

CHE 2060: Principles of Organic Chem



3. Conformation and stereochemistry

Introduction: Louis Pasteur and the discovery of molecular chirality

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3. Conformation and stereochemistry



Molecular models are your friend!

Because this chapter deals extensively with concepts that are inherently three-dimensional in nature, it will be very important for you to use a **molecular modeling kit that is specifically intended for organic chemistry**.

Many of the ideas we will be exploring can be extremely confusing if you are limited to the two dimensions of this page.

Be prepared to follow along with these discussions in three dimensions, with a molecular model in your hands!

<https://www.amazon.com/Molymod-MMS-008-Organic-Chemistry-Molecular/dp/B007FAZOVS>

3. Conformation and stereochemistry



Introduction:

Louis Pasteur and the discovery of molecular chirality



Introduction



Can you see that these two crystals are mirror images?
Can you perfectly superimpose them? Imagine rotating them around as much as you like.

Each is about the size of a crystal of table salt. Imagine separating them with a microscope and tweezers. Pasteur was a grind!

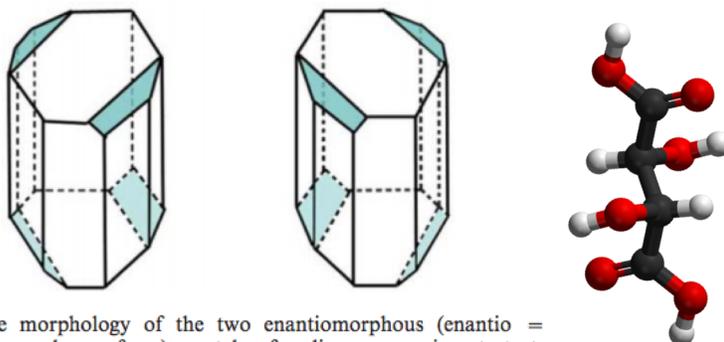


Fig. 1 The morphology of the two enantiomorphous (enantio = opposite, morphe = form) crystals of sodium ammonium tartrate separated by Pasteur in 1848. The hemihedral faces are colored blue (adapted from ref. 3). The shapes of the two crystals are not superimposable by translation or rotation, and are thus chiral.

tartaric acid

CrystEngComm, 2003, 5(26), 140–146 DOI: 10.1039/b304061e

3. Conformation and stereochemistry

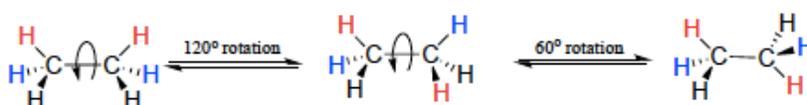
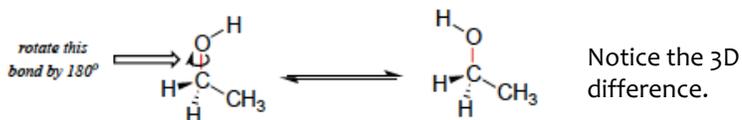


3.1: Conformations of open-chain organic molecules (aka linear molecules)

Rotation around single bonds



Conformational isomerism results from free and rapid rotation around single σ bonds.



Rotation around the C – C σ bond of ethane produces 3 different **conformers** (conformational isomer): *different 3D arrangement of molecular groups in space.*

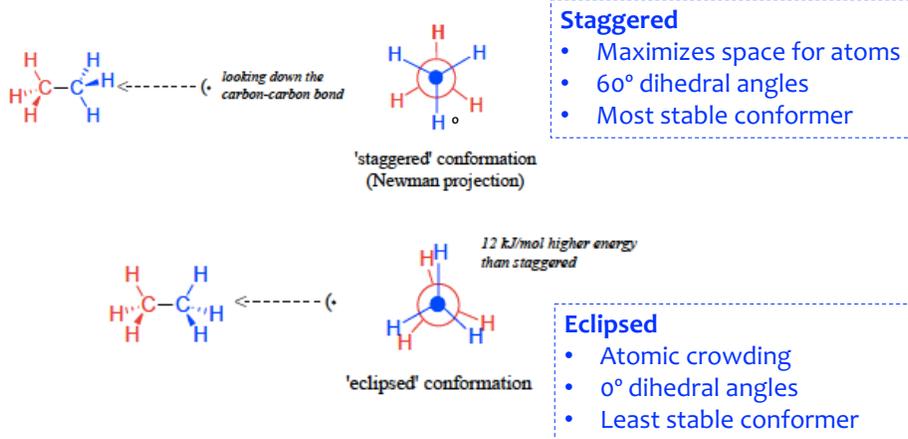
Notice that this 3D difference can't be seen on 2D paper without **dash-wedge** drawings.

Newman projections: ethane



Newman projections are a means of drawing molecules to highlight the difference between staggered and eclipsed conformers.

- Looking down the axis (bond) between two carbon atoms.
- Shows the 3D arrangement of all atoms bonded to those two carbons.

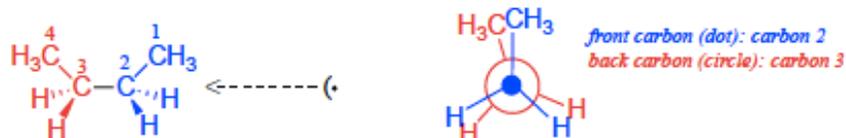


Newman projections: butane



Note that butane's Newman projection is a bit **more complex**.

- Looking down from C2 – C3
- C1 and C4 are shown as methyl groups (CH₃)
- All carbons must be shown!



Is eclipsed butane more or less stable than eclipsed ethane? And why?

Eclipsed butane is less stable than eclipsed ethane because the overlapping methyl groups are larger, causing more steric hindrance.

How many eclipsed butane conformers are there?

Three: methyl 1 can 'eclipse' any of the three atoms attached to carbon 3; the red atoms.

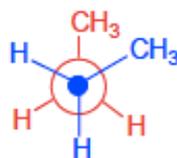
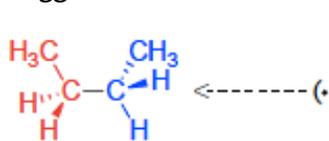
Which of the eclipsed conformers are more and less stable?

The methyl-methyl eclipsed conformer is less stable than the methyl-hydrogen eclipsed conformers.

Gauche vs anti?

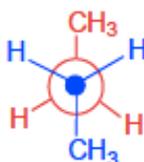
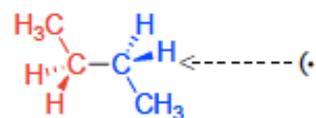


Just as there are several eclipsed conformations of butane, there are **several staggered conformations** as well.



gauche

Gauche is staggered when the two largest groups are **not** directly opposite on another.



anti

Anti is staggered when the two largest groups are **directly** opposite on another.

Which staggered butane more or less stable? And why?

Anti is more stable than gauche since the two large methyl groups are furthest apart.

Steric strain (aka steric hinderance)



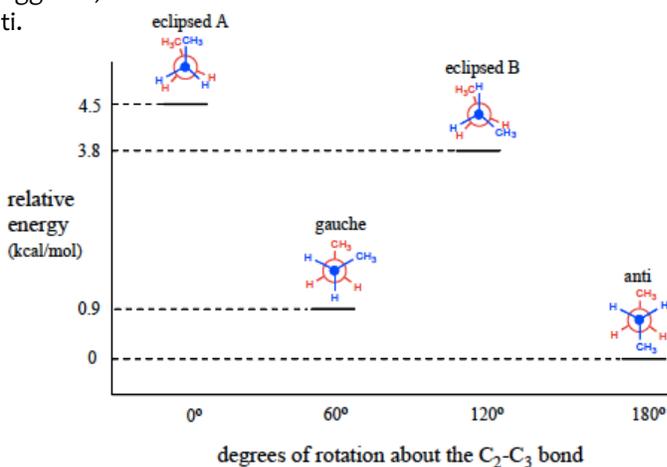
Steric strain (aka steric hinderance) is the loss of stability, or increase in energy, caused by spatial crowding of molecular groups in specific conformations.

This is the force responsible for the higher energy and lower stability of:

- Eclipsed vs. staggered; and
- Gauche vs. anti.

Note that the **energy diagram** of butane has two different peaks and two different valleys.

Can you explain why?



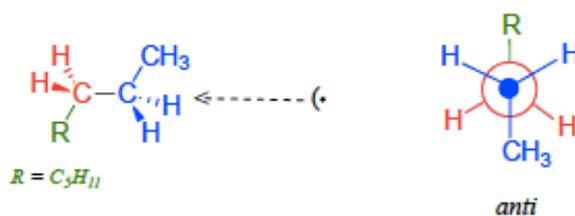
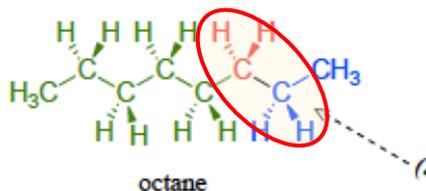
[Butane interactive](#)

Newman projections of larger molecules



Newman projections and dash-wedge drawings can be used to **focus on one C – C bond** of octane (C₂ – C₃).

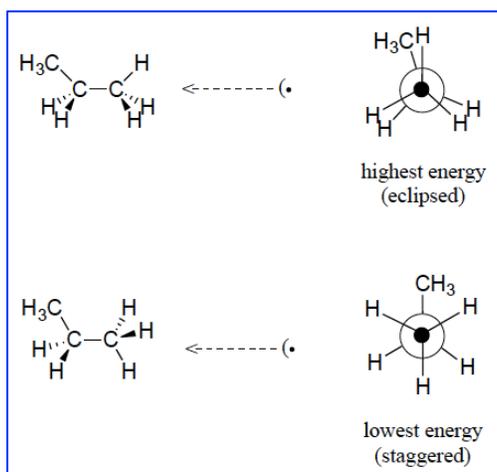
- Note the use of 'R' to abbreviate large sections of the molecule, outside of the area of focus.



Try this:



Draw Newman projections of the lowest and highest energy conformations of propane.



Can you?



- (1) Visualize free rotation around σ bonds?
- (2) Define the term 'conformer'?
- (3) Use dash-wedges to clearly show the different 3D structure of conformers?
- (4) Use Newman projections to show staggered and eclipsed conformations?
- (5) Describe 'steric hindrance' and how it determines the energy levels – and therefore stability – of different conformers?

3. Conformation and stereochemistry



3.2: Conformations of cyclic organic molecules

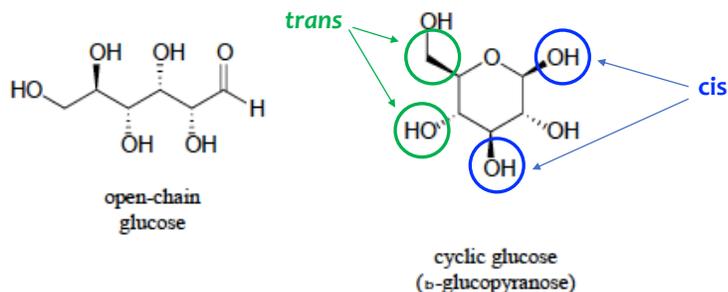
Cyclic molecules: *cis*, *trans* isomerism



This section focuses on cyclic, but **not aromatic**, structures.

Many molecules, like glucose, have both open-chain and cyclic structures.

- For both, dash-wedge allows us to see 3D structure.



Groups on the **same side** of the ring (both pointing up/towards) are **cis**.

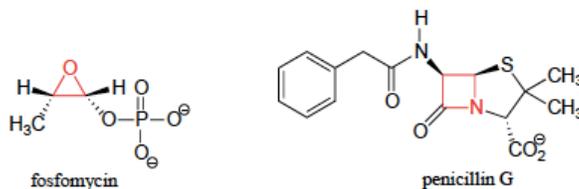
Groups on the **opposite side** of the ring (one towards/one away) are **trans**.

Ring number, strain and reactivity



Most cyclic biomolecules have **5 or 6 atoms** in their rings and are **stable**.

- **Angle strain** makes rings with **fewer atoms are less stable, more reactive**.
- These angles are far less than the 'comfortable' 109.5° .



The small rings, and resulting angle strain, make these two antibiotics effective as they react quickly once they find their bacterial targets.

Fosfomycin disrupts cell wall synthesis by inhibiting phosphoenolpyruvate synthetase and thus interferes with the production of peptidoglycan

Penicillin G burst bacterial cell walls by preventing peptidoglycans from cross-linking.

Wikipedia

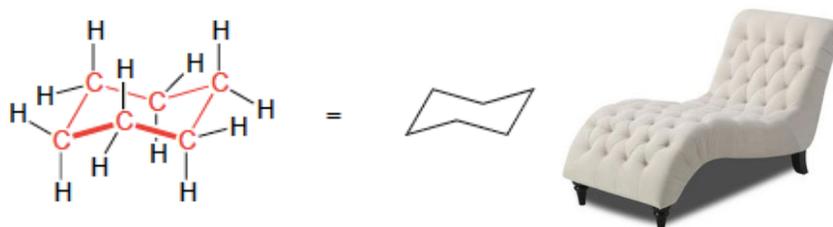
6-atom rings: puckered, thus stable



Rings with six atoms are **very stable** because of their favored **109.5° angles**.

The ring **'puckers'** to achieve that perfect angle.

- A flat six-membered ring would have very high energy levels.



Chair conformation is the most stable conformer for a six-atom ring.

- The 'bowtie' is the line-bond abbreviation for the chair.

Chairs can flex, invert and bow

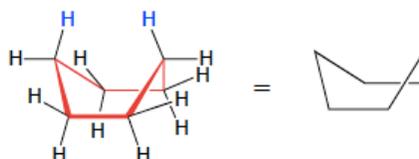


Because the C – C bonds of cyclohexane are single (σ) they can **flex or invert**.

- **Energy** increases the rate at which σ bonds rotate, so rate of flexion.
 - At room temperature, inversion happens constantly.
- The head of the chair can become the feet.



- Both ends can bow up to form bow and stern of a **boat** conformer.
 - The boat conformer has higher energy, and less stability, than the chair conformer.



Can you explain why the boat conformer is less stable than the chair conformer?

1. In the boat hydrogen atoms are eclipsed. They are staggered in chair.
2. 'Flagpole' (bow and stern axial hydrogen atoms) are sterically hindered.

Axial and equatorial positions

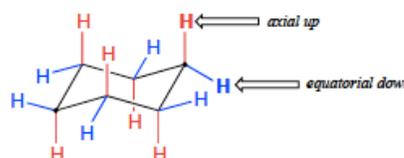


Every carbon of a 6-carbon ring is bonded to two hydrogen atoms. Each occupies positions described as:

Axial: perpendicular to the mean plane of the ring; pointing up or down

Equatorial: in the mean plane of the ring; slightly up or down

- Notice that as you travel around the ring axial hydrogen atoms alternate up and down.
- Likewise, equatorial hydrogen atoms alternate angled up and angled down.
- And, at one carbon, when axial is up, equatorial is down and vv.



When the ring is inverted or 'flipped' all axial positions become equatorial, and vv.

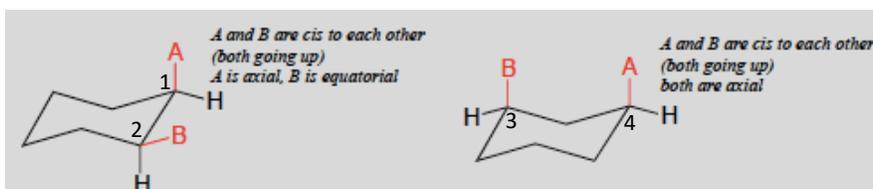
Which position do you think has higher energy, equatorial or axial? And why?

Axial is more crowded than equatorial, so axial is less stable than equatorial.

Axial / equatorial ≠ cis / trans



Both phenomenon happen in rings but mean different things.



What is the relationship between B on C2 and H on C1?

Both are equatorial and they are trans: B is above the mean plane; H is below it.

What is the relationship between A on C1 and H on C2?

Both are axial and they are trans: A is above the mean plane; H is below it.

What is the relationship between H on C3 and H on C4?

Both are equatorial and they are cis: both H atoms are below the mean plane.

What is the relationship between B on C3 and H on C4?

B is axial and H is equatorial.

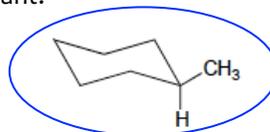
They are trans: B is above the mean plane of the ring and H is below it.

Where do the big groups want to be?



Many rings have substituents larger than hydrogen atoms.

- Which position do these larger groups want?

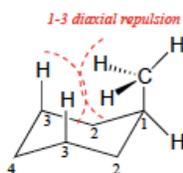


Does the methyl group want to be axial or equatorial? Why?

The methyl group wants to be equatorial because it has more space; it's less sterically hindered or crowded.

Build a model to demonstrate the effects of '1-3 diaxial repulsion'?

- Invert the models to compare methyl groups in the axial vs equatorial positions.

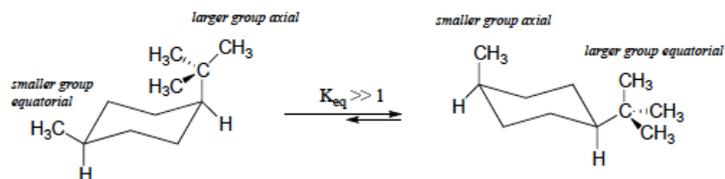


Bigger groups? Stronger preference



Here the ring has both a methyl group and a bulky 'tertbutyl' group.

- IUPAC name for tertbutyl is 1,1-dimethylethyl.
- The bigger, or 'bulkier' group takes the equatorial position.



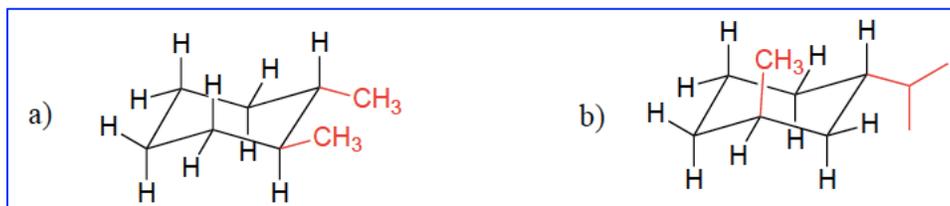
Try this:



Draw the **lower energy chair** conformations of:

- (a) trans-1,2-dimethylcyclohexane
- (b) trans-1-isopropyl-3-methylcyclohexane

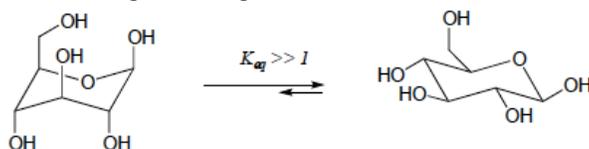
Be sure that axial and equatorial orientation is clear!



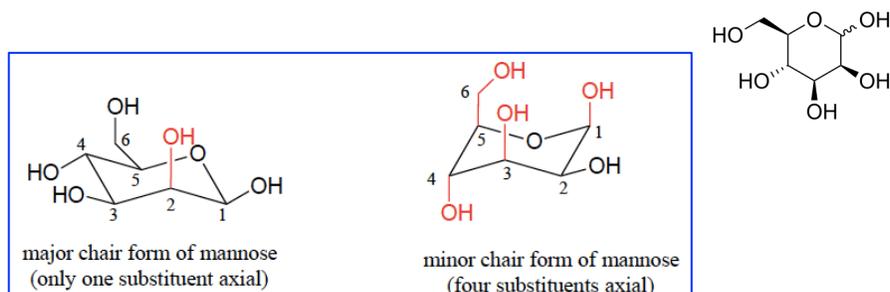
Try this:



One conformer of the ring form of glucose is more stable.



Draw the two chair conformations of the six-carbon sugar mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

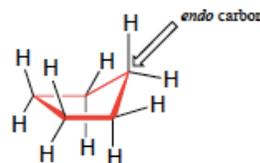


Cyclopentane 'envelope'

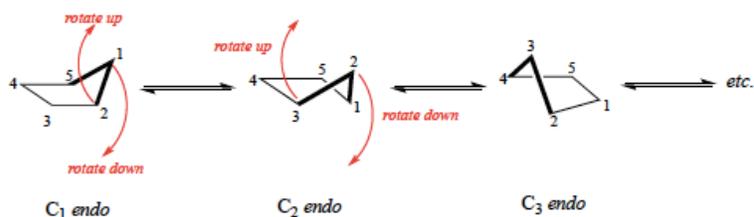


The **lowest energy conformer** of cyclopentane is called an '**envelope**' because the one carbon that is proud of the rectangle formed by the other four looks like the flap of an envelope.

- No axial and equatorial.



At room temperature, inversion causes carbons to take a turn at being endo.



Can you?



- (1) Describe the *cis-trans* isomerism of rings and show it with dash-wedge diagrams?
- (2) Describe 'angle strain' and 'pucker' and why 5- and 6-membered rings are most stable?
- (3) Draw chair and boat forms of cyclohexane so that 'axial' and 'equatorial' positions are clearly shown?
- (4) Flex and invert chairs, changing axial to equatorial and vice versa?
- (5) Describe why chairs are more stable than boats?

3. Conformation and stereochemistry



3.3: Chirality and stereoisomers

What is chiral?



Chiral objects don't have an internal plane of symmetry, aka a **mirror plane** of symmetry.

- When superimposed, chiral objects don't overlap perfectly.

Hands are a chiral, or handed.

What about:

Gloves?

Mittens?

Achiral examples?

Baseball bat

Coffee mug

Many socks



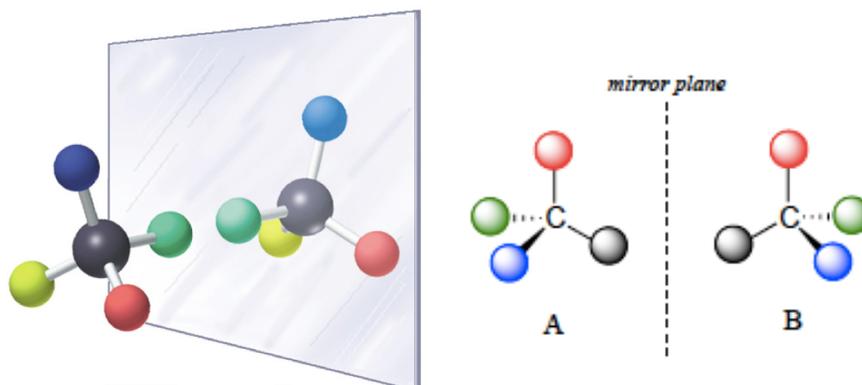
Chiral carbons



Chiral molecules also **lack internal planes of symmetry**, but there are some easier ways to identify them.

The two chiral molecules shown here (A and B) are **mirror images** of one another.

- sp^3 hybridized carbons (aka chiral carbons; chiral centers)
- **4 different substituents**

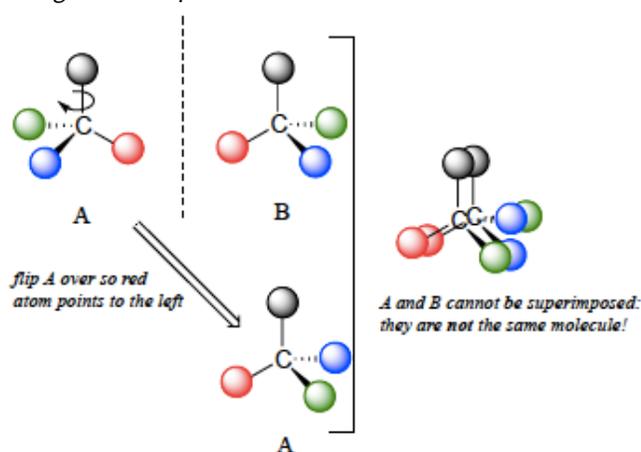


Can't be superimposed



Notice that the two mirror image molecules, A and B, **cannot be superimposed** even after one of them are rotated.

Stereoisomers: same molecular formula & connectivity but different 3D arrangement in space



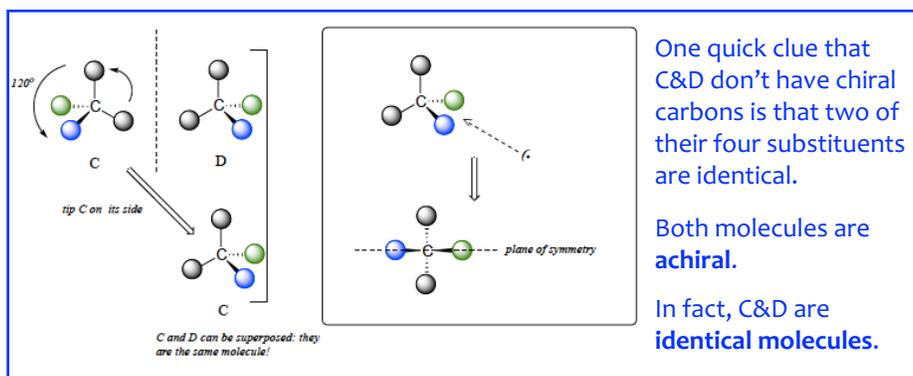
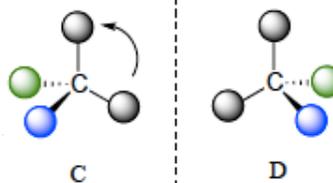
Enantiomers: pair of stereoisomers that are mirror images of each other

- Same physical and chemical properties.
- Different biological properties.

Try this



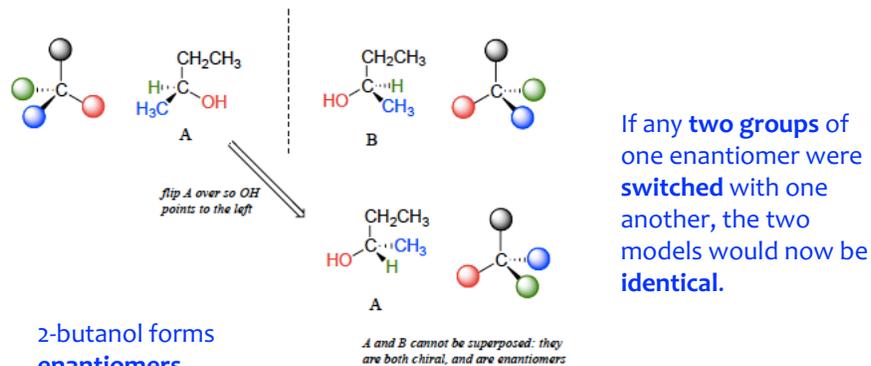
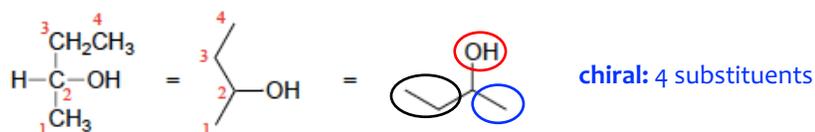
Are C and D **stereoisomers**?



Try this



Is **2-butanol** chiral? Does it have four different substituents?

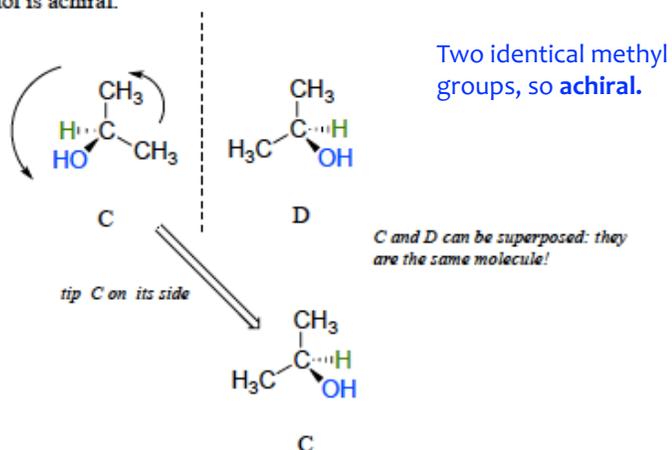


Try this:



Is **2-propanol** chiral? Does it have four different substituents?

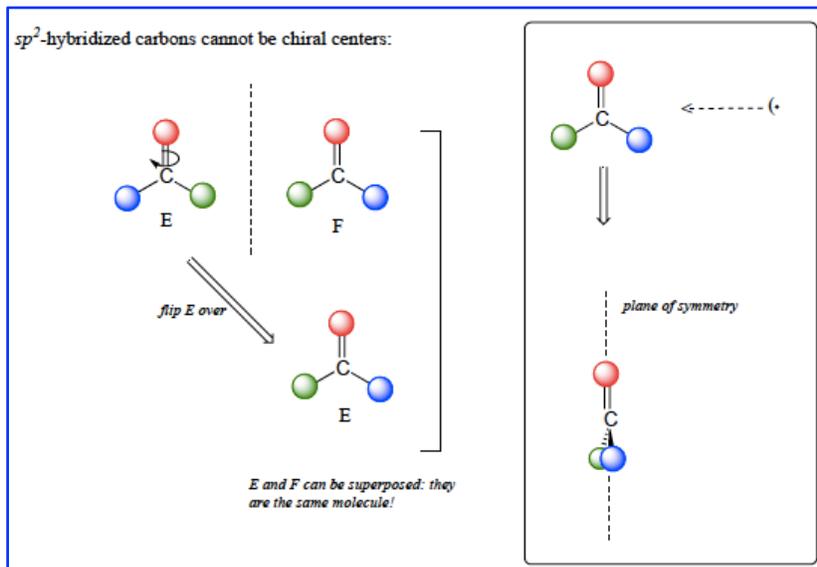
2-propanol is achiral:



Try this:



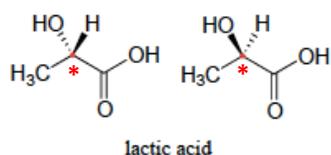
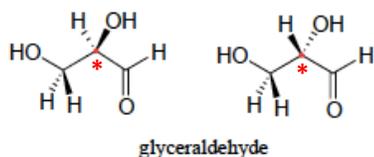
Can a small molecule with a central sp^2 hybridized carbon be chiral?



Examples of enantiomeric pairs



Chiral carbons are shown as red dots.



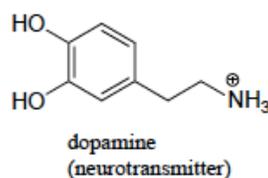
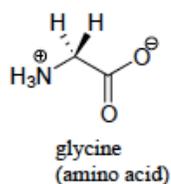
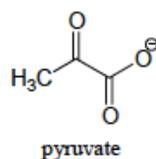
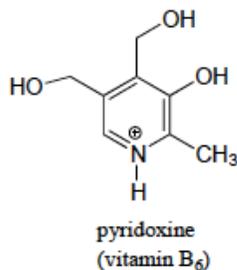
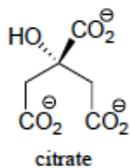
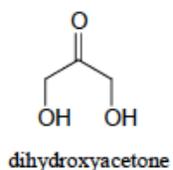
Find the chiral carbons here.

Examples of achiral molecules



Be sure that you can see that **none** of these molecules contains a chiral carbon.

- Remember that dash-wedged carbons don't necessarily correspond to chirality.

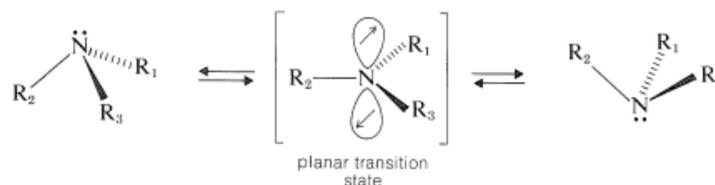


Amines: sometimes chiral

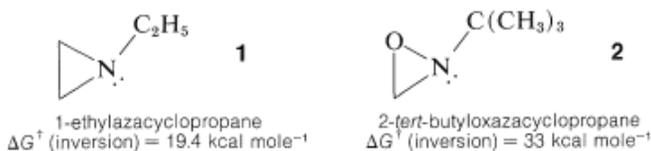


The nitrogen of **acyclic amines** has four 'substituents', so why isn't it chiral? One substituent is a **lone pair**.

- At room temperature, the orientation of the nitrogen **inverts rapidly**, preventing true chirality from occurring.
 - 4 E10 inversions/second



In **small rings (<5 atoms)**, the inversion rates of N is much **slower** and **chirality can occur** at the N even with a lone pair.



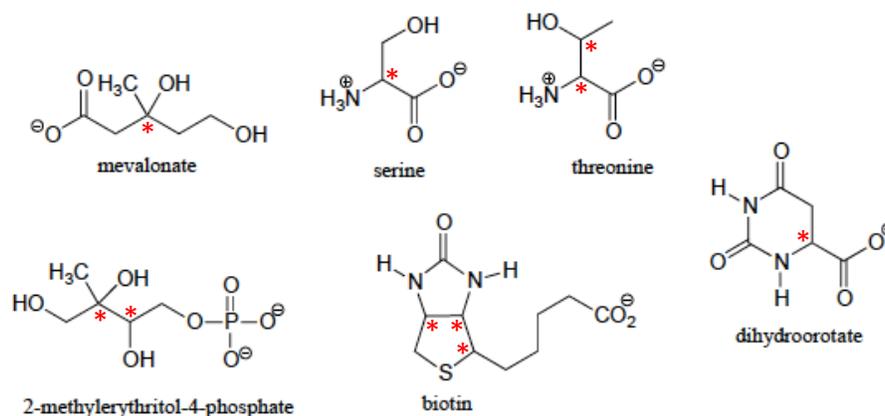
[https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Book%3A_Basic_Principles_of_Organic_Chemistry_\(Roberts_and_Caserio\)/23%3A%3A_Organonitrogen_Compounds_%3A_Amines/23.06%3A_Stereochemistry_of_Amines](https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Book%3A_Basic_Principles_of_Organic_Chemistry_(Roberts_and_Caserio)/23%3A%3A_Organonitrogen_Compounds_%3A_Amines/23.06%3A_Stereochemistry_of_Amines)

Try this:



Locate all **chiral centers**; there may be more than one.

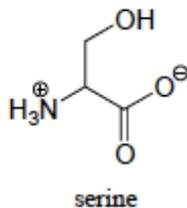
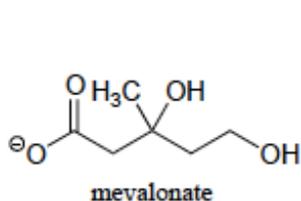
- Remember that some hydrogen atoms aren't shown explicitly.



Try this:

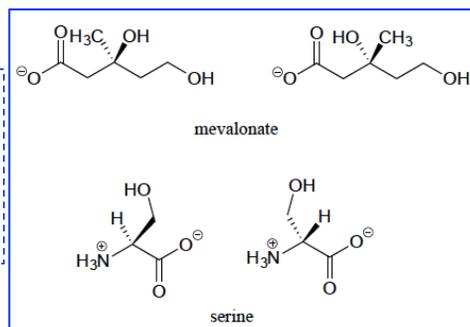


Draw enantiomers of **mevalonate** and **serine**.



How do you approach this problem?

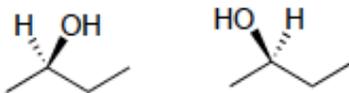
- Find and mark chiral centers.
- Use dash-wedges to show both orientations at chiral centers:
 - switch dash-wedges!



Try this:



Both molecules shown here are 2-butanol. **Are they enantiomers?**



Nope. In both cases, the hydroxyl group comes forward and the hydrogen atom goes backwards.
Make models to convince yourself!

Can you?



- (1) Define the term 'chirality' and give examples of chiral and achiral objects?
- (2) Define the terms 'stereoisomer' and 'enantiomer', and draw enantiomers using dash-wedge conventions?
- (3) Identify chiral centers in molecular structures? Including amine Ns?
- (4) Describe what you would have to change (or switch) to convert one enantiomer to the other?

3. Conformation and stereochemistry



3.4: Labeling chiral centers

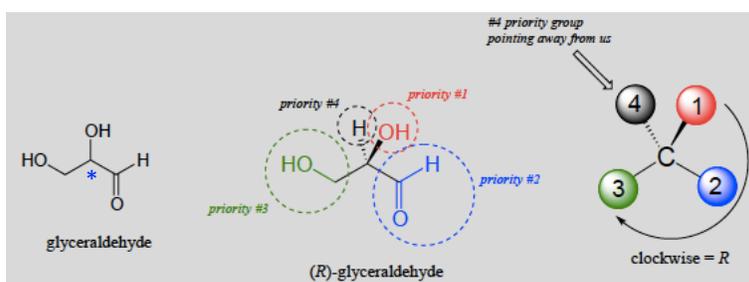
Cahn-Ingold-Prelog labeling: R or S



The **Cahn-Ingold-Prelog labeling system** allows us to identify stereoisomers by describing the 3D orientation of the four substituents of a chiral atom.

Steps:

1. Label substituents from highest (1) to lowest (4) priority by atomic number.
2. Build a model.
3. Hold the model so that substituent 4 faces away from you with 1-3 facing toward you.
4. As you follow substituents from 1 to 3,
 - if you move clockwise the chiral atom has an 'R' conformation.
 - If counterclockwise, then it's an 'S' conformation.



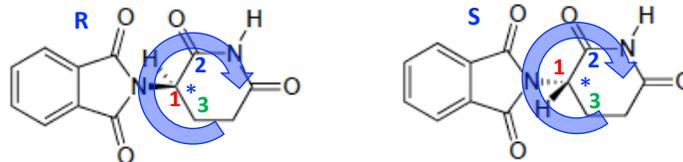
Try this:



Thalidomide was prescribed as a sedative and anti-morning sickness medication for pregnant women in the 1950s. Tragically, one enantiomer caused serious birth defects in children born to some of those women.

- It's now used to treat wasting sickness in patients with HIV and the aggressive blood cancer, multiple myeloma.

Which of these **thalidomide enantiomers** is R and which is S?



Note that the hydrogen (priority 4) is pointing at us, rather than away from us. Flipping the molecule over would 'fix' that and clockwise rotation would become anticlockwise.

While it's believed that the S enantiomer causes the birth defects, an **isomerase** in the body will convert R to S, so birth defects aren't prevented by giving purified R-form. [Interactive model](#)

Regulation prevented more tragedy



In the US, thalidomide wasn't approved for use because of the efforts of a pharmacist at the USDA. **Frances Oldham Kelsey** received the President's Award for Distinguished Civilian Service in 1962.

Richardson-Merrell, the American distributor, demanded approval six times without supplying any test data.

Only 17 children were affected by free samples applied for 'testing purposes'.

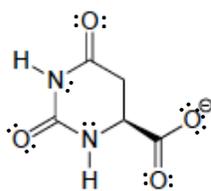
<https://en.wikipedia.org/wiki/Thalidomide>



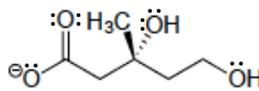
Try this:



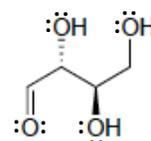
Identify the chiral centers in these biomolecules **and** determine whether conformation is R or S.



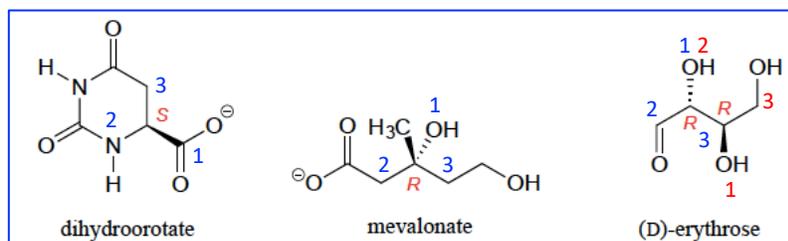
dihydroorotate



mevalonate



(D)-erythrose



dihydroorotate

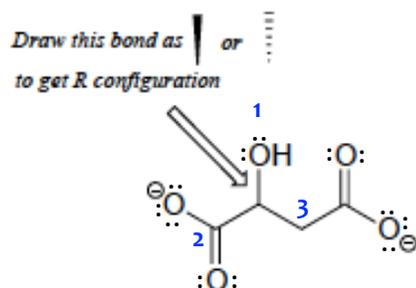
mevalonate

(D)-erythrose

Try this:



Should the R enantiomer of malate have a dash or wedge for its C - O bond?



The C - OH bond should be 'dashed' for the R enantiomer.

Can you?



- (1) Describe the steps of Cahn-Ingold-Prelog prioritization and use it to determine configuration of chiral centers as R or S?
- (2) Use dash-wedge diagrams to draw R or S forms of an organic molecule?

3. Conformation and stereochemistry



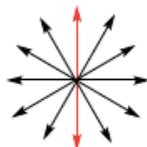
3.5: Optical activity

Plane polarized light



A beam of light is a collection of **electromagnetic waves** traveling through space.

- The waves are **randomly oriented**, or **nonpolarized**.



ordinary
(nonpolarized) light



Without Polarizer



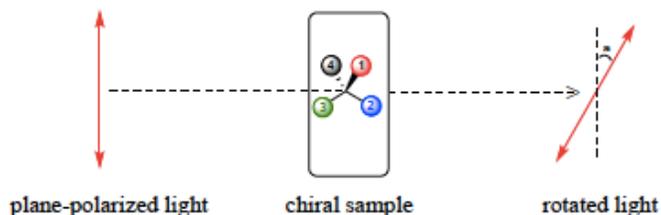
With Polarizer

Chiral molecules rotate polarized light



When plane-polarized light is passed through a solution of chiral molecules the plane of the light is **rotated**.

- This property is called '**optical activity**'.



Dextrorotatory (D+): polarized light is rotated clockwise

Levorotary (L-): polarized light is rotated counterclockwise

D & L are
not related
to R & S.

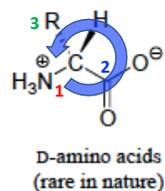
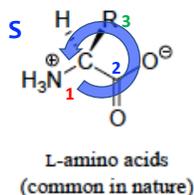
A 50:50 mixture of R and S enantiomers, called a **racemic mixture**, does not appear to rotate plane-polarized light because the rotations are equal and opposite and cancel one another out.

Amino acids: L for 'life'



19 of 20 amino acids have chiral α -carbons, and in nature (or life) they are nearly all L, or levorotary.

- Coincidentally, 18 of 19 are also (S).



R
Seems S, but the H projects forward, so the molecule (and rotation) have to be flipped.

Determine whether each of these amino acids is R or S.

D amino acids are rare in nature, but are used by some bacteria can be useful in biotechnology.

Can you?



- (1) Define the term 'plane-polarized light'?
- (2) Describe the effect of chirality on plane-polarized light?
- (3) Define the terms 'levorotary' and 'dextrorotary'?
- (4) Describe the relationship between L and D and R and S?
- (5) Define the term 'racemic mixture' and explain why it has no apparent optical activity?

3. Conformation and stereochemistry



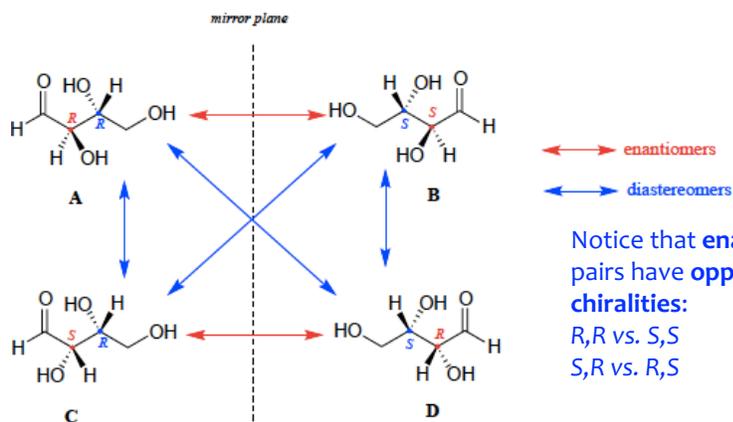
3.6: Molecules with multiple chiral centers

Several chiral centers are common



This four-carbon sugar has two chiral carbons, labelled here with blue and red dots.

- How many possible stereoisomers? 2^n , where n = chiral centers



Diastereomer: stereoisomers that are not enantiomers
Epimers: diastereomers that differ at only one chiral center

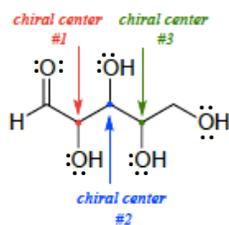
Physical properties may vary.

Try this:



Here's a three-carbon sugar.

- How many possible stereoisomers are possible? $2^3 = 8$
- Draw the R,R,R stereoisomer.
- How would you then draw any of the other stereoisomers?

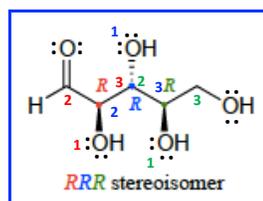


Once you've got one, just switch dashes and wedges where needed.

What was your process?

I have to admit that I tend to prioritize the four substituents, randomly add dashes and wedges and then determine whether I've made R or S. If I'm wrong, I switch the dash and wedge.

Models can be faster!

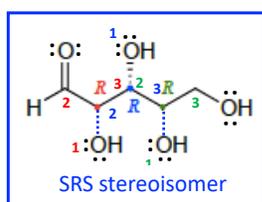


Try this:



Again, refer to the same three-carbon sugar shown in the last problem.

- Draw the SRS stereoisomer.
- List all epimers of the SRS stereoisomer.
- List all non-epimer stereoisomers of SRS.



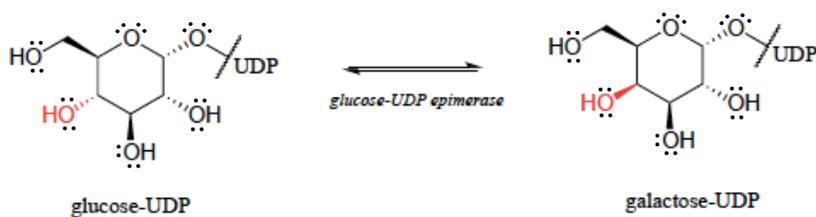
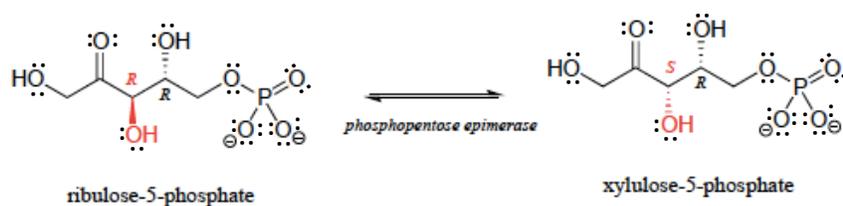
All possibilities ($2^3 = 8$):

RRR	RRS epimer	RSS	SSS epimer
	RSR enantiomer	SRS identical	
	SRR epimer	SSR	

Epimerases



Epimerases: enzymes that 'convert' stereoisomers at one chiral center



Try this:

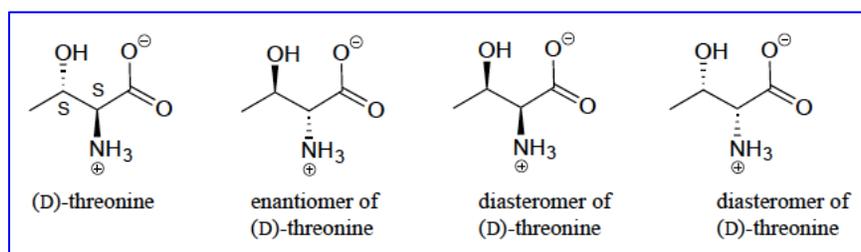
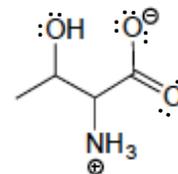


This is the amino acid D-threonine, drawn without stereochemistry.

(a) Draw it as *S,S*-threonine as it is found in nature.

(b) Draw the enantiomer of the natural version.

(c) Draw all possible diastereomers.



Can you?



- (1) Define the term 'diastereomer'?
- (2) Calculate the number of diastereomers that an organic molecule has?
- (3) Define the term 'epimer'?
- (4) Convert the dash-wedge drawing of one stereoisomer to another?
- (5) Describe what an 'epimerase' is and what it does?

3. Conformation and stereochemistry



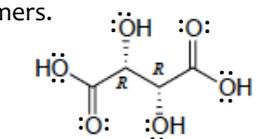
3.7: Meso compounds

Meso compounds

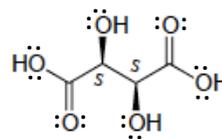


Meso compounds: have chiral centers with equal and opposite chirality, and an *internal plane of symmetry* that renders them *achiral*

Tartaric acid has 2 chiral carbons. It should have 4 stereoisomers.
Here are its enantiomers.



(*R,R*)-(+)-tartaric acid
(‘natural’ isomer from grapes)

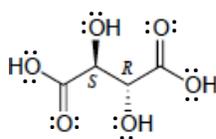


(*S,S*)-(-)-tartaric acid

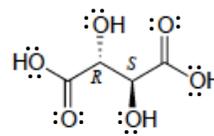
Is this a **second set of enantiomers**?

This is actually one molecule as these ‘two’ forms are superimposable and identical.

- **Meso!**



(*S,R*)-tartaric acid



(*R,S*)-tartaric acid

Seeing meso

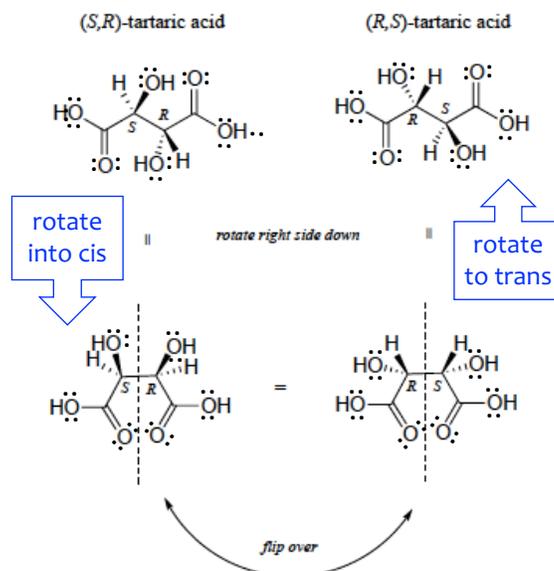


Some meso compounds are obvious, but others are much easier to see if you **build the model(s)**.

So the meso form is an **achiral diastereomer** of the R,R and S,S forms.

Some conformations make the internal mirror image more obvious.

And here flipping the molecule over converts S,R to R,S without making or breaking a single bond.

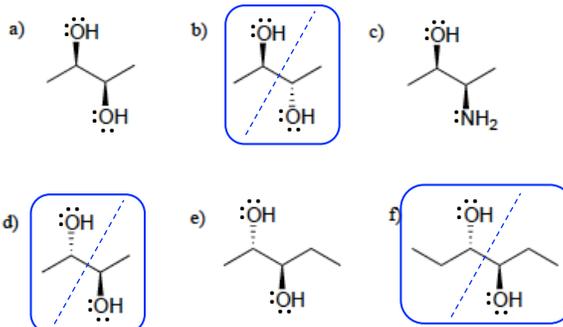


Try this:



Which of these compounds are **meso**?

- Look for internal symmetry and opposite chirality.
- You may want to build models to be sure!



Can you?



- (1) Define the term 'meso' compound and explain how to test for it?
- (2) Understand how the R/S configuration of a compound reflects the internal symmetry characteristic of a meso compound?
- (3) Describe the optical activity of a meso compound?

3. Conformation and stereochemistry



3.8: Fisher and Haworth projections

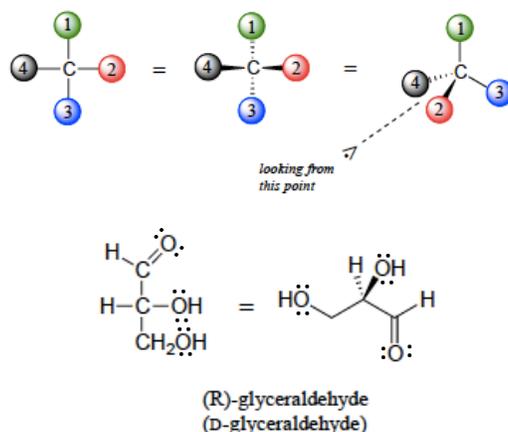
Fischer projections



Fischer projections: show the chirality of organic molecules in the open chain form and don't use dashes and wedges

Horizontal axis points out of the plane, towards the viewer.

Vertical axis points back into the plane, away from the viewer.

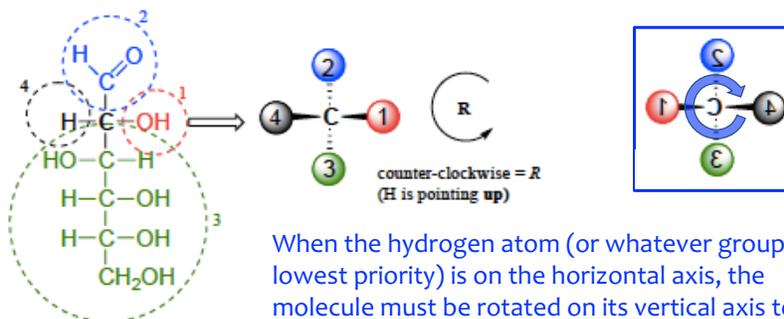


Fischer projections: R or S?



To determine whether each carbon of a Fischer projection is R or S:

- (1) Assign priority to the four substituents;
- (2) Face the hydrogen back away from the viewer;
- (3) Determine whether 1 to 2 to 3 is clockwise or counterclockwise.



When the hydrogen atom (or whatever group is lowest priority) is on the horizontal axis, the molecule must be rotated on its vertical axis to swing the hydrogen to face away from the viewer.

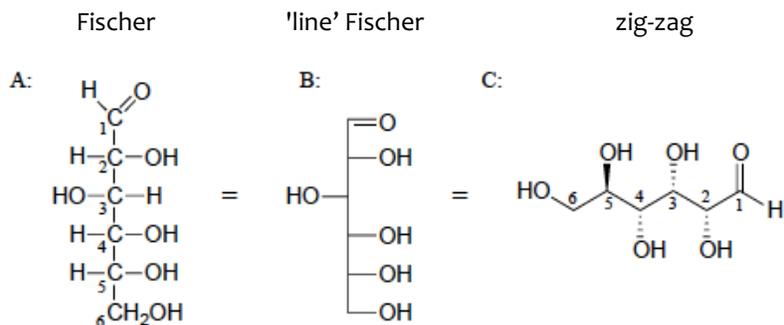
- That twists the other horizontal substituent over to the other side.
- Here the OH (1) ends up on the left.
- Make a model and prove this to yourself.

Translating Fisher to zig-zag



It's wise to determine whether each chiral carbon is R or S to be sure the two types of diagrams actually represent the same molecule.

- Be sure that you can do that here.

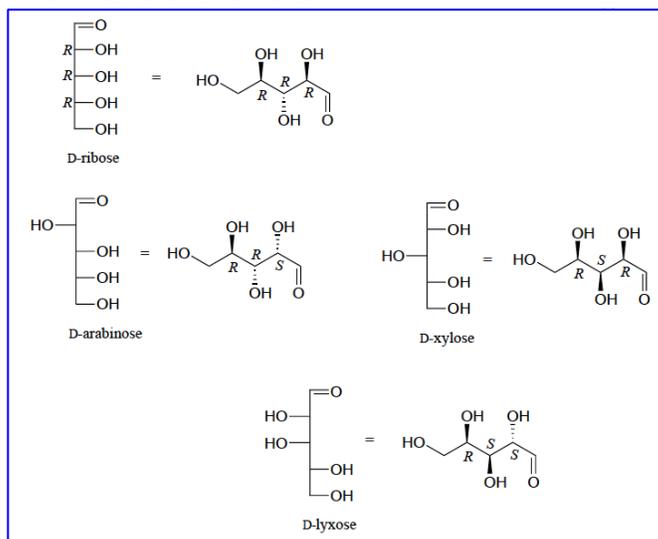


Try this:



For this group of five-carbon sugars:

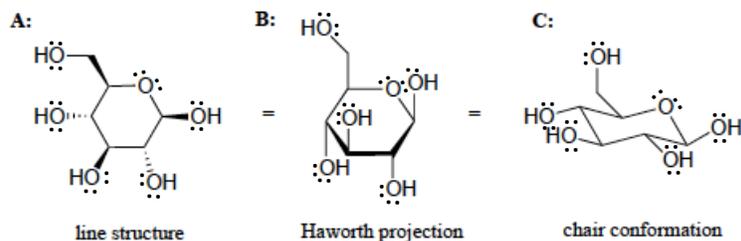
- Label all chiral carbons.
- Determine whether each is R or S.



Haworth projections (Fischer for rings)



The **Haworth diagram** shows stereochemistry like a Fischer diagram.



Chair (or boat) diagrams show both conformation and stereochemistry.

- Most realistic.

Can you?



- (1) Describe the conventions of a Fischer projection?
How does it show 3D structure without dash-wedges?
- (2) Determine whether chiral centers are R or S on Fischer projections?
- (3) Convert Fischer projections to 'zig-zags' and dash-wedge diagrams?
- (4) Describe how a Haworth projection is similar to a Fischer projection?

3. Conformation and stereochemistry



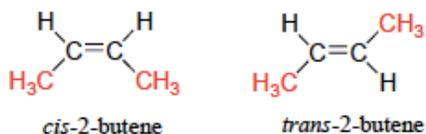
3.9: Stereochemistry of alkenes

Cis-trans isomers



The groups on either side of double bonds can assume different **stereoisomeric conformations** if both carbons share a **common substituent**.

- Here methane and hydrogen are common to both double-bonded carbons.



Cis: both groups are on the **same** side

Trans: the common groups are on **opposite** sides

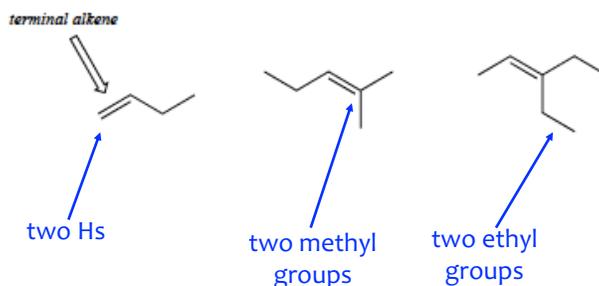
These molecules **aren't chiral** and **don't have chiral carbons**, but they are **stereoisomers**.

- Diastereomers**

Can't be *cis-trans*?



If one of the double-bonded carbons has **two identical substituents**, then the molecule doesn't have stereoisomerism.



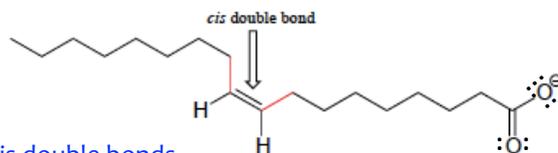
Cis-trans fatty acids



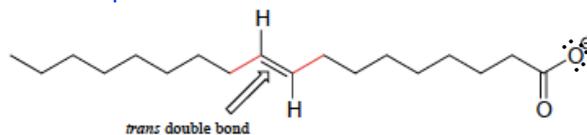
Most **naturally occurring** fatty acids with double bonds are found in the *cis* conformation.

However, when double bonds are introduced into fatty acids using chemistry, their conformation is often **trans**.

- Trans fatty acids are associated with heart disease and other health issues.



Notice that *cis* double bonds create a 'kink' in fatty acid tails. The kink impairs packing and lowers mp.

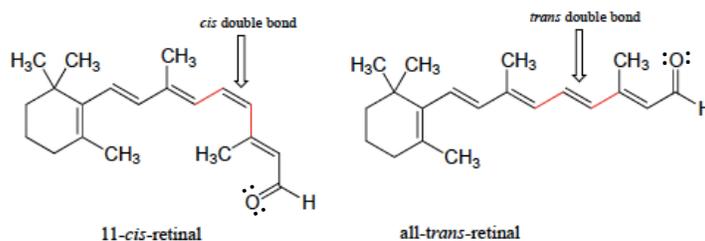


Retinal signals with *cis-trans* change



Retinal is derived from vitamin A and is found in the eye's rod cells.

- Light enters the eye and converts the *cis* stereoisomer to the *trans* form.
- The shape change alters the way retinal binds to the protein rhodopsin.
- This causes a signal to be sent to the vision center of the brain.



E and Z when all groups are unique



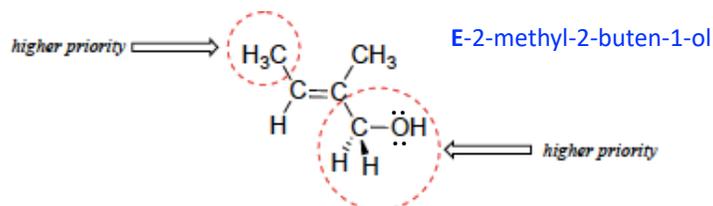
The terms *cis* and *trans* can be used when both double-bonded carbons share a common substituent.

If they don't share a substituent, then the stereoisomerism is described as **E** or **Z**.

- **Use E and Z when all four substituents are different.**

Steps:

1. For each carbon, identify the substituent with the **greater atomic number**.
2. If the 'high' groups are on the **same side** of the double bond: **Z**.
3. If the 'high' groups are on **opposite sides** of the double bond: **E**.

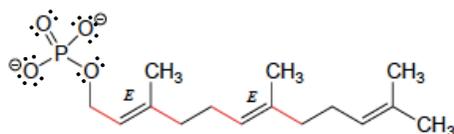
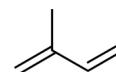


E and Z isoprenoid polymers

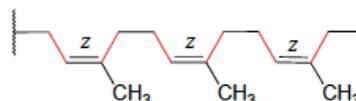


Isoprene units can be polymerized to create large biomolecules.

- Stereoisomerism determines form and function.



E-isoprenoids
(eg. a precursor to cholesterol)

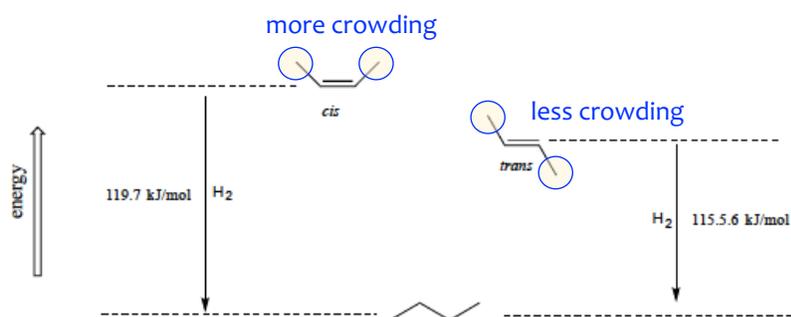


Z-isoprenoids
(eg. rubber)

Which is more stable?



Generally, large substituents prefer to be across the double bond from one another (**trans** or **E**) because that gives them **more space** and **lowers 'steric hindrance'** or crowding.

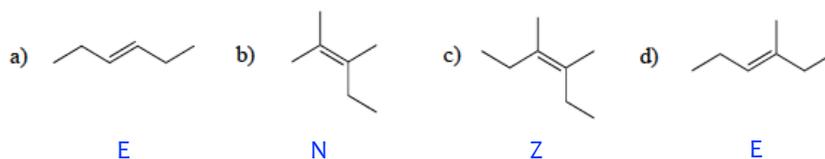


Try this:



Label each molecule as one of the following:

- N (not stereoisomer)
- E
- Z

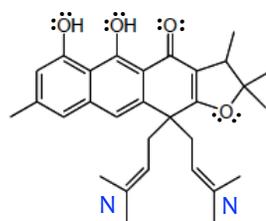


Try this:

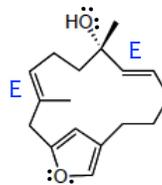


These molecules were isolated from natural sources. For double bonds outside of 5- or 6-membered rings, label the bonds as:

- N (not stereoisomer)
- E
- Z



from Nketto plant in Cameroon
J. Nat. Prod. **2007**, *70*, 600



from tree bark in Thailand
J. Nat. Prod. **2007**, *70*, 659

Can you?



- (1) Define the terms 'cis' and 'trans', and what types of molecules can and cannot be cis-trans?
- (2) Describe the class of stereoisomer that cis-trans isomers are?
- (3) Identify and draw cis-trans isomers?
- (4) Define what 'E' and 'Z' isomers are?
- (5) Identify and draw E and Z isomers?
- (5) Describe whether cis or trans isomers are more stable and why?

3. Conformation and stereochemistry



3.10: Stereochemistry in biology and medicine

Biomolecules are chiral

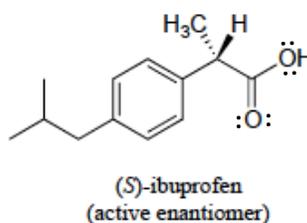
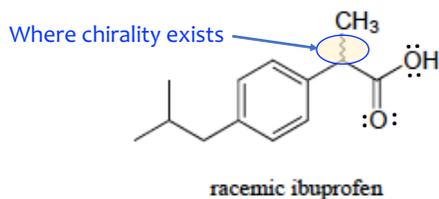


Many, if not most, biomolecules contain chiral centers and are chiral.

Proteins are chiral:

- Receptors send signals to and through cells.
- Enzymes do the chemical work of the cell.
- Antibodies defend the body against invaders.

So the **ligands** that are bound by these proteins must be **chiral and a match**.



The **R enantiomer** doesn't do this.

An enzyme in our bodies **converts** the R form to the S form over time, so it must be considered in dosage.

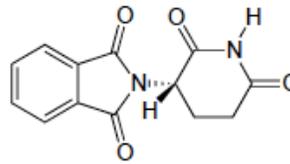
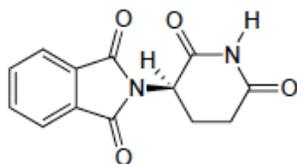
The **S enantiomer** reduces inflammation by **binding to, and inhibiting**, the enzyme prostaglandin H2 synthetase.

Remember thalidomide?



Thalidomide's side effect was teratogenicity: the ability to cause serious birth defects, like missing limbs.

Why did that happen?



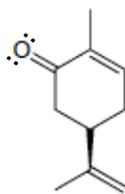
In 2010, Japanese researchers found that thalidomide binds to a protein called **thereblon**.

What does thereblon do? When its production is blocked in zebra fish their offspring have birth defects like those seen in human victims of thalidomide.

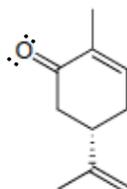
Harmless but spicy enantiomers



Most enantiomers have far more benign differences in biological effects.



(*R*)-carvone
(spearmint odor)



(*S*)-carvone
(caraway odor)

These two enantiomers create the very different odors, and tastes, of two different herbs.

Enzymes bind & create one enantiomer

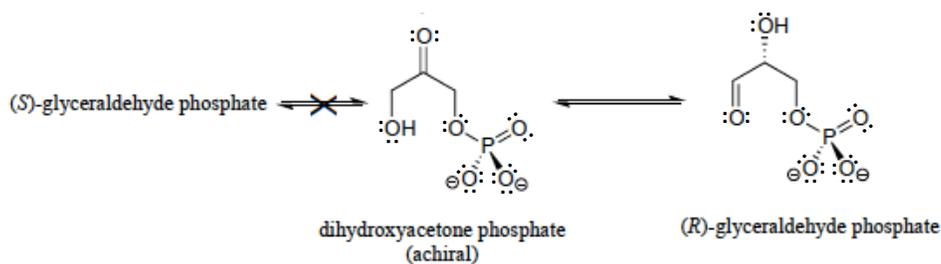


Because **enzymes** are chiral, they bind one enantiomer and **create one chiral product**; either R or S.

- However, **chemical reactions** produce a **mixture of both enantiomers**.

In **glycolysis**, triose phosphate isomerase creates a chiral product from an achiral substrate.

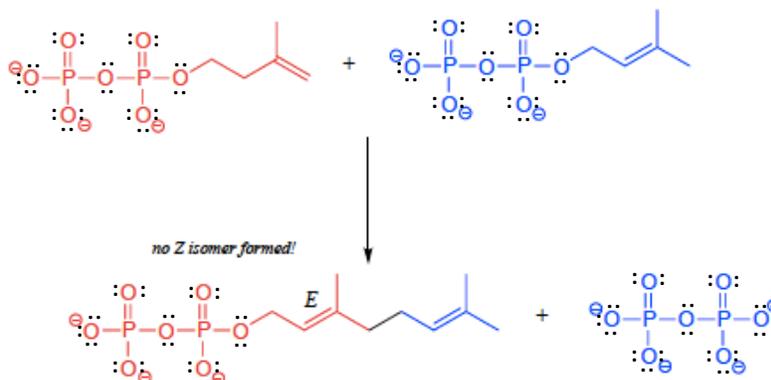
- The R enantiomer is made, but the S enantiomer is not.



Enzymes create one type of bond



Here the enzyme polymerizing (linking) isoprene units creates an **E bond**, but not a Z bond.



Can you?



- (1) Describe why biological molecules are chiral and recognize only one enantiomer?
- (2) Explain why biological processes produce only one enantiomer while chemical reactions produce both?

3. Conformation and stereochemistry



3.11: Prochirality

- Prochiral carbons
- Prochiral nitrogens

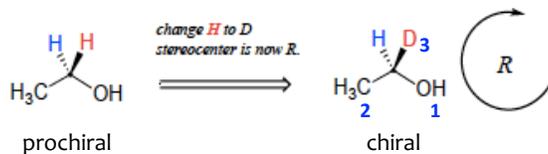
Prochirality



Prochirality: the potential of a tetrahedral (sp^3) carbon to be converted from achiral to chiral by changing one substituent

Enzymes are able to differentiate the 'blue' and 'red' hydrogens because the ethanol molecule fits into the enzyme's binding site in a **particular orientation**.

- For example, the methyl group binds in the left-hand end of the pocket and the hydroxyl group binds in the right-hand end.



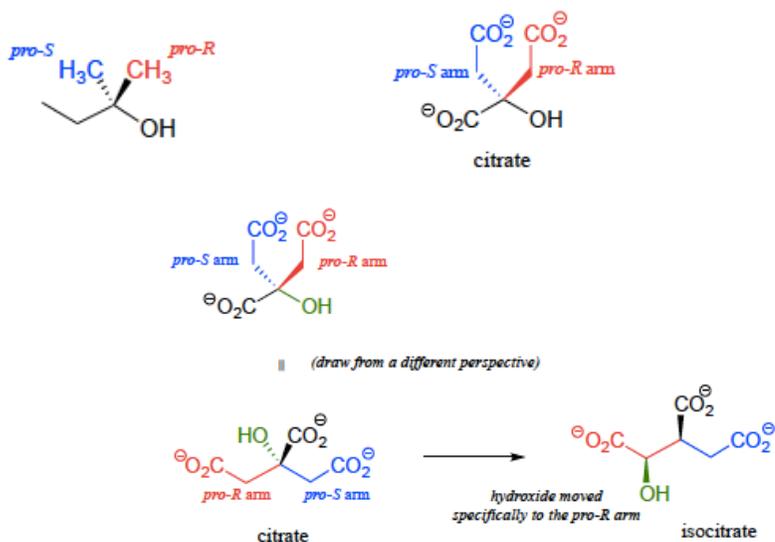
Replacement of the 'red' hydrogen atom with deuterium creates the R enantiomer.

- So the 'red' hydrogen is **pro-R**.
- It follows that the 'blue' hydrogen is **pro-S**.

Prochirality: not just for hydrogen atoms



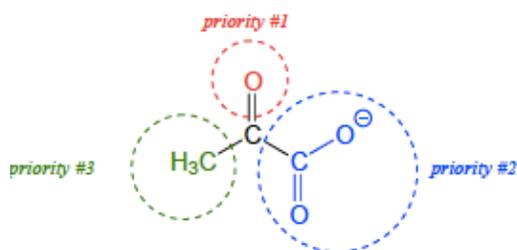
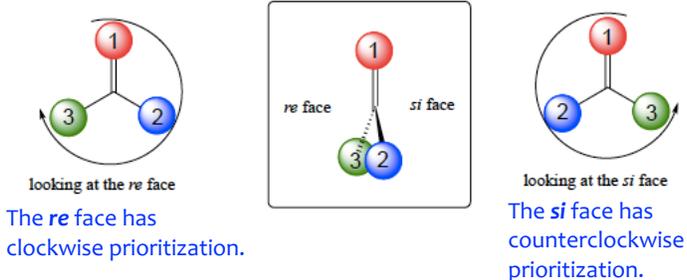
Here methyl groups and carboxylic acid groups have prochirality.



Prochiral carbonyl groups



Carbonyl groups (like ketones) are **flat**, trigonal planar, and therefore have two sides or **two faces**.



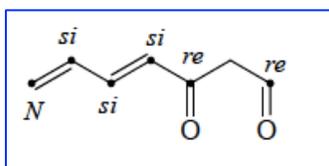
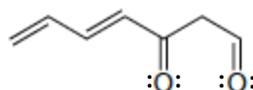
Here we are looking down on the *re* face of pyruvate.

Enzymatic reactions generally 'attack' from one side of the molecule, and thus create **one enantiomer**.

Try this:



The concept of *re* and *si* faces can also be applied to planar alkenes. Assign a designation of *re*, *si*, or *N* (not prochiral) to indicate which face we are looking down on for each of the sp^2 -hybridized carbons in the structure below.



Can you?



- (1) Define the terms 'prochirality', 're' and 'si'?
- (2) Describe how molecular geometry determines prochirality?
- (3) Describe how prochirality affects the chiral outcome of reactions?
- (4) Determine the configuration of prochiral centers?