ChemFactsheet

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Chiral Compounds as Medicines

First, try deciding whether the following statements are true or false.

	Statement	True	False
1	Racemates contain two enantiomers in equal numbers.		
2	The synthesis of single optical isomers, rather than racemates, is less expensive.		
3	Chiral molecules produced naturally by enzymes are usually a racemic mixture		
4	Two enantiomers have identical effects when taken as medicines		
5	If two enantiomers have different effects on the human body, one will be inactive and do nothing		
6	Chiral drugs which are administered as only one enantiomer normally have increased pharmacological activity and reduced side effects.		
7	Naturally occurring chiral molecules such as L-amino acids may be used as starting materials and molecular templates in the manufacture of a drug.		
8	Chiral catalysts may be used to help the reaction and also to confer chirality.		

If you answered true to numbers 1, 6, 7 and 8 and false to 2, 3, 4, and 5, then well done!

In order to succeed in this topic you will need a very sound knowledge of optical isomerism. Remember optical isomers are *non-super imposable mirror images* of each other; they are rather like left and right hand gloves. They behave the same chemically although one optical isomer will rotate the plane of plane-polarized light anti-clockwise and the other optical isomer will rotate it clockwise. They will also act differently in any environment that can distinguish between them; right and left hand gloves fit on a right hand (a chiral environment for the gloves) differently! Such an environment is termed chiral.

A pair of optical isomers are called enantiomers.

Nature in general is chiral! Amino acids, proteins and enzymes are all important examples of this. Enzymes work by substrate(s) binding to the enzyme's ***active site*** which has a definite shape into which the substrate(s) can fit.

Try cutting out an *irregular* shape from a piece of paper – the cut out piece (substrate) will fit into the space (acive site) left, but if you turn it over and form a mirror image, it will not fit.

Chiral drugs are designed to work in a similar way. If one optical isomer can attach itself chemically (or bind) to a given site the other will not. However, the other isomer may still have an effect in the human body.

Although they are chemically identical, two optical isomers or enantiomers will in general behave differently when placed in a chiral environment. The human body is inherently chiral.

*You will need to be able to easily identify **chiral centres** in unfamiliar drug molecules, given the structural formula. A chiral centre is a part of the structure which confers the property of optical activity on the whole molecule. A chiral centre is easily identified by looking for a carbon atom that has **four different** atoms or groups attached to it.*

The two enantiomers of a chiral drug may have very different effects. The most important considerations for exam purposes are:

(1) Only one may be active in producing the desired effect. The other may be inactive and do nothing, however it will still have to be metabolized resulting in an unnecessary burden.

An example is **Ibuprofen**, where only one enantiomer acts as a pain killer.

(2) One may be active and the other may produce undesired side effects

An example is **Thalidomide**, where one enantiomer is safe and effective against insomnia, while the other enantiomer produces defects in unborn babies as they develop in the womb.

Administering drugs which consist of only one enantiomer increases pharmacological activity for a given dose and reduces side effects.

In the past pharmaceutical companies would routinely launch chiral drugs as mixtures containing equal amounts of each optical isomer because mixtures are cheaper and simpler to make. Regulators of drugs realized in the early 1990's the importance of single enantiomers and now will not approve mixtures unless there is a good reason for it not being possible to make it as a single isomer - for example some pairs of enantiomers rapidly interconvert.

A mixture which contains equal amounts of two optical isomers is often called a racemic mixture or racemate.

Note *Not all drugs are best administered as single enantiomers. For example Statins, which are used for lowering serum cholesterol levels. However, when given as a single enantiomer they may cause a potentially fatal muscle side effect in patients. A combination of different single enantiomers is often used.*

Many chiral drugs are still marketed as racemates. Permission may have been granted for their manufacture before new controls were introduced. In some cases the manufacturing licence may expire at a future date and the Company which is manufacturing the drug will then have to reapply, and may have to modify their manufacturing procedure to produce a single enantiomer.

Companies that market racemic versions of drugs and then find that one enantiomer has undesirable side effects may face litigation in the future.

The pharmaceutical companies can either
(a) make a mixture of enantiomers and then separate them or
(b) use a method of production that gives single enantiomers.

Drug companies like to maximize their profits, but optical isomers are difficult to separate and their separation increases production costs.

Separation of Two Enantiomers

(a) A racemic mixture of two crystals with different melting points can be resolved by *differential crystallization*. This means allowing the enantiomer with the higher melting point to crystallize first, while the other is still liquid, and then separating the crystals.
(b) The mixture may be made to react with a chiral organic acid or base. The racemates then separate to form two *diasteromeric salts*. Diasteromeric salts have two chiral centres with one chiral centre identical in each, but the other chiral centre different. The diasteromeric salts are chemically different, and so can be separated.

Chiral compounds made synthetically will often be a mixture of enantiomers, whereas chiral compounds made in nature by enzymes often consist of only one enantiomer. Drug companies actively seek ways of producing single enantiomer drugs.

Practical Routes to the Production of Single Enantiomers

The use of enzymes or bacteria, often called biocatalysts.

Fermentation is used to produce the enzyme or bacterium. The enzyme or bacterium is added to the racemic mixture. The enzyme or bacterium is itself chiral and selectively converts one of the enantiomers into a product molecule at a much faster rate than the other enantiomer. Thus two chemically different molecules are now present, one of the original enantiomers and a new chemically distinct molecule, together with the enzyme. These two can be separated chemically, and the enzyme also separated from the mixture. The useful product must also be further purified.

The use of chiral catalysts

A chiral catalyst is used to help carry out the chemical reaction faster and also to make the product consist of one enantiomer only. The way in which a chiral catalyst does this is by lowering the activation energy for the formation of one of the enantiomers. This enantiomer is then formed rather than the other.

The use of natural chiral molecules, for example L-amino acids or sugars, as starting materials

This is called *asymmetric synthesis* and makes use of the fact that some natural substances are chiral and available as a single enantiomer. For example an L-amino acid will contain only one enantiomer, and is inexpensive and easily available. The chiral starting material undergoes a series of reactions using non-chiral reagents. During these reactions the substance changes chemically, while retaining its own chirality to obtain the desired enantiomer as end product. This type of process has the disadvantage that the synthesis may be complex and so expensive, and also a lot of the chiral starting material will be needed (compared to using a chiral catalyst, where a relatively small amount is needed as the chiral catalyst can be used again and again like a normal catalyst).

The use of a chiral auxiliary

This is a chiral substance which can be chemically attached to the starting material to prevent chemical attack on the important chiral region of the starting molecule. The chiral auxiliary is then removed at the end of the chemical synthesis. It has the disadvantage that two extra steps are needed in the synthesis – one at the beginning to add the chiral auxiliary and one at the end to remove it – this makes the process more expensive and time consuming.

How Science Works

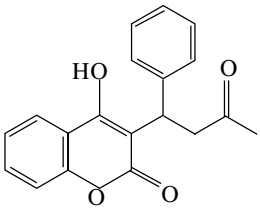
Some techniques are new and complicated, and the examination board will have to give you sufficient details. For example modern direct high performance liquid chromatography analysis is an example of 'How Science Works'. It is a common technique, which is undergoing rapid development. One way of *separating two enantiomers* is by using a '*chiral stationary phase*' - a chiral molecule covalently bonded to an inert silica support. This is rather like immobilizing a catalyst. The racemic mixture flows over the stationary phase and undergoes non-covalent interactions with the chiral stationary phase. The mechanisms involved in these non-covalent interactions are: hydrophobic interactions, electrostatic forces of attraction, and hydrogen bonding between the racemic mixture and the chiral molecule. Only one of the enantiomers will attach itself to the chiral molecule.

The chiral stationary phase may include oligosaccharides (called cyclodextrins) which have hydrophobic (water hating) cavities of exact internal diameters. For example β-cyclodextrin has a cavity of the correct size for the inclusion of aromatic groups such as phenyl (which are attracted as they are also hydrophobic). However, only one enantiomer may fit as the rest of the molecule may prevent the phenyl group of the other enantiomer from entering the cavity.

An advantage of this type of process is that a continuous flow method can be used, which gives 24 hour production with no need to stop and start or clean your equipment between batches. An important consideration is the how well the substances flow, and supercritical CO_2 may be used to achieve the conditions needed to optimize flow.

Practice Questions

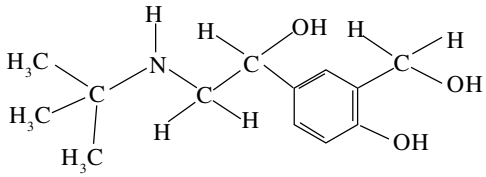
1. (a) The drug Warfarin is an anticoagulating agent ; its structure is shown below. Mark on the structure the feature responsible for stereoisomerism with an asterisk, *. (1 mark)



(b) Outline two important factors that pharmaceutical companies need to consider when manufacturing chiral compounds for use as medicines. (Ignore financial considerations) (2 marks)

(c) How might the pharmaceutical company achieve this with a drug such as Warfarin? (1 mark)

2. Salbutamol (shown below) is a chiral compound used in inhalers to relieve asthma.

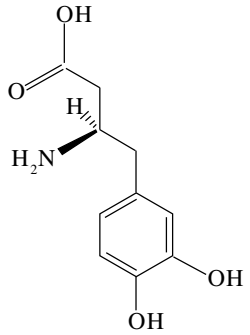


(a) Mark the chiral centre with an asterisk * on the structure above.

(b) When Salbutamol is manufactured to relieve asthma it is made as a single optical isomer. List two reasons why.

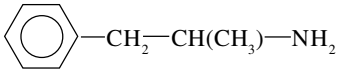
(c) Salbutamol is reacted with $K_2Cr_2O_7/H_2SO_4$ under reflux. Predict the likely organic product of this reaction and draw a displayed formula of this product below.

3. The compound 3-(3,4-dihydroxyphenyl)-alanine, commonly know as DOPA, was initially given to patients suffering from Parkinson's disease. However, this treatment caused serious side effects such as a reduction in white blood cells. Look at the structure of DOPA shown below and suggest a reason why these side effects may have occurred. Refer to a structural feature of the molecule to illustrate your answer. The compound is now used successfully in the treatment of Parkinson's disease. How has the problem been resolved? (3 marks)



DOPA

4. A group of compounds still used in treating some sleeping disorders and hyperactivity in children are the amphetamines. They are stimulants and their side effects include anxiety and restlessness. The simplest member of the group of compounds is amphetamine:

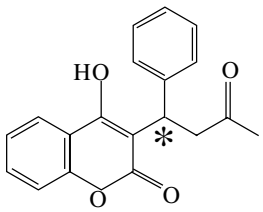


Draw *three-dimensional* structures to show the two stereoisomers of amphetamine. (2 marks)

5. The amino acid arginine can be used as a muscle relaxant. Enzymes in the body cause the breakdown of arginine and the product formed affects the muscles. Only one enantiomer is affected by the enzymes. How does the enzyme catalyze the breakdown of arginine?. Explain why the enzyme only affects one of the enantiomers of arginine. (4 marks)

Answers

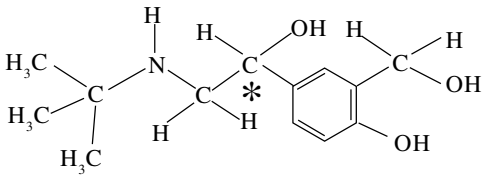
1. (a)



(b) The compound must have good pharmalogical activity and (1 mark) no detrimental side effects (1 mark)

(c) By manufacturing the drug as a single enantiomer. (1 mark)

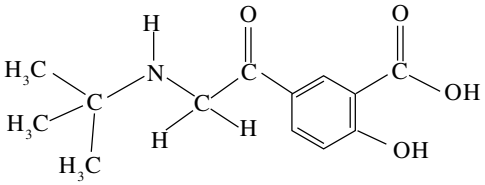
2 (a)



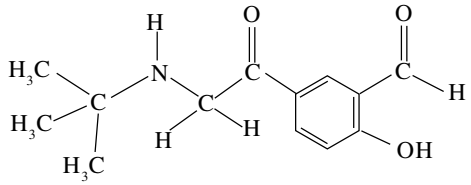
(1 mark)

(b) There may be side effects from other enantiomer (1 mark)
The drug would be more pharmacologically active and so a lower dosage could be used (1 mark)

(c)



The primary alcohol group is oxidized to a carboxylic acid and the secondary alcohol to a ketone.
or (1 mark)



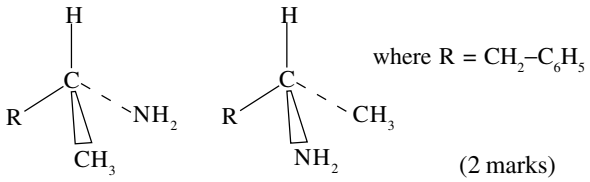
The primary alcohol group is oxidized to an aldehyde and the secondary alcohol to a ketone.

3. The compound has a chiral centre, and so the compound originally manufactured would be racemic, consisting of two enantiomers. (1 mark)

One of the enantiomers would be responsible for the side effects and the other enantiomer would be successful in treating the disease. (1 mark)

The compound is being manufactured only as the single successful enantiomer or the successful enantiomer is isolated after manufacture and given to the patient. (1 mark)

4.



(2 marks)

5. The reaction takes place at an active site on the enzyme which has a certain shape.

The shape of the active site is due to intramolecular forces which determine the tertiary structure (folding) of the enzyme.

The enantiomer which is affected by the enzyme fits into the active site, whereas the other enantiomer does not.

Interactions between enzyme and enantiomer at the active site cause a lowering of the activation energy.
(1 mark for each point = 4 marks)

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