Amides, Amino acids and Chirality

**Naming of Amides**
The amide functional group consists of a carbonyl group bonded to the nitrogen of an amine. Like amines, amides are classified by the number of carbons attached to the nitrogen.

A primary amide is therefore one in which both of the other atoms bonded to the nitrogen are hydrogens: -CONH₂

*Fig. 1.*

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CH₃CH₂CONH₂ propanamide
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(note that the carbon of the carbonyl group is counted in the longest chain, and that they stem is propan- not propyl-)

A secondary amide is a linking group (biologists may refer to this as a peptide link) with the form –CONH- forming the link.

*Fig. 2.*

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CH₃CH₂CONHCH₃ N-methylpropanamide
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A tertiary amide has the carbonyl group and two other carbon atoms attached to the nitrogen.

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HCON(C₂H₅)₂ N,N-diethylmethanamide
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*Fig. 3.*

Note that this type of hybrid between a displayed and a structural formula is OK if you are only required to draw a molecule unambiguously, but NOT if the type of formula is specified in the question as displayed.

**Production of amides**
Amides are produced by the reaction of acyl chlorides (or acid anhydrides) with ammonia or amines. The ammonia or amide acts as a nucleophile, donating the lone pair on the nitrogen to form a dative bond to the δ+ carbon of the acyl chloride.

Primary amides are produced in the reaction with ammonia:

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e.g. CH₃COCl + 2NH₃ → CH₃CONH₂ + NH₄Cl
ethanoyl chloride ethanamide
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Secondary amides are produced in the reaction with a primary amine:

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e.g. CH₃CH₂COCl + 2CH₃NH₂ → CH₃CH₂CONHCH₃ + CH₃⁺NH₃Cl
propanoyl chloride methylamine N-methylpropanamide methylammonium chloride
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Amino Acids
Amino acids are the building blocks for biological molecules called peptides, and for proteins (polypeptides). The body has 20 different amino acids from which to assemble proteins.

Structure
An amino acid contains the functional groups –NH₂ and –COOH (amine and carboxylic acid).

In an α-amino acid (such as the 20 the body uses to make proteins) the –NH₂ and –COOH groups are both bonded to the same carbon atom.

The general formula of an α-amino acid can therefore be written as:

\[ RCH(NH₂)COOH \]

or \[ \text{RCH(NH₂)COOH} \]

The R-group is usually an alkyl group but can contain –OH, -SH, -COOH or –NH₂ groups.

Example of α-amino acids:

- glycine (aminoethanoic acid)
- glutamic acid (2-aminopropanoic acid)
- alanine (2-aminopentanedioic acid)
- serine (2-amino-3-hydroxypropanoic acid)

EXTENSION MATERIAL – NOT ON SPECIFICATION

Zwitterions
The acidic carboxylic acid group can donate a proton to the basic amine group. The result is an internal salt (a molecule having both a positive and a negative charge on different parts of the same molecule) known as a zwitterion.

A zwitterion has no overall charge.

e.g. 

\[ \text{H} \text{N} - \text{C} \text{C} \text{O} \text{H} \]

\[ \rightarrow \text{H}^+ \text{N} - \text{C} \text{C} \text{O} \text{H}^- \]
Each amino acid has a characteristic pH called the ISOELECTRIC POINT at which it exists as a zwitterion. The exact value of pH depends on the nature of the R-group. The presence of an acidic group such as –COOH in the R-group shifts the isoelectric point to a lower (more acidic) pH, while the presence of a basic group such as –NH₂ in the R-group shifts the isoelectric point to higher (more alkaline) pH.

**Amphoteric properties of amino acids**

Amino acids are amphoteric – which means they can react with both acids and bases.

The –NH₂ group, like any amine, is able to act as a base by using the lone pair on the N atom to accept a proton. It can therefore neutralise acids, forming salts.

\[
\text{e.g. } \text{H} \quad \text{C} \quad \text{C} \quad \text{O} \quad \text{H} + \text{HCl} \rightarrow \text{H} \quad \text{N}^+ \quad \text{C} \quad \text{C} \quad \text{O} \quad \text{H} + \text{Cl}^- 
\]

The –COOH group, as in carboxylic acid, can act as a proton donor. The carboxylic acid group in an amino acid therefore can form salts when reacted with alkalis,

\[
\text{e.g. } \text{H} \quad \text{C} \quad \text{O} \quad \text{H} + \text{NaOH} \rightarrow \text{H} \quad \text{N} \quad \text{C} \quad \text{C} \quad \text{O} \quad \text{Na}^+ \quad \text{H} \quad \text{O} \quad \text{H} \quad \text{H}_2\text{O}
\]

and form esters when heated with an alcohol in the presence of concentrated sulphuric acid as a catalyst.

\[
\text{e.g. } \text{H} \quad \text{C} \quad \text{O} \quad \text{H} + \text{C}_2\text{H}_5\text{OH} \rightarrow \text{H} \quad \text{N} \quad \text{C} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{C}_2\text{H}_5\text{O} \quad \text{H}_2\text{O}
\]

Note that because this reaction is carried out under acidic conditions, the amine group in the amino acid (which is a base) will also react with the acid and become protonated.
Chirality and Optical Isomerism

We have already met stereoisomerism in the form of E/Z (and the more specific cis-trans) isomerism. Here the restricted rotation around double bond results in two isomers. These two isomers may have different chemical properties – why might this be?

e.g. The acid HOOCCH=CHCOOH can be extracted from unripe tomatoes and apples, and also from the wild flower Fumaria officinalis. When heated, the acid obtained from unripe tomatoes or apples reacts, forming a cyclic acid anhydride. The acid from the wild flower, however, does not react.

The explanation for this, that the acid from the tomatoes or apples has the acid functional groups on the same side of the double bond where they can react, while the acid from the wild flower has the acid groups on opposite sides of the double bond where restricted rotation around the bond prevents them from reacting, gained van’t Hoff the first Nobel Prize in Chemistry for his contribution of the ideas of cis- and trans-isomers in stereochemistry.

With the exception of glycine, amino acids are examples of molecules that show a different type of stereoisomerism: optical isomerism.

This occurs when a carbon atom in a molecule has four different groups attached to it. For example, the C in an alanine molecule has –H, -CH₃, -NH₂ and –COOH attached to it. We call such a carbon atom chiral.

Because of the tetrahedral arrangement of groups around a carbon with four single bonds, there are two possible arrangements for these groups. They are mirror images of one another. Rotations of the molecule about the carbon atom cannot make one optical isomer the same as the other.

**Definition:** optical isomerism occurs when a molecule has non-superimposable mirror images about a chiral centre. Optical isomers are also referred to as enantiomers.

Optical isomers are chemically identical, although they have different physical properties, in that they rotate plane-polarised light in different directions.

A molecule can have more than one chiral centre. Each produces two optical isomers, so if a molecule has two chiral carbon atoms it will have two pairs of isomers (i.e. four optical isomers).
**Identifying optical isomers**

We find a chiral centre anywhere the four groups attached to a carbon atom are different. This sounds straightforward, but can be made difficult in two ways:

i) when the molecule is presented skeletally (and so hydrogen atoms are hidden)

![Diagram of a molecule](image1)

E.g. in 2-chloro-5-ethyloctane there are two chiral carbons, indicated with *. Hint: it is easier to see chiral carbons if you re-draw the molecule displayed.

ii) when the molecule is large or contains rings - the points of difference can be quite a distance from the chiral carbon, and the whole of the molecule has to be considered.

![Diagram of a molecule](image2)

E.g. this molecule only has one chiral centre, indicated with *. You need to be sure you understand both why this carbon is chiral, and why the others aren’t – especially the carbon two to the right of the chiral one.

**Practice:**

Which of the following molecules has chiral centers, and where are they:

CH₃CH₂CH₂CH₂CH₂OH - no

CH₃CH₂CH(NH₂)CH₃ - yes ³ᵈ C from the left is chiral

CH₃CHClCH₃ - no

CH₃CH(OH)Br - yes ²ᵈ C from left is chiral

- yes, four of them shown with *
**Drawing the optical isomers**
- Structures must be drawn around a correctly-drawn 3D tetrahedral carbon centre
- Each enantiomer is then drawn as the mirror image of the other one
- Structural formulae may be used for attached groups if convenient (and unless told otherwise in the question)
- Use a vertical dotted line to show the mirror plane between the two molecules
- Remember to draw the connecting bonds to the correct atoms on the four groups

\[ \text{CH}_3 \quad \text{OH} \quad \text{H} \quad \text{HOOC} \quad \text{CH}_3 \quad \text{COOH} \]

**Significance of Optical Isomerism**
Optical activity is important in biological systems where frequently only one of the optical isomers is biologically active – only one of the optical isomers will interact with an enzyme due to the specific geometry of the receptor sites on enzymes – we call this being stereospecific. This can result in them having different sensory effects or medical effects.

*e.g.* leucine – an amino acid with R = -CH\(_2\)CH(CH\(_3\))\(_2\)

One optical isomer tastes sweet, the other tastes bitter and is used as a food additive.

*e.g.* Thalidomide (1954)
- prescribed to prevent morning-sickness in pregnant women
- drug was later found to be chiral – only one enantiomer had the required therapeutic effect
- the drug was not marketed in the US because the FDA demanded further testing before licensing, and during this process the activity of the other enantiomer was discovered
- the other optical isomer led to deformities in developing babies – some 10,000 were affected in Europe

*e.g.* Seldane – one of the first antihistamines
- used to relieve hayfever symptoms
- chiral with one enantiomer having the required therapeutic effect
- after testing and licensing, it was found that the “inactive” isomer caused a potentially fatal heart condition in some patients
e.g. Ibuprofen

- one active optical isomer controls pain effectively by blocking messages to the brain and reducing swelling and inflammation
- the other isomer is inactive, but is fortuitously converted into the active isomer in the body, so the whole dose is active