Chapter 4
Stereochemistry

from
Organic Chemistry

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Chapter Outline of the Book

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1. Organic Molecules and Chemical Bonding
2. Alkanes and Cycloalkanes
3. Haloalkanes, Alcohols, Ethers, and Amines
4. Stereochemistry
5. Organic Spectrometry

II. Reactions, Mechanisms, Multiple Bonds

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7. Reactions of Haloalkanes, Alcohols, and Amines. Nucleophilic Substitution
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20. Carbohydrates
21. Lipids
22. Peptides, Proteins, and α–Amino Acids
23. Nucleic Acids

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**Note: Chapters marked with an (*) are not yet posted.*

4: Stereochemistry

(continued next page)

4: Stereochemistry

- *Tetrahedral Carbon Configurations*
- *Stereoisomers and R,S Assignments*
- *The Number and Types of Stereoisomers*
- *Drawing Structures of Stereoisomers*
- *Cyclic Molecules*
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Preview

Nomenclature rules for organic compounds allow us to draw their chemical bonds and show specific positions of atoms and groups on their carbon skeletons. We can draw 3-dimensional structures for these molecules based on the tetrahedral structure of their C atoms and we know that they have many different conformations due to rotation about their chemical bonds.

In this chapter, we will learn that there is a property of tetrahedral carbon atoms that causes some chemical names that we have learned to inadequately describe a unique molecule. For example, there are two different molecules with the name 2-bromobutane because there are two different ways to bond a set of four atoms or groups to a tetrahedral atom. This **stereochemical** property of tetrahedral C is present in all molecules, but only leads to different structures in some of them.

This chapter will vigorously exercise your ability to picture objects in three dimensions. *Your molecular model kit will be a very important aid to learning the material in this chapter.*

4.1 Tetrahedral Carbon Configurations

There are two different ways to bond four different atoms or groups to a tetrahedral carbon.

Two Configurations at Tetrahedral Carbon (4.1A)

We use *bromochlorofluromethane* (CHBrClF) to illustrate the two ways of bonding four different atoms to a tetrahedral C. [graphic 4.1]

Non-Superimposable Mirror Images. The two structures of CHBrClF labelled (A) and (B) are different from each other because no matter how they are each oriented in space, they can never be **superimposed** on each other. If you correctly *superimpose* each of the halogens

atoms of (A) and (B) on each other, you will find that their carbon atoms, and also their hydrogen atoms, are far away from each other as we show in Figure [grapic 4.2]. [graphic 4.2] Alternatively if we superimpose the C atoms and H atoms of (A) and (B) on each other, the halogen atoms do not correctly overlap with each other. As a result, we say that (A) and (B) are **non-superimposable** and that their C atoms have different **configurations**.

We illustrate that (A) and (B) are **mirror images** of each other by showing in Figure [graphic 4.3] that the *mirror image* of one of them is identical to the *other*. [graphic 4.3] If you rotate the *mirror image* of (A) around the axis shown, it is completely *superimposable* on (B). The mirror image of (A) is (B), and the mirror image of (B) is (A).

Handedness and Chirality. (A) and (B) differ from each other like a *right hand* differs from a *left hand*. Right and left hands have the same component parts attached in the same way to each other, but they cannot be superimposed on each other. Like right and left hands, (A) and (B) are *mirror images* of each other. Because of this analogy with hands, chemists say that the two different *configurations* of C in CHBrClF ((A) and (B)) have the property of **handedness**. Chemists use the term **chirality** to refer to the property of *handedness* when it applies to molecules. A molecule is **chiral** if it cannot be superimposed on its mirror image. As a result, the (A) and (B) structures of CHBrClF are *chiral* molecules.

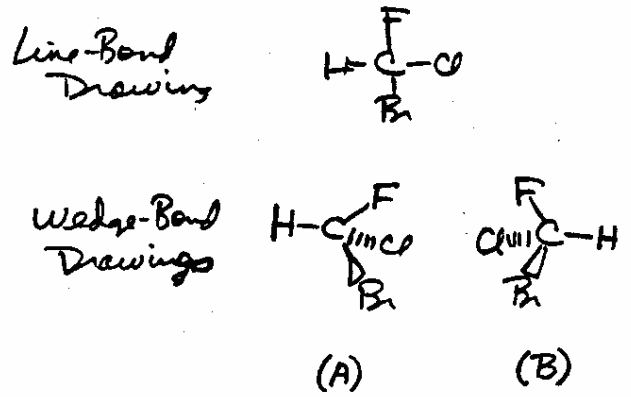
Chiral Atoms (4.1B)

A molecule is usually *chiral* because it contains one or more *chiral atoms*. However we will see below that specialized molecules can be *chiral* even when they have no *chiral* atoms.

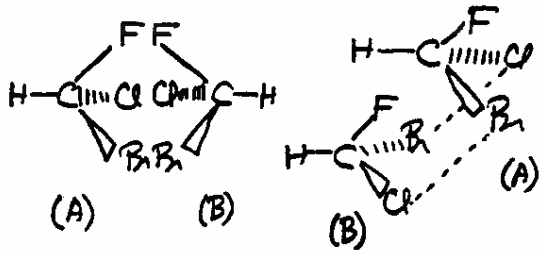
Chiral Carbon Atoms. A carbon atom must have four different atoms or groups bonded to it in order to be *chiral*. If two or more of the groups or atoms on a tetrahedral C are identical, the C cannot be *chiral* and we describe it as **achiral**. While *CHBrClF* has a chiral C, the compound CH_2BrCl is *achiral* because it has a tetrahedral C on which two of the bonded atoms are the same (the two H's). We confirm that CH_2BrCl is not a chiral molecule by showing in Figure [graphic 4.4] that its mirror image is superimposable on the original molecule. [graphic 4.4]

Other Chiral Atoms. Chiral molecules can also result from the presence of chiral atoms other than C such as the chiral N in a tetraalkylaminium ion. [graphic 4.5] The N is chiral because it is an atom with tetrahedral bond angles like C and it has four different alkyl groups bonded to it. As a result, the mirror image of this molecule is non-superimposable on the original structure so it is a chiral molecule.

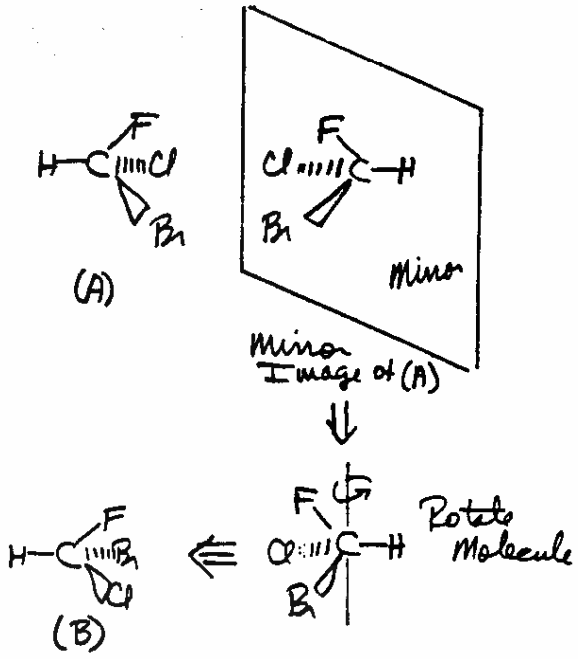
4.1 Bromochlorofluoromethane (CHBrClF)



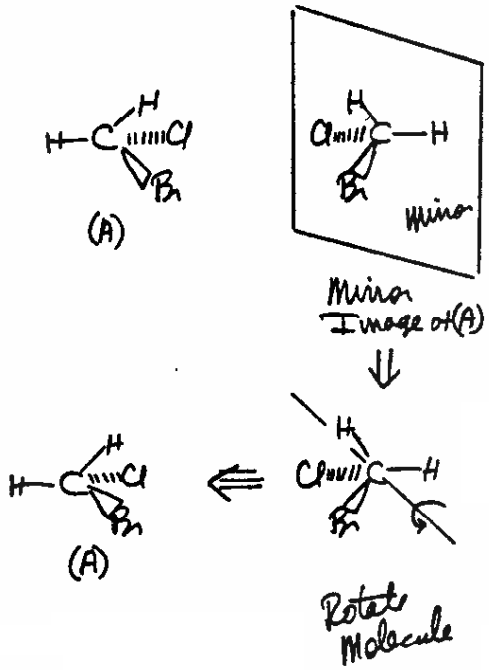
4.2 Structures (A) and (B) of CHBrClF are not superimposable.



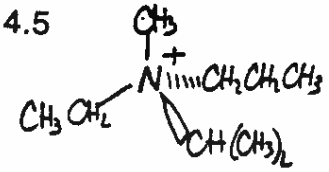
4.3 Structure (B) of CHBrClF is the mirror image of (A).



4.4 The mirror image of CH_2BrCl is identical to the original molecule.



4.5



Amines. The nitrogen atom of an amine (R_3N:) can also be chiral since amines have a tetrahedral (pyramidal) structure. If the three *R* groups are different from each other as shown in Figure [graphic 4.6], the mirror image of an amine is not superimposable on the original amine. [graphic 4.6] The unshared electron pair in the sp^3 orbital is like a fourth "group".

Even when they possess chiral N atoms, amines are not considered chiral compounds because they undergo amine inversion (Chapter 3) at a very rapid rate (about 10^{11} times per second for NH_3) as we show in Figure [graphic 4.7]. [graphic 4.7] This inversion allows an amine to rapidly change into its non-superimposable mirror image. As a result, unlike aminium ions and compounds with chiral C, it is not possible to individually isolate just one of the chiral forms of an amine.

Molecular Chirality Without Chiral Atoms. An example of a chiral molecule without a chiral atom is (A) in Figure [graphic 4.8]. [graphic 4.8] While it has no chiral atoms, this molecule is chiral because it is not superimposable on its mirror image. The mirror image of (A) cannot be superimposed on (A) no matter how it is oriented in space so it is a different compound that we label as (B). You can demonstrate this by making models of (A) and its mirror image (B) using a molecular model set. There are relatively few chiral molecules that have no chiral atoms.

4.2 Stereoisomers and *R,S* Assignments

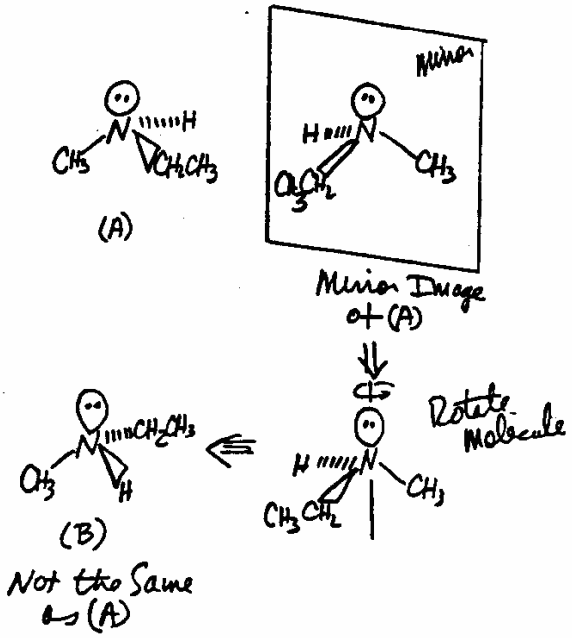
A chiral molecule and the molecule that is its non-superimposable mirror image are **stereoisomers** of each other. Based on the nomenclature rules that we have learned so far, *stereoisomers* have the same chemical name such as the pair of stereoisomers (A) and (B) of CHBrClF that both have the name *bromochlorofluoromethane*. In order to distinguish (A) and (B), we use additional nomenclature that we describe here.

R and S Nomenclature (4.2A)

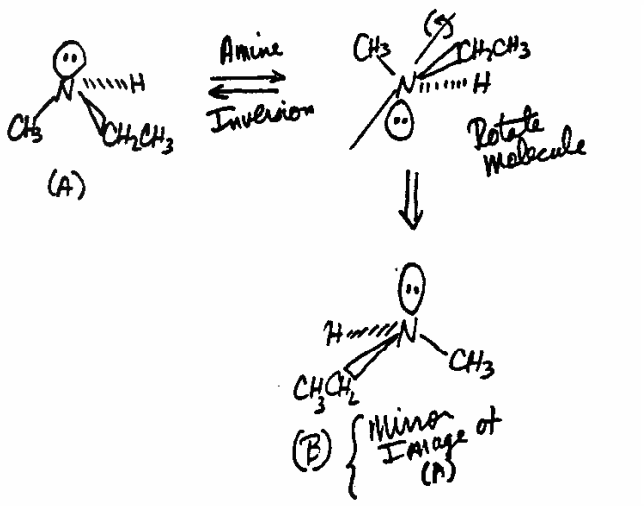
We distinguish the two different stereoisomers of CHBrClF with the prefixes ***R*** or ***S*** so that their complete names are *(R)-bromochlorofluoromethane* and *(S)-bromochlorofluoromethane*. *R* and *S* describe the two different configurations at the chiral C and we will show below how we assign them to the two stereoisomers using a set of rules applicable to any chiral atom.

Clockwise and Counterclockwise Isomers. In order to assign *R* and *S* to a chiral C, we will learn a set of rules that allows us to uniquely give the **priority numbers** "1", "2", "3", and "4" to each atom or group on a chiral C. For the moment, let's not worry about these rules. We first need to recognize that once the *priority numbers* are correctly assigned to the

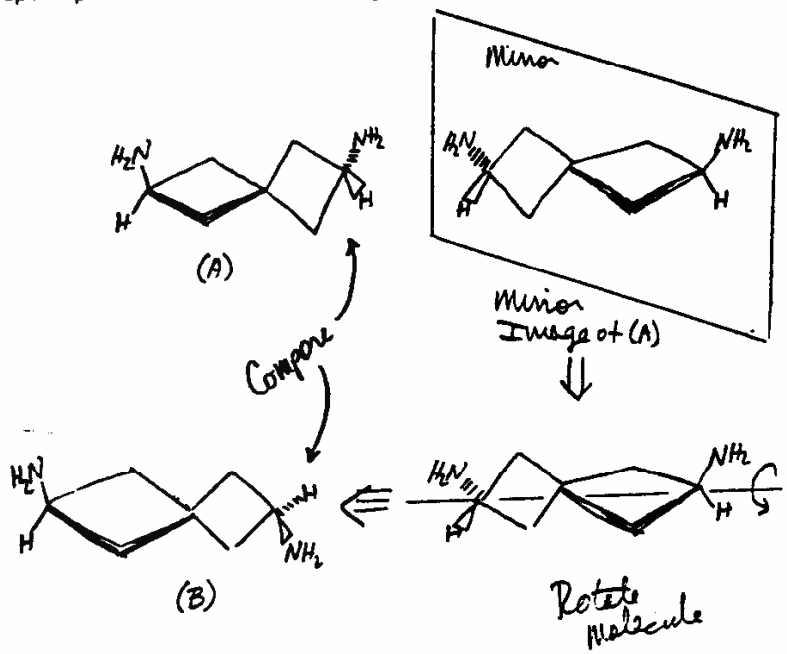
4.6 **The mirror image of an amine with three different R groups is not superimposable on the original amine.**



4.7 **Inversion converts an amine into its mirror image.**



4.8 **A molecule without chiral carbons which is not superimposable on its mirror image.**



four atoms or groups on the chiral C, there are two different ways that these *priority numbers* can appear on the tetrahedral C. [graphic 4.10] When we orient each of these two structures so that "4" is behind the chiral C, our views of these structures when we look at the chiral C's show "1", "2", and "3" progressing "**clockwise**" in one structure and "**counterclockwise**" in the other.

The Assignments of R and S. Chemists use a set of rules called the **Cahn-Ingold-Prelog** system for assigning the *priority numbers* "1" through "4" to the atoms or groups on a chiral C or other chiral atom. After we use these rules to assign the priority numbers to the specific atoms or groups, we refer to the *clockwise* isomer in Figure [graphic 4.10] as the ***R*** isomer, and the *counterclockwise* isomer as the ***S*** isomer.

R comes from the latin word *"rectus"* which means the direction "right". When the numbers "1", "2", and "3" progress in a *clockwise* direction we think of them as progressing toward the "right" as we show in Figure [graphic 4.11]. [graphic 4.11] The letter *S* comes from the latin word "*sinister*" which means the direction "left". When the numbers "1", "2", and "3" progress in a *counterclockwise* direction we think of them as progressing toward the "left". We show in the next section how we use the *Cahn-Ingold-Prelog rules* to assign the numbers "1", "2", "3", and "4" to atoms or groups bonded to a tetrahedral atom.

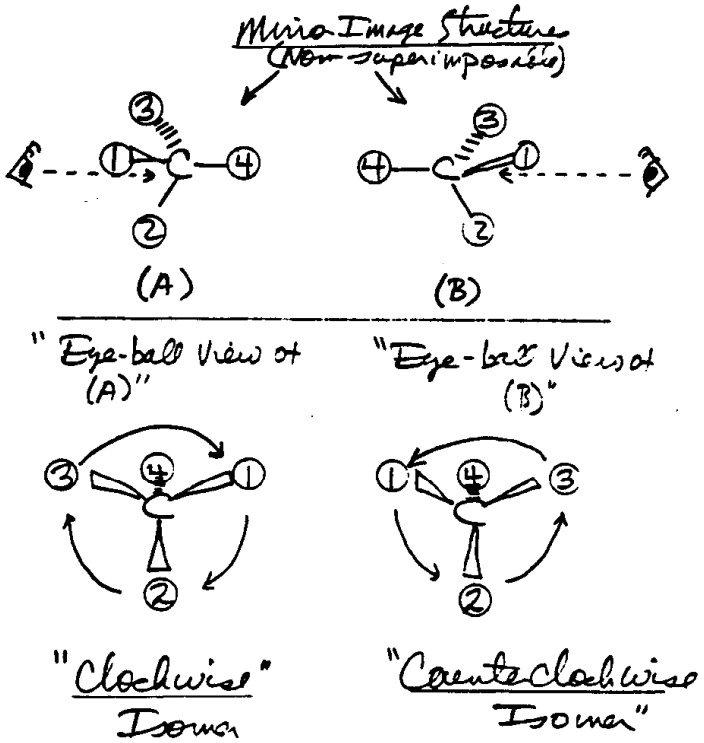
> ***Remembering R and S***. If you have trouble remembering that a "clockwise" progression of the priority numbers is progression to the "right" with respect to direction, you can think of the "clockwise" progression as being "right" with respect to "correctness". That does not mean that "counterclockwise" progression is "wrong", it still is "left"

R and S Assignment Rules (4.2B)

The *Cahn-Ingold-Prelog* method uses the *atomic numbers* of the atoms bonded directly or indirectly to the chiral atom. We illustrate each rule with an example before stating the rule.

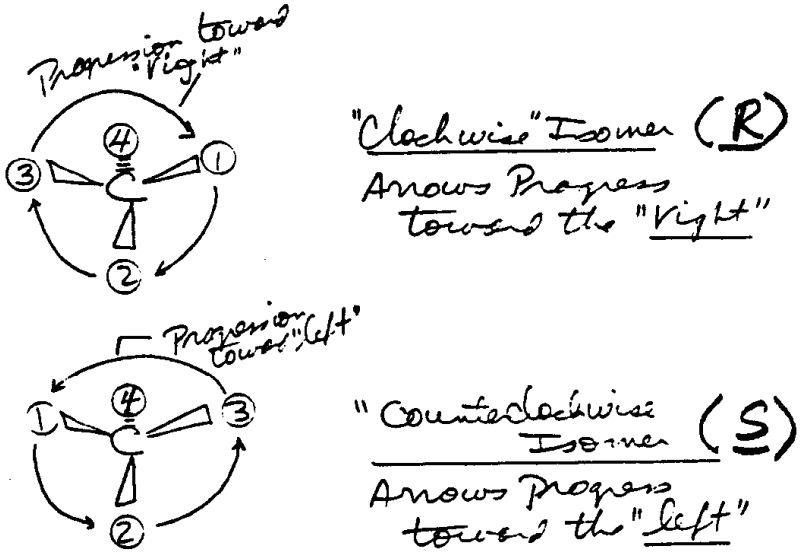
Case 1. Each Atom Directly Bonded to a Chiral C is Different. Our example is CHBrClF that we first used to illustrate a chiral molecule. *Br* has the highest atomic number (35) so we assign it *priority number "1"*, *Cl* has the next highest atomic number (17) so we assign it *priority number "2"*, we assign *priority number "3"* to *F* since it has the third highest atomic number (9), while we assign *priority number "4"* to *H* because it has the lowest atomic number (1).

4.10 **Different views of mirror image structures with four different attached groups or atoms.**



4.11

Relationships between "clockwise" and "counterclockwise" progression and the directions "right" and "left".



When we orient the molecule so that the priority "4" atom (H in this case) points away from us, and then view each stereoisomer along the C-"4" (C-H) bond, we see the two stereoisomers labelled with their respective priority numbers as the views that we show in Figure [graphic 4.12]. [graphic 4.12] The first structure with the *clockwise* progression of the atoms labelled "1", "2", and "3" has the *R* configuration at C. The other structure, with the *counterclockwise* progression has the *S* configuration at C.

Chiral C's directly bonded to four different atoms are easy to designate *R* or *S* even when these atoms are part of a larger group. We show two compounds where we have assigned priority numbers to the groups based only on the atomic numbers of the atoms directly bonded to the chiral C. [graphic 4.13] All of these examples fit the first "***R,S* assignment rule**" that states:

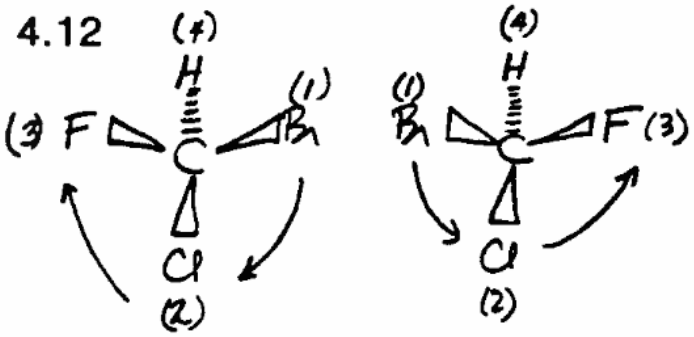
> ***Rule 1***. *Substituents on a chiral atom are given the priority numbers "1", "2", "3", "4" in order of decreasing atomic number of the atom directly connected to the chiral atom.*

Unfortunately, there are not many molecules that fit *Rule 1*. While molecules with chiral C's must have four different groups on each chiral C, two or more of the atoms directly bonded to the chiral C are frequently the same.

Case 2. Two or More Atoms Bonded to a Chiral C are the Same. When a compound has four different groups bonded to the chiral C (labelled as C*), and two or more of the directly bonded atoms are the same (as in 2-bromobutane shown in Figure [graphic 4.14]), you must examine atoms beyond those directly bonded to C* to assign the correct priority numbers. [graphic 4.14] The four different atoms or groups bonded to the C* are Br, H, CH_3, and CH_2CH_3 so the atoms directly bonded to C* are Br, H, C and C. We immediately assign priority number "1" to Br since it has the highest atomic number, and priority number "4" to H since it has the lowest atomic number. However we need another rule to assign priority numbers "2" and "3" to CH_3, and CH_2CH_3 since they both have C bonded to C*.

When we cannot initially distinguish two groups such as CH_3 and CH_2CH_3 because their "**first level**" atoms directly connected to C* are the same (both are C in this case), we look at their "**second level**" atoms. The *second level* of atoms in each group are those bonded to the C directly bonded to C*. For $\underline{C}H_3$, they are the *three H's* that are shaded in Figure [graphic 4.15]. For $\underline{C}H_2CH_3$, they are the *two shaded H's* and the *shaded C* of its CH_3 group. [graphic 4.15]

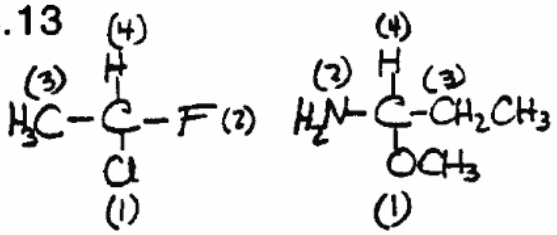
4.12



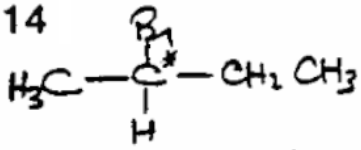
"Clockwise" "Counterclockwise"

R-isomer S-isomer

4.13



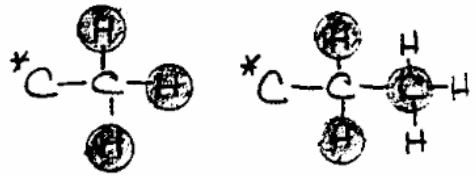
4.14



2-bromobutane

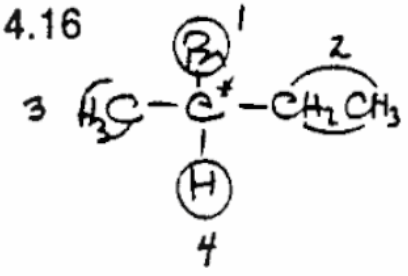
4.15 Second level atoms in CH_3 and CH_2CH_3 groups.

CH_3 Group CH_2CH_3 Group

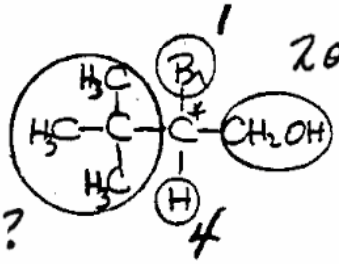


(H, H, H) (C, H, H)

4.16

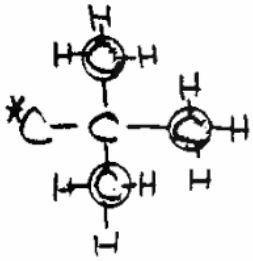


4.17



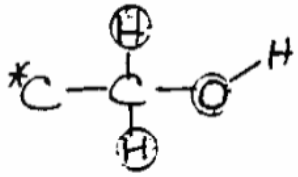
4.18 Second level atoms in $C(CH_3)_3$ and CH_2OH groups.

$C(CH_3)_3$ Group CH_2OH Group



(C, C, C)

Priority "3"



(O, H, H)

Priority "2"

For each of these groups we list these "*second level*" shaded atoms in decreasing order of atomic number and this gives the sequence (*H, H, H*) for CH_3, and (*C, H, H*) for CH_2CH_3. We then compare the atomic numbers of the atoms in these sequences in the order that they are written until we find the first point of difference. In (C, H, H), the first atom (C) has atomic number 6, while in (H, H, H), the first atom (H) has atomic number 1. Since atomic number 6 is higher than 1, we immediately assign the higher priority number "2" to CH_2CH_3 (with the sequence (C,H,H)) and the lower priority number "3" to CH_3 (with the sequence (H,H,H)) without comparing any other atoms in the sequences. [graphic 4.16]

In another example, C* is bonded to Br, CH_2OH, $(CH_3)_3C$, and H. [graphic 4.17] We immediately assign priority numbers "1" and "4" to Br and H, respectively, because they have the highest and lowest atomic numbers of all of the atoms directly bonded to C*, but once again the directly bonded (*first level*) atoms for the other two groups are C. The sequence of "*second level*" atoms bonded to those C's in order of decreasing atomic number is (C, C, C) for $C(CH_3)_3$ and (O, H, H) for CH_2OH as we show in Figure [graphic 4.18]. [graphic 4.18]

When we begin our comparison of the sequences with the first atom in each sequence, O has a higher atomic number than C so we immediately give CH_2OH a higher priority number than $C(CH_3)_3$. Although there are 2 additional C's in the sequence (C, C, C) compared to 2 H's in the sequence (O, H, H), we ignore these additional atoms once we have identified the first point of difference. The assigned priority numbers, and the resulting *R* and *S* isomers, are shown below. [graphic 4.19] These compounds require the use of a second "***R,S* Assignment Rule**" that states:

> ***Rule 2***. *When two or more groups have the same type of atom directly bonded to the chiral atom, their priority numbers depend on the atomic numbers of their "second level" atoms. If the second level atoms in one group are X, Y, and Z, whose order of atomic numbers is X>Y>Z, we group them as (X, Y, Z) and compare them in that order (one at a time) with "second level" atoms arranged in the same way for the other group or groups bonded to the chiral atom. When we find a difference in atomic number, we assign the higher priority number to the group with the higher atomic number atom in the comparison.*

Case 3. ***Groups with Double and Triple Bonds***. There are special rules for molecules with double or triple bonds (eg. C=C, C≡C, C=O, or C≡N) in groups bonded to C*. [graphic 4.20] In the example with C=O, we treat C=O as if it is O-C-O. As a result, the sequence of

"second level" atoms bonded to C in that example is (O, O, H) and these are circled in the structure. Similarly, we treat the C of C≡N as if it has three bonded N atoms so the sequence of "second level" atoms in that example is (N, N, N) and we have circled them. The rule that applies to double and triple bonds in groups bonded to chiral atoms is:

Rule 3. *A double bond to an atom is replaced by two single bonds to the same type of atom and a triple bond to an atom is replaced by three single bonds to the same type of atom.*

More Complex Molecules. In more complex molecules, you will need to go beyond the "second level" of atoms in groups bonded to C* to find the first point of difference. In each case you must compare sequences of atoms at the same level with each other until you find the point of difference as we have described for comparisons of "second level" atoms.

4.3 The Number and Types of Stereoisomers

The maximum number of stereoisomers for a molecule increases exponentially as the number of chiral atoms in the molecule increases.

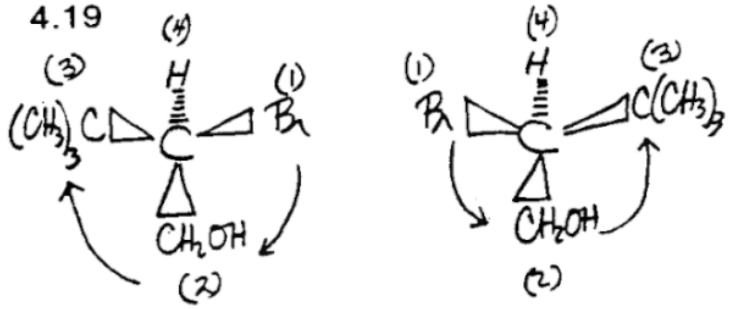
Compounds Can Have 2^n Stereoisomers (4.3A)

We have seen that a molecule with 1 chiral C has 2 stereomers. If a molecule contains 2 chiral C's, it is possible for it to have 4 stereoisomers, while a molecule with 3 chiral carbons can have 8 stereoisomers. A molecule with *n* chiral atoms may have up to 2^n stereoisomers.

2-Bromo-3-chlorobutane. A molecule with 2 chiral C's and 4 stereoisomers is *2-bromo-3-chlorobutane*. [graphic 4.22] C1 and C4 are achiral because they each have 3 H's, but C2 and C3 are chiral because they each have 4 different groups. Those on C2 are $\underline{C}H_3$, H, Br, and $\underline{C}HClCH_3$, while those on C3 are $\underline{C}H_3$, H, Cl, and $\underline{C}HBrCH_3$. [graphic 4.23] We treat C2 and C3 as separate chiral centers, so the fact that some groups on C2 are the same as some on C3 does not affect the individual chirality of C2 or C3.

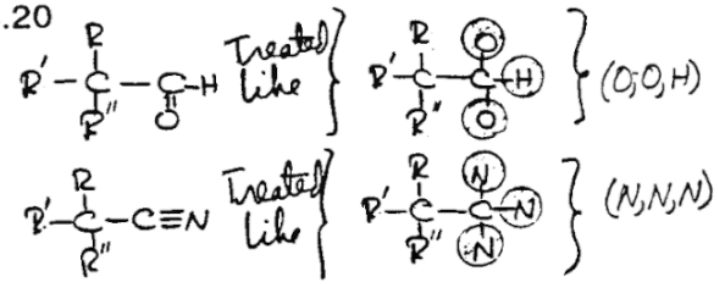
These separate chiral centers (C2 and C3) can each be *R* or *S*, so the names of the four possible stereoisomers are *(2R,3R)-2-bromo-3-chlorobutane*, *(2S,3S)-2-bromo-3-chlorobutane*, *(2R,3S)-2-bromo-3-chlorobutane*, and *(2S,3R)-2-bromo-3-chlorobutane*. [graphic 4.24] For easy comparison, we have shown each stereoisomer in an orientation where C2 and C3 lie on a vertical line, their H's project back into the paper, and their other two groups project out toward you. (We will see later in Section 4.4 that there are other ways to draw these stereoisomers).

4.19

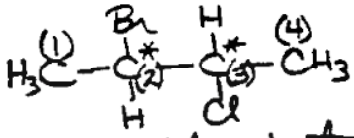


(R)-isomer ("clockwise") (S)-isomer ("counterclockwise")

4.20

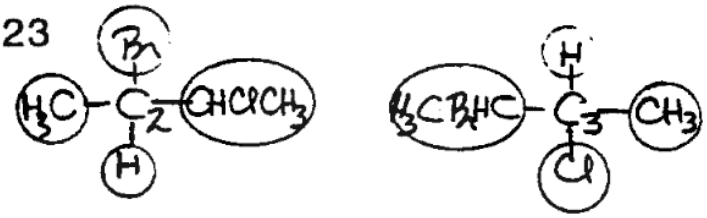


4.22



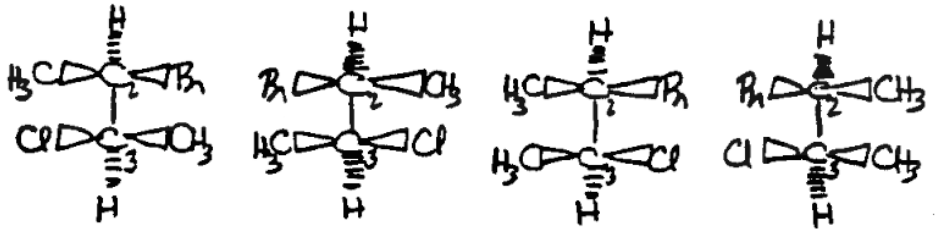
2-Bromo-3-chlorobutane

4.23



Four Groups on C_2 Four Groups on C_3

4.24 The four stereoisomers of 2-bromo-3-chlorobutane



(2R,3R) (2S,3S) (2R,3S) (2S,3R)

Before we discuss the relationships between these four stereoisomers, we need to be sure that we have made the correct assignments of *R* and *S* at C2 and C3 in Figure [graphic 4.24]. We verify this below for C2 of the (2*R*, 3*R*) isomer using the rules that we presented earlier.

Configuration at C2 in the (2R,3R) Isomer. We have taken (2*R*,3*R*)-2-bromo-3-chlorobutane from Figure [graphic 4.24] and redrawn it as structure (1) in Figure [graphic 4.25]. [graphic 4.25] This figure is a stepwise illustration verifying that C2 has the *R* configuration.

The assignment of configuration to C2 does not depend on the configuration of C3 so in the *first step* we remove the wedges and dashes from C3, and write it and its groups simply as $CHClCH_3$ as shown in structure (2). The atoms directly bonded to C2 in order of decreasing atomic number are Br, C, C, and H so in the *second step* we can immediately assign the priority numbers "1" and "4" to Br and H, respectively. However to assign priority numbers "2" and "3", we must analyze the "second level" atoms in the other two groups on C2. These are (H, H, H) for CH_3, and (Cl, C, H) for $CHClCH_3$, so the first atom in each sequence leads us to the assignment of "2" to $CHClCH_3$ and "3" to CH_3 as we show on structure (3).

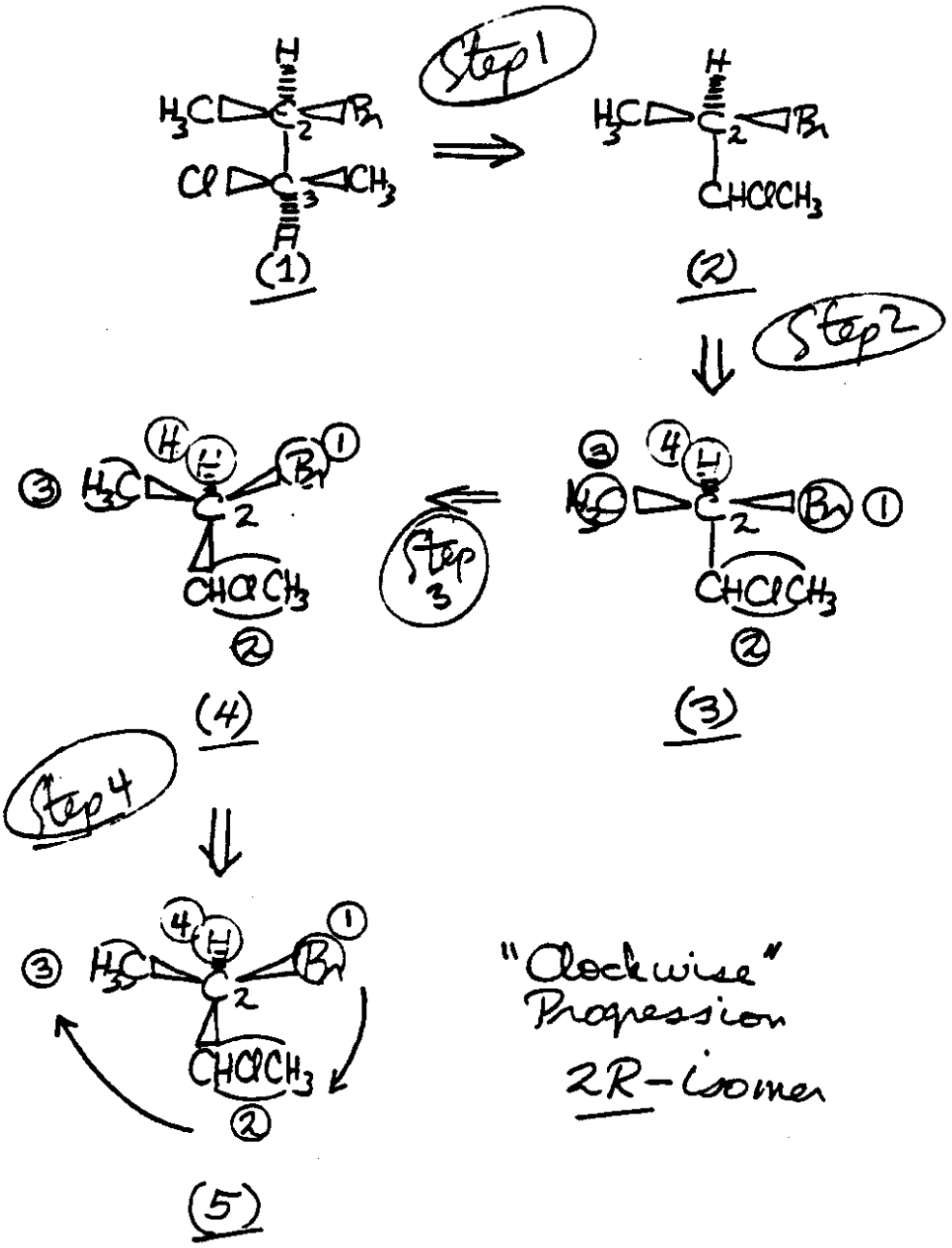
We orient the molecule so that the priority "4" atom (H) is directed away from us by "lifting up" the $CHClCH_3$ group from the plane of the paper in the *third step*. This moves the H further away from us as we show in structure (4). Finally in the *fourth step*, we connect priority numbers "1", "2", and "3" with arrows that show the direction of their progression in structure (5). The "*clockwise*" progression verifies the assignment of *R* to C2 in this (2*R*,3*R*) stereoisomer.

Configuration at C2 in the other Stereoisomers. At this point we can go back and look at C2 in all four stereoisomers of 2-bromo-3-chlorobutane (Figure [graphic 4.24]). By inspecting these structures you should be able to see that the configuration at C2 in the (2*R*,3*S*) isomer is the same as that at C2 in the (2*R*,3*R*) isomer that we just analyzed. You should also be able to see that the configurations at C2 in either (2*S*,3*S*) or (2*S*,3*R*) are th same as each other and are mirror images of the C2 configuration in either (2*R*,3*R*) or (2*R*,3*S*). We ignored the stereochemistry of the C3 group when we analyzed C2, but you can now separately verify the configuration at C3 in the same way that we just described for C2.

Relationships Between Stereoisomers (4.3B)

The four stereoisomers of 2-bromo-3-chlorobutane in Figure [graphic 4.24] differ from each other because of the differences in their configurations at C2 and C3. While we can uniquely

4.25 **Stepwise illustration of *R,S* configurational assignment at C2 in a stereoisomer of 2-bromo-3-chlorobutane.**



refer to each of them by their designations (2*R*,3*R*) *etc*., we also use the general terms **enantiomer** and **diastereomer** to describe their relationships to each other.

Enantiomers. *Enantiomers are stereoisomers that are mirror images of each other, but non-superimposable*. We have seen that (*R*) and (*S*)-*bromochlorofluoromethane* are non-superimposable mirror images, so they are *enantiomers* of each other as we illustrate in Figure [graphic 4.26]. [graphic 4.26]

Among the four stereoisomers of *2-bromo-3-chlorobutane* (Figure [graphic 4.24]), the (2*R*,3*R*) and (2*S*,3*S*) isomers are mirror images of each other, and so are the (2*R*,3*S*) and (2*S*,3*R*) isomers. Since they are also non-superimposable, (2*R*,3*R*) and (2*S*,3*S*) are *enantiomers* of each other, and (2*R*,3*S*) and (2*S*,3*R*) are also *enantiomers* of each other (Figure [graphic 4.26]).

Diastereomers. *Any pair of stereoisomers of a compound that is not a pair of enantiomers is a pair of diastereoisomers*. For example, the (2*R*,3*R*) and (2*R*,3*S*) stereoisomers of 2-bromo-3-chlorobutane are not enantiomers of each other since they are not mirror images. As a result, these two stereoisomers are *diastereomers* of each other. Based on these definitions, a pair of stereoisomers of a compound is either a pair of *enantiomers* or a pair of *diastereomers*. We see this in Table 4.1 that summarizes all of the pair-wise relationships between the stereoisomers of 2-bromo-3-chlorobutane.

Table 4.1. Relationships Between the Stereoisomers of 2-Bromo-3-Chlorobutane

Isomer Pair	Mirror Images?	Super-imposable?	Relationship
(2*R*,3*R*),(2*S*,3*S*)	Yes	No	Enantiomers
(2*R*,3*S*),(2*S*,3*R*)	Yes	No	Enantiomers
(2*R*,3*R*),(2*S*,3*R*)	No	No	Diastereomers
(2*R*,3*R*),(2*R*,3*S*)	No	No	Diastereomers
(2*S*,3*S*),(2*R*,3*S*)	No	No	Diastereomers
(2*S*,3*S*),(2*S*,3*R*)	No	No	Diastereomers

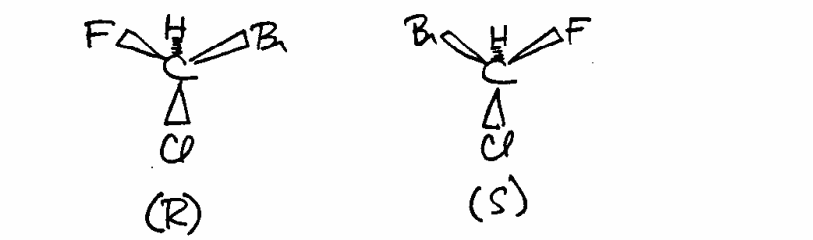
Compounds with Fewer than 2^n Stereoisomers (4.3C)

Some compounds with *n* chiral centers have fewer than 2^n stereoisomers.

2,3-Dibromobutane. Both C2 and C3 in *2,3-dibromobutane* are chiral, and each has an *R* and an *S* configuration. [graphic 4.27] While we can show 4 possible stereoisomers in this figure, we will see that the compound has only 3 different stereoisomers. The (2*R*,3*R*) and (2*S*,3*S*) isomers are mirror images of each other and non-superimposable so they are a pair of

4.26 **Enantiomers of bromochlorofluoromethane and of 2-bromo-3-chlorobutane.**

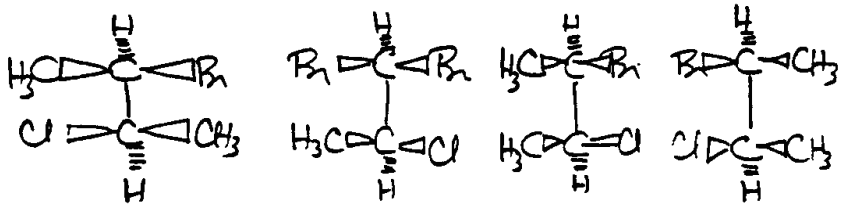
Bromochlorofluoromethane



(R) (S)

Non-Superimposable Mirror Images ≙ Enantiomers

2-Bromo-3-Chlorobutane

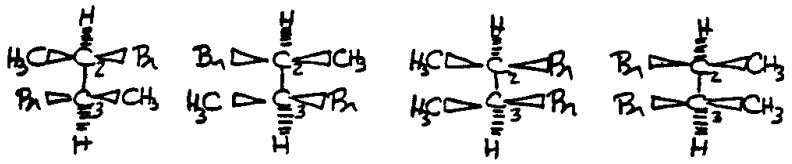


(2R,3R) (2S,3S) (2R,3S) (2S,3R)

Non-Superimposable Mirror Images ≙ Enantiomers

Non-Superimposable Mirror Images ≙ Enantiomers.

4.27 **Possible Stereoisomers of 2,3-dibromobutane**



(2R,3R) (2S,3S) (2R,3S) (2S,3R)

Mirror Images

Mirror Images

enantiomers. In contrast, while the (2*R*,3*S*) and (2*S*,3*R*) structures are also mirror images of each other, we will see that they are superimposable so they are identical to each other. [graphic 4.28]

If you lift the (2*S*,3*R*) structure off of the page and rotate it by 180°, you can superimpose it exactly on top of the (2*R*,3*S*) structure (Figure [graphic 4.28]). These two structures are superimposable because each has a **plane of symmetry** (Figure [graphic 4.29]) in which the groups on C2 (Br, CH_3, H) are chemically identical to, and the exact mirror images of, the groups on C3 (Br, CH_3, H). [graphic 4.29]

Meso Form. Since (2*R*,3*S*) and (2*S*,3*R*)-2,3-dibromobutane (Figures [graphic 4.27] and [graphic 4.28]) are identical to each other (superimposable on each other), they are a single stereoisomer that we call a **meso form** or **meso isomer**. A *meso form* is a stereoisomer of a compound with two or more chiral centers that is superimposable on its own mirror image.

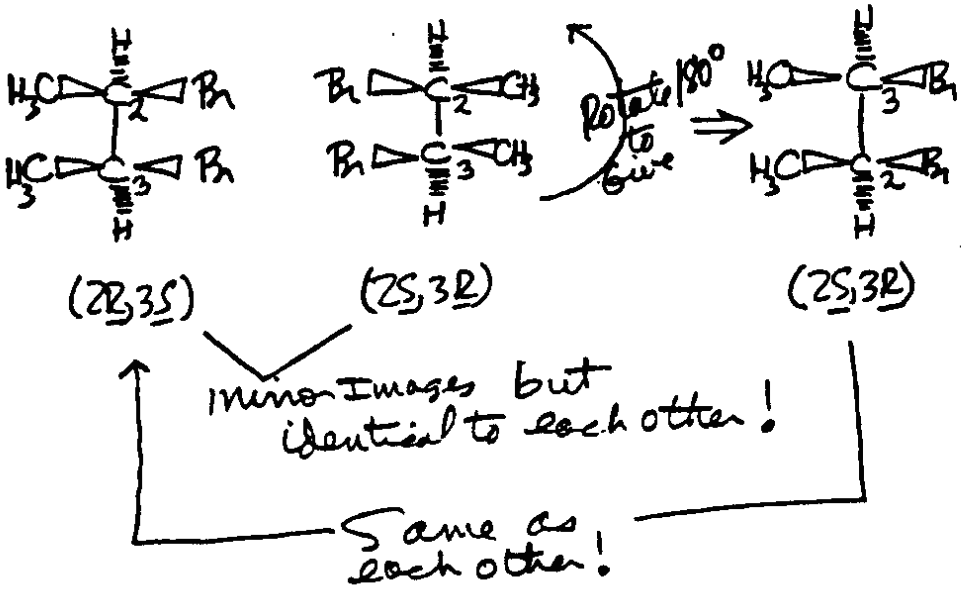
You may wonder why we can refer to this single *meso isomer* as either (2*R*,3*S*) or (2*S*,3*R*). This results from the mirror plane of symmetry that allows us to number the molecule beginning at either terminal CH_3 group. If we reverse the numbers on C2 and C3 of the (2*R*,3*S*) stereoisomer, *without changing the configurations at the two C's,* then (2*R*,3*S*) becomes (3*R*,2*S*). This new designation (3*R*,2*S*) is completely equivalent to the designation (2*S*,3*R*) so we see that the designations (2*R*,3*S*) or (2*S*,3*R*) are completely interchangeable.

Since meso forms are stereoisomers with mirror planes of symmetry, you can identify a *meso* form by identifying its mirror plane. Another way to predict the presence of a mirror plane in a stereoisomer, and its identity as a *meso form*, is to recognize that there are two identical ways to number the carbon atoms when you name the molecule. Because it has a *meso* form, 2,3-dibromobutane has only *3* unique stereoisomers. We summarize the relationships between pairs of its stereoisomers in Table 4.2 [next page].

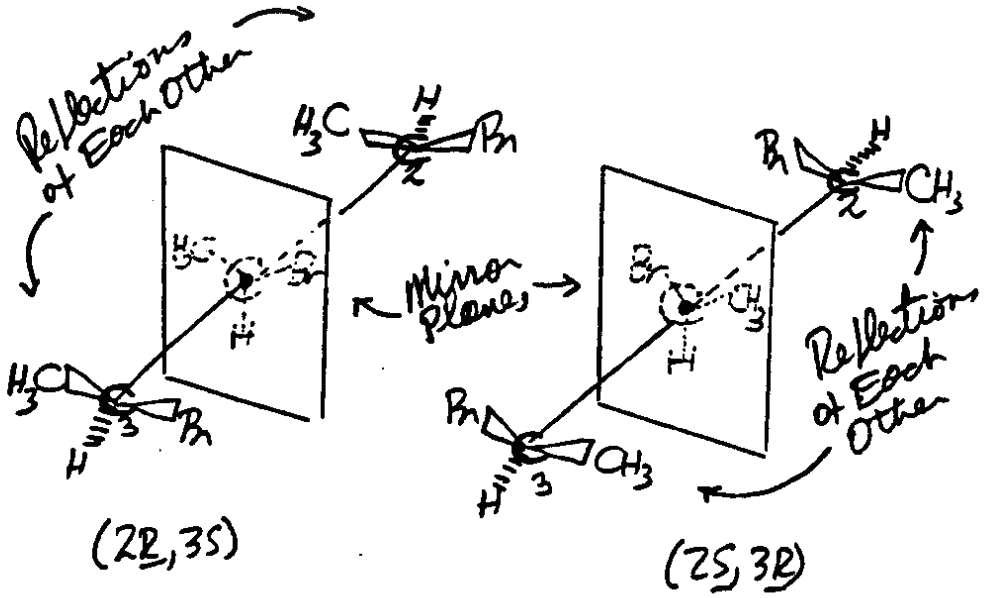
Table 4.2. Relationships Between the Stereoisomers of 2,3-Dibromobutane

Isomer Pair	Mirror Images?	Super-imposable?	Relationship
(2*R*,3*R*),(2*S*,3*S*)	Yes	No	Enantiomers
(2*R*,3*S*),(2*S*,3*R*)	Yes	Yes	Identical (Meso form)
(2*R*,3*R*),(2*S*,3*R*)	No	No	Diastereomers
(2*R*,3*R*),(2*R*,3*S*)	No	No	Diastereomers
(2*S*,3*S*),(2*R*,3*S*)	No	No	Diastereomers
(2*S*,3*S*),(2*S*,3*R*)	No	No	Diastereomers

4.28 **An illustration showing that the (2*R*,3*S*) and (2*S*,3*R*) isomers of 2,3-dibromobutane are identical to each other.**



4.29 **The (2*R*,3*S*) and (2*S*,3*R*) isomers of 2,3-dibromobutane have a mirror plane.**



4.4 Drawing Structures of Stereoisomers

In this section we consider different ways of drawing stereoisomers and methods for interconverting these various types of drawings. This will help us compare stereoisomers and determine their stereochemical relationships to each other.

3-D Conformations of Stereoisomers (4.4A)

There are a variety of ways to draw 3-D structures for stereoisomers since each stereoisomer can be drawn in many different orientations in space, and in different conformations resulting from rotation about C-C and other single bonds in the molecule.

Many Ways to Draw the Same Stereoisomer. All of the structures that we show in Figure [graphic 4.32] are the same stereoisomer (*2R,3S*)-*2-bromo-3-chlorobutane*. [graphic 4.32] While they appear different from each other, we can use the the *R*,*S* assignment rules to confirm in each structure that the configuration at C2 is *R* and that at C3 is *S*. Configurations at a chiral atom do not change when we rotate about C-C bonds, or when we rotate a molecule in space. In order to change a configuration at a chiral C, we must exchange the positions of two atoms and/or groups bonded to that C. This means that we must break the chemical bonds between these two atoms or groups and the chiral center, and then form new bonds to the atoms or groups in the opposite spatial orientation.

3-D Structures for Comparing Stereoisomers. Because it is visually difficult to relate structures of stereoisomers with different conformations (C-C rotation) or different spatial orientations such as those in Figure [graphic 4.32], the best way to draw a complete set of stereoisomers of a compound is to arbitrarily choose one structure for a stereoisomer and model the rest of the stereoisomers on it. We illustrate this for *3-bromo-2-butanol* in Figure [graphic 4.33] starting with four different arbitrary structures for its (2*S*,3*R*) stereoisomer on lines (A) through (D). [graphic 4.33]

We draw the *second structure* in each group as the mirror image of the *first structure*. The configuration at each chiral C in a mirror image is opposite that in the original structure, so the mirror image *second structure* in each case is (2<u>*R*</u>,3<u>*S*</u>)-3-bromo-2-butanol. We draw the *third stereoisomer* in groups (A) through (D) by arbitrarily changing the configuration at one chiral C in each *second structure*. Because we have arbitrarily changed the configuration at C2 from *R* to *S*, the *third structure* in each group is the new stereoisomer (2<u>*S*</u>,3*S*)-3-bromo-2-butanol and it is different from both the *first* structure (2*S*,3*R*) and *second* structure (2*R*,3*S*) in each group.

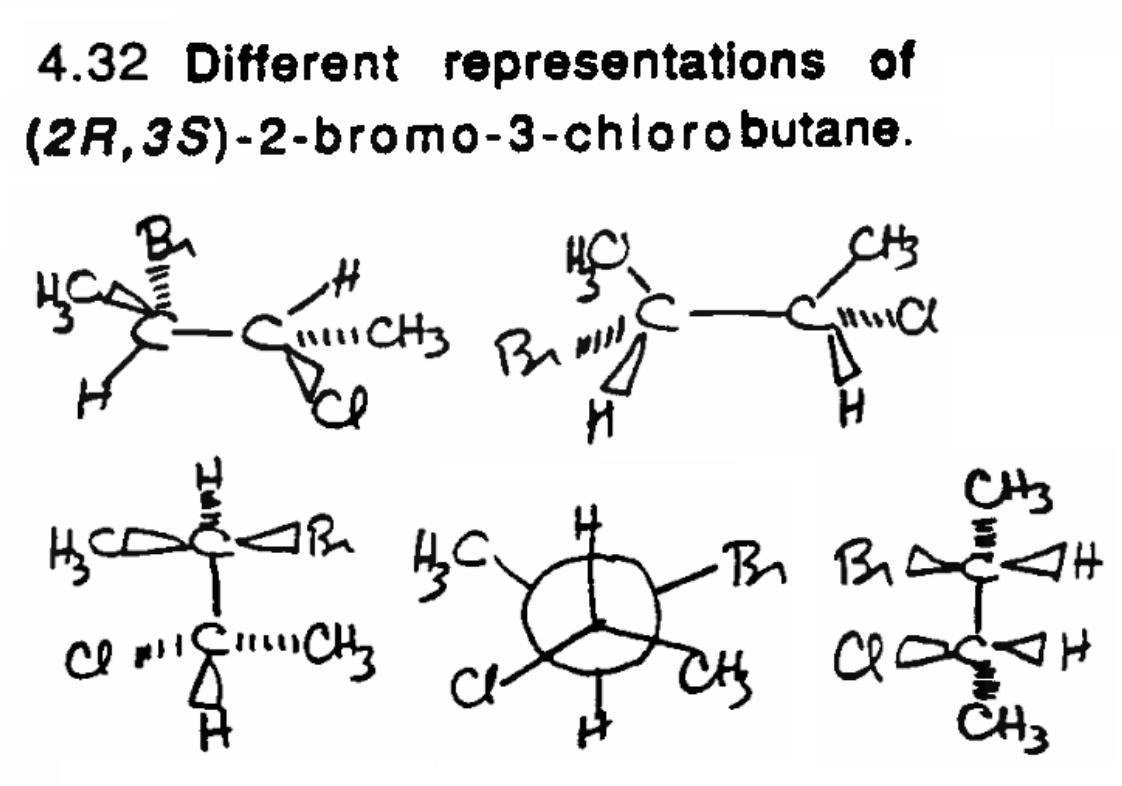
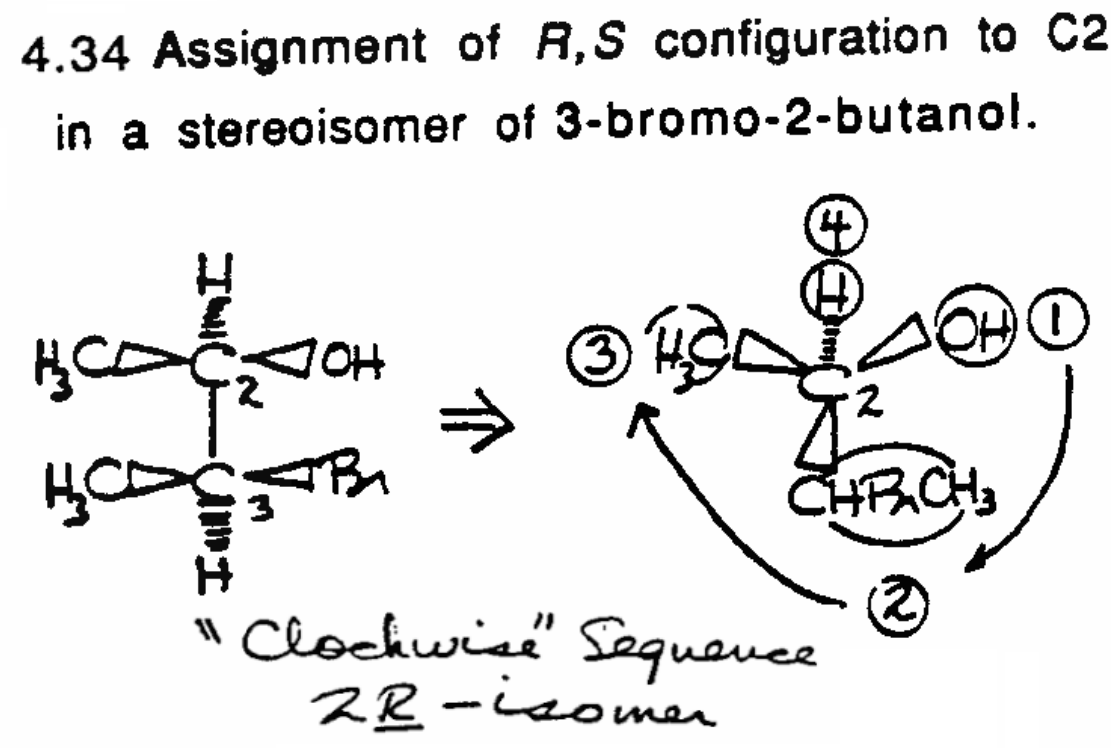
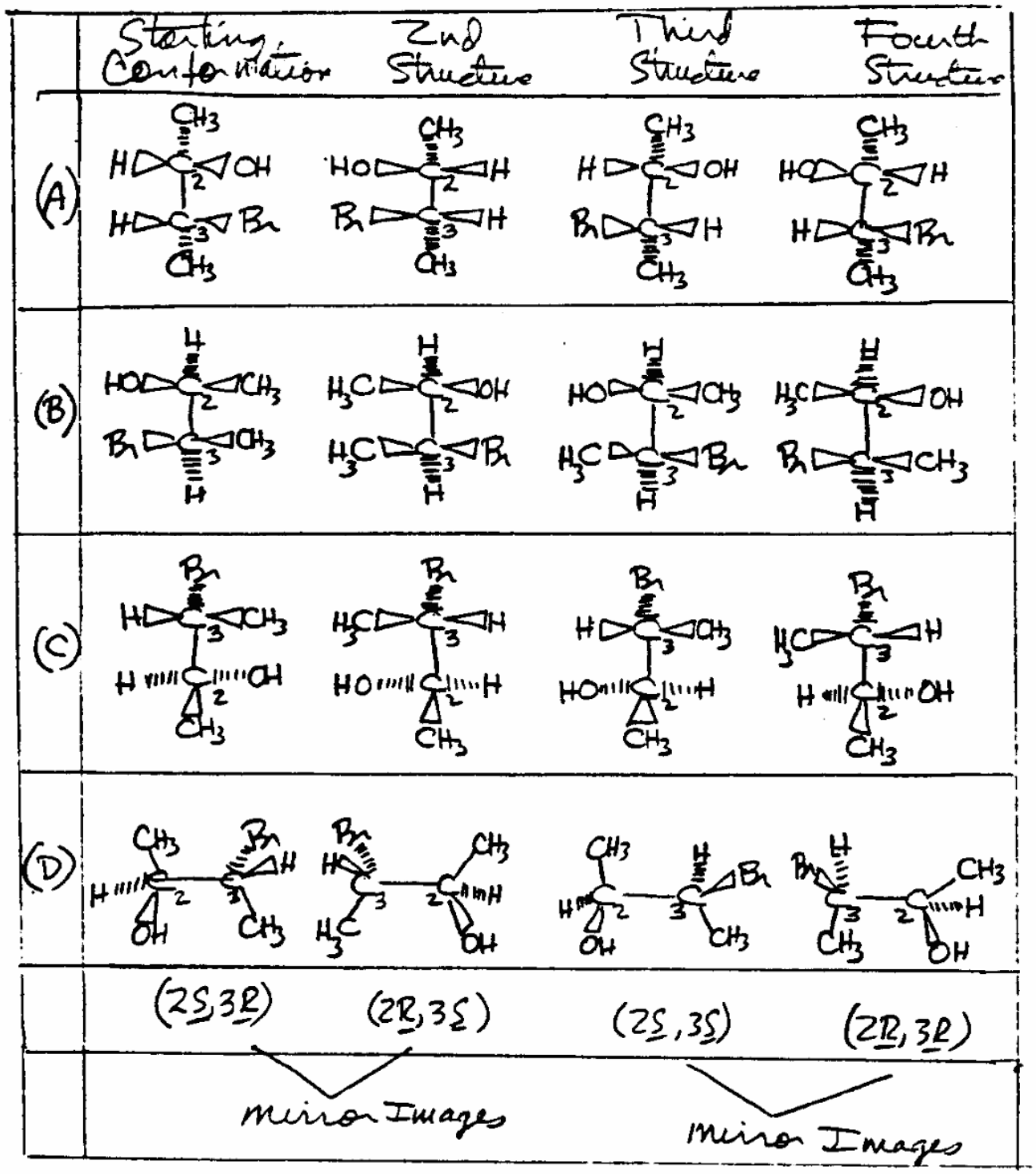


Figure 4.33 (See Next Page)



4.33 Four different presentations of the four stereoisomers of 3-bromo-2-butanol.



We draw the *fourth structure* in each group as the mirror image of the *third structure*. The configuration at each chiral C changes in a mirror image, so all of these *fourth* stereoisomers are (2*R*,3*R*)-3-bromo-2-butanol. Since 3-bromo-2-butanol has no mirror plane, its four stereoisomers (shown in different orientations on lines (A)-(D)) are different from each other and there are no *meso* forms.

Each group of stereoisomers on lines (A)-(D) are valid representations of the four stereoisomers of 3-bromo-2-butanol. However you will frequently see 3-D stereoisomers drawn as wedge-bond structures such as those in groups (A) or (B) in Figure [graphic 4.33] with their chiral C's on a vertical line and their horizontal bonds pointing out from the paper. Organic chemists usually draw groups of stereoisomers with the maximum number of C's on the vertical line as in group (A), while the conformations in group (B) are useful for assigning *R* and *S* configurations to the chiral carbons since they have priority "4" groups on C2 and on C3 at the top and bottom of the structures .

Configuration of C2 in (2R,3R)-3-bromo-2-butanol. Let's verify the assignment of the *R* configuration to C2 in (2R,3S)-3-bromo-2-butanol using the structure from group (B) of Figure [graphic 4.33] that we show again in Figure [graphic 4.34]. [graphic 4.34] Our first step is to assign priority numbers to the atoms and groups on C2. We then want to view this C2 chiral carbon down its C2-"priority '4'-group" bond so we lift the C2-C3 bond from the plane of the paper so that C3 is pointing towards us. As a result, the priority "4" H atom moves further away from us as shown in the second structure of Figure [graphic 4.34]. When we now connect the groups numbered "1" through "3" by arrows, we see that the configuration at C2 is *R* because the arrows rotate in a *clockwise* or "*right*" direction. We can carry out the same process at C3 to verify that it has the *S* configuration.

In more complex molecules, you may find it more challenging to orient a particular chiral C so that you can determine its *R,S* assignment as we describe above. This takes practice and is usually made easier by the use of molecular models. However, molecular models may not always be available, so you need to practice making these configurational assignments both with and without them.

Fischer Projections (4.4B)

Chemists sometimes use **Fischer projections**, rather than 3-D wedge-bond drawings, to represent structures of stereoisomers. We will make extensive use of *Fischer projections* to draw structures of sugars (carbohydrates) in Chapter 20.

Definition of Fischer Projections. We illustrate the definition of a *Fischer projection* with the structures in Figure [graphic 4.35]. [graphic 4.35] A *Fischer projection* symbolizes a 3-D wedge-bond structure whose *horizontal* bonds at each chiral C are *solid wedges* projecting out of the plane of the paper, and whose *vertical* bonds at each chiral C are *dashed wedges* projecting back into the plane of the paper (or lying in the plane of the paper as is the case for the central C-C bond in the structure with two chiral C's).

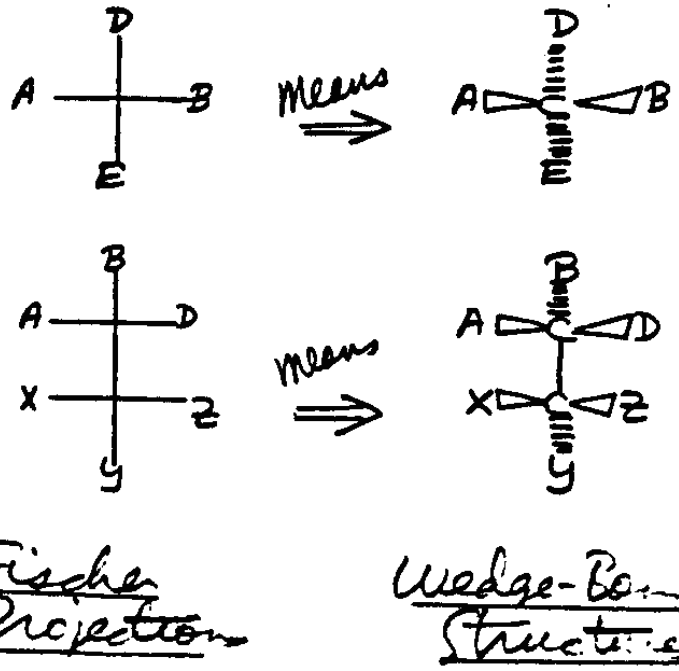
Two stereoisomers of molecules that we have already discussed are shown in Figure [graphic 4.36] using both 3-D wedge-bond structures and their *Fischer projections*. [graphic 4.36] You can see that we have drawn the horizontal bonds in the 3-D wedge-bond structures as solid wedges, and the top and bottom vertical bonds as dashed-wedges. When we draw the 3-D wedge-bond drawings in this way, we are able to immediately draw their adjacent *Fischer projections*. Alternatively, had we first drawn these *Fischer projections*, they would have immediately defined their adjacent 3-D wedge-bond structures.

It is important to realize that we can draw each of these stereoisomers in a variety of different conformations and orientations in space. However, only when we draw wedge-bond structures with horizontal bonds projecting toward us, and vertical bonds projecting away from us, can we immediately convert them into the *Fischer projections*. Note in *Fischer projections* that (1) all of the bonds are solid lines, (2) all of the atoms or groups are in the same relative positions as in the wedge-bond structures, and (3) the chiral C's are <u>not</u> labelled with the letter "C". It is customary <u>not</u> to label the chiral C's with the letter "C" in a Fischer projection in order to distinguish it from line-bond structures such as those shown early in Chapter 1 (see also Figure [graphic 4.1]. *Fischer projections* specify the configuration and stereochemistry at chiral C's, but line-bond structures do not!

Manipulations of Fischer Projections. *Fischer projections* eliminate the need to draw solid and dashed wedge-bonds required in 3-D structures, but without those solid and dashed-wedge bonds we must be very careful how we reorient Fischer projections on a piece of paper. We illustrate in Figure [graphic 4.37] a problem that occurs when we reorient a Fischer projection. [graphic 4.37] When we simply rotate the Fischer projection of (<u>*R*</u>)-CHBrClF in the plane of the paper by 90° (step (A)), it is now (<u>*S*</u>)-CHBrClF! We can verify this by converting that rotated Fischer projection into its wedge-bond structure and assigning a configuration to the chiral C using the *R,S* assignment rules.

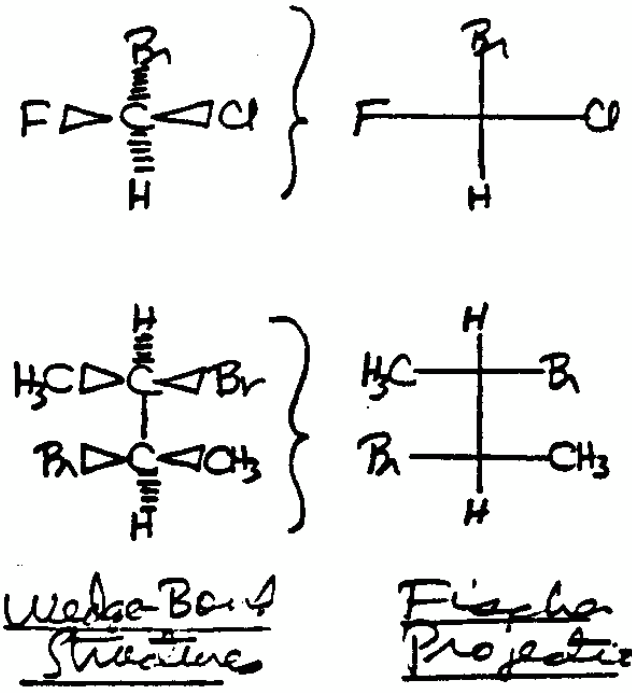
This **inversion of configuration** where *R* becomes *S* at the chiral C upon 90° rotation of a Fischer projection results from the different meaning of its *horizontal* and *vertical* bonds. If

4.35 Definitions of Fischer projections.



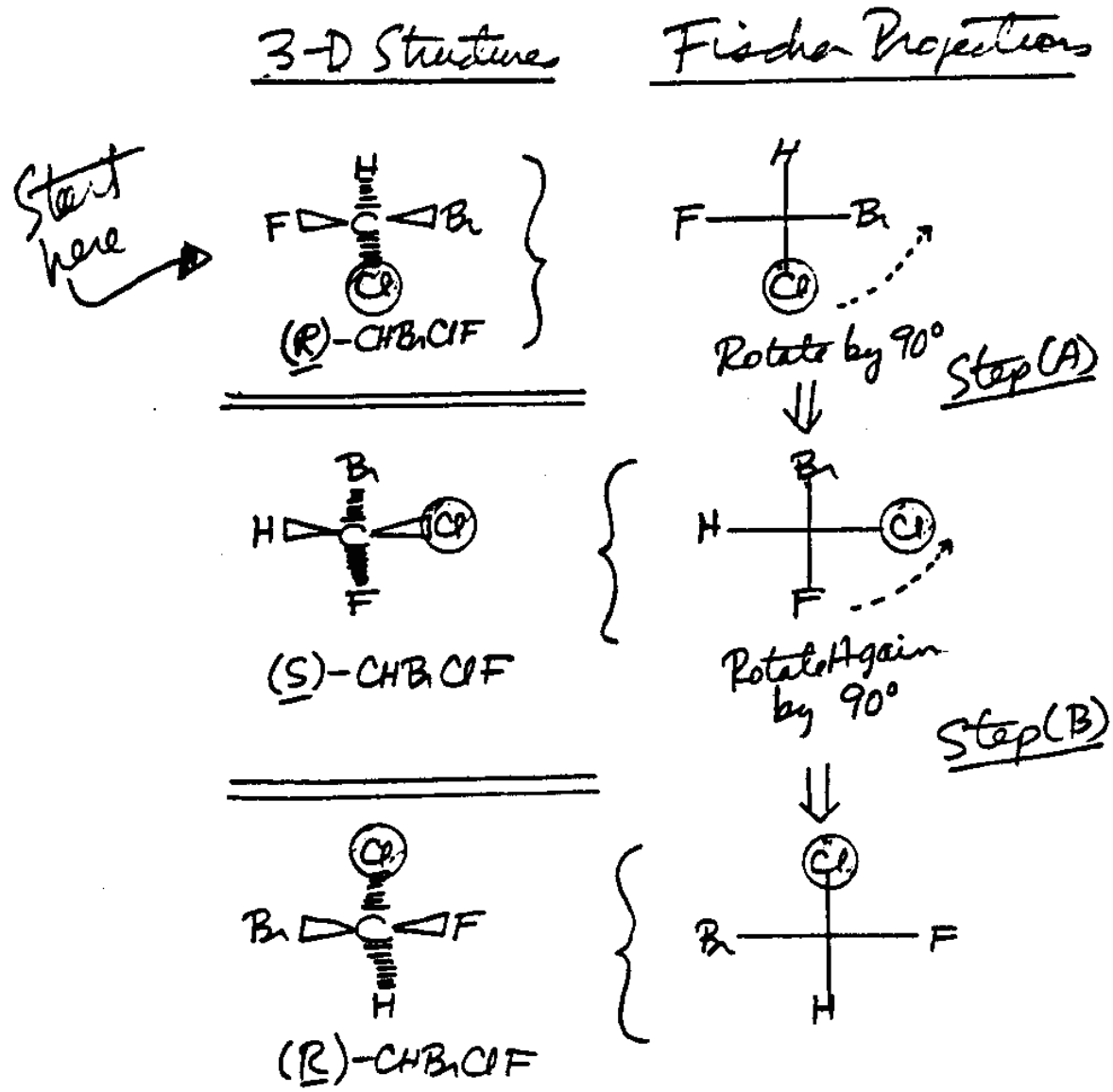
Fischer Projection Wedge-Bond Structure

4.36 Fischer projections of some stereoisomers.



Wedge-Bond Structure Fischer Projection

4.37 **The results of rotation of Fischer projections in the plane of the paper.**



we rotate that middle Fischer projection by another 90° in the plane of the paper (step (B)), we can show by converting it into a wedge-bond structure that it has once again become (*R*)-CHBrClF. This demonstrates that rotation of a Fischer projection by a full 180° in the plane of a piece of paper (the result of two separate 90° rotations), does not change the configuration at its chiral carbons.

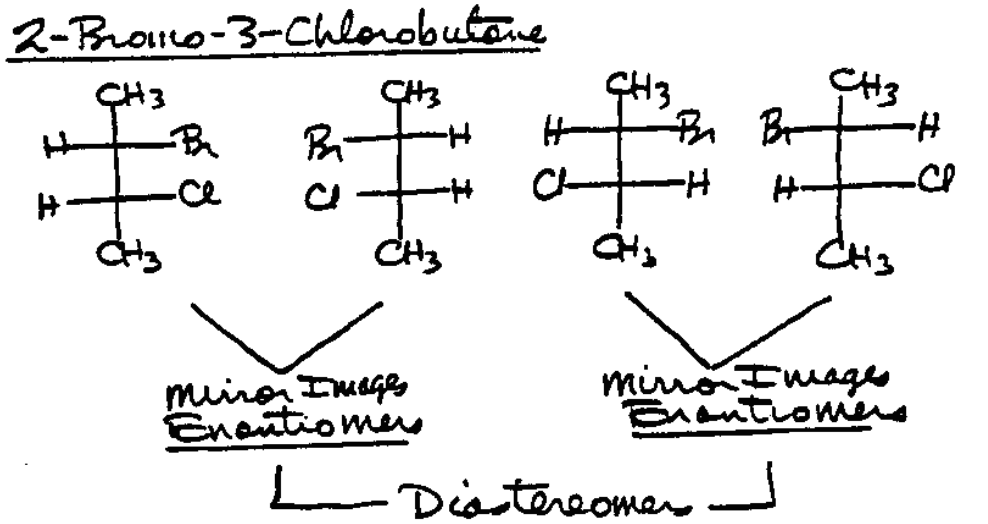
Using Fischer Projections to Draw Stereoisomers. We draw *Fischer projections* in Figure [graphic 4.41] of the possible stereoisomers of *2-bromo-3-chlorobutane* and of *2,3-dibromobutane* that we discussed earlier using wedge-bond drawings. [graphic 4.41] For each compound, we arbitrarily draw the *first* Fischer projection so that the chiral C's and CH_3 groups are on the imaginary vertical line mentioned earlier. The *second* Fischer projections are "mirror images" of the first ones. Since they are also non-superimposable on these first structures, they are *enantiomers* of these first structures. You can verify this by rotating the second structure for each compound by 180° in the plane of the paper and noting that the atoms do not match up with those on the first structures. Remember that a 180° rotation of a Fischer projection does <u>not</u> change the configuration at any chiral C in the molecule.

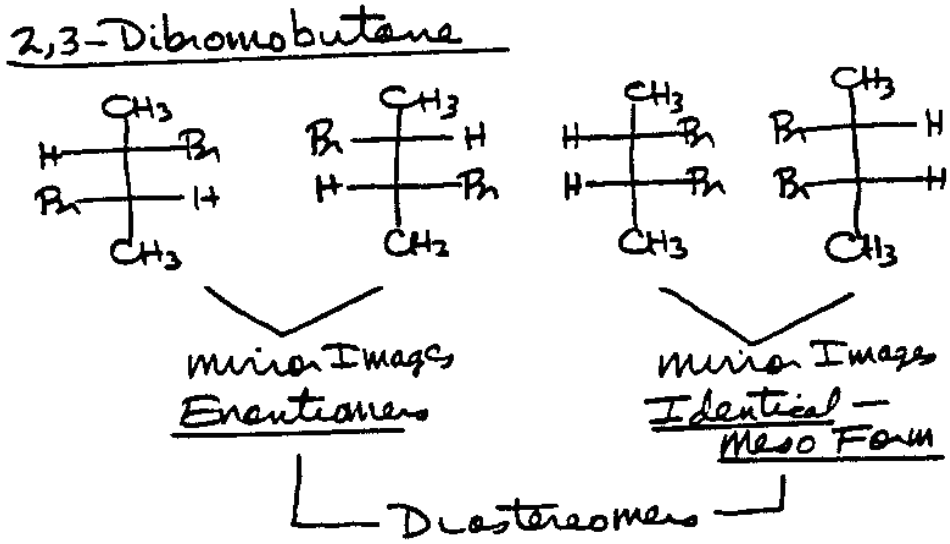
We draw the *third* Fischer projections by changing the configuration at just one C in the *second* structure. As a result, each is a *diastereomer* of the first and second structures of each compound. The *fourth* Fischer projections are mirror images of the *third* Fischer projections. For *2-bromo-3-chlorobutane*, this *fourth* Fischer projection cannot be superimposed on its mirror image (the *third* Fischer projection) so it is an *enantiomer* of the third structure.

The situation is different for *2,3-dibromobutane*. If we rotate its *fourth* Fischer projection by 180° in the plane of the paper, we can superimpose it exactly on the *third* Fischer projection that is its mirror image. Since these *third* and *fourth* Fischer projections of *2,3-dibromo-butane* are *identical* mirror images, they are each a representation of the single *meso* form of 2,3-dibromobutane.

> ***R,S Assignments Using Fischer Projections***. We have shown Fischer projections of the 4 stereoisomers of 2-bromo-3-chlorobutane and the 3 stereoisomers of 2,3-dibromobutane in Figure [graphic 4.41], but have not labelled their chiral C's *R* or *S*. You can provide these assignments by converting each Fischer projection into a wedge-bond structure, and then analyzing each chiral C as we did earlier in this chapter. However, you can also assign *R* or *S* to chiral C's in Fischer projections without converting them to wedge-bond structures.

4.41 **Fischer projections of the stereoisomers of 2-bromo-3-chlorobutane and of 2,3-dibromobutane.**





If the priority "4" group of each chiral C is on the top or bottom position of the Fischer projection, all you need to do is to connect the remaining priority numbers with the curved arrows as shown in Figure [graphic 4.42] because a group on the top or bottom of a Fischer projection is defined as pointing back into the page away from you. [graphic 4.42] However, if the chiral C on which you want to do *R*,*S* assignments in the Fischer projection does not have the lowest priority group at the top or bottom position, you can "move" the priority "4" group to a top or bottom position by exchanging it with one of the other groups bonded to the chiral C using the Exchange Rule that we describe here.

The Fischer Projection Exchange Rule. *Exchanging the positions of any two groups bonded to the same chiral carbon in a Fischer projection changes the configuration at that chiral carbon.* We demonstrate that this is correct below, but first we present a step-by-step outline of how you can use this exchange rule to assign the *R* or *S* configuration to a chiral carbon atom for a stereoisomer of 2,3-dibromobutane, and we illustrate it with the 6 steps in Figure [graphic 4.43]: [graphic 4.43]

(Step 1) Identify the chiral C in a Fischer projection whose *R*,*S* configuration you wish to assign.

(Step 2) Assign priority numbers to the groups on that chiral C.

(Step 3) Put the priority 4 group at the top (or bottom) of the Fischer projection of that chiral C, by exchanging its position with the group already in the top (or bottom) position.

(Step 4) Exchange positions of any two groups on that chiral C other than the priority 4 group.

(Step 5) Connect the priority 1, 2, and 3 groups with arrows and assign *R* or *S* to that chiral C as appropriate.

(Step 6) This *R* or *S* assignment will be the same as that for the original chiral C.

The configuration at the chiral C at the end of this sequence of steps is the same as it was in the original Fischer projection because you made <u>two</u> exchanges. The first (done in step (3)) *inverts* the configuration at the chiral C according to the basic exchange rule, and the second (done in step (4)) returns the *inverted* configuration to the configuration in the original projection.

Confirmation of the Exchange Rule. A way to prove that the exchange of positions of two groups on a chiral C changes configuration at that C is illustrated by the following steps:

(1) Draw a Fischer projection for a chiral C and then convert that into a wedge-bond structure.

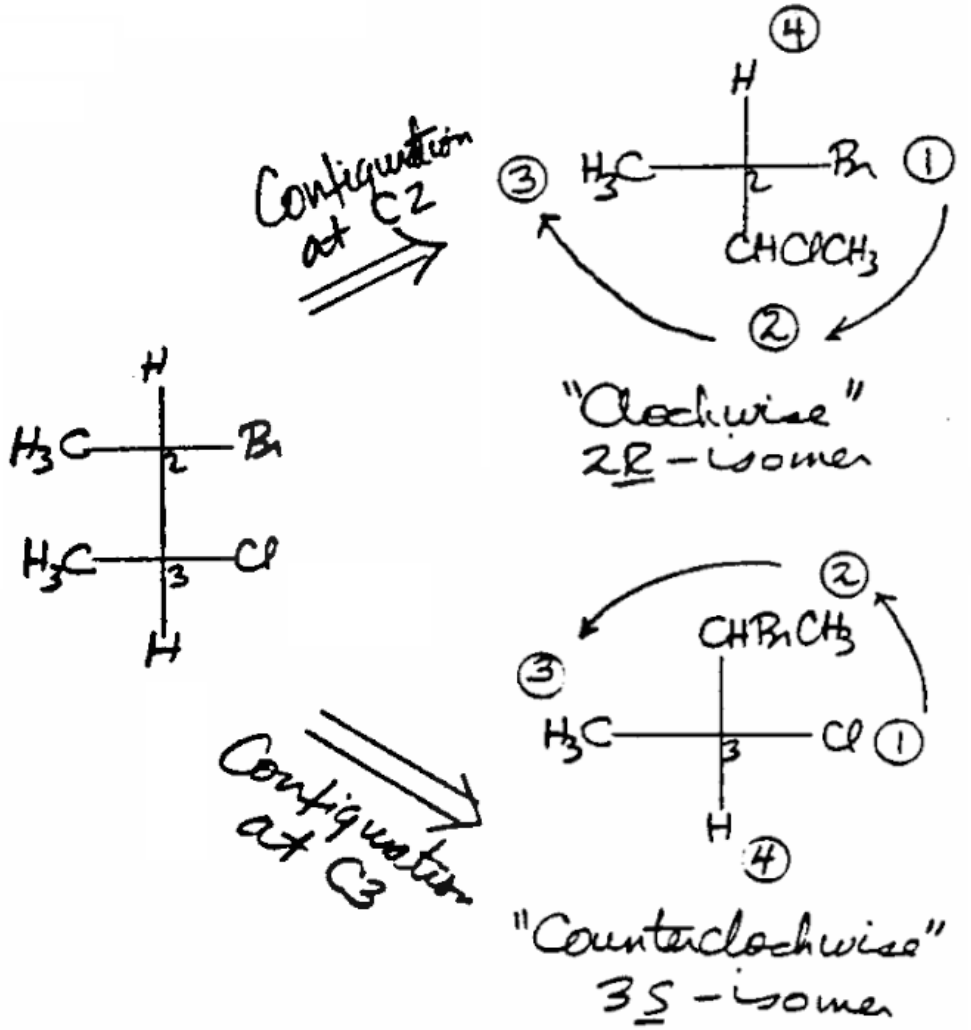
(2) Determine the *R*,*S* configuration at the chiral C using *R*,*S* assignment rules described earlier.

(3) Exchange two groups on the Fischer projection that you drew in (1) and convert this new Fischer projection into a wedge-bond structure.

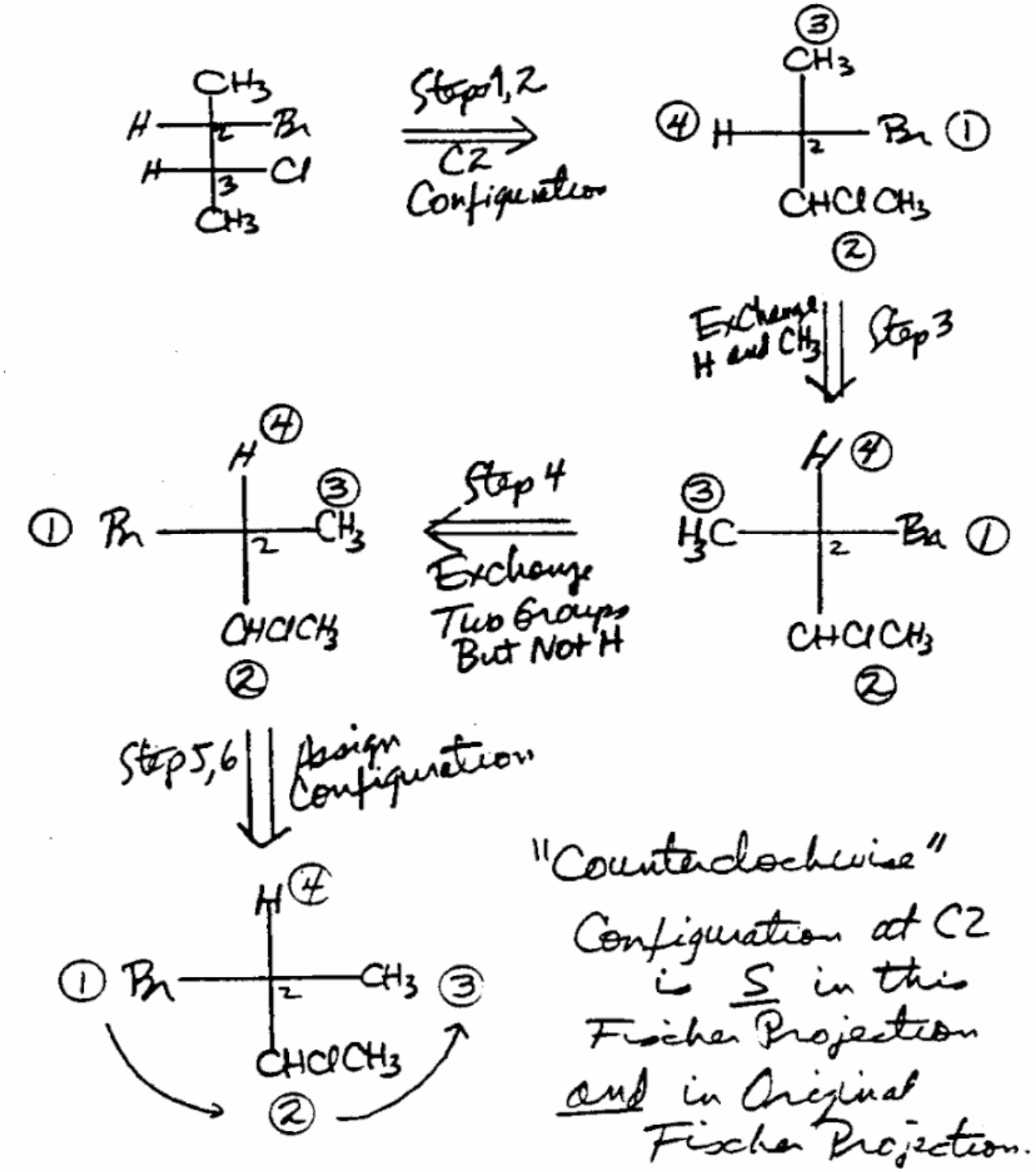
(4) Determine the *R*,*S* configuration at the chiral C in the wedge-bond structure created in (3).

If you do all of this correctly you will find out that the two wedge-bond structures have opposite configurations.

4.42 *R,S* assignments using Fischer projections with lowest priority groups in the "top" and "bottom" positions of the Fischer projection.



4.43 Use of the Fischer projection exchange rule to assign configuration.



4.5 Cyclic Molecules

Cyclic molecules can have chiral centers in the ring or in a group bonded to the ring. [graphic 4.45] When the chiral center is not in the ring (as in (A)), we treat the molecule just like those we have already described. This section describes stereoisomers of molecules that have chiral centers in the ring (as in (B)).

Cyclic Stereoisomers (4.5A)

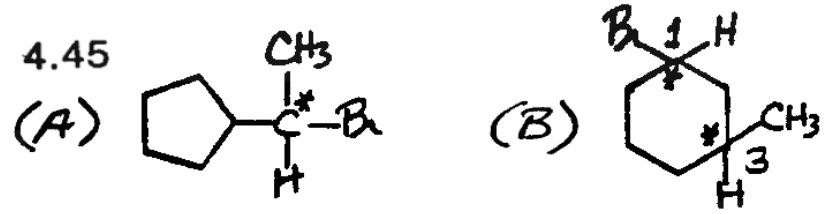
To draw stereoisomers for cyclic systems, we first identify the chiral atom or atoms in the ring just as we did for acyclic systems. As with acyclic molecules, a chiral C in a ring must have four different groups bonded to it.

Chiral Centers in 1-bromo-3-methylcyclohexane. Both C1 and C3 of 1-bromo-3-methylcyclohexane (structure (B) in Figure [graphic 4.45]) are chiral although at first glance you may think that neither of them has four different groups. For example, C1 is bonded to a Br, H, and two ring CH_2's, while C3 is bonded to a CH_3, H, and two ring CH_2's. You may initially think that the two ring CH_2's on C1 or on C3 do not qualify as different groups, but a closer look at the two ring CH_2's on C1 shows that one is CH_2-$CH(CH_3)$-, while the other is CH_2-CH_2-. These two groups differ at the next C bonded to each CH_2. (There is also one more CH_2 group in the ring between the CH_2CH_2- and $CH_2CH(CH_3)$- groups, but we ignore it in our analysis because we found a point of difference before we reached that group). In a similar way, the four groups on C3 are CH_3, H, CH_2CH_2-, and $CH_2CH(Br)$- ([graphic 4.46]).

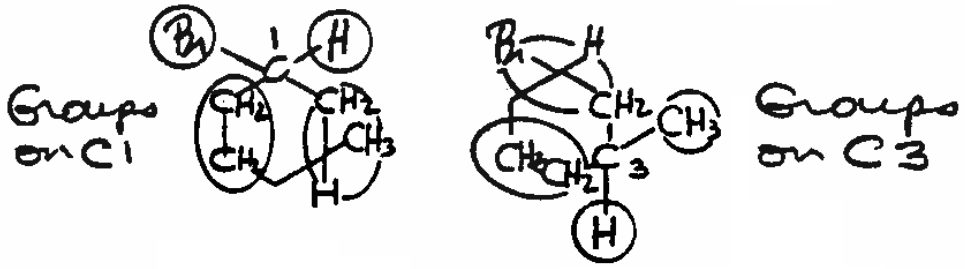
> ***A Method to Identify Chiral Centers in Rings***. If you have difficulty identifying chiral C's in rings, imagine a pair of twins standing on the C in the ring that you are testing for chirality. Allow each of the twins to simultaneously walk in opposite directions on the ring one step at a time using the atoms in the ring as stepping stones. If the two twins encounter a difference in substitution after the same number of steps, the C that they were both originally standing on is chiral. If they meet again without encountering any differences, the original C is *achiral*.

Stereoisomers of 1-bromo-3-methylcyclohexane. Since 1-bromo-3-methylcyclohexane has 2 chiral centers, it can have no more than the four stereoisomers ($2^n = 2^2 = 4$) whose structures we show in Figure [graphic 4.49]. To help determine the relationships between these possible stereoisomers, we have reoriented (B) and (D) in Figure [graphic 4.50] so that you can see more easily that (B) is the mirror image of (A), and (D) is the mirror image of (C). [graphic 4.50] Since (A) and (B) are non-superimposable mirror images (see Figure [graphic 4.49]), they are *enantiomers* of each other, and the same is true for (C) and (D). As a result, (A) and (C) (or (D)) are *diastereomers* like (B) and (C) (or (D)).

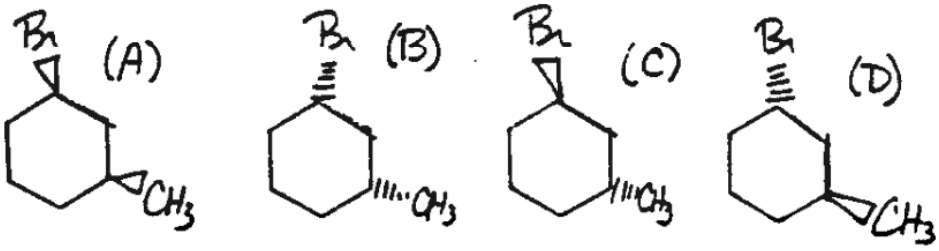
4.45



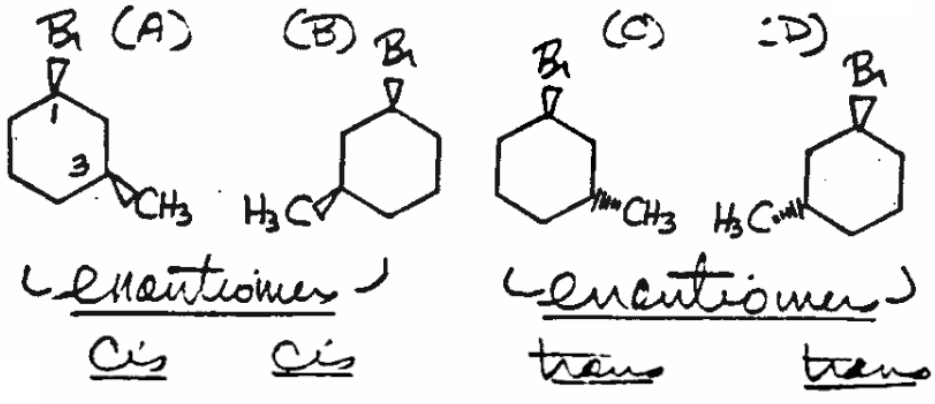
4.46 Identification of the four different groups substituted on C1 and on C3 in 1-bromo-3-methylcyclohexane.



4.49 The four stereoisomers of 1-bromo-3-methylcyclohexane.



4.50 Relationships between the four stereoisomers of 1-bromo-3-methylcyclohexane.



Stereochemical Relationships between cis and trans Isomers. You can also see in Figure [graphic 4.50] that (A) and (B) are both *cis* isomers (Chapter 2) of 1-bromo-3-methylcyclohexane, while (C) and (D) are both *trans* isomers. This means that *cis*-1-bromo-3-methylcyclohexane is the *pair* of enantiomers (A) and (B), while *trans*-1-bromo-3-methylcyclohexane is the *pair* of enantiomers (C) and (D). Since (A) or (B) are each diastereomers of (C) or (D), we can think of *cis* and *trans*-1-bromo-3-methylcyclohexane as *diastereomers* of each other.

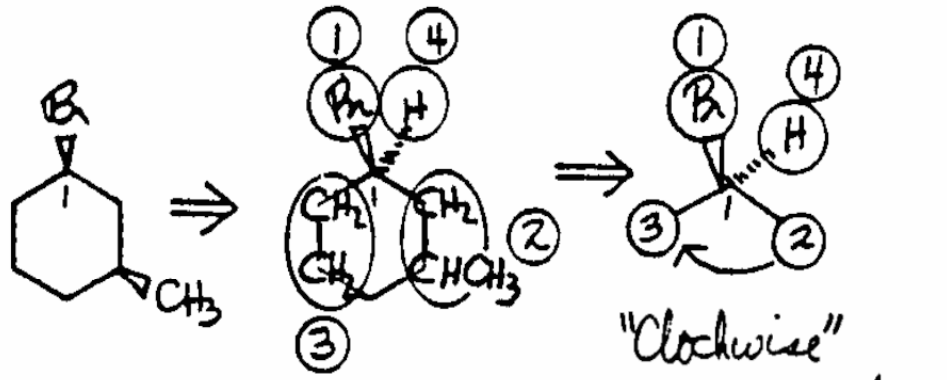
> ***R,S Assignments at Ring Carbons***. You can assign *R* or *S* configurations to the chiral carbons in cyclic systems as we described for acyclic systems. One method is to isolate a specific chiral ring C from a wedge drawing of a stereoisomer and make the assignment on that isolated chiral center. We illustrate this in Figure [graphic 4.51] for the C1 carbon in a stereoisomer of 1-bromo-3-methylcyclohexane. [graphic 4.51]
>
> We first identify the four different groups on C1 and give them priority numbers as we illustrate in the middle structure of Figure [graphic 4.51]. We then extract the C1 carbon from the molecule and identify some of its groups using just priority numbers to make viewing easier as we show in the third structure. Since these priority numbers progress in a clockwise direction using the method outlined for acyclic systems, we have identified the configuration at C1 as *R*.

Isomeric Bromomethylcyclohexanes. There are 3 other bromomethylcyclohexanes that are structural isomers of *1-bromo-3-methylcyclohexane*. Of these, only *1-bromo-2-methylcyclohexane* has chiral carbon atoms. [graphic 4.52]

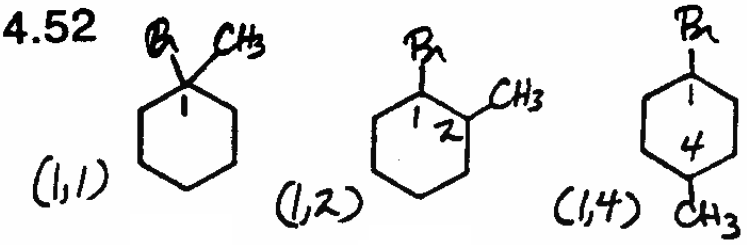
1-Bromo-1-methylcyclohexane is a single compound with two different chair conformations and no chiral C's. Five of the six ring carbons are CH_2 groups that cannot be chiral because they each have two H's. While the C1 center has a Br and a CH_3, its other "two groups" are identical to each other so it is **achiral**.

C1 and C4 of *1-bromo-4-methylcyclohexane* are also *achiral* as are the ring CH_2's. However, 1-bromo-4-methylcyclohexane does have a *cis* and a *trans* isomer that are stereoisomers because they differ only in the spatial arrangement of their Br and CH_3 groups in space. [graphic 4.53] They are *diastereomers* because they are not mirror images, and since each has a mirror plane, they are *meso forms*.

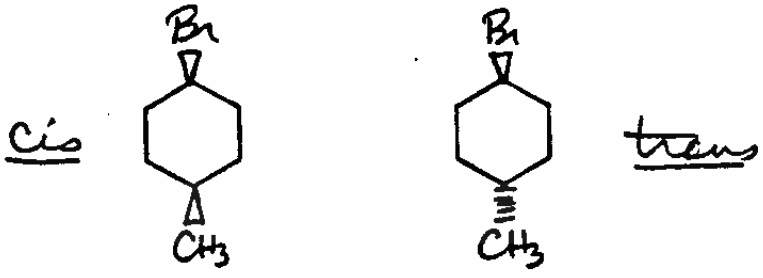
4.51 Determination of *R,S* configuration at C1 of a stereoisomer of 1-bromo-3-methylcyclohexane.



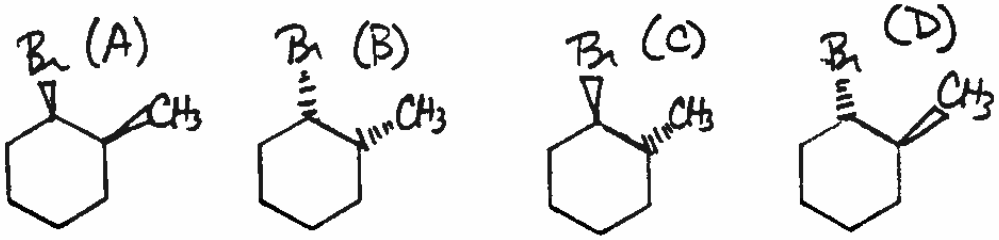
4.52



4.53 The two stereoisomers of 1-bromo-4-methylcyclohexane.



4.54 The four stereoisomers of 1-bromo-2-methylcyclohexane.



In contrast, *1-bromo-2-methylcyclohexane* has two chiral C's and four stereoisomers. [graphic 4.54] You can do a stereochemical analysis of these stereoisomers in a way that is completely analogous to that we have illustrated for 1-bromo-3-methylcyclohexane.

Drawings of Cyclic Stereoisomers (4.5B)

There are several ways to draw cyclic stereoisomers.

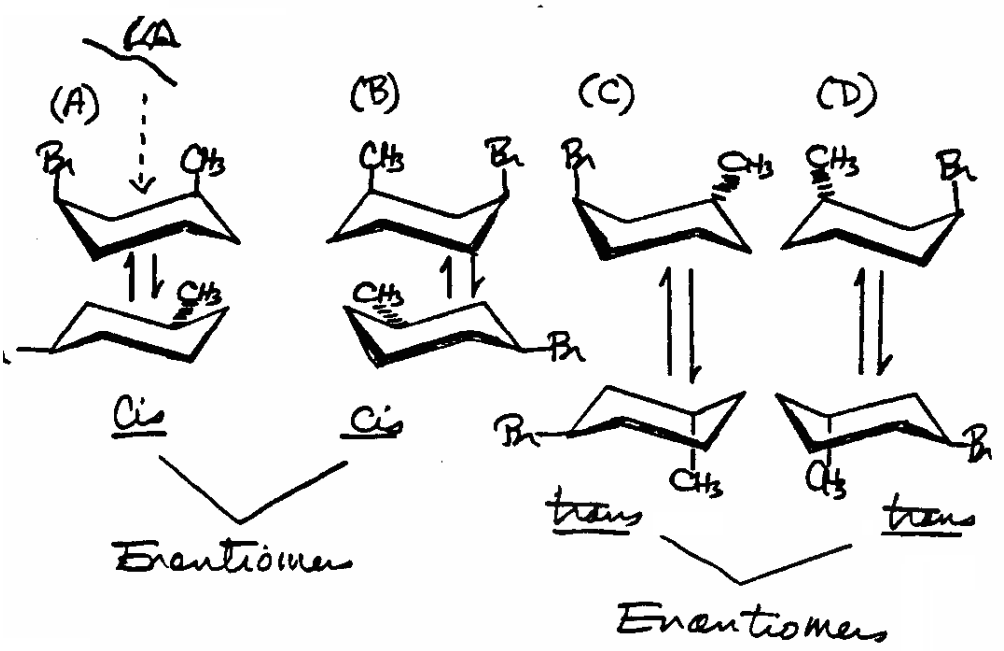
Wedge-Bond Structures. Wedge-bond drawings (Figures [graphic 4.49] and [graphic 4.50]) are the easiest way to depict stereoisomers of cyclic systems. They are simple to draw and we can use them to depict rings of any size as we illustrated in Chapter 2. However, wedge-bond structures do not show 3-dimensional aspects of these stereoisomers.

Chair Forms. Chair forms are the most accurate way to depict the 3-D structures of cyclohexane stereoisomers (Figure [graphic 4.55]). [graphic 4.55] Each wedge-bond structure in Figure [graphic 4.50] corresponds to the view we "see" when we look at the top of each chair form (A) through (D) in Figure [graphic 4.55]. The chair forms remind us that each stereoisomer is an equilibrium mixture of two conformations. This is no different than the situation for acyclic systems, since every acyclic stereoisomer that we have seen is a mixture of different conformations.

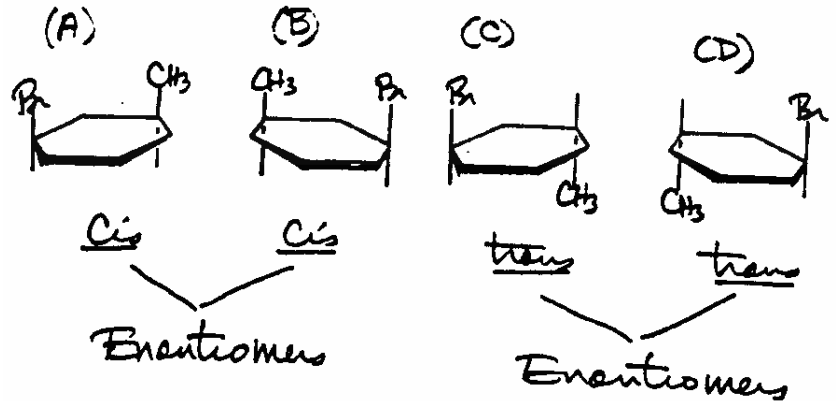
Haworth Projections. Organic chemists sometimes depict stereoisomers of cyclic systems with **Haworth projections** such as those we show for 1-bromo-3-methylcyclohexane in Figure [graphic 4.56]. [graphic 4.56] *Haworth projections* of rings are flat, so they clearly show the *cis* or *trans* relationships between groups on a ring. They also have the advantage that they can be used for rings of any size.

You can see that the *Haworth projections* of (A) and (B) in Figure [graphic 4.56] look very much like the top two *chair conformations* of (A) and (B) in Figure [graphic 4.55] if we flatten the rings in the chair forms. It's harder to see that the Haworth projections for (C) and (D) arise by flattening the rings of the chair conformations of (C) and (D). However you can see this clearly if you make a molecular model of chair (C) or (D) and then carefully flatten its ring. We will use *Haworth projections* to depict sugar molecules (carbohydrates) (Chapter 20) that often have six-membered rings such as that we show for the sugar *α-D-glucose* in Figure [graphic 4.57]. [graphic 4.57]

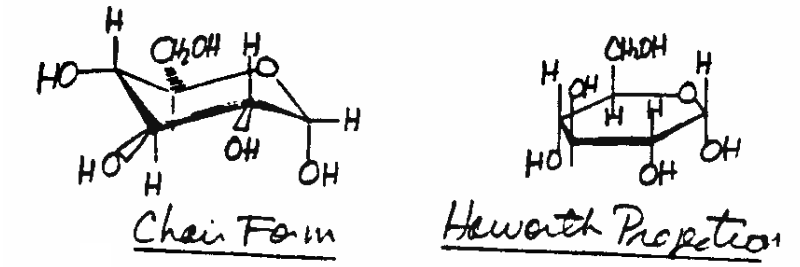
4.55 Chair forms of the four stereoisomers of 1-bromo-3-methylcyclohexane.



4.56 Haworth projections of the four stereoisomers of 1-bromo-3-methylcyclohexane.



4.57 Chair form and Haworth projection of α-D-glucose.



4.6 Optical Activity

Stereoisomers with non-superimposable mirror images are **optically active**. *Optically active* compounds in solution or in the form of pure liquids rotate **plane polarized light**. Organic chemists use *optical activity* to identify stereoisomers, to assess their purity, and to relate stereoisomers to each other.

Rotation of Plane Polarized Light and the Polarimeter (4.6A)

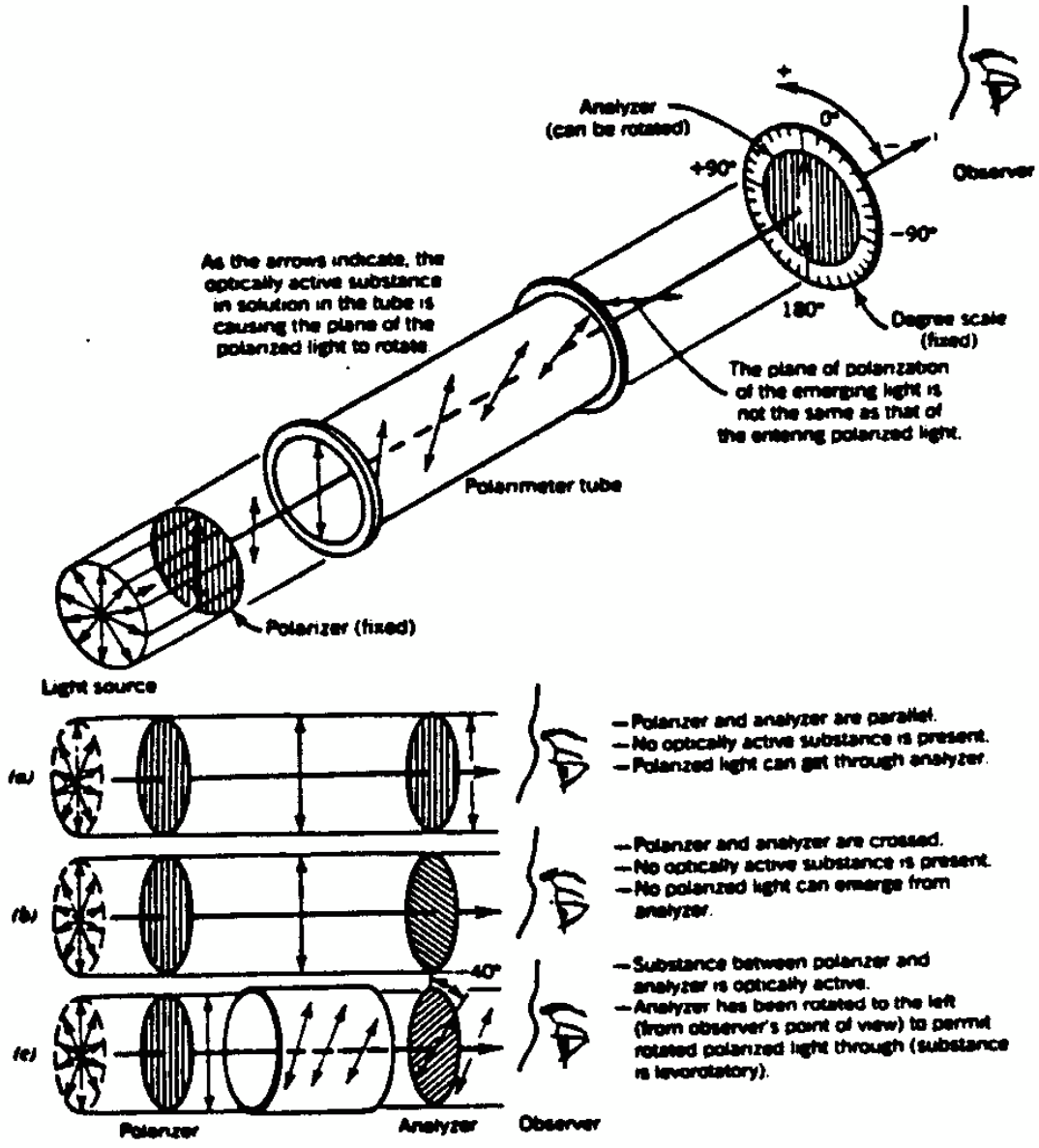
Organic chemists use **polarimeters** to measure *optical activity*.

Polarimeter. We illustrate the general features of a *polarimeter*, and the rotation of *plane polarized light* by an *optically active* compound in the *polarimeter*, in the schematic drawing in Figure [graphic 4.58]. [graphic 4.58] The beam of light from the **light source** oscillates in an infinite series of planes that intersect each other like the intersecting arrows at the center of the *light source* . The **polarizer** allows light in only one of these planes to pass through it, so we say that the light (represented by the single arrow on the right side of the *polarizer*) is *plane polarized*.

Light Rotation by the Sample. As *plane polarized light* passes through the *polarimeter tube* containing the solution or liquid sample of the optically active compound, the compound rotates the plane of the light. We illustrate this with the sequence of tilting arrows in the polarimeter tube. The **analyzer** measures the amount of the rotation and displays it as a **positive (+)** or **negative (-)** rotation between 0° and 180° compared to the plane of the light before it encounters the optically active sample. Chemists use the *(+)* or *(-)* sign of the observed rotation as part of the name of the stereoisomer. For example, (+)-2-bromobutane is the name of the stereoisomer of 2-bromobutane that rotates light in the (+) direction.

> ***Some Cautionary Words***. You may see references to (+) light rotations as "*clockwise*" rotations and (-) rotations as "*counterclockwise*" rotations. However when used to describe light rotation, *clockwise* and *counterclockwise* have no connection with their use in *R* and *S* assignments. In addition, although you can assign *R* or *S* configurations using rules we have presented, you usually cannot predict direction or magnitude of light rotation by an optically active molecule just from its structure. Both the *direction* and *magnitude* of light rotation by an optically compound are physical properties of a compound like its boiling point or melting point.

4.58 Diagram of a polarimeter showing rotation of plane polarized light by an optically active compound.



From Mayo, D. W., Pike, R. M., Trumper, P. K.

Microscale Organic Laboratory, *3rd ed., Wiley: New York, 1994*

Magnitude and Sign of Light Rotation (4.6B)

The number of degrees (°) that an optically active compound rotates light depends on several factors.

Observed versus Specific Rotation. We use the symbol α for the *observed* rotation of plane polarized light that we measure in the polarimeter. α depends on the *wavelength* of the light, any *solvent* that we use, the *temperature* of the sample, the *concentration* of the stereoisomer in a solvent (or the *density* of a pure liquid), and the *length* of the *polarimeter tube* (the **cell** length). The **specific rotation [α]** for the optically active compound is independent of the concentration (or density) of the compound and the *cell pathlength* and we can calculate it from the *observed rotation* α using equation (1)[next page].

$$[\alpha] = \alpha/(c \times l) \qquad (1)$$

α is the observed rotation in degrees (°)

c is the concentration (g/mL) of the chiral compound (or its density (g/mL) if a pure liquid)

l is the pathlength of the cell (decimeters, dm)(1 dm =10 cm)

Chemists usually measure α values at *room temperature* (*20* to *25°C*) using a specific wavelength of light from a **sodium vapor lamp** called the **sodium D line**. It is customary to specify the solvent, temperature, wavelength of light, and concentration when reporting a value of [α]. For example, if you calculated a *specific rotation* of -37° from an *observed rotation* measured at a temperature of 23°C using the sodium D line and a solution of 0.03 g of the compound in 1.00 mL of $CHCl_3$, you should write it as: *$[\alpha]^{23}_D$ = -37° (c, 0.03 in $CHCl_3$)*.

Specific Rotations of Enantiomers. While we cannot predict the actual value of a *specific rotation [α]* for an optically active compound, we do know that the *specific rotation* values for a stereoisomer and its *enantiomer* must have exactly the *same magnitude* with*opposite signs* since the two enantiomers are mirror images. For this reason, chemists historically describe one enantiomer of a pair of enantiomers as the (+) enantiomer and the other as the (-) enantiomer.

Relative and Absolute Configurations. Since the two members of an enantiomeric pair are mirror images, each chiral center in one enantiomer must have a configuration opposite to that of the corresponding chiral center in the other enantiomer. The corresponding chiral centers in the two enantiomers have **opposite relative configurations**.

When we know whether the configuration of a chiral center is *R* or *S* in a stereoisomer for which we also know the sign of its *specific* (or *observed*) rotation, then we know the **absolute configuration** of that center. If we know *absolute configurations* for chiral centers in one stereoisomer, then we know them for the corresponding centers in its enantiomer since they have *opposite relative configurations* at each chiral center. We discuss determination of *absolute configurations* in Appendix C at the end of this chapter.

Specific Rotations of Diastereomers. We can predict the specific rotation [α] of a stereoisomer if we know [α] for its *enantiomer*, but this information usually does not allow us to predict [α] values for its *diastereomers*. *Meso* forms are an exception since they are not optically active. The plane of symmetry of the *meso* form not only causes the *meso* form to be superimposable on its mirror image, but makes its optical rotation 0°. You can imagine that the two mirror image parts of the *meso* form (see Figure [graphic 4.29]) rotate light in equal and opposite directions so that they cancel each other giving a net rotation of 0° for the whole molecule.

d and l Isomers. Chemists have historically referred to (+)-enantiomers as ***d-enantiomers***, and (-)-enantiomers as ***l-enantiomers***. These lower case letters *d* and *l* are derived from the Latin words *dextro* meaning "right" and *levo* meaning "left" and refer to the direction that the stereoisomer rotates plane polarized light. We will refer to optically active stereoisomers exclusively by the designations (+) and (-), however you will encounter *d* and *l* in older books and literature and chemists still use these terms. (In order to have the meaning that we have just described, *d* and *l* must be lower case letters. We will learn in a later Chapter that the upper case letters (capital letters) **D** and **L** have completely different meanings!

> ***Optical Isomers***. Historically, chemists have also referred to *enantiomers* as **optical isomers** because they rotate light in equal but opposite directions. However, this term is confusing because chemists sometimes also use it to describe *diastereomers* of each other. For this reason, authorities in stereochemistry recommend against the use of the term *optical isomer*. Nonetheless, you will encounter it in textbooks and literature, and it continues to be used informally by chemists in their conversations.

Racemic Mixture. Chemists refer to an equimolar mixture of the two enantiomers of an enantiomeric pair as a ***racemic mixture*** or ***racemate*** and often label them as such by placing (±) or "*d,l*" in front of their chemical names. *Racemic mixtures* show no light rotation in a polarimeter. Since the two enantiomers in the *racemic mixture* rotate light in equal and

opposite directions, and are present in the same concentrations in the *racemic mixture*, the net rotation of the mixture as observed in a polarimeter is 0°.

Appendix A: Resolution of Stereoisomers

Chemists often wish to **resolve** (isolate) individual stereoisomers of a compound. One reason is because molecules of biological importance are often single stereoisomers as we describe in the *Feature* at the end of this chapter. **Resolution** of stereoisomers can be more difficult than separation of unrelated organic compounds since most separation methods depend on differences in boiling points, or solubilities in solvents of the components of a mixture. These differences are small or non-existent for stereoisomers because they have the same mass, functional groups, and chemical structures except for configurations at chiral centers.

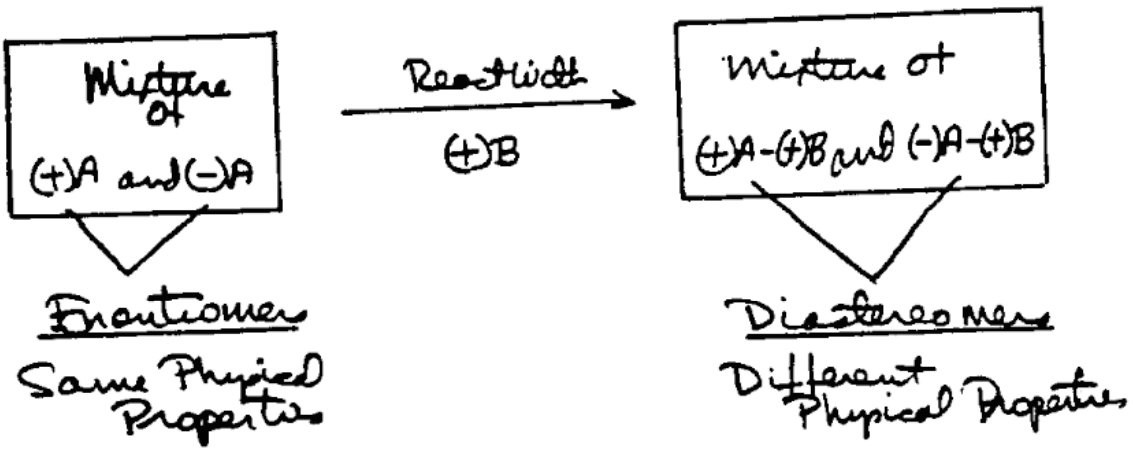
Resolution of Diastereomers. When there is a difference in physical properties between two diastereomers, it is conceivable that they can be separated by **fractional crystallization**, **fractional distillation**, or various types of **chromatography**. *Fractional crystallization* makes use of differences in solubilities of compounds in solvents to aid in their separation while *fractional distillation* uses differences in the boiling points of compounds for the same purpose.

Chromatography is a general term for a number of different techniques used to separate mixtures of compounds. All *chromatographic methods* involve passing a mixture of compounds through a column containing a **stationary phase** that interacts differentially with individual compounds or stereoisomers in the mixture leading to its separation into individual components that can be individually isolated.

Resolution of Enantiomers. Individual *enantiomers* of an enantiomeric pair have identical physical properties, so they cannot be *resolved* by *fractional crystallization* or *fractional distillation*. However, if we chemically convert each *enantiomer* into a new compound with an additional chiral atom of the same configuration, the pair of *enantiomers* becomes a pair of *diastereomers* with different physical properties. We illustrate this schematically in Figure [graphic 4.59] and describe it in more detail below. [graphic 4.59]

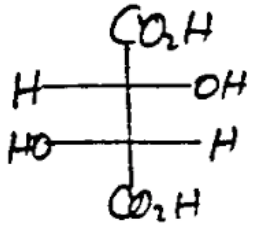
(+)A and *(-)A* are enantiomers of each other so each has identical physical properties (b.p., m.p., *etc.*) except for the direction that they rotate plane polarized light. However, if we react each of them with the same stereoisomeric reagent *(+)B* and the chiral centers in *A* and *B* are not changed, the reaction products are the *diastereomers (+)A-(+)B* and *(-)A-(+)B* with

4.59 Schematic diagram showing a resolution of (+)A and (-)A.

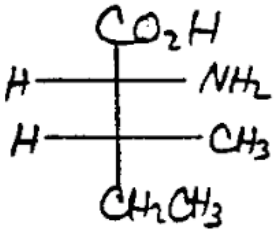


4.60 Fischer projections of (+)tartaric acid and (-)isoleucine.

(+)-tartaric acid (R, R)

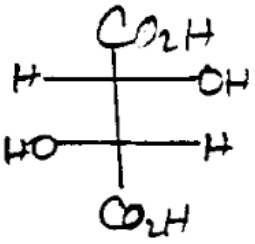


(-)-isoleucine (R, R)

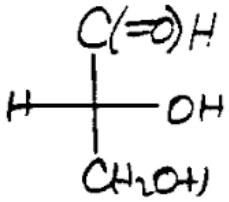


4.61 Fischer projections of (+)tartaric acid and (+)glyceraldehyde.

(+) tartaric acid



(+)-glyceraldehyde



different physical properties. If these different properties allow us to separate (+)A-(+)B from (-)A-(+)B, we can theoretically obtain separate samples of pure (+)A and pure (-)A after we remove the (+)B groups.

Alternatively, we might separate a pair of enantiomers by chromatography using some specific chiral stereoisomer as the stationary phase in the chromatography column. Enantiomers have identical properties in an achiral environment, but we would expect two enantiomers to interact differently with a single stereoisomer in a chromatography column since they will appear as different compounds to the single stereoisomer in the stationary phase.

Some Reported Physical Properties for Stereoisomers. We compare in Table 4.3 some experimentally determined physical properties reported in the chemical literature for stereoisomers of several different compounds.

Table 4.3. Physical Properties of Some Stereoisomers.

Compound	Relationship	$[\alpha]_D$	m.p.(°C)
2,3-butanediol			
(2R,3R)	enantiomeric	-13.0°	19.7
(2S,3S)	pair	+12.4°	25
meso form	diastereomer	(0°)	34.4
3-amino-2-butanol			
(2R,3R)	enantiomeric	-15.84°	15-16
(2S,3S)	pair	+15.69°	7-11
(2R,3S)	enantiomeric	+0.80°	49
(2S,3R)	pair	Data not available	
bromochlorofluoromethane			
(+)	enantiomeric	+0.20°	
(-)	pair	-0.13°	
1,2-cyclohexanediol			
(1R,2R), *trans*	enantiomeric	-46.5°	113-4
(1S,2S), *trans*	pair	+36.7°	108-9
meso form, *cis*	diastereomer	(0°)	98
1,2-cyclohexanediamine			
(1R,2R), *trans*	enantiomeric	-36°	
(1S,2S), *trans*	pair	+34°	
meso form, *cis*	diastereomer	(0°)	

The enantiomers in the enantiomeric pairs should have values of $[\alpha]_D$ with equal magnitudes and opposite signs, but the experimental values are not identical. This probably means that each enantiomer is not absolutely pure, and it may also reflect experimental error in their measurement.

Nonetheless, you can see that the data for each enantiomer in a pair are very similar. The (2*R*,3*R*) and (2*S*,3*S*) enantiomers of *3-amino-2-butanol* have $[\alpha]_D$ values that are close to each other, but significantly different from that of their (2*R*,3*S*) diastereomer. In addition, the m.p.'s of (2*R*,3*R*) and (2*S*,3*S*) are similar, but very different than that of the (2*R*,3*S*) diastereomer. You can also see that m.p.'s of *meso* forms differ more from those of the members of enantiomeric pairs than do the m.p.'s of the individual enantiomers from each other.

Appendix B: Optical Purity

When *specific rotations* of individual enantiomers of an enantiomeric pair do not have the same magnitude (eg. see Table 4.3) when calculated from α values measured under identical conditions, one or both enantiomers may be impure. While the impurity may be a diastereomer or some other compound, if repeated purification does not lead to the same *specific rotation* for each enantiomer the impurity is probably the other enantiomer.

%Optical Purity. Two enantiomers of an enantiomeric pair always have equal but opposite rotations, so contamination by the other enantiomer always leads to an observed rotation that is smaller than that of the pure enantiomer. As a result, you can expect that as the purity of an enantiomer increases, so will the magnitude of its apparent *specific rotation*. We describe the purity of a stereoisomer contaminated with its enantiomer as **%Optical Purity** define it using equations (2) or (3).

$$\%\text{Optical Purity} = ([\alpha]_{expt}/[\alpha]_o) \times 100 \qquad (2)$$

$$\%\text{Optical Purity} = |\%(+) - \%(-)|$$
$$= \%\text{Enantiomeric Excess} = \%\text{ ee} \qquad (3)$$

Equation (2) states that the **%Optical Purity** of a sample contaminated by its enantiomer is proportional to the experimentally determined specific rotation ($[\alpha]_{expt}$) divided by the true specific rotation ($[\alpha]_o$). If a sample of an enantiomer has an $[\alpha]_{expt}$ value of +36.7° while ($[\alpha]_o$) is +46.5°, the *%Optical Purity* is [(36.7)/(46.5)]x100 % or 78.9%.

Since *%Optical Purity* is also equal to the difference in the % of each enantiomer in the sample (*%(+)* and *%(-)* in equation (3)), then the absolute value of the difference $|\%(+) - \%(-)|$ also equals 78.9%. If the sample contains only the two enantiomers, *%(+) - %(-)* must equal 100% so one enantiomer is about 89.4% of the mixture while the other is about 10.6%.

Enantiomeric Excess (%ee). In order to obtain *%Optical Purity* from equation (2), we must know $[\alpha]_o$ and this requires that we have a pure sample of enantiomer. This presents a dilemma since we may not know when we have an absolutely pure enantiomer. Equation (3) provides a solution to this problem since *%Optical Purity* is also equal to the difference in the percentage amounts of the two enantiomers in the mixture (the **%Enantiomeric Excess** or **%ee)** if no other impurities are present.

If we can determine the relative amounts of the two enantiomers (***%ee*)** by a method other than optical activity, then we can calculate *%Optical Purity* from equation (3) and use it in equation (2) along with $[\alpha]_{expt}$ to calculate a value for $[\alpha]_o$. Fortunately, there are instrumental methods widely used today in chemical research that frequently allow us to independently determine %ee values. One of these is **Nuclear Magnetic Resonance** (**NMR**) that we describe in Chapter 5.

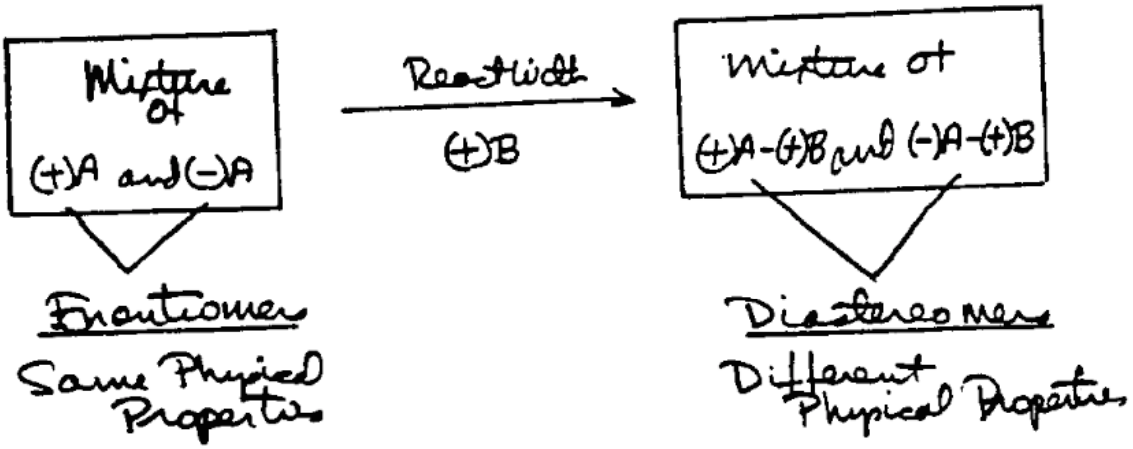
Appendix C: Absolute Configuration

At the beginning of this chapter we saw that *bromochlorofluromethane* (CHBrClF) has two stereoisomers that are its *R* and *S* enantiomers. If you are given each of these enantiomers in a separate unlabelled bottle with no additional information, you would not know which one is *R* and which one is *S* because they have identical properties except for the direction that they rotate plane polarized light.

Because of this difference in light rotation, you can determine which is (+) and which is (-). However without knowing the answer to begin with, you cannot say which is *R* and which is *S* because there is no connection between *R,S* configuration and direction of light rotation. This means that you do <u>not</u> know the *absolute configurations* of these two enantiomers. In order to know the *absolute configuration* of a stereoisomer with a known specific rotation ($[\alpha]$) you must be able to specify the *R* or *S* configuration at each of its chiral centers.

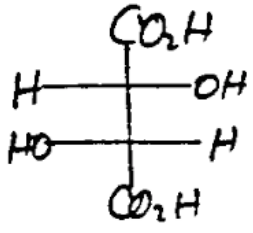
Absolute configurations for chiral centers in compounds were unknown until 1951. In that year a Dutch chemist J. M. Bijvoet (1892-?) reported his use of **X-ray diffraction** to determine that *(+)-tartaric acid* and *(-)-isoleucine* were the (*R,R*) stereoisomers that we show in Figure [graphic 4.60]. [graphic 4.60] These *X-ray diffraction* experiments on *(+)-tartaric acid* and *(-)-isoleucine* also provided *absolute configurations* for chiral centers in other molecules whose *relative configurations* were known with respect to the chiral centers in *(+)-tartaric acid* or *(-)-isoleucine* such as those related to *(+)-tartaric acid* that we show here:

4.59 Schematic diagram showing a resolution of (+)A and (-)A.

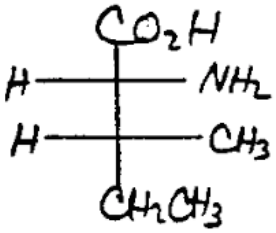


4.60 Fischer projections of (+)tartaric acid and (-)isoleucine.

(+)-tartaric acid (R, R)

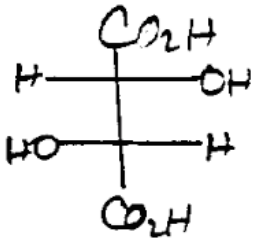


(-)-isoleucine (R, R)

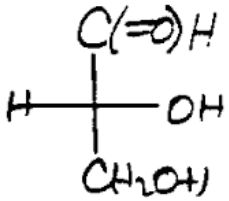


4.61 Fischer projections of (+)tartaric acid and (+)glyceraldehyde.

(+) tartaric acid



(+)-glyceraldehyde



(+)-tartaric acid	HO_2C-C*H(OH)-C*H(OH)-CO_2H
↓	↓
(+)-malic acid	HO_2C-C*H(OH)-CH_2-CO_2H
↓	↓
(+)-isoserine	HO_2C-C*H(OH)-CH_2-NH_2
↓	↓
(-)-glyceric acid	HO_2C-C*H(OH)-CH_2-OH
↑	↑
(+)-glyceraldehyde	H(O=)C-C*H(OH)-CH_2-OH

The configuration at C* is the same in each of these compounds and is not changed by the chemical reactions (indicated by the arrows) that interconvert these compounds. As a result, if C* in (+)-tartaric acid has the configuration shown in Figure [graphic 4.61], then the configuration at C* in (+)-glyceraldehyde is that shown in this same figure. [graphic 4.61] Since Bijovet showed that this Fischer projection for (+)-tartaric acid has the correct absolute configuration at each chiral C, the Fischer projection for (+)-glyceraldehyde also has the correct configuration.

> ***Two Chiral Centers in (+)-Tartaric Acid***. Note that (+)-tartaric acid has two chiral C's while there is only one in (+)-glyceraldehyde. Which chiral C in (+)-tartaric acid becomes the chiral C in (+)-glyceraldehyde? It turns out that it makes no difference since the two chiral C's in (+)-tartaric acid are chemically and configurationally identical (they are both *R*). No matter which C*H(OH)-CO_2H group of tartaric acid becomes CH_2-OH in glyceraldehyde, the stereochemical result for glyceraldehyde is the same.

Long before Bijvoet carried out his experiments, Emil Fischer (1852-1919) arbitrarily assigned the structure in Figure [graphic 4.61] to (+)-glyceraldehyde. [graphic 4.61] He knew that the odds were 50/50 that it was correct, so chemists were pleased when Bijvoet's structure determination of (+)-tartaric acid showed that Fischer's guess was correct.

Chapter Review

Tetrahedral Carbon Configurations. (1) Four different atoms or groups can bond in two different ways to tetrahedral C atoms. (2) These two different *configurations* are non-superimposable mirror images and the C is chiral. (3) Chiral C's can cause molecules containing them to be chiral molecules. (4) Some molecules have structural features causing them to be chiral without chiral atoms.

Stereoisomers and R,S Assignments. (1) ***R*** and ***S*** uniquely identify the two possible configurations at a chiral C. (2) *R,S* assignment rules use priority numbers ("1" through "4") for each atom or group on the chiral C based on the relative atomic numbers of atoms in the groups. (3) Chiral C's with *R* configurations have a *clockwise* progression of priority numbers from "1" to "3" when viewed down the C-"4" bond with "4" in back, while C's with *S* configurations have a *counterclockwise* progression.

The Number and Types of Stereoisomers. (1) Molecules with *n* chiral centers can have up to 2^n stereoisomers. (2) *Enantiomers are* stereoisomers that are non-superimposable mirror images of each other. (3) *Diastereomers* are stereoisomers of the same compound that are not *enantiomers*. (4) A *meso form* is a stereoisomer that has a superimposable mirror image because it has a *plane of symmetry*. (5) Compounds with *meso forms* have fewer than 2^n stereoisomers.

Drawing Structures of Stereoisomers. (1) Solid and dashed wedge-bond drawings are the clearest way to show *R* or *S* configurations at chiral centers. (2) A set of stereoisomers is best drawn starting with one arbitrary conformation for a stereoisomer and interchanging atoms and groups at each chiral center on this conformation to obtain the other stereoisomers. (3) Fischer projections use line bonds to represent wedge-bonds following a set of specific rules. (4) The exchange of any two groups bonded to a single chiral center in a Fischer projection changes the configuration at that chiral center from *R* to *S* (or *S* to *R*).

Cyclic Molecules. (1) Atoms in rings can be chiral, and cyclic molecules with chiral atoms have enantiomers, diastereomers, and meso forms like acyclic molecules. (2) *cis* and *trans* isomers of cyclic molecules are diastereomers of each other. (3) *Haworth projections* of cyclic stereoiomers are useful for comparing configurations at chiral atoms in rings. (4) Conformational changes in rings (*eg*. cyclohexane ring-flipping) do not interconvert stereoisomers nor change configurations at chiral atoms.

Optical Activity. (1) *Chiral molecules* are *optically active* and rotate *plane polarized light*. (2) The magnitude of light rotation **is** measured in degrees (°) using a polarimeter and its sign is **(+)** or **(-)**. (3) $[\alpha] = \alpha/(c \times l)$ where $[\alpha]$ is the *specific rotation*, α is the *observed rotation*, *c* is concentration (or density), and *l* is pathlength. (4) $[\alpha]$ values of pure enantiomers are equal in magnitude but opposite in sign. (5) The *absolute configuration* of a chiral atom is known when it can be assigned as *R* or *S* in a pure stereoisomer. (6) *Relative configurations* of chiral centers in two stereoisomers are known when they can be identified as the same or opposite to each other without knowing which is *R* and *S*. (7) *Meso* forms are *optically inactive* because they possess a plane of symmetry. (8) An equimolar mixture of enantiomers (a *racemate* or a *racemic mixture*) is optically inactive because it contains equal numbers of molecules that rotate light in equal but opposite directions.

What a Difference a Configuration Makes!

The *R,S* configuration at a chiral carbon can have enormous consequences with respect to the biological activity of organic compounds. Frequently, one enantiomer of a pair of enantiomers is biologically active while the other enantiomer is biologically inactive. Sometimes, one enantiomer may actually inhibit the desired function of the other enantiomer. It is also possible that one enantiomer is beneficial while the other enantiomer is hamful to an organism. Examples of these effects of configuration on biological activity are found among amino acids, sugars, sex pheremones, and pharmaceuticals.

Amino Acids and Sugars

The configurations at chiral carbons in amino acids and sugars have dramatic effects on their biological activity. Amino acids, the building blocks of proteins, have the general line-bond structure shown below where the R group has a variety of different structures that we describe in Chapter 22. [graphic 4.62] In all of these amino acids the configuration of the chiral C* must be that shown in the wedge-bond structure (A). [graphic 4.63] The enantiomeric form (B) of each of these amino acids is not incorporated into protein molecules and is therefore not produced by the conversion of protein molecules into their component amino acids.

In a similar way, sugar molecules such as *α-D-glucose* are biologically active and can serve as metabolic energy sources for a variety of organisms including humans. [graphic 4.64]
This is not the case for its enantiomer (*α-L-glucose*) that we and other organisms cannot metabolize. Unlike amino acids that generally have only one chiral center, sugar molecules have several chiral centers. For example α-D-glucose shown above has 5 chiral centers and the configuration at each of these is the mirror image of those in *α-L-glucose*. The importance of all of these chiral centers in determining the characteristics of sugars will be explored in the carbohydrate chapter (Chapter 20). (*D* and *L* designate enantiomers, but we will see in Chapters 20 and 22 that they are defined differently than *d* and *l*).

Sex Pheromones

Pheromones are organic compounds that serve as a means of chemical communication between organisms. Sex pheromones provide a way for a member of one sex of a species to find or attact a member of the opposite sex of the same species. A number of years ago, the compound shown in Figure [graphic 4.65] was isolated from females of the organism *Popillia japonica* (commonly known as *Japanese beetles* because of the country of their origin). [graphic 4.65] Extracts of this compound taken from female beetles were shown to be a powerful attractant to male members of this same species. However, when this compound was synthesized in the laboratory it provided no attraction to the discriminating males of *Popillia japonica*.

Chemists and entomologists (scientists who study insects) determined that the feature responsible for these effects is the chiral carbon C* in the wedge-bond drawings of the two enantiomers of this pheromone shown in Figure [graphic 4.66]. [graphic 4.66] They were able to show that only the *R* enantiomer was a sex attractant.

Of even greater interest was the fact that the presence of the *S* enantiomer actually prevents the *R* enantiomer from serving as an attractant! As a result, a racemic mixture of the *R* and *S* forms is essentially biologically inactive.

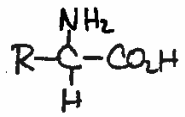
Pharmaceuticals

Pharmaceutical chemists have found that a wide variety of compounds with pharmaceutical properties have one or more chiral atoms. For example the compound *ibuprofen*, which is the active ingredient in such brand name drugs as Advil™, Motrin™, and Nuprin™, has the chemical structure shown here with its chiral carbon designated as C*. [graphic 4.67] It is sold in these preparations as a racemic mixture of the *R* and *S* enantiomers, but only the *S* enantiomer has the desired biological activity. While the *R* enantiomer is biologically inactive, it isomerizes *in vivo* to the biologically active *S* stereoisomer after it is ingested.

While *ibuprofen* appears so far to be a harmless example of the dramatic difference in biological activity of two enantiomers, the case of *thalidomide* is a tragic demonstration of what a difference a configuration can make. [graphic 4.68] This compound with one chiral C* was extensively marketed for a number of years as a sedative, but it was subsequently found to have dreadful side effects on fetal development when taken by women during pregnancy. It is now known that these "teratogenic" side effects are caused by only one of the enantiomers while the other enantiomer possesses only the desired sedative effects for which thalidomide was originally marketed. As a result of these unintended side effects, the drug was removed from the market for a number of years. However as of this writing it has been reintroduced in a carefully controlled manner designed to preclude its use by women who may become pregnant because it has been shown to have significant positive benefits in treatment of conditions for which there are few pharmaceutical options.

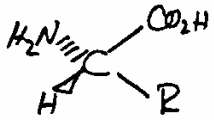
The thalidomide experience served as a major impetus to pharmaceutical companies to take great care in testing drugs with chiral atoms and to avoid racemic mixtures whenever possible. In addition, these companies try to develop pharmaceuticals without chiral atoms wherever possible not only to avoid problems like that described above, but also to reduce costs associated with synthesis of enantiomerically pure compounds and/or large scale resolutions of optical isomers. However because of the chiral character of living systems that we will explore in Chapters 20 ot 23 of this text, it seems certain that many new and effective pharmaceuticals will continue to have chiral atoms.

4.62 General Structure of An Amino Acid



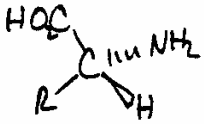
4.63

Amino Acid Enantiomers



(A)

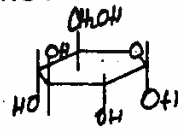
(biologically active)



(B)

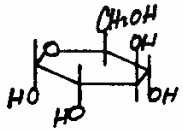
(not biologically active)

4.64



α-D-glucose

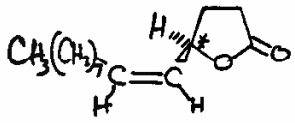
(biologically active)



α-L-glucose

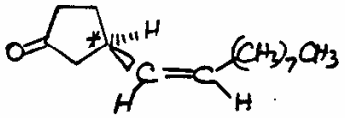
(not biologically active)

4.66 Enantiomers of sex attractant pheromone from Popilla japonica.



(R)-enantiomer

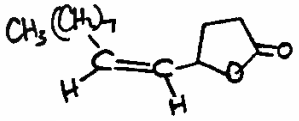
(biologically active attractant)



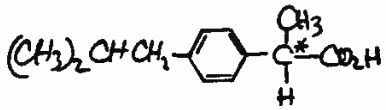
(S)-enantiomer

(inhibitor of the R-enantiomer)

4.65 Sex attractant pheromone from *Popilla japonica*.



4.67 Ibuprofen



4.68 Thalidomide