Faculty of Science
Department & Chemistry

SOME PRINCIPAL ORGANIC REACTIONS AND THEIR MECHANISMS

Prepared by
Moustafa F. Aly

Contents

Introduction

This course deals with the chemistry of some principal organic reactions and their mechanisms, which are very essential for organic chemistry students.

For example knowing how hybridization occurs in C, N and O atoms is a must. Hybridization is a subject dealing with the way of bonding between atoms and the reactivity of compounds during a chemical reaction. It also spots some light on the stability of the transition states through which chemical reactions undergo. The hybridization and rehybridization of the carbon atoms during the transition states of the chemical reactions explains the formation of different products.

The nature of the carbonyl group is explained and also the effect of substituents on its reactivity. Nearly almost reactions of the carbonyl group are discussed in detail:

(a) Nucleophilic addition at the partial positively charged carbon atom of the carbonyl group:

  (i) Grignard addition to the carbonyl group.

  (ii) The hydride H^- addition to the carbonyl group.

  (iii) Acetal and ketal formation.

  (iv) Protection and deprotection of the carbonyl group.

  (v) Esterification of carboxylic acids.

  (vi) Nucleophilic substitution at the carbonyl group.

(b) Nucleophilic substitution at the carbonyl group:

  (i) Imine and oxime formation.

  (ii) Hydrazone and semicarbazone formation.

  (iii) Reduction of C=O to CH_2.

  (iv) Conversion of C=O to CCl_2.

(v) Synthesis of DDT.

(vi) Chloromethylation of aromatic compounds.

The nucleophilic substitution reactions S_N1 and S_N2 and elimination reactions E1 and E2 of alkyl halides are fully studied. Thus, for example MeX, 1° and 2° alkyl halides would be undergoing by S_N2 mechanism, whereas 3° alkyl halide tends to go through another path S_N1. In each reaction the type of RX, nucleophile, concentration of reactants and the used solvent affect both the reaction path and the rate of reaction to a great extent. In the elimination reaction E2 the alkene with the more substituted double bond would be predominant. However, the high steric hindrance in the transition state in E2 would lead to an alkene with the less substituted double bond.

Many sample and study problems are given for each topic.

Chapter 1

Hybridization

Hybrid Orbitals of Carbon:

Carbon atom has two electrons in the first energy level, 1s orbital, which is not used for bonding. The four electrons in the second energy level of carbon are in fact the bonding electrons.

The four atomic orbitals at the second energy level: one atomic orbital 2s and three 2p orbitals. The carbon atom does not use these four orbitals as they are for bonding, but it, hybridizes its four second-level atomic orbitals in one of three different ways for bonding:

1- The sp^3 hybridization, is used when the carbon atom forms four single bonds, Figure 1.

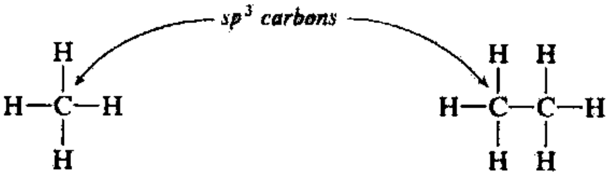


Figure 1

2- The sp^2 hybridization, is used when a double bonded carbon skeleton is formed, Figure 2.

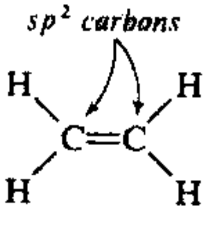


Figure 2

3-The *sp* hybridization, is used only when the carbon atom forms a triple bond or cumulated double bonds (two double bonds on both sides of a single carbon atom). In the latter case the hybridization of the middle carbon atom is known as pseudo sp hybridization. However, the hybridization in the case of the cumulated double bonds is usually called pseudo *sp* hybridization, Figure 3.

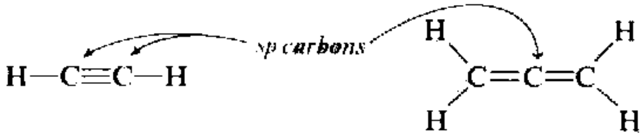


Figure 3

Carbon atom forms compounds with hybrid atomic orbitals rather than with unhybridized atomic orbitals. The hybridization gives stronger bonds due to:

1- The greater overlap, which gives more stable compounds.
2- The lower energy molecules.

In the following pages we will discuss each type of hybridization:

(i) the shape of each hybrid orbital,
(ii) the geometry of the three types of hybrid orbitals.

(A) sp^3 hybridization:

In methane (CH_4), the carbon atom has four equivalent sigma bonds to four hydrogen atoms. The four C–H bonds are equally in bond length and bond dissociation energy. The bond angle between the C–H bonds is 109.5°. This experimental evidence clearly shows that carbon does not form bonds without hybridization of one *s* atomic orbital and three *p* atomic orbitals. Otherwise the four C–H bonds would not be all equivalent.

A new hypothesis was suggested to explain the hybridization process, by which four equivalent bonds are obtained. The hybridization occurs between the one *2s* atomic orbital and the three *2p* atomic orbitals to afford four equivalent orbitals each hybrid atomic orbital is named sp^3. During such process, one of the *2s* electrons would be promoted to the empty *2p* orbital by gaining energy. The energy of the four sp^3 orbitals have equal energies–slightly higher than that of the *2s* orbital, but slightly lower than that of the *2p* orbitals. Each of the obtained four hybridized sp^3 orhitals contains one electron for bonding. The first level non-bonding $1S^2$ is not shown, Figure 4.

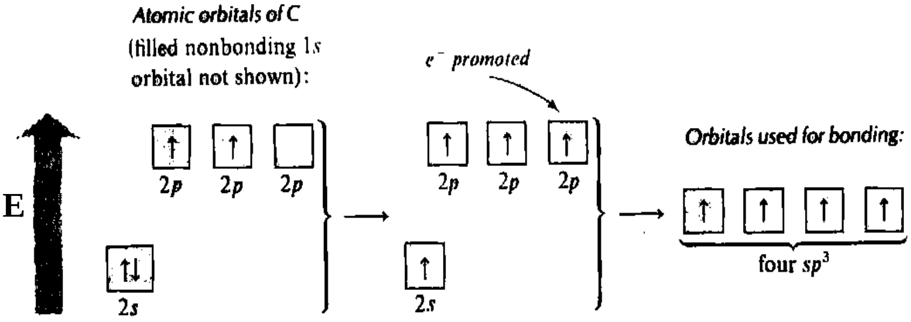


Figure 4

This diagram is called an orbital diagram, in which each box of the diagram represents an orbital. The relative energies of the various orbitals are signified by relating their positions to the energy axis. The electrons in each box are represented by arrows, and the direction of electron spin is indicated by the direction of the arrow.

Figure 5 shows one isolated *sp*^{3} orbital, in which a large lobe and a small lobe with a node at the nucleus. The large end with another orbital gives more complete overlap and forms a stronger bond.

The four *sp*^{3}-hybrid orbitals surround the carbon nucleus, and due to the repulsions between the electrons in the obtained hybrid orbitals, these *sp*^{3} orbitals then must lie far apart from each other as possible and form a regular tetrahedron, Figure 5. It must be noted that the ideal bond angles of the hybridized orbitals is 109.5°. However, *sp*^{3} carbon atom is referred to as a tetrahedral carbon atom because of the geometry of its bonds.

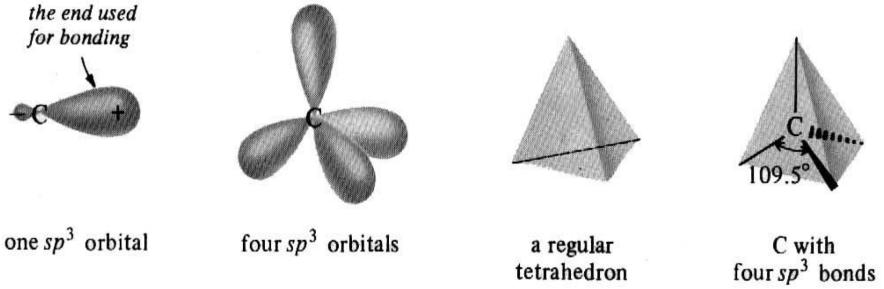
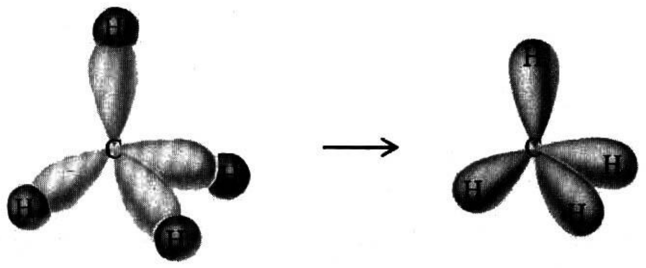


FIGURE 5
The four sp^3-hybrid orbitals of carbon point toward the corners of a regular tetrahedron.

In methane CH_4 Figure 6 shows, an *sp*^{3} carbon atom forms four bonds with four hydrogen atoms and it does so by overlapping each of its four *sp*^{3} orbitals with *1s* orbital from four hydrogen atoms (we must remember that each orbital in turn contains one electron). Each of the formed *sp*^{3}*—s* molecular orbital has a cylinder shape and is known as sigma (σ) bond and is symmetrical around the axis of such cylinder, which is passing through the nuclei of the carbon and the hydrogen. Figures 8 and 9 represent the formation of ethane C_2H_6 (CH_3-CH_3), in which an *sp*^{3}

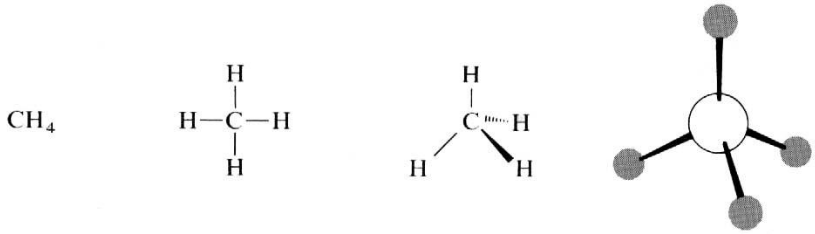
orbital of one carbon atom overlaps with an *sp^3* orbital of the other carbon atom (C-C bond). The other overlapping occurs between the three sp^3 orbitals of each carbon atom with 1s orbital of three hydrogen atoms. All the formed *sp^3-s* and *sp^3-sp^3* bonds are sigma bonds.



one e^- in each atomic or hybrid orbital

two e^- in each molecular orbital

FIGURE 6
Formation of C—H sigma bonds in methane, CH4.
(The small lobes of the sp^3 orbitals are not shown.)



condensed structural formula

complete structural formula

dimensional formula

molecular model

FIGURE 7
Some different ways of representing methane

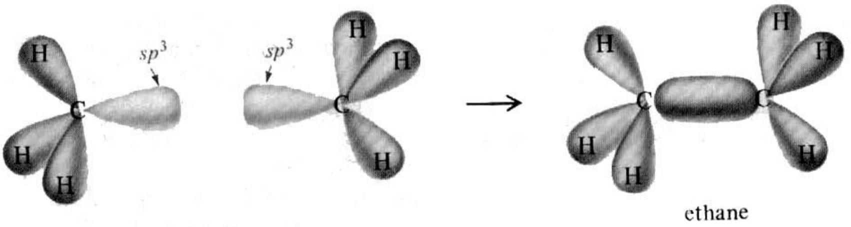
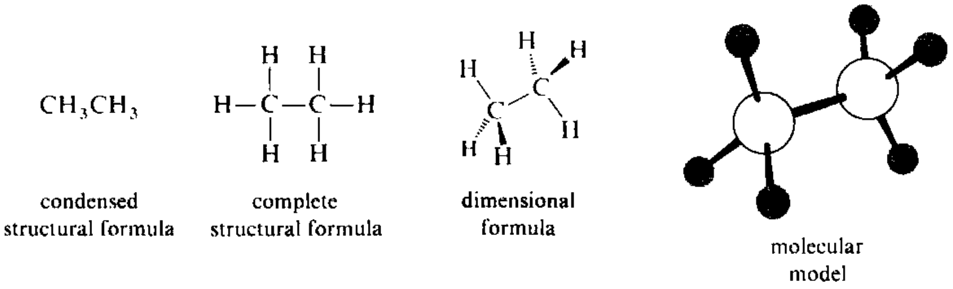


FIGURE 8
Formation of sp^3-sp^3 sigma bond in ethane, CH3CH3



condensed structural formula

complete structural formula

dimensional formula

molecular model

FIGURE 9
Some different ways of representing ethane

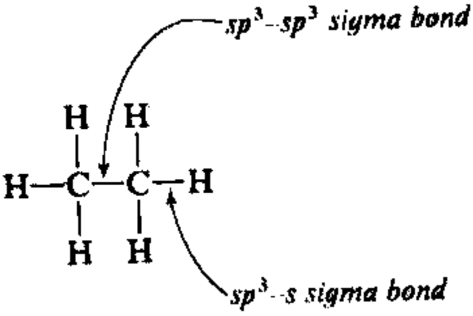
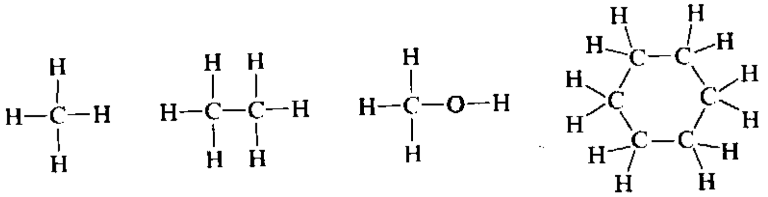


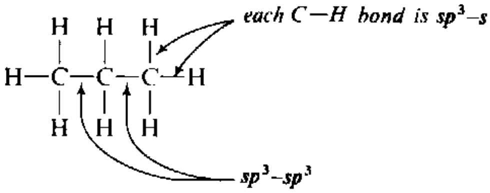
Figure 10

In the saturated hydrocarbons, any carbon atom in the *sp*^{3} hybrid state is bonded to four other atoms, and the formed four bonds are sigma bonds. The bond angle is 109.5°, however, other factors, such as dipole–dipole repulsions or the geometry of a cyclic compound, can cause deviations from this ideal bond angle.

Examples of structures with sp^3 carbons (each C has four sigma bonds):

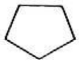


The complete structural formula for propane $CH_3CH_2CH_3$ shows all types of orbitals overlap to form each bond.



Study problem:

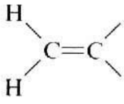
Discuss the complete structural formula for each of the following compounds.

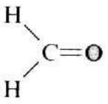
(a) $(CH_3)_3CH$ & (b) 

(B) sp^2 Hybridization:

The carbon atom can be doubly bonded to some other atoms e.g. Alkenes, aldehydes, ketones, acid derivatives and imines (-CH=N-), in such a case the carbon atom is be surrounded by 3 sigma bonds together a *pi* bond, the carbon atom adopts the *sp^2*-hybrid state.

Examples of compounds with sp^2 carbons:


ethylene


formaldehyde

To form sp^2 bonding orbitals, carbon hybridizes its $2s$ orbital with only two of its $2p$ ($2p_x$ and $2p_y$) orbitals. One p orbital ($2p_z$) remains unhybridized. Three atomic orbitals are needed to form the sp^2 orbitals, by which three sp^2-hybrid orbitals are formed. Each sp^2 orbital has a shape similar to that of an sp^3 orbital, but slightly shorter, and contains one electron that can be used for bonding, Figure 11.

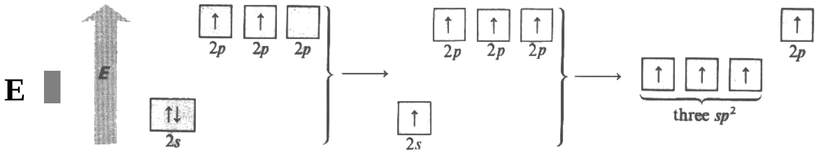
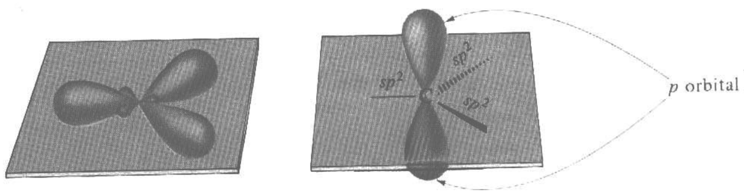


Figure 11

The three sp^2 orbitals around a carbon nucleus lie in a plane, and to be as far apart from one another the angle is nearly 120°. An sp^2-hybridized carbon atom is said to be a trigonal (triangular) carbon. Figure 12 shows a carbon atom with three sp^2 orbitals and the one unhybridized $2p_z$ orbital, which is perpendicular to the sp^2 plane.

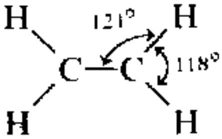


a trigonal carbon; three sp^2 orbitals in a plane with 120° angles between them

p orbital at a right angle to the plane

FIGURE 12
Carbon in the sp^2-hybrid state

In ethylene (CH_2=CH_2), two *sp*^{2} carbons are joined by a sigma bond formed by the overlap of one sp^2 orbital from each carbon atom. This sigma bond is part of the double bond. There are two *sp*^{2} orbitals left on each carbon atom for bonding with hydrogen. Each carbon atom still has a *2p*$_z$ orbital, which is perpendicular to the formed plane of *sp*^{2} orbitals, however it is not shown in the following structure, Figure 13.



Planar sigma-bond structure of ethylene (p orbitals not shown)

Figure 13

The remaining *2p*$_z$ orbital on each carbon has two lobes, one is above the plane of the sigma bonds and the other (of opposite amplitude) is below the plane, and of course each *2p*$_z$ orbital contains one electron. It is well known that when these *2p*$_z$ electrons are paired in a bonding molecular orbital, the energy of the formed system will be lowered. As the *2p*$_z$ orbitals lie side by side in the ethylene molecule, the ends of both orbitals can be overlapped to produce a new type of bonding named the pi (π) bonding, (see Figure 14). The resultant pi bond will be located above and below the plane of the sigma bonds. The double bond is made up from the sigma and the pi bond.

It is obvious that any carbon atom that is bonded to three other atoms must be in the *sp*^{2} hybrid state and is connected to another sp^2 carbon (or a hetero atom, e.g. N or O) by a double bond. In the obtained compounds, the *2p*$_z$

orbital on the *sp*^{2} carbon overlaps with a *2p*$_z$ orbital of the adjacent *sp*^{2} atom.

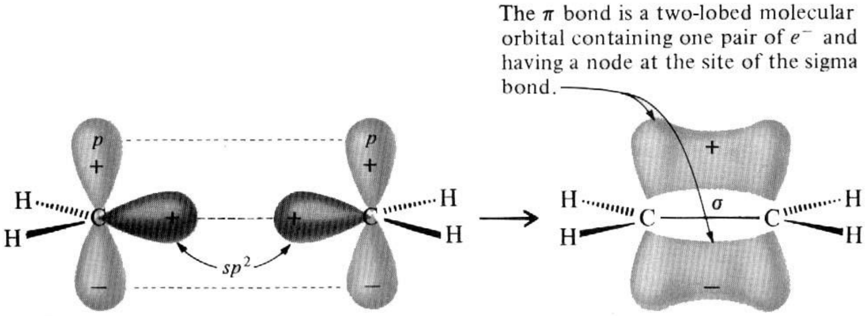
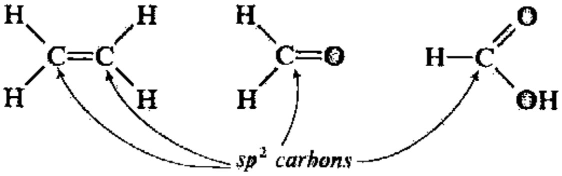

The π bond is a two-lobed molecular orbital containing one pair of e⁻ and having a node at the site of the sigma bond.

FIGURE 14

Formation of the *sp*^{2}–*sp*^{2} sigma bond and the *2p*$_z$–*2*$_z$*p* pi bond in ethylene, CH_2=CH_2. (The + and – are not electrical charges but they refer to phases of the wave functions.)



Some features of the pi bond:

The *pi* bond is made up from a side by side interaction of two *2p*$_z$ orbitals located at two adjacent atoms, and each of the two *2p*$_z$ orbitals has two lobes and has a node at the nucleus. The pi bond is not cylindrically symmetrical as the sigma bond is.

A *2p*$_z$ orbital of carbon is of slightly higher energy than an sp^2 orbital (cf. the energy diagram). It is clearly that the pi bond, which is formed from two 2p$_z$ orbitals, has slightly higher energy and is slightly less stable than the

sigma bond. The bond dissociation energy of the sigma bond of ethylene's C=C double bond is estimated to be 95 kcal/mole, while that of the pi bond is estimated to be only 68 kcal/mole.

The *pi* pond is more affected than the sigma bond, for this reason the pi bond is easily polarized, which makes the pi electrons to be more mobile. If the *pi* bond is attacked by a nucleophile the *pi* electrons will move away.

Rotation around the pi bond is restricted due the geometry of the *pi* bond, and for this to occur the *pi* bond must be broken. (cf. Figure 15).The molecules during a chemical reaction may have sufficient energy (about 68 kcal/mole), which is enough to break up the *pi* bond. In a flask at room temperature, molecules do not have enough energy for this bond breakage to occur, (nearly 20kcal/mole is the maximum energy available to molecules at room temperature). However, it is well known that stirring at room temperature affords enough energy to break down the *pi* bond.

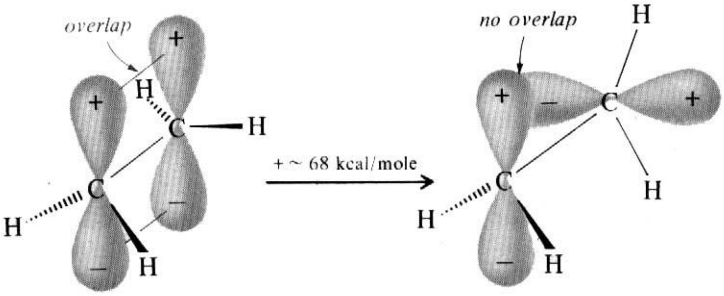
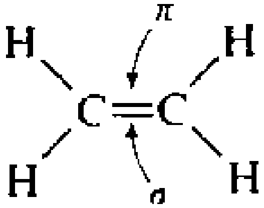
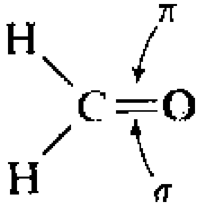


FIGURE 15
The portion of a molecule surrounding a pi bond is held in a planar structure unless enough energy is supplied to break the pi bond.

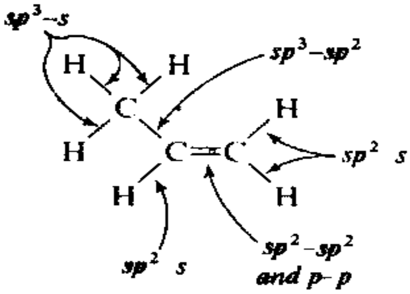
The double bond is represented by two identical lines. We must remember that the double bond is not simply two identical bonds, but that the double line represents one strong sigma bond and one weak *pi* bond.

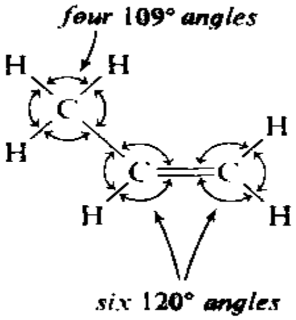




All types of overlap are presented for CH_3–CH=CH_2:

Solution:

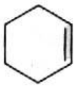




Examples:

(1) Show the complete structural formula for each of the following compounds.

(a) $CH_2{=}C(CH_3)_2$ (b) $CH_2{=}CHCH{=}CH_2$ (c)



(2) For compound (b) in the previous example draw the full structure.

Figure 16 shows the orbital representations of the π_1 and π_2* orbitals of ethylene. Note that besides the node at the σ-bond site, the π_2* orbital has an additional node

between the two carbon nuclei. A minimum of the pi electron density is located between the nuclei in this orbital; thus, the π_2* orbital is of higher energy than the π_1 orbital. In the ground state of ethylene, the pi electrons are found in the lower-energy π_1 orbital.

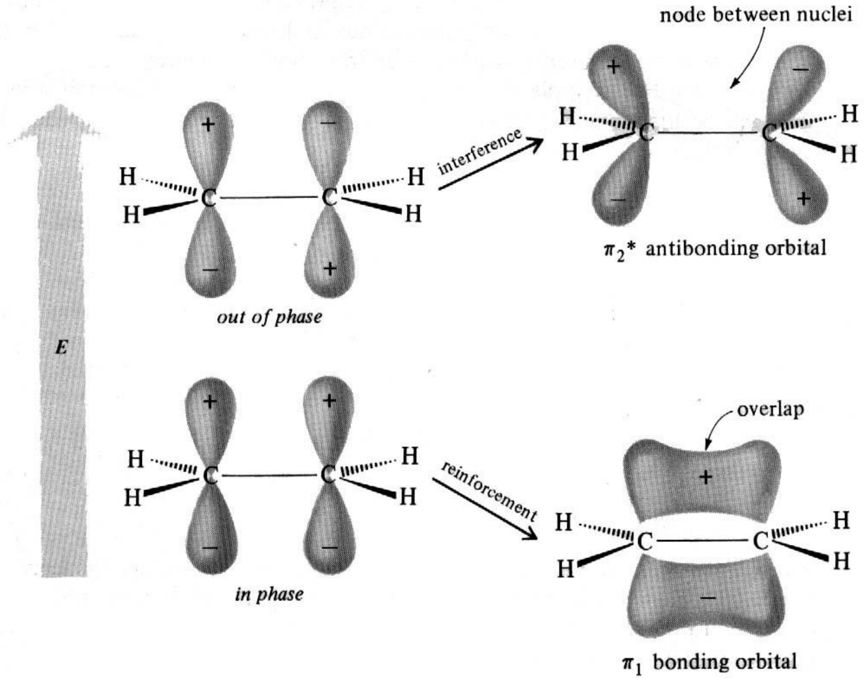


FIGURE 16

The π_1, bonding orbital and the π_2* antibonding orbital of ethylene.

(C) *sp* Hybridization:

In the *sp* hybridization a carbon atom is connected to another carbon atom or a hetero atom e.g. N. Acetylene (CH≡CH), is an example of the *sp* hybridization. In which, one *2s* orbital blends with only one $2p_x$ orbital to form two *sp*-hybrid orbitals. In this case, the two $2p_y$ and $2p_z$ orbitals remain unhybridized, each with one electron, Figure 17.

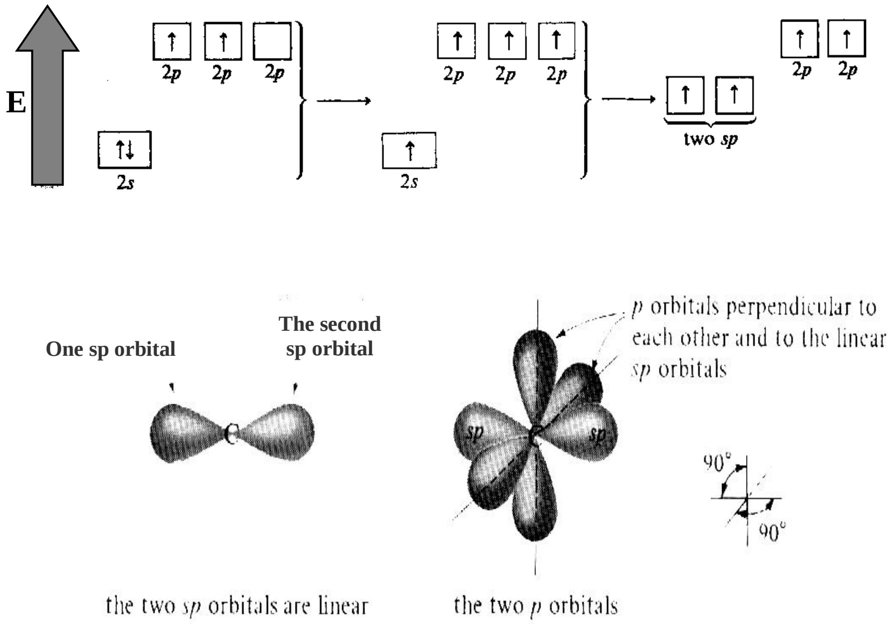


FIGURE 17
Carbon in the sp-hybridstate

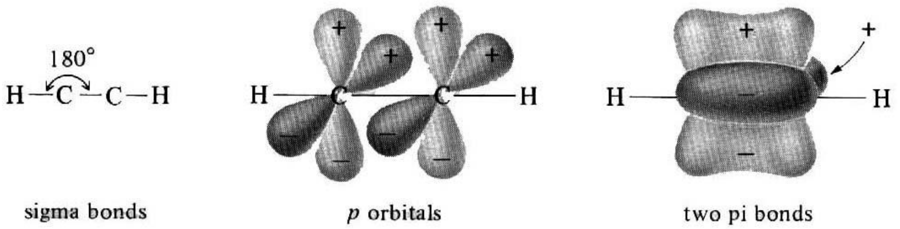
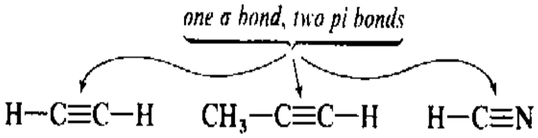


FIGURE 18
Bonding in acetylene, CH≡CH

To avoid any repulsion effect the two *sp* hybrid orbitals would lie as far apart as possible, with an angle of 180° between them. The remaining *p* orbitals ($2p_y$ and $2p_z$) are perpendicular to each other and to the line of the two *sp* hybrid orbitals (see Figure 18).

In $CH\equiv CH$, the two carbon atoms are joined together by a triple bond, which contains an *sp-sp* sigma bond and two *pi* bonds. Each carbon is also bonded to a hydrogen atom by an *sp-s* sigma bond. The two *p* ($2p_y$ and $2p_z$) orbitals of one carbon is then overlapped with the two *p* ($2p_y$ and $2p_z$) orbitals of the other carbon to form two *pi* bonds. One pi bond is above and below the line of the sigma bonds, and the other *pi* bond is located in the front and back of the sigma bond.

As you might guess, the chemical reactions of a compound containing a triple bond are not too different from those of a compound containing a double bond. Instead of one *pi* bond, there are two.



Example:

Show all types of overlap in each carbon-carbon bond for $CH_3\text{–}C\equiv CH$.

<u>Effects of hybridization on bond lengths:</u>

A 2*s* orbital is slightly lower energy than a 2*p* orbital. On the average, 2*s* electrons are found closer to the nucleus than 2*p* electrons. For this reason, a hybrid orbital with a greater proportion of *s* character is of lower energy and is closer to the nucleus than a hybrid orbital with less *s* character.

An *sp*-hybrid orbital is one-half s and one-half *p*; we may say that the sp orbital has 50% *s* character and 50% p character. At the other extreme is the sp^3 orbital, which has only one-fourth, or *25% s* character.

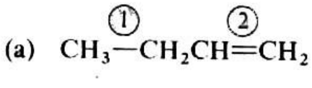
Table 1 shows the differences in bond lengths among the three C–C and C–H bond types.

C–C bonding	**hybrid orbital**	**s character %**
$CH \equiv CH$	sp	**50**
$CH_2 \equiv CH_2$	sp^2	$33\frac{1}{3}$
CH_3CH_3	sp^3	**25**

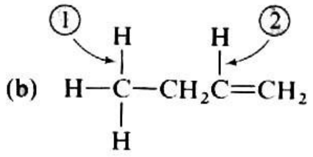
The *sp* hybrid orbital contains more *s* character, so it is closer to its nucleus; it forms shorter and stronger bonds than the sp^3 orbital. The sp^2 orbital is intermediate between *sp* and sp^3 in its *s* character and in the length and strength of the bonds it forms.

Study problem:

Can you list the numbered bonds in order of increasing the bond length in the following compounds:



$\overset{①}{CH_3-}CH_2\overset{②}{CH=}CH_2$



$H-\underset{H}{\overset{H}{C}}-CH_2\overset{H}{C}=CH_2$

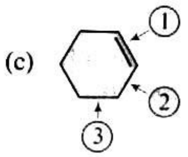
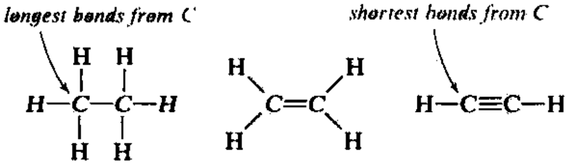


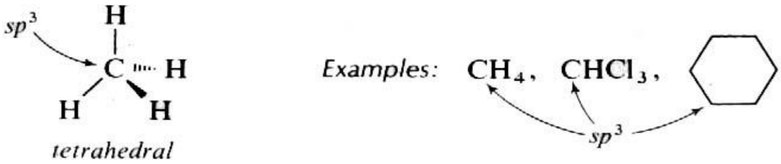
Table 2. Effect of hybridization on bond length



Percent s character:	25	33	50
C—C bond length:	1.54 Å	1.34 Å	1.20 Å
C—H bond length:	1.09 Å	1.08 Å	1.06 Å

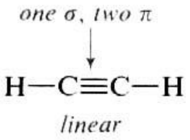
Summary of the hybrid orbitals of carbon:

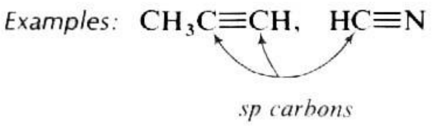
1- In the *sp*^{3} hybridization the carbon atom is surrounded with four equivalent *sp*^{3} orbitals. The *sp*^{3} carbon is tetrahedral and the angle is 109.5º.



2- In the *sp*^{2} hybridization the carbon atom is bonded to 3 other atoms, in which the carbon atom is joined by three *sp*^{2}*-s* hybrid orbitals and *pi* bond. The formed *pi* bond is planar and perpendicular to the plane of the sigma bonds and the angle is 120º.

3- In the *sp* hybridization the carbon bonds to the other two atoms (C or N), are formed from two equivalent *sp* hybrid orbitals. The left two *2p* orbitals ($2p_y$ and $2p_z$) overlap with two *2p* orbitals ($2p_y$ and $2p_z$) of another atom to form two pi bonds. The two *sp* hybrid orbitals form two equivalent and linear sigma bonds.





Functional Groups:

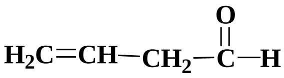
The stable *sp*^{3}–*sp*^{3} carbon–carbon bonds and *sp*^{3}–*s* carbon–hydrogen bonds are common to almost all organic compounds. However these bonds are not greatly involved in organic reactions, (stable and strong). Only compounds containing either *pi* bond or hetero atom (N, O etc…) in an organic structure that show pronounced reactivity. However, the site at which a chemical reaction can occur is called a functional group. Chemical reactions occur readily at a *pi* bond or at an electronegative (or electropositive) atom in an organic molecule. Either one of these is considered a functional group.

Some functional groups (coloured):

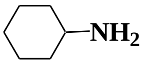
$CH_3CH{=}CH_2$ $CH_3CH_2NH_2$ CH_3CH_2OH

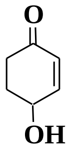
Study problem:

What are the functional groups in the following compounds:

(a) 

$H_2C{=}CH{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}H$

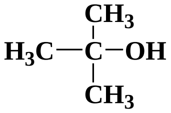
(b) 

(c) 

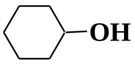
Compounds with the same functional group have the same chemical properties, and undergo the same chemical reactions. For example, alcohols are a class of compounds and each individual contains a hydroxyl group (–OH). These compounds undergo similar reactions.

Some alcohols:

H_3C-CH_2-OH



$$H_3C-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-OH$$



As a result of these similarities in reactivity among compounds with the same functional group, chemists agreed to use a general formula for each series of these compounds. They represent an alcohol as ROH. Table 2 shows some functional groups and some classes of compounds with generalized formulas.

R means an alkyl group, such as CH_3-, CH_3CH_2-
ROH means an alcohol, such as CH_3OH, CH_3CH_2OH

TABLE 2. Some functional groups and compound classes

Functional group		**Class of compound**	
Structure	***Name***	***General formula***	***Class name***
$C=C$	**double bond**	**$R_2C= CR'_2{}^a$**	**alkene**
$C\equiv C$	**triple bond**	**$RC\equiv CR'^a$**	**alkyne**
$-NH_2$	**amino group**	**RNH_2**	**amine**
-OH	**hydroxyl group**	**ROH**	**alcohol**
-OR	**alkoxyl group**	**$R^aO\ R'^a$**	**ether**

[a] R' refers to an alkyl group that may be the same as or different from R.

Example 1:

The following compounds are all amines. Write a general formula for an amine.

CH_3NH_2 $CH_3CH_2NH_2$ $(CH_3)_2CHCH_2NH_2$

Example 2:

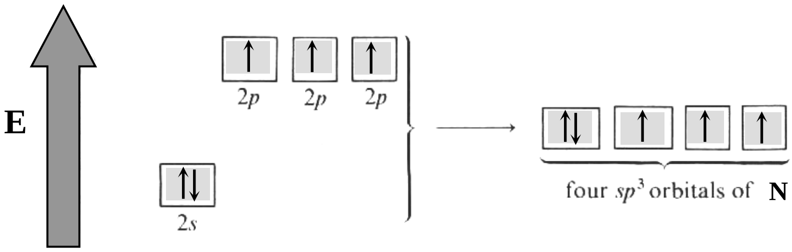
The following compounds are all carboxylic acids. Write a general formula for carboxylic acids.

CH_3COOH, CH_3CH_2COOH, $CH_3CH_2CH_2COOH$

Hybrid Orbitals of Nitrogen and Oxygen:

(A) Amines *sp*^{3}:

As previously mentioned many important functional groups in organic compounds contain nitrogen or oxygen. Like carbon, nitrogen forms bonds by *sp*^{3} hybrid orbitals, and the atomic orbitals of nitrogen hybridize in a manner very similar to those of carbon, *cf*. given orbital diagram:



Nitrogen has five electrons to distribute in four *sp*^{3} orbitals, whereas carbon has four electrons to distribute in four *sp*^{3} orbitals. In the case of nitrogen one of the sp^3 orbitals is filled with a pair of electrons known as unshared pair of electrons, so nitrogen can form only three covalent bonds to other atoms.

The in ammonia *sp*^{3} nitrogen atom is bonded to three hydrogen atoms. Whereas, an amine molecule has a similar structure, in which an *sp*^{3} nitrogen atom is bonded to one or more carbon atoms. In either ammonia or an amine, the nitrogen has one orbital filled with an un shared pair of electrons. The similarities in structure of ammonia and two amines are represented in Figure 19. Note that, the *sp*^{3} angle in nitrogen is different (not 109.5º) compared to that in *sp*^{3} carbon.

The basicity of ammonia and amines is attributed to that unshared pair of electrons in the filled orbital on the nitrogen atom. When ammonia or an amine is treated with an acid, these unshared electrons are used to form a sigma bond with the acid proton to produce an amine salt.

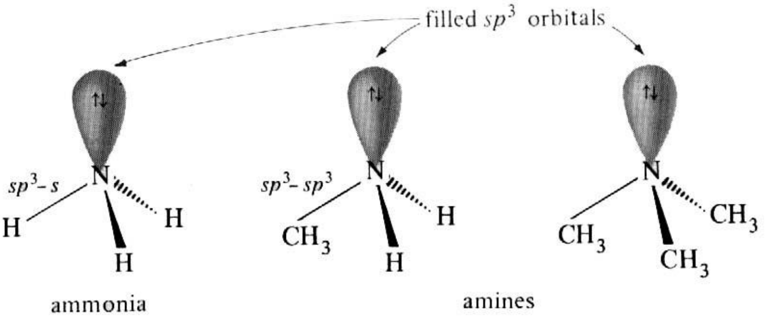
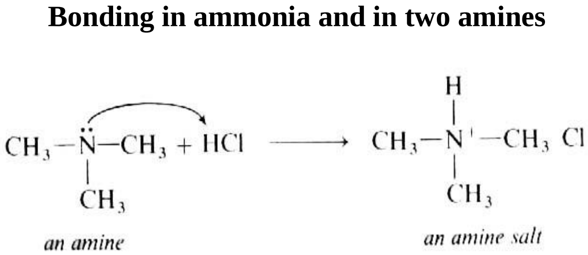


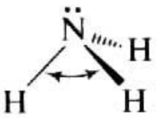
FIGURE 19
Bonding in ammonia and in two amines



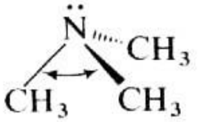
$$\mathrm{CH_3-\underset{CH_3}{\underset{|}{\ddot{N}}}-CH_3 + HCl \longrightarrow CH_3-\overset{H}{\overset{|}{\underset{CH_3}{\underset{|}{N^+}}}}-CH_3\ Cl^-}$$

In fact the H–N–H bond angle in NH$_3$ is not 109.5º, but experimental results showed that the bond angles in NH$_3$

are 107.3°. This is easily explained as the bond angles are compressed by the large size of the filled orbital with its pair of unshared electrons. In trimethyl amine the sp^3 nitrogen is connected to groups bigger than hydrogen atoms, the bond angles become closer to the tetrahedral angle of 108° due to the repulsions between these larger groups.

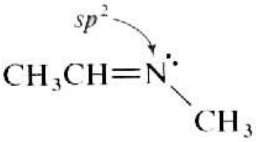


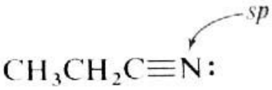
107.3°
ammonia



108°
trimethylamine

Nitrogen is also found in organic compounds in the sp^2- and sp-hybrid states, imines (R–CH=N–) and nitriles (R–C≡CN), respectively. Yet again, in these compounds one of the orbitals of nitrogen is filled with an unshared pair of electrons.





Example:

Give the complete structural formula of each of the following compounds and which type of orbitals overlap to form each bond:

(a) $(CH_3)_2NCH_2NH_2$

(b)

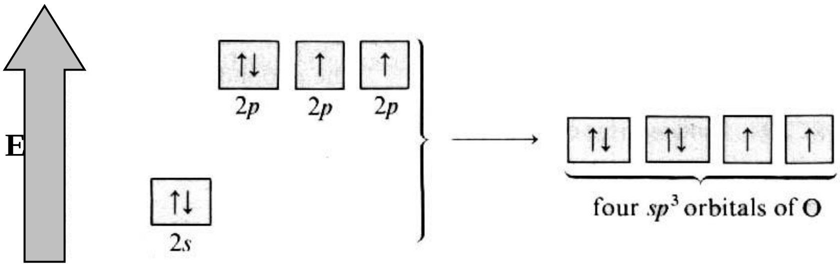
$H_2N\overset{\overset{\displaystyle NH}{\|}}{C}NHCH_2CN$

(c)


(C) Hybridization of oxygen:

(a) Water, alcohols, and ethers:

Oxygen forms only four *sp*^{3}-hybrid orbitals and two of the formed hybrid orbitals are filled with unshared pairs of electrons, (cf. energy diagram).



In water oxygen has four *sp*^{3} hybrid orbitals, two of which are filled with two pairs of unshared electrons. The bond angle in water is found to be 104.5°, which is not the idealized 109.5° (*sp*^{3} compounds). It is clearly that the size of the two filled orbitals with unshared electrons decreases the H-O-H bond angle, just as the filled orbital in ammonia does.

There are a number of classes of organic compounds that contain *sp*^{3} oxygen atoms. For the present, let us consider just two, Alcohols R-OH and ethers R-O-R and ROR$^/$ are examples of the *sp*^{3} oxygen compounds, in which oxygen is similarly bonded to atoms as the bonding in water. We should keep in mind that in each case, the oxygen is has four *sp*^{3} hybrid orbitals, two of which has two pairs of unshared electrons, Figure 20.

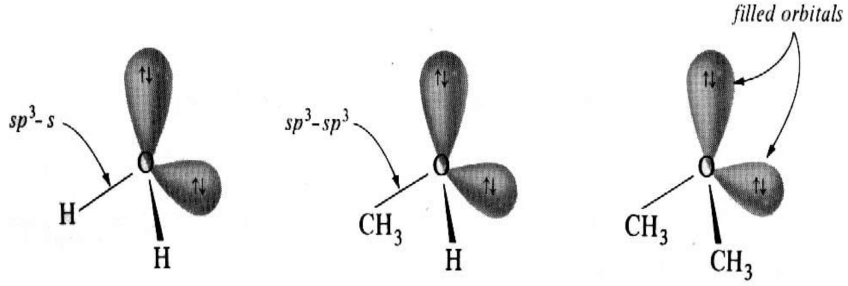


FIGURE 20
Bonding in water, in the alcohol CH3OH and in the ether $CH3OCH_3$

(b) Carbonyl compounds:

The carbonyl group (C=O) contains an *sp*^{2} carbon atom connected to an *sp*^{2} oxygen atom by a double bond.

The carbonyl group is planar and the carbon-oxygen bond contains a pair of exposed *pi* electrons and oxygen also has two pairs of unshared electrons. The geometry of a carbonyl group is represented in Figure 21.

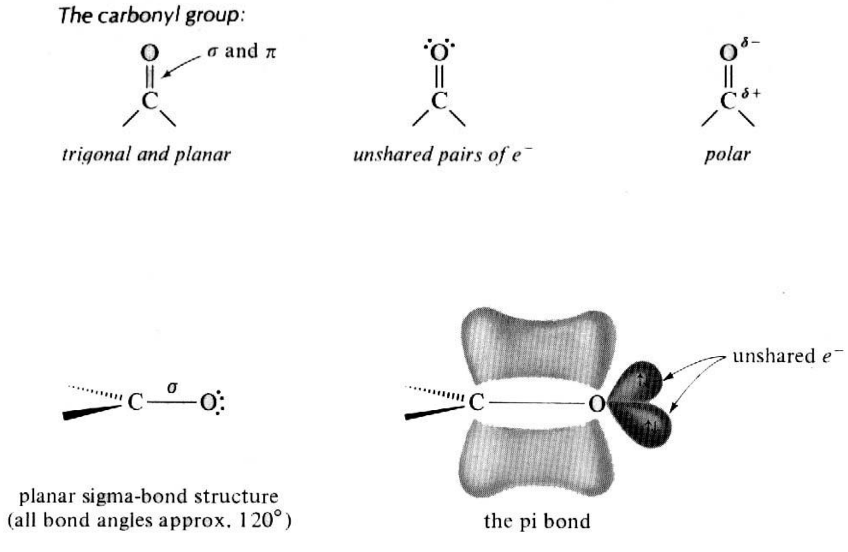
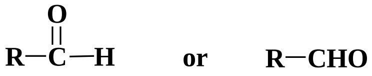


FIGURE 21
Bonding in the carbonyl group

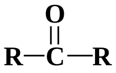
Polarity of the carbonyl group is more pronounced than the C–O group in alcohols or ethers. This enhanced polarity is attributed to the mobile pi electrons, which are more easily drawn toward the electronegative oxygen than are the C–O sigma electrons. The carbonyl group is considered to be the most important group in organic chemistry, at which wide variety of reactions can occur.

Other compounds contain the carbonyl group as a part of their functional groups, e.g. aldehydes (R-CHO), ketones (R-CO-R), acids (R-COOH) and their derivatives.



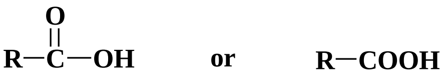
$R-\overset{\overset{\displaystyle O}{\|}}{C}-H$ **or** $R-CHO$

an aldehyde



$R-\overset{\overset{\displaystyle O}{\|}}{C}-R$

a ketone



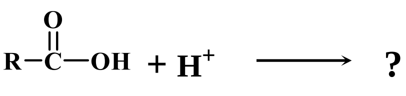
$R-\overset{\overset{\displaystyle O}{\|}}{C}-OH$ **or** $R-COOH$

a carboxylic acid

It is worth mentioning that oxygen atom cannot form *sp* hybridization because the two filled $2s^2$ and $2p_x^2$ orbitals do not participate in such hybridization.

Study problem:

Which oxygen will attack H$^+$ in the following example:



$$R-\overset{\overset{\displaystyle O}{\|}}{C}-OH + H^+ \longrightarrow ?$$

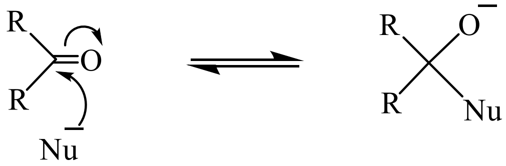
i- If the hetero atom is part of the *pi* system its unshared pair(s) of electrons are available.

ii- If the hetero atom is connected to the *pi* system its unshared pair(s) of electrons are not available.

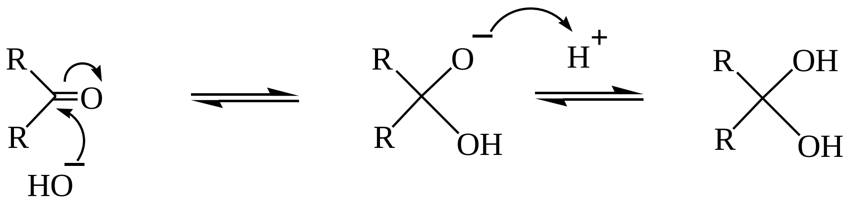
Chapter 2

NUCLEOPHILIC ADDITION TO THE CARBONYL GROUP

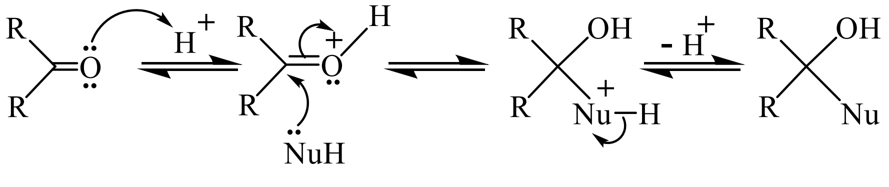
The carbonyl group has a polarizable *pi* bond, and its electrophilic carbon atom can be easily attacked by nucleophiles $N^{\cdot\cdot}$ or N^{-}:



The carbonyl group can be assumed to react with hydroxide anion: However this reaction is in equilibrium and the final dihydroxy alcohol is not exist in the presence of a base (HO^{-}).

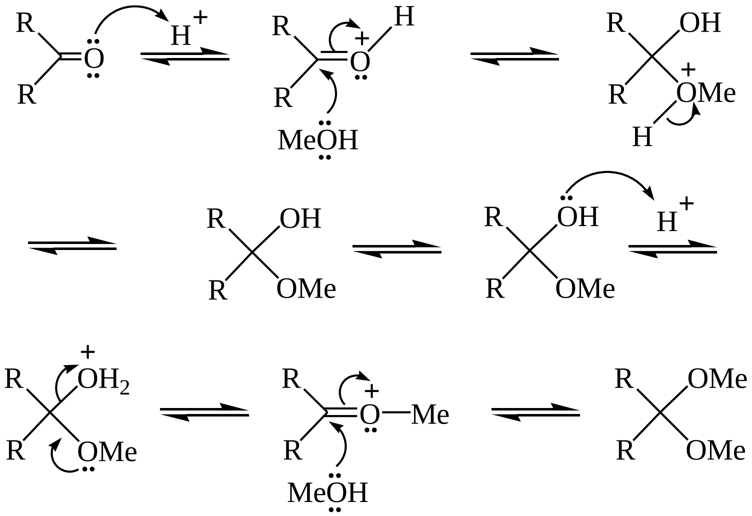


The same reaction can occur in another approach, in which the proton is firstly attacked by the carbonyl oxygen and then the nucleophile adds to the electrophilic carbon:

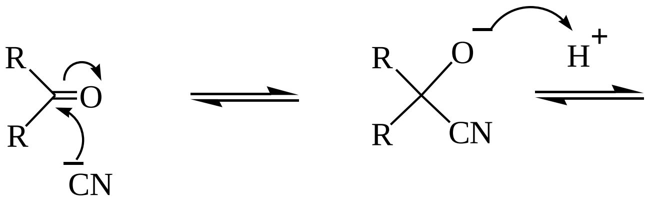


Yet again H_2O cannot be undergoing this reaction even under acid catalysis. However this reaction readily takes place with MeOH in the presence of an acid (MeOH is much better nucleophile than H_2O).

Note that a proton is used first and then regenerated as an example of the acid catalysis. However, using MeOH as nucleophile the corresponding product acetal for aldehydes (ketal for ketones) is formed:

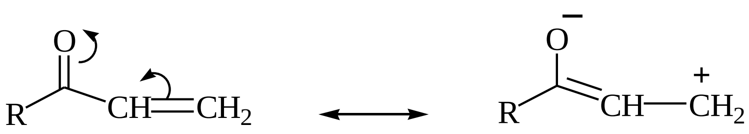


Cyanohydrins $R_2C(OH)(CN)$ are formed by adding excess of NaCN and one mole of acid to the carbonyl compound. The first part of the reaction is in equilibrium, and the acid is added to drive over the equilibrium by protonating the intermediate:

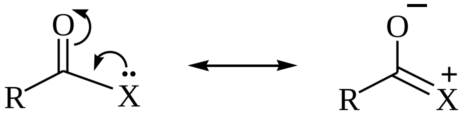


Some substituents stabilize the C=O bond in RCOX and make it less reactive:

(a) Some substituents stabilize RCOX by π-conjugation:

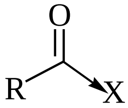


(b) Some others do it by lone pair conjugation:



(X = OEt, NH_2)

On the other hand, some substituents destabilize the C=O bond in RCOX by inductive electron withdrawal:



(X = Cl)

Taking RCHO as standard, we can say that Cl activates the carbonyl group by inductive withdrawal. However, when X = Me the carbonyl group is deactivated by π-delocalization *via* hyper conjugation, whereas NH_2 and OEt by lone pair donation, NH_2 is more effective at this (nitrogen is a soft atom comparing to oxygen). I it is known that ammonia is much more basic than water due to the same reason. The same factors could affect the product as well.

Since the carbonyl group has gone in $R_2C(OH).CN$, we would expect very little effect from any of these substituents. There can be not any conjugation, and inductive effects on the distant O atom will be small. What effect would an inductively withdrawing substituent would have on the equilibrium for cyanohydrin formation?

The inductively withdrawing substituent in the cyanohydrin equilibrium will destabilize the carbonyl compound a lot, and have very little effect on the produced

compoud, it will therefore push the equilibrium over to the product. Consider cyanohydrin formation from:

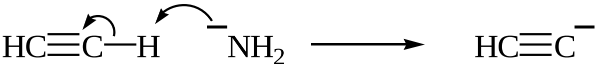
a) MeCHO	**b) PhCHO**
c) $Me_2C=O$	**d) PhCO.Me**
e) $Ph_2C=O$	**f) MeCOOEt**

Compound (a) gives the corresponding cyanohydrin, whilst compounds (e) and (f) give no cycnohydrin at all, <u>comment</u>. In compound (d) there is a strong π-conjugation from the benzene ring, which stabilizes the carbonyl compound (this effect is absent in compound (c)). These results fit in with what we have mentioned above.

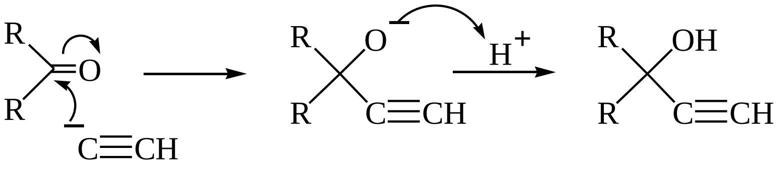
However, it is worth mentioning that formaldehyde H.CO.H (H-CHO) is more reactive than acetaldehyde CH_3.CO.H (CH_3CHO, or aldehyde RCHO) and much more reactive than acetone CH_3.CO.CH_3, due to two reasons:

- **(i) Electronic factor, which lower down the reactivity of the electrophilic carbonyl carbon.**
- **(ii) Steric factor, which retard the nucleophile abroach.**

The acetylide anion is formed by the action of strong base (e.g. the amide anion $^{-}NH_2$) on acetylene:



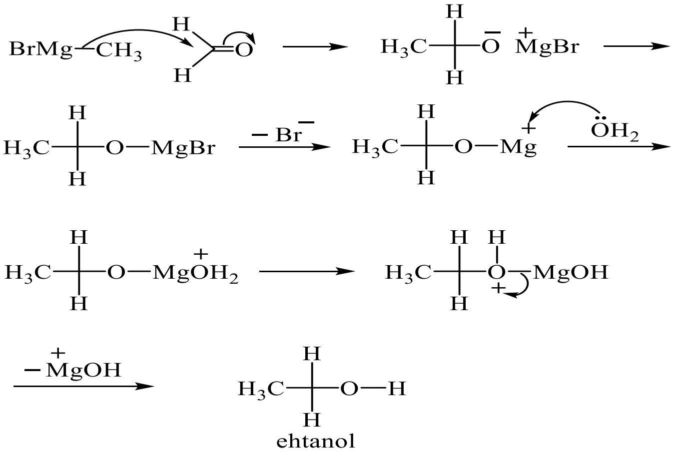
This strong acetylide anion adds easily to the carbonyl group, according to the following equation:



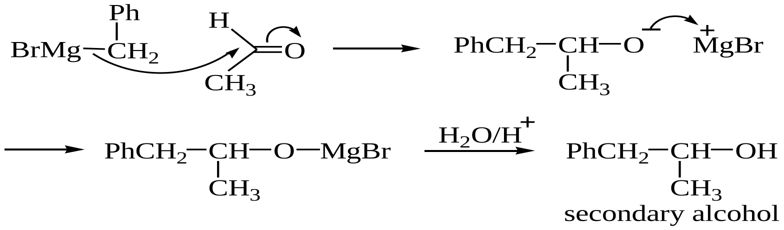
If you know that the pK_a of HCN is 9.15, that of water is 15.7, and that of acetylene is about 25. Which anion, CN^-, HO^-, or acetylide anion, would add fastest to acetone?

It is well known that if HX is a weak acid, X^- is a strong base, so acetylide anion is the fastest then hydroxide, and the cyanide is the slowest.

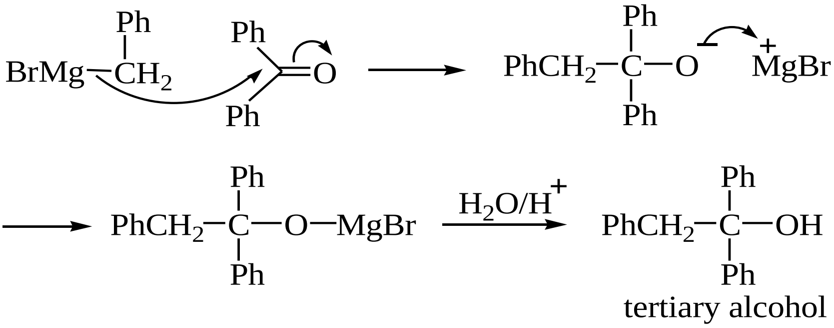
Another type of carbon nucleophile is the Grignard reagent RMgBr made by direct metalation of the organic halide with magnesium metal in dry ether. The alkyl part of these compounds acts as a nucleophile at the electrophilic carbon of the carbonyl group because the electrons in the C-Mg bond polarize towards the carbon atom. Methyl magnesium bromide readily reacts with a carbonyl compound to give the corresponding alcohol after acid hydrolysis according to the following Scheme:



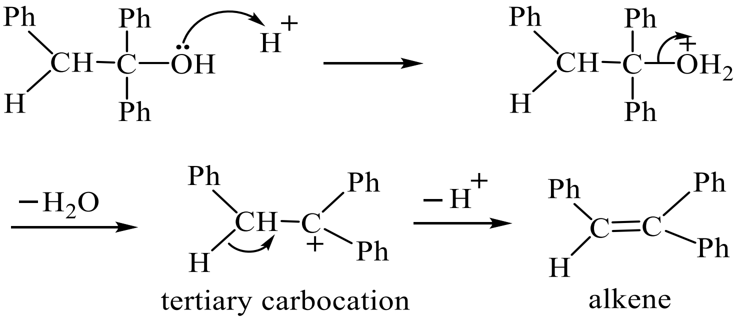
The addition Grignard reagent to formaldehyde gives primary alcohol, when it adds to R.CHO a secondary alcohol is obtained. For example the reaction between benzyl magnesium bromide and acetaldehyde yields to secondary alcohol.



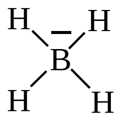
However, if Grignard reagent adds to a ketone a tertiary alcohol will be formed. Again, benzyl magnesium bromide reacts with diphenylketone to give the corresponding tertiary alcohol.

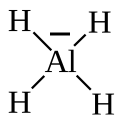


During the work-up in acidic medium, the obtained tertiary alcohol reacts spontaneously with acid and loss of water leads to a stable tertiary carbocation, which loses proton to yield the expected alkene:

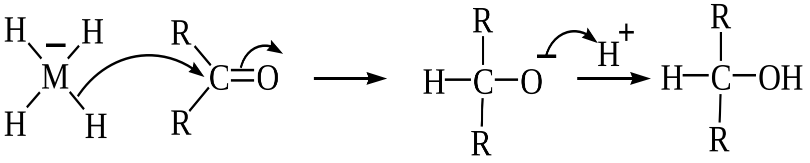


The hydride ion, H^- is considered as a good candidate to attack the carbonyl carbon. Sources of H^- for addition to the C=O bond are $NaBH_4$ and $LiAH_4$, which are the familiar sources for obtaining the hydride ion H^-.





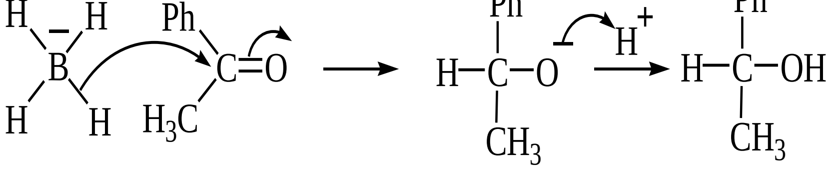
The tetrahedral octet anions MH_4^- (M is Al or B) transfers H^-, which attacks the electrophilic carbon of a ketone as follows:



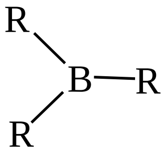
(M = Al, B)

Lithium aluminium hydride $LiAlH_4$ was used for such a long time. But it is highly dangerous to handle and store, thus when it is damp it gives off hydrogen in large quantities, and evolves heat at the same time which results in fire. However, sodium boron hydride $NaBH_4$ is less reactive so it is much safely to be handled and stored, and can be used readily in aqueous solution.

Acetophenone can be easily reduced by the effect of sodium borohydride to give the corresponding secondary alcohol:

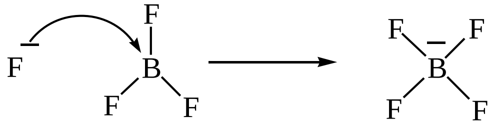


These reagents demonstrate two important proprties of boron and aluminium compounds. The neutral trivalent B and Al compounds are in the sixtet state and electron deficient:



(only six valency electrons: no lone pair)

These trivalent compounds readily accept anion to form stable octet tetravalent anions. For example the reaction between the trivalent BF_3 and a flouride anion F^- forms the tetravalent B^-F_4.

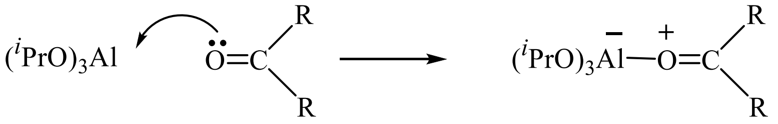


The formed tetravalent anions can transfer an anion to the electrophilic center of another molecule:

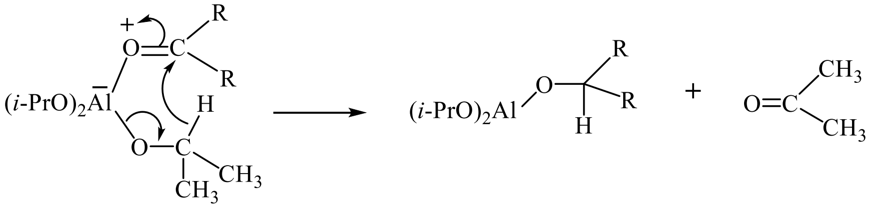
Thus, we can say that trivalent boron and aluminium compounds can accept anions from one molecule and then transfer them to another one.

Meerwein-Ponndorff reduction is a very good example to show such selective reduction. In this reduction process the trivalent compound is aluminium *tri*-iso-propyloxy, $Al(OPr^i)_3$. The unshared pair of electrons on the carbonyl oxygen of a ketone adds to the Al atom of this reagent to form a tetrahedral anion.

We must keep in mind that the trivalent Al atom is electrophilic and therefore it can be attacked by nucleophiles, in this case the carbonyl oxygen of the ketone molecule is the nucleophile.



The reaction goes on according to the following equation:

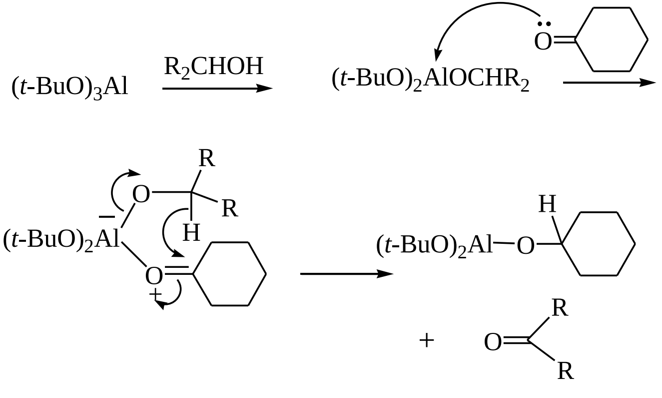


The products so far are acetone and a new aluminium compound. The reaction is done in isopropanol as a solution so that another ^{i}PrO- group displaces the newly formed secondary alcohol from the Al atom:

$$(i\text{-PrO})_2Al{-}OCHR_2 \xrightarrow{i\text{-PrOH}} (i\text{-PrO})_3Al + HOCHR_2$$

The reaction is done at a high temperature enough for the acetone to be distilled off.

Oppenauer oxidation is the reverse reaction, in which aluminium *tri*-tertiarybutyloxy, $Al(tBuO)_3$ is used in cyclohexanone as a solvent to oxidize any secondary alcohol into the corresponding ketone.



According to the mechanism of the previous reactions a great selectivity is noticed in the reduction or oxidation of the carbonyl group with no effect on the other functional groups such as C=C double bonds.

Example:

Discuss the following chemical reactions and draw the structure of (A), (B) and (C):

$$CH_3COCH_2CMe_2CHO \xrightarrow{EtOH/H} (A) \xrightarrow[i\text{-}PrOH]{Al(i\text{-}PrO)_3} (B) \xrightarrow{H_2O/H^+} (C)$$

In the first step the aldehyde group forms the acetal but the ketone group does not form the ketal.

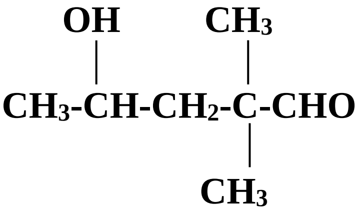
$$CH_3CO.CH_2CMe_2CHO \longrightarrow CH_3CO.CH_2CMe_2CH(OEt)_2$$

It is well documented that the aldehyde group –CHO is much reactive than the ketone group, and we need to reduce the ketone group. In this case it is recommended to protect the aldehyde group *via* the acetal formation.

Only one carbonyl group is now available for Meerwein-Pondorff reduction:

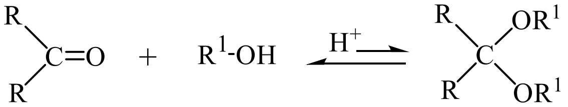
$$CH_3.CO.CH_2.CMe_2.CH(OEt)_2 \longrightarrow CH_3.CH(OH).CH_2.CMe_2.CH(OEt)_2$$

Finally the acetal is hydrolyzed in acidic medium. This example shows that a ktone group is possibly reduced in the presence of the more reactive aldehyde group:

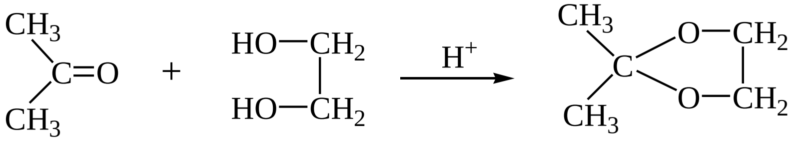


$$CH_3\text{-}\overset{\displaystyle OH}{\overset{|}{C}}H\text{-}CH_2\text{-}\overset{\displaystyle CH_3}{\overset{|}{\underset{\underset{\displaystyle CH_3}{|}}{C}}}\text{-}CHO$$

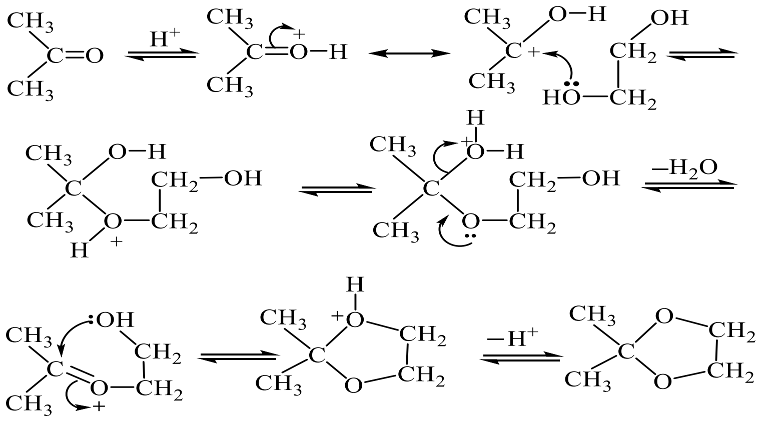
Although acetal formation is a reversible reaction, but the equilibrium constant for acetal formation from a ketone is unfavourable and poor yields are obtained:



However, ethylene glycol is rather very useful for protecting the carbonyl group through obtaining the cyclic acetals:

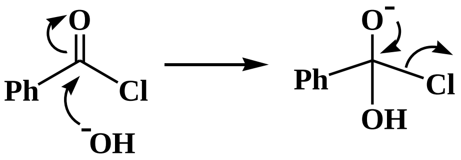


The reaction occurs according to the following mechanism:

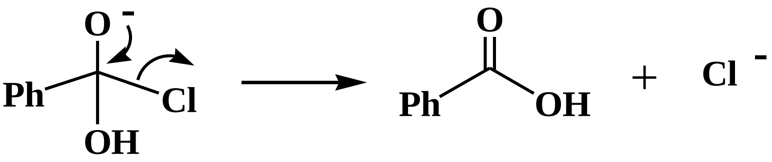


We have discussed in the previous pages only the reactivity of aldehydes and ketones. We are now moving to study the reactivity of the carbonyl group in the full range of structures including carboxylic acids RCOOH, acid chlorides RCOCl, and esters RCOOR. According to our knowledge of the nucleophilic addition, one can imagine the

first reaction between hydroxide ion and benzoyl chloride PhCOCl:



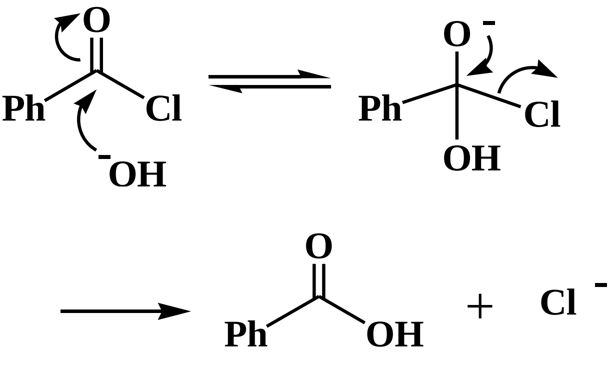
An intramolecular step then occurs, in which the negative charge returns back to restore the C=O double bond with expelling Cl^- anion:



Explain why Cl^- has been expelled and not the ^-OH?

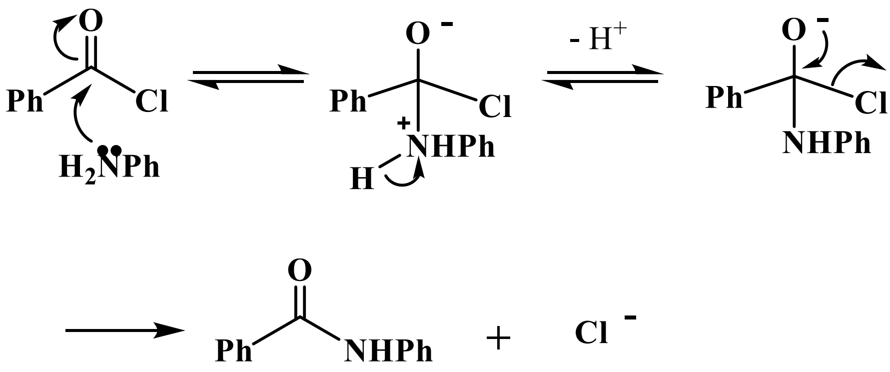
The Cl^- anion has been easily expelled because it is a better leaving group than ^-OH. It is well known that HCl is a stronger acid than HOH and is therefore Cl^- is a weaker base than OH^-. So HCl is much easier to ionize and Cl^- must therefore be more stable than ^-OH, it is known that the stronger base (Nucleophile) substitutes the weaker one.

The whole reaction will be as follows:



This reaction is in fact a nucleophilic substitution reaction, in which OH substitutes Cl.

Aniline $PhNH_2$ reacts readily with benzoyl chloride to form the expected amide. In this reaction aniline is the nucleophile, yet again NHPh substitutes Cl:



As far as the carbonyl group is concerned, molecules are better nucleophiles if they are more basic and worse leaving groups.

Again it can be said that a stronger nucleophile will displace a weaker nucleophile from a carbonyl compound.

Sample problem:

Which of the following reactions would you expect to work well?

(a) $Cl^{-} + CH_3CONH_2 \rightarrow CH_3CO.Cl + NH_2^{-}$

(b) $NH_3 + CH_3CO.OEt \rightarrow CH_3CO.NH_2 + EtOH$

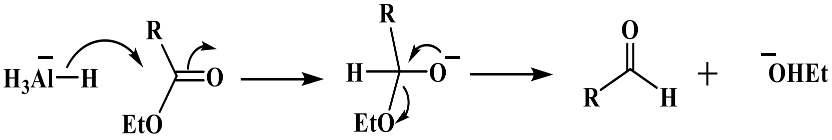
(c) $CH_3CO.O^{-} + CH_3CO.Cl \rightarrow CH_3CO.CH_3 + Cl^{-}$

(b) and (c) would work well, whereas (a) would ont.

Predict the following reaction:

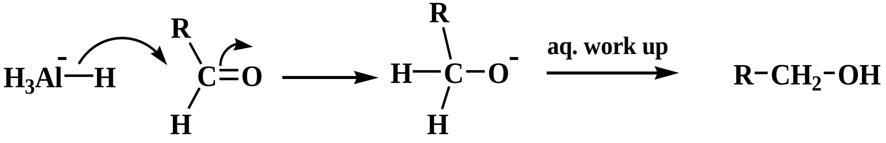
$$RCO.OEt + LiAiH_4 \rightarrow ?$$

Solution:



According to our knowledge AlH_4^- ion delivers H^- as a nucleophile, which will attack the ester carbonyl group.

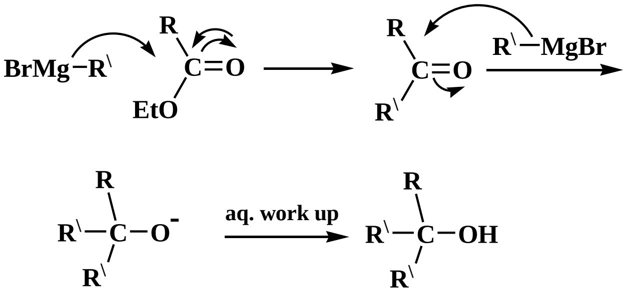
It is well known that EtO^- is less basic than H^-, and so it will be displaced. The produced alaldelyde under the reaction conditions will be further reduced to give the corresponding primary alcohol:



It is well known that the aldehyde is much more reactive than the ester, so it is impossible to stop the reaction at the first stage (the aldehyde formation step). The reduction of any compound by $LiAlH_4$ needs normally an excess amount of the $LiAlH_4$, this explains the formation of the alcohol in the given example.

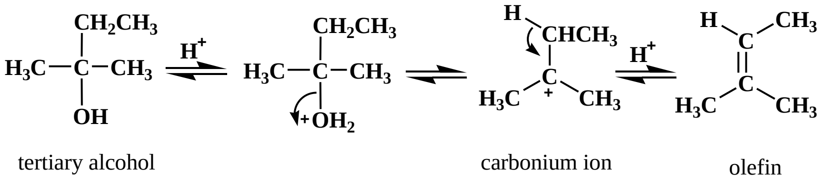
Grignard reagents RMgBr are considered as a very important series of nucleophiles. Let us discuss the reaction of RMgBr with RCOOEt.

The first step converts these carbonyl compounds into reactive carbonyl products (ketones). In such reaction an excess amount of Grignaaard reagent is normally used, therefore the corresponding tertiary alcohols are obtained in good yields:



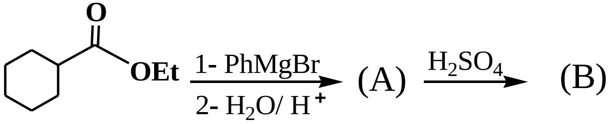
The double headed arrow on the carbonyl group of the ester molecule means two steps, (a) the polarization of the carbonyl group, and (b) the return of the negative charge on oxygen to restore back the carbonyl C=O double bond with expelling away EtO^-. The final product from this reaction is a tertiary alcohol.

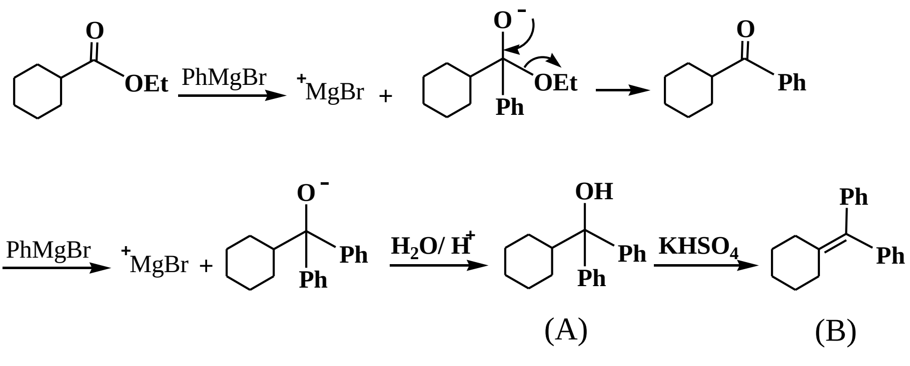
We shall discuss how this reaction finally ends up as an olefin. During the acid work-up the tertiary alcohols are easily converted into carbocations. The formed carbcation can either pick up a nucleophile or lose a proton to give an olefin. The olefin is obtained in good yield by using a strong acid with a weakly nucleophilic anion such as H_2SO_4 or $KHSO_4$.



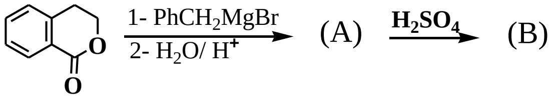
Example:

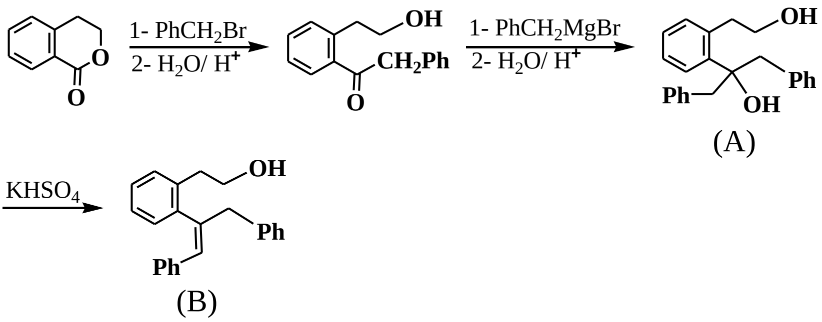
Discuss the following chemical reactions and draw the structure of the compounds (A) and (B):



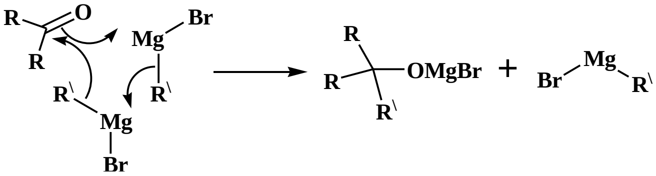


Now let us discuss the reaction between $PhCH_2MgBr$ with a cyclic ester (lactone). The reaction occurs just like that for an acyclic (open chain) ester.

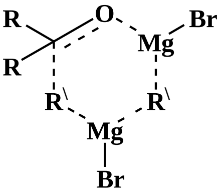




A Grignard reaction is probably an example of the electrophilic catalysis, which involves two molecules of the Grignard reagent, one molecule as a reactant and the other as a catalyst as follows:

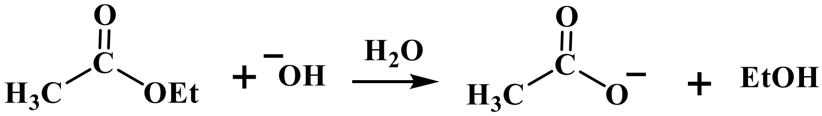


The reaction occurs through a concerted cyclic six-membered transition state:

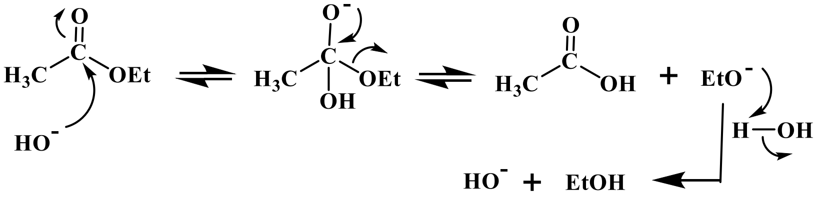


In view of our conclusion (the more basic nucleophile will substitute the less basic nucleophile). In other words the stronger nucleophile substitutes the weaker nucleophile.

The hydrolysis of esters in alkaline solution is considered to be the best example for substituting the more basic $^{-}$OEt by the less basic $^{-}$OH the more basic !!!



This reaction occurs according to the following mechanism:

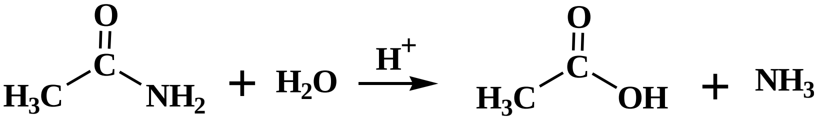


It should be remembered that the hydroxide anion $^{-}$OH reacts with the obtained carboxylic acid to give finally the corresponding carboxylate anion.

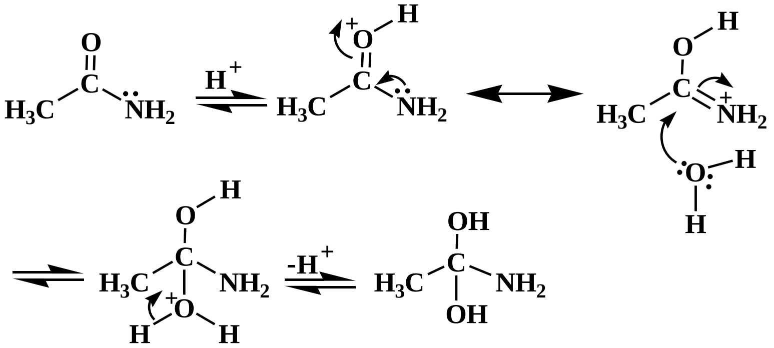
Notice that $^{-}$OH displaces the slightly more basic $^{-}$OEt. Can you give a reason for why this happens so easily?

In this reaction the steps are all in equilibrium, and it is known that the equilibrium can be driven over. The reaction is carried out in water with an excess of the hydroxide anions $^{-}$OH, which drive the reaction forward by the mass action effect. Moreover, $^{-}$OEt is a good leaving group in basic medium. On the other hand, CH_3COOH in basic medium will form CH_3COO^{-} as an unreactive anion, which has no much effect in the equilibrium system.

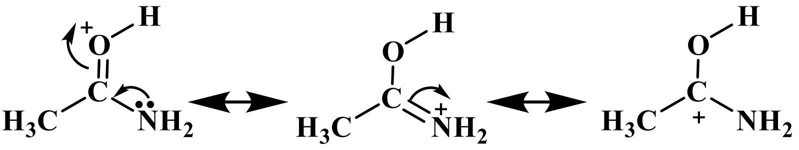
Amides can be readily hydrolyzed in acid solution too:



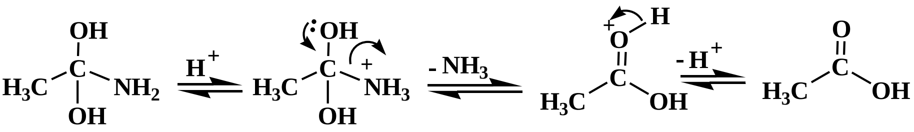
How could acid catalyze the first step of the reaction, the formation of the tetrahedral intermediate?


tetrahedral intermediate

Now using the lone pair of electrons on nitrogen results in the most delocalized cation:



In the tetrahedral intermediate, none of these substituents is good leaving group, but in acid solution the amino group NH_2 would be easily protonated because it is the more basic, and $^+NH_3$ is now a good leaving group.



This reaction is very similar to some of the steps in the acetal formation. So in conclusion, a base catalyzes the hydrolysis of esters or amides in two ways:

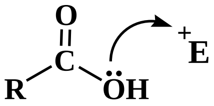
1- By driving over an unfavourable equilibrium using the mass action effect.

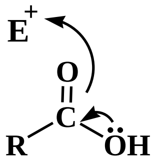
2- By capturing the carboxylic acid product as an unreactive anion compared to $^{-}$OH.

Acid catalyzes the same reaction also in two ways:

1. **It catalyzes the addition of the nucleophile by protonating the carbonyl oxygen.**
2. **It turns a bad leaving group into a good one by protonation.**

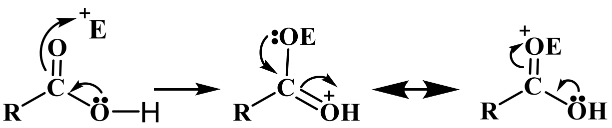
This first catalytic function can be carried out by electrophiles other than the proton. This applies particularly to carboxylic acids. One could say that the electrophile could be attacked by either oxygen atom:



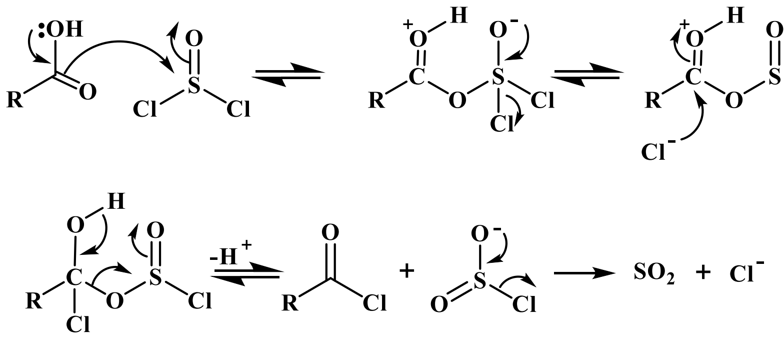


In fact the carbonyl oxygen is the only atom to participate in this electrophilic substitution reaction. The carbonyl oxygen atom will attack E^+ for two reasons:

- **(i) The unshared pair of electrons of the carbonyl oxygen are available. Why?**
- **(ii) The positive charge in the produced cation will be delocalized on both oxygen atoms.**



For example, a carboxylic acid reacts readily with thionyl chloride to form the corresponding acid chloride. Initial attack occurs at the carbonyl oxygen.



We now have within the system:

a) **a reactive carbonyl group, due to protonation.**

b) **a good leaving group, $ClSO_2^-$, which decomposes to SO_2 gas and Cl^- anion.**

c) **a nucleophile, Cl^- anion.**

The net result is that a carboxylic acid has been converted into an acid chloride together with some other byproducts.

In this context, the above reaction resembles the first example of nucleophilic substitution at the carbonyl carbon of a carboxylic acid that we have seen. It is noticed that unless we attack first with an electtrophile, carboxylic acids are very unreactive towards nucleohilic substitution, due to the following reasons:

1- **The acid carbonyl group is rather unreactive.**

2- **The HO^- is a very bad leaving group.**

3- **Nucleophiles are bases, which may remove the acidic proton rather than attack the carbonyl carbon.**

How do we overcome these problems by the reaction with thionyl chloride?

In this reaction the carbonyl group has become more reactive $C=O^+$ due to the protonation of the carbonyl oxygen. A good leaving group is also exist $CISO_2^-$. The

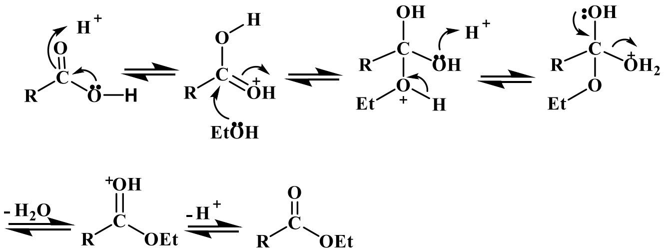
proton will come off and because of the electrophilic assistance we can use a very weak nucleophile, Cl^-. Other reagents, which can give the same acid chloride are $POCl_3$ and PCl_5.

How can we convert a RCOOH into RCOOEt:

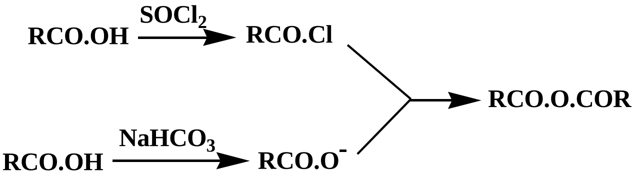
However, it has been known that EtOH reacts with acid chloride to give the corresponding ester under basic conditions. The following scheme represents the whole conversion of acids into esters:

$$\mathrm{RCO.OH} \xrightarrow{SOCl_2} \mathrm{RCO.Cl} \xrightarrow[\mathrm{Base}]{\mathrm{EtOH}} \mathrm{RCO.OEt}$$

It is worth mentioning that a carboxylic acid readily reacts with EtOH under acid catalysis to give the expected ester in good yield. The full mechanism of such esterification is as follows:



How can we convert a carboxylic acid RCOOH into the corresponding anhydride RCO.O.COR? It is apparently clear that the shortest way is to displace Cl^- by $RCO.O^-$:



General questions:

1- Arrange the following compounds in order of reactivity towards water, all reactions are to give the carboxylic acid:

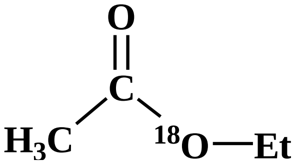
$CH_3CO.OCO.\ CH_3$	$CH_3CO.NH_2$
$CH_3CO.Cl$	$CH_3CO.OEt$

The answer:

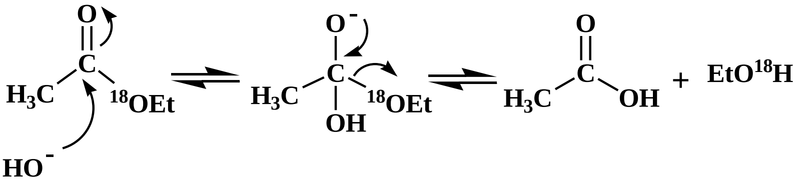
Chloride > anhydride > ester > amide.

In fact the chloride explodes with cold water, the anhydride reacts with cold water, the ester reacts with dilute acid or base but the amide reacts only with boiling 70 % acid or 10 % caustic soda.

2- If you hydrolyzed an ester labeled with heavy oxygen (O^{18}) in acid or base, would the ^{18}O end up in the acetic acid or in the ethanol?



In both acid and base it would end up in the ethanol, this is one of the pieces of evidence used to establish the mechanisms we have been discussing.



3- How would you carry out this multi-step synthesis?

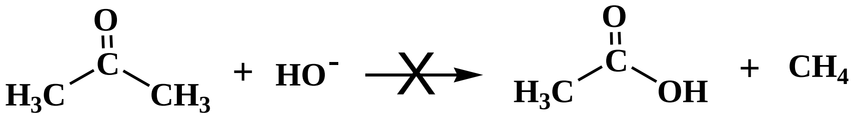
$$PhCH_2CO.OH \longrightarrow PhCH_2CH_2O.COCH_2Ph$$

a) $PhCH_2COOH \xrightarrow{SOCl_2} PhCH_2COCl$

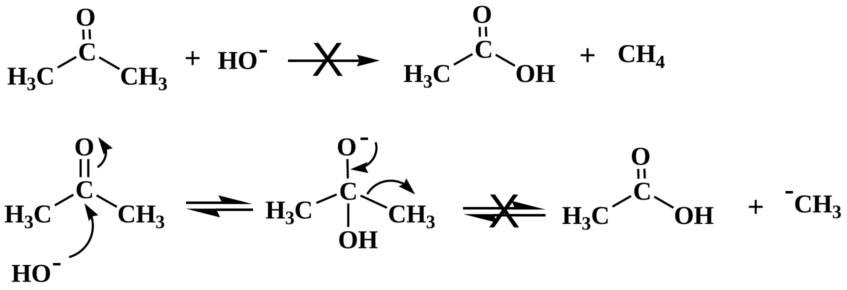
b) $PhCH_2COOH \xrightarrow[H^+]{EtOH} PhCH_2COOEt \xrightarrow{LiAlH_4} PhCH_2CH_2OH$

c) $PhCH_2COCl + PhCH_2CH_2OH \longrightarrow PhCH_2CH_2O.COCH_2Ph$

The following reaction does not occur, why?



The answer:

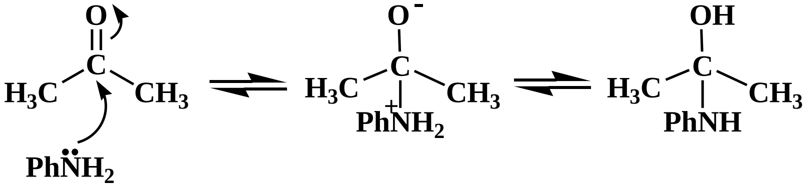


According to the given mechanism it is clear that CH_3^- is far too stronger nucleophile to be substituted by ^-OH.

NUCLEOPHILIC SUBSTITUTION AT THE CARBONYL GROUP LEADING TO COMPLETE REMOVAL OF THE OXYGEN ATOM

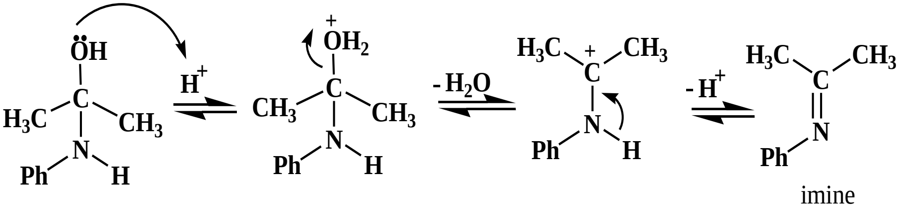
1. **Imine formaation from aldehydes and ketones.**
2. **Oxime formation and the structure of oximes.**
3. **Hydrazone and semicarbazone formation.**
4. **Reduction of C=O to CH_2.**
5. **Conversion of C=O to CCl_2.**
6. **DDT synthesis.**
7. **Chloromethylation of aromatic compounds.**
8. **Review questions.**

Aniline, $PhNH_2$ adds to the carbonyl group of acetone to give a neutral addition product as follows:

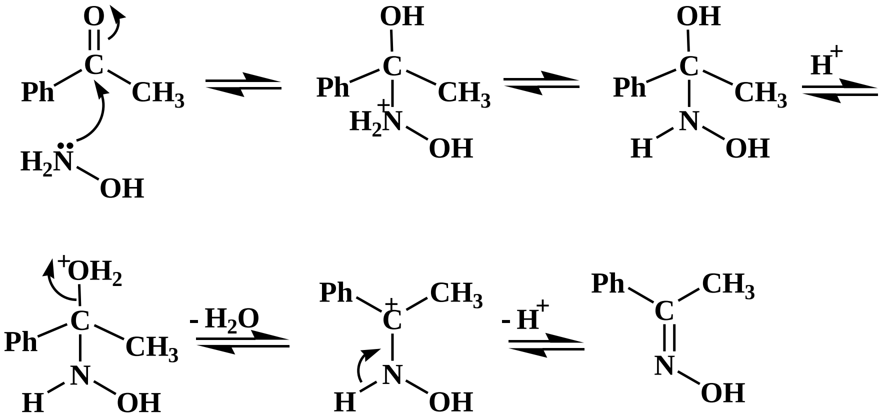


However, the extension of this addition reaction into a substitution one, a leaving group must exist. In fact, CH_3, OH or PhNH are very bad leaving groups.

By protonation (as in amide hydrolysis), if PhNH is protonated and eliminated, we just go back to square one, i.e. the reaction goes back to the starting materials, but if OH is protonated and eliminated, the reaction will yield the corresponding imine.

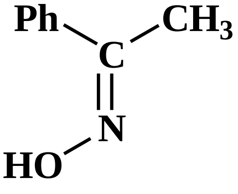


The product of this last reaction is an imine, containing a C=N double bond. The formation of these compounds is in equilibrium and they are very easily hydrolyzed. However, hydroxylamine $HONH_2$ reacts smoothly with the carbonyl compounds to give more stable imines. The reaction between $HONH_2$ and PhCO.Me (using the soft nitrogen atom as a nucleophile) is given below:

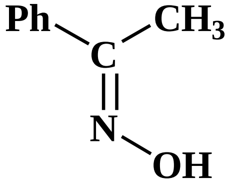


oxime

In fact two isomers are obtained due to the rigidity of the C=N bond, and the obtained two oximes, are called *"syn* " and " *anti* ":



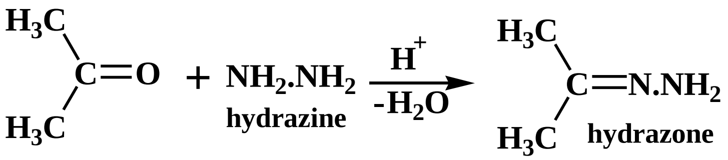
cis (syn)



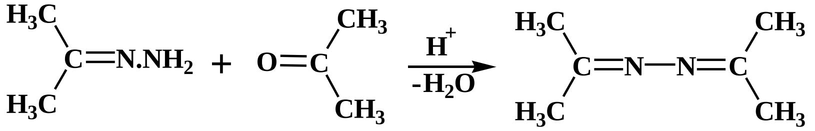
trans (anti)

Similar reactions occur with other amines, for example hydrazine NH_2NH_2 reacts with the carbonyl compounds to form stable crystalline imines known as hydrazones. Hydrazine reacts smoothly with acetone to give

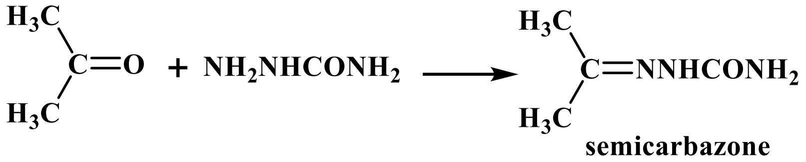
the corresponding hydrazine (the produt depends on the amount of hydrazine):



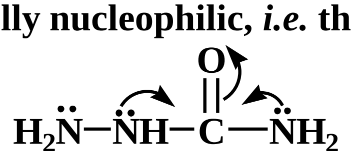
However, the other end of the molecule can react with more acetone to form a condensation product with the other amino group.



Semicarbazide, $NH_2NHCONH_2$ also similarly reacts with the carbonyl compounds to give the corresponding semicarbazones, *e.g.*:



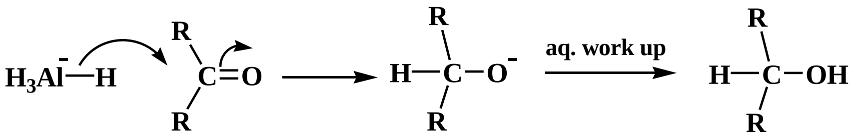
The reaction proceeds through the nitrogen atom of the free amino group, the other two nitrogen atoms have their unshared pairs of electrons interacted with the *pi* C=O bond: they are in fact amide-like. The only terminal nitrogen atom is fully nucleophilic, *i.e.* the only one to react.



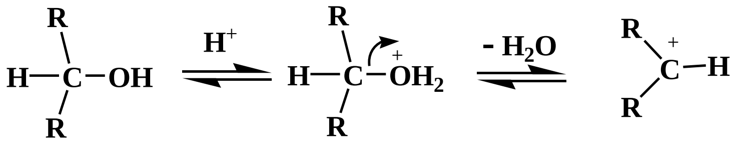
It is well documented that the hydride ion H^- source are $NaBH_4$ and $LiAlH_4$. The hydride ion can be used to remove the carbonyl oxygen atom to form a hydrocarbon:

$$R_2C=O \longrightarrow R_2CH_2$$

The neutral intermediate is found by adding hydride ion H^- to the carbonyl compound in the usual way:



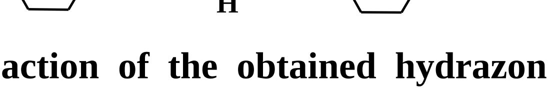
Under strongly acidic conditions this alcohol could give a carbocation:



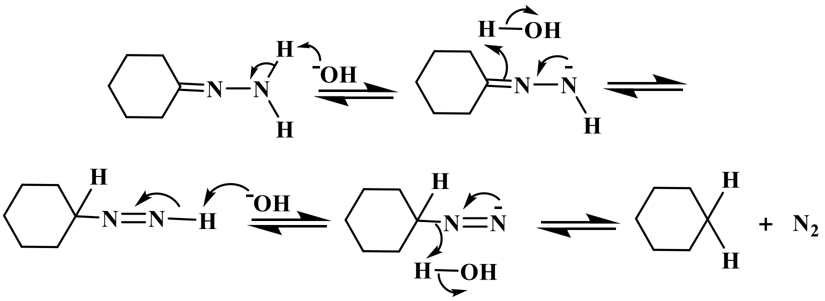
In fact $^-$MH4 are not used in such reactions due some major experimental problems. So the reduction of the carbonyl group into methylene group by the hydride ion H^- is impossible. Therefore Clemmemsen reduction, is used successfully, however its mechanism is unknown in detail:

$$R_2C{=}O + \text{Zn/Hg} + \text{conc. HCl} \longrightarrow R_2CH_2$$

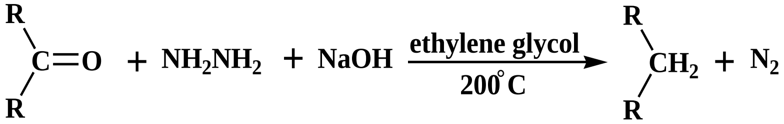
An alternative method begins with the formation of a hydrazone may give the write answer. Cyclohexanone is used here for a change (it is a general reaction for any carbonyl compound):



The reaction of the obtained hydrazone with very strong base gives the expected hydrocarbon (cyclohexane). The full mechanism is given below:

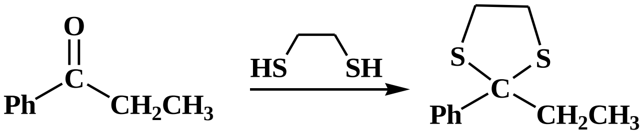


The reaction is usually done at high temperatures in ethylene glycol, a high-boiling polar solvent, and is called the Wolff-Kishner reduction:

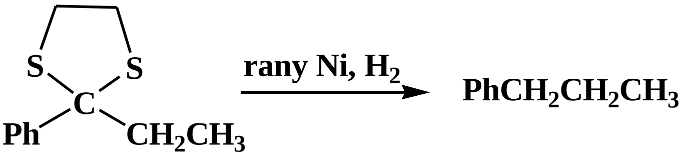


$$R_2C{=}O + NH_2NH_2 + NaOH \xrightarrow[200^{\circ}C]{\text{ethylene glycol}} R_2CH_2 + N_2$$

The reaction of $PhCO.CH_2CH_3$, with $HSCH_2CH_2SH$ gives the ketone dithioketal, a reaction similar to the formation of ketals (it is widely used to protect the carbonyl groups, as it is easily to be deprotected):



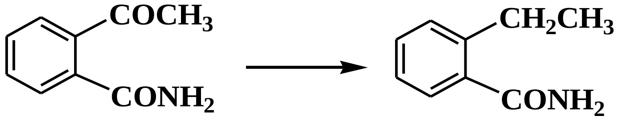
However, the formed dithioketal can be reduced directly to the hydrocarbon by catalytic hydrogenation over Raney nickel:



Up to now we have methods of reducing ketones to hydrocarbons in acidic, alkaline and neutral solutions. This is useful since some molecules, may be sensitive to some of these conditions.

Discuss the following reactions:
Which methods would you use for the following reactions?

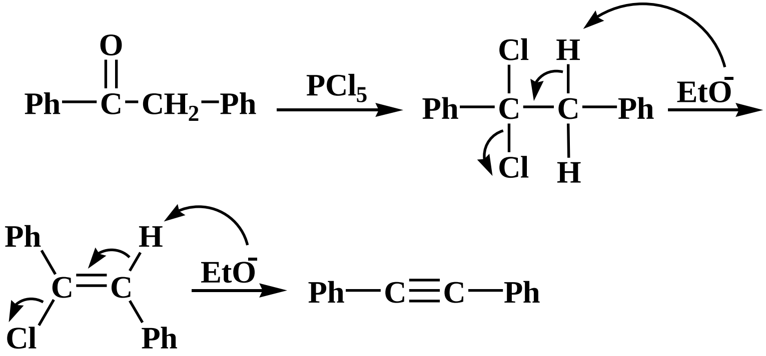
a) $PhCO.CMe_2.CH(OEt)_2 \longrightarrow PhCH_2.CMe_2.CH(OEt)_2$

b)


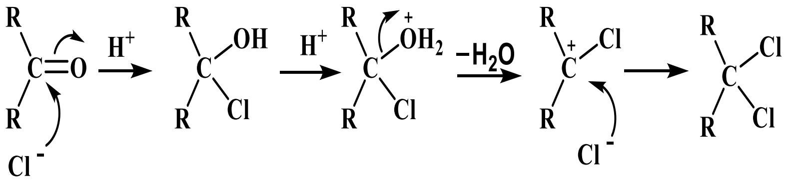
a) **Wolff-Kishner: Clemmensen would destroy the acetal.**
b) **Dithioketal. Either of the other methods would do nasty things to the amide.**

Write down the expected products of the following reaction:

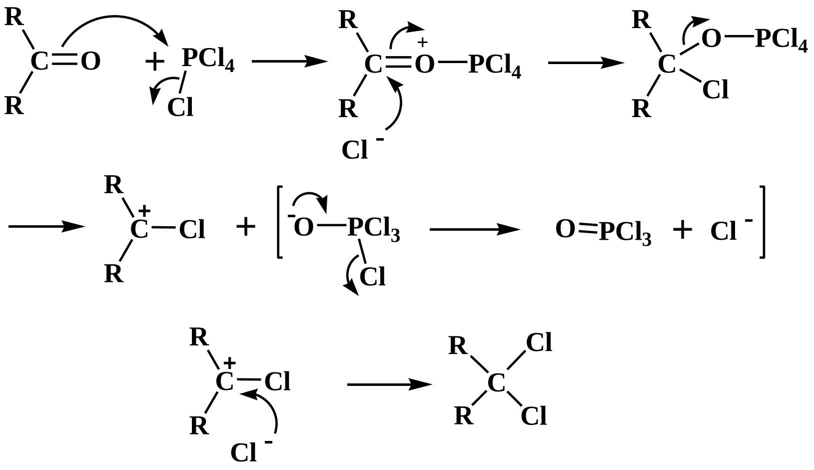
$$PhCOCH_2Ph \xrightarrow{PCl_5} \ ? \xrightarrow[EtOH]{EtO^-} \ ?$$



The idea of adding a nucleophile to a carbonyl compound to give an alcohol and then dehydrating the alcohol to a carbocation in acid solution, and finally adding another nucleophie to the carbocation, could be extended a bit. It was discussed before this idea for H^- as a nucleophile, but it did not work out too well. Now let us discuss the use of Cl^- as a nucleophile on a general ketone $R_2C{=}O$.



Such reaction cannot do this with HCl, in fact stronger electrophilic catalyst PCl_5 is used instead for the first step than the proton. The final products in this reaction are R_2CCl_2, and $POCl_3$. The reaction occurs according the following mechanism:

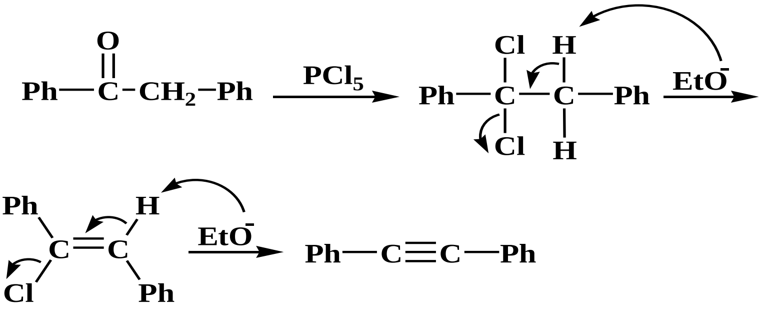


Discuss the following reaction:

$$PhCO.CH_2Ph \quad + \quad PCl_5 \longrightarrow PhCCl_2.CH_2Ph$$

The obtained product reacts with EtO^- in EtOH to give the corresponding alkyne:

$$PhCOCH_2Ph \xrightarrow{PCl_5} ? \xrightarrow[EtOH]{EtO^-} ?$$

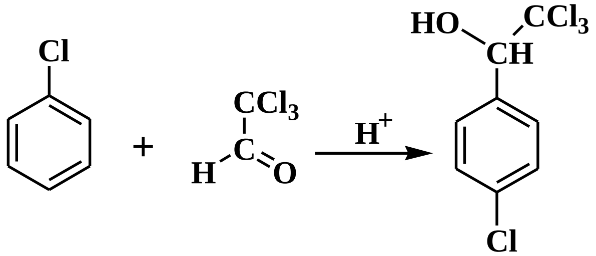


The ethoxide ion EtO$^-$ is very basic and is able to remove protons, even protons attached to carbon atoms (this proton is activated by the leaving Cl$^-$). We also have good leaving groups in the molecule and that combination look like making an elimination reaction. In fact, a double elimination occurs by the E_2 mechanism.

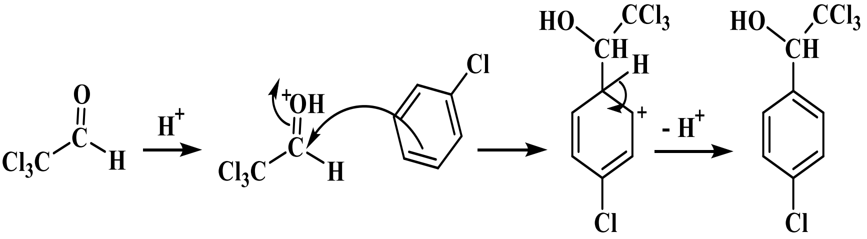
<u>The formation of DDT:</u>

With very reactive carbonyl compounds, such as chloral $Cl_3C.CHO$, we can even do an electrophilic reaction by the aromatic compounds in the presence of strong acid.

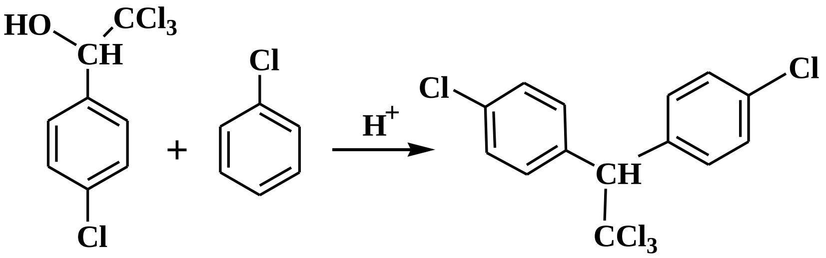
The first step (the alcohol formation):



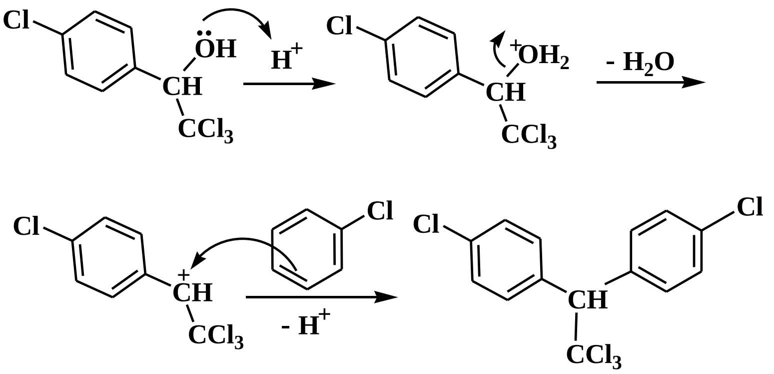
The following scheme represents the mechanism by which the first step occurs:



A second molecule adds on:



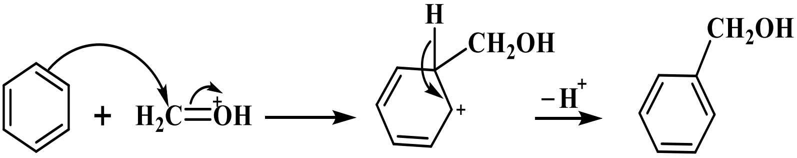
The following mechanism is suggested for the second step:



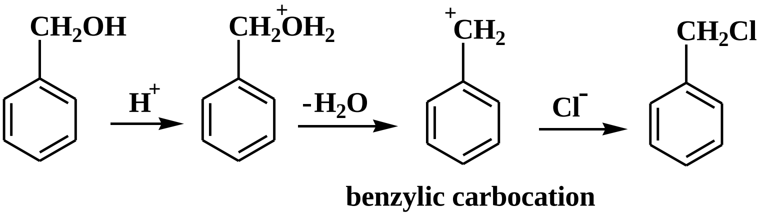
The final product is known as DDT (dichlorodiphenyl trichloroethane, which was used widely as an insecticide. However, it is not valid anymore due to the build-up of the organic chlorocompounds in animals.

Formaldehyde is a very reactive carbonyl compound, which reacts readily with benzene in acid solution to form

the corresponding hydroxymethyl derivative. The reaction mechanism is given below:



If HCl is used as the acid catalyst, Cl^- ion acts as a nucleophile in the second step to yield the chlorobenzyl:

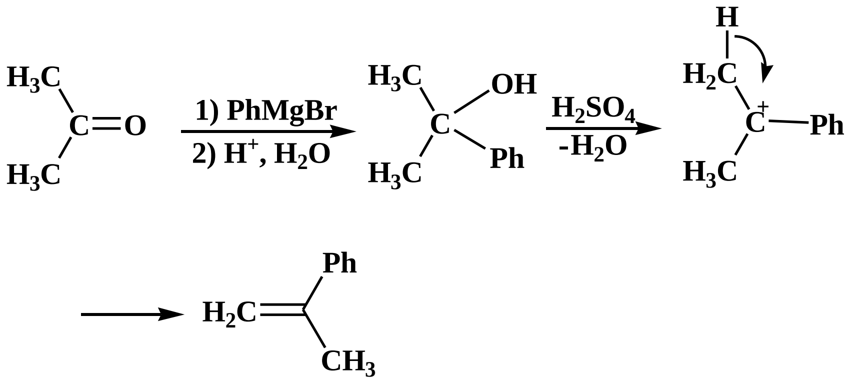


This reaction resembles a general reaction for adding a chloromethyl group $-CH_2Cl$ to an aromatic ring known as chloromethylation. The reaction is carried out in a single step, by adding CH_2O and HCl to the aromatic compound.

However, it should be remembered that the catalyst used for the DDT synthesis was H_2SO_4, whereas that for chloromethylation is HCl. In the DDT synthesis we added two molecules of the aromatic hydrocarbon, but in the chloromethylation the second step had Cl^- as nucleophile.

It is known that H_2SO_4, is an acid with a non-nucleophilic anion in the DDT synthesis, and HCl, an acid with a nucleophilic anion, in chloromethylation.

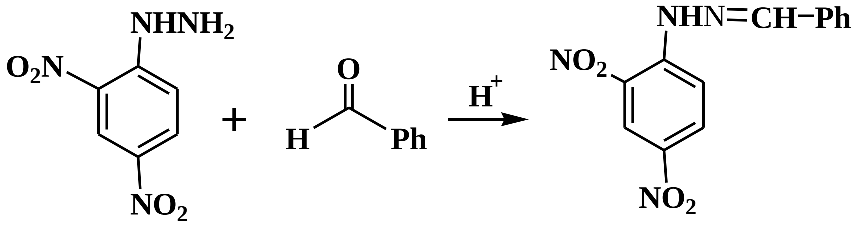
As mentioned earlier sulfuric acid H_2SO_4 is also used for the same reason in the dehydration of the tertiary alcohols produced by the addition of Grignard reagents to ketones. Acetone is used in the following example:



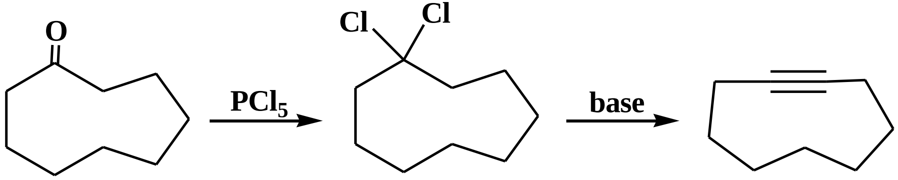
This is the final example of substitution removing the carbonyl oxygen atom completely: here you can see C=O being replaced by C=C.

<u>Review questions</u>:

Aldehydes and ketones are often characterized as 2,4-dinitrophenylhydrazones, as these are usually highly crystalline orange compounds. Draw the formation of this derivative from benzaldehyde giving reagent, catalyst, and the structure of the product.



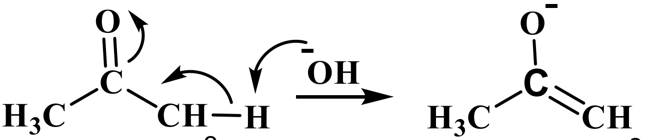
The smallest stable cyclic acetylene is in the nine-membered ring. If you had a sample of a nine-membered ring ketone, how would you attempt to make the cyclic acetylene from it?



CARBANIONS AND ENOLISAATION

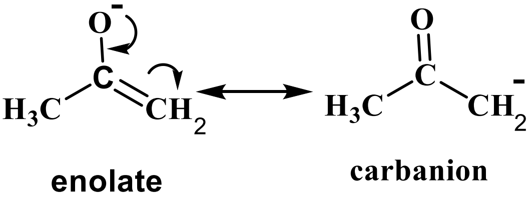
Carbanions
Tautomerism.
Equilibration and racemisation of ketones by enolisation .
Halogenation of ketones.
Formation of bromo-acid derivatives.
Organo-zinic derivatives and their use in synthesis.
Review questions.

Carbanions have a negatively charged carbon atom, they are in general not sable intermediates. However, $^{-}CBr_3$ anion is considered as one of the rare stable simple carbanions. In order to make a carbanion, one needs to remove a proton from carbon. In this case we need to accommodate the formed negative charge somewhere and the carbonyl group is the best candidate to play such a role. In the following example the curly arrows show the formation of an anion from acetone:

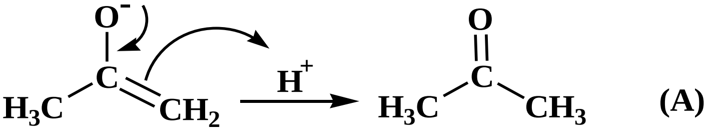


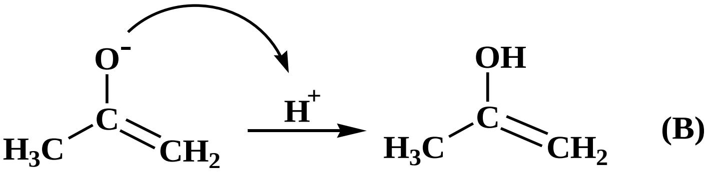
acetone enolate

In the obtained anion, which is recently called a carbonion, and the formed negative charge is delocalized between the oxygen and carbon atoms. The intermediate with the negative charge on oxygen is called enolate, whereas if the negative charge is on carbon the intermediate is called carbanion.

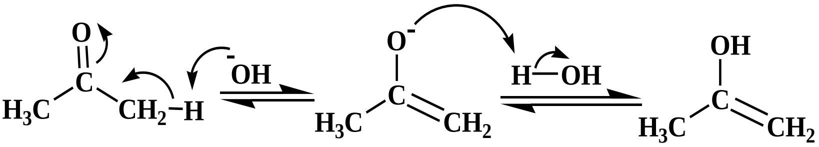


The negative charge can exist on either carbon or oxygen, so this anion can react with a proton on carbon and on oxygen to give two different products:

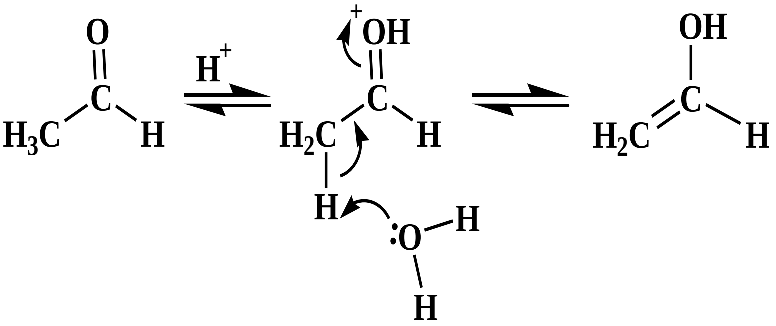




The two products (A) and (B) represent the familiar keto-enol tautomerism, in which (A) is the keto form whereas (B) is the enol form of acetone. The mechanism for the conversion of the keto form to the enol form under basic conditions is represented as follows:



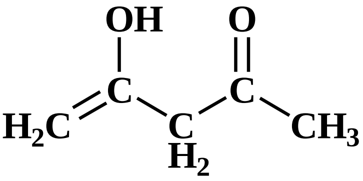
This equilibrium is catalysed by acid as well as by base. How the enol of acetaldehyde could be formed under acid catalysis?

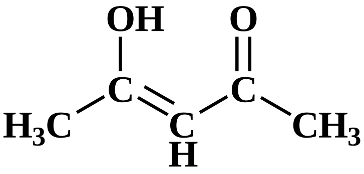


Draw the enol form of the following ketone:

$$CH_3CO.CH_2.COCH_3$$

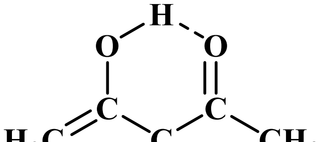
There are in fact two possible enol forms:

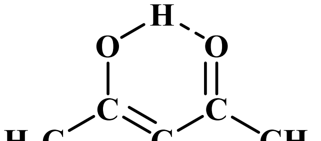




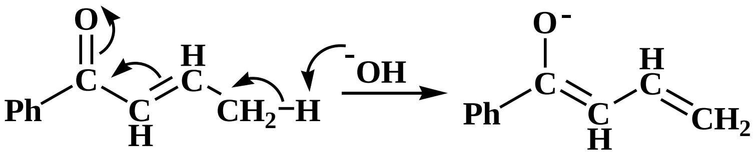
Which form is the more stable and why?

The second: not only because of the intramolecular hydrogen bonding, in fact the conjugation of the formed double bond with the carbonyl group would be more effective. In fact the second enol is stable under normal conditions.

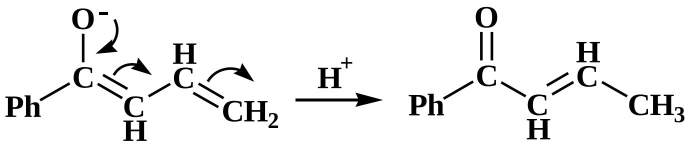




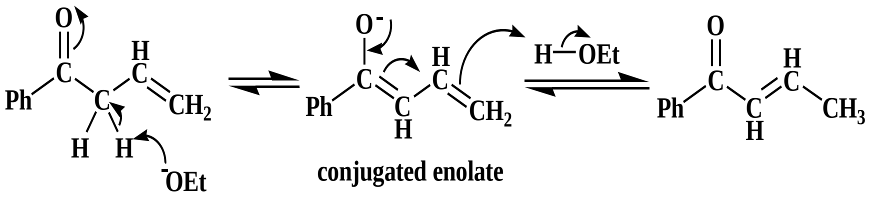
In the α,β-unsaturated ketones we have to remove a rather distant proton due to the cojugation, but the charge still goes to the carbonly oxygen:



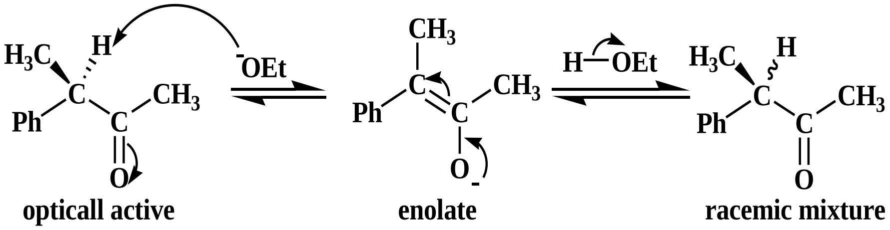
The re-protonation of this enolate will give the original compound.



However, enolization (deprotonation) and reprotonation of β,γ-unsaturated ketones will give α,β-unsaturated ketones due to the formation of conjugated enolates.



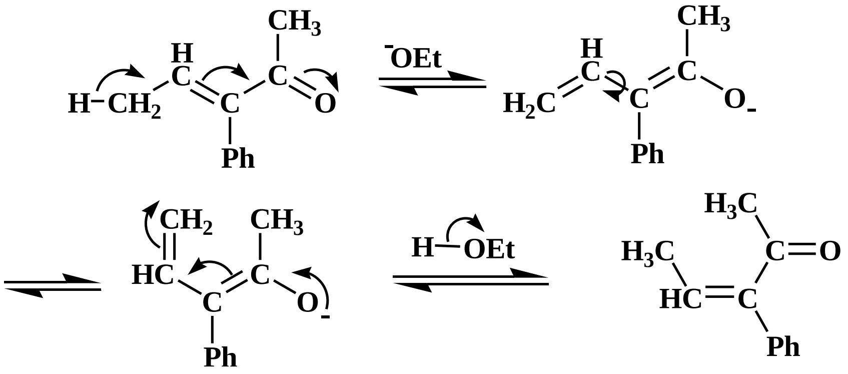
However, an optically active ketone would give racemic mixture under basic conditions, the reaction takes place in ethanol in the presence of catalytic amount of an ethoxide ion:



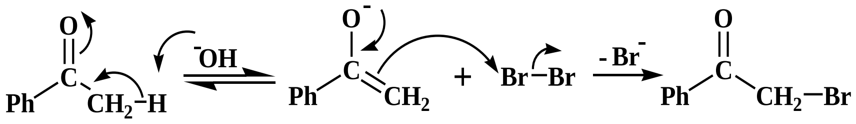
The formed enolate anion is planar (both carbons of C=C double bond are sp^2), which on reprotonation could

give racemic mixture as the proton can add on to either side of the α-carbon.

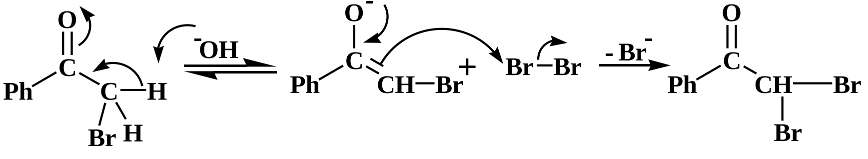
However, treating a *trans* ketone with EtO^- in EtOH will give a mixture of *cis* and *trans* ketones, due to the rotation around a single bond, what was originally a double bond. The re-protonation of the enolate anion would finally give a *cis-trans* mixture.



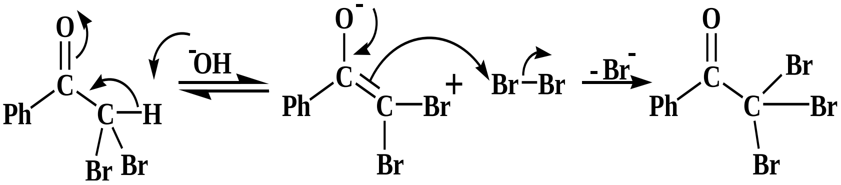
The enolate anons also react with many other electrophiles in the same way. In fact the negatively charged carbon (the carbanion anion) would then attack electrophiles. For example an enolate anion formed from acetophenone PhCO.Me attacks bromine by bringing the negative charge back from the oxygen atom:



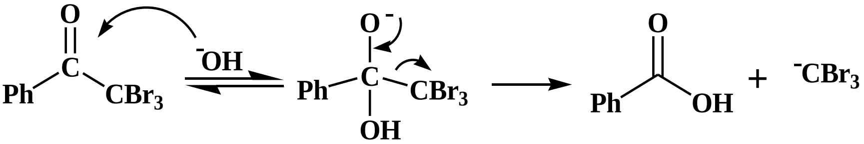
This process similarly takes place with another proton:



In this second step a second α-hydrogen is easily removed due to the inductive effect of the bromine atom. In a similar manner the third hydrogen would be even removed much faster.



So in the presence of enough bromine, the ketone is converted rapidly into the formed *tri*-bromoketone, which under the basic conditions gives benzoic acid together with $^{-}CBr_3$, one of the rare stable simple carbanions.

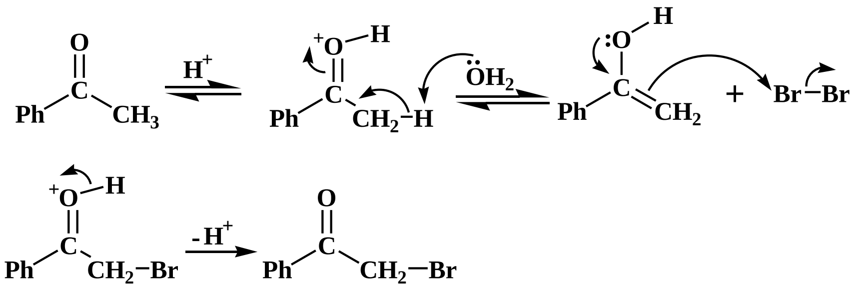


However, even though $^{-}CBr_3$ carbanion, is relatively stable, compared to other carbanions, but it is still capable to pick up a proton from water to give bromoform $CHBr_3$. We must remember that under the used basic conditions a benzoate salt would be formed and not benzoic acid.
A general equation is given below:

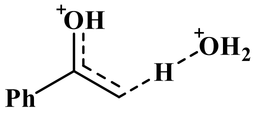
$$\underset{}{PhCO.Me} + \underset{excess}{Br_2} + HO^{-} \longrightarrow PhCO_2^{-} + CHBr_3$$

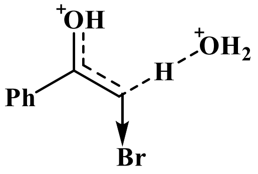
Acetophenone reacts similarly with chlorine or iodine to form chloroform or iodoform.

The synthesis of the monobromo derivative of a ketone is readily occurred in acid solution. Thus reacting aetophenone with Br_2 in acid solution yields the corresponding monobromo derivative according to the given mechanism:



The electron withdrawing effect of Br in the enolisation step (marked *) destabilizes this transition state, so the reaction can be stopped at this stage, as the positive charge is spread over all the atoms connected by the dotted line.



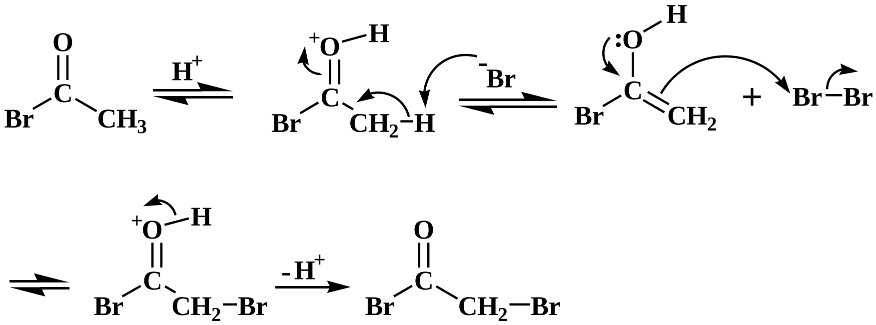


*

We previously showed that the acid chlorides are obtained by the effect of $SOCl_2$ on carboxylic acids RCOOH. Herein, we will discuss the reaction of PCl_5 and PBr_5 with RCOOH:

$$CH_3COOH + PBr_5 \longrightarrow CH_3COBr + POBr_3 + HBr$$

If the reaction is conducted in the presence of bromine the corresponding bromoacetyl bromide would be formed, bearing in mind that the produced HBr, could catalyze the enolisation of the acid bromide CH_3COBr. It means that the acid bromide enolises and reacts with bromine:

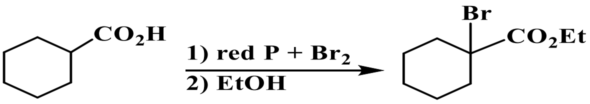


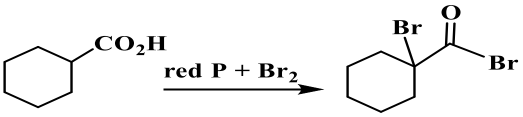
Yet again this is an acid-catalyzed reaction and it can be stopped at this stage. This valuable reaction, known as the Hell-Volhard-Zelinsky (HVZ) reaction, is normally carried out by treating the acid with red phosphorus and bromine. In this reaction PBr_5 is thus obtained in *situ*.

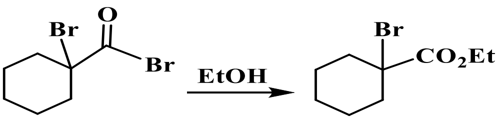
Example 1:

$$PhCH_2COOH \xrightarrow{\text{red P + Br}_2} PhCHBr.COBr$$

Example 2:



(1) 

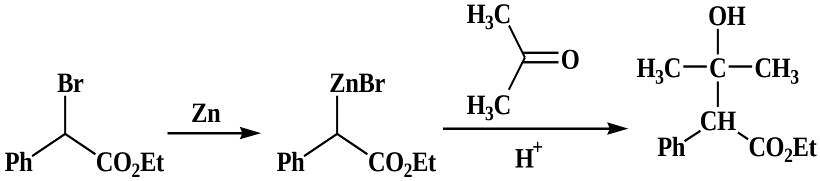
(2) 

We do not usually try to make Grignard reagents from α-bromo esters like this compound.

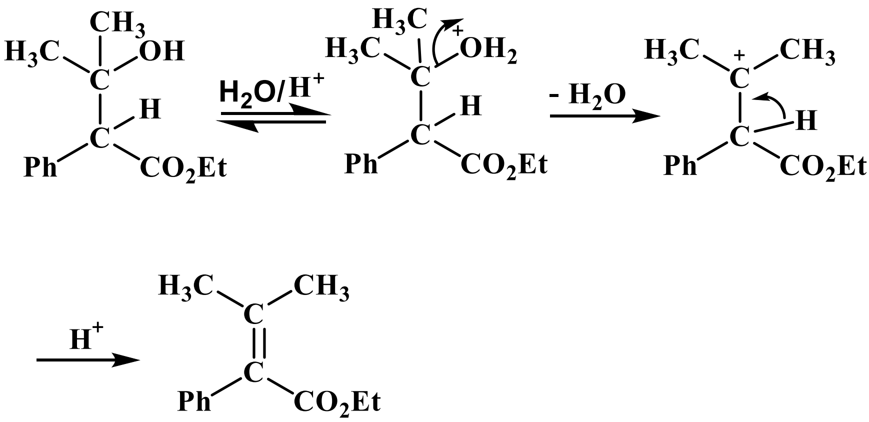
A Grignard reagent from α-bromo esters reacts with itself, because Grignard reagents readily react with esters.

However, α-bromo esters react with zinc in the same way as Grignard reagents to produce the corresponding

zinc compounds RZnBr. These compounds are less reactive to react with themselves, but they react with ketones as in the normal way.



The obtained tertiary alcohol during the acidic work up dehydrates spontaneously to give an α,β-unsaturated ester according to the following mechanism:



α,β-unsaturated ester

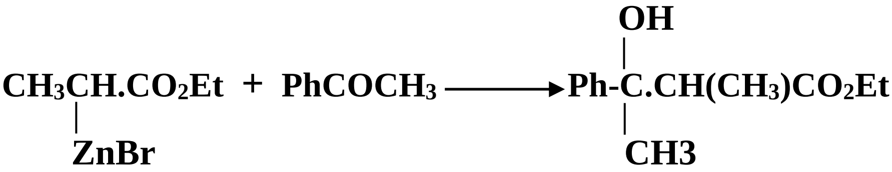
Discuss the mechanism of the following reaction:

$$PhCOCH_3 \longrightarrow PhCMe{=}CMe.CO_2Et$$

The answer:

$$CH_3CH_2COOH \xrightarrow{HVZ} CH_3CHBr.COBr \xrightarrow{EtOH}$$

$$CH_3CHBr.CO_2Et \xrightarrow{Zn}$$

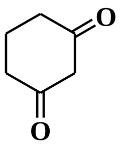


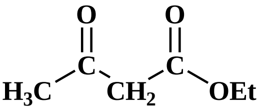
$$\underset{\displaystyle ZnBr}{\underset{|}{CH_3CH}}.CO_2Et + PhCOCH_3 \longrightarrow Ph\text{-}\overset{\displaystyle OH}{\overset{|}{\underset{\displaystyle CH3}{\underset{|}{C}}}}.CH(CH_3)CO_2Et$$

$$\xrightarrow{H^+} PhCMe{=}CMe.CO2Et$$

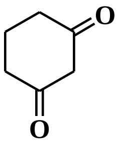
[(HVZ): Hell-Volhard-Zelinsky reaction]

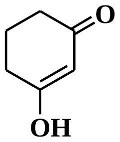
(1) Which is the most stable form in the following compounds:



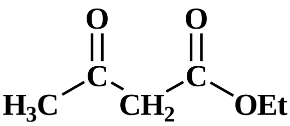


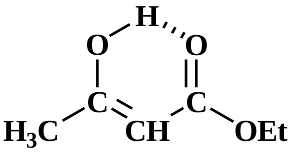
The answer:





conjugated enol





conjugated and H-bonded enol

(2) Arrange these compounds in order of reactivity towards:

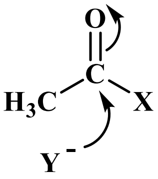
i) nucleophilic addition,
ii) nucleophilic substitution, and
iii) enolisation.

CH_3COOEt CH_3COCl CH_3CONH_2 $CH_3COO.COCH_3$

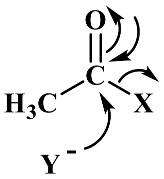
The answer:

The order is the same in each case.
Most reactive: acid chloride, anhydride and ester.
Least reactive: amide.

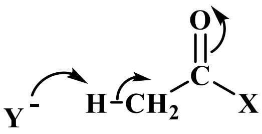
This because each reaction involves negative charge being taken on the carabonyl oxygen atom:



addition



substitution



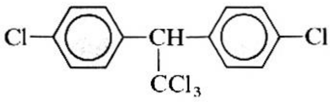
enolisation

Chapter 3

Alkyl Halides
Substitution and Elimination Reactions

Organohalogen compounds are widely used all over the globe. Some of these compounds are used as solvents, plymers *e.g.* PVC (polyvinyl chloride) and some others are used as insecticides. They also play an important role as versatile intermediates in the synthesis of wide variety of other organic compounds. Most of the organohalogen compounds are synthetic and the naturally occurring organohalogen compounds are in fact quite rare.

Organohalogen compounds are toxic and should be used with high caution. For example, the solvent carbon tetrachloride (CCl_4) is recently banned as a solvent, whereas chloroform ($CHCI_3$) is used under very restricted conditions. However, both compounds cause liver damage when inhaled in excess. Insecticides that contain halogens (such as DDT), which have been widely used in agriculture; in recent years their use is not welcome as they cause great danger to environment.



DDT

an insecticide

Compounds containing only carbon, hydrogen, and a halogen atom fall into one of the followings:

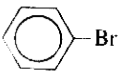
- **(i) alkyl halides,**
- **(ii) aryl halides (in which a halogen is bonded to a carbon of an aromatic ring), and**
- **(iii) vinylic halides (in which a halogen is bonded to a double-bonded carbon).**

A few examples are given:

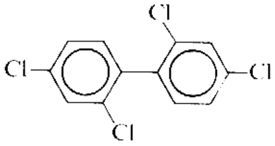
(i) <u>Alkyl halides (RX):</u>

CH_3I	CH_3CH_2Cl
iodomethane	**chloroethane**

(ii) <u>Aryl halides (ArX), and vinylic halides:</u>



bromobenzene



a polychlorinated biphenyl (PCB)

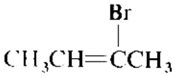
a toxic compound that has been used as a cooling fluid in transformers

Vinylic halides:

$CH_2{=}CHCl$

chloroethene
(vinyl chloride)

the starting material for polyvinyl chloride (PVC), a plastic used for piping, house siding, phonograph records, and trash bags



$CH_3CH{=}\overset{\overset{Br}{|}}{C}CH_3$

2-bromo-2-butene

We have already defined R as the general symbol for an alkyl group. In a similar manner, Ar is the general symbol for an aryl group. A halogen atom (F, CI, Br, or I) may be represented by X. By using such general symbols, an alkyl halide is RX, and an aryl halide is ArX.

A halogen atom in an organic compound is looked at as a functional group, and the C–X bond is a site of chemical reactivity. In this chapter, the discussion will be foxed only on the reactions of the alkyl halides. However, aryl halides and vinylic halides do not undergo the reactions that will be involved in this chapter, due to two reasons: (i) a bond from an *sp*^{2} carbon is stronger than a bond from an *sp*^{3} carbon (ii) secondly the unshared pair of

electrons on the halogen atom would be interacted with the C=C *pi* bond. It is well known that if a hetero atom is a part of a *pi* system, its unshared pair(s) of electrons would be available, but if the hetero atom is connected to a *pi* system, its unshared pair(s) of electrons would not be available. In the latter case the unshared pair(s) of electrons would be rather interacted with the *pi* system.

(1) Bonding in Organohalogen Compounds:

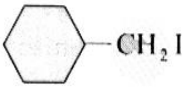
The carbon-halogen sigma bond is formed by the overlap of an orbital of the halogen atom and a hybrid orbital of the carbon atom. There is a lack of information about the hybridization of the halogen atom in an organic halide because the halogen atom forms only one covalent bond and therefore has no bond angle around it. However, carbon uses an *sp*^{3} hybrid orbital to bond to the halogen atom as it does to bond to a hydrogen atom or to another carbon atom:

CH_3-CH_2Br

bromoethane
(ethyl bromide)

$(CH_3)_3C-CH_2Cl$

1-chloro-2,2-dimethylpropane
(neopentyl chloride)



(iodomethyl)cyclohexane

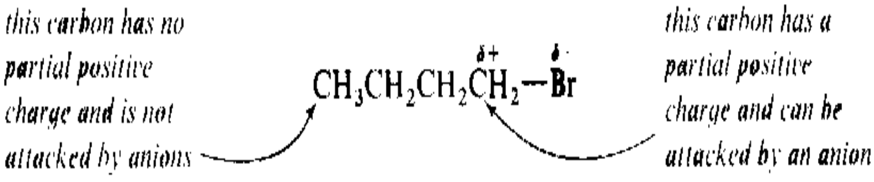
The halogen atom is more electronegative than carbon therefore, alkyl halides are polar compounds.

Dipole moments of the methyl halides:

	CH_3F	CH_3Cl	CH_3Br	CH_3I
$\mu =$	1.81 D	1.86 D	1.78 D	1.64 D

In an alkyl halide, a carbon atom bonded to a halogen atom has a partial positive charge, whereas the halogen atom will have a partial negative charge. The

partial positive charge on this particular carbon atom in an organic molecule makes it an electrophilic center and to be easily attacked by an anion. The attack at this electrophilic carbon is part of the general reactions of alkyl halides.



$CH_3CH_2CH_2\overset{\delta+}{C}H_2{-}\overset{\delta-}{Br}$

SECTION 2:

(2) Physical Properties of Halogenated Alkanes (Alkyl Halides):

The names, boiling points, and densities of several alkyl halides are listed in Table 3. In general halogen atoms are heavier than carbon or hydrogen atoms, only fluorine is the exceptional case. Increasing halogen atoms in alkyl halides causes an increase in the boiling points of a series of these compounds (*cf.*Table 3).

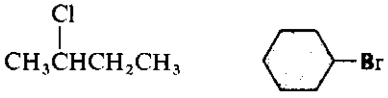
The alkyl halide liquids are heavier than water due to the mass of the halogen atoms, whereas most organic compounds are lighter than water. However, Alkyl halides do not form hydrogen bonds and are insoluble in water.

TABLE 3: Physical properties of some halogenated alkanes

IUPAC name	*Trivial name*	*Formula*	*bp. °C*	*Density, g/cc at 20°*
chloromethane	**methyl chloride**	**CH_3Cl**	**-24**	**gas**
dichloromethane	**methylene chloride**	**CH_2Cl_2**	**40**	**1.34**
trichloromethane	**chloroform**	**$CHCl_3$**	**61**	**1.49**
tetrachloromethane	**carbon tetrachloride**	**$CC1_4$**	**77**	**1.60**
bromomethane	**methyl bromide**	**CH_3Br**	**5**	**gas**
iodomethane	**methyl iodide**	**CH_31**	**43**	**2.28**

(3) Nomenclature and Classification of Alkyl Halides:

In the IUPAC system (International Union of Pure and Applied Chemistry), an alkyl halide is named with a halo-prefix. Many common alkyl halides also have trivial functional-group names. In these names, the name of the alkyl group is given, followed by the name of the halide.



IUPAC:	2-chlorobutane	bromocyclohexane
trivial:	*sec*-butyl chloride	cyclohexyl bromide

The structure of the alkyl portion of an alkyl halide plays an important role during the course of the chemical reactions. Therefore, we need to differentiate the four types of alkyl halides: methyl, primary, secondary, and tertiary.

Methyl halide is a structure in which one hydrogen atom of methane has been replaced by a halogen atom.

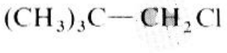
The methyl halides:

CH_3F	CH_3Cl	CH_3Br	CH_3I
Fluoromethane	***Chloromethane***	***bromo methane***	***iodomethane***

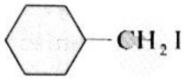
The head carbon of an alkyl halide is the carbon atom bonded to the halogen atom. A primary (1°) alkyl halide (RCH_2X) has a head primary carbon atom attached to the halogen. In the following examples, the head carbons and their hydrogen atoms are circled. A primary carbon is attached directly to only one carbon atom.

Primary alkyl halides (only one carbon atom is attached to the head carbon):

bromoethane
(ethyl bromide)



1-chloro-2,2-dimethylpropane
(neopentyl chloride)

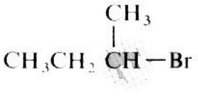


(iodomethyl)cyclohexane

However a secondary (2°) alkyl halide (R_2CHX) has

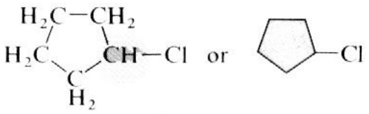
two alkyl groups are attached to the head carbon *i.e.* two carbon atoms are attached to the head carbon, and a tertiary (3°) alkyl halide (R_3CX) has three alkyl groups attached to the head carbon (three carbons are attached to head carbon). However, when a halogen atom is attached directly to a cycloalkane ring the formed alkyl halide will be either secondary or tertiary.

Secondary alkyl halides
(two alkyl groups are attached to head):



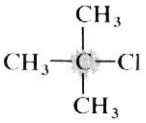
$$CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{CH}-Br$$

2-bromobutane
(*sec*-butyl bromide)



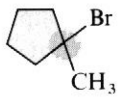
chlorocyclopentane
(cyclopentyl chloride)

Tertiary alkyl halides
(three alkyl groups are attached to head):



$$CH_3-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}-Cl$$

2-chloro-2-methylpropane
(*t*-butyl chloride)

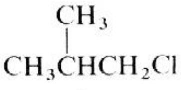


1-bromo-1-methylcyclopentane

In general 1°, 2°, or 3° carbon, means that the carbon atom is attached to one carbon atom, two carbon atoms or three carbon atoms, respectively.

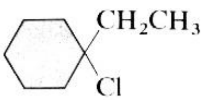
Classify each of the following alkyl halides as 1°, 2°, or 3°:

(a)

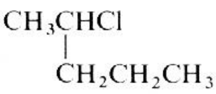


$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_2Cl$$

(b)



(c)



$$CH_3\underset{\underset{\displaystyle CH_2CH_2CH_3}{|}}{C}HCl$$

Solution:

(a) 1° ; (b) 3° ; (c) 2°

1) **Write two names for:**
    - **(a) (CH_3CI)**
    - **(b) (CH_3CH_2CI)**
    - **(c) ($CH_3CH_2CH_2I$)**

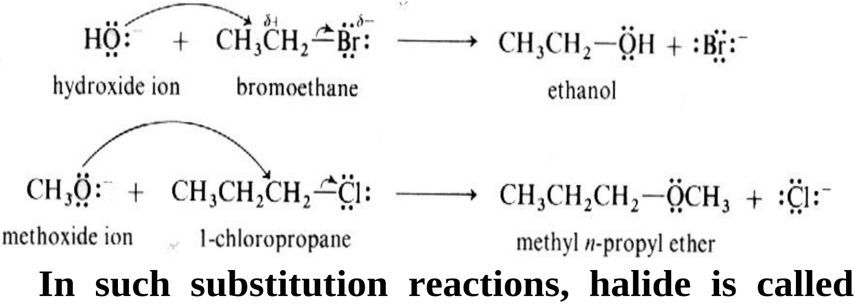
2) **Write structural formulas for:**
    - **(a) 1,1-dibromobutane.**
    - **(b) 3-chloro-1-butene.**
    - **(c) 2-fluoro-1-ethanol.**

(4) Substitution and Elimination Reactions:

(A) Substitution Reactions:

In the substitution reactions of alkyl halides, a nucleophile substitutes a halogen in an alkyl halide. The electrophilic carbon in an alkyl halide could be attacked by an anion or by any other nucleophile that carries an unshared pair of electrons. A nucleophile is defined as an species that attacks a positively charged carbon atom. However, strong nucleophiles substitute the weaker ones at the head carbon atom:

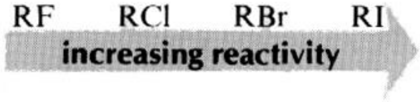
The σ-bond electrons leave with the halogen



In such substitution reactions, halide is called a leaving group, a term meaning any group that can be displaced. It is known that halide ions are very weak bases (nucleophiles), so they are regarded as good leaving groups. Strong bases (nucleophiles), such as ^-OH, are very poor

leaving groups. Strong nucleophiles substitute the weaker ones, whereas strong bases abstract protons from acids or from compounds containing active α-hydrogen. However, only the halides as leaving groups are taken in account.

In substitution reactions of alkyl halides, the iodide ion is the halide most easily displaced, followed by the bromide ion and then the chloride ion. Because F^- is a stronger base than the other halide ions, it is not good a leaving group. Only Cl^-, Br^-, and $I^-$are good leaving groups, which are useful in the substitution reactions. For this reason, RX refers to alkyl chlorides, bromides, and iodides.

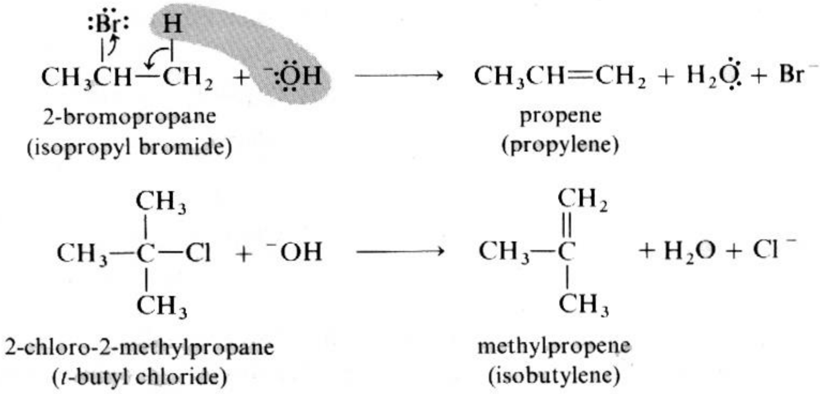


The nucleophile that attacks the head carbon atom in an alkyl halide is often abbreviated as Nü or Nu^-, therefor HO^- and CH_3O^- are considered nucleophiles. Generally, a nucleophile is any species that attacks an electrophilic center; thus, a nucleophile is looked at as a Lewis base. Most nucleophiles are anions; however, some neutral polar molecules, such as H_2O, CH_3OH, and CH_3NH_2, can also act as nucleophiles. These neutral molecules contain unshared pair of electrons that can be used to form sigma bonds. A reaction in which a substitution occurs by nucleophiles is called nucleophilic substitution reaction, or nucleophilic displacement reaction.

The opposite of a nucleophile is an electrophile, which can be readily attacked by a negatively charged carbon atom (carbanion), and is often abbreviated as E^+. An electrophile is in fact looked at as a Lewis acid, such as H^+ or $ZnCl_2$, *etc*.

(B) Elimination reactions:

However, an alkyl halide reacts with a strong base to produce the corresponding alkene via an elimination reaction. An elimination reaction is a reaction by which an alkyl halide molecule loses two atoms or ions at two adjacent carbons to yield the expected unsaturated compounds. Thus, an elimination reaction of an alkyl halide yields an alkene. In this type of elimination reaction, the elements H and X are lost from the alkyl halide; therefore, these particular reactions are also called dehydrohalogenation reactions.



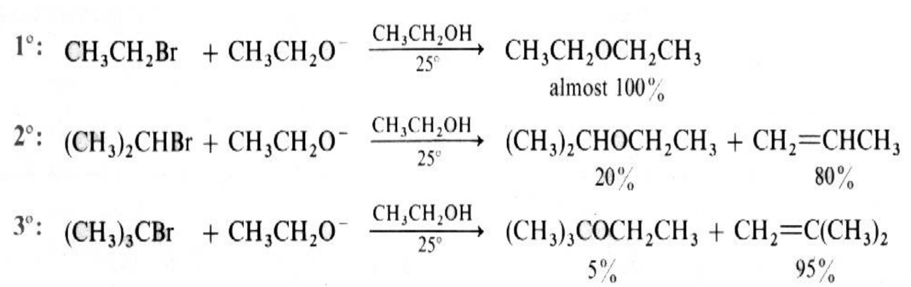
(C) Competing reactions:

However, a hydroxide ion (HO^-) or alkoxide ion (RO^-) can react as a nucleophile in a substitution reaction or as a base in an elimination reaction. The type of reaction actually occurs depends on a number of factors, such as:

(i) the structure of the alkyl halide (1°, 2°, or 3°),
(ii) the strength of the base,
(iii) the nature of the solvent, and
(iv) The temperature.

In fact methyl and primary alkyl halides tend to yield substitution products, and not elimination products.

However, under equivalent conditions, tertiary alkyl halides yield mainly elimination products, and not substitution products. Secondary alkyl halides are intermediate in their behavior; the relative proportion of the substitution product to the elimination product depends, to a great extent, upon the experimental conditions:



$$1^\circ:\ CH_3CH_2Br + CH_3CH_2O^- \xrightarrow[25^\circ]{CH_3CH_2OH} \underset{\text{almost }100\%}{CH_3CH_2OCH_2CH_3}$$

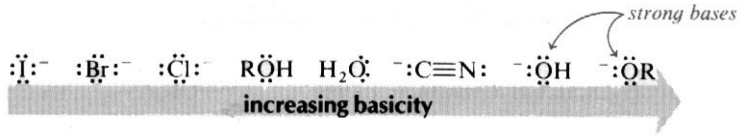
$$2^\circ:\ (CH_3)_2CHBr + CH_3CH_2O^- \xrightarrow[25^\circ]{CH_3CH_2OH} \underset{20\%}{(CH_3)_2CHOCH_2CH_3} + \underset{80\%}{CH_2{=}CHCH_3}$$

$$3^\circ:\ (CH_3)_3CBr + CH_3CH_2O^- \xrightarrow[25^\circ]{CH_3CH_2OH} \underset{5\%}{(CH_3)_3COCH_2CH_3} + \underset{95\%}{CH_2{=}C(CH_3)_2}$$

(D) Nucleophilicity versus basicity :

Before proceeding with the details of substitution and elimination reactions, let us briefly consider the similarities and differences between bases and nucleophiles. Under the proper circumstances, all bases can act as nucleophiles. On the other way round, all nucleophiles can act as bases. In either case, the reagent reacts by donating a pair of electrons to form a new sigma bond.

Basicity can be defined as the ability of a reagent to accept a proton in an acid-base reaction. In other words, how readily the reagent can abstract a proton:



On the other hand, nucleophilicity is known as the ability of a reagent to cause a substitution reaction.

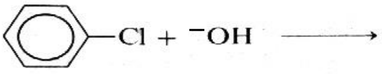
A list of relative nucleophilicities does not exactly parallel to a list of base strengths; however, a stronger base is usually a better nucleophile than a weaker base. For

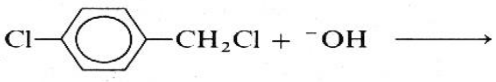
example HO^{-} (a strong base) is a better nucleophile than Cl^{-} or H_2O (weak bases).

Sample problem:

Give the structures of the substitution products (if any) in the following reactions:

(a) $CH_3CH_2CH_2CH_2I + {}^{-}CN \longrightarrow$

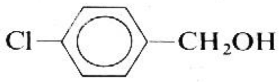
(b)


(c)


Solution:

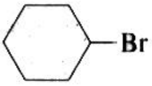
(a) $CH_3CH_zCH_zCH_zCN$;

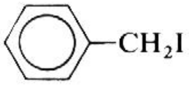
(b) Aryl halide gives no substitution reaction;

(c)


(1) Write equations for the reactions of the following compounds with CH_3O^{-}. Show both substitution and elimination products (if any):

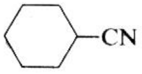
(a) $(CH_3CH_2)_2CHCl$

(b)


(c)


(2) Show by equations how can you prepare the following compounds from alkyl halides and the appropriate nucleophiles? Give two procedures to compound (a).

(a) $CH_3CH_2CH_2OCH_2CH_2CH(CH_3)_2$

(b)


(4) The S_N2 Reaction

(1) The reaction of the primary alkyl halide RX with a hydroxide HO^- ion occurs by an S_N2 mechanism. The reaction takes place in one step through a concerted transition state. The rate of the reaction depends on the concentration of both reactants. It is well documented that any methyl or primary alkyl halide undergoes an S_N2 reaction with any relatively strong nucleophile such as ^-OH, ^-OR, ^-CN. Secondary alkyl halides can also undergo S_N2 reactions; however, tertiary alkyl halides for certain do not. The (S_N2) term means bimolecular nucleophilic substitution reaction. However, an umbrella inversion occurs during the transition state. This phenomena is well pronounced in the reactions of the homo chiral alkyl halides, *vide sobra*. However, such umbrella inversion is called "Walden" inversion after the chemist who discovered it.

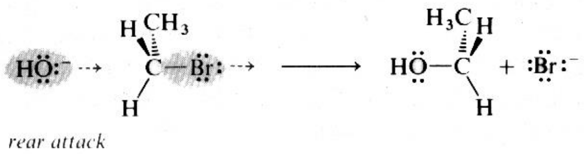
(A) Reaction mechanism:

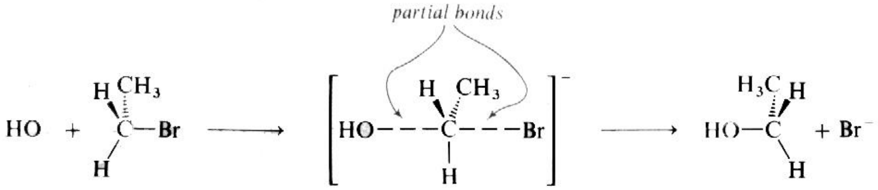
The S_N2 reaction has been studied extensively; there is a large amount of experimental data supporting the reported mechanism.

B) Stereochemistry of an S_N2 reaction

Overall S_N2 reaction:

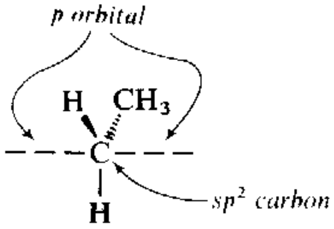
In the reaction between ethyl bromide and hydroxide ion, a typical S_N2 reaction, the oxygen of the hydroxide ion collides with the rear of the head carbon and displaces the bromide ion.



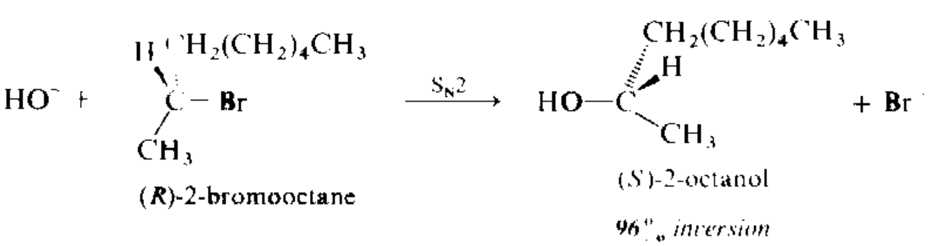


transition state: high potential energy

In the S_N2 reaction, the transition state involves a temporary rehybridization of the head carbon atom from *sp^3* to sp^2 and finally back to sp^3 again. Also, in the transition state, the carbon atom has three planar *sp^2* bonds, with two halfbonds (the two lobes of the *$2p_z$* orbital) perpendicular to the *sp^2* plane:



An umbrella inversion exists as part of the mechanism of an S_N2 reaction has been well explained by the reactions of homo chiral alkyl halides. Thus, the S_N2 reaction of (*R*)-2-bromooctane with ^-OH yields almost exclusively (*S*)-2-octanol:



Study problem:

Write an equation (showing the stereochemistry by using dimensional formulas) for the S_N2 reaction of (*S*)-2-bromobutane with CN^-.

(C) Energy in an S_N2 reaction:

It is well known that any reaction needs energy to occur. The gained energy would exceed the colliding rate of molecules, which is the way for a reaction to occur. Let us take a closer look at these energy requirements in rather more details.

The moving molecules in solution would have an amount of potential energy in their bonds and an amount of kinetic energy from their movement. Of course, all molecules in solution have not exactly the same amount of potential or kinetic energy; however, let us take in account the *average energy* of the molecules. Obviously the total energy of the reaction mixture is increased, usually by stirring or heating the solution. The heated molecules are kinetically energetic, so they will collide more frequently and will be more energetically, and exchange some kinetic energy for potential energy.

Right at the beginning of a reaction, some of the colliding molecules and ions may have enough energy to reach the transition state.

Figure 22: Shows an energy diagram for the progress of an S_N2 reaction. The potential energy, which is required to reach the transition state, forms an energy barrier; it is the point of maximum energy on the graph. For colliding alkyl halide and nucleophile to reach the transition state, they need a certain minimum amount of energy called the energy of activation E_{act}. At the transition state, the

molecules can go back to reactants or go forward to products. The difference between the average potential energy of the reactants and that of the products is the change in enthalpy ΔH for the reaction.**

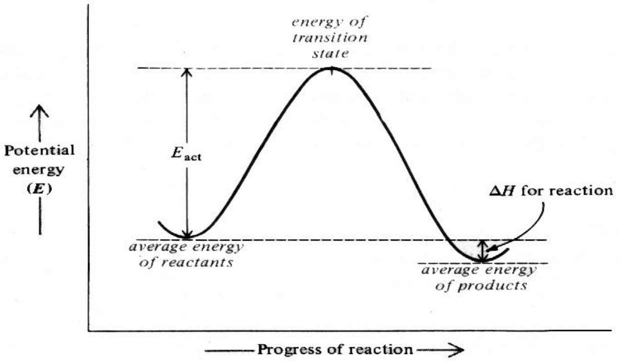


FIGURE 22
Energy diagram of an S_N2 reaction

(D) Rate of an S_N2 reaction:

Each molecule that undergoes a reaction to yield product must go through the transition state. Since the energies of all the molecules are not the same, a certain amount of time is needed for all the molecules to react. This time requirement causes the rate of a reaction. The rate of a chemical reaction is a measure of how fast the reaction proceeds; that is, how fast reactants are consumed and products are formed. In simple words, that means how fast the reactants are converted into products. Reaction kinetics is the term used to describe the study and measurement of reaction rates.

The rate of a reaction depends on many variables, some of which may be held constant for a given experiment (for example temperature and solvent). In this study, we will be concerned with two variables: (i) the concentrations of the reactants, and (ii) the structures of the reactants.

Increasing the concentration of both reactants in an S_N2 reaction increases the rate of the reaction. If all other

variables are held constant and the concentration of either the alkyl halide or the nucleophile is doubled, the rate of product formation is doubled. If either concentration is tripled, the rate is tripled.

$$\mathrm{Nu^- + RX \longrightarrow RNu + X^-}$$

$$\mathrm{S_N2\ rate} = k\,[\mathrm{RX}][\mathrm{Nu^-}]$$

In this equation, [RX] and [Nu$^-$] represent the concenations in moles/liter of the alkyl halide and the nucleophile, respectively. The term *k* is the proportionality constant, called the rate constant, between these concentrations and the measured rate of product formation. The value for *k* is constant for the same reaction under identical experimental conditions e.g. solvent, temperature, *etc*.

Sample problem:

Calculate the rate of the S_N2 reaction of CH_3I with CH_3O^- if the concentrations of both reactants are doubled and all other variables are kept constant.

Solution:

If the concentrations of both reactants are doubled the rate will be four times faster.

Because the rate of an S_N2 reaction depends on the concentrations of both particles [RX] and [Nu$^-$], and the rate is a second order, *i.e.* the S_N2 reactions follow second-order kinetics. The S_N2 reactions are also bimolecular, in fact not all bimolecular reactions are second-order and not all second-order reactions are bimolecular.

(E) Effect of E_{act} on rate and products:

According to the energy diagram, Figure 23, the reaction with the lower E_{act} has the faster rate. It means

that, if less energy is needed for a reaction to take place, a greater number of molecules have enough energy to react.

In the competing reactions of the same starting material, the reaction with the lower-energy transition state is the faster reaction.

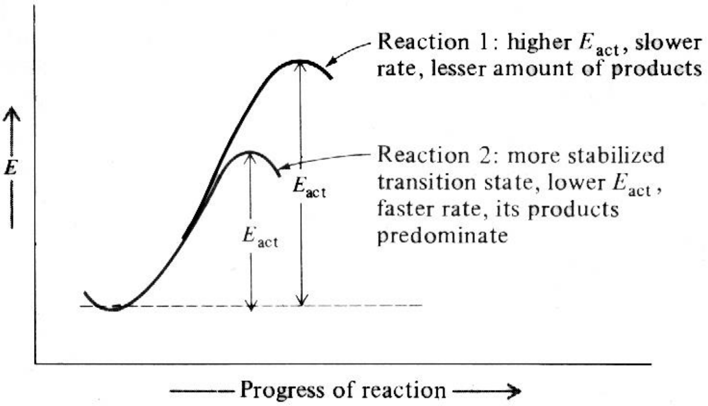


FIGURE 23

In competing reactions of a single starting material, the reaction of the lower E_{act} is the faster one. If the reactions are essentially irreversible, the products of the faster reaction predominate.

(F) Effect of structure on the reaction rate:

Reaction kinetics provides a valuable tool for exploring the effect of structure upon reactivity. Let us consider the following two reactions:

(1) $OH^- + CH_3Br \longrightarrow CH_3OH + Br^-$

bromomethane — *a methyl halide*; methanol

(2) $OH^- + CH_3CH_2Br \longrightarrow CH_3CH_2OH + Br^-$

bromoethane — *a 1° alkyl halide*; ethanol

The two reactions are S_N2 and both yield alcohols. The only difference between the two reactions is the alkyl group of the alkyl halides.

Does this difference in the alkyl group have an effect upon the rate of the S_N2 reaction?

The answer of such a question, will clarify such dilemma. Thus, the two rate constants (k_1 and k_2) are determined or, more commonly, the relative rates are determined.

$$CH_3Br \xrightarrow{OH} CH_3OH \qquad rate_1 = k_1[CH_3Br][OH^-]$$

$$CH_3CH_2Br \xrightarrow{OH} CH_3CH_2OH \qquad rate_2 = k_2[CH_3CH_2Br][OH^-]$$

$$\textit{relative rates of reaction of } CH_3Br \textit{ compared to } CH_3CH_2Br = \frac{rate_1}{rate_2}$$

The experimental results showed that bromomethane is undergoing the substitution reaction 30 times faster than bromoethane. That means if the reaction of bromoethane takes one hour to reach 50 % completion, the bromomethane reaction would take about 1/30 as long, or only two minutes, to reach 50 % completion. It is clear that the size of the alkyl group in the alkyl halides has affected the rate of an S_N2 reaction to a great extent. Table 4 shows some average relative rates (compared to ethyl halides) of S_N2 reactions of alkyl halides.

Table 4. Average relative rates of some alkyl halides in a typical S_N2 reaction

Alkyl halide	*Relative rate*
CH_3X	**30**
CH_3CH_2X	**1**
$CH_3CH_2CH_2X$	**0.4**
$CH_3CH_2CH_2CH_2X$	**0.4**
$(CH_3)_2CHX$	**0.03**
$(CH_3)_3CX$	**~0**

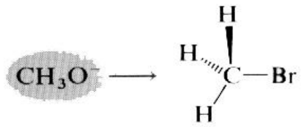
(G) The steric hindrance effect in S_N2 reactions:

Table 4, showed that methyl halides have the fastest rate, followed by primary alkyl halides, then secondary alkyl halides. Finally tertiary alkyl halides do not undergo S_N2 reactions.

3°RX 2°RX 1°RX CH_3X

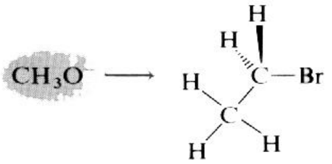
increasing the rate of S_N2 reaction →

As the number of alkyl groups attached to the head carbon atom increases (CH_3X → 1° → 2° → 3°), the transition state becomes increasingly crowded with groups. It is known that in the more crowded transition state would raise the energy of activation, and the nucleophile approach would be greatly retarded. Consider the following examples of reactions of alkyl bromides (RBr) with the methoxide ion (CH_3O^-) as nucleophile: ($CH_3O^- + RBr \rightarrow CH_3OR + Br^-$):



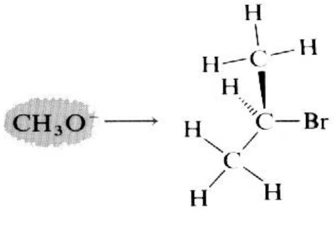
bromomethane

very fast



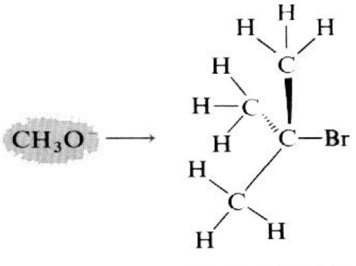
bromoethane

moderate rate



2-bromopropane

very slow



t-butyl bromide

no S_N2 reaction

When large groups are crowded in a small space, repulsion between atoms become severe and therefore the energy of the system gets much higher. Thus, in an S_N2

reaction, the crowded transition state is highly energetic than that with less steric hindrance. Accordingly, rates of the reaction become very slower in the series: methyl, primary, secondary, and tertiary (see Figure 24). The energy of the S_N2 transition state of a tertiary alkyl halide is too much high, and because of that the S_N2 reaction does not proceed.

SAMPLE PROBLEM:

The rate of S_N2 reaction of neopentyl bromide, $(CH_3)_3CCH_2Br$, with sodium ethoxide, $Na^+\ ^-OCH_2CH_3$, proceeds about 0.00001 times as fast as the reaction of bromoethane. Explain.

Solution:

Although neopentyl bromide is a primary alkyl halide the alkyl group attached to the head carbon atom is very bulky. The steric hindrance in the transition state is considerable. Therefore, the E_{act} is high and the rate is slow.

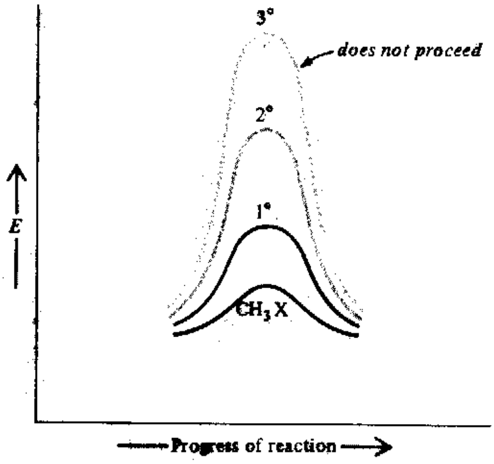
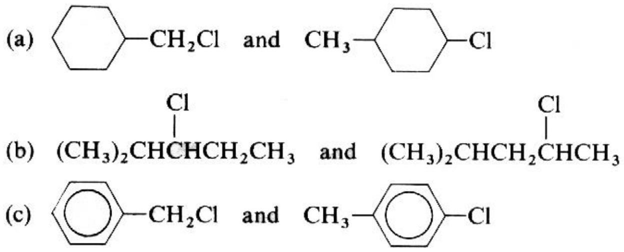


FIGURE 24
Energy diagram for S_N2 reactions of different types of alkyl halides.

Study problem:

Which member of each of the following pairs undergoes the faster S_N2 reaction?



<u>Sumary:</u>

In an S_N2 reaction:

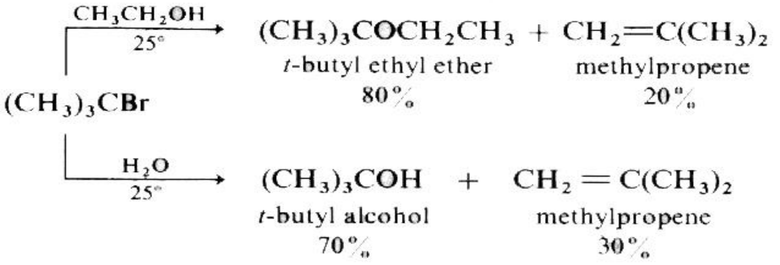
1. **MeX and primary alkyl halides explosively undergo S_N2 reactions, some secondary alkyl halides do, however tertiary alkyl halides do not.**
2. **Strong bases are used *e.g.* HO^- and EtO^-.**
3. **The reaction depends on the concentration of both reactants, the alkyl halide RX and the nucleophile (HO^-).**
4. **The process occurs in one step through a concerted transition state in which a new HO–C bond begins to form, and at the same time the old C–X bond begins to break.**
5. **The rate of an S_N2 reaction is directly proportional to the concentration of the nucleophile.**
6. **The rate of an S_N2 reaction is increased by heating.**
7. **An optical isomer gives its mirror image, i.e. an enantiomer *(R)* gives the enantiomer *(S)*, and vice versa, due to the umbrella inversion. However, such umbrella inversion is called "Walden" inversion after the chemist who discovered it.**

(8) Polar solvents decrease the rate of an S_N2 reaction due to the solvation of the carbanion (nucleophile).

(9) The bulky alkyl groups retard the nucleophile approach and slow down the reaction to a great extent.

(6) The S_N1 Reaction:

Due to the great effect of steric hindrance, t-butyl bromide and other tertiary alkyl halides do not undergo S_N2 reactions. Yet, if *t*-butyl bromide is treated with a nucleophile that is a very weak base (such as H_2O or CH_3CH_2OH), substitution products are formed, together with elimination products:



It is well established that tertiary alkyl halides cannot undergo S_N2 reactions, *vide sobra*. In such a case, tertiary alkyl halides undergo substitution reactions by a different mechanism, called the S_N1 reaction (substitution, nucleophilic and unimolecular). The experimental results obtained in S_N1 reactions are considerably different from those obtained in S_N2 reactions:

(i) The reaction of a pure enantiomer of an alkyl halide containing a chiral C–X carbon undergoes an S_N1 reaction, a *racemic* mixture of substitution products is obtained (in contrast to an S_N2 reaction).

(ii) The concentration of the nucleophile is generally has little effect upon the overall rate of an S_N1 reaction, whereas the rate of an S_N2 reaction is directly proportional to the concentration of the nucleophile.

A typical example of an S_N1 reaction is the reaction of ***t-butyl*** **bromide with water however, the formation of the elimination product is ignored for this reaction:**

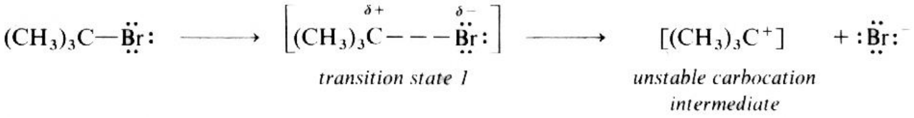
$$\underset{t\text{-butyl bromide}}{(CH_3)_3CBr} + H_2O \longrightarrow \underset{t\text{-butyl alcohol}}{(CH_3)_3COH} + H^+ + Br^-$$

(A) The S_N1 mechanism:

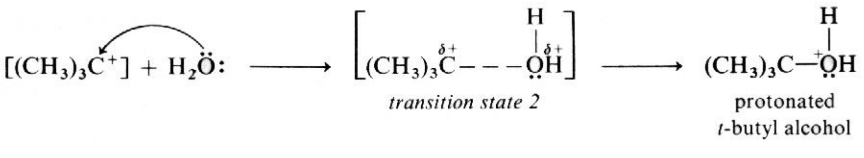
The S_N1 reaction of a tertiary alkyl halide is an *stepwise reaction*:

Step 1, is the ionization step, which gives a carbocation together with Br^- ion. This step occurs slowly and is called the rate determining step. The formed cation in the ionization step in S_N1 reactions is stabilized by polar solvents, *i.e.* the rate of an S_N1 reaction is increased as the polarity of solvents increases.

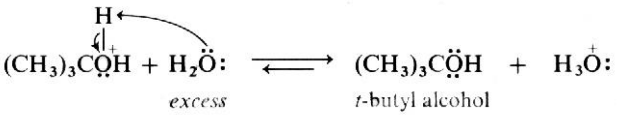
Step 1: is the ionization step:



Step 2: is the nucleophilic attack at the electrophilic center of the carbocation by the nucleophile (H_2O) to yield the initial product, a protonated alcohol:



Step 3: The *ter*-alcohol is finally formed by the loss of H^+:



In fact an S_N1 reaction is considered to take place in two main steps, the first step is the slow ionization step, which produces a carbocation and the other step is the fast nucleophilic attack at the positively charged carbon in the formed carbocation, to yield the corresponding *tert*-alcohol.

Figure 25 represents the energy diagram of an S_N1 reaction:

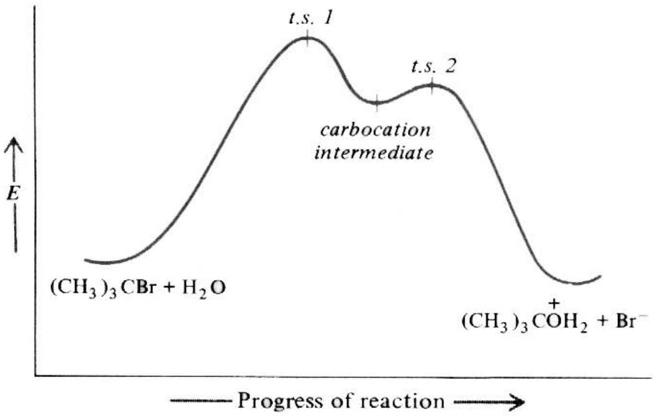


FIGURE 25
Energy diagram for a typical S_N1 reaction.

The overall reaction of *t*-butyl bromide with water is thus actually composed of two separate reactions: the S_N1 reaction (ionization followed by nucleophilic attack at the electrophilic center). The steps could be summarized:

$$\underbrace{(CH_3)_3CBr \xrightarrow[\text{slow}]{-Br^-} [(CH_3)_3C^+] \xrightarrow[\text{fast}]{H_2O} (CH_3)_3\overset{+}{C}OH_2}_{S_N1\ reaction} \underbrace{\xrightarrow[\text{fast}]{-H^+} (CH_3)_3COH}_{acid\ base\ reaction}$$

Typically, Step 1 (the slow ionization step) has a high E_{act} in the overall process. In which, enough energy must be supplied to the tertiary alkyl halide to break the C–X sigma bond (a strong bond) and yield the carbocation and the

halide ion.

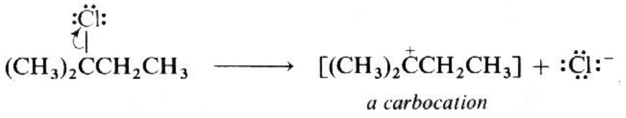
The carbocation is an intermediate in this reaction, a structure that is formed during the reaction and then undergoes further reaction to yield products. We must differentiate between the intermediate and the transition state. An intermediate has a finite lifetime; a transition state does not. At the transition state, molecules undergo bond-breaking and bond-making. A potential energy of a transition state is a high point on a potential-energy curve. On the other hand, an intermediate is a temporary, reactive product of lower energy than transition states, but is of higher energy than the final products. The energy diagram in Figure 25 shows a dip for the carbocation formation; the dip is not a large one because the carbocation is a high-energetic and reactive species.

Step 2 in the sequence of an S_N1 reaction is the nucleophileic attack at the electrophilic center of the formed carbocation. However, the combination process of the carbocation with the nucleophile occurs fast to form products with a low *E_{act}*.

Sample problem:

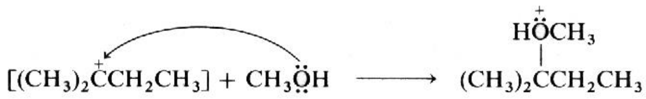
Write equations for the steps in the S_N1 reaction of 2-chloro-2-methylbutane with methanol. (Include the deprotonation step in your answer.)

Step 1 : (slow ionization) :



$$(CH_3)_2\overset{:\ddot{Cl}:}{C}CH_2CH_3 \longrightarrow [(CH_3)_2\overset{+}{C}CH_2CH_3] + :\ddot{Cl}:^-$$

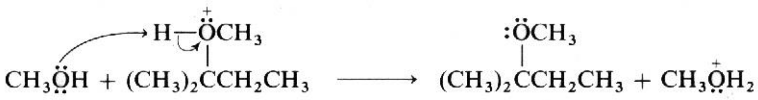
Step 2 (fast combination with Nu^-):



$$[(CH_3)_2\overset{+}{C}CH_2CH_3] + CH_3\ddot{O}H \longrightarrow (CH_3)_2\underset{\textstyle |}{C}(\overset{+}{H\ddot{O}}CH_3)CH_2CH_3$$

a protonated ether

Step 3 (loss of H^+ to solvent):



$$CH_3\ddot{O}H + (CH_3)_2C(H\overset{+}{\ddot{O}}CH_3)CH_2CH_3 \longrightarrow (CH_3)_2C(:\ddot{O}CH_3)CH_2CH_3 + CH_3\overset{+}{\ddot{O}}H_2$$

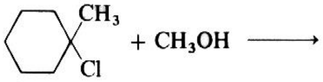
an ether

Study problem:

Complete the following equations for solvolysis reactions:

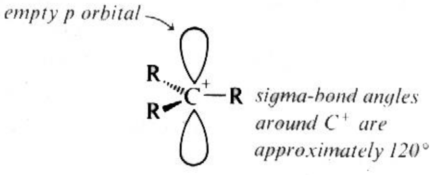
(a) $(CH_3CH_2)_3Cl + H_2O \longrightarrow$

(b)



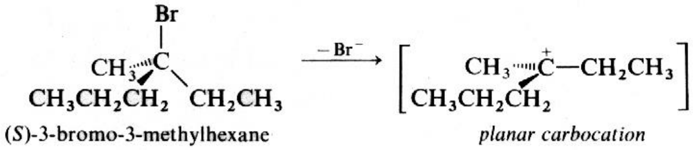
(B) Stereochemistry of an S_N1 reaction:

In a carbocation the carbon atom is rehybridized to *sp*^{2} carbon with only three groups attached and having an empty *p* orbital. The three groups are planar and the bond angles are nearly 120°.



Treating (*S*)-3-bromo-3methylhexane with water yields a racmic mixture of the *(R)* and *(S)* alcohols. The S_N1 mechanism is used to explain this racemization. The first step in this S_N1 reaction is ionization of the alkyl halide to a carbocation and a halide ion:

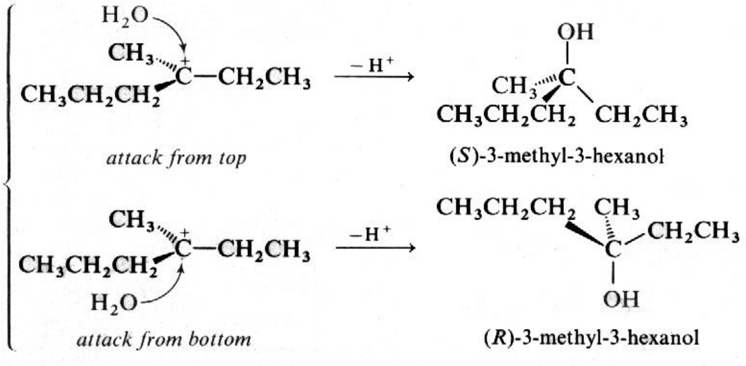
Step 1:



Step 2:

In the second step, H_2O can attack equally the carbocation from the top and the bottom sides through the two lobes of the empty *p* orbital to produce racemic mixture of the two alcohols. If the H_2O molecule attacks the carbocation from the top side, the *(S)*-enantiomer alcohol is formed. Whereas, when H_2O attacks the carbocation from the bottom side the *(R)*-enantiomer is the product. The equal amounts of the *(R)*- and *(S)*-alcohols are produced due to the equal probability of attack from both sides of the carbocation.

Step 2 and Step 3:



(C) Rate of an S_N1 reaction:

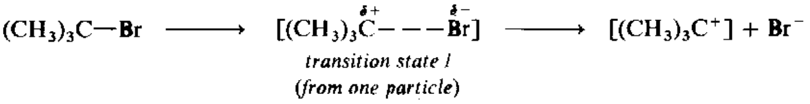
It was mentioned earlier that the rate of a typical S_N1 reaction does not depend on the concentration of the nucleophile, but depends only on the concentration of alkyl halide.

$$S_N1 \text{ rate} = k\,[RX]$$

The reason for this behavior is simply due to the very fast reaction between R^+ and $Nu^{\cdot\cdot}$, but the concentration of R^+ is very low comparing to the concentration of the nucleophile $Nu^{\cdot\cdot}$ (solvent used). The fast combination of R^+ with $Nu^{\cdot\cdot}$, occurs only once the carbocation is formed. Therefore, the rate of the overall reaction is determined entirely by how fast RX could ionize and form R^+ carbocation. This ionization step is called the rate-determining step. However, the rate-determining step in any stepwise reaction is the slowest step in the whole sequence.

An S_N1 reaction is characteristically first order in rate because the rate is proportional to the concentration of only one reactant (RX). It is a unimolecular reaction because only one particle (RX) is involved in the *transition state of the rate-determining step.* (The "1" in S_N1 refers to unimolecular.)

Rate-determining step:



$$(CH_3)_3C{-}Br \longrightarrow [(CH_3)_3\overset{\delta+}{C}{-}{-}{-}\overset{\delta-}{Br}] \longrightarrow [(CH_3)_3C^+] + Br^-$$

transition state I
(from one particle)

(D) Relative reactivities in S_N1 reactions:

Table 5 lists the relative rates of reaction of some alkyl bromides under typical S_N1 conditions (*e.g.* solvolysis in water). Note that a secondary alkyl halide undergoes S_N1 substitution 11.6 times faster than a primary alkyl halide under these conditions, whilst a tertiary alkyl halide undergoes reaction a million times faster than a primary halide!

Methyl bromide:

$$CH_3Br \quad + H_2O \xrightarrow[S_N1]{\text{negligible rate}} CH_3OH \quad + Br^- + H^+$$

1° :

$$CH_3CH_2Br \quad + H_2O \xrightarrow[S_N1]{\text{negligible rate}} CH_3CH_2OH \quad + Br^- + H^+$$

2° :

$$(CH_3)_2CHBr + H_2O \xrightarrow[S_N1]{\text{very slow}} (CH_3)_2CHOH + Br^- + H^+$$

3° :

$$(CH_3)_3CBr \quad + H_2O \xrightarrow[S_N1]{\text{fast}} (CH_3)_3COH \quad + Br^- + H^+$$

The S_N1 reaction rate depends on the energy of activation at which the carbocation is formed. So an S_N1 reaction leads to the more stabilized (lower energy) carbocation would have the faster rate. Tertiary alkyl halides undergo an S_N1 reaction at the fastest rate through a tertiary carbocation. It is well known that the *tert*-carbocation is the most stable (lowest energy) than the carbocation obtained from methyl halide or a primary alkyl halide. Therefor the S_N1 reaction rate of a *tert*- alkyl halide is the fastest comparing to that of methyl halide or a primary alkyl halide.

Table 5: Relative rates of some alkyl bromides under typical S_N1 conditions

CH_3Br	**1.00[a]**
H_3CCH_2Br	**1.00[a]**
$(CH_3)_2CHBr$	**11.6**
$(CH_3)_3CBr$	**1.02×10^6**

***a*: The observed reaction of the methyl or primary bromide probably occurs by a different path (S_N2, not S_N1).**

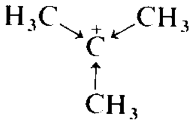
(E) Stability of carbocations:

A carbocation is unstable intermediate and quickly undergoes further reactions. However, let us discuss *the*

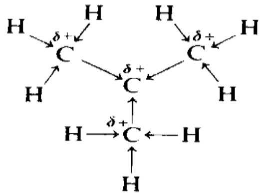
relative stabilities **of carbocations. We will consider some different types of carbocations such as a methyl cation (carbocation resulting from ionization of a methyl halide), primary carbocations (from 1° alkyl halides), secondary carbocations (from 2° alkyl halides) and tertiary carbocations (from 3° alkyl halides):**

$\overset{+}{C}H_3$	$CH_3\text{–}\overset{+}{C}H_2$	$(CH_3)_2\text{–}\overset{+}{C}H$	$(CH_3)_3C^+$
methyl	**1°**	**2°**	**3°**

In general the stability of a positively charged carbon atom is increased by dispersing the positive charge. In other words stable carbocation must accommodate the formed positive charge on the head carbon. The inductive effect of the positively charged carbon would help dispersing the positive charge:



siqma-bonds are drawn toward the positive charge



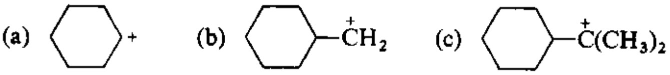
All the atoms help disperse the positive charge.

This example shows that the more substituted positively charged carbon atom would be the more stable carbocation. For this reason methyl halide and primary alkyl halides cannot easily form the corresponding cabocations.

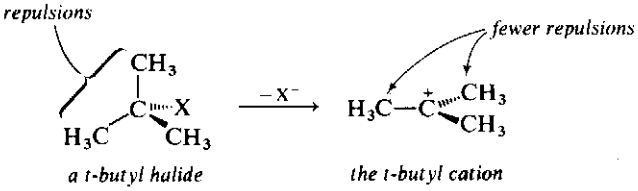
$^+CH_3$	$CH_3\text{-}CH_2^+$	$(CH_3)_2\text{-}CH^+$	$(CH_3)_3\text{-}C^+$
methyl	**1°**	**2°**	**3°**

increasing carbocation stability; increasing S_N1 rate of RX

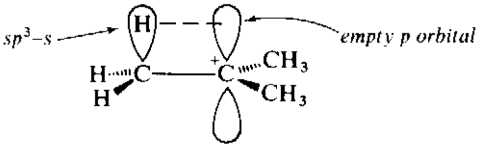
List the following carbocations in order of increasing stability (least stable first):



The steric hindrance in tertiary alkyl halides is another factor that may increase the stability of the formed tertiary carbocations. Thus, repulsions between groups on the *sp*^{3} carbon (the bond angles are nearly less than 109.5°) in an alkyl halide add energy to the neutral molecule due to the repulsion between the alkyl groups. It is easily seen that the energy of the ground-state of a tertiary alkyl halide is higher than that of a primary or secondary alkyl halide. However, such crowding of the groups attached to the positively charged *sp*^{2} carbon would somewhat disappear (the bond angles become 120°). Thus less energy is needed for RX to form the carbocation.



The hyperconjugation can also stabilize carbocation through the partial overlap of an *sp*^{3}– *s* orbital (a C-H bond) with the empty *p* orbital of the positively charged carbon:

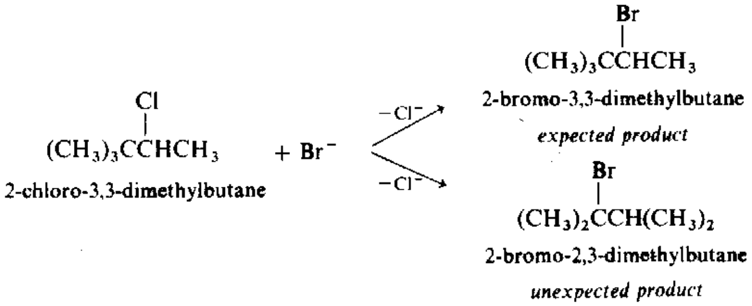


An ethyl cation CH_3-CH_2^+ has only three C-H bonds

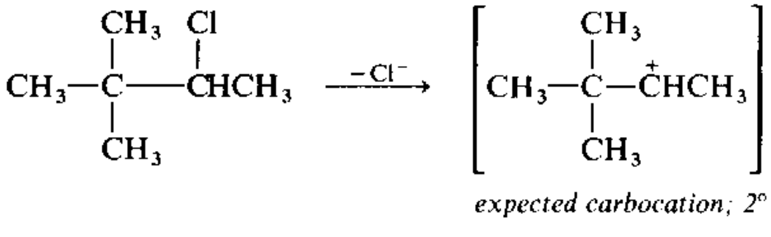
that can overlap with the empty *p* orbital, but the *t-butyl* cation $(CH_3)_3C^+$ has nine C-H bonds that can help dispersing the charge in this way. Therefore, a tertiary carbocation is stabilized by more accommodation of the positive charge.

(F) Rearrangements of carbocations :

Bromide ion as a nucleophile substitutes the chloride ion in 2-Chloro-3,3-dimethylbutane (secondary alkyl chloride) via an S_N1 reaction. Interestingly, in addition to the expected product, another substitution product is observed.



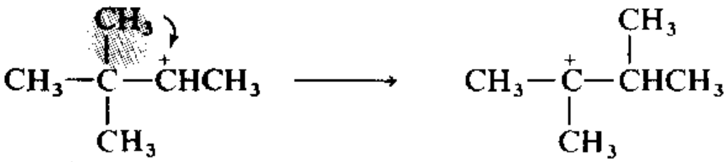
Let us examine the intermediate carbocation in this reaction more carefully. The first formed carbocation is in fact a secondary carbocation:



It is well known that a secondary carbocation is of much higher energy (less stable) than a tertiary carbocation. A lower energy (more stable) tertiary carbocation would be easily obtained by the shift of a

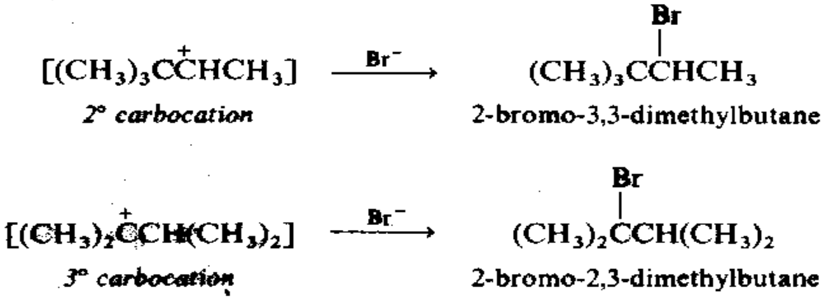
methyl group with its bonding electrons from the adjacent carbon atom, this process is called *methide* ($^-CH_3$) shift. This *methide* shift causes the rearrangement of the secondary carbocation to the more stable tertiary carbocation.

1,2-Methyl shift (*Methide* H_3C^- shit):



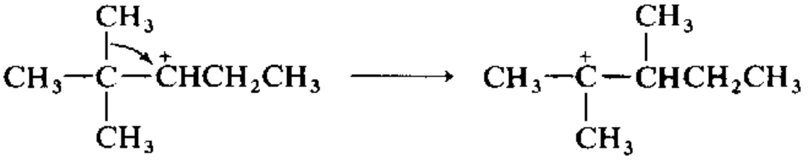
a 2° carbocation a more stable 3° carbocation

A methyl group carrying a negative charge ($^-CH_3$) is called *methide* and it is looked at as a carbanion, and it is obtained *via* a concerted reaction step. The presence of both secondary and tertiary carbocations in solution leads to the formation of the two products, with different skeleton:



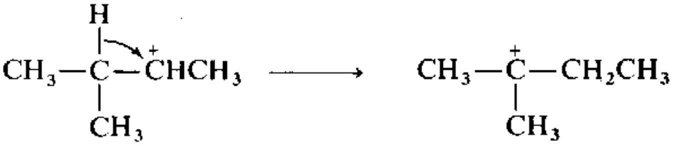
Such 1,2-shift also occurs with hydrogen, methyl or aryl during the rearrangement of a less stable carbocation to yield the more stable one. In each case the attached atom would move with its bonding electrons. The following rearrangements exemplify 1,2-shifts and the formation of more-stable carbocations.

1,2-Methide (H_3C^-) shift:



a 2° carbocation   a more stable 3° carbocation

1,2-Hydride (H^-) shift:

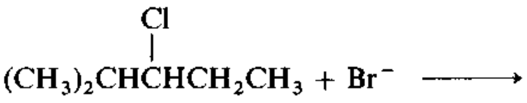


a 2° carbocation   a more stable 3° carbocation

(Notice that any 1,2-shift occurs at an adjacent saturated carbon)

Study problems:

1. **Show by an arrow the 1,2-shift of an alkyl group or a hydrogen and give the structure of the rearranged carbocation:**
   - **a)** $CH_3\ CH_2\ {}^+CHCH_3$
   - **b)** $(CH_3)_2\ CH\ {}^+CHCH_3$
   - **c)** $CH_3{}^+CHCH(CH_3)_2$
2. **How many S_N1 products would be formed in the following reaction?**



$$(CH_3)_2CH\overset{Cl}{\overset{|}{C}}HCH_2CH_3 + Br^- \longrightarrow$$

(7) Substitution Reactions of Allylic Halides and Benzylic Halides:

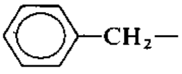
The allylic halides and the benzylic halides behave differently in S_N1 and S_N2 reactions

$CH_2{=}CH{-}CH_2{-}$

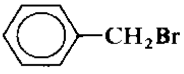
the allyl group

$CH_2{=}CHCH_2Cl$

3-chloro-1-propene
(allyl chloride)



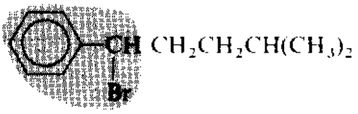
the benzyl group



benzyl bromide

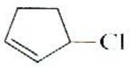
An atom or group that is attached to the carbon atom *adjacent to one of the sp^2 carbon atoms* is said to be in the allylic position or the benzylic position, respectively.

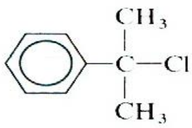
4-chloro-2-pentene
an allylic chloride

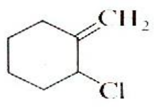


1-bromo-4-methyl-1-phenylpentane
a benzylic bromide

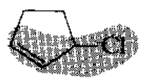
Circle the allylic or benzylic halide grouping in each of the following structures. In addition, classify each as being 1°, 2°, or 3°:

(a) 

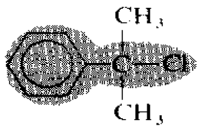
(b) 

(c) 

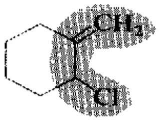
Solution:

(a) 

2°

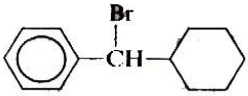
(b) 

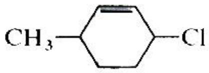
3°

(c) 

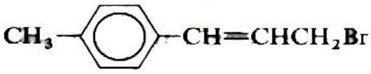
2°

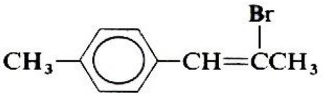
1. **Circle the benzylic or allylic halide grouping in each of the following structures:**

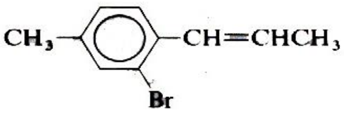
(a) 

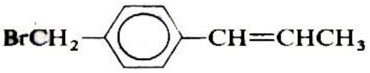
(b) 

2. **Classify each of the following compounds as a vinylic halide, an allylic halide, a benzylic halide, or an aryl halide:**

(a) 

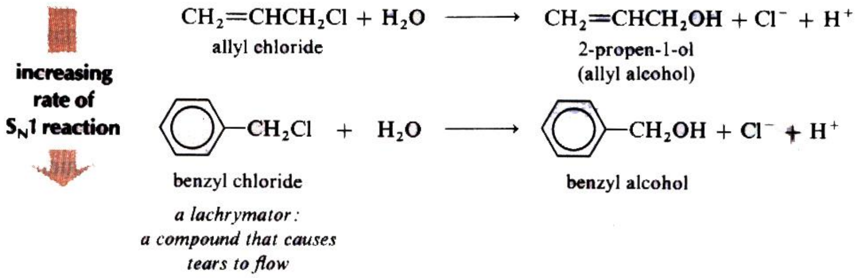
(b) 

(c) 

(d) 

(A) S_N1 reactions:

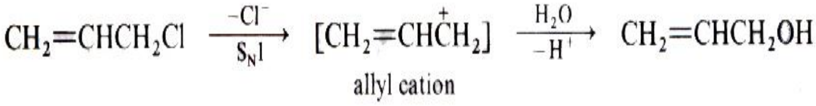
In general primary alkyl halides undergo substitution by the S_N2 mechanism exclusively and do not undergo through the S_N1 path. However, a primary allylic halide or benzylic halide is very reactive in both S_N1 and S_N2 reactions. Table 6 lists the relative reactivities of some halides under typical S_N1 conditions. It can be seen from the table that an allyl halide is about 30 times more reactive than an ethyl halide, and a benzyl halide is almost 400 times more reactive compared to ethyl halide. If two phenyl groups are present, *e.g.* 2,2-diphenyl-1-chloroethane, the halide is 100,000 times as reactive.



Carbocations are stabilized by dispersal of the positive charge. In the case of *Inductive stabilization* involves dispersal of the positive charge through *sigma*

bonds. **As mentioned previously the inductive effect explains the relative stabilities of 1°, *2°*, and 3° carbocations. Stabilization *via* hyper conjugation is must be taken into account, too. On the other hand, *Resonance-stabilization* would be involved in the dispersal of the positive charge through the *pi bonds.***

Let us consider the following S_N1 reaction of allyl chloride with H_2O:



$$CH_2{=}CHCH_2Cl \xrightarrow[S_N1]{-Cl^-} \underset{\text{allyl cation}}{[CH_2{=}CH\overset{+}{C}H_2]} \xrightarrow[-H^+]{H_2O} CH_2{=}CHCH_2OH$$

The two resonance structures for the allyl cation are identical in structure and bonding; therefore, they would have the same energy content and contribute equally to the structure of the actual allyl cation. Because the allyl cation is resonance-stabilized, so the energy of the transition state leading to its formation is relatively low. Accordingly, the rate of its S_N1 reaction is quite fast. A *p*-orbital picture (a composite of the *π* bonding orbitals) of the allyl cation is shown in Figure 26, in which an interaction occurs between the C=C *pi* bond and the empty *$2p_z$* orbital at the positively charged allylic carbon.

TABLE 6: Relative rates of some organic halides under typical S_N1 conditions

Halide	*Relative rate*	
CH_3CH_2X	**1.0 [a]**	
$CH_2{=}CHCH_2$	**33**	
$X\ C_6H_sCH_2X$	**380**	
$(C_6H_s)_2CHX$	**~10^5**	

a **The observed reaction probably proceeds by an S_N2 path.**

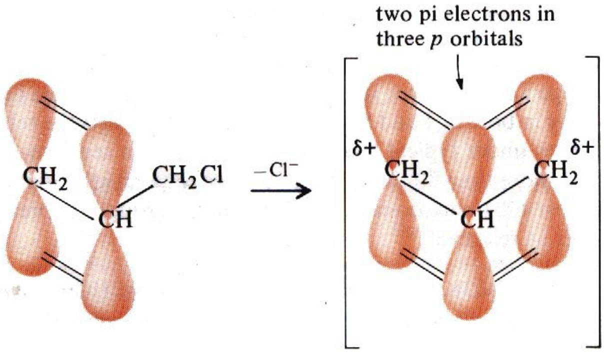
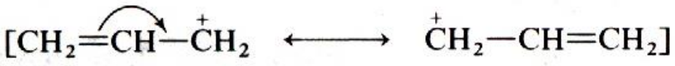


FIGURE 26

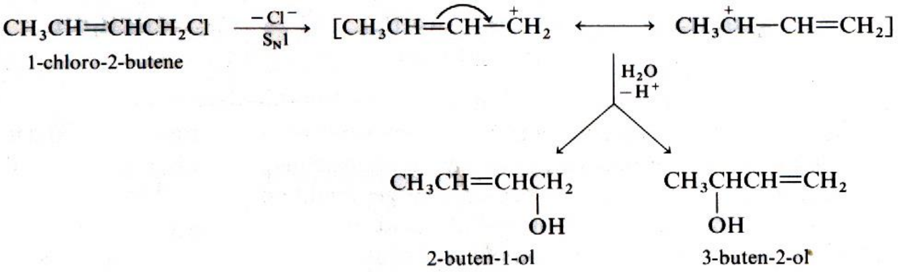
Formation of the allyl cation from allyl chloride.



$$[CH_2{=}CH{-}\overset{+}{C}H_2 \longleftrightarrow \overset{+}{C}H_2{-}CH{=}CH_2]$$

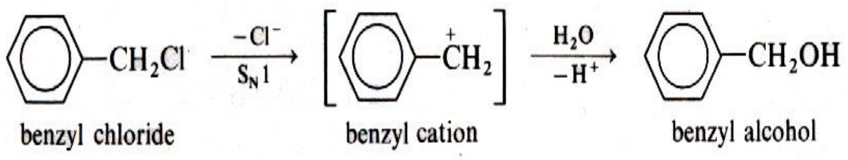
resonance structures for the allyl cation
(*equal contributors*)

Both terminal carbons in the allyl cation have an equal amount of positive charge. In fact both positively charged carbon atom of the allylic carbocation is equally attacked by the nucleophile. On the other hand, the S_N1 reaction of l-chloro-2-butene with H_2O leads again to two products. These two products arise from the attack of H_2O at either of the two partially positive carbon atoms (1° and 2° carbocations):



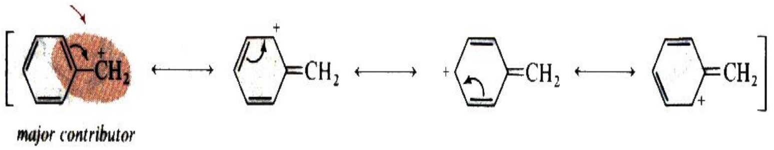
Benzyl halides also show an enhancement of the S_N1

rate due to the resonance stabilization of the transition states. It is well known that the *pi* electrons in the aromatic *pi* cloud of the benzene ring affects dispersing the positive charge to a great extent.

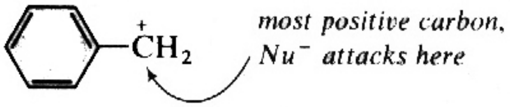


The aromatic *pi* cloud of benzene is usually symbolized by a circle in the ring. However, in the discussion of delocalization of *pi* electrons, Kekule formulas are more convenient for understanding such process. The benzyl cation has four resonance structures, whereas allylic cation has only two. This explains the high enhancement of the rate of solvolysis in the case of the benzyl chloride:

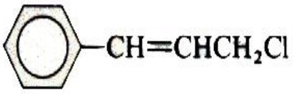
Similar to allylic cation

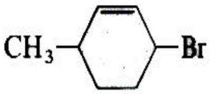


The first resonance structure shown is the major contributor because of the aromatic *pi* cloud stabilization. Therefore, the most positive carbon in the intermediate is the benzylic carbon. This carbon would be redily attacked by the nucleophile. Notice that the aromatic *pi* cloud of the benzene ring stabilizes only the positive charge on the head benzylic carbon atom and the other Kekule resonating structures do not participate in the S_N1 reaction (losing aromaticity is not easily achaived under such reaction conditions).



Predict the products of the solvolysis in water of:

(a) 

(b) 

(B) S_N2 reactions:

Allylic halides and benzylic halides also undergo S_N2 reactions at faster rates than primary alkyl halides or even methyl halides. Table 7 lists the average relative rates of some halides in a typical S_N2 reaction. The reason for this greater S_N2 reactivity of allylic and benzylic halides is that the allylic *pi* bond or the benzene *pi* cloud reduces the energy of the transition state of an S_N2 reaction. In the transition state, the head carbon, which is undergoing the S_N2 reaction changes from the *sp^3-hybrid* state to the *sp^2-hybrid* state and has a *p* orbital. This *p* orbital forms partial bonds with both the incoming nucleophile and the leaving halide ion. Also, in the transition both the nucleophile and the halide ion carry partial negative charge. However, the adjacent *pi* orbitals, in the allylic or benzylic halide, would undergo partial overlap with the transitional *p* orbital of the head carbon. Accordingly the adjacent *pi* orbitals would delocalize the negative charge, which lowers the energy of the transition state. Figure 27 shows the *pi* orbitals of the allylic case; notice that the benzylic is similar.

Table 7: **Average relative S_N2 rates for some organic halides**

Halide	*Relative rate*
CH_3X	30
CH_3CH_2X	1
$(CH_3hCHX$	0.03
$CH_2=CHCH_2X$	40
$C_6H_sCH_2X$	120

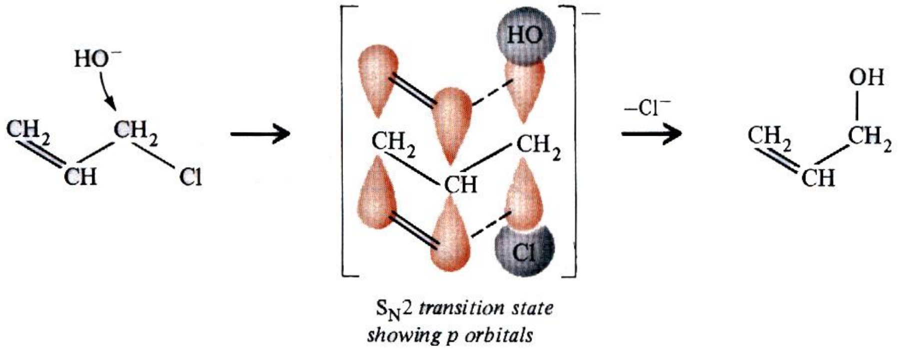
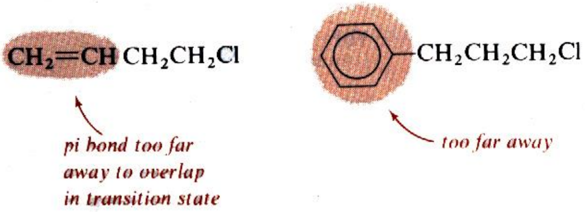


FIGURE 27
Stabilization of the transition state
in an S_N2 reaction of allyl chloride.

The increased stabilization occurs only in either S_N1 or S_N2 reactions of compounds containing *pi* systems, if the *pi* system is *adjacent* to the head carbon. However, if it is distant, it cannot overlap and cannot stabilize the transition state:



Which of the following compounds enhance reactivity in S_N1 and S_N2 reactions due to the resonance stabilization of the partial *p*-orbital overlap?

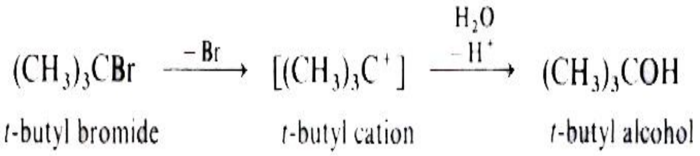
(a) $CH_3CH{=}CHCHBrCH{=}CH_2$
(b) $CH_3CH{=}CHCH_2CHBrCH_2CH_3$
(c) $C_6H_5CH{=}CHCH_2I$
(d) $CH_2{=}CHCH_2CHBrCH{=}CH_2$

Solution: (a), (c), (d)

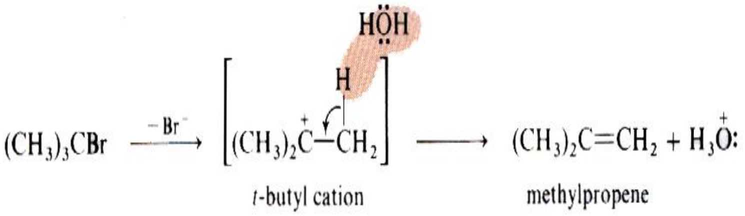
(8) The E1 Reaction:

The S_N1 reaction occurs through a carbocation, which is highly-energetic, unstable intermediate that quickly undergoes a further reaction. One way of a carbocation to reach a stable product is by combining with a nucleophile *via* an S_N1 mechanism. However, there is an alternative path, by which the carbocation can lose a proton to a base to form an alkene *via* an elimination reaction El.

Substitution (S_N1):

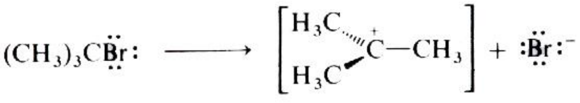


Elimination (E1):



The first step in an E1 reaction is identical to the first step in an S_N1 reaction, in which the ionization of the alkyl halide slowly occurs. This slow step is the rate-determining step of the overall reaction. Like an S_N1 reaction, a typical E1 reaction shows first order kinetics, with the rate of the reaction is dependent on the concentration of only the alkyl halide. Since only one reactant is involved in the transition state of the rate-determining step, the E1 reaction, like the S_N1 reaction, is unimolecular.

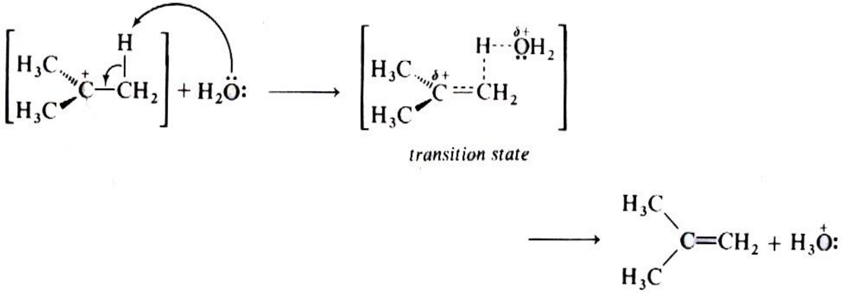
Step 1 (slow):



carbocation intermediate

In the second step of an elimination reaction, the base removes a proton from a saturated carbon that is *adjacent to the positive carbon.* The electrons of that carbon--hydrogen sigma bond shift toward the positive charge, the adjacent carbon rehybridizes from the *sp*^{3} state to the *sp*^{2} state, and an alkene is formed.

Step 2 (fast):



Because an E1 reaction, like an S_N1 reaction, proceeds through a carbocation intermediate, for this reason tertiary alkyl halides undergo this reaction much more rapidly than other alkyl halides. E1 reactions of alkyl halides occur under the same conditions as S_N1 reactions (polar solvent, very weak base, etc.); therefore, S_N1 and El reactions compete with each other. Under the mild conditions needed for these carbocation reactions of alkyl halides, the S_N1 product generally predominates over the E1 product. For this reason, E1 reactions of alkyl halides are relatively unimportant *vide sobra*.

Some tertiary alkyl halides yield mixtures of alkenes as well as a substitution product when they are subjected to S_N1 conditions. Predict all likely products from the reactions of 2-bromo-2-methylbutane with ethanol under S_N1 conditions.

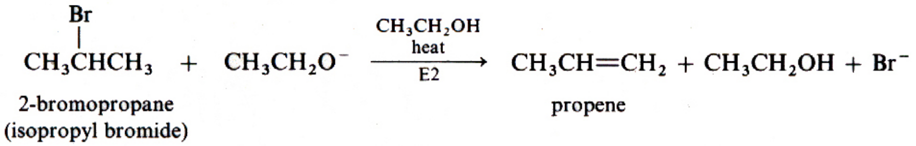
Sumary:

In an S_N1 reaction:

1. **Tertiary alkyl halides, allyl halides and benzyl halides undergo S_N1 reactions.**
2. **The reaction depends on the concentration of RX only.**
3. **Weak bases are used *e.g.* H_2O and EtOH.**
4. **The process occurs through two steps, the first step is the ionization step that yields the carbocation and it is very slow, which is called the rate determining step. The second step is fast, in which the nucleophile attacks the formed positively charged carbon.**
5. **The rate of an S_N1 depends on the concentration of RX.**
6. **An optical isomer gives racemic mixture.**
7. **Polar solvents increase the rate of an S_N1 reaction due to the solvation of the formed carbocation.**
8. **S_N1 reactions are usually competed by elimination reactions E1.**
9. **S_N1 reactions may suffer rearrangement processes.**

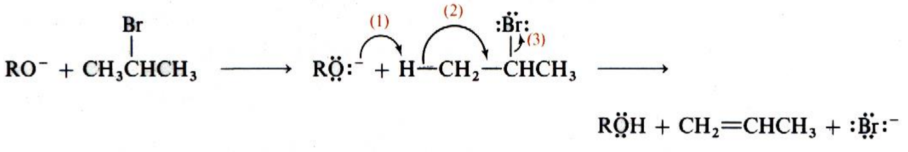
(9) The E2 Reaction:

The most useful elimination reaction of alkyl halides is the E2 reaction (bimolecular elimination). E2 reactions of alkyl halides are favored by using strong bases, e.g. ^-OH or ^-OR, and high temperatures. A typical, an E2 reaction is carried out by heating the alkyl halide with potassium hydroxide $K^+ \, ^-OH$ or sodium ethoxide $Na^+ \, ^-OEt$ in ethanol.



$$CH_3\overset{\overset{Br}{|}}{C}HCH_3 + CH_3CH_2O^- \xrightarrow[E2]{CH_3CH_2OH,\ heat} CH_3CH{=}CH_2 + CH_3CH_2OH + Br^-$$

Because the E2 reaction proceeds in one step through a concerted transition state, a reaction just as an S_N2 reaction does.



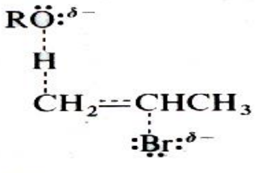
This reaction occurs through the following steps:

(1) The base is forming a bond with the hydrogen.

(2) The C-H electrons are forming the *pi* bond.

(3) The bromine is departing with the pair of electrons from the carbon-bromine sigma bond.

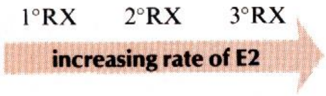
The previous equation shows the mechanism with arrows representing "electron-pushing." The structure of the transition state in this one-step reaction is represented as following transition state:



E2 transition state

In which the new and old bonds are drawn in dotted lines.

Tertiary alkyl halides would be undergoing E2 reaction at the fastest rate, and primary alkyl halides have the slowest rate. However, treating primary alkyl halides with a base usually produce nucleophilic substitution products and little alkenes are formed.

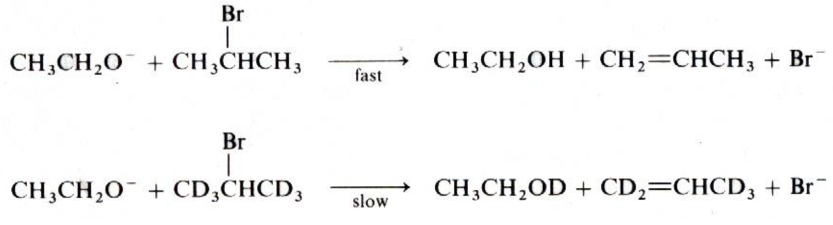


(A) Kinetic isotope effect:

The experimental evidence that supports our understanding of the E2 mechanism is the difference in the rates of elimination of deuteriated and nondeuteriated alkyl halides. Such a difference in the reaction rates of compounds containing different isotopes is called a kinetic isotope effect.

Deuterium ($^{2}_{1}H$, or D) is an isotope of hydrogen with a nucleus containing one proton and one neutron. The C-D bond is stronger than the C-H bond by about 1.2 kcal/mole. It has been postulated that the breaking of the CH bond is an integral part of the rate-determining step (the *only* step) of an E2 reaction. What happens when the H that is eliminated is replaced by D? The stronger C-D bond requires more energy to be broken. For this reason, the E_{acl} is increased (Figure 28) and the rate for the elimination reaction would be slower.

When the 2-bromopropanes are subjected to an E2 reaction with EtO^- as the base, it has been observed that the reaction of the deuteriated compound occurs at *one-seventh* the rate of the ordinary 2-bromopropane, this fact supports the proposed mechanism of the E2 reaction.



$$CH_3CH_2O^- + CH_3\overset{\overset{\displaystyle Br}{|}}{C}HCH_3 \xrightarrow[\text{fast}]{} CH_3CH_2OH + CH_2{=}CHCH_3 + Br^-$$

$$CH_3CH_2O^- + CD_3\overset{\overset{\displaystyle Br}{|}}{C}HCD_3 \xrightarrow[\text{slow}]{} CH_3CH_2OD + CD_2{=}CHCD_3 + Br^-$$

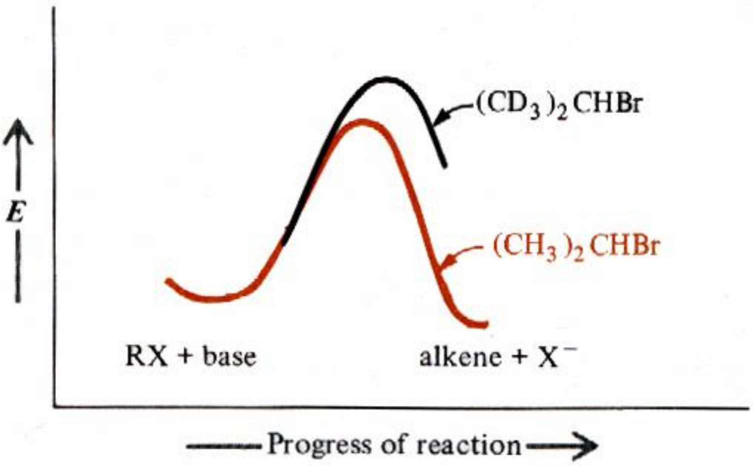


Figure 28

Energy diagrams for the E2 reactions of 2-bromopropane and a deuteriated 2-bromopropane

Sample problem:

Why is a kinetic isotope effect not observed with $(CH_3)_3CBr$ and $(CD_3)_3CBr$ in E1 reactions?

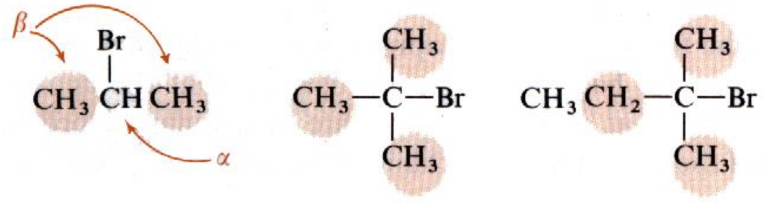
Solution: **The cleavage of a C-H bond is not involved in the rate-determining step of an El reaction (RDS is the ionization step and not the cleavage step).**

(B) Mixtures of alkenes:

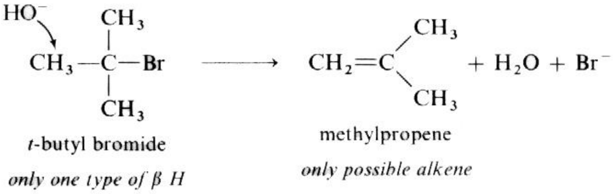
Generally, E1 and E2 reactions are known as beta (*β*) eliminations. This term reflects which hydrogen atom is lost in the reaction. Different types of carbon and hydrogen atoms in a molecule may be labeled as α-, β-, according to the *Latin* alphabet. The carbon atom *attached to the principal functional group* in a molecule is called the alpha (α) carbon, and the adjacent carbon is the beta (*β*) carbon. The hydrogens attached to the α- carbon are called α-hydrogens, while those attached to the *β*-carbon are *β*-hydrogens. In a *β* elimination reaction, a *β*-hydrogen is lost to yield the corresponding alkene, keep in mind that the *β*-hydrogen must be attached to a saturated carbon. (Of

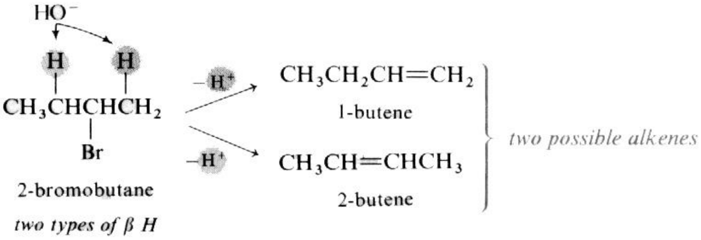
course, an alkyl halide with no *β*- hydrogen cannot undergo a *β* elimination *e.g.* vinyl halides CH_2=CHX.)

***β*-carbons and *β*-hydrogens are circled:**



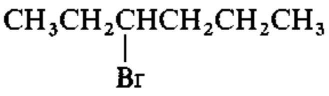
If 2-bromopropane or *t*-butyl bromide undergoes elimination, there is only one possible alkene product. However, if the alkyl groups around the α-carbon are different and there are more than one type of *β*-hydrogens, then more than one alkene could be resulted. The E2 reaction of 2-bromobutane yields two alkenes because two types of hydrogen atoms can be eliminated: *β*-hydrogen from a CH_3 group or a β-hydrogen from a CH_2 group.





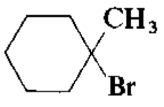
Circle the *β*-carbons and *β*-hydrogens in the following structures:

(a)



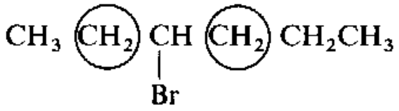
$$CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$$

(b)

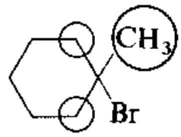


Solution :

(a)



(b)



In the preceding problem, tell how many different types of *β*-hydrogens are in each structure.

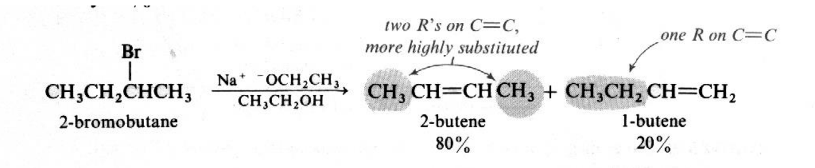
Solution*:*

- **(a) two types;**
- **(b) two types (the ring CH_2 groups are equivalent to each other; the CH_3 is different).**

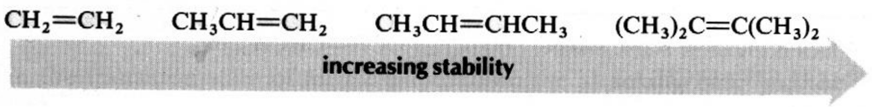
Write the structures of the expected alkenes from the E2 reaction of each of the above alkyl bromides.

(C) Which alkene is formed?

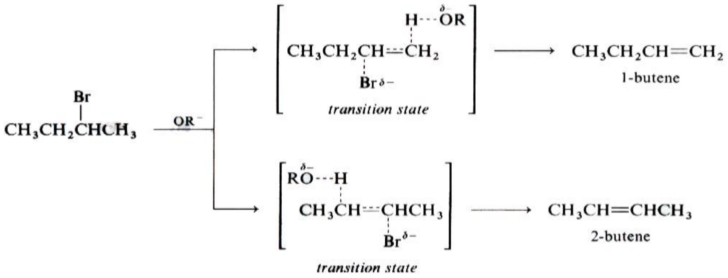
In 1875, the Russian chemist Alexander Saytseff formulated the following rule, now is called the Saytseff rule: *In elimination reactions, the alkene with the greatest number of alkyl groups attached to the doubly-bonded carbon atoms predominates in the product mixture.* We will refer to this alkene as the *more highly substituted alkene.* In other words, the alkene with the more substituted double bond is the more stable, the more predominant product. The Saytseff rule predicts that 2-butene would predominate over 1-butene as a product in the E2 reaction of 2-bromobutane. In the following reaction, the mixture of alkene products consists of 80 % 2-butene and only 20% 1-butene.



The more substituted alkene is the more stable:



The more stable alkene (2-butene) is formed in preference to the less stable alkene (1-butene), due to the lower energy transition state. However, in either transition state, the base is removing a proton and a double bond is being formed, so each transition state has some double-bond character. The old bonds and the new ones in the transitions are shown as dotted lines in the formulas. The transition state leading to the more stable alkene is itself more stabilized and of lower energy. The reaction with the lower-energy transition state would proceed at a faster rate; therefore, the more stable alkene is the predominant product, Figure 29.



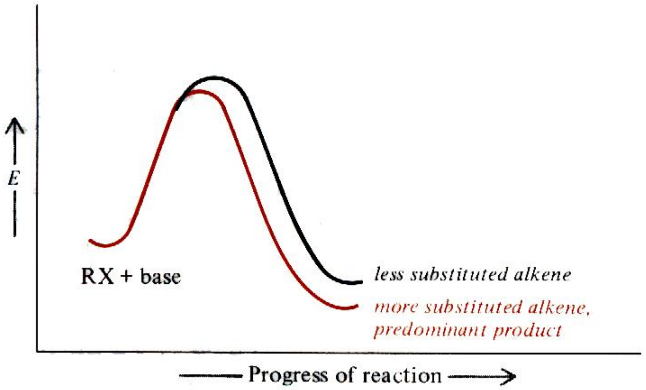


FIGURE 29

Energy diagram for a typical E2 reaction, showing more substituted alkene predominates.

In the following alkenes which is the more stable:

(a) $(CH_3)_3CCH=CHCH_3$ or (b) $CH_3CH=C(CH_3)_2$

Solution:

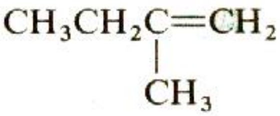
(b) with three groups is more stable than
(a) with only two groups is less stable

Predict the major alkene product of the E2 dehydrohalogenation of $CH_3CH_2C(CH_3)_2Cl$.

Solution:

The two possible alkenes are:

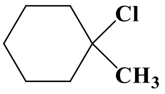
$CH_3CH=C(CH_3)_2$ and



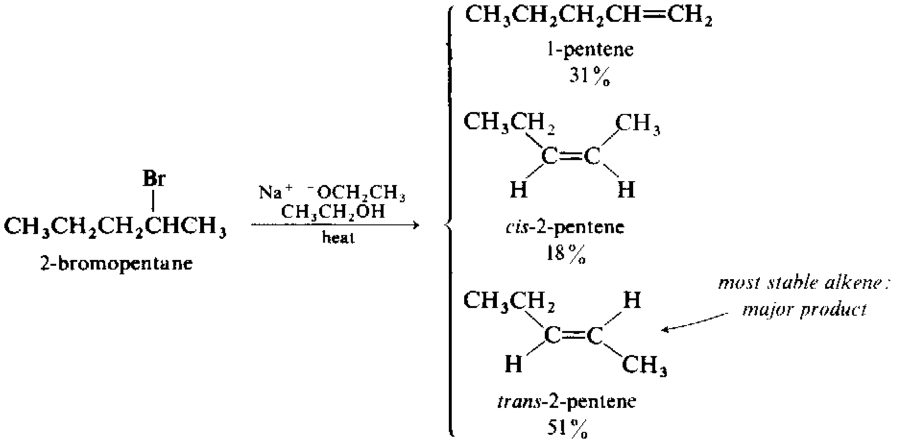
$$CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}=CH_2$$

The first alkene predominates (3 groups versus 2 groups).

Predict the major alkene product of the E2 dehydrohalogenation of l-chloro-l-methylcyclohexane:



It is well documented that the most highly substituted alkene predominates in the product mixture. The most highly substituted alkene can often exist as *cis*- and *trans*-diastereomers (geometric isomers). According to the available exipermental data, it has been determined that the *trans* alkenes are generally more stable than their *cis* isomers, this could be attributed to the less steric hindrance in the *trans* isomers. Therefore, *trans* alkenes are expected to be predominant products of E2 reactions, due to the more stabilized transition state. The following equation presents the results of an E2 reaction of 2-bromopentane:

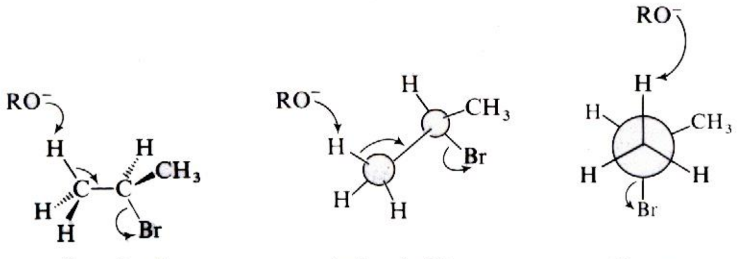


This result confirmed that the more substituted *trans* isomer is the more predominant product than the *cis* isomer.

(D) Stereochemistry of an E2 reaction:

In the transition state of an E2 elimination reaction, the attacking base and the leaving group must be as far apart as possible, or *anti* to each other. For this reason, the E2 elimination is often referred to as *anti*-elimination.

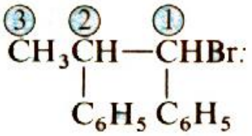
anti-Elimination:



dimensional *ball-and-stick* *Newman*

The *anti*-positioning of H and Br that are lost during an anti-elimination reaction would determine the stereochemistry of the formed alkene. Let us look at the E2

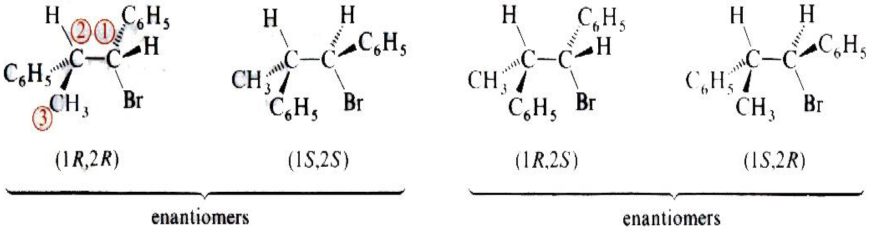
reactions of some stereoisomeric halides. For example 1-bromo-1,2-diphenylpropane, which has two chiral centers (carbons 1 and 2) and four stereoisomers.



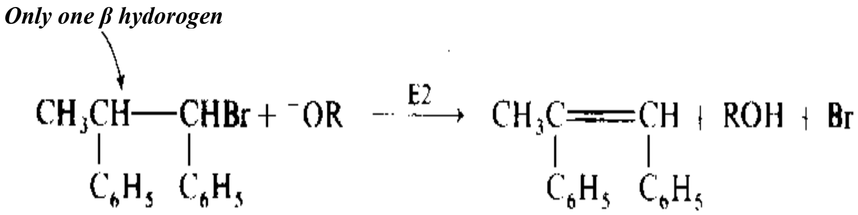
$$\overset{③}{C}H_3\overset{②}{C}H\underset{C_6H_5}{|}—\overset{①}{C}HBr\underset{C_6H_5}{|}$$

1-bromo-1,2-diphenylpropane

The four stereoisomers of 1-bromo-1,2-diphenylpropane, are:



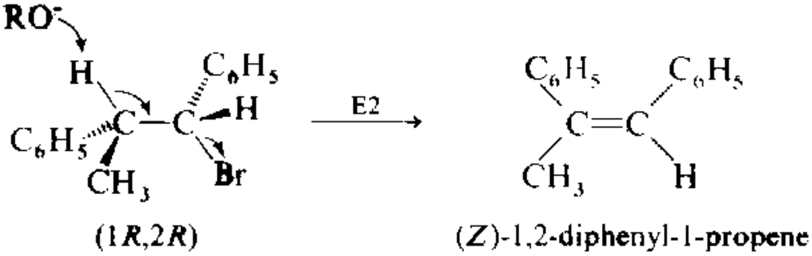
Because there is only one *β*-hydrogen in the starting alkyl halide, anyone of these stereoisomers yields $C_6H_5(CH_3)C{=}CHC_6H_5$. However, geometric isomerism is possible in this product.



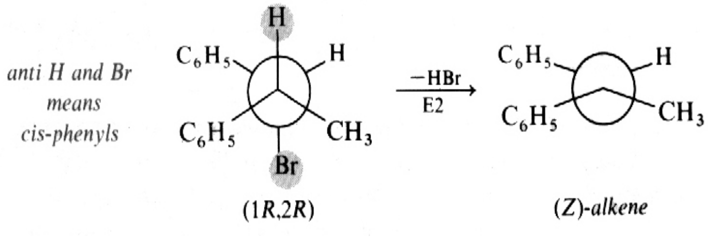
Only one β hydorogen

$$\underset{}{CH_3CH}(C_6H_5)—CHBr(C_6H_5) + {}^{-}OR \xrightarrow{E2} CH_3C(C_6H_5){=}CH(C_6H_5) + ROH + Br$$

When either (lR,2R)-1-bromo-l,2-diphenylpropane or its (lS,2S)-enantiomer undergoes E2 reaction, the (Z)-alkene is formed exclusively; no (E)-alkene is formed.



The reason for obtaining all (*Z*) and no (*E*) product is that, there is only one conformation of either of these enantiomers in which the Br and the beta H are anti. In either the (*1R,2R*) or the (*1S,2S*) enantiomer, the *anti*-positioning of H and Br puts the two phenyl groups on the same side of the molecule, and the (*Z*)-alkene is formed. If the elimination could occur regardless the conformation of the enantiomers, then some (*E*)-alkene would also be observed.



Study problem:

Write equations for the *anti-elimination* of the (*1S,2S*)-enantiomer, as we have done for the (*1R,2R*)-enantiomer.

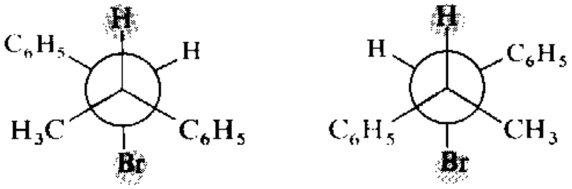
Solution:

The mirror image of the (*1R,2R*)-enantiomer would yield, yet again only the (*Z*)-alkene.

However, the opposite situation is found with the (*1R,2S*)- or (*1S,2R*)-enantiomers. Either of these isomers yields the (*E*)-alkene and not the (*Z*)-alkene. The reason, once again is that, there is only one conformation for each of these enantiomers in which the Br and the single beta H

are in an *anti*-relationship. In these conformations, the phenyl groups are on opposite sides of the molecule.

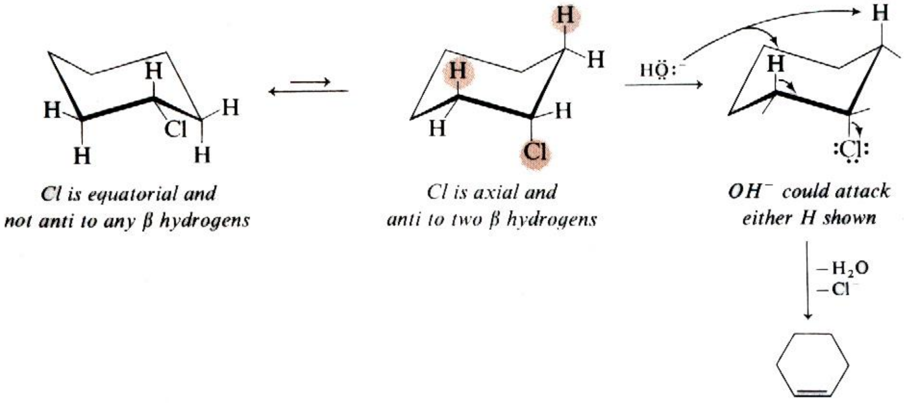
anti H and Br means trans-phenyls



(1*R*,2*S*) (1*S*,2*R*)

Any reaction of different stereoisomers of a reactant yield stereo isomerically different products is said to be a stereospecific reaction. The E2 reaction is typical example of a stereospecific reaction.

Halocycloalkanes, such as chlorocyclohexane, can also undergo E2 reactions. In these cases, the conformation of the ring plays an important role in such a reaction. In order to get an *anti*-elimination reaction on a cyclohexane ring, the leaving group (such as chlorine) and a *β* hydrogen must be 1,*2-trans* and *diaxial.* No other conformation places the H and Cl *anti* to each other. (Using models would be very useful.) Even though this conformation is not the favored one (energy wise), a certain percent of halocycloalkane molecules would adopt this conformation at any given time and could undergo an *anti*-elimination reaction.



Cl is equatorial and not anti to any β hydrogens

Cl is axial and anti to two β hydrogens

OH⁻ could attack either H shown

1- **Draw the dimensional formulas for the conformers of (*1R,2S*)-1-bromo-1,2-diphenylpropane and (*1S,2R*)-1-bromo-1,2-diphenylpropane that undergo E2 reaction.**
2- **1,2-Dibromo-1,2-diphenylethane contains two chiral carbon atoms and has a pair of enantiomers plus a *meso* diastereomer. Any of the stereoisomers of this compound could undergo an E2 reaction to yield 1-bromo-1,2-diphenylethene. The *meso* form yields one geometric isomer of the alkene, while the racemic mixture of enantiomers yields the other geometric isomer. Predict the stereochemistry of the products of these two reactions.**
3- **Write an equation using conformational formulas that illustrate the E2 reaction of trans-1-chloro-2-methylcylohexane in aqueous sodium hydroxide. (*Be sure to show the required conformation of the ring for anti-elimination*.) Using models is recommended.**

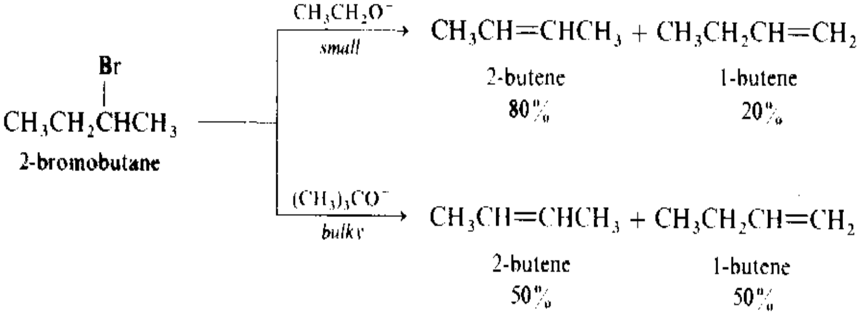
(E) Hofmann products:

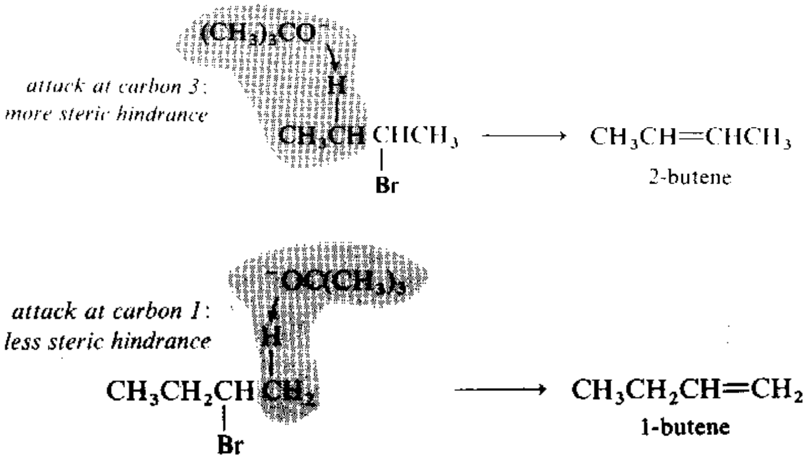
It has been dominstrated that most dehydrohalogenations follow the Saytseff rule, and the more substituted alkene predominates. However, under certain circumstances, the major product of an E2 dehydrohalogenation is the *less substituted, less stable alkene.* When the less substituted alkene is the predominant product, in such a case the reaction would yield the Hofmann product.

A common phenomena leading to the less substituted alkene is the steric hindrance in the transition state that leading to the most substituted alkene. The steric hindrance can greatly raise the energy of this transition state. In such a case the reaction would follow a different path and yield the less substituted alkene trough the less hindered

transition state. The steric hindrance may be caused by anyone of three factors:

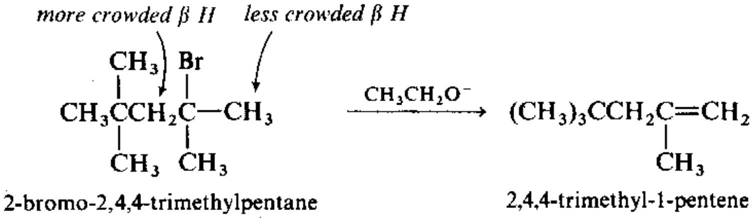
(i) The size of the attacking base may cause such steric hindrance. For example in the elimination reaction of 2-bromobutane with the small ethoxide ion EtO$^-$, the more substituted alkene predominates. Whereas using the more bulky *t*-butoxide ion $(CH_3)_3CO^-$, the 1- and 2-butenes are obtained in equal amounts.





(ii) Steric hindrance might be caused by the bulky groups surrounding the β-H in the alkyl halide. For example the hindered 2-bromo-2,4,4-trimethylpentane yields the less substituted alkene in an E2 reaction as the only product, even with a

small base like the ethoxide ion EtO$^-$.



(iii) If the leaving group itself is large and bulky, the Hofmann product may predominate.

1. **Write the formulas for both the Hofmann and Saytseff products of the E2 reactions of:**
   (a) 3-bromo-2-methylpentane and
   (b) 1-chloro-1-methylcyclohexane.
2. **Predict the major alkene products of the following E2 reactions:**

   (a) $CH_3CH_2CH_2CHBrCH_3 + {}^-OC(CH_3)_3 \rightarrow$

   (b) $CH_3CH_2CHBrCH_3 + OH^- \rightarrow$

(10) Factors Governing Substitution and Elimination Reactions:

The S$_N$1, S$_N$2, E1, and E2 are *competing reactions.* A single alkyl halide could yield substitution, elimination, and rearrangement products all together in the same reaction. If this happens, a mixture of a large number of products can result. However, a chemist can control the products of the reaction to a certain extent by a proper choice of the reagents and reaction conditions.

However, the factors that affect the course of substitution and elimination reactions of alkyl halides are:

1- **the structure of the alkyl halide;**
2- **the nature of the nucleophile or base;**
3- **the nature of the solvent;**
4- **the concentration of the nucleophile or base;**
5- **the temperature.**

(A) The alkyl halide

It has been mentioned that the type of alkyl halide affects greatly the mechanism of the reaction, *cf. infra*. We can summarize how the different alkyl halides act.

(a) *Methyl and primary alkyl halides* **tend to undergo S_N2 reactions. They do not form carbocations and thus cannot undergo S_N1 or E1 reactions. Primary alkyl halides may slowly undergo E2 reactions.**

(b) *Alkyl halides* **can undergo reaction by any path, but S_N2 and E2 are more common than E1 or S_N1. The reactions of secondary alkyl halides are more subject to be controled by conditions in the reaction flask (concentration of nucleophile, solvent, etc.) than are reactions of other alkyl halides.**

(c) Alkyl halides **undergo primarily E2 reactions with a strong base (such as ^-OH or ^-OR), but undergo the S_N1 reaction and some E1 reaction with a very weak base (such as H_2O or EtOH).**

Table 8 shows general equations to summarize the reactions of the different types of alkyl halides.

TABLE 8: The principal reactions of the different types of alkyl halides[a]

Halide			***products***
Methyl and primary	$RCH_2X + Nu^-$	$\xrightarrow{S_N2}$	$RCH_2\ Nu$
Secondary	$R_2CHX + Nu^-$	$\xrightarrow{S_N2 + E2}$	$R_2CH\ Nu$ + alkenes
Tertiary	$R_3CX + H_2O$	$\xrightarrow{S_N1 \text{ and } E1}$	R_3COH + alkenes
	$R_3CX + R'\ OH$	$\xrightarrow{S_N1 \text{ and } E1}$	R_3COR' + alkenes
	R_3CX + base	$\xrightarrow{E2}$	alkenes

a **For an E1 or E2 reaction to occur, the alkyl halide must contain at least one β hydrogen.**

(B) The nucleophile or base:

A strong base is generally considered as a good nucleophile, two other factors may affect the relative nucleophilicities of reactants, to some extent:

(i) The prpoperties of the used solvent, thus the more solvated nucleophile would be less reactive.

(ii) The polarizability of an ion or molecule affects its nucleophilicity. The atomic size is very effective as the outer electrons of larger atoms are quite far from the nucleus and less tightly held than those of smaller atoms. Thus the outer electrons of larger atoms would easily attack the positively charged carbon atom. For this reason, the iodide ion is a better nucleophile than the chloride ion.

The degree of nucleophilicity versus basicity can affect the course of a reaction. Thus, the reaction of a primary alkyl halide with a strong nucleophile (base) follows an S_N2 path. However, for a tertiary alkyl halide, any fairly strong base favors E2 reaction. Only the weakest bases (H_2O, ROH) give substitution products (through an S_N1 path).

For secondary alkyl halides, strong nucleophiles (such

as CN^-) favor S_N2 reactions, while weak nucleophiles (such as H_2O) favor carbocation reactions, S_N1 with some of the competing El. Strong bases (such as ^-OH or ^-OR) favor E2 reactions:

Strong nucleophile : S_N2
Weak nucleophile : S_N1 with some E1
Strong base : E2

Study problem:

Predict which is a better nucleophile CH_3S^- or CH_3O^-. Give an explanation.

(C) The solvent

The effect of solvent on substitution and elimination reactions can be well pronounced according to its ability or inability to solvate ions e.g. carbocations, nucleophiles or bases, and leaving groups. The ability of a solvent to solvate ions is determined by its polarity, which is usually reported as a dielectric constant. The dipole moment is a measure of the polarity of a single molecule, whereas the dielectric constant is a measure of the polarity of a liquid (many molecules with interactions between them). A highly polar solvent has a high dielectric constant. Table 9 lists some common organic solvents, their dielectric constants and the relative rates of a typical S_N1 reaction in that solvent.

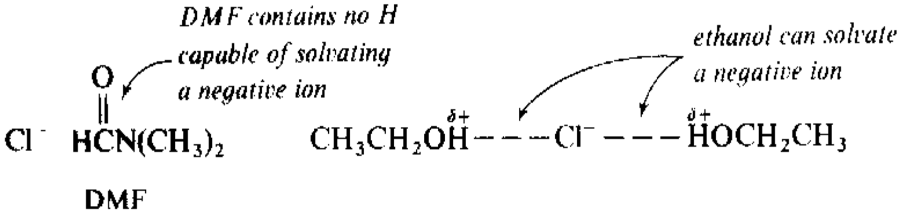
Even though dielectric constants can provide a guide for solvent selection, there are no firm rules about how to predict the best solvent for a given reaction (The solubility of the reactants must be considered too). In general, a *very polar solvent* (such as water) encourages S_N1 reactions by stabilizing the carbocation through solvation. In contrast, a less polar solvent (such as acetone) favors S_N2 and E2

reactions because it does not assist the ionization process.

TABLE 9: Relative rates of typical S_N1 reactions in various solvents

Solvent	*Formula*	*Dielectric Constant*	*Approximate relative rate*
formic acid	**HCO_2H**	**58**	**150**
water	**H_2O**	**78.5**	**4000**
80% aqueous ethanol	**CH_3CH_2OH-H_2O**	**67**	**185**
ethanol	**CH_3CH_2OH**	**24**	**37**
Acetone	**CH_3COCH_3**	**21**	**0.5**

In addition to solvation of a carbocation, the solvation of the nucleophile is very important, too. The choice of solvent can actually change the ranking of nucleophilicity within a group of nucleophiles. A solvent that can solvate (stabilize) an anion reduces its nucleophilicity, the reaction would be undergoing an S_N1 mechanism with higher relative rate. By contrast, a solvent that cannot solvate an anion enhances its nucleophilicity, and the reaction would be undergoing an S_N2 mechanism. For example the chloride ion is far better nucleophile in dimethylformamide (DMF), where it is not solvated, than in ethanol, where it is solvated.



(D) Concentration of the nucleophile or base

Controlling the concentration of a nucleophile or a base, could have a direct control over the rates of S_N2 and

E2 reactions. It is known that increasing the concentration of nucleophile generally has no effect on the rates of S_N1 or El reactions (it should be remembered that the reaction in such case depends only on the formation of carbocation). However, increasing the concentration of a nucleophile or a base increases the reaction rates of S_N2 or E2 proportionally. Thus, a high concentration of nucleophile or base supports S_N2 or E2 reaction, respectively; a low concentration of nucleophile or base favors S_N1 or E1 reactions:

High concentration of Nu^- or base: S_N2 or E2

Low concentration of $Nu^{\cdot\cdot}$: S_N1 or E1

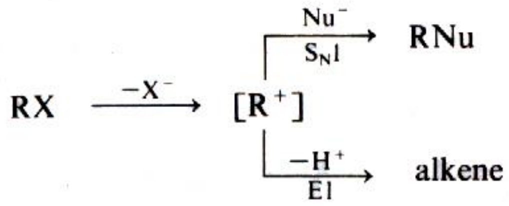
(E) Temperature

It is obvious that any increase in temperature would increase the rates of all substitution and elimination reactions. However, an increase in temperature usually leads to a greater increase in elimination products. (The reason for this is that elimination reactions usually have higher E_{act}'s than do substitution reactions, and higher temperatures enable a greater number of molecules to reach the elimination transition state.)

Summary

An alkyl halide contains a good leaving group (X^-) and can be readily attacked by nucleophiles ($Nu^{\cdot\cdot}$). The reaction may occur by one or more of four possible paths: S_N1, S_N2, El, E2.

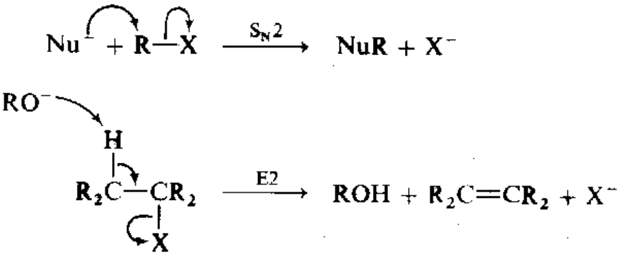
An S_N1 or E1 reaction proceeds through a carbocation intermediate [R^+], which is obtained through the slow rate determining step (RDS):



A carbocation intermediate usually leads to a mixture of products: a substitution product, an alkene, and also rearrangement products. Rearrangement products occur if the carbocation can form a more stable carbocation by a 1,2-shift of H, Ar, or R. If RX is an enantiomer pure alkyl halide, racemic mixture of products would be obtained in an S_N1 reaction.

The rate of a typical S_N1 or EI reaction depends on the concentration of the alkyl halide RX only; for this reason, these reactions are said to be first order. The rate-determining step (slow step) in an S_N1 or EI reaction is the formation of [R^+]. The stability of [R^+] determines the energy of activation of the transition state (E_{act}) in this step because the transition state has carbocation character. The stability of the carbocations will be in the following order: 3° » 2° » 1° » H_3C^+. For this reason, the readiness of RX to undergo S_N1 or EI reaction is: 3° » 2° » I ° » CH_3X. Allylic and benzylic halides undergo S_N1 reactions easily because of resonance-stabilization of the intermediate carbocation.

An S_N2 reaction occurs via a concerted transition state, which leads to Walden inversion. Such inversion is observed when RX is an enantiomer pure alkyl halide. An E2 reaction is also a concerted reaction that occurs through anti-elimination of H^+ and X^- .



Both S_N2 and E2 reactions follow second-order kinetics: the rate depends on the concentrations of both RX and Nu^-, and both reactions are bimolecular because both reactants are involved in the transition state. Due to the steric hindrance in S_N2 reactions, the order of reactivity of RX is: CH_3X » 1° » 2° » 3°.

Because the transition state has double-bond character, the order of reactivity of RX in E2 reactions is: 3° » 2° » 1°, the same order as in the E1 reaction. The most substituted C=C double bond usually predominates in E2 reactions (Saytseff rule) and the *trans* alkene usually predominates over the *cis* alkene. If the steric hindrance is highly effective in the transition state, the formation of the most substituted alkene would be inhibited, and then the least substituted alkene predominates (Hofmann product).

References:

1- **Organic chemistry text book (Second edition 1982), Ralph J. Fessenden and Joan S. Fessenden, Willard Grand press Boston, Massachusetts**

2- **Organic chemistry text book (Second edition 1979), Norman L. Allinger, Michael P. cava, Don C. DE Jongh, Carl R. Johnson, Norman A. Lebel, Calvin L. Stevens, Worth publishers, INC.**

3- **Chemistry of carbonyl group text book, Stuart Warren 1985, John Wiley and Sons.**

4- **A guide book to mechanism in organic chemistry text book (Sixth Edition 1986), longman Scientific and Technical, John Wiley and Sons.**

5- **Link: Google Schoolar (Sep. 2021)**