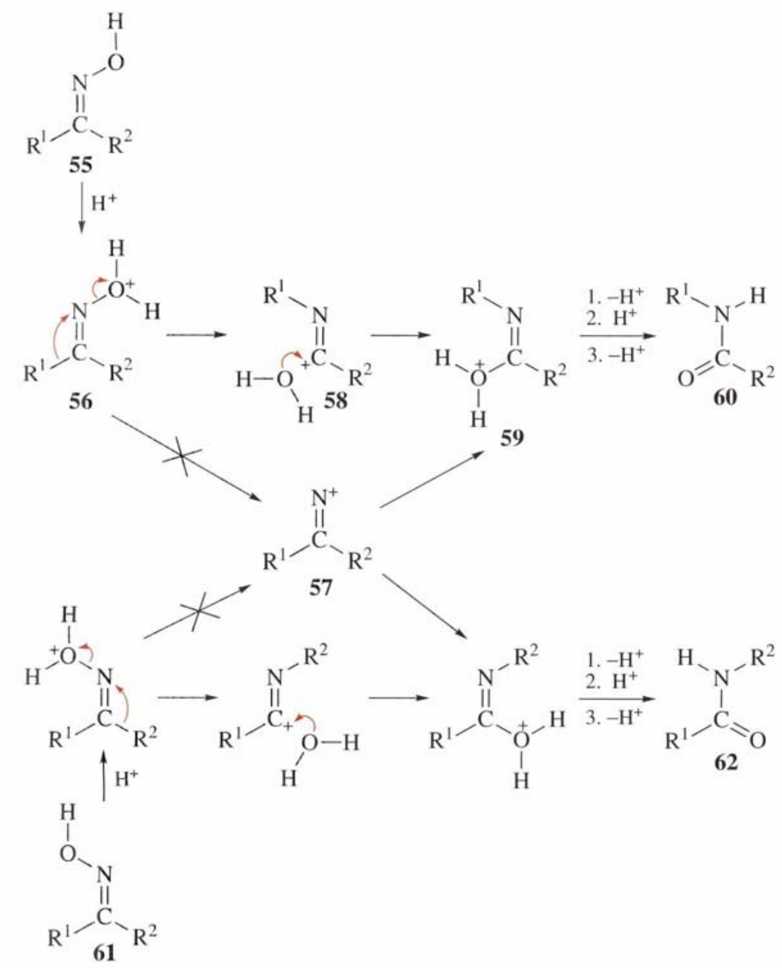
(5.33)

51 **52**

(5.34)

53 **54**

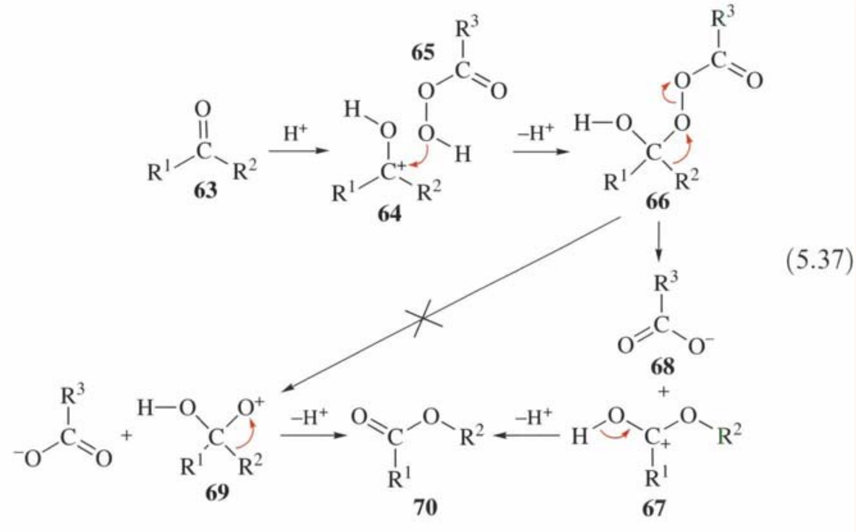
(5.35)



(5.36)

Ketones such as **63** are oxidized by peroxy acids **65** in the **Baeyer–Villiger reaction** (5.37), which involves migration of a carbon-centred group from carbon to oxygen. The protonated ketone **64** reacts with the peroxy acid **65** to give the ester **66**. Migration of R^2 to oxygen takes place as the stabilized carboxylate anion **68** leaves, to give the protonated ester **67**. This loses a proton to give the ester product **70**. The alternative route via the unstable oxygen-centred cation **69** does not take place.

In the Beckmann and Baeyer–Villiger rearrangements, migration of a carbon-centred group from C to N or O takes place synchronously with elimination of a good leaving group. If the leaving group left first, very unstable R_2N^+ or RO^+ intermediates would be formed.

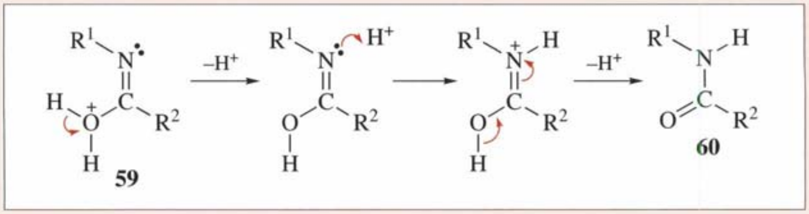


(5.37)

Worked Problem 5.3

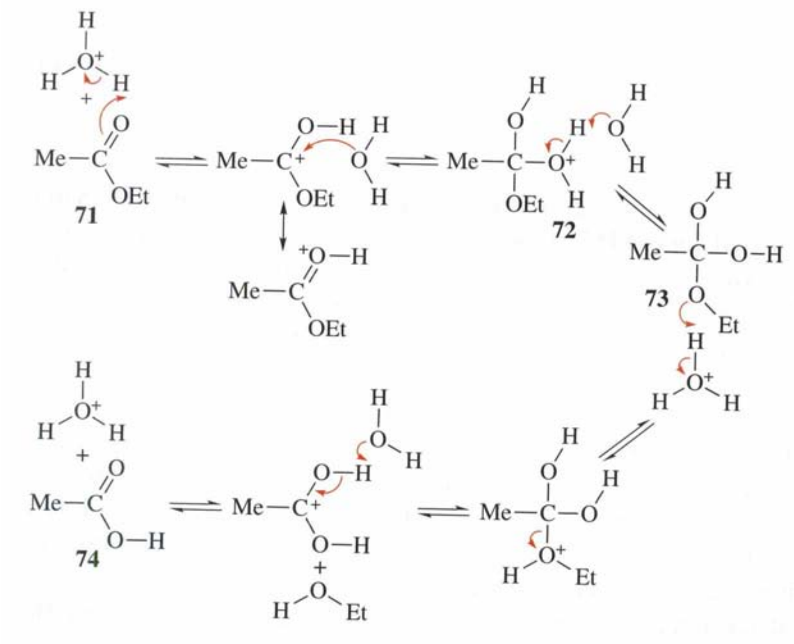
Q Show how the intermediate **59** (reaction 5.36) is converted into the amide **60** in three protonation–deprotonation steps.

A



5.5 Acid-catalysed Reactions

Many reactions are catalysed by acids. Hydrolysis of esters and the reverse reaction, esterification, are important examples both in the laboratory and in living systems (reaction 5.38). In the forward direction, the initial rate is proportional to $[H_3O^+]$[**71**]; in the reverse direction the kinetic dependence is on $[H_3O^+]$[**74**][EtOH]. By the principle of microscopic reversibility (Chapter 1), the reaction must have the same mechanism in both directions. The third-order kinetic dependence of the reverse reaction suggests that the reaction is complex and involves intermediates, because termolecular reactions are rare. The formation of tetrahedral intermediates of type **72** or **73**, involving reversible addition of a water molecule, is supported by the observation that if partial hydrolysis of an ester labelled with ^{18}O in the carbonyl group is carried out and unchanged ester is recovered, oxygen exchange with the solvent water occurs. In both reaction directions, if substituted benzoate esters are used, negative Hammett ρ factors are observed, showing that positive charge is built up during the reaction, and the dependence on σ^+ shows that the charge is conjugated with the ring (see Section 3.3 for an explanation of substituent effects).



(5.38)

The scheme shown in (5.38) is consistent with these observations. Why are so many steps involved? The scheme has been drawn out in detail, including the representation of the solvated proton as H_3O^+ to emphasize that *in each step a bond is formed and a bond is broken. Thus all the steps are approximately thermoneutral, and can take place with low activation energies. The number of steps is immaterial, so long as there is a negative Gibbs free-energy change in the reaction.* Most biological reactions involve sequences of this type.

In general, the fact that a reaction is acid catalysed implies that a substrate molecule is protonated in the first step, and that the protonated molecule reacts further, perhaps with other molecules, to give product molecule(s), regenerating the proton during the process. This route must be faster than alternative schemes which do not involve the catalyst, otherwise no catalysis would have taken place. Two possibilities are shown in reactions (5.39) and (5.40).

$$\mathrm{S} + \mathrm{H}^+ \xrightleftharpoons{\substack{\text{rapid} \\ \text{pre-equilibrium}}} \mathrm{SH}^+ \xrightarrow{\text{slow}} \text{Products} \tag{5.39}$$

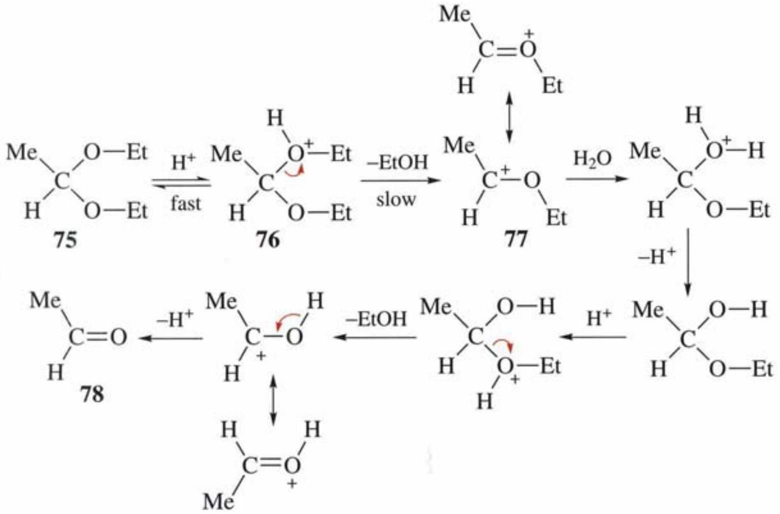
$$\mathrm{S} + \mathrm{H}^+ \underset{\substack{\text{reverse deprotonation} \\ \text{does not compete with} \\ \text{product formation}}}{\rightleftharpoons} \mathrm{SH}^+ \xrightarrow{\text{fast}} \text{Products} \tag{5.40}$$

In (5.39), a rapid pre-equilibrium is set up between the substrate S and its protonated form SH^+, followed by a slow reaction of SH^+ to give products. Alternatively, the protonation may be rate determining, with a rapid reaction of SH^+ to give products being faster than the reverse deprotonation back to S, as in reaction (5.40). There are kinetic consequences of this difference. For reactions of type (5.39), the set-up of an equilibrium between S and SH^+ means that the concentration of SH^+ and thus the rate depends only on the (solvated) hydrogen ion concentration. Reactions of this type are said to undergo **specific acid catalysis**; the rate will depend only on the concentration of solvated protons and not on the concentration of any other acid species present, including water. However, for reactions of type (5.40), where protonation is rate determining, the protonation can be carried out either by the solvated proton (reaction 5.41) or by any other acid present, including water (reaction 5.42). Each route will independently produce SH^+ ions that contribute to product formation. The rate equation will have terms involving all acids present, and the reaction is said to be subject to **general acid catalysis**.

$$\mathrm{S} + \mathrm{H_3O}^+ \longrightarrow \mathrm{SH}^+ + \mathrm{H_2O} \tag{5.41}$$

$$\mathrm{S} + \mathrm{HA} \longrightarrow \mathrm{SH}^+ + \mathrm{A}^- \tag{5.42}$$

An example of specific acid catalysis is the hydrolysis of acetaldehyde diethyl acetal (1,1-diethoxyethane, **75**). Reaction (5.43) was carried out in a formic (methanoic) acid/formate buffer. The formic acid concentration was varied over a factor of 10, whereas the ratio $[HCO_2H]/[HCO_2^-]$ was maintained at a value of 3.0, to give a constant pH and hydrogen ion concentration. The rate of hydrolysis in all the experiments was the same, within experimental error, showing that the rate depended only on the hydrogen ion concentration and not on the formic acid or water concentrations. Thus this reaction is subject to specific acid catalysis. A rapid pre-equilibrium is set up between **75** and its protonated form **76** in the first step. The second and rate-determining step involving loss of an ethanol molecule to give the carbocation **77** is slow, so specific acid catalysis by the solvated proton is observed. The subsequent steps lead to an acetaldehyde (ethanal) molecule **78** in good yield.

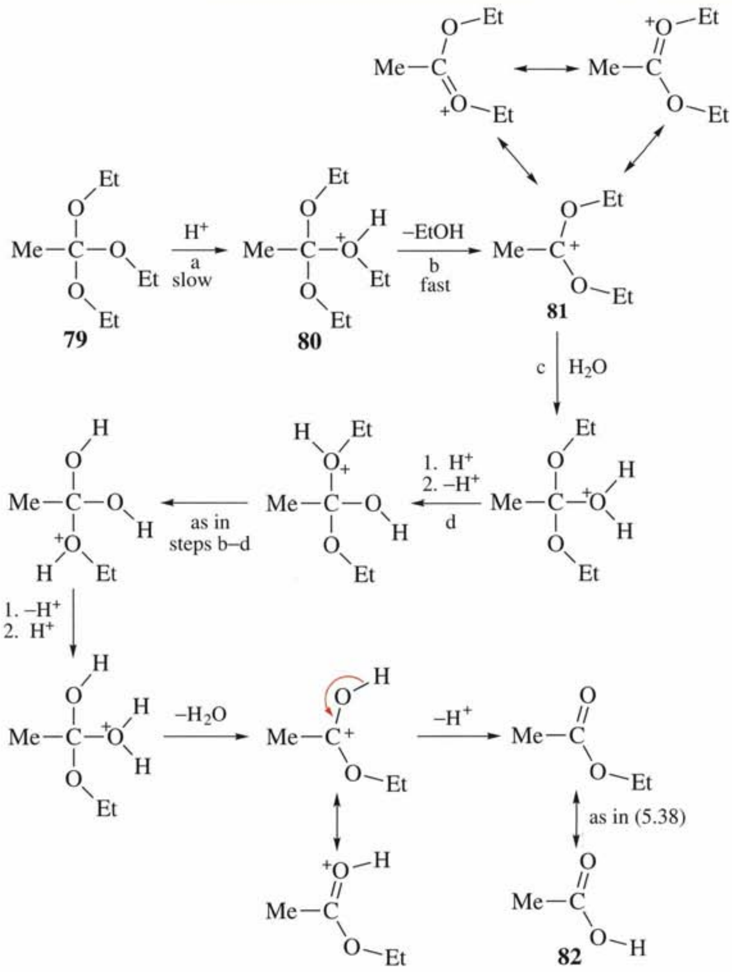


(5.43)

An example of specific acid catalysis.

By contrast, the hydrolysis of 1,1,1-triethoxyethane (ethyl orthoacetate, **79**) to acetic acid (**82**) is subject to general acid catalysis (reaction 5.44), as discussed in Chapter 2 (reaction 2.32). When the reaction is carried out in a *m*-nitrophenol/*m*-nitrophenolate buffer, terms in $[H_3O]^+$, $[m\text{-}O_2NC_6H_4OH]$ and $[H_2O]$ are found in the rate equation. In reaction (5.44), the first step to give the protonated compound **80** is rate determining, followed by a rapid second step.

An example of general acid catalysis.



(5.44)

In acid-catalysed reactions, the first step involves the protonation of a neutral substrate molecule S. If the protonation is rate-determining, general acid catalysis will be observed. If a rapid pre-equilibrium between S and SH^+ is followed by a later rate-determining step, specific acid catalysis will take place.

Why the difference between (5.43) and (5.44)? In reaction (5.43), the carbocation **77** formed in the second step is stabilized by only one oxygen substituent. However, the analogous cation **81** in reaction (5.44) is stabilized by two oxygen substituents, making the fragmentation step more exothermic and therefore faster, so in this case the rate-determining step shifts from the second to the first.

Summary of Key Points

1. Electrophiles react with nucleophiles by accepting an electron pair from the nucleophile to form a covalent bond. Carbocations and solvated protons are strongly electrophilic; many neutral species such as hydrogen halides and halogen molecules are also electrophilic.

2. Important reactions of carbocations are rearrangement, addition to multiple bonds, and elimination. Rearrangements are much more common in carbocations than in carbanions or free radicals; if a carbon skeleton rearrangement has taken place in a chemical reaction, it is likely that a carbocation intermediate is involved.

3. A number of rearrangements of oxygen- or nitrogen-containing organic compounds involve a concerted migration of a carbon-centred group from carbon to oxygen or nitrogen to avoid the production of the very unstable intermediates of type RO^+ or R_2N^+.

4. Many reactions are catalysed by acids; most involve a reversible protonation of a neutral substrate as the first step. In specific acid catalysis the kinetics show a single rate constant which involves the concentration of the solvated proton and one or more substrate molecules. In general acid catalysis, the observed rate involves several terms, each with a different rate constant, one for each acid present in the reaction mixture.

5. Acid-catalysed reactions often involve many steps, in each of which a bond is made and a bond is broken in a concerted manner so that each reaction step is approximately thermoneutral and no high activation energy steps are involved. In these reactions, the intermediates and reagents are either neutral or positively charged. No anions are involved.

Further Reading

T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, HarperCollins, London, 1987.

H. Maskill, *Mechanisms of Organic Reactions*, Oxford University Press, Oxford, 1996.

C. A. Reed, K. -C. Kim, E. S. Stoyanov, D. Stasko, F. S. Tham, L. J. Mueller and P. W. D. Boyd, *Isolating benzenonium ion salts*, in *J. Am. Chem. Soc.*, 2003, **125**, 1796.

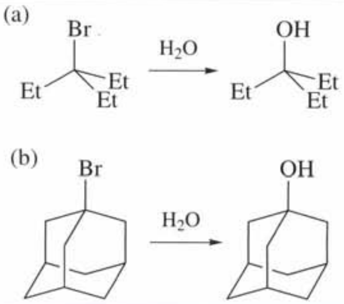
Problems

5.1. Which of the following species are (a) electrophiles, (b) nucleophiles, (c) carbocations, (d) cations. Some species may fit into more than one category, or into none:

Na^+	$CH_2{=}CH_2$	HBr	I_2
OH^-	H_2O	H_3O^+	NO_2^+
Me–Me	MeOMe	MeOH	$AlCl_3$
Me_3C^+	PhO^-	 = $C_6H_6NO_2^+$	 = $C_5H_5^-$

5.2. Would you expect Me_3CBr or $Me_2(Ph)CBr$ to react more rapidly in S_N1 reactions? Why?

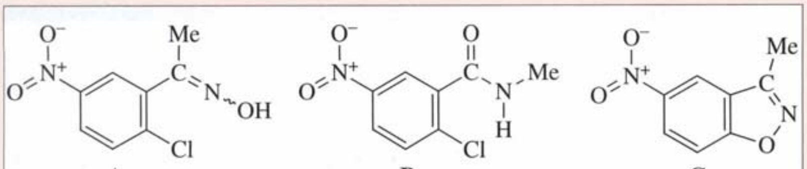
5.3. Explain why although the S_N1 hydrolysis (a) is rapid, the analogous reaction (b) is very slow.



5.4. $PhCHMe–CHMeNH_2$ reacts with nitrous acid (HNO_2) in acetic acid to give a mixture of PhCHMe–CHMeOAc (44%), PhCMe(OAc)–CH_2Me (24%) and PhCH(OAc)–$CHMe_2$ (32%) [Ac=CH_3CO]. It is thought that one of the following is involved as an intermediate: $PhCHMe\text{-}CHMe^+$, $PhCHMe\text{-}CHMe^•$ or $PhCHMe–CHMe^-$. Which is the most likely, and why?

5.5. 1-Fluoropropane in SbF_5 shows a ^1H NMR spectrum consisting of a doublet ($J = 3$ Hz) at $\delta = 5.1$ ppm and a septet ($J = 3$ Hz) at $\delta = 13.5$ ppm, with relative intensities of 6:1. Explain the chemistry that gives rise to the species showing this NMR spectrum, and comment on the chemical shifts observed.

5.6. One of the isomeric oximes **A** rearranges in the presence of acid to give the amide **B**. In the presence of base, the oxime undergoes ring closure to give **C**. Suggest mechanisms for both these reactions and identify which of the stereoisomeric oximes corresponds to **A**. What information about the stereochemistry of the migration of the methyl group in the rearrangement of **A** to **B** is provided by this experiment?

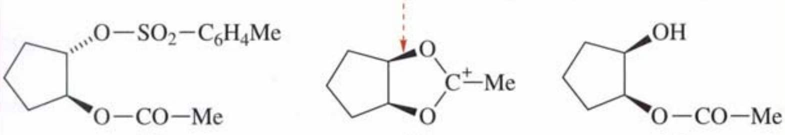


A **B** **C**

Note: ~~~ is a bond whose stereochemistry is uncertain

5.7. The ester **D** is hydrolysed in H_2O/HOAc to give **F**, and it has been suggested that **E** is an intermediate. Devise a plausible mechanism for the reaction which involves **E** on the route and comment on any points of interest. How could you establish if the reaction is acid catalysed, and, if so, whether the catalysis is general or specific? Suggest a trapping experiment to support the intermediacy of **E**.

Note the change in stereochemistry here



D **E** **F**

6
Radicals

Free radicals are species that have an unpaired electron in their valence shell. They tend to be very reactive and are normally only present in tiny concentrations. In solution in non-polar solvents, free radical and molecular reactions play a dominant role to the virtual exclusion of cations and anions. Almost all the reactions that take place in the atmosphere are free radical processes.

Aims

This chapter describes the most common types of radical reaction that occur in the gas phase or in solution, especially in non-polar solvents. By the end of this chapter you should be able to:

- Apply tests to organic reactions to confirm or refute the presence of free radical intermediates
- Understand the basic principles of electron spin resonance and the information that this technique provides about free radical structure
- Understand the importance of free radical chain reactions
- Know the key types of elementary reaction
- Suggest likely mechanisms for reactions known to involve free radical intermediates

6.1 Formation of Free Radicals

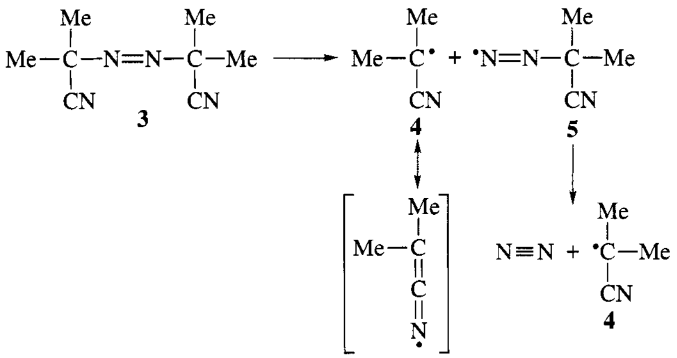
Since most organic molecules have all their electrons paired, conversion into radicals involves homolysis of a covalent bond, or a single electron transfer to or from a molecule.

6.1.1 Thermolysis

For molecules with a weak covalent bond, heating provides enough thermal energy to break the covalent bond **homolytically** (one electron from the covalent bond to each of the two radicals formed); the weaker the bond, the lower the temperature for decomposition. In practice, peroxides and azo compounds are the most practical and cleanest sources, as exemplified by reactions (6.1) and (6.2). Di-*t*-butyl peroxide (**1**) decomposes at temperatures above 100 °C to give two *t*-butoxyl radicals (**2**). The oxygen-oxygen bond is by far the weakest in the molecule, so this bond is the exclusive bond broken in the homolysis, giving a clean reaction. In azobisisobutyronitrile (AIBN, **3**) the C–N bond is the weakest, partly because the product 2-cyanoprop-2-yl radical (**4**) is stabilized by delocalization. The intermediate azo radical **5** quickly loses a nitrogen molecule to give a second 2-cyanoprop-2-yl radical, so reaction (6.2) provides a clean source of these radicals at temperatures above about 80 °C. Hydrocarbons such as 1,2-diphenylethane (**6**), which homolyse to give two stabilized benzyl radicals **7** (reaction 6.3), decompose at temperatures of about 400 °C, too hot to be of practical value for reactions in solution, whereas simple alkanes such as ethane only undergo homolysis at temperatures above 800 °C, making these reactions significant only in high-temperature pyrolyses and combustion reactions (*e.g.* reaction 6.4).

Free radicals have an unpaired electron in the valence shell. They are formed by homolysis of a covalent bond, or by electron gain or loss from molecules which contain only paired electrons.

$$\underset{\mathbf{1}}{\mathrm{Me_3C{-}O{-}O{-}CMe_3}} \longrightarrow \underset{\mathbf{2}}{\mathrm{Me_3C{-}O^\bullet}} + \underset{\mathbf{2}}{\mathrm{{}^\bullet O{-}CMe_3}} \qquad (6.1)$$



(6.2)

$$\underset{\mathbf{6}}{\mathrm{Ph{-}CH_2{-}CH_2{-}Ph}} \longrightarrow \underset{\mathbf{7}}{\mathrm{Ph{-}CH_2^\bullet}} + \underset{\mathbf{7}}{\mathrm{{}^\bullet CH_2{-}Ph}} \qquad (6.3)$$

$$\mathrm{CH_3{-}CH_3} \longrightarrow 2\ \mathrm{CH_3^\bullet} \qquad (6.4)$$

6.1.2 Photolysis

The energy required to break a covalent bond can also be provided by electromagnetic radiation, normally ultraviolet or visible light.

The molecule needs to have a chromophore to absorb the radiation. Chlorine, bromine and iodine molecules absorb visible radiation and are decomposed by a photon of light into two halogen atoms (reaction 6.5). Alkanes do not absorb visible or UV light down to 200 nm, and thus do not undergo photolysis to free radicals. Ketones such as benzophenone (diphenylmethanone, **8**) absorb near-UV light to give an excited molecule **9** in which an electron has been promoted from a non-bonding orbital on oxygen to the π* antibonding orbital of the carbonyl group. This n→π* transition gives an excited ketone molecule **9**, which has enough energy to abstract a hydrogen atom from a solvent (usually alcohol) molecule to give the stabilized $Ph_2\dot{C}OH$ radical **10** and a more reactive alcohol-derived radical $R_2\dot{C}OH$ **11**, both of which can undergo further reactions (reaction 6.6 and Figure 6.1).

$$\begin{gathered} X{-}X \xrightarrow{h\nu} X^{\bullet} + X^{\bullet} \\ X = Cl, Br \text{ or } I \end{gathered} \qquad (6.5)$$

$$\underset{\mathbf{8}}{Ph_2C{=}O} \xrightarrow{h\nu} \underset{\mathbf{9}}{Ph_2\dot{C}{-}\dot{O}} \xrightarrow{HCR_2OH} \underset{\mathbf{10}}{Ph_2\dot{C}{-}OH} + \underset{\mathbf{11}}{\dot{C}R_2OH} \qquad (6.6)$$

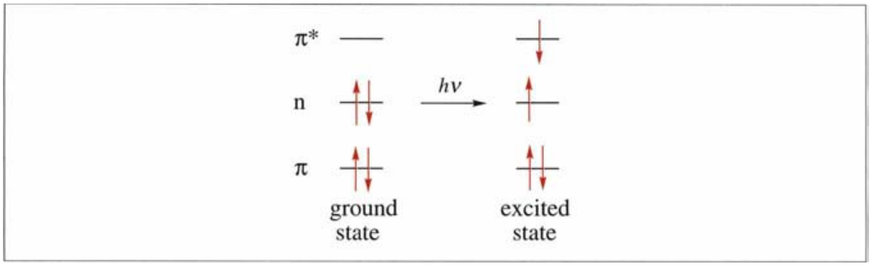
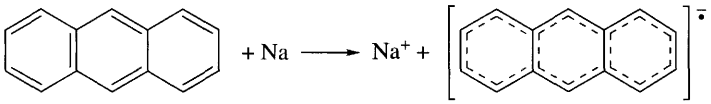


Figure 6.1 n→π* excitation of ketones

6.1.3 Electron Transfer

Many metal atoms can give up a single electron to give a cation with a single positive charge, and many ions can give up or take an electron from an organic molecule to convert it into a radical. Practical examples are shown in reactions (6.7)–(6.9). In (6.7) the silver atom gives up an electron to the chlorotriphenylmethane molecule **12**, which promptly loses a chloride ion to give the triphenylmethyl radical **13**, whereas in (6.8) the electron is transferred from the sodium atom to the lowest antibonding orbital of anthracene (**14**) giving a radical anion **15** which behaves both as a radical and as an anion. Fe(II) salts are readily oxidized to Fe(III) salts by hydrogen peroxide, giving a hydroxide ion and a hydroxyl radical, a convenient source of the latter at room temperature (reaction 6.9).

$$\underset{\mathbf{12}}{Ph_3C{-}Cl} + Ag \longrightarrow \underset{\mathbf{13}}{Ph_3C^{\bullet}} + Ag^{+}Cl^{-} \qquad (6.7)$$



14 **15** (6.8)

$$Fe^{2+} + H{-}O{-}O{-}H \longrightarrow Fe^{3+} + HO^{\bullet} + {}^{-}OH \qquad (6.9)$$

6.1.4 Molecule-induced Homolysis

Some reactions occur thermally at temperatures too low for homolysis of any of the covalent bonds present to provide enough radicals to start the reaction. For example, mixtures of fluorine and methane explode at room temperature, and many hydrocarbons are oxidized slowly by molecular oxygen (see below). It has been postulated that the bimolecular reactions (6.10) and (6.11) are responsible. In (6.10), the formation of the very strong H–F bond makes this reaction much less endothermic than the simple homolysis of the fluorine molecule. In (6.11), a strong O–H bond is formed in the hydroperoxyl radical **18**, whereas two relatively weak bonds are broken, the O=O π bond and the C–H bond in **16** which is weakened by the stabilization of the product benzylic radical **17**. The occurrence of these molecule-induced homolysis reactions is difficult to prove because the compounds formed tend to be swamped by those from the subsequent radical reactions.

$$CH_4 + F{-}F \longrightarrow CH_3^{\bullet} + H{-}F + F^{\bullet} \qquad (6.10)$$

$$\underset{\mathbf{16}}{PhCMe_2H} + O{=}O \longrightarrow \underset{\mathbf{17}}{Ph\dot{C}Me_2} + \underset{\mathbf{18}}{H{-}O{-}O^{\bullet}} \qquad (6.11)$$

6.2 Destruction of Radicals (Termination)

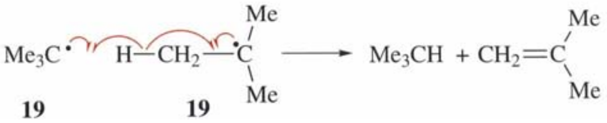
Radicals show a very important difference from anionic and cationic intermediates. Because radicals are uncharged and possess an unpaired electron in an orbital which is capable of forming a covalent bond, they normally react with each other on every collision with little or no activation energy. The bimolecular rate constants are large, in the region of 10^{10} M^{-1} s^{-1}. **Combination** results in a new covalent bond, as in reaction (6.12). If more than one type of radical is present in the system,

cross-combination occurs, for example reaction (6.13), and the final product contains all possible dimers in proportions that depend on the relative concentrations of the radicals. For alkyl radicals such as the *t*-butyl radical **19** with one or more β-hydrogen atoms, an alternative reaction is **disproportionation**, in which one radical abstracts a hydrogen atom from the β-position of the other, leading to an alkane and an alkene product (reaction 6.14). The more β-hydrogen atoms present, the more does disproportionation compete with combination.

Simple free radicals are destroyed rapidly by combination or disproportionation. This means that only very low concentrations of free radicals can be built up.


(6.12)

$$CH_3^\bullet + Cl^\bullet \longrightarrow CH_3\text{–}Cl \qquad (6.13)$$


(6.14)

Half-headed arrows (fish-hooks, ⇀) are used to show the movement of **individual electrons** in free radical reactions, in contrast to the curved arrows (→) used in polar and molecular reactions to show the movement of **electron pairs**.

The rapid rate of radical termination reactions for simple organic radicals means that only very small steady-state concentrations can be maintained, typically 10^{-8} M or lower. However, some larger stabilized radicals do not dimerize readily and therefore larger concentrations can be built up. These stabilized radicals will be considered later in the chapter.

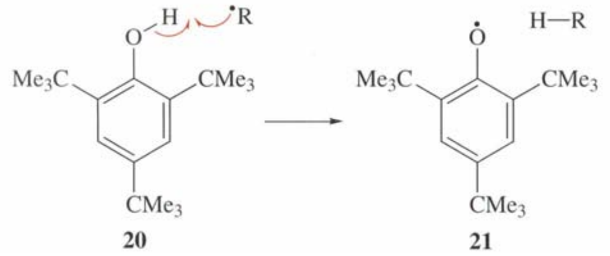
6.3 Detection of Radicals as Reaction Intermediates

Because of the low steady-state concentrations involved, this is not always easy. Evidence for free radical intermediates can be obtained from:

Kinetics. As outlined in Chapter 2, since radicals tend to be formed by first-order processes and destroyed in second-order reactions, steady-state radical concentrations are usually proportional to the square root of the precursor concentration [A]. This often leads to kinetic dependence on $[A]^{0.5}$ or $[A]^{1.5}$, so kinetic dependence of this form is strong evidence for a free radical mechanism.

Influence of light. If a reaction is speeded up by visible or UV light, a free radical mechanism should be considered, though we shall see in the next chapter a variety of molecular photo-induced reactions are also possible. The quantum yield Φ (phi) is a useful parameter, defined as the number of molecules converted from starting materials into products per photon absorbed. A few radical reactions have Φ in the region of 1 or 2, but most radical chain reactions have higher Φ values, often 1000 or more, so a high quantum yields for any reaction taking place in the gas phase or in solution in non-polar solvents is a strong indication of a radical reaction.

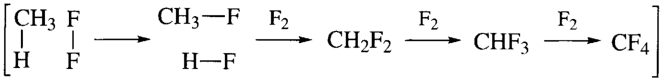
Initiation and inhibition. If a reaction is speeded up by the addition of compounds such as peroxides which are known to produce free radicals, this is evidence for a free radical mechanism. Inhibition (slowing down) of a reaction by compounds such as phenols is also evidence for free radical behaviour. 2,4,6-Tri-*t*-butylphenol (**20**) acts as an inhibitor by hydrogen transfer (reaction 6.15) to one of the chain-carrying radicals involved, giving the phenoxyl radical **21**, which is stabilized by delocalization and may be unable to carry on the chain reaction.



(6.15)

Initiation of polymerization. If styrene (phenylethene, $PhCH{=}CH_2$) or methyl methacrylate (methyl 2-methylpropenoate, $CH_2{=}C(Me)\text{-}CO_2Me$),or preferably an equimolar mixture of the two, is added to the reaction mixture, the production of polymer, which can be precipitated from the mixture by methanol, indicates the presence of radicals. If a mixture of the alkene monomers is used, the product will be a copolymer containing equal quantities of the two alkene monomers. This allows the distinction to be made between the presence of radicals, anions or cations as the reactive species responsible for initiating the polymerization. Cations would give a polymer comprising styrene residues only; anions would give a polymer containing methyl methacrylate residues only. The three possibilities can be readily be distinguished by elemental analysis by combustion, which typically gives the carbon and hydrogen content to about 0.4%. Expected compositions of the polymers formed by these three methods of initiation are shown in Table 4.2 (Section 4.3.4).

By-products. The presence in the products of small quantities of compounds which would arise from combination of free radical intermediates can provide evidence for a free radical process. For example, the explosive reaction of methane with fluorine gives mainly hydrogen fluoride and a mixture of mono-, di-, tri- and tetrafluoromethanes, but small quantities of fluorinated ethanes, including C_2F_6, are also produced. These two-carbon products cannot be readily explained on the basis of possible molecular reactions (see reaction 6.16), but would arise naturally as combination products of the fluorinated methyl radicals produced in a radical chain reaction sequence (reaction 6.17).



$$\left[\begin{array}{cc} CH_3 & F \\ | & | \\ H & F \end{array}\right. \longrightarrow \begin{array}{c} CH_3{-}F \\ \\ H{-}F \end{array} \xrightarrow{F_2} CH_2F_2 \xrightarrow{F_2} CHF_3 \xrightarrow{F_2} \left. CF_4 \right] \tag{6.16}$$

$$\left.\begin{array}{l} CH_4 + F^\bullet \longrightarrow CH_3^\bullet + H{-}F \\ CH_3^\bullet + F{-}F \longrightarrow CH_3{-}F + F^\bullet \\ CH_3F \longrightarrow \dot{C}H_2F \longrightarrow CH_2F_2 \longrightarrow \dot{C}HF_2 \longrightarrow CHF_3 \longrightarrow \dot{C}F_3 \xrightarrow{\dot{C}F_3} CF_3{-}CF_3 \end{array}\right\} \tag{6.17}$$

6.4 Electron Spin Resonance (ESR)

ESR spectra of radicals show some similarities with the NMR spectra of spin-paired molecules. The ESR *g* value corresponds to the NMR chemical shift. Hyperfine splitting in ESR caused by electron-nuclear spin interactions have an NMR counterpart in the splitting of resonances by interactions between two nuclear spins.

With specialized equipment, it is possible to investigate the presence of particular radical species by UV or visible spectroscopy, but the most useful spectroscopic method for free radicals is **electron spin resonance** or **ESR**. This technique depends on the fact that a free electron has a magnetic moment. In a magnetic field, this will line up either with the field or against it. These two orientations have slightly different energies, so if radiation of an appropriate frequency is applied, there will be absorption of energy at a frequency corresponding to the energy difference. The energy gap between the two spin states will be proportional to the magnitude of the applied field (see Figure 6.2a), and equation (6.18) shows the relationship between the frequency of radiation v and the applied magnetic field H. β is the Bohr magneton, a parameter derived from the properties of the electron, h is Planck's constant, and g, the dimensionless g value, has a value of 2.0023 for the free electron. Magnetic fields in the region of 300 mT are used, corresponding to radiation in the microwave region of about 3 cm. At this wavelength, which depends on the size of the cavity of the spectrometer, it is easier to keep the wavelength constant and sweep the magnetic field to achieve the resonance condition at which absorption of radiation can take place. Because of the method of detection, the display is in the form of the derivative of the absorption, giving a spectrum shown in Figure 6.2(b). The g value corresponds to the field at which the derivative curve crosses the baseline. Values of g vary over a small range and are larger for organic radicals with, for example, oxygen substituents. The g value corresponds to the chemical shift in the analogous NMR technique, but is nothing like as useful, since it is difficult to predict the effect of a particular substituent. The g value, is, however, characteristic of a particular radical even if prepared in different ways, provided the solvent and temperature remain the same.

$$E = hv = g\beta H \tag{6.18}$$

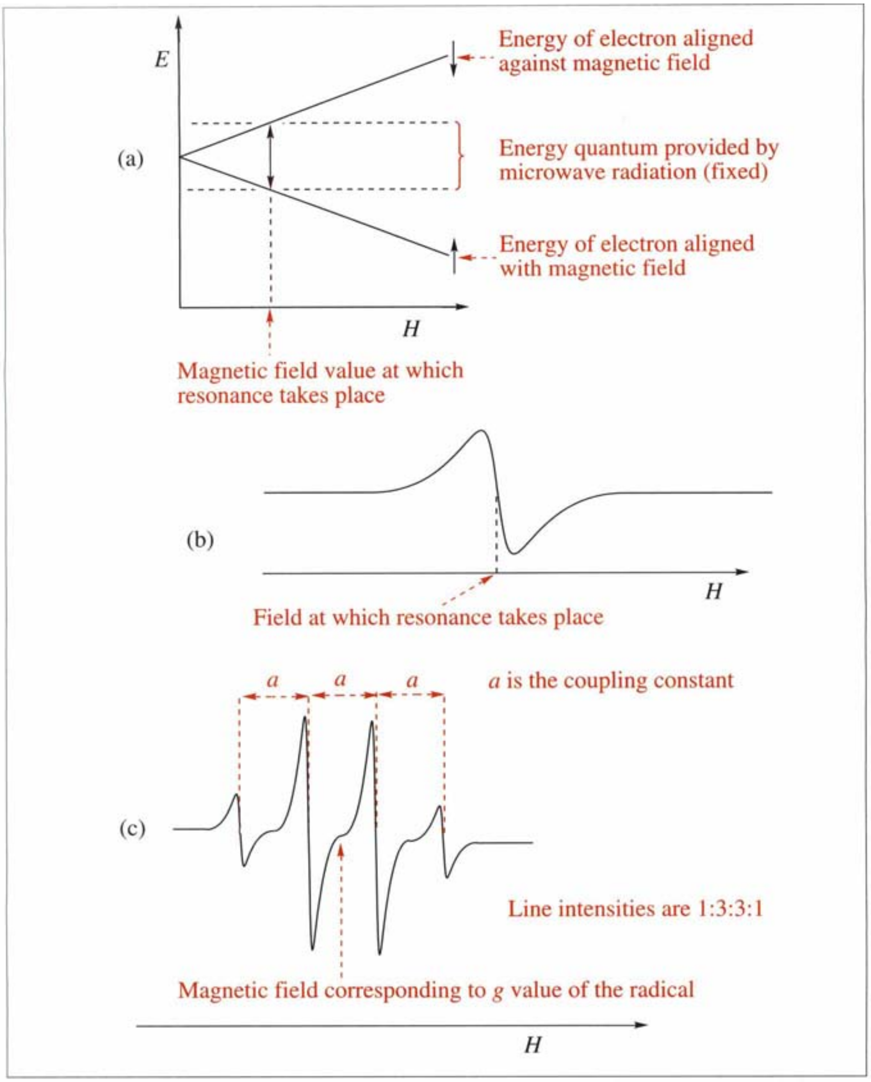


Figure 6.2 Electron spin resonance. (a) Dependence of electron energy on magnetic field. (b) ERS spectrum of a simple free radical. (c) Idealized ESR spectrum of the methyl radical

The presence of an ESR signal is conclusive evidence for the presence of a free radical in the system. The presence of an ESR signal in a reacting system is, however, not by itself conclusive evidence that the main body of the reaction is taking place by a free radical process, since a small amount of a side reaction could lead to a signal. Because of the small magnitude of the radical concentration often present, it is also possible to have a free radical reaction without producing a visible ESR signal.

If *g* values were the only information available from ESR, the technique would have limited use in showing the presence or absence of free radicals in a system. Fortunately, there is another feature. Many atomic nuclei have a nuclear magnetic moment, much smaller than that of the electron.

The most useful is the proton, which has a nuclear spin of ½, as do ^{19}F, ^{31}P and also ^{13}C (which is present in about 1% in natural abundance). ^{14}N has a spin of 1, and both ^{35}Cl and ^{37}Cl have spins of 3/2. ^{16}O has no nuclear spin. A list of common nuclei with nuclear spins is given in Table 6.1.

Table 6.1 Some common nuclei with nuclear spins

Atom	*Nuclear spin*	*Natural abundance* (%)
^{1}H	½	99.98
^{13}C	½	1.1
^{14}N	1	99.6
^{19}F	½	100
^{29}Si	½	4.7
^{31}P	½	100
^{35}Cl	$\frac{3}{2}$	75.5
^{37}Cl	$\frac{3}{2}$	24.5

If an atom with a nuclear spin of ½ is present close to the radical site, it will align with (↑) or against (↓) the magnetic field, augmenting or decreasing the magnetic field "seen" by the electron, so there will be two resonance positions and the spectrum will show a doublet of lines of equal intensity. Two identical atoms in the same environment will behave identically, giving three possible orientations and will therefore produce three lines. However, since the possible orientations are ↑↑, ↑↓, ↓↑ or ↓↓, with equal probabilities, the central line, corresponding to the two situations ↑↓ and ↓↑ where there is no net effect of the two nuclei, will have twice the intensity of the outside lines, leading to a triplet with relative intensities of the lines of 1:2:1, analogously to NMR. Likewise, three hydrogen atoms, for example in a methyl group, will give rise to a quartet with intensities 1:3:3:1, and in general n hydrogen atoms will give $n + 1$ lines. An idealized spectrum of the methyl radical is shown in Figure 6.2(c).

If more than one environment for the hydrogen is present, each type can be considered separately, so that in the ethyl radical $CH_3CH_2^\bullet$, each line of the triplet due to the methylene group is split into quartets by the three hydrogens of the methyl group, giving a spectrum of 12 lines in all.

Atoms such as ^{14}N and deuterium with a nuclear spin of 1 have three possible orientations of the nuclear magnetic moment, either with the field, at right angles to it, or opposed to the field. This gives rise to a 1:1:1 triplet, in contrast to the 1:2:1 triplet caused by two identical protons.

These splitting patterns often allow identification of a radical and to determine the position of attack on a molecule. For example, *t*-butoxyl radicals react with diethyl ether to give a product radical whose spectrum shows a quartet of doublets of triplets, corresponding to three different kinds of hydrogen atoms containing one, two and three atoms, respectively. This accords with attack at the position α to the oxygen atom to give the radical $CH_3\dot{C}H\text{–}O\text{–}CH_2CH_3$, rather than the radical $^{\bullet}CH_2CH_2\text{–}O\text{–}CH_2CH_3$ which would have been formed by β-attack. Figure 6.3 shows the spectrum and how it is analysed.

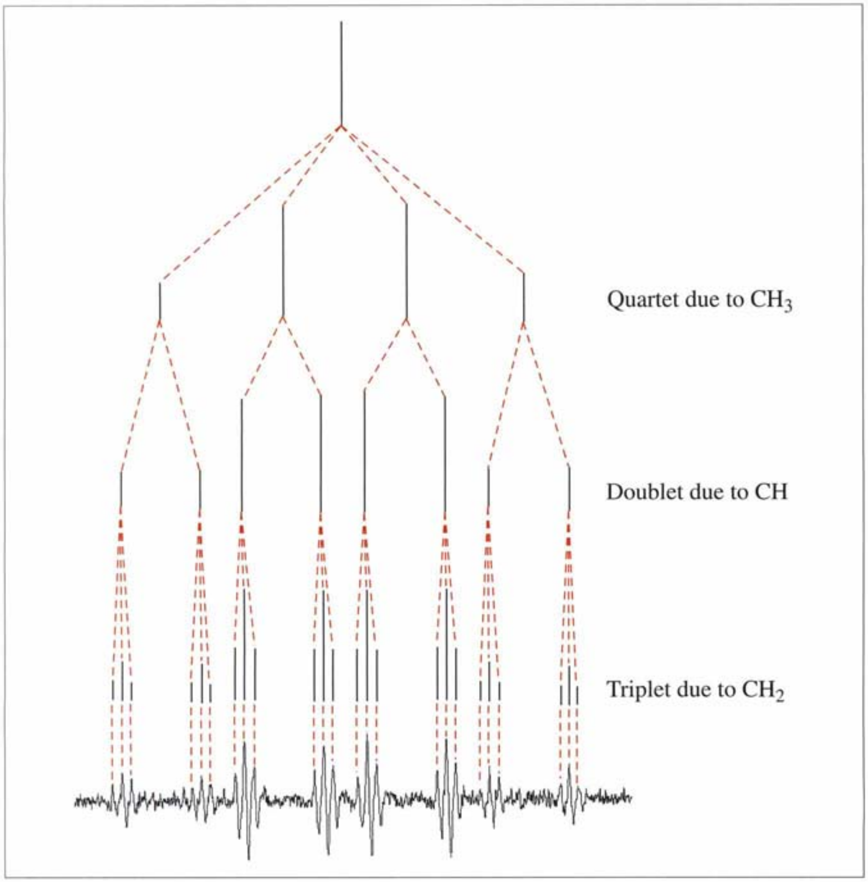


Figure 6.3 ESR spectrum of the $CH_3\dot{C}H\text{–}O\text{–}CH_2CH_3$ radical

The use of ESR to support a radical mechanism is exemplified in the autoxidation of isopropylbenzene (cumene, **16**) by molecular oxygen. The proposed initiation reaction is shown in reaction (6.11), and a mechanism to account for the production of the hydroperoxide **24** as the first stable product is shown in reactions (6.19) and (6.20). The development of a singlet ESR signal in this reaction system is evidence for a free radical reaction, and also suggests that the dominant radical present is the peroxyl radical **23** rather than the cumyl radical **22**. The peroxyl radical has no hydrogen atoms α, β or γ to the radical site, whereas the cumyl radical has six β hydrogen atoms and also hydrogen atoms on the benzene ring which should split the ESR signal into a complex pattern. This suggests that reaction (6.19) is much faster than (6.20): the cumyl radical is rapidly converted into the peroxyl radical, which is only slowly

ESR provides evidence for free radical intermediates in reactions and provides detailed information about radical structures.

reconverted back to the cumyl radical, giving a much higher steady-state concentration of the cumylperoxyl radical **23**.

$$\underset{\mathbf{22}}{\mathrm{Ph\dot{C}Me_2}} + \mathrm{O{=}O} \xrightarrow{\text{fast}} \underset{\mathbf{23}}{\mathrm{PhCMe_2{-}O{-}O^{\bullet}}} \qquad (6.19)$$

$$\mathrm{PhCMe_2{-}O{-}O^{\bullet}} + \underset{\mathbf{16}}{\mathrm{PhCMe_2H}} \xrightarrow{\text{slow}} \underset{\mathbf{24}}{\mathrm{PhCMe_2{-}O{-}O{-}H}} + \mathrm{Ph\dot{C}Me_2} \qquad (6.20)$$

6.5 Structure and Stability of Free Radicals

Methyl and simple alkyl radicals are essentially planar with sp^2 hybridization and the single electron in a p orbital, in contrast to the analogous silyl radicals which are pyramidal with approximately sp^3 hybridization for all the valence orbitals: three bonding and one singly occupied. The evidence is for this comes from ESR and stereochemistry studies.

6.5.1 Coupling Constants for Radicals Centred on an Atom with a Nuclear Spin

In organic and organosilicon free radicals, the predominant carbon and silicon isotopic species, ^{12}C and ^{28}Si, have no nuclear magnetic moment and do not give rise to splitting, but the ^{13}C and ^{29}Si isotopes are present in natural abundances of 1% and 5%, respectively. These isotopes have a nuclear spin of ½ and can couple with the free electron. Thus lower intensity ^{13}C and ^{29}Si satellite spectra are seen for carbon and silicon free radicals, and the relevant coupling constants can be measured.

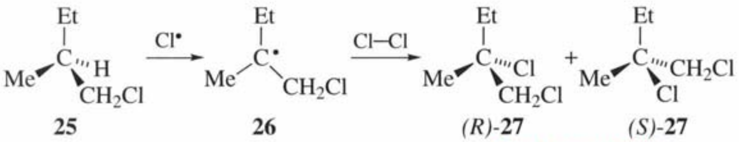
The interaction between the nuclear spin and the electron spin is expected to be proportional to the spin density of the unpaired electron at the nucleus of the central atom. Only s electrons have spin density at the nucleus (in fact this is the position of the highest value of the wave function ψ), whereas p electrons have a node at the nucleus corresponding to zero spin density. Thus the interaction between the nucleus and the electron, and thus the coupling constant, will be proportional to the s character of the orbital. The maximum coupling constants a for an electron in a 2s orbital in ^{13}C and the 3s orbital in ^{29}Si can be calculated to be 111 and 121 mT, respectively. For an electron in an sp^3 orbital, the expected values will be 25% of these figures, *i.e.* 28 and 30 mT, respectively. For an electron in a p orbital, corresponding to sp^2 hybridization of the central atom, the expected values of a will be zero in both cases.

Table 6.2 shows the ^{13}C and ^{29}Si coupling constants for a number of carbon- and silicon-centred radicals. $^{\bullet}SiH_3$ has a ^{29}Si coupling constant close to the region expected for sp^3 hybridization. $^{\bullet}SiMe_3$ also has a substantial ^{29}Si coupling and is therefore pyramidal in shape. The value of the ^{13}C coupling constant in $^{\bullet}CH_3$ is much lower and is consistent with a more planar structure. In fact, $^{\bullet}CH_3$ is considered to be planar with sp^2 hybridization. The non-zero ^{13}C coupling constant is thought to be due to the molecular vibration in and out of the plane (like an umbrella), which means that although the lowest energy of the system is planar, on average there is a small divergence from planarity. Other alkyl radicals are nearly planar. If the central carbon is substituted with electronegative elements such as fluorine, the radical becomes more pyramidal and the ^{13}C coupling constant rises. The ^{13}C coupling constant for $^{\bullet}CF_3$ is close to the predicted value for sp^3 hybridization.

Table 6.2 ^{29}Si and ^{13}C coupling constants *a*

Radical	*a*/mT	*Radical*	*a*/mT
$^{\bullet}SiH_3$	27	$^{\bullet}CH_3$	3.8
$^{\bullet}SiMe_3$	18	$^{\bullet}CMe_3$	4.5
$^{\bullet}SiCl_3$	42	$^{\bullet}CF_3$	27

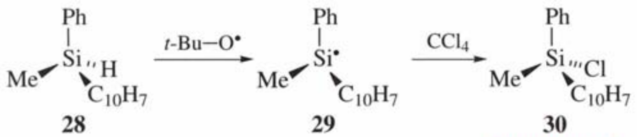
The near planarity of alkyl radicals and the non-planarity of silicon-centred radicals is supported by experiments on optically active compounds. In reaction (6.21) the chiral carbon centre in **25** is converted into a carbon-centred radical **26** with three different substituents, which in turn gives a chlorinated product **27** that has lost its optical activity. This implies that the radical **26** is either planar or, if pyramidal, it undergoes rapid inversion prior to capture to give the product. On the other hand, if the organosilane **28** is converted into **30** via the silicon-centred radical **29** (reaction 6.22), the product is optically active and can be shown to have retained its configuration, proving that, in this case, the intermediate radical has maintained its non-planar structure.



25 **26** *(R)*-**27** *(S)*-**27**

Equal proportions, therefore optically inactive

(6.21)



28 **29** **30**

Retention of configuration

(6.22)

6.5.2 α-Hydrogen Coupling Constants

Conjugated radicals have a conjugated π system of multiple bonds or aromatic rings adjacent to the radical centre. The π overlap allows the unpaired electron to be delocalized over the whole of the conjugated system and leads to greater thermodynamic stability for the radical. The coupling constants of hydrogen atoms attached to sp^2 carbon atoms in a π radical are approximately proportional to the spin density on the carbon atom to which they are attached, and thus provide a measure of the spin density on individual carbon atoms. Figure 6.4 shows the hydrogen coupling constants for methyl (**31**), allyl (**32**) and benzyl (**33**). It can be seen that the coupling constants for the hydrogen atoms attached to the terminal positions of the allyl radical have values of just over half of those of the methyl radical, reflecting the fact that the electron is delocalized equally on the terminal atoms. The *ortho* and *para* hydrogen atoms on the benzene ring of the benzyl radical have coupling constants greater than those at the *meta* positions and those attached to the 2-position of the allyl radical. This reflects the spin density at the various carbon atoms and accords with the predictions of resonance and molecular orbital theory. The resonance structures for the allyl and benzyl radicals are shown in Figure 6.4. No resonance structures can be drawn showing the unpaired electron at the 2-position of allyl or the *meta* positions of benzyl, according with the much lower spin density found at these positions.

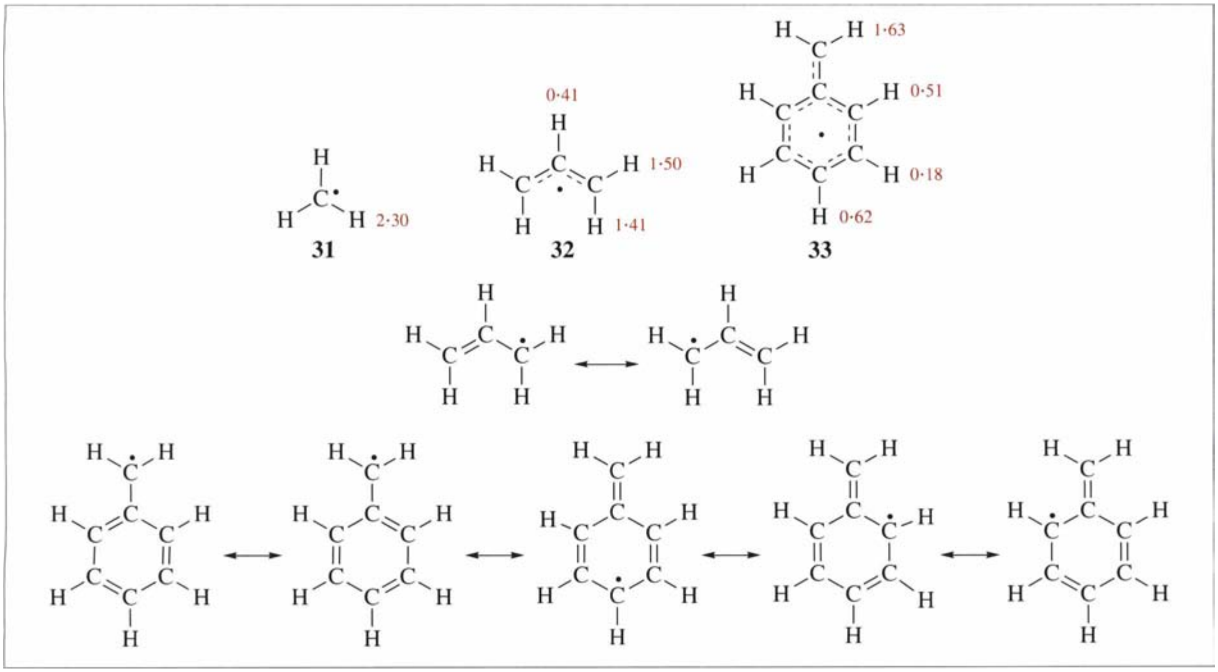


Figure 6.4 Hydrogen coupling constants (*a*, in mT) for π radicals

Worked Problem 6.1

Q The ESR spectrum of the benzene radical anion, $[C_6H_6]^{\bullet -}$, in which the unpaired electron is in a molecular orbital delocalized round the benzene ring, shows a septet, with a coupling constant of 0.375 mT. Comment on the spectrum, in relation to the quartet shown by the methyl radical, with $a(\text{C–H}) = 2.30\,\text{mT}$.

A The quartet in methyl is due to three identical hydrogen atoms; n hydrogens give $n+1$ lines. Six identical hydrogens in benzene should give a septet, as observed. The coupling constant reflects spin density on the appropriate carbon atom. In methyl, the spin density is almost all on the central carbon atom. In the benzene radical anion it will be equally shared on all the carbon atoms, giving a spin density of $^1/_6$ on each carbon atom. The coupling constant should therefore be $23.0/6 = 0.383\,\text{mT}$, in very good agreement with the observed value of 0.375 mT.

6.5.3 β-Hydrogen Coupling Constants

These have the same order of magnitude as the α-coupling constants. For rigid radicals, the value depends critically on the orientation of the C–H bond with the orbital containing the unpaired electron (see Figure 6.5). If the σ-orbital of the C–H bond is exactly aligned with the axis of the p orbital containing the unpaired electron (**34**, dihedral angle $\theta = 0°$), there will be maximum interaction, spin density will be transferred to the hydrogen and a large coupling, in the region of 5 mT, will be observed. If the dihedral angle is 90°, conformation **35**, there will be no interaction and no coupling. For intermediate angles, the coupling constant will depend on $\cos^2\theta$. If there is free rotation round the C–C bond, for example in the ethyl radical, there will be an average over all possible dihedral angles. Since the average value of $\cos^2\theta$ over all angles from 0° to 360° is 0.5, the expected value of the coupling constant would be half the maximum value. The β-C–H coupling constant for ethyl is 2.7 mT, in approximate agreement with the expected value of $0.5 \times 5 = 2.5\,\text{mT}$.

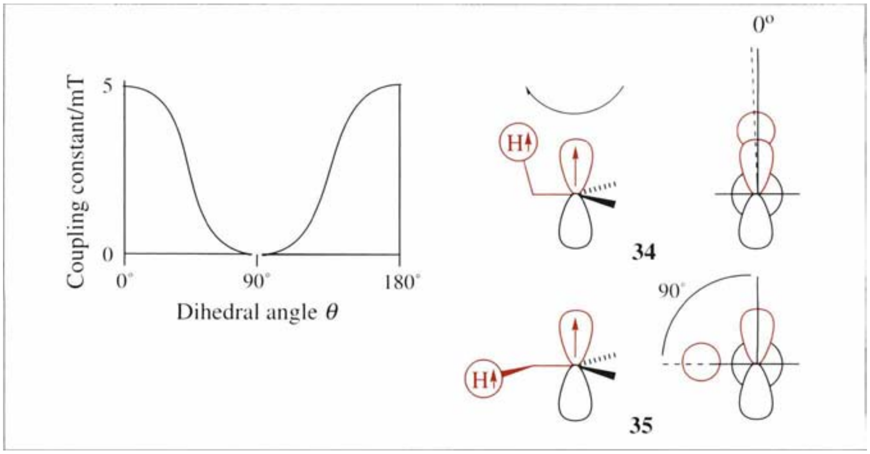
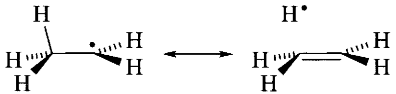


Figure 6.5 Dependence of β-hydrogen coupling constants in organic radicals on the dihedral angle θ

On a resonance picture, we can consider structures such as **36a** and **36b** as contributing to the total structure. Stabilization of this type is referred to as hyperconjugation. It must be stressed that structures such as **36b** only contribute to the structure to a minor extent, so there is no question of the hydrogen atom becoming free and leaving the radical.



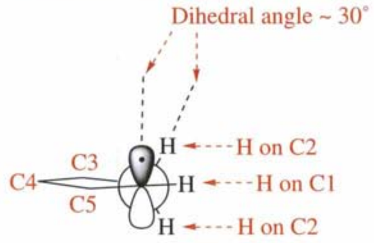
36a **36b**

Hydrogen atoms more remote than the β-position have coupling constants which are typically at least an order of magnitude less than α and β coupling constants, and are usually unimportant.

Worked Problem 6.2

Q The ESR spectrum of the cyclopentyl radical is a doublet ($a = 2.1$ mT) of quintets ($a = 3.5$ mT). What does this show about the structure of the radical? [The ethyl radical shows a triplet ($a = 2.2$ mT) of quartets ($a = 2.7$ mT)].

A Saturated alkyl radicals are approximately planar at the radical centre, with most of the spin density on the central atom, so the doublet splitting, ascribed to the C–H at the radical centre, has a similar value for that of the triplet in ethyl due to the CH_2 group. Because of the ring, the four β-hydrogen atoms in cyclopentyl are not free to rotate. The dihedral angle between the β-hydrogen atoms and the unpaired electron is about 30°. $\cos^2 30° = 0.75$, so the quintet coupling constant due to the four β-hydrogen atoms should be approximately $5 \times 0.75 = 3.75$, in good agreement with the observed value, and larger than $a(CH_3)$ in ethyl, where the free rotation of the methyl groups leads to an average value of $\cos^2\theta = 0.5$.



Newman projection looking along the C1–C2 bond in the cyclopentyl radical

6.5.4 Stability and Persistence

Stability is a thermodynamic concept, and is defined for organic radicals as the difference between the bond dissociation energies of R–H and CH_3–H. Values of D(R–H) for a number of radicals are given in Table 6.3. The stability increases in the order $CH_3^\bullet < CH_3CH_2^\bullet < (CH_3)_2CH^\bullet < (CH_3)_3C^\bullet$. This increase in stability is normally ascribed to hyperconjugation as described above, but the increasing number of alkyl carbon atoms round the free radical centre will also mean that these sp^3–sp^3 C–C bonds will be converted into the stronger sp^3–sp^2 bonds as the branched alkane is converted into the radical, which will decrease the bond dissociation energy and therefore increase the stability of the radical.

Table 6.3 Bond dissociation energies for hydrocarbons, D(R–H)[a]

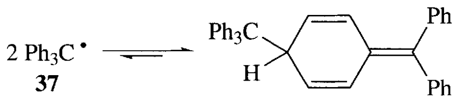
R	$D(R\text{–}H)$/kJ mol^{-1}
$Me^\bullet$	439
$MeCH_2^\bullet$	423
$Me_2CH^\bullet$	412
$Me_3C^\bullet$	404
$CH_2{=}CHCH_2^\bullet$	362
$PhCH_2^\bullet$	370
$Ph_2CH^\bullet$	341
$Ph_3C^\bullet$	298
$H_2C{=}CH^\bullet$	465
$Ph^\bullet$	465
$HC{\equiv}C^\bullet$	556

[a] Secondary and tertiary C–H bonds in alkanes have strengths very similar to those of $MeCH_2^\bullet$, $Me_2CH^\bullet$ and $Me_3C^\bullet$, respectively

The bond from H to sp^2 carbon is stronger than that to sp^3 carbon so the vinyl (ethenyl), ethynyl and phenyl radicals are all less stable than the methyl radical. On the other hand, delocalized radicals such as allyl and benzyl are significantly more stable than methyl. The delocalization is demonstrated by ESR, so that delocalization and stabilization go hand-in-hand. Delocalization is increased if the radical can be spread over more than one ring, as in diphenylmethyl and triphenylmethyl.

Stability as defined in this way is a good guide to reactivity, since the trend in bond strengths to other elements broadly follows the strengths to carbon. Thus the more stabilized the radical, the less reactive it will be towards a particular reagent.

Most radicals react with each other very rapidly by combination and disproportionation to give non-radical products, and if radicals are not continuously introduced into the system, the concentration quickly drops to zero. A minority of radicals do not react with each other rapidly by combination or disproportionation, usually for steric reasons or because no bond of sufficient strength can be formed. Radicals of this type which can maintain their concentration at least for a few hours in solution in inert solvents in the absence of oxygen are said to be **persistent**. Examples of persistent radicals include triphenylmethyl (**37**). Here, the central carbon atom is so crowded that dimerization to hexaphenylethane is impossible. Attack by the central carbon radical centre of one radical on the *para* position of another can take place, giving rise to an alternative dimer **38** that exists in equilibrium with the triphenylmethyl radical (reaction 6.23). Nitroxides such as 2,2,6,6-tetramethylpiperidinoxyl (TEMPO, **39**) are persistent. The lone pair orbital on the nitrogen and the singly occupied orbital on the oxygen interact to form a π bond; since three electrons are involved, one has to go into the π* orbital (Figure 6.6, **39a**). As a result, the N–O bond has a bond order of 1 ½, and this strength would be reduced to 1 in any addition or abstraction reaction of the oxygen atom.



37 **38**

(6.23)

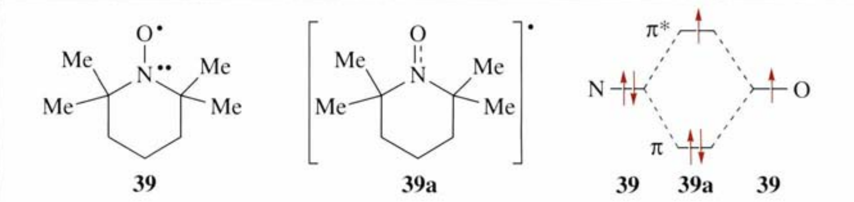


Figure 6.6 The TEMPO radical

Radicals can be stable without being persistent; the benzyl radical **33** is stabilized by delocalization of the electron onto the *ortho* and *para* positions of the benzene ring, but it is not persistent since dimerization can readily take place at the unhindered CH_2 group.

6.6 Radical Chain Reactions

The high reactivity and fast recombination rate of most radicals ensures that however rapidly radicals are introduced into a system, the steady-state concentration of radicals remains low. Under these conditions, a radical will meet thousands of molecules before it is destroyed on meeting another radical, offering excellent opportunities for reaction. Because of the single electron involved, reaction of a radical with an electron paired molecule must produce another radical, which in turn can react with another molecule to produce another radical, and so on, until eventually the radical is destroyed on encounter with another radical. If the radical is reactive and the radical concentration is very low, many thousands of molecules may be converted for each radical introduced into the system. Reactions of this type are called **chain reactions**: almost all free radical reactions of synthetic or environmental importance are chain reactions. Because of their importance, a terminology for chain reactions has been developed. **Initiation** reactions are those in which a radical or radicals are introduced into the system (see Section 6.1). **Termination** reactions are those in which radicals are destroyed, usually combination and disproportionation (Section 6.2). **Propagation** reactions are the radical–molecule reactions in which all the useful chemistry takes place, in favourable cases at least 99%, leaving less than 1% of by-products from termination reactions. There are two important classes of propagation reactions: radical transfer and addition to a multiple bond (and its reverse, fragmentation).

Almost all useful radical reactions are chain reactions. The major products are determined by the propagation steps. Only minor amounts of by-products come from initiation or termination reactions.

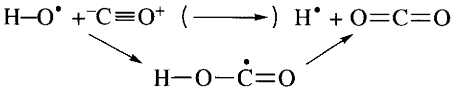
6.6.1 Chain Reactions involving Radical Transfer

Radical transfer reactions involve abstraction of an atom or group B by a radical A from a molecule B–C (reaction 6.24). B is nearly always an atom; transfer of a group, which would correspond to substitution at a polyvalent atom, though important in nucleophilic and electrophilic reactions, is very uncommon in radical reactions. The atom transferred is almost always a hydrogen or a halogen atom.

$$A^{\bullet} + B{-}C \longrightarrow A{-}B + C^{\bullet} \qquad (6.24)$$

B is normally a hydrogen or a halogen atom

Reactions such as (6.25) which involve transfer of an oxygen atom are important in atmospheric chemistry. They are thought to involve addition of the hydroxyl radical to form an intermediate **40**, which then loses a hydrogen atom.



40

(6.25)

Reactions such as (6.26) involve transfer of a hydrogen atom from a radical to a multiply bonded atom, and can be seen as hopping of a hydrogen atom between a C=O and an O=O double bond.

$$^{\bullet}O\text{–}CH_2\text{–}H + O{=}O \longrightarrow O{=}CH_2 + H\text{–}O\text{–}O^{\bullet} \qquad (6.26)$$

Radical transfer reactions involved in chain reactions are almost always exothermic. Endothermic reactions would be faster in the reverse direction. This principle can sometimes be used to generate a more stable radical from a less stable radical. Thus the non-stabilized *t*-butoxyl radical **41** reacts with toluene to give *t*-butanol and the benzyl radical **42** (reaction 6.27).

$$\underset{\mathbf{41}}{Me_3C\text{–}O^{\bullet}} + H\text{–}CH_2\text{–}Ph \longrightarrow Me_3C\text{–}O\text{–}H + \underset{\mathbf{42}}{^{\bullet}CH_2\text{–}Ph} \qquad (6.27)$$

Halogenation

Halogenations of alkanes provide good examples of chain reactions where all the chain steps involve radical transfer. Initiation is by photolysis of the halogen (reaction 6.28; X = Cl or Br) or, for fluorine, by molecule-induced homolysis (reaction 6.10). There are two propagation steps. The first (6.29) involves abstraction of a hydrogen atom from the alkane (illustrated here by methane). The alternative reaction to give the halomethane and a hydrogen atom does *not* take place: this would involve attack at a multivalent centre which is very uncommon for organic compounds without electropositive substituents, and the reaction would be 90 kJ mol^{-1} endothermic for Cl$^{\bullet}$, which would lead to an activation energy of at least that amount. The second propagation step (6.30) involves abstraction of a halogen atom from a halogen molecule by the methyl radical. Termination involves combination reactions of X$^{\bullet}$ and CH$_3^{\bullet}$ to give X–X, CH$_3$X and CH$_3$CH$_3$. The feasibility of the chain reaction depends on both propagation steps being fast. This is partly controlled by the thermochemistry; heats of reaction for both steps of the chain reaction are shown in Table 6.4 for all four halogens.

$$X\text{–}X \xrightarrow{h\nu} X^{\bullet} + X^{\bullet} \qquad (6.28)$$

X = Cl or Br

$$CH_3\text{–}H + X^{\bullet} \longrightarrow CH_3^{\bullet} + H\text{–}X \qquad (6.29)$$

$$CH_3^{\bullet} + X\text{–}X \longrightarrow CH_3\text{–}X + X^{\bullet} \qquad (6.30)$$

Table 6.4 Heats of reaction for halogenation of methane (kJ mol^{-1})

	Halogen *F*	*Cl*	*Br*	*I*
ΔH for reaction (6.29); hydrogen abstraction by $X^\bullet$	−133	+3	+69	+136
ΔH for reaction (6.30); reaction of $CH_3^\bullet$ with X–X	−298	−103	−99	−82
ΔH overall	−431	−100	−30	+54

For fluorine, both steps are highly exothermic. Each step is fast; the reaction is explosive. For chlorine, the first reaction is approximately thermoneutral, but the extra activation energy barrier is not high, and the first step is fast. The second step is substantially exothermic and fast; the overall exothermicity ensures that there is no tendency for the reaction to reverse. For bromine, the first step is substantially endothermic, and the activation energy must be greater than this. The reaction is therefore much slower than chlorination, even though the second step is highly exothermic, and will be expected to be fast. The overall exothermicity of the whole process will ensure that the reaction goes to completion. For iodine, the endothermicity of the first step makes it too slow for reaction to proceed. Additionally, the exothermicity of the second step is not sufficient to balance the endothermicity of the first step, so the reaction is endothermic overall. In fact, the reaction can be operated in reverse: hydrogen iodide will reduce iodoalkanes to alkanes with iodine as the other product.

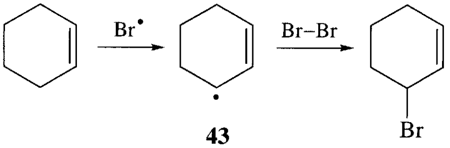
For hydrocarbons with more than one type of C–H bond, halogenation will give mixtures of products. The position of attack is determined by the abstraction step, and the heat of reaction (and also the activation energy) will reflect the strength of the bond broken. Table 6.3 shows that bond strengths fall from primary > secondary > tertiary > allylic or benzylic carbon atoms, and we may therefore expect reactivity to rise in the same order, as the bond becomes easier to break. The situation was discussed in Chapter 3. For the very exothermic reactions of fluorine, there will be an early transition state (Figure 3.1c), which will be very close to the starting materials. There will be little development of radical character on the alkyl group, so there will be little differentiation because of the different stabilities of the incipient alkyl radicals. Thus attack will be essentially random (see Table 6.5). On the other hand, attack by bromine atoms will have a late transition state with a structure near that of the products, so that any radical stabilization will be almost fully developed. Bromination will therefore be highly selective, and the different reactivities of different positions enable useful preparative chemistry to be carried out.

Table 6.5 Relative selectivity in hydrogen abstraction from alkanes by halogen atoms at 300 K[a]

Halogen	$-CH_3$	$>CH_2$	$-CH<$
F	1	1.2	1.4
Cl	1	4.4	6.7
Br	1	80	1600
I	1	1850	210,000

[a] Relative selectivities are for a single hydrogen of the type indicated.

Allylic positions are even more reactive, so that, for example, although cyclohexene has three types of hydrogen atom, bromination takes place almost exclusively at the 3-position via the allylic radical **43** (reaction 6.31).



43

(6.31)

Organotin Hydride Reductions

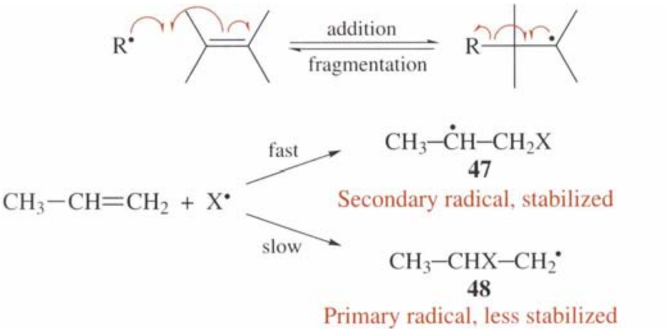
Tin forms strong covalent bonds to halogens but only a weak bond to hydrogen. This feature can be exploited in a radical chain reaction that results in reduction of haloalkanes to alkanes by organotin hydrides; the chain steps are shown in reactions (6.32) and (6.33). In the initiation step, a radical from homolysis of an azo compound (*e.g.* reaction 6.2) abstracts the weakly bound hydrogen atom from the tin centre of **44**. The organotin radical **45** preferentially abstracts a halogen atom from the haloalkane to give the alkyl radical, and does not react with the C–H bonds because the Sn–H bond is so weak. In the second step, the alkyl radical preferentially abstracts a hydrogen atom from the Sn–H bond, the weakest bond in the two molecules. Thus haloalkanes can be reduced to alkanes **46** in good yields, and the reaction can be carried out in the presence of groups such as the carbonyl group, which is readily reduced by polar reagents such as lithium aluminium hydride, $Li^+[AlH_4]^-$.

$$\underset{\mathbf{45}}{Bu_3Sn^\bullet} + Br{-}R \longrightarrow Bu_3Sn{-}Br + R^\bullet \qquad (6.32)$$

$$R^\bullet + \underset{\mathbf{44}}{H{-}SnBu_3} \longrightarrow \underset{\mathbf{46}}{R{-}H} + \underset{\mathbf{45}}{{}^\bullet SnBu_3} \qquad (6.33)$$

6.6.2 Chain Reactions involving Addition to Multiple Bonds (and Fragmentation)

The second important type of propagation reaction is addition to multiple bonds; addition to C=C is particularly important. In reaction (6.34), R can be an atom or a group centred on carbon or any element which forms a bond stronger than the π bond which is broken in the reaction (about 250 kJ mol^{-1}). If the alkene is unsymmetrical, addition can in principle take place at either end of the double bond. Addition normally takes place at the end of the double bond which will generate the more stable free radical. Thus for addition of a halogen atom to propene, attack at the CH_2 position will give the secondary radical **47** (reaction 6.35) rather than attack at the central carbon atom which would give the less stable primary radical **48** (reaction 6.36).



(6.34)

(6.35)

(6.36)

The most favourable approach for attack by a radical appears to be along the line on which the new bond is being formed (Figure 6.7). For the intramolecular addition of the hex-5-enyl radical **49**, this results in the formation of the less stable primary cyclopentylmethyl radical **50** by reaction (6.37) rather than the more stable secondary cyclohexyl radical **51** by reaction (6.38).

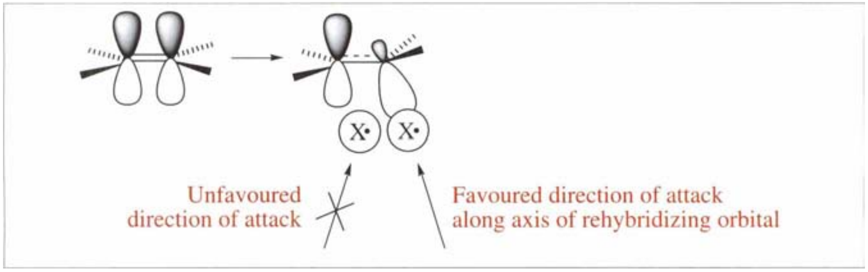
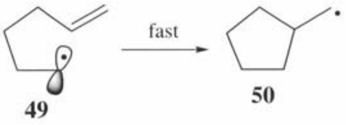
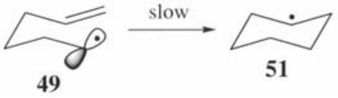


Figure 6.7 Direction of approach of a radical to a double bond



(6.37)



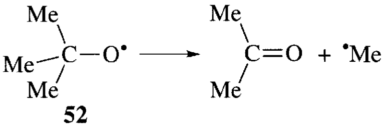
(6.38)

Fragmentation

Addition reactions differ from radical transfer reactions in one very important respect: two reactants react to give one product radical. This decrease in number of particles means that entropy is decreased during addition. The reverse reaction, fragmentation, involves an increase in the number of particles and therefore in the entropy. Since the free energy of reaction, ΔG, and therefore the position of equilibrium is governed by equation (6.39), however exothermic the addition reaction is, at a sufficiently high temperature the $T\Delta S$ term will outweigh ΔH and fragmentation will take place. t-Butoxyl radicals **52** fragment to methyl radicals and acetone at 140 °C (reaction 6.40), and fragmentation of alkyl radicals will be considered in the next section on polymerization.

Negative ΔG values correspond to equilibria that lie to the right.

$$\Delta G = \Delta H - T\Delta S = -RT\ln K \qquad (6.39)$$

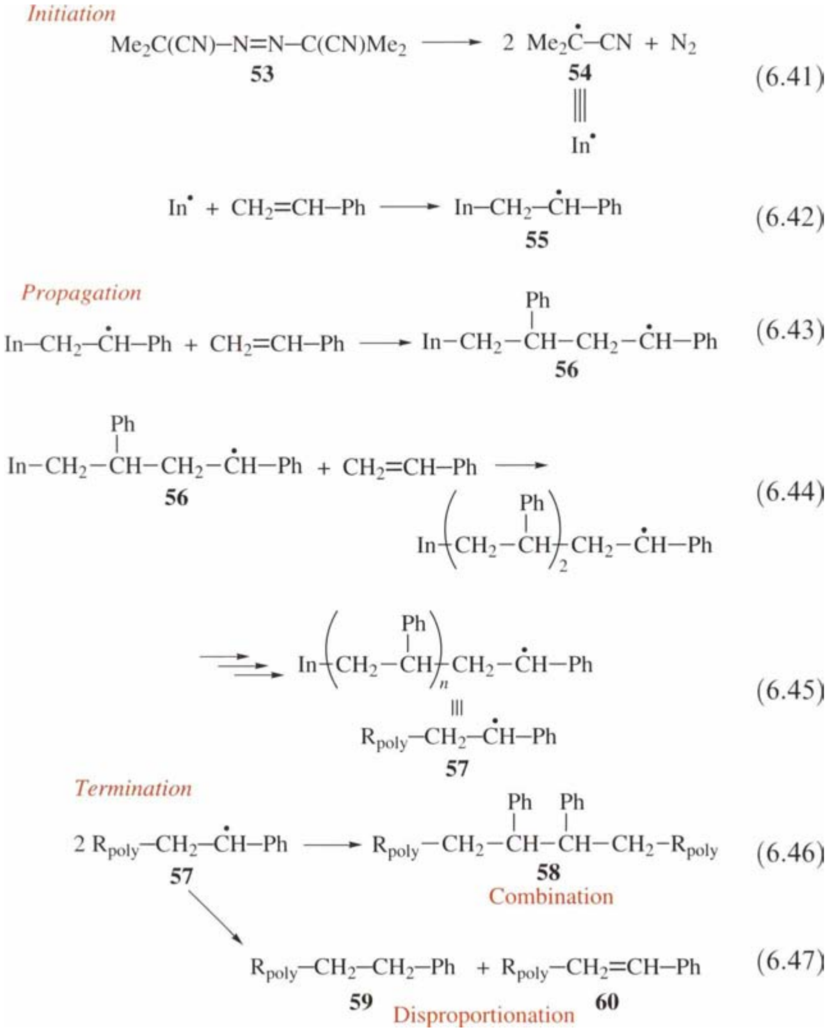


$$\mathrm{Me_3C{-}O^{\bullet}} \longrightarrow \mathrm{Me_2C{=}O} + {}^{\bullet}\mathrm{Me} \qquad (6.40)$$

52

Polymerization

The radical product of addition to a double bond may itself be able to add to a new alkene molecule to give a longer-chain radical, and this process may be repeated in a chain reaction consisting only of radical additions to give a long-chain polymer radical. The process to give the polymer is completed by termination steps involving combination or disproportionation of two polymer radicals. This chain-reaction free radical polymerization process is exemplified in reactions (6.41)–(6.47) for the polymerization of styrene initiated by azobisisobutyronitrile (**53**). The 2-cyanoprop-2-yl radical **54** adds to the CH_2 group of a styrene molecule to give the stabilized radical **55** (reaction 6.42). The adduct radical **55** in turn adds to the CH_2 group of another styrene molecule to give the radical **56** (reaction 6.43), and by successive additions (6.44 and 6.45) a long-chain polymer radical **57** is produced, as a straight chain with phenyl substituents on alternate backbone carbon atoms. Termination takes place by combination (reaction 6.46) to give a dimeric polymer **58**, or by disproportionation where one polymer radical **57** abstracts a hydrogen atom from a second radical to give an alkane **59** and an alkene **60** polymer molecule (reaction 6.47), both with shorter chain lengths than polymer molecules produced by combination. Useful polymers tend to have chain lengths of at least 1000. Most alkenes that can be readily polymerized have a terminal CH_2 or CF_2 group.



The average chain length of polymers can be reduced by adding small quantities of **chain transfer agents** such as thiols. These react with the growing polymer chain by hydrogen transfer (reaction 6.48), to form a polymer molecule **59** and a thiyl radical, which can re-initiate further polymerization. Thus each original initiator radical results in several shorter chain polymer molecules rather than one long one. This enables the chain lengths of polymers to be controlled.

Chain transfer

$$\underset{\mathbf{57}}{R_{poly}{-}CH_2{-}\dot{C}H{-}Ph} + RSH \longrightarrow \underset{\mathbf{59}}{R_{poly}{-}CH_2{-}CH_2{-}Ph} + RS^{\bullet} \qquad (6.48)$$

Polymerizations are carried out at relatively low temperatures. Since the propagation steps (6.44) and (6.45) involve two starting molecules giving one product molecule, entropy is lost when the reaction goes in the forward direction. Equation (6.39) shows that as the temperature rises, so does the $T\Delta S$ contribution to the free energy of reaction, so that at a sufficiently high temperature the reverse of steps (6.44) and (6.45) will be faster than the forward reactions. Above this **ceiling temperature** polymer molecules will degrade to monomer molecules by fragmentation. Ceiling temperatures are different for different polymers; for polystyrene [poly(phenylethene)] the temperature is 310 °C.

Addition of HBr to Alkenes

In the presence of a radical initiator, alkenes react with reactive molecules such as hydrogen bromide to give simple 1:1 adducts rather than a polymer. The initiator radical reacts rapidly with an HBr molecule to give a bromine atom (6.49), which starts the chain reaction. In the first propagation step, the bromine atom adds to the alkene **61** to give the adduct radical **62** (reaction 6.50). Since **62** abstracts a hydrogen atom from HBr by reaction (6.51) more rapidly than it would add to the alkene to form a polymer radical as in (6.43), the chain continues with reactions (6.50) and (6.51) as the propagating steps, and the product is the primary bromo compound **63**. This **anti-Markovnikov** addition is in the reverse direction to the polar addition discussed in Chapter 5. Since the radical chain reaction is faster than the polar reaction, the anti-Markovnikov product dominates if radicals are present. If the Markovnikov product is required, the reaction must be carried out in the dark, in the absence of free radical initiators, and preferably with a radical inhibitor present.

$$In^{\bullet} + H{-}Br \longrightarrow In{-}H + {}^{\bullet}Br \qquad (6.49)$$

$$\left.\begin{aligned} &\underset{\mathbf{61}}{R{-}CH{=}CH_2} + {}^{\bullet}Br \longrightarrow \underset{\mathbf{62}}{R{-}\dot{C}H{-}CH_2{-}Br} \\ &\underset{\mathbf{62}}{R{-}\dot{C}H{-}CH_2{-}Br} + H{-}Br \longrightarrow \underset{\mathbf{63}}{R{-}CH_2{-}CH_2{-}Br} + {}^{\bullet}Br \end{aligned}\right\} \text{Propagation} \qquad \begin{aligned}(6.50)\\(6.51)\end{aligned}$$

Worked Problem 6.3

Q Photolysis of a mixture of CCl_3Br and the alkene $PhCH{=}CH_2$ gives $PhCHBr{-}CH_2CCl_3$ as the major product. Write a plausible chain reaction scheme to account for this product.

A

$$\text{Br–CCl}_3 \xrightarrow{h\nu} \text{Br}^\bullet + {}^\bullet\text{CCl}_3 \qquad \text{Initiation}$$

$$\text{Ph–CH=CH}_2 + {}^\bullet\text{CCl}_3 \longrightarrow \text{Ph–}\dot{\text{C}}\text{H–CH}_2\text{–CCl}_3$$

addition at CH_2 gives the more stable radical

$$\text{Ph–}\dot{\text{C}}\text{H–CH}_2\text{–CCl}_3 + \text{Br–CCl}_3 \longrightarrow \text{Ph–CHBr–CH}_2\text{–CCl}_3 + {}^\bullet\text{CCl}_3$$

univalent bromine atom is transferred

Propagation

What happens to the bromine atom produced in the initiation step? It will react with the alkene as shown below, and the adduct radical will react with CCl_3Br to give a $^\bullet CCl_3$ radical, which will continue the chain as shown above. One molecule of the dibromide will be produced as a by-product, along with termination products. Provided that the chain is long, these will be insignificant.

$$\text{Ph–CH=CH}_2 + {}^\bullet\text{Br} \longrightarrow \text{Ph–}\dot{\text{C}}\text{H–CH}_2\text{–Br}$$

$$\text{Ph–}\dot{\text{C}}\text{H–CH}_2\text{–Br} + \text{Br–CCl}_3 \longrightarrow \text{Ph–CHBr–CH}_2\text{–Br} + {}^\bullet\text{CCl}_3$$

6.7 Atmospheric Reactions

Almost all the chemistry that takes place in the atmosphere is free radical in nature. An important area is the oxidative degradation of organic matter, ultimately to carbon dioxide, with formaldehyde (methanal) and carbon monoxide as key intermediates. The hydroxyl radical is the main daytime initiating radical, formed principally by the photolysis of NO_2 to give an oxygen atom which reacts with water to give two hydroxyl radicals (reaction 6.52). A simplified scheme for oxidation of methane to formaldehyde in an unpolluted atmosphere is shown in reactions (6.53)–(6.57). This sequence of five elementary steps involves two hydrogen transfer reactions, an addition to a double bond, a disproportionation reaction and a photolysis, all of which are analogous to reactions already considered in this chapter. The overall result (equation 6.58) is the oxidation of one molecule of methane by a molecule of oxygen to formaldehyde and a water molecule. One photon is required, and the ${}^{\bullet}\mathrm{OH}$, $\mathrm{CH_3O^{\bullet}}$ and $\mathrm{CH_3OO^{\bullet}}$ radicals which are formed during the reaction sequence are destroyed in other steps. The disproportionation reaction (6.55) is thought to be the way peroxyl radicals are destroyed: simple combination would lead to a molecule containing a chain of four oxygen atoms which would be unstable and immediately break in the centre to re-form the peroxyl radicals.

$$\mathrm{NO_2} \xrightarrow[\lambda < 400\ \mathrm{nm}]{h\nu} \mathrm{NO} + \mathrm{O} \xrightarrow{\mathrm{H_2O}} 2\,{}^{\bullet}\mathrm{OH} \tag{6.52}$$

$$\mathrm{CH_4} + {}^{\bullet}\mathrm{OH} \longrightarrow \mathrm{CH_3^{\bullet}} + \mathrm{H_2O} \tag{6.53}$$

$$\mathrm{CH_3^{\bullet}} + \mathrm{O{=}O} \longrightarrow \mathrm{CH_3{-}O{-}O^{\bullet}} \tag{6.54}$$

$$\mathrm{CH_3{-}O{-}O^{\bullet}} + {}^{\bullet}\mathrm{O{-}O{-}H} \longrightarrow \mathrm{CH_3{-}O{-}O{-}H} + \mathrm{O{=}O} \tag{6.55}$$

$$\mathrm{CH_3{-}O{-}O{-}H} \xrightarrow{h\nu} \mathrm{CH_3{-}O^{\bullet}} + {}^{\bullet}\mathrm{O{-}H} \tag{6.56}$$

$$\mathrm{H{-}CH_2{-}O^{\bullet}} + \mathrm{O{=}O} \longrightarrow \mathrm{CH_2{=}O} + {}^{\bullet}\mathrm{O{-}O{-}H} \tag{6.57}$$

$$\mathrm{CH_4} + \mathrm{O_2} \xrightarrow{h\nu} \mathrm{H_2CO} + \mathrm{H_2O} \tag{6.58}$$

Chemistry in the atmosphere is almost entirely free radical reactions.

Formaldehyde and other aldehydes and ketones formed during the atmospheric oxidation of more complex organic compounds are photolysed with a loss of a hydrogen atom or an alkyl radical. Photolysis of ketones (6.59) provides one way in which C–C bonds break; another is the fragmentation of alkoxyl radicals mentioned earlier (reaction 6.40). Eventually, all organic compounds end up as carbon dioxide and water.

$$\mathrm{CH_3{-}CO{-}CH_3} \xrightarrow{h\nu} \mathrm{CH_3^{\bullet}} + {}^{\bullet}\mathrm{CO{-}CH_3} \longrightarrow \mathrm{CO} + {}^{\bullet}\mathrm{CH_3} \tag{6.59}$$

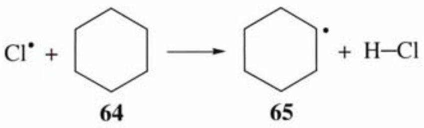
6.8 Non-chain Radical Reactions

Most useful free radical reactions are chain reactions and for photochemical reactions a large number of starting molecules are converted into products for every photon absorbed. A few photochemical processes are non-chain reactions, in which only one or two initial molecules are converted into products for each photon absorbed.

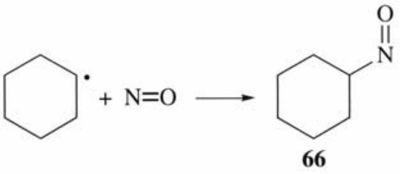
6.8.1 Nitrosation of Cyclohexane

The reaction of cyclohexane with nitrosyl chloride (NOCl) is a commercially important photochemical reaction, used in the first stage of nylon-6 manufacture. The UV light is absorbed by the NOCl (cyclohexane does not absorb UV light with $\lambda > 200\,\text{nm}$) to give NO and $Cl^\bullet$ (reaction 6.60). The NO, though a radical, is unreactive, but the chlorine readily abstracts a hydrogen atom from cyclohexane (**64**) to give the cyclohexyl radical **65** (reaction 6.61). The cyclohexyl radical undergoes a combination reaction (6.62) with the NO, to give nitrosocyclohexane (**66**). One photon is required to produce one molecule of product; thus it is not a chain reaction. The remaining steps in the process to give the oxime **67**, the lactam **68** and eventually nylon-6 (**69**) are ionic. They are shown as reaction (6.63), but are not considered here.

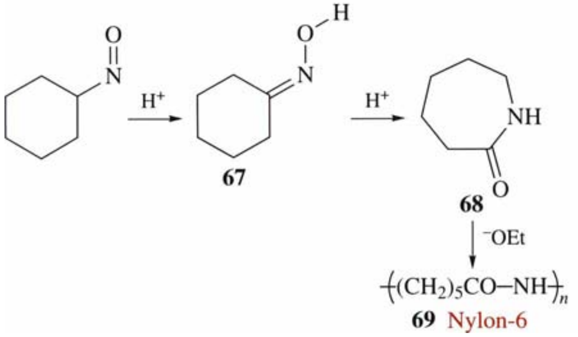
$$\text{Cl–N=O} \xrightarrow{h\nu} \text{Cl}^\bullet + {}^\bullet\text{N=O} \qquad (6.60)$$



(6.61)



(6.62)



(6.63)

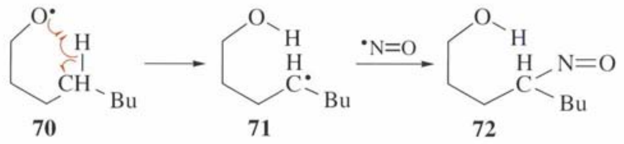
6.8.2 Intramolecular Hydrogen Abstraction: the Barton Reaction

Most organic compounds have more than one type of C–H bond, and hydrogen abstraction by radicals usually proceeds in an unselective manner, giving complex mixtures of products. An exception is when the abstraction is intramolecular, when for example a long-chain alkoxyl

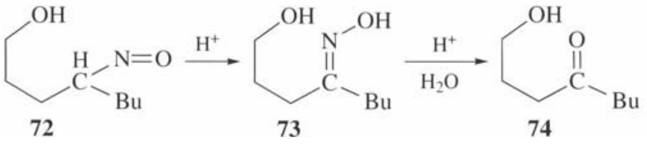
Derek H. R. Barton shared the Nobel Prize for Chemistry in 1969 for his work on conformations of organic molecules.

radical **70**, produced in reaction (6.64), abstracts a hydrogen from its own chain to give **71**, as in reaction (6.65). Here the reaction takes place almost exclusively at the δ-position. The radical **71** combines with N=O to give the nitroso compound **72**. This is readily isomerized by acid to the oxime **73**, which can be hydrolysed to the ketone **74** (reaction 6.66). This allows the remote functionalization of a C–H group, and has been particularly useful in steroid chemistry. Yields are ~30%.

$$C_8H_{17}{-}OH \xrightarrow{Cl{-}N{=}O} C_8H_{17}{-}O{-}N{=}O \xrightarrow{h\nu} \underset{\mathbf{70}}{C_8H_{17}{-}O^\bullet} + {}^\bullet N{=}O \qquad (6.64)$$



(6.65)

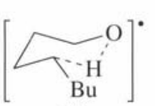


(6.66)

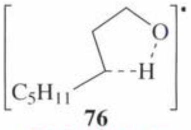
This reaction is not a chain reaction. One photon is required for each molecule of nitrite converted. The nitric oxide produced in the photolytic step is too unreactive to start a chain reaction, and simply combines with the rearranged radical.

A few non-chain reactions are significant. They usually involve radical intermediates such as NO, which can combine with other radical intermediates, but are too stable to react with molecules in propagation steps.

The preferential abstraction of a δ-hydrogen atom corresponds to a six-membered transition state, which can adopt the unstrained cyclohexane chair-type conformation **75**. The alternative γ-hydrogen abstraction, which would require a five-membered transition state **76**, is not usually observed. By analogy with cyclopentane, this would be approximately planar, involving significant angle strain and eclipsing interactions which would raise the energy.



75
Favourable six-membered transition state



76
Unfavourable five-membered transition state

Summary of Key Points

1. Most radical reactions are chain reactions. Initiation is usually by thermolysis of a weak bond or photolysis of a molecule with a suitable chromophore to absorb the light.

2. The most important reactions of radicals are atom abstraction and addition to multiple bonds. Atom abstraction is almost always hydrogen or halogen.

3. Fragmentation, the reverse of addition, becomes more important at higher temperatures.

4. Characteristics of free radical reactions include acceleration by free radical initiators or light, inhibition by compounds such as phenols, kinetics including half-powers of concentrations, and the production of small quantities of by-products resulting from radical combination.

5. Electron spin resonance is often helpful in deciding whether or not a reaction is free radical in character, and may identify intermediates.

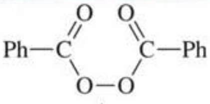
6. Using these principles you should be able to devise possible reaction steps for a reaction that may involve free radical intermediates, and to devise tests to determine whether or not the reaction is free radical in nature.

Further Reading

D. C. Nonhebel and J.C. Walton, *Free-radical Chemistry*, Cambridge University Press, Cambridge, 1974.
R. P. Wayne, *Chemistry of Atmospheres*, Oxford University Press, Oxford, 2000.

Problems

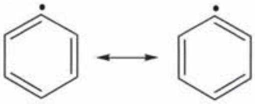
6.1. When dibenzoyl peroxide **A** is heated in toluene (methylbenzene), the products include benzoic acid, benzene, carbon dioxide and 1,2-diphenylethane. Account for the formation of these products and comment on the reaction steps you propose.



A

6.2. Methyl groups stabilize carbocations whereas nitro groups, $-NO_2$, stabilize carbanions. Provide an explanation, using the idea of delocalization, why both these substituents stabilize a radical centre conjugated with them.

6.3. The bond dissociation energies in Table 6.3 show that there is no significant stabilization of the phenyl radical compared with the vinyl (ethenyl) radical, $CH_2{=}CH^\bullet$, in spite of the fact that two structures **B1** and **B2** can be drawn for the phenyl radical. Explain this.



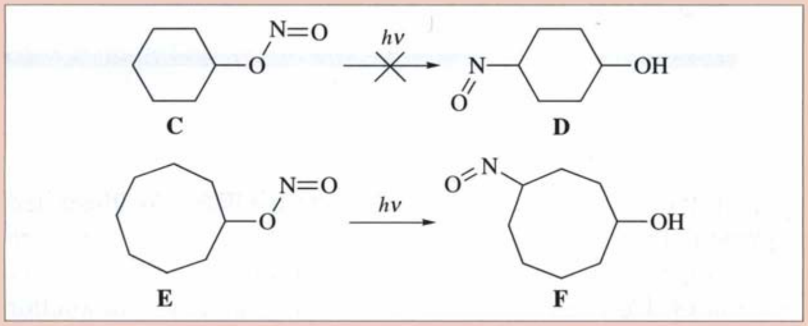
B1 **B2**

6.4. Dibenzylmercury in octane solution decomposes thermally to give a quantitative yield of mercury, with 1,2-diphenylethane as the major organic product. However, traces of toluene and 1,2,3-triphenylpropane are also produced. Suggest a mechanism. What other experiments could you carry out which might provide support for your mechanism?

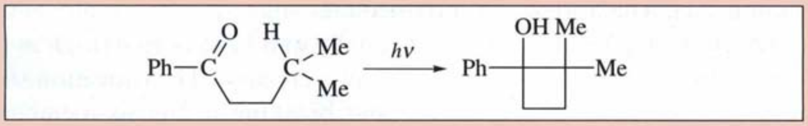
6.5. When 2-methylprop-1-ene (isobutene, $Me_2C{=}CH_2$) is heated with thiophenol (benzenethiol, PhSH) in the presence of a small amount of di-*t*-butyl peroxide, the major product is $Ph{-}S{-}CH_2CHMe_2$. Suggest a mechanism for this reaction.

6.6. The ESR spectrum of the cyclohexyl radical consists of a doublet ($a = 2.1$ mT) of triplets ($a = 3.9$ mT) of triplets ($a = 0.5$ mT). What light does this show on the structure of the radical?

6.7. When cyclohexyl nitrite **C** is photolysed, there is no intramolecular hydrogen transfer to give the nitroso compound **D** of the type found in reaction (6.44), whereas cyclooctyl nitrite **E** gives some rearranged product **F**. Why is this? [*Hint*: consider possible conformations].



6.8. Suggest a mechanism for the following photochemical reaction [*Hint*: consider reactions (6.6) and (6.65)]:

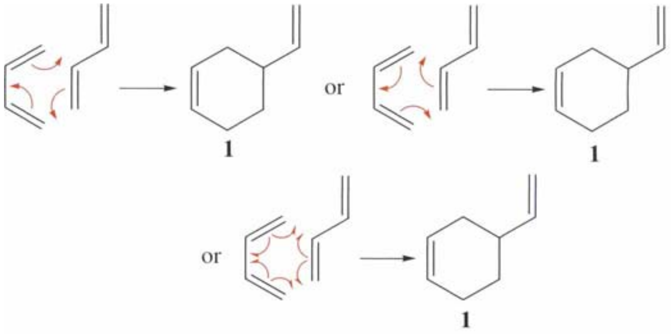


7

Molecular Reactions: Cyclic Transition States

The great majority of reactions involve intermediates, as illustrated in the previous three chapters. A smaller number of uni- or bimolecular reactions appear to proceed from reagents to products without detectable intermediates. These reactions take place in the gas phase or in solution in non-polar solvents. The absence of substantial solvent effects (Chapter 3) indicates little build up of charge in the transition state.

Butadiene dimerizes to 4-vinylcyclohexene (4-ethenylcyclohexene, **1**) (reaction 7.1). The absence of intermediates suggests a cyclic movement of three electron pairs, (which could equally well have been written in the opposite direction, or as single electron movements). The transition state would involve partial bond-making and breaking in the six-membered transition state as shown. Reactions involving such cyclic transition states are known as **pericyclic reactions**.However, ethene does not dimerize to cyclobutane (reaction 7.2) under thermal conditions, even though a cyclic movement of two pairs of electrons could have been invoked.



(7.1)

(7.2)

This chapter explores the reasons why some molecular reactions take place whereas others do not, and introduces the concepts of frontier orbitals and transition state aromaticity.

Aims

Having worked through this chapter, you should:

- Understand the concept of frontier orbitals, HOMO and LUMO, and be able to determine the HOMOs and LUMOs of organic molecules
- Understand the key importance of HOMO–LUMO interactions
- Understand the importance of Hückel and Möbius cyclic transition states
- Be able to apply these ideas to predict whether particular molecular reactions will or will not occur, and the stereochemical outcomes of such reactions

7.1 Frontier Orbitals

When two atoms approach, the atomic orbitals from the individual atoms begin to overlap, giving rise to molecular orbitals. The overlap is either in phase, giving rise to a lowering of energy resulting in bonding if the orbital is occupied by electrons, or out of phase, giving rise to an increase of energy and antibonding. This is illustrated in Figure 7.1 for two hydrogen atoms, each of which brings one 1s electron, both of which can be accommodated in the resulting bonding sigma (σ) orbital.

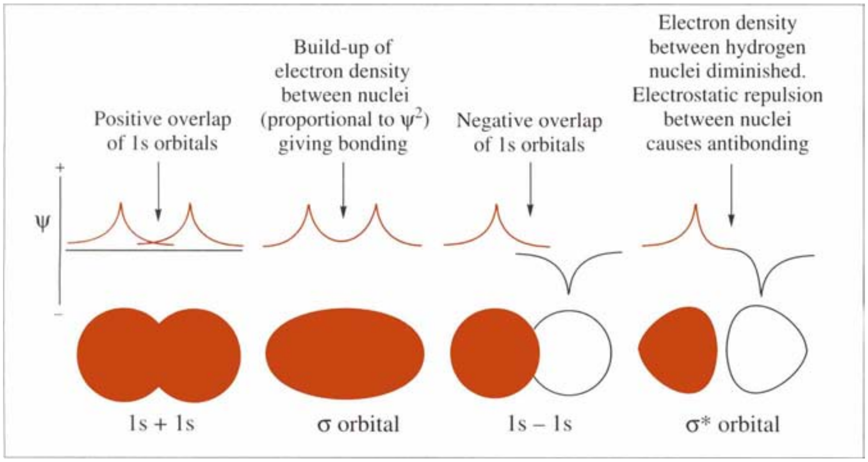


Figure 7.1 Overlap of the atomic orbitals of hydrogen. Positive phase for wave functions (orbitals) shown red, negative as white

Overlap of orbitals applies to molecules as well as atoms. In Figure 7.2 we see the approach of two hydrogen molecules end on. As the molecules approach, the σ orbitals interact to give two molecular orbitals, one with lower and one with higher energy. Since both original orbitals are occupied, with a total of four electrons, both the new molecular orbitals will be occupied. To a first approximation, the extra bonding and antibonding will cancel out, although because of electron repulsion the antibonding effect will be somewhat larger than the bonding effect.

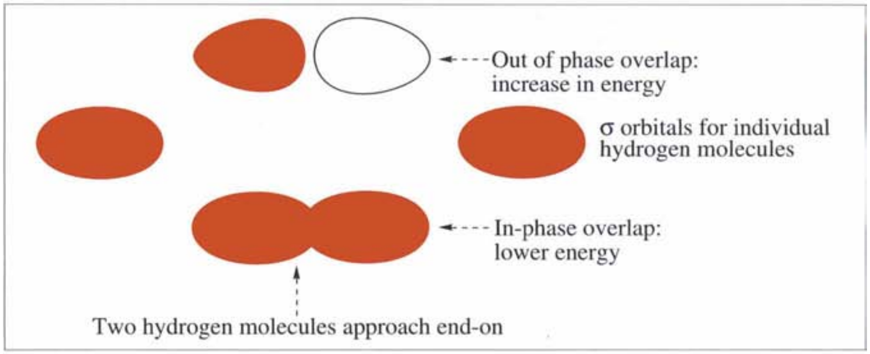
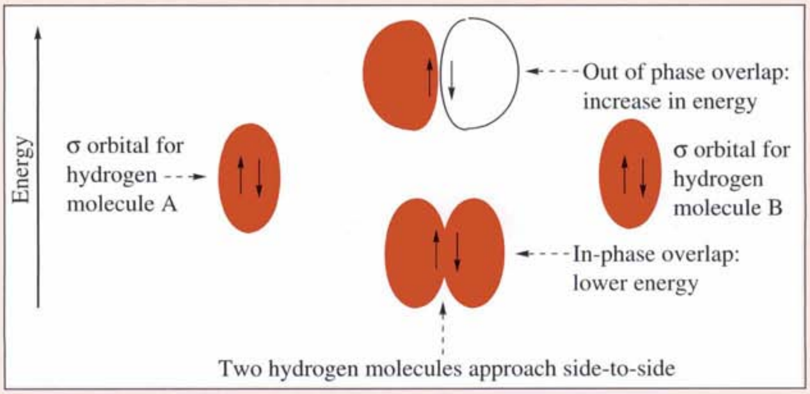


Figure 7.2 Overlap of the molecular orbitals of two hydrogen molecules

Worked Problem 7.1

Q What will happen to the σ orbital energies if two hydrogen molecules approach side to side?

A As the molecules approach, their σ orbitals will overlap. Two orbitals will result: the one with the phases the same will have a lower energy, whereas the one with different phases will have a higher energy. Since four electrons are involved, both new orbitals will be filled, so there will be no net increase in bonding.



In most molecules, all the electrons are paired: orbitals are either filled with two electrons or empty. If two molecules approach each other, all the orbitals in one molecule will interact with all those in the other. For complex molecules with a large number of orbitals, this gives rise to a very large number of interactions. Fortunately, it turns out that only one or two are important.

The interactions are of three types: occupied–occupied, occupied–unoccupied and unoccupied–unoccupied (Figure 7.3). For occupied–occupied interactions, because four electrons are involved, both the resulting orbitals are filled. One goes down in energy, the other goes up, so there is no significant change in energy (Figure 7.3a). For unoccupied–unoccupied interactions there will be no energy consequences since neither of the new orbitals is occupied (Figure 7.3b). Only for occupied–unoccupied interactions is there a significant energy difference. Because only the more bonding new orbital is occupied, there will be a significant reduction in energy (Figure 7.3c).

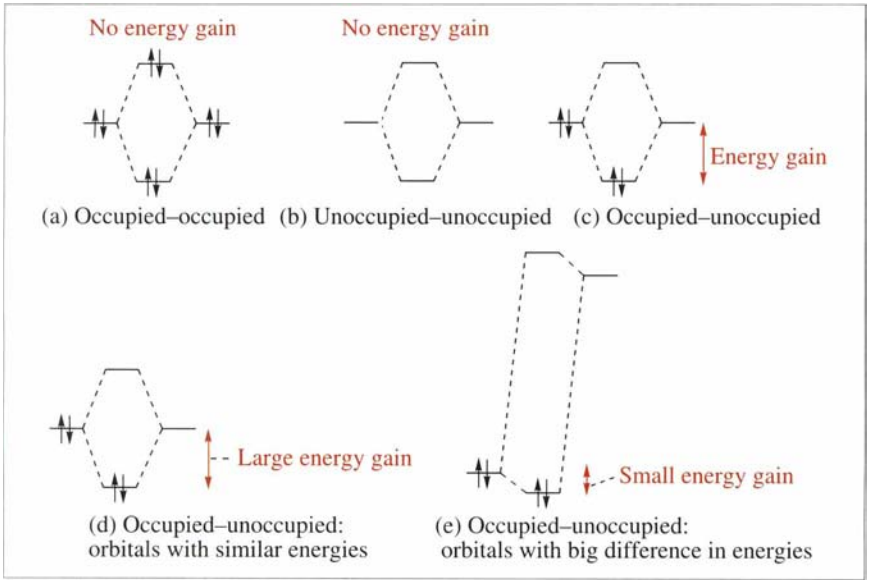
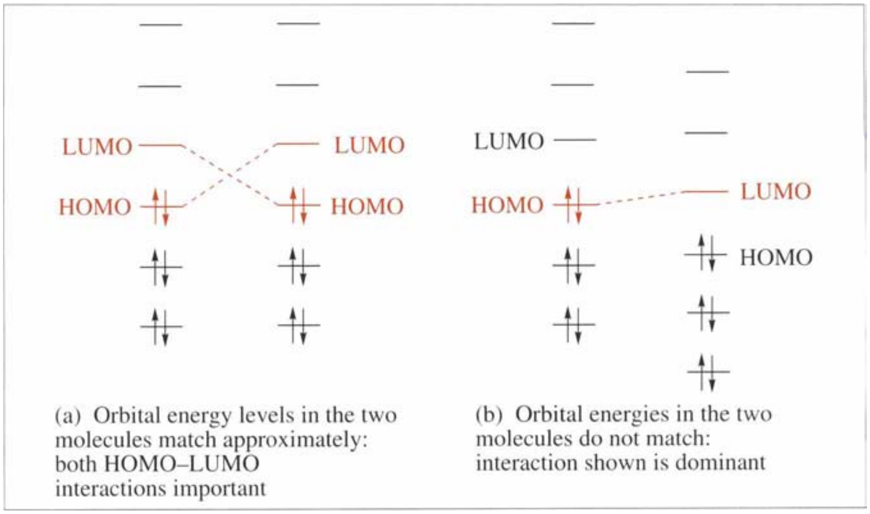


Figure 7.3 Energy consequences of the interaction between orbitals

Thus we should focus on occupied–unoccupied interactions. Interactions between orbitals are greater if the individual energies are similar, and less if they are significantly different (Figure 7.3d and 7.3e). *Thus the largest (favourable) energy interactions occur when there is the least energy difference between the interacting orbitals.* These correspond to interactions between the **highest occupied molecular orbital (HOMO)** of one molecule and the **lowest unoccupied molecular orbital (LUMO)** of the other (Figure 7.4). If the two reacting molecules have similar energy levels, the HOMO–LUMO interactions in each direction will both contribute significantly (Figure 7.4a), whereas if the levels are different in energy, the dominant interaction will be the one where there is the lesser difference in energies (Figure 7.4b).



(a) Orbital energy levels in the two molecules match approximately: both HOMO–LUMO interactions important

(b) Orbital energies in the two molecules do not match: interaction shown is dominant

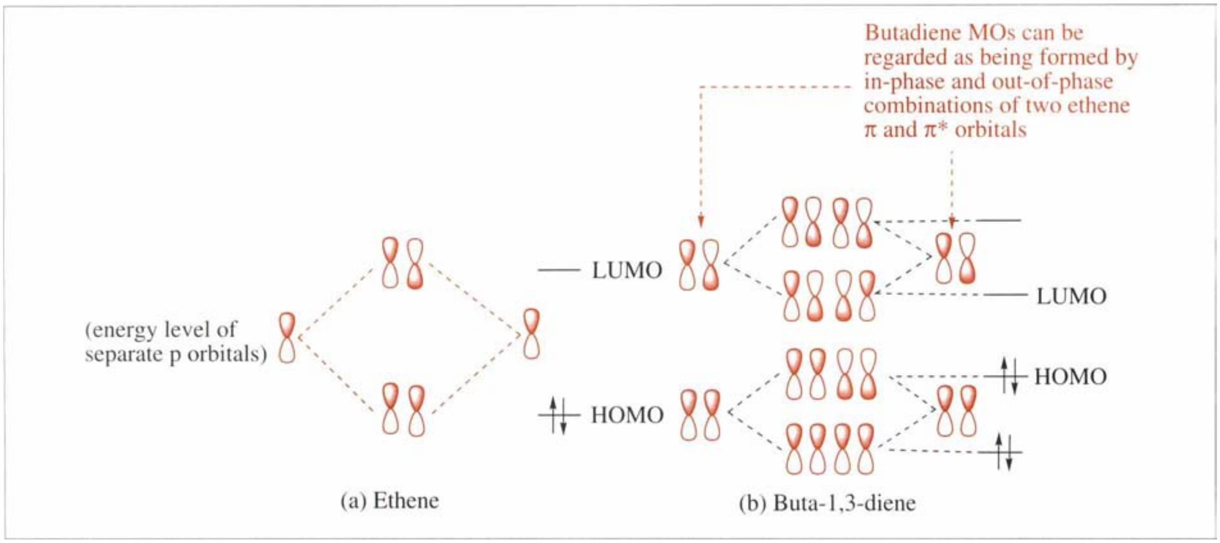
Figure 7.4 Frontier orbitals

It turns out that we can usually neglect all other orbital interactions between molecules and focus our attention only on these **frontier orbitals** (HOMOs and LUMOs) when considering interactions between molecules, and in particular pericyclic reactions. This insight gained the relatively unknown Japanese chemist Kenichi Fukui a share in the Nobel Prize for Chemistry in 1981.

How do we determine the frontier orbitals? We only need to consider the bonds that are actually reacting. For example, in reactions involving addition to ethene, we only need to consider the C–C π bond. The π orbital is the HOMO and the π^* orbital is the LUMO. For buta-1,3-diene with four orbitals in the π system, the HOMO and LUMO are shown in Figure 7.5b; note that there is a smaller HOMO–LUMO gap than for ethene (Figure 7.5a). In general, the antibonding level is approximately as far above the non-interacting level (separate atomic orbitals) as the bonding orbital is below this level.

HOMO-LUMO interactions determine whether or not a particular thermal pericyclic reaction will take place.

In reaction (7.1), one of the butadiene molecules is reacting across its ends, so the HOMO and LUMO are for the whole conjugated system, but the other molecule is only reacting across one of the double bonds. The second double bond is unchanged in the reaction, so plays no part in the primary electronic interactions and can be regarded as a substituent of a reacting *ethene* molecule.



Butadiene MOs can be regarded as being formed by in-phase and out-of-phase combinations of two ethene π and π^* orbitals

(a) Ethene

(b) Buta-1,3-diene

Figure 7.5 Molecular orbitals of ethene and buta-1,3-diene

In the next section we will see how the ideas of frontier orbitals can be applied to cycloaddition reactions.

7.1.1 Cycloadditions

A simple (though not very efficient or convenient) cycloaddition reaction is the reaction of buta-1,3-diene with ethene to give cyclohexene (reaction 7.3). The reaction does not appear to involve significant charge build-up in the transition state, and it appears that both new bonds are being formed at the same time, since the reaction is stereospecific with *cis* addition across both unsaturated systems.


(7.3)

It can be seen in Figure 7.6 that there is favourable (same phase) overlap between both ends of the HOMO of the butadiene molecule with the LUMO of the ethene molecule, and *vice versa*. Accordingly, as the molecules approach, there is a favourable energy change and the reaction takes place readily.

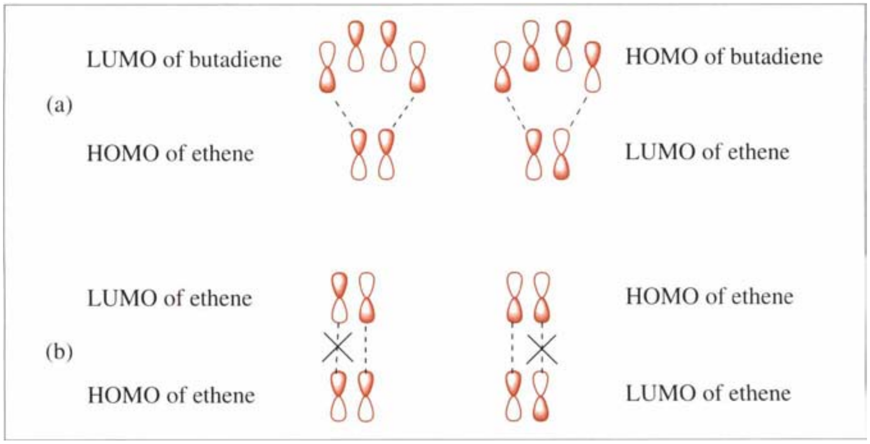


Figure 7.6 HOMO–LUMO interactions for (a) ethene with buta-1,3-diene and (b) ethene with ethene

However, for reaction (7.2), the dimerization of ethene to cyclobutane, the HOMO–LUMO interactions are unfavourable; if there is in-phase (favourable) interaction at one end, it will be unfavourable at the other. Thus the interactions cancel out, there is no overall favourable frontier orbital interaction, and the reaction does not take place thermally.

Other Cycloadditions

Provided that there is a favourable interaction at both ends between the HOMO of one component and the LUMO of the other component, reactions with a cyclic transition state should be possible for many other systems. Figure 7.7 shows the basic structures available for π systems containing between two and four overlapping p orbitals.

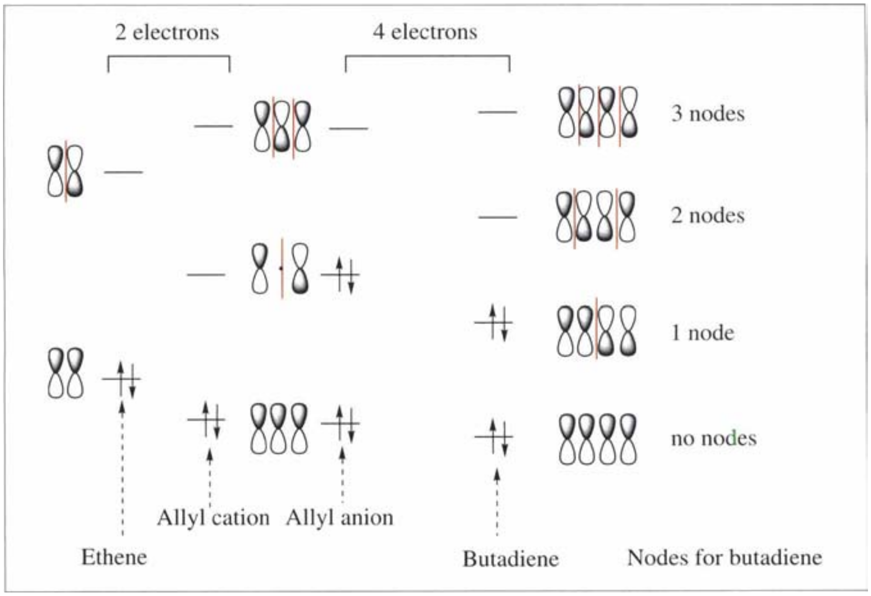


Figure 7.7 Molecular orbitals derived from two, three and four p orbitals. Nodes are shown in red. Orbital phases are shown as shaded and white

Inspection of Figure 7.7 shows that whatever the size of the system, the lowest, most bonding orbital has all the constituent orbitals in phase. Thus the components at the two ends necessarily have the same phase. For the next orbital up, there is a reversal of phase in the middle of the molecule, giving rise to antibonding at this point for systems with even numbers of orbitals, or non-bonding if there is an odd number of constituents. This change of phase or node results in the two end component orbitals being out of phase. For ethene (two atomic orbitals in ⇒ two molecular orbitals out) there are no further orbitals, but for systems with three or more constituent orbitals the next orbital up in energy will have two nodes, and the end orbital components will be back in phase again. This alternation of sign will continue as we go to higher and higher energies. Since electrons go into the lowest orbital available, a system with two electrons will have its HOMO with the end component orbitals in phase irrespective of the number of atomic orbitals involved. For four electrons, the HOMO will have the end components out of phase, for six, they will be back in phase, and so on. Thus for systems with $4n+2$ electrons the end components will be in phase, and for $4n$ electrons the ends will be out of phase. Since the LUMO is the next orbital above the HOMO, the phases will be opposite, with $4n+2$ electrons resulting in out-of-phase end components, and $4n$ in-phase. The position is summarized in Table 7.1, which enables the phases at the ends of molecular orbitals to be easily determined without having to construct all the molecular orbitals.

Table 7.1 Phases at ends of frontier orbitals

Frontier orbital	*4n+2 electrons*	*4n electrons*
HOMO	Same phase	Opposite phase
LUMO	Opposite phase	Same phase

The atoms need not be carbon: it is the orbitals that matter. Charged species can be involved, for example the allyl cation $CH_2{=}CH{-}CH_2^+$ has two π electrons (formally two from the double bond and none from the carbocation centre), the allyl anion $CH_2{=}CH{-}CH_2^-$ has four π electrons (two from the double bond and two from the lone pair on the negatively charged carbon). Ozone, $O{=}O^+{-}O^-$, is isoelectronic with the allyl anion, and will also bring four π electrons to the reaction (two from the double bond and two from the lone pair on the negatively charged oxygen).

For conjugation to be effective in π systems, approximate planarity needs to be maintained so that each p-type orbital can overlap with the next. The two points of attack on the π system can be on the same surface (top or bottom), in which case the attack is said to be **suprafacial** (supra = above) for that π system (Figure 7.8). Less commonly, attack can take place on opposite surfaces, in which case it is said to be **antarafacial** (possibly from antae, antarum = columns on either side of a door).

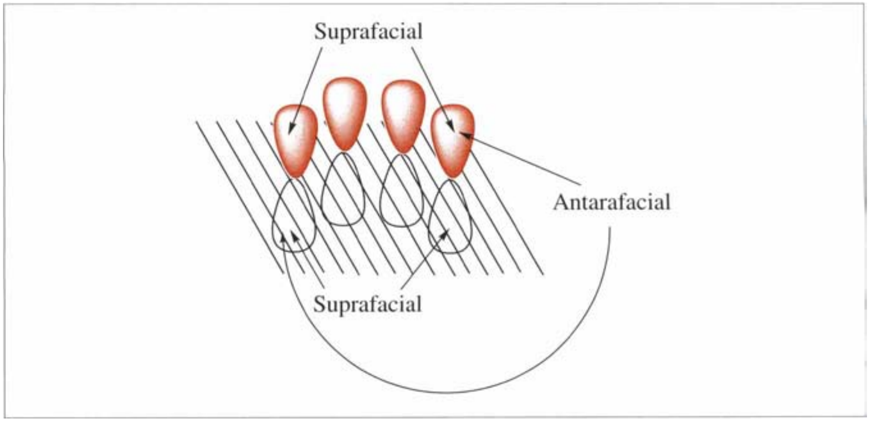
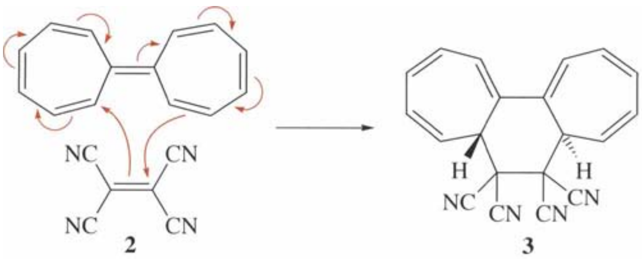


Figure 7.8 Suprafacial and antarafacial attack

Suprafacial cycloadditions are favourable if $4n+2$ electrons are involved.

Almost all cycloadditions are suprafacial for both components. For these fully suprafacial reactions, inspection of Table 7.1 shows that for the ends of the HOMO and LUMO to both be in phase (or both to be out of phase) and therefore to give favourable interactions at both ends, one component needs $4x$ electrons and the other needs $4y+2$, *i.e.* a total of **$4n+2$ electrons** $(n = x + y)$.

In a very small number of reactions, the twisted geometry of one of the components makes it possible for antarafacial attack to take place on one of the components. In these rare cases, since the opposite lobe of the antarafacial component is being used, the $4n+2$ rule is broken, and $4n$ electrons becomes the favoured total. Heptafulvalene (**2**) has a twisted structure (Figure 7.9) and reacts antarafacially with tetracyanoethene to give the adduct **3** (reaction 7.4).



(7.4)

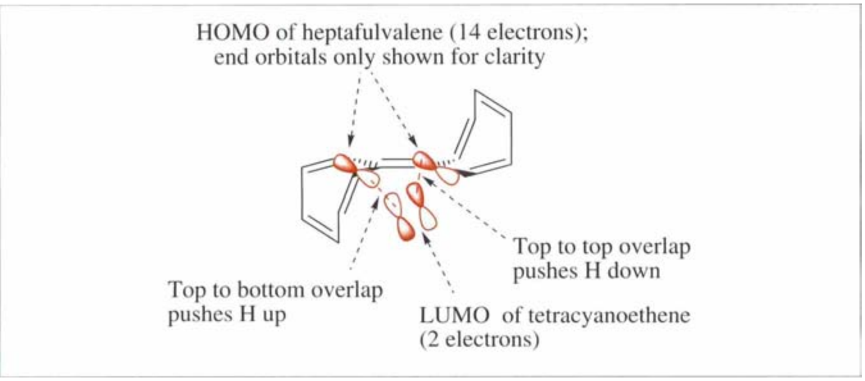


Figure 7.9 Antarafacial attack of tetracyanoethene on heptafulvalene

7.2 The Aromatic Transition State

The frontier orbital arguments outlined above strictly apply only to the initial stages of the reaction when the molecules come into contact and the orbitals start interacting. We have shown that there will be favourable HOMO–LUMO interactions if $4n+2$ electrons are involved in a fully suprafacial reaction or $4n$ electrons if one antarafacial component is involved. It does not necessarily follow from this that there will be a lowering of energy in the transition state. *However, in the transition state of all fully suprafacial pericyclic reactions, there is a cyclic overlap of the atomic orbitals involved in the bonds being formed and broken in the reaction, and we may expect, by analogy with cyclic conjugated structures, that delocalization and hence stabilization will be involved if there are the correct number of electrons.*

7.2.1 Hückel Systems

For all common aromatic systems, the overlap of the constituent p-type atomic orbitals is continuous around the cyclic system (no phase change). This leads in every case to a uniquely stable orbital with in-phase overlap between each of the adjacent orbitals in the cyclic system, as shown for three-, four-, five- and six-membered ring systems in Figure 7.10. This orbital can accommodate two electrons. The next most-stable orbitals will have a node where the phase changes, causing antibonding across this plane. Because the molecule is cyclic, there are *two* ways of introducing this nodal plane, at right angles to each other. This results in two orbitals of equal energy, which can between them accommodate four electrons. For the larger ring sizes, the higher orbitals will have two, three or more nodes, still occurring in pairs which can accommodate four electrons. Thus aromatic systems will have $4n + 2$ electrons, the **Hückel number**. Figure 7.10(b) and (d) shows that, for even numbered ring sizes, there is a unique most antibonding orbital with out-of-phase overlap between all

For suprafacial pericyclic reactions, the cyclic transition state is stabilized if a Hückel number of electrons, $4n+2$, is involved. This will give faster reaction rates.

next-neighbouring orbitals, but an orbital of this type is impossible for rings with odd numbers of atoms as in (a) and (c). For a three-membered ring, the aromatic number of two electrons can be achieved by loss of an electron from the neutral cyclopropenyl radical $C_3H_3^\bullet$ to give the cyclopropenyl cation $C_3H_3^+$ (**4**). For a five-membered ring, six electrons can be achieved by the neutral cyclopentadienyl radical $C_5H_5^\bullet$ gaining an electron to give the cyclopentadienyl anion $C_5H_5^-$ (**6**), or in the case of pyrrole (**7**) by the contribution of two electrons from the lone pair on the nitrogen atom. Cyclobutadiene (**5**) should be a triplet with an electron in each of the equivalent orbitals if the molecule is delocalized. In fact, molecules of this type distort to give alternate single and double bonds. Benzene (**8**) is the archetypal aromatic molecule, with an unstrained ring system with sp^2 hybridization, 120° bond angles and six π electrons that can be accommodated in the three bonding molecular orbitals.

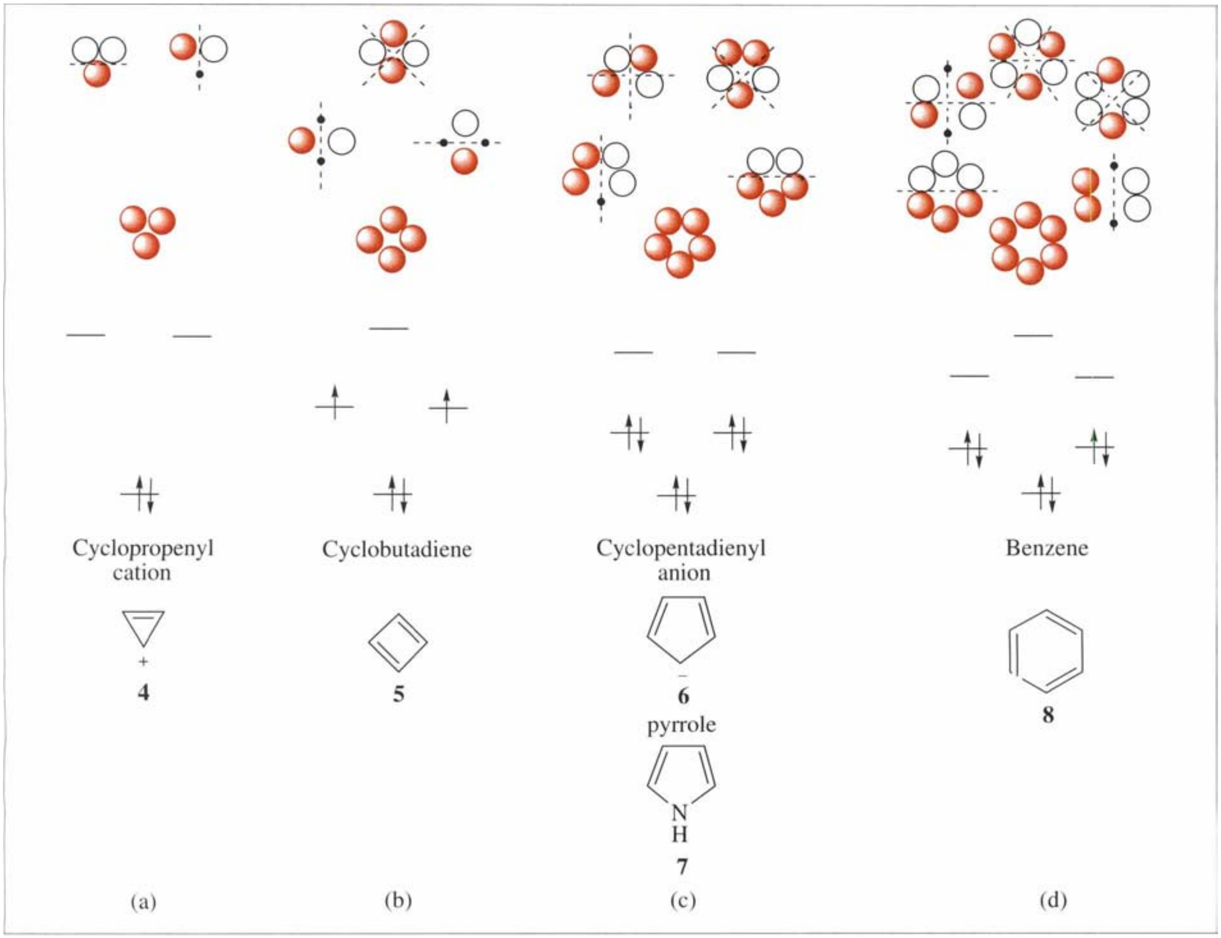


Figure 7.10 Orbitals and energy levels for cyclic conjugated systems

7.2.2 Möbius Systems: Rings with a Twist

In a large cyclic conjugated system, we could envisage a small angular deviation between the p orbitals of adjacent atoms, which if continued in the same direction round the ring could eventually reach a 180° total as we get back to the original atom, giving an out-of-phase antibonding interaction at this point. Systems of this type are rare, but it has been suggested that the cyclononatetraenyl cation $C_9H_9^+$ (**9**) may be a system of this type (Figure 7.11). They are named **Möbius systems** after the topological structure known as the Möbius strip, which can be constructed by joining the ends of a long thin strip of paper into a loop, but turning one end through 180° before joining.

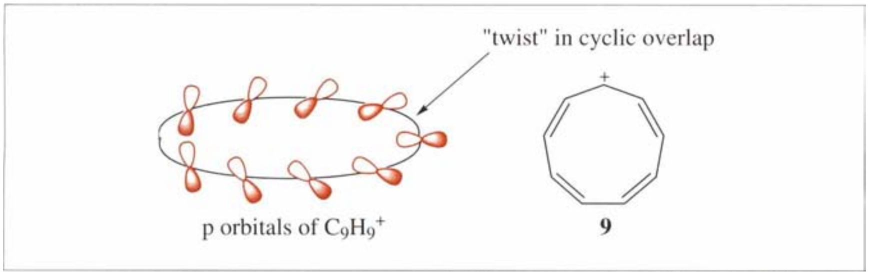


Figure 7.11 Orbital overlap in a Möbius system

Although Möbius molecules are rare, Möbius transition states, with one antarafacial component, are relatively common. For these systems, 4*n* electrons is the favourable number, giving a stabilized transition state and a faster reaction rate.

Since there is a "twist" in the system, there is no uniquely favourable orbital with positive overlap all the way round the ring, a crucial difference from Hückel molecules. The change of phase at a position on the opposite side of the molecule to that of the first molecular orbital (Figure 7.12a) will result in another orbital (Figure 7.12b) with positive overlap between all but one pairs of adjacent atoms, and with the same energy. These two orbitals will accommodate four electrons. We can put further nodes in the system, always in pairs, giving a succession of pairs of orbitals which can accommodate four electrons. Finally, if there is an odd number of atoms in the ring, there will be an unique high-energy orbital, with out-of-phase overlap between all pairs of adjacent orbitals. Since the orbital levels occur in pairs which can accommodate four electrons, Möbius systems will be stabilized if they have ***4n electrons*** and destabilized with $4n+2$, the opposite to Hückel systems. The molecular orbitals for a hypothetical Möbius cyclobutadiene are shown in Figure 7.12; the generalized progression of orbital levels is shown for both Hückel and Möbius systems in Figure 7.13.

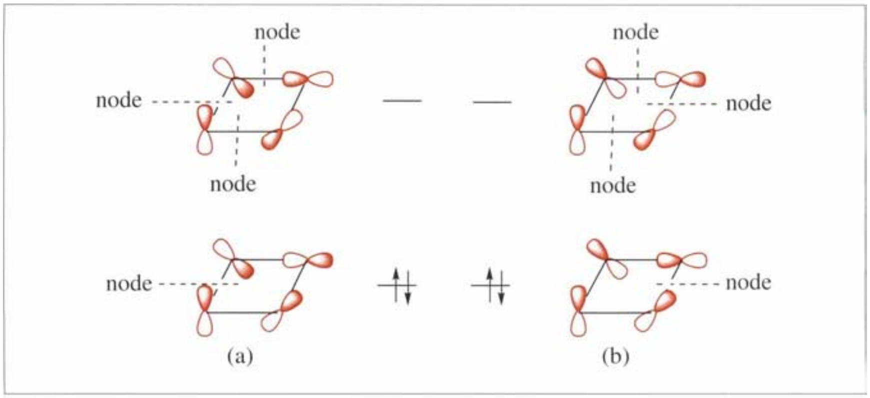


Figure 7.12 Molecular orbitals for the (hypothetical) Möbius cyclobutadiene

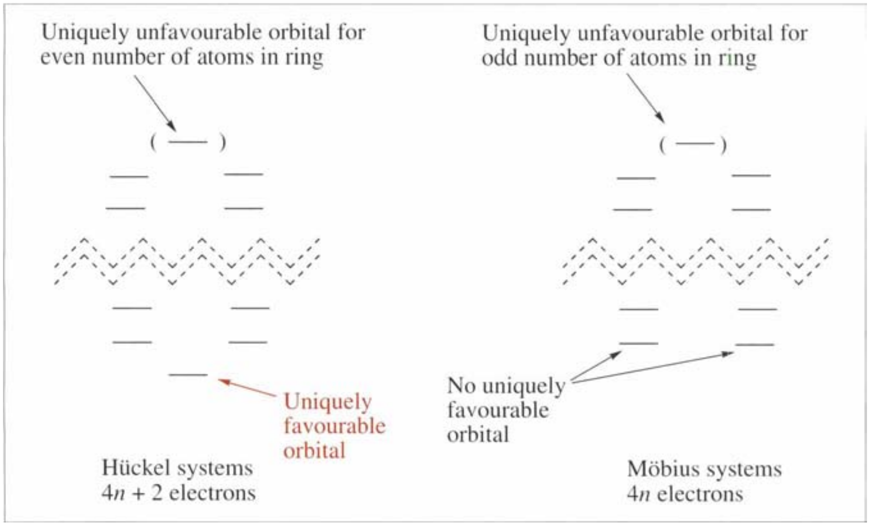


Figure 7.13 Progression of molecular orbitals in conjugated cyclic systems

7.2.3 The Link between the "Frontier Orbital" and the "Aromatic Transition State" Approaches

We have established earlier in the chapter that there will be favourable Frontier Orbital HOMO–LUMO interactions when two molecules approach for a cycloaddition reaction if there are $4n+2$ electrons involved in a fully suprafacial reaction, or $4n$ electrons if there is an antarafacial component. For delocalization of electrons in the transition state, the fully suprafacial cycloaddition reaction will result in a continuous cyclic overlap of atomic orbitals in the transition state without a phase change, for which $4n+2$ electrons will give aromatic stabilization. For a cycloaddition with one antarafacial component, the cyclic overlap of orbitals will give a Möbius system for which $4n$ electrons will provide stabilization. Thus the two approaches, Frontier Orbitals and the Aromatic Transition State will always be in agreement: favourable

HOMO–LUMO interactions as the molecules approach will always be accompanied by a lowering of the energy of the transition state, corresponding to a much faster reaction, as shown in Figure 7.14.

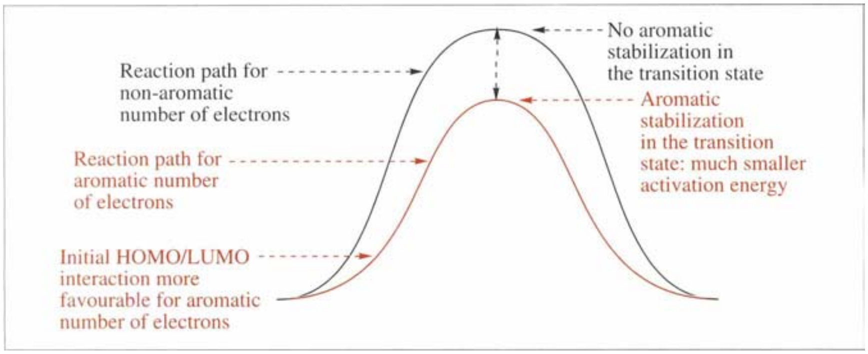


Figure 7.14 Reaction paths for pericyclic reactions involving aromatic and non-aromatic numbers of electrons. Number of aromatic electrons is $4n+2$ for Hückel systems with no antarafacial components, or $4n$ electrons for Möbius systems with one antarafacial component

7.3 Application of the Idea of the Aromatic Transition State to Pericyclic Reactions

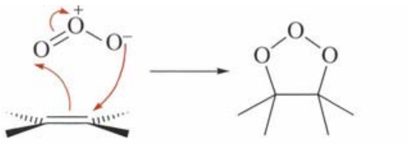
In the remainder of this chapter we will consider further cycloaddition reactions and other examples of pericyclic reactions. We will use the aromatic transition state approach for simplicity, although in all cases an approach based on HOMO–LUMO interactions would give the same result.

7.3.1 Cycloadditions

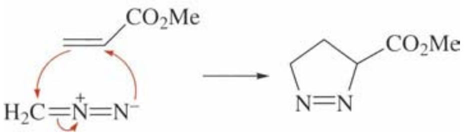
Entirely Suprafacial Reactions with $4n+2$ Electrons

Diels–Alder reactions (for example 7.1 and 7.3) are important six-electron systems which can be used synthetically. The six-membered transition state is unstrained, and the probability of both molecules colliding with the correct orientation is reasonably favourable.

Reactions involving a five-membered transition state are even more favoured on entropy grounds, although there is some angle strain in the transition state and the products. The first step in the reaction of ozone with alkenes is a reaction of this type (7.5), as is the reaction of diazomethane with alkenes such as methyl acrylate (methyl propenoate) (reaction 7.6). In each case, six p-type electrons are involved, a Hückel number, so the reactions will be favoured as long as the reactions are entirely suprafacial. The movement of three pairs of electrons (six in total) is shown by the curved arrows, and corresponds to the bonds broken and formed during these two reactions.

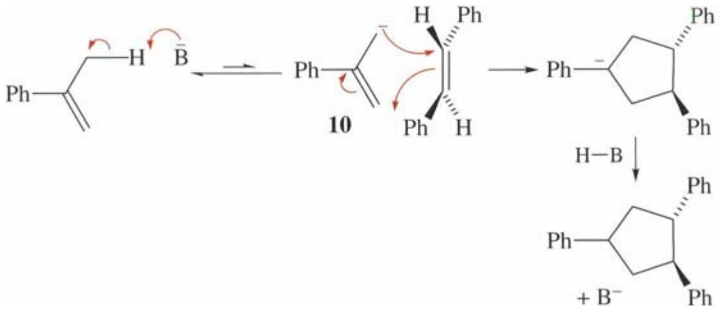


(7.5)



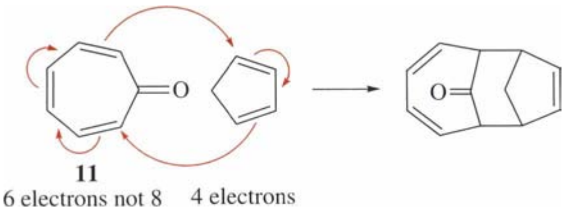
(7.6)

Reaction (7.7) involves the reversible removal of a proton from an allylic position by a base to give the stabilized anion **10,** which then reacts suprafacially with *trans*-1,2-diphenylethene to give the cyclopentane product in which the relative stereochemistry of the two phenyl groups has been preserved.



(7.7)

Suprafacial cycloadditions involving 10, 14, *etc.*, electrons are possible, but for open chain systems the probability of getting conformations of the two molecules in which interaction at both ends of both π systems takes place at once is very small, making the reactions impractical. However, if the molecules are constrained to give a favourable transition state geometry, for example by being part of a ring system, such reactions are feasible. In reaction (7.8), both components are constrained by being part of ring systems. The cyclic ketone **11** only brings six electrons to the reaction; the C=O group, though conjugated, does not react and is present in the product. The involvement of 10 electrons, a Hückel number, is shown by the five curved arrows.



(7.8)

Cycloadditions with an Antarafacial Component

These are rare. We have already met a 16-electron system in reaction (7.4), where the bicyclic geometry of the 14-electron system holds the ends of its π system close together and at an angle which facilitates antarafacial attack by the substituted ethene molecule.

Two ethene molecules do not react thermally to give cyclobutane (reaction 7.2). This 4π system has the wrong number of electrons for suprafacial attack to take place, and geometric reasons make it impossible for overlap to take place from a p-orbital lobe away from the direction of approach to give an antarafacial component (Figure 7.15).

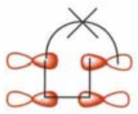
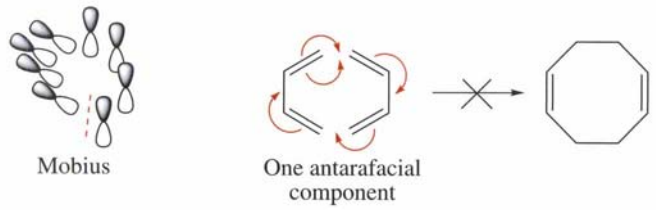


Figure 7.15 Impossibility of antarafacial attack in ethene dimerization

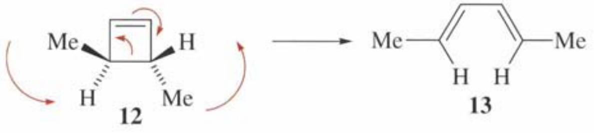
In principle, two buta-1,3-diene molecules could react to give cycloocta-1,5-diene (reaction 7.9), but this would involve an eight-membered transition state, with a low probability of the correct orientation for reaction. Instead, reaction can take place more readily via a six-membered Hückel transition state to give 4-vinylcyclohexene (reaction 7.1).



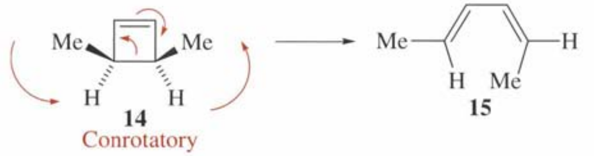
(7.9)

7.3.2 Electrocyclic Reactions

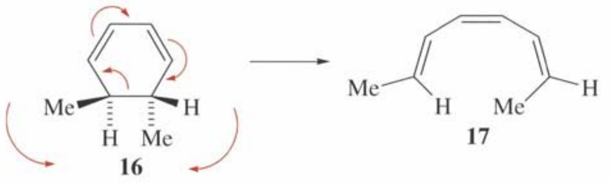
Pericyclic reactions can involve σ as well as π bonds. Electrocyclic ring opening (or closure) reactions are exemplified by reactions (7.10) and (7.11).



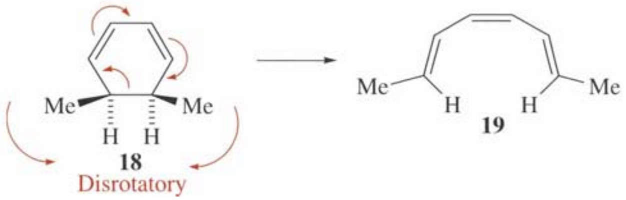
(7.10a)



(7.10b)



(7.11a)



(7.11b)

These reactions involve breakage of a σ bond. As the bond breaks, the sp^3 orbitals gradually rehybridize to p orbitals, and rotation takes place so that the incipient p orbitals can overlap with the p orbitals of the π system in the ring, resulting in one more double bond in the open-chain product. The reactions are stereospecific: *trans*-3,4-dimethylcyclobutene (**12**) gives *trans,trans*-hexa-2,4-diene (**13**), whereas the *cis* isomer (**14**) gives *cis,trans*-hexa-2,4-diene (**15**).

In reactions (7.10a) and (7.10b), the rotations are both in the same direction and are shown as anti-clockwise. For (7.10b), the rotations could have equally well been both clockwise, but for (7.10a), clockwise rotation would have given rise to the less stable *cis,cis* isomer which would be energetically less favourable. Where the rotations are in the same direction, the reaction is said to be **conrotatory**.

By contrast, the cyclohexadiene isomers in reaction (7.11) undergo ring opening with rotations in opposite directions as shown. These reactions are termed **disrotatory**.

These electrocyclic reactions and their conrotatory or disrotatory nature can be readily understood on the basis of aromaticity in the transition state (Figure 7.16). For the conrotatory mode, the rotations of the breaking σ orbitals bring about a phase change in the cyclic transition state: continuous red-to-red overlap cannot be maintained. Thus the transition state is Möbius, and is favoured for 4 (or any multiple of 4) electrons in the reacting system, as in Figure 7.16a. The distrotatory mode (Figure 7.16b) would have continuous in-phase overlap, giving a Hückel system, for which 4*n* electrons is unfavourable.

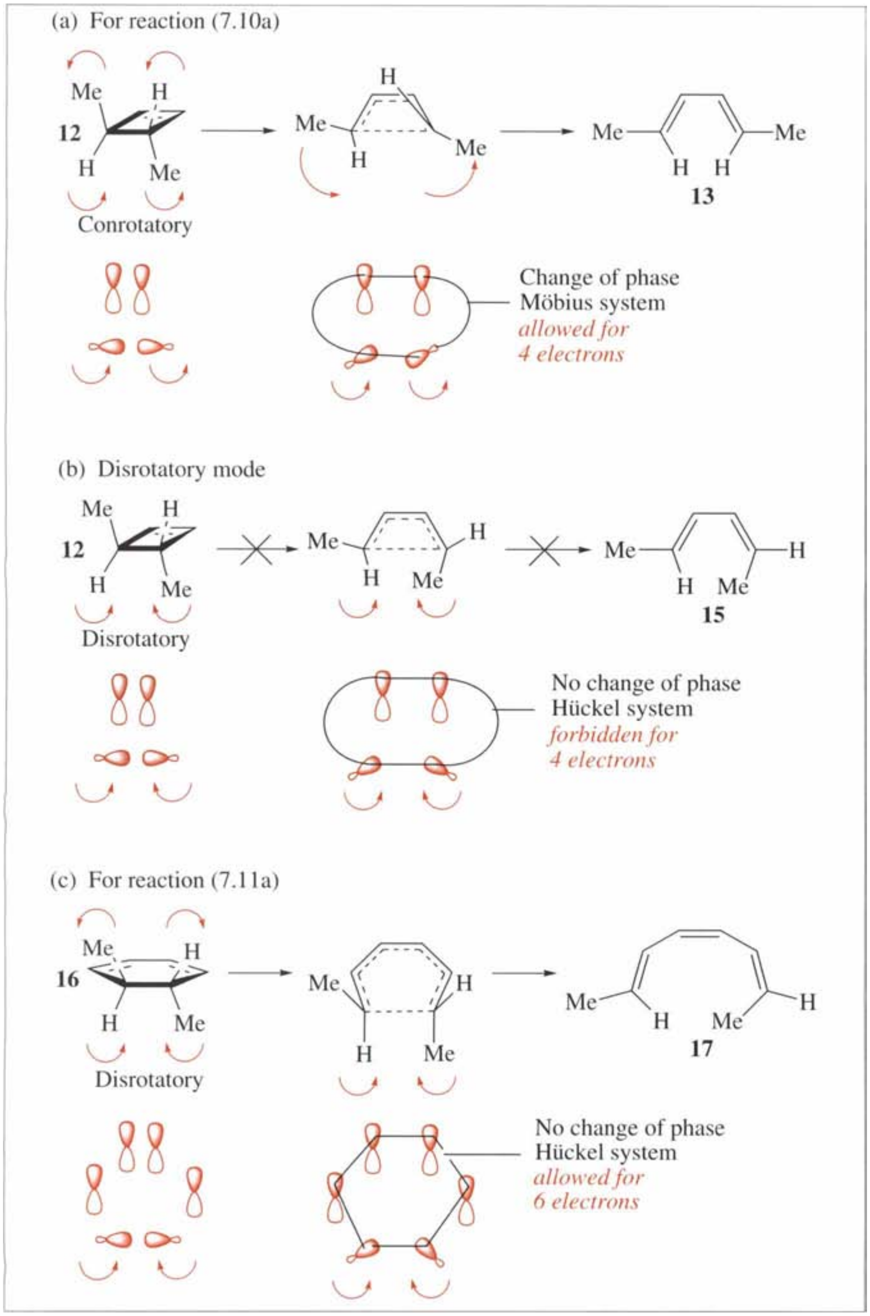


Figure 7.16 Conrotatory and disrotatory ring opening of cyclobutenes and cyclohexadienes

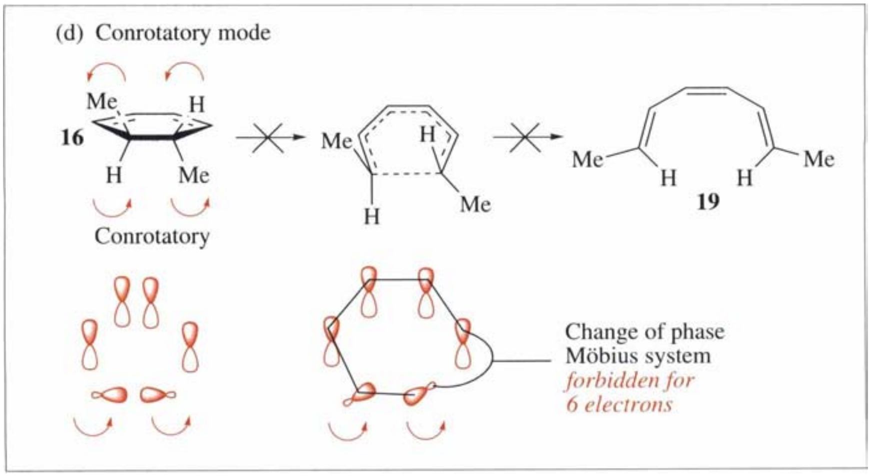


Figure 7.16 (Continued)

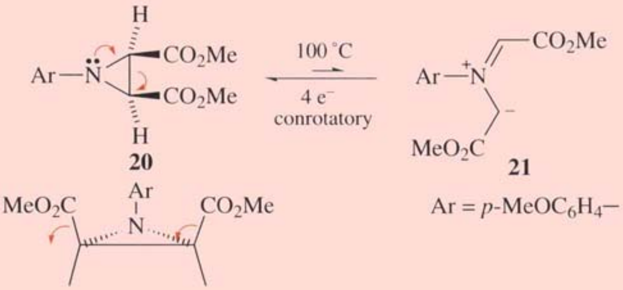
In contrast, ring opening of the cyclohexadiene isomers **16** and **18** to give **17** and **19** are both disrotatory. For this reaction, with a Hückel transition state involved, $4n+2$ electrons is the favoured number, and for this number of electrons the conrotatory mode which would give a Möbius transition state is not favoured.

A worked problem follows and several examples of electrocyclic reactions occur in the problems at the end of the chapter. The important principle is that for $4n$ electrons, conrotation will give the favoured Möbius transition state, whereas for $4n+2$ electrons, disrotation will give the favoured Hückel transition state.

Electrocyclic ring opening and closure will be disrotatory for $4n+2$ electrons, but conrotatory for $4n$ electrons. Many examples of both types are known.

Worked Problem 7.2

Q On heating, the aziridine **20** undergoes ring opening to the dipolar product **21** in reaction (7.12). Explain why the conrotatory mode shown is favoured.



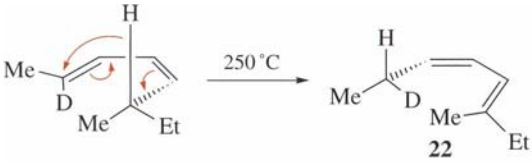
Ar = p-$MeOC_6H_4$–

(7.12)

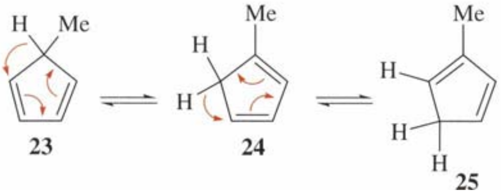
A Four electrons are involved in this ring-opening reaction: two from the lone pair on the nitrogen and two from the σ bond which breaks, as shown by the curved arrows. Thus a Möbius transition state is favoured, resulting in conrotatory ring opening.

7.3.3 Sigmatropic Rearrangements

In these reactions, a σ bond moves across a π system to a new site. An example is reaction (7.13), where the stereochemistry of the product **22** shows that the reaction is suprafacial. The reaction is designated [1,5] because a σ bond to a single atom moves from one end to the other of a 5-atom system. Another interesting example of this is the rearrangement and interconversion of the methylcyclopentadiene isomers **23**, **24** and **25**, which is rapid at room temperature (reaction 7.14).



(7.13)



(7.14)

Figure 7.17 shows the cyclic overlap of the orbitals for a [1,5] suprafacial shift. This will be favourable for Hückel systems with $4n+2$ electrons, as in reactions (7.13) and (7.14). Antarafacial migration will be possible for systems with $4n$ electrons; these are relatively uncommon. Hydrogen atoms do not migrate across an allyl system (reaction 7.15). The suprafacial migration is forbidden; the allowed antarafacial process cannot take place for geometric reasons which prevent the hydrogen orbital from overlapping simultaneously with the orbitals on carbon atoms 1 and 3 in an antarafacial manner.

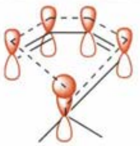
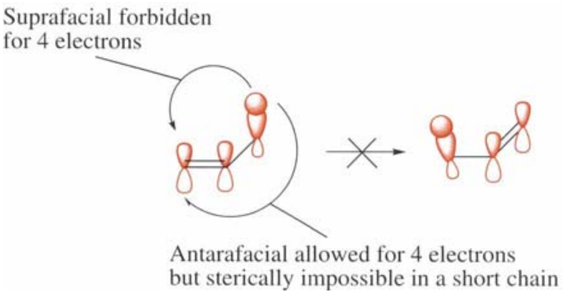


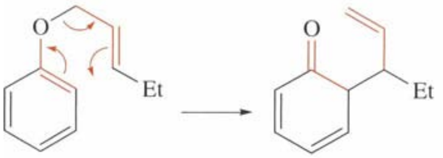
Figure 7.17 Cyclic overlap of orbitals in a [1,5] sigmatropic shift



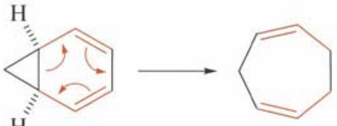
(7.15)

Sigmatropic rearrangements will be suprafacial for $4n + 2$ electrons, but antarafacial for $4n$ electrons. Antarafacial reactions are rarer, since antarafacial movement is often impossible geometrically.

A number of [3,3] rearrangements are interesting, including the rearrangement of allyl phenyl ethers **26** to dienones such as **27** (reaction 7.16). The designation [3,3] indicates that there are two 3-atom components of the system, shown in red in (7.16) and (7.17), which are joined at one end in the starting molecule, and at the other end in the products. The Cope rearrangement of **28** to **29** (reaction 7.17) is another example of a [3,3] rearrangement.



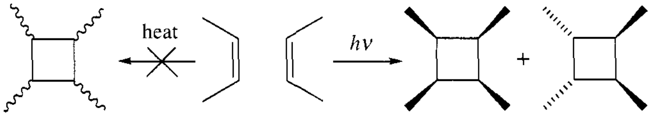
26 **27** (7.16)



28 **29** (7.17)

7.4 Photochemical Reactions

All the examples so far in this chapter have been thermal reactions. Many reactions which do not go thermally, such as (7.2), can be made to take place photochemically. If the alkenes are disubstituted, the stereochemistry of the products is consistent with entirely suprafacial attack, as shown in reaction (7.18).



(7.18)

Frontier orbital treatment provides a good explanation. For the thermal reaction of two ethene molecules, HOMO–HOMO and

LUMO–LUMO are unable to contribute stabilizing influences as the reagents collide, as shown in Figure 7.18(a). For this four-electron system, HOMO–LUMO interactions are also unfavourable because the orbitals at the ends of the two π systems are out of phase. In the photochemical reaction, one of the ethene molecules has an electron promoted to a higher orbital, usually from the HOMO to the LUMO. This dramatically alters the possible interactions, as shown in Figure 7.18(b). We designate as "HOMO" and "LUMO" the orbitals that were the HOMO and LUMO before excitation. The orbitals themselves will be virtually unchanged by the change in occupancy. The "HOMO" with one electron will be able to interact with the HOMO of another molecule (two electrons) to give bonding and antibonding combinations of molecular orbitals. Two electrons will go into the bonding orbital, one in the antibonding, giving a net bonding interaction. Likewise the "LUMO" with one electron interacts with the LUMO of the second molecule (no electrons) to give bonding and antibonding combinations. The single electron available goes into the bonding combination with a reduction in energy. Thus for this system, which is thermally forbidden, both "HOMO"–HOMO and "LUMO"–LUMO reactions are favourable and the reaction is photochemically allowed.

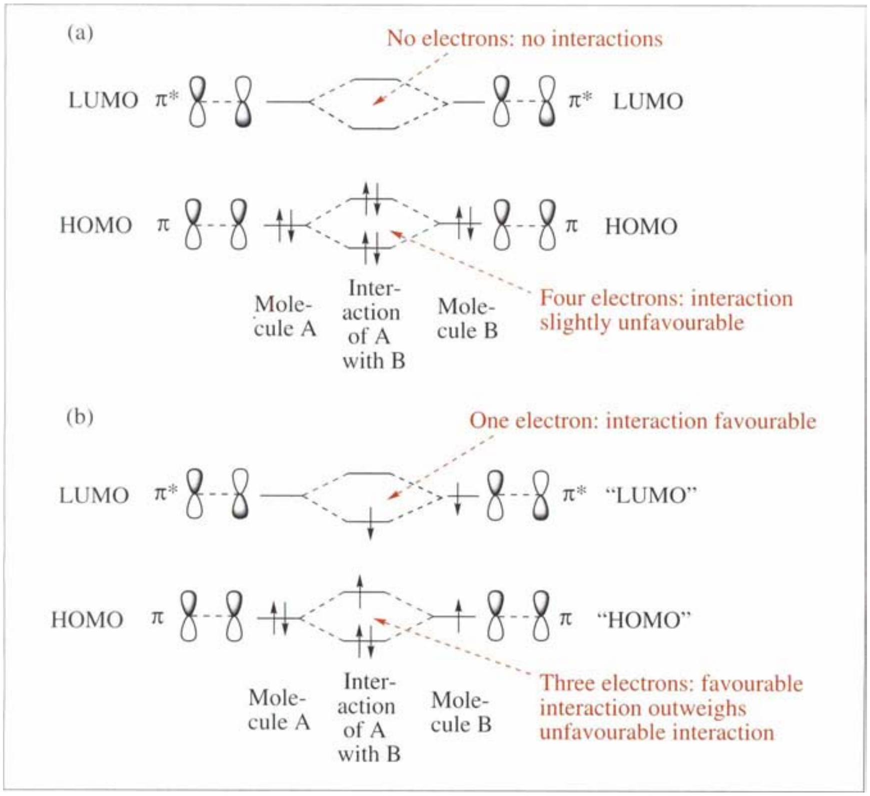


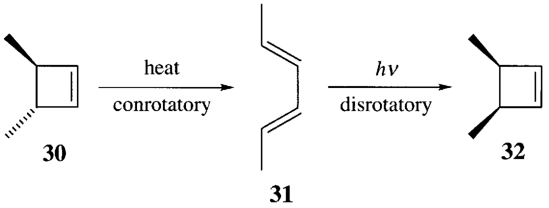
Figure 7.18 Molecular orbitals involved in thermal and photochemical reactions (a) Thermal: overall interaction slightly unfavourable. (b) Photochemical: one electron in molecule B promoted to "LUMO"; overall interactions favourable

For photochemical reactions, HOMO–"HOMO" and LUMO–"LUMO" interactions dominate, in contrast to the HOMO–LUMO interactions involved in thermal reactions. The rules for numbers of electrons involved in photochemical pericyclic reactions are the reverse of those for thermal reactions.

The conclusion is general: reactions which are forbidden thermally are allowed photochemically and *vice versa*. For a particular number of electrons, cycloadditions that go entirely suprafacially under thermal conditions will require an antarafacial component photochemically and *vice versa*. For electrocyclic reactions that are conrotatory under thermal conditions, the corresponding photochemical reactions will be disrotatory and *vice versa*.

The **Woodward–Hoffmann rules** are a general expression of this. *A pericyclic reaction which is entirely suprafacial is allowed thermally if 4n+2 electrons are involved (Hückel transition state), but forbidden for 4n electrons. If there is one antarafacial component, the reaction will be allowed thermally if 4n electrons are involved (Möbius transition state), but forbidden for 4n+2 electrons. For photochemical reactions, these rules are reversed.* Roald Hoffmann shared the Nobel prize for Chemistry with Kenichi Fukui in 1981 for his contribution to this concept; Robert Burns Woodward had already won the prize in 1965.

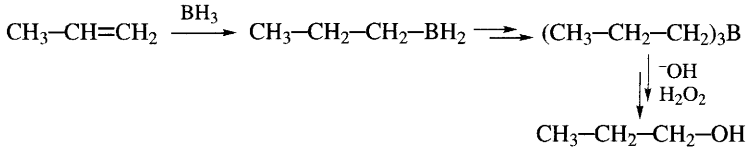
The different stereochemistry of thermal and photochemical reactions can sometimes be exploited, where reactions are reversible, to cause isomerization between stereoisomers. The thermal conrotatory ring opening of *trans*-3,4-dimethylcyclobutene (**30**) to *trans*,*trans*-hexa-2,4-diene (**31**) goes effectively to completion, since the product **31** is more stable because of the relief of the ring strain (reaction 7.19). The photochemical ring closure is also very effective: the diene **31** because of its conjugation absorbs light at longer wavelengths than the mono-ene product *trans*-3,4-dimethylcyclobutene (**32**) which is photochemically inert to normal UV radiation, and the photon of light provides plenty of energy to make the endothermic reaction proceed. By this sequence of reactions, **30** can be transformed into its geometric isomer **32** in good yield.



(7.19)

7.5 Molecular Reactions with Non-cyclic Transition States

The reaction of diborane, B_2H_6 (which reacts as BH_3), with alkenes gives adducts that can be used further in synthetic schemes, for example to give alcohols; this is important synthetically. Reaction (7.20) shows that the overall effect is to give addition in the opposite sense to that given by direct hydration of alkenes.



$$CH_3{-}CH{=}CH_2 \xrightarrow{BH_3} CH_3{-}CH_2{-}CH_2{-}BH_2 \rightrightarrows (CH_3{-}CH_2{-}CH_2)_3B \xrightarrow[H_2O_2]{^-OH} CH_3{-}CH_2{-}CH_2{-}OH \qquad (7.20)$$

The B–H bond has a polarity which is reversed compared with most H–X bonds, with the $\delta+$ on boron and $\delta-$ on the hydrogen atom. However, the reaction does not seem to be a normal electrophilic addition to the C=C double bond. Addition is suprafacial, suggesting a molecular reaction, which at first sight might appear to be a forbidden four-electron process. The movement of electrons shown in Figure 7.19(a) would indeed be forbidden, but there is an alternative involving the empty p orbital on boron. The movement of electrons shown in Figure 7.19(b) shows overlap between the sp^2 hybrid orbital on boron with the hydrogen, thence to the p orbitals on the two carbon atoms and back to the vacant p orbital on boron. However, there is no overlap between the p orbital on boron with the original sp^3 hybrid orbital; these are strictly orthogonal (no overlap), and hence there is no cyclic conjugation in the transition state. Thus the reaction is a non-cyclic concerted reaction involving the flow of two electron pairs.

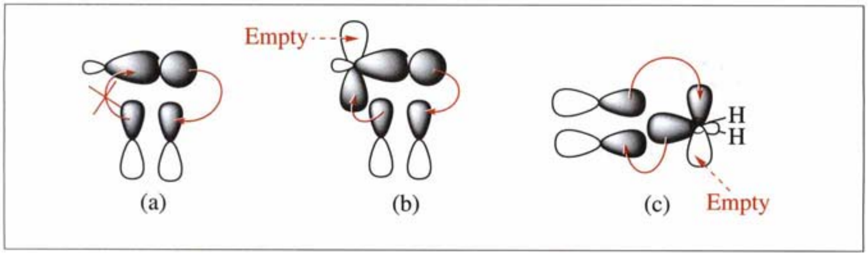
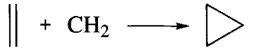


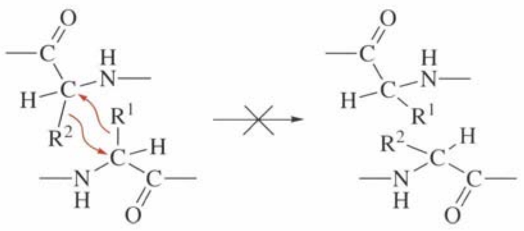
Figure 7.19 Non-cyclic transition states

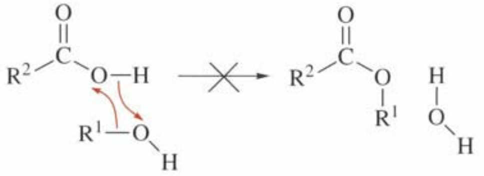
A similar situation occurs in the addition of carbenes to alkenes to give cyclopropanes, another synthetically useful reaction shown in its simplest form in reaction (7.21). Figure 7.19(c) shows the movement of electrons for this reaction, which is similarly concerted but does not involve a cyclic transition state.



(7.21)

As a footnote, the stability and integrity of ordinary organic compounds containing nitrogen, oxygen and halogen atoms towards direct exchange of groups depends on the absence of empty accessible orbitals. Thus reactions of types (7.22) and (7.23), for example, which would have to involve a cyclic Hückel transition state with four electrons, do not take place. Peptides do not exchange side chain groups directly, and esterification of carboxylic acids has to take place by lengthier processes involving intermediates, as discussed in previous chapters.


(7.22)


(7.23)

Summary of Key Points

1. The concepts of frontier orbital HOMO–LUMO interactions, the idea of an aromatic transition state, and the alternative concept of conservation of orbital symmetry (not developed in this chapter) all lead to the same result: for pericyclic reactions which involve a cyclic overlap of orbitals in the transition state, thermal reactions are allowed for reactions involving $4n+2$ electrons in Hückel systems (no change in phase between overlapped orbitals in the cyclic transition state) or for $4n$ electrons in Möbius systems (phase between overlapped orbitals in the cyclic transition state changes once on going round the ring). For photochemical systems, these rules are reversed.

2. The impossibility of suprafacial four-electron pericyclic reactions explains why simple interchange of groups between organic molecules does not readily take place, and why many reactions take place *via* intermediates, as described in earlier chapters.

Further Reading

I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, 1976, Chapters 4 and 6.

R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, 1971.

M. Mauksch, V. Gogonea, H. Jiao and P. von R. Schleyer, $(CH)_9{}^+$, in *Angew. Chem. Int. Ed. Engl.*, 1988, **37**, 2395.

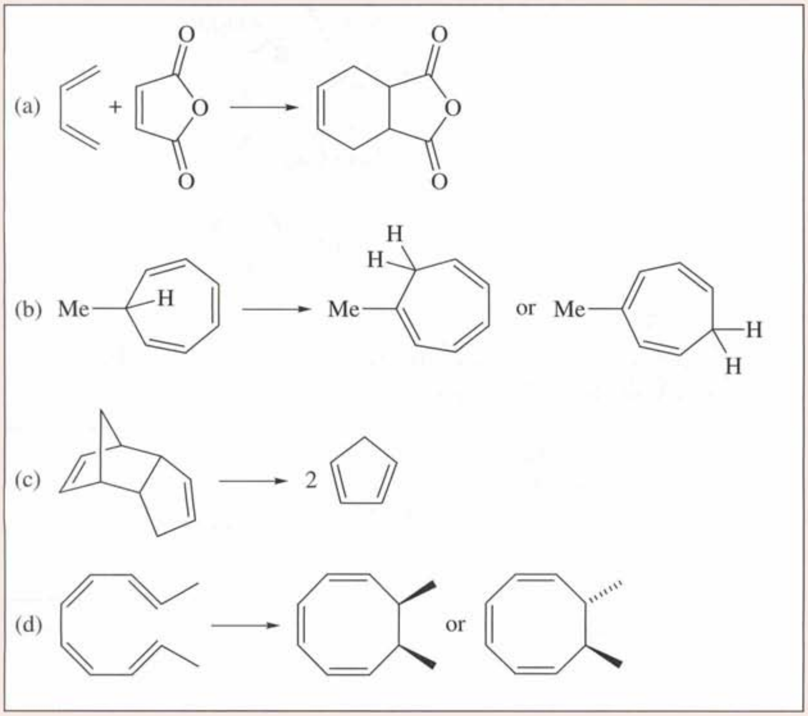
Problems

7.1. Using arguments based on frontier orbitals, show why two molecules of ethene do not react thermally to give cyclobutane, but ethene will react with buta-1,3-diene to give cyclohexene.

7.2. Using the concept of the aromatic transition state, show that, for pericyclic thermal reactions, $4n+2$ electrons need to be involved if the reaction is entirely suprafacial, whereas $4n$ electrons are needed for reactions with one antarafacial component.

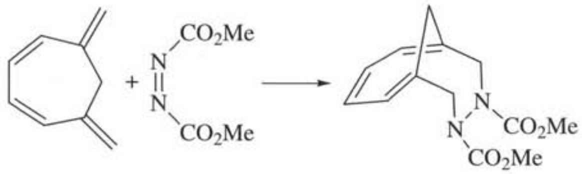
7.3. Using the formation of cyclobutane from ethene as an example, show that pericyclic reactions that are forbidden thermally are allowed photochemically and *vice versa*.

7.4. Classify the following six reactions as cycloaddition, sigmatropic, or electrocyclic. Use curved arrows to identify the number of electrons involved, and rationalize the results in terms of the Woodward–Hoffmann rules. If more than one possible product is listed, predict which of them will be formed. All reactions are thermal unless stated otherwise.



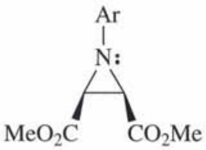
(e) As (d) but photochemical

(f)

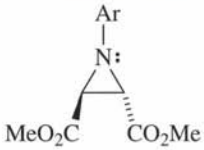


7.5. What products would you expect from the photochemical reaction of *trans*-but-2-ene? [Hint: compare reaction (7.18)]

7.6. On heating in CCl_4, the aziridine **A** slowly isomerizes to **B**, showing first-order kinetics, and giving eventually the equilibrium mixture. If dimethyl acetylenedicarboxylate (dimethyl butynedioate, **C**) is added, the isomerization does not take place, but instead the adduct **D** is formed. Explain these results. [Hint: consider reaction (7.12)]



A

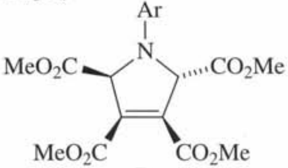


B

Ar = *p*-$MeOC_6H_4-$

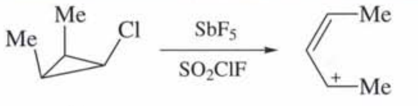
$MeO_2C-C\equiv C-CO_2Me$

C



D

7.7. Explain the formation of the cation **F** from the chloro compound **E** in the following reaction:

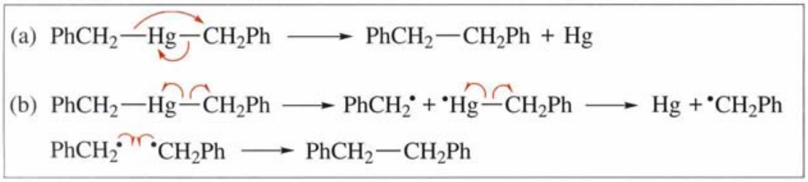


E **F**

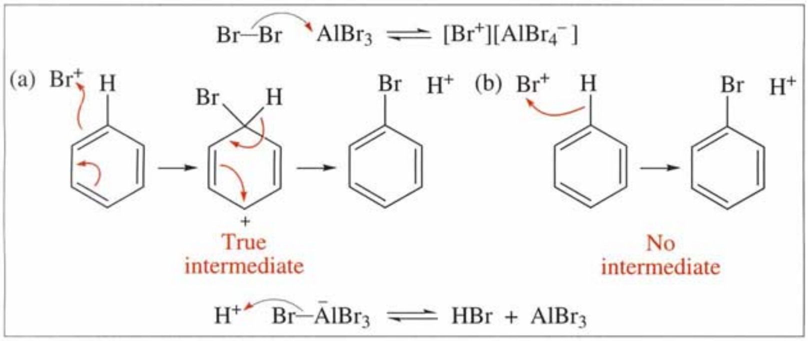
Answers to Problems

Chapter 1

1.1.



1.2.



1.3. (a) Unlikely. Reaction would involve four molecules interacting in one step. Also, the $Ni(CN)_2$ molecule is not used. A catalyst molecule must be involved in the reaction mechanism; if not, the reaction would go equally well in its absence.

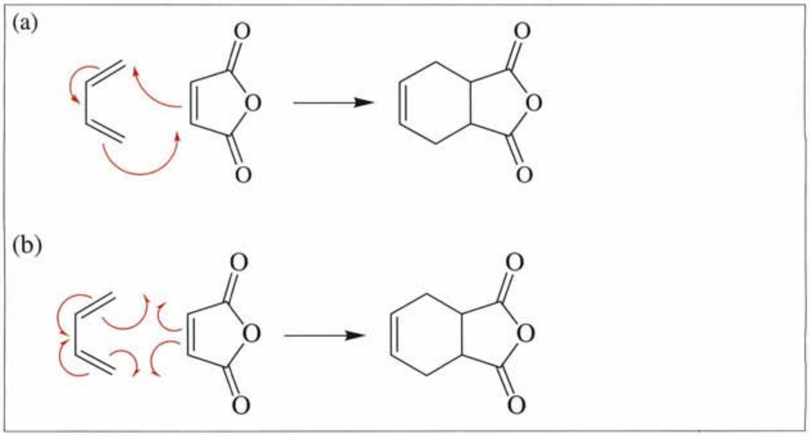
(b) The reverse reaction would involve the interaction of five species: highly unlikely. Since the forward and back reactions of an elementary process must follow the same route, this reaction is unlikely because of the principle of microscopic reversibility. The reaction is more likely to proceed homolytically by steps in which one C-Pb bond is broken at a time.

(c) Quite plausible. Only two molecules are involved, and in the concerted process shown, three bonds are broken at the same time as three new bonds are formed, so the reaction will not be highly endothermic.

(d) Unlikely. If two bonds are formed simultaneously, they must be to the same face of the molecule. This would give the other stereoisomer.

(e) Unlikely. The nitrogen radical intermediate proposed would have nine electrons in its valence shell (two each for the four covalent bonds and one for the single electron that would make it a free radical).

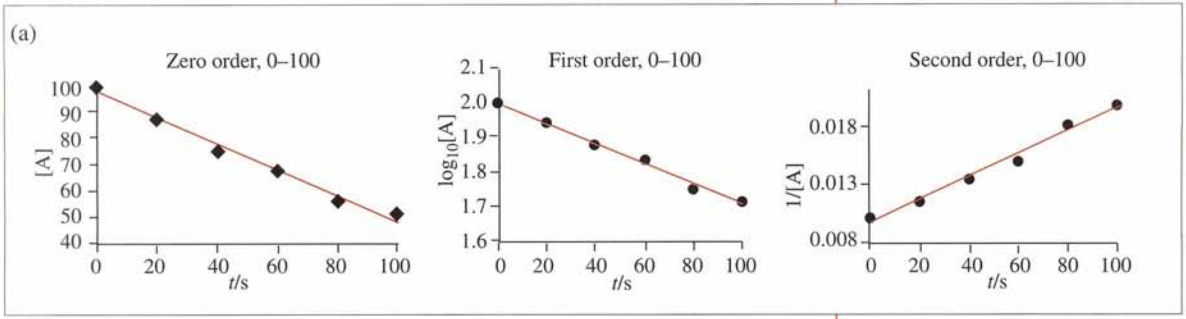
1.4.



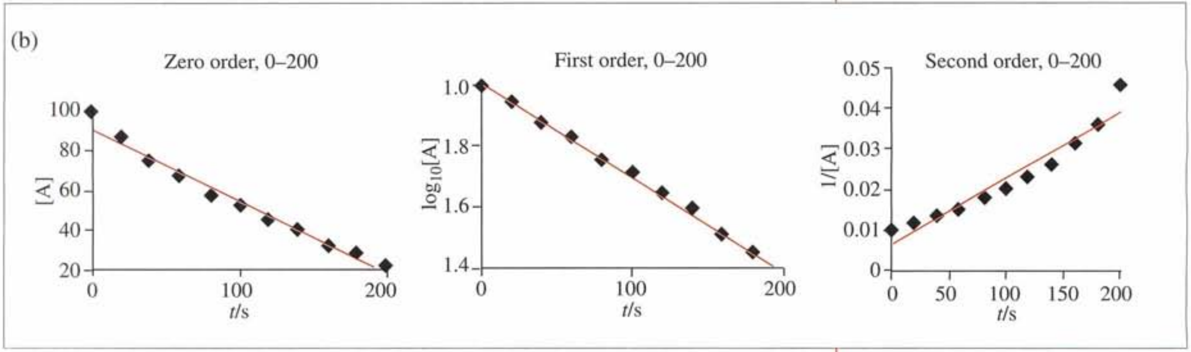
1.5. The central carbon atom has four shared electrons in the covalent bonds to the two hydrogens, and two unshared electrons. The total number of electrons formally associated with the carbon in its valence shell is thus $(4/2)+2=4$. This balances the $4+$ charge that a carbon atom with no electrons in its valence shell would have, making it electrically neutral.

Chapter 2

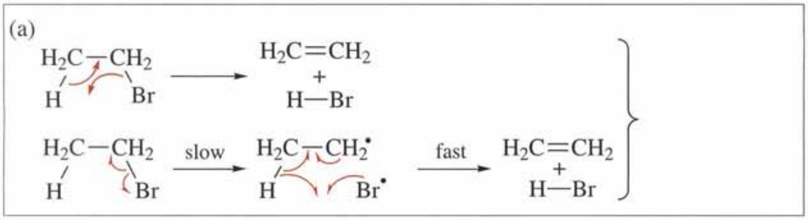
2.1. (a) Plots of [A], $\log_{10}$[A] and 1/[A] against time, made on a spreadsheet, are shown below. Because of the relatively small range of concentrations measured and the scatter of points, it is impossible to be sure which plot gives the best straight line.

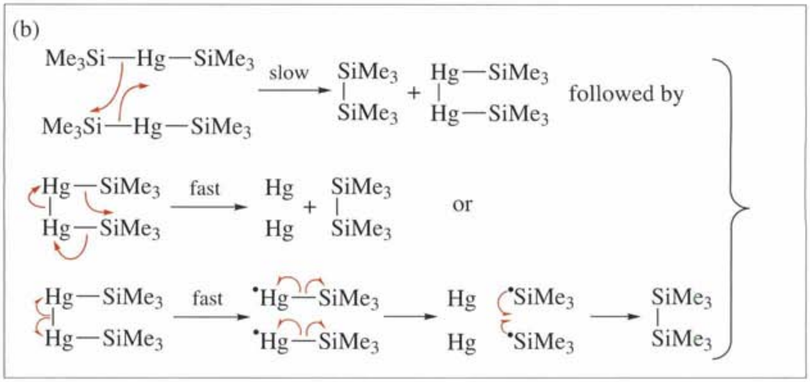


(b) The extended data are plotted below. The zero- and second-order plots both show pronounced curvature, whereas the first order plot is a much better straight line. These data support first-order dependence on [A], and show the importance of following a reaction for at least two half-lives if possible.

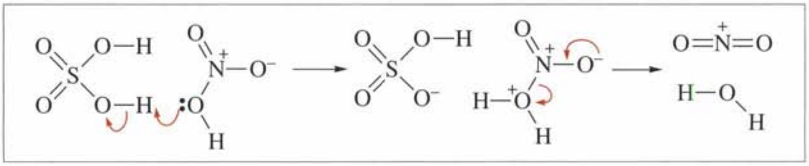


2.2.





2.3. The nitric acid and sulfuric acid must react slowly to give an intermediate which reacts rapidly with benzene to form the product. Spectroscopic and other evidence shows this intermediate to be the nitronium ion, NO_2^+, formed by the reaction:



2.4. Since reaction p1 is fast, all $R^\bullet$ radicals, formed by reaction i, are rapidly converted into $ROO^\bullet$ radicals. Reaction p2 does not contribute to the loss of $ROO^\bullet$ radicals because they are immediately regenerated by p1. Thus in the steady state:

$$d[ROO^\bullet]/dt = 2k_i[\text{initiator}] - 2k_t[ROO^\bullet]^2 = 0$$

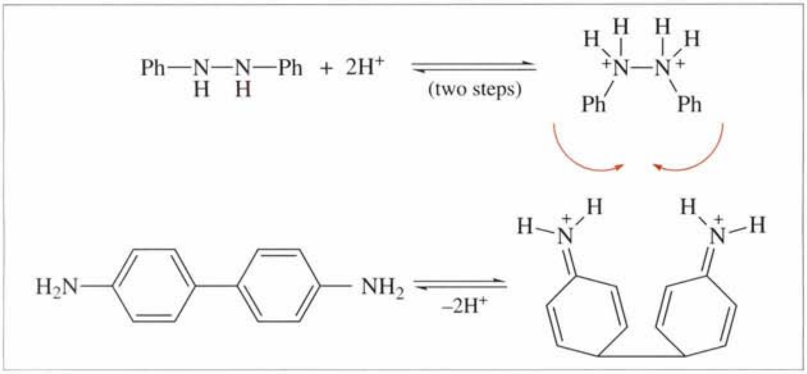
$$\therefore [ROO^\bullet] = (k_i/k_t)^{0.5}[\text{initiator}]^{0.5}$$

Product is only formed by p2, so:

$$d[ROOH]/dt = (k_i/k_t)^{0.5}k_{p2}[\text{initiator}]^{0.5}[RH]$$

Since the reaction of alkyl radicals with oxygen (p_1) is much faster than reaction p_2, most of the radicals present in the system at a particular time will be peroxyl radicals, $ROO^\bullet$, so the main route for destruction of the radicals will be the bimolecular reaction between the peroxyl radicals, *i.e.* k_t.

2.5.



2.6. Mechanism (a) is a molecular reaction with a "tight" transition state, whereas the rate determining step in (b) is homolysis into two radicals with a "loose" transition state, which would give a larger Arrhenius *A* factor. The observed *A* factor falls within the range expected for molecular reactions shown in Table 2.1; thus (a) is favoured.

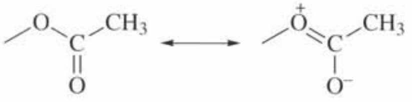
2.7. In the transition state of a molecular reaction, the molecules will have approached each other closer than the van der Waals contact distances, but the bond lengths of the bonds being formed between the terminal carbon atoms of the two molecules will still be much longer than typical C–C bond lengths, so there is significant bond breakage at these positions. However, the C2 and C3 atoms are changing their bonding, from single in one direction and double in the other, to the reverse arrangement in the product. The bond lengths will be intermediate between single and double, and little bonding will have been lost at these positions. Thus the observed isotope effect will be small, and in this example it is effectively unity.

2.8. Both mechanisms involve the breakage of C–H bonds in the transition state, so either would give significant hydrogen isotope effects, and no distinction between these mechanisms can be reached. However, in mechanism (a), no breakage of the C–N bond takes place in the transition state, whereas in the concerted reaction (b) the C–N bond is partially broken. Thus the nitrogen isotope effect favours route (b).

Chapter 3

3.1. The first reaction involves spreading a charge in the transition state; the second involves creation of charge. Thus the first will be decreased in rate by increasing the ionizing power of the solvent; the second will be increased (by a larger amount).

3.2. At the *meta* position, the inductive withdrawal of electrons by the oxygen atom outweighs the resonance release of electrons, so the net effect is electron withdrawal, shown by the small positive σ value. In the O–CO–Me group, there is a contribution to the structure from **L**:



L

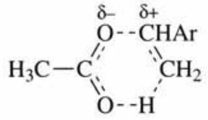
This produces a partial positive charge on the non-carbonyl oxygen of the group, which will make it more electron deficient. Hence it will withdraw electrons inductively more effectively than the OMe group, and will have a larger positive ρ value.

3.3. Examples:

σ_p^+	NH_2	NMe_2	OH	OMe	SMe	Cl
σ_p^-	CHO	COMe	CO_2Me	CN	NO_2	

3.4. Route (a) involves creation of positive charge in the intermediate formed in the rate-determining step, so ρ will be negative. The charge is conjugated with the aromatic ring, so σ^+ will be followed. Route (b) involves creation of negative charge in the intermediate formed in the rate-determining step, so ρ will be positive. The charge is not conjugated with the aromatic ring, so σ will be followed. Experimentally, ρ is found to be +2.33 and σ is followed, supporting mechanism (b).

3.5. The negative ρ value indicates that positive charge is being built up near the aromatic ring; the σ^+ dependence shows that this charge is conjugated with the aromatic ring and is therefore likely to be at the α-position, as shown below. The low ρ value indicates that the molecule is not fully ionized. A transition state of the type shown below is indicated.



3.6. See Table 3.4, which defines the six categories. Choose other reactions whose mechanisms have been established and assign them to the six categories.

3.7. Introduction of the first *t*-butyl group only increases the rate by a factor of 1.2. The second *t*-butyl group increases the rate by the much larger factor of $18.4/1.2=15.3$. This increasing effect of successive substituents is characteristic of steric effects.

3.8. Introduction of the first phenyl group increases the rate by a factor of $5.2\times10^{-5}/1.76\times10^{-5}=3.0$. The second phenyl group increases the rate by the smaller factor of $1.15\times10^{-4}/5.2-10^{-5}=2.2$. This decreasing effect of successive substituents is characteristic of electronic effects.

3.9. Br and OH have the highest priority. Ethyl and methyl are both centred on carbon, but ethyl has the higher priority because of the second carbon atom attached to the first. The conformations shown here have the hydrogen atom of lowest priority at the back; if a structure were shown that did not have the hydrogen atom at the back, it would be necessary to rotate the molecule round any of the bonds except the C–H bond, to bring the H atom to the back. Going round the groups from Br > Et > Me shows an anti-clockwise sense for the isomer on the left; therefore this is the (*S*) enantiomer. In the product on the right, OH > Et > Me has a clockwise sense, so this is the (*R*) enantiomer.

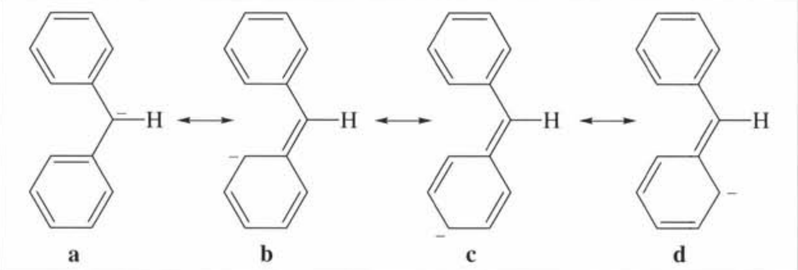
3.10. All the L-α-amino acids shown in Figure 3.7 have NH_2 as the highest and H as the lowest priority groups. For almost all the α-amino acids, the CO_2H group takes precedence over the R group (also carbon atom centred) because of the two oxygen atoms attached to the carbon atom in the CO_2H group, giving the (*S*) configuration. In cysteine, $R=CH_2SH$, with a sulfur attached to carbon. Since sulfur has a higher atomic number than oxygen, CH_2SH will take priority over CO_2H. This reverses the priorities of these two groups, so the molecule will have the opposite configuration, on this convention, *i.e.* (*R*).

3.11. In **X**, all the chlorine atoms are equatorial, so there is no hydrogen attached to an adjacent carbon atom in the *anti* conformation (the ring bonds are occupying this 180° dihedral angle orientation). Thus, with no favourable *anti* conformation available, reaction will be slow. The situation would not be improved if the molecule were to flip to the alternative chair conformation with all Cl atoms axial, since here all the *anti* positions would be occupied by chlorine atoms. **Y** has two axial chlorine atoms each with an adjacent axial hydrogen atom in an *anti* conformation, so reaction is faster. **Z** has two axial chlorine atoms, each with two adjacent axial hydrogen atoms in an *anti* conformation, so there are more possibilities for *anti* elimination, and reaction is faster still.

Chapter 4

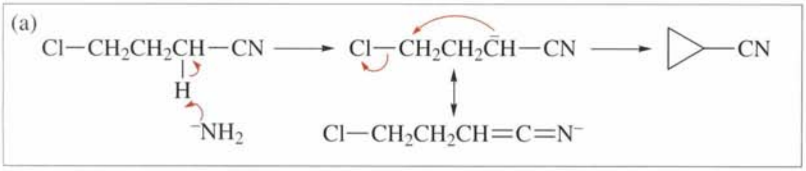
4.1. See Sections 4.1, 4.2, 4.3 and 4.3.3 for definitions; alternatively, look in the index for relevant page numbers. The main types of reactions of carbanions and carbenes are listed in Section 4.3.3.

4.2. The three possible structures for the Ph_2CH^- anion with a negative charge on one of the benzene rings are shown as **b**, **c** and **d**. Similar structures can be drawn with the charge on the other ring, making seven structures altogether, including **a** which has the charge on the central atom. The Ph_3C^- anion has three benzene rings, hence 10 structures, three for each ring and one with the charge on the central carbon atom. Thus Ph_3C^- is more stabilized and Ph_3CH is more acidic than Ph_2CH_2. *Structures with alternative dispositions of the double bonds in uncharged rings will not contribute to extra stabilization of anions, since these structures are also available for the parent hydrocarbons.*

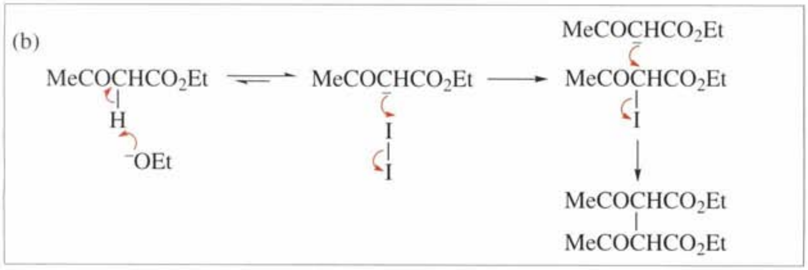


4.3. Loss of a proton from CH_3CH_3 gives the alkyl anion $CH_3CH_2^-$. This has the charge on the not-very-electronegative carbon atom and no stabilization by delocalization. Thus CH_3CH_3 is an extremely weak acid. For CH_3COCH_3, the anion $CH_3COCH_2^-$ is delocalized, with one structure having the charge on the electronegative oxygen atom. Thus this anion is stabilized and CH_3COCH_3, though a weak acid, is much stronger than CH_3CH_3. CH_3CO_2Et has an intermediate acidity. Although the anion $^-CH_2CO_2Et$ has a structure analogous to that of $CH_3COCH_2^-$ with a negative charge on oxygen, the parent ester is stabilized by the structure $CH_3C(O^-)=\overset{+}{O}Et$ (similar to **9**), which decreases the *extra* stabilization in the ion.

4.4. (a) The first step involves abstraction of a proton from the chloronitrile by the strong base NH_2^-. The proton is abstracted from the carbon next to the nitrile group because the resultant anion is stabilized. The anion undergoes an internal nucleophilic substitution, closing the ring and expelling the chloride anion:

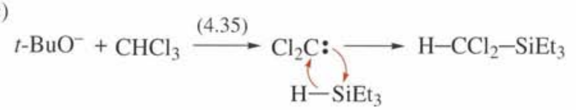


(b) The first step involves abstraction of a proton from the keto ester by the strong base EtO^-. As in (a) the proton is abstracted from the position which gives the most stable anion. The anion reacts by a S_N2 reaction with the iodine molecule to give the iodinated intermediate, which in turn undergoes a S_N2 reaction with the anion to give the dimeric product, with the displacement of an iodide anion:



(c) Dichlorocarbene is formed as in reaction (4.35). This reacts by insertion into the reactive Si–H bond:

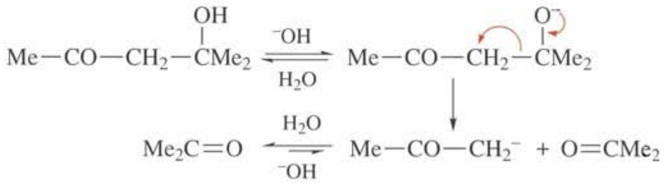
(c)



4.5. (a) The three reactions prior to the rate-determining step are all reversible, so the hydroxynitrile anion **A** will be formed with an equilibrium concentration proportional to the two reagents, *i.e.* [PhCHO][CN^-]. The overall kinetics will be determined by the rate-determining step, with a kinetic dependence on [**A**][PhCHO] or $[PhCHO]^2[CN^-]$, third order overall.

(b) The carbanion **A** is stabilized, with a structure involving negative charge on the nitrogen atom [compare Problem 4.4(a)]. No such stabilization is available for the corresponding hydroxide adduct, so although the hydroxide ion adds reversibly to the carbonyl group, an anion analogous to **A** cannot be formed, and the condensation cannot take place.

4.6. The reaction is likely to be a reverse of the aldol condensation (*e.g.* reaction 4.20). The first step involves equilibration of the keto alcohol with its anion. This is followed by a rate-determining fragmentation of the anion to acetone and the acetone anion, which will rapidly be converted by water into a second acetone molecule. Since the second step will be rate determining, the rate will be proportional to the concentration of the anion formed in the first step, which will be proportional to $[OH^-][Me_2C(OH)CH_2COMe]$:



Chapter 5

5.1. Electrophiles: HBr, I_2, H_2O, H_3O^+, NO_2^+, MeOH, $AlCl_3$, Me_3C^+, $C_6H_6NO_2^+$.

Nucleophiles: $CH_2{=}CH_2$, OH^-, H_2O, Me_2O, MeOH, PhO^-, $C_5H_5^-$.

Carbocations: Me_3C^+, $C_6H_6NO_2^+$.

Cations: Na^+, H_3O^+, NO_2^+, Me_3C^+, $C_6H_6NO_2^+$.

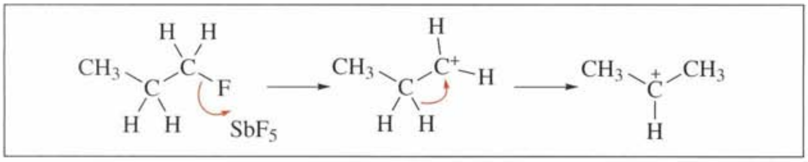
5.2. $Me_2(Ph)CBr$ will react more rapidly in S_N1 reactions. The intermediate tertiary carbocation is further stabilized by delocalization of the positive charge onto the *ortho* and *para* positions on the benzene ring, which will lower the activation energy required for its formation.

5.3. Reaction (a) involves the S_N1 hydrolysis of a tertiary bromide. The planar tertiary carbocation formed as an intermediate is stabilized by the three alkyl substituents. The S_N1 hydrolysis of 1-bromoadamantane in (b) would lead to a cation that could not have coplanar geometry at the carbocation centre. The cation would therefore have a high energy, and the reaction is very slow.

5.4. The presence in the products of compounds with both rearranged and unrearranged carbon skeletons suggests that a carbocation intermediate is formed. Anionic or radical intermediates do not normally rearrange. The mechanism is likely to involve the reaction of $PhCHMe{-}CHMeNH_2$ with HNO_2 to give $PhCHMe{-}CHMe^+$. This will give $PhCHMe{-}CHMeOAc$ by reaction with an acetic acid molecule. Rearrangement of the carbocation by a 1,2-hydrogen or -methyl shift will give the rearranged cations $PhMeC^+{-}CH_2Me$ or $Ph\overset{+}{C}H{-}CHMe_2$, respectively, which react with acetic acid to give $PhCMe(OAc){-}CH_2Me$ and $PhCH(OAc){-}CHMe_2$.

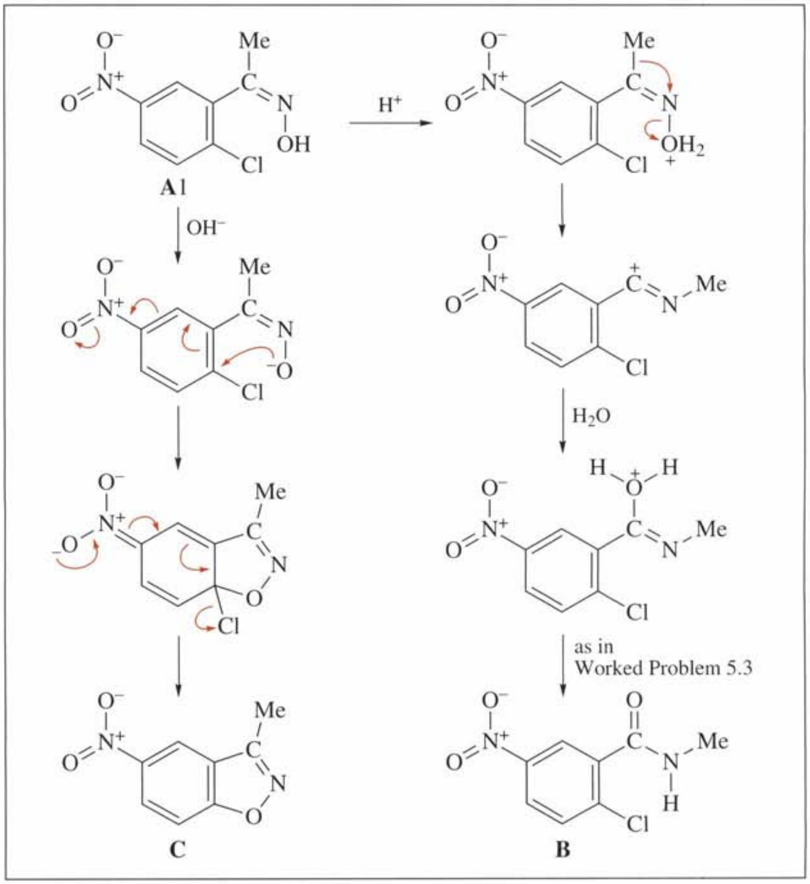
Carbocations rearrange readily, but carbanions and radicals do not rearrange so readily, so an intermediate of these types is much less likely. See Box 5.1. Anionic intermediates are very unlikely in acid solutions.

5.5. 1-Fluoropropane reacts with SbF_5 as shown below:



SbF_5 is a Lewis acid and can form a strong bond to another fluorine atom: the fluorine atom leaves the 1-fluoropropane with the electron pair from the bond, leaving behind the *n*-propyl (prop-1-yl) cation. This is a primary cation, which quickly rearranges by a proton shift to give the more stable prop-2-yl cation (a typical carbocation rearrangement). The secondary carbon bearing the formal charge is highly deshielding, so the attached proton shows its NMR peak at the very high δ value of 13.5 ppm. It is split into a septet by the six hydrogen atoms of the two adjacent methyl groups. The methyl hydrogens are not directly attached to a formally positively charged carbon atom, so the deshielding is less, but still significant. The peak is split into two by the single proton on the adjacent carbon atom. The intensity for the six protons is six times that of the single C–H proton. The coupling constants are the same because in a $H_a{-}C{-}C{-}H_b$ system the influence of H_a on H_b through the two carbons is the same as that of H_b on H_a.

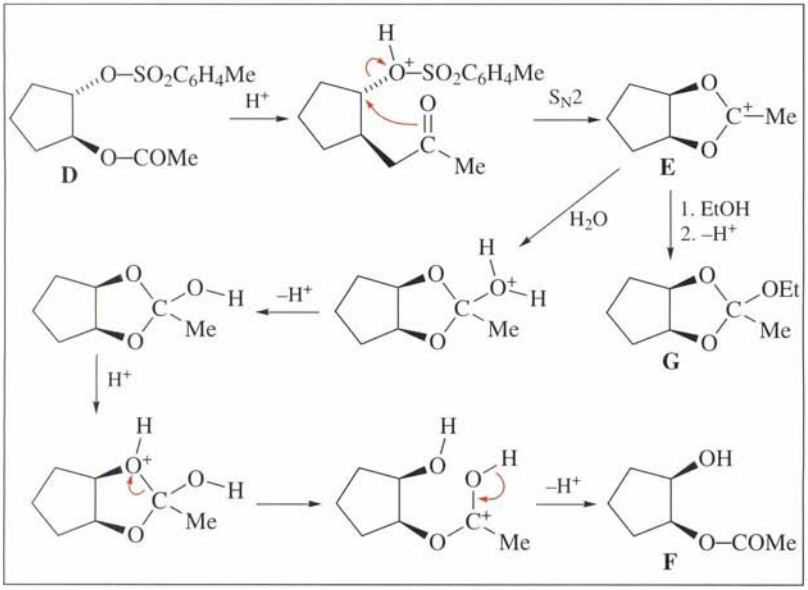
5.6. Mechanisms:



The oxime must have the structure **A1**, since ring closure takes place in the presence of base to give **C** by a nucleophilic substitution reaction. In the other isomer, the oxime oxygen atom would be too far away from the C–Cl bond for ring closure to be possible. This allowed the stereochemistry of these oxime isomers to be established long before X-ray analysis was available. The acid-catalysed rearrangement starts with the protonation of the oxime OH group. The resulting cation loses a water molecule in the second step. If the N–O bond were the only one to break, a very unstable NR_2^+ intermediate would be formed: most unlikely, and if it did, a mixture of amides would be expected from a symmetrical intermediate. Thus the methyl group migrates synchronously with the loss of the water molecule, giving the rearranged carbocation, which is converted by addition of water and proton shifts into the observed amide **B**.

This experiment shows that the group *trans* to the OH group in the oxime is the one that migrates in the Beckmann rearrangement.

5.7. Mechanism:

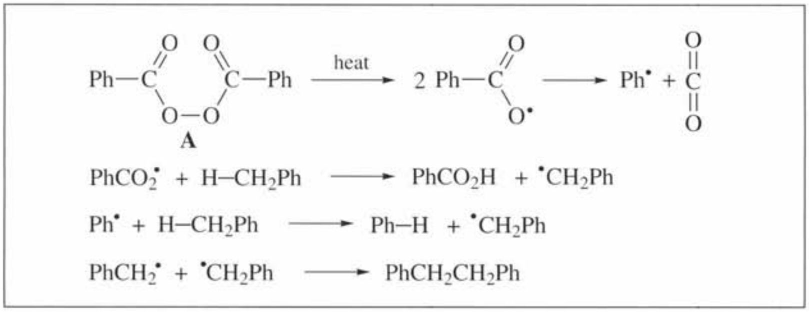


The first step is protonation. The second step is the displacement by the carbonyl oxygen of the $HOSO_2C_6H_4Me$ group by a S_N2 process to give **E**. Since it is an S_N2 reaction, the stereochemistry of the carbon is inverted. The new bond is formed from the top as the sulfonic acid leaves from the bottom. The remaining steps to give the product are typical of ester hydrolysis and involve no further possibility of stereochemical change on the cyclopentane ring, since no reaction takes place at either of the chiral carbon atoms.

To establish if the reaction is acid catalysed, carry out the reaction in the presence of different concentrations of acetic acid. If there is no acid catalysis, there will be no change in rate. If the rate is affected by acid concentration, try the reaction in buffer solutions of acetic acid/sodium acetate with a fixed ratio of [HOAc]/AcO^-]. This will keep [H_3O^+] constant, so if the reaction is specifically catalysed by H_3O^+, there will be no change in rate. If the increase in buffer concentration does cause an increase in rate, the reaction is subject to general acid catalysis, with a kinetic term involving [HOAc] as well as one involving [H_3O^+]. If ethanol is added to the mixture, **G** will be formed by the nucleophilic ethanol trapping the carbocation **E**.

Chapter 6

6.1. Mechanism:



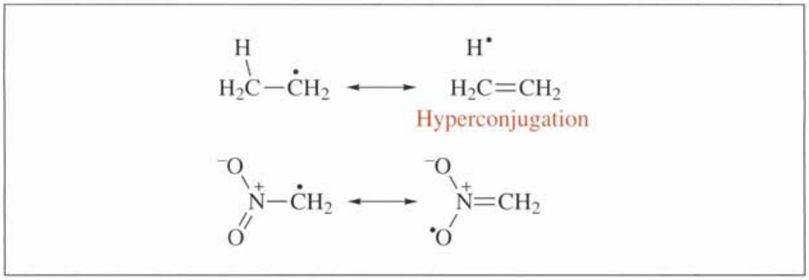
$PhCO_2^\bullet + H\text{–}CH_2Ph \longrightarrow PhCO_2H + {}^\bullet CH_2Ph$

$Ph^\bullet + H\text{–}CH_2Ph \longrightarrow Ph\text{–}H + {}^\bullet CH_2Ph$

$PhCH_2^\bullet + {}^\bullet CH_2Ph \longrightarrow PhCH_2CH_2Ph$

Homolysis of the weak O–O bond in the peroxide **A** gives two benzoyloxyl radicals. These will either fragment to give the phenyl radical and carbon dioxide, or abstract a hydrogen atom from the methyl group of a toluene molecule to give the stabilized benzyl radical and benzoic acid. The unstable phenyl radical will also readily abstract a hydrogen atom from toluene molecule to give the stabilized benzyl radical and benzene. The stabilized benzyl radicals have no radical-molecule reactions open to them, so they combine to give 1,2-diphenylethane.

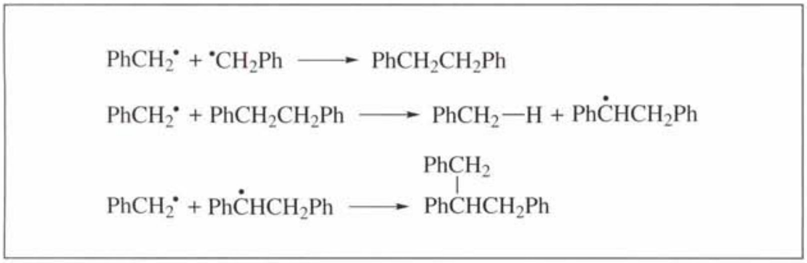
6.2. The following structures can contribute:



The diagrams refer to a substituted methyl radical, but similar stabilization would be available for any radical where the radical is conjugated with the reaction centre.

6.3. Although structures **B1** and **B2** can be written for the phenyl radical, two similar structures can be written for the benzene molecule, so there is no extra stabilization obtained when benzene loses a hydrogen atom to give the phenyl radical. No structures can be written where the unpaired electron is on a different atom, so the electron is localized in the sp^2 orbital on one carbon atom.

6.4. Mechanism:



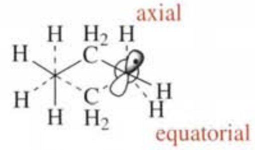
$$\begin{aligned}
\mathrm{PhCH_2^{\bullet}} + {}^{\bullet}\mathrm{CH_2Ph} &\longrightarrow \mathrm{PhCH_2CH_2Ph} \\
\mathrm{PhCH_2^{\bullet}} + \mathrm{PhCH_2CH_2Ph} &\longrightarrow \mathrm{PhCH_2{-}H} + \mathrm{Ph\dot{C}HCH_2Ph} \\
\mathrm{PhCH_2^{\bullet}} + \mathrm{Ph\dot{C}HCH_2Ph} &\longrightarrow \mathrm{Ph\overset{\overset{\textstyle PhCH_2}{|}}{C}HCH_2Ph}
\end{aligned}$$

Add 1,2-diphenylethane to the reaction mixture. This should increase the amount of 1,2,3-triphenylpropane produced. Alternatively, add a thiol or other radical trap. This should cut down the amount of both 1,2-diphenylethane and 1,2,3-triphenylpropane.

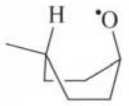
6.5. Mechanism:

$$\begin{aligned}
t\text{-Bu–O–O–Bu-}t &\longrightarrow 2t\text{-Bu–O}^{\bullet} \\
\text{PhS–H} + {}^{\bullet}\text{O–Bu-}t &\longrightarrow \text{PhS}^{\bullet} + \text{H–O–Bu-}t \\
&\left.\begin{aligned}
\text{PhS}^{\bullet} + \text{CH}_2\text{=CMe}_2 &\longrightarrow \text{PhS–CH}_2\text{–}\dot{\text{C}}\text{Me}_2 \\
\text{PhS–CH}_2\text{–}\dot{\text{C}}\text{Me}_2 + \text{PhS–H} &\longrightarrow \text{PhS–CH}_2\text{–CHMe}_2 + \text{PhS}^{\bullet}
\end{aligned}\right\}\text{Propagation}
\end{aligned}$$

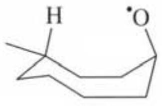
6.6. The doublet is from the C–H at the radical centre, with a coupling constant similar to other alkyl radicals. The cyclohexyl radical will be expected to have the normal chair conformation, though with an sp^2 hybridized radical centre. A Newman projection (below) looking from C1 to either C2 or C6 will show an axial hydrogen nearly eclipsing the p orbital with the unpaired electron, giving a large coupling constant, and an equatorial C–H with a dihedral angle close to 90°, giving a very small coupling constant. There will be two equivalent hydrogens of both types, giving triplets.



6.7. Abstraction of H4 in the cyclohexyloxyl radical from **C** would require the boat conformation **C′**, which is a very high-energy conformation. Cyclooctane is much more flexible, with considerable rotation round the C–C bonds, and conformations such as **E′** will be significant, allowing hydrogen abstraction to take place.

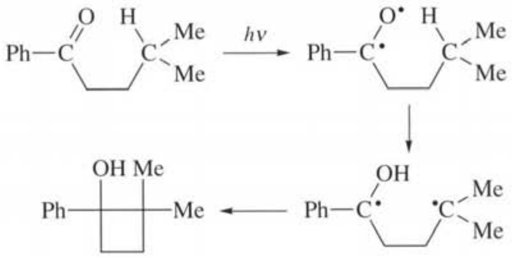


C′



E′

6.8. Mechanism:



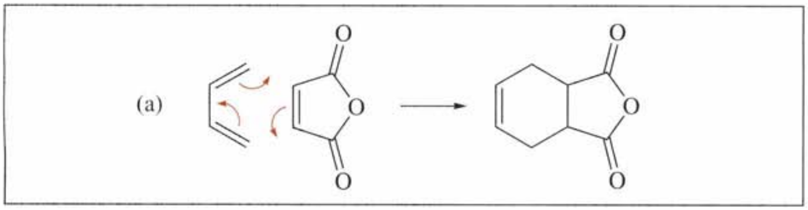
Chapter 7

7.1. Define frontier orbitals as in Section 7.1 and (referring to Figure 7.7 if necessary) establish that the HOMO of buta-1,3-diene has opposite phases at the end of its π system, as does the LUMO of ethene. Thus when these two molecules react in a cycloaddition, the phases match at both ends, giving favourable interactions. For two ethene molecules the HOMO has the same phase at the two ends but the LUMO has opposite phases, so there will be a favourable interaction at one end but unfavourable at the other.

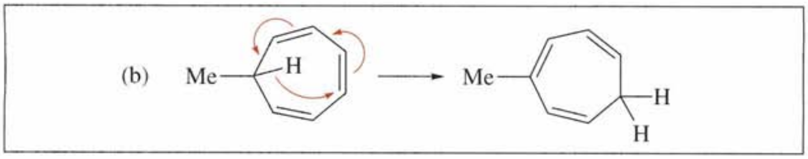
7.2. In an entirely suprafacial system, there is positive overlap between all next-neighbour orbitals in the cyclic transition state. This will be delocalized, with a uniquely favourable molecular orbital with positive overlap all the way around the ring, which can hold two electrons. Higher orbitals occur in pairs (see Figures 7.10 and 7.13), holding four electrons in each level. Thus stabilization of the transition state (and rapid reaction) will take place if $4n+2$ electrons (the Hückel number) are involved. If there is a change in phase in the cyclic overlap (an antarafacial component), there is no uniquely favourable orbital, and since the orbitals occur in pairs with the same energy, $4n$ electrons will be favourable for these Möbius systems. See Section 7.2.

7.3. In thermal reactions, HOMO–LUMO interactions are the most important, for the reasons expounded in Answer 7.1. In photochemical reactions, since an electron has been promoted, HOMO–"HOMO" and LUMO–"LUMO" interactions will be favourable, and since the energy gap is small or zero, these interactions will dominate. Thus for reactions that have the wrong number of electrons for a thermal reaction, the photochemical reaction will take place; conversely, if the correct number of electrons for a thermal reaction is present, the photochemical reaction will not take place.

7.4. (a) Cycloaddition, six electrons, entirely suprafacial, thermally allowed:

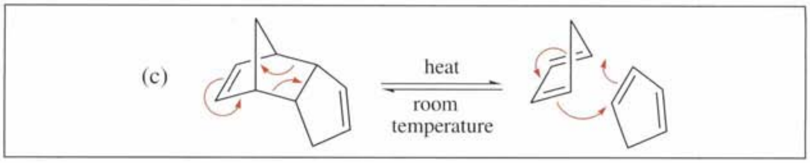


(b) [1,5] sigmatropic reaction. Six electrons, so suprafacial process involving migration of the hydrogen atom is thermally allowed:



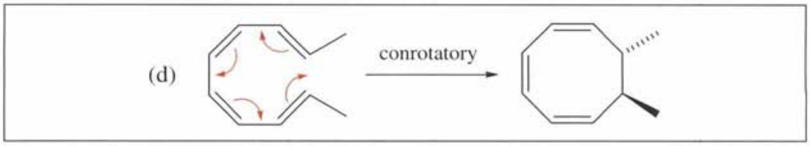
The other isomer would come from a [1,7] shift. This would be allowed for an antarafacial shift, but would be impossible geometrically.

(c) Reverse of cycloaddition, six electrons, suprafacial, so thermally allowed:



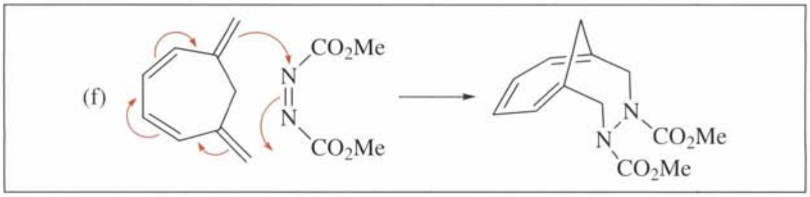
Proceeds to the right on heating (more entropy), but the reaction reverses at room temperature [favoured by energy (enthalpy)]. The pathway of an elementary reaction must be the same in both directions (microscopic reversibility).

(d) Electrocyclic ring closure. Eight electrons, so antarafacial component needed; hence conrotatory. Looking at the molecule from the right-hand side, both the terminal methyl groups point outwards. Conrotation in the clockwise sense will bring one up, the other down, as shown:

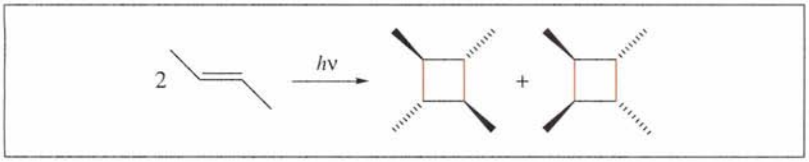


(e) Since the thermal reaction is conrotatory, the photochemical reaction must be disrotatory, giving the other (*cis*) isomer.

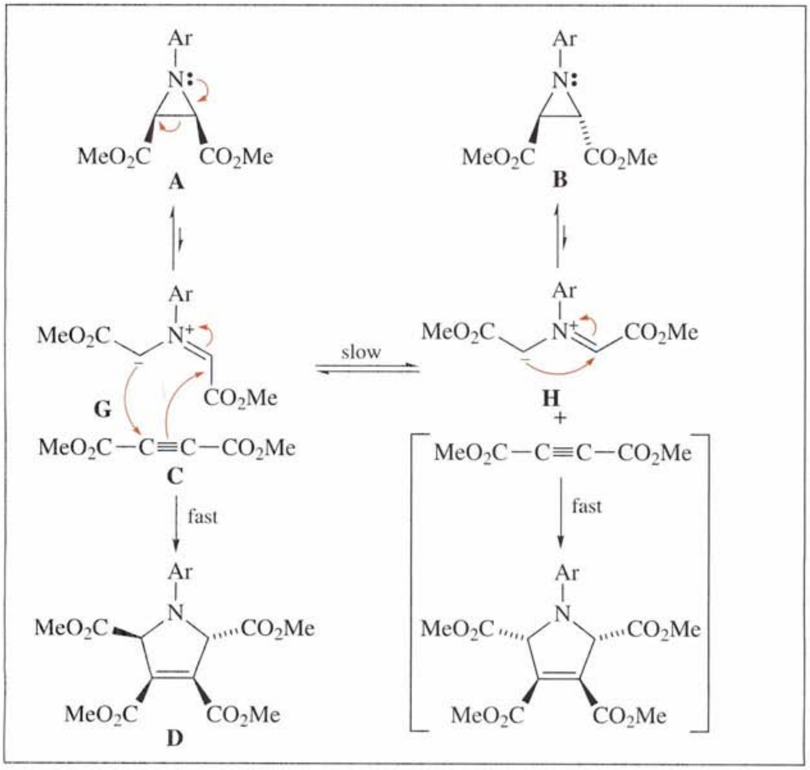
(f) Cycloaddition, 10 electrons, so suprafacial reaction allowed thermally:



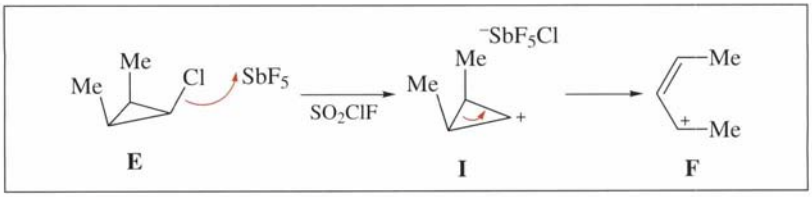
7.5. This photochemical four-electron process is suprafacial. The two but-2-ene molecules can approach each other in two ways; the two new bonds are shown in red.



7.6. The aziridine **A** undergoes a reversible electrocyclic ring opening on heating. Since four electrons are involved, this is conrotatory. The equilibrium favours the starting compound **A**. The open-chain product **G** slowly isomerizes to **H** by rotation about a C–N bond. Since **G** and **H** are stabilized by delocalization, whereas the transition state between them (in which one of the C–N bonds has been rotated through 90°) is not, there will be a considerable activation energy for this isomerization. **H** will rapidly undergo ring closure to give **B**. If **C** is present, a rapid six-electron cycloaddition takes place. The suprafacial attack preserves the orientation of the CO_2Me groups, giving **D**:



7.7. In the polar aprotic solvent SO_2ClF, SbF_5 abstracts a chloride ion from **E** to give the cyclopropyl cation **G**. This rapidly undergoes electrocyclic ring opening to give the cation **I**, whose stereochemistry is established by NMR. Since two electrons are involved in the ring opening, the reaction is disrotatory:



Subject Index

An increasing knowledge and understanding of organic reaction mechanisms has been a major factor in the rapid advance of organic chemistry, biochemistry and pharmacology in the last century. It therefore forms a vital part of today's chemistry courses.

Mechanisms in Organic Reactions helps students to make sensible proposals for the mechanisms of particular organic reactions, and then how to distinguish between different possible mechanisms. Techniques for this include product studies, kinetics, and the identification of intermediates. Three chapters on intermediates discuss likely points of attack on molecules by anions, radicals and cations, and the important role of acid- and base-catalysed reactions and radical chain reactions. The prediction of reaction rates and the effects of structural changes on reaction rate are also covered.

It concludes with a discussion of molecular reactions, both thermal and photochemical - reactions which provide deep and beautiful insights into the reasons why some reactions go and others do not, and why the majority of real-life reactions involve multi-step processes.

The book provides both illuminating insights into fundamental chemistry, and also practical value for students who will go on to teach, research, or be involved in other scientific roles (administration, policy making or journalism).

ISBN 0-85404-642-9

9 780854 046423 >