1 STEREOCHEMISTRY

1.1 INTRODUCTION

- Stereoisomers are molecules whose atomic connectivity is the same but whose three-dimensional arrangement of atoms in space is different.
- This 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.
- 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 in order to study and understand the structural features that give rise to stereoisomerism.

1.2 OBJECTIVES

- Recognise a stereogenic (chiral) centre in a molecular structure.
- Use the sequence rules for specification of configuration to identify and name correctly stereoisomers and individual stereogenic (chiral) centres having *R* or *S* absolute configurations.
- To be able to predict, identify and distinguish between enantiomers and diastereoisomers.
- To recognise a meso compound given its structure.
- To be able to recognise other structural features that can give rise to chirality, including quadrivalent chiral atoms, tervalent chiral atoms, restricted rotation, and helical shape.

1.3 GETTING STARTED

- Open the interactive WebCSD teaching database by going to the following URL:

  http://webcsd.ccdc.cam.ac.uk/teaching_database_demo.php

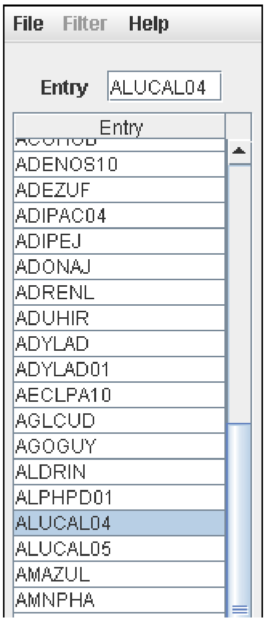
- This demo version of WebCSD allows you to browse all 500 entries in the teaching subset of the Cambrdige Structrual Database.
- Reference codes (refcodes) of the structures in the teaching set will appear in a list on the left hand side of the WebCSD page. Only those refocde beginning with "A" are displayed intially. To show those refcodes starting with "B" click on the > button.
- To view a structure select the corresponding refcode in the list by left-clicking on it.

Alternatively, you can type a refocde in the **Entry** box above the structure list.

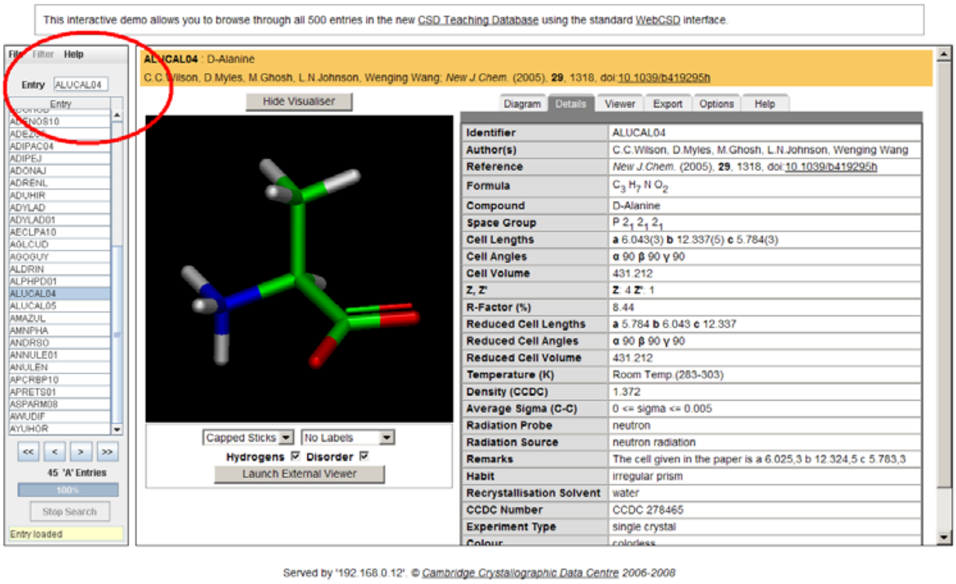
1.4 STEPS REQUIRED

1.4.1 Investigate the structure of the amino acid alanine.

- Examine and compare two crystal structures of alanine (refcodes *LALNIN23* and *ALUCAL05*). To display a structure type it's reference code (refcode) in the **Entry** box above the structure list on the left hand side of the WebCSD page:



Entry: ALUCAL04



This interactive demo allows you to browse through all 500 entries in the new CSD Teaching Database using the standard WebCSD interface.

Entry: ALUCAL04

ALUCAL04 : D-Alanine

C.C.Wilson, D.Myles, M.Ghosh, L.N.Johnson, Wenging Wang; *New J.Chem.* (2005), **29**, 1318, doi:10.1039/b419295h

Identifier	ALUCAL04
Author(s)	C.C.Wilson, D.Myles, M.Ghosh, L.N.Johnson, Wenging Wang
Reference	*New J.Chem.* (2005), **29**, 1318, doi:10.1039/b419295h
Formula	$C_3 H_7 N O_2$
Compound	D-Alanine
Space Group	$P 2_1 2_1 2_1$
Cell Lengths	**a** 6.043(3) **b** 12.337(5) **c** 5.784(3)
Cell Angles	**α** 90 **β** 90 **γ** 90
Cell Volume	431.212
Z, Z'	**Z**: 4 **Z'**: 1
R-Factor (%)	8.44
Reduced Cell Lengths	**a** 5.784 **b** 6.043 **c** 12.337
Reduced Cell Angles	**α** 90 **β** 90 **γ** 90
Reduced Cell Volume	431.212
Temperature (K)	Room Temp.(283-303)
Density (CCDC)	1.372
Average Sigma (C-C)	0 <= sigma <= 0.005
Radiation Probe	neutron
Radiation Source	neutron radiation
Remarks	The cell given in the paper is a 6.025,3 b 12.324,5 c 5.783,3
Habit	irregular prism
Recrystallisation Solvent	water
CCDC Number	CCDC 278465
Experiment Type	single crystal
Colour	colorless

Capped Sticks | No Labels

Hydrogens ☑ Disorder ☑

45 'A' Entries

Entry loaded

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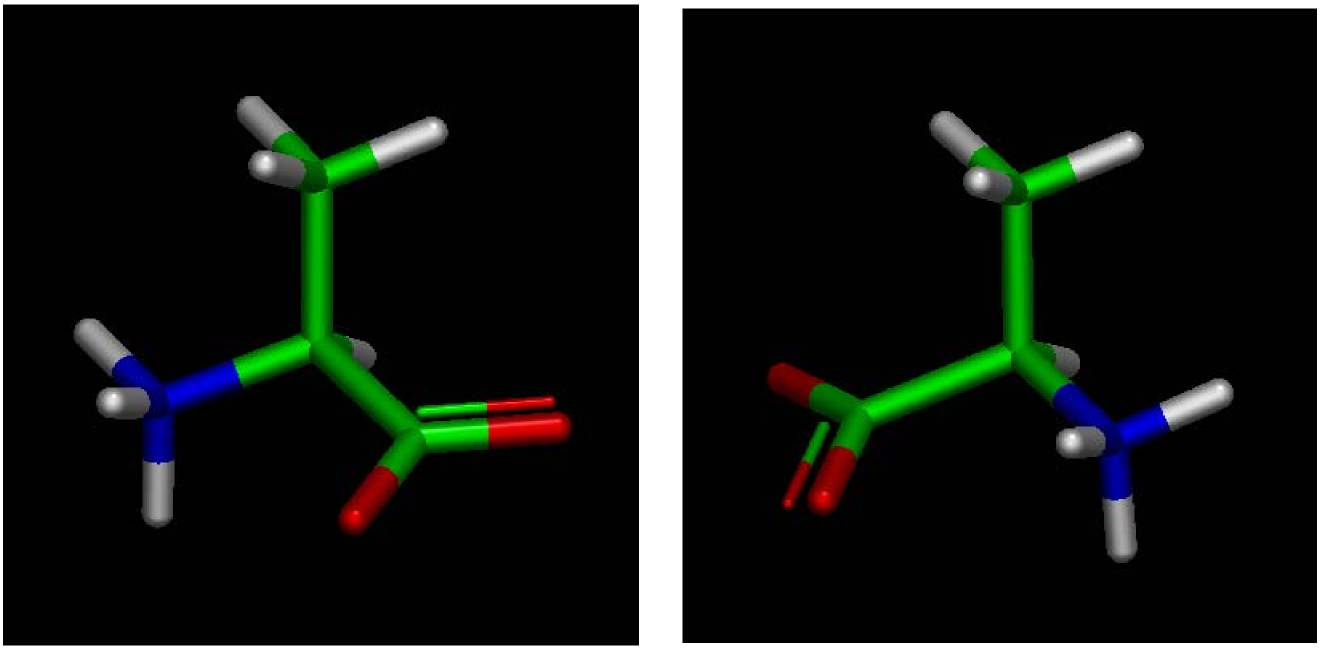
- What is the relationship between these two structures, are they identical?



left: Alanine (LALNIN23); right: Alanine (ALUCAL05)

To manipulate structures in the 3D viewer:

1. Structures can be rotated by moving the cursor in the display area while keeping the left-hand mouse button pressed down.

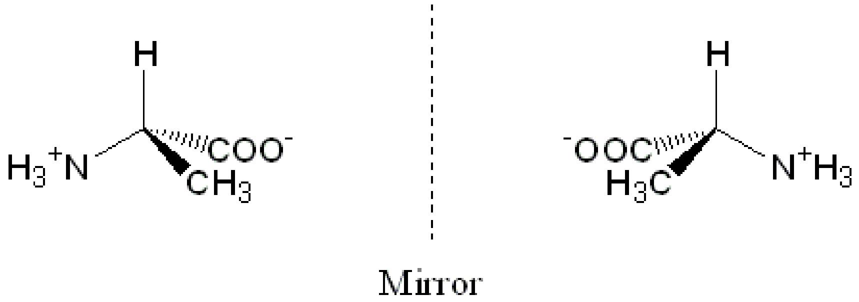
2. To zoom in and out move the cursor up and down in the display area while keeping both the shift key and the left-hand mouse button pressed down.

3. To translate structures move the cursor in the display area while keeping both the left-hand mouse button and the keyboard Ctrl key pressed down.

4. At any stage the display area can be returned to the default view by hitting the r button on the keyboard.

- Although the two structures initially look identical, after careful inspection, we can see they are not the same. The structures are non-superimposable. However we orientate the structures we cannot directly overlay one onto the other such that all four substituents align. *Note that if you have full access to the Cambridge Structural Database then you will be able to display both structures together and manipulate them independently within Mercury. Try to overlay one structure onto the other. However the structures are orientated all four substituents cannot be aligned.*
- In fact, the two structures are mirror-images of each other. If we reflected *LALNIN23* in a mirror,

we would get a structure that is identical to *ALUCAL05*.



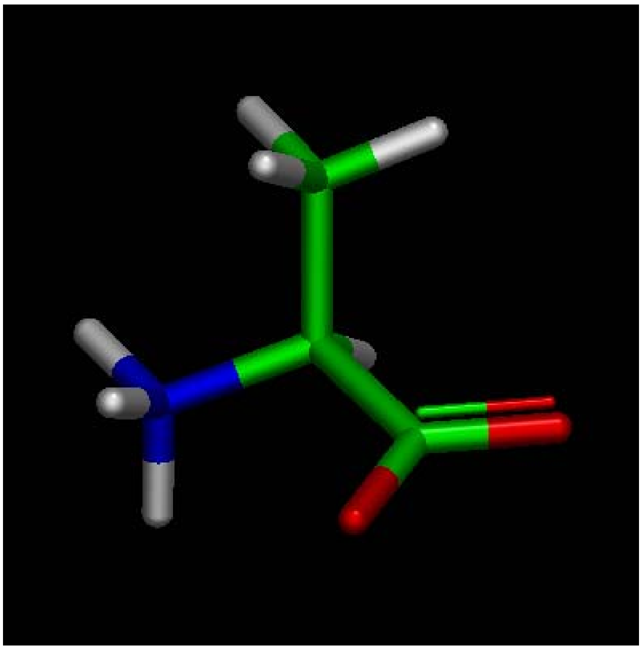
- Two structures that are not identical, but are mirror images of each other are called enantiomers. Structures that are not superimposable on their mirror image and can therefore exist as two enantiomers are called chiral.
- Enantiomers are identical in all physical properties except for the direction in which they rotate the plane of polarised light. Compounds that are able to rotate the plane of polarized light are said to be optically active.

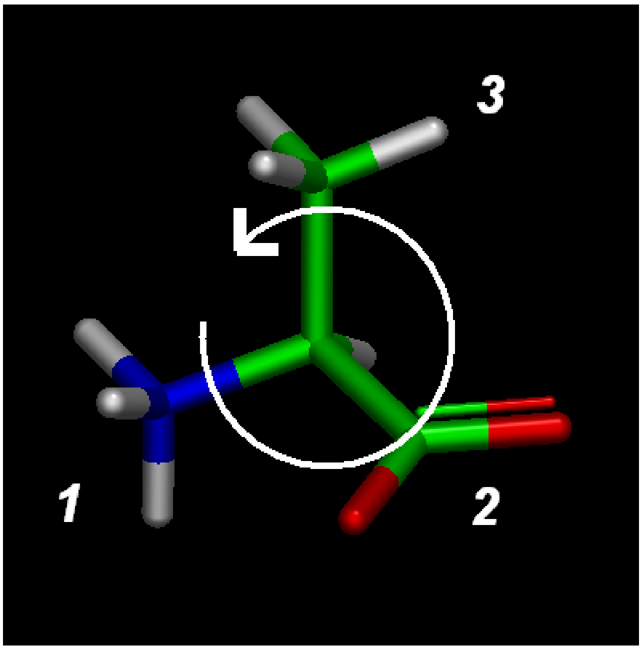
1.4.2 Identifying chirality.

- How can we predict whether or not a molecule is chiral?
- A molecule can't be chiral if it contains a plane of symmetry. If a molecule has a plane of symmetry then it will be superimposable on its mirror image and will be achiral.
- Any molecule containing a carbon atom carrying four different groups will not have a plane of symmetry and must therefore be chiral. Such carbon atoms are know as stereogenic or chiral centers.
- All amino acids have a carbon carrying an amino group, a carboxyl group, a hydrogen atom and an R group (for alanine R=methyl). Therefore, all amino acids (except for glycine where R=H, see refcode *GLYCIN*) are chiral.
- 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 and is referred to as being racemic. In fact, nearly all chiral molecules in living systems are found as single enantiomers not as racemic mixtures.
- Examine each of the following structures and determine whether or not they are chiral.
  - Toluene (refcode: *TOLUEN*)
  - Lactic acid (refcode: *YILLAG*)
  - Citric acid (refcode: *CITARC*)
  - 2,2,2-Trifluoro-1-(9-anthryl)ethanol (refcode: *SOCLIF*)

1.4.3 Describing the configuration of a chiral centre.

- 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.
- Once again, display the structure of alanine (refcode: *LALNIN23*).
- First, look at the four atoms directly attached to the stereogenic centre and assign priorities in order of decreasing atomic number. The group with the highest atomic number is ranked first, the lowest atomic number is ranked fourth. If two or more of the atoms are identical, then we assign priorities by assessing the atoms attached to those atoms, continuing on as necessary until a difference is found.
- So, we assign priority 1 to the NH_3 group. Priorities 2 and 3 will be assigned to the CO_2 and CH_3 groups respectively since the CO_2 group carries oxygen atoms whereas the CH_3 only carries hydrogen atoms. Finally, priority 4 is assigned to the hydrogen atom.
- Now, orientate the molecule in the display so that the lowest priority substituent (the hydrogen) is pointed away from you. The hydrogen should be almost eclipsed by the chiral carbon atom.
- Next, mentally trace a path from substituent priority 1 (NH_3) to 2 (CO_2) to 3 (CH_3). If we are moving in a clockwise direction, then we assign the label *R* to the chiral centre; if we move in an anticlockwise direction, we assign the label *S*.



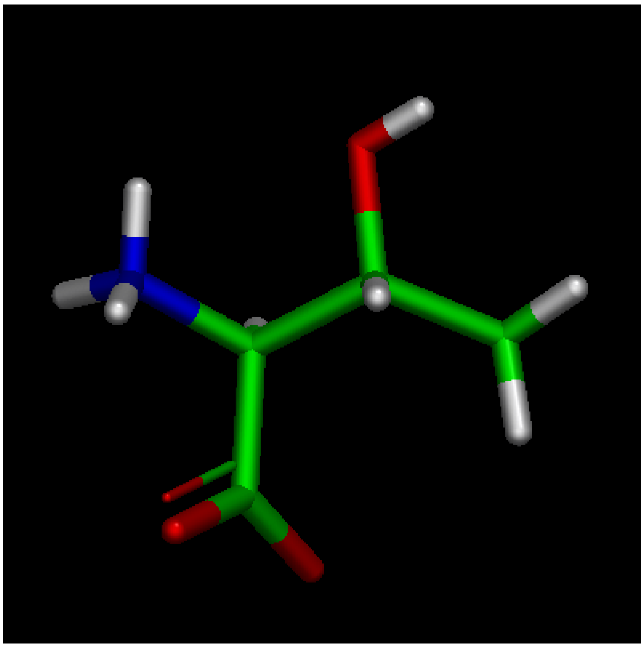


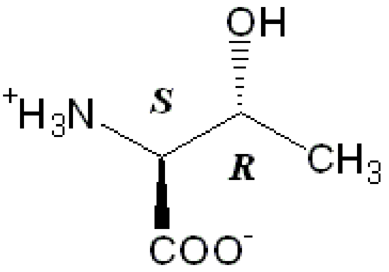
- What is the configuration of our alanine molecule? Is it the (*S*)-alanine, or (*R*)-alanine enantiomer?
- Some further examples of chiral molecules are provided. Identify the chiral centre in each of the following molecules and assign their configuration using *R* and *S* notation:
  - Carvone (spearmint oil) (refcode: *RERXIV*)

- Adrenaline (refcode: *ADRENL*)
- Ibuprofen (refcode: *JEKNOC10*).

1.4.4 Compounds containing more than one stereogenic center.

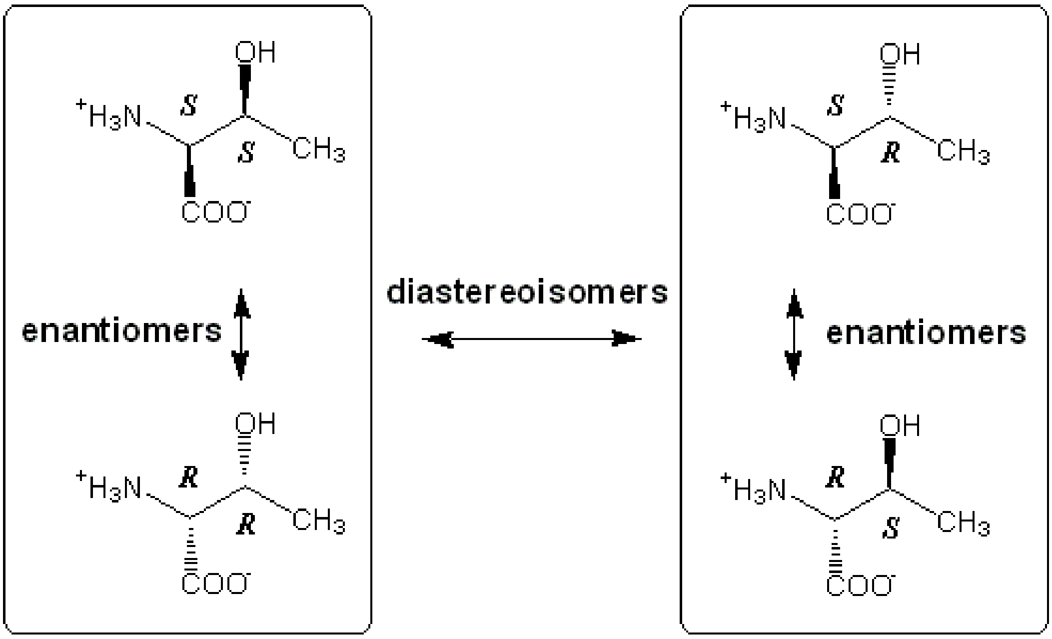
- Alanine is relatively simple to deal with, it contains only one chiral center and can therefore only exist in two enantiomeric forms.
- Now, examine the structure of threonine (2-amino-3-hydroxybutanoic acid) (refcode: *LTHREO01*). You will see that threonine has two stereogenic centers (on C2 and C3). Assign *R* and *S* configuration to each stereogenic center.
- You should find that *LTHREO01* has a (2S,3R) configuration. This can be drawn in 2D as shown below:





(2S,3R)-threonine

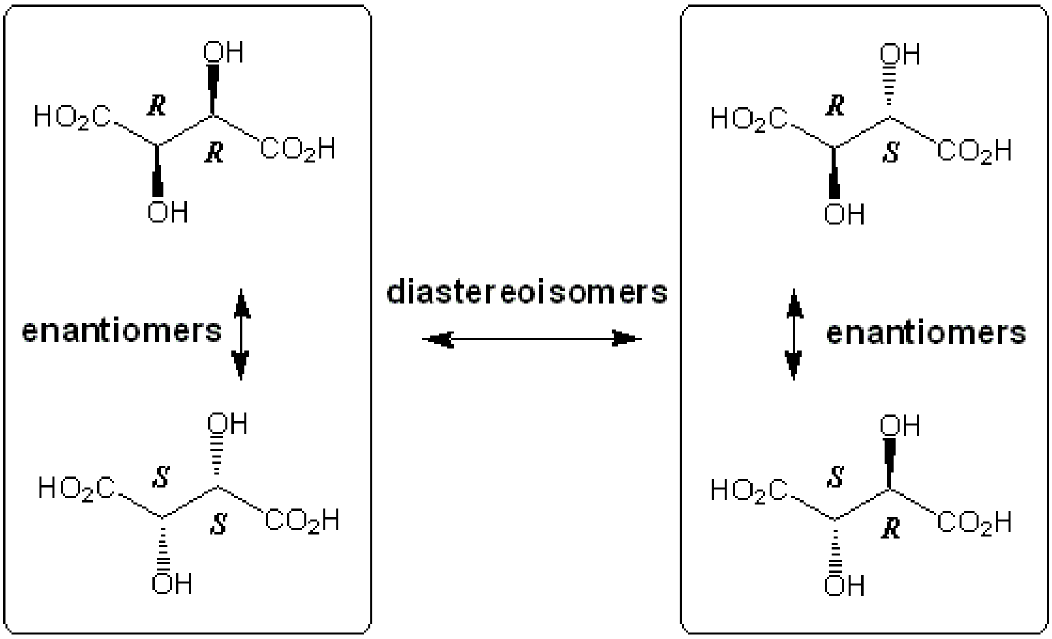
- What other stereoisomers could exist for threonine? Draw all possible stereoisomers, identifying the configuration at each chiral center. What is the relationship between these stereoisomers?
- There are four stereoisomers of threonine. These can be classified into two mirror image pairs of enantiomers. The 2R,3R stereoisomer is the mirror image of 2S,3S, and the 2R,3S stereoisomer is the mirror image of 2S,3R. But what is the relationship between any two configurations that are not mirror images (e.g. between 2R,3R and 2R,3S)?
- Stereoisomers that are not mirror images are called diastereoisomers. Note the difference between enantiomers and diastereoisomers: enantiomers must have opposite (mirror image) configurations at all stereogenic centers; diastereoisomers must have opposite configurations at some stereogenic centers, but the same configuration at others. These relationships are summarised below:



- Lets look at another example. Ephedrine (refcode: *EPHEDR01*) and pseudoephedrine (refcode: *PSEPED01*) each contain two stereogenic centers and are stereoisomers. Ephedrine is used in nasal sprays as a decongestant and pseudoephedrine is the active component of the decongestant Sudafed.
- Examine these two structures in detail, identify the two chiral centres in each molecule and assign their configuration using *R* and *S* notation. Describe the relationship between these two stereoisomers.

1.4.5 Compounds that contain stereogenic centers but are achiral.

- Tartaric acid, like threonine, contains two stereogenic centers so again we might expect four stereoisomers: two diastereoisomers, each existing as a pair of enantiomers:



- However, we actually find there are only three stereoisomers of tartaric acid (refcodes: *TARTAC*, *TARTAL04* and *TARTAM*). Can you determine why this is? Examine all three structures closely. For each structure, assign the configuration at both stereogenic centers 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, this can be seen by rotating one structure 180 degrees. The identity of the *R,S* and *S,R* structures results from the fact that the molecule has a plane of symmetry. This plane cuts through the C2-C3 bond, making one half of the molecule a mirror image of the other.
- Compounds that contain stereogenic centers but are achiral (due to a symmetry plane) are called meso compounds. Tartaric acid therefore exists as three stereoisomers: two enantiomers (refcodes: *TARTAC* and *TARTAL04*) and one achiral meso form (refcode: *TARTAM*).

1.5 ADVANCED EXCERCISE

- 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.

1.5.1 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 example of a compound with a quadrivalent chiral Si atom see refcodes: *YONMET* and *YONMIX*.

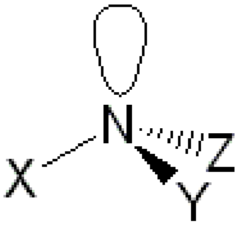
- Examine each of these two stereoisomers in turn. Assign *R* or *S* configuration to the Si atom in each structure.

1.5.2 Substituted adamantanes.

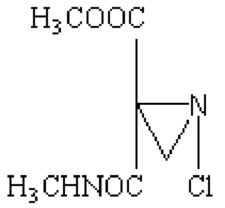
- Molecules that resemble an expanded tetrahedron will have the same symmetry properties as a regular tetrahedral atom and can therefore be chiral. For example, adamantanes containing four different substituents at the bridgehead positions are chiral and optically active.
- Display the structure of 1-bromo-3-chloro-5-fluoro-7-iodoadamantane by entering refcode *XUKFIS*.
- Inspect the structure. Click on the **Packing** tick box in the bottom left-hand corner of the main window to display the unit cell of the structure. Notice that both the *R* and *S* enantiomers are present in the unit cell.

1.5.3 Compounds with tervalent chiral atoms.

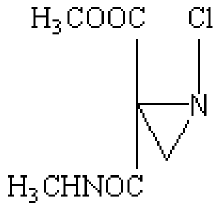
- Pyramidal nitrogen atoms might be expected to give rise to optical activity if they are connected to three different groups. This is because the unshared pair of electrons is analogous to a fourth group and necessarily different from the others:



- In practice, chirality is rarely observed in such systems due to pyramidal inversion. This is the rapid movement of the unshared pair from one side of the *XYZ* plane to the other which thus interconverts the molecule into its enantiomer.
- However, inversion is less rapid for nitrogen atoms in a three membered ring, and for nitrogen atoms connected to an atom with an unshared electron pair. When both of these 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 tervalent nitrogen atom.
- An example of this is 1-chloro-2-methoxycarbonyl-2-methylcarbamoylaziridine, for which both the *cis*- and *trans* epimers have been isolated:



trans *CSD refcode: KIRCOD*

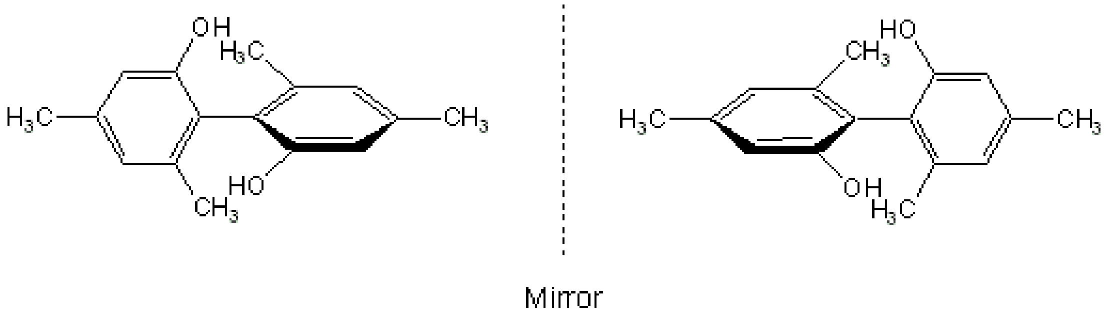


cis *CSD refcode: KUBZOW*

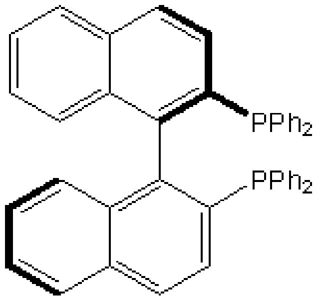
- Examine each of these two stereoisomers in turn (refcodes: *KIRCOD* and *KUBZOW*).
- You should be able to see that *KIRCOD* has a (1R,2R) configuration at the chiral N(l) and C(2) atoms, whereas the crystal structure of *KUBZOW* is made up of racemic pairs of discrete molecules with (1S,2R) and (1R,2S) configurations.

1.5.4 Chirality due to restricted rotation,

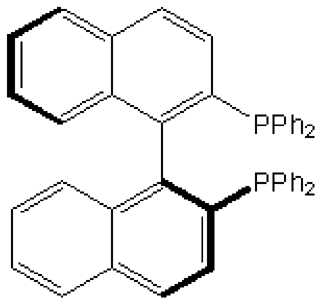
- Some compounds are chiral, yet have no stereogenic centres. Consider 2,2'-dihydroxy-4,4',6,6'-tetramethylbiphenyl, the mirror images (enantiomers) shown below are not superimposable and so the molecule is chiral:



- The presence of the ortho substituents means that the central bond linking the two phenyl groups cannot rotate freely due to steric hindrance. This hindered rotation prevents the enantiomers from interconverting and therefore gives rise to chirality.
- Examine this molecule for yourself (refcodes: *NIYQUH* and *NIYRAO*). The crystal structure of *NIYQUH* consists of a single enantiomer, whereas the crystal structure of *NIYRAO* has both enantiomers present in the unit cell (unit cell packing can be displayed using the free visualiser Mercury).
- Another example of a molecule that is chiral by virtue of restricted rotation is 2,2-bis(diphenylphosphino)-1,1'-binaphthyl*,* known as *BINAP* (refcodes: *PASRAC* and *HUZGUE*). This is an important ligand used in asymmetric hydrogenation reactions.

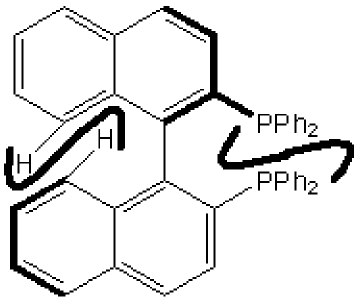


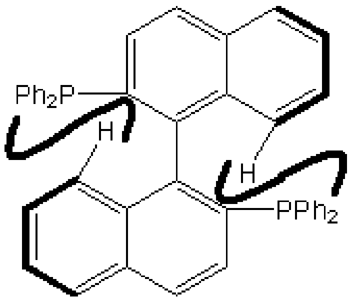
(R)-BINAP



(S)-BINAP

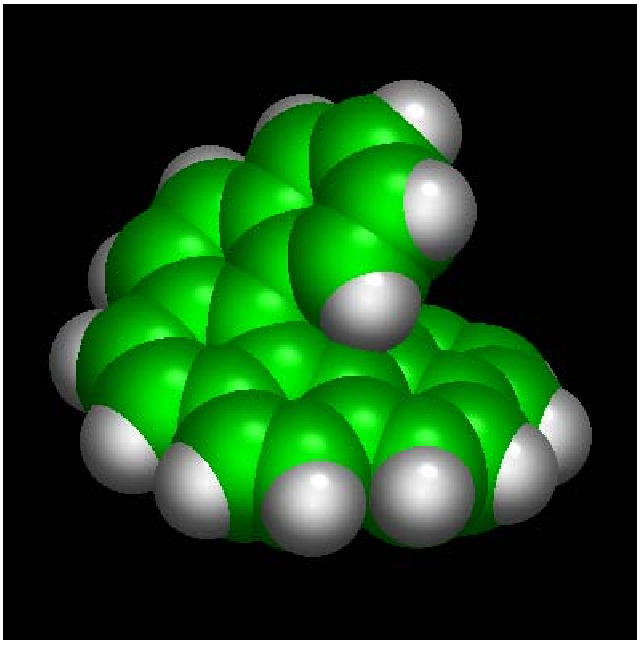
- In order for the enantiomers of *BINAP* to interconvert, the PPh_2 group would have to force its way past either the other PPh_2 group or past the hydrogen. Both pathways are too strained for racemization to occur:





1.5.5 Chirality due to helical shape.

- Helicenes are a further another example of compounds that lack asymmetric carbon atoms yet are chiral. Helicenes' chirality results from the fact that clockwise and counterclockwise helices are non-superimposable.
- Examine the following hexahelicenes (refcodes: *HEXHEL* and *MEHXHE*). In both structures see how one side of the molecule must lie above the other because of crowding.



1.6 SUMMARY OF KEY CONCEPTS

- 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 center.
- Compounds that contain such stereogenic centers 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 center can be described as either R or S by applying sequence rules.
- Diastereoisomers are stereoisomers that are not mirror images. Diastereoisomers have different spectra and physical properties.
- Some molecules have more than one stereogenic center. Enantiomers have opposite configuration at all stereogenic centers, whereas diastereoisomers have the same configuration in at least one center but opposite configurations at the other(s).
- Compounds that contain stereogenic centers 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, tervalent chiral atoms, restricted rotation about a particular bond, and helical shape.