4

Stereochemistry

In Chapter 3 the reasons why drugs behave as weak acids or weak bases were discussed and strategies were developed to exploit differences in physicochemical properties to separate components of a mixture. In this chapter, the three-dimensional shapes of molecules will be introduced and, in particular, the unusual geometry that arises around a carbon atom with four different substituents attached to it – an *asymmetric carbon atom*. The study of the three-dimensional shape of molecules is absolutely fundamental to a student's understanding of complex topics such as biochemistry, medicinal chemistry and drug design.

Chemical compounds that have the same molecular formula but different structural formulas are said to be *isomers* of each other. These constitutional isomers (or structural isomers) differ in their bonding sequence, i.e. their atoms are connected to each other in different ways. Stereoisomers have the same bonding sequence, but they differ in the orientation of their atoms in space. Stereoisomerism can be further divided into optical isomerism (*enantiomerism*) and *geometrical isomerism* (*cis–trans* isomerism). The relationships between the different types of isomerism are shown in Figure 4.1.

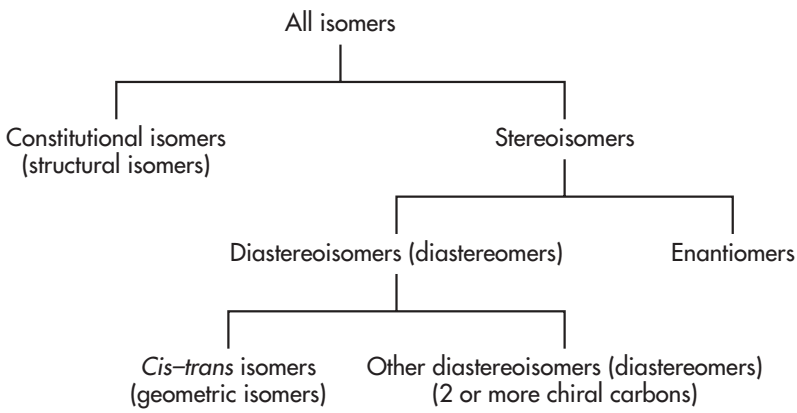


Figure 4.1 Different types of isomerism.

There are a number of atoms that display optical isomerism, including nitrogen and phosphorus, but the simplest case to consider, and the most commonly encountered in drugs, is that of an sp^3 hybridised carbon atom with four different substituents attached to it (Figure 4.2). A carbon like this is said to be *chiral* and to display the property of *chirality*. If the four substituents are different, a pair of non-superimposable mirror image forms can be drawn. These two isomers are called *enantiomers*. A chiral compound always has an enantiomer, whereas an achiral compound has a mirror image that is the same as the original molecule.

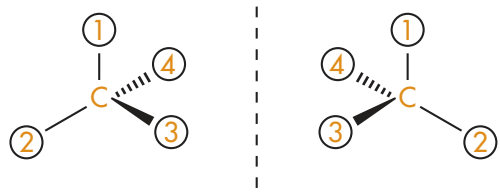


Figure 4.2 Chiral carbon atoms.

Enantiomers have identical or nearly identical physical properties unless a reagent or technique is used that is itself chiral. For example, the two enantiomers in Figure 4.2 will have the same boiling point, melting point, refractive index and density since these are bulk effects and cannot discriminate between the two enantiomers. Differences between enantiomers only become apparent when they interact with chiral reagents such as the active sites of enzymes or the chiral stationary phase of a HPLC column.

In the laboratory, the technique of *polarimetry* is used to distinguish between enantiomers and to measure the extent to which each enantiomer rotates the plane of plane-polarised light.

Polarimetry

Most of the light detected by our eyes is not polarised: that is the light waves vibrate randomly in all directions perpendicular to the direction of propagation of the wave. If normal light of this type is passed through a material that is itself chiral (e.g. the mineral Icelandic spar, or the compound, 'Polaroid', used in sunglasses) then the waves of light interact with the chiral material to produce light that is oscillating in only one plane. This light is called *plane-polarised light*. When plane-polarised light is passed through a solution containing an optically active substance, the chiral compound causes the plane of vibration of the light to rotate (the origin of

the expression *optical activity*). If a second piece of chiral material fitted with a measuring protractor is now placed in the light path, the number of degrees of rotation can be measured and read off a calibrated scale. This is a description of an instrument called a polarimeter, which is used to measure the angle of rotation of plane-polarised light (Figure 4.3).

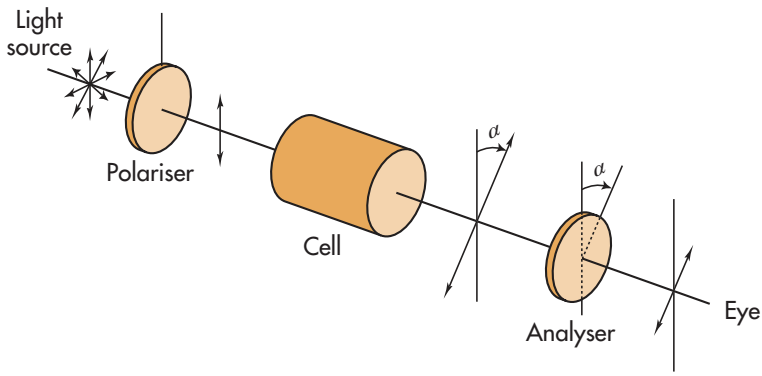


Figure 4.3 A diagram of a polarimeter.

The light source used in polarimetry is usually a sodium vapour lamp, which emits yellow light of a characteristic wavelength (the sodium D line, 589.3 nm). This light is polarised by a fixed filter (the polariser) and passed through a sample cell containing a solution of the optically active substance. The plane of the light is rotated by the chiral compound and emerges from the sample cell, whereupon it enters a second, movable filter (the analyser). This filter has a scale marked out in degrees and allows the operator to measure the angle between the two filters and hence the angle of rotation of the light, α. Once the angle of rotation has been measured the *specific optical rotation* [α] of the substance may be calculated.

$$[\alpha] = \frac{100\alpha}{lc} \tag{4.1}$$

where [α] = specific optical rotation, α = measured rotation in degrees, l = length of sample tube in decimetres (1 dm = 10 cm), c = concentration of sample in % w/v.

Values of [α] are quoted in *British Pharmacopoeia* (BP) monographs for chiral drugs and reagents, and limits are set within which drugs of BP quality must comply. The specific optical rotation of a solid is always expressed with reference to a given solvent and concentration.

The specific optical rotation of a liquid is obtained from equation (4.2), where d = relative density of the liquid.

$$[\alpha] = \frac{a}{ld} \tag{4.2}$$

Compounds that rotate the plane of polarised light towards the right (clockwise) are called *dextrorotatory*, while compounds that rotate the plane to the left, or anticlockwise, are called *laevorotatory*. The direction of rotation is often specified by the symbols (+) for dextrorotatory and (−) for laevorotatory and the direction is considered with the operator facing the light source.

If a sample cell in a polarimeter contains equal amounts of the (+) and the (−) enantiomers, the angle of rotation due to one enantiomer will be equal and opposite to the angle due to the other and the net observed rotation will be zero. Such a mixture is called a *racemic mixture* or a *racemate* and is often encountered in the laboratory as a result of a non-chiral organic synthesis. The common synthesis of adrenaline (epinephrine), the 'fight or flight' hormone, yields a racemic mixture, which has precisely 50% of the biological activity of the natural hormone. Once the racemate is *resolved* into the two pure enantiomers, the (*R*)-(−)-adrenaline is found to be identical to the natural hormone produced by the adrenal medulla, while the other enantiomer, the (*S*)-(+) isomer, has little or no biological activity (Figure 4.4). (The meaning and use of the (*R*) and (*S*) notation is described later in this chapter.)

Occasionally, the specific rotation of a compound can change over time. This phenomenon called *mutarotation* and is caused by a change in the molecular structure of the chiral compound. A good example of this can be seen with the monosaccharide glucose. α-D-(+)-Glucose has an [α] value of +110°, while β-D-(+)-glucose has an [α] value of +19.7°. If freshly prepared solutions of α-D-(+)-glucose and β-D-(+)-glucose are allowed to stand, however, the [α] value of each compound slowly changes until an [α] value of +52.5° is reached. This is the [α] value for the equilibrium mixture of the two anomeric forms (which differ in configuration at carbon-1) of glucose. Both the α- and the β-pyranose forms of D-glucose are in equilibrium with a common open-chain form and this allows interconversion between the two cyclic forms. The equilibrium mixture obtained due to mutarotation of D-glucose has the approximate composition 33% α, 66% β and 1% open-chain aldehyde (Figure 4.5).

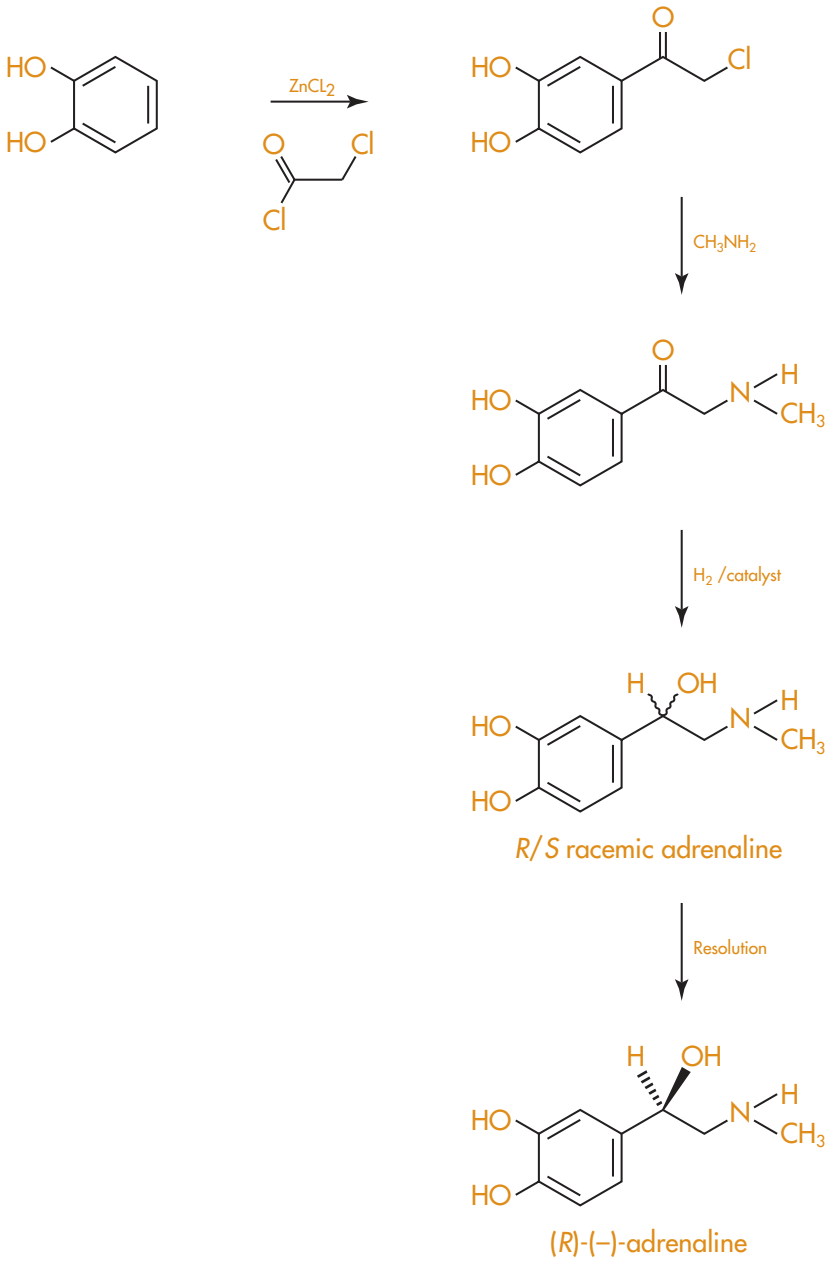


Figure 4.4 A synthesis of adrenaline (epinephrine).

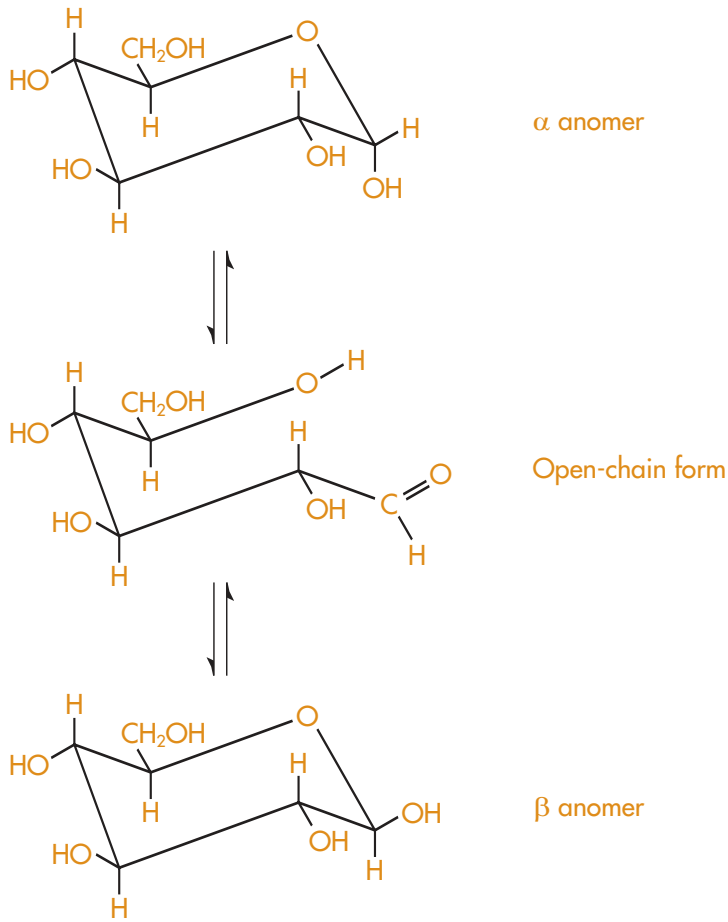


Figure 4.5 Mutarotation of D-glucose.

Biological systems

It is very important to realise that when drugs or medicines are administered to the body there is the opportunity for chiral interactions. This is because the human body is composed of enzymes and receptors that are protein in nature. These proteins are polymers of 20 or so naturally occurring amino acids. With the exception of glycine, all of these amino acids are chiral (all are L-series amino acids – see later) and it must be expected that a chiral drug will interact with these chiral receptors differently from its enantiomer. It is often the case that if a racemic mixture of a chiral drug is administered, only one enantiomer will be active, while the other will be

less active or inactive, or may even be toxic. There is a school of thought among analysts that if a racemate is administered, and only one enantiomer is active at the receptor, then the patient has paid for and received 50% impurity and a clever lawyer may be able to pursue a claim!

A simple, non-invasive example of chiral discrimination can be seen using the smell of volatile compounds. (−)-Carvone is a natural product with the smell of spearmint oil. (+)-Carvone, the enantiomer, has the odour of caraway seeds (Figure 4.6). The fact that our noses can detect a different smell for the tiny concentration of each enantiomer present proves that our sense of smell is stereospecific. This is an example of a general rule, which is that the body is chiral and body systems can discriminate between enantiomers of chiral drugs. The history of drug development is littered with examples where the implications of stereochemistry were ignored (perhaps most tragically with the sedative thalidomide). Students of pharmacy and chemistry must expect the enantiomers of chiral drugs to interact differently with chiral receptors and enzymes.

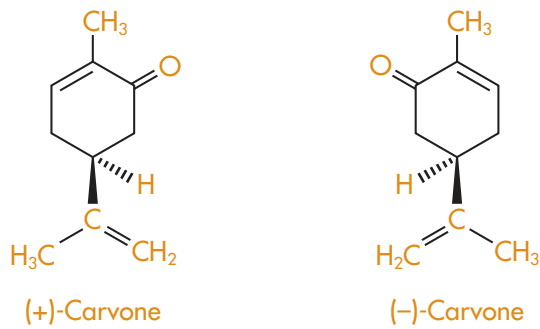


Figure 4.6 The structures of (+)- and (−)-carvone.

Fischer projections

It is sometimes useful to be able to draw a schematic diagram of the stereochemistry around a chiral carbon, especially when a molecule contains more than one chiral centre. The German chemist Emil Fischer solved this problem and his method of representing chiral centres is now called a Fischer projection.

A Fischer projection looks like a cross, with the chiral centre at the point where the lines cross. The horizontal lines are considered to be bonds projecting *towards* the viewer, while the two vertical lines are considered to project *away* from the viewer. In this way the tetrahedral arrangement of

groups around an sp^3 hybridised carbon, for example, may be represented on a page in two dimensions. The other rule to remember when drawing a Fischer projection is to draw the carbon chain of the compound vertically *with the most oxidised carbon atom at the top*. An example of a Fischer projection of lactic acid, the acid produced when milk turns sour, is shown in Figure 4.7.

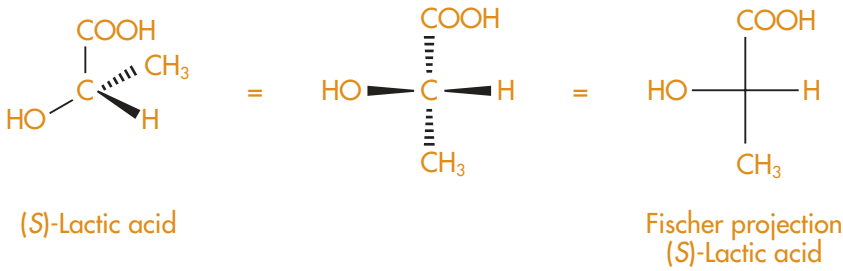
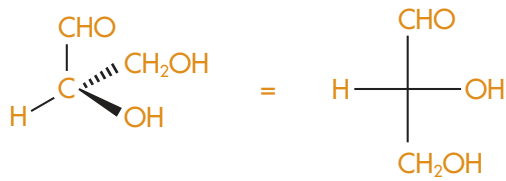


Figure 4.7 Fischer projection of lactic acid.

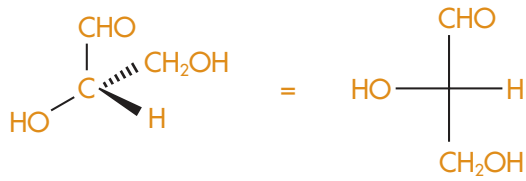
D and L configurations

The Fischer projection allows the stereochemistry around a chiral centre to be conveniently and accurately represented in two dimensions. Using the Fischer projection, a different system of describing the configuration (i.e. the arrangement in space of the atoms or groups attached to a chiral carbon) of groups around a chiral centre can now be introduced, the D and L convention. This method of describing absolute configuration is widely used in biochemistry and organic chemistry, particularly for carbohydrates and amino acids.

The simplest aldehyde-containing sugar (or aldose) is glyceraldehyde and this compound was selected as the standard compound for assigning the configuration of all carbohydrates. The dextrorotatory isomer of glyceraldehyde, (+)-glyceraldehyde, was arbitrarily assigned the absolute configuration shown in Figure 4.8. This was a lucky guess on the part of the chemists making the choice. They could not know at the time, with the analytical techniques at their disposal, how the atoms of glyceraldehyde were arranged in space around the chiral centre. Much later, when the technique of X-ray diffraction became available, it was possible to check the orientation of atoms in space in glyceraldehyde and it was found that the original guess had been correct.



D-(+)-Glyceraldehyde



L-(−)-Glyceraldehyde

Figure 4.8 D and L forms of glyceraldehyde.

The Fischer projection of D-(+)-glyceraldehyde is shown in Figure 4.8. The carbon chain is drawn vertically, with the most oxidised carbon (the aldehyde) at the top. The OH group on the chiral centre is drawn on the *right-hand side* for the D isomer and on the *left-hand side* for the L isomer. It follows that any sugar that has the same stereochemistry as D-glyceraldehyde belongs to the D-series of sugars (e.g. D-glucose, D-galactose), while any sugar that has the same stereochemistry as L-glyceraldehyde belongs to the L-series of sugars.

For amino acids the situation is analogous. When the Fischer projection is drawn (carbon chain vertical with most oxidised carbon at the top) all of the 'natural' amino acids found in human proteins are found to have the NH_3^+ group on the left-hand side of the Fischer projection and are therefore similar in configuration to L-(−)-glyceraldehyde. These amino acids are consequently known as L-series amino acids (Figure 4.9).

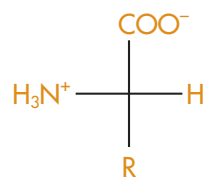
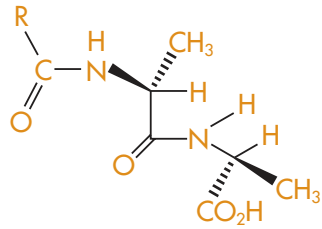


Figure 4.9 Fischer projection of L-series amino acids.

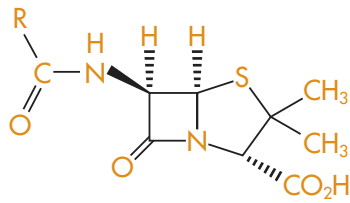
Amino acids of the opposite, D, configuration are known and do occur naturally in microorganisms. Indeed, the mode of action of penicillin antibiotics depends on the opposite stereochemistry of bacterial amino acids. In penicillin-sensitive bacteria, the organism manufactures a cell wall to contain the high osmotic pressure produced inside the bacterial cell. The bacterial cell wall consists of a polysaccharide (called *peptidoglycan*), which is reinforced by structural cross-linking of chains of polypeptide. The situation is fairly complex, but the final step of the cross-linking is achieved by attaching the terminal amino acid of the cell wall, a glycine, to a D-alanine residue on an adjacent peptide chain. This cross-linking is catalysed by an enzyme called *transpeptidase* (or transaminase). Penicillins can inhibit the enzyme transpeptidase and prevent the formation of structural cross-links in the bacterial cell wall. The cell is weakened, becomes unable to contain the high internal osmotic pressure and bursts. Penicillin is able to inhibit the enzyme because of the close structural similarity between the penicillin antibiotic and the D-alanine-D-alanine dipeptide from the cell wall. Penicillins are non-toxic to humans because we possess L-alanine, the amino acid with the opposite stereochemistry, in our proteins. This is an example of an important concept in drug design called *selective toxicity*, which arises when a drug is poisonous to one type of organism or cell (a bacterium in this case) but harmless to another (human cells). Penicillins are a good example of selectively toxic drugs and, assuming the patient is not allergic to them, they are remarkably free of toxic side-effects. If a patient is allergic to penicillins, the macrolide antibiotic erythromycin is usually prescribed instead. The structures of penicillin and the D-alanine-D-alanine dipeptide are shown in Figure 4.10.

Penicillins and the structurally similar class of antibiotic, the cephalosporins, are known collectively as β-*lactam antibiotics*. The β-lactam ring is the 4-membered cyclic amide ring common to both classes of antibiotics and fundamental to the molecular mode of action of the drugs. The β-lactam ring is under immense strain and opens easily if attacked by a nucleophile. This is because amides contain sp^2 hybridised carbon atoms, which normally have a bond angle of 120°. The bond angle of the amide in a β-lactam ring approaches 90°. A serine residue present in the active site of transpeptidase can attack the β-lactam ring, using the lone pair of electrons on the —OH, open the ring and so acylate the active site of the enzyme and prevent cell wall cross-linking (Figure 4.11).

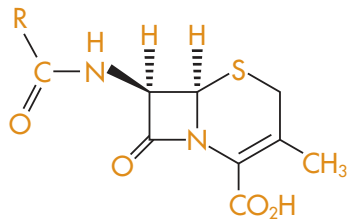
Unfortunately, other nucleophiles can open a β-lactam ring and inactivate penicillins. Attack by water renders the penicillin unstable in aqueous solution (see Chapter 8 for more information) and some bacteria have evolved mechanisms to overcome penicillins and are said to be *resistant* to



Acyl-D-Ala-D-Ala



Penicillin



Cephalosporin

Figure 4.10 The structures of D-alanine-D-alanine dipeptide, penicillin and cephalosporin.

the drug. A large number of hospital-acquired infections are now resistant to treatment by penicillin, including the notorious MRSA or meticillin (formerly methicillin) resistant *Staphylococcus aureus*. This 'super bug' produces an enzyme, β-lactamase, which hydrolyses the β-lactam ring and inactivates the penicillin. Organisms which are resistant to treatment with antibiotics pose one of the greatest threats to modern pharmacy and medicine. At the moment, drugs such as the glycopeptide derivatives vancomycin and teicoplanin are reserved for use against difficult infections,

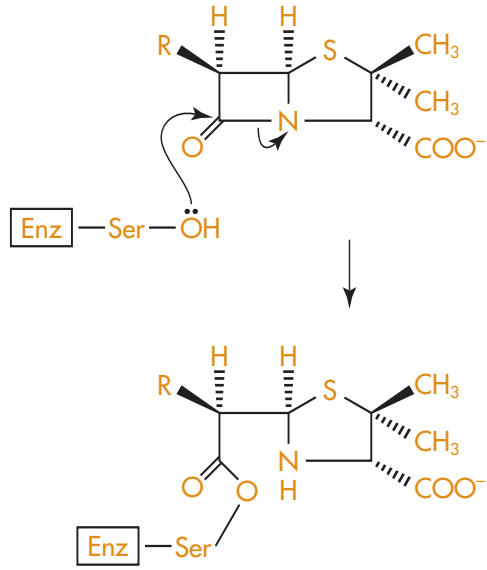


Figure 4.11 Mode of action of β-lactam antibiotics.

but vancomycin resistance has been reported and it is only a matter of time before organisms work out how to inactivate teicoplanin.

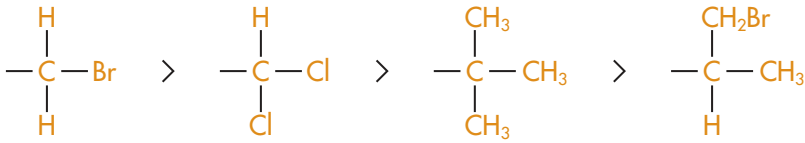
R and *S* configurations

The absolute configuration of atoms around a chiral centre may be drawn accurately by use of a Fischer projection and may be described (particularly in biochemistry for chiral carbohydrates and amino acids) by the D/L convention. The most successful system for displaying configuration of general compounds, however, is the Cahn–Ingold–Prelog convention, named for the three chemists who first described it. This system assigns each chiral centre in a molecule a letter (*R* or *S*) and is the method of choice when assigning the configuration of chiral centres of drug molecules.

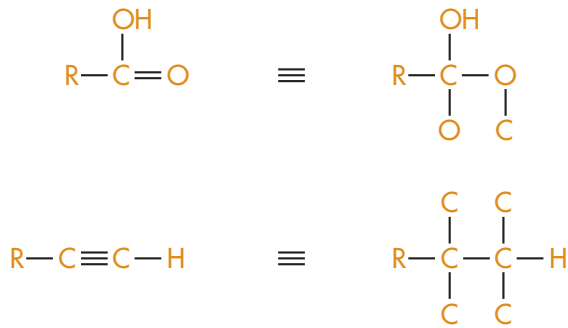
To use the Cahn–Ingold–Prelog convention, a 'priority' is assigned to each group attached to the chiral centre according to the *atomic number* of the atom in question (N.B. not atomic weight – a common mistake). The numbering follows the atomic numbers in the periodic table, with heavy isotopes of the same atom taking priority over lighter ones. Hydrogen comes last, for example:

$$I > S > O > N > {}^{13}C > {}^{12}C > Li > {}^{3}H > {}^{2}H > {}^{1}H$$

If two groups cannot be distinguished on the basis of atomic number, the next atom of the group attached to the chiral centre is considered, and so on until the priorities are clear.



If a double- or triple-bonded group appears in the sequence, then each double bond is counted twice and each triple bond is counted three times, for example:



Once all the priorities around the chiral centre have been assigned, the molecule is viewed from the side *opposite the group with lowest priority* (usually hydrogen). If the order of the group priorities is arranged *clockwise* around the chiral centre, the chiral carbon receives the (*R*) configuration (from the Latin *rectus*). If the priority of groups is *anticlockwise* when viewed from the side opposite the group with lowest priority, the chiral centre is assigned (*S*) (from the Latin *sinister*, meaning 'to the left' – something to think about, all you readers who are left-handed!).

Students often find stereochemistry and the assigning of absolute configuration around a chiral centre difficult. This is usually because of difficulties picturing the arrangement of groups in space. The use of molecular models can be beneficial and they are recommended, particularly for beginners.

A number of worked tutorial examples and problems can be found on p. 101–104.

Molecules with more than one chiral centre

Since there are two possible configurations for an asymmetrically substituted carbon atom, a structure containing n such centres will, in theory, possess 2^n stereoisomers. The actual number of stereoisomers that exist may be less than this due to steric effects. Compounds that have the same stereochemistry at one chiral centre but different stereochemistry at the others are known as *diastereoisomers* (diastereomers); a good example is given by the alkaloids ephedrine and pseudoephedrine. Ephedrine (the (1*R*, 2*S*) diastereoisomer) is a natural product isolated from Ephedra (the *Ma Huang* plant) and known to Chinese medicine for over 3000 years. It was used in the last century for the treatment of asthma. Pseudoephedrine (the (1*S*, 2*S*) diastereoisomer) is a decongestant and a constituent of several 'over-the-counter' cold and flu remedies (Figure 4.12).

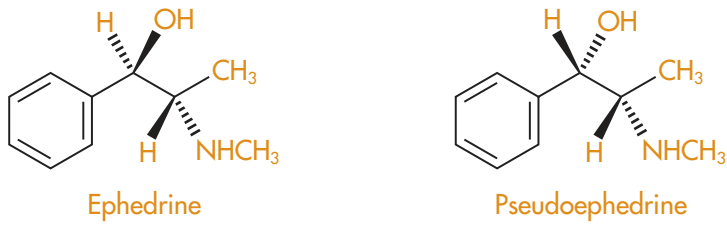


Figure 4.12 The structures of ephedrine and pseudoephedrine.

Diastereoisomers (unlike enantiomers) have different physical properties such as boiling point, density, etc. These differences between diastereoisomers can be exploited to resolve (or separate) mixtures of enantiomers. The principle behind this technique is to resolve the mixture of enantiomers by chemically converting them into a pair of diastereoisomers. This is achieved by reacting the racemic mixture with an optically pure reagent. These reagents are usually natural products; for example, if the racemic mixture contains acidic compounds, reaction is with an optically pure alkaloid such as strychnine or brucine.

Similarly, if the racemic mixture is composed of basic drugs, use is made of camphor-10-sulfonic acid, a natural product obtainable as an optically pure enantiomer. An example of the type of reactions involved is shown in Figure 4.13, where a pair of enantiomeric alcohols is resolved by reaction with phthalic anhydride and an optically pure base to form a pair of diastereoisomeric salts. Reactions of this type can be tedious to perform and, with the advent of HPLC with chiral stationary phases, are gradually being replaced.

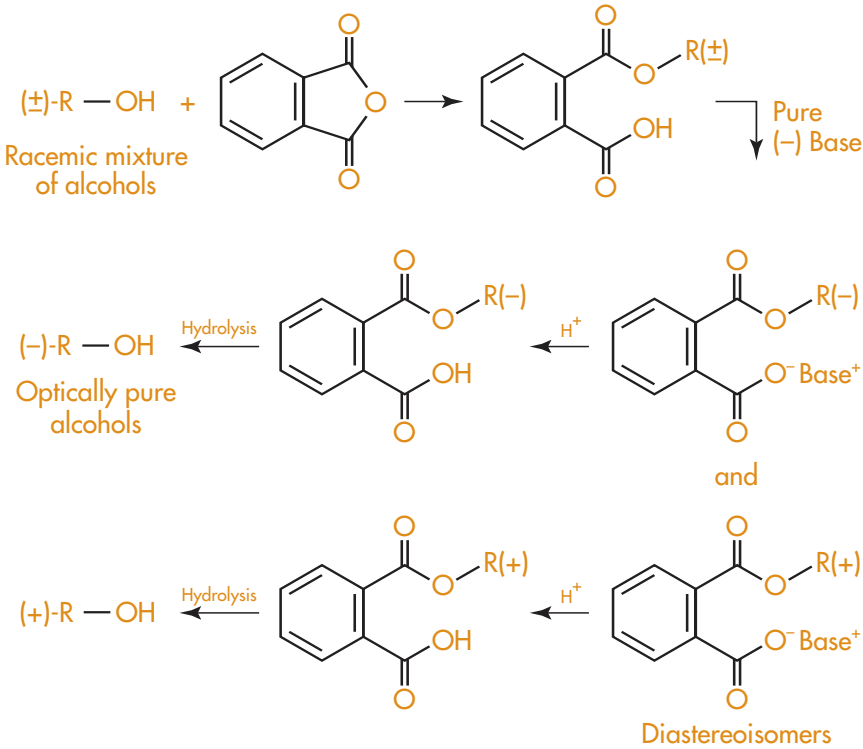


Figure 4.13 Resolution of a racemic mixture of alcohols.

Stereochemistry case study: thalidomide

The thalidomide disaster was the most serious drug-induced medical accident of the last 50 years. The drug was first marketed in Germany as a sedative with apparently few side-effects. It was considered safe and was indicated for the treatment of morning sickness associated with pregnancy. The drug was very popular and thousands of women around the world took thalidomide during their pregnancies. In the late 1950s and early 1960s a number of children were born with a serious congenital abnormality called *phocomelia*, characterised by deformities in limb structure or, in some cases, a total absence of a limb. Initially it was impossible to say what had caused the birth deformity, but eventually it was realised that all of the mothers involved had taken thalidomide at some time during their pregnancy. Official estimates put the number of children affected by thalidomide at 12 000, but this figure does not include the women who miscarried as a result of drug-induced damage to the fetus, so the true total is probably

much higher. Thalidomide caused birth deformities when tested (retrospectively) in rabbits and in primates, as well as in humans, but tragically, the initial toxicology screen for the drug had been carried out in rats. It is now known that rats metabolise the drug differently from humans and, as a result, birth defects were not detected in the animal testing. The structure of thalidomide is shown in Figure 4.14 with the chiral centre indicated.

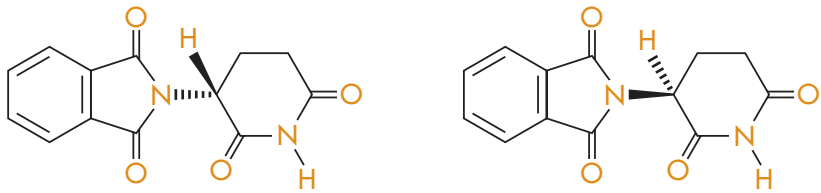


Figure 4.14 The enantiomers of thalidomide.

The drug was administered as the racemic mixture but, whereas the (*R*) isomer was an effective sedative, the opposite (*S*) isomer was found to have teratogenic properties and to cause deformities in the developing fetus. The toxic effect of thalidomide is most profound on new blood vessels developing in the fetus, a process called *angiogenesis*. The drug damages these delicate structures, transport of essential nutrients to the growing limbs is prevented, and the limbs do not develop properly. The period of pregnancy when the symptoms of morning sickness are most severe coincides almost exactly with the period of most rapid limb growth in the fetus, so, unfortunately, the drug was taken at the worst possible time during the pregnancy to damage the fetus. In cases of drug toxicity like this when one enantiomer is active (often called the *eutomer*) and the opposite enantiomer is toxic (called the *distomer*), the obvious solution is to resolve the racemic mixture into the two enantiomers and administer only the safe (*R*) isomer as a pure enantiomer. Unfortunately, it is now known that, in the case of thalidomide, administration of the enantiomerically pure (*R*) isomer would not have prevented the disaster since this isomer undergoes racemisation *in vivo*; in other words, administration of the pure enantiomer results in formation of a 50/50 racemic mixture in the bloodstream. The half-life for this reaction has been determined as 566 minutes at 37°C and pH 7.4. This means that even if pure (*R*) isomer had been given, in a little less than 10 hours half of it would have been converted into the toxic enantiomer.

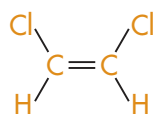
The situation is (even) more complicated because thalidomide is metabolised in the body and the metabolites themselves may be toxic. The

drug was withdrawn from the market as soon as evidence of the birth defects became known and for many years thalidomide disappeared from the Pharmacopoeia. Recently, however, thalidomide has undergone something of a renaissance and is now the drug of choice for erythema nodosum leprosum, a very severe inflammatory condition associated with leprosy. The drug is used only in male patients or in female patients who are not of child-bearing age.

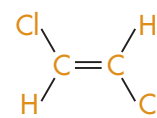
Thalidomide is also undergoing trials as an adjuvant to cancer treatment, where the inhibition of angiogenesis may be employed to damage a tumour's blood supply and, hence, starve the tumour of oxygen and nutrients. There are also reports that the drug may possess immunomodulatory activity and may be of benefit in the treatment of autoimmune diseases such as Crohn disease. It will be interesting to see whether thalidomide, after all the damage and misery it has caused, can become a useful and beneficial drug in the future.

Geometrical isomerism

Compounds that possess a multiple bond do not rotate easily about the bond. This gives rise to a type of isomerism called *geometrical* (or *cis–trans*) isomerism. If the substituents around the double bond are similar and both are on the same side of the double bond, the term *cis* is used to describe the molecule. If the same groups are on opposite sides of the double bond, the term *trans* is used to describe the configuration, as illustrated in Figure 4.15.



cis-Dichloroethene



trans-Dichloroethene

Figure 4.15 Examples of *cis* and *trans* isomerism.

The *cis–trans* convention is perfectly adequate for the description of simple compounds; however, for more complex examples a system based on the Cahn–Ingold–Prelog rules has been developed. The groups surrounding the double bond are assigned a Cahn–Ingold–Prelog priority depending on the atomic numbers of the substituents. The configuration in which the high-priority substituents are on the same side of the double bond is called the (*Z*) isomer (from the German *zusammen* meaning together). The alternative configuration, with the high-priority groups on

opposite sides of the double bond, is described as (*E*) (also from the German, *entgegen* or opposite). Examples of (*Z*) and (*E*) isomers are shown in Figure 4.16.

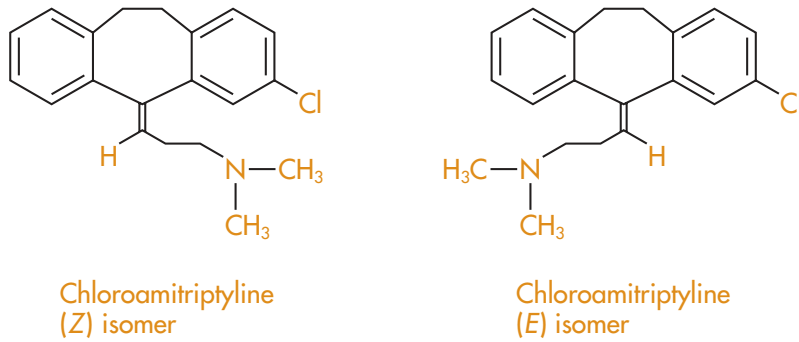


Figure 4.16 Examples of (*Z*) and (*E*) isomers.

It should be obvious that the *cis* isomer is *usually* also the (*Z*) isomer, while the *trans* isomer is *usually* also the (*E*) isomer. This useful arrangement is not foolproof, however, and the anticancer drug tamoxifen is a notable example of a drug that is *trans* with respect to the phenyl groups, but also (*Z*) when the Cahn–Ingold–Prelog priorities are used (Figure 4.17).

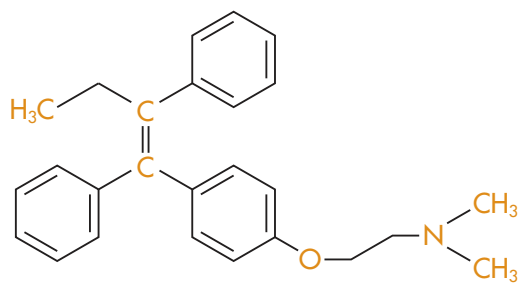


Figure 4.17 The structure of tamoxifen.

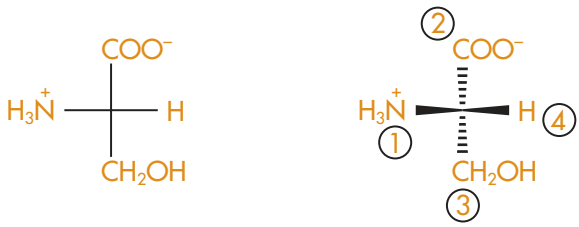
Tutorial examples

Q *1 The structure of the amino acid serine is shown in Figure 4.18. Draw a Fischer projection of the naturally occurring* L *isomer and determine the configuration using the Cahn–Ingold–Prelog convention.*

$HOCH_2CH(\overset{+}{N}H_3)COO^-$

Figure 4.18 The structure of serine.

A 1 A Fischer projection of serine is shown in Figure 4.19. The carbon chain is drawn vertical with the most oxidised carbon at the top. For the amino acid to be a member of the L-series, the NH group must be on the *left* of the Fischer projection. The priorities for the Cahn–Ingold–Prelog convention are also shown in Figure 4.19.



(*S*)-Serine

Figure 4.19 Fischer projection and Cahn–Ingold–Prelog convention for serine.

The highest priority is the NH_3^+, since the atomic number of nitrogen is 7; the second priority is COO^-; the third priority is the side-chain of the amino acid —CH_2OH; and the lowest priority (as always) is the hydrogen. The direction of rotation is therefore clockwise when viewed in the Fischer projection, but the Cahn–Ingold–Prelog convention demands that the chiral centre is viewed from the side *opposite* the group of lowest priority; therefore this molecule is (*S*). In fact, *all the common* L*-series amino acids are* (*S*) *unless the side-chain contains a sulfur atom*. This is because the group with the second priority is always the COO^- group unless there is an atom of higher atomic number than oxygen in the side-chain. In the case of the amino acid L-cysteine,

the Cahn–Ingold–Prelog convention is (*R*) since one sulfur atom in the side-chain takes priority over the two oxygens in the COO^- group.

Q

2 Draw Fischer projections of $HOH_2C—CH(OH)—CH(OH)—CH_2OH$ *to illustrate*

(a) A pair of enantiomers

(b) A pair of diastereoisomers

(c) A meso compound

A

2 The answers are shown in Figure 4.20. Structures (1) and (2) are enantiomeric pairs. Structures (1) and (3) and structures (2) and (3) are pairs of diastereoisomers (or diastereomers), while structure (3) is a meso compound. A meso compound is optically inactive since it possesses a plane of symmetry and is superimposable on its mirror image. It does, however, contain two chiral carbon atoms. This reminds us that *not all compounds that contain chiral centres are optically active*.

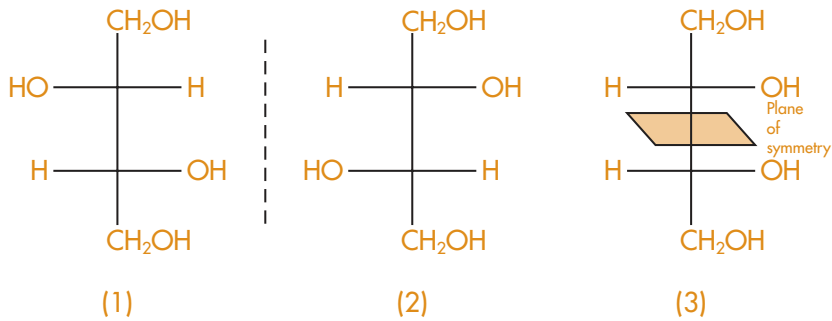


Figure 4.20 Enantiomers, diastereoisomers and a meso compound.

Problems

Q4.1 Four representations of the antidote dimercaprol, used in the treatment of heavy-metal poisoning, are shown in Figure 4.21. Assign each as either (*R*) or (*S*). Bonds projecting *out* of the page towards the reader are shown as solid wedges, while bonds projecting *into* the page are represented as dotted lines.

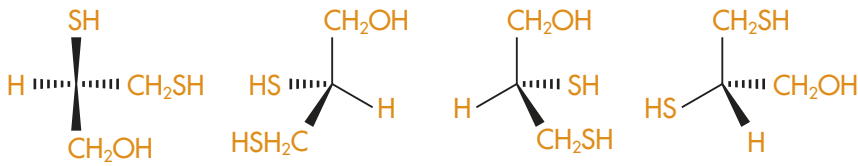


Figure 4.21 Representations of dimercaprol.

Q4.2 Designate each of the structures in Figure 4.22 as either (*E*) or (*Z*).

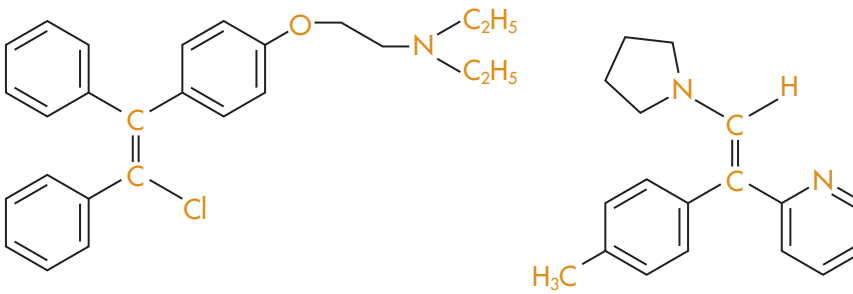


Figure 4.22 Structures of compounds that have geometrical isomers.

Q4.3 The structure of naloxone hydrochloride is shown in Figure 4.23. Assign the stereochemistry at the 5- and 14-positions using the Cahn–Ingold–Prelog convention.

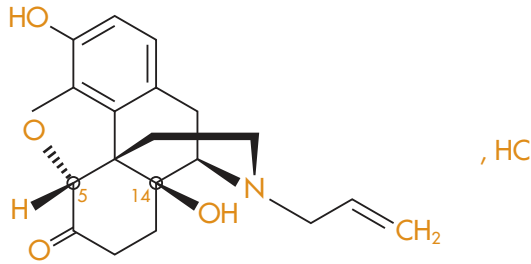


Figure 4.23 Structure of naloxone hydrochloride.

(Answers to problems can be found on pp. 258–259.)