Organic Chemistry I

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Organic Chemistry, *Structure and Function* **(7th edition)**

By *P. Vollhardt* and *N. Schore*, Elsevier, 2014

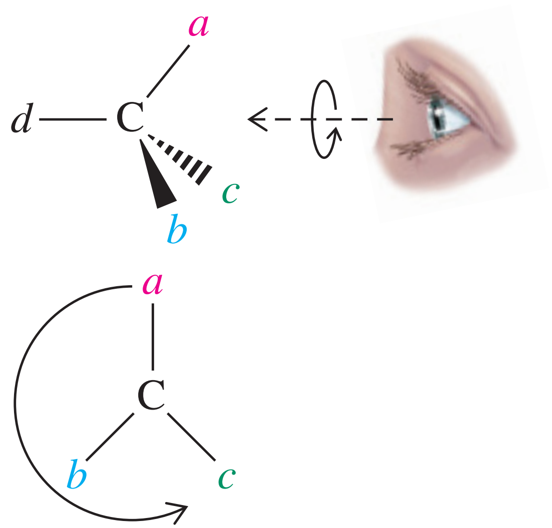
Stereocenters are labeled *R* or *S*

A system was developed by Cahn, Ingold, and Prelog allows us to indicate the handedness in the molecule, a sort of “left-hand” versus “right-hand” nomenclature.

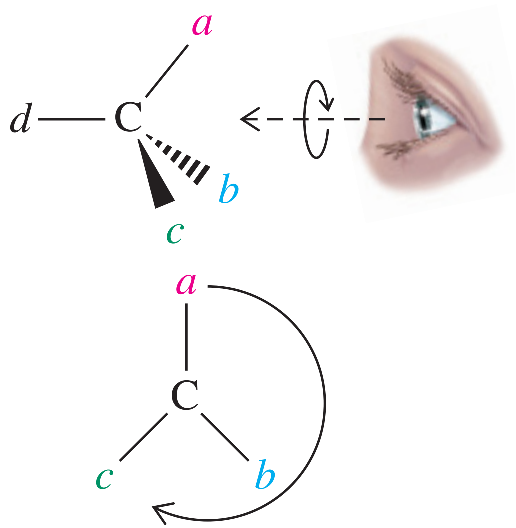
The first step is to rank all four substituents, around an asymmetric carbon atom, in the order of decreasing priority. Substituent *a* has the highest priority, *b* the second highest, *c* the third, and *d* the lowest.

Next, we position the molecule so that the lowest-priority substituent is placed as far away from us as possible. This process results in two possible arrangements of the remaining substituents.

If the progression from *a* to *b* to *c* is counter-clockwise, the configuration at the stereocenter is named ***S*** (*sinister,* Latin, left). Conversely, if the progression is clockwise, the center is ***R*** (*rectus,* Latin, right).



Counterclockwise: *S*



Clockwise: *R*

The symbol *R* or *S* is added as a prefix in parentheses to the name of the chiral compound, as in (*R*)-2-bromobutane and (*S*)-2-bromobutane.

A racemic mixture can be designated *R*,*S*, as in (*R*,*S*)-bromochlorofluoromethane. The sign of the rotation of plane-polarized light may be added if it is known, as in (*S*)-(+)-2-bromobutane and (*R*)-(-)-2-bromobutane.

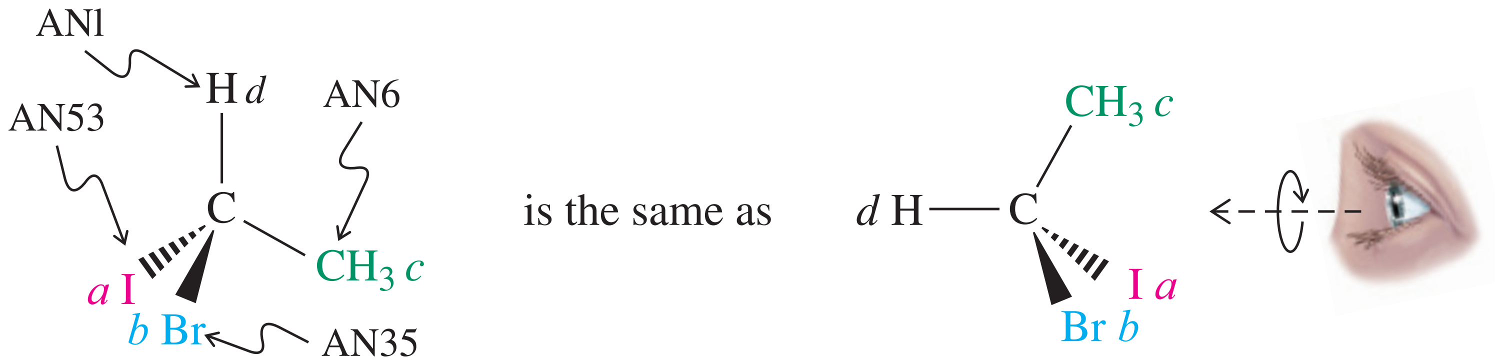
It is important to remember that the symbols *R* and *S* are *not* necessarily correlated with the sign of α.

Sequence rules assign priorities to substituents

Before applying the *R*,*S* nomenclature to a stereocenter, we must first assign priorities by using sequence rules.

Rule 1. We look first at the atoms attached directly to the stereocenter. A substituent atom of higher atomic number takes precedence over one of lower atomic number. Consequently, the substituent of lowest priority is hydrogen.

In regard to isotopes, the atom of higher atomic mass receives higher priority.

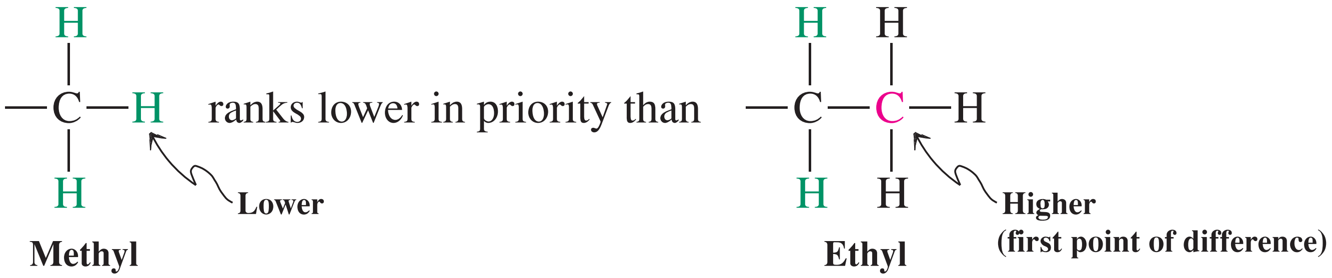


AN = atomic number

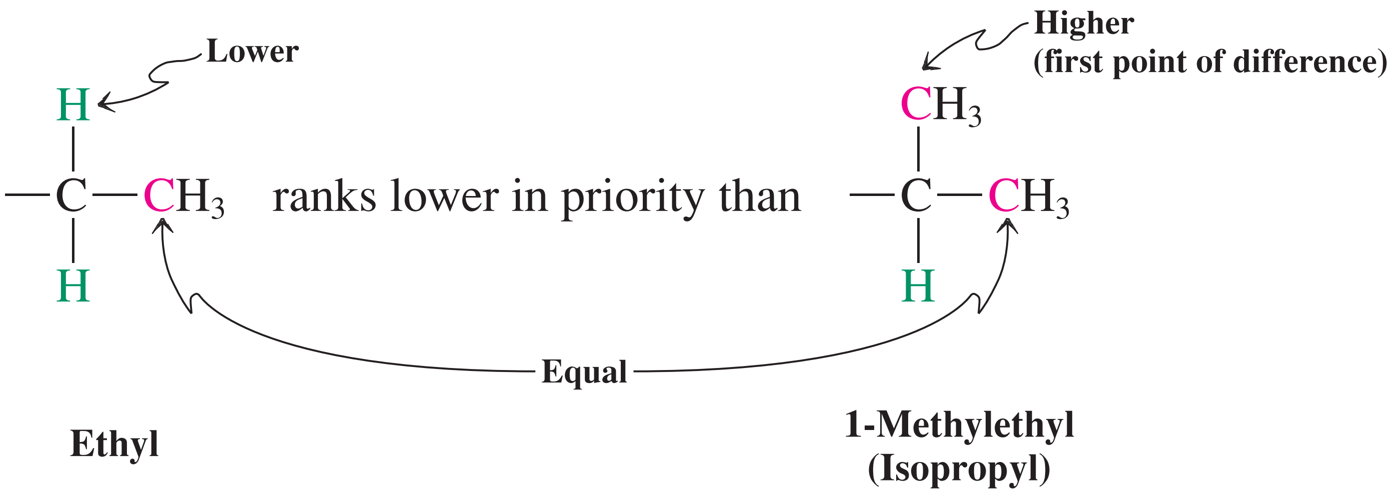
(*R*)-1-Bromo-1-iodoethane

Rule 2. What if two substituents have the same rank when we consider the atoms directly attached to the stereocenter? In such a case, we proceed along the two respective substituent chains until we reach a point of difference.

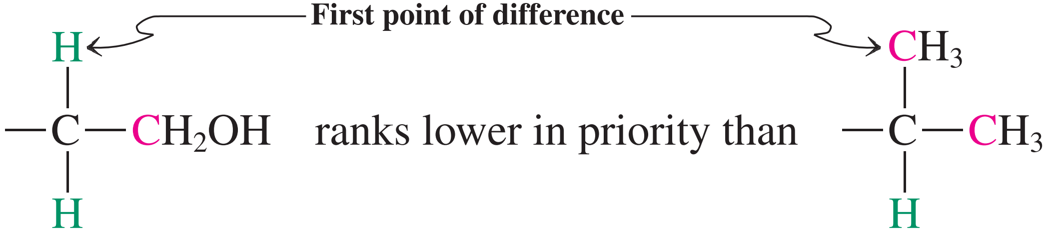
For example, an ethyl substituent takes priority over methyl. At the point of attachment to the stereocenter, each substituent has a carbon nucleus, equal in priority. Farther from that center, methyl has only hydrogen atoms, but ethyl has a carbon atom (higher in priority).



However, 1-methylethyl takes precedence over ethyl because, at the first carbon, ethyl bears only one other carbon substituent, but 1-methylethyl bears two.

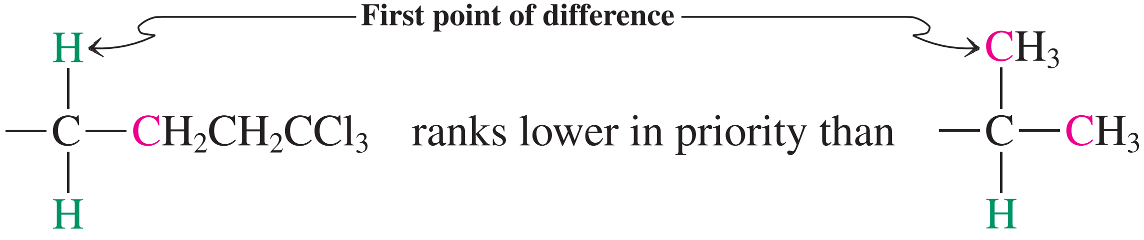


We must remember that the decision on priority is made at the *first* point of difference along otherwise similar substituent chains. When that point has been reached, the constitution of the remainder of the chain is irrelevant.



$-\overset{H}{\underset{H}{C}}-CH_2OH$ ranks lower in priority than $-\overset{CH_3}{\underset{H}{C}}-CH_3$

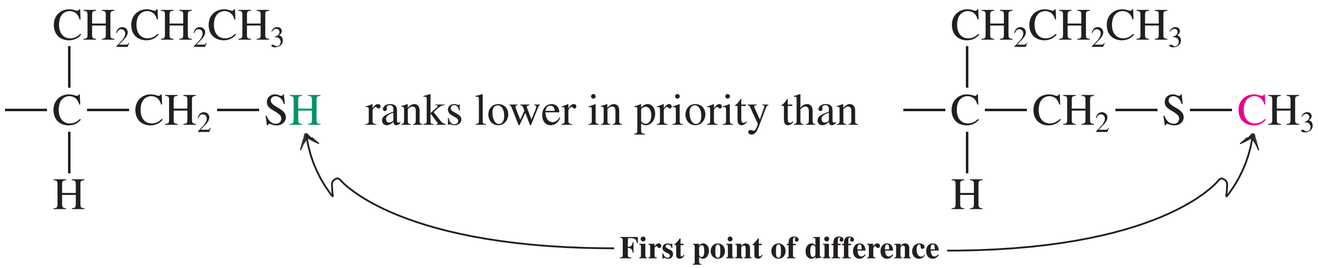
First point of difference



$-\overset{H}{\underset{H}{C}}-CH_2CH_2CCl_3$ ranks lower in priority than $-\overset{CH_3}{\underset{H}{C}}-CH_3$

First point of difference

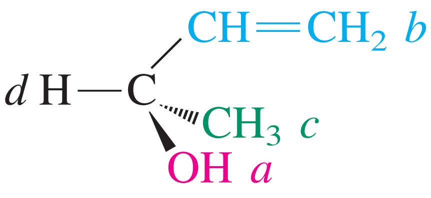
When we reach a point along a substituent chain at which it branches, we choose the branch that is higher in priority. When two substituents have similar branches, we rank the elements in those branches until we reach a point of difference.



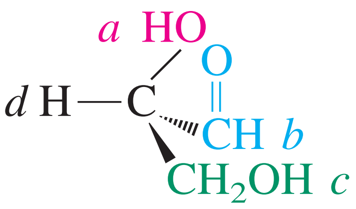
$-\overset{CH_2CH_2CH_3}{\underset{H}{C}}-CH_2-SH$ ranks lower in priority than $-\overset{CH_2CH_2CH_3}{\underset{H}{C}}-CH_2-S-CH_3$

First point of difference

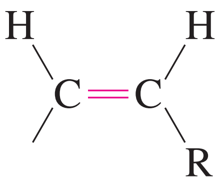
Rule 3. Double and triple bonds are treated as if they were single, and the atoms in them are duplicated or triplicated at each end by the respective atoms at the other end of the multiple bond.



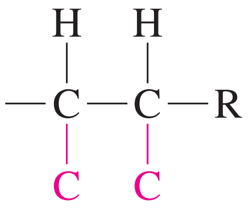
R



R

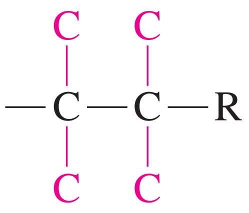


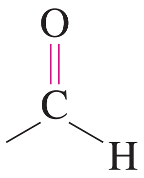
is treated as



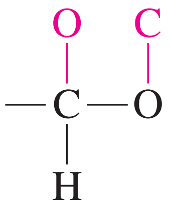
$-C\equiv C-R$

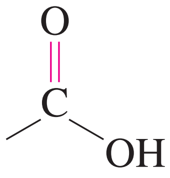
is treated as



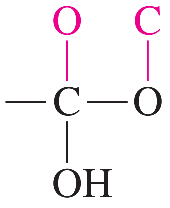


is treated as





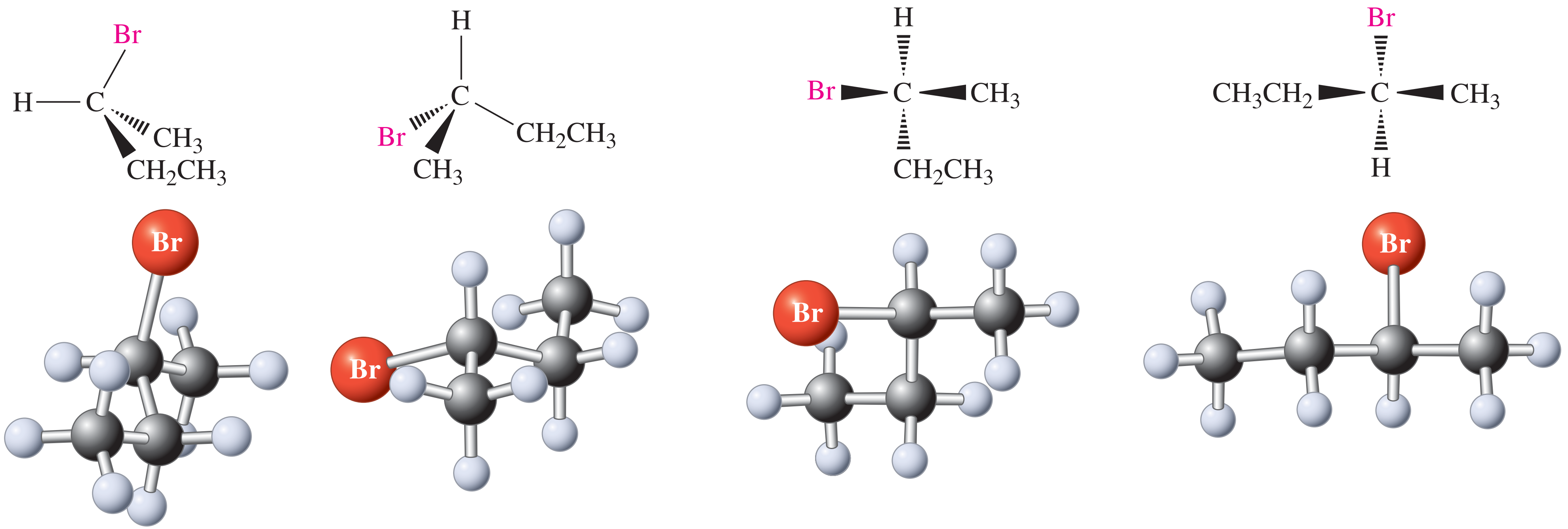
is treated as



To assign correctly the stereostructure of stereoisomers, we must develop a fair amount of three-dimensional “vision,” or “stereo-perception.”

In most of the structures that we have used to illustrate the priority rules, the lowest-priority substituent is located at the left of the carbon center and in the plane of the page, and the remainder of the substituents at the right, the upper-right group also being positioned in this plane.

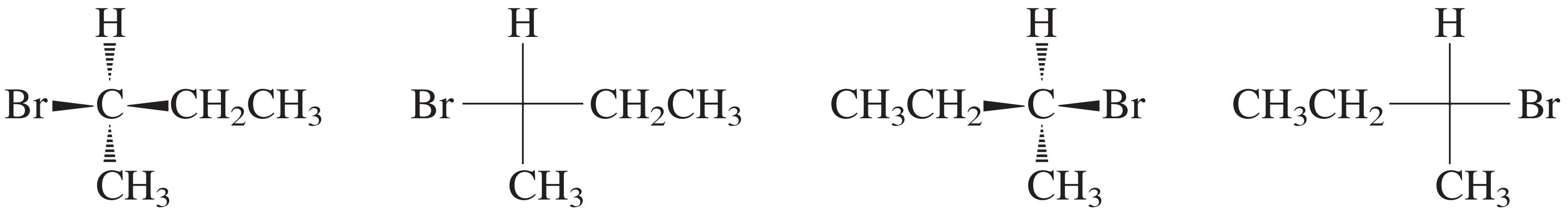
Four (of Many) Ways of Depicting (*S*)-2-Bromobutane



FISCHER PROJECTIONS

A **Fischer projection** is a simplified way of depicting tetrahedral carbon atoms and their substituents in two dimensions. The molecule is drawn in the form of a cross, the central carbon being at the point of intersection. The horizontal lines signify bonds directed *toward* the viewer; the vertical lines are pointing *away*.

Conversion of the Hashed-Wedged Line Structures of 2-Bromobutane into Fischer Projections (of the Stereocenter)



Hashed-wedged line structure — **Fischer projection**

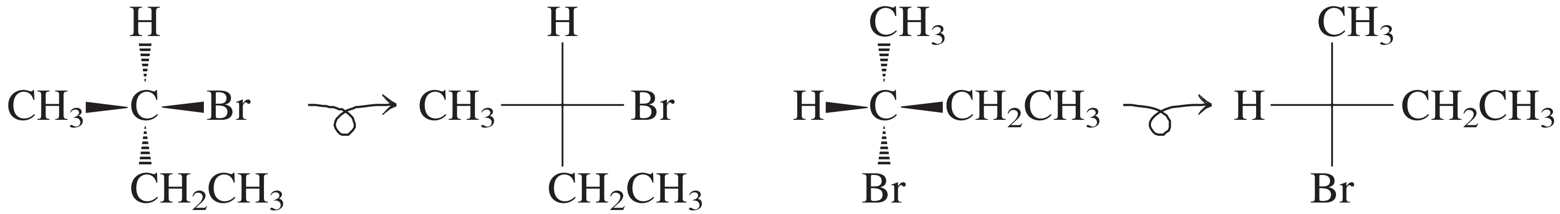
(*R*)-2-Bromobutane

Hashed-wedged line structure — **Fischer projection**

(*S*)-2-Bromobutane

There are several ways of depicting a molecule in the hashed-wedged line notation:

Two Additional Projections of (*R*)-2-Bromobutane



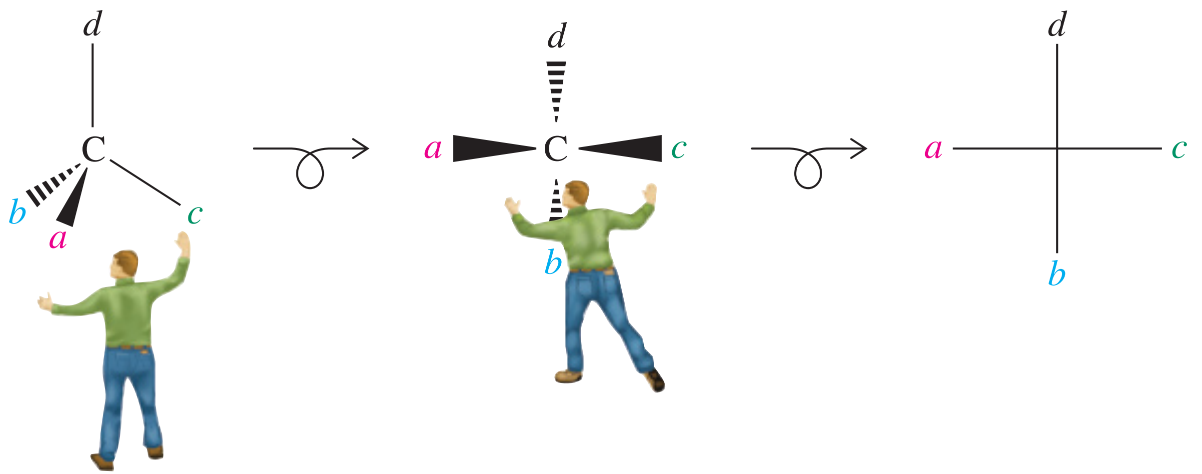
You can change one Fischer projection into another of the same molecule by using certain manipulations: rotations and substituent switches.

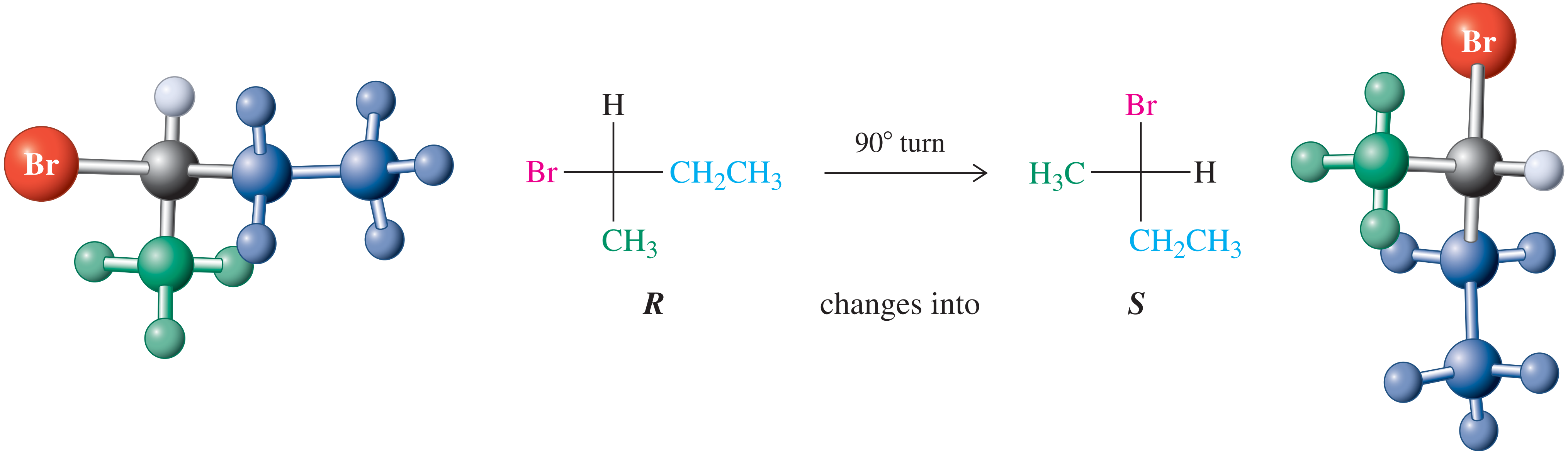
Rotating a Fischer projection may or may not change the absolute configuration

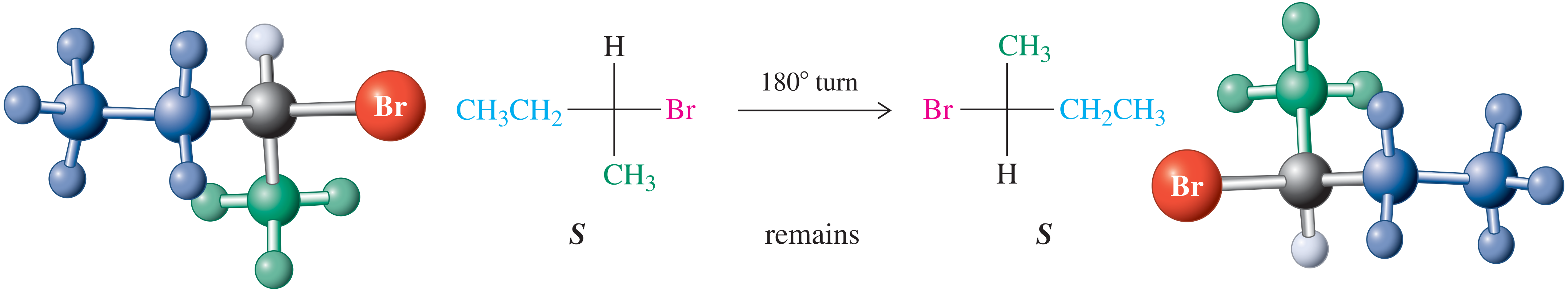
When we rotate a Fischer projection in the plane of the page by 90°, horizontal bonds are pointed above, vertical ones below the plane of the page. This rotation has *switched* the relative spatial disposition of the two sets: The result is a picture of the enantiomer.

Rotation by 180° is fine, because horizontal and vertical lines have not been interchanged: The resulting drawing represents the same enantiomer.

A Simple Mental Exercise:
Conversion of Hashed-Wedged Line Structures into Fischer Projections



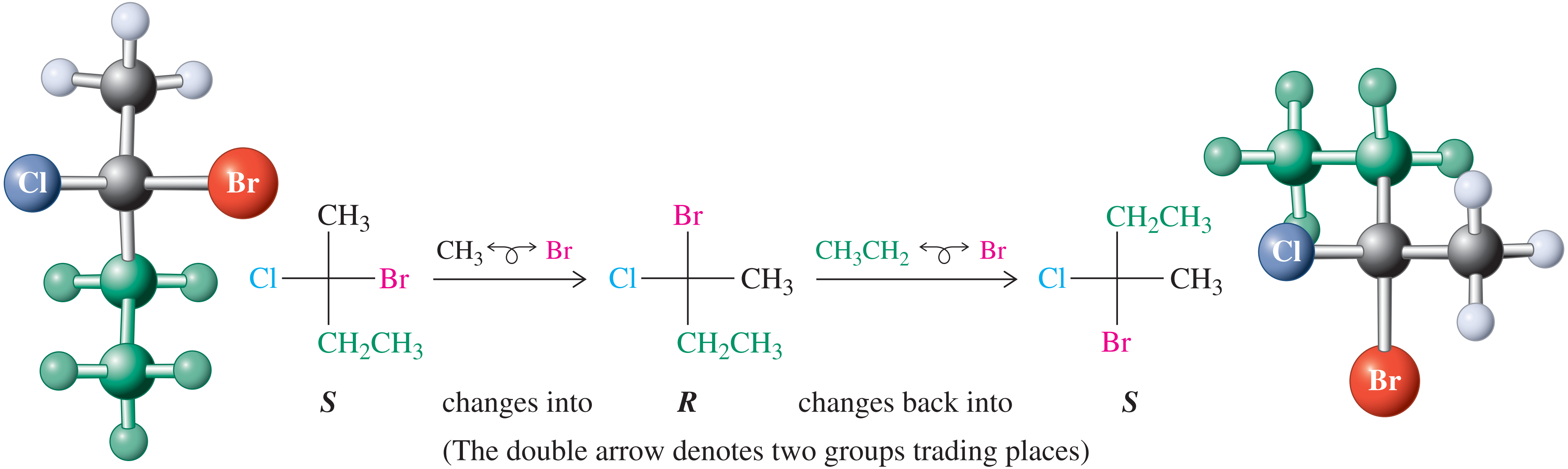

Br
H
Br
CH2CH3
CH3
R
90° turn
changes into
Br
H3C
H
CH2CH3
S
Br


Br
H
CH3CH2
Br
CH3
S
180° turn
remains
CH3
Br
CH2CH3
H
S
Br

Exchanging substituents in a Fischer projection also changes the absolute configuration

Any *single* such exchange turns one enantiomer into its mirror image. Two such exchanges produce the original absolute configuration.

If the conversion of one structure into another takes an even number of exchanges, the structures are identical. If it requires an odd number of such moves, the structures are mirror images of each other.



(The double arrow denotes two groups trading places)

Fischer projections tell us the absolute configuration

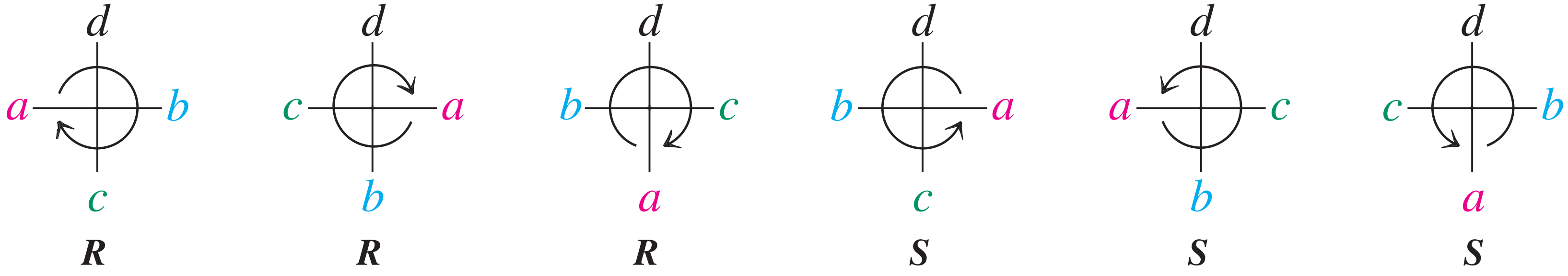
Fischer projections allow us to assign absolute configurations without having to visualize the three-dimensional arrangement of the atoms. For this purpose:

First draw the molecule as any Fischer projection.

Next, we rank all the substituents in accord with the sequence rules.

Finally, if necessary, we place group *d* on top by a double exchange.

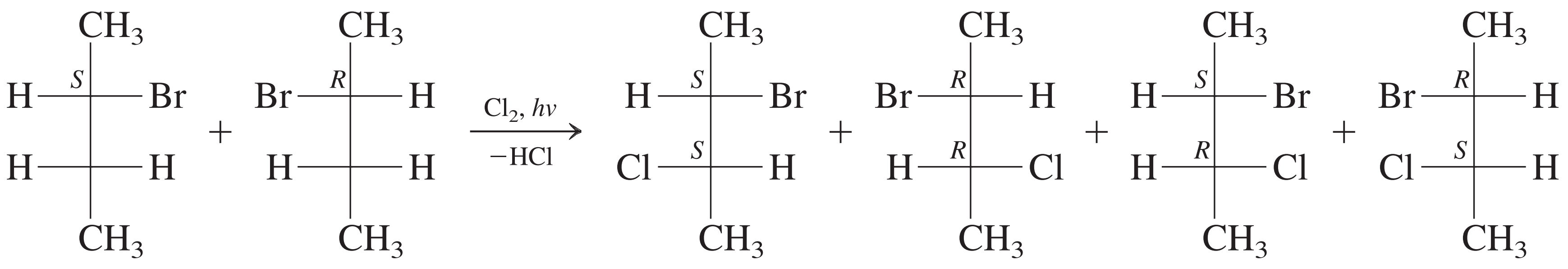
With *d* at the top, the three groups of priority *a*, *b*, and *c* can adopt only two arrangements: either clockwise or counter-clockwise. The first corresponds to the *R*, the second to the *S* configuration.



MOLECULES INCORPORATING SEVERAL STEREOCENTERS: DIASTEREOMERS

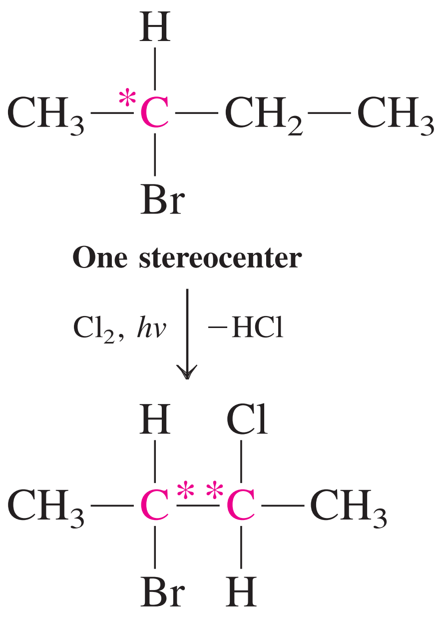
Many molecules contain several stereocenters. Because the configuration about each center can be *R* or *S*, several possible structures emerge, all of which are isomeric.

Two stereocenters can give four stereoisomers: chlorination of 2-bromobutane at C3

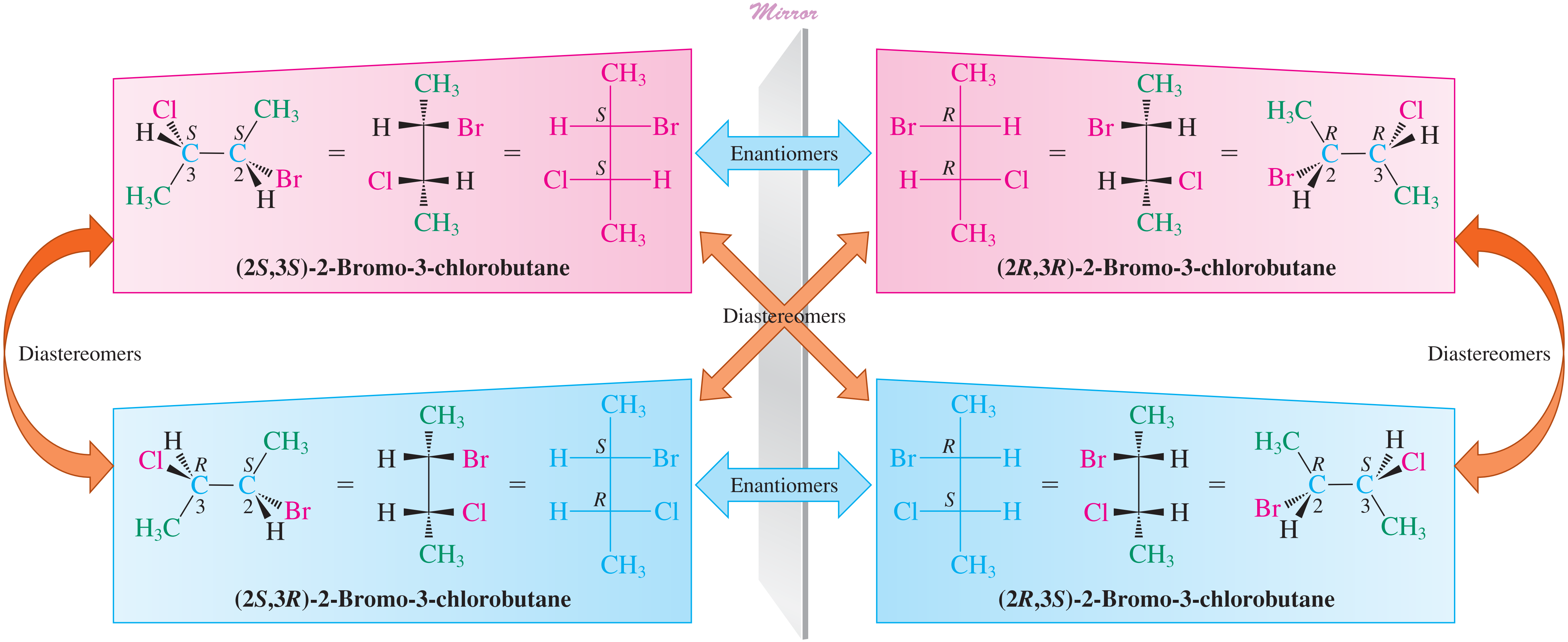


Racemic 3-bromobutane

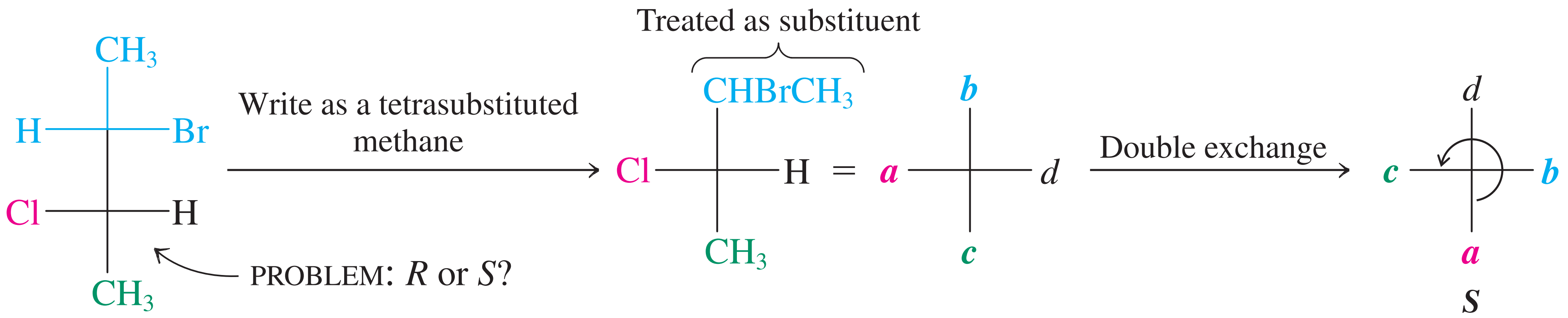
Four stereoisomers of 2-bromo-3-chlorobutane



2-Bromo-3-chlorobutane

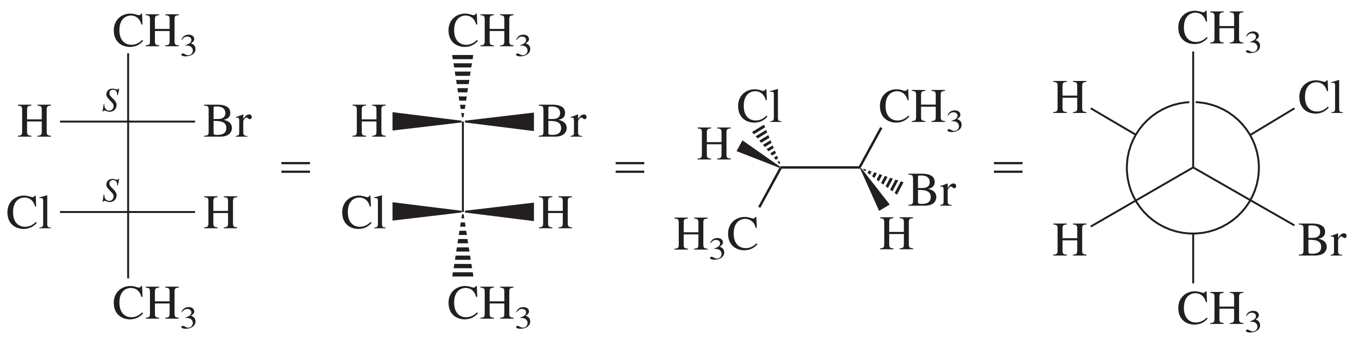


There are two related pairs of compounds: an *R*,*R*/*S*,*S* pair and an *R*,*S*/*S*,*R* pair. The members of each individual pair are mirror images of each other and therefore enantiomers. Conversely, each member of one pair is not a mirror image of either member of the other pair; they are **diastereomers** (*dia,* Greek, across).



Because all horizontal lines in Fischer projections signify bonds directed toward the viewer, the Fischer stencil represents an *eclipsed* conformation and therefore does not depict the molecule in its most stable form, which is *anti.*

(2*S*,3*S*)-2-Bromo-3-chlorobutane: From Eclipsed Fischer Projection to *anti* Conformation



Fischer projection

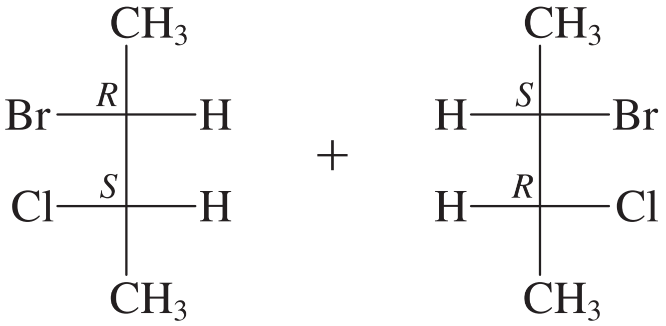
***anti*-Hashed-wedged line structure**

Newman projection

In contrast with enantiomers, diastereomers are molecules with *different physical and chemical properties*. Their steric interactions and energies differ.

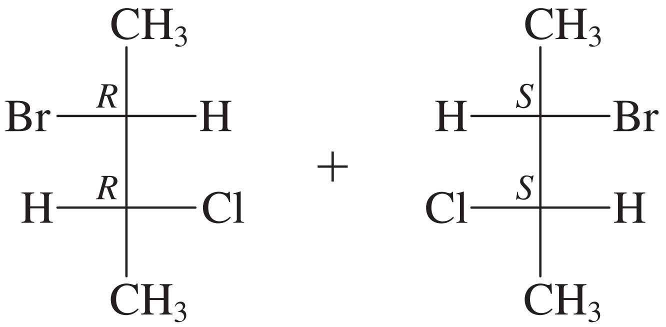
They can be separated by fractional distillation, crystallization, or chromatography. They have different melting and boiling points and different densities.

In addition, they have different specific rotations.



2-Bromo-3-chlorobutane

***R*,*S*/*S*,*R*-Racemate:**
b.p. 31–33°C (at 16 torr)

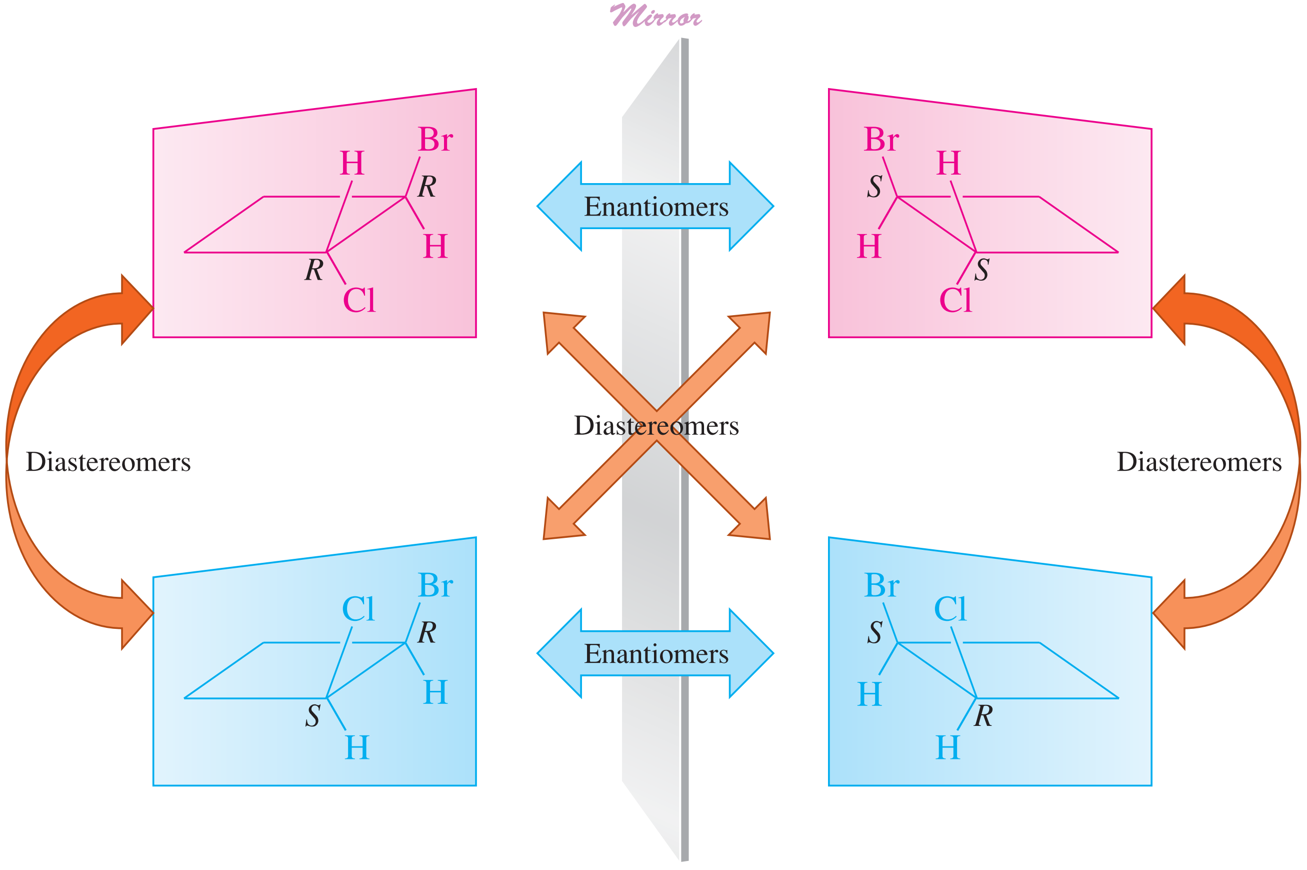


2-Bromo-3-chlorobutane

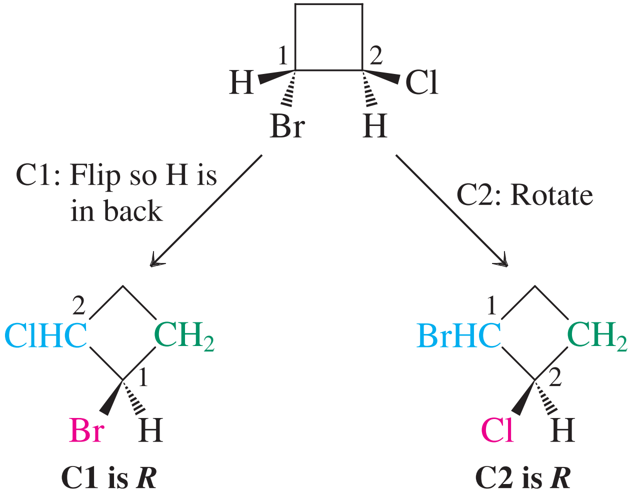
***R*,*R*/*S*,*S*-Racemate:**
b.p. 38–38.5°C (at 16 torr)

Cis and trans isomers are cyclic diastereomers

In 1-bromo-2-chlorocyclobutane, there are four stereoisomers: *R*,*R*, *S*,*S*, *R*,*S*, and *S*,*R*. The stereoisomeric relation of the first pair to the second is easily recognized: One pair has cis stereochemistry, the other trans.



A



C1 is *R*

C2 is *R*

B

More than two stereocenters means still more stereoisomers

For a compound having three stereocenters, a total of eight stereoisomers exists in four enantiomer pairs of diastereomers:

Image	*RRR*	*RRS*	*RSS*	*SRS*
Mirror image	*SSS*	*SSR*	*SRR*	*RSR*

Generally, *a compound with n stereocenters can have a maximum of* 2^n *stereoisomers.*

Powers of 2

n	2^n
0	1
1	2
2	4
3	8
4	16
10	1,024
20	1,048,576
30	1,073,741,824