Raffles Institution
Year 6 H2 Chemistry 2025
Lecture Notes 20
Nitrogen Compounds – Amines, Amides, Amino Acids & Proteins

Content

Amines (exemplified by ethylamine and phenylamine)

(i) their formation
(ii) salt formation
(iii) other reactions of phenylamine

Amides (exemplified by ethanamide)

(i) formation from acyl chlorides
(ii) neutrality of amides
(ii) hydrolysis (under acidic and basic conditions)

Amino acids (exemplified by aminoethanoic acid)

(i) their acid and base properties
(ii) zwitterion formation

Proteins

(i) formation of proteins
(ii) hydrolysis of proteins

Condensation Polymers

(i) polyamides and polyesters

Learning outcomes

Candidates should be able to:

(a) describe the formation of amines as exemplified by ethylamine (through amide and nitrile reduction) and by phenylamine (through the reduction of nitrobenzene)

(b) describe the reaction of amines in the formation of salts

(c) describe and explain the basicity of primary, secondary and tertiary amines in the gaseous phase (interpret as Lewis bases)

(d) explain the relative basicities of ammonia, ethylamine and phenylamine, in aqueous medium, in terms of their structures

(e) describe the reaction of phenylamine with aqueous bromine

(f) describe the formation of amides from the condensation reaction between RNH_2 and $R'COCl$

(g) explain why an amide is neutral in terms of delocalisation of the lone pair of electrons on nitrogen

(h) describe the chemistry of amides, exemplified by the following reactions:
  (i) hydrolysis on treatment with aqueous alkali or acid
  (ii) reduction to amines with lithium aluminium hydride

(i) describe the acid/base properties of amino acids and the formation of zwitterions
[knowledge of isoelectric points is **not** required]

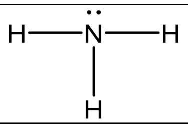
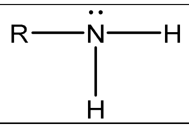
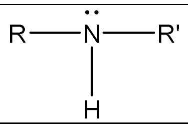
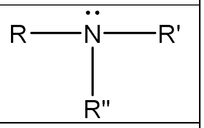
(j) describe the formation of peptide (amide) bonds between α-amino acids, and hence explain protein formation

(k) describe the hydrolysis of proteins

Amines RNH_2 | 1 – Introduction

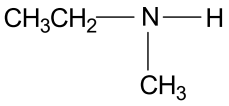
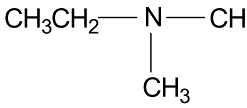
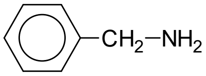
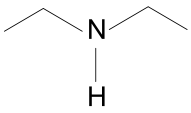
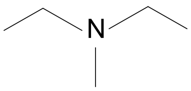
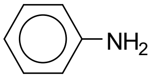
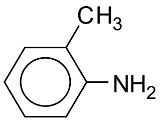
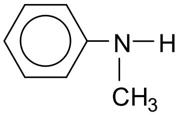
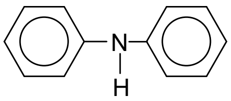
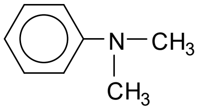
1.1 What are amines?

- Amines are derivatives of ammonia in which one or more hydrogen atoms of the ammonia molecule have been substituted by alkyl or aryl groups.
- Amines are classified as primary, secondary or tertiary amines depending on the number of alkyl or aryl groups attached to the nitrogen atom.

Type of amine	Ammonia (**not amine**)	Primary (1°)	Secondary (2°)	Tertiary (3°)
Structure				
Number of R groups attached to N	0	1	2	3

1.2 Nomenclature

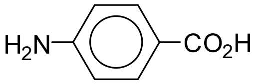
- In the common names of amines, the **names of the alkyl/aryl groups** bonded to nitrogen are given first, followed by the suffix **-amine**.

	primary (1°) amine	**secondary (2°) amine**	**tertiary (3°) amine**
Aliphatic amines	$CH_3–NH_2$ methylamine $CH_3CH_2–NH_2$ ethylamine $CH_3CH_2CH_2–NH_2$ propylamine	 *N*-methylethylamine (ethylmethylamine)	 *N*,*N*-dimethylethylamine (ethyldimethylamine)
	$H_2N–CH_2CH_2–NH_2$ ethane-1,2-diamine  (phenylmethyl)amine	 diethylamine	 *N*-methyldiethylamine (diethylmethylamine)
Aromatic amines - Aromatic amines are amines in which the nitrogen atom is attached directly to the aromatic ring.	 **phenylamine** (aniline)  2-methylphenylamine	 *N*-methylphenylamine  diphenylamine	 *N*,*N*-dimethylphenylamine

- In naming amines with more complicated structures or in compounds in which other functional groups are of higher priority, the $–NH_2$ group becomes the prefix (substituent) and is called the **amino group**.

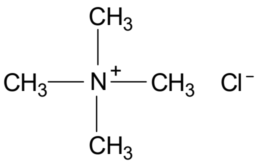
$H_2N–CH_2CH_2–COOH$
3-aminopropanoic acid

$H_2N–CH_2CH_2–OH$
2-aminoethanol

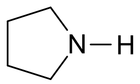

4-aminobenzoic acid

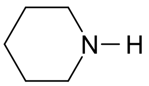
- **Quaternary ammonium salts** ($R_4N^+X^–$) are the organic equivalent of ammonium compounds (e.g. NH_4Cl). They have **four alkyl/aryl groups bonded to the nitrogen atom**.

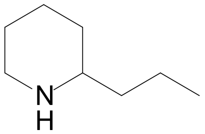
$(CH_3)_4N^+Cl^–$
tetramethylammonium chloride


$CH_3–N^+(CH_3)_2–CH_3 \; Cl^-$

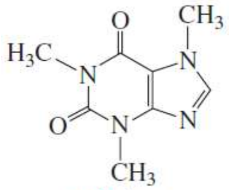
- **Cyclic amines** exist. Some examples are given below.

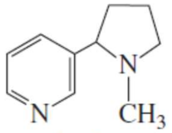

pyrrolidine

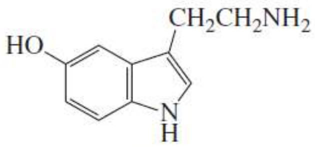

piperidine

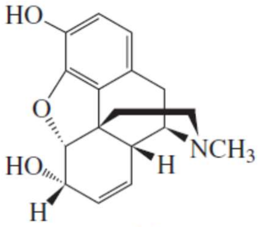

coniine

- Some naturally occurring amines.


caffeine

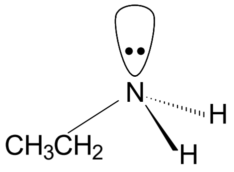

nicotine


serotonin


morphine

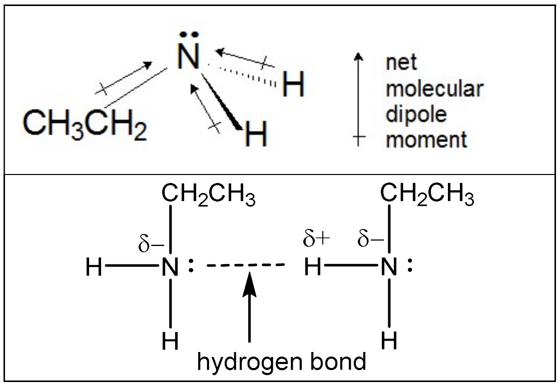
1.3 Structure of amines

- Similar to ammonia, the N atom of most amines is sp^3 hybridised.
- Consider the ethylamine molecule.

$CH_3CH_2–NH_2$ 	What is the shape of the ethylamine molecule with respect to the N atom? • There are 4 electron pairs around the N atom in an amine molecule. • They must be directed in a tetrahedral manner in order to minimise repulsion. • Since there are 3 bond pairs and 1 lone pair, the shape of the amine molecule is trigonal pyramidal with respect to the N atom.

Amines RNH_2 | 2 – Physical Properties

- Amines are polar compounds.



	contains N–H bond?	hydrogen bonding among own molecules?
1° amine		
2° amine		
3° amine		

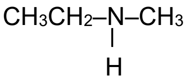
2.1 Boiling point

- The smaller aliphatic amines are gases (e.g. CH_3NH_2 and $CH_3CH_2NH_2$) or liquids with low-boiling points (e.g. $CH_3CH_2CH_2NH_2$ and $CH_3CH_2CH_2CH_2NH_2$).

(a) For a particular class of amines, boiling point generally increases with increasing M_r.

Amine	**M_r**	**melting point/ °C**	**boiling point / °C**	**Reason**
CH_3NH_2	31	–94	– 6	• **larger and more polarisable electron cloud** • **increasing strength of instantaneous dipole-induced dipole interactions**
$CH_3CH_2NH_2$	45	–81	17	
$CH_3CH_2CH_2NH_2$	59	–83	48	
$CH_3CH_2CH_2CH_2NH_2$	73	–51	78	
$C_6H_5NH_2$	93	–6	184	

(b) Among <u>isomeric</u> amines, boiling point increases in the following order: **3° < 2° < 1° amines**.

Amine	**Class**	**boiling point / °C**	**Points to note**
$CH_3CH_2CH_2–NH_2$	1° amine	48	• instantaneous dipole-induced dipole forces • permanent dipole-permanent dipole forces • **hydrogen bonding**
 $CH_3CH_2–N(H)–CH_3$	2° amine	34	• instantaneous dipole-induced dipole forces • **hydrogen bonding** • **less polar** than $CH_3CH_2CH_2–NH_2$ ⇒ **weaker permanent dipole-permanent dipole forces (compared to 1° amines)**
$(CH_3)_3N$	3° amine	3	• instantaneous dipole-induced dipole forces • **permanent dipole-permanent dipole forces** • **no hydrogen bonding** among the molecules.

(c) In general, amines have **<u>higher boiling points</u>** than alkanes of similar electron cloud size.

Compound	**M_r**	**boiling point / °C**	**predominant intermolecular forces**
$CH_3CH_2NH_2$	45	17	• hydrogen bonding
$CH_3CH_2CH_3$	44	–42	• instantaneous dipole-induced dipole forces

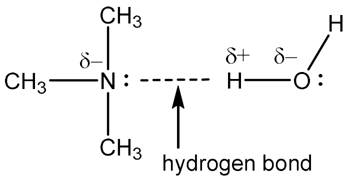
(d) In general, amines have **lower boiling points** than alcohols of similar electron cloud size.

Compound	M_r	**boiling point / °C**	**Reason**
$CH_3CH_2NH_2$	45	17	• the N atom is less electronegative than the O atom • the N–H bond is less polar than the O–H bond • the N–H······N hydrogen bond is **weaker** than the O–H·······O hydrogen bond
CH_3CH_2OH	46	78.5	
$CH_3CH_2CH_2NH_2$	59	48	
$CH_3CH_2CH_2OH$	60	97	

2.2 Solubility

- All three classes of amines **can form hydrogen bonds with water**.
- Why are the lower members very soluble in water?
  - their molecules can interact with water molecules via hydrogen bonding
  - their molecules have relatively small non-polar hydrocarbon portions
- The higher members have poor solubility in water because they have relatively large non-polar hydrocarbon portions. Borderline solubility in water is reached at about six carbon atoms.

Hydrogen bonding between trimethylamine (a 3° amine) and water.



http://www.humantouchofchemistry.com/node/10

Why do fish smell when you buy them?

Heard of the saying "something smells fishy"? Have you noticed how a fresh fish smells different from one that is not so fresh? Yes, once again it is chemistry that is the reason behind this.

The cause of the stink

Fishes smell because of a natural process of decay. Bacterial enzymes attack the flesh of the fish. This triggers an oxidation reduction reaction. The muscle of the fish contain a substance called trimethylamine oxide (TMAO) which is broken down by decomposition. The result is trimethylamine and dimethylamine. The mixing of these two amines results in that characteristic fishy smell. In fact, it is the presence of trimethylamine that is used as an indicator of how fresh a fish is.

Do you know you can use lemon, vinegar and baking soda to reduce the smell of the fish?

Removing the smell

If you do have a very smelly fish and need to remove the fish smell, then chemistry can come to your aid once again. Using lemon, vinegar or baking soda will reduce the smell of the mixing amines. Amines are alkaline based and lemon juice is acidic in nature, thus mixing the two neutralizes the effect of each other. This is why lemon is added to fish preparations to remove the strong smell of fish.

2.3 Odour

- The smell of the early members of the amine series is similar to that of ammonia, though with a slightly fishy character.
- Dimethylamine and trimethylamine are found in rotting fish and are partly responsible for its peculiar smell.
- Putrescine (butane-1,4-diamine) and cadaverine (pentane-1,5-diamine) are found in decaying animal flesh.

2.4 Aromatic amines

- Aromatic amines are liquids or solids with high boiling points. They are generally toxic.
- Phenylamine is only sparingly soluble in water due to its large non-polar benzene ring which interferes with the formation of hydrogen bonding between the –NH_2 group and water.
- Phenylamine has appreciable solubility in non-polar organic solvents. Its ability to dissolve in fats means that it is readily absorbed through the skin.

3.1 Amines as bases

- An amine, like ammonia, can act as a **Br∅nsted-Lowry base** (i.e. a proton acceptor) and **a Lewis base** (i.e. an electron-pair donor).

An amine can be a **Br∅nsted-Lowry base**

because it has a **lone pair of electrons** on the nitrogen atom which is available to form a dative covalent bond with **a proton**.

■ See Examples 1 to 4 below.

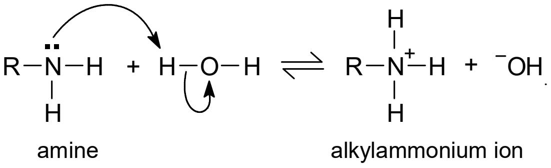
An amine can be a **Lewis base**

because it has a **lone pair of electrons** on the nitrogen atom which is available to form a dative covalent bond with **an electron-deficient species**.

■ See Examples 1 to 5 below.

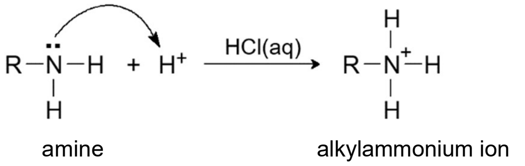
- **Examples**

Example 1 – Reaction with H_2O



$R\text{–}NH_2(aq) + H_2O(l) \rightleftharpoons R\text{–}NH_3^+(aq) + OH^-(aq)$

Example 2 – Reaction with HC*l*(aq)

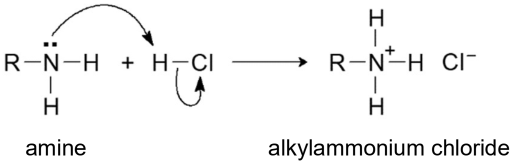


$R\text{–}NH_2(aq) + H^+(aq) \longrightarrow R\text{–}NH_3^+(aq)$

Example 3 – Reaction with $CH_3CO_2H(aq)$

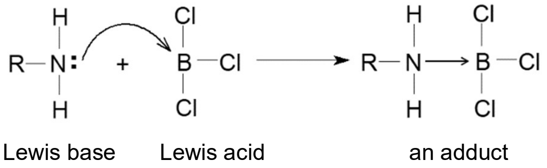
$R\text{–}NH_2 + CH_3CO_2H \rightleftharpoons R\text{–}NH_3^+ + CH_3CO_2^-$

Example 4 – Reaction with HC*l*(g)



$R\text{–}NH_2(g) + HCl(g) \longrightarrow R\text{–}NH_3^+Cl^-$

Example 5 – Reaction with BC*l*$_3$



$R\text{–}NH_2(g) + BCl_3(g) \longrightarrow RH_2N{\rightarrow}BCl_3$

- **Note:**

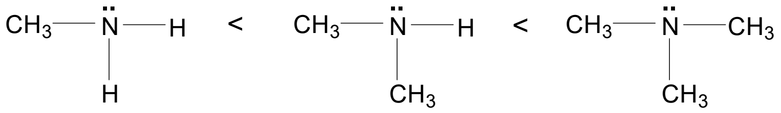
The strength of an amine as Br∅nsted-Lowry base is dependent on the **availability of the lone pair of electrons on the nitrogen atom** to form a dative covalent bond with a proton.

The strength of an amine as a Lewis base is dependent on the **availability of the lone pair of electrons on the nitrogen atom** to form a dative covalent bond with an electron-deficient species.

- To compare the basicity of amines, keep in mind the following:
  - any factor that <u>increases the electron density</u> on the N atom <u>increases the basicity</u> of the amine,
  - any factor that <u>decreases the electron density</u> on the N atom <u>decreases the basicity</u> of the amine.

3.2 Relative basicities of primary, secondary and tertiary amines in the gaseous phase

- The basicities of methylamine, dimethylamine and trimethylamine in the gaseous phase increase in the following order:



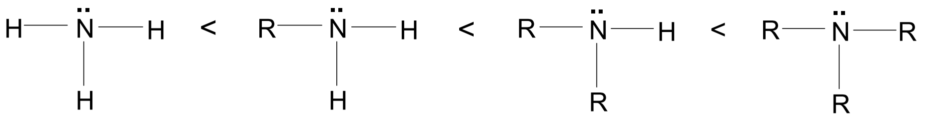
$CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$

methylamine (a 1° amine)	dimethylamine (a 2° amine)	trimethylamine (a 3° amine)
weakest Lewis base		strongest Lewis base

- Explanation:
  - The basicity of each given amine depends on the availability of the lone pair of electrons on the N atom to form a dative covalent bond with an electron-deficient species.
  - The methyl group is electron-donating. It increases the electron-density at the N atom, making the lone pair of electrons on the N atom more readily available for coordination to an electron-deficient species.
  - Since the number of electron-donating methyl groups bonded to the N atom increases from CH_3NH_2 to $(CH_3)_2NH$ to $(CH_3)_3N$, the strength of the given amines as Lewis bases in the gaseous phase increases in the following order:

$$CH_3NH_2 < (CH_3)_2NH < (CH_3)_3N$$

- **Note:** In general, the strength of ammonia and aliphatic amines as Lewis bases **in the gaseous phase** increases in the following order:



$NH_3 < RNH_2 < R_2NH < R_3N$

ammonia	1° aliphatic amine	2° aliphatic amine	3° aliphatic amine

$\xrightarrow{\hspace{10cm}}$

increasing strength as a Lewis base in the gaseous phase

- increasing number of electron-donating alkyl groups (R–)
- increasing electron density at the N atom
- increasing availability of the lone pair of electrons to form a dative covalent bond with an electron-deficient species

3.3 Relative basicities of amines in aqueous solution

- Amines are relatively **weak bases** in aqueous solution. Each amine has its characteristic **base dissociation constant, K_b.**

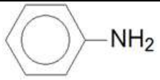
$$\mathbf{R{-}NH_2 + H_2O \rightleftharpoons R{-}NH_3^+ + OH^-}$$

$$K_b \text{ of } RNH_2 = \frac{[RNH_3^+][OH^-]}{[RNH_2]}$$

$$pK_b = -\lg K_b$$

- The K_b of an amine is a measure of the basicity of the amine. It is a measure of the extent of ionisation of the amine in water.
- The larger the K_b value of an amine (or the smaller the pK_b value), the more basic the amine.

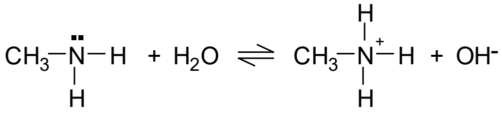
- The relative basicities of amines in aqueous solution can be compared using their K_b or pK_b values. The K_b values of ammonia and some amines are shown below.

Base		NH_3	$CH_3CH_2NH_2$	$(CH_3CH_2)_2NH$
Name	phenylamine	ammonia	ethylamine	diethylamine
K_b at 25 °C/mol dm^{-3}	4.2×10^{-10}	1.8×10^{-5}	5.1×10^{-4}	1.0×10^{-3}

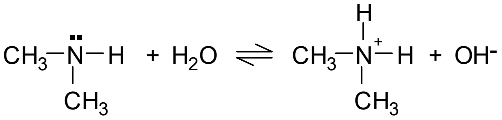
(a) Relative basicities of methylamine and dimethylamine in aqueous solution

- $(CH_3)_2NH$ (pK_b = 3.28) is a stronger base than CH_3NH_2 (pK_b = 3.36). Explain.

- The basicity of each given amine depends on the availability of its lone pair of electrons on the nitrogen atom to form a dative covalent bond with a proton.



$$CH_3{-}\ddot{N}H{-}H + H_2O \rightleftharpoons CH_3{-}\overset{+}{N}H_2{-}H + OH^-$$



$$CH_3{-}\ddot{N}(CH_3){-}H + H_2O \rightleftharpoons CH_3{-}\overset{+}{N}H(CH_3){-}H + OH^-$$

- In CH_3NH_2, there is **one electron-donating –CH_3 group** bonded to the N atom.
- In $(CH_3)_2NH$, there are **two electron-donating –CH_3 groups** bonded to the N atom.
- With more electron-donating alkyl groups, the **electron density at the N atom** of $(CH_3)_2NH$ is increased to a greater extent, making the lone pair of electrons at the N atom more readily available to coordinate with a proton.
- Hence $(CH_3)_2NH$ is a stronger base than CH_3NH_2.

- **Note:** In general, the basicity of ammonia and aliphatic amines **in aqueous solution** increases in the following order:

$$\mathbf{NH_3 < 1^o \text{ aliphatic amine} < 2^o \text{ aliphatic amine}}$$

$$\xrightarrow{\hspace{6cm}}$$

increasing basicity in aqueous solution

- increasing number of electron-donating alkyl groups
- increasing electron density at the N atom
- increasing availability of the lone pair of electrons for coordination with a proton

Remark:
- The basicity of 3° aliphatic amine is **<u>not</u>** included here.
- This is because another factor i.e. the ease with which a protonated amine can undergo hydration in aqueous medium (hence stabilising it) needs to be included for discussion.
- This factor will **<u>not</u>** be discussed here.

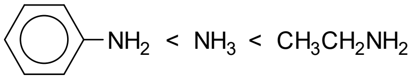
(b) Relative basicities of phenylamine, ammonia and ethylamine in aqueous solution

Worked Example:

Arrange the following compounds in order of increasing basicity and explain the order: $C_6H_5NH_2$, NH_3 and $CH_3CH_2NH_2$.

Suggested answer:

- The given compounds can be arranged in the following order of increasing basicity:



- The basicity of the given compounds depends on the availability of the lone pair of electrons on the nitrogen atom to form a dative covalent bond with a proton. The greater this availability, the more basic the compound.

- Ethylamine is a **stronger base** than NH_3.

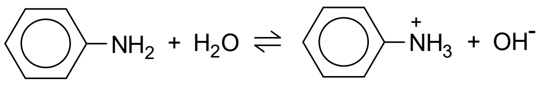
$$CH_3CH_2{-}NH_2 + H_2O \rightleftharpoons CH_3CH_2{-}NH_3^+ + OH^-$$

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

Reason:

- In ethylamine, the $-CH_2CH_3$ group is electron-donating.
- It increases the electron density at the nitrogen atom, making the lone pair of electrons on the nitrogen atom more readily available for coordination to a proton than that in ammonia.
- Hence ethylamine is a stronger base than ammonia.

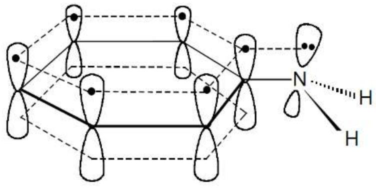
- Phenylamine is a **weaker base** than NH_3.

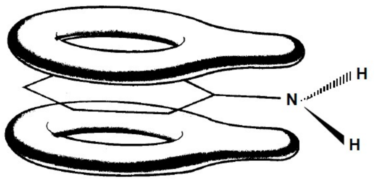


$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$$

Reason:

- In phenylamine, the orbital containing the lone pair of electrons on the nitrogen atom overlaps with the π electron cloud of the benzene ring.
- Thus the lone pair of electrons on the nitrogen atom is delocalised into the benzene ring and is less available for coordination to a proton than that in ammonia.
- Hence phenylamine is a weaker base than ammonia.





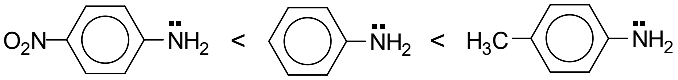
3.4 Effect of substituents on the basicity of aromatic amines

Worked Example:

Arrange the following compounds in order of increasing basicity and explain the order: phenylamine, 4-nitrophenylamine and 4-methylphenylamine.

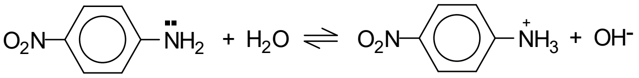
Suggested answer:

- The given compounds can be arranged in the following order of increasing K_b value:



- The basicity of the given compounds depends on the availability of the lone pair of electrons on the nitrogen atom to form a dative covalent bond with a proton. The greater this availability, the more basic the compound.

- 4-Nitrophenylamine is a **weaker base** than phenylamine.

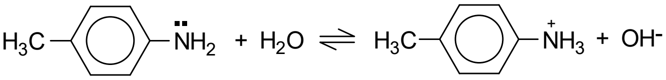


- In 4-nitrophenylamine, the $–NO_2$ group is **electron-withdrawing**.

- It **decreases the electron density** at the nitrogen atom of the $–NH_2$ group, making the **lone pair of electrons less available for coordination to a proton** as compared to that in phenylamine.

- Hence 4-nitrophenylamine is a weaker base than phenylamine.

- 4-Methylphenylamine is a **stronger base** than phenylamine.



- In 4-methyphenylamine, the $–CH_3$ group is **electron-donating**.

- It **increases the electron density** at the nitrogen atom of the $–NH_2$ group, making the **lone pair of electrons more available for coordination to a proton** as compared to that in phenylamine.

- Hence 4-methylphenylamine is a stronger base than phenylamine.

4.1 Reaction of ammonia with halogenoalkane *(Refer to Halogen Derivatives lecture notes)*

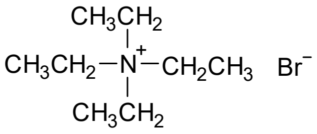
- Alkylamines are, in principle, capable of being prepared by nucleophilic substitution reactions of halogenoalkanes with ammonia.

$\text{R–X} + \text{NH}_3 \xrightarrow[\text{heat in sealed tube}]{\text{excess conc. NH}_3\text{ (in ethanol)}} \underset{1^\circ\text{ amine}}{\text{R–NH}_2} + \text{HX}$	• For simplicity, this equation is commonly used to represent the reaction.

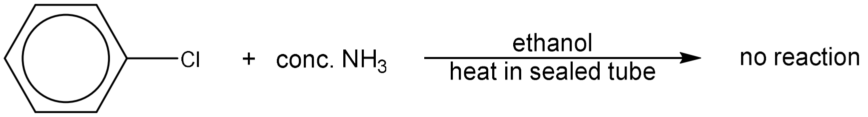
- A problem encountered with this method of preparation of amines: a mixture of products is obtained due to polyalkylation. The use of excess NH_3 in the reaction discourages polyalkylation.

$NH_3 + CH_3CH_2Br \longrightarrow CH_3CH_2NH_2 + HBr$	• Since the 1° amine formed is also nucleophilic, it may undergo further reaction giving a 2° amine.
$CH_3CH_2NH_2 + CH_3CH_2Br \longrightarrow (CH_3CH_2)_2NH + HBr$	• By further alkylation, the 3° amine and even the quaternary ammonium compound may be formed.
$(CH_3CH_2)_2NH + CH_3CH_2Br \longrightarrow (CH_3CH_2)_3N + HBr$	• The actual result is a complex mixture of products.
$(CH_3CH_2)_3N + CH_3CH_2Br \longrightarrow \mathbf{(CH_3CH_2)_4N^+\ Br^-}$	• On an industrial scale, the products are separated by the addition of alkali to liberate the free amines, followed by fractional distillation.

- **Note:**

$CH_3CH_2Br \xrightarrow[\text{sealed tube, heat}]{\textbf{excess}\text{ conc NH}_3\text{ (in alcohol)}} CH_3CH_2NH_2 + HBr$	• Intended product is $CH_3CH_2NH_2$.
$\underset{\textbf{(excess)}}{CH_3CH_2Br} \xrightarrow[\text{sealed tube, heat}]{\text{conc. NH}_3\text{ in alcohol}}$  $CH_3CH_2-\overset{CH_3CH_2}{\underset{CH_3CH_2}{\overset{+}{N}}}-CH_2CH_3\ \ Br^-$ quaternary ammonium salt	• Intended product is $(CH_3CH_2)_4N^+Br^-$.

- This method is limited to the preparation of aliphatic amines because aryl halides will not undergo nucleophilic substitution reactions with ammonia under such conditions.

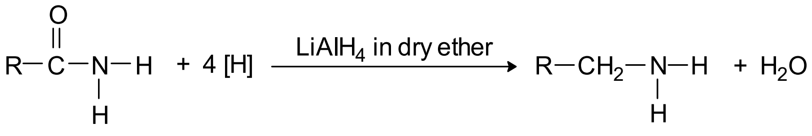
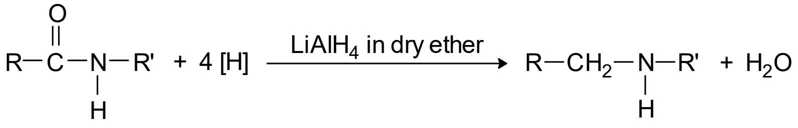
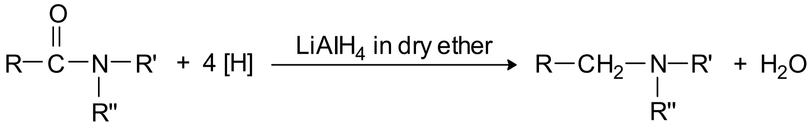


- a p-orbital of C*l* overlaps with the π electron cloud of the benzene ring
- lone pair of electrons on C*l* delocalises into the benzene ring
- the C–C*l* bond acquires partial double bond character
- the C–C*l* bond is strengthened and is not easily broken

4.2 Reduction of nitriles

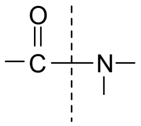
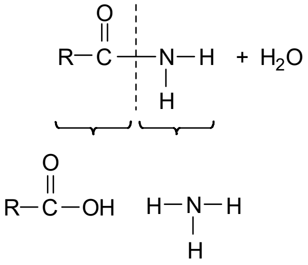
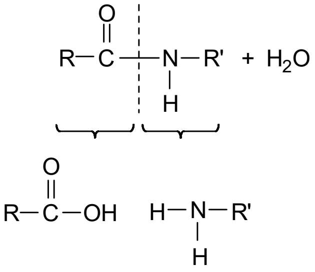
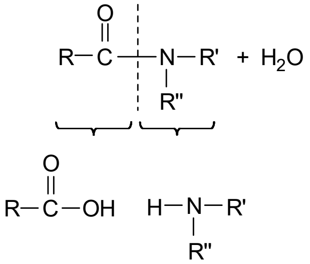
$R{-}C{\equiv}N + 4[H] \xrightarrow{\text{LiA/H}_4\text{ in dry ether}} R{-}CH_2{-}NH_2$ (a 1° amine)	- This method is limited to the preparation of <u>primary</u> aliphatic amines.
$R{-}C{\equiv}N + 2H_2 \xrightarrow{H_2\text{, Ni, heat}} R{-}CH_2{-}NH_2$ (a 1° amine)	

4.3 Reduction of amides

 $R-\overset{O}{\overset{\|}{C}}-\underset{\underset{H}{\vert}}{N}-H + 4[H] \xrightarrow{\text{LiAlH}_4\text{ in dry ether}} R-CH_2-\underset{\underset{H}{\vert}}{N}-H + H_2O$ 1° amide 1° amine	- The C=O group in the amide is reduced to a –CH₂– group.
 $R-\overset{O}{\overset{\|}{C}}-\underset{\underset{H}{\vert}}{N}-R' + 4[H] \xrightarrow{\text{LiAlH}_4\text{ in dry ether}} R-CH_2-\underset{\underset{H}{\vert}}{N}-R' + H_2O$ 2° amide 2° amine	
 $R-\overset{O}{\overset{\|}{C}}-\underset{\underset{R''}{\vert}}{N}-R' + 4[H] \xrightarrow{\text{LiAlH}_4\text{ in dry ether}} R-CH_2-\underset{\underset{R''}{\vert}}{N}-R' + H_2O$ 3° amide 3° amine	

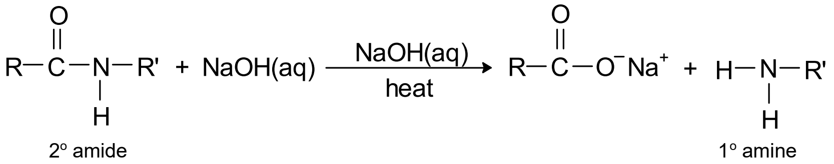
- **Note:** H_2, Ni, heat and $NaBH_4$ cannot be used to reduce amides.

4.4 Hydrolysis of 2° and 3° amides

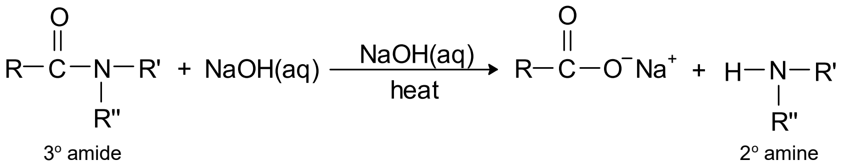
	1° amide	2° amide	3° amide
	 ammonia	 1° amine	 2° amine

Note: Whether the carboxylate salt or ammonium/protonated amine is formed depends on the whether the reaction medium is basic or acidic.

(a) Basic hydrolysis



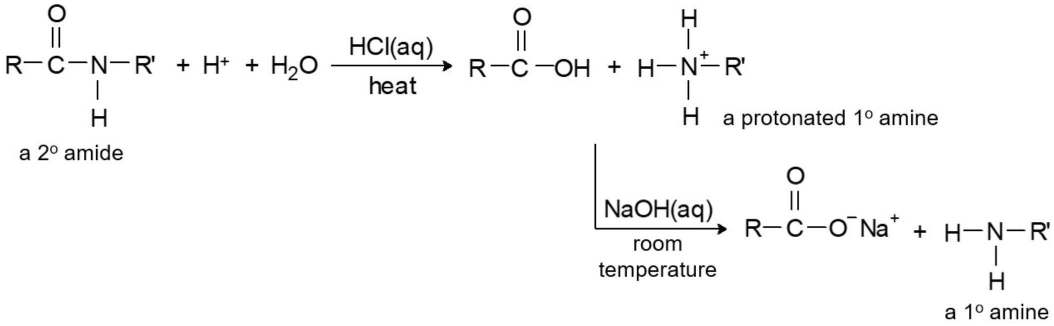
$RCONHR' + NaOH(aq) \xrightarrow[\text{heat}]{NaOH(aq)} RCOO^-Na^+ + H_2NR'$



$RCONR'R'' + NaOH(aq) \xrightarrow[\text{heat}]{NaOH(aq)} RCOO^-Na^+ + HNR'R''$

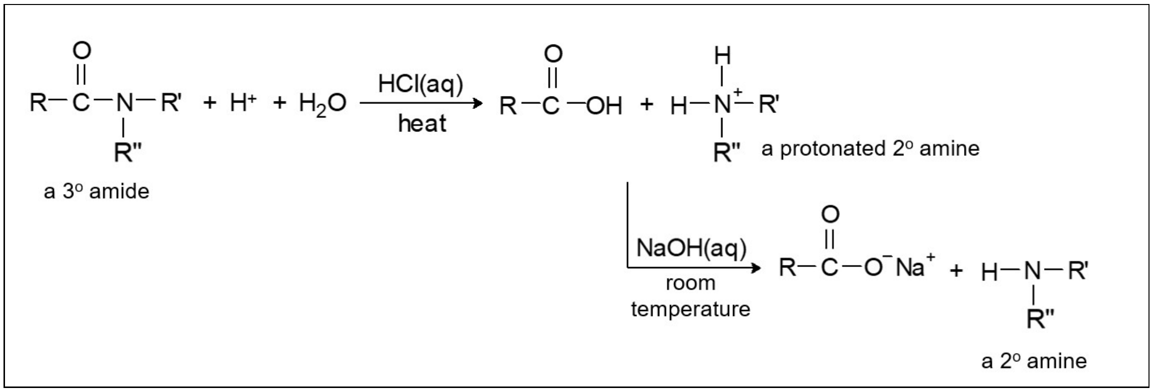
Note: Primary amides can also undergo basic hydrolysis to produce a carboxylate salt and ammonia. (*Refer to Amides Section 5.1*)

(b) Acidic hydrolysis



$RCONHR' + H^+ + H_2O \xrightarrow[\text{heat}]{HCl(aq)} RCOOH + H_3N^+R'$

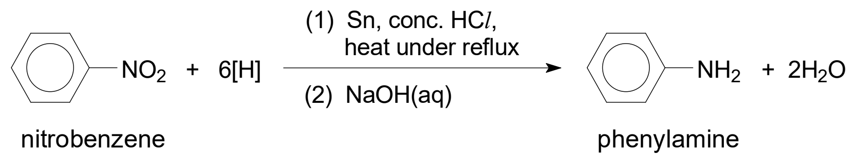
$\xrightarrow[\text{room temperature}]{NaOH(aq)} RCOO^-Na^+ + H_2NR'$



Note: Primary amides can also undergo acidic hydrolysis to produce a carboxylic acid and ammonium salt. (*Refer to Amides Section 5.1*)

4.5 Reduction of nitrobenzene

- This method is usually used in the preparation of **primary aromatic amines**.
- Phenylamine is usually prepared in the laboratory by reducing nitrobenzene using granulated tin and concentrated hydrochloric acid.



Step (1): Reduction

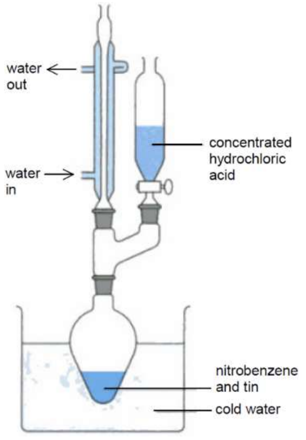
- Nitrobenzene is reduced to form $\mathbf{C_6H_5NH_3^+}$ under the acidic medium.

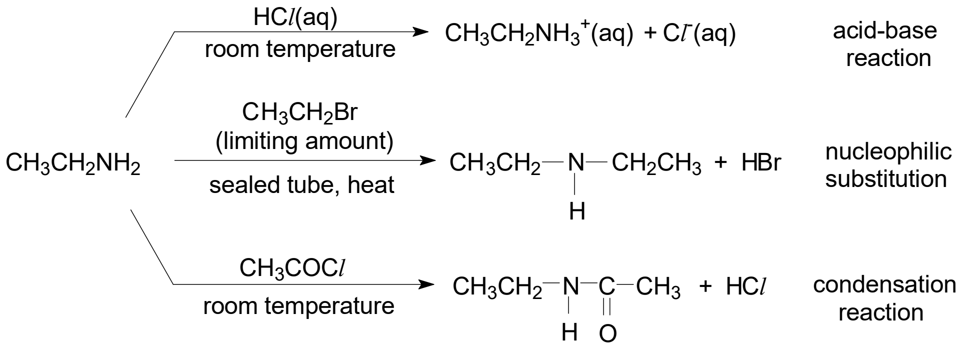
Step (2): Acid-Base reaction

- **NaOH(aq)** is added to the mixture **to liberate phenylamine**.

$$C_6H_5NH_3^+ + OH^- \longrightarrow C_6H_5NH_2 + H_2O$$

Experiment set-up:



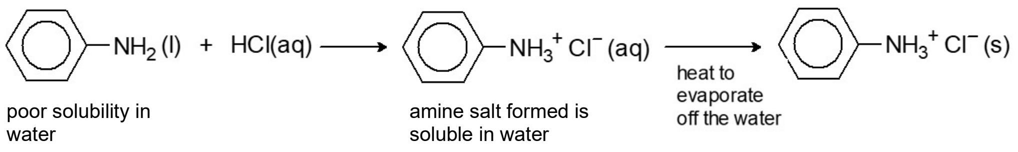
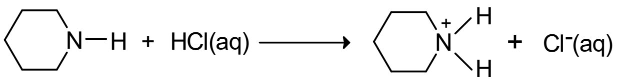
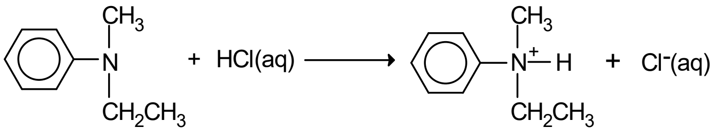


5.1 Reaction with acids

- Amines can act as Bronsted-Lowry bases (i.e. proton acceptors) because of the **availability of a lone pair of electrons on the nitrogen atom** to form a dative covalent bond with a proton.
- Both aliphatic amines and phenylamine form stable crystalline salts with mineral acids.

$\underset{\text{1° amine}}{R{-}NH_2} + HCl(aq) \longrightarrow \underset{\text{amine salt}}{R{-}NH_3^+Cl^-(aq)} \xrightarrow[\text{heat to evaporate off the water}]{} \underset{\text{amine salt or alkylammonium salt}}{R{-}NH_3^+Cl^-(s)}$	• Type of reaction: **acid-base reaction** • The reaction involves the formation of a water-soluble amine salt.

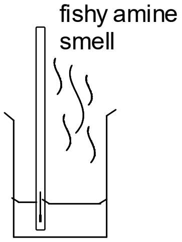
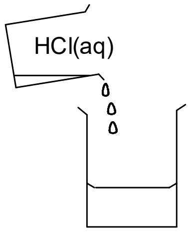
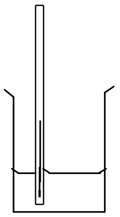
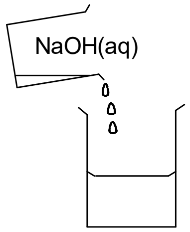
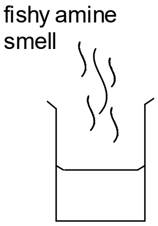
- **Examples:**

$CH_3CH_2NH_2(g) + HCl(aq) \longrightarrow CH_3CH_2NH_3^+(aq) + Cl^-(aq) \xrightarrow[\text{heat to evaporate off the water}]{} CH_3CH_2NH_3^+Cl^-(s)$
 poor solubility in water; amine salt formed is soluble in water
$CH_3CH_2NH_2 + H_2SO_4(aq) \longrightarrow CH_3CH_2NH_3^+(aq) + HSO_4^-(aq)$
$R{-}NH_2 + CH_3CO_2H \longrightarrow R{-}NH_3^+ + CH_3CO_2^-$ (**Note:** Amines undergo acid-base reaction with carboxylic acids to form a **salt**, i.e. **no amide** is formed.)
 2° amine
 3° amine

- The amine can be **regenerated** from the amine salt by reacting the salt with an alkali (e.g. NaOH).

$$\mathrm{CH_3CH_2NH_3^+\,C\mathit{l}^-(aq)} + \mathbf{NaOH(aq)} \longrightarrow \mathrm{CH_3CH_2NH_2(aq) + NaC\mathit{l}(aq) + H_2O(l)}$$

- The diagrams below illustrate an experiment in which acid is added to a solution of ethylamine.

(a) 	(b) 	(c) 	(d) 	(e) 
Solution of ethylamine with characteristic smell.	Add dilute hydrochloric acid to produce the non-volatile amine salt. Temperature increases since the acid-base reaction is exothermic. Smell disappears since the amine salt is non-volatile.		Add excess aqueous sodium hydroxide to regenerate the volatile ethylamine. Smell of amine returns and is easily detected when the solution is warmed.	

Worked Example:

Suggest a simple chemical test which can be used to test for the $CH_3CH_2NH_3^+$ ion.

Reagent and condition: Add NaOH(aq) to the sample and warm the mixture gently.

Observation: Pungent $CH_3CH_2NH_2(g)$ evolved and turns damp red litmus paper blue.

Explanation:

In an aqueous solution of $CH_3CH_2NH_3^+\,C\mathit{l}^-$, the following equilibrium exists:

$$\mathbf{CH_3CH_2NH_3^+(aq) + H_2O(l) \rightleftharpoons CH_3CH_2NH_2(aq) + H_3O^+(aq)} \text{ ----------(1)}$$

- Addition of NaOH(aq) removes H_3O^+ ions by neutralisation reaction. This causes $[H_3O^+]$ to decrease and hence the equilibrium position of reaction (1) shifts right in accordance to Le Chatelier's principle. This produces more $CH_3CH_2NH_2(aq)$.
- $CH_3CH_2NH_2$ is soluble in water. Warming the mixture gently helps to force more $CH_3CH_2NH_2$ out of the reaction mixture i.e. produces more $CH_3CH_2NH_2(g)$ which will turn damp red litmus paper blue.

Note:

The test for the $CH_3CH_2NH_3^+$ ion is identical to the test for the **NH_4^+ ion**:

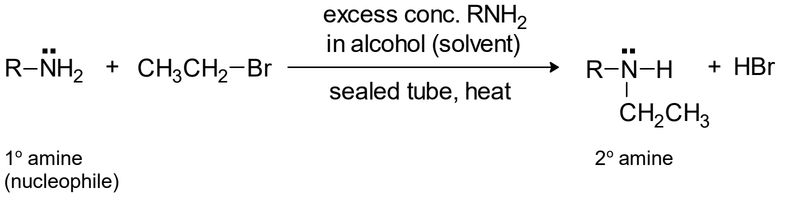
Add NaOH(aq) and warm the mixture.

- Some properties of amines and amine salts are tabulated below. The formation of amine salts can be used to isolate and characterise amines. It is used to separate amines from neutral or acidic organic compounds.

Amines		**Amine Salts**
RNH_2 R_2NH R_3N	$\xrightarrow{\mathrm{HC\mathit{l}(aq)}}$ $\xleftarrow[\mathrm{NaOH(aq)}]{}$	RNH_3^+ $R_2NH_2^+$ R_3NH^+
• water insoluble (except for amines with low M_r)		• ionic salts, high melting points • relatively more water soluble
• soluble in organic solvents		• generally insoluble in non-polar organic solvents
• some are volatile • pungent / fishy odour		• non-volatile solids • no odour

5.2 Reaction with halogenoalkanes

- An amine can undergo alkylation with halogenoalkane with the amine acting as the nucleophile. The reaction involves **nucleophilic substitution** mechanism. *(Refer to Amines Section 4.1 and Halogen Derivatives lecture notes)*



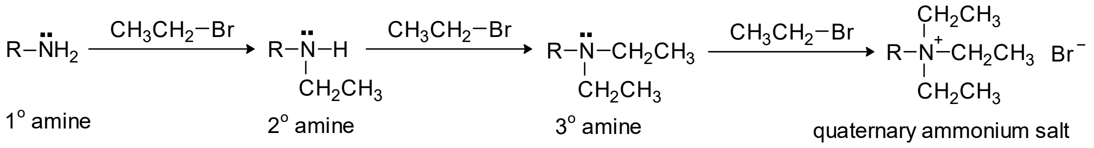
$$R\!-\!\ddot{N}H_2 + CH_3CH_2\!-\!Br \xrightarrow[\text{sealed tube, heat}]{\text{excess conc. } RNH_2 \text{ in alcohol (solvent)}} R\!-\!\ddot{N}(CH_2CH_3)\!-\!H + HBr$$

1° amine (nucleophile)

2° amine

- Type of reaction: **nucleophilic substitution**
- For simplicity, this equation is commonly used to represent the reaction.

- Polyalkylation can occur. The reaction can proceed until a quaternary ammonium salt is obtained because the 2° amine and 3° amine produced in the reaction mixture are also able to act as nucleophiles since each possesses a lone pair of electrons on the nitrogen atom.



$$R\!-\!\ddot{N}H_2 \xrightarrow{CH_3CH_2-Br} R\!-\!\ddot{N}(CH_2CH_3)\!-\!H \xrightarrow{CH_3CH_2-Br} R\!-\!\ddot{N}(CH_2CH_3)\!-\!CH_2CH_3 \xrightarrow{CH_3CH_2-Br} R\!-\!\overset{+}{N}(CH_2CH_3)_2\!-\!CH_2CH_3\ Br^-$$

1° amine

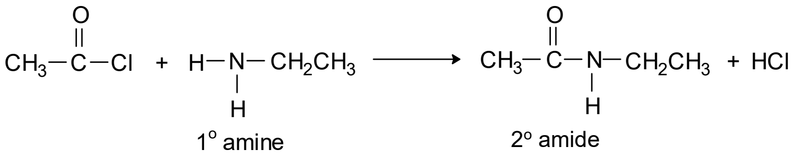
2° amine

3° amine

quaternary ammonium salt

5.3 Reaction with acid halides

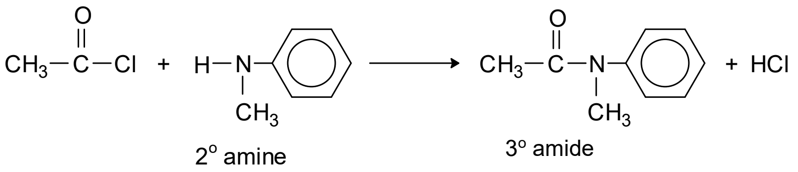
- Amines can undergo **condensation** with acid halides (i.e. acyl halides) to produce **amides**. Anhydrous condition must be used because acid halides react readily with water.



$$CH_3\!-\!\overset{O}{\overset{\|}{C}}\!-\!Cl + H\!-\!N(H)\!-\!CH_2CH_3 \longrightarrow CH_3\!-\!\overset{O}{\overset{\|}{C}}\!-\!N(H)\!-\!CH_2CH_3 + HCl$$

1° amine

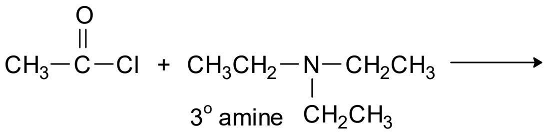
2° amide



$$CH_3\!-\!\overset{O}{\overset{\|}{C}}\!-\!Cl + H\!-\!N(CH_3)\!-\!C_6H_5 \longrightarrow CH_3\!-\!\overset{O}{\overset{\|}{C}}\!-\!N(CH_3)\!-\!C_6H_5 + HCl$$

2° amine

3° amide



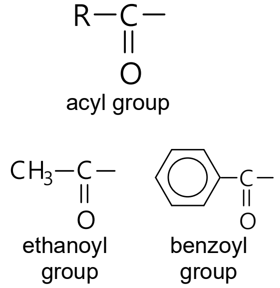
$$CH_3\!-\!\overset{O}{\overset{\|}{C}}\!-\!Cl + CH_3CH_2\!-\!N(CH_2CH_3)\!-\!CH_2CH_3 \longrightarrow$$

3° amine

- no H atom bonded to N in the 3° amine
- no amide formation

- Type of reaction: **condensation**

Note:



acyl group

ethanoyl group

benzoyl group

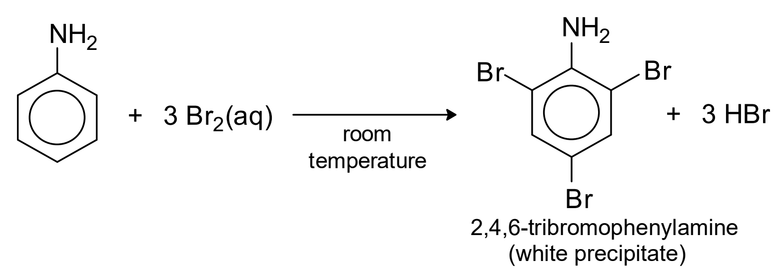
Note: Acid halides can also react with ammonia to form 1° amide *(Refer to Amides Section 4)*.

Note: Amines are basic and will undergo acid-base reaction with carboxylic acids to form a salt *(Refer to Amines Section 5.1)*. Hence, an amide can only be formed by reacting NH_3/1° amine/2° amine with an acid halide.

5.4 Ring reactions of phenylamine

(a) Formation of 2,4,6-tribromophenylamine

- Bromination of the benzene ring in phenylamine using $Br_2(aq)$ occurs at room temperature and without the use of a Lewis Acid catalyst.



Type of reaction: **electrophilic substitution**

Note:

- The $–NH_2$ group is strongly activating.
- The $–NH_2$ group is 2,4-directing.

Observations:

- Orange $Br_2(aq)$ decolourised
- A white precipitate of 2,4,6-tribromophenylamine is formed

Why does the reaction between phenylamine and aqueous bromine occur readily?

- The $–NH_2$ group increases the electron density in the benzene ring as the lone pair of electrons on the nitrogen atom is delocalised into the benzene ring.
- This makes the benzene ring in phenylamine more electron rich and susceptible to **electrophilic** attack.

Note:

- This reaction is a useful **distinguishing test** for phenylamine or other aromatic amines.
- But **phenol** also undergoes a similar reaction and gives the same observations.

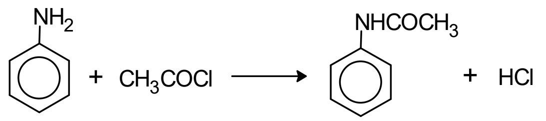
Note:

- **$Cl_2(aq)$** also reacts similarly to form 2,4,6-trichlorophenylamine.

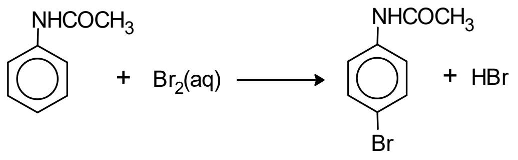
(b) Formation of 2-bromophenylamine and 4-bromophenylamine

- To get a mono-brominated phenylamine, it is necessary to reduce the electron density and hence the reactivity of the aromatic ring in phenylamine.
- This can be achieved by acylation of the strongly activating $–NH_2$ group with ethanoyl chloride to produce the moderately activating $–NHCOCH_3$ group.
- Note: The $–NHCOCH_3$ group is 2,4-directing. *(Refer to Section 8 of Data Booklet)*
- After reaction with aqueous bromine, the ethanoyl group can then be removed by hydrolysis using hot NaOH(aq).

Step 1: Condensation

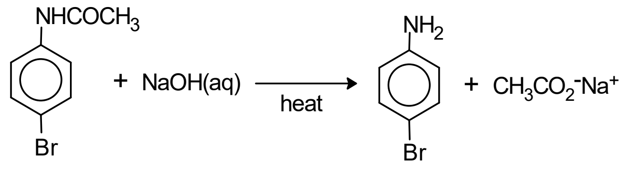


Step 2: Electrophilic substitution

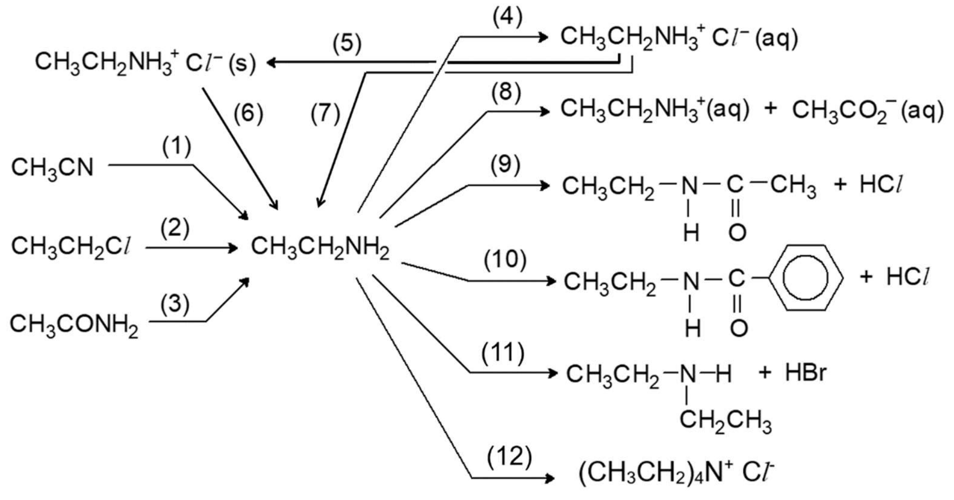


Note: The 1,2-isomer is also produced but not shown here.

Step 3: Base hydrolysis



6.1 Preparation and reactions of ethylamine



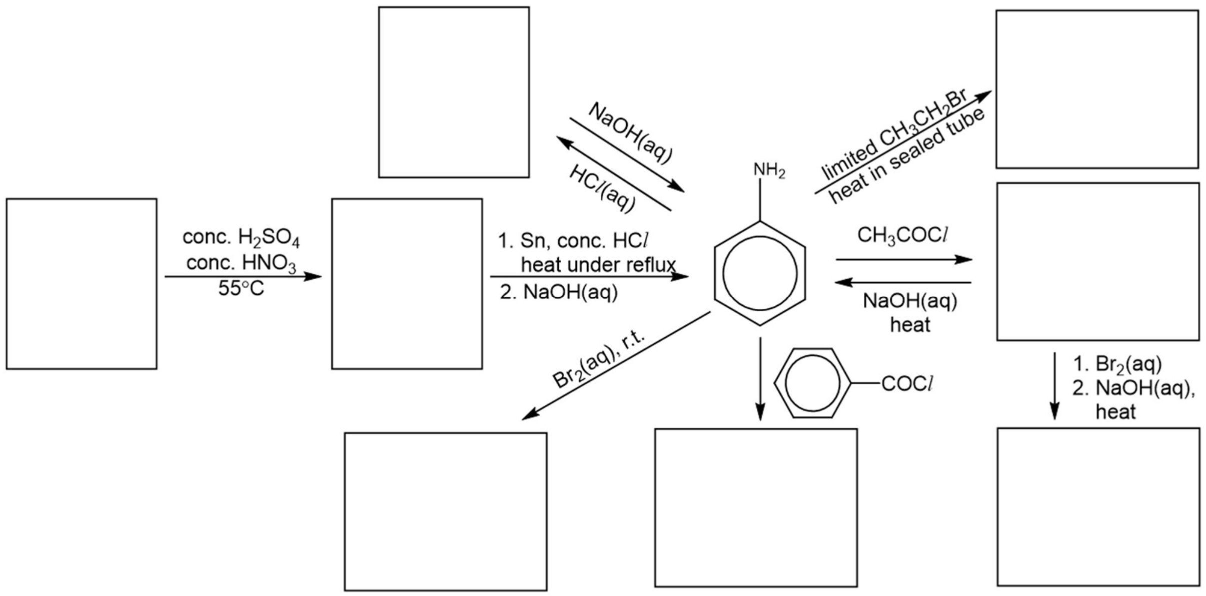
Reactions of ethylamine

- acid-base reaction
- nucleophilic substitution
- condensation reaction

	Reagents and conditions
(1)	LiA*l*H$_4$ in dry ether (or H$_2$, Ni, heat)
(2)	Excess conc. NH$_3$ in ethanol, heat in sealed tube
(3)	LiA*l*H$_4$ in dry ether
(4)	HC*l*(aq)
(5)	Heat to evaporate off the water
(6)	NaOH(aq)

	Reagents and conditions
(7)	NaOH(aq)
(8)	CH$_3$COOH(aq)
(9)	CH$_3$COC*l*
(10)	C$_6$H$_5$COC*l*
(11)	Limiting CH$_3$CH$_2$Br, heat in sealed tube
(12)	Excess CH$_3$CH$_2$C*l*, heat in sealed tube

6.2 Preparation and reactions of phenylamine



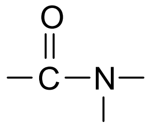
6.3 Relativity basicity

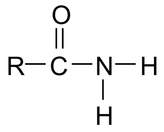
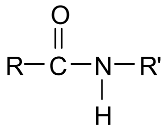
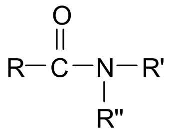
- Basicity increases in the following order: **phenylamine < ammonia < ethylamine**

Amides RCONH2 | 1 – Introduction

1.1 General Formulae

Amides are derivatives of carboxylic acids that contain the following group:


$$-\overset{\overset{O}{\|}}{C}-\underset{|}{N}-$$

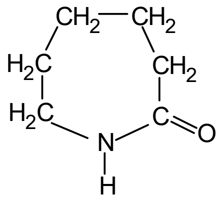
Amides are classified as primary, secondary or tertiary according to the number of alkyl groups bonded to the nitrogen atom of the amide group.	 $\mathrm{R-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{\vert}}{N}-H}$	 $\mathrm{R-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{\vert}}{N}-R'}$	 $\mathrm{R-\overset{\overset{O}{\|}}{C}-\underset{\underset{R''}{\vert}}{N}-R'}$
	$RCONH_2$	R–CONHR’	R–CONR’R”
	primary (1°) amide	secondary (2°) amide *N*-substituted amide	tertiary (3°) amide *N,N*-disubstituted amide

1.2 Nomenclature

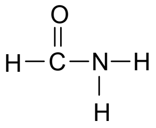
- To name a 1° amide, first name the corresponding acid. Drop the -ic acid or -oic acid suffix from the name of the carboxylic acid, and substitute the suffix **-amide**.
- 2° and 3° amides are named by treating the alkyl groups on nitrogen as substituents, specifying their positions by the prefix *N*-.
- A cyclic amide is termed a **lactam**.

Example:

caprolactam
(6-aminohexanoic acid lactam)

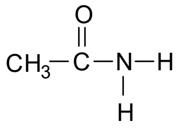


1° amides


$\mathrm{H-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{\vert}}{N}-H}$

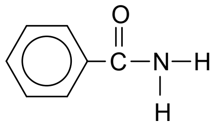
$HCONH_2$

methanamide
(formamide)


$\mathrm{CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{\vert}}{N}-H}$

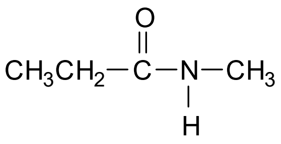
CH_3CONH_2

ethanamide
(acetamide)



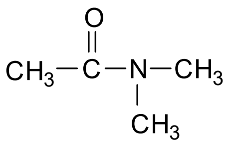
benzenecarboxamide
(benzamide)

2° amides


$\mathrm{CH_3CH_2-\overset{\overset{O}{\|}}{C}-\underset{\underset{H}{\vert}}{N}-CH_3}$

N-methylpropanamide

3° amides


$\mathrm{CH_3-\overset{\overset{O}{\|}}{C}-\underset{\underset{CH_3}{\vert}}{N}-CH_3}$

N,N-dimethylethanamide

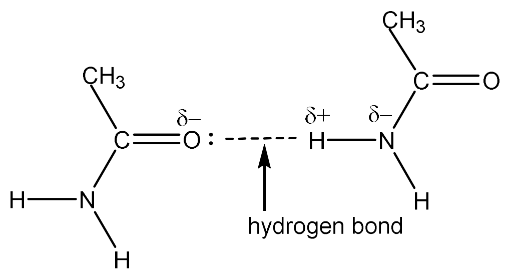
Amides $RCONH_2$ | 2 – Physical Properties

2.1 Boiling and melting points

Name	Formula	m.p./°C	b.p./°C
Methanamide	$HCONH_2$	3	193
Ethanamide	CH_3CONH_2	82	221
Benzenecarboxamide	$C_6H_5CONH_2$	132	290

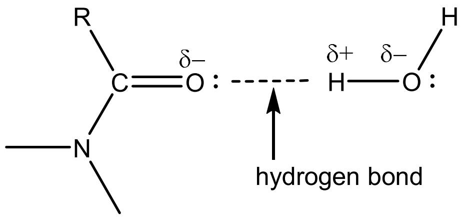
- Amides are polar organic compounds.
- All primary amides except methanamide are crystalline solids due to fairly strong intermolecular hydrogen bonding.
- Compared to 3° amides, 1° and 2° amides have higher melting and boiling points due to the presence of hydrogen bonding between molecules.
- 3° amide molecules do not form hydrogen bonds with each other since there are no hydrogen atoms directly bonded to the electronegative N atom.

Hydrogen bonding between ethanamide molecules



2.2 Solubility

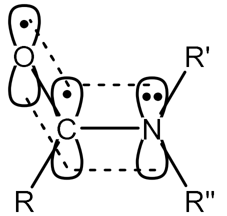
- Lower members of aliphatic amides are soluble in water because the amide molecules can interact with water molecules via hydrogen bonding.



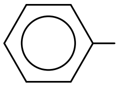
- Solubility of amides in water decreases with increasing size of the non-polar hydrocarbon chain.

Amides $RCONH_2$ | 3 – The Lack of Basicity

- The simple amide structure shows a lone pair of electrons on the nitrogen atom. Unlike amines, however, amides are only very weakly basic. In fact, we regard the amide functional group to be **neutral**. Amides are neutral to litmus.
- Why is the amide functional group **effectively neutral**?

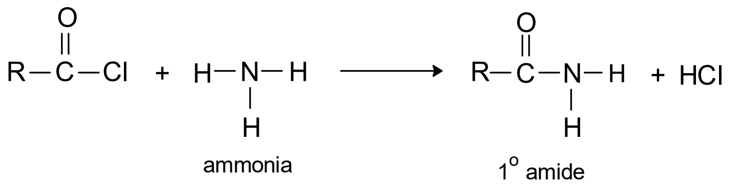
The lack of basicity in amides arises because the orbital containing the **lone pair of electrons on the nitrogen atom** overlaps with the π electron cloud of the adjacent C=O bond and the lone pair of electrons is **delocalised**. Hence, this lone pair of electrons on the nitrogen atom is not available for coordination to a proton.	

- **Note:** Relative basicity of ethanamide, phenylamine, ammonia and ethylamine

CH_3CONH_2 <  NH_2 < NH_3 < $CH_3CH_2NH_2$

4 – Laboratory Preparation

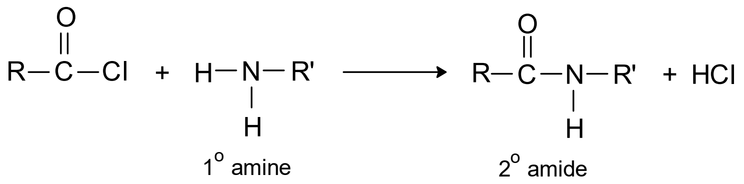
- Amides can be obtained from the acylation of ammonia, primary amines or secondary amines at room temperature. *(Refer to Amines Section 5.3 and Carboxylic Acids and Derivatives notes)*
- Acylation of NH_3 produces a primary amide



$$R-\overset{\overset{\displaystyle O}{||}}{C}-Cl + H-\underset{\underset{\displaystyle H}{|}}{N}-H \longrightarrow R-\overset{\overset{\displaystyle O}{||}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-H + HCl$$

Type of reaction:
condensation

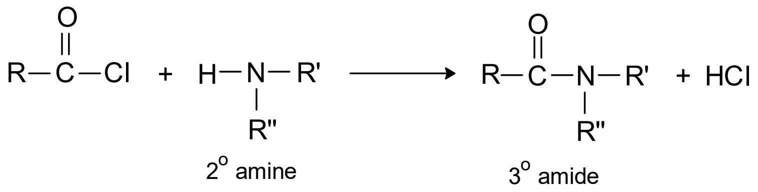
- Acylation of a primary amine produces a secondary amide



$$R-\overset{\overset{\displaystyle O}{||}}{C}-Cl + H-\underset{\underset{\displaystyle H}{|}}{N}-R' \longrightarrow R-\overset{\overset{\displaystyle O}{||}}{C}-\underset{\underset{\displaystyle H}{|}}{N}-R' + HCl$$

Type of reaction:
condensation

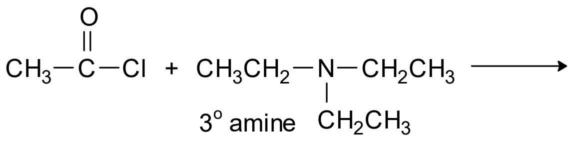
- Acylation of a secondary amine produces a tertiary amide



$$R-\overset{\overset{\displaystyle O}{||}}{C}-Cl + H-\underset{\underset{\displaystyle R''}{|}}{N}-R' \longrightarrow R-\overset{\overset{\displaystyle O}{||}}{C}-\underset{\underset{\displaystyle R''}{|}}{N}-R' + HCl$$

Type of reaction:
condensation

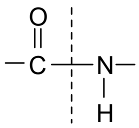
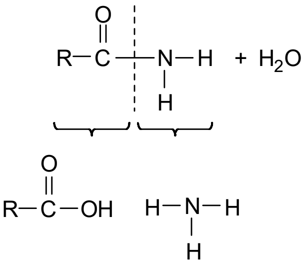
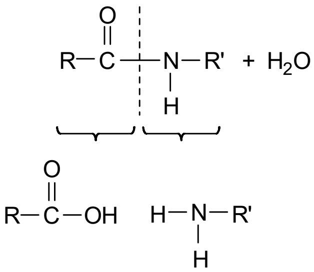
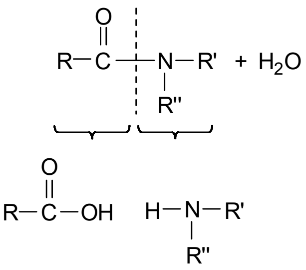
- **Note:** Acid halides (or acyl halides) do not react with tertiary amines to give amides.



$$CH_3-\overset{\overset{\displaystyle O}{||}}{C}-Cl + CH_3CH_2-\underset{\underset{\displaystyle CH_2CH_3}{|}}{N}-CH_2CH_3 \longrightarrow$$

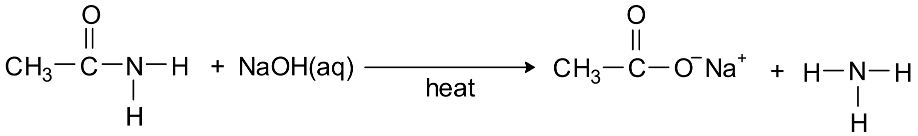
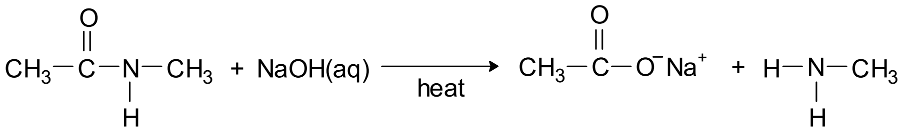
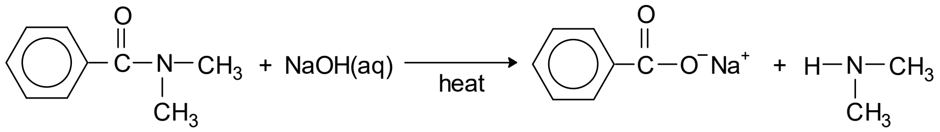
- no H atom bonded to N in the 3° amine
- no amide formation

5.1 Hydrolysis (*Refer to Amines Section 4.4.*)

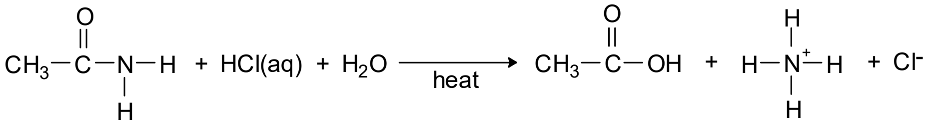
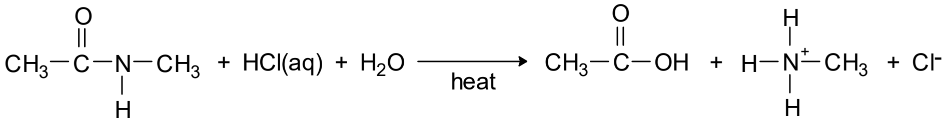
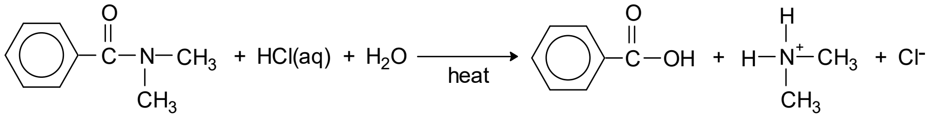
	1° amide	2° amide	3° amide
	 ammonia	 1° amine	 2° amine

Note: Whether the carboxylate salt or ammonium/protonated amine is formed depends on whether the reaction medium is basic or acidic.

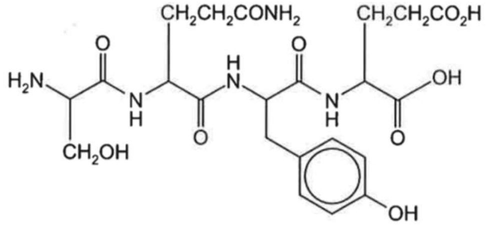
(a) Basic Hydrolysis

 $CH_3-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{\|}{N}}-H + NaOH(aq) \xrightarrow[heat]{} CH_3-\overset{O}{\overset{\|}{C}}-O^-Na^+ + H-\underset{H}{\underset{\|}{N}}-H$	This reaction can be used as a distinguishing test for amides (*Refer to Amines Section 4.4*). Amides require **strong heating** to hydrolyse to amines and carboxylate salts.
 $CH_3-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{\|}{N}}-CH_3 + NaOH(aq) \xrightarrow[heat]{} CH_3-\overset{O}{\overset{\|}{C}}-O^-Na^+ + H-\underset{H}{\underset{\|}{N}}-CH_3$	
	

(b) Acidic hydrolysis

 $CH_3-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{\|}{N}}-H + HCl(aq) + H_2O \xrightarrow[heat]{} CH_3-\overset{O}{\overset{\|}{C}}-OH + H-\overset{H}{\overset{\|}{\underset{H}{\underset{\|}{N^+}}}}-H + Cl^-$	This reaction cannot be used as a distinguishing test as ammonium salt formed is non-volatile.
 $CH_3-\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{\|}{N}}-CH_3 + HCl(aq) + H_2O \xrightarrow[heat]{} CH_3-\overset{O}{\overset{\|}{C}}-OH + H-\overset{H}{\overset{\|}{\underset{H}{\underset{\|}{N^+}}}}-CH_3 + Cl^-$	
	

Exercise 1 (N2014/P1/Q22)
The following diagram shows the structure of the tetrapeptide T.



T

When 0.1 mole of T is heated under reflux with NaOH(aq) until no further reaction occurs, how many moles of NaOH(aq) will react?

A 0.4 **B** 0.5 **C** 0.6 **D** 0.7

5.2 Reduction

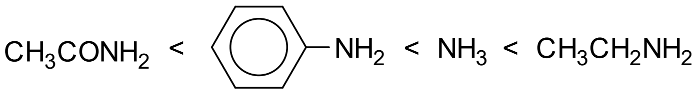
- Amides can undergo **reduction** to form amines using $LiAlH_4$ in dry ether.
(*Refer to Amines Section 4.3*)

- **Note:** H_2, Ni, heat and $NaBH_4$ cannot be used to reduce amides.

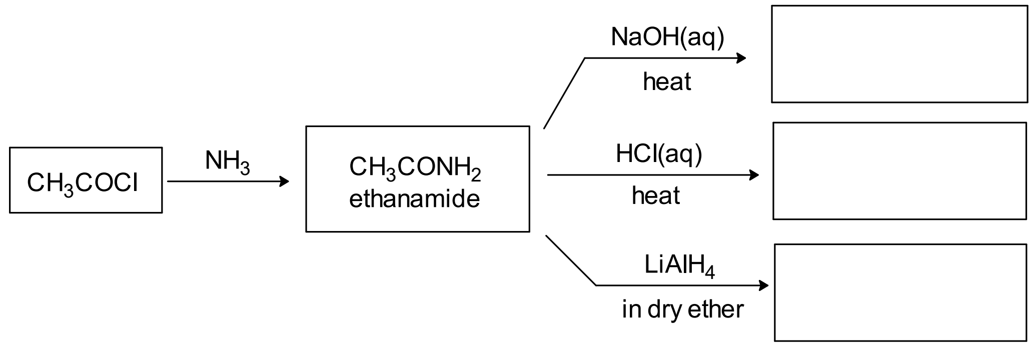
Amides RCONH$_2$ | 6 – Summary

- Amides are effectively neutral. Amides are not basic because the orbital containing the lone pair of electrons on the nitrogen atom overlaps with the π electron cloud of the adjacent C=O bond and the lone pair of electrons is delocalised. This lone pair of electrons on the nitrogen atom is therefore not available for coordination to a proton.

- Relative basicity of ethanamide, phenylamine, ammonia and ethylamine



- Preparation and reactions of ethanamide



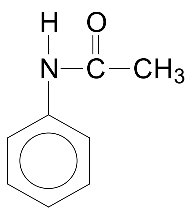
7 – Distinguishing Tests for Amines, Amides and Ammonium Salts

Functional Group		**Amine (5 C or less)**	**Amine (6 C or more)**	**Phenylamine**	**Amide**	**Ammonium Salt**
Example		$CH_3CH_2CH_2NH_2$	$CH_3(CH_2)_5NH_2$	$C_6H_5NH_2$	$CH_3CH_2CONHCH_3$	$CH_3CH_2COO^- CH_3NH_3^+$
Physical State and Volatility		Liquid, high volatility	Liquid, low volatility	Liquid, low volatility	Solid, low volatility	Solid, low volatility
Solubility in water		Soluble	Insoluble	Sparingly soluble	Soluble	Soluble
Moist red litmus paper		Turns moist red litmus paper blue			Moist red litmus paper does <u>not</u> turn blue	
Dilute acid e.g. HC*l*(aq)	Add dilute HC*l* to a mixture of water and the compound.	No observable change. Amine is already soluble in water.	Amine reacts with HC*l*(aq) to form a water-soluble salt. Hence the amine dissolves to form a homogeneous solution.		No observable change. Amide (low M_r) is already soluble in water.	No observable change. Salt is already soluble in water.
NaOH(aq)	Add NaOH(aq) to compound. **Warm gently**. Test any gas evolved with moist red litmus paper.	Pungent gas evolved turns moist red litmus blue. Amine is volatile and leaves the mixture on heating. **Note**: Addition of NaOH(aq) is not needed here. Warming the solution will force the volatile amine out of the solution. (*Refer to Worked Example under Amides Section 7 on page 26*)	No pungent gas detected. (Amine is not volatile)	No pungent gas detected. (Phenylamine is not volatile)	No pungent gas detected. (Amide needs **strong heating** to hydrolyse to amine and carboxylate salt)	Pungent gas evolved on gentle warming turns moist red litmus blue if amine formed is volatile (5 C or less) Or An oily layer separates out if non-volatile amine formed (has 6 or more C). $RNH_3^+ + OH^- \rightarrow RNH_2 + H_2O$ (volatile amine will vaporise on gentle warming)
	Add NaOH(aq) to compound. **Heat strongly** in a boiling water bath for a few minutes. Test any gas evolved with moist red litmus paper.				Pungent gas evolved turns moist red litmus blue if amine formed is volatile (5 C or less) Or An oily layer separates out if non-volatile amine formed (6 or more C). $R'CONHR + OH^- \rightarrow RNH_2(g) + R'COO^-$	
Br_2(aq)	Add Br_2(aq) at room temperature.	No decolourisation of orange Br_2(aq).	No decolourisation of orange Br_2(aq).	White ppt formed. Decolourisation of orange Br_2(aq).	No decolourisation of orange Br_2(aq).	No decolourisation of orange Br_2(aq).

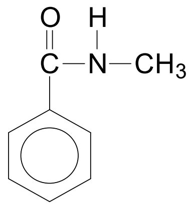
- **Worked Example:**

Suggest a chemical test to distinguish the following compounds.

(a)

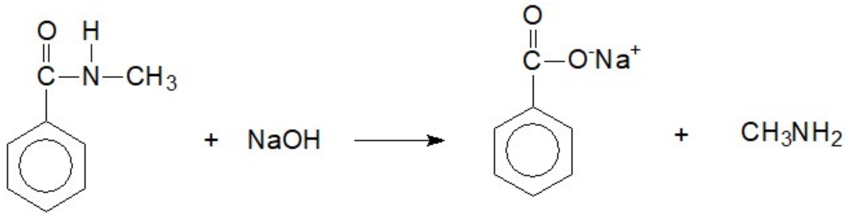


and

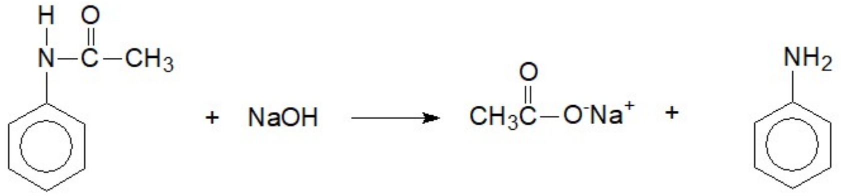


Add NaOH(aq) to each sample in a test-tube and **heat strongly**.

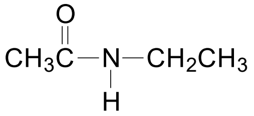
For $C_6H_5CONHCH_3$, there will be evolution of pungent CH_3NH_2 gas which turns damp red litmus paper blue.



For $C_6H_5NHCOCH_3$, there will not be any CH_3NH_2 gas evolved / damp red litmus paper does not turn blue.



(b)



$CH_3\overset{O}{\overset{\|}{C}}-\underset{H}{\underset{|}{N}}-CH_2CH_3$ and $[CH_3CH_2NH_3]^+ [CH_3COO]^-$

Add NaOH(aq) to each sample in a test-tube and **heat gently/warm** for about a minute.

For $CH_3CH_2NH_3^+$ $CH_3CO_2^-$, there will be evolution of pungent $CH_3CH_2NH_2$ gas which turns damp red litmus paper blue.

$$CH_3CH_2NH_3^+ CH_3COO^- + NaOH \longrightarrow CH_3CH_2NH_2 + CH_3COO^-Na^+ + H_2O$$

For $CH_3CONHCH_2CH_3$, there will not be any $CH_3CH_2NH_2$ gas evolved / damp red litmus paper does not turn blue.

Note:
$CH_3CH_2NH_2$ gas can only evolve if there is **strong heating** such that amide hydrolysis occurs.

Amino Acids $H_2N\text{-}CHR\text{-}CO_2H$ | 1 – Introduction

1.1 2-Amino Acids

- Amino acids are organic compounds that contain at least one amino group ($–NH_2$) and one carboxylic acid group (–COOH).

- Amino acids can be classified as α, β, λ, and so on, according to the location of the amine group on the carbon chain that contains the carboxylic acid group.

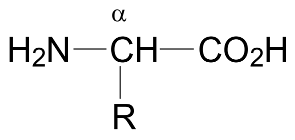
$H_2N-\overset{\alpha}{CH_2}-COOH$ an α-amino acid	$H_2N-\overset{\beta}{CH_2}-\overset{\alpha}{CH_2}-COOH$ a β-amino acid	$H_2N-\overset{\gamma}{CH_2}-\overset{\beta}{CH_2}-\overset{\alpha}{CH_2}-COOH$ a γ-amino acid

- Although more than 700 different amino acids are known to occur naturally, a group of 20 of them commands special attention. These 20 are the amino acids that are normally present in proteins.

- All the 20 amino acids from which proteins are derived from are **α-amino acids (or 2-amino acids)** i.e. the amine group is attached to the α carbon atom i.e. the carbon atom that is bonded to the carboxylic acid group.

Our focus will be the **α-amino acids (or 2-amino acids).**

- They are the **basic building blocks of proteins.**
- They differ only in the substituent (–R) attached to the α carbon atom.

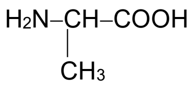
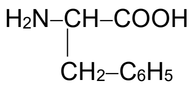
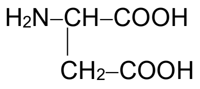
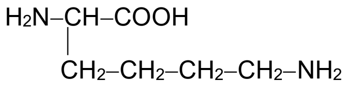


$$H_2N-\underset{\displaystyle R}{\underset{|}{\overset{\alpha}{CH}}}-CO_2H$$

- The 20 amino acids commonly present in protein structure are shown on the next page.

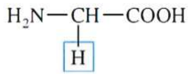
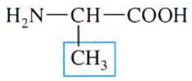
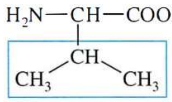
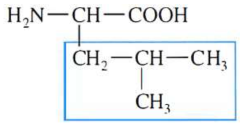
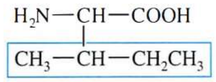
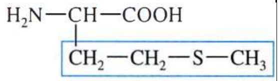
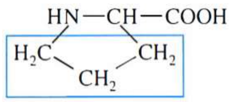
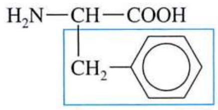
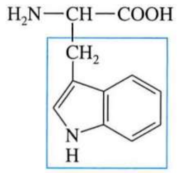
1.2 Nomenclature and Classification

- Amino acids are named systematically by considering them as amino derivatives of carboxylic acids. However, many are still referred to by their original names.

Name	Abbreviation	Structure
glycine (aminoethanoic acid)	Gly	H_2N-CH_2-COOH
alanine (2-aminopropanoic acid)	Ala	 $H_2N-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-COOH$
phenylalanine (2-amino-3-phenylpropanoic acid)	Phe	 $H_2N-\underset{\displaystyle CH_2-C_6H_5}{\underset{\vert}{CH}}-COOH$
aspartic acid (2-aminobutanedioic acid)	Asp	 $H_2N-\underset{\displaystyle CH_2-COOH}{\underset{\vert}{CH}}-COOH$
lysine (2,6-diaminohexanoic acid)	Lys	 $H_2N-\underset{\displaystyle CH_2-CH_2-CH_2-CH_2-NH_2}{\underset{\vert}{CH}}-COOH$

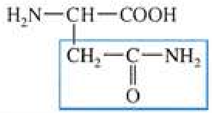
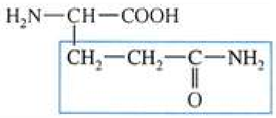
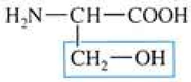
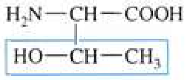
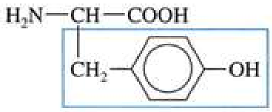
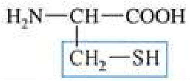
- Amino acids may be classified as neutral, basic or acidic according to the number of amino and carboxyl groups they contain. The neutral amino acids contain an equal number of amino and carboxyl groups (usually one of each). The basic amino acids contain an extra amino group. The acidic amino acids contain an extra carboxyl group.

- The structures of the twenty amino acids that are commonly found in proteins are shown below.

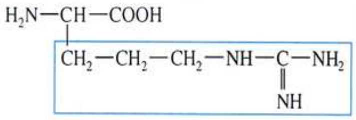
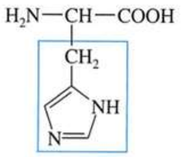
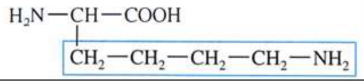
Name		**Structure**
glycine	Gly	 $H_2N-\underset{\boxed{H}}{\underset{\vert}{CH}}-COOH$
alanine	Ala	 $H_2N-\underset{\boxed{CH_3}}{\underset{\vert}{CH}}-COOH$
valine	Val	
leucine	Leu	
isoleucine	Ile	 $H_2N-\underset{\boxed{CH_3-CH-CH_2CH_3}}{\underset{\vert}{CH}}-COOH$
methionine	Met	 $H_2N-\underset{\boxed{CH_2-CH_2-S-CH_3}}{\underset{\vert}{CH}}-COOH$
proline	Pro	
phenylalanine	Phe	
tryptophan	Trp	

- Some of these amino acids are **essential amino acids**. They are not biosynthesised by the human body and must be provided for in the diet.
- A deficiency in any one of these essential amino acids prevents growth and may even cause death.

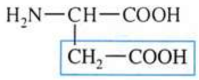
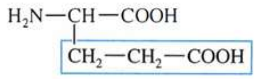
2-amino acids with polar side chain

Name		**Structure**
asparagine	Asn	
glutamine	Gln	
serine	Ser	 $H_2N-\underset{\boxed{CH_2-OH}}{\underset{\vert}{CH}}-COOH$
Threonine	Thr	 $H_2N-\underset{\boxed{HO-CH-CH_3}}{\underset{\vert}{CH}}-COOH$
Tyrosine	Tyr	
Cysteine	Cys	 $H_2N-\underset{\boxed{CH_2-SH}}{\underset{\vert}{CH}}-COOH$

2-amino acids with basic side chain

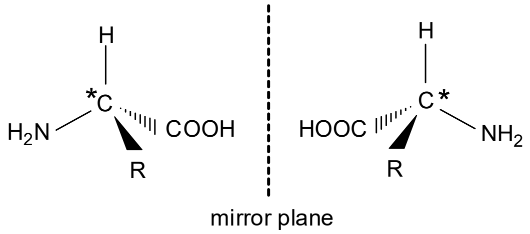
Name		**Structure**
arginine	Arg	
histidine	His	
lysine	Lys	 $H_2N-\underset{\boxed{CH_2-CH_2-CH_2-CH_2-NH_2}}{\underset{\vert}{CH}}-COOH$

2-amino acids with acidic side chain

Name		**Structure**
aspartic acid	Asp	 $H_2N-\underset{\boxed{CH_2-COOH}}{\underset{\vert}{CH}}-COOH$
glutamic acid	Glu	 $H_2N-\underset{\boxed{CH_2-CH_2-COOH}}{\underset{\vert}{CH}}-COOH$

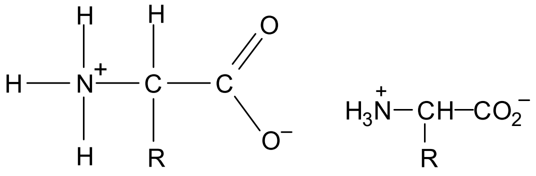
2.1 Optical Activity

- With the sole exception of aminoethanoic acid (glycine), all 2-amino acids contain at least a chiral carbon atom and consequently display enantiomerism and can exist in optically active forms.

 **Note**: ∗ denotes chiral carbon atom	2-amino acids (exception: glycine) isolated from natural sources • consist purely of one enantiomeric form • are optically active 2-amino acids (exception: glycine) synthesised in the laboratory • usually consist of racemic mixture • and hence are optically inactive

2.2 Formation of zwitterions

- Although we commonly write amino acids with an intact carboxylic acid group (–COOH) and amine group ($–NH_2$), their actual structure in the dry solid state is **zwitterionic**.
- The amino acid undergoes an internal acid-base reaction in which
  - the carboxylic acid group loses a proton, giving a carboxylate ion ($–COO^–$),
  - and the amine group is protonated to an aminium group ($–NH_3^+$).

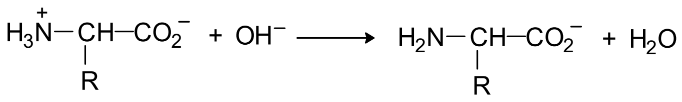
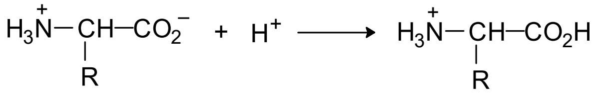
• Amino acids exist as **zwitterions.** • The zwitterion is also often referred to as a **dipolar ion**. Note, however, that it is not an ion but an electrically neutral molecule with oppositely charged ends.	
• A **zwitterion** is an electrically neutral molecule with oppositely charged ends	

- The zwitterionic nature of amino acids gives them some unusual properties as described below.

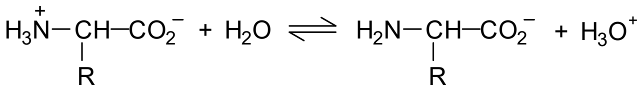
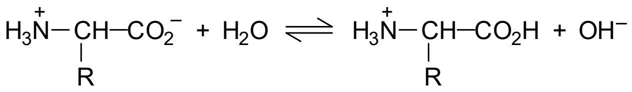
• Amino acids are crystalline solids with **high melting points** or decomposition points, usually above 200 °C. • Example: Glycine has a melting point of 262 °C.	• In solid amino acid, the lattice particles are zwitterions held together by strong **ionic bonding**. • The strong electrostatic forces of attraction between oppositely charged ends of neighbouring zwitterions require a large amount of heat energy to overcome. • Hence the melting points or decomposition points of amino acids are relatively high.
• Amino acids are **much more soluble in water** than in non-polar solvents.	• The oppositely charged ends of the zwitterions can interact with water molecules via **ion-dipole interactions.** • This causes the amino acids to be more soluble in a polar solvent like water than in a non-polar organic solvent like benzene.
• Amino acids are **less acidic** than most carboxylic acids and **less basic** than most amines.	The acidic part of an amino acid is the $–NH_3^+$ group. • K_a of $–NH_3^+$ < K_a of –COOH The basic part of an amino acid is the $–COO^–$ group. • K_b of $–COO^–$ < K_b of $–NH_2$

3.1 Acidic and basic groups in amino acids

- Amino acids are **amphoteric** (i.e. having both acidic and basic properties) since they contain both acidic and basic groups.

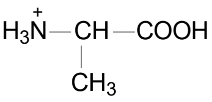
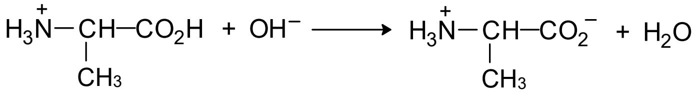
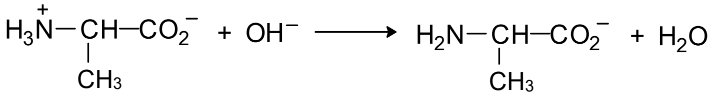
as a Bronsted-Lowry acid	 $H_3\overset{+}{N}-\underset{R}{CH}-CO_2^- + OH^- \longrightarrow H_2N-\underset{R}{CH}-CO_2^- + H_2O$	**Note:** The acidic part of an amino acid molecule is the $-NH_3^+$ group.
as a Bronsted-Lowry base	 $H_3\overset{+}{N}-\underset{R}{CH}-CO_2^- + H^+ \longrightarrow H_3\overset{+}{N}-\underset{R}{CH}-CO_2H$	**Note:** The basic part of an amino acid molecule is the $-COO^-$ group.

- Consider an aqueous solution of an amino acid.

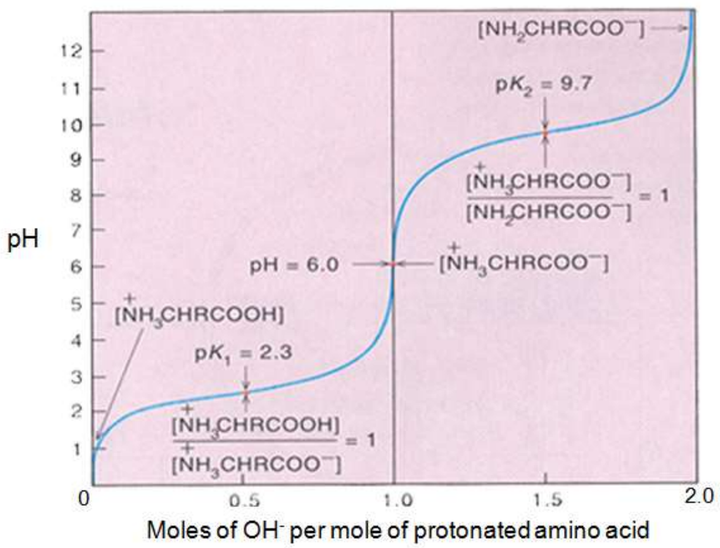
For simplicity, assume that the –R group is neither acidic nor basic. **Questions:** • Is the solution acidic or alkaline? • Does the amino acid behave as an acid or as a base?	 $H_3\overset{+}{N}-\underset{R}{CH}-CO_2^- + H_2O \rightleftharpoons H_2N-\underset{R}{CH}-CO_2^- + H_3O^+$
	 $H_3\overset{+}{N}-\underset{R}{CH}-CO_2^- + H_2O \rightleftharpoons H_3\overset{+}{N}-\underset{R}{CH}-CO_2H + OH^-$
Note: • For glycine (aminoethanoic acid), K_a of $-NH_3^+ = 1.6 \times 10^{-10}$ mol dm^{-3} and K_b of $-COO^- = 2.5 \times 10^{-12}$ mol dm^{-3}. • Since $K_a > K_b$, an aqueous solution of glycine is **weakly acidic**.	

3.2 Titration curve of a protonated amino acid

- Consider the **protonated form of 2-aminopropanoic acid (i.e. protonated alanine)**. It is considered to be a dibasic acid with two pK_a values of 2.3 and 9.7. It can donate two protons during its complete titration with a solution of a base.

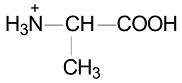
 $H_3\overset{+}{N}-\underset{CH_3}{CH}-COOH$ **acidic** **acidic** pK_{a2} = 9.7 pK_{a1} = 2.3	**Step 1:**  $H_3\overset{+}{N}-\underset{CH_3}{CH}-CO_2H + OH^- \longrightarrow H_3\overset{+}{N}-\underset{CH_3}{CH}-CO_2^- + H_2O$ cation zwitterion
	Step 2:  $H_3\overset{+}{N}-\underset{CH_3}{CH}-CO_2^- + OH^- \longrightarrow H_2N-\underset{CH_3}{CH}-CO_2^- + H_2O$ zwitterion anion

- The graph below shows the titration curve for protonated alanine. The pK_{a1} and pK_{a2} of protonated alanine are sufficiently far apart such that two equivalent points can be seen in the titration curve.
- The first equivalence point corresponds to the completion of Step 1 above while the second equivalence point corresponds to the completion of Step 2 above.



Suggest the major species present in a solution of alanine at the following pH values:

- pH = 1.5
- pH = 5.0
- pH = 11.0

pH	Predominant species	Remarks
pH = initial pH	 $H_3\overset{+}{N}-\underset{\displaystyle CH_3}{\underset{\vert}{C}H}-COOH$	The amino acid is fully protonated.
pH = pK_{a1} = 2.3		A buffer solution of maximum buffering capacity. [cation] = [zwitterion]
pH at 1st equivalence point		The first equivalence point of the titration is reached.
pH = pK_{a2} = 9.7		A buffer solution of maximum buffering capacity. [zwitterion] = [anion]
pH at 2nd equivalence point		The second equivalence point of the titration is reached.

4.1 Acid base reaction

Reaction with an acid:

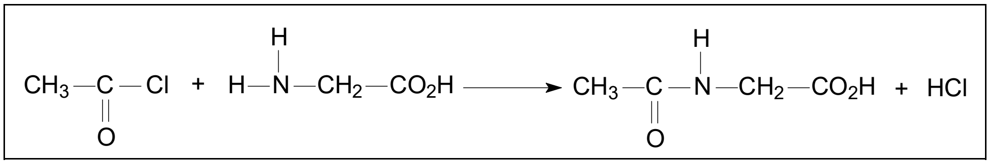
$^+H_3N–CH_2–COO^-(aq) + HCl(aq) \longrightarrow {}^+H_3N–CH_2–COOH(aq) + Cl^-(aq)$

Reaction with a base:

$^+H_3N–CH_2–COO^-(aq) + NaOH(aq) \longrightarrow H_2N–CH_2–COO^-(aq) + Na^+(aq) + H_2O(l)$

4.2 Condensation reaction with acid chloride

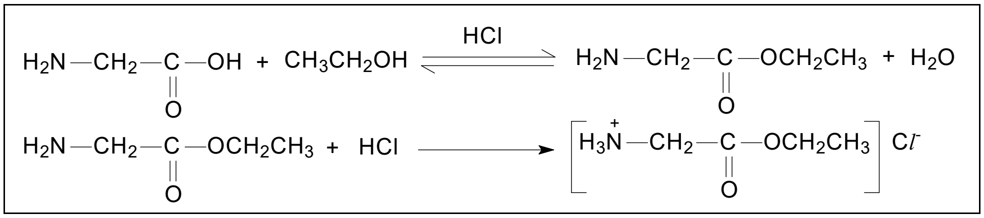
- The amine group in amino acids can react with an acid chloride, e.g. ethanoyl chloride, to form amide.



$$CH_3-\underset{\underset{O}{\|}}{C}-Cl + H-\overset{\overset{H}{|}}{N}-CH_2-CO_2H \longrightarrow CH_3-\underset{\underset{O}{\|}}{C}-\overset{\overset{H}{|}}{N}-CH_2-CO_2H + HCl$$

4.3 Condensation reaction with alcohols

- This reaction is fundamentally similar to the reactions of carboxylic acids, with the exception that the mineral acid catalyst ultimately reacts with the $–NH_2$ group.



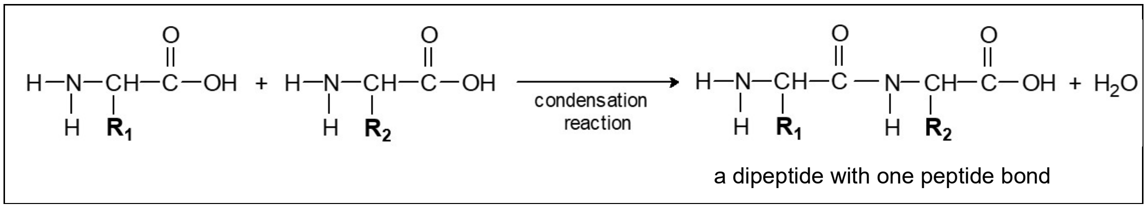
$$H_2N-CH_2-\underset{\underset{O}{\|}}{C}-OH + CH_3CH_2OH \overset{HCl}{\rightleftharpoons} H_2N-CH_2-\underset{\underset{O}{\|}}{C}-OCH_2CH_3 + H_2O$$

$$H_2N-CH_2-\underset{\underset{O}{\|}}{C}-OCH_2CH_3 + HCl \longrightarrow \left[H_3\overset{+}{N}-CH_2-\underset{\underset{O}{\|}}{C}-OCH_2CH_3\right] Cl^-$$

4.4 Peptide formation

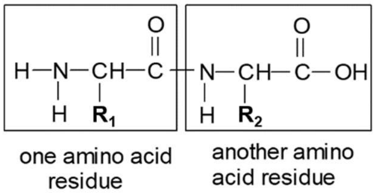
- Having both an $-NH_2$ group and a –COOH group, an amino acid is ideally suited to form an amide linkage. Under the **proper conditions**, the $-NH_2$ group of one molecule condenses with the –COOH group of another to form an amide bond.

- Consider the formation of a **dipeptide**.

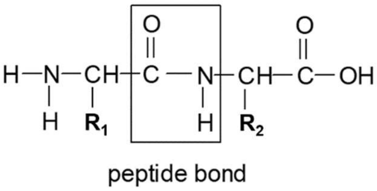


a dipeptide with one peptide bond

- The product is an amide called a **dipeptide** because it consists of two amino acid residues.



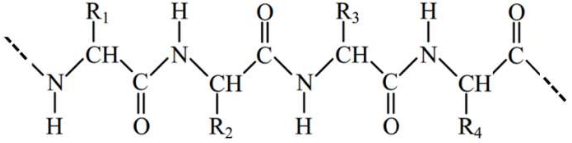
- The amide linkage (i.e. –CO–NH– structural unit) between the amino acid residues is called a **peptide bond**.



- A **peptide bond** (or peptide linkage) is the special name given to the amide bond (or amide linkage) formed between the alpha $-NH_2$ group of an α-amino acid and the alpha –COOH group of another α-amino acid.

1.1 Peptides and Proteins

- A **peptide** is a compound containing two or more amino acid residues linked by peptide bonds between the α-amino group of each amino acid and the α-carboxyl group of the neighbouring amino acid.
- Each amino acid unit in the peptide is called an **amino acid residue**.
- **Note:** Any number of amino acids can undergo condensation to form a peptide.

Number of amino acids undergoing condensation	Product	Number of amino acid residues	Number of peptide bond(s)
2	dipeptide	2	1
3	tripeptide	3	2
4	tetrapeptide	4	3
n	polypeptide	n	n – 1
			

- In living systems, amino acids undergo condensation reaction to form polypeptides and proteins with the aid of enzymes that form peptide bonds (i.e. amide linkages or amide bonds) between the α-amino group of one amino acid to the α-carboxyl group of another.
- In general

$$\text{amino acids} \longrightarrow \text{peptides} \longrightarrow \underset{(M_r < 5000)}{\text{polypeptides}} \longrightarrow \underset{(M_r\text{: } 6000 - 40\,000\,000)}{\text{proteins}}$$

Note:
- Proteins are polyamides.
- Proteins are condensation polymers.
- Proteins are biopolymers of α-amino acids (i.e. 2-amino acids).
- Proteins are macromolecules consisting of one or more polypeptide chains.
- Proteins are polypeptides that have some biological function.
- Proteins are naturally occurring polypeptides made up of 40 to 4000 amino acids.

- Proteins play a central role in biological systems and are essential for life in all living organisms. They serve many functions in living systems as shown in the table below.

Type of protein	Function	Example
Enzymes	Catalyse metabolic processes which produce energy, build up new cell structures or destroy old ones.	Proteases such as *pepsin, trypsin, chymotrypsin*
Transport proteins	Move metabolites around the cell or around the whole organism.	*Haemoglobin* & *myoglobin* – transport and store oxygen
Structural proteins	Provide the framework which defines the shape and size of cells.	*Keratin* in hair and fingernails *Collagen* in cartilage
Contractile proteins	Involve in muscle and cell movement and contraction	*myosin* and *actin* in muscles
Hormones or regulatory proteins	Control the level and type of cell functions including metabolism and reproduction.	*Insulin – to control blood sugar*
Immunoproteins	Involve in the functioning of immune system	Antibodies

- Regardless of their function, all proteins have a fundamentally similar structure and are made up of many amino acids linked together in a long chain. However, each protein differs from another protein in the number, type and sequence of constituent amino acids.

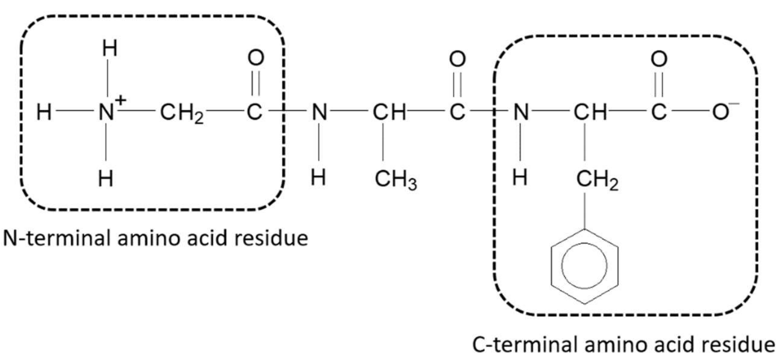
1.2 Structure and nomenclature of peptides

- Consider a tripeptide with the structure as shown below.

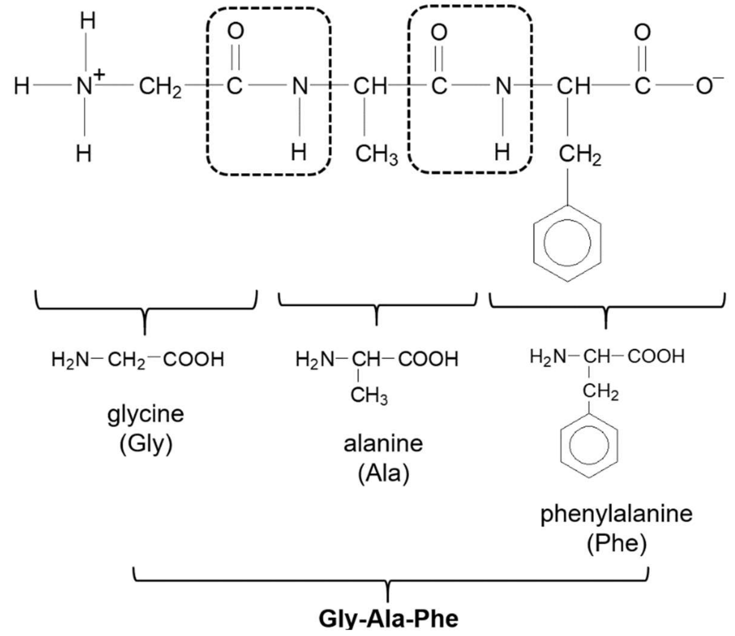
By convention, the structure of a peptide is written with

- the **N-terminal** amino acid residue (i.e. the one that has a free –NH_3^+ group) on the **left** and

- the **C-terminal** amino acid residue (i.e. the one that has a free –CO_2^- group) on the **right**.



- The name of a simple peptide can be denoted by a combination of the **3-letter abbreviations** listed for each amino acid in the table on page 28.
- For example, the given tripeptide can be identified as **Gly-Ala-Phe**.



Note:

- For any given peptide, to identify its constituent amino acids, locate the peptide bonds first.
- Then "cleave" each peptide bond to allow the structural formulae of the constituent amino acids to be seen more clearly.

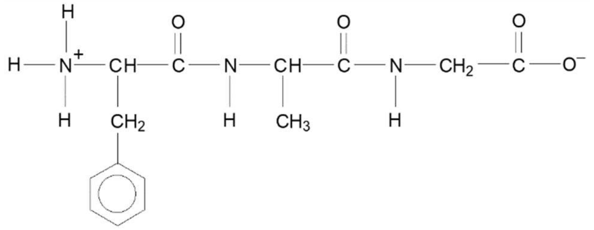
- Other tripeptides with the same three constituent amino acids are

Gly-Phe-Ala

Ala-Gly-Phe
Ala-Phe-Gly

Phe-Ala-Gly
Phe-Gly-Ala

- **Worked example:**
  Draw the tripeptide, **Phe-Ala-Gly**.

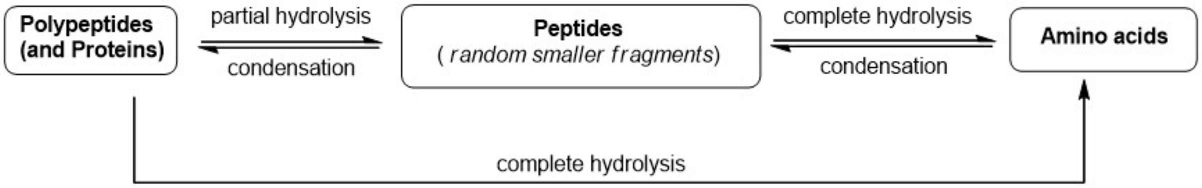


Note:

Gly-Ala-Phe
is **<u>not</u>** the same as
Phe-Ala-Gly.

2.1 Hydrolysis of Peptides and Proteins

- Peptides, polypeptides and proteins can undergo **hydrolysis** where the peptide bonds are broken. This reaction is the similar to the hydrolysis of amides (*Refer to Amides Section 5.1*).



- The hydrolysis carried out can be complete hydrolysis or partial hydrolysis.

Complete Hydrolysis	Partial hydrolysis
• The complete hydrolysis of a protein gives the number and relative amounts of different types of amino acids. • However, this method does not provide any information about the order in which the amino acids are joined together.	• Partial hydrolysis of a protein gives smaller peptide fragments which still retain some sequence information. • When these fragments are separated and identified, the overall amino acid sequence of the protein may be deduced from overlaps of the peptide sequences.
• The complete hydrolysis of a polypeptide or protein into individual amino acids, is usually done by heating the sample with 6 mol dm^{-3} HC*l* at 100–120 °C for 24 hours in an evacuated tube.	• The partial hydrolysis of a polypeptide or protein into smaller peptides is usually carried out by enzymatic hydrolysis using a suitable enzyme.

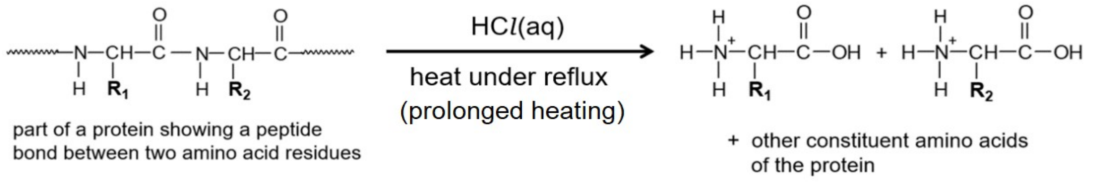
2.2 Chemical hydrolysis

- In the laboratory, the complete hydrolysis of a sample of protein or peptide into its constituent amino acids is usually carried out by **prolonged heating** using **aqueous hydrochloric acid or sulfuric acid** of a higher concentration (e.g. 6 mol dm^{-3} HC*l*).

Acid hydrolysis

Reagent: HC*l*(aq) or H_2SO_4(aq)

Condition: Heat under reflux (for a few hours / prolonged heating)

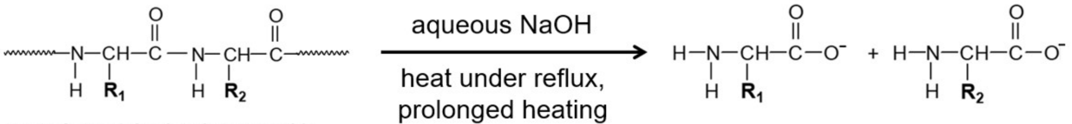


- In the laboratory, hydrolysis of a sample of peptide or protein using **aqueous sodium hydroxide** of a higher concentration under **prolonged heating** is also possible.

Base hydrolysis

Reagent: NaOH(aq)

Condition: Heat under reflux (for a few hours / prolonged heating)

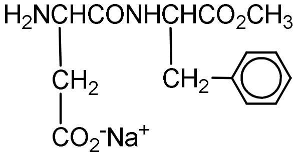


part of a protein showing a peptide bond between two amino acid residues

+ other constituent amino acids of the protein

Exercise 2 [N2005/I/Q12]

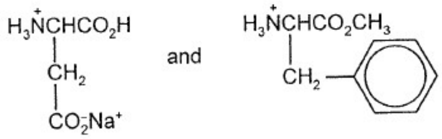
Aspartame is a dipeptide derivative used as an artificial sweetening agent in many soft drinks. Its general usefulness is restricted because it loses its sweetness after hydrolysis.



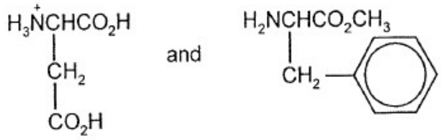
aspartame

Which products would be formed after prolonged acid hydrolysis?

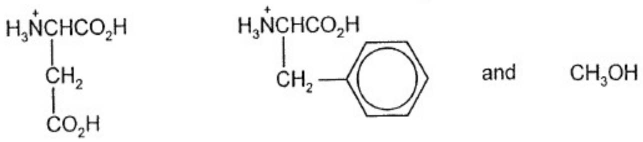
A



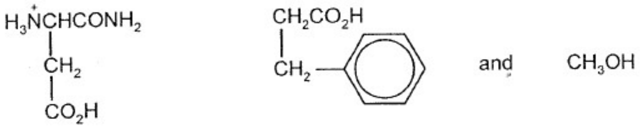
B



C



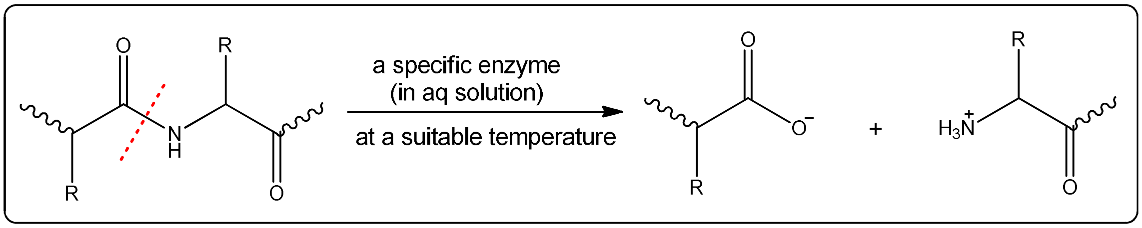
D



2.3 Enzymatic hydrolysis

- For peptides containing more than 50 residues, the use of chemical hydrolysis is generally not practical because unwanted side products may accumulate and interfere with the results.

- Enzymatic hydrolysis using enzymes known as proteases/peptidases (e.g. trypsin, chymotrypsin and pepsin) is usually employed as these enzymes selectively hydrolyse specific peptide bonds.



- For example, trypsin only catalyses the hydrolysis of the peptide bond at the carboxyl end of the basic amino acids, arginine and lysine.

Ala-Phe-Lys-Pro-Met-Tyr-Gly-Arg-Ser-Trp-Leu-His $\xrightarrow{\text{Trypsin}}$ Ala-Phe-Lys
Pro-Met-Tyr-Gly-Arg
Ser-Trp-Leu-His

- By using a variety of proteases, multiple overlapping fragments are formed and this can be used for primary sequence determination of proteins.

Exercise 3

Partial hydrolysis of a hexapeptide gives the following fragments:
Gly-Pro-Arg, Arg-Ala, Pro-Leu-Gly.

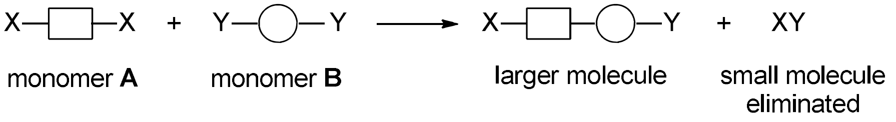
What is the structure of the hexapeptide?

Condensation Polymers

1.1 Condensation polymers

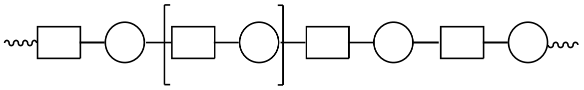
> *Recall from Introduction to Organic Chemistry, Lecture Notes 9 Section 6.3,*
> *For a condensation reaction:*
> - *Two molecules react together to form a bigger molecule with the elimination of small molecules such as H_2O or HCl.*
> - *Degree of unsaturation remains unchanged.*

Condensation Reaction:



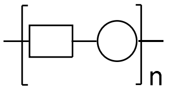
where X : -COOH Y : -OH, $-NH_2$

In the above reaction, the larger molecule formed still contains X and Y which can undergo further condensation reactions with monomers **B** and **A** respectively. The reaction continues to form a polymer:

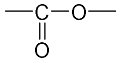
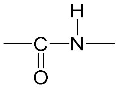


repeating unit

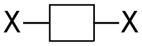
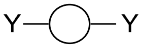
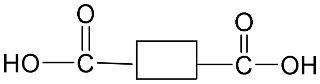
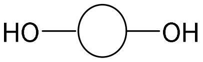
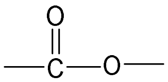
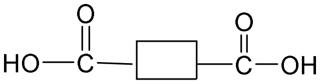
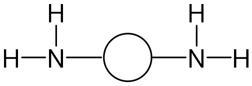
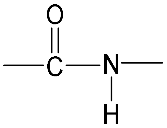
also represented as



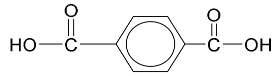
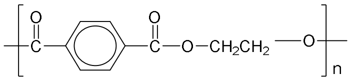
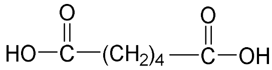
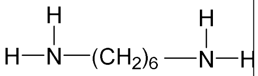
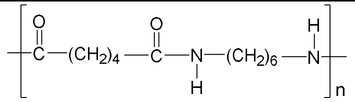
n = number of repeat units

- Thus, condensation polymers are formed when monomers containing <u>two functional groups</u> come together and <u>lose a small molecule</u> such as H_2O or HC*l*.
- The bonds between the repeat units are usually either the ester ( $\underset{\underset{O}{\|}}{-C}-O-$) or the amide ( $\underset{\underset{O}{\|}}{-C}-\overset{\overset{H}{|}}{N}-$) bond.
- Examples of condensation polymers: polyesters and polyamides

The two types of condensation polymers

Monomer structure 	**Monomer structure** 	**Bond between repeat units**	**Molecule eliminated**
 dicarboxylic acid	 diol	 ester	H_2O
 dicarboxylic acid	 diamine	 amide	H_2O

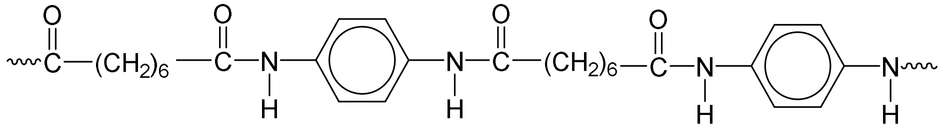
Common condensation polymers and their uses

Name of polymer	Monomer structure X–☐–X	Monomer structure Y–○–Y	Polymer structure	Uses
poly(ethylene terephthalate) (PET)	 benzene-1,4-dicarboxylic acid	$HO-CH_2CH_2-OH$ ethane-1,2-diol	 polyester	Terylene fabric, PET bottles, surgical sutures, Mylar film in balloons
(nylon 6,6)	 $HOOC-(CH_2)_4-COOH$ hexane-1,6-dicarboxylic acid	 $H_2N-(CH_2)_6-NH_2$ 1,6-diamino-hexane	 polyamide	backpacks

A carboxylic acid can only react with an amine to form an amide in the presence of a coupling reagent (this is beyond the scope of the H2 syllabus). Otherwise, an acid-base reaction will occur.

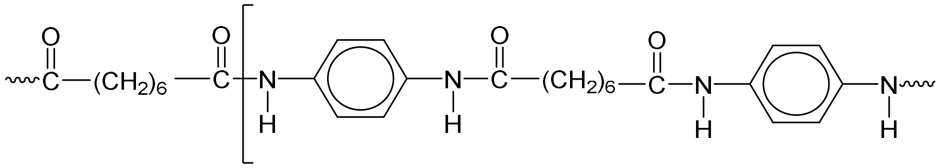
1.2 Deducing the repeat units and monomers in condensation polymers

A typical condensation polymer is shown below:

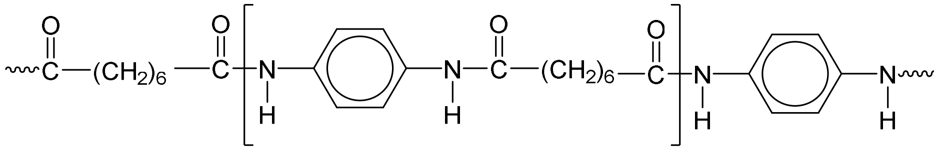


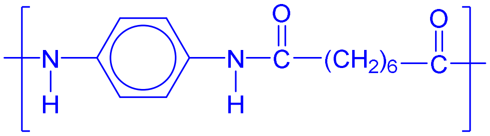
(a) To determine the **repeat unit**:

Step 1: Draw a bracket line between the C–N bond of the amide group (–CO–NH–) of the polyamide or between the C–O bond of the ester group (–CO–O–) of the polyester



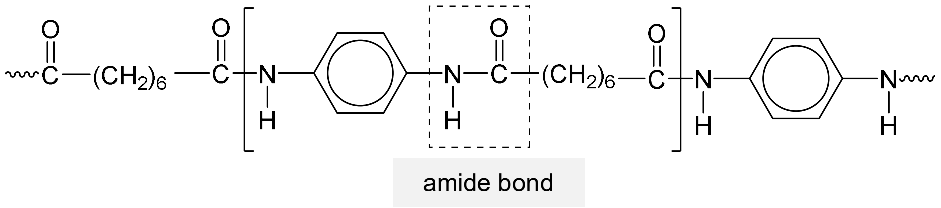
Step 2: Follow the chain until you come to just before this is about to repeat itself and draw the other bracket.



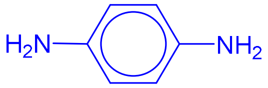


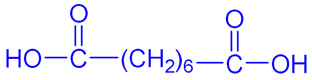
repeat unit

(b) To determine the **monomer units**:
Step 1: Locate the amide or ester bond within a repeat unit.



Step 2: What are the two monomers on either side of this bond?


monomer 1

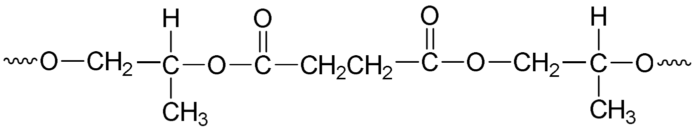

$HO-\overset{\displaystyle O}{\overset{\|}{C}}-(CH_2)_6-\overset{\displaystyle O}{\overset{\|}{C}}-OH$

monomer 2

To form an amide bond, one monomer must be a <u>diamine</u> and the other a <u>dicarboxylic acid</u>.

- **Worked Example:**

The following formula represents a portion of a polymer:


$\sim O-CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle H}{C}}-O-\overset{\displaystyle O}{\overset{\|}{C}}-CH_2CH_2-\overset{\displaystyle O}{\overset{\|}{C}}-O-CH_2-\underset{\displaystyle CH_3}{\overset{\displaystyle H}{C}}-O\sim$

(a) State the type of polymerisation involved in the formation of this polymer.

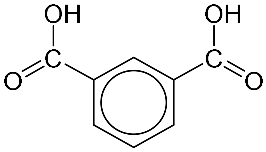
(b) Draw the structural formulae of the monomers which undergo polymerisation to form this polymer.

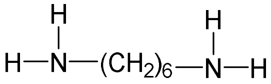
<u>Solution</u>

- **Worked Example:**

Draw the polyamide formed from each pair of monomers.

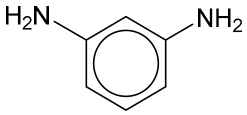
(a)

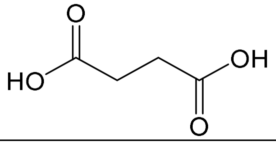




$\mathrm{H{-}\overset{H}{\overset{|}{N}}{-}(CH_2)_6{-}\overset{H}{\overset{|}{N}}{-}H}$

(b)





Solution