ANDERSON SERANGOON JUNIOR COLLEGE
JC 2 H2 CHEMISTRY
NITROGEN COMPOUNDS

Content	Resources
1 Amines 1.1 Structure & Classification 1.2 Nomenclature 1.3 Physical Properties of amines 1.4 Basic Properties of amines 1.5 Preparation of amines 1.6 Reactions of amines	**Lecture 1** • Mode: F2F • Lecture note: Pg 2 to 11 • SLS quiz: Q1 – 2
2 Amides 2.1 General formula & Structure 2.2 Nomenclature 2.3 Physical Properties of amides 2.4 Preparation of amides 2.5 Reactions of amides	**Lecture 2** • Mode: F2F • Lecture note: Pg 12 to 18 • SLS quiz: Q3 – 6
3 Amino Acids (continued) 3.1 Introduction to amino acid 3.2 General Properties of amino acids 4 Polypeptides and Proteins 4.1 Polypeptides 4.2 Hydrolysis of polypeptides/proteins	**Lecture 3** • Mode: F2F • Lecture note: Pg 18 to 30 • SLS quiz: Q7 – 10

LEARNING OUTCOMES

Candidates should be able to:

(a) describe the formation of amines as exemplified by ethylamine (through amide and nitrile reduction; see also Section 11.4) 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'COC*l*
(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:
    - hydrolysis on treatment with aqueous alkali or acid
    - reduction to amines with lithium aluminium hydride
(i) describe the acid/base properties of amino acids and the formation of zwitterions
(j) describe the formation of peptide (amide) bonds between α-amino acids, and hence explain protein formation
(k) describe the hydrolysis of proteins

REFERENCES

1. Organic Chemistry; K. Peter C. Vollhardt
2. Organic Chemistry; Francis A. Carey
3. Organic Chemistry; Morrison and Boyd
4. Organic Chemistry; John McMurry
5. Chemistry In Action; Michael Freemantle
6. Chemistry; J.G.R. Briggs
7. Biology for Advanced Level; Glenn and Susan Toole
8. Principles of Biochemistry; David L. Nelson
9. H2 Chemistry Teaching and Learning Guide

1 AMINES

1.1 STRUCTURE & CLASSIFICATION

- Amines are **organic derivatives of ammonia** where one or more hydrogen atoms is/are replaced by the corresponding number of **alkyl** or **aryl** group(s).

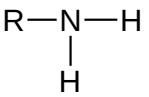
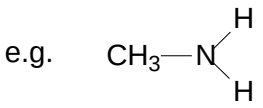
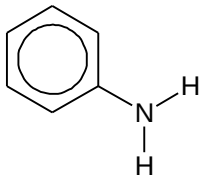
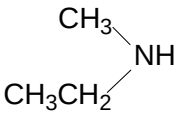
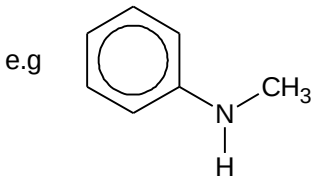
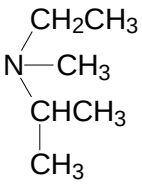
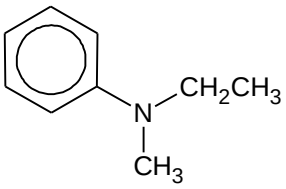
- Can be classified according to their **degree of substitution on the nitrogen atom** (i.e. the number of **R group** substituents on the **nitrogen** atom)

  i.e. primary (1°) – **one** group substituted on **N atom**

  secondary (2°) – **two** groups substituted on **N atom**

  tertiary (3°) – **three** groups substituted on **N atom**

E.g.

Class	Functional Group	Aliphatic amine	Aromatic amine (N atom is directly bonded to the benzene ring)
1°	$-NH_2$	 	**Ar**NH_2 
2°		**R$_2$**NH or **RR'**NH 	**Ar$_2$**NH or **ArR**NH 
3°		**R$_3$**N or **RR'R''**N 	**Ar$_3$**N or **Ar$_2$R**N or **ArR'R''**N 

- Quaternary (4°) ammonium compounds

  - four groups substituted on N atom which is **tetravalent**

  - named as ammonium salts

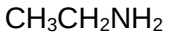
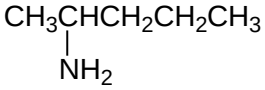
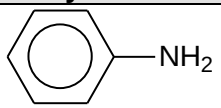
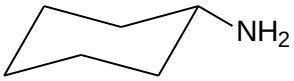
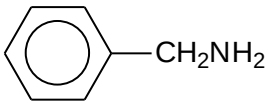
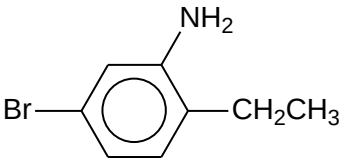
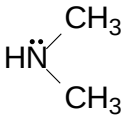
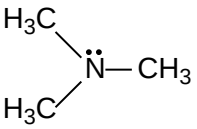
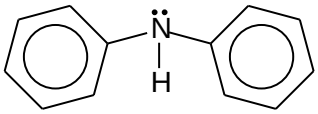
  E.g. $(CH_3)_4\overset{+}{N}\ \ Cl^-$

  tetramethylammonium chloride

1.2 NOMENCLATURE

- For simple amines
  - suffix ***–amine*** is added to the name of the alkyl group that is bonded to the N atom

E.g.

Alkylamines		Arylamines
 **ethylamine**	 **2-pentylamine**	 **phenylamine**
 **cyclohexylamine**	 **(phenylmethyl)amine / benzylamine**	 **5-bromo-2-ethylphenylamine***
 **dimethylamine**	 **trimethylamine**	 **diphenylamine**

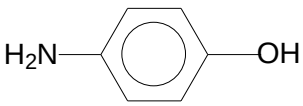
***Recall**: Substituents on the benzene ring are listed in alphabetical order and direction of numbering is governed by the usual rule "smallest possible numbers to the substituents".*

- For polyfunctional amines with other functional groups of higher priority,
  - treat the amine group as a substituent and add the prefix ***–amino*** to the parent compound

E.g.

H_2NCH_2COOH

2-aminoethanoic acid



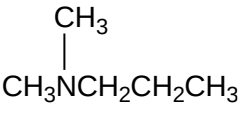
4-aminophenol

- For **2° and 3° amines** with alkyl substituents on the nitrogen atom:
  - named as *N*- substituted derivatives of primary amines
  - the parent amine is taken to be the one with the longest carbon chain
  - the prefix *N*- is added to identify substituents **on the amino nitrogen**.

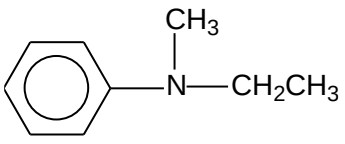
E.g.

$CH_3NHCH_2CH_3$

***N*-methylethylamine**



***N,N*-dimethylpropylamine**



***N*-ethyl-*N*-methylphenylamine**

1.3 PHYSICAL PROPERTIES OF AMINES

(a) Boiling / Melting Points (SDL)

- Lower alkylamines are gases (with odours similar to ammonia) or low boiling liquids (with characteristic fishy smell). Amines with high molecular mass are solids.

E.g. CH_3NH_2 b.p. = -7°C (gas)
$CH_3CH_2NH_2$ b.p. = 17°C (gas)
$CH_3CH_2CH_2NH_2$ b.p. = 49°C (liquid)

- Boiling points of amines are higher than the alkanes of similar relative molecular masses.

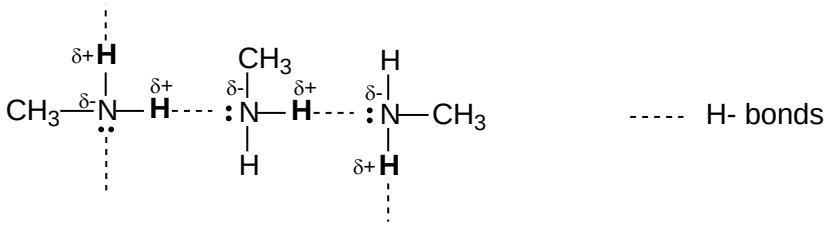
E.g. $CH_3CH_2CH_3$ (M_r = 44), b.p. = - 42°C
$CH_3CH_2NH_2$ (M_r = 45), b.p. = 17°C

Reason: Amines are polar compounds and can form **intermolecular hydrogen bonds**. Large amount of energy is required to overcome the stronger hydrogen bonds between amine molecules.

- Among isomeric amines, primary amines have the highest boiling points, and tertiary amines the lowest.

Reason: Tertiary amines have no N−H bond, they are unable to form intermolecular hydrogen bonds between molecules of tertiary amine.

Only 1° and 2° amines can form intermolecular hydrogen bonds. WHY?



Reason: For 1° and 2° amines, the H atom bonded to N can form H-bonding with the lone pair of electrons on N atom of another molecule. However, molecules of 3° amines lack a H atom bonded to the electronegative N atom, hence they can only form weaker permanent dipole–permanent dipole attractions between the molecules.

- For molecules with similar number of electrons, amines have lower boiling point than alcohols.

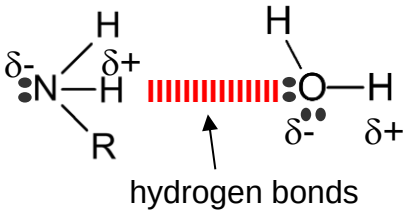
Reason: Since N atom is less electronegative than O atom, the N−H bond in amines is less polar than the O−H bond in alcohols. Hence, hydrogen bonding between amines is weaker than the hydrogen bonding between alcohols.

Compound	Functional Group	Mr	Boiling point / °C	Predominant intermolecular forces of attraction
CH_3CH_3	Alkane	30	−89	Instantaneous dipole – induced dipole attractions
CH_3NH_2	Amine	31	−6	Hydrogen bonding
CH_3OH	Alcohol	32	65	Hydrogen bonding

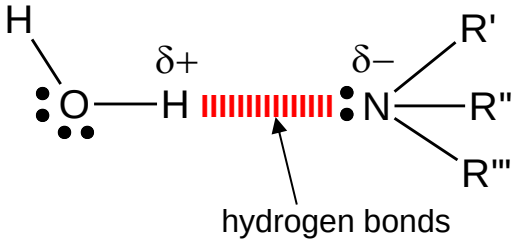
(b) Solubility (SDL)

- Lower alkylamines (usually amines with fewer than 5 carbon atoms) are **soluble in water**

  Reason: All amines (1°, 2°, 3°) can form **hydrogen bonds** with water molecules.



  Tertiary amines, though they do not contain a H atom bonded to a N atom, can **form hydrogen bonds with water** as well (as shown in the diagram below).



- However, solubility in water **decreases** as molecular mass **increases**.

  E.g. Phenylamine has limited solubility in water.

> **Recall:**
> For a solute to dissolve in a solvent, the energy released from the solute-solvent interactions ≥ energy required to overcome the solute-solute interactions and solvent-solvent interactions.

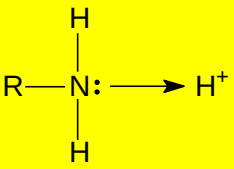
Reason: As molecular mass increases due to **increase** in number of C atoms in the hydrocarbon chain, there will be **stronger** instantaneous dipole–induced dipole (i.d.–i.d.) attractions (as number of electrons increases) between amine molecules.

Hence, energy released from the formation of hydrogen bonds between the amine and water molecules is not enough to compensate for the energy required to overcome the stronger i.d.–i.d. attraction between amine molecules and hydrogen bonding between water molecules.

1.4 BASIC PROPERTIES OF AMINES

- Amines like ammonia are weak **Lewis bases** in which the **lone pair of electrons** on the **N atom** can form a **co-ordinate (dative)** bond with a proton from an acid (i.e. act as electron pair donor).

E.g.



> A Lewis base is an **electron pair donor**.

The **basic strength** of an amine depends on the **availability of the lone pair of electrons on N atom** to form a dative bond to H^+ (or to accept a proton).

Relative Basicity of Amines in GASEOUS medium

In general, the relative basicities in gaseous medium:

3˚ amine > 2˚ amine > 1˚ amine > NH_3

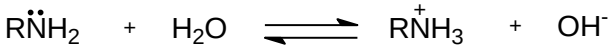
The extra alkyl groups in 2˚/3˚ amine exerts a greater electron donating effect and increase the electron density on N atom. This increases the availability of the lone pair of electrons on N atom to accept a proton.

Relative Basicity of Amines in AQUEOUS medium

- **Recall from *Acid–Base Equilibria***:

  The strength of a base is indicated by the extent to which the dissociation equilibrium lies to the right and this is represented by the base dissociation constant, **K_b**.

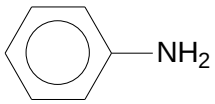
  E.g. When an amine is dissolved in water, equilibrium is established in which the lone pair on N atom of the amine accepts a proton from water. Water is acting as an acid.



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

  ⇒ The **more readily** the lone pair of electrons on N atom accepts a proton
  ⇒ the **larger** the value of K_b
  ⇒ the **stronger** the base

- Compare K_b of ammonia, ethylamine and phenylamine:

Bases	Structure	K_b
Ammonia	$H—NH_2$	1.8×10^{-5}
Ethylamine	$CH_3CH_2—NH_2$	5.6×10^{-4}
Phenylamine		4.2×10^{-10}

- Why does the base dissociation constant, K_b, values differ for different compounds?

- What are the other factors that can affect the basicity of a compound?

(1) Ethylamine is a stronger base than ammonia

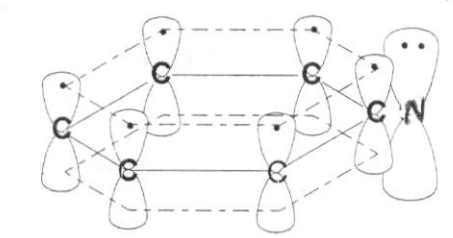
- Ethyl (or in general, alkyl) group is **electron-donating** and increases the electron density around the N atom.

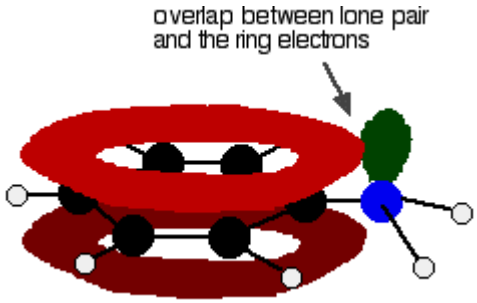
- This **increases** the **availability of the lone pair of electrons on N atom to accept a proton** (or to form a dative bond to a proton).

- Resulting in a stronger base than ammonia.

(2) Phenylamine is a weaker base than ammonia

- Lone pair of electrons on N atom in phenylamine is **delocalised** into the π electron cloud of the benzene ring.





- This **decreases** the **availability of the lone pair of electrons on N atom to accept a proton** (or to form a dative bond to a proton).

- Resulting in a weaker base than ammonia.

- Conclusion:

In general, the relative basicities in aqueous medium:
RNH_2 (alkylamines) > NH_3 > $C_6H_5NH_2$ (phenylamine)

Effect of substituents on basicity

Electron-**donating** substituent	Electron-**withdrawing** substituent
CH_3 NH_2 + H_2O ⇌ $CH_3NH_3^+$ + OH^-	CH_2(**C*l***)NH_2 + H_2O ⇌ CH_2(C*l*)NH_3^+ + OH^-
Increases the **availability of the lone pair of electrons on N atom to accept a proton.**	**Reduces** the **availability of the lone pair of electrons on N atom to accept a proton.**
Increase in basicity	**Decrease** in basicity
(i) **No. of** electron-donating / withdrawing substituents: • Greater no of electron-donating / withdrawing substituents • Greater increase / decrease in basicity (ii) **Proximity** of electron-donating / withdrawing substituent to NH_2 group: • Nearer to amino group, • Greater electron donating / withdrawing effect • Greater increase / decrease in basicity	

SUMMARY:
Effect of electron–donating and electron–withdrawing substituents on strength of base

	Electron-**donating** substituent	Electron-**withdrawing** substituent
For **bases**:	Increases the availability of the lone pair of electrons on N atom to accept a proton ⇒ **increase** basicity	Reduces the availability of the lone pair of electrons on N atom to accept a proton ⇒ **decrease** basicity

1.5 PREPARATION OF AMINES

(a) Preparation of aliphatic amine

(i) Reduction of nitriles (RCN)

(Refer to Halogen Derivatives Lecture Notes for more details)

Type of reaction	Reduction
Reagents & Condition	$LiAlH_4$ in dry ether, room temperature Or H_2(g), nickel catalyst, heat (Catalytic hydrogenation)
General Equation	$CH_3CN + 4[H] \xrightarrow[\text{room temp}]{LiAlH_4 \text{ in dry ether}} CH_3CH_2NH_2$ $CH_3CN + 2H_2 \xrightarrow[\text{heat}]{\text{Ni catalyst}} CH_3CH_2NH_2$

(ii) Reduction of amides

- Will be covered later under amides

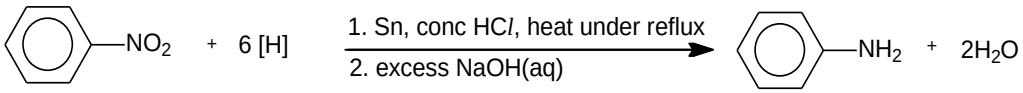
(iii) Nucleophilic substitution of halogenoalkanes, RX

(Refer to Halogen Derivatives Lecture Notes for more details)

Type of reaction	Nucleophilic substitution
Reagents & Condition	NH_3 in ethanol, heat in sealed tube
General Equation	$CH_3CH_2I + \dot{N}H_3 \longrightarrow CH_3CH_2\dot{N}H_2 + HI \xrightarrow{CH_3CH_2I} (CH_3CH_2)_2\dot{N}H + HI$ $(CH_3CH_2)_2\dot{N}H \xrightarrow{CH_3CH_2I} (CH_3CH_2)_3\dot{N} + HI$ $(CH_3CH_2)_3\dot{N} \xrightarrow{CH_3CH_2I} (CH_3CH_2)_4N^+ + I^-$

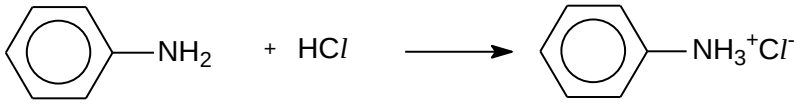
- Not a good preparation method as a mixture of 1°, 2°, 3° amines and 4° ammonium salts are formed.

(b) Preparation of aromatic amines – Reduction of nitrobenzene

Type of reaction	Reduction
Reagents & Condition	1) Granulated tin (Sn), concentrated HC*l*, heat under reflux 2) Followed by excess NaOH (aq)
General Equation	

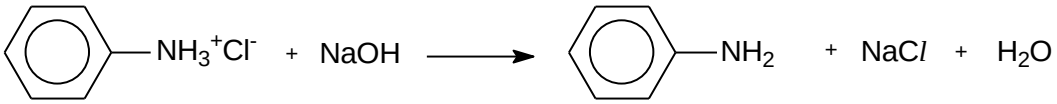
Product formed after step 1

- Phenylamine formed after the first step is basic and reacts with the conc. HC*l* to form an ammonium salt solution.



Product formed after step 2

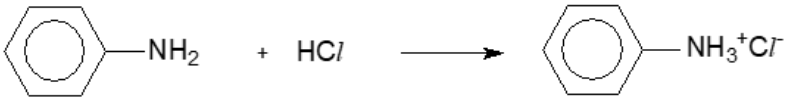
- Phenylamine is liberated by adding excess aqueous sodium hydroxide.



1.6 REACTIONS OF AMINES

(a) Reaction of the $-NH_2$ group: Salt formation (Acid-Base reaction)

- Aliphatic amines and phenylamines, which are basic, react with mineral acids to form soluble **ammonium salts**.

Type of reaction	Acid-base
Reagent & Condition	$HCl(aq)$ OR $H_2SO_4(aq)$, room temperature
General Equation	$CH_3CH_2NH_2 + HCl \longrightarrow CH_3CH_2NH_3^+Cl^-$ 

- These ammonium salts are obtained as **white crystals**, on evaporating their aqueous solutions.
- The amines can be re-generated from the aqueous salt solutions by adding **excess aqueous sodium hydroxide**.

E.g. $CH_3CH_2NH_3^+Cl^- + NaOH(aq) \longrightarrow CH_3CH_2NH_2 + NaCl(aq) + H_2O(l)$

(b) Reaction of the $-NH_2$ group with acyl chlorides: Formation of amides

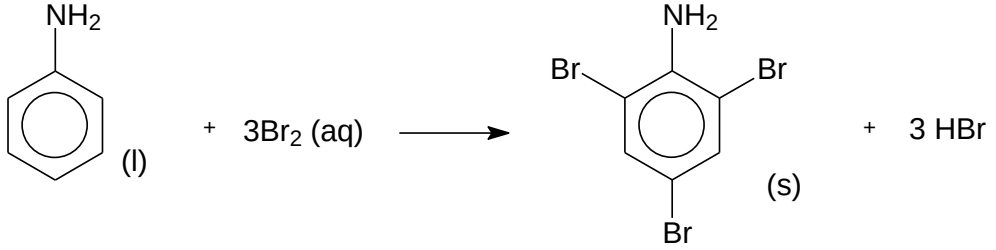
- Will be covered later under amides

(c) Reaction of the benzene ring in phenylamine: Electrophilic substitution (Bromination)

- The $-NH_2$ group in phenylamine is **ring-activating** and **-2,4 directing**. The lone pair of electrons on the N atom is delocalised into the benzene ring, making the benzene ring more electron rich. (*Recall: similar to phenols*)

  As a result, phenylamine is **more susceptible** to electrophilic substitution than benzene.

- Phenylamine reacts with **aqueous bromine, $Br_2(aq)$**, to give a **white precipitate** of 2,4,6-tribromophenylamine. Catalyst (Fe or $FeBr_3$) is not required.



white ppt
2,4,6-tribromophenylamine

Observations: Orange aqueous bromine is decolourised.
A white precipitate is formed.

The reaction with $Br_2(aq)$ can be used to **distinguish phenylamine from benzene**.
Observation when $Br_2(aq)$ is added to benzene: orange bromine remains.

Recall that
1. $-NH_2$ is electron-donating by resonance and activates the benzene ring so multiple substitution will occur.
2. Phenol gives the same observations as phenylamine with aqueous Br_2.

EXERCISE 1

Describe the reaction of phenylamine with

(i) dilute hydrochloric acid
(ii) aqueous bromine

For each reaction, write a balanced equation and draw the structural formula of the product.

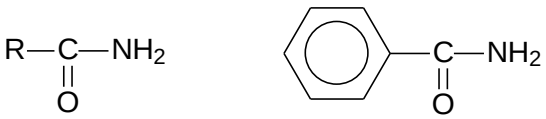
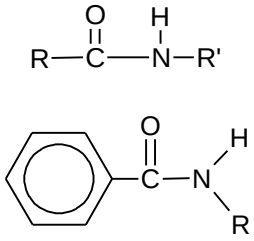
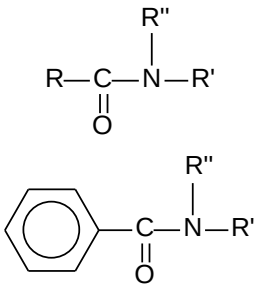
Solution

(i) Acid-base reaction

(ii) Electrophilic substitution

2 AMIDES

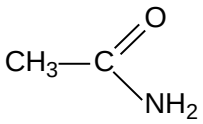
2.1 GENERAL FORMULA & STRUCTURE

Simple primary (1°) amides	Substituted amides	
	2° (secondary)	3° (tertiary)
		

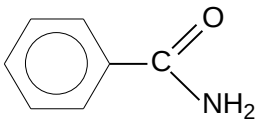
2.2 NOMENCLATURE

- Amides are carboxylic acid derivatives, where the acyl group is bonded to the N atom. Named by replacing the *"–oic acid"* of a carboxylic acid with *"–amide"*

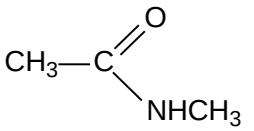
E.g.



ethanamide

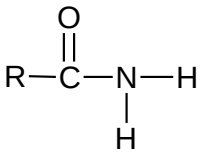
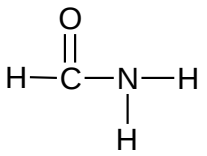
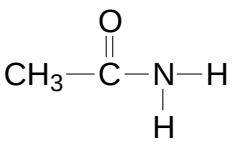
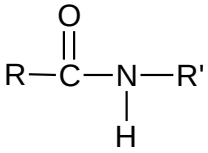
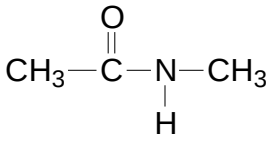
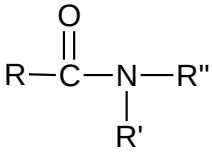
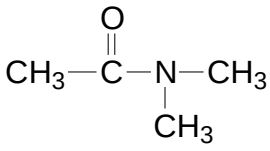


benzamide



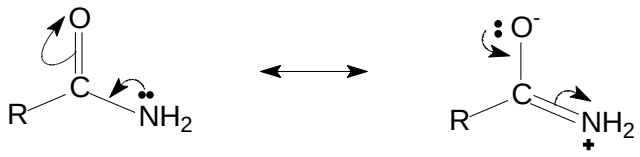
N-methylethanamide

- Substituted amides can have **one or two alkyl groups** in place of the hydrogen atoms normally attached to the **N atom**.

Classification of Amides	General Formula	Examples
Primary Amides (**0 R gp** attached to N)		 methanamide  ethanamide
Secondary Amides (**1 R gp** attached to N)		 N-methylethanamide
Tertiary Amides (**2 R gps** attached to N)		 N,N-dimethylethanamide

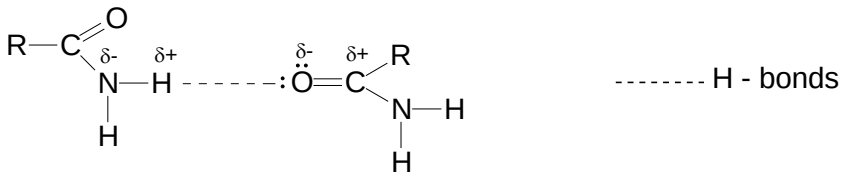
2.3 PHYSICAL PROPERTIES

- Amides are **neutral** solids, because the lone pair of electrons on nitrogen atom is delocalised into the π bond of the adjacent C=O by resonance, **hence not available to accept a proton**.



- Amides have high melting and boiling points due to **intermolecular hydrogen bonding**. (Note that tertiary amides have no N-H group, so they are unable to form intermolecular hydrogen bonding.)

  Methanamide, $HCONH_2$, is a liquid at room temperature, while all other amides are white crystalline solids.



- **Lower aliphatic** amides (≤ C_4) are **soluble** in water due to formation of **hydrogen bonds** with water.
- **Higher aliphatic** (≥ C_5) and **aromatic** amides are **insoluble** in water due to **large non polar** alkyl / aryl groups present.

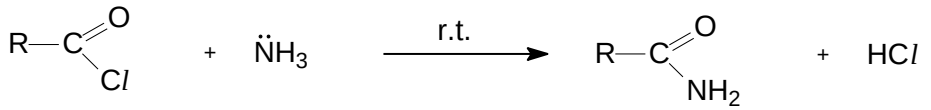
- All amides are soluble in common organic solvents.

2.4 PREPARATION OF AMIDES

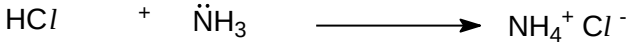
From acyl chlorides

- Acyl chlorides undergo **nucleophilic (acyl) substitution/ condensation** to give amides.
- The carbonyl C is **highly electron deficient** as it is bonded to **two electronegative atoms** – chlorine and oxygen.
- **Two** molar equivalents of reagents (NH_3 / RNH_2) are involved in the reaction with acyl chlorides
  - one molecule of the reagent acts as a nucleophile,
  - the second molecule acts as a Bronsted base.

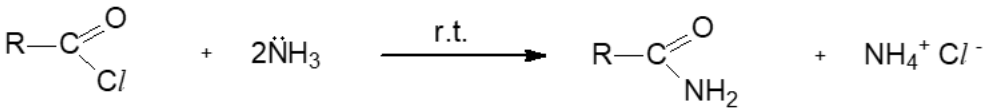
E.g.

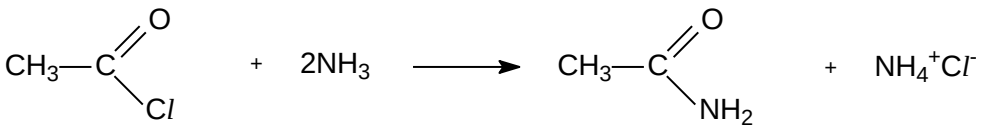


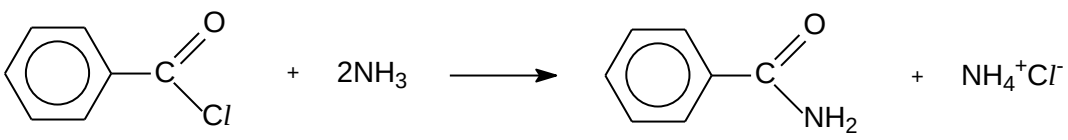
R = alkyl or aryl



(i) Acyl chlorides with ammonia, NH_3 – to form 1° amide

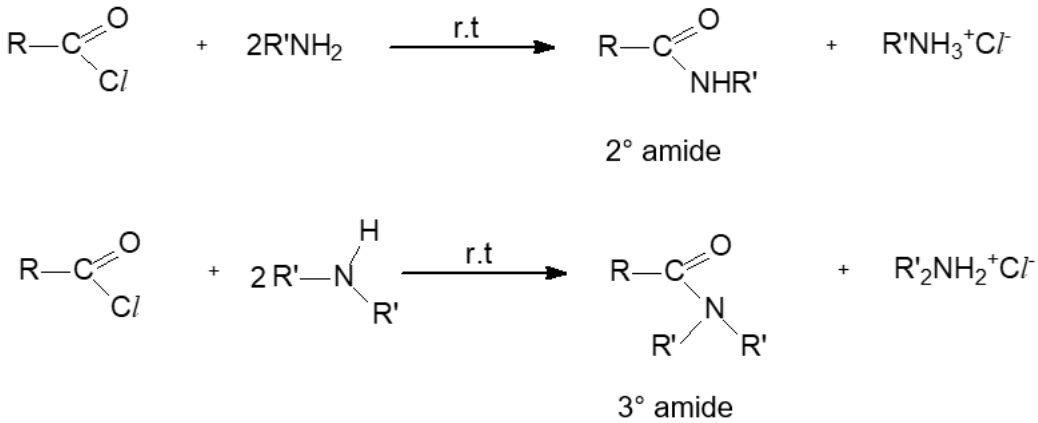
Type of reaction	nucleophilic (acyl) substitution/ condensation
Reagent & Condition	NH_3, room temperature
General Equation	 R = alkyl or aryl

E.g. 

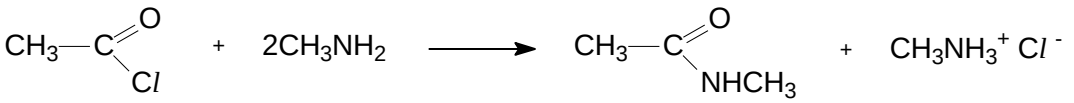


(ii) <u>Acyl chlorides with 1º & 2º amines – to form 2º & 3º amides</u>

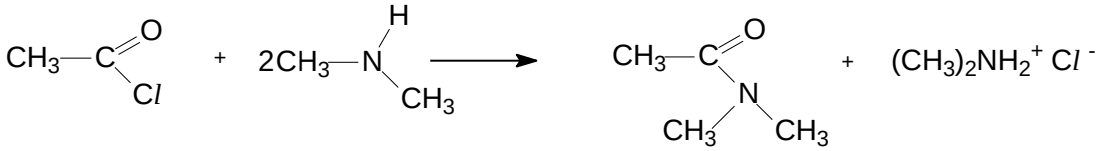
- Acyl chlorides react with primary or secondary amines to give N-substituted amides.

Type of reaction	nucleophilic (acyl) substitution/ condensation
Reagent & Condition	R^1NH_2 / $R^1{}_2NH$, room temperature
General Equation	 R, R^1 = alkyl or aryl

E.g.



2^o amide



3^o amide

- Tertiary amines do not undergo nucleophilic (acyl) substitution with acyl chloride because they do not have any replaceable H atoms.

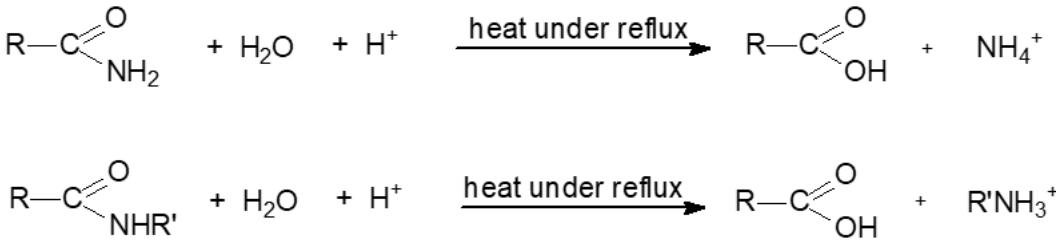
2.5 REACTIONS OF AMIDES

(a) Hydrolysis

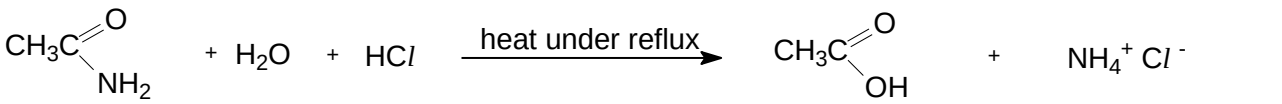
- Amides are neutral solids and are fairly stable in water. The amide bond is cleaved on **heating** in the presence of **strong acids or bases** – acid / base hydrolysis.

(i) Acid hydrolysis

- Acidic hydrolysis of amides produces a **carboxylic acid** and an **ammonium salt**.

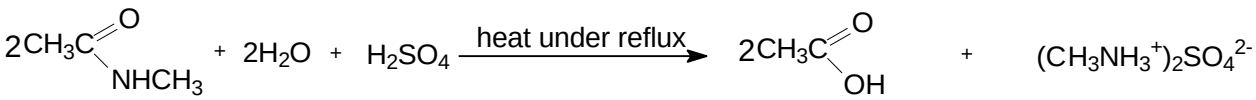
Type of reaction	acidic hydrolysis
Reagent & Condition	dilute HC*l* or dilute H_2SO_4, heat under reflux
General Equation	 R = alkyl or aryl

E.g.



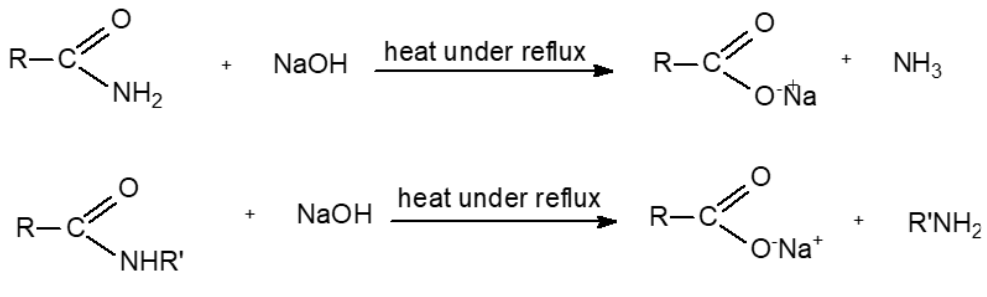
ethanamide — ethanoic acid — ammonium chloride

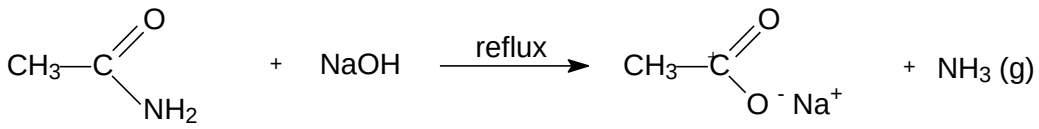
E.g.



(ii) Base hydrolysis

- Base hydrolysis of **primary amides** yields a **carboxylate salt** and **liberates ammonia**.
- Base hydrolysis of **substituted (secondary & tertiary) amides** yields a **carboxylate salt** and **amine**.

Type of reaction	base hydrolysis
Reagent & Condition	dilute NaOH *l* or dilute KOH, heat under reflux
General Equation	 R = alkyl or aryl

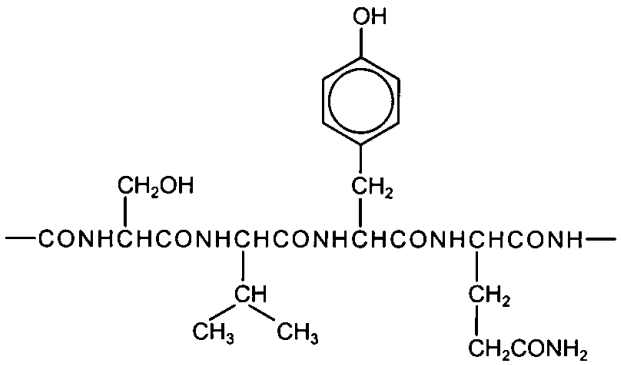
E.g. 

ethanamide sodium ethanoate

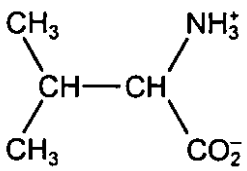
Note: Amides are more resistant to hydrolysis compared to esters as the lone pair of electrons on nitrogen is more easily delocalise into the C=O group, which reduces the partial positive charge on the carbonyl carbon and strengthens the C–N bond. This makes the carbonyl carbon less attractive towards nucleophiles.

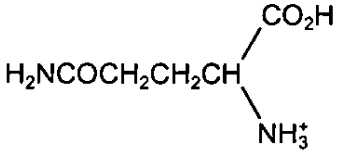
EXERCISE 2

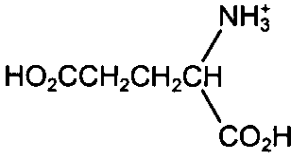
Part of the chain of the hormone insulin is shown below.

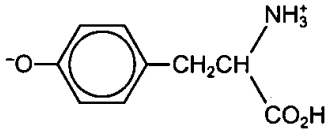


When insulin is heated in 6 mol dm^{-3} HC*l* for a prolonged period, which is a product that is obtained?

A 

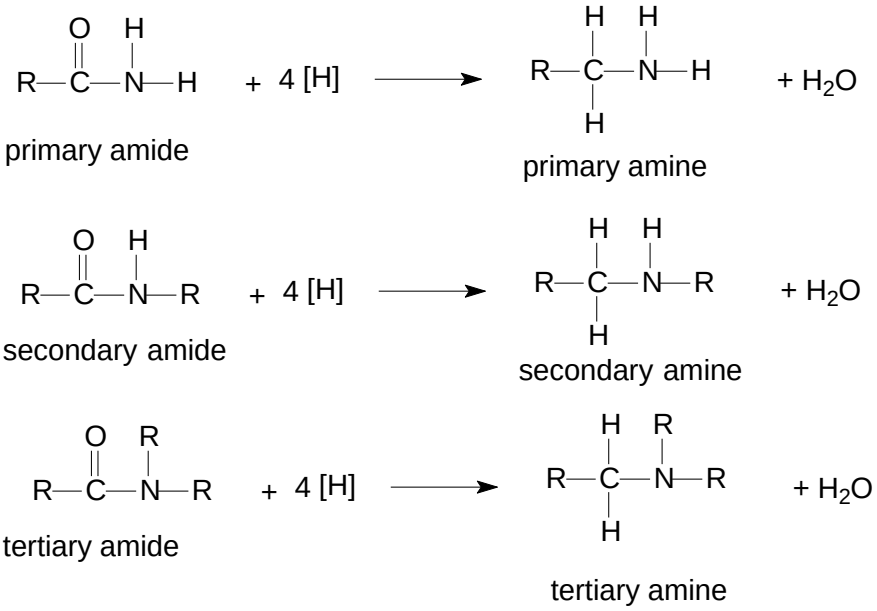
B 

C 

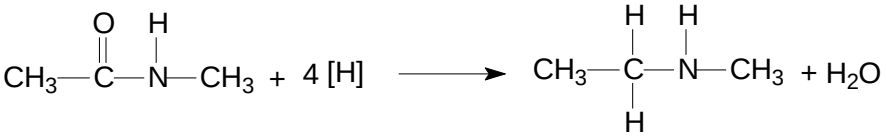
D 

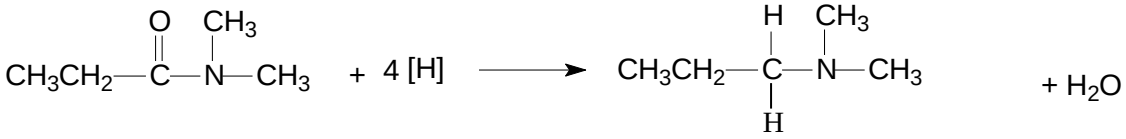
J2009/I/29

(b) Reduction of Amide

Type of reaction	reduction
Reagent & Condition	$LiAlH_4$, room temperature
General Equation	

Eg:





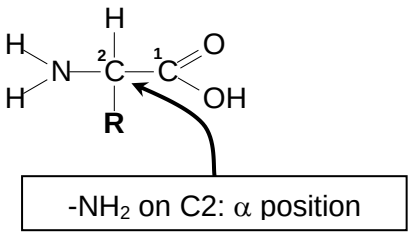
3 AMINO ACIDS

3.1 INTRODUCTION TO AMINO ACIDS

- Amino acids are the building blocks of proteins. Of the 20 amino acids needed to make up our proteins, eight cannot be synthesised in our bodies. These eight are called essential amino acids and must be part of our diet.
- An amino acid molecule has two functional groups, a **carboxylic acid group**, –COOH, and a basic **amino group**, $-NH_2$.
- There are **two types** of amino acids: **Naturally Occurring** and **Synthetic**.

- Naturally occurring amino acids **<u>can</u>** be synthesised in the human body while synthetic ones cannot.

- All naturally occurring amino acids are **<u>α-amino acids</u>** where the α-carbon is directly bonded to BOTH –COOH and – NH_2 groups. The general structure of an α-amino acid is shown below:



- The side chain, **R**, varies considerably in the 20 naturally occurring α-amino acids (see p 24 – 25). The composition of the **R** group confers an individual set of properties to each amino acid, which affects the properties of the proteins in which they are found.

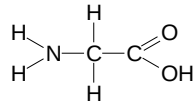
  If the **R** group contains **one or more carboxyl group**, –COOH: **<u>acidic</u>** amino acid.

  If the **R** group contains **one or more amino group**, –NH_2: **<u>basic</u>** amino acid.

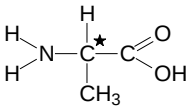
  If the **R** group contains **neutral group(s)**: **<u>neutral</u>** amino acid.

- All amino acids, except aminoethanoic acid (glycine), have 4 different groups attached to the α-carbon.
  ⇒ exhibit enantiomerism
  (*Recall:* enantiomers *are non-superimposable mirror images of each other, rotate plane polarised light*)

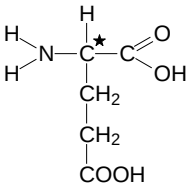
  E.g.



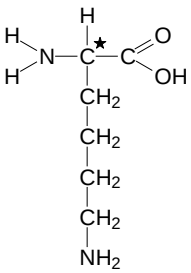
aminoethanoic acid
(glycine)



2-aminopropanoic acid
(alanine)



glutamic acid



lysine

- Synthetic amino acids (β-amino acids) are rare in nature and are **<u>not</u>** found in proteins.
  The **–NH_2** and **–COOH** groups of **β-amino acids** are **<u>not</u>** attached to the **same C atom**.

Fun Facts

The isomer that rotates plane polarised light clockwise (or to the right) is classified as *dextrorotatory* (D-isomer).

Hence, the other isomer (its mirror image), which rotates plane polarised light anti-clockwise (or to the left), is classified as *levorotatory* (L-isomer).

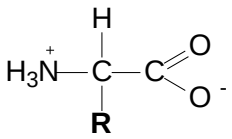
Only **L-amino acids** are found in proteins.

3.2 GENERAL PROPERTIES OF AMINO ACIDS

(a) Zwitterion Formation

- The basic amino group and the acidic carboxyl group can react with each other.

  A proton from –COOH can be donated to the $–NH_2$ group of the same molecule to give a **zwitterion**, a molecule that carries both a positive and a negative charge.



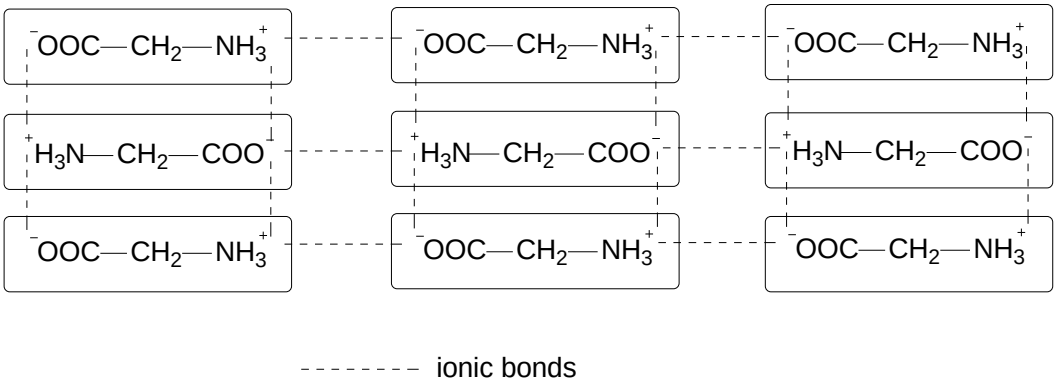
- Amino acids exist as zwitterions in solid state and in neutral solutions.

(b) Physical Properties of amino acids

- Amino acids are **crystalline solids** with **very high melting points** (e.g. m.p. of aminoethanoic acid is 235^{o}C).

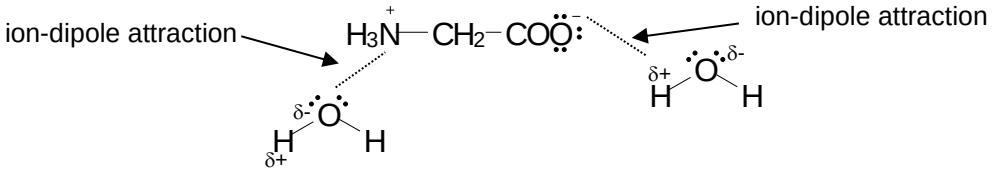
  Reason: This is due to the presence of **strong electrostatic forces of attraction (ionic bonds)** between the oppositely charged ends of neighbouring zwitterions in a **giant ionic** lattice structure.

  Simplified structure of solid aminoethanoic acid:



- Amino acids are very soluble in water (and other polar solvents) but not in non-polar solvents.

  Reason: The charged ends of the zwitterions can form strong **ion-dipole attractions** with water molecules.



(c) Acid-base Properties of amino acids

- Amino acid zwitterions are **amphoteric** since they contain an acidic functional group and a basic functional group

  - acidic functional group is the ammonium ion : $-NH_3^+$
  - basic functional group is the carboxylate ion : $-COO^-$

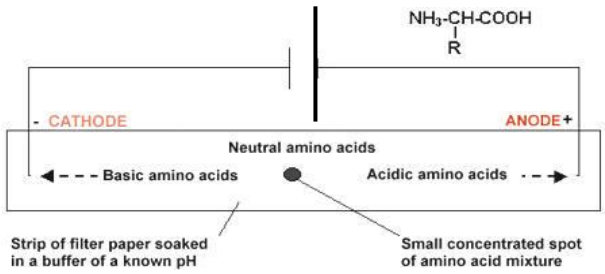
- The acid / base behaviour of an amino acid depends on the **pH** of the solution it is dissolved in.
- By varying the pH of the solution used, a mixture of amino acids can be separated by a process known as electrophoresis.

Fun Facts

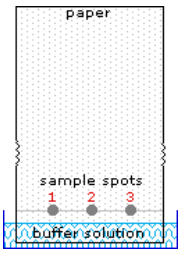
Separation of Amino Acids

Different amino acids can exist as zwitterions, positive ions or negative ions, depending on the pH of the solution. To separate the amino acids, the pH of the solution is varied slightly over time and the different amino acids will migrate to the electrodes at different pH values.

Amino acids can also be separated by paper chromatography. The different amino acids are separated based on different solubilities in a solvent as well as their molecular masses. Amino acids which are more soluble will move faster, and lighter amino acids will move faster than heavier amino acids. A reagent, ninhydrin, is then used to indicate the position of amino acids by the observation of a blue or purple colouration.



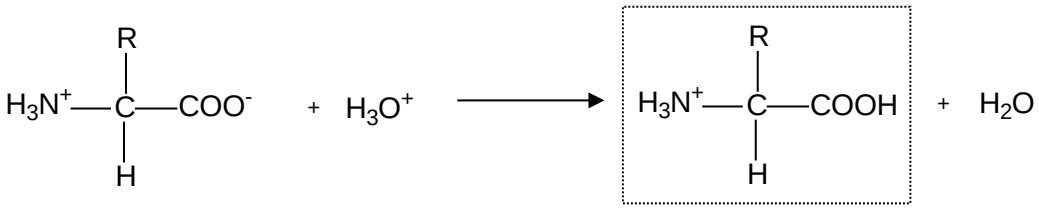
paper electrophoresis



paper chromatography

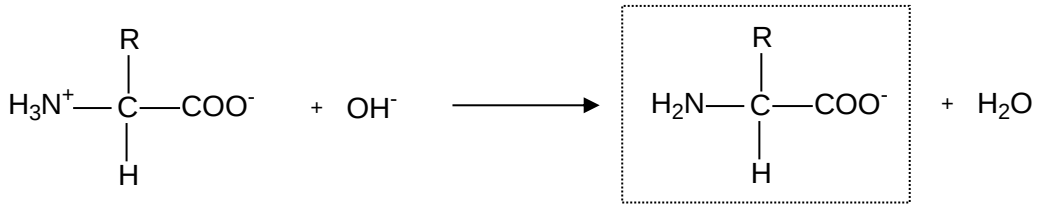
(1) <u>In acidic solution – low pH</u>

- Zwitterions act as a **<u>base</u>** by **<u>accepting a proton</u>** from the acid to form a positive ion, which migrates to the **<u>negative</u>** electrode (cathode) in an electric field.



(2) <u>In alkaline solution – high pH</u>

- Zwitterions act as an **<u>acid</u>** by **<u>donating a proton</u>** to the base to form a negative ion, which migrates to the **<u>positive</u>** electrode (anode) in a electric field



- Hence, zwitterions can act as a **<u>buffer</u>** as it is able to resist small changes in pH when small amounts of acid or base are added. (*Recall: acid-base equilibrium - buffers*)

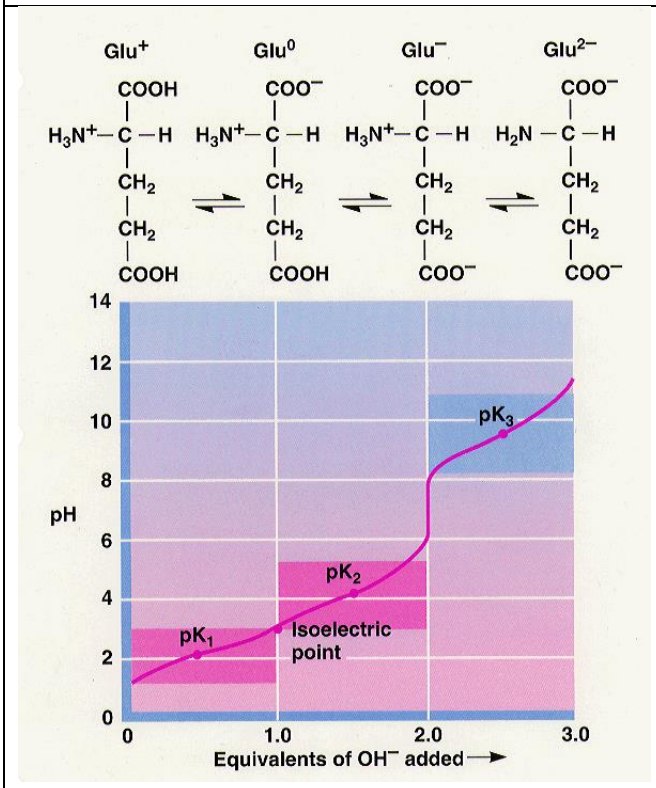
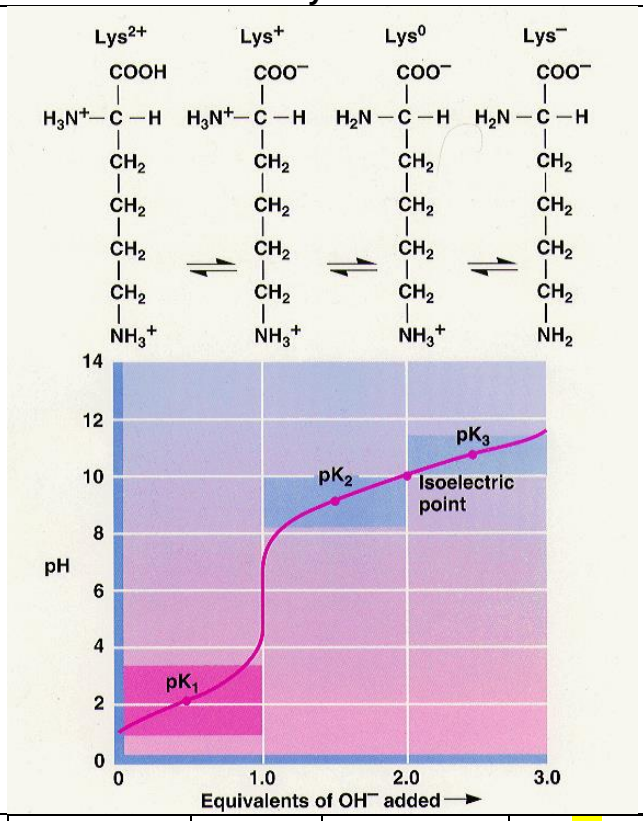
(3) <u>Isoelectric Points (p*I*) – *(FYI – Not in syllabus)*</u>

- The pH at which an amino acid carries **<u>no net charge</u>** is known as the **<u>isoelectric point</u>**.

- Different amino acids have different isoelectric points.

In summary, all amino acids can exist in 3 forms, depending on the pH of the solution.

pH of solution	Structure of molecule	Charge of molecule	Migration in the presence of electric field
pH < p*I*	Its weakly basic $–COO^-$ group (along with the basic R-group if any) will react with H^+ ions in the more acidic condition to form the following structure: $H_3N^+ – CH(R) – COOH$	positive	negative electrode
pH = p*I*	$H_3N^+ – CH(R) – COO^-$	neutral	no migration
pH > p*I*	Its weakly acidic $–NH_3^+$ group (along with the acidic R-group if any) will react with OH^- ions in the more basic condition to form the following structure: $H_2N – CH(R) – COO^-$	negative	positive electrode

Glutamic acid				Lysine			
							
pK_a α-COOH	**pK_a α-NH_3^+**	**pK_a side chain**	**p*I***	**pK_a α-COOH**	**pK_a α-NH_3^+**	**pK_a side chain**	**p*I***
2.19	**9.67**	**4.25**	**3.22**	**2.18**	**8.95**	**10.53**	**9.74**

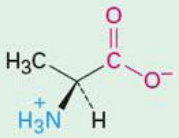
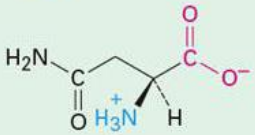
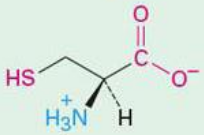
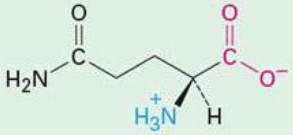
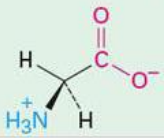
- **Amino acids will always exist in their most protonated form before they are subjected to neutralization**
- **pH = pK_a @ ½ equivalence point.**

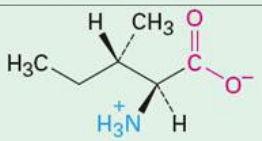
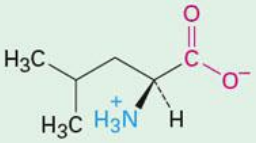
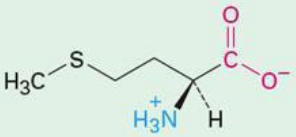
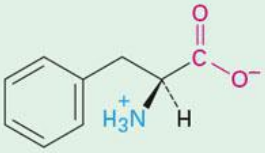
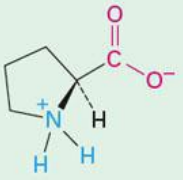
How are the pK_a values assigned to the various acidic groups in glutamic acid and lysine?

pK_a	Group	Reason
lowest (most acidic) ↓ highest (least acidic)	α–COOH	due to its closer proximity to the electron–withdrawing α–NH_3^+ group. $RCO_2H + H_2O \rightleftharpoons RCO_2^- + H_3O^+$ This disperses the negative charge of the anion (conjugate base) and stabilises it to a greater extent. Hence dissociation to form H^+ is more favoured.
	R–COOH (in glutamic acid)	
	α–NH_3^+	due to its closer proximity to the electron–withdrawing α–COOH group. $RNH_3^+ + H_2O \rightleftharpoons R\text{-}NH_2 + H_3O^+$ This decreases the availability of the lone pair of electron on N atom in the amine to accept a proton, hence the position of above equilibrium lies to the right, favouring the formation of H_3O^+.
	R–NH_3^+ (in lysine)	

The structures, pK_a and pI values of the 20 naturally occurring amino acids are shown below.

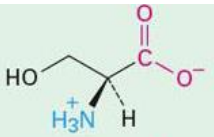
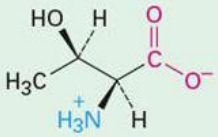
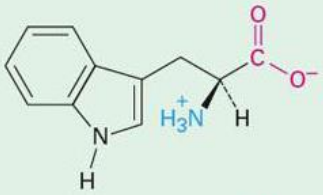
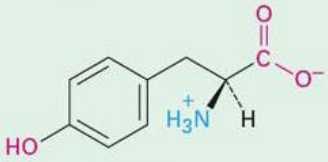
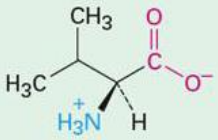
The 20 Common Amino Acids in Proteins

Name	Abbreviations		MW	Stucture	pK_a α-CO_2H	pK_a α-NH_3^+	pK_a side chain	pI
Neutral Amino Acids								
Alanine	Ala	A	89		2.34	9.69	—	6.01
Asparagine	Asn	N	132		2.02	8.80	—	5.41
Cysteine	Cys	C	121		1.96	10.28	8.18	5.07
Glutamine	Gln	Q	146		2.17	9.13	—	5.65
Glycine	Gly	G	75		2.34	9.60	—	5.97

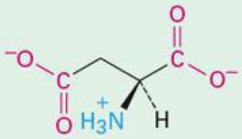
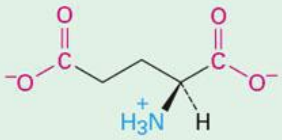
Name	Abbreviations		MW	Stucture	pK_a α-CO_2H	pK_a α-NH_3^+	pK_a side chain	pI
Isoleucine	Ile	I	131		2.36	9.60	—	6.02
Leucine	Leu	L	131		2.36	9.60	—	5.98
Methionine	Met	M	149		2.28	9.21	—	5.74
Phenylalanine	Phe	F	165		1.83	9.13	—	5.48
Proline	Pro	P	115		1.99	10.60	—	6.30

continued

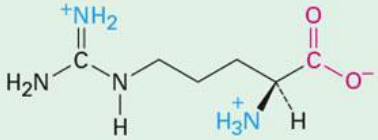
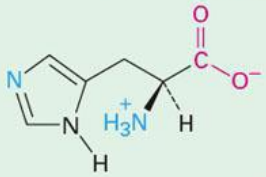
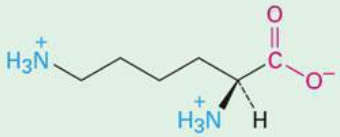
Neutral Amino Acids *continued*

Serine	Ser	S	105		2.21	9.15	—	5.68
Threonine	Thr	T	119		2.09	9.10	—	5.60
Tryptophan	Trp	W	204		2.83	9.39	—	5.89
Tyrosine	Tyr	Y	181		2.20	9.11	10.07	5.66
Valine	Val	V	117		2.32	9.62	—	5.96

Acidic Amino Acids

Aspartic acid	Asp	D	133		1.88	9.60	3.65	2.77
Glutamic acid	Glu	E	147		2.19	9.67	4.25	3.22

Basic Amino Acids

Arginine	Arg	R	174		2.17	9.04	12.48	10.76
Histidine	His	H	155		1.82	9.17	6.00	7.59
Lysine	Lys	K	146		2.18	8.95	10.53	9.74

Source: Organic Chemistry by John McMurry, 7th Edition

EXERCISE 3

(a) Amino acids exist as zwitterions.

(i) Draw the structural formula of the zwitterion from glycine (aminoethanoic acid)

(ii) Write equations to show how the zwitterionic form of glycine can react as a buffer.

(iii) How would you expect the melting point and the solubility in water, of an unionised covalent form of glycine to compare with the actual properties of the zwitterionic form?

N96/I/10

Solution

(a) (i)

(ii)

(iii) The unionised covalent form of glycine will have a _____ in water compared to the zwitterionic form.

Melting point

_____ energy is needed to break the intermolecular hydrogen bonding between the unionised covalent form compared to the _____ between oppositely charged ends of the zwitterionic form.

Solubility

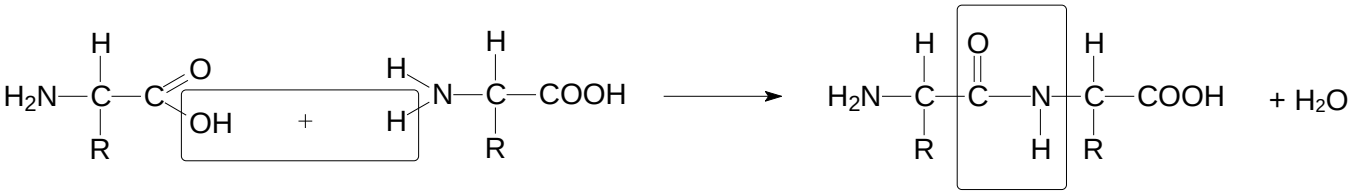
The intermolecular hydrogen bonding between the covalent form and water is weaker than the _____ between the zwitterionic form and water.

4 POLYPEPTIDES & PROTEINS

4.1 POLYPEPTIDES

- When two amino acids react together, the compound formed is known as a **dipeptide**.
- This is a **condensation reaction** between the –COOH group of one α-amino acid with the $–NH_2$ group of the other α-amino acid to eliminate a (small) molecule of water.

  By convention, the amino acid that contains the **free $–NH_2$ group** is always placed on the **left**.



peptide linkage

- The CO–NH group is also an amide functional group.

  The term **peptide linkage/bond** is used when the amide functional group is formed between the α–COOH and α– NH_2 of two **amino acids**.

- When either end of a dipeptide reacts with another amino acid, a **tripeptide** is formed.

  Amino acids can keep reacting to form longer and longer amino acid chains, known as **polypeptides**.

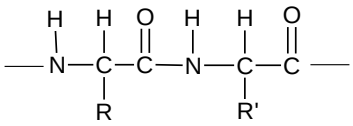
- Proteins are made up of one or more long polypeptide chains.

  The amino acids that make up the proteins are called **residues**.

  The **R** groups of the individual amino acids in a protein chain are called **side chains**.

- Proteins are **polymers of high M_r** made up of **long polypeptide chains** of amino acid residues.
- Proteins have **open ends** structure unlike peptides.

Example:



Fun Facts

- **Types** of Proteins:

(a) Classification according to their **composition**:

Simple Proteins	Conjugated Proteins
yield **only α-amino acids** upon hydrolysis	yield **amino acids and other compounds** (carbohydrates, fats or nuclei acids) upon hydrolysis

(b) Classification according to their **solubility in water**:

Globular Proteins	Fibrous Proteins
• **soluble** in water • **coiled** and **spherical** shape (**α helix** structure) • maintains **metabolic** functions in cells. e.g. enzymes and hormones	• **insoluble** in water • **parallel** polypeptide chains arranged side by side in **long filaments** (**β pleated sheets**) • maintains **structural** functions in cells. e.g. fingernails, horns and muscles

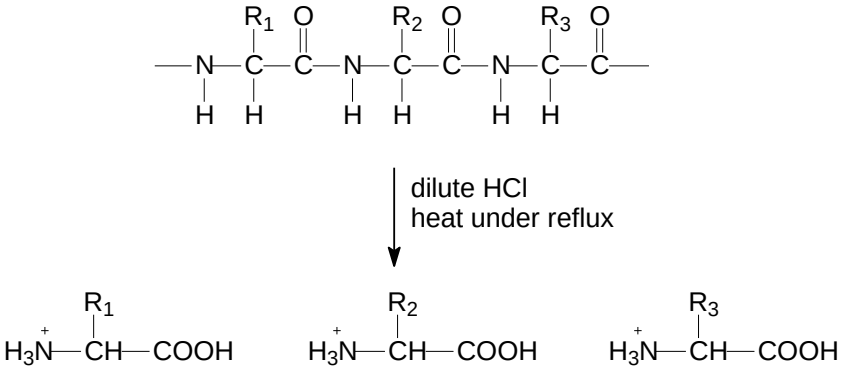
- **Functions of Proteins**

Types of Protein		Example(s)	Function(s)
Fibrous	Structural	keratin, collagen	Hair, wool, nails, horns, hoofs, tendons, cartilage
Globular	Enzymes	amylase	Biological catalyst promotes the breakdown of starch to simple sugars, glucose
	Hormones	insulin, glucagon	Regulates the use of blood sugar
	Storage	ferritin	Stores iron in spleen
	Transport	haemoglobin, serum albumin	Carries oxygen in blood Carries fatty acids in blood
	Immunological	antibodies	Get rid of foreign proteins in body

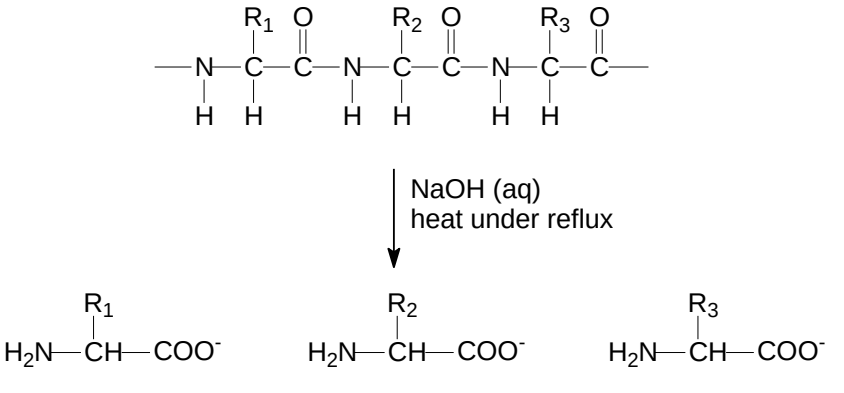
4.2 Hydrolysis of Polypeptides / Proteins

- The peptide bond in a protein or polypeptide can be **cleaved** / broken by hydrolysis to yield a mixture of amino acids. This can be done by using dilute acids or alkali.

(a) Acid hydrolysis

Type of reaction	Acid hydrolysis
Reagent & Condition	HC*l*(aq) or dilute H_2SO_4(aq), heat under reflux for **several hours**
General Equation	

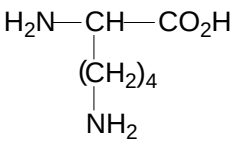
(b) Base hydrolysis

Type of reaction	Base hydrolysis
Reagent & Condition	NaOH(aq) or KOH(aq), heat under reflux for **several hours**
General Equation	

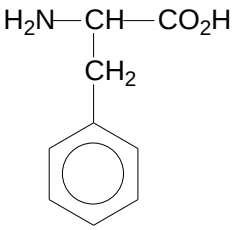
EXERCISE 4

On hydrolysis, a tripeptide produced the following amino acids in equimolar amounts.

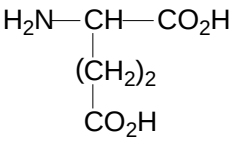
B



C



D



(a) In how many different ways can these three amino acids be coupled by peptide bonds to form a tripeptide?

(b) Draw the structural formula of one such tripeptide.

Indicate what happens when this tripeptide is dissolved, in

(i) **cold** dilute aqueous sodium hydroxide,
(ii) **cold** dilute hydrochloric acid.

Solution

(a)

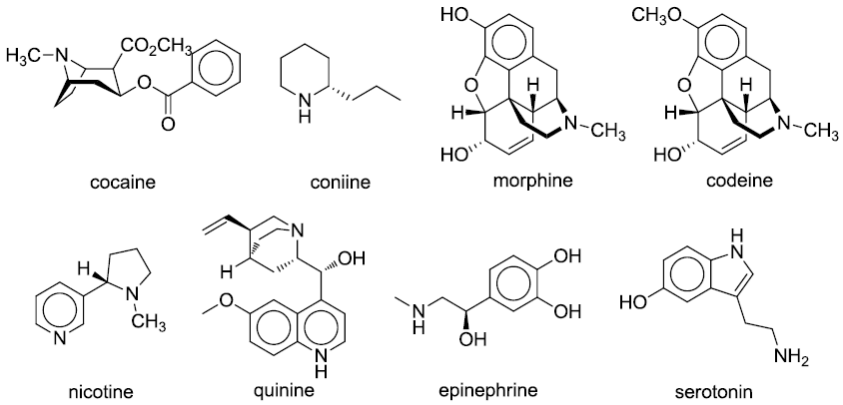
(b)

Recall: By convention, the amino acid that contains the free –NH_2 group is always placed on the left.

(i) Acid–base reaction takes place between the _____ to form salt.	**(ii)** Acid-base reaction takes place between the _____ to form amine salt.

Fun Facts:
Application in real life

The ease with which amines are extracted into an aqueous acid, combined with their regeneration on treatment with a base, makes it a simple matter to separate amines from other plant materials, and nitrogen-containing natural products were among the earliest organic compounds to be studied. Their properties led amines obtained from plants to be called alkaloids.



Several naturally occurring amines mediate the transmission of nerve impulses and are referred to as neurotransmitters. Two examples are epinephrine and serotonin. (Strictly speaking, these compounds are not classified as alkaloids, because they are not isolated from plants.)

The most common class of amino acids in nature is the α-amino acids, which are all chiral except for aminoethanoic acid (glycine). One notable example of a non- α-amino acid is γ-aminobutanoic acid (GABA), which is the chief inhibitory neurotransmitter in the mammalian central nervous system, playing a role in regulating neuronal excitability throughout the nervous system.