19 Extension Topic – Organic Chemistry Nitrogen Compounds

GUIDING QUESTIONS

Amines

- How are amines synthesised?
- What types of reactions do amines undergo and why?

Phenylamines

- How are phenylamines synthesised?
- What types of reactions do phenylamines undergo and why?
- What are the effects of the delocalisation of the lone pair of electrons on nitrogen of phenylamine into the benzene ring?

Amides

- How are amides synthesised?
- Why are amides neutral?
- What types of reactions do amides undergo and why?

Amino Acids

- What are the properties of amino acids?
- What types of reactions do amino acids undergo and why?

How do we compare the basicity of organic nitrogen compounds?

LEARNING OUTCOMES

Students should be able to:

19(a) describe the formation of amines as exemplified by ethylamine (through amide and nitrile reduction; refer to Topic 13 Halogen Derivatives) and by phenylamine (through the reduction of nitrobenzene)

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

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

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

19(e) describe the reaction of phenylamine with aqueous bromine

19(f) describe the formation of amides from the condensation reaction between RNH_2 and R'COC*l*

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

19(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

19(i) describe the acid/base properties of amino acids and the formation of zwitterions

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

19(k) describe the hydrolysis of proteins

REFERENCES

1. Peter Cann & Peter Hughes (2014). *Chemistry*, Hodder Education, Chapter 27
2. John McMurry (2012). *Organic Chemistry*. 9th Edition, Cengage Learning, Chapter 24

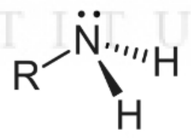
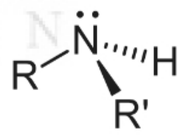
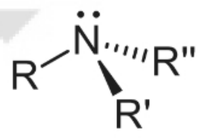
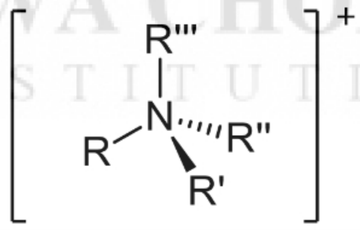
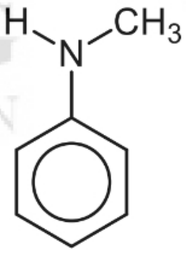
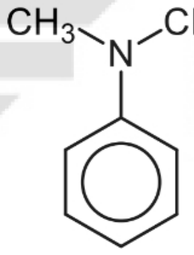
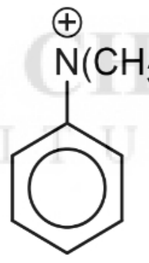
1 INTRODUCTION

Nitrogen Compounds

Amines

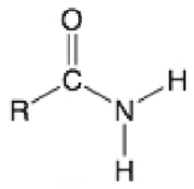
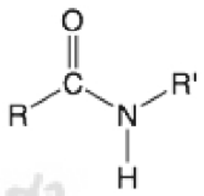
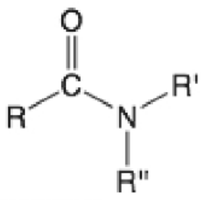
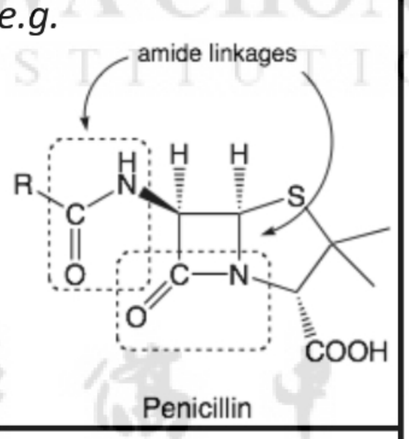
Amines are derivatives of ammonia, NH_3, in which one or more hydrogen atoms are replaced by alkyl or aryl groups.

Amines are classified as **primary**, **secondary** and **tertiary** according to the number of carbon atoms directly attached to the N atom.

	Primary (1°) amines	**Secondary (2°) amines**	**Tertiary (3°) amines**	**Quaternary ammonium ions**
				
Aliphatic	*e.g.* $CH_3CH_2NH_2$ ethylamine	*e.g.* $CH_3CH_2NHCH_3$ N-methyl ethylamine	*e.g.* $(CH_3)_3N$ trimethylamine	*e.g.* $(CH_3)_4N^+$ Tetramethyl-ammonium ion
Aromatic	 *e.g.* phenylamine	 *e.g.* *N*-methylphenyl amine	 *e.g.* *N*,*N*-dimethyl phenylamine	 *e.g.* *N*,*N*,*N*-trimethyl phenyl-ammonium ion
	For aromatic amine, the nitrogen atom is <u>directly</u> attached to the benzene ring			

Amides

Amides are derivatives of carboxylic acids.

Primary amides	**Substituted amides**		*e.g.*
			 Penicillin

Amino Acids

Amino acids contain both an acidic carboxyl group ($-CO_2H$) and a basic amino group ($-NH_2$) on the same molecule.

Table 1. Various functional groups of nitrogen compounds

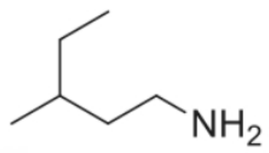
1.1 Nomenclature

1.1.1 Amines

Simple amines are named by adding the suffix *–amine* to the name of the longest alkyl group that is attached to the nitrogen atom.

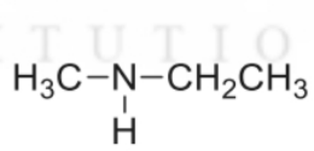
The longest carbon chain containing the amine group is considered the parent structure. Number the alkane chain beginning at the end nearer the amine group.

Note: An alternative way of naming amines is to replace the final *–e* in the name of the parent compound with the suffix *–amine*.

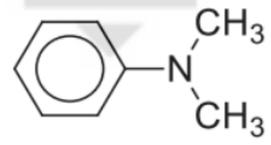


3-methylpentan-1-amine

In secondary and tertiary amines, the capital N denotes the location of the substituents directly attached to the nitrogen atom.

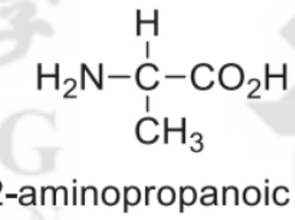


N-methylethylamine



N,*N*-dimethylphenylamine

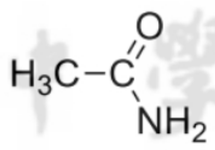
If there is a functional group of higher priority, the $–NH_2$ group can be considered as an *amino* substituent in the prefix.



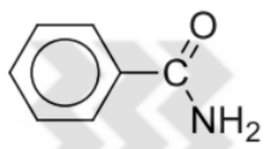
2-aminopropanoic acid

1.1.2 Amides

Primary amides with an unsubstituted $–NH_2$ group are named by replacing the *–oic acid* of the parent carboxylic acid with *–amide*.

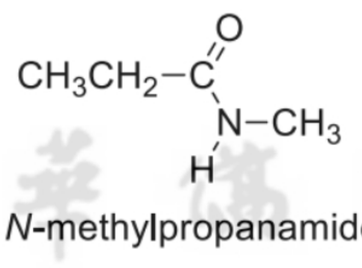


ethanamide

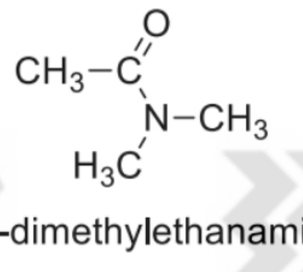


benzamide

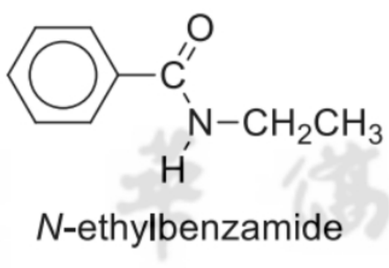
If the nitrogen atom is further substituted, the location of the substituent group is denoted by a capital N.



N-methylpropanamide



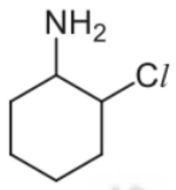
N,*N*-dimethylethanamide



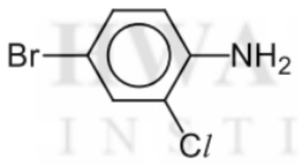
N-ethylbenzamide

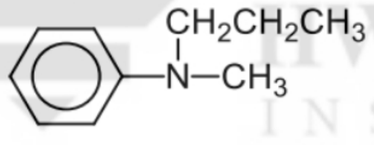
Lecture Exercise 1.1

Name the following compounds and indicate whether it is a primary, secondary or tertiary amine:

1. 

2. $CH_3CH_2NHCH_2CH_2CH_3$

3. 

4. 

2 PHYSICAL PROPERTIES OF AMINES AND AMIDES

2.1 Odour

The aliphatic amines of lower molecular weight have a characteristic pungent smell whereas the higher members have strong "fishy" odours. Sometimes even "foul smelling" is an understatement, and two of the amines produced in decaying flesh are named cadaverine and putresine.

2.2 Boiling points

Name	Structural formula	Number of electrons in the molecules	b.p. / °C	Predominant Intermolecular forces
Methylamine	CH_3NH_2	18	–6	hydrogen bonding
Ethylamine	$CH_3CH_2NH_2$	26	17	hydrogen bonding
Propylamine	$CH_3CH_2CH_2NH_2$	34	50	hydrogen bonding
N-methylethanamine	$CH_3CH_2NHCH_3$	34	34	hydrogen bonding
N,N-dimethylmethanamine	$(CH_3)_3N$	34	3	permanent dipole-permanent dipole interactions

Table 2. Boiling points of some amines

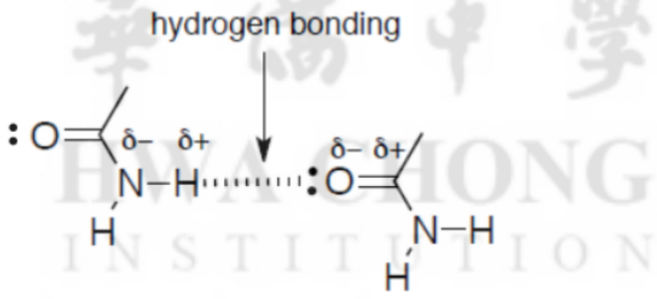
- Comparing methylamine, ethylamine and propylamine, as the number of carbon atoms and electrons increases, more energy is required to overcome the increasing strength of dispersion forces between the molecules. Thus, boiling point increases with increasing number of carbon atoms.
- Primary and secondary amines have higher boiling points than tertiary amines. Since tertiary amines have no N—H bond, they are unable to form hydrogen bonds. Their molecules are held together by weaker permanent dipole – permanent dipole interaction which requires less energy to overcome as compared to stronger hydrogen bonds between molecules of primary and secondary amines.

Name	Structural formula	Number of electrons in the molecules	b.p. / °C	Predominant Intermolecular forces
Methylamine	CH_3NH_2	18	–6	hydrogen bonding
Ethane	CH_3CH_3	18	–89	dispersion forces
Methanol	CH_3OH	18	65	hydrogen bonding

Table 3. Boiling points of corresponding alkane, alcohol and amine (similar no. of electrons in the molecules)

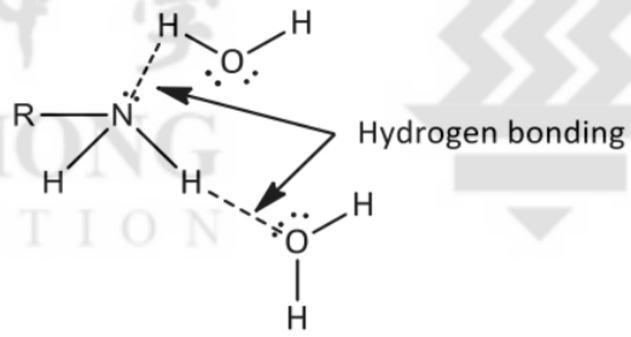
- Methylamine, CH_3NH_2, has a considerably higher boiling point compared to its corresponding alkane (ethane) due to the presence of stronger intermolecular hydrogen-bonding compared to only weaker dispersion forces in the alkane.
- However, boiling point of CH_3NH_2 is lower than that of the corresponding alcohol (methanol), since the N-H bond is less polar than the O-H bond. Hence, the intermolecular hydrogen-bonds in alcohols are stronger than those between amine molecules and require more energy to overcome.

Amides are white crystalline solids at room temperature, apart from methanamide, which is a liquid. Amides can form extensive intermolecular hydrogen bonds as a result of the polar nature of the N–H bond, and these hydrogen bonds result in relatively high melting and boiling points.



2.3 Solubility in water

Aliphatic amines with four carbon atoms or fewer are readily soluble in water due to their ability to form strong hydrogen bonds with water molecules.



Phenylamines and amines with increasing length of hydrocarbon chain are virtually insoluble in water because the energy released from hydrogen bonding formed between these amines with water is less able to overcome the energy required to overcome the increasing strength of dispersion forces between larger hydrocarbon chains, as well as the existing hydrogen bonding in water. In addition, the non-polar large hydrocarbon skeletons also disrupt the hydrogen bonding with water molecules. These compounds do dissolve, though, in organic solvents, e.g. benzene.

For amides, their ability to form extensive hydrogen bonds with water also means that simple amides are very soluble in water.

Self-Practice Question 2.1

a) Propylamine is highly soluble in water. Draw a diagram to illustrate how a molecule of propylamine interacts with a molecule of water.

b) Explain why $H_2NCH_2CH_2NH_2$ has a boiling point of 116°C while propylamine has a boiling point of 50°C.

3 BASICITY OF NITROGEN COMPOUNDS

LO 19(c): describe and explain the basicity of primary, secondary and tertiary amines in the gaseous phase (interpret as Lewis bases)
LO 19(d): explain the relative basicities of ammonia, ethylamine and phenylamine, in aqueous medium, in terms of their structures

3.1 Amines

Like ammonia, amines contain a lone pair of electrons on the nitrogen atom that can form a co-ordinate (dative covalent) bond with a proton. Hence, amines can act as proton-acceptors or Bronsted-Lowry bases. Amines can also act as Lewis bases by donating this electron pair to an acid. (Refer to Topic 4 Reactions and Stoichiometry for the theories of acids and bases.) The basicity of amines depends on the availability of the lone pair of electrons on nitrogen for protonation (or donation to an acid).

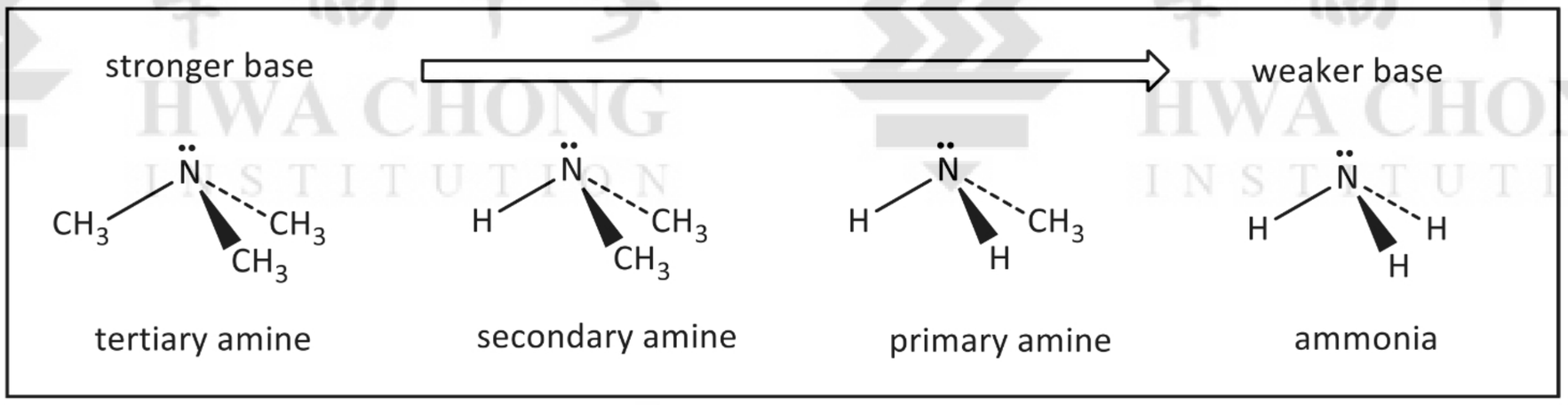
There are two factors affecting the basicity of amines:

1. **Inductive effect:** Presence of electron-donating groups such as alkyl groups increases the electron density on the nitrogen atom and increases availability of the lone pair of electrons on the N atom for donation to an acid.
2. **Steric hindrance:** Bulky groups attached to the N atom hinder the donation of its lone pair to form a dative bond with an acid.

3.1.1 Basicity of amines in the gaseous phase (Lewis bases)

In the gaseous phase, aliphatic amines are more basic than ammonia because alkyl groups are electron-donating; they increase the electron density on nitrogen atom, making the lone pair of electrons more available to form a dative bond with an acid.

Therefore,



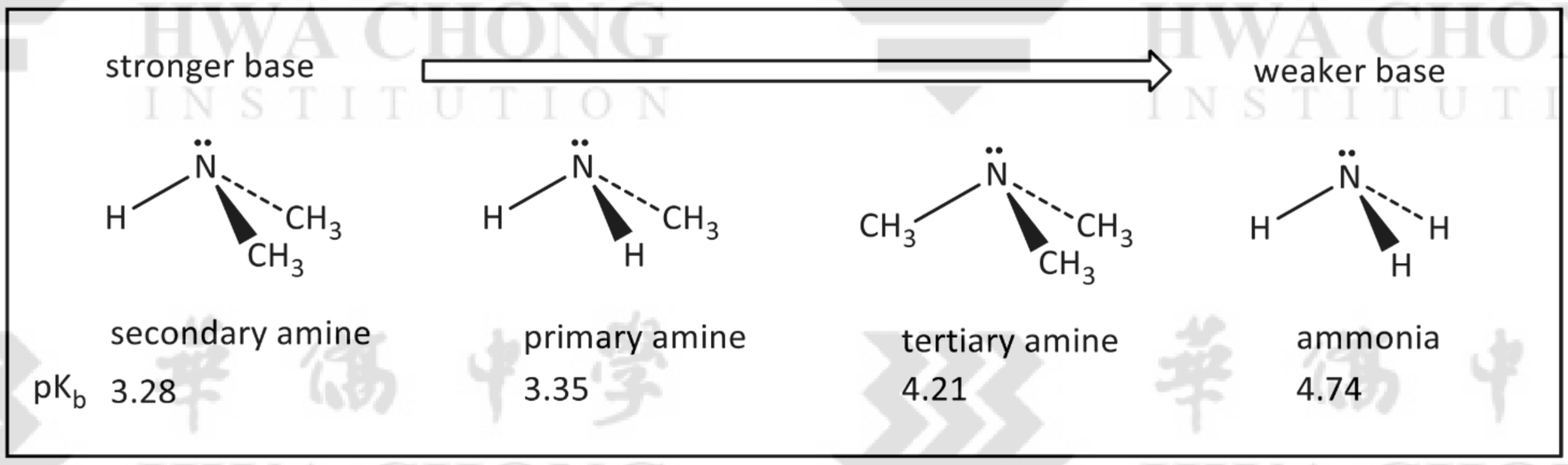
3.1.2 Basicity of amines in the aqueous medium

When amines are dissolved in water, an equilibrium is established in which the water donates a hydrogen ion to the amine. The extent of this reaction is a measure of the amine's basicity.

$$\underset{\text{Base}}{RNH_2} + H_2O \rightleftharpoons \underset{\text{Conjugate acid}}{RNH_3^+} + OH^-$$

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

The larger the K_b values, the greater its basicity; the smaller the pK_b, the stronger the base.



In the aqueous medium, the basicity trend in ammonia, primary and secondary amine is the same as in gaseous phase. However, tertiary amines are less basic than secondary and primary amines in aqueous medium because:

1. The bulky alkyl groups attached directly to N atom hinder the donation of its lone pair to form a bond with a proton.
2. The resulting conjugate acids are not as effectively solvated through hydrogen bonding by the surrounding water molecules (absent in gaseous phase) as compared to conjugate acids of primary and secondary amines. Thus, the conjugate acids are less stable, resulting in tertiary amines to ionise in water to a smaller extent.

3.2 Phenylamines

Phenylamines are considerably less basic than ammonia. This is because in phenylamine, the lone pair of electron on nitrogen is delocalized into the benzene ring. This decreases the electron density on the nitrogen atom, making the lone pair of electrons less available to form a dative bond with a proton.

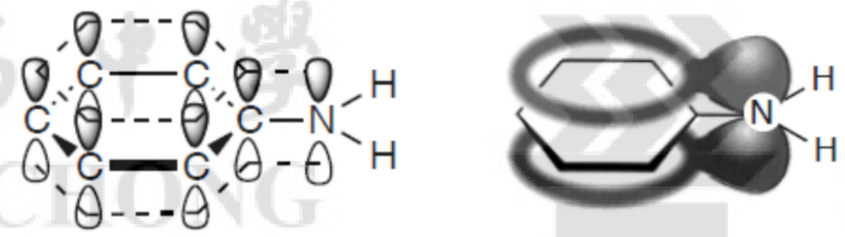


Figure 1. Extended delocalized π- electron cloud is present in phenylamines

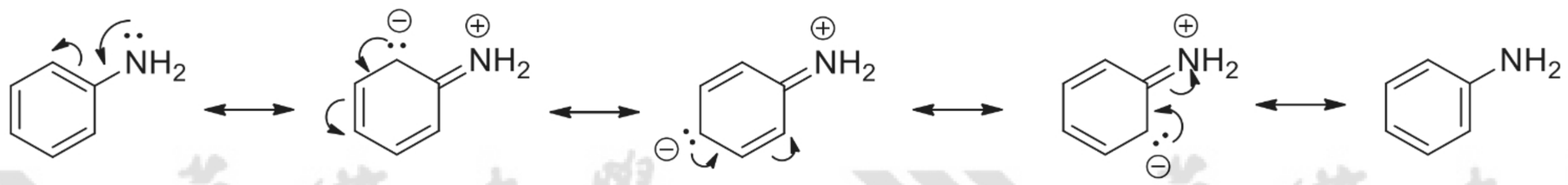
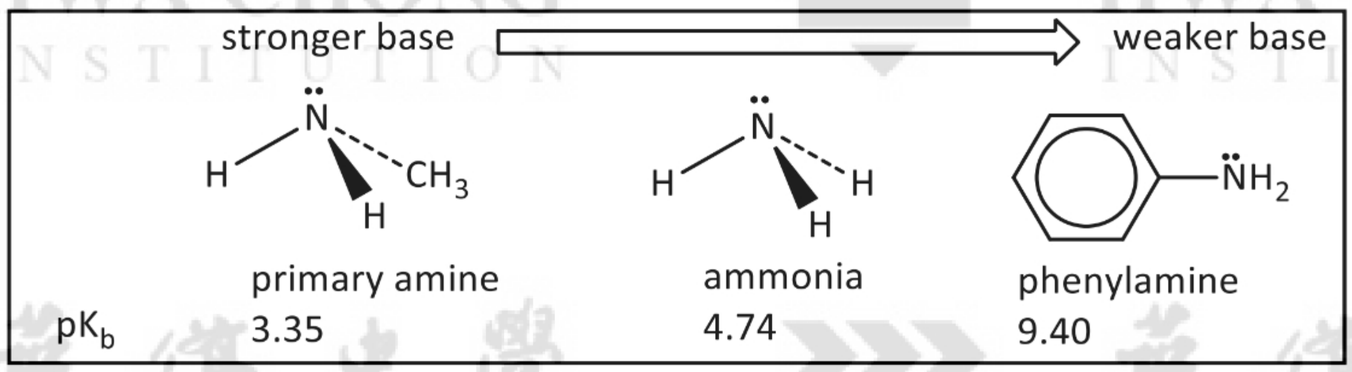


Figure 1. Resonance structure of phenylamines

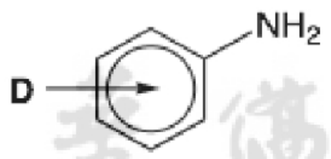
Therefore,



3.2.1 Substituted Phenylamines

Their relative basicity depends on the nature of the substituent attached to the benzene ring.

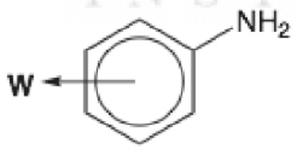
D = electron-donating group



D
$-NH_2$
–OH
–OR
–R(alkyl)

Electron-donating groups increase electron density on the benzene ring, making the lone pair of electrons on nitrogen atom more available for donation to an acid. Hence these substituted phenylamines are more basic than phenylamine.

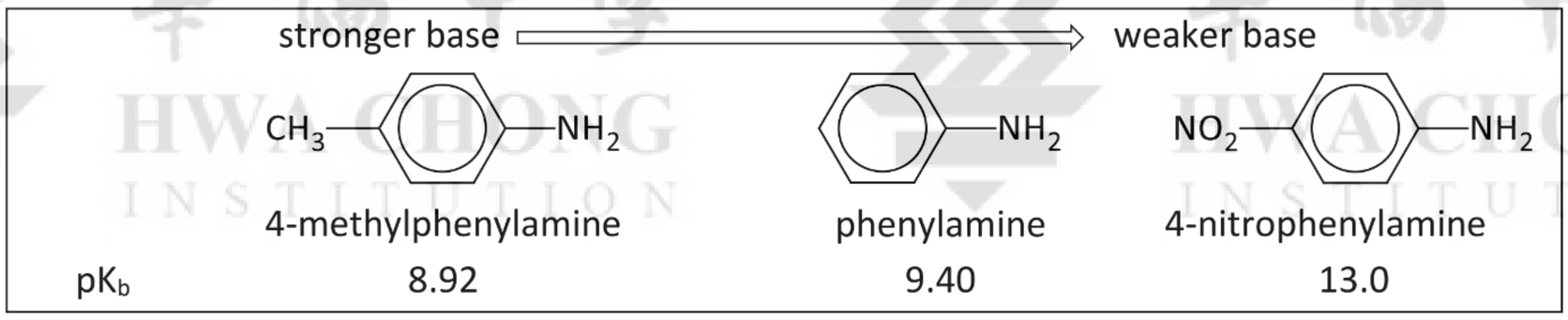
W = electron-withdrawing group



W
–X (X = F, Cl, Br)
–CHO
–COR
$-CO_2H$
$-CO_2R$
$-SO_3H$
$-NO_2$

Electron-withdrawing groups decrease electron density on the benzene ring, making the lone pair of electrons on nitrogen atom less available for donation to an acid. Hence, these substituted phenylamines are less basic than phenylamine.

Therefore,

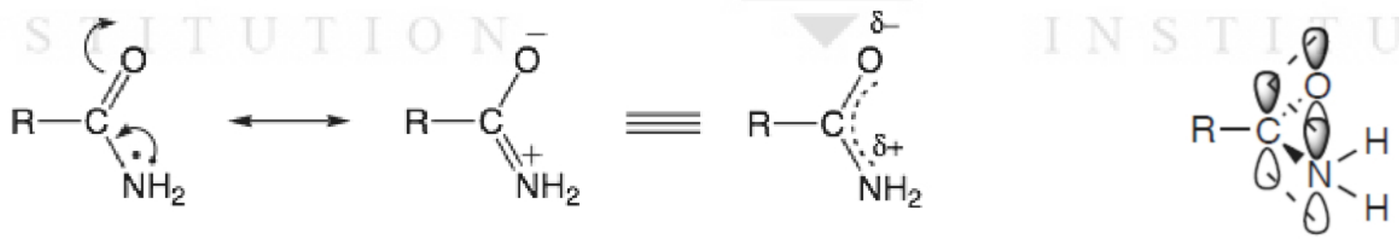


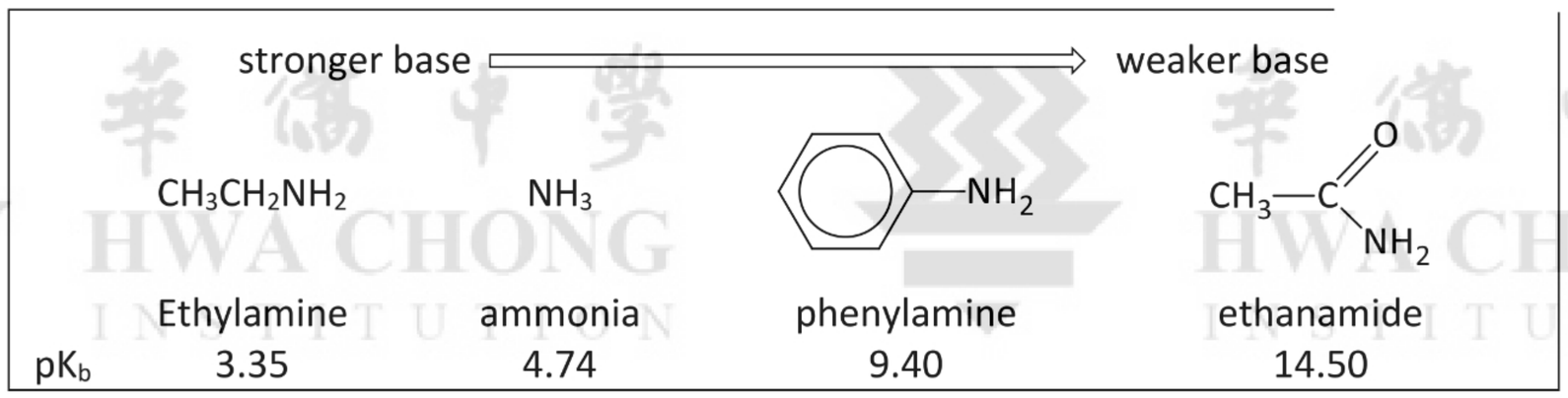
3.3 Amides

LO 19(g): explain why amide is neutral in terms of delocalisation of the lone pair of electrons on nitrogen

Amides give neutral solutions in water (not basic). The delocalisation of the lone pair of electrons on the nitrogen atom over the C=O bond reduces the electron density on the nitrogen atom such that the lone pair of electrons on the nitrogen atom is not available for protonation.

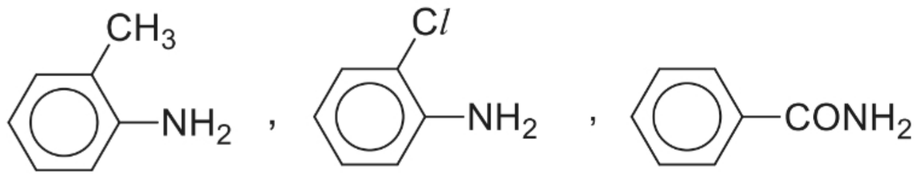
Therefore,





Lecture Exercise 3.1

Arrange the following compounds in order of increasing basicity, giving your reasoning.



A **B** **C**

4 PREPARATION OF AMINES AND AMIDES

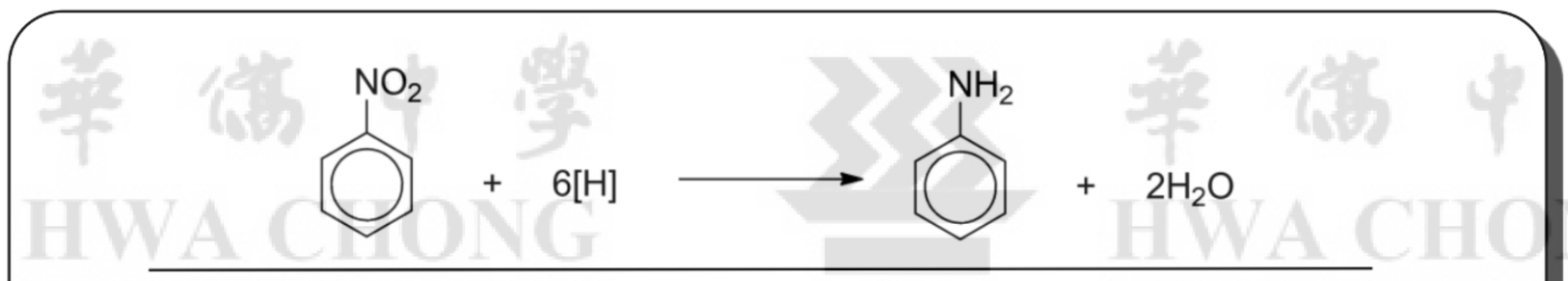
LO 19(a): describe the formation of amines as exemplified by ethylamine and by phenylamine
LO 19(f): describe the formation of amides from the condensation reaction between RNH_2 and R'COCl

Amines can be prepared from:

- Nucleophilic substitution of halogenoalkanes (Topic 13: Halogen Derivatives)

- Reduction of nitriles (Topic 13: Halogen Derivatives) and amides (to be covered later in this topic)

- Reduction of nitrobenzene
  Phenylamine can be prepared by reduction of aromatic nitro-compounds using tin and excess concentrated hydrochloric acid. The product first forms as a salt, $C_6H_5NH_3^+Cl^-$ and excess NaOH(aq) is then added to liberate the free phenylamine. Aliphatic nitro-compounds are not reduced using the same reagent.



Reagents & Conditions: 1. Sn, excess concentrated HC*l*, heat
2. NaOH(aq)

$LiAlH_4$ and $NaBH_4$ are **not** used in this above reaction because $NaBH_4$ does not reduce nitro groups at all, while $LiAlH_4$ will reduce nitrobenzene to azo compounds instead, giving $C_6H_5–N=N–C_6H_5$.

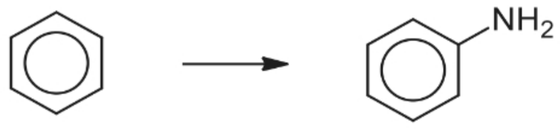
Amides can be prepared from:

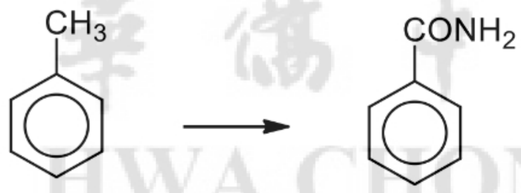
- Condensation of acyl chlorides (Topic 18: Carboxylic Acids & Derivatives)

  Note: Carboxylic acids cannot be used in the preparation of amides. This is because they react with amines/ammonia in an acid-base reaction instead. E.g. $CH_3CO_2H + NH_3 \rightarrow CH_3CO_2^-NH_4^+$.

Self-Practice Question 4.1

Give the reagents and conditions that you would use in the following conversions:

a) 

(b) 

(c) $CH_2{=}CH_2 \longrightarrow CH_3CH_2CH_2NH_2$

5 REACTIONS OF AMINES AND AMIDES

5.1 Amines

The chemistry of amines is dominated by the lone pair of electrons on nitrogen atom. They can behave:

- as bases (donating the lone pair to a H^+ ion or an acid)
- as good nucleophiles (being able to attack at the partial positive end of a polarized bond)
- as excellent ligands (with transition metals) – refer to Topic 22: Chemistry of the Transition Elements

5.1.1 Reaction with acids

LO 19(b): describe the reaction of amines in the formation of salts

Amines (both aliphatic and phenylamines) can act as a base to react with acids (mineral or carboxylic acids) to form salts.

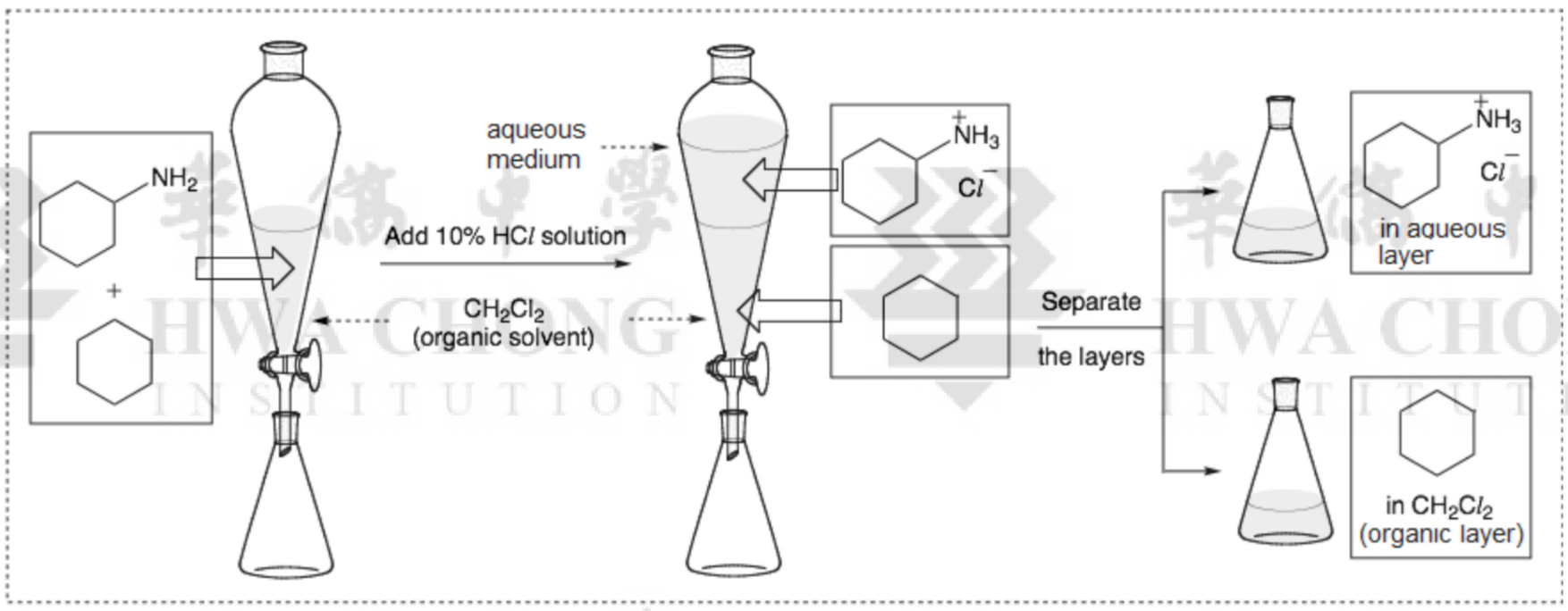
$$RNH_2 + HCl \longrightarrow RNH_3^+ Cl^-$$

Reagents & conditions: Mineral acids or carboxylic acids, room temperature

Comment: The salts are soluble in aqueous solution. On evaporating this solution, the salts can be obtained as white crystalline solids.

Amines with bulky R-groups are insoluble in water (forming two immiscible layer when mixed) due to the presence of non-polar hydrocarbon skeleton which hinder the formation of hydrogen bonds with water molecules.

However, soluble ionic salts are formed through acid-base reaction when acids are added. The ionic salts are soluble in water (forming a homogeneous solution as they can form favourable ion-dipole interaction with water molecules) but insoluble in organic solvents. Thus an amine can be separated from other organic compounds by converting it to a water-soluble ammonium salt. You may refer to Topic 8: Introduction to Organic Chemistry on the details of the extraction procedure.



The amines can be regenerated from their corresponding salts by using strong bases, such as NaOH(aq).

$$\underset{\textbf{Stronger acid}}{RNH_3^+} + \underset{\textbf{Stronger base}}{OH^-} \longrightarrow \underset{\textbf{Weaker base}}{RNH_2} + \underset{\textbf{Weaker acid}}{H_2O}$$

5.1.2 Nucleophilic substitution

Primary, secondary and tertiary amines can act as a nucleophile to react with halogenoalkanes and form secondary amines, tertiary amines and quaternary ammonium salts respectively (refer to Topic 13: Halogen Derivatives).

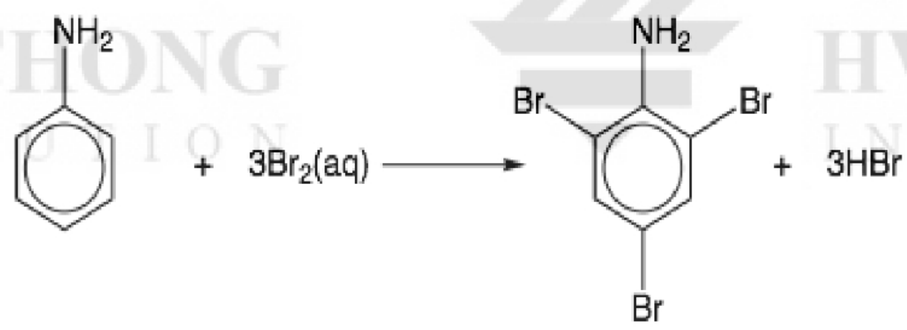
5.1.3 Condensation

Primary and secondary amines (both aliphatic and phenylamines) can act as a nucleophile to react with acid chlorides to form amides (refer to Topic 18: Carboxylic Acids & Derivatives).

5.1.4 Electrophilic substitution of phenylamine

LO 19(e): describe the reaction of phenylamine with aqueous bromine

Phenylamine reacts very quickly with aqueous bromine via an electrophilic substitution mechanism to form a white precipitate. This is similar to the reaction of phenol with bromine (refer to Topic 16: Hydroxy Compounds). Aliphatic amines do not react with bromine.



Reagents & Conditions: Aqueous bromine, room temperature

Observations: Yellow-orange solution decolourise; white ppt formed
(White fumes of HBr may not be observed as HBr dissolved in aqueous solution.)

Comments: 2,4,6-tribromophenylamine is formed because the $-NH_2$ group is 2,4-directing.
No Lewis acid catalyst (halogen carrier) is required for this reaction, unlike bromination of benzene (which requires $AlCl_3$ or $FeCl_3$).

Explanation: Like phenol, the lone pair of electrons on the nitrogen atom is delocalised into the benzene ring, the electron density in the ring is greatly increased, making it much more susceptible to electrophilic attack than benzene. Hence, the presence of the $-NH_2$ group highly activates the benzene ring towards electrophilic substitution and no catalyst is required.

5.2 Amides

LO 19(h): describe the chemistry of amides, exemplified by the following reactions:

(i) hydrolysis on treatment with aqueous alkali or acid

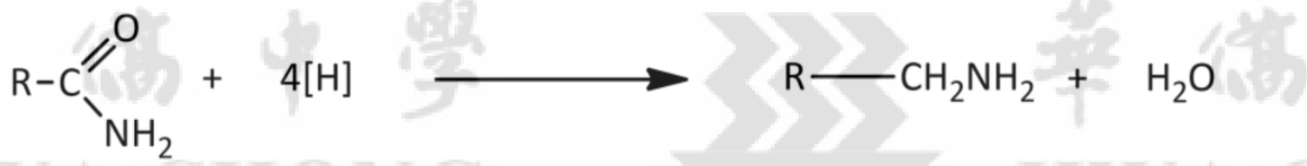
(ii) reduction to amines with lithium aluminium hydride

In amides, the lone pair of electrons on the nitrogen atom is delocalised into the adjacent C=O bond. Thus, the electron density on the nitrogen atom is reduced, making it unable to act as a nucleophile, unlike amines.

The delocalization also gives good stability to amides and makes them the least reactive of the carboxylic acid derivatives.

5.2.1 Reduction of amides

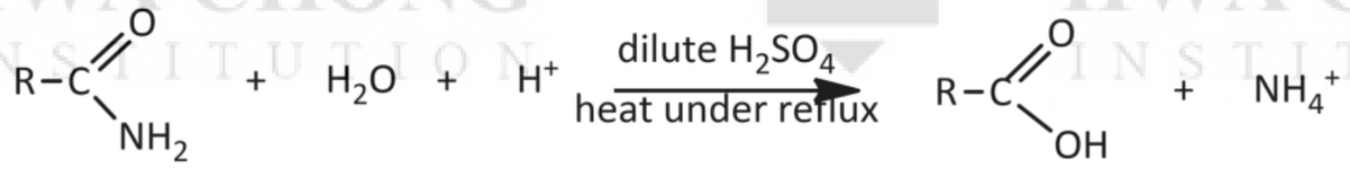
Amides can be reduced to amines by lithium aluminium hydride.



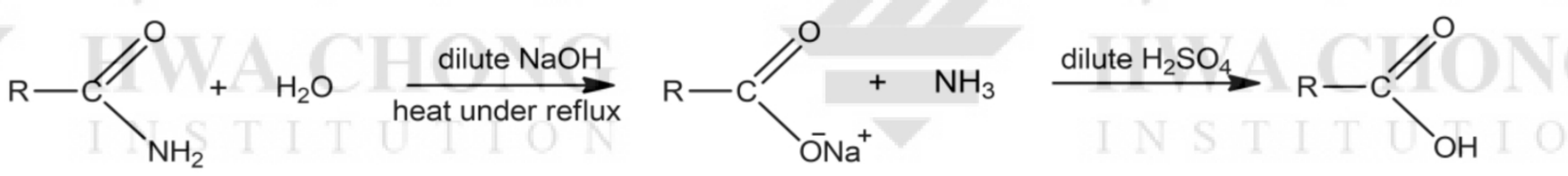
Reagents & Conditions: $LiAlH_4$ in dry ether

5.2.2 Hydrolysis of amides

Amides can be hydrolysed by aqueous acids (e.g. dil H_2SO_4) or alkalis (e.g. dil NaOH) when heated under reflux to yield the carboxylic acid or salt respectively. Although the exact same bond is cleaved in both acidic and alkaline hydrolysis, the products of hydrolysis depend on the pH of the environment.



Reagents and conditions: dilute H_2SO_4, heat under reflux



Reagents and conditions: dilute NaOH, heat under reflux, followed by acidification with dilute H_2SO_4 to yield the carboxylic acid

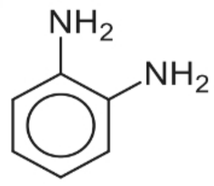
Comments: Ammonia will be produced if the primary amides undergo alkaline hydrolysis (a distinguishing test). For substituted amides, amines are formed instead.

Lecture Exercise 5.2

Predict the products of the following reactions:

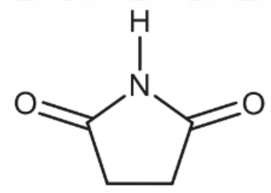
a) N,N-dimethylamine, $(CH_3)_2NH$, and ethanoic acid at room temperature

b)



and Br_2 (aq)

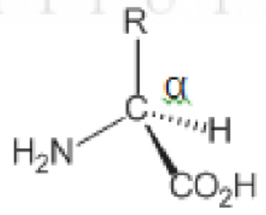
c)



and NaOH(aq) heat

6 AMINO ACIDS

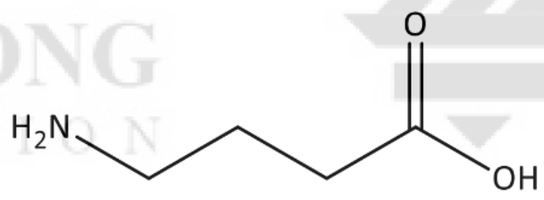
α-Amino acids are the building blocks for all the proteins in the human body. Naturally occurring amino acids are **α-amino acids** where the amino and carboxyl groups are bonded directly to the same α-carbon. The general formula of an α-amino acid is as follows:



There are 20 naturally occurring α-amino acids (as shown in the next two pages), differing only in the identity of the R group bonded to the α-carbon. The R group is called the side chain of the amino acid. The simplest amino acid, called glycine, has R = H. Except for glycine, all other α-amino acids are chiral and exist in optically active forms (enantiomers).

For your information

There are some non-α-amino acids in nature apart from the 20 common α-amino acids. One notable example is γ-aminobutanoic acid (GABA), which is the chief inhibitory neurotransmitter in the mammalian central nervous system. Note that the amino and carboxyl groups are attached to different carbons.

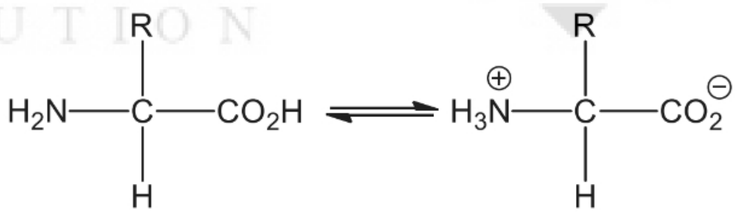


γ-aminobutanoic acid

6.1 Formation of zwitterion

LO 19(i): describe the acid/base properties of amino acids and the formation of zwitterions

Amino acids can undergo an intramolecular acid-base reaction, and exist as dipolar ions with no overall electrical charge called **zwitterions**.



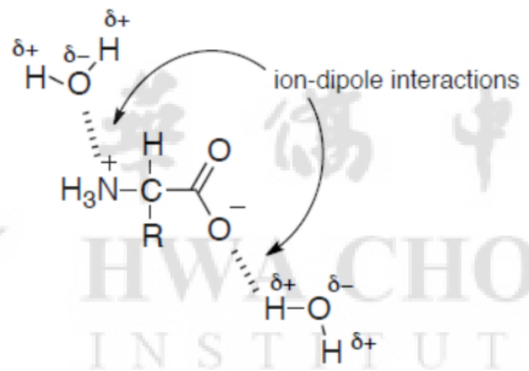
un-ionised form zwitterion

Amino acids exist as zwitterions in aqueous solutions and in the solid state. Therefore, many physical properties of amino acids resemble that of ionic compounds.

6.2 Physical properties of amino acids

The formation of zwitterions gives amino acids some unusual properties:

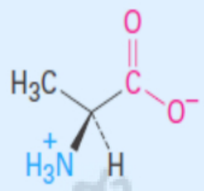
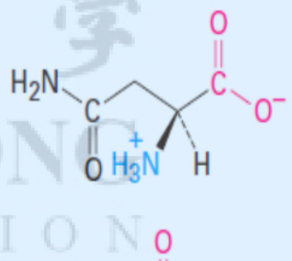
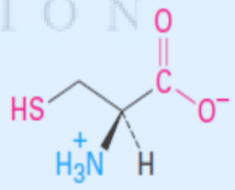
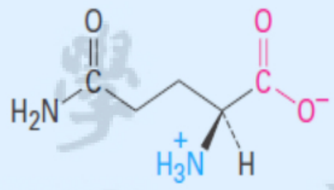
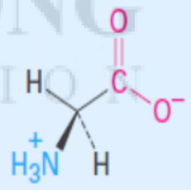
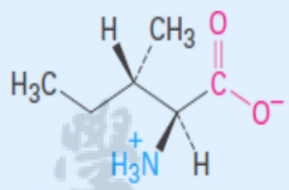
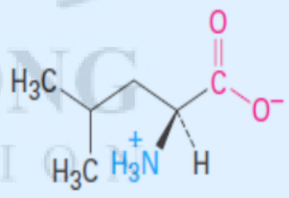
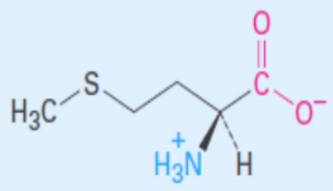
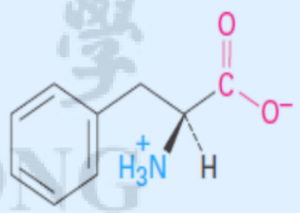
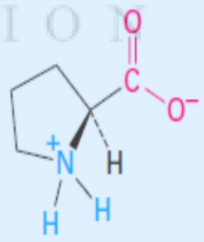
- Amino acids are crystalline solids with **high melting points**, *e.g.* glycine has a melting point of 262°C. This is due to strong electrostatic forces of attraction between the dipolar zwitterions in the solid lattice structure. Large amount of energy is required to overcome the **strong ionic bonds between oppositely charged ions**.



- Amino acids are **more soluble in water than in organic solvents**. This is due to the **strong ion-dipole interaction between the zwitterions and water molecules**.

For your information

Here are 20 naturally occurring α-amino acids and their names can be represented by either a one-letter or a three-letter abbreviation as shown in the table.

Name	Abbreviations		MW	Structure at pH = 7.3	pK_a α-CO_2H	pK_a α-NH_3^+	pK_a side chain	p*I*
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
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

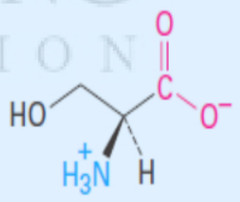
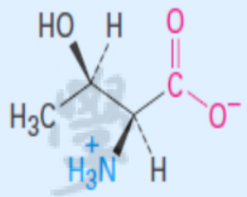
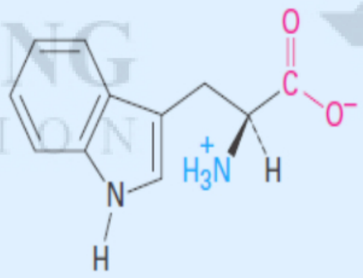
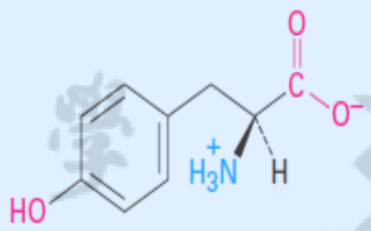
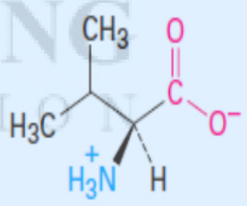
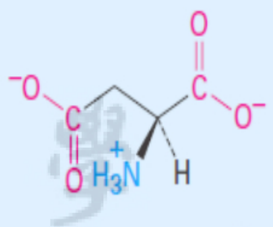
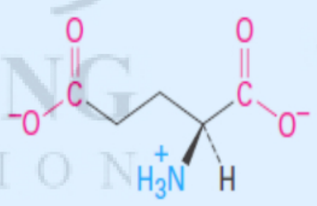
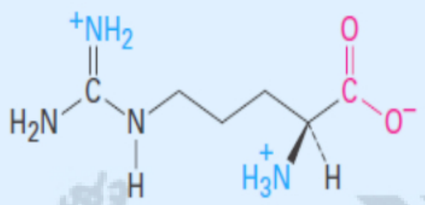
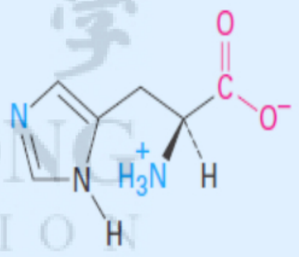
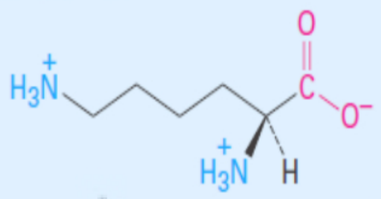
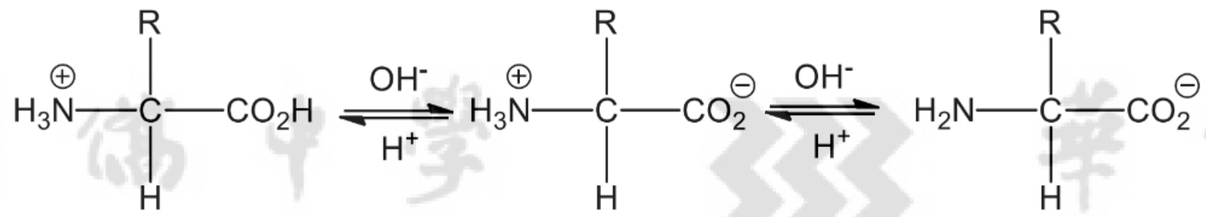
Neutral Amino Acids *(continued)*							
Serine	Ser	S	105		2.21	9.15	—	5.68
Threonine	Thr	T	119		2.09	9.10	—	5.60
Tryptophan	Trp	W	204		2.83	9.39	—	5.89
Tyrosine	Tyr	Y	181		2.20	9.11	10.07	5.66
Valine	Val	V	117		2.32	9.62	—	5.96
Acidic Amino Acids								
Aspartic acid	Asp	D	133		1.88	9.60	3.65	2.77
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

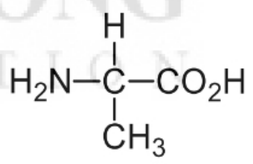
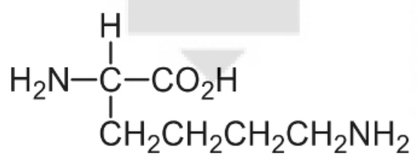
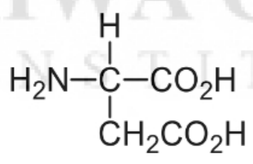
Table 4. 20 naturally occurring amino acids (at pH = 7.3). Extracted from McMurry J., Organic Chemistry. *8th ed. USA: Brooks/Cole*

6.3 Acid-Base behaviour

Having both the acidic and basic groups, amino acids are amphoteric, reacting with both acids and bases to form ionic salts.



Isoelectric point (pI) of an amino acid (or protein) is the pH at which the overall net charge on the amino acid is zero and it exists primarily as the neutral zwitterion. This isoelectric pH depends on the nature of the side chain, R.

Amino acid	Alanine	Lysine	Aspartic acid
Structure			
Nature of side-chain	neutral	basic	acidic
Isoelectric point	6.01	9.74	2.77

At a pH below isoelectric point (pH << pI), the amino acid exists predominantly as cations. However, when pH >> pI, the amino acid exists predominantly as anions.

Lecture Exercise 6.1

Draw the structures of the major species of lysine that can exist in aqueous solution of various pH. Start with the species in a solution of very low pH and consider the change in structure as pH increases. Hence identify the major species that exists at isoelectric point.

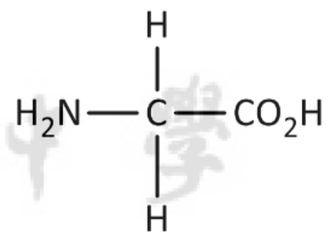
Structure				
pH	Very low pH			Very high pH

Increasing pH

6.4 Titration curves of amino acids (Application Example)

Titration of amino acids are very similar to the titration of polyprotic acids. Refer to Topic 15 Acid-Base Equilibria for titration curves and polyprotic acids.

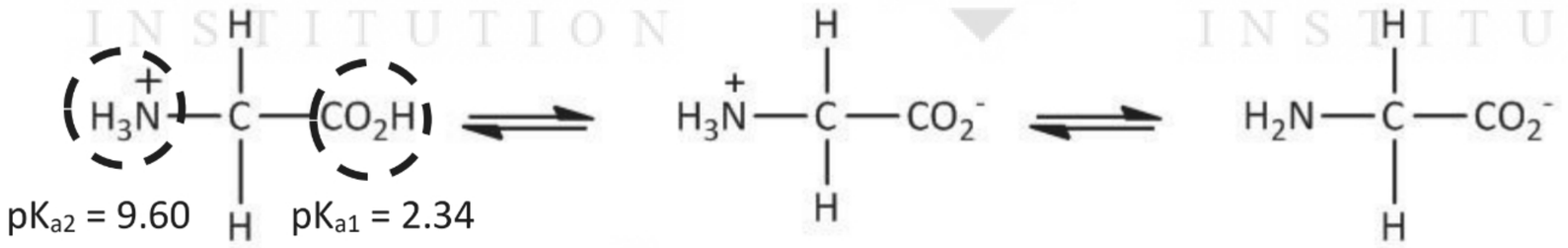
Using glycine as an example,



Glycine

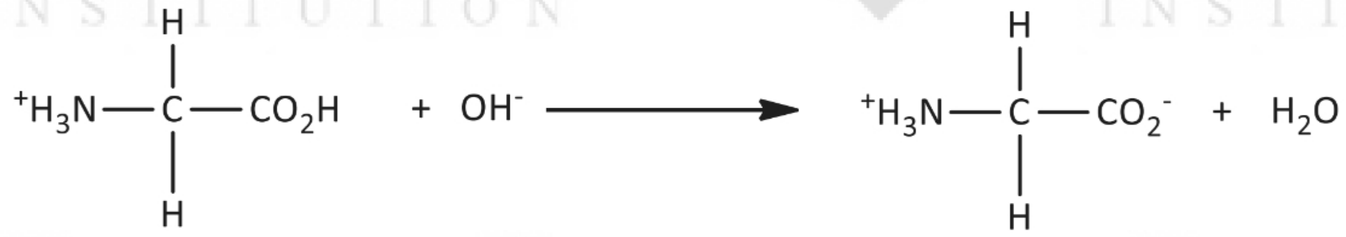
pK_{a1}= 2.34

pK_{a2}= 9.60



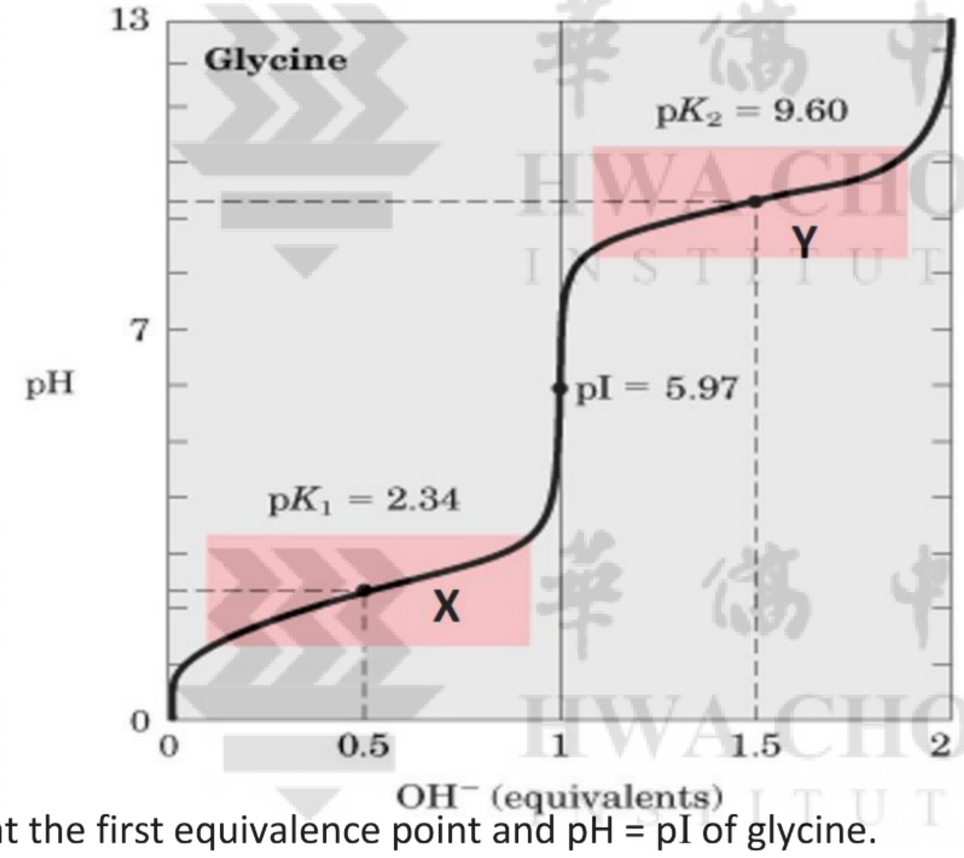
pH < 2.34 2.34 < pH < 9.60 9.60 < pH

At pH < 2.34, all possible sites of glycine are protonated. Since $–CO_2H$ group is a stronger acid than $–NH_3^+$ group, the stronger acidic $–CO_2H$ group will be neutralised first by the addition of base, $OH^–$, followed by the $–NH_3^+$ group. The reaction is as follows:



In the titration curve, the protonated (cationic) form of glycine was titrated against NaOH of same concentration. The cationic form predominates at low pH before $OH^–$ is added. When some $OH^–$ is added, a portion of the cationic form undergoes neutralisation to form zwitterion, resulting in buffer region **X** (mixture of cationic form and zwitterion).

Note that when 0.5 equivalent of $OH^–$ is added, amount of cationic form unreacted = amount of zwitterion formed. This is the maximum buffering capacity where pH=pK_{a1}.



The solution only contains zwitterion when at the first equivalence point and pH = pI of glycine.

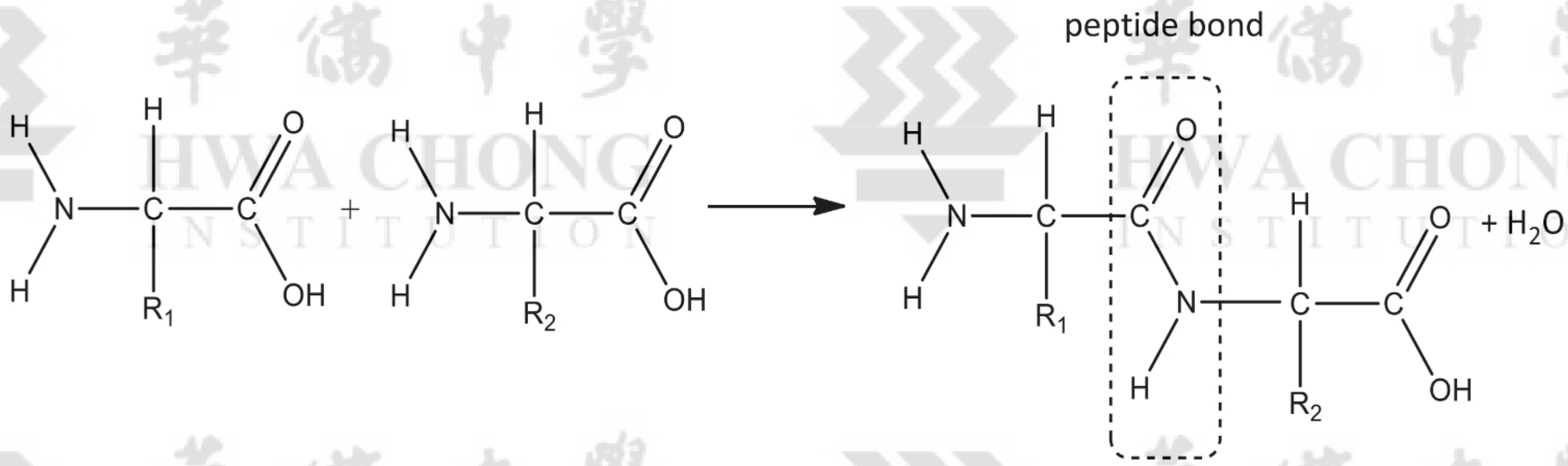
As more $OH^–$ is added, the $–NH_3^+$ group is neutralised to form the anionic form, leading to a new buffer mixture containing zwitterion and the anionic form in region **Y**. Note that when 1.5 equivalent of $OH^–$ is added, amount of zwitterion unreacted = amount of anionic form produced. This is the maximum buffering capacity where pH=pK_{a2}.

At the second equivalence point and beyond, all sites are de-protonated and the solution only contains the anionic form of glycine.

6.5 Peptide bond formation to form polypeptides and proteins

LO 19(j): describe the formation of peptide (amide) bonds between α-amino acids and, hence, explain protein formation

Amino acids are the basic units of polypeptides and proteins. An amide bond between amino acids is also called a peptide bond. Peptide bonds are formed from the condensation reaction between the $–CO_2H$ and the $–NH_2$ groups on two amino acids through the elimination of a water molecule. In this manner, any number of amino acids can be bonded in a continuous chain.



A **dipeptide** is the result of 2 amino acid molecules condensing together to form a peptide bond with the elimination of a water molecule while a **tripeptide** results from 3 amino acids molecules doing so with the formation of two peptide bonds and the elimination of two water molecules, and so on.

Lecture Exercise 6.2

A small peptide **X** is hydrolysed according to the following reaction.

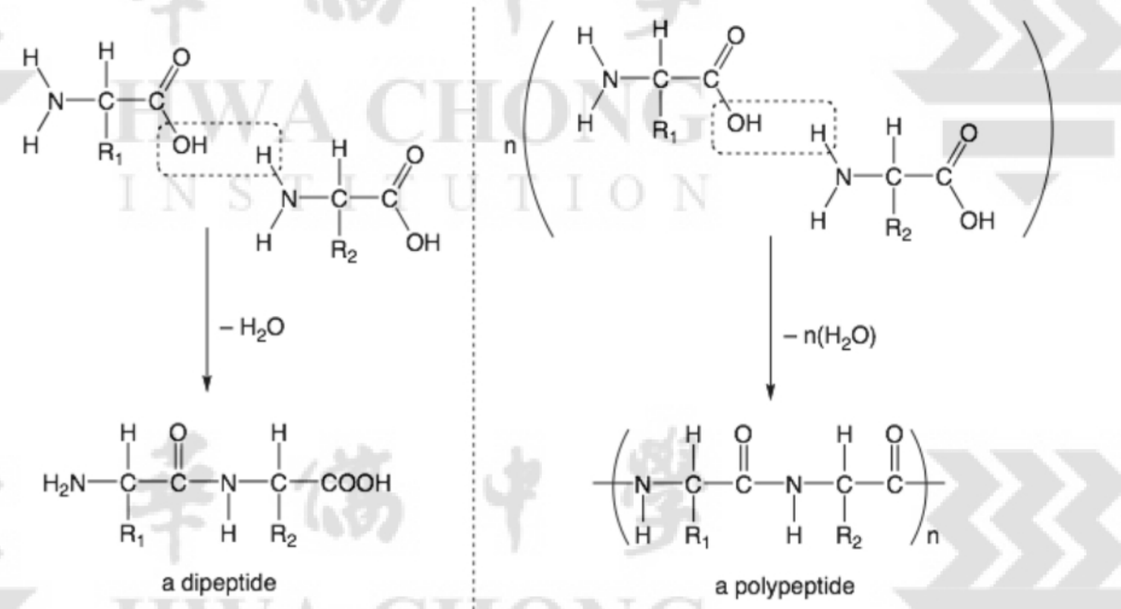
$$\mathbf{X} \xrightarrow{\text{hydrolysis}} 2NH_2CH_2CO_2H + NH_2CH(CH_3)CO_2H + 2NH_2CH(CH_2OH)CO_2H$$

$M_r = 75$ $M_r = 89$ $M_r = 105$

What is the M_r of **X**?

(N2009/I/30)

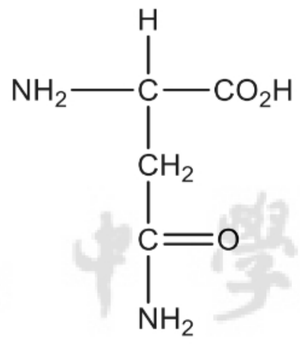
Peptides made from the condensation of up to about 50 amino acid molecules are called **polypeptides (or polyamides)**. Anything larger is classified as a **protein molecule**.



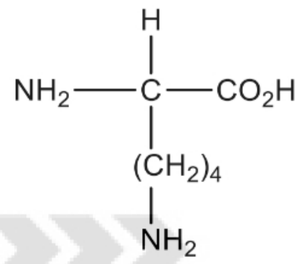
Note: In the lab, the reaction between a carboxylic acid and an amine would result in salt formation, but living organisms employ *enzymes* to form peptide bonds.

Lecture Exercise 6.3

Draw the structural formula of a dipeptide with the sequence asn-lys, showing the ionic form which it would exist at pH 3.

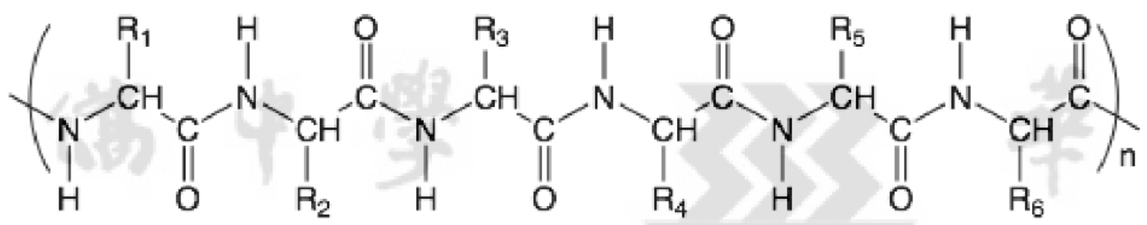


Asparagine (asn)



Lysine (lys)

7 PROTEINS



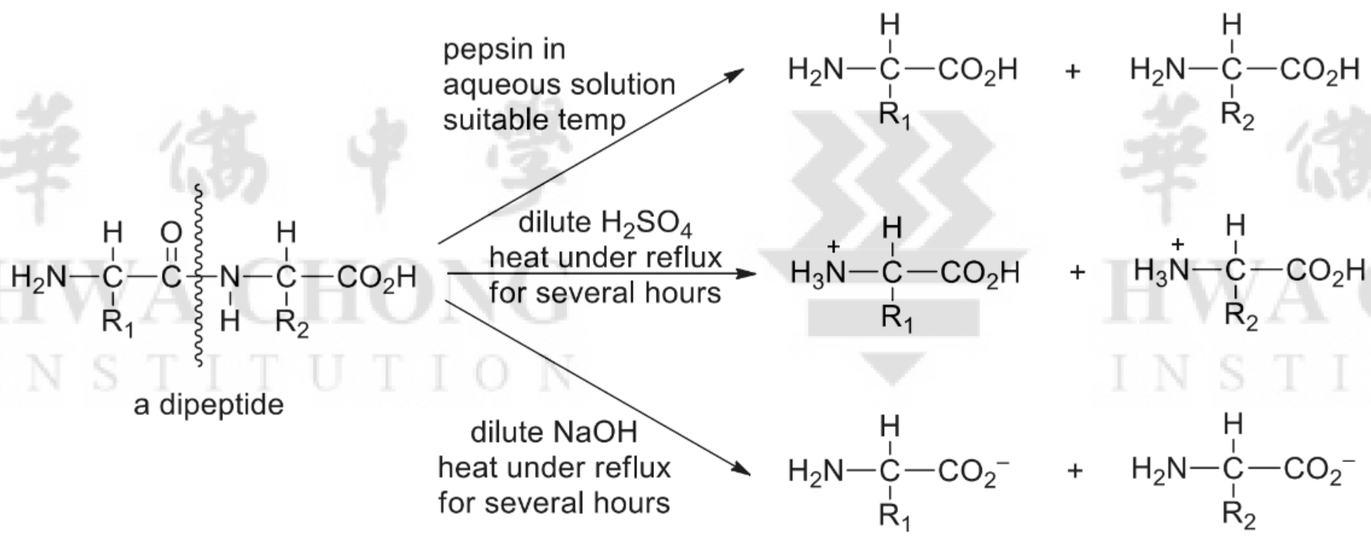
Proteins are naturally occurring polypeptides of molecular weight > 5000 and are formed when over 10^5 amino acids condense together, all linked by peptide bonds. They are essential for life in all living organisms and have many biological functions in the body, for example:

Type of Protein	Function	Examples
Structural proteins	Provide the framework which defines the size and shape of cells	Keratin is the protein of hair, nails, horns and feathers. Collagen and elastin provide a fibrous framework in animal connective tissues
Catalytic proteins (enzymes)	Accelerate metabolic processes to produce energy, build new cell structures and destroy old ones	Pepsin, trypsin and chymotrypsin which hydrolyses proteins in our diets so that subunits can be absorbed for use by our cells.

7.1 Hydrolysis of Proteins

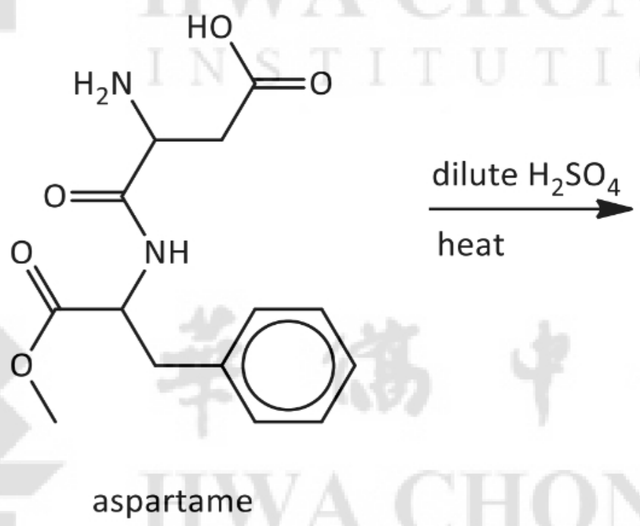
LO 19(k): describe the hydrolysis of proteins

Proteins can by hydrolysed into their constituent amino acids either by an appropriate enzyme or heating under reflux in the presence of aqueous acid or alkali for several hours in the laboratory.



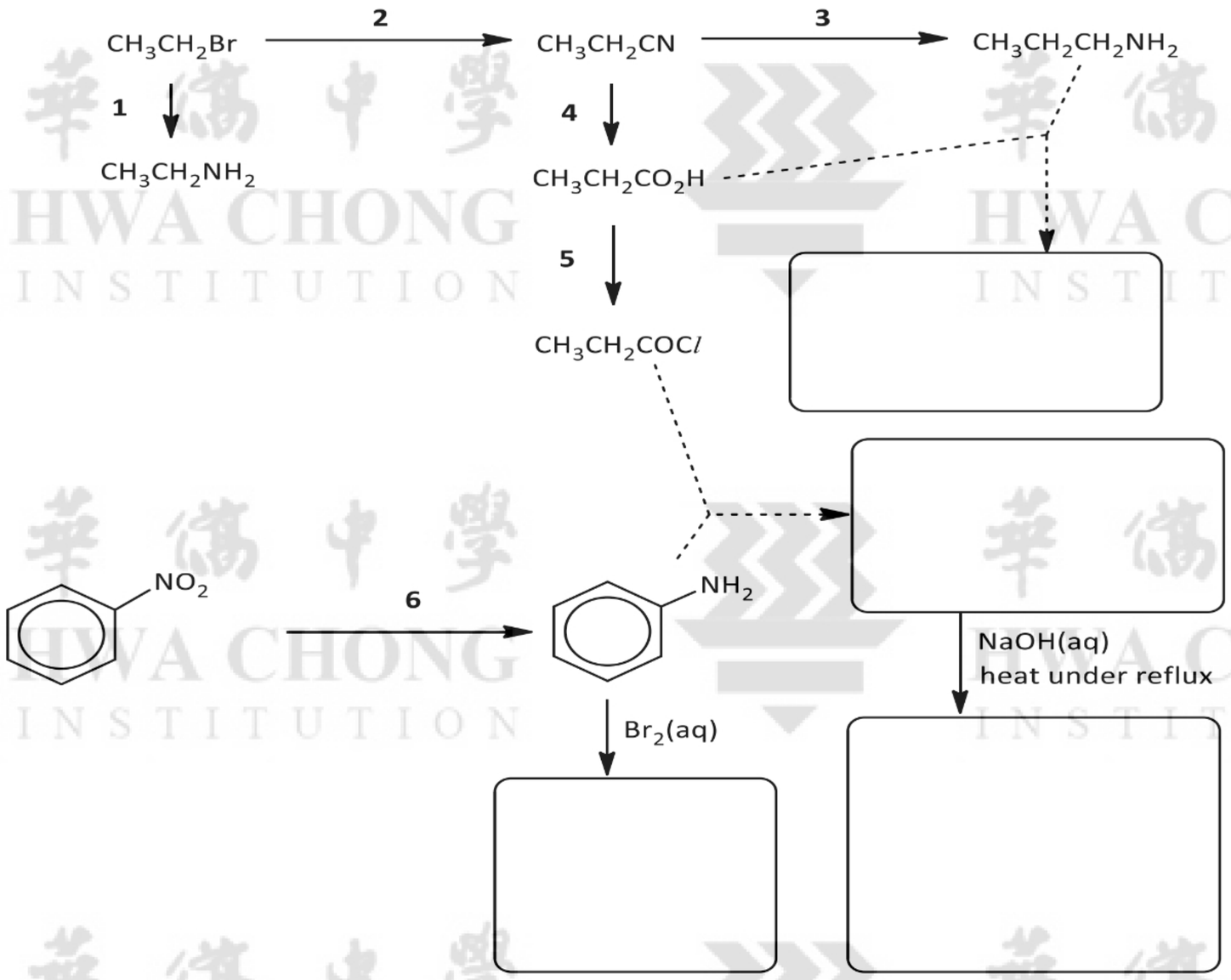
Lecture Exercise 7.1

Aspartame is the name for an artificial sweetener used as a sugar substitute in many foods and beverages. Draw the structural formulae of all the organic products obtained when aspartame is heated with dilute H_2SO_4.



Summary of reactions of amines and amides

State the reagents and conditions needed for the conversions on the arrows below. Draw the structure of the organic products formed in the boxes.



Summary of oxidising and reducing agents

Functional groups	Ability to be oxidised by			Ability to be reduced by		
	$KMnO_4$, dilute NaOH, cold	$KMnO_4$, dilute H_2SO_4, heat	$K_2Cr_2O_7$, dilute H_2SO_4, heat	H_2 / Ni high P	$LiAlH_4$ in dry ether	$NaBH_4$ in methanol
alkenes	√	√	X	√	X	X
alkylbenzenes		√	X			
nitriles (-CN)				√	√	X
1° & 2° alcohol		√	√			
aldehydes		√	√	√	√	√
ketones		X	X	√	√	√
carboxylic acids		X	X	X	√	X
esters		X	X			
amides		X	X		√	X

Note that nitrobenzene may be reduced to phenylamine using Sn, conc HC*l*, heat followed by dilute NaOH.

LOOKING AHEAD

In our study of the extension topic on organic chemistry, we have learnt the general concepts in organic chemistry (Topic 8 Introduction and Topic 9 Isomerism) and the nature & reactions of specific functional groups, which exemplify these general concepts as well as earlier concepts of structure and bonding, thermodynamics and kinetics. As we move on to the next topic of Electrochemistry and Transition Elements, bear in mind that organic compounds can undergo redox reactions and act as fuels in electrochemical cells (e.g. methane and ethanol). Organic molecules are also common ligands in transition metal complexes as many contain electron-rich centers e.g. alcohols, phenols, carboxylic acids, amines, alkenes and arenes.