# 18: Organic Chemistry III

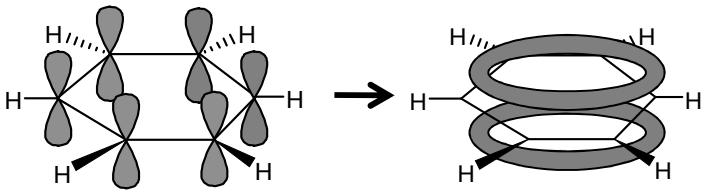
## 18A. Arenes

There are two major classes of organic chemicals
**aliphatic** : straight or branched chain organic substances
**aromatic or arene**: includes one or more ring of six carbon atoms with delocalised bonding.

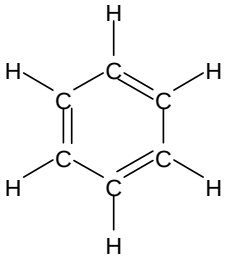
All of the organic substances we have looked at so far have been aliphatic

Benzene belongs to the aromatic class.

**Benzene's Structure**
The simplest arene is benzene. It has the molecular formula $C_6H_6$
Its basic structure is six C atoms in a hexagonal ring, with one H atom bonded to each C atom
Each C atom is bonded to two other C atoms and one H atom by single covalent σ-bonds. This leaves one unused electron on each C atom in a p orbital, perpendicular to the plane of the ring.
The Six p electrons are delocalised in a ring structure above and below the plane of carbon atoms

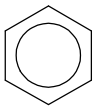


In 1865 Kekule suggested the following structure for Benzene consisting of alternate single and double covalent bonds between the carbon atoms

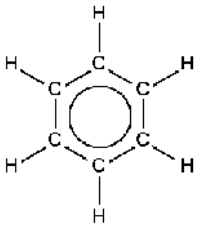


This structure is not correct. Evidence suggests that all the C-C bonds are the same length.

In formulae we draw a circle to show this delocalised system



Abbreviated formula



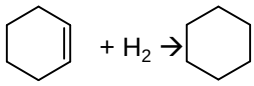
Displayed formula

The six electrons in the pi bonds are delocalised and spread out over the whole ring. Delocalised means not attached to a particular atom.

Benzene is a **planar** molecule.The evidence suggests all the C-C bonds are the same and have a length and bond energy between a C-C single and C=C double bond

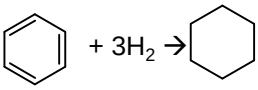
The H-C-C bond angle is 120° in Benzene

**Enthalpies of Hydrogenation**



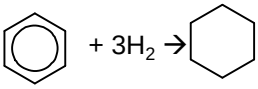
$\Delta H = -120$ kJ/mol

cyclohexene cyclohexane ↓ x3



$\Delta H = -360$ kJ/mol

Non delocalised structure



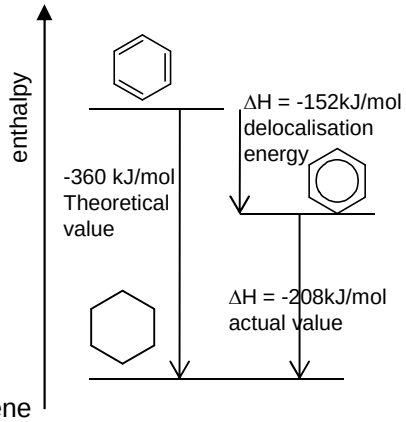
$\Delta H = -208$kJ/mol

delocalised structure

Theoretically because there are 3 double bonds one might expect the amount of energy to be 3 times as much.

However, the real amount of energy is less. The 6 pi electrons are delocalised and not arranged in 3 double bonds

This when represented on an energy level diagram shows that the delocalised benzene is more thermodynamically stable.

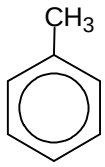



The increase in stability connected to delocalisation is called the **delocalisation energy**

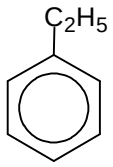
**Reactions of Benzene**
Benzene does not generally undergo addition reactions because these would involve breaking up the delocalised system. Most of Benzene's reactions involve substituting one H for another atom or group of atoms. Benzene has a high electron density and so attracts electrophiles. It reactions are usually **electrophilic substitutions**

**Naming aromatic molecules**

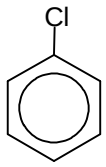
Naming aromatic compounds can be complicated. The simplest molecules are derivatives of benzene and have benzene at the root of the name



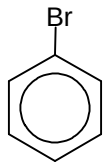
Methylbenzene



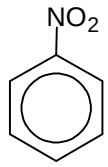
ethylbenzene



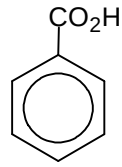
chlorobenzene



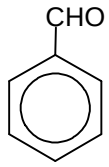
bromobenzene



nitrobenzene

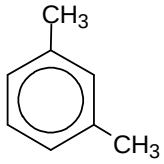


benzenecarboxylic acid

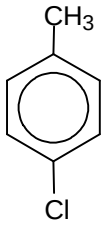


benzaldehyde

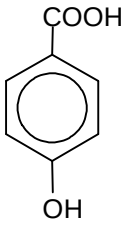
If two or more substituents are present on the benzene ring, their positions must be indicated by the use of numbers. This should be done to give the lowest possible numbers to the substituents. When two or more different substituents are present, they are listed in alphabetical order and di, tri prefixes should be used.



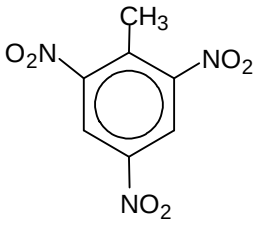
1,3-dimethylbenzene



1-chloro- 4-methylbenzene

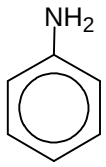


4-hydroxybenzenecarboxylic acid

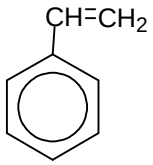


2,4,6-trinitromethylbenzene

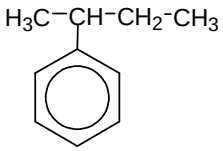
In other molecules the benzene ring can be regarded as a substituent side group on another molecule, like alkyl groups are. The $C_6H_5$- group is known as the **phenyl** group.



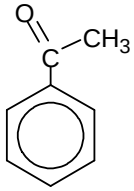
phenylamine



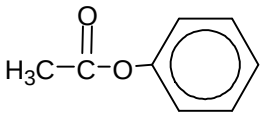
phenylethene



2-phenylbutane



phenylethanone



phenylethanoate

**Toxicity of Benzene**
Benzene is a carcinogen (cancers causing molecule) and is banned for use in schools.

Methylbenzene is less toxic and also reacts more readily than benzene as the methyl side group releases electrons into the delocalised system making it more attractive to electrophiles

## Reactions of Benzene

### Combustion

Benzene + oxygen → carbon dioxide + water

$C_6H_6$ (l) + 7.5 $O_2$ → 6 $CO_2$ + 3 $H_20$

Benzene will combust with a very sooty flame. The lower the carbon to hydrogen ratio the sootier the flame.

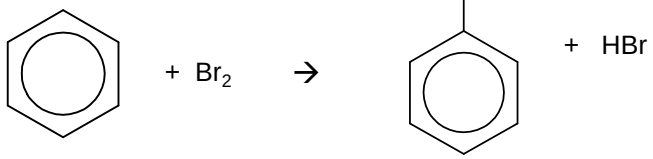
## Halogenation of Benzene

**Change in functional group**: benzene → Bromobenzene
**Reagents**: Bromine
**Conditions**: iron(III) bromide catalyst $FeBr_3$
**Mechanism**: Electrophillic Substitution

This reaction can be done with chlorine.
The catalyst can be $AlCl_3$ or $FeCl_3$

It is possible to create the iron(III) bromide in situ by reacting iron with bromine

**Overall Equation for reaction**

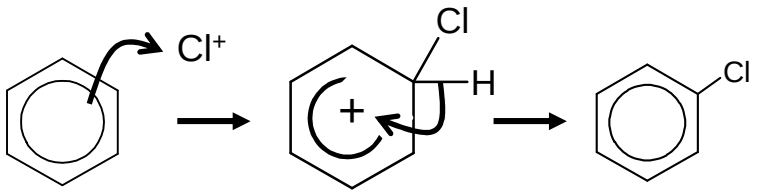



**Equation for Formation of electrophiles: (Learn!)**

$AlCl_3 + Cl_2 \rightarrow AlCl_4^- + Cl^+$

$FeBr_3 + Br_2 \rightarrow FeBr_4^- + Br^+$

**Mechanism**




The $H^+$ ion reacts with the $AlCl_4^-$ to reform $AlCl_3$ catalyst and HCl.

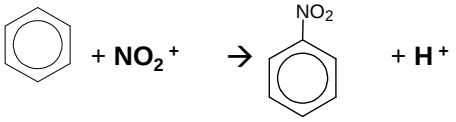
$H^+ + AlCl_4^- \rightarrow AlCl_3 + HCl$

## Nitration of Benzene

**Change in functional group:** benzene → nitrobenzene
**Reagents:** conc nitric acid in the presence of concentrated sulphuric acid (catalyst)
**Mechanism:** Electrophilic Substitution
**Electrophile: $NO_2^+$**

**Importance of this reaction**
Nitration of benzene and other arenes is an important step in synthesising useful compounds
e.g. explosive manufacture (like TNT, trinitrotoluene/ 2,4,6-trinitromethylbenzene)
and formation of amines from which dyestuffs are manufactured. (The reaction for this is covered in the amines section.)

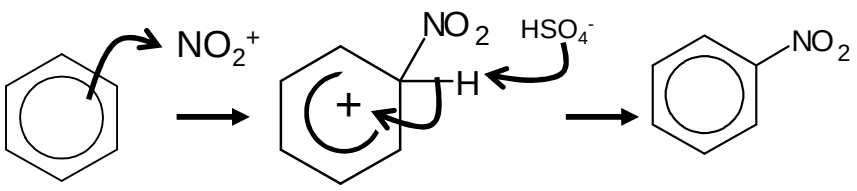
**Overall Equation for reaction**




**Equation for Formation of electrophile: (Learn!)**

$HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + 2HSO_4^- + H_3O^+$

**Mechanism**




The horseshoe shape of the intermediate must not extend beyond C's 2 to 6

The $H^+$ ion rejoins with the $HSO_4^-$ to reform $H_2SO_4$ catalyst.

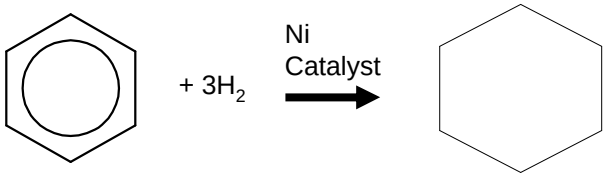
$H^+ + HSO_4^- \rightarrow H_2SO_4$

This reaction is done at 60°C. On using higher temperatures a second nitro group can be substituted onto different positions on the ring

If the benzene ring already has a side group e.g. methyl then the Nitro group can also join on different positions. A-level does not require knowledge of what positions the groups go on.

## Hydrogenation of Benzene

**Reaction:** benzene → cyclohexane
**Reagents:** Hydrogen
**Conditons:** Nickel catalyst at 200C and 30 atm
**Type of reaction**: Addition and reduction



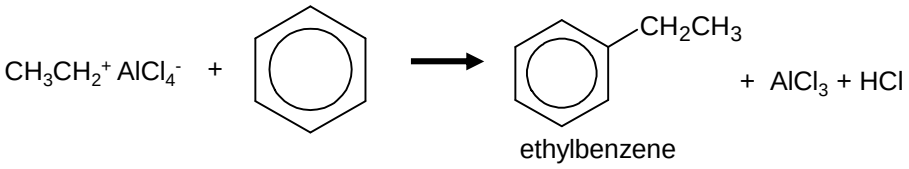

## Friedel Crafts Alkylation

**Change in functional group:** benzene → alkylbenzene
**Reagents:** chloroalkane in the presence of anhydrous aluminium chloride catalyst
**Conditions:** heat under reflux
**Mechanism:** Electrophilic Substitution

Any chloroalkane can be used RCl where R is any alkyl group Eg $-CH_3$ , $-C_2H_5$.
The electrophile is the $R^+$.

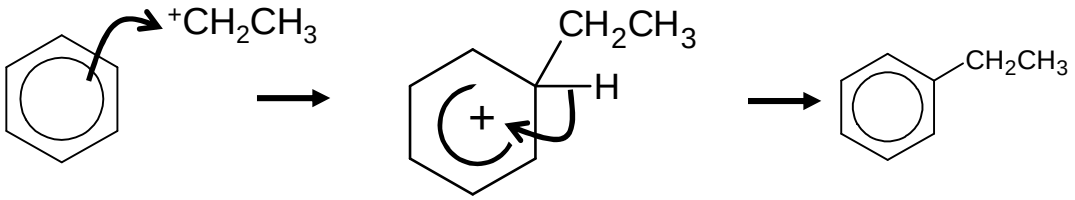
**Formation of the electrophile.**
$AlCl_3 + CH_3CH_2Cl \rightarrow CH_3CH_2^+ AlCl_4^-$

**Overall Equation for reaction**




ethylbenzene

**Mechanism**




The $H^+$ ion reacts with the $AlCl_4^-$ to reform $AlCl_3$ catalyst and HCl.

$H^+ + AlCl_4^- \rightarrow AlCl_3 + HCl$

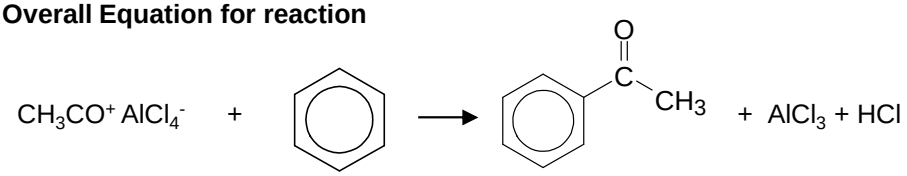
## Friedel Crafts Acylation

**Change in functional group:** benzene → phenyl ketone
**Reagents:** acyl chloride in the presence of anhydrous aluminium chloride catalyst
**Conditions:** heat under reflux (50$^{O}$C)
**Mechanism:** Electrophilic Substitution

Any acyl chloride can be used RCOCl where R is any alkyl group e.g. $-CH_3$ , $-C_2H_5$. The electrophile is the $RCO^+$.

**Equation for Formation of the electrophile.**
$AlCl_3 + CH_3COCl \rightarrow CH_3CO^+ AlCl_4^-$

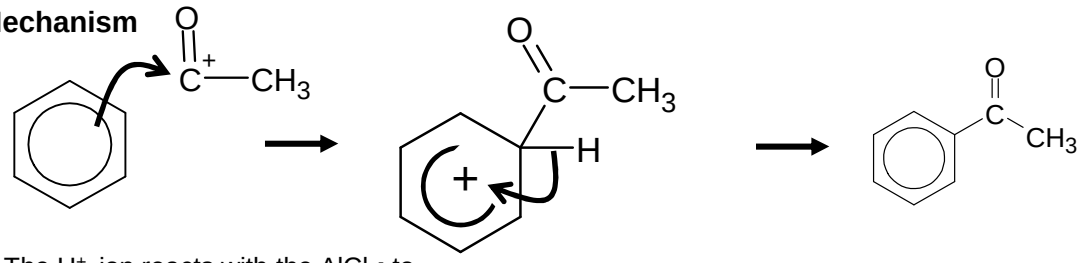
**Overall Equation for reaction**




phenylethanone

These are important reactions in organic synthesis because they introduce a reactive functional group on to the benzene ring

**Mechanism**




The $H^+$ ion reacts with the $AlCl_4^-$ to reform $AlCl_3$ catalyst and HCl.

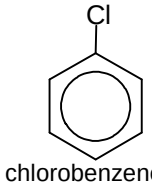
$H^+ + AlCl_4^- \rightarrow AlCl_3 + HCl$

### Effect of side groups on benzene ring

Electron releasing side groups such as alkyl groups, phenols and amines releases electrons into the delocalised system making a higher electron density in the ring and it more attractive to electrophiles. They will therefore carry out the substitution reactions more readily with milder conditions

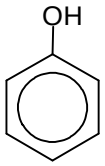
### Effect of delocalisation on side groups with lone pairs

If a –OH group, a Cl atom or an $NH_2$ group is directly attached to a benzene ring the delocalisation in the benzene ring will extend to include the lone pairs on the N,O and Cl. This changes the properties and reactions of the side group



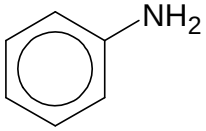

chlorobenzene

The C-Cl bond is made stronger. Typical halogenoalkane substitution and elimination reactions do not occur. Also the electron rich benzene ring will repel nucleophiles




phenol

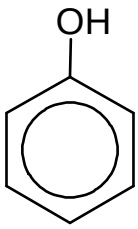
Delocalisation makes the C-O bond stronger and the O-H bond weaker. Phenol does not act like an alcohol- it is more acidic and does not oxidise




phenylamine

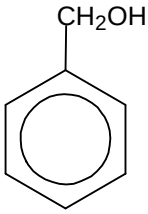
Less basic than aliphatic amines as lone pair is delocalised and less available for accepting a proton

## Phenols



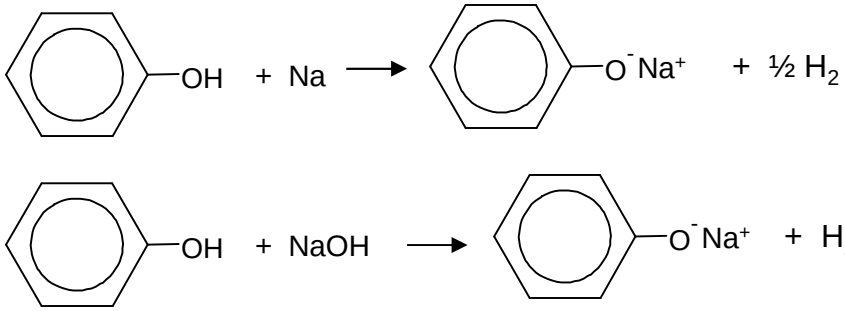

In a phenol the OH group is directly attached to the benzene ring.

In a phenol the lone pair of electrons on the oxygen is delocalised with the electron charge cloud of the arene ring.
The delocalised bonding changes the reactivity of the OH group and the arene ring.




This is not a phenol, but is an alcohol because the OH group is attached to an alkyl group rather than the benzene ring.

Phenols are very weakly acidic. They are weaker acids than carboxylic acids. Both phenols and carboxylic acids will react with sodium metal and sodium hydroxide. Only carboxylic acids will react with sodium carbonate as a phenol is not strong enough an acid to react.

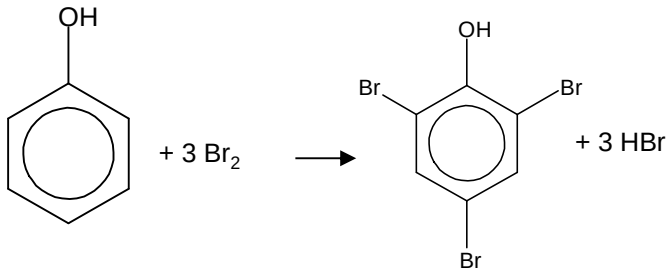



sodium phenoxide

The sodium phenoxide compound is more soluble than the original phenol. So the solid phenol dissolves on addition of NaOH

### Reaction of phenol with Bromine

**Reagents**: Bromine water
**Conditions**: room temp




2,4,6 –tribromophenol

Phenol does not need a $FeBr_3$ catalyst like benzene and undergoes multiple substitution whereas benzene will only add one Br.

The product in this reaction is a white solid

In phenol the lone pair of electrons on the oxygen (p- orbital) is partially **delocalised** into the ring. The electron density increases and the $Br_2$ is more polarised

Phenols are used in the production of plastics, antiseptics, disinfectants and resins for paints.

# 18B. Amines, Amides and Amino Acids

## Naming

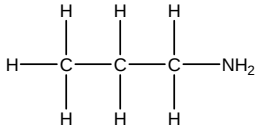
**Amines**

These end in **–amine**.

There is, however, rather confusingly two ways of using this suffix.

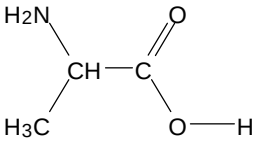
The exam board tend to use the common version where the name stem ends in **-yl** prop**yl**amine.

The IUPAC version of the same chemical is propan-1-amine. (This is used in the same way as naming alcohols)



prop**yl**amine
Or propan-1-amine

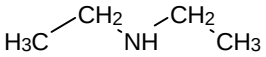
If there is another priority functional group as well as the amine group then the prefix amino is used.



2-aminopropanoic acid.

If the amine is secondary and has two alkyl groups attached to the nitrogen, then each chain is named and the smaller alkyl group is preceded by an –N which plays the same role as a number in positioning a side alkyl chain

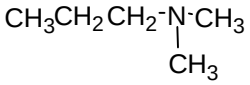
$CH_3CH_2CH_2NHCH_3$
N-methylpropylamine (common name)
N-methylpropan-1-amine (IUPAC name)



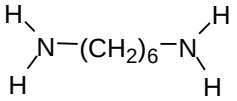
Diethylamine (common name- does not use N if chains are same length)
N-ethylethanamine (IUPAC name does still use N)

In the common naming version if the chain lengths are the same an –N is not used

If a tertiary amine similar rules apply, and each alkyl side group is given an N



N,N-dimethylpropylamine (common name)
N,N-dimethylpropan-1-amine (IUPAC name)

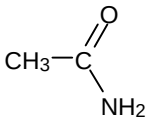


It could also be named 1,6-diaminohexane

hexane-1,6-diamine

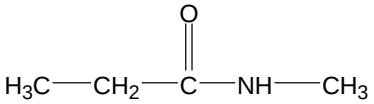
**Amides**

Add **–amide** to the stem name

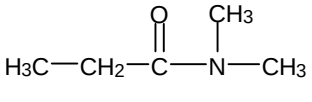


ethanamide

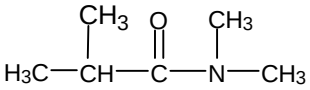
Secondary and tertiary amides are named differently to show the two (or three) carbon chains. The smaller alkyl group is preceded by an –N which plays the same role as a number in positioning a side alkyl chain



N-methylpropanamide



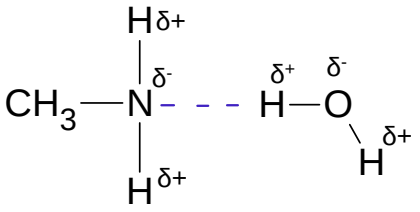
*N*,*N*-dimethylpropanamide



*N*,*N*,2-trimethylpropanamide

## Properties of Amines

Amines have a characteristic fishy smell



Small amines can form hydrogen bonds with water and therefore can dissolve readily in water.

**Base Properties**

Primary aliphatic amines act as Bronsted-Lowry Bases because the lone pair of electrons on the nitrogen is readily available for forming a dative covalent bond with a $H^+$ and so accepting a proton.

$CH_3NH_2 + H_2O \rightarrow CH_3NH_3^+ + OH^-$

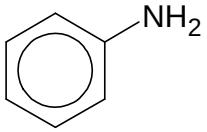
Primary aliphatic amines are stronger bases than ammonia as the alkyl groups are electron releasing and push electrons towards the nitrogen atom and so make it a stronger base.

$NH_{3\,(aq)} + H_2O_{\,(l)} \rightarrow NH_4^+{}_{(aq)} + OH^-{}_{(aq)}$

Secondary amines are stronger bases than primary amines because they have more alkyl groups that are substituted onto the N atom in place of H atoms. Therefore more electron density is pushed onto the N atom (as the inductive effect of alkyl groups is greater than that of H atoms).
One might expect using the same trend that tertiary amine would be the strongest amine base but the trend does not hold. The tertiary amines and corresponding ammonium salts are less soluble in water and this makes them less strong bases than the secondary amines. (This point will not be examined)

**Base strength of aromatic amines**

Primary aromatic amines such as Phenylamine do not form basic solutions because the lone pair of electrons on the nitrogen delocalise with the ring of electrons in the benzene ring. This means the N is less able to accept protons.



phenylamine

**Reactions with acids**

Amines as bases react with acids to form ammonium salts.
$CH_3NH_{2\,(aq)} + HCl_{\,(aq)} \rightarrow CH_3NH_3^+Cl^-{}_{(aq)}$
Methylamine methylammonium chloride
$2CH_3NH_{2\,(aq)} + H_2SO_{4\,(aq)} \rightarrow (CH_3NH_3^+)_2\,SO_4^{2-}{}_{(aq)}$

Addition of NaOH to an ammonium salt will convert it back to the amine

These ionic salts will be solid crystals, if the water is evaporated, because of the strong ionic interactions.

The ionic salts formed in this reaction means that the compounds are soluble in the acid.
e.g. Phenylamine is not very soluble in water but phenylammonium chloride is soluble

**Making a basic buffer from an amine**

Basic buffers can be made from combining a weak base with a salt of that weak base
e.g. Ammonia and ammonium chloride
Methylamine and methylammonium chloride
Ethylamine and ethylammonium chloride

### Formation of complex ions

The lone pair of electrons on the nitrogen enable amines to act as ligands and form dative covalent bonds into transition metal ions to form coloured complex ions.

$$4\,CH_3CH_2NH_2 + Cu(H_2O)_6^{2+} \rightleftharpoons [Cu(CH_3CH_2NH_2)_4(H_2O)_2]^{2+} + 4H_2O$$

This is a similar ligand exchange reaction to the one where ammonia acts as the ligand

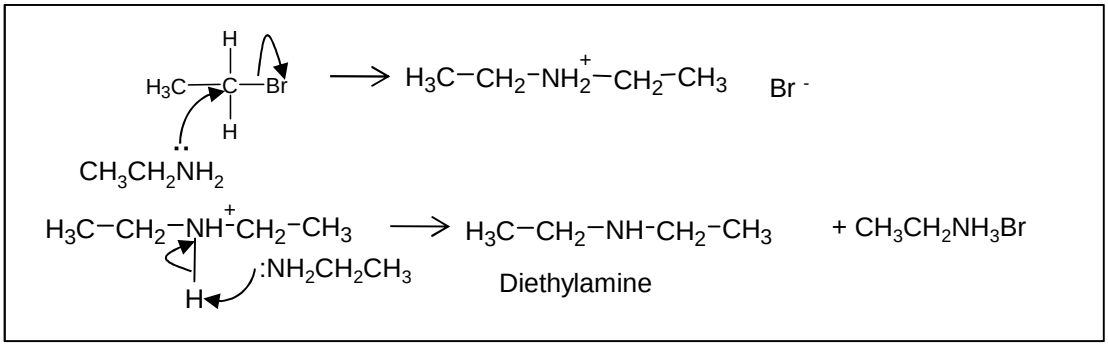
$$4NH_3 + Cu(H_2O)_6^{2+} \rightleftharpoons [Cu(NH_3)_4(H_2O)_2]^{2+} + 4H_2O$$

light blue solution — deep blue solution

**Reaction of primary Amines with halogenoalkanes forming secondary amines**

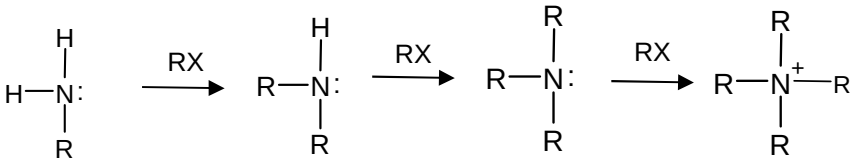
Amines will react with halogenoalkanes in a similar way to the reaction of ammonia with halogenoalkanes via a nucleophilic substitution reaction

$2CH_3CH_2NH_2 + CH_3CH_2Br \rightarrow CH_3CH_2NH_2CH_2CH_3 + CH_3CH_2NH_3Br$




The secondary amine formed can also then react with more halogenoalkane to form a tertiary amine and subsequently on to what is called a quaternary ammonium salt

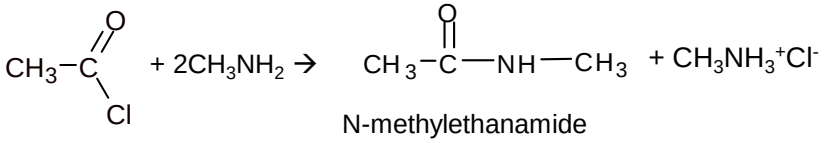
Where RX is the haloalkane



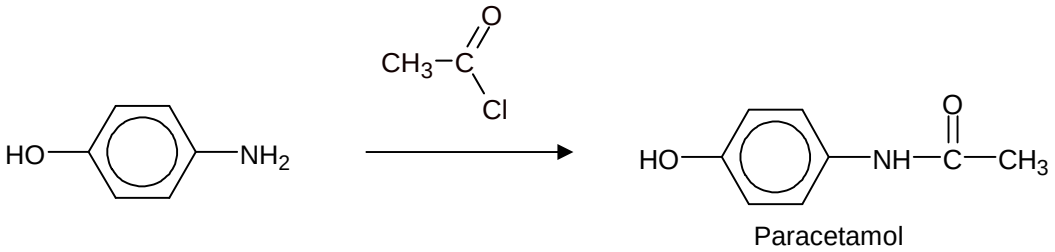

**Reaction with primary amines with acyl chlorides**

Change in functional group**: acyl chloride → secondary amide**
Reagent: **primary amine**
Conditions: **room temp.**

$RCOCl + 2CH_3NH_2 \rightarrow RCONHCH_3 + CH_3NH_3^+Cl^-$




Paracetamol is made by the reaction of an aromatic amine with an acyl chloride to produce an amide



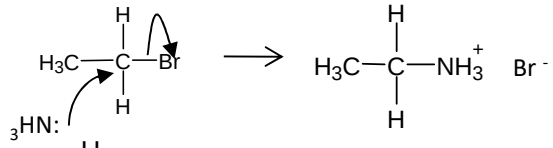
## The preparation of primary aliphatic amines

### 1. Forming a primary amine in a one step reaction of halogenoalkanes with ammonia

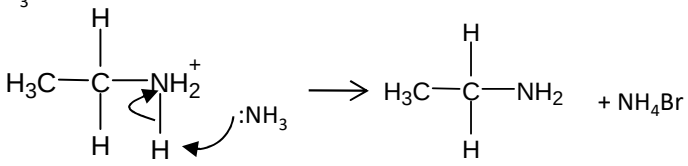
Primary amines can be formed by the **nucleophilic substitution** reaction between halogenoalkanes and ammonia in a **one step reaction**. However, as the lone pair of electrons is still available on the N in the amine formed, the primary amine can react in the same nucleophilic way in a successive series of reactions forming secondary, tertiary amines and quaternary ammonium salts.
This is therefore not a good method for making a primary amine because of the further reactions. It would mean the desired product would have to be separated from the other products.

$CH_3CH_2Br + 2NH_3 \rightarrow CH_3CH_2NH_2 + NH_4Br$

Ammonia dissolved in ethanol is the initial nucleophile



In the first step of the mechanism the nucleophile attacks the halogenoalkane to form an intermediate



In the second step of the mechanism a second ammonia removes a proton from the intermediate (acts as base) to form the amine

Using an **excess of Ammonia** can limit the further subsequent reactions and will **maximise the amount of primary amine** formed

### 2. Preparing Amines from Nitriles

Using the method above of reacting halogenoalkanes and ammonia is not an efficient method for preparing a high yield of the primary amine because of the further substitution reactions that occur.

A better method is to use the following reactions

Step 1. convert **halogenoalkane to nitrile** by using KCN in ethanol (heat under reflux)

$CH_3CH_2Br + CN^- \rightarrow CH_3CH_2CN + Br^-$

Step 2. reduce **nitrile to amine** by using **$LiAlH_4$ in ether** or by reducing with $H_2$ using a Ni catalyst

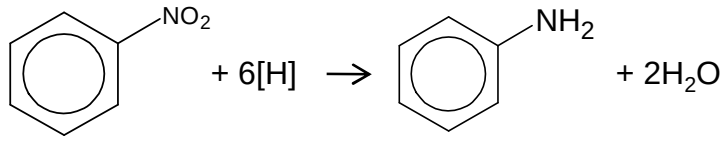
$CH_3CH_2CN + 4[H] \rightarrow CH_3CH_2CH_2NH_2$

A disadvantage of this method is that it is a two step reaction that may therefore have a low yield. Also KCN is toxic.

**Reducing nitroarenes to aromatic amines**

The nitro group on an arene can be reduced an amine group as follows

**Reagent**: Sn and HCl or Fe and HCl
**Conditions**: Heating
**Mechanism**:reduction




nitrobenzene phenylamine

As the reaction is carried out in HCl the salt $C_6H_5NH_3^+Cl^-$ will be formed. Reacting this salt with NaOH will give phenylamine.

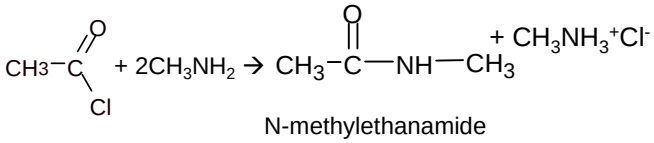
The phenylamine formed in this reaction is best separated from the reaction mixture by steam distillation.

**Forming Amides**

Aliphatic amines and phenylamine can react with acyl chlorides to form amides in a nucleophilic addition-elimination reaction- see chapter 17C for more details.

Change in functional group**: acyl chloride → secondary amide**
Reagent: **primary amine**
Conditions: **room temp.**

$$RCOCl + 2CH_3NH_2 \rightarrow RCONHCH_3 + CH_3NH_3^+Cl^-$$




N-methylethanamide

**Condensation Polymerisation**

The two most common **types** of condensation polymers are **polyesters** and **polyamides** which involve the formation of an **ester** linkage or an **amide** linkage.

In condensation polymerisation there are two different monomers that add together and a small molecule is usually given off as a side-product e.g. $H_2O$ or HCl.

The monomers usually have the same functional group on both ends of the molecule e.g. di-amine, di carboxylic acid, diol, diacyl chloride.

Forming polyesters and polyamide uses these reactions we met earlier in the course

Carboxylic Acid + Alcohol → Ester + water

Acyl chloride + Alcohol → Ester + HCl

Carboxylic Acid + Amine → amide + water

Acyl chloride + Amine → amide + HCl

If we have the same functional group on each end of molecule we can make polymers so we have the analogous equations:

dicarboxylic acid + diol → poly(ester) + water

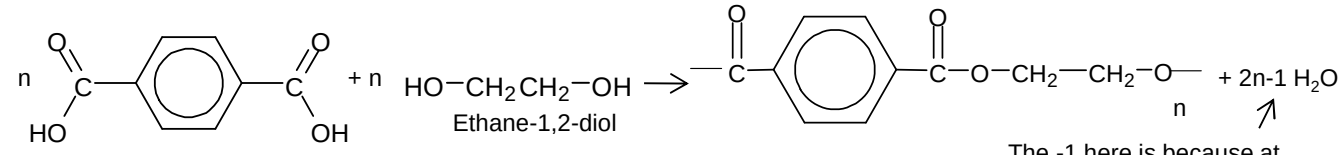
diacyl dichloride + diol → poly(ester) + HCl

dicarboxylic acid + diamine → poly(amide) + water

diacyl dichloride + diamine → poly(amide) + HCl

Using the carboxylic acid to make the ester or amide would need an acid catalyst and would only give an equilibrium mixture. The more reactive acyl chloride goes to completion and does not need a catalyst but does produce hazardous HCl fumes.

**Terylene- a common polyester**

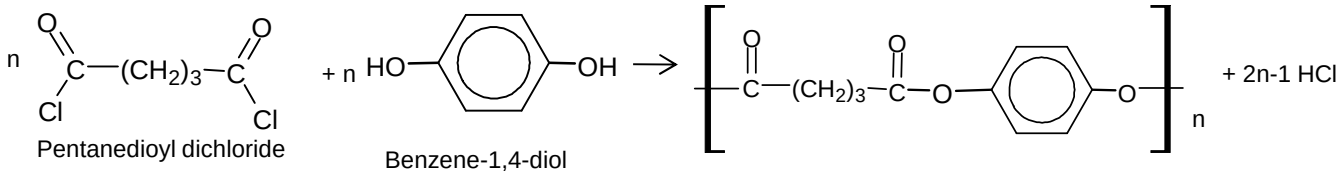



Benzene-1,4-dicarboxylic acid

Ethane-1,2-diol

The -1 here is because at each end of the chain the H and OH are still present

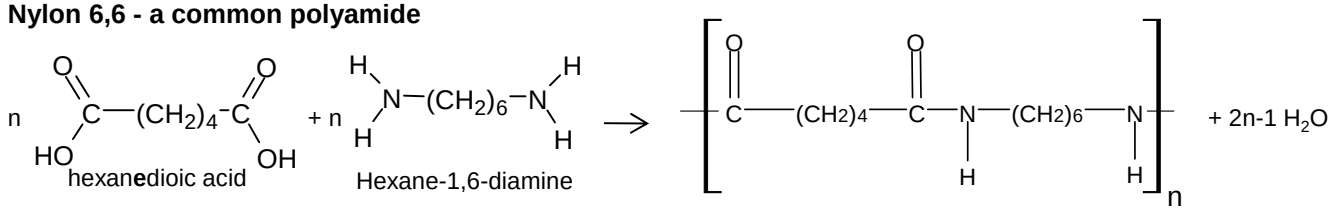
Terylene fabric is used in clothing, tire cords




Pentanedioyl dichloride

Benzene-1,4-diol

**Nylon 6,6 - a common polyamide**

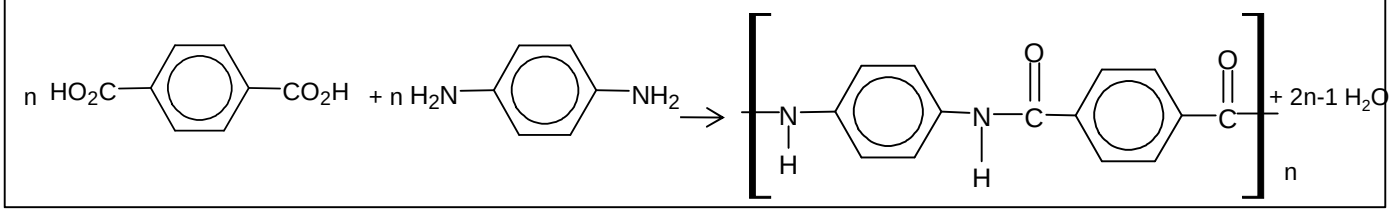



hexan**e**dioic acid

Hexane-1,6-diamine

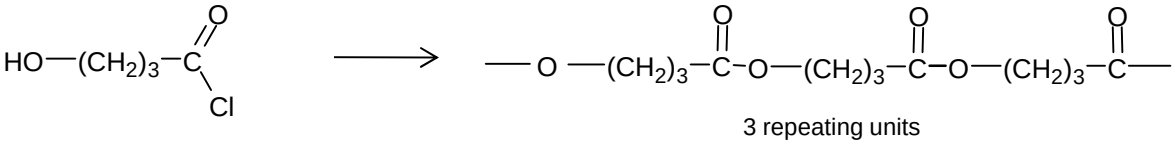
The 6,6 stands for 6 carbons in each of the monomers. Different length carbon chains produce different polyamides

**Kevlar- a common polyamide**

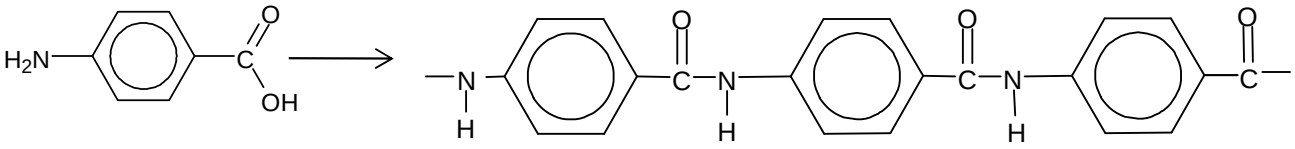


**Note on classification for condensation polymers**
If asked for **type of polymer**: It is polyamide or polyester
Whereas **type of polymerisation** is **condensation**

It is also possible for polyamides and polyesters to form from **one** monomer, if that monomer contains both the functional groups needed to react




3 repeating units




3 repeating units

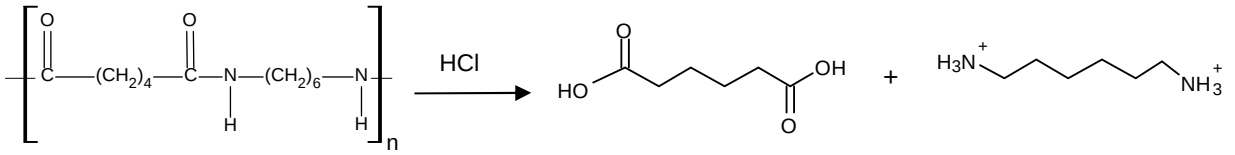
**Chemical reactivity of condensation polymers**

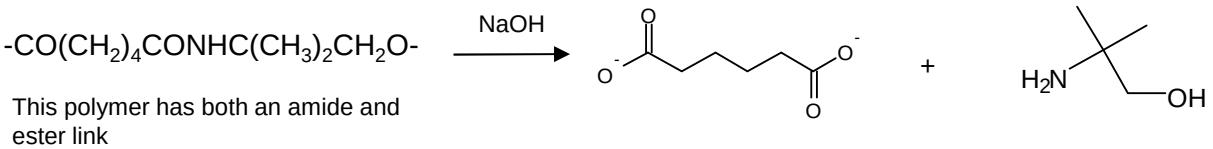
polyesters and polyamides can be broken down by **hydrolysis** and are, therefore, biodegradable

The reactivity can be explained by the presence of **polar bonds** which can attract attacking species such as nucleophiles and acids

**Hydrolysis**

Polyesters and polyamides can be hydrolysed by acid and alkali
The hydrolysis will result in the original monomers forming- although the carboxylic acid or amine group will be in salt form depending on whether the conditions are alkaline or acidic



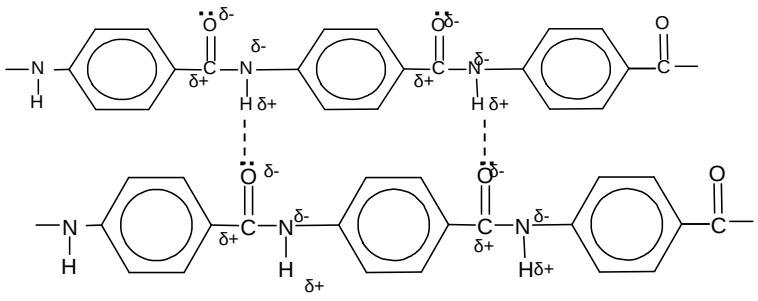




This polymer has both an amide and ester link

**Intermolecular bonding between condensation polymers chains**

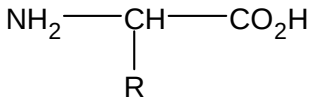
Polyesters have permanent dipole forces between the $C^{\delta+}=O^{\delta-}$ groups in the different chains in addition to the London forces between the chains.

Polyamides (and proteins) have **hydrogen bonding** between the lone pairs on oxygen in $C^{\delta+}=O^{\delta-}$ groups and the H in the $N^{\delta-}—H^{\delta+}$ groups in the different chains.
There are also **Permanent dipole-permanent dipole forces b**ecause the polar C=O bond and polar C-N bond
There are also **London forces** which are large because there are many electrons in the molecule
Polyamides will therefore have higher melting points than polyesters.



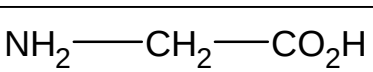
## Amino Acids

**General structure of an amino acid**



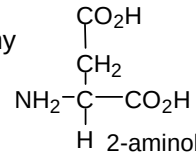
The R group can be a variety of different things depending on what amino acid it is.

The simplest amino acid is glycine, where the R is an H

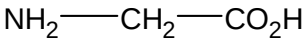


**Naming amino acids**

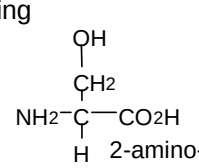
You do not need to know any common names for the 20 essential amino acids. We should, however, be able to name given amino acids using IUPAC organic naming



2-aminobutanedioic acid

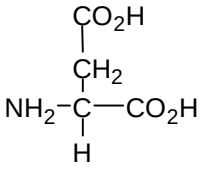


(2-)aminoethanoic acid

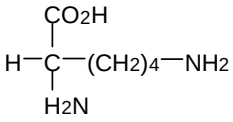


2-amino-3-hydroxypropanoic acid

Some amino acids have an extra carboxylic acid or an amine group on the R group. These are classed as acidic or basic (respectively) amino acids



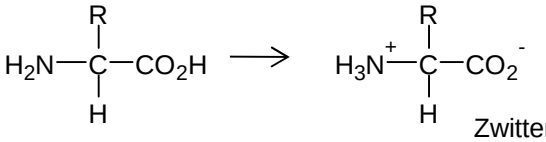
Aspartic acid



Lycine (basic)
2,6-diaminohexanoic acid

**Zwitterions**

The no charge form of an amino acid never occurs. The amino acid exists as a dipolar zwitterion.



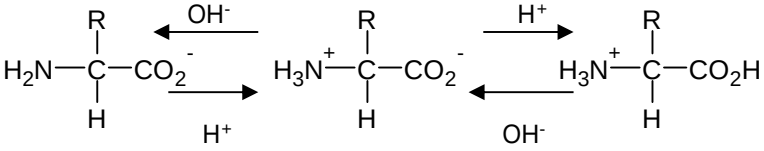
Zwitterion

Amino acids are often **solids**

The **ionic interaction** between zwitterions explains the relatively high melting points of amino acids as opposed to the weaker hydrogen bonding that would occur in the no charge form.

**Acidity and Basicity**

The amine group is basic and the carboxylic acid group is acidic.



**Species in alkaline solution High pH**

**Species in neutral solution**

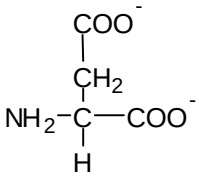
**Species in acidic solution Low pH**

Amino acids act as weak buffers and will only gradually change pH if small amounts of acid or alkali are added to the amino acids.

$^{+}NH_3\text{-}CH_2\text{-}CO_2^{-} + HCl \rightarrow Cl^{-}\ NH_3^{+}\text{-}CH_2\text{-}CO_2H$

$^{+}NH_3\text{-}CH_2\text{-}CO_2^{-} + NaOH \rightarrow\ NH_2\text{-}CH_2\text{-}CO_2^{-}Na^{+} + H_2O$

The extra carboxylic acid or amine groups on the R group will also react and change form in alkaline and acid conditions



Aspartic acid in high pH

## Chromatography of Amino Acids

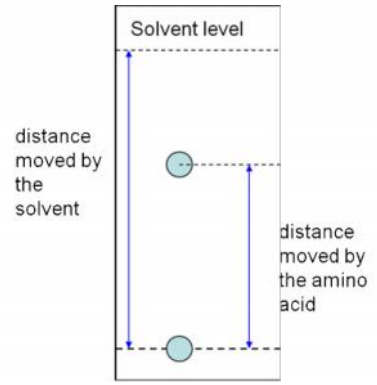
A mixture of amino acids can be separated by chromatography and identified from the amount they have moved.

$R_f$ value = distance moved by amino acid / distance moved by the solvent

Each amino acid has its own $R_f$ value. Compare an unknown amino acid's Rf value with known values in a data book to identify the amino acid

**Method**

Take chromatography paper and draw a pencil line 1.5cm from bottom.
With a capillary tube put a small drop of amino acid on pencil line
Roll up paper and stand it in a large beaker.
The solvent in the beaker should be below the pencil line.
Allow to stand for 20 mins and mark final solvent level
Spray paper with ninhydrin and put in oven

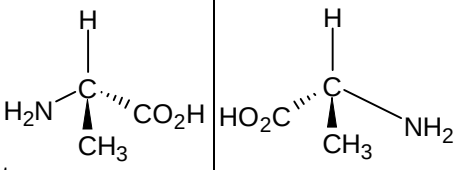



If ninhydrin is sprayed on an amino acid and then heated for 10 minutes then red to blue spots appear. This is done because amino acids are transparent and cannot be seen.

**Optical Activity**

All amino acids, except glycine, are chiral because there are four different groups around the C

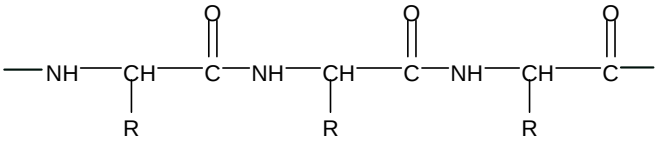
They rotate plane polarised light.

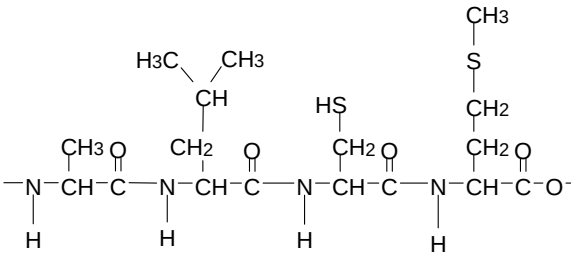


Optical isomers have similar physical and chemical properties, but they rotate plane polarised light in different directions.

## Proteins

Proteins are polymers made from combinations of amino acids.
The amino acids are linked by peptide links, which are the amide functional group.

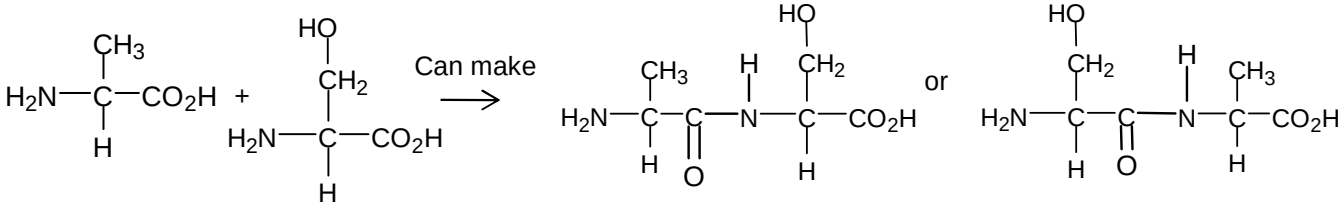




## Dipeptides

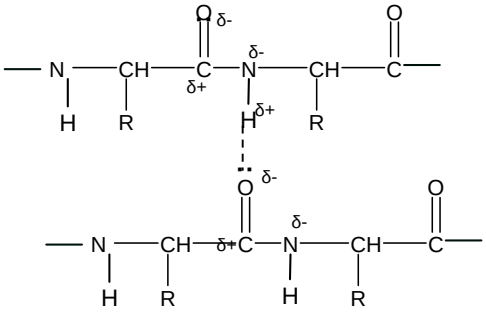
Dipeptides are simple combination molecules of two amino acids with one amide (peptide) link.

For any two different amino acids there are two possible combinations of the amino acids in the dipeptide.



**Importance of hydrogen bonding in proteins**

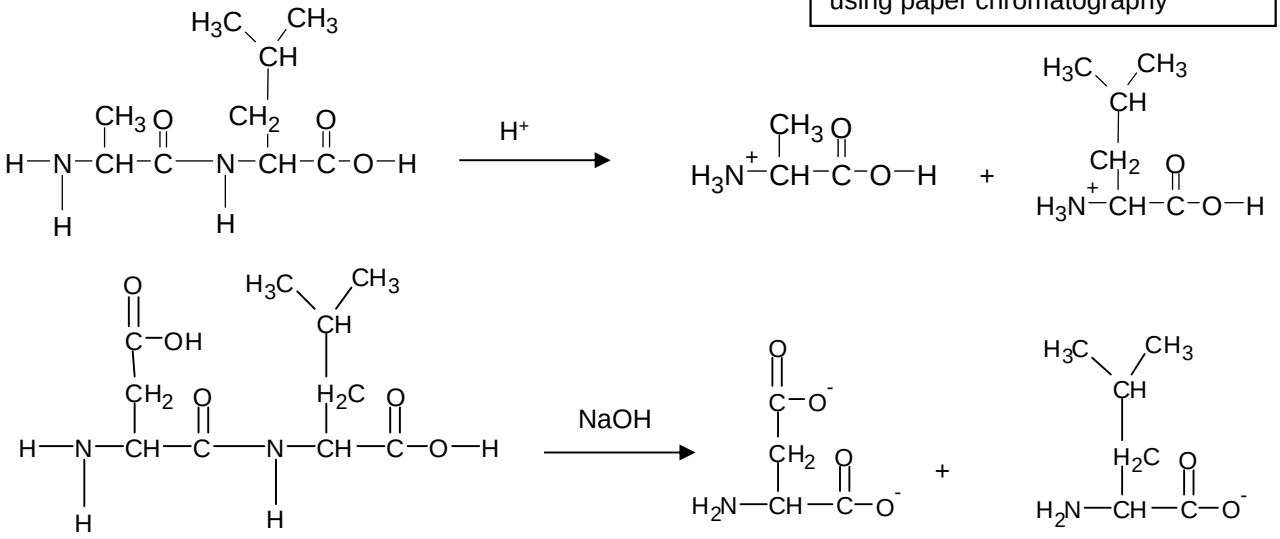
The 3D arrangement of amino acids with the polypeptide chain in a corkscrew shape is held in place by Hydrogen bonds between the H of $-N^{\delta-}-H^{\delta+}$ group and the –O of $C^{\delta+}=O^{\delta-}$



**Hydrolysis of di-peptides/proteins**

If proteins are heated with dilute acid or alkali they can be hydrolysed and split back in to their constituent amino acids.

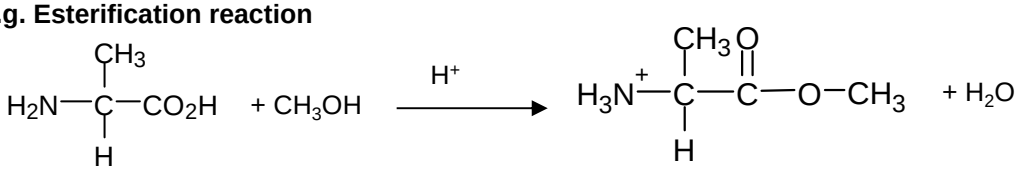
The composition of the protein molecule may then be deduced by using paper chromatography

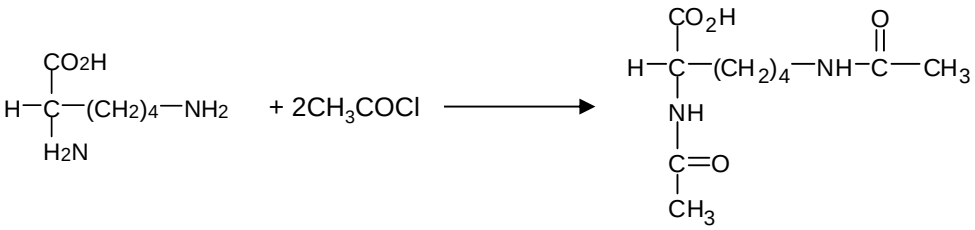



**Other reactions of amino acids**

The carboxylic acid group and amine group in amino acids can undergo the usual reactions of these functional groups met in earlier topics. Sometimes questions refer to these.

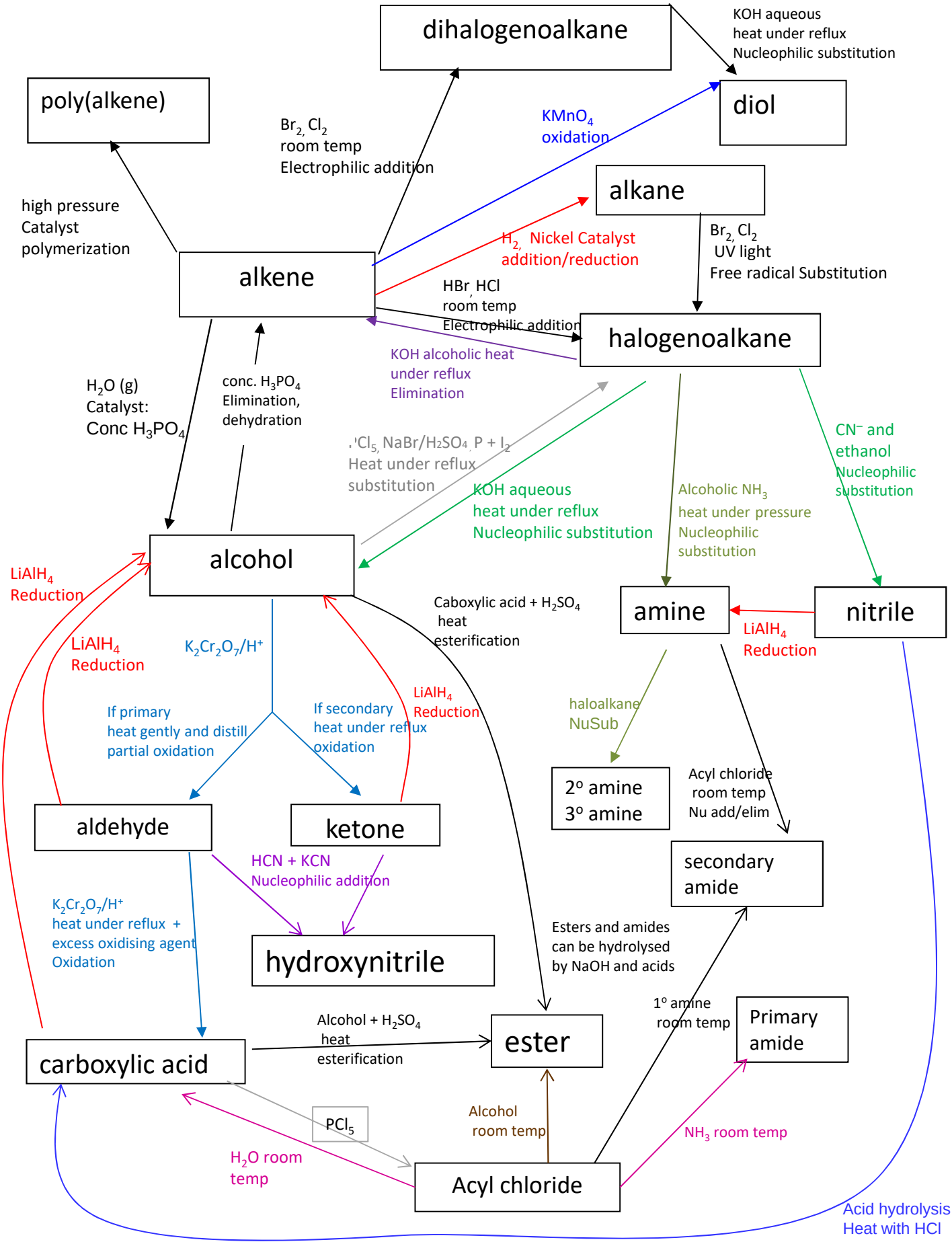
**e.g. Esterification reaction**



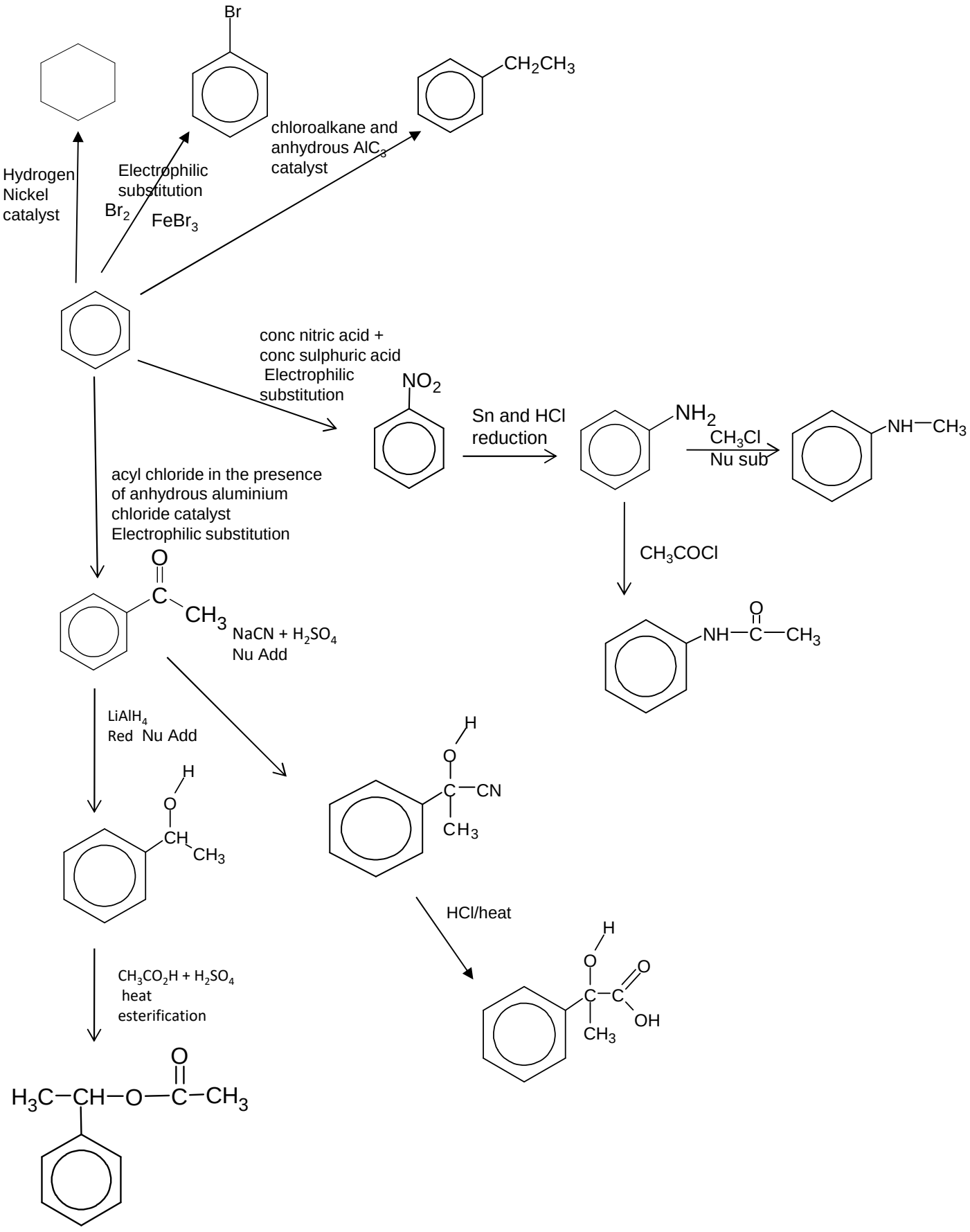




If the R group contains a amine or carboxylic acid then these will do the same reactions as the **α** amine and carboxylic groups

# 18C. Synthetic Routes



## Aromatic synthetic routes



# Grignard Reactions

Grignard Reagent is used to increase the length of the carbon chain in a molecule

## Preparing Grignard Reagent

A halogenoalkane is dissolved in dry ether and reacted with magnesium to produce the reactive Grignard Reagent

$CH_3CH_2I + Mg \rightarrow CH_3CH_2MgI$

Ethyl magnesium iodide
Grignard Reagent

This Grignard reagent is highly reactive and the alkyl group can be considered to have a negative charge. The $R^-[^+MgI]$ and so contains a nucleophilic carbon atom

## Reactions of Grignard Reagent

### Reactions with carbonyls

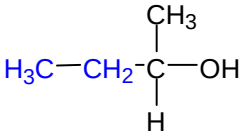
With methanal will produce a **primary alcohol**

$$CH_3CH_2MgI + HCHO \xrightarrow{H_2O} CH_3CH_2CH_2OH + Mg(OH)I$$

$$RMgI + HCHO \rightarrow RCH_2OH + Mg(OH)I$$

With other aldehydes will produce **secondary alcohols**

$$CH_3CH_2MgI + CH_3CHO \xrightarrow{H_2O}$$

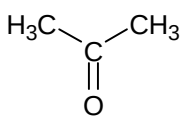


$+ Mg(OH)I$

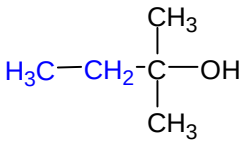
$$RMgI + R'CHO \xrightarrow{H_2O} RCH(OH)R' + Mg(OH)I$$

With ketones will produce **tertiary alcohols**

$CH_3CH_2MgI +$



$\xrightarrow{H_2O}$



$+ Mg(OH)I$

$$RMgI + R'COR'' \xrightarrow{H_2O} RR'C(OH)R'' + Mg(OH)I$$

### Reaction with carbon dioxide

With $CO_2$ will produce a **carboxylic acid**

$$CH_3CH_2MgI + CO_2 \xrightarrow{H_2O} CH_3CH_2CO_2H + Mg(OH)I$$

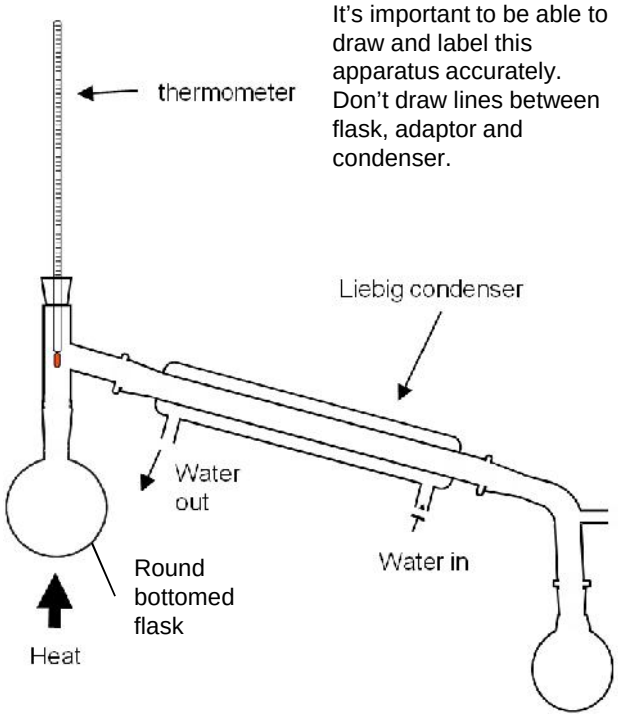
The carbon chain can also be increased by the introduction of a nitrile group into a compound by either reacting a halogenoalkane with KCN (see chapter 6D) or producing hydroxynitriles from carbonyls (see chapter 17B)

## Organic techniques

### Distillation

In general used as separation technique to separate an organic product from its reacting mixture. Need to collect the distillate of the approximate boiling point range of the desired liquid.

**Classic AS reaction using distillation**
**Reaction**: primary alcohol → aldehyde
**Reagent**: potassium dichromate (VI) solution and dilute sulphuric acid.
**Conditions**: use a limited amount of dichromate and **warm gently and distil** out the aldehyde as it forms [This prevents further oxidation to the carboxylic acid]
$CH_3CH_2CH_2OH + [O] \rightarrow CH_3CH_2CHO + H_2O$
**Observation**
Orange dichromate solution changes to green colour of $Cr^{3+}$ ions



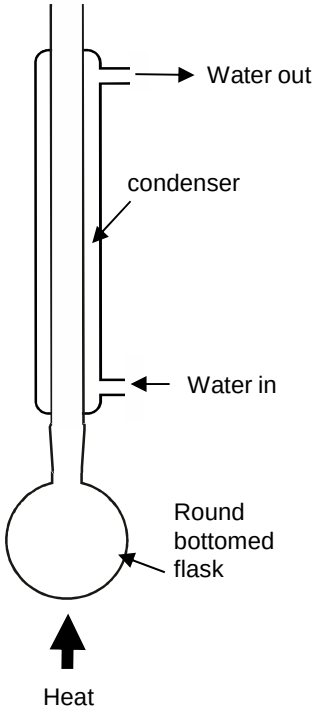

It's important to be able to draw and label this apparatus accurately. Don't draw lines between flask, adaptor and condenser.

### Reflux

Reflux is used when heating organic reaction mixtures for long periods. The condenser prevents organic vapours from escaping by condensing them back to liquids.

**Never seal the end of the condenser** as the build up of gas pressure could cause the apparatus to explode. This is true of any apparatus where volatile liquids are heated

**Classic AS reaction using reflux**
**Reaction**: primary alcohol → carboxylic acid
**Reagent**: potassium dichromate(VI) solution and dilute sulphuric acid
**Conditions**: use an excess of dichromate, and **heat under reflux**: (distill off product after the reaction has finished using distillation set up)
$CH_3CH_2CH_2OH + 2[O] \rightarrow CH_3CH_2CO_2H + H_2O$
**Observation**
Orange dichromate solution changes to green colour of $Cr^{3+}$ ions




Anti-bumping granules are added to the flask in both distillation and reflux to prevent vigorous, uneven boiling by **making small bubbles** form instead of large bubbles

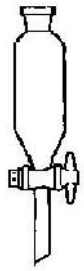
It's important to be able to draw and label this apparatus accurately.
- Don't draw lines between flask and condenser.
- Don't have top of condenser sealed
- Condenser must have outer tube for water that is sealed at top and bottom
- Condenser must have two openings for water in and out that are open

## Purifying an organic liquid **General method**

- Put the distillate of impure product into a separating funnel
- wash product by adding either
  - sodium hydrogencarbonate solution , shaking and releasing the pressure from $CO_2$ produced.
  - Saturated sodium chloride solution

Sodium hydrogencarbonate will neutralise any remaining reactant acid.

Sodium chloride will help separate the organic layer from the aqueous layer



Separating funnel

•Allow the layers to separate in the funnel, and then run and discard the aqueous layer.

The layer with lower density will be the upper layer. This is usually the organic layer

•Run the organic layer into a clean, dry conical flask and add three spatula loads of drying agent (e.g. anhydrous sodium sulphate, calcium chloride) to dry the organic liquid. When dry the organic liquid should appear clear.

The drying agent should
- be insoluble in the organic liquid
- not react with the organic liquid

- Carefully decant the liquid into the distillation flask

Decant means carefully pour off organic liquid leaving the drying agent in the conical flask

•Distill to collect pure product

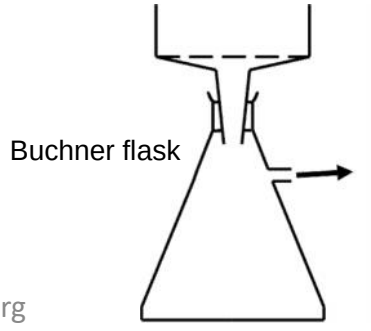
## Purifying an organic solid: Recrystallisation

Used for purifying aspirin

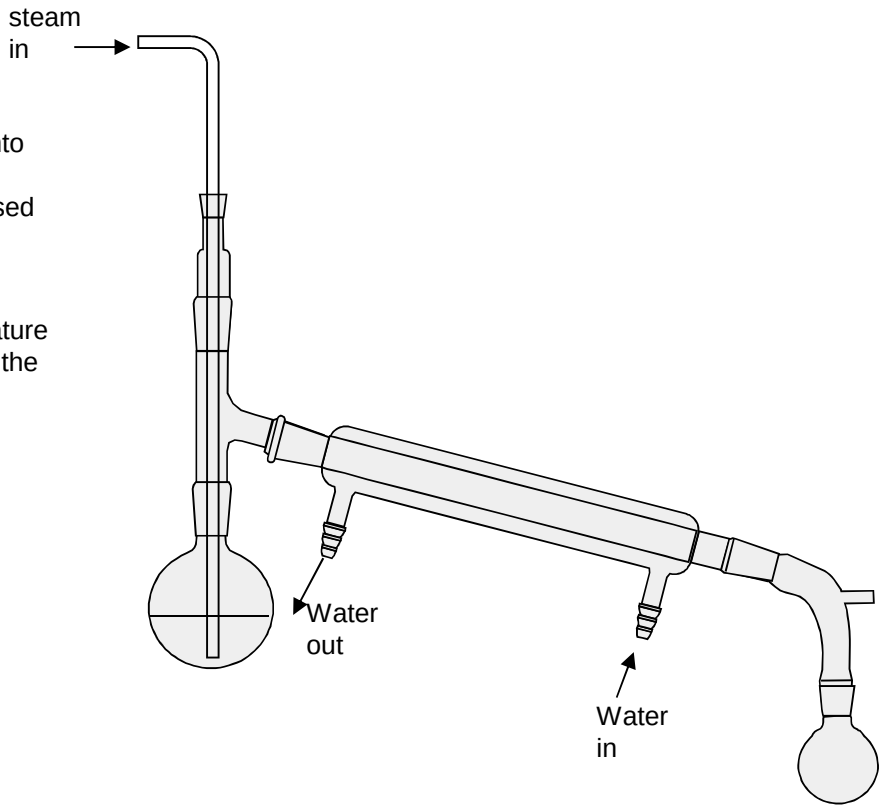
| Step | Reason |
|---|---|
| 1. Dissolve the impure compound in a **minimum volume** of **hot** (near boiling) **solvent**. | An appropriate solvent is one which will dissolve both compound and impurities when hot **and** one in which the compound itself does not dissolve well when cold. The minimum volume is used to obtain saturated solution and to enable crystallisation on cooling (If excess (solvent) is used, crystals might not form on cooling) |
| 2. **Hot filter** solution through (fluted) filter paper quickly. | This step will remove any insoluble impurities and heat will prevent crystals reforming during filtration |
| 3. **Cool** the filtered solution by inserting beaker **in ice** | Crystals will reform but soluble impurities will remain in solution form because they are present in small quantities so the solution is not saturated with the impurities. Ice will increase the yield of crystals |
| 4**. Suction filtrate** with a buchner flask to separate out crystals | The water pump connected to the Buchner flask reduces the pressure and speeds up the filtration. |
| 5 Wash the crystals with distilled water | To remove soluble impurities |
| 6. Dry the crystals between absorbent paper | |

**Loss of yield in this process**
- Crystals lost when filtering or washing
- Some product stays in solution after recrystallisation
- other side reactions occurring

If the crystals are not dried properly the mass will be larger than expected which can lead to a percentage yield >100%



## Steam distillation

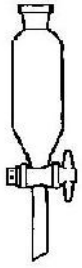



In steam distillation steam is passed into the mixture and the product vapour is distilled off with the water and condensed

**Advantage of steam distillation:**
The product distils at a lower temperature which can prevents decomposition of the product if it has a high boiling point

## Solvent extraction

Mix organic solvent and oil-water mixture in a separating funnel then separate the oil layer.
Distil to separate oil from organic solvent
Add anhydrous $CaCl_2$ to clove oil to dry oil
Decant to remove $CaCl_2$




## Safety and hazards

A **hazard** is a substance or procedure that can has the potential to do harm.
Typical hazards are toxic/flammable /harmful/ irritant /corrosive /oxidizing/ carcinogenic

**RISK:** This is the probability or chance that harm will result from the use of a hazardous substance or a procedure

Irritant - dilute acid and alkalis- wear googles
Corrosive- stronger acids and alkalis wear goggles
Flammable – keep away from naked flames
Toxic – wear gloves- avoid skin contact- wash hands after use
Oxidising- Keep away from flammable / easily oxidised materials

Hazardous substances in low concentrations or amounts will not pose the same risks as the pure substance.

## Measuring melting point

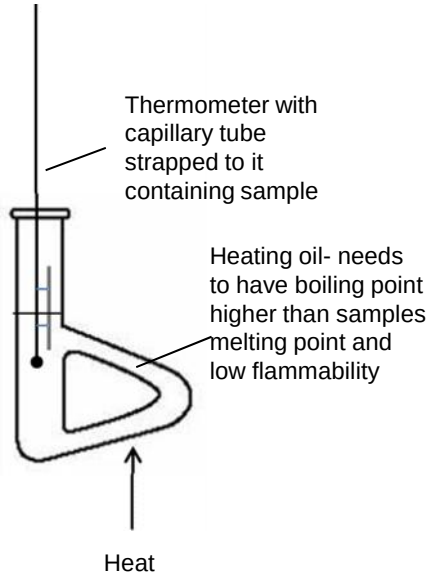
One way of testing for the degree of purity is to determine the melting "point", or melting range, of the sample.

If the sample is very pure then the melting point will be a sharp one, at the same value as quoted in data books.

If **impurities** are present (and this can include solvent from the recrystallisation process) the **melting point will be lowered** and the sample will **melt over a range** of several degrees Celsius

Melting point can be measured in an electronic melting point machine or by using a practical set up where the capillary tube is strapped to a thermometer immersed in some heating oil.

In both cases a small amount of the salt is put into a capillary tube.




Comparing an experimentally determined melting point value with one quoted in a data source will verify the degree of purity.

Sometimes an error may occur if the temperature on the thermometer is not the same as the temperature in the actual sample tube.

## Measuring boiling point

Purity of liquid can be determined by measuring a boiling point. This can be done in a distillation set up or by simply boiling a tube of the sample in an heating oil bath.

Pressure should be noted as changing pressure can change the boiling point of a liquid

Measuring boiling point is not the most accurate method of identifying a substance as several substances may have the same boiling point.

To get a correct measure of boiling point the thermometer should be above the level of the surface of the boiling liquid and be measuring the temperature of the saturated vapour.

## Combustion Analysis

0.328 g of a compound containing C,H and O was burnt completely in excess oxygen, producing 0.880 g of carbon dioxide and 0.216 g of water. Use these data to calculate the empirical formula of the compound.

Work out moles of $CO_2$ = Mass of $CO_2$/Mr of $CO_2$

= 0.88/44
=0.02mol

Moles of C in compound = moles of $CO_2$ → Mass of C in compound = mol of C x 12
= 0.02 mol =0.02 x12
=0.24g

Work out moles of $H_2O$ = Mass of $H_2O$ /Mr of $H_2O$

= 0.216/18
=0.012mol

Moles of H in compound = 2 x moles of $H_2O$ → Mass of H in compound = mol of H x 1
= 0.024 mol =0.024 x1
=0.024g

Work out mass of O in compound = mass of compound – mass of C – mass of H
= 0.328 – 0.24 -0.024
=0.064

Work out moles of O in compound = Mass of O /Ar of O
= 0.064/16
= mol 0.004

Work out molar ratio of 3 elements (divide by smallest moles)

C = 0.02/0.004
=5

H = 0.024/0.004
=6

O = 0.004/0.004
= 1

**empirical formula = $C_5H_6O$**

See notes in chapter 19 on spectroscopy for mass spec, IR, and NMR

**Bringing it all together**

1. Work out empirical formula

Elemental analysis C 66.63% H 11.18% O 22.19%

| C | H | O |
|---|---|---|
| 66.63/12 | 11.18/1 | 22.19/16 |
| =5.5525 | =11.18 | =1.386875 |
| =4 | =8 | =1 |

2. Using molecular ion peak m/z value from mass spectrum calculate Molecular formula

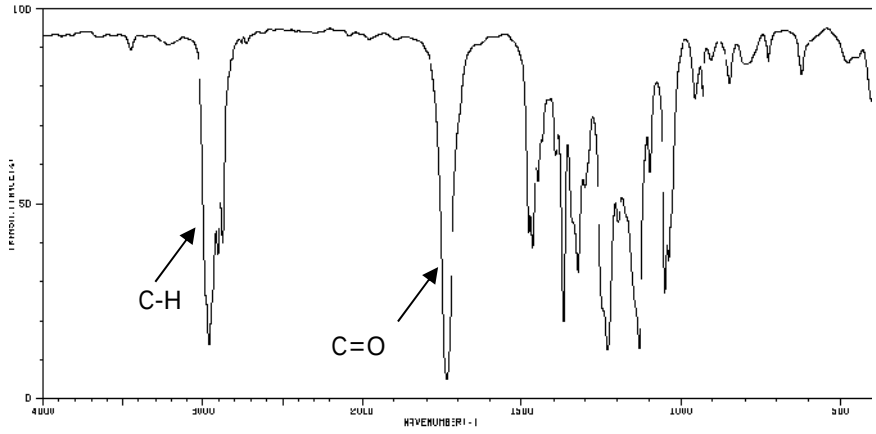
molecular ion peak m/z value= 144

Mr empirical formula $C_4H_8O$ = 72

If Mr molecular formula 144 then compound is $C_8H_{16}O_2$

3. Use IR spectra or functional group chemical tests to identify main bonds/functional group

$C_8H_{16}O_2$ could be an ester, carboxylic acid or combination of alcohol and carbonyl. Look for IR spectra for C=O and O-H bonds

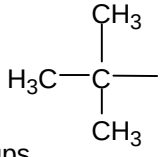



There is a C=O but no O-H absorptions, so must be an ester.

4. Use NMR spectra to give details of carbon chain

4 peaks – only 4 different environments.

singlet of area 9
At δ =0.9
Means 3 $CH_3$ groups



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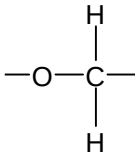
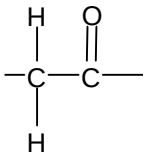
Peak at δ 4 shows H–C–O

Area 2 suggests $CH_2$
Quartet means next to a $CH_3$

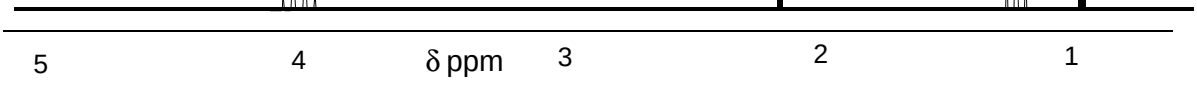


Peak at δ 2.2 shows H–C=O

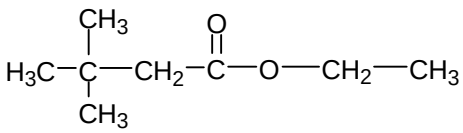
Area 2 suggests $CH_2$
Singlet means adjacent to C with no hydrogens



Peak at δ 1.2 shows R-$CH_3$
Area 3 means $CH_3$
Triplet means next to a $CH_2$




Put all together to give final structure



## Testing for Organic Functional Groups

| Functional group | Reagent | Result |
|---|---|---|
| Alkene | Bromine water | Orange colour decolourises |
| Alcohols + carboxylic acids | $PCl_5$ | Misty fumes of HCl produced |
| Alcohols, phenols, carboxylic acids | Sodium metal | Efferevesence due to $H_2$ gas |
| Carbonyls | 2,4,DNP | Orange/red crystals produced |
| Aldehyde | Fehlings solution | Blue solution to red precipitate |
| Aldehyde | Tollens Reagent | Silver mirror formed |
| Carboxylic acid | Sodium carbonate | Effervescence of $CO_2$ evolved |
| $1^o$ $2^o$ alcohol and aldehyde | Sodium dichromate and sulphuric acid | Orange to green colour change |
| chloroalkane | Warm with silver nitrate | Slow formation of white precipitate of AgCl |
| Acyl chloride | Silver nitrate | Vigorous reaction- steamy fumes of HCl- rapid white precipitate of AgCl |

### Tollen's Reagent

**Reagent:** Tollen's Reagent formed by mixing aqueous ammonia and silver nitrate. The active substance is the complex ion of $[Ag(NH_3)_2]^+$ .

**Conditions:** heat gently

**Reaction: aldehydes only** are oxidised by Tollen's reagent into a carboxylic acid and the silver(I) ions are reduced to silver atoms

**Observation:** with aldehydes, a silver mirror forms coating the inside of the test tube. Ketones result in no change.

$CH_3CHO + 2Ag^+ + H_2O \rightarrow CH_3COOH + 2Ag + 2H^+$

### Fehling's solution

**Reagent:** Fehling's Solution containing blue $Cu^{2+}$ ions.

**Conditions:** heat gently

**Reaction: aldehydes only** are oxidised by Fehling's Solution into a carboxylic acid and the copper ions are reduced to copper(I) oxide .

**Observation: Aldehydes :**Blue $Cu^{2+}$ ions in solution change to a red precipitate of $Cu_2O$. **Ketones do not react**

$CH_3CHO + 2Cu^{2+} + 2H_2O \rightarrow CH_3COOH + Cu_2O + 4H^+$

The presence of a carboxylic acid can be tested by addition of **sodium carbonate**. It will fizz and produce carbon dioxide

$2CH_3CO_2H + Na_2CO_3 \rightarrow 2CH_3CO_2^-Na^+ + H_2O + CO_2$