ADVANCED ORGANIC CHEMISTRY

Part A: Structure and Mechanism 5th Edition

Francis A. Carey and Richard J. Sundberg

Kluar Academic / Plenum Publishers

Ebrahim Ahmadi

REFERENCES

1. Advanced Organic Chemistry, Part A: "Structure and Mechanisms"

Francis A. Carey & Richard J. Sundberg

4rd Edition, Plenum Press, 1990.

2. Advanced Organic Chemistry: "Reactions, Mechanisms and Structure"

Jerry March

3rd Edition, John Wiley & Sons, 1985.

3. Introduction to streochemistry

Kurt Mislow

Table of Contents:

Chapter 1: Chemical Bonding and Molecular Structure

Chapter 2: Stereochemical Principles

Chapter 3: Conformational, Steric, and Stereo Electronic Effects

Chapter 4: Study and Description of Organic Reaction Mechanisms

Chapter 5: Nucleophilic Substitution

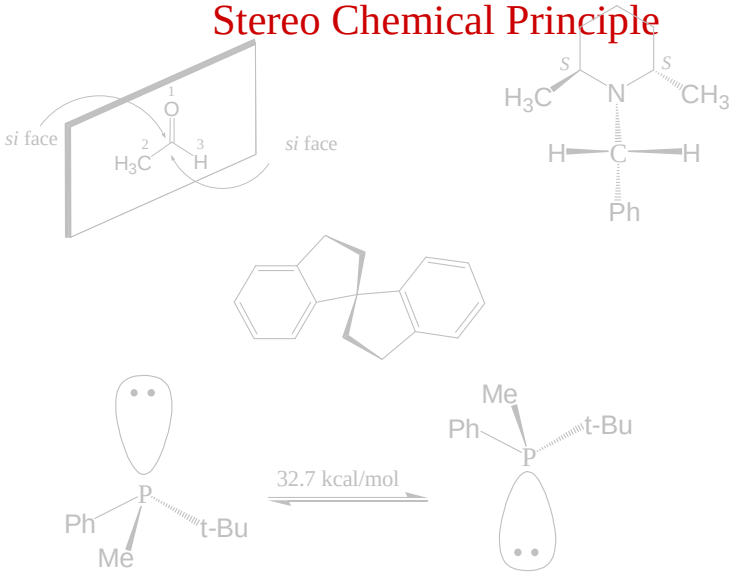
Chapter 6: Polar Addition and Elimination Reactions

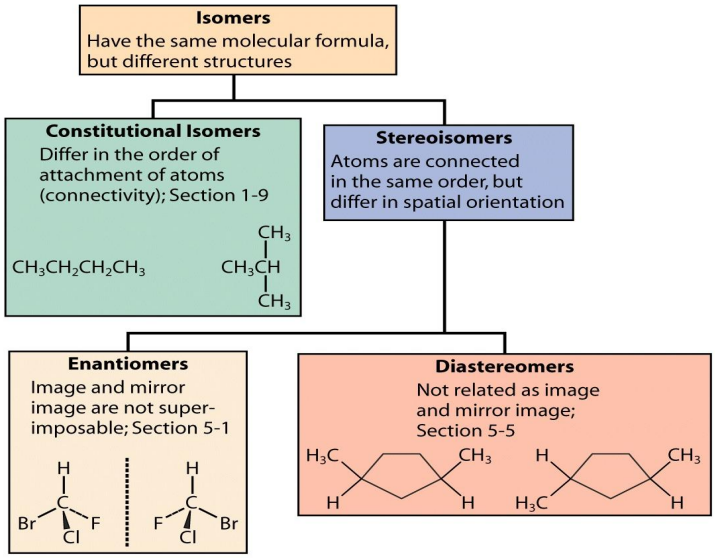
Chapter 7: Carbanions and Other Nucleophilic Carbon Species

Chapter 9: Aromaticity

CHAPTER 2

Stereo Chemical Principle





Terms and Definitions

Stereoisomers: Constructions with different spatial arrangement.

Chiral Objects: non superimpasible with the mirror image.

Chirality: Property of molecules that have not super imposable mirror images

Enantiomers: Stereoisomers that have not super imposable mirror images.

Homochiral: Samples containing only one enantiomer.

Optically Pure: Samples that have only one of the enantiomers.

Diastereomers: Stereoisomers that are not enantiomers.

Racemic Mixture: Samples containing equal amount of two enantiomer. They show zero net rotation.

Conformation: Different molecular spatial arrangement as a result of facile **rotation about single bond.**

Atropisomers: Stereoisomers that rotation about single bond is restricted by steric or other factors. The different conformations can be separated.

2.1 Enantiomeric Relationship

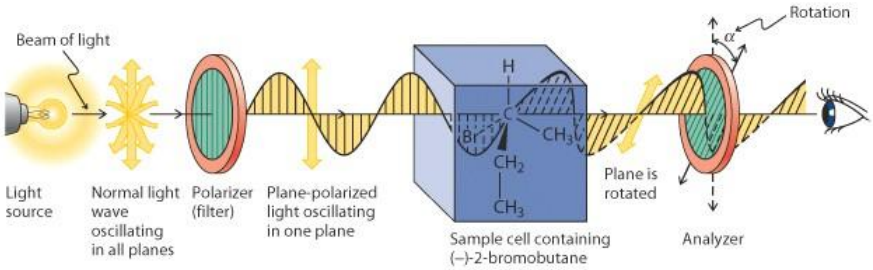
They have the same solubility, physical, and spectroscopic properties and the same chemical reactivity toward achiral reagents.

Enantiomers also differ in a specific physical property, namely the rotation of plane polarized light.

The property of rotating plane polarized light is called optical activity

هنگامی که نور پلاریزه مسطح از یک مولکول کایرال عبور کند، بر همکنش میدان الکتریکی موجب خواهد شد، نور در جهت راست یا جهت چپ منحرف شود. به این اثر فعالیت نوری و به این مولکولها فعال نوری می گویند.

فعالیت نوری با پالاریمتر اندازه گیری می شود.



چرخش اندازه گیری شده (بر حسب درجه)، چرخش نوری مشاهده شده، α، نمونه است.

مقدار α وابسته است به:

- ساختار مولکول کایرال
- غلظت مولکول کایرال
- طول سل نمونه
- طول موج نور
- حلال استفاده شده
- دما

چرخش ویژه، [α]، برای هر مولکول کایرال با معادله زیر محاسبه می شود و تنها به حلال بستگی دارد:

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

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)

چرخش ویژه همانند نقطه جوش، نقطه ذوب، چگالی و غیره از ثابت های فیزیکی می باشد.

Sign and Magnitude of Optical Rotation

- a) Temperature
- b) Solvent
- c) Wave Length of the Light Source

Convention: Emission line of sodium lamp at l = 589 nm (Sodium D line)

Measured Rotation : $[a]_D$

Optical Purity

$$\text{Optical Purity } (\%) = \frac{[\alpha]_{\text{mixture of enantiomers}}}{[\alpha]_{\text{pure enantiomer}}} \times 100$$

Enantiomeric Excess:

$$(\text{ee } \%) = \left[X_{\text{Major Enantiomer}} - X_{\text{Minor Enantiomer}}\right] \times 100$$

Where X is Mole Fraction

The OP is numerically equivalent to enantiomeric excess.

Optical Rotatory Dispersion (ORD):

Measurement of rotation as function of wavelength.

Use:

Specifying the configuration of a molecule by relating it to similar molecules of known configuration.

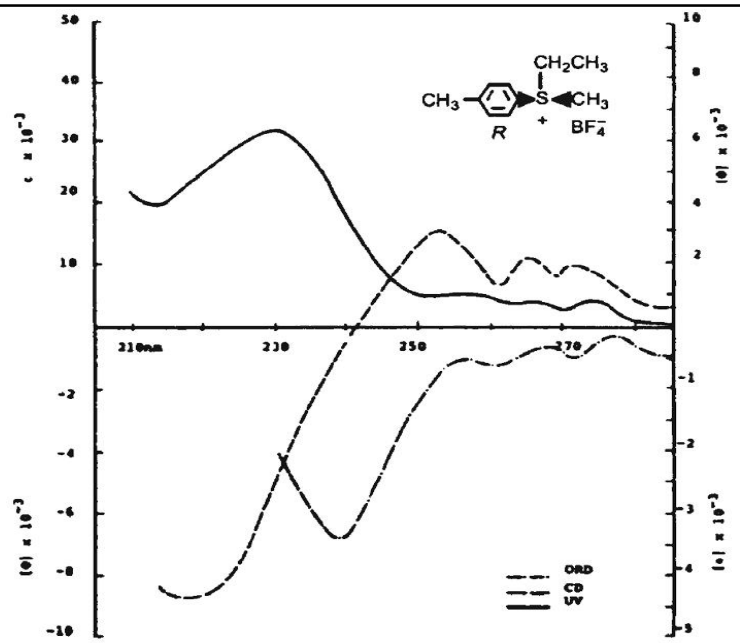


Fig. 2.2. UV absorption, ORD, and CD curves of (R)-ethyl methyl p-tolyl sulfonium tetrafluoroborate.

Circular Dichroism (CD): Absorption of circularly polarized light by two enantiomers.

Circularly polarized light can be obtained by passing plane-polarized radiation through an anisotropic crystal. These materials transmit radiation at different velocities in different directions.

$$\theta = 3330(\varepsilon_L - \varepsilon_R)$$

ε_L and ε_R: Extinction coefficient of the left and right Circularly Polarized Light.

Use:

CD is quantitatively expressed molecular ellipticity. Two enantiomers have molecular ellipticity exactly opposite in values at each wavelength (like specific rotation).

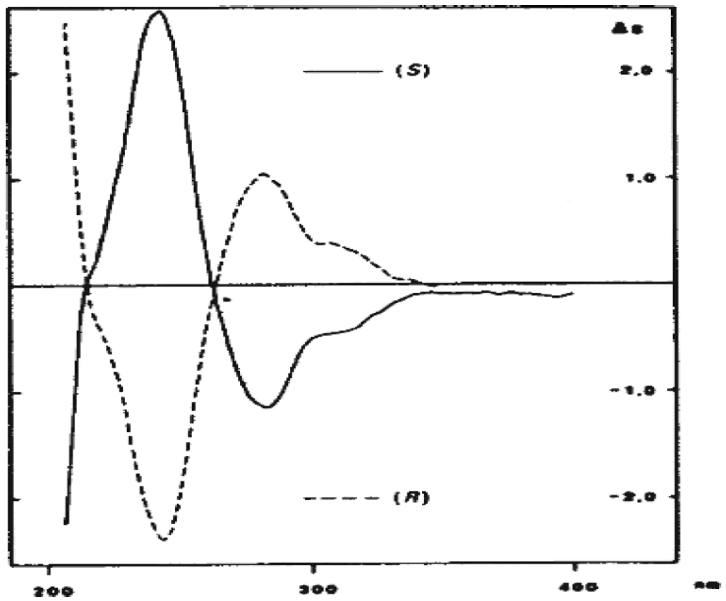


Fig. 2.3. CD spectra of (S)- and (R)-2-amino-1-phenyl-1-propanone hydrochloride.

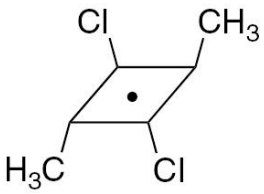
The Relationship between Chirality and Symmetry

What kinds of molecules display optical activity:

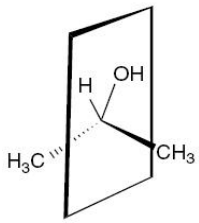
a) Not have plane of symmetry

b) Not have center of symmetry

For example, trans, trans, cis-2,4-dichloro-1,3-dimethylcyclobutane has a center of symmetry, but no plane of symmetry. It is achiral.

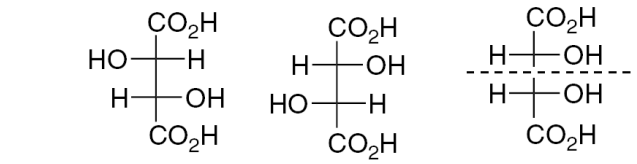


center of symmetry

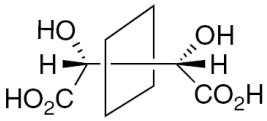


2-propanol

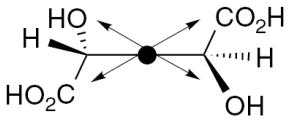
plane of symmetry



D-tartaric acid L-tartaric acid *meso*-tartaric acid

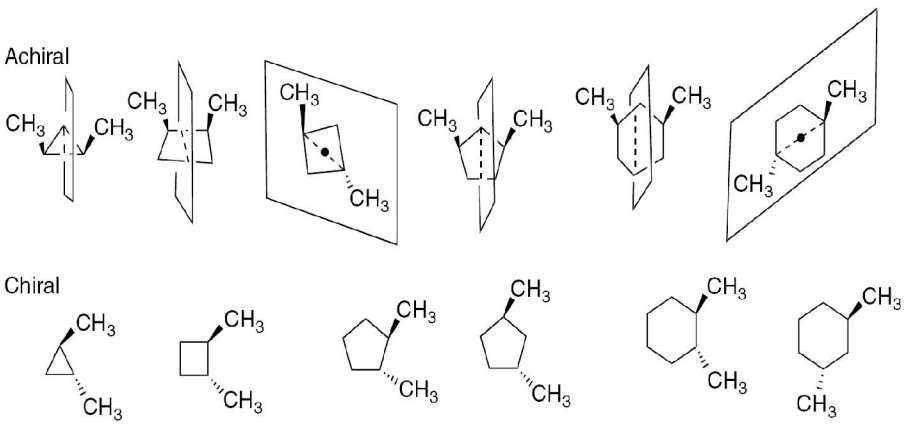


Plane of symmetry in the eclipsed conformation of *meso*-tartaric acid



Center of symmetry in the *anti* staggered conformation of *meso*-tartaric acid

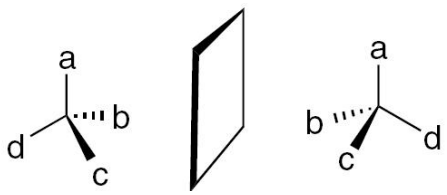
Chiral and Achiral Disubstituted Cycloalkanes



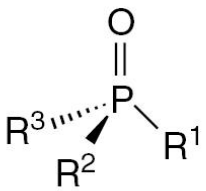
Chiral compounds in organic chemistry

1) Compounds with a chral carbon atoms.
2) Compounds with other Quadrivalent chiral atoms.
3) Compounds with Trivalent chiral atoms.
4) Suitably substituted adamantens.
5) Restricted rotation giving rise to perpendicular dissymmetric planes.
6) Chirality due to a helical shape.
7) Chirality caused by restricted rotation of other type.

1) Compounds with a chiral carbon atoms.

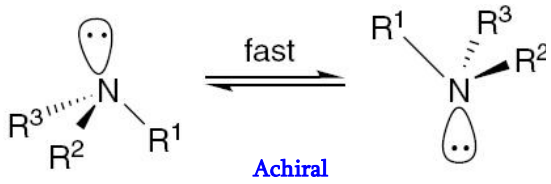


2) Compounds with other tetravalent chiral atoms.



phosphine oxide

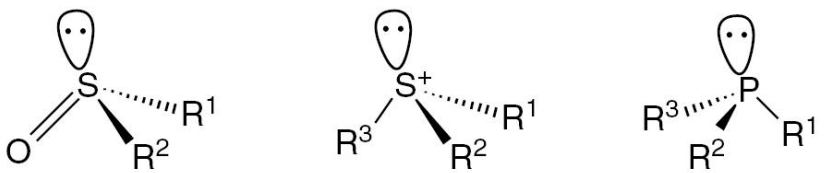
3) Compounds with Trivalent chiral atoms.



Umbrella effect = Pyramidal inversion

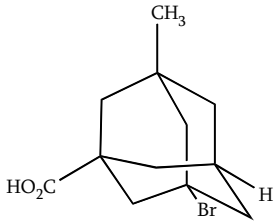
1) Nitrogen atoms in a three-member ring.
2) Nitrogen atoms connected to another atom bearing an unshared electron pair.
3) Nitrogen atoms in bridgehead bicycle systems.

Sulfonium salts, sulfoxides, and phosphines can be obtained as pure enantiomers, Because there is a relatively high energy barrier to inversion of these tetrahedral molecules,



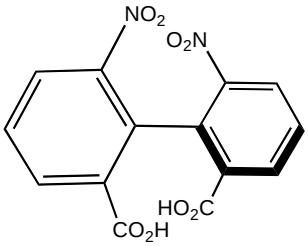
sulfoxide sulfonium ion phosphine

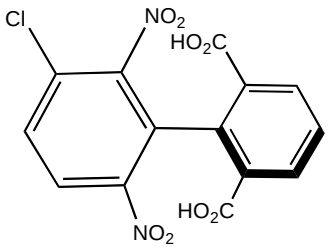
4) Suitably substituted adamantens.



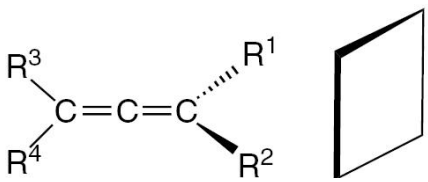
5) Restricted rotation giving rise to perpendicular dissymmetric planes.

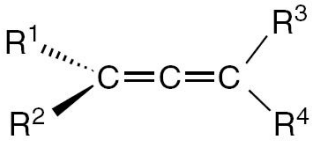
a) 1 1'-biphenyl compounds: Stericinteractions between the orto hydrogens prevent these molecules from being planar.



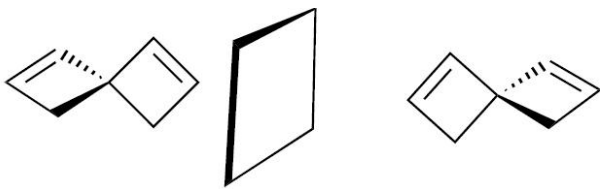


b) Allenes can be chiral.



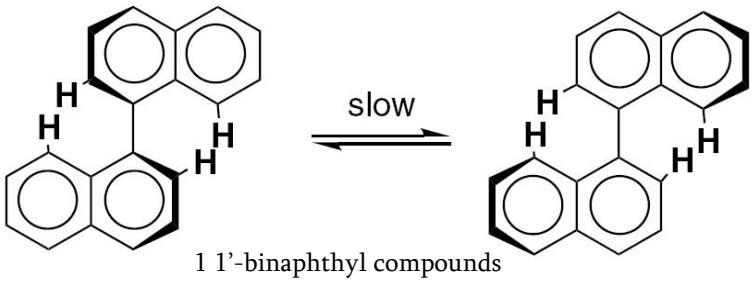


c) Many spiro compounds are chiral.



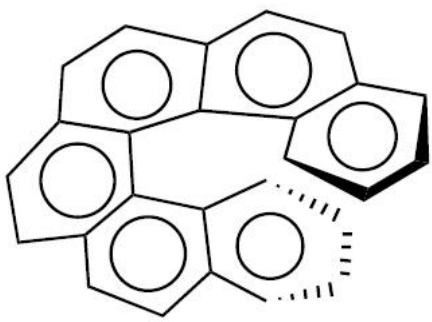
S-(+)-spiro[3,3]hepta-1,5-diene

6) Chirality due to a helical shape.



1 1'-binaphthyl compounds

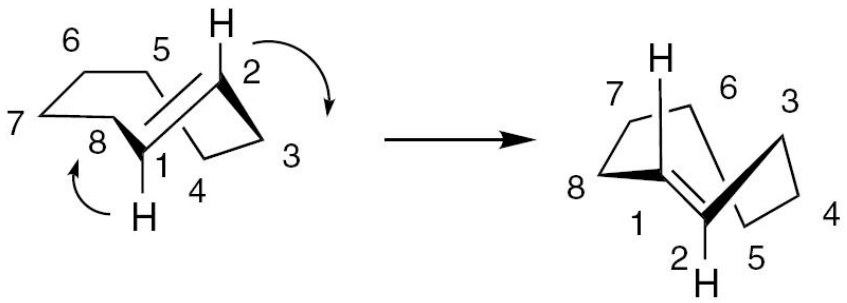
Steric interactions between the 2 and 8' hydrogens prevent these molecules from being planar.



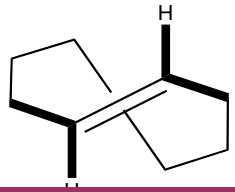
Hexahelicene

The activation energy required is 36.2 kcal/mol.

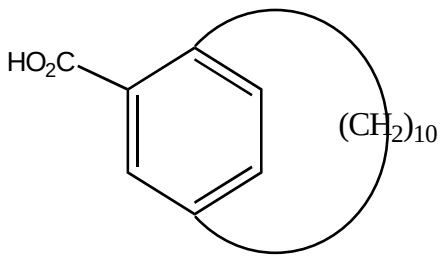
For E-cyclooctene the half-life is 1 h at 183.9 ^{0}C.
The activation energy is 35.6 kcal/mol.



E-cyclononene, racemizes much more rapidly.
The half-life is 4 min at 0 ^{0}C, with an activation energy of about 20 kcal/mol.



7) Chirality caused by restricted rotation of other type.



Specifying The Configuration

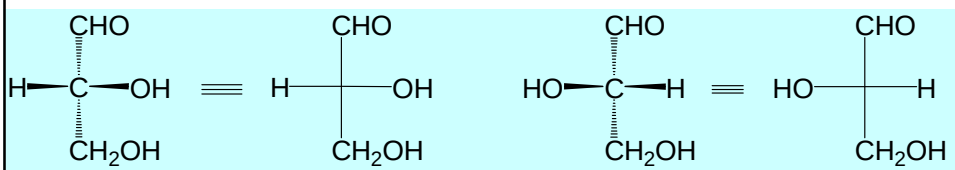
- Fischer Convention
- Cahn-Ingold-Perlog Convention

Fischer Convention (D and L description) for the configuration of carbohydrates and natural substances.

D= dextrorotary

L= levorotary

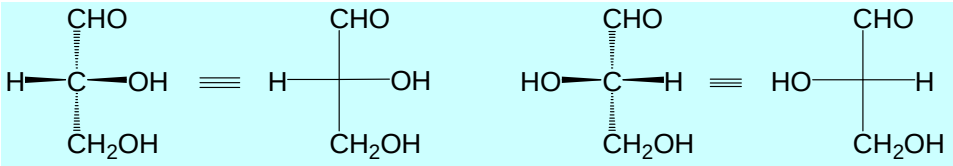
Two enantiomers of glyceraldehyde were originally **arbitrarily** assigned the configuration D and L. This assignment was then confirmed by X-Ray crystallography.



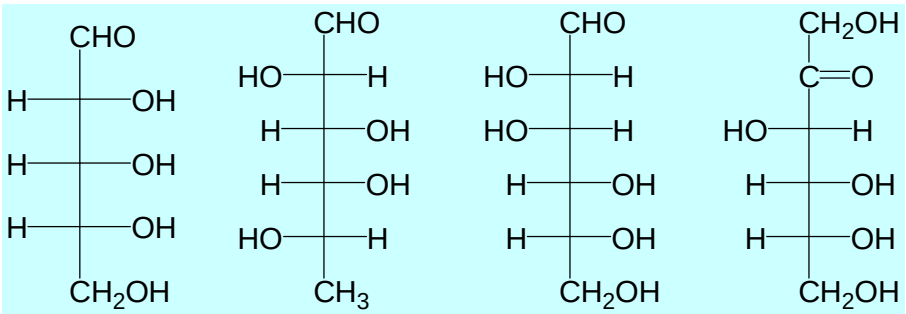
D-(+)-glyceraldehyde L-(-)-glyceraldehyde

Rules

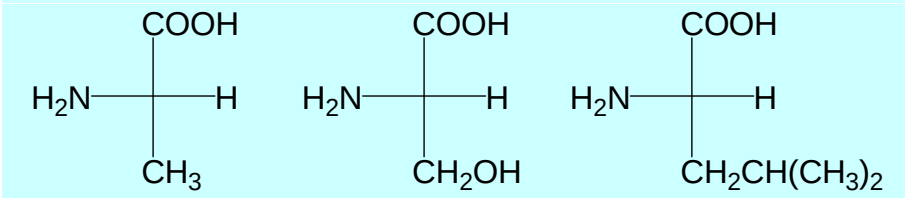
1. Major carbon chain align vertically.
2. The most oxidized terminal carbon at the top.
3. The horizontal bonds are directed forward to the viewer.
4. The vertical bonds are directed back, away from the viewer.
5. Notice to the largest group on the chiral atom at the lowest position in the Fischer projection.



D-(+)-glyceraldehyde L-(-)-glyceraldehyde



D-Ribose L-Fucose D-Mannose D-Fructose

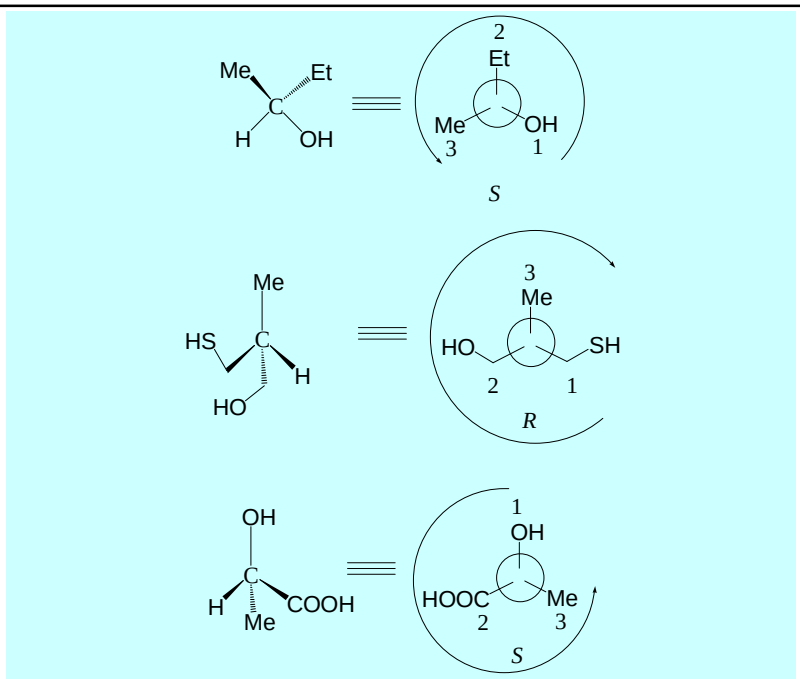


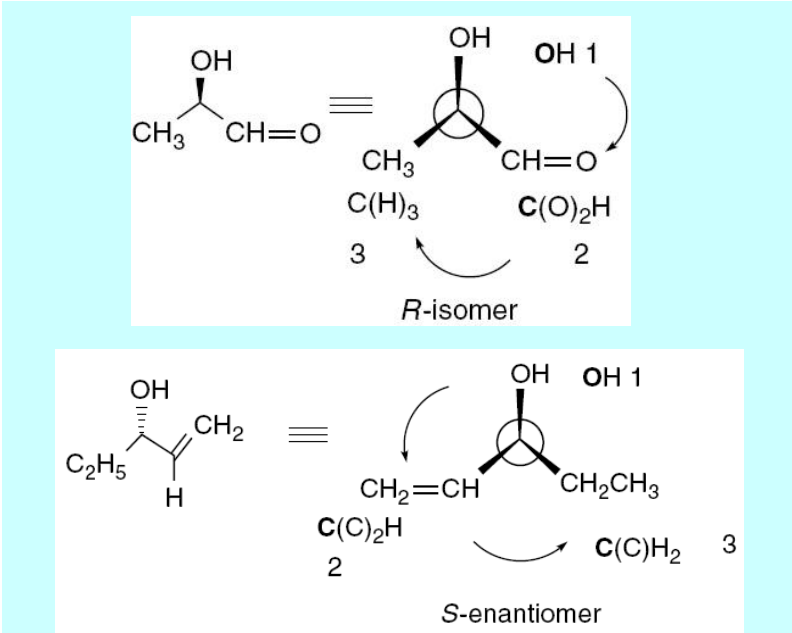
L-Alanine L-Serine L-Leucine

All amino acids found in proteins have the L – configuration.

Cahn-Ingold-Perlog Convention (*R* and *S* description):

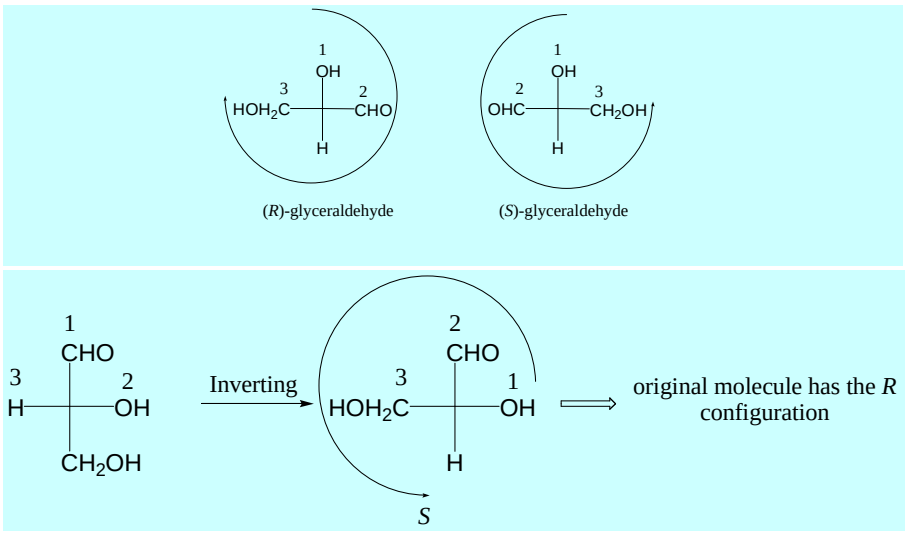
1. **Sequence Rule:** The substituents atoms are assigned decreasing priority in the order of decreasing atomic number.
2. The lowest priority substituent viewed **BEHIND** the chiral center.
3. Clockwise Decreasing The Priority: *R* (for Rectus)
4. Counterclockwise Decreasing The Priority: *S* (for Sinister)



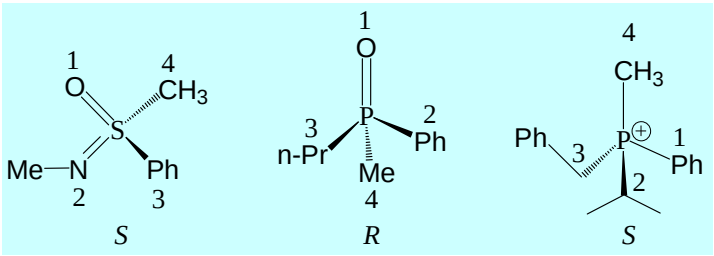


Determination of Configuration on Fischer Projection

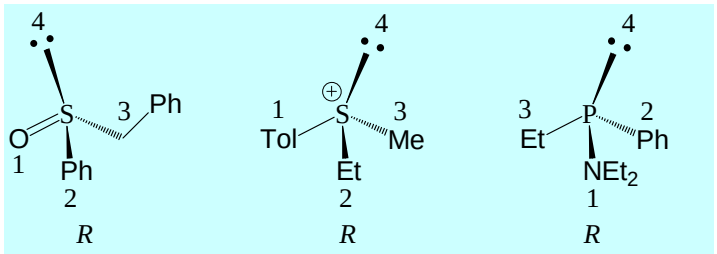
Lowest ranking group at the bottom:



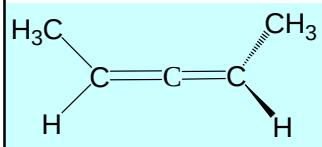
Chiral Centers Other Than Carbon



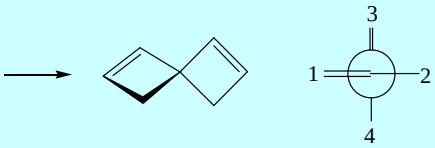
Phantom Atom with atomic number zero for tricoordinate chiral centers such as sulfoxides, sulfonium salts and phosphines.



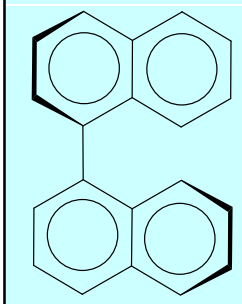
Chiral Molecules Having No Asymmetric Center

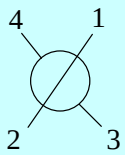


R-(-)-Dimethylallene

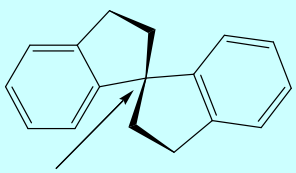


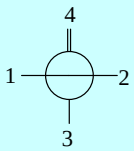
S-(+)-Spiro[3,3]-hepta-1,5-diene





S-(+)-1,1'-Binaphthyl





R-(+)-1,1'-Spirobiindane

Determination of Absolute Configuration

No direct relationship between the configurational descriptors *R* and *S* or D and L and the sign of the optical rotation of the molecule.

Approaches:

1. Chemical Process

2. Biochemical process

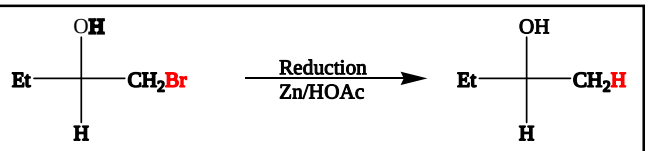
3. Optical Comparsion

4. Correlation with the **CD** and **ORD** curves of the molecules whose absolute configurations are known.

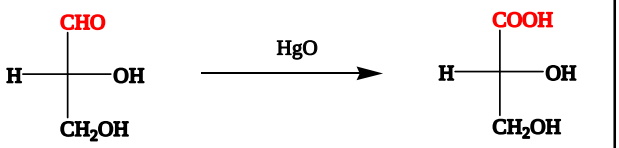
5. **X-Ray**

1. Chemical Process

A: Attacked to Neighborhood Chiral Carbon

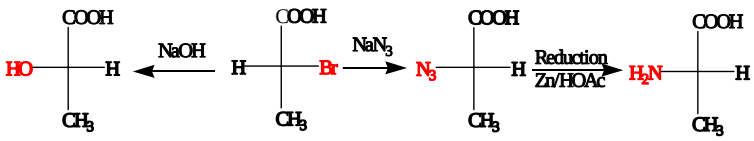


(R)-1- Bromo-2-Butanol (S)-2- Butanol



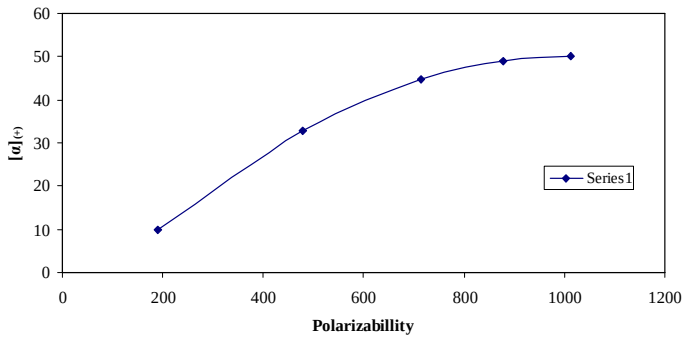
(R)-(+)- Glycer aldehyde (R)-(-)- Glyceric acid

B: Attacked to Chiral Carbon



(S)-(+)-Luctic acid (R)-(-)-2-bromo-propanoic acid (S) (S)-(+)-Alanine

3. Optical Comparsion

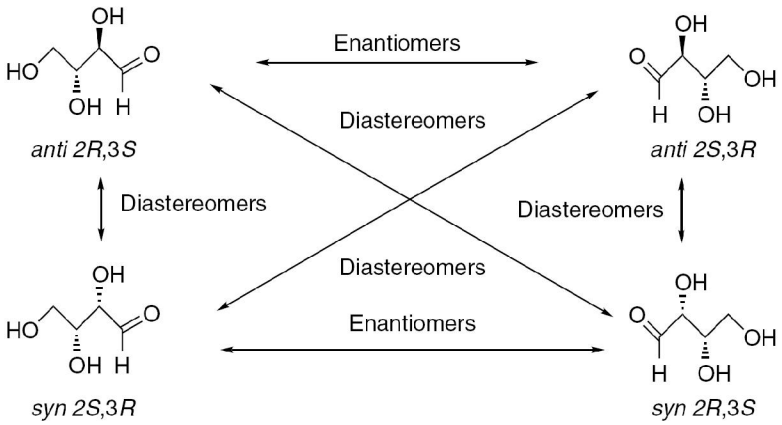


Molecules with Multiple Stereogenic Centers

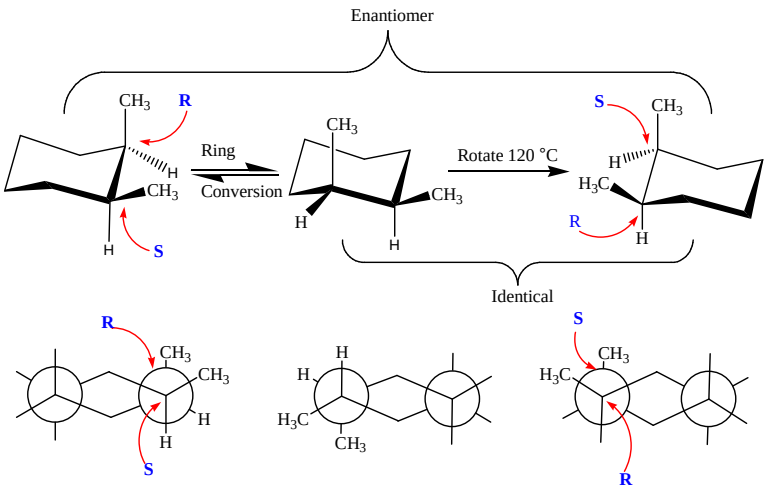
Molecules can have several stereogenic centers, including double bonds with Z or E configurations and asymmetrically substituted tetrahedral atoms. The maximum number of stereoisomers that can be generated from n stereogenic centers is 2^n.

There are several ways of representing molecules with multiple stereogenic centers.

The configuration at each center is specified as R or S. The isomers can also be characterized as syn or anti.



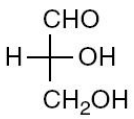
Extended chain representation of all stereoisomers of 2,3,4-trihydroxybutanal.



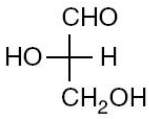
Another means of representing molecules with several stereocenters is by Fischer projection formulas.

Fischer projection formulas represent a completely eclipsed conformation of the vertical chain.

Fischer projection formulas may be reoriented only in the plane of the paper. In the conventional orientation, D-substituents are to the right and L-substituents are to the left.

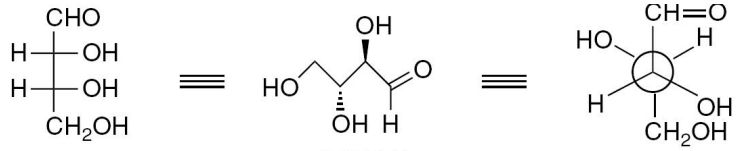


D-(+)-glyceraldehyde



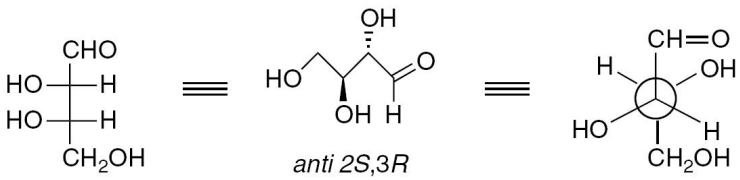
L-(-)-glyceraldehyde

The stereochemistry of adjacent stereocenters can also be usefully represented by Newman projection formulas. The relative configuration of adjacent substituents in a Fischer projection formula are designated *erythro* if they are on the same side and *threo* if they are on the opposite side.



2*R*,3*R*
(D-erythrose)

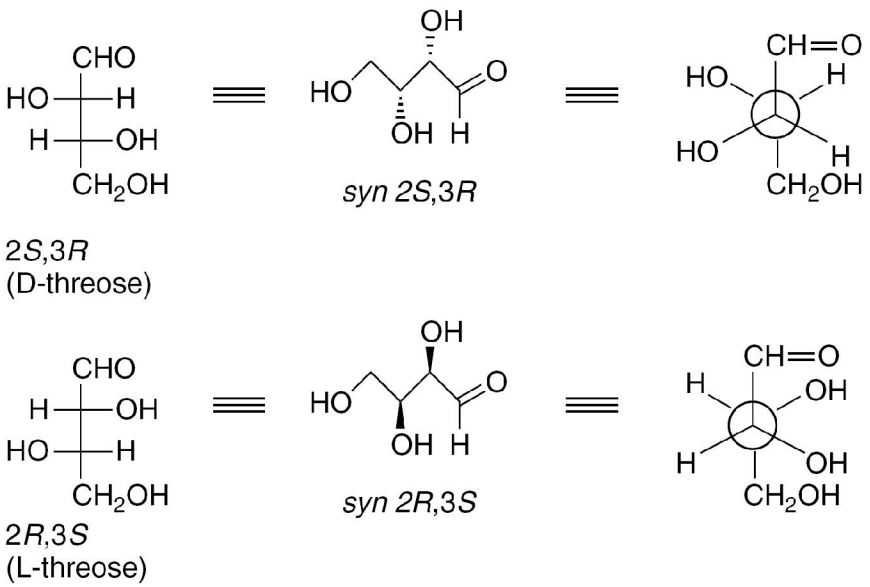
anti 2*R*,3*R*



2*S*,3*S*
(L-erythrose)

anti 2*S*,3*R*

Fischer, extended, and Newman projection representations of the stereoisomers of 2,3,4-trihydroxybutanal.



Fischer, extended, and Newman projection representations of the stereoisomers of 2,3,4-trihydroxybutanal.

Configuration at Prochiral Centers

Prochiral centers have two identical ligands, such as two hydrogens, and are achiral. In many situations, however, these identical ligands are *topologically nonequivalent* or *heterotopic*. This occurs when the other two substituents are different.

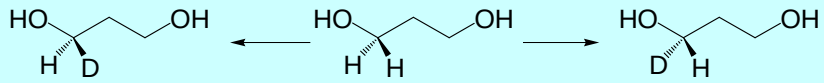
If either of the identical groups is replaced by a different ligand, a stereogenic center is created. The two positions are called *enantiotopic*. The position, which if assigned a higher priority, gives an R configuration is called pro-R. The position, which if assigned a higher priority, gives an S configuration is called pro-S.

Propane-1,3-diol is an example of a prochiral molecule. The C(1) and C(3) positions are prochiral, but the C(2) is not, because its two hydroxymethyl ligands are identical.

1. Homotopic
2. Enantiotopic
3. Diastreotopic

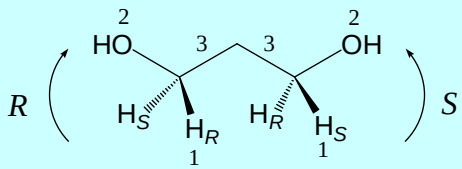
Distinguishing between identical ligands:

Enantiotopic Protons



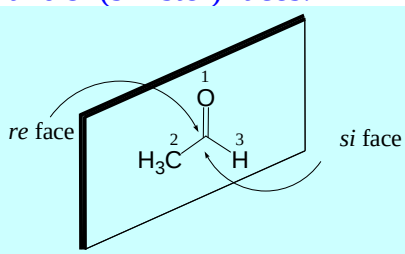
(*R*)-1-deutrio-1,3-propandiol (*S*)-1-deutrio-1,3-propandiol

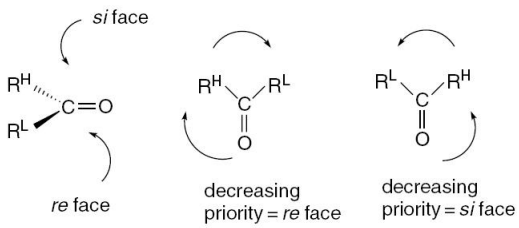
Assignment Enantiotopic Protons: Sequence rule, Pro-*R* and Pro-*S*



The carbonyl group is said to have an re face and an si face.
The enzyme-catalyzed interconversion of acetaldehyde to ethanol.

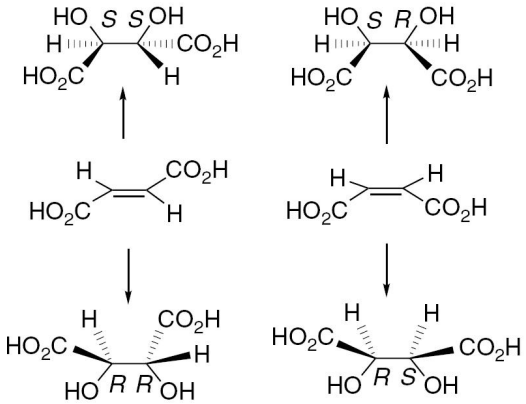
Prochiral *re* (rectus) and *si* (sinister) faces:





Other trigonal centers, including carbon-carbon double bonds, present two prochiral faces. For example, E- and Z-butenedioic acid (maleic and fumaric acid) generate different stereoisomers when subjected to *syn*-dihydroxylation.

If the reagent that is used is chiral, the E-isomer will generate different amounts of the R,R and S,S products. The S,R and R,S forms generated from the Z-isomer are *meso* forms and will be achiral, even if they are formed using a chiral reagent.



Two identical ligands at enantiotopic centers are in *chemically equivalent environments*. Enantiotopic protons do not show separate NMR signals. Two diastereotopic protons give rise to a more complex NMR pattern. Because of their chemical shift difference, they show a geminal coupling. An example of this effect can be seen in the proton NMR spectra of 1-phenyl-2-butanol, as shown in under Figure The C(1) CH_2 group appears as a quartet near 2.8 ppm with further coupling to the C(2) proton. The C(1) hydrogens are diastereotopic. The C(3) hydrogens are also diastereotopic, but their nonidentity is not obvious in the multiplet at about 1.6 ppm.

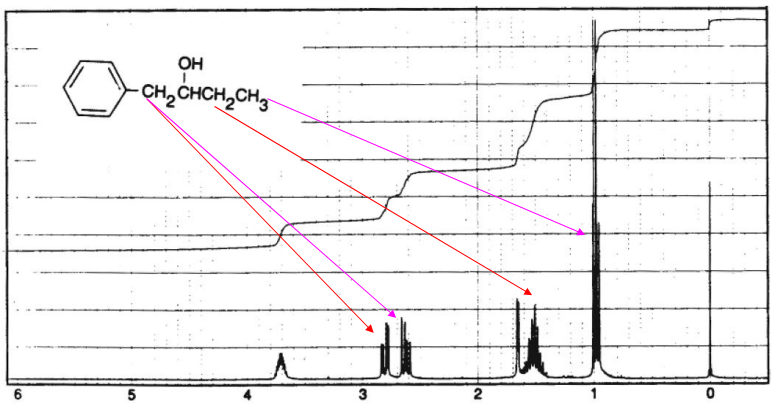
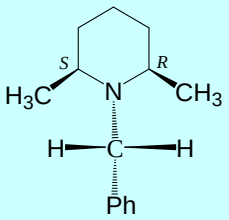


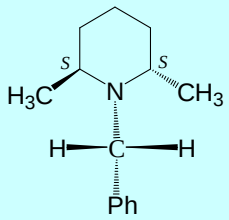
Fig. 2.6. NMR spectrum of 1-phenyl-2-butanol showing the diastereotopic nature of C(1) protons. Reproduced from *Aldrich Library of*^{13} *C and* ^{1}*H NMR Spectra*, Vol. 2, 1993, p. 386.

Diastereotopic protons are chemically nonequivalent and can be distinguished by physical probes especially NMR spectroscopy.

1-benzyl-cis(trans)-2,6-dimethylpiperidine



Enantiotopic Protons (singlet)
(molecule is Achiral)



Diastereotopic Protons (AB-Quartet)
(molecule is Chiral

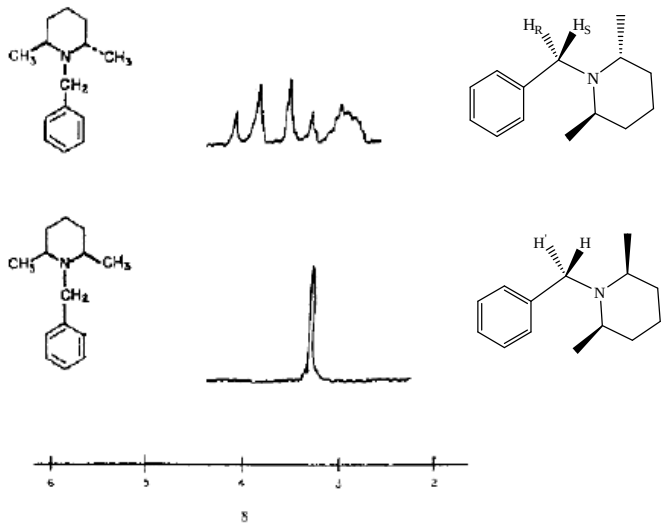
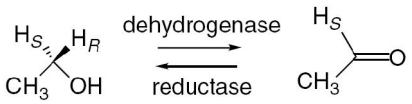


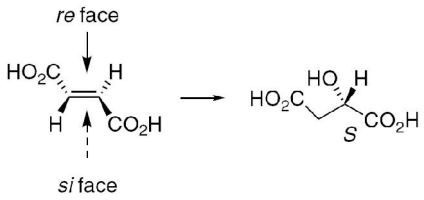
Fig. 2.8. Equivalent benzyl CH_2 protons in 1-benzyl-*cis*-2,6-dimethylpiperidine compared with nonequivalent protons in the *trans* isomer. [Reproduced from *Tetrahedron* **21**:2015 (1965) by permission of Elsevier Science.]

Enantiotopic protons are equivalent in all chemical and physical respects **EXCEPT** toward a chiral reagent. e.g.:

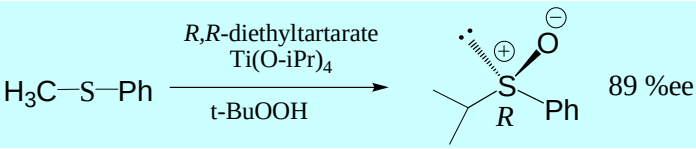
Because biological reactions involve chiral enzymes, enantiotopic groups and faces typically show different reactivity. For example, the two methylene hydrogens in ethanol are enantiotopic. Enzymes that oxidize ethanol, called *alcohol dehydrogenases*, selectively remove the pro-R hydrogen. This can be demonstrated by using a deuterated analog of ethanol in the reaction.

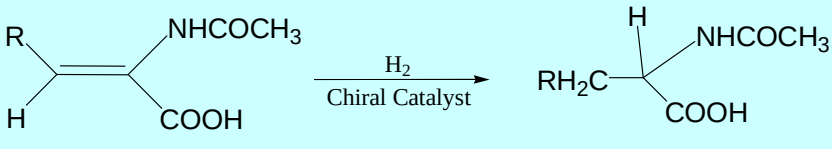


Conversely, *reductases* selectively reduce acetaldehyde from the *re* face. Fumaric acid is converted to L-malic acid (S-2-hydroxybutanedioic acid) by the enzyme *fumarase*. The hydroxyl group is added stereospecifically from the *si* face of the double bond.

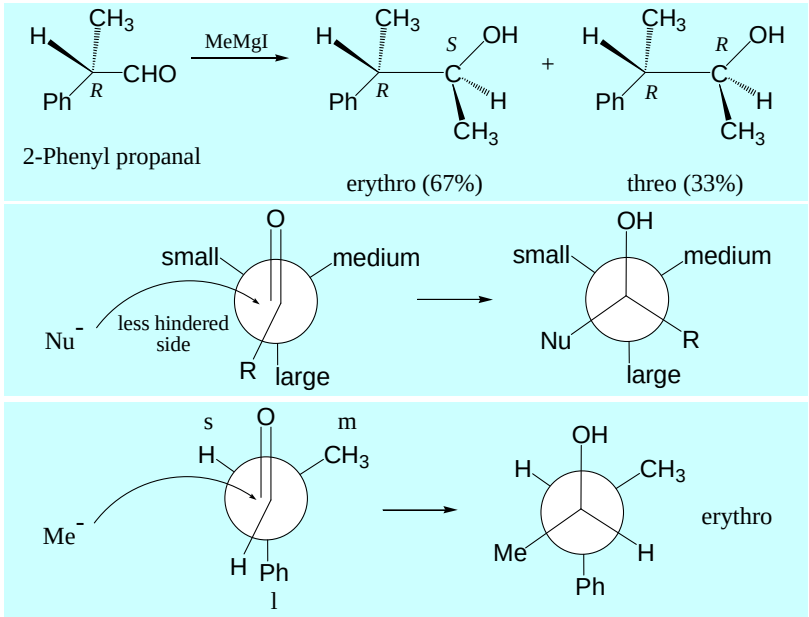


L-phenylalanine is converted to cinnamic acid by the enzyme *phenylalanine ammonialyase*. The reaction occurs by an *anti* elimination involving the amino group and the 3-*pro-R* hydrogen.





Cram's Rule



Resolution—The Separation of Enantiomers

1. Converting the mixture of enantiomers into a mixture of diastereomers: Reaction with a pure enantiomer of a second reagent.

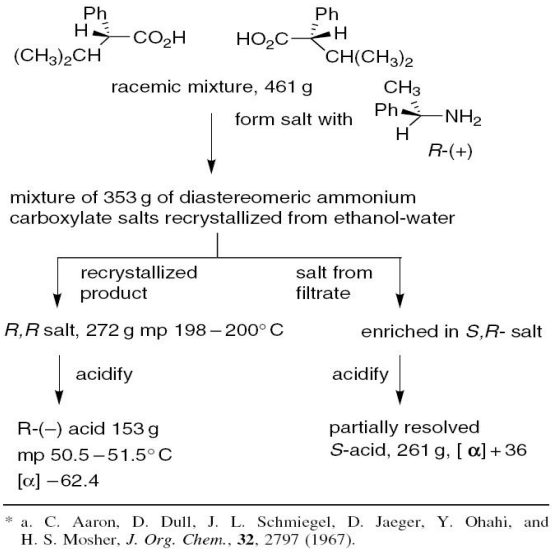
2. **Kinetic Resolution:** Incomplete reaction of two enantiomers with a chiral reagent.

3. **Enzymatic Resolution**: They are chiral and derived from L-amino acids (making diastereomeric relationship with enantiomers upon interaction).

4. Noncovalent binding with chiral substances (Chiral HPLC or GLC).

Conceptual Representation of Resolution through Separation of Diastereomeric Derivatives

Scheme 2.3. Resolution of 3-Methyl-2-Phenylbutanoic Acid[a]



[a] a. C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohahi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967).

Kinetic Resolution

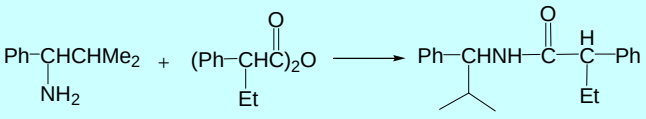
S enantiomer + *R* enentiomer

incomplete reaction with an enantiomerically pure reagent

if rate of the reaction of $R > S$ | if rate of the reaction of $R < S$

unreacted material enriched in *S*
product enriched in *R*

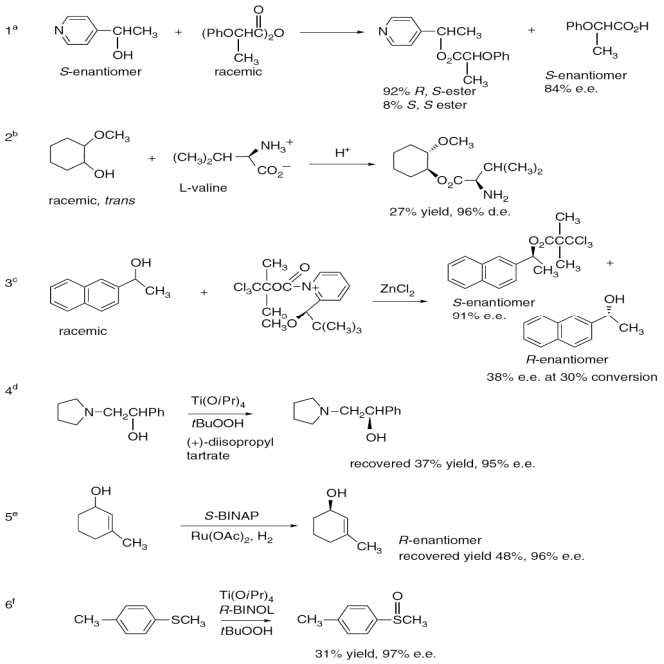
unreacted material enriched in *R*
product enriched in *S*



R, S *S* *(R, S) / (S, S)* = 1.75 with 0.25 eq. anhydride

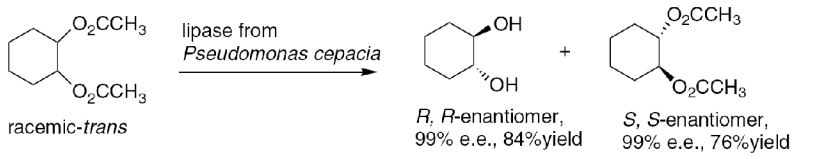
Bull. Chem. Soc. JPN. 57, 1570 (1984)

Scheme 2.5. Examples of Kinetic Resolution



Enzymatic Resolution

Two examples are shown below. The main restriction on enzymatic resolution is the relatively limited range of reactions and substrates to which it is applicable.

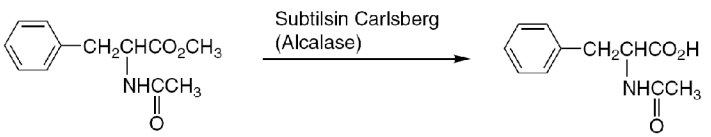


racemic-*trans*

R, R-enantiomer, 99% e.e., 84%yield

S, S-enantiomer, 99% e.e., 76%yield

Ref. 13



S-enantiomer, 98% e.e.

Ref. 14

Stereochemistry of Dynamic Process

Dynamic Stereochemistry: Topological features of processes which affect the molecular shape.

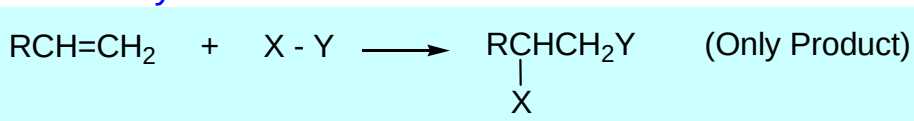
Stereo Specific Reaction: Stereomeric starting materials afford stereo chemically different products under same condition.

Stereo Selective Reaction: A single reactant has the capacity of forming two Stereomeric products in a particular reaction but one is formed preferentially.

Retention of Configuration: A process in which the relative spatial arrangement at the reaction center is the same in the reactant and the product.

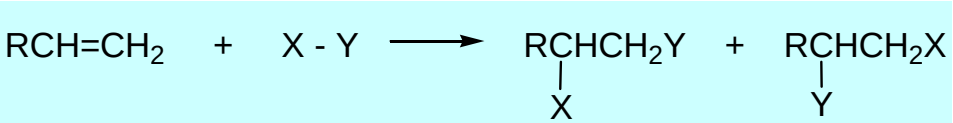
Inversion of Configuration: A process in which the configuration of the reaction center is inversed.

Regiospecific Reaction: One products is formed exclusively.



Regiospecific Reaction

Regioselective Reaction: One products is formed a predominantly.



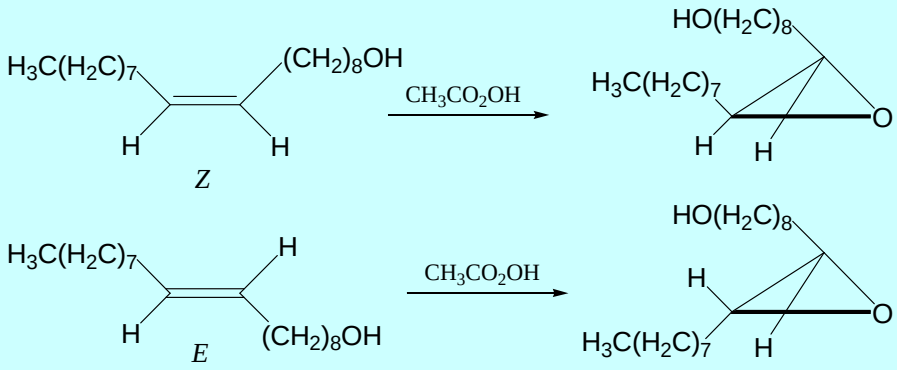
Regioselective Reaction

Racemization: A process which generate both possible enantiomers from a single enantiomer.

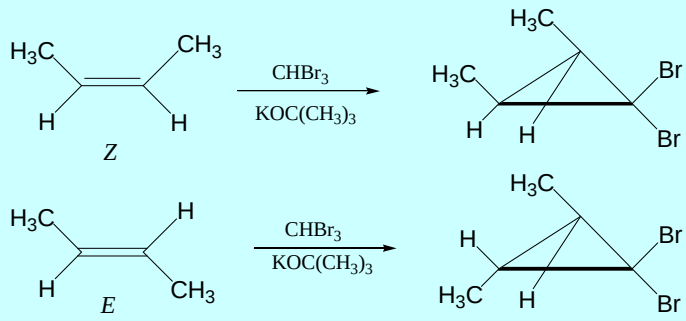
Epimerization: Occurring the racemization in a single chiral center in a diastereomer.

Some Examples for Stereo Specific Reactions:

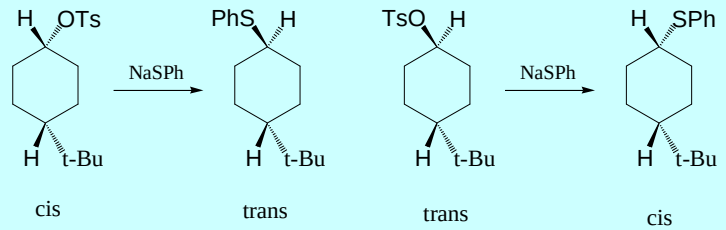
Epoxidatin of Alkenes:



Addition to Dibromocarbene

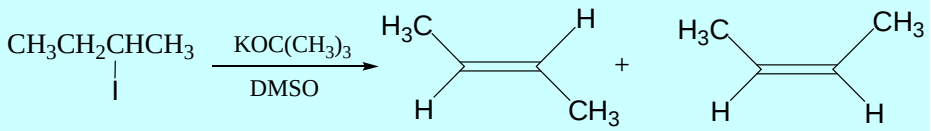


Nuclephilic Substitution (invertion of Configuration)



Some Examples for Stereo Selective Reactions

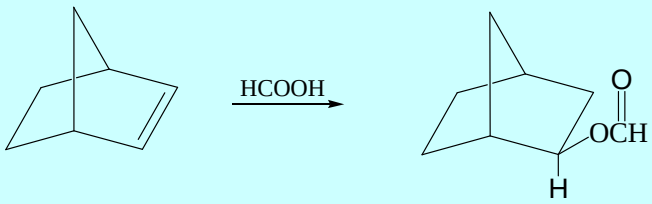
Dehydrohalogenation



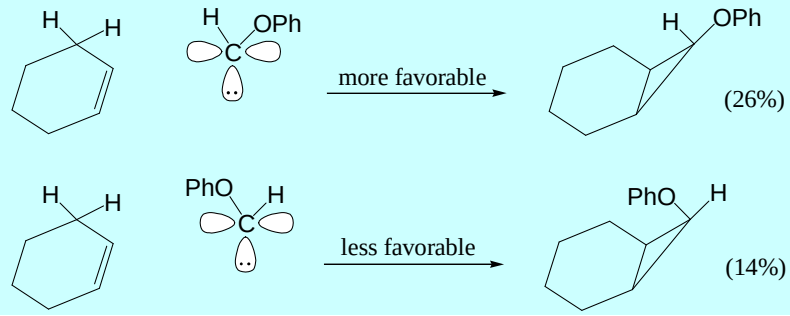
(60%) (20%)

+ $CH_3CH_2CH=CH_2$ (20%)

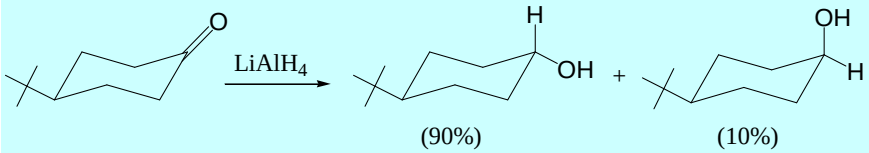
Addition of Formic Acid to Norbornene



Addition of Phenoxycarbene to Cyclohexene



Addition to Carbonyl Groups



Racemization

a) Cleavage of one ligand and formation of planar in tricoordinate intermediate.

b) Pyramidal inversion at trivalent N, S or P compounds.

Rate of Racemization: Barrier to the inversion process.

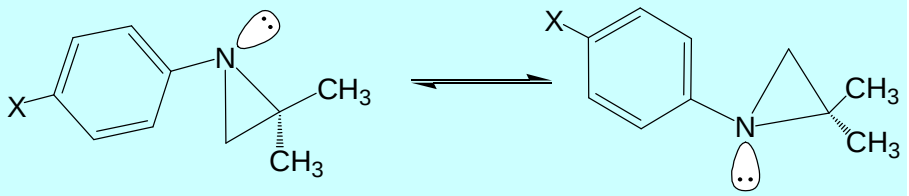
N containing compounds: The barrier is low

Inversion is too rapid

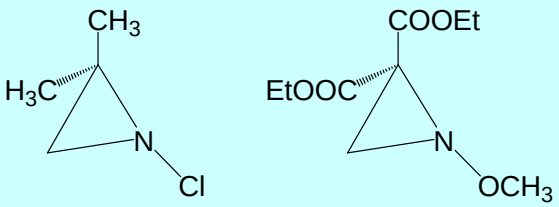
The enantiomers can be separated rarely

It can be shown by NMR

Aziridines:



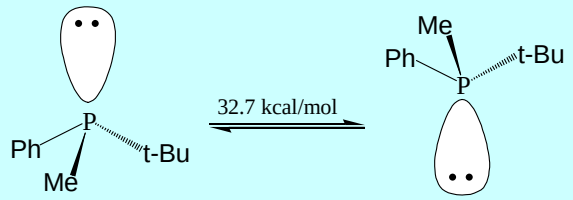
Inversion barrier 8-12 kcal/mol depending on X



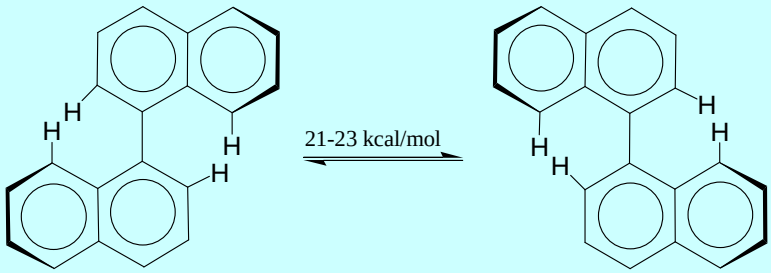
separated

Inversion in Heavier Atoms: Higher Barrier

Phosphines

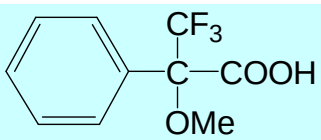


1,1'-Binaphthyl



Determination of Enantiomeric Purity

NMR Spectroscopy: Chiral Shift Reagents (making diastereomeric relationship with enantiomers upon interaction)



Mosher's Reagent

Lanthanide Complexes

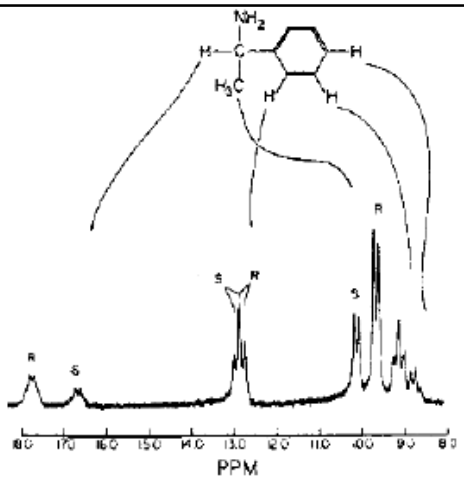


Fig. 2.7. NMR spectrum of 1-phenylethylamine in the presence of a chiral shift reagent, showing differential chemical shift of methine and methyl signals and indicating ratio of *R*- to *S*-enantiomers. [Reproduced from *J. Am. Chem. Soc.* **93**:5914 (1971) by permission of the American Chemical Society.]