CHEM 212: Organic Chemistry II (3Credits)

Chapter 1 Amines and Its Derivatives

1.1 **Amines**

- Organic Nitrogen compounds are compounds that contain Carbon and nitrogen bonds: of which the amines is an example. Other nitrogen compounds include: ammonia, amides, nitriles, nitro, azo, diazo etc

- Nitrogen has variable oxygen states hence, organic nitrogen compounds are many

1.2 Types and Nomenclature of Amines

- Classification of amines is based on the number of alkyl or aryl group attached to nitrogen. The number is important in determining the type of reaction that is possible at the nitrogen atom

- NH_3 (ammonia), RNH_2 (primary amine) R_2NH (secondary amine), R_3N (tertiary amine), $R_4N^+ X^-$ (quaternary amine) e.g. $(CH_3)_3CNH$ - t-butyl amine

- Amino compounds are named either as an ammonia derivatives or as amino substituted compounds ($HOCH_2CH_2NH_2$ = 2-hydroxyethylamine or 2-aminoethanol. Conventionally, the hydroxyl group takes precedence over the amine as the functional group, hence the better name is 2-aminoethanol. With halogens, the amine is the preferred functional group, 2-chloroethylamine)

- Salts of amines with inorganic or organic acid are named as ammonium salts: $CH_3N^+H_3Cl^-$ - methyl ammonium chloride, $CH_2=CH-CH_2-NH^+(CH_3)_2{}^-OCCH_3$ (allydimethylammonium acetate). Sometimes, the name of the acid is used in conjunction with the corresponding amine: $CH_3N^+H_3Cl^-$ (methylammonium hydrochloride)

1.3 Physical Properties of Amines

-**Hydrogen Bond:** Properties of amines depend on the degree of substitution of the nitrogen atom: tertiary amines do not have N-H bond hence it cannot form NH stretching bonds or form hydrogen bonds.

- **Bond Strength**: N-H-N bonds are weaker compare to that of O-H-O- or F-H-F because the electronegativity of N<O<F

-**Boiling Point/Volatility**: Primary and secondary amines forms extensive H-bonding and it decreases its volatility but increases its boiling point relative to those of hydrocarbons of similar size, shape and weight:

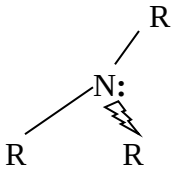
C-C-C-C-C-NH_2 C-C-C-C-C-C

MW= 87, BP=130^0C MW = 86, BP = 69^0C

- **Solubility**: Low molecular weight amines are more soluble in water relative to alcohols of comparable MW because of its extensive hydrogen bonding with water
- **IR**- 1^0 (two bands)and 2^0 (one band) amines has moderately weak characteristic N-H stretching vibrations at 3500-3300 cm^{-1}
- C-N vibrations are less identifiable but aromatic compounds shows absorption at 1300 cm^{-1}
- **NMR**: Has characteristic H-C-N proton shift at 2.7 ppm. The N-H protons are not easily identifiable and varies greatly among the amines due to various degrees of hydrogen bonding

1.4 Stereochemistry of Amines

- Bond angles: Nitrogen bond angles (pyramidal) are closer to tetrahedral (109.5^0) than to 90^0 which is expected of pure p bonds. This may be due to repulsion between the bonding and non bonding electrons on Nitrogen. If R's are different substituent, then an optical isomer is formed with N as the center of asymmetry



1.5 Amines as Acids and Bases

- Primary and secondary amines can act as a base as well as an acid

- When reacting as a base it accepts a proton: $RNH_2 + H_2O \leftrightarrow RNH_3^+$. The basic strength of aliphatic amines approximately the value of it equilibrium constant

$^-$ donates hydrogen when acting as a base: $(C_2H_5)_2NH + C_6H_5Li \rightarrow (C_2H_5)_2NLi + C_6H_6$

1.5 Methods of Preparation of Amines

- **alkylation:** Reaction of an alkyl halide with ammonia: $CH_3I + NH_3 \rightarrow CH_3N^+H_3I^-$

- Alkylation of ammonia with primary alcohols:

$$CH_3OH + NH_3 \xrightarrow[300^0C]{Zn,NH_4Cl} CH_3NH_2 + H_2O$$

- **The Beckman Rearrangement**: rearrangement of oximes of ketones to amines

$(R_2)C=N\text{-}OH + H_2SO_4 \rightarrow R\text{-}C=\bar{N}\text{-}R$

- **Reduction of Nitro Compounds**

$$CH_3NO_2 + 3H_2 \rightarrow CH_3NH_2 + 2H_2O$$

1.6 Reactions of Amines

- **Salt Formation**: amines are soluble in organic solvents and forms salts easily. Pyridine is a tertiary amine that is soluble in water and hydrocarbons ($K_b \sim 10^{-9}$).

$RNH_2 + H^+ \rightarrow RNH_3^+$

- Acylation: The lone pair of electrons on the Nitrogen plays a key role in the reactions of amines by losing a proton and elimination of X^- ion

$$C_6H_5C(=O)X + CH_3NH_2 \leftrightarrow C_6H_5C(=O)NHCH_3 + HX$$

- **Halogenation:** Primary amine reacts with halogens to form mono and disubstituted products. Secondary gives mono halo amines:

$$RNH_2 + Cl_2 \xrightarrow{^-OH} RNHCl$$

- **Reactions with Nitrous Acid (HONO)**

Nitrous acid reacts differently with primary, secondary and tertiary amines. It reacts with primary amines to liberate nitrogen, forms insoluble yellow liquid or solid with secondary amine, dissolve without evolving nitrogen to give complex derivatives

Oxidation

- **Tertiary Amines**: Amine oxides are formed when agents such as hydrogen peroxide (H_2O_2) and percarboxylic acid incorporate six electron oxygen into the amine.

$(C_2H_5)_3N: + [:O:] \rightarrow (C_2H_5)_3N\text{-}O^-$

- Amine oxides decompose to give alkenes when strongly heated and will not undergo inversion at N. So, amine oxides with three different R can be resolved into optically active form

$(CH_3CH_2)_2N^+(O^-)\text{---}CH_2\text{---}CH_2\text{—}H \rightarrow (CH_3CH_2)_2NOH + CH_2CH_2$

- 1^0 or 2^0 amines reacts with peroxide or peracid to form amine oxide intermediates which rearranges to form hydroxylamine
-
- $CH_3CH_2NH_2 + [\ddot{O}:] \rightarrow [CH_3CH_2\overset{O^-}{\underset{|}{N^+}}H_2] \rightarrow CH_3CH_2\overset{OH}{\underset{|}{N}}H$

Chapter 2 Chemistry of the Carbonyl group

2.1 Carbonyl Functional Group

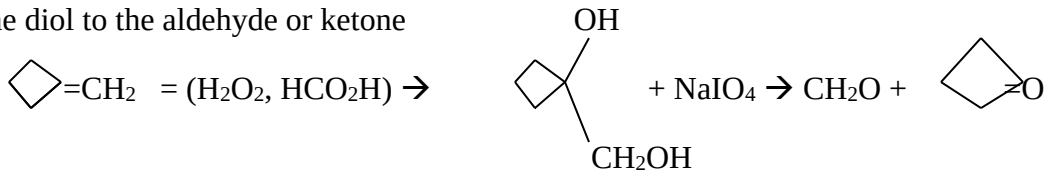
- Carbonyl compounds are carbon compounds that has C=O group in its structure
- There are two types of carbonyl compounds: RHC=O (Aldehydes) and $R_2C=O$ (ketones)
- Reactions can occur at the C=O carbon or the C=O itself can activate adjacent carbons (α-carbon) to make it undergo different types of reactions.

2.2 Preparation of Aldehydes and Ketones

- **I**: Ozonization of alkenes and hydration of alkynes will result into the formation of aldehydes and ketones

- **II Oxidation of 1, 2 Diols and Alkenes**

The reaction is a two-step reaction: (1) oxidation of alkene to a 1, 2 diol (2) oxidative cleavage of the diol to the aldehyde or ketone



III Reduction of Carboxylic Acids to Aldehydes (Rosenmund Reduction)

Acids are general difficult to reduce, hence, they are general first of all converted to derivatives that can easily be reduced or to a substance that can be converted to an aldehyde

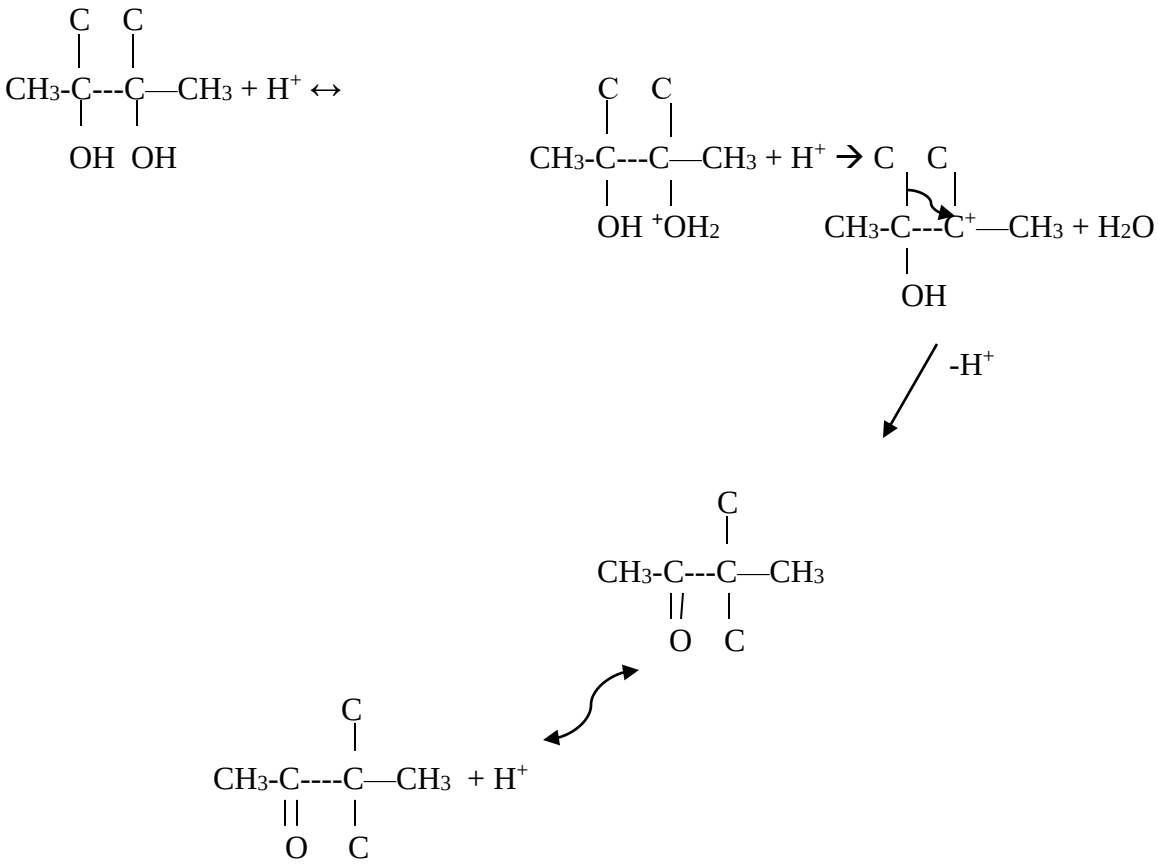
- **Rosenmund Reduction**: An acid is first converted to an acyl chloride which is then reduced to an aldehyde
- **(**H_2, Pd)

$$RCO_2H + SOCl_2 \rightarrow RCOCl + SO_2 + HCl \rightarrow RHC=O + HCl$$

- **IV 1,2 Glycol Rearrangement Reaction (Pinacol-Pinacolone Rearrangement)**
- Acid catalyzed rearrangements of 1,2 Glycols can result into carbonyl compounds

For example,2,3-dimethyl-2,3-butanediol(pinacol) to 3,3- dimethyl-2-butanone

(Pinacolone)



2.3 Characteristics of Carbonyl Groups of Aldehydes and Ketones

- The C=O group is very strong and reactive. Its bond energy (179 kJ) is more than that of a C=C (145 kJ) and C-O (161 kJ)

- For example formaldehyde will react rapidly with water while ethylene will not

$CH_2=O + H_2O \leftrightarrow HOCH_2OH$

- The reactivity of the C=O group is due to the polarity of the bond and the ability tautomerise (form resonance): $C=O \leftrightarrow C^+---O^-$
- The polarity allows the addition of polar compounds (HCl, H_2O, R^--Mg^+ X, etc) to be very easy.
- Polarity also increases the boiling point especially the lower members of the series (50-80^0 higher than hydrocarbons of the same molecular mass.) It also increases their solubility in water

2.4 Physical Properties

- **IR**: Stretching frequencies of aldehydes and ketones – 1705-1740 cm^{-1}

- **UV:** Absorption maximum is seen around 1560- 2800 cm^{-1}

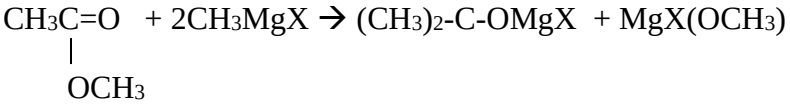
- **NMR:** C=O chemical shift is around 2.3 ppm

2.5 Reactions of the C=O Group

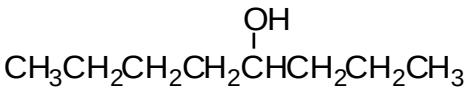
- C=O group reacts by addition reaction

- Factors such as steric hindrance, size of substituent's, cyclisation, electrical effects etc affect the reactivity of the C=O group

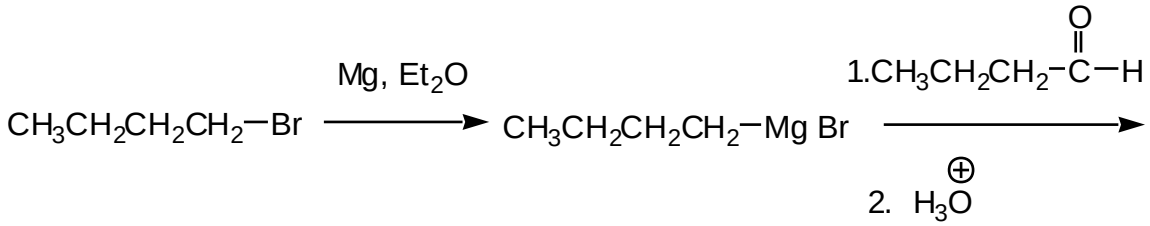
- **Grignard Reagents:** Grignard reagents can be represented as $R^{-}Mg^{+}$ X and can undergo addition reaction with the C=O bond

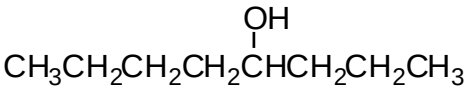


Example: Sketch an efficient synthesis of the target compound shown below using any organic compound having four carbon atoms or less, and any inorganic reagents, solvents and reaction conditions necessary.

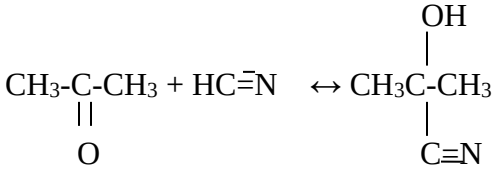


Answer:



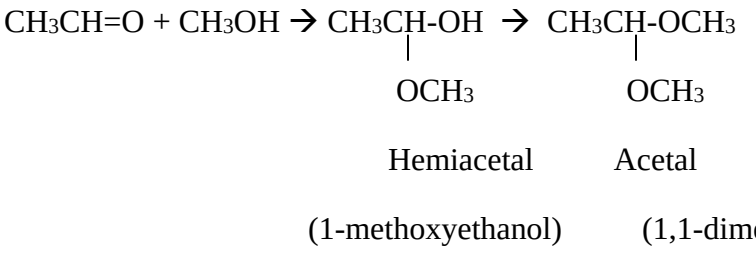


- **Cyanohydrins Formation:** Addition of HCN to aldehydes or ketone forms cyanohydrins
-

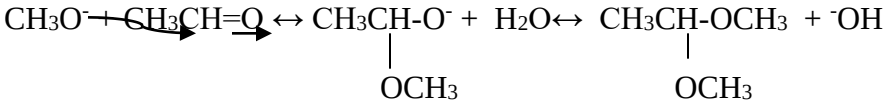


- **Hemiacetal and Acetal Formation**

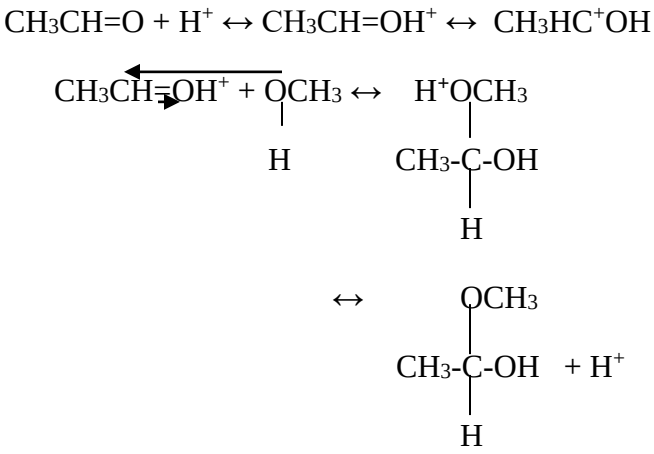
  Hemiacetal and acetal are formed by adding alcohols to aldehydes and ketones



- Hemiacetal formation can be catalyzed by acids or a base
- **Base catalyses**: $CH_3OH + {}^-OH \leftrightarrow CH_3O^- + H_2O$



- **Acid catalyses**



- **Halogenation**
- $CH_3CH=O + HCl \leftrightarrow CH_3ClCH\text{-}OH$

$CH_3CH=O + PCl_5 \rightarrow CH_3CHCl_2 + POCl_3$

- **Reduction of Carbonyls**

$CH_3CH=O + (H_2/Pd, 1000\ psi, 50^0) \rightarrow CH_3CH\text{-}OH$

- **Cannizaro Reaction:** occurs with aldehydes with no α-hydrogen by self-redox process in the presence of a strong base
- $2CH_2{=}O + NaOH\ (heat, H_2O) \rightarrow CH_3OH + H\text{-}C(=O)ONa$
- **2.6 Reactions Involving the Substituent Groups**
- **Halogenation of Saturated Aldehydes and Ketones:** Halogenation of saturated aldehydes or ketones occur by replacement of hydrogen alpha to the carbonyl group

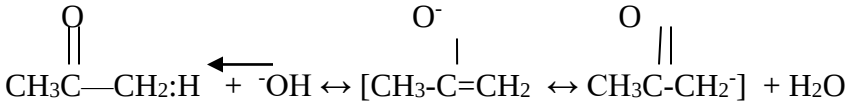
  $CH_3C{=}OCH_3 + Cl_2 \rightarrow ClCH_2C{=}OCH_3 + HCl$

  Acetone chloroacetone

- Chlorination of acetone can be base or acid catalyzed

2.6.1 Base Catalyzed Reaction: Enolate ion Formation

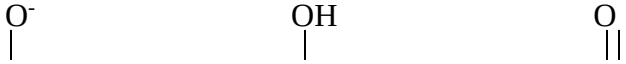
- First step is the removal of a α-proton form acetone by the base to form the enolate ion



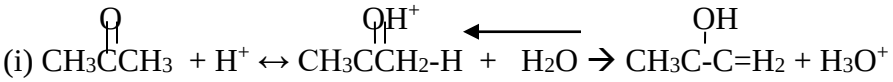
- This step is very slow so that the enolate ion can pick up a proton to form an enol

- Enolate enol

- Either the enolate ion or the enol can rapidly react with the halogen to form the halo ketone



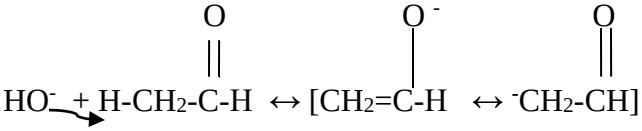
-
- **Haloform Reaction:** The remaining alpha protons are now more acidic and highly labile and can all be replaced by the halogen in a very fast reaction to form **trihaloketones**: $CH_3COCH_2Br + Br_2 \rightarrow CH_3COCBr_3 + 2HBr$
- The reaction can go further by the base converting the trihaloketones to a haloform and a carboxylic acid:
- $CH_3COCBr_3 + {}^-OH \rightarrow CH_3COOH + HCBr_3$
- Carboxylic acid bromoform
-
- **2. 6.2. Acid Catalyzed Reaction: Enol Formation**

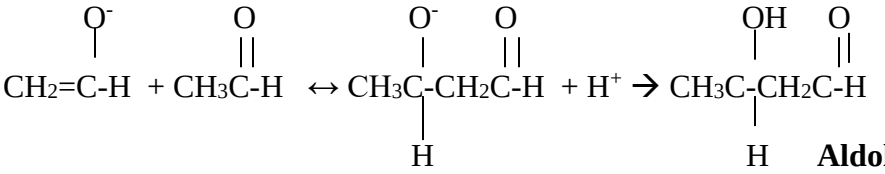
- Reaction is in two steps: (i) formation of oxonium salt (ii) removal of alpha proton by a proton acceptor e.g. water
- 
- (i) $CH_3CCH_3 + H^+ \leftrightarrow CH_3CCH_2\text{-}H + H_2O \rightarrow CH_3C\text{-}C=H_2 + H_3O^+$
- Protonation of the C=O oxygen makes the alpha hydrogen very acidic and very labile. The enol can then react with a halogen to form the haloketone

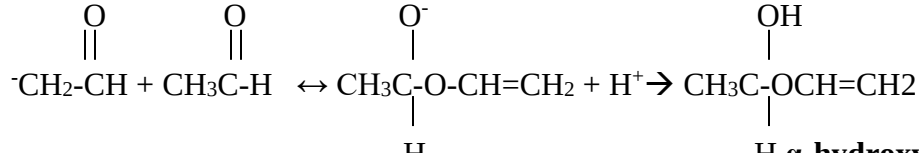
- $CH_3C\text{-}C=H_2 + Br_2 \rightarrow CH_3C\text{-}CH_2Br + HBr$
- Acid based catalysis is the preferred method with monohalogenation is desired

2.7 Reactions of Enolate Anions: Aldol Condensation Reaction

- Enolate ion is a very good synthetic intermediate. It can be added to C=C bonds or used as reagents in nucleophilic substitution reactions
- when the addition is to a C=O bond, it is called **aldol condensation addition reaction**
- Aldol condensation reaction is a two step reaction: (i) formation of the enolate ion (ii) addition of the enolate ion to another carbonyl carbon
- Using acetaldehyde as an example:

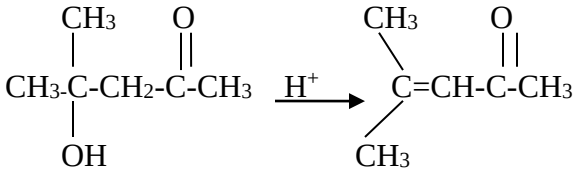
- 
- $HO^- + H\text{-}CH_2\text{-}C\text{-}H \leftrightarrow [CH_2=C\text{-}H \leftrightarrow {}^-CH_2\text{-}CH]$

- The enolate ion can react in two ways (i) add to the form a C-C bond by attacking the carbon of the C=O of another acetaldehyde molecule (aldol formation) (ii) form a C-O bond by attacking with the O of the enolate ion to form an α-hydroxyethyl vinyl ether
- 
- $CH_2=C\text{-}H + CH_3C\text{-}H \leftrightarrow CH_3C\text{-}CH_2C\text{-}H + H^+ \rightarrow CH_3C\text{-}CH_2C\text{-}H$ **Aldol**



- ${}^-CH_2\text{-}CH + CH_3C\text{-}H \leftrightarrow CH_3C\text{-}O\text{-}CH=CH_2 + H^+ \rightarrow CH_3C\text{-}OCH=CH2$
- **α-hydroxyethyl vinyl ether**

- Formation of the aldol is more thermodynamically favored over the formation of the α-hydroxyethyl vinyl ether
-
- **2.7.1 Mixture of Carbonyl Compounds**
- Aldol reaction requires an electron pair acceptor and an electron pair donor
- The example we have discussed involves only one type of reagent. It is possible to have mixed condensation with different reagents: (i) one acting as an electron acceptor (one that does not have an α-hydrogen in its structure and hence cannot form an enolate ion, e.g. formaldehyde) (ii) the other acting as an electron-pair donor (has α-hydrogen and can form enolate ion e.g. acetone)
- $CH_3C{=}OCH_3 + CH_2{=}O \xrightarrow{HO^-} CH_3C{=}OCH_2CH_2OH$ (acetaldol)
- The reaction needs to be controlled in order to get the mono product or else all the six α-hydrogen of the acetone will be replaced by CH_2OH (from formaldehyde) which might be dehydrated in the presence of an acid to α, ϭ unsaturated carbonyl compound e.g.



Diacetone 4-methyl, 3-penten-2-one (mesityl oxide)

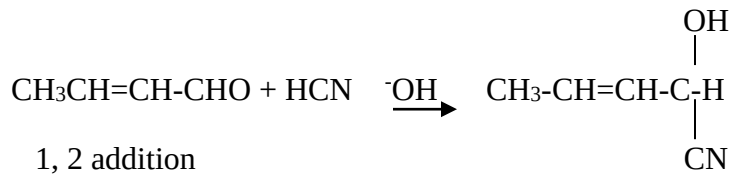
2.8 α,ϭ Unsaturated Aldehydes and Ketones

- α, ϭ unsaturated carbonyl compounds can be formed by the dehydration of aldol compounds.

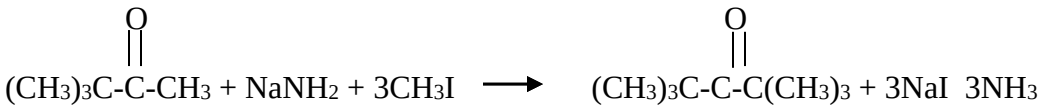
- the double bond conjugated to the carbonyl group has profound effect on the spectroscopic properties of these compounds (UV, nmr)

- α, ϭ unsaturated compounds undergoes addition and condensation reactions at the C=O (1,2 addition) or at the C=C carbons (1,4 addition)

- Usually, aldehydes gives 1, 2 addition products and ketones gives 1,4 addition products



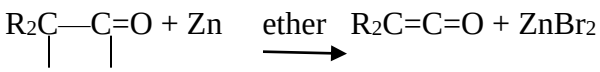
1, 2 addition



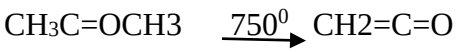
1, 4 addition

2.9. Ketenes

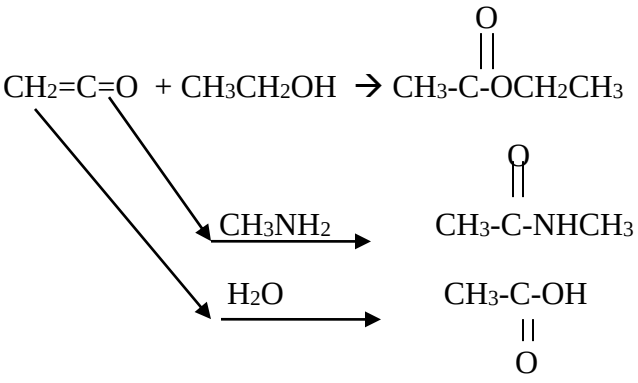
- Ketenes have C=O and C=C consecutively bonded to each other: RC=C-C=O (R= H, alkyl, aryl)
- When R = H, the compound is called ketene
- Monosubstituted products are called aldolketenes and the disubstituted are called ketoketenes
- Ketenes can be prepared by treating α-bromo acyl bromide with Zn



- Ketene itself can be prepared by passing acetone vapor over heated coil in a vacuum



- Ketenes are good acylating agents



WHY IS BASE-CATALYSIS INEFFECTIVE IN CONVERTING HEMIACETALS TO ACETALS??

- Recall that **hydroxide ion is a rather poor leaving group**, whereas **water is a good leaving group**.

- Refer to step 2 of the mechanism for the conversion of a hemiacetal to an acetal, noting the analogy to an S_N1 reaction, with water as the leaving group. In the absence of acid, the leaving group would have to be a hydroxide anion, which is a poor leaving group.

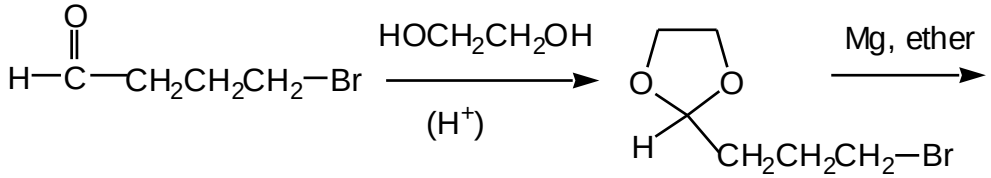
- It is also important to note that the converse is alsotrue, that is, that **an acetal cannot be converted to a hemiacetal in base**.

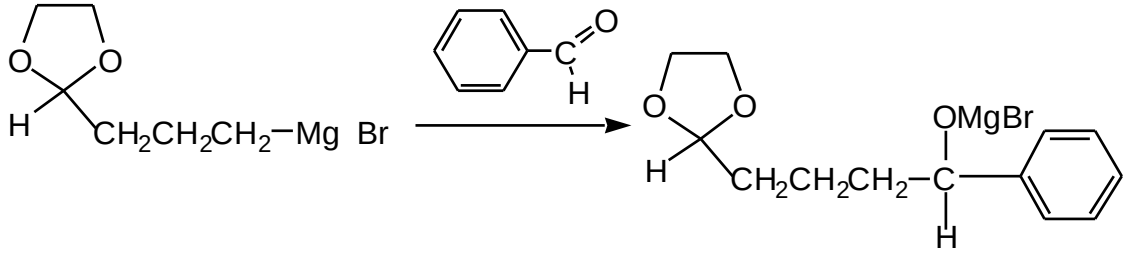
- Thus, the acetal function is especially **synthetically useful** because it is stable in basic solutions and contains only two relatively unreactive ether functionalities. On the other hand**, it is readily converted back to the precursor carbonyl compound by acid-catalyzed hydrolysis.** The mechanism is the reverse of acid-catalyzed acetal formation (start with the product and read backward in the mechanism).

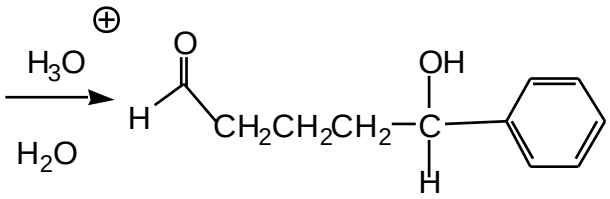
SYNTHETIC APPLICATIONS OF ACETALS: THE PROTECTING GROUP STRATEGY

- The ability to smoothly convert reactive aldehyde or ketone functionality to relatively inert acetal functionality is highly useful in organic synthesis. The acetal functionality is, in effect, a **protected carbonyl group**.

- An excellent example of the use of the acetal protecting group strategy is the formation of a Grignard reagent from a bromoaldehyde, as shown below. If the aldehyde functionality were not protected, this Grignard reagent could not be formed in a synthetically useful manner, because it would quickly react with a molecule of the aldehyde. However, if the aldehyde functionality is first protected as an acetal function, the Grignard can be prepared quite nicely, and the protected Grignard reagent can then be used for whatever synthetic purpose may be desired. In the example shown, the Grignard is used to react with benzaldehyde to give, after hydrolysis, a hydroxyaldehyde.





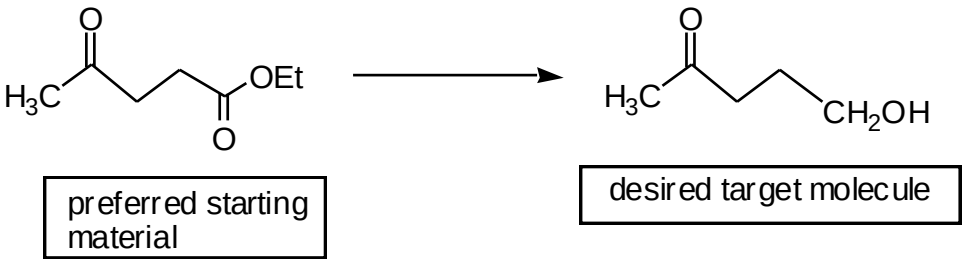


- Note that there are essentially **three requirements** for an effective protecting group.
    - It must be formed in high yield
    - In the protected form it must be unreactive
    - The protected functionality must be efficiently re-converted to the original functionality. This step is called "**de-protection**".

- The de-protection step is very facile in the case of an acetal, because in the course of acidic, aqueous workup it is quickly hydrolyzed to the carbonyl functionality.

CONSIDER ANOTHER EXAMPLE OF THE PROTECTING GROUP STRATEGY:

- In the case of the synthetic transformation below, the preferred starting material is a **keto ester**, and it is desired to selectively reduce the ester functionality to an alcohol functionality, without affecting the ketone function (the target molecule retains the ketone function).



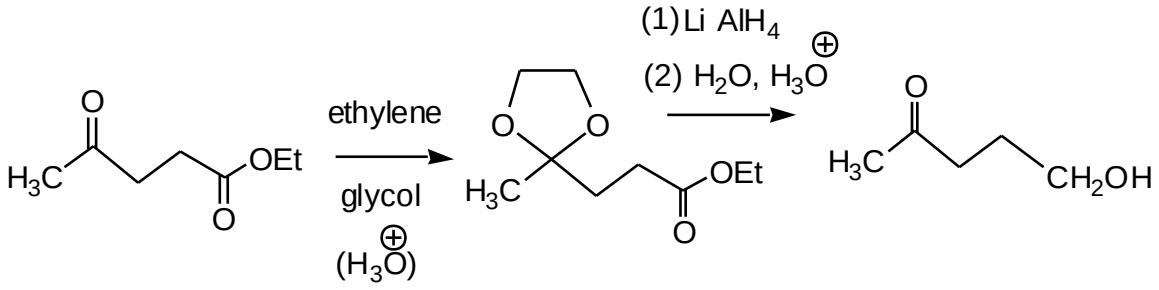
preferred starting material

desired target molecule

- It is known that lithium aluminum hydride will efficiently reduce an ester function in the manner desired (see later), but we also know that it will reduce the ketone function, in this case to a secondary alcohol. This would not lead to the desired product, if both functionalities were reduced.

- There is an even more serious problem. If we were to attempt to use only the stoichiometric amount of the hydride reagent necessary to **selectively** reduce one of the functionalities, the ketone would be the one preferentially reduced, because the ester function is resonance stabilized (see later), and therefore less reactive than the ketone. (By the way, LAH is highly reactive, and not very selective, anyway, but any selectivity would favor reaction with the ketone function.

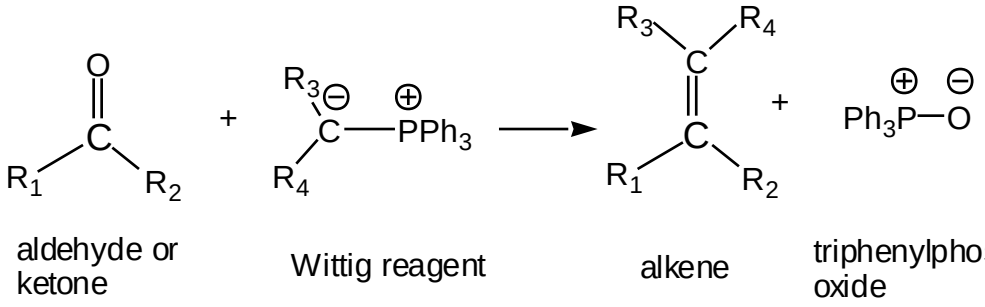
- We must therefore adopt a protecting group strategy, as shown below. Again, note that the acidic, aqueous workup required for LAH reductions is also that required to de-protect the acetal functionality.



THE WITTIG REAGENT

- .The so-called "Wittig reagent" is another reagent containing nucleophilic carbon, and which can add readily to a carbonyl group. The reagent, as illustrated below, has extensive **carbanion character**, and thus is quite **nucleophilic**.

- This reagent is rather unique in that it allows the formation of a new **doubly bonded carbon**. The net result is the conversion of an aldehyde on ketone to an alkene of choice. The overall reaction is illustrated below. It can be used to form mono-, di-, tri-, or tetrasubstituted alkenes. A mixture of *cis* and *trans* alkene isomers are usually formed.

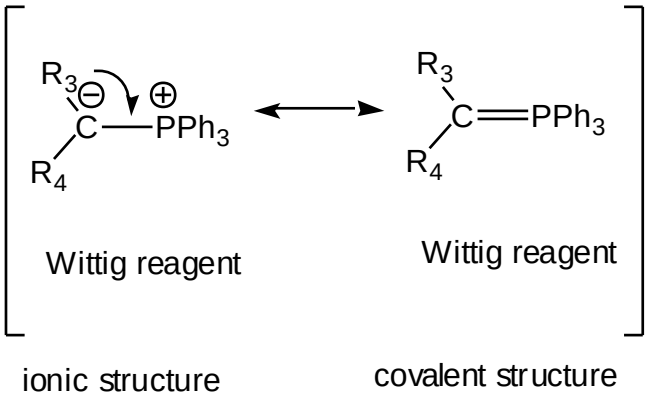


- It is very important to note that the conversion of a arbonyl function to an alkene double bond is thermodynamically unfavorable by at least 20 kcal/mol, as we have seen in this chapter. What is thermodynamic "driving force" which makes this reaction possible? (That is, which provides more than 20 kcal/mol of negative free energy change?)

- It is, of course, the conversion of the Wittig reagent to triphenylphosphine. In particular, the Wittig reagent has **carbanion character**, but the phosphine oxide has **oxyanion character**, the latter being very much more favorable for stabilization of the negative charge.

Resonance Treatment of the Wittig Reagent.

- The canonical structure written above for the Wittig reagent places negative charge on carbon and positive charge on the tetravalent phosphorous atom. Why not move the electron pair of the carbanion center in between the carbon and phosphorous atom to form a second bond, i.e., a pi bond?



- Actually, for phosphorous this covalent structure is a valid (i.e., legal) canonical structure, because phosphorous is a third row element which has vacant 3d orbitals. Although it has already used all of its valence shell 3s and 3p AO's to form four sp^3 covalent bonds (three to phenyl groups and one to the carbanion carbon), it still has 3d AO's, which are vacant and can overlap with the filled carbon 2p AO which contains the electron pair. We thus can have a two electron pi bond structure.

- Normally, since the covalent structure has one additional covalent bond, one would think that this structure would be the lower energy structure, but in this case, interestingly, **the ionic structure is the one of lower energy**. There are two reasons for this:

- First, the pi bond which is formed is very weak indeed, because the 3d AO is quite high in energy, and overlap with that orbital yields relatively little stabilization.

- Secondly, the first structure, although lacking a pi covalent bond, does have a relatively strong **ionic (i.e., electrostatic) pi bond**. Of course, ionic bonding can be quite strong.

- Consequently, we usually draw the ionic structure to represent the Wittig reagent, but you should know that a covalent structure also contributes to the resonance hybrid, so that carbon doesn't have a full unit of negative charge.

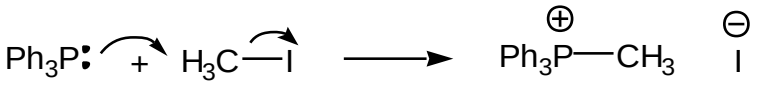
- Suppose we had an analogous reagent in which the phosphorous was replaced by nitrogen? Would the covalent structure be valid? The answer is NO! Nitrogen is in the second row of the Periodic Table and the valence shell is the second main shell, which has no d type orbitals.

Preparation of the Wittig Reagent.

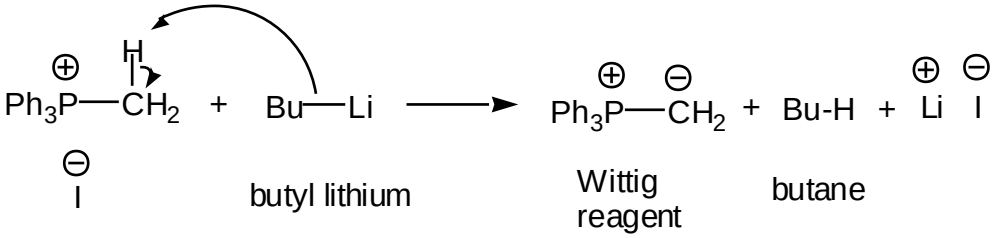
- Some Wittig reagents are commercially available, but most are preferably synthesized prior to use in the laboratory. There are two steps in the generation of an appropriate Wittig reagent:

- **Step 1**: Reaction of triphenylphosphine with an alkyl halide, in an S_N2 reaction. Recall that P, as a heavier atom, is especially nucleophilic, although not very basic (the

"polarization" effect), so these displacement reactions work very efficiently. This reaction results in the formation of a stable **phosphonium salt** (tetravalent phosphorous is analogous to tetravalent nitrogen of ammonium salts). The simplest case, reaction with methyl iodide, is illustrated below, but analogous reactions with primary or secondary halides are feasible.



- **Step 2**: Removal of a modestly acidic proton from the carbon atom alpha to the positively charged phosphorous atom. This proton is removable because the resulting "carbanion" will be substantially stabilized by the resulting electrostatic bond present in the Wittig reagent and to a modest extent by the weak pi bonding present in the Wittig reagent. Any of a variety of bases can be used, but relatively strong ones like **butyl lithium** are more commonly used.



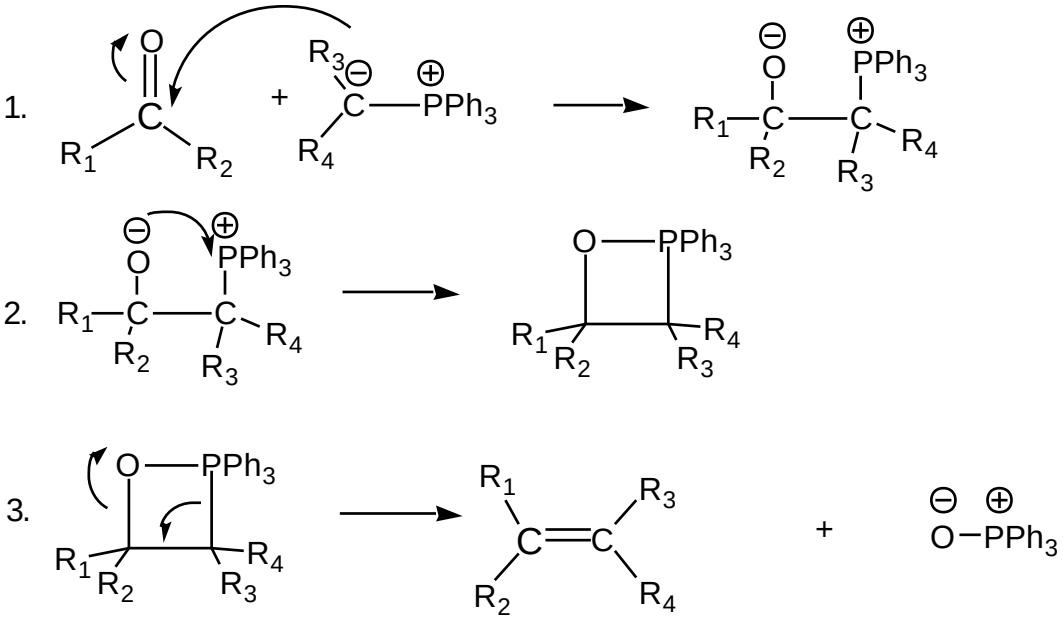
methyltriphenylphosphonium iodide

butyl lithium

Wittig reagent

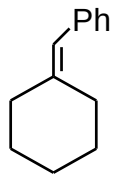
butane

Mechanism of the Wittig Reaction.

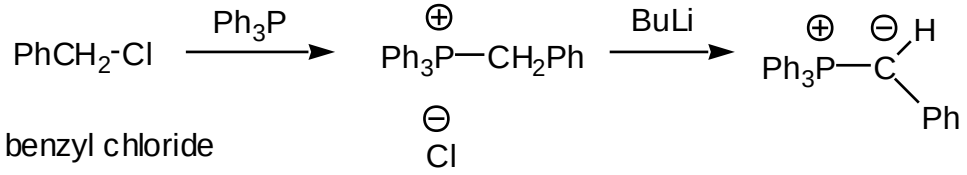


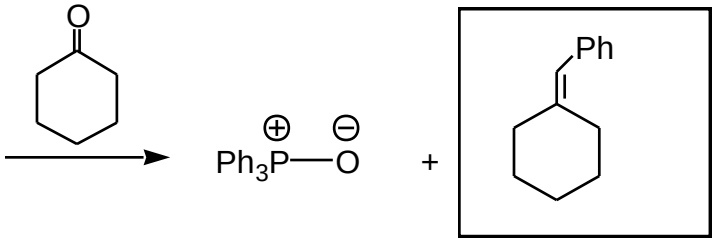
AN EXAMPLE:

- Sketch an efficient synthesis of the following alkene:

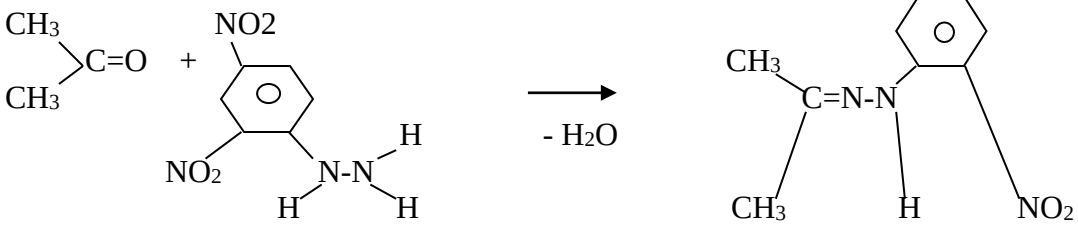


- Answer:





Test for Aldehydes and Ketones
The DNP Test



2,4-nitrophenylhydrazine

orange crystal hydrazine of acetone

Chapter 3 Substitution Nucleophilic (S_N) and Elimination Reaction

3.1 S_N Reactions

- Alkyl derivatives, alcohols, ethers, esters and "onium ions" can undergo nucleophilic displacement reactions of the type:
- RX + Y → RY + X

- Examples of "onium ions": R_4N^+, R_4P^+, R_4O^+, R_4S^+, $R_4N{=}\overline{N}^+$
- tetraalkylammonium, tetraalkylphosonium, tetraalkyloxonium, tetraalkylsulfonium tetraalkyldiaxonium
- The displacement is caused by nucleophiles (electron pair donor) at the C or the alkyl derivative. Overall, the reaction is an ionic or polar reaction:
- $CH_3Br + {}^-OH \rightarrow CH_3OH + Br^-$
- A nucleophile can be an anion, X^-,or a neutral molecule, Y: or HY:
- Common nucleophiles include: CN^-, ^-OH, halogen, $^-OCH_3$, $^-NH_2$, $^-N^+{=}N^-$, NO_2^-
- Solvents that will dissolve the nucleophiles and the nucleophilic reagent are required. Usually, highly polar nucleophilic agents hardly dissolve in the solvents that dissolve slightly polar organic compounds
- Common solvents that dissolves both include: acetone, ethanol, aqueous dioxane, water, aqueous acetone, acetic acid-ethanol, DMSO, liquid ammonia, N,N dimethyl formamide, acetone-ethanol mixture.

3.2 Mechanism of S_N Reactions

- There are 2 different types of mechanism that can be used to describe S_N reactions

- **Mechanism A**: is a two step reaction mechanism: (1) dissociation of organic compound into a cation and an anion (slow step) and

$$CH_3Br \leftrightarrow CH_3^+ + Br^-$$

(2) Reaction between the cation and the nucleophile (fast step): $CH_3^+ + {}^-OH \rightarrow CH_3OH$

- **Mechanism B:** the reaction is a single step reaction: the nucleophile attacks the carbon of the organic compound while the anion departs at the same time

$$CH_3Br + {}^-OH \rightarrow CH_3OH + Br^- \text{ (slow step)}$$

- The slow steps determines the rate of each type of reaction
- The rate of reaction of Mechanism A is determined by the concentration of $[CH_3Br]$ (moles/volume x time (s))
- i.e. $r = k[CH_3Br]$ (1) k = specific rate constant in unit of s^{-1}
- We can determine the order of a reaction either with respect to the a specific reactant or to the overall order of reaction (sum of all order of reactions of all reagent or products)
- The order of a reaction is the power to which the concentration of a reactant is raised to have direct proportionality between concentration and the reaction rate.
- In this reaction mechanism, the order is first order to all reactant and the product. The overall order of reaction is one and it is called a **unimolecular nucleophilic substitution or S_N1 reaction**

- The rate of reaction of Mechanism B is determined by the concentration of [CH_3Br] and [^-OH], hence,
- r= k[CH_3Br][^-OH]
- The order of reaction is first order to all reactant and overall order of 2
- This mechanism is classified as **bimolecular nucleophilic** substitution or **S_N2 reaction**
- When the solvent serves as the nucleophile, the reaction is called **solvolysis (**hydrolysis (water), ethanolysis (ethanol), acetolysis (acetone)

3.3 How to Differentiate between S_N1 and S_N2 reactions

- if the solvent serves as the nucleophile, a little bit of a stronger nucleophile is added

- if the rate of reaction remains the same, then the reaction is an S_N1 reaction

- If the rate of reaction increases significantly, then the reaction is an S_N2 reaction

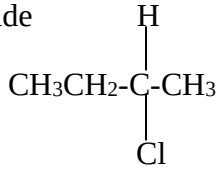
3.4 Stereochemistry of S_N Reactions

- **S_N2 Reactions:** the incoming nucleophile may attack from the front (where the leaving anion is attached or from the backside that leads to inversion of configuration

- The front side attack yields cis product while the backside attack yields the trans- product for cyclic compounds

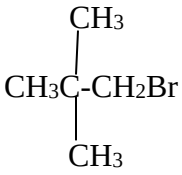
- For open chain analogs, the trans- analog is predominantly formed

- Consider an optical isomer with four different groups attached to one carbon, e.g. *s*-butyl chloride



- The isomer can exist as the right and left handed isomers
- These isomers have the same physical properties except in their response to plane polarized light
- When plane polarized light is passed through their solutions, one isomer rotate the plane of the polarized light around the axis of the beam in one direction
- The other isomer rotates the plane equally but in opposite direction
- In the S_N2 reaction of *s*-butyl chloride with ^-OH, the ^-OH can attack s-butyl chloride from the front side to form a product (alcohol) that retains its *s*-configuration
- Attack from the backside will invert the configuration of *s*-butyl chloride to form the opposite optical isomer of *s*-butyl chloride
- This inversion process is called **Walden inversion**

- In general, S_N2 reaction always reacts by **Walden inversion**, i.e. it react by back-side attack of the incoming nucleophile to produce a single optical isomer
- **S_N1 Reactions:** reacts to produce both isomers **but the inversion product is always the predominant product**
- The extent of configurational change depends on the amount of shielding (bulkiness) provided by the leaving group and the associated solvent to the reactive carbon
- If the leaving group is still attached to the reacting carbon when the incoming group attacks the reacting carbon, then backside attack will prevail and a product with inverted configuration will be formed e.g. solvolysis of 2-octylp-toulenesulfonate is 100%
- However, the amount of inversion decreases as the stability of the intermediate carbonium ion increases.
- The type of solvent used also determines the stability of the reacting species and hence, influences what happens (type of product) in S_N1 reactions. The more polar (higher dielectric constant) the solvent the better stability it gives to the intermediate carbonium ion and S_N1 reaction prevails
- **3.4 Structural and Solvent Effects in S_N Reactions**
- **Structure of Alkyl Groups:** The rate of reaction of S_N2 reactions of a simple alkyl-derivatives, RX, follows the order: $1^0 > 2^0 > 3^0$
- S_N2 reactions works very well with primary and secondary alkyl derivates and not with the tertiary derivative
- Bulkiness of the alkyl group causes steric hindrance that prevents back-side reaction by the incoming nucleophile and hence favors S_N1 reactions. Therefore, steric hindrance plays an important role in determining the rates of reaction of S_N2 reactions
- For example, neopentyl halides do not react by S_N2 mechanism because of the steric hindrance to the ẟ-carbon:

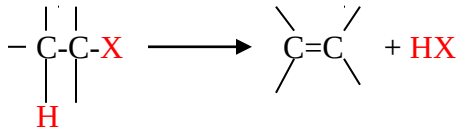


- Steric hindrance does not affect S_N1 reactions because it does not depend on the incoming nucleophile
- For S_N1 reactions the rate of reaction will follow the order: $3^0 > 2^0 > 1^0$
- **Leaving Group**: The reactivity of an alkyl derivative RY either in S_N1 or S_N2 reactions depends partly on the acid strength of HY i.e. the strongest acid gives the best leaving group. For halide acids, the acidity follows the following order: HI>HBr>HCl>HF, hence the leaving group (Y) in alkyl derivatives following the same order: SO_3Ph> I>Br>Cl>F
- Alcohols are unreactive in S_N reactions except if an acid is present to catalyze the reaction because ^-OH is a poor leaving group. The acid donates a proton the ^-OH group to form water which is a better leaving group
- The same thing happens to ethers and esters, they are reacting only when they are acid catalyzed

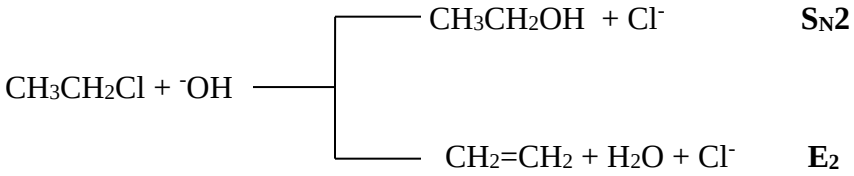
- Heavy metals such as Cu, Ag, Hg catalyzes S_N1 reactions (in a similar way that acid catalyzes S_N reactions) by forming a complex with the unshared electrons of the leaving group. The leaving group is now a metal complex instead of been a halide ion and hence, makes it a better leaving group
- The rate of reaction of alkyl halides with heavy metals follow the following order: $3^0 > 2^0 > 1^0$, i.e. tertiary halides precipitates rapidly at room temperature more than a primary halide (needs warming)
- **Nucleophilicity:** is the defined as the S_N2 reactivity of a reagent towards an alkyl derivative i.e. it is the ability of the reagent to donate a pair of electron to an alkyl carbon. This is different from the **basicity** of a reagent which is defined as the ability to donate a pair of electron a proton. A strong base is a good nucleophile but might be a poor leaving group while a weak base may be a poor nucleophile but a good leaving group. Therefore basicity does not parallel nucleophilicity
- **Nature of Solvent:** Rates of S_N1 reaction changes with solvent change because the ionizing power of a solvent (ability of a solvent to form ions) determines its ability to form ions: $RY \rightarrow R^+ + Y^-$
- Ionizing ability of a solvent depends on 2 factors: (1) Dielectric constant: the force between charge particles depends inversely on the dielectric constant of a solvent. Therefore, high dielectric constant value increases the ionizing power of a solvent (2) ability of the solvent to solvate the separated ions. Cations are better solvated by elements or molecules with unshared electrons (ammonia, water, alcohols, carboxylic acids, sulfur dioxide, DMSO while anions are better solvated by molecules that have hydrogen attached to a strong electronegative element e.g. water

Elimination Reactions

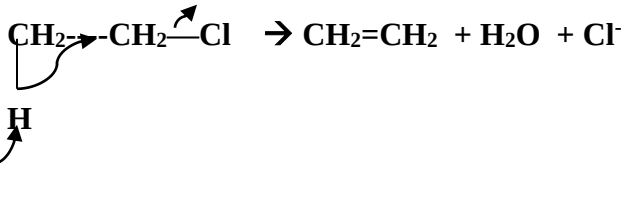
- Elimination reaction involves removal of ions (Cl^-), group of ions (SO_4^-) or alkyl groups from a saturated organic compound to form an unsaturated organic compound. It is the opposite of addition reactions.
- In general, an organic compound such as R_2-CH-CR_2-X (R= H or alkyl, X= halides, hydroxyl, ester, onium, $^+SR_2$, $^+NR_3$, $^+OH_2$, $RCOO^+$) will lose X and a hydrogen ion on the adjacent carbon atom.

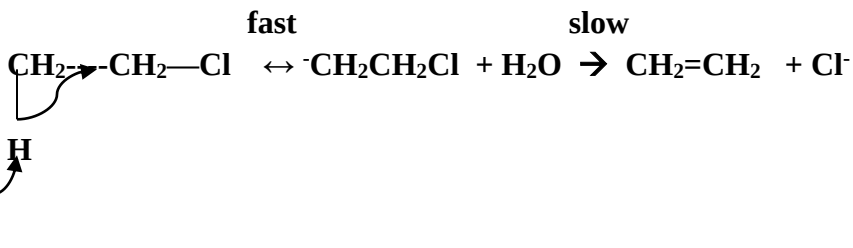


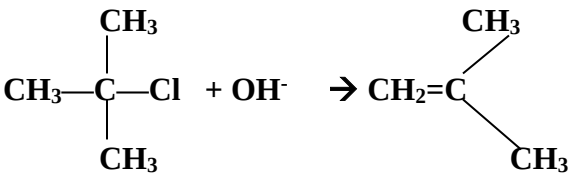
- Elimination and substitution occur at the same time in an organic reaction and their mechanisms are closely alike. Therefore, it requires adequate control on which of the products is desired
- Just like the S_N reactions, there are two types of elimination reactions: E_1 and E_2

- **E_2 Reactions**
- Taking the following reaction as an example, S_N2 reaction which produces ethanol
- 

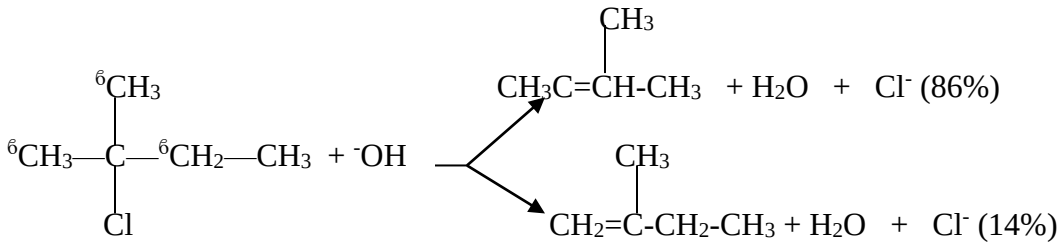
  competes with the E_2 reaction that produces ethylene

- **Mechanism of E_2 Reaction**
- In this reaction the rate of elimination is proportional to the concentration of ethyl chloride and the hydroxyl ion which makes it a second order reaction
- The mechanism of the reaction is as follow: (i) the hydroxyl ion removes a proton from the ϐ-carbon and simultaneously forms a double bond and (ii) losses the chloride ion at the same time
-
- 

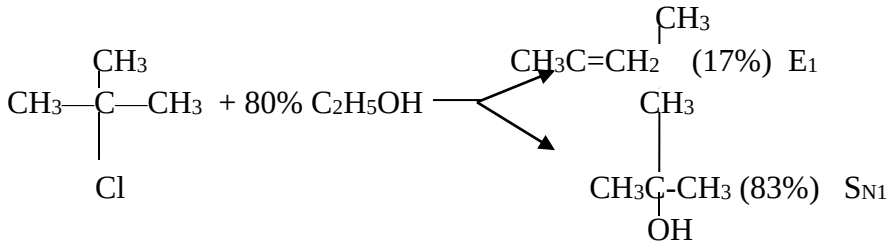
- An alternative reaction mechanism is as follow
-
- 

- *Structure of the organic halide affects E_2 reaction* as follow: (i) for a given R, the rate of elimination varies with X in the order $I^- > Br^- > Cl^- > F^-$ and (ii) for a give X, the ease of elimination follows the order $3^0 > 2^0 > 1^0$ R.
- *Steric hindrance slightly affects E_2 reaction relative to S_{N2} reaction* but it is prominent with tertiary halides
-
-
-
- 

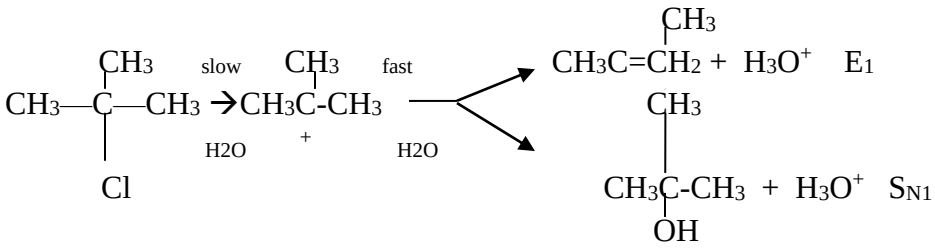
- The *strength of the base determines how effective it will be in conducting the E_2 reaction*: $^-NH_2 > {}^-OC_2H_5 > {}^-OH > {}^-OCCH_3$
- *High temperature* favors elimination reaction over S_N reactions
- *Halides with unsymmetrical alkyl group, R,* may yield 2 or more different alkenes depending on which δ-hydrogen that is removed in the rate determining step
- Most halides yields the most stable or substituted alkene
- The most unstable alkene may also be eliminated if: (1) the base itself is bulky (2) the leaving group is bulky or has a highly electron attracting power
-



- **E_1 Reactions**
- With many 2^0 and 3^0 halides, S_{N1} reactions compete with E_1 reactions in neutral or acidic solutions. For example,
-



- Usually but not always, the E_1 and S_{N1} reactions have a common rate determine step with each one of them having the same kinetic order with respect to the concentration of the t-butyl halide (slow ionization of the halide to form a carbonium ion)
- The initial step involves the slow formation of an intermediate carbonium ion and then followed by the fast step of attack by the solvent either by E_1 (attack at the δ hydrogen) or S_{N1} (attack at the carbonium carbon) mechanism.
-



- Structural influences on E_1 reactions are the same with S_{N1} reactions: Rate order for X = I > Br > Cl > F and 3^0 R > 2^0 R > 1^0R

Example 1

- In the reaction shown above (t-butyl alcohol), would you expect the ratio of t-butyl alcohol to isobutylene to vary significantly with the nature of the leaving group in the t-

butyl derivative [Cl, Br, or $S(CH_3)_2$] Why?. Would you expect the same behavior if elimination were occurring by the E_2 mechanism with the solvent acting as the base? Explain.

- Answer: The ratio will be significant depending on the nature of the leaving group. The rate order for the leaving group is I > Br > Cl > F and 3^0 R > 2^0 R > 1^0R for the alkyl. This determines the rate at which the intermediate carbonium ion is formed. Hence, the rate of formation of the intermediate carbonium ion will also depend on the nature of the leaving group.

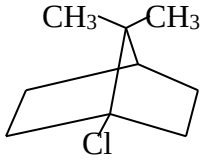
  Similarly, the rate order of E_2 reaction for a given R is I > Br > Cl > F and 3^0 R > 2^0 R > 1^0R which will affect the ratio of the products formed.

Example 2

Write the equations and mechanism for all the products that might reasonably be expected from the reaction of s-butyl chloride with a solution of potassium hydroxide in ethanol?

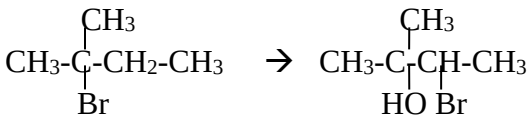
Example 3

Why is apocamphyl chloride practically inert toward hydroxide ion?

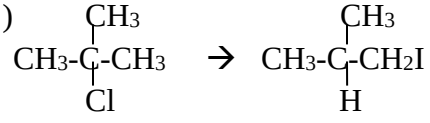


Answer: The leaving group (chlorine) and the carbonium carbon are located at the foot of the bridge which means that the double bond formed during elimination reaction is going to lie across the bridge. According to Breath Rule, no double bond can be formed across a bridge; therefore reaction of apocamphyl chloride will not happen

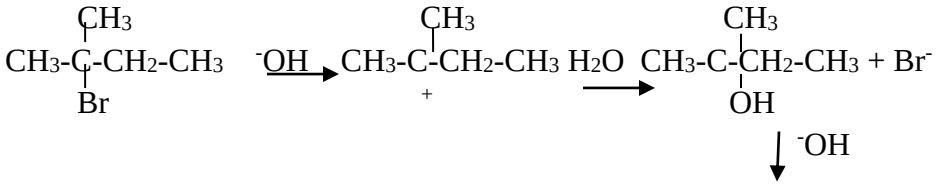
- Example 4
- Show how the following conversions may be achieved (specify reagents and conditions; not that several steps may needed). Write a mechanism for each reaction you use.
- (a)

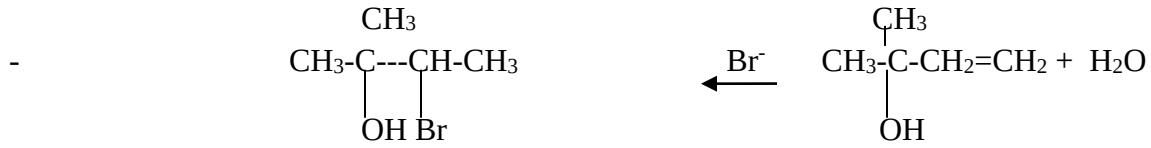


- (b))



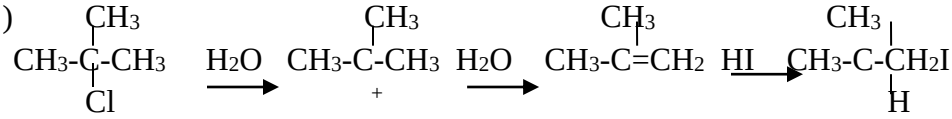
- Answer (a)





(Markownikoff's addition)

(b))



(antimarkownikoff'addition)

Chapter 4 The Carboxylic Group

4.1. Introduction

- The carboxyl group is represented by –C=O and it produces acidic reaction when it dissolves in water: $RCO_2H + H_2O \rightarrow RCO_2^- + H_3O^+$
- The carboxylic acids can be represented by R-COOH where R = H, alkyl, alkenyl, aryl, heterocyclic etc. When R= H, the acid is called formic acid
- The ionization is weak and incomplete, therefore, it produces a weak acid
- Examples of carboxylic acids are: CH_3COOH (acetic or ethanoic acid), CH_3CH_2COOH, CH_3CHCO_2H (alanine, α-aminopropanoic acid), CH_2COOH (Succinic acid)
  NH_2 CH_2COOH
- When R= alkyl or alkenyl, the carboxylic acids are called **fatty acids (FA).** Fatty acids occur naturally as esters in nature are found as fats, waxes and oils in plants and animals
- The most common FA's are: palmitic- $CH_3(CH_2)_{14}COOH$,
  Stearic acid- $CH_3(CH_2)_{16}COOH$
  Oleic acid $CH_3(CH_2)_7CH=CH(CH_2)_7COOH$
  Linoleic acid $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7COOH$
- These acids can be found as **glycerides** (esters of trihydric alcohol, called **glycerol)**

$$\begin{array}{l} CH_2COR \\ | \\ CHCOR \\ | \\ CHCOR \end{array} + NaOH \rightarrow \begin{array}{l} CH_2OH \\ | \\ CH_2OH \\ | \\ CH_2OH \end{array} + 3RCO_2^-Na + H^+ = 3RCOOH$$

Glyceride (fat) glycerol soap fatty acid

4.2 Nomenclature of Carboxylic Acids

- Carboxylic acids are called alkanoic acids
- The suffix 'oic' is added to the longest straight chain hydrocarbon in the molecule that includes the carboxyl group

4.3 Physical Properties of Carboxylic Acids

- Carboxylic acids has considerable amount of hydrogen bonding in its structure. The hydrogen bonding is stronger than those of alcohols because the O-H bond is more polarized. The hydrogen bonding could be inter or intra (with self carbonyl group)
- The hydrogen bonding is responsible for carboxylic acids: high boiling and melting point, high water solubility.
- The solubility decreases as the size of R increases and also as branching increases
- **IR:** broad OH-absorption band at 3000 cm^{-1} and broad CO absorption at 1740 cm^{-1}
- **UV:** Carboxylic acids absorb UV between 200-290 cm^{-1}
- **NMR:** carboxylic proton- chemical shift at 5.5 ppm

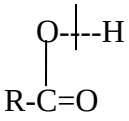
Example: Explain why the chemical shift of the acidic proton of a carboxylic acid, dissolved in a nonpolar solvent like carbon tetrachloride, show less variation with concentration than that of the OH proton of an alcohol under the same conditions

Answer: The extent of hydrogen bonding and chemical shift increases with concentration of alcohols due increase in the association of the molecules. The carbonyl function of the carboxylic acids makes the hydrogen bonding stronger and therefore makes association of the molecules less. Therefore, the chemical shift variation with concentration of the carboxylic acid will be less compared to that of the alcohol

4.2 Chemical Reactions of Carboxylic Acids

Carboxylic acids react by four different processes

- (1) Reactions involving cleavage of the O-H bond: acid dissociation, solvolytic reactions



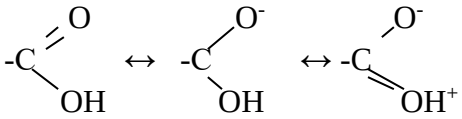
4.2.1 Dissociation of Carboxylic Acids

- (a) **Resonance Effect**: Carboxylic acids are weak acids when compared to mineral acids such as HCl, perchloric acid, nitric, sulfuric acids etc. The extent of dissociation in water is very small with the acidity or dissociation constants in the range of 10^{-5}

$$RCO_2H + H_2O \leftrightarrow RCO_2^- + H_3O^+$$

$$K_A = [RCO_2^-][H_3O^+]/[RCO_2H] \sim 10^{-5} \text{ for } R = CH_3(CH_2)_n$$

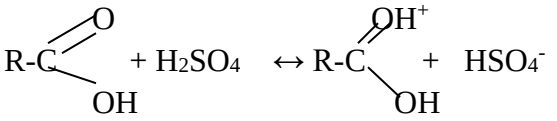
However, the fatty acids are many orders stronger than the corresponding alcohols because of the polar nature of the carbonyl group present in its structure. The polarity is due to the resonance effect of the carboxylic group which stabilizes the carboxylate ion

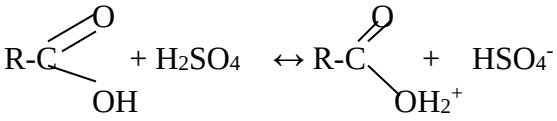


better than the alkoxide ion of the alcohols

(b)**Inductive Effect:** substitution on the α-carbon to the carboxyl group has a profound effect on the acidity (acid strength) of the carboxylic group. For example, trifluoroacetic acid is very much stronger than acetic acid itself. This effect is called ***inductive effect*** which is different from the resonance effect. It is symbolized as ±I. It is takes as (-) it is acid enhancing and (+) if acid weakening. Acid enhancing substituents like the halogens have electron withdrawing power and acid weakening substituent's like the alkyl (R^-), alkoxy (RO^-) group have electron donating power. The inductive effect falls as the distance of the substituent's from the carboxyl group increases (α>β>γ etc)

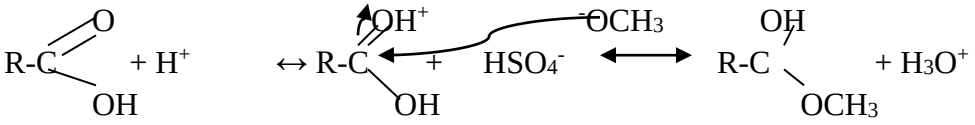
(c) Carboxylic acids can also act as a weak base by the carboxyl oxygen or the hydroxyl oxygen accepting a proton from a strong acid like mineral acids (H_2SO_4, $HClO_4$)





4.2.2 Reactions at the Carbonyl Carbon

- Reactions at the carbonyl carbon involve nucleophilic attack on the carbonyl carbon with subsequent cleavage of the C-O bond of the hydroxyl group, e.g. esterification, reduction by hydrides. These reactions are often acid catalyzed are happens by acids protonating the carbonyl oxygen and hence makes the carbonyl carbon more electropositive and susceptible to nucleophilic attack.

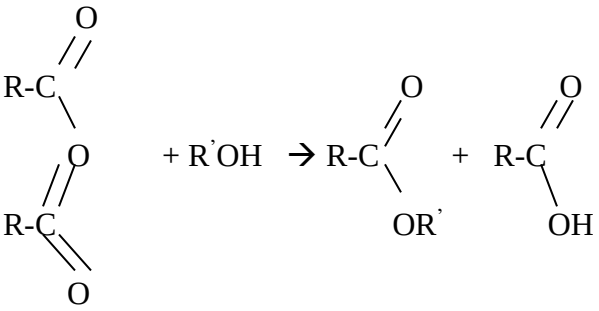


(esterification)

Other examples include formation of acyl chlorides (RCOCl) and reduction of the carboxylic group to an alcohol by hydrides ($LiAlH_4$)

$RCO_2H + PCl_5 \rightarrow RCOCl + POCl_3 + HCl$

$RCO_2H + SOCl_2 \rightarrow RCOCl + SO_2 + HCl$



$RCH_2CO_2H + LiAlH_4 \rightarrow \xrightarrow{H^+, H_2O} RCH_2CH_2OH$

Exercise

By analogy with ester hydrolysis, propose a mechanism for each of the following reactions?

(1) $C_6H_5CO_2CH_3 + C_2H_5OH \xrightarrow{H^+} C_6H_5CO_2C_2H_5 + CH_3OH$

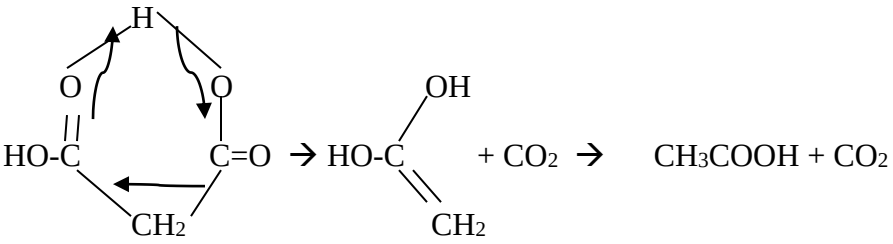
(2) $(CH_3CO)_2O + CH_3OH \xrightarrow{H^+} CH_3CO_2CH_3 + CH_3COOH$

(3) $CH_3CONH_2 + {}^-OH \longrightarrow CH_3CO_2^- + NH_3$

4.2.3 Decarboxylation

Decarboxylation, for example occurs in Kolbe electrolysis. Most Decarboxylation involves loss of carbon dioxide by simple heating. Thermal decomposition occurs easily when the α-carbon carries an electron withdrawing substituent (- inductive effect) e.g. $O_2N\text{-}CH_2COOH$, $HOOC\text{-}CH_2COOH$ etc.

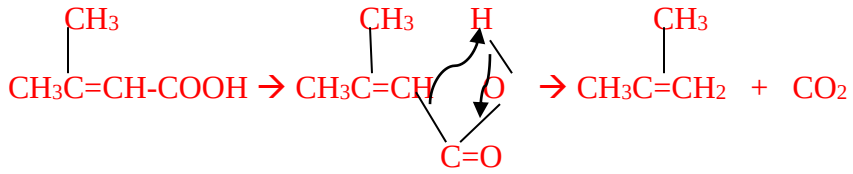
Decarboxylation may occur by cyclic processes (β,γ-unsaturated acids) or by stepwise steps in which carboxylate radical is formed ($RCO_2^{\cdot}$)



malonic acid enol form of acetic acid acetic acid

Example: Predict the product of Decarboxylation of 2-methyl-3-butenoic acid?

Answer



4.2.4 Reactions at the α-Carbon of Carboxylic Acid Derivatives

Reactions at the α-carbon involve the reactions of α-substituted carboxylic acids such as:

(1) The acidic properties of Esters with α-hydrogen's: Formation of C-C bonds occur in synthetic reactions that lead to formation of esters. These reactions occur because the α-hydrogen of an ester is weakly acidic (negative inductive effect of the carbonyl oxygen) and the resonance stability of the resulting anion. A strong base such as sodium ethoxide can produce a significant amount of the ester anion in equilibrium

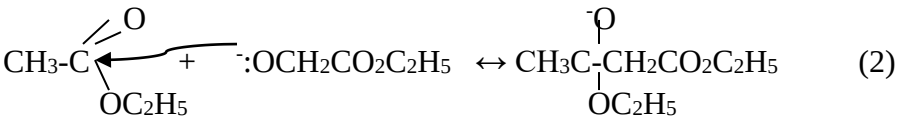
$RCH_2CO_2C_2H_5 + C_2H_5O^- \rightarrow RC^-HCO_2C_2H_5 + C_2H_5OH$

A second electron withdrawing group on the α-carbon of the ester makes the α-hydrogen more acidic.

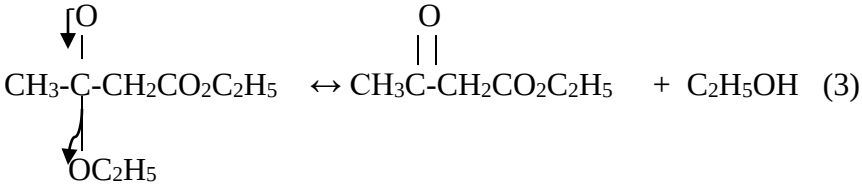
Examples include $O_2NCH_2CO_2C_2H_5$ (ethyl nitroacetate), $C_2H_5O_2CCH_2CO_2C_2H_5$ (diethyl malonate) etc.

(2) The Claisen Condensation: Involves self condensation reaction of ethyl acetate in the presence of a strong alkoxide (sodium ethoxide) to from ethyl acetoacetate. The reaction is theoretically thermodynamically unfavorable but can be achieved if one of the products is continuously removed from the reaction vessel (ethyl alcohol using excess ethoxide). The mechanism of this reaction is a combination of aldol reactions and nucleophilic attack as shown below:

$C_2H_5O^- + H\text{-}CH_2CO_2C_2H_5 \leftrightarrow {}^-\!:OCH_2CO_2C_2H_5 + C_2H_5OH$ (1)



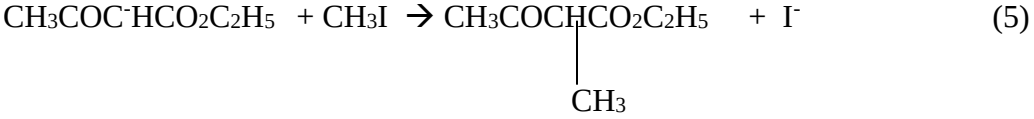
(2)



(3)

(3) Alkylation of Acetoacetic and Malonic Esters: alkyl halides can be added to the anion of acetoacetate and diethyl malonate. These reactions are used in the synthesis of carboxylic acids and ketones. The reaction involves formation of the anion of the ester followed by SN_2 addition of the alkyl halide

$CH_3COCH_2CO_2C_2H_5 + C_2H_5O^- \leftrightarrow CH_3COC^-HCO_2C_2H_5 + C_2H_5OH$ (4)



(5)

-

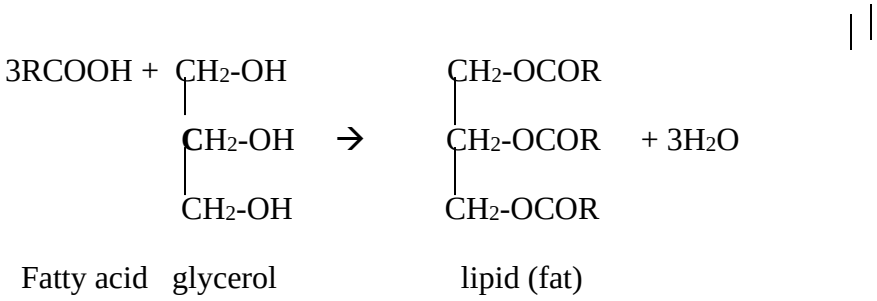
Chapter 5 Some Important types of Natural Products: Lipids, Carbohydrates

5.1 Lipids

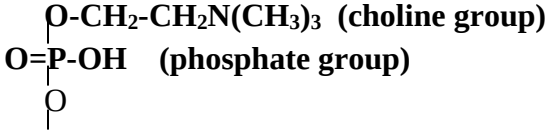
- Lipids are water insoluble organic biomolecules

- They can be classified into four major groups: triglycerides, phosphoglyceride, steroids and prostaglandins

- **Triglycerides (TG, Neutral fats):** TG's are the most abundant lipids are they serve as the most concentrated source of energy. The structure consists of three molecules of a fatty acid chemically joined to one molecule of glycerol (glycerin, trihydric alcohol).

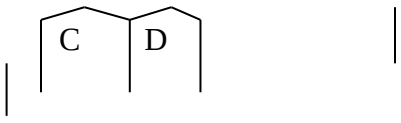


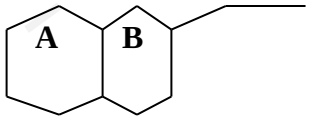
- The fatty acid could be a saturated acid (palmitic acid ($C_{15}H_{31}COOH$), stearic acid ($C_{17}H_{35}COOH$)) or an unsaturated fatty acid (oleic acid ($C_{17}H_{33}COOH$). Oleic acid is classified as polyunsaturated acid which is the most abundant polyunsaturated fatty acid
- Polyunsaturated fatty acid is claimed to be good for our diet compared to saturated fatty acids. It is claimed to reduced the level of cholesterol in our blood which in turn reduces our risk for heart diseases and high blood pressure
- Two other polyunsaturated fatty acids; linoleic acid ($C_{17}H_{31}COOH$) and linolenic acid ($C_{17}H_{29}COOH$) are classified as essential fatty acids because our body needs it but cannot make it itself. Therefore, these two acids need to be ingested and should be included in our diet.
- **Phosphoglycerides:** are lipids that contain a phosphorous group (as the head) and a flexible tail (consisting of two FA). The head is hydrophilic and the tail hydrophobic. An example is Phosphatidycholine (lecithin) which is an abundant phosphoglyceride found in the cell membrane. They form a double layer in cell membranes with their tails pointing to each other and protein molecules embedded on and in between these layers.
- **Transportation**: Lipids are transported in the blood as ***chylomicrons*** (fat droplets = triglycerides + cholesterol + phospholipids), FA and lipoproteins. During fat absorption, the blood contains my chylomicrons to the extent that the blood may look yellowish. This clears out within 4 hours after a meal when all the fats move into the adipose tissue cells.



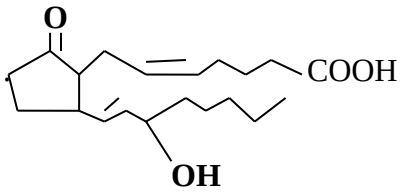
CH_2——CH——CH_2 (glycerol)
O O
C=O C=O (fatty acid)
$C_{15}H_{31}$ $C_{17}H_{33}$ (lecithin)

- **Post Absorptive State**: When all the chylomicrons have moved to the adipose tissue, the blood still contains some lipids called ***lipoproteins*** (triglycerides + cholesterol + phospholipids + proteins).
- ***There are 3 types of lipoproteins***: very low density (VLDL) low density (LDL) and high density (HDL) lipoproteins and all are produced in the liver.
- Diet containing saturated FA's and cholesterol promotes formation of LDL (bad lipoproteins) which may cause coronary disease and atherosclerosis.
- Blood with high concentration of HDL (good lipoproteins) is believed to reduce coronary diseases. Exercise tends to increase the level of HDL in the blood
- *Lipid catabolism* takes place in the liver and it involves many processes such as glycolysis, Krebs cycle, beta-oxidation etc. to produce energy.
- The amount of energy produced by lipids is twice as much as the energy produced by carbohydrates. (1.0 g of carbohydrate = 4.1 kcal, 1.0 g of lipid = 9 kcal)
- High rate of fat catabolism, patients with diabetes or during fasting results into excessive production of acetyl-*CoA* which the liver convert to *Acetoacetic acid* (ketone bodies = acetone + beta hydroxybutyric acid).
- Excessive amount of ketone bodies in the blood is called *Ketosis* with sign and symptoms of *acetone breath* and *ketonuria*
- *Lipid anabolism* involves synthesis of triglycerides, phospholipids, cholesterol and prostaglandins.
- *Triglycerides* can be synthesized from FA and glycerol or from excess glucose and amino acids. Therefore, fat can be gotten form other forms of food apart from fat. Extent of fat storage has no limit and it serves as the largest reserve of energy.
- *Lipid Control*: fat metabolism is inversely related to carbohydrate metabolism and is controlled by the following hormones: insulin, growth hormone, ACTH and glucocorticoids
- **Steroids:** compounds with the steroid structure as their nucleus. They are large molecules with no FA's in their structure. Examples include: cholesterol, male and female sex hormones and adrenocorticoids





- **Prostaglandins:** are lipids containing a 20-carbon FA that contains 5-carbon ring. There are 14 types of prostaglandins in the semen alone. Others are present in many tissues and it plays a very important role in some hormones



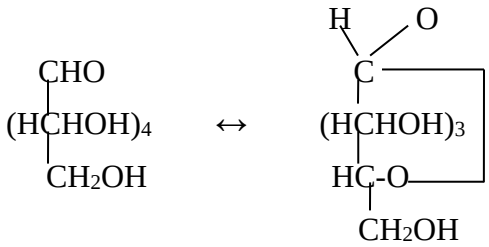
- **5.2 Carbohydrates**
- Carbohydrates are produced in green plants by photosynthesis using carbon dioxide and water as the ingredients in the presence of sunlight

$$\mathbf{yCO_2} + yH_2O \xrightarrow{\text{sunlight, green plants}} (CH_2O)_y + yO_2$$

- Photosynthesis is an enzyme catalyzed reaction that includes chlorophyll and a series of redox reactions that culminates into formation of simple sugars such as glucose ($C_6H_{12}O_6$) and complex starches and cellulose $(C_6H_{10}O_5)_n$ ($n \geq 1000$)

5.3 Classification of Carbohydrates

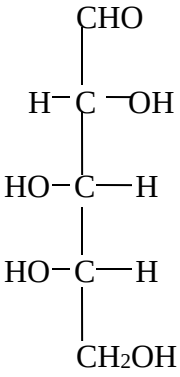
- **Monosaccharides**: this is the simplest unit of a carbohydrate that can be described as polyhydric alcohols. They are also called simple sugars with 5, 6, 7 or 8 carbon atoms
- The structure also contain carbonyl functional group that may form cyclic structures (hemiacetal or hemiketal) with one of the hydroxyl group to form a ring structure (α or β-anomer)

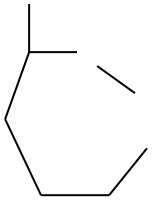


Aldohexose (open chain) 1,5-cyclic hemiacetal of an aldohexose

- The cyclic structures (pyranose for 5-C sugars) are more stable than the open chain form

- Examples of the 5-carbon sugars (pentoses or aldopentoses) are L-arabinose, d-ribose, 2-deoxy-D-ribose, and D-xylose
- The 6-carbon sugars are called hexoses or aldohexoses except D-fructose which is a ketohexose.
- Examples of hexose sugars are: D-glucose, D-fructose, D-galactose, and D-mannose
- Open chain structure Cyclic oxide structure





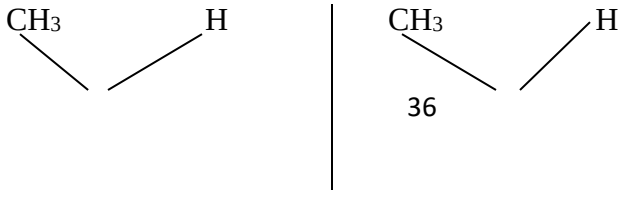
- Example of a seven carbon sugar (heptoses) is D-sedoheptulose
- **Oligosaccharides:** these are low molecular weight polymers of monosaccharides with 2-9 units of the monomer.
- **Oligosaccharides** are often hexose sugars.
- There are many disaccharides which include sucrose $(C_6H_{12}O_5)O(C_6H_{12}O_5)$, maltose (glucose + galactose) and lactose (galactose + glucose) which can be hydrolyzed to glucose and fructose :
- $(C_6H_{12}O_5)O(C_6H_{12}O_5) + H_2O \rightarrow C_6H_{12}O_6 + C_6H_{12}O_6$

  Sucrose D-glucose D-fructose

- **Polysaccharide:** are high molecular weight polymers of sugar made by condensation of the monomers (≥ 10 monomers).
- Examples are starch, cellulose, agar, and carbohydrate gums (plants) and glycogen (animals)
- **Glycosides:** these are sugars attached to non-sugars compounds such as hydroxylated compounds or nitrogen bases

5.3 Optically Active Compounds

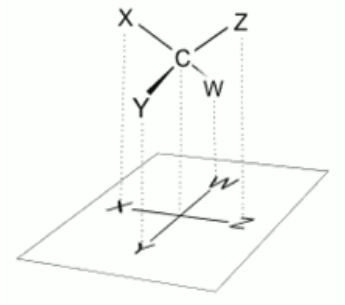
- A carbon center surrounded by 4 substituent's that are the same is said to be a symmetrical carbon
- A carbon center surrounded by 4 different substituent's is said to be an asymmetrical carbon
- An electromagnetic radiation has an electrical and magnetic component that move in perpendicular direction to each other and to the direction of propagation of the radiation.
- In plane polarized light the electrical and magnetical component of radiation are contained in a fixed plane but are both perpendicular to each other and to the direction of propagation of the light.
- This is what is called a plane polarized light
- When a plane polarized light is passed through an optically active compound, an observer looking towards the beam can see the light rotated either clockwisely or counterclockwise
- If the observer noticed that the light is rotated clockwisely (to the right)will define the compound as ***dextrorotatory($_D$)*** and the angle of rotation is taken to be positive ***(+)***
- If the observer noticed that the light is rotated counterclockwise (to the left) will define the compound as ***levorotatory($_L$)*** and the angle of rotation is taken to be negative ***(-)***
- Usually, a structure always have an image that is superimposable on the original structure when place in front of a mirror, e.g. left and right hand
- However, there are some molecules with nonsuperimposable mirror images of each other
- Such compounds have asymmetric centers and are said to be optically active
- Examples include s-butyl alcohol and glucose
- Such mirror images are called ***enantiomers***
- If the mirror images are formed in equal numbers, the net rotation is zero and the mixture is called a ***racemic*** mixture. Each enantiomers is called a ***racemate***
- Separation of enantiomers in a racemic mixture is called ***resolution***
- Conversion of molecule of one enantiomers to a racemic mixture is called ***racemization***
- A 1:1 mixture of enantiomers gives a stronger packing than either enantiomers separately. For example right and left handed objects usually can be packed in a box better than all right or all left handed objects.



s-butyl alcohol

5.4 Fishers Projection

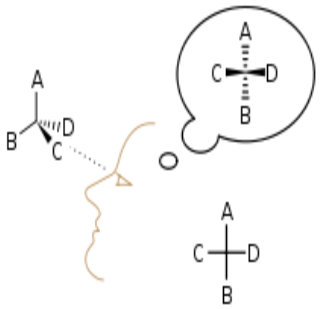
- The **Fischer projection**, devised by Hermann Emil Fischer in 1891, is a two-dimensional representation of a three-dimensional organic molecule by projection. Fischer projections were originally proposed for the depiction of carbohydrates and used by chemists, particularly in organic chemistry and biochemistry but can also be used for amino acids or for other organic molecules. Since Fischer projections depict the stereochemistry (three-dimensional structure) of a molecule, they are very useful for



Projection of a tetrahedral molecule on a plane

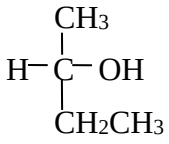
differentiating between enantiomers of chiral molecules

- All bonds are depicted as horizontal or vertical lines.
- All vertical lines goes back behind of the plane of the page (projects away from the viewer) and are represented by broken lines
- All horizontal lines are coming out of the plane of the page (projects towards the viewer) and are represented by the dark wedges (lines)



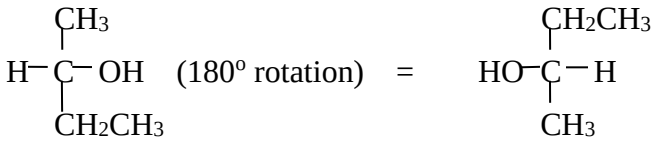
Fisher's projection of a tetrahedral molecule

- Fisher's convection makes the all carbons (carbon chain) to be written in a vertical row with carbon atoms represented by the center of crossing lines.

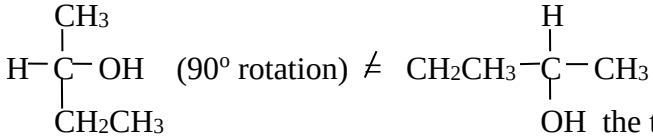


- The orientation of the carbon chain is so that the C1 carbon is at the top.
- In an aldose, the carbon of the aldehyde group is C1
- In a ketose the carbon of the ketone group has the lowest possible number (usually C2).

If a Fishers projection is rotated by 180^0, the stereochemistry (configuration) remains unchanged. Swapping two pairs of groups attached to the central carbon atom still represents the same molecule as was represented by the original Fischer projection.

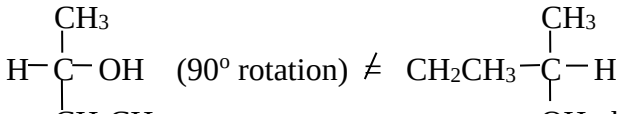


- If a Fisher's projection is rotated 90º, -90º and 270º, the configuration (stereochemistry) will be inverted and enantiomers will be formed

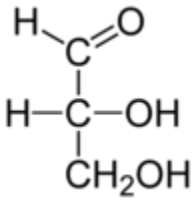


the two compounds are enantiomers

- One group of the Fisher's projection can be held constant while others are rotated to form enantiomers

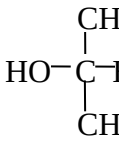


- the two compounds are enantiomers
- A Fischer projection is used to differentiate between L- and D- molecules.
- On a Fischer projection, the penultimate (last but one) carbon of D- sugars are depicted with ***hydrogen on the left and hydroxyl on the right***.



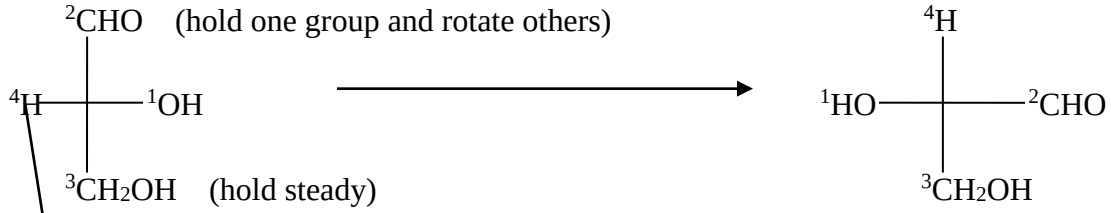
D-glyceraldehyde

- L sugars will be shown with the ***hydrogen on the right and the hydroxyl on the left***



L- glyceraldehyde

- **Assigning R and S-configurations to Fischer projections**
- Assign priorities to the four substituent's according to the Cahn-Ingold-Prelog convention.
- Perform the two allowed manipulations of the Fischer projection to place the lowest priority group on one of the vertical positions (either top or bottom)
- If the priorities of the other three groups (1-2-3) proceed clockwise, the stereogenic center is assigned as R.
- If the priorities of the other three groups (1-2-3) proceed counter clockwise, the stereogenic center is assigned as S.



(lowest priority. Move to a vertical position) The priorities of the other group (1-2-3) is clockwise. The stereogenic center is R

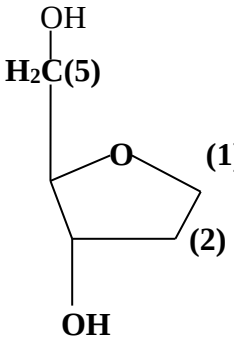
-

5.5 The Structure and Properties of $_D$-Glucose

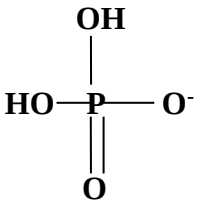
- Glucose is the most abundant monosaccharide.
- It is found in: fruits, plants, honey, urine, blood of animals and combined in may disaccharides, polysaccharides and glycosides
- Glucose is an aldohexose with a terminal aldehyde group
- CHO
- *CHOH
- * CHOH
- *CHOH
- *CHOH
- CH_2OH
- The carbons labeled with asterisks are asymmetrical and hence can form 2^4 configurations or 16 optically active forms.
- All the 16 forms are known. Some occur naturally and some are synthesized
- Emil Fisher developed a projection system of identifying all the 16 optical isomers
-

Chapter 6 Chemistry of Amino Acids and Proteins

1.2 Nucleic Acids: survival of living things including man depends on nucleic acids. There are two types of nucleic acids: Deoxyribose nucleic (DNA) and Ribonucleic acids (RNA). The nucleic acids are polymers of small molecules called nucleotides. The deoxyribonucleotide is present in DNA (structural units of DNA) and ribonucleotide in RNA (structural units of RNA). DNA consists of a pentose sugar (deoxyribose), a nitrogenous base (adenine or cytosine or thymine or guanine) and a phosphate group. RNA consists of pentose sugar (ribose) a nitrogenous base (adenine or cytosine or uracil or guanine) and a phosphate group.

- 

(1) A base is attached to carbon-1 and a phosphate to carbon-5

Phosphate group: 

($H_2PO_4^-$)

- Adenine and guanine are called **purine bases** and cytosine and thymine are called **pyrimidine bases**
- Linkages (polynucleotide chain) in the nucleotide is from carbon-3 of one sugar to the phosphate group and attached to carbon-5 on another sugar
- DNA has 2 very long strands of polynucleotide chain s (> 100 milli0n) while RNA has one. The strands of the DNA coil around each other to form a **double helical shape** (a spiral shape of a spring) with its phosphate group pointing outwardly while the bases points inwardly. Hydrogen bonding joins the base in one strand to another base in the other strand to form a **base pair**. Therefore, the base pairs holds (appears like steps of a staircase) together the two strands of DNA
- There are two types of base pairs in a DNA: Adenine-Thymine (A-T) and Guanine-Cytosine (G-C).

- The base pair sequence in a DNA are the same in an individual but different in other individuals

Chapter 7 Organosulfur and its Compounds