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ORGANIC CHEMISTRY

Textbook

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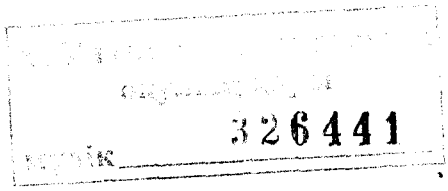
This tutorial includes the methods of synthesizing, the basic physical and chemical properties of organic compounds. Material benefits are stated clearly, consistently, accompanied by illustrative material. At the present level in an interesting, accessible way the fundamentals of organic chemistry, with specific examples shown the connection of science with industry, etc. the Original form of the material, highlight key terms, objectives, and key concepts, the clarity of diagrams and equations facilitates easy assimilation of the material.



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Preface

Since ancient times mankind has known about some substances, now classified as organic compounds, although their pure forms were only obtained much later. Even prehistoric peoples at a primitive stage of culture knew the skill of turning fermented sugary juices into alcoholic beverages, grapes into wine; barley was turned into a special kind of beer by the ancient Egyptians and Germans, honey – alcoholic beverage, also called honey. The process of "distilling" when alcohol is released from liquids by distillation became known only much later, at the time of alchemy (about 900). The name alcohol (al-Kohol), used by ancient Arabs to denote all the highly volatile substances in general, was first given to alcohol by Paracelsus; it is still used at the present day.

Until the end of the first decades of XIX century there was a notion that the compounds formed in plants and animals were generated by a special so-called vital force, and that "gross and simple inorganic forces" causing transformations of inorganic matter do not play any role in the living organism. According to this view, organic substances differ from inorganic ones in that their formation depends on this particular "vital force"; therefore, their artificial production using the methods of inorganic chemistry was considered impossible.

Gradually it was established that the composition of all "organic" substances necessarily includes carbon and, therefore, the presence of this element is characteristic for them. In 1848, Gmelia in his textbook pointed out that carbon is the only essential constituent of organic compounds. This concept was the basis for a new division of chemistry into inorganic and organic chemistry: organic chemistry is a chemistry of carbon compounds, inorganic chemistry covers the compounds of all other elements.

This definition includes some transitional substances, as a result of which the boundary between organic and inorganic chemistry is smoothed out. For example, carbon monoxide CO, carbon dioxide CO_2, as well as carbonic acid H_2CO_3 and its salts are so closely related to the inorganic world that they are usually considered by inorganic chemistry. Hydrocarbons, on the contrary, are considered to be organic compounds, and these substances are the basis of the systematics of organic compounds.

The variety of carbon compounds is an amazing and unique phenomenon, therefore the exceptional position of carbon in chemistry will be explained in further chapters.

This textbook is for students of colleges and universities, workers of chemical industry. It can also be useful to everyone who wants to get acquainted in a short and accessible form with the modern state of organic chemistry.

The book presents the basic information on organic chemistry in an informative form. Theoretical bases of organic chemistry, methods of preparation and properties of organic compounds are considered. Fundamentals of the nomenclature of organic compounds and the most important sources of information on organic chemistry are given.

1 Alkanes

Alkanes are compounds of carbon and hydrogen only, without double bonds, triple bonds, or rings. They all conform to the general formula C_nH_{2n+2} and sometimes are called paraffin hydrocarbons, open-chain saturated hydrocarbons, or acyclic hydrocarbons.

1.1 Physical properties of alkanes. The concept of homology

The series of straight-chain alkanes, in which *n* is the number of carbons in the chain, shows a remarkably smooth gradation of physical properties (see table 1.1 and figure 1.1). As *n* increases, each additional CH_2 group contributes a fairly constant increment to the boiling point and density, and to a lesser extent to the melting point. This makes it possible to estimate the properties of an unknown member of the series from those of its neighbors. For example, the boiling points of hexane and heptane are 69° and 98°, respectively. Thus a difference in structure of one CH_2 group for these compounds makes a difference in boiling point of 29°; we would predict the boiling point of the next higher member, octane, to be 98°+ 29°= 127°, which is close to the actual boiling point of 126°.

Table 1.1 *Physical properties of alkanes*

n	Name	Bp, °C (760 mm)	Mp °C	Density at 20° d_4^{20}, g ml^{-1}
1	Methane	−161.5	−183	0.424
2	Ethane	−88.6	−172	0.546
3	Propane	−42.1	−188	0.501
4	Butane	−0.5	−135	0.579
5	Pentane	36.1	−130	0.626
6	Hexane	68.7	−95	0.659
7	Heptane	98.4	−91	0.684
8	Octane	125.7	−57	0.703
9	Nonane	150.8	−54	0.718
10	Decane	174.1	−30	0.730
11	Undecane	195.9	−26	0.740
12	Dodecane	216.3	−10	0.749
15	Pentadecane	270.6	10	0.769
20	Eicosane	342.7	37	0.786
30	triacontane	446.4	66	0.810

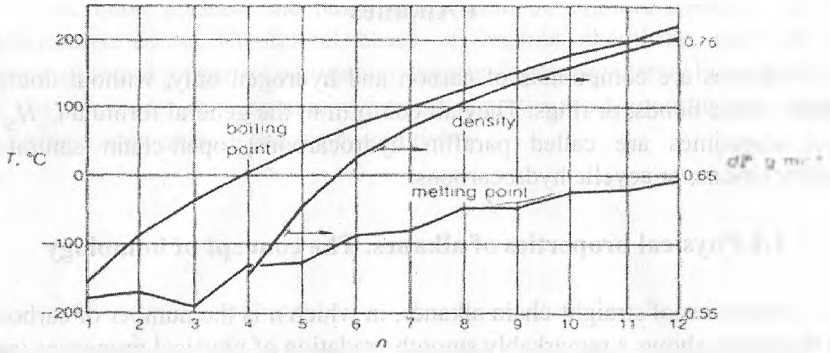


Figure 1.1 *Dependence on n of melting points, and densities of continuous-chain alkanes, $CH_3(CH_2)_{n-1}H$*

Members of a group of compounds, such as the alkanes, that have similar chemical structures and graded physical properties, and which differ from one another by the number of atoms in the structural backbone, are said to constitute a homologous series. When used to forecast the properties of unknown members of the series, the concept of homology works most satisfactorily for the higher-molecular-weight members because the introduction of additional CH_2 groups makes a smaller relative change in the overall composition of such molecules. This is better seen from figure 1.2, which shows

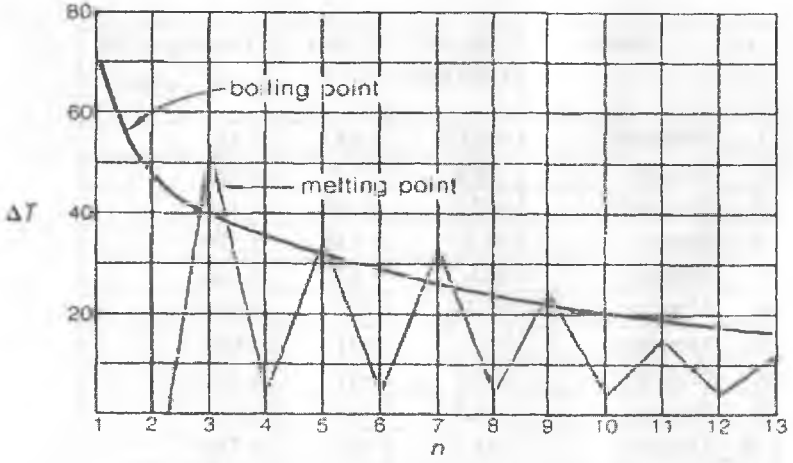


Figure 1.2 *Dependence of (difference in boiling and melting points between consecutive members of the series of continuous-chain alkanes) on n (number of carbon atoms) how , the differences in boiling points and melting points between consecutive members of the homologous series of continuous-chain alkanes, changes with the number of carbons, n.*

Branched-chain alkanes do not exhibit the same smooth gradation of physical properties as do the continuous-chain alkanes. Usually there is too great a variation in molecular structure for regularities to be apparent. Nevertheless, in any one set of isomeric hydrocarbons, volatility increases with increased branching. This can be seen from the data in table 1-2, which lists the physical properties of the five hexane isomers. The most striking feature of the data is the 19° difference between the boiling points of hexane and 2,2-dimethylbutane.

Table 1.2 *Physical properties of hexane isomers*

Isomer	structure	Bp °C	Mp °C	Density At 20°, d_4^{20} g ml^{-1}
Hexane	$CH_3(CH_2)_4CH_3$	68.7	−94	0.659
3-methylpentane	$CH_3CH_2CH(CH_3)CH_2CH_3$	63.3	−118	0.664
2-methylpentane	CH_3OH	60.3	−154	0.653
2,3-dimethylbutane	$CH_3CH(CH_3)CH(CH_3)CH_3$	58.0	-129	0.661
2,2-dimethylbutane	$CH_3C(CH_3)_2CH_2CH_3$	49.7	-98	0.649

1.2 Chemical reactions of alkanes. Combustion of alkanes

Homology hardly can be overestimated as a practical aid for the organic chemist to cope with the large numbers of compounds with which he works. In the simplest approximation, the members of a homologous series are assumed to have essentially the same properties, except for increases in boiling point and melting point as shown in Figure 1-1 for alkanes. This generally will be true, except when the number of carbons is small and when the hydrocarbon

chain has polar substituents. To explain briefly, consider compounds such as alcohols, ROH, which have polar $\overset{\ominus}{O}\text{---}\overset{\oplus}{H}$ groups. As we indicated in Section 1-3, polarity causes molecules to associate with one another, which decreases their volatility, raises melting points, increases solubility in polar liquids, and decreases solubility in nonpolar liquids. This explains why methanol, CH_3OH is much less volatile and much more water-soluble than methane, CH_4. But we find that the water-solubility of alcohols falls off rapidly with the length of the carbon chain, certainly faster than expected for a simple homologous series effect. Whereas methanol,CH_3OH, and ethanol, CH_3CH_2OH are completely soluble in water, butanol, $CH_3CH_2CH_2CH_2OH$, is only slightly soluble. This illustrates the conflicting properties conferred on molecules by polar groups compared to nonpolar hydrocarbon groups, and points up that large changes in physical properties can be expected in the early part of a homologous series until the hydrocarbon chain is sufficiently long, usually six or more carbons, so that the hydrocarbon parts dominate over the polar parts of the molecules.

As a class, alkanes generally are unreactive. The names saturated hydrocarbon, or "paraffin," which literally means "not enough affinity" [L. *par(um),* not enough, *+affins,* affinity], arise because their chemical "affinity" for most common reagents may be regarded as "saturated" or satisfied. Thus none of the C-H or C-C bonds in a typical saturated hydrocarbon, for example ethane, are attacked at ordinary temperatures by a strong acid, such as sulfuric acid (H_2SO_4), or by an oxidizing agent, such as bromine (in the dark), oxygen, or potassium permanganate($KMnO_4$). Under ordinary conditions, ethane is similarly stable to reducing agents such as hydrogen, even in the presence of catalysts such as platinum, palladium, or nickel.

However, all saturated hydrocarbons are attacked by oxygen at elevated temperatures and, if oxygen is in excess, complete combustion to carbon dioxide and water occurs. Vast quantities of hydrocarbons from petroleum are utilized as fuels for the production of heat and power by combustion, although it is becoming quite clear that few of the nations of the world are going to continue to satisfy their needs (or desires) for energy through use of petroleum the way it has been possible in the past.

Petroleums differ considerably in composition depending on their source. However, a representative petroleum[1] on distillation yields the following fractions:

1. *Gas* fraction, boiling point up to 40°, contains normal and branched alkanes from C_1 to C_5. Natural gas is mainly methane and ethane. "Bottled" gas (liquefied petroleum gas) is mainly propane and butane.

2. *Gasoline*, boiling point from 40° to 180°, contains mostly hydrocarbons

from C_6 to C_{10}. Over 100 compounds have been identified in gasoline, and these include continuous-chain and branched alkanes, cycloalkanes, and alkylbenzenes (arenes). The branched alkanes make better gasoline than their continuous-chain isomers because they give less "knock" in high-compression gasoline engines.

3. *Kerosine*, boiling point 180° to 230°, contains hydrocarbons from C_{11} to C_{12}. Much of this fraction is utilized as jet engine fuels or is "cracked" to simpler alkanes (and alkenes). *Light gas oil*, boiling point 230°C to 305°C, C_{13} to C_{17}, is utilized as diesel and furnace fuels. *Heavy gas oil and light lubricating distillate*, boiling point 305° to 405°, C_{18} to C_{25}. *Lubricants,* boiling point 405° to 515°, C_{26}, to C_{17}, familiarly encountered as paraffin wax and petroleum jelly (Vaseline). The distillation residues are known as asphalts. The way in which petroleum is refined and the uses for it depend very much on supply and demand, which always are changing.

1.3 Combustion. Heats of reaction. Bond energies

All hydrocarbons are attacked by oxygen at elevated temperatures and, if oxygen is in excess, complete combustion occurs to carbon dioxide and water:

$$CH_4 + 2O_2 \rightarrow CO_2 + 2H_2O$$

The heat evolved in this process the heat of the combustion reaction, ΔH- is a measure of the amount of energy stored in the C-C and C-H bonds of the hydrocarbon compared to the energy stored in the products, carbon dioxide and water. It can be measured experimentally with considerable accuracy and generally is reported as $\Delta H°$ the amount of heat (in kilocalories) liberated on complete combustion of one mole of hydrocarbon when the reactants and the products are in standard states, and at the same temperature, usually 25°. Not all chemical reactions that occur spontaneously liberate heat some actually absorb heat. By convention, $\Delta H°$ is given a *negative* sign when heat is evolved (exothermic reaction) and a *positive* sign when heat is absorbed (endothermic reaction). The heat evolved or absorbed also is called the enthalpy change.

The task of measuring the heats of all chemical reactions is a formidable one and about as practical as counting grains of sand on the beach. However, it is of practical interest to be able to estimate heats of reaction, and this can be done quite simply with the aid of bond energies. The necessary bond energies are given in table 1.3, and it is important to notice that they apply only to complete dissociation of gaseous substances to gaseous atoms at 25°C.

Table 1.3 *Bond energies (kcal mole^{-1} at 25 ^{o}C)*

Diatomic molecules					
H — H	104.2	F — F	37.5	H — F	135.9
A — A	118.9	Cl — Cl	58.1	H — Cl	103.1
N≡N	226.8	Br — Br	46.4	H — B	87.4
C — O	257.3	J — J	36.5	H — J	71.4
Polyatomic molecules					
C — H	98.7	C — C	82.6	C — F	116
N — H	93.4	C=C	145.8	C — C	81
O — H	110.6	C≡C	199.6	C — B	68
S — H	83	C — N	72.8	C — J	51
P — H	76	C=N	147	C — S	65
N — N	39	C≡N	212.6	C=S	128
N=N	100	C — O	85.5	C — F	65
O — O	35	C=O	192.0	N — C	46
S — S	54	C=O	166	O — F	45
N — O	53	C=O	176	O — C	52
N=O	145	C — O	179	O — B	48

It is important to recognize that the bond energies listed in table 1-3 for all molecules other than diatomic molecules are *average* values. That the C — H bond energy is stated to be 98.7 kcal does not mean that, if the hydrogens of methane were detached one by one, 98.7 kcal would have to be put in at each step. Actually, the experimental evidence is in accord with quite different energies for the separate dissociation steps:

$$CH_4 \longrightarrow CH_3\cdot + H\cdot \quad \Delta H^\circ = 104 \text{ kcal}$$

$$CH_3\cdot \longrightarrow CH_2\cdot + H\cdot \quad \Delta H^\circ = 111 \text{ kcal}$$

$$\cdot CH_2\cdot \longrightarrow \cdot CH + H\cdot \quad \Delta H^\circ = 101 \text{ kcal}$$

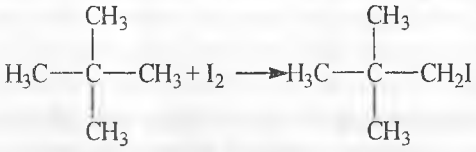
$$\cdot CH \longrightarrow \cdot C\cdot (g) + H\cdot \quad \Delta H^\circ = 81 \text{ kcal}$$

$$CH_4 \longrightarrow \cdot C\cdot (g) + H\cdot \quad \Delta H^\circ = 397 \text{ kcal at } 25^\circ$$

Comparing isomers in table 1.4, we see that 2-methylpropane and 2,2,3,3-tetramethylbutane give off less heat when burned than do butane andoctane, and this is a rather general characteristic result of chain branching.

Cyclopropane has a $\Delta H°$ of combustion 27.7 kcal mole^{-1}*greater* than expected from bond energies, and this clearly is associated with the abnormal C-C-C bond angles in the ring. These matters will be discussed in detail in Chapter 12. For cyclohexane, which has normal bond angles, the heat of combustion is close to the calculated value.

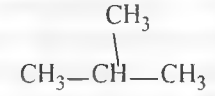
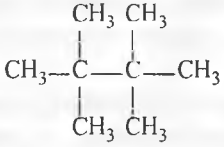
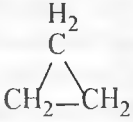
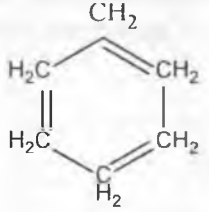
Suppose $\Delta G°$ is positive, what hope do we have of obtaining a useful conversion to a desired product? There is no simple straightforward and general answer to this question. When the reaction is reversible the classic procedure of removing one or more of the products to prevent equilibrium from being established has many applications in organic chemistry, as will be seen later. When this approach is inapplicable, a change in reagents is necessary. Thus, iodine does not give a useful conversion with 2,2-dimethylpro-pane, to give 1-iodo-2,2-dimethylpropane, 2, because the position of equilibrium is too far to the left ($K_{eq} \cong 10^{-5}$)



Alternative routes with favorable $\Delta G°$ values are required. Development of ways to make indirectly, by efficient processes, what cannot be made directly is one of the most interesting and challenging activities of organic chemists.

Table 1.4 *Calculate and experimental heats of combustion of gaseous Hydrocarbons at 25 ^0C*

Hydrocarbon	$\Delta H°$ of combustion calculated from bond energies kcal mole^{-1}	$\Delta H°$ of combustion experimental values kcal mole^{-1}	Discrepancy kcal mole^{-1}
CH_4	-193.8	-191.8	-2.0
$CH_3—CH_2—CH_2—CH_3$	-634.4		+0.7

	-634.4	-1223.0	-1.3
$CH_3(CH_2)_2CH_3$	-1221.8	-1218.9	+1.2
	-440.6	-468.3	-2.9
	-881.1	-881.6	+27.7
	-881.1	-881.8	+0.7

To reach an understanding of why methane and chlorine do not react in the dark, we must consider the details of *how* the reaction occurs-that is, the *reaction mechanism.* The simplest mechanism would be for a chlorine molecule to collide with a methane molecule in such a way as to have chloromethane and hydrogen chloride formed directly as the result of a *concerted* breaking of the Cl — Cl and C — H bonds. The failure to react indicates that there must be an energy barrier too high for this mechanism to operate.

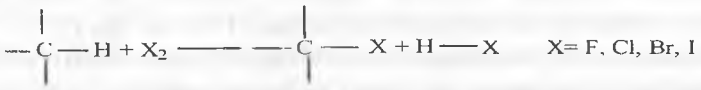
1.4 Practical halogenations. Problems of selectivity

Given the knowledge that a particular reaction will proceed at a suitable rate, a host of practical considerations are necessary for satisfactory operation.

These considerations include interference by possible side reactions that give products other than those desired, the ease of separation of the desired products from the reaction mixture, and costs of materials, apparatus, and labor. We shall consider these problems in connection with the important synthetic reactions discussed in this book.

The chlorination of saturated hydrocarbons can be induced by light, but also can be carried out at temperatures of about 300° in the dark. Under such circumstances the mechanism is similar to that of light-induced chlorination, except that the chlorine atoms are formed by thermal dissociation of chlorine molecules. Solid carbon surfaces catalyze thermal chlorination, possibly by aiding in the cleavage of the chlorine molecules.

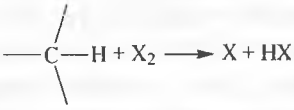
Direct monohalogenation of saturated hydrocarbons works satisfactorily only with chlorine and bromine. For the general reaction



the calculated $\Delta H°$ value is negative and very large for fluorine, negative and moderate for chlorine and bromine, and positive for iodine (see table 1.5). With fluorine, the reaction evolves so much heat that it may be difficult to control, and products from cleavage of carbon-carbon as well as of carbon-hydrogen bonds may be obtained. The only successful, direct fluorination procedure for hydrocarbons involves diffusion of minute amounts of fluorine mixed with helium into liquid or solid hydrocarbons at low temperatures, typically -78° (Dry Ice temperature). As fluorination proceeds, the concentration of fluorine can be increased. The process is best suited for preparation of completely fluorinated compounds, and it has been possible to obtain in this way amounts of and $(CF_3)_3—C(CF_3)_3$ from 2,2-dimethyl-propane and 2,2,3,3-tetramethylbutane corresponding to 10-15% yields based on the fluorine used.

Bromine generally is much less reactive toward hydrocarbons than chlorine is, both at high temperatures and with activation by light. Nonetheless, it usually is possible to brominate saturated hydrocarbons successfully. Iodine is unreactive.

Table 1.5 *Calculated Heats of Reaction for Halogenation of Hydrocarbons*

X	$\Delta H°$(kcal mole^{-1})[a]	
F	-116	
Cl	-27	
Br	-10	
I	13	

The chlorination of methane does not have to stop with the formation of chloromethane (methyl chloride). It is usual when chlorinating methane to obtain some of the higher chlorination products: dichloromethane (methylene

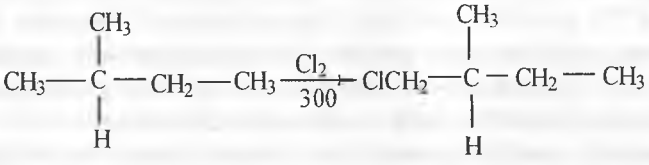
chloride), trichloromethane (chloroform), and tetrachloromethane (carbon tetrachloride):

$$CH_4 \rightarrow \underset{\text{chloro-methane}}{CH_3Cl} \rightarrow \underset{\text{dichioro-methane}}{CH_2Cl_2} \rightarrow \underset{\text{trichioro-methane}}{CHCl_3} \rightarrow \underset{\text{tetrachloro methane}}{CCl_4}$$

In practice, one can control the degree of substitution to a considerable extent by controlling the methane-chlorine ratio. For example, for monochlorination to predominate, a high methane-chlorine ratio is necessary such that the chlorine atoms react with CH_4 and not with CH_3Cl

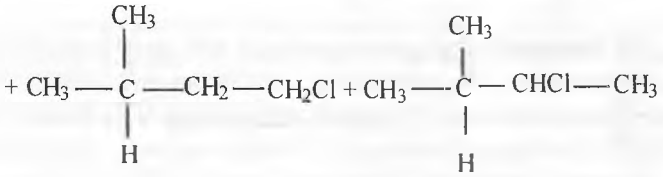
1.5 Selectivity in alkane halogenation

For propane and higher hydrocarbons for which more than one monosubstitution product is generally possible, difficult separation problems may arise when a particular product is desired. For example, the chlorination of 2-methyl-butane 3 at 300°C gives all four possible monosubstitution products, 4, 5, 6, and 7:



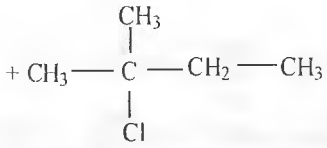
2-methylbutane
3

1-chloro-2-methylbutane (30%)[4]



1-chloro-3-methylbutane (15%)
5

3-choloro-2-methylbutane (33%)
6



2-chloro-2-methylbutane
(22%)

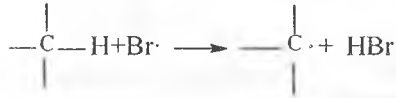
7

On a purely statistical basis, we may expect the ratio of products from 3 to correlate with the number of available hydrogens at the various positions of substitution. That is, 4, 5, 6, and 7 would be formed in the ratio 6:3:2:1 (50%:25%:17%:8%). However, as can be seen from Table 1-6, the strengths of hydrogen bonds to primary, secondary, and tertiary carbons are not the same and, from the argument we would expect the weaker C-H bonds to be preferentially attacked by Cl·. The proportion of 7 formed is about three times that expected on a statistical basis which is in accord with our expectation that the tertiary C-H bond of 2-methylbutane should be the weakest of the C-H bonds.

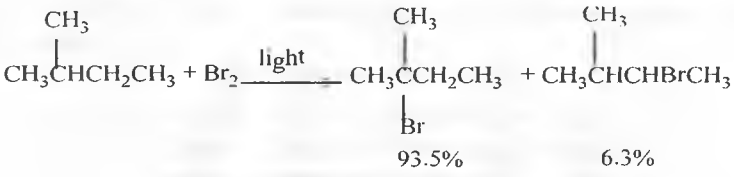
The factors governing selectivity in halogenation of alkanes follow:

1. The rates at which the various C-H bonds of 2-methylbutane are broken by attack of chlorine atoms approach 1: 1: 1 as the temperature is raised above 300°. At higher temperatures both chlorine atoms and hydrocar bons become more reactive because of increases in their thermal energies. Ultimately, temperatures are attained where a chlorine atom essentially re-moves the first hydrogen with which it collides regardless of position on the hydrocarbon chain. In such circumstances, the composition of monochlorination products will correspond to that expected from simple statistics.

2. Bromine atoms are far more selective than chlorine atoms. This is not unexpected because not unexpected because



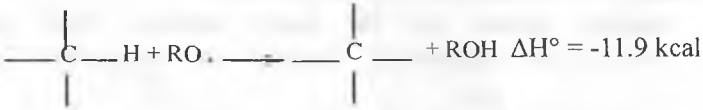
reactions with a chlorine atom usually are exothermic. Bromine removes only those hydrogens that are relatively weakly bonded to a carbon atom. As predicted, attack of Br. on 2-methyl-butane leads mostly to 2-bromo-2-methylbutane, some secondary bromide, and essentially no primary bromides:



3. The selectivity of chlorination reactions carried on in *solution* is increased markedly in the presence of benzene or alkyl-substituted benzenes because benzene and other arenes form loose complexes with chlorine atoms. This substantially cuts down chlorine-atom reactivity, thereby making the chlorine atoms behave more like bromine atoms.

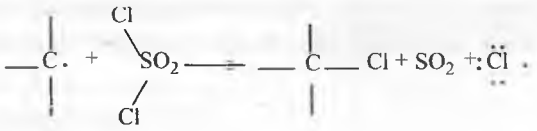
It is possible to achieve chlorination of alkanes using sulfuryl chloride (SO_2Cl_2, bp 69°) in place of chlorine:

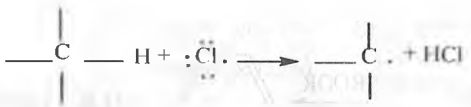
The reaction has a radical-chain mechanism and the chains can be initiated by light or by chemicals, usually peroxides, ROOR. Chemical initiation requires an *initiator* with a weak bond that dissociates at temperatures between 40-80°. Peroxides are good examples. The O-O bond is very weak (30-50 kcal) and on heating dissociates to alkoxyl radicals, RO. which are reactive enough to generate the chain-propagating radicals from the reactants. The exact sequence of chemical initiation is not always known, but a plausible route in the present case would have RO. abstract hydrogen from the alkane:



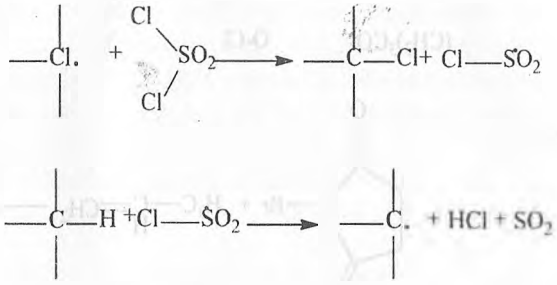
$mole^{-1}$

The propagation steps that would follow are

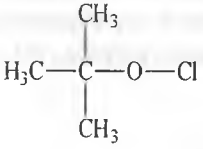




Chlorination with sulfuryl chloride of alkanes with more than one kind of hydrogen gives a mixture of alkyl chlorides resembling that obtained with chlorine itself. However, in some circumstances the mixture of chlorides is not the same mixture obtained with chlorine itself and when this is true, the hydrogen-abstraction step probably involves $\bullet SO_2Cl$ rather than $Cl\bullet$. The alternative propagation steps then are



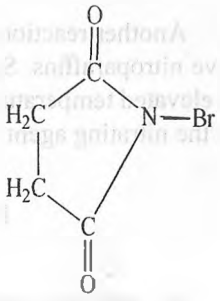
Different product ratios are expected from $Cl\bullet$ and $ClSO_4$ for the same reason that $Cl\bullet$ and $Br\bullet$ lead to different product ratios. Other reagents that sometimes are useful halogenating agents in radical-chain reactions include



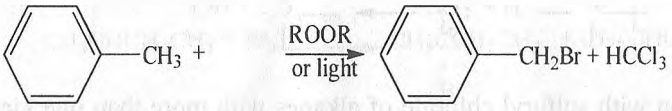
tert- butyl hypochlorite

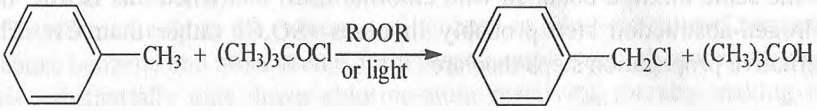
$BrCCl_3$

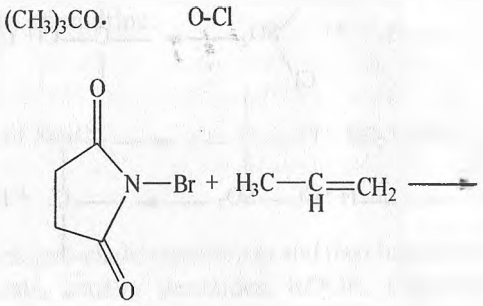
bromotrichloromethane



N- bromosuccinimide





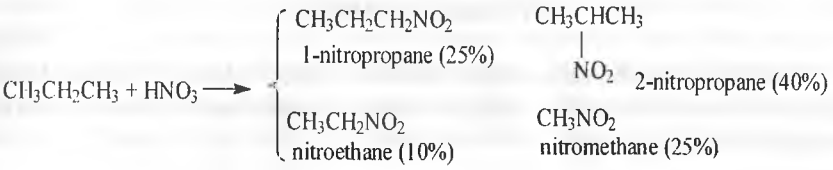


1.6 Nitration of alkanes

Another reaction of commercial importance is the nitration of alkanes to give nitroparaffins. Such reactions usually are carried out in the vapor phase at elevated temperatures using nitric acid (HNO_3) or nitrogen tetroxide (N_2O_4) as the nitrating agent:

$$RH + HNO_3 \xrightarrow{\sim 425} RNO_2 + H_2O$$

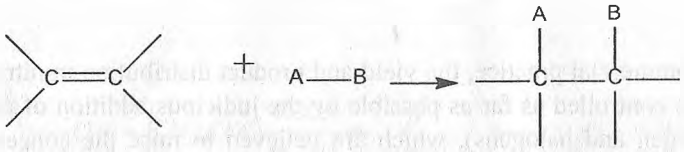
All available evidence points to a radical mechanism for nitration, but many aspects of the reaction are not fully understood. Mixtures are obtained; nitration of propane gives not only 1- and 2-nitropropanes but nitroethane and nitromethane:



In commercial practice, the yield and product distribution in nitration of alkanes is controlled as far as possible by the judicious addition of catalysts (e.g., oxygen and halogens), which are believed to raise the concentration of alkyl radicals. The products are separated from the mixtures by fractional distillation.

2 Alkenes and alkynes

Carbon-carbon double and triple bonds undergo a wide variety of addition reactions in which one of the multiple bonds is broken and two new bonds to carbon are formed:



The importance of such reactions to synthetic organic chemistry is paramount. It is our intention in this and the following chapter to show the great diversity, utility, and specificity of addition reactions of alkenes and alkynes.

We will begin with a brief discussion of the physical and spectroscopic properties of alkenes and alkynes. But the major emphasis in the chapter is on two main types of reactions, ionic addition and radical-chain addition. For ionic additions we will make extensive use of the classification of reagents as electrophiles and nucleophiles.

2.1 Physical properties of alkenes and alkynes

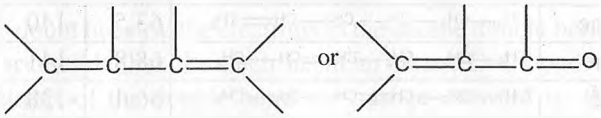
In general, the physical properties of alkenes are similar to those of alkenes. The data of Table 2.1 allow comparison of the boiling points, melting points, and densities of several alkenes with the corresponding alkenes that have the same carbon skeleton. Like the continuous-chain alkenes, the 1-alkenes form a homologous series of compounds that show regular changes in physical properties with increasing chain length.

The boiling points, melting points, and densities of the simple alkynes (also included in table 2.1) are somewhat higher than those of the corresponding alkenes or alkenes, and these properties also show regular changes as the chain length is increased.

2.2 Spectroscopic properties of alkenes and alkynes

The infrared spectra of alkenes are sufficiently different from those of alkenes in most instances to make it possible to recognize when a double bond is present. For example, in the infrared spectrum of 1-butene the absorption band near 1650 cm^{-1} is characteristic of the stretching vibration of the double bond. In general, the intensity and position of this band depends on the structure of the alkenes; it varies with the degree of branching at the double bond.

with the presence of a second unsaturated group in conjugation with the first and with the symmetry of the substitution of the double bond. However, in many cases the absorption bands caused by the various modes of vibration of the alkenic C–H bonds frequently are more useful for detecting a double bond and identifying its type than is the absorption band caused by C=C stretch.



With 1-butene, absorptions arising from the C-H vibrations of the terminal $=CH_2$ group occur near 3100 cm^{-1}, 1420 cm^{-1}, and 915 cm^{-1}, and those of the –CH= grouping near 3020 cm^{-1}. 1420 cm^{-1} are due to inplane bending. The other intens absorptions, near 1460 cm^{-1} and 3000 cm^{-1}, are due to C–H vibrations of the CH_3CH_2– group. These illustrate a further point namely, the positions of the infrared absorptions of alkyl C-H bonds are significantly different from those of alkenic C–H bonds.

The double bonds of an alkene with no alkenic hydrogens are difficult to detect by infrared spectroscopy and in such cases Raman spectroscopy is helpful.

Table 2.1 *Comparison of Physical properties of alkanes, alkenes and alkynes*

Hydrocarbon	Formula	B_p,°C	M_p,°C	Density, d_4^{20}
ethane	$CH_3—CH_3$	-88,6	-183	
ethene	$H_2C=CH_2$	-105	-169	
ethyne	$HC\equiv CH$	-83	-81	
propane	$H_3C—CH_2—CH_3$	-42,1	-187	0,501
propene	$CH_3—CH=CH_2$	-47,8	-185	0,514
propyne	$CH_3—C\equiv CH$	-23,2	-102,7	0,706
butane	$CH_3—CH_2—CH_2—CH_3$	-0,5	-138	0,579
1 - butene	$CH_3—CH_2—CH=CH_2$	-6,3	-185	0,595
2 - butene	$CH_3—CH=CH—CH_3$	3,7	-139	0,621
1 – butyne	$CH_3—CH_2—C\equiv CH$	8,1	-126	0,65
2 – butyne	$CH_3—C\equiv C—CH_3$	27,0	-32	0,691
pentane	$CH_3—CH_2—CH_2—CH_2—CH_3$	36,1	-129	0,626
1 – pentene	$CH_3—CH_2—CH_2—CH=CH_2$	30,0	-165	0,641

Continuation of table 2.1

2 - pentene	$CH_3—CH_2—CH=CH—CH_3$	37,9	-151	0,656
1 - pentyne	$CH_3—CH_2—CH_2—C\equiv CH$	40,2	-106	0,690
2 - pentyne	$CH_3—CH_2—C\equiv C—CH_3$	56,1	-109	0,711
hexane	$CH_3—CH_2—CH_2—CH_2—CH_2—CH_3$	68,7	-95	0,659
1 – hexane	$CH_3—CH_2—CH_2—CH_2—CH=CH_2$	63,5	-140	0,674
2 - hexene	$CH_3—CH_2—CH_2—CH=CH—CH_3$	68,8	-141	0,687
3- hexene	$CH_3—CH_2—CH=CH—CH_2—CH_3$	66,4	-138	0,680
1 – hexyne	$CH_3—CH_2—CH_2—CH_2—C\equiv CH$	71	-132	0,716
2 – hexyne	$CH_3—CH_2—CH_2—C\equiv C—CH_3$	84,0	-88	0,732
3- hexene	$CH_3—CH_2—C\equiv C—CH_2—CH_3$	81,8	-105	0,724

Spectroscopic properties of alkynes. The infrared spectrum of a monosubstituted alkyne such as ethynylbenzene, $C_6H_5C\equiv CH$, has a strong band near 3300 cm^{-1}, which is characteristic of the carbon-hydrogen stretching vibration in the grouping ≡C–H. At a lower frequency (longer wavelength) around 2100 cm^{-1}, there is a band associated with the stretching vibration of the triple bond. Therefore the presence of the grouping – C≡CH in a molecule may be detected readily by infrared spectroscopy. However, the triple bond of a disubstituted alkyne, R–C≡C–R, is detected less easily because there is no ≡C–H absorption near 3300 cm^{-1}, and furthermore the C≡C absorption sometimes is of such low intensity that it may be indiscernible. Raman spectroscopy or chemical methods must then be used to confirm the presence of a triple bond. The difference in chemical shift between the two types of protons is considerably larger than between alkenic and aromatic protons and, in general, alkynic protons come into resonance at higher magnetic fields than alkenic or aromatic protons. In fact, the ≡C–H protons of alkynes have chemical shifts approaching those of alkyl protons.

Alkynes, like alkenes, undergo electronic absorption strongly only at wavelengths in the relatively inaccessible region below 200 nm. However, when the triple bond is conjugated with one or more unsaturated groups, radiation of longer wavelength is absorbed. To illustrate, ethyne absorbs at 150 nm and 173 nm, whereas 1-buten-3-yne ($CH_2 = CH–C \equiv CH$) absorbs at 219 nm and 227.5 nm.

The mass spectra of alkenes and alkynes usually give distinct molecular ions; however, the fragmentation is often complex and not easily interpreted.

2.3 Electrophilic additions to alkenes

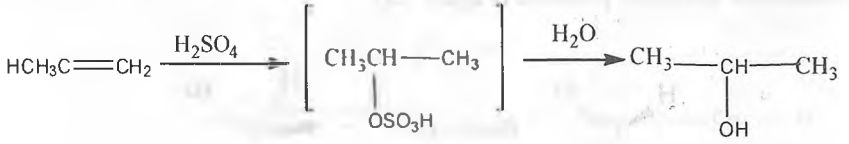
The reactions of alkanes are homolytic processes, which means that the bonds are made and broken through radical or atomic intermediates. In contrast,

the S_N and E reactions of alkyl halides, involve heterolytic bond cleavage and ionic reagents or products. An especially important factor contributing to the differences between the reactions of the alkanes and alkyl halides is the slight ionic character of C–H bonds compared to C – halide bonds. The alkenes are like the alkanes in being nonpolar compounds and it may come as a surprise that many important reactions of alkenes are heterolytic reactions. Why should this be so? No doubt because the electrons in the alkene double bonds are more exposed and accessible than the electrons in an alkane C–C bond.

The electrons of the double bond are pushed outward by their mutual repulsions, and their average positions are considerably farther from the bond axis than the electron positions of a single bond. In such circumstances, electrophilic reagents, which act to acquire electrons in chemical reactions, are expected to be particularly reactive. This is actually the case. Furthermore, reagents that are primarily nucleophilic (electron-donating) are notoriously poor for initiating reactions at carbon-carbon double bonds. Exceptions occur when the double bonds carry substituents with a sufficiently high degree of electron-attracting power to reduce the electron density in the double bond enough to permit attack by a nucleophilic agent.

Examples of electrophilic reagents that normally add to carbon-carbon double bonds of alkenes to give saturated compounds include halogens (Cl_2, Br_2 and I_2), hydrogen halides (HCl and HBr), hypohalous acids (HOCl and HOBr), water, and sulfuric acid.

The mechanisms of these reactions have much in common and have been studied extensively from this point of view. They also have very considerable synthetic utility. The addition of water to alkenes (hydration) is particularly important for the preparation of a number of commercially important alcohols. Thus ethanol and 2-propanol (isopropyl alcohol) are made on a very large scale by the hydration of the corresponding alkenes (ethene and propene) using sulfuric or phosphoric acids as catalysts. The nature of this type of reaction will be described later.



2-propanol

2.4 The stepwise ionic mechanism. Halogen addition

We shall give particular attention here to the addition of bromine to alkenes because this reaction is carried out very conveniently in the laboratory

and illustrates a number of important points about electrophilic addition reactions. Much of what follows applies to addition of the other halogens, except fluorine.

A significant observation concerning bromine addition is that it and many of the other reactions listed on page 26 proceed in the dark and are not influenced by radical inhibitors. This is evidence against a radical-chain mechanism of the type involved in the halogenation of alkanes. However, it does not preclude the operation of radical-addition reactions under other conditions, and, as we shall see later in this chapter, bromine, chlorine, and many other reagents that commonly add to alkenes by ionic mechanisms also can add by radical mechanisms.

One alternative to a radical-chain reaction for bromine addition to an alkene would be the simple four-center, one-step process shown in Figure 2.1.

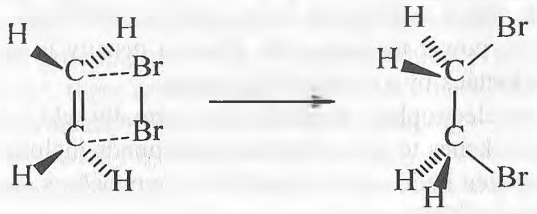


Figure 2.1 *Representation of a one-step suprafacial mechanism for addition of bromine to ethane. Gas-phase additions appear to proceed in this manner.*

The mechanism of Figure 2.1 cannot be correct for bromine addition to alkenes in solution for two important reasons. First, notice that this mechanism requires that the two C-Br bonds be formed on the same side of the double bond, and hence produce suprafacial addition. However, there is much evidence to show that bromine and many other reagents add to alkenes to form clntaraficial additiorz products (Figure 2.2).

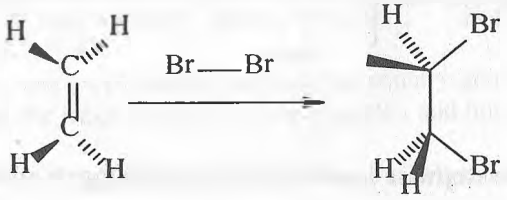
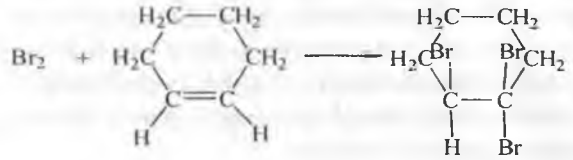


Figure 2.2 *Antarafacial addition of bromine to ethane; usually observed in solution*

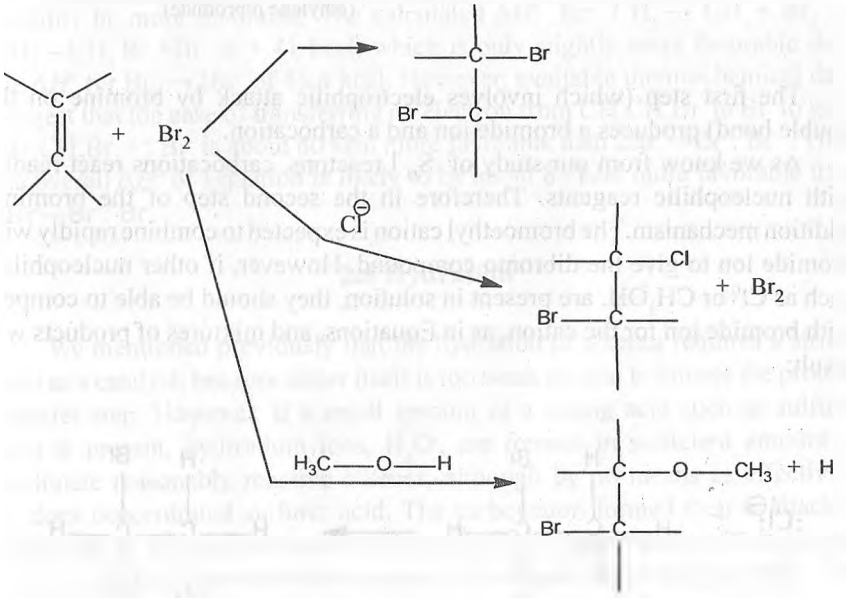
Cyclohexene adds bromine to give trans- 1,2 – dibromocyclohexane:



trans-1,2-dibromocyclohexene

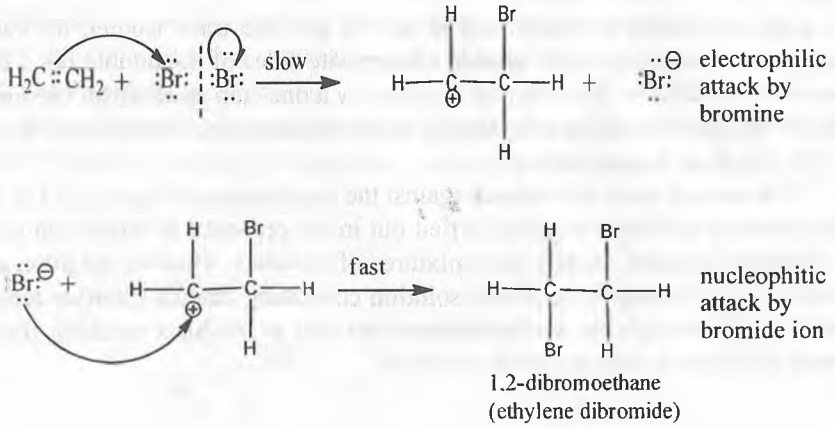
The cis isomer is not formed at all. To give the trans isomer, the two new C–Br bonds have to be formed on opposite sides of the double bond by antarafacial addition. But this is impossible by a one-step mechanism because the Br–Br bond would have to stretch too far to permit the formation of both C–Br bonds at the same time.

The second piece of evidence against the mechanism of Figure 2.2 10^{-7} is that bromine addition reactions carried out in the presence of more than one nucleophilic reagent usually give mixtures of products. Thus the addition of bromine to an alkene in methanol solution containing lithium chloride leads not only to the expected dibromoalkane, but also to products resulting from attack by chloride ions and by the solvent:



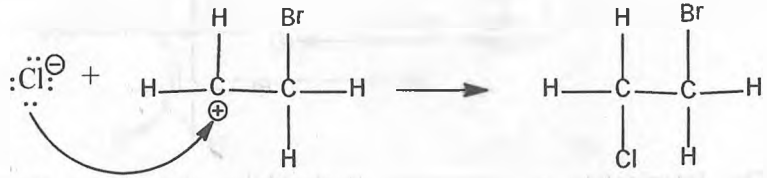
The intervention of extraneous nucleophiles suggests a stepwise mechanism in which the nucleophiles compete for a reactive intermediate formed in one of the steps.

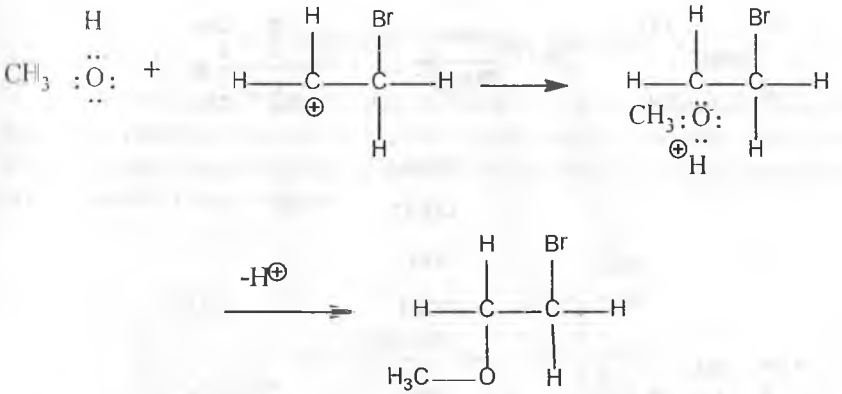
A somewhat oversimplified two-step mechanism that accounts for most of the foregoing facts is illustrated for the addition of bromine to ethene. In the formulation shown below, the curved arrows are not considered to have real mechanistic significance, but are used primarily to show which atoms can be regarded as nucleophilic (donate electrons) and which as electrophilic (accept electrons). The arrowheads always should be drawn to point to the atoms that are formulated as accepting a pair of electrons.



The first step (which involves electrophilic attack by bromine on the double bond) produces a bromide ion and a carbocation.

As we know from our study of S_N l reactons, carbocations react readily with nucleophilic reagents. Therefore in the second step of the bromine-addition mechanism. The bromoethyl cation is expected to combine rapidly with bromide ion to give the dibromo compound. However, if other nucleophiles, such as Cl^0 or CH_3OH, are present in solution, they should be able to compete with bromide ion for the cation, as in Equations, and mixtures of products will result:





To account for the observation that all of these reactions result in antarafacial addition, we must conclude that the first and second steps take place from opposite sides of the double bond.

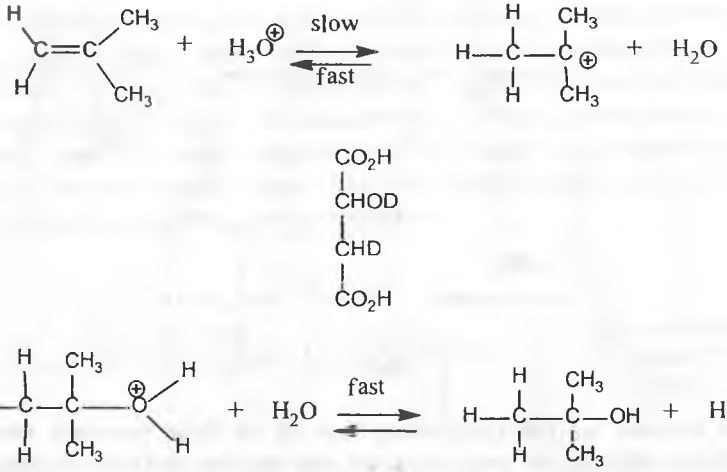
An alternative to Equation would be to have Br_2 ionize to Br^+ and Br^-, with a subsequent attack of Br^+ on the double bond to produce the carbocation. The fact is that energy required for such an ionization of Br, is prohibitively large even in water.

Solution ($\Delta H^\circ \geq 80$ kcal). One might well wonder why Equation could possibly be more favorable. The calculated ΔH° for $CH_2 \rightarrow CH_2 + Br_2 \rightarrow CH_2 - CH_2Br + Br$ is + 41 kcal, which is only slightly more favorable than the ΔH° for $Br_2 \rightarrow 2Br$ of 46.4 kcal. However, available thermochemical data suggest that the ease of transferring an electron from CH_2CH_2Br to Br to give $CH_2CH_2Br + :Br^-$ is about 80 kcal more favorable than $2Br^- \rightarrow Br^+ : Br^-$. Thus the overall ΔH° of Equation is likely to be about 85 kcal more favorable than $2Br^- \rightarrow Br^+ : Br^-$.

2.5 Hydration

We mentioned previously that the hydration of alkenes requires a strong acid as a catalyst, because water itself is too weak an acid to initiate the proton-transfer step. However, if a small amount of a strong acid such as sulfuric acid is present, hydronium ions, H_3O^+, are formed in sufficient amount to protonate reasonably reactive alkenes, although by no means as effectively as does concentrated sulfuric acid. The carbocation formed then is attacked rapidly by a nucleophilic water molecule to give the alcohol as its conjugate acid, 2 which regenerates hydronium ion by transferring a proton to water. The reaction sequence follows for 2-methylpropene:

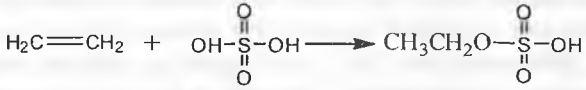
$$H_2SO_4 + H_2O \rightleftharpoons H_3O^\oplus + HSO_4^\ominus$$



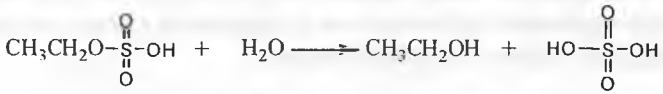
In this sequence, the acid acts as a catalyst because the hydronium ion used in the proton addition step is regenerated in the final step.

Sulfuric acid (or phosphoric acid) is preferred as an acid catalyst for addition of water to alkenes because the conjugate base, HSO_4^- (or H_2PO_4), is a poor nucleophile and does not interfere in the reaction. However, if the water concentration is kept low by using concentrated acid, addition occurs to give sulfate (or phosphate) esters. The esters formed with sulfuric acid are either alkyl acid sulfates R-OSO_3H or dialkyl sulfates $(RO)_2SO_2$. In fact, this is one of the major routes used in the commercial production of ethanol and the terms conjugate acid and conjugate base are very convenient to designate substances that are difficult to name simply as acids, bases, or salts. The conjugate acid of a compound X is XH^+ and the conjugate base of HY is Y^+ Thus H_2O is the conjugate acid of water, while OH^+ is its conjugate base. Water itself is then both the conjugate base of H_3O and the conjugate acid of OH^-

2-propanol. Ethene and sulfuric acid give ethyl hydrogen sulfate, which reacts readily with water in a second step to give ethanol:



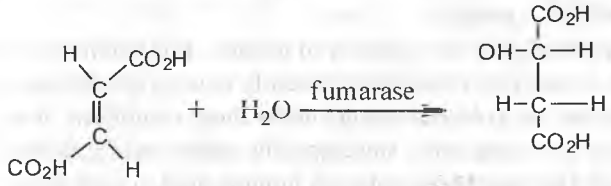
ethene sulfuric acid ethyl hydrogen sulfate



ethyl hudrogen sulfate ethanol sulfuric acid

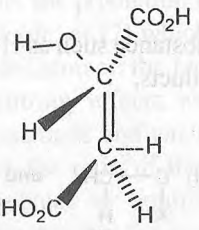
2.6 A biological hydration reaction

The conversion of fumaric acid to malic acid is an important biological hydra-tion reaction. It is one of a cycle of reactions (Krebs citric acid cycle) involved in the metabolic combustion of fuels (amino acids and carbohydrates) to CO_2 and H_2O in a living cell.



trans-butenedioic acid
(fumaric acid)

2-hydroxybutanedioic acid
(L-malic acid)



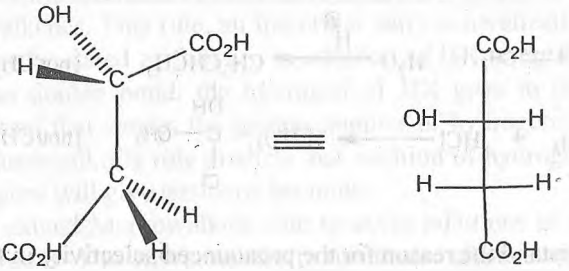


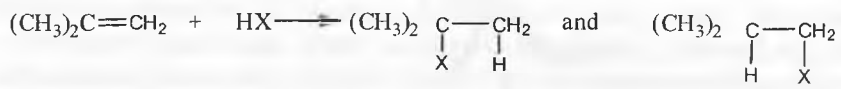
Figure 2.3 *Representation of the course of enzyme-induced hydration of femaric acid (trans butenedic acid) o give L-malic acid (L-2-hydroxybunadiodic acid).*

If the enzyme complexes with either $-CO_2H$ (carbohyl) group of fumaric, and then adds wash from its right hand and H from its left, the proper stereosomer (L) is produced by antarafacial addition to the double bond. At least three particular points of contact mast occur between enzyme and substrate to provide the observed stereospecificity of the addition. Thus, if the enzyme funtions equally well with alcenic hydrogen of the carboxyl toward its mouth (as shown in the drawing) the reaction still will give antarafacial addition, but D, L-malic acid will be the product.

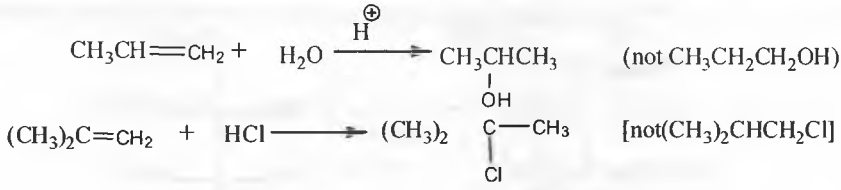
The reaction is remarkable for a number of reasons. It is readily reversible and is catalyzed by an enzyme (fumarase) at nearly neutral conditions (pH = 7). Without the enzyme, no hydration occurs under these conditions. Also, the enzymatic hydration is a completely stereospecific antarafacial addition and creates L-malic acid. The enzyme operates on fumaric acid in such a way that the proton adds on one side and the hydroxyl group adds on the other side of the double bond of fumaric acid. This is shown schematically in Figure 2.3.

2.7 Orientation in addition to alkenes

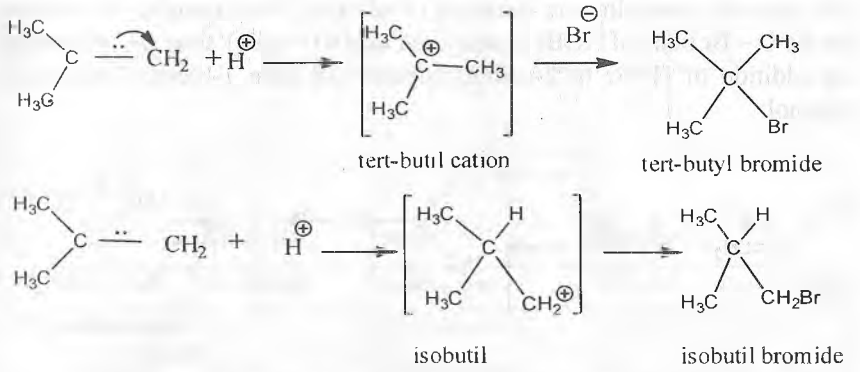
Addition of an unsymmetrical substance such as H X to an unsymmetrical alkene theoretically can give two products,



but both seldom are formed in equal amounts; in fact, one isomer usually is formed to the exclusion of the other. For example, the hydration of propene gives 2-propanol (not 1-propanol), and hydrogen chloride adds to 2-methylpropene to give tert-butyl chloride (not isobutyl chloride):



To understand the reason for the pronounced selectivity in the orientation of addition of electrophiles, it will help to consider one example, hydrogen bromide addition to 2-methylpropene. Two different carbocation intermediates could be formed by attachment of a proton to one or the other of the double-bond carbons:



Subsequent reactions of the cations with bromide ion give tertbutyl bromide and isobutyl bromide. In the usual way of running these additions, the product is very pure tert-butyl bromide.

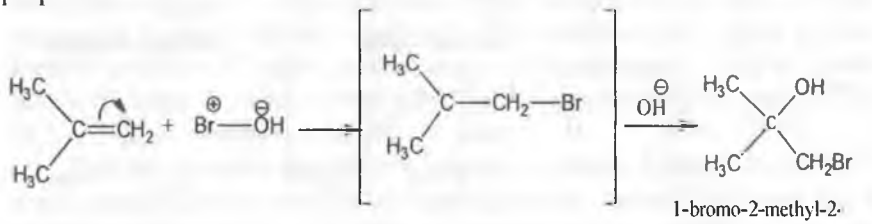
How could we have predicted which product would be favored? The first step is to decide whether the prediction is to be based on (1) which of the two products is the more stable, or (2) which of the two products is formed more rapidly. If we make a decision on the basis of product stabilities, we take into account ΔH° values, entropy effects, and so on, to estimate the equilibrium constants $K_,$ for the reactants and each product. When the ratio of the products is determined by the ratio of their equilibrium constants, we say the overall reaction is subject to equilibrium (or thermodynamic) control. Equilibrium control requires that the reaction be reversible.

When a reaction is carried out under conditions in which it is not reversible, the ratio of the products is determined by the relative rates of formation of the various products. Such reactions are said to be under kinetic control.

A rather simple rule, formulated in 1870 and known as Markownikoffs rule, correlates the direction of kinetically controlled additions of HX to unsymmetrical alkenes. This rule, an important early generalization of organic reactions, may be stated as follows: In addition of HX to an unsymmetrical carbon-carbon double bond, the hydrogen of HX goes to that carbon of the double bond that carries the greater number of hydrogens. It should be clear that Markownikoffs rule predicts that addition of hydrogen bromide to 2-methylpropene will give tert-butyl bromide.

We can extend Markownikofs rule to cover additions of substances of the general type X–Y to unsymmetrically substituted alkenes when a clear-cut decision is possible as to whether X or Y is the more electrophilic atom of X–Y. If the polarization of the X–Y bond is such that X is positive, then X will be expected to add as X^+ to the alkene to form the more stable carbocation.

This step will determine the direction of addition. For example, if we know that the O – Br bond of HOBr is polarized as $(HO)^{-}-(Br)^{+}$ then we can predict that addition of HOBr to 2-methylpropene will give 1-bromo-2-methyl-2-propanol:

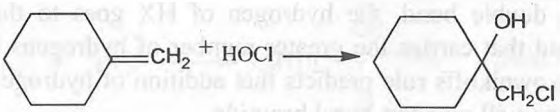


1-bromo-2-methyl-2-propanol

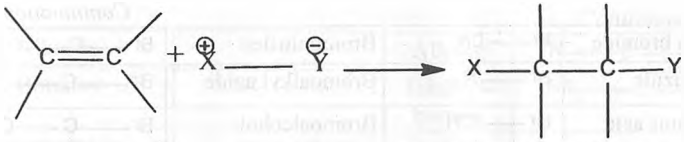
The polarization of X–Y bonds may be predicted by considering the electron-attracting powers, or electronegativities, of the various elements and groups. The general problem of assigning electronegativities to the various elements has been considered in detail by Pauling. In the Pauling electronegativity chart the elements of each horizontal row in the periodic table are arranged in order of increasing electronegativity from left to right. In a given horizontal row of the periodic table, electronegativity increases with increasing atomic number. However, electronegativity decreases with increasing atomic number in a given vertical column of the periodic table.

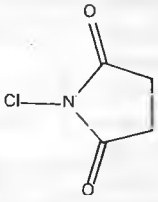
Pauling's value for the electronegativity of carbon makes it slightly more electron-attracting than hydrogen. However, we expect that the electron-attracting power of a carbon atom (or of other elements) will depend also on the electronegativities of the groups to which it is attached. In fact, many experimental observations indicate that carbon in methyl or other alkyl groups is significantly less electron-attracting than hydrogen. Conversely, the CF_3– group is, as expected, far more electron-attracting than hydrogen.

We then can predict that, in the addition of HOCl to an alkene, the chlorine will add preferentially to form the more stable of two possible carbon cations. Generally, this means that chlorine will bond to the carbon carrying the greater number of hydrogens:

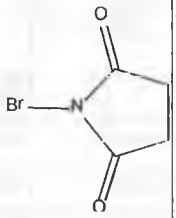


A number of reagents that are useful sources of electrophilic halogen are included in Table. Some of these reagents, notably those with O – halogen or N – halogen bonds, actually are sources of hypohalous acids, HOX, and function to introduce halogen and hydroxyl groups at carbon. There are very few good fluorinating agents whereby the fluorine is added as Fa^{+}.

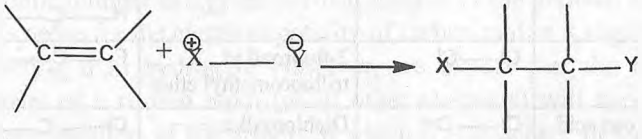


Reagents ($\overset{\oplus}{X}-\overset{\ominus}{Y}$)		Adduct	
Name	Structure	Name	Structure
Sulfuric acid	H—OSO_3H	Sulfate ester	H—C—C—OSO_3H
Hydrogen fluoride	H—F	Fluoroalkane	H—C—C—F
Hydrogen chloride	H—Cl	Chloroalkane	H—C—C—Cl
Water	H—Br	Bromoalkane	H—C—C—Br
Alchol	H—OH	Alcohol	H—C—C—OH
Carboxylic acid	H—OR O ‖ H—OCR	Ether	H—C—C—OR
Tri	F—O—CF_3	Carboxylic ester	O ‖ H—C—C—OCR
Chlorine	Cl—Cl	2-fluoroalkyl trifluoromethyl ether	F—C—C—OCF_3
Hyprochlorous acid	Cl—OH	Dichloroalkane	Cl—C—C—Cl
Tert-butil hypochiorite	Cl—$OC(CH_3)_3$	choloroalcohol	Cl—C—C—OH
N- chlorosuc-cinimide		choloroalcohol	Cl—C—C—OH
N- chlorosuc-cinimide And hydrogen fluoride		choloroalcohol	C—C—C—F
Bromine	Br—Br	dibromoalkane	Br—C—C—Br
Bromine chloride	Br—Cl	Bromo-chloroalkane	Br—C—C—Cl

Continuation of table

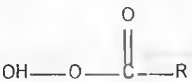
Cyanogen bromide	Br—CN	Bromonitrile	Br—C—C—CN
Bromine azide	Br—N_2	Bromoalkyl azide	Br—C—C—N_3
Hypobromus acid	Br—OH	Bromoalcohol	Br—C—C—OH
N-bromosuc-cinimide		Bromoalcohol	Br—C—C—OH
N-bromosuccinimide and hudrogen fluoride		Bromofluoroalkane	Br—C—C—F
iodine	I—I	Diiadoalkane	I—C—C—I
Iodine chloride	I—Cl	Chloroiodoalkane	I—C—C—Cl
Hypoiodous acid	I—OH	iodoalcohol	I—C—C—OH

Reagents that add to Alkenes by Electrophilic Attack:

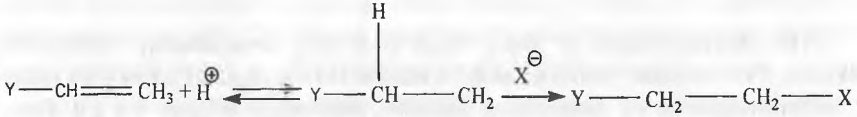


Reagents ($\overset{\oplus}{X}-\overset{\ominus}{Y}$)		Adduct	
Name	Structure	Name	Structure
N-iodosuccinimide and hydrogen floride		iodof-luoroal-kane	—C—C—F
Sulfenyl chlorides	SR—Cl	Chloro-thioether	SR—C—C—Cl
Nitrosyl chloride	O=N—Cl	Chloro-nitro-soalkane	O=N—C—C—Cl
Nitrul iodide	NO_2—I	Nitroio-doal-kane	NO_2—C—C—I
Mercuris salts	HgX—X	Alkylmer-curic compound	HgX—C—C—X
Thallium salts	TlX—X	Alkylthal-lium compound	TlX—C—C—X

Continuation of table

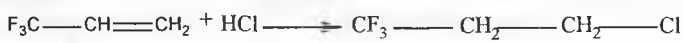
Alkanes	R—H	Alkane	R—C—C—H
Boranes	BR_2—H	Trialkyl-borane	BR_2—C—C—H
Peroxyacids		oxirane	

For alkenes that have halogen or similar substituents at the doubly bonded carbons, the same principles apply as with the simple alkenes. That is, under kinetic control the preferred product will be the one derived from the more stable of the two possible intermediate carbon cations. Consider a compound of the type Y-CH=CH_2. If Y is move electron-attracting than hydrogen, then hydrogen halide should add in such a way as to put the proton of HX on the YCH= end and X on the =CH_2 end. The reason is that the positive carbon is expected to be more favorably located if it is not attached directly to an electron-attracting substituent:

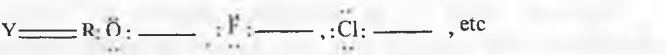


Y is more electron attracting than hydrogen

The addition goes as predicted, provided that the atom directly attached t o the carbon of the double bond carries no unshared (nonbonding) electron pairs. For example,

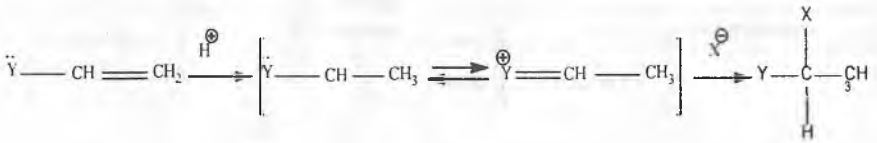


Such substituents are relatively uncommon, and most of the reported H-X additions have been carried out with Y groups having unshared electron pairs on an atom connected directly to a carbon of the double bond:

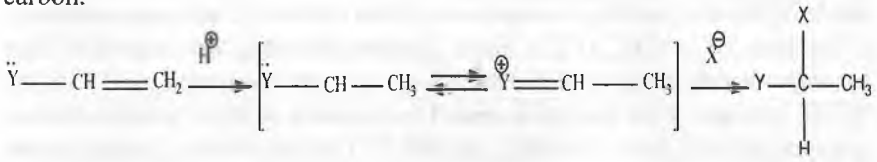


These substituents usually are strongly electronegative relative to

hydrogen, and this often causes diminished reactivity of the double bond toward electrophiles. Nonetheless, the preferred orientation of HX addition situates the positive charge of the intermediate carbocation next to the substituent:

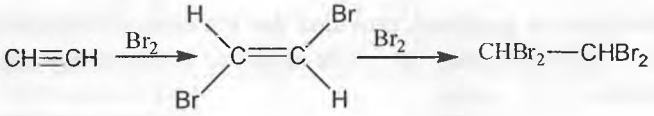


The electron-attracting power of the substituent is more than counterbalanced by stabilization of the intermediate cation by the ability of the substituents to delocalize their unshared electrons to the adjacent positive carbon.



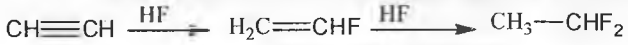
2.8 Electrophilic addition reactions of alkynes

The alkynes behave in many ways as if they were doubly unsaturated alkenes. For example, bromine adds to ethyne in two stages-first to give trans-1,2-dibromoethene by antarafacial addition, and finally to give 1,1,2,2,-tetra-bromoethane:



trans-1,2-dibromoethene 1,1,2,2-tetrabromoethane

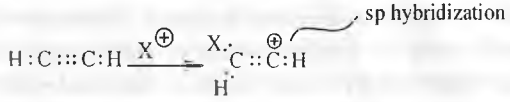
Likewise, anhydrous hydrogen fluoride adds first to give fluoroethene and ultimately to give 1,l-difluoroethane:

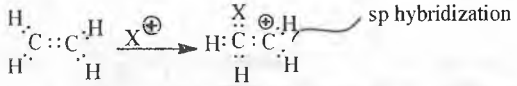


fluoroethene 1,1-difluoroethane

However, there is an interesting contrast in reactivity. Alkynes are substantially less reactive than corresponding alkenes toward many electrophiles. This is perhaps surprising because the electrons of a triple bond, like those of a double bond, are highly exposed, which suggests that the reactivity (nucleophilicity) of a triple bond should be high. Evidently this is not the case.

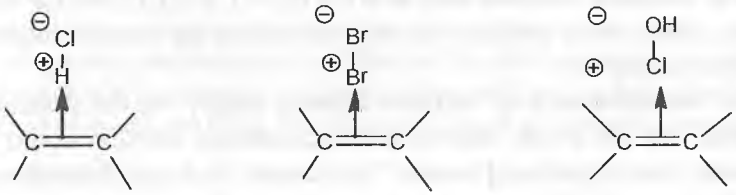
A simple but reasonable explanation is that the carbocation formed from the alkyne is less stable than that from the alkene because it cannot achieve the sp^2 hybrid-orbital configuration expected to be the most stable arrangement for a carbocation.



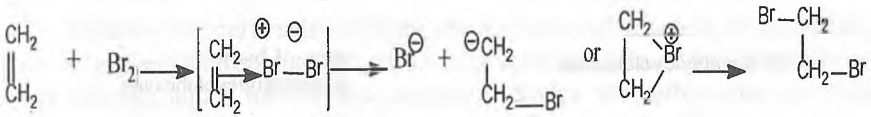


Complexes of electrophilic agents with double bonds. There is a further aspect of polar additions to alkenes that we should consider, namely, that electrophilic reagents form loose complexes with the *n* electrons of the double bonds of alkenes prior to reaction by addition. Complexes of this type are called charge-transfer complexes (or π complexes). Formation of a complex between iodine and cyclohexene is demonstrated by the fact that iodine dissolves in cyclohexene to give a brown solution, whereas its solutions in cyclohexane are violet. The brown solution of iodine in cyclohexene slowly fades as addition occurs to give colorless trans- 1, 2-diiodocyclohexane.

Precise Lewis structures cannot be written for charge-transfer complexes, but they commonly are represented as

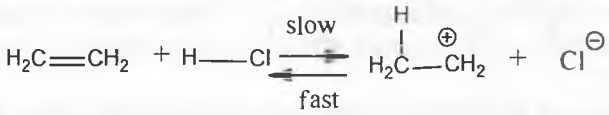


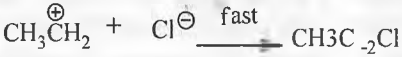
with the arrow denoting that electrons of the double bond are associated with the electrophile. These complexes probably represent the first stage in the formation of addition products by a sequence such as the following for bromine addition:



Addition of proton acids. We have seen that electrophiles can react with

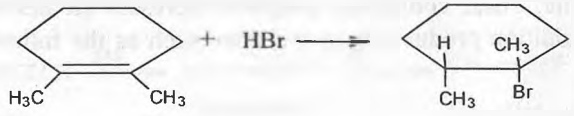
alkenes to form carbon-halogen bonds by donating positive halogen, Br^+, Cl^+ or I^+ Likewise, carbon-hydrogen bonds can be formed by appropriately strong proton donors, which, of course, are typically strong proton acids. These acids are more effective in the absence of large amounts of water because water can compete with the alkene as a proton acceptor. Hydrogen chloride addition to ethene occurs by way of a proton-transfer step to give the ethyl cation and a chloride ion followed by a step in which the nucleophilic chloride ion combines with the ethyl cation:





All of the hydrogen halides (HF, HC1, HBr, and HI) will add to alkenes. Addition of hydrogen fluoride, while facile, is easily reversible. However, a solution of 70% anhydrous hydrogen fluoride and 30% of the weak organic base, pyridine, which is about 1/10,000 times as strong as ammonia, works better, and with cyclohexene gives fluorocyclohexane. With hydrogen iodide, care must be taken to prevent I, addition products resulting from iodine formed by oxidation reactions such as $4HI + O_2 \rightarrow 2I_2 + 2H_2O$. With hydrogen bromide, radical-chain addition may intervene unless the reaction conditions are controlled carefully.

The stereochemistry of addition depends largely on the structure of the alkene, but for simple alkenes and cycloalkenes, addition occurs predominantly in an antarafacial manner. For example, hydrogen bromide reacts with 1, 2-dimethylcyclohexene to give the antarafacial addition product:



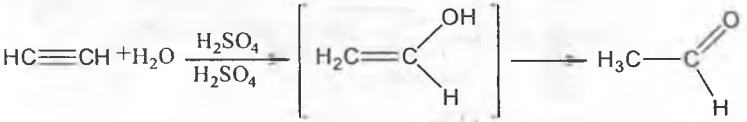
1,2-dimethylcyclohexene

trans - 1 bromo- 1,2-dimemethylcyclohexane

2.9 Hydration of alkynes

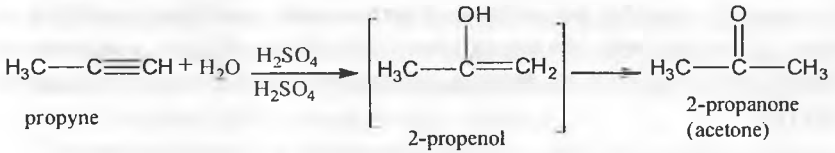
Alkynes, unlike alkenes, are not hydrated readily in aqueous acid unless a mercuric salt is present as a catalyst. Also, the products that are isolated are either aldehydes or ketones instead of alcohols.

Even though the addition of one molecule of water to ethyne probably gives ethenol (vinyl alcohol) initially, this compound is unstable relative to its structural isomer (ethanal) and rapidly rearranges:



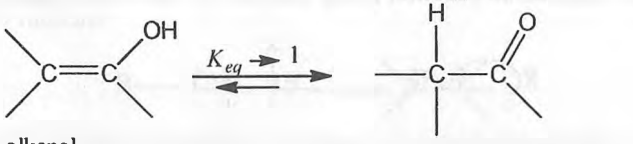
ethenol (unstable) — ethanal (acetaldehyd)

Similarly, addition of water to propyne leads to 2-propanone by way of its unstable isomer, 2-propenol:



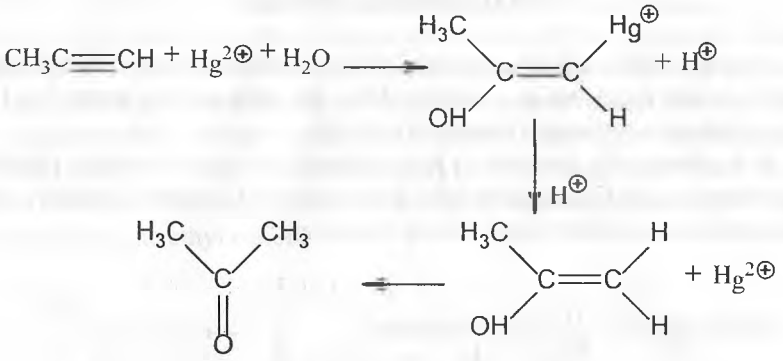
propyne — 2-propenol (unstble) — 2-propanone (acetone)

In general, the position of equilibrium for interconversion of a carbonyl compound with the corresponding alkenol (or enol), having the hydroxyl group attached to the double bond, lies far on the side of the carbonyl compound:



alkenol — alkanone or alkanal

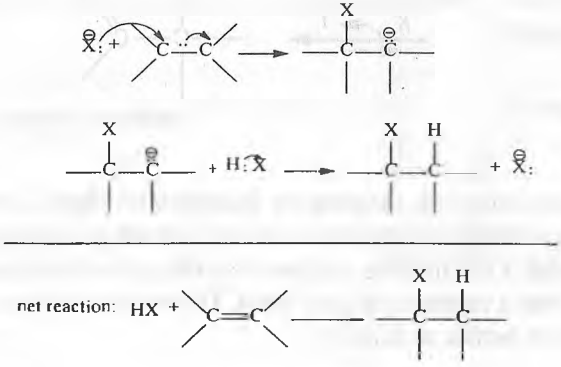
Because mercuric salts catalyze the hydration of alkynes, they probably are acting as electrophiles. Mercuric salts are known to add to both alkenes and alkynes, and if the reaction mixture is acidic, the carbon-mercury bond is cleaved to form a carbon-hydrogen bond. The overall sequence in propyne hydration may be written as follows:



2.10 Nucleophilic addition reactions

When a stepwise ionic addition reaction involves nucleophilic attack at carbon as a first step, it is described as a nucleophilic addition. Reactions of this type often are catalyzed by bases, which generate the required nucleophile. For example, consider the addition of some weakly acidic reagent HX to an alkene. In the presence of a strong base ($^{-}$OH), HX could give up its proton to form the conjugate base X^{-}, which is expected to be a much better nucleophile than HX:

What can follow with an alkene is an ionic chain reaction with the following two propagating steps. First, the nucleophile attacks at carbon to form a carbon anion (carbanion) intermediate. Second, electrophilic transfer of a proton from HX to the carbanion forms the adduct and regenerates the nucleophile). The overall reaction is the addition of HX to the double bond:



2.11 Radical-chain addition reactions to alkenes

Much of the uncertainty on the addition of hydrogen bromide was removed by the classical researches of M.S. Kharasch and F.R. Mayo (1933) who showed that there must be two reaction mechanisms, each giving a different product. Kharasch and Mayo found, in the presence of radical inhibitors, hydrogen bromide adds to propene in a rather slow reaction to give pure 2-bromopropane:

$$HCH_3C{=}CH_2 + HBr \xrightarrow[\text{radical inhibitors}]{\text{slow}} CH_3CHCH_3 \quad (Br)$$

With light, peroxides, radical initiators, and in the absence of radical inhibitors a rapid radical-chain addition of hydrogen bromide occurs to yield 80% or more of 1- bromopropane:

$$HCH_3C{=}CH_2 + HBr \xrightarrow[\text{peroxides}]{\text{fast}} CH_3CH_2CH_2Br$$

Similar effects have been noted occasionally with hydrogen chloride, but never with hydrogen iodide or hydrogen fluoride. A few substances apparently add to alkenes only by radical mechanisms, and always add in the opposite way to that expected for electrophilic ionic addition.

The ionic addition of hydrogen bromide and will not be considered further at this point. Two questions with regard to the so-called abnormal addition will be given special attention. Why does the radical mechanism give a product of different structure than the ionic addition? Why does the radical addition occur readily with hydrogen bromide but rarely with the other hydrogen halides?

The abnormal addition of hydrogen bromide is catalyzed strongly by peroxides, which have the structure R – O – O – R and decompose thermally to give RO radicals:

$$R{-}\ddot{O}{:}\ddot{O}{-}R \longrightarrow 2R{-}\ddot{O}\cdot$$

The RO radicals can react with hydrogen bromide in two ways, to abstract either hydrogen atoms or bromine atoms:

$$RO + HBr \begin{cases} \longrightarrow ROH + Br & \Delta H^\circ = -23 \text{ kcal} \\ \longrightarrow ROBr + H & \Delta H^\circ = +23 \text{ kcal} \end{cases}$$

Clearly, the formation of ROH and a bromine atom is energetically more favorable. The overall process of decomposition of peroxide and attack on hydrogen bromide, which results in the formation of a bromine atom, can initiate a radical-chain addition of hydrogen bromide to an alkene.

chain propagation

$HCH_3C{=}CH_2 + Br \longrightarrow HCH_3C{-}CH_2Br \qquad \Delta H°=-5$ kcal

$CH_3CH_2{-}CH_2Br + HBr \longrightarrow CH_3CH_2CH_2Br + Br \qquad \Delta H°=-11$ kcal

chain propagation $\quad R`\cdot + R`\cdot \longrightarrow R`{-}R` \qquad R`\cdot =$ atom or radical

The two chain-propagating steps, taken together, are exothermic by 16 kcal and have a fairly reasonable energy balance between the separate steps. The reaction chains apparently are rather long, because the addition is strongly inhibited by radical traps and only traces of peroxide catalyst are needed.

Orientation of addition. The direction of addition of hydrogen bromide to propene clearly depends on which end of the double bond the bromine atom attacks. The important question is which of the two possible carbon radicals that may be formed is the more stable, the 1-bromo-2-propylradical, 5, or the 2-bromo- 1-propyl radical, 6:

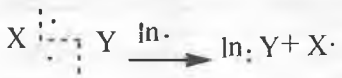
$CH_3{-}CH_2{-}CH_2{-}Br$ $\qquad$ $CH_3{-}\underset{\displaystyle Br}{\underset{|}{CH}}{-}CH_2$

5 $\qquad$ 6

From C – H bond-dissociation energies of alkanes, the ease of formation and stabilities of the carbon radicals is seen to follow the sequence tertialy > secondary > primary. By analogy, the secondary 1-bromo-2-propyl radical, 5, is expected to be more stable and more easily formed than the primary 2-bromo-1-propyl radical, 6. The product of radical addition should be, and indeed is, 1-bromopropane:

$$CH_3CH{=}CH_2 + Br. \longrightarrow CH_3CHCH_2Br \xrightarrow{HBr} CH_3CH_2CH_2BrH + Br.$$

Other reagents, such as the halogens, also can add to alkenes and alkynes by both radical-chain and ionic mechanisms. Radical addition usually is initiated by light, whereas ionic addition is favored by low temperatures and no light. Nevertheless, it often is difficult to keep both mechanisms from operating at the same time. This is important even when the alkene is symmetrical because, although the adduct will then have the same structural formula regardless of mechanism, the stereochemical configurations may differ. Electrophilic addition of halogens generally is a stereospecific antarafacial addition, but radical-chain additions are less stereospecific .There are many reagents that add to alkenes only by radical-chain mechanisms. A number of these are listed in table 2.3. They have in common a relatively weak bond, X–Y, that can be cleaved homolytically either by light or by chemical initiators such as peroxides. In the propagation steps, the radical that attacks the double bond does so to produce the more stable carbon radical. For addition to simple alkenes and alkynes, the more stable carbon radical is the one with the fewest hydrogens or the most alkyl groups at the radical center.



(In· is an initiator radical, with ROOR as initiator, In· is RO)

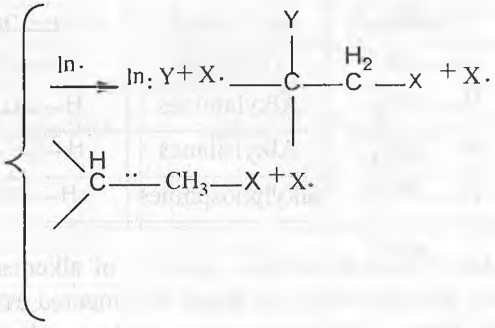
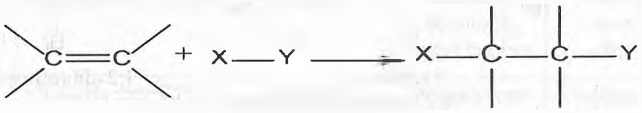
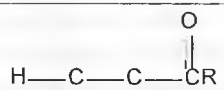


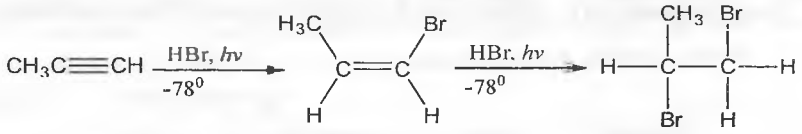
Table 2.3

Reagents than add to Alkenes and Alkynes by Radical-Chain Mechanisms



Name	Reagent (X-Y) structure	Name	Structure
Hydrogen bromide	H—Br	Bromoalkane	H—C—C—Br
Bromine	Br—Br	Dibromoalkane	Br—C—C—Br
Polyhalo-methanes	Cl—CCl_3	Polyhaloalkanes	Cl—C—C—Br
	Br—CCl_3		Br—C—C—CCl_3
	I—CF_3		I—C—C—CF_3
Sulfonyl halides	Cl—SO_2R	Halosulfones	Cl—C—C—SO_2R
Alcohols			
Methanol	H—CH_2OH	Primary alcohol	H—C—C—CH_2OH
Primary	H—CHROH	Secondary alcohol	H—C—C—CHROH
Secondary	H—CR_2OH	Tertiary alcohol	H—C—C—CR_2OH
Carboxyl acids	H—CR_2CO_2H	Carboxylic acids	H—C—C—CR_2CO_2H
Aldehydes		Ketones	
Thiols	H—SR	Thioethers	H—C—C—SR
amines	H—NR_2	Alkylamines	H—C—C—NR_2
Silanes	H—SiR_3	Alkylsilanes	H—C—C—SR_3
phosphines	H—PR_2	alkylphosphines	H—C—C—PR_2

The principles of radical addition reactions of alkenes appear to apply equally to alkynes, although there are fewer documented examples of radical additions to triple bonds. Two molecules of hydrogen bromide can add to propyne first to give cis-1-bromopropene (by antarafacial addition) and then 1,2-dibromopropane:

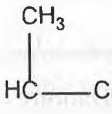


cis adduct
by antarafacial addition

1,2-dibromopropane

2.12 Polymerization of alkenes

One of the most important technical reactions of alkenes is their conversion to higher-molecular-weight compounds or polymers (table 2.4). A polymer is defined as a long-chain molecule with recurring structural units. Thus polymerization of propene gives a long-chain hydrocarbon with recurring



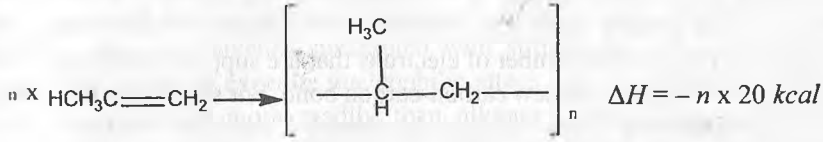


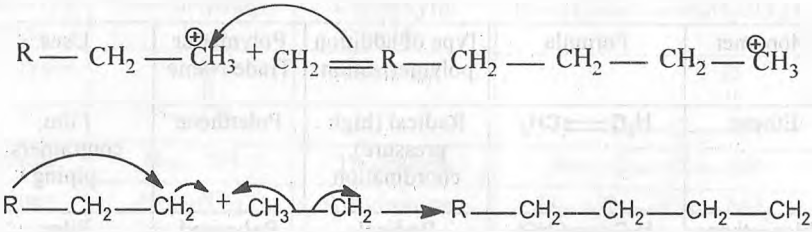
Table 2.4 *Alkene monomers and their polymers*

Monomer	Formula	Type of addition polymerization	Polymer or Trade Name	Uses
Ethene	$H_2C{=}CH_2$	Radical (high pressure), coordination	Poletthene	Film, contrainers, piping
Chloroethene (vinyl chloride)	$H_2C{=}CHCl$	Radical	Polyvinyl chloride (PVC)	Film, insulation, piping, leatherette
Fluoroethene	$H_2C{=}CHF$	Radical	Tedlar	Coatings
Chlorotrif-luoroethene	$F_2C{=}CFCl$	Radical	Kel-F	gaskets, insulation
Tetrafluo-roethene	$F_2C{=}CF_2$	Radical	Teflon	Gaskets, valves, insulation, coatings
Propene	$HCH_3C{=}CH_2$	coordination	Polypropene, herculon	Fibers, molded, articles
2-methyl-propone	$C(H_3C)_2{=}CH_2$	Cationic	Vistanex, oppanol, butyl rubber	Pressure-sensitive adhesives
Strene	$HCC_6H_5{=}CH_2$	Radical	Polystyrene	Molded articles

Continuation of table 2.4

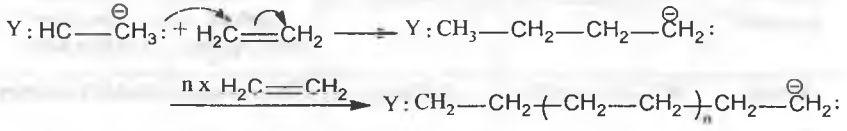
Propen-enitrile (acrylonitile)	$H_2C{=}CHCN$	Radical	Orlon, acrilan	Acrylic fibers
Methyl 2-methyl-propenoate (methyl methacrylate)	$H_2C{=}C(CH_3)CO_2CH_3$	Radical anionic	Lucite, plexglass	Coatings, molded articles

Most technically important polymerizations of alkenes occur by chain mech-anisms and may be classed as anion, cation, or radical reactions, depending upon the character of the chain-carrying species. In each case, the key steps involve successive additions to molecules of the alkene, the differences being in the number of electrons that are supplied by the attacking agent for formation of the new carbon-carbon bond. For simplicity, these steps will be illustrated by using ethene, even though it does not polymerize very easily by any of them:

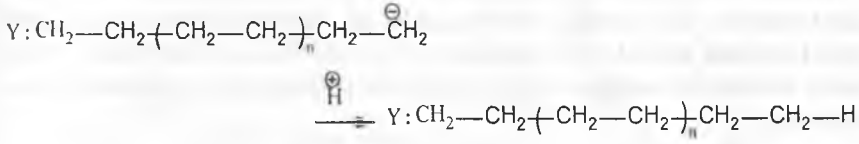


Anionic polymerization. Initiation of alkene polymerization by the anion-chain mechanism may be formulated as involving an attack by a nucleophilic reagent $Y:^{\ominus}$ on one end of the double bond and formation of a carbanion:

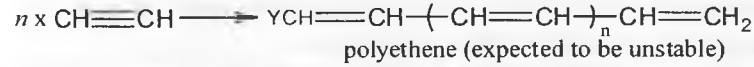
Attack by the carbanion on another alkene molecule would give a four-carbon carbanion, and subsequent additions to further alkene molecules would lead to a high-molecular-weight anion:



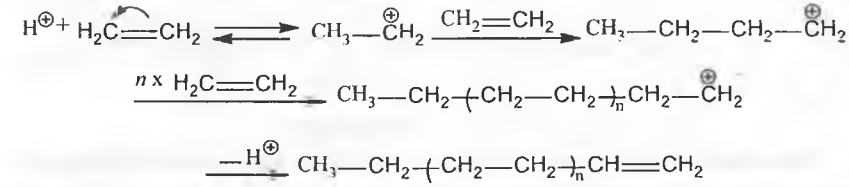
The growing chain can be terminated by any reaction (such as the addition of a proton) that would destroy the carbanion on the end of the chain:



Anionic polymerization of alkenes is quite difficult to achieve because few anions (or nucleophiles) are able to add readily to alkene double bonds. Anionic polymerization occurs readily only with alkenes sub Anionic polymerization of alkenes is quite difficult to achieve because few anions (or nucleophiles) are able to add readily to alkene double bonds. Anionic polymerization occurs readily only with alkenes substituted with sufficiently powerful electron-attracting groups to expedite nucleophilic attack. By this reasoning, alkynes should polymerize more readily than alkenes under anionic conditions, but there appear to be no technically important alkyne polymerizations in operation by this or any other mechanism. Perhaps this is because the resultant polymer would be highly conjugated, and therefore highly reactive, and may not survive the experimental conditions:

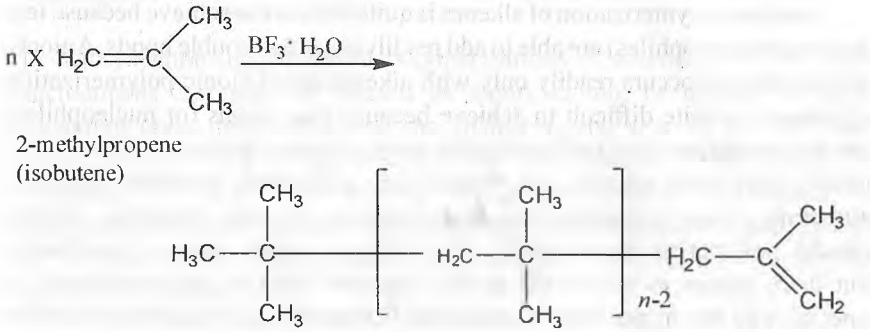


Cationic polymerization. Polymerization of an alkene by acidic reagents can be formulated by a mech-anism similar to the addition of hydrogen halides to alkene linkages. First, a proton from a suitable acid adds to an alkene to yield a carbocation. Then, in the absence of any other reasonably strong nucleophilic reagent, another alkene molecule donates an electron pair and forms a longer-chain cation. Continua-tion of this process can lead to a high-molecular-weight cation. Termination can occur by loss of a proton. The following equations represent the overall reaction sequence:



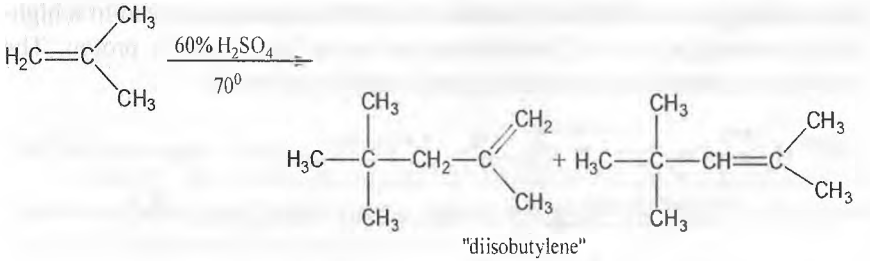
Ethene does not polymarerize by cationic mechanism because it does not polymerize by the cationic mechanism because it does not have sufficiently

effective electron-donating groups to permit easy forma-tion of the intermediate growing-chain cation. 2-methylpropene has electron-donating alkyl groups and polymerizes much more easily than ethene by this type of mechanism. The usual catalysts for cationic polymerization of 2-methylpropene are sulfuric acid, hydrogen fluoride, or a complex of boron trifluoride and water. Under nearly anhydrous conditions a very long chain polymer called polyisobutylene is formed.



Polyisobutylene fractions of particular molecular weights are very tacky and are used as adhesives for pressure-sealing tapes.

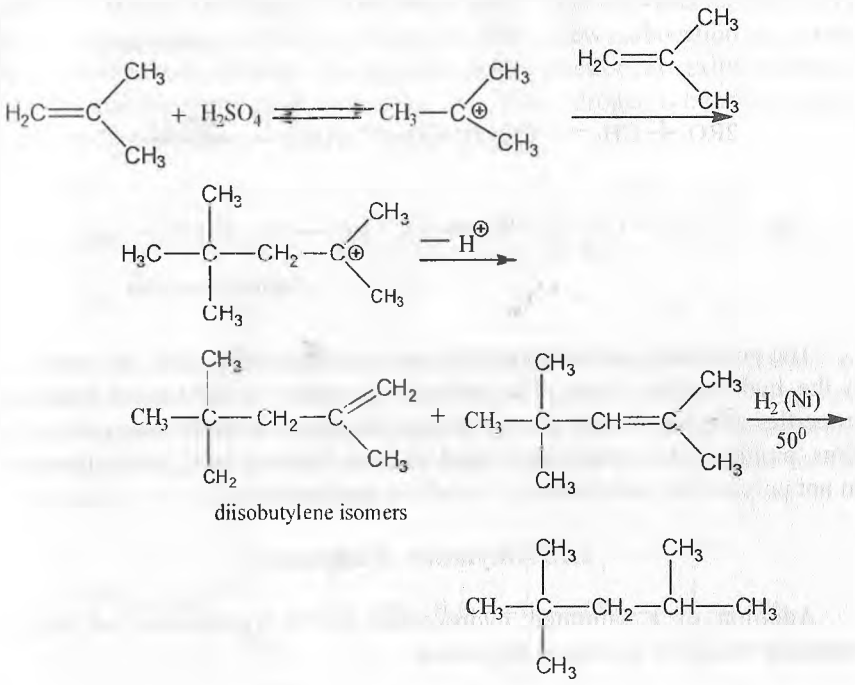
In the presence of 60% sulfuric acid, 2-methylpropene is not converted to a long-chain polymer, but to a mixture of eight-carbon alkenes. The mechanism is like that of the polymerization of 2-methylpropene under nearly anhydrous conditions, except that chain termination occurs after only one 2-methylpropene molecule has been added:



The short chain length is due to the high water concentration; the intermediate carbocation loses a proton to water before it can react with another alkene molecule.

The proton can be lost in two different ways, and a mixture of alkene isomers is obtained. The alkene mixture is known as «diisobutylene» and has

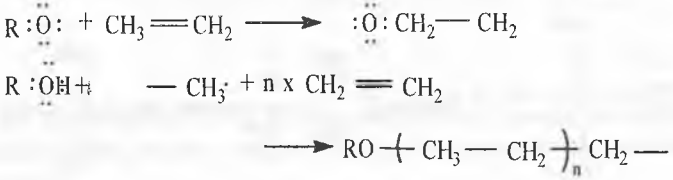
a number of commercial uses. Hydrogenation yields 2,2,4-trimethylpentane (often erroneously called «isooctane»), which is used as the standard «100 antiknock rating» fuel for internal-combustion gasoline engines:



Radical polymerization. Ethene can be polymerized with peroxide catalysts under high pressure (1000 atm or more, literally in a cannon barrel) at temperatures in excess of 100». The initiation step involves formation of radicals, and chain propagation entails stepwise addition of radicals to ethene molecules.

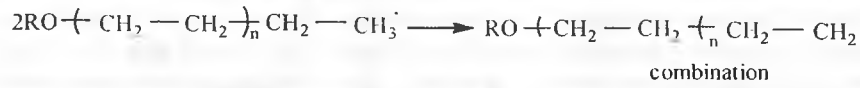
initiation

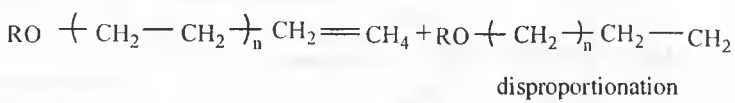
propagation



Chain termination can occur by any reaction resulting in combination or disproportionation of free radicals.

termination :

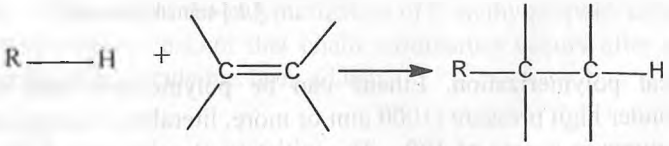




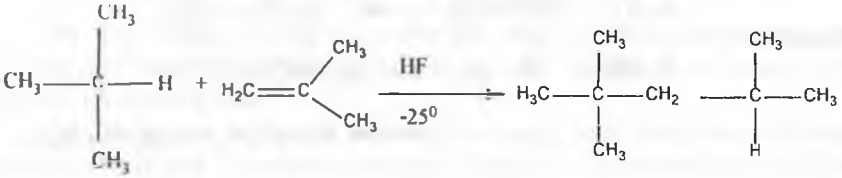
The polyethene produced in this way has from 100 to 1000 ethene units in the hydrocarbon chain. The polymer possesses a number of desirable properties as a plastic and is used widely for electrical insulation, packaging films, piping, and a variety of molded articles. Propene and 2-methylpropene do not poly-merize satisfactorily by radical mechanisms.

2.13 Alkylation of alkenes

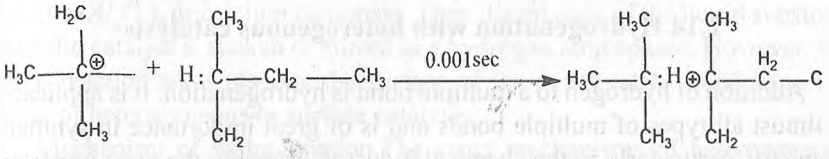
Addition of a saturated hydrocarbon (R-H) hydrocarbon of higher molecular weight is known as alkylation:



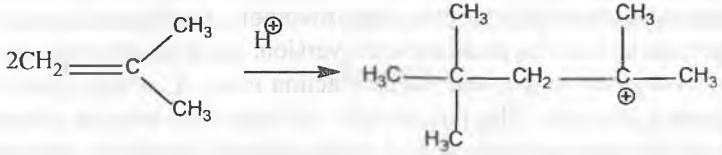
Such reactions are used by the petroleum industry to produce medium-molecular-weight hydrocarbons from smaller molecules. A particularly important example is afforded by the addition of 2-methylpropane to 2-methyl-propene in the presence of sulfuric acid or anhydrous hydrogen fluoride to yield 2,2,4-trimethylpentane:



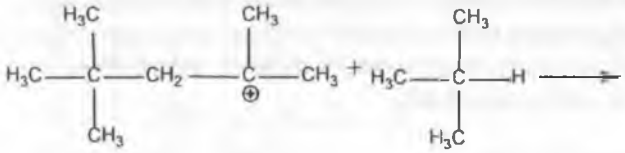
The overall reaction appears to be different from any so far discussed, because it involves addition of a nonpolar reagent (RH) to an alkene bond. The key to the mechanism of hydrocarbon alkylation was provided by the discovery by P. D. Bartlett, in 1940, that a carbocation can react rapidly with a hydrocarbon having a tertiary hydrogen to yield a new carbocation and a new hydrocarbon. Some of these «hydrogen-transfer» reactions are extra-ordinarily fast and may be complete in seconds or less. The hydrogen is transferred with both bonding electrons (H: $^-$). For example,

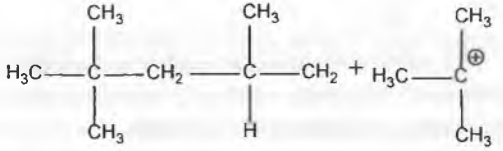


With the knowledge that the hydrogen transfer is fast, the alkylation of 2-methylpropene with 2- methylpropane can be formulated as involving first polymerization of two 2-methylpropene molecules under the influence of the sulfuric acid catalyst to give the same octyl cation as was postulated for the dimerization of 2-methylpropene:

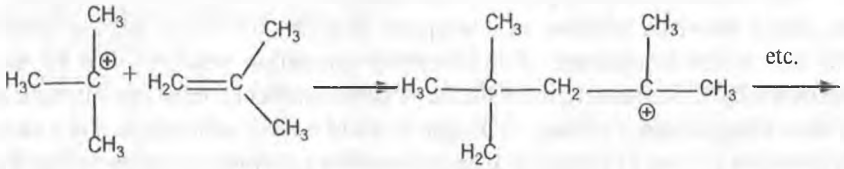


The octyl cation then can undergo a hydrogen-transfer reaction with 2-methyl-propane to furnish 2,2,4-trimethylpentane and a tert-butyl cation:





Attack by the tert-butyl cation on another molecule of 2-methylpropene pro-duces an eight-carbon tertiary cation, which then proceeds to another molecule of «alkylate»:



This is an important example of a cationic chain reaction.

2.14 Hydrogenation with heterogenous catalysts

Addition of hydrogen to a multiple bond is hydrogenation. It is applicable to almost all types of multiple bonds and is of great importance in synthetic chemistry, particularly in the chemical industry. Probably the most important technical example is production of ammonia by the hydrogenation of nitrogen:

$$3H_2 + N \equiv N = 2NH_3 \qquad \Delta H^\circ = -22.0 \text{ kcal } (25^0)$$
$$\Delta G^\circ = -8.0 \text{ kcal } (25^0)$$

This may appear to be a simple process, but in fact it is difficult to carry out because the equilibrium is not very favorable. High pressures (150-200 atm) are required to get a reasonable conversion, and high temperatures (430-510°) are necessary to get reasonable reaction rates. A catalyst, usually iron oxide, also is required. The reaction is very important because ammonia is used in ever-increasing amounts as a fertilizer either directly or through conversion to urea or ammonium salts.

Production of ammonia requires large quantities of hydrogen, most of which comes from the partial oxidation of hydrocarbons with water or oxygen. A simple and important example is the so-called "methane-steam gas" reaction, which is favorable only at very high temperatures because of the entropy effect in the formation of H2 (see Section 4-4B)

$$CH_4 + H_2O \longrightarrow CO + 3H_2 \qquad \Delta H^\circ = +51.0 \text{ kcal } (25^0)$$
$$\Delta G^\circ = +33.9 \ (25^0)$$

Therefore the fertilizer industry is allied closely with the natural gas and pe-troleum industries, and for obvious reasons ammonia and hydrogen often are produced at the same locations.

Alkenes and alkynes add hydrogen much more readily than does nitrogen. For example, ethene reacts rapidly and completely with hydrogen at ordinary pressures and temperatures in the presence of metal catalysts such as nickel, platinum, palladium, copper, and chromium:

$$H_2C{=}{=}CH_2 + H_2 \xrightarrow{\text{metal catalyst}} CH_3CH_3 \qquad \Delta H^\circ = -32.7 \text{ kcal } (25^0)$$
$$\Delta G^\circ = -24.1 \text{ kcal } (25^0)$$

These reactions are unlike any we have encountered so far. They are hetero-geneous reactions, which means that the reacting system consists of two or more phases. Usually, the metal catalyst is present as a finely divided solid suspension in the liquid or solution to be reduced. Alternatively, the metal is deposited on an inert solid support such as carbon, barium sulfate, alumina (Al_2O_3), or calcium carbonate. Then the mixture of the liquid substrate and solid catalyst is shaken or stirred in a hydrogen atmosphere. However, the actual reaction takes place at the surface of the metal catalyst and is an example of heterogeneous or surface catalysis.

Mechanism of hydrogenation.The exact mechanisms of heterogeneous reactions are difficult to determine, but much interesting and helpful information has been obtained for catalytic hydrogenation. The metal catalyst is believed to act by binding the reactants at the surface of a crystal lattice. As an example, consider the surface of a nickel crystal (Figure 2.4). The nickel atoms at the surface have fewer neighbors (lower covalency) than the atoms in the interior of the crystal. The surface atoms therefore have residual bonding capacity and might be expected to combine with a variety of substances.

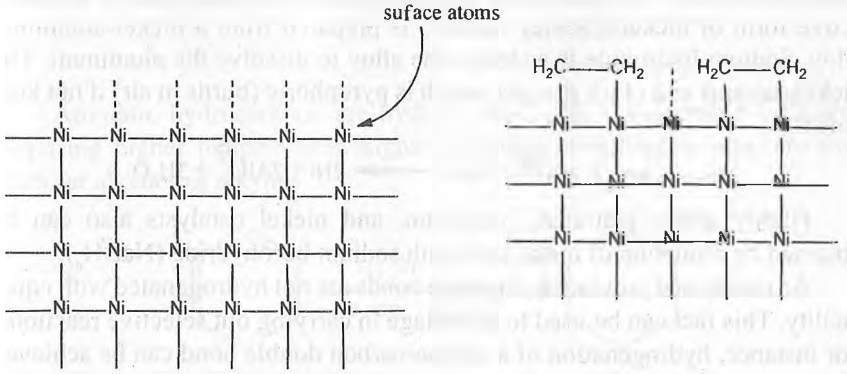


Figure 2.4 *Figure left: Schematic representation of a nickel crystal in cross section showing residual valences at the surface atoms.*

Right: Adsorption of ethene on the surface of the nickel crystal with formation of C-Ni bonds.

It has been shown experimentally that ethene combines exothermically (ΔH° = -60 kcal mole^{-1}) and reversibly with a metal surface. Although the

precise structure of the ethene-nickel complex is unknown, the bonding to nickel must involve the electrons of the double bond because saturated hydrocarbons, such as ethane, combine only weakly with the nickel surface. A possible structure with carbon-nickel a bonds is shown in Figure 2.4.

Hydrogen gas combines with nickel quite readily with dissociation of the H-H bonds and formation of Ni-H bonds (nickel hydride bonds). The overall hydrogenation process is viewed as a series of reversible and sequential steps. First the reactants, hydrogen and ethene, are adsorbed on the surface of the metal catalyst. The energies of the metal-hydrogen and metal-carbon bonds are such that, in a second step, a hydrogen is transferred to carbon to give an ethyl attached to nickel. This is the halfway point. In the next step, the nickel-carbon bond is broken and the second carbon-hydrogen bond is formed. Hydrogenation is now complete and the product is desorbed from the catalyst surface.

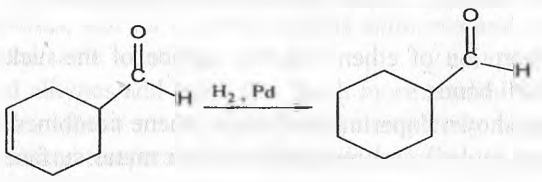
Ethane has a low alffinity for the metal surface and, when desorbed, creates a vacant space for the adsorption of new ethene and hydrogen molecules. The cycle continues until one of the reagents is consumed or some material is adsorbed that "poisons" the surface and makes it incapable of further catalytic activity. Because the reaction occurs only on the surface, small amounts of a catalyst poison can completely stop the reaction.

For maximum catalytic activity, the metal usually is prepared in a finely divided state. This is achieved for platinum and palladium by reducing the metal oxides with hydrogen prior to hydrogenation of the alkene. A specially active form of nickel ("Raney nickel") is prepared from a nickel-aluminum alloy. Sodium hydroxide is added to the alloy to dissolve the aluminum. The nickel remains as a black powder which is pyrophoric (burns in air) if not kept moist:

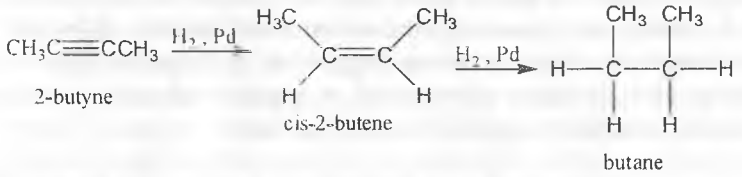
$$2Ni{-\!\!-}AlH_2 + 2OH^{\ominus} + 2H_2O \longrightarrow 2Ni + 2AlO_2^{\ominus} + 3H_2O$$

Highly active platinum, palladium, and nickel catalysts also can be obtained by reduction of metal salts with sodium borohydride ($NaBH_4$).

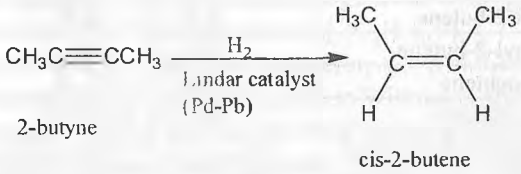
As mentioned previously, multiple bonds are not hydrogenated with equal facility. This fact can be used to advantage in carrying out selective reactions. For instance, hydrogenation of a carbon-carbon double bond can be achieved without simultaneously reducing a carbonyl bond in the same molecule. For example the carbon double bond of the following aldehyde can be reduced selectively:



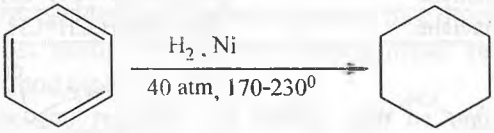
Alkynes are hydrogenated more easily than alkenes mainly because alkynes are adsorbed more readily on the catalyst surface. Hydrogenation proceeds in stages, first to the cis-alkene and then to the alkane. For example,



Normally, it is not possible to stop the hydrogenation of an alkyne at the alkene stage, but if the catalyst is suitably deactivated, addition to the triple bond can be achieved without further addition occurring to the resulting double bond. The preferred catalyst for selective hydrogenation of alkynes is palladium partially «poisoned» with a lead salt (Lindlar catalyst). This catalyst shows little affinity for adsorbing alkenes and hence is ineffective in bringing about hydrogenation to the alkane stage:



Aromatic hydrocarbons are hydrogenated with considerable difficulty, requiring higher temperatures, higher pressures, and longer reaction times than for alkenes or alkynes



Heats of hydrogenation. In addition to having synthetic applications, catalytic hydrogenation is useful for analytical and thermochemical purposes. The analysis of a substance for the number of carbon-carbon double bonds it contains is carried out by measuring the uptake of hydrogen for a known amount of sample. Measurement of the heat evolved in the hydrogenation of alkenes gives information as to the relative stabilities of alkenes, provided that the differences in $\Delta S°$ values are small.

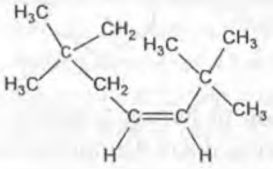
The experimental values of $\Delta H°$ for hydrogenation of a number of alkenes

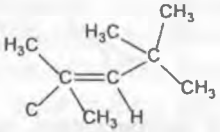
and alkynes are listed in table 2.5. The ΔH° calculated from average bond energies is -30 kcal mole^{-1} for a double bond and -69 kcal mole^{-1} for a triple bond. The divergences from these values reflect the influence of structure on the strengths of multiple bonds. Some important generalizations can be made:

1. The more alkyl groups or other substituents there are on the multiple bond, the less heat is evolved on hydrogenation. Because less heat evolved signifies a stronger, more stable bond, it appears that alkyl substitution increases the stability (strength) of the multiple bond.

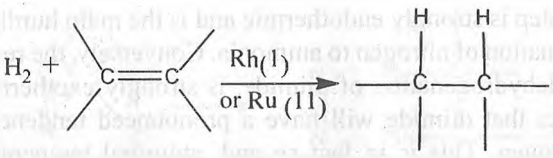
Table 2.5 *Heats of hydrogenation of gaseous alkenes and alkynes (kcal mole^{-1}, atm. 25^0)*

Compound	Formula	$-\Delta H^\circ$
Ethene	$CH_2=CH_2$	32,8
Propene	$CH_3CH=CH_2$	30,1
1-butene	$CH_3CH_2CH=CH_2$	30,3
Cis-2-butene	$CH_3CH=CHCH_3$	28,6
Trans-2-butene	$CH_3CH=CHCH_3$	27,6
2-methyl-2-butene	$(CH_3)_2C=CHCH_3$	26,9
2,3-dimethyl-2-butene	$(CH_3)_2C=C(CH_3)_2$	26,6
Cis-2-pentene	$CH_3CH=CHC_2H_5$	28,6
Trans-2-pentene	$CH_3CH=$ CHC2H5	27,6
Cis-2,2,5,5-tetramethyl-3-hexene	$(CH_3)_3C—CH=CH—C(CH_3)_3$	36,2
Trans-2,2,5,5-tetramethyl-3-hexene	(CH3)3C—CH=CH—C(CH3)3	26,9
ehyne	CH≡CH	74,4
propyne	$CH_3C=CH$	69,1
1,2-propadiene	$CH_2=C=CH_2$	71,3
1,3-butadiene	$CH_2=CH—CH=CH_2$	57,1
1,3-pentadiene	$CH_3CH=CH—CH=CH_2$	54,1
1,4-pentadiene	$CH_2=CHCH_2CH=CH_2$	60,8

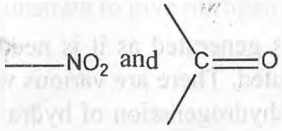




Hydrogenation and homogenous catalysts. Hydrogen addition to multiple bonds is catalyzed by certain complex metal salts in solution. This may be described as homogeneous catalysis and, com-pared to heterogeneous catalysis, is a relatively new development in the area of hydrogenation reactions. Rhodium and ruthenium salts appear to be generally useful catalysts:



At present, homogeneous catalysis for routine hydrogenation reactions offers little advantage over the convenience and simplicity of heterogeneous catalysis. Suprafacial addition of hydrogen is observed with both types of catalytic sys-tems. However, greater selectivity can be achieved with homogeneous catalysts because they appear to be more sensitive to steric hindrance and are less likely to cause rearrangement. dissociation, and hydrogenation of other bonds



The most thoroughly investigated homogeneous hydrogenation catalyst is the four-coordinate rhodium complex $Rh[(C_6H_5)_3P]_3$ C1. This catalyst is called Wilkinson's catalyst after its discoverer, G. Wilkinson. In 1973, the Nobel Prize in chemistry was awarded jointly to Wilkinson and E. 0. H. Fischer for their respective contributions to the field of ovganometallic chemistry. As you will see in this and later chapters, compounds with carbon-metal bonds (organometallic compounds) are extremely useful reagents, reactive intermediates, or catalysts in organic reactions. To a very large extent, the work of Fischer and Wilkinson created the current interest and developments in the field of transition-metal organic chemistry.

Hydrogenation with diimide. There are alternative ways to add hydrogen to a multiple bond besides the catalytic methods described in the previous sections. The most useful of these are homogeneous reactions utilizing diimide, HN=NH, and diborane, B_2H_6.

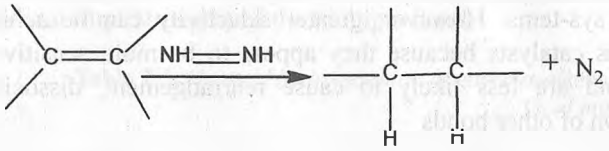
The behavior and reactivity of diimide can be understood best by considering the thermochemistry of hydrogenation of nitrogen:

$$N \equiv N + H_2 \rightarrow \underset{\text{dimide}}{HN = NH} \qquad \Delta H^\circ = +43.2 \text{ kcal}$$

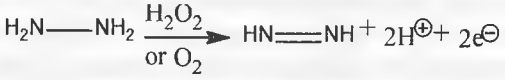
$$HN = NH + H_2 \rightarrow \underset{\text{Hydrazine}}{H_2NNH_2} \qquad \Delta H^\circ = +\text{-}21.6 \text{ kcal}$$

$$H_2NNH_2 + H_2 \rightarrow 2\,NH_3 \qquad \Delta H^\circ = -\,43.6 \text{ kcal}$$

The first step is strongly endothermic and is the main hurdle to overcome in the hydrogenation of nitrogen to ammonia. Conversely, the reverse reaction, which is the dehydrogenation of diimide, is strongly exothermic. Therefore we may expect that diimide will have a pronounced tendency to revert to molecular nitrogen. This is in fact so and, atnormal temperatures, diimide exists only as a transient intermediate that cannot be isolated. It is extremely reactive and readily transfers hydrogen to carbon-carbon multiple bonds:

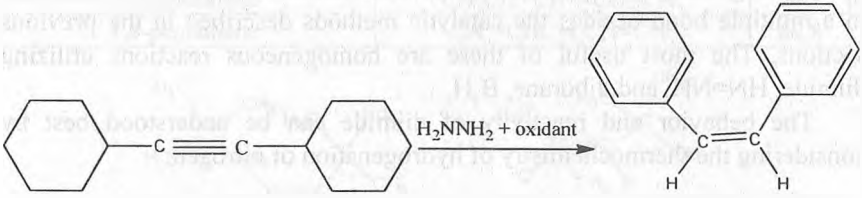


In practice, diimide is generated as it is needed in the presence of the compound to be hydrogenated. There are various ways to do this, but one of the simplest methods is dehydrogenation of hydrazine with oxidizing agents such as atmospheric oxygen or hydrogen peroxide:



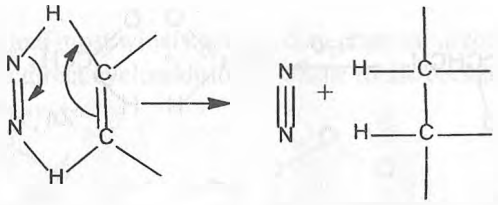
Hydrazine actually has been used as a hydrogenating agent for over sixty years, but it was not until the 1960's that the diimide intermediate in such reactions was recognized.

The hydrogenation step is stereospecific and transfers hydrogen in the suprafacial manner. For example, alkynes are converted to cis-alkenes

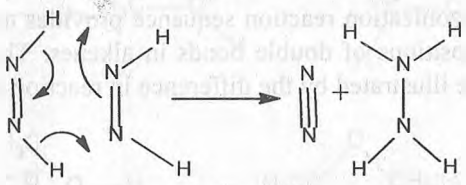


cis-1,2.diphenylethene
(cis-stilbene)

There are no detectable intermediate stages or rearrangements in diimide hydrogenation. The reaction is visualized as a six-center (pericyclic) process in which the bonds are broken and made in a concerted fashion:

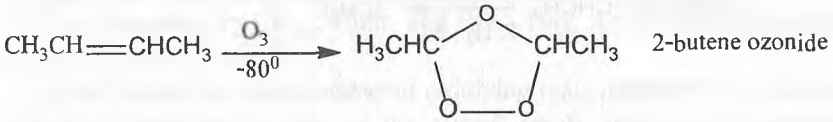


An important difference between diimide hydrogenation and catalytic hydrogenation is that diimide will react only with symmetrical or nonpolar bonds (C=C, C=C, N=N), whereas hydrogen can add, albeit reluctantly, to polar bonds (C=O, C=N) . Diimide does not attack the stronger polar bonds probably because it does not survive long enough to do so. It self-destructs in the absence of a reactive substrate to give nitrogen and hydrazine:



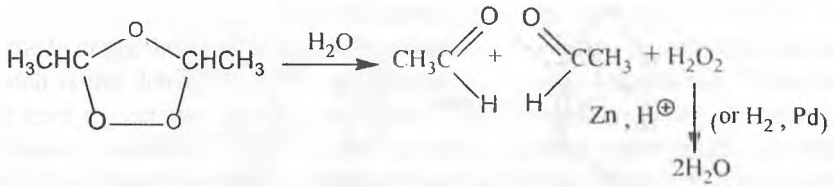
2.15 Oxidation reactions

Ozonization. Most alkenes react readily with ozone (O_3), even at low temperatures, to yield cyclic peroxidic derivatives known as ozonides. For example,

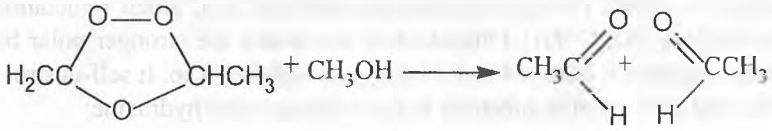


2-butene ozonide

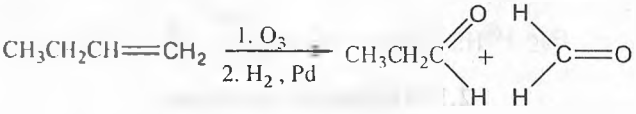
These substances, like most compounds with peroxide (O—O) bonds, may explode violently and unpredictably. Therefore ozonizations must be carried out with appropriate caution. The general importance of these reactions derives not from the ozonides, which usually are not isolated, but from their subsequent products. The ozonides can be converted by hydrolysis with water and reduction, with hydrogen (palladium catalyst) or with zinc and acid, to carbonyl compounds that can be isolated and identified. For example, 2-butene gives ethanal on ozonization, provided the ozonide is destroyed with water and a reducing agent which is effective for hydrogen peroxide:



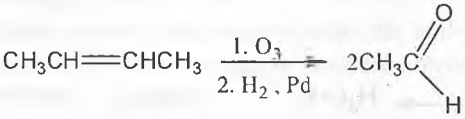
An alternative procedure for decomposing ozonides from di- or trisubstituted alkenes is to treat them with methanol (CH_3OH). The use of this reagent results in the formation of an aldehyde or ketone and a carboxylic acid:



The overall ozonization reaction sequence provides an excellent means for locating the positions of double bonds in alkenes. The potentialities of the method may be illustrated by the difference in reaction products from the 1-and 2-butenes:



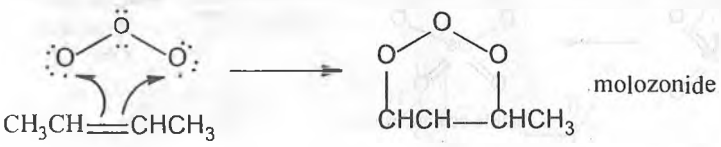
1-butene propanol methanal



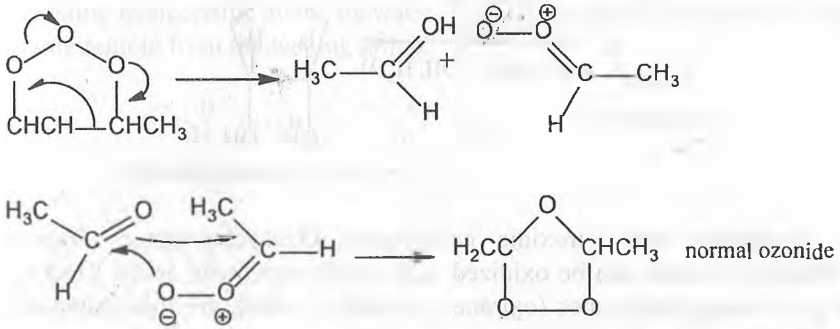
2-butene ethanal

Mechanism of ozanization. Ozonization of alkenes has been studied extensively for many years, but there still is disagreement about the mechanism (or mechanisms) involved because some alkenes react with ozone to give oxidation products other than ozonides. It is clear that the ozonide is not formed directly, but by way of an unstable intermediate called a molozonide. The molozonide then either isomerizes to the «normal» ozonide or participates in other oxidation reactions. Although the structure of normal ozonides has been established beyond question, that of the molozonide, which is very unstable even at -100°, is much less certain.

The simplest and most widely accepted mechanism involves formation of a molozonide by a direct cycloaddition of ozone to the double bond.

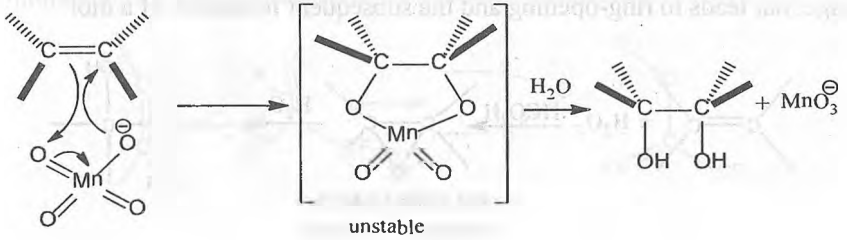


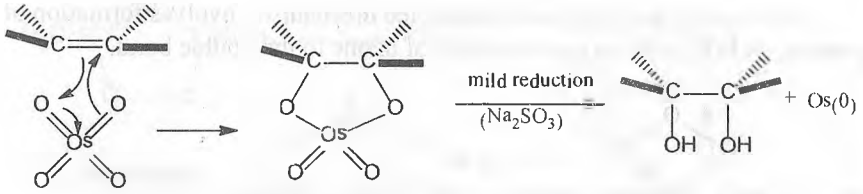
Isomerization of the molozonide appears to occur by a fragmentation-recombination reaction, as shown in:



The ozone structure shown here with single electrons having paired spins on the terminal oxygens accords both with the best available quantum mechanical calculations and the low dipole moment of ozone, which is not consonant with the conventional $O{=}\overset{\oplus}{O}{-}\overset{\ominus}{O}$ structure. See W. A. Goddard 111, T. H. Dunning, Jr., W. J. Hunt, and P. J . Hay, Accounts of Chemical Research 6, 368 (1973).

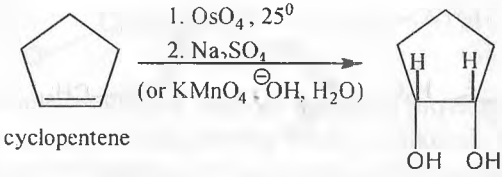
Hydroxylation of alkenes. Several oxidizing reagents react with alkenes under mild conditions to give, as the overall result, addition of hydrogen peroxide as HO—OH. Of particular importance are alkaline permanganate (MnO_4) and osmium tetroxide (OsO_4), both of which react in an initial step by a suprafacial cycloaddition mechanism like that postulated for ozone.





stable osmate ester

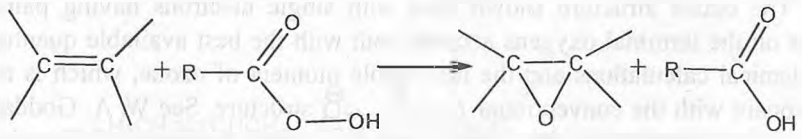
Each of these reagents produces cis-1,2-dihydroxy compounds (diols) with cycloalkenes:



cyclopentene

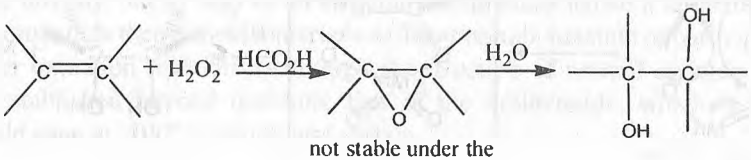
cis-1,2-cyclopentanediol

Oxidation with peroxidic compounds. Oxacyclopropane (Oxirane) formation. Alkenes can be oxidized with peroxycarboxylic acids, RCO_3OH, to give oxacy-clopropanes (oxiranes, epoxides), which are three-membered cyclic ethers:



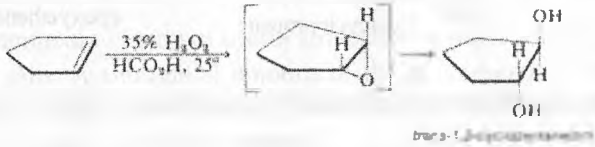
an oxacyclopropane
(oxirane, epoxide)

The reaction, known as epoxidation, is valuable because the oxacyclopropane ring is cleaved easily, thereby providing a route to the introduction of many kinds of functional groups. In fact, oxidation of alkenes with peroxymethanoic acid (peroxyformic acid), prepared by mixing methanoic acid and hydrogen peroxide, usually does not stop at the oxacyclopropane stage, but leads to ring-opening and the subsequent formation of a diol:

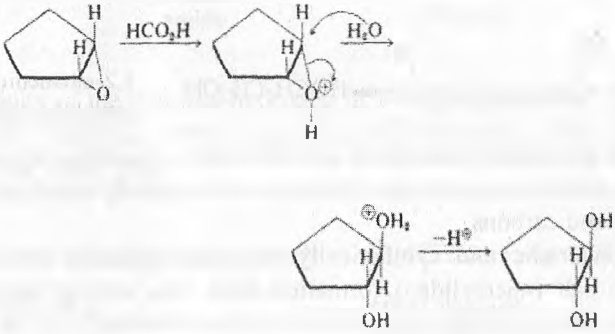


not stable under the
reaction conditions

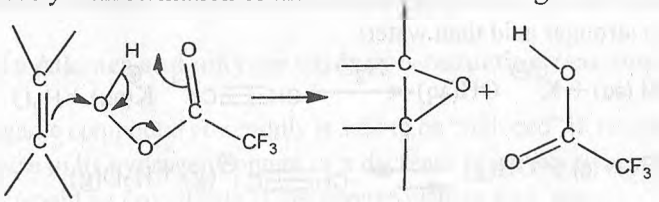
This is an alternative scheme for the hydroxylation of alkenes. However, the overall stereochemistry is opposite to that in permanga-nate hydroxylation. For instance, cyclopentene gives trans- 1,2-cyclopen-tanediol. First the oxirane forms by suprafacial addition and then undergoes ring opening to give the trans product:



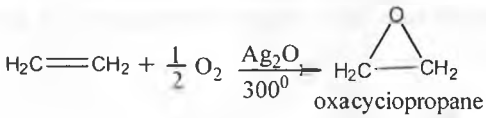
The ring opening is a type of Sp2 reaction. Methanoic acid is sufficiently acidic to protonate the ring oxygen, which makes it a better leaving group, thus facilitating nucleophilic attack by water. The nucleophile always attacks from the side remote from the leaving group:



The peroxyacids that are used in the formation of oxacyclopropanes include peroxyethanoic CH_3CO_3H, peroxybenzoic (C, H, CO, H) , and trifluoroperoxyethanoic (CF_3CO_3H) acids. A particularly useful peroxyacid is 3-chloroperoxybenzoic acid, because it is relatively stable and is handled easily as the crystalline solid. The most reactive reagent is trifluoroperoxyethanoic acid, which suggests that the peroxyacid behaves as an electrophile (the electronegativity of fluorine makes the CF_3 group strongly electron-attracting). The overall reaction can be viewed as a cycloaddition, in which the proton on oxygen is transferred to the neighboring carbonyl oxygen more or less simultaneously with formation of the three-membered ring:



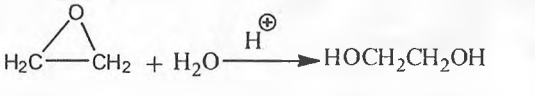
A reaction of immense industrial importance is the formation of oxacyclopropane itself (most often called



(oxirane, ethylene oxide, 1,2-epoxyethene)

ethylene oxide) by oxidation of ethene with oxygen over a silver oxide catalyst at 300°:

Oxacyclopropane is used for many purposes, but probably the most important reaction is ring opening with water to give 1,2-ethanediol (ethylene glycol, bp 197°). This diol, mixed with water, is employed widely in automotive cooling systems to provide both a higher boiling and lower freezing coolant than water alone:

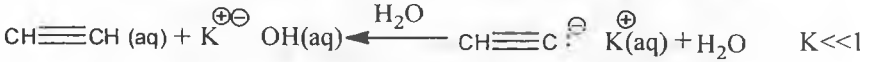


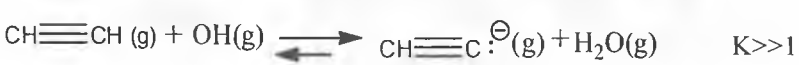
1,2-ethanediol (ethylene dlycol)

Propene and higher alkenes are not efficiently epoxidized by oxygen and Ag_2O in the same way as ethene is because of competing attack at other than the double-bond carbons.

A characteristic and synthetically important reaction of ethyne and 1-alkynes is salt («acetylide») formation with very strong bases. In such reactions the alkynes behave as acids in the sense that they give up protons to suitably strong bases:

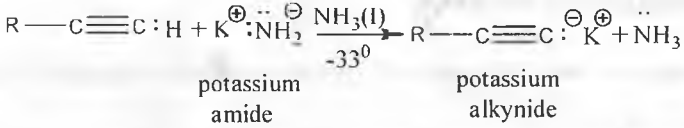
Water is too weak a base to accept protons from alkynes; consequently no measurable concentration of H_3O is expected from the ionization of alkynes in dilute aqueous solutions. Therefore we have no quantitative measure of 1-alkyne acidity in aqueous solution other than that it probably is about 10^{1} times less acidic than water, as judged from measurements in other solvents to be discussed shortly. In the gas phase, however, the situation is reversed, and ethyne is a stronger acid than water:



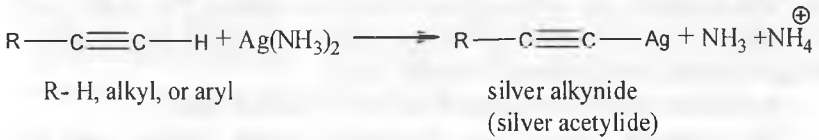


This reversal is of little practical value because organic reactions involving ions normally are not carried out in the gas phase. However, it should alert us to the tremendous role that solvents play in determining acidities by their abilities (some much more than others) to stabilize ions by the property known as solvation.

Liquid ammonia is a more useful solvent than water for the preparation of 1-alkyne salts. A substantial amount of the alkyne can be converted to the conjugate base by amide anions (potassium or sodium amide) because a 1-alkyne is a stronger acid than ammonia.



The acidity of the terminal hydrogen in 1-alkynes provides a simple and useful test for 1-alkynes. With silver-ammonia solution ($AgNO_3$ in aqueous ammonia), 1-alkynes give

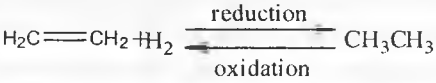


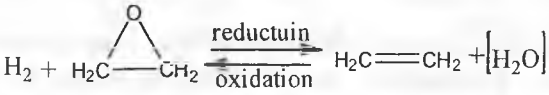
insoluble silver salts, whereas disubstituted alkynes do not:

The silver «acetylides» appear to have substantially covalent carbon-metal bonds and are less ionic than sodium and potassium alkynides. Silver-ammonia solution may be used to precipitate 1-alkynes from mixtures with other hydrocarbons. The 1-alkynes are regenerated easily from the silver precipitates by treatment with strong inorganic acids. It should be noted, however, that silver alkynides may be shock sensitive and can decompose explosively, especially when dry.

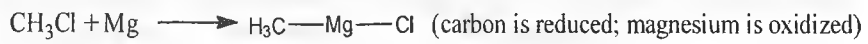
2.16 Alkenes and alkynes oxidation-reduction reactions

An organic compound commonly is said to be "reduced" if reaction leads to an increase in its hydrogen content or a decrease in its oxygen content. The compound would be «oxidized» if the reverse change took place.





This is a very unsatisfactory definition because many oxidation-reduction or redox reactions do not involve changes in hydrogen or oxygen content, as the following example illustrates:



Redox reactions are better defined in terms of the concept of electron transfer. Thus an atom is said to be oxidized if, as the result of a reaction, it experiences a net loss of electrons; and is reduced if it experiences a net gain of electrons. This simple definition can be used to identify oxidation or reduction processes at carbon in terms of a scale of oxidation states for carbon based on the electronegativities of the atoms attached to carbon. The idea is to find out whether in a given reaction carbon becomes more, or less, electronrich. We will use the following somewhat arbitrary rules:

1.Elementary carbon is assigned the zero oxidation state.

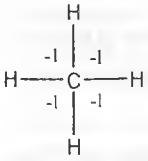
2.The oxidation state of any chemically bonded carbon may be as signed by adding -1 for each more electropositive atom and + 1 for each more electronegative atom, and 0 for each carbon atom bonded directly to the carbon of interest for the Pauling electronegativity scale. That is, -1.for electropositive atoms, H, B, Na, Li, Mg +1 for electronegative atoms, halogens, O, N, S 0 for carbon.

The rationale for this mode of operation can be seen if was look more closely at the example of $CH_3Cl + Mg \longrightarrow CH_3—Mg—Cl$. Chlorine is more electronegative than either carbon or magnesium. Carbon is more electronegative than magnesium. Thus CH_3Cl is written properly with a polar bond as CH_3---Cl, whereas the C-Mg bond is oppositely polarized, CH_3--Mg

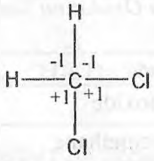
3. In compounds with multiple bonds), ($>C=O_+ - C \equiv N$) the attached heteroatom is counted twice or three times, depending on whether the bond is double or triple.

4. A formal positive charge on carbon changes the oxidation state by +1, and a formal negative charge by -1 ; an odd electron on carbon leaves the oxidation state unchanged.

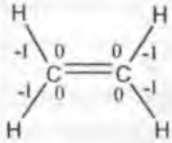
To illustrate, the oxidation state of carbon in four representative examples is determined as follows:



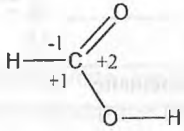
Oxidation state: 4 x (-1) = -4



2 x (-1) + 2 x (+1) = 0

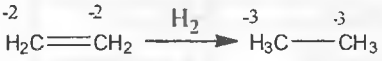


2 x (-1) +2 x (0) = - 2

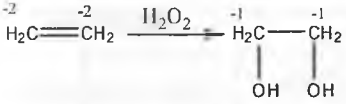


(-1) + (+1) + (+2) = +2

Using this approach, we can construct a carbon oxidation scale. Any reaction that increases the degree of oxidation of carbon corresponds to a loss of electrons (oxidation), and a reaction that decreases the oxidation level corresponds to a gain of electrons (reduction). Two examples follow:



net decrease in carbon oxidation srate of 2 per molecule (reduction)

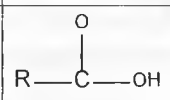


net increase in carbon oxidation state of 2 per molecule (oxidation)

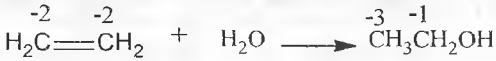
We recommend this scheme of oxidation states only as an aid to identify and balance redox reactions. Also, the terminology «redox» should not be confused with the mechanism of a reaction, as there is no connection between them. A moment of the reflection also will show that virtually all reactions theoreti-cally can be regarded as redox reactions, because in almost every reaction the reacting atoms experience some change in their electronic environments. Traditionally, however, reactions are described as redox reactions of carbon only when there is a net change in the oxidation state of

the carbon atoms involved. An indication of just how arbitrary this is can be seen by the example

Table 2.6 *Carbon Oxidation States of Representative Organic Compounds (R=alkyl) of addition of water to ethene.*

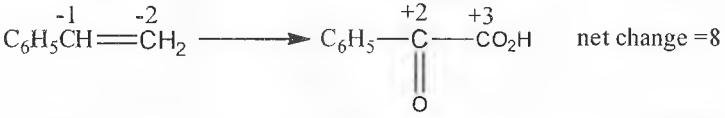
Compound	Structure	Oxidation state
Carbon dioxide	O—C—O	+4
tetrachloromethane	CCl_4	+4
isocyanates	CR—C—O	+4
carboxylic acids		+3
nitriles	CR≡N	+3
ketones	$R_2C{=}O$	+2
trichloromethane	$CHCl_3$	+2
ketenes	$R_2C{=}C^*{-}O$	+2(*)
tert-alcohols	R_3COH	+1
aldehydes	HCR=O	+1
methanol	CH_2—O	0
michloromethane	CH_2Cl_2	0
alkanes	R_2C	0
benzene	C_4H_6	-1 (per carbon)
alkanes	R_3CH	-1
ethyne	HC≡CH	-1 (per carbon)
alkanes	R_2CH_2	-2
ethene	$H_2C{=}CH_2$	-2 (per carbon)
chloromethane	CH_3Cl	-2
methanol	CH_3OH	-2
methyl cation	$CH_3^{\oplus}$	-2
methyl radical	CH_3	-3
alkanes	RCH_3	-3
methyl anion	$CH_3^{\ominus}$	-4
methane	CH_4	-4

This reaction usually is not regarded as an oxidation-reduction reaction because there is no net change in the oxidation state of the ethene carbons, despite the fact that, by our rules, one carbon is oxidized and the other reduced:

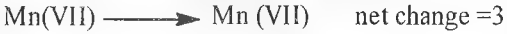


Apart from indicating when oxidation or reduction occurs, the oxidation scale is useful in balancing redox equations. For example, consider the following oxidation of ethenylbenzene (styrene) with potassium permanganate:

To determine how many moles of permanganate ion are required to oxidize one mole of styrene in this reaction, first determine the net change in oxidation state of the reacting carbons:



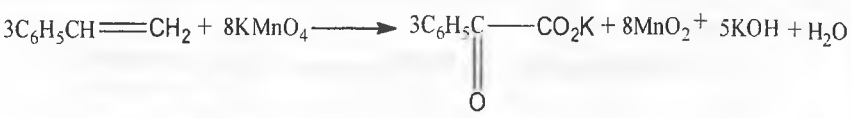
Second, determine the net change in oxidation state of manganese for $MnO_4 \rightarrow MnO_4$;



Therefore we need three moles of styrene for every eight moles of permanganate:

To get the overall atom and electrical balance for Equation 11-1, the requisite amounts of H_2O must be added, but the 3:8 ratio will remain unchanged:

Becouse KOH reacts in a nonoxidative- way with carboxylic acids to form carboxylate salts ($RCO_2H + 2H + KOH \rightarrow RCO_2K + H_2O$), the final equation is



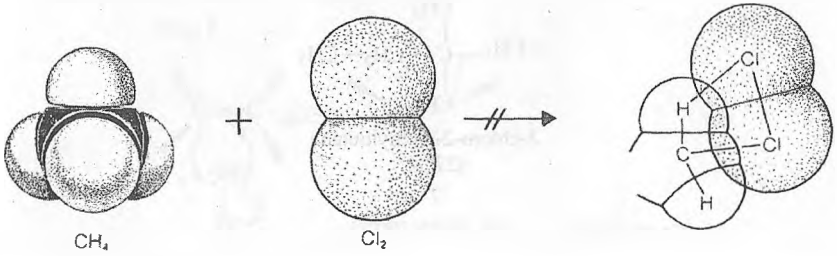
3 Halogenation

Halogenation of alkanes. The economies of the highly industrialized nations of the world are based in large part on energy and chemicals produced from petroleum. Although the most important and versatile intermediates for conversion of petroleum to chemicals are compounds with double or triple bonds, it also is possible to prepare many valuable substances by substitution reactions of alkanes. In such substitutions, a hydrogen is removed from a carbon chain and another atom or group of atoms becomes attached in its place. A simple example of a substitution reaction is the formation of chloromethane from methane and chlorine:

$$CH_4 + CL_2 \longrightarrow CH_3CL + HCL$$

Presumably, methane could react with chlorine to give chloromethane and hydrogen chloride, or chloromethane could react with hydrogen chloride to give methane and chlorine. If conditions were found for which both reactions proceeded at a finite rate, equilibrium finally would be established when the rates of the reactions in each direction became equal.

$$CH_4 + CL_2 \longrightarrow CH_3CL + HCL$$

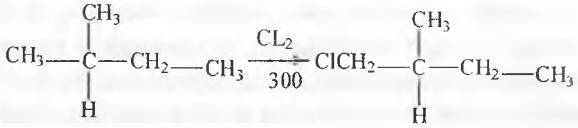


Models showing the degree of atomic compression required to bring a chlorine molecule to within bonding distance of carbon and hydrogen of methane.

The chlorination of methane does not have to stop with the formation of chloromethane (methyl chloride). It is usual when chlorinating methane to obtain some of the higher chlorination products: dichloromethane (methylene chloride), trichloromethane (chloroform), and tetrachloromethane (carbon tetrachloride):

$$CH_4 \longrightarrow \underset{\text{chloro-methane}}{CH_3CL} \longrightarrow \underset{\text{dichioro-methane}}{CH_2Cl_2} \longrightarrow \underset{\text{trichloro-methane}}{CHCl_3} \longrightarrow \underset{\text{tetrachioro-methane}}{CCl_4}$$

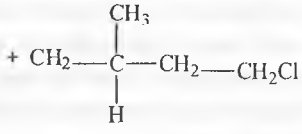
For propane and higher hydrocarbons for which more than one monosubstitution product is generally possible, difficult separation problems may arise when a particular product is desired. For example, the chlorination of 2-methylbutane 3 at 300" gives all four possible monosubstitution products, 4, 5, 6, and 7:



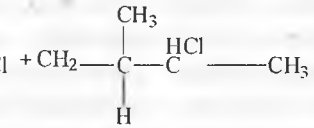
2-methylbutane

3

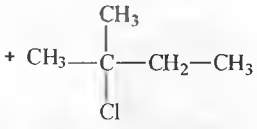
1-chloro-2-methylbutane
(30%)
4



1-chloro- 3-methylbutane
(15%)
5

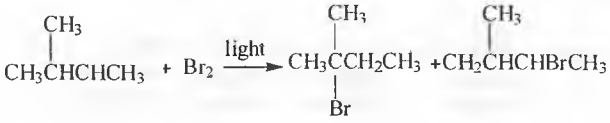


3-chloro-2-methylbutane
(33%)
6

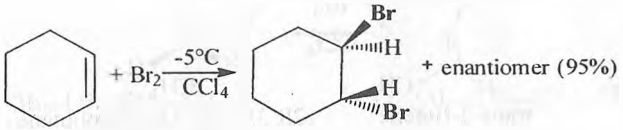


2-chloro-2-methylbutane
(22%)
7

Bromine atoms are far more selective than chlorine atoms. This is I I not unexpected because -C-H 4- Bra -+ -C. d- HBr is endothermic, I I whereas corresponding reactions with a chlorine atom usually are exothermic. Bromine removes only those hydrogens that are relatively weakly bonded to a carbon atom. As predicted, attack of Br. on 2-methylbutane leads mostly to 2-bromo-2-methylbutane, some secondary bromide, 4 Alkanes and essentially no primary bromides:

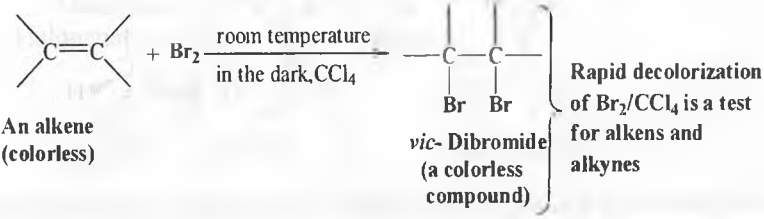


Halogenation of alkenes (Alkynes). Alkenes readily accept Br2 or Cl2 to form vicinal dihalides:



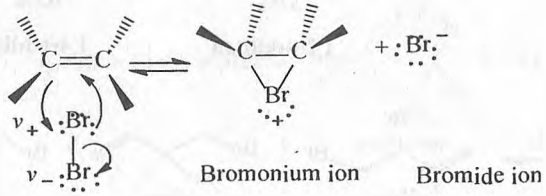
trans-1,2-Dibromocyclohexane
(as a racemic form)

Used as a test for alkenes because the red color of the bromine reagent disappears when an alkene (or alkyne) is present:

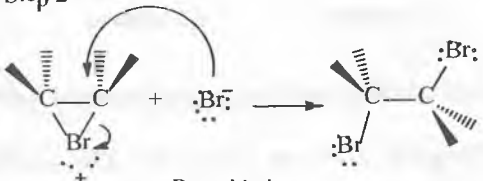


Mechanism of Halogen Addition:

Step 1

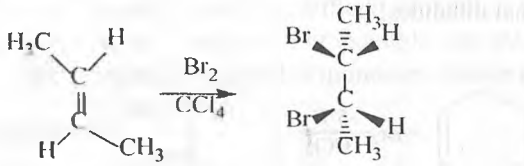


Step 2

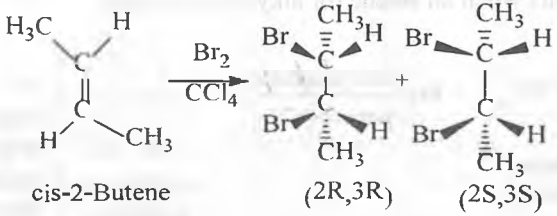


Halogenation of double bonds is stereospecific.A reaction is stereospecific if a particular stereoisomeric form of the starting material reacts in such a way that it gives a specific stereoisomeric form of the product l Example: cis- and trans-2-butene give stereoisomeric products when halogenated:

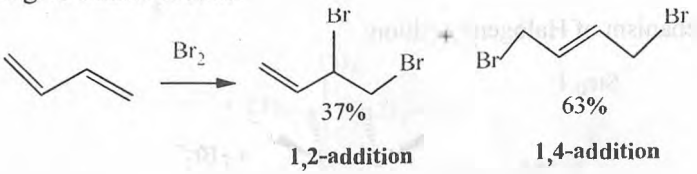
Reaction 1

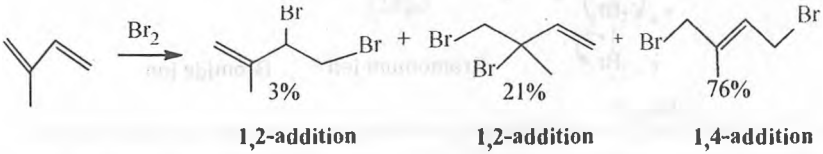


Reaction 2

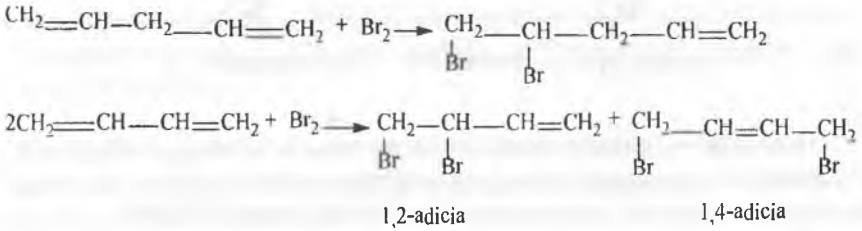


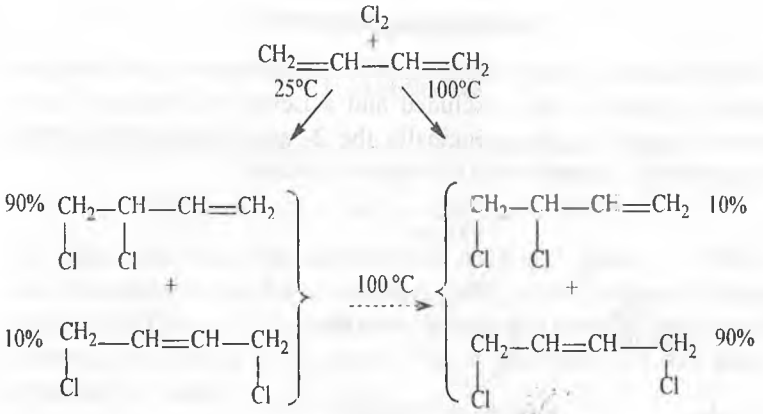
Halogenation of alkadienes. Electrophilc additions of other electrophile to dienes give similar results:



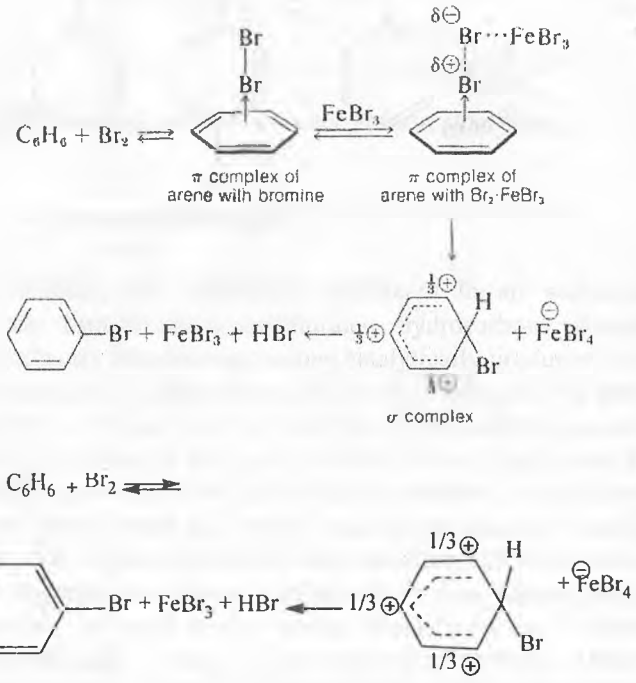


Regioselectivity of addition reactions on conjugated 1,3-alkadienes





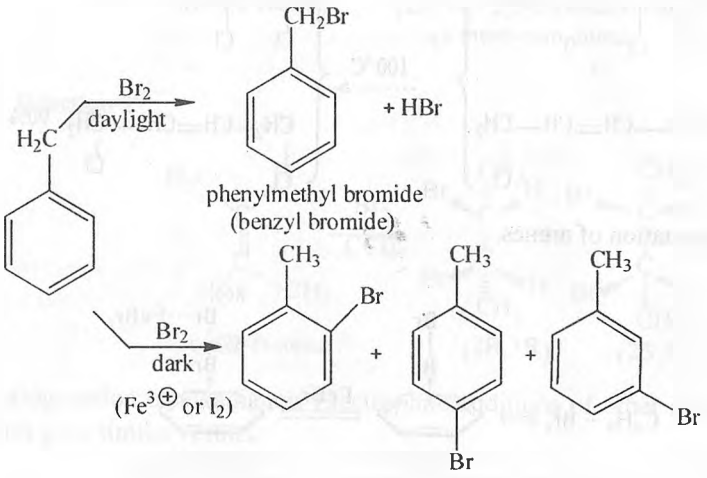
Halogenation of arenes.



The order of reactivity of the halogens is F, > Cl, > Br, > I,. Fluorine is too reactive to be of practical use for the preparation of aromatic fluorine. Iodine usually is unreactive. It has been stated that iodination fails because the reaction is reversed as the result of the reducing properties of the hydrogen iodide that is formed:

$$C_6H_6 + I_2 \rightleftharpoons C_6H_5I + HI$$

Methylbenzene reacts with bromine when illuminated to give phenylmethyl bromide, but when light is excluded and a Lewis acid catalyst is present, substitution occurs to give principally the 2- and 4-bromomethylbenzenes. Much less of the 3-bromomethyl benzene is formed:



bromomethylbenzenes

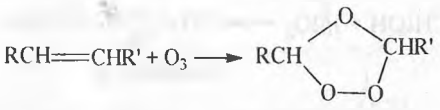
4 Aldehydes and ketones

4.1 Aldehydes

The oxidation of primary alcohols to aldehydes is as follows:

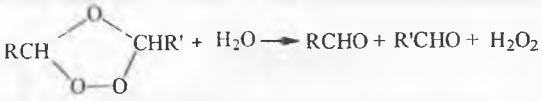
$$RCH_2OH + 1/2O_2 \longrightarrow R{-}CH{=}O + H_2O$$

All aldehydes have the characteristic carbonyl group, – CH=O The general structural formula for an aldehyde is R – CHO, where R represents any alkyl group: CH_3–, C_2H_5–, and so on. Aldehydes can also be formed from unsaturated hydrocarbons by ozonation. The hydrocarbons are first converted to an ozonide by ozone.



An ozonide

The ozonides react readily with water to form aldehydes.



These reactions are particularly significant in air pollution, where aldehydes are formed when unsaturated hydrocarbons discharged in automobile exhausts combine with ozone catalytically produced by reactions of oxygen with sunlight in the presence of oxides of nitrogen. The aldehydes so formed cause eye irritation, one of the most serious problems associated with air pollution. The oxides of nitrogen required for catalyzing ozone formation are produced in great quantities during high-temperature combustion of fossil fuels in steam power plants and internal combustion engines. Automobile and truck engine exhaust gases are a particularly significant source because of wide distribution at ground level where contact with human, animal, and plant life is most probable. Although a wide variety of aldehydes can be formed from primary alcohols, only a few are of commercial importance. Aldehydes can also be produced by reduction of carboxylic acids. Formaldehyde is formed by the oxidation of methanol.

$$CH_3OH + 1/2O_2 \longrightarrow H_2C{=}O + H_2O$$

Formaldehyde

It is used extensively in organic synthesis. It is very toxic to microorganisms,

and, because of this property, it is used in embalming fluids and fluids used for the preservation of biological specimens. Industrial wastes containing formaldehyde were considered at one time to be too toxic for treatment by biological methods.

Through dilution of such wastes to reduce the concentration of formaldehyde below 1500 mg/L, it was found that microorganisms could use the formaldehyde as food and oxidize it to carbon dioxide and water. This experience has led to the concept of *toxicity thresholds* in industrial waste treatment practice. It means that below certain concentrations all materials are nontoxic. The completely mixed activated sludge system is designed to take advantage of this concept.

Acetaldehyde. Acetaldehyde is formed by the oxidation of ethanol.

$$CH_3CH_2OH + 1/2O_2 \longrightarrow CH_3-\underset{H}{C}=O + H_2O$$

Acetaldehyde

The suffix -al is zppended to the name of the hydrocarbon corresponding to the longest carbon chain that includes the aldehyde carbon.

Remember that alkane- + -al becomes alkanal with the e omitted, and because the al function is necessarily at C1, the -1- is redundant and is omitted:

$CH_3CH_2CH_2CH_2CH_2CHO$

hexanal

$HC\equiv CCH_2CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CHO$

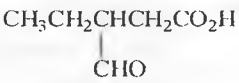
3 - methyl-6-heptynal

Dialdehydes are named as -dials. Thus OHCCH,CH,CH,CH,CHO is hexanedial. The simplest aldehyde is methanal, HCHO, which is familiarly known as formaldehyde. However, when aldehydes are named as derivatives of methanal, they usually are called carbaldehydes, and the suffix «carbaldehyde» refers to the -CHO group. This system is used where the hydrocarbon group is not a chain, but a ring, and the CHO group can be thought of as a one-carbon chain:

cyclohexanecarbaldehyde

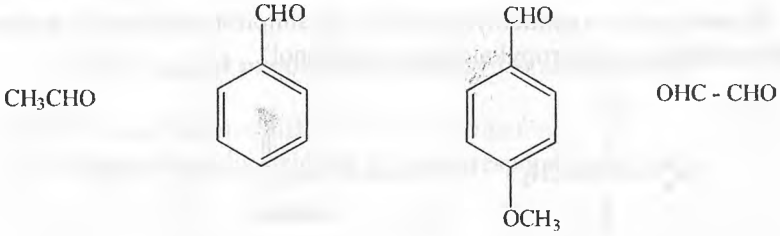
1,4 - benzenedicarbaldehyde

3. When the -CHO group is a substituent on the parent chain or ring and it ranks below another functional group, it properly is designated by the prefix methnnoyl. However, the prefix fovmyl also is used:



3 - methanoylpentanoic acid
(3 - formylpentanoic acid)

Trivial names are used for many simple aldehydes, some of which are shown below in parentheses:



ethanal (acetaldehyde)

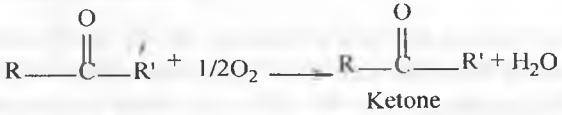
benzenecarbaldehyde (benzaldehyde)

4 - methoxy-benzenecarbaldehyde (anisaldehyde)

ethanedial (glyoxal)

4.2 Ketones

Ketones are prepared by the oxidation of secondary alcohols.



Ketone

Ketones have two alkyl groups attached to the carbonyl group, —C(=O)—, while aldehydes have one R group and a hydrogen atom. The R groups in ketones may be the same or different.

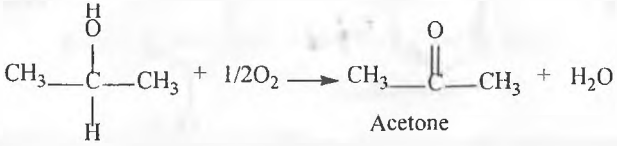
Table 4.1 *Common aldehydes*

Common name	IUPAC name	Formula
Formaldehyde	Methanol	HCHO
Acetaldehyde	Ethanal	CH_3CHO
Propionaldehyde	n – Propanal	C_2H_5CHO
Butyraldehyde	n – Butanal	C_3H_7CHO

Continuation of table 4.1

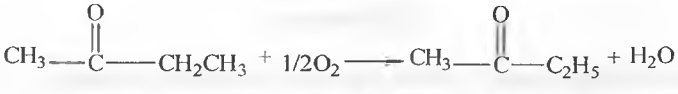
Valeraldehyde	n – Pentanal	C_4H_9CHO
Caproaldehyde	n – Hexanal	$C_5H_{11}CHO$
Heptaldehyde	n – Heptanal	$C_6H_{13}CHO$
Acrolein		$CH_2 = CHCHO$
Citral		$C_9H_{15}CHO$
Citronellal		$C_9H_{17}CHO$

Acetone Acetone (dimethyl ketone) is the simplest ketone and is produced by the oxidation of isopropyl alcohol (2-propanol).



Acetone

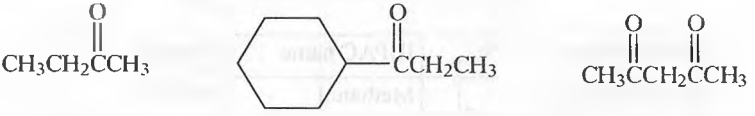
Methyl ethyl ketone Methyl ethyl ketone is prepared by the oxidation of 2-butanol.



Methyl ethyl ketone

Ketones are used as solvents in industry and for the synthesis of a wide variety of products. The names of a few ketones are given in Table 4.2.

The IUPAC system employs the suflix -one added to the prefix identifying the longest carbon chain of RCOR' that includes the carbonyl group. The chain is numbered to give the carbonyl group the lowest possible number. In the examples given, the names in parentheses correspond to a less systematic nomenclature of ketones by which the R groups each are named separately:



2 - butanone (methyl ethyl ketone)

1 - cyclohexyl - 1 - propanone (cyclohexyl ethyl ketone)

2,4 - pentanedione

When the doubly bonded oxygen is regarded as a substituent along the parent chain or ring, it is called an *oxo* group. = O;

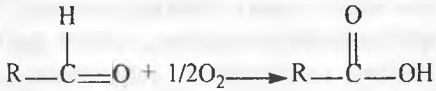
4-oxopentanal
(Notice in Table 7 - 1 that
-al is ahead of - one.)

4 - oxocyclohexanecarboxylic acid

4.3 Chemical properties of aldehydes and ketones

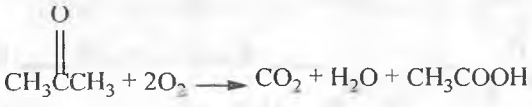
Aldehydes and ketones differ in ease of oxidation.

1. Aldehydes are easily oxidized to the corresponding acids.



2. Ketones are more difficult to oxidize. This is because there is no hydrogen attached to the carbonyl group. As a result, further oxidation must initiate in one of the alkyl groups, the molecule is cleaved, and two or more acids are produced.

3.



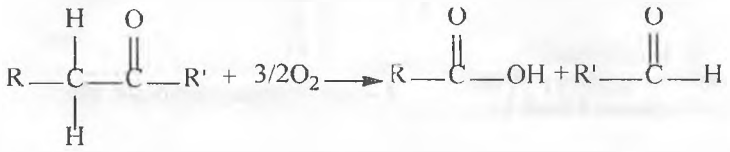
Acetone

Acetic acid

Table 4.2 *Common ketones*

Common name	IUPAC name
Acetone	Propanone
Methyl ethyl ketone	Butanone
Diethyl ketone	3 – Pentanone
Methyl propyl ketone	2 – Pentanone
Methyl isopropyl ketone	3 – Methyl – 2 - butanone
n – Butyl methyl ketone	2 – Hexanone
Ethyl propyl ketone	3 – Hexanone
Dipropyl ketone	4 - Heptanone
Dibutyl ketone	5 – Nonanone

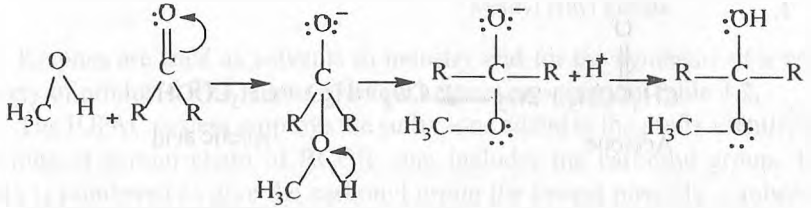
In the case of acetone, carbon dioxide and acetic acid are formed. Theoretically, formic acid should be formed, but it is so easily oxidized that it is generally converted under the prevailing conditions to carbon dioxide and water. Higher ketones such as diethyl ketone (3-pentanone) are oxidized as follows:



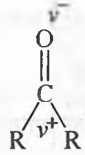
Oxidation of both aldehydes and ketones to organic acids is accomplished readily by many microorganisms. However, since the organic acids serve as a good food supply, the ultimate end products under aerobic conditions are carbon dioxide and water.

Reactions of aldehydes and ketones. Aldehydes and ketones undergo a variety of reactions that lead to many different products. The most common reactions are nucleophilic addition reactions, which lead to the formation of alcohols, alkenes, diols, cyanohydrins, and imines, to mention a few representative examples.

Reactions of carbonyl groups.The main reactions of the carbonyl group are nucleophilic additions to the carbon-oxygen double bond. As shown below, this addition consists of adding a nucleophile and a hydrogen across the carbon-oxygen double bond.



Due to differences in electronegativities, the carbonyl group is polarized. The carbon atom has a partial positive charge, and the oxygen atom has a partially negative charge.

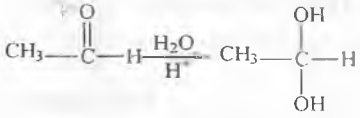


Aldehydes are usually more reactive toward nucleophilic substitutions

than ketones because of both steric and electronic effects. In aldehydes, the relatively small hydrogen atom is attached to one side of the carbonyl group, while a larger R group is affixed to the other side. In ketones, however, R groups are attached to both sides of the carbonyl group. Thus, steric hindrance is less in aldehydes than in ketones.

Electronically, aldehydes have only one R group to supply electrons toward the partially positive carbonyl carbon, while ketones have two electron-supplying groups attached to the carbonyl carbon. The greater amount of electrons being supplied to the carbonyl carbon, the less the partial positive charge on this atom and the weaker it will become as a nucleus.

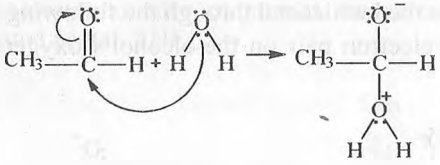
Addition of water.The addition of water to an aldehyde results in the formation of a hydrate.



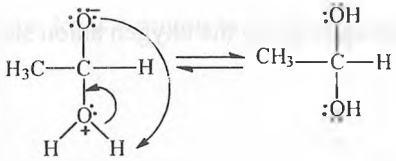
hydrate

The formation of a hydrate proceeds via a nucleophilic addition mechanism.

1. Water, acting as a nucleophile, is attracted to the partially positive carbon of the carbonyl group, generating an oxonium ion.



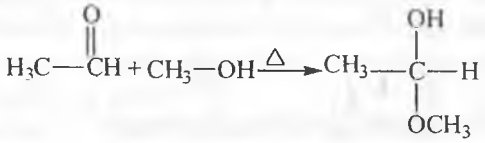
2. The oxonium ion liberates a hydrogen ion that is picked up by the oxygen anion in an acid-base reaction.



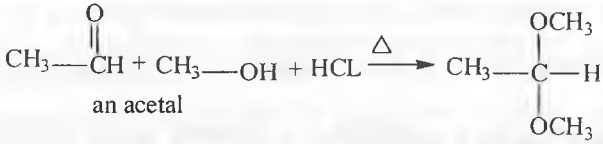
Small amounts of acids and bases catalyze this reaction. This occurs because the addition of acid causes a protonation of the oxygen of the carbonyl group, leading to the formation of a full positive charge on the carbonyl

carbon, making the carbon a good nucleus. Adding hydroxyl ions changes the nucleophile from water (a weak nucleophile) to a hydroxide ion (a strong nucleophile). Ketones usually do not form stable hydrates.

Addition of alcohol.Reactions of aldehydes with alcohols produce either hemiacetals (a functional group consisting of one – OH group and one – OR group bonded to the same carbon) or acetals (a functional group consisting of two – OR groups bonded to the same carbon), depending upon conditions. Mixing the two reactants together produces the hemiacetal. Mixing the two reactants with hydrochloric acid produces an acetal. For example, the reaction of methanol with ethanal produces the following results:



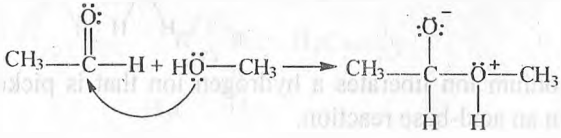
a hemiacetal



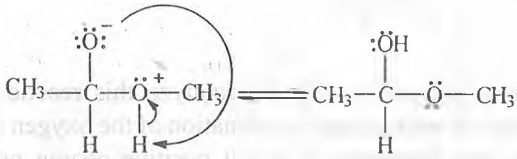
an acetal

A nucleophilic substitution of an OH group for the double bond of the carbonyl group forms the hemiacetal through the following mechanism:

3. An unshared electron pair on the alcohol's oxygen atom attacks the carbonyl group.

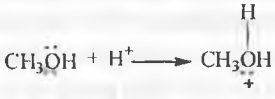


4. The loss of a hydrogen ion to the oxygen anion stabilizes the oxonium ion formed in Step 1.

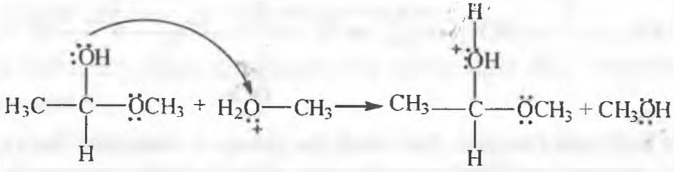


The addition of acid to the hemiacetal creates an acetal through the following mechanism:

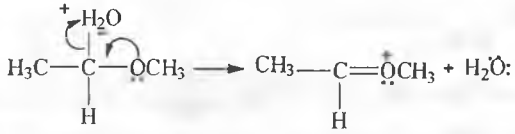
5. The proton produced by the dissociation of hydrochloric acid protonates the alcohol molecule in an acid-base reaction.



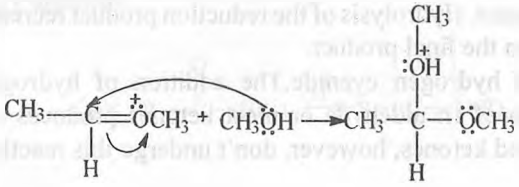
6. An unshared electron pair from the hydroxyl oxygen of the hemiacetal removes a proton from the protonated alcohol.



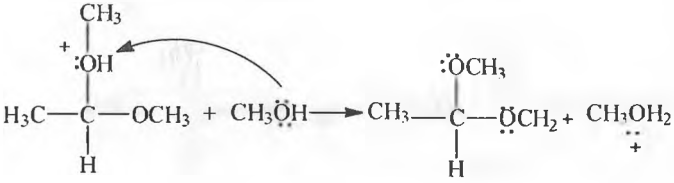
7. The oxonium ion is lost from the hemiacetal as a molecule of water.



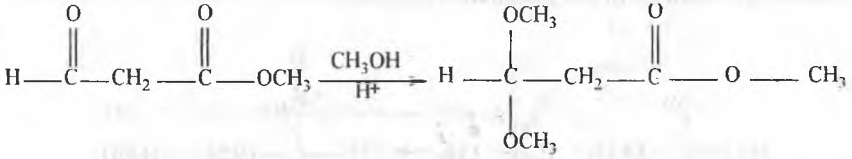
8. A second molecule of alcohol attacks the carbonyl carbon that is forming the protonated acetal. EHEE



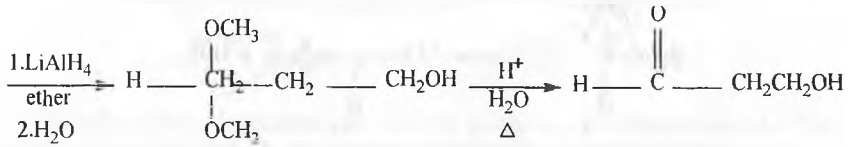
7. The oxonium ion loses a proton to an alcohol molecule, liberating the acetal.



Stability of acetals.Acetal formation reactions are reversible under acidic conditions but not under alkaline conditions. This characteristic makes an acetal an ideal protecting group for aldehyde molecules that must undergo further reactions. A protecting group is a group that is introduced into a molecule to prevent the reaction of a sensitive group while a reaction is carried out at some other site in the molecule. The protecting group must have the ability to easily react back to the original group from which it was formed. An example is the protection of an aldehyde group in a molecule so that an ester group can be reduced to an alcohol.

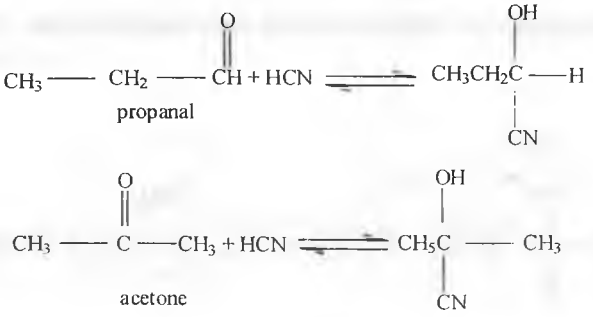


In the previous reaction, the aldehyde group is converted into an acetal group, thus preventing reaction at this site when further reactions are run on the rest of the molecule.



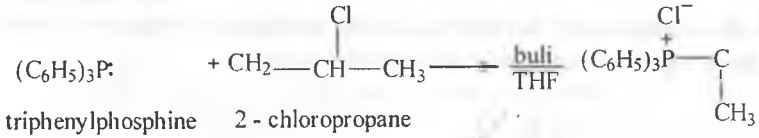
Notice in the previous reaction that the ketone carbonyl group has been reduced to an alcohol by reaction with $LiAlH_4$. The protected aldehyde group has not been reduced. Hydrolysis of the reduction product recreates the original aldehyde group in the final product.

Addition of hydrogen cyanide.The addition of hydrogen cyanide to a carbonyl group of an aldehyde or most ketones produces a cyanohydrin. Sterically hindered ketones, however, don't undergo this reaction.



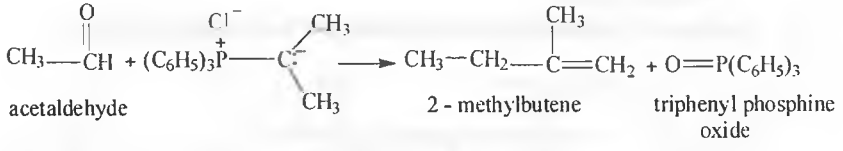
The mechanism for the addition of hydrogen cyanide is a straightforward nucleophilic addition across the carbonyl carbony oxygen bond.

Addition of ylides (the Wittig reaction).The reaction of aldehydes or ketones with phosphorus ylides produces alkenes of unambiguous double-bond locations. Phosphorous ylides are prepared by reacting a phosphine with an alkyl halide, followed by treatment with a base. Ylides have positive and negative charges on adjacent atoms.



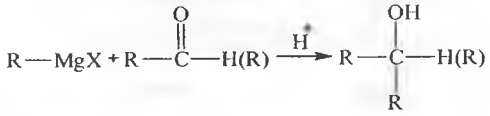
triphenylphosphine 2 - chloropropane

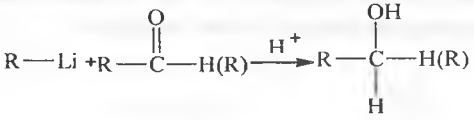
The following illustration shows the preparation of 2 methylbutene by a Wittig reaction.

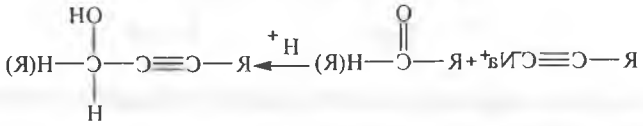


acetaldehyde dimethyitriphenylphosphonium chloride anion 2 - methylbutene triphenyl phosphine oxide

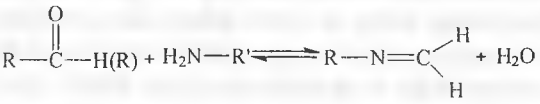
Addition of organometallic reagents.Grignard reagents, organolithium compounds, and sodium alkynides react with formaldehyde to produce primary alcohols, all other aldehydes to produce secondary alcohols, and ketones to produce tertiary alcohols.





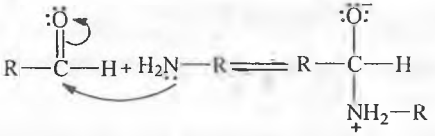


Addition of ammonia derivatives. Aldehydes and ketones react with primary amines to form a class of compounds called imines

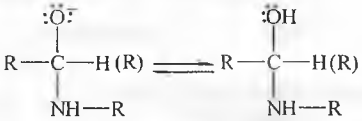


The mechanism for imine formation proceeds through the following steps:

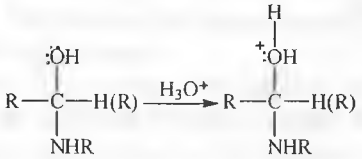
1. An unshared pair of electrons on the nitrogen of the amine is attracted to the partial-positive carbon of the carbonyl group.



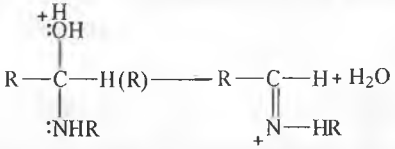
2. A proton is transferred from the nitrogen to the oxygen anion.



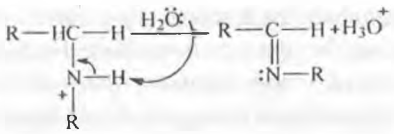
3. The hydroxy group is protonated to yield an oxonium ion, which easily liberates a water molecule.



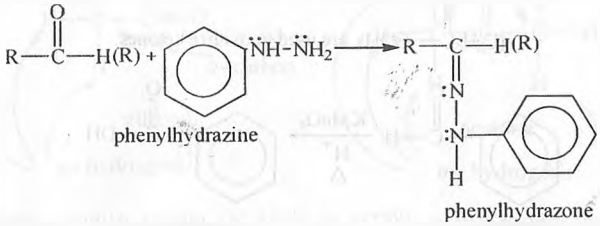
4. An unshared pair of electrons on the nitrogen migrate toward the positive oxygen, causing the loss of a water molecule.

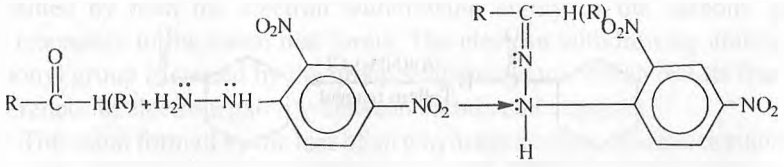


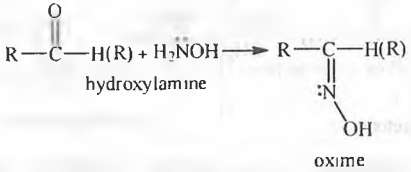
A proton from the positively charged nitrogen is transferred to water, leading to the imine's formation.

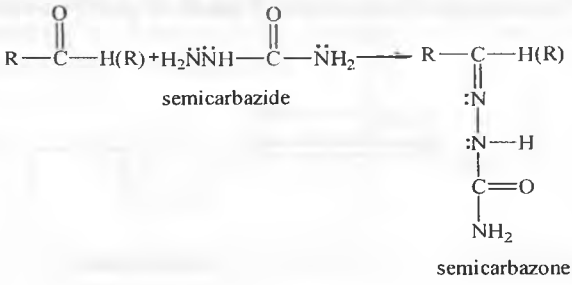


Imines of aldehydes are relatively stable while those of ketones are unstable. Derivatives of imines that form stable compounds with aldehydes and ketones include phenylhydrazine, 2,4-dinitrophenylhydrazine, hydroxylamine, and semicarbazide.



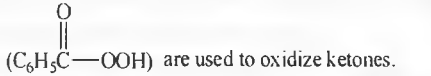


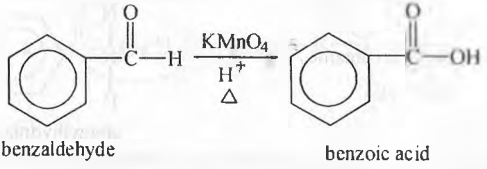


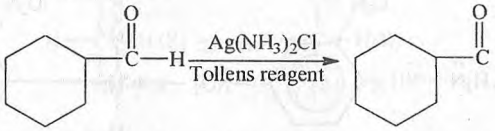


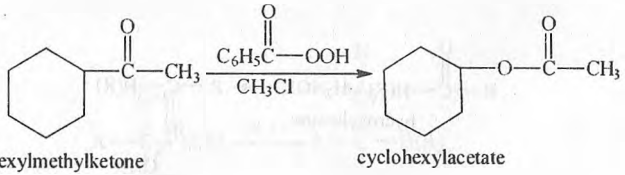
Oximes, 2,4-dinitrophenylhydrazones, and semicarbazones are often used in qualitative organic chemistry as derivatives for aldehydes and ketones.

Oxidations of aldehydes and ketones. Aldehydes can be oxidized to carboxylic acid with both mild and strong oxidizing agents. However, ketones can be oxidized to various types of compounds only by using extremely strong oxidizing agents. Typical oxidizing agents for aldehydes include either potassium permanganate ($KMnO_4$) or potassium dichromate ($K_2Cr_2O_7$) in acid solution and Tollens reagent. Peroxy acids, such as peroxybenzoic acid:

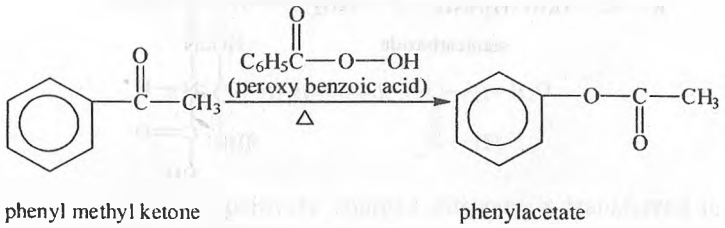




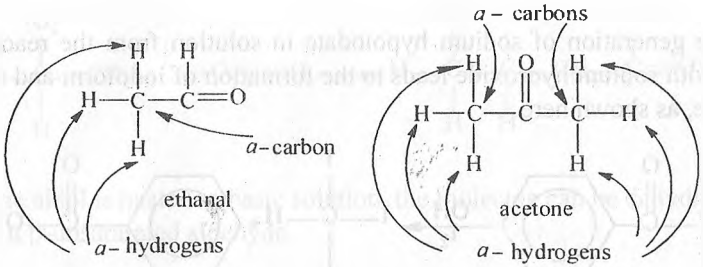




Baeyer-Villiger oxidation is a ketone oxidation, and it requires the extremely strong oxidizing agent peroxybenzoic acid. For example, peroxybenzoic acid oxidizes phenyl methyl ketone to phenyl acetate (an ester).

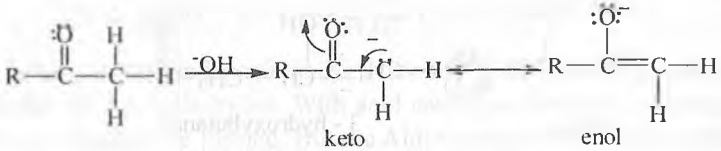


Aldol reactions. In addition to nucleophilic additions, aldehydes and ketones show an unusual acidity of hydrogen atoms attached to carbons alpha (adjacent) to the carbonyl group. These hydrogens are referred to as α hydrogens, and the carbon to which they are bonded is an α carbon. In ethanal, there is one α carbon and three α hydrogens, while in acetone there are two α carbons and six α hydrogens.



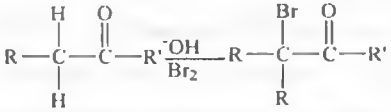
Although weakly acidic ($K_a 10^{-19}$ to 10^{-20}), α hydrogens can react with strong bases to form anions. The unusual acidity of α hydrogens can be explained by both the electron withdrawing ability of the carbony group and resonance in the anion that forms. The electron withdrawing ability of a carbonyl group is caused by the group's dipole nature, which results from the differences in electronegativity between carbon and oxygen.

The anion formed by the loss of an α hydrogen can be resonance stabilized because of the mobility of the π electrons that are on the adjacent carbonyl group.

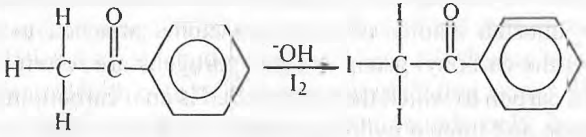


The resonance, which stabilizes the anion, creates two resonance structures — an enol and a keto form. In most cases, the keto form is more stable.

Halogenation of ketones.In the presence of a base, ketones with α hydrogens react to form α haloketones.

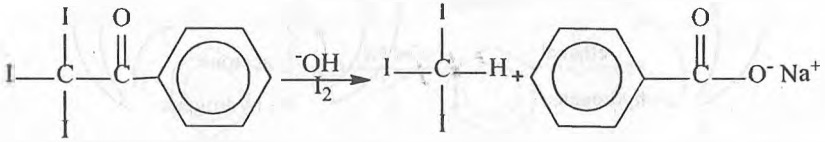


Likewise, when methyl ketones react with iodine in the presence of a base, complete halogenation occurs.



methyl phenyl ketone triiodomethyl phenyl ketone

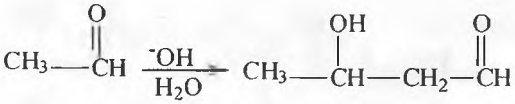
The generation of sodium hypoiodate in solution from the reaction of iodine with sodium hydroxide leads to the formation of iodoform and sodium benzoate, as shown here.



iodoform sodium benzoate

Because iodoform is a pale yellow solid, this reaction is often run as a test for methyl ketones and is called the iodoform test.

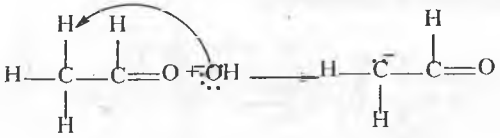
Aldol condensation.Aldehydes that have α hydrogens react with themselves when mixed with a dilute aqueous acid or base. The resulting compounds, β-hydroxy aldehydes, are referred to as aldol compounds because they possess both an aldehyde and alcohol functional group.



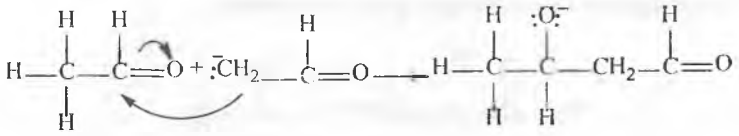
ethanal 3 - hydroxybutanal

The aldol condensation proceeds via a carbanion intermediate. The mechanism of base-catalyzed aldol condensation follows these steps:

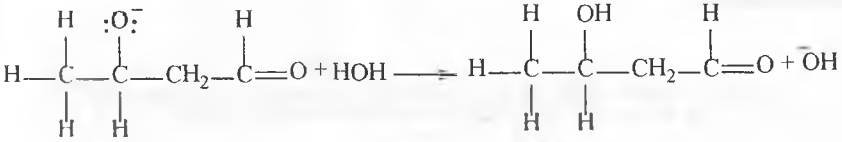
1. The base removes an α hydrogen.



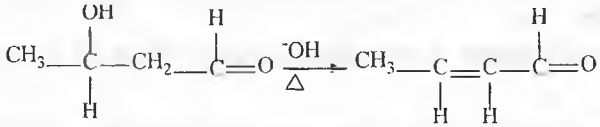
2. The carbanion undergoes nucleophilic addition with the carbonyl group of a second molecule of ethanal, which leads to formation of the condensation product.



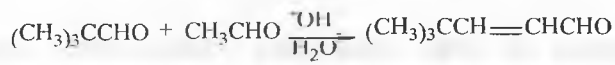
3. A reaction with water protonates the alkoxide ion.



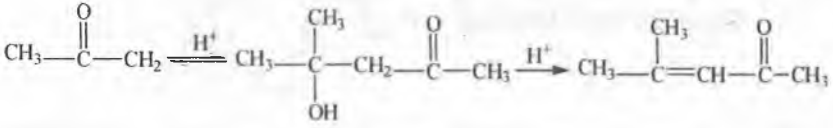
If the aldol is heated in basic solution, the molecule can be dehydrated to form an α β-unsaturated aldehyde.



Cross-aldol condensation. An aldol condensation between two different aldehydes produces a cross-aldol condensation. If both aldehydes possess α hydrogens, a series of products will form. To be useful, a cross-aldol must be run between an aldehyde possessing an α hydrogen and a second aldehyde that does not have α hydrogens.



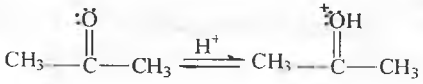
Ketonic aldol condensation. Ketones are less reactive towards aldol condensations than alde-hydes. With acid catalysts, however, small amounts of aldol product can be formed. But the Aldol product that forms will rapidly dehydrate to form a resonance-stabilized product. This dehydration step drives the reaction to completion.



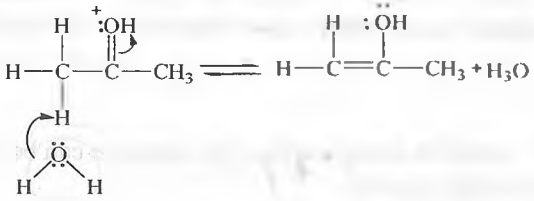
2 - propanone 4- hydroxy- 4- methyl - 2 -pentanone 4 - methyl -3-pentene-2-one

The acid-catalyzed aldol condensation includes two key steps: the conversion of the ketone into its enolic form, and the attack on a protonated carbonyl group by the enol. The mechanism proceeds as follows:

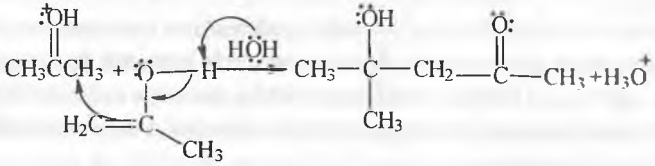
1. The oxygen of the carbonyl group is protonated.



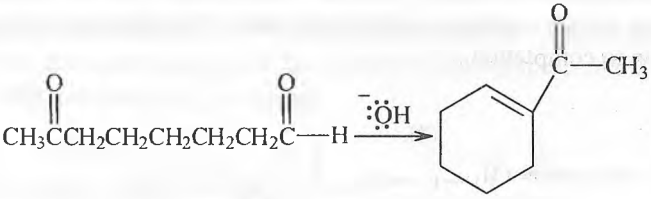
2. A water molecule acting as a base removes an acidic α hydrogen, which leads to an enol.



3. The enol attacks a protonated carbonyl group of a second ketone molecule.

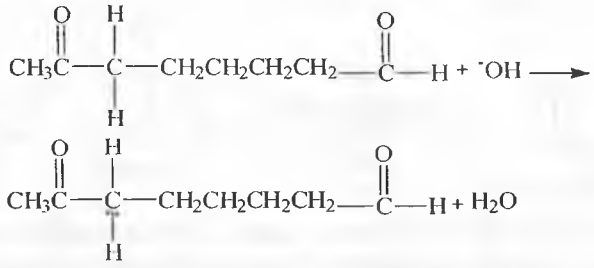


Cyclizations via aldol condensation. Internal aldol condensations (condensations where both carbonyl groups are on the same chain) lead to ring formation.

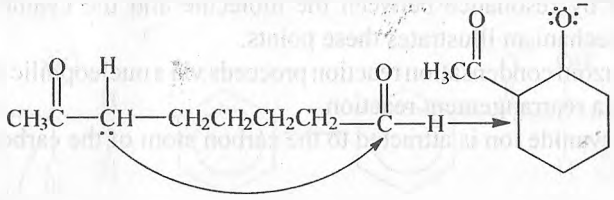


The mechanism for cyclization via an aldol proceeds through an enolate attack on the aldehyde carbonyl.

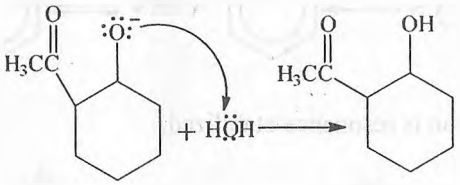
1. The hydroxy ion removes a hydrogen ion α to the ketone carbonyl.



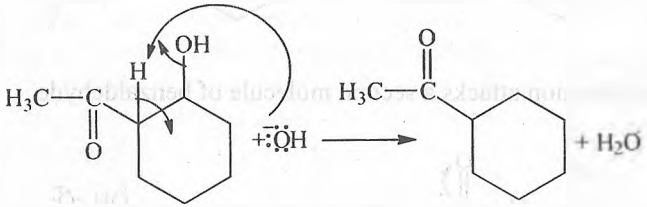
2. The enolate ion attacks the aldehyde carbonyl, closing the ring.



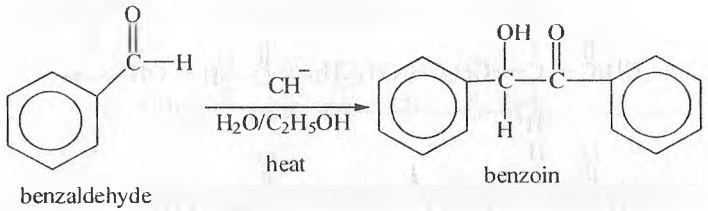
3. The alkoxide ion abstracts a proton from water in an acid-base reaction.



4. The base removes a hydrogen ion to form a resonance-stabilized molecule.



The benzoin condensation. Aromatic aldehydes form a condensation product when heated with a cyanide ion dissolved in an alcohol-water solution. This condensation leads to the formation of α hydroxy ketones.

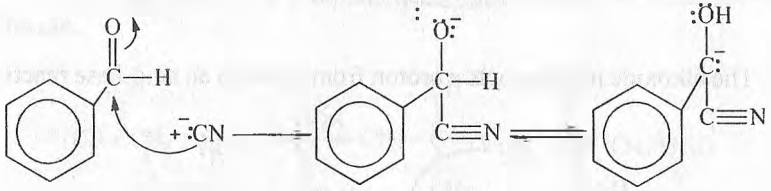


benzaldehyde benzoin

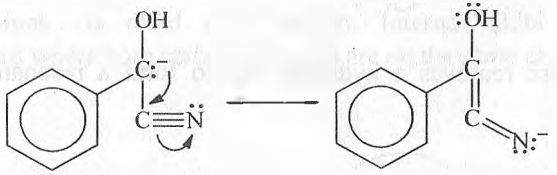
The cyanide ion is the only known catalyst for this condensation, because the cyanide ion has unique properties. For example, cyanide ions are relatively strong nucleophiles, as well as good leaving groups. Likewise, when a cyanide ion bonds to the carbonyl group of the aldehyde, the intermediate formed is stabilized by resonance between the molecule and the cyanide ion. The following mechanism illustrates these points.

The benzoin condensation reaction proceeds via a nucleophilic substitution followed by a rearrangement reaction.

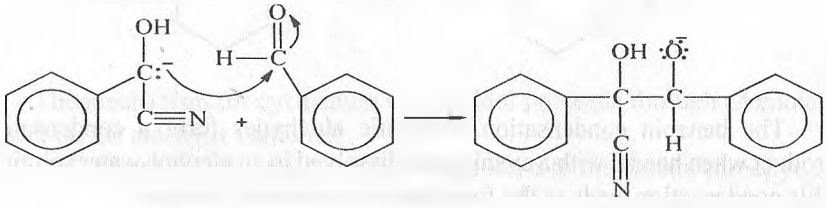
1. The cyanide ion is attracted to the carbon atom of the carbonyl group.



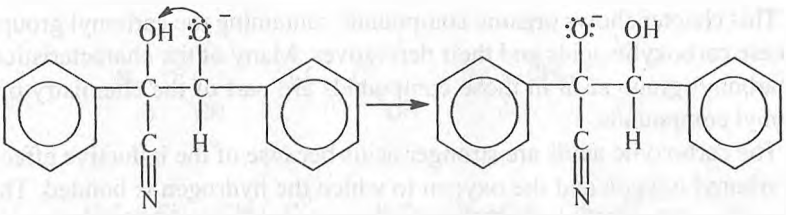
2. The carbanion is resonance-stabilized.



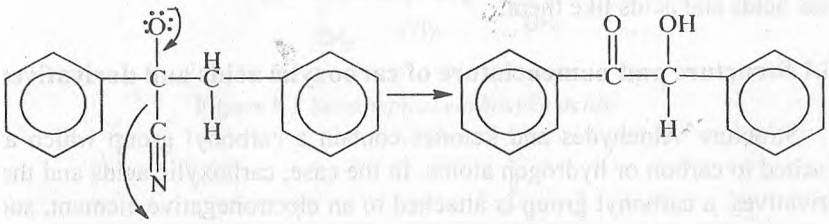
3. The carbanion attacks a second molecule of benzaldehyde.



4. The alkoxide ion removes a proton from the hydroxide group.



5. A pair of electrons on the alkoxide ion are attracted to the carbon bonded to the cyanide group, which then leaves to generate the product.



5 Carboxylic acids and their derivatives

This chapter shows organic compounds containing the carbonyl group; in this case carboxylic acids and their derivatives. Many of the characteristics of the carbonyl group seen in those compounds are part of the chemistry of all carbonyl compounds.

The carboxylic acids are stronger acids because of the inductive effect of the carbonyl oxygen and the oxygen to which the hydrogen is bonded. These carboxylic acids are the most important organic acids. You find them in citrus fruits (citric acid), vinegar (acetic acid), aspirin (acetylsalicylic acid), and numerous other natural and synthetic compounds, as well on numerous organic exams. In this chapter you explore the structure, synthesis, and reactions of these acids and acids like them.

5.1 Structure and nomenclature of carboxylic acids and derivatives

Structure. Aldehydes and ketones contain a carbonyl group which are attached to carbon or hydrogen atoms. In the case, carboxylic acids and their derivatives, a carbonyl group is attached to an electronegative element, such as: oxygen, chlorine or nitrogen. The presence of these elements tends to increase the "+" charge on the carbonyl carbon, which makes the carbon atom more susceptible to nucleophilic attack.

The general formula for a carboxylic acid is RCOOH, where R may be hydrogen or any alkyl or aryl group. The derivatives vary slightly from that formula:

in esters, the -OH is replaced with a -OR'.

in acyl chlorides, the -OH is replaced with a -Cl.

in acid anhydrides, two carboxylic acid molecules join (with the removal of a water molecule) to produce a molecule where an oxygen atom joins two carbonyl groups.

Finding out how carboxylic acids are called. When naming carboxylic acids, the final -e of the hydrocarbon is replaced with either -ic acid (common name) or -oic acid (IUPAC name). The carbonyl carbon on the acid is the position one. When naming the salts, the -ic of the acid name is replaced with -ate.

Figure 5.1 shows the structures of some carboxylic acids, and their common names and IUPAC names are given in the following list. Figure 5.2 shows the structures and names of some of carboxylic acid salts.

(I) formic acid or methanoic acid

(II) acetic acid or ethanoic acid

(III) propionic acid or propanoic acid

(IV) butyric acid or butanoic acid

(V) valeric acid or pentanoic acid
(VI) 4-methylpentanoic acid

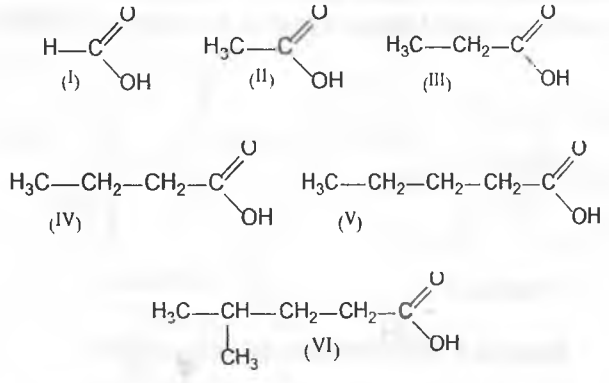


Figure 5.1 *Some typical carboxylic acids*

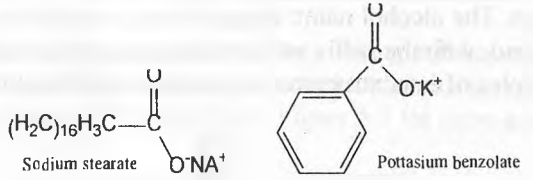


Figure 5.2 *Two carboxylic acid salts*

Designating dicarboxylic acids.Molecules may contain more than one carboxylic acid group. The dicarboxylic acids,which contain two carboxylic acid groups are very important in areas such as organic synthesis. Many dicarboxylic acids have the general formula HOOC-$(CH_2)_n$-COOH. Table 5.1 lists how the names of the dicarboxylic acids relate to the value of n.

Table 5.1 *Some Dicarboxylic Acids (HOOC-(CH2)n-COOH)*

Value of n	Dicarboxylic Acid
n = 0 Oxalic acid	Oxalic acid
n = 1 Malonic acid	Malonic acid
n = 2 Succinic acid	Succinic acid
n = 3 Glutaric acid	Glutaric acid
n = 4 Adipic acid	Adipic acid

A few important unsaturated dicarboxylic acids are shown in Figure 5.3. The position of the acid groups in a dicarboxylic acid is significant:

If the two acid groups are ortho, the acid is phthalic.
The phthalic acids are examples of aromatic dicarboxylic acids.
If the two acid groups are meta, the acid is isophthalic.
If the two carboxylic acid groups are para, the acid is terephthalic.

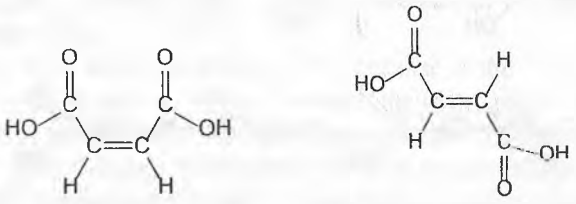


Figure 5.3 *Two unsaturated dicarboxylic acids.*

Examining the nomenclature of esters."Uniting acids and alcohols to make esters", esters come from an alcohol and an acid. The name of an ester reflects this origin. The alcohol name appears first (as an alkyl), and the acid name comes second, with the suffix -ate replacing the -ic acid part of the acid name. Two examples of ester structures and names are in Figure 5.4.

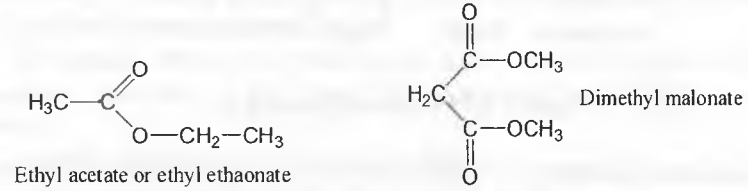


Figure 5.4 *Examples of two esters with their names.*

Naming acid anhydrides.Acid anhydrides are formed by joining two acids together. When naming, replace the word acid with the word anhydride. For example, two acetic acid molecules are joined to form acetic anhydride. Dicarboxylic acids may react internally to form an acid anhydride. See Figure 5.5 for some examples.

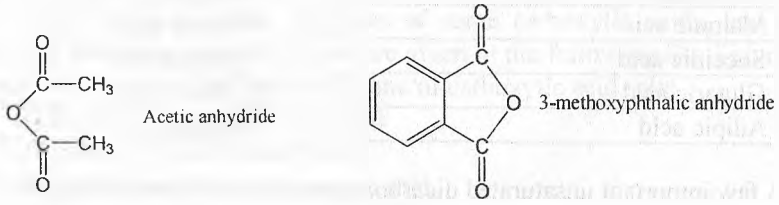


Figure 5.5 *Examples of two acidanhydrides with their names.*

Labeling acyl chlorides.When naming an acylchloride, you need to replace -ic acid with –yl chloride. See Figure 5.6 for three examples.

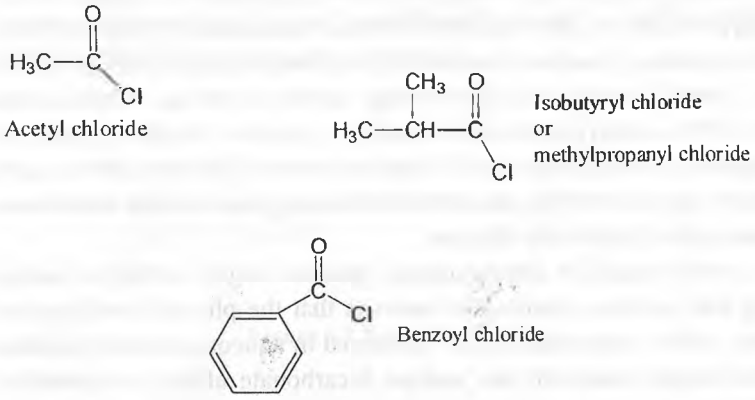


Figure 5.6 *Examples of three acyl chlorides with their names.*

Clarifying amide nomenclature.When naming amides, replace the *-ic* (or *-oic*) *acid* with *amide*. Each R group attached to the nitrogen is represented by an N at the beginning of the name. See Figure 5.7 for some examples.

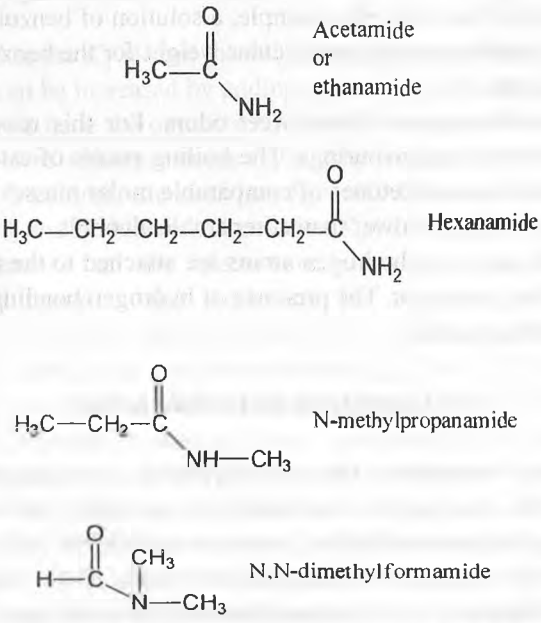


Figure 5.7 *Examples of amides with their names.*

5.2 Physical properties of carboxylic acids and derivatives

Physical properties of carboxylic acids and derivatives include solubility, melting point, boiling point and a few other characteristics. In this section we will examine each class and discuss the most important physical properties.

Carboxylic acids with six or fewer carbon atoms are soluble in water because of the polarity of the acid functional group and the ability of the acidic hydrogen atom to hydrogen bond. Carboxylic acids with more than six carbon atoms are reacted with and dissolved in either aqueous sodium bicarbonate or aqueous sodium hydroxide solution.

A useful means of distinguishing between larger carboxylic acids and phenols that are not dissolved in water is that the phenols are dissolved in aqueous sodium hydroxide but are dissolved in aqueous sodium bicarbonate. Neither sodium hydroxide nor sodium bicarbonate affects the solubility of alcohols.

In general, the carboxylic acids have disagreeable odors, high melting points, and high boiling points. The high melting and boiling points are due to hydrogen bonding. In some cases the hydrogen bonding is sufficient to hold two carboxylic acids molecules together as a *dimer* (two molecules held together). When this occurs, the molecular weight (MW) appears to be about twice the weight of the acid. For example, a solution of benzoic acid (MW = 122 g/mol) in naphthalene has a molecular weight for the benzoic acid dimer of about 244 g/mol.

Esters.In general, esters have sweet odors. For this reason, many are useful in perfumes or as flavourings. The boiling points of esters are similar to those of aldehydes and ketones of comparable molar masses, which means that the boiling points are lower than comparable alcohols.

Amides.If one or two hydrogen atoms are attached to the nitrogen atom, hydrogen bonding can occur. The presence of hydrogen bonding increases the melting and boiling points.

5.3 Acidity of carboxylic acids

The carboxylic acids are the most important of the organic acids. The Ka values (acid dissociation constants) are normally between 10^{-4} and 10^{-5}, indicating that an equilibrium has been established with only a small percentage of the weak acid in its dissociated form. As for acids, they have a sour taste. (Vinegar a 4- to 5-percent solution of acetic acid.) Two factors enhance the acid behaviour of the carboxylic acids. The first factor is an

inductive effect (see Figure 5.8), which is a result of the electron-withdrawing power of the two oxygen atoms. *Note:* The arrows in the figure indicate the electron-withdrawing power of the two oxygen atoms. The other factor is the resonance stabilization of the carboxylate ion (see Figure 5.9). Remember that resonance stabilizes the molecular structure.

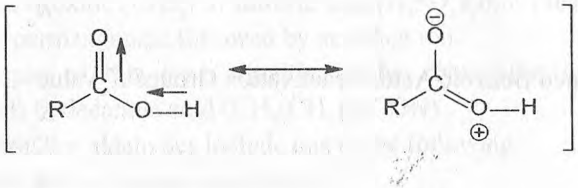


Figure 5.8 *The inductive effect.*

Figure 5.9 *Resonance stabilization of the carboxylate ion.*

The higher the K_a (lower the pK_a) value is, the stronger the acid will be. The acidity can be increased by adding electron-withdrawing groups to the R electron donors have the opposite effect). For example, the acidity of acetic acid increases as chlorine atoms replace hydrogen atoms. Acetic acid has $K_a=1.76\times10^{-5}$, chloroacetic acid has $K_a=1.40\times10^{-3}$, dichloroacetic acid has $K_a=3.32\times10^{-2}$, and trichloroacetic acid has $K_a=2.00\times10^{-1}$.

The distance at the electron-withdrawing group from the carboxylic acid group is also important. For example, butanoic acid has $K_a=1.5\times10^{-5}$, 4-chlorobutanoic acid has $K_a=3\times10^{-5}$, 3-chlorobutanioic acid has $K_a=8.9\times10^{-5}$, and 2-chlorobutanoic acid has $K_a=1.4\times10^{-3}$. This shows that the chlorine is more effective, the closer it gets to the carboxylic acid group.

For the aromatic carboxylic acids, substituents on the aromatic ring may also influence the acidity of the acid. Benzoic acid, for example, has $K_a=4.3\times10^{-5}$. The placements of various activating groups on the ring decrease the value of the equilibrium constant, and deactivating groups increase the value of the equilibrium constant. Table 5.2 illustrates the influence of a number of para-substituents upon the acidity of benzoic acid.

Table 5.2 *Comparison of K_a Values of Benzoic Acid to Para-Substituted Benzoic Acids*

Benzoic acid	$K_a = 4.3\times10^{-5}$
Para-Substituted Benzoic Acid, Activating Groups K_a Value	
-OH	$K_a = 2.8\times10^{-5}$
-OCH3	$K_a = 3.5\times10^{-5}$
-CH3	$K_a = 4.3\times10^{-5}$
Para-Substituted Benzoic Acid, Deactivation Groups K_a Value	
-Br/-Cl	$K_a = 1.1\times10^{-4}$
-CHO	$K_a = 1.8\times10^{-4}$
-CN	$K_a = 2.8\times10^{-4}$
-NO2	$K_a = 3.9\times10^{-4}$

The dicarboxylic acids have two K_a values with $K_a1 >> K_a$. The second K_a value is lower because the loss of the first acidic hydrogen leaves an anion, which can back-donate electron density (inductive effect). The difference between the K_a values decreases as the value of n increases for the series $HOOC(CH_2)_nCOOH$.

5.4 Synthesis of carboxylic acids and derivatives

The syntheses of carboxylic acids and their derivatives are important reactions in organic chemistry. In this section you have a look at several ways to make these compounds.

Synthesizing carboxylic acids.A number of methods are used in the synthesis of carboxylic acids. Most of these methods involve the oxidation of some organic molecule, but other methods can be also used. In this section we take a look at a few of these methods.

Oxidation of alkenes.The synthesis of carboxylic acids by the oxidation of alkenes is a two-step process. In the first step, a hot basic potassium permanganate ($KMnO_4$) solution oxidizes an alkene, and in the second step, the oxidized alkene is acidified. The process cleaves the carbon backbone at the carbon-carbon double bond to produce two smaller carboxylic acid molecules. For example, oleic acid ($CH_3(CH_2)_7CH=CH(CH_2)_7COOH$) yields of mixture of nonanoic acid ($CH3(CH_2)_7COOH$) and nonadioic acid ($HOOC(CH_2)_7COOH$). Oxidation of aldehydes and primary alcohols

The oxidation of either primary alcohols or aldehydes does not change the carbon backbone, so you end up with a carboxylic acid containing the

same number of carbon atoms as the aldehyde or alcohol. Alcohols require considerably stronger oxidizing conditions than aldehydes do.

The oxidation of a secondary alcohol gives a ketone, and neither ketones nor tertiary alcohols readily oxidize.

The oxidants for alcohols include one of the following:

Hot acidic potassium dichromate ($K_2Cr_2O_7$);

Chromium trioxide (CrO_3) in sulfuric acid (H_2SO_4)(Jones reagent);

Hot basic permanganate followed by acidification.

An example of this type reaction is the conversion of 1-decanol ($CH_3(CH_2)_8OH$) to decanoic acid ($CH_3(CH_2)_8COOH$).

The oxidants for aldehydes include one of the following:

any reagent that can oxidize an alcohol;

cold dilute potassium permanganate;

a number of silver compounds including $Ag(NH_3)_2OH$ and Ag_2O in base followed by acidification;

air (over a long period of time).

An example of this type of reaction is the conversion of hexanal ($CH_3(CH_2)_4CHO$) to hexanoic acid ($CH_3(CH_2)_4COOH$).

Oxidation of alkyl benzene. Strong oxidizing agents are capable of attacking alkyl benzenes if the carbon atom nearest the ring has at least one hydrogen atom attached. When this occurs, the oxidation removes all of the alkyl group except the carbon atom closest to the ring. Oxidizing agents include the following:

hot acidic potassium dichromate solution;

hot (95 degrees Celsius) potassium permanganate solution followed by acidification.

Figure 5.10 illustrates the reaction of *p*-nitrotoluene to form *p*-nitrobenzoic acid.

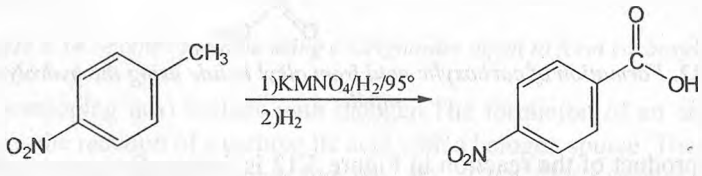


Figure 5.10 *The oxidation of p-nitrotoluene to p-nitrobenzoic acid.*

Oxidation of methyl ketones.In general, ketones do not undergo oxidation; however, methyl ketones undergo a haloform reaction. In a haloform reaction, the oxidation converts the methyl group to a haloform molecule (usually

iodoform (CHI_3)), which leaves the carbon backbone one carbon atom shorter. The oxidant in a haloform reaction is sodium hypohalite (NaOX), which forms by the reaction of sodium hydroxide (NaOH) with a halogen (X_2, where X = Cl, Br, or I). Figure 5.11 illustrates the oxidation of a methyl ketone.

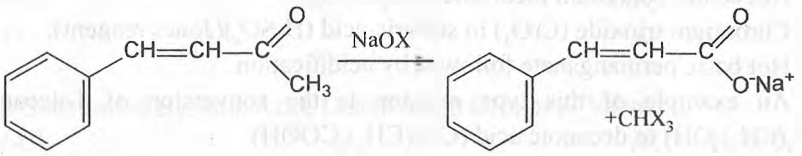


Figure 5.11 *The oxidation of amethyl ketone.*

Hydrolysis of cyanohydrins and other nitriles.The basic hydrolysis (reaction with water) of a nitrile (R-CN) followed by acidification yields a carboxylic acid. In general, an S_N reaction (nucleophilic substitution) of an alkyl halide is used to generate the nitrile before hydrolysis. Figure 5.12 illustrates the formation of a carboxylic acid beginning with an alkyl halide.

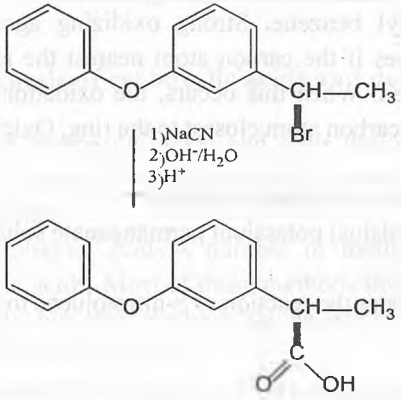


Figure 5.12. *Formation of carboxylic acid from alkyl halide using the hydrolysis of a nitrile.*

The product of the reaction in Figure 5.12 is fenoprofen, an antiarthritic agent.

Carbonation of Grignard reagents. After multiple steps, an organic halide can be converted to a carboxylic acid. The organic halide converts to a Grignard reagent, which reacts with carbon dioxide and then acidification forms the acid. Figures 5.13 and 5.14 illustrate the steps in this process.

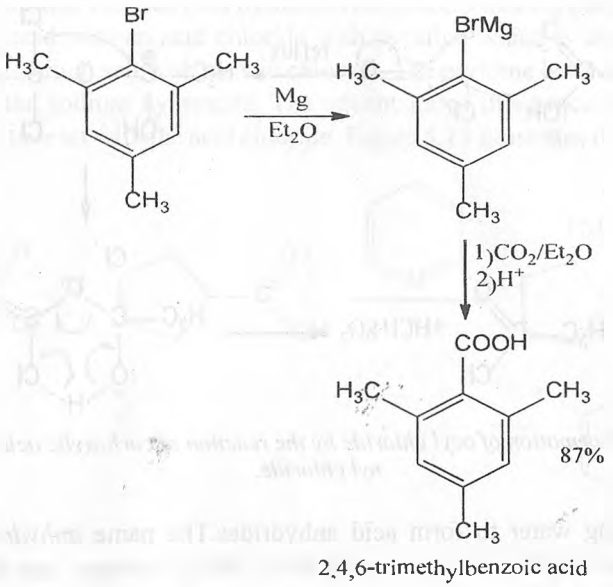


Figure 5.13 *The use of a Grignardre agent to form carboxylic acid.*

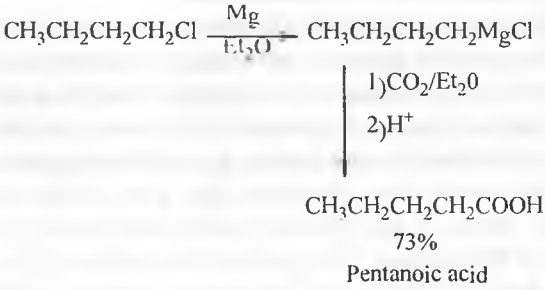


Figure 5.14 *Another example using a Grignardre agent to form carboxylic acid.*

Developing acyl halides with halogen.The formation of an acyl halide involves the reaction of a carboxylic acid with a halogen source. The common halogen sources are compounds like PX_3, PX_5, ClOCCOCl (oxalyl chloride), or SOX_2, where *X* is a halogen. The most commonly used acyl halides are the chlorides, and the simplistic reaction is RCOOH → RCOCl. Figure 5.15 illustrates the mechanism using thionyl chloride ($SOCl_2$) as the halogen source. One aid in the reaction is the formation of a transition state containing a six-membered ring. This reaction works because the $-SO_2Cl$ is a better leaving group than Cl–.

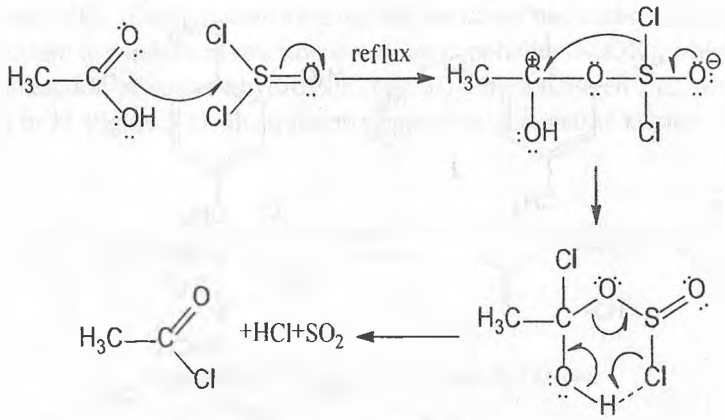


Figure 5.15 *Formation of acyl chloride by the reaction of carboxylic acid with thionyl chloride.*

Removing water to form acid anhydrides.The name *anhydride* means *without water,* so that makes it pretty clear that the general idea behind the formation of an acid anhydride is to remove water from a carboxylic acid. Both acyl chlorides and acid anhydrides are very effective at removing water. In some cases, heat can be used to remove water.

Sodium salt plus acid chloride.The reaction of a carboxylic acid with sodium hydroxide (NaOH) produces the sodium salt of the carboxylic acid. The sodium salt then reacts with an acid chloride to form the anhydride. Figure 5.16 illustrates the final step in this process. In this reaction, the carboxylate ion behaves as a nucleophile and attacks the carbonyl carbon atom of the acid chloride. The reaction of a carboxylic acid with sodium hydroxide also generates water, which, if not removed, reacts with the acid chloride and lowers the yield of the reaction. This synthesis can produce either a *symmetric anhydride* (both acids the same) or an *asymmetric anhydride* (different acids).

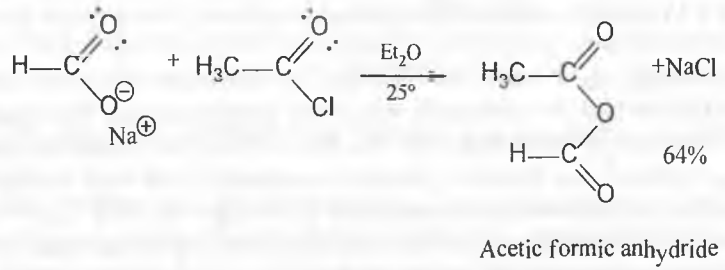


Figure 5.16 *The reaction of sodium salt of carboxylic acid (sodium formate) with acid chloride.*

Acid plus acid chloride plus pyridine.This process that happens when you combine an acid with an acid chloride with pyridine which is similar to the reaction of a sodium salt with an acid chloride. The pyridine behaves as a base in place of the sodium hydroxide. The advantage of this process is that no water forms to react with the acid chloride. Figure 5.17 illustrates this reaction.

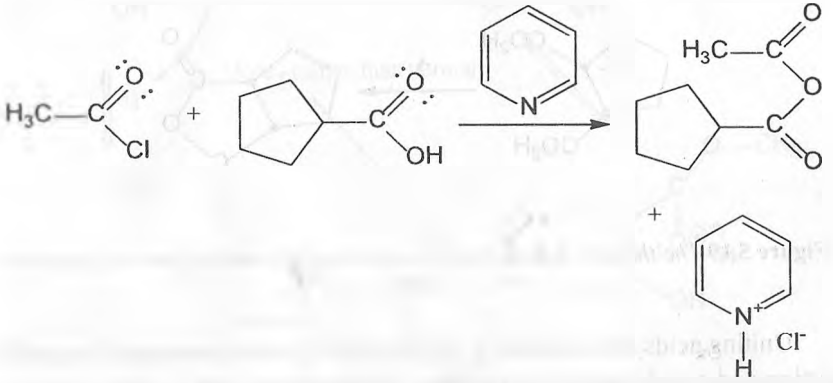


Figure 5.17 *Acid an hydride formed by the reaction of acid chloride with carboxylic acid in the presence of pyridine.*

Acetic anhydride plus acid.The dehydrating properties of an acid anhydride can be used to produce another acid anhydride. This is an equilibrium process. By heating the mixture, the more volatile acid vaporizes to shift the equilibrium toward the products. Acetic acid, from acetic anhydride, is useful because it's more volatile than most other carboxylic acids. Figure 5.18 illustrates this reaction.

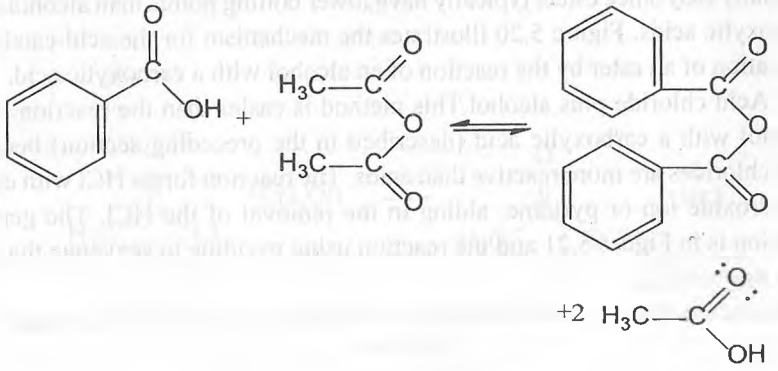


Figure 5.18 *Formation of acid an hydride by the reaction of carboxylic acid with acetic anhydride.*

Cyclic anhydrides. A cyclic anhydride can be formed from a dicarboxylic acid by heating if the anhydride forms has a five- or six-membered ring. If the dicarboxylic acid contains a ring, only a *cis* isomer (not the *trans* isomer) reacts. Figure 5.19 illustrates this type of reaction. The black circles in the figure indicate that the *cis*-isomer is reacting to form a *cis* product.

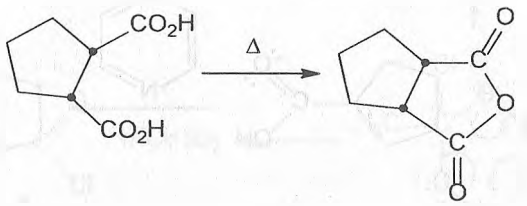


Figure 5.19 *The thermal dehydration of a dicarboxylic acid to form a cyclic anhydride.*

Uniting acids and alcohols to make esters. An ester consists of an alcohol portion and a carboxylic acid portion. In the synthesis of an ester, these two portions need to be brought together. The simplest method is to react an acid with an alcohol in the presence of another alcohol, but as you see in the following sections, other methods are useful as well.

Acid plus alcohol.This method is called the Fischer esterification. It is a condensation reaction where the loss of a water molecule accompanies the joining of the alcohol portion to the acid portion. The acid gives up the OH and the alcohol gives up the H to make the water molecule. All steps in the mechanism are reversible (that means, it establishes an equilibrium), so removing the ester is helpful as soon as it is formed. Removal of the ester is normally easy since esters typically have lower boiling points than alcohols and carboxylic acids. Figure 5.20 illustrates the mechanism for the acid-catalyzed formation of an ester by the reaction of an alcohol with a carboxylic acid.

Acid chloride plus alcohol.This method is easier than the reaction of an alcohol with a carboxylic acid (described in the preceding section) because acid chlorides are more reactive than acids. The reaction forms HCl with either a hydroxide ion or pyridine, aiding in the removal of the HCl. The general reaction is in Figure 5.21 and the reaction using pyridine to scavenge the HCl is in Figure 5.22.

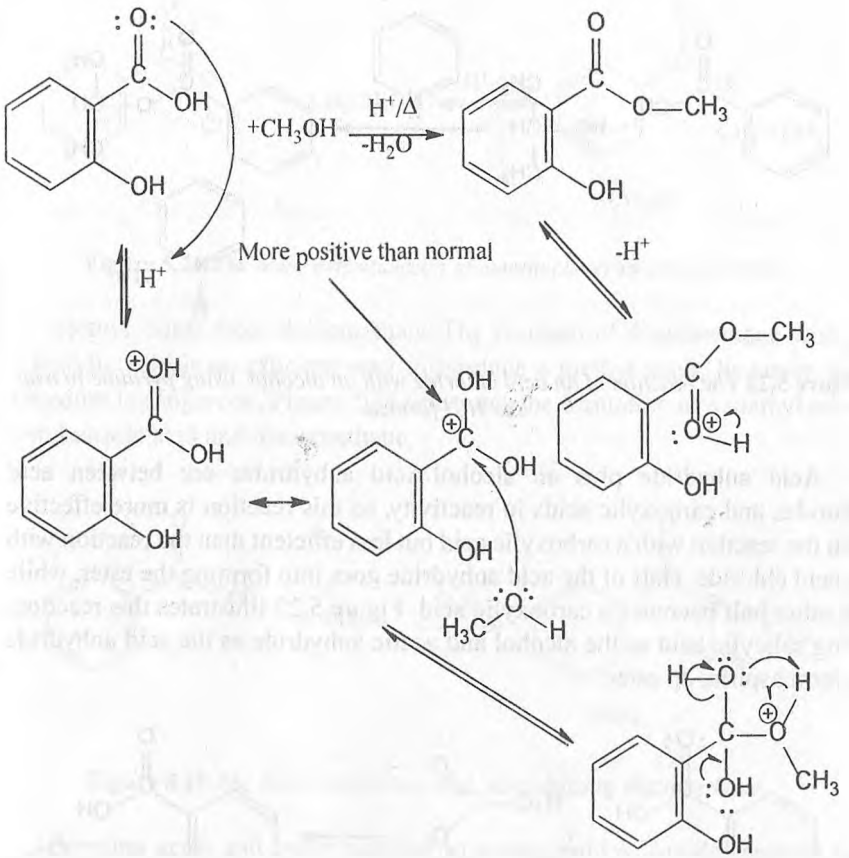


Figure 5.20 *Acidcatalyzed formation of an ester from an alcohol and a carboxylic acid.*

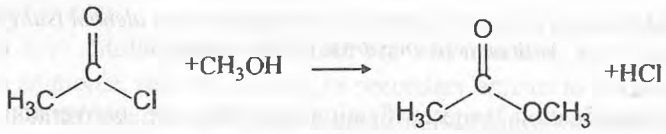


Figure 5.21 *The general method forester synthesis from an alcohol and an acid chloride.*

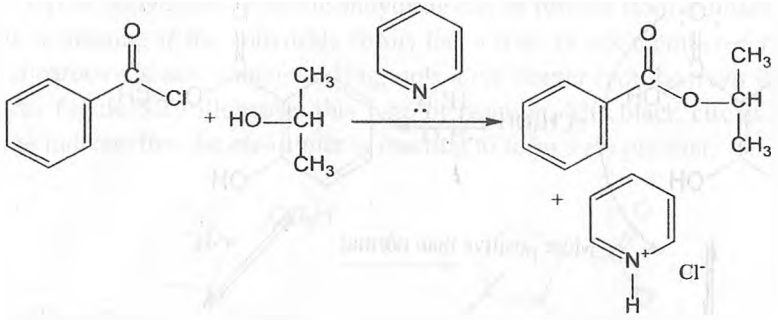


Figure 5.22 *The reaction of an acid chloride with an alcohol, using pyridine to trap the HCl formed.*

Acid anhydride plus an alcohol.Acid anhydrides are between acid chlorides and carboxylic acids in reactivity, so this reaction is more effective than the reaction with a carboxylic acid but less efficient than the reaction with an acid chloride. Half of the acid anhydride goes into forming the ester, while the other half becomes a carboxylic acid. Figure 5.23 illustrates this reaction, using salicylic acid as the alcohol and acetic anhydride as the acid anhydride to form aspirin, an ester.

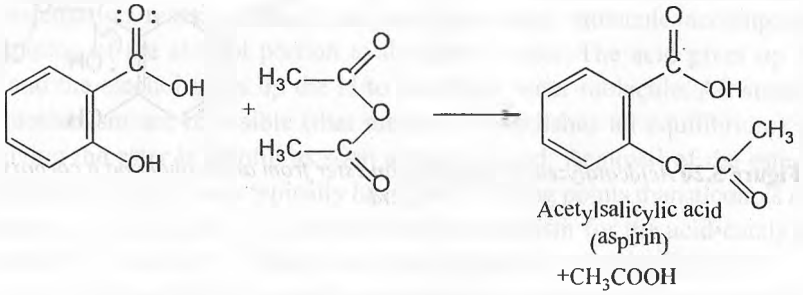


Figure 5.23 *Forming an ester (aspirin) by the reaction of an alcohol (salicylic acid) with an acid anhydride (acetic anhydride).*

Transesterification.Tranesterification involves the conversion of one ester into another. In this process, a less volatile alcohol replaces a more volatile alcohol. For example, heating is an excess of ethanol with a methyl ester while rapidly removing the more volatile methanol as it forms results in transesterification. An acid catalyst facilitates the reaction, which is illustrated in Figure 5.24. To produce a propyl ester, the action of propanol on either a methyl ester or an ethyl ester would work.

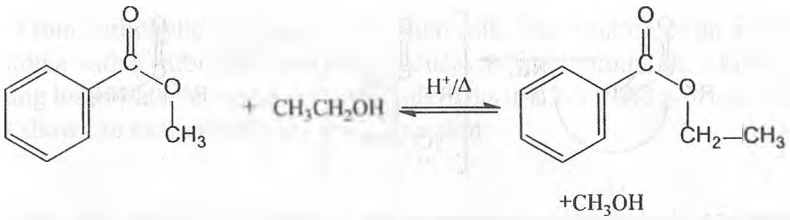


Figure 5.24 *The trans esterification of amethyl ester to an ethylester.*

Methyl esters from diazomethane.The reaction of diazomethane with a carboxylic acid is an efficient way to produce a methyl ester; however, the procedure is dangerous. Figure 5.25 illustrates the formation of a methyl ester from benzoic acid and diazomethane.

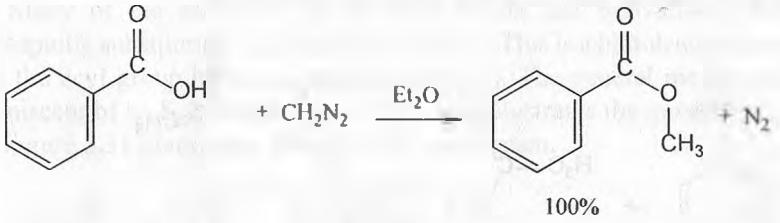


Figure 5.25 *The formation of amethyl ester utilizing diazomethane.*

Bringing acids and bases together to create amides. Amides contain an acid portion and an amine portion. However, unlike the formation of an ester, the reaction of a carboxylic acid with an amine is not an efficient method for preparing an amide, because, as you see in this section, the simple reaction of an acid (carboxylic acid) with a base (amine) causes interference. Fortunately, methods similar to many of the other ester synthesis methods are useful in the synthesis of amides.

From acid chlorides.Acid chlorides are very reactive, and they readily react with ammonia, primary amines, or secondary amines to form an amide. Figure 5.26 illustrates the reaction of an acid chloride with ammonia. Replacing one or two of the hydrogen atoms of ammonia with an organic group will result in an N-substituted amide. Tertiary amines react with acid chlorides to form a carboxylic acid and an ammonium salt.

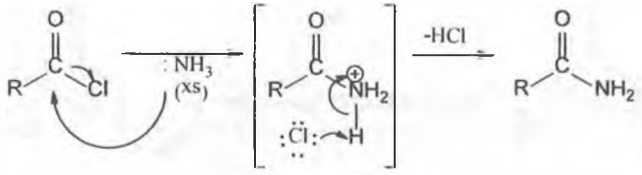


Figure 5.26 *The formation of anamide by the reaction of an acid chloride with ammonia.*

From acid anhydrides.This process is similar to the formation of an ester by the action of an acid anhydride on an alcohol. Half the acid anhydride forms the amide; the other half is a leaving group. Ammonia, primary amines and secondary amines react to produce amides. Figure 5.27 shows the industrial preparation of phenacetin by the reaction of an amine with an acid anhydride. The mechanism for this reaction is similar to the mechanism for the reaction of an acid chloride with an amine (refer to Figure 5.26).

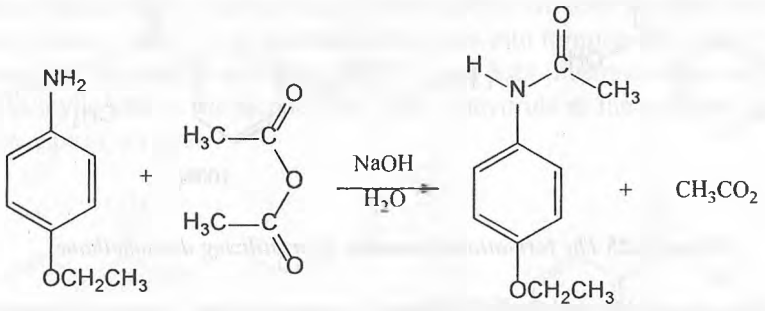


Figure 5.27 *The preparation of phenacetin by the reaction of an amine with an acid anhydride.*

From esters.Amines also react with esters by a method similar to the reaction of an acid chloride with an amine. Figure 5.28 illustrates the formation of benzamide by this type of reaction, using ammonia and methyl benzoate. Again, the mechanism is similar to the reaction of an acid chloride with an amine (Figure 5.26).

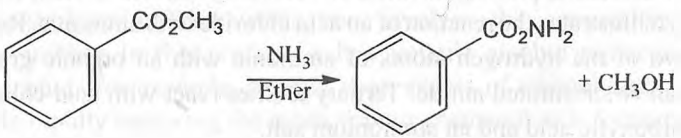


Figure 5.28 *The formation of benzamide by the reaction of ammonia with methyl benzoate.*

From carboxylic acids and ammonium salts.The reaction of an amine or ammonia with a carboxylic acid first produces an ammonium salt, which upon heating loses water and produces an amide. This is a low yield process. Figure 5.29 shows an example of this type of reaction.

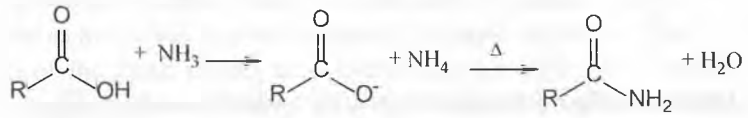


Figure 5.29 *The reaction of ammonia with a carboxylic acid to eventually form an amide.*

5.5 Exploring reactions

Many of the reactions of carboxylic acids and derivatives involve nucleophilic substitution at the acyl carbon atom. This is a bimolecular process with the acyl group having a leaving group (L). The general mechanism is reminiscent of an S_N2 mechanism. Figure 5.30 illustrates the general process and Figure 5.31 gives more details on the mechanism.

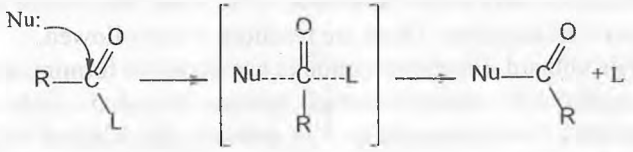


Figure 5.30 *Nucleophilic attack at the acylcarbon atom showing its relationship to an S_N2 process.*

The various carboxylic acid derivatives vary in their reactivity (stability of the leaving group). Acid chlorides, for example, are more reactive than anhydrides.A summary of the relative reactivities appears in Figure 5.32.

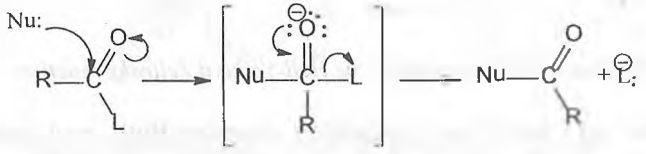


Figure 5.31 *The general mechanism for the nucleophilic attack on an acyl carbon atom.*

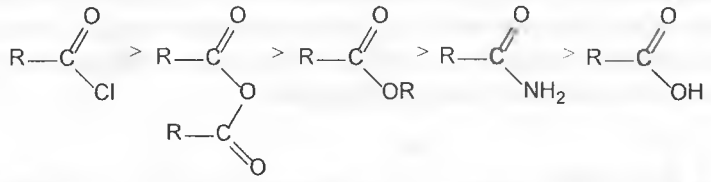


Figure 5.32 *The relative reactivities of the carboxylic acid derivatives.*

The sequence in Figure 5.32 does not only represents the general reactivity of carboxylic acid derivatives but also gives information on the ease of synthesis. The more reactive a species is, the more difficult it is to get prepared (and vice versa). From this series, you can see that synthesizing a less reactive acyl compound from a more reactive acyl compound is always possible.

Generous carboxylic acids.This section gives your brain a rest with some simple materials: Carboxylic acids are acids. Acids donate a hydrogen ion, H+, to other species. Therefore, that's the fundamental reaction of carboxylic acids. As you have seen previously, these are weak acids (although they're stronger than most other organic acids). In this chapter we have seen a variety of other reactions, such as the formation of an ester, that utilize carboxylic acids as one of the reactants. There are reactions to be followed.

The Hell-Volhard Zelinsky reaction is a method for forming α-halo acid. This is a synthetically useful procedure because the α-halo acids are useful starting materials for other reactions. For example, the addition of hydroxide ion leads to the replacement of the halogen with an -OH group. The reaction with ammonia replaces the halogen with $-NH_2$. The reaction with cyanide ion, CN–, converts the halide to a nitrile. Figure 5.33 illustrates this reaction.

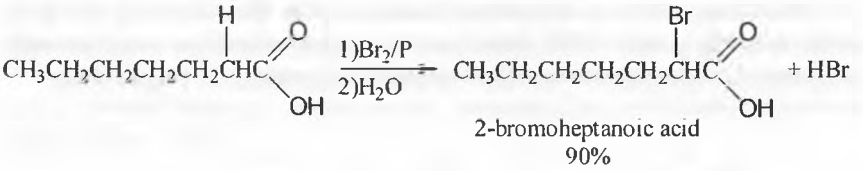


Figure 5.33 *An example of the Hell-Volhard Zelinsky reaction.*

Simple acyl halide and anhydride reactions.Both acyl halides and anhydrides react with water (hydrolysis). Acyl halidesreact to form one mole of the carboxylic acid and one mole of the hydrohalic acid, HX. Anhydrides react to form two moles of carboxylic acid.

Acyl halides and anhydrides are important reactants for the formation of other carbonyl compounds, but you don't need to take up valuable brain space with information about any other acyl halide or anhydride reactions at this time.

Hydrolysis of esters. Esters can undergo hydrolysis using either an acid or a base as a catalyst. Hydrolysis always produces an alcohol from the alkyl portion of the ester. During acid hydrolysis, the acid portion of the ester yields a carboxylic acid. During base hydrolysis of an ester, which is called *saponification,* the acid portion of the ester yields the carboxylate ion.

Acid hydrolysis. Acid hydrolysis is the reverse of the Fischer esterification. Figure 5.34 illustrates the mechanism. Base hydrolysis (saponification) Saponification (base hydrolysis) follows a simpler mechanism (see Figure 5.35).

In the reaction, one mole of hydroxide generates one mole of alcohol and one mole of carboxylate ion from one mole of ester. Based on this stoichiometry (the mole relationship as defined by the balanced chemical equation), if the number of moles of base is known, then the amount of ester will be known. This stoichiometry is the saponification equivalent, used to determine the equivalents of ester.

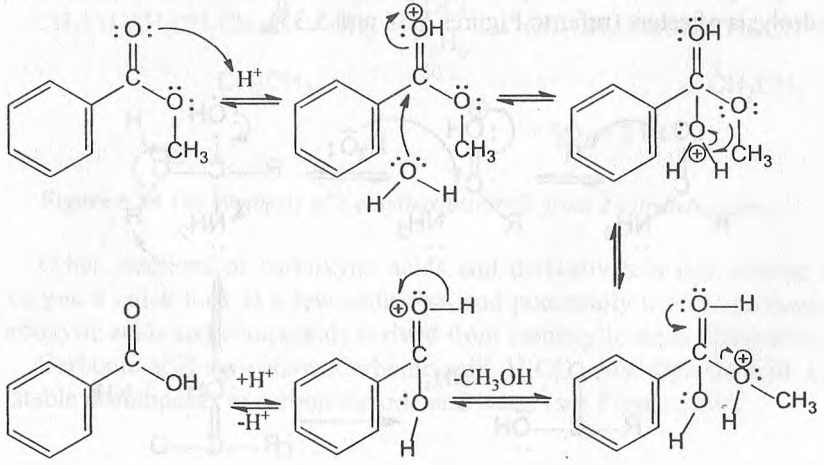


Figure 5.34 *The mechanism for acid hydrolysis of an ester.*

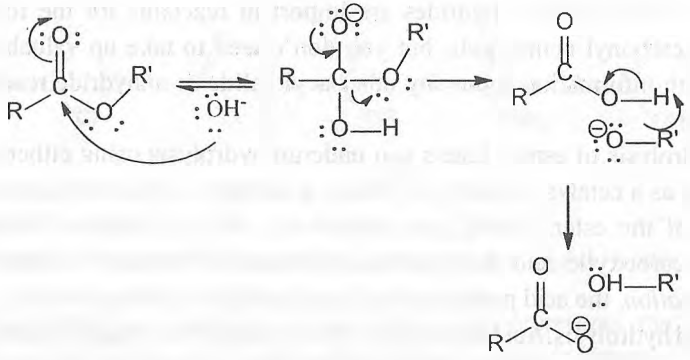


Figure 5.35 *The mechanism for base hydrolysis of an ester.*

Amide reactions.The reactions of amides have similarities to those of esters. Specifically, the reactions covered in this section involve the loss or gain of water (dehydration or hydrolysis).

Acid- or base-catalyzed hydrolysis.Acid hydrolysis of an amide yields a carboxylic acid and an ammonium ion. The mechanism for acid hydrolysis is shown in Figure 5.36. Base hydrolysis of an amide, on the other hand, yields ammonia and a carboxylate ion. You can see this mechanism in Figure 5.37. To identify similarities, compare these mechanisms to the mechanisms for the hydrolysis of esters (refer to Figures 5.34 and 5.35).

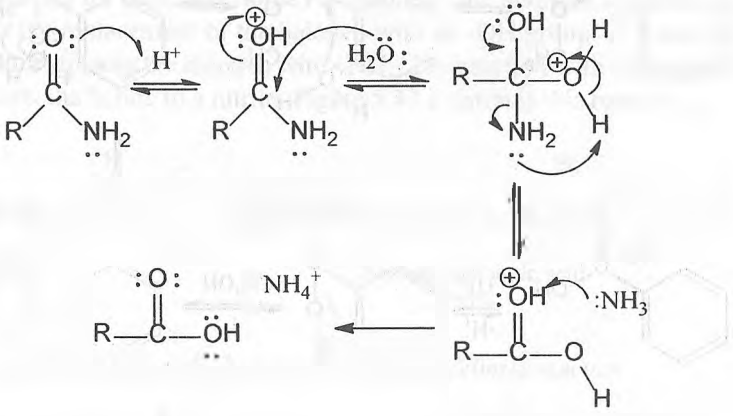


Figure 5.36 *The mechanism for the acid hydrolysis of an amide.*

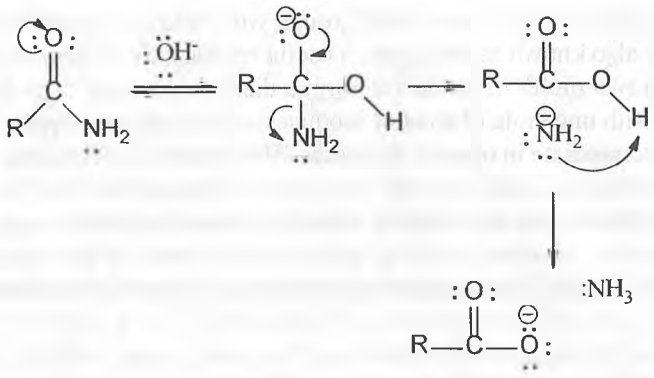


Figure 5.37 *The mechanism for the base hydrolysis o fan amide.*

Dehydration. Amides undergo dehydration. Useful dehydrating agents include $SOCl_2$, P_4O_{10} (P_2O_5), $(AcO)_2O$, and $POCl_3/\Delta$. The product is a nitrile, and in fact, dehydration of an amide is one method to produce aryl nitriles. Figure 5.38 shows the synthesis of 2-ethylhexanenitrile from 2-ethylhexanamide with a 94-percent yield.

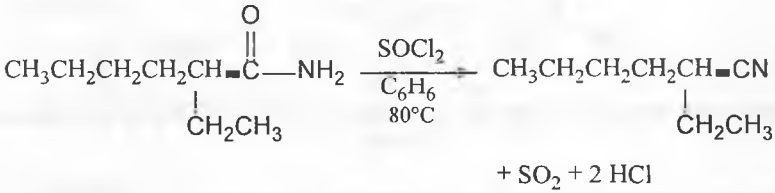


Figure 5.38 *The synthesis of 2-ethylhexanenitrile from 2-ethylhexanamide.*

Other reactions of carboxylic acids and derivatives.In this section we give you a quick look at a few additional and potentially useful reactions of carboxylic acids and compounds derived from carboxylic acids (derivatives).

Carbonic acid derivatives.Carbonic acid, H_2CO_3, is a diprotic acid. It is unstable decomposes to carbon dioxide and water (see Figure 5.39).

Figure 5.39 *The decomposition of carbonic acid.*

The replacement of both -OH groups with chlorine produces carbonyl dichloride, also known as *phosgene,* a useful reactant. For example, phosgene reacts with two moles of alcohol to form a dialkyl carbonate. The reaction of phosgene with one mole of alcohol produces an alkyl chloroformate, which is a useful intermediate in organic syntheses. The reaction of phosgene with four moles of ammonia yields urea and two moles of ammonium chloride, NH_4Cl. Figure 5.40 shows the structures of some of these compounds.

One useful reaction utilizing alkyl chloroformate is the reaction with an amine in base to form a carbamate (urethane). Figure 5.41 illustrates this reaction.

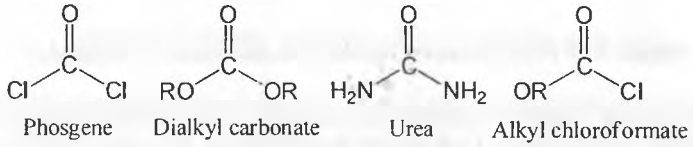


Figure 5.40 *Some important carbonic acid derivatives.*

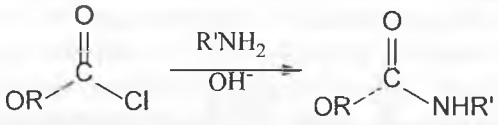


Figure 5.41 *The reaction of an alkyl chloroformate with an amine in the presence of a base.*

Another useful carbonic acid derivative is carbamic acid. Like carbonic acid, carbamic acid is unstable (see Figure 5.42).

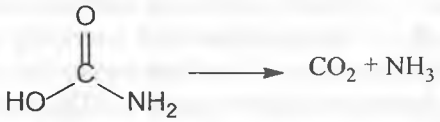


Figure 5.42 *The decomposition of carbamic acid*

Decarboxylation is the loss of carbon dioxide, which happens easily because of the stability of CO_2. Heating β-keto acids to between 100 and 150 degrees Celsius is one example of a decarboxylation reaction. The mechanism for the decarboxylation of a β-keto acid is in Figure 5.43.

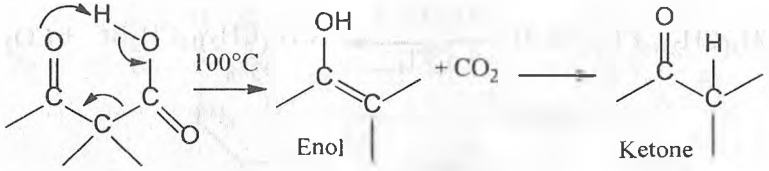


Figure 5.43 *The mechanism for the decarboxylation of a β-keto acid.*

Hunsdiecker reaction.The Hunsdiecker reaction is a free-radical reaction for the synthesis of an alkyl halide. The starting material comes from the reaction of a silver carboxylate with a solution of a halogen in a solvent such as carbon tetrachloride (see Figure 5.44). The overall free-radical mechanism is shown in Figure 5.45.

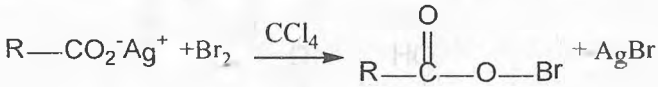


Figure 5.44 *The formation of the starting material for the Hunsdiecker reaction.*

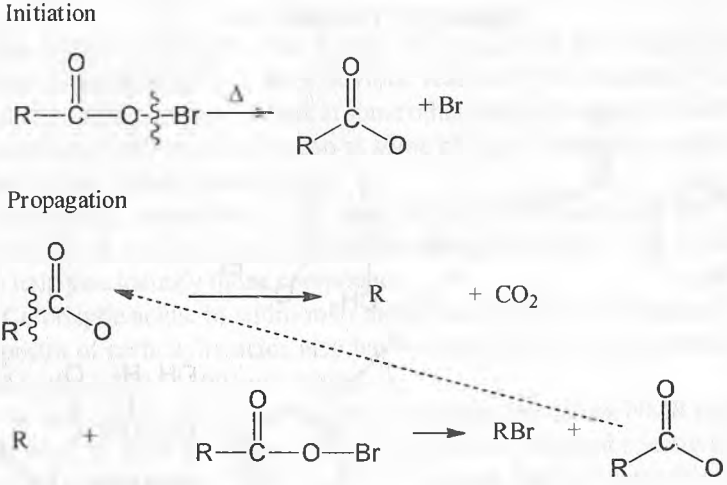


Figure 5.45 *The free radical mechanism of the Hunsdiecker reaction.*

Other reagents can be used in the Hunsdiecker reaction, as shown in Figure 5.46.

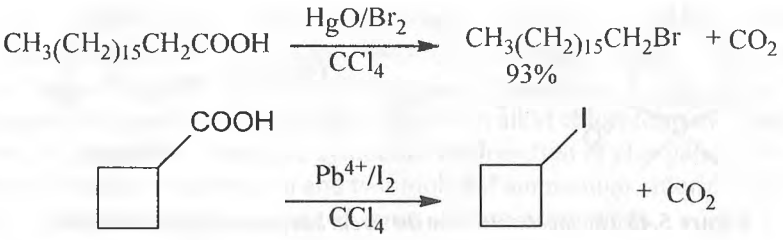


Figure 5.46 *Additional examples of the Hunsdiecker reaction.*

The Reformatsky reaction.The Reformatsky reaction uses an organozinc intermediate to form &-hydoxy esters (see Figure 5.47). The general Reformatsky reaction is in Figure 5.48 and the mechanism is in Figure 5.49.

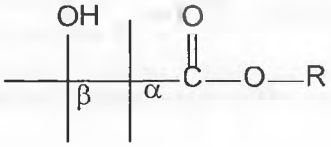


Figure 5.47 *A β-hydoxy ester.*

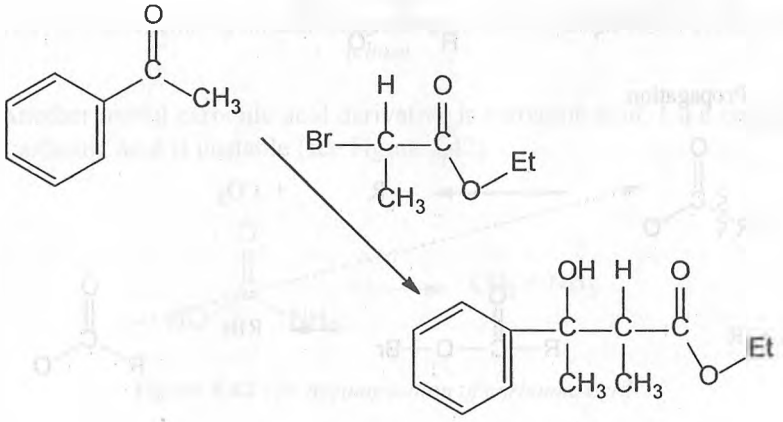


Figure 5.48 *The Reformatsky reaction.*

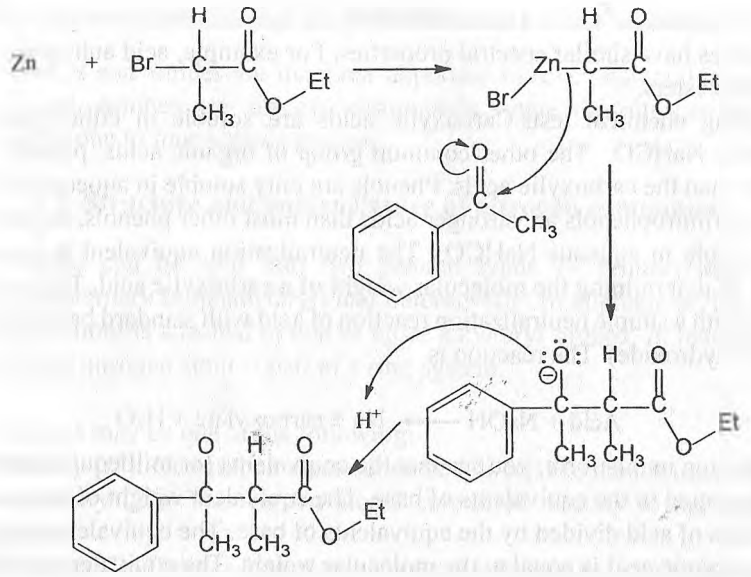


Figure 5.49 *The mechanism for the Reformatsky reaction.*

5.6 Spectroscopyand chemical tests

The carbonyl stretch in the 1,700 cm^{-1} region of the infrared spectra of carbonyl compounds is a very obvious feature of the spectrum for these compounds. In this section we look at some other spectral features of carboxylic acids and their derivatives, and also at some chemical tests that can help you determine what you're dealing with.

Identifying compounds with spectral data.You can use the unique spectroscopy of carboxylic acids and derivatives, described in the following list, to help you identify those compounds.

"Carboxylic acids: In addition to the carbonyl stretch, the infrared

spectra of carboxylic acids also have a broad OH stretch, which is often shifted to the 3,300–2,500 cm^{-1} region.

The acid hydrogen is in the" = 10–12 region of the proton NMR spectrum.

"Esters: In addition to the carbonyl st-etch, the infrared spectra contains two C-O stretches in the 1,300–1,050 cm^{-1} region. This is the result of having two different R groups attached to the singly bonded oxygen atom.

"Acyl chlorides: In acyl chlorides, the carbonyl stretch appears in the

1,850–1,780 cm^{-1} region.

"Amides: The carbonyl stretch of amides is in the 1,690–1,630 cm^{-1} region. If one hydrogen atom is attached to the nitrogen atom, the amide has an N-H stretch. If two hydrogen atoms are attached to the nitrogen, it will have

two N-H stretches. The N-H stretches are in the 3,500-3,300 cm^{-1}region. Other derivatives have similar spectral properties. For example, acid anhydrides are similar to esters.

Using chemical tests.Carboxylic acids are soluble in either aqueous NaOH or $NaHCO_3$. The other common group of organic acids, phenols, are weaker than the carboxylic acids. Phenols are only soluble in aqueous NaOH. Di- and trinitrophenols are stronger acids than most other phenols, so they are also soluble in aqueous $NaHCO_3$. The neutralization equivalent is a useful means of determining the molecular weight of a carboxylic acid. The process begins with a simple neutralization reaction of acid with standard base (usually sodium hydroxide). The reaction is

$$\text{Acid} + \text{NaOH} \longrightarrow \text{Na} + \text{carboxylate} + H_2O$$

Written in this form, you see that the equivalents (or milliequivalents) of acid are equal to the equivalents of base. The equivalent weight of the acid is the grams of acid divided by the equivalents of base. The equivalent weight of monoprotic acid is equal to the molecular weight. The equivalent weight of diprotic acid is equal to half the molecular weight.

6. Amines

Amines and amides are the most important nitrogen-containing organic compounds. Amines are nitrogen compounds where the nitrogen atom is attached to one to four organic groups.

6.1 Structure and nomenclature of nitrogen compounds

Amines can be split into two general types — primary/secondary/ tertiary/quaternary (aliphatic/aryl) and heterocyclic. In aliphatic/aryl amines, a nitrogen atom is attached to one or more alkyl/aryl groups. In heterocyclic amines, the nitrogen atom is part of a ring system.

Amines may be one of the following:
primary (1°): One carbon atom connected directly to the nitrogen atom;
secondary (2°): Two carbon atoms connected directly to the nitrogen atom;
tertiary (3°): Three carbon atoms connected directly to the nitrogen atom;
quaternary (4°): Four carbon atoms connected to the nitrogen atom.

Primary amines.The common names of primary amines consist of the name of the alkyl branch followed by the name *amine*. The systematic (IUPAC) name of primary amines consists of the name of the alkane with the *-e* replaced by the suffix *-amine*. Some examples of primary amines appear in Figure 6.1. If more than one amine group is present, you need to use the appropriate prefix.

For example, $H_2NCH_2CH_2CH_2CH_2NH_2$ is 1,4-butandiamine, because the amino groups are attached to the first and fourth carbons.

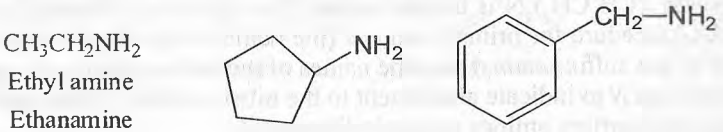


Figure 6.1 *Some examples of primary amines.*

Aniline is a simple aromatic compound composed of an amino group attached to a benzene ring. Other aromatic amines are aniline derivatives. Some examples of aromatic amines are shown in Figure 6.2.

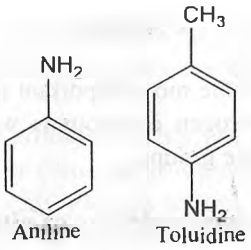


Figure 6.2 Some aromatic amines.

The amine group has a lower priority in numbering the ring positions around the ring than -OH and other oxygen-containing groups. Some examples showing the lower priority of the amine group are in Figure 6.3.

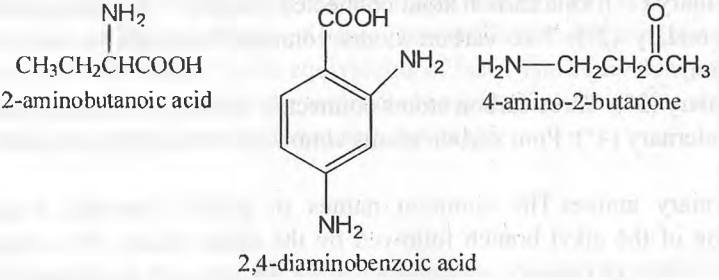


Figure 6.3 *Some primary amines containing other functional groups*

Secondary and tertiary amines.The common names of secondary and tertiary amines are an extension of the common names of primary amines, where the organic groups are named as branches followed by the word *amine.* For example, $(CH_3CH_2)_3N$ is triethyl amine. The systematic (IUPAC) names utilize the procedure for primary amines (the name of the alkane with the *-e* replaced by the suffix *-amine)* plus the names of the remaining organic groups preceded by an *N* to indicate attachment to the nitrogen atom. Some names of secondary and tertiary amines appear in Figure 6.4.

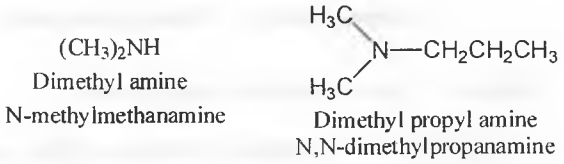
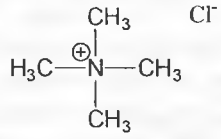
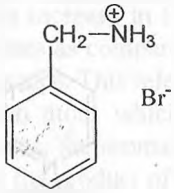


Figure 6.4 *Some secondary and tertiary amines.*

Quaternary amines (quaternary ammonium salts).Ammonium salts contain a nitrogen atom with four bonds that has a positive charge. Four-bonded nitrogen atoms derived from amines are ammonium ions (if they're derived from aniline, they're anilinium ions). If the four bonds are all to carbon atoms, the nitrogen atom is quaternary. Salts contain a cation (named first) and an anion (named last). Typical anions include Cl– (chloride), Br– (bromide), HSO_4– (hydrogen sulfate or bisulfate), and NO_3 – (nitrate).



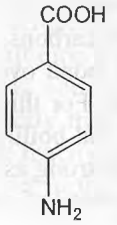
Tetramethylammonium chloride



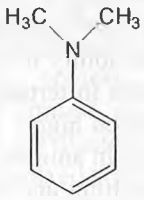
Benzylammonium bromide

Figure 6.5 *Two examples containing ammonium ions.*

Two additional examples of amine nomenclature are shown in Figure 6.6. Note that in the *p*-aminobenzoic acid the oxygen-containing group takes precedence in the naming, so that the compound is then named as a substituted benzoic acid and not a substituted aniline, as is done in the N,N-dimethylaniline beside it.



p-aminobenzoic acid



N,N-dimethylaniline

Figure 6.6 Two addition al examples of amine nomenclature.

Heterocyclics.Heterocyclics are ring systems containing something other than carbon in the ring. The names of some nitrogen-containing heterocyclic compounds (with a single nitrogen) are listed in Figure 6.7. Heterocyclic systems may contain more than one nitrogen atom, though, and some examples are shown in Figure 6.8. These heterocyclics are important in biological and biochemical systems

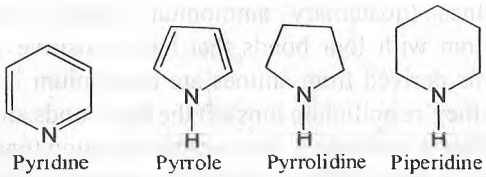


Figure 6.7 *Some examples of nitrogen containing heterocyclic compounds.*

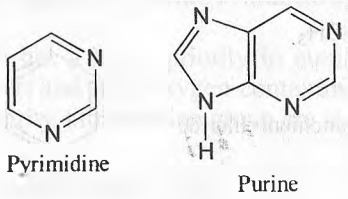


Figure 6.8 *Some examples of nitrogen containing heterocyclic compounds containing more than one nitrogen atom.*

6.2 Physical properties of amines

The high electronegativity of the nitrogen atom means that the carbonnitrogen bond of amines is polar. This results in an attraction between two polar molecules (dipole-dipole intermolecular forces), which increases the melting and boiling points above those of hydrocarbons. However, in primary and secondary amines the ability to hydrogen bond overshadows the simple dipole-dipole forces present in tertiary amines. For this reason, primary and secondary amines have much higher melting and boiling points than tertiary amines. Hydrogen bonding in amines is not as strong as hydrogen bonding in alcohols; therefore, the melting and boiling points of amines are lower than those of comparable alcohols.

In general, amines with up to about six carbon atoms are soluble in water. Primary, secondary and tertiary amines react with acids to produce ammonium ions. These ammonium ions and quaternary ammonium ions are also soluble in water. Amines can be separated from other organic compounds by treating the mixture with an aqueous acid, converting the amines to ammonium ions. These ammonium ions dissolve in the aqueous acid, leaving the other organic materials behind. Separating the aqueous layer results in an acid extract containing the ammonium ions. Adding base to the acid extract until the solution is basic converts the ammonium ions back to the free amines, which then separate from the aqueous layer. Many amines have a very distinctive odor, like dead fish or worse.

6.3 Basicity of nitrogen compounds

Primary, secondary and tertiary amines react with acids to form amine salts. This is because of the basic nature of the amines.

Amines are both Brønsted-Lowry bases (they accept hydrogen ions from acids) and Lewis bases (they furnish an electron pair to Lewis acids). As Brønsted-Lowry bases they have K_b values. Aliphatic amines have K_b values of approximately 10^{-4}, and aromatic amines have values near 10^{-10}. (These values compare to a value of $\approx 10^{-5}$ for ammonia.) The increase in the K_b values of aliphatic amines (thus making them stronger bases as compared to ammonia) is due to the electron-releasing nature of alkyl groups. This release of electrons "pumps" electron density back to the nitrogen atom which stabilizes the positive charge. Compared to the aliphatic amines, the aromatic amines have lower K_b values. This lower value indicates that the product of the protonation of aromatic amines is less stable. The decrease in stability is due to a loss in resonance stabilization of the protonated form. An amine group attached to an aromatic ring is an activating *o-p*-director.

The lone pair of electrons on the nitrogen atom makes the amines Lewis bases. As Lewis bases, they may behave as nucleophiles. Because aromatic amines are resonance stabilized, they're weaker nucleophiles than alkyl amines.

6.4 Synthesis of nitrogen compounds

Amines can be prepared a number of ways. These methods include nucleophilic substitution reactions, reduction reactions, and oxidation reactions.

Nucleophilic substitution reactions. Synthesizing amines with nucleophilic substitution reactions is normally an S_N2 process. This means that methyl amines react more readily than primary amines, and secondary and tertiary amines show very little reactivity. Figure 6.9 illustrates the basic reaction. The resultant amine may react further to give a mixed group of products as shown in the following reaction. Using a large excess of ammonia minimizes the chances for multiple alkylations.

$$H_3N: \curvearrowright R \!-\!\!-\! \overset{\curvearrowright}{X} \xrightarrow{S_N2} \overset{\oplus}{N}H_3R \quad X^- \xrightarrow[\text{or } NH_3]{OH^-} NH_2R$$

$$CH_3(CH_2)_6CH_2Br + NH_3 \longrightarrow CH_3(CH_2)_6CH_2NH_2 \text{ octylamine (45\%)}$$
$$+ [CH_3(CH_2)_6CH_2]_2NH \text{ (dioctylamine [43\%])}$$
$$+ [CH_3(CH_2)_6CH_2]_3N \text{ (trioctylamine [trace])}$$
$$+ [CH_3(CH_2)_6CH_2]_4N^+ \text{ (trace)}$$

Figure 6.9 *The basic reaction for a nucleophilic substitution reaction to produce an amine.*

Aromatic halides don't react unless an electron-withdrawing group is attached to the ring. For example, bromobenzene doesn't react. An example showing the reaction when an electron-withdrawing group is present is illustrated in Figure 6.10, the nucleophilic substitution attack on *p*-bromonitrobenzene.

The azide ion is a better nucleophile than amines, but it has to be reduced to the amine after nucleophilic substitution. Lithium aluminum hydride ($LiAlH_4$) in ether followed by treatment with water reduces the azide ion to the amine. Figures 6.11 and 6.12 illustrate two examples of this reaction.

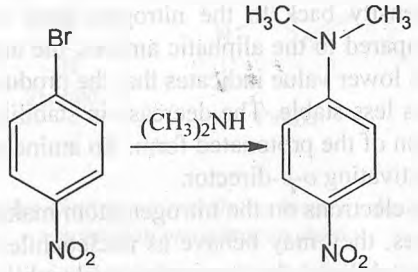


Figure 6.10 *The nucleophilic substitution attack on p-bromonitro benzene.*

Azides are explosive, releasing nitrogen gas. That's why they're used to inflate car air bags.

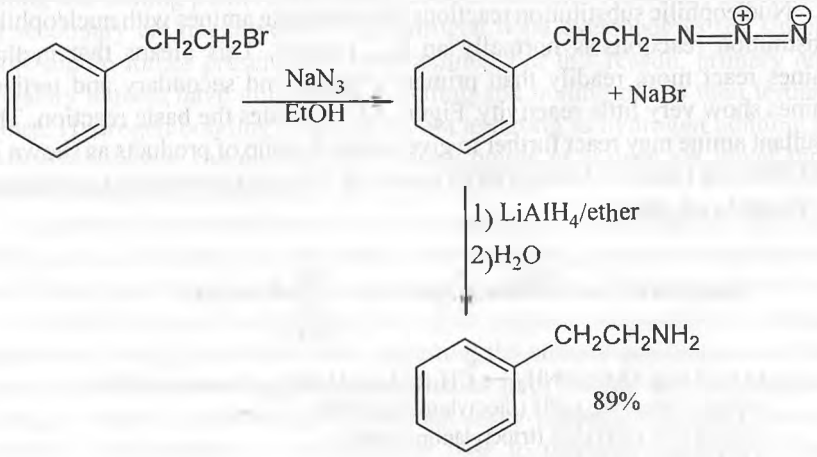


Figure 6.11 *The preparation of an amine from an azide.*

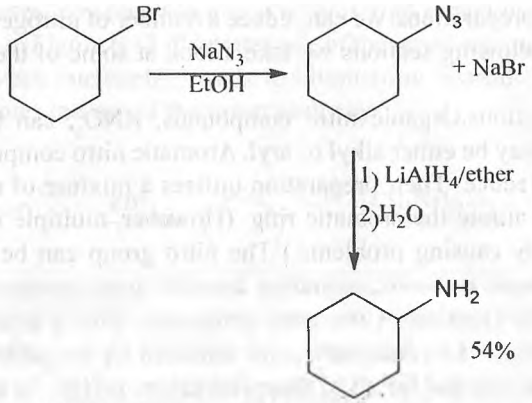


Figure 6.12 *Another preparation of an amine from an azide.*

The *Gabriel synthesis* of amines uses potassium phthalimide (prepared from the reaction of phthalimide with potassium hydroxide). The structure and preparation of potassium phthalimide is shown in Figure 6.13. The extensive conjugation (resonance) makes the ion very stable. An example of the Gabriel synthesis is in Figure 6.14. (The N_2H_4 reactant is hydrazine.) The Gabriel synthesis employs an S_N2 mechanism, so it works best on primary alkyl halides and less well on secondary alkyl halides. It doesn't work on tertiary alkyl halides or aryl halides.

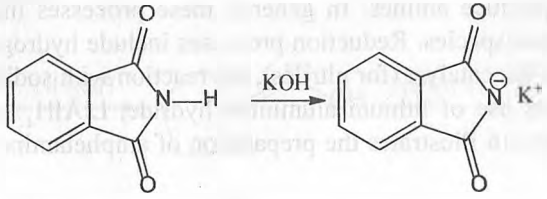


Figure 6.13 *The preparation of potassium phthalimide from phthalimide and potassium hydroxide.*

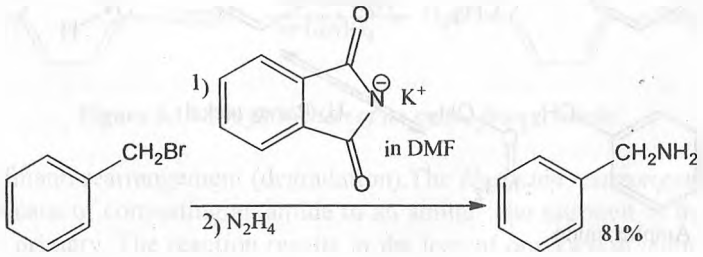


Figure 6.14 *Using the Gabriel synthesis to produce an amine.*

Reduction preparations. We can reduce a number of nitrogen species to an amine. In the following sections we take a look at some of the methods that can be used.

Nitro reductions. Organic nitro compounds, RNO_2, can be reduced to amines. The R may be either alkyl or aryl. Aromatic nitro compounds are easy to prepare and reduce. Their preparation utilizes a mixture of nitric acid and sulfuric acid to nitrate the aromatic ring. (However, multiple nitrations may occur, potentially causing problems.) The nitro group can be reduced with a number of simple methods, including catalytic hydrogenation of the nitro compound or the reaction of the nitro compound with a metal (Fe, Zn, or Sn) in the presence of hydrochloric acid followed by the addition of excess base. The generic symbol for all of these reductions is [H]. An example of the formation of a nitro compound followed by reduction is shown in Figure 6.15.

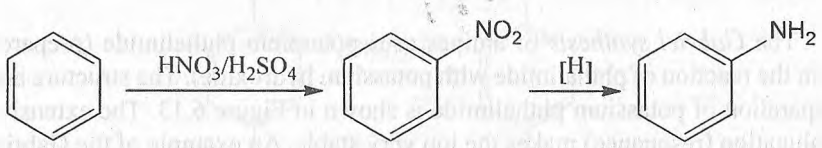


Figure 6.15 *The preparation of a nitro compound followed by reduction to an amine.*

Reductive amination. A number of organic species, including amides, oximes, and nitriles, undergo *reductive amination,* a variety of reduction reactions that produce amines. In general, these processes involve imines, R=N-R, or related species. Reduction processes include hydrogenation using Raney nickel as the catalyst (for nitriles), the reaction with sodium/EtOH (for oximes), and the use of lithium aluminum hydride, $LiAlH_4$ (for amides or nitriles). Figure 6.16 illustrates the preparation of amphetamine by reductive amination.

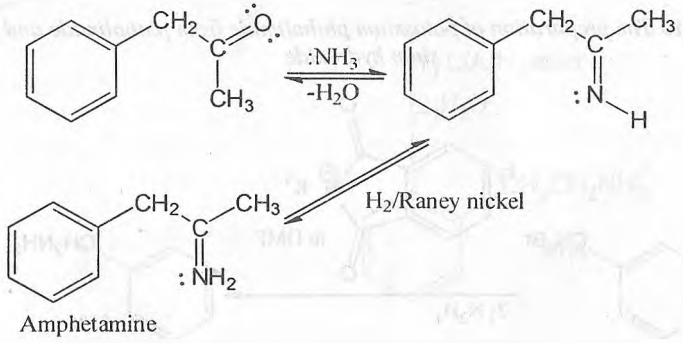


Figure 6.16 *The preparation of amphetamine by reductive amination.*

In some cases, you may run into problems with reductive amination. The upper pathway in Figure 6.17 illustrates one of the problems (a secondary alkyl halide and a weak nucleophile leads to elimination instead of substitution), which necessitates the use of the lower pathway.

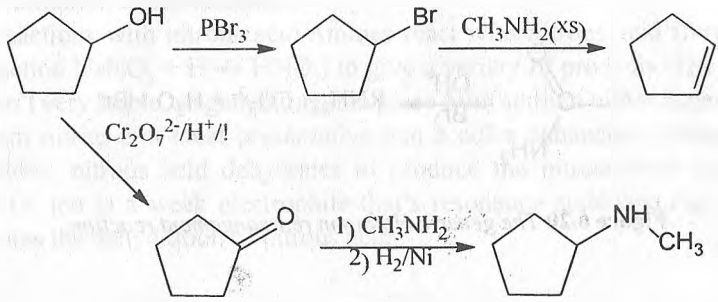


Figure 6.17 *In the upper pathway, reductive amination fails. The lower path way works.*

Another type of reductive amination is shown in Figure 6.18. This reaction illustrates the formation of an amine from a ketone through the formation of an intermediate oxime. Figure 6.19 shows the conversion of a nitrile to an amine. (The nitrile can be formed by the action of cyanide ion, CN–, on a halide via an S_N2 mechanism.)

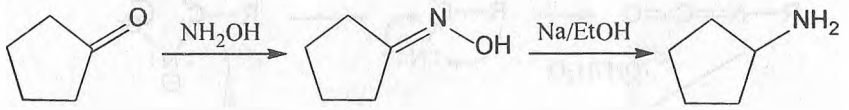


Figure 6.18 *The formation of an amine from a ketone via an oxime.*

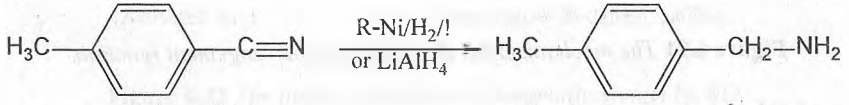


Figure 6.19 *The formation of an amine from a nitrile.*

Hofmann rearrangement (degradation).The *Hofmann rearrangement* is a useful means of converting an amide to an amine. The nitrogen of the amide must be primary. The reaction results in the loss of one carbon atom. Figure 6.20 illustrates the generic Hofmann rearrangement reaction, and the generic

mechanism of the Hofmann rearrangement reaction is shown in Figure 6.21. In the reaction, an intermediate isocyanate forms. The R in Figure 6.21 may be alkyl or aryl. The first intermediate in the mechanism is resonance stabilized, which promotes the reaction (it's similar in structure to an enolate). In addition, the third intermediate is also resonance stabilized.

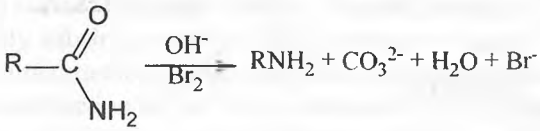


Figure 6.20 *The generic Hofmann rearrangement reaction.*

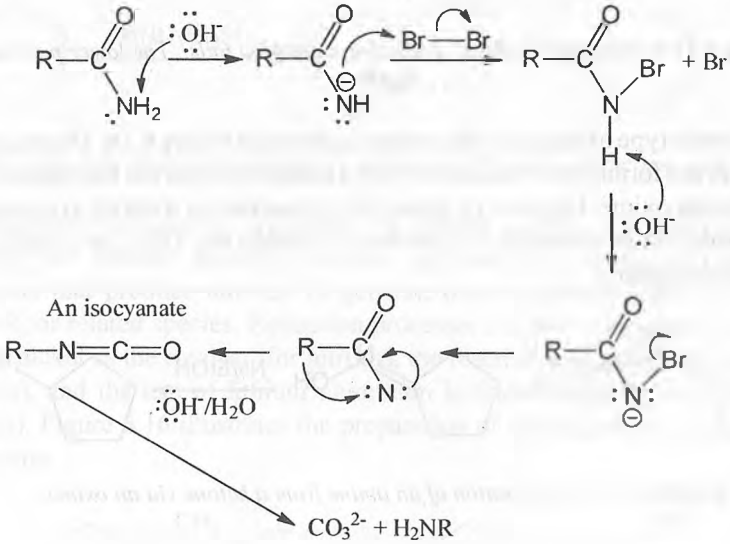


Figure 6.21 *The mechanism for the Hofmann rearrangement reaction.*

A related reaction is the *Curtius rearrangement,* which replaces the amide with an azide, RCO-N_3. The azide can be formed by the reaction of an acyl chloride with sodium azide.

6.5 Chemical properties of nitrogen compounds

Primary, secondary, and tertiary amines behave as Brønsted-Lowry bases.

These amines react like ammonia, adding H^+ to produce an ammonium ion. Amines may also behave as nucleophiles (Lewis bases). Primary amines are stronger nucleophiles than secondary amines, which, in turn, are stronger nucleophiles than tertiary amines. As nucleophiles, amines attack acid chlorides to form amides. Later in this chapter you see that they're important in the formation of sulfonamides.

Reactions with nitrous acid.Amines react with nitrous acid (formed by the reaction $NaNO_2 + H^+ \rightarrow HNO_2$) to give a variety of products. The nitrous acid isn't very stable, so generating it in place from sodium nitrite is necessary. (Sodium nitrite is a meat preservative and a color enhancer.) Under acidic conditions, nitrous acid dehydrates to produce the nitrosonium ion, NO^+. The NO^+ ion is a weak electrophile that's resonance stabilized.Figure 6.22 illustrates the dehydration of nitrous acid.

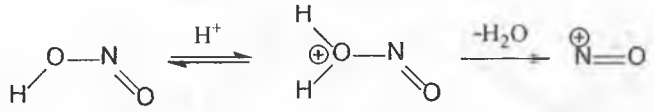


Figure 6.22 *The dehydration of nitrous acid.*

Tertiary amines don't react directly with acidic sodium nitrite. However, as seen in Figure 6.23, even though the tertiary amine doesn't react, its presence activates an aromatic system leading to attack by NO^+.

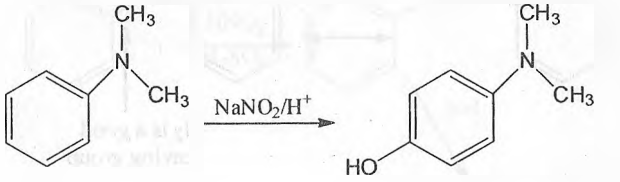


Figure 6.23 *The attack of an activate daromatic system by NO .*

As seen in Figure 6.24, secondary amines react directly with acidic sodium nitrite to form a nitrosamine. (These compounds are very, very toxic.) Primary amines react under similar conditions to form unstable diazonium salts (see Figure 6.25). Diazonium salts readily lose the very stable N_2 to form reactive carbocations that are useful in a number of synthetic pathways. Figure 6.26 shows the resonance stabilization of a diazonium ion.

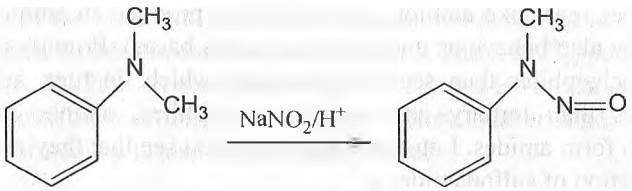


Figure 6.24 *The formation of a nitrosamine by the reaction of a secondary amine with acidic sodium nitrite.*

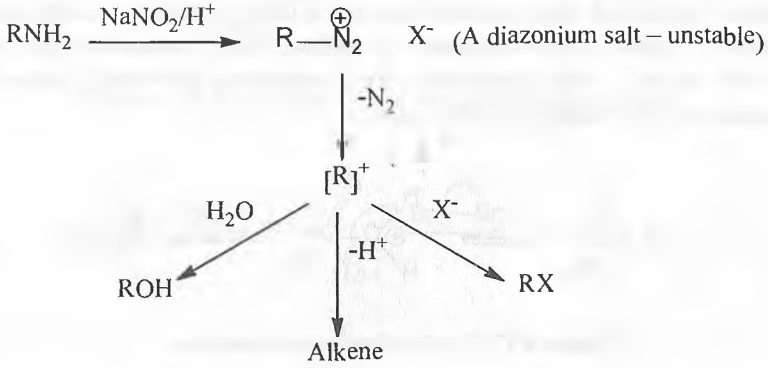


Figure 6.25 *The formation of a diazonium salt, its decomposition ,and several possible outcomes of the carbocation formed by decomposition.*

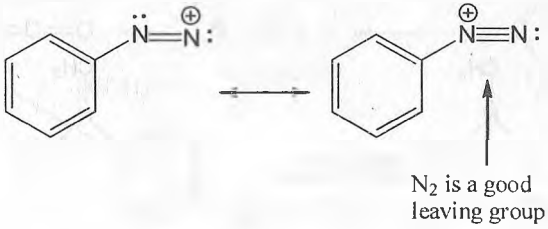


Figure 6.26 *Resonance stabilization of a diazoniumion.*

Replacement reactions.Many kinds of replacement reactions involve nitrogen compounds. A good many of these processes, described in the following sections, utilize diazonium salts.

Sandmeyer reaction.The *Sandmeyer reaction* utilizes a diazonium salt to produce an aryl halide. The process begins by converting an amine to a diazonium salt. Decomposition of the diazonium salt in the presence of a copper (I) halide places the halide ion into the position originally occupied by

the amine. The most useful copper (I) halides are CuCl and CuBr; in addition, the copper (I) pseudohalides, such as CuCN, also works by placing a nitrile in the position originally occupied by the amine. Figure 6.27 shows an example of the Sandmeyer reaction.

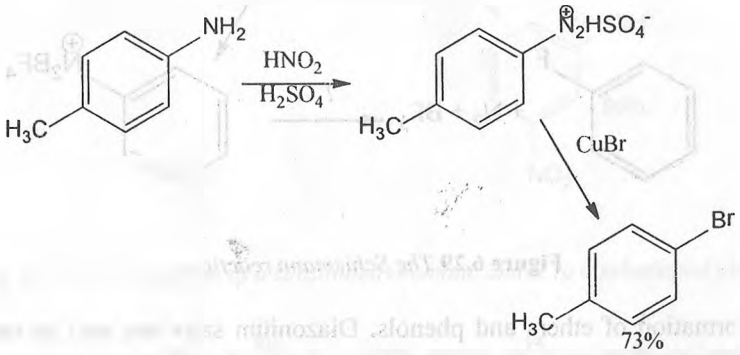


Figure 6.27 *An example of the Sandmeyer reaction.*

Replacement by iodide ion.This reaction is similar to the Sandmeyer reaction, but the halide source is potassium iodide (KI). Figure 6.28 illustrates this reaction.

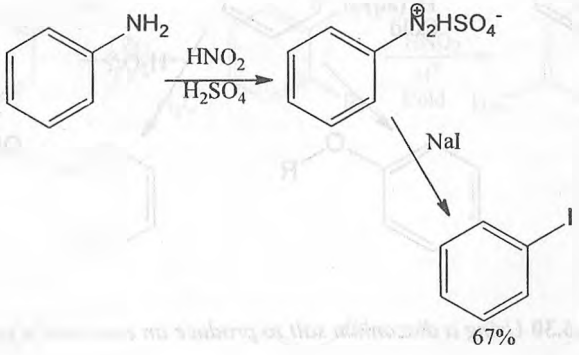


Figure 6.28 *The preparation of an aryl iodide.*

Schiemann reaction.The *Schiemann reaction* is a means of preparing aryl fluorides. The process is similar to the Sandmeyer reaction. The source of the fluoride is fluoroboric acid, HBF_4. Figure 6.29 illustrates the Schiemann reaction.

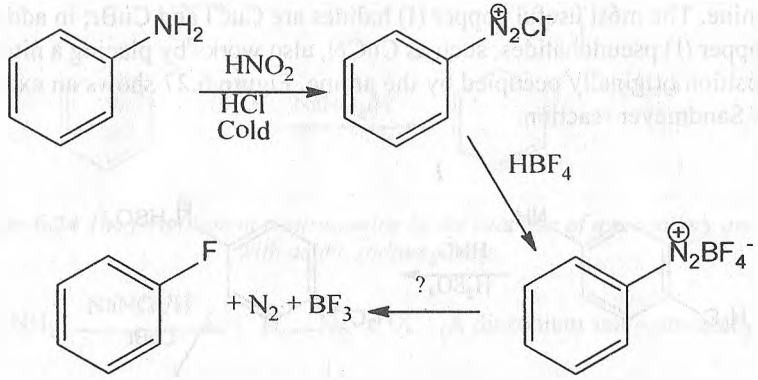


Figure 6.29 *The Schiemann reaction.*

Formation of ethers and phenols. Diazonium salts can also be used to form ethers and phenols. Reaction of diazonium salt with an alcohol generates an ether, while thermal hydrolysis of the diazonium salt yields a phenol. Figure 6.30 illustrates both formations. As seen in Figure 6.31, this process also works on substituted aromatic systems.

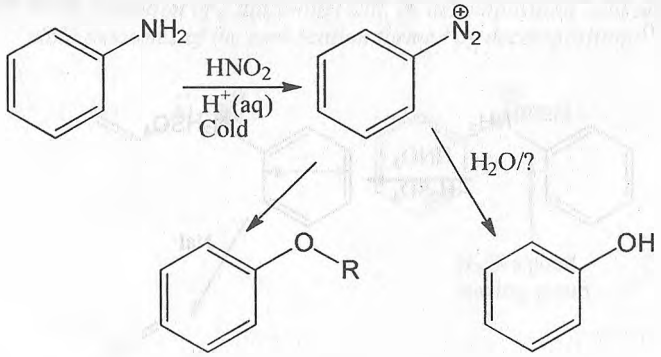


Figure 6.30 *Using a diazonium salt to produce an ether and a phenol.*

Deamination replaces the amine group with a hydrogen atom. This process normally uses hypophosphorous acid, H_3PO_2. The general process for deamination is in Figure 6.32. This is a synthetically useful technique that leads to different products than other replacement methods. Figure 6.33 illustrates the formation of two different dibromotoluenes.

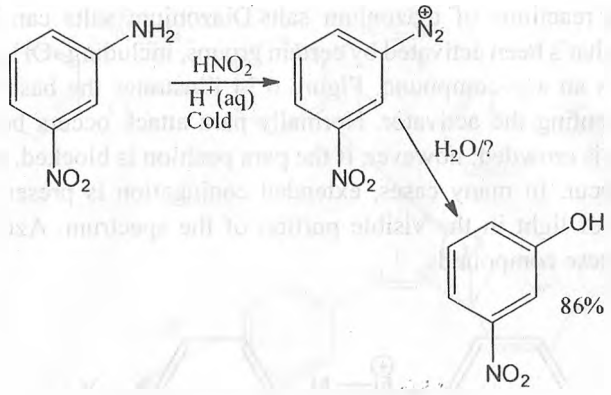


Figure 6.31 *The conversion of a substituted aromatic amine to a substituted phenol.*

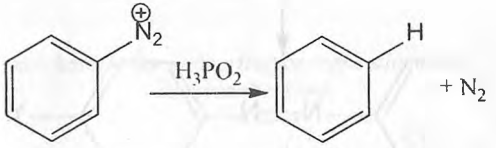


Figure 6.32 *The general process for deamination.*

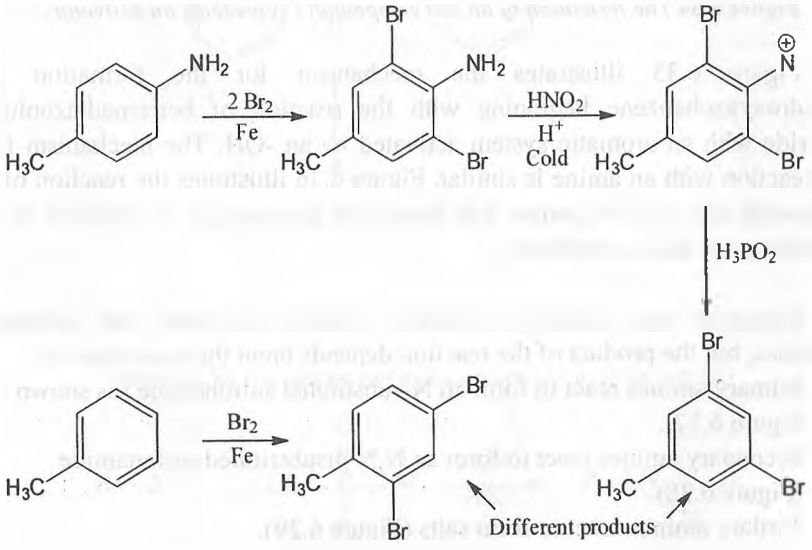


Figure 6.33 *The formation of two different dibromotoluenes.*

Coupling reactions of diazonium salts.Diazonium salts can attack an aromatic ring that's been activated by certain groups, including -OH and $-NR_2$. The product is an azo compound. Figure 6.34 illustrates the basic reaction, with Y representing the activator. Normally para attack occurs because the ortho position is crowded; however, if the para position is blocked, then ortho attack may occur. In many cases, extended conjugation is present, leading to absorption of light in the visible portion of the spectrum. Azo dyes are examples of these compounds.

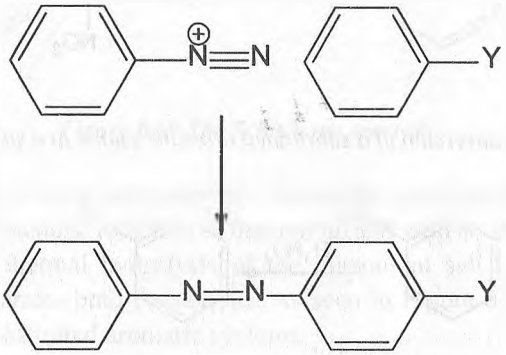


Figure 6.34 *The formation of an azo compound(Y represents an activator).*

Figure 6.35 illustrates the mechanism for the formation of *p*-hydroxyazobenzene beginning with the reaction of benzenediazonium chloride with an aromatic system activated by an -OH. The mechanism for the reaction with an amine is similar. Figure 6.36 illustrates the reaction of a diazonium salt with an amine. The product of the reaction in Figure 6.36 is *p*-(dimethylamino) azobenzene.

Reactions with sulfonyl chlorides. Amines can react with sulfonyl chlorides, but the product of the reaction depends upon the type of amine.

Primary amines react to form an N-substituted sulfonamide (as shown in Figure 6.37).

Secondary amines react to form an N,N-disubstituted sulfonamide (Figure 6.38).

Tertiary amines react to form salts (Figure 6.39).

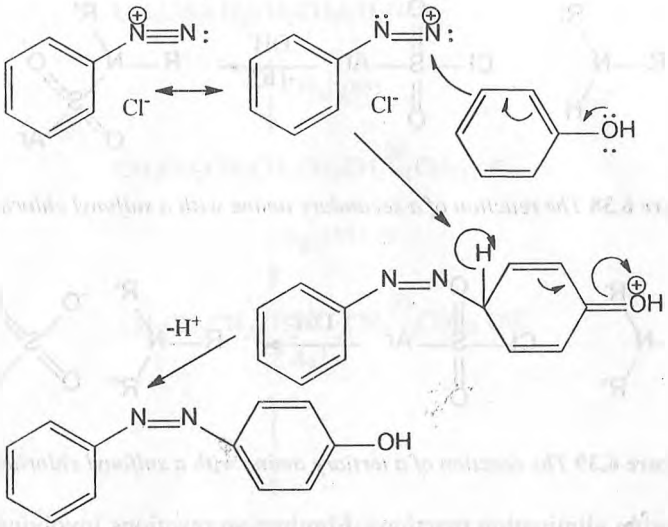


Figure 6.35 *The mechanism for converting benzene diazonium chloride to p-hydroxyazobenzene.*

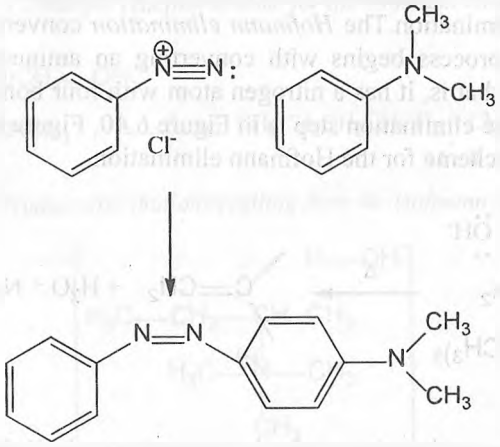


Figure 6.36 *The reaction of a diazonium salt with an amine.*

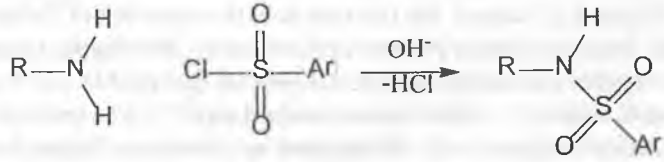


Figure 6.37 *The reaction of a primary amine with a sulfonyl chloride.*

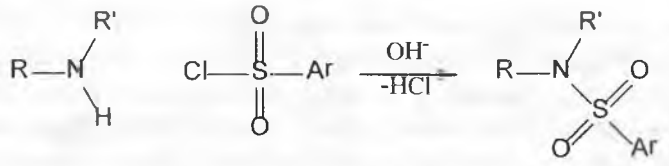


Figure 6.38 *The reaction of a secondary amine with a sulfonyl chloride.*

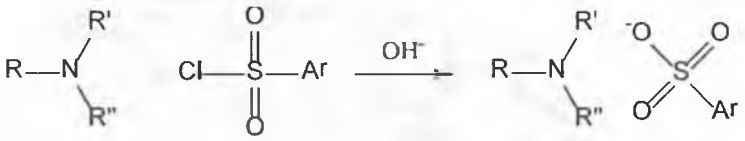


Figure 6.39 *The reaction of a tertiary amine with a sulfonyl chloride.*

Exploring elimination reactions. Elimination reactions involving amines are important synthetic methods.

They can be used to make a variety of useful organic compounds, including alkenes. We examine a few of them in this section.

Hofmann elimination.The *Hofmann elimination* converts an amine into an alkene. The process begins with converting an amine to a quaternary ammonium salt (that is, it has a nitrogen atom with four bonds). The general mechanism for the elimination step is in Figure 6.40. Figure 6.41 illustrates a sample reaction scheme for the Hofmann elimination.

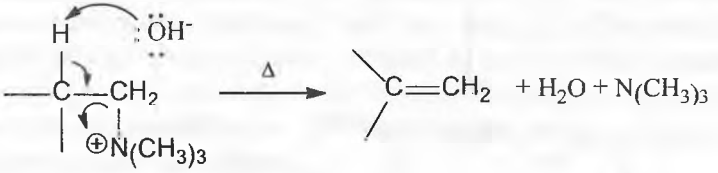


Figure 6.40 *The general mechanism for the elimination in the Hofmann elimination.*

As you know,more highly substituted double bond is more stable (Zaitsev's rule). As Figure 6.42 shows, the reaction does the opposite of Zaitsev's rule. That is, the least-substituted product predominates. This happens because the transition state has carbanion character (shown in Figure 6.43). (A 1° carbanion is more stable than a 2°, which is more stable than a 3°.) The process involves anti-elimination (opposite side elimination as shown in Figure 6.44). The geometry requires the bulky groups to have the greatest separation.

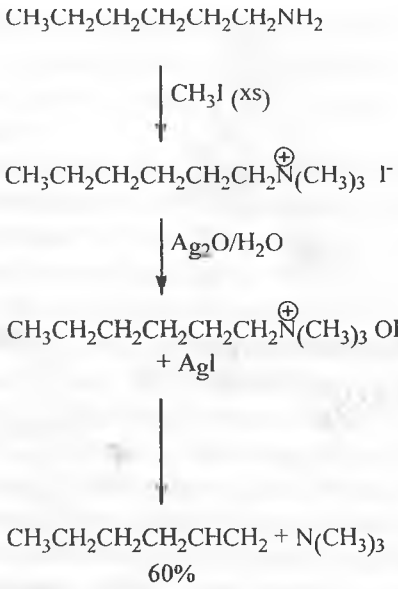


Figure 6.41 *A sample reaction scheme for the Hofmann elimination.*

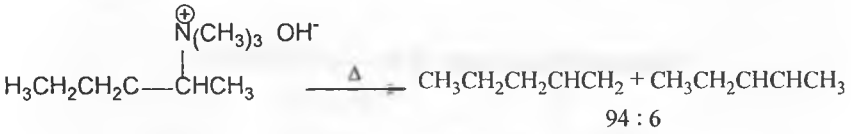


Figure 6.42 *Product distribution resulting from the Hofmann elimination.*

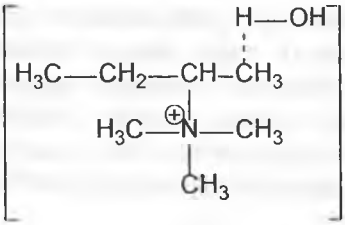


Figure 6.43 *The intermediate in the Hofmann elimination.*

Cope elimination.In the Cope elimination, thirty percent hydrogen peroxide H_2O_2, is used to produce an amine oxide, which upon heating undergoes elimination. This is a syn-elimination process. Figure 6.45 illustrates the general reaction, while Figure 6.46 shows the mechanism of the syn-elimination step.

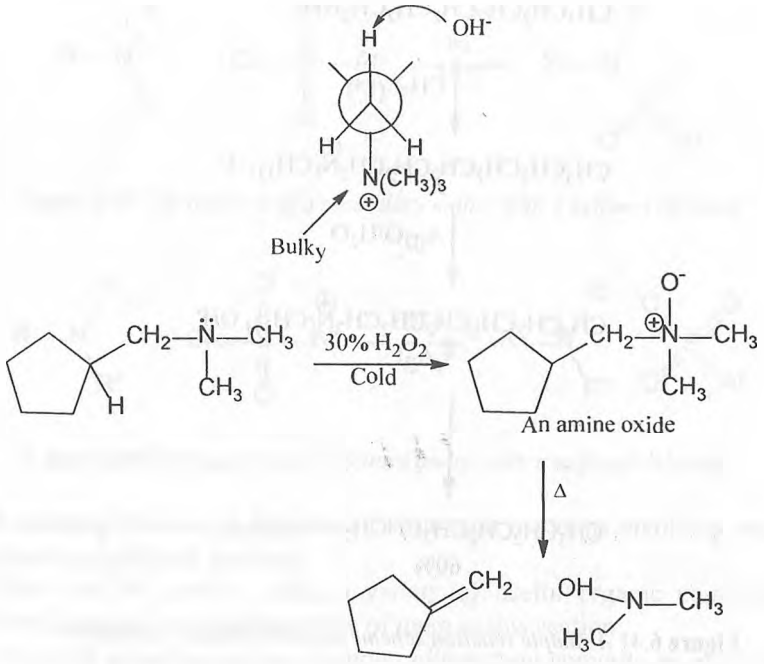


Figure 6.45 *An example of the Cope elimination.*

6.6 Multistep synthesis

In many cases, a desired compound cannot be synthesized directly from readily available materials. In these cases, a multistep synthesis must be performed. Figure 6.47 illustrates a multistep synthesis. (A similar type of problem appears on many Organic chemistry exams; they're retrosynthetic analysis problems.) For aromatic amines, -NR_2 is activating *o-p*-directors, and -N+R_2H is deactivating (that is, it may interfere with the reactions).

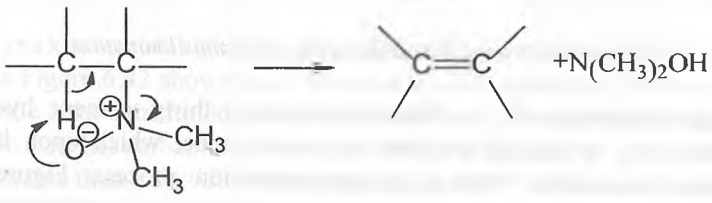


Figure 6.46 *The mechanism of the syn-elimination step in the Cope elimination.*

When attacking a retrosynthetic analysis problem, you often know only the formula of the starting material and the desired product (in addition, the instructor may impose a few other rules). The answer to the problem should resemble Figure 6.47.

You have many options for attacking multistep synthesis problems. In general, you should begin with the desired product and work backwards. After you determine the identity of the reactant, you back up one step and determine which reactant can produce the amide given in Figure 6.47. After this, you back up another step and repeat the procedure until you reach the starting material. If you get lost, you may need to retrace your steps and redo one or more steps. Only try to work from the beginning as a last resort.

The formation of sulfa drugs is another example of a multistep synthesis. The sulfa drugs are bactericides, effective against a wide variety of bacteria because they mimic *p*-aminobenzoic acid (Figure 6.48). Many bacteria require *p*-aminobenzoic acid, which they are unable to synthesize, and need to synthesize folic acid. Many types of sulfa drugs exist, and most of them involve the substitution of one of the hydrogen atoms on the $-SO_2-NH_2$. Prontosil (Figure 6.49) was the first commercially available sulfa drug. The metabolism of prontosil produced sulfanilamide.

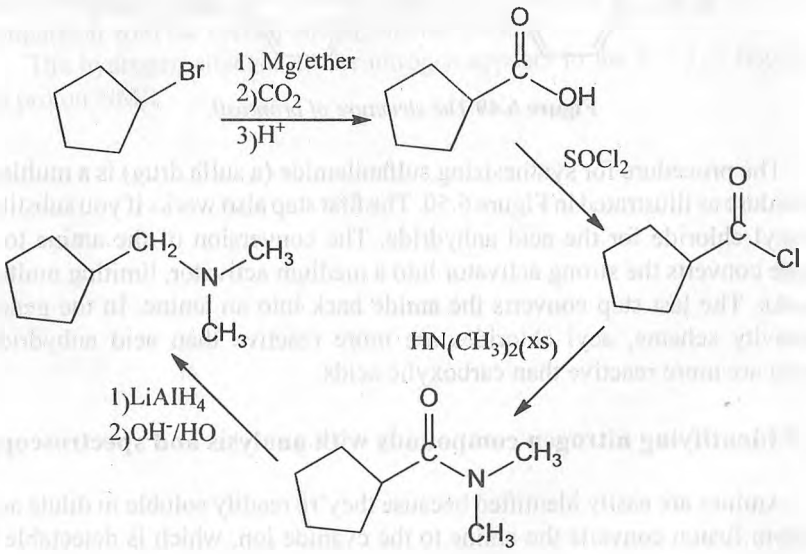


Figure 6.47 *An example of a multistep synthesis.*

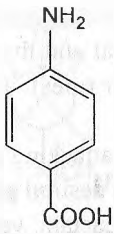


Figure 6.48 *The structure of p-aminobenzoic acid.*

The procedure for synthesizing sulfanilamide (a sulfa drug) is a multistep procedure as illustrated in Figure 7-50. The first step also works if you substitute an acyl chloride for the acid anhydride. The conversion of the amine to an amide converts the strong activator into a medium activator, limiting multiple attacks. The last step converts the amide back into an amine.

In the general reactivity scheme, acyl chlorides are more reactive than acid anhydrides, which are more reactive than carboxylic acids.

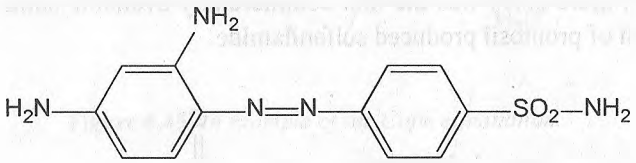


Figure 6.49 *The structure of prontosil.*

The procedure for synthesizing sulfanilamide (a sulfa drug) is a multistep procedure as illustrated in Figure 6.50. The first step also works if you substitute an acyl chloride for the acid anhydride. The conversion of the amine to an amide converts the strong activator into a medium activator, limiting multiple attacks. The last step converts the amide back into an amine. In the general reactivity scheme, acyl chlorides are more reactive than acid anhydrides, which are more reactive than carboxylic acids.

6.7 Identifying nitrogen compounds with analysis and spectroscopy

Amines are easily identified because they're readily soluble in dilute acid. Sodium fusion converts the amine to the cyanide ion, which is detectable by a variety of methods. The ready formation and decomposition of diazonium salts leads to the identification of primary amines. The Hinsberg test (see the nearby sidebar) is useful in identifying amines.

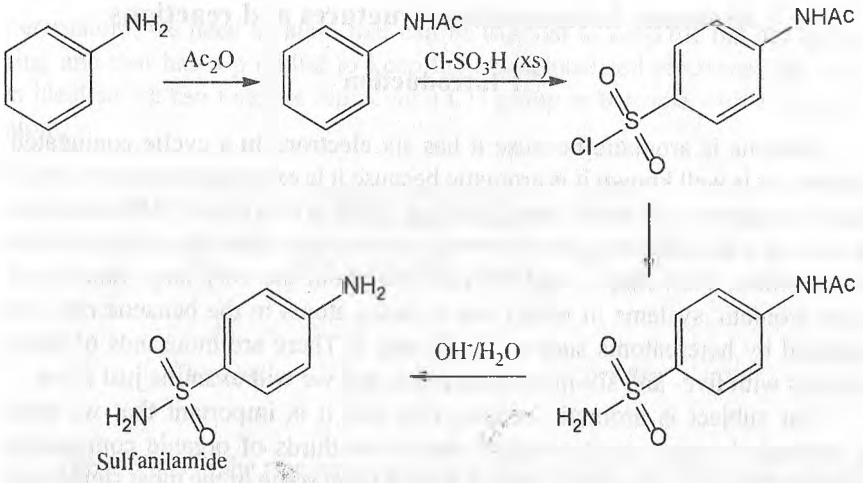


Figure 6.50 *The multistep synthesis of sulfanilamide.*

The infrared spectra of amines show one or two N-H stretches in the 3500–3200 cm^{-1} region. Primary amines usually have two bands, while secondary amines usually have one band. Obviously, since there are no N-H bonds, tertiary amines have no N-H stretch. The bands are small and sharp in comparison with the corresponding alcohol peaks.

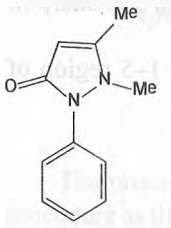
The hydrogen attached to the nitrogen appears in the # = 1–5 region of the proton NMR.

7 Aromatic heterocycles: structures and reactions

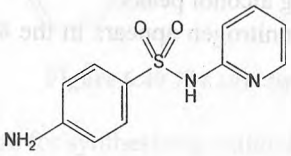
7.1 Introduction

Benzene is aromatic because it has six electrons in a cyclic conjugated system. As is well known it is aromatic because it is exceptionally stable and it has a ring current and hence large chemical shifts in the proton NMR spectrum as well as a special chemistry involving substitution rather than addition with electrophiles. This chapter and the next are about the very large number of other aromatic systems in which one or more atoms in the benzene ring are replaced by heteroatoms such as N, O, and S. There are thousands of these systems with five- and six-membered rings, and we will examine just a few.

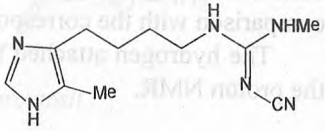
Our subject is aromatic heterocycles and it is important that we treat it seriously because most probably about two-thirds of organic compounds belong to this class, and they number among them some of the most significant compounds for human beings. Even in the sixteenth century quinine was used to prevent and treat malaria, though the structure of the drug was not known. The first synthetic drug was antipyrine (1887) for the reduction of fevers. The first effective antibiotic was sulfapyridine (1938). The first multi-million pound drug (1970s) was Tagamet, the anti-ulcer drug.



antipyrine



sulfapyridine



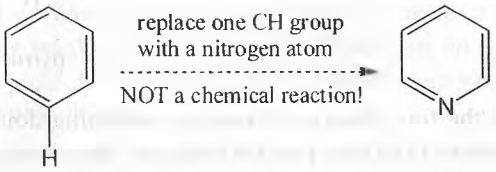
Tagamet

All these compounds have heterocyclic aromatic rings shown in black. Three have single rings, five- or six-membered, two have five- or six-membered rings fused together. The number of nitrogens in the rings varies from one to four. We will start by looking at the simple six-membered ring with one nitrogen atom. This is pyridine and the drug sulfapyridine is an example.

7.2 Aromatic nitrogen heterocycles

There is no doubt that benzene is aromatic. Now we must ask: how can we insert a heteroatom into the ring and retain aromaticity? What kind of atom is needed? If we want to replace one of the carbon atoms of benzene with a

heteroatom, we need an atom that can be trigonal to keep the flat hexagonal ring and that has a p orbital to keep the six delocalized electrons. Nitrogen is ideal so we can imagine replacing a CH group in benzene with a nitrogen atom.

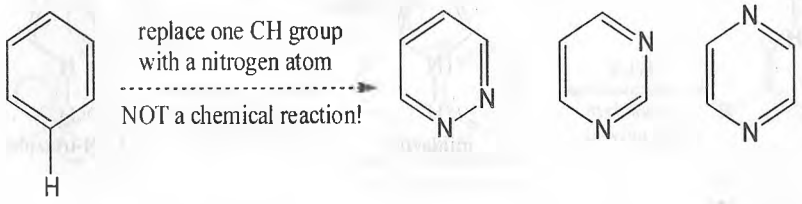


benzene pyridine

The orbitals in the ring have not changed in position or shape and we still have the six electrons from the three double bonds. One obvious difference is that nitrogen is trivalent and thus there is no NH bond. Instead, a lone pair of electrons occupies the space of the C–H bond in benzene.

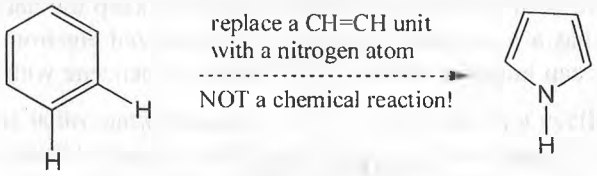
In theory then, pyridine is aromatic. But is it in real life? The most important evidence comes from the proton NMR spectrum. The six protons of benzene resonate at dH 7.27 p.p.m., some 2 p.p.m. downfield from the alkene region, clear evidence for a ring current. Pyridine is not as symmetrical as benzene but the three types of proton all resonate in the sameregion.

As we will see, pyridine is also very stable and, by any reasonable assessment, pyridine is aromatic. We could continue the process of replacing, on paper, more CH groups with nitrogen atoms, and would find three new aromatic heterocycles–pyridazine, pyrimidine. and pyrazine:



pyridine pyridazine pyrimidine pyrazine

There is another way in which we might transform benzene into a heterocycle. Nitrogen has a lone pair of electrons so we could replace a CH=CH unit in benzene by a nitrogen atom providing that we can use the lone pair in the delocalized system. This means putting it into a p orbital.

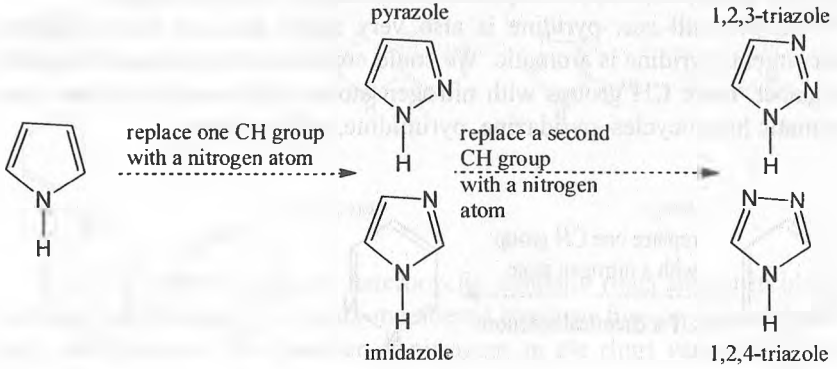


benzene pyrrole

You still have the four electrons from the remaining double bonds and, with the two electrons of the lone pair on nitrogen, that makes six in all. The nitrogen atom must still be trigonal with the lone pair in a p orbital so the N–H bond is in the plane of the five-membered ring.

The NMR of pyrrole is slightly less convincing as the two types of proton on the ring resonate at higher field (6.5 and 6.2 p.p.m.) than those of benzene or pyridine but they still fall in the aromatic rather than the alkene region. Pyrrole is also more reactive towards electrophiles than benzene or pyridine, but it does the usual aromatic substitution reactions (Friedel–Crafts, nitration, halogenation) rather than addition reactions: pyrrole is also aromatic.

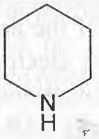
Inventing heterocycles by further replacement of CH groups by nitrogen in pyrrole leads to two compounds, pyrazole and imidazole, after one replacement and to two triazoles after two replacements.



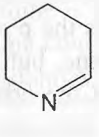
All of these compounds are generally accepted as aromatic too as they broadly have the NMR spectra and reactivities expected for aromatic compounds. As you may expect, introducing heteroatoms into the aromatic ring and, even more, changing the ring size actually affect the chemistry a great deal. It must be now returned to pyridine and work our way more slowly through the chemistry of these important heterocycles to establish the principles that govern their behaviour.

7.3 Pyridine

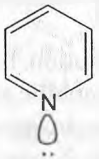
The nitrogen atom in the pyridine ring is planar and trigonal with the lone pair in the plane of the ring. This makes it an imine. Most of the imines you have met before, have been unstable intermediates in carbonyl group reactions, but in pyridine we have a stable imine - stable because of its aromaticity. All imines are more weakly basic than saturated amines and pyridine is a weak base with a pK_a of 5.5. This means that the pyridinium ion as about as strong an acid as a carboxylic acid.



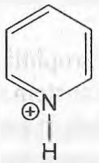
piperidine
pKa 11.2



typical imine
pKa~9

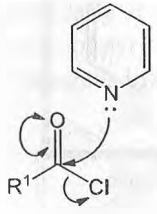


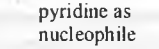
pyridine

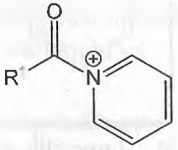


pyridinium ion

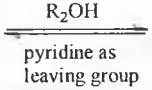
Pyridine is a reasonable nucleophile for carbonyl groups and is often used as a nucleophilic catalyst in acylation reactions. Esters are often made in pyridine solution from alcohols and acid chlorides

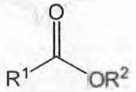






acyl pyridinium ion
reactive intermediate



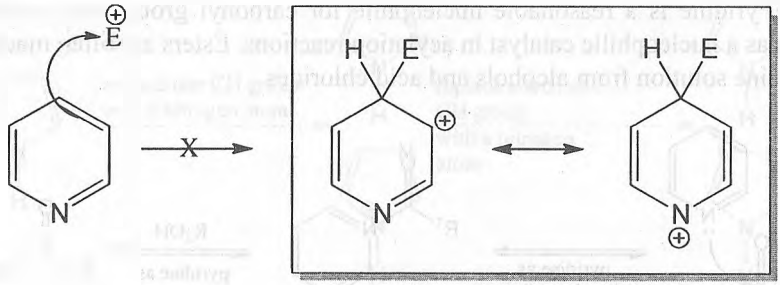


Pyridine is nucleophilic at the nitrogen atom because *the lone pair of electrons on nitrogen cannot be delocalized around the ring* . They are in an sp2 orbital orthogonal to the p orbitals in the ring and there is no interaction between orthogonal orbitals. Try it for yourself, drawing arrows. All attempts to delocalize the electrons lead to impossible results!

attempts to delocalize lone pair
lead to ridiculous results

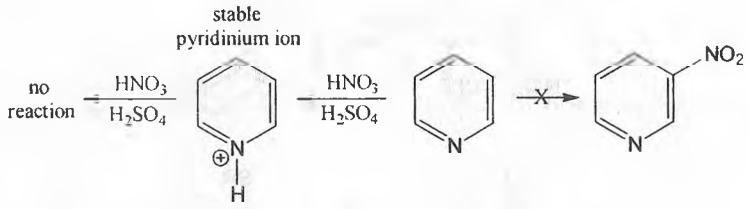
The main interest must be this: what does the nitrogen atom do to the rest of the ring? The important orbitals the p orbitals of the aromatic system are superficially the same as in benzene, but the more electronegative nitrogen atom will lower the energy of all the orbitals. Lower-energy filled orbitals mean a *less* reactive nucleophile but a lower-energy LUMO means a *more* reactive electrophile. This is a good guide to the chemistry of pyridine. It is less reactive than benzene in electrophilic aromatic substitution reactions but nucleophilic substitution, which is difficult for benzene, comes easily to pyridine.

Pyridine is bad at electrophilic aromatic substitution.The lower energy of the orbitals of pyridine's p system means that electrophilic attack on the ring is difficult. Another way to look at this is to see that the nitrogen atom destabilizes the cationic would-be intermediate, especially at the 2- and 4-positions.

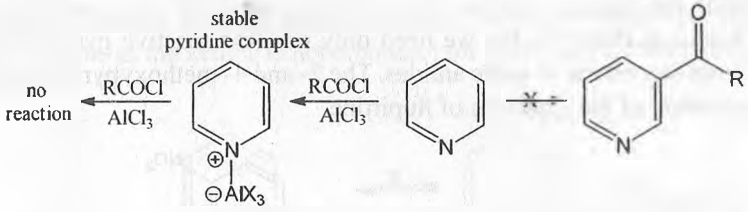


unstable electron-deficient cation

An equally serious problem is that the nitrogen lone pair is basic and a reasonably good nucleophil this is the basis for its role as a nucleophilic catalyst in acylations. The normal reagents for electrophilic substitution reactions, such as nitration, are acidic. Treatment of pyridine with the usual mixture of HNO_3 and H_2SO_4 merely protonates the nitrogen atom. Pyridine itself is not very reactive towards electrophiles: the pyridinium ion is totally unreactive.

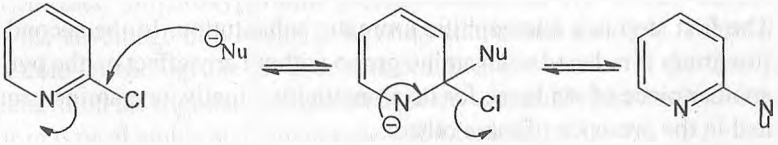


Other reactions, such as Friedel–Crafts acylations, require Lewis acids and these too react at nitrogen. Pyridine is a good ligand for metals such as Al(III) or Sn(IV) and, once again, the complex with its cationic nitrogen is completely unreactive towards electrophiles.

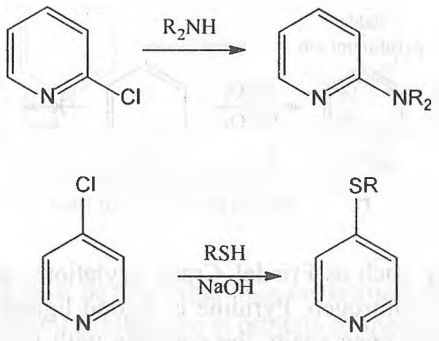


Pyridine does not undergo electrolytic substitution. Aromatic electrophilic substitution on pyridine is not a useful reaction. The ring is unreactive and the electrophilic reagents attack nitrogen making the ring even less reactive. Avoid nitration, sulfonation, halogenation, and Friedel–Crafts reactions on simple pyridines.

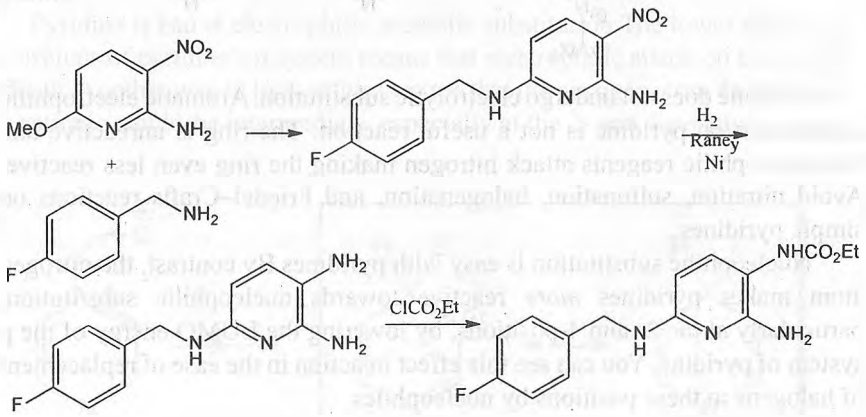
Nucleophilic substitution is easy with pyridines.By contrast, the nitrogen atom makes pyridines *more* reactive towards nucleophilic substitution, particularly at the 2- and 4-positions, by lowering the LUMO energy of the p system of pyridine. You can see this effect in action in the ease of replacement of halogens in these positions by nucleophiles.



The intermediate anion is stabilized by electronegative nitrogen and by delocalization round the ring. These reactions have some similarity to nucleophilic aromatic substitution but are more similar to carbonyl reactions. The intermediate anion is a tetrahedral intermediate that loses the best leaving group to regenerate the stable aromatic system. Nucleophiles such as amines or thiolate anions work well in these reactions.

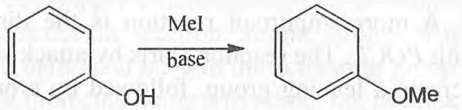


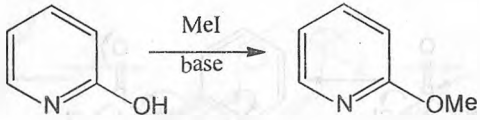
The leaving group does not have to be as good as chloride in these reactions. Continuing the analogy with carbonyl reactions, 2- and 4-chloropyridines are rather like acid chlorides but we need only use less reactive pyridyl ethers, which react like esters, to make amides. The 2- and 4- methoxypyridines allow the completion of the synthesis of flupirtine.



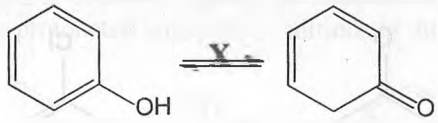
The first step is a nucleophilic aromatic substitution. In the second step the nitro group is reduced to an amino group without any effect on the pyridine ring another piece of evidence for its aromaticity. Finally, one amino group is acylated in the presence of three others.

Pyridones are good substrates for nucleophilic substitution.The starting materials for these nucleophilic substitutions (2– and 4– chloro or methoxypyridines) are themselves made by nucleophilic substitution on pyridines and we need now to discuss these interesting molecules. If you were asked to propose how 2-methoxypyridine might be made, you would probably suggest, by analogy with the corresponding benzene compound, alkylation of a phenol. Let's have a look at this in detail



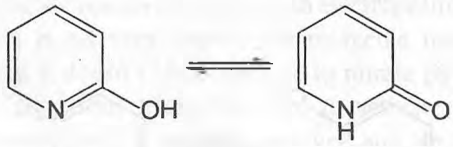


The starting material for this reaction is a 2-hydroxypyridine that can tautomerize to an amidelike structure by the shift of the acidic proton from oxygen to nitrogen. In the phenol series there is no doubt about which structure will be stable as the ketone is not aromatic; for the pyridine both structures are aromatic.



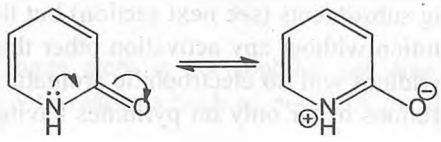
stable phenol

unstable non-aromatic

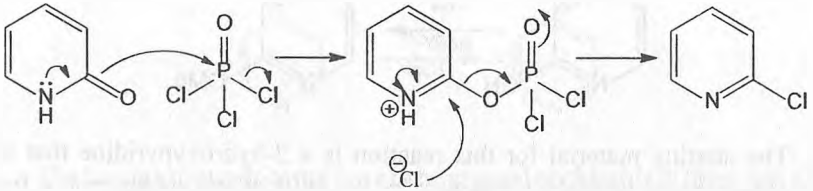


In fact, 2-hydroxypyridine prefers to exist as the 'amide' because that has the advantage of a strong C=O bond and is still aromatic. There are two electrons in each of the C=C double bonds and two also in the lone pair of electrons on the trigonal nitrogen atom of the amide. Delocalization of the lone pair in typical amide style makes the point clearer.

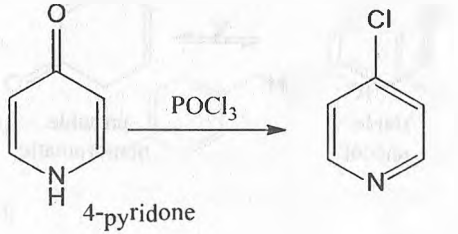
aromatic 2-pyridone



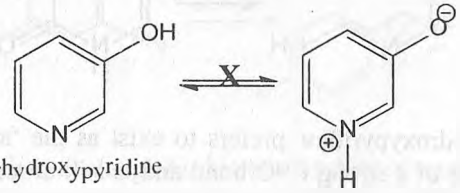
Pyridones are easy to prepare and can be alkylated on oxygen as predicted by their structure. A more important reaction is the direct conversion to chloropyridines with $POCl_3$. The reaction starts by attack of the oxygen atom at phosphorus to create a leaving group, followed by aromatic nucleophilic substitution. The overall effect is very similar to acyl chloride formation from a carboxylic acid.



The same reaction occurs with 4-pyridone, which is also delocalized in the same way and exists in the 'amide' form; but not with 3-hydroxypyridine, which exists in the 'phenol' form.



4-pyridone

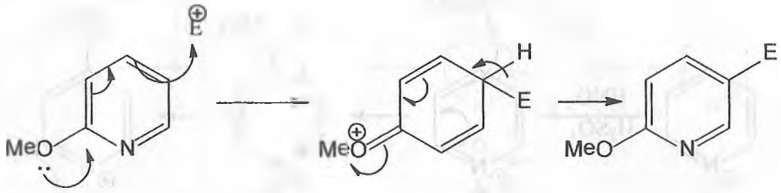


3-hydroxypyridine

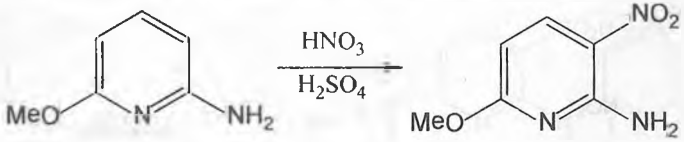
Pyridines undergo nucleophilic substitution

Pyridines can undergo *electrophilic* substitution only if they are activated by electron-donating substituents (see next section) but they readily undergo *nucleophilic* substitution without any activation other than the ring nitrogen atom. Activated pyridines will do electrophilic aromatic substitution Useful electrophilic substitutions occur only on pyridines having electron-donating

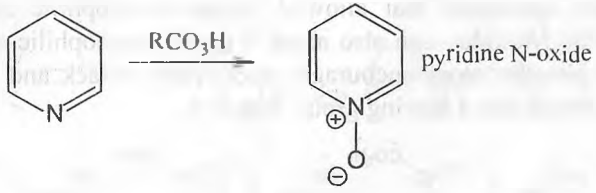
substituents such as NH_2 or OMe. These activate benzene rings too but here their help is vital. They supply a nonbonding pair of electrons that becomes the HOMO and carries out the reaction. Simple amino- or methoxypyridines react reasonably well *ortho* and *para* to the activating group. These reactions happen in spite of the molecule being a pyridine, not because of it.



A practical example occurs in the manufacture of the analgesic flupirtine where a doubly activated pyridine having both MeO and NH_2 groups is nitrated just as if it were a benzene ring. The nitro group goes in *ortho* to the amino group and *para* to the methoxy group. This sequence is completed in the next section. The activation is evidently enough to compensate for the molecule being almost entirely protonated under the conditions of the reaction.

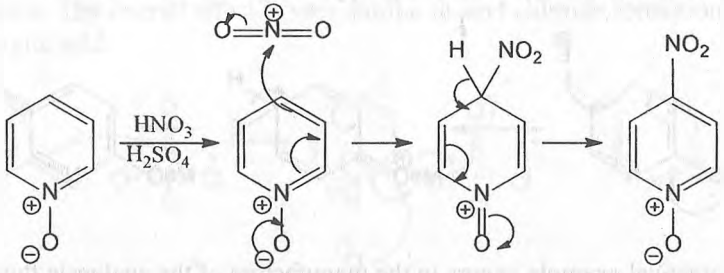


Pyridine *N*-oxides are reactive towards both electrophilic and nucleophilic Substitution.This is all very well if the molecule has such activating groups, but supposing it doesn't? How are we to nitrate pyridine itself? The answer involves an ingenious trick. We need to activate the ring with an electron-rich substituent that can later be removed and we also need to stop the nitrogen atom reacting with the electrophile. All of this can be done with a single atom!

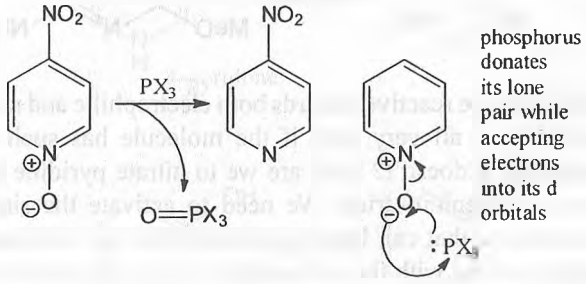


Because the nitrogen atom is nucleophilic, pyridine can be oxidized to pyridine *N*-oxide with reagents such as *m*-CPBA or just H_2O_2 in acetic

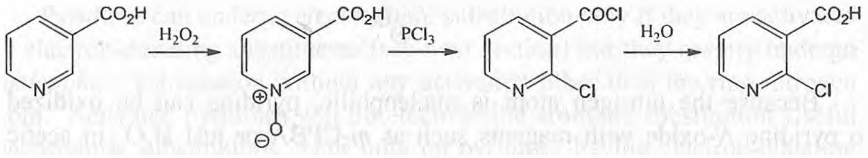
acid. These *N*-oxides are stable dipolar species with the electrons on oxygen delocalized round the pyridine ring, raising the HOMO of the molecule. Reaction with electrophiles occurs at the 2- (‘*ortho*’) and 4- (‘*para*’) positions, chiefly at the 4-position to keep away from positively charged nitrogen.



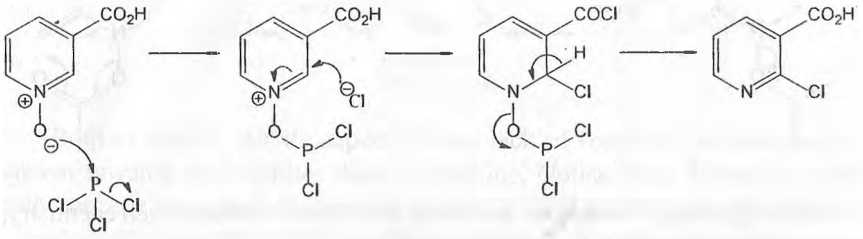
Now the oxide must be removed and this is best done with trivalent phosphorus compounds such as $(MO)_3P$ or PCl_3. The phosphorus atom detaches the oxygen atom in a single step to form the very stable P=O double bond. In this reaction the phosphorus atom is acting as both a nucleophile and an electrophile, but mainly as an electrophile since PCl_3 is more reactive here than $(MO)_3P$.



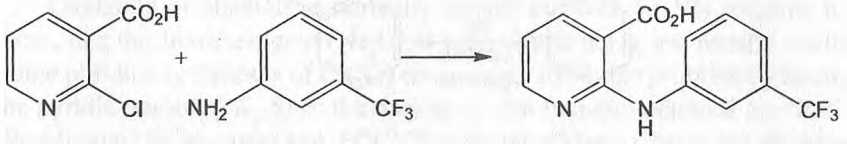
The same activation that allowed simple electrophilic substitution–oxidation to the *N*-oxide– can also allow a useful nucleophilic substitution. The positive nitrogen atom encourages nucleophilic attack and the oxygen atom can be turned into a leaving group with PCl_3.



The *N*-oxide reacts with PCl_3 through oxygen and the chloride ion released in this reaction adds to the most electrophilic position between the two electron-withdrawing groups. Now a simple elimination restores aromaticity and gives a product looking as though it results from chlorination rather than nucleophilic attack.



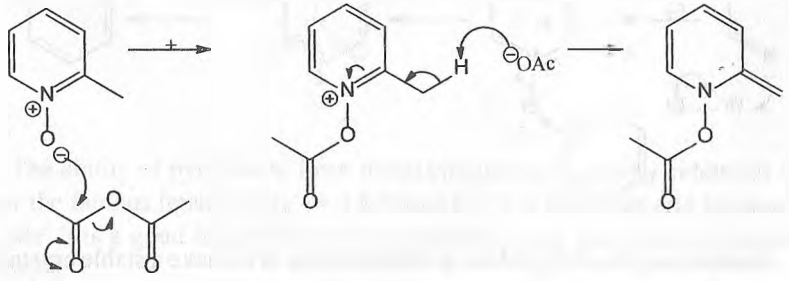
The reagent PCl_3 also converts the carboxylic acid to the acyl chloride, which is hydrolysed back again in the last step. This is a useful sequence because the chlorine atom has been introduced into the 2-position from which it may in turn be displaced by, for example, amines.



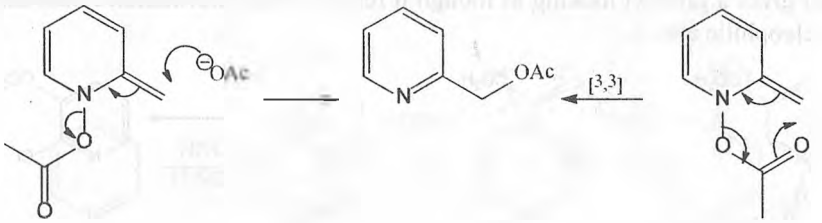
nifluminic acid - analgesic

Pyridine-N-oxides.Pyridine *N*-oxides are useful for both electrophilic and nucleophilic substitutions on the same carbon atoms (2-, 4-, and 6-) in the ring.

Nucleophilic addition at an even more distant site is possible on reaction with acid anhydrides if there is an alkyl group in the 2-position. Acylation occurs on oxygen as in the last reaction but then a proton is lost from the side chain to give an, uncharged intermediate.

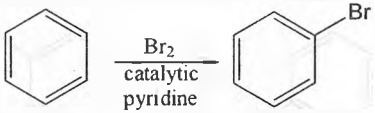


This compound rearranges with migration of the acetate group to the side chain and the restoration of aromaticity. This may be an ionic reaction or a [3,3]-sigmatropic rearrangement.

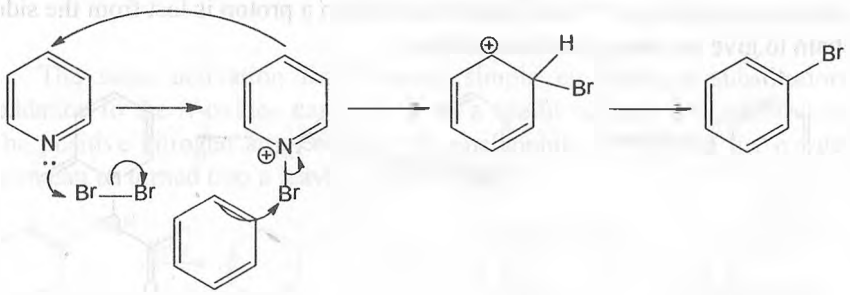


Since pyridine is abundant and cheap and has an extremely rich chemistry, it is not surprising that it has many applications.

Some applications of pyridine chemistry.One of the simplest ways to brominate benzenes is not to bother with the Lewis acid is just to add liquid bromine to the aromatic compound in the presence of a small amount of pyridine.

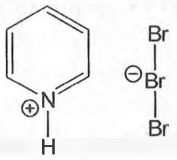


Only about one mole per cent is needed and even then the reaction has to be cooled to stop it getting out of hand. Pyridine attacks electrophiles through its nitrogen atom. This produces the reactive species, the *N*-bromo-pyridinium ion, which is attacked by the benzene. Pyridine is a better nucleophile than benzene and a better leaving group than bromide. This is another example of nucleophilic catalysis.



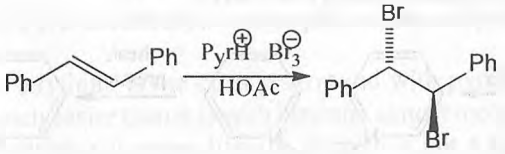
Another way to use pyridine in brominations is to make a stable crystalline compound to replace the dangerous liquid bromine. This compound, known

by names such as pyridinium tribromide, is simply a salt of pyridine with the anion Br_3^-. It can be used to brominate reactive compounds such as alkenes.

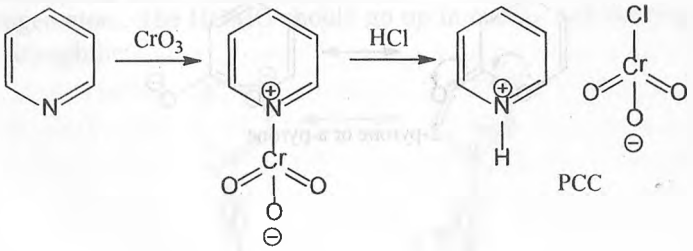


pyridinium
Ph tribromide

Both of these methods depend on the lack of reactivity of pyridine's p system towards electrophiles such as bromine. Notice that, in the first case, both benzene and pyridine arepresent together. The pyridine attacks bromine only through nitrogen (and reversibly at that) and never through carbon.

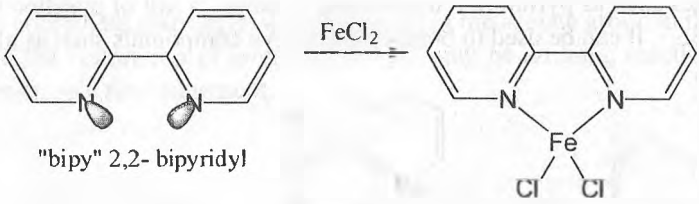


Oxidation of alcohols is normally carried out with Cr(VI) reagents but these, like the Jones' reagent ($Na_2Cr_2O_7$) in sulfuric acid), are usually acidic. Some pyridine complexes of Cr(VI) compounds solve this problem by having the pyridinium ion (pK_a 5) as the only acid. The two most famous are 'PDC' (Pyridinium DiChromate) and 'PCC' (Pyridinium Chloro- Chromate). Pyridine forms a complex with CrO_3 but this is liable to burst into flames. Treatment with HCl gives PCC, which is much less dangerous. PCC is particularly useful in the oxidation of primary alcohols to aldehydes as overoxidation is avoided in the only slightly acidic conditions.



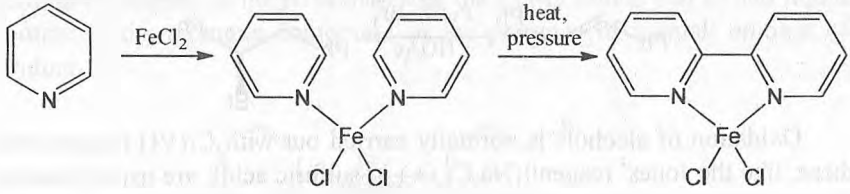
PCC

The ability of pyridine to form metal complexes is greatly enhanced in a dimer the famous ligand 'bipy' or 2,2-bipyridyl. It is bidentate and because of its 'bite' it is a good ligand for many transition metals but shows a partiality for Fe(II).



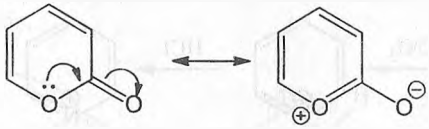
"bipy" 2,2- bipyridyl

It looks like a rather difficult job to persuade two pyridine rings to join together in this way to form bipy. It is indeed very difficult unless you make things easier by using a reagent that favours the product. And what better than Fe(II) to do the job? ICI manufacture bipy by treating pyridine with $FeCl_2 \cdot 4H_2O$ at high temperatures and high pressures. Only a small proportion of the pyridine is converted to the Fe(II) complex of bipy (about 5%) but the remaining pyridine goes back in the next reaction. This is probably a radical process in the coordination sphere of Fe(II).

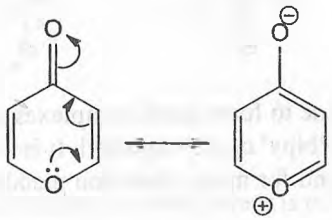


7.4 Six-membered aromatic oxygen heterocycles

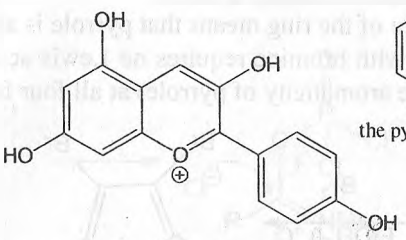
Though pyridine is overwhelmingly the most important of the six-membered aromatic heterocycles, there are oxygen heterocycles, pyrones, that resemble the pyridones. The pyrones are aromatic, though a-pyrone is rather unstable.



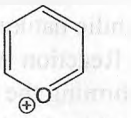
2-pyrone or a-pyrone



The pyrilium salts are stable aromatic cations and are responsible as metal complexes for some flower colours. Heterocycles with six-membered rings based on other elements (for example, P) do exist but they are outside the scope of this book.



a red pyrilium flower pigment



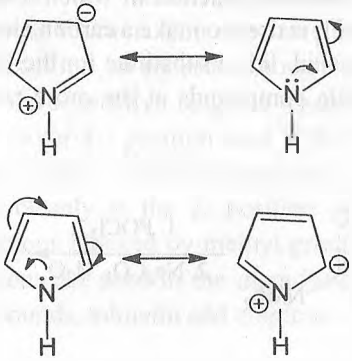
the pyrilium cation

7.5 Five-membered nucleophiles heterocycles

Just about everything is the other way round with pyrrole. Electrophilic substitution is much easier than it is with benzene almost too easy in fact while nucleophilic substitution is more difficult. Pyrrole is not a base nor can it be converted to an *N*-oxide. We need to find out why this is.

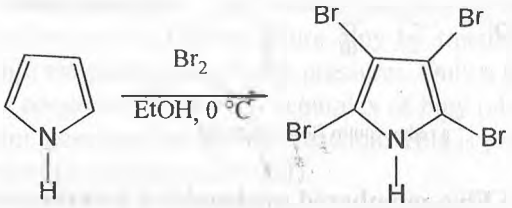
The big difference is that the nitrogen lone pair is delocalized round the ring. The NMR spectrum suggests that all the positions in the ring are about equally electron-rich with chemical shifts about 1 p.p.m. smaller than those of benzene. The ring is flat and the bond lengths are very similar, though the bond opposite the nitrogen atom is a bit longer than the others.

The delocalization of the lone pair can be drawn equally well to any ring atom because of the five membered ring and we shall soon see the consequences of this. All the delocalization pushes electrons from the nitrogen atom into the ring and we expect the ring to be electron-rich at the expense of the nitrogen atom. The HOMO should go up in energy and the ring become more nucleophilic.

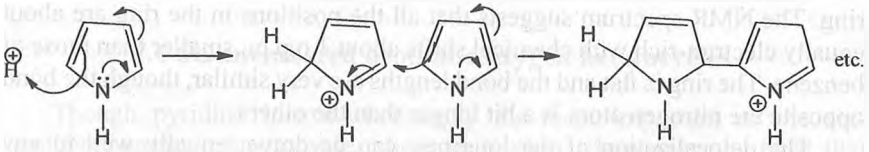


An obvious consequence of this delocalization is the decreased basicity of the nitrogen atom and the increased acidity of the NH group as a whole. In fact, the p*K*a of pyrrole acting as a base is about 4 and protonation occurs at carbon. The NH proton can be removed by much weaker bases than those that can remove protons on normal secondary amines.

The nucleophilic nature of the ring means that pyrrole is attacked readily by electrophiles. Reaction with bromine requires no Lewis acid and leads to substitution (confirming the aromaticity of pyrrole) at all four free positions.



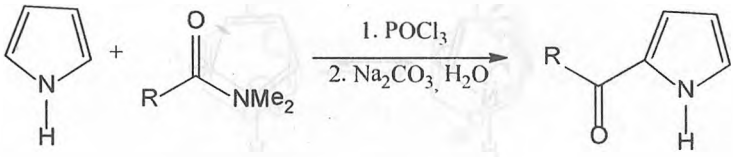
This is a fine reaction in its way, but we don't usually want four bromine atoms in a molecule so one problem with pyrrole is to control the reaction to give only monosubstitution. Another problem is that strong acids cannot be used. Though protonation does not occur at nitrogen, it does occur at carbon and the protonated pyrrole then adds another molecule like this.



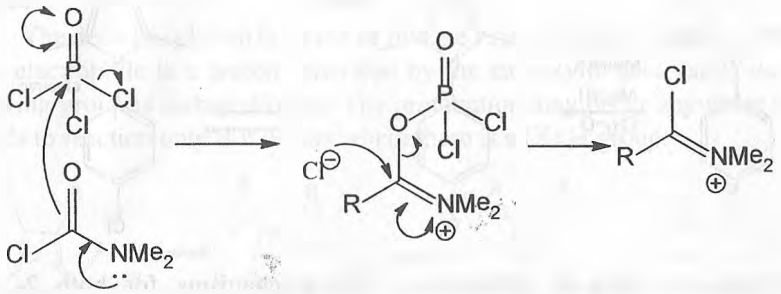
reaction continues to give polymer

Pyrrole polymerizes.Strong acids, those such as H_2SO_4 with a pK_a of less than 4, cannot be used without polymerization of pyrrole.

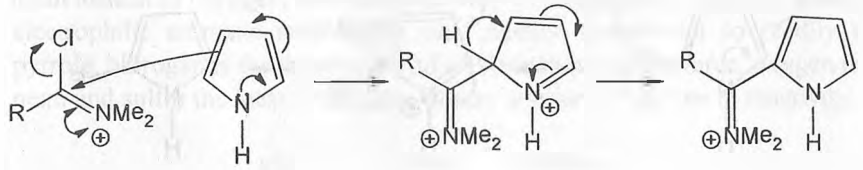
Some reactions can be controlled to give good yields of monosubstituted products. One is the Vilsmeier reaction in which a combination of an *N,N*-dimethylamide and $POCl_3$ is used to make a carbon electrophile in the absence of strong acid or Lewis acid. It is a substitute for the Friedel–Crafts acylation, and works with aromatic compounds at the more reactive end of the scale (where pyrrole is).



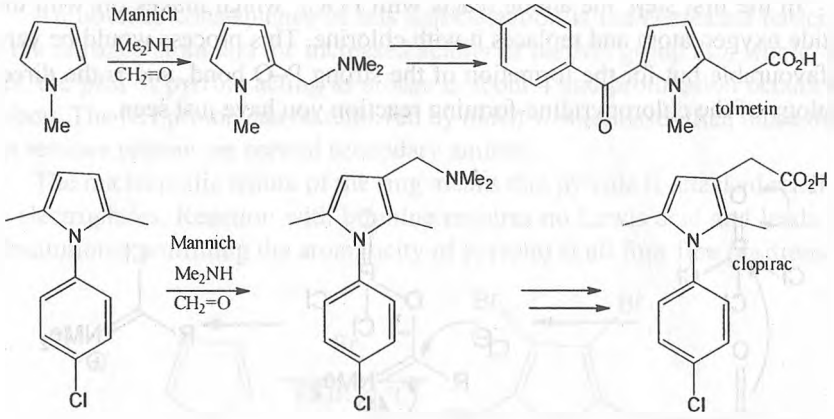
In the first step, the amide reacts with $POCl_3$ which makes off with the amide oxygen atom and replaces it with chlorine. This process would be very unfavourable but for the formation of the strong P–O bond, and is the direct analogy of the chloropyridine-forming reaction you have just seen.



The product from this first step is an iminium cation that reacts with pyrrole to give a more stable iminium salt. The extra stability comes from the conjugation between the pyrrole nitrogen and the iminium group.

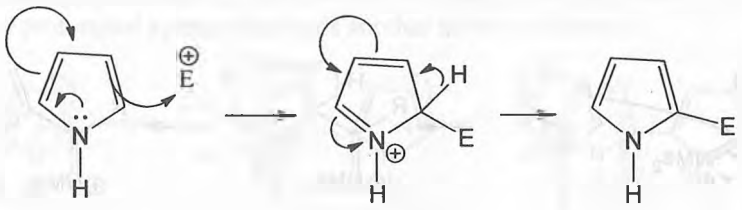


The work-up with aqueous Na_2CO_3 hydrolyses the imine salt and removes any acid formed. This method is particularly useful because it works well with Me_2NCHO (DMF) to add a formyl (CHO) group. This is difficult to do with a conventional Friedel–Crafts reaction. You may have noticed that the reaction occurred only at the 2-position on pyrrole. Though all positions react with reagents like bromine, more selective reagents usually go for the 2- (or 5-) position and attack the 3- (or 4-) position only if the 2- and 5-positions are blocked. A good example is the Mannich reaction .In these two examples *N*-methylpyrrole reacts cleanly at the 2- position while the other pyrrole with both 2- and 5-positions blocked by methyl groups reacts cleanly at the 3-position. These reactions are used in the manufacture of the nonsteroidal anti-inflammatory compounds, tolmetin and clopirac.



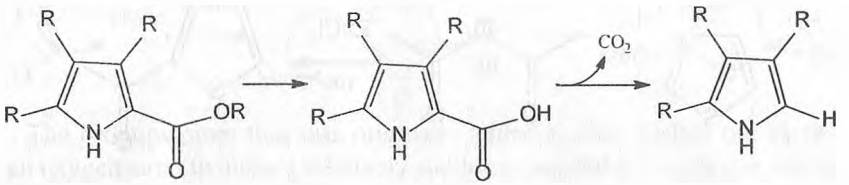
Now we need an explanation. The mechanisms for both 2- and 3-substitutions look good and we will draw both, using a generalized E^+as the electrophile.

reaction with electrophiles in the 2-position

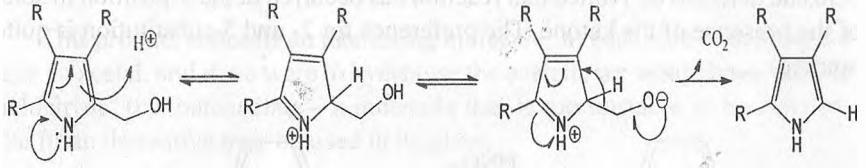


Both mechanisms can occur very readily. Reaction in the 2-position is somewhat better than in the 3-position but the difference is small. Substitution is favoured at *all* positions. Calculations show that the HOMO of pyrrole does indeed have a larger coefficient in the 2-position but that is very much a theoretical chemist's answer, which organic chemists cannot reproduce easily. One way to understand the result is to look at the structure of the intermediates. The intermediate from attack at the 2-position has a linear conjugated system. In both intermediates the two double bonds are, of course, conjugated with each other, but only in the first intermediate are both double bonds conjugated with N^+. The second intermediate is 'cross-conjugated', while the first has a more stable linear conjugated system.

Since electrophilic substitution on pyrroles occurs so easily, it can be useful to block substitution with a removable substituent. This is usually done with an ester group. Hydrolysis of the ester releases the carboxylic acid, which decarboxylates on heating.



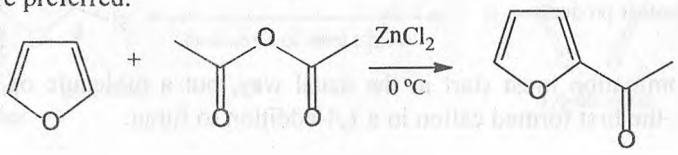
The decarboxylation is a kind of reverse Friedel–Crafts reaction in which the electrophile is a proton (provided by the carboxylic acid itself) and the leaving group is carbon dioxide. The protonation may occur anywhere but it leads to reaction only if it occurs where there is a CO_2H group.

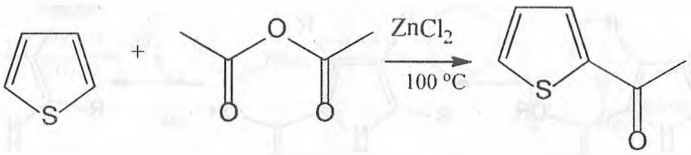


7.6 Furan and thiophene are oxygen and sulfur analogues of pyrrole

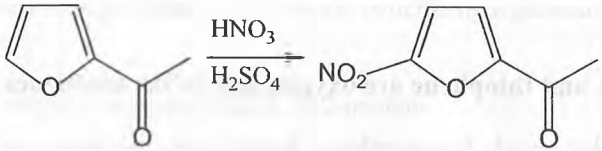
The other simple five-membered heterocycles are furan, with an oxygen atom instead of nitrogen, and thiophene with a sulfur atom. They also undergo electrophilic aromatic substitution very readily, though not so readily as pyrrole. Nitrogen is the most powerful electron donor of the three, oxygen the next, and sulfur the least. Thiophene is very similar to benzene in reactivity.

You may be surprised that thiophene is the least reactive of the three but this is because the p orbital of the lone pair of electrons on sulfur that conjugates with the ring is a **3p** orbital rather than the **2p** orbital of N or O, so overlap with the 2p orbitals on carbon is less good. Both furan and thiophene undergo more or less normal Friedel–Crafts reactions though the less reactive anhydrides are used instead of acid chlorides, and weaker Lewis acids than AlCl3 are preferred.



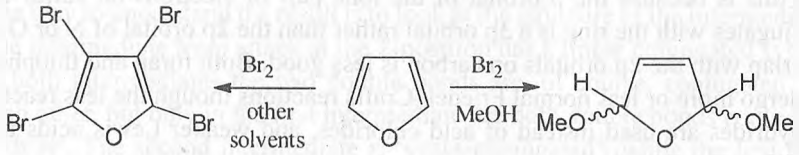


Notice that the regioselectivity is the same as it was with pyrrole the 2-position is more reactive than the 3-position in both cases. The product ketones are less reactive towards electrophiles than the starting heterocycles and deactivated furans can even be nitrated with the usual reagents used for benzene derivatives. Notice that reaction has occurred at the 5-position in spite of the presence of the ketone. The preference for 2- and 5-substitution is quite marked.



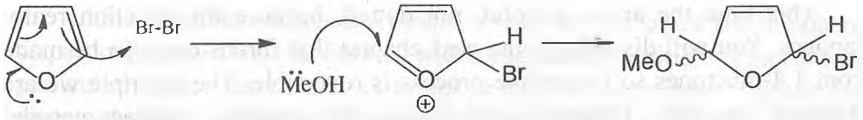
So far, thiophenes and furans look much the same as pyrrole but there are other reactions in which they behave quite differently and we shall now concentrate on those.

Electrophilic addition may be preferred to substitution with furan. Furan is not very aromatic and if there is the prospect of forming stable bonds such as C–O single bonds by addition, this may be preferred to substitution. A famous example is the reaction of furan with bromine in methanol. In nonhydroxylic solvents, polybromination occurs as expected, but in MeOH no bromine is added at all!

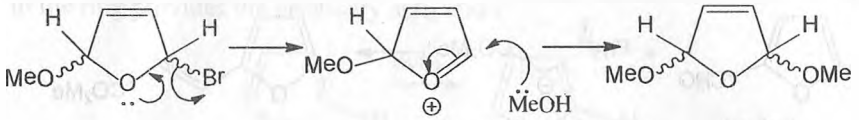


and other products

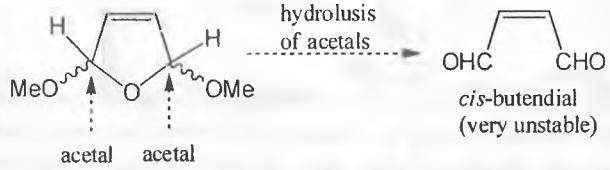
Bromination must start in the usual way, but a molecule of methanol captures the first formed cation in a 1,4-addition to furan.



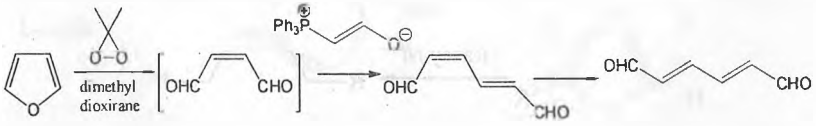
The bromine atom that was originally added is now pushed out by the furan oxygen atom to make a relatively stable conjugated oxonium ion, which adds a second molecule of methanol.



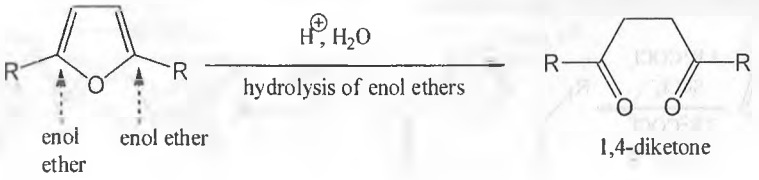
This product conceals an interesting molecule. At each side of the ring we have an acetal, and if we were to hydrolyse the acetals, we would have 'maleic dialdehyde' (*cis*-butenedial) – a molecule that is too unstable to be isolated. The furan derivative may be used in its place.



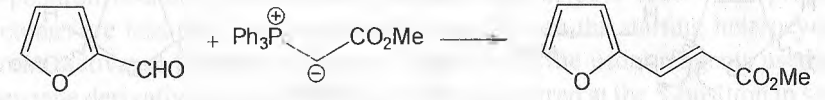
The same 1,4-dialdehyde can be made by oxidizing furan with the mild oxidizing agent dimethyldioxirane, which you met on p. 000. In this sequence, it is trapped in a Wittig reaction to give an *E, Z* diene, which is easily isomerized to *E, E*.



We can extend this idea of furan being the origin of 1,4-dicarbonyl compounds if we consider that furan is, in fact, an enol ether on both sides of the ring. If these enol ethers were hydrolysed we would get a 1,4-diketone.

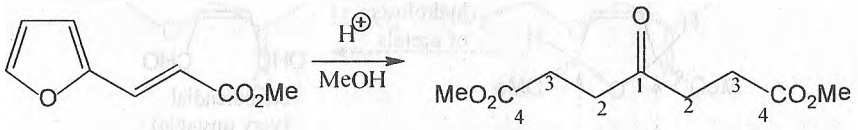


This time the arrow is solid, not dotted, because this reaction really happens. You will discover in the next chapter that furans can also be made from 1,4-diketones so this whole process is reversible. The example we are choosing has other features worth noting. The cheapest starting material containing a furan is furan-2-aldehyde or 'furfural', a by-product of breakfast cereal manufacture. Here it reacts in a typical Wittig process with a stabilized ylide.

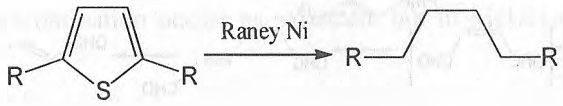


furfural stabilized phosphorus ylid

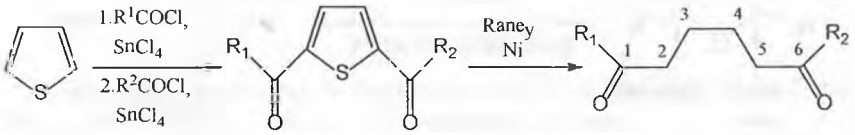
Now comes the interesting step: treatment of this furan with acidic methanol gives a white crystalline compound having two 1,4-dicarbonyl relationships.



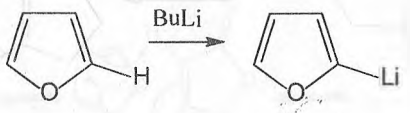
The thiophene ring can also be opened up, but in a very different way. Reductive removal of the sulfur atom with Raney nickel reduces not only the C–S bonds but also the double bonds in the ring and we are left with a saturated alkyl chain.

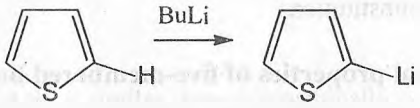


If the reduction follows two Friedel–Crafts reactions on thiophene the product is a 1,6-diketone instead of the 1,4-diketones from furan. Thiophene is well behaved in Friedel–Crafts acylations, and reaction occurs at the 2- and 5-positions unless these are blocked.

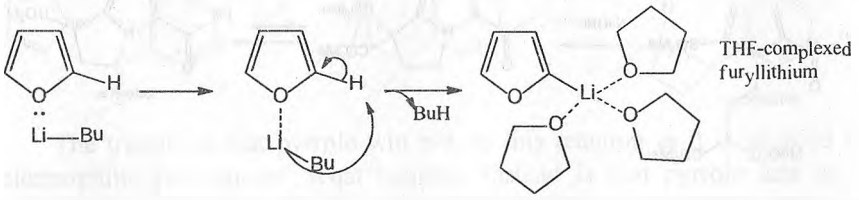


Lithiation of thiophenes and furans. A reaction that furans and thiophenes do particularly well and that fits well with these last two reactions is metallation, particularly lithiation, of a C–H group next to the heteroatom and we will discuss this next. Lithiation of benzene rings is carried out by lithium halogen (Br or I) exchange a method that works well for heterocycles too as we will see later with pyridine or by directed ('*ortho*') lithiation of a C–H group next to an activating group such as OMe. With thiophene and furan, the heteroatom in the ring provides the necessary activation.

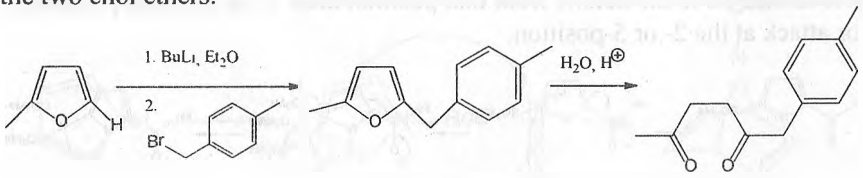




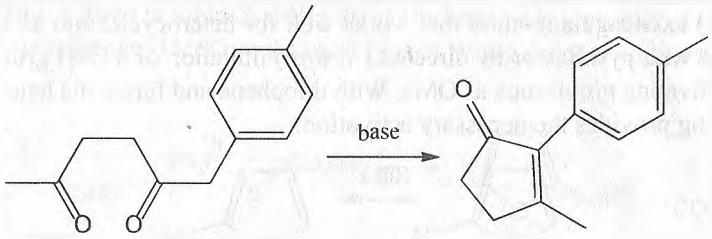
Activation is by coordination of O or S to Li followed by proton removal by the butyl group so that the by-product is gaseous butane. These lithium compounds have a carbon lithium s bond and are soluble in organic solvents with the coordination sphere of Li completed by THF molecules.



These lithium compounds are very reactive and will combine with most electrophiles–in this example the organolithium is alkylated by a benzylic halide. Treatment with aqueous acid gives the 1,4-diketone by hydrolysis of the two enol ethers.



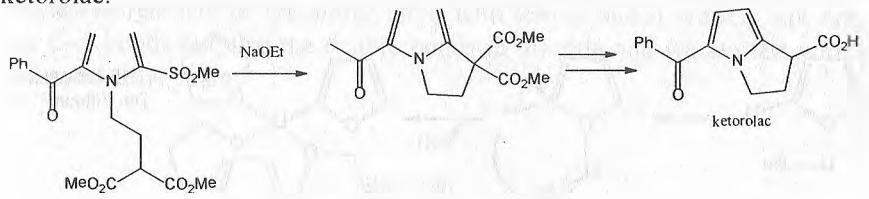
Treatment of this diketone with *anhydrous* acid would cause recyclization to the same furan but it can alternatively be cyclized in base by an intramolecular aldol reaction to give a cyclopentenone.



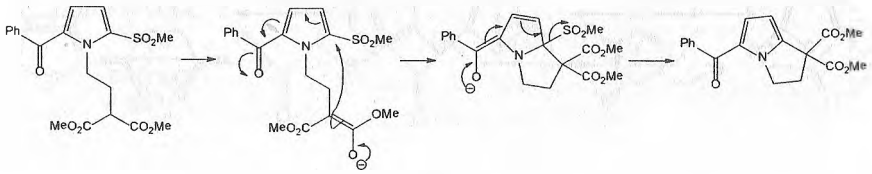
This completes our exploration of chemistry special to thiophene and furan and we now return to all three heterocycles (pyrrole in particular) and look at nucleophilic substitution.

7.7 Chemical properties of five-membered heterocycles

Nucleophilic substitution requires an activating group. Nucleophilic substitution is a relatively rare reaction with pyrrole, thiophene, or furan and requires an activating group such as nitro, carbonyl, or sulfonyl, just as it does with benzene. Here is an intramolecular example used to make the painkiller ketorolac.

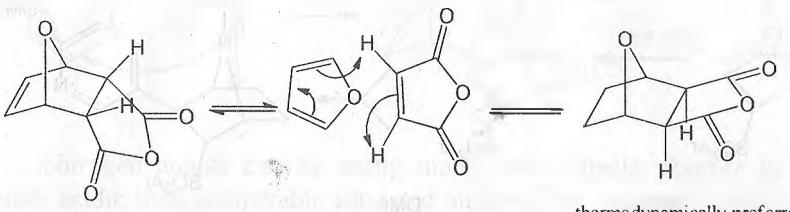


The nucleophile is a stable enolate and the leaving group is a sulfinate anion. An intermediate must be formed in which the negative charge is delocalized on to the carbonyl group on the ring. Attack occurs at the 2-position because the leaving group is there and because the negative charge can be delocalized on to the ketone from that position there is no inherent preference for attack at the 2- or 5-position.



So far, all of the reactions we have discussed have been variations on reactions of benzene. These heterocycles also do reactions totally unlike those of benzene and we are now going to explore two of them.

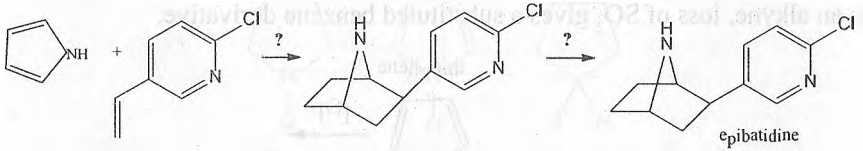
Five-membered heterocycles act as dienes in Diels–Alder reactions. Furan is particularly good at Diels–Alder reactions but it gives the thermodynamic product, the *exo* adduct, because with this aromatic diene the reaction is reversible.



kinetically preferred
endo adduct

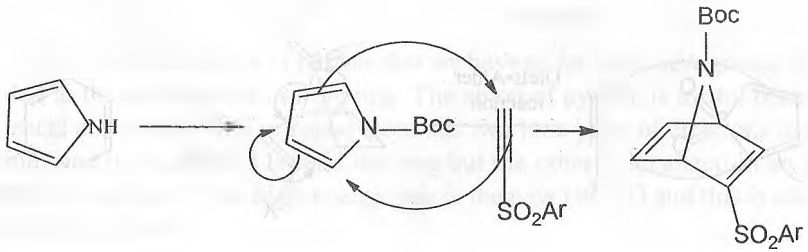
thermodynamically preferred
exo adduct

If pyrrole would do a similar thermodynamically controlled *exo* Diels–Alder reaction with a vinyl pyridine, a short route to the interesting analgesic epibatidine could be imagined, with just a simple reduction of the remaining alkene left to do. The reaction looks promising as the pyridine makes the dienophile electron-deficient and pyrrole is an electron-rich 'diene'.

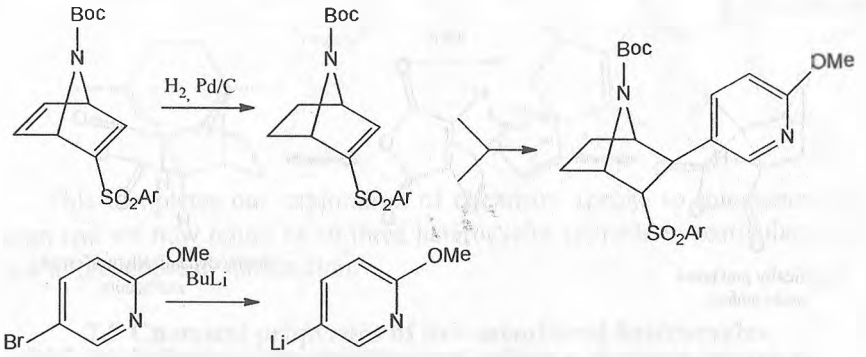


epibatidine

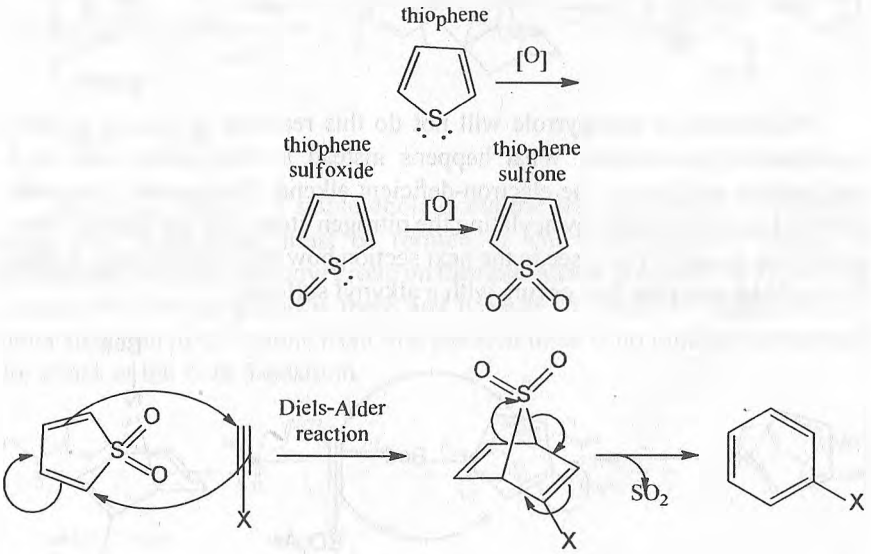
The trouble is that pyrrole will not do this reaction as it is so good at electrophilic substitution. What happens instead is that pyrrole acts as a nucleophile and attacks the electron-deficient alkene. The answer is to make pyrrole less nucleophilic by acylating the nitrogen atom with the famous 'Boc' protecting group. We will see in the next section how this may be done. A good Diels–Alder reaction then occurs with a alkynyl sulfone.



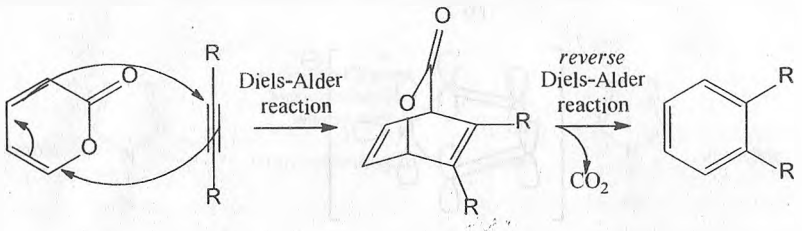
It is then possible to reduce the nonconjugated double bond chemoselectively and add a pyridine nucleophile to the vinyl sulfone. Notice in this step that a lithium derivative can be prepared from a bromopyridine. In general, heterocycles form lithium derivatives rather easily. The skeleton of epibatidine is now complete and you will find some further reactions from the rest of the synthesis in the problems at the end of this chapter.



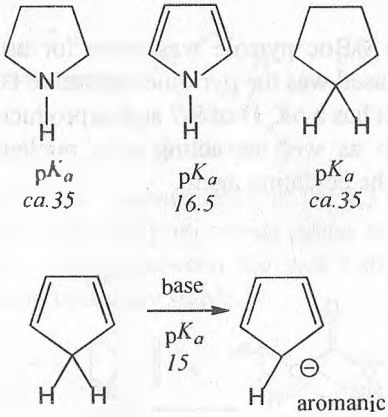
Aromaticity prevents thiophene taking part in Diels-Alder reactions, but oxidation to the sulfone destroys the aromaticity because both lone pairs become involved in bonds to oxygen. The sulfone is unstable and reacts with itself but will also do Diels-Alder reactions with dienophiles. If the dienophile is an alkyne, loss of SO_2 gives a substituted benzene derivative.



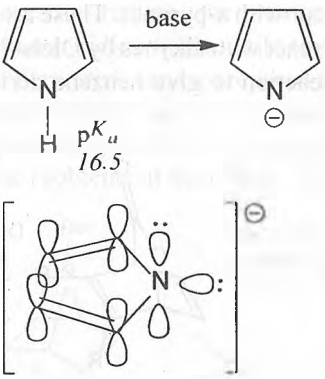
Similar reactions occur with a-pyrones. These are also rather unstable and barely aromatic and they react with alkynes by Diels–Alder reactions followed by reverse Diels-Alder reaction to give benzene derivatives with the loss of CO_2 rather than SO_2.



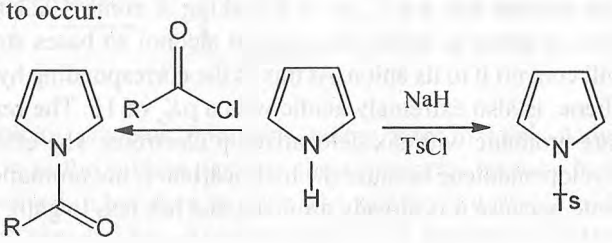
Nitrogen anions can be easily made from pyrrole. Pyrrole is much more acidic than comparable saturated amines. The pK_a of pyrrolidine is about 35, but pyrrole has a pK_a of 16.5 making it some 1023 times more acidic! Pyrrole is about as acidic as a typical alcohol so bases stronger than alkoxides will convert it to its anion. At this as the corresponding hydrocarbon, cyclopentadiene, is also extremely acidic with a pK_a of 15. The reason is that the anions are aromatic with six delocalized p electrons. The effect is much greater for cyclopentadiene because the hydrocarbon is not aromatic and much less for pyrrole because it is already aromatic and has less to gain.



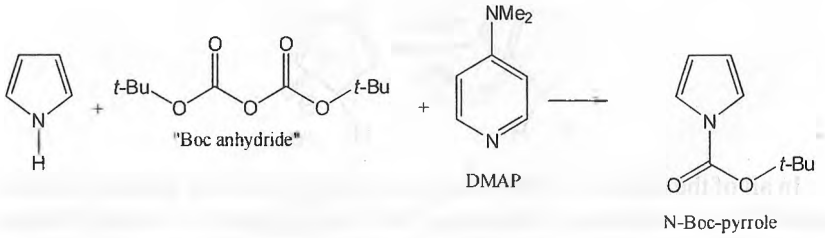
In all of the reactions of pyrrole that we have so far seen, new groups have added to the carbon atoms of the ring. The anion of pyrrole is useful because it reacts at nitrogen. The nitrogen atom has two lone pairs of electrons in the anion: one is delocalized around the ring but the other is localized in an sp2 orbital on nitrogen. This high-energy pair is the new HOMO and this is where the molecule reacts.



N-acylated derivatives in general can be made in this way. A commonly used base is sodium hydride (NaH) but weaker bases produce enough anion for reaction to occur.



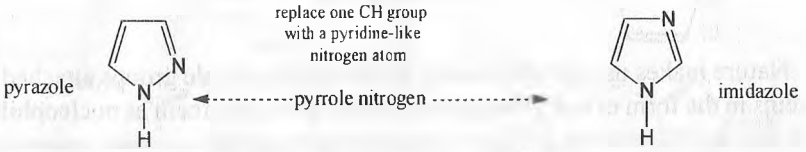
This is how the *N*-Boc pyrrole was made for use in the synthesis of epibatidine. The base used was the pyridine derivative DMAP, which you met earlier in the chapter. It has a pK_a H of 9.7 and so produces small, equilibrating amounts of the anion as well as acting as a nucleophilic catalyst. 'Boc anhydride' is used as the acylating agent.



Anion formation is important in the next main section of this chapter, which is about what happens when we insert more nitrogen atoms into the pyrrole ring.

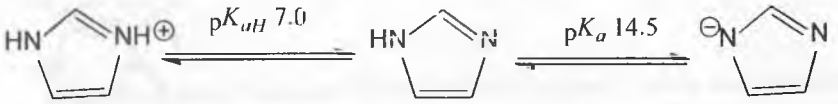
7.8 Five-membered rings with two or more nitrogen atoms

Imidazole. At the beginning of this chapter we imagined adding more nitrogen atoms to the pyrrole ring and noticed then that there were two compounds with two nitrogen atoms: pyrazole and imidazole.



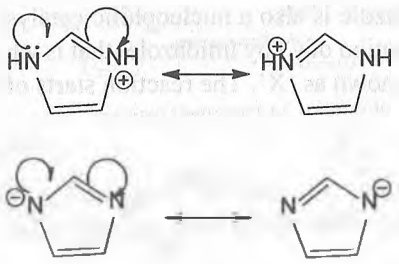
Only one nitrogen atom in a five-membered ring can contribute two electrons to the aromatic sextet. The other replaces a CH group, has no hydrogen, and is like the nitrogen atom in pyridine. The black nitrogens are the pyrrole-like nitrogens; the green ones are pyridine-like. The lone pairs on the black nitrogens are delocalized round the ring; those on the green nitrogens are localized in sp2 orbitals on nitrogen. We can expect these compounds to have properties intermediate between those of pyrrole and pyridine.

Imidazole is a stronger base than either pyrrole or pyridine it has a pK_aH of almost exactly 7, meaning that it is 50% protonated in neutral water. It is also more acidic than pyrrole.

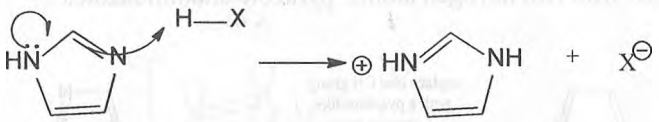


imidazole

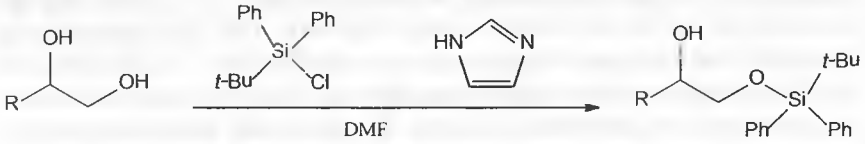
These curious results are a consequence of the 1,3 relationship between the two nitrogen atoms. Both the (protonated) cation and the (deprotonated) anion share the charge equally between the two nitrogen atoms they are perfectly symmetrical and unusually stable.



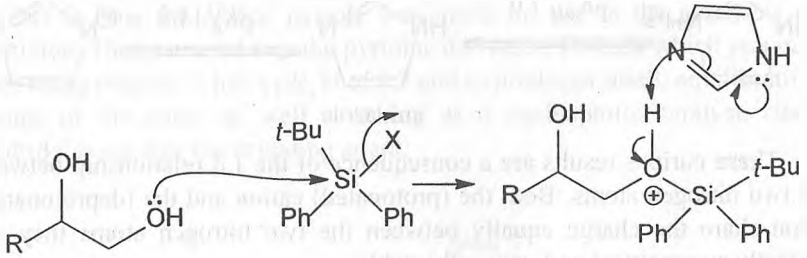
Another way to look at the basicity of imidazole would be to say that both nitrogen atoms can act at once on the proton being attacked. It has to be the pyridine-like nitrogen that actually captures the proton but the pyrrole nitrogen can help by using its delocalized electrons like this.



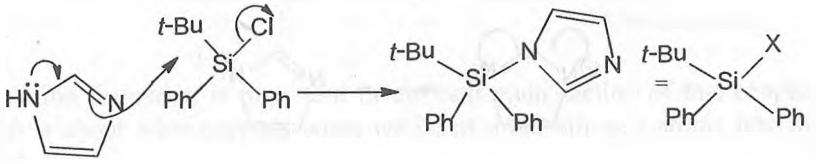
Nature makes use of this property by having imidazole groups attached to proteins in the form of the amino acid histidine and using them as nucleophilic, basic and acidic catalytic groups in enzyme reactions.We use this property in the same way when we add a silyl group to an alcohol. Imidazole is a popular catalyst for these reactions.



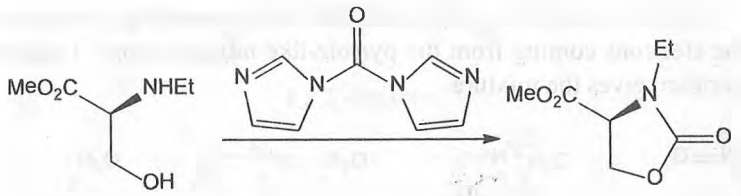
A weakly basic catalyst is needed here because we want to discriminate between the primary and secondary alcohols in the diol. Imidazole is too weak (pK_aH 7) to remove protons from an alcohol ($pK_a \sim 16$) but it can remove a proton after the OH group has attacked the silicon atom.



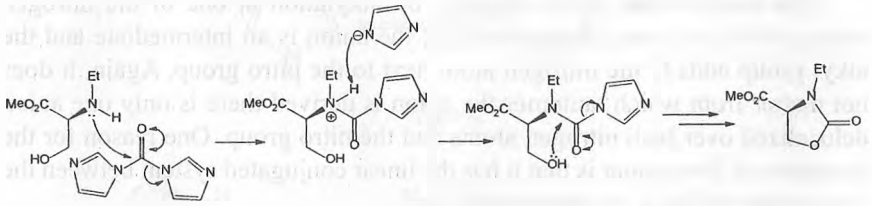
In fact, the imidazole is also a nucleophilic catalyst of this reaction, and the first step is substitution of Cl by imidazole–that is why the leaving group in the last scheme was shown as 'X'. The reaction starts off like this.



The same idea leads to the use of Carbonyl Dilmidazole (CDI) as a double electrophile when we want to link two nucleophiles together by a carbonyl group. Phosgene ($COCl_2$) has been used for this but it is appallingly toxic (it was used in the First World War as a poison gas with dreadful effects). CDI is safer and more controlled. In these reactions imidazole acts (twice) as a leaving group.



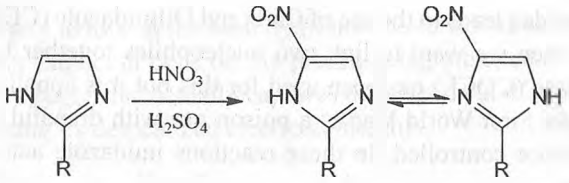
The amino group probably attacks first to displace one imidazole anion, which returns to deprotonate the ammonium salt. The alcohol can then attack intramolecularly displacing the second imidazole anion, which deprotonates the OH group in its turn. The other product is just two molecules of imidazole.



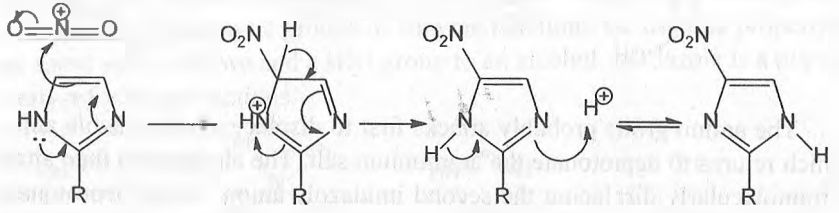
The relationship between the delocalized imidazole anion and imidazole itself is rather like that between an enolate anion and an enol. It will come as no surprise that imidazole tautomerizes rapidly at room temperature in solution. For the parent compound the two tautomers are the same, but with unsymmetrical imidazoles the tautomerism is more interesting.

two identical tautomers of imidazole

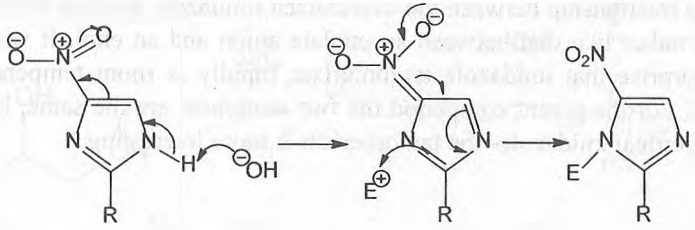
Imidazoles with a substituent between the two nitrogen atoms can be nitrated with the usual reagents and the product consists of a mixture of tautomers.



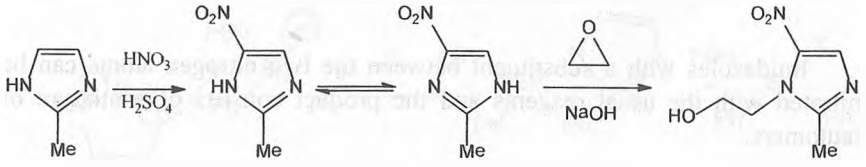
The initial nitration may occur at either of the remaining sites on the ring with the electrons coming from the pyrrole-like nitrogen atom. Tautomerism after nitration gives the mixture.



The tautomerism can be stopped by alkylation at one of the nitrogen atoms. If this is done in basic solution, the anion is an intermediate and the alkyl group adds to the nitro group. Again, it does not matter from which tautomer the anion is derived there is only one anion delocalized over both nitrogen atoms and the nitro group. One reason for the formation of this isomer is that it has the linear conjugated system between the pyrrole-like nitrogen and the nitro group.

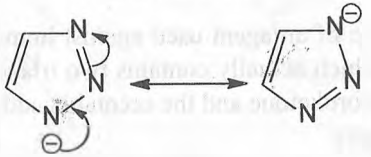


Important medicinal compounds are made in this way. The antiparasitic metronidazole comes from 2-methyl imidazole by nitration and alkylation with an epoxide in base.



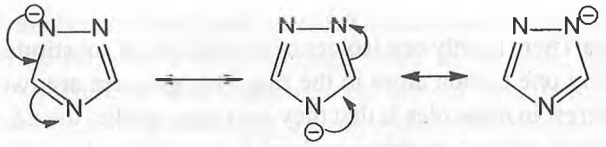
The triazoles.There are two triazoles, and each has one pyrrole-like nitrogen and two pyridine-like nitrogens. Both triazoles have the possibility of tautomerism (in 1,2,3-triazole the tautomers are identical) and both give rise to a single anion.

1,2,3,-triazole



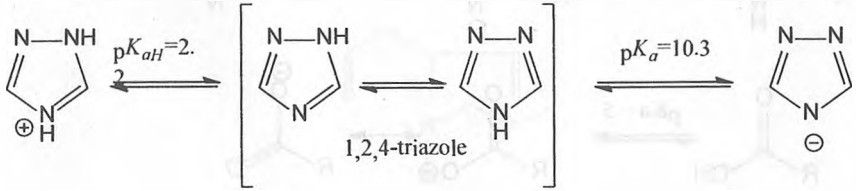
delocalized anion

1,2,4-triazole

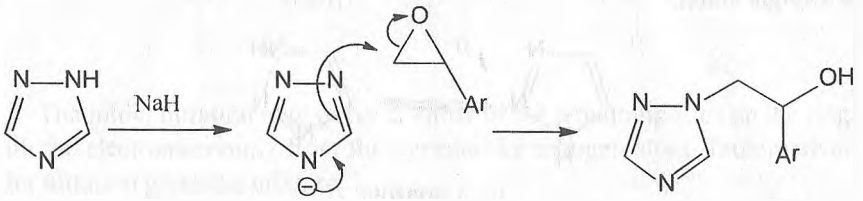


delocalized anion

The 1,2,4-triazole is more important because it is the basis of the best modern agricultural fungicides as well as drugs for fungal diseases in humans. The extra nitrogen atom makes it more like pyridine and so more weakly basic, but it increases its acidity so that the anion is now easy to make.

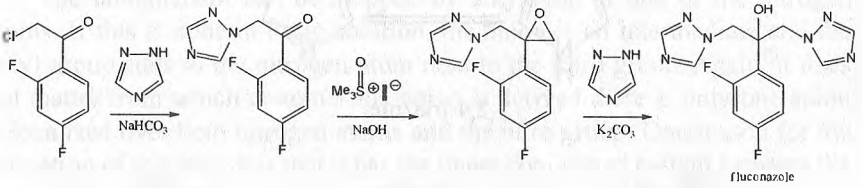


The fungicides are usually made by the addition of the triazole anion to an epoxide or other carbon electrophile. The anion normally reacts at one of the two linked nitrogen atoms (it does not matter which the product is the same).

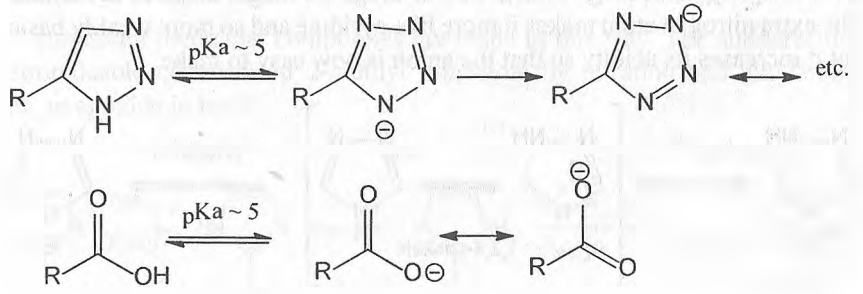


A modern example of an agent used against human fungal infections is Pfizer's fluconazole, which actually contains two triazoles. The first is added as the anion to an a-chloroketone and the second is added to an epoxide made with sulfur ylid chemistry.

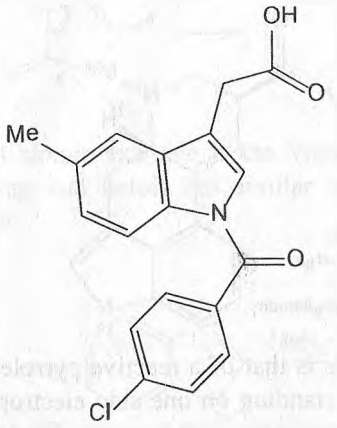
Note that weak bases were used to catalyse both of these reactions. Triazole is acidic enough for even $NaHCO_3$ to produce a small amount of the anion.



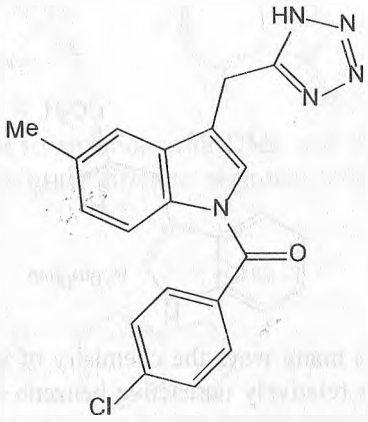
Tetrazole.There is only one isomer of tetrazole or of substituted tetrazoles, as there is only one carbon atom in the ring, though there are two tautomers. The main interest in tetrazoles is that they are rather acidic: the pK_a for the loss of the NH proton to form an anion is about 5, essentially the same as that of a carboxylic acid. The anion is delocalized over all four nitrogen atoms (as well as the one carbon atom), and four nitrogen atoms do the work of two oxygen atoms.



Because tetrazoles have similar acidities to those of carboxylic acids, they have been used in drugs as replacements for the CO_2H unit when the carboxylic acid has unsatisfactory properties for human medicine. A simple example is the anti-arthritis drug indomethacin whose carboxylic acid group may be replaced by a tetrazole with no loss of activity.



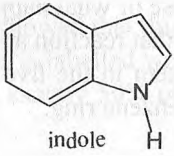
indomethacin



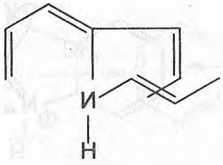
tetrazole substitute for indomethacin

7.9 Benzo-fused heterocycles

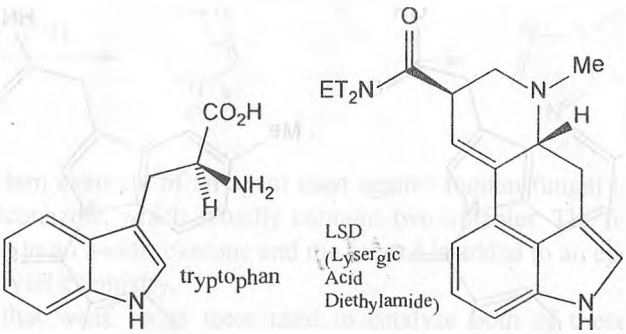
Indoles are benzo-fused pyrroles.Indomethacin and its tetrazole analogue contain pyrrole rings with benzene rings fused to the side. Such bicyclic heterocyclic structures are called indoles and are our next topic. Indole itself has a benzene ring and a pyrrole ring sharing one double bond, or, if you prefer to look at it this way, it is an aromatic system with 10 electrons eight from four double bonds and the lone pair from the nitrogen atom.



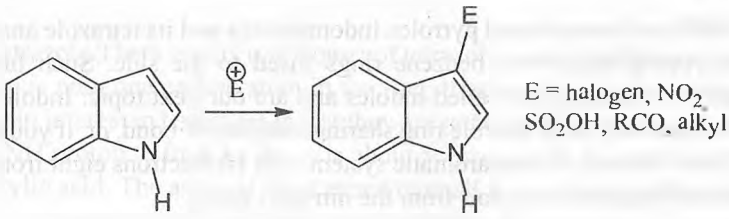
indole



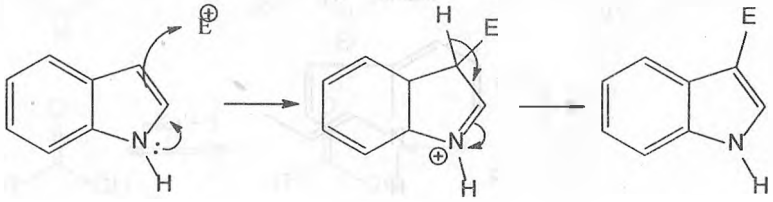
Indole is an important heterocyclic system because it is built into proteins in the form of the amino acid tryptophan, because it is the basis of important drugs such as indomethacin, and because it provides the skeleton of the indole alkaloids biologically active compounds from plants including strychnine and LSD.



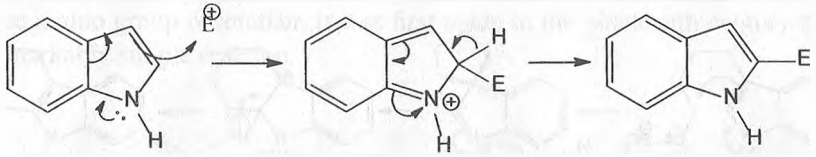
In many ways the chemistry of indole is that of a reactive pyrrole ring with a relatively unreactive benzene ring standing on one side electrophilic substitution almost always occurs on the pyrrole ring, for example. But indole and pyrrole differ in one important respect. In indole, electrophilic substitution is preferred in the 3-position with almost all reagents. Halogenation, nitration, sulfonation, Friedel-Crafts acylation, and alkylation all occur cleanly at that position.



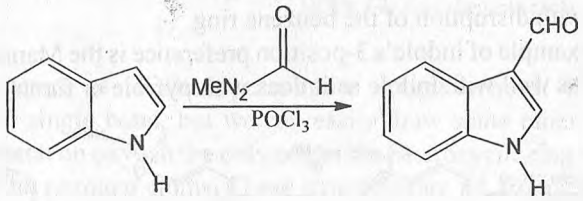
This is, of course, the reverse of what happens with pyrrole. Why should this be? A simple explanation is that reaction at the 3-position simply involves the rather isolated enamine system in the five-membered ring and does not disturb the aromaticity of the benzene ring.



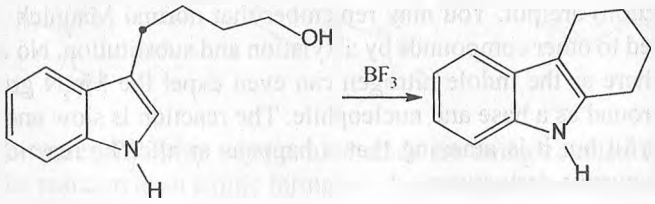
The positive charge in the intermediate is, of course, delocalized round the benzene ring, but it gets its main stabilization from the nitrogen atom. It is not possible to get reaction in the 2-position without seriously disturbing the aromaticity of the benzene ring.



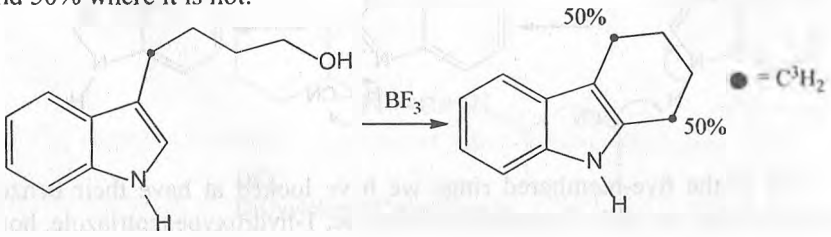
A simple example is the Vilsmeier formylation with DMF and $POCl_3$ showing that indole has similar reactivity, if different regioselectivity, to pyrrole.



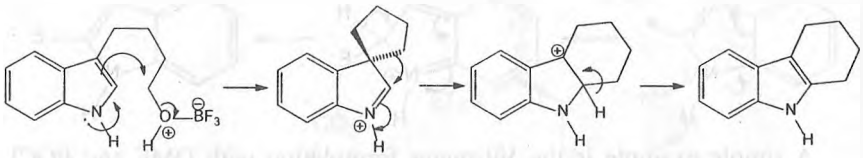
If the 3-position is blocked, reaction occurs at the 2-position and this at first seems to suggest that it is all right after all to take the electrons the 'wrong way' round the five-membered ring. This intramolecular Friedel-Crafts alkylation is an example.



An ingenious experiment showed that this cyclization is not as simple as it seems. If the starting material is labelled with tritium (radioactive 3H) next to the ring, the product shows exactly 50% of the label where it is expected and 50% where it is not.

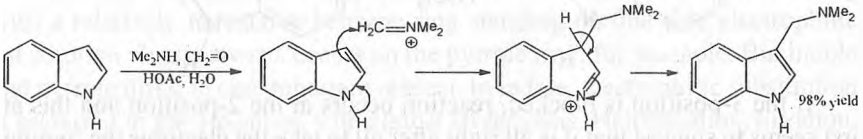


To give this result, the reaction must have a symmetrical intermediate and the obvious candidate arises from attack at the 3-position. The product is formed from the intermediate *spiro* compound, which has the five-membered ring at right angles to the indole ring–each CH_2 group has an exactly equal chance of migrating.

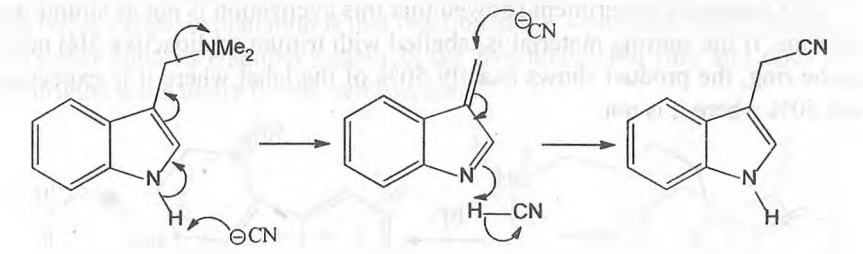


The migration is a pinacol like rearrangement. It is now thought that most substitutions in the 2-position go by this migration route but that some go by direct attack with disruption of the benzene ring.

A good example of indole's 3-position preference is the Mannich reaction, which works as well with indole as it does with pyrrole or furan.



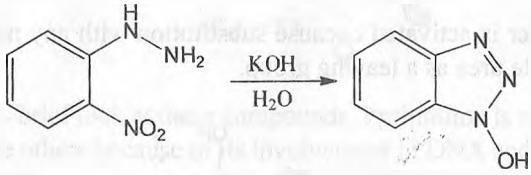
The electron-donating power of the indole and pyrrole nitrogens is never better demonstrated than in the use to which these Mannich bases (the products of the reaction) are put. You may remember that normal Mannich bases can be converted to other compounds by alkylation and substitution. No alkylation is needed here as the indole nitrogen can even expel the Me_2N group when NaCN is around as a base and nucleophile. The reaction is slow and the yield not wonderful but it is amazing that it happens at all. The reaction is even easier with pyrrole derivatives.



All of the five-membered rings we have looked at have their benzo-derivatives but we will concentrate on just one, 1-hydroxybenzotriazole, both

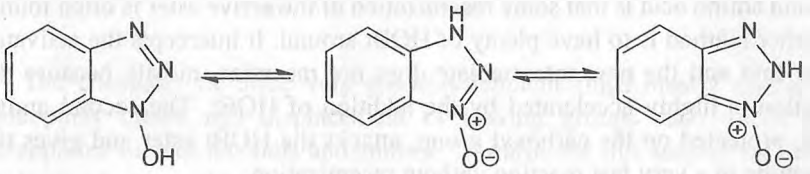
because it is an important compound and because we have said little about simple 1,2,3-triazoles.

HOBt is an important reagent in peptide synthesis. 1-Hydroxybenzotriazole (HOBt) is a friend in need in the lives of biochemists. It is added to many reactions where an activated ester of one amino acid is combined with the free amino group of another. It was first made in the nineteenth century by a remarkably simple reaction.

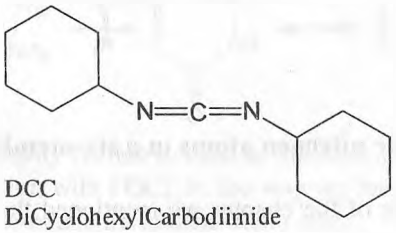


HOBt, 1-hydroxybenzotriazole

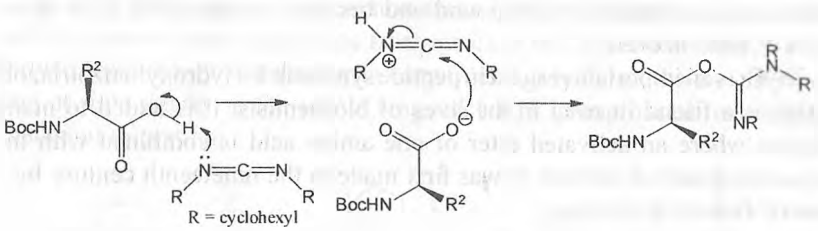
The structure of HOBt appears quite straightforward, except for the unstable N-O single bond, but we can easily draw some other tautomers in which the proton on oxygen the only one in the heterocyclic ring can be placed on some of the nitrogen atoms. These structures are all aromatic, the second and third are nitrones, and the third structure looks less good than the other two.



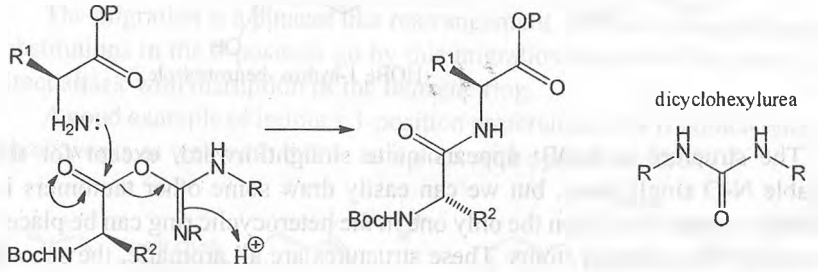
HOBt comes into play when amino acids are being coupled together in the lab. The reaction is an amide formation. It even more common to form the activated ester in the coupling reaction, using a coupling reagent, the most common being 'DCC', dicyclohexylcarbodiimide. DCC reacts with carboxylic acids like this.



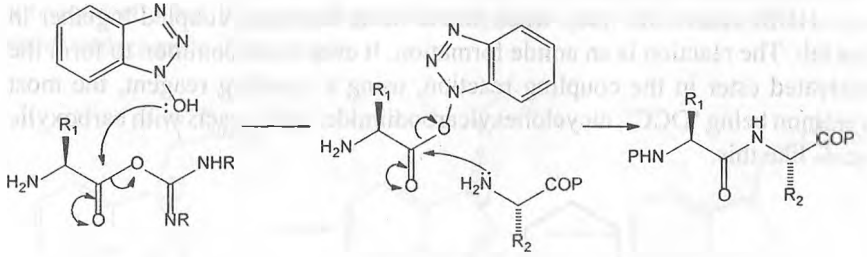
DCC
DiCyclohexylCarbodiimide



The product ester is activated because substitution with any nucleophile expels this very stable urea as a leaving group.



The problem with attacking this ester directly with the amino group of the second amino acid is that some racemization of the active ester is often found. A better method is to have plenty of HOBt around. It intercepts the activated ester first and the new intermediate does not racemize, mostly because the reaction is highly accelerated by the addition of HOBt. The second amino acid, protected on the carboxyl group, attacks the HOBt ester and gives the dipeptide in a very fast reaction without racemization.

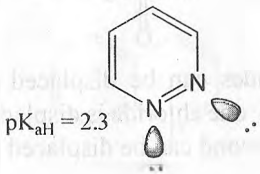


7.10 More nitrogen atoms in a six-membered ring

At the beginning of the chapter we mentioned the three six-membered

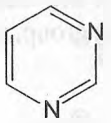
aromatic heterocycles with two nitrogen atoms pyridazine, pyrimidine, and pyrazine. In these compounds both nitrogen atoms must be of the pyridine sort, with lone pair electrons not delocalized round the ring.

pyridazine



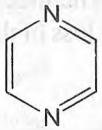
Here is brief look at these compounds. Pyrimidine is more important than either of the others because of its involvement in DNA and RNA you will find this in. All three compounds are very weak bases hardly basic at all in fact. Pyridazine is slightly more basic than the other two because the two adjacent lone pairs repel each other and make the molecule more nucleophilic.

pyrimidine



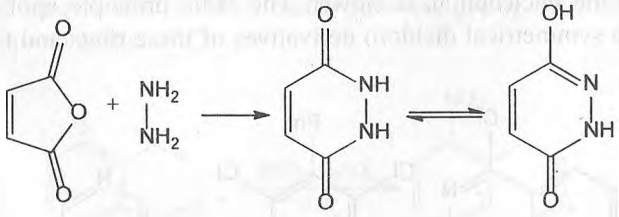
$pK_{aH} = 1.3$

pyrazine

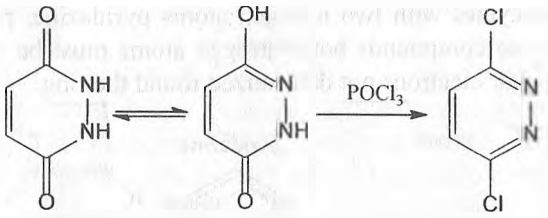


$pK_{aH} = 0.65$

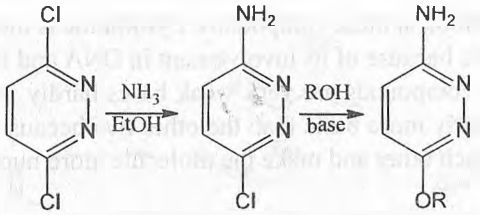
The chemistry of these very electron-deficient rings mostly concerns nucleophilic attack and displacement of leaving groups such as Cl by nucleophiles such as alcohols and amines. To introduce this subject we need to take one heterocyclic synthesis at this point, though these are properly the subject of the next chapter. The compound 'maleic hydrazide' has been known for some time because it is easily formed when hydrazine is acylated twice by maleic anhydride.



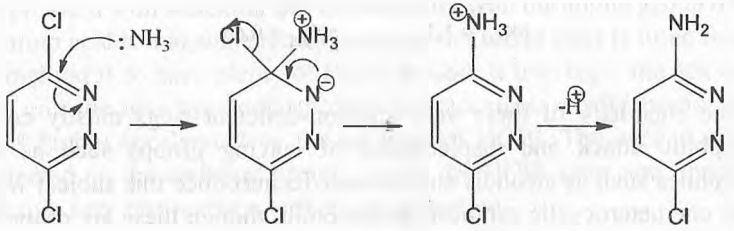
The compound actually prefers to exist as the second tautomer, which is 'more aromatic'. Reaction with $POCl_3$ in the way we have seen for pyridine gives the undoubtedly aromatic pyridazine dichloride.



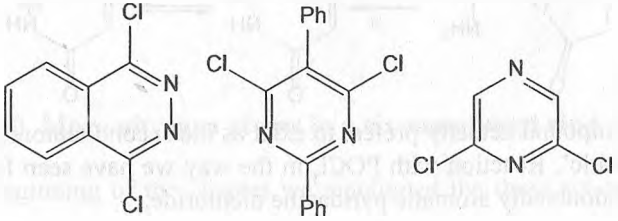
Each of these chlorides can be displaced in turn with an oxygen or nitrogen nucleophile. Only one chloride is displaced in the first reaction, if that is required, and then the second can be displaced with a different nucleophile.



How is this possible? The mechanism of the reactions is addition to the pyridazine ring followed by loss of the leaving group, so the first reaction must go like this.

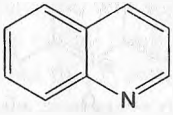


When the second nucleophile attacks it is forced to attack a less electrophilic ring. An electron withdrawing group (Cl) has been replaced by a strongly electron-donating group (NH_2) so the ratedetermining step, the addition of the nucleophile, is slower. The same principle applies to other easily made symmetrical dichloro derivatives of these rings and their benzo-analogues.



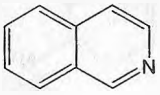
7.11 Fusing rings to pyridines: quinolines and isoquinolines

A benzene ring can be fused on to the pyridine ring in two ways giving the important heterocycles quinoline, with the nitrogen atom next to the benzene ring, and isoquinoline, with the nitrogen atom in the other possible position.

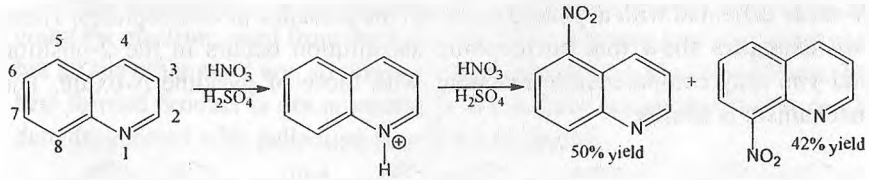


quinoline

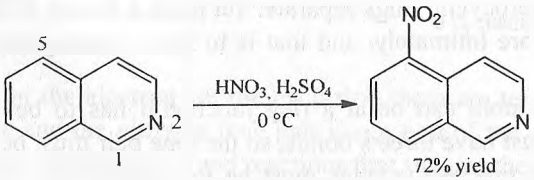
Quinoline forms part of quinine (structure at the head of this chapter) and isoquinoline forms the central skeleton of the isoquinoline alkaloids. Electrophilic substitution favours the benzene ring and nucleophilic substitution favours the pyridine ring. So nitration of quinoline gives two products the 5- nitroquinolines and the 8-nitroquinolines in about equal quantities (though you will realize that the reaction really occurs on protonated quinoline.



isoquinoline

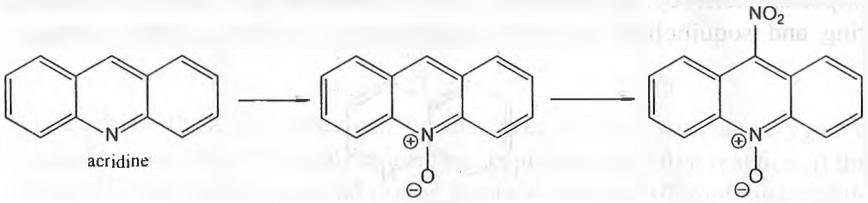


This is obviously rather unsatisfactory but nitration is actually one of the better behaved reactions. Chlorination gives ten products (at least!), of which no fewer than five are chlorinated quinolines of various structures. The nitration of isoquinoline is rather better behaved, giving 72% of one isomer (5-nitroisoquinoline) at 0 °C.

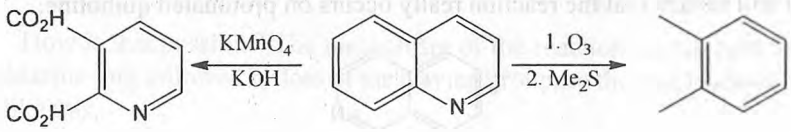


To get reaction on the pyridine ring, the *N*-oxide can be used as with pyridine itself. A good example is acridine, with two benzene rings, which

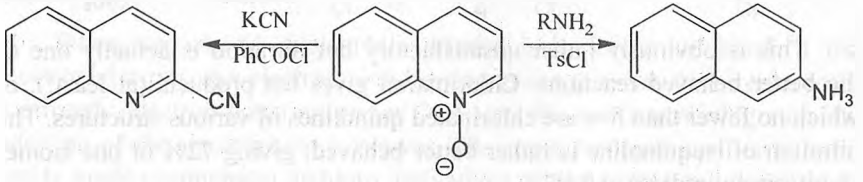
gives four nitration products, all on the benzene rings. Its *N*-oxide, on the other hand, gives just one product in good yield nitration takes place at the only remaining position on the pyridine ring.



In general, these reactions are of not much use and most substituents are put into quinolines during ring synthesis from simple precursors as we will explain in the next chapter. There are a couple of quinoline reactions that are unusual and interesting. Vigorous oxidation goes for the more electronrich ring, the benzene ring, and destroys it leaving pyridine rings with carbonyl groups in the 2- and 3-positions.

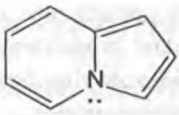


A particularly interesting nucleophilic substitution occurs when quinoline *N*-oxide is treated with acylating agents in the presence of nucleophiles. These two examples show that nucleophilic substitution occurs in the 2-position and you may compare these reactions with those of pyridine *N*-oxide. The mechanism is similar.



In considering quinolines and indoles with their fused rings we kept the benzene and heterocyclic rings separate. Yet there is a way in which they can be combined more intimately, and that is to have a nitrogen atom at a ring junction.

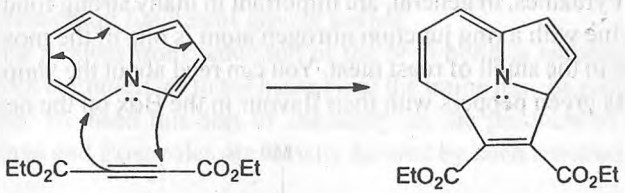
A nitrogen atom can be at a ring junction.It has to be a pyrrole-type nitrogen as it must have three s bonds, so the lone pair must be in a p orbital. This means that one of the rings must be five-membered and the simplest member of this interesting class is called indolizine it has pyridine and pyrrole rings fused together along a C–N bond.



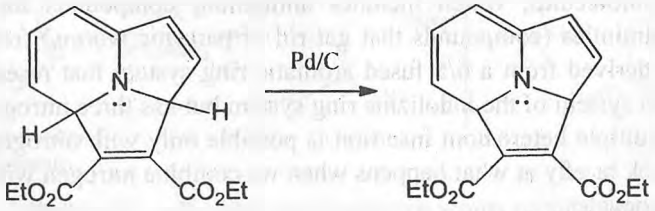
indolizine

If you examine this structure you will see that there is definitely a pyrrole ring but that the pyridine ring is not all there. Of course, the lone pair and the p electrons are all delocalized but this system, unlike indole and quinoline, is much better regarded as a ten-electron outer ring than as two six-electron rings joined together.

Indolizine reacts with electrophiles on the five-membered rings by substitution reactions as expected but it has one special reaction that leads dramatically to a more complex aromatic system. It does a cycloaddition with diethyl acetylenedicarboxylate to give a tricyclic molecule.



The dienophile is the usual sort of unsaturated carbonyl compound but count the electrons used from the indolizine. The nitrogen lone pair is not used but all the other eight are, so this is a most unusual [2 + 8] cycloaddition. The first formed product is not aromatic (it is not fully conjugated) but it can be dehydrogenated with palladium to make a cyclazine.

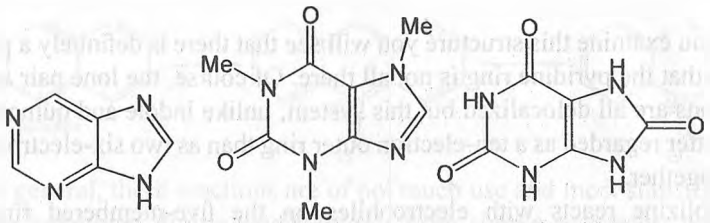


a cyclazine

Now count the electrons in the cyclazine there are ten electrons round the outer edge and the nitrogen lone pair is not part of the aromatic system. Cyclazines have NMR spectra and reactions that suggest they are aromatic.

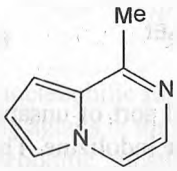
Fused rings with more than one nitrogen.It is easily possible to continue to insert nitrogen atoms into fused ring systems and some important compounds

belong to these groups. Simple purines play an important part in our lives. Coffee and tea owe their stimulant properties to caffeine, a simple trimethyl purine derivative. It has an imidazole ring fused to a pyrimidine ring and is aromatic in spite of the two carbonyl groups.



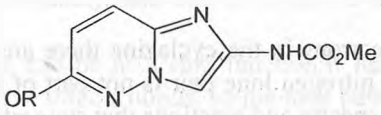
purine caffeine uric acid

Other fused heterocycles have very attractive flavour and odour properties. Pyrazines, in general, are important in many strong food flavours: a fused pyrazine with a ring junction nitrogen atom is one of the most important components in the smell of roast meat. You can read about the simple pyrazine that provides green peppers with their flavour in the Box on the next page.



smell of roast meat

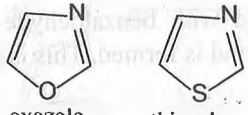
Finally, the compounds in the margin form a medicinally important group of molecules, which includes antitumour compounds for humans and anthelmintics (compounds that get rid of parasitic worms) for animals. They are derived from a 6/5 fused aromatic ring system that resembles the tenelectron system of the indolizine ring system but has three nitrogen atoms. All this multiple heteroatom insertion is possible only with nitrogen and we need to look briefly at what happens when we combine nitrogen with oxygen or in heterocycles.



useful medicinal compounds

7.12 Nitrogen and oxygen heterocycles

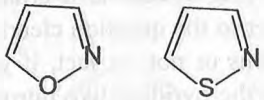
A neutral oxygen or sulfur atom can have only two bonds and so it can never be like the nitrogen atom in pyridine it can only be like the nitrogen atom in pyrrole. We can put as many pyridine-like nitrogens as we like in an aromatic ring, but never more than one pyrrole-like nitrogen. Similarly, we can put only one oxygen or sulfur atom in an aromatic ring. The simplest examples are oxazoles and thiazoles and their less stable isomers.



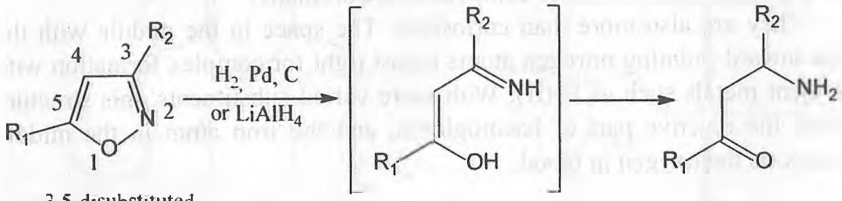
oxazole thiazole

The instability of the 'iso-' compounds comes from the weak O–N or S–N bond. These bonds can be cleaved by reducing agents, which then usually reduce the remaining functional groups further.

The first product from reduction of the N-O bond is an unstable imino-enol. The enol tautomerizes to the ketone and the imine may be reduced further to the amine. We used this sort of chemistry on the products of 1,3-dipolar cycloadditions and isoxazoles are usually formed by such reactions.

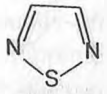


isoxazole isothiazole

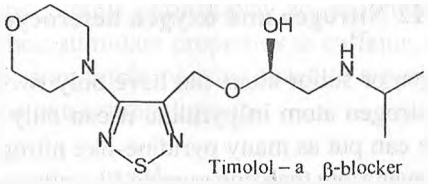


3,5-disubstituted isoxazole

Such heterocycles with even more nitrogen atoms exist but are relatively unimportant and we shall mention just one, the 1,2,5-thiadiazole, because it is part of a useful drug, timolol.



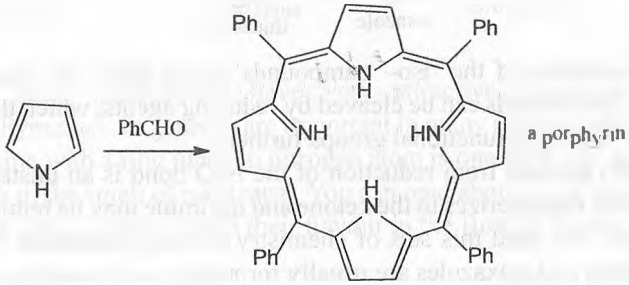
1,2,5-thiadiazole



Timolol – a β-blocker

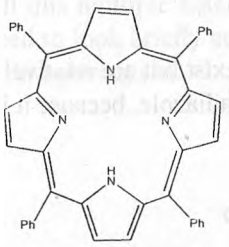
7.13 Polyaromatic heterocycles

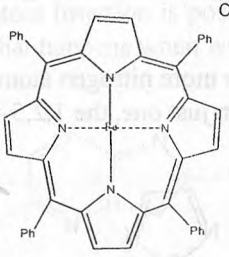
If pyrrole is combined with benzaldehyde a good yield of a highly coloured crystalline compound is formed. This is a porphyrin.

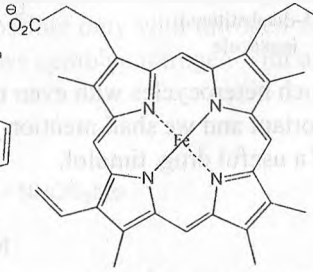


Now, what about this ring system is it aromatic? It's certainly highly delocalized and your answer to the question clearly depends on whether you include the nitrogen electrons or not. In fact, if you ignore the pyrrole-like nitrogen atoms but include the pyridine-like nitrogens and weave round the periphery, you have nine double bonds and hence 18 electrons a $4n + 2$ number. Most people agree that these compounds are aromatic.

They are also more than curiosities. The space in the middle with the four inward-pointing nitrogen atoms is just right for complex formation with divalent metals such as Fe(II). With more varied substituents, this structure forms the reactive part of haemoglobin, and the iron atom in the middle transports the oxygen in blood.

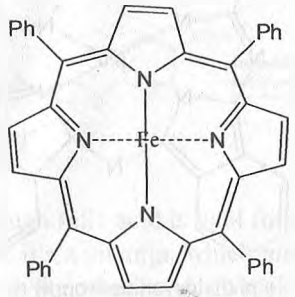

the 18 α-electron system of a porphyrin


an iron–porphyrin complex

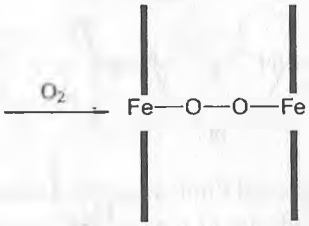


the iron porphyrin in haemoglobin

Iron prefers to be octahedral with six bonds around it and in one of these spare places in haemoglobin that is occupied by oxygen. If you try and make an oxygen complex of the simple porphyrin with four phenyl groups around the edge you get a sandwich dimer that oxidizes itself.



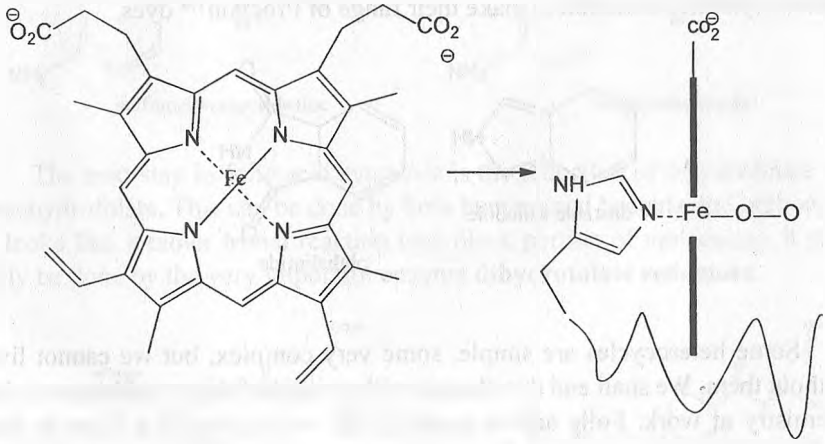
an iron–porphyrin complex



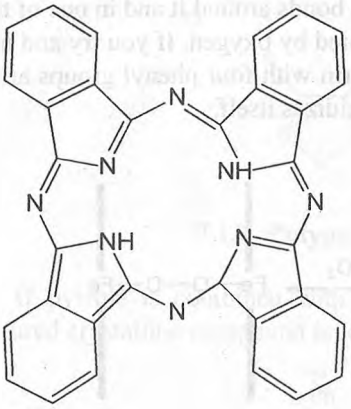
porphyrin rings side-on

The porphyrin in blood avoids this problem by having another heterocycle to hand.

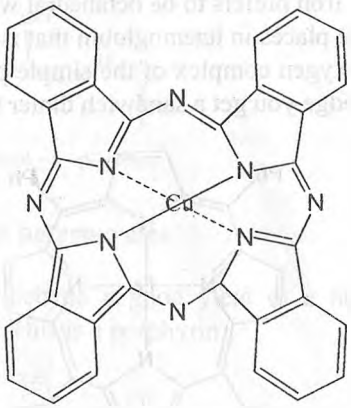
Haemoglobin consists of the flat porphyrin bound to a protein by coordination between an imidazole in the protein and the iron atom. This leaves one face free to bind oxygen and makes the molecule far too big to dimerize.



Haem–metal complexes are strongly coloured the iron complex is literally blood red. Some related compounds provide the familiar blue and green pigments used to colour plastic shopping bags. These are the phthalocyanine –metal complexes, which provide intense pigments in these ranges. The basic ring system resembles a porphyrin.

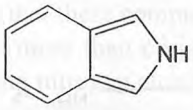


a simple phthalocyanine

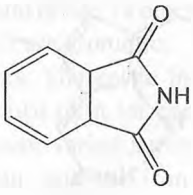


a phthalocyanine–copper complex

The differences are the four extra nitrogen atoms between the rings and the fused benzene rings. These compounds are derivatives of phthalimide, an isoindole derivative that has a nonaromatic five-membered ring. The metal most commonly used with phthalocyanines is Cu(II), and the range of colours is achieved by halogenating the benzene rings. The biggest producer is ICI at Grangemouth in Scotland where they do the halogenation and the phthalocyanine formation to make their range of Procyon™ dyes.

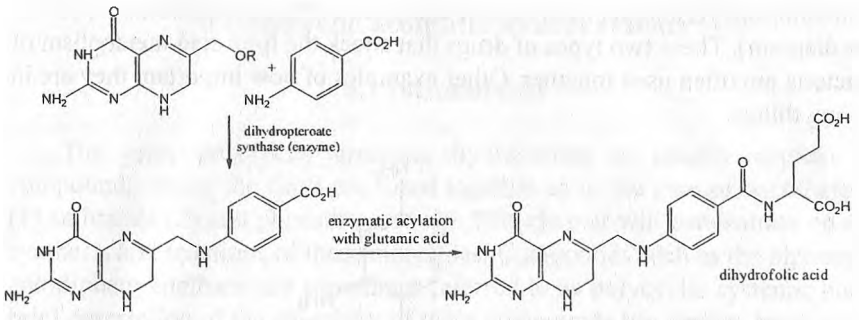


unstable isoindole

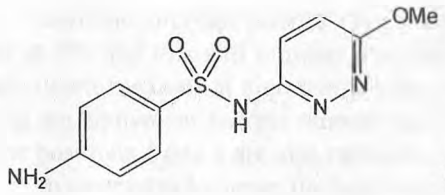


phthalimide

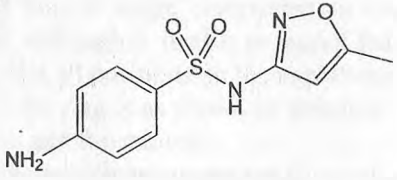
Some heterocycles are simple, some very complex, but we cannot live without them. We shall end this chapter with a wonderful story of heterocyclic chemistry at work. Folic acid is much in the news today as a vitamin that is particularly important for pregnant mothers, but that is involved in the metabolism of all living things. Folic acid is built up in nature from three pieces: a heterocyclic starting material (red), *p*-aminobenzoic acid (black) and the amino acid glutamic acid (brown). Here you see the precursor, dihydrofolic acid.



Although folic acid is vital for human health, we don't have the enzymes to make it: it's a vitamin, which means we must take it in our diet or we die. Bacteria, on the other hand, do make folic acid. This is very useful, because it means that if we inhibit the enzymes of folic acid synthesis we can kill bacteria but we cannot possibly harm ourselves as we don't have those enzymes. The sulfa drugs, such as sulfamethoxypyridazine or sulfamethoxazole, imitate *p*-aminobenzoic acid and inhibit the enzyme dihydropteroate synthase. Each has a new heterocyclic system added to the sulfonamide part of the drug.

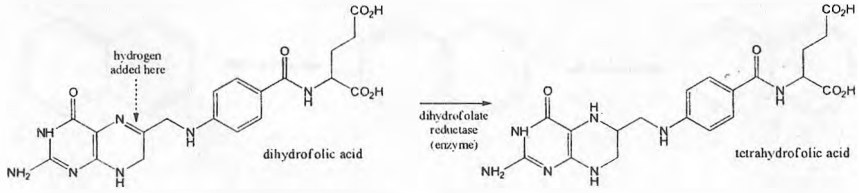


sulfamethoxypyridazine



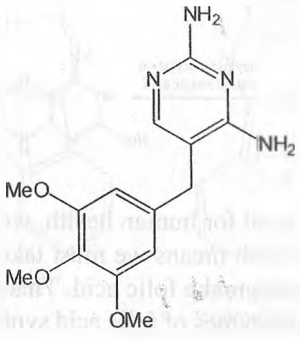
sulfamethoxazole

The next step in folic acid synthesis is the reduction of dihydrofolate to tetrahydrofolate. This can be done by both humans and bacteria and, although it looks like a rather trivial reaction (see black portion of molecules), it can only be done by the very important enzyme **dihydrofolate reductase**.



Though both bacteria and humans have this enzyme, the bacterial version is different enough for us to attack it with specific drugs. An example is

trimethoprim yet another heterocyclic compound with a pyrimidine core (black on diagram). These two types of drugs that attack the folic acid metabolism of bacteria are often used together. Other examples of how important they are in living things.

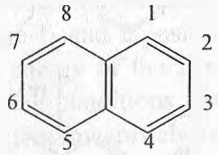


trimethoprim

8 Polycyclic aromatic hydrocarbons

8.1 Introduction

The term polycyclic aromatic hydrocarbon is usually applied to compounds where the rings are fused together as in the case of naphthalene (1),anthracite (2) and phenatherene (3). This chapter will concentrate on the synthesis and reactions of these molecules. Compounds such as the biphenyls and diphenylmethane are sometimes referred to as polycyclic systems, but a brief description of the chemistry of these compounds has already been given in.



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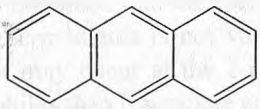
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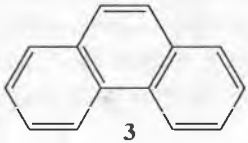
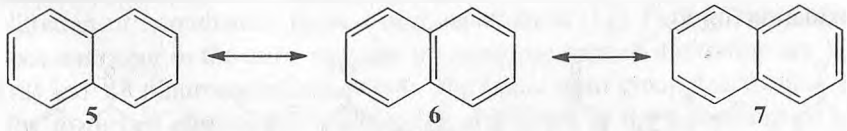

3

8.2 Chemistry of naphthalene

Introduction.Naphthalene (1) is the largest single component of coal tar at 9% and this still remains a source, although it is also produced from petroleum fractions at high temperature. Not all positions on the naphthalene ring are equivalent and the numbering of the ring is as shown in structure 1. The positions 1 and 2 are also called the *a*- and P-positions.

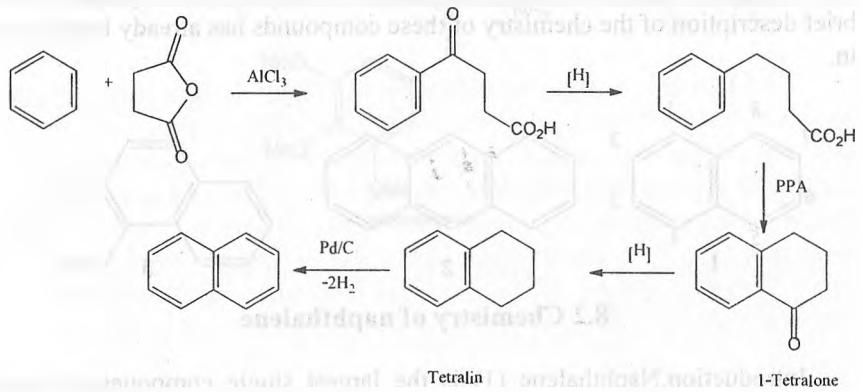
In contrast to benzene, the bond lengths in naphthalene are not all equal, as illustrated in 4. The resonance energy of naphthalene is 255 kJ mol^{-1} which is higher than, though not twice that of, benzene (151 kJ mol^{-1}). In the canonical forms 5 and 7 that contribute to the valence bond structure for naphthalene, only one of the two rings is fully benzenoid. Naphthalene is less aromatic than benzene, which accounts for its higher reactivity towards electrophilic attack compared with benzene.


5 6 7

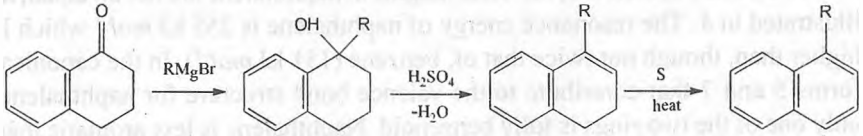
Synthesis of Naphthalene.There are two main synthetic routes to naphthalene: the Haworth synthesis and a Diels-Alder approach. In the Haworth synthesis, benzene is reacted under Friedel-Crafts conditions with succinic anhydride (butanedioic anhydride) to produce 4-oxo-4-phenylbutanoic acid,

which is reduced with either amalgamated zinc and HCl (the Clemmensen reduction) or hydrazine, ethane- 1,2-diol and potassium hydroxide (the Wolff-Kischner reaction) to 4-phenylbutanoic acid. Ring closure is achieved by heating in polyphosphoric acid (PPA). The product is 1-tetralone and reduction of the carbonyl group then gives 1,2,3,4-tetrahydronaphthalene (tetralin). Aromatization is achieved by dehydrogenation over a palladium catalyst.

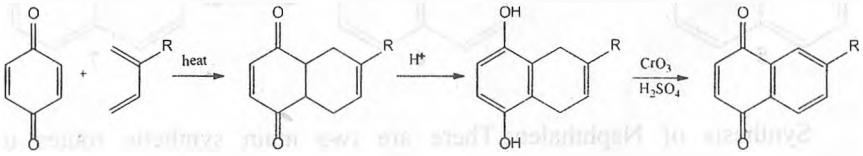
This route to naphthalenes is versatile. Alkyl and aryl substituents can be introduced into the 1-position through reaction of 1-tetralone with a



Grignard reagent, followed by dehydration and aromatization. The use of substituted benzenes in the first stage of the sequence enables variously substituted derivatives of naphthalene to be obtained. Of course, the substituents should not interfere with the Friedel-Crafts reaction with succinic anhydride.

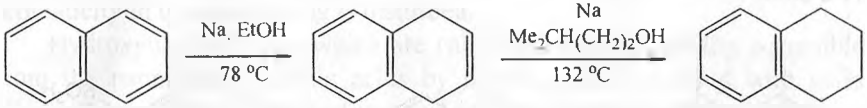


The Diels-Adler reaction of benzo- 1,4-quinone with 1,3-dienes produces adducts that may be converted to naphtho- 1,4-quinones via enolization and oxidation (fig 5).



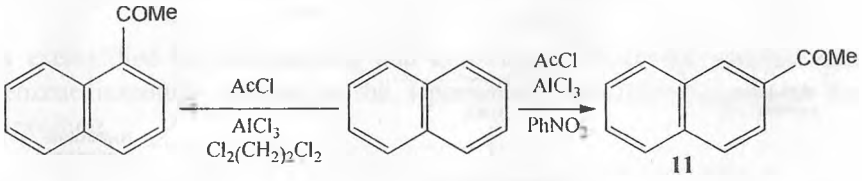
Reactions of Naphthalene. Naphthalene is readily hydrogenated to tetrahydronaphthalene, which is used as a paint solvent, but further reduction

to produce decahydronaphthalene (decalin) requires forcing conditions (Raney nickel catalyst at 200°C:). The first step in the reduction of naphthalene can be achieved by reaction with sodium in boiling ethanol, which produces 1,4-dihydronaphthalene. The tetrahydro compound is formed in the higher-boiling 3-methylbutanol (isopentyl alcohol).



Electrophilic substitution in naphthalene was discussed, when consideration of the stability of the cationic intermediates arising from attack at the 1- and 2-positions indicated that the former is favoured. Nevertheless, the energy of the two intermediates is not vastly different and under more forcing conditions attack may occur at the 2-position. Naphthalene is more reactive towards electrophiles than is benzene and hence milder conditions are generally employed.

In the case of Friedel-Crafts reactions, mild conditions are essential, since binaphthyls are formed under vigorous conditions. Reaction with acetyl chloride in tetrachloroethane in the presence of aluminium chloride gives 1 -acetylnaphthalene although in nitrobenzene the 2-acetyl derivative 11 is the major product. Attack at the less hindered 2-position is preferred in the latter case because of the larger size of the solvated acylating species.

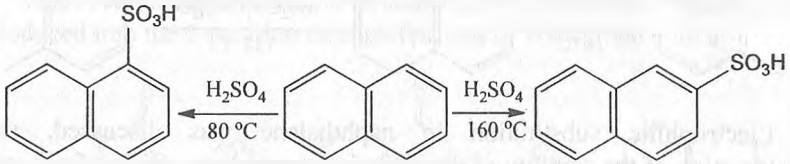


11

Naphthalene is also easily halogenated. For example, bromination in the presence of aluminium chloride results in a 99% yield of 1-bromo- naphthalene. Nitration of naphthalene gives 1-nitronaphthalene (12). Further substitution does not occur in the same ring and the main products of dinitration are 1,5- (13) and 1,8 dinitronaphthalenes (14). The initial nitro group deactivates that ring to further electrophilic substitution and attack at the a-positions of the other ring therefore takes place.

The sulfonation of naphthalene by concentrated sulfuric acid at 80 °C gives naphthalene-1-sulfonic acid. At 160 °C, naphthalene-2-sulfonic acid predominates .The 1-isomer is the more readily formed and is stable at the reaction temperature of 80 °C. However, at 160 °C, not only is naphthalene-

1-sulfonic acid desulfonated, but also there is sufficient energy to convert naphthalene into the 2 sulfonic acid, which is stable even at the higher temperature. The 2-substituted isomer is more stable, probably because there is less steric hindrance between the bulky sulfonic acid group and the adjacent *ortho* H atoms (H-1 and H-3) than between the 1-sulfonic acid and the *peri* H-8 atom.



This process illustrates the concept of kinetic *versus* thermodynamic control of a reaction, with naphthalene- 1 -sulfonic acid being the kinetic product and the 2-sulfonic acid the thermodynamic product. The energy changes associated with these processes are illustrated in.

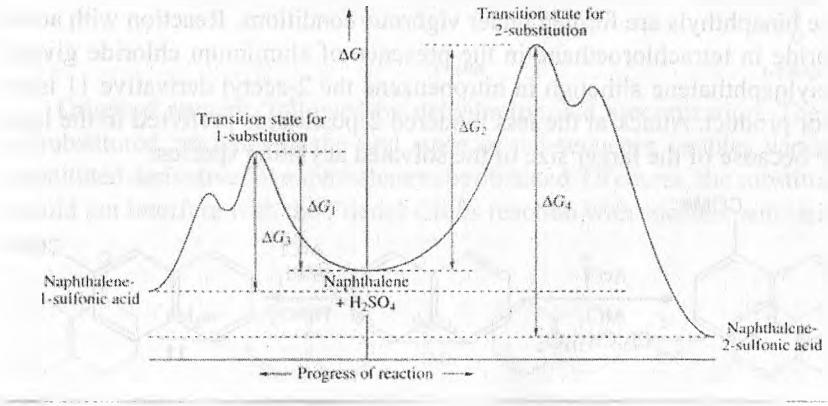


Figure 8.1 *Energy profile for the sulfonation of naphthalene.*
AG_1 = energy of activation for 1- substitution; AG_2 = energy of activation for 2-substitution; $AG_1 < AG_2$, so naphthalene-1–sulfonic acid is the more easily formed and is the kinetic product. AG_3 = energy required to reverse formation of naphthalene-1 – sulfonic acid; AG_4 = energy required to reverse formation of naphthalene- 2-sulfonic acid; $AG_4 > AG_1$, so naphthalene-2-sulfonic acid is thermodynamically more stable than the 1-sulfonic acid

The orientation of disubstitution in naphthalene follows a similar pattern to that encountered in benzene:

Electron-donating substituents at the 1-position activate the 2- and

4-posi, tions

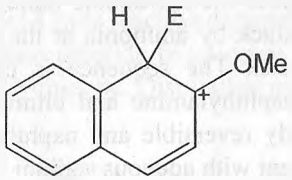
Electron-donating substituents at the 2-position activate the

1 -position

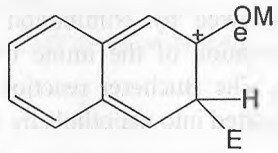
Electron-withdrawing substituents direct attack to the second ring

With an electron-donating substituent at C-2, attack at C-1 is preferred since attack at C-3 would produce a Wheland intermediate in which the aromaticity in the second ring is disturbed.

Hydroxynaphthalenes, which are called napthols are readily accessible from the naphthalenesulfonic acids by heating them to fusion with solid alkali. They are also available from coal tar. The reactions of both 1-naphthol and 2-naphthol closely resemble those of phenols. For example, both can be acylated and alkylated. 2- Naphthol is more reactive than 1-naphthol. The hydroxyl group activates the ring to electrophilic substitution. Thus, in addition to attack by the usual electrophiles, reaction with weaker electrophiles can occur,

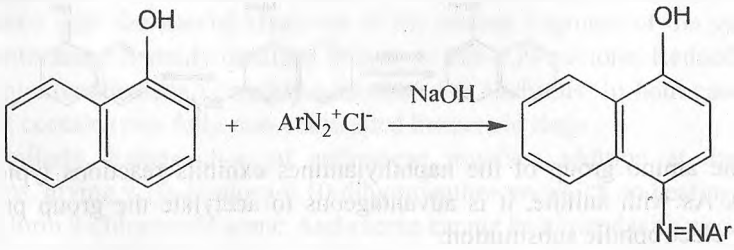


aromaticity retained in one ring following attack at the 1-position



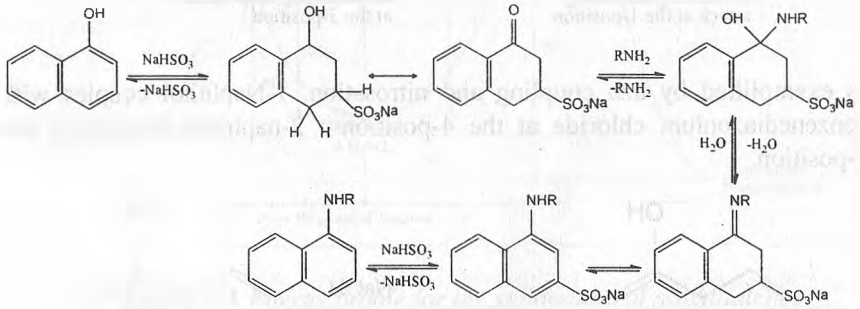
aromaticity is not retained in either ring after attack at the 3-position

as exemplified by azo coupling and nitrosation. 1-Naphthol couples with benzenediazonium chloride at the 4-position : 2-naphthol couples at the 1-position.



Treatment of 1- and 2-naphthol with nitrous acid results in the introduction of a nitroso group at the expected positions. The products exist as a mixture of the nitroso and oxime tautomers, conjugated with the enol and keto functions, respectively.

The naphthylamines may be prepared by reduction of the corresponding nitro compound, but they are readily accessible from naphthols by the Bucherer reaction The naphthol is heated, preferably under pressure in an autoclave, with ammonia and aqueous sodium hydrogen sulfite solution, when an addition-elimination sequence occurs. The detailed mechanism is not completely elucidated, but the Bucherer reaction is restricted to those phenols that show a tendency to tautomerize to the keto form, such as the naphthols and 1,3-dihydroxybenzene (resorcinol). Using 1-naphthol for illustration, the first step is addition of the hydrosulfite across the 3,4-double bond of either the enol or keto tautomer. Nucleophilic attack by ammonia at the carbonyl group is followed by elimination of water. The sequence is completed by tautomerization of the imine to the naphthylamine and elimination of hydrosulfite. The Bucherer reaction is fully reversible and naphthylamines may be converted into naphthols by treatment with aqueous sodium hydrogen sulfite.

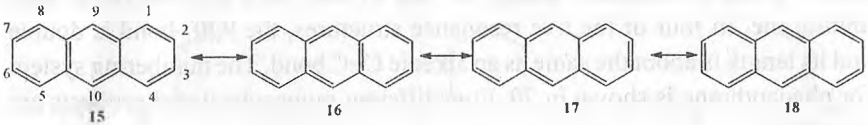


The amino group of the naphthylamines exhibits reactions typical of aniline. As with aniline, it is advantageous to acetylate the group prior to further electrophilic substitution.

8.3 Chemistry of anthracene

Valence bond theory considers that anthracene is best regarded as a resonance hybrid of the four structures 15-18. The resonance energy of

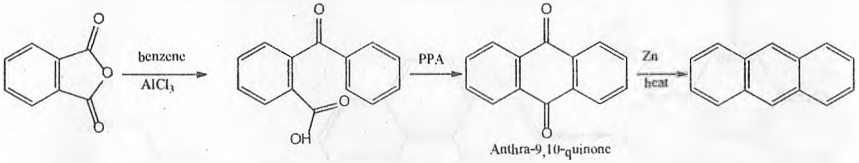
anthracene is 351 kJ mol^{-1}. Examination of the canonical forms indicates that the three rings cannot all be benzenoid at the same time. It can also be seen that the central ring contains a four-carbon fragment with a relatively high degree of double bond character. The numbering system, shown in 15, is a little unusual and was introduced during early chemical studies to indicate the special character associated with the 9- and 10- positions.



15 16 17 18

Synthesis of anthracene. Although it is possible to synthesize anthracene in a number of ways using Friedel-Crafts methodology, the usual routes involve either an adaptation of the Haworth synthesis of naphthalene or a Diels-Adler reaction using naphtho- 1,4-quinone as the dienophile.

Friedel-Crafts reaction of phthalic anhydride with benzene in the presence of aluminium chloride followed by cyclization under acidic conditions gives anthra-9,10-quinone. Distillation over zinc dust gives anthracene.



Anthra-9,10-quinone

Anthra-9,10-quinone is the eventual product from the cycloaddition of buta- 1,3-diene to naphtho- 1,4-quinone after oxidation of the tetrahydroanthraquinone adduct.

Reactions of anthracene. Much of the chemistry of anthracene is associated with the special character of the central fragment of the system. Thus anthracene is easily oxidized to form anthra-9,10-quinone. Reduction to 9,10-dihydroanthracene is readily achieved with Na/EtOH. In both cases the product contains two fully non-conjugated benzenoid rings.

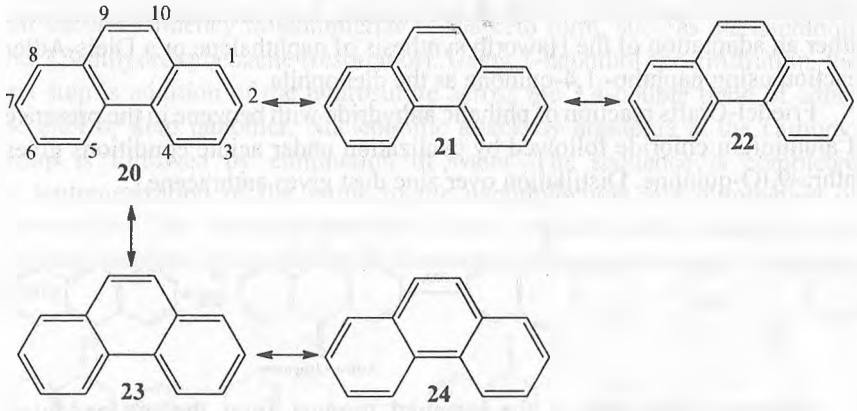
Similarly, halogenation of anthracene involves addition at the 9,10 positions, giving 9,10-dichloro-9,10-dihydroanthracen which on heating loses HCl to form 9-chloroanthracene. Anthracene cannot be nitrated with nitric acid because of its easy oxidation to anthraquinone, although 9-nitroanthracene can be isolated from nitration in acetic anhydride at room temperature.

The dienic character of the central ring is illustrated by the reaction of anthracene with dienophiles in Diels-Alder reactions. For example, cis-butenedioic anhydride (maleic anhydride) reacts readily; when benzyne is generated in the presence of anthracene, triptycene (19) is produced.

Derivatives of anthraquinone are important as dyestuffs for the coloration of a variety of fabrics.

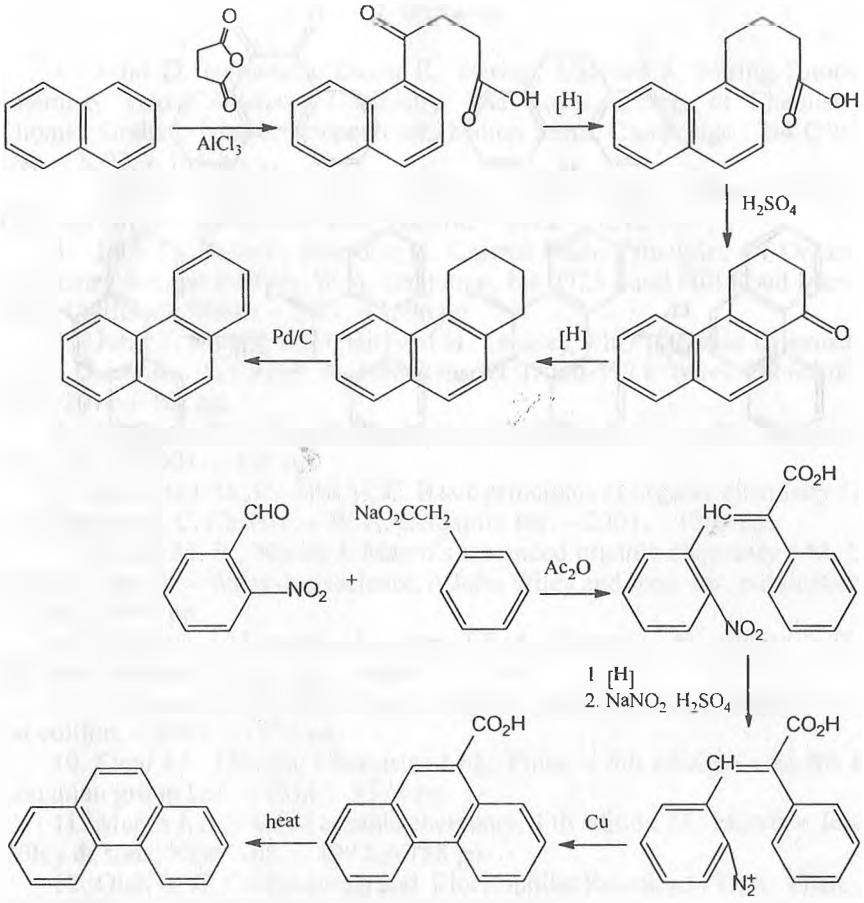
8.4 Chemistry of phenanthrene

Phenanthrene is best represented as a hybrid of the five canonical forms 20-24. It has a resonance energy of 380 kJ mol^{-1} and is more stable than anthracene. In four of the five resonance structures, the 9,10 -bond is double and its length is about the same as an alkenic C=C bond. The numbering system for phenanthrene is shown in 20. Five different monosubstituted products are possible.

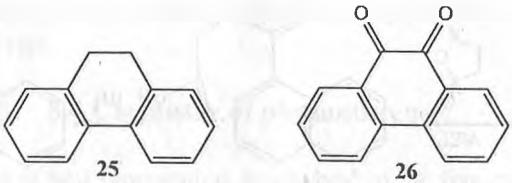


Synthesis of phenanthrene.There are two major routes to phenanthrene, both of which can be used to prepare substituted derivatives. In the Haworth synthesis, reaction of naphthalene with succinic anhydride yields an oxobutanoic acid which is reduced under Clemmensen conditions to the butanoic acid. Cyclization in sulfuric acid and reduction of the resulting ketone is followed by dehydrogenation over palladium-on-carbon to phenanthrene. Alkyl or aryl derivatives can be obtained by treatment of the intermediate ketone with a Grignard reagent prior to dehydration and oxidation.

In the Pchorr synthesis a Perkin reaction between 2-nitrobenzaldehyde and sodium phenylacetate in the presence of acetic anhydride yields 3-(2-nitrophenyl)-2-phenylpropenoic acid. Reduction of the nitro group and deamination of the resulting amine *via* its diazonium salt is accompanied by cyclization. Thermal decarboxylation completes the sequence.



Reactions of phenanthrene.Both reduction (H_2, Pt catalyst) and oxidation (CrO_3, AcOH) of the 9,10 bond are readily accomplished, yielding 9,10-dihydrophenanthrene (25) and phenanthra-9,10-quinone (26), respectively. In acetic acid solution, phenanthrene undergoes addition of chlorine to give a mixture of *cis*- and trans-9,10-dichloro-9,10-dihydrophenanthrenes. The accompanying formation of an acetoxy derivative suggests that the normal electrophilic addition to a double bond is occurring. The dichloro addition compound eliminates hydrogen chloride to give 9-chlorophenanthrene. However, reaction with bromine in refluxing tetrachloromethane produces 9-bromophenanthrene and an alternative mechanism is probably operating. Other electrophilic substitution reactions of phenanthrene lead to mixtures of products.



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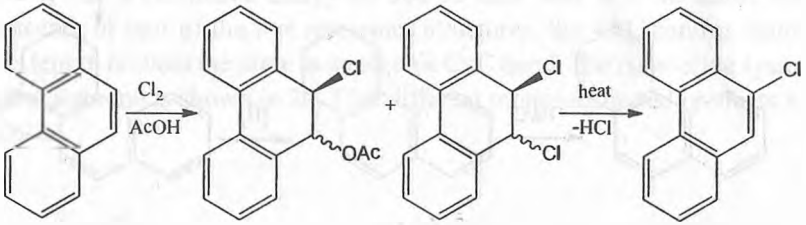

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