2023 JC2 H2 CHEMISTRY (9729)
EXTENSION TOPIC – ORGANIC CHEMISTRY
Nitrogen Compounds

Name: ____ Civics Group: 22-_________

Students 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 $R'COCl$
(g) explain why an amide is neutral in terms of delocalisation of the lone pair of electrons on nitrogen
(h) describe the chemistry of amides, exemplified by the following reactions:
  (i) hydrolysis on treatment with aqueous alkali or acid
  (ii) reduction to amines with lithium aluminium hydride
(i) describe the acid/base properties of amino acids and the formation of zwitterions
(j) describe the formation of peptide (amide) bonds between α-amino acids, and hence explain protein formation
(k) describe the hydrolysis of proteins

LECTURE CONTENT

AMINES

REFERENCES

1 **A-Level Chemistry (4th ed), E.N. Ramsden**
2 **Organic Chemistry (6th ed), R.T. Morrison, R.N. Boyd**
3 **Organic Chemistry – Structure and Reactivity (4th ed), S.N. Eğe**
4 **Organic Chemistry (5th ed), F.A. Carey**
5 http://www.chemguide.co.uk/organicprops/aminemenu.html

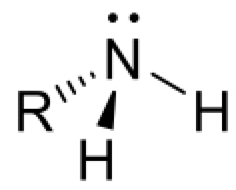
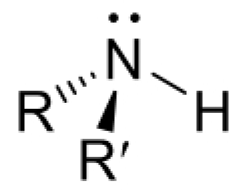
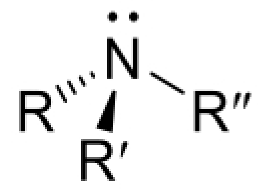
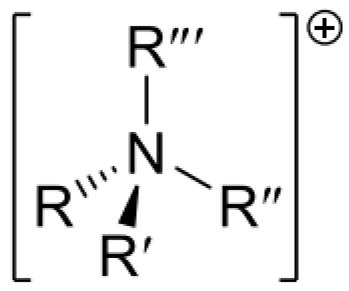
AMINES

1 Introduction

1.1 Structure and classification

- Amines are derivatives of ammonia where one or more hydrogen atoms of the ammonia molecule have been substituted by alkyl or aryl groups.

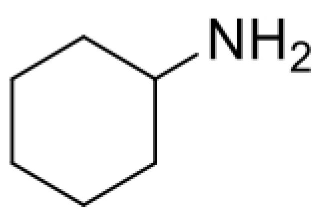
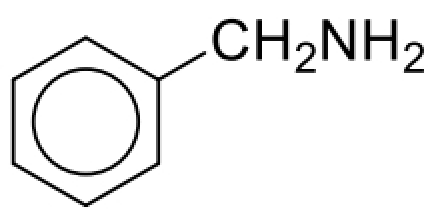
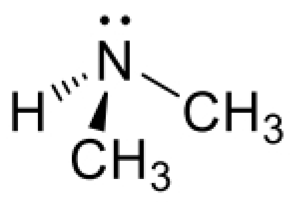
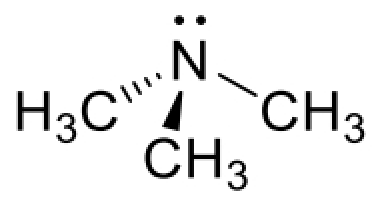
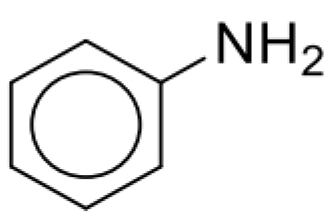
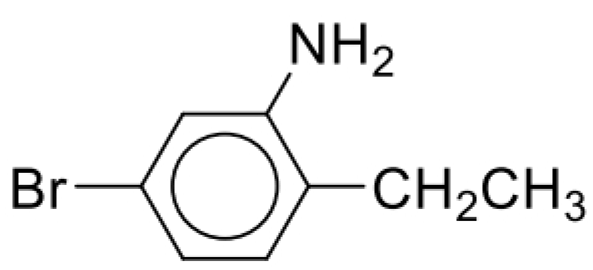
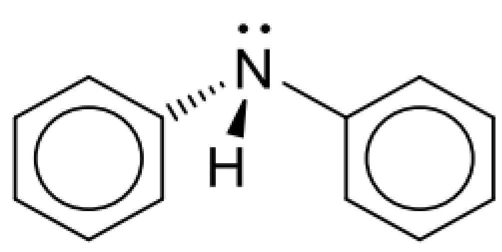
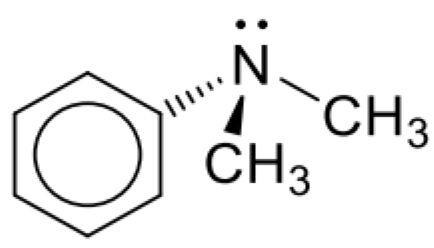
- Amines may be classified as **primary** (1º), **secondary** (2º) or **tertiary** (3º), depending on the **number of alkyl/ aryl groups** attached to the **N atom**.

				
Classification	primary	secondary	tertiary	quaternary ammonium salt
No. of R groups attached to N	**1 R** group attached to N atom	**2 R** groups attached to N atom	**3 R** groups attached to N atom	**4 R** groups attached to N atom

1.2 Nomenclature

- Many **aliphatic amines** are named by specifying the alkyl groups attached to the N atom, following by the suffix ***-amine***.

- Many **aromatic amines** are named as derivatives of the simplest aromatic amine, e.g. **phenylamine (aniline).**

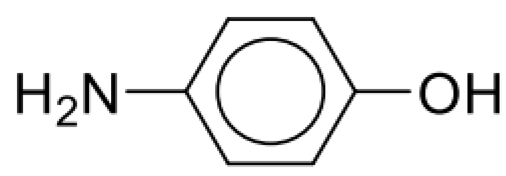
	primary (1º)		secondary (2º)	tertiary (3º)
Aliphatic amines	 **cyclohexylamine**	 **phenylmethanamine**	 **dimethylamine**	 **trimethylamine**
Aromatic amines – amino N is attached directly to benzene ring	 **phenylamine**	 **5-bromo-2-ethyl-phenylamine**	 **diphenylamine**	 ***N,N*-dimethyl-phenylamine**

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

e.g.

H_2NCH_2COOH

2-aminoethanoic acid

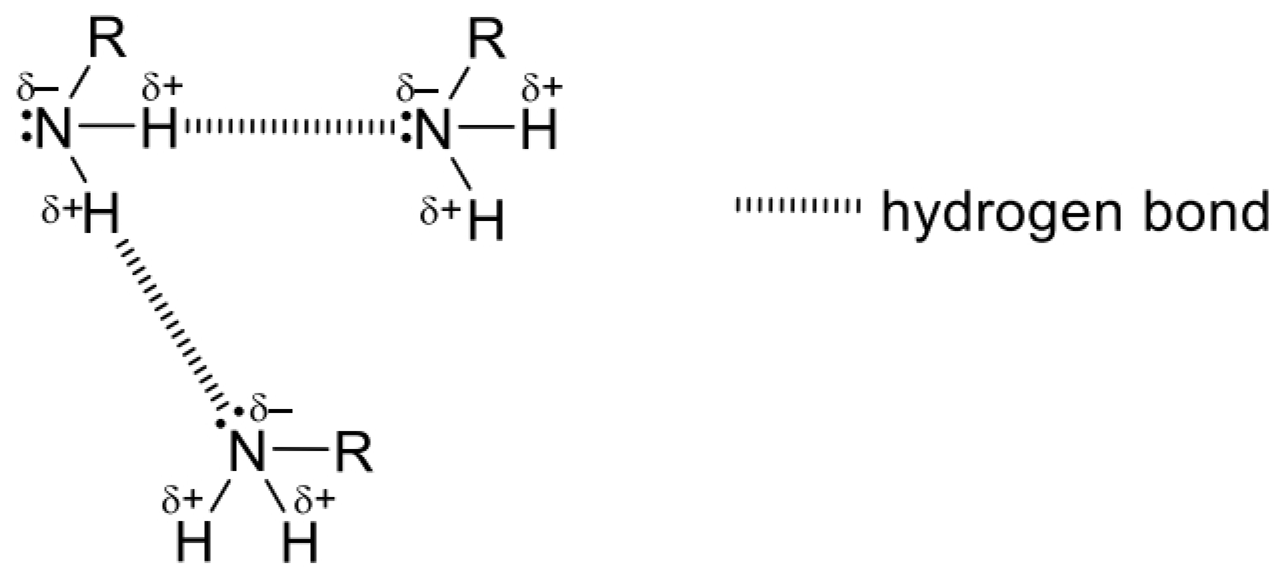


4-aminophenol

1.3 Physical properties

(a) Boiling point

- Amines have **higher boiling points** than hydrocarbons with similar M_r due to **stronger hydrogen bonding** (except for 3° amines).



- However, amines have **lower boiling points** than **alcohols** of similar M_r due to the **hydrogen bonds** in amines being **weaker** than those in alcohols since the **N–H bond is less polar than O–H bond**.

compound	M_r	b.p. / °C
$CH_3CH_2CH_2NH_2$ (amine)	59	48
$CH_3CH_2CH_2OH$ (alcohol)	60	97

- Amines which are constitutional isomers, have boiling points which increases in the order:
  3° amines < 2° amines < 1° amines

amine	classification	b.p. / °C	intermolecular forces of attraction
$CH_3CH_2CH_2NH_2$	primary	48	**hydrogen bonding** instantaneous dipole-induced dipole
$CH_3CH_2NHCH_3$	secondary	34	**hydrogen bonding (less extensive)** instantaneous dipole-induced dipole
$(CH_3)_3N$	tertiary	3	no hydrogen bonding between molecules **permanent dipole-permanent dipole (weaker)** instantaneous dipole-induced dipole

- Think: Why is the hydrogen bonding in secondary amines less extensive than that of primary amines?

  Answer: With one more R group bonded directly to the N atom in secondary amines, there is greater steric hindrance which makes the lone pair of electrons on the N atom is less accessible for hydrogen bonding as compared to primary amines. Hence, the hydrogen bonding in secondary amines is less extensive.

Self Check 1A

Arrange the following compounds in order of increasing boiling points.

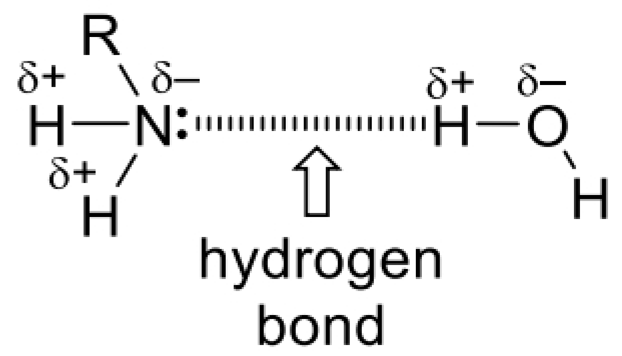
compound	M_r
$(CH_3)_3N$	59
$(CH_3)_3CH$	58
$CH_3CH_2CH_2NH_2$	59

Answer:

(b) Solubility in water

- Amines with **small molecular size** are soluble in water.

Reason: Amines can **form hydrogen bonds with water molecules**. The hydrogen bonds formed between amines and water molecules **releases sufficient energy to overcome the strong hydrogen bonds** between amines and water molecules.

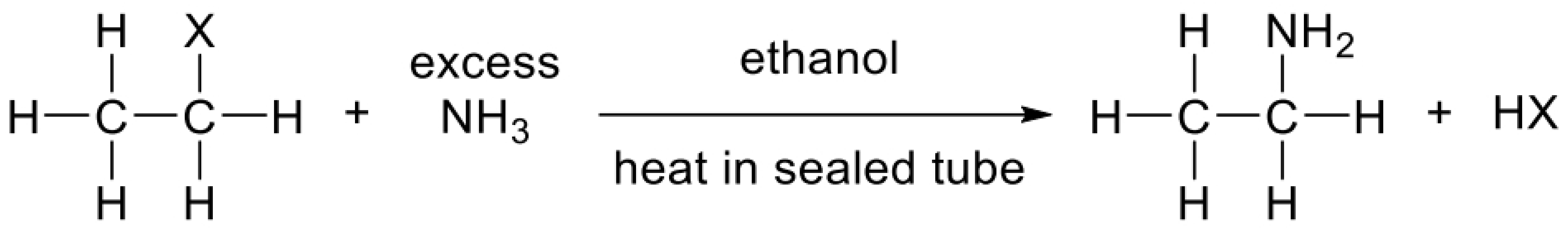


However, as the **alkyl group(s) becomes bulkier/heavier**, the **solubility in water decreases** because of the **greater non-polar nature of the R group.**

Reason: The **permanent dipole-induced dipole interactions** between the larger non-polar alkyl group and water molecules **do not release sufficient energy to overcome the strong hydrogen bonds** between amines and water molecules. In addition, the larger alkyl group also **hinders the formation of hydrogen bonds between the amine functional group and water molecules**.

2 Preparation of Amines

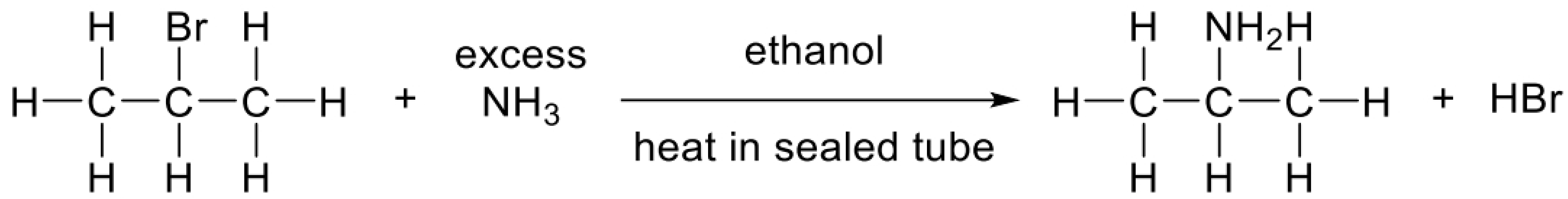
2.1 Nucleophilic substitution of halogenoalkane



Reagents and conditions: excess NH_3 in ethanol, heat in a sealed tube

Type of reaction: Nucleophilic Substitution

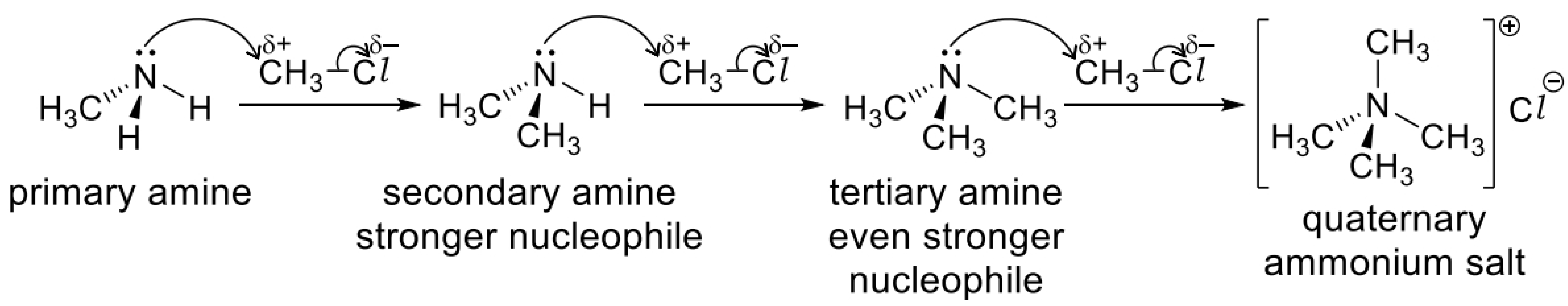
Example: Nucleophilic substitution of 2-bromopropane



- A **primary amine** (RNH_2) is formed in the reaction. Excess ammonia is used to **ensure high yield** of the primary amine.
- Without excess ammonia, secondary and tertiary amines (R_2NH and R_3N respectively), or even quaternary ammonium salts ($R_4N^+X^-$) may be obtained as the primary amines formed are **stronger nucleophiles** than ammonia and further nucleophilic substitution reaction may occur.
- In general,

$$RX + NH_3 \longrightarrow \underset{\text{primary amine}}{RNH_2} \xrightarrow{RX} \underset{\text{secondary amine}}{R_2NH} \xrightarrow{RX} \underset{\text{tertiary amine}}{R_3N} \xrightarrow{RX} \underset{\text{quaternary ammonium salt}}{R_4N^+X^-}$$

Example: *Reaction of excess chloromethane with ammonia*



- This method is limited to preparation of aliphatic amines as halogenoarenes will not undergo nucleophilic substitution reactions with ammonia under these conditions. Why?

  Recall from the topic of Halogen Derivatives:

  - ➢ The p-orbital of the halogen atom can have a **side-on overlap** with the π electron cloud of the benzene ring. As a result, the lone pair of electrons on the halogen atom can **delocalise** into the benzene ring.
  - ➢ Therefore, there **is partial double bond character** in the C–X bond and is thus stronger and not easily broken.

Self Check 2A

Predict with reasoning, the solubility of the end-product formed from the reaction of excess chloromethane with ammonia, in water.

Answer:

LO (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)

2.2 Reduction of nitriles

- Nitriles can be reduced to primary amines only.

$$R-C\equiv N \;+\; 4\,[H] \longrightarrow R-CH_2NH_2 \quad \text{[Using (1)]}$$

$$R-C\equiv N \;+\; 2\,H_2 \longrightarrow R-CH_2NH_2 \quad \text{[Using (2)]}$$

Reagents and conditions:
(1) $LiAlH_4$ in dry ether, r.t. *OR*
(2) H_2 with Ni / Pd / Pt catalyst, r.t.

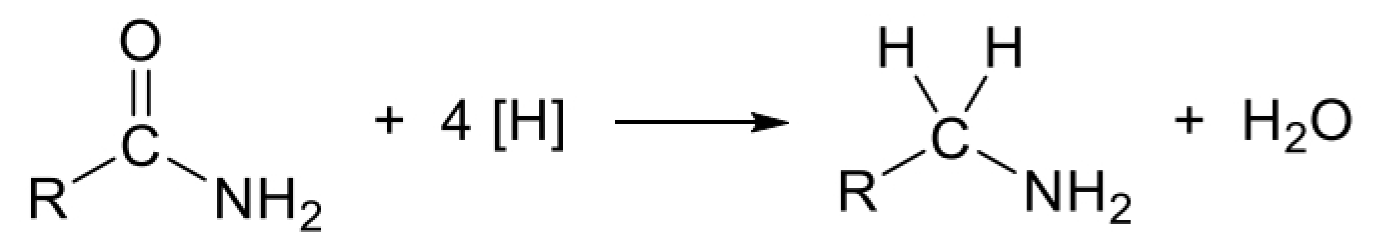
Type of reaction: Reduction

Example: Reduction of propanenitrile

$$CH_3CH_2\mathbf{CN} \;+\; 4\,[H] \xrightarrow[\text{r.t.}]{LiAlH_4 \text{ in dry ether}} CH_3CH_2\mathbf{C}H_2\mathbf{N}H_2$$

2.3 Reduction of amides

- The C=O group in the amide is reduced to a methylene group, $-CH_2-$.



primary amide **primary amine**

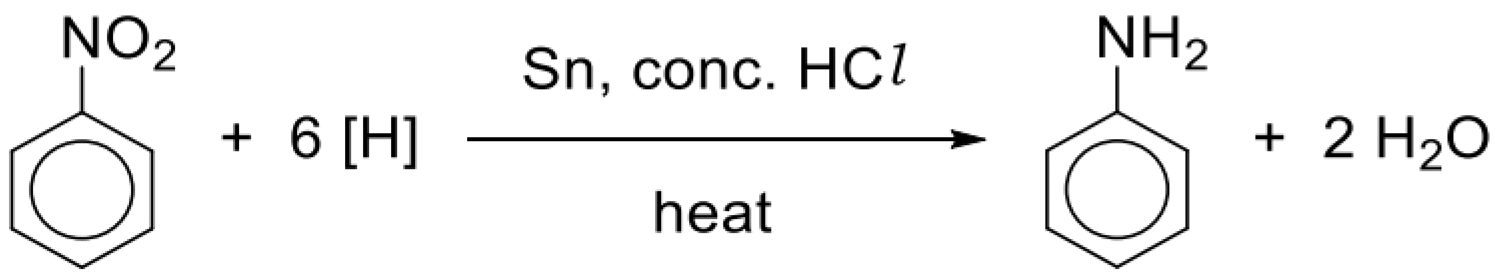
Reagents and conditions: $LiAlH_4$ in dry ether, r.t.

Type of reaction: Reduction

Example: Reduction of ethanamide

$$CH_3CONH_2 \;+\; 4\,[H] \xrightarrow[\text{r.t.}]{LiAlH_4 \text{ in dry ether}} CH_3CH_2NH_2 \;+\; H_2O$$

2.4 Reduction of nitrobenzenes (preparation of aromatic amines)



Reagents and conditions: Sn, concentrated HCl, heat

Type of reaction: Reduction

- The product of the reduction of nitrobenzene is phenylamine.
- Due to the highly acidic concentrated HCl used, the basic phenylamine is obtained in the form of its ammonium salt, $C_6H_5NH_3^+Cl^-$.
- To free the phenylamine, NaOH(aq) can be added to neutralise the acid.

$$C_6H_5NH_3^+(aq) + NaOH(aq) \rightarrow C_6H_5NH_2(l) + H_2O(l)$$

3 Basicity of Amines

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

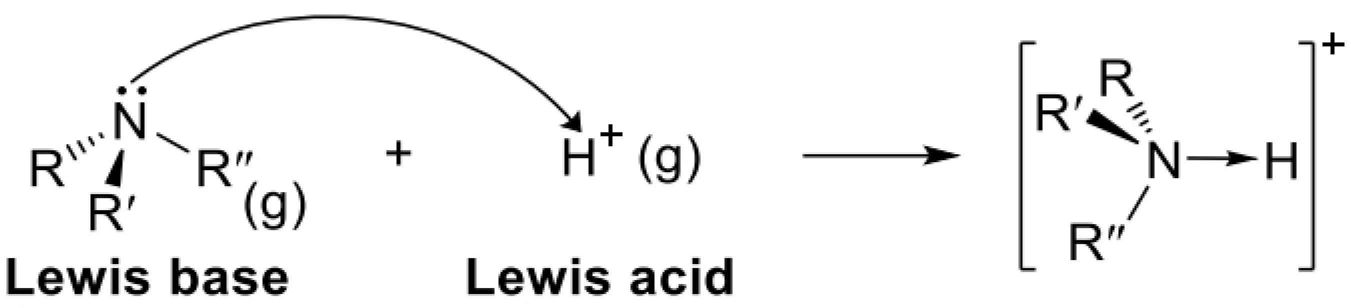
3.1 Amines as bases in gaseous phase

- In the **gaseous phase**, amines behave like a **Lewis base** *i.e.* **electron-pair donor**. This is due to the availability of the lone pair of electrons on the nitrogen atom for donation to an electron pair acceptor (Lewis acid), like H^+ ion.

- Their **basic strength** increases with the **availability of the lone pair of electrons** on the nitrogen atom for **donation** to an electron pair acceptor.

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

- Basicity of tertiary amine > secondary amine > primary amine > ammonia



$$NH_3(g) + H^+(g) \rightarrow NH_4^+(g) \qquad \Delta H_{protonation} = -858 \text{ kJ mol}^{-1}$$

$$CH_3NH_2(g) + H^+(g) \rightarrow CH_3NH_3^+(g) \qquad \Delta H_{protonation} = -896 \text{ kJ mol}^{-1}$$

$$(CH_3)_2NH(g) + H^+(g) \rightarrow (CH_3)_2NH_2^+(g) \qquad \Delta H_{protonation} = -923 \text{ kJ mol}^{-1}$$

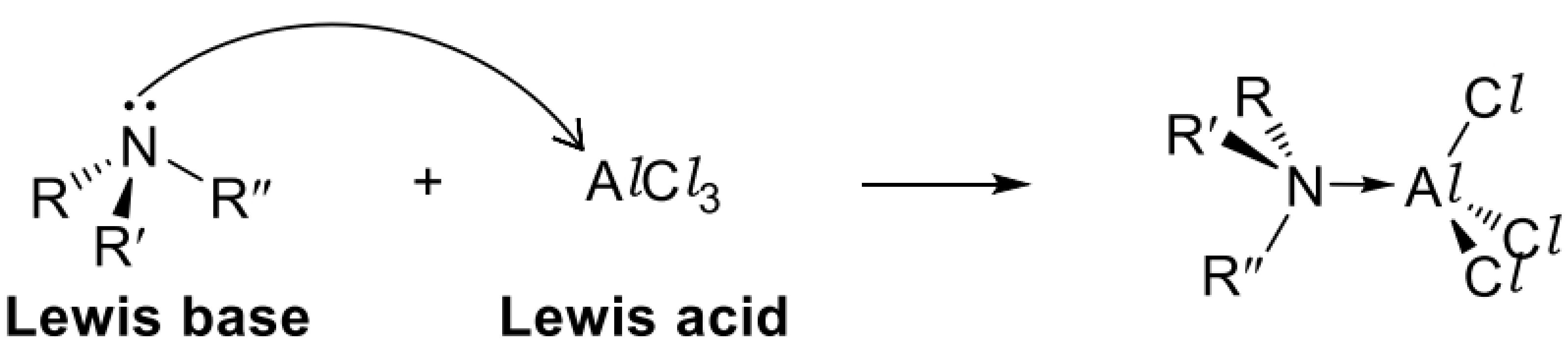
$$(CH_3)_3N(g) + H^+(g) \rightarrow (CH_3)_3NH^+(g) \qquad \Delta H_{protonation} = -938 \text{ kJ mol}^{-1}$$

Order of base strength (in gas phase):

trimethylamine > **dimethylamine** > **methylamine** > **ammonia**
most basic ... least basic

Reason

- From methylamine to trimethylamine, the **number of electron-donating alkyl groups attached to the N atom increases**.
- This **increases** the **electron density on N atom** of the amine. Hence, the **lone pair of electrons on N atom** is **more available for donation** to a Lewis acid.
- Thus basicity of tertiary amine > secondary amine > primary amine > ammonia.
- The same order of basicity is seen in the reaction of amines with other Lewis acids, such as $AlCl_3$:



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

3.2 Amines as bases in aqueous medium

- Amines are **weak bases** in aqueous medium.
- In the **aqueous medium**, amines behave like a **Bronsted-Lowry base** *i.e.* **proton acceptor**. This is due to the ability of the **lone pair of electrons on N atom** to **accept a proton** from H_2O.

e.g. $CH_3CH_2NH_2(aq) + H_2O(l) \rightleftharpoons CH_3CH_2NH_3^+(aq) + OH^-(aq)$

ethylamine → ethylammonium ion

- Their **basic strength increases** with the **availability** of the **lone pair of electrons** on the nitrogen atom for **donation** to a proton.

3.2.1 Relative basicity of ammonia, ethylamine and phenylamine in water

- The base dissociation constant, K_b, of an amine is a measure of the base strength of an amine. It is a measure of the extent of ionisation of the amine in water.
- The larger the K_b or the lower the pK_b, the stronger the base.

Comparing the base dissociation constant, K_b:

compound	K_b / mol dm^{-3}
ethylamine	5.6×10^{-4}
ammonia	1.8×10^{-5}
phenylamine	4.3×10^{-10}

Order of base strength: **ethylamine** (most basic) **>** **ammonia** **>** **phenylamine** (least basic)

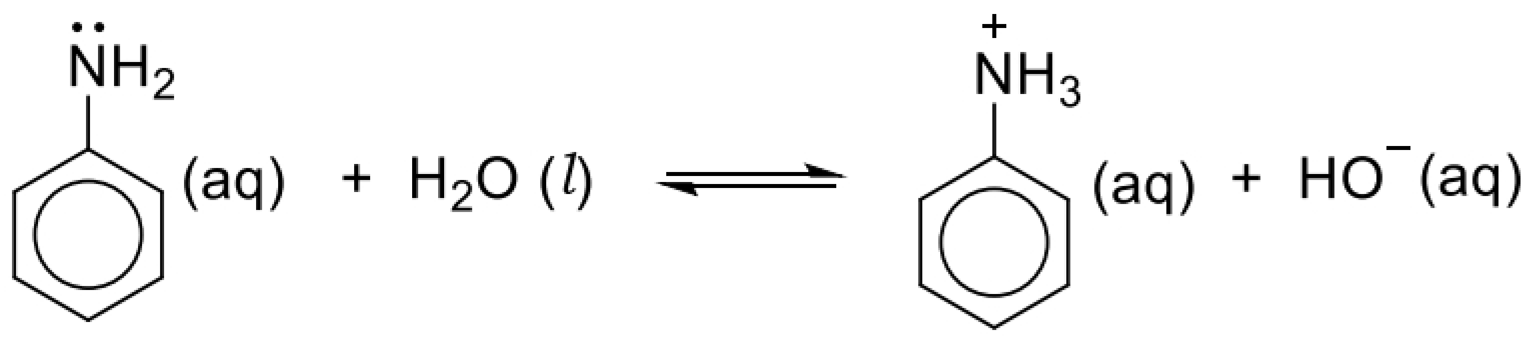
Why is ethylamine a stronger base than ammonia?

$$CH_3CH_2\ddot{N}H_2(aq) + H_2O(l) \rightleftharpoons CH_3CH_2NH_3^+(aq) + OH^-(aq)$$

$$\ddot{N}H_3(aq) + H_2O(l) \rightleftharpoons NH_4^+(aq) + OH^-(aq)$$

- ➢ The **electron-donating** ethyl group (CH_3CH_2–) **increases** the **electron density of the lone electron pair on N atom** of ethylamine. Hence, the **lone electron pair on N atom** is **more available for donation to a proton**.
- ➢ However, ammonia does not have any electron-donating group attached to its N atom. Hence, ammonia is a weaker base than ethylamine.

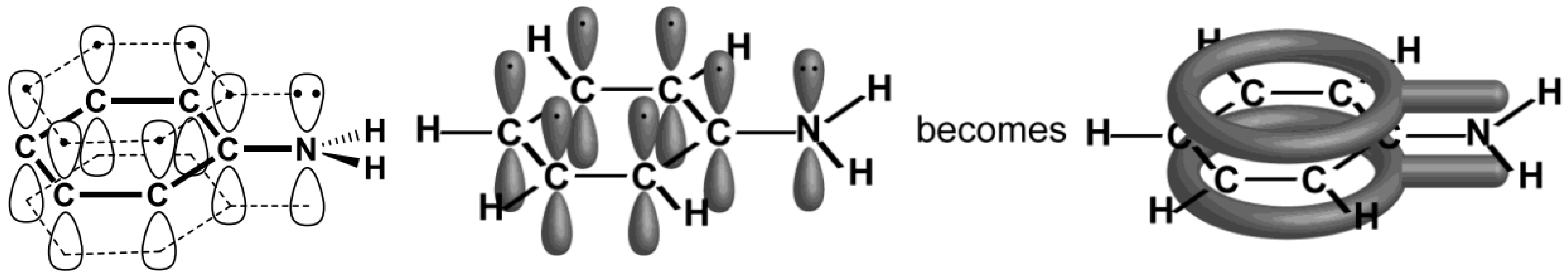
Why is phenylamine a weaker base than ammonia?



$$\ddot{N}H_3\,(aq) + H_2O(l) \rightleftharpoons NH_4^+\,(aq) + OH^-\,(aq)$$

- In phenylamine, the **lone pair of electrons** on the **nitrogen atom is delocalised into the benzene ring** due to the p-orbital of the nitrogen atom having a **side-on overlap** with the π electron cloud of the benzene ring.

- The **delocalisation of the lone pair** on N atom makes it **less available** for **donation to a proton**.



3.2.2 Effect of substituents on basicity

- **Electron-donating substituents cause an increase in basicity**

  The **electron-donating group** increases the electron density at the N atom of the amine group, making **the lone pair of electrons on N atom more available** for donation to a proton. Hence, the amine is **more basic.**

  E.g.

compound	K_b / mol dm^{-3}
CH_3NH_2	4.38×10^{-4}
NH_3	1.8×10^{-5}

- **Electron-withdrawing substituents cause a decrease in basicity**

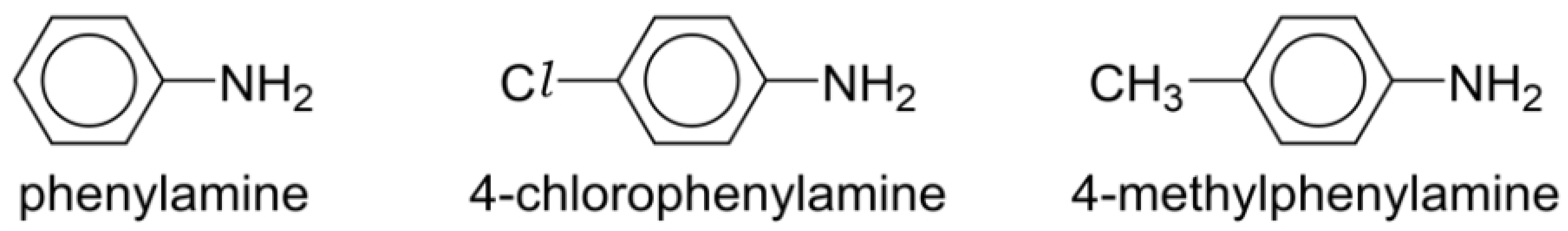
  The **electron-withdrawing group** decreases the electron density at the N atom of the amine group, making **the lone pair of electrons on N atom less available** for donation to a proton. Hence, the amine is **less basic**.

  E.g.

compound	K_b / mol dm^{-3}
NH_3	1.8×10^{-5}
NH_2NH_2	1.7×10^{-6}

Example 3A

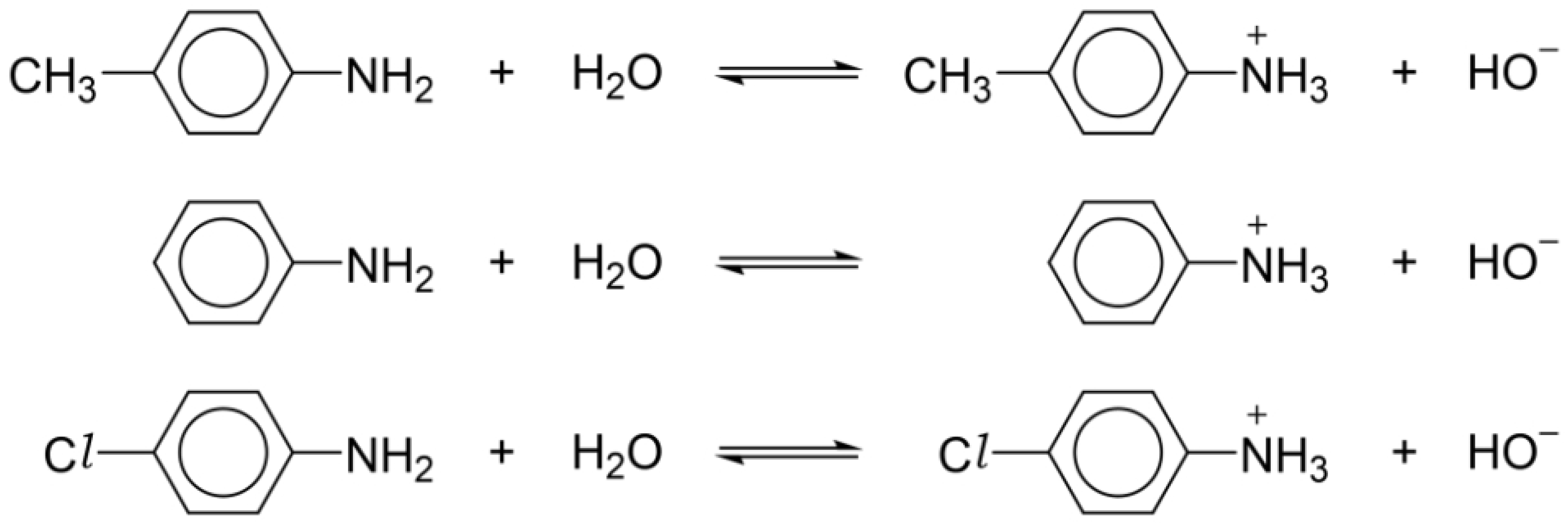
State and explain the relative base strength of phenylamine, 4-chlorophenylamine and 4-methylphenylamine



Answer:

Order of basicity:

Equations to represent basicity



Comparing basicity of 4-methylphenylamine and phenylamine

- The **electron-donating** $-CH_3$ group **increases the electron density** of the benzene ring. Hence, the **lone pair** on N atom is **less delocalized into the benzene ring** and **more available for donation** to a proton.

  ⇒ 4-methylphenylamine is the *strongest* base.

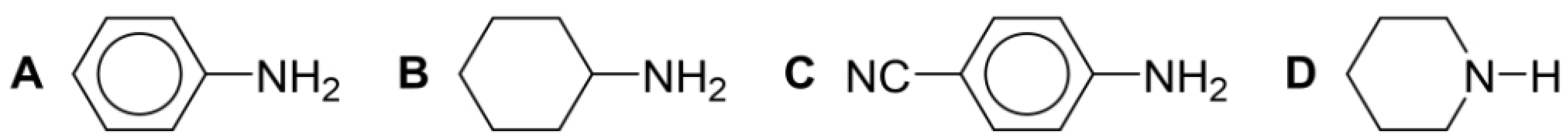
Comparing basicity of 4-chlorophenylamine and phenylamine

- The **electron-withdrawing** $-Cl$ group **decreases the electron density** of the benzene ring. Hence, the **lone pair** on N atom is **more delocalized into the benzene ring** and **less available for donation** to a proton.

  ⇒ 4-chlorophenylamine is the *weakest* base.

Self Check 3A

Arrange the following compounds in order of increasing pK_b.



Answer:

Example 3B – Comparison of Acidity and Basicity of Salts

RECALL: The stronger the base, the weaker the conjugate acid.
The stronger the acid, the weaker the conjugate base.

Which salt will be the most acidic in aqueous solution?

A $C_2H_5NH_3^+Cl^-$ **B** $C_6H_5NH_3^+Cl^-$

C K^+Cl^- **D** $NH_4^+Cl^-$

Explanation:

For Option C: KCl is a neutral salt as both $K^+(aq)$ and $Cl^-(aq)$ do not undergo hydrolysis.

For Option A, B, D:

$$\underset{\text{base}}{RNH_2} + H_2O \rightleftharpoons \underset{\text{conjugate acid}}{RNH_3^+} + OH^-$$

Since basicity:

Hence, acidity of the conjugate acid:

3.3 Comparison of basicity of amine in gas phase and aqueous phase (for enrichment)

- In the **gas phase** basicity of the methyl amines is of the order:

	trimethylamine	>	**dimethylamine**	>	**methylamine**	>	**ammonia**	
$\Delta H_{protonation}$	–938		–923		–896		–858	kJ mol^{-1}
	most basic						least basic	

- However in **aqueous** solution, the basicity as measured by the **pK_b** is of the order:

	dimethylamine	>	**methylamine**	>	**trimethylamine**	>	**ammonia**
pK_b	3.27		3.38		4.22		4.74
	most basic						least basic

There are 3 factors affecting the basicity of amines.

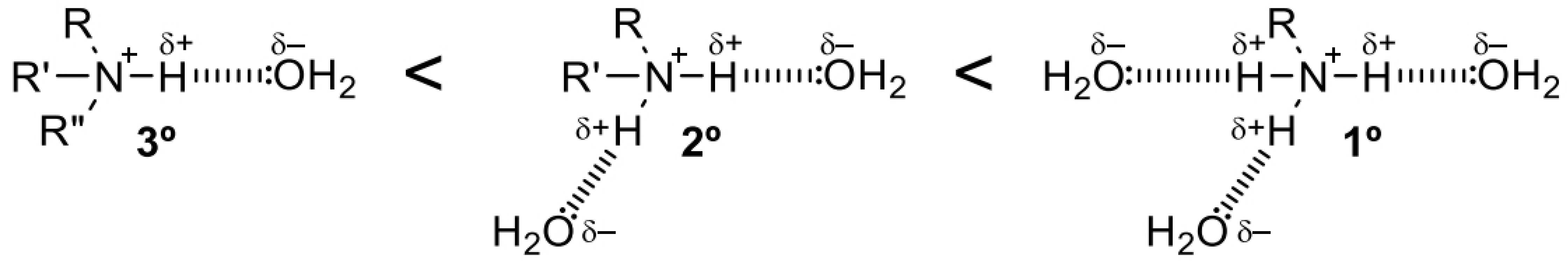
(1) **Inductive effect** of substituents on N. Alkyl groups will increase the basicity as they exert electron–donating inductive effect.

(2) **Solvation Effect** which is the degree of solvation of the protonated amine. More N–H groups allow for more extensive hydrogen bonds between the protonated amine and water molecules, leading to greater degree of solvation and thus greater stability of the protonated amine and greater ease of formation. Thus, basicity of amine will increase.

(3) **Steric hindrance** offered by the groups on N. Bulky groups hinder formation of hydrogen bond between N and the approaching H^+ ion.

- In the aqueous phase, the substituted ammonium cations get stabilised not only by electron-donating effect of the alkyl group **(inductive effect)** but also by solvation with water molecules *via* hydrogen bonding **(solvation effect)**. More N-H groups allow for more extensive hydrogen bonds and greater degree of solvation.

  Thus the order of stability of ions are as follows:



- In addition, when the alkyl group is small, like $-CH_3$ group, there is no **steric hindrance** to hydrogen bonding. In the case where the alkyl group is bigger than CH_3 group, the bulky group hinders the formation of hydrogen bonding.

  Hence aqueous basicity of the ethyl substituted amines follows the order:

	diethylamine	>	**triethylamine**	>	**ethylamine**	>	**ammonia**
pK_b	3.00		3.25		3.29		4.74
	most basic						least basic

- Hence, there is a subtle interplay of the ***inductive effect*****,** ***solvation effect*** **and** ***steric hindrance*** of the alkyl group which decides the basic strength of alkyl amines in the aqueous solution.

4 Reactions of Amines

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

4.1 Formation of salts

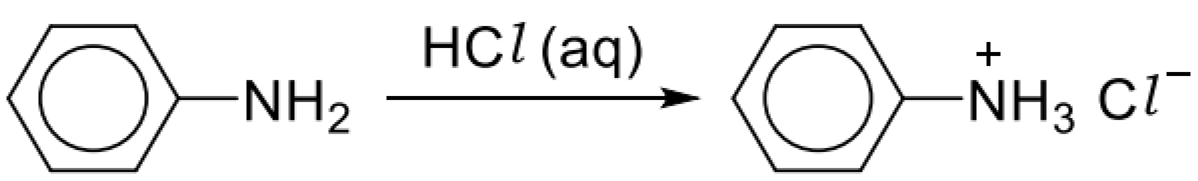
$$R{-}NH_2 + H^+ \longrightarrow R{-}NH_3^+$$

Reagents and condition: HC*l* (aq) or H_2SO_4 (aq), r.t.

Type of reaction: acid-base reaction or neutralisation

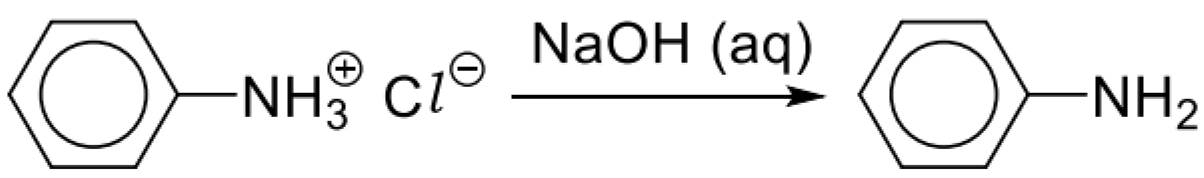
- Both aliphatic amines and phenylamines form stable crystalline salts with mineral acids. The amine salt is soluble in water.

Example: Reaction of phenylamine with hydrochloric acid



Phenylamine is only slightly soluble in water, but it dissolves readily in hydrochloric acid because a salt is formed. The salt is an *ionic compound* and dissolves due to **ion-dipole interactions** formed with water molecules. Evaporation of the salt solution gives a **white solid** of phenylammonium chloride.

- The amine can be regenerated from the amine salt by reacting the salt with a strong alkali e.g. NaOH.



Addition of alkali to this salt solution causes phenylamine to be released.

Self Check 4A

1 A liquid **P** is sparingly soluble in water but dissolves readily in cold hydrochloric acid. Evaporation of this solution yields a crystalline solid.

Which of the following could be **P**?

A $C_6H_5COCH_3$ **B** C_6H_5CN **C** $C_6H_5NH_2$ **D** C_6H_5OH

Example 4A

Which method is able to separate benzene from a mixture of benzene and phenylamine?

A extracting the phenylamine with ethanol

B nitrating the benzene with a nitrating mixture

C shaking the mixture with dilute aqueous acid

D shaking the mixture with dilute aqueous alkali

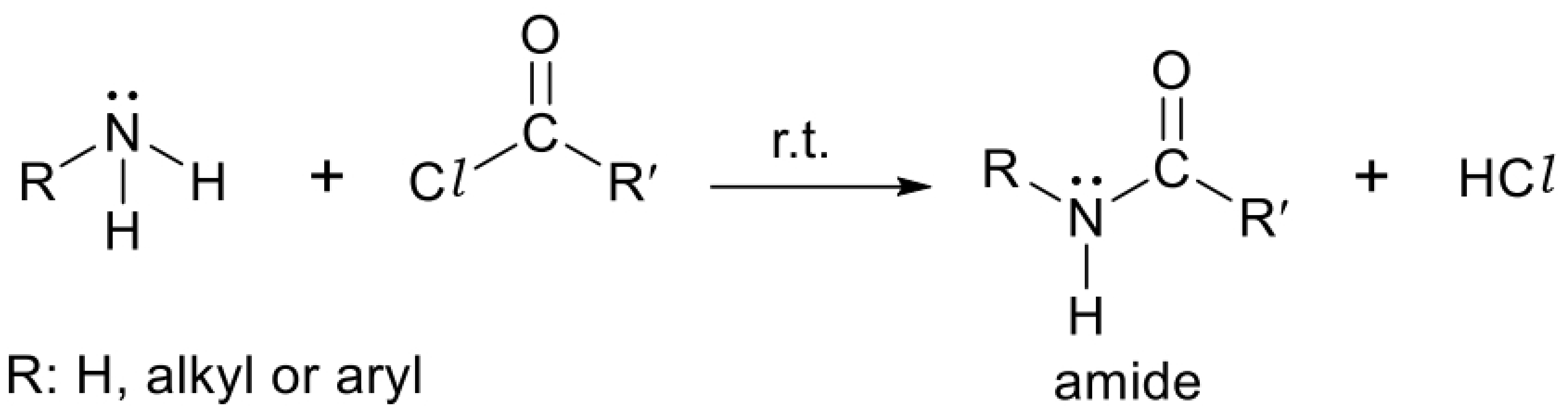
4.2 Nucleophilic substitution with halogenoalkane (See Section 2.1)

- Amines can react halogenoalkanes in a nucleophilic substitution with the amine acting as the nucleophile.

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

4.3 Nucleophilic substitution/ condensation reaction with acyl chloride

- Amines can undergo nucleophilic substitution / condensation with acyl chlorides to form amides.

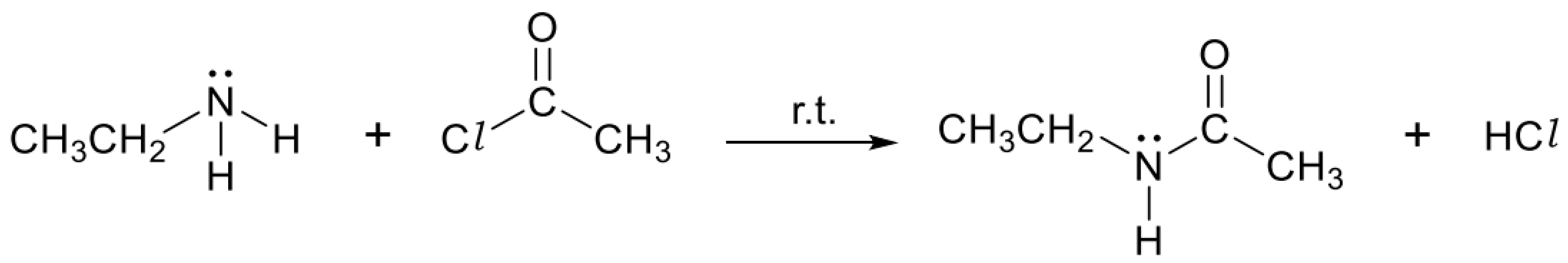


Reagents and condition: anhydrous acyl chloride, RCOC*l*, room temperature

Type of reaction: nucleophilic (acyl) substitution / condensation

Observations: white fumes of HC*l*

Example:

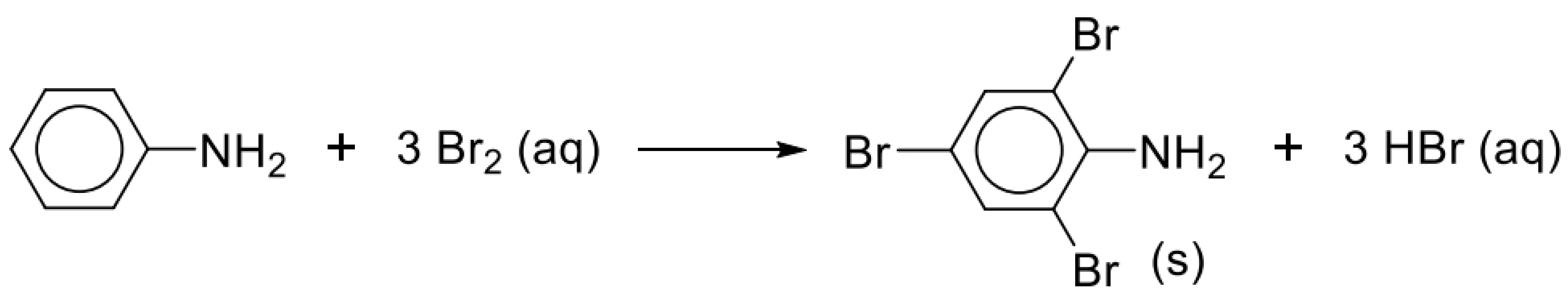


- Other acyl halides can be used to form amides. e.g. acyl bromide.
- Anhydrous condition is required for the reaction as acyl halides react readily with water.
- The reaction of acyl halides with ammonia, primary amines and secondary amines is the **ONLY** method to synthesise amides.
- Carboxylic acids cannot react with amines to form amide. Why?
  - Amines are basic and would undergo acid-base reaction with carboxylic acids to form a salt instead.

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

4.4 Electrophilic substitution of phenylamine

- Bromination of the benzene ring of phenylamine can be done using aqueous bromine at room temperature without the use of a Lewis acid catalyst.
- This is due to the $–NH_2$ group increasing the electron density of the benzene ring as the lone pair of electrons on N atom is delocalised into the benzene ring, making it more susceptible to electrophilic attack as the benzene ring is now more electron-rich.



white ppt of
2,4,6-tribromophenylamine

Reagents and condition: aqueous bromine

Type of reaction: electrophilic substitution

Observations: orange bromine solution decolourises with the formation of a white ppt (of 2,4,6-tribromophenylamine) and white fumes (of HBr) evolved

- Phenol and phenylamine react similarly with Br_2 (aq) to give the same observations.
How can phenol and phenylamine be distinguished?

Test: Add aqueous neutral $FeCl_3$ solution separately to each unknown compound.

Observation: Phenol – forms a violet complex

Phenylamine – does not form a violet complex

- Can phenylamine react with *dilute* nitric acid like phenol to give 2-nitrophenylamine or 4-nitrophenylamine?

____

____

____

- Think: How to synthesise 2-nitrophenylamine or 4-nitrophenylamine from phenylamine?
(Hint: Convert the basic $–NH_2$ group into a neutral functional group that is still 2,4-directing)

Checkpoint for Amines:

Section 1: Introduction

- To know the structure and classification (primary (1°), secondary (2°) or tertiary (3°)) of amines.
- To interpret and use the nomenclature, general formulae and displayed formulae of amines.
- To describe and explain the physical properties (boiling point, solubility) of amines.

Section 2: Preparation of Amines

- To describe the formation of amines in the following reactions:
    - nucleophilic substitution of halogenoalkanes
    - reduction of nitriles
    - reduction of amides
    - reduction of nitrobenzenes (for preparation of aromatic amines)

Section 3: Basicity of Amines

- To describe amines as Lewis bases in the *gaseous* phase, and explain their relative basicity using the availability of the lone pair of electrons on N atom for donation.
- To describe amines as Bronsted-Lowry bases in the *aqueous* phase, and explain their relative basicity using the ability of the lone pair of electrons on N atom to accept a proton.
- To understand the effects of substituents (electron-donating or electron-withdrawing) on the basicity of amines.

Section 4: Reactions of Amines

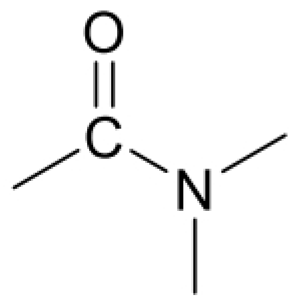
- To describe the following reactions of amines:
    - acid-base reaction to form salts
    - nucleophilic substitution with halogenoalkanes (also refer to section 2)
    - nucleophilic (acyl) substitution with acyl halides (condensation reaction).
    - electrophilic substitution of phenylamine

AMIDES

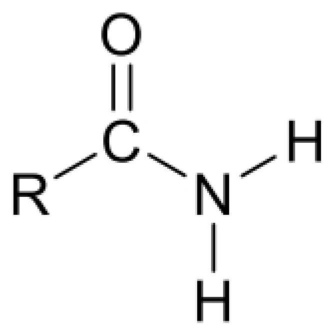
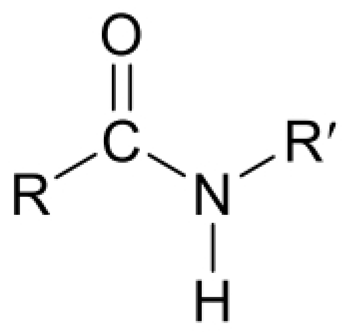
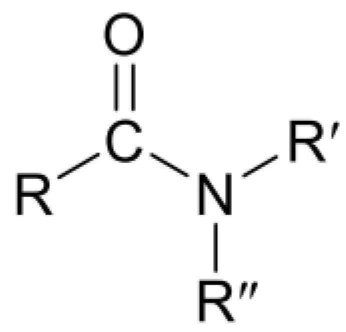
1 Introduction

1.1 General formulae

- Amides are derivatives of carboxylic acids that contain a trivalent nitrogen bonded to a carbonyl group. They contain the following group:



- Amides are classified as primary, secondary, or tertiary according to the number of alkyl groups bonded to the nitrogen atom of the amide group.

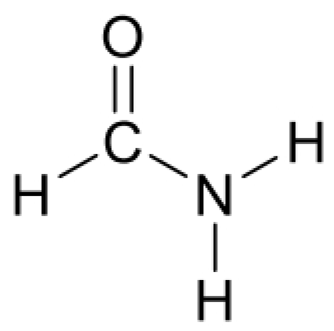
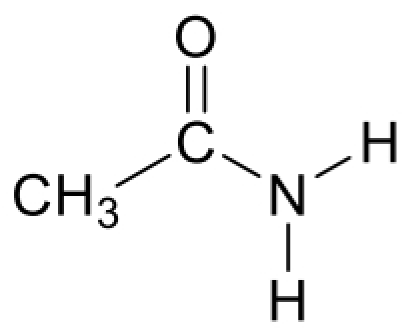
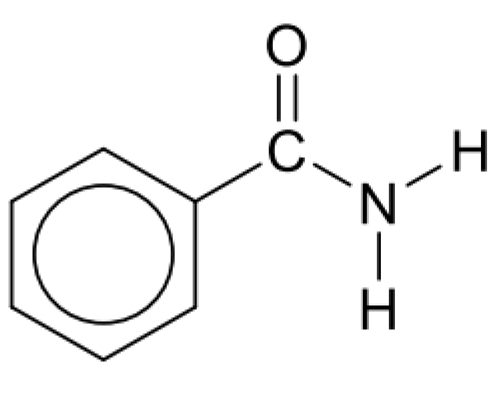
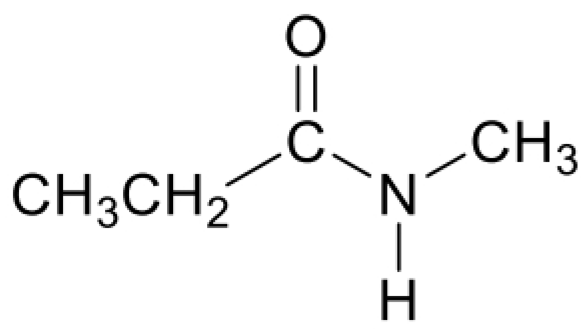
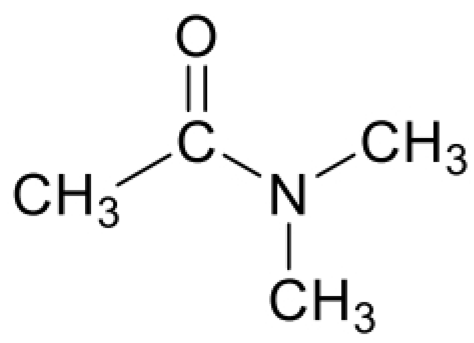
		
$R-CONH_2$	$R-CONHR'$	$R-CONR'R''$
primary (1º) amide	secondary (2º) amide *N*-substituted amide	tertiary (3º) amide *N*,*N*-disubstituted amide

1.2 Nomenclature

- To name a primary amide, first name the corresponding acid. Drop the -ic acid or -oic acid suffix from the name of the carboxylic acid, and substitute the suffix **-amide**.

- Secondary and tertiary amides are named by treating the alkyl groups on nitrogen as substituents, specifying their positions by the prefix *N*-.

Example:

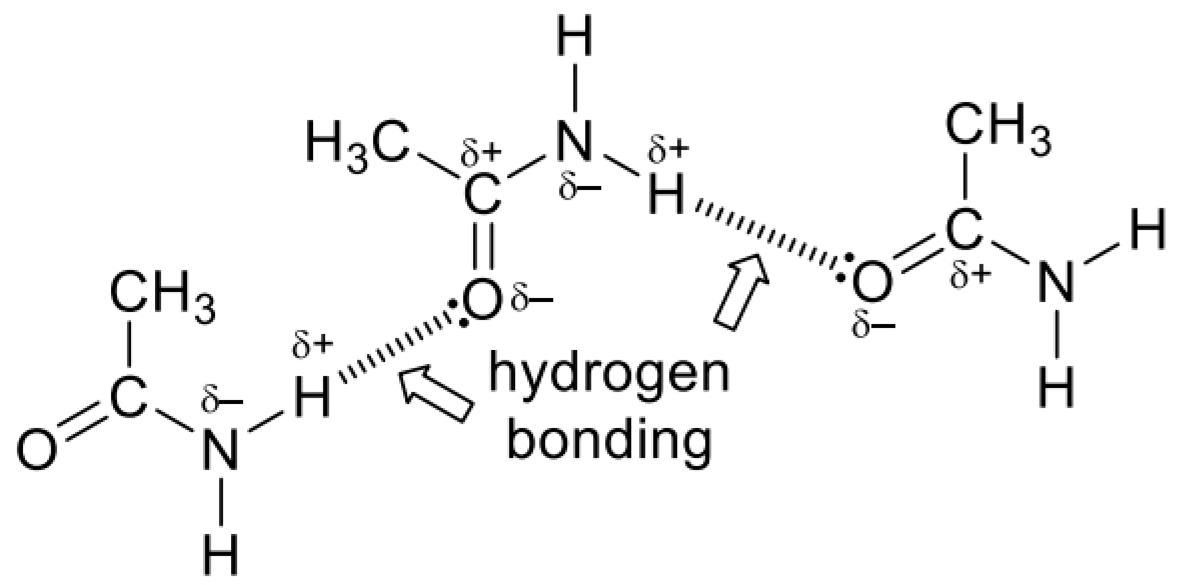
primary (1º)	secondary (2º)	tertiary (3º)
 methanamide  ethanamide  benzamide	 *N*-methylpropanamide	 *N*,*N*-dimethylethanamide

1.3 Physical properties

(a) Boiling and melting points

name	formula	classification	m.p. / ºC	b.p. / ºC
methanamide	$HCONH_2$	primary	3	193
ethanamide	CH_3CONH_2	primary	82	221
benzenecarboxamide	$C_6H_5CONH_2$	primary	132	290
N,*N*-dimethylethanamide	$CH_3CON(CH_3)_2$	tertiary	–20	166

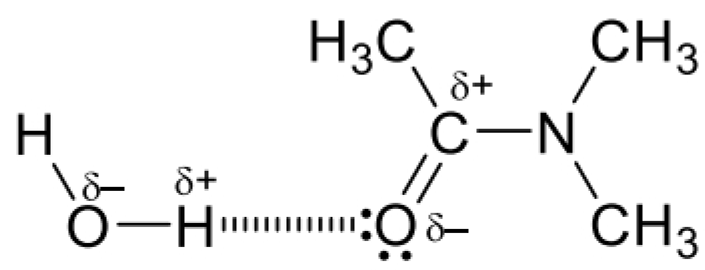
- Amides are polar organic compounds.
- All primary amides except methanamide are crystalline solids due to fairly strong hydrogen bonding.
- 1º and 2º amides have high melting points and boiling points due to the presence of hydrogen bonding between molecules.



- 3º amide molecules do not form hydrogen bonds with each other since there are no hydrogen atoms directly bonded to the electronegative N atom.

(b) Solubility in water

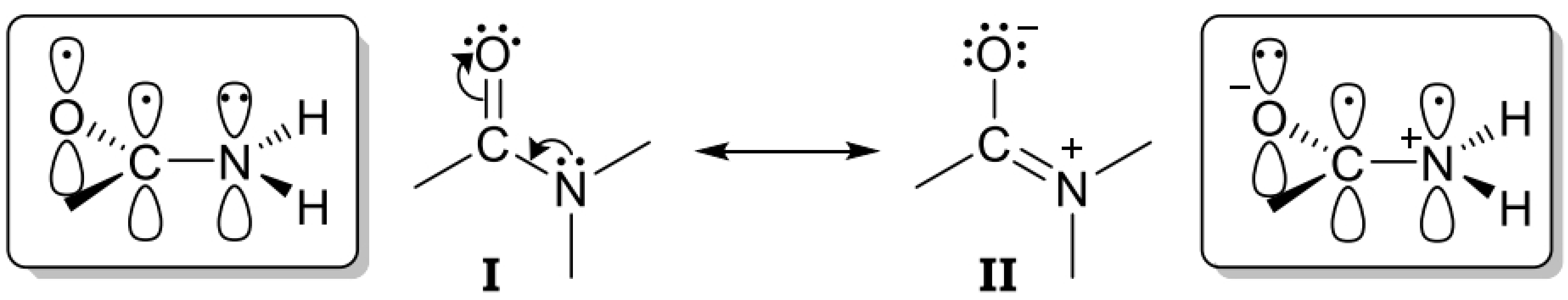
- Aliphatic amides with a small number of carbon atoms are soluble in water because the amide molecules can interact with water molecules via hydrogen bonding.
- Solubility of amides in water decreases with increasing size of the non-polar hydrocarbon chain.



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

2 Lack of Basicity

- The simple amide structure shows a lone pair of electrons on the nitrogen atom. However, unlike amines, the amide functional group is considered to be **neutral**. Amides are neutral to litmus.
- Why is the amide functional group **effectively neutral**?
  - Amide is neutral because the **lone pair of electrons on the nitrogen atom delocalises into** the **π-electron cloud of the adjacent C=O bond**. The lone pair of electrons on the nitrogen atom is therefore not available for donation to a proton.

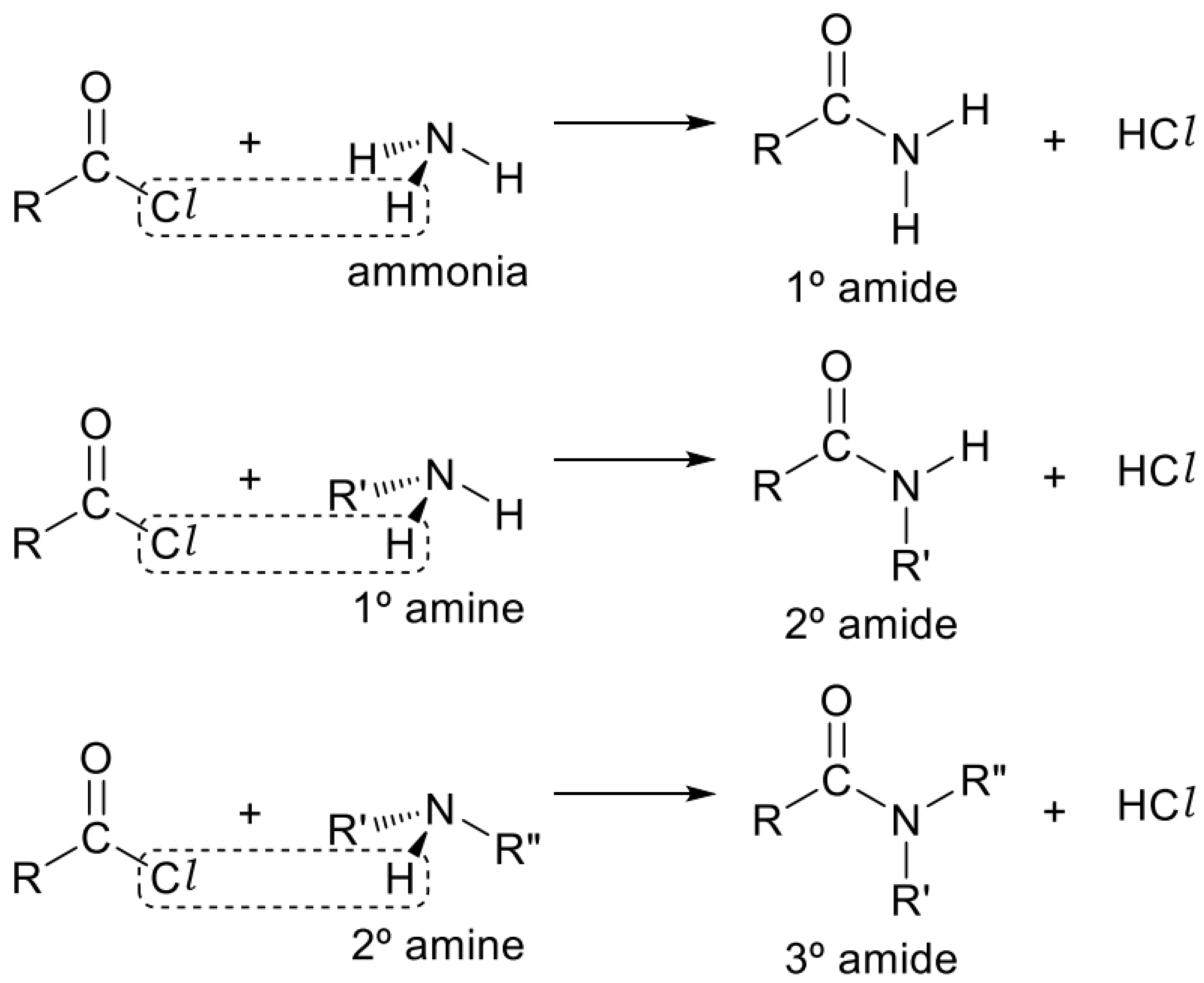


3 Preparation of Amides

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

3.1 Nucleophilic substitution/ condensation with acyl chloride

- Amides can be obtained from the nucleophilic (acyl) substitution of acyl chloride with ammonia, primary amines or secondary amines at room temperature. See Amines Section 4.3.



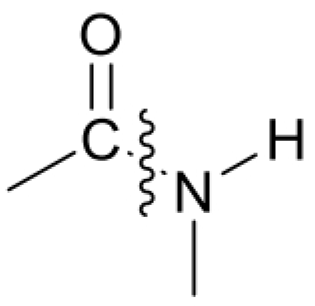
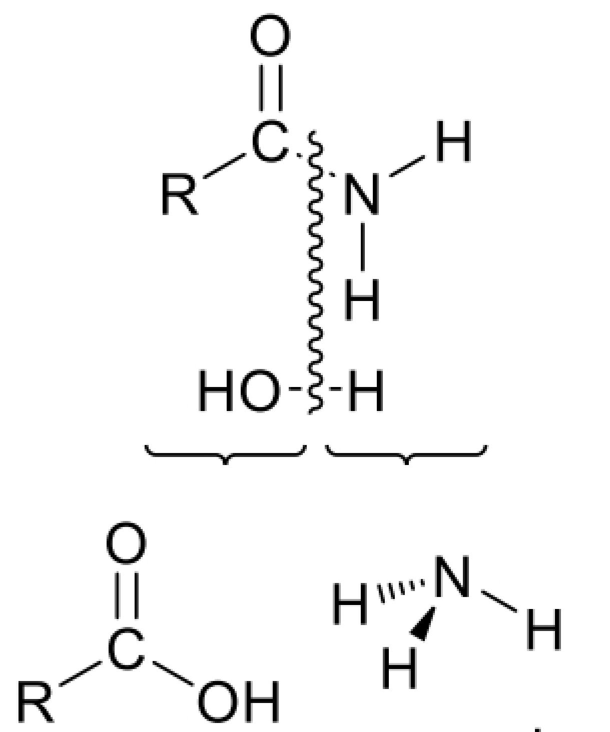
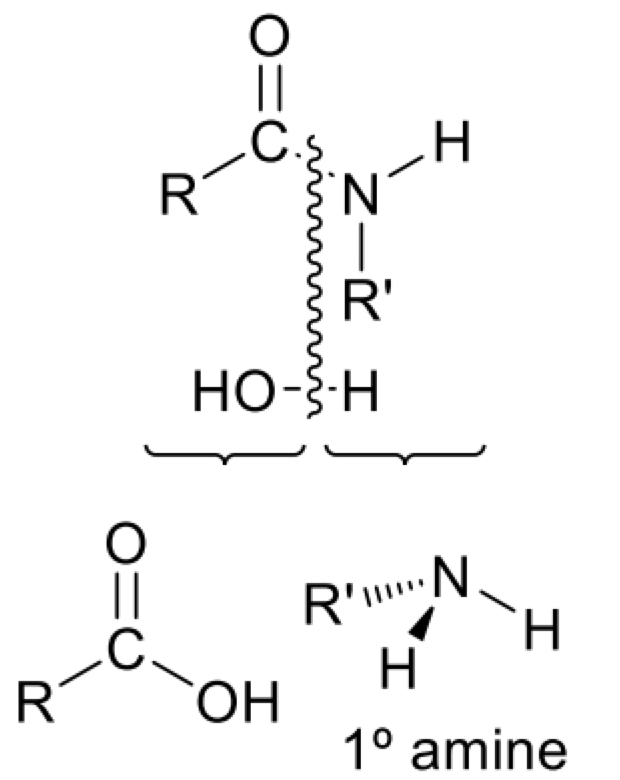
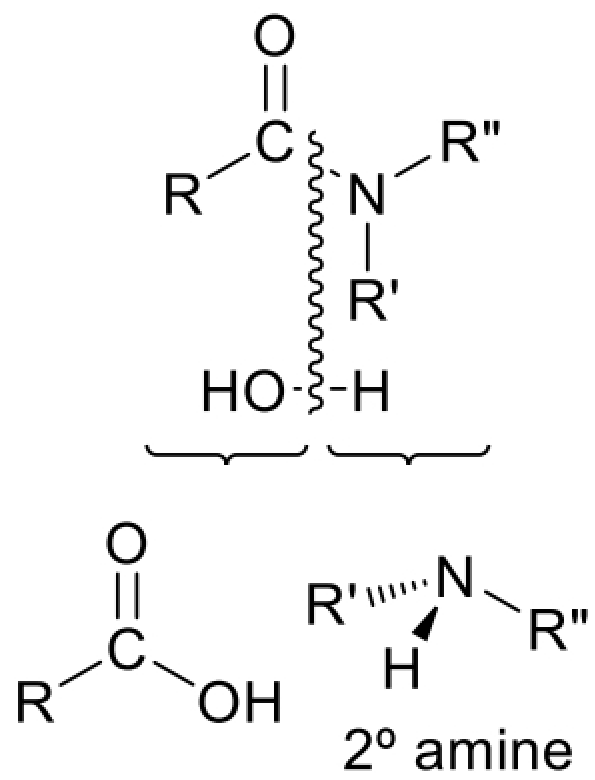
- 3º amine does not react with acyl chloride (No H atom bonded to N)

4 Reactions of Amides

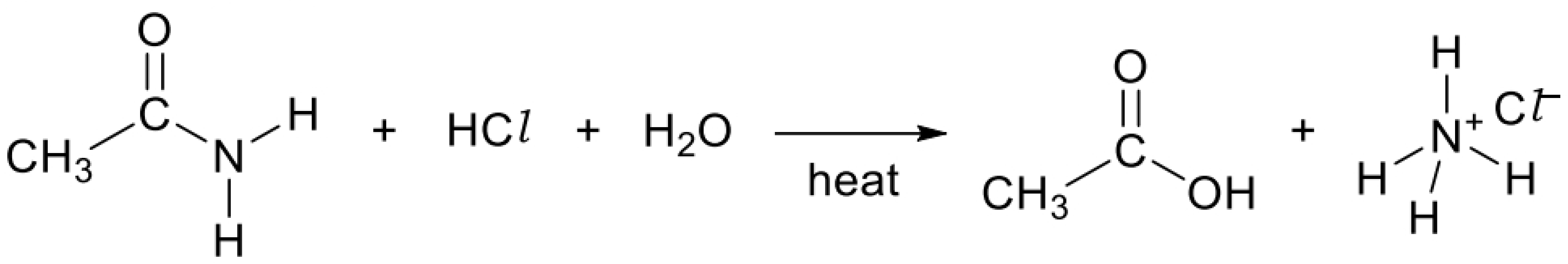
LO (h) describe the chemistry of amides, exemplified by the following reactions:
(i) hydrolysis on treatment with aqueous alkali or acid
(ii) reduction to amines with lithium aluminium hydride

4.1 Hydrolysis

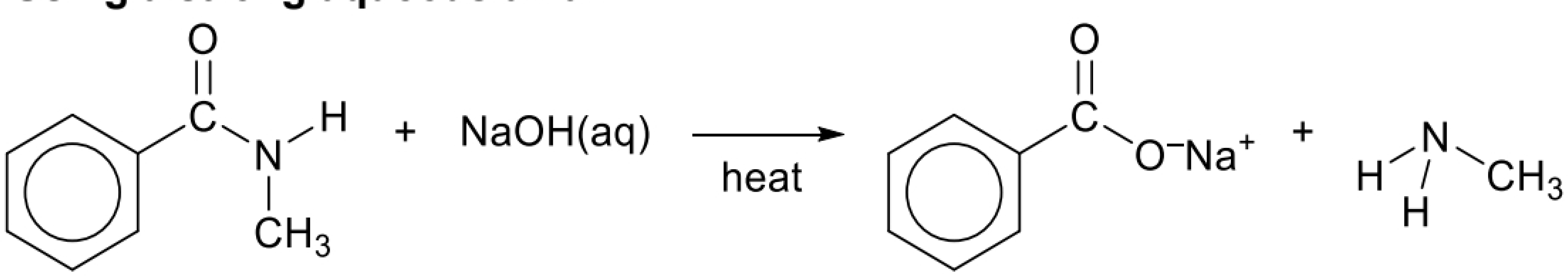
- Amides can undergo hydrolysis when heated in a strong acid or strong alkali. The C–N bond in the amide group is cleaved during hydrolysis.

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

(a) Using a strong aqueous acid



(b) Using a strong aqueous alkali

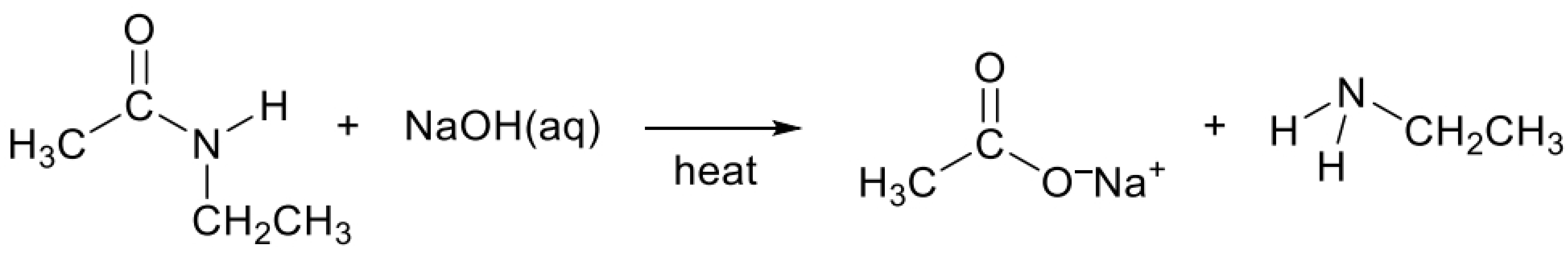


Reagents and condition: HC*l* (aq) or H_2SO_4(aq), heat
OR NaOH (aq) or KOH (aq), heat

Type of reaction: acidic hydrolysis OR alkaline/base hydrolysis

- Heating is required to hydrolyse amides.
- The alkaline/base hydrolysis reaction can be used as a **distinguishing test** for amides.

Example:

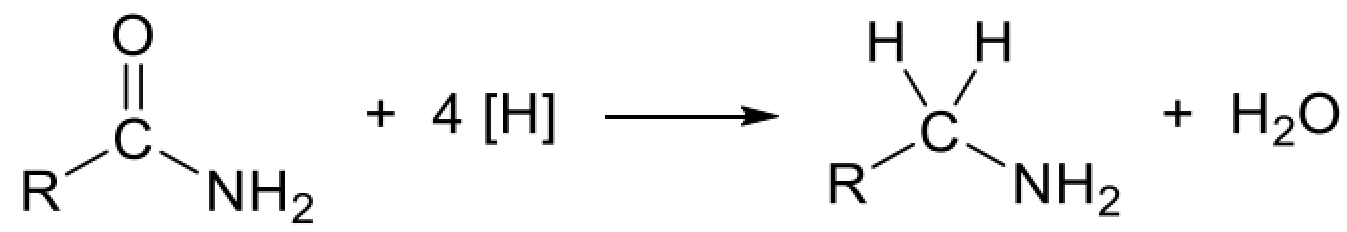


Observations: Pungent gas, $CH_3CH_2NH_2$, evolves that turns moist red litmus paper blue.

This test works if amines produced contain 5 carbons or less as these amines are volatile enough to be vapourised by the heat.

4.2 Reduction

- Amides can undergo **reduction** to form amines using $LiAlH_4$ in dry ether at r.t.
- The C=O group in the amide is reduced to a methylene group, $–CH_2–$.



primary amide **primary amine**

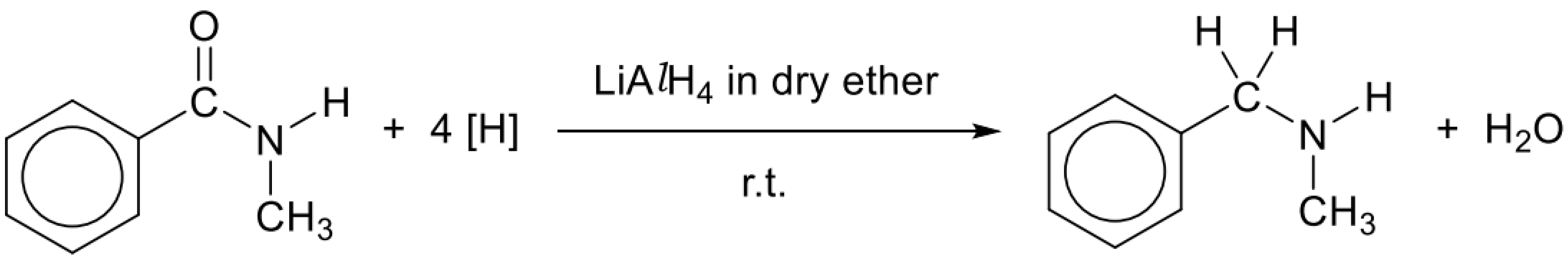
Reagents and conditions: $LiAlH_4$ in dry ether, r.t.

Type of reaction: Reduction

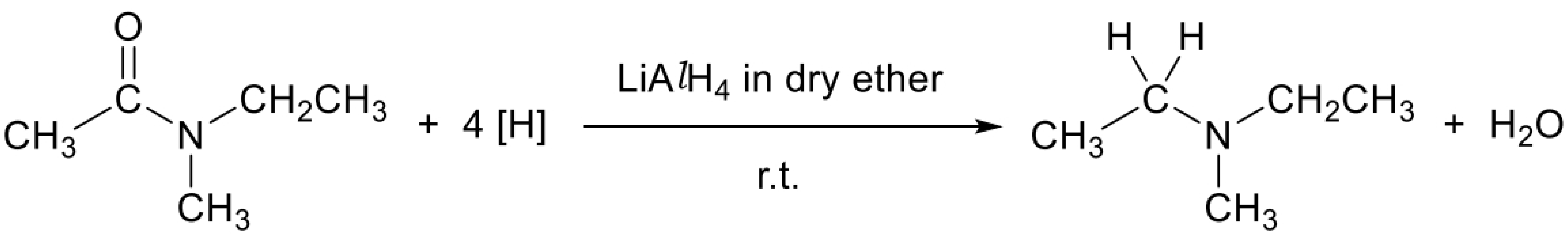
Example: Reduction of ethanamide

$$CH_3CONH_2 + 4\,[H] \xrightarrow[\text{r.t.}]{LiAlH_4 \text{ in dry ether}} CH_3CH_2NH_2 + H_2O$$

- Secondary amides and tertiary amides are reduced to secondary and tertiary amines respectively.



2° amide 2° amine



3° amide 3° amine

- Catalytic hydrogenation (H_2, Ni) and $NaBH_4$ **cannot** be used to reduce amides.

Checkpoint for Amides:

Section 1: Introduction
- To interpret and use the nomenclature, general formulae and displayed formulae of amides.
- To describe and explain the physical properties (boiling and melting point, solubility) of amides.

Section 2: Lack of Basicity
- To explain that an amide is neutral due to the delocalisation of the lone pair of electrons on N atom into the π-electron cloud of the adjacent C=O bond.

Section 3: Preparation of Amides
- To describe how amides can be formed from the nucleophilic (acyl) substitution of acyl chloride with ammonia, primary amines, or secondary amines at room temperature (condensation reaction).

Section 4: Reactions of Amides
- To describe the following reactions of amides:
  - hydrolysis using a strong acid or alkali
  - reduction to form amine

AMINO ACIDS

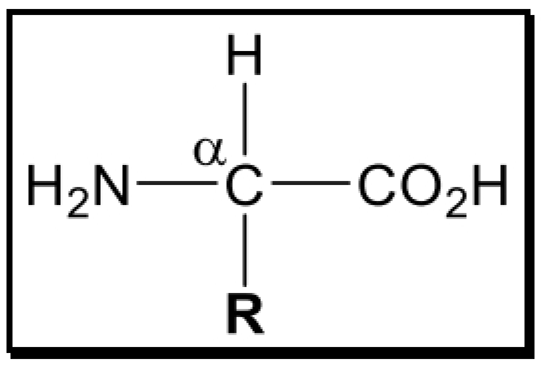
1 Introduction

- Amino acids are 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.

1.1 α-amino acids

- An amino acid contains at least 1 carboxylic acid group ($–CO_2H$) and 1 amino group ($–NH_2$).
- The C atom to which the $–CO_2H$ group is bonded to is called **α-carbon**.
- *Definition of α-amino acid*: **An amino-acid where both the $–NH_2$ and the $–CO_2H$ group are directly bonded to the same C atom** (α-carbon).

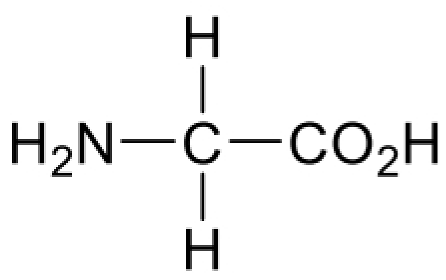
General formula of **α-amino acids:**



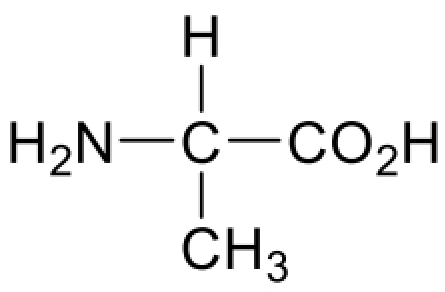
- The side chain, **R**, varies considerably in the 20 naturally occurring α-amino acids. The composition of the **R** group confers an individual set of properties to each amino acid, which affects the properties of the proteins in which they are found (see Table 1).
  - **Acidic** amino acid : **R** group contains **one or more carboxyl group**, $–CO_2H$
  - **Basic** amino acid : **R** group contains **one or more amino group**, $–NH_2$
  - **Neutral** amino acid : **R** group contains **neutral group(s)** (neutral groups could be polar or non-polar)

1.2 Nomenclature of amino acids

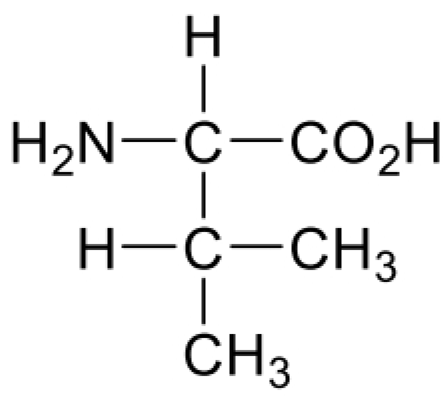
- Amino acids are named as amino derivatives of carboxylic acids. However, they are still often referred to using their common names (in brackets).



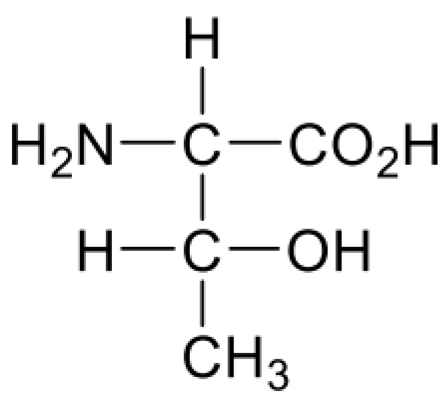
2-aminoethanoic acid (glycine)



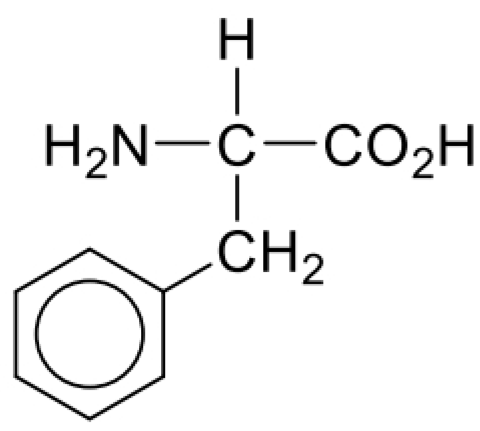
2-aminopropanoic acid (alanine)



2-amino-3-methylbutanoic acid (valine)

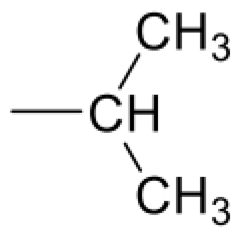
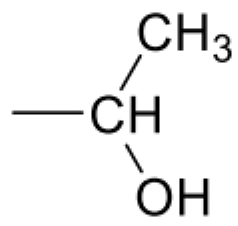
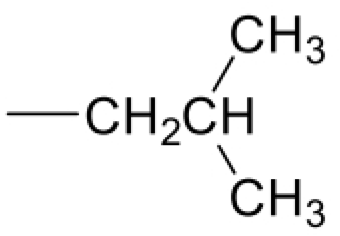
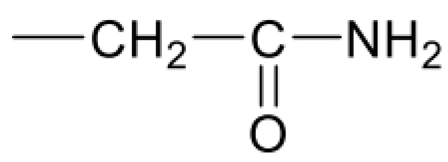
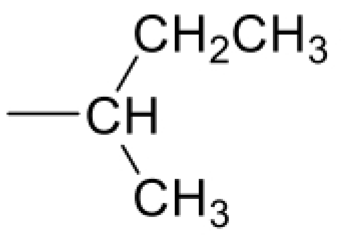
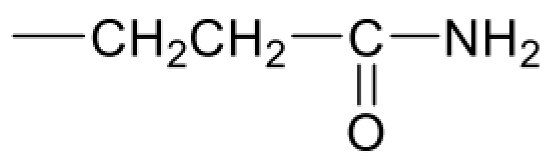
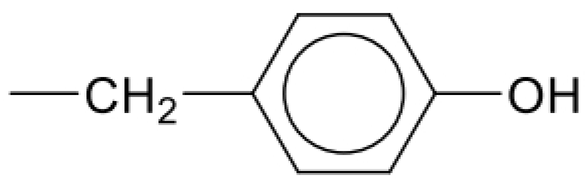
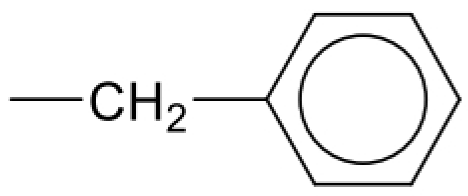
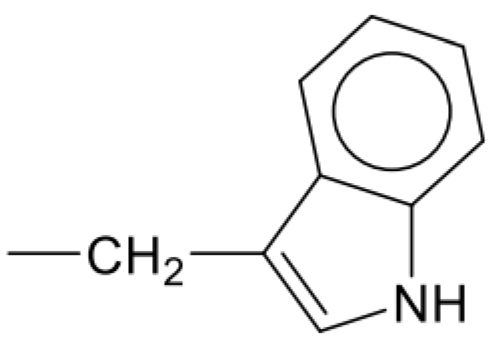
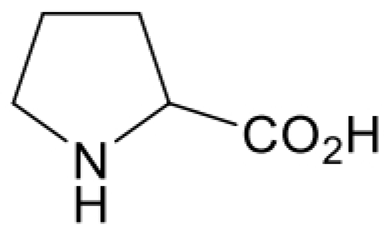
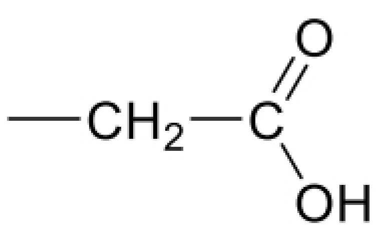
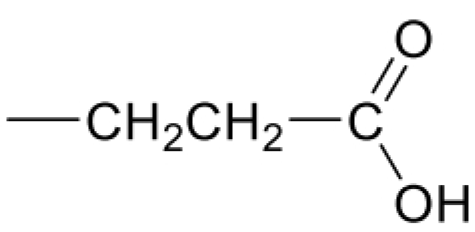
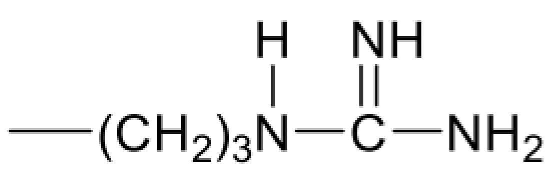
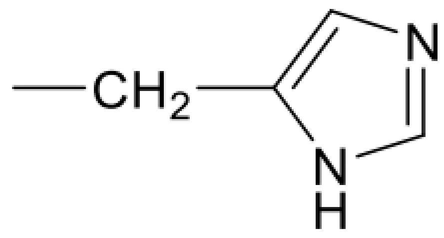


2-amino-3-hydroxybutanoic acid (threonine)



2-amino-3-phenylpropanoic acid (phenylalanine)

Table 1 α-Amino acids

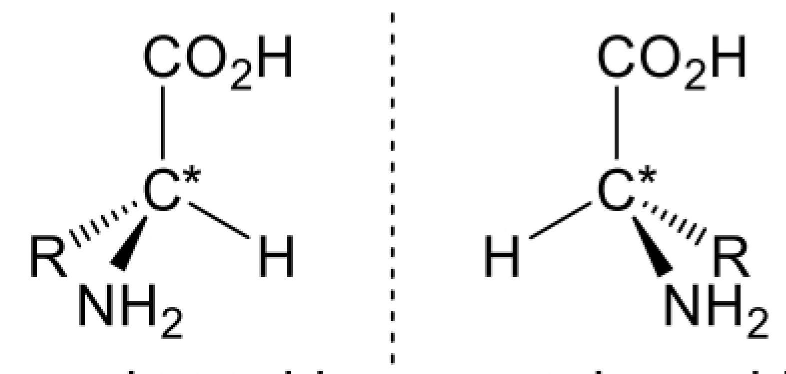
amino acid	abbre	R	amino acid	abbre	R
non-polar neutral R group			**polar neutral R** group		
glycine	gly	$-H$	serine	ser	$-CH_2OH$
alanine	ala	$-CH_3$	cysteine	cys	$-CH_2SH$
valine	val		threonine	thr	
leucine	leu		asparagine	asn	
isoleucine	ile		glutamine	gln	
methionine	met	$-CH_2CH_2-S-CH_3$	tyrosine	tyr	
phenylalanine	phe				
tryptophan	trp				
proline*	pro				
acidic R group			**basic R** group		
aspartic acid	asp		lysine	lys	$-CH_2CH_2CH_2CH_2NH_2$
glutamic acid	glu		arginine	arg	
			histidine	his	

* The full structure of proline is shown as it is the only amino acid that possesses a secondary amine for its amino group.

2 Physical Properties of Amino Acids

2.1 Optical activity

- All α-amino acids found in our bodies have at least 1 **chiral C centre** (except aminoethanoic acid (glycine) where R = H) with no plane of symmetry, thereby exhibiting **enantiomerism**.



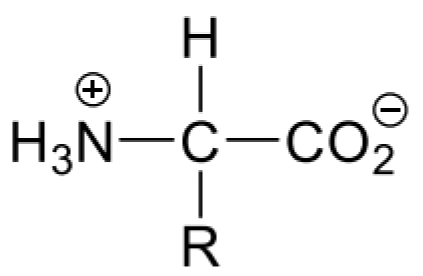
L-amino acid D-amino acid

- α-amino acids (except glycine) that are obtained from natural sources usually consist purely of one enantiomeric form (the L-form) thus it will exhibit optical activity (or is said to be optically active).
- However, α-amino acids synthesised in the laboratory are usually racemic mixtures and hence it **does not** exhibit optical activity (or is said to be optically inactive).

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

2.2 Formation of zwitterion

- Amino acids readily exist as **electrically neutral compounds that contain unit electrical charges of opposite sign** called ***zwitterions***.



zwitterion

How are zwitterions formed?

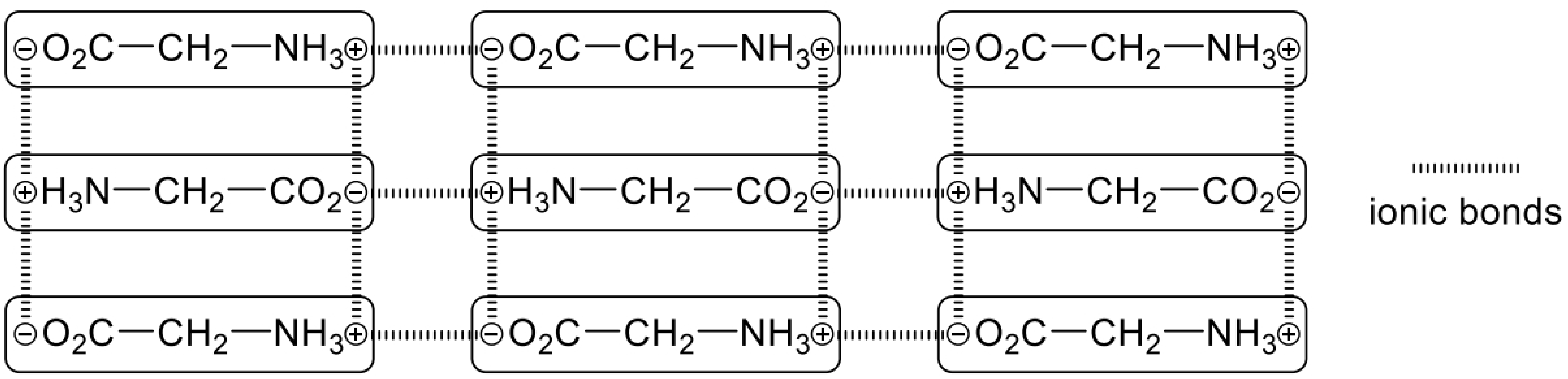
- The **zwitterion** is formed as a result of an **intramolecular acid-base reaction**, in which the **most acidic group** (usually a carboxyl group) **donates a proton to the most basic group** (usually an amino group).

Physical properties due to zwitterionic nature of amino acids

(a) Amino acids exist as crystalline solids with high melting points (above 200 °C)

Reason: **High amount of energy** is required to overcome the **strong electrostatic forces of attraction between the oppositely charged ends of neighbouring zwitterions.**

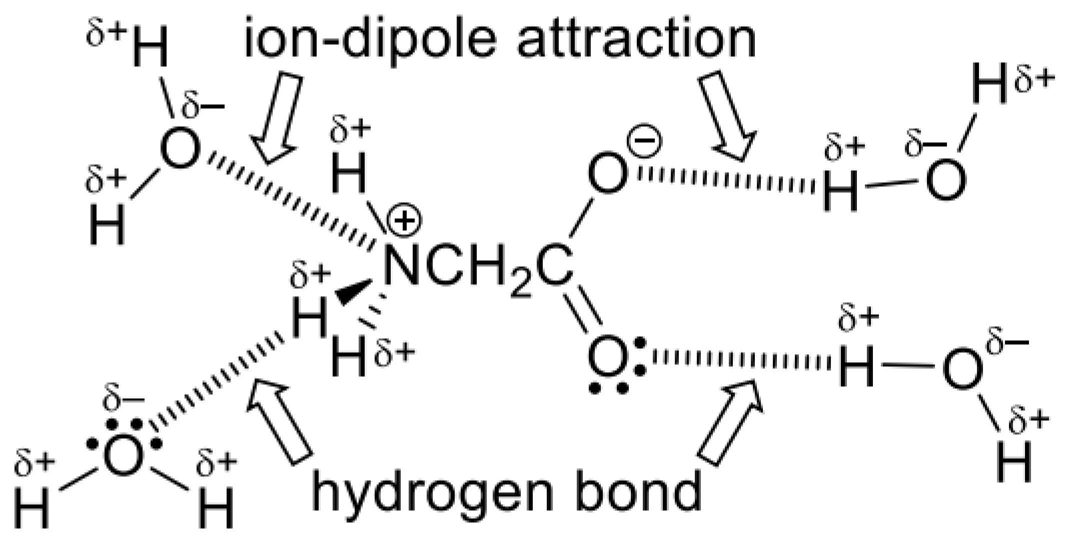
Simplified structure of solid aminoethanoic acid:



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

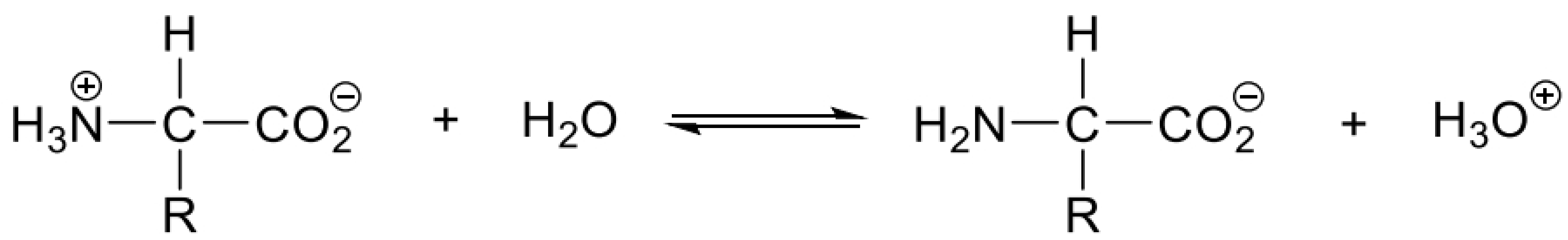
Reason: The charged ends of the zwitterions can form strong **ion-dipole interactions with the water molecules** which results in the **release of sufficient energy** to overcome the **ionic bonds between the zwitterions for hydration**.

Amino acids can also form **hydrogen bonds** with water molecules.



(c) Amino acids are amphoteric in nature $\Rightarrow$ can act as both acids and bases

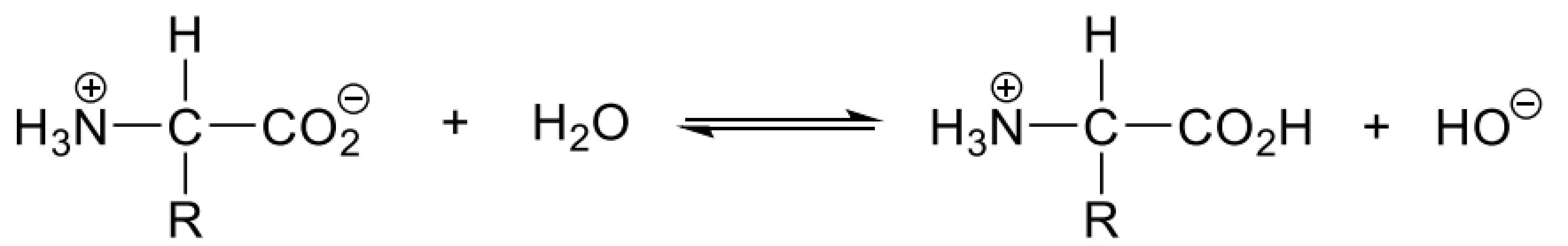
As an acid: The **$-NH_3^+$** group is responsible for its acidic properties.



$pK_a = 8.80 - 10.60$

acid (proton donor) **conjugate base**

As a base: The **$-CO_2^-$** group is responsible for its basic properties.



$pK_b = 11.17 - 12.18$

base (proton acceptor) **conjugate acid**

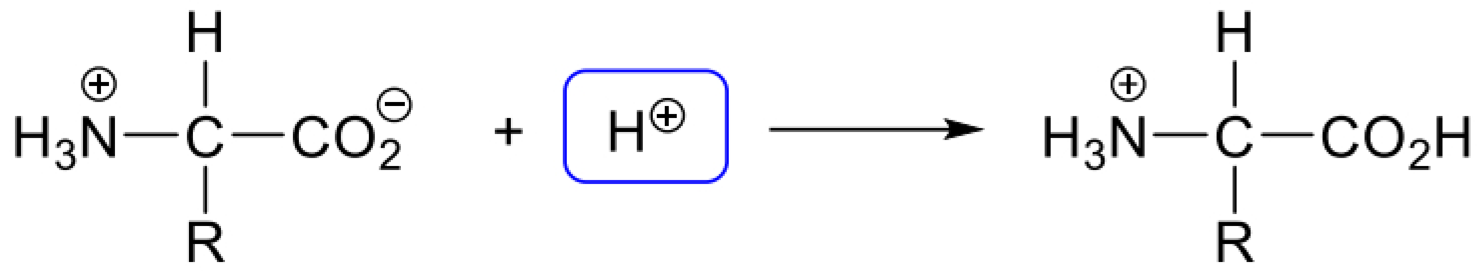
- The α-NH_3^+ group of amino acids are much *less* acidic than most carboxylic acids (since pK_a of $-NH_3^+$ > pK_a of $-CO_2H$, e.g. $pK_a(CH_3CO_2H) = 4.76$)
  - If side chain **R** contains acidic functional group, e.g. aspartic and glutamic acid, the aqueous solution will be **acidic** (see Table 1).
- The α-CO_2^- group of amino acids are much *less* basic than most amines (since pK_b of $-CO_2^-$ > pK_b of $-NH_2$, e.g. $pK_b(CH_3NH_2) = 3.36$)
  - If side chain **R** contains basic functional group, e.g. lysine and histidine, the aqueous solution will be **basic** (see Table 1).
- "Neutral" amino acids that does not possess any acidic or basic functional group in the side chain **R**, are thus **weakly acidic** (refer to Section 2.3) since there will be a slight excess of H^+ resulting from dissociation of the α-NH_3^+ than OH^- from the α-CO_2^- group.

  Consider a 1.0 mol dm^{-3} solution of the amino acid in water,

  $\left[H^+\right]$ from the least acidic $\alpha\text{-}NH_3^+ \approx \sqrt{10^{-10.60} \times 1.0} = 5.0 \times 10^{-6}$ mol dm^{-3}

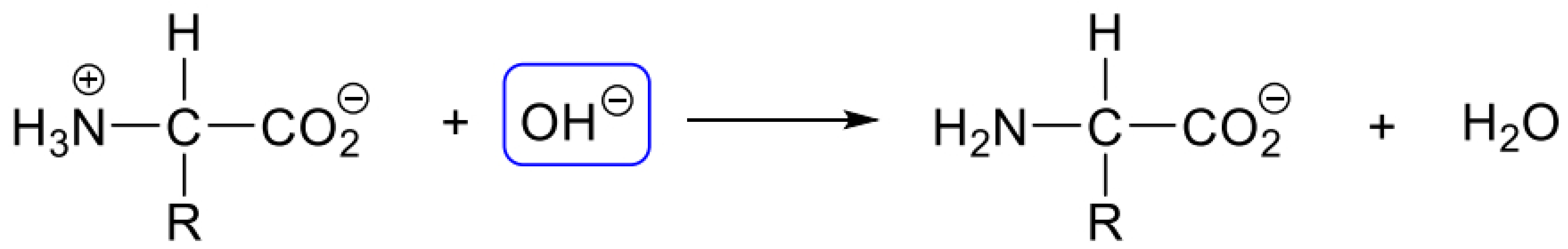
  $\left[OH^-\right]$ from the most basic $\alpha\text{-}CO_2^- \approx \sqrt{10^{-11.17} \times 1.0} = 2.6 \times 10^{-6}$ mol dm^{-3}

- Amino acids (and zwitterions) can act as a buffer solution.
  - On addition of **small amount of H^+**:



H^+ is removed and hence $[H^+]$ does not change much and pH remains fairly constant.

  - On addition of **small amount of OH^-**:



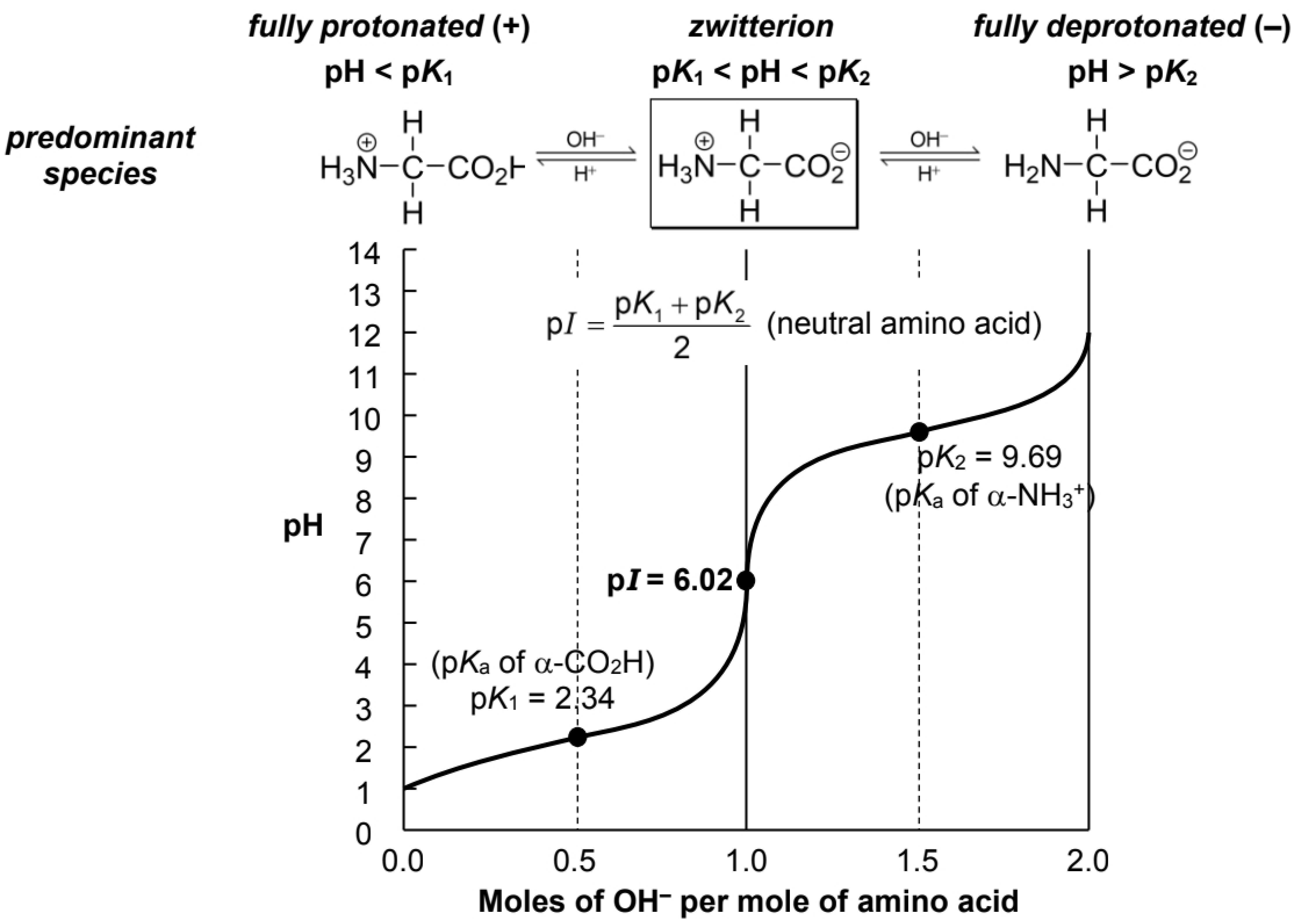
OH^- is removed and hence $[OH^-]$ does not change much and pH remains fairly constant.

2.3 Isoelectric point (p*I*) of an amino acid (for enrichment)

- The **pH at which the amino acid** exists predominantly in the form of its **zwitterions** is called the **isoelectric point (p*I*).** At this pH, the amino acid will not migrate under the influence of an electric field as it has a **net charge of zero**.
- Every amino acid has a characteristic isoelectric point. The difference in isoelectric point can be used to separate amino acids by a technique called **electrophoresis**, in which an amino acid will move towards the cathode or anode depending on the pH of the solution in which the amino acids are dissolved in.

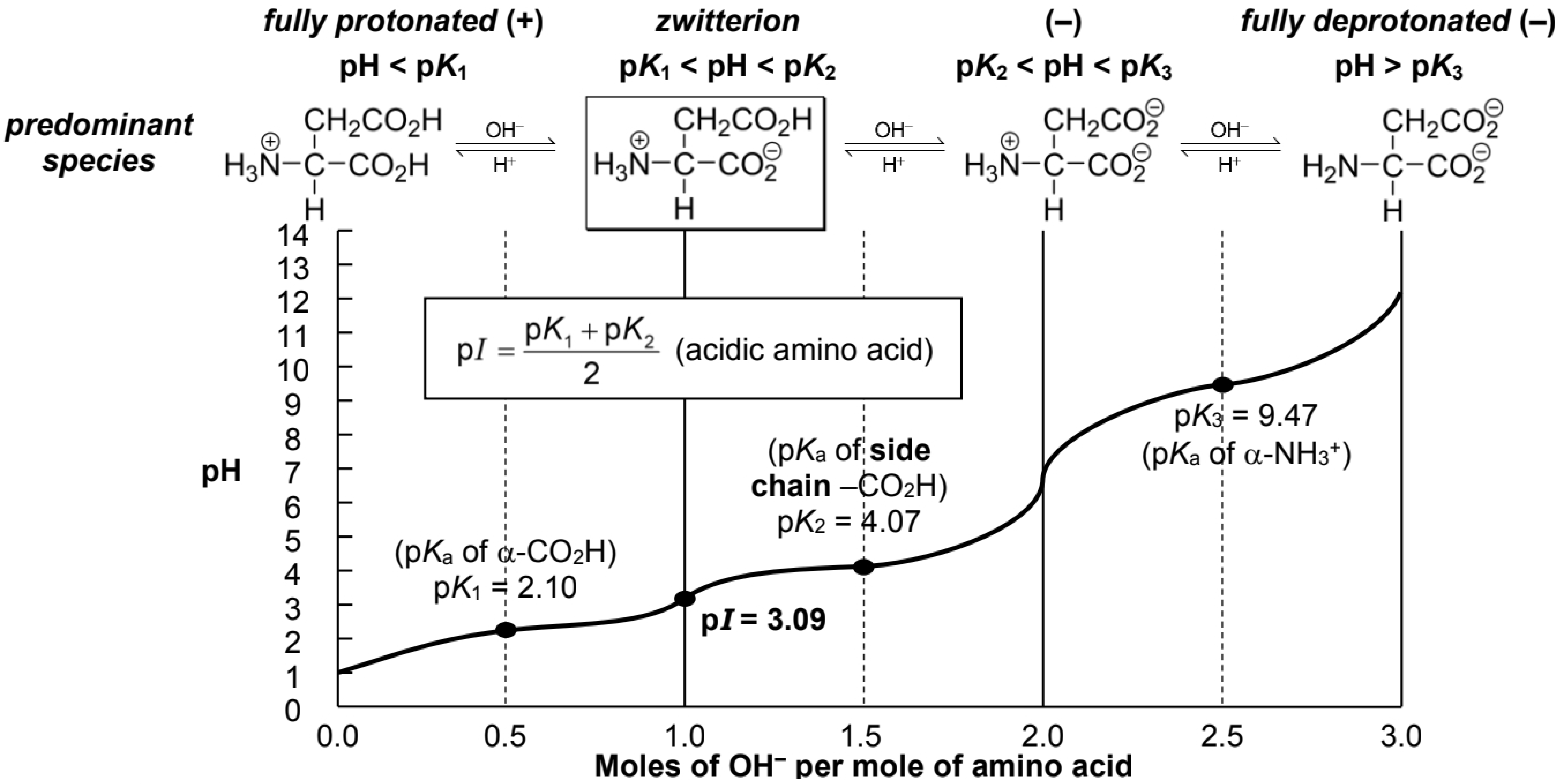
Neutral amino acids

- Fully protonated neutral amino acid is a **dibasic** acid as it has 2 acidic groups; **α-CO_2H** and **α-NH_3^+.**



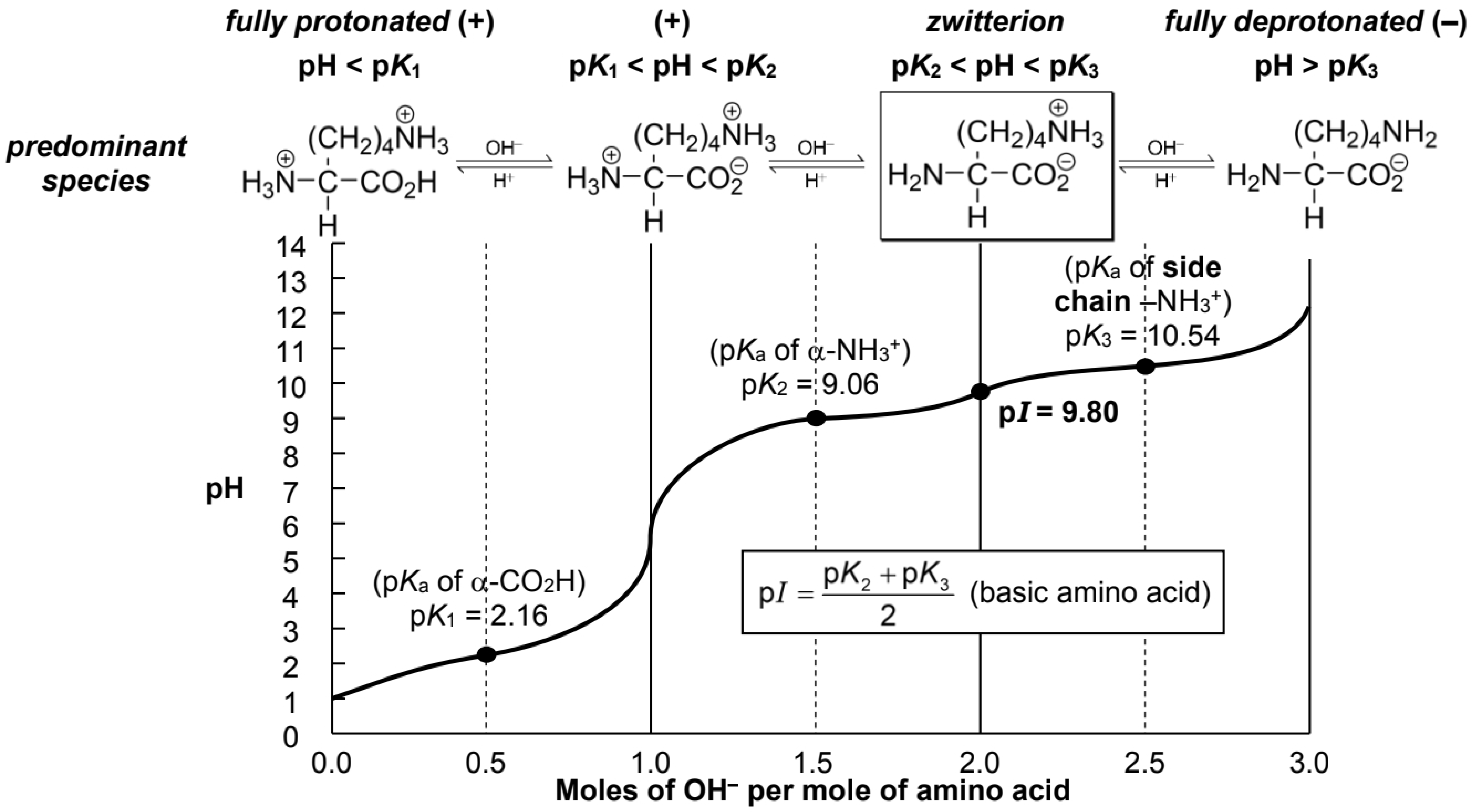
Acidic amino acid

- Fully protonated acidic amino acid has **3** acidic groups: **α-CO_2H, side chain-CO_2H and α-NH_3^+.**
- CO_2H is **more acidic** than **NH_3^+** due to **resonance stabilisation** of the CO_2^- produced.
- α-CO_2H is **more acidic** than the side chain-CO_2H as it is closer to the **α-NH_3^+** which exerts an **electron-withdrawing inductive effect**, leading to further **dispersal** of **negative charge** on the α-CO_2^- produced, thus stabilising it.



Basic amino acid

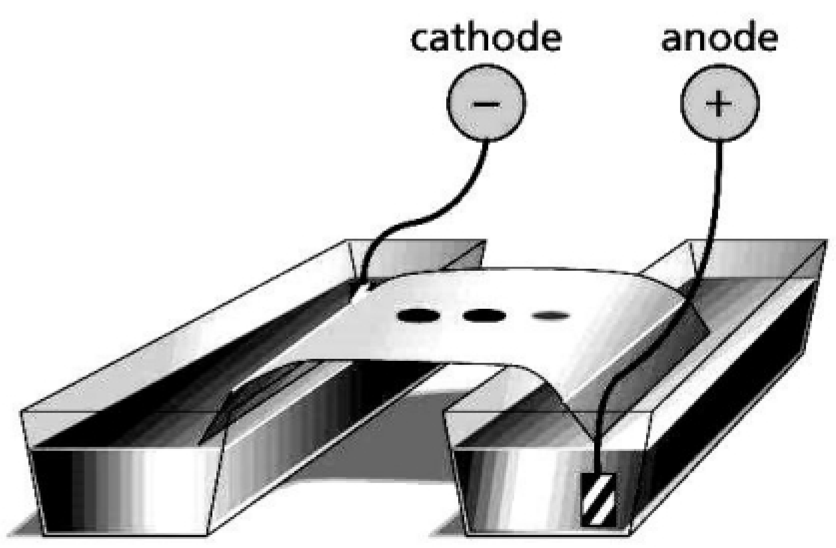
- Fully protonated basic amino acid has **3** acidic groups: **α-CO_2H, α-NH_3^+ and side chain-NH_3^+**
- CO_2H is **more acidic** than **NH_3^+** due to **resonance stabilisation** of the CO_2^- produced.
- **α-NH_3^+** group is **more acidic** than side-chain-**NH_3^+** as it is closer to the **α-CO_2^-** group which exerts an **electron-withdrawing inductive effect**, leading to intensification of the **positive charge** on the **α-NH_3^+**, thus destabilising it.

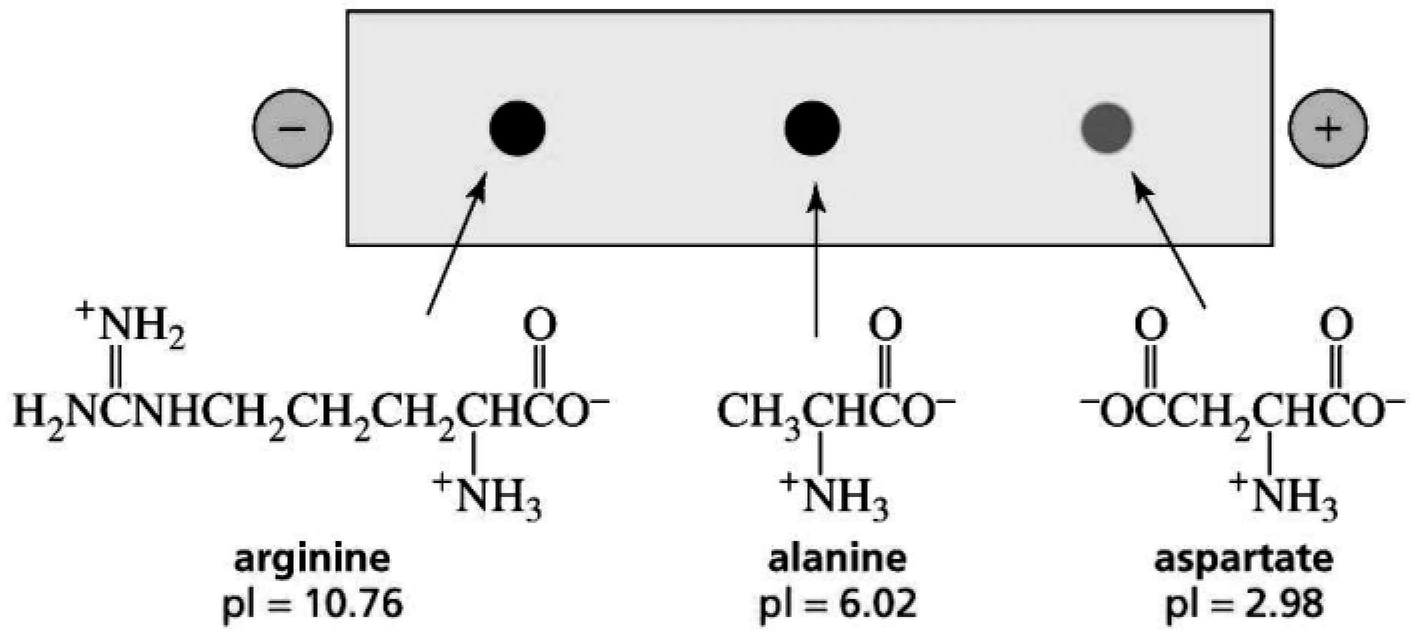


For Information Only

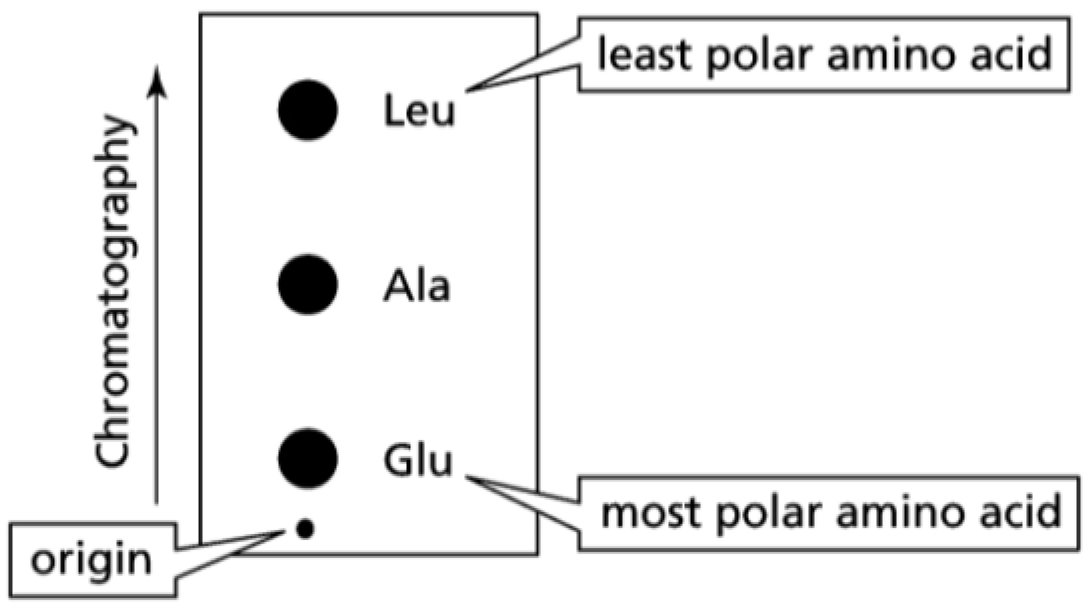
Separation of Amino Acids

- Amino acids can be separated according to their pI values using **electrophoresis**.
- When pH of the electrophoresis buffer = pI of the amino acid, the amino acids will be in the zwitterionic form ⇒ **electrically neutral** ⇒ **does not migrate** under the electric field
- When pH of electrophoresis buffer < pI of the amino acid, the relatively more acidic environment will cause the zwitterion to be protonated ⇒ **positively charge** ⇒ migrate toward the **negative electrode** (cathode)
- When pH of electrophoresis buffer > pI of the amino acid, the relatively more basic environment will cause the zwitterion to be deprotonated ⇒ **negatively charge** ⇒ migrate toward the **positive electrode** (anode)
- 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

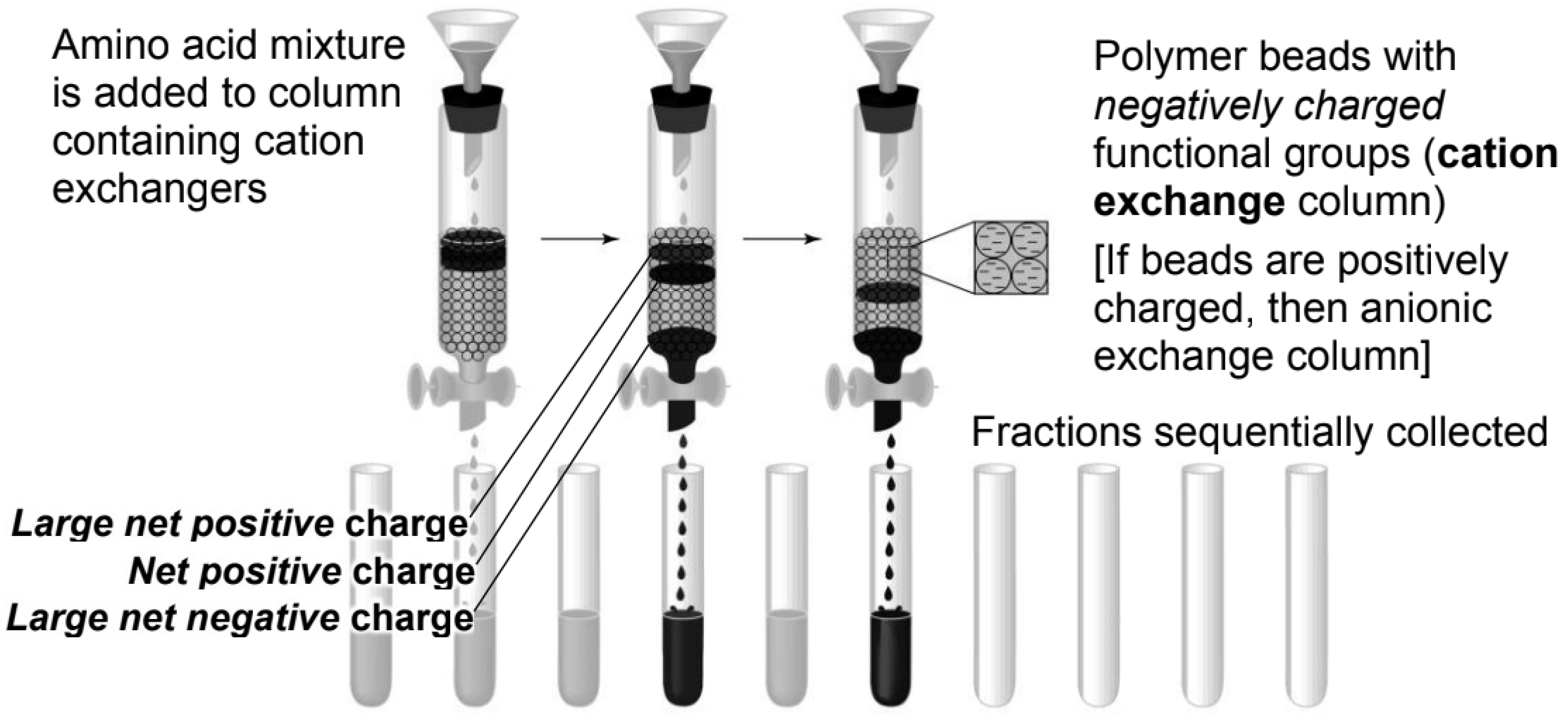




Amino acids can also be separated by **paper chromatography**. The different amino acids are separated based on different solubilities in a solvent as well as their molecular masses. Amino acids which are more soluble will move faster, and lighter amino acids will move faster than heavier amino acids.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



Ion exchange chromatography



Amino acids move through column at rates determined by their **net charge** at the pH used. With cation exchangers, amino acids with a *more negative net charge* move *faster* and elute earlier

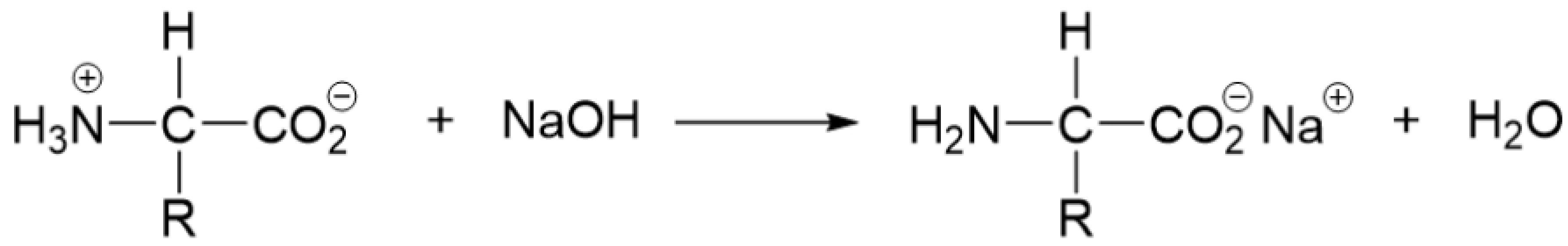
3 Reactions of Amino Acids

Due to the amphoteric nature of amino acids, they undergo **neutralisation** reactions at the respective $–CO_2^-$ or $–NH_3^+$ groups in the zwitterion form.

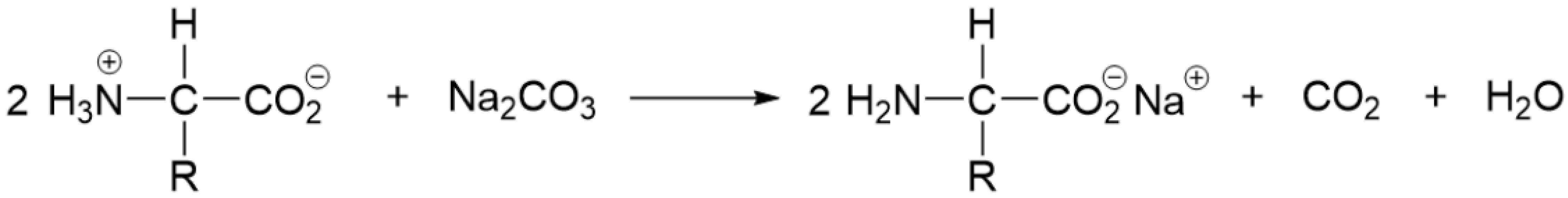
3.1 Reactions of the acidic group

Amino acids form **salts** with alkalis and carbonates due to reaction with the acidic **$–NH_3^+$ group**.

3.1.1 Reaction with alkalis



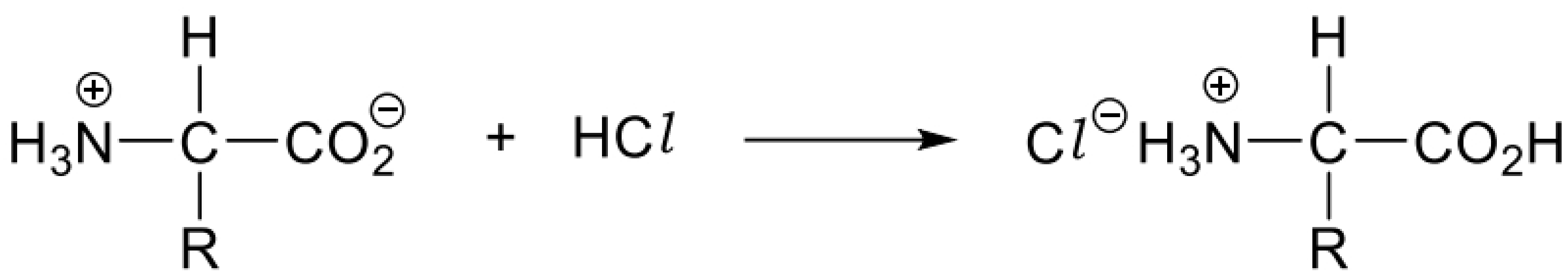
3.1.2 Reaction with carbonates (and hydrogencarbonates)



3.2 Reactions of the basic group

Amino acids form **salts** with acids due to reaction with the basic **$–CO_2^-$ group**.

3.2.1 Reaction with acids



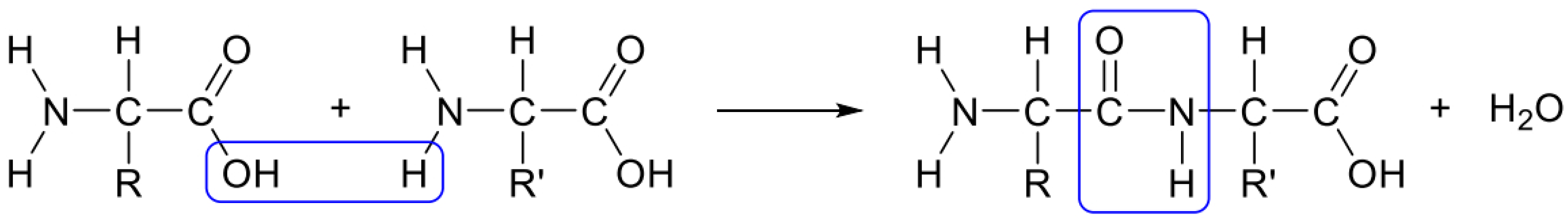
LO (j)	describe the formation of peptide (amide) bonds between α-amino acids, and hence explain protein formation

3.3 Formation of peptide (amide) bond between amino acids

- In the human body, amino acids are capable of undergoing **self-condensation** or **condensation reaction** with other amino acid molecules to form **peptide/ amide linkages**.

- The process involves the **elimination of a water molecule** between the **carboxylic acid group** of one amino acid molecule and the **amino group** of another molecule.

Example:

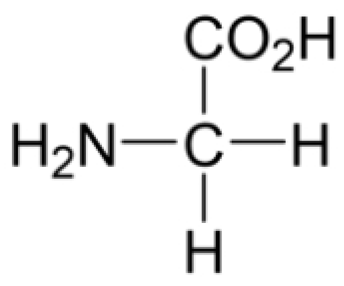


peptide bond

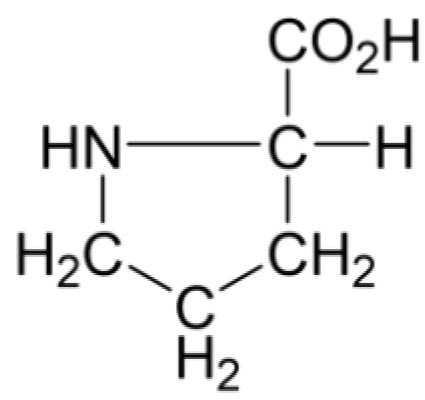
- The peptide formed may vary in terms of the **number of amino acids**:
  - 2 amino acids joined together: dipeptide (only 1 peptide bond)
  - 3 amino acids joined together: tripeptide (only 2 peptide bonds)
  - many amino acids joined together: polypeptide
- Polypeptides containing more than 40 amino acid residues are termed proteins.

Example 3A

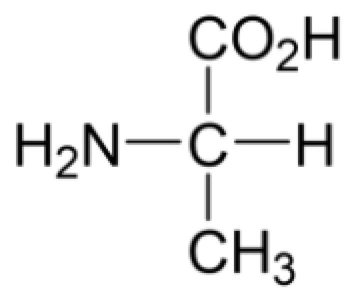
The formulae of three amino acids are given.



glycine
gly



proline
pro



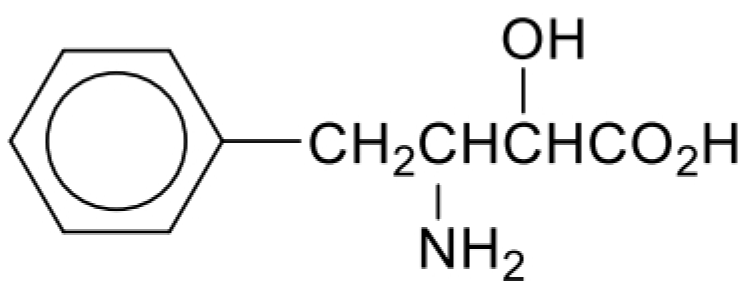
alanine
ala

Draw the displayed formula of the tripeptide, gly-pro-ala.

Note: *By convention, the free NH_2 group is on the left and the free CO_2H group is on the right of the peptide chain.*

Self Check 3A

An anti-HIV drug is made by combining **A**, which is an amino acid, with the amino acid, glycine, $H_2NCH_2CO_2H$. Draw the structures of two different compounds that could be formed when one molecule of A reacts with one molecule of glycine.



compound **A**

N2006/II/4(f)

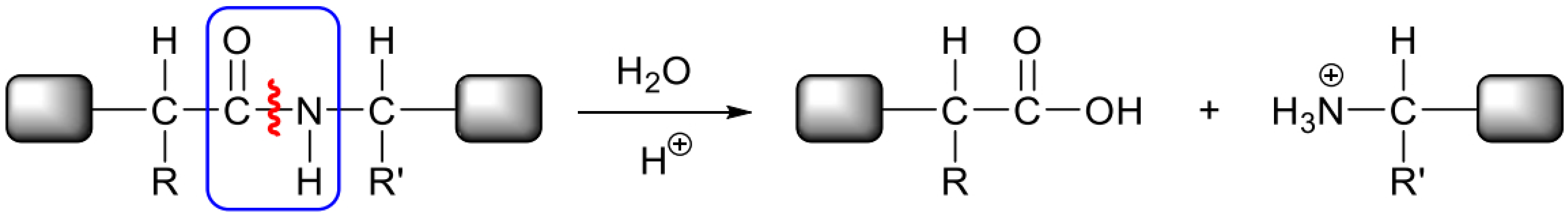
4 Hydrolysis of Peptide Bond

LO (k) describe the hydrolysis of proteins

- In protein, peptide bonds can be broken by **hydrolysis** in presence of suitable **enzymes**, or **prolonged heating** in **acidic or alkaline solution.**

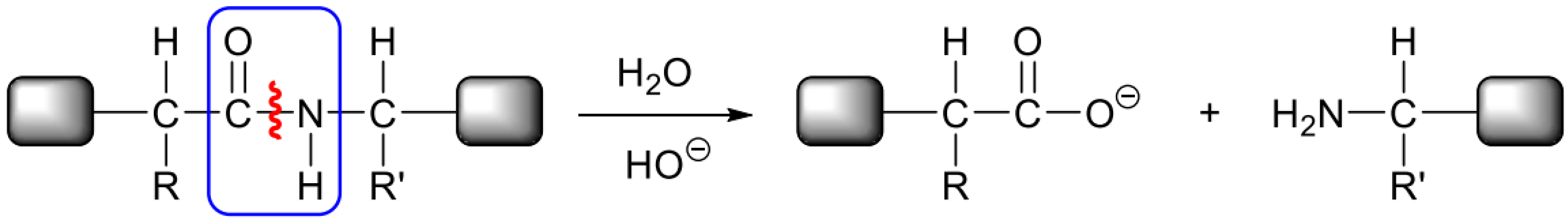
- There are 2 types of hydrolysis of peptide bonds – acidic hydrolysis or alkaline hydrolysis, depending on the reagent used.

(a) Using a strong aqueous acid – acidic hydrolysis



carboxylic acid **ammonium salt**

(b) Using a strong aqueous alkali – basic hydrolysis



carboxylate salt **amine**

Reagents and condition: HCl (aq) or H_2SO_4(aq)
OR NaOH (aq) or KOH (aq)

Type of reaction: acidic hydrolysis
OR alkaline/base hydrolysis

Self Check 4A

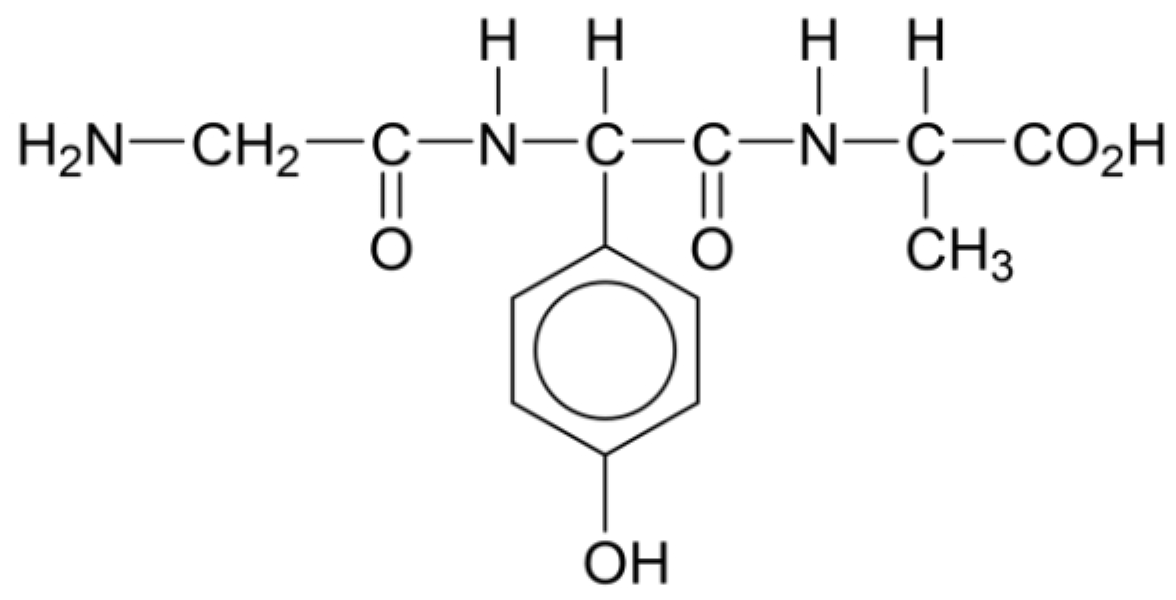
Upon hydrolysis, a tripeptide **X** forms the constituent amino acids according to the equation:

$$\mathbf{X} \xrightarrow{\text{hydrolysis}} \underset{(M_r=75)}{H_2NCH_2CO_2H} + \underset{(M_r=103)}{H_2NCH(CH_2CH_3)CO_2H} + \underset{(M_r=105)}{H_2NCH(CH_2OH)CO_2H}$$

What is the M_r of **X**?

Example 4A

1 The following shows a tripeptide.



Note: By convention, the free NH_2 group is on the left and the free CO_2H group is on the right of the peptide chain.

Give the structure of the product(s) when the tripeptide is
(a) placed in a ***cold*** aqueous solution of pH 2, and **(b)** ***boiled*** with sodium hydroxide.

Checkpoint for Amino Acids:

Section 1: Introduction

- To interpret and use the general formulae and displayed formulae of α-amino acids.

Section 2: Physical Properties of Amino Acids

- To describe optical activity of α-amino acids.
- To describe the acid/base properties of amino acids and the formation of zwitterions.

Section 3: Reactions of Amino Acids

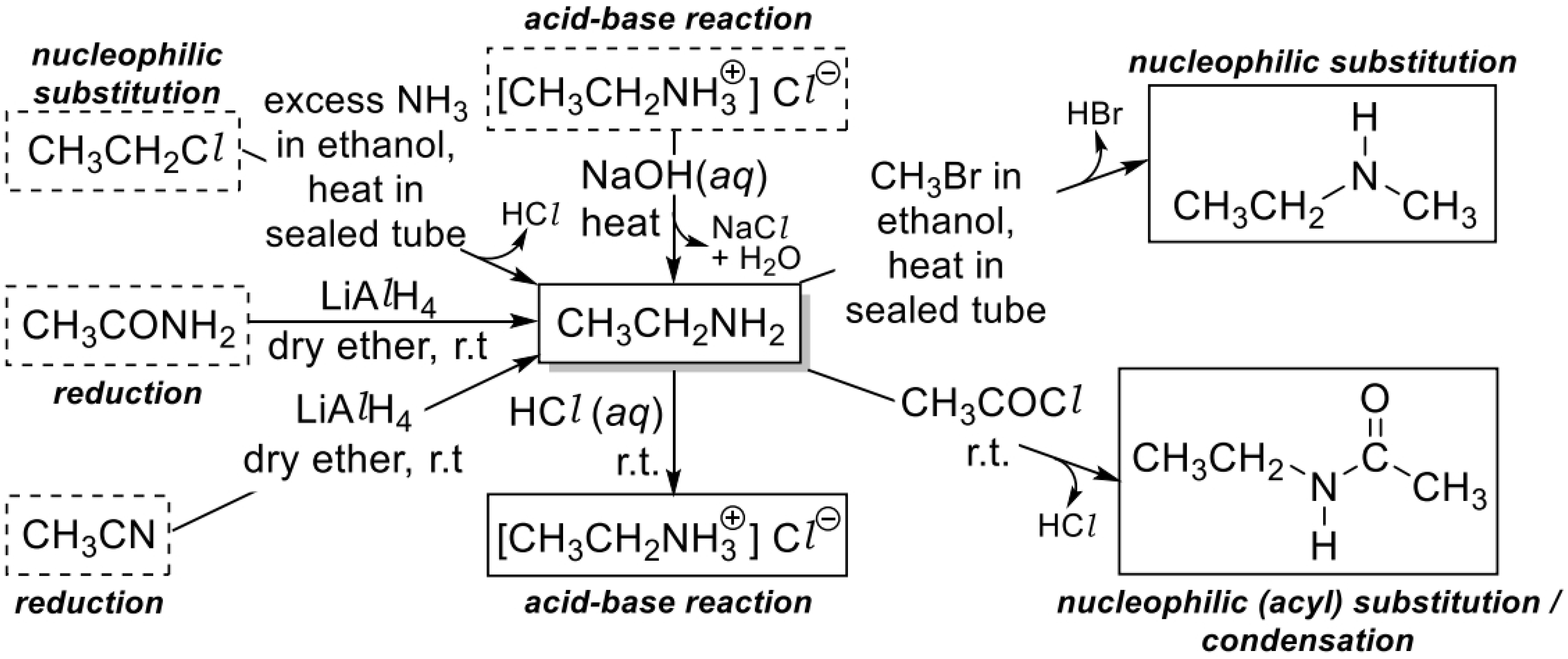
- To describe the following reactions of amino acids:
    - reactions of the acidic group
    - reactions of the basic group
    - formation of peptide bonds leading to the formation of proteins

Section 4: Hydrolysis of Peptide Bond

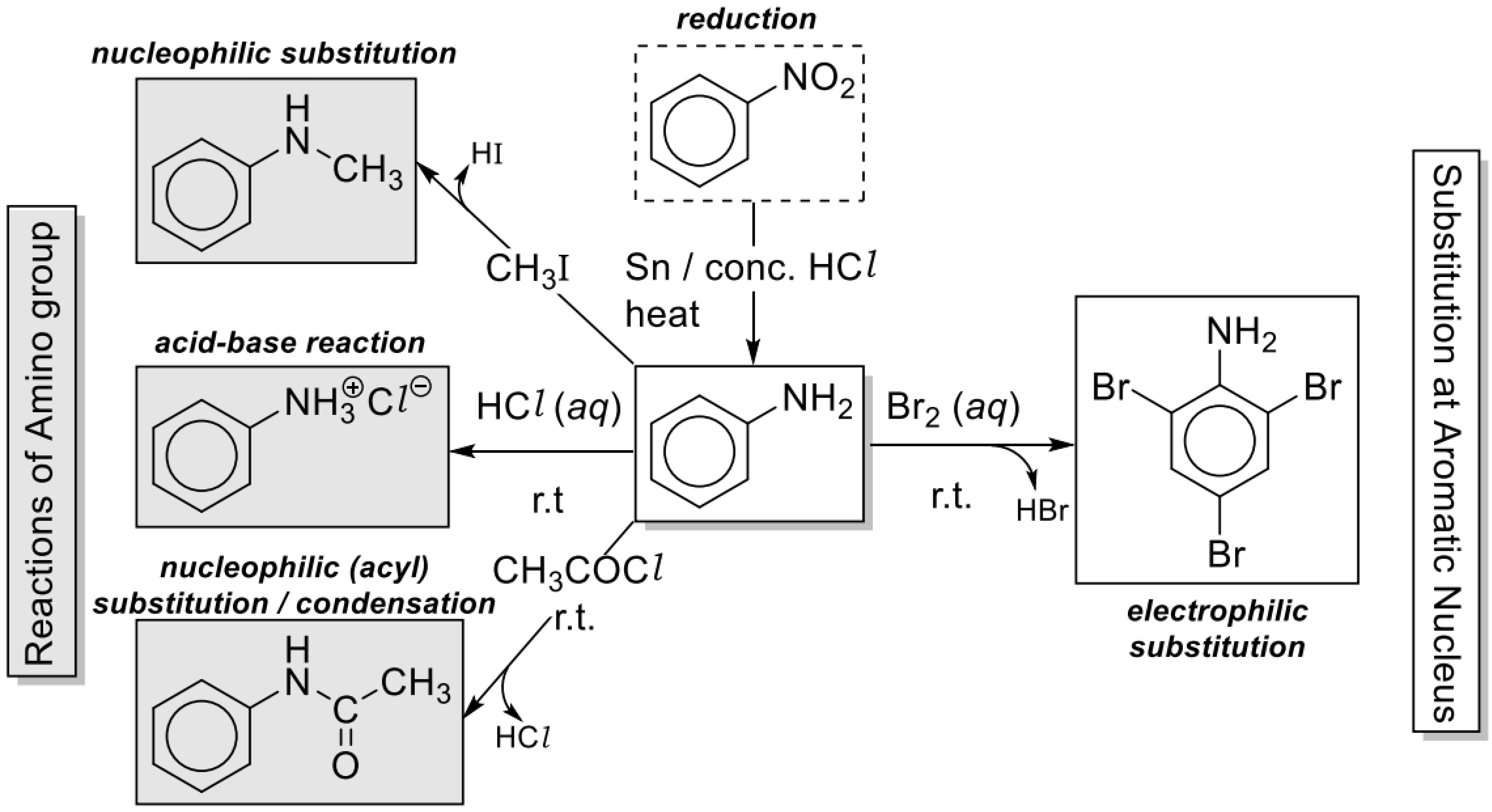
- To describe the hydrolysis of peptide bonds, either in acidic or basic conditions.

Summary

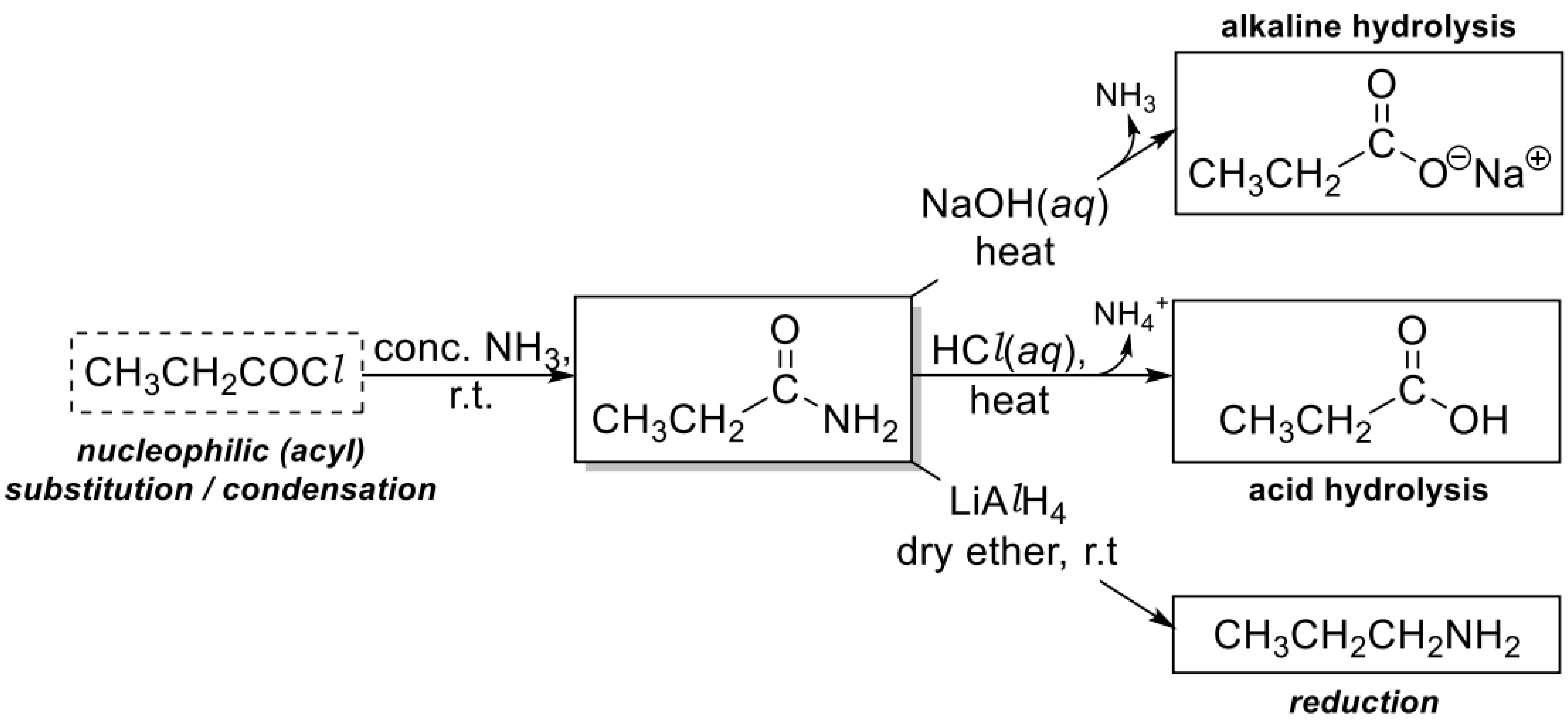
Aliphatic amines



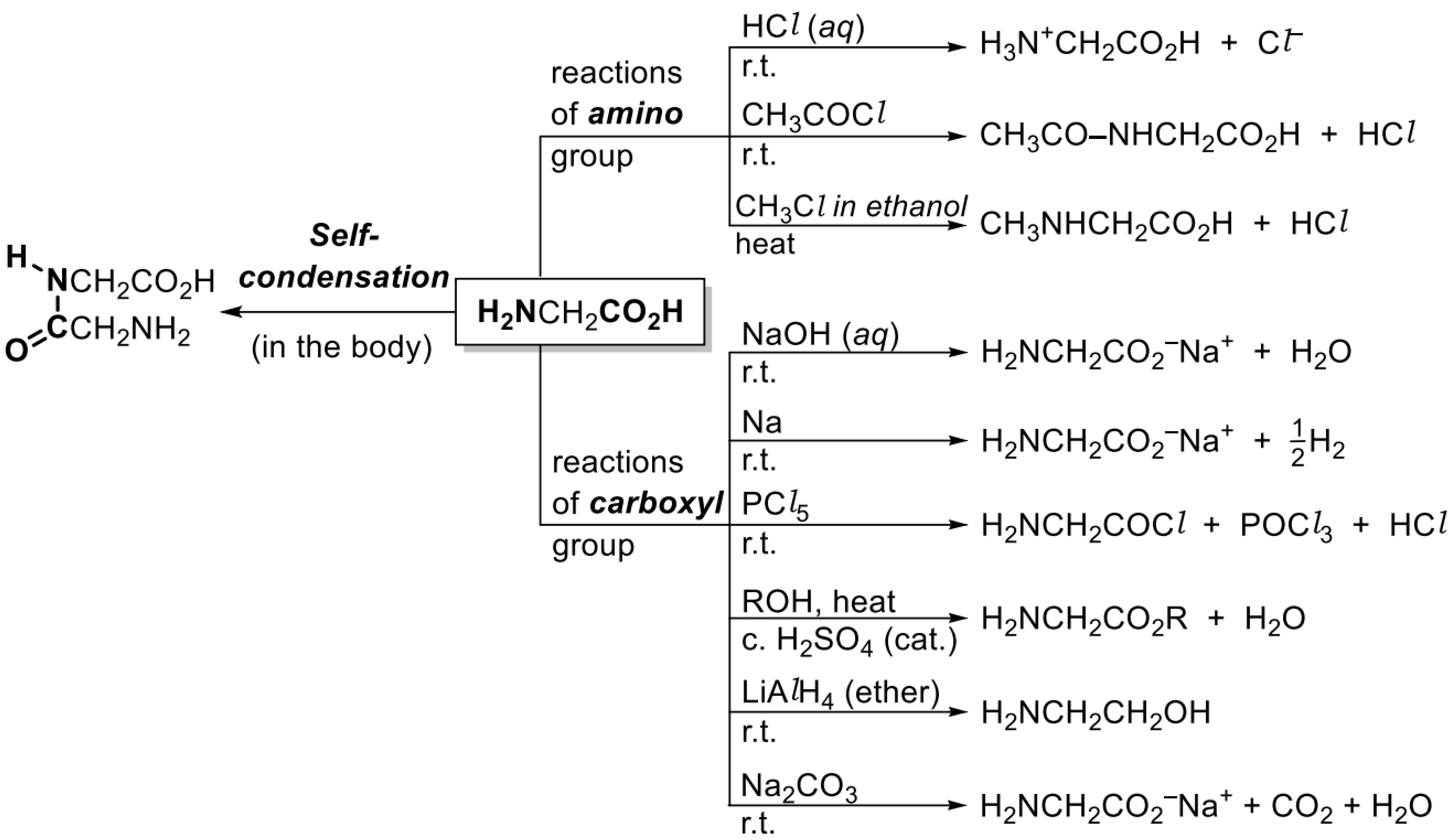
Phenylamine



Amides



Amino acids



Self Check Answers

Amines

1A **$(CH_3)_3CH$ < $(CH_3)_3N$ < $CH_3CH_2CH_2NH_2$**

compound	polarity	type of intermolecular forces of attraction
$(CH_3)_3N$	Polar	Permanent dipole – permanent dipole attraction
$(CH_3)_3CH$	Non-polar	Instantaneous dipole – induced dipole attraction
$CH_3CH_2CH_2NH_2$	Polar	Hydrogen bonding

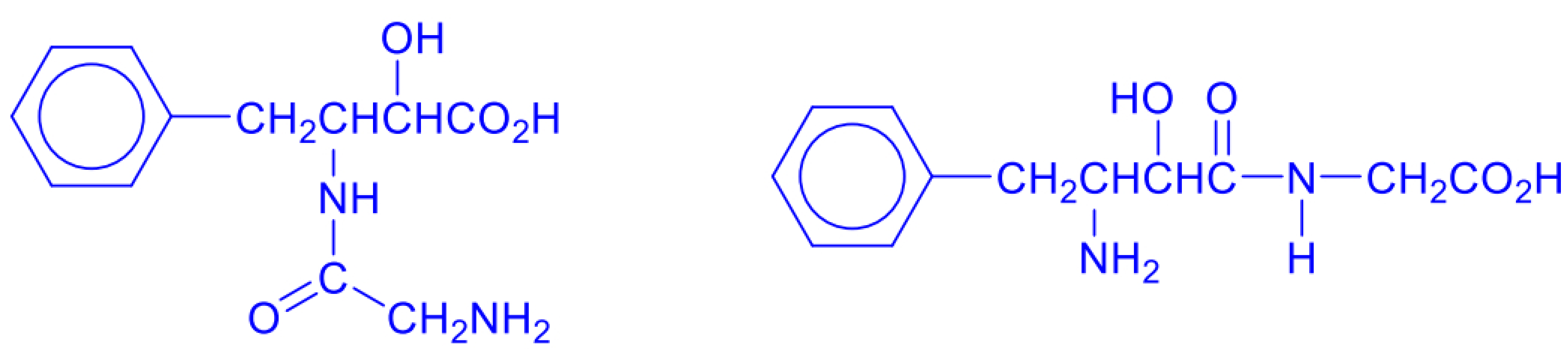
2A The ammonium salt is soluble in water. The **ionic** quaternary ammonium salt can **form ion-dipole interactions** with water molecules which **releases sufficient energy to overcome the ionic bonds in the crystal lattice for solvation**.

3A D < B < A < C

4A **C**

Amino Acids

3A



4A A tripeptide has 2 peptide bonds. (*n* amino acid residue has (*n*–1) peptide bonds)

When peptide bonds are formed, a water molecule (M_r = 18) is lost.

M_r of X = 75 + 103 + 105 – (2 × 18)

= 247.0