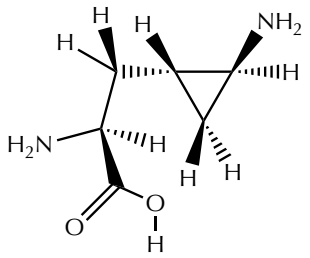
This TIB #7 question was used on a U-M exam back in 2003. It did not make the cut for the book, but there are plenty of comparable examples in what you need to know about the identification, labelling, and assignment of stereoisomers.

A. Compound A is an amino acid that was prepared during the synthesis of Belactosin A, a substance that shows modest antitumor activity.

(a) Circle each stereocenter in Compound A and provide the configurational label.

Compound A



(b) Is Compound A optically active? Circle one: yes no cannot predict

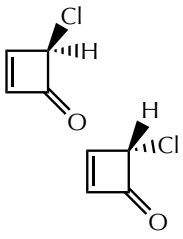
(c) Is Compound A dextrorotatory? Circle one: yes no cannot predict

(d) Is there a compound that is enantiomeric to Compound A? Circle one: yes no cannot predict

(e) Is there at least one compound that is diastereomeric to Compound A? Circle one: yes no cannot predict

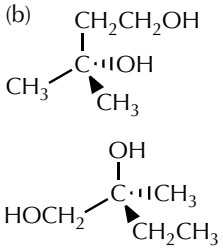
B. For each of the following pairs, check all of the classifications that apply (no partial credit).

(a)



- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active
- ☐ conformers

(b)



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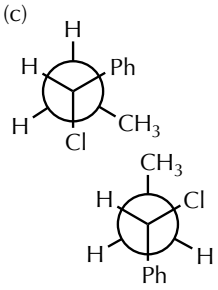
(c)



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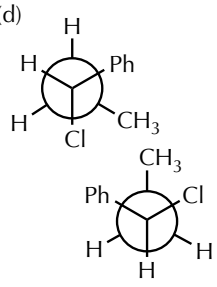
(d)



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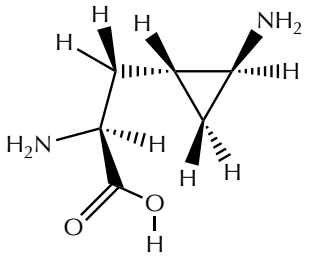


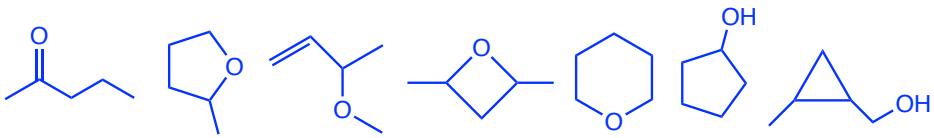
The topic of stereoisomerism is a highly rule-based set of conventions about identifying, drawing, labelling, and specifying the relationships between molecules, derived from an understanding more about molecular structure than issues related to reactions (at least at this point). This topic also completes the fundamental introduction to different *molecular structures* for organic chemistry

Molecular structure in Organic Chemistry

(a) molecular formula: *units of unsaturation* (e.g., $C_5H_{10}O$ has one unit of unsaturation - a ring or a double bond)

(b) structural or constitutional isomerism: the molecular formula provides the constitution, or make-up, of a molecule; different molecules with the same molecular formula are possible because of differences in connectivity; these are called structural isomers of this molecular formula, and also structural isomers of one another

some $C_5H_{10}O$ structural isomers, differing according to different connectivities

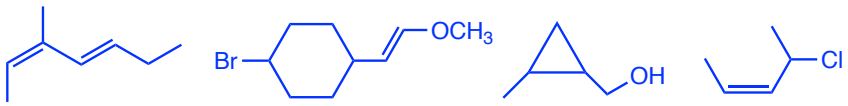


(c) stereoisomerism: some connectivities can represent an array of different molecules based on fixed (i.e., rigid, non-interconverting) three dimensional arrangements; these different molecules are called stereoisomers of a given connectivity, and the structural features that can result in stereoisomers are architectural in nature, not chemical, in that the predictions about stereoisomers and their relationships depend more on physical geometry than chemical identity

there are many different structural features that can result in stereoisomerism; three of these features make up the usual introduction to this topic (this list is for molecules with only one of the structural features; *the resulting generalizations apply to 100% of molecules that fit into the identifiable case!*)

1. double bonds with dissimilar end-atom pairs - two stereoisomers result, they:
   - are both achiral (optically inactive)
   - can be named with the labels (*E*)- and (*Z*)- [or *cis*- and *trans*- if hydrogen atoms are being compared]
   - are diastereomers (stereoisomers that are not enantiomers)
   - significantly different properties expected
2. symmetrical, even-sized rings with dissimilar atom pairs at opposite vertices - two stereoisomers result, they:
   - are both achiral (optically inactive)
   - can be named with the labels *cis*- and *trans*- if hydrogen atoms are being compared
   - are diastereomers (stereoisomers that are not enantiomers)
   - significantly different properties expected
3. asymmetrical tetrahedral atoms with 4 dissimilar groups (“stereocenters”) - two stereoisomers result, they:
   - are both chiral (optically active)
   - can be named with the labels (*R*)- and (*S*)-
   - are enantiomers (non-identical mirror images)
   - properties in an achiral environment are identical; properties are different in a chiral environment

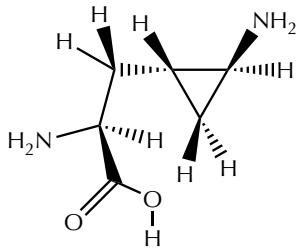
connectivities with more than one of these structural features have more than two stereoisomers; because each feature creates 2 stereoisomers, the presence of any two dissimilar features creates 2x2 or 4 stereoisomers; for example:



A. Compound A is an amino acid that was prepared during the synthesis of Belactosin A, a substance that shows modest antitumor activity.

(a) Circle each stereocenter in Compound A and provide the configurational label.

Compound A



the presence of any two dissimilar features creates 2x2 or 4 stereoisomers, and the generalizations depend on the specific pairings of structural features; although this means (for CHEM 210) six different cases of pairing up two of the three cases, the generalizations that result are universally applicable to the hundreds of thousands of molecules that fit into the case — the generalizations in this grid are *derivable* from the basic principles of chirality as applied to the molecules that are created in each case (that is, the grid is not at all something to be recalled, but it represents a way to know that you understand the basic ideas because you can also carry out the analysis and get the same result)

	a double bond with dissimilar end-atom pairs	*symmetrical, even-sized rings with dissimilar atom pairs at opposite vertices*	*asymmetical tetrahedral atoms with 4 dissimilar groups ("stereocenters")*
a double bond with dissimilar end-atom pairs	4 stereoisomers result - all 4 achiral - (*E, E*), (*E, Z*), (*Z, E*), (*Z, Z*) - all pairings are diastereomers	4 stereoisomers result - all 4 achiral - (*E, cis*), (*E, trans*), (*Z, cis*), (*Z, trans*) - all pairings are diastereomers	4 stereoisomers result - all 4 chiral - (*E, R*), (*E, S*), (*Z, R*), (*Z, S*) - (*E, R*), (*E, S*) enantiomers - (*Z, R*), (*Z, S*) enantiomers - other pairings are diastereomers
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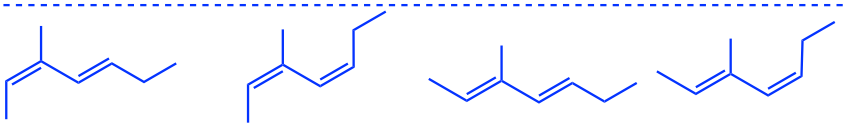
asymmetical tetrahedral atoms with 4 dissimilar groups ("stereocenters")			4 stereoisomers result - all 4 chiral - (*R, R*), (*R, S*), (*S, R*), (*S, S*) - (*R, R*), (*S, S*) enantiomers - (*S, R*), (*R, S*) enantiomers - other pairings are diastereomers

4 stereoisomers result
- all 4 achiral
- (*E, E*), (*E, Z*), (*Z, E*), (*Z, Z*)
- all pairings are diastereomers



4 stereoisomers result
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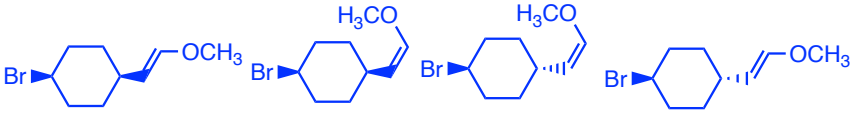
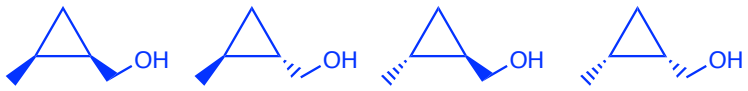
- (*E, cis*), (*E, trans*), (*Z, cis*), (*Z, trans*)
- all pairings are diastereomers



4 stereoisomers result
- all 4 chiral
- (*R, R*), (*R, S*), (*S, R*), (*S, S*)
- (*R, R*), (*S, S*) enantiomers
- (*S, R*), (*R, S*) enantiomers
- other pairings are diastereomers



4 stereoisomers result
- all 4 chiral
- (*cis, R*), (*cis, S*), (*trans, R*), (*trans, S*)
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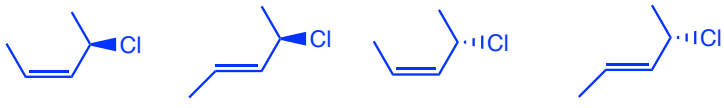
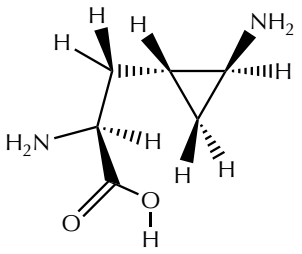


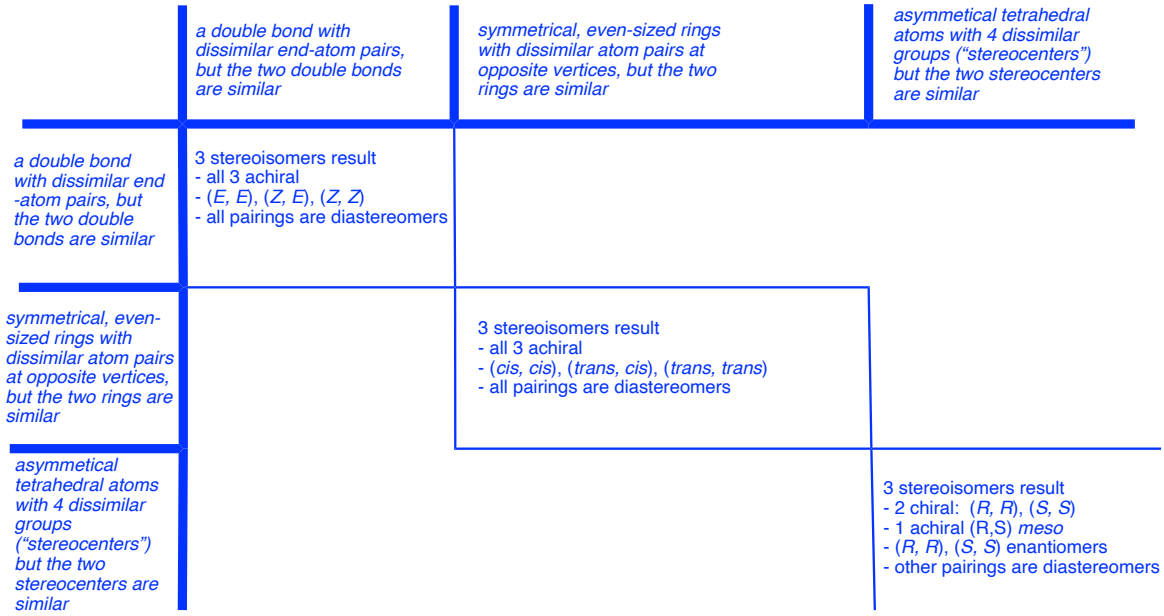
A. Compound A is an amino acid that was prepared during the synthesis of Belactosin A, a substance that shows modest antitumor activity.

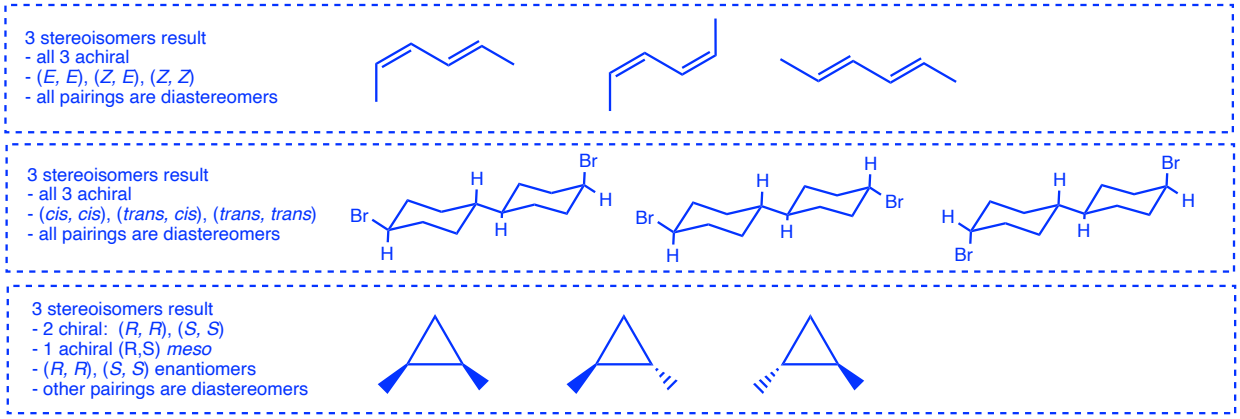
(a) Circle each stereocenter in Compound A and provide the configurational label.

Compound A



when there are two of these structural units that are similar, the total number of stereoisomers drops to three because of a degeneracy due to the increased molecular symmetry (this is exactly comparable to the difference between tossing two different coins, where there are 4 observably different outcomes, and tossing two of the same coin, where there are only 3 observably different outcomes: heads-heads, tails-tails, and heads-tails which looks the same as tails-heads when the coins are identical)





when there are three or more completely dissimilar structural units that give rise to stereoisomers, the number of stereoisomers is 2^n where "n" is the number of dissimilar units. A molecule with 4 dissimilar stereocenters has 16 stereoisomers. All 16 are chiral. One of these, for example, might be the (*R, R, R, R*)- compound. It has one enantiomer (*S,S,S,S*)- and the remaining 14 stereoisomers are diastereomers of both the (*R, R, R, R*)- and (*S,S,S,S*)- isomers (e.g., *RRRS, RSSR, SRSR, etc)*

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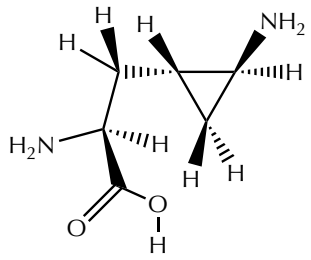
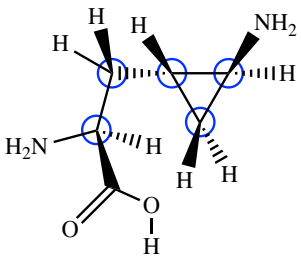
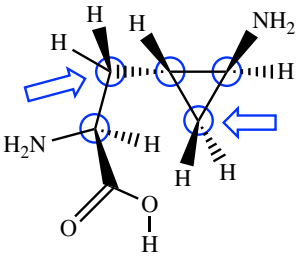


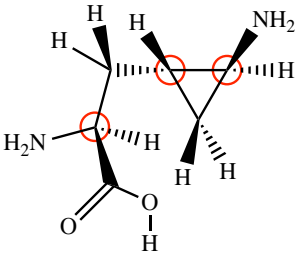
The instructions need to be quite explicit here because there are so many different questions that can be posed about this molecule. The conclusion from these instructions, before even looking at the molecule, is that you are expecting only one category of the structural features that result in stereoisomers: stereocenters (other features are not mentioned, so even if they were present, they are not relevant to part (a). Thus, you are looking for asymmetical tetrahedral (sp^3) atoms with 4 dissimilar groups attached. There are 5 potential candidates:



And of these 5:

3 of them have 4 dissimilar groups, and 2 of them have only 3 (the two H's that are the same are shown explicitly), so the other 3 of them need to be circled

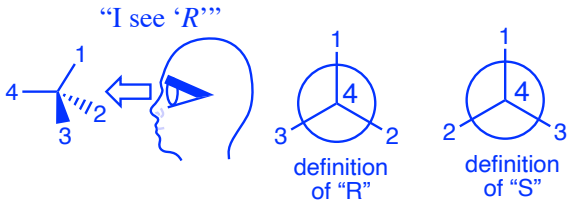




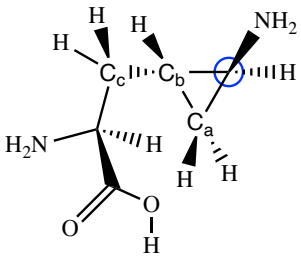
To "provide the configurational label" means to assign the "R" or "S" geometry to the stereocenter. This process is rule-driven and can be applied to every stereocenter that exists.

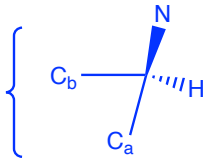
(1) assign the priorities, based on atom number of the directly attached atom, to the 4 groups

(2) assign the geometry by (i) viewing the stereocenter along the bond, where the stereocenter atom is in the front and the lowest priority group (#4) is in the back; this leaves the direction of turning for priority 1 -> 2 -> 3 to either be in the (+)-clockwise direction, in which case the geometry is called "R," or the (-)-counterclockwise direction, in which case the geometry is called "S"

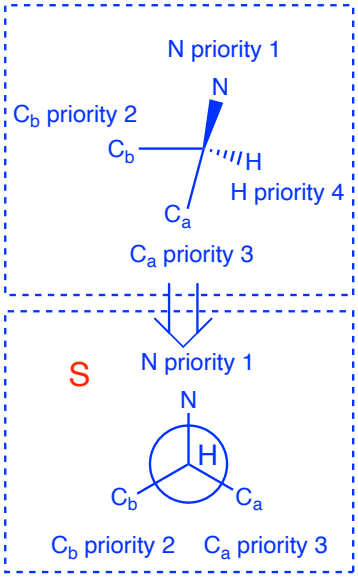


There are numerous strategies for visualing these assignments, but they all boil down to these definitions (they have to!).

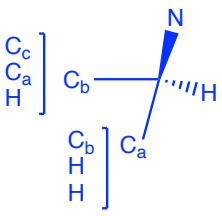




C_a atomic #6 : priority 2 or 3
C_b atomic #6 : priority 2 or 3
H atomic #1 : priority 4



break the C_a/C_b tie with next tier of atoms:



C_a is attached to H, H, and C_b
C_b is attached to H, C_a and C_b
• the highest priority for each one in these groups is a "C", the second highest for C_a is an "H" while the second highest for C_b is a "C", so C_b gets priority 2 and C_a gets priority 3

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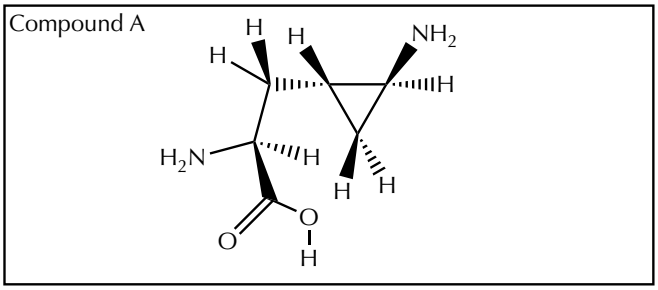
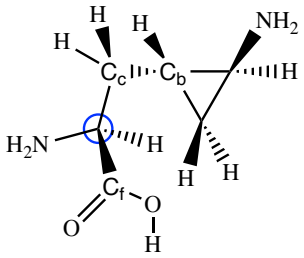
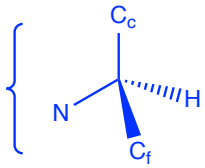
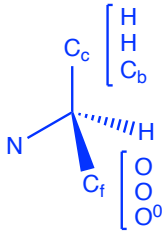




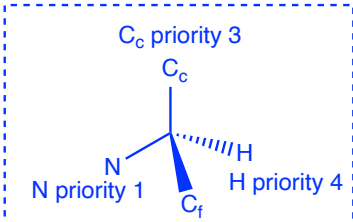


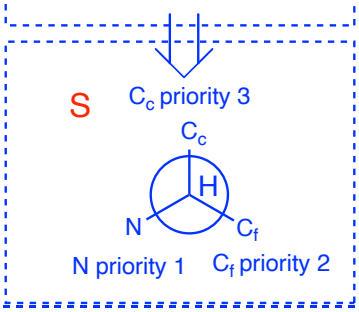
N atomic #7 : priority 1
C_c atomic #6 : priority 2 or 3
C_f atomic #6 : priority 2 or 3
H atomic #1 : priority 4

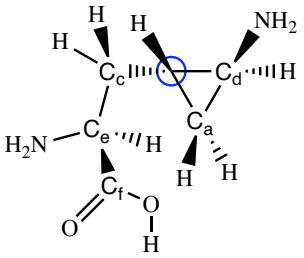
break the C_c/C_f tie with next tier of atoms:

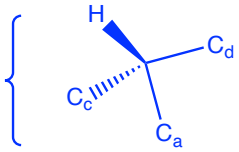


all atoms are treated as tetravalent, so the C_f is attached to oxygen 3 times, two "real" ones and one phantom O which is given an atomic number of zero; and so then the highest priority in that group (a real O) has a higher atomic number than the highest one in the C_c group (C_b), and then C_f gets priority 2



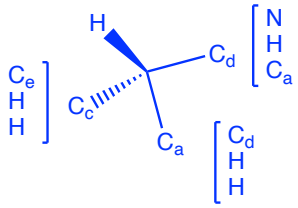




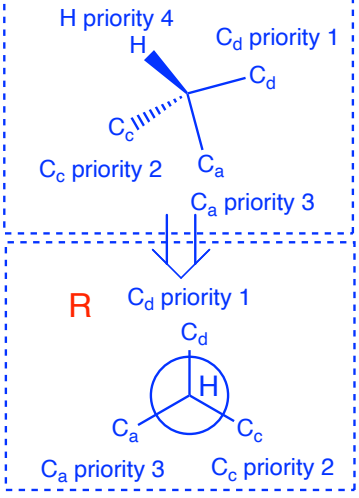


C_d atomic #6 : priority 1, 2 or 3
C_a atomic #6 : priority 1, 2 or 3
C_c atomic #6 : priority 1, 2 or 3
H atomic #1 : priority 4

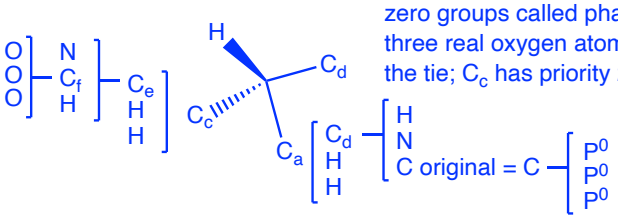
try to break the 3-way C_a/C_c/C_d tie with next tier of atoms:

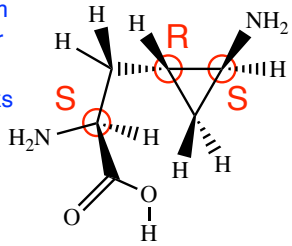


the N in C_d has the highest atomic number in that group, and is higher than C_e and C_d; C_c and C_a are still tied, however, so you need to go out to the next group along the C's (below):



C_e has N, C_f and H, while C_d has N, H, and the original C!!!, it has already been accounted for, so the 3rd atom attached to C_d is an "auxiliary C" with 3 atomic number zero groups called phantom atoms (P^0), while C_f has three real oxygen atoms with atomic #8 and that breaks the tie; C_c has priority 2, and C_a is 3

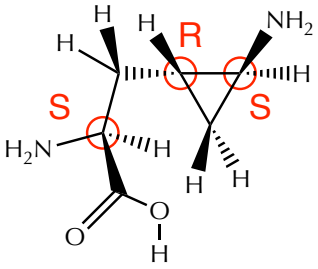




A. Compound A is an amino acid that was prepared during the synthesis of Belactosin A, a substance that shows modest antitumor activity.

(a) Circle each stereocenter in Compound A and provide the configurational label.

Compound A



The molecule has 3 dissimilar stereocenters. There is a single, general solution to the questions about this case that can be asked. Concretely, then, for all molecules with 3 dissimilar stereocenters (including this one):

(a) there are 2^3 stereoisomers = 8 stereoisomers (and this is one of them)
(b) all 8 are chiral
(c) all 8 are optically active, but the sign & magnitude of the rotation cannot be known without experimental data
(d) there is one with all R's: RRR;
one with all S's: SSS
three with 2R's and 1S: RRS, RSR, SRR
and three with 1R and 2 S's: RSS, SRS, SSR
(e) the 4 enantiomeric relationships are RRR:SSS, RSS:SRR, RSR:SRS, and SSR:RSS
all other pairwise relationships are diastereomeric

Therefore, the answer to these next questions (b)-(e) has nothing to do with this molecule, in particular, except as an example of a 3 dissimilar stereocenter molecule!

(b) Is Compound A optically active?
statement (c)

Circle one: [yes] no cannot predict

(c) Is Compound A dextrorotatory?
statement (c)

Circle one: yes no [cannot predict]

(d) Is there a compound that is enantiomeric to Compound A?
statement (e)

Circle one: [yes] no cannot predict

(e) Is there at least one compound that is diastereomeric to Compound A?
statement (e)

Circle one: [yes] no cannot predict

B. For each of the following pairs, check all of the classifications that apply (no partial credit).

this problem is complex because it requires you to do three things at once:

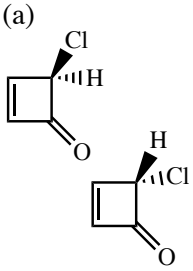
(1) analyze 2 structures for their relationship

(2) understand the features of all these terms

(3) combine these two distinct understandings

on top of that, the terms are themselves linked internally; to be a "same" or a "different" molecule is absolutely linked with most of these terms, and that is useful to understand, too:

(a)



- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active
- ☐ conformers

- molecules that are always "different molecules":
  enantiomers, diastereomers, constitutional isomers, stereoisomers
- molecules that are always "the same molecule": conformers
- a pair of molecules that are both optically active could be the same or different

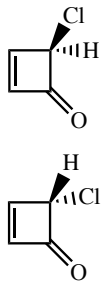
B. For each of the following pairs, check all of the classifications that apply (no partial credit).

the relationship between two molecules means first figuring out:

(a) do they have the same molecular formula? if no, then they are simply different molecules altogether with no isomeric relationship

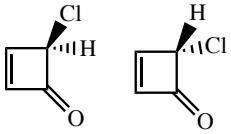
(b) if they have the same molecular formula and different connectivities, then they are constitutional isomers with no other isomeric relationship; but if they have the same connectivity, they could be stereoisomers (different molecules), conformers (different conformations of the same molecule), or identical conformers (the same conformation of the same molecule)

(a)



- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active
- ☐ conformers

(c) if they have the same connectivity, then they need to be assessed for structural units that can create stereoisomers (stereocenters, double bonds with E/Z, oppositely substituted even-sized rings) as well as how many of these there are, and whether they are similar or dissimilar if there is more than one; if stereoisomers are possible, then the two molecules could be stereoisomers (different molecules) or they could be the same molecule, and if they are the same molecule, they could be conformers (different conformations of the same molecule), or identical conformers (the same conformation of the same molecule)



this pair of drawings is quickly assessed as representing the same connectivity, so you can jump to statement (c); and it is a molecule with one structural unit that can create stereoisomers, the stereocenter with the chlorine atom on it (the double bond), because it is trapped inside the small ring, cannot have both an E and Z geometry, so the double bond does not count as a source of stereoisomers here

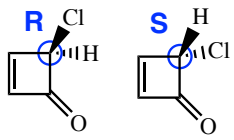
having one stereocenter is a general case, and from the first page, the analytical result from having one stereocenter is a fixed answer:

3. asymmetrical tetrahedral atoms with 4 dissimilar groups ("stereocenters") - two stereoisomers result, they:
   - are both chiral (optically active)
   - can be named with the labels (*R*)- and (*S*)-
   - are enantiomers (non-identical mirror images)
   - properties in an achiral environment are identical; properties are different in a chiral environment

and that means that either these two molecules have two different stereoisomers (one R, the other S), in which case all of the above relationships hold,

or the two molecules are the same stereoisomer (the same molecules, both of them R or both S), in which case they could be the same or different conformation of that same molecule

sometimes you can tell this by inspecting the drawings, immediately, but the most foolproof way to compare a pair of possible stereoisomers is to assign the geometrical labels (R/S, E/Z, cis/trans)



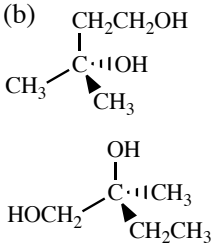
the two stereocenters are different, so they represent two molecules with the characteristics associated with that general case:

two stereoisomers result (different molecules), they:
- are both chiral (optically active)
- can be named with the labels (*R*)- and (*S*)-
- are enantiomers (non-identical mirror images)
- properties in an achiral environment are identical; properties are different in a chiral environment

two stereoisomers result (different molecules), they:
- are both chiral (optically active)
- can be named with the labels (*R*)- and (*S*)-
- are enantiomers (non-identical mirror images)
- properties in an achiral environment are identical; properties are different in a chiral environment

- ☒ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☒ stereoisomers
- ☒ different molecules
- ☒ both are optically active
- ☐ conformers

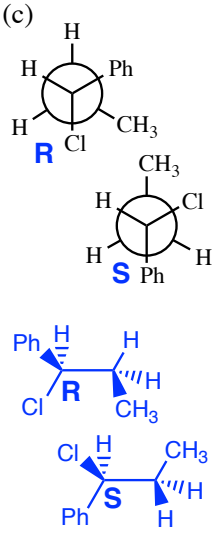
(b)



At a glance, the molecules have different connectivities (the OH or alcohol groups are 3 atoms away from one another on the top, and 2 atoms away from one another on the bottom. So these are not stereoisomers nor are they conformers. They are different molecules, and the only question is whether they have the same molecular formular or not, to determine if they are constitutional isomers. The top molecule is $C_5H_{12}O_2$, and the bottom one is $C_5H_{12}O_2$ … so they are indeed constitutional isomers.

- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☒ constitutional isomers
- ☐ stereoisomers
- ☒ different molecules
- ☐ both are optically active
- ☐ conformers

(c)



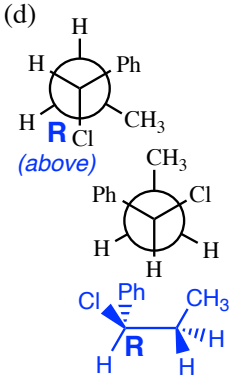
Just because the drawings are Newman projections does not automatically mean that these are conformers. You must step down the identification process. First, they have the same connectivity, so they could be stereoisomers, they could be the same molecule, and they might or might not be conformers of the same molecule.

There is one source of stereoisomers: the front carbon is a stereocenter, so these could be enantiomers (one R the other S) or identical molecules (both R, both S). If you assign R and S, you find out there is one of each. Redrawing to the line/dash/wedge form might be necessary, depending on your ability to visualize the 3D structure. It's actually not necessary, because all that matters is that they are different, and that can be assessed by looking at them. Comparing the top to the bottom drawings, two of the groups at the stereocenter have been exchanged (the Ph and Cl change places, and that would interconvert an "R" and an "S")

As a pair of enantiomers, this question is exactly the same as part (a): they are both optically active, and the fact that they are drawn as Newman projections is irrelevant because stereoisomers are different molecules and cannot be conformers of one another.

- ☒ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☒ stereoisomers
- ☒ different molecules
- ☒ both are optically active
- ☐ conformers

(d)



It makes the analysis of this comparison a lot easier when you take a moment to recognize that the top molecule here is the same as the top molecule in part (c), so much of that analysis can repeat itself. You already know this is the "R" isomer.

The bottom molecule has the same connectivity, so the question is the same as above: is the stereocenter the same molecule "R" or the different molecule "S"? The 3D can be assigned (it is "R") or you can notice that the front carbon atom in the bottom drawing is just a rotation of the one on the top, so it is the same molecule.

As the same (optically active) "R" molecule, the only remaining question is whether or not they are different conformers of that molecule or exactly the same conformer. The Newman projection provides the easiest way to inspect the internal relationships. In both drawings, the 3 anti relationships are the same (H/Cl, H/CH_3, and H/Ph), as are the clustered gauche interactions Ph/CH_3/Cl), indicating that these are exactly the same conformation of the "R" molecule, so they are not conformers.

- ☐ enantiomers
- ☒ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☒ both are optically active
- ☐ conformers