Stereochemistry: Introduction to Optical Isomerism

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1 Introduction

This teaching module introduces you to important concepts in stereochemistry, including chirality and conventions for describing stereocentres and the distinction between enantiomers and diastereomers, as well as recognising molecules which are not chiral by virtue of internal symmetry using examples of structures taken from the Cambridge Structural Database.

1.1 Learning outcomes

At the end of this module, you will:

- be able to recognise a stereogenic centre in a molecular structure
- be able to use the sequence rules for specification of configuration to identify and name correctly stereoisomers and individual stereogenic centres having *R* or *S* absolute configurations
- be able to predict, identify and distinguish between enantiomers and diastereomers
- be able to recognise a *meso* compound given its structure
- be able to identify chirality arising from certain trivalent atoms and stereocentres with coordination number greater than four.

1.2 Materials

The structures needed to complete this module are available from the online Web service Access Structures.

https://www.ccdc.cam.ac.uk/structures/

This provides you with all the features required to complete this teaching module. Alternatively, you may prefer to use the structure visualization program Mercury, which you can download for free. Instructions for obtaining this software and links to resources to support you using it are given at the end of this document. This teaching module uses entries in the Teaching Subset; you can find out more about the Teaching Subset here: https://www.ccdc.cam.ac.uk/community/education-and-outreach/education/teaching-subset/.

1.3 Pre-required skills

No prior knowledge of crystallography is required to complete this teaching module however a basic understanding of molecular geometry is required.

2 Introduction to optical isomerism

Stereoisomers are molecules whose atomic connectivity is the same but whose three-dimensional arrangement of atoms in space is different. Stereoisomers can be of different types and include enantiomers, diastereomers, geometric isomers and conformational isomers. The first three of these belong to the configurational isomer class; their stereochemistry cannot be changed without breaking and reforming bonds. Conformational stereoisomers differ in spatial arrangement but can be converted by rotation about single bonds. This teaching module covers enantiomers and diastereomers but is limited to point chirality, by which we generally mean chirality centred on a single atom.

Chirality has sweeping implications in biological systems. For example, most drugs are often composed of a single stereoisomer of a compound, and while one stereoisomer may have positive effects on the body (since it has the right three-dimensional shape to bind to the protein receptor), another stereoisomer may not bind or could even be toxic. An example of this is the drug thalidomide which was used during the 1950s to suppress morning sickness. The drug, unfortunately, was prescribed as a mixture of stereoisomers, and while one stereoisomer actively worked on controlling morning sickness, the other stereoisomer caused serious birth defects. Ultimately the drug was pulled from the marketplace (stereoisomers interconverted in the body making it impossible to avoid the toxic form). Because of these implications, a great deal of work done by synthetic organic chemists is in devising methods to synthesize compounds that are purely one stereoisomer. The ability to visualise and manipulate molecules in three-dimensions is vitally important to study and understand the structural features that give rise to stereoisomerism.

2.1 A note about crystal structures used in this handout

Crystal structures have at the bare minimum translational symmetry, however they may (and most often do) have other types of symmetry. Symmetry can generate more stereoisomers that are visible in the molecular unit. The structures in this handout have been chosen so that the default molecular view displayed in the Web viewer provides the molecule with chosen features. Bear in mind that if you explore larger sections of a structure, for example, the unit cell, you might find other stereoisomers depending on the crystal symmetry. We recommend using the default view unless you are instructed to do otherwise, or if you are confident with crystal symmetry.

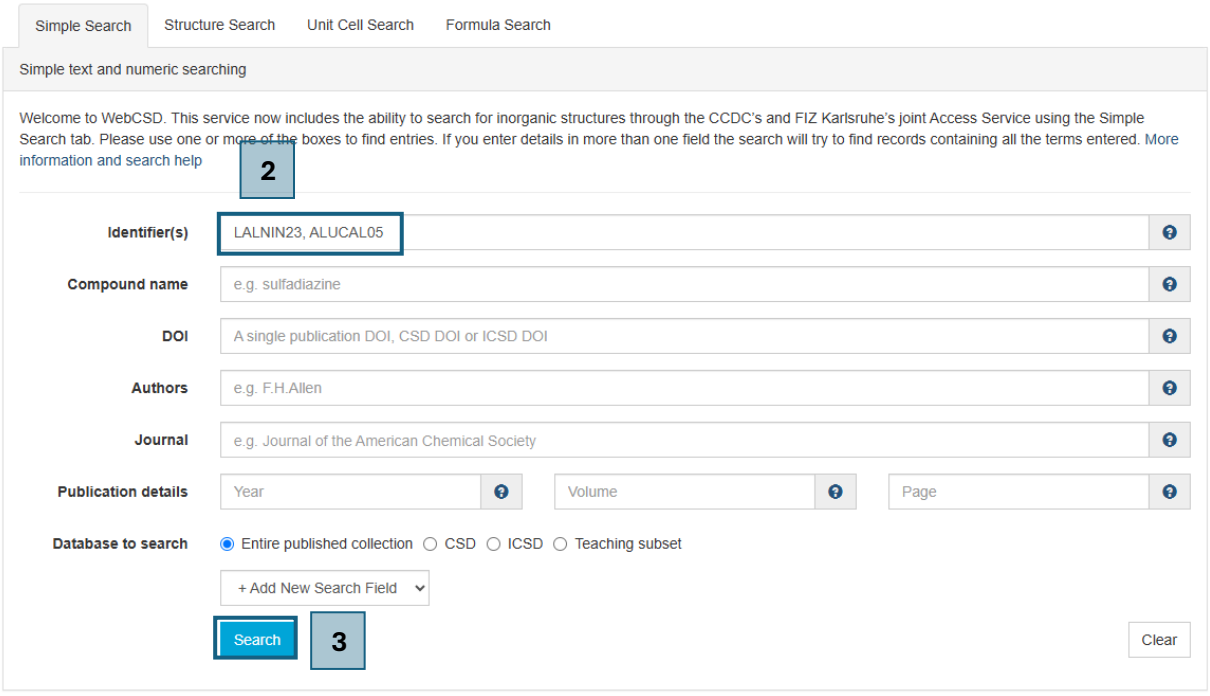
It is also important to note that the crystal structure of a flexible molecule gives a ‘frozen’ view of the molecule in a particular conformation. In the conditions that chemists typically use for reactions and spectroscopic measurements, flexible molecules will typically change conformations rapidly and average out any special stereoisomerism associated with its specific shape in the crystal form. In this teaching module we will disregard potential instances of this.

2.2 Investigating the structure of the amino acid alanine

We will first examine two CSD entries of the molecule alanine (2-aminopropanoic acid), which is the simplest amino acid after glycine.

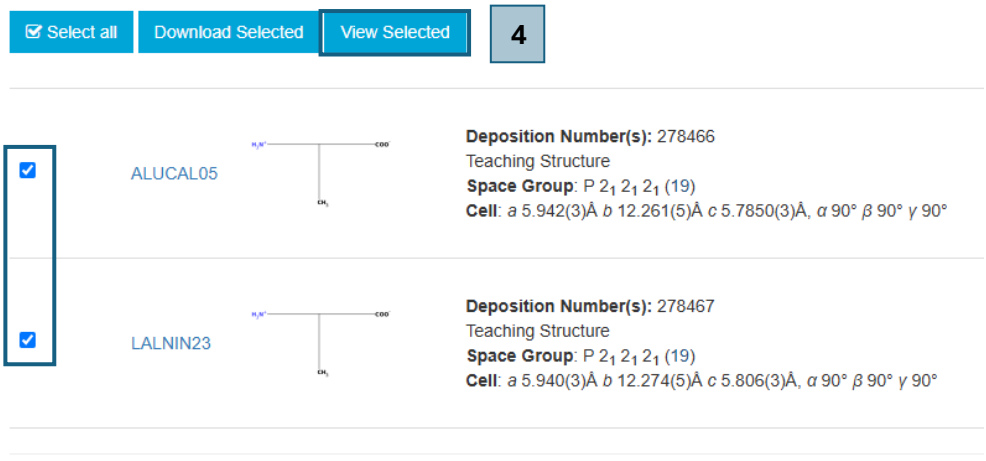
1. On a Web browser, visit https://www.ccdc.cam.ac.uk/structures/

2. In the *Identifier(s)* field, type "LALNIN23, ALUCAL05" (these 6-8 character codes are database identifers, referred to as *refcodes*)

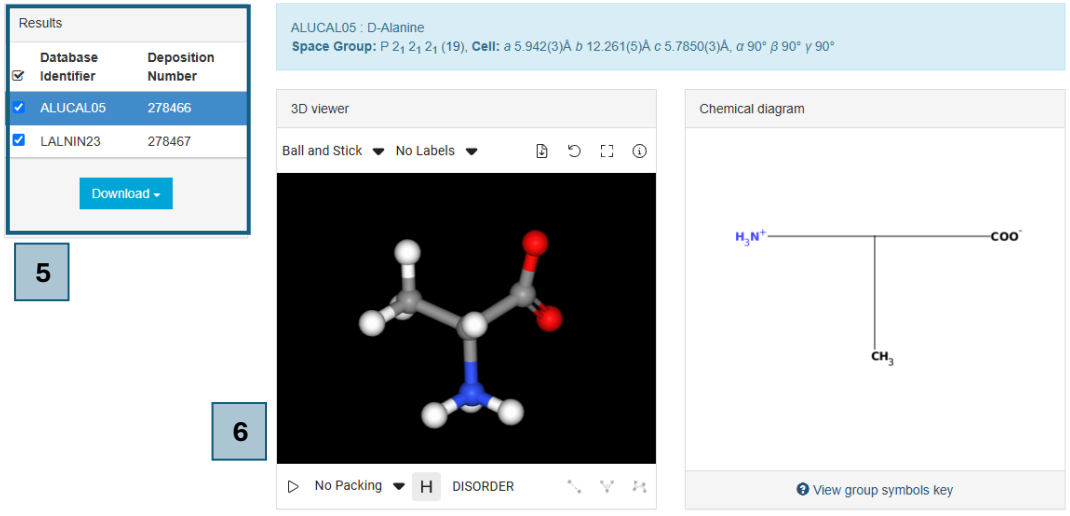


3. Press **Search**

4. Ensure that both entries are selected in the results page and click **View Selected**.

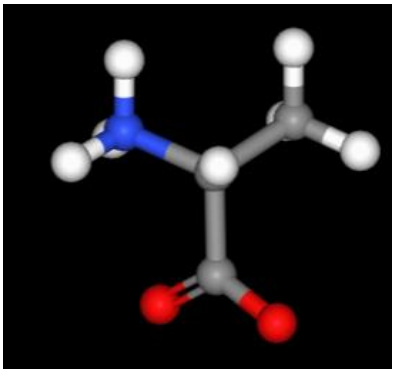


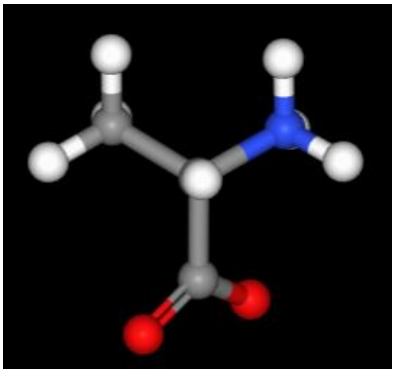
5. In the detailed view, you can see a 2D and a 3D diagram. You can move between the two structures by clicking on the *Database Identifier* (the refcode) in the *Results* list.



6. To manipulate the structure:
    - Left click and drag to rotate the structure.
    - Right click and drag to translate the structure.
    - Scroll up/down with the mouse wheel to zoom in/out.
    - At any time, hit ↺ to reset the viewer.

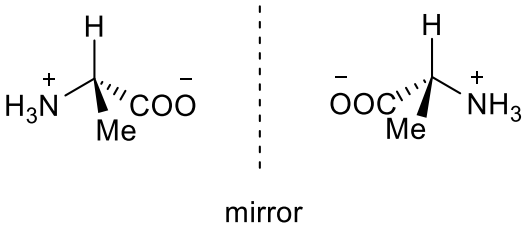
Can you see any differences between them? Are they identical? You should be able to see from the images below that, whilst they are chemically identical – same atoms, same bonds – they are not spatially identical.





Left: CSD entry ALUCAL05 (D-alanine). Right: CSD entry LALNIN23 (L-alanine).

Notice that with the C–H bond on the central carbon directed out of the plane of the page, the molecules appear to be mirror images of one another.



Structures which cannot be superimposed upon their mirror images are chiral and are said to be *enantiomers*. Enantiomers are identical in all physical properties except for the direction in which they rotate plane polarised light. Compounds that are able to rotate plane polarised light are said to be optically active. Enantiomorphism can lead to differences in other properties such as smell, and crystals of enantiomers may form crystal shapes which are mirror images of one another.

How can we predict whether or not a molecule is chiral? There are a couple of key points to consider:

- Any molecule which lacks a mirror symmetry plane or a centre of inversion (inversion can be defined as an operation consisting of a twofold rotation and reflection in a perpendicular mirror plane) may be chiral.
- A common reason for organic molecules to lack mirror/inversion symmetry is for them to contain a carbon atom with four different substituents.
- Whilst we usually talk about chiral *molecules*, it is useful to have a term for the focus of chirality in a molecule (e.g. the tetrasubstituted carbon described above). We call the focus of chirality a *chiral centre* if it coincides with an atom.
- Another frequently used term is stereogenic centre or *stereocentre*. Interchanging any two substituent groups at a stereocentre will generate a new stereoisomer but the stereoisomers need not be chiral.

All amino acids have a carbon atom carrying an amino group, a carboxyl group, a hydrogen atom and an R group (for alanine, R = methyl). Therefore, all amino acids are chiral (except for glycine where R = H, see CSD refcode GLYCIN). Natural alanine, extracted from plants, consists of one enantiomer only. Samples of chiral molecules that contain only one enantiomer are called enantiomerically pure. However, alanine produced in the lab from achiral starting materials will be a 50:50 mixture of enantiomers which is referred to as being racemic. In fact, nearly all chiral molecules in living systems are found as single enantiomers, not as racemic mixtures.

Exercise 1

Examine the structures in the table and determine if they are chiral.

Compound	**CSD refcode**	**Chiral?**
Toluene	TOLUEN	
Lactic acid	YILLAG	
Citric acid	CITRAC10	
2,2,2-trifluoro-1-(9-anthryl)ethanol	SOCLIF	

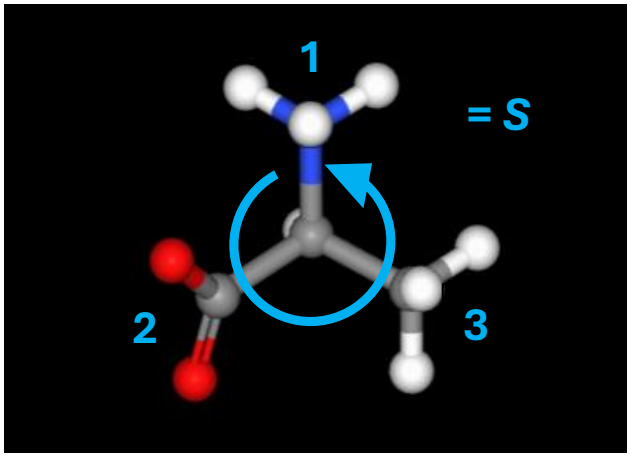
2.3 Describing the configuration of a chiral centre: the Cahn-Ingold-Prelog system

How do chemists explain which enantiomer they are talking about? One way is to use a set of rules to assign a letter *R* or *S*, to describe the configuration of groups at a chiral centre. The letters come from the Latin *rectus* (right) and *sinister* (left). The method used to assign the configuration at a chiral centre is called the Cahn-Ingold-Prelog (CIP) system. There three steps: (1) identifying chiral centres, (2) prioritising the attached groups and (3) assigning an *R* or *S* descriptor. Let's return to alanine to see how they are applied. We will use CSD structure LALNIN23.

1. The only atom which bears four different groups is the central carbon atom of alanine (called the *α*-carbon in amino acids like alanine), therefore this molecule has only one chiral centre.

2. Prioritisation of the groups attached to the chiral centre is done using atomic number, where priority increases with atomic number. If the atoms immediately attached to a chiral centre are of the same element, move along the chain until there is a point of difference.[1] In alanine, the groups attached to the α-carbon are methyl (carbon, atomic number 6), carboxylate (carbon, atomic number 6), ammonium (N, atomic number 7) and hydrogen (atomic number 1). NH_3^+ therefore takes priority 1. Comparing CH_3 and COO^-, moving to the next position from carbon, we find hydrogen (atomic number 1) and oxygen (atomic number 8) for CH_3 and COO^-, respectively. Carboxylate therefore takes priority 2 and methyl takes priority 3. Finally, the hydrogen directly attached to the *α*-carbon takes priority 4. Summary: $NH_3^+ > COO^- > CH_3 > H$.

3. Orientate the molecule so that the bond to the lowest priority group is pointing down the line of sight (the back side, into the plane of the page). This is C–H in alanine. If the remaining groups occur in the order 1-2-3 in a clockwise sense, the configuration is *R*; if they occur in this order in an anticlockwise direction, the configuration is *S*. We can see in the case of LALNIN23 that NH_3^+ - COO^- - CH_3 occurs in an anticlockwise sense, hence the stereocentre is *S*. This is illustrated in the picture below.



Application of the CIP priority rules to alanine in CSD entry LALNIN23.

[1] This is described as moving through *spheres*. The first sphere includes atoms one bond away from the chiral centre, the second contains atoms two bonds away and so on.

Since CSD structure ALUCAL05 is the enantiomer of this molecule, its configuration at the equivalent chiral centre should be *R*. Apply the CIP priority rules to confirm that this is the case.

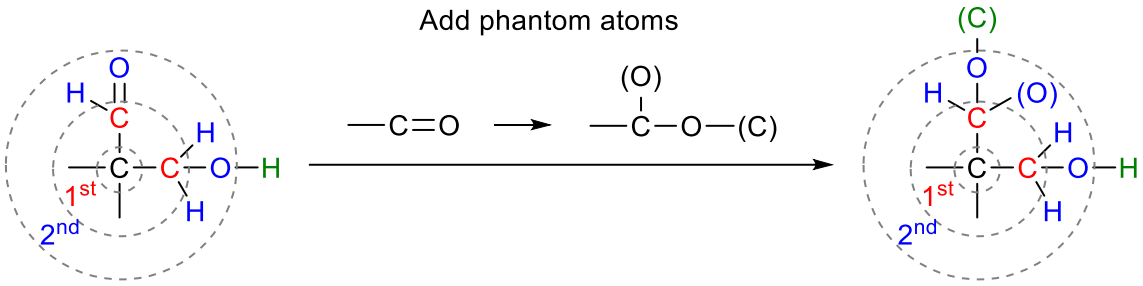
Exercise 2

Identify the chiral centre in molecules in the table below and determine their configuration.

CSD refcode	**Chiral atom label**	***R/S***
RERXIV		
ADRENL		
JEKNOC10		

2.3.1 CIP rules for multiple bonds

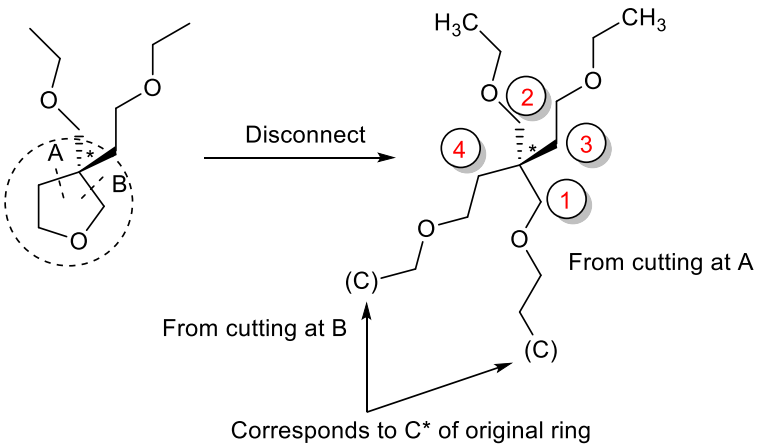
Which of CH_2OH (alcohol) or CH=O (aldehyde) would have higher priority if both functional groups were attached to the same central carbon atom? In the Cahn-Ingold-Prelog system, this is decided by using so-called phantom atoms. The double bond is represented single bonds and phantom atoms by duplicating the atoms of the double bond and attaching these phantom atoms to the atoms of the double bond. The phantom atoms are considered not to be bonded to any further atoms. In the case of the carbonyl group, this would involve adding a phantom oxygen atom to the existing carbon atom and a phantom carbon atom to the existing oxygen one.



Now exploring the branches of the tree graph shown above in the second sphere (atoms coloured in blue) we see encounter two oxygen atoms and one hydrogen (expanded representation of aldehyde) *vs* two hydrogen and one oxygen (primary alcohol), therefore the aldehyde has precedence.

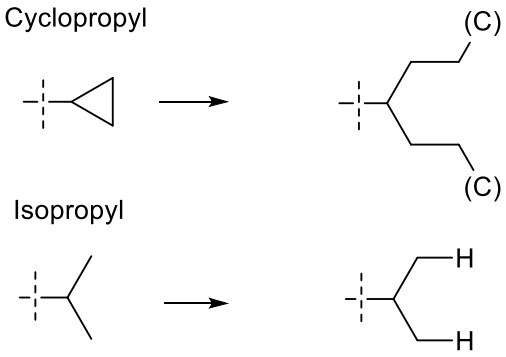
2.3.2 CIP rules for cyclic compounds

When are rings are considered, they are severed at the branch point and the atom at the branch point is then complemented at the end of the chain resulting from the disconnection using a phantom atom. This is best illustrated with an example. In the tetrahydrofuran derivative below, the 5-membered ring is cut either to side of the chiral centre to give the two chains ending in the phantom C atoms.



Now looking at the substituents, there are two with oxygen in second positions along the chain, so these will get priorities 1 and 2. Following the chains along to the fifth position we find either H or (C). The phantom carbon, (C) takes precedence so that chain gets highest priority. The remaining two chains pose a similar choice; however, we find that the chain resulting from ring deconstruction has no substituents once the phantom carbon is reached. On the other hand, the true acyclic ligand has hydrogens attached, so it will get higher priority. This example thus has configuration *S* at the starred carbon.

Using this method, you should be able to see that a cyclic alkyl would be a higher priority group than the linear alkyl of the same length e.g. cyclopropyl has higher priority than isopropyl.



Combining the multiple bond and ring rules, you will see that phenyl (which contains double bonds in Kekulé form) takes precedence over cyclohexyl.

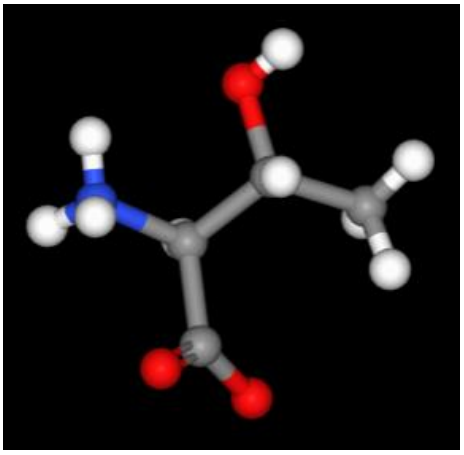
Exercise 3

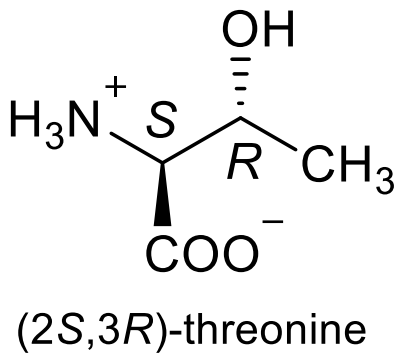
Look up CSD refcode DIWDIW on Access Structures. Use the CIP system to determine the configuration.

2.4 Compounds containing more than one stereocentre

Alanine is relatively simple to deal with, it contains only one chiral centre and can therefore only exist in two enantiomeric forms. Now, examine the structure of threonine (2-amino-3-hydroxybutanoic acid, refcode: LTHREO01). You will see that threonine has two stereocentres (on C2 and C3). What is

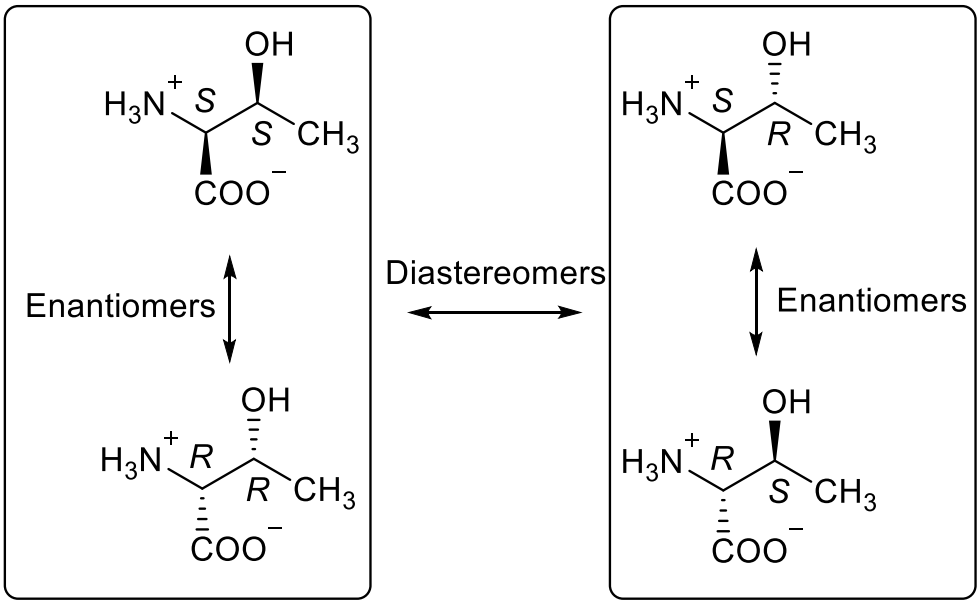
the configuration at each of these stereocentres? You should find that C2 has configuration *S*, whilst C3 has configuration *R*, which can be written succinctly as (2*S*,3*R*). This is shown below.





Left: the structure of L-threonine, CSD entry LTHREO01. Right: 2D chemical diagram with stereocentres labelled.

Since there are two stereocentres in threonine, there are four possible combinations of *R* and *S* and thus up to four stereoisomers. If the stereochemistry of both chiral centre is inverted (changed from *R* to *S* and vice versa), the stereoisomers are enantiomers. i.e. (2*S*,3*R*) and (2*R*,3*S*), and (2*R*,3*R*) and (2*S*,3*S*) are enantiomeric pairs. But what is the relationship between any two configurations that are not mirror images – e.g. between (2*R*,3*R*) and (2*R*,3*S*)? Stereoisomers that are not enantiomers are called diastereoisomers (usually shorted to diastereomers); they differ by the configuration of one or more, but not all, stereocentres. The relationships are summarised below.

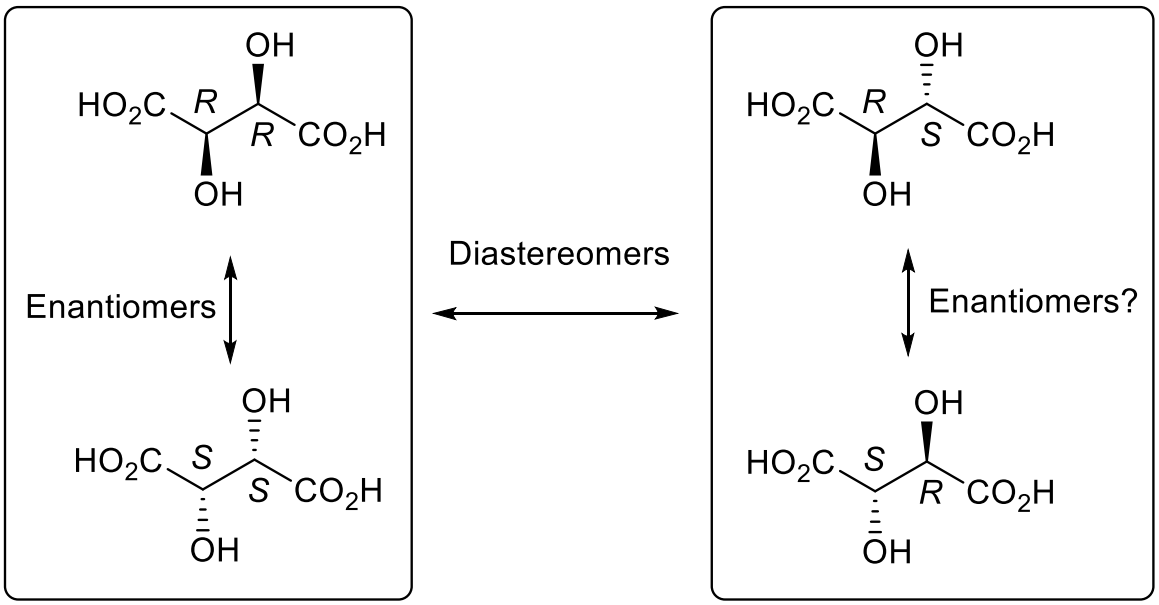


Exercise 3

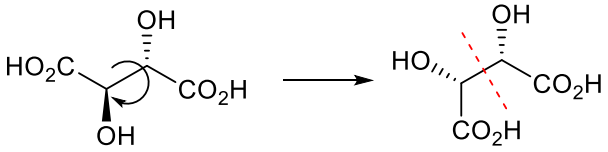
Ephedrine (refcode: EPHEDR01) and pseudoephedrine (refcode: PSEPED01) each contain two stereogenic centres and are stereoisomers. Ephedrine is used in nasal sprays as a decongestant and pseudoephedrine is the active component of the decongestant Sudafed. Find these structures on Access Structures and examine their stereochemistry. Assign *R*/*S* configuration to their chiral centre(s) and describe their stereochemical relationship.

2.5 Compounds that contain stereogenic centres but are achiral

Tartaric acid, like threonine, contains two stereogenic centres so again we might expect four stereoisomers: two diastereomers, each existing as a pair of enantiomers as shown below.



However, only three stereoisomers are found (CSD refcodes TARTAC, TARTAL04 and TARTAM). Can you explain why this is? Examine all three structures closely. For each structure, assign the configuration at both stereogenic centres and match the structure with the corresponding stereoisomer in the diagram above. You should find that TARTAM can be matched against both the *R,S* and *S,R* configurations shown in the diagram above: *R,S*-tartaric acid and *S,R*-tartaric acid are identical. The identity of the *R,S* and *S,R* structures results from the fact that the molecule has symmetry. It's easier to see this if the molecule is rotated about the central C–C bond, as shown below.



Rotate the molecule about the central C–C bond to reveal mirror symmetry.

The molecule then appears to be divided in two halves by a mirror plane. Compounds that contain stereogenic centres but are achiral due to symmetry are called *meso* compounds. Tartaric acid therefore exists as three stereoisomers: two enantiomers (TARTAC and TARTAL04) and one achiral *meso* form (TARTAM).

Conclusions

In this section we have seen that a carbon atom bearing four different substituents is chiral and leads to stereoisomerism in the molecule it is found in. Molecules can have multiple stereocentres so a systematic way of distinguishing them is required; in practice, the Cahn-Ingold-Prelog priority rules are used, to classify each stereocentre as *R* or *S*. Pairs of molecules which differ by configuration at only some chiral centres are called diastereomers and do have different physical properties. Epimers are a subset of these which differ only by the configuration of a single chiral centre. We have also seen that it is possible for molecules which contain chiral centres to be non-chiral when considered as a whole; these situations arise due to internal symmetry and the molecules are designated *meso*. This may seem like an overwhelming variety of possibilities but so long as we keep track of the configurations at individual stereogenic centres, relationships are easily established.

3 Non-carbon stereocentres

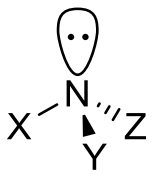
So far, we have only considered compounds containing chiral carbon atoms. However, other kinds of molecules can also display chirality. In the following sections, we will look at some examples of these.

3.1 Compounds with quadrivalent chiral atoms other than carbon

Any molecule containing an atom that has four bonds orientated towards the corners of a tetrahedron will be optically active if the four groups are different. For an examples of compounds with a quadrivalent chiral silicon atom see refcodes: YONMET and YONMIX. Examine each of these two stereoisomers in turn. You should find that the configuration at Si in YONMET is *R*, whereas in YONMIX, it is *S*.

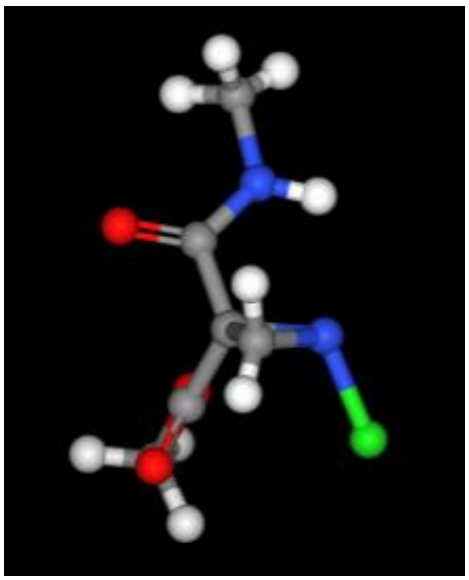
3.2 Compounds with trivalent chiral atoms

Pyramidal nitrogen atoms might be expected to give rise to optical activity if they are connected to three different groups. This is because the unshared pair of electrons is analogous to a fourth group and necessarily different from the others.

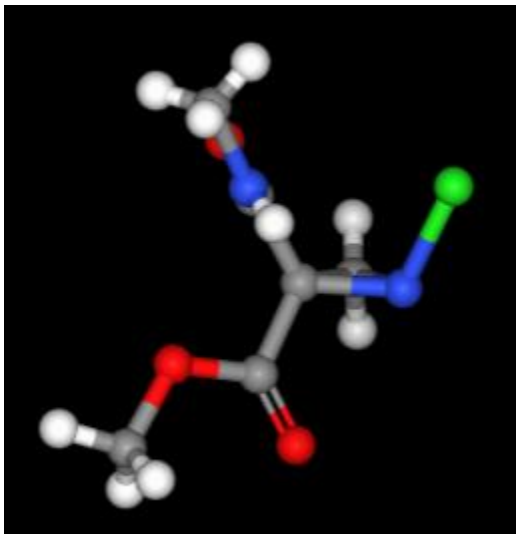


In practice, chirality is rarely observed in such systems due to pyramidal inversion. This is the rapid movement of the lone pair from one side of the *XYZ* plane to the other which thus interconverts the configuration of the chiral nitrogen centre. However, inversion is less rapid for nitrogen atoms in a

three membered ring, and for nitrogen atoms connected to an atom with a lone electron pair. When both features are present in a molecule the barrier to inversion is sufficient to allow isolation of separate isomers. This can result in compounds which are optically active due to a chiral trivalent nitrogen atom. An example of this is 1-chloro-2-methoxycarbonyl-2-methylcarbamoylaziridine, for which both the *cis* (CSD refcode KUBZOW) and *trans* (KIRCOD) epimers have been isolated (see overleaf). The use of *cis* and *trans* terminology here is a convenient way to describe the Cl group being on one 'side' of the ring or the other (the ester group is being used an arbitrary reference in this case). Within the CIP framework, a *phantom atom* with low priority is used to represent the lone pair position. Can you determine whether the ring nitrogen atoms are *R* or *S*?



CSD entry KUBZOW



CSD entry KIRCOD

Although the configuration at the chiral ring carbon differs (*S* in KUBZOW and *R* in KIRCOD), the configuration at the ring nitrogen is *R* in both cases.

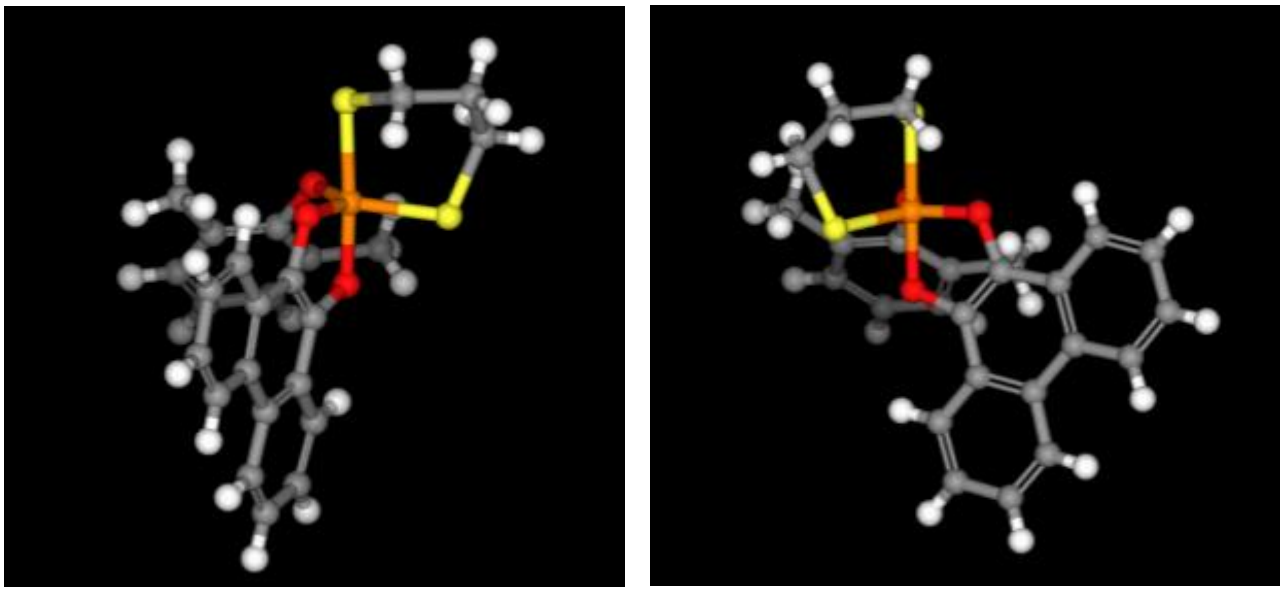
For heavier atoms (from 3rd period or above) with lone pairs, the barrier to inversion is rather larger than for amines. Phosphines and sulfoxides are common examples of potentially chiral groups with the central group possessing a lone pair.

Exercise 4

Look up CSD refcode APUMAC and assign the configuration at stereocentres present.

3.3 Chiral centres with coordination number greater than four

Chirality may be observed at centres with more than four substituents or ligands attached providing the condition for the lack of internal symmetry is met. This includes a wide range of coordination compounds. There are a greater number of possibilities for stereoisomerism at such polyhedral centres, incorporating both geometrical and optical types. A full discussion is beyond the scope of this module but by way of example, examine CSD entries SIDJEU and SIDJEU01.[2] The phosphorus atom in these molecules is in a trigonal bipyramidal environment.



Left: CSD entry SIDJEU (configuration *C* at phosphorus). Right: CSD entry SIDJEU01 (configuration *A* at phosphorus). The phosphorus centre is chiral, and the two molecules shown are enantiomers.

A stereochemical descriptor can be assigned to the above example by assigning priorities to the ligands as follows:

1. Rank the substituents using CIP rules as usual.
2. Look down onto the trigonal plane from the side of the axis with highest priority substituent.
3. If moving from the highest to second-highest priority substituent in the plane occurs clockwise, the label *C* applies. If it occurs in an anticlockwise sense, the label *A* applies.

Based on those rules, the molecules shown, from SIDHEU and SIDJEU01, are *C* and *A*, respectively.

If you would like to learn more about other polyhedral stereocentres, we recommend reading H. A. Favre and W. H. Powell, in *Nomenclature of Organic Chemistry*, Royal Society of Chemistry, 2013, ch. 9, pp 1156 – 1292.

[2] These structures actually both contain *C* and *A* isomers when crystal symmetry is applied but the default view chosen for the molecular unit by the crystallographer is opposite which is why they are used in this example.

3.4 Conclusions

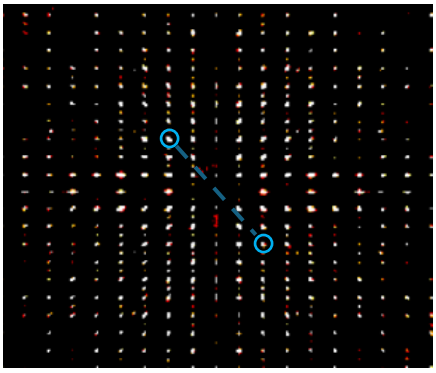
In this section we have seen that chirality at non-carbon tetravalent centres is a straightforward extension the normal rules. Replacement of one substituent with a lone pair, as seen in trivalent Group 5 compounds, also leads to chirality, but only in the absence of rapid inversion. Amines are rarely chiral due to this phenomenon; however, phosphines are normally stable to inversion and often do exhibit optical isomerism. Lastly, chirality can be observed for centres with *more* than four attached groups/ligands.

4 Experimental determination of chirality

As noted, enantiomers do not differ from one another in their physical properties such as melting point, however they do differ in the way they interact with certain type of light. They also differ in their interactions (and reaction) with other chiral molecules. Interaction with other chiral molecules forms the basis of chiral separation whilst chiral derivatisation makes use of chemical reactions between chiral molecules. Chiral separation and derivatisation are complex topics which are beyond the scope of this module. We shall focus on physical techniques: X-ray diffraction and polarimetry.

4.1 X-ray diffraction: absolute configuration

X-rays are a type of electromagnetic radiation with a very short wavelength. They interact with optically pure (consisting of one enantiomer) compounds in a way that allows the absolute configuration of chiral centres to be determined.[3] X-ray diffraction patterns are normally symmetrical in terms of the intensity of equivalent points in opposite directions, but chiral crystals can cause slight differences in intensity (see below for an example X-ray diffraction pattern). Once collected, X-ray diffraction data are processed and solved to give a model with the relative 3D positions of atoms. This model is then refined to optimise accuracy. If the crystal structure is chiral then the 3D model can have one of two handedness – just like enantiomers. During the refinement process it is usually possible to check that the model has the correct handedness by making use of the small intensity differences mentioned previously. Hence it is possible to determine the correct stereochemistry of individual molecules. This is called the Bijvoet method.



A typical X-ray diffraction pattern. Chirality can cause small differences in intensity between related spots, which can be used to determine absolute configuration.

4.2 Polarimetry: relative configuration

On the other hand, if a crystal is not available, it is still possible to identify enantiomers with respect to a reference of the same compound using techniques based on polarised light. For example, if we have a pure sample of (1*R*,4*R*)-camphor and a second sample of camphor whose chirality is unknown, we can determine if the unknown sample is *R* or *S* using a technique called polarimetry. Polarimetry uses plane polarised light (also called linearly polarised light). You will most likely have

[3] The effect that allows discrimination between chiral structures is called resonant scattering. Most textbooks on X-ray diffraction cover this topic. For example, see William Clegg in *X-ray Crystallography*, Oxford University Press, Oxford, 2nd edition, 2015, ch. 9, pp. 61–62.

encountered plane polarised light before in sunglasses, where it is induced by a polariser to reduce glare. Light consists of oscillating electric (E) and magnetic (B) fields as shown in **A** overleaf. The E- and B-fields are always perpendicular so we can just focus on the E-field (in red). Notice that the red E-field wave oscillates up and down only in *z* direction – it is polarised in this direction. In unpolarised light the oscillation varies along random directions, so filters called polarisers are needed in polarimeters to polarise the light. Chiral compounds are able to rotate the direction of polarisation away from the initial direction of polarisation; the second polariser in the polarimeter can then be rotated to determine by what angle the direction of polarisation has changed by, making use of the fact that a polarising filter will not allow light through it if the direction of polarisation is perpendicular to its own polarising direction.

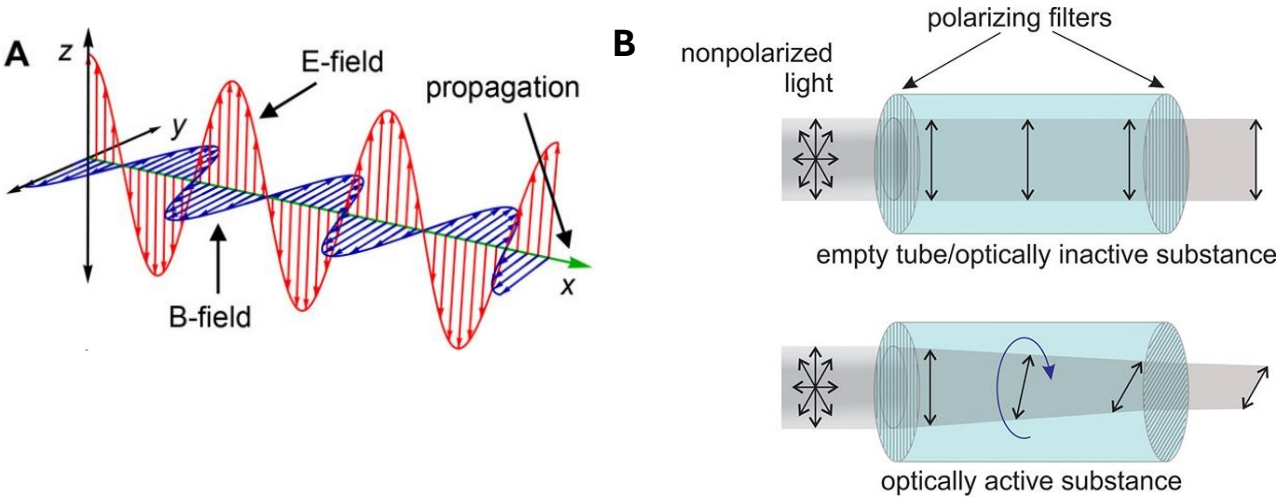
For a substance the specific rotation can be calculated from the measured angle:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \cdot \rho}$$

where l is the path length in decimetres, ρ is the density in grams per millilitre and α is the measured rotation in degrees. If the measurement is made for a solution, the specific rotation can be calculated from the modified equation:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \cdot c}$$

where c is the concentration in grams per millilitre. Note that specific rotation is dependent on wavelength and temperature, which must normally be specified. For standard measurements, the light source is often the sodium D-line, for which λ = 589 nm, and the temperature, T, is normally 20 °C. In such circumstances, the specific rotation may be written $[\alpha]_D$. A positive specific rotation indicates the sample rotates plane polarised light in a clockwise direction (dextrorotatory) whilst a negative specific rotation indicates (laevorotatory).



A: a polarised light wave, showing the directions of oscillation of the E- and B-fields do not change with propagation. Adapted with permission from Journal of Chemical Education, 2020, 97, 12,

4370–4376. Copyright 2020 American Chemical Society. **B**: schematic of the basic operation of a polarimeter. Adapted with permission from Journal of Chemical Education, 2020, 97, 4, 1162–1166. Copyright 2020 American Chemical Society.

Returning to the example of camphor, if $[\alpha_{obs}] = +45°$ for (1*R*,4*R*)-camphor (10 % in ethanol) at a given wavelength and another sample of camphor under the same conditions gives $[\alpha_{obs}] = -45°$, then it must be the enantiomer, (1*S*,4*S*)-camphor. On the other hand, if it was found that $[\alpha_{obs}] = 0$, this would suggest a racemic mixture – the signals of the enantiomers have opposite signs and the same magnitude and so cancel out. Intermediate values would indicate an unequal mixture of isomers which can be quantified by an enantiomeric excess, which is the absolute difference between the mole fraction of each enantiomer. It is usually expressed as a percentage:

$$\%ee = |F_R - F_S| \times 100$$

Where F_R and F_S are the mole fractions of the *R* and *S* isomers, respectively.

With (1*R*,4*R*)-camphor as the reference:

$$\frac{[\alpha_{obs}]}{[\alpha_R]} = \frac{F_R[\alpha_R] + F_S[\alpha_s]}{[\alpha_R]}$$

However, since $[\alpha_S] = -[\alpha_R]$,

$$\frac{[\alpha_{obs}]}{[\alpha_R]} = \frac{F_R[\alpha_R] - F_s[\alpha_R]}{[\alpha_R]} = F_R - F_S$$

hence,

$$\%ee = \left|\frac{[\alpha_{obs}]}{[\alpha_R]}\right| \times 100$$

Given that the sign of $[\alpha_R]$ is known from the reference, (1*R*,4*R*)-camphor, by omitting the modulus from the above equation, it is possible to determine *which* enantiomer is in excess. Say, for example that a sample was measured and $[\alpha_{obs}]$ was found to be −15°, we would calculate:

$$\frac{[\alpha_{obs}]}{[\alpha_R]} = \frac{-15°}{45°} = \frac{-1}{3}$$

Since this is less than zero, it tells you than the enantiomer with the configuration opposite to the reference (i.e. 1*S*,4*S*)-camphor) is in excess, and the %*ee* is 33.3%. This can be generalised to

$$\%ee = \left|\frac{[\alpha_{obs}]}{[\alpha_{pure}]}\right| \times 100$$

where $[\alpha_{pure}]$ is the specific rotation of a reference sample. Note that the measurement conditions must be the same for the sample and the reference.

5 Summary

In this module you have explored two types of chirality: optical isomerism and diastereoisomerism. To summarise the key points covered:

- A molecule that is not superimposable on its mirror image is said to be chiral.
- A chiral molecule is one that does not contain a plane of symmetry. The most common cause of chirality is the presence of a tetrahedral sp^3-hybridised carbon atom bonded to four different groups; this is referred to as a stereogenic centre.
- Compounds that contain such stereogenic centres can exist as a pair of non-superimposable mirror image stereoisomers called enantiomers.
- Enantiomers are identical in all physical properties except for the direction in which they rotate the plane of polarised light.
- The configuration of a stereogenic centre can be described as either *R* or *S* by applying the Cahn-Ingold-Prelog sequence rules.
- Diastereomers are stereoisomers that are not mirror images. Diastereomers have different spectra and physical properties.
- Some molecules have more than one stereogenic centre. Enantiomers have opposite configuration at all stereogenic centres, whereas diastereomers have the same configuration in at least one centre but opposite configurations at the other(s).
- Compounds that contain stereogenic centres but are achiral (due to a symmetry plane) are called *meso* compounds.
- Molecules can also display optical activity due to other structural features, including: quadrivalent chiral atoms other than carbon, trivalent chiral atoms.
- Absolute configuration can be experimentally determined with X-ray diffraction using the Bijvoet method, if crystals are available.

The chirality we have covered in this handout arises from a specific point in a molecule. However, this is not the only way that chirality can arise – after all the only requirement for enantiomers is that they lack internal mirror symmetry. Enantiomers can still occur in molecules lacking stereogenic centres if a rotation cannot interconvert them. This is called axial chirality and is covered elsewhere.

5.1 Next steps

If you would like to study the structures presented in this teaching sheet further, we suggest viewing them in Mercury, where you can customize the view of the molecules and make more advanced measurements. A free-for academic use version of Mercury is available for educational use. To learn more about Mercury, we recommend trying the online module "Visualization 101 – Visualizing Structural Chemistry Data with Mercury". You can find the structures used in this module in the Teaching Subset, which is pre-loaded into Mercury. See the links below for more information.

https://www.ccdc.cam.ac.uk/solutions/software/free-mercury/
https://www.ccdc.cam.ac.uk/community/training-and-learning/csdu-modules/visualization-101/
https://www.ccdc.cam.ac.uk/community/education-and-outreach/education/teaching-subset/

If you wish to explore the CSD further and search for structures of interest to you, you can find a number of training resources, including self-guided workshops, online courses and videos to you get started from the CCDC's Training and Learning Web pages.

https://www.ccdc.cam.ac.uk/community/training-and-learning/

If you have found this module useful, you might like to explore other topics in stereochemistry such as axial chirality.

Answers to exercises

Exercise 1

Compound	**CSD refcode**	**Chiral?**
Toluene	TOLUEN	No
Lactic acid	YILLAG	Yes
Citric acid	CITRAC10	No
2,2,2-trifluoro-1-(9-anthryl)ethanol	SOCLIF	Yes

Exercise 2

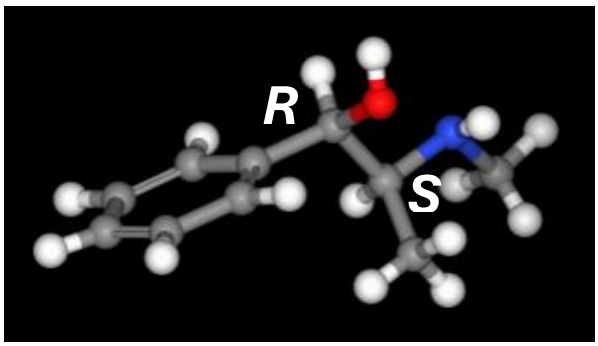
CSD refcode	**Chiral atom label**	***R/S***
RERXIV	C4	*R*
ADRENL	C7	*R*
JEKNOC10	C2 (or C15)	*S*

Exercise 3

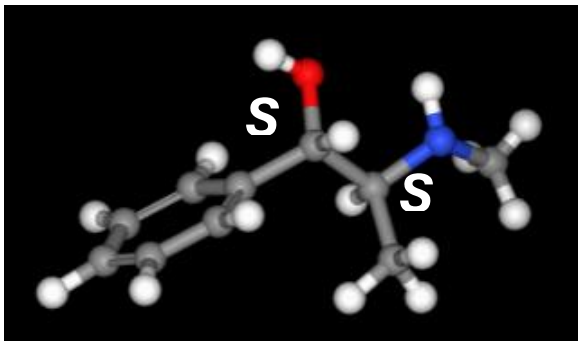
2-Cyclohexyl-1-(4-methoxyphenyl)-2-phenylethanone (CSD entry DIWDIW) contains one chiral centre, which bears the following substituents: phenyl, cyclohexyl and ketone. Application of the double bond and ring rules gives C=O > Ph > Cy. Hence, the stereocentre is *S*.

Exercise 4

The two isomers of ephedrine are shown below.



Ephedrine (CSD refcode EPHEDR01)



Pseudoephedrine (CSD refcode PSEPED01)

Since the two molecules differ only at one stereocentre they are diastereomers. A specific term for isomers differing at only one chiral centre, like this pair, is epimers.