Intermediate Organic Chemistry

B D Pearson

Butterworths

Pearson

Intermediate Organic Chemistry

Intermediate Organic Chemistry

B. D. PEARSON, B.SC., PH.D., F.R.I.C.
Central Institute of Technology,
Petone, New Zealand
(Formerly Senior Lecturer in Organic Chemistry,
Derby and District College of Technology)

LONDON
BUTTERWORTHS

THE BUTTERWORTH GROUP

ENGLAND
Butterworth & Co (Publishers) Ltd
London: 88 Kingsway, WC2B 6AB

AUSTRALIA
Butterworth & Co (Australia) Ltd
Sydney: 20 Loftus Street
Melbourne: 343 Little Collins Street
Brisbane: 240 Queen Street

CANADA
Butterworth & Co (Canada) Ltd
Toronto: 14 Curity Avenue, 374

NEW ZEALAND
Butterworth & Co (New Zealand) Ltd
Wellington: 49/51 Ballance Street
Auckland: 35 High Street

SOUTH AFRICA
Butterworth & Co (South [illegible]
Durban: 33/35 Beach Grove

First published 1970

Suggested U.D.C. No.: 547
ISBN 0 408 70041 6
Filmset and Printed in England by Page Bros. (Norwich) Ltd., Norwich

Preface

In the past twenty-five years the products of organic chemistry have been increasingly encountered by the community at large. Polymers, plastics, pesticides and the wonder-drugs have all become part of everyday life. The products of organic chemistry are seen in objects as diverse as carpets, containers, drain-pipes and shoes.

Organic chemistry encompasses very many disciplines, e.g. biochemistry, food, rubber and textile chemistry. Its practice demands the cooperation of a variety of skills. The postgraduate research worker, the graduate development chemist, the skilled technician, the librarian, the plant-worker and many others all have a part to play.

The skilled technician plays a number of important roles, e.g. the maintenance of analytical services, quality control, technical services, assistance with research, etc. The trainee technician usually starts an H.N.C. or H.N.D. course having already obtained two 'A' Level passes at school or an O.N.C. by part-time study. The Higher National course provides a general course of study for the field in which the technician is working. In many cases he will then complete his formal education (for the time being?) with a supplementary course in Analytical Techniques or another field. With a good H.N.C. he may leave the technician ranks by working for the Grad. R.I.C. examination.

In the author's experience, textbooks for the Honours degree standard are not particularly satisfactory for the average H.N.C. student, since they provide far more than the required amount of information. By the very nature of his part-time study the Higher National student has little time for general reading. In this text the author has tried to provide a reasonable balance between factual information and theory, as appropriate to the H.N.C. standard. A prior knowledge of organic chemistry to 'A' Level or O.N.C. standard is assumed.

In the first three chapters the framework of organic chemistry is developed—chemical bonding, elementary stereochemistry and reaction mechanisms. Elementary spectroscopy of organic molecules is considered in Chapter 4 and the reactions and formation of bonds between carbon and other elements in Chapters 5–10, i.e. the C—H C—Hal, C—O, C—N and C—S bonds. No attempt has been made to differentiate between aliphatic and aromatic compounds but emphasis has been laid on the hybridisation state of the carbon atom forming the bond. Interaction between adjacent groups is considered in Chapters 11 and 12, and the stereochemistry of more complex molecules in Chapter 13. Simple heterocyclic compounds are covered in Chapter 14, mainly from the viewpoint of the effect of the electronegativity of the heteroatom on the aromatic properties of the ring system. Important naturally occurring compounds, i.e. carbohydrates, proteins and lipids (Chapter 15) and polymers (Chapter 16) have been briefly considered. In many parts of the text a number of reactions have been combined into a single reaction scheme. Whilst this helps to emphasize the comparative aspects of organic chemistry it does lead to over-simplification in some cases. Some problems of Higher National standard and suggested references for further reading are included at the end of the book. No details of practical methods of synthesis, etc., have been included as the student at this level will almost certainly pursue a parallel course of practical work.

Whilst the text is specifically intended for students preparing for Higher National examinations it should also be of value for other courses of study, e.g. University or C.N.A.A. B.Sc (Ordinary) degrees or courses where organic chemistry is an ancillary subject to another Honours subject. Much of the material required for the Grad. R.I.C., Part I, and Parts I and II of the B.Sc. General (London–External) examinations is also included. Students preparing for University Scholarship examinations should find the first three chapters and parts of Chapter 5–10 of value.

The author is indebted to his wife for help with the preparation of the manuscript and many of the figures and to Drs. A. W. Bamford, C. D. Johnson and R. A. Knaust for reading the manuscript and providing many valuable suggestions.

B. D. Pearson

Contents

1

Chemical Bonding in Organic Molecules

INTRODUCTION

The study of organic chemistry is largely a consideration of the properties of covalent bonds between carbon and other elements. In this chapter the polarisation and polarisability of C—X bonds is briefly discussed. This is followed by a description of hydridisation and the resulting geometrical arrangement of bonds between carbon, nitrogen, oxygen and other elements. Using these ideas the electronic structures of some simple molecules can be described and the electrical interactions, i.e. inductive and mesomeric effects, between atoms and groups considered. Lastly the effects of polarisation and other bonding forces between molecules are considered in relation to observed physical properties.

1.1 POLARISATION AND POLARISABILITY OF BONDS

Carbon lies at the middle of the Periodic Table. To form ionic bonds carbon would have to either gain or lose four electrons to produce the ions $C^{4\ominus}$ or $C^{4\oplus}$. The formation of either of these ions has a very large energy requirement, which is not recouped in the binding energy of the ionic structure, and so carbon shares electrons with other elements and thus forms covalent bonds.

Two atoms joined together by a covalent bond share a pair of electrons. If the two atoms are different, or are similar but joined to different groups, then the pair of bonding electrons will not be equally shared. One of the atoms will acquire a small positive charge and the other a small negative charge. The bond is then said to be polarised and may be written as $\overset{\delta\oplus}{X}—\overset{\delta\ominus}{Y}$. Three types of bond can be envisaged:

(1) $H_3C—CH_3$	similar atoms joined to similar groups—equal sharing of the bonding electrons,
(2) $H_3C—OH$	different atoms—unequal sharing of the bonding electrons,
(3) $H_3C—CH_2OH$	similar atoms joined to different groups—unequal sharing of the bonding electrons.

In simple molecules, such as diatomic molecules, the bond between the atoms will possess polar character if the atoms have different affinities for electrons, i.e. different electronegativities. Relative electronegativities for the typical elements of the Periodic Table are given below. Fluorine is the most electronegative element.

			H 2·1			
Li 1·0	Be 1·5	B 2·0	C 2·60	N 3·05	O 3·50	F 3·90
Na 0·9	Mg 1·2	Al 1·5	Si 1·9	P 2·5	S 2·60	Cl 3·15

The numerical electronegativity values should only be considered as approximate but nevertheless form a useful guide.

It is interesting to consider the effect of bond polarisation and atomic size on chemical reactivity. The carbon–halogen bonds form a useful series where the order of electronegativity of the halogens is:

$$\underset{3{\cdot}90}{\mathrm{F}} > \underset{3{\cdot}15}{\mathrm{Cl}} > \underset{2{\cdot}95}{\mathrm{Br}} > \underset{2{\cdot}65}{\mathrm{I}}$$

The carbon–fluorine bond is the most polarised of the four carbon–halogen bonds.

$$\overset{\delta\oplus}{\mathrm{C}}\text{——}\overset{\delta\ominus}{\mathrm{F}} > \overset{\delta\oplus}{\mathrm{C}}\text{——}\overset{\delta\oplus}{\mathrm{Cl}} > \overset{\delta\oplus}{\mathrm{C}}\text{——}\overset{\delta\ominus}{\mathrm{Br}} > \overset{\delta\oplus}{\mathrm{C}}\text{——}\overset{\delta\ominus}{\mathrm{I}}$$

Evidence for bond polarisation can be obtained from dipole moments. In a non-polar molecule the centre of negative charge can be considered to coincide with the centre of positive charge. However, in a polar molecule the two centres of charge (of magnitude e, e.s.u) are separated by a distance d, Å*, and the dipole moment, μ (in Debye units, D) is given by:

$$\mu = e \times d \text{ Debye}$$

---

* 1 Å = 100 pm.

The dipole moments, bond lengths and bond dissociation energies for the carbon–halogen bonds in halomethanes are given in *Table 1.1*. The C—F bond, although the most polar bond, is the least reactive of the four towards hydroxide ions in the reaction:

$$CH_3Hal + OH^{\ominus} \rightarrow CH_3OH + Hal^{\ominus}$$

Table 1.1. PROPERTIES OF THE C—Hal BOND IN HALOMETHANES

Bond	C—F	C—Cl	C—Br	C—I
Dipole moment, D	1·82*	1·87	1·79	1·64
Internuclear distance, Å	1·38	1·78	1·94	2·14
Bond dissociation energy, kJ/mol	448	335	280	222
Reactivity towards nucleophiles, e.g. OH$^{\ominus}$	increasing reactivity →			

* Fluorine compounds often show lower dipole moments than expected.

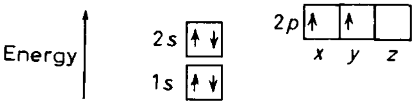
Indeed considerably more energy is required to break the C—F bond (448 kJ/mol) than the other carbon–halogen bonds. As a general rule it can be stated that the shortest bonds are the strongest and have the highest bond dissociation energies.

The carbon–fluorine bond is a short, rigid bond and so is not easily distorted by the approach of the reagent, i.e. the polarisability of the bond is low because the nucleus of the fluorine atom keeps the valency electrons firmly under its control. By comparison the carbon–iodine bond is easily distorted by the reagent, i.e. it has a high polarisability. Iodine is a large atom and the bonding electrons are shielded from the nucleus by 46 inner electrons. Polarisability is, therefore, proportional to atomic size. Bond polarisability is important because when a bond is easily distorted, by the approach of a reagent, the formation of the reaction transition state (Section 3.3) is facilitated. In other words when a bond is easily distorted the energy of activation for reaction is low.

1.2 COVALENT BONDS WITH CARBON—

(a) THE ELECTRONIC CONFIGURATION OF CARBON

The electronic configuration of the most stable state of carbon is:



↑ and ↓ represent the two possible spin orientations of an electron, ↓↑ represents opposed or paired electron spins.

The two electrons in the lowest energy level (1) are closest to the nucleus and in a spherically symmetrical (*s*) orbital (*Figure 1.1*). In the next highest energy level (2) a further two electrons are in an *s* orbital and two more electrons are in separate* *p* orbitals which have a somewhat higher energy than the 2*s* orbital. The 2*s* orbital is somewhat larger than the 1*s* orbital but of the same shape. The three possible *p* orbitals are arranged perpendicular to one another, i.e. directed along the *x*, *y* and *z* axes, and have dumb-bell like shapes (*Figure 1.1*).

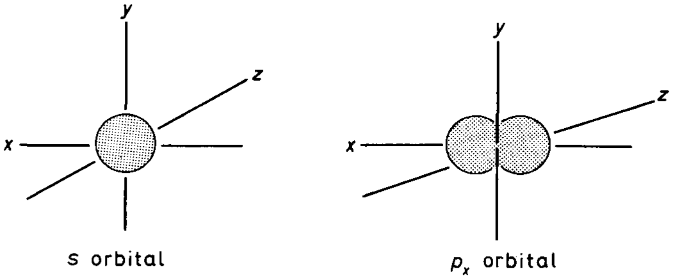


Figure 1.1. Approximate shapes of s *and* p *orbitals*

(b) THE FORMATION OF COVALENT BONDS BY OVERLAP OF ATOMIC ORBITALS

Pauli in 1925 put forward a statement which has become known as the Pauli Exclusion Principle—'only two electrons can occupy one atomic orbital and the two electrons must have opposite spins'. Thus a covalent bond can only be formed with two electrons having opposed spins (↑↓). Electrons with like spins repel one another.

The formation of a molecule such as methane or ethane can be imagined to involve the overlap of carbon atomic orbitals with hydrogen atomic orbitals (*Figure 1.2*). The dot and cross represent electrons of opposite spin. The degree, i.e. volume, of atomic orbital overlap is a measure of the strength of the bond; the greater the overlap the stronger the bond. In the new C—H molecular orbitals each electron has a greater volume in which to move than in its former atomic orbital. Less energy is required to constrain the electrons in their new molecular orbitals than in their former atomic orbitals and so the molecule is more stable than its component atoms.

---

* Hund's rule: electrons distribute themselves amongst a set of orbitals of the same energy so as to leave as many unpaired electrons as possible.

The combination of atoms into molecules evolves energy—the Heat of Reaction, and conversely the breakdown of a bond in a molecule requires energy—the Bond Dissociation Energy.

The overlap of atomic orbitals can take place in several ways. In the case of ethane the overlap of the two carbon atomic orbitals is directly along the bond axis. The resulting bond is termed a σ-bond and it is approximately cylindrical in shape, about the bond axis (*Figure 1.2*). The overlap of *p* atomic orbitals takes place parallel to, and above and below the bond axis as for example in ethylene or acetylene; this is termed a π-bond (*Figures 1.6* and *1.9*). The shapes, directional properties, etc., of bonds formed by carbon are best explained in terms of the hybridisation of atomic orbitals.

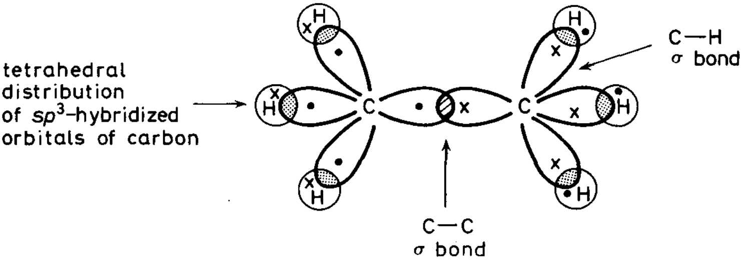


Figure 1.2. Formation of a σ bond between two sp^3*-hydridised carbon atoms in the molecule ethane,* $CH_3 \cdot CH_3$

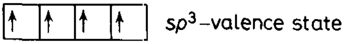
1.3. HYBRID ORBITALS OF CARBON, NITROGEN AND OXYGEN

Three types of hybridisation will be considered.

(a) sp^3-HYBRIDISATION

In the ground state carbon has the structure $(1s)^2$ $(2s)^2$ $(2p)^2$ which in no way explains the formation of a molecule such as methane, CH_4, where carbon has four chemically equivalent bonds to hydrogen atoms. To obtain four equivalent orbitals, that will produce bonds equal in strength and reactivity, it can be imagined that energy must first be supplied to raise carbon to a valence state. The addition of energy promotes an electron from the 2*s* to the 2*p* energy level:

The one *s* and three *p* orbitals are then mixed or hybridised to produce four equivalent hybrid orbitals:



This is termed the sp^3-hybridisation state of carbon.

Obviously the four hybrid orbitals will position themselves such that the repulsive forces between the orbitals are minimised. The formation of stronger hybridised bonds more than compensates for the energy required for electron promotion. The preferred shape for four bonds to be equally spaced is tetrahedral, i.e. where the four orbitals are directed towards the corners of a regular tetrahedron and the bond angles are 109·5° (*Figure 1.3*).

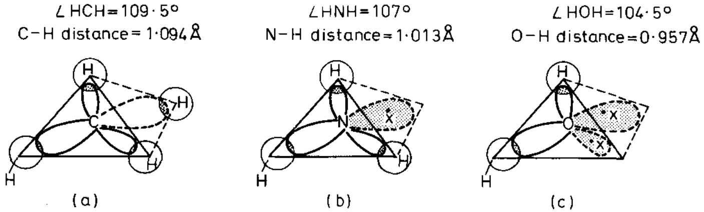


Figure 1.3. Tetrahedral arrangement of orbitals in the molecule (a) methane, (b) ammonia and (c) water

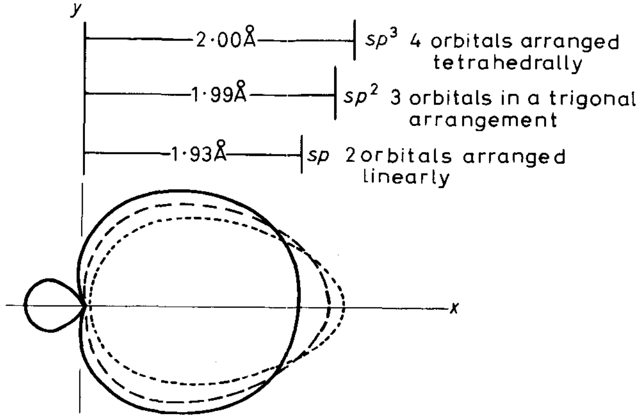
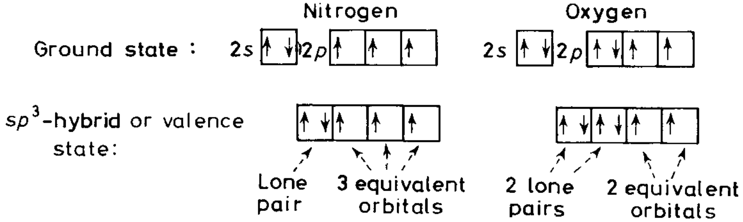


Figure 1.4. Representation of the shapes of sp^3, sp^2 *and* sp-*hydrid orbitals*

Although each sp^3-hybrid orbital is represented as a single lobe the shape is really more complex as shown in *Figure 1.4*. In practice the small rearward pointing lobe may be neglected. Thus in any carbon compound CX_4 the bond angles will be exactly 109·5°. When complete symmetry is lost, as in CX_3Y, slight deviations from the tetrahedral angle will occur, e.g. in bromomethane CH_3Br, the ∠HCBr is 107° 14′.

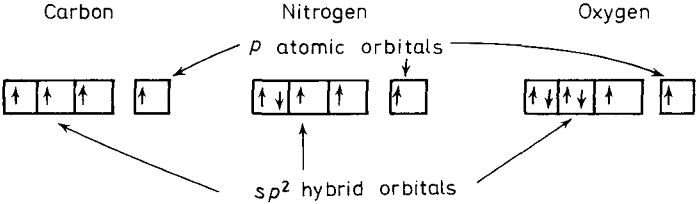
The concept of hybrid orbitals is not confined to carbon. Hybridisation of the sp^3 type can be put foward for nitrogen and oxygen.



sp^3-Hybridisation explains the shapes of nitrogen and oxygen compounds, such as ammonia and water which are approximately tetrahedral (*Figure 1.3*). Notice that in these two molecules lone pairs of electrons occupy hybrid orbitals.

(b) *sp*²-HYBRIDISATION

Just as the most stable electronic configuration of carbon does not provide for the formulation of the methane molecule neither does it provide an understanding of the structure of the ethylene molecule. One explanation is to use the concept of sp^2-hybridisation. This involves the production of three equivalent hybrid orbitals from one *s* and two *p* atomic orbitals:



In each case the three sp^2-hybrid orbitals lie in a plane with 120° between each orbital to minimise repulsion forces, i.e. a trigonal arrangement of the orbitals. The remaining *p* atomic orbital is situated with its axis at right angles to this plane (*Figure 1.5*).

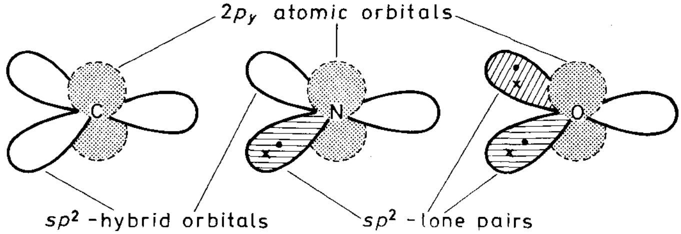


Figure 1.5. Representation of sp²*-hydridised carbon, nitrogen and oxygen atoms*

From the arrangements of orbitals in the sp^2-hybridisation state (*Figure 1.5*) the structure of double bonds can be explained.

(*i*) *The* >C=C< *bond of alkenes*

In a molecule such as ethylene the overlap of two sp^2-hybrid orbitals from two carbons atoms forms a σ-bond. The p atomic orbitals also overlap but to form a π-bond (*Figure 1.6*).

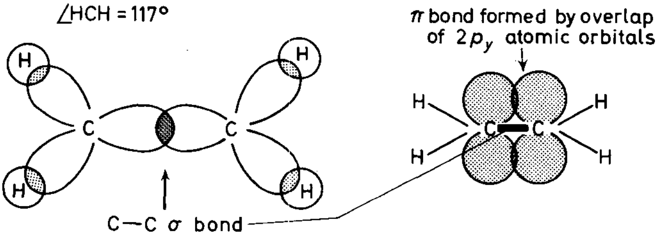
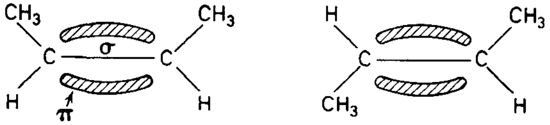


Figure 1.6. Structure of the ethylene molecule

The two carbon and four hydrogen atoms all lie in the same plane with the π-bond above and below this plane and situated parallel to the >C=C< σ-bond. The combination of the σ and π-bonds makes the >C=C< bond a rigid bond, i.e. the $=CH_2$ residues cannot rotate relative to one another and so *cis–trans* isomerism is possible:

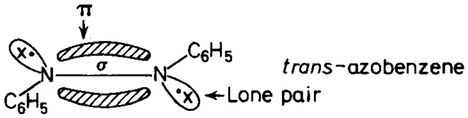


Cis and *trans*–2–butenes

The *trans* isomer cannot be converted to the *cis* isomer and vice versa, unless the π-bond is broken and then reformed.

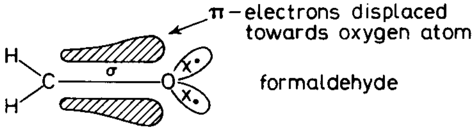
(*ii*) *The* >N=N< *bond of azo compounds*

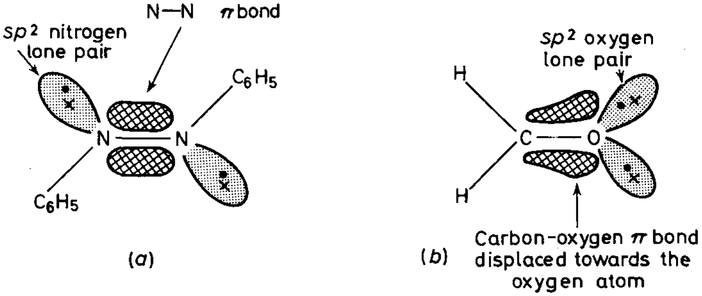
Azobenzene can also exist as *cis* and *trans* isomers because the azo linkage is comprised of a σ and a π-bond.



*(iii) The >C=O bond of carbonyl compounds**

A simple carbonyl compound such as formaldehyde can be represented with both the carbon and oxygen atoms in the sp^2-hybridisation state. As the oxygen atom is more electronegative than the carbon atom the electrons in both the σ and π-bonds are displaced towards the oxygen atoms.





(*a*) (*b*)

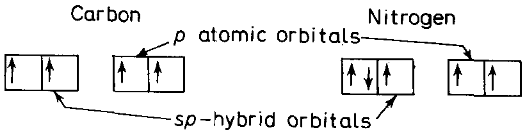
Figure 1.7. Structures of (a) trans-azobenzene and (b) formaldehyde

(c) *sp*-HYBRIDISATION

A third type of hybridisation for carbon and nitrogen is postulated to explain the formulation of triple bonds. This is *sp*-hybridisation in which two equivalent hybrid orbitals are produced from one *s* and one *p* atomic orbital:

---

* An alternative explanation of the structure of the carbonyl group is that the oxygen atom is in its most stable state—$(1s)^2$ $(2s)^2$ $(2p)^4$. This would mean that the lone pairs could be expected to have different properties and indeed there is some evidence to support this view. However, in water, alcohols, phenols and ethers the oxygen atom is probably sp^3-hybridised since the observed bond angles are closer to the tetrahedral value of 109·5° than the value of 90° required for the ground state configuration.



The two *sp*-hybrid orbitals assume a linear arrangement so that they become as far apart as possible. The two remaining *p* atomic orbitals are at right angles to each other and to the axis of the two linearly disposed hybrid orbitals. *sp*-Hybrid orbitals can be used to account for the structure (and properties) of compounds containing —C≡C— and —C≡N bonds.

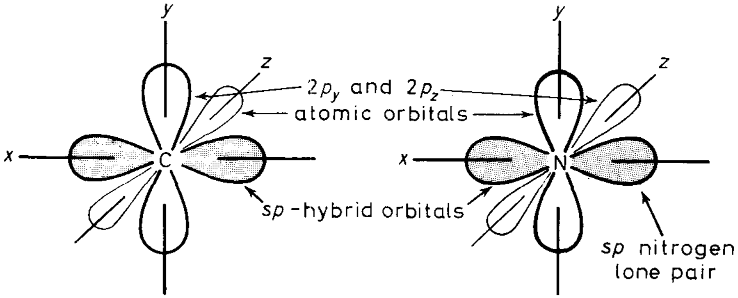


Figure 1.8. Representation of sp*-hybridised carbon and nitrogen atoms*

(*iv*) *The* —C≡C— *bond of alkynes*

In acetylene, the overlap of two *sp*-hybrid orbitals between two carbon atoms forms a σ-bond. The two p_y atomic orbitals overlap to form a π_y-bond and the p_z atomic orbitals similarly form a π_z-molecular orbital.

(*v*) *The* —C≡N *bond as in cyanomethane*

Again π_y and π_z-bonds are formed, together with a σ-bond, between the carbon and nitrogen atoms. The structure of cyanomethane is illustrated in *Figure 1.9b*.

A summary of the variation of bond lengths and bond energies of carbon, nitrogen and oxygen bonded to hydrogen is given in *Table 1.2*. Similar values for various carbon–carbon bonds are quoted in *Table 1.7*.

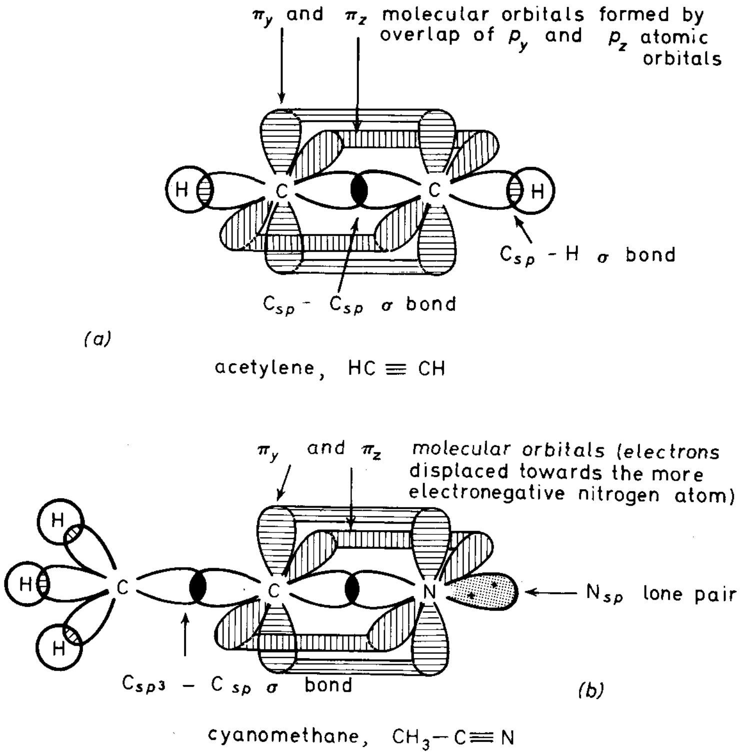


Figure 1.9. Representation of triple bonds in (a) acetylene and (b) cyanomethane

Table 1.2. LENGTHS AND DISSOCIATION ENERGIES OF BONDS BETWEEN HYDROGEN AND THE ELEMENTS CARBON, NITROGEN AND OXYGEN

Bond	*Hybridisation state*	*Percentage s character*	*Arrangement of bonds*	*Length* (Å)	*Bond energy* (*kJ/mol*)*
C—H	sp^3	25	Tetrahedral	1·094	406
N—H				1·013	431
O—H				0·957	494
C—H	sp^2	33	Trigonal	1·086	421
C—H	sp	50	Linear	1·057	458

* The SI unit of energy is the joule, which is related to the calorie by 1 cal = 4·184 J

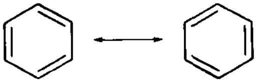
One unexpected consequence of the different hybridisation states is that for any element there is an apparent increase in electronegativity as the percentage of *s* character in the bond increases:

$$\xrightarrow[\text{Apparent decrease in electronegativity}]{X_{sp} > X_{sp^2} > X_{sp^3}}$$

However, this is simply a result of the different shapes of the hybrid orbitals (*Figure 1.4*). As the percentage of *s* character, i.e. spherical symmetry, in the hybrid orbital increases so the bonding electrons move closer to the atom X. This means that the bond length decreases and the bond dissociation energy increases. In the case of the carbon–hydrogen bonds the C_{sp}—H bond of alkynes is noticeably more acidic than the C_{sp^2}—H bond of alkenes because of this movement of the bonding electrons closer to the carbon atom with increasing *s* character. Thus hybridisation provides an interpretation of the properties of many bonds.

1.4 DELOCALISATION OF ELECTRONS IN MOLECULES

In the previous section it has been shown how the structures of some fairly simple molecules can be interpreted in terms of hybrid orbitals. Aromatic compounds form another particularly interesting case because they show a greater degree of resistance to substitution, addition and oxidation than their formal valence bond structures would suggest. The Kekulé structures:



showing alternate double and single bonds suggest that hydrogen bromide should add to benzene as it does to alkenes, i.e. benzene should react as a cyclohexatriene but in practice such behaviour is not observed.

All six carbon atoms of benzene are sp^2-hybridised, all bond lengths are equal, and the trigonal arrangement of the bonds is in agreement with the observed bond angles of 120° found in benzene. A feature of benzene not shown by the valence bond (Kekulé) structures is that the six *p* atomic orbitals from the carbon atoms all interact together to form a continuous π-molecular orbital extending all round the hexagonal structure. The six electrons from the *p*-atomic orbitals can thus move over the entire benzene ring and they are said to be delocalised. This degree of freedom for the electrons makes for a very stable structure.

The hybrid orbital structure for benzene (*Figure 1.10*) shows that there is no need to consider benzene as two resonating valence bond structures. Instead the two structures must be considered to

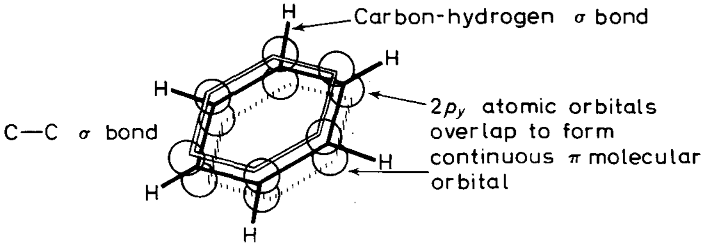
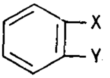
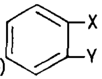
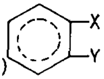


Figure 1.10. Representation of the structure of benzene

be simultaneously superimposed, i.e. Ia plus Ib. This explains the early observation that benzene produces only one *ortho* isomer and not two as inferred by the valence bond structures, Ia and Ib.

(Ia)


(Ib)


(II)


In normal practice benzene is represented by either of the structures Ia or Ib but it must be emphasised that these structures refer to a delocalised molecule. The representation II is really more accurate in the case of benzene but is usually retained for various intermediates encountered in the reactions of aromatic compounds. The delocalised electronic structure of benzene permits an explanation of how groups such as $-NH_2$, —OH, —Hal, $-NO_2$, —C=O and —C≡N interact with the π and σ-bonds and this is considered in the next section.

1.5 INDUCTIVE AND MESOMERIC EFFECTS

In aniline an sp^3-hybridised nitrogen atom is joined to an sp^2 carbon atom. The nitrogen atom is more electronegative than the carbon and so will have a greater share of the σ-bond electrons. The tendency of an atom, or group of atoms, to attract or repel electrons due to differences in electronegativity of the atoms forming the bond is called the Inductive Effect (I effect). In a bond C—X when X is more electronegative than carbon then X is said to exert a negative inductive effect (−I) which is represented as C→X. Conversely if X is less electronegative than carbon then it exerts a positive inductive effect (+I) represented as C←X.

The inductive effects of some commonly encountered groups are shown in *Table 1.3*. For convenience alkyl groups are included with the +I groups although the reasons for the electron releasing properties of alkyl groups are not completely understood.

Table 1.3. INDUCTIVE EFFECTS OF SOME ATOMS AND GROUPS

−I Groups (C$\gg$X)	*+I Groups* ($C \ll X$)
—Halogen (F > Cl > Br > I)	$—S^{\ominus}$, $—O^{\ominus}$, $—NH^{\ominus}$
$—NH_2$, $—NR_2$, etc.	—MgHal, —Na, —Li, etc.
$—\overset{\oplus}{N}H_3$, $—\overset{\oplus}{N}H_2R$, etc.	$—C(CH_3)_3 > —CH(CH_3)_2 > —CH_2CH_3 > —CH_3$
$—NO_2$, —NO	
—OH, $—OCH_3$, etc.	
$—\overset{\oplus}{O}H_2$, $—\overset{\oplus}{O}HR$	
$\rangle C{=}O$, $\rangle C{=}N—$, $—C{\equiv}N$	

(All relative to —H which is assumed to have no inductive effect.)

The nitrogen atom in aniline thus attracts electrons along the σ-bond by an effect termed the −I effect. However, the sp^3-hybridised lone pair of the nitrogen is of the correct symmetry to interact with the π-molecular orbital system of the benzene nucleus. This lone pair/π-electron system interaction is termed a Mesomeric Effect and can be positive or negative with the same meaning as for the inductive effect. The amino group of aniline releases some fraction of its lone pair to the π-molecular orbital system and so this is a +M effect and is represented by a curved arrow (see *Figure 1.11*).

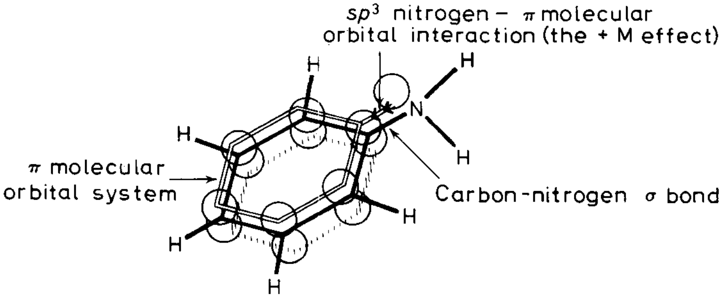


Figure 1.11. Representation of the structure of aniline

A mesomeric effect can occur between a π-molecular orbital system and a lone pair or between two π-molecular orbital systems. The mesomeric effects of a number of groups are given in *Table 1.4.*

(a) THE INDUCTIVE EFFECT

An inductive effect is not simply confined to the polarisation of the one bond C > X. The effect is transmitted to other carbon

Table 1.4. MESOMERIC EFFECTS OF SOME ATOMS AND GROUPS

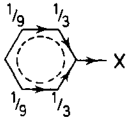
−M Groups $(C-\overset{\curvearrowright}{Y})$	*+M Groups* $(C-\overset{\curvearrowleft}{\ddot{Y}})$
$-NO_2$, $-NO$	—Halogen (F > Cl > Br > I)
$>C=O$, $>C=N-$, $-C\equiv N$	$-NH_2$, $-NR_2$, etc.
$-C\equiv C-$, $-\overset{\oplus}{N}\equiv N$	$-OH$, $-OCH_3$, etc. $-O^{\ominus}$, $-CH_3$

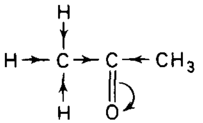
(Again relative to —H which has no mesomeric effect.) Electron release from a $-CH_3$ group to a π-electron system is often termed hyperconjugation.

atoms, probably through the σ-bonds but possibly by normal electrostatic forces. The inductive effect

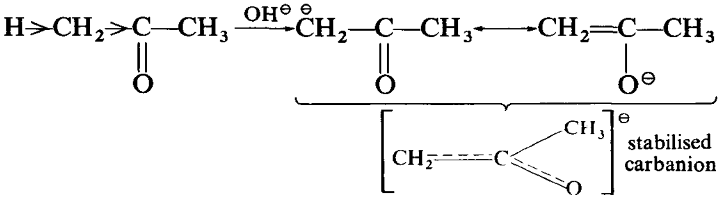
$$\underset{\frac{1}{9}}{\overset{\delta\oplus}{CH_3}}\rightarrow\underset{\frac{1}{3}}{\overset{\delta\oplus}{CH_2}}\rightarrow\!\!\rightarrow\underset{1}{\overset{\delta\oplus}{CH_2}}\rightarrow\!\!\rightarrow\!\!\rightarrow\overset{\delta\ominus}{Cl}$$

decreases rapidly with distance and is reduced by about one third at each carbon atom. After three carbon atoms the effect is negligible. Thus in 1-chloropropane if the effect is unity at the first carbon atom it will be about $\frac{1}{3}$ on the second carbon atom, etc. In a benzene ring the ortho positions suffer the greatest changes from the inductive effects of substituent groups.





An inductive effect is not confined to carbon–carbon bonds; electrons in carbon–hydrogen bonds will also be displaced as indicated in the acetone molecule above. A strong base can remove a weakly acidic hydrogen atom from acetone and produce a carbanion which is stabilised by delocalisation of the negative charge over the carbonyl group.*



$$H\rightarrow CH_2\rightarrow\underset{\underset{O}{\parallel}}{C}-CH_3\xrightarrow{OH^{\ominus}}\overset{\ominus}{C}H_2-\underset{\underset{O}{\parallel}}{C}-CH_3\longleftrightarrow CH_2=\underset{\underset{O^{\ominus}}{|}}{C}-CH_3$$

stabilised carbanion

---

* For other examples of stabilised ions see pages 127, 185, 209 and 221.

The magnitude of the inductive effect varies with the electronegativity of the atom or group, e.g.

$$\mathrm{F} > \overset{\oplus}{\mathrm{O}}\mathrm{H}_2 > \mathrm{OH} > \overset{\oplus}{\mathrm{N}}\mathrm{H}_3 > \mathrm{NH}_2$$

$$\mathrm{F} > \mathrm{Cl} > \mathrm{Br} > \mathrm{I}$$

$$\mathrm{C}_{sp} > \mathrm{C}_{sp^2} > \mathrm{C}_{sp^3}$$

$$\xrightarrow[\text{Decreasing negative inductive effect } (-\mathrm{I})]{\hspace{6cm}}$$

Several physical properties of organic compounds illustrate the importance of the inductive effect. The different dipole moments of the halomethanes have already been mentioned (page 3). The acidities of the α-halocarboxylic acids and the basicities of amines are other examples (*Table 1.5*).

Table 1.5. THE ACIDITIES OF α-HALOCARBOXYLIC ACIDS*

Acid	*Formula*	*I effect of α-substituent*	$K_A(\times 10^{-5})$
acetic acid	$\mathrm{H{-}CH_2COOH}$	0	1·84
propionic acid	$\mathrm{CH_3{-}CH_2COOH}$	+I	1·22
chloroacetic acid	$\mathrm{Cl{-}CH_2COOH}$	−I	155
bromoacetic acid	$\mathrm{Br{-}CH_2COOH}$	−I	138
iodoacetic acid	$\mathrm{I{-}CH_2COOH}$	−I	73
β-chloropropionic acid	$\mathrm{ClCH_2{-}CH_2COOH}$	−I	8·2
γ-chlorobutyric acid	$\mathrm{ClCH_2CH_2{-}CH_2COOH}$	−I	3·0
dichloroacetic acid	$\mathrm{Cl_2{-}CHCOOH}$	−I (×2)	5140
trichloroacetic acid	$\mathrm{Cl_3{-}CCOOH}$	−I (×3)	30000

* The acid dissociation constant, K_A, is the equilibrium constant, in aqueous solution, for the reaction:

$$\mathrm{HA} \rightleftharpoons \mathrm{H}^{\oplus} + \mathrm{A}^{\ominus}$$

$K_A = [\mathrm{H}^{\oplus}][\mathrm{A}^{\ominus}]/[\mathrm{HA}]$. Similarly the basic strengths of amines, K_B, correspond to the equilibrium constant of the reaction:

$$\mathrm{RNH_2} + \mathrm{H_2O} \rightleftharpoons \mathrm{R}\overset{\oplus}{\mathrm{N}}\mathrm{H_3} + \overset{\ominus}{\mathrm{O}}\mathrm{H}$$

$(K_A . K_B = 10^{-14})$.

The electronegative halogen atoms (a) attract the bonding electrons in the —O—H bond of the carboxyl group and (b) stabilise the carboxylate anion by spreading the negative charge. These two effects assist the formation of the carboxylate anion and so aid the dissociation process. The K_A values increase with the magnitude of the −I effect. Electron releasing groups have the reverse effects.

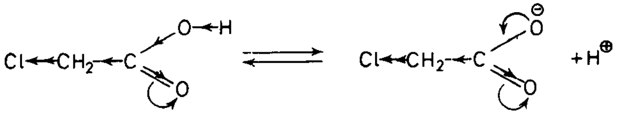
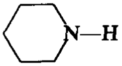
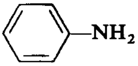
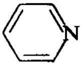


Table 1.6. THE BASICITIES OF AMINES*

Base	*Formula*	*I effect*	K_B
Ammonia	H—NH_2	0	$1{\cdot}8 \times 10^{-5}$
Methylamine	CH_3—NH_2	+I	44×10^{-5}
Ethylamine	$CH_3CH_2NH_2$	+I	47×10^{-5}
Diethylamine	$(CH_3CH_2)_2NH$	+I (×2)	95×10^{-5}
Triethylamine	$(CH_3CH_2)_3N$	+I (×3)	55×10^{-5}
Piperidine		+I (×2)	160×10^{-5}
Aniline		+I (and −M)	$4{\cdot}2 \times 10^{-10}$
Pyridine		+I (but sp^2 N)	23×10^{-10}

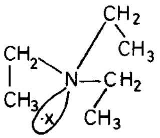
---

* See footnote to Table 1.5.

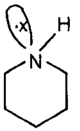
The basic strength of an amine depends on the ease with which a proton can combine with the nitrogen lone pair:

$$RNH_2 + H^{\oplus} \rightleftharpoons R\overset{\oplus}{N}H_3$$

Electron releasing alkyl groups increase the availability of the lone pair and hence increase the basic strength of the amine. An exception to this rule is triethylamine (and similar amines) which is a weaker base than either diethylamine or piperidine. The reason is probably that three large ethyl groups act in a 'flailing' manner around the site of the lone pair and severely restrict the direction of approach of the proton. No doubt this effect also occurs in diethylamine to some extent but is absent in the piperidine molecule because there the 'alkyl groups' are part of a ring system.



triethylamine



piperidine

Aniline is a weaker base than the other amines because the lone pair is partly delocalised over the aromatic nucleus (+M effect) and also the nitrogen atom is attached to an sp^2-hybridised carbon atom. Pyridine is a slightly stronger base than aniline even though the nitrogen atom is sp^2-hybridised; however, in this case the lone pair projects out of the ring and cannot interact with the π-molecular orbital system.

(b) THE MESOMERIC EFFECT

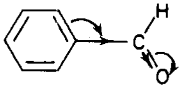
The head of the curved arrow, used to represent the mesomeric effect, indicates the direction of movement of a pair of electrons. Electron release by the mesomeric effect will be greatest when (a) the orbitals overlapping are of a similar size so that the volume of overlap is a maximum, and (b) the electronegativity of the group attached to the molecular orbital system is a minimum.

$$\mathrm{NH_2 > O^{\ominus} > OH > F} \qquad \xrightarrow{\text{increasing electronegativity}}$$

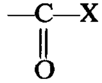
$$\mathrm{F > Cl > Br > I} \qquad \xrightarrow[\text{carbon due to increasing size of halogen}]{\text{decreasing orbital overlap with}}$$

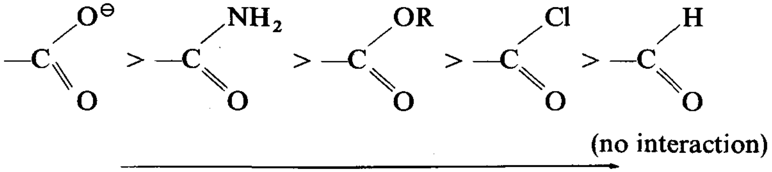
$$\xrightarrow[\text{decreasing +M effect}]{}$$

Groups such as $-NO_2$, $-C{=}N-$, $-C{=}O$ and $-SO_3H$ exert $-$M effects due to the high electronegativities of the sp^2-hybridised nitrogen and oxygen atoms. Thus $-C{=}O$ exerts a larger $-$M effect than $-C{=}N-$, etc. The nitro and carbonyl groups both exert $-$I and $-$M effects and strongly withdraw electrons from an aromatic system, e.g. benzaldehyde.



When groups exerting opposite mesomeric effects are efficiently conjugated through a system the result is a very polar molecule, e.g. p-nitroaniline (dipole moment, 6·10 D, cf. nitrobenzene, 4·01 D and aniline, 1·53 D). The conjugation of the amino and nitro groups results in the first electronic transition of p-nitroaniline appearing in the visible region at 26 700 cm^{-1} (375 nm). Hence an aqueous solution of this amine is bright yellow in colour. The order of efficiency for conjugation of two groups through an aromatic ring is: *para* > *ortho* ≫ *meta* (see also page 56).

Mesomeric effects can also operate within a single functional group, e.g. esters, amides, etc. In the group  $-\underset{\underset{\displaystyle O}{\|}}{C}-X$ the order of mesomeric interaction between the +M group, X, and the $-$M carbonyl group is:



(no interaction)

decreasing interaction between the groups

1.6 BOND ENERGIES, BOND LENGTHS AND STABILISATION ENERGIES

Bond energies and bond lengths are interrelated. As has already been mentioned the shortest bonds are the strongest bonds. The case of the different reactivities of carbon–halogen bonds towards hydroxide ions was discussed on page 3.

In the case of hybrid orbitals an increase in *s* character produces a shortening of the bond and an increase in bond energy. The bond lengths and bond energies, corrected to 0 K, for various bonds to carbon are given in *Table 1.7*. The values show that a single bond (C_{sp^3} linked to C_{sp^3}, C_{sp^2} or C_{sp}) can vary in length from 1·544 to 1·460 Å and in energy from 354 to 421 kJ/mol. It is, therefore, essential when examining a molecular structure to determine the hybridisation state of each atom in the molecule. It is insufficient simply to examine the representation of the molecule on paper.

Table 1.7. LENGTHS AND ENERGIES OF BONDS FORMED BY CARBON*

Bond	*Typical molecule*	*Bond length* (Å)	*Bond energy* (kJ/mol)
C_{sp^3}—C_{sp^3}	Ethane	1·544	353·8
C_{sp^3}—H		1·094	405·9
C_{sp^2}—C_{sp^2}	Ethylene	1·334	545·8
C_{sp^2}—H		1·086	420·6
C_{sp}—C_{sp}	Acetylene	1·205	713·6
C_{sp}—H		1·057	458·0
C_{sp^3}—C_{sp^2}	Propene	1·517	374·8
C_{sp^3}—C_{sp}	Propyne	1·460	421·5
C_{sp^3}—Cl	Chloromethane	1·78	334·7
C_{sp^2}—Cl	Vinyl chloride	1·74	435·1

* Dewar, M. J. S., *Hyperconjugation*, Ronald Press Co., New York, 1962, page 66.

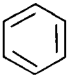
Attempts have been made, using bond energy values, to calculate the stabilisation energy† of benzene due to the delocalisation of

---

† Also termed the resonance energy.

the six electrons in the π-molecular orbital. For this purpose benzene is compared with cyclohexatriene.

benzene 

1,3,5-cyclohexatriene 

Cyclohexatriene has six C_{sp_2}—H bonds (6 × 420·6 kJ/mol), three C_{sp^2}—C_{sp^2} single bonds (3 × 397·5) and three C_{sp^2}—C_{sp^2} double bonds (3 × 545·8), making the total calculated heat of formation 5353·0 kJ/mol. The difference between this value and the observed value (5470·2 kJ/mol) is 117·2 kJ/mol. Higher stabilisation energies for benzene, of up to 171 kJ/mol, have been obtained in calculations which failed to take into account the correct nature of the hybrid bonds in cyclohexatriene. In cases where electron delocalisation in molecules is not possible the agreement between calculated and observed heats of formation is generally good, e.g. propene—calculated 3400, observed 3398 kJ/mol.

1.7 THE HYDROGEN BOND AND PHYSICAL PROPERTIES OF ORGANIC MOLECULES

Physical properties such as boiling point, melting point and water solubility might be expected to depend largely on molecular weight. In substances where the most important forces between molecules are van der Waals forces this is indeed so, e.g. the boiling points of alkanes:

	CH_4	C_3H_8	C_6H_{14}	C_9H_{20}	$C_{12}H_{26}$
Mol. wt.	16	44	86	128	170
B. pt.	−162°	−42°	69°	151°	216°

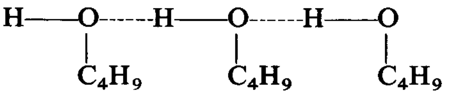
Melting points show more irregularity since this property is dependent upon the ease and efficiency with which molecules pack into crystals.

When the boiling points of a range of different substances, having similar molecular weights are examined, some inconsistencies appear:

	Hydrocarbon		*Alcohol*	*Thiol*
	C_5H_{12}	C_6H_6	C_4H_9OH	C_3H_7SH
Mol. wt.	72	78	74	76
B. pt.	36°	80°	118°	68°

	Aldehyde C_3H_7CHO	*Acid* $C_2H_5CO_2H$	*Ether* $(C_2H_5)_2O$
Mol. wt.	72	74	74
B. pt.	76°	140°	35°

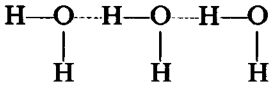
The alcohol and carboxylic acid have significantly higher boiling points than the other substances. Now as a substance boils individual molecules escape from the surface of the liquid. The energy, normally in the form of heat, applied to the liquid must be sufficient to break all the forces between molecules at the surface of the liquid. These forces include van der Waals forces and dipole–dipole interactions. However, the alcohol, C_4H_9OH, has a lower dipole moment (1·63 D) than the aldehyde, C_3H_7CHO (2·72 D). Some other bonding forces must operate in the case of the alcohol. In particular hydrogen bonds, indicated by dotted lines, produce weak electrostatic interactions between the hydrogen atom of the hydroxyl group of one alcohol molecule and the oxygen atom of a second molecule.



$$\mathrm{H{-}\underset{\underset{C_4H_9}{|}}{O}\cdots H{-}\underset{\underset{C_4H_9}{|}}{O}\cdots H{-}\underset{\underset{C_4H_9}{|}}{O}}$$

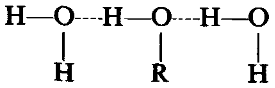
The energy of a hydrogen bond is low, i.e. of the order of 21 kJ/mol. This value is much less than the energy of a covalent bond but is greater than that due to dipole–dipole interactions.

Hydrogen bonding has been shown to occur when the hydrogen atom is attached to a small electronegative atom such as nitrogen, oxygen or fluorine. Water is a good example of a hydrogen bonded liquid; the molecular weight is only 18 but the boiling point is 100°. In liquid water the molecules are bonded together in straight and cyclic chains:

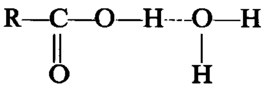


$$\mathrm{H{-}\underset{\underset{H}{|}}{O}\cdots H{-}\underset{\underset{H}{|}}{O}\cdots H{-}\underset{\underset{H}{|}}{O}}$$

Hydrogen bonds are also in part responsible for the solubility of many substances in water, e.g. alcohols and acids.

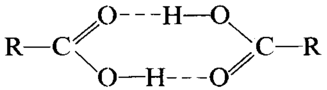


$$\mathrm{H{-}\underset{\underset{H}{|}}{O}\cdots H{-}\underset{\underset{R}{|}}{O}\cdots H{-}\underset{\underset{H}{|}}{O}}$$

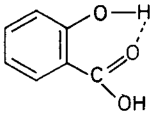


$$\mathrm{R{-}\underset{\underset{O}{\|}}{C}{-}O{-}H\cdots\underset{\underset{H}{|}}{O}{-}H}$$

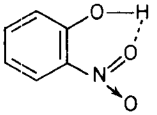
Carboxylic acids can form dimers due to hydrogen bonding:



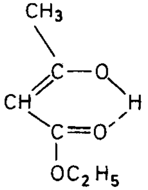
Hydrogen bonds linking two separate molecules, e.g. an alcohol and a water molecule, are said to be intermolecular. Hydrogen bonding can also occur between two groups within the same molecule and this is termed an intramolecular hydrogen bond.



salicylic acid



o-nitrophenol



ethyl acetoacetate (enol form)

Physical evidence for hydrogen bonding can be obtained from a number of sources. Infra-red spectra (section 4.1) are particularly useful, dipole moments and n.m.r. spectra (section 4.2) are also of value.

Physical properties of substances depend on many factors which include van der Waals forces, dipole–dipole interactions, hydrogen bonding and attractions between ions and dipolar molecules. Many of these factors are involved in hydration and other solvation processes. As a general rule concerning solubility, non-polar substances are soluble in non-polar solvents and polar substances are soluble in polar solvents, e.g. naphthalene is soluble in benzene and ethanol in water. In the alcohols the hydroxyl group confers water solubility provided that the carbon content of the molecule is low. As the carbon content of alcohols rises their water solubility decreases.

Molecules with two opposing functions, a water soluble portion and a non-polar fragment, e.g. $CH_3(CH_2)_{14}CO\overset{\ominus}{O}\}Na^{\oplus}$ have the important property of acting as soaps and detergents. Such sub-

Table 1.8. SOLUBILITY OF ALCOHOLS IN WATER

	Methanol, ethanol, propanols	1-butanol	1-pentanol	1-hexanol	1-heptanol
Sol. in water, g/l	∞	79	23	6	2

stances lower surface tension and disperse oil, fat, dirt, etc. into stable, water soluble 'micelles' (*Figure 1.12*). The polar end of the soap is held in the surface of the oil droplet by the non-polar alkyl group and the polar group is hydrogen bonded to the bulk of the aqueous solution. The chemical nature and manufacture of soaps are described in Chapter 15.

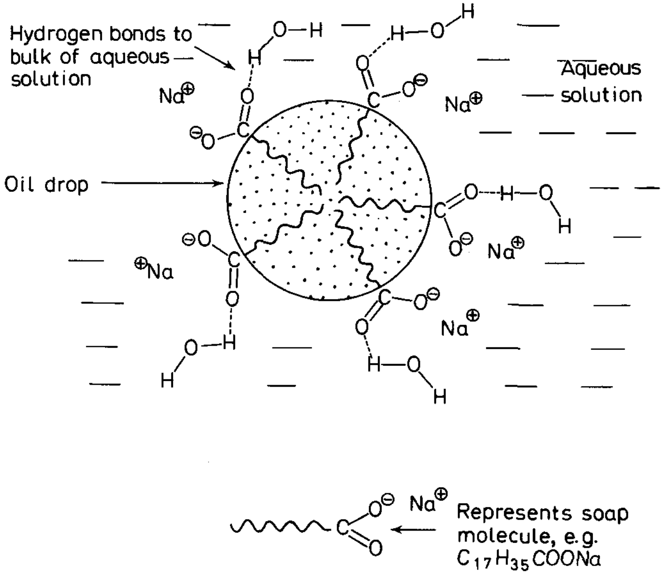


Figure 1.12. Solubilisation of oil drop in water by formation of water soluble 'micelle'

2

Stereochemistry I

2.1 CONFORMATION OF ALKANES

Although organic molecules can be represented diagrammatically on a flat sheet of paper they are really three-dimensional structures. Stereochemistry deals with the three-dimensional properties of molecules and considers how molecular shapes influence physical and chemical properties. Even a simple molecule such as ethane has different possible arrangements of the atoms in space. Each spatial arrangement of the atoms of a particular molecular structure, produced by the rotation or twisting of single bonds, but not the breaking of bonds, is termed a conformation. Conformation generally refers to systems in mobile equilibrium whilst the term configuration is used for a particular molecular arrangement of atoms, i.e. a stereoisomer, which can be isolated.

In a molecule such as ethane the rotation of one carbon atom relative to the other about the σ bond produces two extreme conformations. These have slightly different energies but cannot

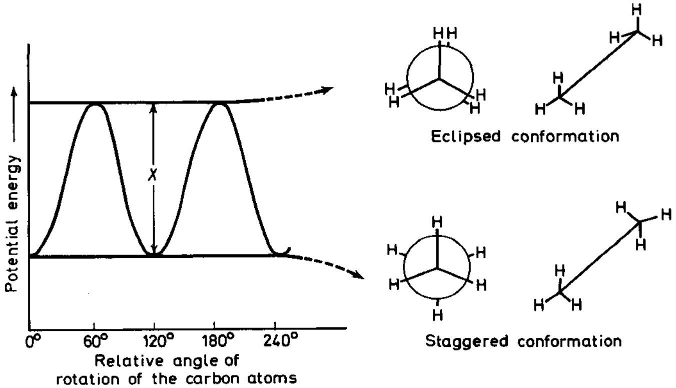


Figure 2.1. Conformations of ethane

be separated. The rotational conformations of ethane are shown in circular or 'Newman' projections and in ordinary line form. The accompanying energy diagram (*Figure 2.1*) shows that the so-called 'eclipsed' and 'staggered' conformations are separated by a small energy barrier (x). For ethane the value of the barrier is about 12·6 kJ/mol. The staggered conformation is the more stable because the six hydrogen atoms are as far apart from one another as possible and so the repulsive interactions are minimised. Thus there is an energy restriction, to completely free rotation of the two carbon atoms relative to one another around the σ bond, of about 12·6 kJ/mol. At room temperatures thermal energy provides 2·5 kJ/mol and so any energy barrier greater than this value will produce some degree of restriction to free rotation. However, to eliminate all free rotation the energy barrier must be 84–126 kJ/mol.

Any molecule such as ethane suffers from some degree of restricted rotation and at equilibrium a preponderance of the molecules will be in the staggered conformation. If some of the hydrogen atoms of ethane are replaced by larger atoms or groups the energy barrier to free rotation increases, e.g. the rotational conformations of n-butane (*Figure 2.2*).

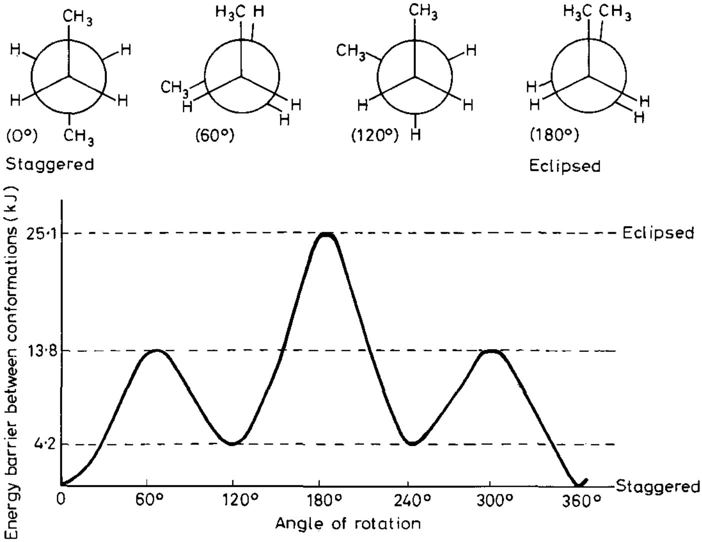


Figure 2.2. Conformations of n-butane

Interactions between the methyl groups and the hydrogen atoms of n-butane are at a minimum in the staggered form and at a maximum in the eclipsed conformation. Intermediate conformations are produced after 60° and 120° rotation (taking the staggered form as 0°). Physical methods such as x-ray diffraction analysis confirm that straight chain alkanes tend to assume their most staggered conformation.

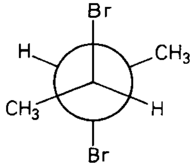
More complicated molecules, such as substituted biphenyls (section 13.2), have higher barriers to rotation and when $x =$ 84–126 kJ/mol separation of the two configurations is possible at room temperature. Different conformations which cannot be separated at room temperature may be separable at low temperatures when the thermal energy of the molecules is lowered relative to the barrier to free rotation.

An example of the effect of conformations on reactivity is found in the debromination of the different 2,3-dibromobutanes.

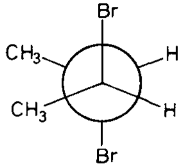
$$CH_3CHBrCHBrCH_3 \xrightarrow[\text{heat}]{Zn/CH_3OH} CH_3CH{=}CHCH_3$$

cis and *trans*-2-butene

2,3-Dibromobutane can exist in meso and racemic forms (these terms are explained in sections 13.1 and 2.4 respectively).



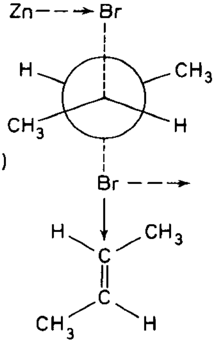
Meso form (I)



Racemic form (II)

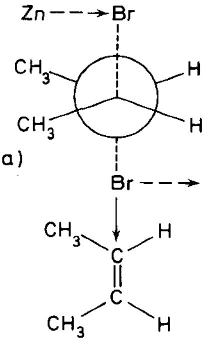
Elimination (section 3.7) is a concerted process, for as zinc begins to bond to one bromine atom, the other carbon–bromine bond begins to break and simultaneously the alkene double bond forms.

(Ia)



trans-2-butene

(IIa)

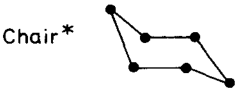


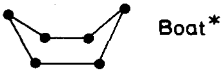
cis-2-butene

Of the two configurations encountered during the concerted elimination, structure Ia involves less repulsive energy than structure IIa. Hence the change I → Ia requires less energy than II → IIa and *trans*-2-butene should be formed faster from meso-2,3-dibromobutane than the *cis*-alkene is formed from the racemic dibromide. In practice it has been observed that the *trans* isomer is formed twice as fast as the *cis* isomer.

2.2 CONFORMATION OF CYCLOHEXANE

Cyclohexane is a non-planar molecule because the six sp^3-hybridised carbon atoms have the normal tetrahedral angle of 109·5° between bonds. Two quite different non-planar forms of cyclohexane, termed the Chair and Boat conformations, can be written.





At room temperature the two conformations undergo rapid interconversion and cannot be separated. The chair conformation is much more stable than the boat form and comprises more than 99 per cent of the equilibrium mixture.

In order to understand the greater stability of the chair conformation the positions and interactions of the hydrogen atoms must be examined. In the chair conformation all the carbon–hydrogen bonds on adjacent carbon atoms are staggered. The end-on view of the chair form of cyclohexane (*Figure 2.3*), neglecting hydrogen atoms on carbon atoms 1 and 4, shows that the hydrogen atoms on carbon atoms 2,3 and 5,6 are completely staggered. The boat conformation (*Figure 2.4*) is less stable than the chair form because (*a*) the eight hydrogen atoms on the sides of the boat are eclipsed and (*b*) two hydrogen atoms attached to the 1 and 4 carbon atoms are so close together (1·83 Å) compared with 2·46 Å for

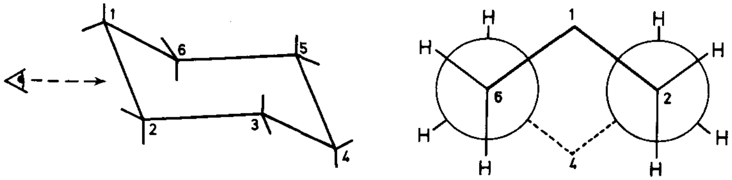


Figure 2.3. Side and end-on views of the chair conformation of cyclohexane

* Neglecting the hydrogen atoms.

staggered hydrogens and 2·27 Å for eclipsed hydrogens, that they are subject to considerable steric repulsion.

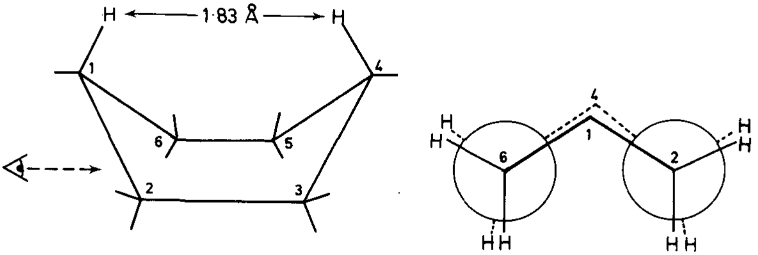


Figure 2.4. Side and end-on views of the boat conformation of cyclohexane

Actually the boat conformation is flexible (the chair form is rigid) to a degree which permits the hydrogen atoms on the 1 and 4 carbon atoms to move slightly further apart than 1·83 Å. At the same time the hydrogen atoms on the sides of the boat become partly staggered. This intermediate conformation is termed the twist-boat form. The energy barrier between the chair and twist-boat conformations is about 46 kJ/mol and a diagram representing the energy barriers between the three forms is shown in *Figure 2.5.*

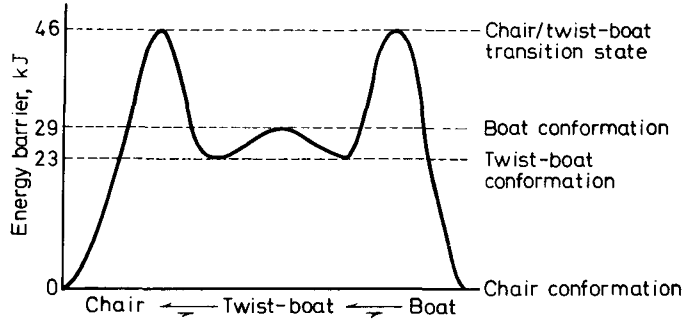
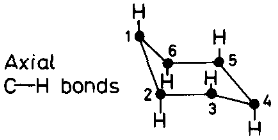
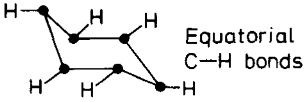


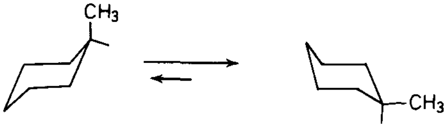
Figure 2.5. Energy barriers between the chair, boat and twist-boat conformations of cyclohexane

A close inspection of the chair conformation of cyclohexane shows that the twelve carbon–hydrogen bonds can be divided into two types. (*a*) The six axial C—H bonds which are all parallel to one another. These bonds are approximately at right angles to the 'seat' of the chair. (*b*) The six equatorial C—H bonds which extend outwards from the sides of the chair.





Note that the axial bonds are more crowded than the equatorial bonds. Whilst this is of no importance in the case of hydrogen, a bulky axial group such as methyl in the 1-position is crowded by the 3 and 5-position hydrogen atoms. Equatorial groups are not subject to such crowding but are more exposed and more accessible to reagents than axial groups.



axial and equatorial methylcyclohexanes

In principle two forms of methylcyclohexane should exist but in practice the equatorial and axial forms are in equilibrium. The equatorial conformation is about 7·5 kJ/mol more stable than the axial form of methylcyclohexane and at room temperature approximately 95 per cent of the chair form has the methyl group equatorial. A rapid interconversion between the equatorial and chair conformations of methylcyclohexane takes place via ring inversion, i.e. as one end of the chair goes up the other moves down.

A problem related to the conformations of cycloalkanes is that of ring strain in such systems. Cyclohexane is a strain-free puckered ring where the carbon bonds are situated at their normal valency angle of 109·5°. Cyclopropane and cyclobutane must be strained as the normal tetrahedral angle cannot be achieved. The concept of ring strain was put forward by Baeyer in 1885; he also suggested that rings larger than cyclohexane were similarly strained and that this could account for difficulties encountered in synthesising such compounds. Sachse (1890) and Mohr (1918) realised that much of the strain in large rings is eliminated by puckering but that the C_7–C_{12} rings have of necessity some eclipsed C—H bonds and so cannot attain strain-free conformations like the chair form of cyclohexane. Strain-free conformations can be realised by rings of more than twelve carbon atoms as all the C—H bonds can again be staggered.

Strains in ring compounds have been evaluated from their observed heats of combustion. A value of 658·6 kJ/mol is allowed for each $—CH_2—$, this being the value for straight chain alkanes, and the total is subtracted from the measured heat of combustion (see *Table 2.1*).

Table 2.1.

Cycloalkane $(\text{—CH}_2\text{—})_n$	n	*Ring strain* (kJ/mol) (*Ht. of comb.* − 658·6n)
cyclopropane	3	115·5
cyclobutane	4	110·5
cyclopentane	5	27·2
cyclohexane	6	0·0
cycloheptane	7	26·4
cyclooctane	8	40·2
cyclononane	9	46·9
cyclodecane	10	50·2
cyclopentadecane	15	6·3

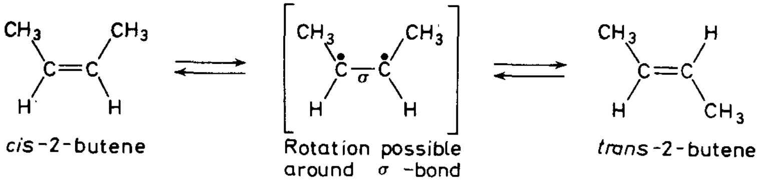
The strain values for cyclopropane and cyclobutane are probably exaggerated because the hybridisation of the carbon atoms may not be pure sp^3 and also some degree of σ-bond bending may occur. These two cycloalkanes should, therefore, really be regarded as special cases.

2.3 GEOMETRICAL ISOMERISM

Geometrical isomers contain some rigid elements such as a double bond or a rigid ring system. Such isomers have the same structures, groups, etc., but differ with respect to the positions of some atoms or groups relative to the double bond or ring system. Geometrical isomerism is usually associated with the bonds $\rangle C{=}C\langle$, $\rangle C{=}N\diagup$, $\diagdown N{=}N\diagdown$ or with certain cycloalkanes.

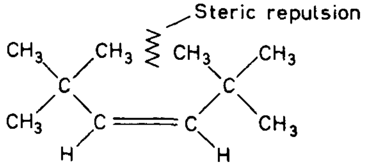
2-butene provides a straightforward example of geometrical isomerism. The configuration in which the two methyl groups are on the same side of the double bond is termed *cis* and that in which the groups are on opposite sides is called *trans*. At room temperature the two configurations are stable and separable. Interconversion *cis* $\rightleftharpoons$ *trans* only occurs when the π-bond is broken and then reformed, e.g. at elevated temperatures or in the presence of ultra-violet light or free radicals.

A double bond is a rigid bond because of the 'locking effect' of the σ- and π-bonds. With a σ-bond alone, i.e. a single bond, free rotation is usually possible and as has already been shown in



section 2.1 this leads to different conformations. Configurational isomers such as *cis–trans* isomers are stable and separable whilst conformational isomers are in mobile equilibrium and inseparable.

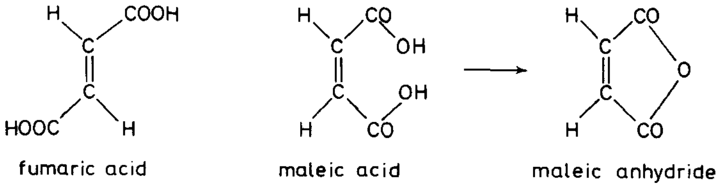
As a general rule *trans* are more stable than *cis* configurations. The reason for this is that a *cis* arrangement of groups can lead to steric hindrance, particularly if the groups are bulky. For example, in 2,2,5,5-tetramethyl-*cis*-3-hexene considerable repulsion occurs between methyl groups in the 2- and 5-positions and so this isomer is much less stable than the *trans* isomer.



Some other examples of geometrical isomerism are given below.

(a) FUMARIC AND MALEIC ACIDS (see also page 213)

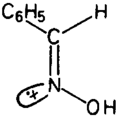
These two unsaturated, dicarboxylic acids form the classical example of geometrical isomerism.



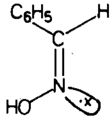
The two acids may be distinguished chemically, for only the *cis*-isomer, maleic acid, in which the two carboxyl groups are close together, produces a cyclic anhydride when gently heated. Maleic acid is converted into the more stable *trans* isomer when boiled for several hours with dilute hydrochloric acid or when exposed to sunlight in the presence of a trace of bromine.

(b) OXIMES

These substances contain the rigid bond $>C{=}N-$ and so geometrical isomerism is possible, e.g. benzaldoxime.



trans-benzaldoxime



cis-benzaldoxime

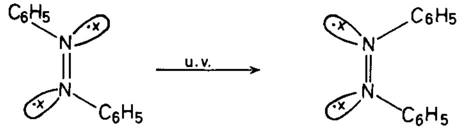
The situation is thus very similar to that of an alkene except that the fourth position about the rigid bond is occupied by a lone pair of electrons rather than an atom or group. In general any oxime will exhibit geometrical isomerism provided that in

$$R.R'{-}C{=}NOH$$

R and R′ are different groups.

(c) AZO COMPOUNDS

Azobenzene normally exists in the *trans* form but irradiation with ultra-violet light brings about some conversion to the *cis*-isomer. *Cis* and *trans*-azobenzenes are readily separated by column chromatography on alumina using petroleum ether as the eluting solvent.



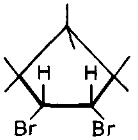
trans-azobenzene *cis*-azobenzene

(d) CYCLOALKANES

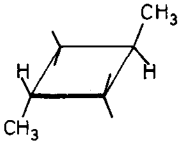
Cyclopropane is a rigid three-membered ring system capable of forming geometrical isomers in just the same way as the carbon–carbon double bond of an alkene.

cis and *trans*-1,2-dimethylcyclopropanes

Cyclobutane and cyclopentane are not perfectly planar but can be considered flat in this context and both ring systems are capable of forming *cis* and *trans*-isomers.



cis-1,2-dibromocyclopentane

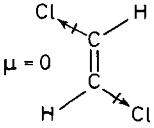


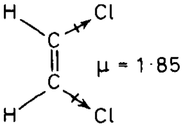
trans-1,3-dimethylcyclobutane

The situation in cyclohexane and other non-planar ring systems is more complicated because conformational isomerism is possible as well as geometrical isomerism. In such cases the favoured conformation is the one in which steric interactions are minimised. This means that bulky groups, such as the t-butyl group, normally take up an equatorial position.

Geometrical isomers can often be separated by crystallisation, fractional distillation or chromatography. *Cis* isomers usually have lower melting but higher boiling points than the *trans* isomers. Physical methods such as dipole moment, optical activity measurements, and infra-red or nuclear magnetic resonance spectra provide evidence for the structure of a particular isomer.

Trans isomers have zero or lower dipole moments than *cis* isomers. For example in *trans*-1,2-dichloroethylene the bond moments of the two opposing carbon–chlorine bonds cancel and so the dipole moment (μ) is zero. However, the *cis* isomer has a dipole moment of 1·85 D because the vector sum of the bond moments is positive. Dipole moment measurements only provide a satisfactory assignment of configuration when the moments of the *cis* and *trans* forms are significantly different. An example of structure determination by optical activity measurements is described in section 13.1.



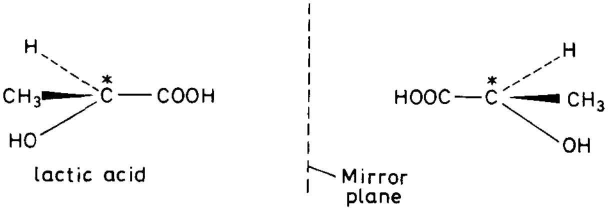


Infra-red spectroscopy is useful for differentiating between *cis* and *trans* isomers of the type RCH═CHR′. The *trans* isomer possesses a strong absorption band near 965 cm^{-1} which is absent from the spectrum of the *cis* isomer. Proton coupling constants (*J*) derived from n.m.r. spectra can also be used to help distinguish between the *cis* and *trans* isomers of 1,2-disubstituted alkenes.

2.4 ASYMMETRY, DISSYMMETRY AND OPTICAL ISOMERISM

Conformational isomers are in mobile equilibrium and inseparable; geometrical isomers have different structures, due to some rigid element in the molecule, and are usually separable. A third type of isomerism is optical isomerism. Pairs of optical isomers have identical physical properties and differ only in their behaviour towards plane polarised light, and in their rates of reaction with reagents that are themselves asymmetric. Each optical isomer rotates the plane of such light by the same amount but the pair of isomers rotate the light in opposite directions.

In order to exhibit optical activity a molecule must not be superimposable on its own mirror image, e.g. lactic acid.



In the above diagram normal lines represent bonds in the plane of the paper, dotted bonds project behind the paper and the thickened bonds are directed out of the paper. The central carbon atom, marked with an asterisk, is said to be asymmetrically substituted since it is bonded to four different atoms or groups, i.e. the molecule has no element of symmetry. Molecules which cannot be superimposed on their mirror images are termed *dissymmetric*. The two optically active, non-superimposable mirror images are called *enantiomers* and can be likened to a right hand and a left hand glove. Molecules may contain asymmetric carbon atoms and yet be non-dissymmetric, i.e. not optically active (see page 235). Alternatively a molecule can be dissymmetric and yet not contain an asymmetrically substituted carbon atom (see page 236).

Pairs of mirror image molecules, or enantiomers, have identical physical properties, apart from their action on plane polarised light, and their chemical properties will also be similar except when reacted with optically active reagents. The enantiomer which rotates the plane of polarised light in a clockwise direction (observer looking towards the light source) is termed *dextrorotatory* and given the prefix (+). The other enantiomer, which produces an anticlockwise rotation, is termed *levorotatory* (or laevorotatory) and indicated (−). Thus (+)-lactic acid has a specific rotation of +3·8° and (−)-lactic acid −3·8°. A mixture of equal parts of the two enantiomers is of course optically inactive as their respective optical activities cancel out. Such a mixture is termed a *racemic* modification and is indicated by the prefix (±), e.g. (±)-lactic acid.

(a) SPECIFIC ROTATION

The angle by which the plane of polarised light is rotated by an optically active substance depends on four factors: (i) the number of molecules the light encounters and their structure, (ii) the wavelength (or frequency) of the light, λ (iii) the temperature, $t°$ and (iv) the solvent, if any, used for the measurements. All these factors are combined in the *specific rotation*, $[\alpha]$. For an optically active substance in solution:

$$[\alpha]_{\lambda}^{t°} = \frac{100\,\alpha}{cl}$$

where α is the measured rotation from the polarimeter, l is the length of the cell used in dm and c is the concentration in g/100 ml of solvent;
or for a pure optically active liquid:

$$[\alpha]_{\lambda}^{t°} = \frac{100\,\alpha}{d\,.\,l}$$

where d is the density of the liquid in g/ml.

The term *molecular rotation* $[M]$ is also used:

$$[M]_{\lambda}^{t°} = \frac{1}{100}\,.\,[\alpha]_{\lambda}^{t°} \times \text{Mol. Wt. of the optical isomer.}$$

Thus $[\alpha]_{D}^{20°} = +57°$ ($c = 2{\cdot}0$, H_2O) refers to a specific rotation of +57° as measured with sodium D light for a solution of concentration 2·0 g/100 ml water, maintained at 20°C.

(b) INTERACTION BETWEEN PLANE POLARIZED LIGHT AND AN OPTICALLY ACTIVE SUBSTANCE

A useful description of plane-polarised light is to consider the plane beam to be the vector resultant of two oppositely rotating beams of circularly polarised light (*Figure 2.6*). The electric vectors, rotating in opposite directions, produce a resultant which describes a planar sine wave and in effect, therefore, behaves as a plane polarised light beam. When plane polarised light passes through a large number of dissymmetric molecules the interaction between the two forms of circularly polarised light and the molecules, producing some degree of molecular polarisation, will be unequal. Hence the vector resultant of the two circularly polarised beams will shift and the plane of polarisation will rotate through some angle. In a racemic modification both the right and left hand circularly polarised beams will interact with molecules to the same but opposite extents and so their vector resultant will be unchanged.

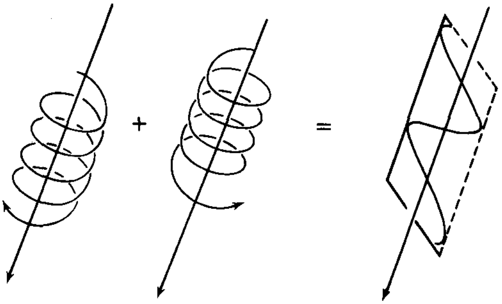
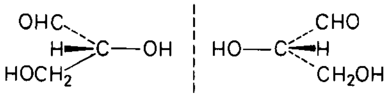


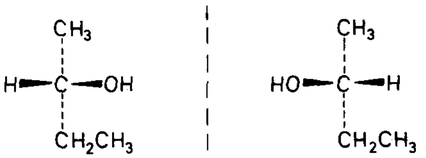
Figure 2.6. Plane polarised light as the vector resultant of two circularly polarised beams

2.5 OPTICALLY ACTIVE SUBSTANCES CONTAINING ONE ASYMMETRIC CARBON ATOM

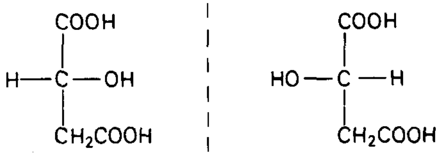
To rotate the plane of polarised light a molecular species must have a structure such that it cannot be superimposed upon its mirror image. One example of a molecule having an asymmetric carbon atom has already been mentioned, i.e. lactic acid. Other examples are glyceraldehyde, 2-butanol and malic acid.



(*a*) glyceraldehyde

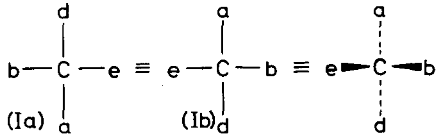


(*b*) 2-butanol

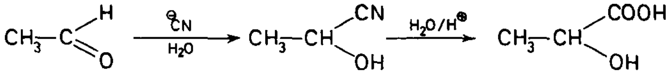


(*c*) malic acid (hydroxysuccinic acid)

Different methods have been used for the presentation of the three examples. The thickened line type of formula (examples *a* + *b*) presents a more three-dimensional image of the molecule than the ordinary line formula and is very useful for simple structures. In more complex structures the Fischer projection, as used for malic acid (*c*), is in common usage. By convention the horizontal bonds of the Fischer projection extend out of the plane of the paper and vertical bonds extend behind the paper. The carbon chain is always written vertically and rotation of a Fischer projection through 180°, in the plane of the paper, leaves the configuration unchanged (Ia and Ib).



As normally synthesised, substances such as lactic acid are racemic:



(±)-lactic acid m.p. 18°

(+)-Lactic acid can be obtained from meat extracts and (−)-lactic acid from the fermentation of sucrose; both forms melt at 26°.

Substances containing two asymmetric carbon atoms are discussed in Chapter 13; compounds which are dissymmetric and yet contain no asymmetric carbon atoms are also described.

3

Mechanisms of Organic Reactions

3.1 INTRODUCTION

A large number of organic reactions have been studied with the aim of elucidating the precise mechanism by which the reactants change into the products. Usually the rate of reaction is investigated at various initial concentrations of the reactants so that a rate equation can be established. When the rate of reaction is proportional to the concentration of just one reactant, i.e. Rate $= k[\text{Reactant}_1]$, the reaction is said to be first order. Where two molecules of the reactants determine the rate of reaction, i.e. Rate $= k[\text{Reactant}_1][\text{Reactant}_2]$ or possibly $= k[\text{Reactant}]^2$, then the reaction is termed second order.

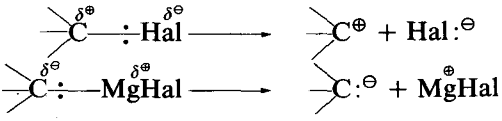
In some cases reaction intermediates can be studied by physical methods such as infra-red, Raman, nuclear magnetic resonance or electron spin resonance spectroscopy, e.g. the nitronium ion, $\overset{\oplus}{N}O_2$, was shown to be the electrophile in the nitration of a number of aromatic hydrocarbons. Isotope techniques and gas liquid chromatography are used to analyse reaction mixtures accurately, e.g. in the study of *ortho*, *meta* and *para* ratios. Many reactions involve an inversion of the configuration of a reactant and this can be studied by changes in specific rotation or optical rotatory dispersion curves. X-ray diffraction analysis, particularly with the aid of computers, can provide a complete solution to the geometry of a molecule.

The mechanisms described in the following pages are some of those frequently encountered in organic chemistry. Divergences do of course occur from these 'basic' mechanisms, particularly in complex compounds.

3.2 HOMOLYTIC AND HETEROLYTIC PROCESSES

During reaction a bond C—X of an organic molecule breaks and is replaced by a new bond C—Y. The bond C—X may break in either of two ways.

(1) Heterolytic bond breaking may occur, in which case both of the bonding electrons are retained by either the carbon atom or X, e.g.

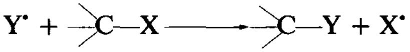


In each case the more electronegative atom of the two atoms forming the bond retains the pair of bonding electrons. Ionic processes of this type are favoured by polar solvents, e.g. aqueous ethanol.

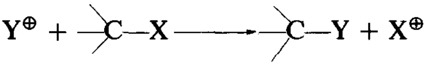
(2) Homolytic bond breaking may occur and then the bonding electrons are equally divided between the carbon atom and X.

Two electrically neutral, free radicals are formed. Homolytic processes are favoured by non-polar solvents, high temperatures and ultra-violet radiation but can take place alongside heterolytic reactions.

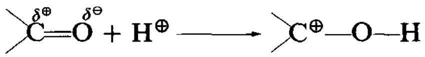
Conversely the new bond C—Y can be formed in two ways, either from free radicals,



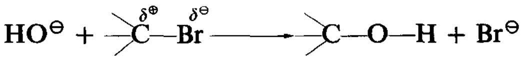
or from ionic species,



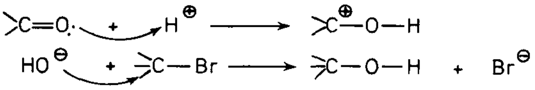
In the latter case the direction of polarisation of the C—X bond will determine the direction of reaction, e.g.



or

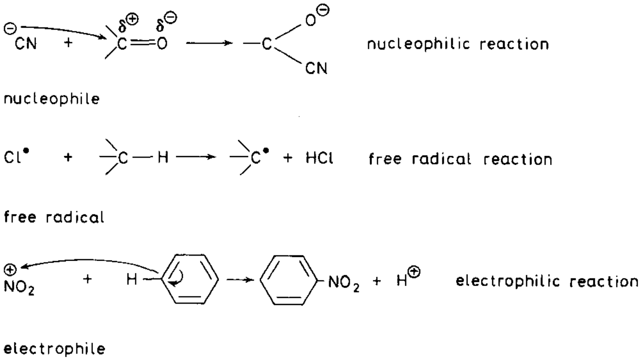


These processes may also be written:



the 'curly arrow' indicating the direction of movement of two electrons. The feasibility of reaction taking place is determined not by the polarity of the bond but by the activation energy (E_{act}) required for reaction. The carbon atom where the reaction occurs is called the reaction centre.

Reagents are classified as *nucleophiles*, *free radicals* or *electrophiles* depending on whether they contribute two, one or no electrons to a bond.



Each type of reagent will now be considered in turn.

(a) ELECTROPHILES

In order to form a covalent bond with a reactant an electrophile must have an empty orbital and be capable of accepting a share in a pair of electrons. Examples of cations which fulfil these requirements are $H^{\oplus}$, $NO_2^{\oplus}$, $NO^{\oplus}$, $CH_3\overset{\oplus}{C}{=}O$ and $Ph{-}\overset{\oplus}{N}{\equiv}N$. Metal cations such as $Li^{\oplus}$ and $Na^{\oplus}$ are not electrophiles because they already have a noble gas configuration.

Some apparently neutral molecules can also act as electrophiles, e.g. Cl_2, Br_2, HCl, HBr and SO_3. Such molecules do not possess empty orbitals but prior to reaction become polarised. At the time of reaction some of them may split out a stable fragment, leaving an electrophile, e.g.

$$\mathrm{Cl_2} \longrightarrow \overset{\delta\oplus}{\mathrm{Cl}}\text{----}\overset{\delta\ominus}{\mathrm{Cl}} \longrightarrow \mathrm{Cl}^{\oplus} + {}^{\ominus}\mathrm{Cl}$$

$$\mathrm{HBr} \longrightarrow \overset{\delta\oplus}{\mathrm{H}}\text{----}\overset{\delta\ominus}{\mathrm{Br}} \longrightarrow \mathrm{H}^{\oplus} + {}^{\ominus}\mathrm{Br}$$

$$\mathrm{HOCl} \longrightarrow \overset{\delta\oplus}{\mathrm{Cl}}\text{----}\overset{\delta\ominus}{\mathrm{OH}} \longrightarrow \mathrm{Cl}^{\oplus} + {}^{\ominus}\mathrm{OH}$$

(b) NUCLEOPHILES

In order to provide the two electrons of opposite spin for a covalent bond a nucleophile must have an available, i.e. not too strongly bound, pair of electrons and must be able to undergo an increase in covalency by one unit. Therefore, anions and neutral molecules with an unshared (available) pair of electrons act as nucleophiles.

Examples of such anions are: $Cl^{\ominus}$, $C_2H_5O^{\ominus}$, $CH_3O^{\ominus}$, $CH_3COO^{\ominus}$, $HO^{\ominus}$ and $PhO^{\ominus}$. All simple anions are bases and nucleophiles. However, the nucleophilic strength of a reagent, i.e. the ability to donate an electron pair to carbon, may not be the same as the basicity, which is the ability to donate an electron pair to a proton. Thus the hydroxyl ion, $HO^{\ominus}$, is a strong base and a good nucleophile whereas the iodide ion, $I^{\ominus}$, is a very weak base but a strong nucleophile.

Examples of neutral molecules which behave as nucleophiles are: NH_3, CH_3NH_2, H_2O, C_2H_5OH and H_2S. Nitrogen, oxygen and sulphur (Group 5 and 6 elements) in the sp^3-hybridisation state are capable of acting as nucleophiles. The halogens (Group 7), in substances such as alkyl halides, do not act as nucleophiles because the nucleus attracts the three unshared electron pairs too strongly for them to be available for bonding. For a similar reason water is a weaker nucleophile than ammonia because the unshared electrons are more strongly attracted to the nucleus in oxygen than in nitrogen.

(c) FREE RADICALS

These are normally very reactive and attack a wide range of neutral molecules, besides combining with other free radicals, to form covalent bonds. Free radicals are usually electrically neutral and possess one unpaired electron. They can react either as:

$$A^{\bullet} + B^{\bullet} \longrightarrow A \div B$$

or with a neutral molecule via a chain reaction:

$$Br_2 \xrightarrow{\text{u.v.}} 2Br^{\bullet}$$

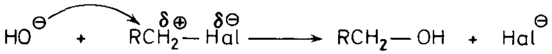
$$Br^{\bullet} + CH_4 \longrightarrow CH_3^{\bullet} + HBr$$

$$CH_3^{\bullet} + Br_2 \longrightarrow CH_3Br + Br^{\bullet}$$

3.3 UNIMOLECULAR AND BIMOLECULAR NUCLEOPHILIC SUBSTITUTION

Reactions of this type are most commonly encountered in aliphatic systems and the substitution is then said to be at a saturated (sp^3) carbon atom. Nucleophilic substitution also takes place at unsaturated (sp^2) carbon atoms, although usually with more difficulty, and this type of reaction will be dealt with at the end of the section.

The alkaline hydrolysis of alkyl halides has been thoroughly investigated by Ingold, Hughes and their co-workers (mainly in the period 1927–1935) and two distinct nucleophilic processes were demonstrated for the reaction:



$$HO^{\ominus} + \overset{\delta\oplus}{RCH_2}-\overset{\delta\ominus}{Hal} \longrightarrow RCH_2-OH + Hal^{\ominus}$$

In general terms attack by a nucleophile, Y:, takes place on an sp^3-hybridised carbon atom and a substituent, X, is displaced.

$$Y: + RCH_2-X \longrightarrow RCH_2-Y + X:$$

Kinetic studies of the alkaline hydrolysis of alkyl halides were interpreted in terms of two extreme types of reaction rate equations. These are:

(1) rate of formation of product $= k[RCH_2-Hal]$ and

(2) rate of formation of product $= k[RCH_2-Hal]\,[HO^{\ominus}]$ where k is the specific rate constant for each reaction.

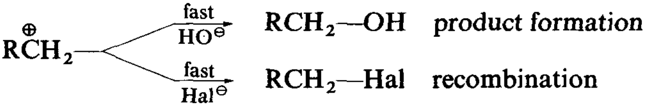
The first order reaction rate, equation (*a*), corresponds to a unimolecular (1) process of nucleophilic (N) substitution (S). This is usually abbreviated to S_N1.

(a) MECHANISM OF S_N1 SUBSTITUTION

The rate of reaction is independent of the concentration of the base and so the rate determining step is the rate of ionisation of the alkyl halide,

$$\underset{}{RCH_2{-}Hal} \xrightarrow{slow} \underset{\text{carbonium ion}}{R\overset{\oplus}{C}H_2} + Hal^{\ominus}$$

The carbonium ion can then react in two ways.



$$R\overset{\oplus}{C}H_2 \xrightarrow[HO^{\ominus}]{fast} RCH_2{-}OH \quad \text{product formation}$$

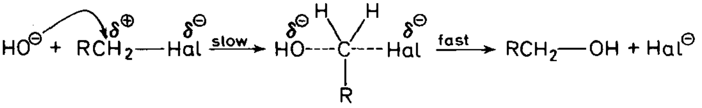
$$R\overset{\oplus}{C}H_2 \xrightarrow[Hal^{\ominus}]{fast} RCH_2{-}Hal \quad \text{recombination}$$

An example of this type of reaction is the alkaline hydrolysis of 2-chloro-2-methylpropane (t-butyl chloride).

$$HO^{\ominus} + (CH_3)_3C{-}Cl \rightleftarrows (CH_3)_3^{\oplus} \rightarrow (CH_3)_3C{-}OH$$

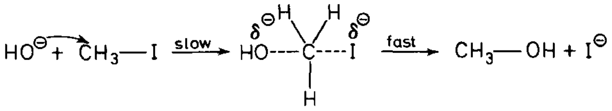
(b) MECHANISM OF S_N2 SUBSTITUTION

The second order reaction rate, equation (*b*), corresponds to a bimolecular (2) process of nucleophilic (N) substitution (S). Abbreviated to S_N2, this means that the rate determining step involves the formation of a transition state from two reactant molecules.



Transition state

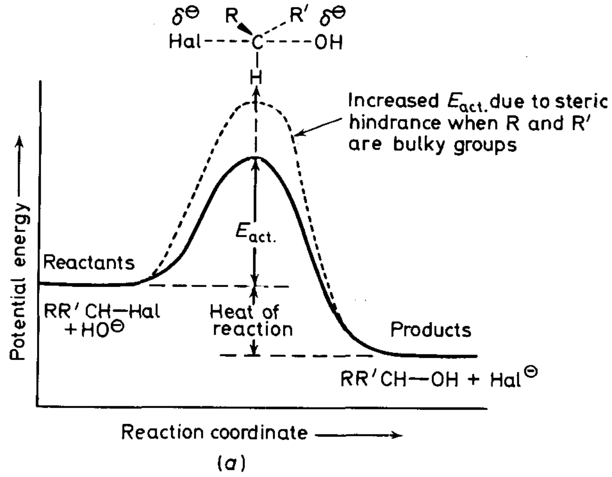
The O--C bond forms as the C--Hal bond breaks but at some stage both groups are partly bonded to the carbon atom. This is termed the transition state. The energy changes which take place during S_N2 substitution are shown in *Figure 3.1*(*a*). The alkaline hydrolysis of iodomethane is an example of this type of reaction.



(c) STEREOCHEMISTRY OF NUCLEOPHILIC SUBSTITUTION

(*i*) S_N1 *Substitution*

When the carbonium ion, produced by the initial ionisation



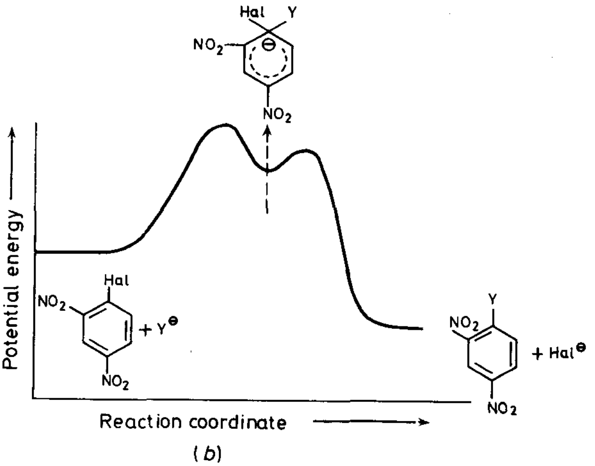
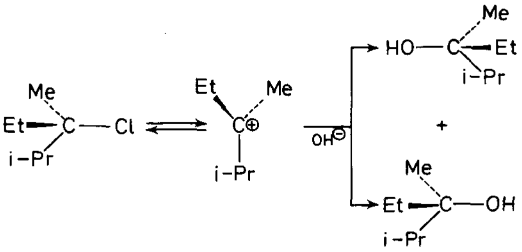
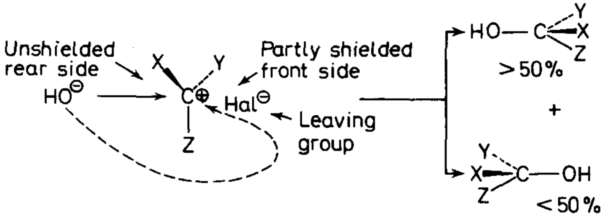


Figure 3.1. Potential energy changes during the progress of S_N2 *substitution in (a) aliphatic and (b) aromatic compounds*

process, is fairly stable, i.e. not too short lived, the product of S_N1 substitution will be a racemate if the reacting molecule was optically active. This is because the carbonium ion is planar, the $C^{\oplus}$ atom is sp^2-hybridised and the nucleophile can attack either side in a random manner.

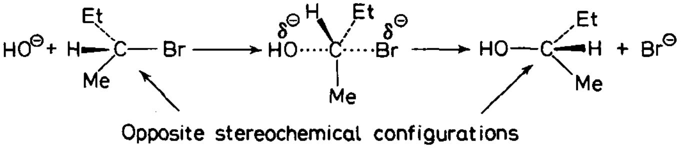


With very short lived carbonium ions the product may be optically active due to a preponderance of inversion of configuration. This happens when attack by the nucleophile on the carbonium ion commences before the leaving group has completely departed. Hence the front side is partly shielded by the leaving group and more than 50 per cent of the nucleophiles attack the rear side of the carbonium ion.



(ii) S_N2 *Substitution*

The transition state forms as the hydroxyl ion approaches the reaction centre, along the line of the carbon–halogen bond, keeping as far as possible from the halogen atom due to the development of the $\delta^{\ominus}$ charges. When the carbon–halogen bond breaks the configuration of the molecule is inverted. This change in stereochemistry, which occurs when a group directly attached to an asymmetric centre is displaced by the S_N2 mechanism, is often referred to as the Walden Inversion

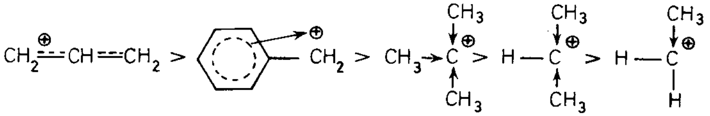


(d) S_N1 v. S_N2 REACTIVITY

In S_N1 substitution the order of reactivity of different halides towards nucleophiles is:

alkyl > benzyl > tertiary ≫ secondary > primary.

This parallels the order of stability of the carbonium ions which these halides produce, i.e.

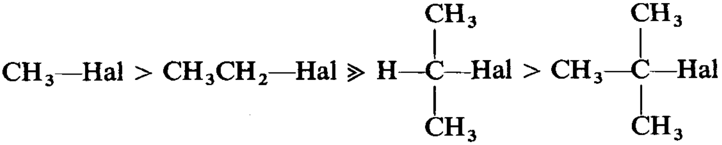


The allyl and benzyl carbonium ions are stabilised by the spread of positive charge over the adjacent π molecular orbital system (section 6.2). In the tertiary carbonium ion three alkyl groups spread the positive charge by virtue of their +I effects. The more stable the carbonium ion the lower the activation energy required to bring about its formation and so the faster the parent compound ionises.

In contrast the rate of S_N2 substitution is largely governed by steric factors in the transition state.

	Reactants →	Transition State →	Products
Number of groups about reaction centre	4	5	4
	increasing steric resistance	steric assistance	

As the number and size of the alkyl groups attached to the reaction centre increases so the activation energy required to form the transition state increases (*Figure 3.1*). This explains the observed order of S_N2 reactivity in alkyl halides, i.e.



$$CH_3\text{—}Hal > CH_3CH_2\text{—}Hal \gg H\text{—}\underset{CH_3}{\overset{CH_3}{C}}\text{—}Hal > CH_3\text{—}\underset{CH_3}{\overset{CH_3}{C}}\text{—}Hal$$

Thus primary halides usually react by the S_N2 route and tertiary halides by the S_N1 mechanism. Secondary halides form an intermediate case and react simultaneously by both mechanisms although at an overall rate slower than that for either primary or tertiary halides.

(e) SOLVENT AND SALT EFFECTS

Because the rate determining step in S_N1 processes is one of ionisation, reactions proceeding by this mechanism are assisted by polar solvents. In other words an S_N1 reaction is speeded up by increasing the polarity, i.e. the dielectric constant and solvation ability, of the solvent in which the reaction is proceeding. Thus tertiary alkyl halides hydrolyse rapidly in water/ethanol mixtures containing a high proportion of water. As the proportion of water is decreased the rate of reaction falls until in pure ethanol the mechanism changes to S_N2. Bimolecular nucleophilic substitution reactions do not involve an ionisation step and so are not much affected by the polarity of the solvent.

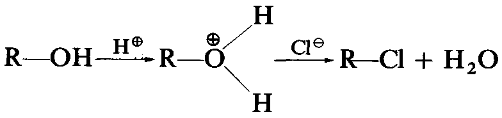
Inorganic salts can alter rates of reactions proceeding by the S_N1 mechanism.

$$R_3C\text{—}Cl \xrightleftharpoons[2.\ +Cl^{\ominus}]{1.\ -Cl^{\ominus}} R_3C^{\oplus} \xrightarrow{3.\ +OH^{\ominus}} R_3C\text{—}OH$$

As the above reaction proceeds, by steps 1 and 3, the concentration of chloride ion in solution increases. Then the reverse step 2 becomes more important and the rate of product formation decreases. Therefore, the addition of chloride ions to the reaction mixture will slow down the formation of the alcohol; this is termed 'Common Ion Retardation'. The addition of non-common ions, e.g. bromide or sulphate ions in the above example, will not slow down alcohol formation, in fact the reverse will tend to occur. The reaction rate will increase slightly because the added non-common ions raise the ionising power of the solution and so increase the rate of step 1; this is termed an 'Ionic Strength Effect'.

(f) EFFECT OF FUNCTIONAL GROUP ON THE REACTIVITY OF ALIPHATIC COMPOUNDS

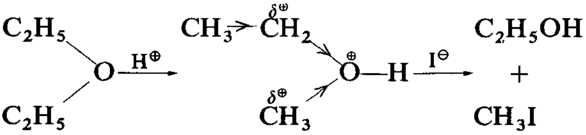
For a particular alkyl group, R, in aliphatic compounds R—X, it is instructive to enquire how the functional group, X, affects attack by nucleophiles. When the C—X bond is easily distorted, i.e. has a high polarisability (section 1.1), the S_N2 transition state will be easily formed and reaction will be rapid. There is a relationship between the acidity of H—X and the S_N2 reactivity of R—X. If H—X is a strong acid and easily dissociates into $H^{\oplus}$ and $X^{\ominus}$ then R—X will react readily with nucleophiles. Thus with the hydrogen halides the order of acidity is HI > HBr > HCl > HF and the order of S_N2 reactivity of alkyl halides is RI > RBr > RCl > RF. Similarly alcohols, ammonia and water, R′OH, HNH_2 and HOH, are very weak acids and so ethers, ROR′, amines, RNH_2, and alcohols, ROH, are unreactive towards nucleophiles. In such cases acid catalysis is normally used to increase the reactivity of the alkyl compound.



The electronegativity of $—\overset{\oplus}{O}H_2$ is greater than that of —OH and so the reaction centre in $R—\overset{\oplus}{O}H_2$ is rendered more positive than that in R—OH and hence more susceptible to nucleophilic attack

$$R'CH_2 \rightarrow OH \qquad R'CH_2 \twoheadrightarrow \overset{\oplus}{O}H_2$$

Protonation explains the use of hydrogen iodide to cleave ethers, for $I^{\ominus}$ is the most powerful nucleophile that can be obtained in strongly acidic solution.

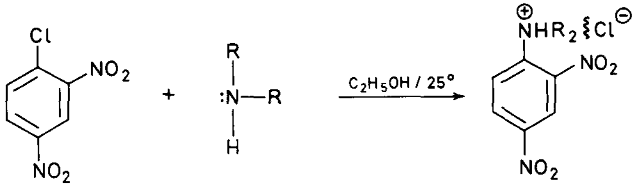


The $—CH_2—$ of the ethyl group is the least positive of the two possible reaction centres and so at room temperature a mixture of iodomethane and ethanol is formed. At higher temperatures the ethanol reacts further to yield iodoethane.

(g) AROMATIC NUCLEOPHILIC SUBSTITUTION

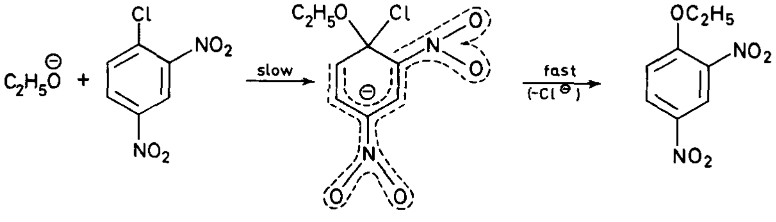
Bimolecular nucleophilic substitution at unsaturated (sp^2) carbon atoms is difficult to achieve unless the atom or group to be displaced is activated by a strongly electron withdrawing group, such as

$-NO_2$, $-NO$, $-\overset{\oplus}{N}\equiv N$ or $-C\equiv N$, in the *ortho* and/or *para* position. Thus second order kinetics have been observed for many substitution reactions of *p*-chloronitrobenzene, 2,4-dinitrochlorobenzene and the corresponding bromo compounds.



Other strong bases, such as $C_2H_5O^{\ominus}$ and $HO^{\ominus}$, also displace the halogen atom in the above compounds, whereas chlorobenzene, under the same conditions, is completely unreactive.

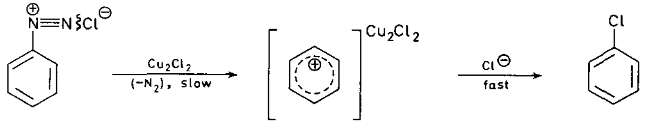
The mechanism of substitution is similar to that encountered previously except that the negative charge is transferred to the benzene ring.



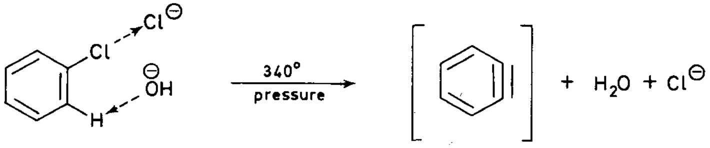
In the reaction intermediate, which lies in a small energy trough—*Figure 3.1(b)*, the carbon atom attacked becomes sp^3-hybridised, temporarily destroying the delocalised aromatic system (cf. electrophilic aromatic substitution, page 51). Electron withdrawing groups reduce the π electron density at the carbon atom attacked, facilitate the approach of the nucleophile and perhaps most important of all stabilise the reaction intermediate by delocalising the negative charge.

Vinyl halides resemble aryl halides in possessing a low reactivity towards nucleophiles (cf. section 6.2). They do, however, undergo free radical polymerisation, e.g. vinyl chloride polymerises to polyvinyl chloride (section 16.2).

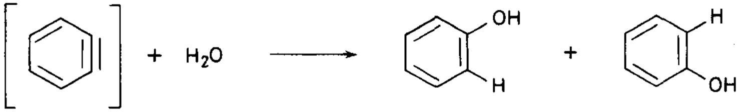
Unimolecular nucleophilic substitution (S_N1) is uncommon in unsaturated systems although the replacement reactions of aromatic diazonium compounds can be considered to fall into this category. The decomposition of the diazonium cation to the carbonium ion is rate determining but, unlike S_N1 substitution in saturated compounds, this step is irreversible.



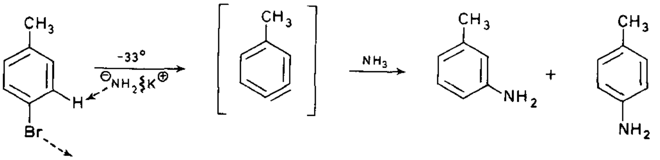
Simple halogenobenzenes, which do not contain activating groups, react with nucleophiles only at elevated temperatures. Thus phenol is produced commercially by the reaction between chlorobenzene and aqueous sodium hydroxide at 340°. This reaction is a process of elimination followed by addition, plus a small amount of direct nucleophilic substitution. Hydrogen chloride is first eliminated (cf. E2 elimination, page 67).



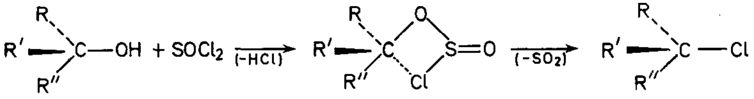
A very reactive intermediate, termed benzyne, is produced and this rapidly adds a nucleophile. Often the nucleophile is the solvent in which the reaction is carried out.



The nucleophile can add to benzyne in two ways and so a mixture of products may arise from a substituted halogenobenzene. Thus the reaction of *p*-bromotoluene with potassium amide, in liquid ammonia as solvent, produces a mixture of *m*- and *p*-toluidines and not just the *p*-isomer as would be expected from normal nucleophilic substitution.



Some bimolecular nucleophilic substitution reactions are known which proceed with retention of configuration. An example is the replacement of the —OH group of alcohols by —Cl using thionyl chloride. Reaction proceeds via a four-membered, cyclic intermediate involving the asymmetric centre, oxygen, sulphur and chlorine. Hence the configuration of the centre must be retained. This is termed an *internal* nucleophilic substitution reaction, usually abbreviated to S_Ni.



3.4 ELECTROPHILIC AROMATIC SUBSTITUTION

Electrophilic substitution is rarely encountered in saturated aliphatic systems but is the predominant mode of substitution in aromatic compounds. Addition, by an electrophilic process, to the multiple bonds of alkenes and alkynes is frequently observed (section 3.5). The common factor in electrophilic substitution and addition is that the systems which are attacked have exposed π molecular orbitals (*Figures 1.6* and *1.10*).

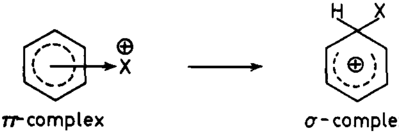
For a bond to be formed between benzene and an electrophile two electrons, from the π molecular orbital system, must be localised on a carbon atom. Any substituent already attached to the conjugated ring system will affect the energy required to localise two electrons on the different carbon atoms of the nucleus. As a result either predominantly *ortho/para* or *meta* substitution is generally observed in mono-substituted benzenes.

(a) MECHANISM OF ELECTROPHILIC SUBSTITUTION

The electrophile initially forms a weak interaction with the π electron system of the aromatic nucleus. This is termed a π-complex. The bonding between the two species in π-complexes is very weak and they can only be isolated at low temperatures (about −80°C) although complexes between benzene and iodine can be observed at room temperature.

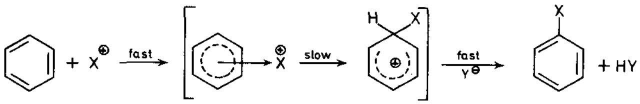
π-complex

The π-complex changes by an unknown but probably rate determining route to a σ-complex. Thus the general bonding of the electrophile, $X^{\oplus}$, to the π electron system changes so that X becomes specifically bonded to one carbon atom of the nucleus. This is the step that requires the localisation of two π electrons on to the carbon atom that is attacked.



The σ-complex is no longer aromatic but is an unstable cation in which four electrons are delocalised over five sp^2-hybridised carbon atoms. The carbon atom attacked by the electrophile has changed from the sp^2 to the sp^3-hybridisation state.

Lastly the σ-complex loses a proton to a base such as $HSO_4^{\ominus}$, $FeBr_4^{\ominus}$ or $AlCl_4^{\ominus}$. All six ring carbon atoms are then once more sp^2-hybridised and the substitution product of benzene has been formed. A driving force of this last step is the restoration of a fully conjugated aromatic system which is accompanied by a gain in stabilisation energy due to delocalisation of the six p electrons. The overall process of electrophilic aromatic substitution is indicated below and some examples of the reaction will be considered.



(i) *Nitration*

The nitronium ion, $O{=}\overset{\oplus}{N}{=}O$, is formed in mixtures of concentrated sulphuric and nitric acids.

$$\underset{}{HNO_3 + 2H_2SO_4 \rightleftarrows} \underset{\text{electrophile}}{\overset{\oplus}{N}O_2 + H_3\overset{\oplus}{O}} + \underset{\text{base}}{2HS\overset{\ominus}{O}_4}$$

The presence of any appreciable concentration of water pushes the equilibrium over to the left and suppresses the formation of the nitronium ion. Fuming nitric acid and oleum are used to nitrate unreactive substances, e.g. nitrobenzene. Acetic anhydride and nitric acid form acetyl nitrate, $CH_3CO\overset{\ominus}{O}\}\overset{\oplus}{N}O_2$, which is a useful reagent for reactive compounds such as pyrrole. Phenol is nitrated via a process of nitrosation with the nitrosonium ion, $NO^{\oplus}$, followed by oxidation (page 141).

(ii) *Halogenation*

Chlorination or bromination of the less reactive aromatic compounds only occurs in the presence of a Lewis acid such as $FeCl_3$, $AlCl_3$, $ZnCl_2$ or $FeBr_3$. The Lewis acid either accepts an electron pair from the halogen or polarises a halogen molecule.

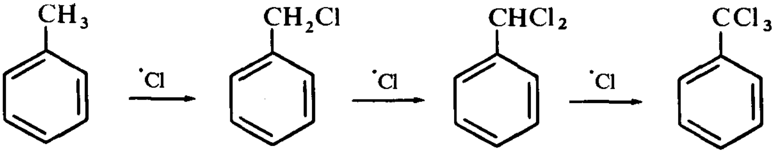
$$FeCl_3 + Cl_2 \rightarrow Fe\overset{\delta\ominus}{Cl_4}\text{-----}\overset{\delta\oplus}{Cl}$$

or

$$FeCl_3 + Cl_2 \rightarrow \underset{\text{electrophile}}{Cl^{\oplus}} + \underset{\text{base}}{FeCl_4^{\ominus}}$$

Arenes with some diene character, such as anthracene, polarise the halogen molecule sufficiently for reaction to occur without the necessity to introduce a Lewis acid.

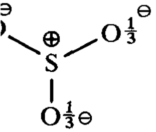
In the absence of a halogenation catalyst but in the presence of strong sunlight, halogen radicals are produced which either add to the ring carbon atoms or substitute any alkyl side chains present.



benzyl chloride benzal chloride benzotrichloride

(iii) *Sulphonation*

Sulphonation of arenes is achieved with either concentrated sulphuric acid or oleum. In either case sulphur trioxide is the electrophilic reagent, although not formally charged it can be considered to be electron deficient.

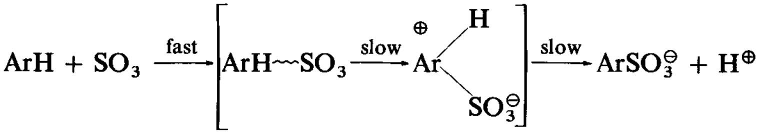


$$2H_2SO_4 \rightleftharpoons SO_3 + H_3O^{\oplus} + HSO_4^{\ominus}$$

Sulphonation differs from other electrophilic substitution reactions in that (i) it is a reversible process:

$$\mathrm{ArH} + \mathrm{H_2SO_4} \underset{\text{dilute } \mathrm{H_2SO_4}}{\overset{\text{conc. } \mathrm{H_2SO_4}}{\rightleftarrows}} \mathrm{ArSO_3H} + \mathrm{H_2O}$$

and (ii) the loss of a proton from the σ-complex is not much faster than the formation of this complex. By comparison in nitration, halogenation, alkylation, etc., the final loss of a proton is much faster than the formation of the σ-complex.

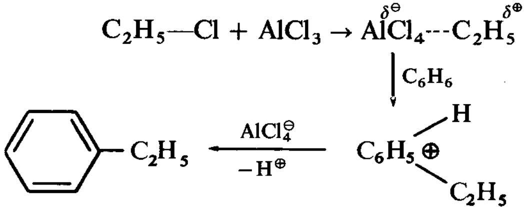


(*iv*) *Friedel–Crafts alkylation and acylation*

Again a Lewis acid is used to polarise the reagent. In the case of an alkyl halide and aluminium chloride a free carbonium ion may be formed in some cases but a polarised intermediate can also be the effective reagent.

$$\mathrm{C_2H_5{-}Cl} + \mathrm{AlCl_3} \rightleftarrows \underset{\substack{\text{carbonium ion}\\ \text{electrophile}}}{\mathrm{C_2^{\oplus}H_5}} + \underset{\text{base}}{\mathrm{AlCl_4^{\ominus}}}$$

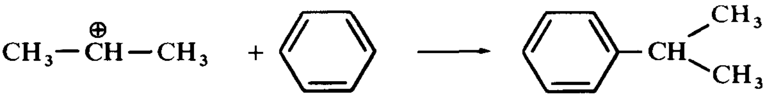
or



ethyl benzene

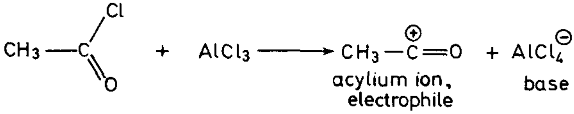
Other Lewis acids, or strong acids such as HF, H_2SO_4 or H_3PO_4, can be used and alkylation with alkenes or alcohols is possible, e.g.

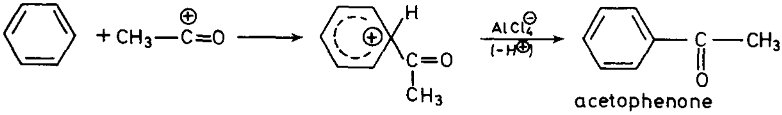
$$\mathrm{CH_3{-}CH{=}CH_2} + \mathrm{H^{\oplus}} \xrightarrow{\mathrm{H_3PO_4}} \mathrm{CH_3{-}\overset{\oplus}{C}H{-}CH_3}$$



iso-propylbenzene (cumene)

Acylation with an acyl halide and aluminium chloride probably takes place via an acylium ion, e.g.





(b) FURTHER ELECTROPHILIC SUBSTITUTION IN AN ALREADY SUBSTITUTED BENZENE RING

Aromatic substances can be classified as *Activated* or *Deactivated* relative to benzene, depending on whether they undergo electrophilic substitution faster or slower than benzene. Electron withdrawing groups produce deactivated arenes because they lower the overall π electron density of the nucleus and destabilise any σ-complex. The π electron density is lowered more at the *ortho* and *para* positions

Table 3.1. EFFECT OF SUBSTITUENTS ON PRODUCT ORIENTATION AND RATE OF ELECTROPHILIC SUBSTITUTION IN ARENES

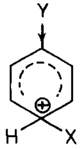
Substituent	*Electrical effects*	*Typical substance*	*Activated or deact. (A or D)*	*Rate of substn. relative to C_6H_6 (+ or −) and Prod. Orientation*
—R	+I	toluene	A	+ *o/p*
—Ar	+I +M	biphenyl	A	+ *o/p*
$—NH_2$ or $—NR_2$	−I +M	aniline	A	+ *o/p*
—OH or —OR	−I +M	phenol	A	+ *o/p*
$—O^{\ominus}$	+I +M	sodium phenoxide	A	+ *o/p*
—Hal	−I +M	chlorobenzene	D (weak)	− *o/p*
$—CH_2Cl$	−I	benzyl chloride	D (weak)	− *o/p*
$—\overset{\oplus}{N}H_3$ or $—\overset{\oplus}{N}R_3$	−I	aniline hydrochloride	D	− *m*
$—CHal_3$	−I	benzotrichloride	D	− *m*
—CHO or >C=O	−I −M	benzaldehyde	D	− *m*
—COOH or $—SO_3H$	−I −M	benzoic acid	D	− *m*
—C≡N	−I −M	cyanobenzene	D	− *m*
$—NO_2$	−I −M	nitrobenzene	D	− *m*

N.B. Halogens and the group $—CH_2Cl$ are anomalous in that they weakly deactivate the nucleus but at the same time produce *ortho*/*para* substitution.

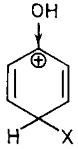
than at the *meta* position. Hence further electrophilic substitution occurs mainly at the *meta* position.

Conversely electron releasing groups produce activated arenes, stabilise any σ-complex and raise the π electron density over the whole ring system, particularly at the *ortho* and *para* positions. A summary of product orientation and substitution rates for some monosubstituted benzenes is given in *Table 3.1.*

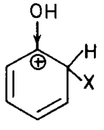
Electron releasing groups increase the stability of the σ-complex, I, and so decrease the activation energy required for this rate determining process of the substitution reaction. The effects of electron release are felt most strongly at the *ortho* and *para* positions, resonance hybrid structures II → IV are particularly stable, and so substitution occurs at these positions.



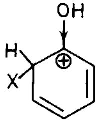
(I)



(II)

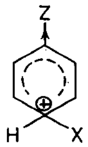


(III)

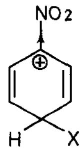


(IV)

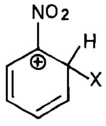
Electron attracting groups decrease the stability of the σ-complex, V, and thus increase the activation energy required to bring about reaction. Resonance hybrid structures leading to *ortho/para* substitution are particularly destabilised, i.e. structures such as VI and VII, and so further substitution occurs at the *meta* positions.



(V)



(VI)



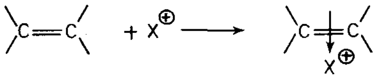
(VII)

3.5 ELECTROPHILIC AND FREE RADICAL ADDITION TO CARBON–CARBON DOUBLE BONDS

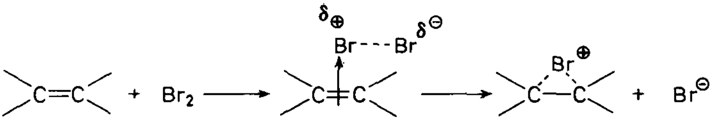
As has already been mentioned in the previous section the π molecular orbital systems of arenes and alkenes expose high concentrations of negative charge above and below the trigonal plane of the sp^2-hybridised carbon atoms. Ionic attack by electrophiles is, therefore, the first stage in polar additions to alkenes and is favoured by polar solvents. Free radical addition also occurs and is favoured by non-polar solvents, the presence of other radicals and sunlight.

(a) MECHANISM OF ELECTROPHILIC ADDITION

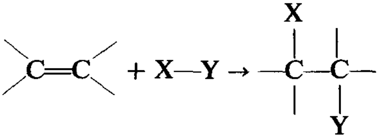
The initial step is the same as in electrophilic aromatic substitution, i.e. a π-complex is formed.



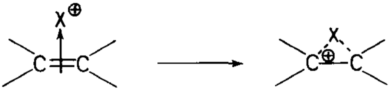
In the case of neutral addenda the electrophile is formed by the polarising influence of the π electron system on the reagent.



The π-complex then changes to a σ-complex but a complication arises at this stage because electrophilic addition to alkenes almost always produces a *trans* product.

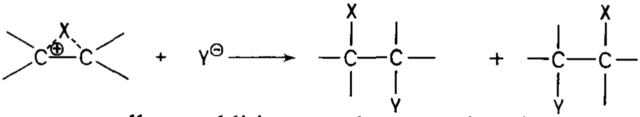


In order to explain this observation the σ-complex is considered to have a cyclic structure.



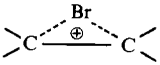
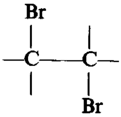
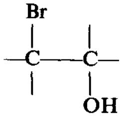
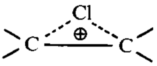
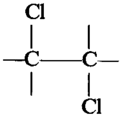
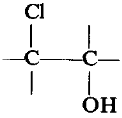
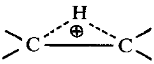
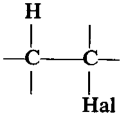
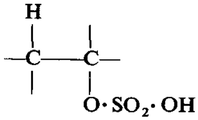
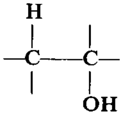
The bonding in this cyclic σ-complex cannot be of the normal covalent type but is 'electron deficient' in that one electron pair bonds three atomic centres.

The last step in the addition process is nucleophilic attack on the cyclic σ-complex. Whichever carbon atom is attacked the result is always a *trans* addition product.

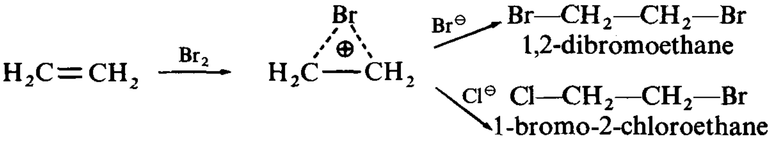


Some common alkene addition reactions are given in *Table 3.2.*

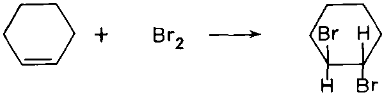
Table 3.2. ADDITION REACTIONS OF ALKENES

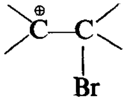
Reagent	*Electrophile or polarised reagent*	*σ-complex*	*Nucleophile*	*Product*
Br_2 or HOBr	$Br^{\oplus}$		$Br^{\ominus}$	 $-\overset{\mathrm{Br}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{Br}}{\underset{\vert}{\overset{\vert}{C}}}-$
			$HO^{\ominus}$	 $-\overset{\mathrm{Br}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{OH}}{\underset{\vert}{\overset{\vert}{C}}}-$
Cl_2 or HOCl	$Cl^{\oplus}$		$Cl^{\ominus}$	 $-\overset{\mathrm{Cl}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{Cl}}{\underset{\vert}{\overset{\vert}{C}}}-$
			$HO^{\ominus}$	 $-\overset{\mathrm{Cl}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{OH}}{\underset{\vert}{\overset{\vert}{C}}}-$
H Hal H_2SO_4 $H_3O^{\oplus}$	$H^{\oplus}$		$Hal^{\ominus}$	 $-\overset{\mathrm{H}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{Hal}}{\underset{\vert}{\overset{\vert}{C}}}-$
			$HSO_4^{\ominus}$	 $-\overset{\mathrm{H}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{O\cdot SO_2\cdot OH}}{\underset{\vert}{\overset{\vert}{C}}}-$
			H_2O	 $-\overset{\mathrm{H}}{\overset{\vert}{\underset{\vert}{C}}}-\underset{\mathrm{OH}}{\underset{\vert}{\overset{\vert}{C}}}-$

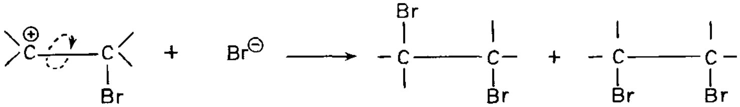
Evidence that a positively charged intermediate exists for a finite time during an electrophilic addition reaction can be obtained from the bromination of ethylene in a polar solvent containing sodium chloride. A mixture of dibromo and bromochloroethanes is formed.



Evidence for overall *trans* addition is best obtained from cyclic alkenes such as cyclohexene or cyclopentene.



The ring system prevents free rotation about the $>$CBr—CBr$<$ bond which normally takes place with $BrCH_2$—CH_2Br and other non-cyclic compounds. It is because of free rotation about a σ-bond that a cyclic σ-complex is a proposed intermediate in the reaction scheme. An open chain σ-complex of the type  $>\overset{\oplus}{C}-\underset{\underset{Br}{|}}{C}<$ should undergo free rotation about the carbon–carbon bond before attack by the nucleophile can take place and this would lead to a mixture of *cis* and *trans* isomers. In practice this mixture of isomers is not formed.



As with aromatic compounds electron releasing groups attached to one or both of the carbon atoms forming the double bond increase the π electron density and activate the molecule towards electrophilic attack. Electron withdrawing substituents attached to the double bond deactivate alkenes and so the rate of electrophilic addition relative to ethylene is reduced.

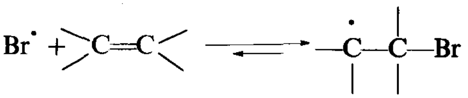
(b) MECHANISM OF FREE RADICAL ADDITION (see also section 16.2)

Addition of free radicals to alkenes is more difficult to study than electrophilic addition. Intensive precautions must be taken to prevent the more normal electrophilic addition, e.g. polar sites such as water and glass vessel walls must be eliminated. Free radical addition is usually initiated by ultra-violet light or by the thermal decomposition of a peroxide such as benzoyl peroxide, PhCO.O—O.OCPh. Under such conditions chlorine and bromine react readily with alkenes by a chain mechanism. Iodine is unreactive and fluorine reacts explosively.

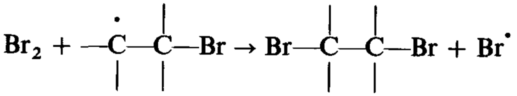
The first step in the chain reaction is that the halogen molecule dissociates into two radicals

$$\mathrm{Br_2} \xrightarrow[\text{peroxide}]{\text{u.v. or}} 2\mathrm{Br}^{\bullet}$$

The bromine radical then propagates the chain reaction:

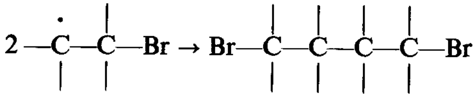


and the carbon radical reacts with another halogen molecule.



$$\mathrm{Br_2} + -\dot{\mathrm{C}}-\mathrm{C}-\mathrm{Br} \rightarrow \mathrm{Br}-\mathrm{C}-\mathrm{C}-\mathrm{Br} + \mathrm{Br}^{\bullet}$$

As the carbon radical is not a cyclic structure the product can be a mixture of *cis* and *trans* isomers. Finally some step such as the combination of two radicals terminates the reaction.

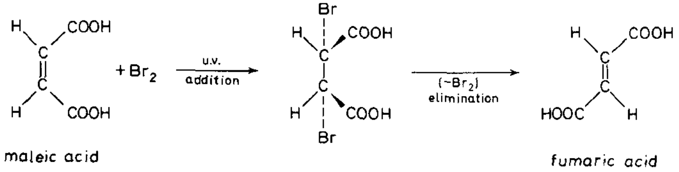


$$2\,-\dot{\mathrm{C}}-\mathrm{C}-\mathrm{Br} \rightarrow \mathrm{Br}-\mathrm{C}-\mathrm{C}-\mathrm{C}-\mathrm{C}-\mathrm{Br}$$

The free radical addition of halogens to alkenes is a reversible process. Below 200° the addition of chlorine is irreversible but between 200° and 450° the reaction is reversible and above 450° allyl position chlorination occurs.

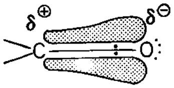
$$\underset{\text{allyl chloride}}{\mathrm{Cl{-}CH_2{-}CH{=}CH_2}} \xleftarrow{>450^\circ} \underset{\text{propene}}{\mathrm{CH_3{-}CH{=}CH_2}} \underset{200\text{–}450^\circ}{\overset{<200^\circ}{\rightleftharpoons}} \underset{\text{1,2-dichloropropane}}{\mathrm{CH_3{-}CHCl{-}CH_2Cl}}$$

With bromine the addition is often reversible at room temperature. Thus if the alkene is mixed with a trace of bromine and exposed to sunlight then conversion of the less stable *cis* isomer to the more stable *trans* isomer takes place, e.g. maleic acid is converted to fumaric acid.

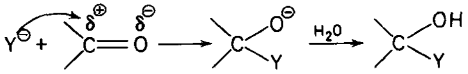


3.6 NUCLEOPHILIC AND ELECTROPHILIC ADDITION TO THE CARBONYL GROUP

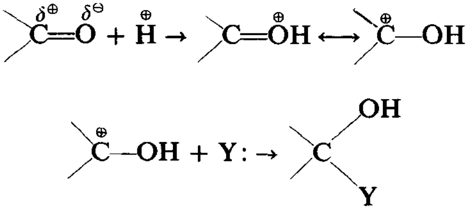
The carbonyl group is strongly polarised. The carbon atom forms a site for attack by nucleophiles and the lone pairs of the oxygen are easily protonated by acids or coordinated to Lewis acids.



Attack by nucleophiles is favoured because in the reaction transition state the oxygen atom can easily support the developing negative charge.



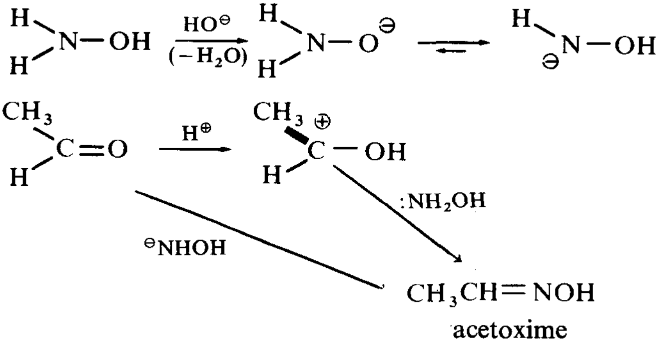
In acid conditions the oxygen atom is protonated, the positivity of the carbon atom is increased and attack by nucleophiles is enhanced.



The operation of the two modes of attack on the carbonyl group is well illustrated by the reaction of hydroxylamine with acetaldehyde. In acid solutions the rate of reaction reaches a maximum near pH = 5 and then falls at higher acid concentrations due to the protonation of the reagent:

$$NH_2OH + H^{\oplus} \rightleftharpoons \overset{\oplus}{N}H_3OH$$

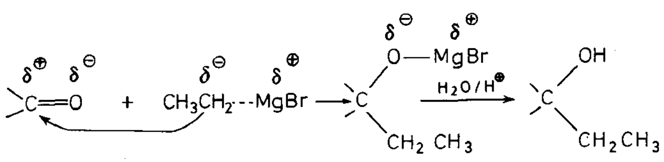
As the solution is made alkaline the rate of reaction again rises owing to the formation of the more powerful nucleophile $\overset{\ominus}{N}HOH$.



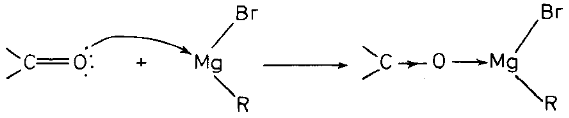
The addition reactions of aldehydes and ketones are summarised in section 8.2 but three further examples of the mechanisms of such reactions are mentioned below.

(i) Addition of Grignard reagents

The alkyl group of the Grignard reagent behaves as the nucleophile.

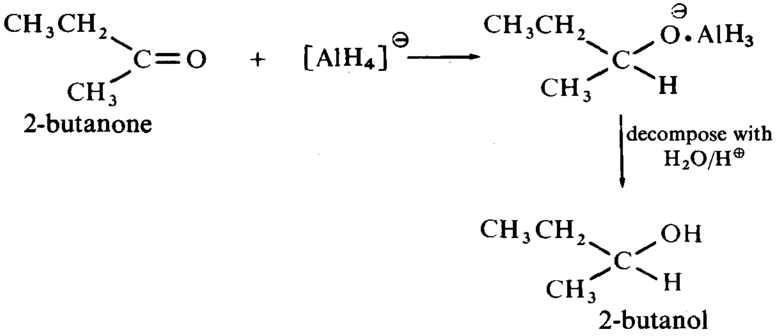


The reagent may also act as a Lewis acid and increase the positivity of the reaction centre.



(*ii*) *Reduction with lithium aluminium hydride*

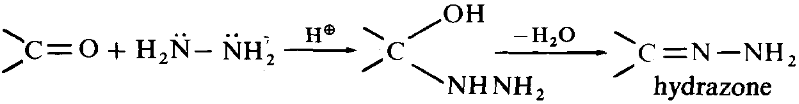
Aldehydes and ketones (and carboxylic acids, esters and amides) are reduced by this reagent to primary and secondary alcohols. The nucleophile is the hydride ion, $H^{\ominus}$, which is transported by the alminium hydride ion, $[AlH_4]^{\ominus}$.



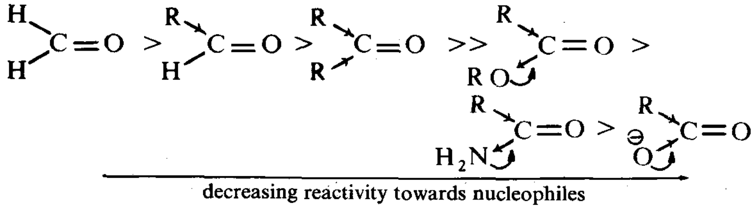
Sodium borohydride, $NaBH_4$, reduces aldehydes and ketones only, by a similar reaction.

(*iii*) *Addition of hydrazine*

This addition is acid catalysed and water is eliminated from the initial addition product to form a carbon–nitrogen double bond.

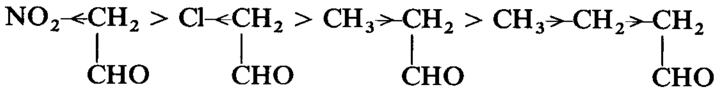


For maximum reactivity towards nucleophiles the carbonyl carbon atom should be as positive as possible and not sterically hindered by adjacent groups. Thus electron donating groups destabilise the transition state and reduce the rate of addition of nucleophiles to the carbonyl group.



Formaldehyde is more reactive than other aldehydes which in turn are more reactive than ketones. In amides and esters the $-$I effects of the $-NH_2$ and $-OR'$ groups are outweighed by their +M effects. The negatively charged oxygen atom of the carboxylate anion exerts both a +I and a +M effect.

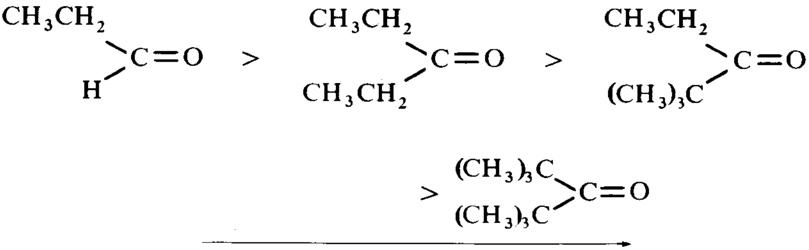
The reactivity of carbonyl compounds is decreased when an aromatic nucleus is directly attached to the carbonyl carbon atom but substituents attached to the nucleus will interact with the carbonyl group in the normal way. Thus benzaldehyde is less reactive than acetaldehyde but *p*-nitrobenzaldehyde is more reactive than benzaldehyde due to the electron withdrawing properties ($-$I and $-$M) of the nitro group. The following change in reactivity is found with a series of aliphatic aldehydes.



$$\mathrm{NO_2{\leftarrow}\underset{\underset{CHO}{|}}{CH_2}} > \mathrm{Cl{\leftarrow}\underset{\underset{CHO}{|}}{CH_2}} > \mathrm{CH_3{\rightarrow}\underset{\underset{CHO}{|}}{CH_2}} > \mathrm{CH_3{\rightarrow}CH_2{\rightarrow}\underset{\underset{CHO}{|}}{CH_2}}$$

decreasing reactivity towards nucleophiles

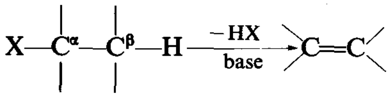
Bulky groups about the carbonyl group increase the activation energy required to form the transition state and decrease the rate of reaction with nucleophiles. Cyclic ketones react faster than open chain ketones because in the former the bulky alkyl groups are held away from the reaction centre by the cyclic structure.



decreasing reactivity towards nucleophiles

3.7 UNIMOLECULAR AND BIMOLECULAR ELIMINATION REACTIONS

Elimination reactions are those in which two groups are removed from a molecule without being replaced by other groups.



$$X-\overset{|}{\underset{|}{C^{\alpha}}}-\overset{|}{\underset{|}{C^{\beta}}}-H \xrightarrow[\text{base}]{-HX} \rangle C=C\langle$$

(e.g. X = —Cl, —Br, —I, —$\overset{\oplus}{N}R_3$, —$\overset{\oplus}{O}H_2$)

This is termed a β-elimination because the base removes a proton from the β-carbon atom as group X leaves the α-carbon atom. Some examples of elimination reactions are:

(1) base induced dehydrohalogenation,

$$RCH_2-CH_2-Br \xrightarrow{HO^{\ominus}} RCH=CH_2 + H_2O + Br^{\ominus}$$

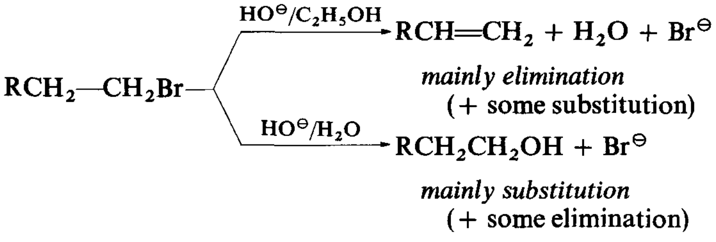
(2) acid catalysed dehydration of alcohols,

$$RCH_2CH_2OH \xrightarrow{H^{\oplus}} RCH_2CH_2\overset{\oplus}{O}H_2 \rightarrow RCH=CH_2 + H_3\overset{\oplus}{O}$$

(3) Hofmann degradation of quaternary alkylammonium hydroxides.

$$RCH_2-CH_2-\overset{\oplus}{N}R_3\{\overset{\ominus}{O}H \xrightarrow{HO^{\ominus}} RCH=CH_2 + H_2O + R_3N$$

Elimination reactions have been shown to take place by either a unimolecular or bimolecular mechanism, designated E1 and E2 respectively (cf., S_N1 and S_N2). Elimination and substitution reactions usually proceed together.



$$RCH_2-CH_2Br \xrightarrow{HO^{\ominus}/C_2H_5OH} RCH=CH_2 + H_2O + Br^{\ominus}$$

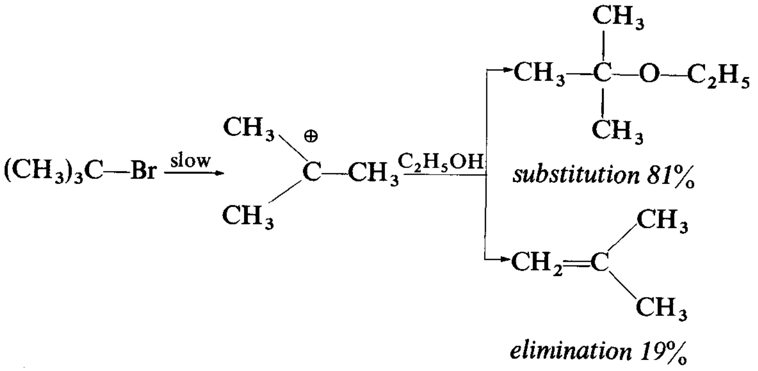
mainly elimination
(+ some substitution)

$$RCH_2-CH_2Br \xrightarrow{HO^{\ominus}/H_2O} RCH_2CH_2OH + Br^{\ominus}$$

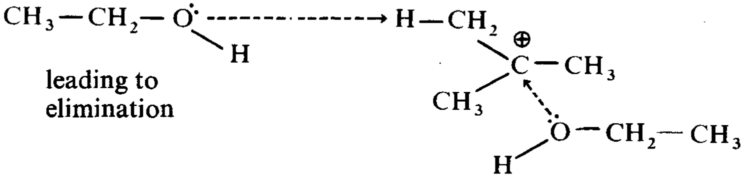
mainly substitution
(+ some elimination)

(a) UNIMOLECULAR ELIMINATION (E1)

Alkene formation often accompanies substitution but does not alter the overall kinetics of the reaction. Thus the ethanolic solvolysis of t-butyl bromide produces a mixture of 2-methylpropene and t-butyl ethyl ether but the rate determining process is the slow ionisation of the bromide. The overall rate of reaction = $K[(CH_3)_3C{-}Br]$.

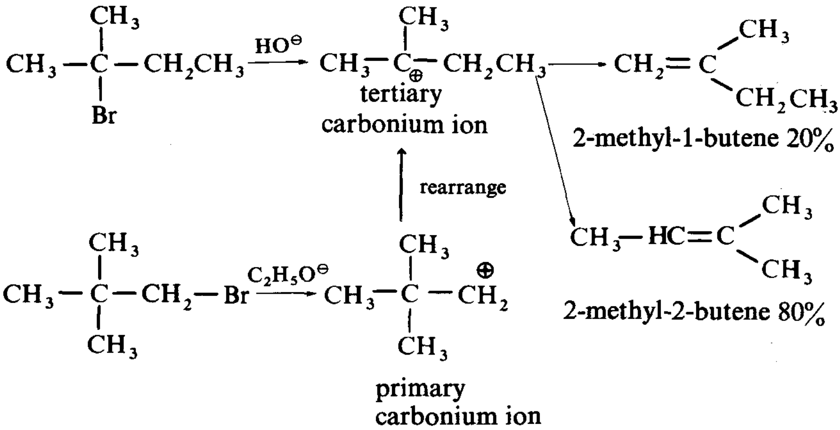


To produce substitution a nucleophile, i.e. ethanol, attacks the positively charged carbon atom of the carbonium ion but for elimination the nucleophile attacks and detaches a hydrogen atom.



leading to substitution

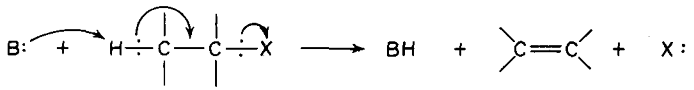
Unimolecular elimination is the major alkene forming route when a stable carbonium ion can be formed, i.e. it is normally only encountered with tertiary halides. In reactions which can give rise to a number of alkenes the most stable alkene, which is normally the most highly branched alkene, usually predominates. However, a further complication is that the intermediate carbonium ion may rearrange to a more stable form which in turn will produce its most stable alkene. Thus a number of alkenes, which may exist as *cis* and *trans* isomers in some cases, can be obtained from a single elimination reaction.



(b) BIMOLECULAR ELIMINATION (E2)

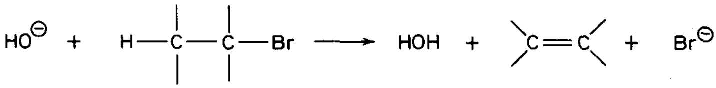
Bimolecular elimination often accompanies bimolecular nucleophilic substitution. With primary and secondary alkyl halides, and hydroxide ion as the base, a mixture of an alkene and an alcohol is formed. The overall reaction exhibits second order kinetics, i.e. rate = $K[RCH_2CH_2Hal]\,[HO^{\ominus}]$.

Bimolecular elimination is a one-step process and the mechanism is said to be *concerted* because as the base removes a β-hydrogen atom the double bond forms and the leaving group, X, simultaneously departs from the α-carbon atom.



$$B: + H-C-C-X \longrightarrow BH + \rangle C{=}C\langle + X:$$

e.g.

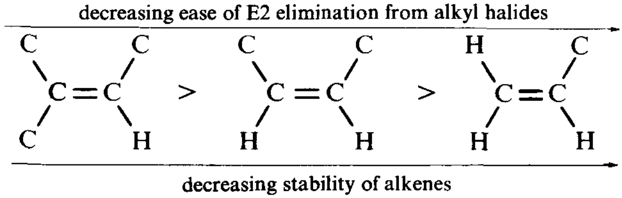


$$HO^{\ominus} + H-C-C-Br \longrightarrow HOH + \rangle C{=}C\langle + Br^{\ominus}$$

The base attacks an exposed hydrogen atom. A five centre transition state, as found in S_N2 substitution, is not encountered and so E2 eliminations are not subject to steric hindrance. In fact the ease of

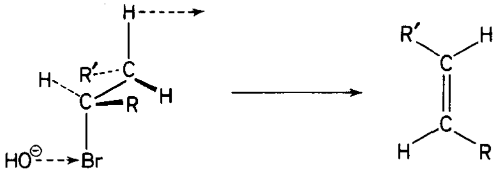
E2 elimination from alkyl groups parallels the stability of the alkenes produced, i.e.

tert. > sec. > primary



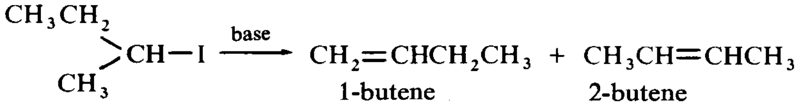
The above order of reactivity is the reverse of that for S_N2 substitution.

Whilst E2 elimination is not subject to steric hindrance it is subject to the steric requirement that the eliminated groups (H and X) shall be *trans* to one another. In this way H, C^{β}, C^{α} and X are coplanar and the developing *p* atomic orbitals form in the same plane.



This is very similar to the attacking nucleophile keeping as far away as possible from the leaving group during the formation of an S_N2 transition state. *Cis* elimination only occurs in a few special cases.

For the different halogens the ease of E2 elimination is in the order I > Br > Cl for the same base. Only strong bases bring about E2 elimination and the ratio of bimolecular elimination to bimolecular substitution increases with strength of the base.



$$\begin{matrix}CH_3CH_2 \\ \quad\quad > CH{-}I \\ CH_3\end{matrix} \xrightarrow{\text{base}} \underset{\text{1-butene}}{CH_2{=}CHCH_2CH_3} + \underset{\text{2-butene}}{CH_3CH{=}CHCH_3}$$

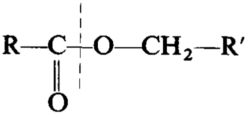
+ substitution products

Increasing strength of base →	$HO^{\ominus}$	$C_2H_5O^{\ominus}$	$(CH_3)_3CO^{\ominus}$
Ratio $E2/S_N2$ =	32	49	99

3.8 ESTERIFICATION OF ACIDS AND HYDROLYSIS OF ESTERS

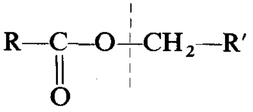
There are three important variables in the reactions involving esterification and ester hydrolysis.

(1) The reaction can be uni- or bimolecular (1 or 2).
(2) The carbon–oxygen bond of the ester linkage can be made or broken in two ways:



$$R-\underset{\underset{O}{\|}}{C}\,\vdots\,O-CH_2-R'$$

Acyl–oxygen bond fission or formation (AC)



$$R-\underset{\underset{O}{\|}}{C}-O\,\vdots\,CH_2-R'$$

Alkyl–oxygen bond fission or formation (AL)

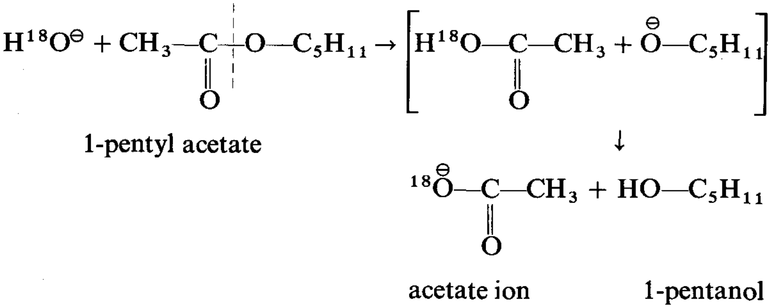
(3) Ester hydrolysis can proceed in basic solution (B) when the ester itself, $RCOOCH_2R'$, is attacked, or in acid solution (A) when the conjugate acid of the ester, $R-\underset{\underset{OH}{|}}{\overset{\oplus}{C}}-O-CH_2R'$, is attacked.

Esterification only proceeds in acid solution (A) because in basic solution the carboxylate anion, $RCOO^{\ominus}$, will not undergo attack by nucleophiles. If all the above variables are taken into account then there are eight possible mechanisms of ester hydrolysis and four of esterification. Two of the most commonly encountered mechanisms will be considered.

(a) BIMOLECULAR BASIC HYDROLYSIS OF ESTERS WITH ACYL-OXYGEN FISSION (usually abbreviated to $B_{AC}2$)

Second order kinetics have been observed for this type of reaction and so the transition state must contain one ester molecule and one hydroxyl ion, i.e. rate of hydrolysis $= K[RCOOCH_2R'][H\overset{\ominus}{O}]$. Acyl–oxygen bond fission was proven using $H_2{}^{18}O$ in the hydrolysis of 1-pentyl acetate. The acetate ion contained the ^{18}O and so the acyl–oxygen bond must have broken at some stage in the reaction.

The heavy isotope of oxygen, ^{18}O, is not radioactive but can be detected by mass spectrometry.

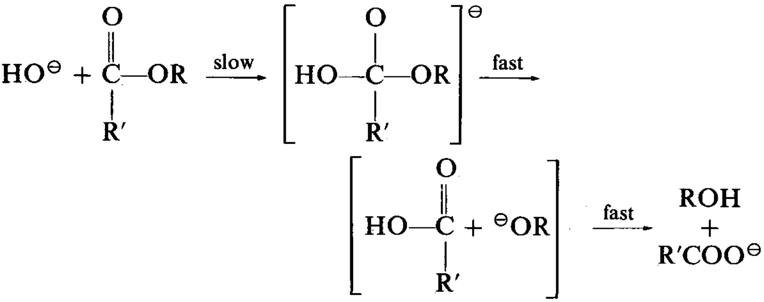


$$H^{18}O^{\ominus} + CH_3-\underset{\underset{O}{\|}}{C}-O-C_5H_{11} \rightarrow \left[H^{18}O-\underset{\underset{O}{\|}}{C}-CH_3 + \overset{\ominus}{O}-C_5H_{11}\right]$$

$$\downarrow$$

$$^{18}\overset{\ominus}{O}-\underset{\underset{O}{\|}}{C}-CH_3 + HO-C_5H_{11}$$

A mechanism consistent with nucleophilic attack on the neutral ester is:



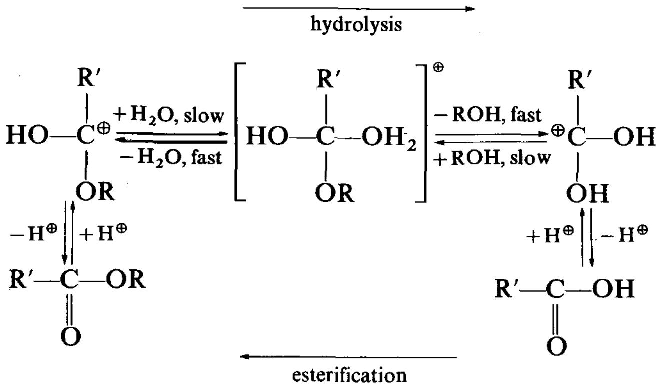
$$HO^{\ominus} + \overset{\overset{O}{\|}}{\underset{\underset{R'}{|}}{C}}-OR \xrightarrow{\text{slow}} \left[HO-\overset{\overset{O}{|}}{\underset{\underset{R'}{|}}{C}}-OR\right]^{\ominus} \xrightarrow{\text{fast}}$$

$$\left[HO-\overset{\overset{O}{\|}}{\underset{\underset{R'}{|}}{C}} + {}^{\ominus}OR\right] \xrightarrow{\text{fast}} \begin{matrix}ROH\\+\\R'COO^{\ominus}\end{matrix}$$

The overall reaction is irreversible and the transition state is more sterically crowded than the free ester so that ester hydrolysis by this mechanism is slowed down if R and R′ are bulky groups.

(b) BIMOLECULAR ACID HYDROLYSIS AND ESTERIFICATION WITH ACYL–OXYGEN FISSION ($A_{AC}2$)

Most esterification reactions and the hydrolysis of esters derived from primary and secondary alcohols proceed by this mechanism. The main difference between the $B_{AC}2$ and $A_{AC}2$ mechanisms is that the former is irreversible whilst the latter is reversible. Therefore, hydrolysis and esterification by the $A_{AC}2$ mechanism must proceed through the same intermediate. A reversible mechanism involving the conjugate acids of both the ester and the carboxylic acid is:



The slow step in each reaction is the addition of water and alcohol to the conjugate acids of the ester and the carboxylic acid respectively. The addition and removal of protons occurs rapidly. The reaction intermediate, which is a complex of a proton and an ester and water molecule, is subject to steric crowding if R and R′ are bulky groups. This steric effect is illustrated by the rates of $A_{AC}2$ esterification of the following acids with methanol at 20°.

$x =$	CH_3COOH	C_3H_7COOH	$(CH_3)_3CCOOH$	$(C_2H_5)_3CCOOH$
$\frac{Kx}{K_{CH_3COOH}}$	1·0	0·5	0·037	0·00016

4

Spectroscopic Methods in Organic Chemistry

4.1 INFRA-RED SPECTRA

Infra-red spectra can provide so much information about an organic compound in such a short time that the measurement of these spectra has become a standard technique in most chemistry laboratories. Relatively inexpensive commercial infra-red spectrophotometers are available to cover the range 4000–625 cm^{-1} (2·5–16 μ) which is of greatest interest to the organic chemist.

Units of infra-red and ultra-violet spectroscopy:

metre	cm	mm	μ	nm	Å
1	10^{-2}	10^{-3}	10^{-6}	10^{-9}	10^{-10}

Wavelength and frequency are inversely proportional, i.e.

$\nu = c/\lambda$, where ν = frequency, Hz (cycles/s)
λ = wavelength, cm
c = velocity of light (3×10^{10} cm/s)

The frequency and energy of the radiation are directly related,

$E = h\nu$, where E = energy of radiation, ergs
h = Planck's constant.

Electromagnetic spectra are best described by some function of frequency (or energy) and the number of waves per cm is the term normally used for this purpose, i.e. $\bar{\nu} = 1/\lambda\ \mathrm{cm}^{-1}$ and then $E = 119{\cdot}7 \times 10^{-4}\bar{\nu}$ kJ/mol.

The approximate positions of the infra-red, visible and ultra-violet regions of the spectrum, in the overall electromagnetic spectrum, are shown in *Figure 4.1*. Nearly all infra-red and many ultra-violet spectrophotometers are now of the recording, double beam type so that absorption by the cell, solvent, water vapour or atmosphere is balanced out in the reference beam. Monochromatic radiation is normally produced by a plastic replica diffraction grating; this has largely displaced the rock salt (NaCl) prism.

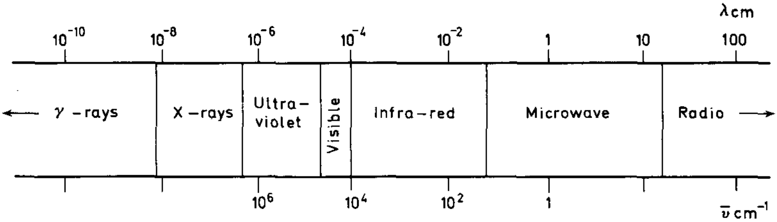
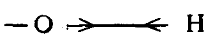


Figure 4.1

Energy levels in a molecule are quantised, i.e. have discrete rather than continuous values, and the total energy of a molecule is made up of three parts, the rotational energy, the vibrational energy and the electronic energy. The energy required to bring about purely rotational changes in a molecule is small and lies in the microwave region of the spectrum. Microwave spectra of simple molecules provide accurate values for bond lengths and angles but the technique is specialised and not often used by the organic chemist.

Vibrational changes in a molecule require energy falling in the region 4000–1000 cm^{-1} and are associated with the bonds X—H, where X = C, O or N, C═Y, where Y = C, O or N and C≡Z, where Z = C or N.



Absorption of energy also takes place in the region 1000–625 cm^{-1}, but this is associated with complex coupled vibrational and rotational energy changes. Whilst interpretation of each absorption peak in the 1000–625 cm^{-1} region is often difficult the overall pattern of absorption can provide conclusive evidence that two or more chemical samples are identical or different. The reason for complex absorption patterns is that a molecule has 3*N*-6 degrees of freedom of movement (*N* is the number of atoms in the molecule) and whilst all the resulting vibrations do not absorb in the infra-red a great many do appear. Slight differences in structure produce marked differences in an overall absorption pattern and so the 1000–625 cm^{-1} region is often called the 'finger-print' region.

The observed stretching frequencies of a number of groups in the region 4000–1000 cm^{-1} are shown in *Table 4.1*.

Table 4.1. INFRA-RED ABSORPTION FREQUENCIES (4000–1000 CM^{-1})

Bond	*Typical compound*	*Frequency* (cm^{-1})	*Intensity of absorption**
X—H			
C_{sp^3}—H	alkanes, CH_3—CH_2—	2850–2960	s
C_{sp^2}—H	alkenes, CH=CH_2	3010–3090	m
C_{sp}—H	alkynes	3280–3320	s
C_{conj}—H	arenes	3010–3030	w
C_{sp^3}—D	deuterated alkanes	near 2200	s
O—H free		3590–3640	v
O—H intermol. H-bonds	alcohols	3200–3600	s
	and		
O—H intramol. H-bonds	phenols	2700–3200	v broad
O—H	carboxylic acids	2500–3000	characteristic group of bands
N—H_2	amines	3200–3500	m
$\overset{\oplus}{N}H_3$	amine salts	3000–3130	m
S—H	thiols	2550–2600	w
C=Y			
C=C	alkenes	1620–1680	v
C=C—(C=O)	α,β-unsaturated carbonyl compounds	1590–1640	s
C=N	oximes	1640–1690	w
C=O	aldehydes, ketones, etc. (see *Table 4.2*)	1600–1860	s
C≡Z			
C≡C	alkynes	2100–2260	v
C≡N	cyanides	2200–2260	v
C—O	alcohols, ethers, etc.	1080–1300	s
NO_2	nitro compounds	two bands 1520–1560 1340–1380	s
Aromatic ring	arenes	two or three bands: 1500–1600	m

* Intensities, w—weak, m— medium, s—strong, v—variable.

The stretching vibrations of bonds can be written $—C\leftrightarrow H$ and the energy (frequency) absorbed in the process depends mainly on the masses of the atoms involved and to a lesser extent on the electrical properties (I and M effects) in the molecule. Thus the C—D bond has a much lower absorption frequency than the C—H bond. More complex groups have different stretching patterns, e.g. the nitro and amino groups

symmetric and antisymmetric stretching frequencies

Thus the two stretching modes of the nitro group absorb at different frequencies and so two bands are observed near 1350 and 1550 cm^{-1} respectively. The carbonyl group in different classes of organic compounds always produces a strong absorption band in the region 1600–1860 cm^{-1}. The wide range illustrates the different electrical effects operative in a series of carbonyl compounds. Reference to *Table 4.2* shows that a number of carbonyl compounds can be differentiated without performing a single chemical test.

Table 4.2. VARIATIONS IN THE CARBONYL GROUP STRETCHING FREQUENCY

Bond	*Typical compound*	*Frequency* (cm^{-1})	*Intensity*
C=O	all carbonyl compounds	1600–1860	s
aldehydes, satd.	propionaldehyde	1720–1740	
aldehydes, aryl	benzaldehyde	1695–1715	
ketones, satd.	2-butanone	1705–1725	
ketones, α.β-unsatd.	2-methyl-2-penten-4-one (mesityl oxide)	1665–1685	
ketones, aryl	acetophenone	1680–1700	
carboxylic acids, satd.	propionic acid	1700–1725	
carboxylic acids, aryl	benzoic acid	1680–1700	
carboxylic acids, α-halo	bromoacetic acid	1720–1740	
esters, satd.	ethyl acetate	1735–1750	
anhydrides, satd.	acetic anhydride	1800–1850 1740–1790 } two bands	
acyl halides	acetyl chloride	1790–1815	
amides (primary)	propionamide	1690	

The hydroxyl group is very subject to strong hydrogen bonding and the free O—H absorption is only observed for alcohols, etc., in dilute solutions in a non-polar solvent. In fact a distinction can often be made between inter- and intramolecular hydrogen bonding by infra-red spectroscopic studies. The broad intramolecular hydrogen bonded absorption near 3000 cm^{-1} is not affected by dilution of the solution. Intermolecular hydrogen bonds are, however, broken as a solution is progressively diluted and the broad band near 3300 cm^{-1} gradually disappears, to be replaced by a sharp peak near 3600 cm^{-1} due to the free O—H absorption.

The infra-red spectra of aromatic compounds exhibit weak C—H stretching frequencies near 3030 cm^{-1} and two or three absorption bands between 1500 and 1600 cm^{-1} due to the movement of the ring carbon atoms. Sometimes the substitution pattern of the ring (1,2-, 1,3- or 1,4-, etc.) can be deduced from the C—H out of plane bending vibrations in the region 730–900 cm^{-1}. Alternatively the general shapes of the very weak overtone bands in the

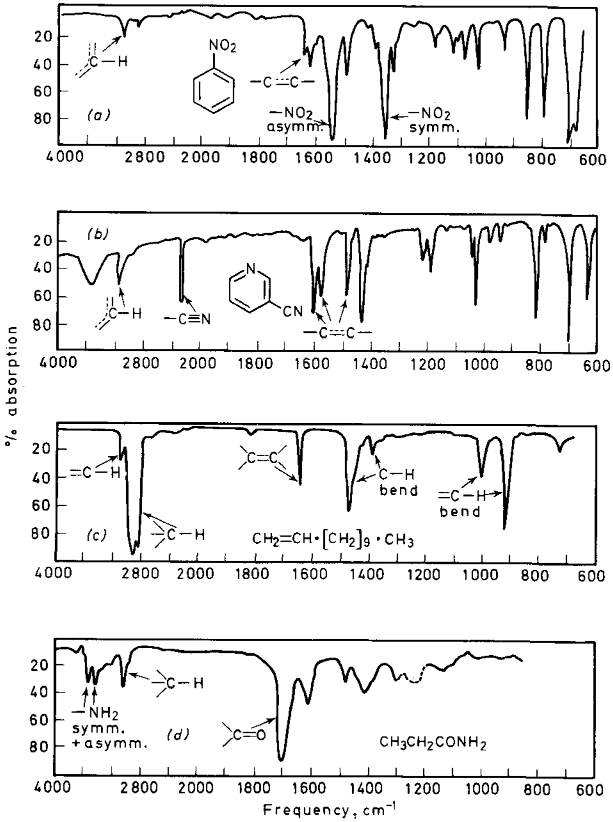


Figure 4.2. Infra-red spectra of (*a*) *nitrobenzene,* (*b*) *3-cyanopyridine,* (*c*) *1-dodecene,* (*d*) *propionamide*

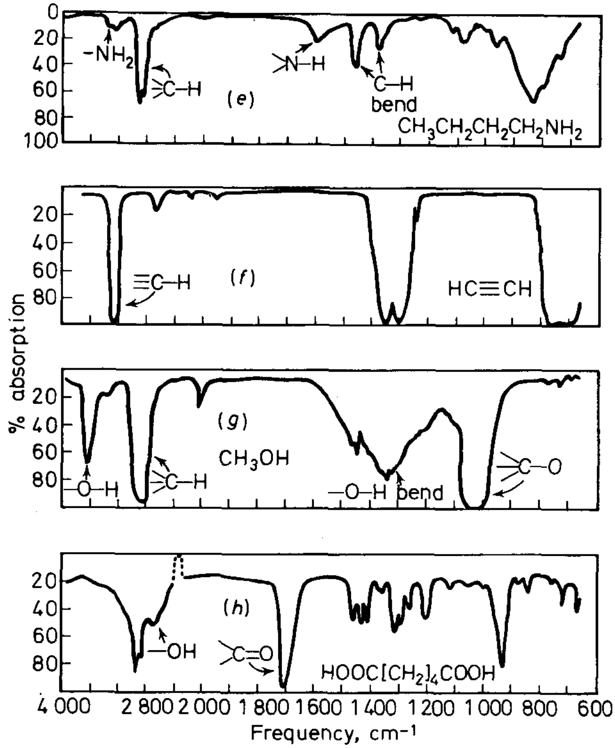


Figure 4.2. Infra-red spectra of (e) n-butylamine, (f) acetylene, (g) methanol, (h) adipic acid

1600–2000 cm^{-1} region can, by reference to patterns for known compounds, produce similar information.

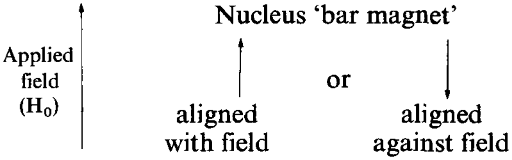
The infra-red spectra of adipic acid, acetylene, n-butylamine, 3-cyanopyridine, 1-dodecene, methanol, nitrobenzene and propionamide are illustrated in *Figure 4.2(a)–(h)*. Some of the characteristic absorption bands mentioned in this section are marked on the figures.

4.2 NUCLEAR MAGNETIC RESONANCE SPECTRA

(a) INTRODUCTION

Some atomic nuclei behave like very small, spinning bar magnets.

In the presence of a uniform, applied magnetic field the nucleus 'bar magnet' can become aligned either with or against this field.



Alignment with the field is the low energy position and against the field the high energy orientation. If a nucleus in the low energy orientation absorbs a quantum of suitable radiation ($h\nu$) then a transition to the higher energy state will occur. In practice for an applied field of 9000–14000 gauss the radiation required ($h\nu$) lies in the radiofrequency range of 30–60 MHz.

Nuclei which can behave like small bar magnets are those having a spin quantum number, $I \neq 0$. The nuclei ^1H, ^{19}F and ^{31}P all have $I = \frac{1}{2}$ and give rise to useful n.m.r. spectra. The first of these, ^1H, is by far the most important for the organic chemist. All nuclei which have a mass number exactly divisible by four possess zero spin quantum numbers. Therefore, the nuclei ^{12}C and ^{16}O do not give rise to n.m.r. spectra. This is just as well for if they did the resultant n.m.r. spectra of most organic compounds would probably be too complex to interpret.

(b) MEASUREMENT OF N.M.R. SPECTRA

To measure an n.m.r. spectrum the applied magnetic field, which must be uniform in the region around the sample, is kept constant and the radiofrequency varied sufficiently to allow each type of proton in the molecule to absorb radiation. Alternatively the radiofrequency can be kept constant and the applied field varied. An outline diagram of the apparatus used is shown in *Figure 4.3*. Any absorption of the applied radiofrequency signal by the sample is detected by a sensitive radiofrequency receiver.

The radiofrequency at which a proton will absorb and change energy states is proportional to the magnetic field. With an applied field of approximately 9300 gauss most of the protons encountered in organic molecules absorb in the radiofrequency region 40 MHz ±200 Hz (or 60 MHz ±300 Hz at 14100 gauss). Thus the n.m.r. spectrometer must be able to resolve 1 Hz in 10^5 but in practice the resolution can be as high as 1 in 10^8, *relative to an internal standard.*

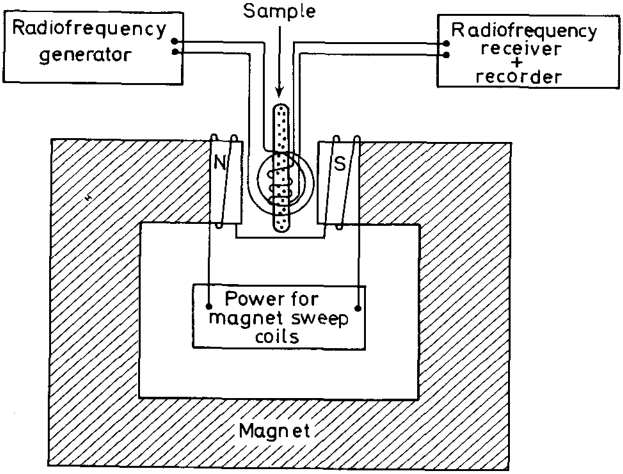


Figure 4.3. Outline diagram of n.m.r. spectrometer

The internal standard most frequently used is tetramethylsilane, $(CH_3)_4Si$. The silicon atom releases electrons to the more electronegative carbon atoms and so the protons of the methyl groups are more shielded than most protons in organic compounds. Other useful features of tetramethylsilane (TMS) as a reference standard are:

(*i*) the twelve equivalent protons give rise to a single sharp absorption line and so only a low concentration of the substance (<1 per cent) is necessary.
(*ii*) it is an inert liquid which does not bond or complex with organic substances.

(c) THE CHEMICAL SHIFT

The statement made above that the frequency (ν) of radiation absorbed by a proton is proportional to the applied field (H_0) is not strictly correct. This is because the local magnetic field (H) experienced by the proton will be less than the applied field by a factor σ, i.e.

$$H = H_0(1 - \sigma)$$

The term σ is called the screening constant and is a measure of the shielding of a proton by the surrounding electrons. The value of the screening constant depends on the magnitude of the electrical (I + M) effects and magnetic effects of adjacent atoms and groups.

When the tetramethylsilane frequency (ν_{TMS}) is subtracted from the frequency of the sample proton (ν_S) and the result divided by the mean operating frequency of the spectrometer, a term, δ, called the chemical shift, is obtained.

$$\delta = \frac{(\nu_S - \nu_{TMS})\,\text{Hz} \times 10^6}{\text{Frequency of instrument, Hz}}\ \text{p.p.m.}$$

The shift, δ, has units of p.p.m. and on this basis the tetramethylsilane frequency assumes an arbitrary zero on the scale. Alternatively the TMS signal can be given the value 10 p.p.m. and the

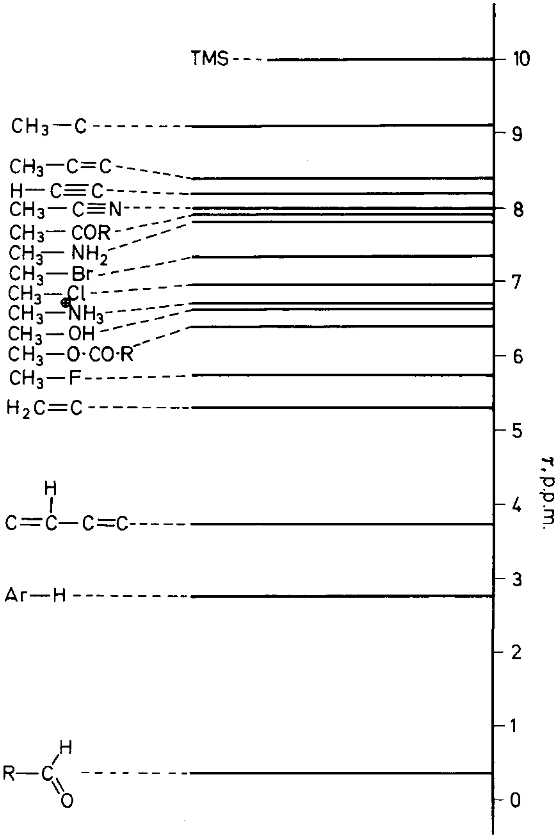


Figure 4.4. Chemical shifts, τ, of various types of protons encountered in organic molecules.

chemical shift the symbol τ, then $\tau = 10 - \delta$ p.p.m. Both the δ and τ scales are widely used but the latter has the advantage that τ values increase as the shielding of the nucleus by the surrounding electrons increases. In this section τ values are used and the chemical shifts for a variety of protons encountered in organic molecules are presented in diagrammatic form in *Figure 4.4*.

Each proton in an organic molecule shares two electrons with a carbon or other atom. The rotational movement of these two electrons about the nucleus creates a local magnetic field opposed to the applied field. The diamagnetism of these circulating electrons thus shields the nucleus. Any outside influence on the electrons alters the degree of shielding. One obvious influence is the inductive effect and this is illustrated by the τ values for the halomethane protons.

	CH_3—H	CH_3—I	CH_3—Br	CH_3—Cl	CH_3—F
τ p.p.m.	9·1	7·84	7·35	6·98	5·74

$$\xrightarrow[\text{by the halogen atom}]{\text{increasing electronegativity and hence deshielding}}$$

A further influence acting on a proton is the circulation of electrons in nearby bonds. In particular circulating electrons in π bonds can create strong magnetic fields which may either oppose or strengthen the applied field. Some examples of π bond systems which influence nearby protons are aromatic rings, carbonyl groups and carbon–carbon double and triple bonds. In the benzene nucleus the magnetic field of the π molecular orbital electrons reinforces the applied field. Hence aromatic protons are deshielded and have the low τ value of 2·73 p.p.m. The reverse effect is found with acetylenic protons, where the field due to electrons circulating in the π bonds opposes the applied field, for the τ value is 7·65 p.p.m.

(d) SOLVENTS AND DEUTERATION

Solvents which contain protons, such as chloroform or dioxan, add their own absorption lines to the measured spectrum. The net result is that part of the useful spectral region is obscured by strong solvent absorption. A hydrogen-free solvent such as carbon tetrachloride, deuterochloroform ($CDCl_3$) or other deuterated liquid is preferred. Complications can also arise from ^{13}C, which gives rise to an n.m.r. signal, but fortunately is only present at one-hundredth of the concentration of ^{12}C.

The τ values for protons attached to oxygen (O—H) or nitrogen

(N—H) can vary over a wide range due to hydrogen bonding, e.g. the hydroxyl proton of alcohols can have a τ value as low as 6·0 or as high as 9·5 p.p.m. Such a situation can obviously lead to misinterpretation of n.m.r. spectra. In these cases the process of deuteration can be helpful. The substance is shaken with deuterium oxide, D_2O, which converts —OH to —OD by an exchange reaction. Deuterium does not absorb in the proton magnetic resonance range and so interpretation of the n.m.r. spectra is simplified.

(e) SPIN–SPIN COUPLING

Nuclear magnetic resonance spectra measured under high resolution conditions show a group of lines, termed multiplet structure, for some protons instead of just a single line, e.g. bromoethane (*Figure 4.5*). In this case the triplet signal, centred at 8·33 p.p.m., arises from the methyl, $—CH_3$, group and the quartet of lines (6·57 p.p.m.) from the $—CH_2—$ group.

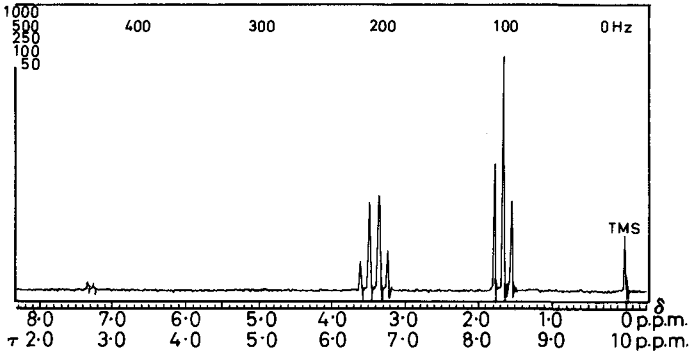
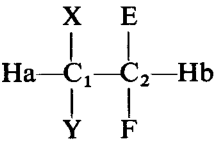


Figure 4.5. N.M.R. spectrum of bromoethane, $CH_3—CH_2—Br$

To explain the reason for this line splitting a simple example will be considered:



$$\begin{array}{ccccccc} & & X & & E & & \\ & & | & & | & & \\ Ha & — & C_1 & — & C_2 & — & Hb \\ & & | & & | & & \\ & & Y & & F & & \end{array}$$

Protons Ha and Hb are in different magnetic environments because the carbon atoms C_1 and C_2 are attached to different groups.

Therefore, an n.m.r. spectrum of the type shown in *Figure 4.6(a)* with just two absorption lines would be expected from such a compound. In practice, under high resolution conditions, four lines divided into two equally spaced pairs would be observed, *Figure 4.6(b)*. The spacing, J Hz, between each pair of lines is termed the coupling constant. The magnitude of J depends on the precise electrical environments of the protons Ha and Hb.

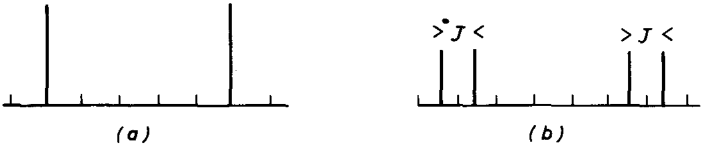
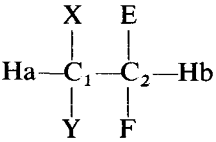


Figure 4.6. (a) expected and (b) observed n.m.r. spectra of a compound of the type



$$\begin{array}{ccccc} & X & & E & \\ & | & & | & \\ Ha- & C_1 & - & C_2 & -Hb \\ & | & & | & \\ & Y & & F & \end{array}$$

Provided that the chemical shift is large compared with J then the spin–spin coupling can be interpreted in a straightforward manner. Thus the local magnetic field experienced by the proton Ha will be influenced by the proton H_0 for this latter proton may be aligned either with or against the field H_0 (*Figure 4.7*). Thus the absorption line of Ha will split into two lines because this proton experiences two local fields, $H\uparrow$ and $H\downarrow$. Similarly Hb will form two lines due to the influence of Ha. The fields $H\uparrow$ and $H\downarrow$ have equal probability and so the lines of each multiplet should have equal intensities. Protons in identical magnetic environments do not exhibit spin–spin coupling.

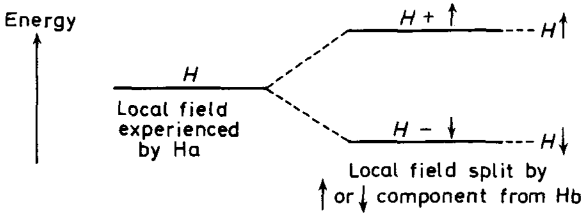


Figure 4.7. Modification to the local field of proton Ha *due to interaction by proton* Hb

Two further examples of spin–spin coupling will be considered using ethanol and 1,1-dibromoethane as examples.

(*i*) *Ethanol* (*Figure 4.8*)

The methyl group protons are observed as a triplet centred at 8·78 p.p.m. and the —CH_2— protons as a quartet at 6·30 p.p.m.

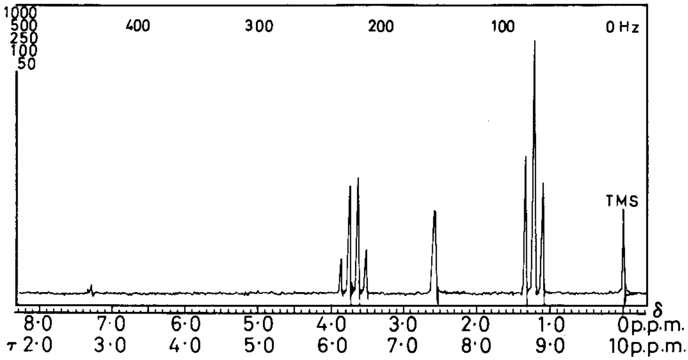


Figure 4.8. N.M.R. spectrum of ethanol, CH_3—CH_2—OH

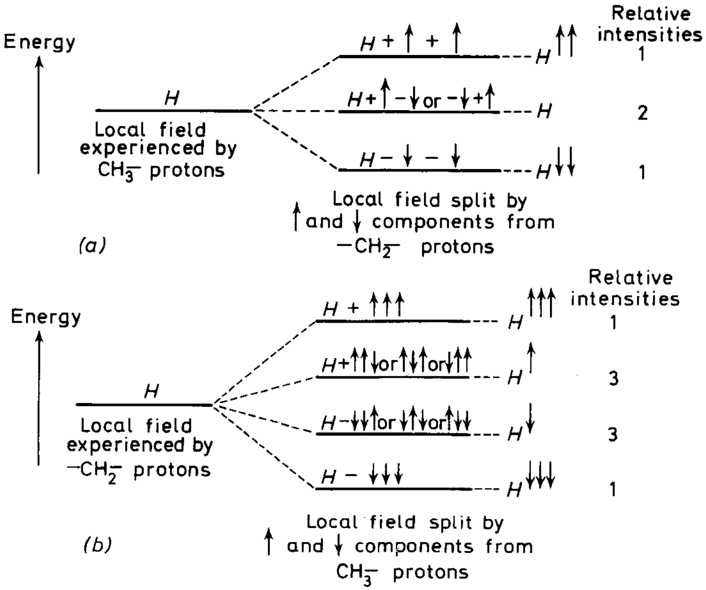


Figure 4.9. Spin–spin coupling between the methyl and methylene group protons in the ethanol molecule. (*a*) *Methyl group triplet formed by spin–spin coupling with the two protons of the methylene group;* (*b*) *methylene group quartet formed by spin–spin coupling with the three protons of the methyl group*

The hydroxyl proton absorption (7·42 p.p.m.) is dependent on hydrogen bonding and other factors but does not couple with the —CH_2— protons.

Consider first the effect of the two methylene protons on the local field experienced by the three equivalent methyl protons; this produces a triplet structure, *Figure 4.9(a)*. Similarly the influence of the three methyl protons on the local field experienced by the two equivalent methylene protons produces a quartet of lines, *Figure 4.9(b)*.

(ii) 1,1-*Dibromoethane* (*Figure 4.10*)

The methyl group protons are observed as a pair of lines at 7·53 p.p.m. and the —CH— group proton as a quartet at 4·14 p.p.m. This line splitting is in agreement with the examples already worked out in *Figures 4.7* and *4.9(b)*.

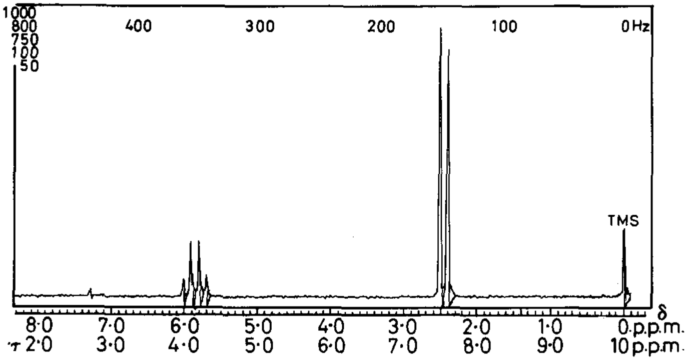


Figure 4.10. N.M.R. spectrum of 1,1-*dibromoethane*, CH_3—CH—Br_2

Thus the number of lines in a multiplet, and the approximate relative intensities of the lines, can be deduced from the number of protons attached to the groups adjacent to the group under examination. If the number of protons on these adjacent groups is X then the number of lines in the multiplet will be $(X + 1)$.

(f) PEAK AREAS

The area of an absorption peak, or set of peaks in the case of spin–spin coupling, in an n.m.r. spectrum is proportional to the number of protons producing the peak. Peak areas can be integrated and recorded electronically at the same time as the actual absorption peaks are recorded. The ratio of the integrated areas for the peaks in a spectrum represents the ratio of the number of protons in each of the possible magnetic environments. When the molecular formula of the compound is known the proton ratio, rounded off to the nearest whole number, can be fitted into the total number of protons in the molecule.

4.3 ULTRA-VIOLET AND VISIBLE SPECTRA

The energy absorbed by molecules in this region of the spectrum produces electronic transitions. This means that electrons are promoted from their ground state energy level to a higher energy level. Considerably more energy is involved in this region than in the infra-red part of the spectrum.

Wavelengths are normally measured in nm or Å but as with infra-red spectra frequency is really a better term, being directly proportional to the amount of energy absorbed. Frequency is used as the principal term in this section but wavelengths are given in parentheses. The ultra-violet region stretches from 54000 to 30000 cm^{-1} (185–330 nm) and the visible spectrum from 30000 to 13000 cm^{-1} (330–770 nm).

The amount of energy corresponding to absorption in the ultra-violet or visible region can be calculated from the expression:

$$E(\text{kJ/mol}) = 119{\cdot}7 \times 10^{-4}(\bar{\nu}) \quad \text{or} \quad 119{\cdot}7 \times 10^{3}(1/\lambda).$$

Thus absorption at 35000 cm^{-1} (286 nm) corresponds to a transition involving 418 kJ/mol. This large amount of energy is similar to, or even greater than, the strengths of many covalent bonds and so it is not surprising that many organic reactions are promoted by ultra-violet radiation.

The amount of radiation absorbed, at a particular frequency, depends on the electronic structure of the molecule. Absorption will vary between 0 and 100 per cent and to eliminate such factors as path length and solution concentration the term ε, based on the Beer–Lambert laws, is used:

$$\varepsilon = \frac{\log I_0/I}{l\,.\,c} = \frac{\text{optical density (or absorbance)}}{l\,.\,c}$$

The Molar Extinction Coefficient (ε) is normally expressed without units although these in fact represent area per molecule. Optical density is normally recorded from the spectrophotometer (I_0 and

I are the intensities of the incident and transmitted radiation respectively) for the solution of path length l cm and concentration c mol/l. The amount of radiation absorbed at each frequency, i.e. a record of ε against cm^{-1}, is characteristic of each organic substance in the infra-red, visible and ultra-violet regions of the spectrum. Unfortunately it is difficult to measure ε with precision in the infra-red.

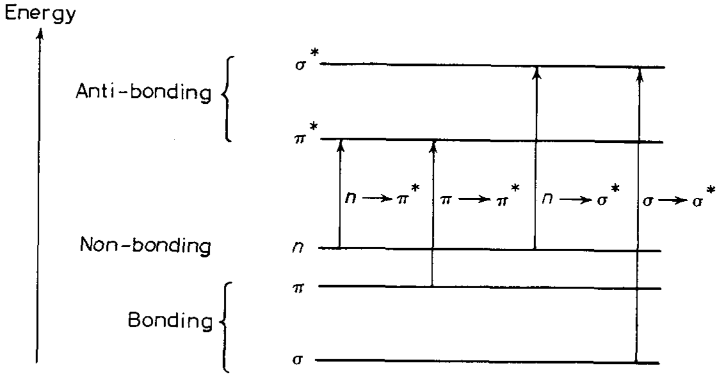


Figure 4.11. Possible electronic transitions in organic molecules

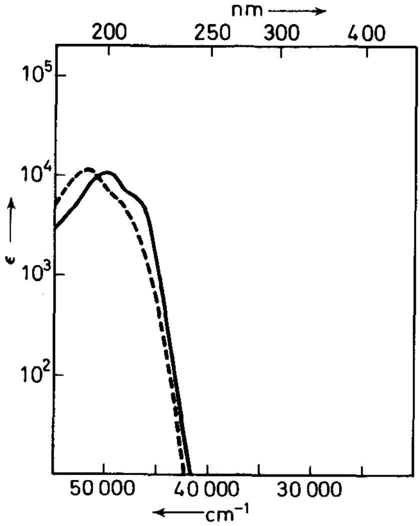


Figure 4.12. Ultra-violet absorption spectra of cis-1,2-dichloroethylene (– – –) and trans-1,2-dichloroethylene (——)

Electronic transitions which can take place in an organic molecule, and so lead to the absorption of radiation at a particular frequency, depend on the types of bonding and non-bonding electrons that are present. Non-bonding, lone pair (*n*) electrons of an oxygen atom require about 395 kJ/mol to undergo a transition to the unstable, anti-bonding (π*) orbital of a carbon–oxygen double bond. This is termed *n* → π* transition. Electronic transitions are accompanied by vibrational and rotational changes within the molecule and so the result is not a sharp absorption peak but a broad band, e.g. see *Figure 4.16*. Similarly a transition can take place from a bonding π orbital to an anti-bonding level (π*), i.e. a π → π* transition. In bonding energy levels π electrons have

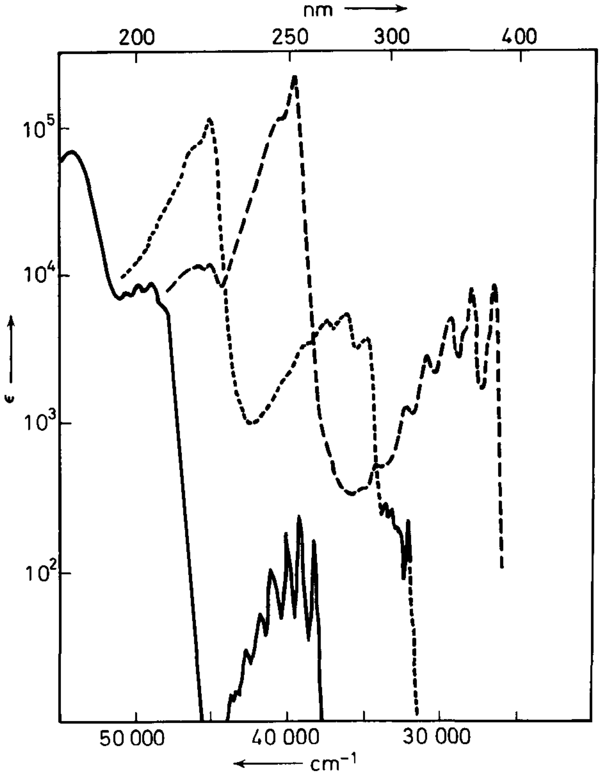


Figure 4.13. Ultra-violet absorption spectra of anthracene (– – –), benzene (——) and naphthalene (. . . . .)

higher energies than σ electrons but in anti-bonding levels this order is reversed. Possible transitions between the various energy levels are shown in *Figure 4.11*; the relative lengths of the transition 'arrows' provide some idea of the different transition energies involved. The transition $n \rightarrow \sigma^*$ occurs with C—Hal, C—O and C—N bonds and normally requires rather more energy than a $\pi \rightarrow \pi^*$ transition. Alkanes exhibit only $\sigma \rightarrow \sigma^*$ transitions which require very large amounts of energy (ca. 840 kJ/mol) and hence are observed in the vacuum ultra-violet region around 60–70000 cm^{-1}. An isolated double bond absorbs in the ultra-violet near 51000 cm^{-1} (195 nm) due to a $\pi \rightarrow \pi^*$ transition. Interaction with a second double bond lowers the energy requirement of the transition, e.g. the $\pi \rightarrow \pi^*$ of 1,3-butadiene is near 46000 cm^{-1} (217 nm)·

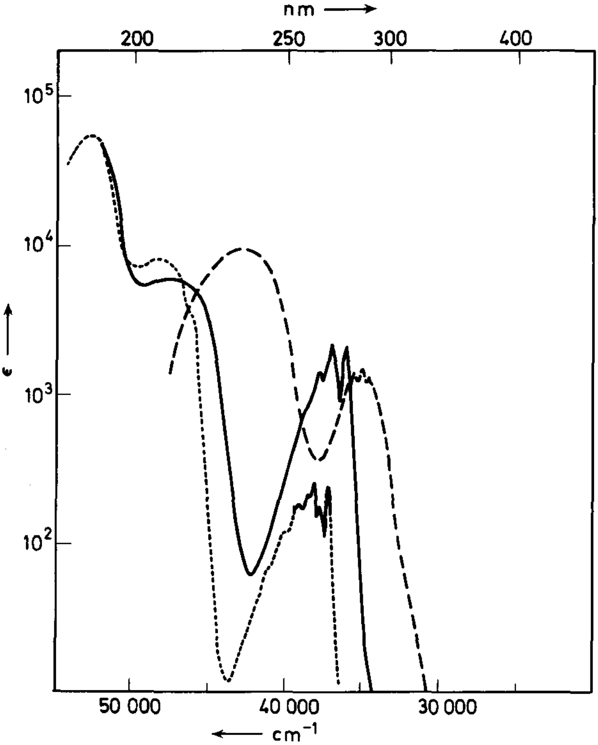


Figure 4.14. Ultra-violet absorption spectra of aniline (– – –), phenol (——) and toluene (. . . . .)

In a series of polyenes, of type R—(CH=CH)$_y$-R′, the energy requirement of the $\pi \rightarrow \pi^*$ transition decreases as y increases. Also the value of ε increases from approximately 10^4 when $y = 1$ to 10^5 when $y = 5$. *Cis* and *trans* isomers of alkenes have slightly different ultra-violet absorption spectra, e.g. *cis* and *trans*-1,2-dichloroethylenes (*Figure 4.12*).

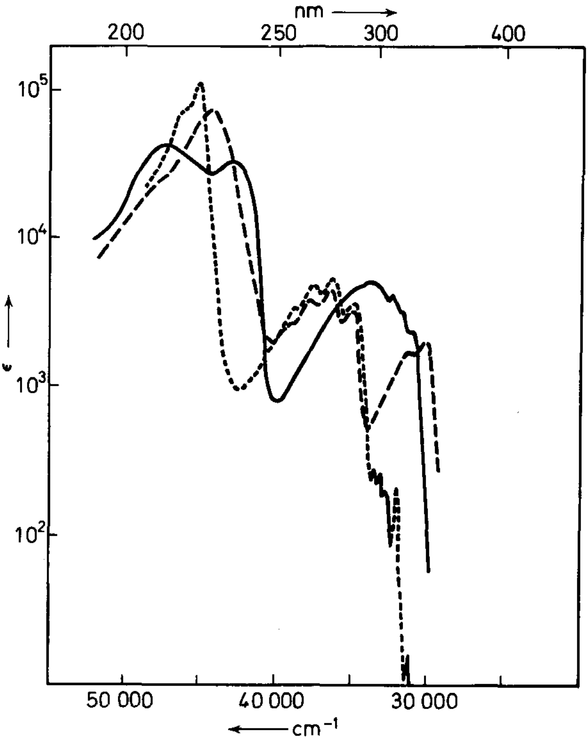


Figure 4.15. Ultra-violet absorption spectra of naphthalene (.....), *1-naphthol* (——) *and 2-naphthol* (– – –)

As a general rule the frequency of an absorption band decreases as the length of a conjugated system increases, cf. benzene, naphthalene and anthracene (*Figure 4.13*). The spectra of aniline, phenol and toluene are shown in *Figure 4.14*. Compared with benzene the first absorption band of these substances shows a move to lower frequencies coupled with some loss of fine structure. Groups which exert only an inductive effect produce little or no change in an ultra-violet spectrum. For example aniline hydrochloride has an ultra-violet spectrum almost identical with that of benzene.

In more complex aromatic hydrocarbons, such as naphthalene, substituents may produce different effects from alternative positions in the nucleus. Thus 1-naphthol has a spectrum similar to that of naphthalene whilst 2-naphthol has quite a different spectrum (*Figure 4.15*).

When a strongly electron attracting (−M) group and an electron releasing group (+M) are attached to a conjugated system the

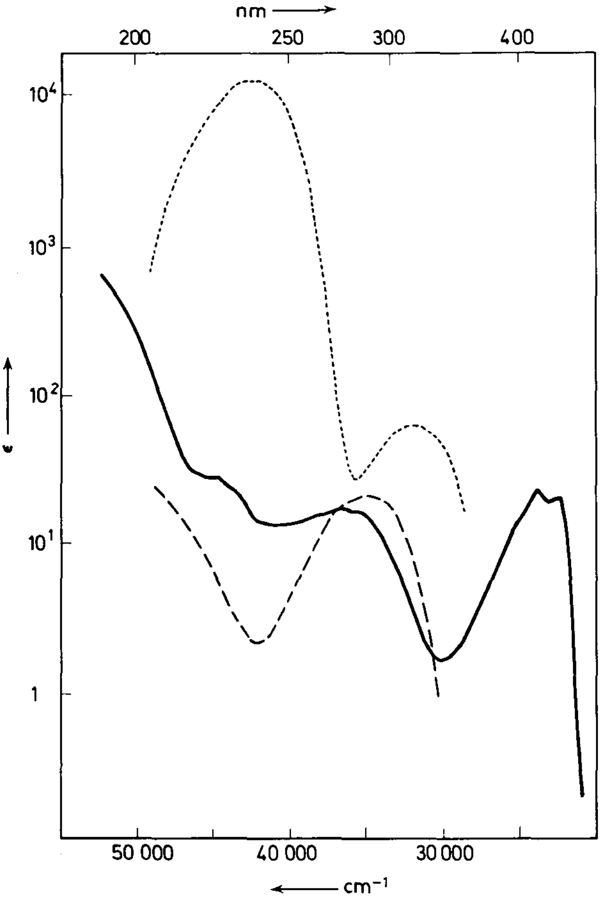


Figure 4.16. Ultra-violet absorption spectra of 2,3-*butanedione* (——), 3,3-*dimethyl*-2-*butanone* (– – –) *and* 4-*methyl*-3-*penten*-2-*one* (. . . . .)

first absorption band often lies in the visible region. Thus the *ortho*, *meta* and *para*-nitroanilines are all yellow in colour although both aniline and nitrobenzene are almost colourless when pure. The extinction coefficients of these three isomers decrease in the order *para* > *ortho* > *meta*, a sequence which parallels the normal order of conjugation through an aromatic nucleus.

First Absorption Maxima of o, m and p-nitroanilines (ethanol)

	para	*ortho*	*meta*
Maxima, cm^{-1}	26600	24800	26700
Extinction coefficient, ε	15000	5200	1300

The carbonyl $n \rightarrow \pi^*$ absorption occurs as a weak absorption band ($\varepsilon = 10$–100) between about 33000 and 36000 cm^{-1} (280–300 nm). The conjugation of a double bond with a carbonyl group, as in α,β-unsaturated ketones, lowers this absorption frequency to 33000–28600 cm^{-1} (300–350 nm) and raises the extinction coefficient. The spectra of 3,3-dimethyl-2-butanone and 4-methyl-3-penten-2-one illustrate these effects (*Figure 4.16*). The interaction of two adjacent carbonyl groups, as in 2,3-butanedione ($CH_3COCOCH_3$), gives rise to two $n \rightarrow \pi^*$ transitions. One of these transitions stretches into the visible part of the spectrum and accounts for the yellow colour of this and similar diketones, e.g. benzil and *p*-benzoquinone.

The combination of infra-red, n.m.r. and ultra-violet spectroscopic methods provide much valuable information about the structure of an isolated or synthesised organic substance. Not only do these techniques provide information quickly but, because only mg quantities of material are required for measurement, structure determinations can be achieved with far less material than is needed for classical chemical methods. Another increasingly important analytical technique is mass spectrometry. References to comprehensive works covering the application of spectroscopic methods to organic chemistry are given in the Further Reading section (page 300).

5

Hydrocarbons—Alkanes, Alkenes, Alkynes and Arenes

5.1 INTRODUCTION AND NOMENCLATURE

Hydrocarbons, as the name implies, contain only carbon and hydrogen. Within the broad classification of aliphatic and aromatic compounds alkanes, alkenes and alkynes belong to the former and arenes to the latter group.

Alkanes (or paraffins) contain only single bonds, alkenes (or olefins) have double and single bonds and alkynes (or acetylenes) triple and single bonds. The simplest arene (or aromatic hydrocarbon) is benzene and higher members of this series are formed by combining together further benzene rings.

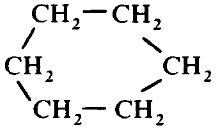
Hydrocarbons are non-polar substances, insoluble in water. They cannot form hydrogen bonds. Their boiling points depend largely on the number of carbon atoms present (see page 20). Thus hexane, cyclohexane, hexene, hexyne and benzene, containing six carbon atoms, all boil within the range 62–82°. Hydrocarbons with four or less carbon atoms boil below room temperature.

The nomenclature of branched chain aliphatic hydrocarbons is built up from that of the alkanes. The first ten alkanes are:

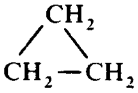
methane, CH_4
ethane, CH_3CH_3
propane, $CH_3CH_2CH_3$
butane, $CH_3(CH_2)_2CH_3$
pentane, $CH_3(CH_2)_3CH_3$
hexane, $CH_3(CH_2)_4CH_3$
heptane, $CH_3(CH_2)_5CH_3$
octane, $CH_3(CH_2)_6CH_3$
nonane, $CH_3(CH_2)_7CH_3$
decane, $CH_3(CH_2)_8CH_3$

Cyclic alkanes simply use the prefix cyclo- before the name of the hydrocarbon, e.g.

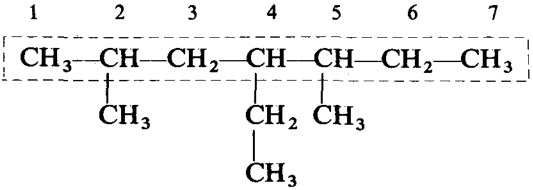
cyclohexane



cyclopropane

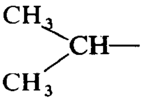


Obviously very many isomers become possible as the number of carbon atoms increases. In such cases the longest carbon chain is selected and this provides the basic name of the hydrocarbon. Side chain substituents are then arranged in alphabetical order and numbered in such a direction on the basic hydrocarbon chain that the sum of these numbers is kept to a minimum.

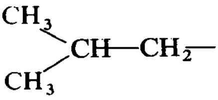


Basic hydrocarbon (dotted): heptane
Side chain substituents: dimethyl (i.e. 2 × methyl), ethyl
Numbering: 2,5-dimethyl-4-ethylheptane (sum 11) or
3,6-dimethyl-4-ethylheptane (sum 13). The former is correct.

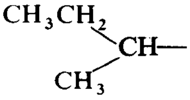
Side chain substituents may be more complex than those above and trivial names are widely used, e.g.



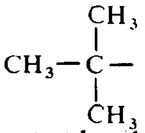
iso-propyl



iso-butyl



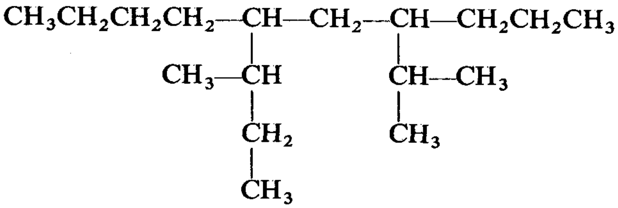
sec-butyl



tert-butyl

The term iso- refers to two methyl groups at the end of a straight hydrocarbon chain. These trivial names for alkyl radicals are particularly useful in discussions concerning the reactivity of organic compounds.

Side chain substituents can also be named systematically from the longest chain of the substituent, numbering commencing at the carbon atom attached to the basic hydrocarbon chain, e.g.



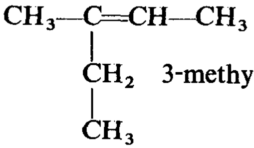
$$\begin{array}{rcccl}
\mathrm{CH_3CH_2CH_2CH_2{-}} & \mathrm{CH} & \mathrm{{-}CH_2{-}} & \mathrm{CH} & \mathrm{{-}CH_2CH_2CH_3}\\
 & | & & | & \\
\mathrm{CH_3{-}} & \mathrm{CH} & & \mathrm{CH} & \mathrm{{-}CH_3}\\
 & | & & | & \\
 & \mathrm{CH_2} & & \mathrm{CH_3} & \\
 & | & & & \\
 & \mathrm{CH_3} & & &
\end{array}$$

Basic hydrocarbon: decane
Side chain substituents: sec-butyl or 1-methylpropyl and iso-propyl or 1-methylethyl
Numbering: from the right the sum is 10 and from the left 12.
Hence numbering from the right the possible names are 6-sec-butyl-4-isopropyldecane or 6-(1-methylpropyl)-4-(1-methylethyl)-decane.

Alkenes are named in the same way as alkanes except that the *–ane* of the corresponding alkane becomes *–ene*, i.e. hexane becomes hexene. The first member of the series is usually called ethylene and the following members are propene, butene, pentene, etc. The longest chain is chosen to include the multiple bond and numbering arranged so that the first carbon atom bearing this bond takes the lowest possible number.

$CH_3CH_2CH{=}CH_2$

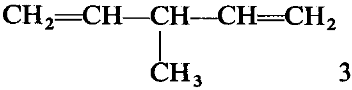
1-butene



$$\begin{array}{rcl}
\mathrm{CH_3{-}} & \mathrm{C} & \mathrm{{=}CH{-}CH_3}\\
 & | & \\
 & \mathrm{CH_2} & \\
 & | & \\
 & \mathrm{CH_3} &
\end{array}$$

3-methyl-2-pentene

The endings *-diene* and *-triene* are used for compounds containing two and three double bonds respectively.

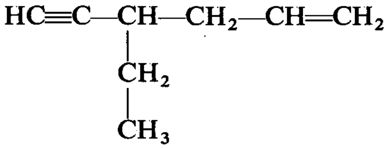


$$\begin{array}{rcl}
\mathrm{CH_2{=}CH{-}} & \mathrm{CH} & \mathrm{{-}CH{=}CH_2}\\
 & | & \\
 & \mathrm{CH_3} &
\end{array}$$

3-methyl-1,4-pentadiene

The term allene is normally used to describe $CH_2{=}C{=}CH_2$ (rather than propadiene) and $CH_2{=}CH{-}CH_2Cl$ is called allyl chloride. Vinyl is used to describe $CH_2{=}CH{-}$, e.g. $CH_2{=}CH{-}Cl$ is vinyl chloride.

Alkynes are also named in the same way as alkanes except that the *-ane* of the corresponding alkane becomes *-yne*. The first member of the series is usually called acetylene and the following members are propyne, butyne, pentyne, etc. Numbering is as for the alkenes but when double and triple bonds are present in the same molecule the former take precedence as shown in the following example:



$$HC{\equiv}C{-}\underset{\substack{|\\CH_2\\|\\CH_3}}{CH}{-}CH_2{-}CH{=}CH_2$$

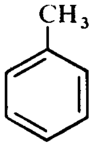
4-ethyl-1-hexen-5-yne

$CH_3—CH_2—C{\equiv}C—CH_3$

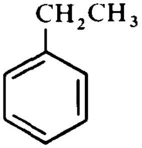
2-pentyne

The simple arenes are usually referred to by trivial names:

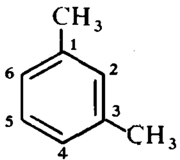
benzene



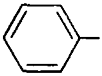
toluene

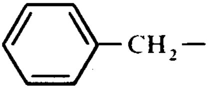


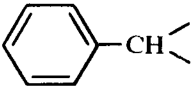
ethylbenzene



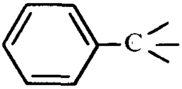
m-xylene

The relative positions of two substituents may be denoted by *ortho* (1,2-), *meta* (1,3-) and *para* (1,4-). The arene radical  or C_6H_5— is usually referred to as phenyl which abbreviates to Ph; Ar similarly stands for any arene radical and R for any aliphatic radical. Benzyl, benzal and benzo refer respectively to:

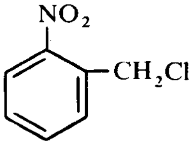




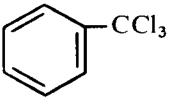
and



e.g.



o-nitrobenzyl chloride



benzotrichloride

In substituted hydrocarbons, whether aliphatic or aromatic, the hydrocarbon is taken as the basic unit. Functional groups are then placed before or after the name of the hydrocarbon. Examples of nomenclature are given at the beginning of each chapter.

5.2 ALKANES

The first member of the homologous series of alkanes, which have the general formula C_nH_{2n+2}, is methane, CH_4. The carbon atom in methane, like all the carbon atoms in alkanes, is sp^3-hybridised and the molecule has tetrahedral symmetry (section 1.3).

Chemically alkanes are inert substances because the carbon and hydrogen atoms have similar electronegativities and hence the C—H bonds have little polar character. The C_{sp^3}—H bond is short (1·09 Å) and strong (406 kJ/mol). The carbon atom is not attacked by nucleophiles or electrophiles because (1) of the lack of polar character and low polarisability of the bond and (2) there is no possibility of stabilising a transition state by spreading a positive or negative charge over several atoms. Alkanes, therefore, react mainly with the neutral, highly reactive species called free radicals. Free radical reactions of alkanes take place, usually at high temperatures, with oxygen, fluorine, chlorine, bromine or nitric acid vapour.

(a) OXIDATION OF ALKANES

Methane is the major constituent of Natural Gas which is a most important source of energy. The process of combustion of alkanes is a complex, stepwise, free radical, chain process. When sufficient energy is provided to start the reaction, e.g. by a flame, then enough heat is evolved to allow the reaction to continue. In the case of methane:

$$CH_4(g) + 2O_2(g) \xrightarrow{\text{flame}} CO_2(g) + 2H_2O(g) + 803\ \text{kJ/mol}$$

or in general terms:

$$C_nH_{2n+2} + \left(\frac{3n+1}{2}\right)O_2 \xrightarrow{\text{flame}} nCO_2 + (n+1)H_2O$$
$$+\ \text{heat of combustion}$$

The oxidation of alkanes does not have to proceed to completion. For example, the partial oxidation of methane at 1500° with a deficiency of oxygen yields acetylene, carbon monoxide and hydrogen.

$$6CH_4 + O_2 \xrightarrow{1500^\circ} 2HC{\equiv}CH + 2CO + 4H_2$$

The carbon monoxide and hydrogen are in the correct proportion for conversion to methanol. This route to acetylene is displacing the traditional route from calcium carbide. Methane will also react with steam at high temperatures:

$$CH_4 + H_2O \xrightarrow[Ni]{850°} CO + 2H_2$$

Petroleum is an abundant source of alkanes. The crude oil is separated by distillation into various fractions. The lower boiling fractions are blended to produce petrol, etc. The high boiling fractions containing higher alkanes may be broken down by various thermal and catalytic cracking processes to the more commercially valuable lower alkanes.

(b) HALOGENATION OF ALKANES

Fluorine reacts with alkanes at room temperature. All the hydrogen atoms may be replaced by fluorine and as the heat of reaction is very high an inert gas is normally added so that the process can be controlled.

Chlorination and bromination of alkanes are free radical, chain processes. Chlorine molecules first break up into chlorine atoms with energy gained from heat or ultra-violet light.

$$Cl_2 \xrightarrow[\text{or u.v.}]{250\text{–}350°} 2Cl^{\bullet}$$

This initiation step of the reaction requires about 243 kJ/mol. The reaction is then propagated by:

$$CH_4 + Cl^{\bullet} \rightarrow CH_3^{\bullet} + HCl \text{ plus about 4·2 kJ/mol}$$

and

$$CH_3^{\bullet} + Cl_2 \rightarrow CH_3Cl + Cl^{\bullet} \text{ plus about 96 kJ/mol}$$

This chain process continues until the free radicals are lost in some termination step such as; $2CH_3^{\bullet} \rightarrow C_2H_6$, $2Cl^{\bullet} \rightarrow Cl_2$ or $CH_3^{\bullet} + Cl^{\bullet} \rightarrow CH_3Cl$.

Reaction does not cease with the formation of chloromethane but proceeds to dichloromethane, etc.

$$CH_4 \xrightarrow{Cl_2} CH_3Cl \rightarrow CH_2Cl_2 \rightarrow CHCl_3 \rightarrow CCl_4$$

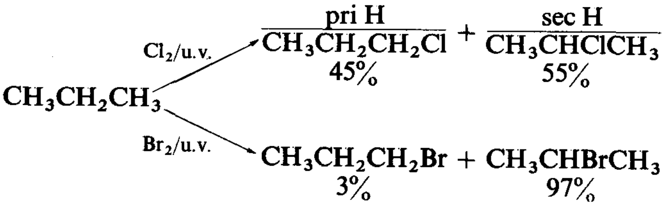
CH_3Cl chloromethane	dichloromethane (methylene chloride)	trichloromethane (chloroform)	tetrachloromethane (carbon tetrachloride)

The mixture of products is separated by distillation. The starting ratio of chlorine to methane to some extent determines the composition of the mixture of products.

Bromination of alkanes follows a similar path to chlorination but takes place less readily. Iodine does not react with alkanes. In alkanes which have more than two carbon atoms the different hydrogen atoms show the following order of reactivity towards halogens:

$$\underset{\xleftarrow[\text{increasing reactivity towards halogens}]{\hspace{12em}}}{\text{tert H} > \text{sec H} > \text{pri H}}$$

The difference in reactivity is not important with the reactive halogen chlorine but bromine is much more selective as the following example shows.



$$CH_3CH_2CH_3 \xrightarrow{Cl_2/u.v.} \underset{45\%}{\overset{\text{pri H}}{CH_3CH_2CH_2Cl}} + \underset{55\%}{\overset{\text{sec H}}{CH_3CHClCH_3}}$$

$$CH_3CH_2CH_3 \xrightarrow{Br_2/u.v.} \underset{3\%}{CH_3CH_2CH_2Br} + \underset{97\%}{CH_3CHBrCH_3}$$

(c) NITRATION OF ALKANES

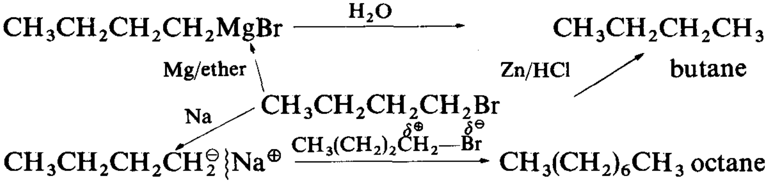
Alkanes react with nitric acid in the vapour phase at 400–500°. The reaction appears to be a free radical process and the mixture of nitroalkanes formed can be separated by fractional distillation.

$$CH_3CH_2CH_3 + HNO_3 \xrightarrow{450^\circ} \underset{25\%}{CH_3CH_2CH_2NO_2}$$
$$+ \underset{40\%}{CH_3CHNO_2CH_3} + \underset{10\%}{CH_3CH_2NO_2} + \underset{25\%}{CH_3NO_2}$$

(d) PREPARATION OF ALKANES

Alkanes containing up to nine carbon atoms are obtained by the careful fractionation of petroleum. More complex members of the series have to be synthesised. Some methods of alkane synthesis are as follows:

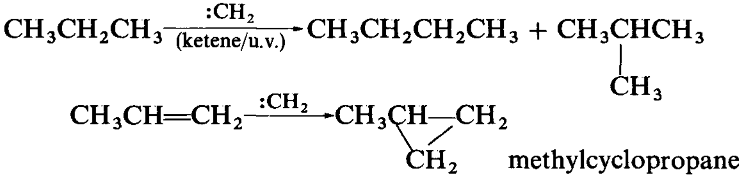
(i) From Alkyl Halides—The halide is either reduced (Zn/acid), converted to a Grignard reagent and hydrolysed, or treated with sodium in ether solution (the Wurtz Reaction).



(ii) From Alkenes or Alkynes—Multiple bonds may be hydrogenated with hydrogen over a catalyst.

$$R{-}CH{=}CH{-}R + H_2 \xrightarrow[\text{(Ni, Pt, etc.)}]{\text{catalyst}} R{-}CH_2{-}CH_2{-}R$$

(iii) From the Insertion of Methylene (:CH_2) into C—H Bonds—Methylene, generated from diazomethane or ketene, is a very reactive species which will insert into C—H bonds or add to double bonds.



$$CH_3CH_2CH_3 \xrightarrow[\text{(ketene/u.v.)}]{:CH_2} CH_3CH_2CH_2CH_3 + CH_3\underset{\substack{|\\ CH_3}}{C}HCH_3$$

(iv) Cycloalkanes can be prepared by ring closure or alteration of an existing ring structure. For example benzene hydrogenates to cyclohexane with hydrogen over a nickel catalyst.

5.3 ALKENES

Alkenes have the general formula C_nH_{2n} and contain double bonds. The structure of double bonds was discussed in section 1.3. Alkenes containing more than one double bond may be classified as non-conjugated, conjugated or cumulated, e.g.

$CH_2{=}CH{-}CH_2{-}CH{=}CH_2$, 1,4-pentadiene, non-conjugated—at least one C_{sp^3} between the double bonds.

$CH_2{=}CH{-}CH{=}CH_2$, 1,3-butadiene, conjugated—alternate single and double bonds.

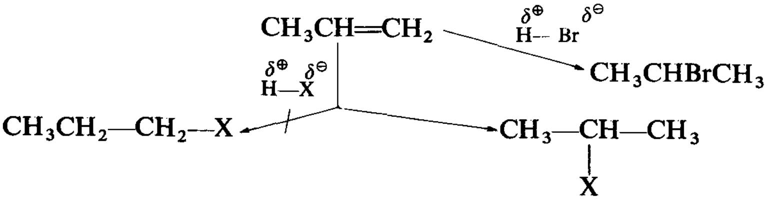
$CH_2{=}C{=}CH_2$, allene (propadiene), cumulated—adjacent double bonds, central carbon atom *sp*-hybridised.

Conjugated dienes show many of the properties of non-conjugated dienes but in addition have some special properties which will be discussed later. Suitably substituted cumulative alkenes possess interesting stereochemical features (section 13.2).

The most important feature of the chemistry of alkenes is their electrophilic and free radical reactions which result in addition across the double bond (mechanisms, section 3.5).

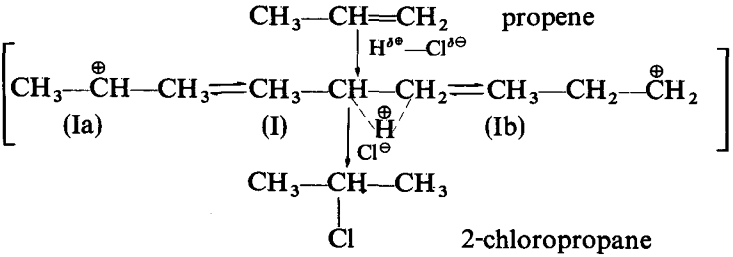
Most of the addition reactions listed in *Table 5.1* are electrophilic in character and addition occurs with the evolution of approximately 126 kJ/mol. As has already been mentioned in section 3.5 electrophilic addition to a double bond is normally *trans* due to an intermediate cyclic cation. Free radical addition is favoured by peroxides and addition by nucleophiles does not occur unless the double bond is conjugated to a strongly electron withdrawing group such as $—C{=}O$, $—C{=}N—$ or $—NO_2$ (see addition to α, β-unsaturated carbonyl compounds, section 12.5).

Addition to unsymmetrical alkenes can lead to a number of products. From a study of many additions to alkenes Markownikoff (1869) suggested that the negative part of the adding reagent adds to the carbon atom of the alkene bearing the smaller number of hydrogen atoms (Markownikoff's Rule).



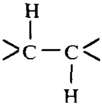
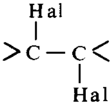
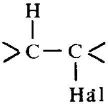
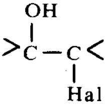
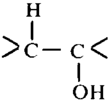
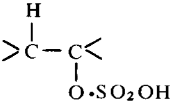
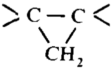
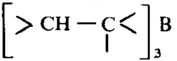
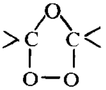
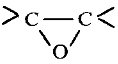
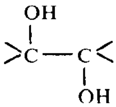
Whilst the rule is not always reliable in predicting the direction of addition it does form a useful guide.

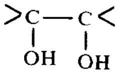
In mechanistic terms the explanation of Markownikoff's rule would seem to depend on the structure of the intermediate cation. For the addition of hydrogen chloride to propene:



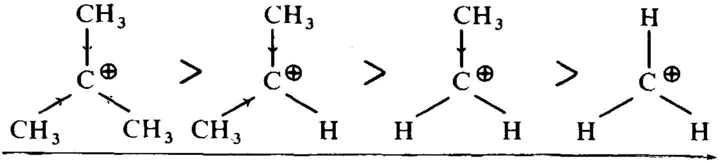
The carbonium ions Ia and Ib do not explain the overall *trans*

Table 5.1. ADDITION REACTIONS OF AN ALKENE $>C=C<$

Addendum	*Product*	
Hydrogen (in presence of Pt, Pd, or Ni catalyst)	Alkane	 $>\overset{H}{\overset{\vert}{C}}-\underset{H}{\underset{\vert}{C}}<$
Halogens (Cl_2, Br_2 or sometimes I_2)	1,2-Dihaloalkane	 $>\overset{Hal}{\overset{\vert}{C}}-\underset{Hal}{\underset{\vert}{C}}<$
Hydrogen halides (HCl, HBr or HI)	Haloalkane	 $>\overset{H}{\overset{\vert}{C}}-\underset{Hal}{\underset{\vert}{C}}<$
Hypohalous acids (HOCl or HOBr)	Haloalcohol (halohydrin)	 $>\overset{OH}{\overset{\vert}{C}}-\underset{Hal}{\underset{\vert}{C}}<$
Water ($H_2O/H^{\oplus}$)	Alcohol	 $>\overset{H}{\overset{\vert}{C}}-\underset{OH}{\underset{\vert}{C}}<$
Sulphuric acid	Alkyl hydrogen sulphate	 $>\overset{H}{\overset{\vert}{C}}-\underset{O\cdot SO_2OH}{\underset{\vert}{C}}<$
Methylene ($:CH_2$) and other carbenes	A cyclopropane	
Diborane (B_2H_6)	Trialkylboranes	 $\left[>CH-\underset{\vert}{C}<\right]_3B$
Ozone	Ozonides (then aldehydes, ketones, etc.)	
Oxygen (O_2/Ag catalyst/250°)	Epoxide	
Peracids, perbenzoic acid	Epoxides	
performic and peracetic acids	*trans*-1,2-Diols	 $>\overset{OH}{\overset{\vert}{C}}-\underset{OH}{\underset{\vert}{C}}<$

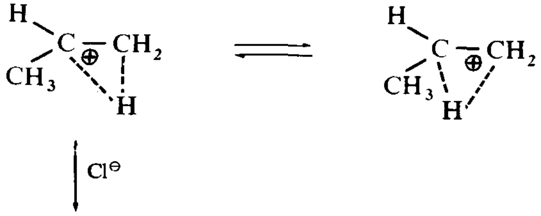
Osmium tetroxide or cold, dilute potassium permanganate	*cis*-1,2-Diols	 $>\underset{OH}{C}-\underset{OH}{C}<$
High temperatures and high pressures, catalyst	Polymerized alkenes	

addition but their ease of formation and stability goes some way towards explaining the observed product orientation.



decreasing ease of formation + stability of carbonium ion

The tertiary carbonium ion is the most stable because the positive charge is spread over the three methyl groups, by their inductive effects. Hence the sec-carbonium ion, Ia, will be more stable than the primary ion, Ib. The chloride ion will, therefore, attack some form of ion, I, which approaches Ia rather than Ib. A representation of this situation is:



2-chloropropane

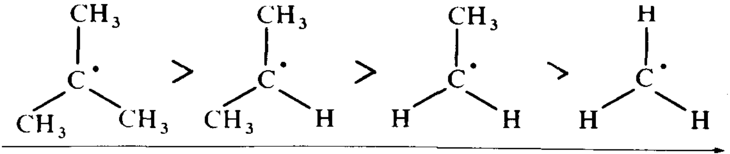
In a number of addition reactions to alkenes, particularly those involving hydrogen bromide, just the reverse product orientation is observed to that predicted by Markownikoff's rule.

$$CH_3CH_2CH_2Br \xleftarrow[\text{fast addn.}]{\text{HBr, u.v./peroxides}} CH_3CH{=}CH_2 \xrightarrow[\text{slow addn.}]{\text{HBr, polar solvent}} CH_3CHBrCH_3$$

1-bromopropane (by free radical addition)

2-bromopropane (by electrophilic addition)

The above example shows the different types of reaction. It is the free radical which leads to the 'anti-Markownikoff' product. The product orientation is now determined by the stability of the intermediate carbon free radicals.



decreasing ease of formation + stability of carbon free radicals

The tertiary free radical is the most stable because the effects of the unshared electron can be dispersed over three carbon atoms. The magnitude of the difference in stability of the four types of free radical is less than that of the four carbonium ions.

The free radical, chain addition process is:

$$\text{H—Br} \xrightarrow[\text{or light}]{\text{peroxide}} \text{H}^{\bullet} + \text{Br}^{\bullet}$$

$$\text{Br}^{\bullet} + \text{CH}_3\text{CH{=}CH}_2 \rightarrow \text{CH}_3\dot{\text{C}}\text{HCH}_2\text{Br} \rightleftharpoons \text{CH}_3\text{CHBr}\dot{\text{C}}\text{H}_2$$

sec. free radical more stable than pri. radical

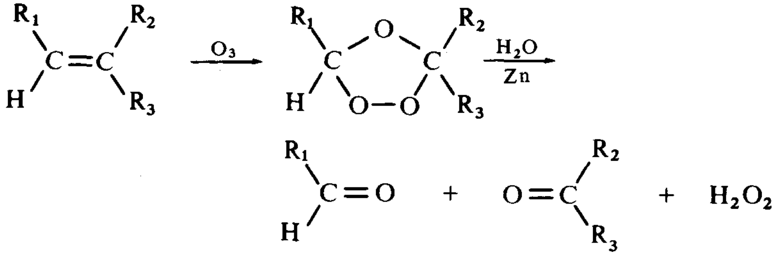
$$\text{CH}_3\dot{\text{C}}\text{HCH}_2\text{Br} + \text{HBr} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{Br}^{\bullet}$$

1-bromopropane

The initial addition of Br$^{\bullet}$ to the alkene is energetically much more favourable than the addition of H$^{\bullet}$.

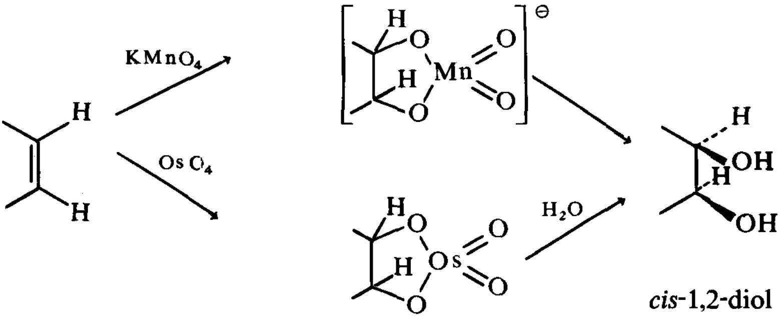
Hydroboronation of alkenes with diborane leads to the 'anti-Markownikoff' alcohol (section 7.6). Carbenes, such as methylene, add to some alkenes to produce cyclopropanes. Polymers of alkenes, such as polyethylene and polypropylene, are produced in large quantities and are of great commerical importance (section 16.3). Double bonds of alkenes are easily reduced with hydrogen and a catalyst but are usually unaffected by lithium aluminium hydride.

Ozonolysis is used to determine the structure of complex alkenes. The ozonide is decomposed with water in the presence of zinc dust (or other reducing agent) to aldehydes, ketones, etc. In the absence of a reducing agent hydrogen peroxide is formed and this oxidises any aldehydes to carboxylic acids.



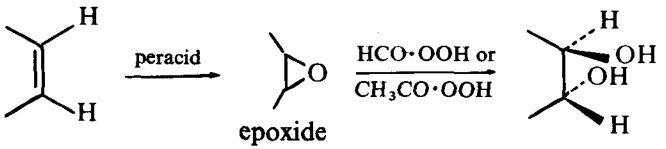
Identification of the carbonyl compounds leads to the structure of the alkene.

Hydroxylation of an alkene, i.e. conversion to a 1,2-diol (or glycol), can take two courses. With potassium permanganate or osmium tetroxide the *cis*-1,2-diol is formed because reaction proceeds via a cyclic intermediate containing both the oxygen atoms.



cis-1,2-diol

On the other hand performic and peracetic acids, like perbenzoic acid, first form an epoxide. Subsequent reaction adds another oxygen atom and produces the *trans*-1,2-diol.



trans-1,2-diol

PREPARATION OF ALKENES

(*a*) *Cracking of petroleum*

The higher distillates from crude petroleum are rapidly passed, either alone or mixed with steam, through a reaction vessel maintained at a high temperature (up to 1000°C). The issuing gases, which contain ethylene, propene, butadiene and other hydrocarbons, are cooled and the constituents separated by fractional distillation.

(*b*) *Elimination reactions*

(*i*) Dehydrohalogenation of alkyl halides (ease—tert > sec > pri)

$$CH_3CHBrCH_2CH_3 \xrightarrow{C_2H_5OH/KOH} CH_3CH{=}CHCH_3 + CH_2{=}CHCH_2CH_3$$

(*ii*) Dehydration of alcohols (ease—tert > sec > pri)

$$CH_3CH_2OH \xrightarrow[180^\circ]{H_2SO_4} CH_2{=}CH_2$$

(*iii*) From tetralkylammonium hydroxides (Hofmann degradation)

$$CH_3CH_2CH_2CH_2\overset{\oplus}{N}(CH_3)_3 \wr \overset{\ominus}{O}H \xrightarrow{\text{heat}} CH_3CH_2CH{=}CH_2 + (CH_3)_3N$$

(*iv*) Dehydrohalogenation of vic-dihalides; zinc powder is added to a solution of the dibromide or diiodide in methanol.

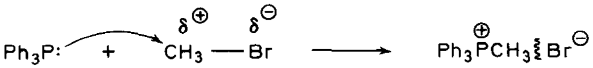
$$CH_3{-}CHBr{-}CH_2Br \xrightarrow{Zn/CH_3OH} CH_3{-}CH{=}CH_2$$

(*c*) *Reduction of alkynes*

May yield predominantly the *cis* or *trans* alkene, see section 5.5.

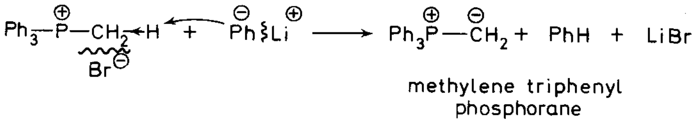
(*d*) *The Wittig synthesis*

Alkyl bromides react with triphenylphosphine to yield an alkyltriphenylphosphonium bromide.

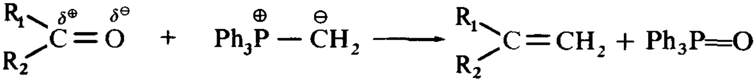


$$Ph_3P{:} + \overset{\delta\oplus}{CH_3}{-}\overset{\delta\ominus}{Br} \longrightarrow Ph_3\overset{\oplus}{P}CH_3 \wr Br^{\ominus}$$

With a strong base (C_2H_5ONa or PhLi) the above phosphonium compound yields an Ylide, i.e. a carbanion having a heteroatom adjacent to the carbon atom carrying the negative charge.

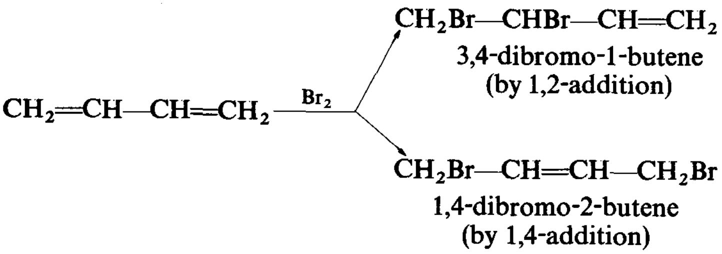


Phosphorane ylides react smoothly with aldehydes and ketones to form alkenes.

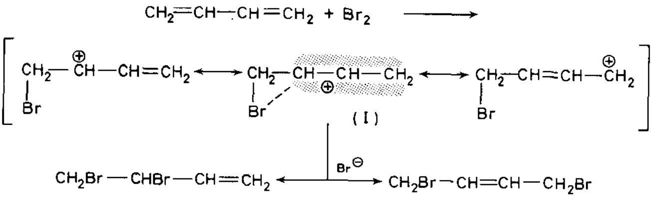


5.4 CONJUGATED DIENES

Non-conjugated dienes simply show normal double bond properties twice over. Conjugated dienes, however, are more reactive than normal alkenes and also exhibit some abnormal properties, e.g. in addition reactions. Thus addition of any of the usual reagents such as halogens, hydrogen halides, etc., to 1,3-butadiene yields two products.



The two products arise by 1,2 and 1,4-addition of the halogen to the diene. Addition probably takes place via an allyl-type carbonium ion, I, (S_N1 substitution of allyl halides, page 128).



The carbonium ion, I, probably includes some contribution from the bromonium ion form mentioned previously with regard to the addition reactions of alkenes (section 3.5).

The ratio of the 1,2- to 1,4-addition products of 1,3-butadiene varies with temperature. Low temperatures favour 1,2-addition, high temperatures favour 1,4-addition. Further, the 1,2-addition product is converted into the 1,4-product at high temperatures, i.e. the 1,4-product is thermodynamically more stable than the 1,2-product. This situation can be represented by a potential energy diagram, *Figure 5.1.*

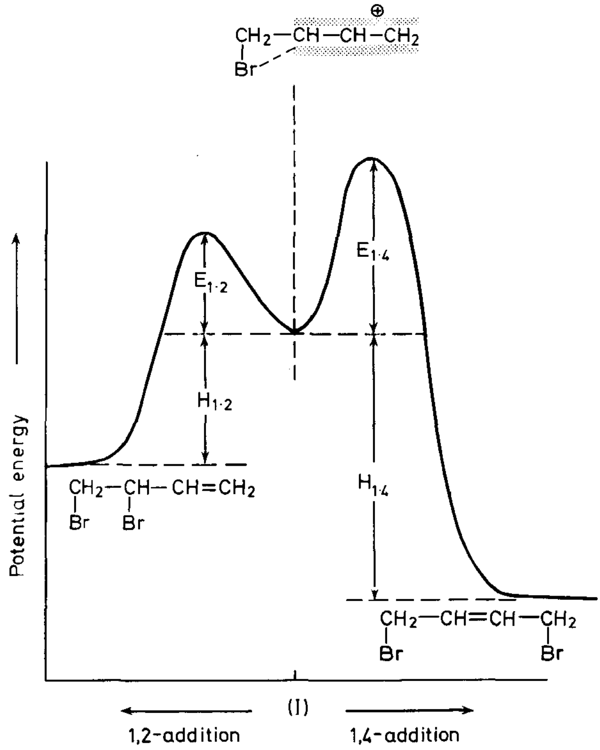
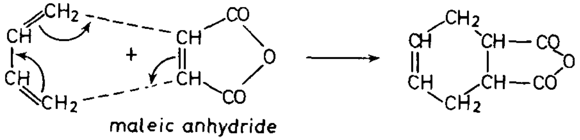


Figure 5.1. Potential energy changes during the formation of 1,2 and 1,4-addition products from 1,3-butadiene

The energy of activation for the 1,2-compound ($E_{1\cdot2}$) is lower than that for the 1,4-compound ($E_{1\cdot4}$). Hence the former is preferentially formed at low temperatures where the energy available is low. However, the heat of reaction for the 1,4-compound ($H_{1\cdot4}$) is greater than that for the 1,2-compound ($H_{1\cdot2}$) and so the former is the more stable isomer. This type of behaviour is described as *kinetic* control of the reaction at low temperatures and *thermodynamic* control at high temperatures.

Conjugated dienes undergo 1,4-addition with substances which contain a double bond activated by one or more electron withdrawing groups. The reaction, which has considerable synthetic importance, is termed the Diels–Alder reaction.



The addition of the activated alkene, termed the dienophile, is to the 1,4-positions of the diene; the remaining double bond of the diene moves to the 2,3-position. Dienophiles need not necessarily be of the cyclic anhydride type. Other dienophiles are $CH_3—CH{=}CH—X$ and $C_6H_5—CH{=}CH—X$, where the group X has powerful $-I$ and $-M$ effects, e.g. —COOH, —CHO, $—NO_2$ and $—C{\equiv}N$. Tetracyanoethylene, $(CN)_2C{=}C(CN)_2$, acrolein, $CH_2{=}CH—CHO$, and vinyl cyanide (acrylonitrile),

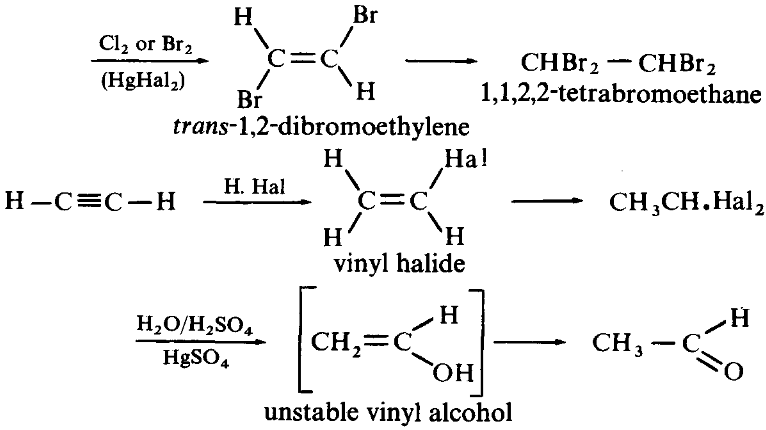
$$CH_2{=}CH—C{\equiv}N,$$

are powerful dienophiles.

1,3-Butadiene is manufactured from the butane fraction of petroleum distillate or the 1-butene fraction of 'cracked' petroleum. Either of these hydrocarbons dehydrogenates to 1,3-butadiene when passed over heated chromic oxide. Polybutadienes find wide application as synthetic rubbers (see section 16.3).

5.5 ALKYNES

Alkynes have the general formula C_nH_{2n-2} and contain a triple bond which comprises one σ and two π-bonds. The π-bonds of alkynes, like those of alkenes, react by addition. The addition is electrophilic in character and again like the alkenes, the overall addition is *trans*.



The addition of halogens is catalysed by metal halides but iodine only reacts as far as the diiodide stage. Alkynes decolorise dilute potassium permanganate solutions and yield diones rather than the diols formed from alkenes.

Alkynes having at least one hydrogen atom attached to the triple bond, i.e. H—C≡C—C but not C—C≡C—C, form metal acetylides with heavy metal ions, particularly $Ag^{\oplus}$, $Cu^{\oplus}$ and $Hg^{\oplus}$.

$$\text{H—C}\equiv\text{C—H} + Cu_2Cl_2 \xrightarrow{NH_4OH} \underset{\text{cuprous acetylide (red)}}{\text{Cu—C}\equiv\text{C—H}}$$

Metal acetylides are explosive when dry but their formation provides a useful test for the H—C≡C— group.

Alkynes are weaker acids than alcohols but stronger acids than amines or ammonia. The approximate K_A values for some commonly encountered compounds are: CH_3COOH, 2×10^{-5}; H_2O, 10^{-16}; C_2H_5OH, 10^{-18}; H—C≡C—H, 10^{-22}; NH_3, 10^{-35}; $H_2C{=}CH_2$, 10^{-40}; $CH_3{-}CH_3$, $<10^{-40}$. An alkyne hydrogen atom is, therefore, removed by $NH_2^{\ominus}$ but not by $OEt^{\ominus}$.

$$\text{H—C}\equiv\text{C—H} + NaNH_2 \xrightarrow[\text{liquid } NH_3]{\text{ether or}} \text{H—C}\equiv\text{C}^{\ominus}\}Na^{\oplus} + NH_3$$

Hydrogen atoms of alkynes show this acidic reaction due to, (*a*) the electronegativity of the *sp*-hybridised carbon atom (see page 11) and (*b*) the stabilisation of the acetylide ion by delocalisation of the negative charge.

The acetylide ion is a carbanion and a powerful nucleophile. Thus it reacts with alkyl halides to yield higher alkynes.

$$H{-}C{\equiv}C^{\ominus}|Na^{\oplus} + CH_3\overset{\delta\oplus}{C}H_2{-}\overset{\delta\ominus}{Br} \rightarrow \underset{\text{1-butyne}}{CH_3CH_2{-}C{\equiv}CH} + NaBr$$

Another method of building up alkynes is via 'oxidative coupling'.

$$2\,CH_3{-}C{\equiv}CH \xrightarrow[\text{air}]{Cu_2Cl_2,\ NH_4Cl} \underset{\text{2,4-hexadiyne}}{CH_3{-}C{\equiv}C{-}C{\equiv}C{-}CH_3}$$

PREPARATION OF ALKYNES

(*a*) Industrial preparation of acetylene, (*i*) from calcium carbide:

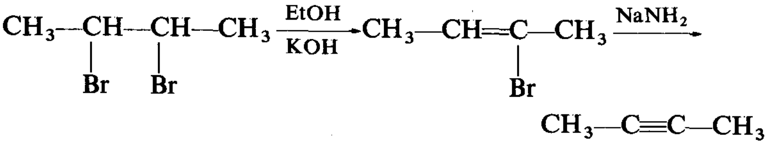
$$CaO + 3C \xrightarrow{2000^\circ} CaC_2 + CO$$

$$CaC_2 + 2H_2O \longrightarrow HC{\equiv}CH + Ca(OH)_2$$

(*ii*) by partial oxidation of methane:

$$6CH_4 + O_2 \xrightarrow{1500^\circ C} 2\,HC{\equiv}CH + 2CO + 4H_2$$

(*b*) Elimination of hydrogen halide (2 moles) from vic-dihalides.



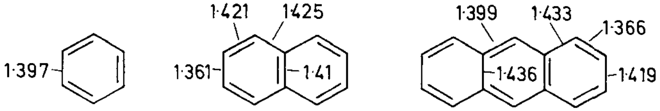
$$CH_3{-}\underset{Br}{\underset{|}{CH}}{-}\underset{Br}{\underset{|}{CH}}{-}CH_3 \xrightarrow[KOH]{EtOH} CH_3{-}CH{=}\underset{Br}{\underset{|}{C}}{-}CH_3 \xrightarrow{NaNH_2} CH_3{-}C{\equiv}C{-}CH_3$$

The second mole of hydrogen halide is difficult to remove and a stronger base may be necessary for this step.

(*c*) Synthesis via attack of the acetylide ion on alkyl halides or by 'oxidative coupling', as described above.

5.6 ARENES

The basic arene, or aromatic hydrocarbon, is benzene. Higher members of the series are formed by combining together benzene rings, e.g. naphthalene, anthracene or phenanthrene. Benzene and the higher arenes, and their derivatives, are said to exhibit aromatic character. Initially the term aromatic referred to the 'fragrant' odour of benzene and some of its derivatives, e.g. benzaldehyde. Nowadays the term aromatic or aromatic character refers to those substances which resist oxidation and substitution to a greater extent than their valence bond structures would suggest. Thus the carbon–carbon bonds in benzene are all the same length and do not alternate double and single as the valence bond formula suggests. Unlike an alkene, benzene does not easily add hydrogen halides or halogens nor does it form glycols with aqueous potassium permanganate. An alternative modern meaning of the term aromatic is that it refers to substances which have approximately uniform carbon–carbon bond lengths within a ring structure and also have a high stabilisation energy due to π-electron delocalisation. These two meanings of the term aromatic are not necessarily compatible.



Bond lengths (Å) in benzene, naphthalene and anthracene

The molecular structure of benzene has already been described (section 1.4). A π-molecular orbital containing six delocalised electrons extends above and below the hexagonal ring (or nucleus) formed by the six sp^2-hybridised carbon atoms. All the carbon–carbon bond lengths are the same (1·397 Å) as are all the carbon–hydrogen distances (1·084 Å). Once the symmetry of the isolated hexagonal structure of benzene is lost then bond lengths show definite variations, e.g. naphthalene and anthracene. In such cases some positions in the ring system show greater reactivity than others towards electrophiles. Also some bonds may exhibit alkene characteristics. Thus, anthracene, like a conjugated diene, undergoes a Diels–Alder reaction and adds maleic anhydride across the 9,10-positions. This type of behaviour is not shown by benzene, naphthalene or phenanthrene.

Aromatic character in monocyclic, planar systems has been studied mathematically by Hückel using the molecular orbital method. He concluded that such substances which have $(4n + 2)$ π-electrons, i.e. 6, 10, 14, 18, etc., are characterised by a high stabilisation energy and are unreactive because a high activation energy is required to form a transition state. This is a reasonable explanation of the general lack of reactivity of benzene, naphthalene, etc., when compared with alkenes. Some variations in the behaviour of individual arenes are described in the following pages.

(a) REACTIONS OF ARENES

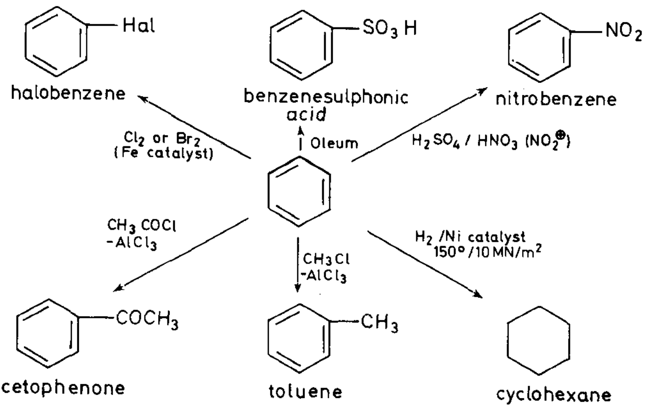
Benzene shows no additive diene properties; it does not react with hydrogen bromide, bromine in carbon tetrachloride or cold aqueous potassium permanganate. Hydrogenation only occurs under vigorous conditions. A variety of electrophilic reagents substitute the benzene nucleus and lead to nitration, halogenation, sulphonation, alkylation and acylation products by the general mechanism of electrophilic aromatic substitution mentioned in section 3.4.

Naphthalene, due to the loss of complete symmetry, requires a lower activation energy for reaction than benzene and is thus more reactive than benzene. For example, nitration of naphthalene occurs 400 times faster than for benzene under the same conditions. Electrophiles react at the 1-position of naphthalene much more readily than at the 2-position. The partial rate factors, i.e. the rate of substitution at a given position relative to any one of the six equivalent positions in benzene, for the nitration of naphthalene at the 1- and 2-positions are 470 and 50 respectively. Naphthalene oxidises quite easily with chromic acid to 1,4-naphthaquinone, reduces with sodium and ethanol to 1,4-dihydronaphthalene and will undergo halogenation without a catalyst.

Anthracene and phenanthrene are less resistant to oxidation and reduction than naphthalene. Substitution tends to take place via addition followed by elimination. The 9,10-positions of both compounds show a degree of reactivity more associated with alkenes than arenes and, as already mentioned, Diels–Alder addition occurs in the case of anthracene. This alkene-type behaviour is observed because addition to, say, the 9 and 10 positions of anthracene, produces two isolated benzene rings which are very nearly as stable as the original anthracene or phenanthrene molecule.

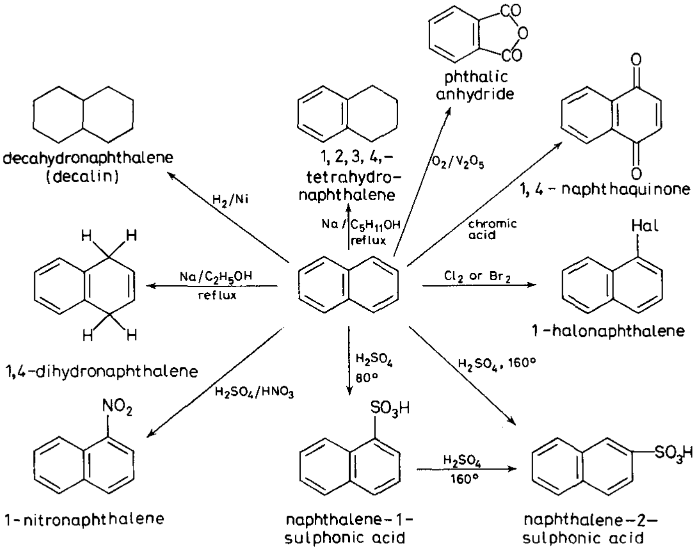
(b) SUMMARY OF ARENE REACTIONS

(*i*) *Benzene*



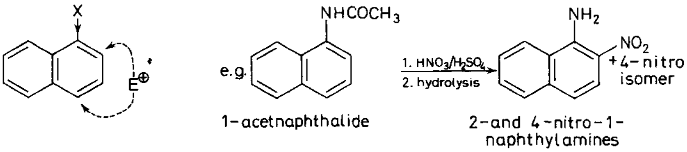
(*ii*) *Naphthalene*

The sulphonation reactions of naphthalene resemble the addition of halogens to 1,3-butadiene. At low temperatures (80°) sulphonation is kinetically controlled and at high temperatures (160°) thermodynamically controlled.

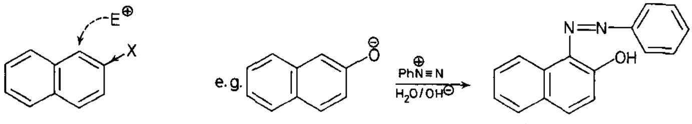


Further substitution in naphthalene (cf. benzene, page 55) may be summarised as follows:

(*A*) An activating group in the 1-position directs incoming electrophiles to the 2- and/or 4-positions, i.e. corresponding to ortho/para substitution in benzene.

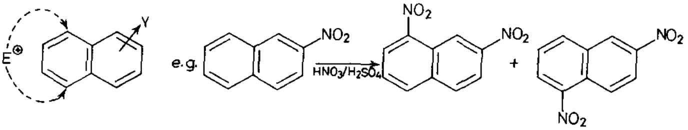


(*B*) An activating group in the 2-position directs electrophiles to the 1-position. This is accompanied by some substitution at the 6- and 8-positions but it should be noted that no substitution occurs at the 3-position.



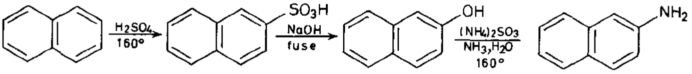
1 - benzeneazo-
2 - naphthol

(*C*) Deactivating substituents in the 1- or 2-positions reduce the electron density so much in their own ring that electrophiles attack the other ring in the 5- and 8-positions.



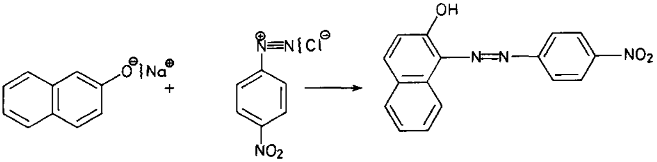
1,7-and 1,6-dinitronaphthalenes

Many other naphthalene derivatives can be prepared by normal chemical methods from compounds already mentioned. Thus 1-naphthylamine, prepared by reduction (Fe/HCl/H_2O) of 1-nitronaphthalene, forms diazonium compounds which undergo the usual replacement reactions (section 9.5). 2-Naphthylamine behaves similarly but is prepared by an unusual method from 2-naphthol since 2-nitronaphthalene is not readily available. Termed the Bucherer reaction, 2-naphthol is heated with ammonia and ammonium sulphite under pressure.



2 - naphthylamine

The naphthols, formed by alkali fusion of the sulphonic acids, readily couple in alkaline solution with diazonium salts and many important dyestuffs are prepared in this way, e.g.



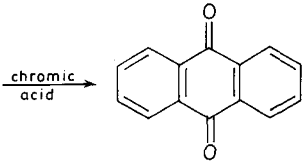
sodium 2-naphthoxide
(apply in solution to
cloth and dry)

p-nitrobenzene
diazonium chloride
(pour solution over
previously
impregnated cloth)

red azo dye –
p-nitrobenzeneazo-
2-naphthol
(formed on cloth
fibres)

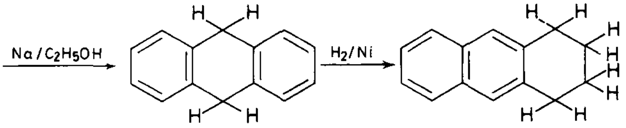
(*iii*) *Anthracene*

Oxidation



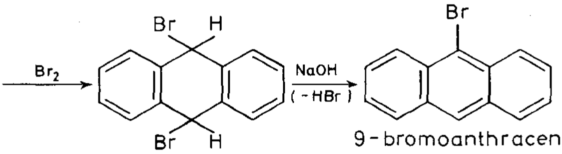
anthraquinone

Reduction



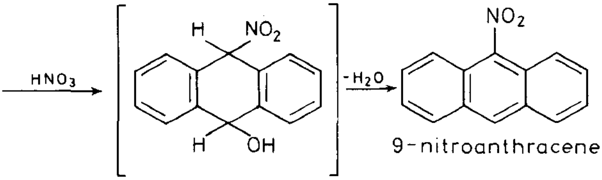
9,10-dihydro- and 1,2,3,4-tetrahydro-
anthracenes

Halogenation



9-bromoanthracene

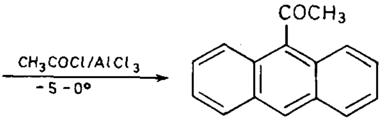
Nitration



9-nitroanthracene

Sulphonation $\xrightarrow{\text{oleum}}$ anthracene-1-sulphonic acid (50%) and
anthracene-2-sulphonic acid (30%)

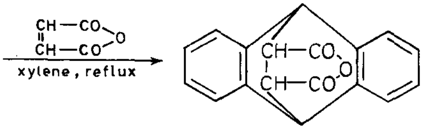
Friedel–Crafts acylation



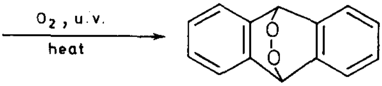
9-acetylanthracene

(more vigorous conditions lead to acylation at the 1- and 2-positions)

Diels–Alder addition

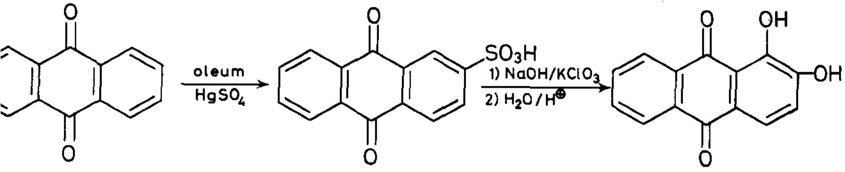


Peroxide formation



The diene-type properties of the 9,10-positions of anthracene are exhibited during halogenation, nitration, peroxide formation and Diels–Alder addition. Anthracene undergoes electrophilic substitution, at the 9-position, very much faster than either benzene or naphthalene.

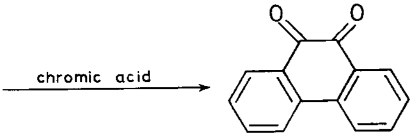
Anthraquinone is a starting material for many important dyestuffs. The two carbonyl groups are strongly electron withdrawing and so anthraquinone is a stable, deactivated substance which only undergoes electrophilic substitution with difficulty. Sulphonation of anthraquinone with oleum in the presence of mercury (II) sulphate yields anthraquinone-2-sulphonic acid. The red dyestuff alizarin, which can be isolated from the root of the madder plant, is synthesised by heating this sulphonic acid with alkali in the presence of potassium chlorate. Alizarin becomes chemically attached to a cloth by forming chelate compounds with the fibre and an added metal (Al, Cr or Fe) salt.



1,2-dihydroxyanthraquinone
(alizarin)

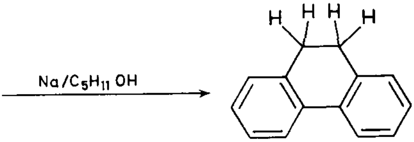
(iv) Phenanthrene

Oxidation



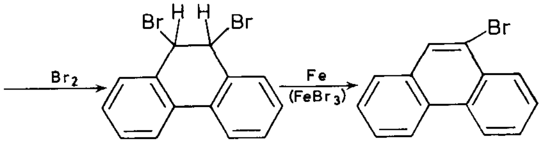
9,10-phenanthraquinone

Reduction



9,10-dihydrophenanthrene

Halogenation

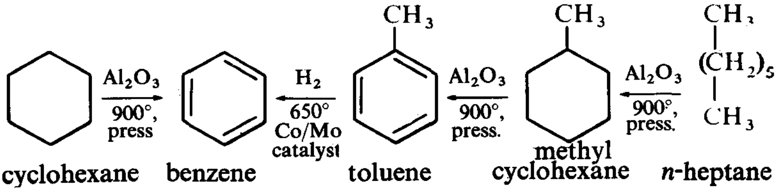


9-bromophenanthrene

Sulphonation (H_2SO_4 at 120°) and Friedel–Crafts acylation ($CH_3COCl/AlCl_3$) produce substitution mainly at the 2- and 3-positions of phenanthrene. Nitration produces a mixture consisting mainly of the 1, 2 and 9-nitrophenanthrenes and substitution at the 9-position is approximately 500 times faster than in benzene.

(c) OCCURRENCE AND SYNTHESIS OF ARENES

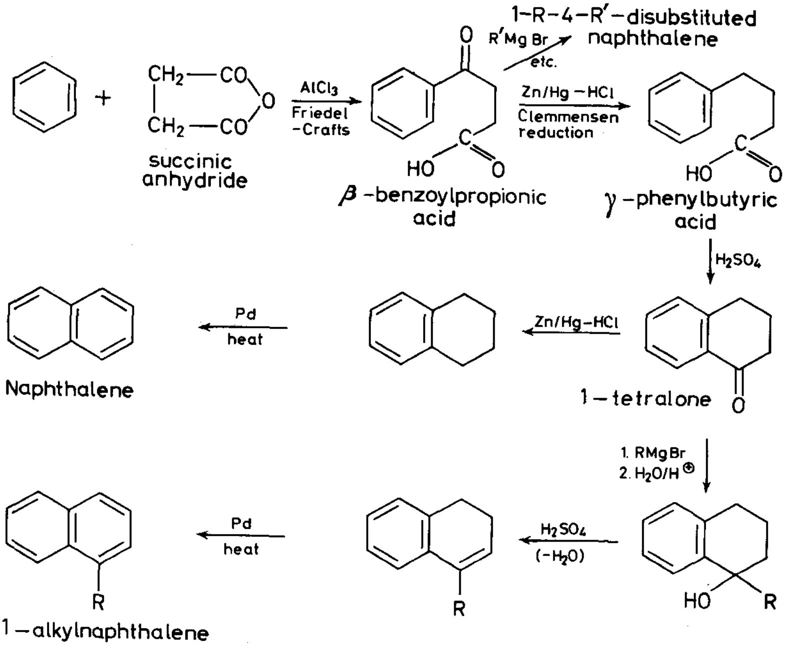
Coal tar yields all the arenes mentioned in this section and many more besides. Naphthalene is present in the largest amount but benzene, toluene and the xylenes are also recovered although only present in small amounts. With a continually increasing demand for arenes, particularly benzene, routes have been developed from petroleum fractions such as cyclohexane and methylcyclohexane:



(*i*) *Naphthalene*

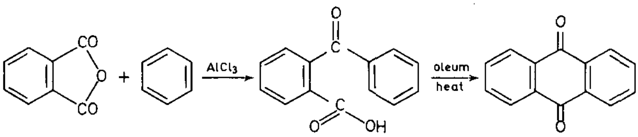
Approximately one-tenth of coal tar is naphthalene. After distillation of the tar, naphthalene solidifies in the middle fraction and is collected. Impurities are removed by washing with mineral acid and then alkali before the naphthalene is finally purified by redistillation. Methylnaphthalenes are produced in some petroleum refinery processes and these can be converted into naphthalene in the same way that toluene is demethylated to benzene.

Synthetic routes to a number of naphthalene derivatives have already been indicated via substitution reactions. Another route is via ring closure; the route due to Haworth (1932) forms an elegant example of this technique. A second ring is built on to a benzene as follows:



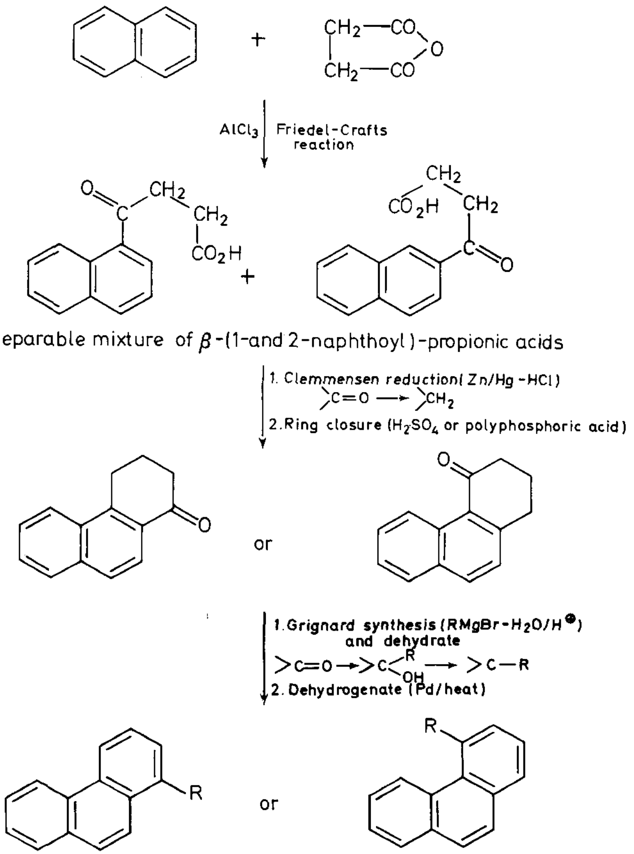
(*ii*) *Anthracene*

Anthracene can be obtained from coal tar or synthesised via a Friedel–Crafts reaction between benzene and phthalic anhydride.



o-benzoylbenzoic acid

Anthraquinone, which is often required in the dyestuffs industry rather than anthracene itself, reduces easily to anthracene with zinc and alkali. Some anthracene derivatives can be made by direct electrophilic substitution of the hydrocarbon but ring closure



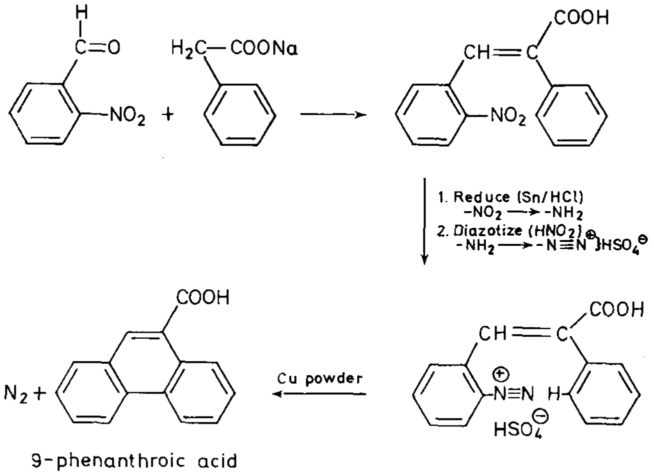
1-or 4-substituted phenanthrene

methods, using substituted benzenes or phthalic anhydrides in the above Friedel–Crafts method, are frequently employed.

(*iii*) *Phenanthrene*

Most substituted phenanthrenes are made by ring closure. The Haworth synthesis, starting from naphthalene and succinic anhydride, is a particularly useful method (see opposite page).

An interesting method of constructing the phenanthrene ring system is the Pschorr synthesis. Reaction between *o*-nitrobenzaldehyde and sodium phenylacetate in acetic anhydride forms one link between two benzene rings. The second bond is formed by the free radical decomposition of a diazonium compound (the Gomberg reaction, section 9.4).

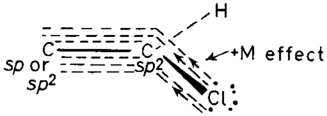


6

The Carbon–Halogen Bond—Alkyl, Alkenyl and Aryl Halides

6.1 INTRODUCTION AND NOMENCLATURE

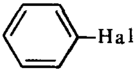
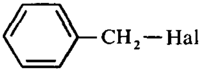
Carbon–halogen bonds are polarised in the direction $>\overset{\delta\oplus}{C}-\overset{\delta\ominus}{\text{Hal}}$. The carbon atom is, therefore, susceptible to attack by nucleophiles. When the carbon atom is sp^3-hybridised the halogen atom can only exert an inductive effect. However, with an sp^2 or sp-hybridised carbon atom, interaction with a lone pair of electrons on the halogen atom can also take place, i.e. both the $-$I and the $+$M effect of the halogen are then operative.

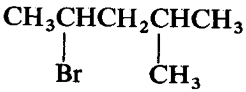


The dissociation energies and lengths of carbon–halogen bonds vary considerably depending on the particular halogen and the hybridisation state of the carbon atom to which it is attached (see *Table 6.1*). In general terms as the bond dissociation energy decreases the bond length increases and so the bond becomes more easily polarised and more reactive towards nucleophiles.

Organic halides are named from their parent alkanes. The halogen is prefixed to the alkane and numbered so as to take precedence over alkyl side chains, e.g.

Table 6.1. BOND DISSOCIATION ENERGIES AT 0 K AND BOND LENGTHS OF CARBON—HALOGEN BONDS

	Bond	*Dissociation energy* (kJ/mol)	*Length* (Å)
CH_3—Hal			
	C—F	448	1·38
	C—Cl	335	1·78
	C—Br	280	1·94
	C—I	222	2·14
CH_2=CH—Hal			
	C—F	—	1·34
	C—Cl	435	1·74
	C—Br	—	1·89
	C—I	—	2·09
			
	C—F	—	1·33
	C—Cl	360	1·69
	C—Br	297	1·86
	C—I		2·08
CH_2=CH—CH_2 Hal			
	C—Cl	251	1·82
	C—Br	193	2·00
	C—I	—	2·18
			
	C—Cl	285	—
	C—Br	213	—



$CH_3\underset{Br}{CH}CH_2\underset{CH_3}{CH}CH_3$ 2-bromo-4-methylpentane

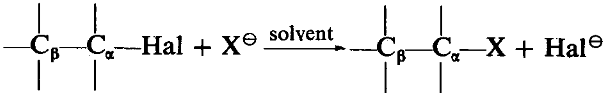
$Cl_2CHCH_2CH_3$ 1,1-dichloropropane

$ICH_2CH_2CH{=}CH_2$ 4-iodo-1-butene

Note that the last example is not termed 1-iodo-4-butene because the multiple bond always takes the lowest possible number.

6.2 REACTIONS OF ORGANIC HALIDES WITH NUCLEOPHILES

The general mechanisms for nucleophilic attack on carbon atoms, the S_N1 and S_N2 mechanisms, have already been described in section 3.3. The overall reaction equation for these processes is:



$$-\overset{|}{\underset{|}{C_\beta}}-\overset{|}{\underset{|}{C_\alpha}}-\mathrm{Hal} + X^{\ominus} \xrightarrow{\text{solvent}} -\overset{|}{\underset{|}{C_\beta}}-\overset{|}{\underset{|}{C_\alpha}}-X + \mathrm{Hal}^{\ominus}$$

The halogen atom has been displaced by the nucleophile, $X^{\ominus}$, to yield a substitution product. One or more alkenes may also be formed in the accompanying elimination reaction.

Many factors affect the overall rate of nucleophilic substitution. Some of these are:

(*a*) the positivity of the α-carbon atom,
(*b*) the polarisability of the C—Hal bond and hence its susceptibility to heterolysis (S_N1),
(*c*) the activation energy required for the formation of any transition state (S_N2),
(*d*) the solvation energies of the nucleophile and the halide,
(*e*) the structure of the carbon skeleton to which the halogen is attached.

This last factor (*e*) is particularly important and is determined by the type of organic halide involved. Three basic types of carbon skeleton are considered.

(a) THE $-\overset{|}{\underset{|}{C_{sp^3}}}-\overset{|}{\underset{|}{C_{sp^3}}}-$ HALOGEN BOND

This type of bond is found in alkyl halides, e.g.

$CH_3—CH_2—Br$	$CH_3—CH_2—CHCl—CH_3$,
bromoethane	2-chlorobutane

The halogen atom exerts only an inductive effect in both the ground state of the molecule and any transition state. Organic halides of this type are fairly reactive towards a wide range of nucleophiles (see *Table 6.2*). Alkyl iodides are the most reactive whilst alkyl fluorides are fairly inert, in agreement with the observed bond lengths and dissociation energies.

$$\xrightarrow[\text{decreasing rate of attack by } X^{\ominus}]{\mathrm{RI} > \mathrm{RBr} > \mathrm{RCl} > \mathrm{RF}}$$

Table 6.2. EXAMPLES OF NUCLEOPHILIC DISPLACEMENT OF A HALOGEN ATOM

$$R—Hal + X^{\ominus} \rightarrow R—X + Hal^{\ominus}$$

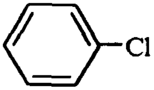
	Nucleophile		*Product*	*Notes*
$C_2H_5Cl +$	$Br^{\ominus}$	$\longrightarrow$	C_2H_5Br bromoethane	
	$I^{\ominus}$		C_2H_5I iodoethane	
	$\overset{\ominus}{O}H$		C_2H_5OH ethanol	or $\overset{\ominus}{O}R$
	$\overset{\ominus}{O}C_2H_5$		$C_2H_5OC_2H_5$ diethyl ether	solvent— ethanol
	$:NH_3$		$C_2H_5\overset{\oplus}{N}H_3\}\overset{\ominus}{Cl}$ ethylammonium chloride	or RNH_2 or $RR'NH$
	$\overset{\ominus}{N}H_2$		$C_2H_5NH_2$ ethylamine	solvent— liquid NH_3
	$CH_3CO{\cdot}O^{\ominus}$		$CH_3CO{\cdot}OC_2H_5$ ethyl acetate	
	$HC{\equiv}C^{\ominus}$		$HC{\equiv}C—CH_2—CH_3$ 1-butyne	solvent— liquid NH_3
	$Ph_3P:$		$C_2H_5—\overset{\oplus}{P}—Ph_3\}\overset{\ominus}{Cl}$ triphenylethyl phosphonium chloride	solvent— ether or benzene
	$\overset{\ominus}{C}{\equiv}N$		$C_2H_5C{\equiv}N$ cyanoethane	
	$\overset{\ominus}{S}H$		C_2H_5SH ethanethiol	

Notes. (*i*) Nucleophilic displacement reactions are usually carried out in ethanol, acetone or water, or a mixture of these solvents. Some exceptions are noted in the table. (*ii*) See also the reactions of halogen compounds with nucleophiles derived from ethyl acetoacetate or diethyl malonate (pages 210 and 223).

Primary alkyl halides will normally react by the S_N2 mechanism whilst tertiary alkyl halides react S_N1 and secondary alkyl halides react by a mixture of the two processes (pages 46–47).

(b) THE C_{sp^2}—C_{sp^2}— HALOGEN BOND

Alternatively C_{sp}—C_{sp}—Hal as in alkenyl and aryl halides, e.g.



$CH_2{=}CHBr$ $CH{\equiv}CCl$

chlorobenzene
(an aryl halide)

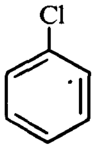
vinyl bromide chloroacetylene
(alkenyl halides)

Both the −I and +M effects of the halogen atom are operative in these molecules and organic halides of this type are characteristically inert towards nucleophiles. The reasons for this lack of reactivity are twofold.

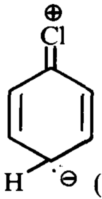
(*i*) Because the α-carbon atom is sp^2 (or sp)-hybridised the +M effect of the halogen can operate and donate some fraction of an electron pair to the π molecular orbital system existing over the π and other carbon atoms. The net result is that the C_α—Hal bond is strengthened and shortened (*Table 6.1*).

(*ii*) The effect of the increase in the percentage of *s*-character in sp^2 and sp-hybridised carbon atoms is to make them appear more electronegative than sp^3 carbon atoms (page 11).

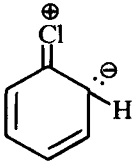
The overall inference from points (*i*) and (*ii*) is that in aryl and alkenyl halides the carbon–halogen bonds are shorter and stronger than in alkyl halides and that also the relative positivity of the α-carbon atom is reduced. The reduced reactivity of these compounds towards nucleophiles can also be explained by hybrid structures, such as I–V, where some degree of double bond character in the carbon–halogen bond is suggested.



(I)



(II)



(III)

$CH_2{=}CH{-}Cl$
(IV)

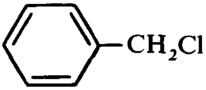
$\overset{\ominus}{C}H_2{-}CH{=}\overset{\oplus}{Cl}$
(V)

The reactivity of aryl halides towards nucleophiles follows the normal order (PhI > PhBr > PhCl > PhF) except when electron withdrawing groups, particularly nitro groups, are situated *ortho* and/or *para* to the halogen atom. The reverse order of reactivity is then observed, e.g. 2,4-dinitrofluorobenzene is more reactive than 2,4-dinitrochlorobenzene.

As aryl halides show such low reactivity towards nucleophiles substitution also takes place by a process of elimination and addition, involving the benzyne intermediate. This mechanism has already been described on page 50.

(c) THE $>C_{sp^2}—C_{sp^3}—$ HALOGEN BOND

Alternatively $—C_{sp}—C_{sp^3}—$Hal, as in alkenyl and benzyl halides, e.g.



benzyl chloride

$CH_2{=}CH—CH_2—Br$

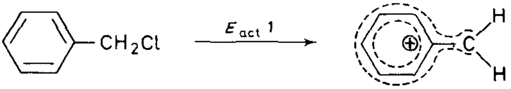
3-bromopropene
(allyl bromide)

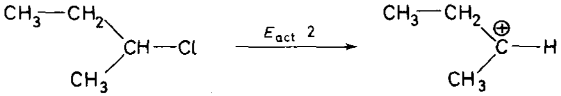
$CH{\equiv}C—CH_2—Cl$

3-chloropropyne

Only the −I effect of the halogen is operative in the ground state of this class of compound, but the +M effect comes into play in carbonium ion intermediates. Compounds of this type are normally the most reactive of the organic halides (except for acyl halides, section 8.8) by both the S_N1 and S_N2 routes.

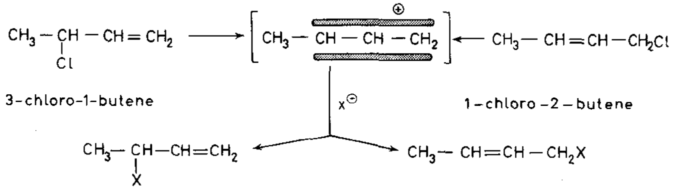
Their high S_N1 reactivity is due to the ease of formation of a carbonium ion:





In the above examples $E_{act}2 > E_{act}1$ and so benzyl chloride is more reactive than 2-chlorobutane. The benzyl carbonium ion is stabilised because the positive charge can be spread, via the π molecular orbital system, over seven carbon atoms. The sec-butyl carbonium ion is less stable because the charge is practically localised on the one carbon atom.

A consequence of charge delocalisation in allyl cations is that the nucleophile can attack either of two carbon atoms and so two reaction products are formed.

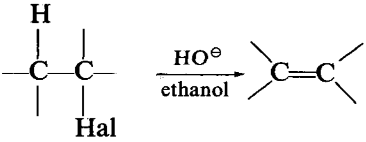


Notice that in this example two different reactants have both yielded the same delocalised carbonium ion and hence they will both yield the same two products.

The high S_N2 reactivity of allyl and benzyl halides is probably due to the increased polarizability of the carbon–halogen bonds. Hence the transition state will be very easily formed.

6.3 ELIMINATION REACTIONS OF ORGANIC HALIDES

The E1 and E2 elimination mechanisms have already been discussed (page 64). In the case of alkyl halides the overall reaction is:

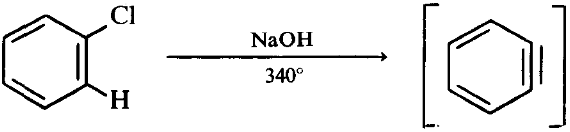


and the highest yields of the alkene are obtained with hot, concentrated solutions of ethanolic alkali. Alkenyl halides will also undergo elimination but the reaction is slower than with the corresponding alkyl halides.

$$CH_2{=}CH{-}CH_2Cl \longrightarrow \underset{\text{allene}}{CH_2{=}C{=}CH_2}$$

$$CH_2{=}CHCl \longrightarrow HC{\equiv}CH$$

Benzyl halides cannot undergo elimination since there is no hydrogen attached to the β-carbon atom. Halobenzenes react with alkali at high temperatures to yield the reactive benzyne intermediate (page 50).



6.4 OTHER REACTIONS OF THE CARBON–HALOGEN BOND

The reduction of halogen compounds to hydrocarbons and the replacement of the halogen atom by a metal are particularly important reactions. In both cases alkyl, allyl and benzyl halides are considerably more reactive than vinyl or aryl halides.

(*a*) *Reduction*—Normally for this reaction either hydrogen and a catalyst (nickel, platinum, palladium, etc.) or a metal and an acid (Zn/HCl, Sn/HCl, etc.) are used. Sodium in ethanol and lithium aluminium hydride in ether are also effective.

$$C_2H_5Br + H_2 \xrightarrow{Ni} C_2H_6$$

$$CH_3CHBrCH_3 \xrightarrow{Zn/HCl} CH_3CH_2CH_3$$

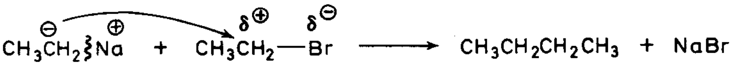
(*b*) *Metallation*—Sodium, lithium, magnesium and zinc all react directly with organic halides. Ethers (diethyl ether, tetrahydrofuran, etc.) are the normal solvents and the reactions are often carried out under nitrogen. Iodides are the most reactive of the halides and fluorides the least reactive ($RI > RBr > RCl \gg RF$).

$$CH_3CH_2CH_2CH_2Br + 2Li \rightarrow \underset{\text{n-butyllithium}}{CH_3CH_2CH_2CH_2Li} + LiBr$$

$$CH_3CH_2Br + Mg \xrightarrow{(C_2H_5)_2O} \underset{\substack{\text{ethylmagnesium bromide} \\ \text{(a Grignard reagent)}}}{CH_3CH_2MgBr}$$

Sodium alkyls are very reactive and combine with the alkyl halide to yield an alkane (the Wurtz reaction).

$$CH_3CH_2Br + 2Na \xrightarrow[\text{reflux}]{(C_2H_5)_2O} \underset{\text{ethylsodium}}{CH_3CH_2Na} + NaBr$$

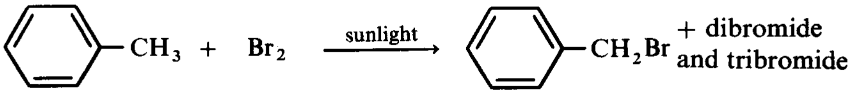


6.5 METHODS OF FORMING CARBON–HALOGEN BONDS

(a) VIA FREE RADICAL REACTIONS

(*i*) Halogenation of hydrocarbons with chlorine or bromine (see also pages 59, 98).

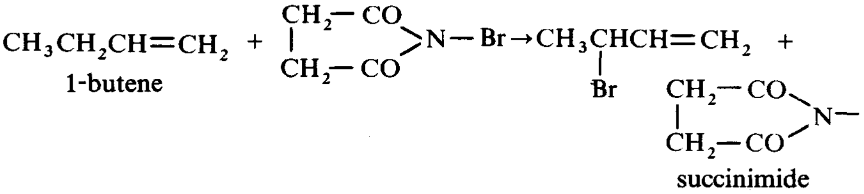
$$CH_4 + Cl_2 \rightarrow CH_3Cl \xrightarrow{Cl_2} CH_2Cl_2 \xrightarrow{Cl_2} CHCl_3 \xrightarrow{Cl_2} CCl_4$$



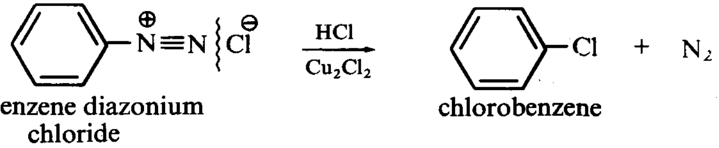
(*ii*) Addition of hydrogen halides to alkenes (mechanism, page 59)

$$CH_3CH{=}CH_2 + HBr \xrightarrow{\text{peroxide}} CH_3CH_2CH_2Br$$

(*iii*) Allyl position halogenation of alkenes with N-bromosuccinimide

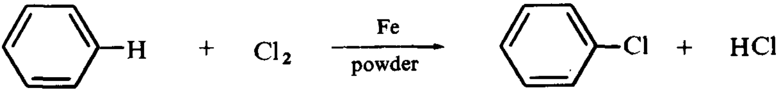


(*iv*) Decomposition of diazonium compound (see also page 183)



(b) VIA ELECTROPHILIC SUBSTITUTION OR ADDITION (mechanisms, page 50)

(*i*) Halogenation of alkenes and aromatic hydrocarbons



$$CH_2{=}CH_2 + Cl_2 \longrightarrow ClCH_2CH_2Cl$$

(*ii*) Addition of hydrogen halides to alkenes

$$CH_3CH{=}CH_2 + HBr \longrightarrow CH_3CHBrCH_3$$

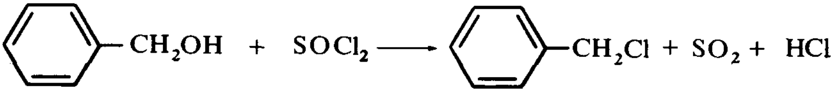
(c) VIA NUCLEOPHILIC SUBSTITUTION OF THE —OH GROUP IN ALCOHOLS

(*i*) With hydrogen halides—The reactions are catalysed by concentrated sulphuric acid or zinc chloride. Rearrangement can occur during the reaction. The order of reactivity of various alcohols is allyl > benzyl > tert > sec > pri.

$$\mathrm{ROH}-\left\{\begin{matrix}\mathrm{H_2SO_4}\\ \mathrm{HBr}\\ \mathrm{HI}\end{matrix}\right\}\rightarrow \overset{\oplus}{\mathrm{R\,O}}\mathrm{H_2}-\left\{\begin{matrix}\mathrm{Cl^{\ominus}}\longrightarrow \mathrm{RCl}\\ \mathrm{Br^{\ominus}}\longrightarrow \mathrm{RBr}\\ \mathrm{I^{\ominus}}\longrightarrow \mathrm{RI}\end{matrix}\right.$$

(*ii*) With phosphorus halides or thionyl chloride—This method avoids the rearrangement encountered in (*i*) but complex by-products are formed with phosphorus pentahalides.

$$3C_2H_5OH + PBr_3 \longrightarrow 3C_2H_5Br + H_3PO_3$$



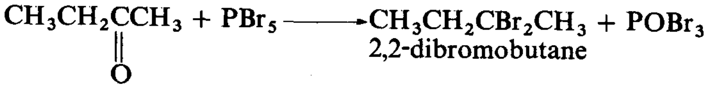
(d) VIA ELIMINATION OF HYDROGEN HALIDE FROM A DIHALIDE

With concentrated ethanolic alkali (mechanism, page 65)

$$\left.\begin{matrix}\mathrm{CH_3{-}CHCl_2}\\ \\ \mathrm{CH_2Cl{-}CH_2Cl}\end{matrix}\right\}\xrightarrow[\mathrm{C_2H_5OH}]{\mathrm{HO^{\ominus}}} \mathrm{CH_2{=}CHCl}$$

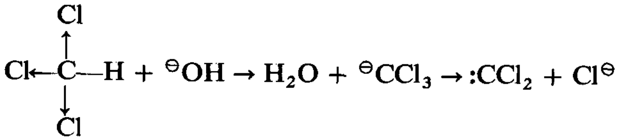
6.6 POLYHALOGEN COMPOUNDS

Di-, tri- and tetrachloromethanes are obtained from the direct chlorination of methane. Dihalogenoalkanes may also be prepared by the addition of halogens to alkenes or by the reaction of phosphorus pentahalides with aldehydes or ketones.



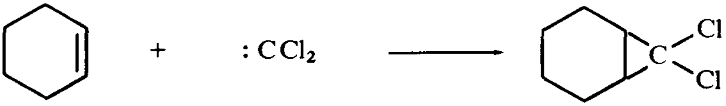
$$\mathrm{CH_3CH_2}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}\mathrm{CH_3} + \mathrm{PBr_5} \longrightarrow \underset{\text{2,2-dibromobutane}}{\mathrm{CH_3CH_2CBr_2CH_3}} + \mathrm{POBr_3}$$

In trichloromethane (chloroform) the electron attracting properties of the chlorine atoms render the hydrogen atom slightly acidic and hence subject to attack by strong bases.



$$\mathrm{Cl}\!\leftarrow\!\underset{\underset{\mathrm{Cl}}{\downarrow}}{\overset{\overset{\mathrm{Cl}}{\uparrow}}{\mathrm{C}}}\!-\!\mathrm{H} + {}^{\ominus}\mathrm{OH} \rightarrow \mathrm{H_2O} + {}^{\ominus}\mathrm{CCl_3} \rightarrow :\!\mathrm{CCl_2} + \mathrm{Cl^{\ominus}}$$

The carbanion, $^{\ominus}CCl_3$, loses a chloride ion to form the reactive intermediate dichlorocarbene, $:CCl_2$. This carbene is electrically neutral but is electron deficient as it has only six valence electrons and so behaves as an electrophile towards alkenes, reactive heterocycles (page 249), activated aromatic compounds (page 142), etc.



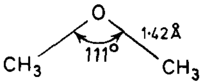
Dichlorocarbene is also formed in the Carbylamine Reaction (primary amine/chloroform/sodium hydroxide) when the nauseating odour of an isocyanide is produced.

7

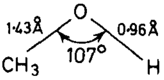
The Carbon–Oxygen Bond, I—Alcohols, Phenols and Ethers

7.1 INTRODUCTION AND NOMENCLATURE

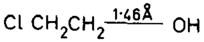
Carbon–oxygen bonds are polarised in the direction $>\!\overset{\delta\oplus}{\mathrm{C}}\text{——}\overset{\delta\ominus}{\mathrm{O}}$. The carbon atom is subject to attack by nucleophiles and the oxygen atom to electrophilic attack, usually protonation, or co-ordination by Lewis acids such as zinc chloride. The oxygen atom is sp^3-hybridised (page 7) producing the normal tetrahedral bond angles of approximately 109·5°. The carbon atom forming the C—O bond may be sp^3, sp^2 or sp-hybridised; the hybridisation state of this atom plays a large part in determining the chemical properties of the alcohol or phenol. Bond lengths also vary with the state of hybridisation of this carbon atom:



dimethyl ether

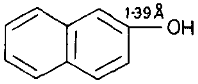


methanol



$$\mathrm{Cl\,CH_2CH_2}\overset{1{\cdot}46\,\text{Å}}{\text{———}}\mathrm{OH}$$

2–chloroethanol
(ethylene chlorohydrin)



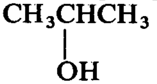
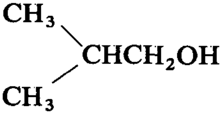
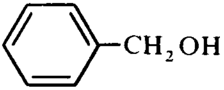
2 – naphthol

Besides undergoing nucleophilic displacement of the —OH group, a further feature of the chemistry of alcohols and phenols is their weak acidity due to cleavage of the oxygen–hydrogen bond.

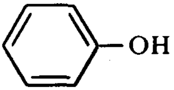
Alcohols are named by replacing the final 'E' of the name of their parent hydrocarbon with-*ol*, e.g.

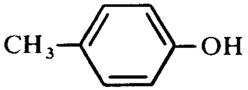
ethane, CH_3CH_3 ethanol, CH_3CH_2OH

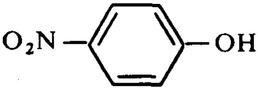
In the following examples trivial names are given in parentheses and trivial names in common usage are marked with an asterisk.

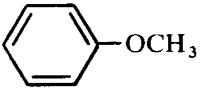
CH_3CH_2OH	ethanol	(ethyl alcohol)
$CH_3CH_2CH_2OH$	1-propanol	(n-propyl alcohol)
 $\underset{\displaystyle OH}{CH_3\underset{\vert}{C}HCH_3}$	2-propanol	(iso-propyl alcohol)
$CH_3CH_2CH_2CH_2OH$	1-butanol	(n-butyl alcohol)
$CH_3CH_2CHOHCH_3$	2-butanol	(sec-butyl alcohol)
	2-methyl-1-propanol	(iso-butyl alcohol)
$(CH_3)_3COH$	2-methyl-2-propanol	(tert-butyl alcohol)
$CH_2{=}CH{-}CH_2OH$	propen-3-ol	(allyl alcohol*)
$CH_2{=}CH{-}CHOHCH_3$	1-buten-3-ol	
	benzyl alcohol	

(The term *Carbinol* is sometimes used to describe CH_3OH so that $MeCPh_2OH$ could be called diphenylmethyl carbinol. The name 1,1-diphenylethanol is, however, more precise and is to be preferred.)


phenol

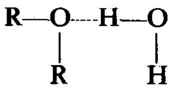

p-cresol*


p-nitrophenol


anisole*

$C_2H_5OC_2H_5$	diethyl ether
$CH_3OC(CH_3)_3$	methyl-t-butyl ether

The lower alcohols and ethers, containing up to about five carbon atoms, and simple phenols are moderately soluble in water due to hydrogen bonding (page 21).



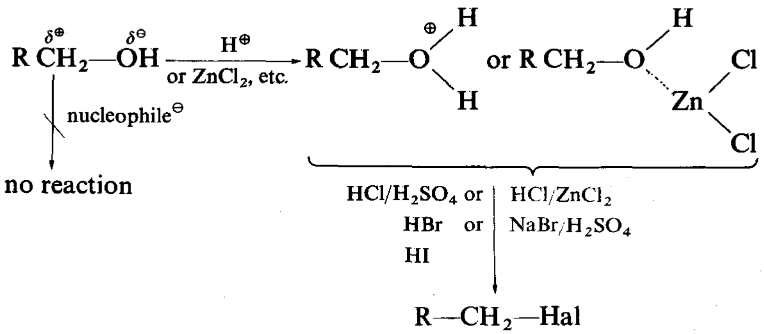
$$\underset{R}{R—O} \cdots \underset{H}{H—O}$$

Ether molecules cannot associate by hydrogen bonding since they have no hydrogen atoms directly attached to oxygen and so ethers have lower boiling points than either alcohols or phenols.

7.2 NUCLEOPHILIC DISPLACEMENT OF THE —OH GROUP IN ALCOHOLS AND PHENOLS

(a) THE C_{sp^3}—OH BOND

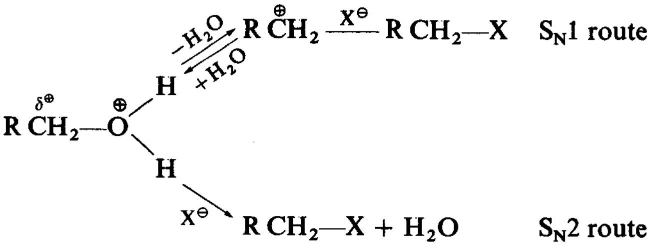
In a neutral alcohol molecule nucleophilic displacement of the hydroxyl group does not usually occur. Protonation of, or coordination to, the oxygen atom, however, increases the reactivity of the C—O bond so that displacement may take place with even weak nucleophiles.



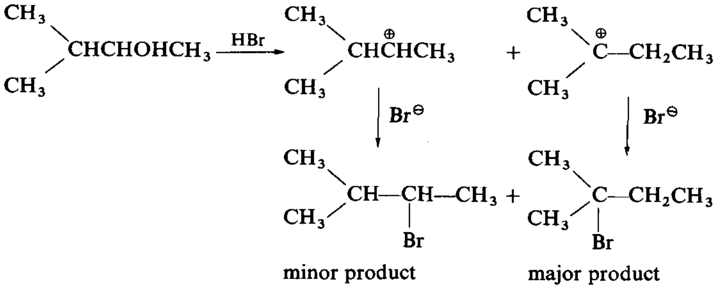
The acid catalysed reactions of alcohols may proceed by either the S_N1 or S_N2 route. Most primary alcohols react by the S_N2 route whilst other alcohols react by the S_N1 mechanism. The order of reactivity for the various types of alcohols is:

$$\underset{\text{decreasing rate of acid catalysed reaction with nucleophiles}}{\xrightarrow{\text{allyl > benzyl > tertiary > secondary > primary}}}$$

The high reactivity of allyl and benzyl alcohols should be compared with that of the corresponding halides (page 127).



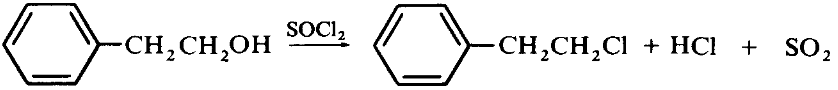
The S_N1 route, shown above, involves a carbonium ion and as has been shown previously (page 127) such reactions often involve rearrangement so that the major product is derived from the most stable carbonium ion, e.g.



The order of reactivity of the hydrogen halides (HI > HBr > HCl) towards alcohols parallels their ease of dissociation to $H^{\oplus}$ and a halide ion, and the order of nucleophilic reactivity of the halide ions ($I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$). The choice of the actual reagent and conditions depends on the individual alcohol. Thus t-butyl alcohol reacts with hydrochloric acid at room temperature whereas primary and secondary alcohols require the addition of concentrated sulphuric acid or zinc chloride.

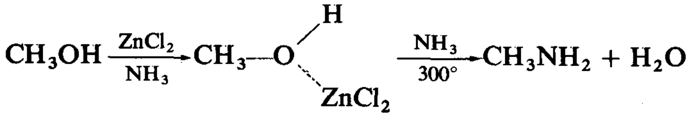
Rearrangement via a carbonium ion, in the replacement of the hydroxyl group of an alcohol by halogen, can be avoided by the use of thionyl chloride, phosphorus tribromide or phosphorus triiodide.

$$3C_2H_5OH + PI_3 \longrightarrow 3C_2H_5I + H_3PO_3$$



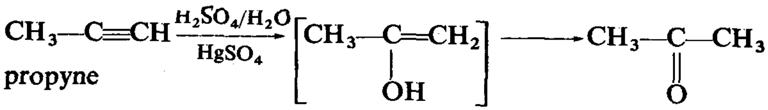
2-phenylethanol

The hydroxyl group can also be displaced by ammonia in the presence of a Lewis acid catalyst. This forms the basis of the manufacture of methylamine from methanol:



(b) THE C_{sp^2}—OH BOND

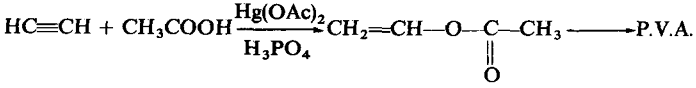
Simple vinyl alcohols, RCH═CHOH, are unstable and as yet have not been isolated although vinyl esters have been prepared. Reactions such as the acid catalysed addition of water to alkynes, which should be expected to produce vinyl alcohols, instead produce carbonyl compounds by tautomeric change (section 11.3).



$$CH_3{-}C{\equiv}CH \xrightarrow[HgSO_4]{H_2SO_4/H_2O} \left[CH_3{-}\underset{\displaystyle OH}{\underset{|}{C}}{=}CH_2\right] \longrightarrow CH_3{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH_3$$

propyne

Polymerised vinyl acetate (P.V.A.) is commercially important in paints and adhesives.

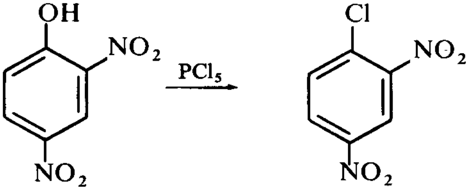


$$HC{\equiv}CH + CH_3COOH \xrightarrow[H_3PO_4]{Hg(OAc)_2} CH_2{=}CH{-}O{-}\underset{\displaystyle O}{\underset{\|}{C}}{-}CH_3 \longrightarrow P.V.A.$$

vinyl acetate

Phenol contains the C_{sp^2}—OH bond system but the carbon atom is part of a conjugated benzene ring system. The oxygen atom attracts bonding electrons from the ring (−I effect) but releases lone pair electrons by the mesomeric route (+M effect). The latter effect is greater than the former and so the —OH group in phenol is electron donating. Some results of this are that (*i*) the C—OH bond in phenols is stronger than in alcohols, cf. alkyl and aryl halides, (*ii*) phenols are weaker nucleophiles than alcohols.

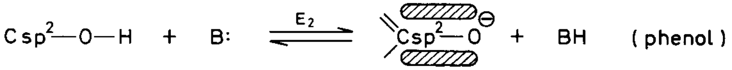
Phenol does not react with hydrogen halides, thionyl chloride or phosphorus trihalides although some reaction takes place with phosphorus pentachloride. Nitro and other deactivating groups, especially when *ortho* or *para* to the hydroxyl group, increase the reactivity of the —OH group and nucleophilic displacement may then occur.



7.3 ACIDITY OF ALCOHOLS AND PHENOLS; CLEAVAGE OF THE O—H BOND

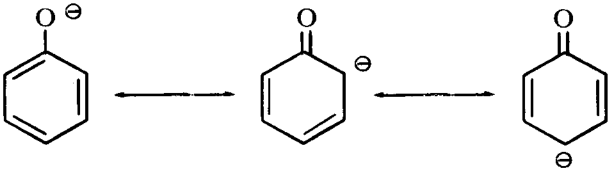
The dissociation processes for alcohols and phenols may be written:

$$\mathrm{Csp^3{-}O{-}H} + \mathrm{B:} \underset{}{\overset{E_1}{\rightleftharpoons}} \mathrm{{>}Csp^3{-}O^{\ominus}} + \mathrm{BH} \quad \text{(alcohol)}$$



$$\mathrm{Csp^2{-}O{-}H} + \mathrm{B:} \overset{E_2}{\rightleftharpoons} \mathrm{{>}Csp^2{-}O^{\ominus}} + \mathrm{BH} \quad \text{(phenol)}$$

In the phenoxide ion the negative charge is delocalised from the oxygen atom over the aromatic ring whereas in the alkoxide ion the charge is localised on the oxygen atom.



Thus the energy of formation, E_1, is greater than that for the phenoxide ion, E_2, and so the phenol ionises more readily than the alcohol. Phenols are, therefore, stronger acids than alcohols.

$$\underset{\text{ethanol}}{\mathrm{C_2H_5OH}} + \mathrm{Na\ or\ NaH\ or\ NaNH_2/liq.\ NH_3} \rightarrow \underset{\text{sodium ethoxide}}{\mathrm{C_2H_5\overset{\ominus}{O}\{\overset{\oplus}{Na}}}$$

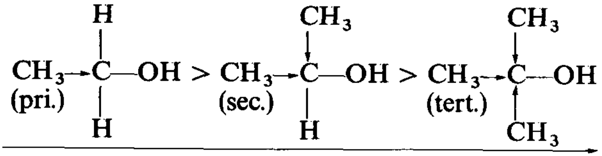
phenol sodium phenoxide

As ethanol is very weakly acidic (K_A about 10^{-18}), strong bases such as sodium hydride or sodamide are required to produce dissociation whereas phenol (K_A about 10^{-10}) is sufficiently acidic to react with sodium hydroxide. Alkoxide ions are rather unstable because the charge is localised on the oxygen atom and so they react with water.

$$C_2H_5\overset{\ominus}{O}\}\overset{\oplus}{Na} + H_2O \longrightarrow C_2H_5OH + NaOH$$

Phenoxide ions are stable, and do not react with water, because their charge is delocalised. Conversely alkoxides are more powerful nucleophiles than phenoxides.

A further reason why phenols are more acidic than alcohols is that the sp^2-hybridised carbon atom, to which the —OH group is attached, is more electronegative (page 11) than an sp^3 carbon atom. Similarly electron withdrawing groups will increase the acidity of alcohols and phenols. Thus 2,4-dinitrophenol is a stronger acid than phenol and will liberate carbon dioxide from sodium hydrogen carbonate solutions. Conversely electron releasing groups decrease the acidity, so that for a series of alcohols:



$$\underset{\text{(pri.)}}{CH_3\!\rightarrow\!\overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle H}{|}}{C}}\!-\!OH} > \underset{\text{(sec.)}}{CH_3\!\rightarrow\!\overset{\overset{\displaystyle CH_3}{\downarrow}}{\underset{\underset{\displaystyle H}{|}}{C}}\!-\!OH} > \underset{\text{(tert.)}}{CH_3\!\rightarrow\!\overset{\overset{\displaystyle CH_3}{\downarrow}}{\underset{\underset{\displaystyle CH_3}{\uparrow}}{C}}\!-\!OH}$$

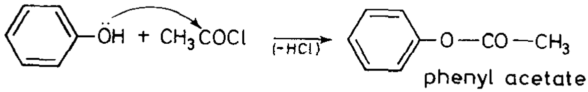
decreasing acidity

7.4 OTHER REACTIONS OF ALCOHOLS AND PHENOLS

(a) ESTER FORMATION

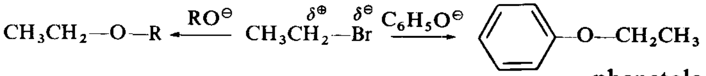
Alcohols and phenols both form esters with acid chlorides and anhydrides. In addition alcohols react with carboxylic acids directly in the presence of a mineral acid catalyst (mechanism, page 69).

$$C_2H_5OH + C_2H_5COOH \xrightarrow{H_2SO_4} \underset{\text{ethyl propionate}}{C_2H_5COOC_2H_5}$$



(b) ETHER FORMATION

Alcohols and phenols are only weak nucleophiles and so do not react at an appreciable rate with alkyl halides. Alkoxide and phenoxide ions are stronger nucleophiles and will react with alkyl halides to form ethers.



phenetole

This type of reaction is termed the Williamson synthesis of ethers.

(c) ALKENE FORMATION—ELIMINATION

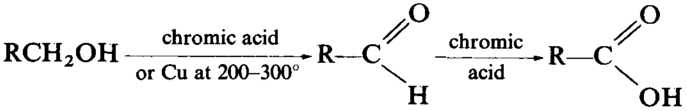
Elimination of water from an alcohol to form an alkene occurs with concentrated mineral acids (section 3.7). The ease of dehydration of alcohols follows the order: tert. > sec. > pri.

$$CH_3CH_2CH_2OH \xrightarrow{H^\oplus} CH_3CH{=}CH_2$$

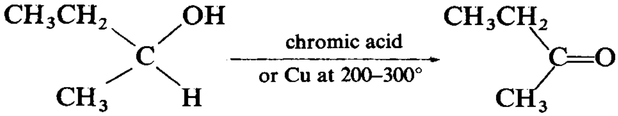
Phenols do not undergo elimination but when strongly heated with zinc dust lose their oxygen atom and form a hydrocarbon, e.g. phenol forms benzene.

(d) OXIDATION

The products of oxidation depend on the type of alcohol. Primary alcohols yield aldehydes first but these oxidise rapidly to carboxylic acids unless removed from the reaction vessel by some process such as distillation.



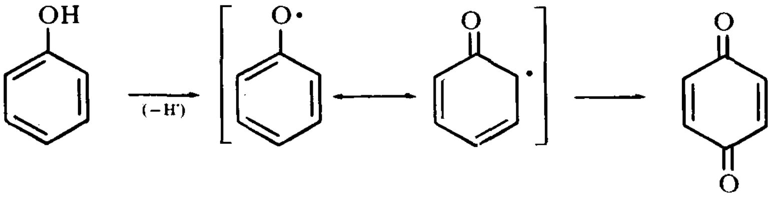
Secondary alcohols are oxidised to ketones.



2-butanone

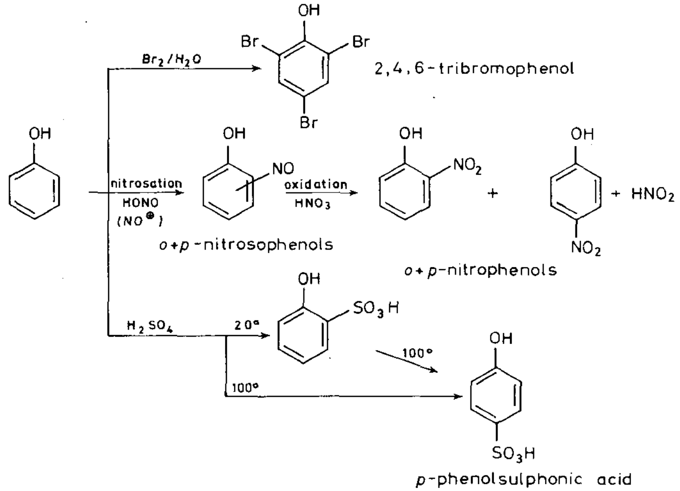
Tertiary alcohols are only oxidised under acid conditions. Dehydration to an alkene occurs first and the alkene is then oxidised.

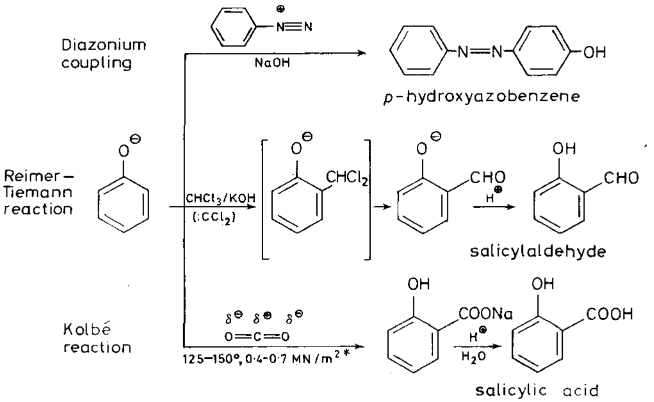
Oxidation of a phenol starts by removing the hydroxyl hydrogen atom but subsequent reactions are complex. With chromic acid phenol forms *p*-benzoquinone.



(e) SUBSTITUTION OF THE AROMATIC NUCLEUS IN PHENOL

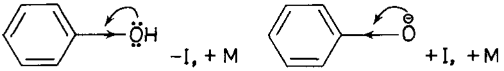
The activating effect of the hydroxyl group on the ring, due to the interaction of the oxygen lone pair electrons with the π molecular orbital system, directs attacking electrophiles to the *ortho* and *para* positions, and the rate of reaction is much greater than for benzene.





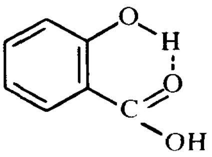
* The SI unit of pressure is the Newton per square metre, where 1 atm = 101·3 kN/m² or 1000 atm = 100 MN/m² approx.

The diazonium cation, dichlorocarbene and carbon dioxide are only weak electrophiles and react with the phenoxide ion rather than phenol itself. Due to the greater availability of electrons the phenoxide ion is a more powerful nucleophile than the neutral phenol molecule.

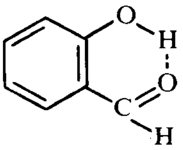


The Kolbé reaction involves the attack of the electron deficient carbon atom of carbon dioxide on phenol. At 125–150° the *ortho* position is substituted yielding salicyclic acid but at higher temperatures (250–300°) *p*-hydroxybenzoic acid is formed.

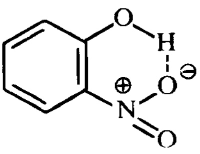
Many *ortho* substituted phenols are intramolecularly hydrogen bonded, i.e. chelated.



salicylic acid



salicylaldehyde

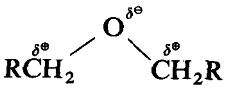


o-nitrophenol

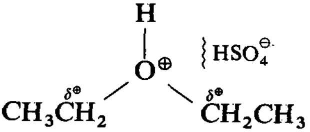
Chelation renders these *ortho* isomers less soluble in water than the *meta* or *para* isomers but makes them volatile in steam. Steam distillation, therefore, provides a method for the separation of, for example, the *ortho* and *para*-nitrophenols.

7.5 REACTIONS OF ETHERS

Ethers are chemically very different from alcohols or phenols. As they have no hydrogen atom attached to the oxygen they exhibit no acidic properties. Also the electron demand of the oxygen atom is spread over two carbon atoms and so neither carbon atom is very positive.



neutral ether

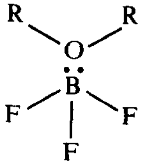


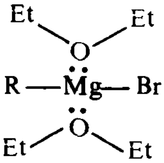
protonated ether
(diethyl oxonium sulphate)

Hence, in the neutral form ethers are chemically inert and are only attacked by the most powerful nucleophiles, such as $\underset{..}{C}H_3^{\ominus}$ derived from methyl sodium (CH_3Na). For this reason alkanes must normally be used as solvents for metal alkyls.

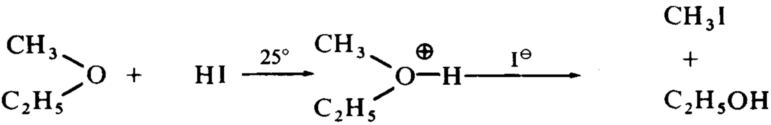
Cold, concentrated, mineral acids protonate ethers and form oxonium salts which are soluble in the acids. By this means a mixture of an alkane and an ether may be separated chemically. The mixture is shaken with cold, concentrated sulphuric acid; the oxonium salt of the ether dissolves in the acid leaving the alkane as a distinct layer which is separated off. Dilution of the acid layer with water destroys the oxonium salt and liberates the ether as a separate layer.

Ethers also form coordination complexes with Lewis acids, with Grignard reagents and boron trifluoride.





Hydriodic acid is often used for the cleavage of ethers as the iodide ion is one of the most powerful nucleophiles to exist in acidic media.



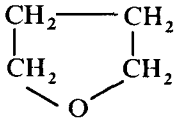
ethylmethyloxonium iodide

The reaction of iodide ion with the oxonium iodide may be S_N1 or S_N2, in this case it would be the latter. The alcohol formed in the cleavage may react again with hydriodic acid, especially at higher temperatures, to yield a second alkyl iodide (see page 48).

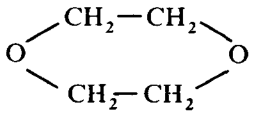
In the presence of air ethers slowly form dangerously explosive peroxides. When shaken with iron (II) ammonium sulphate and potassium thiocyanate a peroxide contaminated ether produces a red colour. Prior to the purification of ethers by distillation any peroxides should be removed by washing with aqueous iron (II) ammonium sulphate solution.

In aromatic ethers such as anisole the —OR group activates the nucleus to electrophilic substitution, which takes place at the *ortho* and *para* positions. Although anisole is less reactive towards electrophiles than phenol it is much more reactive than toluene.

Of the cyclic ethers tetrahydrofuran finds considerable use as a solvent for Grignard reactions and 1,4-dioxane is a good, general purpose solvent, although rather toxic.



tetrahydrofuran



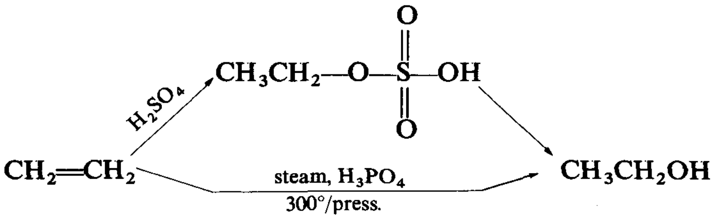
1,4-dioxane

7.6 PREPARATION OF ALCOHOLS

(a) HYDRATION OF ALKENES

This is an industrially important process for the preparation of ethanol from ethylene, 2-propanol from propene and 2-methyl-2-

propanol from 2-methylpropene. The alkene may either be absorbed in concentrated sulphuric acid or reacted directly with steam in the presence of phosphoric acid.

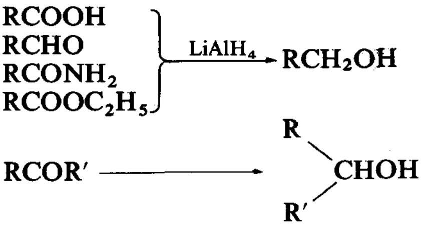


Markownikoff's rule is obeyed in that the alcohol produced is derived from the most stable carbonium ion intermediate.

(b) HYDROLYSIS OF ALKYL HALIDES

$$\text{R Hal} + \text{aq. NaOH} \longrightarrow \text{ROH} + \text{NaHal}$$

(c) REDUCTION OF ACIDS, ALDEHYDES, AMIDES, ESTERS AND KETONES

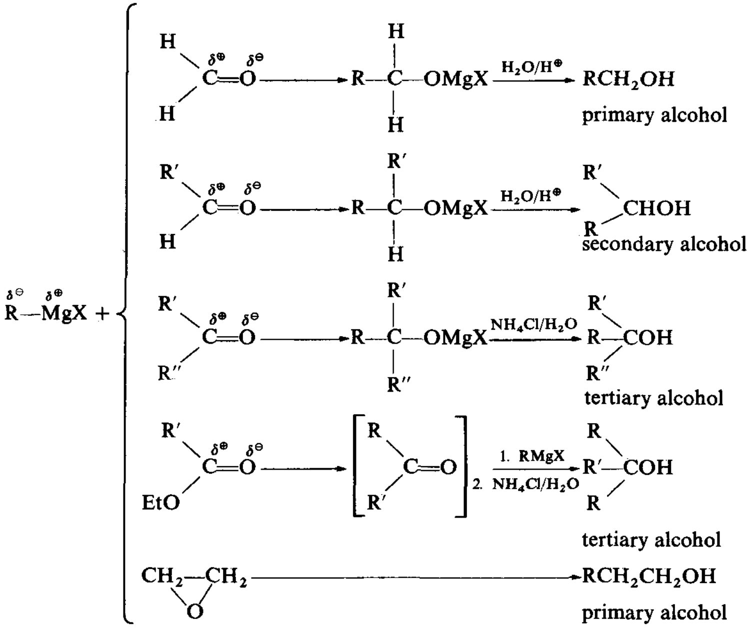


$$\left.\begin{array}{l}\text{RCOOH}\\ \text{RCHO}\\ \text{RCONH}_2\\ \text{RCOOC}_2\text{H}_5\end{array}\right\}\xrightarrow{\text{LiAlH}_4}\text{RCH}_2\text{OH}$$

$$\text{RCOR}' \longrightarrow \begin{array}{l}\text{R}\\ \quad\diagdown\\ \quad\ \text{CHOH}\\ \quad\diagup\\ \text{R}'\end{array}$$

Lithium aluminium hydride is a good reducing agent for the above functional groups and does not reduce double bonds. Sodium borohydride is a milder reagent but useful for aldehydes and ketones. Hydrogenation over a nickel catalyst is a widely used technique but any multiple bonds present are also reduced.

(d) GRIGNARD SYNTHESES



(e) HYDROBORONATION

Diborane reacts with alkenes to yield initially alkyl boranes which oxidise readily with alkaline hydrogen peroxide to alcohols. The synthetic value of the hydroboronation reaction is twofold. Firstly rearrangement does not occur during the reaction and secondly the anti-Markownikoff product is obtained. Thus propene yields 1-propanol, 2-methylpropene yields 2-methyl-1-propanol, etc.

$$6CH_3CH{=}CH_2 + (BH_3)_2 \rightarrow 2(CH_3CH_2CH_2{-})_3B \xrightarrow[{}^{\ominus}OH]{H_2O_2} 6CH_3CH_2CH_2OH$$

Hydroboronation is carried out in ether solution. The diborane can be generated *in situ* by reacting boron trifluoride etherate with sodium borohydride.

$$3NaBH_4 + 4F_3B{:}O(C_2H_5)_2 \xrightarrow{(C_2H_5)_2O} 2(BH_3)_2 + 3NaBF_4$$

(f) ETHANOL FROM FERMENTATION PROCESSES

The fermentation of sugars derived from starch, grains, etc, is economically of great importance for the production of beer, spirits and wine.

(g) METHANOL FROM CARBON MONOXIDE AND HYDROGEN

(see also pages 97–98)

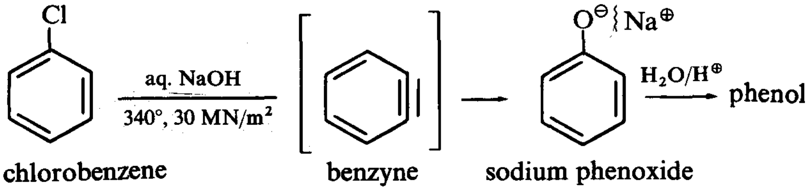
$$\mathrm{CO} + 2\mathrm{H}_2 \xrightarrow[350\text{–}400°,\ 20\ \mathrm{MN/m^2}]{\text{Zn and Cr oxides}} \mathrm{CH_3OH}$$

7.7 PREPARATION OF PHENOLS

(a) COMMERCIAL PREPARATION

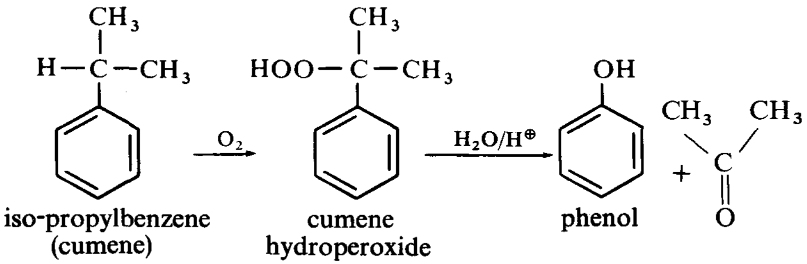
Some phenol is obtained from coal tar but with increasing demand, particularly to make phenol–formaldehyde polymers (section 16.3), two important synthetic routes have been developed.

(i) The Dow process (mechanism, section 3.3)



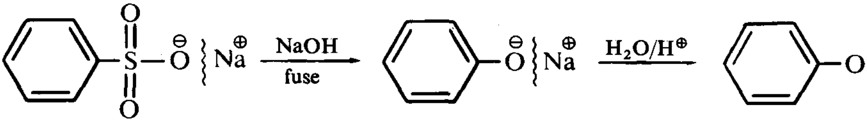
(ii) The cumene-hydroperoxide process

Iso-propylbenzene (cumene) is readily obtained from a Friedel–Crafts reaction between benzene and propene using aluminium chloride as catalyst. Atmospheric oxidation of cumene yields cumene-hydroperoxide which is rearranged and cleaved by aqueous acid to phenol and acetone.



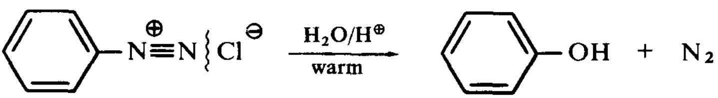
Acetone is an important by-product and renders the process commercially viable.

(b) NUCLEOPHILIC DISPLACEMENT OF THE SULPHONIC ACID GROUP



sodium benzenesulphonate

(c) NUCLEOPHILIC DISPLACEMENT OF THE DIAZONIUM GROUP



benzene diazonium chloride

This reaction is of considerable value in the laboratory as only mild conditions are required and it permits the synthesis of a wide range of substituted phenols.

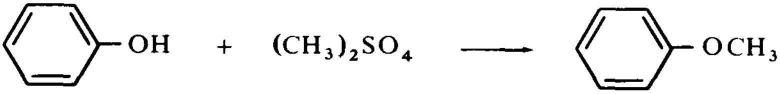
7.8 PREPARATION OF ETHERS

(a) THE WILLIAMSON SYNTHESIS

An alkyl halide is reacted with an alkoxide or phenoxide (page 125).

(b) METHYLATION OF AN ALCOHOL OR PHENOL

Dimethyl sulphate and diazomethane both react with phenols, where the hydrogen atom is fairly acidic, to form methyl ethers.



anisole

Diazomethane will also react with alcohols in the presence of a catalyst which can coordinate with the oxygen atom and increase the acidity of the hydrogen atom, e.g. aluminium alkoxides.

$$\mathrm{ROH} \xrightarrow[\text{aluminium alkoxide}]{\mathrm{CH_2N_2}} \mathrm{ROCH_3}$$

8

The Carbon–Oxygen Bond, II—Aldehydes, Ketones and Carboxylic Acids

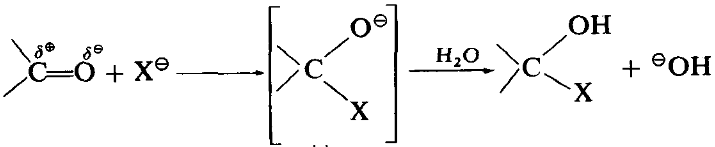
A. ALDEHYDES AND KETONES

8.1 INTRODUCTION AND NOMENCLATURE

The structure of the carbonyl group has already been discussed in sections 1.3 and 3.6. The group is polarised:

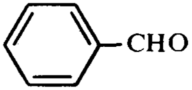
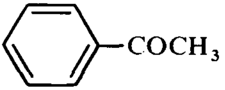
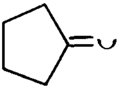
$$\overset{\ominus}{X} \dashrightarrow \overset{\delta\oplus}{>C}=\overset{\delta\ominus}{O} \dashleftarrow \overset{\oplus}{E}$$

and has a dipole moment of over 2 D. Nucleophiles attack the carbon atom ($\delta^{\oplus}$) and electrophiles or Lewis acids the oxygen atom ($\delta^{\ominus}$). Nucleophilic attack at the carbon atom is enhanced because the oxygen atom can readily support a negative charge as a reaction transition state develops, e.g.



Despite the high chemical reactivity of the carbonyl group the bond between the carbon and oxygen atoms is strong (736 kJ/mol) stronger in fact than a carbon–carbon double bond (544 kJ/mol).

The trivial names of aldehydes are derived from those of the carboxylic acids to which they may be oxidised. On the I.U.P.A.C. system the longest chain, including the carbonyl group, becomes the parent hydrocarbon and to this is added *–al*. Ketones are given trivial names according to the hydrocarbon groups attached to the carbonyl group; alternatively on the I.U.P.A.C. system the function $=O$ is denoted by the suffix *–one* (or the prefix *oxo–*).

Formula	*Trivial Name*	*I.U.P.A.C. Name*
$HCHO$	formaldehyde	methanal
CH_3CHO	acetaldehyde	ethanal
$CH_3CH_2CH_2CHO$	butyraldehyde	butanal
$CH_2{=}CHCHO$	acrolein	propenal
	benzaldehyde	
CH_3COCH_3	acetone	propanone
$CH_3COCH_2CH_3$	ethylmethylketone	2-butanone
$CH_3COCH{=}CH_2$	methylvinylketone	1-buten-3-one
	acetophenone	
	cyclopentanone	

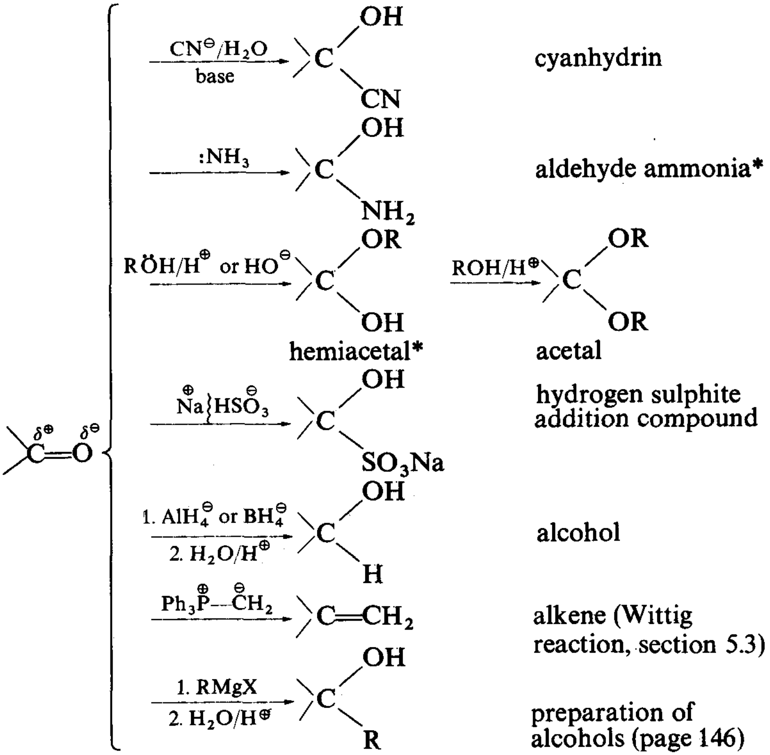
8.2 REACTIONS OF ALDEHYDES AND KETONES

(a) ADDITION TO THE CARBONYL GROUP

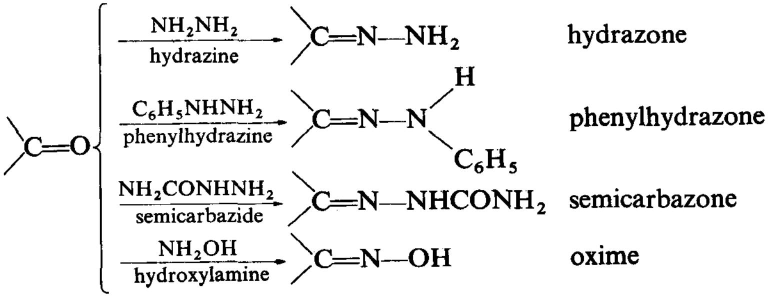
The general mechanisms of these reactions and the effects of structure on the reactivity of carbonyl compounds have already been discussed in section 3.6.

The reactions shown on page 152 apply to both aldehydes and ketones except those marked with an asterisk which are for aldehydes only. Further, the formation of hydrogen sulphite addition compounds is limited to aldehydes, methyl ketones and some cyclic ketones. Ketones are less reactive than aldehydes due to (*i*) steric interference with reactions from the second alkyl group of ketones and (*ii*) electron release from this second alkyl group reduces the positivity of the carbonyl carbon atom and destabilises the reaction transition state.

Aldehydes and ketones react with a number of amine derivatives

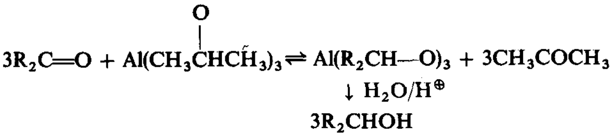


to yield good crystalline solids which are often used for characterisation purposes. The initial nucleophilic addition of the amine derivative may be catalysed by acids or bases. This is followed by the elimination of water to produce an azomethine bond ($\gt C{=}N{-}$).



(b) REDUCTION OF $>C{=}O$ TO —CHOH OR $>CH_2$

The reduction of aldehydes and ketones, to primary and secondary alcohols respectively, with lithium aluminium hydride or sodium borohydride is a nucleophilic reaction (section 3.6). Carbon–carbon double bonds are unaffected under the conditions used. Reduction involving hydride ion transfer can also be achieved by the Meerwein–Ponndorf–Oppenauer–Verley method. The carbonyl compound is refluxed with aluminium 2-propoxide in 2-propanol.



$$3R_2C{=}O + Al(CH_3\overset{\overset{\textstyle O}{|}}{C}HCH_3)_3 \rightleftharpoons Al(R_2CH{-}O)_3 + 3CH_3COCH_3$$
$$\downarrow H_2O/H^{\oplus}$$
$$3R_2CHOH$$

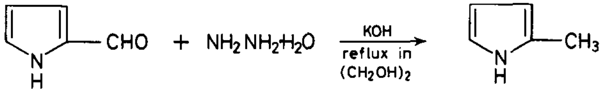
The reaction is driven to completion by slowly distilling off the acetone; again double bonds are unaffected by the reaction conditions. On a large industrial scale hydrogen with a catalyst is preferred but then double bonds are reduced.

The chemical reduction of $>C{=}O$ to $>CH_2$ is carried out with amalgamated zinc and concentrated hydrochloric acid (Clemmensen reduction method).

$$C_6H_5COCH_3 \xrightarrow{Zn/Hg\ -\ HCl} C_6H_5CH_2CH_3$$

acetophenone ethylbenzene

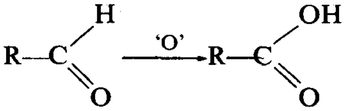
If the carbonyl compound is acid sensitive then the modified Wolff–Kishner procedure using hydrazine hydrate and alkali may bring about reduction.



2-methylpyrrole

(c) OXIDATION OF ALDEHYDES AND KETONES

Aldehydes are readily oxidised to carboxylic acids either slowly by atmospheric oxygen or rapidly by reagents such as chromic acid, potassium permanganate or ammoniacal silver nitrate (Tollen's reagent).



Tollen's reagent may be used as a test for aldehydes. The formation of a silver mirror indicates the presence of an aldehyde or other reducing agent.

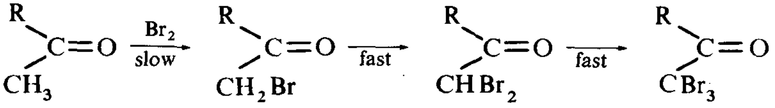
$$CH_3CHO + Ag(NH_3)_2^{\oplus}\{\overset{\ominus}{OH} \rightarrow Ag + CH_3CO\overset{\ominus}{O} + 2NH_3 + H_2O$$

Other tests for aldehydes include (*a*) the restoration of the magenta colour to Schiff's reagent, and (*b*) the production of an orange precipitate of copper (I) oxide when boiled with Fehling's reagent.

Ketones are very difficult to oxidise because such a process must involve the breakage of carbon–carbon bonds. Oxidation of ketones can be achieved via enolisation (see the Haloform Reaction below).

(d) HALOGENATION OF ALDEHYDES AND KETONES

Halogenation takes place on the carbon atom next to the carbonyl group.

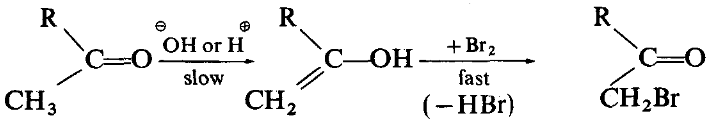


The reaction is catalysed by acids and bases but occurs more rapidly with the latter. The introduction of the first halogen atom is slow but further substitution takes place more rapidly due to additional electron withdrawal by the halogen atom already present.

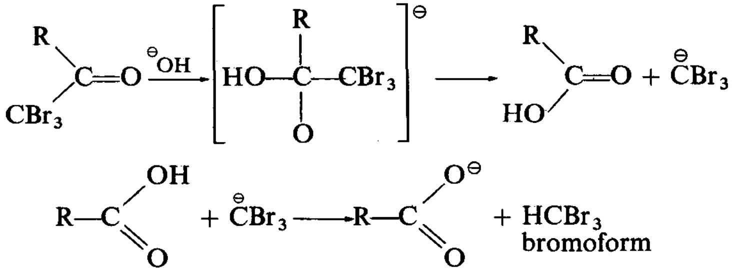
Kinetic studies show that the rate of halogenation is dependent on the concentration of acid or base catalyst but is independent of the halogen concentration.

$$\text{Rate of Halogenation} = k[\text{Ketone}]\,[\text{Acid or Base}]$$

The accepted interpretation of this equation is that the first step is enolisation, i.e. conversion of the ketone to the enol form:



Acid catalysis should be used if the monohaloketone is required as the overall rate of halogenation is slower than with a basic catalyst. A further complication with base catalysis is that the group —$CHal_3$ readily undergoes nucleophilic displacement:

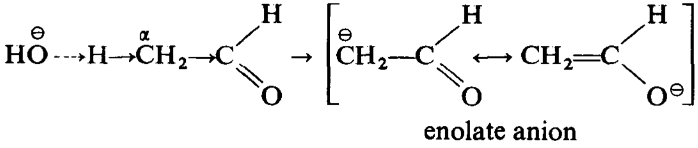


The cleavage of a methyl ketone in this way to an acid salt and a haloform, using halogen and alkali, is termed the Haloform Reaction. The reaction is a useful synthetic process and also provides a means of detecting methyl ketones (CH_3COR), acetaldehyde and compounds such as CH_3CHOHR and CH_3CH_2OH which are oxidised to the appropriate carbonyl compounds under conditions used for the reaction. Iodine and alkali are often used as the yellow, crystalline solid, iodoform, is then precipitated (the Iodoform Test).

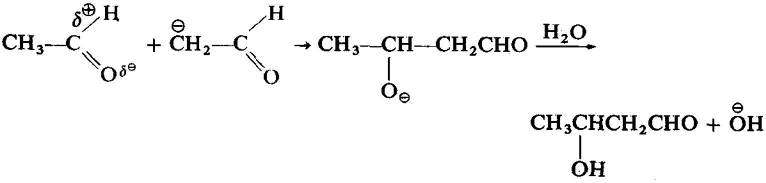
(e) OTHER REACTIONS OF ALDEHYDES AND KETONES INVOLVING ENOLATE ANIONS

(*i*) *The Aldol condensation*

Two molecules of aldehyde or ketone, which must have at least one hydrogen atom on the carbon atom adjacent to the carbonyl group, condense in the presence of dilute alkali to a β-hydroxyaldehyde or ketone respectively.

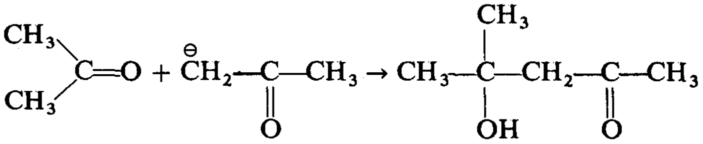


The hydrogen atom on the α-carbon atom of the aldehyde or ketone is somewhat acidic due to the electron attracting power of the carbonyl group, and is removed by the base to form an enolate anion. In this anion the negative charge is spread over two carbon and one oxygen atoms, all three atoms being sp^2-hybridised. In the second step of the reaction the enolate anion behaves as a nucleophile and attacks the carbonyl group of a second molecule of aldehyde or ketone:



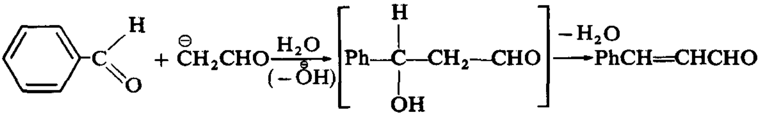
3-hydroxybutanal
(acetaldol)

Similarly acetone yields 4-hydroxy-4-methyl-2-pentanone (diacetone alcohol).



β-Hydroxyaldehydes and ketones are readily dehydrated when heated with mineral acids to yield α,β-unsaturated aldehydes and ketones (section 12.5). Aldol condensations can also be brought about with dilute acids.

Crossed aldol condensations are sometimes feasible where the various possible products can be separated, e.g.

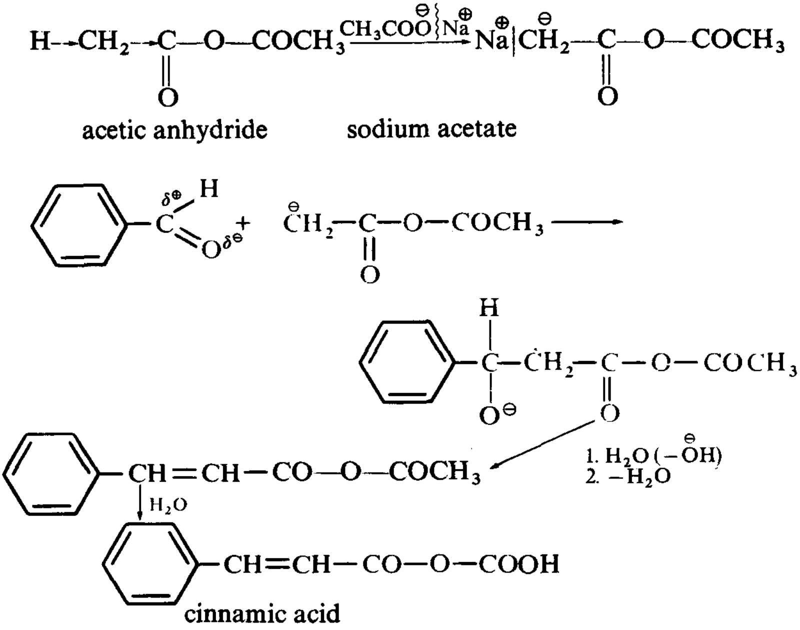


benzaldehyde
(cannot form enolate
anion)

cinnamaldehyde

(ii) The Perkin reaction

This is one of a number of variations on the aldol condensation. It is really a crossed aldol reaction between an aromatic aldehyde and an enolate anion derived from an acid anhydride and an acid salt. After dehydration and hydrolysis the product is an α,β-unsaturated acid.

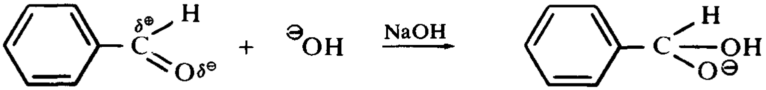


(iii) The Cannizzaro reaction

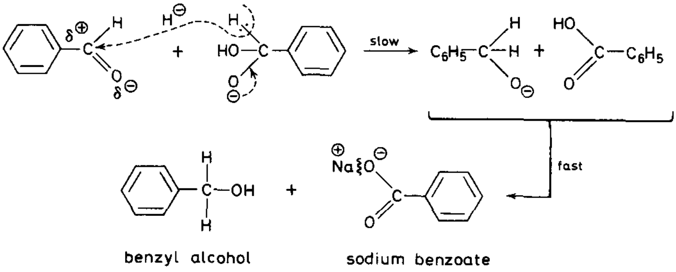
Aldehydes lacking hydrogen atoms on the α-carbon atom, e.g. benzaldehyde and formaldehyde, cannot form enolate anions with dilute alkalis. However, such substances will react with concentrated solutions of a base to yield an alcohol and an acid salt.

$$2HCHO + NaOH \xrightarrow[\text{heat}]{H_2O} CH_3OH + HCO\overset{\ominus}{O}\}Na^{\oplus}$$

Initially the nucleophile $^{\ominus}OH$ attacks the carbonyl group:

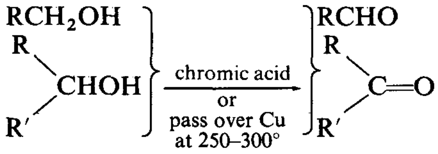


and a hydride ion is next donated to a second molecule of aldehyde:

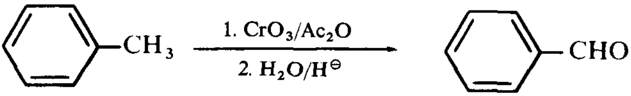


8.3 PREPARATION OF ALDEHYDES AND KETONES

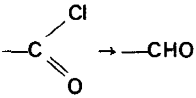
(a) OXIDATION (OR DEHYDROGENATION) OF AN ALCOHOL, —CHOH → >C=O

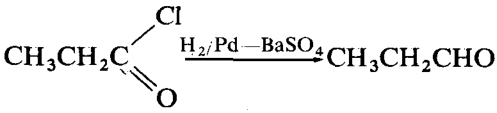


(b) OXIDATION OF A METHYL GROUP ATTACHED TO AN AROMATIC RING, —CH_3 → —CHO



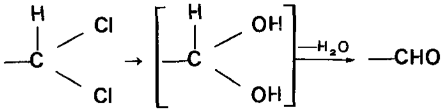
(c) REDUCTION OF AN ACID CHLORIDE,

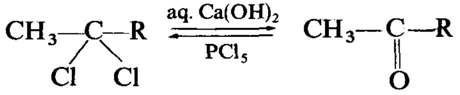


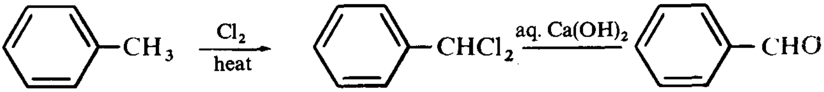


The barium sulphate lowers the activity of the palladium catalyst and prevents the further reduction of the aldehyde to an alcohol.

(d) HYDROLYSIS OF GEM-DIHALIDES,





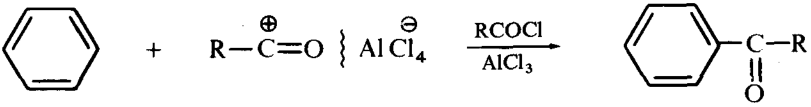


benzal chloride

Note also the Reimer–Tiemann reaction for the preparation of phenolic aldehydes (section 7.4e).

(e) FRIEDEL–CRAFTS KETONE SYNTHESIS

Electrophilic substitution by an acylium cation (R—$\overset{\oplus}{C}$=O) (see pages 54–55).



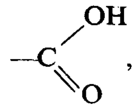
(f) SYNTHESIS OF KETONES VIA ETHYL ACETOACETATE (section 12.2)

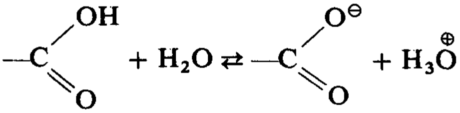
(g) INDUSTRIAL SYNTHESIS OF ACETALDEHYDE AND FORMALDEHYDE

$$HC{\equiv}CH + H_2O \xrightarrow{H_2SO_4/HgSO_4} CH_3CHO \xleftarrow[300]{Cu} C_2H_5OH$$
$$CH_3OH + O_2 \xrightarrow{Cu,\ 600^\circ} HCHO + H_2O$$

B. CARBOXYLIC ACIDS

8.4 INTRODUCTION AND NOMENCLATURE

The carboxyl group, , can give rise to weak or strong acids depending on the electrical properties of other groups which are in a position to influence the dissociation process (section 1.5). The acidic reaction in aqueous solution is due to the ionisation process:



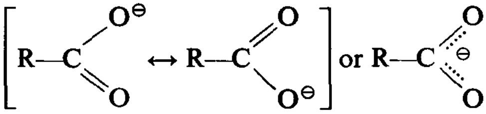
Dissociation will be enhanced, i.e. acid strength increased, by any group which can (*a*) attract electrons from the carboxyl group and so ease the removal of the proton, and (*b*) stabilise the resulting anion by delocalising the negative charge. Conversely electron releasing groups decrease the strength of an acid. Some effects of substituent groups upon acidity have already been given in *Table 1.5* and further values are given in *Table 8.1*.

Table 8.1. NOMENCLATURE AND ACIDITY CONSTANTS OF SOME CARBOXYLIC ACIDS

Formula	*Trivial Name*	*I.U.P.A.C. Name*	*Acids* K_A ($\times 10^{-5}$)
HCOOH	formic acid	methanoic acid	17·7
CH_3COOH	acetic acid	ethanoic acid	1·84
FCH_2COOH	fluoroacetic acid	fluoroethanoic acid	260·0
$CH_3(CH_2)_2COOH$	butyric acid	butanoic acid	1·5
C_6H_5COOH	benzoic acid		6·3
$C_6H_5CH_2COOH$	phenylacetic acid		4·9
p-$NO_2C_6H_4COOH$	*p*-nitrobenzoic acid		36·0
p-ClC_6H_4COOH	*p*-chlorobenzoic acid		10·3
p-$CH_3C_6H_4COOH$	*p*-toluic acid		4·2
p-$NH_2C_6H_4COOH$	*p*-aminobenzoic acid		1·4
p-$CH_3OC_6H_4COOH$	*p*-methoxybenzoic acid		3·3

On the I.U.P.A.C. system carboxylic acids are known as alkanoic acids, i.e. the suffix –*oic* is added to the name of the parent hydrocarbon. In practical terms this system is little used at the present time and trivial names are accepted, at least for the simple acids containing up to five carbon atoms.

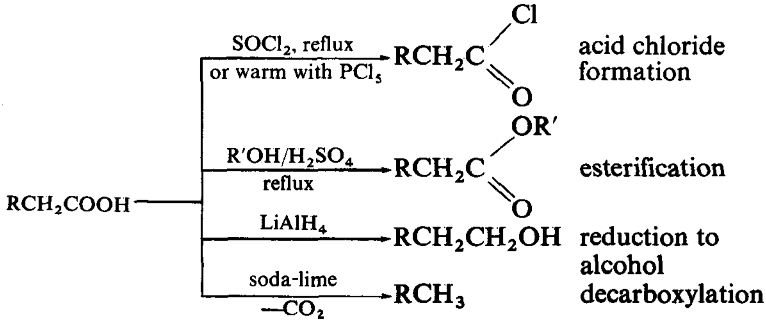
A further factor assisting the dissociation of carboxylic acids is that the carboxylate anion is stabilised by electron delocalisation.



In the anion the three *p* atomic orbitals from the one carbon and two oxygen atoms overlap to form a π molecular orbital and so the negative charge is delocalised over three atoms. This interpretation of the structure of the carboxylate anion is supported by evidence from electron and x-ray diffraction measurements. These show that the two —C—O bonds in sodium formate are of equal length (1·27 Å) whilst those in formic acid are different (1·23 and 1·36 Å for —C═O and —C—OH respectively).

A study of the acidity constants (*Tables 1.5* and *8.1*) of some carboxylic acids shows that formic acid is stronger than acetic acid which in turn is slightly stronger than propionic or butyric acids. The acidities of the haloacetic acids are in accord with the electronegativities of the halogen atoms. Movement of the halogen atom away from the carboxyl group reduces the acidity (see Inductive Effect, section 1.5). Benzoic acid is nearly four times more acidic than acetic acid due to the possibility of further delocalising the charge from the anion over the ring system. Ring substituents have the expected effects, e.g. the electron attracting *para* nitro group strengthens the acid approximately nine-fold. In contrast the electron releasing methoxy group in *p*-methoxybenzoic acid considerably reduces the acid strength.

8.5 REACTIONS OF THE CARBOXYL GROUP



Esterification, reduction and acid chloride formation probably all involve nucleophilic attack on the carbonyl carbon atom. In the case of esterification prior protonation of the carboxylic acid with a strong mineral acid increases its reactivity towards weak nucleophiles (mechanism, section 3.8). Soda-lime decarboxylation of carboxylic acids is not an efficient process. However, some acids lose carbon dioxide simply on heating to 100–200°; such a case is malonic acid where the ease of decarboxylation confers important uses for the acid in synthesis reactions (section 11.3).

$$\underset{\text{malonic acid}}{\mathrm{HOOCCH_2COOH}} \xrightarrow[150^\circ]{\text{heat}} \mathrm{CH_3COOH + CO_2}$$

8.6 REACTIONS AT THE α-CARBON ATOM OF CARBOXYLIC ACIDS

Bromine in the presence of red phosphorus readily and specifically displaces the α-position hydrogen atoms of a carboxylic acid. Phosphorus tribromide is first formed. This produces an acyl bromide which is then brominated.

$$\mathrm{2P + 3Br_2 \rightarrow 2PBr_3}$$

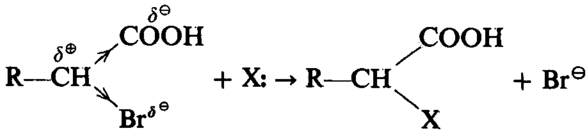
$$\mathrm{RCH_2COOH + PBr_3 \rightarrow RCH_2COBr + POBr + HBr}$$

$$\mathrm{RCH_2COBr + Br_2 \rightarrow RCHBrCOBr \xrightarrow{RCH_2COOH} RCHBrCOOH + RCH_2COBr,\ etc.}$$

$$\mathrm{RCHBrCOOH \xrightarrow{Br_2/red\ P} RCBr_2COOH}$$

Chlorine is not quite so specific to the α-position as bromine although with acetic acid it produces monochloro-, dichloro- and finally trichloroacetic acid. These important reactions for the halogenation of the α-position of carboxylic acids are known as Hell–Volhard–Zelinsky reactions.

Halogen atoms in the α-positions of carboxylic acids readily undergo S_N2 nucleophilic displacement due to the additional electron attracting properties of the carboxyl group.

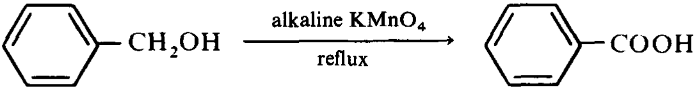


Nucleophile, X:	*Product*	
$I^{\ominus}$	α-iodo	carboxylic acids
$C{\equiv}N^{\ominus}$	α-cyano	
$^{\ominus}OH$ (or $^{\ominus}OR$ or $^{\ominus}OPh$)	α-hydroxy	
$:NH_3$	α-amino	

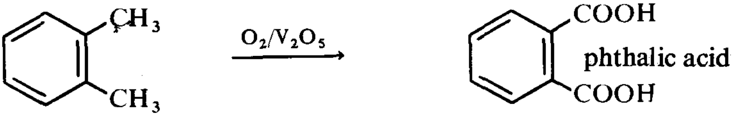
8.7 PREPARATION OF CARBOXYLIC ACIDS

(a) OXIDATION OF A PRIMARY ALCOHOL, AN ALDEHYDE OR AN ALKYLBENZENE

$$\underset{\text{propionaldehyde}}{CH_3CH_2CHO} \xrightarrow{\text{chromic acid}} \underset{\text{propionic acid}}{CH_3CH_2COOH}$$



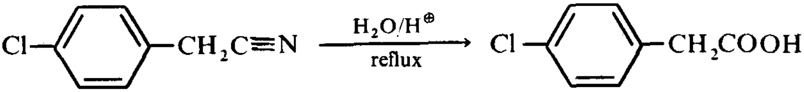
benzyl alcohol benzoic acid



phthalic acid

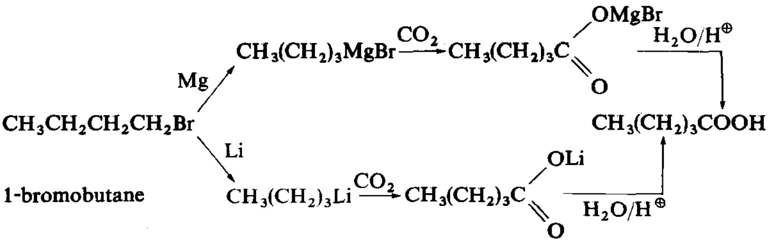
(b) HYDROLYSIS OF CYANIDES AND ACID DERIVATIVES

Alkyl and aryl cyanides are hydrolysed in refluxing acid or alkaline solutions.



p-chlorobenzyl cyanide *p*-chlorophenylacetic acid

(c) VIA ORGANOMETALLIC COMPOUNDS

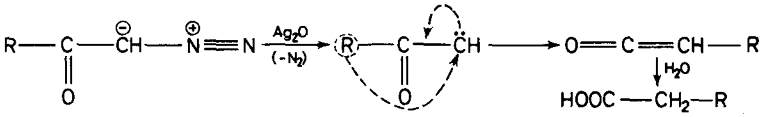


1-bromobutane

(d) CHAIN LENGTHENING OF AN EXISTING ACID—THE ARNDT–EISTERT REACTION

$$\underset{\text{acid}}{RCOOH} \xrightarrow{SOCl_2} \underset{\text{acid chloride}}{RCOCl} \xrightarrow{CH_2N_2} \underset{\text{diazoketone}}{RCOCHN_2} \xrightarrow{Ag_2O/H_2O} RCH_2COOH + N_2$$

The diazoketone is formed by reaction of diazomethane with the acid chloride. Silver oxide causes the diazoketone to lose nitrogen and produce a carbene which rearranges to a ketene. Addition of water to the ketene forms the next higher carboxylic acid, cf. nitrene rearrangements, page 177.

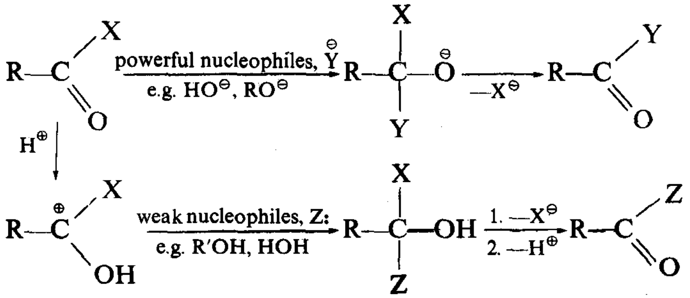


diazoketone

(e) SYNTHESIS VIA DIETHYL MALONATE OR ETHYL ACETOACETATE (sections 11.3 and 12.2 respectively)

8.8 DERIVATIVES OF CARBOXYLIC ACIDS—ACYL HALIDES, AMIDES, ANHYDRIDES AND ESTERS

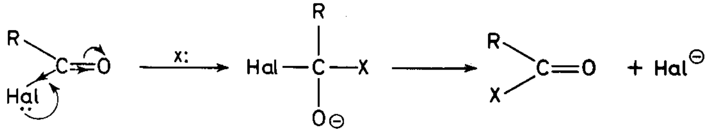
These derivatives are all easily hydrolysed to the corresponding acid. Their chemistry is controlled by the carbonyl group such that they are more reactive towards nucleophiles than the corresponding alkyl halide, amine or ether. In the neutral form these derivatives react with powerful nucleophiles but in order for esters to react with weak nucleophiles the conjugate acid of the carbonyl compound must be formed:

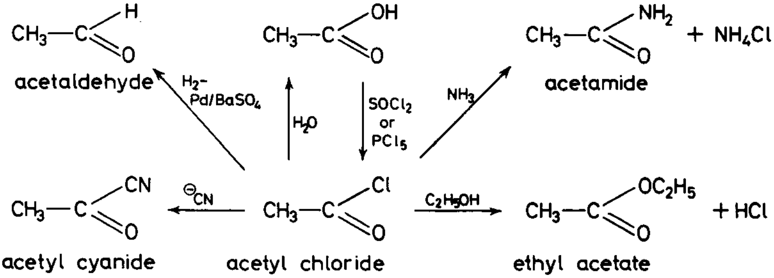


In these reactions the carbonyl group is regenerated by the expulsion of $X^{\ominus}$. The reactivity of RCO.X parallels the ease of loss of X as $X^{\ominus}$, i.e. $Cl^{\ominus} > {}^{\ominus}O.CO.CH_3 > {}^{\ominus}OCH_3 > {}^{\ominus}OH > O^{\ominus}$.

(a) ACYL HALIDES

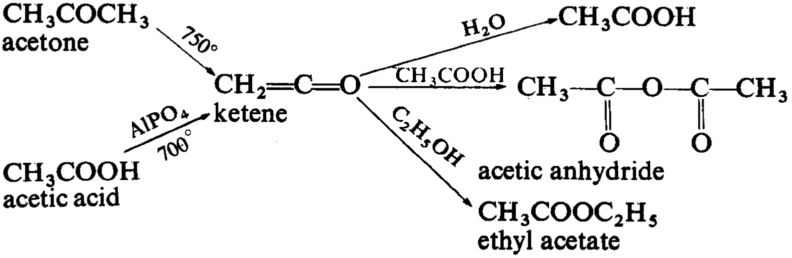
Acyl halides are much more susceptible to nucleophilic attack than alkyl halides due to (*i*) the greater positivity of their reaction centre (*ii*) the reaction centre is sp^2-hybridised and hence less crowded than the sp^3-hybridised reaction centre in alkyl halides, and (*iii*) the transition state is stabilised because the oxygen atom can readily support a negative charge.



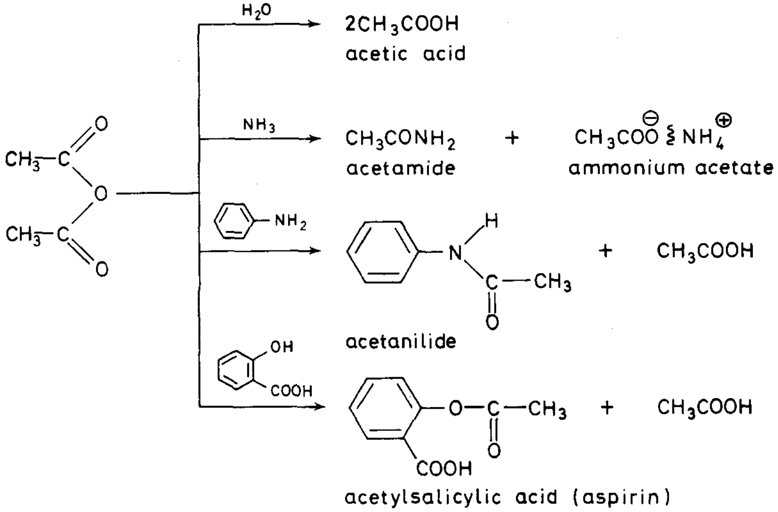


(b) ACID ANHYDRIDES

As the name suggests these substances are dehydration products of carboxylic acids. Acetic anhydride, a pungent smelling liquid, is the most important commerical anhydride and is prepared from the reaction between ketene and acetic acid.

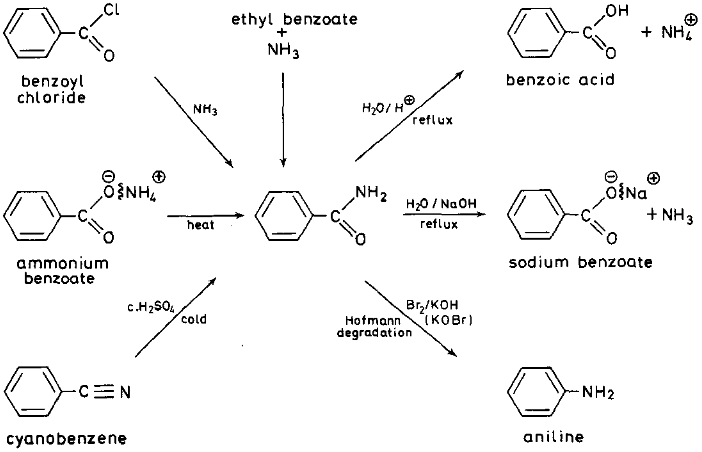


Some reactions of acetic anhydride are indicated below.



(c) AMIDES

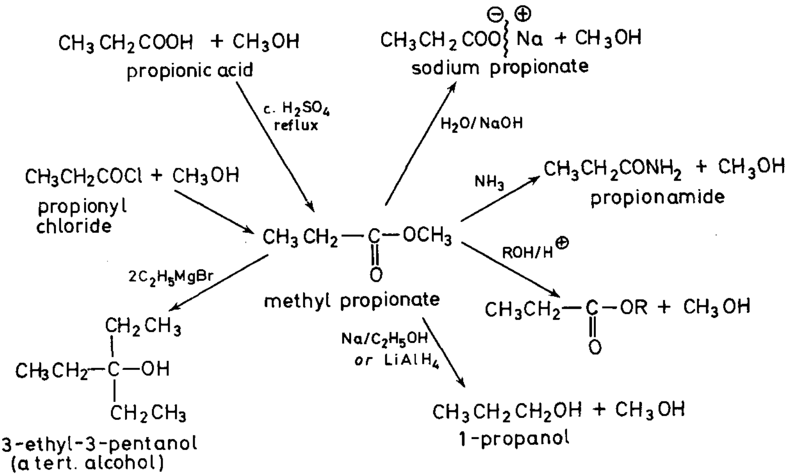
The —NH_2 group in amides is easily displaced by nucleophiles in contrast to the difficulty of replacing the same group in amines. Again this is a consequence of the activating effect of the carbonyl group as has already been outlined for acyl halides. Some reactions and preparations of the amide, benzamide, are indicated below.



The Hofmann reaction, i.e. the conversion of an amide to an amine containing one carbon atom less using bromine and alkali (alkaline hypobromite), is a particularly useful reaction (page 177).

(d) ESTERS

Esters are usually prepared from the reaction of a carboxylic acid with an alcohol in the presence of a small amount of concentrated sulphuric acid, dry hydrogen chloride, boron trifluoride or other similar coordinating agent.



Esters react with Grignard reagents to yield first a ketone, which cannot normally be isolated, and then a tertiary alcohol. The processes of ester hydrolysis ($^{\ominus}OH$), ammonolysis (NH_3) and alkyl group exchange in the above reaction scheme, are all examples of nucleophilic substitution in which the group $—OCH_3$ is displaced.

Esters isolated from animal and vegetable sources are termed lipids. They occur as fats, oils and waxes and find many uses, e.g. as foodstuffs and materials for the preparation of soaps (section 15.3).

9

The Carbon–Nitrogen Bond—Amino, Azo, Cyano, Diazo and Nitro Compounds

9.1 INTRODUCTION AND NOMENCLATURE

There are a number of variations on the simple $-\mathrm{C}-\mathrm{N}<$ bond because nitrogen can exhibit a variety of oxidation levels. Some of the functional groups involving nitrogen are shown below.

(a) AMINES, $>\mathrm{C}-\mathrm{NH}_2$

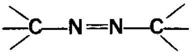
These also include $-\mathrm{C}-\mathrm{NHR}$, $-\mathrm{C}-\mathrm{NR}_2$ and ammonium salts $-\mathrm{C}-\overset{\oplus}{\mathrm{N}}\mathrm{H}_3$. The groups (including a lone pair) are tetrahedrally distributed about the *sp*^{3}-hybridised nitrogen atom. If the carbon atom of the bond is *sp*^{3}-hybridised then nitrogen exerts only a $-\mathrm{I}$ effect but if the carbon atom is *sp*^{2} or *sp* the amino group exerts a $-\mathrm{I}$ and a $+\mathrm{M}$ effect and is an activating group in electrophilic aromatic substitution.

Amines are named either as derivatives of ammonia or as amino substituted carbon compounds, depending on the other groups present, e.g.

$\mathrm{C_2H_5NH_2}$	ethylamine
$\mathrm{(C_2H_5)_2NH}$	diethylamine
$\mathrm{H_2NCH_2CH_2OH}$	2-aminoethanol
$\mathrm{BrCH_2CH_2NH_2}$	2-bromoethylamine

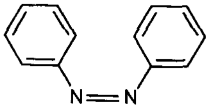
Amine salts are usually named as ammonium compounds, e.g. $(\mathrm{CH_3})_2\overset{\oplus}{\mathrm{N}}(\mathrm{C_2H_5})_2\}\overset{\ominus}{\mathrm{Br}}$ diethyldimethylammonium bromide.

(b) AZO COMPOUNDS,

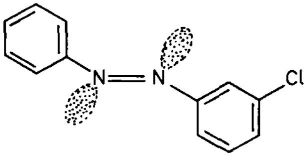


$$>C-N=N-C<$$

The groups and lone pair about the sp^2-hybridised nitrogen are in a planar, trigonal arrangement. *Cis-trans* isomerism is possible about the —N=N— bond which is strongly electron withdrawing.

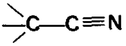


cis-azobenzene



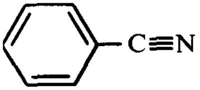
trans-3-chloroazobenzene

(c) CYANIDES,

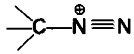


$$>C-C\equiv N$$

The *sp*-hybridised carbon and nitrogen atoms are arranged in a linear manner (see *Figure 1.9*). The cyano group is electron withdrawing. Organic cyanides, also referred to as nitriles, are named in the same way as halides, i.e. cyano is prefixed to the name of the hydrocarbon.

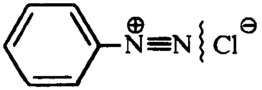
$CH_3C\equiv N$	cyanomethane (acetonitrile)
$CH_3CH_2C\equiv N$	cyanoethane (propionitrile)
$(CN)_2C=C(CN)_2$	tetracyanoethylene
	cyanobenzene

(d) DIAZONIUM COMPOUNDS

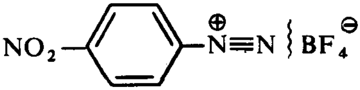


$$>C-\overset{\oplus}{N}\equiv N$$

The linear group $-\overset{\oplus}{N}\equiv N$ is strongly electron attracting and only forms stable compounds when the positive charge can be delocalised over, for example, an aromatic system. Diazonium compounds show a strong tendency to decompose with the evolution of nitrogen.



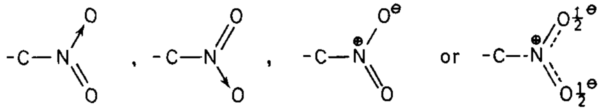
benzene diazonium chloride



p-nitrobenzene diazonium fluoborate

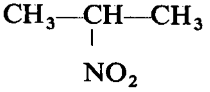
(e) NITRO COMPOUNDS $>C{-}NO_2$

The nitro group can be written:

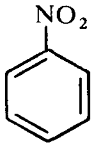


The last representation is probably the best since measurement has shown that both N—O bonds are the same length (1·21 Å). The nitro group is a powerful electron withdrawing group and nitro compounds, like cyanides and halides, are named as derivatives of hydrocarbons.

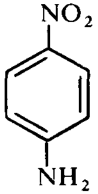
CH_3NO_2 nitromethane



$CH_3CH(NO_2)CH_3$ 2-nitropropane



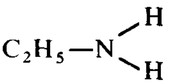
nitrobenzene



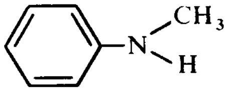
p-nitroaniline

9.2 REACTIONS AND PREPARATION OF AMINES

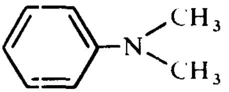
Aliphatic and aromatic amines may be primary, secondary or tertiary.



ethylamine
(primary)

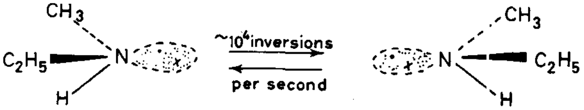


N-methylaniline
(secondary)



N, N-dimethylaniline
(tertiary)

The nitrogen atom in amines is sp^3-hybridised and the angle between each pair of bonds is very close to the tetrahedral value of 109·5°. The three valency bonds are directed towards three corners of a tetrahedron and the lone pair towards the fourth corner. The system is in a constant state of oscillation:



In aliphatic amines (C_{sp^3}—N) the nitrogen atom is more electronegative than the carbon atom and attracts electrons along the σ bond (−I effect). However, in aromatic amines (C_{sp^2}—N) the nitrogen lone pair interacts with the π molecular orbital system of the nucleus and so the amino group is electron donating ($+M > -I$). In aromatic amines the amino group is an activating group for electrophilic substitution. These different electrical effects are reflected in the chemistry of aliphatic and aromatic amines.

(a) BASIC PROPERTIES OF AMINES

Amines readily form salts with acids due to protonation of the nitrogen lone pair electrons.

$$RNH_2 + HCl \rightleftharpoons R\overset{\oplus}{N}H_3\{\overset{\ominus}{Cl}$$

The lone pair of electrons in aromatic amines is partly donated to the π molecular orbital system and so is less available for protonation than the lone pair in aliphatic amines. Therefore, aromatic amines are weaker bases than aliphatic amines. Similarly any group in an amine which attracts the lone pair will decrease the basicity, e.g. *p*-nitroaniline, compared with the unsubstituted amine, whilst an electron releasing group will increase the basicity, e.g. *p*-methoxyaniline (see *Table 9.1* below and also *Table 1.6*).

Table 9.1. BASICITY CONSTANTS (K_B) OF SOME ALIPHATIC AND AROMATIC AMINES

Base	*Formula*	K_B
ammonia	NH_3	1·8 × 10^{-5}
ethylamine	$C_2H_5NH_2$	47 × 10^{-5}
diethylamine	$(C_2H_5)_2NH$	95 × 10^{-5}
aniline	$C_6H_5NH_2$	4·2 × 10^{-10}
p-nitroaniline	*p*-$NO_2C_6H_4NH_2$	0·001 × 10^{-10}
p-chloroaniline	*p*-$ClC_6H_4NH_2$	1·5 × 10^{-10}
p-methoxyaniline	*p*-$CH_3OC_6H_4NH_2$	15 × 10^{-10}

(b) ACIDITY OF AMINES

Primary and secondary amines are extremely weak acids (K_A approximately 10^{-30}), i.e. weaker acids than either alcohols

$$RNH_2 \rightleftharpoons R\overset{\ominus}{N}H + \overset{\oplus}{H}$$

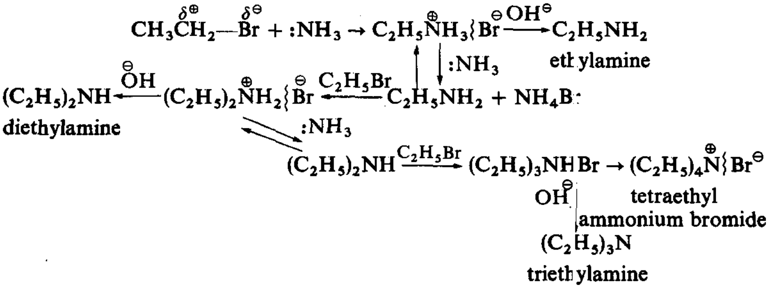
or alkynes. They will however, form salts with very strong bases such as phenyl lithium.

$$\underset{\text{diethylamine}}{(C_2H_5)_2NH} + \underset{\text{phenyl lithium}}{C_6\overset{\ominus}{H}_5\}\overset{\oplus}{Li}} \rightarrow \underset{\text{diethylamino lithium}}{(C_2H_5)_2\overset{\ominus}{N}\}\overset{\oplus}{Li}} + C_6H_6$$

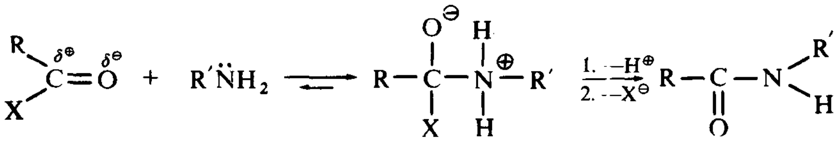
The anion $(C_2H_5)_2N^{\ominus}$ is an extremely powerful base.

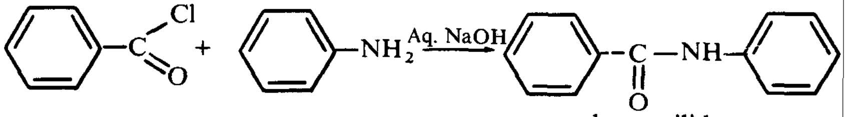
(c) ACYLATION AND ALKYLATION OF AMINES

Amines and ammonia act as nucleophiles towards acyl and alkyl halides.

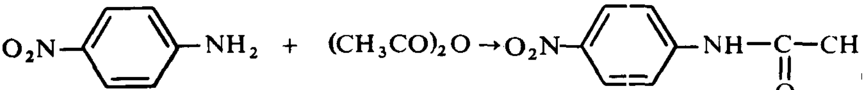


On an industrial scale the mixture of mono-, di- and trialkylamines is separable by fractional distillation. Similar products are obtained from the reaction of ammonia with an alcohol (section 7.2) and such a process is used to prepare mono-, di- and trimethylamines from methanol.





benzanilide



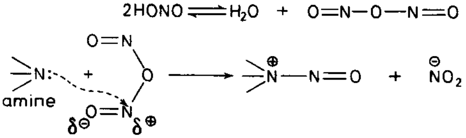
p-nitroacetanilide

Primary and secondary amines react with acyl halides, acid anhydrides and esters to yield amides. In each case the nucleophilic amine attacks the carbon atom of the carbonyl group.

Benzoylation with benzoyl chloride in the presence of aqueous sodium hydroxide is termed the Schotten–Baumann technique.

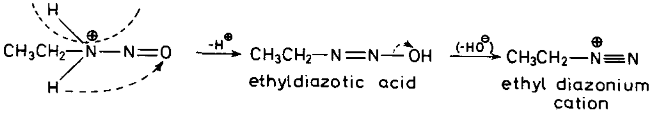
(d) REACTIONS OF AMINES WITH NITROUS ACID

This important reaction is used to differentiate between primary, secondary and tertiary amines. The initial reaction is between the amine lone pair and N_2O_3 (or $\overset{\oplus}{N}O$). Subsequent reactions depend on the type of amine but all involve the loss of a proton.

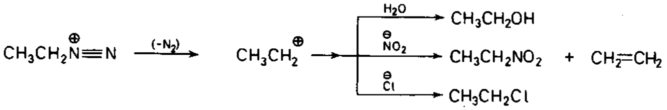


(i) Primary amines

E.g. ethylamine + nitrous acid



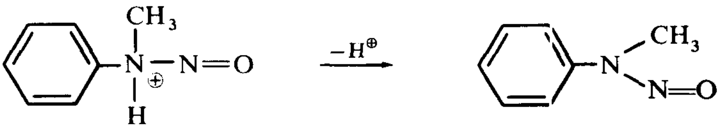
Alkyl diazonium cations are unstable because the positive charge is localized on the nitrogen atoms. They react with any nucleophiles in solution such as water, nitrite ions, etc., to yield substitution and elimination products.



On the other hand aryl diazonium cations are relatively stable at 0–5° because the positive charge is delocalised over the aromatic nucleus. They undergo important displacement reactions (section 9.5).

(ii) Secondary amines

Alkyl and aryl secondary amines form stable N-nitrosoamines which separate as yellow liquids on the surface of the nitrous acid solution.

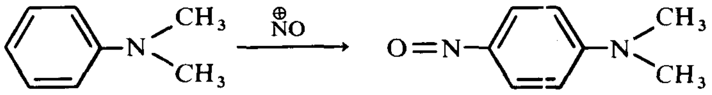


N-methyl-N-nitrosoaniline

Nitrosoamines, and hence indirectly secondary amines, may be recognised by the characteristic green colour they produce when warmed with phenol and concentrated sulphuric acid (Liebermann's nitrosoamine reaction).

(*iii*) *Tertiary amines*

Aliphatic tertiary amines form a variety of products with nitrous acid including aldehydes and ketones, due to the loss of an alkyl group from the nitrogen atom. Tertiary aromatic amines usually undergo nitrosation, due to electrophilic substitution by $\overset{\oplus}{N}O$, in the *para* position because the group $—NR_2$, like the —OH group, is strongly electron releasing (cf. the nitration of phenols via nitrosation and oxidation, (page 141).

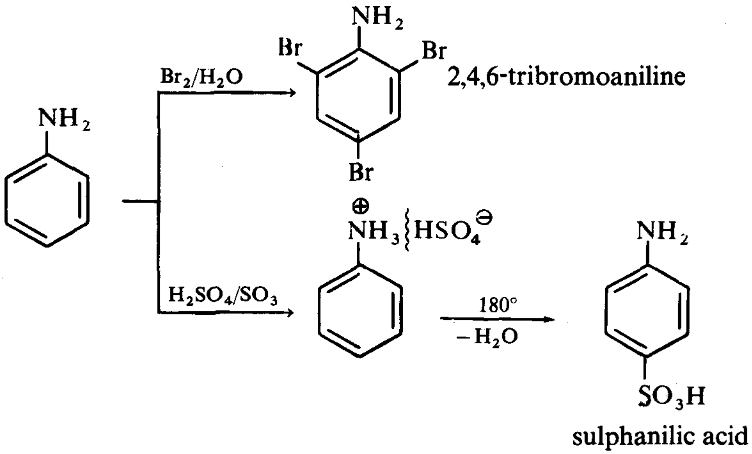


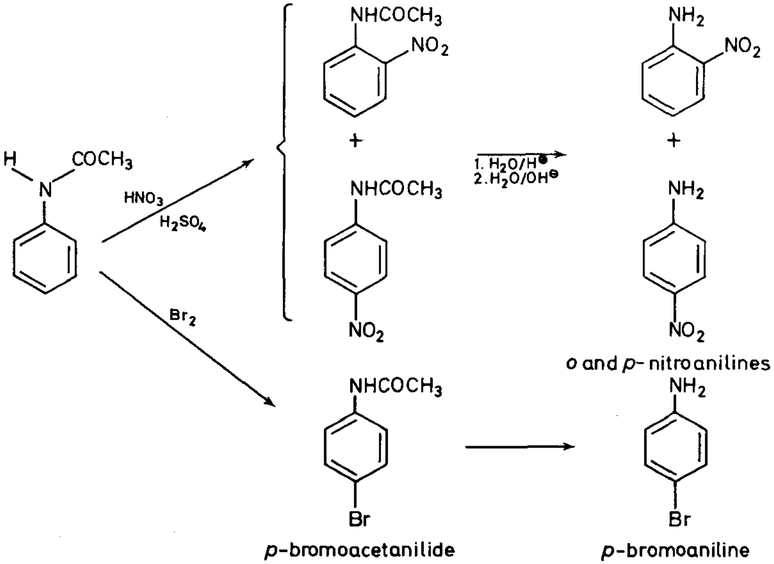
N,N-dimethylaniline *p*-nitroso-N,N-dimethylaniline

(e) SUBSTITUTION OF THE AROMATIC NUCLEUS IN AROMATIC AMINES

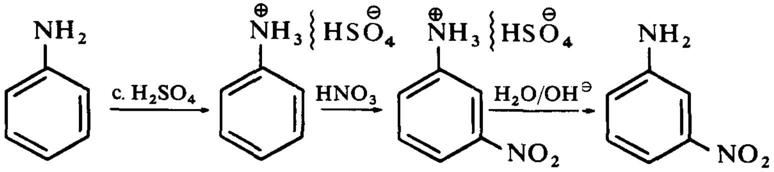
The groups $—NH_2$, —NHR and $—NR_2$ are all strongly activating and direct incoming electrophiles to the *ortho* and *para* positions. The amino group of aniline is very easily oxidised by nitric acid and so the acetyl derivative, acetanilide, is subjected to nitration rather than the free amine. The amide group, $—NHCOCH_3$, is less activating than the amino group but is still *ortho–para* directing.

Protonation of an aromatic amine stops the nitrogen lone pair electrons from interacting with the aromatic nucleus and removes the +M effect. However, the −I effect of the $—\overset{\oplus}{N}H_3$ group is greater than that of the amino group so that in aniline sulphate $—\overset{\oplus}{N}H_3$





is strongly deactivating and *meta* directing for electrophilic aromatic substitution.



aniline sulphate

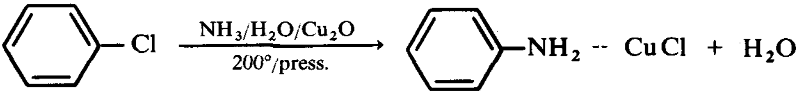
m-nitroaniline

(f) PREPARATION OF AMINES

(i) Nucleophilic displacement of a halogen atom or hydroxyl group (page 172)

$-C_{sp^3}-X + NH_3 \rightarrow$ pri., sec. + tert. amines (X = —Cl, —Br, —I or —OH).

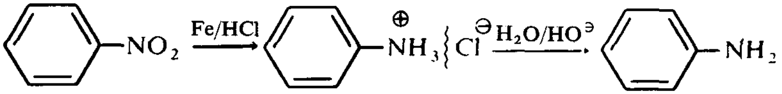
The reaction is of less value for aryl halides owing to the low reactivity of the C_{sp^2}—Hal bond (section 6.2) unless activated by an electron withdrawing group. Without such activating groups intensive conditions are necessary.



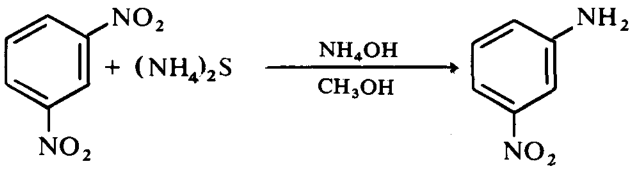
(ii) Reduction of nitro and other compounds

$$RNO_2 + 6\text{'H'} \rightarrow RNH_2 + 2H_2O$$

This is a particularly important method for the commercial preparation of aromatic amines. The reducing agent is often iron and hydrochloric acid but other reagents include hydrogen and a catalyst, tin or zinc and acid, tin(II)chloride and hydrochloric acid or boiling aqueous iron(II)ammonium sulphate.



One nitro group can sometimes be reduced in the presence of another such group; tin(II)chloride and hydrochloric acid or methanolic ammonium sulphide are often used for such reactions.



Amides, cyanides and oximes can also be reduced to amines.

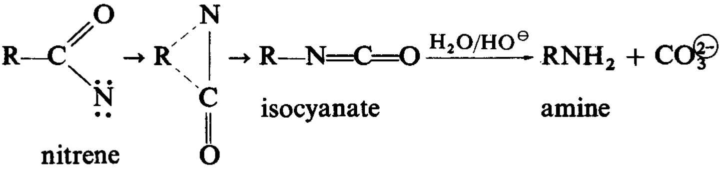
$$R\text{—}C\equiv N \rightarrow RCH_2NH_2$$

$$RCONH_2 \rightarrow RCH_2NH_2 + H_2O$$

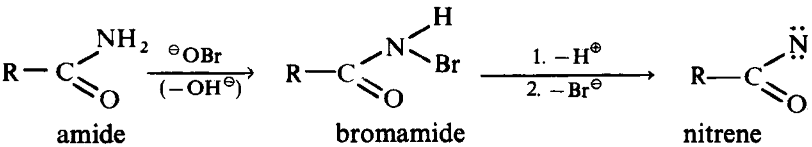
$$R_2C\text{=}NOH \rightarrow R_2CHNH_2 + H_2O$$

(*iii*) *Degradation of an amide or azide—The Hofmann, Schmidt and Curtius reactions*

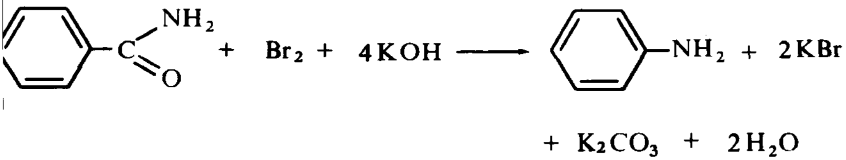
These three reactions pass through a common intermediate, a nitrene. The nitrene, like a carbene, is electron deficient and it rapidly rearranges to an isocyanate which hydrolyses in aqueous alkali to an amine.



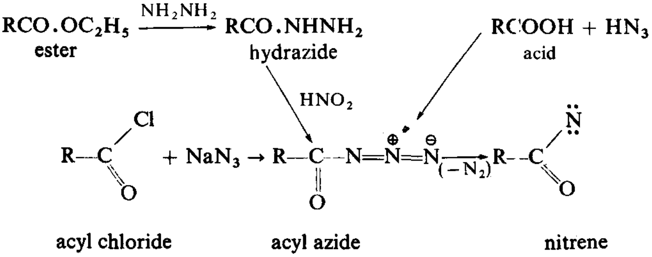
In the Hofmann reaction a bromamide is first formed, by the action of bromine and alkali on an amide, and this loses first a proton and then bromide ion to produce the unstable nitrene.



e.g.

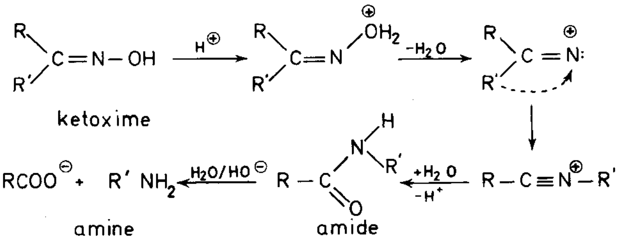


The Schmidt and Curtius reactions both involve the loss of nitrogen from an acyl azide to form the nitrene. The acyl azide for the Schmidt reaction is formed by the action of hydrazoic acid on a carboxylic acid. The variation for the Curtius reaction is that the azid is formed either by the action of sodium azide on an acyl chloride or by nitrous acid on the hydrazide.

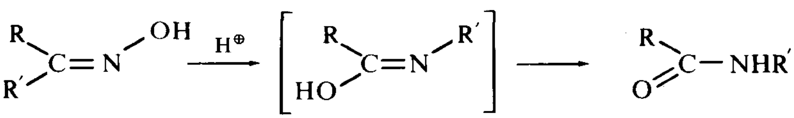


(*iv*) *Beckmann rearrangement of an oxime*

A ketoxime rearranges, when warmed with polyphosphoric acid or concentrated sulphuric acid, to an amide. This is known as the Beckmann rearrangement.



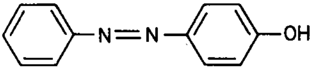
Alkaline hydrolysis of the amide produces the free amine. The rearrangement possesses the interesting feature that *trans* migration of the groups nearly always occurs:

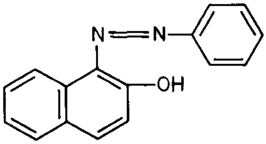


(*v*) *The Gabriel synthesis of primary amines via phthalimide* (see page 214).

9.3 AZO COMPOUNDS

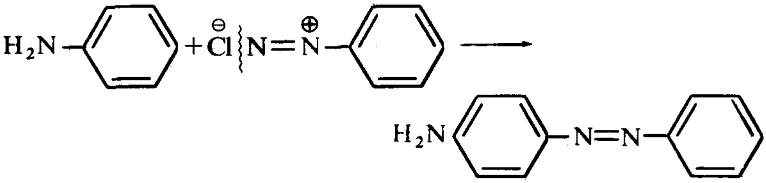
Azo compounds contain the group —N═N— in which both nitrogen atoms are sp^2-hybridised. As has already been mentioned in section 2.3 azo compounds exhibit geometrical isomerism and the *cis* and *trans* isomers can often be separated by chromatography. The energy requirement for the $\pi \rightarrow \pi^*$ transition of the entire conjugated system of azo compounds often falls within the visible region of the spectrum. Azo compounds are, therefore, often highly coloured and the colour can be changed by altering some part of the conjugated system.

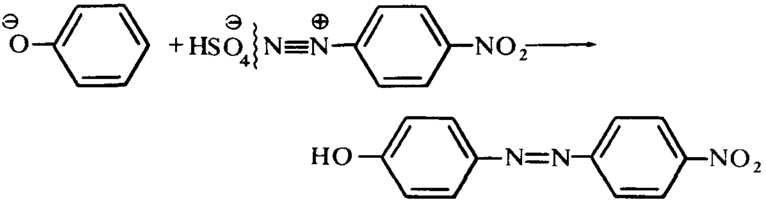

p-hydroxyazobenzene
(orange)

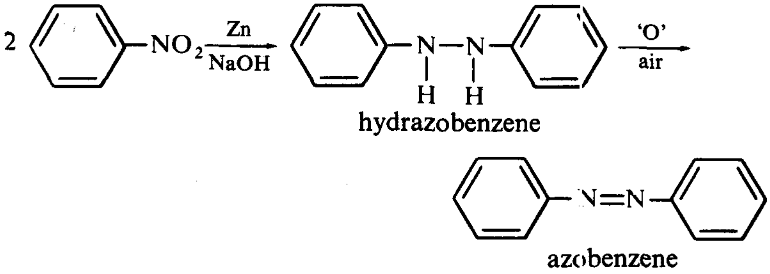

benzeneazo-2-naphthol
(red)

Some of the important reactions and methods of preparing azo compounds are summarised below.

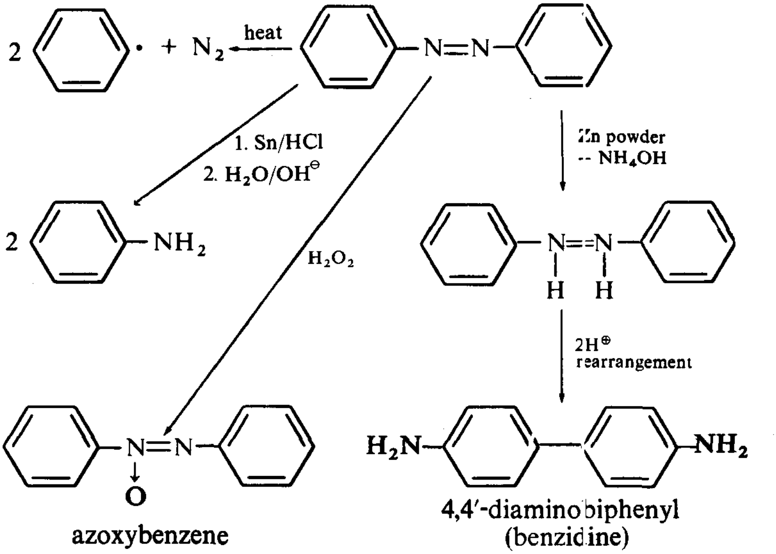
(a) PREPARATIONS


p-aminoazobenzene


p-hydroxy-*p*′-nitroazobenzene

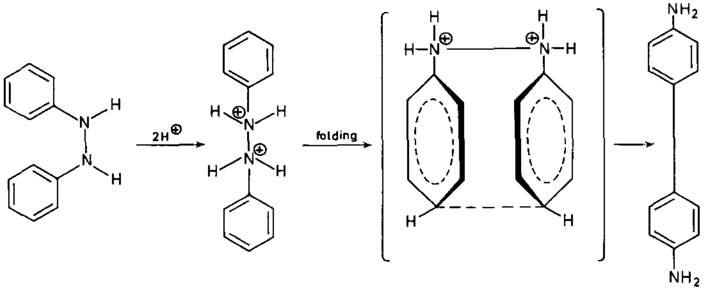


(b) REACTIONS



The preparation of azo compounds via the coupling of diazonium compounds is an important reaction for the dyestuffs industry.

The rearrangement of hydrazobenzene under acid conditions to benzidine, termed the benzidine rearrangement, is an interesting reaction. Two protons are known to be involved in the transition state for the rate of rearrangement = k[Hydrazobenzene] $[H^{\oplus}]^2$ The protonated molecule then appears to fold:



The two protons reduce the electron densities over the aromatic nuclei so that the nuclei may approach one another and then electron shifts simultaneously form new carbon–carbon bonds and break the nitrogen–nitrogen bond.

9.4 CYANIDES

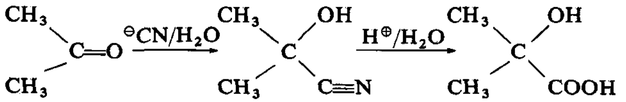
The bond —C≡N ($\overset{4{\cdot}0\ \text{D}}{\longmapsto}$) is highly polar and so differs considerably from the —C≡C— bond. Thus cyanides, unlike alkynes, are good solvents of high dielectric constant and are fairly soluble in water. The group is strongly electron attracting (−I and −M) and like the carbonyl and nitro groups it renders hydrogen atoms on an adjacent carbon atom slightly acidic. Cyanides may also be referred to as nitriles.

A useful synthetic property of the cyanide group is that hydrolysis occurs, in boiling acid or alkaline solutions, to produce the carboxyl group or the carboxylate anion respectively.

(a) REACTIONS OF CYANIDES

(i) Complete hydrolysis

E.g. the preparation of α-hydroxyacids

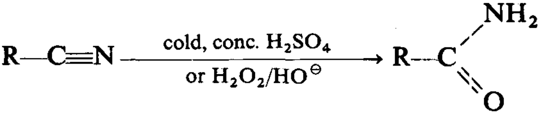


$$(CH_3)_2C{=}O \xrightarrow{^{\ominus}CN/H_2O} (CH_3)_2C(OH)C{\equiv}N \xrightarrow{H^{\oplus}/H_2O} (CH_3)_2C(OH)COOH$$

α-hydroxy-α-methyl
propionic acid

(*ii*) *Partial hydrolysis*

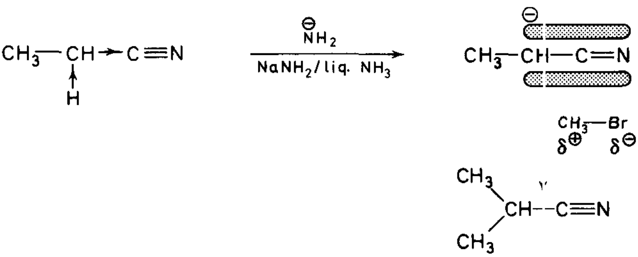
The formation of an amide:



(*iii*) Reduction

$$RCH_2C\equiv N \xrightarrow{Zn/CH_3COOH \text{ or } LiAlH_4} RCH_2CH_2NH_2$$

(*iv*) Alkylation



2-cyanopropane

(b) PREPARATION OF CYANIDES

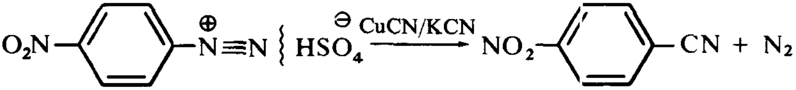
(*v*) *Dehydration of amides*

$$CH_3CH_2CONH_2 \xrightarrow{P_2O_5} CH_3CH_2C\equiv N$$

(*vi*) *Nucleophilic displacement of halogen*

$$R\overset{\delta\oplus}{C}H_2-\overset{\delta\ominus}{Br} + \overset{\ominus}{C}N \xrightarrow{KCN/C_2H_5OH} RCH_2C\equiv N$$

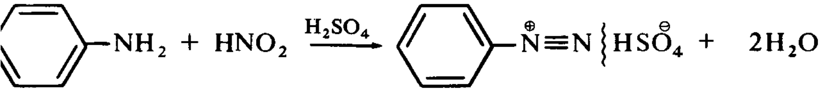
(*vii*) *Aryl cyanides via replacement of the diazonium group*



p-cyanonitrobenzene

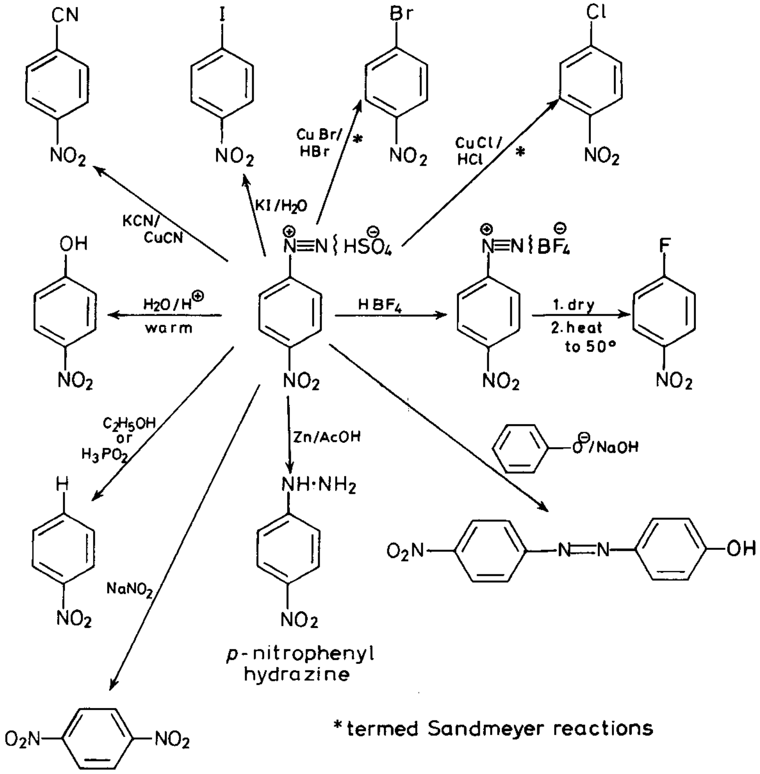
9.5 DIAZONIUM COMPOUNDS

Diazonium compounds are formed by the reaction of a primary aromatic amine with nitrous acid, usually at a low temperature (0–5°).



benzene diazonium sulphate

Many variations on the basic diazotisation technique are known, e.g. a solution of a weakly basic amine in acetic acid can be poured into nitrosyl sulphuric acid ($NaNO_2$ in conc. H_2SO_4). The diazonium

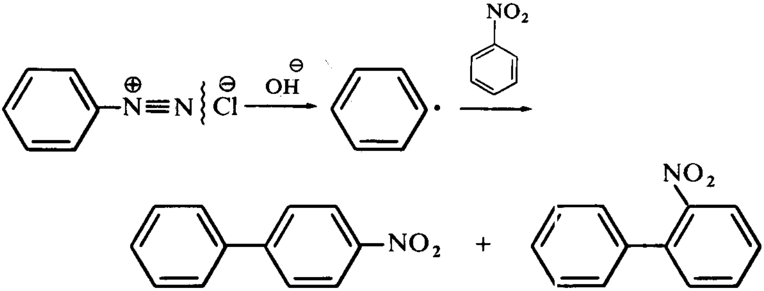


*termed Sandmeyer reactions

salt is normally used in solution as soon as possible after preparation so as to minimise decomposition. Many dry diazonium salts are explosive.

The diazonium group ($-\overset{\oplus}{N}\equiv N$) may be replaced by —Hal, $-C\equiv N$, $-NO_2$, —OH or —H; loss of nitrogen yields a free radical. Alternatively the nitrogen–nitrogen linkage may be retained as in diazo coupling to yield an azo compound, or by reduction to form a hydrazine. Many diazo reactions are catalysed by copper salts, particularly cuprous salts.

Aryl radicals are formed when solutions of diazonium salts are made alkaline. Coupling to a second molecular species can then occur with the formation of a new carbon–carbon bond, this is termed the Gomberg Reaction.



4 and 2-nitrobiphenyls

9.6 NITRO COMPOUNDS

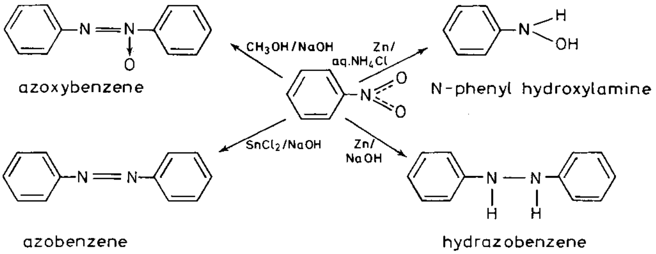
The nitro group is strongly electron attracting (−I and −M effects) with the result that these compounds have high dipole moments (3–4 D). Even so nitro compounds are practically insoluble in water. Nitro compounds are unstable substances, hence their use as explosives, e.g. 2,4,6-trinitrotoluene (T.N.T.).

Aromatic nitro compounds are particularly useful chemical intermediates because the nitro group is easily reduced to an amino group and the latter can be converted via a diazonium compound to a wide range of substances (see previous section). Aliphatic nitro compounds do not have the same synthetic value as aliphatic diazonium compounds do not undergo replacement reactions.

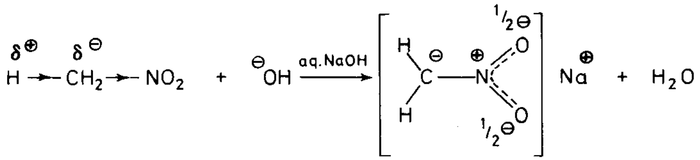
Complete reduction of the nitro group can be brought about by many reagents (section 9.2, f).

$$—NO_2 + 6\text{'H'} \rightarrow —NH_2 + 2H_2O$$

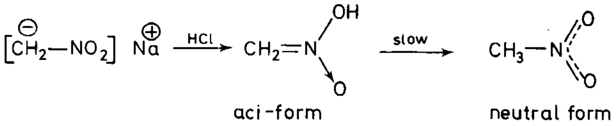
Under neutral or alkaline conditions partial reduction of the nitro group can occur yielding azo, azoxy and hydrazobenzenes or phenyl hydroxylamines.



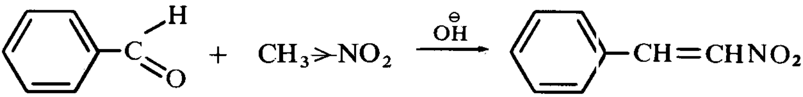
The nitro group may activate other atoms or groups in the same molecule, e.g. in 2,4-dinitrochlorobenzene the chlorine atom is activated towards nucleophilic displacement (section 3.3). A similar effect is found in aliphatic nitro compounds where hydrogen atoms attached to the carbon atom adjacent to the nitro group become strongly acidic, e.g. nitromethane dissolves in aqueous sodium hydroxide.



The sodium nitromethane salt is stabilised, like phenoxide and enolate anions, by delocalisation of the negative charge. When acidified the salt liberates the aci or acid form of nitromethane which slowly reverts to the normal neutral form.



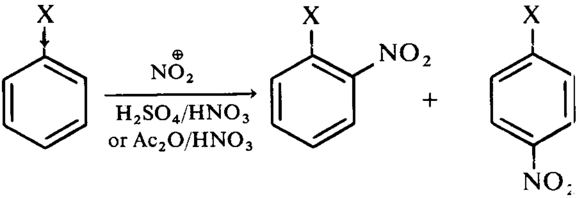
The activating effect of the nitro group on the methyl group of nitromethane is similar to that of the carbonyl group in acetaldehyde and in fact alkyl nitro compounds will undergo aldol type reactions.



2-nitrophenylethylene

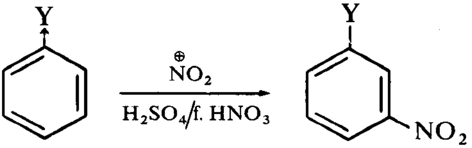
PREPARATION OF NITRO COMPOUNDS

(*a*) *Direct electrophilic substitution by the* —NO_2 *group*



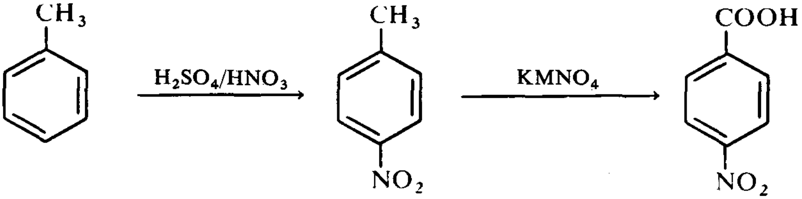
X = —OH, —NHCOR,
—Hal, —R, etc.

The *ortho* and *para* isomers can usually be separated by crystallisation, steam distillation or chromatography.



Y = —NO_2, —CN,
—COOH, —CHO,
etc.

To obtain a particular product the reactant must be chosen so as to give the correct group orientation even if one or more groups have to be subsequently altered chemically, e.g.

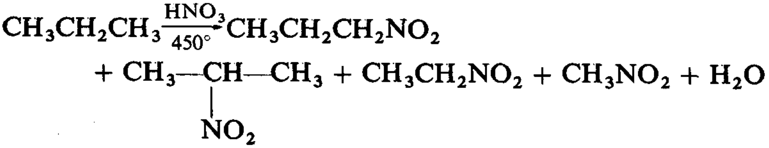


p-nitrotoluene (after separation of) the *o* and *p*-isomers)

p-nitrobenzoic acid

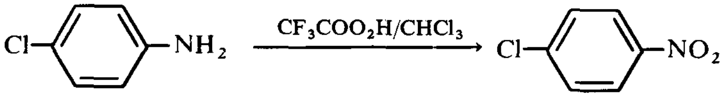
Nitration of benzoic acid would have produced the *meta* and not *para* orientation of the substituents.

(*b*) *Vapour phase nitration of alkanes*



$$CH_3CH_2CH_3 \xrightarrow[450°]{HNO_3} CH_3CH_2CH_2NO_2 + CH_3-\underset{\displaystyle NO_2}{\underset{|}{CH}}-CH_3 + CH_3CH_2NO_2 + CH_3NO_2 + H_2O$$

(*c*) *Oxidation of an amino group with trifluoroperacetic acid*



(*d*) *Introduction of* —NO_2 *via a diazonium replacement reaction* (section 9.5)

(*e*) *Nucleophilic displacement of halogen*

$$CH_3CH_2\overset{\delta\oplus}{CH_2}-\overset{\delta\ominus}{Br} + \overset{\ominus}{NO_2} \xrightarrow{AgNO_2/ether} CH_3CH_2CH_2NO_2$$

Reaction may be brought about with either silver nitrite in ether solution or sodium nitrite in N,N,-dimethylformamide ($HCONMe_2$). Some nitrite ester, $CH_3CH_2CH_2—O—N{=}O$, may also be formed in the reaction.

10

The Carbon–Sulphur Bond —Thiols, Thioethers and Sulphonic Acids

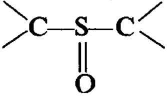
10.1 INTRODUCTION AND NOMENCLATURE

The carbon–sulphur bond is different from the carbon–oxygen bond in at least three ways:

(1) sulphur is less electronegative than oxygen (2·6 and 3·5 respectively),

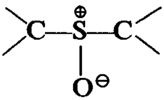
(2) sulphur does not readily form double bonds with carbon because a 3*p* orbital of sulphur cannot overlap efficiently with a 2*p* orbital of carbon and so the $>\!C{=}S$ is a weak bond,

(3) the valence octet of sulphur can be expanded, by utilising unoccupied *d* orbitals, to accept an electron pair from an oxygen atom. In effect a π-bond is produced between sulphur and oxygen in addition to the σ-bond. Systems like



$>\!C{-}\underset{\underset{\displaystyle O}{\|}}{S}{-}C\!<$

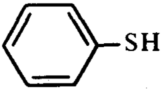
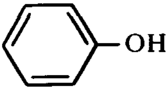
can then be formed. These are highly polar and some contribution from the form



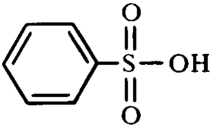
$>\!C{-}\underset{\underset{\displaystyle O^{\ominus}}{|}}{\overset{\oplus}{S}}{-}C\!<$

can be envisaged.

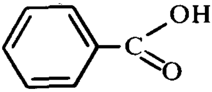
Whereas compounds containing the group $>\!C{-}OH$ are termed alcohols (or phenols), the corresponding sulphur compounds are termed thioalcohols (or thiophenols). Similarly the sulphur counterparts of ethers ($>\!C{-}O{-}C\!<$) are thioethers ($>\!C{-}S{-}C\!<$).

C_2H_5SH	ethanethiol	C_2H_5OH	ethanol
	thiophenol		phenol
$C_2H_5SC_2H_5$	diethyl thioether	$C_2H_5OC_2H_5$	diethyl ether

Sulphonic acids resemble carboxylic acids and are named in a similar manner:



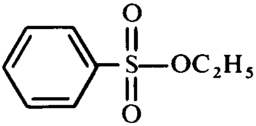
benzene sulphonic acid



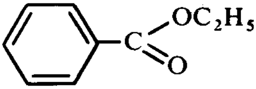
benzoic acid

$CH_3CH_2SO_3H$ ethanesulphonic acid

Both types of acid give rise to esters.



ethyl benzenesulphonate



ethyl benzoate

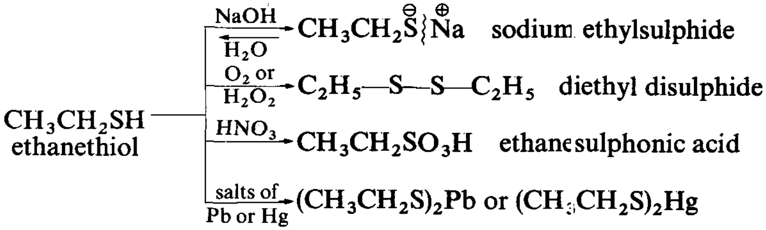
10.2 THIOLS

Thiols are volatile liquids having very unpleasant odours. Their boiling points are lower than those of the corresponding alcohols. This can be explained by very much weaker intermolecular hydrogen bonding between hydrogen and sulphur atoms than between hydrogen and oxygen.

Chemically three important differences between alcohols and thiols are, (1) thiols are much more acidic than alcohols (K_A approximately 10^{-11} for C_2H_5SH and 10^{-17} for C_2H_5OH) which is not unexpected since hydrogen sulphide is considerably more acidic than water,

(2) alcohols and thiols behave differently towards oxidising agents; thiols readily form disulphides,

(3) thiols form salts with aqueous solutions of heavy metal salts.



$$CH_3CH_2SH \xrightleftharpoons[H_2O]{NaOH} CH_3CH_2\overset{\ominus}{S}\}\overset{\oplus}{Na}$$ sodium ethylsulphide

$$CH_3CH_2SH \xrightarrow[H_2O_2]{O_2 \text{ or}} C_2H_5{-}S{-}S{-}C_2H_5$$ diethyl disulphide

$$CH_3CH_2SH \xrightarrow{HNO_3} CH_3CH_2SO_3H$$ ethanesulphonic acid

$$CH_3CH_2SH \xrightarrow[\text{Pb or Hg}]{\text{salts of}} (CH_3CH_2S)_2Pb \text{ or } (CH_3CH_2S)_2Hg$$

ethanethiol

Thiophenols undergo the same reactions as thiols and just as thiols are more acidic than alcohols so thiophenol is a stronger acid than phenol.

Thiols are readily prepared by the nucleophilic displacement of the halogen atom in alkyl halides with $SH^{\ominus}$.

$$CH_3Br + KSH \xrightarrow[\text{reflux}]{C_2H_5OH} CH_3SH + KBr$$

potassium
hydrogen sulphide

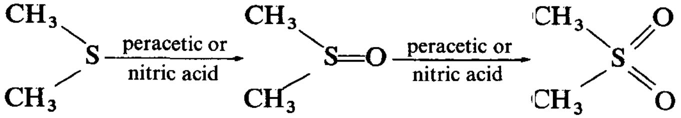
Alternatively an alcohol can be treated directly with hydrogen sulphide in the presence of a catalyst.

$$ROH + H_2S \xrightarrow[300\text{–}400°]{ThO_2} RSH + H_2O$$

10.3 THIOETHERS

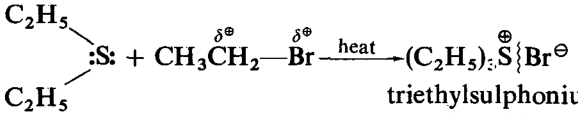
Thioethers, like ethers, are fairly inert chemically except in two respects.

(1) Thioethers are easily oxidised forming first a sulphoxide and then a sulphone. Either substance can become the major product by adjusting the reaction conditions.



dimethyl thioether dimethyl sulphoxide dimethyl sulphone

(2) Thioethers act as nucleophiles towards alkyl halides.



$$(C_2H_5)_2S{:} + CH_3\overset{\delta\oplus}{C}H_2{-}\overset{\delta\ominus}{Br} \xrightarrow{\text{heat}} (C_2H_5)_3\overset{\oplus}{S}\}Br^{\ominus}$$

triethylsulphonium
bromide

Trialkylsulphonium hydroxides undergo elimination when heated.

The reaction is very similar to the Hofmann degradation of quaternary alkylammonium hydroxides (section 3.7).

Thioethers may be obtained from a reaction similar to the Williamson ether synthesis, i.e. between a sodium alkyl sulphide and an alkyl halide.

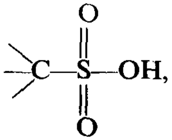
$$C_2H_5\overset{\ominus}{S}\,\wr Na^{\oplus} + \overset{\delta\oplus}{C}H_3\text{—}\overset{\delta\ominus}{Br} \longrightarrow CH_3\text{—}S\text{—}C_2H_5 + NaBr$$

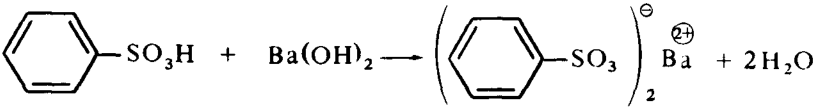
Alternatively a thiol will add to an alkene in the presence of peroxides.

$$C_2H_5SH + CH_2{=}CHCH_3 \xrightarrow{\text{peroxides}} C_2H_5SCH_2CH_2CH_3$$

Sulphoxides and sulphones are particularly good solvents. Like N,N-dimethylformamide they strongly solvate cations. This property can have important repercussions, e.g. in some elimination reactions the use of dimethylformamide as solvent produces alkene ratios very different from those observed with more usual solvents such as ethanol.

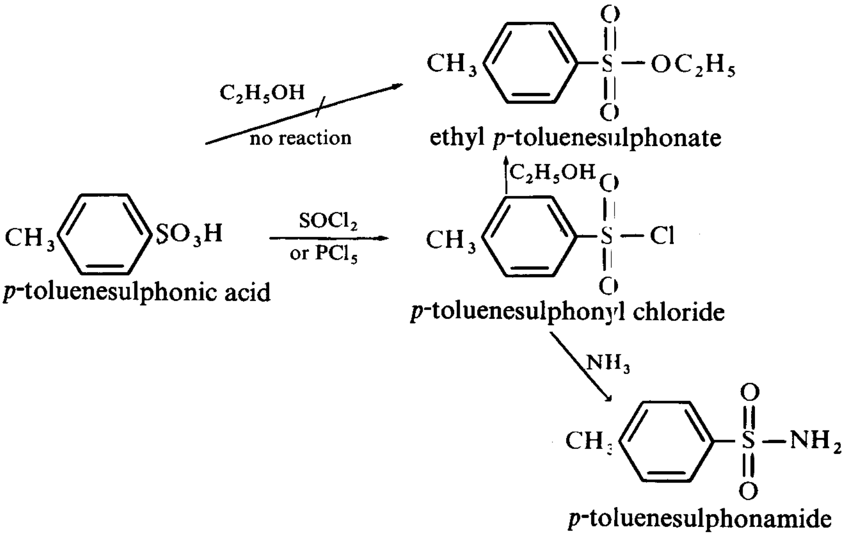
10.4 SULPHONIC ACIDS

Sulphonic acids contain the group  $\rangle C\text{—}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}\text{—}OH$, where the carbon fragment can be aliphatic or aromatic. The aliphatic sulphonic acids are viscous liquids whilst the aromatic acids are colourless, crystalline solids. The —SO$_3$H group is highly polar and as a result sulphonic acids are very soluble in water. They are fairly strong acids, considerably stronger than carboxylic acids, readily form salts with bases and liberate carbon dioxide from sodium hydrogen carbonate solutions. Sulphonic acids are often isolated as their insoluble barium or calcium salts.

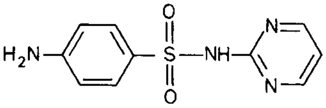


The more water soluble sodium sulphonate is often the usual commercial product as free sulphonic acids are difficult to isolate and are often hygroscopic.

The esters of sulphonic acids, unlike those of carboxylic acids, cannot be prepared directly from the reaction of the acid with an alcohol. Instead esterification of a sulphonic acid is achieved via the acid chloride.

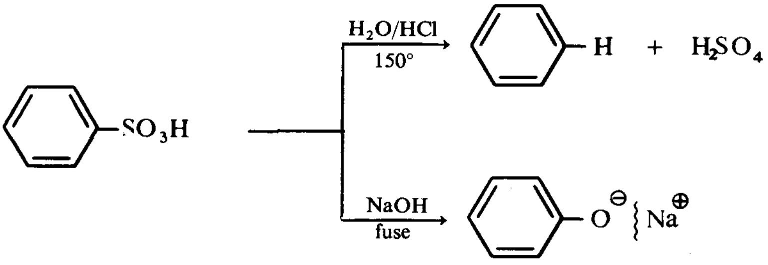


Sulphonyl chlorides react with amine derivatives to yield sulphonamides. The so-called 'Sulpha Drugs' are sulphonamides. They are bacteriostatic agents which assist the natural defences of the host to overcome bacterial infection. Such a substance is 'Sulphadiazine':



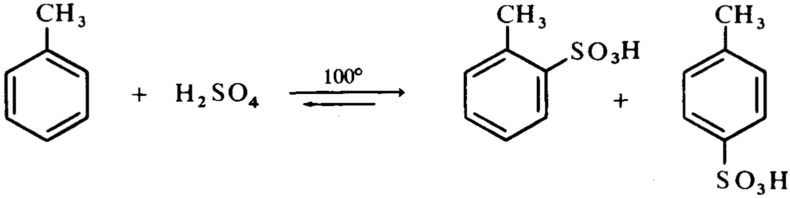
In the body, sulpha drugs break down to *p*-aminobenzenesulphonamide which interferes with the enzyme system of the bacteria.

Aromatic, but not alkylsulphonic acids, lose the —SO_3H group when either heated with hydrochloric acid at 150–200° under pressure or fused with sodium hydroxide. Due to the electronegative oxygen atoms the sulphonic acid group is electron attracting and *meta* directing, in electrophilic aromatic substitution, when attached to an aromatic nucleus.

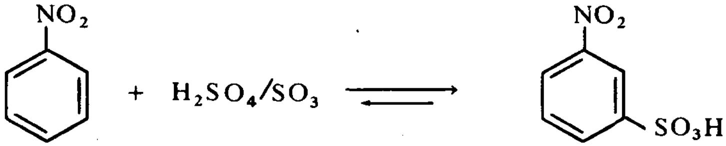


sodium phenoxide

Arylsulphonic acids are usually prepared by the direct electrophilic substitution of the hydrocarbon with sulphuric acid, in the case of activated compounds like toluene, or with oleum for deactivated compounds like nitrobenzene.



o + *p*-toluenesulphonic acids



m-nitrobenzenesulphonic acid

Alkylsulphonic acids can be made by the oxidation of thiols (section 10.2). Alternative methods are:

(1) the direct nucleophilic replacement of the halogen atom in reactive alkyl halides using sodium sulphite (the Strecker reaction):

$$CH_3CH_2Br + \text{aq. } Na_2SO_3 \xrightarrow[\text{displacement}]{S_N2} CH_3CH_2S\overset{\ominus}{O_3}\left\{\overset{\oplus}{Na}\right. + NaBr$$

sodium
ethanesulphonate

(2) the addition of sodium hydrogen sulphite to alkenes in the presence of oxygen or peroxides.

$$CH_3CH{=}CH_2 + \text{aq. } NaHSO_3 \xrightarrow[\text{peroxides}]{O_2\text{ or}} CH_3CH_2CH_2S\overset{\ominus}{O}_3\left\{ \overset{\oplus}{Na} \right.$$

sodium 1-propanesulphonate

As might be expected, under these conditions the direction of addition does not obey Markownikoff's rule.

Solutions of sodium salts of sulphonic acids are in widespread use as detergents (page 277). The ability of these substances to solubilise oil droplets in micelles has already been mentioned in section 1.7.

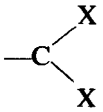
11

Polyfunctional Compounds I —Dialdehydes, Dicarboxylic Acids, Diketones and Diols

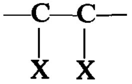
INTRODUCTION

In this and the following chapter organic compounds containing two functional groups are discussed. Compounds with two similar groups are mentioned in this chapter and those with two different functional groups in Chapter 12.

When functional groups are joined directly together, e.g. —CO·CO—, or are joined to the same carbon atom, e.g. $—COCH_2CO—$, then some degree of interaction may occur between the groups. Irrespective of the structure of the complete molecule the relative positions of functional groups, X, are described as follows:

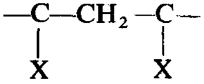


gem disubstitution, both groups attached to the same carbon atom



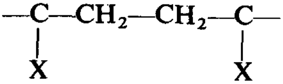
$$—\underset{X}{\underset{|}{C}}—\underset{X}{\underset{|}{C}}—$$

vic or 1,2- or α-disubstitution, two groups attached to adjacent carbon atoms



$$—\underset{X}{\underset{|}{C}}—CH_2—\underset{X}{\underset{|}{C}}—$$

1,3- or β-disubstitution



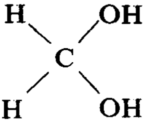
$$—\underset{X}{\underset{|}{C}}—CH_2—CH_2—\underset{X}{\underset{|}{C}}—$$

1,4- or γ-disubstitution

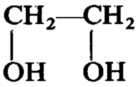
Four types of disubstituted compounds will be discussed, diols, dialdehydes, diketones and dicarboxylic acids (X = —OH, —CHO, —C═O, and —COOH respectively).

11.1 DIOLS (AND TRIOLS)

The simplest stable diol, or dihydric alcohol, is 1,2-ethanediol which is also commonly referred to as ethylene glycol (diol = glycol). Methanediol, like all simple gem-diols, is unstable. 1,2,3-Propanetriol, more usually called glycerol, is a commercially important substance and a constituent of many natural occurring esters (section 15.3).

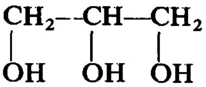


methanediol
(methylene glycol)



$\underset{\mathrm{OH}}{\mathrm{CH_2}}-\underset{\mathrm{OH}}{\mathrm{CH_2}}$

1,2-ethanediol
(ethylene glycol)

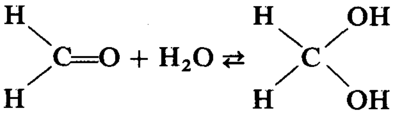


$\underset{\mathrm{OH}}{\mathrm{CH_2}}-\underset{\mathrm{OH}}{\mathrm{CH}}-\underset{\mathrm{OH}}{\mathrm{CH_2}}$

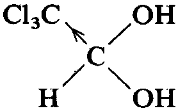
1,2,3-propanetriol
(glycerol)

(a) METHANEDIOL

An aqueous solution of formaldehyde contains this diol due to the equilibrium:



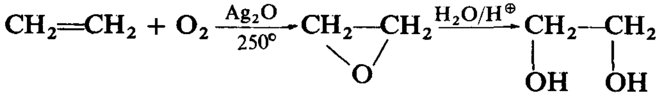
Attempts to isolate methanediol produce only the dehydration product. The gem-diol structure is, however, stabilised by strong electron attracting groups, e.g. chloral hydrate.



(b) 1,2-ETHANEDIOL

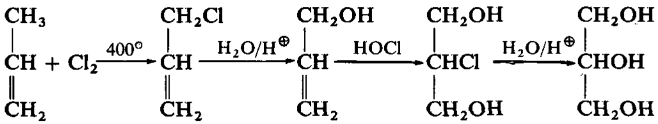
This colourless, water miscible liquid (b.p. 197°, f.p. −16°)

is a commercially important antifreeze for the cooling systems of cars, etc. 1,2-Ethanediol is manufactured from ethylene:



(c) 1,2,3-PROPANETRIOL

Alkaline hydrolysis of glyceride fats produces this trihydric alcohol which has a wide variety of uses, not the least of which is conversion to the explosive, nitroglycerine. An alternative route to the triol is from propene.

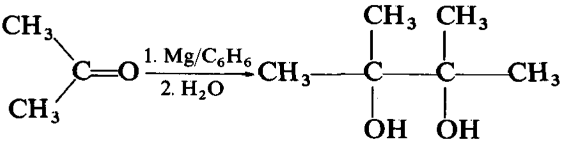


$$\begin{array}{c}CH_3\\|\\CH\\\|\\CH_2\end{array} + Cl_2 \xrightarrow{400^\circ} \begin{array}{c}CH_2Cl\\|\\CH\\\|\\CH_2\end{array} \xrightarrow{H_2O/H^{\oplus}} \begin{array}{c}CH_2OH\\|\\CH\\\|\\CH_2\end{array} \xrightarrow{HOCl} \begin{array}{c}CH_2OH\\|\\CHCl\\|\\CH_2OH\end{array} \xrightarrow{H_2O/H^{\oplus}} \begin{array}{c}CH_2OH\\|\\CHOH\\|\\CH_2OH\end{array}$$

allyl position
chlorination

(d) REACTIONS AND GENERAL PREPARATIONS OF 1,2-DIOLS

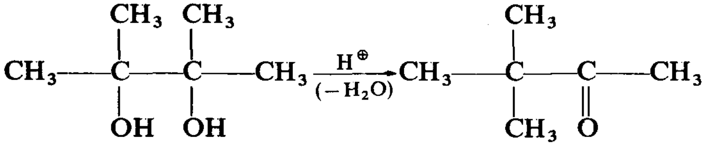
Hydroxylation of the double bond of alkenes with potassium permanganate, osmium tetroxide or peracids yields 1,2-diols (section 5.3). Normal preparative methods for alcohols such as the hydrolysis of 1,2-dihaloalkanes may also be useful. One specific method is the reduction of aldehydes and ketones with magnesium:



$$\begin{array}{l}CH_3\\ \quad C{=}O\\ CH_3\end{array} \xrightarrow[2.\ H_2O]{1.\ Mg/C_6H_6} CH_3-\begin{array}{c}CH_3\\|\\C\\|\\OH\end{array}-\begin{array}{c}CH_3\\|\\C\\|\\OH\end{array}-CH_3$$

2,3-dimethyl-
2,3-butanediol
(pinacol)

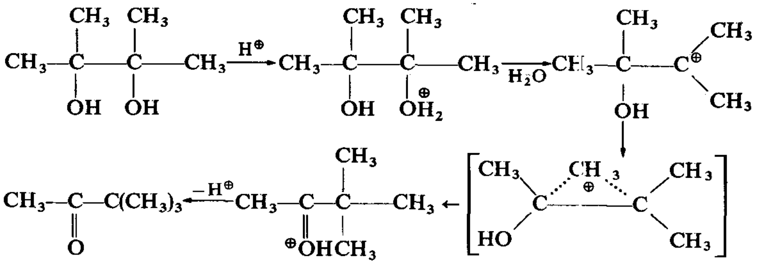
Under the influence of acids many tertiary 1,2-diols undergo dehydration and rearrangement to yield a carbonyl compound.



$$CH_3-\begin{array}{c}CH_3\\|\\C\\|\\OH\end{array}-\begin{array}{c}CH_3\\|\\C\\|\\OH\end{array}-CH_3 \xrightarrow[(-H_2O)]{H^{\oplus}} CH_3-\begin{array}{c}CH_3\\|\\C\\|\\CH_3\end{array}-\begin{array}{c}C\\\|\\O\end{array}-CH_3$$

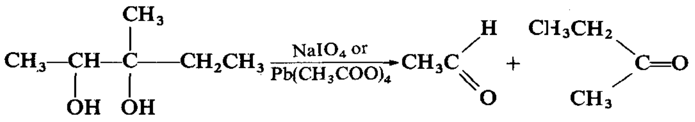
3,3-dimethyl-2-butanone (pinacolone)

This is often termed the Pinacol–Pinacolone rearrangement. The rearrangement step normally takes place through the most stable carbonium ion intermediate.



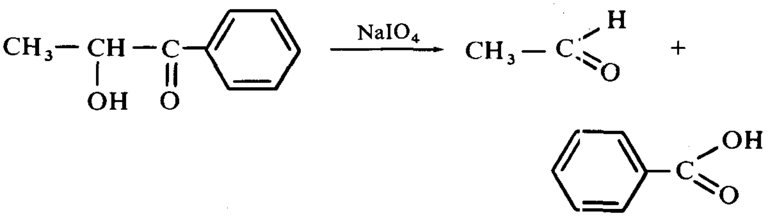
The migrating methyl group does not become completely free from the system but rearranges via the 'bridged intermediate' shown above in square brackets.

The carbon–carbon bond between two adjacent carbon atoms bearing —OH groups can be broken with either lead tetraacetate or sodium periodate. With the latter reagent the cleavage is often quantitative.



3-methyl-2,3-pentanediol

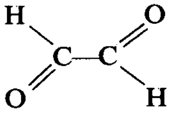
The structure of an alkene can be determined by the reaction sequence (*a*) hydroxylation of the double bond and (*b*) glycol cleavage with sodium periodate followed by identification of the oxidation products. Besides oxidising the group —CHOHCHOH sodium periodate also oxidises —CO·CO— and —CO·CHOH— groups.



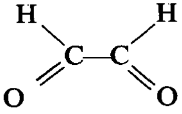
11.2 DIALDEHYDES

Ethanedial (glyoxal), CHO·CHO, is the simplest dialdehyde. Both the carbon atoms are sp^2-hybridised and so a continuous molecular orbital extends over the two carbon and the two oxygen atoms. Of the two possible conformations the *trans* form is probably favoured for then repulsive forces between the oxygen atoms are at a minimum.

trans

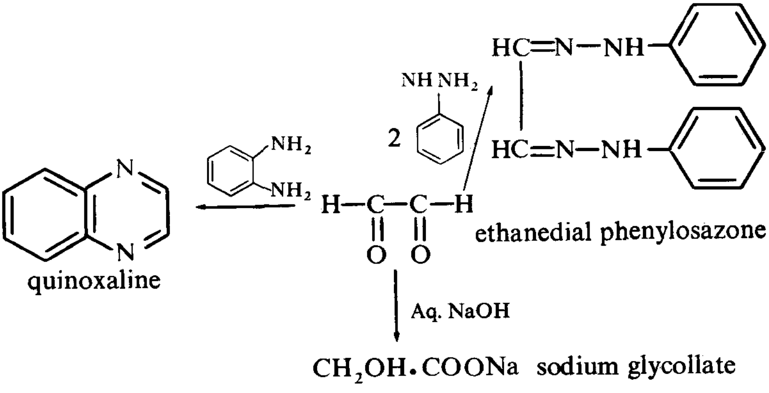


cis

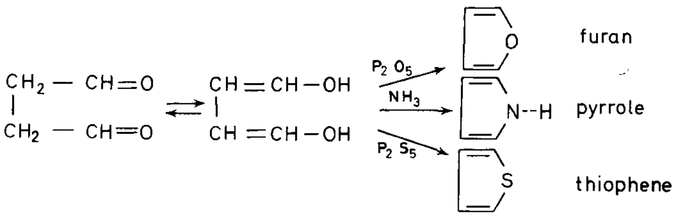


As with other 1,2-dicarbonyl compounds the electronic energy levels of the extended molecular orbital are such that the first absorption band ($n \rightarrow \pi^*$) lies in the visible part of the spectrum (22000 cm^{-1}, 450 nm). Most 1,2-dicarbonyl compounds are pale yellow in colour.

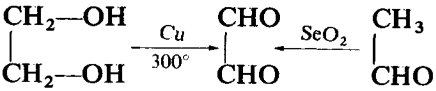
Ethanedial shows most of the usual addition reactions and reducing properties of aldehydes (section 8.2) although it does not reduce Fehling's solution. Most 1,2-dicarbonyl compounds condense with *o*-phenylenediamine to form a quinoxaline. Ethanedial forms an osazone with phenylhydrazine and undergoes an intramolecular Cannizzaro reaction with alkali.



Butanedial (succindialdehyde) has normal aldehyde properties because two sp^3-hybridised carbon atoms separate the aldehyde groups. Butanedial readily forms five-membered ring heterocyclic compounds, reaction possibly taking place via the enol form (cf. section 14.5).



Dialdehydes can be prepared by dehydrogenating diols over copper or by oxidising a methylene group in an existing aldehyde with selenium dioxide.

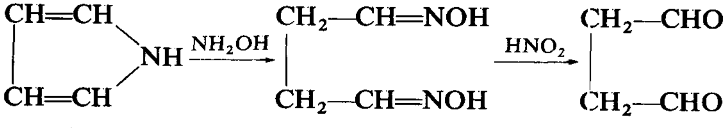


$$\begin{matrix} CH_2-OH \\ | \\ CH_2-OH \end{matrix} \xrightarrow[300^\circ]{Cu} \begin{matrix} CHO \\ | \\ CHO \end{matrix} \xleftarrow{SeO_2} \begin{matrix} CH_3 \\ | \\ CHO \end{matrix}$$

Selenium dioxide specifically oxidises a methyl or methylene group adjacent to a carbonyl group:

$$-CH_2\cdot CO- \xrightarrow{SeO_2} -CO\cdot CO-$$

Butanedial reacts with ammonia to form pyrrole but the latter undergoes a ring opening reaction with hydroxylamine to reform the dialdehyde via the dioxime.



pyrrole

butanedial

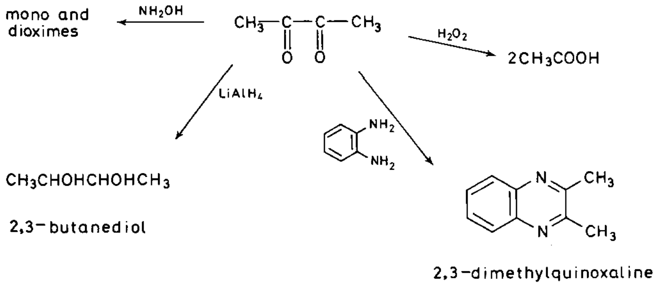
11.3 DIKETONES

Some of the simple diketones are indicated below.

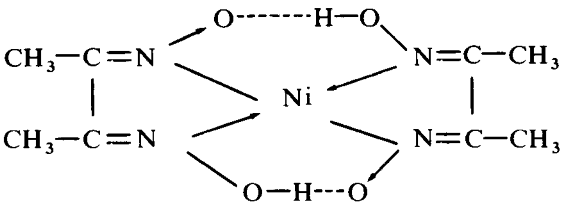
$CH_3COCOCH_3$	2,3-butanedione (biacetyl)	—1,2-diketones
$C_6H_5COCOC_6H_5$	benzil	
$CH_3COCH_2COCH_3$	2,4-pentanedione (acetylacetone)	—1,3-diketone
$CH_3COCH_2CH_2COCH_3$	2,5-hexanedione (acetonyl acetone)	—1,4-diketone

(a) 1,2- or α-DIKETONES

2,3-Butanedione, like ethanedial, is yellow in colour due to conjugation between the carbonyl groups. The diketone is an oil which exhibits most of the normal reactions of ketones but also undergoes condensation with *o*-phenylenediamine. The carbon–carbon bond between the carbonyl groups is easily cleaved with hydrogen peroxide to yield two moles of acetic acid.

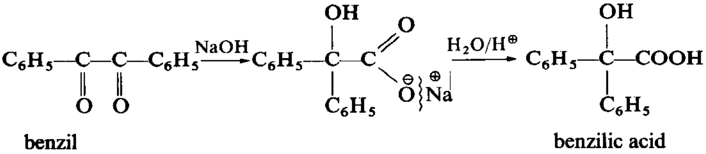


The dioxime of 2,3-butanedione forms coordination compounds with many metals. In particular the dioxime is used for the quantitative estimation of nickel, with which it forms a red chelate compound.

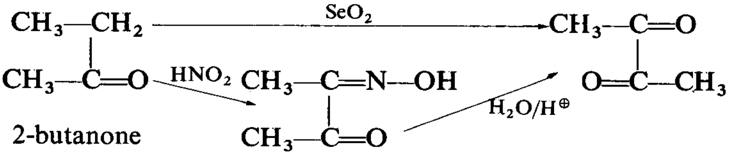


nickel dimethylglyoxime

With sodium hydroxide benzil rearranges to benzilic acid by an intramolecular Cannizzaro reaction similar to that undergone by ethanedial. This reaction is known as the Benzilic Acid Rearrangement.



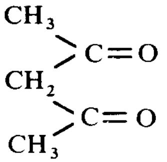
One general method of making 1,2-diketones has already been mentioned, i.e. the oxidation of a methylene group adjacent to a carbonyl group with selenium dioxide. An alternative route is via the corresponding oxime, formed from the reactive methylene group with nitrous acid liberated from isopentyl nitrite and hydrochloric acid



2-butanone

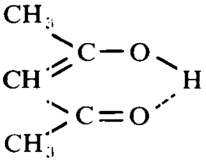
(b) 1,3- or β-DIKETONES

The typical member of this series is 2,4-pentanedione. This is a colourless substance because direct interaction between the carbonyl groups cannot occur as they are separated by a —CH$_2$—group. Due to the rapid interchange of a hydrogen atom between the methylene group and a carbonyl group 1,3-diketones exhibit keto–enol tautomerism.



keto form

(gives $>$C=O reactions)

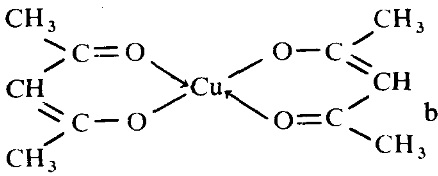


enol form

(colour with FeCl$_3$)

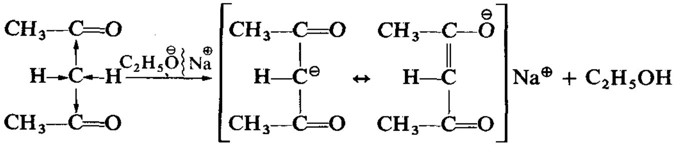
Polar solvents shift the equilibrium in favour of the keto form as this tautomer has two carbonyl groups available for intermolecular bonding to the solvent. Non-polar solvents favour the enol form, for an intramolecular bond is produced when bonding to the solvent is not possible. Nuclear magnetic resonance spectra clearly indicate the equilibrium between the keto and enol forms. When only a proton shift is involved the term prototropic change is often used instead of tautomerism.

The enol form of 2,4-pentanedione yields coordination compounds with a number of metal salts, e.g. copper, iron and beryllium. Thus the copper chelate, which is soluble in organic solvents such as ether, benzene and chloroform but insoluble in water, has the formula:



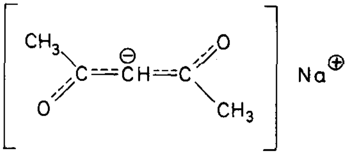
bis-(2,4-pentanedionato)-copper (II)

The methylene group of 1,3-diketones, sandwiched between two electron withdrawing carbonyl groups, is 'activated'. That is the hydrogen atoms of this —CH_2— are weakly acidic and can be removed by a strong base such as sodium ethoxide. Reaction is assisted by the stabilisation of the carbanion produced, due to electron delocalisation.



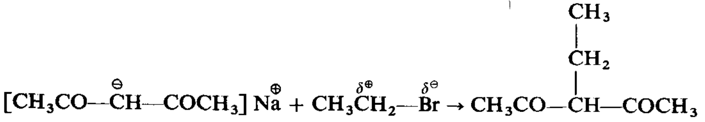
(I) (II)

The anion II is probably an extreme form because most subsequent reactions occur via structure I. The central carbon atom changes hybridisation states from sp^3 in the neutral molecule to sp^2 in the anion. The negative charge can then be spread, i.e. delocalised, over a molecular orbital linking three carbon and two oxygen atoms:



stabilized anion III

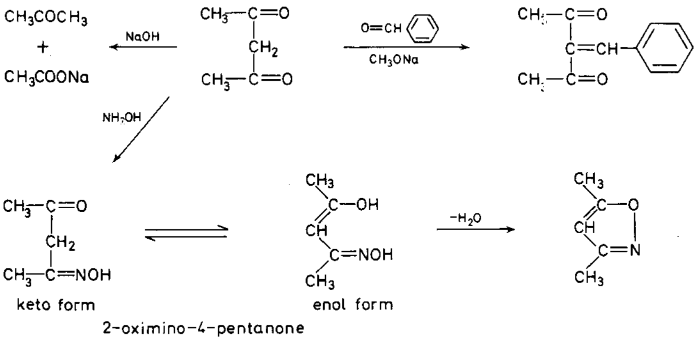
This stabilised anion, III, behaves as a nucleophile and reacts with alkyl halides, etc.



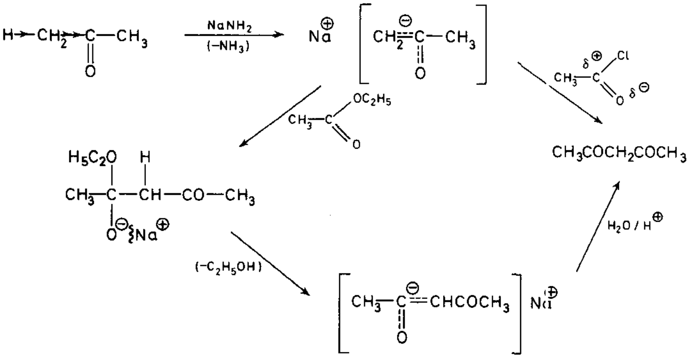
$$[CH_3CO-\overset{\ominus}{C}H-COCH_3]\overset{\oplus}{Na} + CH_3CH_2\overset{\delta\oplus}{-}\overset{\delta\ominus}{Br} \rightarrow CH_3CO-\underset{}{\overset{CH_3CH_2}{CH}}-COCH_3$$

3-ethyl-2,4-pentanedione

Other reactions of 2,4-pentanedione include (1) the condensation of the reactive methylene group with aldehydes in the presence of a base, (2) the formation of heterocyclic compounds from the mono-oxime, hydrazone and phenylhydrazone and (3) the cleavage of the molecule to acetone and sodium acetate with sodium hydroxide.



Two methods of preparing 2,4-pentanedione are (4) the reaction of acetyl chloride with sodio ethyl acetoacetate (page 223) and (5) reaction of the sodium salt of acetone with acetyl chloride or ethyl acetate.

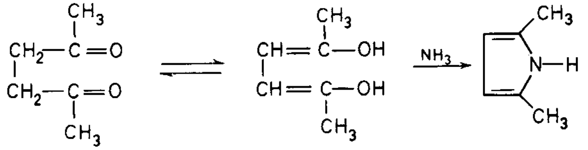


The reaction (5) above involving ethyl acetate is a Claisen condensation and besides initial nucleophilic attack, E2 elimination subsequently takes place to remove a molecule of ethanol. The ketone is more acidic than the ester, due to the +M effect of the

—OC_2H_5 group, and so reaction occurs as shown. In the absence of a ketone, ethyl acetate condenses with itself to form ethyl acetoacetate (page 224).

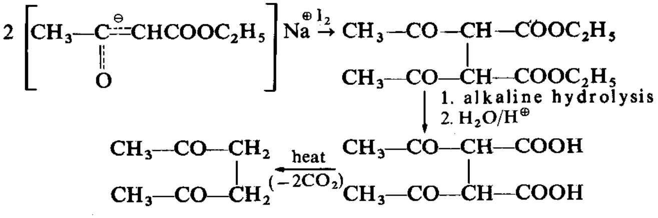
(c) 1,4 or γ-DIKETONES

2,5-Hexanedione is a colourless liquid possessing normal ketone properties. The hydrogen atoms of the central methylene groups are little more acidic than those of normal ketones and stabilised anions of the type encountered with 2,4-pentanedione are not formed. Keto-enol tautomerism is possible and reaction with NH_3, P_2S_5 or P_2O_5, to produce 2,5-dimethylpyrrole, thiophene and furan respectively, probably takes place via the enol form (The Paal–Knorr synthesis, page 254).



keto form   enol form   2,5-dimethylpyrrole

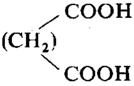
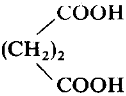
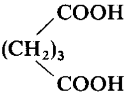
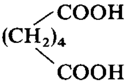
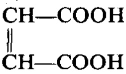
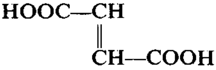
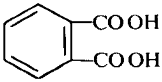
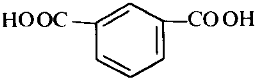
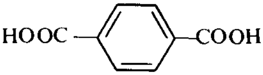
2,5-Hexanedione can be prepared by (1) reacting bromoacetone with sodio ethyl acetoacetate (page 223) or (2) condensing together two molecules of sodio ethyl acetoacetate with iodine. A new carbon–carbon bond is formed, the diester hydrolysed and the dicarboxylic acid decarboxylated by heat.



2,5-hexanedione

11.4 DICARBOXYLIC ACIDS

The structures of the simple dicarboxylic acids with their first and second acid dissociation constants (K_A1 and K_A2) are shown below. Trivial names are in common usage but it would seem sensible to use systematic names, particularly for the higher acids.

Formula	*Trivial Name*	*Systematic Name*	K_A1 $(\times 10^{-5})$	K_A2 $(\times 10^{-5})$
$(COOH)_2$	oxalic acid	ethanedioic acid	5000	5·3
 $(CH_2)\begin{smallmatrix}\diagup COOH\\ \diagdown COOH\end{smallmatrix}$	malonic acid	propanedioic acid	150	0·22
 $(CH_2)_2\begin{smallmatrix}\diagup COOH\\ \diagdown COOH\end{smallmatrix}$	succinic acid	butanedioic acid	6·4	0·25
 $(CH_2)_3\begin{smallmatrix}\diagup COOH\\ \diagdown COOH\end{smallmatrix}$	glutaric acid	pentanedioic acid	4·5	0·38
 $(CH_2)_4\begin{smallmatrix}\diagup COOH\\ \diagdown COOH\end{smallmatrix}$	adipic acid	hexanedioic acid	3·7	0·39
 $\begin{matrix}\mathrm{CH{-}COOH}\\ \Vert\\ \mathrm{CH{-}COOH}\end{matrix}$	maleic acid	*cis*-butenedioic acid	1000	0·055
 $\begin{matrix}\mathrm{HOOC{-}CH} & \\ \Vert & \\ \mathrm{CH{-}COOH} & \end{matrix}$	fumaric acid	*trans*-butenedioic acid	96	4·1
	phthalic acid	*o*-benzene-dicarboxylic acid	110	0·4
	isophthalic acid	*m*-benzene-dicarboxylic acid	24	2·5
	terephthalic acid	*p*-benzene-dicarboxylic acid	29	3·5

(a) PHYSICAL PROPERTIES

Maleic, malonic and glutaric acids are particularly soluble in water whilst adipic, oxalic and succinic acids are only moderately soluble. Water solubility decreases with increasing molecular weight.

Where the two acid groups are close together, as in fumaric, maleic, malonic, oxalic and phthalic acids, either the inductive effect or direct electrostatic interaction of the two carboxyl groups gives K_A1 a high value. At the same time K_A2 is often lower than normal in such cases.

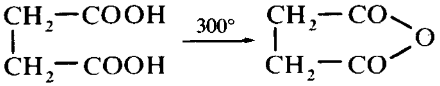
(b) ACTION OF HEAT

At about 150° malonic and oxalic acids undergo decarboxylation.

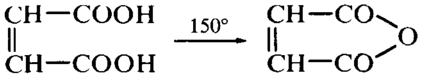
$$\mathrm{HOOC{-}COOH} \longrightarrow \mathrm{HCOOH} + \mathrm{CO_2}$$

$$\mathrm{HOOC{-}CH_2{-}COOH} \longrightarrow \mathrm{CH_3COOH} + \mathrm{CO_2}$$

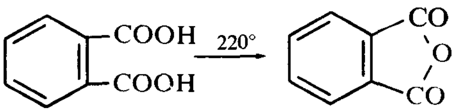
Glutaric, maleic, phthalic and succinic acids lose water on heating to produce the corresponding anhydride.



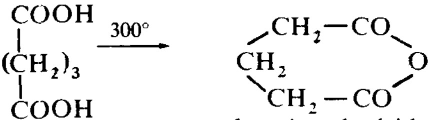
succinic anhydride



maleic anhydride

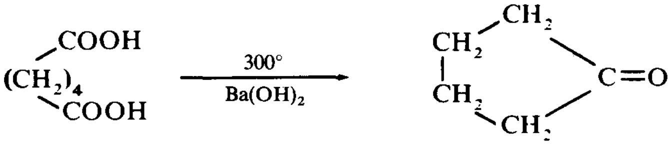


phthalic anhydride



glutaric anhydride

Adipic acid, however, loses carbon dioxide and water to produce the five-membered ring ketone, cyclopentanone.

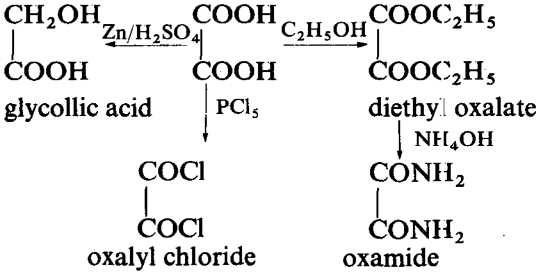


(c) OXALIC ACID

Oxalic acid crystallises from water as the dihydrate, $(COOH)_2.2H_2O$. The acid is easily oxidised and is used as a reducing agent in a number of volumetric determinations, e.g. with acidified potassium permanganate solution at 60°:

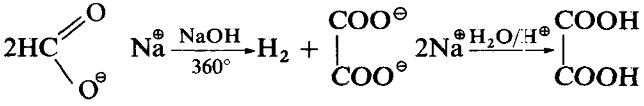
$$3KMnO_4 + 3H_2SO_4 + 5(COOH)_2 \rightarrow 2MnSO_4 + K_2SO_4 + 10CO_2 + 8H_2O$$

Oxalic acid is more reactive than most carboxylic acids; it reacts with ethanol to yield diethyl oxalate without a mineral acid catalyst. The ester, diethyl oxalate, is also a reactive substance and rapidly precipitates the di-amide, oxamide, with ammonia.



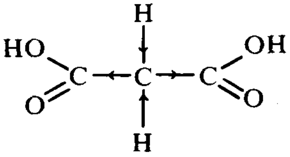
Oxalic acid is one of the final degradation products of starch, sugars, etc., and can be prepared in the laboratory by the oxidation of sucrose with nitric acid. Industrially sodium formate is heated with alkali at 360°.

$$\underset{\text{sucrose}}{C_{12}H_{22}O_{11}} \xrightarrow{HNO_3} 6(COOH)_2 + 5H_2O$$

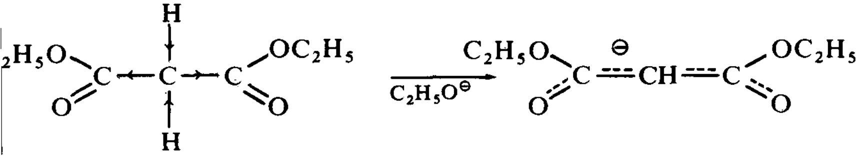


(d) MALONIC ACID

Two properties make malonic acid a useful intermediate for the synthesis of mono- and dicarboxylic acids and to a lesser extent of keto-acids. First, heating malonic acid or a derivative of the acid produces decarboxylation with the loss of one —COOH group. Secondly malonic acid, like 2,4-pentanedione, possesses an activated methylene group.



In practice the dicarboxylic acid is inconvenient to use for synthetic purposes and so reactions are carried out with the ester, diethyl malonate. With bases such as sodium ethoxide, sodamide or sodium hydride a proton is detached from diethyl malonate and a stabilised anion is formed.



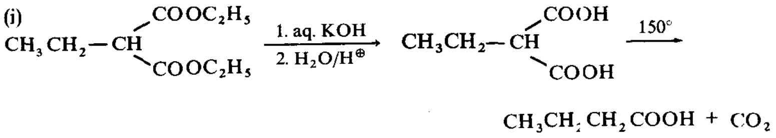
diethyl malonate stabilised anion

This stabilised anion acts as a nucleophile towards alkyl and acyl halides and in most cases behaves, at the time of reaction, as though the negative charge is located on the middle carbon atom.

$$[\overset{\ominus}{C}H(COOC_2H_5)_2]\,\overset{\oplus}{Na} + CH_3\overset{\delta\oplus}{C}H_2—\overset{\delta\ominus}{Br} \rightarrow CH_3CH_2—CH(COOC_2H_5)_2$$

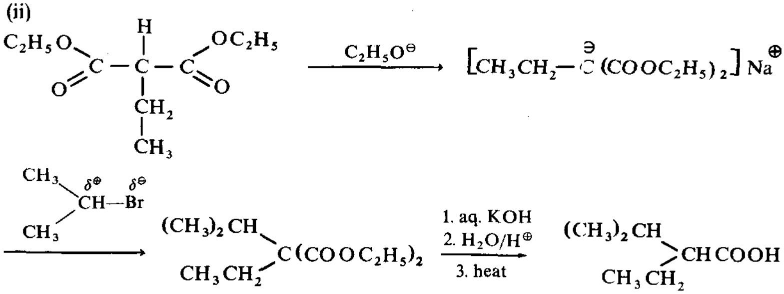
The monoalkyl diethyl malonate can be either hydrolysed and decarboxylated to a monocarboxylic acid, or a second alkyl group can be introduced prior to hydrolysis and decarboxylation.

(i)



$$CH_3CH_2-CH(COOC_2H_5)_2 \xrightarrow[2.\ H_2O/H^{\oplus}]{1.\ aq.\ KOH} CH_3CH_2-CH(COOH)_2 \xrightarrow{150^{\circ}} CH_3CH_2CH_2COOH + CO_2$$

(ii)

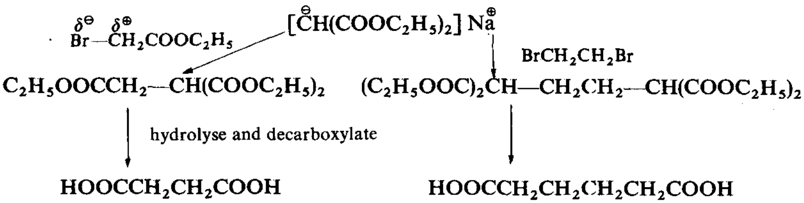


$$C_2H_5O-C(=O)-CH(CH_2CH_3)-C(=O)-OC_2H_5 \xrightarrow{C_2H_5O^{\ominus}} [CH_3CH_2-\overset{\ominus}{C}(COOC_2H_5)_2]\,\overset{\oplus}{Na}$$

$$\xrightarrow{(CH_3)_2\overset{\delta\oplus}{CH}-\overset{\delta\ominus}{Br}} (CH_3)_2CH(CH_3CH_2)C(COOC_2H_5)_2 \xrightarrow[3.\ heat]{1.\ aq.\ KOH\quad 2.\ H_2O/H^{\oplus}} (CH_3)_2CH(CH_3CH_2)CHCOOH$$

2-(isopropyl)-butaneoic acid

(iii) Diethyl malonate can also be used to prepare dicarboxylic acids and keto-acids as follows. Reaction of sodio diethyl malonate with a bromoacid ester or a dibromalkane produces a dicarboxylic acid.



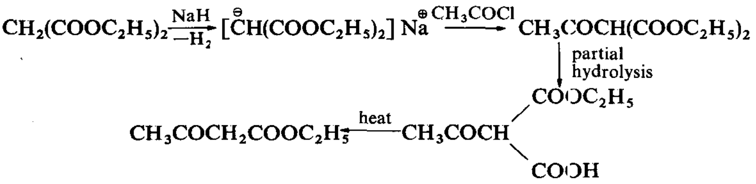
$$[\overset{\ominus}{C}H(COOC_2H_5)_2]\,\overset{\oplus}{Na} \xrightarrow{\overset{\delta\ominus}{Br}-\overset{\delta\oplus}{C}H_2COOC_2H_5} C_2H_5OOCCH_2-CH(COOC_2H_5)_2 \xrightarrow{\text{hydrolyse and decarboxylate}} HOOCCH_2CH_2COOH$$

$$[\overset{\ominus}{C}H(COOC_2H_5)_2]\,\overset{\oplus}{Na} \xrightarrow{BrCH_2CH_2Br} (C_2H_5OOC)_2CH-CH_2CH_2-CH(COOC_2H_5)_2 \longrightarrow HOOCCH_2CH_2CH_2CH_2COOH$$

succinic acid

adipic acid

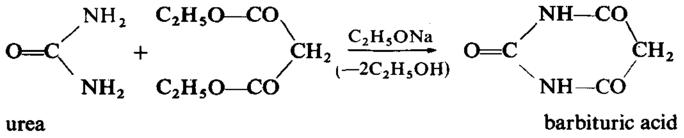
Reaction with an acyl halide, using sodium hydride as the base, followed by careful partial hydrolysis, may yield a β-ketoester. Sodium ethoxide cannot be used as the base because the ethanol produced in the reaction would react with the acyl halide.



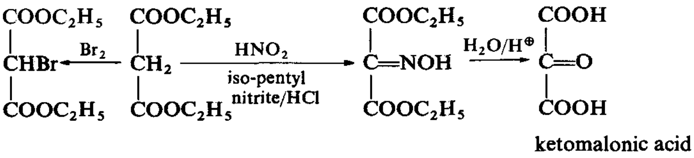
$$CH_2(COOC_2H_5)_2 \xrightarrow[-H_2]{NaH} [\overset{\ominus}{C}H(COOC_2H_5)_2]\,\overset{\oplus}{Na} \xrightarrow{CH_3COCl} CH_3COCH(COOC_2H_5)_2 \xrightarrow{\text{partial hydrolysis}} CH_3COCH(COOC_2H_5)(COOH) \xrightarrow{heat} CH_3COCH_2COOC_2H_5$$

ethylacetoacetate

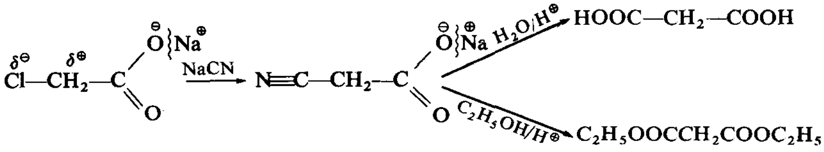
(iv) Diethyl malonate reacts with urea to form the parent of the class of compounds known as Barbiturates.



(v) The activated methylene group of diethyl malonate also reacts with a number of reagents, e.g. bromine or nitrous acid.

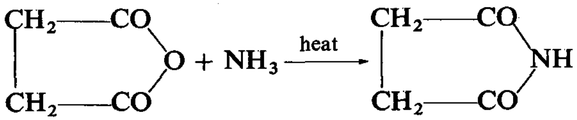


Malonic acid is readily prepared from the hydrolysis of cyanoacetic acid which is produced by the action of sodium cyanide on sodium chloroacetate.

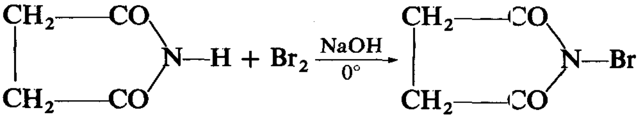


(e) SUCCINIC ACID

As already mentioned the action of heat on succinic acid yields succinic anhydride. The latter reacts with ammonia to give succinimide:

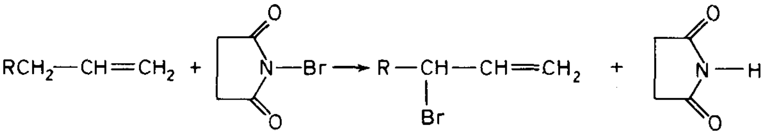


The nitrogen atom of succinimide is subject to electron withdrawal by the two adjacent carbonyl groups (−I and −M effects). The nitrogen–hydrogen bond is, therefore, weakened and the hydrogen atom easily replaced by bromine, yielding N-bromosuccinimide.



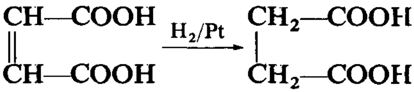
N-bromosuccinimide

N-Bromosuccinimide is a useful brominating agent, particularly for the allyl position of alkenes



The action of this brominating agent may be free radical, for the process is frequently initiated by light or peroxides, or the reagent may simply provide a low concentration of bromine.

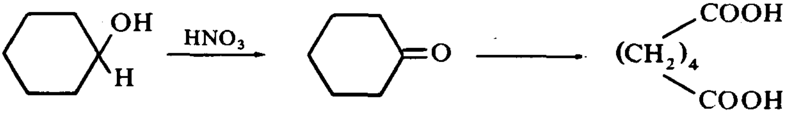
Succinic acid is produced by the catalytic reduction of maleic acid.



$$\begin{array}{l} CH-COOH \\ \| \\ CH-COOH \end{array} \xrightarrow{H_2/Pt} \begin{array}{l} CH_2-COOH \\ | \\ CH_2-COOH \end{array}$$

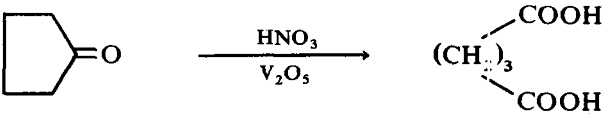
(f) GLUTARIC AND ADIPIC ACIDS

Adipic acid is particularly important for the manufacture of Nylon (6.6) (section 16.3) and is prepared via the oxidation of cyclohexanol with nitric acid.



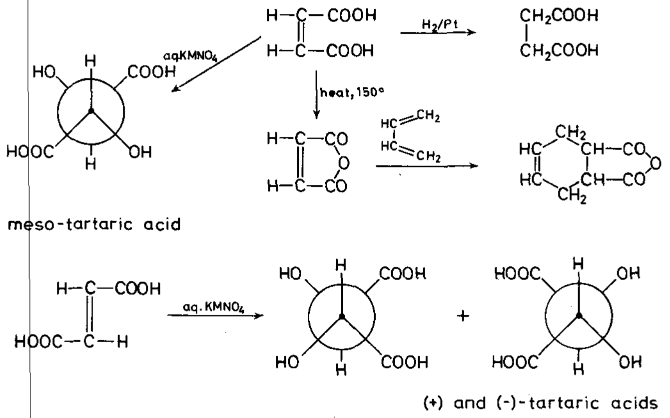
cyclohexanol cylohexanone adipic acid

Glutaric acid is made by oxidising cyclopentanone with nitric acid over vanadium pentoxide.

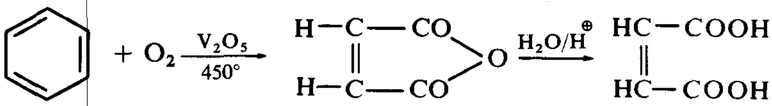


(g) MALEIC AND FUMARIC ACIDS

Both of these acids reduce to succinic acid and hydroxylate to tartaric acid. However, maleic acid yields meso-tartaric acid whilst fumaric acid forms (±)-tartaric acid. Another difference between the two acids is that maleic readily forms the anhydride, maleic anhydride, on heating at about 150° whilst furmaric acid only slowly forms the same anhydride at 250°. Maleic anhydride is a useful dienophile in Diels–Alder syntheses (section 5.4).



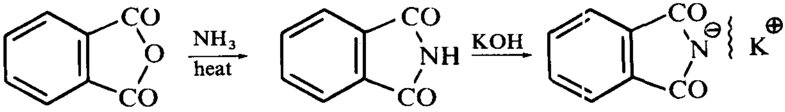
Maleic acid is manufactured via the catalytic oxidation of benzene to maleic anhydride.



Fumaric acid is produced by boiling maleic acid with dilute acid or alkali or by the action of bacteria on glucose or other carbohydrates.

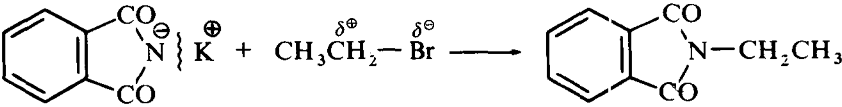
(h) PHTHALIC ACID

Phthalic anhydride is formed by the action of heat on phthalic acid and, like succinic anhydride, it yields an imide when heated with ammonia.



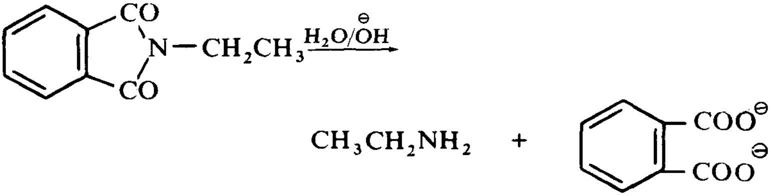
phthalic anhydride phthalimide potassium phthalimide

The hydrogen atom attached to the nitrogen atom of phthalimide is rendered acidic by the electron withdrawing carbonyl groups and the resultant anion is stabilised by electron delocalisation. Thus reaction of phthalimide with aqueous potassium hydroxide produces the salt, potassium phthalimide, in which the phthalimide anion is capable of acting as a nucleophile towards alkyl halides.



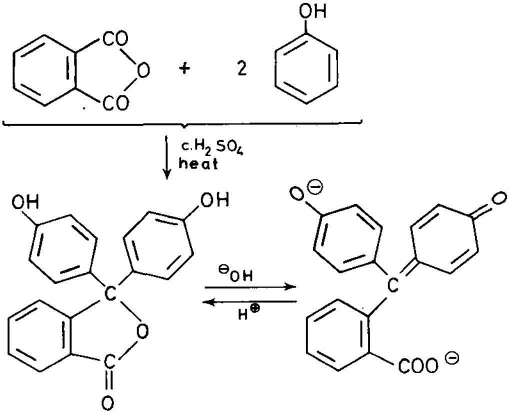
N-ethyl phthalimide

N-Alkyl phthalimides hydrolyse with aqueous alkali to give a pure primary amine.



These last two reactions together form the Gabriel Phthalimide synthesis of primary amines.

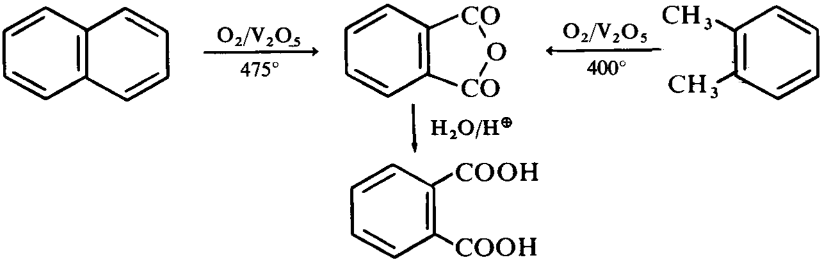
Another feature of the chemistry of phthalic anhydride is that it forms phthaleins when heated with phenols in the presence of a strong acid. One of the best known of these is the acid–base indicator phenolphthalein.



phenolphthalein
(colourless)

phenolphthalein
(red in dilute alkali)

Phthalic acid is manufactured via the catalytic oxidation of either naphthalene or *o*-xylene. Condensation of phthalic acid or the anhydride with glycerol produces an alkyd resin (section 16.3).

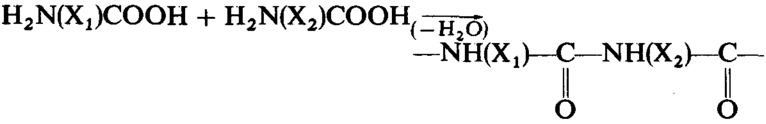


12

Polyfunctional Compounds II —Amino, Keto, Halogeno and Hydroxy Acids, α,β-Unsaturated Carbonyl Compounds

12.1 AMINO ACIDS

As the name suggests, amino acids contain an amino group and a carboxyl group. These two groups can condense together to form amide linkages:



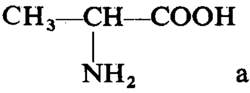
$$H_2N(X_1)COOH + H_2N(X_2)COOH \xrightarrow[(-H_2O)]{} -NH(X_1)-\underset{\underset{O}{\|}}{C}-NH(X_2)-\underset{\underset{O}{\|}}{C}-$$

This condensation product, which is termed a peptide or protein depending on chain length (section 15.2), can be isolated from many natural sources. In principle the amino group may be in any position relative to the carboxyl group, i.e. α, β, γ, etc. However, all the amino acids isolated from natural sources are of the α-type.

To illustrate the properties and reactions of amino acids, discussions will be confined to the simple acids, glycine and alanine.

NH_2CH_2COOH

glycine



$$CH_3-\underset{\underset{NH_2}{|}}{CH}-COOH$$

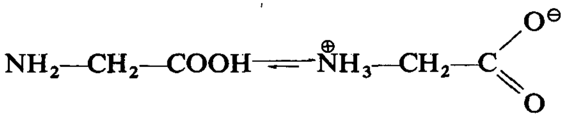
alanine

Amino acids can be named systematically, e.g. alanine is 2-aminopropanoic acid, but in practice they are always referred to by their trivial names.

The attachment of a carbonyl group and an amino group to the same carbon atom confers special properties on the molecule. Some of these properties, as illustrated by glycine, are as follows.

(*a*) In aqeous solution glycine has a very large dipole moment.
(*b*) Glycine is quite soluble in water but insoluble in non-polar solvents.
(*c*) α-Amino acids are high melting solids, melting with decomposition.
(*d*) Glycine is about 10^5 weaker as an acid than acetic acid and also about 10^8 weaker as a base than ethylamine.

These properties are consistent with α-amino acids existing in a dipolar or *zwitterion* form.



$$NH_2{-}CH_2{-}COOH \rightleftharpoons \overset{\oplus}{N}H_3{-}CH_2{-}C\begin{matrix}\diagup O^{\ominus}\\ \diagdown\!\!\diagdown O\end{matrix}$$

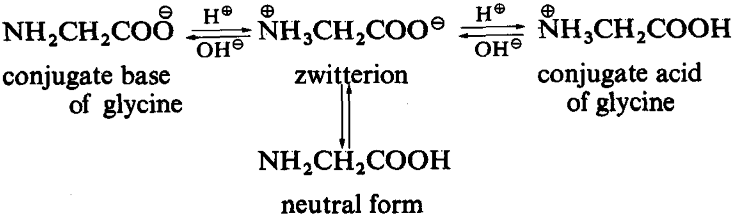
The observed physical properties can be interpreted on the basis of this internal salt form. Thus acidity refers to the ammonium ion:

$$R\overset{\oplus}{N}H_3 + H_2O \rightleftharpoons H_3\overset{\oplus}{O} + RNH_2$$

and basicity to the carboxylate ion:

$$RCOO^{\ominus} + H_2O \rightleftharpoons \overset{\ominus}{O}H + RCOOH$$

Glycine is a slightly stronger acid ($K_A = 1{\cdot}6 \times 10^{-10}$) than it is a base ($K_B = 2{\cdot}5 \times 10^{-12}$) so that in aqueous solution the concentration of the anion, $NH_2CH_2COO^{\ominus}$, exceeds that of the cation, $\overset{\oplus}{N}H_3CH_2COOH$. Addition of a little acid will correct this situation and at pH 6·0 glycine is entirely in the zwitterion or neutral form.



$$\begin{tikzcd} NH_2CH_2CO\overset{\ominus}{O} \arrow[r, shift left, "H^{\oplus}"] & \overset{\oplus}{N}H_3CH_2COO^{\ominus} \arrow[l, shift left, "OH^{\ominus}"] \arrow[r, shift left, "H^{\oplus}"] \arrow[d, shift left] & \overset{\oplus}{N}H_3CH_2COOH \arrow[l, shift left, "OH^{\ominus}"] \\ & NH_2CH_2COOH \arrow[u, shift left] & \end{tikzcd}$$

conjugate base of glycine

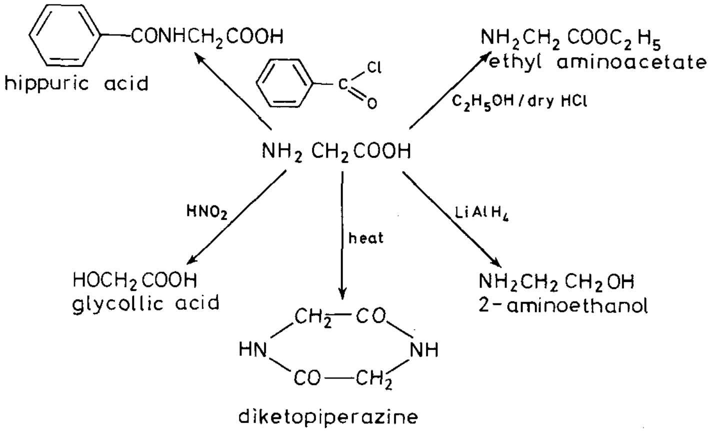
zwitterion

conjugate acid of glycine

neutral form

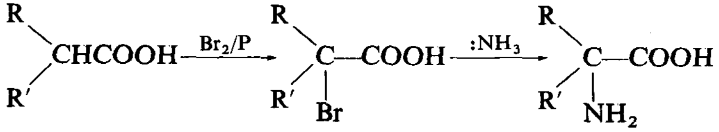
The pH at which an amino acid is fully in the zwitterion form is termed the Isoelectric Point. At this pH the amino acid will not migrate to either a positive or negative electrode if a potential is applied to the solution. The minimum solubility of an amino acid in water normally occurs at the isoelectric point.

Chemically amino acids exhibit reactions of both the amino and carboxyl groups. The amino group can be acetylated with acetic anhydride, benzoylated with benzoyl chloride or reacted with nitrous acid to give, amongst other products, a hydroxy acid. The carboxyl group can be esterified or reduced. The action of heat on an amino acid often causes two molecules to condense with the loss of water and formation of two amide linkages within a cyclic structure, e.g. two molecules of glycine form diketopiperazine.



Amino acids can be synthesised in many ways but two general methods will be considered here.

(1) Halogenation of a carboxylic acid with bromine and red phosphorus yields the α-bromo acid (the Hell–Volhard–Zelinsky reaction, page 162). Nucleophilic displacement of the bromine atom with ammonia produces the α-amino acid.

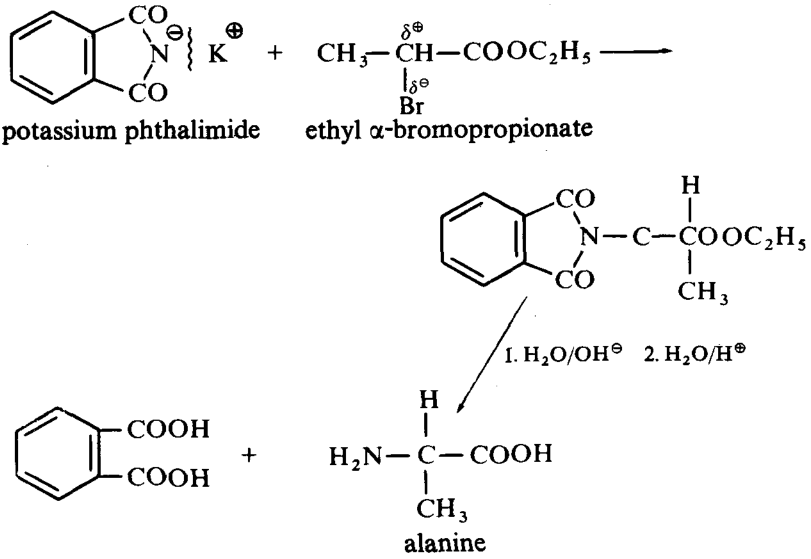


$$RR'CHCOOH \xrightarrow{Br_2/P} RR'C(Br)COOH \xrightarrow{:NH_3} RR'C(NH_2)COOH$$

A suitably substituted carboxylic acid for the reaction could be produced via either the diethyl malonate or ethyl acetoacetate synthesis (page 210 or 223).

(2) The Gabriel phthalimide synthesis of primary amines (section

11.4) may be modified so that the nucleophilic phthalimide anion is reacted with an α-halo-ester instead of an alkyl halide. Subsequent hydrolysis yields an α-amino acid.



Preparation of an amino acid by either of the above routes yields an optically inactive product which must be resolved (section 13.3) if the optically active forms are required.

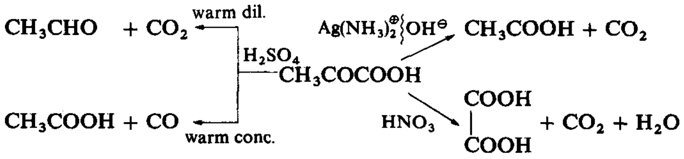
12.2 KETO ACIDS

Keto acids could be expected to show reactions of both the carbonyl group and the carboxyl group. The degree to which this occurs depends on the separation of the two groups. In α-keto acids as in α-diketones the two groups interact together to produce some reactions peculiar to the system as a whole. Beta-keto acids, like both β-diketones and 1,3-dicarboxylic acids, exhibit keto–enol tautomerism and react with bases to form stabilised anions. Gamma-keto acids show the more usual reactions of the two groups although these substances tend to eliminate water to produce cyclic compounds. The typical α, β, and γ-keto acids are indicated below.

$CH_3CO—COOH$	2-oxopropanoic acid or pyruvic acid
$CH_3CO—CH_2—COOH$	3-oxobutanoic acid or acetoacetic acid
$CH_3CO—CH_2CH_2—COOH$	4-oxopentanoic acid or laevulic acid

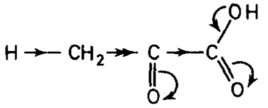
(a) 2-OXOPROPANOIC ACID OR PYRUVIC ACID

The carbonyl and carboxyl groups in this molecule directly influence one another and as a result the keto acid is very easily oxidised. The oxidation products with ammoniacal silver nitrate, nitric acid and sulphuric acid are shown below.

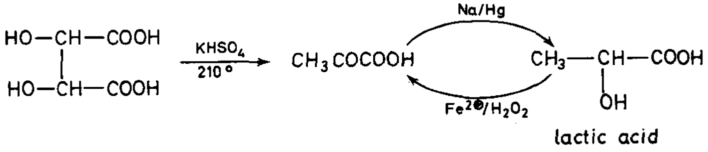


The different reactions with warm dilute and concentrated sulphuric acids are typical of α-keto acids.

The hydrogen atoms attached to the methyl group of 2-oxopropanoic acid are more acidic than the corresponding hydrogen atoms of ketones and undergo condensation more readily.



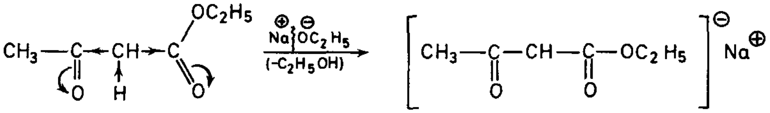
The carbonyl group will react independently, e.g. to form an oxime, and can be reduced, without involving the carboxyl group, to yield lactic acid. Conversely oxidation of lactic acid with iron (II) sulphate and hydrogen peroxide (Fenton's reagent) yields 2-oxopropanoic acid although the best method of preparation is to heat tartaric acid with potasssium hydrogen sulphate.



(b) 3-OXOBUTANOIC ACID OR ACETOACETIC ACID

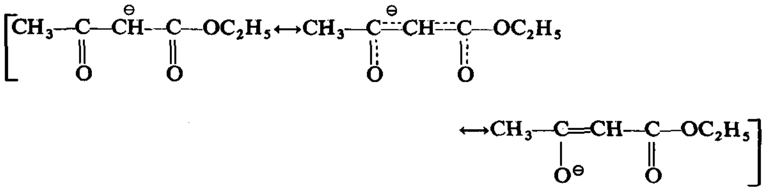
Acetoacetic acid and malonic acid both possess an activated methylene group and both are useful reagents in organic synthesis reactions. For this purpose both substances are normally used as their ethyl esters rather than as the free acids. Acetoacetic acid readily decomposes to carbon dioxide and acetone.

Reaction of ethyl acetoacetate with a strong base such as sodium ethoxide produces sodio ethyl acetoacetate.



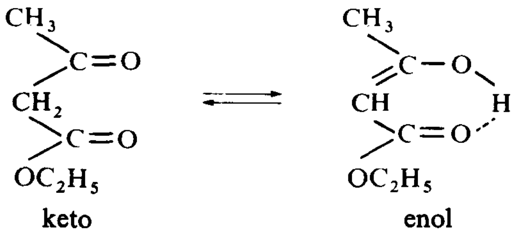
$$CH_3-\underset{O}{\underset{\|}{C}}-\underset{H}{\underset{|}{C}}H-\overset{OC_2H_5}{\underset{O}{\underset{\|}{C}}} \xrightarrow[(-C_2H_5OH)]{\overset{\oplus}{Na}\overset{\ominus}{O}C_2H_5} \left[CH_3-\underset{O}{\underset{\|}{C}}-CH-\underset{O}{\underset{\|}{C}}-OC_2H_5\right]^{\ominus} Na^{\oplus}$$

The ethyl acetoacetate anion behaves as a nucleophile towards alkyl and acyl halides; like the diethyl malonate anion it is stabilised by delocalisation of the negative charge.



$$\left[CH_3-\underset{O}{\underset{\|}{C}}-\overset{\ominus}{C}H-\underset{O}{\underset{\|}{C}}-OC_2H_5 \longleftrightarrow CH_3-\underset{O}{\underset{\vdots}{\overset{\ominus}{C}}}\text{---}CH\text{---}\underset{O}{\underset{\vdots}{C}}-OC_2H_5 \longleftrightarrow CH_3-\underset{O^{\ominus}}{\underset{|}{C}}=CH-\underset{O}{\underset{\|}{C}}-OC_2H_5\right]$$

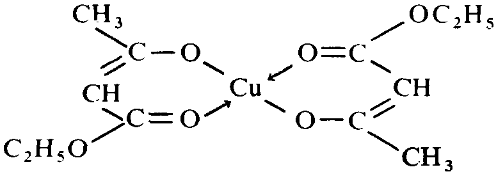
Ethyl acetoacetate exists in keto and enol forms.



Interconversion between the keto and enol forms is catalysed by acids and bases. Even the weakly alkaline reaction of a glass surface will catalyse a keto–enol tautomeric change. Quartz apparatus must be used for the separation of the keto and enol forms by fractional distillation (enol, b.p. 41°; keto, b.p. 33°, both at 2 mm pressure). The enol form is subject to intramolecular hydrogen bonding and is found in non-polar solvents, whilst the keto form forms intermolecular hydrogen bonds and predominates in polar solvents.

	Ethyl Acetoacetate	
Solvent	*% Keto form*	*% Enol form*
water	99·6	0·4
ethanol	89·5	10·5
hexane	53·6	46·4

The presence of the keto form can be demonstrated by the formation of an oxime with hydroxylamine and of an addition compound with sodium bisulphite. The enol form gives a red colour with ferric chloride, reacts with sodium, adds bromine across the double bond and, like 2,4-pentanedione, forms coordination compounds with metals.



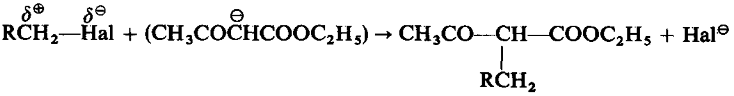
bis-(ethyl 3-oxobutanoato)copper(II)

Some of the most important reactions of ethyl acetoacetate are those of its stabilised anion with primary and secondary alkyl halides, acyl halides, haloketones and haloesters. The nucleophilic displacement of halogen atoms in these compounds produces mono- or disubstituted ethyl acetoacetates which may be hydrolysed so as to yield either a carboxylic acid or a ketone as the major product. The use of these reactions for the synthesis of acids and ketones is illustrated below in reactions (*a*)–(*c*).

(*a*) Formation of sodio ethyl acetoacetate.

$$CH_3COCH_2COOC_2H_5 \xrightarrow[\text{or NaH}]{NaOC_2H_5,\ NaNH_2} [CH_3COCHCOOC_2H_5]^{\ominus}Na^{\oplus}$$

(*b*) Reaction with an alkyl or acyl halide, etc.



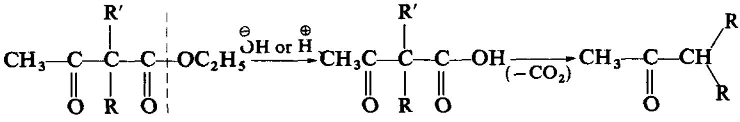
$$\overset{\delta\oplus}{RCH_2}-\overset{\delta\ominus}{Hal} + (CH_3CO\overset{\ominus}{C}HCOOC_2H_5) \rightarrow CH_3CO-\underset{\substack{|\\ RCH_2}}{CH}-COOC_2H_5 + Hal^{\ominus}$$

monoalkyl ethyl
acetoacetate

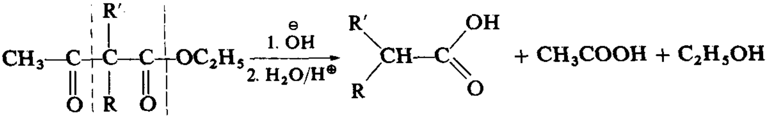
Steps (*a*) and (*b*) can be repeated on the monoalkyl ethyl acetoacetate to form a dialkyl derivative.

(*c*) Hydrolysis of the product from step (*b*) with dilute acid or alkali liberates a β-keto acid which loses carbon dioxide to form a ketone. Alkaline hydrolysis with concentrated alkali brings attack by hydroxyl ion at both carbonyl groups and the products, after acidification, are acetic and another carboxylic acid.

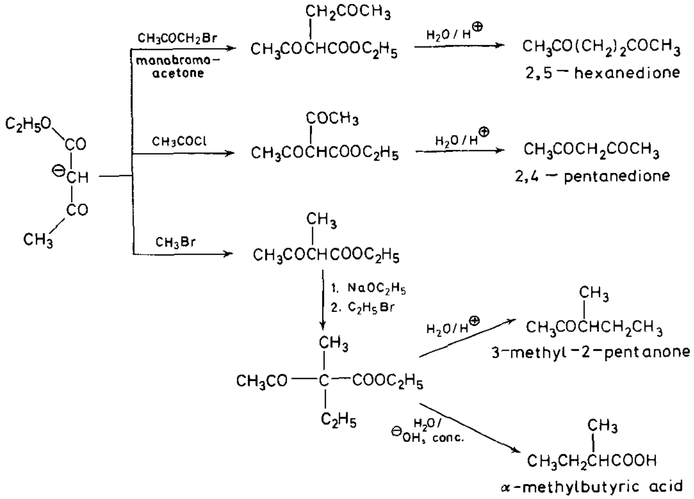
Dilute Acid or Alkali:



Concentrated Alkali:

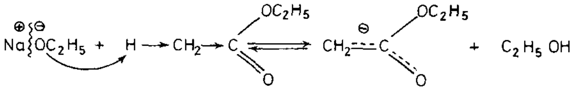


Thus ethyl acetoacetate can be used to prepare ketones of the type R′RCH—CO—CH_3 and carboxylic acids such as R′RCH—COOH, e.g.

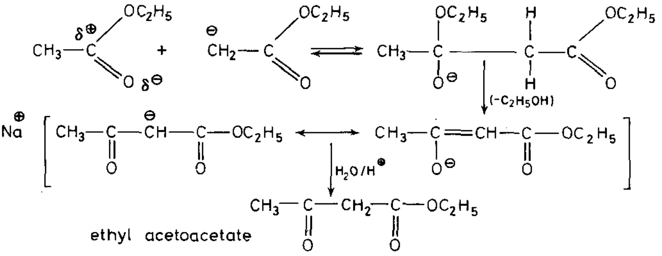


The diethyl malonate synthesis (page 210) is to be preferred for the synthesis of carboxylic acids since higher yields are normally obtained than with the ethyl acetoacetate route.

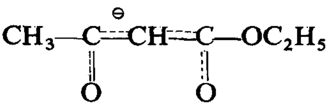
In the laboratory, ethyl acetoacetate is prepared from the self condensation of two molecules of ethyl acetate in the presence of a strong base. The process is termed the Claisen condensation and should be compared with the preparation of 2,4-pentanedione from sodio acetone and ethyl acetate (page 204). The base, which is often sodium ethoxide, detaches one of the weakly acidic hydrogen atoms from the methyl group adjacent to the carbonyl group.



The stabilised anion which is produced attacks a second molecule of ethyl acetate.

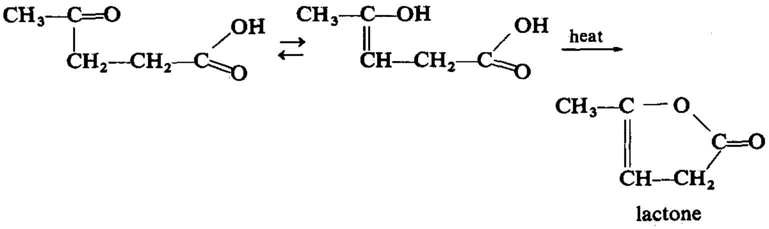


The condensation only proceeds to give a reasonable yield at equilibrium if the ethanol eliminated during the reaction is removed by reaction with sodium. As this last reaction evolves hydrogen, which is lost from the system, the equilibrium is displaced. To undergo the Claisen condensation an ester must have at least one hydrogen atom attached to the carbon atom adjacent to the carbonyl group otherwise it cannot form a stabilised anion.

The Aldol (section 8.2) and Claisen condensations are similar in mechanism. The only difference is that in the Claisen condensation the elimination of a second molecule of ethanol to form  $CH_3-\overset{\ominus}{\underset{\underset{O}{\|}}{C}}\cdots CH\cdots\underset{\underset{O}{\vdots}}{C}-OC_2H_5$ is spontaneous whereas the reaction can be halted prior to elimination in the Aldol condensation.

(c) 4-OXOPENTANOIC ACID OR LAEVULIC ACID

This acid is a stable, crystalline solid which gives independent reactions for a carbonyl group (formation of oximes, etc.) and for a carboxyl group (ester formation, etc.). As in 1,4-diketones the central —CH_2— groups are little more acidic than normal. However, the carbonyl and carboxyl groups are now sufficiently spaced to form stable, cyclic esters or lactones. Dehydration to the lactone occurs on prolonged heating and probably takes place via the enol form.



4-Oxopentanoic acid can be prepared by heating sucrose with concentrated hydrochloric acid or by reacting sodio ethyl acetoacetate with ethyl bromoacetate followed by ketonic hydrolysis with dilute acid or alkali.

12.3 HALOGENO ACIDS

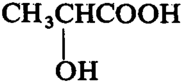
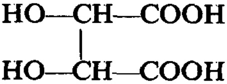
The hydrogen atoms attached to a carbon atom adjacent to a carboxyl group are specifically displayed by bromine in the presence of red phosphorus (section 8.2).

$$RCH_2\text{—}COOH \xrightarrow{Br_2/P} RCHBr\text{—}COOH$$

Displacement also occurs with chlorine and red phosphorus but reaction is not confined to the α-carbon atom and some substitution may occur at other carbon atoms. This method of preparing α-bromo or chlorocarboxylic acids is termed the Hell–Volhard–Zelinsky reaction. The reaction is of great value because the halogen atoms of α-halo acids readily undergo nucleophilic displacement (S_N2) by $I^{\ominus}$, $CN^{\ominus}$, $OH^{\ominus}$, NH_3 and other nucleophiles; a summary of these reactions is given on page 162.

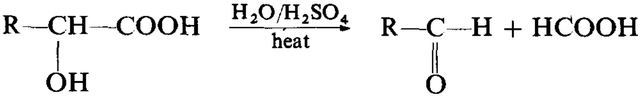
12.4 HYDROXY ACIDS

Hydroxy acids contain a hydroxyl group and a carboxyl group. The two groups may be α, β and γ, etc., to one another as illustrated by the following compounds.

$HOCH_2COOH$	hydroxyacetic acid or glycollic acid
 $CH_3\underset{\displaystyle OH}{\underset{\vert}{C}}HCOOH$	α-hydroxypropionic acid or lactic acid
 $CH_3\underset{\displaystyle OH}{\underset{\vert}{C}}HCH_2COOH$	β-hydroxybutyric acid
 $\begin{array}{l} HO{-}CH{-}COOH \\ \quad\;\; \vert \\ HO{-}CH{-}COOH \end{array}$	dihydroxysuccinic acid or tartaric acid

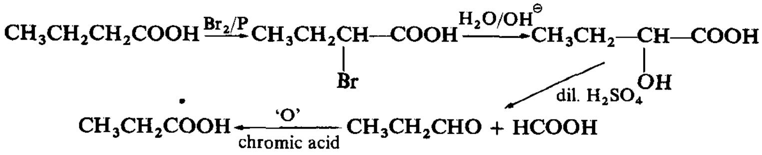
Hydroxy acids are water soluble compounds and like the amino acids many are optically active. Their reactions are those of a hydroxyl group and a carboxyl group, although the latter group can be masked by esterification, together with a few special reactions when the groups are α or β to one another. Ring closure, to form lactones, readily occurs with γ-hydroxy acids.

Oxidation of hydroxy acids with iron (II) sulphate and hydrogen peroxide (Fenton's reagent) produces keto acids. Hot dilute sulphuric acid cleaves α-hydroxy acids to an aldehyde and formic acid (cf. the behaviour of α-keto acids with this reagent, page 220).



$$R{-}\underset{\displaystyle OH}{\underset{\vert}{CH}}{-}COOH \xrightarrow[\text{heat}]{H_2O/H_2SO_4} R{-}\underset{\displaystyle O}{\underset{\Vert}{C}}{-}H + HCOOH$$

This reaction can form the basis of a method for descending a homologous series of carboxylic acids, e.g.

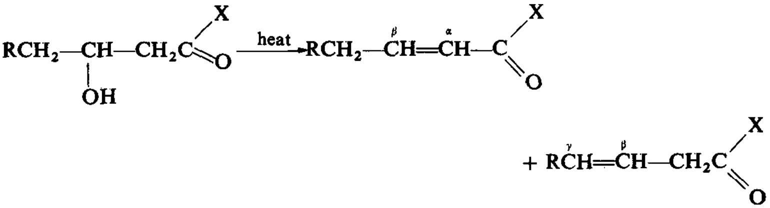


$$CH_3CH_2CH_2COOH \xrightarrow{Br_2/P} CH_3CH_2\underset{\displaystyle Br}{\underset{\vert}{CH}}{-}COOH \xrightarrow{H_2O/OH^{\ominus}} CH_3CH_2{-}\underset{\displaystyle OH}{\underset{\vert}{CH}}{-}COOH \xrightarrow{\text{dil. } H_2SO_4} CH_3CH_2CHO + HCOOH$$

$$CH_3CH_2COOH \xleftarrow[\text{chromic acid}]{\text{'O'}} CH_3CH_2CHO + HCOOH$$

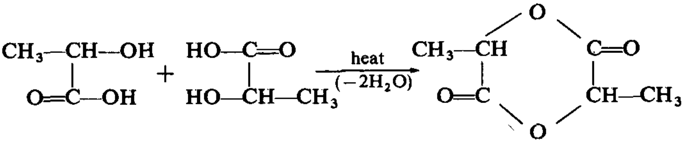
(Procedures for ascending a series of acids, see page 164.)

Beta-hydroxy carbonyl compounds readily lose water when either heated alone or with acid or base.

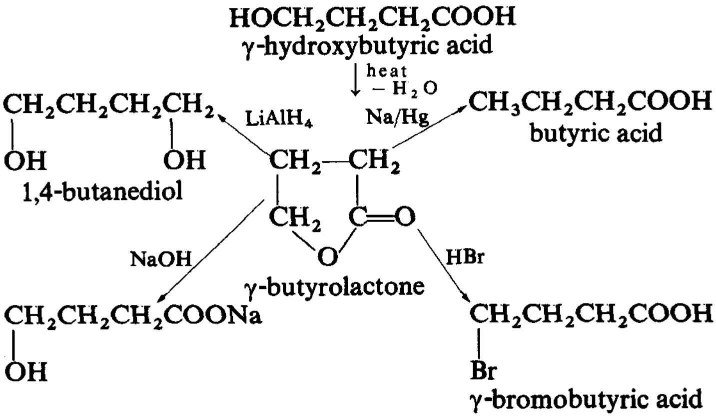


X = R′, H, OR′ or OH

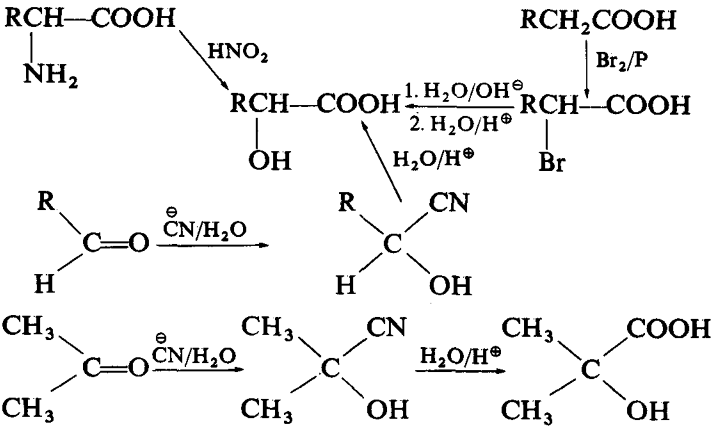
The product is largely an α,β-unsaturated carbonyl compound, but some of the β,γ-isomer is also formed. In contrast the action of heat on an α-hydroxy acid brings about dimerisation with the loss of two molecules of water. The product is a cyclic diester called a lactide.



Gamma-hydroxy acids also lose water when heated but this time from within one molecule, and the product is a cyclic ester or lactone. Beta-hydroxy acids undergo a similar reaction under special conditions. Lactones are reduced by lithium aluminium hydride to diols and by sodium amalgam to carboxylic acids. Aqueous alkali opens the lactone ring and reforms the hydroxy acid whilst a hydrogen halide forms a halogeno acid.

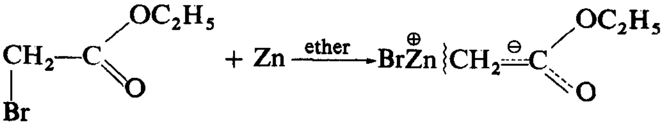


Hydroxy acids can be prepared by any of the routine methods used for the introduction of hydroxyl or carboxyl groups, e.g. hydrolysis of a halogeno acid, treatment of an amino acid with nitrous acid or hydrolysis of a cyanhydrin derived from an aldehyde or ketone.



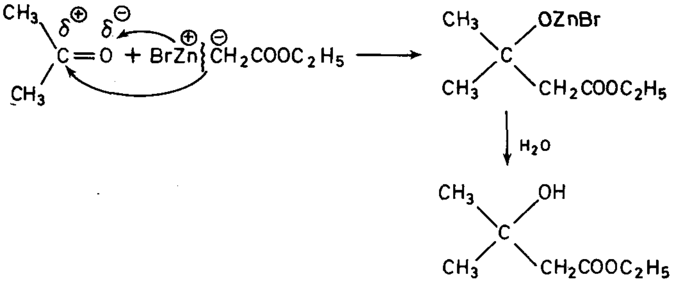
α-hydroxy-α-methyl-propionic acid

Hydroxy acids of the β and γ-type are more easily obtained by reducing the corresponding keto acids. The Reformatsky reaction, however, provides a direct route to β-hydroxy acids. An α-bromoester is reacted with zinc and an aldehyde or ketone in dry ether solution. Organozinc compounds are first produced, e.g.



bromoacetic ester

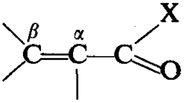
The organozinc compound behaves like a Grignard reagent and adds to the carbonyl group of the aldehyde or ketone. The organozinc derivative is used in preference to the organomagnesium compound because the latter would react with the ester grouping (page 146).



ethyl β-hydroxy-β-methylbutyrate

12.5 α,β-UNSATURATED CARBONYL COMPOUNDS

All the compounds described in this section possess the group:



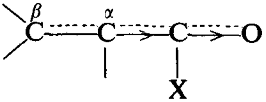
where X = H, R, Ar, OH, or OR.

The three carbon atoms are sp^2-hybridised so that the carbonyl group and the carbon–carbon double bond are conjugated due to some degree of overlap between their π molecular orbital systems. α,β-Unsaturated carbonyl compounds exhibit reactions of the carbonyl group and of the alkene double bond plus some reactions of the conjugated system, cf. 1,4-addition to 1,3-butadiene (section 5.4).

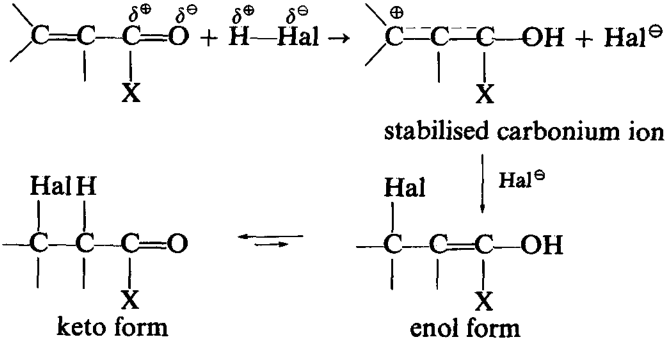
Many α,β-unsaturated carbonyl compounds are known by trivial names and these, together with systematic names, are listed below for some of the commonly encountered compounds of this class.

Formula	*Systematic name*	*Trivial name*
$CH_2{=}CH{-}CHO$	propenal	acrolein
$CH_3CH{=}CH{-}CHO$	2-butenal	crotonaldehyde
$C_6H_5CH{=}CH{-}CHO$	3-phenylpropenal	cinnamaldehyde
$CH_2{=}CH{-}COOH$	propenoic acid	acrylic acid
$CH_3CH{=}CH{-}COOH$	2-butenoic acid	crotonic acid
$C_6H_5CH{=}CH{-}COOH$	3-phenylpropenoic acid	cinnamic acid
$CH_2{=}\underset{\displaystyle CH_3}{\underset{\vert}{C}}{-}COOH$	2-methylpropenoic acid	methacrylic acid
$CH_2{=}CH{-}CO{-}CH_3$	1-buten-3-one	methyl vinyl ketone
$C_6H_5CH{=}CH{-}CO{-}CH_3$	1-phenyl-1-buten-3-one	benzal acetone

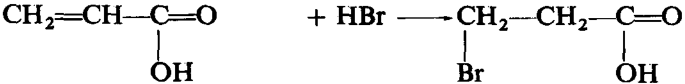
In the α,β-unsaturated carbonyl system:

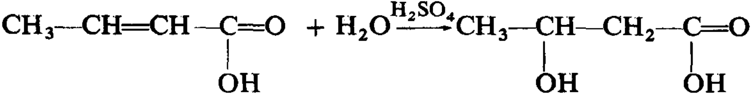


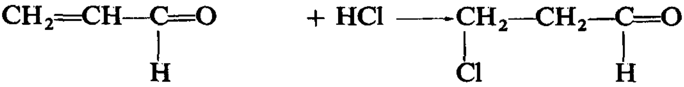
the carbonyl group attracts electrons by both the inductive and mesomeric routes. Therefore, electrophiles add more slowly to the carbon–carbon double bond in α,β-unsaturated carbonyl compounds than to isolated double bonds. Addition is of the 1,4-type with the positive end of the addendum attacking the most negative centre, i.e. the carbonyl group. The carbonium ion initially produced is stabilised by the delocalisation of the positive charge over three carbon atoms.

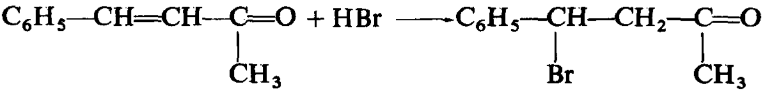


The most stable product is then formed by the addition of halide ion to the β-position. Finally enol → keto tautomerism takes place since the keto is normally more stable than the enol form. Some examples of addition reactions to α,β-unsaturated carbonyl compounds are as follows.

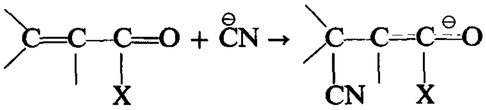

$$CH_2{=}CH{-}\underset{\displaystyle OH}{C}{=}O + HBr \longrightarrow \underset{\displaystyle Br}{CH_2}{-}CH_2{-}\underset{\displaystyle OH}{C}{=}O$$


$$CH_3{-}CH{=}CH{-}\underset{\displaystyle OH}{C}{=}O + H_2O \xrightarrow{H_2SO_4} CH_3{-}\underset{\displaystyle OH}{CH}{-}CH_2{-}\underset{\displaystyle OH}{C}{=}O$$

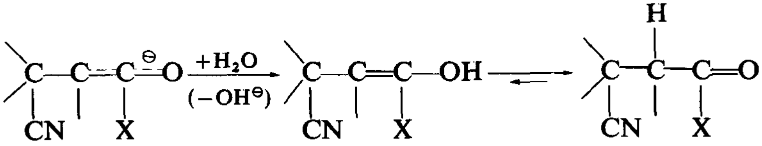

$$CH_2{=}CH{-}\underset{\displaystyle H}{C}{=}O + HCl \longrightarrow \underset{\displaystyle Cl}{CH_2}{-}CH_2{-}\underset{\displaystyle H}{C}{=}O$$


$$C_6H_5{-}CH{=}CH{-}\underset{\displaystyle CH_3}{C}{=}O + HBr \longrightarrow C_6H_5{-}\underset{\displaystyle Br}{CH}{-}CH_2{-}\underset{\displaystyle CH_3}{C}{=}O$$

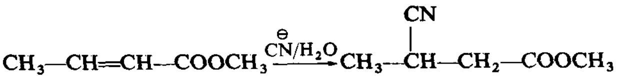
A second mode of attack on α,β-unsaturated carbonyl compounds is by nucleophiles. The electron withdrawing carbonyl group reduces the electron density at the double bond to such an extent that nucleophiles will attack the β-carbon atom. The resulting anion is stabilised by delocalisation of the negative charge.



The most negative atom of the stabilised anion, i.e. the oxygen atom, then abstracts a proton from the solvent and enol → keto tautomerism gives the final product.

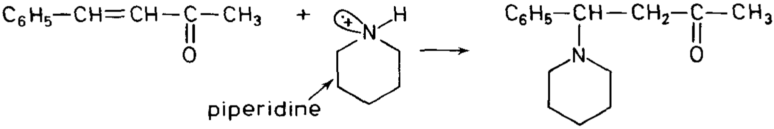


This reaction takes place with nucleophiles such as $\overset{\ominus}{C}N$, NH_3, NH_2R, NH_2OH, $\overset{\ominus}{C}H(COOC_2H_5)_2$ and $CH_3CO\overset{\ominus}{C}HCOOC_2H_5$, e.g.

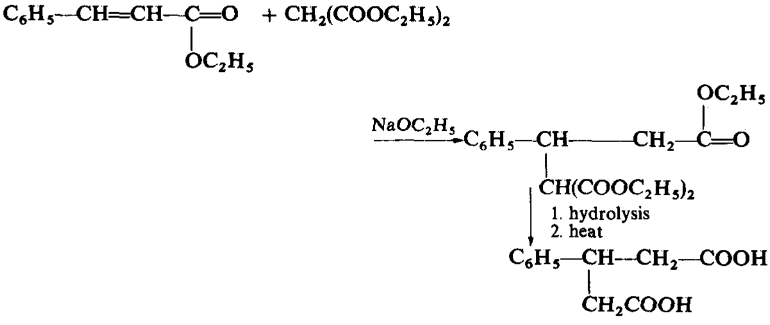


$$CH_3{-}CH{=}CH{-}COOCH_3 \xrightarrow{\overset{\ominus}{C}N/H_2O} CH_3{-}\overset{\overset{CN}{|}}{C}H{-}CH_2{-}COOCH_3$$

methyl 2-butenoate　　　methyl 3-cyanobutanoate



The nucleophilic addition of diethyl malonate or ethyl acetoacetate anions to α,β-unsaturated carbonyl compounds is known as the Michael Addition reaction, e.g. the addition of diethyl malonate to ethyl cinnamate in the presence of sodium ethoxide.

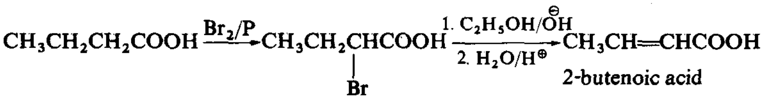


$$C_6H_5-CH=CH-\underset{\substack{|\\OC_2H_5}}{C}=O + CH_2(COOC_2H_5)_2 \xrightarrow{NaOC_2H_5} C_6H_5-\underset{\substack{|\\CH(COOC_2H_5)_2}}{CH}-CH_2-\overset{\substack{OC_2H_5\\|}}{C}=O \xrightarrow[\text{2. heat}]{\text{1. hydrolysis}} C_6H_5-\underset{\substack{|\\CH_2COOH}}{CH}-CH_2-COOH$$

β-phenylglutaric acid

Hydrolysis and decarboxylation of the initial product gives a dicarboxylic acid.

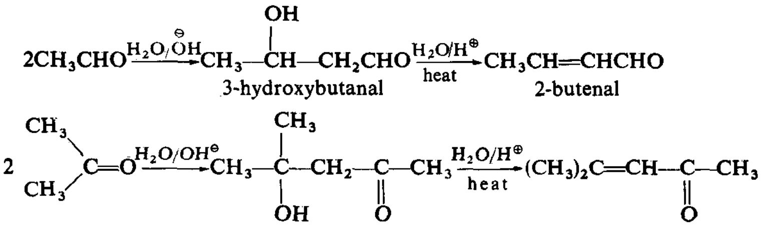
α,β-Unsaturated carbonyl compounds can be prepared by normal synthetic methods, e.g. elimination of hydrogen halide to produce a double bond.



$$CH_3CH_2CH_2COOH \xrightarrow{Br_2/P} CH_3CH_2\underset{\substack{|\\Br}}{C}HCOOH \xrightarrow[2.\ H_2O/H^\oplus]{1.\ C_2H_5OH/\overset{\ominus}{O}H} CH_3CH=CHCOOH$$

2-butenoic acid

Some specific reactions are also important. Thus the Aldol condensation reaction (page 155), after dehydration of the initial product, yields α,β-unsaturated aldehydes and ketones.



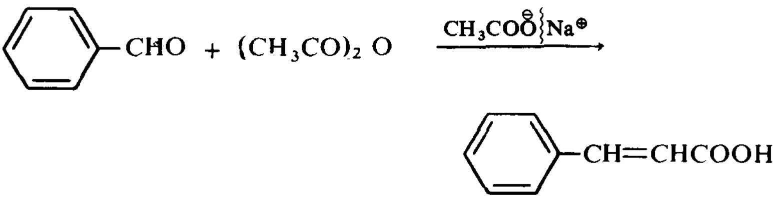
$$2CH_3CHO \xrightarrow{H_2O/\overset{\ominus}{O}H} CH_3-\overset{\substack{OH\\|}}{C}H-CH_2CHO \xrightarrow[\text{heat}]{H_2O/H^\oplus} CH_3CH=CHCHO$$

3-hydroxybutanal 2-butenal

$$2\ (CH_3)_2C=O \xrightarrow{H_2O/OH^\ominus} CH_3-\overset{\substack{CH_3\\|}}{\underset{\substack{|\\OH}}{C}}-CH_2-\underset{\substack{\|\\O}}{C}-CH_3 \xrightarrow[\text{heat}]{H_2O/H^\oplus} (CH_3)_2C=CH-\underset{\substack{\|\\O}}{C}-CH_3$$

2-methyl-2-penten-4-one
(mesityl oxide)

The Perkin Reaction (page 157) produces α,β-unsaturated carboxylic acids.



cinnamic acid

13

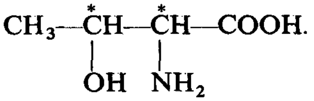
Stereochemistry II

13.1 OPTICALLY ACTIVE SUBSTANCES WITH TWO ASYMMETRIC CARBON ATOMS

In Chapter 2 the origin of optical activity in substances containing one asymmetric carbon atom was briefly described. Substances containing two or more asymmetric atoms are not, however, necessarily optically active. The optical activity of the various asymmetric centres in the molecule may cancel out. For convenience, substances pòssessing two asymmetric centres may be divided into two types (*a*) those with two different asymmetric centres and (*b*) those with two similar centres.

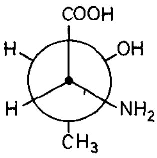
(a) SUBSTANCES HAVING TWO DIFFERENT ASYMMETRIC CENTRES

Compounds of this type can be represented in a general way as Ca b d . Ca b e or Ca b d . Cx y z, etc. Many examples of such compounds could of course be described but this discussion will be restricted to the amino acid, threonine (page 272).

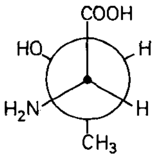


$$CH_3-\underset{\displaystyle OH}{\underset{|}{\overset{*}{C}H}}-\underset{\displaystyle NH_2}{\underset{|}{\overset{*}{C}H}}-COOH.$$

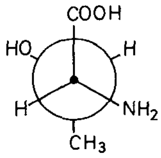
Four different configurations can be written for this compound.



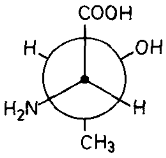
(Ia)



(Ib)



(IIa)

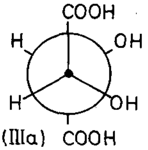


(IIb)

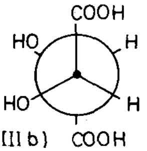
All the configurations result in optical activity and Ia and Ib are *enantiomers* as are IIa and IIb. Structures Ia and IIa are related in that their front carbon atoms have the same configuration; they are stereoisomers but not mirror images and are termed *diastereoisomers.* Rotation of the rear asymmetric carbon atom of IIa does not produce Ia; structure IIa can only be converted into Ia by the breaking and reforming of bonds. Diastereoisomers usually have substantially different physical properties whereas enantiomers are identical except in their behaviour towards polarised light and optically active reagents. Thus threonine exists in four stereoisomeric forms and in general a molecule having N different asymmetric centres will have 2^N optical isomers.

(b) SUBSTANCES WITH TWO SIMILAR ASYMMETRIC CENTRES

The representation Ca b d . Ca b d may be used for this type of substance, e.g. 2,3-dibromobutane, $CH_3—CHBr—CHBr—CH_3$, tartaric acid (dihydroxysuccinic acid) COOH—CHOH—CHOH—COOH and *cis*-1,2-cyclopentanediol. These substances exist in three stereoisomeric forms of which only two are optically active, e.g. tartaric acid.

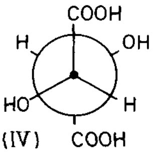


(IIIa)



(IIIb)

(±)-tartaric acids

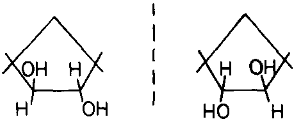


(IV)

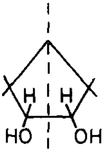
meso-tartaric acid

Configurations IIIa and IIIb are enantiomers and represent (+) and (−)-tartaric acids (m.p. 170°). These configurations contain no plane or centre of symmetry and are dissymmetric. Configuration IV is optically inactive and is called *meso*-tartaric acid (m.p. 140°). Meso compounds are said to be internally compensated, for the optical activity of one asymmetric centre cancels out that of the other centre. This is easily demonstrated, for if the rear carbon atom of structure IV is rotated by 180° then the front half of the molecule becomes the mirror image of the rear half, i.e. the molecule contains a plane of symmetry. In addition structure IV has a centre of symmetry mid-way between the two asymmetric carbon atoms; from this point a line drawn to an atom or group on one side of the C—C bond will meet a similar atom or group when projected by a similar distance on the other side of the bond.

In the case of the *cis* and *trans*-1,2-cyclopentanediols the *cis* isomer is the meso form since this configuration contains a plane of symmetry. The *trans* isomer is dissymmetric and so forms a pair of enantiomers which can be separated. Thus one method of distinguishing between the *cis* and *trans* isomers of this diol is that only the *trans* isomer undergoes resolution into two optically active forms.



trans-1,2-cyclopentanediols
(resolvable)



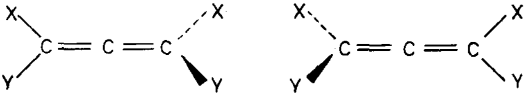
cis-1,2-cyclopentanediol
(meso form)

13.2 OPTICALLY ACTIVE COMPOUNDS HAVING NO ASYMMETRIC CARBON ATOMS

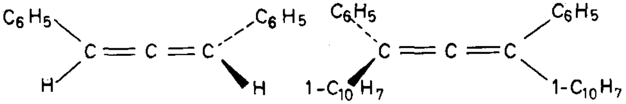
The three classes of compounds usually described in this context are allenes, biphenyls and spiranes.

(a) ALLENES

Substituted allenes, of the type shown below, can in principle undergo resolution into a pair of enantiomers providing that X and Y are different atoms or groups.



In practice the preparation and resolution of suitable allenes is a difficult task. Allenes such as 1,3-diphenylallene and 1,3-diphenyl-1,3-di(1-naphthyl)allene have been prepared and separated into their dextro and levorotatory forms.



The reason for the dissymmetry of allenes is that the two terminal groups lie in planes at right angles to one another due to the *sp*-hybridisation of the central carbon atom (*Figure 13.1*).

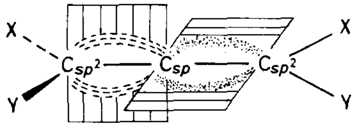
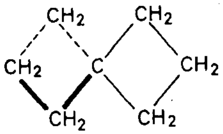


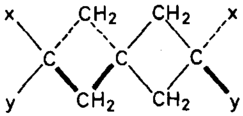
Figure 13.1. Spatial arrangement of groups in an allene

(b) SPIRANES

Spiranes are bicyclic compounds in which the two rings are fused at one sp^3-hybridised carbon atom, e.g. spiro[3.3]heptane.

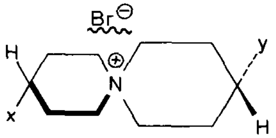


The two rings are held rigidly at right angles to one another due to the tetrahedral symmetry of the central carbon atom. Substitution of both rings in the same way as for allenes leads to dissymmetry.

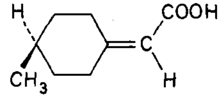


Examples of substituted spiro[3.3]heptanes that have been resolved are the 2,5-dicarboxylic acid (x = H, y = COOH) and the 2,5-diamine (x = H, y = NH_2).

More complex examples of optical activity associated with spiranes are known. For example the atom used to fuse the two rings need not be carbon; spiro ammonium compounds like the salt V have been resolved. Similarly alkylidenecycloalkanes, such as the acid VI, which is in effect half spirane and half allene, have been resolved into their optically active forms.



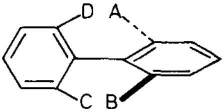
a spirobispiperidinium bromide (V)



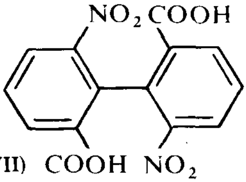
4-methylcyclohexylidene acetic acid (VI)

(c) BIPHENYLS

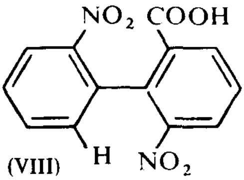
In unsubstituted biphenyl free rotation is possible about the 1,1′-bond. The molecule has a plane of symmetry and so does not exhibit optical activity.



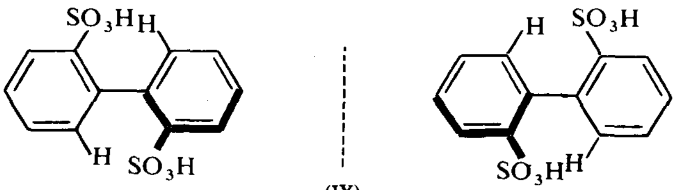
If, however, bulky groups are attached to at least the 2 and 2′ positions, and possibly also the 6 and 6′, then free rotation about the 1,1′-bond is prevented. Then, providing that A is different from B and C from D, no plane of symmetry will exist in the molecule. For example the dicarboxylic acid VII, the carboxylic acid VIII and the disulphonic acid IX have all been resolved.



(VII)

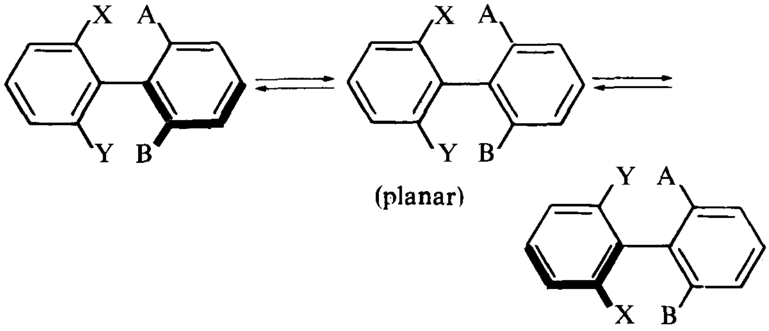


(VIII)



(IX)

The ease of racemisation of an optically active biphenyl depends on the size of the groups in the 2, 2′, 6 and 6′ positions. The smaller these groups are the more easily a planar conformation, which leads to racemisation, can be achieved.



To sum up, dissymmetry in allenes and spiranes results from the directional properties of bonds and this is associated with the hybridisation states of certain atoms. In biphenyls optical activity can result from steric hindrance which prevents free rotation about a single bond, so forcing the molecule into a dissymmetric configuration.

13.3 RACEMIC MODIFICATIONS, RESOLUTION AND RACEMISATION

(*a*) A racemic modification contains equal amounts of the dextro and levorotatory enantiomers. The optical activity of the two forms cancels out and so the racemic modification is optically inactive.

Racemic modifications can exist in three physical forms. (*i*) *The Racemic Mixture*—This consists of equal amounts of the dextro and levo crystalline forms. Two distinct phases are present. Racemic modifications rarely form the two types of crystal that can be identified as mirror images of one another. Pasteur in 1848 observed that sodium ammonium tartrate existed in mirror image crystalline forms and separated the two forms using tweezers and a hand lens. The two types of crystal produced equal but opposite specific rotations. This marked the first resolution of an optically inactive material into its optically active enantiomers.

(*ii*) *The Racemic Compound*—In this case each crystal contains equal amounts of the dextro and levorotatory forms.

(*iii*) *The Racemic Solid Solution*—The enantiomers are isomorphous and crystallise in the same crystal to give a solid solution.

In the racemic compound and solid solution only one phase is present and so Pasteur's method of mechanical separation cannot be applied. Other methods of resolution must then be attempted.

(b) The resolution or separation of a racemic modification into its optically active components is often a difficult problem. As the enantiomers have identical physical properties they cannot be separated by fractional distillation, crystallisation, etc. The yields of each optical isomer from the resolution process are frequently poor and several methods may have to be tried before a satisfactory procedure is found.

(*i*) *Resolution by Mechanical Separation*—This technique can only be applied to a small number of racemic mixtures, such as sodium ammonium tartrate.

(*ii*) *Resolution by Selective Adsorption*—Column chromatography is sometimes successful when the adsorbent is optically active. The racemic modification is dissolved in a solvent and applied to the column. The column is then eluted with the same or a different solvent and the enantiomers are desorbed at different rates and collected as separate fractions. A number of adsorbents have been used, e.g. lactose or (+)-camphorsulphonic acid coated on silica. In paper chromatography optically active cellulose has been used and in gas–liquid chromatography optically active stationary phases can produce resolution.

(*iii*) *Resolution by Conversion into Diastereoisomers*—This is the most general and widely used method for the resolution of enantiomers. The enantiomers are reacted with a suitable optically active substance so as to convert them into diastereoisomers. The two diastereoisomers usually have different physical properties. e.g. solubilities, and can be separated by physical methods such as fractional crystallisation. The outline scheme for racemic acids and bases is:

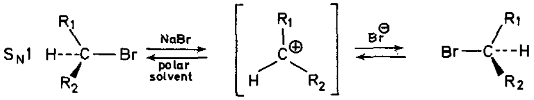
Enantiomers	*Resolving agent*	*Diastereoisomers*
[(+)-acid, (−)-acid] +	2(+)-base →	[(+)-acid, (+)-base] +
		+ [(−)-acid, (+)-base]
[(+)-base, (−)-base] +	2(+)-acid →	[(+)-base, (+)-acid] +
		+ [(−)-base, (+)-acid]

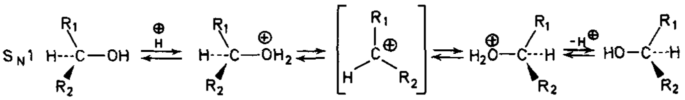
When the diastereoisomers have been separated the enantiomers must be regenerated with acid or alkali in such a way that racemisation does not occur. The alkaloids brucine, strychnine and quinine are naturally occurring, optically active bases which can be used to separate racemic acids. Optically active acids such as tartaric acid, camphor-10-sulphonic acid and malic acid are used to resolve racemic bases. Several resolving agents may have to be tried before separable diastereoisomers are obtained. Alternatively one diastereoisomer may be obtained pure whilst the other may have to be decomposed and the product resolved again with a second resolving agent.

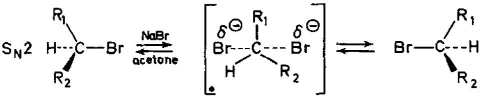
Resolution by conversion into diastereoisomers is not confined to acids and bases. For example racemic alcohols can be esterified with an optically active acid or converted to an acid-ester with phthalic anhydride and then resolved in the same way as a racemic acid.

(*c*) Racemisation, that is the conversion of an optically active substance into an inactive mixture of enantiomers, can occur in a variety of ways depending on the chemical properties of the substance. The process is illustrated by the following examples.

(*i*) Optically active alkyl halides and alcohols racemise via S_N1 and S_N2 substitution.

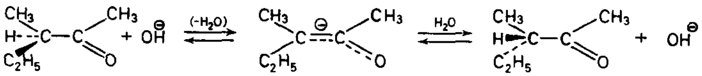






In each case the continual interconversion between the two forms eventually produces equal amounts of each enantiomer and racemisation is then complete.

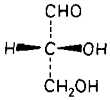
(*ii*) Compounds containing a carbonyl group adjacent to an asymmetric centre are racemised by acids or bases due to their catalytic effect on the keto ⇌ enol interconversion.



(*iii*) Optically active biphenyls racemise when rotation occurs about the 1,1′-bond, i.e. when a planar conformation is attained (page 238). Racemisation can usually be brought about by heat or ultra-violet radiation.

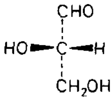
13.4 ABSOLUTE AND RELATIVE CONFIGURATIONS

Until as recently as 1949 it was not known which configurational isomer of any pair of enantiomers corresponded to the dextro or levorotatory forms. The Absolute Configuration of a (+) or (−) optical isomer was unknown. To get round this difficulty (+)-glyceraldehyde had quite arbitrarily been assigned the structure X and hence the (−) isomer had the configuration XI.



$$\begin{array}{c} CHO \\ H-C-OH \\ CH_2OH \end{array}$$

D-(+)-glyceraldehyde (X)



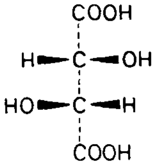
$$\begin{array}{c} CHO \\ HO-C-H \\ CH_2OH \end{array}$$

L-(-)-glyceraldehyde (XI)

The letters D and L refer to the absolute configuration; D indicates the case where the substituent, in this case the —OH group, is on the right of the asymmetric centre and L to where the group is on the left.

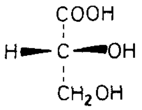
Quite by chance the configurations assigned to glyceraldehyde turned out to be correct. The configuration of sodium rubidium (+)-tartrate was determined by x-ray diffraction techniques and this showed that the absolute configuration of (+)-tartaric acid is:

D-(+)-tartaric acid

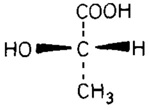


$$\begin{array}{c} COOH \\ H-C-OH \\ HO-C-H \\ COOH \end{array}$$

Now optically active compounds can be converted into other substances and the configuration about the asymmetric centre will remain unchanged providing that none of the bonds to the centre are broken. Alternatively if such bonds are broken but the mechanism of the reaction is known then the resulting configuration may be deduced, e.g. S_N2 substitution would produce an inversion of configuration. In this way the configurations of a series of compounds can be related and it was known that (+)-glyceraldehyde had the same configuration as D-(+)-tartaric acid. Optical isomers related to D-(+)-glyceraldehyde need not be dextrorotatory, e.g. D-(−)-glyceric acid and L-(+)-lactic acid.



D-(−)-glyceric acid



L-(+)-lactic acid

Many substances which are produced from natural sources such as sugars and amino acids (Chapter 15) often have a complex structure and may possess a number of asymmetric centres. The particular centre chosen for relation to D-(+)-glyceraldehyde is, therefore, somewhat random and the assigned configuration is relative rather than absolute. As might be expected, some ambiguity can arise when the configurations of such compounds are compared. A more precise method of dealing with configurations has been suggested and is known as the Cahn–Ingold–Prelog Sequence Rule [see *Stereochemistry of Carbon Compounds* by Eliel, (Further Reading section, page 300)].

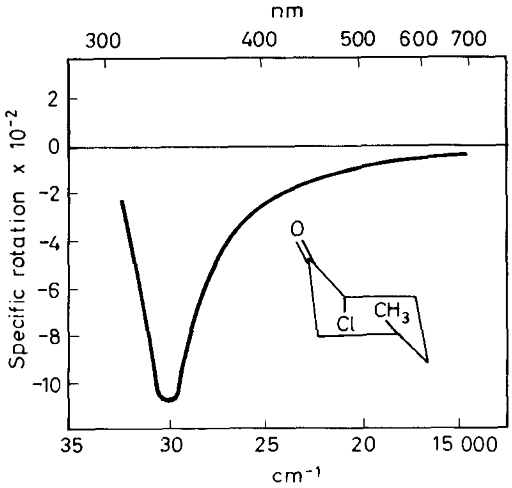


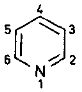
Figure 13.2. Optical rotatory dispersion curve of trans-*2-chloro-5-methylcyclohexanone*

For most optical isomers the specific rotation at the sodium D line (17000 cm^{-1}, 589 nm) is small compared with that at higher frequencies where the molecule absorbs radiation. An example is the record of specific rotation against frequency for the ketone, *trans*-2-chloro-5-methylcyclohexanone (*Figure 13.2*). This is termed an Optical Rotatory Dispersion curve. The $n \rightarrow \pi^*$ transition (section 4.3) of the carbonyl group is associated with a zero specific rotation and this would occur near 33000 cm^{-1} (300 nm). A large negative specific rotation is observed at 30000 cm^{-1}.

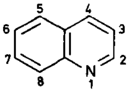
14

Heterocyclic Aromatic Compounds

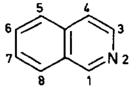
The heterocyclic compounds discussed in this chapter exhibit aromatic properties in varying degrees. They contain only one heteroatom, i.e. nitrogen, oxygen or sulphur, in a ring with four or five carbon atoms.



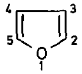
pyridine



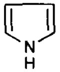
quinoline



iso-quinoline



furan



pyrrole

thiophene

There are many examples of much more complex heterocyclic systems and some of these are of great biological importance (see page 275). The five and six membered ring systems are treated separately and their reactions compared with those of various benzene derivatives.

A. FIVE MEMBERED RING SYSTEMS WITH ONE HETEROATOM

14.1 OCCURRENCE OF PYRROLE, FURAN AND THIOPHENE

Pyrrole is found in coal tar and bone oil distillates. The system of four pyrrole rings linked together as in haemin occurs in many natural substances, e.g. alkaloids and chlorophyll. A characteristic reaction of pyrrole and its derivatives is the bright red colour which it imparts to pine wood moistened with mineral acid.

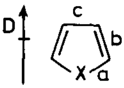
Furan is prepared commerically from furan-2-aldehyde (furfural). This aldehyde is the mineral acid dehydration product of pentose sugars present in oat husks.

Thiophene can be isolated from the benzene fraction of coal tar and is also present in crude oil. With isatin and concentrated sulphuric acid thiophene gives a characteristic blue colour. This colour reaction led to the discovery of thiophene in benzene distilled from coal tar since a synthetic sample of benzene did not give the colour reaction.

14.2 STRUCTURE OF PYRROLE, FURAN AND THIOPHENE

The molecular dimensions, dipole moments and boiling points of the three heterocycles are set out in *Table 14.1*.

Table 14.1

		Bond lengths (Å)			Dipole moment (D)	B.Pt. (°C)	Electro-negativity of X
		a	*b*	*c*			
	Pyrrole	1·38	1·37	1·43	1·8	131	3·05
	Furan	1·37	1·35	1·44	0·7	32	3·50
	Thiophene	1·72	1·35	1·45	1·8	84	2·60

(a) PYRROLE

All three heterocycles can in principle form a sextet of electrons (page 112) and should, therefore, exhibit aromatic properties. Their chemistry is governed by the ease with which this sextet of electrons is formed and in turn this largely depends on the electronegativity of the heteroatom.

In pyrrole the four carbon atoms are sp^2-hybridised and the overlap of their p atomic orbitals with the unshared pair of the nitrogen atom produces a π molecular orbital containing six electrons, as in benzene (see *Figure 14.1*).

However, delocalisation is not as efficient in pyrrole as in benzene

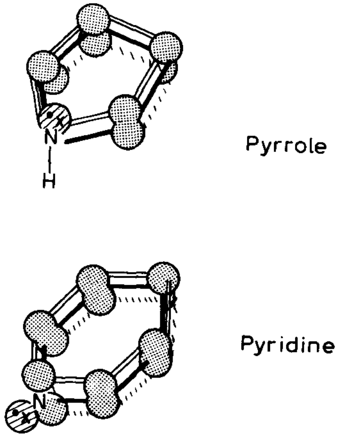


Figure 14.1. Structure of pyrrole and pyridine

because the nitrogen atom is more electronegative than the carbon atoms. In spite of this the dipole moment of 1·8 D indicates that a considerable fraction of the lone pair is donated to the molecular orbital system of the ring. Protonation of the lone pair of course destroys any aromatic properties as then it is no longer possible to form a sextet of electrons.

(b) FURAN

Furan has a similar structure to pyrrole except that the electron pair, required to form the aromatic sextet, comes from oxygen rather than nitrogen. Oxygen is more electronegative than nitrogen and so donates an unshared pair less readily. Furan, therefore, has more difficulty in forming an aromatic sextet than pyrrole and so shows fewer aromatic properties. In agreement with this view the dipole moment of furan is only 0·7 D whilst that of pyrrole is 1·8 D.

(c) THIOPHENE

In thiophene the electron pair comes from sulphur. Sulphur donates electrons more readily than either oxygen or nitrogen since it is the least electronegative of these three elements. On the other hand the lone pair of sulphur ($3sp^3$) will overlap less well with the carbon atomic orbitals ($2p$) than the lone pairs of either oxygen or nitrogen ($2sp^3$). The C—S bonds are longer than either the C—O or C—N bonds and so thiophene is less regular in shape than the pyrrole or furan ring systems.

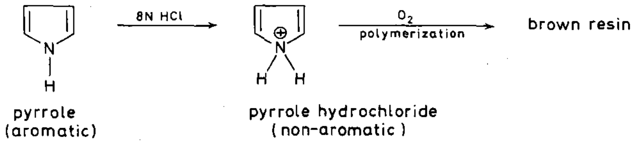
14.3 CHEMICAL REACTIONS OF PYRROLE, FURAN AND THIOPHENE

(a) PYRROLE

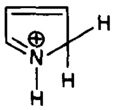
Pyrrole is both a weak base and a weak acid. The heterocycle possesses some aromatic character in neutral or weakly acidic solutions. Electrophilic substitution occurs very readily and thus is successful with mild reagents. The high reactivity of pyrrole towards electrophiles indicates resemblances to phenol and the phenoxide ion.

(*i*) *Acidic and basic properties of pyrrole*

With hydrochloric acid (8N) pyrrole exhibits basic characteristics and forms a crystalline hydrochloride. This salt is only stable in the absence of oxygen, for otherwise polymerisation rapidly occurs to produce a brown resin.



There is evidence that pyrrole hydrochloride may be



rather than

.

Pyrrole is an extremely weak acid but forms salts with solid potassium hydroxide or potassium metal. The pyrryl anion may be slightly stabilised by delocalisation of the negative charge over the ring but, like alkoxides, pyrryl potassium is instantly hydrolysed by water. The pyrryl anion acts as a nucleophile, e.g. towards alkyl halides.

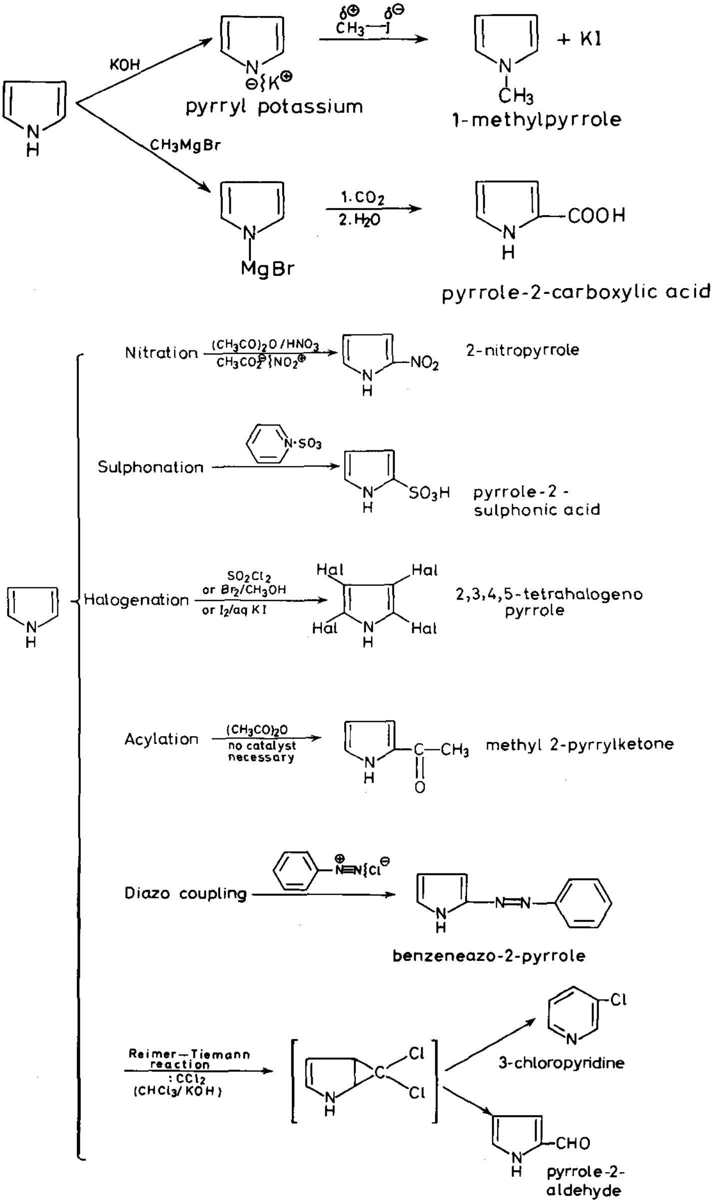

KOH
δ⊕ δ⊖ CH3—I
pyrryl potassium
+ KI
1-methylpyrrole
CH3MgBr
MgBr
1. CO2
2. H2O
COOH
pyrrole-2-carboxylic acid
Nitration
(CH3CO)2O / HNO3
CH3CO2⊖{NO2⊕
NO2
2-nitropyrrole
N·SO3
Sulphonation
SO3H
pyrrole-2-sulphonic acid
Halogenation
SO2Cl2
or Br2/CH3OH
or I2/aq KI
Hal
2,3,4,5-tetrahalogeno pyrrole
Acylation
(CH3CO)2O
no catalyst necessary
methyl 2-pyrrylketone
Diazo coupling
N≡N{Cl⊖
benzeneazo-2-pyrrole
Reimer—Tiemann reaction
:CCl2
(CHCl3/KOH)
Cl
3-chloropyridine
CHO
pyrrole-2-aldehyde

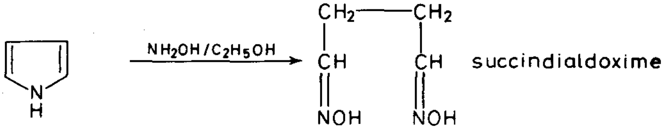
Figure 14.2

(*ii*) *Electrophilic substitution*

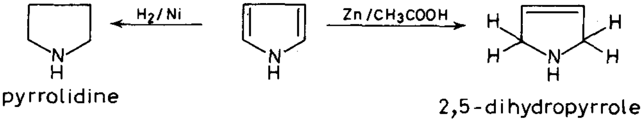
Electrophilic substitution takes place at the 2 position or, if this is blocked, at the 3 position. Calculations indicate that the π electron density at the 2 position (1·096) is higher than at the 3 position. Substitution is only successful if strongly acidic solutions, leading to protonation and hence polymerisation, are avoided (see *Figure 14.2*).

(*iii*) *Ring opening and other reactions*

Boiling ethanolic hydroxylamine opens the pyrrole ring to yield the dioxime of succindialdehyde.



The 1,3-diene behaviour of pyrrole is very limited, unlike that of furan. Maleic anhydride does not add to pyrrole. Reduction of pyrrole with zinc and acetic acid does, however, yield 2,5-dihydropyrrole. Catalytic reduction completely hydrogenates the ring system and produces pyrrolidine.

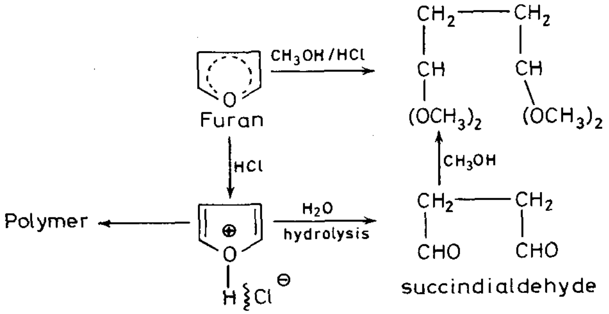


(b) FURAN

Furan, like pyrrole, is a weak base. Furan is less aromatic in character than pyrrole and shows more properties of a 1,3-diene, e.g. furan undergoes a Diels–Alder reaction.

(*i*) *Basic properties*

Furan forms unstable salts with mineral acids. These salts may polymerise or alternatively hydrolyse to succindialdehyde. With methanol and hydrochloric acid the diacetal of succindialdehyde is formed.



(ii) *Electrophilic substitution*

Electrophilic substitution takes place extremely readily and the 2 position is attacked. Decomposition of the ring system occurs with all but the mildest reagents (*Figure 14.3*).

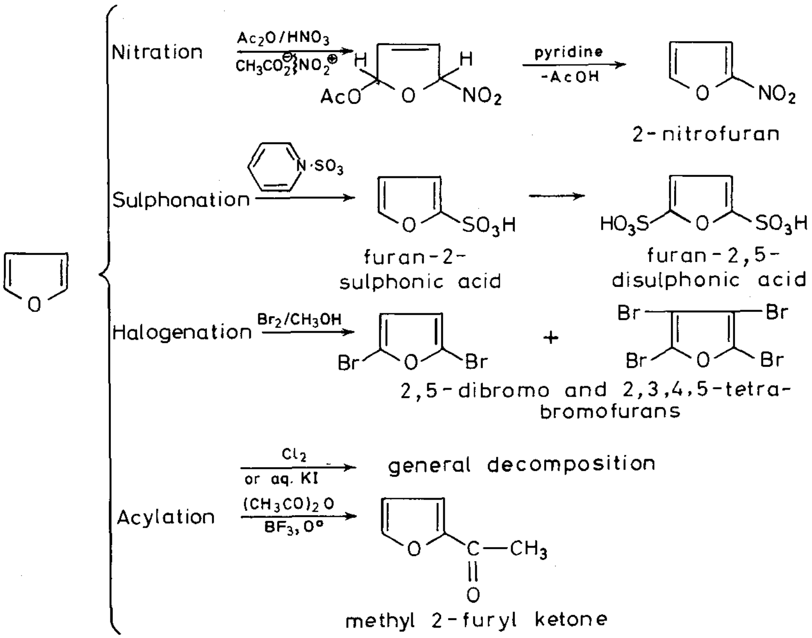
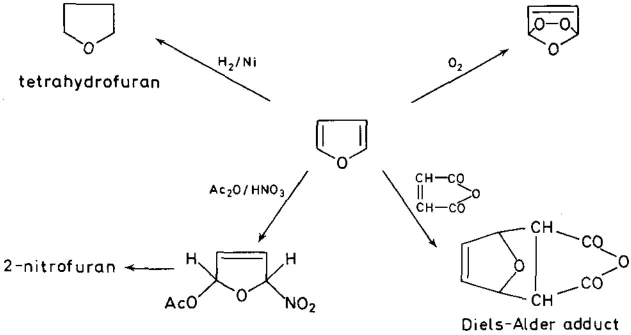


Figure 14.3

(*iii*) *Addition and other reactions*

Furan has sufficient diene character to undergo Diels–Alder addition by maleic anhydride across the 2 and 5 positions. With air or oxygen a peroxide can be isolated and the first step in nitration (acetic anhydride/nitric acid) involves addition at the 2 and 5 positions. These reactions closely resemble the addition of the same reagents to the 9 and 10 positions in anthracene (section 5.6).

Complete hydrogenation of furan yields the cyclic ether tetrahydrofuran, a useful solvent for Grignard reactions.



(c) THIOPHENE

Thiophene does not show any basic properties although protonation of the sulphur atom may occur in the course of some reactions. Thiophene is much more stable to acids than either pyrrole or furan, e.g. sulphonation of the nucleus with concentrated sulphuric acid is possible at room temperature, polymerisation only occurring at much higher temperatures. Thiophene exhibits a lower reactivity towards electrophiles than the other two heterocycles; this greater degree of aromaticity can be attributed to the lower electronegativity of the sulphur atoms.

(*i*) *Electrophilic substitution* (see *Figure 14.4*)

(*ii*) *Addition reactions*

Thiophene does not react with atmospheric oxygen and is stable towards many oxidising reagents. The π electron system is too

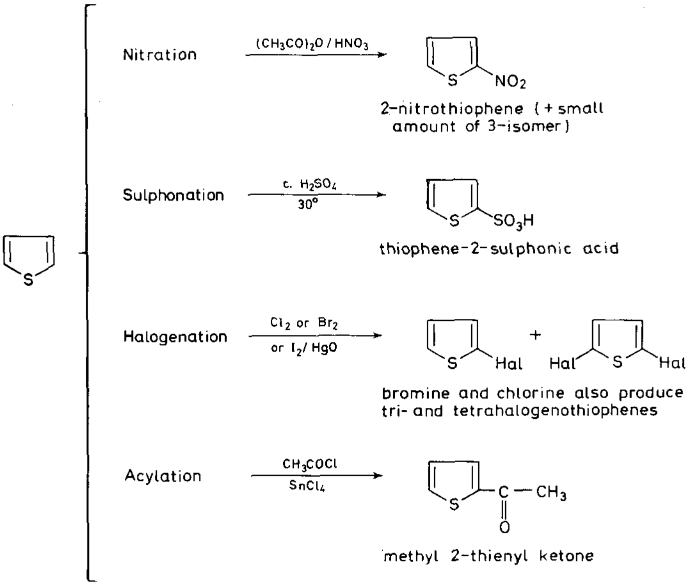
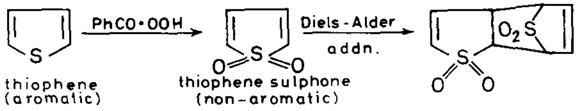


Figure 14.4

delocalised to allow thiophene to undergo Diels–Alder addition. However, like a thioether, thiophene forms a sulphone with perbenzoic acid. The sulphone cannot be aromatic as the sulphur lone pair electrons are engaged in bonding to oxygen atoms and so a Diels–Alder type addition occurs and produces a dimer.



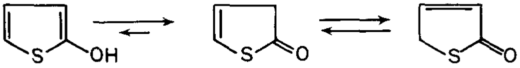
14.4 AROMATICITY AND EFFECTS OF SUBSTITUENTS IN PYRROLE, FURAN AND THIOPHENE

Aromaticity in the normal sense, i.e. resistance to oxidation and electrophilic substitution is certainly found in thiophene and to some extent in pyrrole. Thiophene, like an alkylbenzene, is more reactive than benzene but reacts normally with many of the reagents used in benzene chemistry. On the other hand pyrrole requires very mild reagents if decomposition is to be avoided.

Pyrrole resembles phenol or rather the phenoxide ion, in ease of electrophilic substitution. Thus pyrrole, like phenoxide compounds, couples with diazonium compounds and undergoes the Reimer–Tiemann reaction. Both pyrrole and phenol are substituted by mild reagents and form polyhalogeno compounds with halogens.

Furan is even more reactive and so less aromatic than pyrrole. Even mild reagents bring about extensive decomposition. Also 1,3-diene behaviour is present, for furan adds both maleic anhydride and oxygen at the 2 and 5 positions. These positions show similar additive properties to the 9 and 10 positions of anthracene.

Substituents have the expected effects. Electron attracting groups, e.g. —NO_2, —COOH, —COR, which draw the lone pair electrons of the heteroatoms more firmly into the ring, stabilise the system. Thus thiophene-2-carboxylic acid resembles benzoic acid. Even furan-2-carboxylic acid is a perfectly stable compound which undergoes nitration and sulphonation with normal reagents. Electron releasing groups have the reverse effect. Strongly electron releasing groups, e.g. —OH and —NH_2, make these ring systems so reactive that tautomerism to a non-aromatic carbonyl form occurs.

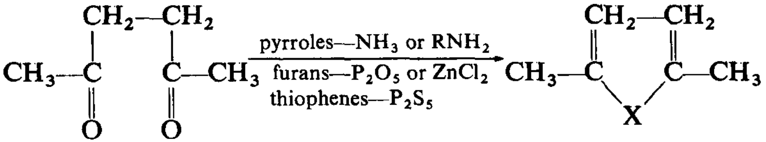


Thus the infra-red spectra of 2 and 3-hydroxythiophenes indicate the presence of a carbonyl group, in agreement with the above equilibrium. 2-Hydroxypyrrole probably exists in a similar equilibrium. Neither 2 nor 3-hydroxyfuran has yet been isolated.

14.5 SYNTHESIS OF PYRROLE, FURAN AND THIOPHENE

(a) THE PAAL–KNORR SYNTHESIS

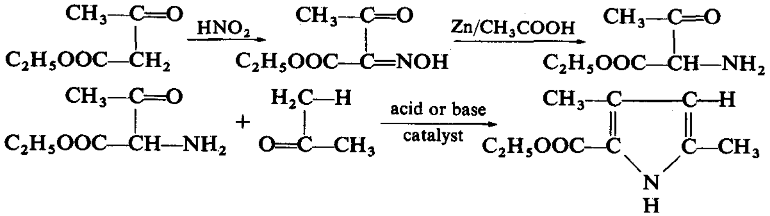
A 1,4-diketone, diacid or keto acid is reacted with one of the reagents shown below. The procedure is very useful for all three types of heterocycle.



2,5-hexanedione

(b) THE KNORR PYRROLE SYNTHESIS

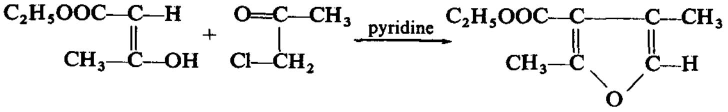
This is the most general method of making pyrroles. An α-aminoketone, often prepared *in situ*, is condensed with a ketone or keto ester.



2-carbethoxy-3,5-di methylpyrrole

(c) THE FEIST FURAN SYNTHESIS

An α-chloroketone is condensed with a β-keto ester in pyridine solution.

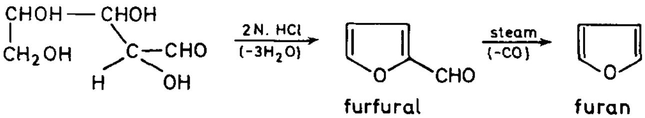


3-carbethoxy-2,4-dimethylfuran

(d) INDUSTRIAL METHODS

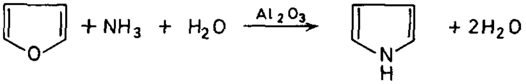
(*i*) *Furan*

The steam distillation of oat husks, which contain pentose sugar residues, with hydrochloric acid (2N) yields furfural. This aldehyde undergoes catalytic decomposition in steam to yield furan.



(*ii*) *Pyrrole*

Furan, ammonia and steam are passed over a heated alumina catalyst.



(*iii*) *Thiophene*

Butane, butenes or 1,3-butadiene yield thiophene when passed rapidly over sulphur at 560°.

B. SIX MEMBERED RING SYSTEMS WITH ONE HETEROATOM

14.6 OCCURRENCE OF PYRIDINE AND QUINOLINE

Pyridine is a hygroscopic liquid (b.p. 115°) possessing a rather unpleasant odour. Pyridine reacts with sodium and so should be dried over solid potassium hydroxide. The heterocycle can be extracted from coal tar distillates with mineral acid. Pyridine-3-carboxylic acid (nicotinic acid) is the chromic acid oxidation product of the alkaloid nicotine. The amide of this acid, nicotinamide, is a vitamin.

Quinoline (b.p 238°) was first obtained by decomposing the alkaloid quinine with alkali. Both quinoline and iso-quinoline can be isolated from coal tar.

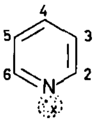
14.7 STRUCTURE OF PYRIDINE AND QUINOLINE

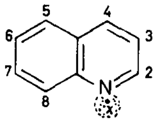
(a) PYRIDINE

Pyridine possesses a sextet of delocalised electrons; one electron is donated from the *p* atomic orbital of each of the five sp^2-hybridised carbon atoms and a further electron from the sp^2-hybridised nitrogen atom. The unshared electron pair of the nitrogen atom lie in the plane of the ring and project outwards (see *Figure 14.1*).

Like nitrobenzene, pyridine is a deactivated aromatic compound very resistant to both electrophilic substitution and oxidation. Protonation of the nitrogen lone pair, to form a pyridinium salt, increases the electron attracting power of the nitrogen atom but does not interfere with the aromatic properties of the molecule (cf. pyrrole).

The nitrogen atom is more electronegative than the carbon atoms and so attracts electrons through both the σ and π bonds of the molecule. The dipole moment of 2·3 D acting towards the nitrogen atom confirms this view of pyridine. The 2, 4 and 6 positions (*ortho* and *para* to nitrogen) are deactivated more than the 3 and 5 positions (*meta* to nitrogen).





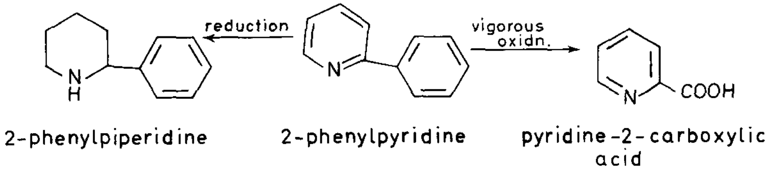
(b) QUINOLINE

This is similar in structure to pyridine except for the additional benzene ring. The deactivating effect of the nitrogen atom is felt most strongly at the 2 and 4 positions and least at the 3 position. There are no positions equivalent to the 5 and 6 positions of pyridine. The 8 position of quinoline is closer to the nitrogen atom than a normal ortho position and this gives rise to peculiar coordination possibilities between the 1 and 8 positions (page 263).

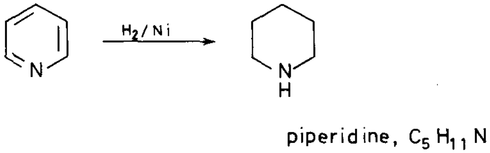
14.8 CHEMICAL REACTIONS OF PYRIDINE AND QUINOLINE

(a) PYRIDINE

The chemistry of pyridine is similar to that of nitrobenzene or a dinitrobenzene but is modified by the unshared pair of electrons attached to the nitrogen atom. Although more resistant to oxidation than benzene, the pyridine system is more easily reduced as illustrated by the reactions of 2-phenylpyridine.



Pyridine is reduced by sodium/ethanol, hydrogen/catalyst or even lithium aluminium hydride to piperidine.



Reactions of pyridine can be conveniently divided into three types (*i*) reactions of the unshared pair, (*ii*) electrophilic substitution and (*iii*) nucleophilic substitution.

(*i*) *Reactions of the nitrogen unshared pair electrons*

Pyridine is a much weaker base than aliphatic amines (*Table 1.6*,

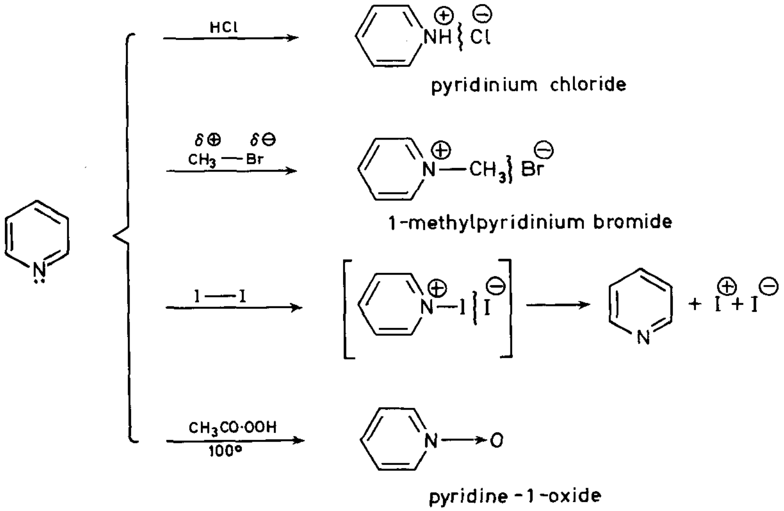
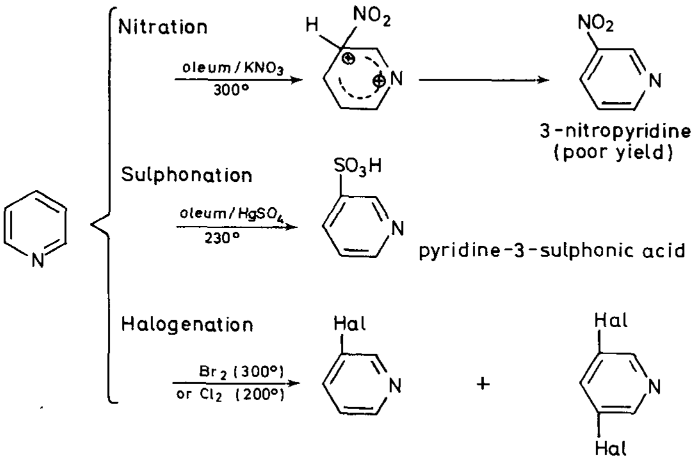


Figure 14.5

page 17). This is because in pyridine the nitrogen lone pair is in an sp^2 hybrid orbital whereas in aliphatic amines the nitrogen atom is sp^3-hybridised. Pyridine is only a weak nucleophile but will react with reactive substances such as alkyl and acyl halides. Thus, with primary halides salts are formed but with tertiary halides the base brings about elimination. Pyridine forms unstable adducts with halogens and these may be a source of the weak electrophile, $Hal^{\oplus}$. This would explain the observed catalytic effect of pyridine in some halogenation reactions. Peracids form pyridine-1-oxide. None of these reactions of the nitrogen lone pair alter the aromatic properties of the pyridine nucleus as the two electrons are not part of the aromatic sextet of electrons (see *Figure 14.5*).

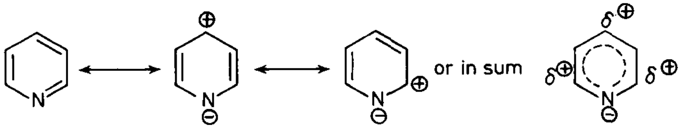
(ii) *Electrophilic substitution of pyridine*

Pyridine only undergoes electrophilic substitution with difficulty. Substitution takes place meta to the nitrogen, i.e. at the 3 and 5 positions, just as further substitution of nitrobenzene occurs at the meta positions. In acidic media, where the nitrogen lone pair is protonated, electrophilic substitution is rendered even more difficult due to the increased electron demand of the nitrogen atom. Neither pyridine nor nitrobenzene undergo Friedel–Crafts substitution.

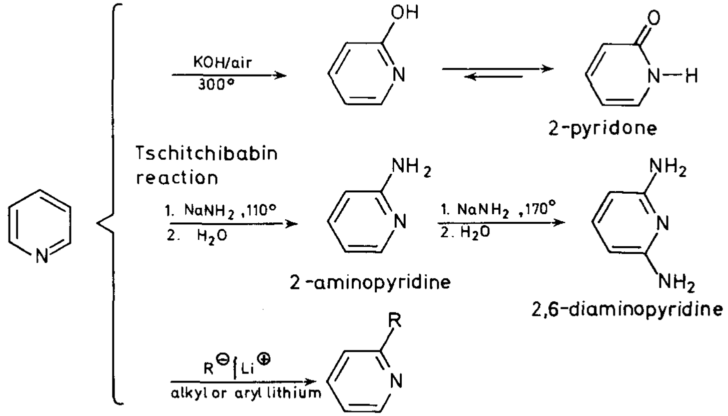


(iii) Nucleophilic substitution of pyridine

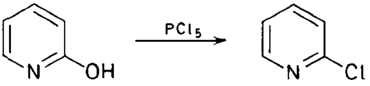
The nitrogen atom strongly withdraws electrons, particularly from the 2, 4 and 6 positions of pyridine. This situation may be represented as follows:



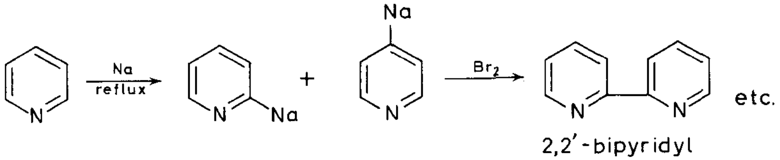
Powerful nucleophiles can, therefore, be expected to displace hydrogen atoms or other substituents from these activated 2, 4 and 6 positions.



In the above reactions the hydrogen atom is displaced from the pyridine nucleus as a hydride ion.



As mentioned in section 14.6, pyridine reacts with sodium; 2 and 4-pyridyl sodium are formed and these substances react with halogens to give bipyridyls.



(b) QUINOLINE

Quinoline shows many of the reactions of pyridine but the electrophilic substitution pattern is modified by the added benzene ring. Thus, reactions at the nitrogen lone pair and nucleophilic substitution follow the same pattern as for pyridine. Electrophilic substitution, however, takes place in the benzene ring since this ring is not much affected by the nitrogen atom and substitution is similar to that in naphthalene. Thus nitration takes place at the 5 and 8 positions of quinoline and the position of sulphonation, as with naphthalene, is temperature dependent (*Figure 14.6*).

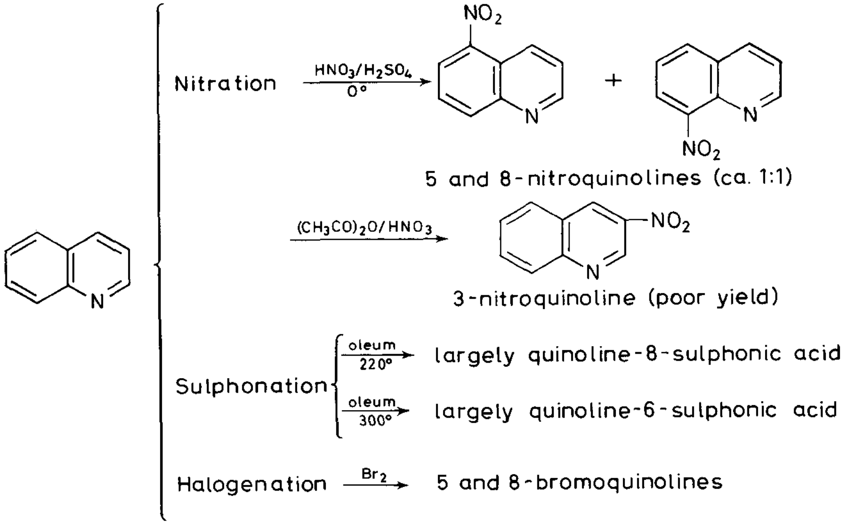
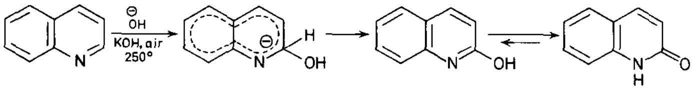


Figure 14.6

Nucleophilic reagents react with quinoline more readily than with pyridine because the added benzene ring serves to spread the negative charge and so stabilise the transition state. Substitution is largely at the 2 position.



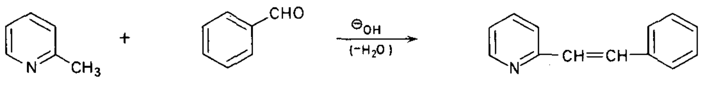
2-quinolone

14.9 AROMATICITY AND EFFECTS OF SUBSTITUENTS IN PYRIDINE AND QUINOLINE

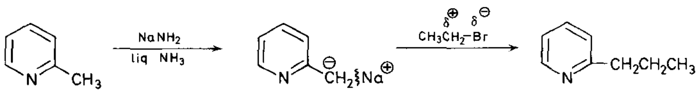
The reactions of pyridine and quinoline, described in the previous section, show that these heterocycles, like nitrobenzene, resist oxidation and electrophilic substitution. They are much more aromatic than either pyrrole or furan.

The powerful electron attracting properties of the nitrogen are transmitted most strongly to the *ortho* and *para* positions, i.e. the 2, 4 and 6 positions in pyridine and the 2 and 4 positions in quinoline. Therefore, substituents at these positions are influenced more strongly by this electron withdrawal, and consequently activated for reaction, than the same substituents at the 3 or 5 positions. Some examples of this behaviour are given below.

(*a*) In the methylpyridines (also termed α, β and γ-picolines), the methyl group, particularly in the 2 and 4 isomers, releases electrons to the ring and so makes the system more reactive towards electrophiles. At the same time the electron attraction of the ring confers a weak degree of acidity on the hydrogen atoms of the methyl groups and so makes condensation and other reactions possible, e.g.



stilbazole

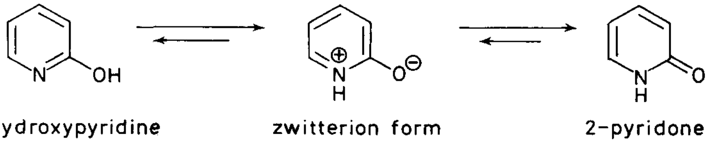


2-(n-propyl)-pyridine

The activating effect on the methyl group in pyridines decreases in the order 4 > 2 > 3. Methyl groups are similarly activated in ketones, nitroalkanes, cyanides, etc.

(*b*) The aminopyridines also illustrate a strong conjugative effect between the nitrogen atom and an amino group in the 2, 4 or 6 positions. In contrast the amino group of 3-aminopyridine behaves normally, e.g. this amine undergoes normal diazonium replacement reactions. The 2 and 4-aminopyridines react with nitrous acid to yield only 2-pyridone. As in aniline the amino group of aminopyridines activates the pyridine nucleus so that electrophilic substitution takes place more readily than in the parent substance.

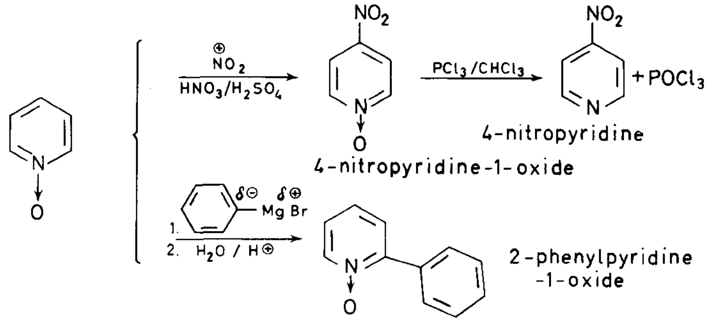
(*c*) The 2 and 4-hydroxypyridines, like the hydroxypyrroles and thiophenes, exist largely in the pyridone form, as indicated by infra-red absorption in the carbonyl region at 1660 cm^{-1}.



Presumably the situation where the more electronegative sp^2-hybridised oxygen attracts electrons from an sp^3-hybridised nitrogen atom is more stable than that in which the hybridisation states are reversed. The 2- and 4-pyridones show some reactions of both phenols and cyclic amides but 3-hydroxypyridine is completely phenolic in character.

8-Hydroxyquinoline (Oxine) forms chelate compounds with a number of metals and in particular is used for the gravimetric determination of aluminium. Bonding to the aluminium atom takes place from the hydroxyl group and the nitrogen lone pair electrons.

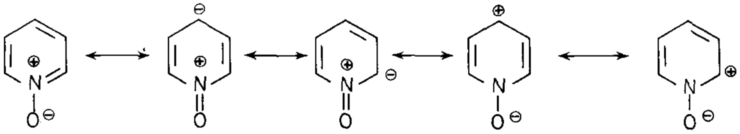
(*d*) The halogen atoms in 2- and 4-halopyridines are easily displaced by nucleophiles due to the activating effect of the nitrogen atom. This situation can be compared with the similar high reactivity of the chlorine atom in 2,4-dinitrochlorobenzene. 3-Halopyridines behave more like the normal unreactive aryl halides, e.g. 3-bromo-



pyridine is only a little more reactive towards nucleophiles than bromobenzene.

Pyridine-1-oxide is an interesting compound as the oxygen atom appears to be capable of either releasing or withdrawing electrons from the nucleus, depending on the demand of the reagent. Thus nitration takes place readily at the 4-position whilst Grignard reagents attack the 2-position.

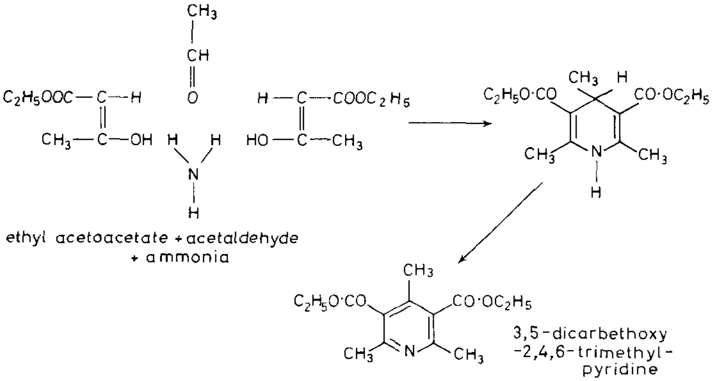
The following structures, which contribute to the resonance hybrid, give some explanation of the different reactions of pyridine-1-oxide.



14.10 SYNTHESES OF PYRIDINE AND QUINOLINE

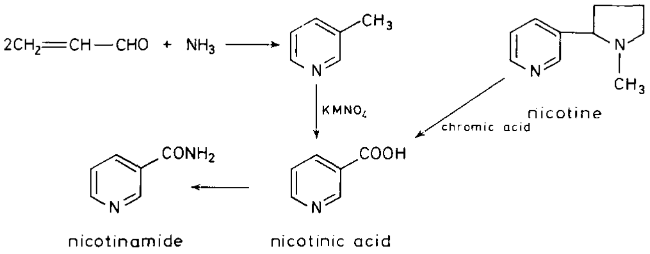
(a) THE HANTZSCH PYRIDINE SYNTHESIS

A β-keto ester or a β-diketone is condensed with an aldehyde and ammonia, e.g. ethyl acetoacetate, acetaldehyde and ammonia.



There is no practical, direct synthesis of pyridine. The heterocycle can be obtained, in quantities sufficient to satisfy demand, from coal tar.

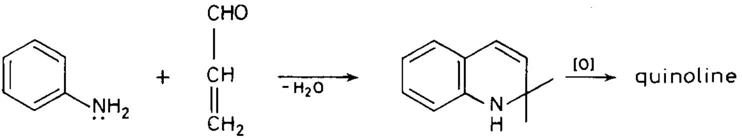
(*b*) Nicotinamide and nicotinic acid are important B group vitamins. The amide is an important biological substance as it is a substituent group of some enzymes. Nicotinic acid was first obtained from the alkaloid nicotine but is now synthesised from acrolein.



(c) SKRAUP QUINOLINE SYNTHESIS

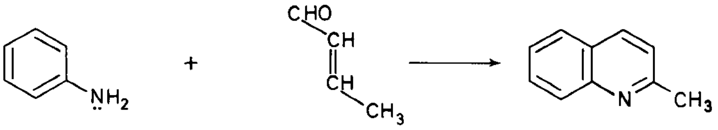
A primary aromatic amine adds to an α,β-unsaturated carbonyl compound. This is followed by cyclisation and oxidation to produce the quinoline system. Aniline, glycerol, concentrated sulphuric acid and an oxidising agent, such as arsenic pentoxide or nitrobenzene, yield quinoline. Acrolein is generated *in situ* from the glycerol.

$$CH_2OH{\cdot}CHOH{\cdot}CH_2OH \xrightarrow{H_2SO_4} CH_2{=}CH{-}CHO$$



The Doebner von Miller synthesis is a variation on the Skraup procedure. The amine is heated with an aldehyde in the presence of zinc chloride and hydrochloric acid. The first step is probably an Aldol condensation.

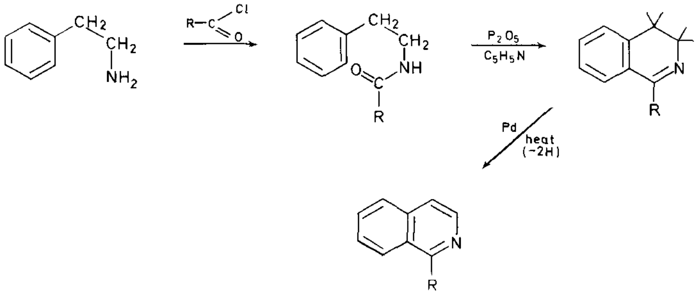
$$2CH_3CHO \xrightarrow[(-H_2O)]{H^{\oplus}} CH_3CH{=}CHCHO$$



2-methylquinoline

(d) THE BISCHLER–NAPIERALSKI SYNTHESIS OF ISO-QUINOLINE

An acyl derivative of 2-phenylethylamine is cyclised with phosphorous pentoxide in pyridine solution.



The 1 position in iso-quinoline exhibits a reactivity similar to that of the 2 and 4 positions in quinoline. The 3 position is far less reactive than the 1 position.

15

Organic Compounds Derived from Natural Sources

15.1 CARBOHYDRATES

Carbohydrates are formed by photosynthesis in green plants. The plant takes in carbon dioxide from the atmosphere and, with the aid of the green pigment chlorophyll, combines this with water from the root system. The energy required to bring about the reaction is supplied by sunlight.

$$x\cdot CO_2 + x\cdot H_2O \xrightarrow[\text{light}]{\text{chlorophyll}} \underset{\text{carbohydrate}}{(CH_2O)_x} + x\cdot O_2$$

During the process of photosynthesis the plant gives out oxygen. Green plants are, therefore, essential for the maintenance of the carbon dioxide/oxygen balance of the atmosphere. The process of photosynthesis is extremely complex and involves phosphates, enzymes and many reaction paths.

Carbohydrates form the major part of all plants, trees, etc., and include sugars, cellulose and starch. These substances comprise much of the food eaten by animals and man. They also supply many other essential requirements, e.g. paper is made from cellulose derived from certain trees.

The simplest carbohydrates are sugars. Most sugars contain five or six carbon atoms and are termed pentose and hexose sugars respectively. Carbohydrates are classified as mono-, di- and polysaccharides. Sugars such as fructose, glucose or ribose are monosaccharides, i.e. basic units which cannot be hydrolysed to smaller units. Disaccharides, such as sucrose, lactose or maltose, can be hydrolysed to produce two monosaccharide molecules. Similarly polysaccharides such as cellulose or starch, hydrolyse to a large number of monosaccharide units. One example of each type of carbohydrate will be briefly described.

(a) GLUCOSE—A MONOSACCHARIDE

Glucose is a hexose sugar with the molecular formula $C_6H_{12}O_6$ and is dextrorotatory. Glucose is one of the first products of photosynthesis and occurs uncombined in many fruits and plants. Animals use glucose and other carbohydrates as a source of energy, for they metabolise such substances to carbon dioxide and water.

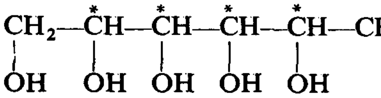
The structure of glucose was deduced from a number of reactions of the sugar. Some of these reactions are listed below.

(*i*) Reduction of glucose with hydrogen iodide and red phosphorus liberated n-hexane indicating that all six carbon atoms must be joined together in a linear and not a branched manner.

(*ii*) Reaction of the sugar with acetyl chloride produced a penta-acetate showing that five hydroxyl groups are involved in the structure.

(*iii*) Glucose forms an oxime and a phenylhydrazone indicating the presence of a carbonyl group. Glucose is also termed a reducing sugar by virtue of positive reactions with both Fehling's and Tollen's reagents. The carbonyl group must, therefore, be part of an aldehyde group.

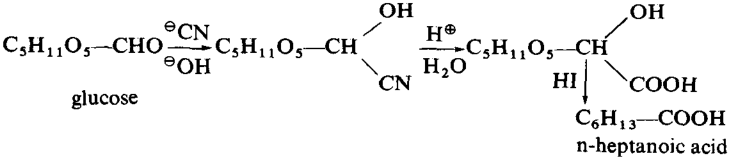
(*iv*) An aldehyde group can only be a terminal group and so the structure of glucose would appear to be:



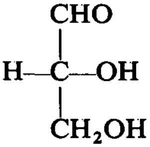
$$\underset{\text{OH}}{\underset{|}{CH_2}}-\underset{\text{OH}}{\underset{|}{\overset{*}{C}H}}-\underset{\text{OH}}{\underset{|}{\overset{*}{C}H}}-\underset{\text{OH}}{\underset{|}{\overset{*}{C}H}}-\underset{\text{OH}}{\underset{|}{\overset{*}{C}H}}-CHO$$

(I)

Proof of the position of the aldehyde group was obtained by reaction with cyanide and alkali to give a cyanhydrin which hydrolysed to a carboxylic acid. Reduction of this acid with hydrogen iodide gave n-heptanoic acid.

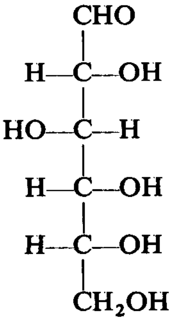


The basic structure of glucose must be that shown by structure I but the four carbon atoms marked with asterisks are asymmetric centres. Altogether there are 2^4, i.e. 16 possible configurations of glucose, only one of which corresponds to the (+)-glucose isolated from natural sources. However, Emil Fischer deduced that the stereochemical arrangement of glucose is configuration II and he related the sugar to D-(+)-glyceraldehyde, III (see section 13.4).



$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

D-(+)-glyceraldehyde (III)

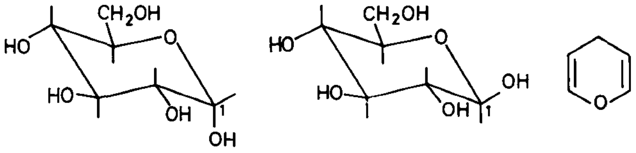


$$\begin{array}{c} \mathrm{CHO} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{HO{-}C{-}H} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{H{-}C{-}OH} \\ | \\ \mathrm{CH_2OH} \end{array}$$

D-(+)-glucose (II)

The straight chain structure, II, does not explain all the chemical properties of glucose, e.g. glucose does not form the expected hydrogen sulphite addition compound. Also a freshly prepared solution of glucose in water has a specific rotation of +113° but on standing this gradually falls until a constant value of +52° is reached. This change in specific rotation is termed *mutarotation*. The crystallisation of glucose from different solvents yields two forms of the sugar. The so-called α-form is obtained by crystallisation from ethanol ($[\alpha]_D = +113°$) whilst pyridine yields the β-form ($[\alpha]_D = +19°$). An aqueous solution of either the α or β-form undergoes mutarotation.

The above properties have been explained by cyclic hemiacetal structures (hemiacetals, page 152). For α and β-glucose (IV and V) x-ray diffraction studies confirm this view. To undergo reaction with Fehling's or Tollen's reagents the ring structure must open under the influence of the reagent and temporarily form the open chain structure, II.



α-D-(+)-glucose (IV) β-D-(+)-glucose (V) pyran

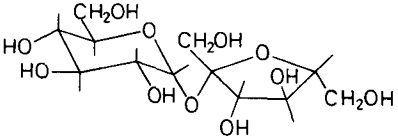
Glucopyranose structures of glucose

The pyran-like ring structures of glucose are termed the glucopyranose forms. The α and β-glucose isomers differ only in the configuration of the hydroxyl group at carbon 1.

(b) SUCROSE—A DISACCHARIDE

(+)-Sucrose is the ordinary 'sugar' of commerce and is isolated from sugar cane and sugar beet. Like many carbohydrates found in nature sucrose contains two hexose monosaccharide units. Sucrose is a non-reducing sugar, i.e. it does not reduce Fehling's or Tollen's reagents. Hydrolysis of sucrose with aqueous acids or the enzyme invertase yields equal amounts of D-(+)-glucose and D-(−)-fructose. Honey is mainly hydrolysed sucrose.

X-ray studies and total synthesis have shown that sucrose is α-D-glucopyranose linked to β-D-fructofuranose. The term furanose is derived from that of the five-membered ring heterocycle, furan (section 14.1).



sucrose

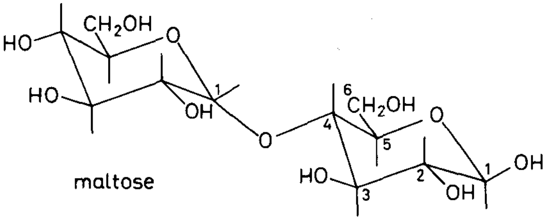
α-D-glucopyranose + β-D-fructofuranose ═ sucrose

Other disaccharides are (+)-maltose, (+)-cellobiose and (+)-lactose.

(c) STARCH AND CELLULOSE—POLYSACCHARIDES

Starch occurs as granules and is the reserve carbohydrate of plants, e.g. of the potato. The form of starch granules is characteristic of the plant from which the material was obtained, e.g. wheat starch, rice starch, etc. Complete hydrolysis of starch gives an almost quantitative yield of D-(+)-glucose indicating that starch is a polymer of the monosaccharide. Partial hydrolysis of starch with the enzyme amylase give the disaccharide maltose in high yield and this indicates the mode of connection of the glucose units in starch.

The structure of starch is more complex than this simple picture suggests, for treatment of the polysaccharide with hot water gives a



maltose

α-D-glucopyranose + β-D-glucopyranose ═ maltose

soluble fraction—Amylose, and leaves an insoluble portion—Amylopectin. The two fractions are in the ratio of approximately 1 : 4. Amylose contains between 60 and 300 glucose units arranged in a linear manner and linked carbon 1 to carbon 4 as in maltose. Amylopectin has a more branched structure and contains between 1000 and 6000 glucose units linked mainly 1 and 4 but with some 1 and 6 links.

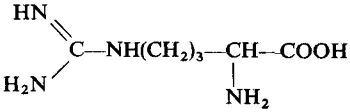
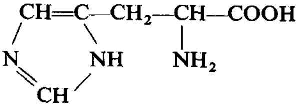
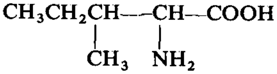
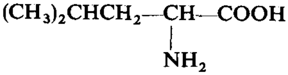
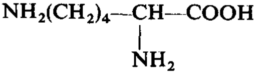
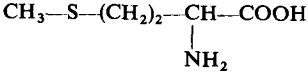
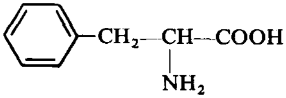
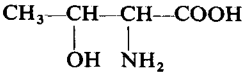
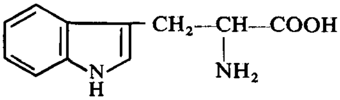
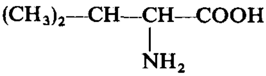
Cellulose is widely distributed in wood and plants, and cotton in particular is almost pure cellulose. In wood the cellulose is deposited with lignin and the latter must be removed if the wood pulp is to be converted into paper. Cellulose is a very high molecular weight (up to 10^6), linear polymer of β-glucose molecules linked entirely by the 1 and 4 positions. The linear nature of the polymer means that the chains can pack together easily and hydrogen bond one to the other. The result is that cellulose occurs as long fibres which have very good wear resistance properties.

15.2 PROTEINS

Proteins are high molecular weight polymers of various amino acids. The amino acid molecules condense in 'head to tail' fashion so that the essential linkage in proteins is the amide group. Proteins are the most important building material for nearly all parts of the animal body, e.g. blood, muscle, nerves, etc. They also act as hormones which regulate body processess, e.g. insulin, as enzymes which bring about many chemical reactions in the body and as oxygen carriers, e.g. haemoglobin. Many disease-causing enemies of animals and man are also largely protein in character, e.g. viruses.

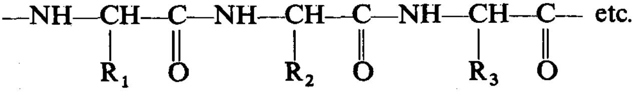
So far twenty-six amino acids have been isolated from the degradation products of proteins. These are all α-amino acids and with the exception of glycine they are optically active. Some amino acids are essential to life processes and a selection of these is shown in *Table 15.1*. Obviously twenty-six amino acids can be combined,

Table 15.1. ESSENTIAL AMINO ACIDS

Abbreviation	*Full Name*	*Formula*
Arg	(+)-arginine	
His	(−)-histidine	
Ileu	(+)-isoleucine	 $\underset{\displaystyle CH_3}{CH_3CH_2CH}—\underset{\displaystyle NH_2}{CH}—COOH$
Leu	(−)-leucine	 $(CH_3)_2CHCH_2—\underset{\displaystyle NH_2}{CH}—COOH$
Lys	(+)-lysine	 $NH_2(CH_2)_4—\underset{\displaystyle NH_2}{CH}—COOH$
Met	(−)-methionine	 $CH_3—S—(CH_2)_2—\underset{\displaystyle NH_2}{CH}—COOH$
Phe	(−)-phenylalanine	
Thr	(−)-threonine	 $CH_3—\underset{\displaystyle OH}{CH}—\underset{\displaystyle NH_2}{CH}—COOH$
Try	(−)-tryptophane	
Val	(+)-valine	 $(CH_3)_2—CH—\underset{\displaystyle NH_2}{CH}—COOH$

cross linked, etc. in an enormous number of ways so that in principle very many different proteins are possible.

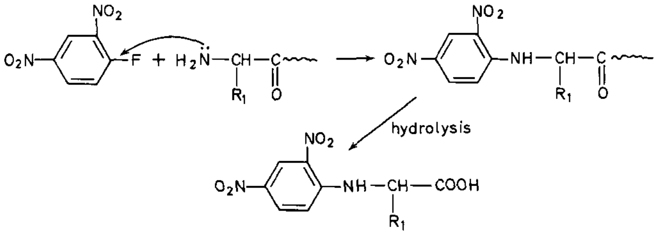
Related to proteins are the peptides. Both are polymers of α-amino acids but peptides are less complex than proteins and have molecular weights of less than 10000. The amide linkages in both proteins and peptides can be written:



$$-NH-\underset{R_1}{\underset{|}{CH}}-\underset{O}{\underset{\|}{C}}-NH-\underset{R_2}{\underset{|}{CH}}-\underset{O}{\underset{\|}{C}}-NH-\underset{R_3}{\underset{|}{CH}}-\underset{O}{\underset{\|}{C}}-\text{ etc.}$$

To determine the amino acids present in a protein the material is subjected to acid hydrolysis. The free amino acids can be identified by paper chromatography. The amount of each acid in the hydrolysate can be determined by gas chromatographic analysis of their methyl esters. The molecular weight of the material is found by physical methods such as osmotic pressure.

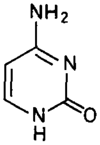
By far the most difficult part in the structure determination of a protein is finding the sequence of the amino acids. Partial hydrolysis of the material with acid or enzymes yields fragments containing three or four amino acids. The amino acid sequence in these small fragments can be found more easily and reassembly of the fragments in the manner of a jigsaw gives the structure of the protein. Special reagents are used to determine the amino acids at each end of the protein chain, e.g. 2,4-dinitrofluorobenzene. This reagent is used because the fluorine atom readily undergoes nucleophilic displacement by the free amino group of a terminal amino acid.



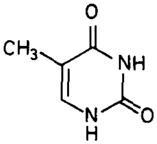
The amino acid labelled with the 2,4-dinitrophenyl group can be separated from the other acids and identified. The terminal amino acid at the other end of the protein chain will have a free carboxyl group and this acid can be selectively hydrolysed with an enzyme and identified.

In recent years one of the most intricate problems which scientists have been attempting to solve is the mechanism by which proteins are synthesised, i.e. how the amino acids are assembled in the required order. The agents primarily responsible for this assembly are found in the chromosomes of cell nuclei and are called deoxyribonucleoproteins. These substances are proteins bonded to deoxyribonucleic acids (DNA).

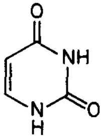
DNA consists of pentose sugar molecules linked together by phosphate groups, and an organic base (adenine, guanine, cytosine or thymine) is linked to each of the sugar residues.



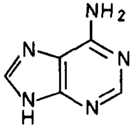
cytosine
(2-oxo-4-aminopyrimidine)



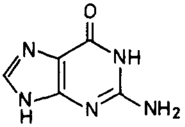
thymine



uracil



adenine
(6-aminopurine)



guanine

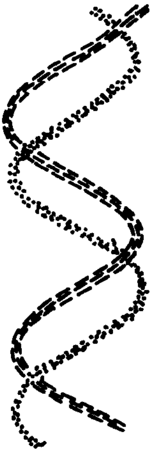
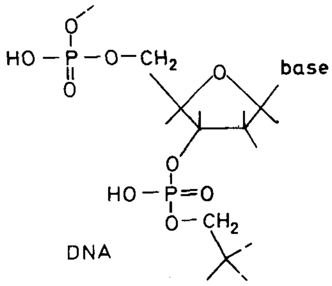


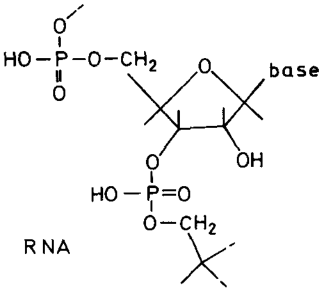
Figure 15.1. Double-helix structure of DNA. The chains are held together by hydrogen bonds between organic bases

The molecular weight of each DNA chain is several million and in the cell two such chains twist together in a double helix structure (*Figure 15.1*). The two chains are held together by hydrogen bonds between the bases such that the diameter of the helix is about 20 Å. Guanine in one chain is always bonded to cytosine in the other chain and similarly adenine is bonded to thymine.

In the cell nucleus the DNA appears to be responsible for the synthesis of ribonucleic acid (RNA). RNA is similar to DNA except that the sugar residue has gained a further hydroxyl group to become D-ribofuranose and the base thymine in DNA is replaced by uracil.



DNA



RNA

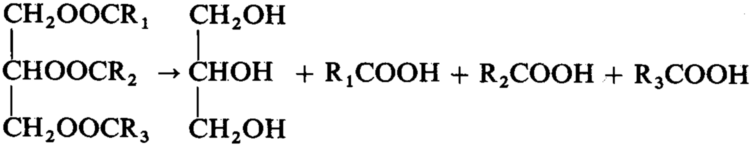
There appear to be different types of RNA which have different functions in the synthesis of proteins.

After synthesis from DNA in the cell nucleus, the RNA moves into the cell cytoplasm and becomes associated with the ribosomes. Protein synthesis now occurs. The order of the bases on the RNA polymer chain is able to determine the order of arrangement of the amino acids on the developing protein chain. The movement of the amino acids to their correct site on the RNA chain and the formation of the amide linkages are probably enzyme induced reactions. Although much is known about the formation of proteins many problems remain for the moment unanswered.

15.3 LIPIDS—FATS, OILS AND WAXES

Lipids are esters isolated from animal and vegetable sources. The rather hard solids are termed waxes, the soft solids fats and the liquids oils. All lipids are insoluble in water but soluble in a number of organic solvents. Lipids together with carbohydrates and proteins are the principle sources of food for animals. Lipids in particular are sources of stored energy which an animal may draw upon, if necessary, over a considerable period of time. On the other hand plants have their reserve energy in the form of starch. Substances such as butter, milk, lard and margarine are all lipids, i.e. esters of the trihydric alcohol, glycerol, $CH_2OH\cdot CHOH\cdot CH_2OH$ and a number of carboxylic acids. Fats and oils derived from glycerol are often termed *glycerides.*

Hydrolysis of most fats and oils with alkali, acid or enzymes yields glycerol and a mixture of carboxylic acids.



$$\begin{array}{lcl} CH_2OOCR_1 & & CH_2OH \\ | & & | \\ CHOOCR_2 & \rightarrow & CHOH \quad + R_1COOH + R_2COOH + R_3COOH \\ | & & | \\ CH_2OOCR_3 & & CH_2OH \end{array}$$

The carboxylic acids obtained are almost completely straight chain compounds and most contain an even number of carbon atoms in the range 10–20. The acids may be saturated or contain up to three double bonds, e.g.

Formula	*Name*
$CH_3(CH_2)_{12}COOH$	myristic acid
$CH_3(CH_2)_{14}COOH$	palmitic acid
$CH_3(CH_2)_{16}COOH$	stearic acid
$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$	oleic acid
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$	linoleic acid

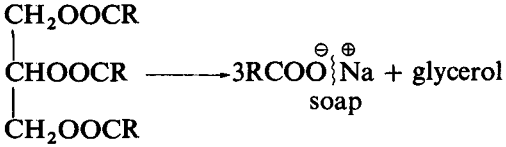
Glyceride esters contain these and other carboxylic acid residues in various proportions. The higher the proportion of unsaturated acid residues the lower the melting point of the lipid. Oils, therefore, contain more unsaturated acid residues than fats.

A few fats and waxes isolated from natural sources are esters of monohydric alcohols, e.g. beeswax is the ester of myricyl alcohol, $C_{30}H_{61}OH$, and palmitic acid, $C_{15}H_{31}COOH$. Waxes are harder than fats and find considerable application as polishes.

Lipids are important starting materials for soaps. Oils are hydrogenated to produce more acceptable fats, such as margarine and cooking fats. Highly unsaturated oils find use as drying oils in paints.

(a) SOAP AND DETERGENTS

The alkaline hydrolysis of lard, tallow and other natural fats is termed *saponification.* The products are soap and glycerol:



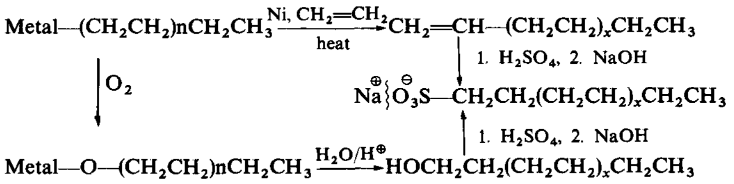
$$\begin{array}{l} CH_2OOCR \\ | \\ CHOOCR \longrightarrow 3RCO\overset{\ominus}{O}\}\overset{\oplus}{Na} + \text{glycerol} \\ | \qquad\qquad\qquad\qquad \text{soap} \\ CH_2OOCR \end{array}$$

The soap is precipitated with salt, washed, mixed with colours, perfumes, etc., dried and then pressed into the article of commerce, the bar of soap. The function of soap in dispersing oil, in the form of stable, water soluble 'micelles' has already been described (section 1.7).

Detergents function in the same way as natural soaps but have a sulphonate grouping in place of the carboxylate anion, e.g.

$$CH_3CH_2(CH_2CH_2)_x\,SO_3^{\ominus}\}Na^{\oplus},$$

where $x = 5 \rightarrow 8$. The advantage of this arrangement is that the cations $Ca^{2\oplus}$ and $Mg^{2\oplus}$, present in most water supplies, form water soluble sulphonate salts whereas the carboxylate salts of these cations are insoluble and produce 'scum'. Detergents can be synthesised from ethylene by Ziegler–Natta polymerisation (page 286). Metal alkyls such as triethyl aluminium and ethylene react to form straight chain alkenes or alcohols and these can be sulphonated to produce the detergent.



(b) HYDROGENATION OF OILS

The hydrogenation of double bonds in oils such as soya-bean oil raises their melting point and yields a commercially valuable fat. The product can be used as cooking fat or, when mixed with colouring and flavouring materials, as margarine.

Hydrogenation can be carried out over a finely divided nickel catalyst, termed *Raney nickel*. When the reaction is complete the catalyst is removed from the melted fat by filtration. The hydrogenation conditions are mild so the ester linkages are not affected.

(c) DRYING OILS

Some oils, such as linseed oil, harden on exposure to air and form a tough skin which resists weather, etc. Suitable admixture of such oils with pigments produces paints. Drying oils contain a large proportion of unsaturated acid residues. Oxygen from the atmosphere brings about polymerisation of the double bonds by the free radical mechanism so that the final paint layer is really a highly cross-linked polymer containing a pigment in suspension.

16

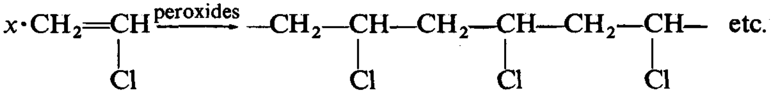
Polymers

16.1 STRUCTURE OF POLYMERS

Polymers contain the continuously repeating structural unit of a monomer (M). The monomer molecules are induced by a process called polymerisation to link together.

$$\underset{\text{monomer}}{x\cdot \mathrm{M}} \xrightarrow{\text{polymerization}} \underset{\text{polymer}}{\mathrm{—M—M—M—M—M—M—M—}}$$

e.g.



$$x\cdot \mathrm{CH_2{=}\underset{\underset{Cl}{|}}{CH}} \xrightarrow{\text{peroxides}} \mathrm{—CH_2—\underset{\underset{Cl}{|}}{CH}—CH_2—\underset{\underset{Cl}{|}}{CH}—CH_2—\underset{\underset{Cl}{|}}{CH}—}\ \text{etc.}$$

vinyl chloride polyvinyl chloride (P.V.C.)

The resulting polymer molecules will normally have a fairly wide range of molecular weights. The physical properties of the polymer will depend on the average and spread of the molecular weights, on the structure of the monomer and the method of polymerisation. A considerable degree of control is now possible over these three factors and to some extent polymers can be designed and made to fulfil predetermined requirements.

The example above of polyvinyl chloride shows that polymer molecules form long chains. However, links may be formed between the chains and these bonds considerably increase the molecular weight of the polymer and also limit the movement of the polymer chains relative to one another. These two factors have a great influence on the physical properties of a polymer.

The three classes of polymer are recognised.

(*i*) Elastomers—These consist of long polymer chains with few cross links. The polymer chains can compress, expand and move relative to one another and so elastomers are pliable, rubbery substances which do not harden.

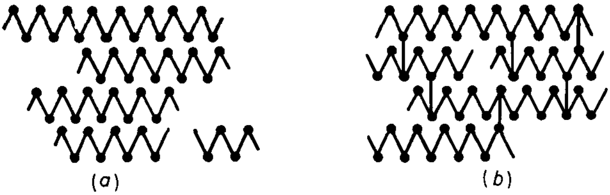
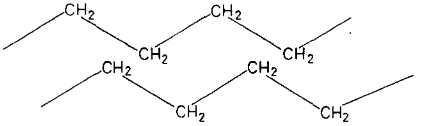


Figure 16.1. (a) Polymer chains without cross linkages, i.e. held together by van der Waals' forces. (b) cross-linked polymer chains

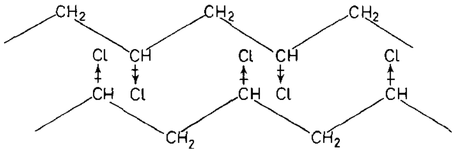
(*ii*) Thermoplastic Polymers—These again consist of long polymer chains with few cross links but the forces between the polymer chains are much greater than in elastomers. Heat is necessary to increase the motion between the polymer chains and cause the material to flow. On cooling in a mould the thermoplastic sets in the shape required.

(*iii*) Thermosetting Polymers—A fairly fluid, low molecular weight material with unlinked or only partly linked chains is transferred to a mould and heated. This causes the polymer chains to cross link and the molecular weight to rise and so the product is a hard polymer.

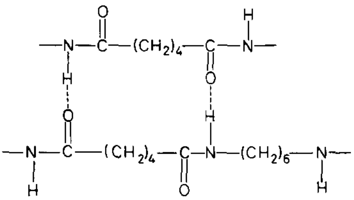
The forces between polymer chains depend on the atoms and groups present and the steric arrangement of the chains. In polyalkenes, such as polyethylene and polypropylene, the only forces



Polyethylene—van der Waals forces only



Polyvinyl chloride—van der Waals forces and probably dipole–dipole interactions



Nylon 6·6—hydrogen bonding between chains in addition to other physical forces between the alkane chains are van der Waals forces. When halogen atoms are introduced into the alkane chains, as in polyvinyl chloride, then dipole–dipole interactions become possible. In a polyamide, such as Nylon (6.6), hydrogen bonding is possible between the polymer chains.

Although a material like polyethylene consists simply of long chains of $—CH_2—$ groups, having average molecular weights of around 20000, the substance is not completely amorphous. The polymer chains line up with one another to form regions having definite crystallinity which are termed *crystallites*. The strength of a polymer is considerably dependent on this degree of crystallinity. An amorphous polymer, such as an elastomer, has a low physical strength because the polymer chains have a random orientation and so forces between the chains are at a minimum. A polymer possessing considerable areas of crystallinity (*Figure 16.2*) will be stronger than an amorphous polymer but the maximum strength of the material will only be achieved when all the crystallites are orientated in the same direction. Orientation of the crystallites in nylon is brought about by stretching the filament to approximately four times its original length.

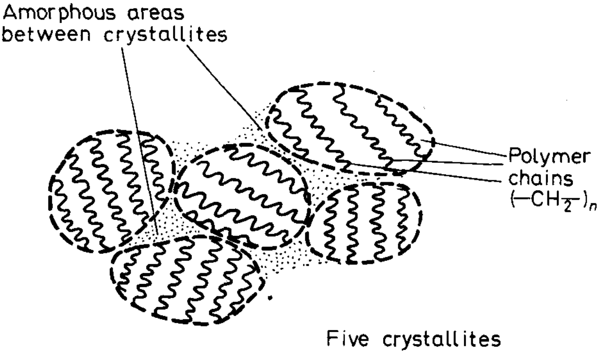
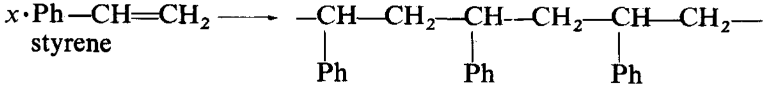


Figure 16.2. Representation of regions of crystallinity within a polyalkene.

The structure of a polymer depends to a large extent on the method used to bring about polymerisation. Polystyrene illustrates this clearly. When styrene is polymerised by free radicals in solution a semi-crystalline polystyrene is produced which is soluble in many solvents, e.g. chloroform, and melts below 200°. This is called *atactic* polystyrene. However, polymerisation of styrene with Ziegler catalysts produces a harder polystyrene which is much less soluble in chloroform and melts at 230°; this is termed *isotactic* polystyrene. The difference between the two forms lies in the orientation of the benzene rings about the addition centres.

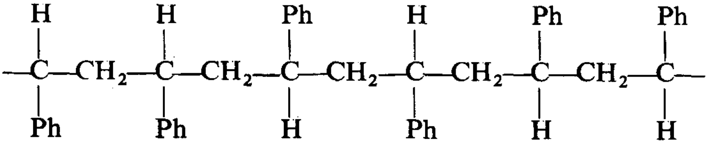


$$x\cdot \mathrm{Ph{-}CH{=}CH_2} \longrightarrow -\underset{\mathrm{Ph}}{\mathrm{CH}}-\mathrm{CH_2}-\underset{\mathrm{Ph}}{\mathrm{CH}}-\mathrm{CH_2}-\underset{\mathrm{Ph}}{\mathrm{CH}}-\mathrm{CH_2}-$$

styrene

polystyrene

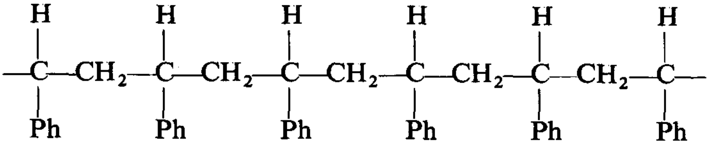
In the atactic configuration the benzene rings are randomly distributed on either side of the alkane chain:



$$-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{Ph}}{\underset{\mathrm{H}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{Ph}}{\underset{\mathrm{H}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{Ph}}{\underset{\mathrm{H}}{\mathrm{C}}}-$$

atactic polystyrene

The isotactic form differs from the above in that all the benzene rings are on the same side of the alkane chain:



$$-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-\mathrm{CH_2}-\overset{\mathrm{H}}{\underset{\mathrm{Ph}}{\mathrm{C}}}-$$

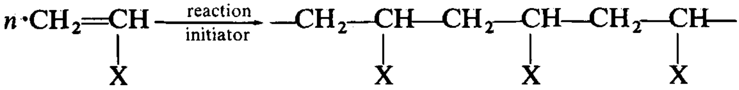
isotactic polystyrene

Other stereochemical arrangements of polymers are possible, e.g. groups may be arranged alternately on one side and then on the other side of an alkane chain. This is termed the *syndiotactic* configuration.

16.2 THE POLYMERISATION PROCESS

Polymerisation processes can be divided into two types. Addition across alkene double bonds is termed *addition polymerisation* and the combination of different sorts of monomer molecules with elimination of water or other simple molecules is termed *condensation polymerisation.*

In addition polymerisation the general reaction involved is:



$$n\cdot CH_2{=}\underset{\displaystyle X}{\underset{|}{CH}} \xrightarrow[\text{initiator}]{\text{reaction}} {-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH}}{-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH}}{-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH}}{-}$$

monomer polymer

Some monomers and their polymerisation products are indicated below.

X	*Monomer*	*Polymer*
H	$CH_2{=}CH_2$	polyethylene
CH_3	$CH_2{=}CHCH_3$	polypropylene
Cl	$CH_2{=}CHCl$	polyvinyl chloride
Ph	$CH_2{=}CHPh$	polystyrene
$C{\equiv}N$	$CH_2{=}CHC{\equiv}N$	polyacrylonitrile
$OOCCH_3$	$CH_2{=}CHOOCCH_3$	polyvinylacetate

Other hydrogen atoms about the double bond may also be replaced, e.g. tetrafluorethylene, $CF_2{=}CF_2$, polymersis to polytetrafluoroethylene. Further examples of polymers based on substituted alkene monomers are given in the next section.

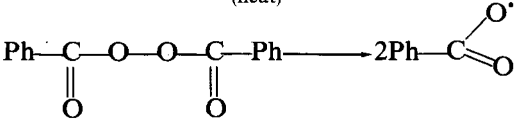
Addition polymerisation can be brought about by free radicals, cations, anions or organometallic reagents called Ziegler catalysts.

(a) FREE RADICAL POLYMERISATION

To start a free radical chain polymerisation process an initiator, or source of free radicals, usually a peroxide, must be added to the monomer. The initiating step is:

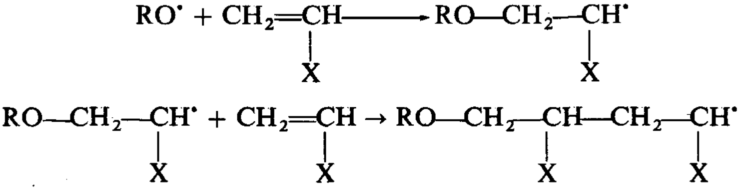
$$RO\cdot OR \xrightarrow[\text{(heat)}]{} 2RO^{\bullet}$$

e.g.



benzoyl peroxide

Polymerisation then follows by a chain mechanism:

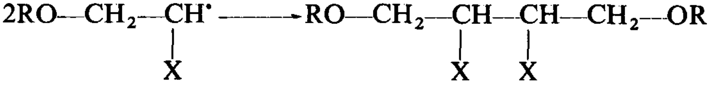


$$RO^{\bullet} + CH_2{=}\underset{\displaystyle X}{\underset{|}{CH}} \longrightarrow RO{-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH^{\bullet}}}$$

$$RO{-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH^{\bullet}}} + CH_2{=}\underset{\displaystyle X}{\underset{|}{CH}} \rightarrow RO{-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH}}{-}CH_2{-}\underset{\displaystyle X}{\underset{|}{CH^{\bullet}}}$$

etc. to polymer

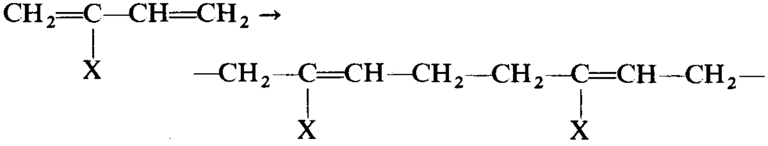
Polymerisation is easily stopped by reaction of the radicals with impurities, or dimerisation, e.g.



$$2RO{-}CH_2{-}\underset{\textstyle X}{\underset{|}{CH^{\bullet}}} \longrightarrow RO{-}CH_2{-}\underset{\textstyle X}{\underset{|}{CH}}{-}\underset{\textstyle X}{\underset{|}{CH}}{-}CH_2{-}OR$$

Hence the monomers used in these reactions must be extremely pure if the polymer is to have consistent physical properties.

Ethylene, but not propene, can be successfully polymerised in the presence of peroxides at 100–200 MN/m^2 pressure and 100–250°. Conjugated dienes readily undergo free radical polymerisation. In the case of 1,3-butadienes the addition is mainly to the 1 and 4-positions.



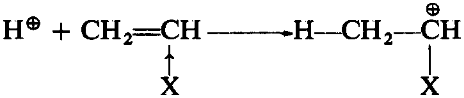
$$CH_2{=}\underset{\textstyle X}{\underset{|}{C}}{-}CH{=}CH_2 \rightarrow {-}CH_2{-}\underset{\textstyle X}{\underset{|}{C}}{=}CH{-}CH_2{-}CH_2{-}\underset{\textstyle X}{\underset{|}{C}}{=}CH{-}CH_2{-}$$

X	*Monomer*	*Polymer*
H	1,3-butadiene	polybutadiene (a rubber)
Cl	2-chloro-1,3-butadiene (chloroprene)	Neoprene rubber
CH_3	2-methyl-1,3-butadiene (isoprene)	synthetic rubber

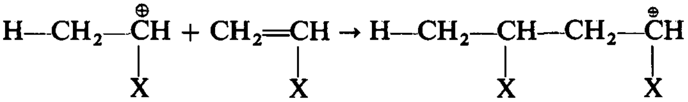
The important feature of polybutadiene and related compounds is that the polymer still possesses double bonds which makes vulcanisation, i.e. cross linking the polymer chains with sulphur atoms, possible. Natural rubber is largely the *cis* form of polyisoprene with small amounts of protein and other impurities. Addition polymerisation is possible between different types of monomer molecules, e.g. a very satisfactory synthetic rubber (Buna or S.B.R. rubber) is obtained when 1,3-butadiene and styrene are polymerised in the ratio of 3:1. This type of process is termed *copolymerisation.*

(b) CATIONIC POLYMERISATION

These processes involve positive ions and so the reactions are catalysed by acids, e.g. H_2SO_4, HF or Lewis acids such as $AlCl_3$ or BF_3.



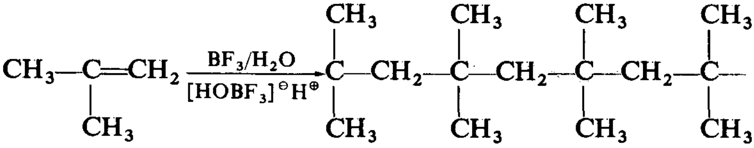
$$H^{\oplus} + CH_2{=}\underset{\textstyle X}{\underset{\uparrow}{CH}} \longrightarrow H{-}CH_2{-}\underset{\textstyle X}{\underset{|}{\overset{\oplus}{C}H}}$$



$$\mathrm{H{-}CH_2{-}\overset{\oplus}{C}H(X) + CH_2{=}CH(X) \rightarrow H{-}CH_2{-}CH(X){-}CH_2{-}\overset{\oplus}{C}H(X)}$$

etc. to polymer

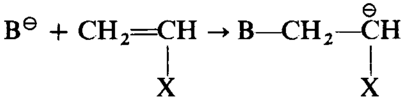
The polymerisation process terminates when the proton is lost from the intermediate carbonium ion. For successful polymerisation by this route electron releasing groups, X, should be attached to the double bond in order to stabilise the developing carbonium ion. Hence ethylene does not polymerise by this route but 2-methylpropene (iso-butylene) produces a very useful synthetic rubber (butyl rubber).



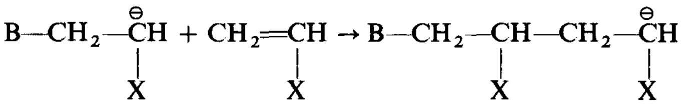
$$\mathrm{CH_3{-}C(CH_3){=}CH_2 \xrightarrow[{[HOBF_3]^{\ominus}H^{\oplus}}]{BF_3/H_2O} {-}C(CH_3)_2{-}CH_2{-}C(CH_3)_2{-}CH_2{-}C(CH_3)_2{-}CH_2{-}C(CH_3)_2{-}}$$

(c) ANIONIC POLYMERISATION

As the term implies, this type of polymerisation involves negative ions. Typical basic catalysts are n-butyl lithium ($C_4H_9^{\ominus}\{Li^{\oplus}$), sodamide in liquid ammonia or sodium in liquid biphenyl. In the last case the sodium produces an anion by transferring an electron to the aromatic hydrocarbon.



$$\mathrm{B^{\ominus} + CH_2{=}CH(X) \rightarrow B{-}CH_2{-}\overset{\ominus}{C}H(X)}$$



$$\mathrm{B{-}CH_2{-}\overset{\ominus}{C}H(X) + CH_2{=}CH(X) \rightarrow B{-}CH_2{-}CH(X){-}CH_2{-}\overset{\ominus}{C}H(X)}$$

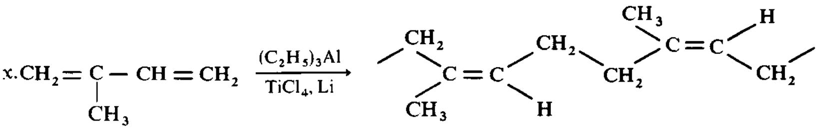
etc. to polymer

Just as cationic polymerisation requires electron releasing groups in the molecule to stabilise the developing carbonium ion so anionic polymerisation takes place with monomers which contain electron attracting groups, e.g. —C≡N and —COOR as in acrylonitrile and methyl methacrylate respectively.

(d) ORGANOMETALLIC REAGENTS

Ziegler and Natta in the 1950s developed catalysts from triethyl aluminium and titanium tetrachloride, which bring about the polymerisation of alkenes in alkane solvents at ordinary pressures and temperatures. The polymers obtained are of high molecular weight, have unbranched chains and often a regular stereochemistry. As has already been mentioned, polymerisation of polystyrene with these catalysts produces an isotactic polymer whereas free radical polymerisation produces the atactic form. Ziegler catalysts usually produce a more crystalline, harder polymer than free radical polymerisation. Propylene will not produce a useful polymer under free radical conditions but with organometallic catalysts yields a commercially important, hard polymer.

With the above Ziegler catalysts plus finely divided lithium metal 2-methyl-1,3-butadiene (isoprene) polymerises almost completely in the *cis* configuration to give a product nearly identical with natural rubber.



cis-1,4-polyisoprene

The mechanism of polymerisation on Ziegler catalysts is not clearly understood but probably involves coordination of the alkene with titanium and progressive stepwise addition of other alkene molecules to the growing polymer chain at this metal atom.

16.3 SYNTHETIC POLYMERS

(a) ADDITION POLYMERS

(i) Polyethylene (Polythene)

Semi-crystalline polyethylene is produced by the free radical polymerisation of ethylene at 100–200 MN/m^2 and up to 250°. The reaction is initiated by peroxides. The polymer has molecular weights of up to 50000 and melts at 110°. Polyethylene is widely used to make colourless sheeting and films (transparent to u.v.), tubing, toys, buckets, etc. Apart from the disadvantage of a low softening point the polymer has outstanding electrical insulation properties and good resistance to chemicals.

Isotactic or crystalline polyethylene is formed by the polymerisation of ethylene with Ziegler catalysts in an alkane solvent at 60°. This so-called high density polyethylene is more rigid and has a better temperature resistance (m.p. 136°) than the semi-crystalline or normal density polymer. The property of resistance to boiling water possessed by high density polyethylene outweighs the somewhat higher cost of this material.

(*ii*) *Polypropylene*

The polymerisation of propene (propylene) with Ziegler catalysts produces a highly crystalline polymer, m.p. 165°C, which is largely isotactic. In fibre form the polymer is extremely strong and impervious to moisture. Polypropylene is harder and more rigid than polyethylene and finds application in a wide range of moulded articles.

(*iii*) *Polytetrafluoroethylene* (*P.T.F.E., Fluon or Teflon*)

Free radical polymerisation of tetrafluoroethylene, $CF_2{=}CF_2$, forms a crystalline fluorocarbon polymer which melts at 330° and is useful up to 300°. The polymer has a low coefficient of friction and also of adhesion and is used for non-stick surfaces. The electrical insulation properties of the polymer are excellent. The cost of polytetrafluoroethylene is high; it is also a difficult material to fabricate and so only finds outlets in specialised applications, e.g. non-stick surfaces for rollers and cooking utensils.

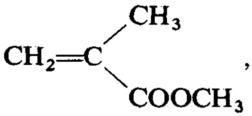
(*iv*) *Polyvinyl chloride* (*P.V.C.*)

Polymerisation of vinyl chloride by the radical mechanism produces an atactic, semi-crystalline material, m.p. 180°. In this form, termed 'rigid P.V.C.', the polymer is manufactured into drain pipes, sheet, rods, etc., and finds wide use where chemical resistance is required. Flexible P.V.C. sheeting for flooring, curtaining, etc., is only obtained when a large amount of plasticiser is incorporated into the rigid form of the polymer. The function of the plasticiser, which is often a high boiling, viscous liquid such as dibutyl phthalate, is to space out the polymer chains and so permit them to move relative to one another.

(*v*) *Polystyrene*

As has already been mentioned, free radical polymerisation of styrene produces an atactic, semi-crystalline polymer. The material softens about 100°, melts below 200°C and is soluble in many organic solvents. Polystyrene is widely used for producing moulded articles and is also used as a foam for heat insulation. The foam is produced by heating polystyrene with a 'blowing agent' which produces large volumes of gas and expands the polymer.

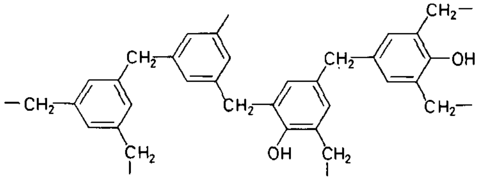
(*vi*) *Polymethyl methacrylate* (*Perspex*)

Methyl methacrylate,  $CH_2{=}C(CH_3)COOCH_3$, is normally polymerised by the radical process to an amorphous, atactic, transparent material which softens at about 95°. The polymer is rather soft but is easily moulded and finds application where a highly transparent polymer is required. Anionic polymerisation produces crystalline, isotactic and syndiotactic polymethyl metacrylates.

(b) CONDENSATION POLYMERS

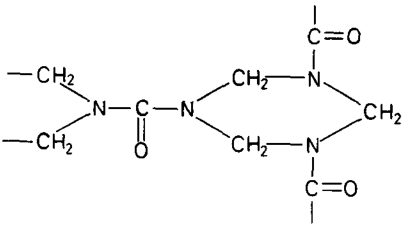
(*vii*) *Phenol-formaldehyde and urea–formaldehyde resins*

Bakelite or phenol-formaldehyde resin was one of the first thermosetting materials to find commercial application. Phenol and formaldehyde are condensed to a low stage of polymerisation; this material is then placed in a mould and heated so that a polymer cross linked in all three dimensions is formed.



structure of phenol-formaldehyde resin

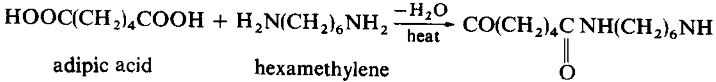
Bakelites are cheap, rigid, stable and good electrical insulators but are only available in dark colours. Urea-formaldehyde resins are more expensive than bakelites but are available in a wider range of colours.



structure of urea-formaldehyde resin

(*viii*) *Polyamides* (*Nylons*)

Polyamides can be obtained in a number of ways but the industrial routes favour condensation of a diamine with a dicarboxylic acid or condensation between amino-acid molecules. Thus hexamethylene diamine and adipic acid condense at 220–280°C to give Nylon (6.6). The designation (6.6) indicates six carbon atoms from each component.



$$HOOC(CH_2)_4COOH + H_2N(CH_2)_6NH_2 \xrightarrow[\text{heat}]{-H_2O} CO(CH_2)_4\underset{\underset{O}{\|}}{C}NH(CH_2)_6NH$$

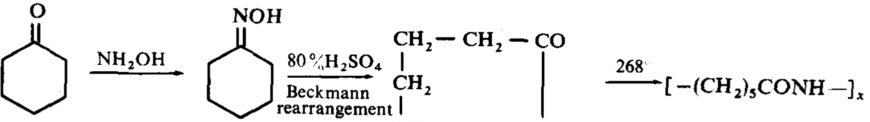
adipic acid

hexamethylene diamine

Nylon (6.6)

The polymer, m.p. 280°C, can be extruded above its melting point through fine holes to form a fibre. This is further processed by stretching to improve the crystal orientation and hence the strength of the fibre. The polymer can also be moulded and has many applications in this form, e.g. nylons have partly replaced brass for light duty bearings. Nylon (6.6) is used in very large quantities as a textile fibre in both the filament and bulked forms.

Nylon (6) can be made from 6-aminohexanoic acid (ε-aminocaproic acid) or the corresponding lactam. The lactam is manufactured from cyclohexanone.



cyclohexanone

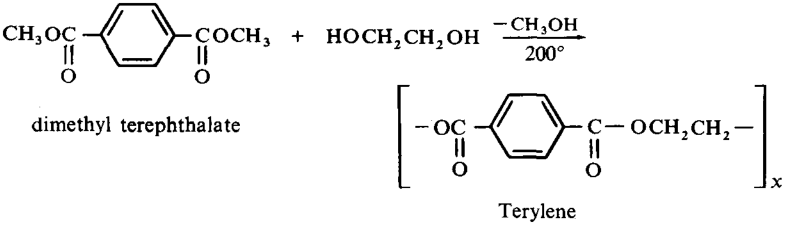
caprolactam

Nylon (6)

This polyamide is also used for textile fibres and is a little softer than Nylon (6.6).

(*ix*) *Polyesters*

A number of polyester condensation polymers are manufactured. Polyethylene terephthalate (Terylene) finds considerable use for fibres and films. Condensation is achieved by heating dimethyl terephthalate with ethylene glycol.



The polymer, m.p. 250°, is amorphous when formed but heat treatment produces crystallisation. Stretching the fibre orientates the crystallites to give a strong filament which is either used alone or blended with other fibres, e.g. wool or cotton.

Alkyd resins are derived from polyhydric alcohols and dibasic acids, e.g. glycerol or glycols are condensed with phthalic, maleic or succinic acids or their anhydrides. Glycerol (2 moles) and phthalic anhydride (3 moles) are heated together to give a tough, highly cross-linked resin called Glyptal. This is widely used as a protective film for it has good resistance to water, light and heat. Alkyd resins can also be moulded but are appreciably more expensive than phenol–formaldehyde resins.

(c) SYNTHETIC RUBBERS

Chemically, natural rubber is largely *cis*-1,4-polyisoprene (page 286). This polymer is amorphous but when stretched the polymer chains straighten and become more orientated. When the restraining force is released the chains resume their previous positions, hence the elastic properties of the material. The polymerisation of isoprene over a Ziegler catalyst to give a product almost identical with natural rubber has already been described.

Styrene–butadiene rubber (S.B.R.) produced from the copolymerisation of 1,3-butadiene and styrene (3:1) finds very wide application for automobile tyres, tubing, hoses, etc. This synthetic rubber has a very good resistance to wear.

Neoprene rubber, formed by the free radical polymerisation of

2-chloro-1,3-butadiene (chloroprene), is almost completely in the *trans* form. The outstanding property of the polymer is its resistance to oil and oxidation. For this reason neoprene rubber is used for oil and petrol hoses and also finds application in chemical manufacturing plant.

Butyl rubber is produced by the cationic polymerisation, with aluminium chloride, of 2-methylpropene (iso-butylene) containing a small percentage of 2-methyl-1,3-butadiene (isoprene). The polymer has good thermal and oxidation resistance properties but poor mechanical strength. An outstanding feature of butyl rubber, is low permeability to gases and for this reason the rubber is used for tyre inner-tubes.

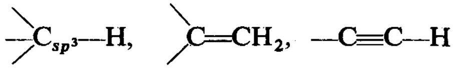
Problems

1. Explain the following:
   - (*a*) ethanethiol has a lower boiling point than ethanol;
   - (*b*) benzene and 1-pentanol have similar molecular weights but very different boiling points;
   - (*c*) the infra-red spectra, measured in solution, of compounds subject to intermolecular hydrogen bonding, change as the solution is progressively diluted.

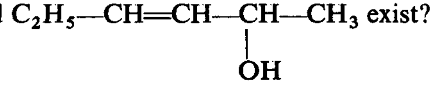
2. Why do the basicity constants of the following bases decrease in the order shown?

   $(C_2H_5)_2NH > (C_2H_5)_3N > C_6H_5NH_2 > p\text{-}NO_2C_6H_4NH_2$

3. Discuss the reactivities of the following types of carbon–hydrogen bonds:



4. What is meant by the terms (*a*) enantiomer, (*b*) specific rotation and (*c*) mirror image? How many stereoisomeric forms of the compound



$$C_2H_5\text{—}CH\text{=}CH\text{—}\underset{\displaystyle OH}{\underset{|}{CH}}\text{—}CH_3$$

   exist?

5. Describe the stereoisomerism associated with (*a*) lactic acid, (*b*) tartaric acid and (*c*) chlorohydroxysuccinic acid. Indicate how a racemic mixture of any one of these acids could be separated by conversion into diastereoisomers.

6. Explain, using suitable examples, the terms asymmetric and dissymmetric. How are optically active substances converted into inactive racemic modifications?

7. Compare the stereochemical changes which occur in the following reactions:

   (*a*) addition of bromine to fumaric and maleic acids;
   (*b*) hydroxylation of the double bond in cyclohexene;
   (*c*) replacement of the halogen atom in 2-bromobutane using aqueous alkali.

8. Draw the possible conformations of (*a*) 2-methylbutane and (*b*) 2,3-dimethylbutane.

9. Explain the observation that the rate of racemisation of (+)-2-iodooctane, in contact with $^{131}I^{\ominus}$ in acetone solution, is twice as fast as the rate of exchange of iodine atoms:

$$RI + {}^{131}I^{\ominus} \rightarrow R^{131}I + I^{\ominus}.$$

10. Compare the addition reactions of the carbon–carbon double bond with those of the carbon–oxygen double bond.

11. What is the general mechanism of nitration of (*a*) benzene and (*b*) benzene substituted by a powerful electron releasing group such as —OH? Give examples to show that the further electrophilic substitution of a monosubstituted benzene is predominantly either *ortho*/*para* or *meta*.

12. Explain why the chemical reactivity of a compound $R_1R_2CH—Br$ is to some extent determined by the sizes of the groups R_1 and R_2. Why does 2-bromopropane react more slowly with nucleophiles than 1-bromopropane under the same reaction conditions?

13. The colourless liquid (A) showed a weak absorption band in the infra-red at 3500 and strong bands at 1760 and 1740 together with a band of medium intensity at 1630 cm^{-1}. The n.m.r. spectrum showed a triplet centred at 8·78, a quartet at 5·85 and strong single lines at 7·8 and 6·7 p.p.m. Treatment of (A) with sodium ethoxide followed by iodomethane gave (B) $C_7H_{12}O_3$ whilst condensation with phenylhydrazine produced a cyclic compound (C) $C_{10}H_{10}N_2O$ and ethanol. Use this evidence to assign a structure to the liquid (A).

14. Substance (A) contained carbon (81·8%), hydrogen (6·06%) and oxygen only. In the infra-red (A) exhibited absorption bands 3000 (w), 2900 (w), 2850 (w), 1670 (s), 1620 (m), 1600 (sh), 1570 (w), 1480 (m) cm^{-1}. Reaction of (A) with semicarbazide hydrochloride and alkali yielded a white solid (C), m.p. 215°C and mild oxi-

dation gave a solid (B), m.p. 133°, which dissolved in potassium hydrogen carbonate solution with effervescence. Explain these observations and assign structures to (A), (B) and (C). (Melting point data for this and other problems can be obtained from a number of sources, e.g. *Qualitative Organic Chemical Analysis* by W. J. Criddle and G. P. Ellis, Butterworths, London, 1967).

15. Substance (A) ($C_7H_7NO_2$) exhibited strong absorption bands in the infra-red at 1520 and 1350 cm^{-1} and in the n.m.r. a singlet at 7·53 and doublets at 2·70 and 1·90 p.p.m. Oxidation of (A) with potassium permanganate produced an acidic substance (B) ($C_7H_5NO_4$) whilst reduction with tin and hydrochloric acid, followed by basification of the solution, gave substance (C) (C_7H_9N), m.p. 45°. Assign structures to substances (A), (B) and (C).

16. The liquid (A) boiled at 218°C and contained 78·6% carbon and 8·2% hydrogen. The infra-red spectrum showed a strong, broad band at 3340 and other bands at 3010 (w), 2970 (m), 1605 (m) and 1500 (s) cm^{-1}. With ferric chloride solution (A) gave a strong coloration and reaction with an alkaline solution of chloroacetic acid, followed by acidification gave a crystalline solid (B) of composition $C_{10}H_{12}O_3$ and m.p. 97°. Identify the liquid (A).

17. What do you understand by the term 'aromatic character'? Illustrate your answer by reference to benzene, anthracene, quinoline and thiophene.

18. Describe the structures of methane, ethylene, acetylene and benzene. How and under what conditions does each of these hydrocarbons react with (*a*) nitric acid, (*b*) chlorine and (*c*) sulphuric acid?

19. Compare the aromatic properties of benzene, naphthalene and anthracene. How could 1-ethyl-4-methylnaphthalene be synthesised, starting from benzene?

20. Compare the addition reactions of bromine and hydrogen bromide to (*a*) propene and (*b*) 1,3-butadiene. Comment on the mechanism of each addition process.

21. How would you distinguish between the following pairs of substances:

(*a*) bromoethane and bromobenzene;
(*b*) benzyl chloride and acetyl chloride;
(*c*) 2-bromobutane and t-butyl bromide?

22. Describe a number of ways in which benzene can be converted into a halogenobenzene. In what ways do the following differ in their reactivity towards nucleophiles: (*a*) chlorobenzene, (*b*) benzyl chloride, (*c*) *p*-nitrochlorobenzene?

23. What is an 'allyl position' in an organic compound? How are allyl compounds prepared and why are allyl halides very reactive towards nucleophiles?

24. Summarise methods of forming carbon–halogen bonds. Why does the type of halogen play a large part in determining the reactivity of an organic halide?

25. Describe methods of making alcohols. Account for the different reactivities of primary, secondary and tertiary alcohols in acid catalysed, alkene-forming elimination reactions.

26. Indicate, with relevant mechanistic detail, methods which may be used to synthesis phenol. Why does *p*-chlorotoluene react with aqueous alkali at high temperatures to give a mixture of *meta* and *para*-cresols?

27. Suggest chemical methods for separating the following pairs of substances:

    (*a*) benzoic acid and phenol; (*b*) hexane and ether;
    (*c*) benzamide and aniline and (*d*) ethyl acetate and acetone.

28. Review the uses of Grignard reagents in organic synthesis. How could the following be prepared using organometallic reagents: (*a*) 2-methyl-1-butanol, (*b*) 3-methylbutanoic acid, (*c*) 2-phenyl-2-pentanol and (*d*) ethyl 3-hydroxy-3-methylpentanoate?

29. Summarise methods of making carboxylic acids. Why do the acidities of the following acids decrease in the order shown?

$$Cl_3CCOOH \gg FCH_2COOH > p\text{-}NO_2C_6H_4COOH > C_6H_5COOH$$

30. 'A number of reactions of aldehydes and ketones are catalysed by both acids and bases.' Explain this statement in terms of reaction mechanisms.

31. Indicate, by means of reaction schemes and brief notes, the chemical differences between aldehydes and ketones. Why is formaldehyde more reactive than either acetaldehyde or acetone?

32. Summarise the reactions of diazonium compounds. How, using a diazonium compound at some stage in the synthesis, would you prepare the following, starting in each case from benzene: (*a*) *m*-nitrophenol, (*b*) *p*-nitrobenzoic acid (*c*) 3,3′-dinitrobiphenyl?

33. Compare the chemical reactions of aliphatic and aromatic amines and account, where possible, for any differences in the reactions of the two types of amine.

34. Explain, with the aid of suitable examples, why the decomposition of alkyl or aryl diazonium compounds in a solution containing a number of different nucleophiles, e.g. water and bromide ions, can give rise to a number of products.

35. Describe the chemical properties and synthetic value of aromatic nitro compounds.

36. Discuss the reactions of (*a*) diketones and (*b*) α,β-unsaturated ketones, in terms of interactions between the groups.

37. Compare the reactions of aliphatic amides and amines ($RCONH_2$ and RNH_2) and of acyl and alkyl halides ($RCOCl$ and RCl). Emphasise the influence of the carbonyl group in modifying the normal properties of the amine and halogen groups.

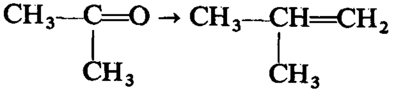
38. Explain what is meant by the term 'activated methyl or methylene groups'. Why are compounds containing such groups useful in organic synthesis reactions?

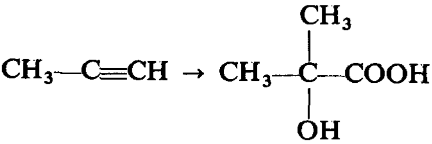
39. Describe the preparation and general uses in organic synthesis of ethyl acetoacetate. Using this reagent how would you synthesise (*a*) 3-methyl-2-pentanone, (*b*) methylsuccinic acid, (*c*) 2,5-hexanedione?

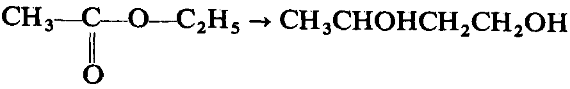
40. 'Ethyl acetoacetate exhibits keto–enol tautomerism.' Explain and give evidence to support this statement. Write down at least three other compounds which exhibit tautomerism.

41. How would you bring about the following transformations in the minimum number of steps?

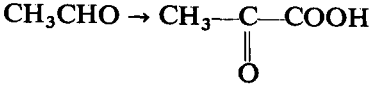
(*a*) $CH_3CH_2CH_2Br \rightarrow CH_3CHOHCH_3$

(*b*)

$CH_3-\underset{CH_3}{\underset{|}{C}}=O \rightarrow CH_3-\underset{CH_3}{\underset{|}{CH}}=CH_2$

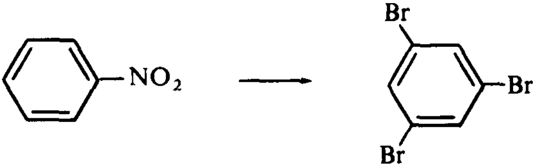
(*c*)

$CH_3-C\equiv CH \rightarrow CH_3-\overset{CH_3}{\overset{|}{\underset{OH}{\underset{|}{C}}}}-COOH$

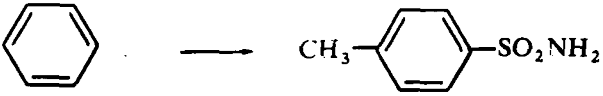
(*d*)

$CH_3-\underset{O}{\underset{\|}{C}}-O-C_2H_5 \rightarrow CH_3CHOHCH_2CH_2OH$

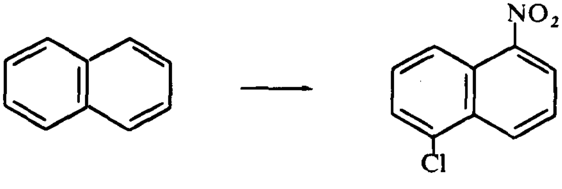
(*e*) $CH_3-CHBr-CH=CH_2 \rightarrow CH_3-CH=CH-CH_2Br$

(*f*)

$CH_3CHO \rightarrow CH_3-\underset{O}{\underset{\|}{C}}-COOH$

(*g*)


(*h*)


(*i*)


(*j*)


42. 'Pyridine and pyrrole are deactivated and activated compounds respectively.' Provide chemical evidence to support this statement.

43. Describe the structure of pyrrole. Chemically pyrrole is considered to resemble phenol. List some chemical reactions of the two substances which support this view.

44. Why are pyridine and nitrobenzene particularly resistant to electrophilic substitution whilst some of their derivatives readily undergo nucleophilic substitution?

45. Differentiate between thermosetting and thermoplastic polymers. Compare the structures of nylons and naturally occurring proteins.

46. Write notes on, and provide examples of (*a*) the polymerisation of alkenes, (*b*) the mechanisms of polymer forming reactions and (*c*) the commercial uses of polymers.

47. Substance (A) is a pale brown oil containing 78·5% carbon, 8·4% hydrogen and 13·1% nitrogen. It reacted with nitrous acid; one portion of the resulting solution gave a dyestuff with an alkaline solution of phenol, another portion reacted with KCN/CuCN to give a liquid (B). When (B) was refluxed with aqueous hydrochloric acid and the solution cooled, a white solid (C), m.p. 110°, precipitated. Deduce the structures of (A), (B) and (C).

48. The liquid (A), b.p. 129°, was weakly basic, Analysis indicated 77·4% carbon, 7·53% hydrogen and 15·0% nitrogen and the mol. wt. was approximately 94. Vigorous oxidation of (A) with potassium permanganate yielded white needles, m.p. 136°C, of an acidic substance (B), $C_6H_5NO_2$. Reaction of (A) with n-butyl lithium and then bromoethane gave a liquid (C) which had a somewhat higher boiling point than (A) but otherwise had similar physical and chemical properties. Explain these observations.

49. The colourless liquid (A) boiled at 94°C and formed an oxime but gave no reaction with Fehling's solution. Reaction with bromine and alkali, followed by ether extraction, separation and acidification of the alkaline layer produced an oil (B), $C_4H_8O_2$. Reaction of (B) with first thionyl chloride and then

ammonia gave a white solid (C), m.p. 129°C, which reacted with bromine and alkali to give a strong base (D). Draw up a reaction scheme to explain these observations.

50. Reaction of (A) with ozone followed by hydrolysis of the ozonide with water and zinc powder yielded only one product (B). With an alkaline solution of sodium cyanide (B) was converted into (C) and the latter yielded lactic acid when refluxed with aqueous hydrochloric acid. Identify substances (A), (B) and (C).

Suggested References for Further Reading

GENERAL

Coulson, C. A., *Valence*, 2nd ed., Oxford University Press, 1961

Cram, D. J. and Hammond, G. S., *Organic Chemistry*, McGraw-Hill, New York, 1959

Dewar, M. J. S., *Hypercongugation*, Ronald Press, New York, 1962

Finar, I. L., *Organic Chemistry*, Vol. I, 5th ed., Longmans, London, 1967

Morrison, R. T. and Boyd, R. N., *Organic Chemistry*, 2nd ed., Allyn and Bacon, Boston, 1966

Pauling, L., *The Nature of the Chemical Bond*, Cornell University Press, Ithaca, N.Y., 1960

Roberts, J. D. and Caserio, M. C., *Basic Principles of Organic Chemistry*, W. A. Benjamin, New York, 1964

STEREOCHEMISTRY

Eliel, E. L., *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, 1962

Hallas, G., *Organic Stereochemistry*, McGraw-Hill, London, 1965

Newman, M. S. (Ed.), *Steric Effects in Organic Chemistry*, Wiley, New York, 1956

REACTION MECHANISMS

Gould, E. S., *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York, 1959

Sykes, P., *A Guidebook to Mechanism in Organic Chemistry*, Longmans, London, 1961

SPECTROSCOPIC METHODS

Silverstem, R. M. and Bassler, G. C., *Spectrometric Identification of Organic Compounds*, Wiley, New York, 1963

Williams, D. H. and Fleming, I., *Spectroscopic Methods in Organic Chemistry*, McGraw-Hill, London, 1966

HETEROCYCLIC CHEMISTRY

ALBERT, A., *Heterocyclic Chemistry: An Introduction,* Athlone Press, London, 1959

KATRITZKY, A. R. and LAGOWSKI, J. M., *Principles of Heterocyclic Chemistry,* Methuen, London, 1967

NATURAL PRODUCTS

FINAR, I. L., *Organic Chemistry,* Vol. II, 4th. ed., Longmans, London, 1968

POLYMERS

MOORE, W. R., *An Introduction to Polymer Chemistry,* University of London Press, London, 1963

ORGANIC CHEMISTRY PROBLEMS

BUSBY, R. E. and SHAW, C. J. G., *Organic Chemistry Problems,* Butterworths, London, 1967

HUTCHINSON, D. W., *Study Problems in Organic Chemistry,* Addison-Wesley, London, 1968

WILLIAMS, D. H. and FLEMING, I., *Spectroscopic Problems in Organic Chemistry,* McGraw-Hill, London, 1967

Index

Page numbers in italic refer to illustrations or tables

Intermediate Organic Chemistry

This text has been written mainly for the H.N.C. student but it will also be useful to those on General degree and Grad. R.I.C. courses, and those studying chemistry as an ancillary subject.

The early chapters cover fundamental theory, including chemical bonding, elementary stereochemistry, reaction mechanisms and spectroscopy. Following chapters discuss the general types of compounds and interactions between adjacent groups. The final section of the book deals with the stereochemistry of more complex molecules, and also polymers and naturally occurring compounds. The author has included a number of relevant problems as well as a useful bibliography.

As this book is designed primarily for the needs of H.N.C. and similar courses, it will be more useful than the average textbook of organic chemistry, which is mainly written for the specialist.

THE BUTTERWORTH GROUP 88 KINGSWAY WC2B 6AB

48s net (£2.40) in UK only

Pearson

Intermediate Organic Chemistry