Stereochemistry

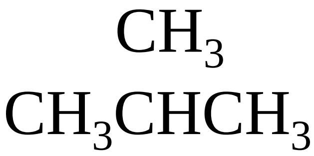
chemistry in three dimensions

Isomers – different compounds with the same molecular formula.

Structural Isomers – isomers that differ in which atoms are bonded to which atoms.

eg. C_4H_{10} $CH_3CH_2CH_2CH_3$

n-butane

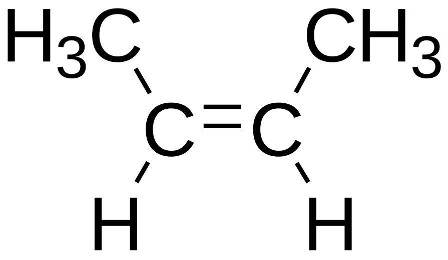


$CH_3\overset{CH_3}{CH}CH_3$

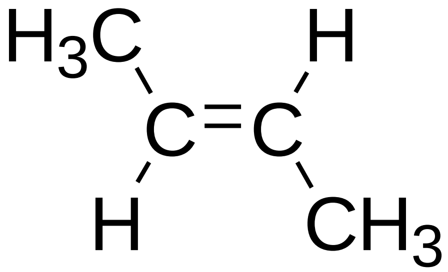
isobutane

Stereoisomers – isomers that differ in the way the atoms are oriented in space, but not in which atoms are bonded to which atoms.

eg. *cis*-2-butene



trans-2-butene



Stereochemistry:

importance:

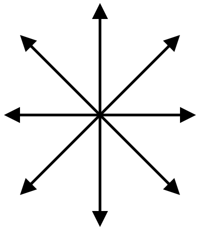
biochemicals

medicine

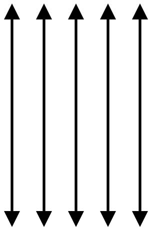
tool for studying mechanisms

optical activity – when a substance rotates the plane of plane polarized light. (1815 by Biot)

plane polarized light – light that has been passed through a nicol prism or other polarizing medium so that all of the vibrations are in the same plane.

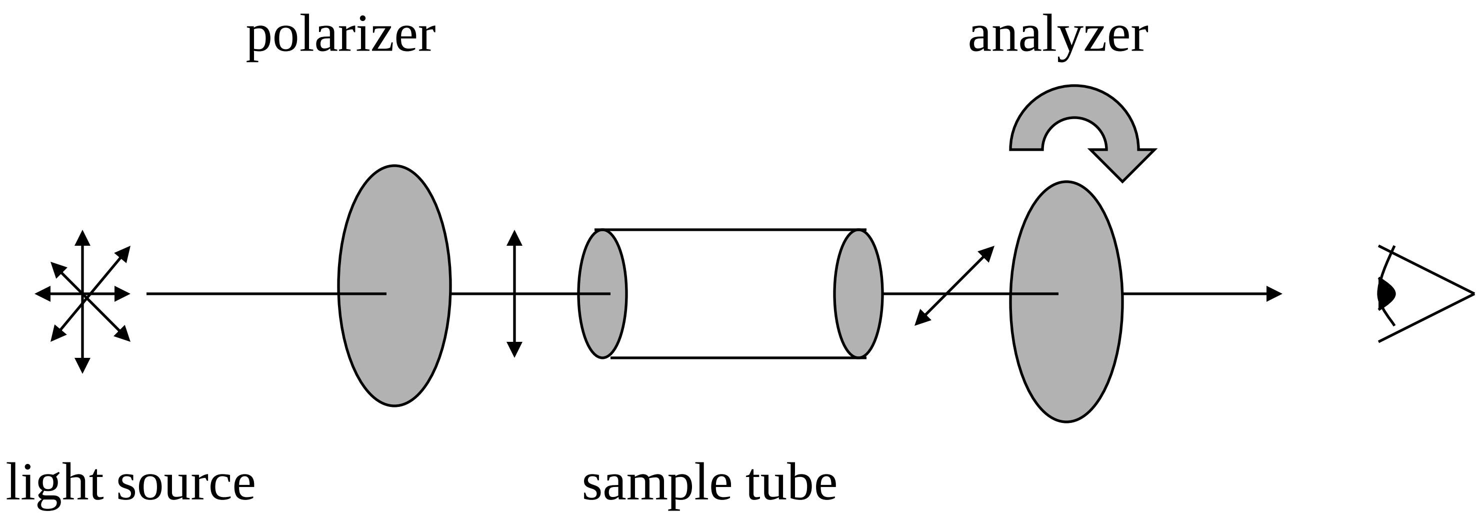


non-polarized



polarized

polarimeter – an instrument used to measure optical activity.



dextrorotatory – when the plane of polarized light is rotated in a clockwise direction when viewed through a polarimeter.

(+) or (*d*) do not confuse with D

levorotatory – when the plane of polarized light is rotated in a counter-clockwise direction when viewed through a polarimeter.

(-) or (*l*) do not confuse with L

The angle of rotation of plane polarized light by an optically active substance is proportional to the number of atoms in the path of the light.

specific rotation – the angle of rotation of plane polarized light by a 1.00 gram per cm^{-3} sample in a 1 dm tube. $[\alpha]_D$ (D = sodium lamp, λ = 589 mμ).

$$[\alpha]_D = \frac{\alpha}{l * d}$$

where α = observed rotation

l = length (dm)

d = concentration (g/cc)

(+)-alanine $[\alpha]_D = +8.5$

(-)-lactic acid $[\alpha]_D = -3.8$

Why are some substances optically active and others not? Can we predict which ones will be and which ones won’t?

Louis Pasteur (1848) recrystallized sodium ammonium tartrate (optically inactive). He noticed that the crystals were of two types which he physically separated. The two types of crystals were optically active, but rotated the plane of polarized light in opposite directions. He proposed that the molecules came in two forms, “left handed” and “right handed”. Together, the mixture of the two forms is optically inactive.

enantiomers - mirror-image stereoisomers.

The physical and chemical properties of enantiomers are identical, except 1) the direction of rotation of the plane of plane polarized light and 2) how they react with optically active reagents.

chiral center– is a carbon that is bonded to four different groups of atoms. (do not confuse with “chiral”)

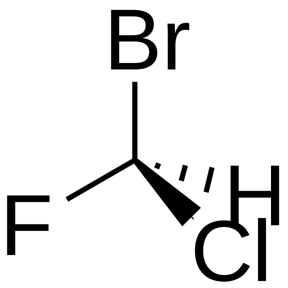
$CH_3CH_2\overset{*}{C}HBrCH_3$ $(CH_3)_2CHCH_2OH$

$CH_3\overset{*}{C}HBr\overset{*}{C}HBrCH_3$

configuration – the arrangement in space of the four different groups about a chiral center.

How do we show configurations?

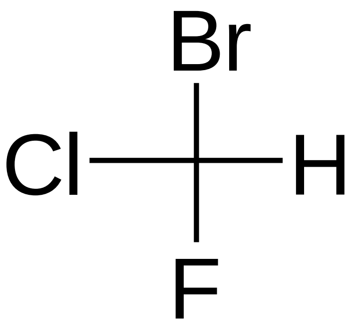
“wedge” formulas



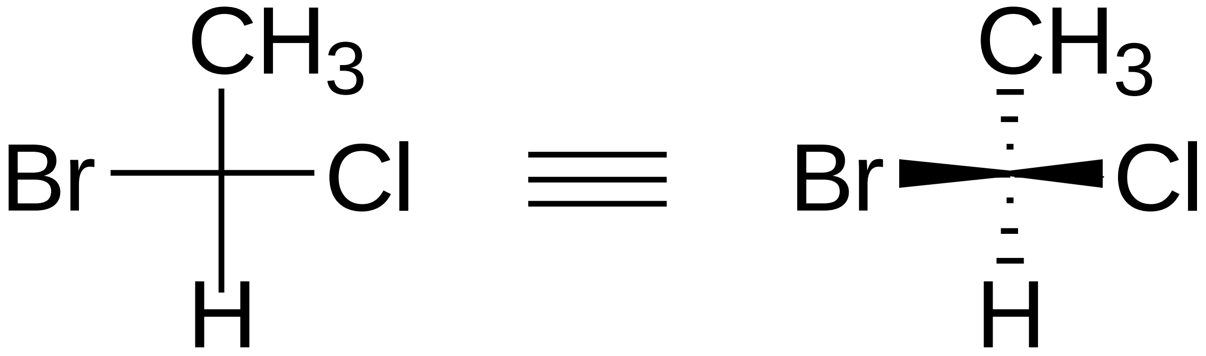
Fischer projections

“cross structures”

use only for chiral centers!



In the Fischer projection, the horizontal bonds to the chiral center are always above the plane and the vertical bonds to the chiral center are below the plane. (the horizontals are “hugging you.”



chiral – not superimposeable on the mirror image (“handedness”)

achiral – superimposeable on the mirror image; not chiral.

Test for optical activity: chiral molecules are optically active.

racemic modification – equimolar molar mixture of enantiomers (will be optically inactive) (±).

- compounds with one chiral center will show optical activity

- compounds without chiral centers do not normally show optical acitivity

- compounds with more than one chiral center may or may not show optical activity depending on whether or not they are non-superimposable on their mirror image (chiral) or superimposable (achiral).

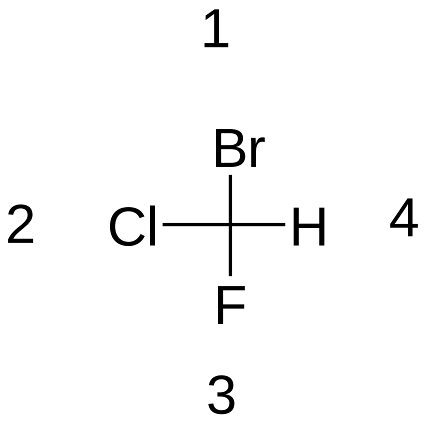
specification of configuration: The **R/S system**.

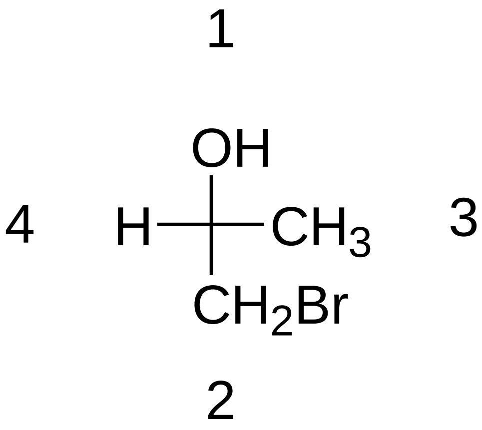
Cahn, Ingold, Prelog sequence rules:

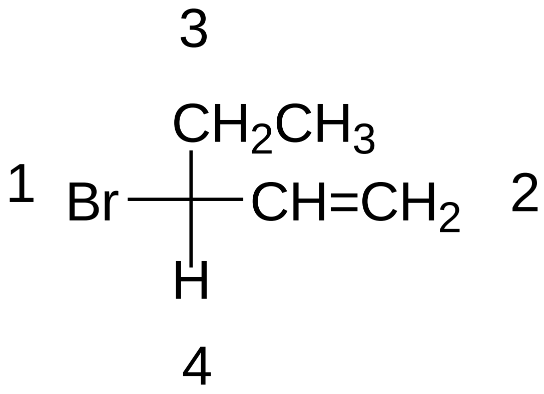
sequence rule 1: the atom attached to the chiral center with the highest atomic number = 1, next = 2, etc.

sequence rule 2: if the four atoms attached to the chiral center are not all different, the sequence is determined at the first point of difference.

sequence rule 3: =X is equal to two –X, etc.


1
Br
2
Cl
H
4
F
3

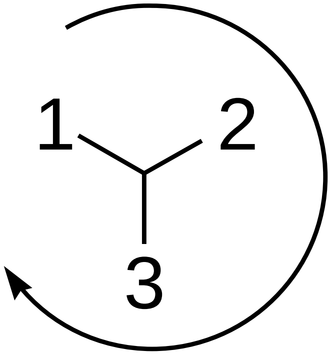

1
OH
4
H
CH3
3
CH2Br
2


3
CH2CH3
1
Br
CH=CH2
2
H
4

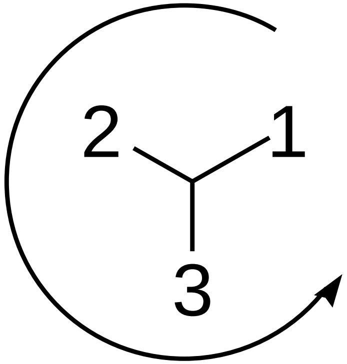
R/S:

1. Using the Cahn, Ingold, Prelog sequence rules, assign numbers to each of the four groups attached to the chiral center.
2. Rotate the number 4 group away from you and observe the sequence 1 → 2 → 3 for the remaining groups.
3. If going from 1 → 2 → 3 is clockwise, then the configuration is R (rectus). If the sequence 1 → 2 → 3 is counter-clockwise, then the configuration is S (sinister).

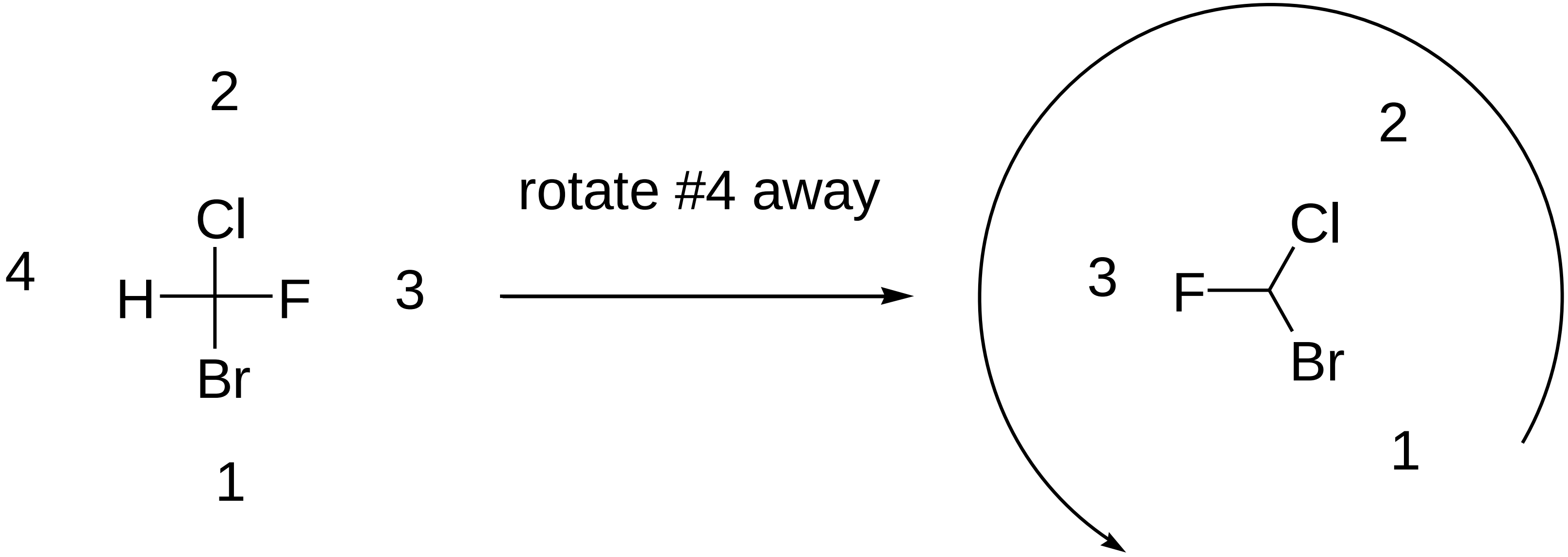
With group #4 rotated away:



R



S



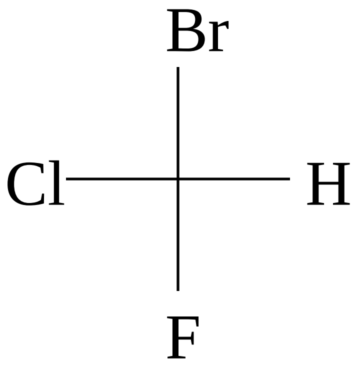
(*S*)-configuration

Using R/S problems on the web:

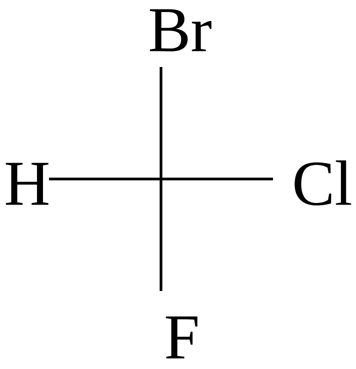
http://chemistry2.csudh.edu/organic/startnewrands.html

Angew. Chem. Int. Ed. Engl. **36**, 1057 (1997).

absolute configuration for bromochlorofluoromethane:



(*R*)-(-)-



(*S*)-(+)-

aldohexose

$$\underset{OH}{CH_2}-\overset{*}{\underset{OH}{CH}}-\overset{*}{\underset{OH}{CH}}-\overset{*}{\underset{OH}{CH}}-\overset{*}{\underset{OH}{CH}}-CH=O$$

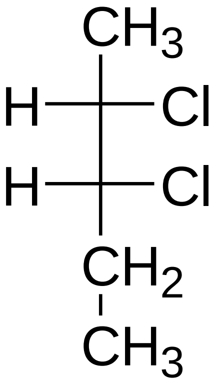
n chiral centers → 2^n maximum stereoisomers

$n = 4 \rightarrow 2^4 = 16$ stereoisomers

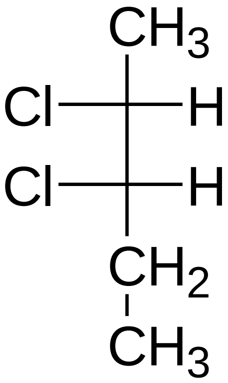
2,3-dichloropentane

$$CH_3\overset{*}{\underset{Cl}{CH}}\overset{*}{\underset{Cl}{CH}}CH_2CH_3$$

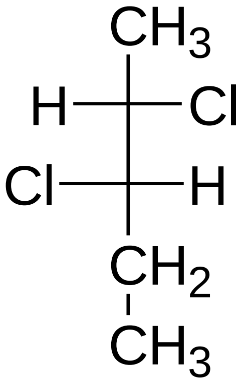
$n = 2 \rightarrow 2^2 = 4$ stereoisomers



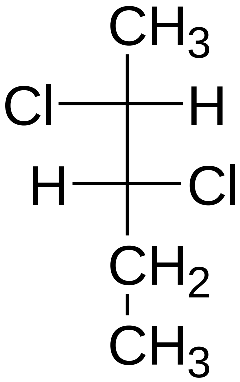
I



II



III

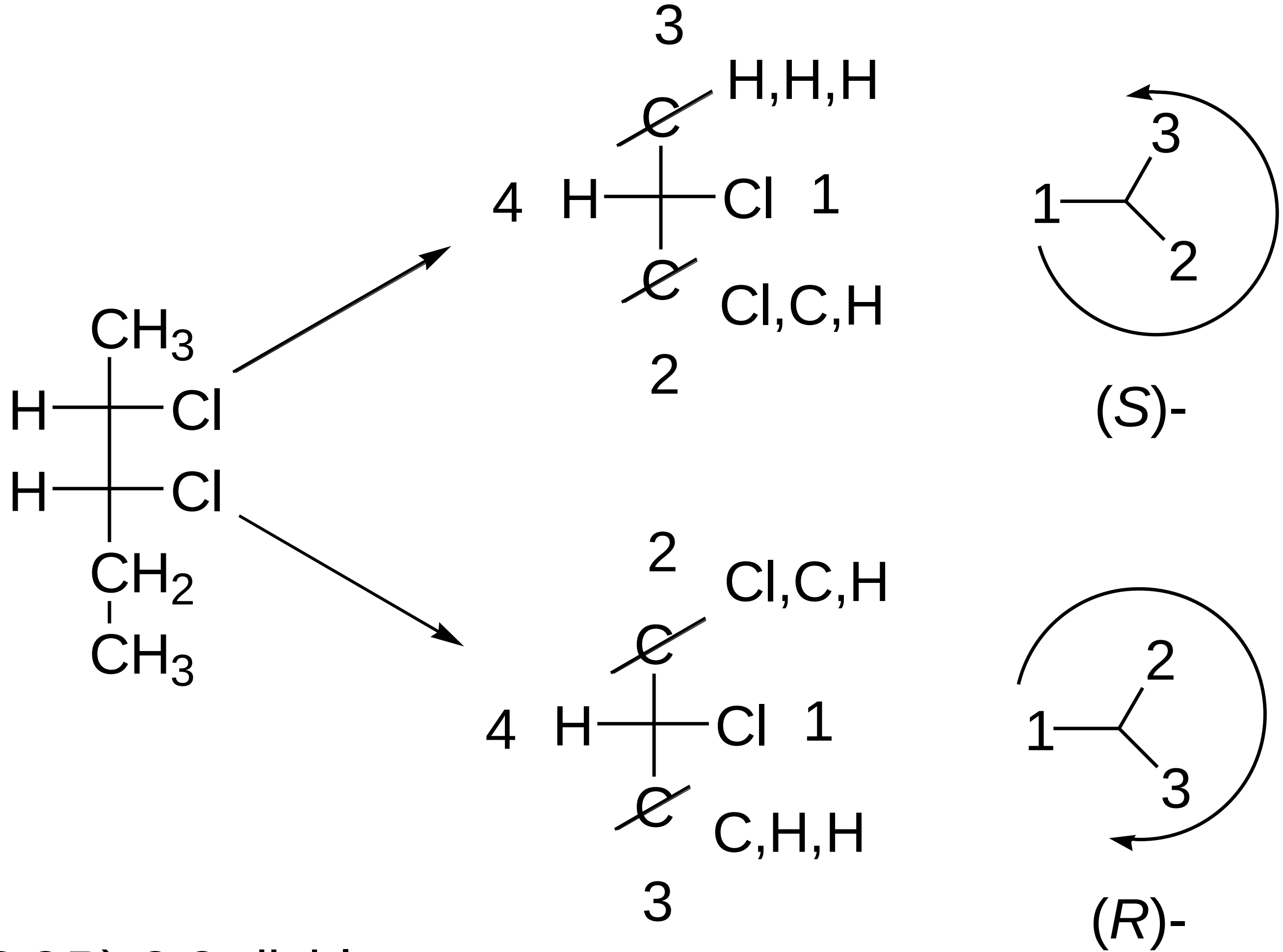


IV

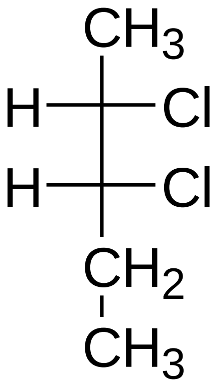
I & II are enantiomers; III & IV are enantiomers; I & III are diastereomers; I & IV are diastereomers…

diastereomers – non-mirror image stereoisomers.

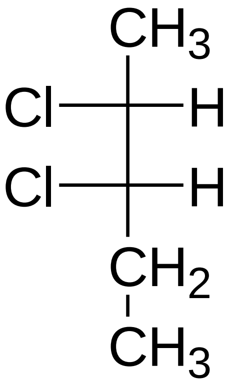
(the physical and chemical properties of diastereomers are different.)



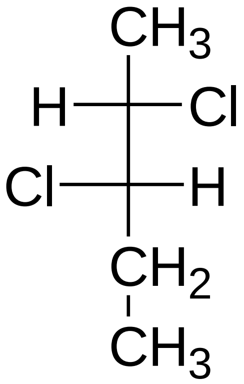
(2*S*,3*R*)-2,3-dichloropentane



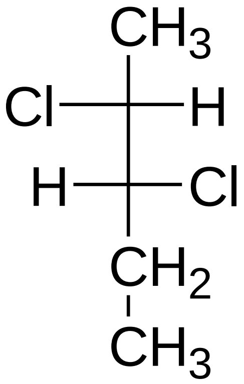
(2*S*,3*R*)-



(2*R*,3*S*)-



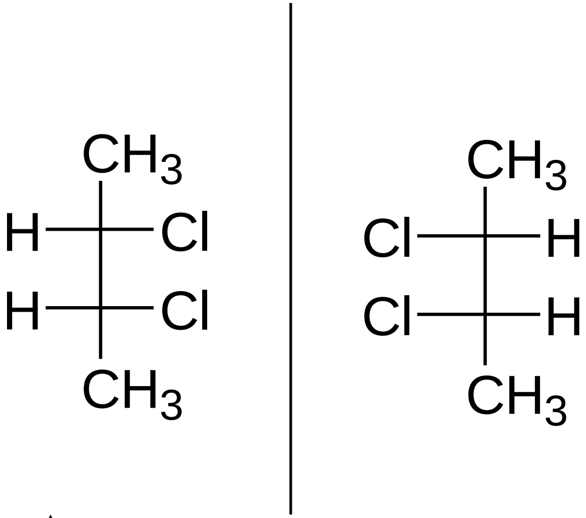
(*S*,*S*)-



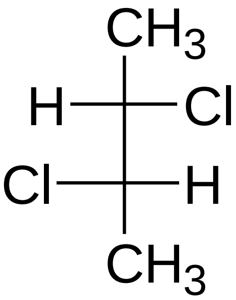
(*R*,*R*)-

2,3-dichlorobutane

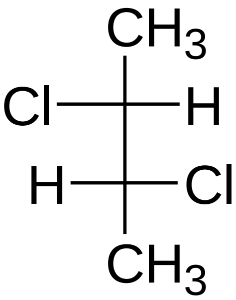
$$\overset{\ \ \ \ *\ \ \ \ *}{CH_3\underset{Cl}{C}H\underset{Cl}{C}HCH_3}$$



I



II



III

***meso*-compound** – a compound that has chiral centers but is not chiral (optically inactive).

Reactions involving stereoisomers:

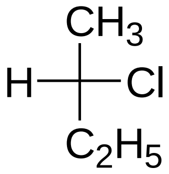
(a) the conversion of an achiral molecule into a chiral molecule, with the generation of a chiral center.

n-butane + Cl_2, hv → *sec*-butyl chloride + etc.

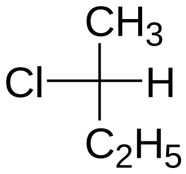
achiral

chiral

$CH_3CH_2\overset{*}{C}HClCH_3$



(*S*)-(+)-*sec*-butyl chloride



(*R*)-(-)-*sec*-butyl chloride

product is optically inactive → racemic modification

The synthesis of chiral compounds from achiral reactants always yields the racemic modification.

Why? ‡ R is enatiomeric to ‡S

Eact (R) = Eact (S)

rate (R) = rate (S)

→ equimolar amounts

racemic modification

optically inactive

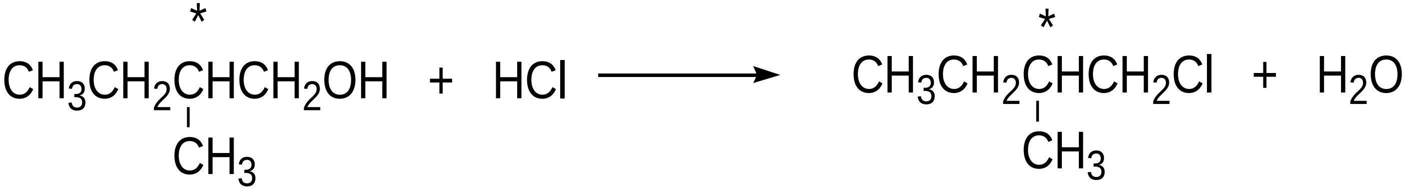
(b) reaction of a chiral molecule where bonds to the chiral center are not broken.

$$\mathrm{CH_3CH_2\overset{*}{C}HClCH_3} \quad + \quad \mathrm{Cl_2},\ hv \quad \rightarrow \quad \mathrm{CH_3CH_2\overset{*}{C}HClCH_2Cl}$$

$$+ \quad \text{etc.}$$

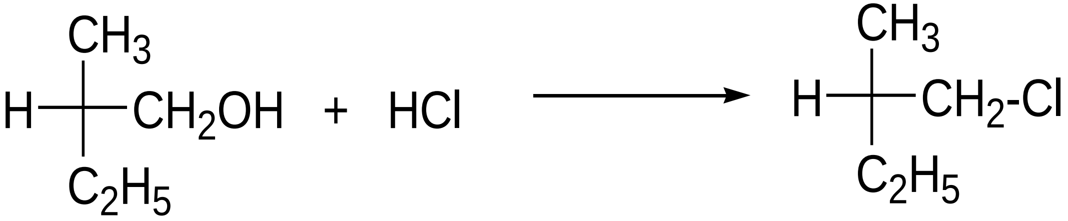
A reaction that does not involve the breaking of a bond to a chiral center proceeds with retention of configuration about the chiral center.

Can be used to “relate” configurations. If a compound can be synthesized by such a reaction from a compound of known configuration, then the configuration is known in the product.



$$\overset{*}{\mathrm{CH_3CH_2\underset{\substack{|\\ CH_3}}{C}HCH_2OH}} + \mathrm{HCl} \longrightarrow \mathrm{CH_3CH_2\underset{\substack{|\\ CH_3}}{\overset{*}{C}}HCH_2Cl} + \mathrm{H_2O}$$

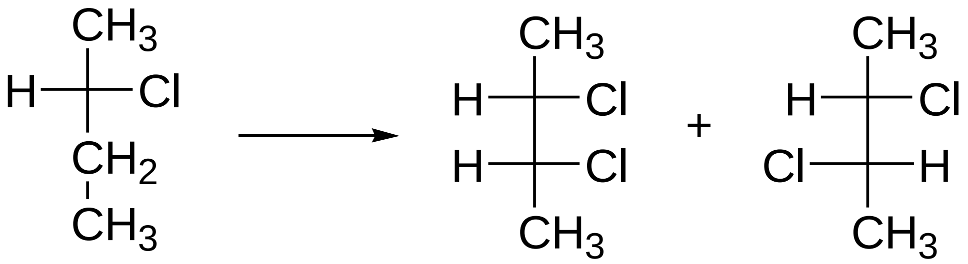
It is known from X-ray crystallography that (-)-2-methyl-1-butanol is the (*S*)-isomer. When pure (-)-2-methyl-1-butanol is reacted with HCl, the product is dextrorotatory. Since no bonds to the chiral center were broken in the reaction, the (+)-1-chloro-2-methyl butane is now known to be the (*S*)-isomer.



(c) reactions like (b) in which a second chiral center is generated:

$$CH_3CH_2\overset{*}{C}HClCH_3 \quad + \quad Cl_2\text{, hv} \;\rightarrow\; CH_3\overset{*}{C}HCl\overset{*}{C}HClCH_3$$

$$+ \text{ isomers}$$



(*S*)- (*R*,*S*)- (*S*,*S*)-

diastereomers in unequal amounts

The transition states are “diastereomeric”, the Eact’s are not equal, the rates are different.

(d) reactions of chiral compounds with optically active reagents.

Enantiomers have the same physical properties and cannot be separated by normal separation techniques like distillation, etc.

Enantiomers differ in reaction with optically active reagents.

Enantiomeric acids or bases can be reacted with an optically active base or acid to form salts that are diastereomers. Since diastereomers have different physical properties they can be separated by physical methods. The salts can then be converted back into the free acids or bases.

Resolution – the separation of enantiomers.

$(+)\text{-HA} \quad + \quad (-)\text{-Base} \quad \rightarrow \quad [(-)\text{-baseH}^{+},(+)\text{A}^{-}] \quad +$

$(-)\text{-HA} \qquad\qquad\qquad\qquad\qquad\qquad [(-)\text{-baseH}^{+},(-)\text{A}^{-}]$

(enantiomers)   (diastereomers, separable)

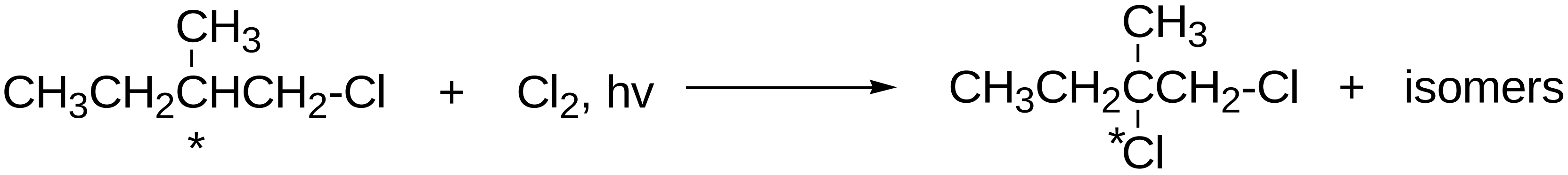
$[(-)\text{-baseH}^{+},(+)\text{-A}^{-}] \quad + \quad \text{H}^{+} \quad \rightarrow \quad (+)\text{-HA} \quad + \quad (-)\text{-baseH}^{+}$

$[(-)\text{-baseH}^{+},(-)\text{-A}^{-}] \quad + \quad \text{H}^{+} \quad \rightarrow \quad (-)\text{-HA} \quad + \quad (-)\text{-baseH}^{+}$

A racemic modification is converted by optically active reagents into a mixture of diastereomers which can then be separated. (resolved)

(e) a reaction of a chiral compound in which a bond to a chiral center is broken…

In a reaction of a chiral compound in which a bond to a chiral center is broken, the stereochemistry depends on the mechanism of the reaction.

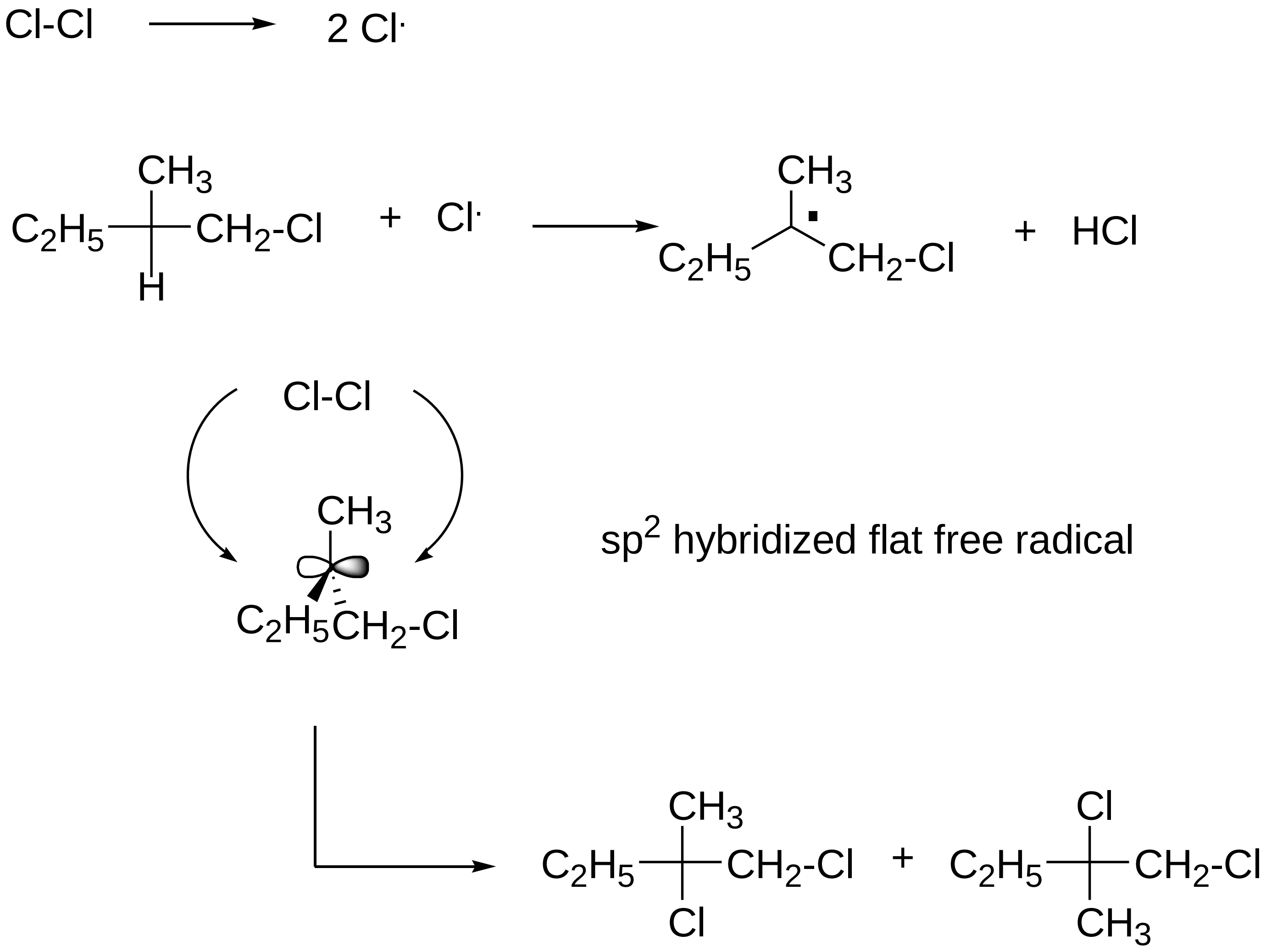


$$CH_3CH_2\underset{*}{\overset{CH_3}{C}}HCH_2\text{-}Cl + Cl_2,\ hv \longrightarrow CH_3CH_2\underset{*Cl}{\overset{CH_3}{C}}CH_2\text{-}Cl + \text{isomers}$$

(*S*)-(+)-1-chloro-2-methylbutane

racemic-1,2-dichloro-2-methylbutane

optically inactive mixture



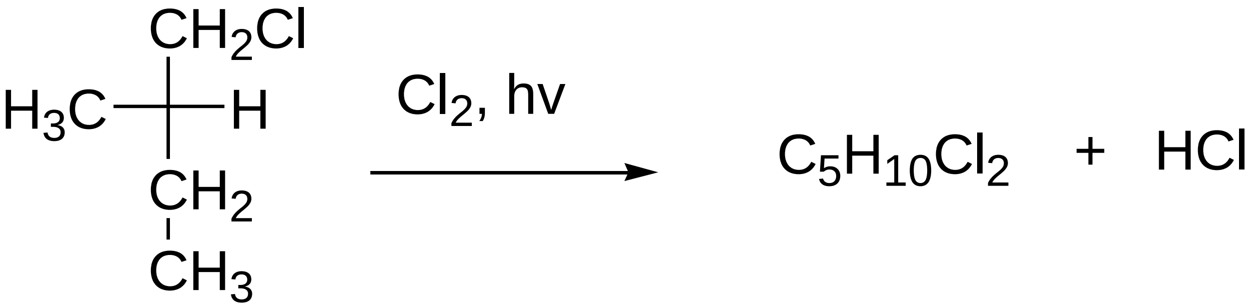
$Cl\text{-}Cl \longrightarrow 2\ Cl\cdot$

sp^2 hybridized flat free radical

In a reaction of a chiral compound in which a bond to a chiral center is broken, the stereochemistry depends on the mechanism of the reaction. This means that we can use the stereochemistry of such a reaction to give us information about the mechanism for that reaction.

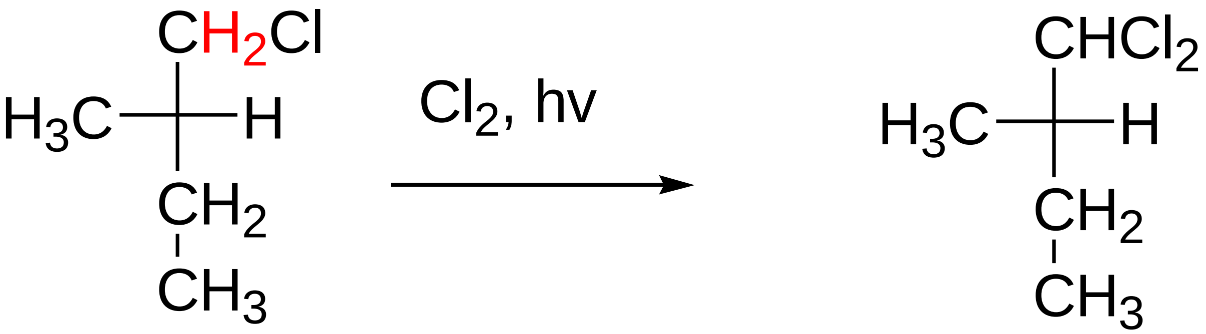
Homework problem 4.24

“Altogether, the free radical chlorination of (*S*)-(-)-1-chloro-2-methylbutane gave six fractions of formula $C_5H_{10}Cl_2$. Four fractions were found to be optically active, and two fractions optically inactive. Draw structural formulas for the compounds making up each fraction. Account in detail for optical activity or inactivity in each case.”



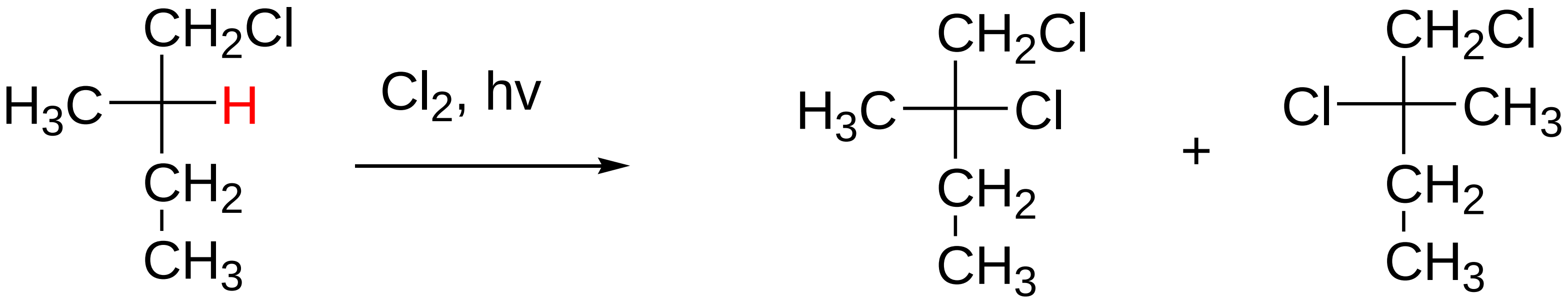
(*S*)-(-)-1-chloro-2-methylbutane

six fractions:
- four optically active
- two optically inactive



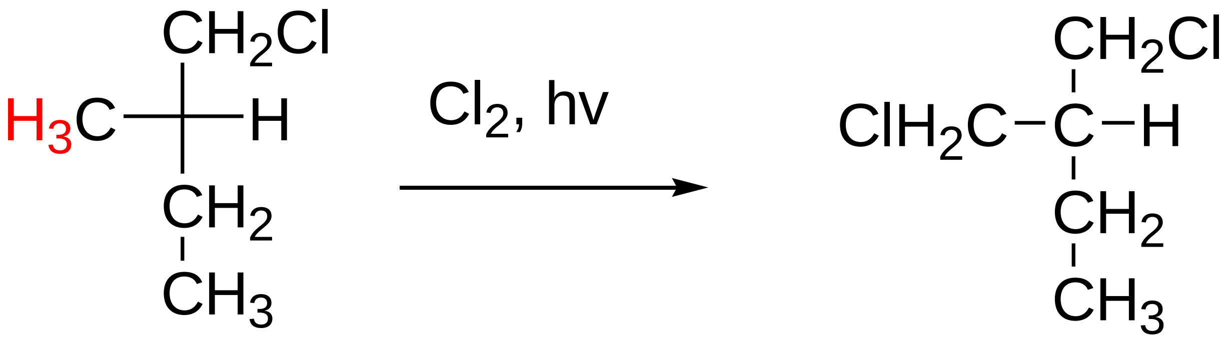
A

No bonds to the chiral center are broken, configuration is retained. Product is optically active



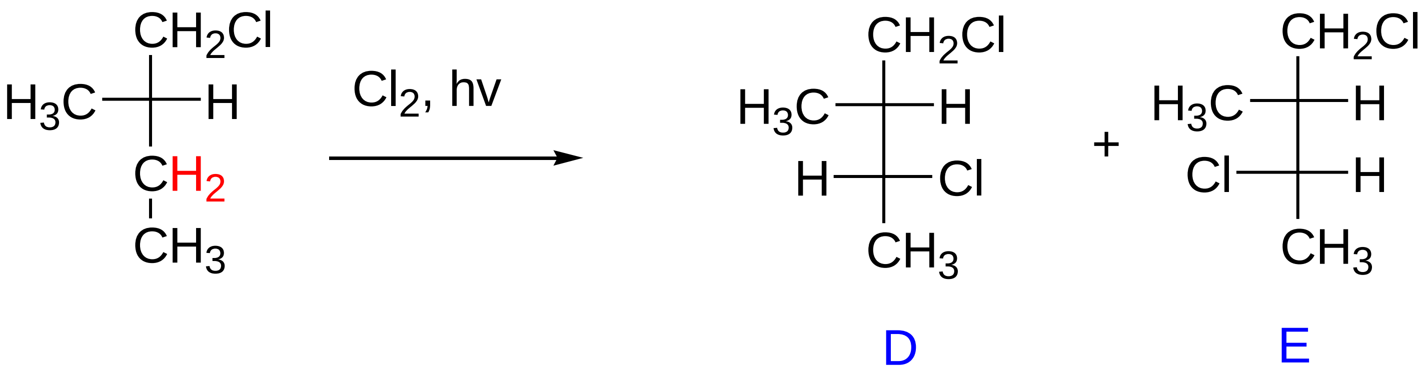
B

A bond is broken to the chiral center. Stereochemistry depends on the mechanism. Here, the intermediate free radical is flat and a racemic modification is formed. This fraction is optically inactive.

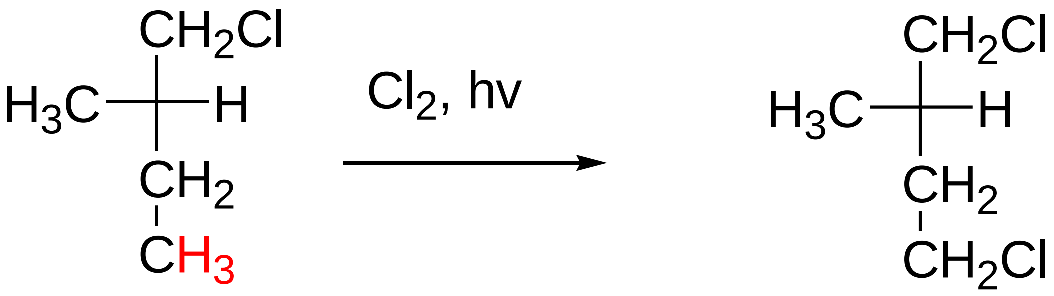


C

The product no longer has a chiral center. It is achiral and optically inactive.

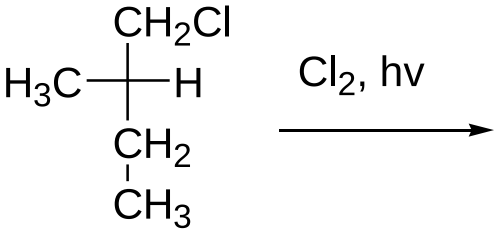


No bond is broken to the chiral center and a new chiral center is formed. The products are diastereomers and each fraction is optically active.

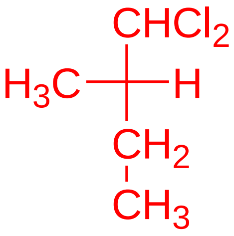


F

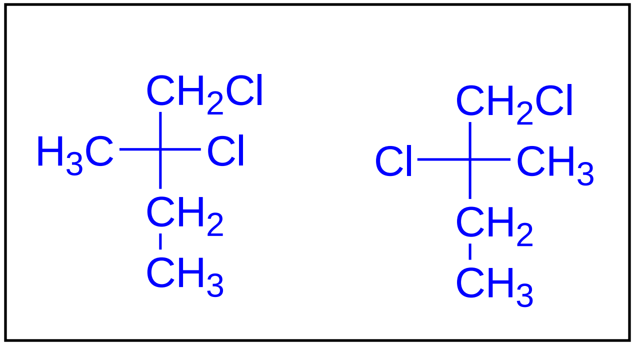
No bonds to the chiral center are broken, configuration is retained. Product is optically active



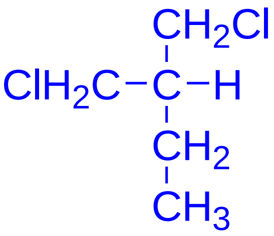
(*S*)-(-)-1-chloro-2-methylbutane



A



B



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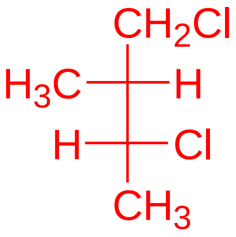

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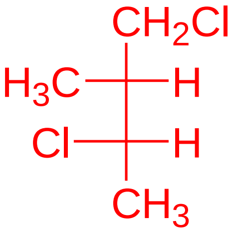

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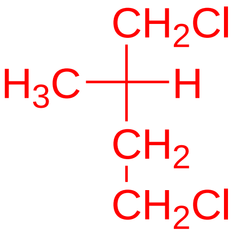

F

optically active
optically inactive