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16th April, 2024

Alkenes

Class

Alkanes are non-reactive, and they are called paraffins, Par = affinis

Alkenes/Olefins → Addition reactions

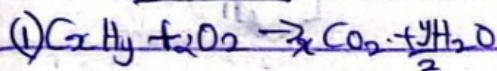
- (1) hydrogenation
- (2) halogenation
- (3) hydration
- (4) hydrohalogenation

→ Oxidation reactions

- (5) hydroxylation
- (6) Ozonolysis

→ Polymerization

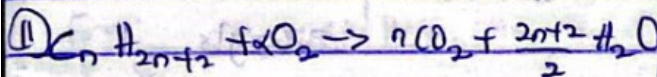
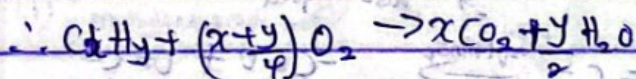
Combustion



LHS = RHS

$$2x = 2x + \frac{y}{2}$$

$$x = x + \frac{y}{4}$$

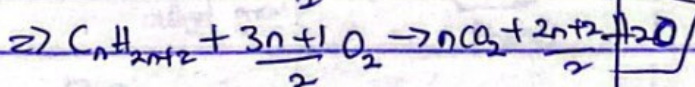


$$2x = 2n + \frac{2n+2}{2}$$

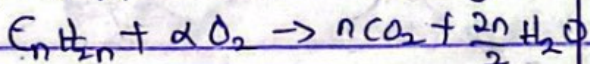
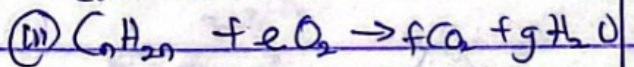
$$2x = 2n + n + 1$$

$$2x = 3n + 1$$

$$x = \frac{3n+1}{2}$$



class work



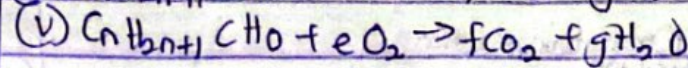
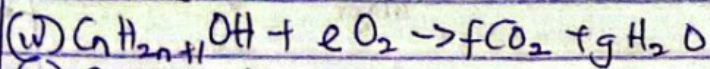
$$2x = 2n + \frac{2n}{2}$$

$$2x = 2n + n$$

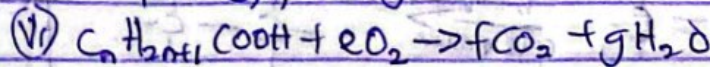
$$x = \frac{3n}{2}$$

$$C_nH_{2n} + \frac{3n}{2} O_2 \rightarrow nCO_2 + \frac{2n}{2} H_2O$$

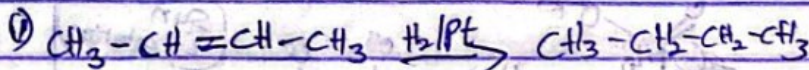
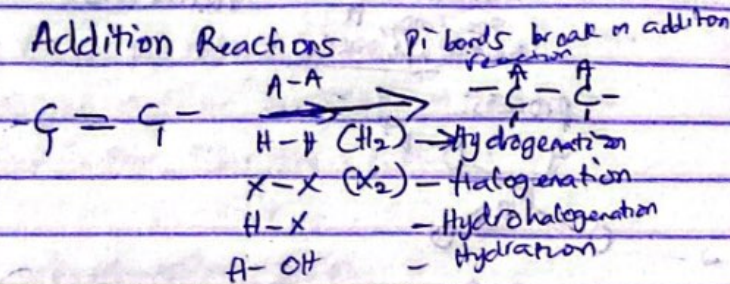
Assignment



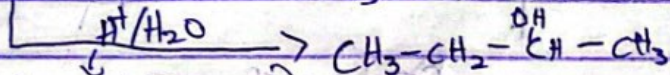
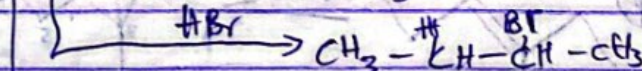
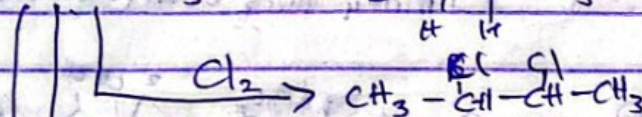
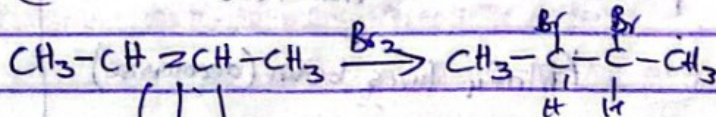
find e, f and g



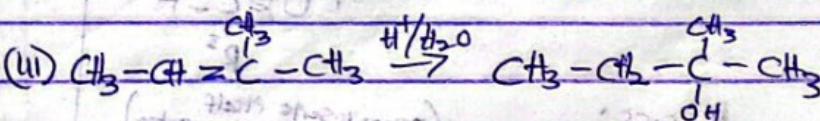
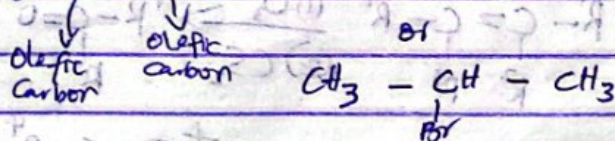
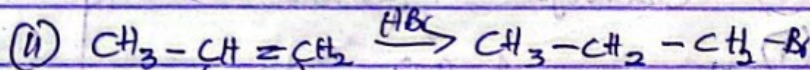
Addition Reactions



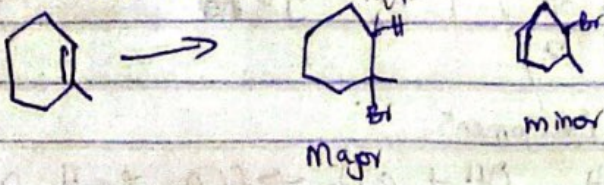
(Anytime there is addition reaction, you use transition metal catalyst)



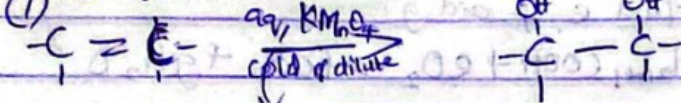
(It must be under acidic condition)



18th April, 2024
using Markovnikov rule

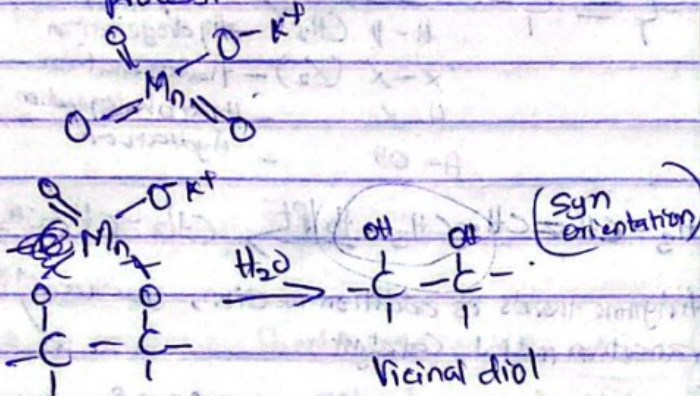


Oxidation reaction

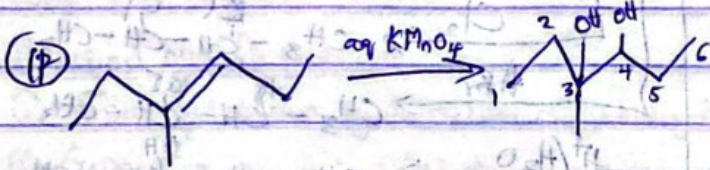


Whenever you see KMnO₄, it is called hydroxylation

Process:



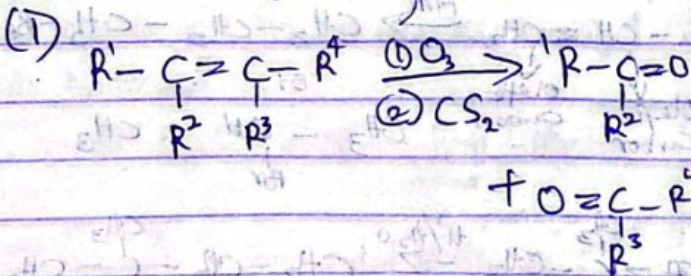
KMnO₄ turns brown (decolourise)



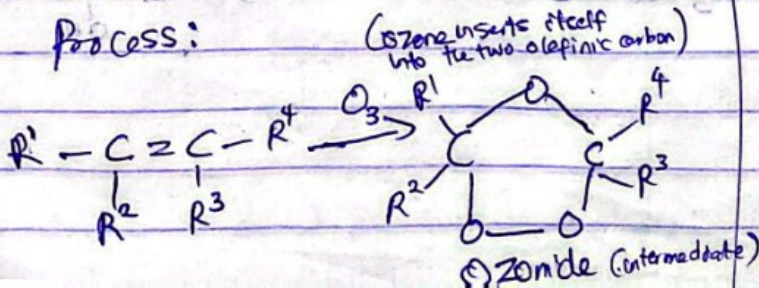
Oxidative Cleavage

Ozonolysis

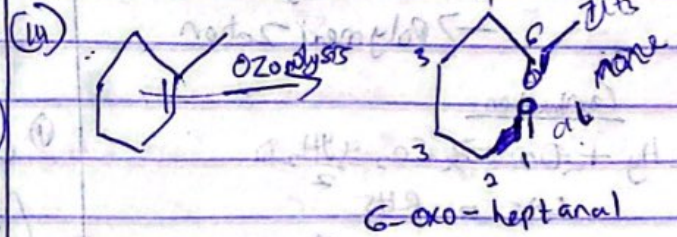
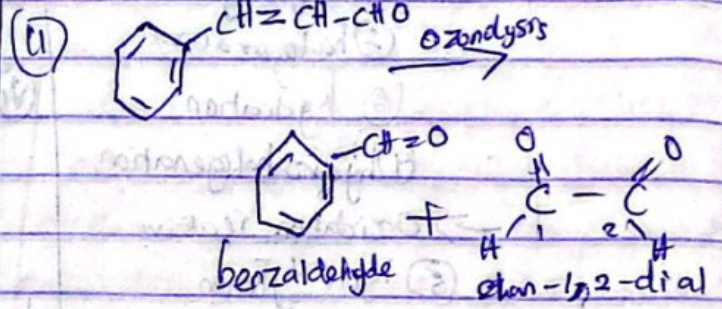
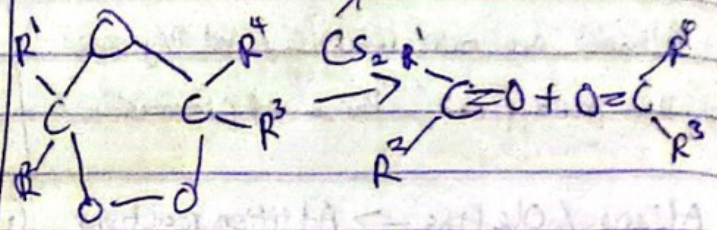
This will give intermediate



Process:

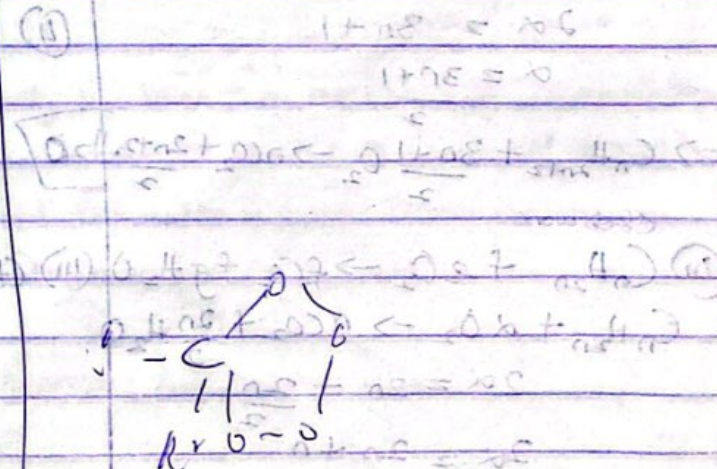
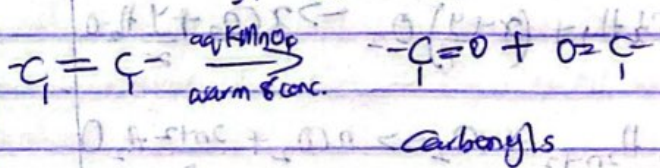


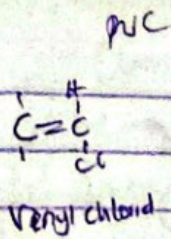
(Other reagents can be used)



Note:

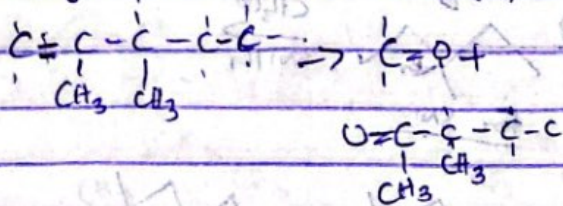
Note that OsO₄ can also be used



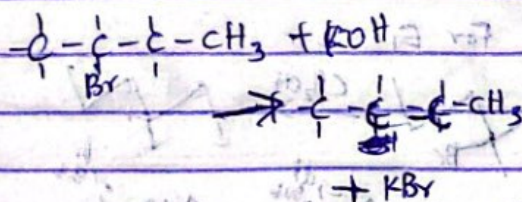


Questions

(1) Ozonolysis products of 2,3-dimethyl pentane



(2) Product when $\text{CH}_3\text{CHBrCH}_2\text{CH}_3$ reacts with KOH



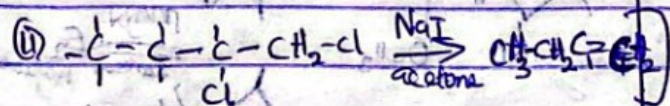
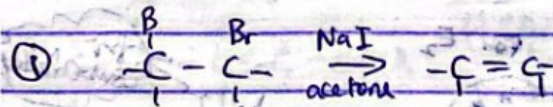
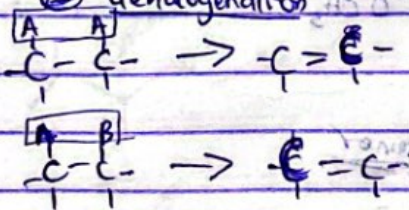
Class

22nd April, 2024

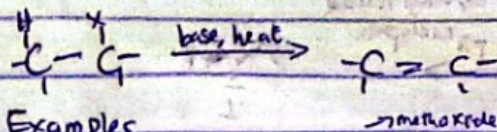
Preparation/Synthesis of Alkenes

- (1) dehydrohalogenation
- (2) dehalogenation
- (3) dehydration

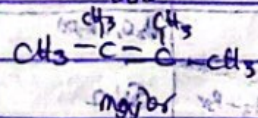
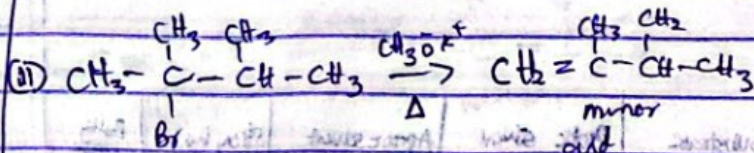
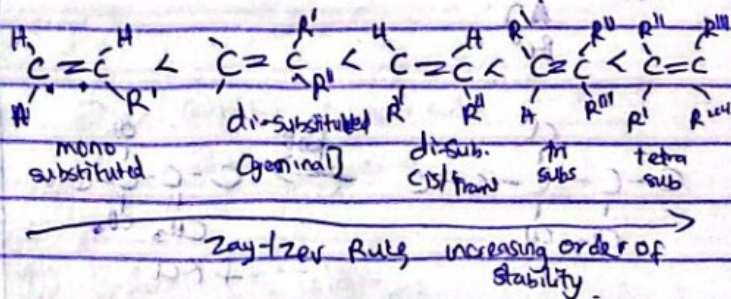
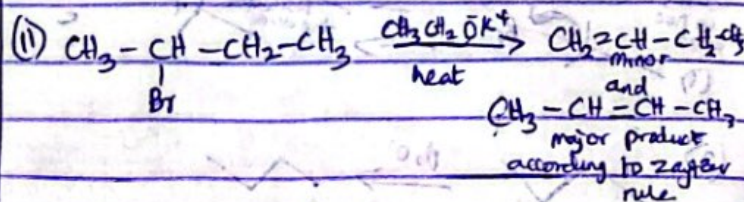
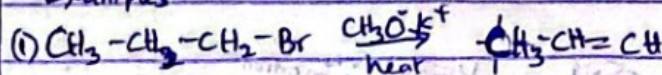
(A) dehalogenation



(2) dehydrohalogenation



Examples

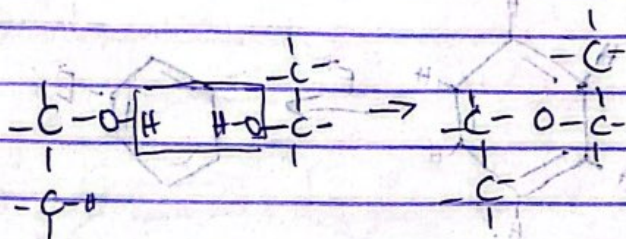
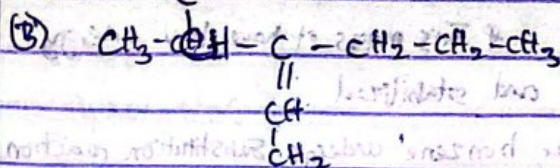
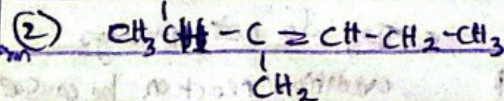
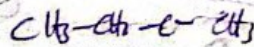
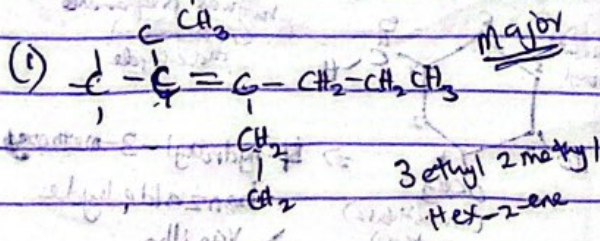
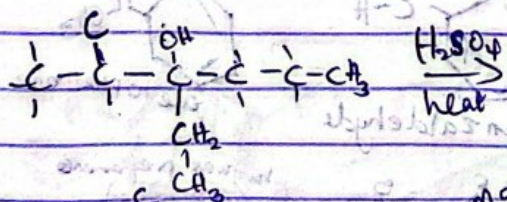
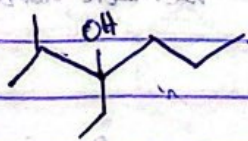
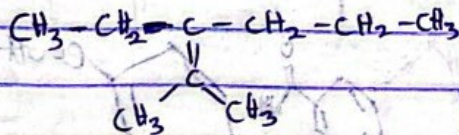
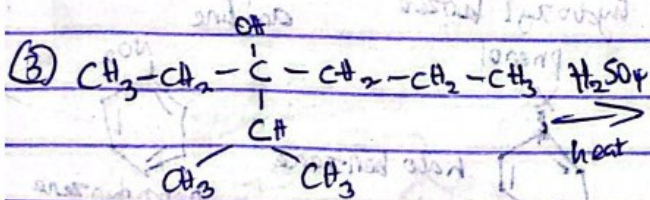
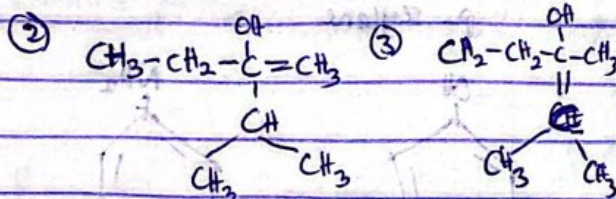
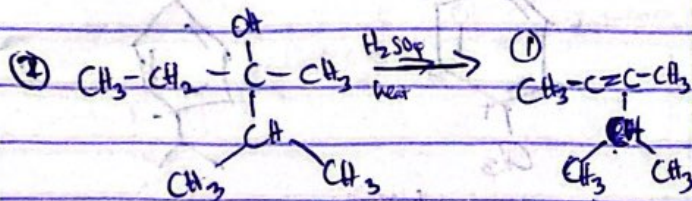
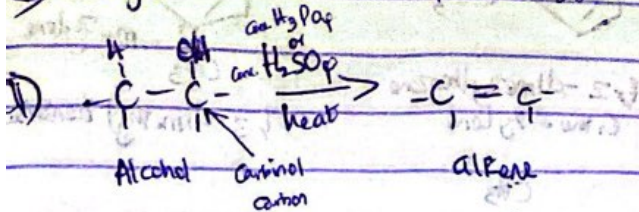


Class

⊛ what temp will you get alkene and what temp will you get ether?

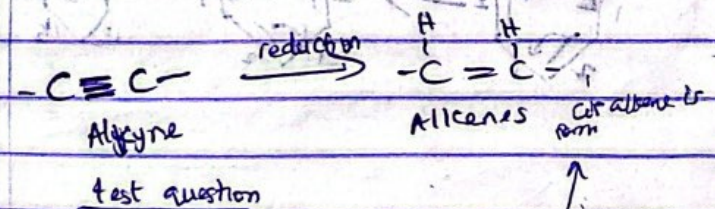
3rd April, 2024

③ Dehydration: Removal of water \rightarrow E1 mechanism



Ether can be formed under certain condition of temperature.

⊛ Reduction of alkynes



* There are times that reduction of alkynes gives cis alkene or trans alkene, it depends on the reagent. Find out the reagent to be used to produce cis and trans alkenes.

* Study Wittig reaction

Stereochemistry of Alkenes

⊛ Cahn-Ingold-Prelog Convention

↓ cis alkene is formed when Pd/BaSO₄ in the presence of quinoline is used as reagent
Trans alkene is formed when Na and Liq. NH₃ is used as reagent

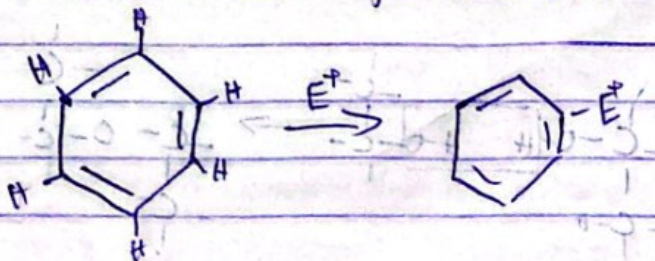
Benzene and Derivatives



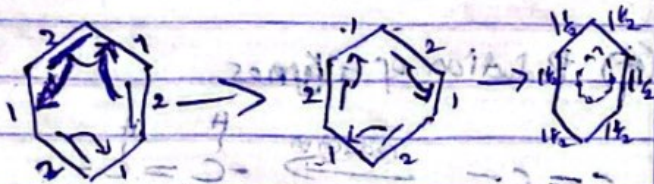
They do not undergo addition reaction because the pi-bonds are delocalized

This makes it have low energy and stabilized

Rather, benzene undergoes substitution reaction

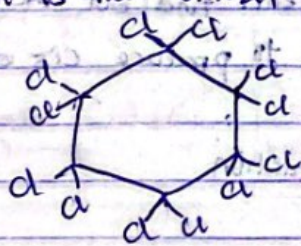


The double bond are not really really, they are pseudo

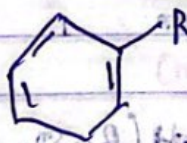


25th April, 2024

Benzene ~~may~~ undergo addition reaction but it is not normal



Derivatives of Benzene and Nomenclature

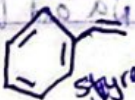


Alkyl benzene



methyl benzene

Toluene

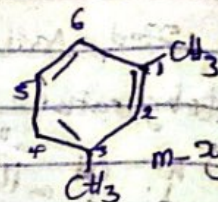


styrene/vinyl benzene

O=ortho, m=meta, p=para



1,2-dimethylbenzene
ortho-xylene



1,3-dimethylbenzene
m-xylene



1,4-dimethylbenzene
p-xylene



Cumene



hydroxyl benzene

phenol



aniline



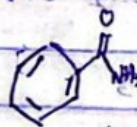
halo benzene



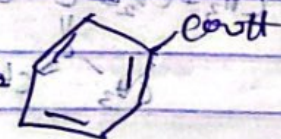
nitro benzene



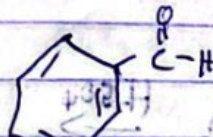
methoxy benzene
anisole



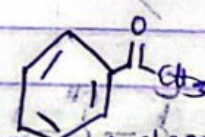
Benzamide



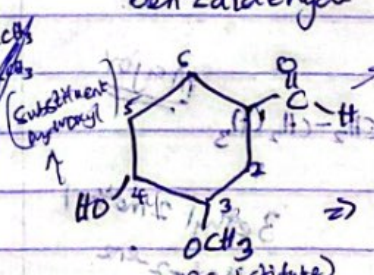
benzoic acid



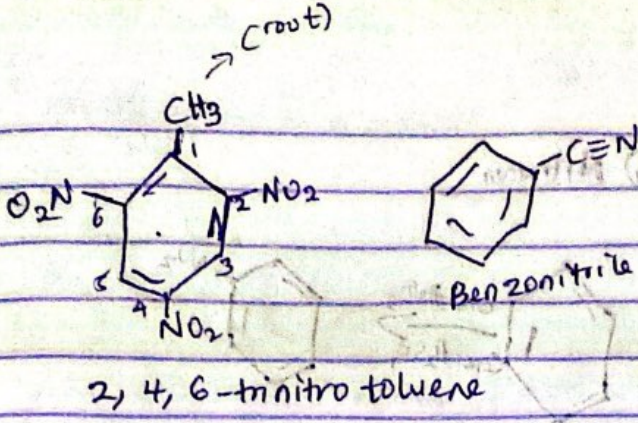
benzaldehyde



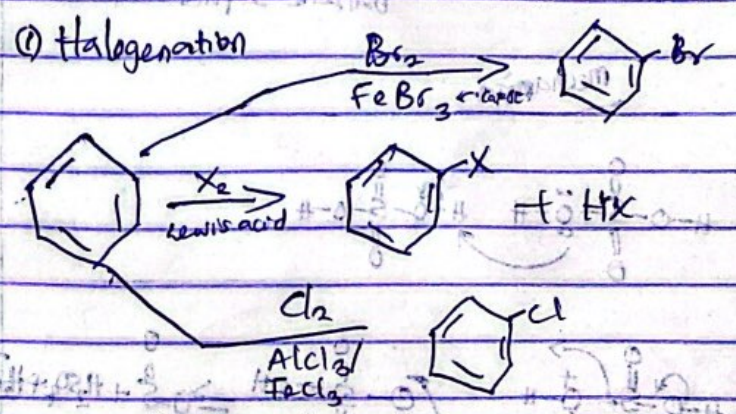
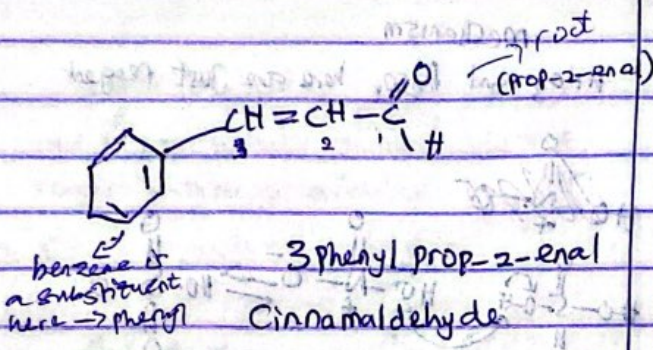
acetyl phenone



highes preference (IUPAC name)
aldehyde
⇒ hydroxyl-3-methoxy benzaldehyde
⇒ Vanillin



- Halogenation
- Alkylation (Friedel-Crafts)
- Acylation (Friedel-Crafts)
- Nitration
- Sulphonation

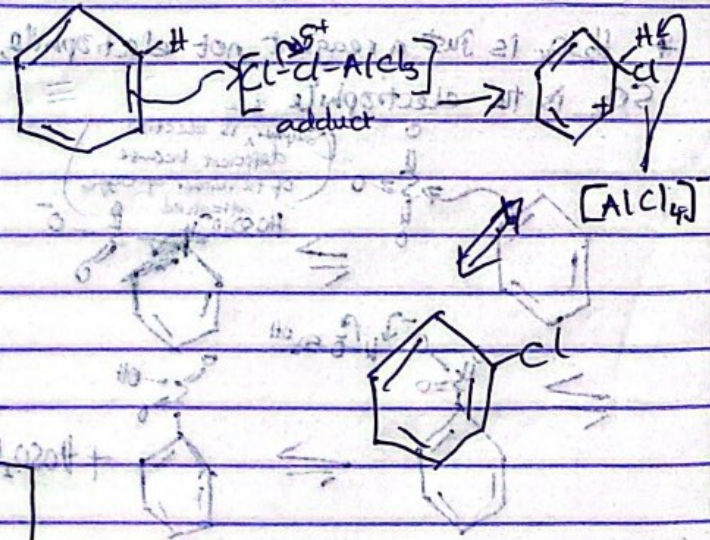
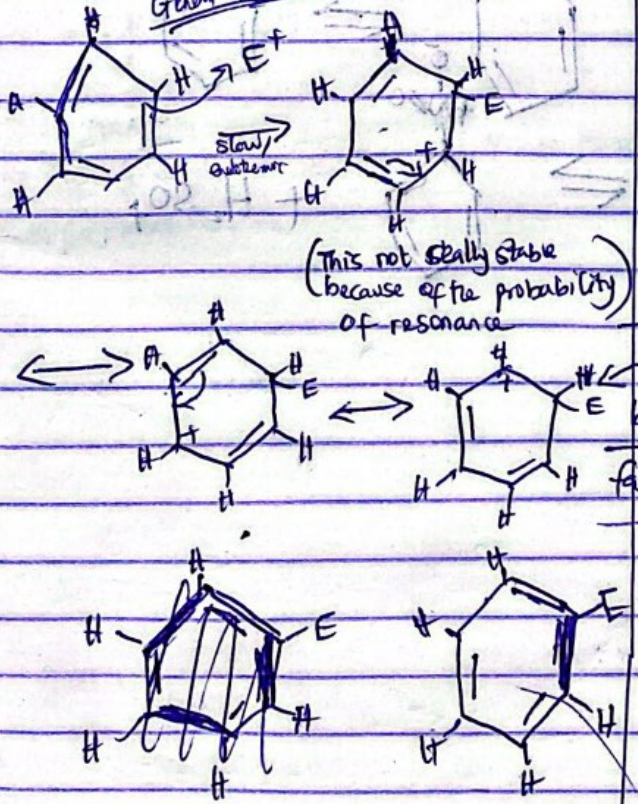


Reactions of Benzene

(i) Electrophilic Substitution reaction:

Benzene is ^{as} nucleophile, having 6 π electron.

General mechanism

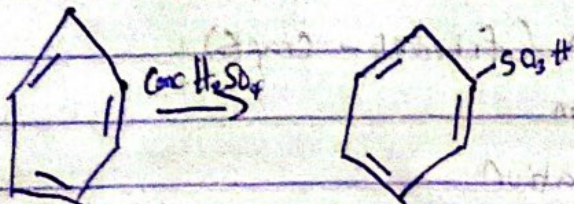


9JABAZING

Class

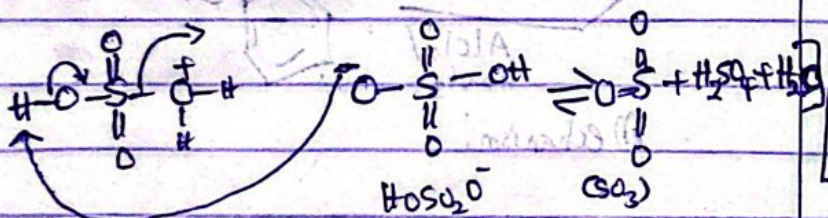
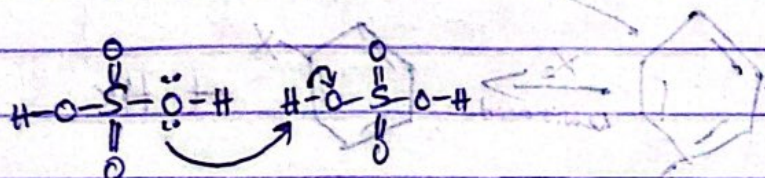
26th April, 2024

② Sulphonation

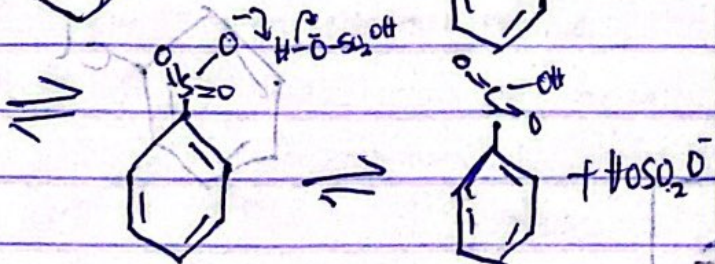
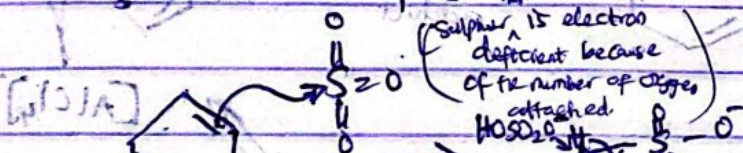


Benzene Sulfonic acid

Mechanism

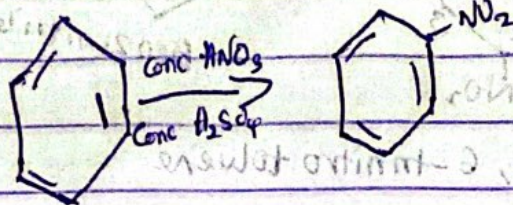


* H_2SO_4 is just a reagent not electrophile, SO_3 is the electrophile here



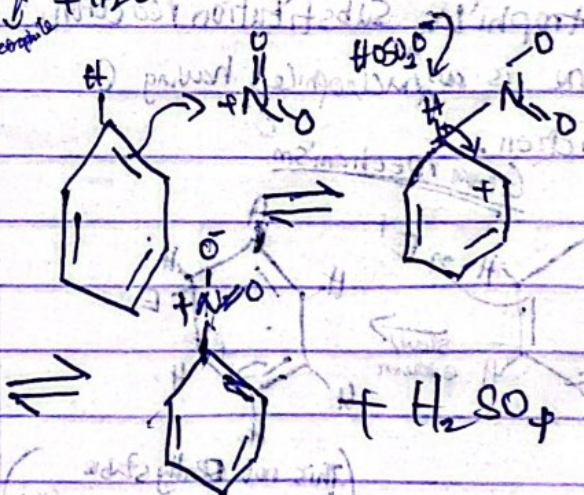
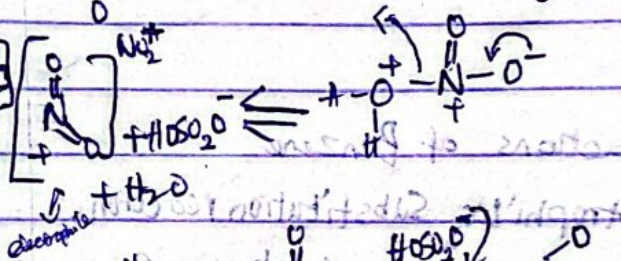
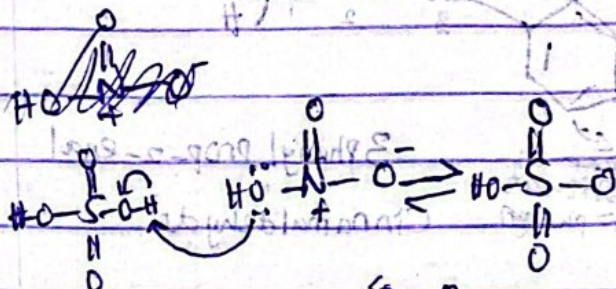
Benzene sulfonic acid

③ Nitration

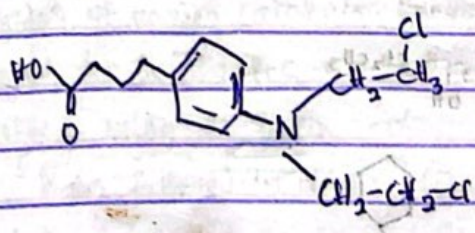


Mechanism

HNO_3 and H_2SO_4 here are just reagent



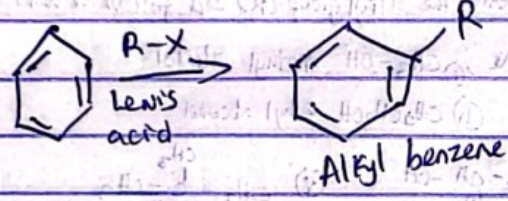
Why organic chemistry is important



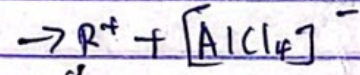
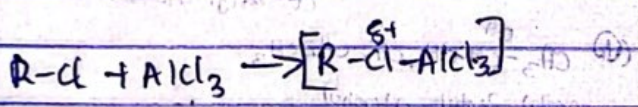
Chlorambucil

used in cancer patients. It undergoes SN2 reaction with the DNA/purine.

(14) Friedel-Crafts Alkylation



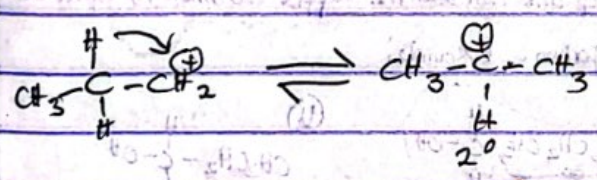
Mechanism



Carbocation electrophile

If R = CH₃ or CH₃CH₂, it will not form a carbocation, it will be unstable

Hydride Shift



29th April 2029

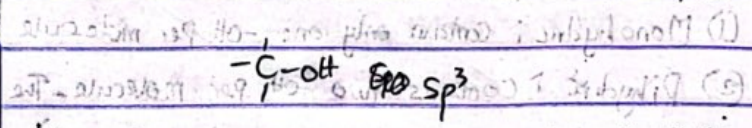
Hydroxyl Compounds

Hydroxyl compounds are compounds with one or more hydroxyl functional groups (-OH) attached to a saturated carbon atom.

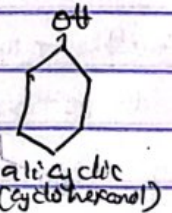
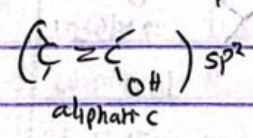
The Saturated carbon atom or a simple alkyl group

Alkanols (Alcohols)

Alkanol are hydroxyl compounds of general formula of R-OH. The -OH group is attached or bonded to a saturated carbon atom (sp³)



While there are some in which OH will attach to sp² hybridized carbon. Carbon in which their OH group is attached to vinylic sp²'s called "enol" while those in which the -OH is bonded to a benzene ring are referred to as phenols



However enols and phenols behave differently from alcohols

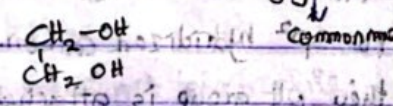
Classification

Alkanols are classified into 3 on the basis of which the OH group is bonded or attached to.

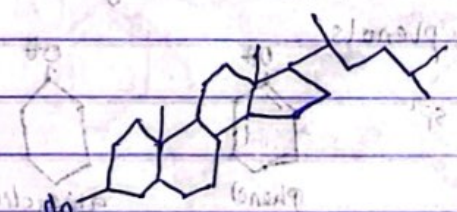
| Class | Gen. Formula | Functional Group | Examples |
|--|---------------------------------|------------------|--|
| must have 2 hydrogen | 1° $R-CH_2-OH$ | $-CH_2-OH$ | $H-CH_2-OH$, CH_3CH_2OH |
| must have two hydrogen and 2 alkyl group | 2° $R-CH(OH)-R'$ | $-CH(OH)-$ | $CH_3CH(OH)CH_3$, $CH_3CH(OH)CH_2CH_3$ |
| no hydrogen, 3 alkyl group | 3° $R-C(OH)(R')(R'')$ | $>C-OH$ | $CH_3-C(OH)(CH_3)_2$, α -terpineol |

Alcohols can be further classified on the basis of the number of hydroxyl groups per molecule or attached to different carbon atoms:

- (1) Monohydric: contain only one -OH per molecule
- (2) Dihydric: contains two -OH per molecule. The simplest form is Ethane-1,2-diol, (glycol)



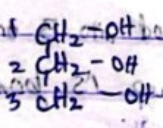
Example of 2°



Cholesterol 2° alcohol

- (3) Trihydric: contains 3-OH per molecule

Example: Propan-1,2,3-triol, (glycerol)



- (4) Polyhydric: More than 3 or many -OH per molecule

Nomenclature

There are three important system used in name alcohols:

(1) Use of common names, systems or functional class system

This is good for simple alcohols. How? Name the alkyl group (R) and follow the word alcohol

Example: (i) CH_3-OH methyl alcohol

(ii) CH_3CH_2OH ethyl alcohol

(iii) $CH_3-CH(OH)-CH_3$ iso propyl alcohol

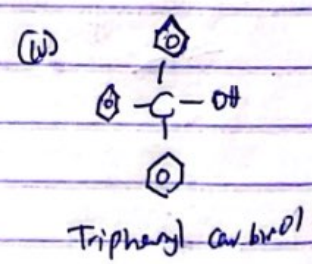
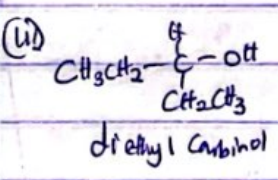
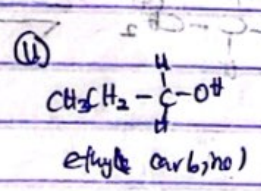
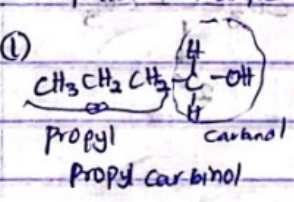
(iv) $CH_3-C(CH_3)_2-CH_2-OH$ tert-butyl alcohol

(v) $CH_3-CH_2-CH_2-CH_2-CH_2-OH$ methyl pentyl alcohol

(2) CARBINOL SYSTEM: This system of naming alcohol

considers all alcohols to have been derived from methyl alcohol by the replacement of one or more hydrogen atoms by other groups: RULOS!

(1) Name the group(s) attached to the carbon bearing the OH group and then add the suffix carbinol to depict the C-OH portion. Example:



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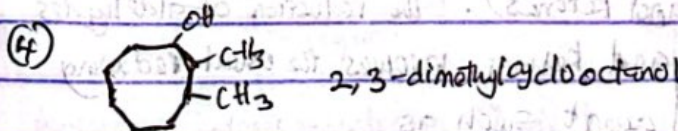
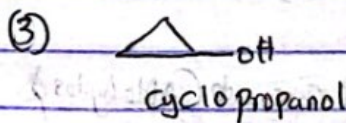
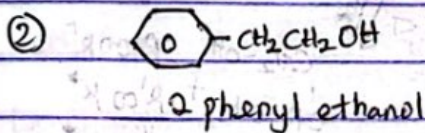
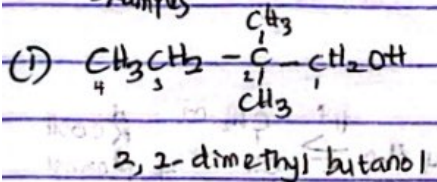
(3) IUPAC SYSTEM: This is the most versatile system of naming alcohols. Simple alcohols are named by the IUPAC as derivatives of parent alkane using the suffix -ol.

Rules Followed in Naming using IUPAC

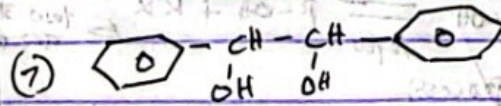
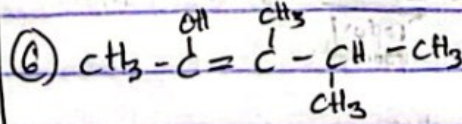
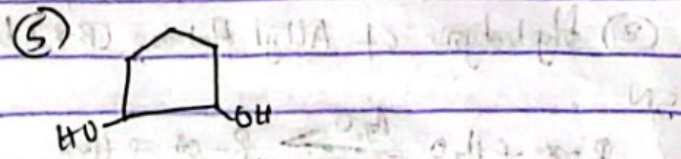
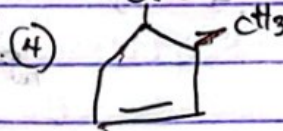
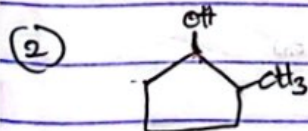
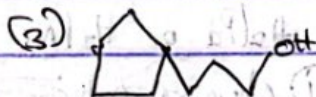
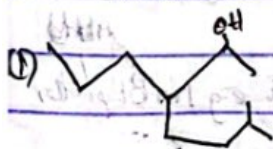
(1) Select or consider the longest, or continuous carbon chain containing the -OH group in deriving the parent name

(2) Number the alkane chain, beginning and the end nearer the -OH group, so as to give carbon atom to which the -OH functional group is attached the lowest possible numbers

Examples



Questions



Physical Properties of Alkanols

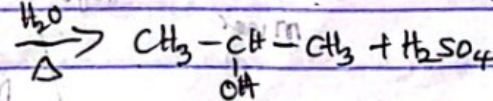
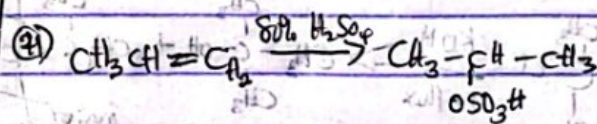
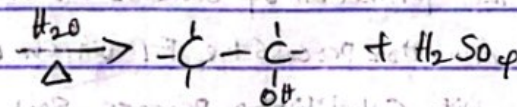
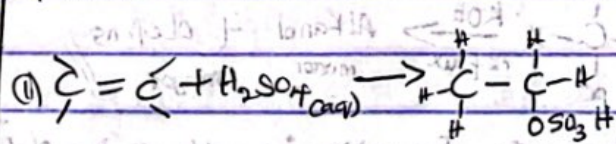
(1) Alkanols have high boiling points at room temperature

(2) They are miscible or soluble in water

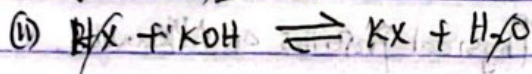
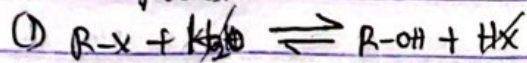
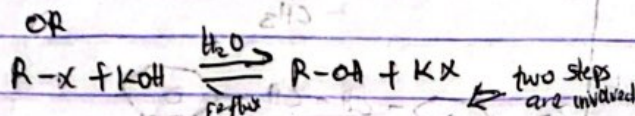
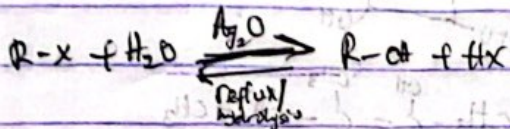
All these physical properties can be explained in terms of intermolecular hydrogen bond

(3) Preparations of Alkanols

(1) Hydration of Olefins/Alkenes: This involves treatment of olefins or alkenes with cold H_2SO_4 followed by addition of water and heat.

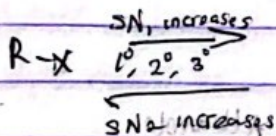


② Hydrolysis of Alkyl Halides (R-X) by SN

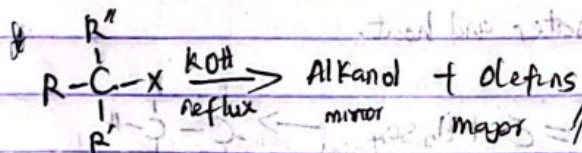


Mechanism of Hydrolysis

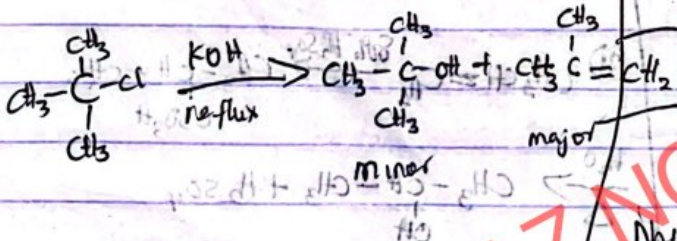
The mechanism of alkaline hydrolysis can be SN1 or SN2



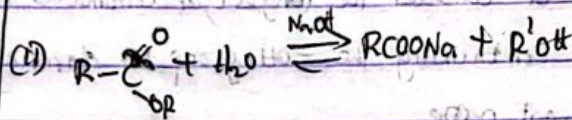
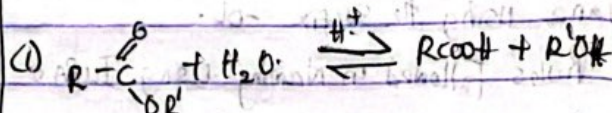
For tertiary alkyl halides, mixtures are often found with the major product being alkenes



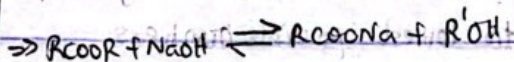
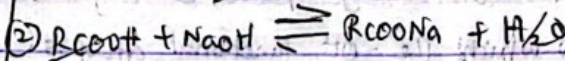
Here, the formation of alkenes or olefins is by elimination process i.e. E1 which is competing with substitution process, SN1



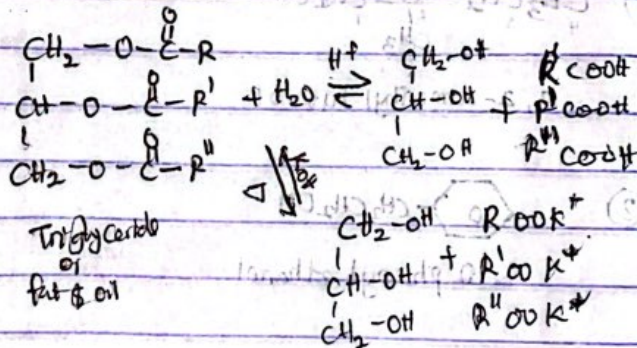
③ Hydrolysis of Esters: This hydrolysis can be acid catalyzed or alkaline catalyzed



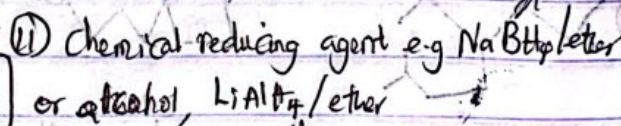
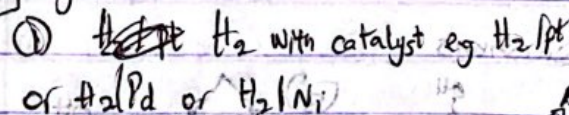
This also involves two steps



Example



Reduction of Carbonyl Compounds (Aldehydes and ketones): The reduction of aldehydes and ketones involves the usual reducing agent such as



Note that LiAlH₄ is a very powerful reducing agent. It reduces -CHO, C=O, aldehyde, ketone

9JABAZING

R^1COOR^2 and $\text{C}=\text{C}$
ester olefins

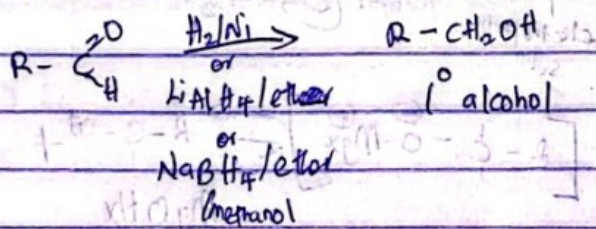
However, NaBH_4 is milder than LiAlH_4
 reduces $-\text{CHO}$, $\text{R}-\text{C}(=\text{O})-\text{R}'$, but no effect
aldehyde ketone

On R^1COOR^2 as well as $\text{C}=\text{C}$
ester olefins

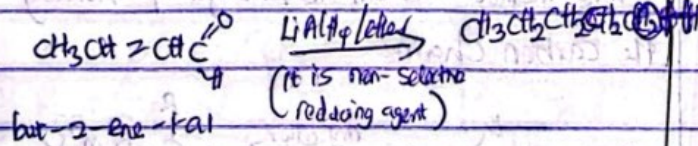
2nd May, 2024

*** ALDEHYDES:**

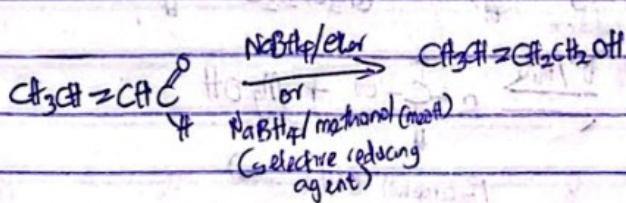
On reduction



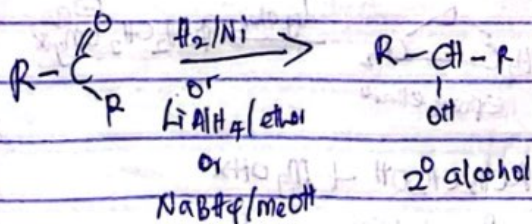
e.g.



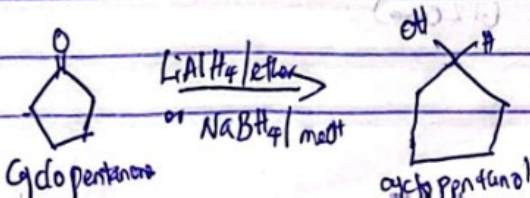
but-3-ene-2-al



ketones: Ketones on reduction will yield
 Secondary alcohols

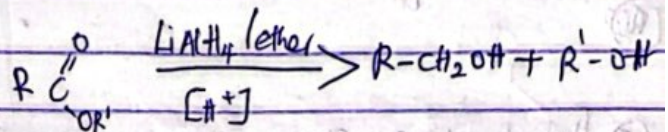


e.g.



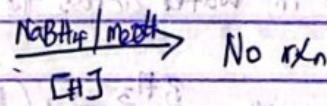
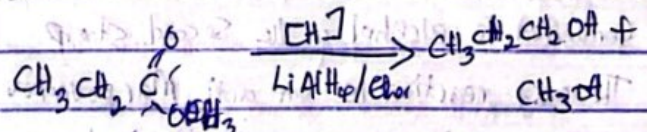
Esters: Esters will yield two types of
 alcohols with powerful reducing agents.
 If ~~NaBH4~~ NaBH_4 (a mild
 reducing agent) is used. No reaction occurs
 or reduction may be very slow.

Hence, medium aluminium hydride is used

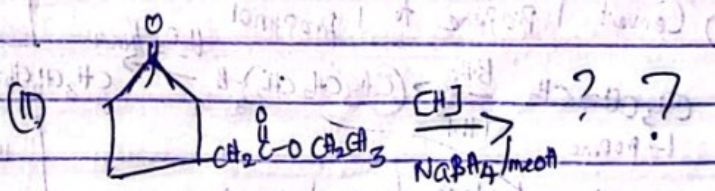
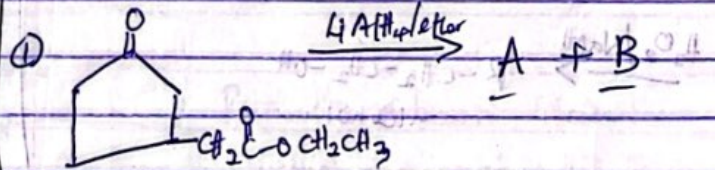


Note that one of the products must be a
 primary alcohol, while the others depends
 on the nature of the R'

e.g.



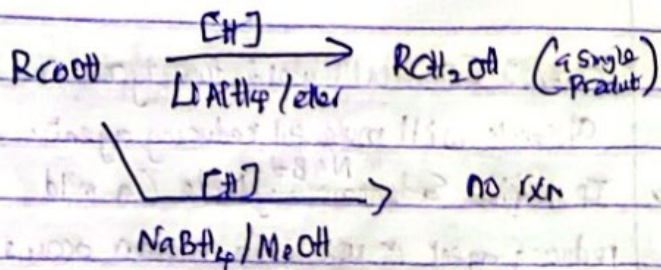
Exercise



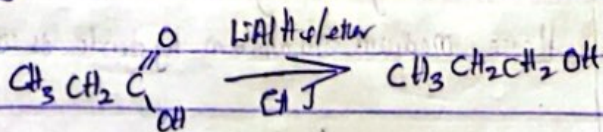
(6) Reduction of Carboxylic acid

They behave in a similar manner to esters.

Carboxylic acids are reduced to primary alcohols
 (a single product) with LiAlH_4 in ether while
 there is no reaction with NaBH_4 in MeOH



e.g

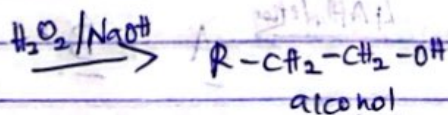
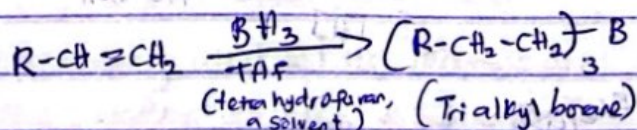


⑥

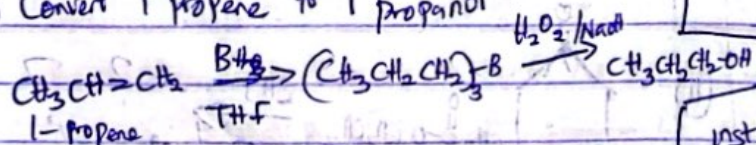
⑦ Hydroboration: This reaction is also used to convert alkene to alcohols.

It is a two step reaction process, in that the first step is conversion of alkene into trialkyl borane. Again, this is converted to alcohol in the second step.

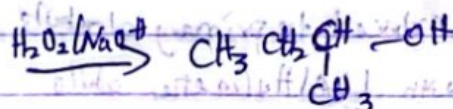
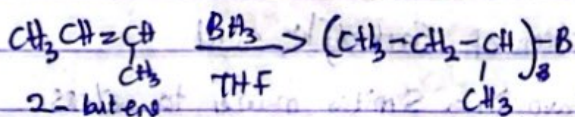
The next reaction is an anti Markovnikov addition in water across the double bond.



① Convert 1 propene to 1 propanol



② Convert 2-butene to 2-butanol

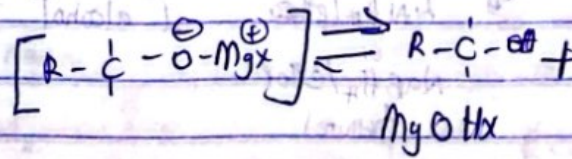
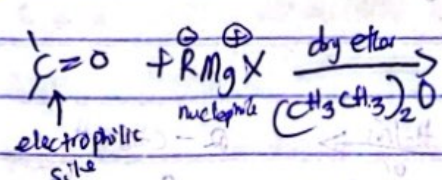


⑧ Preparation of Alcohol From Grignard

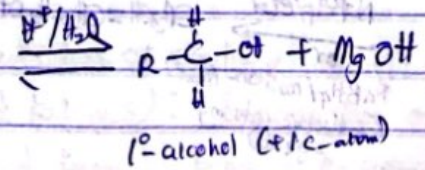
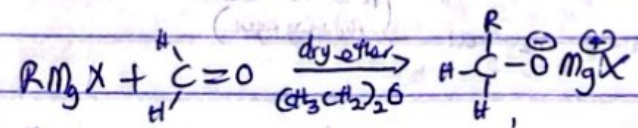
Reagent: Grignard reagent is used in the synthesis in the preparation of all the three type of alcohols (1°, 2°, 3°)

The grignard reagent (R⁻Mg⁺X) are reacted with carbonyl compound (aldehydes and ketones), esters, epoxide to form intermediate which are further hydrolyzed to alcohols.

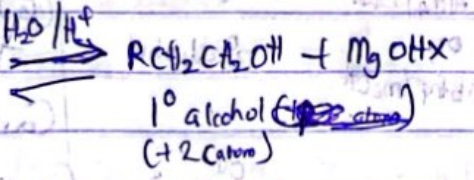
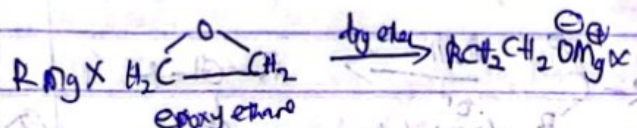
① With aldehydes & ketones

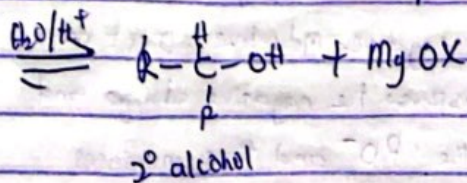
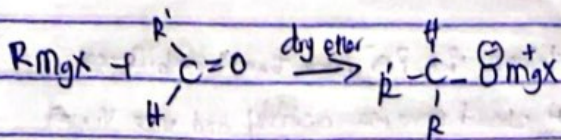


This method has an advantage of extending the carbon chain.



Epoxide ether (ethylene oxide) may be used instead of methanol



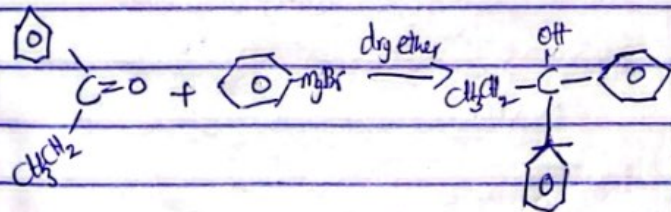
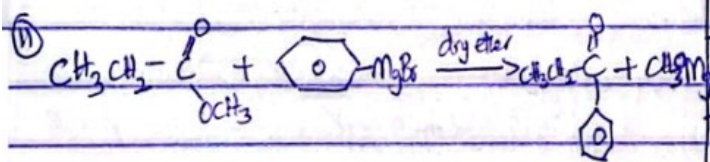
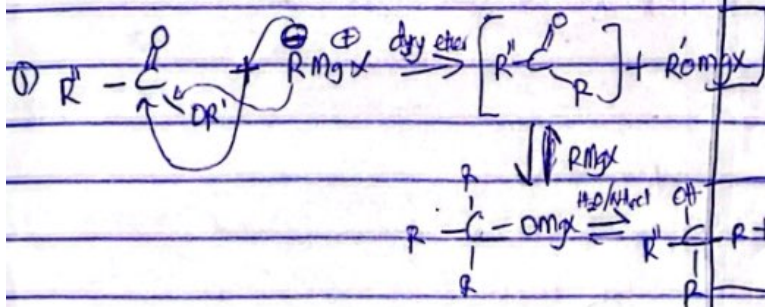


3rd May, 2024

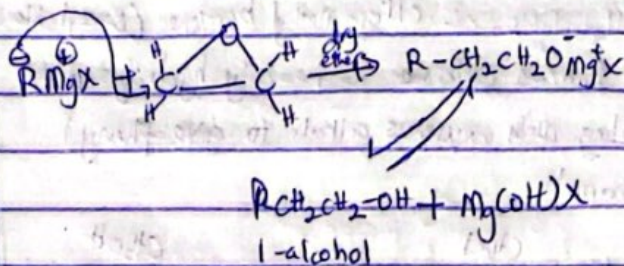
In the preparation of tertiary alcohol, aqueous $NaOH$ is used for hydrolysis as dilute acid brings about dehydration (H_2O/H^+) of the alcohol to alkene.

② With Esters

The reaction of Grignard reagent and esters gives tertiary alcohol as the product. It is a two step reaction. The first step, gives ketone.



With Epoxide: The reaction of Grignard reagent and epoxide gives a primary alcohol with two carbon atoms added.



How do you prepare propanol from a named Grignard reagent?

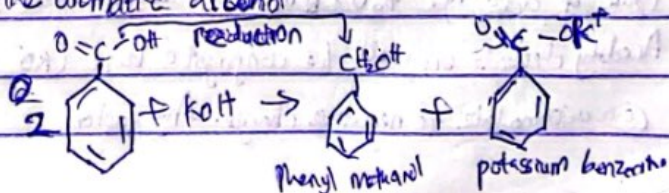
In Summary:

- Grignard Reagent + Methanal \rightarrow 1° alcohol
- " + other aldehyde \rightarrow 2° alcohol
- " + Ketone \rightarrow 3° alcohol
- " + esters \rightarrow ketone \rightarrow 3° alcohol
- " epoxide \rightarrow 1° alcohol

Preparation of Aromatic Alcohol

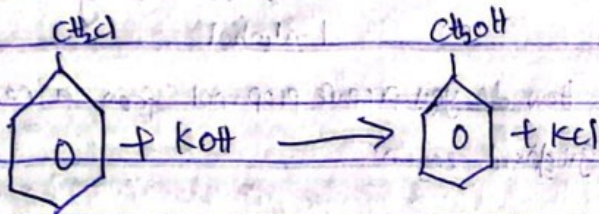
① Aromatic alcohol can be prepared by Cannizzaro reaction. Aromatic aldehyde, such as benzaldehyde, $\begin{matrix} O \\ || \\ C-H \\ | \\ C_6H_5 \end{matrix}$ when shaken with

aqueous KOH , it undergoes simultaneous oxidation and reduction (disproportionation reaction) yielding the potassium salt of the corresponding carboxylic acid together with the aromatic alcohol.



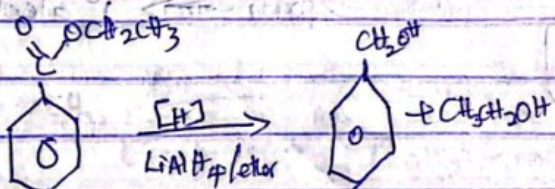
The potassium salt is dissolved in water and the alcohol is extracted with ethoxy ethane (diethyl ether) using separating funnel.

② Hydrolysis of chloromethyl benzene (Benzyl chloride)
Benzyl chloride is readily hydrolysed on boiling with aqueous alkali to give phenyl ethanol



③ By reduction of Benzene Carboxylate (Benzoate)

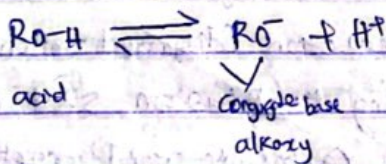
Benzoyl carboxylic acid (benzoic acid) or ether benzoate can be reduced to the alcohol by using LiAlH_4 (reducing agent)



Chemical Reactivities of Alkanol

① Alkanols have Amphoteric behaviour. Alkanols can act as an acid and a base

② As an acid: An alcohol releases a proton



Order of acidity: $\text{H}_2\text{O} > \text{CH}_3\text{OH} > 1^\circ \text{alcohol} > 2^\circ \text{alcohol} > 3^\circ \text{alcohol}$
Acidity depends on well the conjugate base (RO^-) can accommodate the negative charge. Any factor

that stabilizes the RO^- more than it stabilizes the ROH should increase acidity and vice versa

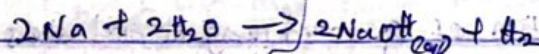
Therefore negative inductive effect in

R should disperse the negative charge and stabilizes the RO^- and thus increases acidity. On the other hand, positive

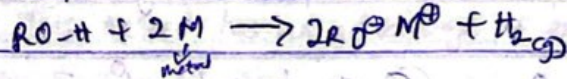
inductive effect in R should intensify

the negative charge on (RO^-) , then stabilizes the anions (RO^-) and thus decreases acidity

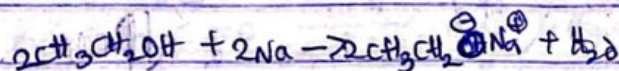
The acidity of alkanols is shown by their reaction with active metals to liberate H_2 gas and give the metal alkoxides



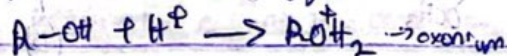
Example



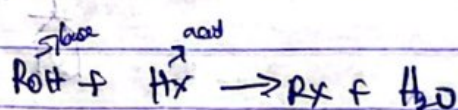
Where M is metal



③ As a base. Alkanol accepts a proton using a lone pair of electron on oxygen atom.



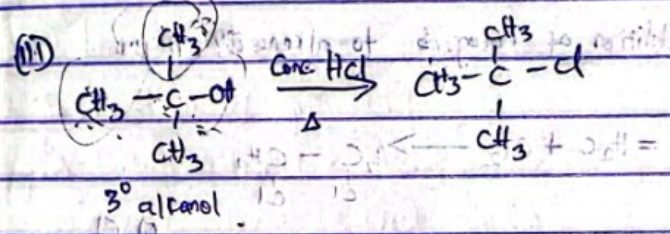
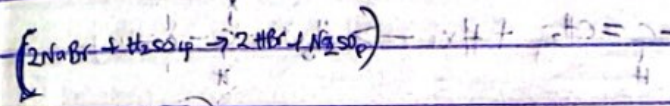
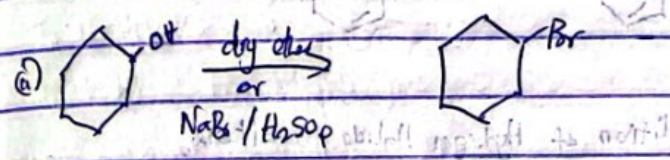
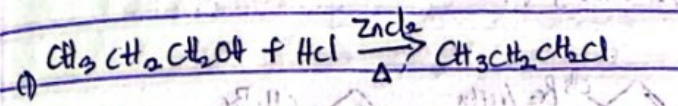
The basicity of alkanol is shown by the fraction of hydrogen halides to give alkyl halides (RX)



HI reacts most rapidly; while HCl reacts least rapidly and requires the presence of ZnCl_2 for reaction with

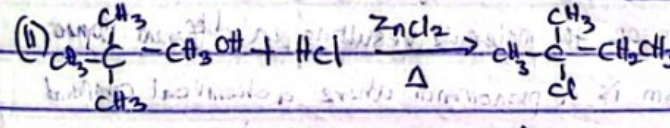
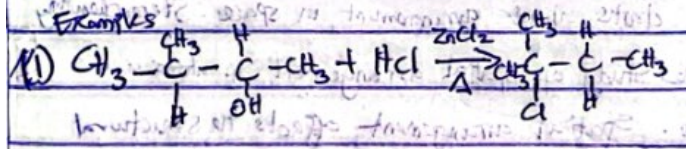
only
homogeneous
layer

Primary and secondary alkanol.
But conc HCl at room temperature is right for
tertiary alkanols. This test is called
Lucas test for alkanols

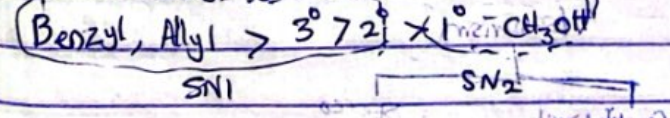


Note: The reaction is catalyzed by acid. eg
conc. H₂SO₄

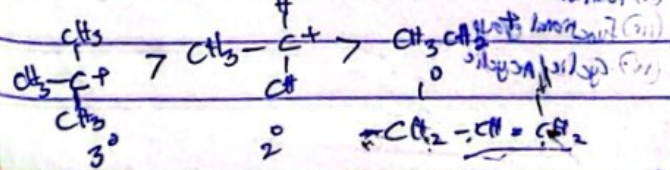
(ii) Rearrangement of alkyl group may occur
except with some primary alkanol



Order of Reactivity of Alkanol toward
Hydrogen Halides



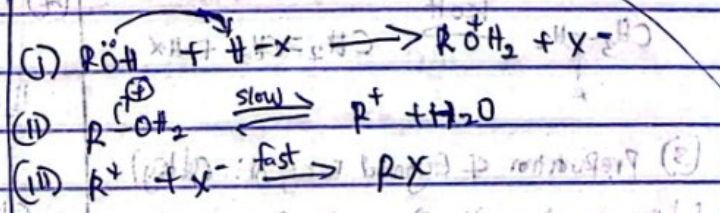
-CH₂-CH=CH₂ - Allylic
-CH=CH₂ - Vinyllic



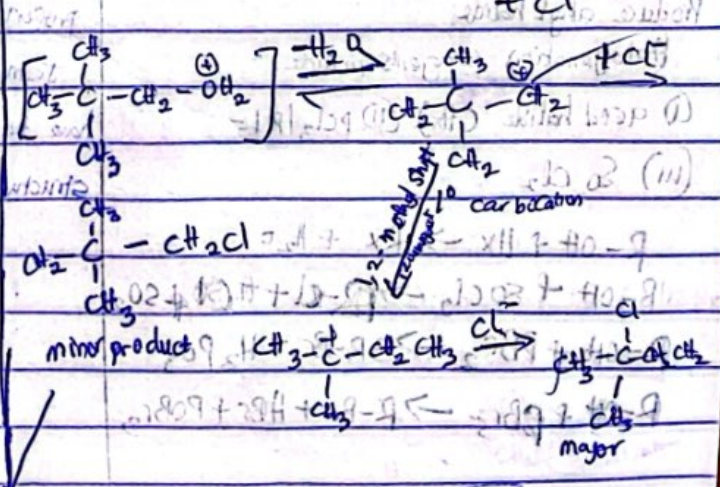
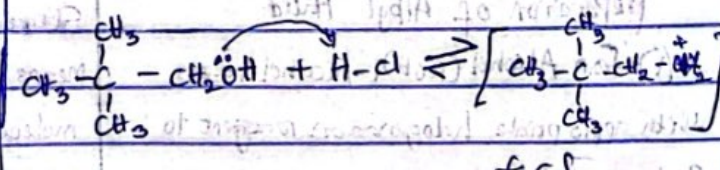
Mechanism of Reaction

The mechanism of the reaction between an
alkanol and HX is SN1 except for
methanol and most primary alkanol where
SN2 is preferred.

The SN1 mechanism involves 3 major steps:
(i) Protonation of Alkanol to form oxonium
ion (R-OH₂⁺)
(ii) Dissociation of the protonated Alkanol into
Water and a carbocation
(iii) Combination of the carbocation or rearranged
carbocation with halide ion (X⁻) to
form the alkyl halide

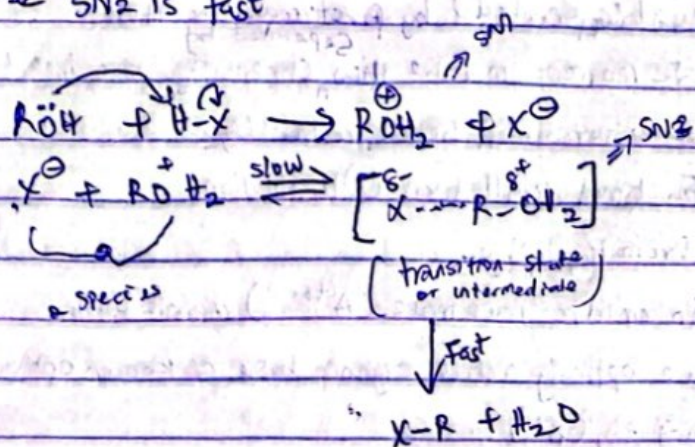


The slow one is the rate determining step
consisting of only one molecule i.e. (R-OH₂⁺). Hence
it is SN1 (unimolecular)



For most primary alkanol and methanol the formation of
primary carbocation is very slow because of the poor accommodation
of positive charge. Hence, bimolecular attack is un hindered

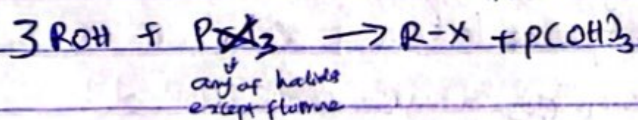
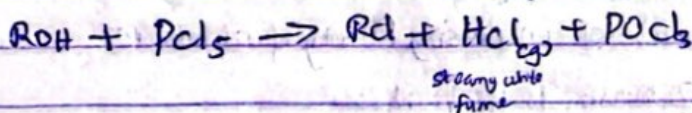
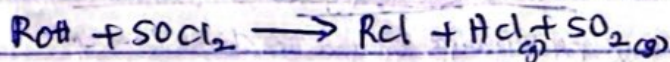
1-2 SN2 is fast



2 species in the slow step showing that the mechanism is bimolecular.

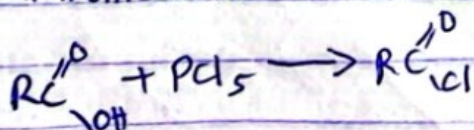
7th May, 2024

Alcohol can also be converted to alkyl halides by reaction with thionyl chloride (SOCl₂) or phosphorus pentachloride (PCl₅) or PCl₃



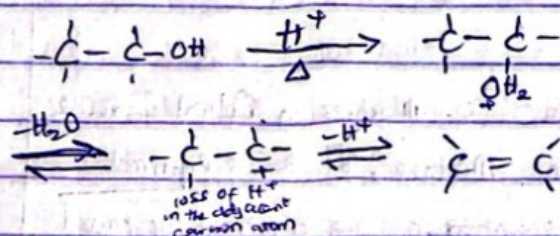
The advantage of the ~~fast~~ ^{third} reaction over others is that it does not contain contaminant as gases.

The steamy white fumes with PCl₅ indicates presence of OH group in a compound, especially alcohols and alkanonic acid

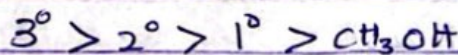


② Dehydration of Alcohols: ~~It~~ It gives alkenes, if there is a total dehydration or alkoxyalkanes if there is partial dehydration.

The common reagent for dehydration is conc. H₂SO₄ or H₃PO₄ (orthophosphoric acid or phosphoric acid). Also, alumina (Al₂O₃), with heat

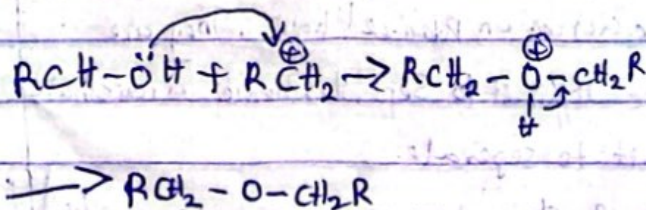


* Order of dehydration

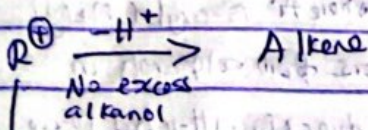
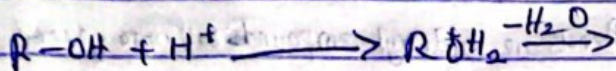


The reaction in the absence of a nucleophile (excess conc. H₂SO₄) gives olefin. The intermediate carbocation may rearrange to a more stable one in form of 1, 2 hydride shift or 1, 2, allyl shift before losing a proton in the adjacent carbon atom to form olefin.

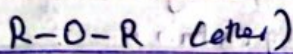
The above carbocation is susceptible to attack by nucleophile, hence if excess alcohol is used, the alcohol may act as the nucleophile because of the excess lone pair of lone pair of electron on the oxygen atom



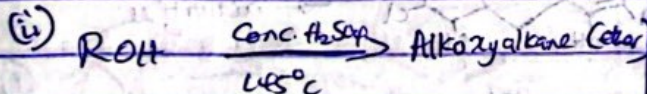
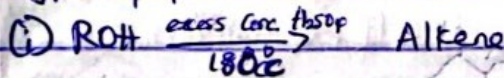
General Reaction



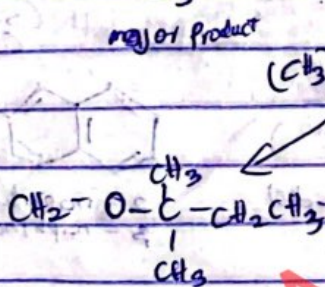
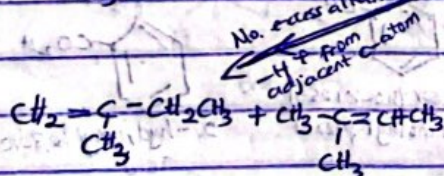
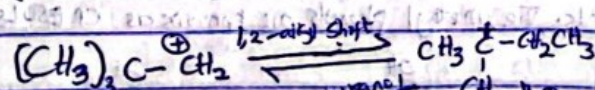
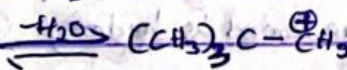
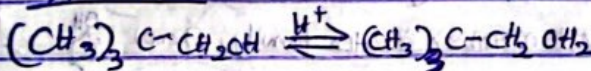
with excess alcohol (ROH)



Depending on the condition of dehydration, alcohols may give two types of product

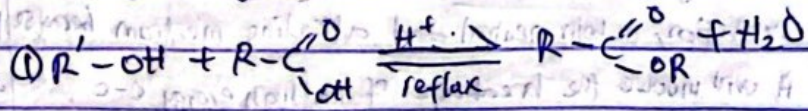


Examples

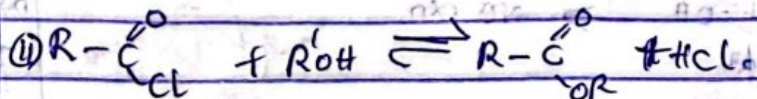


(3) Formation of Esters (Esterification)

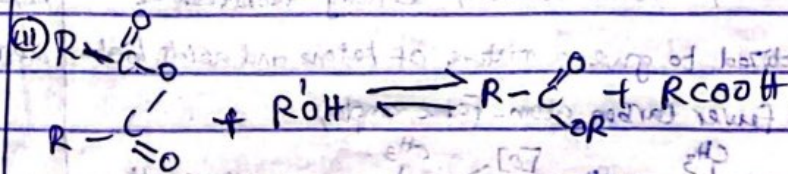
Alcohols and carboxylic acid reacts in the presence of mineral acid e.g. conc. H_2SO_4 as a catalyst to give esters



Alcohol can also react with acid chloride



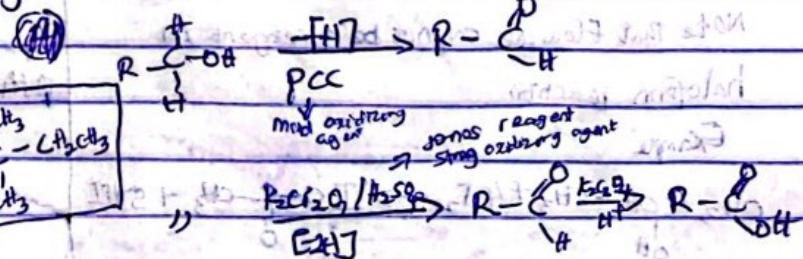
acid chloride



acid anhydride

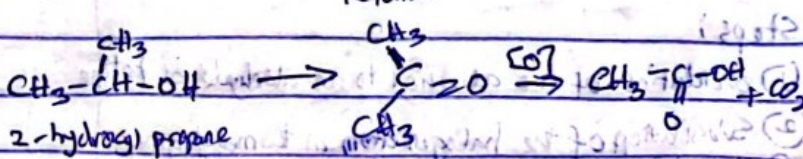
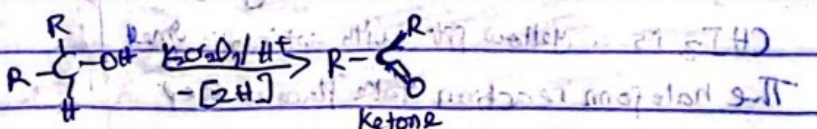
8th May 2024

Oxidation
Alcohols can be oxidized by various oxidizing agent; (i) Aldehyde (ii) ketone (iii) carboxylic acid, depending on the nature of the alcohol and the strength of the oxidizing agent used



Secondary alcohol are oxidized to ketone

Under normal condition

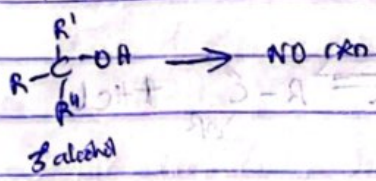


9JABAZING

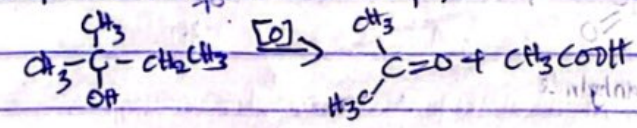
The ketone formed has to undergo prolonged and

drastic treatment because it can be broken down into carbonyl compounds with smaller number of carbon atoms

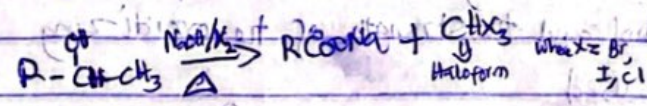
Tertiary alcohols are normally resistant to oxidation, in both neutral and alkaline medium because it will involve the breakage of the high energy C-C bonds in the alcohol



However, in acidic solutions, tertiary alcohol can be oxidized to give a mixture of ketone and acids, both with fewer carbon atom. For example,

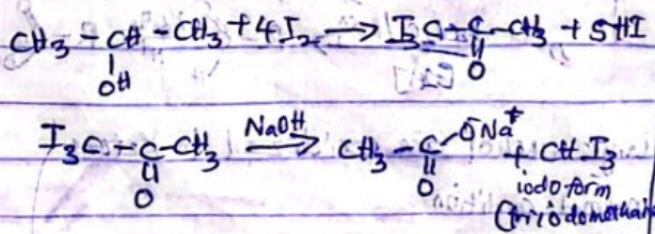


⑤ **Haloform Reaction:** Alcohols which contain the group $CH_3CH(OH)$ can be oxidized under suitable conditions to $CH_3C(=O)$. This group of alcohol will readily undergo haloform reaction.



Note that Fluorine cannot be a reagent in haloform reaction

Example



CHI_3 is a yellow ppt with antiseptic smell

The haloform reaction take place in step

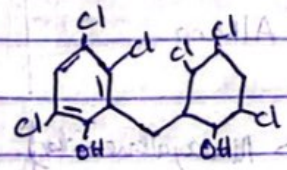
steps:

- oxidation of the alcohol to an aldehyde or ketone
- substitution of the halogen atom in the methyl group
- hydrolysis under alkaline condition to form the haloform.

Phenol

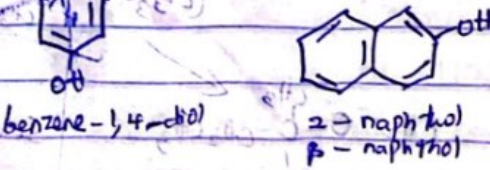
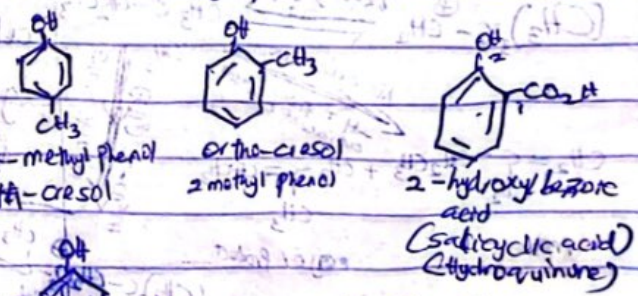
Phenols are hydroxyl compounds with general formula $Ar-OH$, where Ar is aryl or phenyl group. Phenols, differs from alcohols in having the -OH group directly attached to an aromatic ring. Like alcohols, they may be monohydric or polyhydric, depending on the number of OH group that they contain.

The chemistry of phenol is very different from that of alcohols. A phenolic compound hexachlorophene is constituent of mouth washes, deodorant soap and medicinal skin cleanser



Acts on anti-bacteria activities

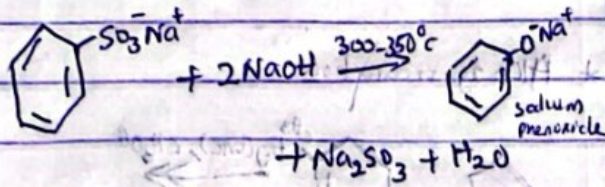
Phenols are generally named as derivatives of the simplest member of the family, phenol. Occasionally, phenols are named as hydroxy compounds. The methyl phenols are known as CRESOLS



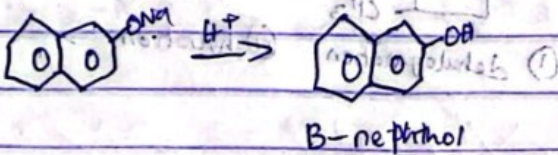
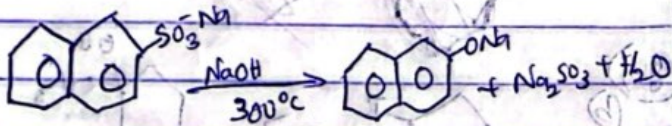
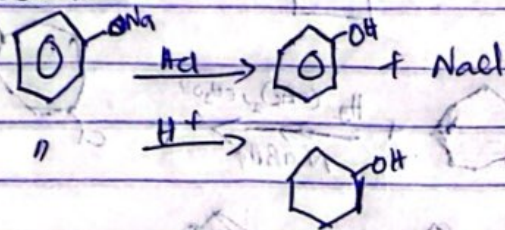
10th May, 2024

Preparation of Phenol

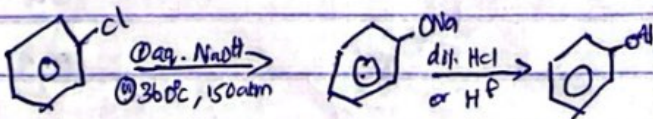
(1) By Diffusion of Aromatic Sulphonic salt with an alkaline solution e.g. NaOH



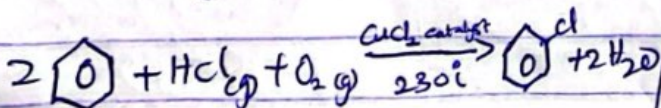
The phenol is obtained as an oily liquid by dissolving sodium phenoxide in a solution of water and acidified.



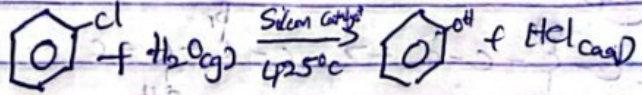
(2) By hydrolysis of chlorobenzene: Hydrolysis of chlorobenzene by aqueous NaOH at 360°C and 150 atm



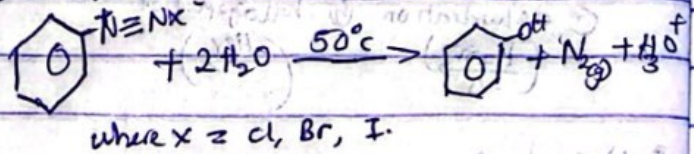
(3) By Raschig process: Here, benzene is chlorinated by passing the vapour together with HCl gas and air over a heated CuCl_2 catalyst at 230°C



The chlorobenzene formed is then catalytically hydrolysed by passing it with steady steam over silicon catalyst at 425°C

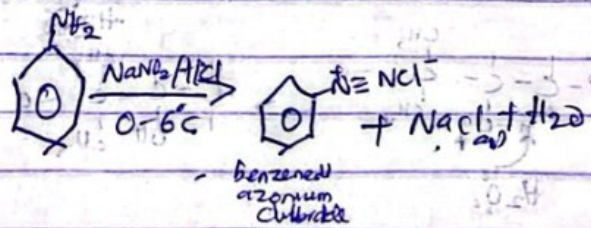


(4) By hydrolysis of diazonium salt: In the Lab, heating of solution of benzene diazonium salt in a water bath at 50°C yields phenol

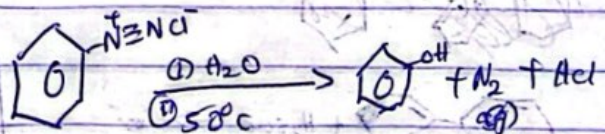


The phenol is recovered by steam distillation and extracted with methoxyethane (diethyl ether) using separating funnel

Primary aromatic amine with cold nitrous acid in the presence of strong mineral acids to give diazonium salt. The process is known as diazotization



Reaction of diazonium salt with water will now give us phenol



Reactions of phenol

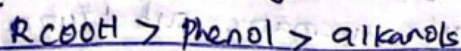
The reactions of phenol includes the following:

- (i) Acidity of Phenol
- (ii) Ether formation (Williamson synthesis)
- (iii) Ester formation
- (iv) Ring substitution reaction e.g. Nitration, Sulphonation, hydrogenation, Friedel-Crafts acylation, coupling with diazonium salt, carbonylation, formylation.

Acidity of Phenol

Phenols are tremendously more acidic than alkanol but Carboxylic acid.

Order of acidity:



This shows that the OH group attached to an aromatic ring is ^{so} more acidic than that attached to an alkyl group.

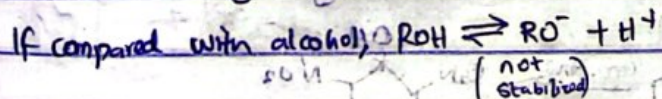
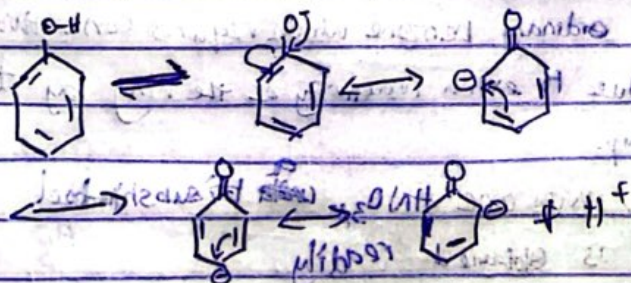
~~Alcohol~~

13th May, 2020

Phenol as an acid:



The reason why phenol is more acidic is because of stabilization of phenoxide ion.



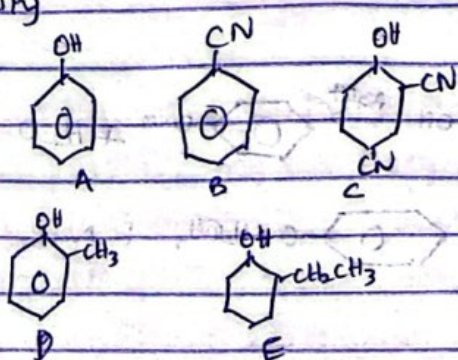
In the resonance stabilization of phenoxide ions, position 2, 4 and 6 i.e. ortho and para position

are more activated than other position, therefore electrophilic attack of the benzene ring will occur at ortho and para position.

Electron withdrawing group such as CN^- , Cl^- , CO_2^- , NO_2 , attached to ortho and para position stabilizes the phenoxide and thus increase acidity.

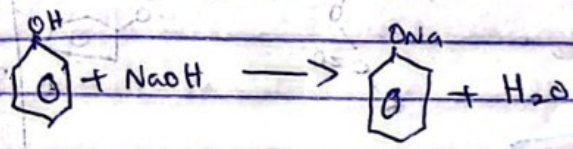
On the hand, electron donating group (EDG) attached to ortho and para

position of phenol destabilizes the phenoxide ion and therefore decreases acidity.

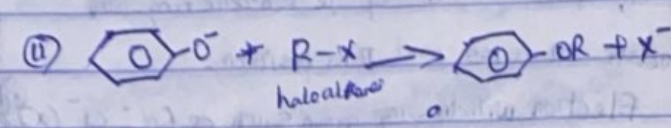
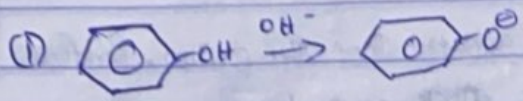


Order of acidity $E < D < A < B < C$

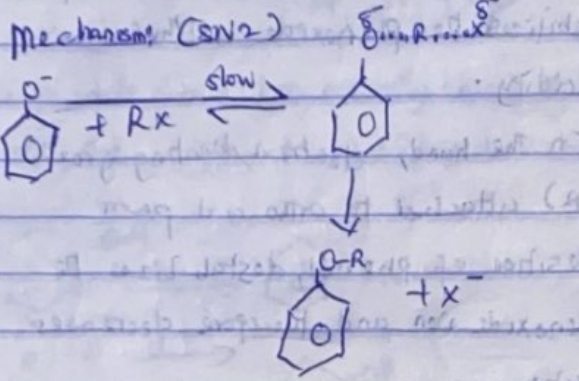
The acidity of phenol is demonstrated by its ability to form salts with alkaline bases such as NaOH / KOH.



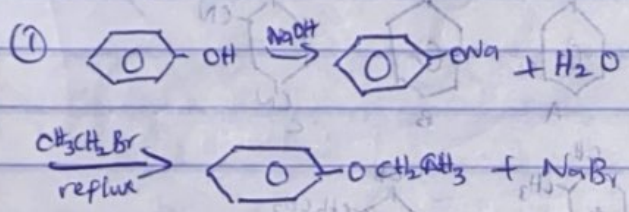
(2) Williamson's Synthesis (formation of ether); phenols in the presence of alkaline base (NaOH / KOH) reacts with haloalkane to form alkyl phenyl ether.



This is an SN2 reaction

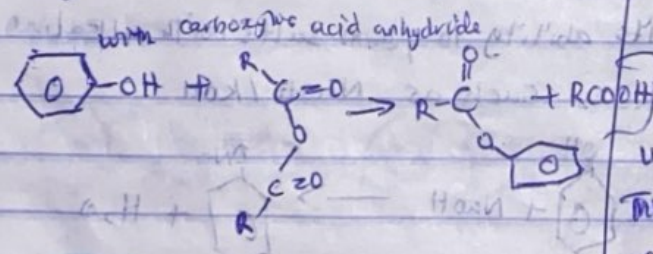


Example

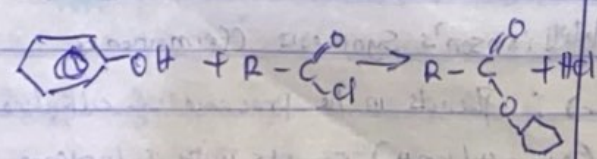


(5) Ester formation

Phenols reacts with carboxylic acid anhydride (RCO)₂, acetyl chloride R-CO-Cl to form esters



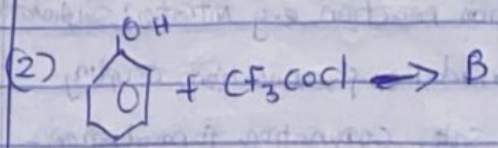
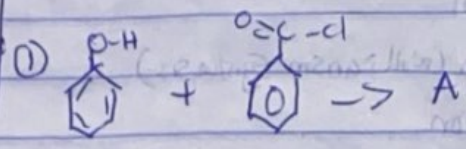
with acetyl chloride



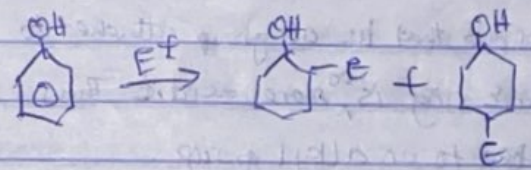
The second reaction is preferable because it does not need separation of products

ortho & para position are between phenol

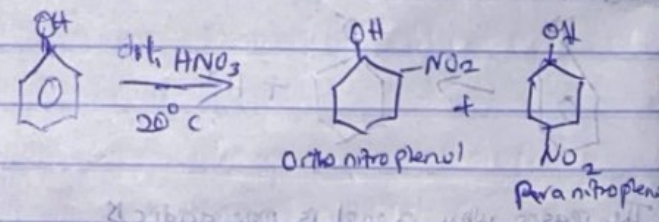
as HCl has been eliminated as a gas



(H) Ring Substitution: The OH group attached to the benzene ring in phenol activate the ring powerfully and direct ortho and para in electrophilic aromatic substitution

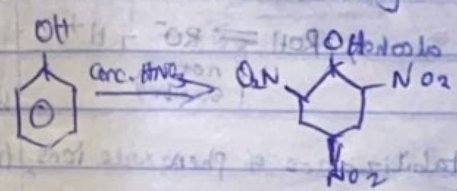


① Nitration: Monosubstituted compound is obtained with dilute HNO₃ at room temperature



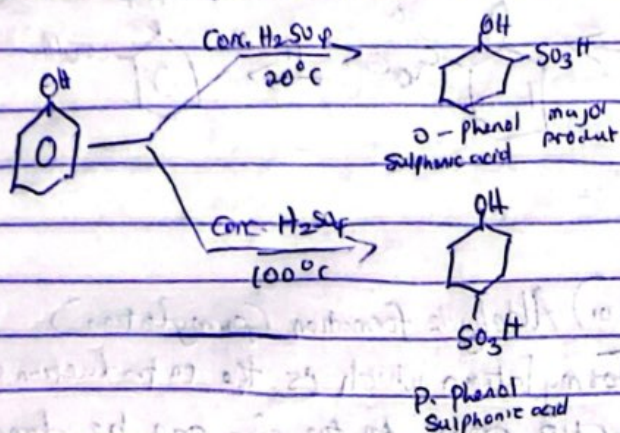
Dilute HNO₃ at 20°C will activate the reaction unlike ordinary benzene which requires conc. HNO₃. This is due to extra reactivity of the ring by the -OH group.

However, with conc. HNO₃ a trisubstituted product is obtained readily



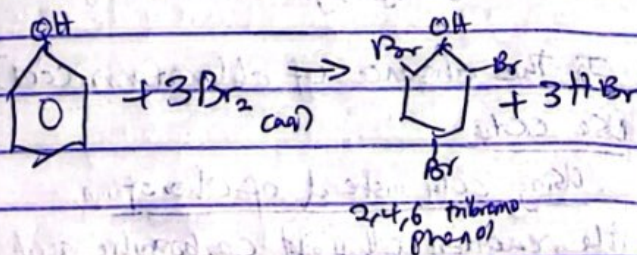
2, 4, 6 trinitrophenol

(i) Sulphonation: When phenol is treated with conc. H_2SO_4 . Different substituted product will be obtained depending on the reaction temperature.

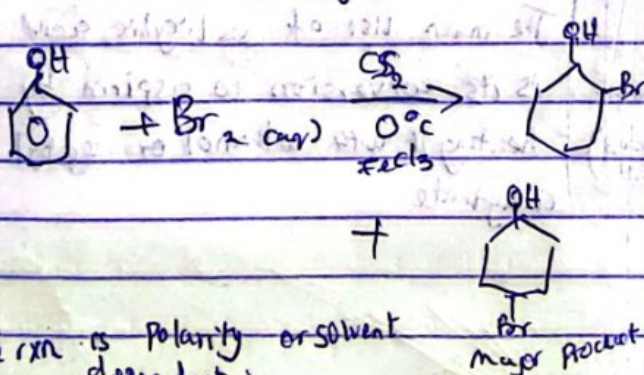


The product is temperature dependent. Raising the temperature of the product to $100^\circ C$ will yield the para product.

(ii) Halogenation: Phenol reacts with aqueous solution of halogens to give polysubstituted product.



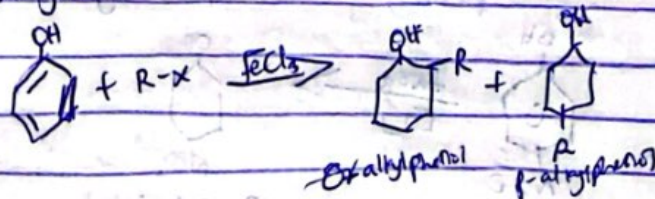
If the reaction is carried out in a solvent of low polarity such as CCl_4 , CS_2 and chloroform ($CHCl_3$) the reaction can be limited to monohalogenation.



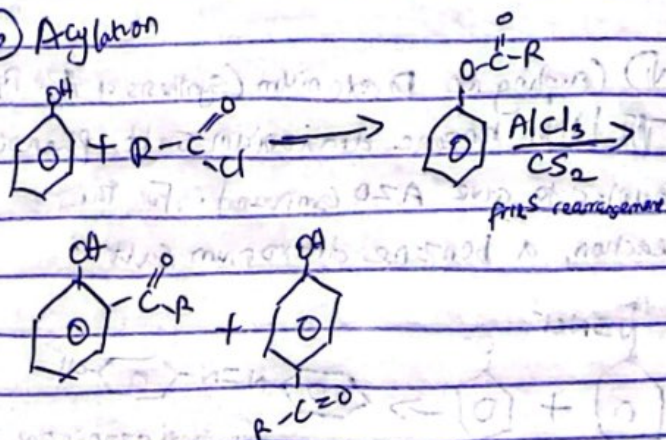
The rxn is polarity or solvent dependent.

(iv) Friedal-Crafts Alkylation/Acylation

(a) Alkylation



(b) Acylation



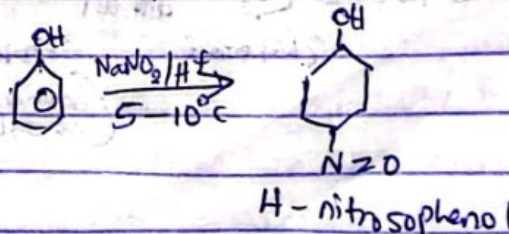
Acylation is used for the preparation of phenolic ketones and this preparation occurs by means of Fries rearrangement instead of direct substitution on the ring.

It goes through two steps;

- (1) formation of ~~ortho~~ phenyl ester
- (2) migration of the acyl group from the phenolic oxygen to the ortho and para position of the ring.

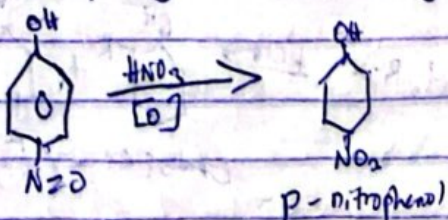
The rearrangement appears to involve generation of acylium ion ($R-C^+=O$) which then attacks the ring, as in ordinary Friedal-Craft reaction.

(v) Nitrosation

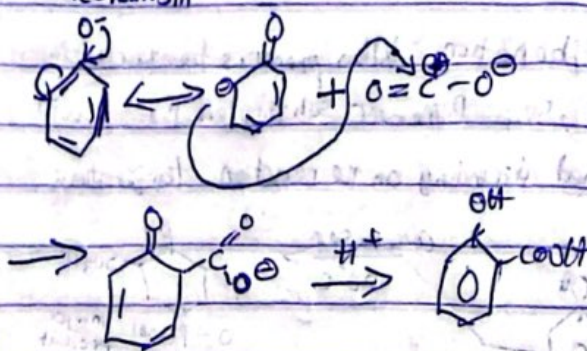


The nitroso product is readily oxidized to

the corresponding nitro compound by HNO_3

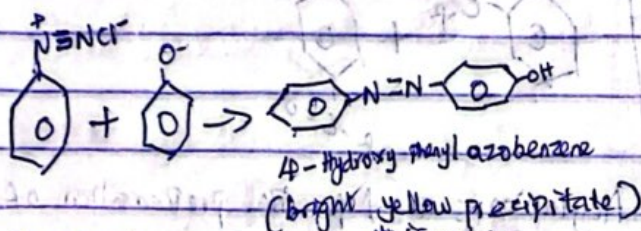


Mechanism



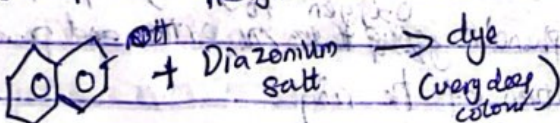
(vi) Coupling of Diazonium (Synthesis of Azo Dyes)

When benzene diazonium salt, phenol couples to give Azo compound. For this reaction, a benzene diazonium salt



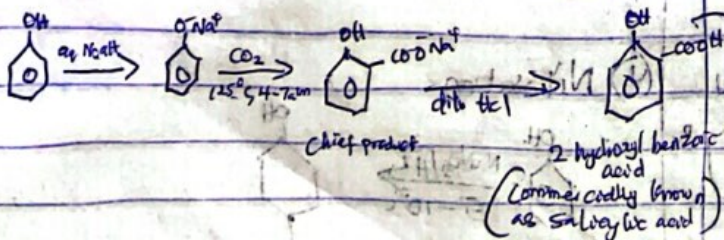
Note: In preparation of dye
 Any phenol + Diazonium salt \rightarrow dye

This reaction is very important in dye stuff industry because Azo compounds have very deep colors



(vii) Carbonation (Kolbe-Schmitt reaction)

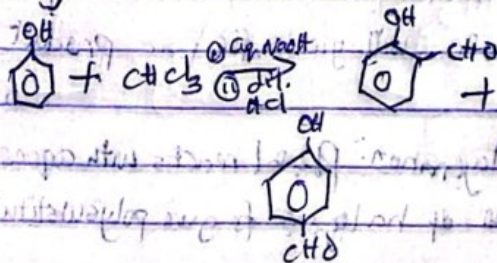
Sodium phenoxide is heated with carbon dioxide



(viii) Aldehyde formation (Formylation)

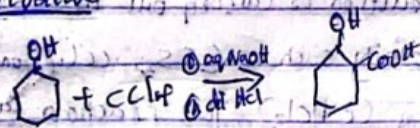
Formylation which is the introduction of $-CHO$ group to the ring can be done in two ways

(a) By Reimer-Tiemann reaction

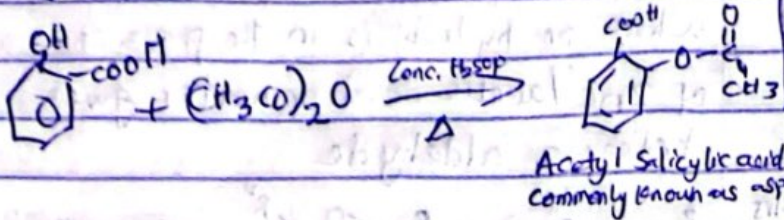
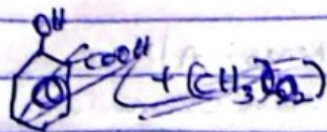


In the absence of chloroform (CCl_4) use CCl_4

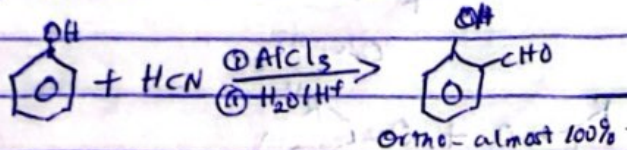
Using CCl_4 instead of chloroform, the reaction will yield carboxylic acid derivative



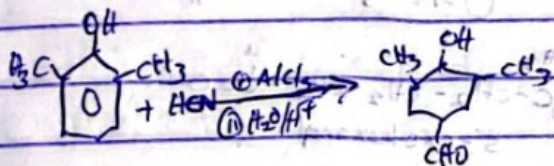
The main use of salicylic acid is its conversion to aspirin by heating it with ethanol or acetyl anhydride



(b) Gattermann-Koch reaction

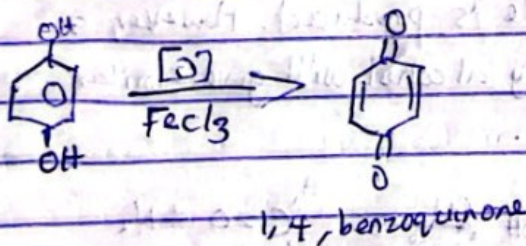


If the ortho position of phenol is blocked by a group, then, formylation may be caused to form at the para position.

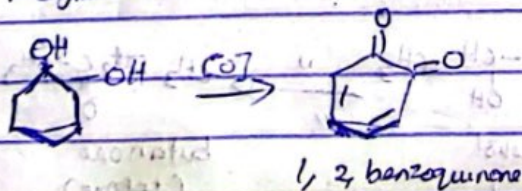


(12) Oxidation

Phenols are easily oxidized by $FeCl_3$ or $K_2Cr_2O_7/H^+$ to quinones

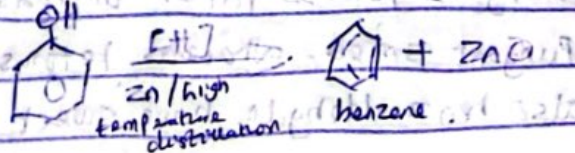


Assignment



Reduction

Phenols are reduced to the corresponding aromatic hydrocarbon by distilling it at high temperature

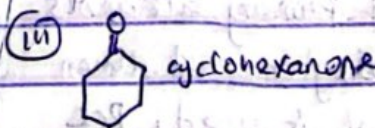
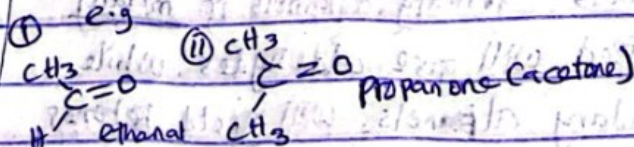
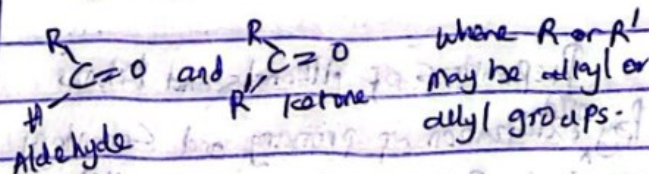


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Carbonyl Compounds

Carbonyl compounds consists of aldehydes and ketones as they both contain $C=O$ functional group.

This carbonyl functional group in both aldehyde and ketone are sp^2 hybridized



Therefore, they have σ and π bonds.

They are generally very reactive because of the π bond and the polarization of $C=O$ bond. However, aldehydes are generally more reactive, being more easily oxidized and also more susceptible to nucleophilic addition reaction i.e. electrophile

Physical Property of Aldehyde & Ketone

Note interest

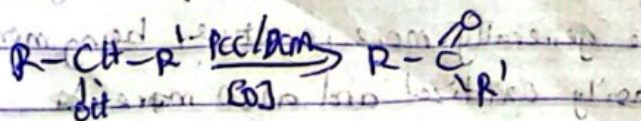
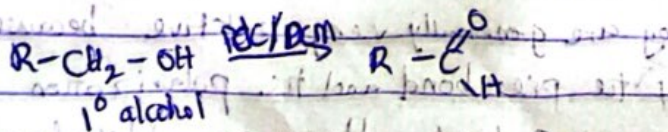
① They are mostly colourless liquid at room temperature, especially the simple aldehydes and ketone. The lower aldehydes possess rather unpleasant pungent smell, whereas ketones and also benzaldehyde have sweet odours.

② The lower aldehydes and ketones are appreciably soluble (miscible) in water due largely to their ability to form hydrogen bond with the water molecule.

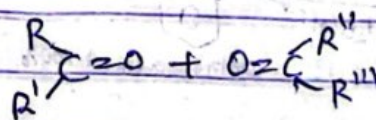
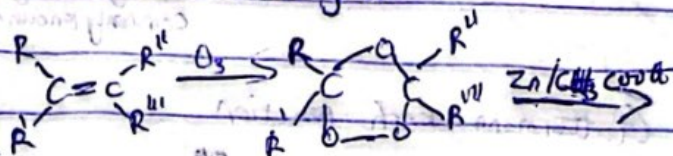
③ The lower aliphatic aldehyde and ketones have higher boiling points because of hydrogen bonding.

Preparations of Alkanals and Ketones

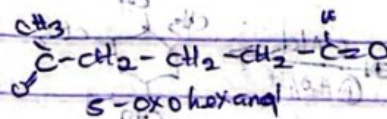
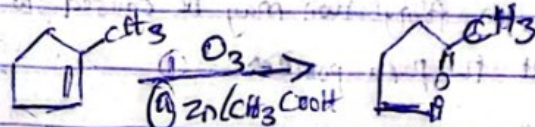
① By mild oxidation of primary and secondary alcohols: Primary alcohols if mildly oxidized will give aldehydes while secondary alcohols will yield ketones. However, oxidation of primary alcohols often lead to carboxylic acid when strong oxidizing agent is used, PCC or PDCM is a better oxidizing agent on the conversion of alcohols.



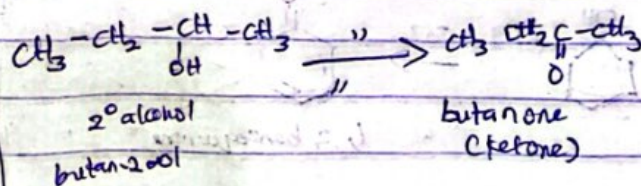
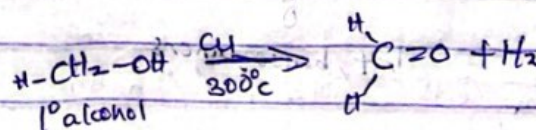
② By ozonolysis of Alkenes: Alkenes reacts with ozone to form ozonide which on hydrolysis in the presence of zinc/acetic acid or water gives ketone or aldehyde.



e.g

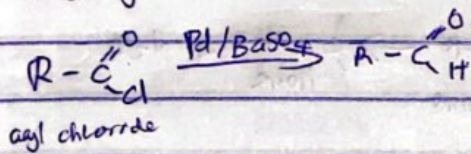


③ Catalytic hydrogen of alkanol: When vapour of primary alcohol is passed over heated copper, a corresponding aldehyde is produced. However, a secondary alcohol will give similar reaction.



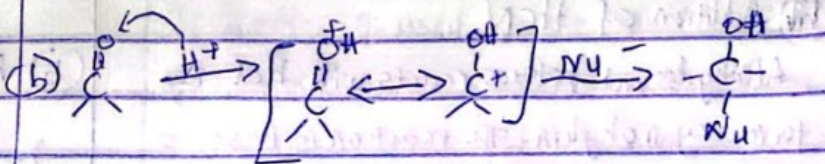
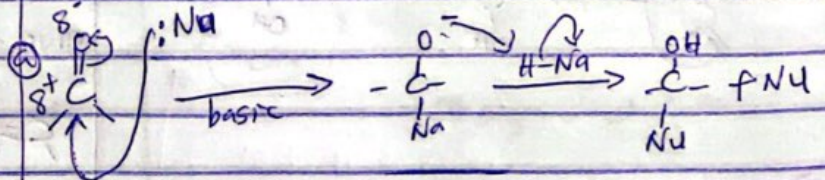
17th May, 2023

(4) Reduction of Acyl chloride (For aldehydes only): Ketones can not be prepared with this method. Acyl chloride is hydrogenated in the presence of Pd supported over $BaSO_4$. In practice, the Pd catalyst is poisoned with sulphur to prevent the reduction process from going to alcohol.



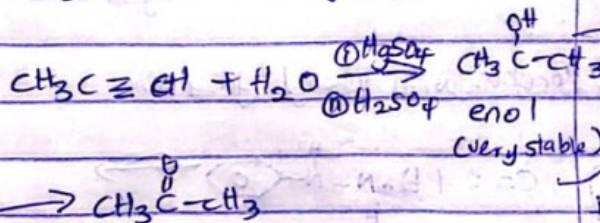
This reaction is referred to Rosenmund reduction

Chemical Reactions of Aldehydes & Ketones
 (1) Nucleophilic Addition: Aldehydes and ketones undergo mostly nucleophilic addition. This is the addition of nucleophile and proton across the polarized $C=O$, the nucleophilic addition can occur in both basic and acidic medium

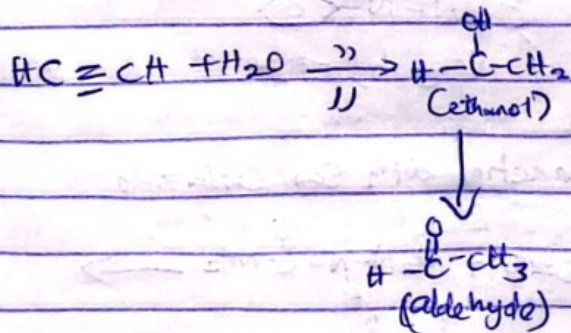


(5) Hydration of Alkyne: Methyl ketones can be prepared by hydration of terminal alkynes in the presence of Mercury salt as catalyst

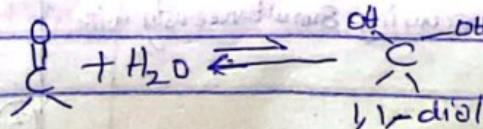
(A) Based catalyzed addition: Here, a strong nucleophile attacks the carbonyl to form an alkoxide which is then protonated.



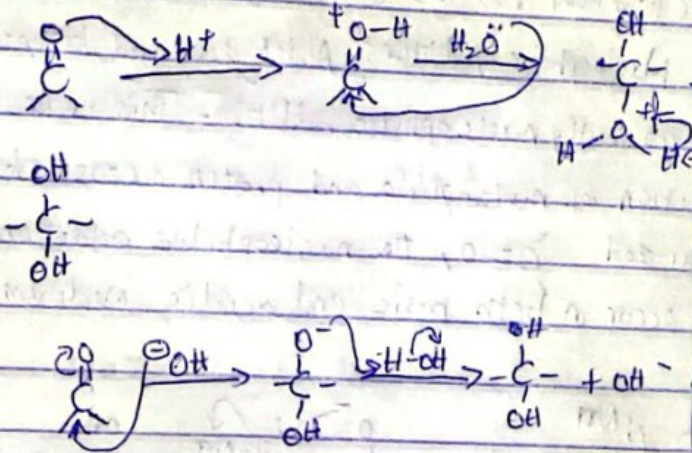
(B) Acid catalyzed addition: Here, the acid protonates the carbonyl oxygen after which weak nucleophile attacks the carbonyl



(P) Hydration of Aldehydes and Ketones: Aldehydes and ketones react with water in both acidic and basic medium to form 1,1, diols, i.e. a geminal diol. The reaction is reversible and the backward reaction is more favoured.



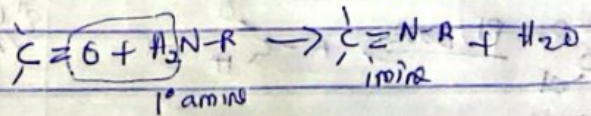
Mechanism



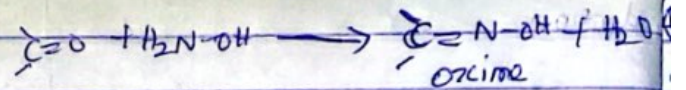
② Reaction of Ammonia Derivatives

Some derivative of ammonia reacts with aldehyde and ketone to form compound with elimination of water molecule

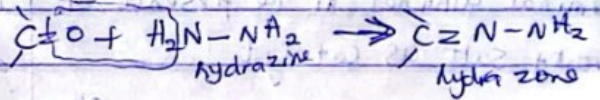
(a) Reaction with Primary Amine: Primary amine reacts with aldehyde and ketone to give imine



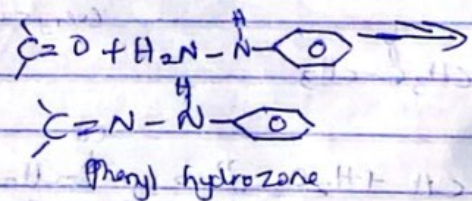
(b) Reaction with hydroxylamine (H₂N-OH)



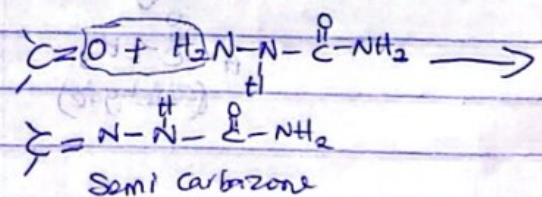
(c) Reaction with hydrazine (H₂N-NH₂)



(d) Reaction with phenyl hydrazine



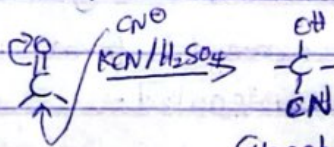
(e) Reaction with semi carbazide



(3) Reaction with Alcohol: Aldehyde and ketone react with equivalent alcohol to form acetals

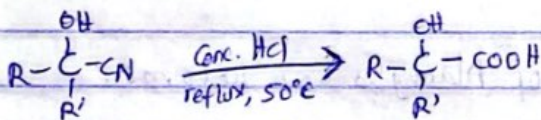
(i) Addition of HCN

Aldehydes and ketones reacts with HCN to form cyanohydrin. The reaction is base catalyzed, a poisonous gas is generated in situ by the action of dilute H₂SO₄ on KCN or NaCN

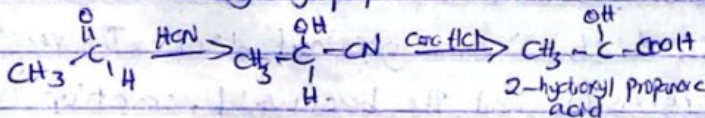


Cyanohydrin (hydroxy alkanonitrile)

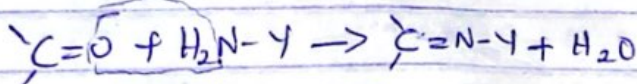
Like other nitriles, 2-hydroxy alkanonitrile can be hydrolyzed to form the carboxylic acid derivative. In this case, the 2- or α-hydroxy acids



To form 2-hydroxy propanoic acid

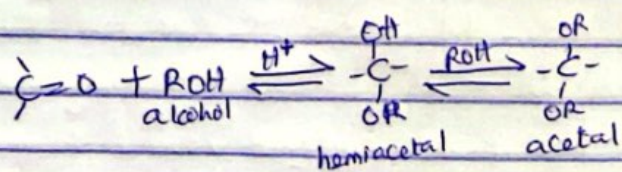


(ii) Addition reaction occurring simultaneously with the loss of water

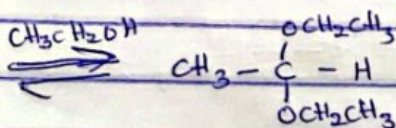
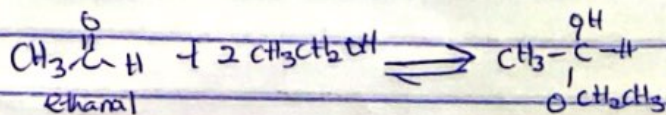


Y = 2,4 DNP
 = OH (H₂N-OH) - hydroxylamine
 = NH₂ (H₂N-NH₂) - hydrazine

which are geminal di'ether

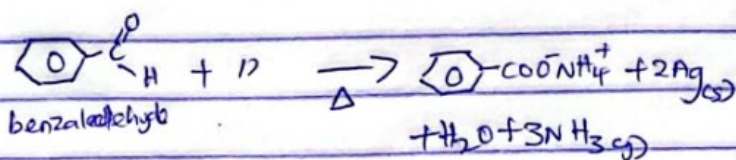
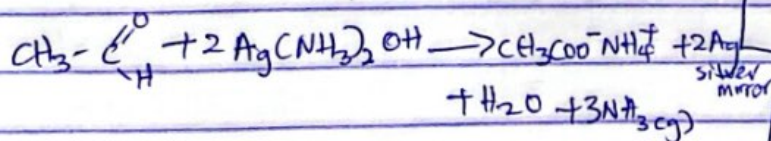


Example



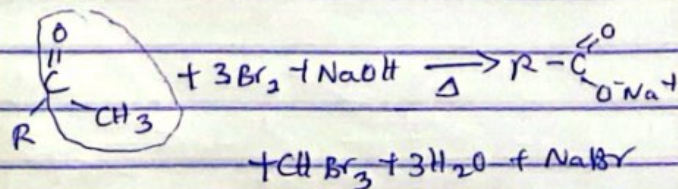
Ⓐ Reactions with Tollen's Reagent: This reaction is for aldehydes only. Aldehyde reacts with Tollen's reagent to give a deposit of silver (silver mirror test), to differentiate between aldehydes and ketones. The reagent consists of a solution of silver nitrate in excess ammonia solution. Aldehydes reduce the Ag^+ to Ag, which is precipitated and forms a mirror effect in the bottom of a test tube.

Ethanal reacts almost immediately, but with benzaldehyde, the reaction mixture requires warming, but ~~does not~~



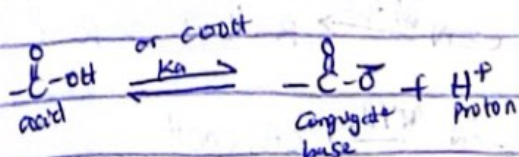
Ⓐ Halofrom Reaction: Compounds with methyl carbonyl group such as ethanal and

Methyl ketones or any group that can be oxidized with alcohol will react rapidly with halogen ($\text{Cl}_2, \text{Br}_2, \text{I}_2$) to form haloform and a salt of carboxylic acid

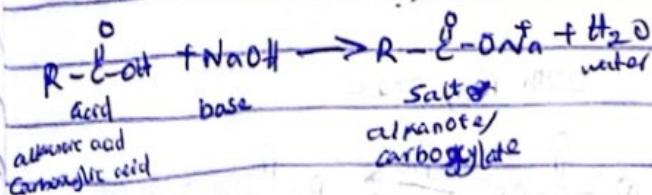


If Iodine is used, it gives yellow precipitate with a characteristic, ~~odour~~ and distinguishable odour. This is a diagnostic test for methyl carbonyl compound.

Carboxylic Acid

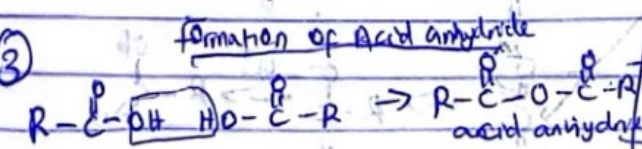
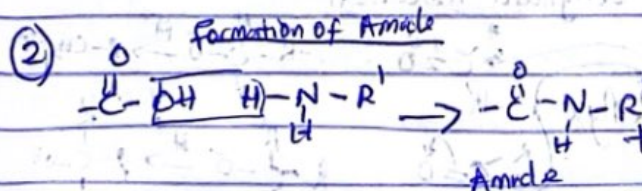
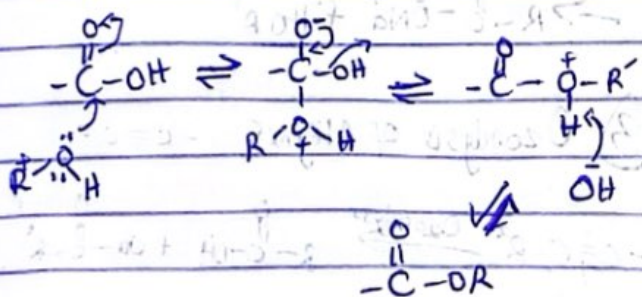
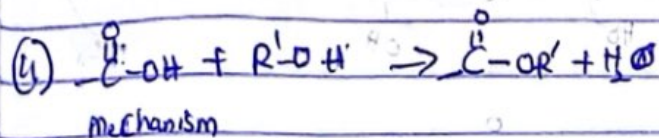
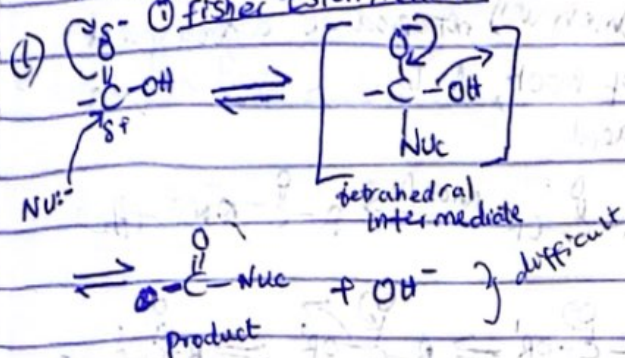


cooh can be involved in acid-base reaction



Nucleophilic Acyl Substitution

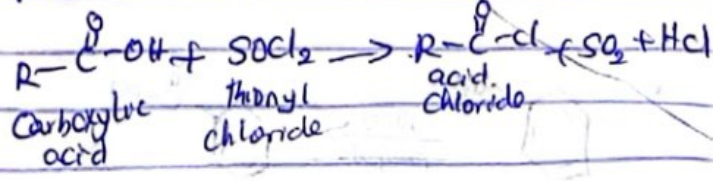
Fischer Esterification



Formation of Acid Chloride

Assignment
Write the mechanism for the formation of acyl chloride.

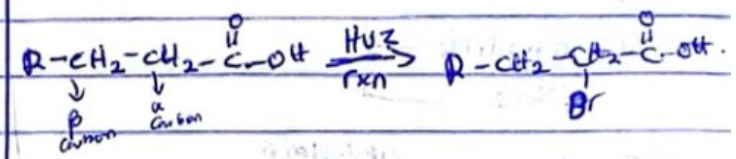
PCl₅ Reaction



Fischer esterification is difficult, this is easy
Carboxylic acid \rightarrow acid chloride \rightarrow ester

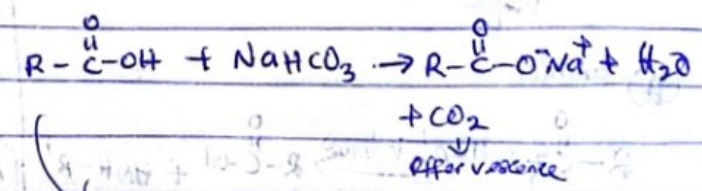
23rd May, 2021

Hell-Volhard-Zelinsky Reaction



Assignment

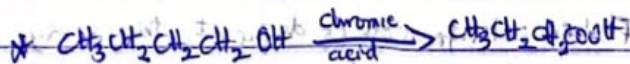
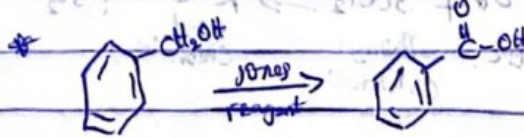
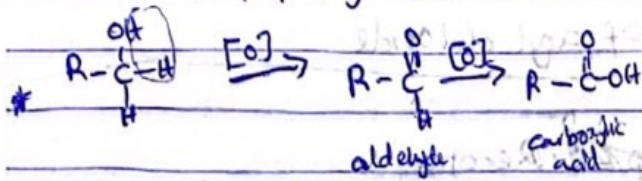
Write the mechanism for Hell-Volhard-Zelinsky reaction



This reaction is used to test for Carboxylic acid.

Preparation of Carboxylic Acid

① Oxidation of primary alcohol



② Hydrolysis of Carboxylic acid derivatives

Carboxylic acid derivatives;

ester

amide

acid chloride

acid anhydride

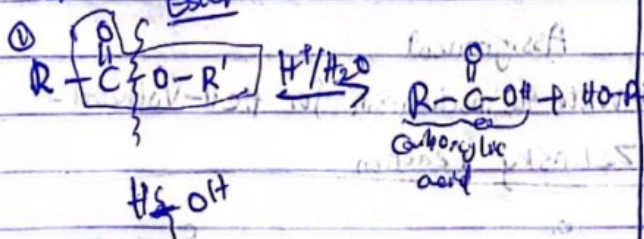
Nitrile

hydrolysis

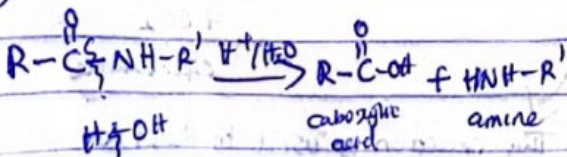


using water to split

Example

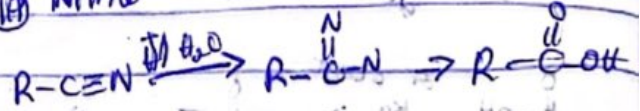


② amide

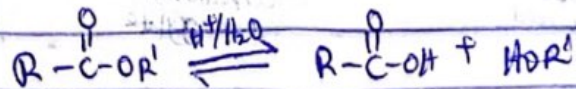


Hydrolysis of esters happens faster than amides

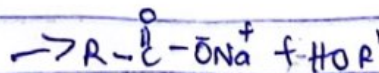
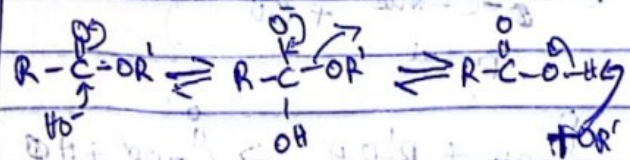
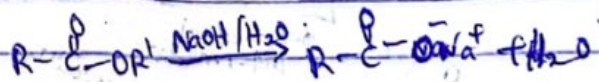
③ Nitrile



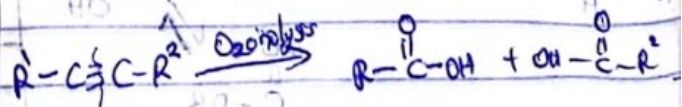
27th May, 2024



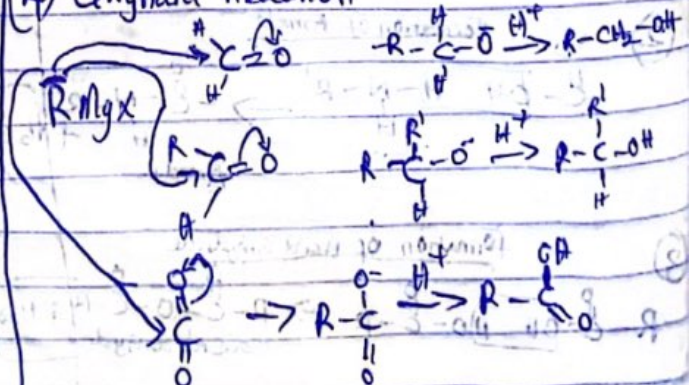
This reaction occurs at equilibrium which will not produce a good yield of RCOOH. A base is used instead of acid.

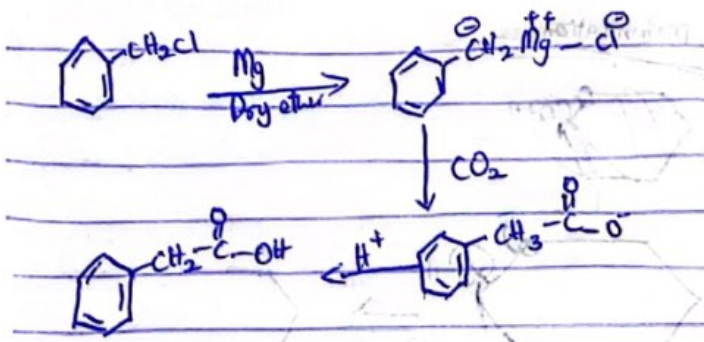


③ Ozonolysis of Alkynes -C≡C-

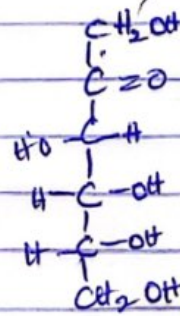


④ Cannizzaro Reaction



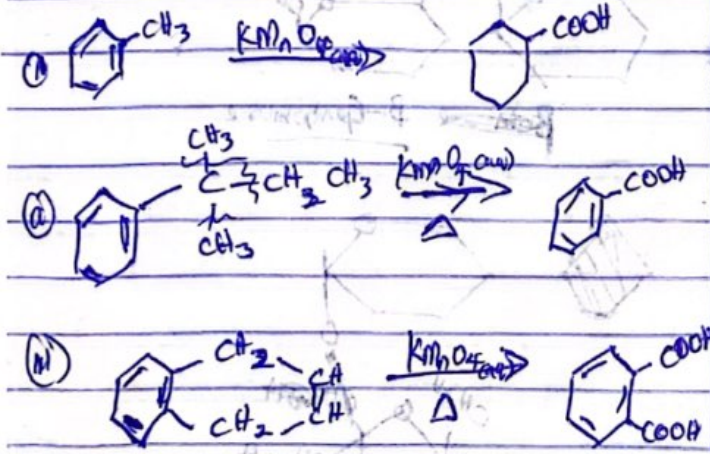


Keto-hexose

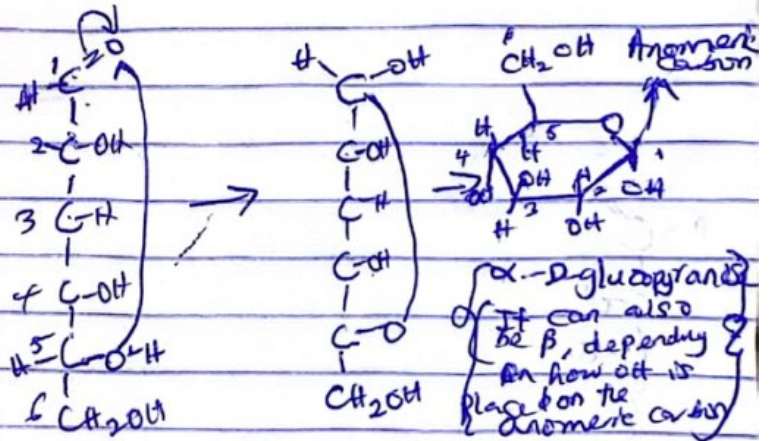


α -fructose

5) Oxidation of benzenes with Alkyl Substitution



(1) mutarotation : fisher \rightarrow Haworth



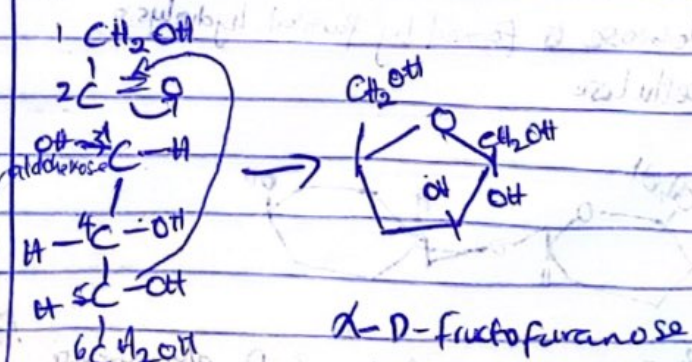
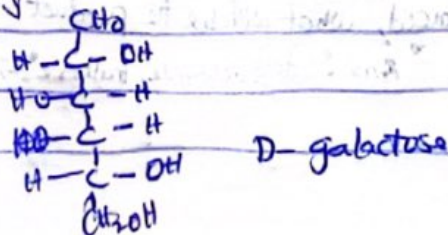
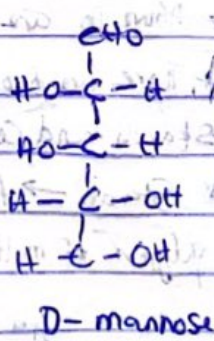
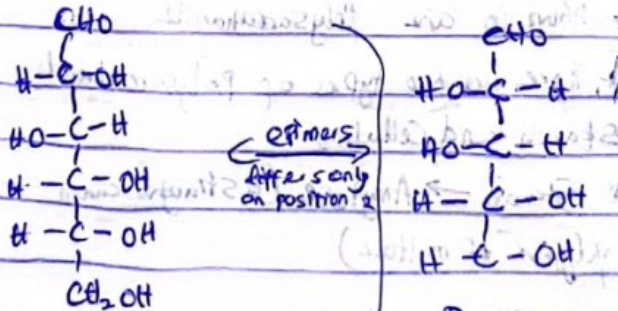
α -D-glucopyranose
 It can also be β , depending on how OH is placed on the anomeric carbon

Carbohydrates

Classification of carbohydrate can be based on functional group (aldehyde and ketone) which are aldoses or ketoses.

Anomeric reaction or hemiacetal reaction

β -D-glucopyranose - 64%
 α -D-glucopyranose - 36% } because of anomeric effect



1.0 CHEMISTRY OF CARBOHYDRATES (SECTION ONE)

This section gives a simple treatment of the Chemistry of Carbohydrates. It provides concise information on this class of Chemistry and suitable for beginners.

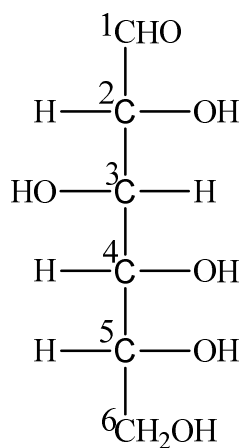
Carbohydrates are natural products with general a formula $C_n(H_2O)_n$. Other names for carbohydrates are also saccharides. This very large family includes monomers - called simple sugars or monosaccharides up to very large molecules (complex) called polymers which are made up of these simple sugars. The polymers are also called polysaccharides such as starch, cellulose, dextrin and glycogen.

1.1 *Classification and nomenclature of monosaccharide*

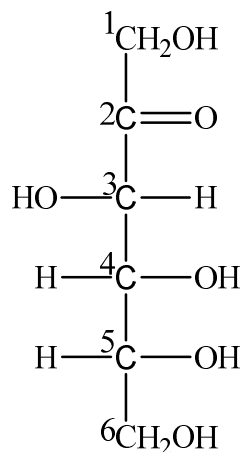
1.1.1 *Monosaccharides*

Monosaccharides are chiral polyhydroxyalkanals or polyhydroxyalkanones which are the cyclic hemiacetal forms of these sugars. This class of saccharide is divided into two major groups depending on whether their acyclic forms contain an aldehyde functional group or a keto functional group which are aldoses or ketoses, respectively.

Aldoses and Ketoses: All monosaccharides have their names end with “*ose*” hence, they are divided into aldoses that is aldehyde plus ose) and ketoses (ketone plus ose). For example, glucose is an, aldose while fructose is a ketose (Figures 1.0 a & b).



Glucose "a" (an aldose)



Fructose "b" (a ketose)

Figure 1.1 a & b: Structures of D-glucose and D-fructose

The above structures are the *Fischer projections* of these monosaccharides. The aldehyde functional group (carboxaldehyde carbon) of an aldose is assigned number 1 and the primary alcohol group (-CH₂OH) assigned the last number.

The simple sugars can also be classified according to the number of carbons that they contain. Both glucose and fructose given in Figure 1.1 a & b above contain six carbons each, hence they are both **hexoses**. If both classifications (functional groups and number of carbons) are combined, then glucose will become an **aldohexose** and fructose a **ketohehexose**.

1.2 *Glyceraldehyde and dihydroxyacetone*

The simplest carbohydrates - glyceraldehyde and dihydroxyacetone, which are **aldotriose** and a **ketotriose**, respectively (Figure 1.2 a & b). All series of aldoses and ketoses are built from glyceraldehyde and dihydroxyacetone, respectively.



Figure 1.2 a & b: Structures of a glyceraldehyde and dihydroxyacetone

1.3 D - and L - Monosaccharides

Using Fischer projection, the first carbon is a carbonyl carbon for aldose and the second carbon is carbonyl for ketose. If the last **chiral carbon** has its hydroxyl group on the right, the sugar is designated **D - sugar** but if it is on the left, it is a **L - sugar**. See Figure 1.3.1 a & b below:

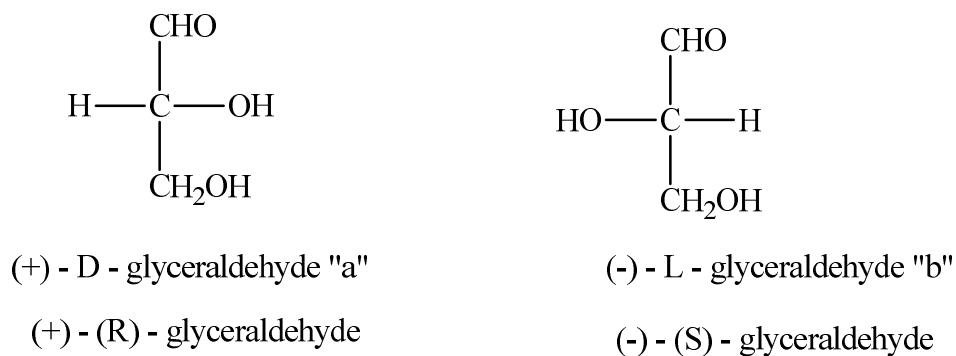


Fig 1.3.1 a & b: Structures of D- and L - glucose

The Figure 1.3 a & b shows that L - Glucose is an enantiomer of D - Glucose.

The simplest sugar is glyceraldehyde (C₃H₆O₃). Because it contains three carbons, it is a triose, and it is an aldotriose because its first carbon is an alkanal.

Emil Fischer assigned the configuration (-) - glyceraldehyde to glyceraldehyde drawn using Fischer projection if the hydroxyl group of the only chiral carbon is on the left which called “**L**” (*laevo*). When the hydroxyl group is on the right of the chiral carbon, he called it “**D**” (*dextro*).

These two enantiomers of glyceraldehyde were later assigned “**S**” (*sinister*) for L - configuration and “**R**” (*recutum*) for D - configuration.

Any molecule that contains n chiral centres will have 2^n stereoisomers provided no meso compounds are present. For example, if there two chiral centres, hence $2^2 = 4$, which means four carbon sugars (aldotetrose). Their structures are given in Figure 1.3.2 a, b, c & d below:

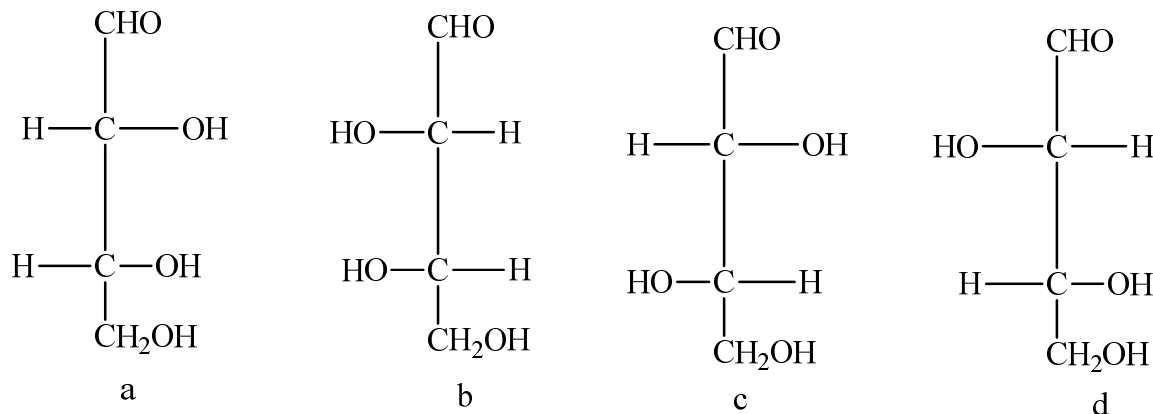


Figure 1.3.2 a, b, c & d: Structure of the stereoisomers of aldotetrose

These four aldotetroses were obtained by inserting **-HCOH-** between carbonyl carbon and the next chiral carbon of both L - glyceraldehyde and D - glyceraldehyde and the mirror image of each will give the other two compounds to make four aldotetroses given above.

1.3 Epimers

An epimer is one of a pair of **diastereomers**. Epimer occurs when two molecules have different configuration at only one chiral centre. That is all other chiral centres in the molecule are the same except one chiral centre. Examples are D - Glucose and D - Mannose (Figure 1.4 a & b).

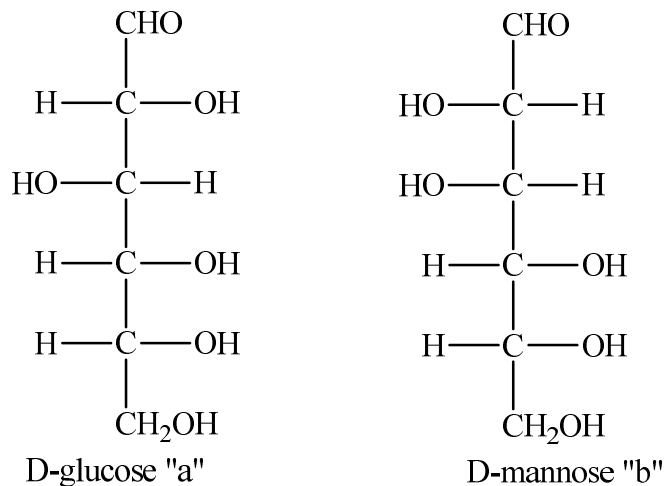


Figure 1.4 a & b: D-glucose and D-mannose

Diastereomer

This term is used to describe two molecules that are stereoisomers with the same formula, connectivity but different arrangement of atoms in space but are not enantiomers. That is the two molecules are not mirror images of each other or non-identical stereoisomers. They occur when two or more stereoisomers of compound for example sugar have different arrangement of atoms at one or more chiral centres but not at all centres which makes them not to be superimposable. If this different is at only one chiral centre, they are called *epimers*.

The simplest ketose, dihydroxyacetone (Figure 1.5) lacks a chiral centre. Insertion of **-CH(OH)-** unit between the carbonyl carbon (carbon number 2) and the third carbon creates erythrulose (Figure 1.6). The D isomer of erythrulose is the bases of the D-ketose sugar series.

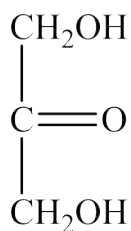


Figure 1.5: Dihydroxyacetone

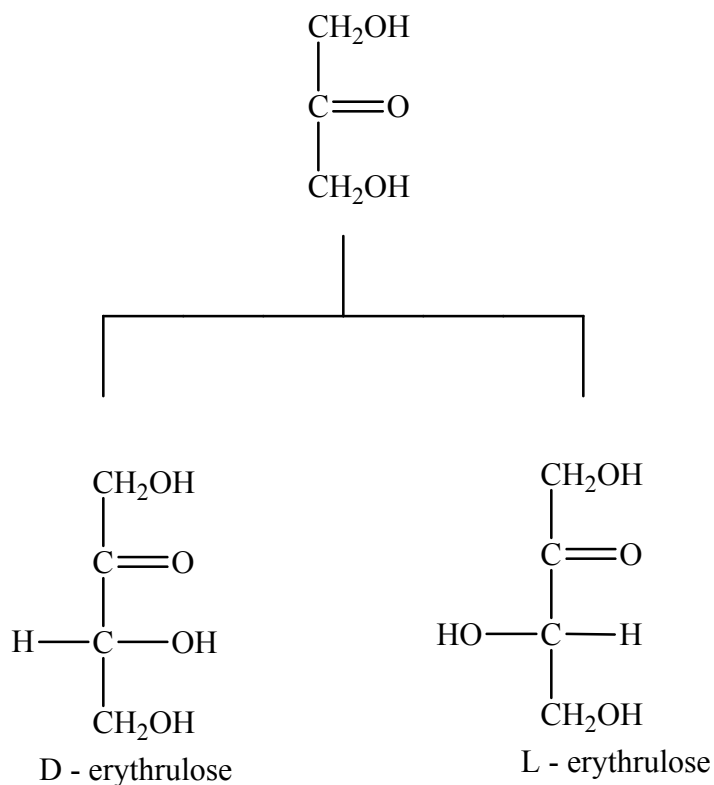


Figure 1.6: Formation of erythrulose from dihydroxyacetone

Ring structure of Monosaccharides

Glucose and other sugars can exist as cyclic hemiacetals or hemiketals. They are formed from intra-molecular reaction of a hydroxy group with a carboxyl group. Glucose and other aldohexoses form their most stable acetal by using the hydroxy group on carbon number 5, and the six-membered ring compound obtained is called the pyranose because it resembles tetrahydropyran (Figure 1.7). Hence, the cyclic form of D-glucose is called D-glucopyranose.

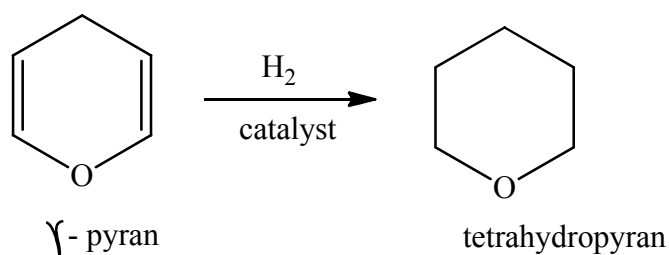


Figure 1.7: Tetrahydropyran from hydrogenation of γ -pyran

The hemiacetal formation or *anomeric reaction* creates a new chiral centre called *anomeric carbon or anomeric centre* that is carbon number one (Figure 1.8). This reaction results in two diastereomeric products that differed in configuration on the anomeric carbon. The two products are also called *Anomers*. These anomers are designated – α or – β depending upon the relative configuration of the anomeric carbon (Figure 1.9 a and b).

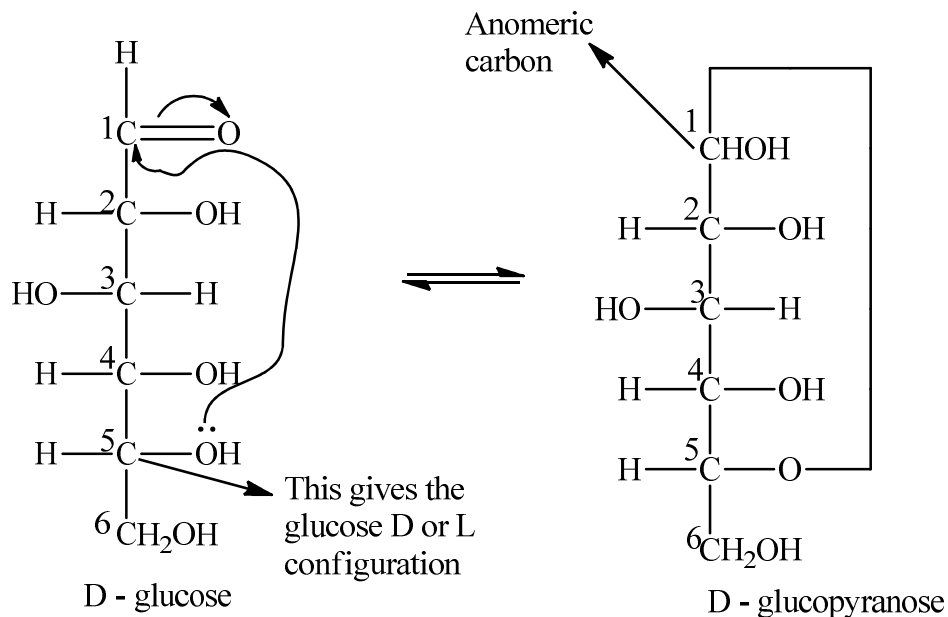


Figure 1.8: Anomeric reaction in D-Glucose (anomerization reaction)

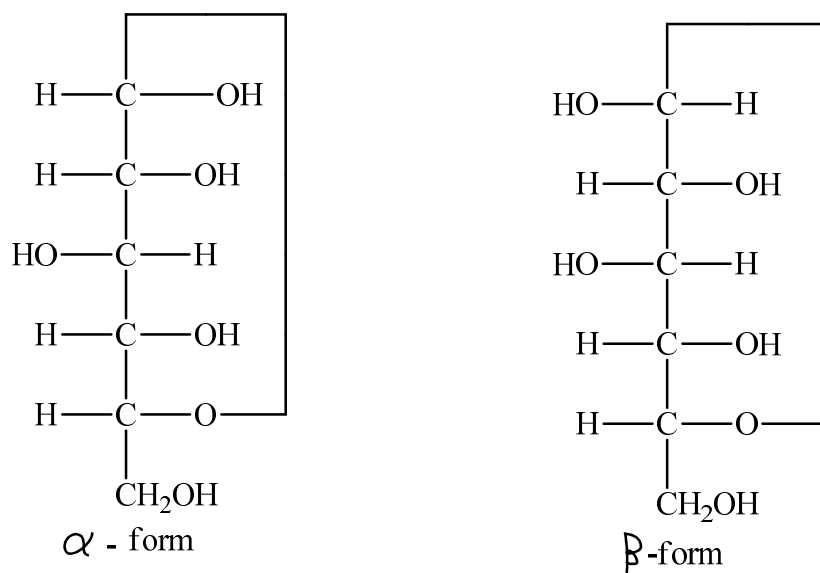


Figure 1.9: The α -form and the β -form of the glucose in ring forms

The structures in the Figure 1.9 above resemble the hydrogenated γ -Pyran (Figure 1.7) above, hence, D-glucose in ring form is named after pyran that is α - or β - D – glucopyranose (Figure 1.10 a and b).

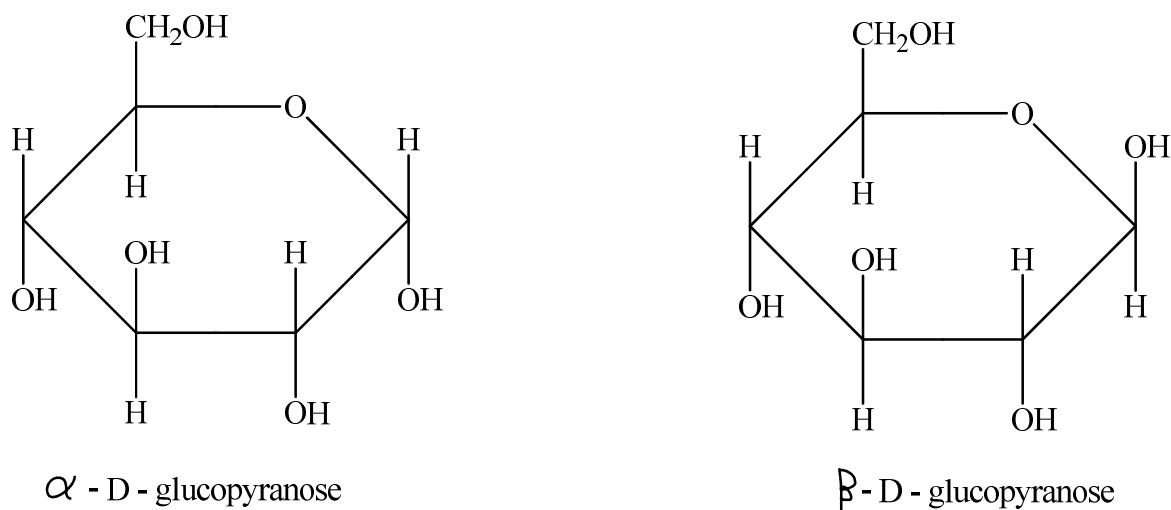


Figure 1.10 a & b: α - D – glucopyranose and β - D – glucopyranose

Ketohexoses also undergo the same intramolecular reaction described above for aldohexose using hydroxy on carbon number 5 (Figure 1.11). This anomeric reaction leads to the formation

of five membered ring compound named after tetrahydrofuran because it resembles hydrogenated Furan (Figure 1.12). The reaction leads to the formation of two products which are also called *Anomers*. These anomers like glucopyranose are designated - α or - β depending upon the relative configuration of the anomeric carbon. The ring forms of D-Fructose resemble hydrogenated Furan (Figure 1.12), hence, the ring structure of D-Fructose is named after Furan that is α - or - β - D-Fructofuranose (Figure 1.13 a and b).

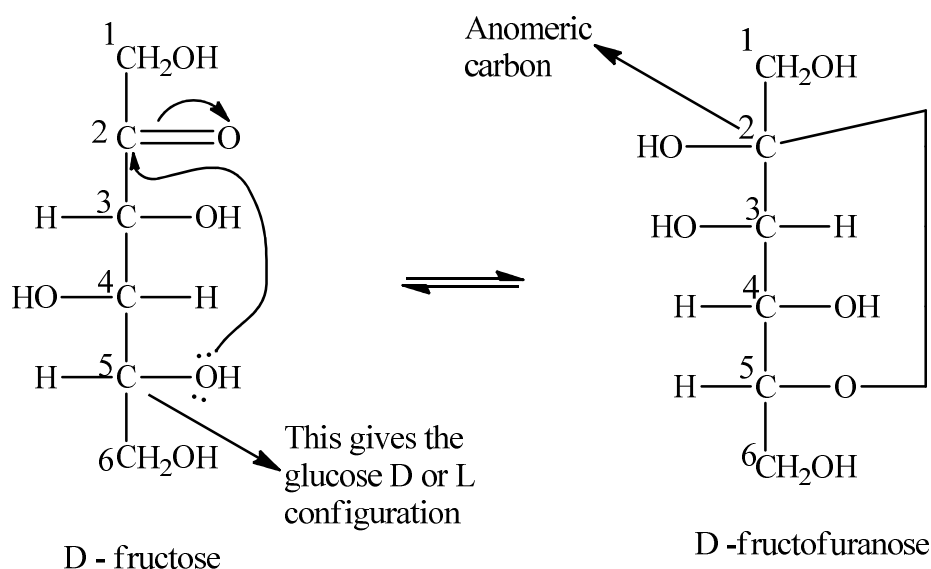


Figure 1.11: Anomeric reaction in D-Fructose (anomerization reaction)

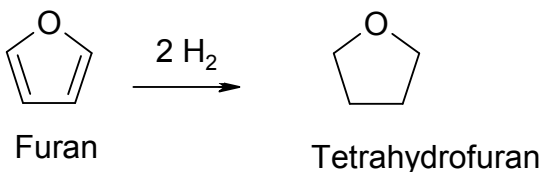
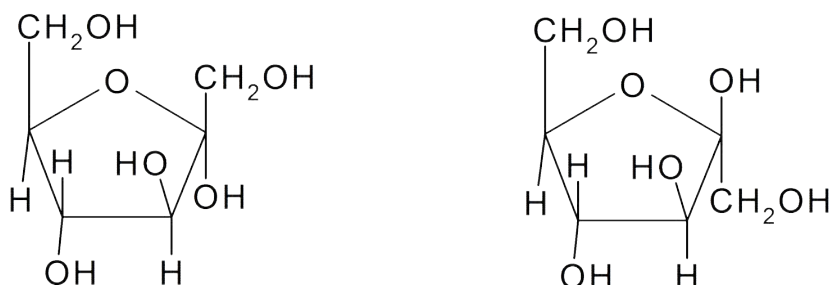


Figure 1.12: Hydrogenation of Furan



α - D-Fructofuranose (a)

β - Fructofuranose (b)

Figure 1.13 a and b: α - or - β - D-Fructofuranose

The ratio of the α - D- glucopyranose to β - D- glucopyranose is 36 : 64% in nature. This is because the beta form is more stable than the alpha anomer. This stability can be explained using the *anomeric effect*.

This effect arises from the orbital interaction between oxygen (heteroatom) and the anomeric carbon that is the CO bond. This reaction occurs when the anomeric hydroxy is in the *axial position* (Figure 1.14) that is **α -form** but this destabilizing reaction is not possible with the OH group in the *equatorial position* (Figure 1.15) that is **β -form**.

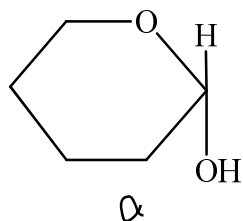


Figure 1.14: Figure showing OH group drawn in the axial position

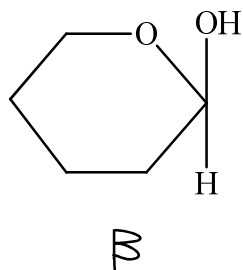


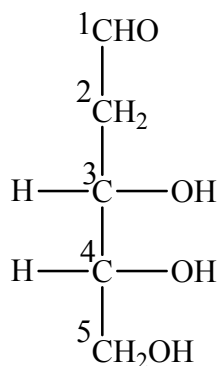
Figure 1.15: Figure showing OH group drawn in the equatorial position

Any ring substituents that are drawn perpendicularly to this axis of symmetry are called *equatorial* while those drawn parallel are referred to as *axial*. For example, the OH group and other substituents on the β - D - glucopyranose are perpendicular to this axis. This reduces steric

hindrance, hence, the β - form is more stable than the α - form. This is another explanation for the reason why β - and α - forms are 64 and 36 % in nature, respectively.

Deoxy and Amino Sugars

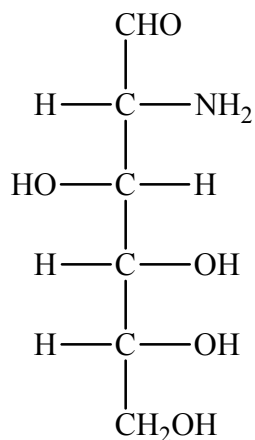
In nature, sugars can have one or more of their OH group(s) replaced by some substituents. Of these, substituents, H and $-\text{NH}_2$ are the most common. A Deoxy sugar has $-\text{CH}_2-$ group in place of a $-\text{CH}(\text{OH})-$ group. The most common deoxy sugar in nature is 2-deoxy—D—ribose (Figure 1.16) which is the sugar moiety of deoxyribonucleic acid (DNA).



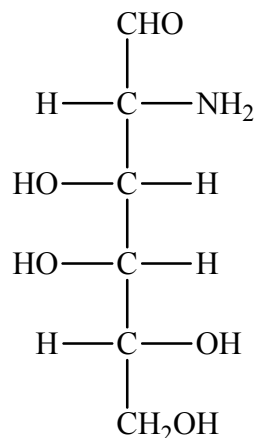
2 - deoxy - D - ribose

Figure 1.16: 2–deoxy-D-ribose

Amino sugar on the other hand has a $-\text{CH}(\text{NH}_2)-$ group replacing a $-\text{CH}(\text{OH})-$ group. Examples of important amino sugars are D - galactosamine and D - glucosamine (Figure 1.17 a & b).



D - glucosamine
(2 - amino - 2 - deoxy - D - glucose)



D - galactosamine
(2 - amino - 2 - deoxy - D - galactose)

Figure 1.17 a & b: D-glucosamine and D-galactosamine

1.3 SOME REACTIONS OF MONOSACCARIDES

1.3.1 Reduction to glucitols

Aldose monosaccharides such as D-glucose can be reduced glycitols. For example, D-glucose can be reduced to D-glucitol (Sorbitol) using a reducing agent such as Sodium borohydride in water ($\text{NaBH}_4/\text{H}_2\text{O}$) (Figure 1.18).

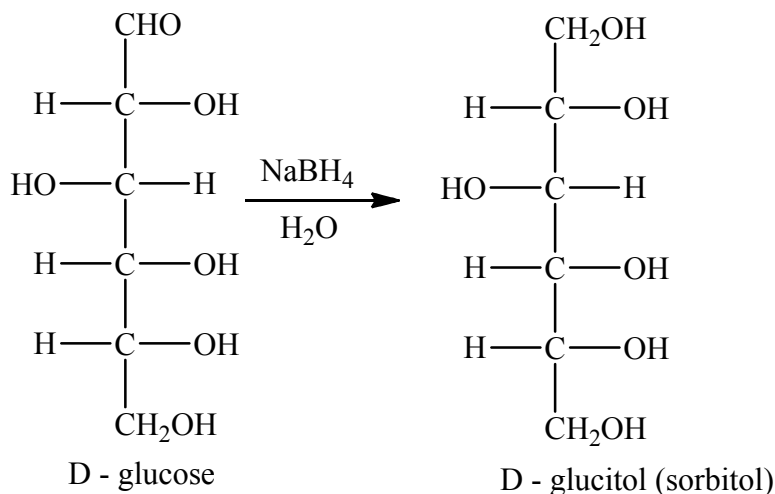


Figure 1.18: Reduction of D-glucose to D-Glucitol

1.3.2 Oxidation to gluconic acids

Aldoses are oxidized to glyconic acids using mild oxidants such as bromine water. For example, D-glucose is oxidized to D-gluconic acid (Figure 1.19).

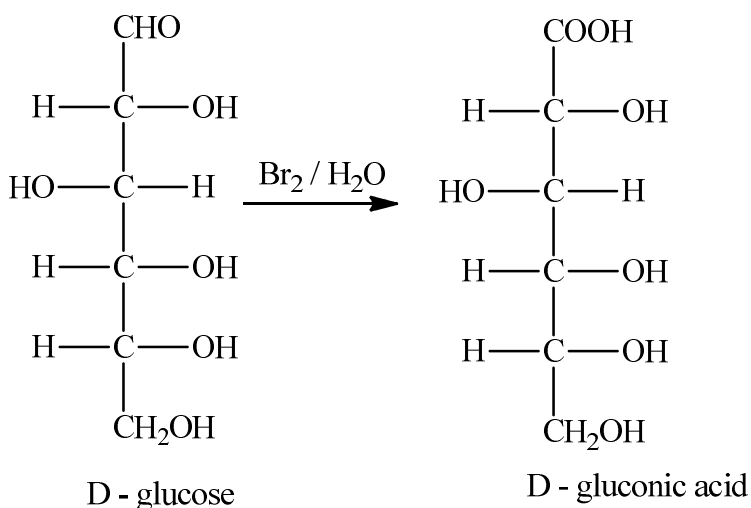


Figure 1.19: Oxidation of D-glucose with mild oxidant to D-gluconic acid

1.3.3 Oxidation to glucaric acids

The oxidation of aldoses to glucaric acids can only be carried out using strong oxidants such as HNO_3 . If D-glucose is oxidized with strong oxidant, it will give D-glucaric acid (Figure 1.20).

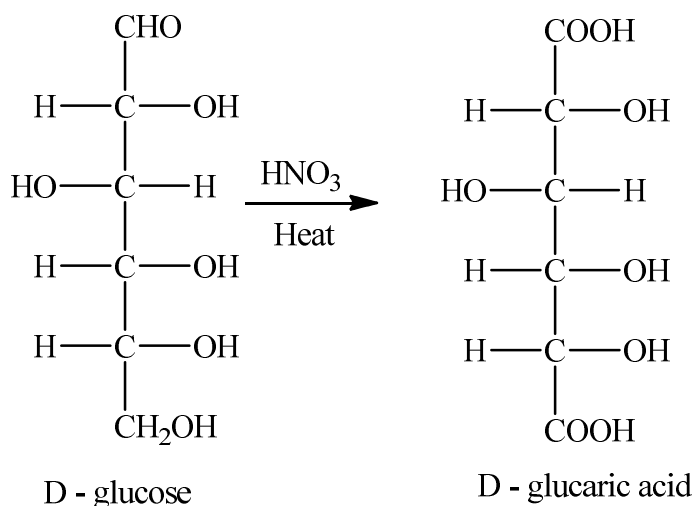
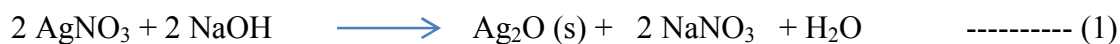


Figure 1.20: Oxidation of D-glucose with strong oxidant to D-glucaric acid

1.3.4 (i) *Reaction with Tollens' reagent*

The Tollens' reagent is prepared according the chemical equations (1 & 2) given below:



The brown Silver (I) oxide precipitate formed is then dissolved in excess aqueous ammonia to give a clear solution of diammoniasilver (I) complex according to equation 2 given below:



The reaction between D-glucose and Tollens' reagent is given in equation 3 below:

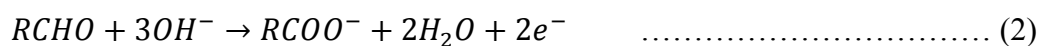
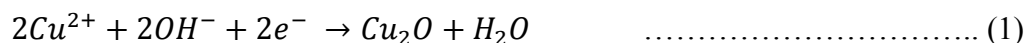
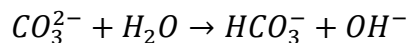


This reaction is the popular mirror image test used for the confirmation of alkanal.

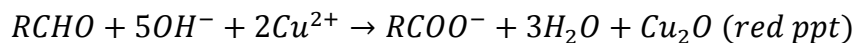
1.3.4 (ii) *Reaction with Fehling's and Benedict's Solutions*

Fehling's solution is made up of the following reagents: copper (II) ions complexed with tartrate ions. Both reagents are prepared in NaOH solution. On the other hand, Benedict's solution contains copper (II) ions with citrate ions instead of tartrate ions. It is prepared with Na₂CO₃ solution as against NaOH solution used for the Fehling's solution.

Both Fehling's and Benedict's solutions provide hydroxy ions that reacts with Cu²⁺ in complex form (equation 1). These hydroxy ions are provide by the NaOH and Na₂CO₃ used in the preparation Fehling's and Benedict's solutions, respectively. In the case of Benedict's solution, OH⁻ is obtained when CO₃²⁻ reversibly reacts with H₂O as follows:



(1) + (2) gives the overall chemical equation for the oxidation of the alkanal



Only reducing sugars (aldoses) like D-glucose can be positive to Tollens', Fehling's and Benedict's tests. But it was observed that Fructose, a non-reducing sugar gives positive Tollens' test. This was made possible because a base catalyzed equilibrium takes place between glucose, mannose and fructose. The alkaline nature of this reagent provides this base catalyst and the rearrangement is called *Lobry de Bruyn-Van Ekenstein rearrangement*. The mechanism for the conversation is given by the following chemical equations (Figure 1.21).

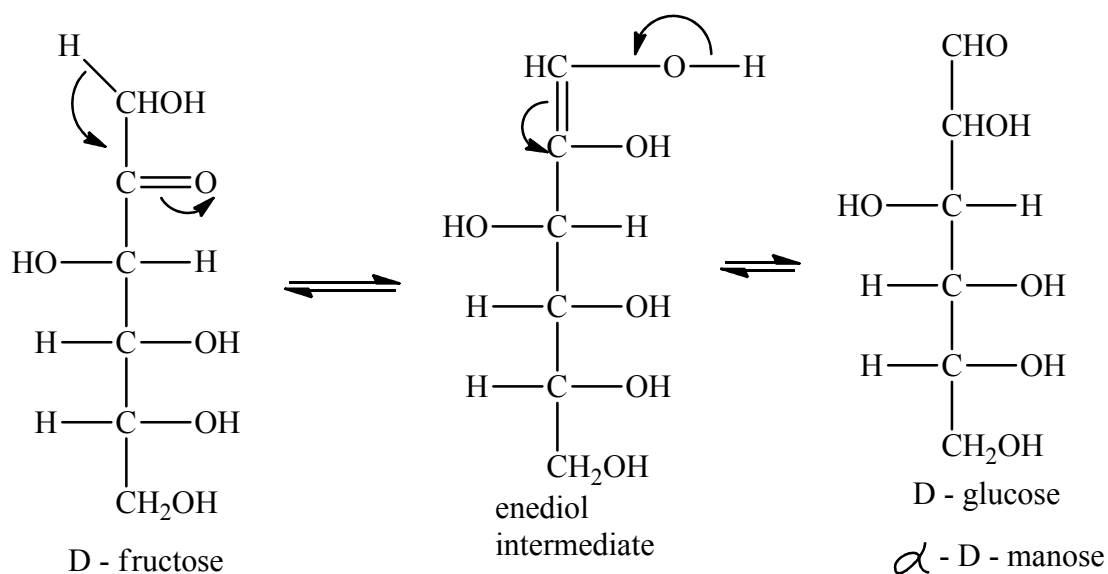


Figure 1.21: The base catalyzed equilibrium between glucose, mannose and fructose

1.3.5 Reaction with hydrogen cyanide (HCN)

Hydrogen cyanide reacts with reducing sugars the same way it reacts with alkanals (aldehydes) by attacking the carbonyl carbon to give a hydroxynitrile compound. An example of this reaction is given below (Figure 1.22):

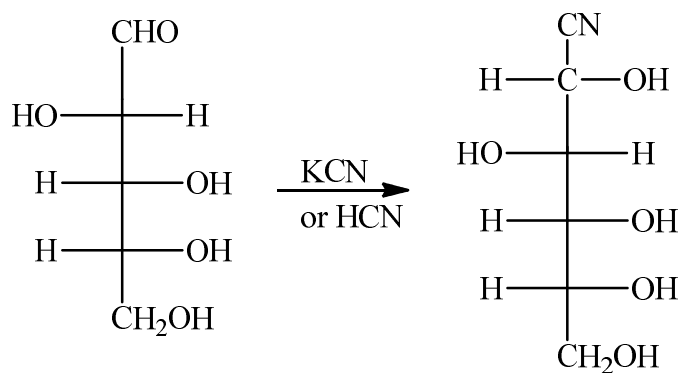


Figure 1.22: Reaction of reducing sugar with Cyanide to form hydroxynitrile compound

It should be noted that hydrogen cyanide is extremely poisonous gas; hence, it is not used directly. The aldehyde / ketone is reacted with a solution of sodium or potassium salt of cyanide in water along with little sulphuric acid to give a solution with a pH of between 4 and 5.

The Mechanisms of the Reaction

The mechanism is through nucleophilic addition. The mechanism is given below (Figure 1.23):

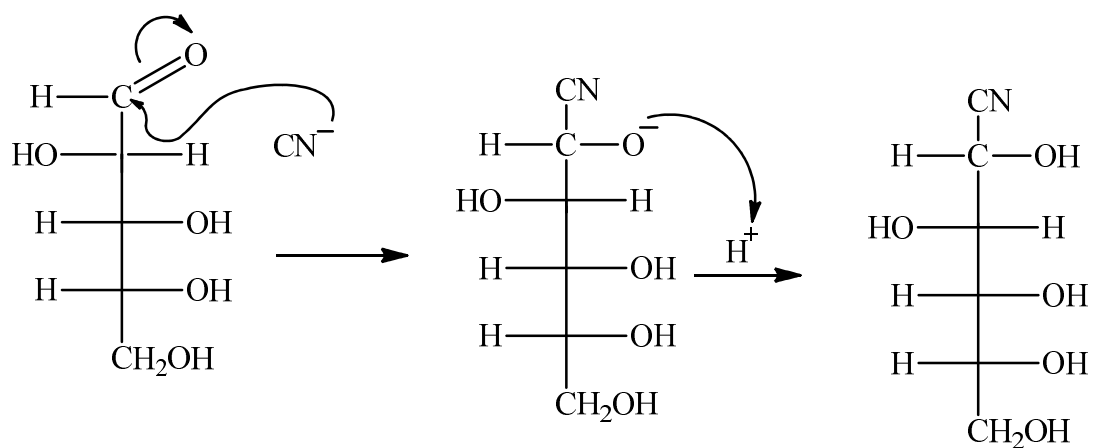
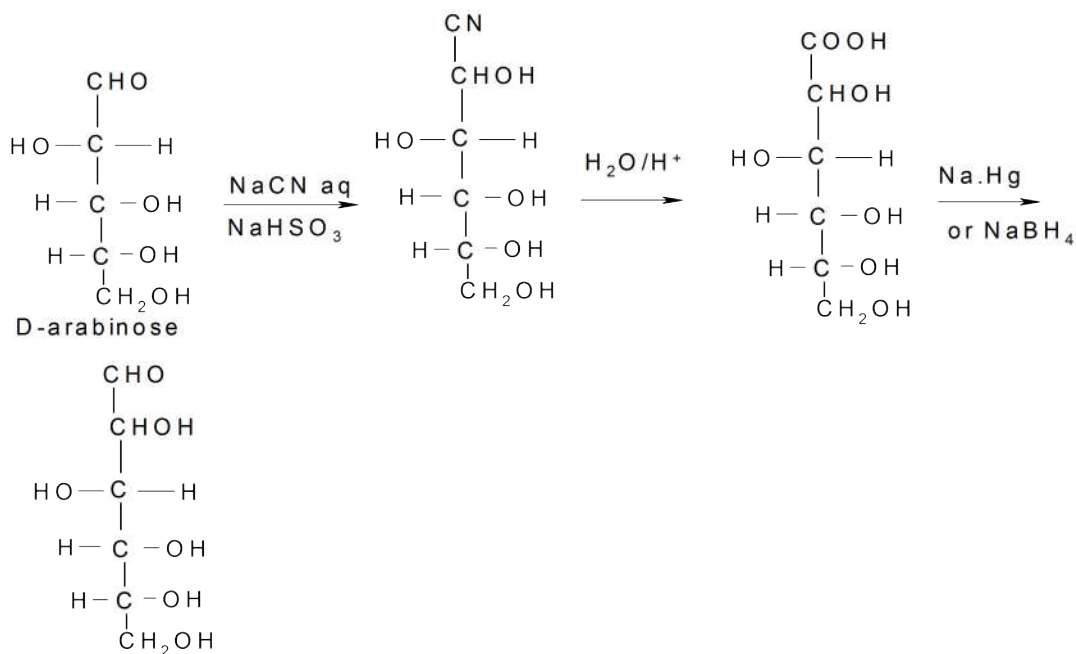


Figure 1.23: Mechanism for the reaction of reducing sugar with Cyanide

A typical example of this reaction is the reaction of D-arabinose with the solution of sodium cyanide given below. The reaction is called *cyanohydrin*. This reaction is also used in

carbohydrate synthesis for increasing the chain length of a sugar by one carbon for example the mixture of D-glucose and D-mannose from D-arabinose (Figure 1.24).



Mixture of D-glucose and D-mannose depending on spartial arrangement on carbon 2

Figure 1.24: Synthesis of D-glucose and D-mannose from D-arabinose

1.3.6 Ruff Degradation

Ruff degradation is a method used for reducing the chain length of a carbohydrate by one carbon. In this method, the sugar to be shortened is first converted to gluconic acid using bromine water followed by decarboxylation (removal of CO_2) using ferric salt. Example is the conversion of D-glucose to D-arabinose (Figure 1.25)

Questions

1. Show using a suitable chemical equations how D-fructose forms hemiacetal.
2. Draw the structures of the following sugars: (a) D-ribose, (b) D-arabinose (c) D-mannose and (d) D-galactose.

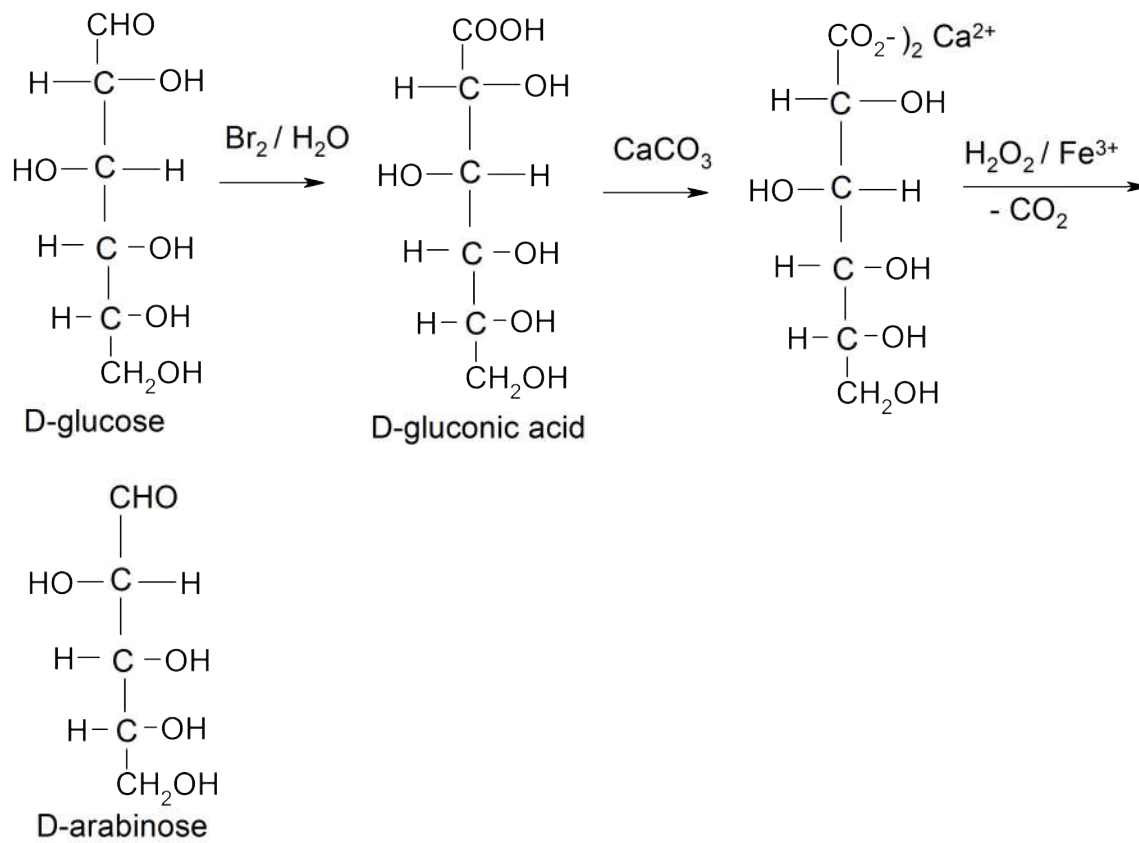


Figure: 1.25: Ruff degradation reaction for converting D-glucose to D-arabinose

1.3.7 Periodic acid oxidation

This is another method for determining the ring size of glycosides. It proceeds stoichiometrically and is a measure of the number of adjacent free hydroxyl groups. In this method, the moles of periodic acid (or sodium metaperiodate) consumed and the moles of formaldehyde and formic acid produced during the oxidation of a known weight of the saccharide under investigation are determined. One mole of the oxidant is reduced (consumed) when two adjacent OH groups are oxidized with cleavage of the C-C bond joining them to yield two aldehyde groups. Terminal hydroxyl group yields formaldehyde while secondary hydroxyl group yields another aldehyde or formic acid if the 2^o hydroxyl group is flanked on both sides by hydroxy groups (i.e. is oxidized twice). From the results, it is possible to determine the number and type (1^o or 2^o) of adjacent

hydroxyl groups present in a molecule. The general reactions are given below (Figures 2.6 A to

F)

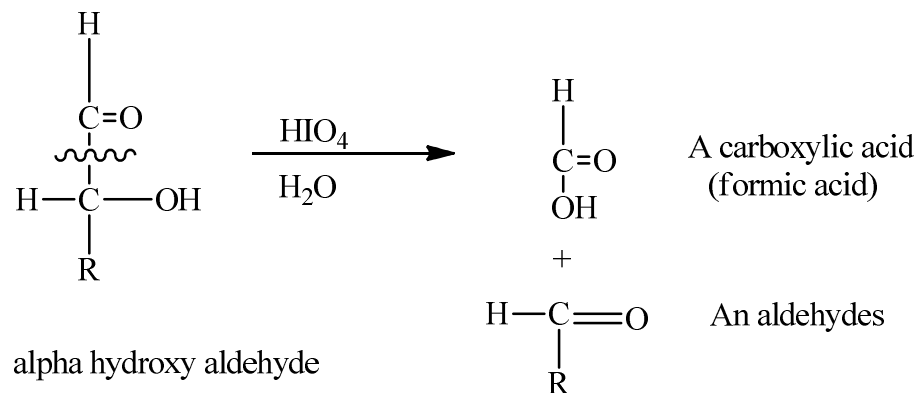


Figure 2.6 A

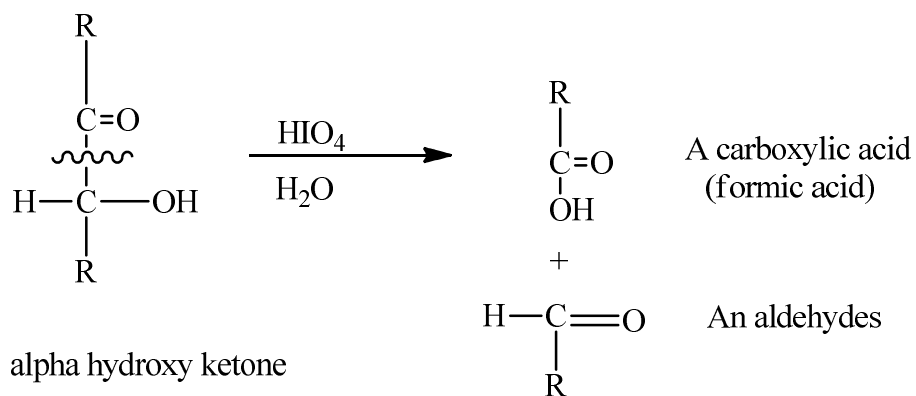


Figure 2.6 B

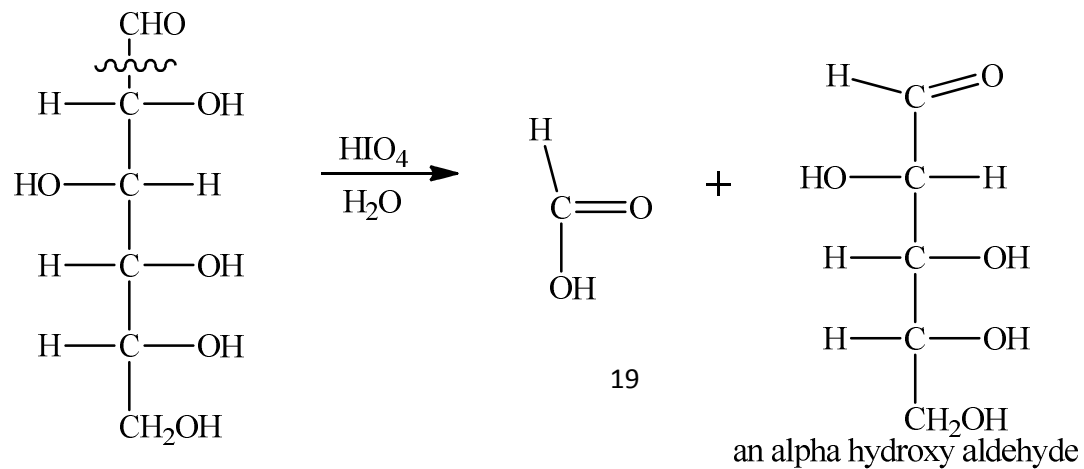


Figure 2.6 C

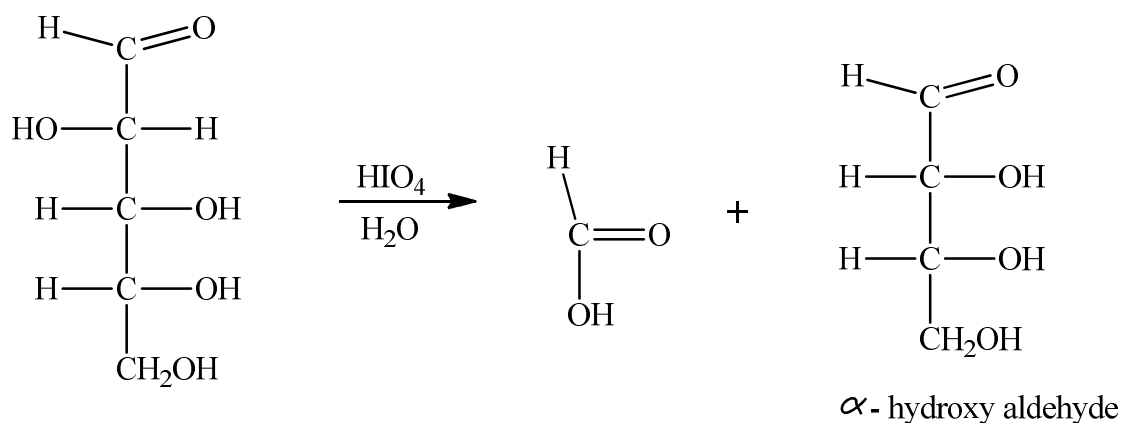


Figure 2.6 D

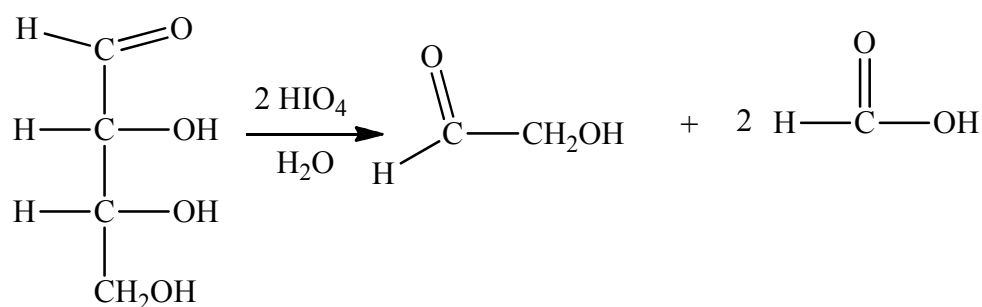


Figure 2.6 E

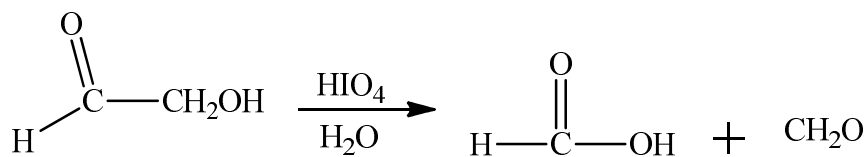


Figure 2.6 F

When all the steps are added up glucose will produce five times as much methanoic acid as methanal.

This type of degradation has played a vital role in understanding the structures of many carbohydrates. The degradation of α -D-glucopyranose by periodic acid is given below (Figure 2.7).

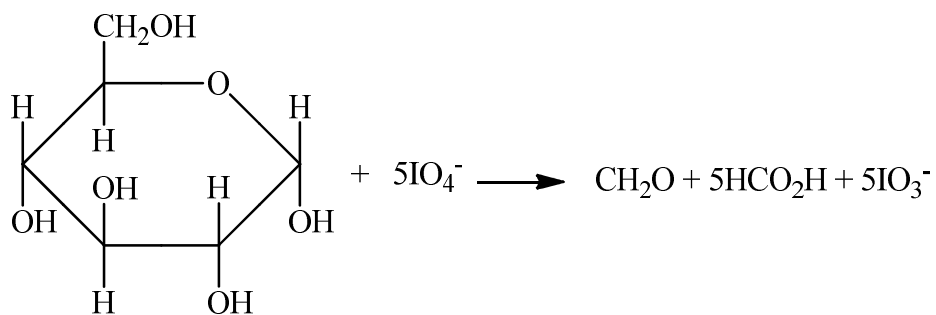


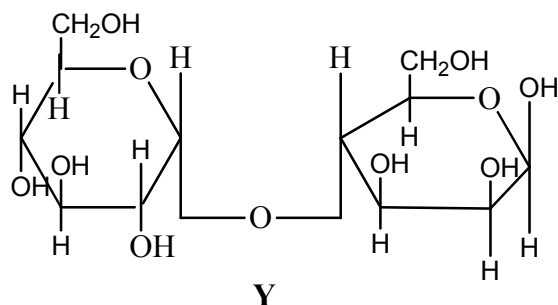
Figure 2.7: The degradation of Alpha - D - glucopyranose by periodic acid

1.4 Disaccharides

According to the name, they all consist of two simple sugars held together by a *glycosidic bond*.

Like monosaccharides, disaccharides are also simple sugars which are water soluble. Some typical examples of disaccharide are maltose, sucrose, lactose, cellobiose, getiobiose etc.

They have two simple sugars held together by a glycosidic bond. The most common involves the anomeric carbon of one sugar and non – anomeric carbon of the other (Compound Y)..



MALTOSE

β – Maltose carries the impressive systematic name O – α – glucopyranosyl – (1,4) – β – D – glucopyranose. The disaccharide contains two latent carbonyl carbons. The one in the ring at the upper left is tied up in the glycosidic linkage. The other is in the ring at the lower right and is still a hemiacetal. The position of the free hemiacetal hydroxy group determines if it is β or α , which must appear in any name of the compound.

See the structure given in the class

Note, the structure of maltose is compound Y above.

Cellobiose and Gentiobiose

These are disaccharides that contains β – D glucopyranose bonded to a second β – D glucopyranose residue via a glycosidic bond. Cellobiose possesses a glycosidic bond between C1 and C4 of two simple sugars, while gentiobiose has a glycosidic between C1 and C6 of two simple sugars.

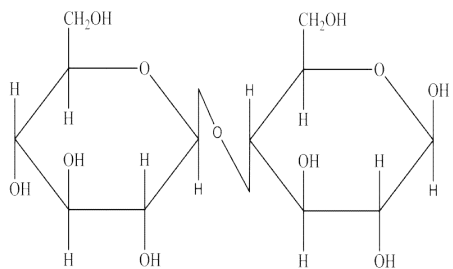


Figure 3.4: β -D - glucopyranosyl-1,4- β -D - glucopyranose (β - Cellobiose)

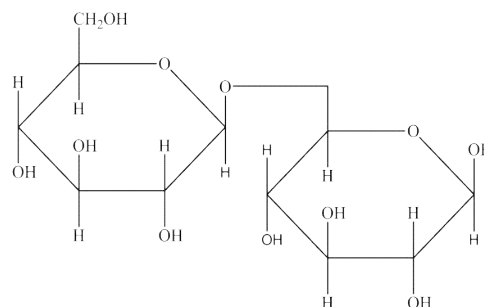
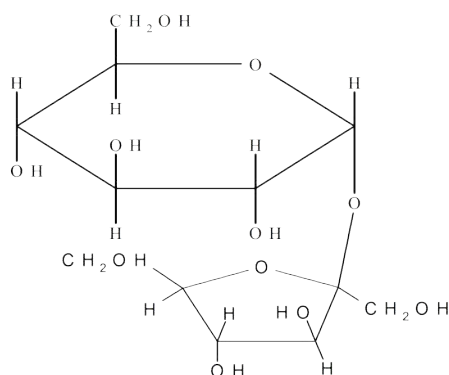


Figure 3.5: β -D - glucopyranosyl-1,6- β -D - glucopyranose (β - Gentiobiose)

SUCROSE

The alternative names of sucrose are cane sugar or beet sugar. It is the common table sugar, α - β - D - glucopyranosyl - (1,2) - β - D - fructofuranoside. This sugar is different from other disaccharides, thus, far studied because its glycoside linkage involves the anomeric centre of both sugars.



Alpha-D - glucopyranosyl-1,2-beta-D - fructofuranoside [Sucrose]

Sucrose, unlike maltose, Lactose, Cellobiose, and gentiobiose, doesn't exist as readily - inter - converted α and β - forms.

The fructose position of the name ends in "oside" in order to indicate that C2 of fructose is involved in the glycoside bond,

Because both anomeric carbons are involved in acetal formation, sucrose is a non-reducing sugar. It is negative to Tollen's reagent and Fehling's solution or Benedict's solution. Moreover, sucrose does not form an osazone, does not exist on anomeric forms and does not show mutarotation in solution. All these facts indicate that sucrose does not contain a "free" aldehyde or ketone group. When sucrose is hydrolysed by dilute aqueous acid or enzyme invertase (from yeast), equal amounts of α - D glucopyranose and β - D - fructofuranose are produced.

POLYSACCHARIDES

Polysaccharides are polymers containing as many as several thousands monosaccharide unit per molecule. As with other saccharides, it is important to know the following:

- (a) Which specific monomer are involved in the polymer formation
- (b) The method of linkage between the monomer
- (c) The gross structure of the polymer.

If the polymer contains more than one type of monosaccharides, then the sequence of the sugars is also important.

Of all the naturally occurring polysaccharides, starch and cellulose are the most important. Both are products of photosynthesis. Cellulose play a tremendous role in our society. As wood, cellulose provides shelter, as pulp, it is the major constituent of cotton which is a natural fibre. Starch is the mainstay of many diets since it is the major compound in rice, potatoes, wheat and corn.

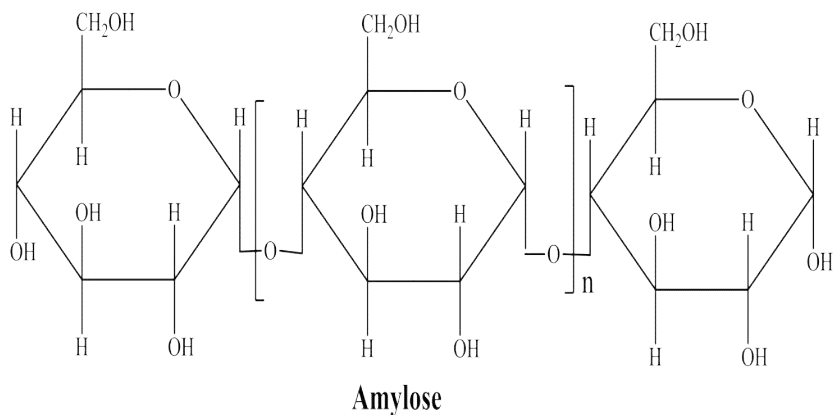
STARCH

This is the major source of energy in plant cells. When intact, starch granules are insoluble in cold water; if the outer membrane has been broken by grinding, the granules swell in cold water and form a gel. When the intact granule is treated with warm water, a soluble portion of the starch diffuse through the granule wall, in hot water the granules swell and then burst. Starch contains two major fractions: amylose ($\approx 20\%$) and amylopectin ($\approx 80\%$). Both can be hydrolysed in acidic medium to give on D – glucose, since both polymer contains the same monomer, the important differences between them must exist in the bonding within these polymers.

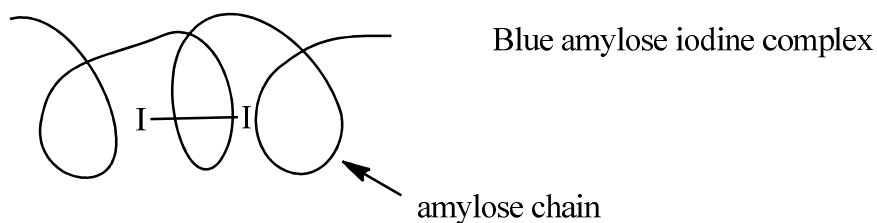
AMYLOSE

Maltose is the only disaccharide produced upon hydrolysis of amylose. The absence of cellobiose suggests that amylose is a linear polymer of D – glucose molecule, each bonded by an α – glycosidic linkage to C 4 of the adjacent glucose unit. If cellobiose had been produced, the β – glycosidic linkage would have been produced.

Amylose then is believed to be made up of long chains, each containing 1000 or more α – D glucopyranose units joined together by α – linkage as in maltose.



α – Amylose is the fraction of starch that gives the intense blue colour with iodine. X – ray analysis shows that the chain coiled in the form of helix (spiral staircase) inside which is just enough to accommodate iodine molecule; the blue colour is due to entrapped iodine molecules.

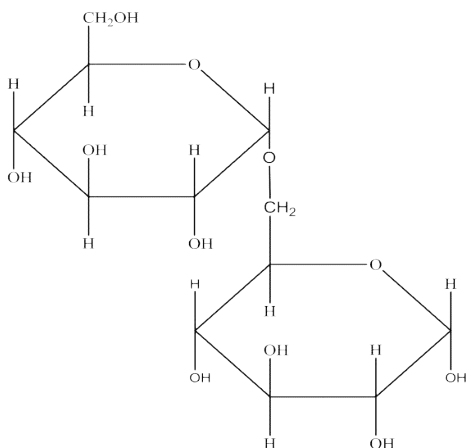


AMYLOPECTIN

Amylopectin is a branched polymer containing about 1000 D – glucose units. The main chain consists of an α – 1, 4 – D glycosidic linkage while branching occurs with an α – 1, 6 – D glycosidic bond. Branching is moderate with perhaps twenty five α – D glucopyranose units occurring between branching points.

The partial hydrolysis of amylopectin produces large molecules called dextrans. Dextrans are used to prepare mucilage, pastes and fabric sizing. (sizes are materials used to fill pores in cloth, paper; etc.). printing inks is often thickened by the addition of dextrans.

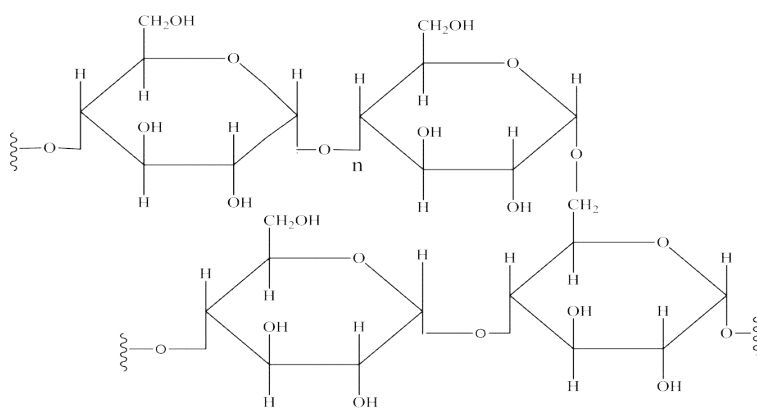
The major disaccharide produced by the hydrolysis of amylopectin is maltose, the glucose unit at each point has C – 1 and C – 6 – OH groups involved in glycosidic linkages. This leads to small amount of isomaltose upon hydrolysis.



Alpha-D-glucopyranosyl-(1,6)-alpha-D-glucopyranose (Alpha Isomaltose)

Structure of amylopectin

Amylopectin is hydrolysed to a single disaccharide maltose; the sequence of methylation and hydrolysis yields chiefly 2,3,6 – tri – o – methyl – D – glucose. Like amylose, amylopectin is made up of chains of α – D glucopyranose units, each unit joined by alpha – glucosidic linkage to C – 4 of the next one. However, its structure is more complex than that of amylose.

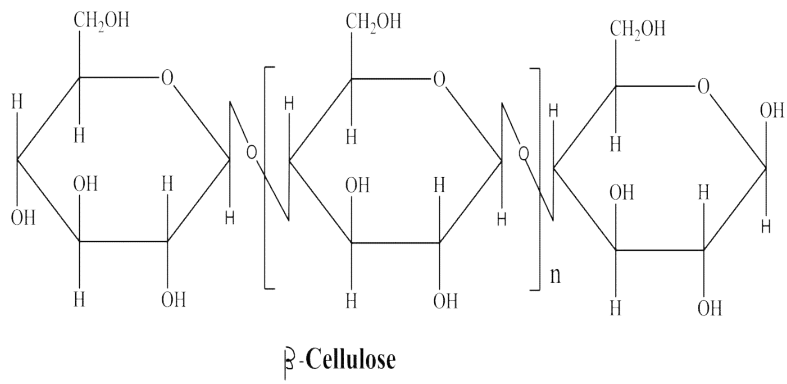


Amylopectin

CELLULOSE

Cellulose is an unbranched polymer of β – D – glucose which occurs in most plants. Most animals, including man and cattle, cannot hydrolyse the β – glycosidic link in cellulose

Cotton which is the most important natural fibre, is about 98% cellulose. Acetal linkage in cellulose are hydrolysed by acids but not by bases.



PROTEINS Polymers formed by

Proteins are naturally occurring ^{condensation} ~~of polymers~~ of α -amino acids. Hydrolysis of proteins with acids, bases or enzymes produces a mixture of α -amino acids. In proteins the amino acid units are linked by peptide linkages (-CO-NH-).

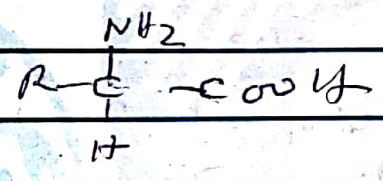
Amino acids

There are ~~twenty~~ ^{twenty three} amino acids of general occurrence in all proteins.

Structures of amino acids

~~Some~~

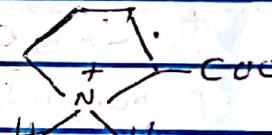
The general structure is given below:



Some of these

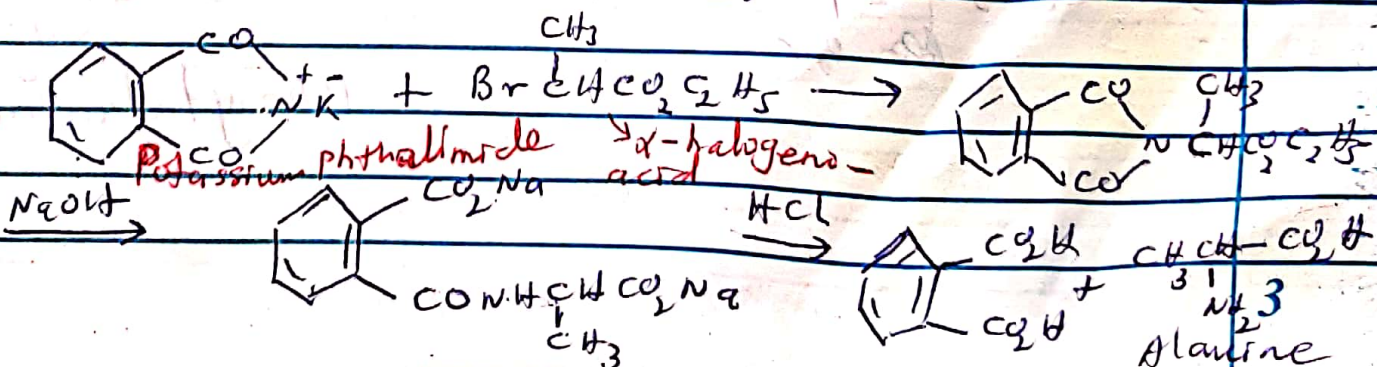
The structures of some of these amino acids are given below:

| Name | Abbreviation | Formula |
|------------|--------------|---|
| 1 Glycine | Gly (G) | $\text{H}-\overset{\text{NH}_2}{\underset{\text{H}}{\text{C}}}-\text{COOH}$ |
| 2 Alanine | Ala (A) | $\text{CH}_3-\overset{\text{NH}_2}{\underset{\text{H}}{\text{C}}}-\text{COO}^-$ |
| 3 Arginine | Arg (R) | $\text{H}_2\text{N}-\underset{\text{NH}_2}{\text{C}}(\text{NH}_2)-\text{CH}_2-\text{CH}_2-\overset{\text{NH}_2}{\underset{\text{H}}{\text{C}}}-\text{COOH}$ |

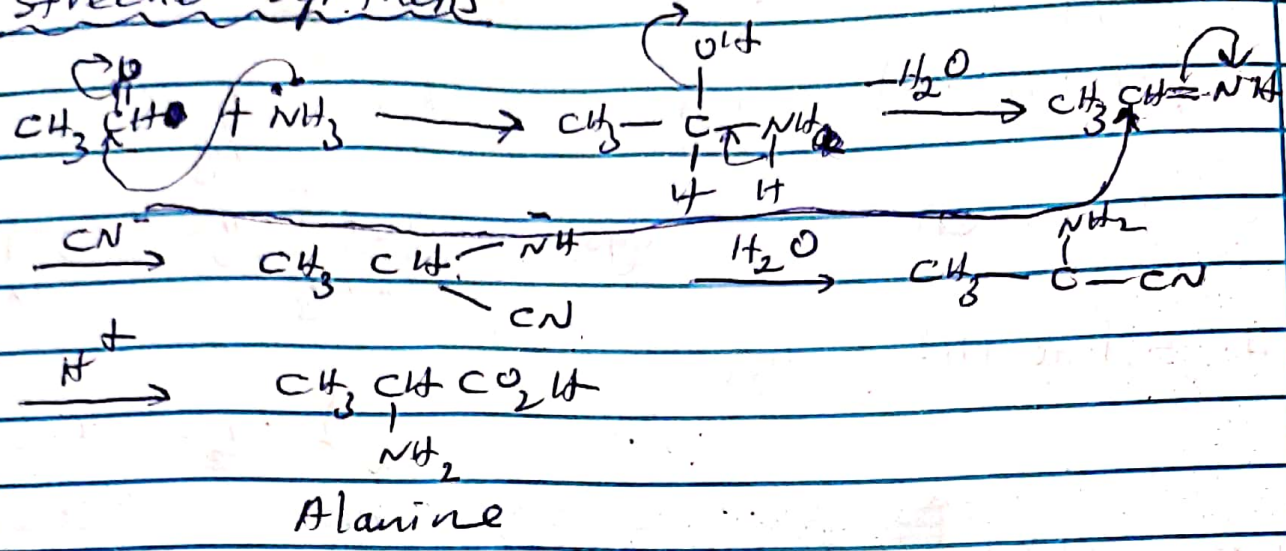
| Name | Abbr. | Formula |
|---------------------|-----------|---|
| 4 Aspartic acid (D) | ASP | $\text{HOOCCH}_2 - \underset{\text{NH}_3^+}{\text{CH}} - \text{COO}^-$ |
| 5 Cysteine (C) | Cys | $\text{HSCH}_2 - \underset{\text{NH}_3^+}{\text{CH}} - \text{COO}^-$ |
| 6 Cystine | cys - cys | $\text{OOCCH}(\text{NH}_3^+) - \text{CH}_2 - \text{S} - \text{S} - \text{CH}_2 - \text{CH}(\text{NH}_3^+) - \text{COO}^-$ |
| 7 Histidine (H) | His | $\text{Imidazole ring} - \text{CH}_2 - \underset{\text{NH}_3^+}{\text{CH}} - \text{COO}^-$ |
| 8 Lysine (K) | Ly.s | $\text{H}_3\text{N}^+ - (\text{CH}_2)_4 - \underset{\text{NH}_3^+}{\text{CH}} - \text{COO}^-$ |
| 9 Methionine (M) | Met | $\text{CH}_3\text{SCH}_2\text{CH}_2 - \underset{\text{NH}_3^+}{\text{CH}} - \text{COO}^-$ |
| 10 Proline (P) | Pro |  |
| 11 Tryptophan (W) | Try | $\text{Indole ring} - \text{CH}_2 - \underset{\text{NH}_3^+}{\text{CH}} - \text{COO}^-$ |

Preparation of amino acids

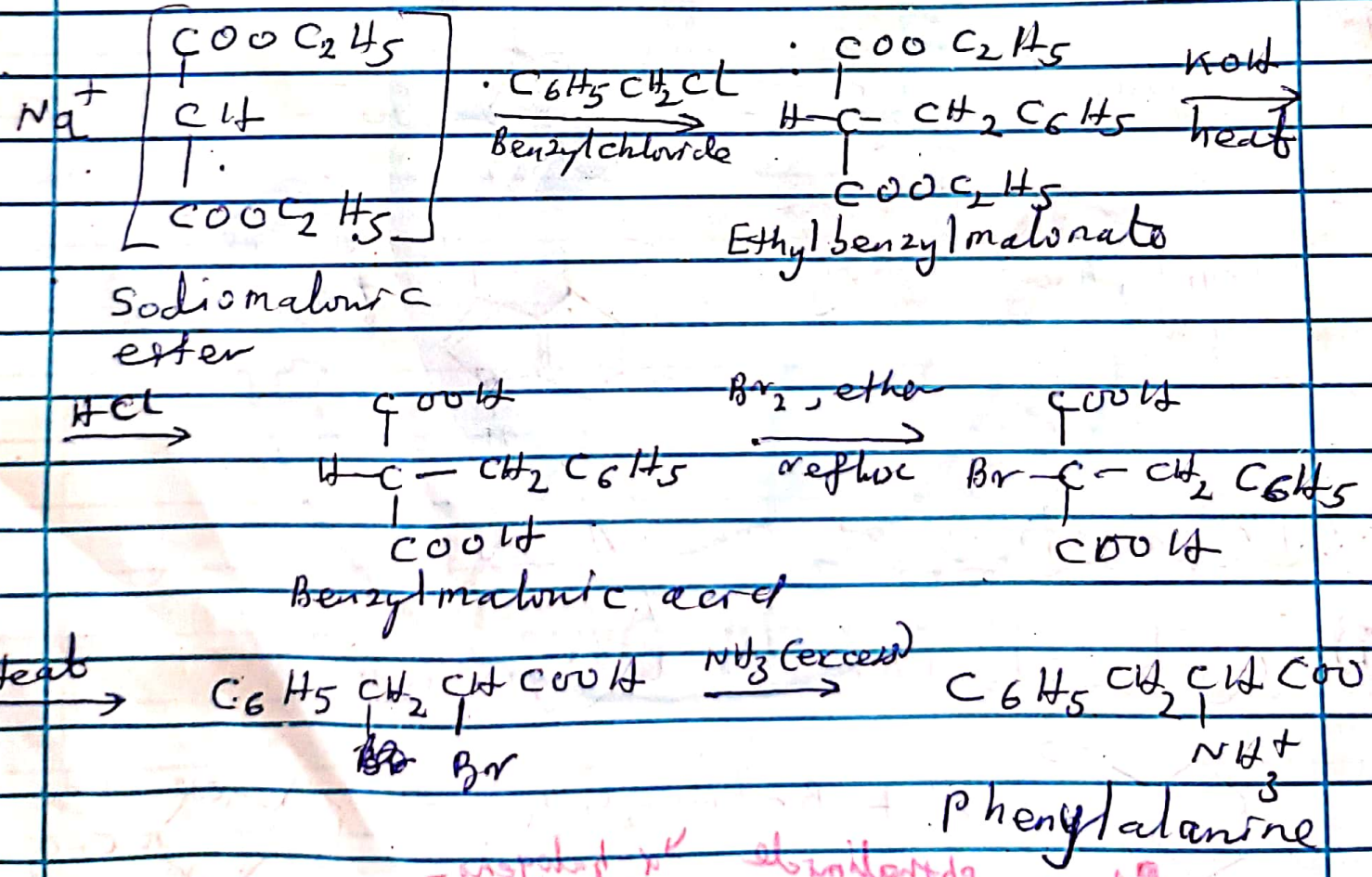
(i) Gabriel's Phthalimide synthesis



(ii) Strecker Synthesis

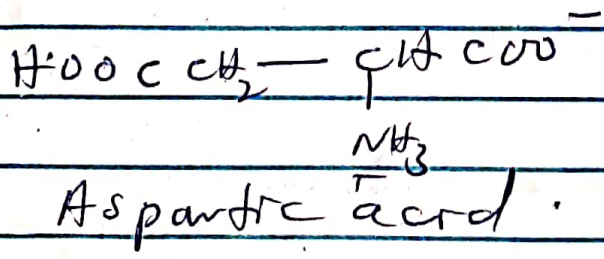
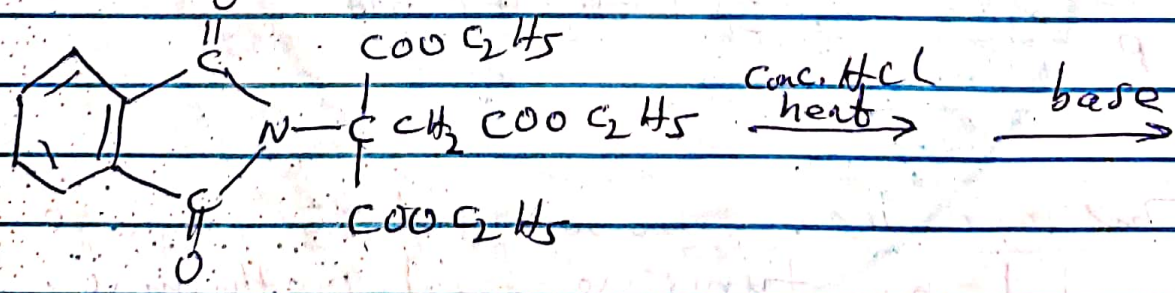
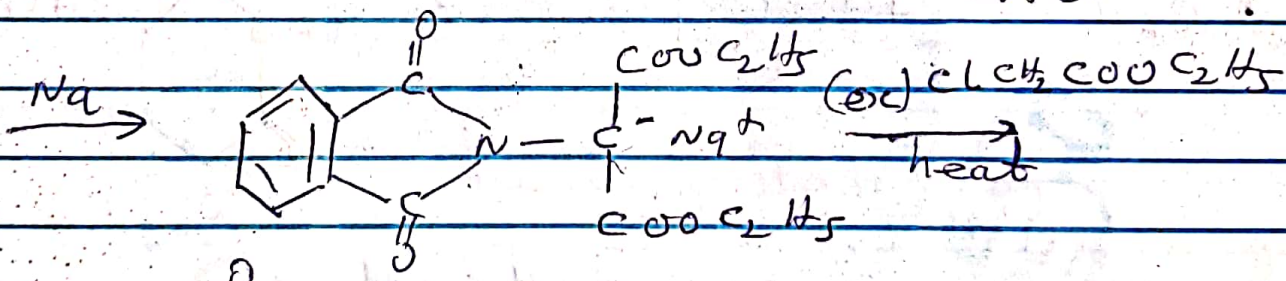
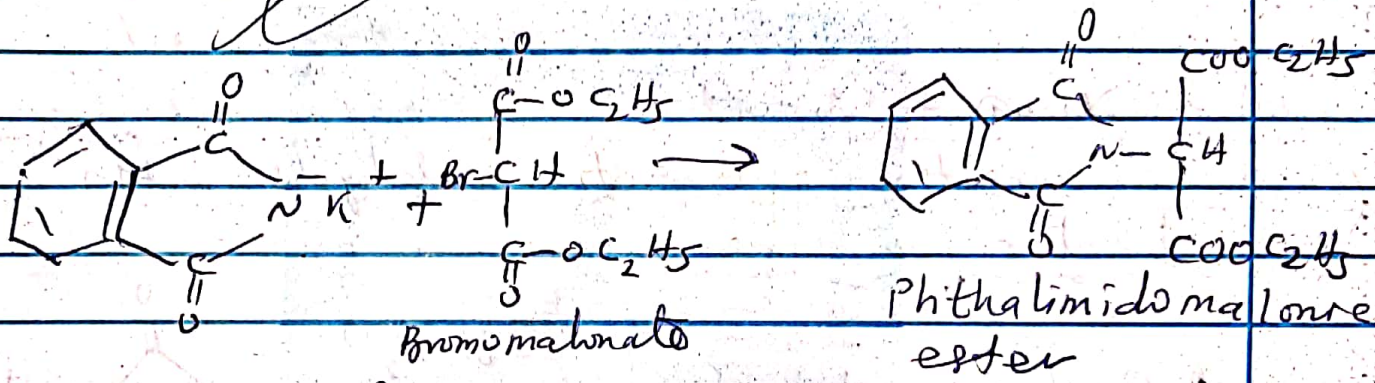
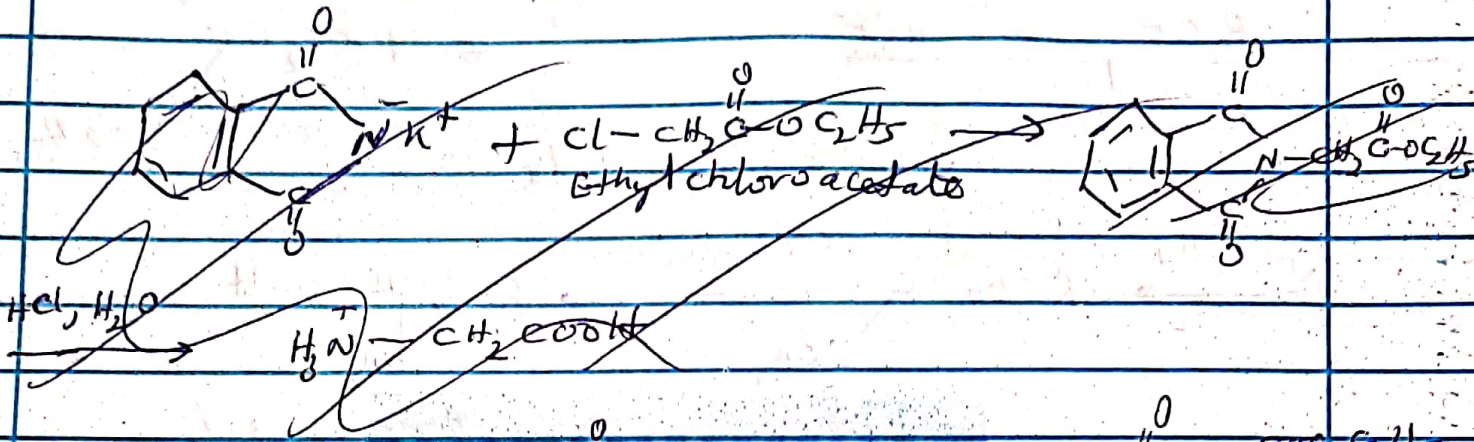


(iii) Malonic ester synthesis of Amino Acids



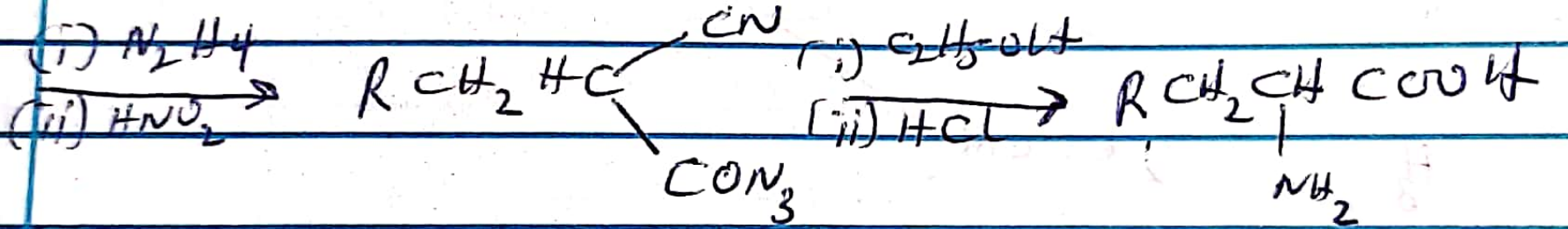
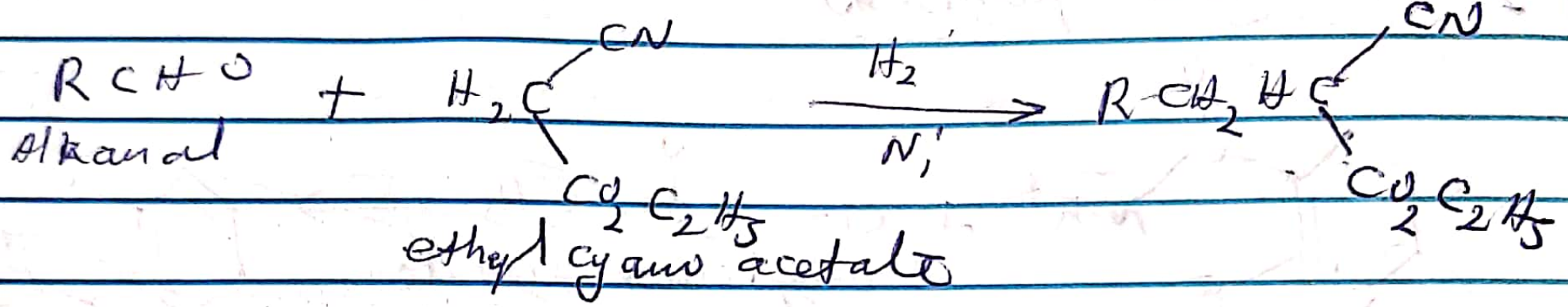
Handwritten notes in red ink:
 - amino acid
 - amino acid
 - amino acid

✓ (IV) Synthesis of Aspartic acid (Gabriel phthalimide synthesis)



Question.....

✓ (v) Darapsky Synthesis



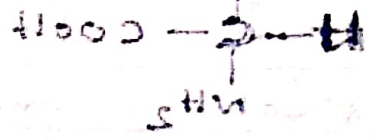
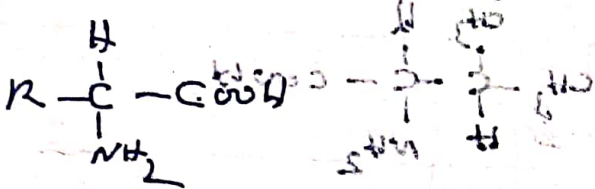
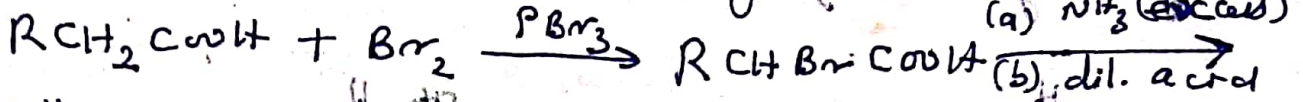
Amino acid

vi) Synthesis of Aromatic

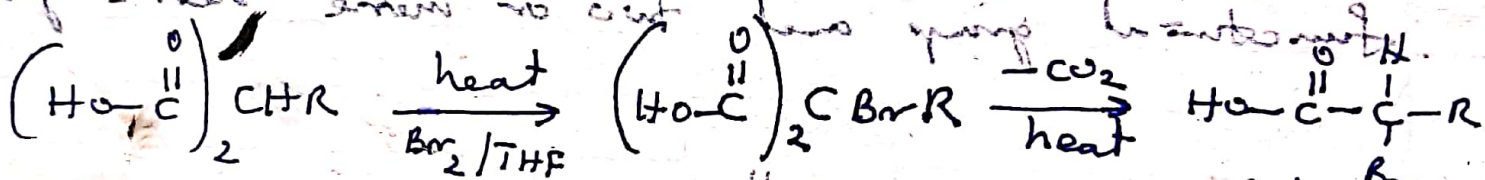
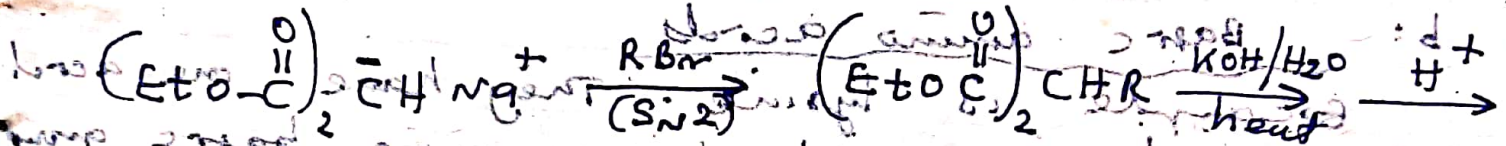
Synthesis of amino acids

(a) Amination of α -Halo acid

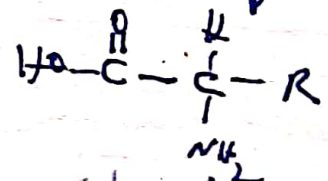
The halo acid is made by



Bromination can also be accomplished using Malonic acid.



(a) NH_3 (ex)
(b) dil. acid

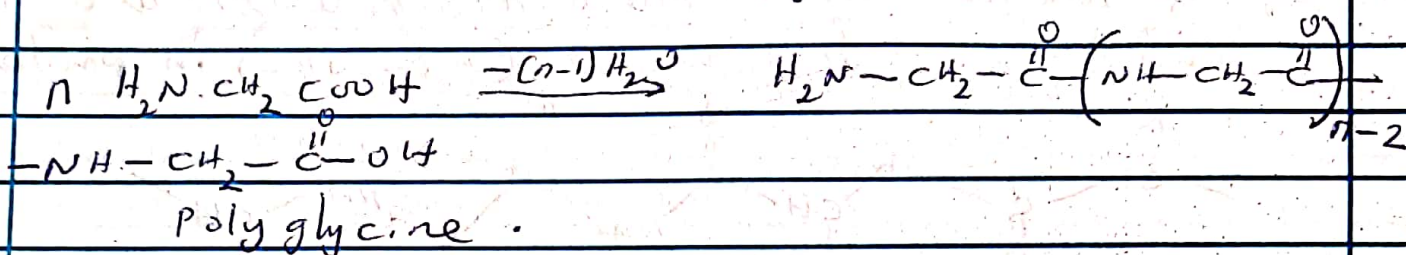


(b) Gabriel synthesis

... amino acid ...

Peptides

When amino acids polymerized they form polyamide. The polyamides derived from α -amino acids are called peptides or polypeptides.

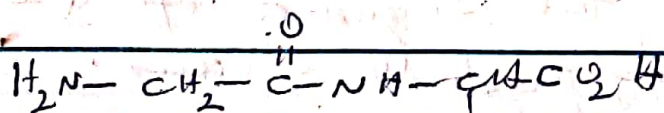
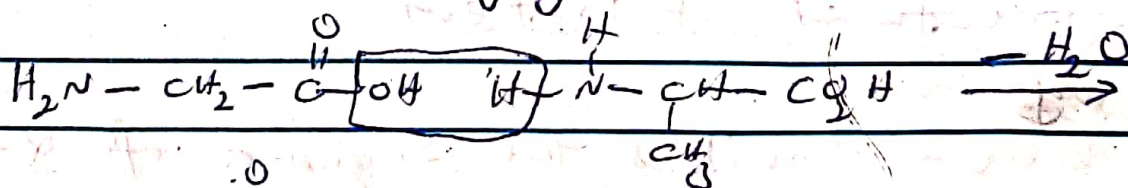


The amido linkage in the polymer is called peptide bond or peptide linkages.

In a heteropolyamide, the amino acid at the end of the polymer bearing a free NH_2 -group is called the "N-terminal amino acid". The amino acid with free carboxyl group is called "C-terminal amino acid". Amino acid residue in a peptide are numbered starting from the N-terminal amino acid.

Polypeptides are named as derivatives of C-terminal amino acid, the N-terminal amino acid being listed first and the C-terminal last.

Example is glycylalanine

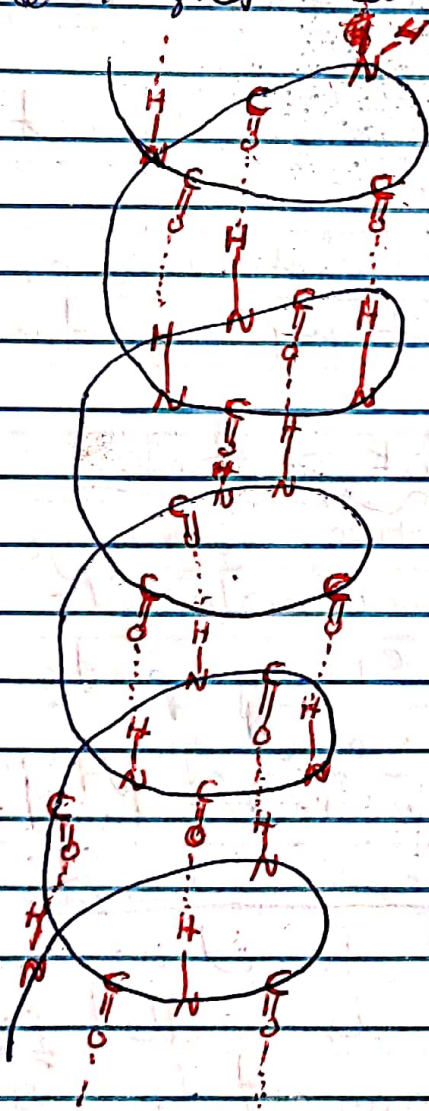


N-terminal Glycylalanine C-terminal

(ii) Secondary structure

It describes

its conformation or molecular shape. It has been proved that the polypeptide chains have helical conformations in their crystal lattices. The helices are stabilized by intramolecular hydrogen bonds involving $-NH-C=O$ groups. The α -helix is right handed.



α -Helix

(III) Tertiary structure

This term is used to describe the shape or folding resulting from the presence of Sulphur-sulphur cross-links between the polymer chains.

It is the three dimensional shape of a protein. The tertiary structure will have a single polypeptide chain backbone with one or more protein secondary structures, the protein domains.

Amino acid side chains may interact and bond in a number of ways. The interactions and bonds of side chains within a particular protein determine its tertiary structure.

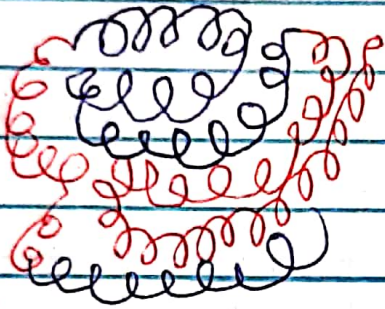
(IV) Quaternary structure of proteins

Quaternary structure is the arrangement of more than one protein molecule in a multi-subunit complex. Many proteins are actually comprised of several polypeptide chains. In this case, the individual polypeptide chains are called protein subunits, and each unit ~~cannot~~ cannot function on its own. These sub-units are also called protomers. These subunits may or may not be identical, and when they are held together by hydrogen bonds, they may be separated by e.g. dissolving.

in water containing water

An example

The figure below is a sketch sketch of the structure of quaternary proteins.



An example of a protein with quaternary structure is hemoglobin. In hemoglobin, one protein binds to oxygen while another binds carbon dioxide. This is how one protein can serve two functions. Another example is holoenzymes, proteins with several subunits. Each subunit of a holoenzyme has a different function. For example, one protein subunit may be the regulatory subunit. Another unit may be the catalytic subunit.

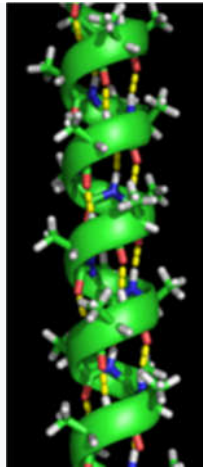
PROTEIN STRUCTURES

Protein primary structure is the linear sequence of amino acids in a peptide or protein. By convention, the primary structure of a protein is reported starting from the amino-terminal (N) end to the carboxyl-terminal (C) end. Protein biosynthesis is most commonly performed by ribosomes in cells. Peptides can also be synthesized in the laboratory.

Isomerisation

The chiral centers of a polypeptide chain can undergo racemization. Although it does not change the sequence, it does affect the chemical properties of the sequence. In particular, the L-amino acids normally found in proteins can spontaneously isomerize at the atom to form D-amino acids, which cannot be cleaved by most proteases. Additionally, proline can form stable trans-isomers at the peptide bond.

Secondary structure



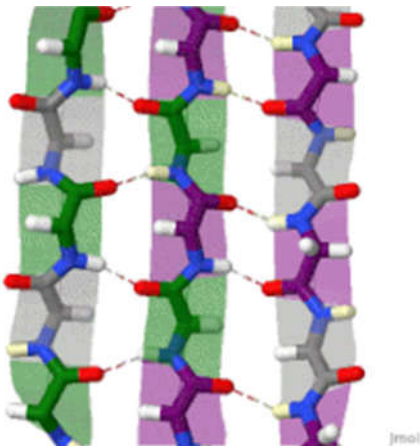
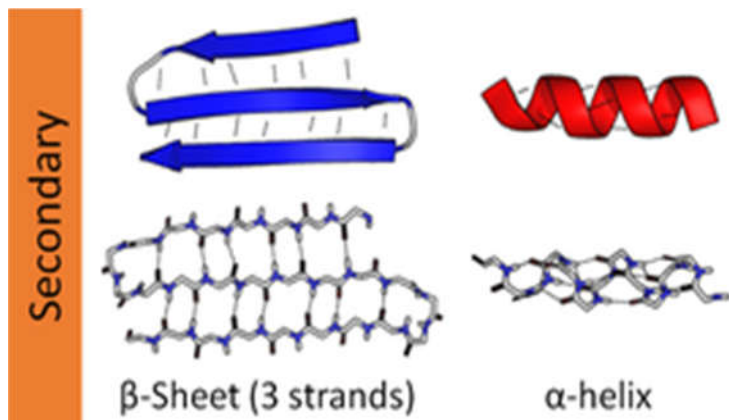
An α -helix with hydrogen bonds (yellow dots)

Secondary structure refers to highly regular local sub-structures on the actual polypeptide backbone chain. Two main types of secondary structure, the α -helix and the β -strand or β -sheets, were suggested in 1951 by Linus Pauling. These secondary structures are defined by patterns of hydrogen bonds between the main-chain peptide groups.

Secondary structure of protein refers to local folded structures that form within a polypeptide due to interactions between atoms of the backbone.

- The proteins do not exist in just simple chains of polypeptides.

- These polypeptide chains usually fold due to the interaction between the amine and carboxyl group of the peptide link.
- The structure refers to the shape in which a long polypeptide chain can exist.
- They are found to exist in two different types of structures α – helix and β – pleated sheet structures.
- This structure arises due to the regular folding of the backbone of the polypeptide chain due to hydrogen bonding between -CO group and -NH groups of the peptide bond.
- However, segments of the protein chain may acquire their own local fold, which is much simpler and usually takes the shape of a spiral an extended shape or a loop. These local folds are termed secondary elements and form the proteins secondary structure.



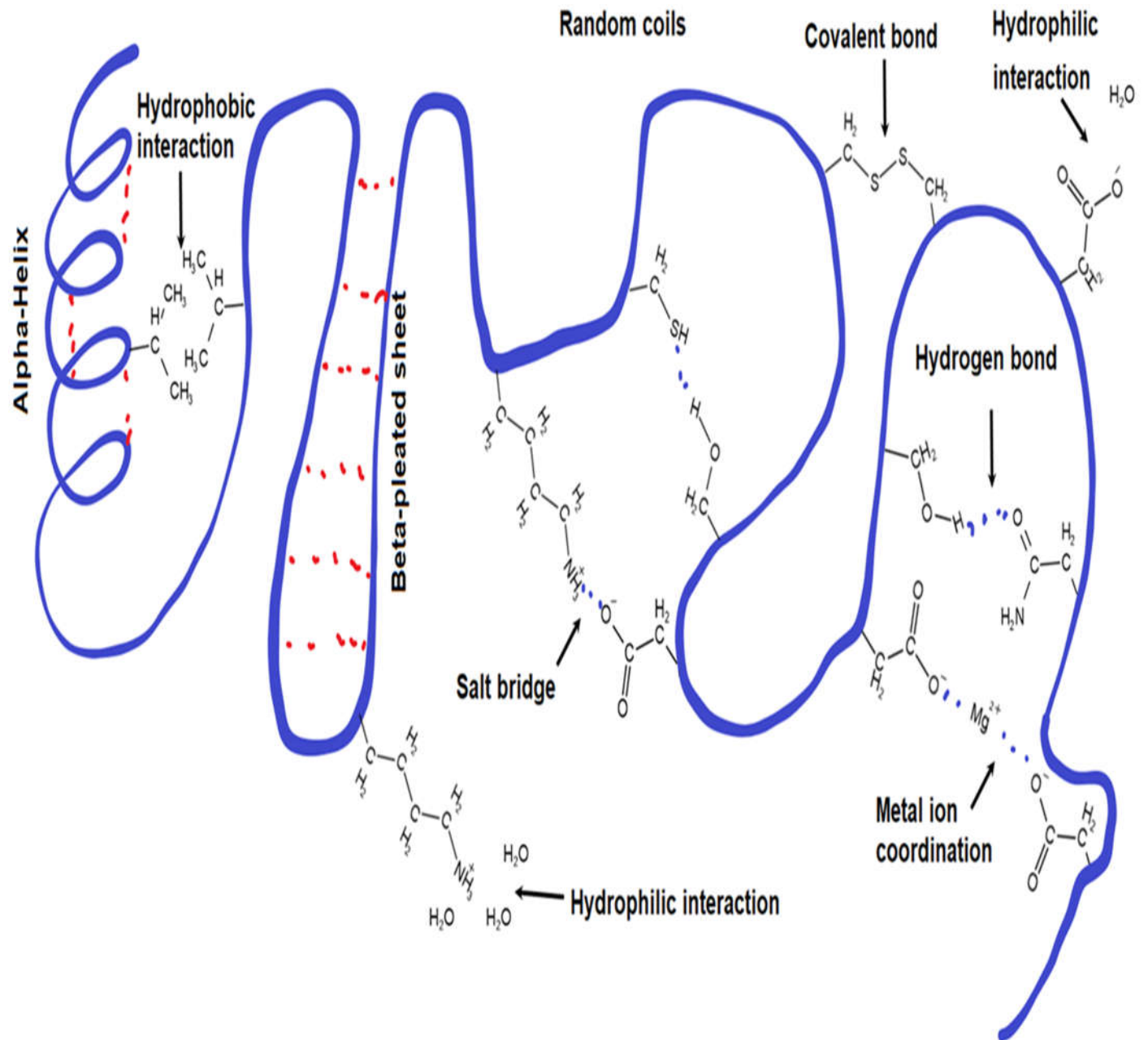
Three-dimensional structure of parts of a beta sheet in [green fluorescent protein](#)

Tertiary Structure of Protein

- This structure arises from further folding of the secondary structure of the protein.
- H-bonds, electrostatic forces, disulphide linkages, and Vander Waals forces stabilize this structure.
- The tertiary structure of proteins represents overall folding of the polypeptide chains, further folding of the secondary structure.
- It gives rise to two major molecular shapes called fibrous and globular.
- The main forces which stabilize the secondary and tertiary structures of proteins are hydrogen bonds, disulphide linkages, van der Waals and electrostatic forces of attraction.

The three-dimensional arrangement of all the atoms of a single polypeptide chain in space, held together by stabilizing interactions between groups on the side chains and between the side chain groups and the backbone groups is called the **tertiary structure of proteins**.

The stabilizing interactions involved in stabilizing the tertiary structure include disulfide linkage, salt bridge, coordinate bonds with metal ions, hydrogen bonding, and hydrophobic interaction, as shown in Fig. and explained below.



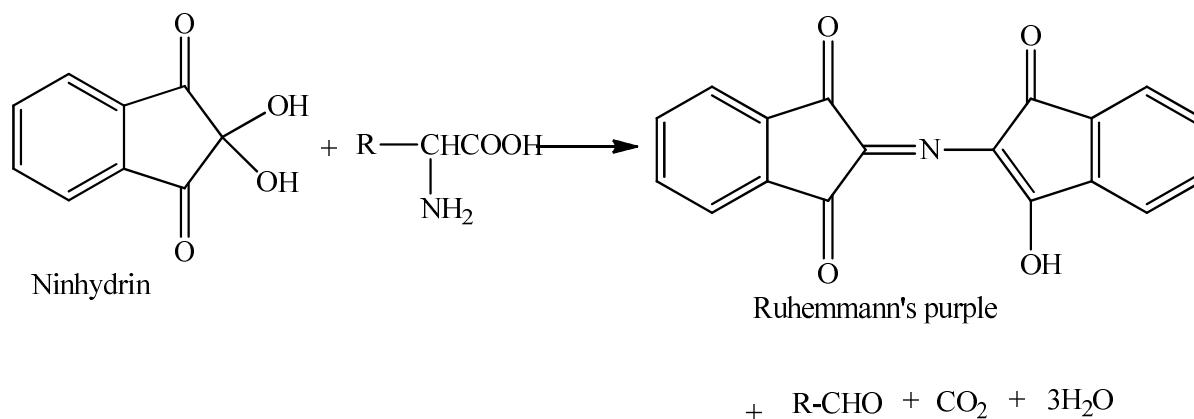
This figure illustrates the disulfide linkage, salt bridge, coordinate bonds with metal ions, hydrogen bonding, and hydrophobic interaction that stabilize the tertiary structure of proteins.

Chemical reactions and interactions of Amino acids and proteins

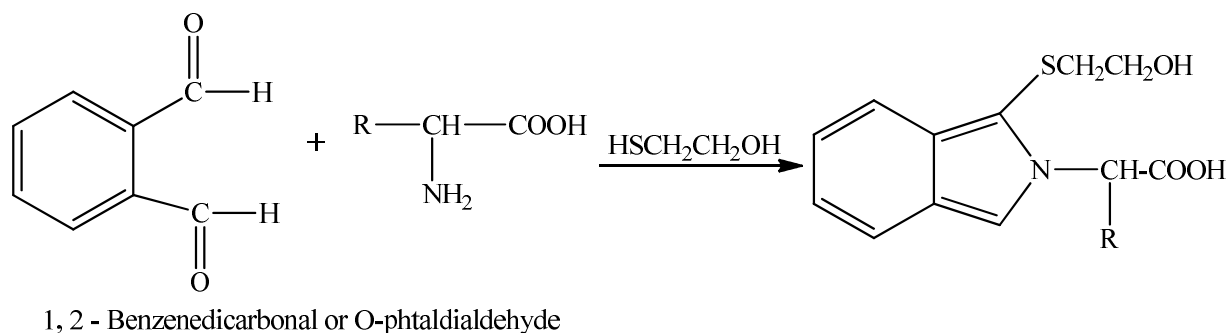
Reactions of various functional groups of amino acids and proteins are used for the chemical estimations.

(i) Reaction with ninhydrin(2,2,-D, hydroxyl-1,3-indandione)

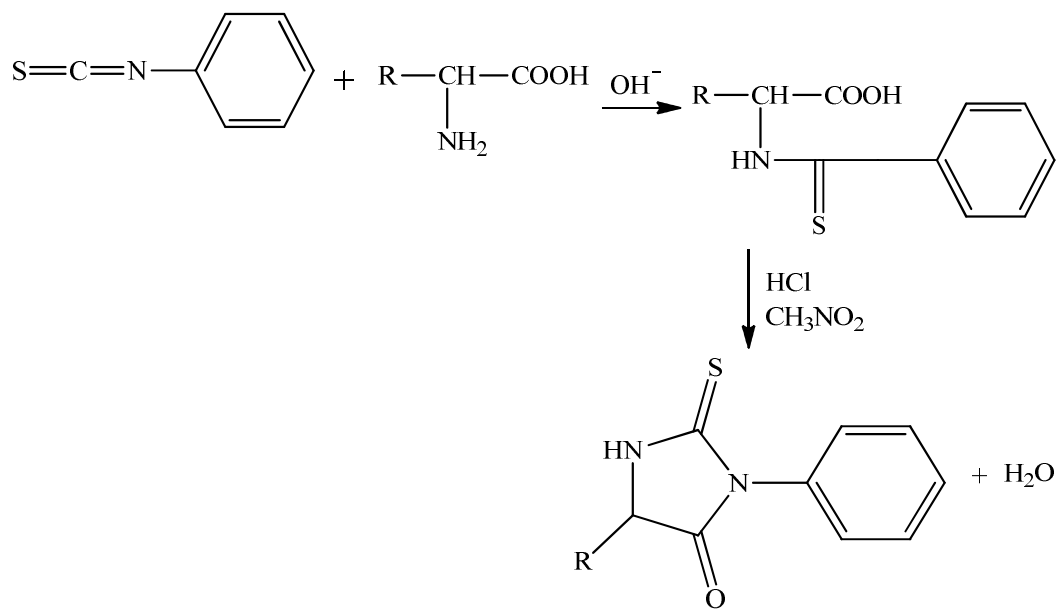
The reaction leads to the formation of coloured complex which is used for quantitative determination of amino acids.



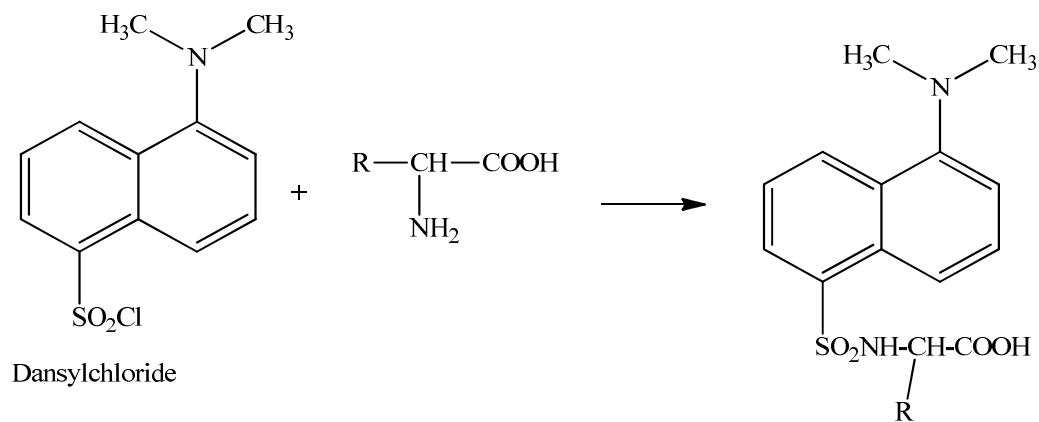
(ii) Reaction with 1,2- Benzene dicarbonyl: 1,2- Benzene dicarbonyl reacts with amino acids to give highly fluorescent isoindole derivatives.



(iii) Reaction with phenylisothiocyanate



(iv) Reaction with Dansyl chloride (1, 1-Dimethyl-aminonaphthalene-5-sulfonyl chloride)



The following reactions are used for the N-terminal analysis of proteins:

A. Sanger's reagent, FDNB (fluorodinitrobenzene), modifies N-terminus for determination via amino acid analysis.

