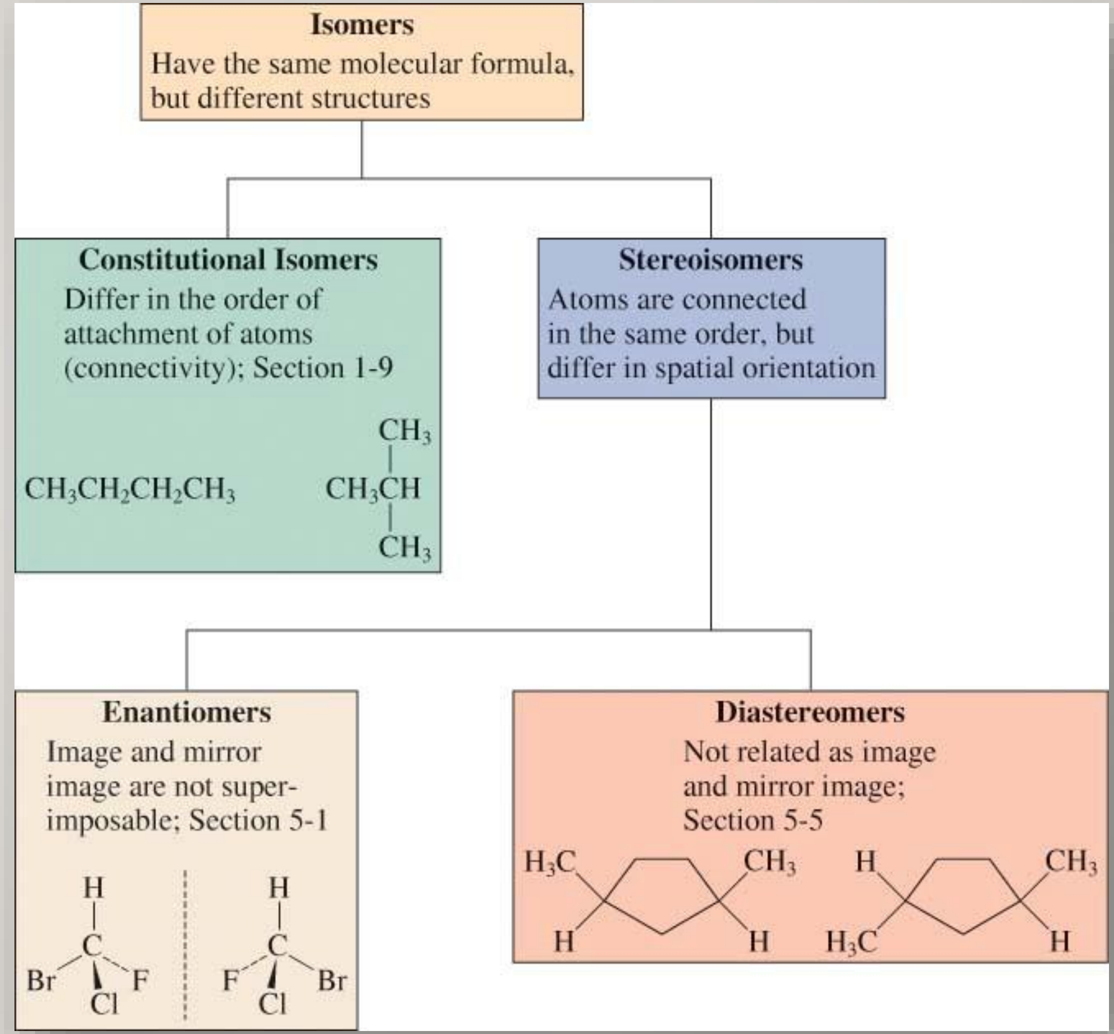
CHM-134 ORGANIC CHEMISTRY
CHAPTER-5: STEREOCHEMISTRY

We have already covered two kinds of isomerism:

- ☐ Constitutional Isomers (structural isomers)
- ☐ Stereoisomers



Isomers
Have the same molecular formula, but different structures

Constitutional Isomers
Differ in the order of attachment of atoms (connectivity); Section 1-9

$CH_3CH_2CH_2CH_3$

$CH_3CH(CH_3)CH_3$

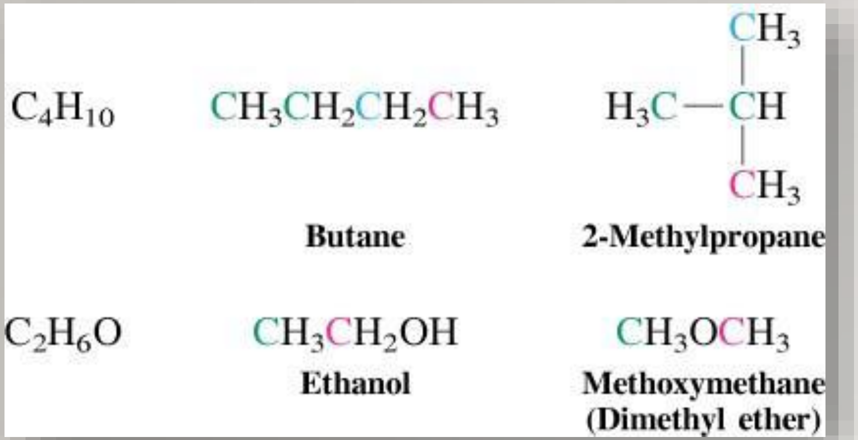
Stereoisomers
Atoms are connected in the same order, but differ in spatial orientation

Enantiomers
Image and mirror image are not superimposable; Section 5-1

Diastereomers
Not related as image and mirror image; Section 5-5

5.1 CONSTITUTIONAL ISOMERISM & STEREOISOMERİSM

Examples of Constitutional Isomers:



C_4H_{10} $CH_3CH_2CH_2CH_3$ **Butane**

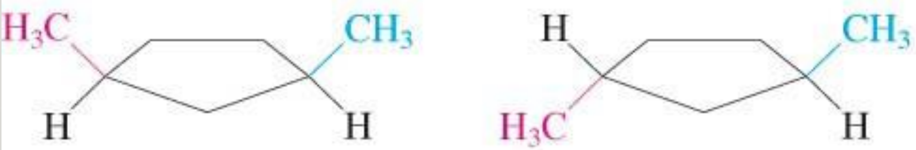
$H_3C-\underset{CH_3}{\overset{CH_3}{CH}}$ **2-Methylpropane**

C_2H_6O CH_3CH_2OH **Ethanol**

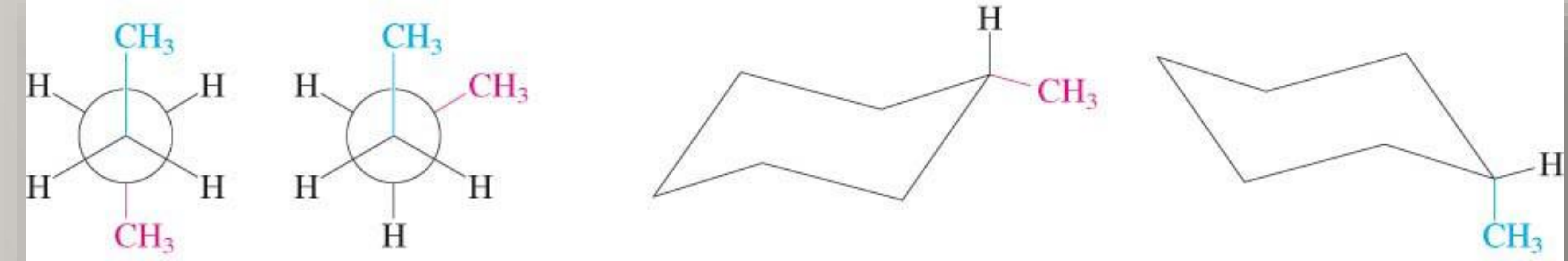
CH_3OCH_3 **Methoxymethane (Dimethyl ether)**

Examples of Stereoisomers:

Stereoisomers



***cis*-1,3-Dimethylcyclopentane** ***trans*-1,3-Dimethylcyclopentane**



***Anti* rotamer of butane**

***Gauche* rotamer of butane**

Equatorial methylcyclohexane

Axial methylcyclohexane

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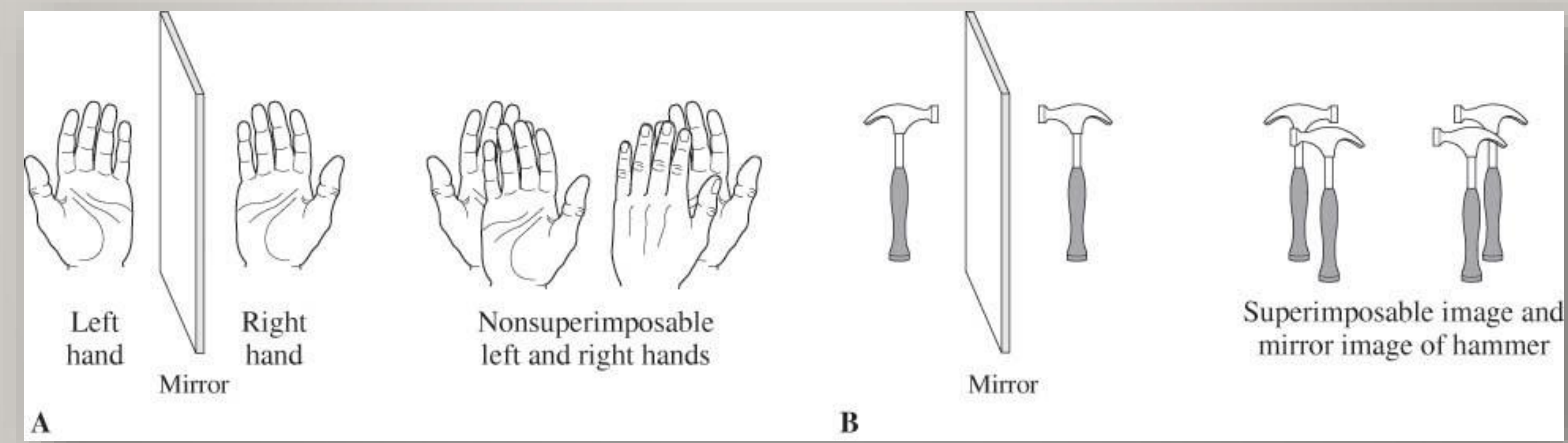
5.1 CONSTITUTIONAL ISOMERISM & STEREOISOMERİSM

Another type of stereoisomerism is called mirror-image stereoisomerism. Mirror-image related stereoisomers are said to be left-handed and right-handed and occur when a molecule and its mirror image are non-superimposable.



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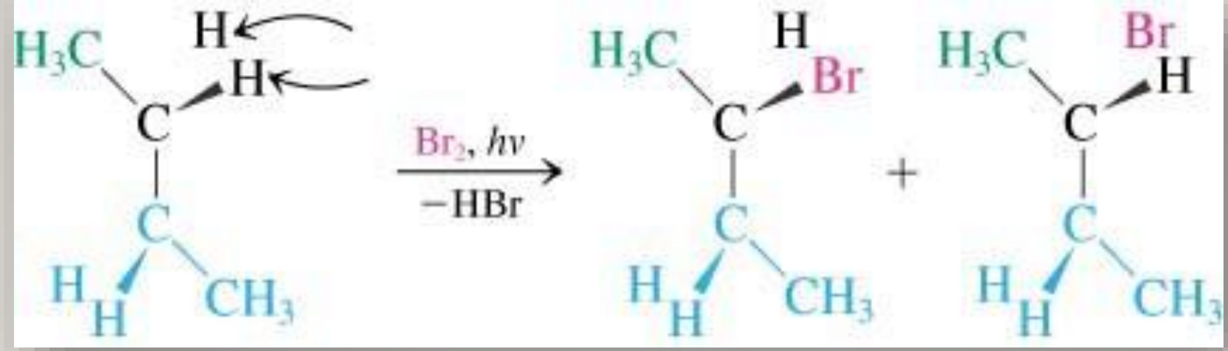
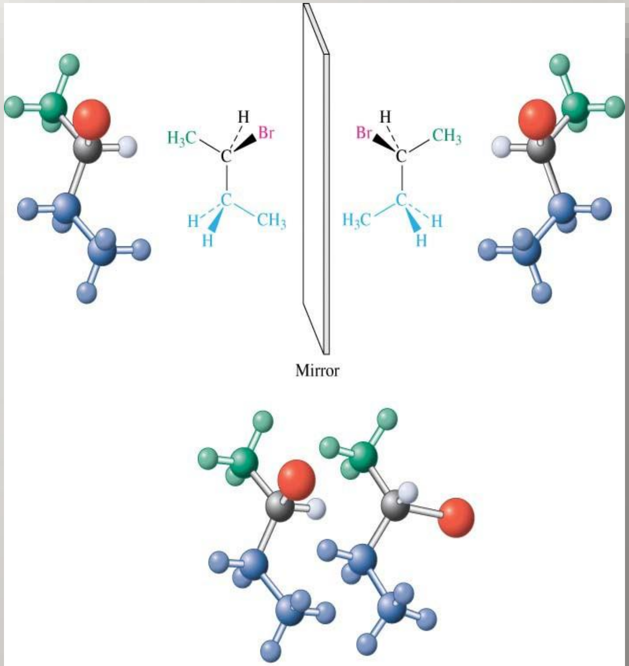
5.2 CHIRAL MOLECULES

The radical bromination of butane to form 2-bromobutane appears to yield a single product:



Chiral molecules cannot be superimposed on their mirror images.



The two enantiomers of 2-bromobutane are nonsuperimposable

The two 2-bromobutane molecules formed by the radical bromination of butane are non-superimposable and are therefore not identical.

A molecule that is not superimposable on its mirror image is said to be chiral.

In this case each isomer is called an enantiomer.

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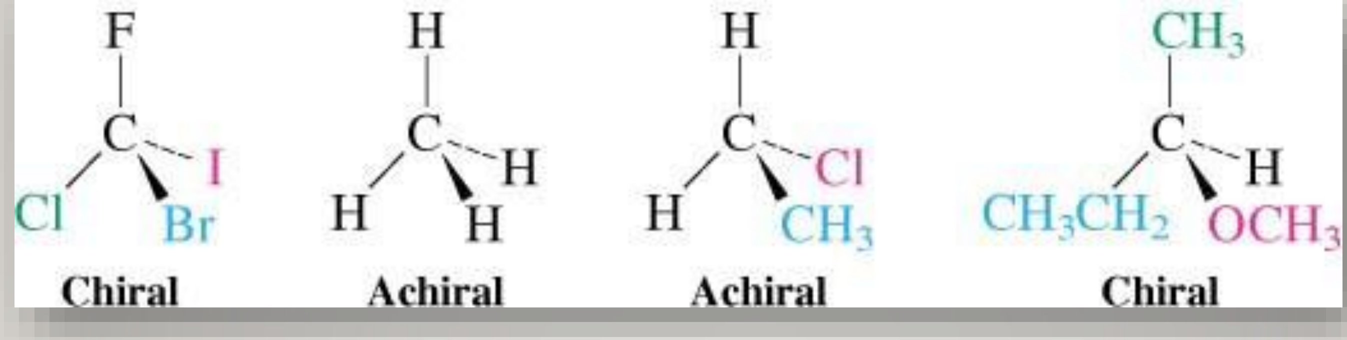
5.2 CHIRAL MOLECULES

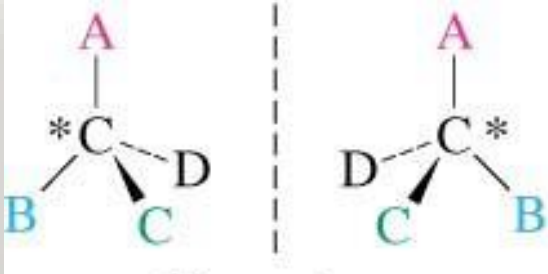
Compounds whose mirror images are superimposable are called achiral.

Examples of chiral and achiral molecules:



Above all, the chiral examples contain an atom that is connected to 4 different substituent groups. This atom is called an asymmetric atom or better as a stereocenter.

Often, asymmetric atoms are marked with an asterisk. Molecules having one stereocenter are always chiral.


Mirror plane

(C* = a stereocenter based on asymmetric carbon)

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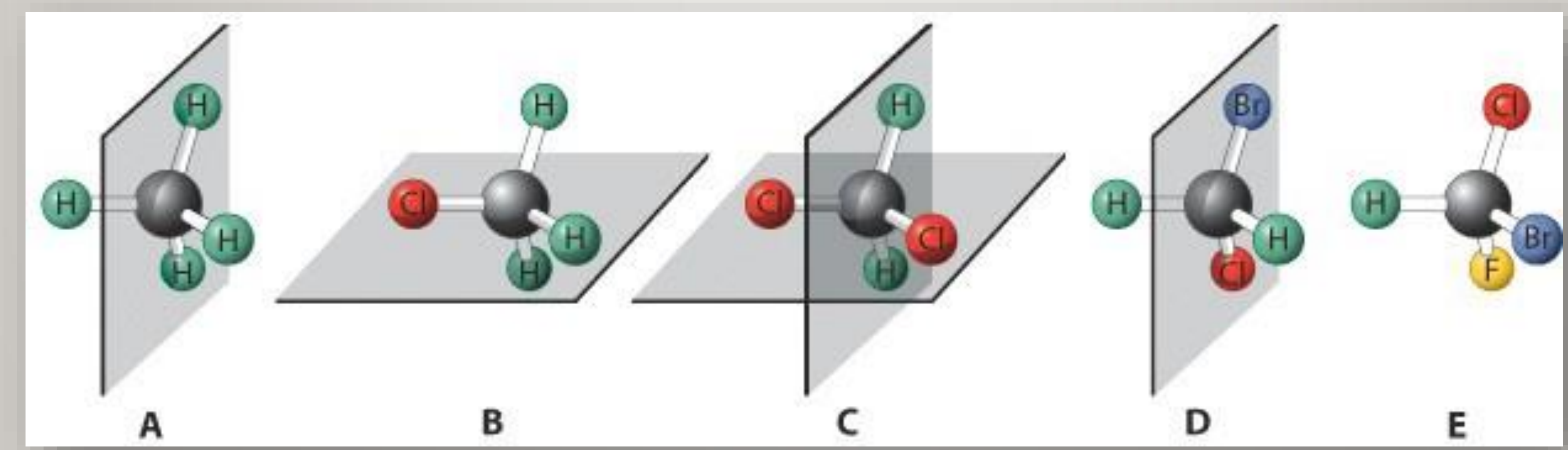
5.2 CHIRAL MOLECULES

The symmetry in molecules helps to distinguish chiral structures from achiral ones.

For most organic molecules, a sufficient test for chirality is absence of a plane of symmetry (mirror plane).

A mirror plane is one that bisects the molecule in such a way that the half of the molecule on one side of the plane is the mirror image of the half on the other side of the plane.

Methane has 6 planes of symmetry, chloromethane has 3, dichloromethane 2, bromochloromethane 1, and bromochlorofluoromethane none:



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5.2 OPTICAL ACTIVITY

- Enantiomers cannot be distinguished on the basis of their physical properties, such as boiling points, melting points, and densities.

- Enantiomers can be distinguished by the way they interact with plane-polarized light.

- When plane-polarized light is passed through a sample of one of the enantiomers, the plane of polarization is rotated either clockwise or counterclockwise. When the experiment is repeated with the other enantiomer, the plane-polarized light is rotated an equal amount, but in the opposite direction.

If facing the light source:

- Clockwise rotation: enantiomer is dextrorotary (+)
- Counterclockwise rotation: enantiomer is levorotary (-)

This interaction with light is called optical activity and enantiomers are often called optical isomers.

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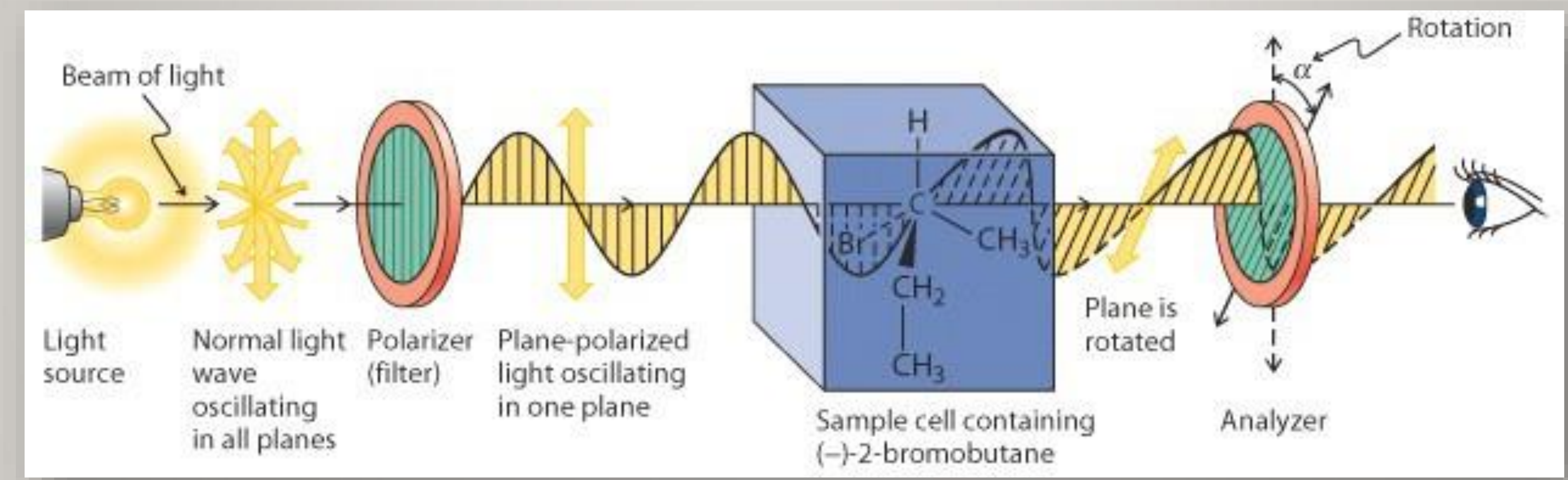
5.2 OPTICAL ACTIVITY

- Optical rotation is measured with a polarimeter.

- Light is electromagnetic radiation that oscillates perpendicular to its direction of motion.
- The oscillation of light can be resolved into two perpendicular components.
- When light is passed through a polarizer, only one of the two perpendicular components of light is passed through. This light is referred to as plane-polarized light.



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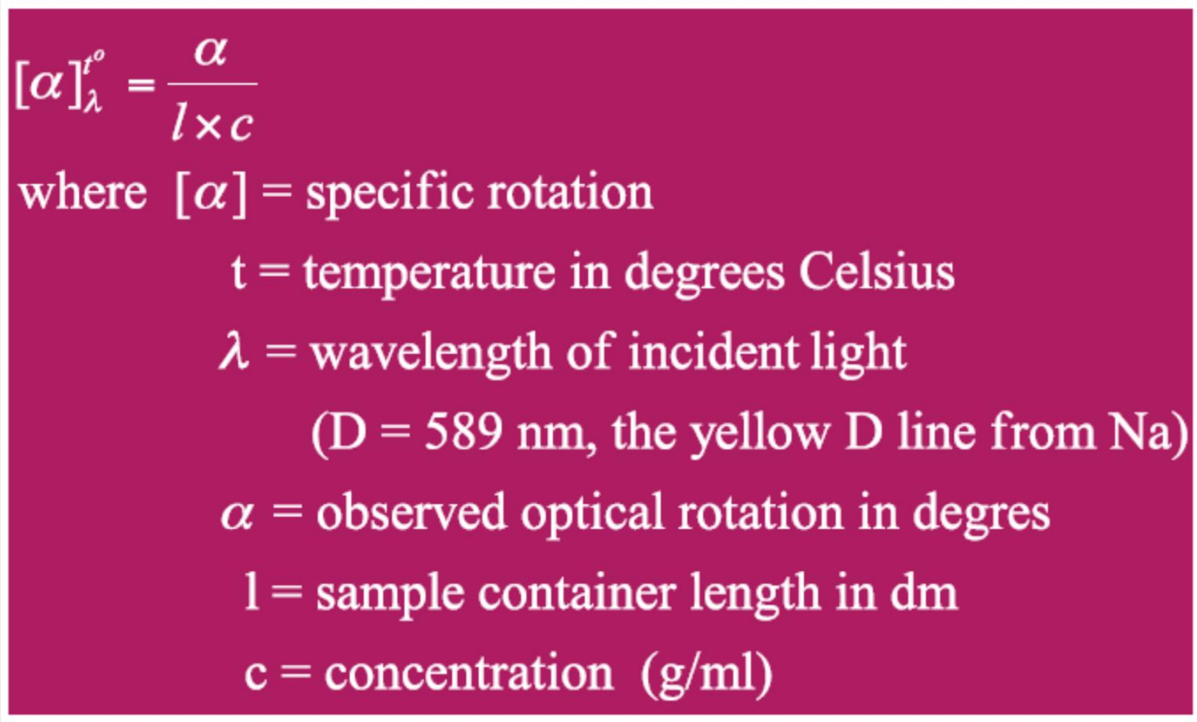
5.2 OPTICAL ACTIVITY

The measured rotation (in degrees) is the observed optical rotation, α, of the sample.

The value of α depends upon:

- Structure of the chiral molecule
- Concentration of the chiral molecule
- Length of the sample cell
- Wavelength of the light
- Solvent used
- Temperature

The specific rotation [α] of a sample is defined for each chiral molecule (the value is solvent dependent):



$$[\alpha]_{\lambda}^{t^{o}} = \frac{\alpha}{l \times c}$$

where $[\alpha]$ = specific rotation

t = temperature in degrees Celsius

λ = wavelength of incident light

(D = 589 nm, the yellow D line from Na)

α = observed optical rotation in degres

l = sample container length in dm

c = concentration (g/ml)

Specific rotation is a physical constant for a substance, as is melting point, boiling point, density, etc.

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5.2 OPTICAL ACTIVITY

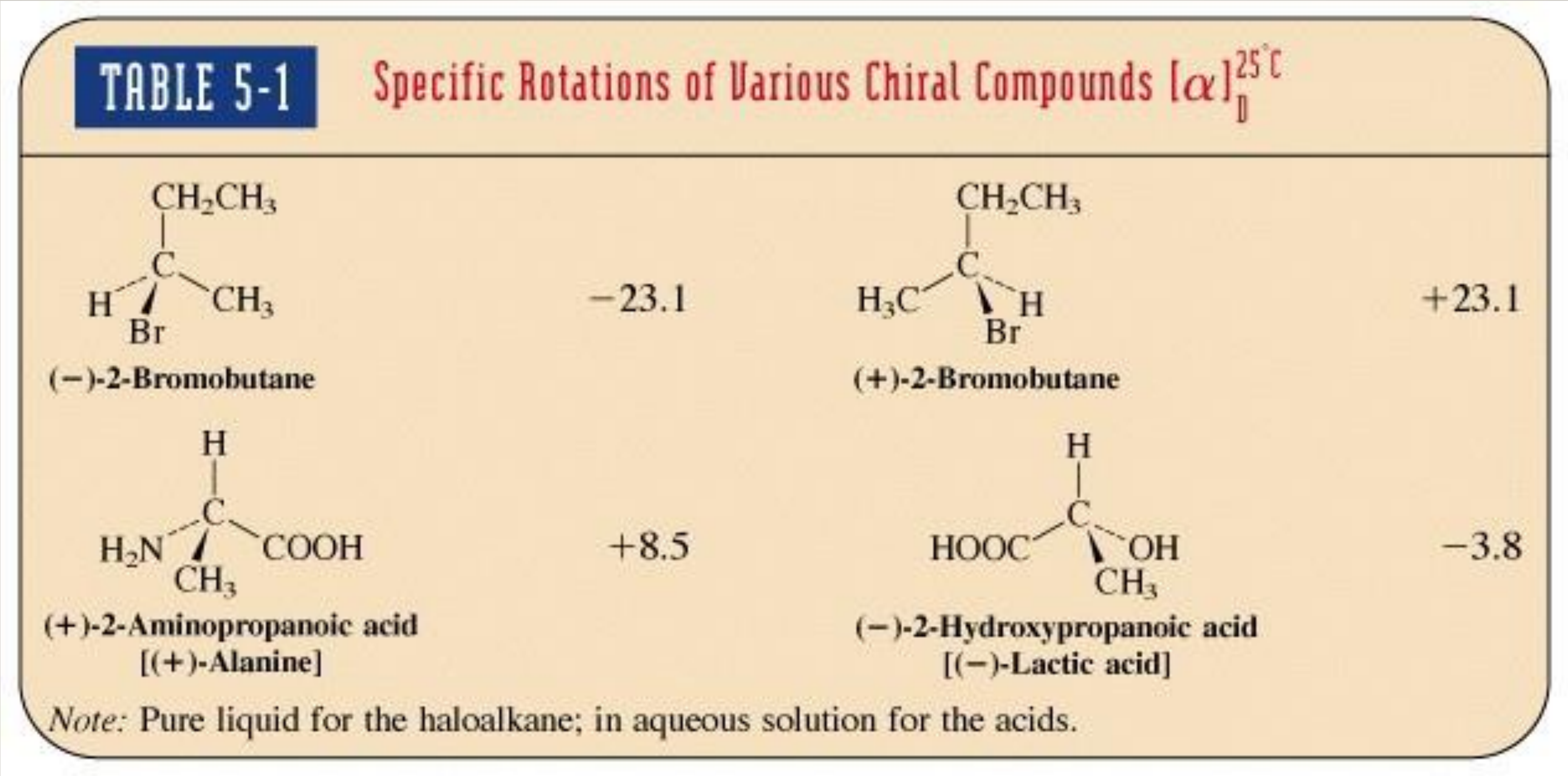

TABLE 5-1 Specific Rotations of Various Chiral Compounds $[\alpha]_{D}^{25^{\circ}C}$

(−)-2-Bromobutane	−23.1	(+)-2-Bromobutane	+23.1
(+)-2-Aminopropanoic acid [(+)-Alanine]	+8.5	(−)-2-Hydroxypropanoic acid [(−)-Lactic acid]	−3.8

Note: Pure liquid for the haloalkane; in aqueous solution for the acids.

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5.2 OPTICAL ACTIVITY

Optical rotation indicates enantiomeric composition

- A racemic mixture is a mixture of equal amounts of the + and – enantiomers of a chiral compound. It shows no net rotation of plane-polarized light.
- When one enantiomer equilibrates with its mirror image, the process is called racemization.
- When one of the two enantiomers of a chiral compound is present in a mixture in excess over the other, there will be a net rotation of plane-polarized light.
- A 50% enantiomer excess would be defined as a mixture of 75% one enantiomer and 25% of the other (50%+ with 25%+ and 25%-). The mixture would be called 50% optically pure.
- The optical purity of an enantiomer is defined:

$$\%\ \text{optical purity} = \left(\frac{[\alpha]_{observed}}{[\alpha]} \times 100 \right) = \text{enantiomer excess}$$

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5.3 R-S SEQUENCE RULES

X-ray diffraction can establish the absolute configuration.

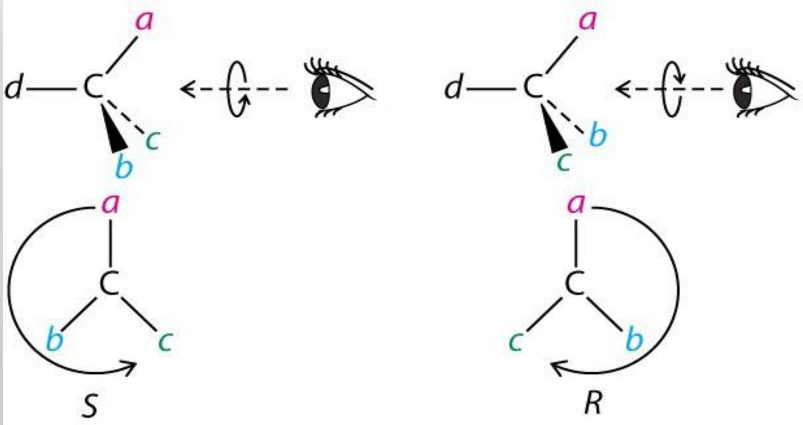
- ✓ The absolute configuration of an enantiomer is the actual spatial arrangement of the substituent groups around the chiral centers.
- ✓ There is no straightforward correlation between the absolute configuration of an enantiomer and the sign of rotation of the molecule.
- ✓ The absolute configuration of an enantiomer can be determined through single crystal X-ray diffraction analysis or through chemical correlation to a molecule whose absolute configuration has already been determined.

Stereocenters are labeled R or S.

The convention for naming enantiomers unambiguously was developed by R.S. Cahn, C. Ingold, and V. Prelog.

The four substituents around the chiral carbon must be first ranked in order of decreasing priority.

- a highest priority
- b second-highest priority
- c third-highest priority
- d lowest priority



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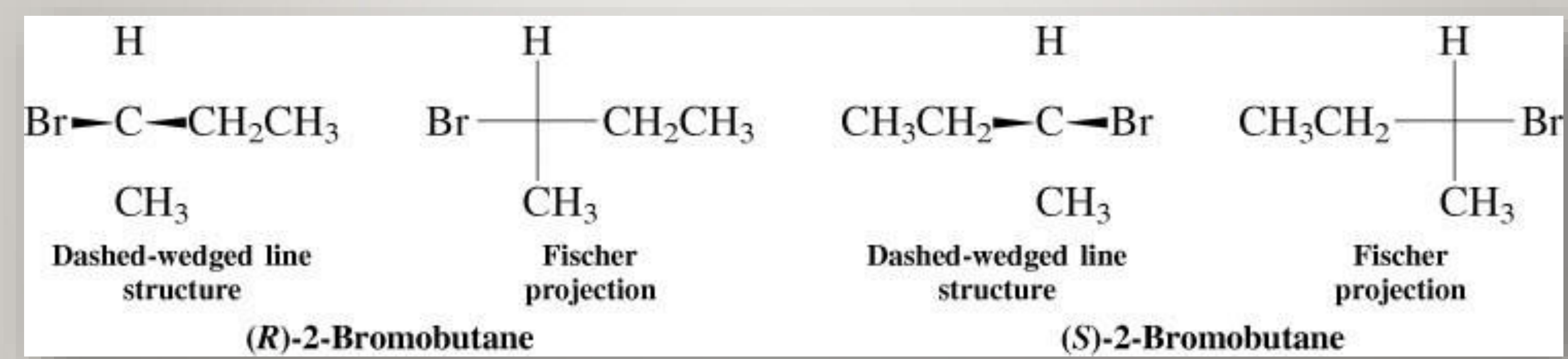
5.4 FISCHER PROJECTIONS

Fischer projection formulas represent 3-D tetrahedral carbon atoms and their substituents in two dimensions.

The molecule is drawn in the form of a cross.

- The tetrahedral carbon is in the plane of the paper at the center of the cross.
- Atoms connected to the tetrahedral carbon by horizontal bonds are behind the plane of the paper.
- Atoms connected to the tetrahedral carbon by vertical bonds are in front of the plane of the paper.



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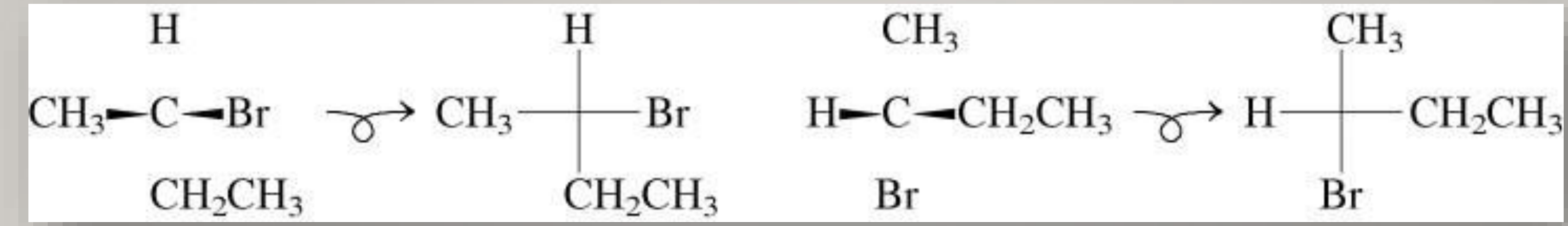
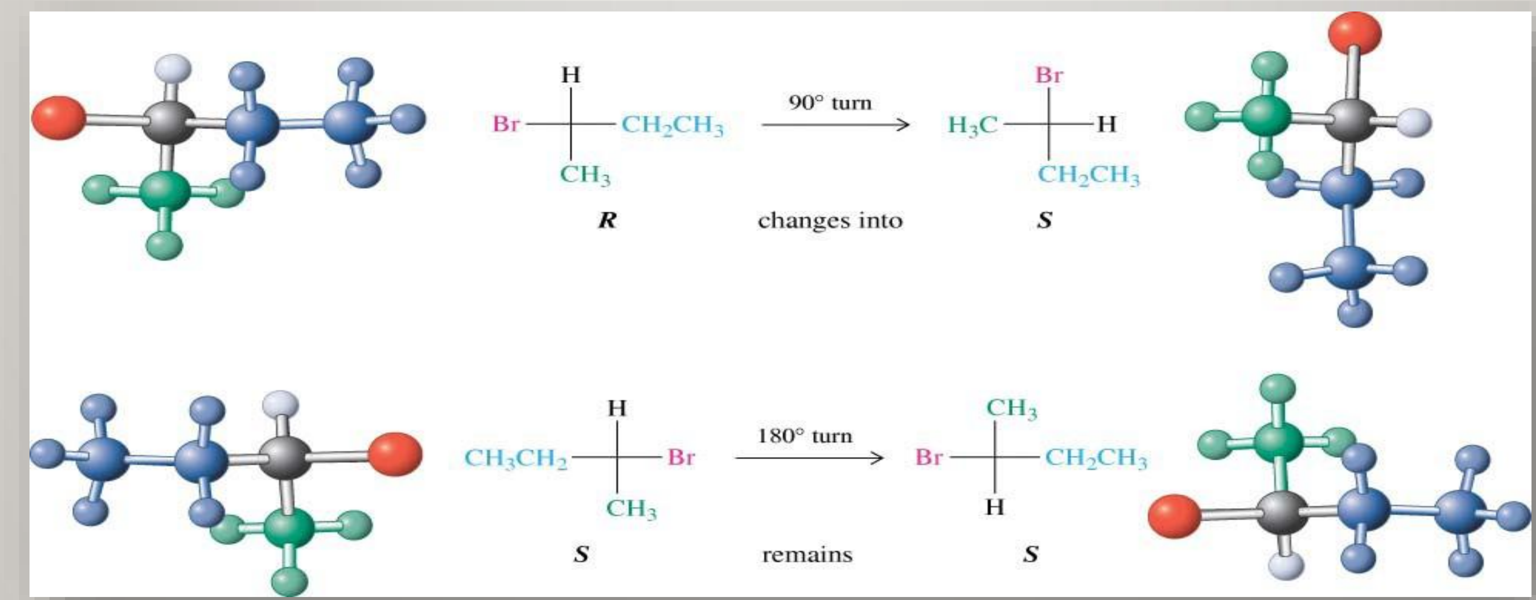
5.4 FISCHER PROJECTIONS

There is more than one correct way to draw a Fischer projection:



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

- Rotating a Fisher projection formula by 90° converts the structure into that of the enantiomer of the molecule originally represented.
- Rotating a Fisher projection formula by 180° keeps the same enantiomer.



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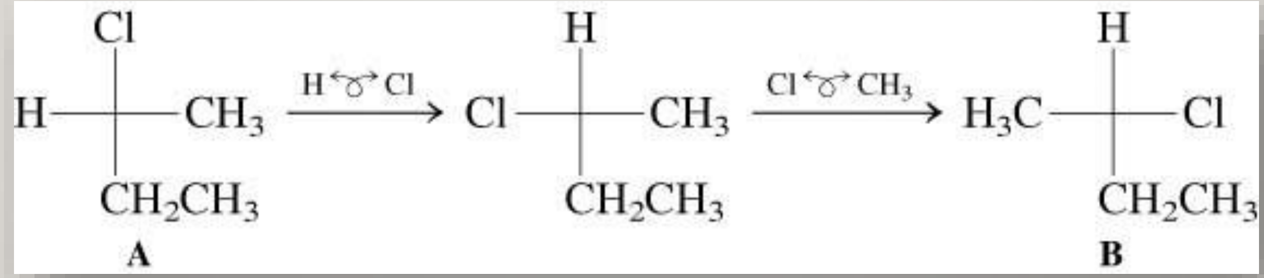
5.4 FISCHER PROJECTIONS

Exchanging substituents in a Fischer projection also changes the absolute configuration.

To compare a Fischer projection to another in a different orientation in order to see if they represent the same enantiomer:

- Exchange any two substituents. This turns the molecule into its mirror image.
- Exchange another two substituents. This then turns the molecule back into the original enantiomer.
- Using a series of exchanges, convert one Fisher formula into the other.
- If an odd number of exchanges are required, the two projection formulas represent different enantiomers.
- If an even number of exchanges are required, the two projection formulas represent the same enantiomer.



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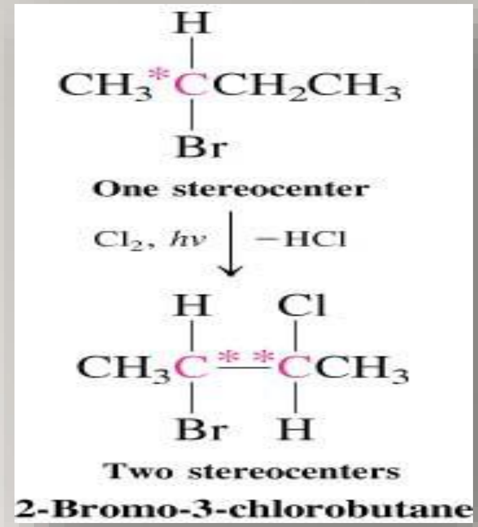
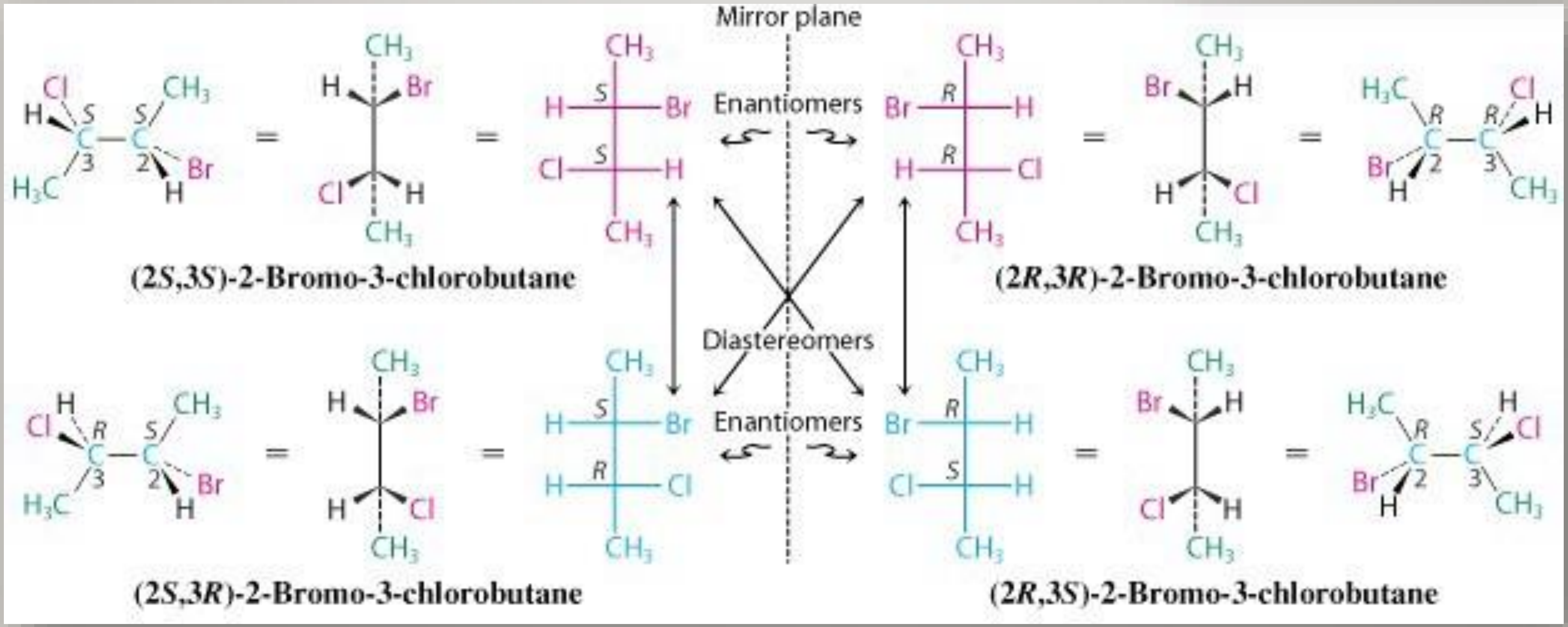
5.5 DIASTEREOMERS

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

- Consider the chlorination of 2- bromobutane. Several products are formed but consider only the 2- bromo-3-chlorobutane.
- A second stereocenter is formed by the addition of the chlorine atom.

The possible combinations are RR, RS, SR, and SS.





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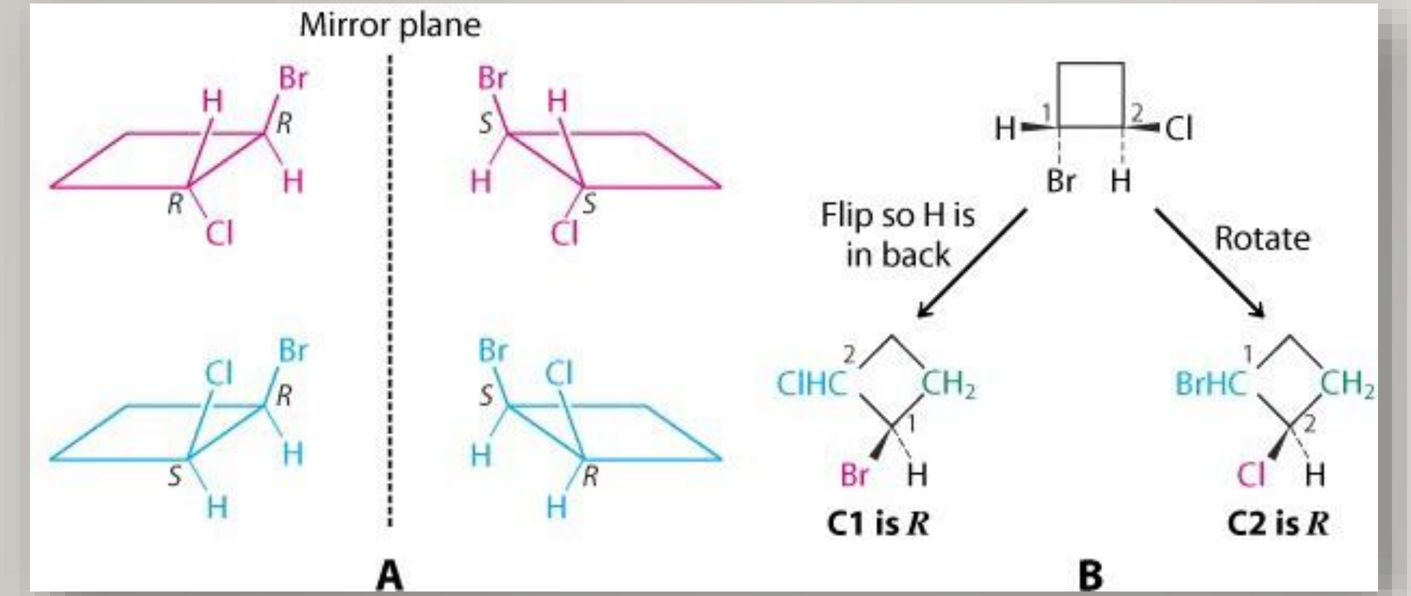
5.5 DIASTEREOMERS

cis and trans isomers are cyclic diastereomers.

Consider 1-bromo-2-chlorocyclobutane:



There are 4 stereoisomers: RR, SS, RS, and SR. The two cis isomers, SR and RS, are enantiomers and the two trans isomers, RR and SS are enantiomers. A cis isomer and a trans isomer are diastereomers of each other.

More than two stereocenters means still more stereoisomers.

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5.5 DIASTEREOMERS

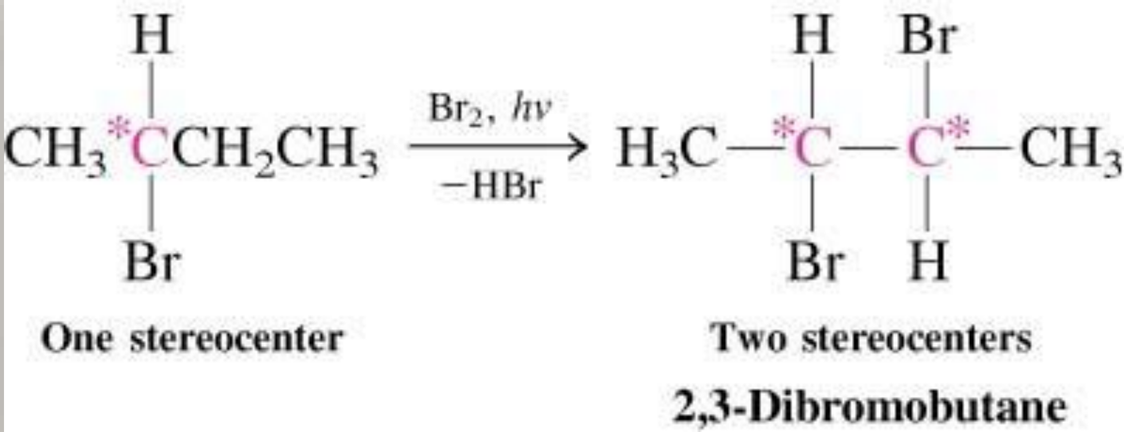
A compound containing 3 stereocenters will exist as 8 stereoisomers which can be grouped into 4 pairs of enantiomers:

RRR | SSS
SRR | RSS
RSR | SRS
RRS | SSR

In general, a compound having n stereocenters can have a maximum of 2^n stereoisomers.

Two identically substituted stereocenters give rise to only three stereoisomers.

Consider the radical bromination of 2-bromobutane:



$$CH_3\overset{H}{\underset{Br}{{}^*C}}CH_2CH_3 \xrightarrow[-HBr]{Br_2,\ h\nu} H_3C-\overset{H}{\underset{Br}{{}^*C}}-\overset{Br}{\underset{H}{C^*}}-CH_3$$

One stereocenter

Two stereocenters

2,3-Dibromobutane

Since there are 2 chiral centers in the product, we might expect 4 distinct stereoisomers: RR, RS, SR, and SS.
These could then be organized into enantiomeric pairs: RR | SS and RS | SR.

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RRR | SSS
SRR | RSS
RSR | SRS
RRS | SSR

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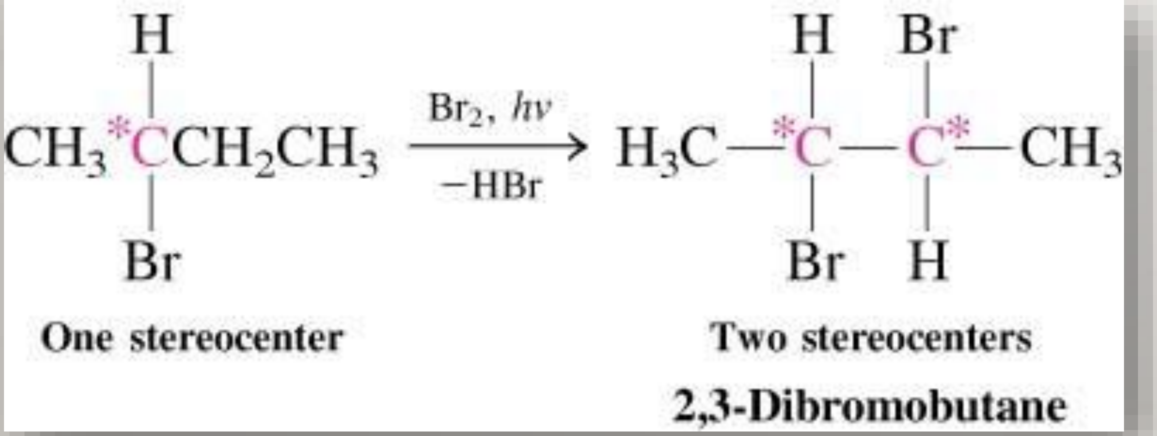

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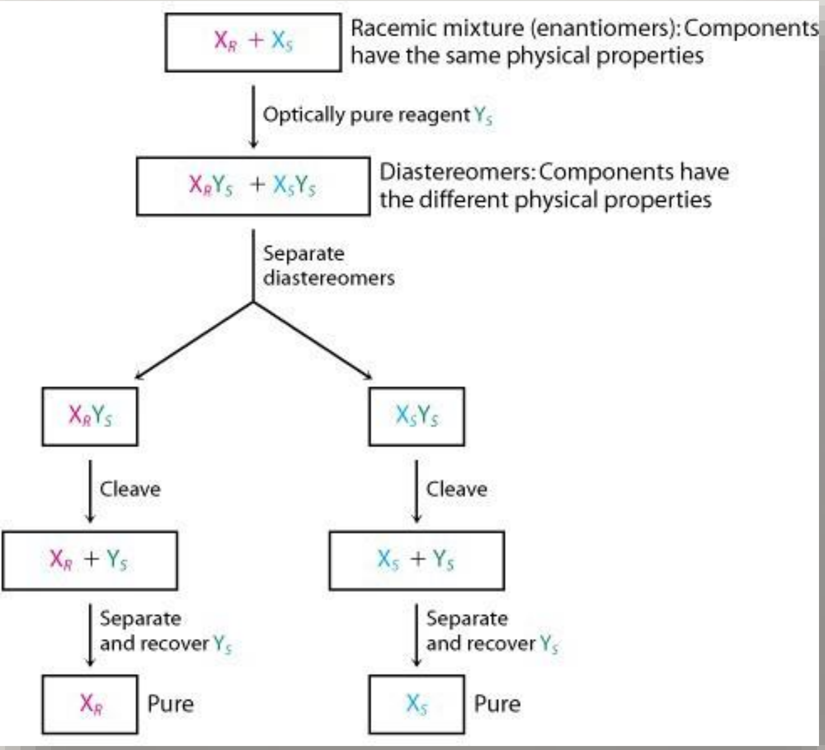
5.6 RESOLUTION: SEPARATION OF ENANTIOMERS

- Pure enantiomers can be obtained by first synthesizing a racemic mixture and then separating the enantiomers formed by a process called resolution.
- Resolution is best carried out by converting a racemate into a mixture of diastereomers by adding an enantiomerically pure reagent. The resulting diastereomers can then be separated by standard techniques.
- Each pure diastereomer can then be separated into one of the original enantiomeric molecules and the optically active reagent, which can be used again to resolve further racemic mixtures.



$X_R + X_S$ Racemic mixture (enantiomers): Components have the same physical properties

Optically pure reagent Y_S

$X_RY_S + X_SY_S$ Diastereomers: Components have the different physical properties

Separate diastereomers

X_RY_S | X_SY_S

Cleave | Cleave

$X_R + Y_S$ | $X_S + Y_S$

Separate and recover Y_S | Separate and recover Y_S

X_R Pure | X_S Pure

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