Stereochemistry: Chirality in the Absence of Chiral Centres

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1 Introduction

This teaching module builds on the Introduction to Optical Isomerism course (see Stereochemistry: Introduction to Optical Isomerism) by focussing on chirality that is associated not with a chiral point (such as an asymmetrically substituted tetrasubstituted carbon centre) but rather by structure as a whole. Using structures taken from the Cambridge Structural Database (CSD) we will explore chirality associated with rotational axes as well as so-called chiral planes.

1.1 Learning outcomes

At the end of this module, you will:

- know the different classes of molecule which can display axial or planar chirality
- be able to recognise axial and planar chirality in 3D structures
- appreciate that conformational stereoisomers may be chiral if rotation about single bonds is restricted
- apply systematic nomenclature rules to describe the configuration of chiral axes and planes.

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-requisite skills

A basic understanding of chirality, as explained in teaching module “Stereoisomerism: Introduction to Optical Isomerism” (Stereochemistry: Introduction to Optical Isomerism) is required. No prior understanding of crystallography is required.

2 Axial chirality

Stereoisomers are molecules whose atomic connectivity is the same but whose stable three-dimensional arrangement of atoms in space is different. Optical isomerism, which concerns enantiomers is most familiar, frequently occurring when atomic centres are asymmetrically substituted. The most common cases arise when tetrahedral carbon centres bear four different substituents. We call this point chirality. However, the only condition for chirality is the non-superimposablility of a molecule upon its mirror image. We shall investigate the ways that this can occur in molecules lacking point chirality, starting with axial chirality.

2.1 Classes of molecules with axial chirality

Several different classes of molecules can possess axial chirality. This includes allenes, alkylidenecycloalkanes, spiranes and certain biphenyls. We will begin using allenes as introduction and discuss the nomenclature for describing axial chirality.

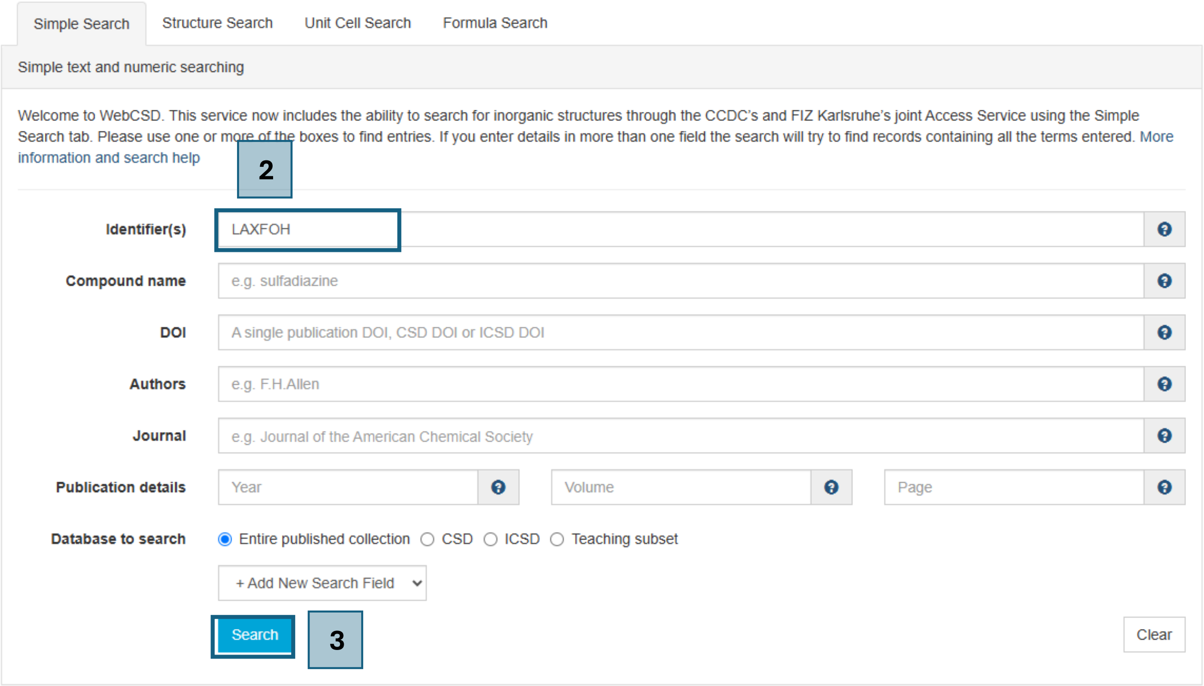
2.1.1 Introduction: allenes and nomenclature

Allenes have two consecutive double bonds. As the π bonds are orthogonal (constructed from adjacent p_x or p_y orbitals), axial chirality can result if there are different substituents on the terminal carbon atoms.

Let's look at an example from the CSD: 1,3-difluoropropadiene.

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

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



Simple text and numeric searching

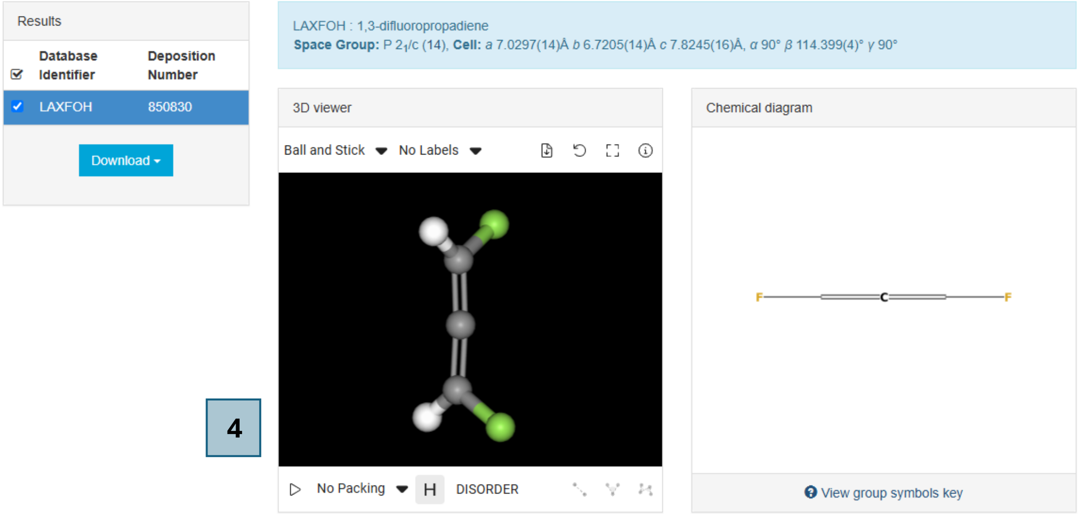
Welcome to WebCSD. This service now includes the ability to search for inorganic structures through the CCDC's and FIZ Karlsruhe's joint Access Service using the Simple Search tab. Please use one or more of the boxes to find entries. If you enter details in more than one field the search will try to find records containing all the terms entered. More information and search help

Identifier(s): LAXFOH

Database to search: ● Entire published collection ○ CSD ○ ICSD ○ Teaching subset

3. Press **Search**

4. In the results page, you can see a 2D and a 3D diagram.



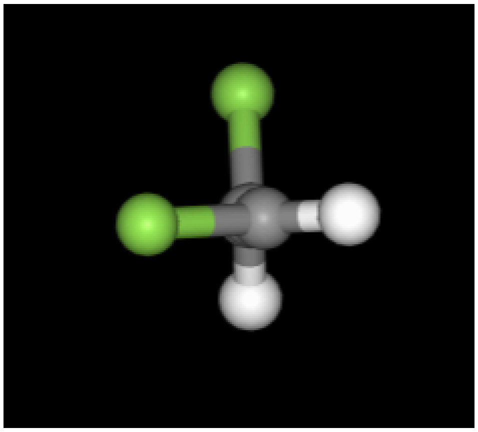
Database Identifier	Deposition Number
LAXFOH	850830

LAXFOH : 1,3-difluoropropadiene

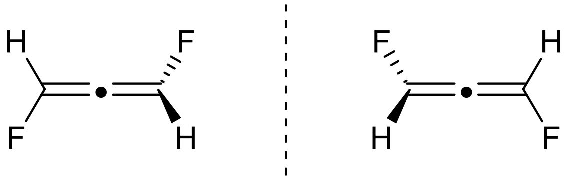
Space Group: P 2_1/c (14), **Cell:** *a* 7.0297(14)Å *b* 6.7205(14)Å *c* 7.8245(16)Å, *α* 90° *β* 114.399(4)° *γ* 90°

5. 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.

Try rotating the structure in 3D. In particular, if you look down the axis of the allene group, you will notice there is a twist which is the same regardless of which end you look from. For example, if you look at the fluorine atoms, you will see that the fluorine farthest away (12 o’clock position in the image below) always occurs in a clockwise turn from the closest one (9 o’clock position in the image below). It follows that a molecule with an anticlockwise twist can exist. Are these superimposable?



CSD entry LAXFOH viewed down the allene axis.

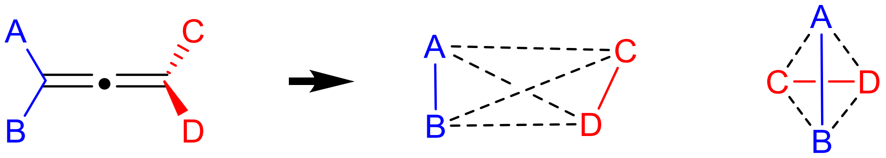


Drawn in 2D you should be able to see that the two mirror images are non-superimposable and are therefore enantiomers.

2.1.2 Nomenclature to describe axial chirality

There are two systems in use for describing axial chirality. This first is an adaption of the familiar Cahn-Ingold-Prelog system which use *R* and *S* notation. In the case of chiral axes these are sometimes prefixed or subscripted to "a" to indicate the axial nature of the chirality.

In the diagram below, the allene is tetrasubstituted and if we ignore the connecting bonds, and simply focus on the pairs of substituents, the *pseudo*tetrahedral arrangement becomes apparent. This gives us a way of adapting the CIP rules for tetrasubstituted centres to axially chiral molecules.

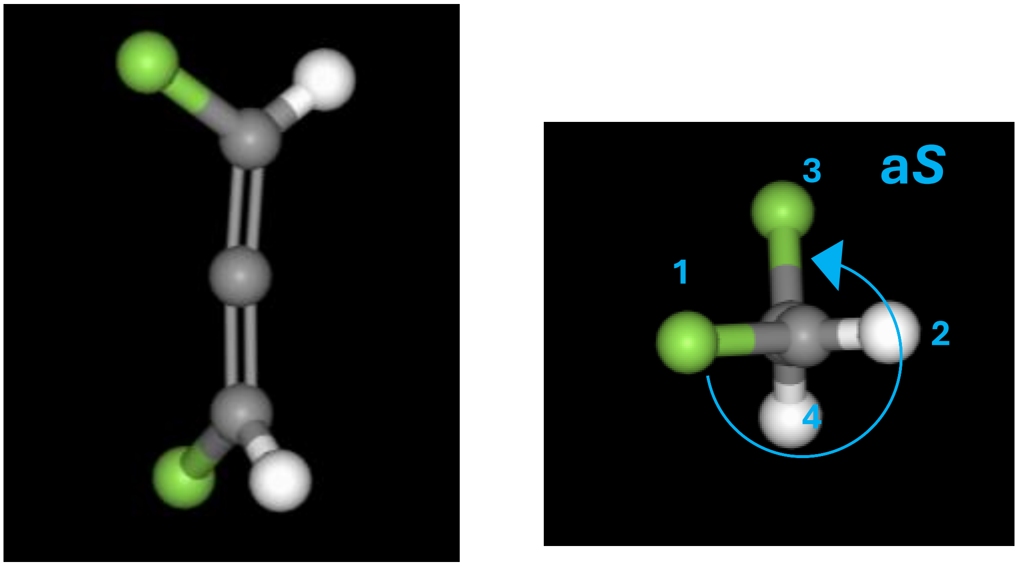


The pseudo tetrahedral arrangement of substituents of an allene. For ease of visualisation, the pairs of substituents are connected in the middle and right-hand diagrams.

To apply the CIP priority rules:

1. Choose a view down the chiral axis to distinguish front from back (it does not matter which end you assign as front and back, so long as a consistent view is maintained).
2. Assign priorities (according to the usual conventions) to the front pair of substituents and rear pair substituents.
3. Assign overall priorities as follows:
    1. Front, higher priority
    2. Front, lower priority
    3. Rear, higher priority
    4. Rear, lower priority
4. Trace the path 1 → 2 → 3. If the sense of rotation is clockwise, the a*R* label applies; if it is anticlockwise, the a*S* label applies (the *a* subscript is sometimes omitted, informally).

Can you match the molecular structure of CSD entry LAXFOH to the *aR* or *aS* isomer?

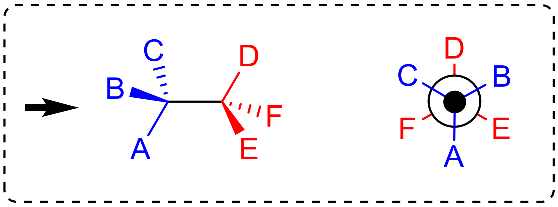


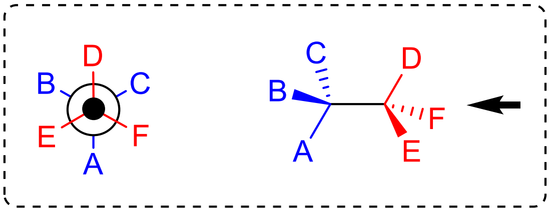
Left: view of CSD entry LAXFOH perpendicular to the allenic axis. Right: view parallel to the allenic axis showing the assignment of the axial stereochemistry descriptor.

The second (arguably simpler) method is by analogy with a helix or screw. A clockwise twist is labelled *P* (for plus, right-handed helicity) whereas an anticlockwise twist is labelled *M* (for minus, left-handed helix). To identify the axial chirality, follow these steps:

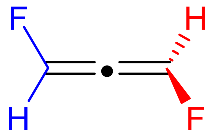
1. Identify the chiral axis.
2. If there are substituents at the end of the axis assign priorities according to the CIP rules. Usually, it is only necessary to focus on the highest priority group at each end.
3. View the molecule down the chiral axis with the end with highest priority substituents on the near side.
4. Trace the shortest path from the highest priority substituent at the near end to the highest at the far end. If the twist is clockwise, the label *P* applies; if it is anticlockwise, the label *M* applies.

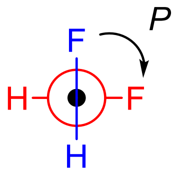
A Newman projection can be a useful tool in these instances. The projection is simply a way of viewing the 'front' and 'back' of a molecule, looking down a specific bond. The front atom is represented by a dot and the back atom by a circle. The substituents are arranged around these. For example:





It doesn't matter from which side we view the molecule as the projection keeps track of it. The principle can be adapted to swap a particular bond for a chiral axis and choosing representative groups that capture the necessary priority information. For example, if we take CSD entry LAXHOF, 1,3-difluoropropadiene, we could represent it as follows:





The direction of rotation from the front F group to the back F group is clockwise, so the label *P* applies.

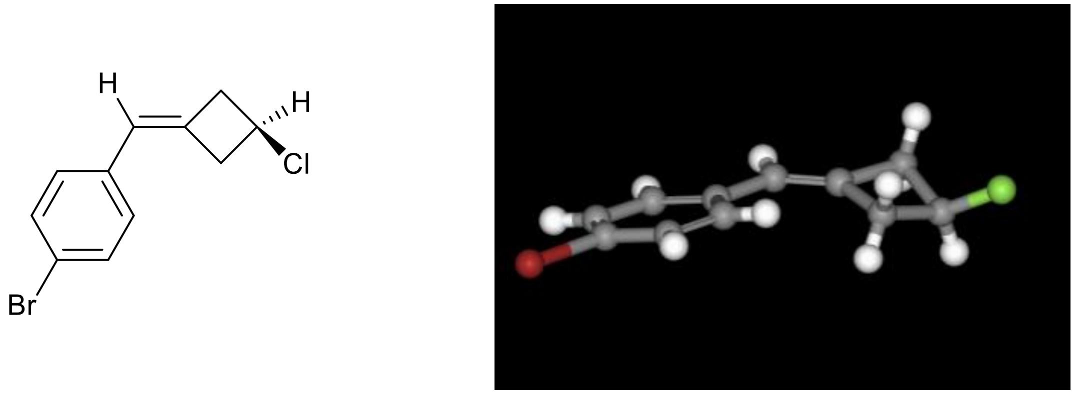
The general relationship between the two systems of nomenclature is that a*S* = *P* and s*R* = *M*. The *M*/*P* system is recommended by IUPAC for systematic naming but the a*S*/a*R* system is still commonly used.

Exercise 1

Look up CSD entry DUFHAR on Access Structures. Assign the stereochemistry as a*R* or a*S*.

2.1.3 Alkylidenecycloalkanes

Alkylidenecycloalkanes contain a double bond directly attached to a ring which is substituted in a certain way which can lead to axial chirality. Look up CSD entry LIRQEJ. Notice that the chlorine and hydrogen atoms are on opposite sides of the four membered ring, leading to a fixed orientation – above and below the plane of the alkene – with respect to the hydrogen atom and the phenyl group attached to the other end of the alkene group.



An example of an alkylidenecycloalkane, CSD entry LIRQEJ (configuration a*R* or *M*).

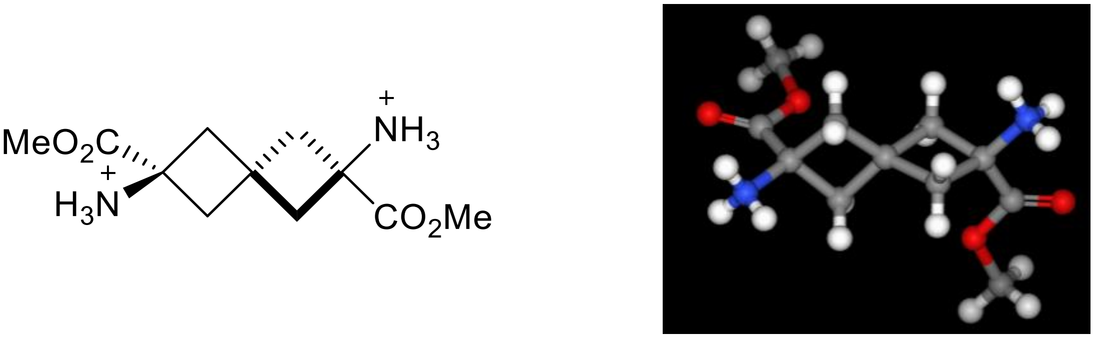
A note on ring conformations: in examples like this you will see in the 3D structure that the ring is not planar. This is generally the case for saturated rings, except 3-membered ones. If the ring conformation were permanent, this could be another source of stereoisomersim (in fact we will see this later). However, in general saturated rings are not rigid; in liquid, solution and gas phases they may flip rapidly. Practically, this means ring conformation won't affect the chirality – you can treat them as flat.

Exercise 2

Look up CSD entry SEWXIB in Access Structures. It is a substituted adamantane. You will see two molecules (make sure No Packing is selected in the 3D viewer). Are the molecules chiral? If they are, determine the chirality.

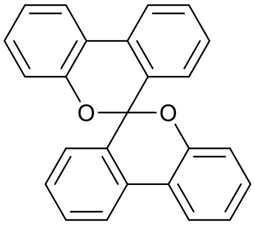
2.1.4 Spiranes

Spiranes are molecules containing rings joined through a single shared atom. If the shared atom has four different substituents, the atom is a normal chiral centre; however, the spiro molecule may be chiral in the absence of four different substituents. Consider, for example dimethyl 2,6-diaminospiro[3.3]heptane-2,6-dicarboxylate bis(hydrochloride), CSD entry LUPMIT below. Its axial chirality can be seen as an extension of that in allenes and alkylidenecycloalkanes; the two perpendicular rings have a rigid relationship, and the stereochemistry can be assigned as a*R* (*P*)

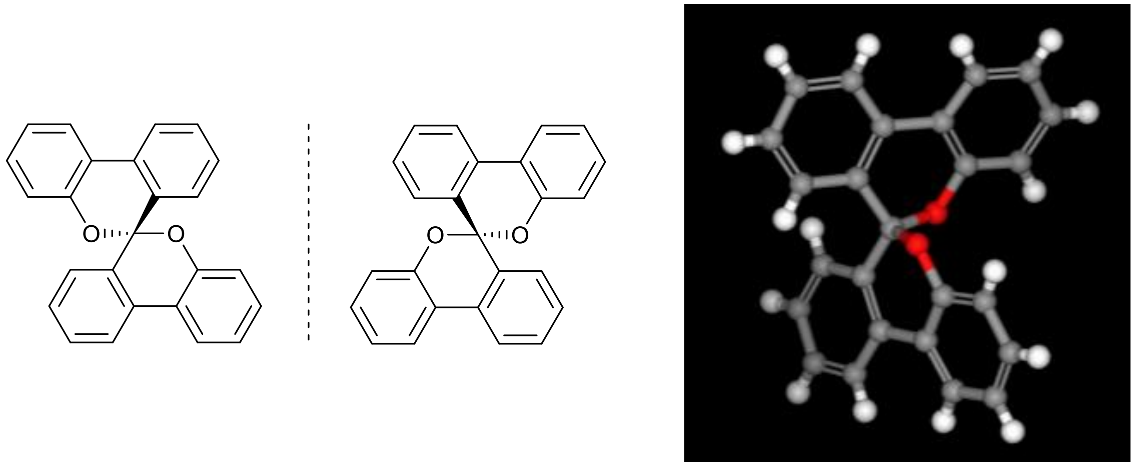


A substituted spiro[3.3]heptane, CSD entry LUPMIT.

As another different example, consider 6,6'-spiro-bi-(benzo(c)chromene) below.



At the centre of the molecule, two oxygen-containing six-membered rings join. There is only one tetrahedral atom, which is the shared one. As there are not four different substituents on this carbon centre, the molecule appears achiral at first. However, when considered in 3D, we see that non-superimposable forms exist. You can see this is CSD entry ADITEN. Of course, it’s possible to have additional chirality when the fused rings are saturated and substituted, as you will find in Exercise 3.

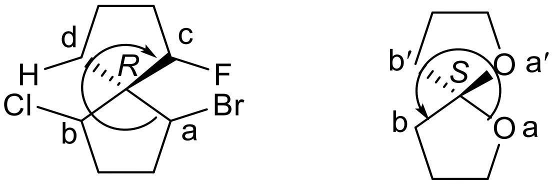


Left: possible enantiomers of 6,6'-spiro-bi-(benzo(c)chromene). Right: CSD entry ADITEN. In this case the central carbon, which is attached to two oxygen atoms and two carbon atoms from separate but identical rings, is the spiro atom.

Since the spiro centre is a regular tetrahedral centre, regular *R*/*S* labels are used to specify the stereochemistry in spirocycles of the class to which ADITEN belongs, even though the spiro centre may not actually be a chiral centre in the conventional sense. A modification of the CIP priority system is needed to assign *R* or *S* configuration to spiro centres in this situation.

1. The labels a and a' are assigned to the higher priority substituents in the two rings of the spirocyclic.
2. The labels b and b' are given to the lower priority substituents, such that a and b are in the same ring (and a' and b' are in the other ring).
3. With b' orientated at the back, the sequence a > a' > b in a clockwise sense gives *R* configuration, whilst an anticlockwise sense gives *S*.

The two scenarios are best illustrated by the following pair of molecules:



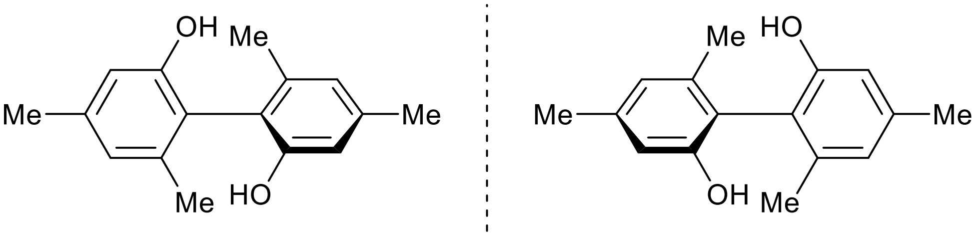
Left: standard priorities according to CIP rules can be applied with this substitution pattern. Right: application of modified CIP rules for two identical fused rings.

Exercise 3

Look up CSD entry WESCAY. Identify the spiro centre and any chiral centres that may be present in addition to it, and determine whether each is *R* or *S*.

2.1.5 Biaryl compounds

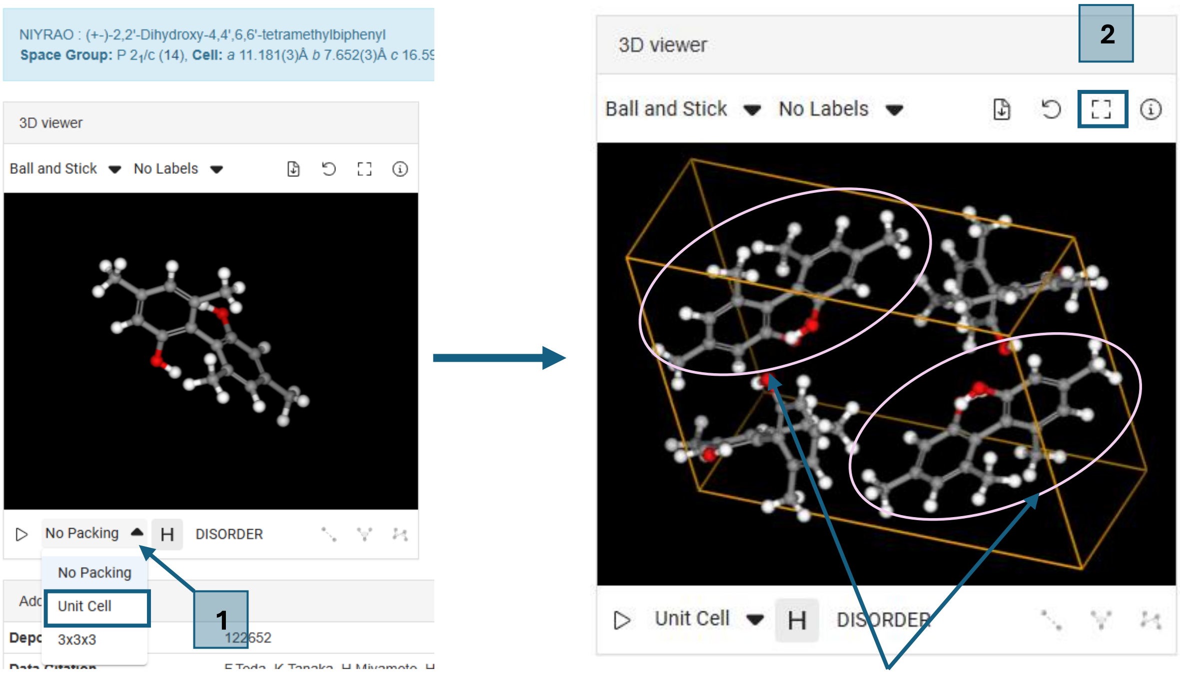
We now move to cases where axial chirality is derived from stable conformation. Consider 2,2'-dihydroxy-4,4',6,6'-tetramethylbiphenyl, the mirror images (enantiomers) shown below are not superimposable and so the molecule is chiral.



Mirror

The presence of the *ortho* substituents means that the central bond linking the two phenyl groups cannot rotate freely due to steric hindrance. This restricted rotation prevents the enantiomers from interconverting and therefore gives rise to chirality. You can examine this molecule yourself; CSD entry NIYQUH consist of a single enantiomer, whereas NIYRAO consists of both enantiomers. Isomers arising from axial chirality due to restricted rotation are called atropisomers. The difference will become apparent in the packed structure – one unit cell's worth of molecules is sufficient. You may wish to expand the visualiser to full screen for a closer look.

You should find that the enantiomers are at the opposite 'corners' of the unit cell.

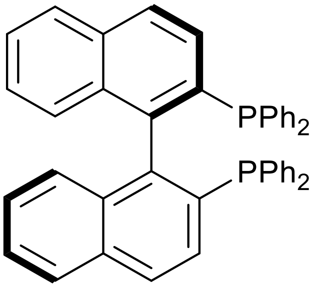

NIYRAO : (+-)-2,2'-Dihydroxy-4,4',6,6'-tetramethylbiphenyl

Space Group: P 2_1/c (14), **Cell:** *a* 11.181(3)Å *b* 7.652(3)Å *c* 16.5

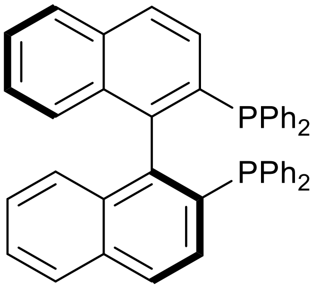
Enantiomers

Another example of a molecule that is chiral by virtue of restricted rotation is 2,2-bis(diphenylphosphino)-1,1'-binaphthyl, known as BINAP (CSD refcodes: PASRAC and HUZGUE).

This is an important ligand used in asymmetric hydrogenation reactions. Note that the "a" associated with *S* and *R* configuration labels is often dropped informally for BINAP and similar compounds.

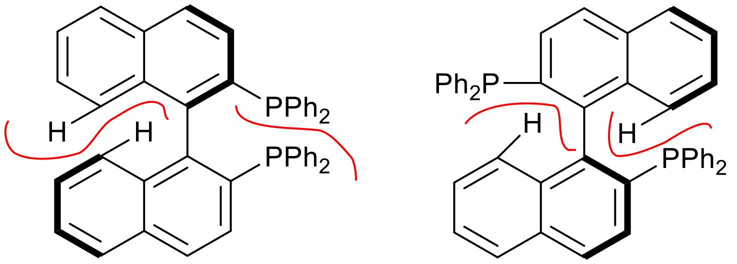


(*R*)-BINAP



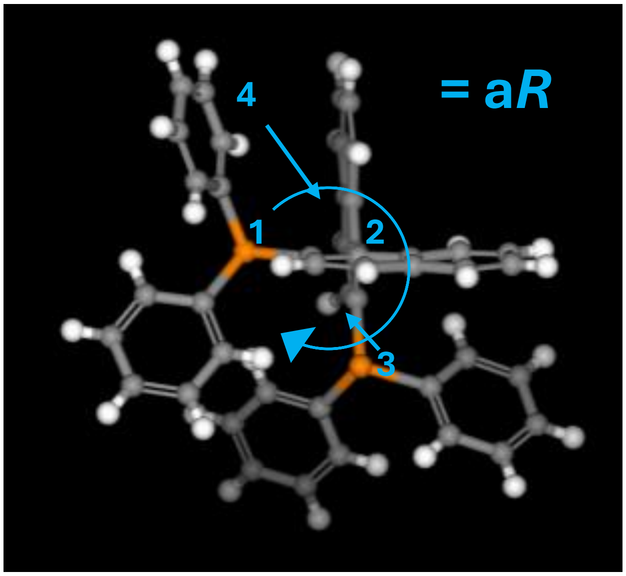
(*S*)-BINAP

In order for the atropisomers 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 racemisation to occur.



Steric clash between hydrogens and/or phosphines prevents racemisation of BINAP enantiomers.

As a further example of applying the CIP rules to axially chiral systems, you can see the procedure for one isomer of BINAP below.

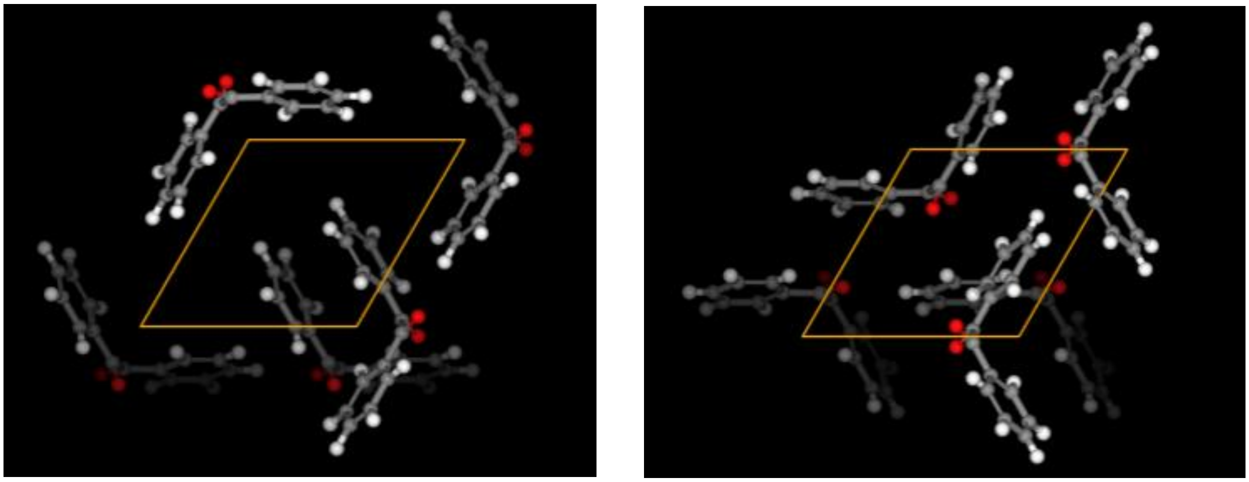


CSD entry PASRAC, showing how the a*R* configuration is assigned.

Exercise 4

Match CSD refcode HUZGUE to a*R* or a*S* stereochemistry.

For the reasons explained above, BINAP retains its chirality under normal conditions. One important feature of the solid state (crystals in this context) is that conformations that are not necessarily stable in other states can be 'frozen out' during crystallisation. An example is benzil $(PhCO)_2$. Unlike BINAP, rotation about the central C−C bond can occur quite easily. As a result, it does not rotate plane polarised light – as a chiral compound must – either in solution or when molten. However, when it crystallises, it forms crystal structures which are mirror images. These are termed enantiomorphic.[1] This is possible because the conformation of benzil in the solid state creates a twist, much like the biphenyls discussed above. To see this, examine BENZIL and BENZIL06. Pack the structures and compare them.



Left: the crystal structure of CSD entry BENZIL. Right the crystal structure of CSD entry BENZIL06. The unit cell and contents are shown in each case.

Exercise 5

Assign *M* and *P* labels to BENZIL and BENZIL06.

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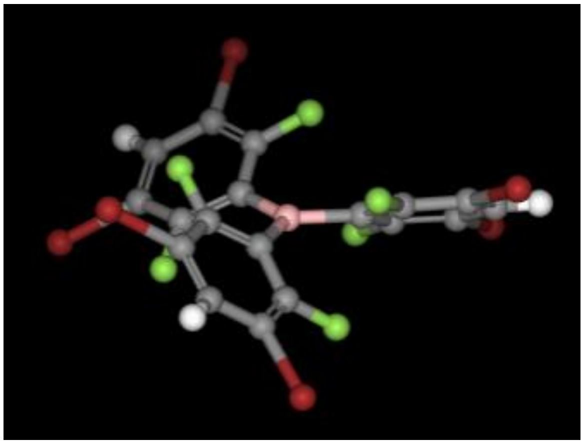
[1] If you are familiar with symmetry in crystallography, BENZIL and BENZIL06 occur in space groups $P3_121$ and $P3_221$, respectively, which are entiomorphous.

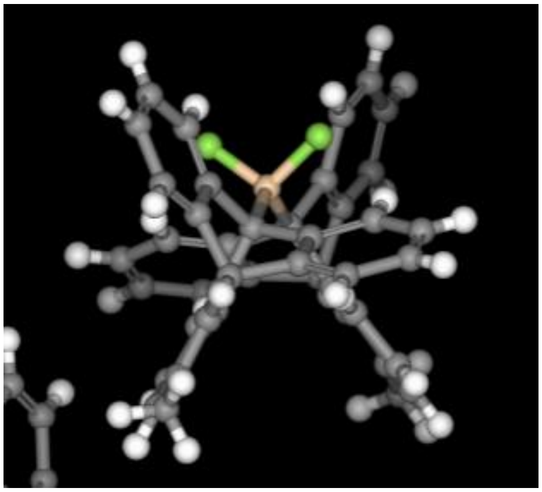
2.1.6 Molecular propellers and gears

The hindered rotation that gives rise to axial chirality in biphenyls applies to other molecular shapes. A couple of interesting examples are molecular propellers and gears. In molecular propellers steric interactions cause (typically) aryl groups to tilt out of the plane of the *ipso* carbons. CSD entry GIWWIW is a simple example of this type of chirality.



CSD entry GIWWIW, a molecular propeller. The aromatic groups must be tilted in the same sense to observe this type of chirality.

Molecular gears have many crowded adjacent groups that are forced to lock together in a particular way. An example is CSD entry SONPER which consist of two 9-tripticyl groups joined by a bridging atom, overall resembling bevel gears. The interlocking of the gears in the chiral isomers means that rotation of the tripticyl groups (which occurs in solution) must be synchronised (as they would be in a mechanical gear).[2]



An example of a molecular gear, CSD entry SONPER.

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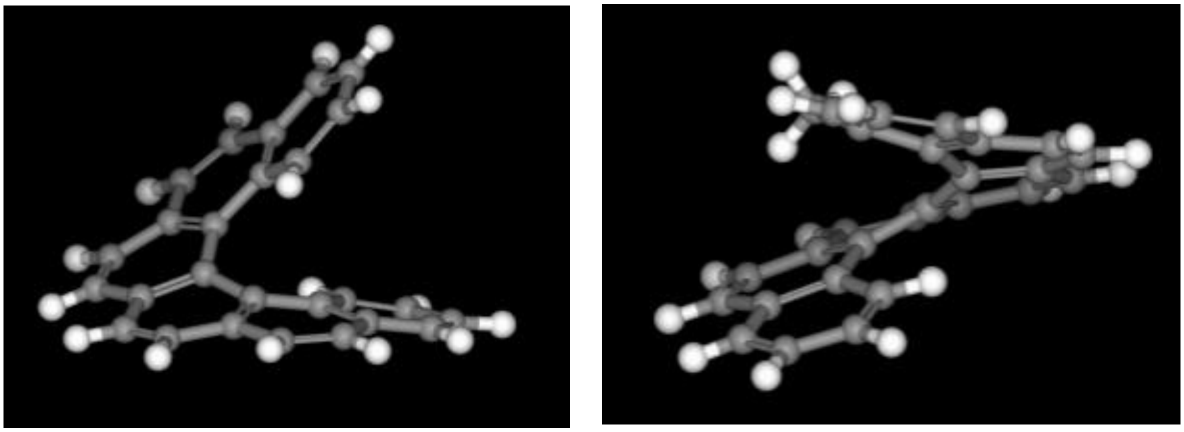
[2] In this case 'gear slippage' can occur (a *meso* isomer can form). See W. Setaka, T. Nirengi, C. Kabuto and M. Kira, *J. Am. Chem. Soc.*, 2008, 130, 47, 15762–15763. DOI: 10.1021/ja805777p.

Exercise 6

Inorganic coordination complexes can display several types of stereoisomerism. For example, when three chelate ligands surround a metal centre, enantiomers can arise. These are called Λ (lambda) and Δ (delta) isomers if they have a left- or right-handed propeller twist (helix), respectively. Look up CSD entry ACACGE and determine whether it has Λ or Δ configuration. What is the correspondence between Λ, Δ, *M* and *P*?

2.1.7 Chirality due to helical shape

Helicenes are a further another example of molecules that lack chiral carbon atoms yet are chiral as molecules overall. Helicenes' chirality results from the fact that clockwise and counterclockwise helices are non-superimposable. Examine the following hexahelicenes: CSD entries HEXHEL and MEHXHE. In both structures see how sequential arene rings must lie above the other because of crowding. This gives rise to the helical structure. Notice that the chiral axis does not coincide with any atom or bond in these structures.



Left: CSD entry HEXHEL. Right: CSD entry MEHXHE. The helix rotates in the same sense (anticlockwise) in both molecules.

Helicenes are an unusual case where there is a general relationship between the absolute configuration and chiroptical properties (properties which arise from interaction between light and chiral molecules).[3] A right-handed (*P*) helicene absorbs left-handed circularly-polarised light more than right-handed circularly-polarised light (a positive *Cotton Effect*), and vice versa for a left-handed (*M*) helicene (a negative Cotton Effect).[4]

Exercise 7

Look up HPTHEL05 on Access Structures and assign its stereochemistry as *P* or *M*.

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[3] Y. Shen and C-F. Chen, *Chem. Rev.*, 112, 2012, 1269–2014. DOI: 10.1021/cr200087r

[4] You can think of circularly polarised light as a kind of chiral light. The associated experimental technique is called circular dichroism spectroscopy. For information, see A. Urbach, *J. Chem. Educ.*, 2010, 87, 891–893. DOI: 10.1021/ed1005954

2.2 Conclusions

In this section we have seen molecules which possess axial chirality. Some of these, such as allenes have groups separated by non-rotatable bonds, whereas others, such as hindered biphenyls owe their atropisomerism to restricted rotation of single bonds. Helicenes are different in that axial chirality is intrinsic to their structure. The axial description leads to a system of nomenclature (*P* and *M* for clockwise and anticlockwise twist) which can be applied generally to molecules axial chirality.

3 Planar chirality

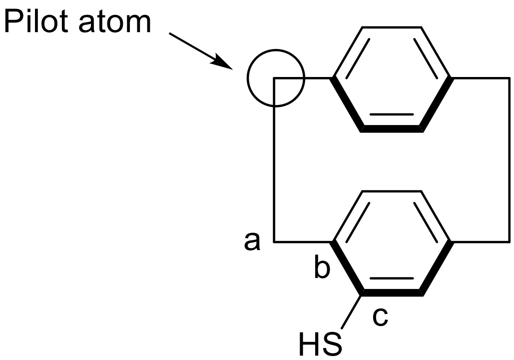
Planar chirality is the term used to describe stereoisomerism resulting from the arrangement of out of plane groups with respect to a plane (called the stereogenic plane). The definition of a chiral plane is less clear than that of a chiral centre or axis. It is a plane of the molecule that contains as many atoms as possible, but not all.

3.1 Types of molecules with planar chirality

The most common examples in organic chemistry are cyclophanes but other examples include annulenes and *trans*-cycloalkenes, whilst in organometallic chemistry, metallocenes and piano stool complexes may show planar chirality. We will begin by studying cyclophanes and learning how to assign configuration.

3.1.1 Introduction: cyclophanes and nomenclature.

If you examine the geometry of CSD entry ILOQIL on Access Structures you will see that the symmetry of the cyclophane is broken by the -SH substituent. Since the structure is rigid – it is not possible for one arene ring to swivel the other – it is chiral. Planar chirality is different from other forms of chirality in that there is no specific stereocentre; it is the asymmetry of the plane itself that matters. The descriptors p*R* and p*S* are used to denote the chirality of the chiral plane (the p prefix is used to signify planar chirality). Consider the follow cyclophane example to see how they are assigned. The simplest method uses a *pilo*t atom.



1. Identify the stereogenic plane, the plane which has the most atoms in it. The ‘plane’ may sometimes be warped and not *precisely* planar. If there are two planes with the same number of atoms, choose the one with the highest priority substituents. In the diagram above, this is the plane containing a, b and c.

2. Identify the pilot atom, which is the atom directly attached to but not in the plane, and closest to the end of the plane with the highest priority atoms.
3. Rank the adjacent three atoms (applying priority rules where there is a choice).
4. If the three atoms a, b and c occur in a clockwise direction in chiral plane when viewed from the pilot atom towards the chiral plane, the configuration is p*R*. If they occur in an anticlockwise sense, the configuration is p*S*.

In the case of the cyclophane in ILOQIL, for which X = SH, this gives *p*R.

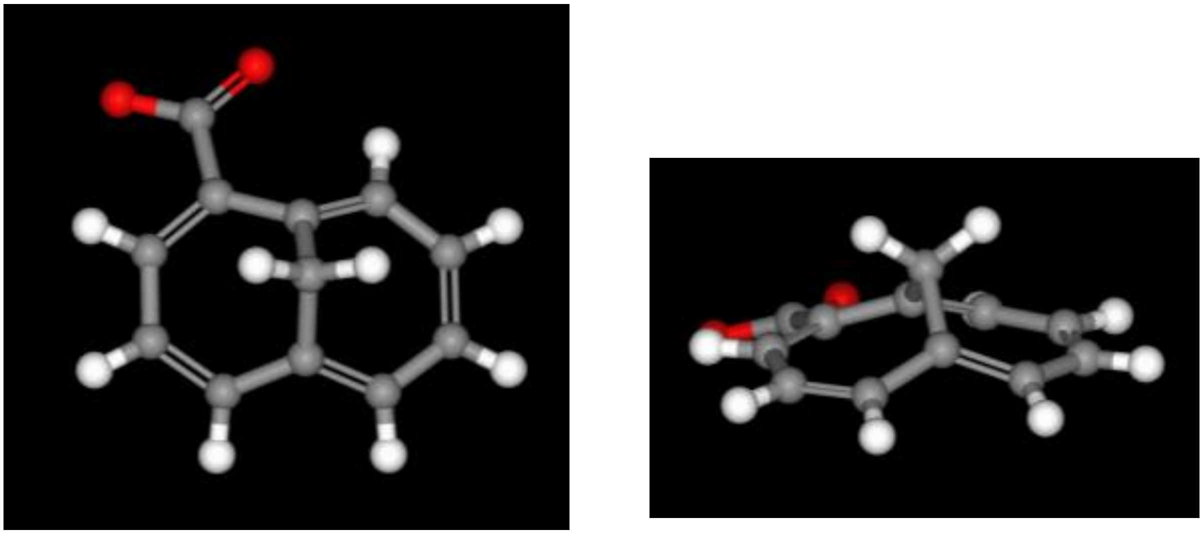
To find the equivalent assignment in terms of *M* and *P*, one looks at pilot-a and b-c and determines the sense of rotation as usual. In the case of the cyclophane shown above, the descriptor *P* would apply. Note that the *pR*-*P*/p*S*-*M* relationship is opposite to the a*R*-*M*/a*S*-*P* relationship shown previously for axial compounds.

Exercise 8

Examine CSD entry VECROL in Access Structures. Determine the chirality of the molecule(s) present using both systems of notation.

3.1.2 Annulenes

Annulenes are cyclic molecules with alternating single and double bonds. In bridged [10]annulenes, the bridge atom cannot pass through the plane containing the annulene. This can lead to chirality with the appropriate substitution pattern. For example, CSD entry MCCARA, the carboxylic acid group causes the molecule to become chiral.



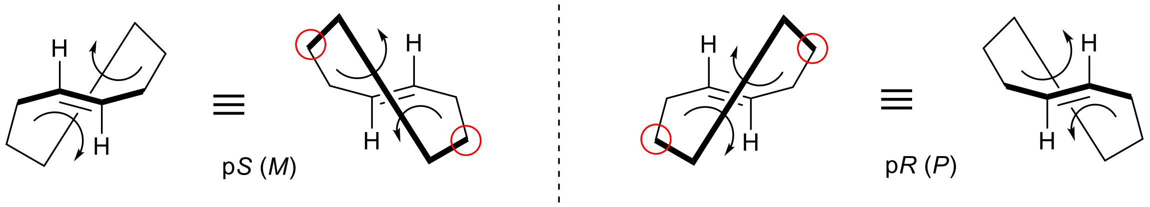
CSD entry MCCARA. The so-called chiral plane is not actually very planar.

Exercise 9

Look up CSD entry JAWVOS on Access Structures. Is it chiral? If it is, assign the stereochemistry.

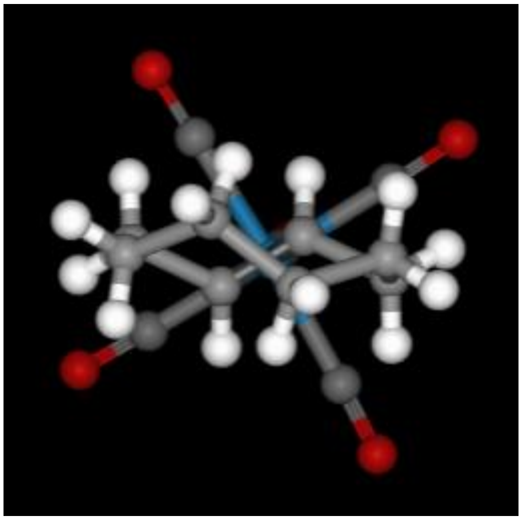
3.1.3 *Trans*-cycloalkenes

A *trans* double bond in a ring can lead to a conformationally stable ring which can exhibit stereoisomers. *Trans* double bonds are not stable in rings with fewer than eight atoms, whilst conformational freedom increases for ring sizes above eight.[5] Thus, for cyclooctene and derivatives it is possible to observe stable enantiomeric conformers.[6] The double bond and directly attached carbon atoms form a plane by which the sense of the displacement of the remaining four atoms may be reckoned, as shown below.



The two enantiomers of *trans*-cyclooctene. Pilot atoms marked in red for reference.

The crystal structure of pure *trans*-cyclooctene is not known, however there are many metal complexes of it. An example is CSD entry QAJCAF which is a tungsten complex. The metal centre provides a useful visual anchor. Looking from the cyclooctene ligand toward the tungsten centre at the back, as shown below, you can see that the conformation matches the p*S* configuration on the diagram above.



CSD entry QAJCAF.

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[5] The optical stability of *trans*-cycloalkenes decreases from trans-cyclooctene ($t_{1/2}$ = 10^5 yr) to *trans*-cyclononene ($t_{1/2}$ = 10 s) to *trans*-cyclodecene ($t_{1/2}$ = 10^{-4} s) at room temperature; see reference **6**.

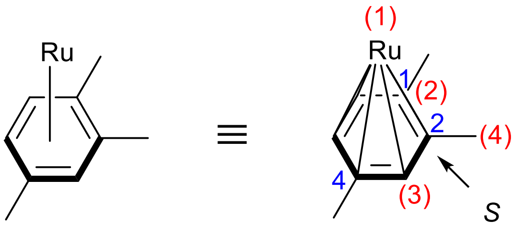
[6] R. D. Bach, U. Mazur, I. Hamama and S. K. Lauderback, *Tetrahedron*, **28**, 1972, 1955–1963. DOI: 10.1016/0040-4020(72)88003-7.

Exercise 10

Look up CSD entry VIJSOW in Access Structures and assign the stereochemistry of the molecule.

3.1.4 Metallocenes and related compounds

Planar chirality can occur in organometallic compounds such as metallocenes if the aromatic ligand is substituted in a way that breaks symmetry. For example, functionalising one Cp ring of ferrocene with different groups at the 1- and 2-positions. Since the metal is the out-of-plane group, it could be treated with p*S*/p*R* descriptors as we have used elsewhere. However, convention is to explicitly draw single bonds between the metal and ring atoms. This way, each ring atom becomes four-coordinate and regular *R*/*S* descriptors can be applied. The highest priority atom in the ring is chosen as the centre to which the descriptor is applied. For example, consider the fragment of a metal-arene complex shown below. The arene is 1,2,4-substituted. The 2-carbon is the centre of precedence (if you start exploring the paths from this carbon you will find the other methyl groups are fewer bonds away than had you chosen the 1-carbon or 4-carbon). The atoms connected to the 2-carbon are ranked by usual priority and thus the configuration is *S*.



Assignment of stereochemistry to coordinated arene. Aromatic ring positions are indicated in blue, priorities are indicated in red.

Exercise 11

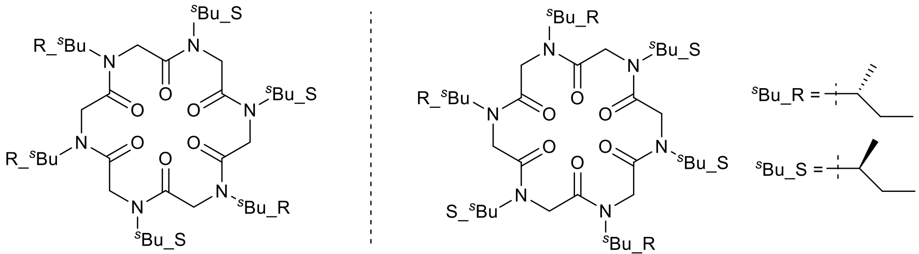
Look up CSD refcode BECKUQ on Access Structures and assign the stereochemistry.

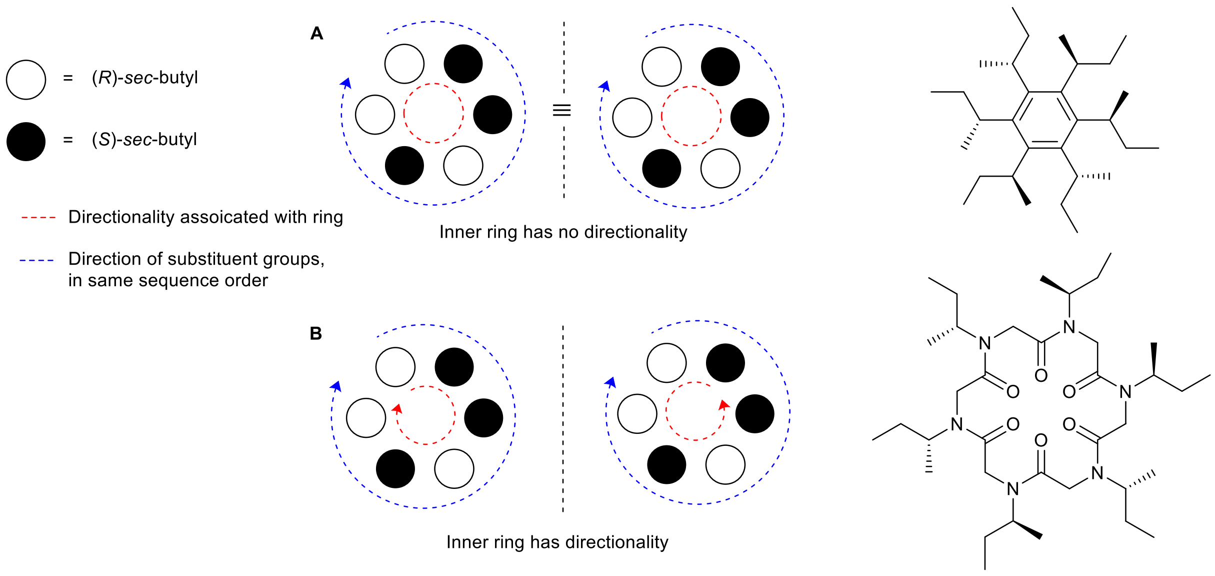
3.2 Conclusions

In this section we have seen that planes (or planar portions of molecules) can become chiral if they are unsymmetrically substituted and have a substituent with a fixed out-of-plane relationship. Whilst this is seen in a small number of distinct types of organic compound, it is very common in organometallic chemistry where coordination of a metal to an appropriately substituted aromatic ligand is sufficient to create it in many cases. It is thus a topic of significant relevance in enantioselective catalysis.

4 Cyclostereoisomerism

Cyclostereoisomerism is a complex topic that will be discussed only briefly here. When constitutionally identical stereocentres occur in a ring, numerous stereoisomers may arise (often with severe degeneracies, i.e. the number of stereoisomers is much less than 2^n where n is the number of stereocentres). This occurs with molecules such as inositol, which has nine stereoisomers – one pair of enantiomers and seven *meso* (achiral) forms – are found (see CSD entries FOPKOK and QIKZUH for the enantiomeric pair). However, cyclostereoisomerism refers to cases where an additional ring directionality can be identified as a source of stereoisomerism. For example, in the pair of enantiomers shown below for hexa-N-*sec*-butylcyclohexaglycyl, the repeat unit is —$\mathrm{N^{*}C(O)CH_2}$— where * indicates the nitrogen is substituted with *R* or *S* *sec*-butyl. If you follow the two stereoisomers round in the direction N→CO→CH the sequence of *R*/*S* *sec*-butyl substituents is reversed going from one enantiomer to the other. By contrast, in a similarly substituted benzene, where no such direction within the ring itself can be identified, interchanging (*R*)- and (*S*)-*sec*-butyl substituents does not lead to a different stereoisomer. Thus, in the case of hexa-N-*sec*-butylcyclohexaglycyl, the directionality of N→CO→CH in the ring leads to an additional stereoisomer, which is called a cyclostereoisomer. The two cases are illustrated in **A** and **B** below.





4.1 Conclusion

Cyclostereoisomerism is a form of non-central chirality which relates to distinguishable 'directions' in rings with chiral elements. It should be noted that this type of stereoisomerism is less well-studied and exact definitions are subject to dispute in the literature.

Exercise 12

Look up CSD entry KATXEL, which is a nanohoop, in Access Structures. Discuss how cyclostereoisomerism might occur in this structure.

5 Summary

In this module we have explored three types of chirality than can occur in the absence of chiral centres, namely axial (or helical) chirality, planar chirality and cyclostereoisomerism. The first two of these represent the most common cases and occur in several well-known types of chemical compound. We have also seen the systems of nomenclature in use to describe the configuration of chiral axes and planes and noted that there are several variations on the well-known *R*/*S* descriptors as well as a more generally more versatile *M*/*P* system which better reflects helicity.

5.1 Next steps

This module covers the main cases of non-central chirality that you are likely to encounter. For a more detailed study, including chemical methods of resolution in the absence of crystal data, we recommend studying. E. L. Eliel and S. H. Wilen, in *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994, ch. 14, pp 1119–1190.

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/

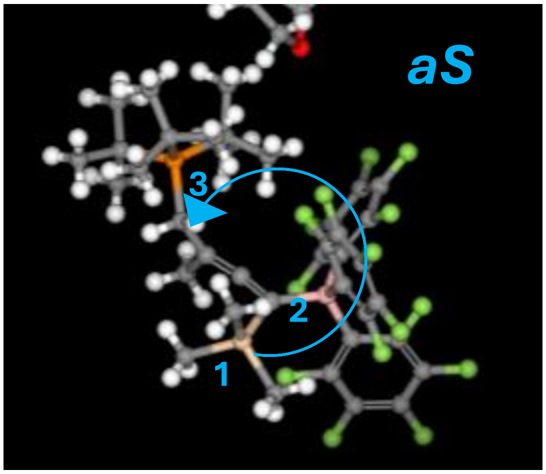
5.2 Acknowledgements

We would like to thank Professor Jonathan M. Goodman (University of Cambridge) for helpful feedback.

6 Answers to exercises

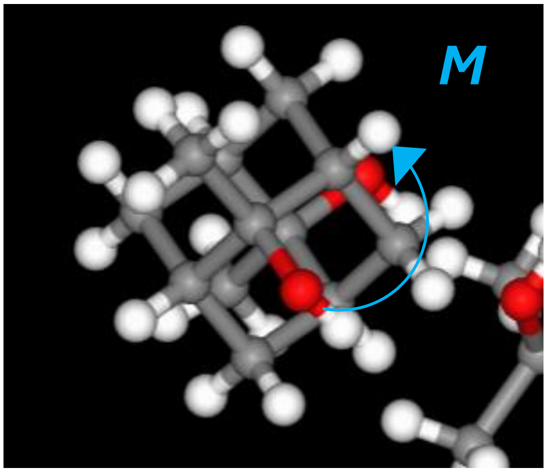
Exercise 1

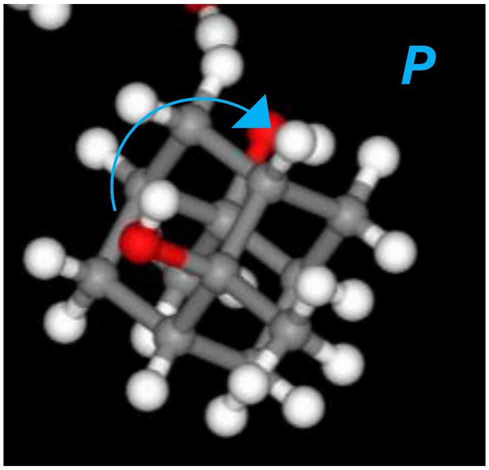
At one end of the allene, there is a SiMe3 group and a $B(C_6F_5)_3$ group. Si has higher priority than B. At the other end of the allene there is a phosphonium ylide and a methyl group. Since both have C in the 1st sphere we move to the next atom which is H for CH_3 and P for the phosphonium ylide, so that latter has priority. Applying the CIP rules for axial chirality this gives a*S*, as shown below.



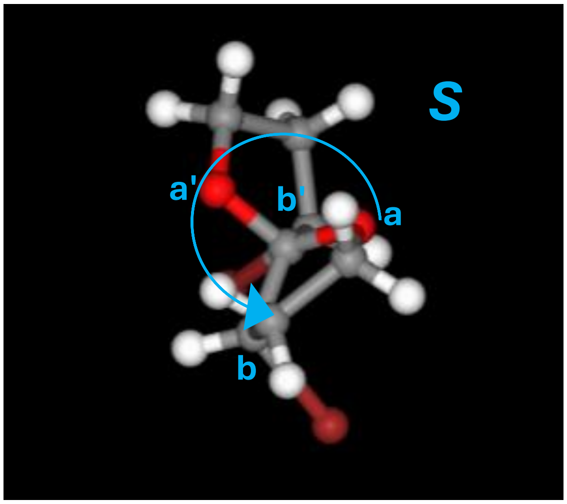
Exercise 2

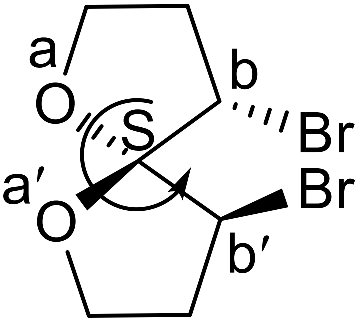
The structure of adamantane ensures that the CH_2 group opposite to one another have a fixed 90° rotation with respect to one another. In this respect the structure fills the same role as the two double bonds of an allene or the double bond plus ring of an alkylidencycloalkane. Since the oxygen atoms have priority over carbon and hydrogen, we can just look at the relative clockwise and counterclockwise rotation of these groups on the top and bottom when looking from of Me(C)OH group to another. In one molecule it is clockwise (*P*) and in the other it is anticlockwise (*M*).





Exercise 3

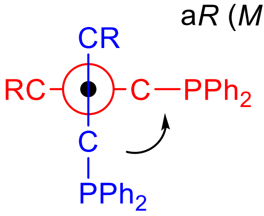




Both bromine-substituted stereocentres are assigned as *S*. According to the modified CIP rules for spiro molecule, the configuration at the spiro centre is also *S*.

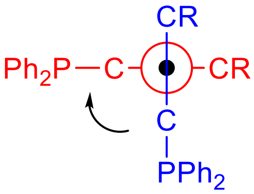
Exercise 4

Drawing a simplified projection of HUZGUE, we find that it has a*S* (*P*) configuration. PASRAC is also shown for comparison.



a*R* (*M*)

PASRAC

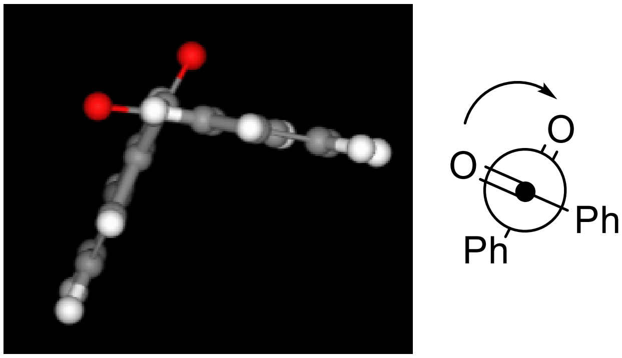


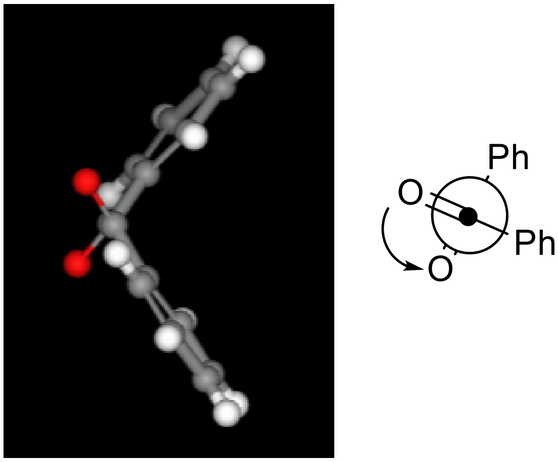
a*S* (*P*)

HUZGUE

Exercise 5

It is helpful to draw a Newman projection as shown below. In the case of BENZIL, a right-handed turn is seen (*P*) whereas a left-handed turn (*M*) is seen in BENZIL06.



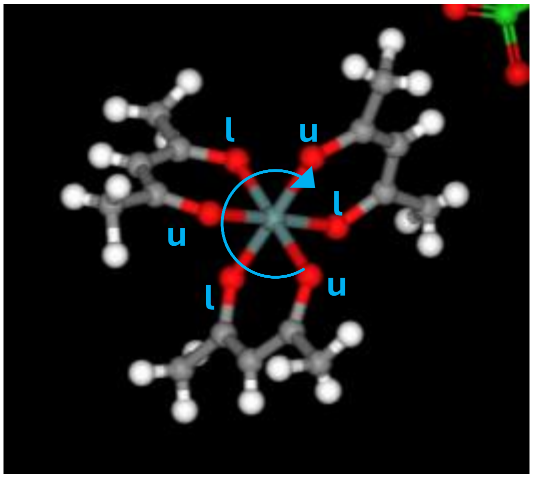


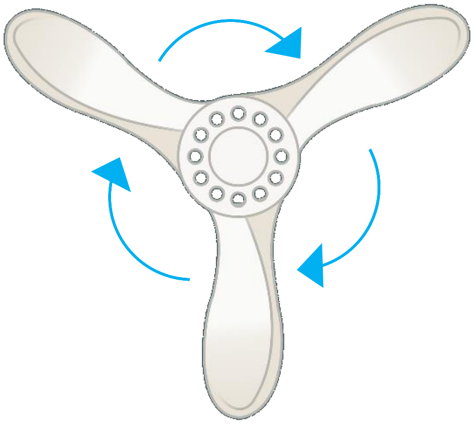
BENZIL: axial chirality: *P*

BENZIL06: axial chirality *M*

Exercise 6

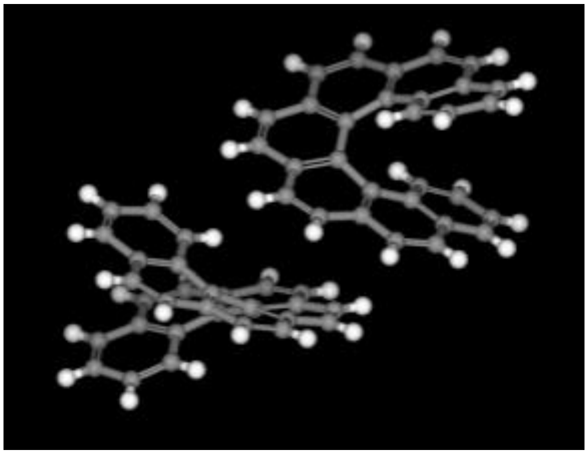
We can compare the cation of ACACGE with the molecular propeller in section 2.2.5 by looking down the direction of 3-fold symmetry as shown below. If we view each acetylacetonate ligand as a blade of the propeller, then the blades tilt downwards in a clockwise direction. This is a right-handed propeller, so the isomer is Δ.





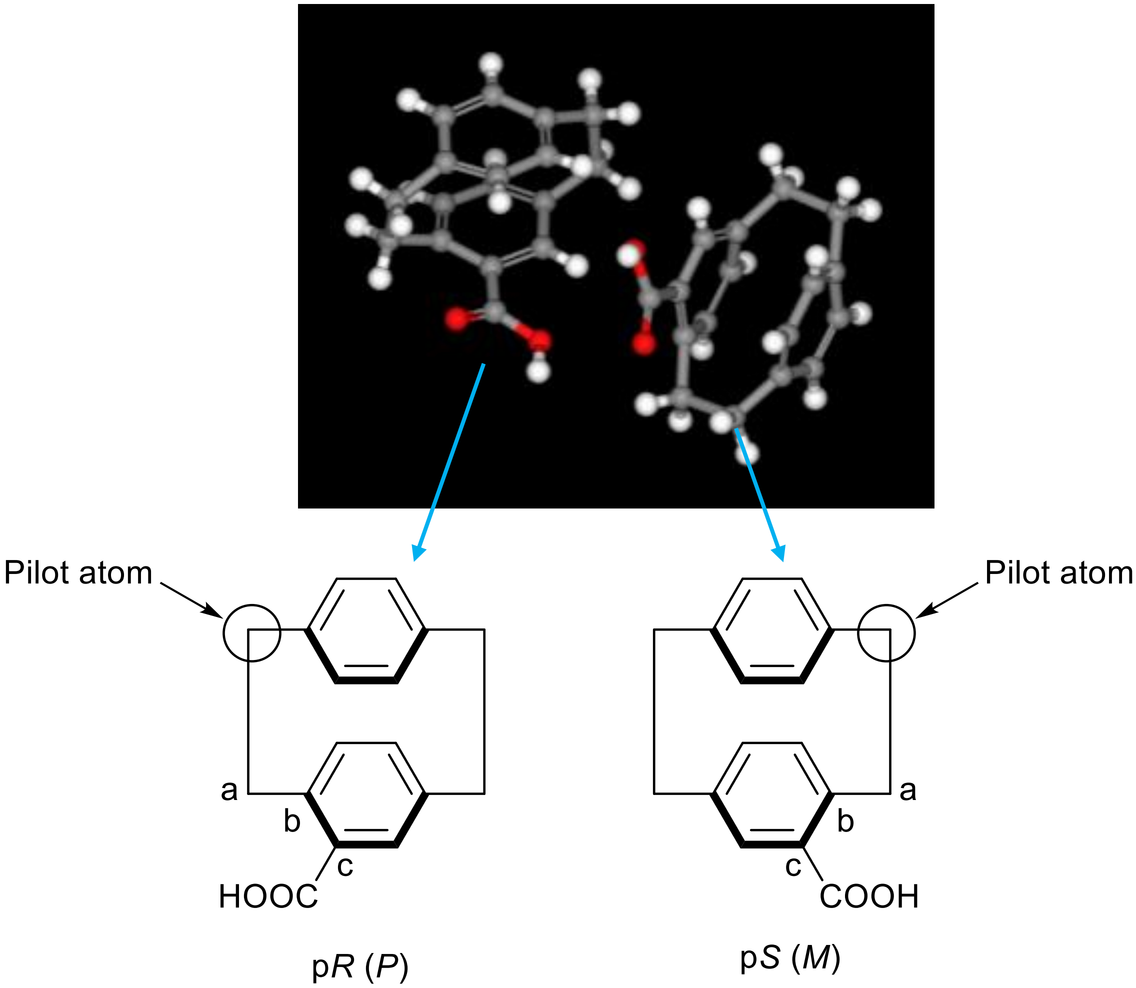
Exercise 7

You will see that there are two molecules in HPTHEL05 visible in the 3D viewer, both twist in an anticlockwise direction, so they are the *M* isomer.



Exercise 8

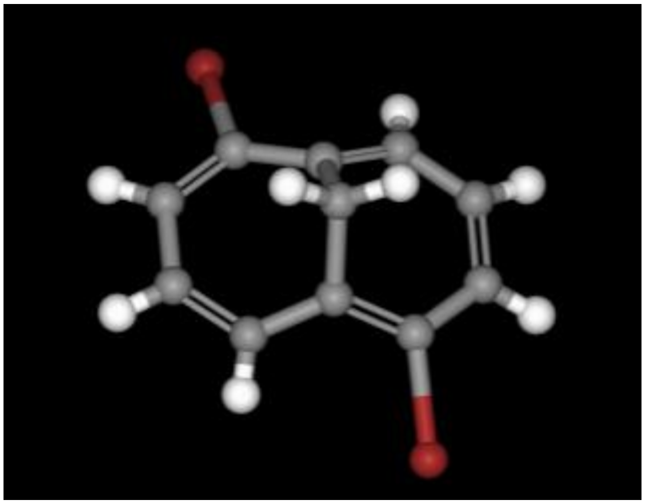
There are two molecules visible in CSD entry VECROL (in default viewer in the visualiser).

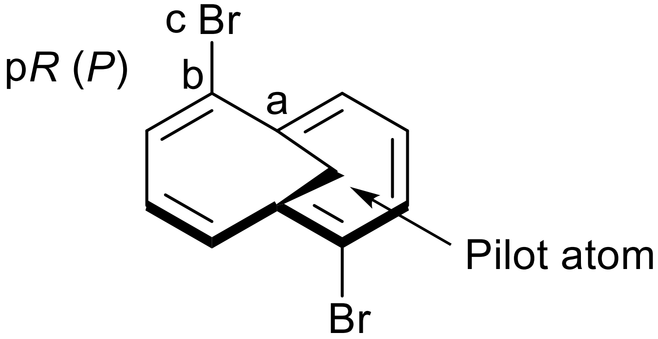


As you can see, both stereoisomers are present.

Exercise 9

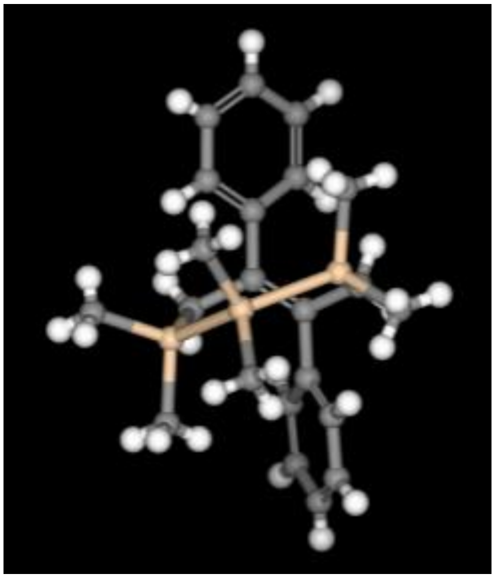
CSD entry JAWVOS is chiral as the bridging CH_2 group is out of the plane of the unsaturated ring (which is itself bent). It does, however, possess twofold rotational symmetry, so although there are two Br atoms present, you should find the same planar chirality regardless of which one you choose. The configuration is p*R* or *P*.

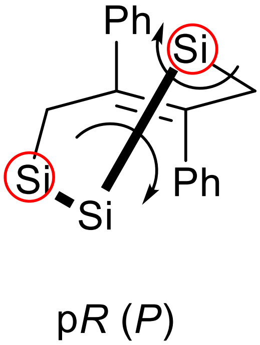




Exercise 10

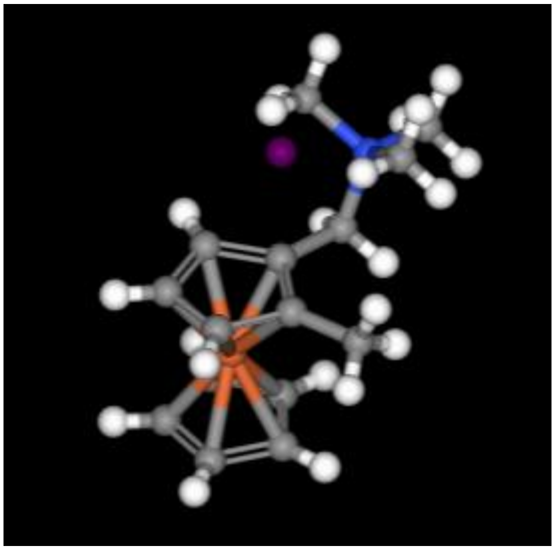
CSD entry VIJSOW is a 7-membered ring with a double bond so the stereochemistry can be determined in a similar way to *trans*-cyclooctene. Thus, it is found to be p*R* or *P*.

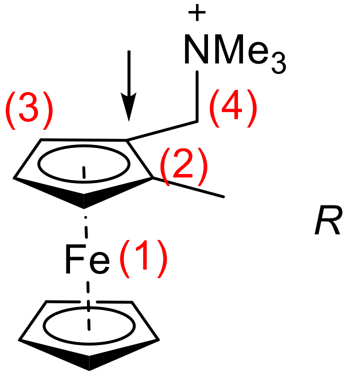




Exercise 11

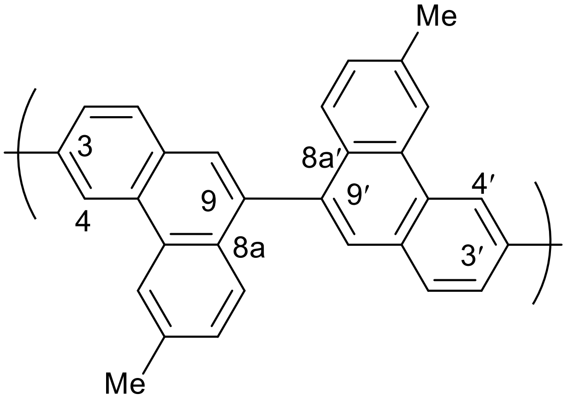
CSD entry BECKUQ contains an unsymmetrically substituted metallocene. Although it possesses planar chirality, we use the *R/S* convention as explained in section 3.1.4, giving the stereochemistry as *R*.



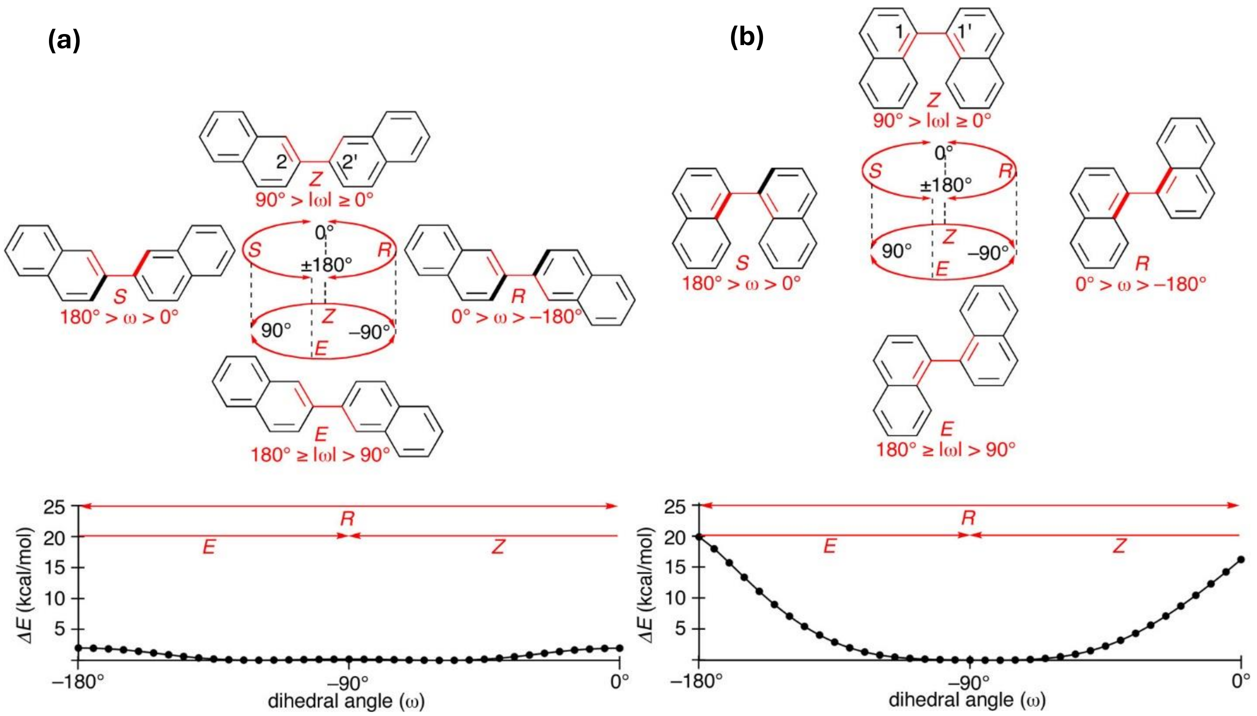


Exercise 12

For a full explanation of the stereoisomerism in CSD entry KATXEL, see P. Sarkar, Z. Sun, T. Tokushira, M. Kotani, S. Sato and H. Isobe, *ACS Cent. Sci.*, 2016, 2, 10, 740-747. The nanoloop is made up of phenanthrene units. There are essentially joined in two different ways (from different ring positions, 9,9' and 3,3') as you traverse the ring as shown below. The 3,3' linkage mimics the biaryl linkage of 2,2'-binaphthyl whilst the 9,9' linkage resembles 1,1'-binaphthyl. *E/Z* and *R/S* can be used (see diagrams for the range of angles covered by these descriptors).



The authors have calculated the energies of rotation about the bonds that give rise to *E/Z* and *R/S* isomers using the binaphthyls as model systems and determined (as you can see from the graphs of energy *vs* dihedral angle) that the energy barriers in the 2,2'-binaphthyl case (a) are very low, essentially giving free rotation, whilst the barrier between *R* and *S* is substantially higher in the case of 1,1'-binaphthyl (b). This substantially higher energy barrier creates stable isomers, which display cyclostereoisomerism due to the *R* or *S* geometry causing the belt shape to twist.



Figures reproduced from P. Sarkar, Z. Sun, T. Tokushira, M. Kotani, S. Sato and H. Isobe, *ACS Cent. Sci.*, 2016, 2, 10, 740-747.

The authors distinguish the pair of enantiomers found in the crystal structure (you will need to view the packed structure to see both) as (*E*,*R*,*E*,*R*,*E*,*R*,*E*,*R*)-[8]CPhen$_{3,9}$ and (*E*,*S*,*E*,*S*,*E*,*S*,*E*,*S*)-[8]CPhen$_{3,9}$ (*E*,*R*,*E*,*R*,*E*,*R*,*E*,*R*)-[8]CPhen$_{3,9}$ is the isomer visible by default in the single molecule view.

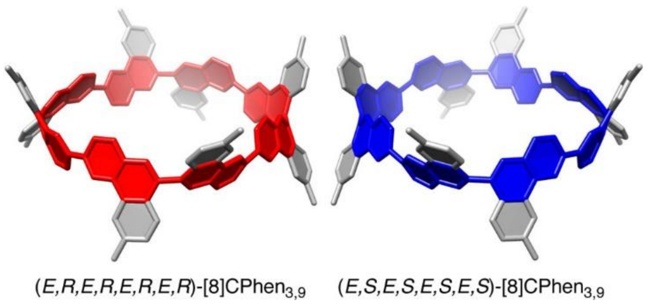


Figure reproduced from P. Sarkar, Z. Sun, T. Tokushira, M. Kotani, S. Sato and H. Isobe, *ACS Cent. Sci.*, 2016, 2, 10, 740-747