South Valley University

Faculty of Education

Chemistry Department

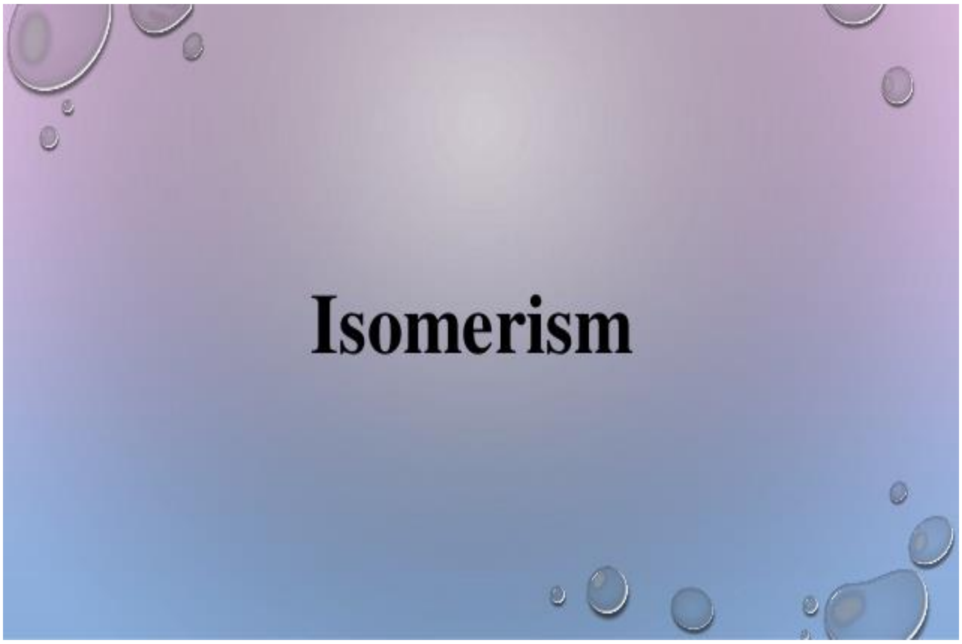
Organic Chemistry II

2nd year students – Faculty of Education

Chemistry group

Second Term 2022/2023

Dr/ Ibrahim Abdul-Motaleb Mousa



Isomerism

2nd year students - Chemistry group – Faculty of Education

Second term – 2022/2023

Dr/ Ibrahim Abdul-Motaleb Mousa

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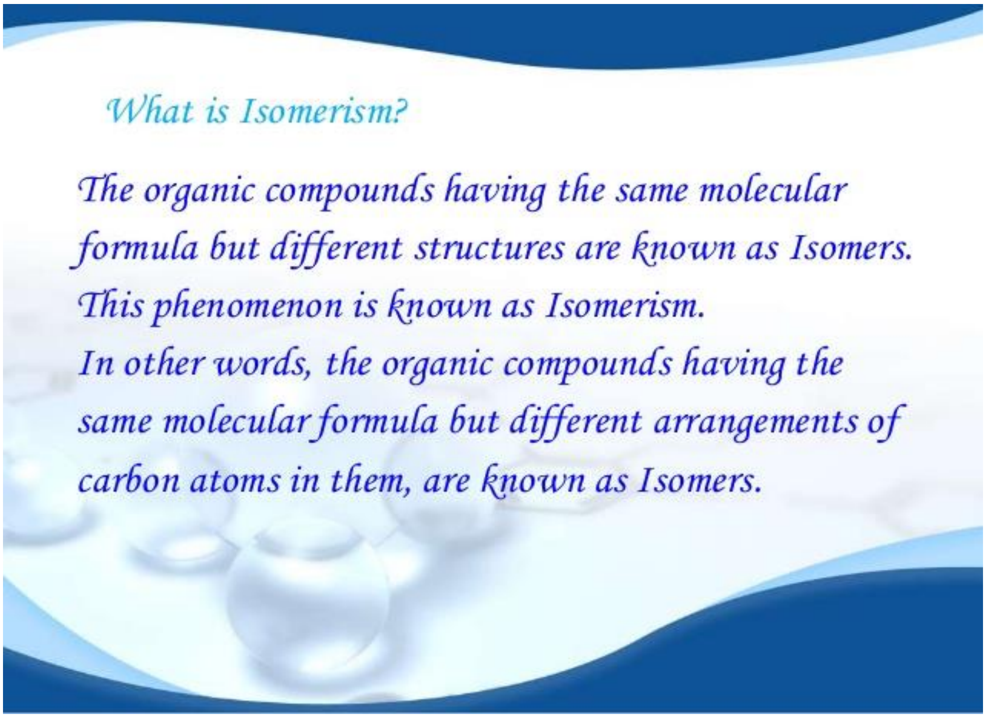
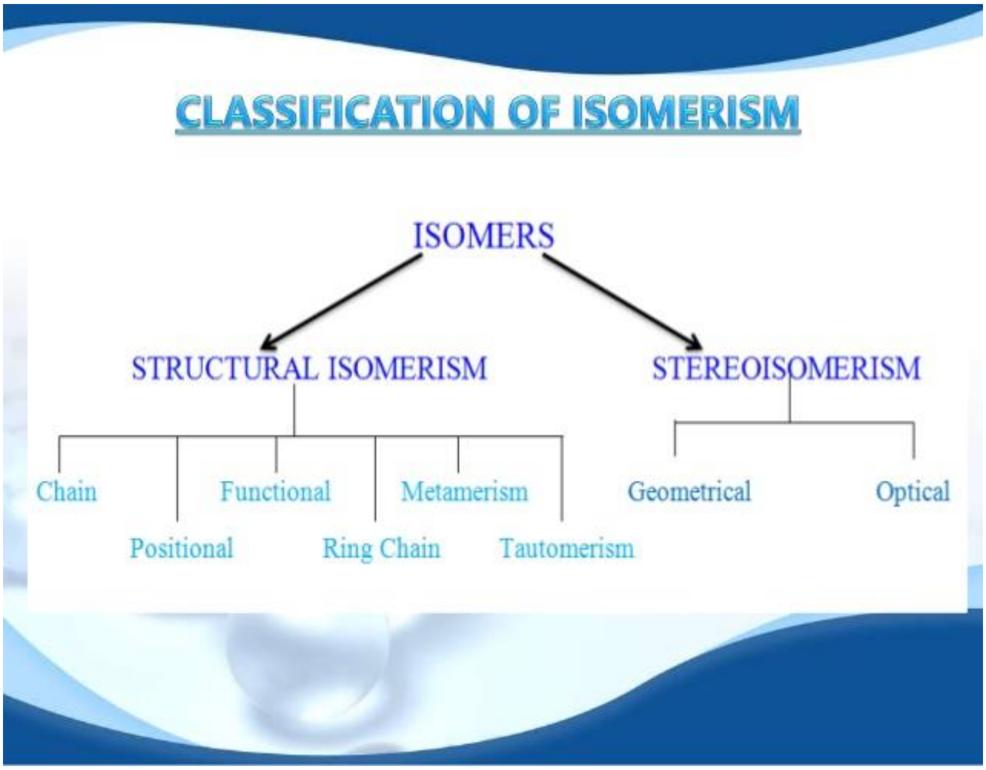


What is Isomerism?

The organic compounds having the same molecular formula but different structures are known as Isomers. This phenomenon is known as Isomerism.

In other words, the organic compounds having the same molecular formula but different arrangements of carbon atoms in them, are known as Isomers.



CLASSIFICATION OF ISOMERISM

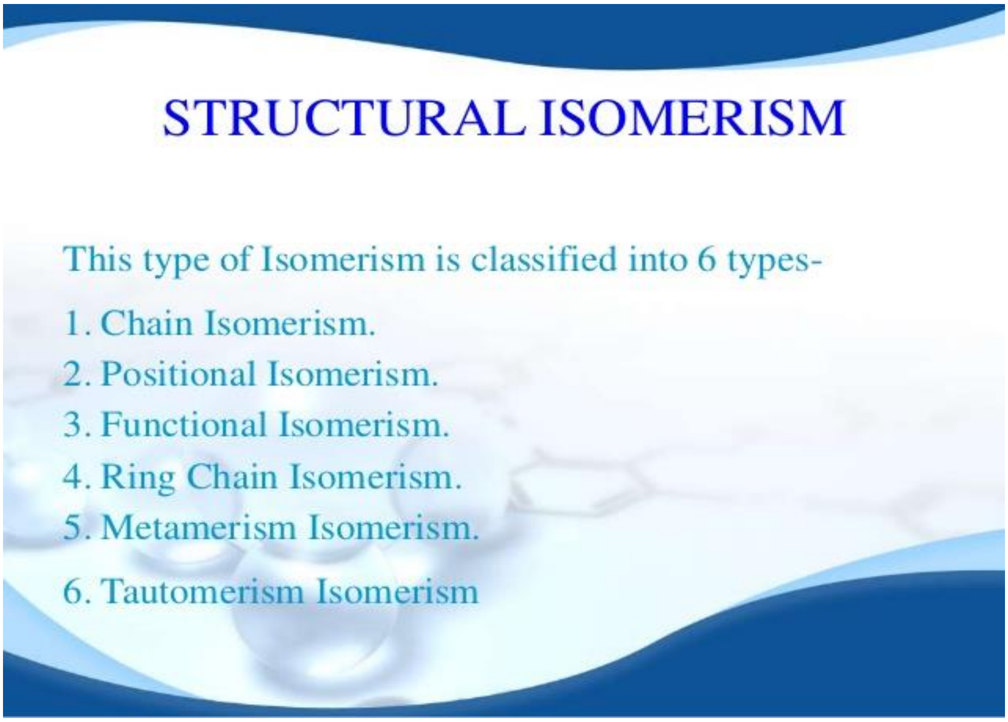
ISOMERS

STRUCTURAL ISOMERISM

- Chain
- Positional
- Functional
- Ring Chain
- Metamerism
- Tautomerism

STEREOISOMERISM

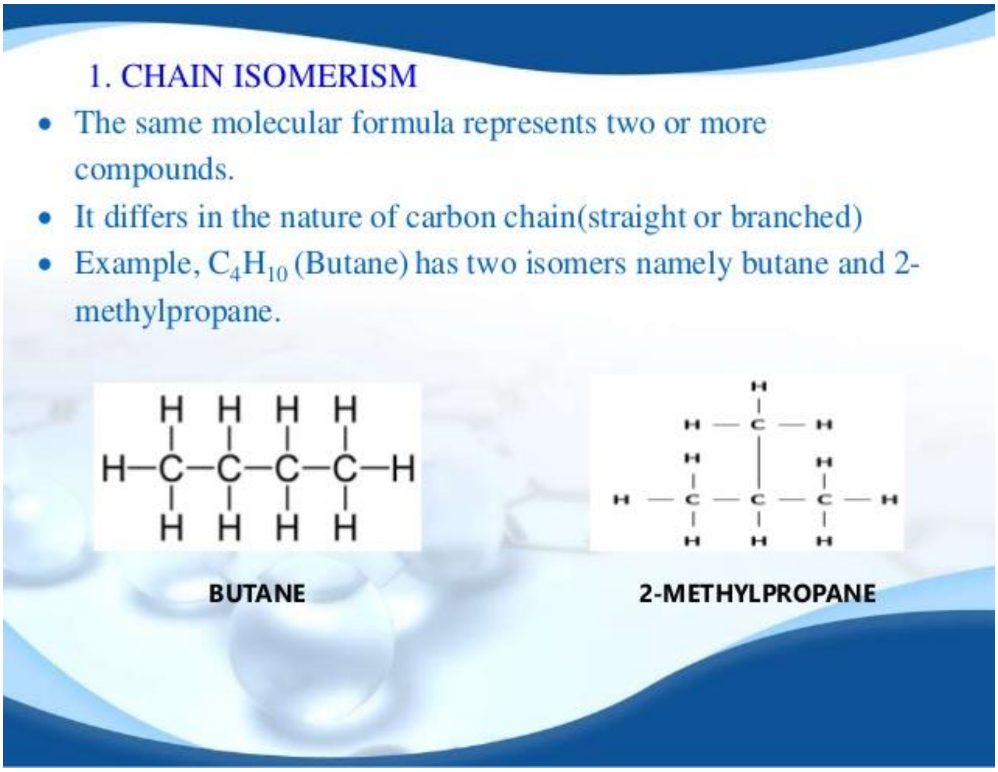
- Geometrical
- Optical



STRUCTURAL ISOMERISM

This type of Isomerism is classified into 6 types-

1. Chain Isomerism.
2. Positional Isomerism.
3. Functional Isomerism.
4. Ring Chain Isomerism.
5. Metamerism Isomerism.
6. Tautomerism Isomerism

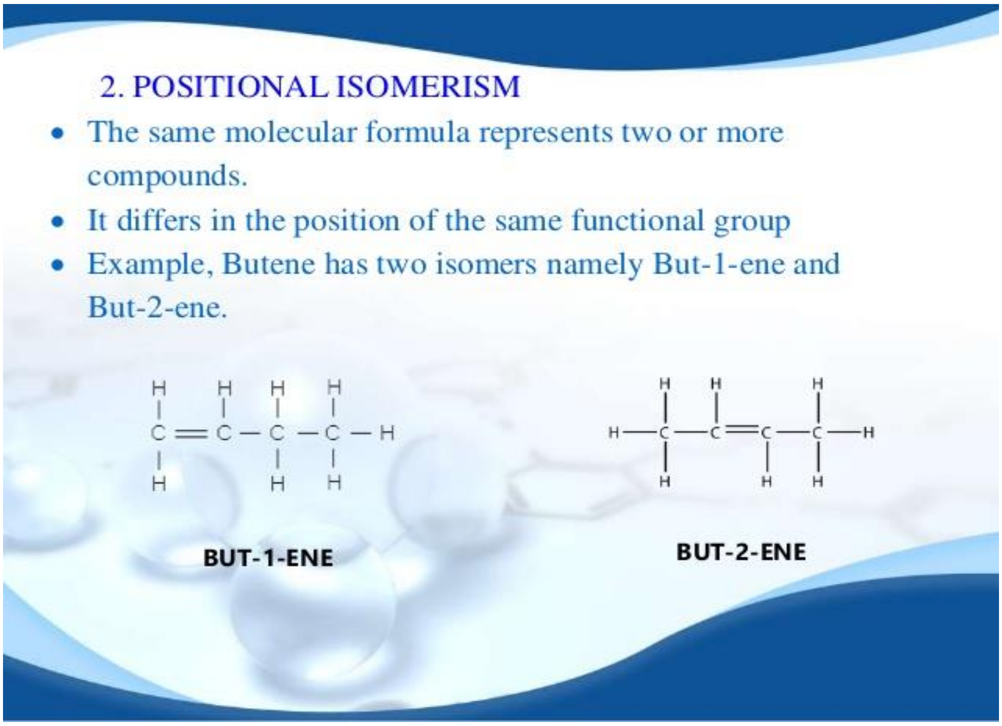


1. CHAIN ISOMERISM

- The same molecular formula represents two or more compounds.
- It differs in the nature of carbon chain(straight or branched)
- Example, C_4H_{10} (Butane) has two isomers namely butane and 2-methylpropane.

BUTANE

2-METHYLPROPANE

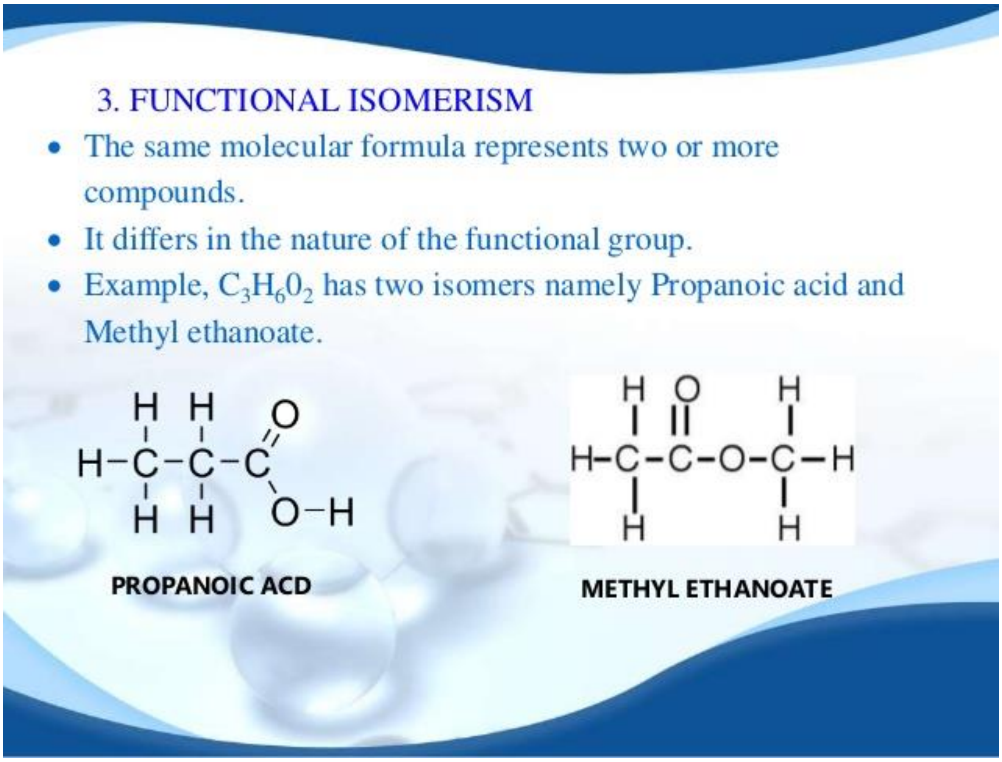


2. POSITIONAL ISOMERISM

- The same molecular formula represents two or more compounds.
- It differs in the position of the same functional group
- Example, Butene has two isomers namely But-1-ene and But-2-ene.

BUT-1-ENE

BUT-2-ENE



3. FUNCTIONAL ISOMERISM

- The same molecular formula represents two or more compounds.
- It differs in the nature of the functional group.
- Example, $C_3H_60_2$ has two isomers namely Propanoic acid and Methyl ethanoate.

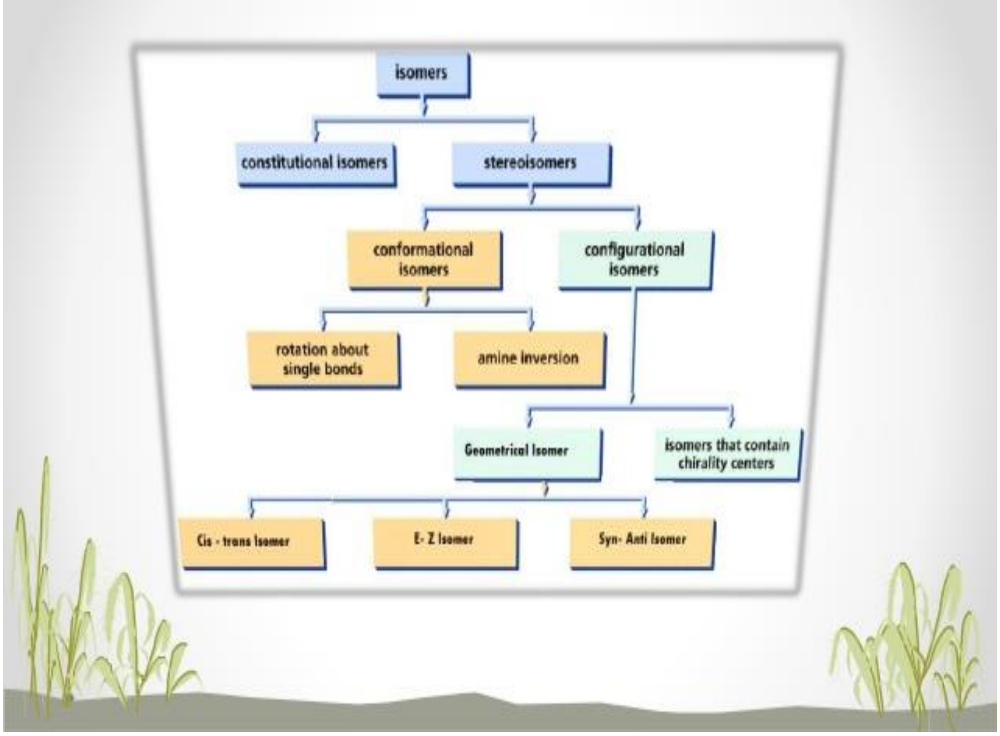
PROPANOIC ACD

METHYL ETHANOATE

Geometrical isomerism

Objective

- What is isomer
- Geometrical isomer
- Cis-trans isomer
- E-Z Isomer
- Syn – anti Isomer



isomers

constitutional isomers

stereoisomers

conformational isomers

configurational isomers

rotation about single bonds

amine inversion

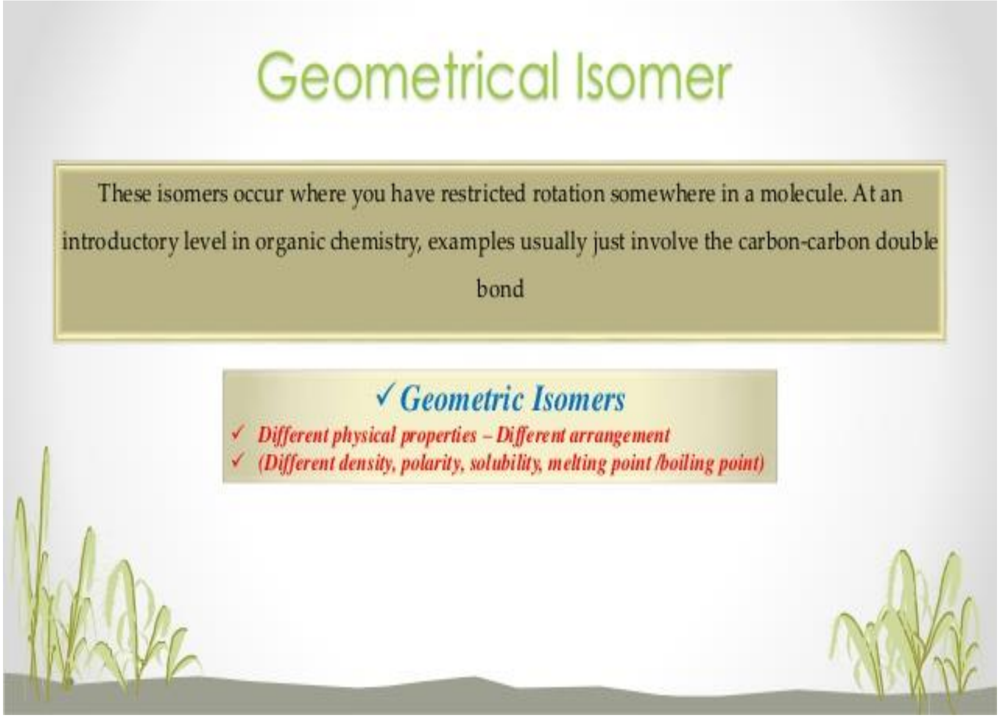
Geometrical Isomer

isomers that contain chirality centers

Cis - trans Isomer

E- Z Isomer

Syn- Anti Isomer

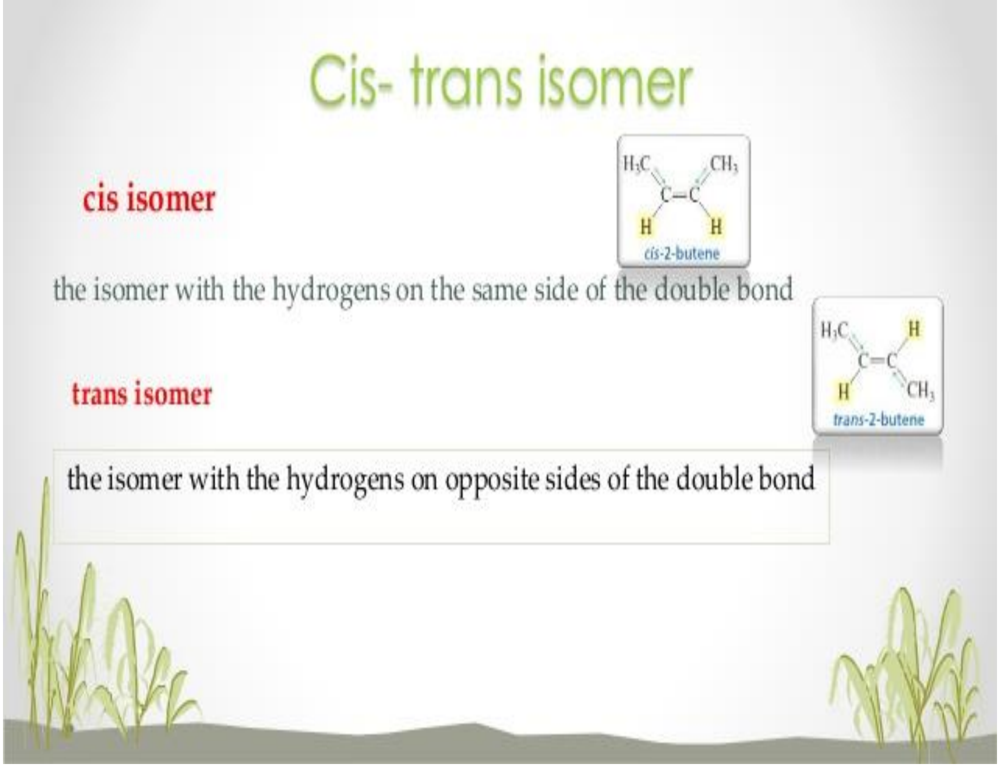


Geometrical Isomer

These isomers occur where you have restricted rotation somewhere in a molecule. At an introductory level in organic chemistry, examples usually just involve the carbon-carbon double bond

✓ *Geometric Isomers*

- ✓ ***Different physical properties – Different arrangement***
- ✓ ***(Different density, polarity, solubility, melting point /boiling point)***



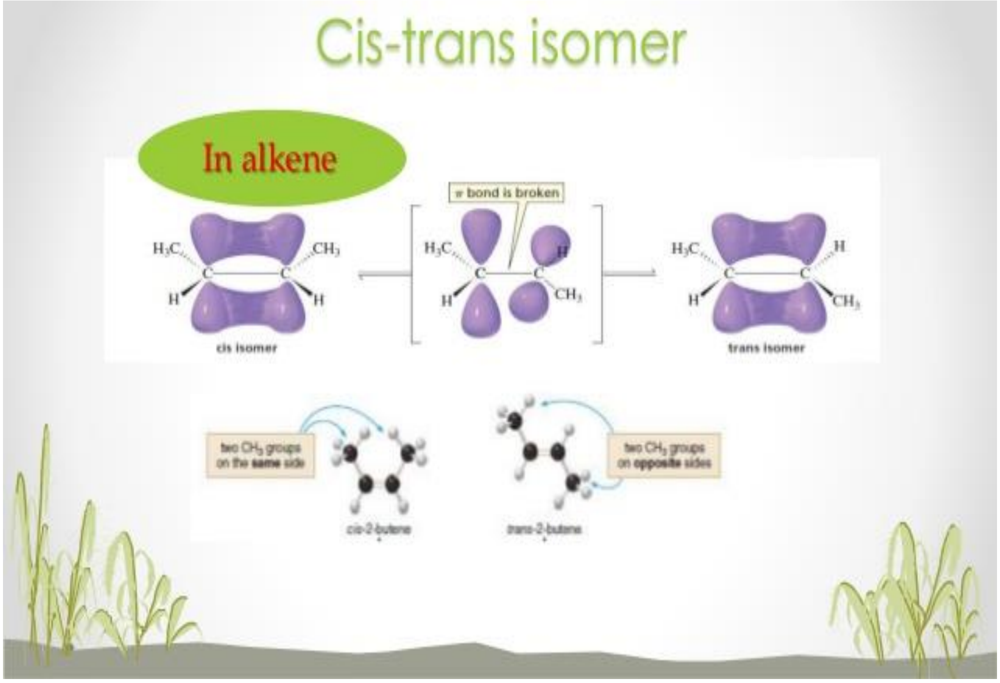
Cis- trans isomer

cis isomer

the isomer with the hydrogens on the same side of the double bond

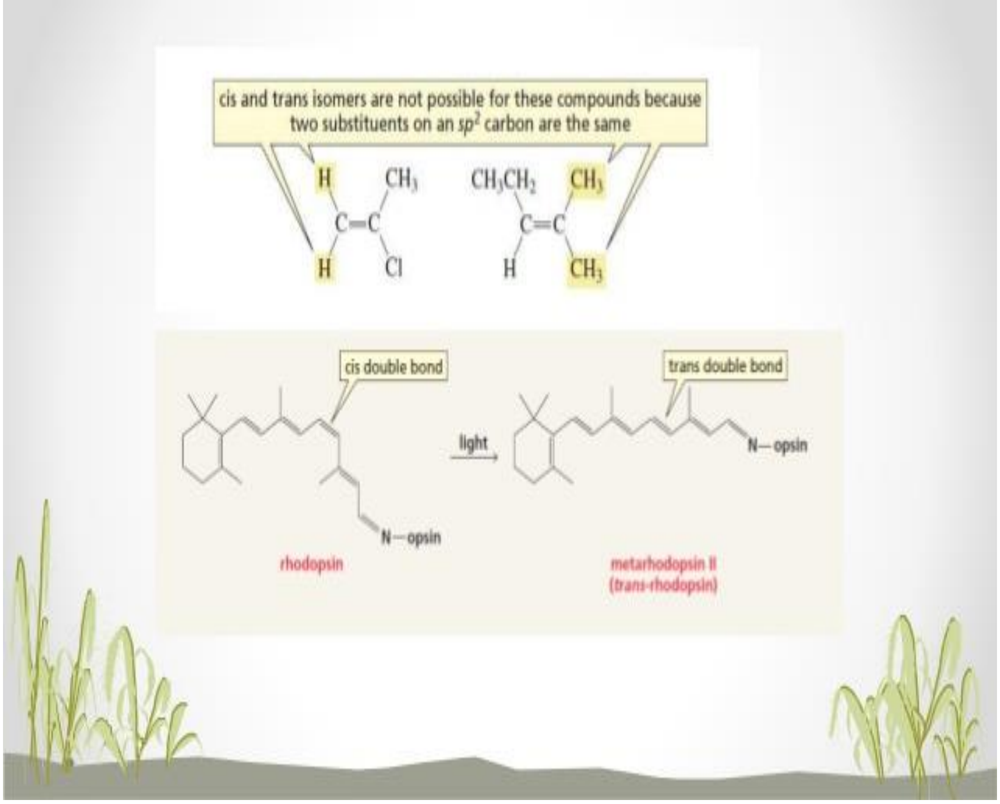
trans isomer

the isomer with the hydrogens on opposite sides of the double bond

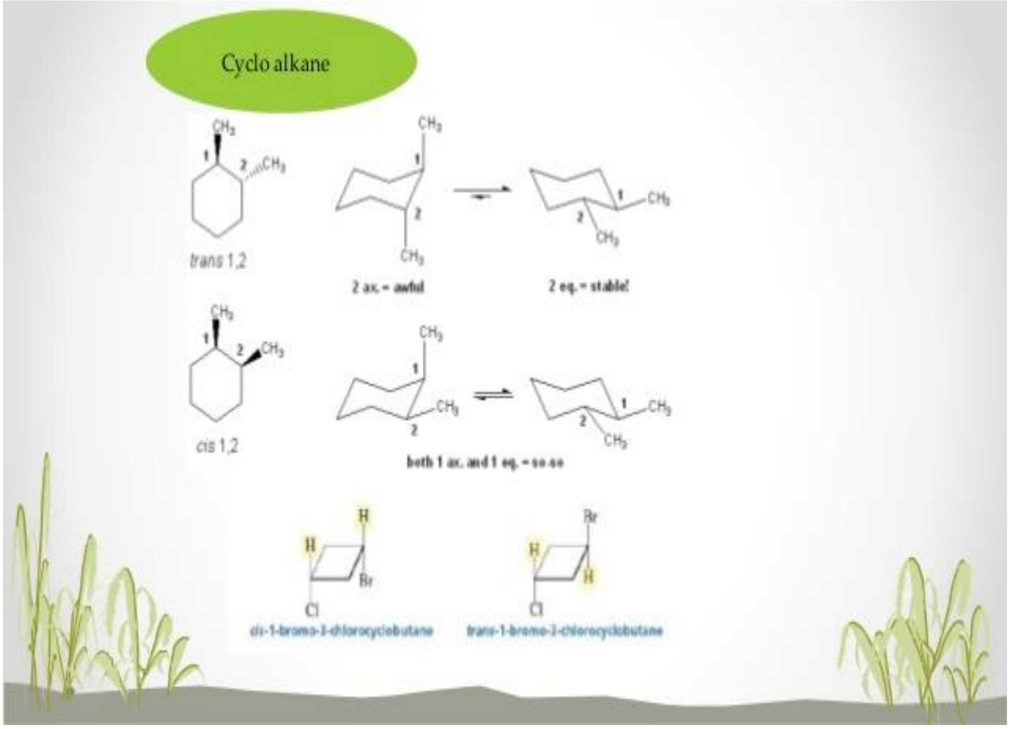


Cis-trans isomer

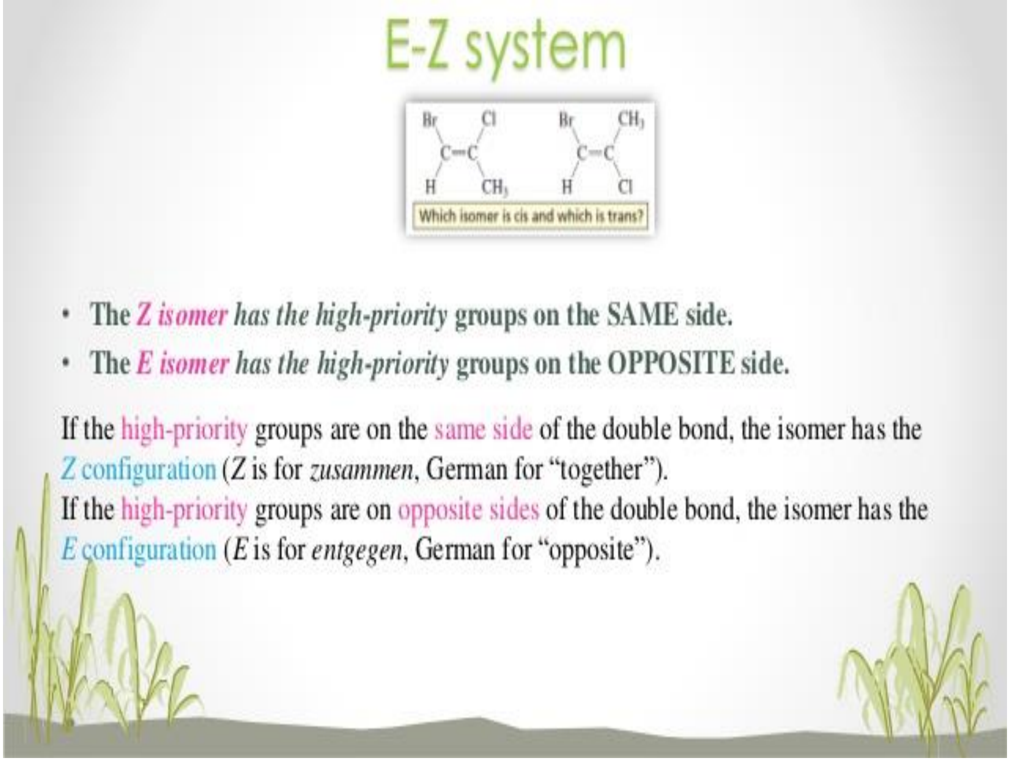
In alkene



cis and trans isomers are not possible for these compounds because two substituents on an sp^2 carbon are the same



Cyclo alkane

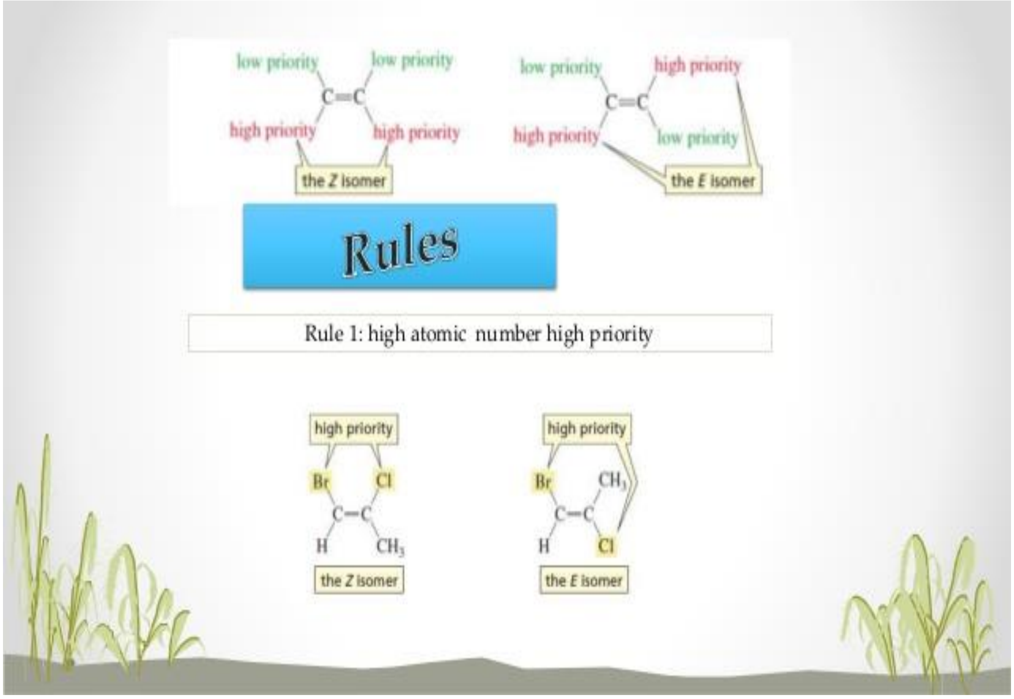


E-Z system

Which isomer is cis and which is trans?

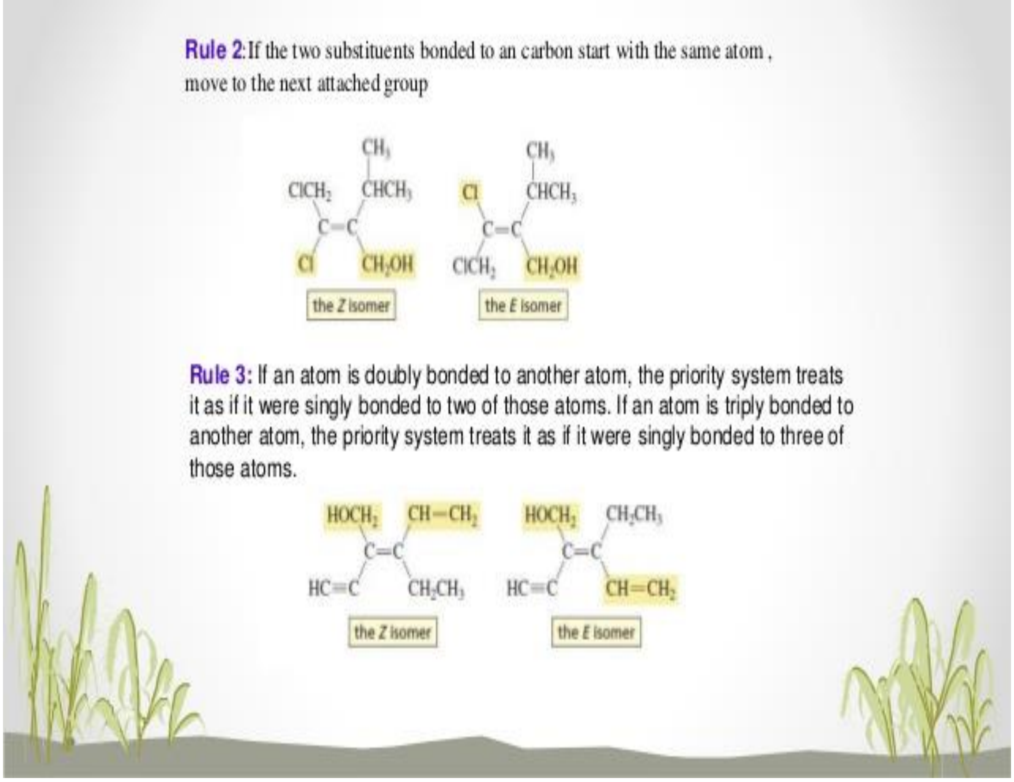
- The *Z isomer has the high-priority* groups on the SAME side.
- The *E isomer has the high-priority* groups on the OPPOSITE side.

If the high-priority groups are on the same side of the double bond, the isomer has the Z configuration (Z is for *zusammen*, German for "together").
If the high-priority groups are on opposite sides of the double bond, the isomer has the E configuration (*E* is for *entgegen*, German for "opposite").



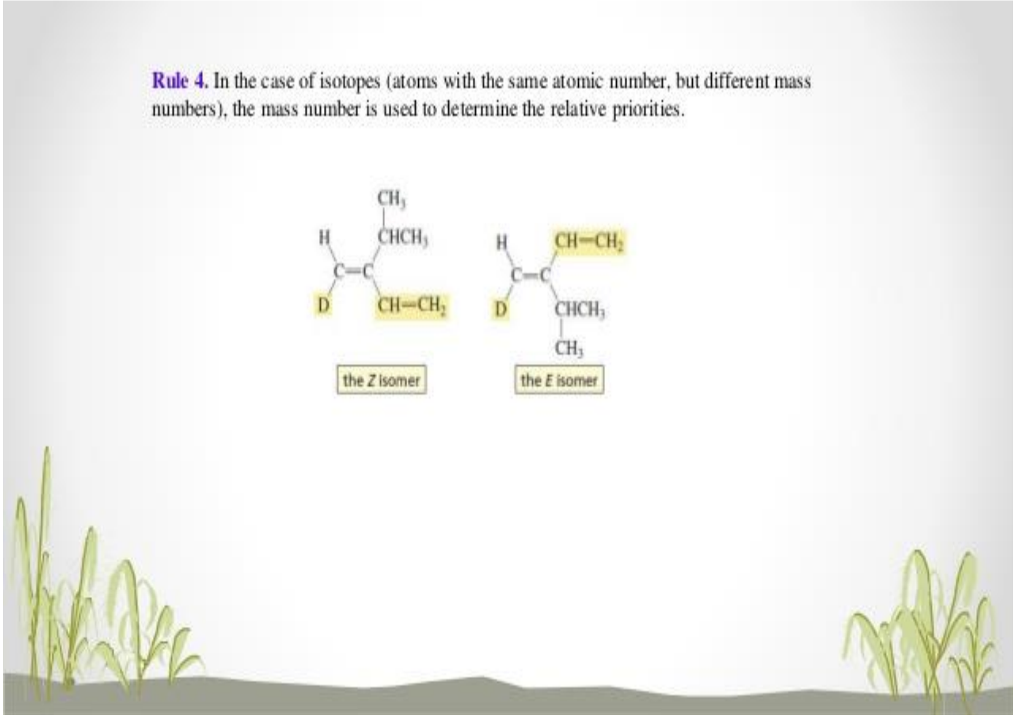
Rules

Rule 1: high atomic number high priority



Rule 2: If the two substituents bonded to an carbon start with the same atom , move to the next attached group

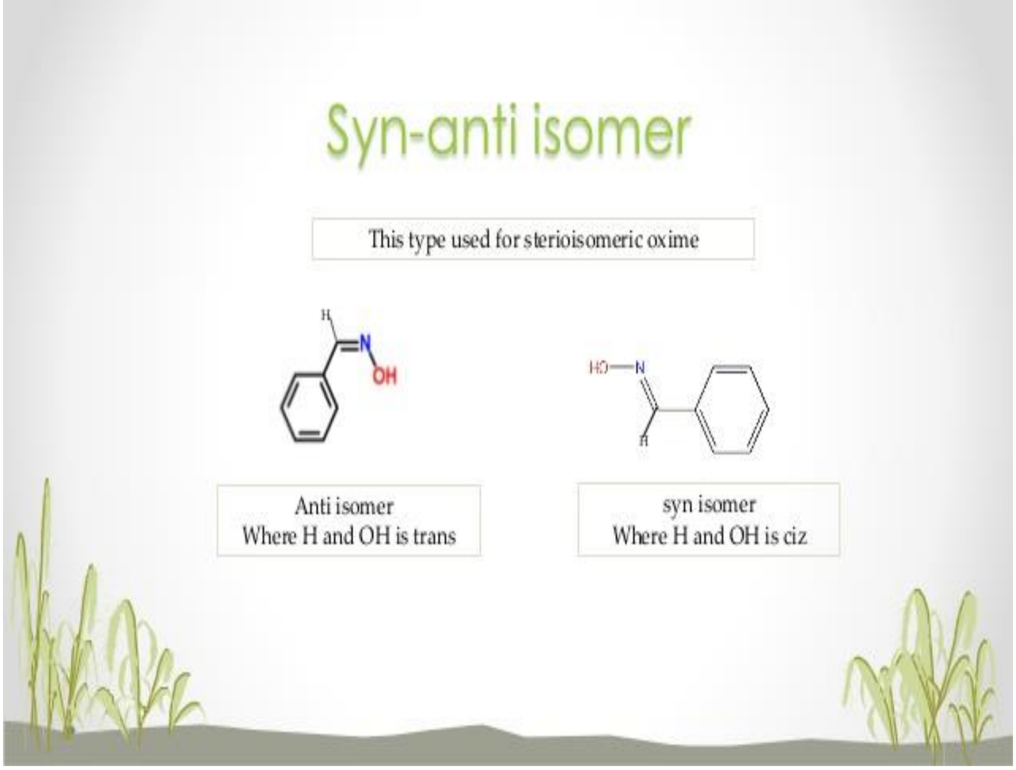
Rule 3: If an atom is doubly bonded to another atom, the priority system treats it as if it were singly bonded to two of those atoms. If an atom is triply bonded to another atom, the priority system treats it as if it were singly bonded to three of those atoms.



Rule 4. In the case of isotopes (atoms with the same atomic number, but different mass numbers), the mass number is used to determine the relative priorities.

the *Z* isomer

the *E* isomer



Syn-anti isomer

This type used for sterioisomeric oxime

Anti isomer
Where H and OH is trans

syn isomer
Where H and OH is ciz

Stereochemistry of Alkanes and Cycloalkanes

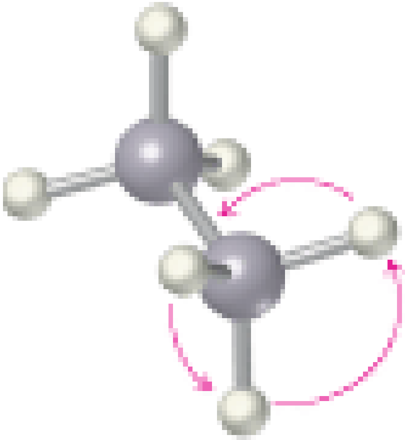
The Shapes of Molecules

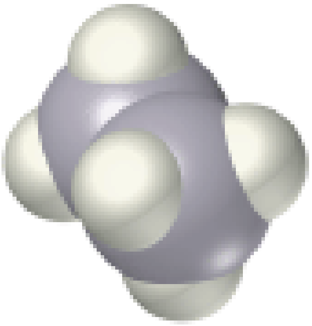
- ☐ **The three-dimensional shapes of molecules result from many forces**
- ☐ **A molecule may assume different shapes, called conformations, that are in equilibrium at room temperature (*the conformational isomers are called conformers*, emphasis on the first syllable)**
- ☐ **The systematic study of the shapes molecules and properties from these shapes is stereochemistry**
- ☐ **The field of stereochemistry is one of the central parts of organic chemistry and includes many important topics**

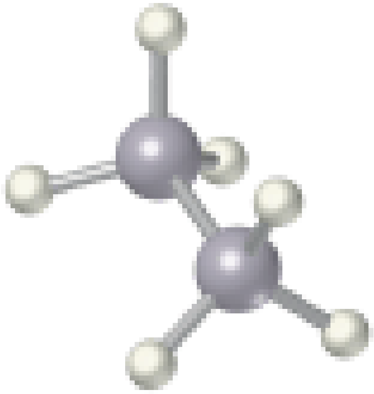
Conformations of Ethane

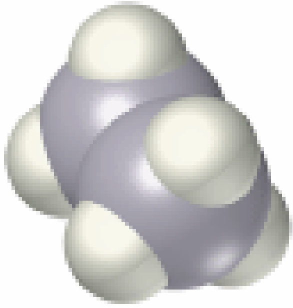
- ☐ **Conformers interconvert rapidly and a structure is an average of conformers**
- ☐ **Molecular models are three dimensional objects that enable us to visualize conformers**

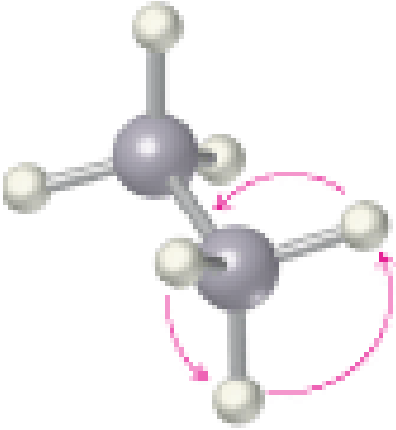
☐ **Representing three dimensional conformers in two dimensions is done with standard types of drawings**



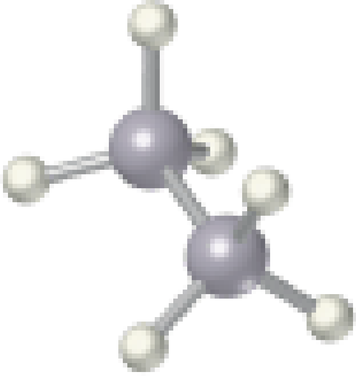






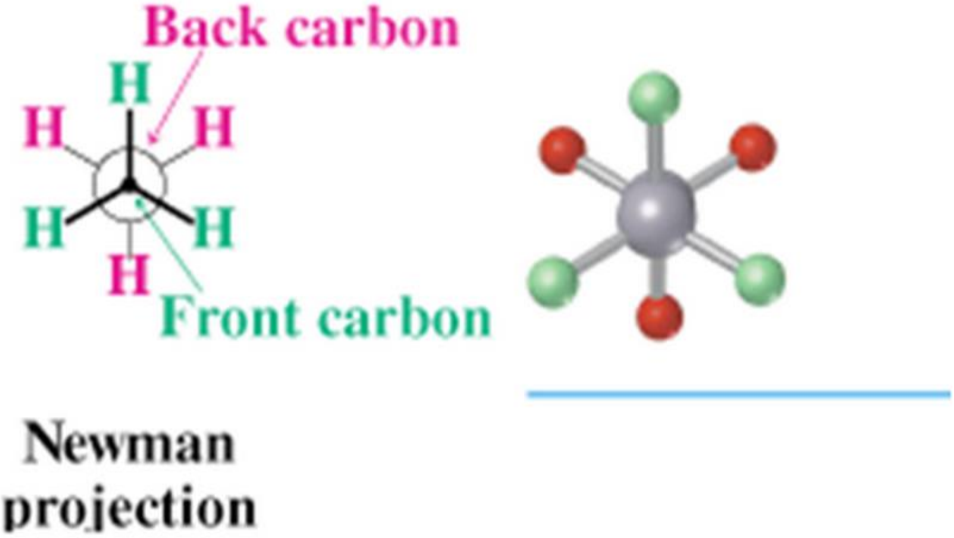


staggered conformation

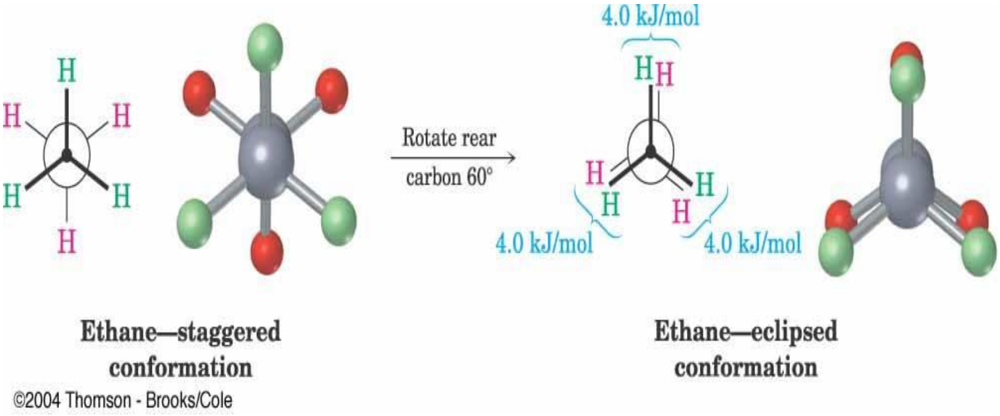


eclipsed conformation

Newman Projections



Ethane’s Conformations

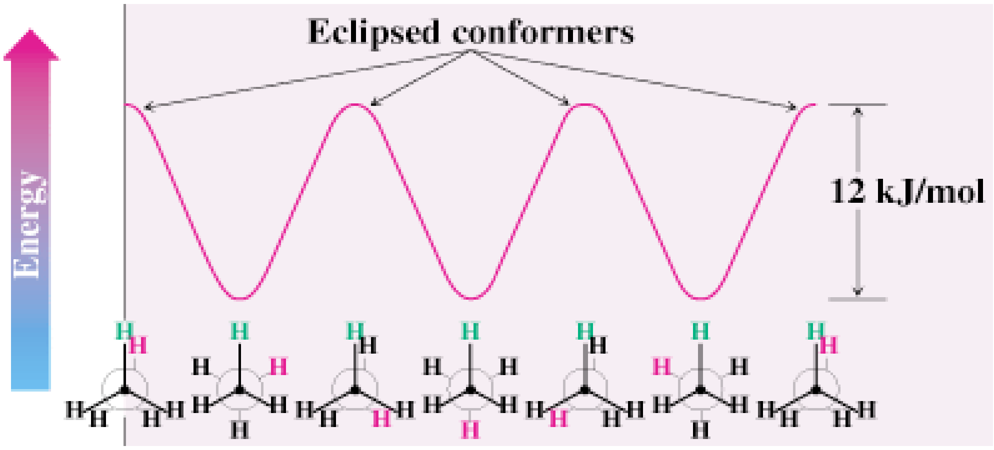


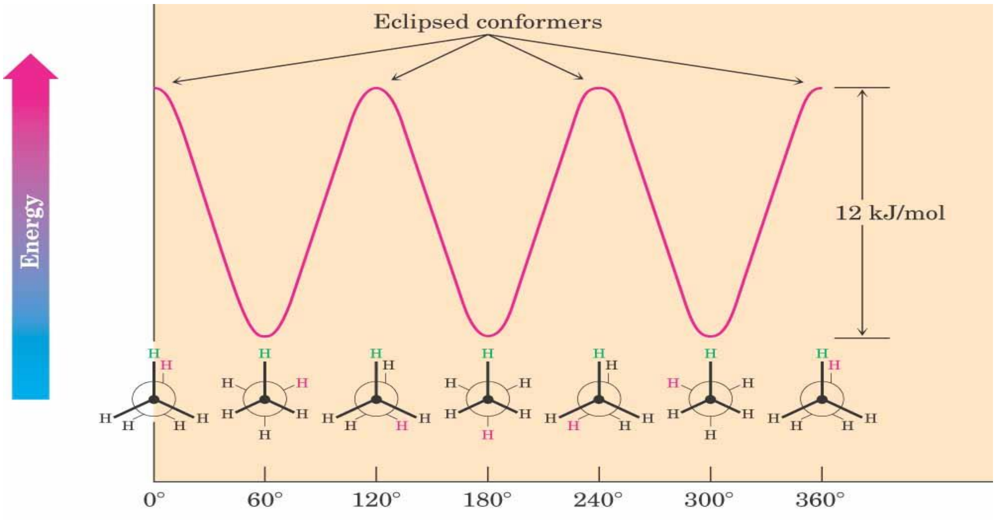
Ethane—staggered conformation

Ethane—eclipsed conformation

- **There barrier to rotation between conformations is small (12 kJ/mol; 2.9 kcal/mol) The most stable conformation of ethane has all six C–H bonds away from each other (staggered)**

- **The least stable conformation has all six C–H bonds as close as possible (eclipsed) in a Newman projection – energy due to torsional strain**





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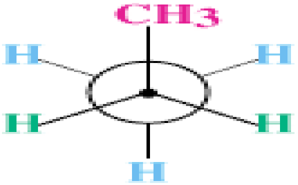
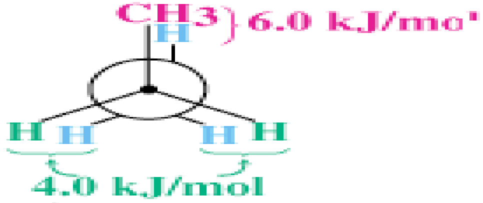
Conformations of Propane

- ☐ **Propane (C_3H_8) torsional barrier around the carbon–carbon bonds 14 kJ/mol**

- ☐ **Eclipsed conformer of propane has two ethane-type H–H interactions and an interaction between C–H and C–C bond**

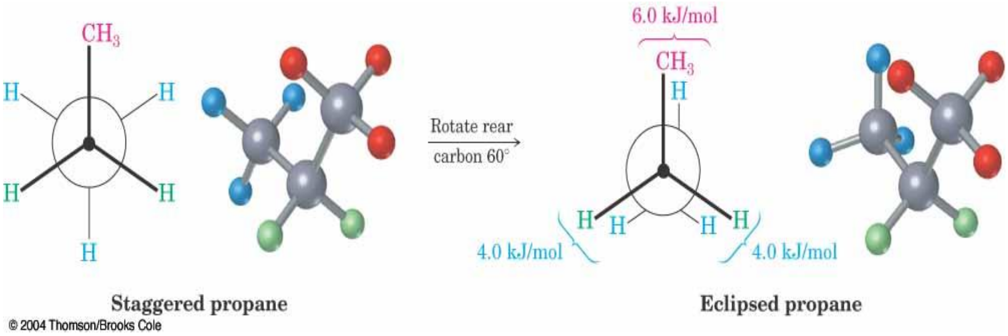


Staggered propane



Eclipsed propane

Propane conformations



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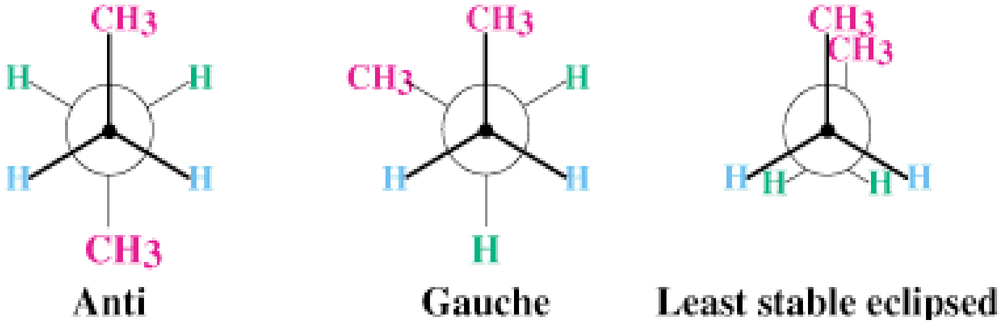
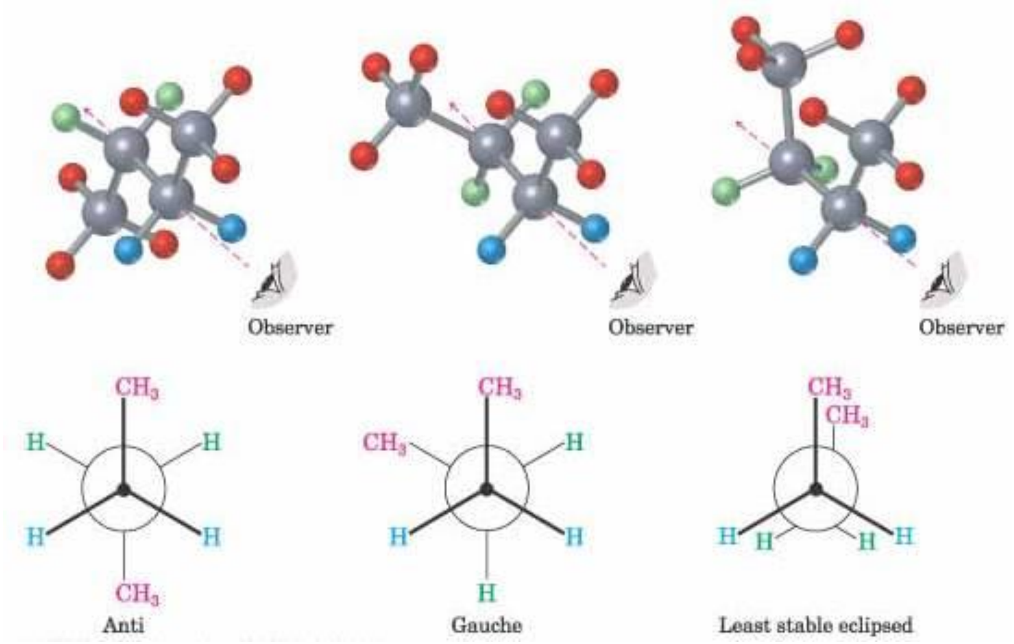
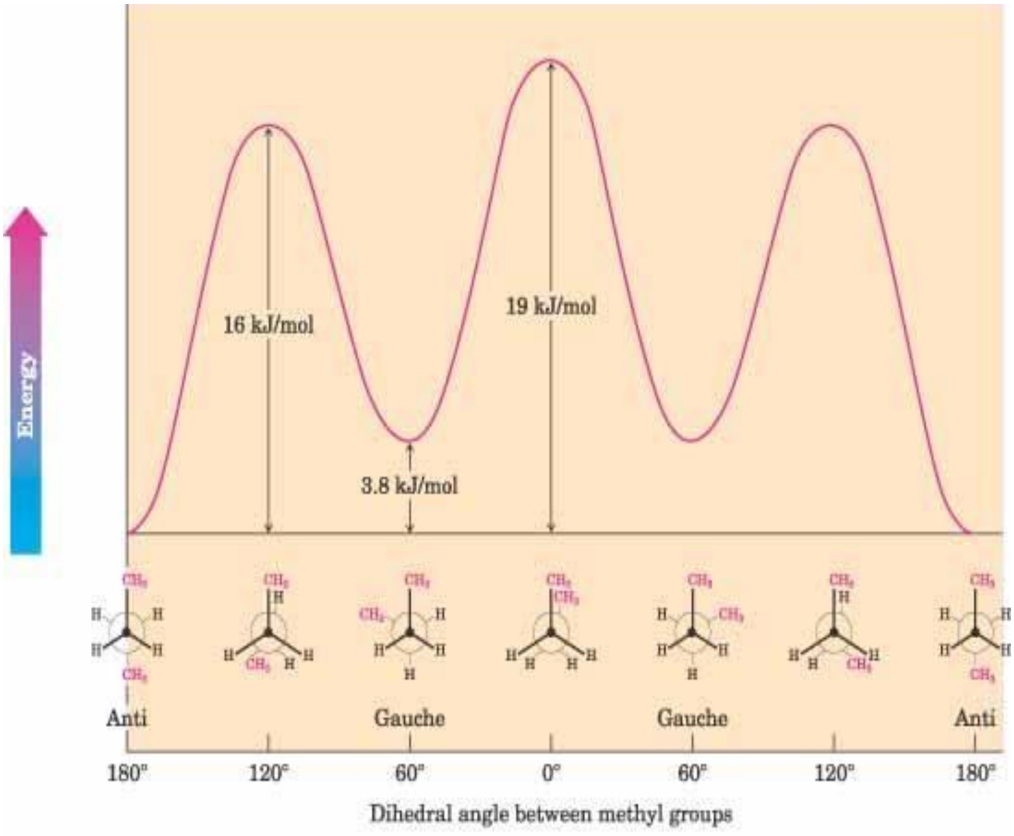
Conformations of Butane

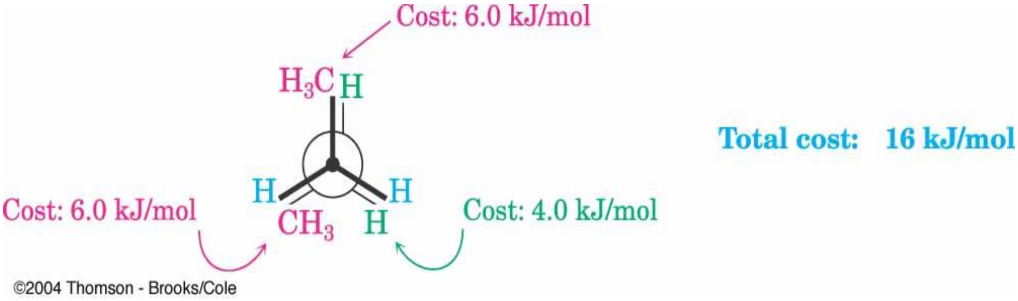
- ☐ anti conformation has two methyl groups 180° away from each other
- ☐ Rotation around the C2–C3 gives eclipsed conformation
- ☐ Staggered conformation with methyl groups 60° apart is gauche conformation




Observer
Observer
Observer
CH_3
H
H
H
H
CH_3
Anti
CH_3
CH_3
H
H
H
H
Gauche
CH_3
CH_3
H
H
H
H
Least stable eclipsed


Energy
16 kJ/mol
19 kJ/mol
3.8 kJ/mol
Anti
Gauche
Gauche
Anti
180°
120°
60°
0°
60°
120°
180°
Dihedral angle between methyl groups

Eclipsed Conformations of Butane



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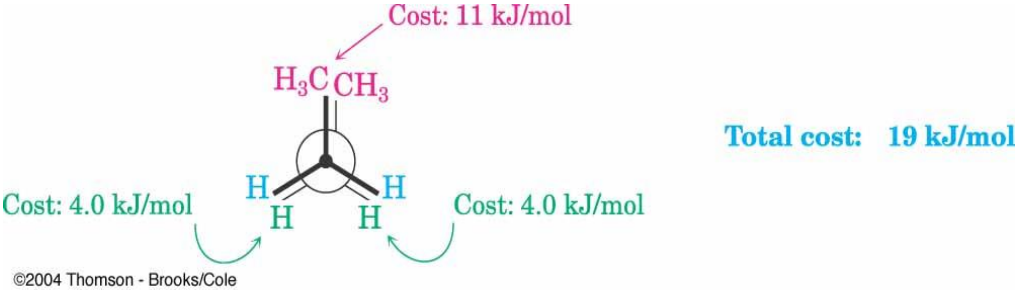

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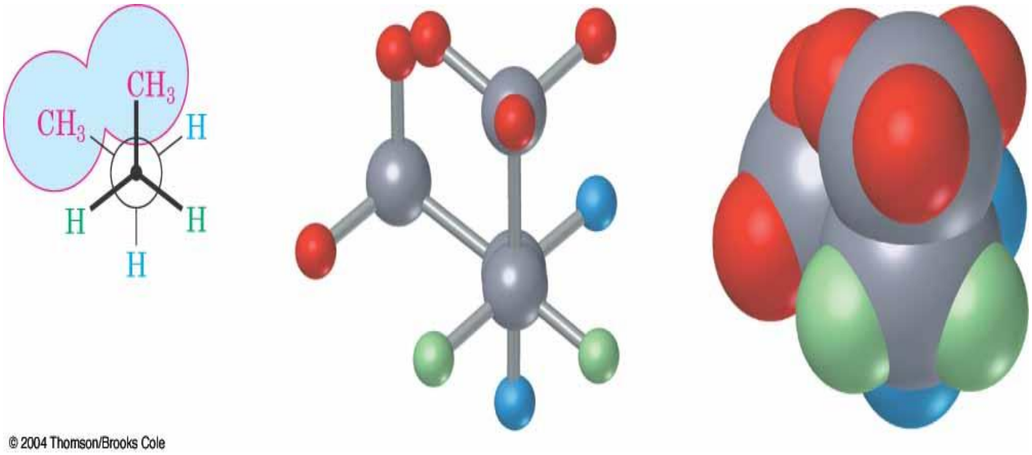
Gauche conformation: steric strain



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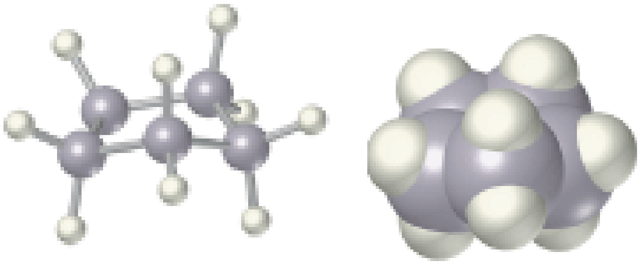
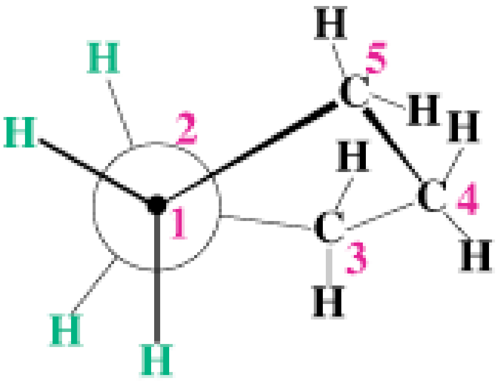
Cyclopentane

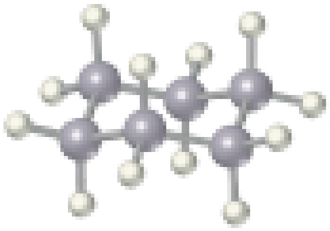
- Planar cyclopentane would have no angle strain but very high torsional strain
- Actual conformations of cyclopentane are nonplanar, reducing torsional strain
- Four carbon atoms are in a plane
    - The fifth carbon atom is above or below the plane – looks like an envelope

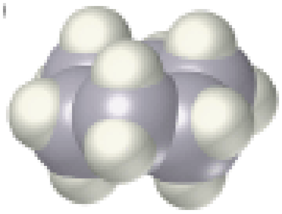


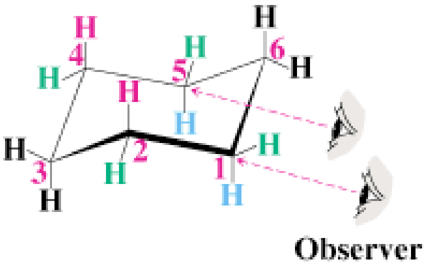


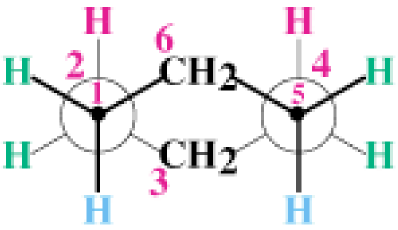
Conformations of Cyclohexane

- **Substituted cyclohexanes occur widely in nature**
- **The cyclohexane ring is free of angle strain and torsional strain**
- **The conformation is has alternating atoms in a common plane and tetrahedral angles between all carbons**
- **This is called a chair conformation**

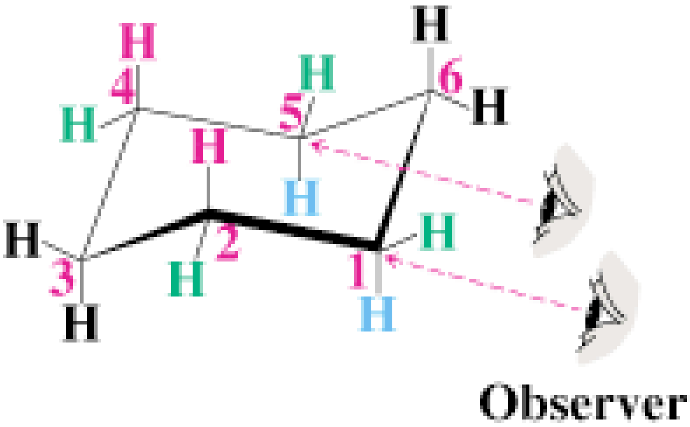


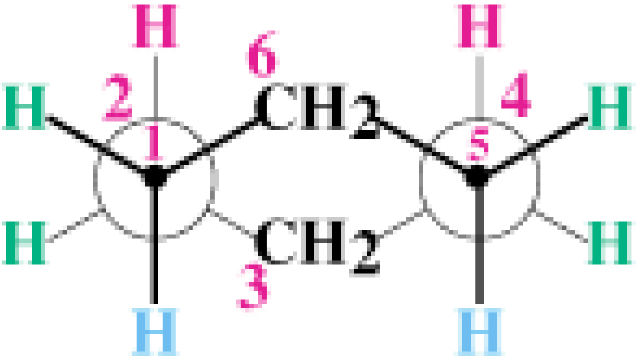






Chair Conformations

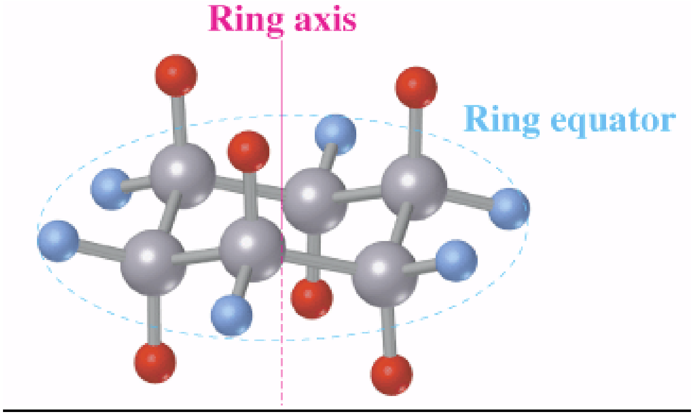


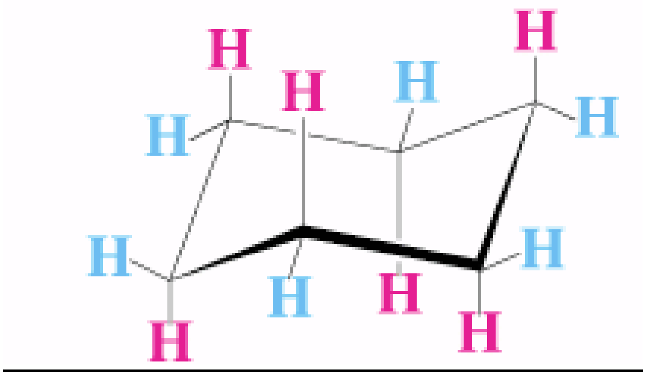


Axial and Equatorial Bonds in Cyclohexane

- ☐ **The chair conformation has two kinds of positions for substituents on the ring: *axial* positions and *equatorial* positions**

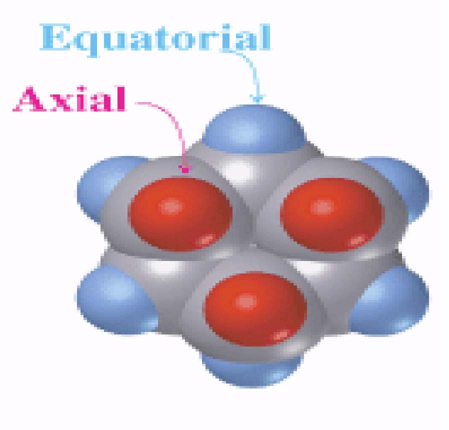
- ☐ **Chair cyclohexane has six axial hydrogens perpendicular to the ring (parallel to the ring axis) and six equatorial hydrogens near the plane of the ring**

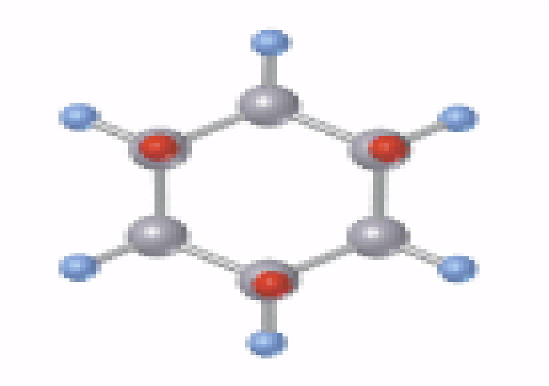


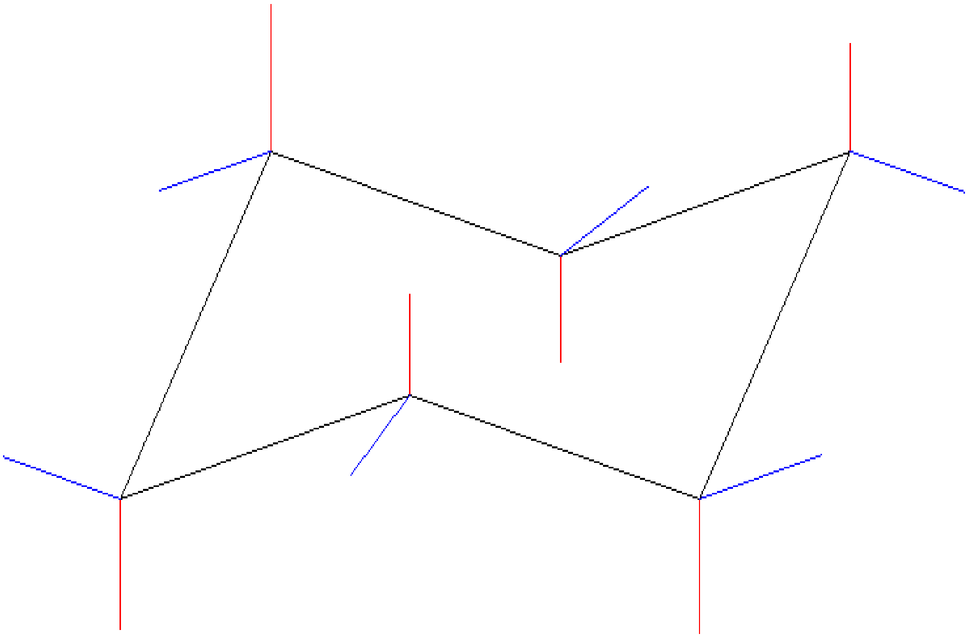


- ☐ **Each carbon atom in cyclohexane has one axial and one equatorial hydrogen**

- ☐ **Each face of the ring has three axial and three equatorial hydrogens in an alternating arrangement**


Equatorial
Axial

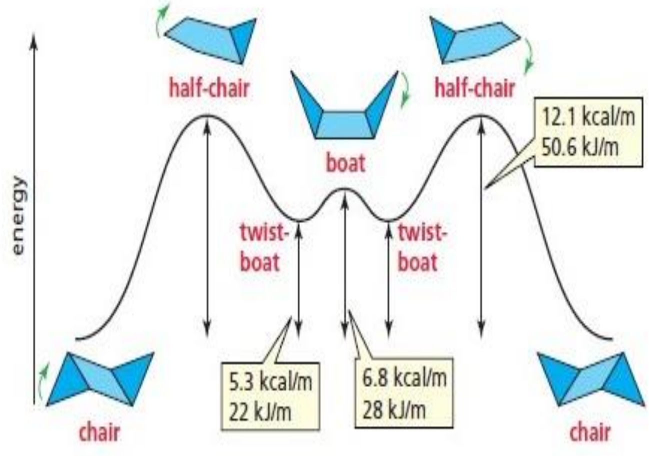


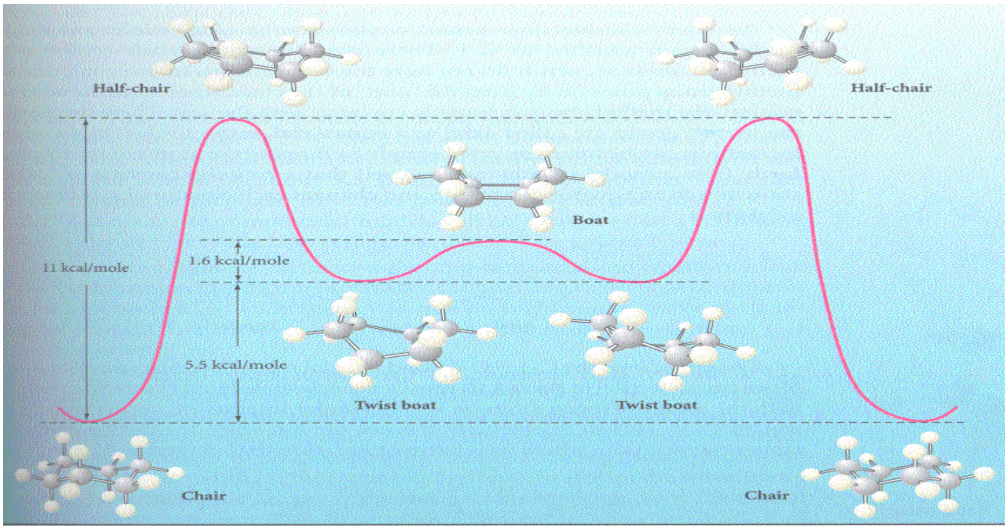


Conformations of Cyclohexane

- ☐ **Chair Conformation**
- ☐ **Boat Conformation**
- ☐ **Twisted Boat Conformation**
- ☐ **Half Chair Conformation**

Stability of Cyclohexane





STEREO CHEMISTRY

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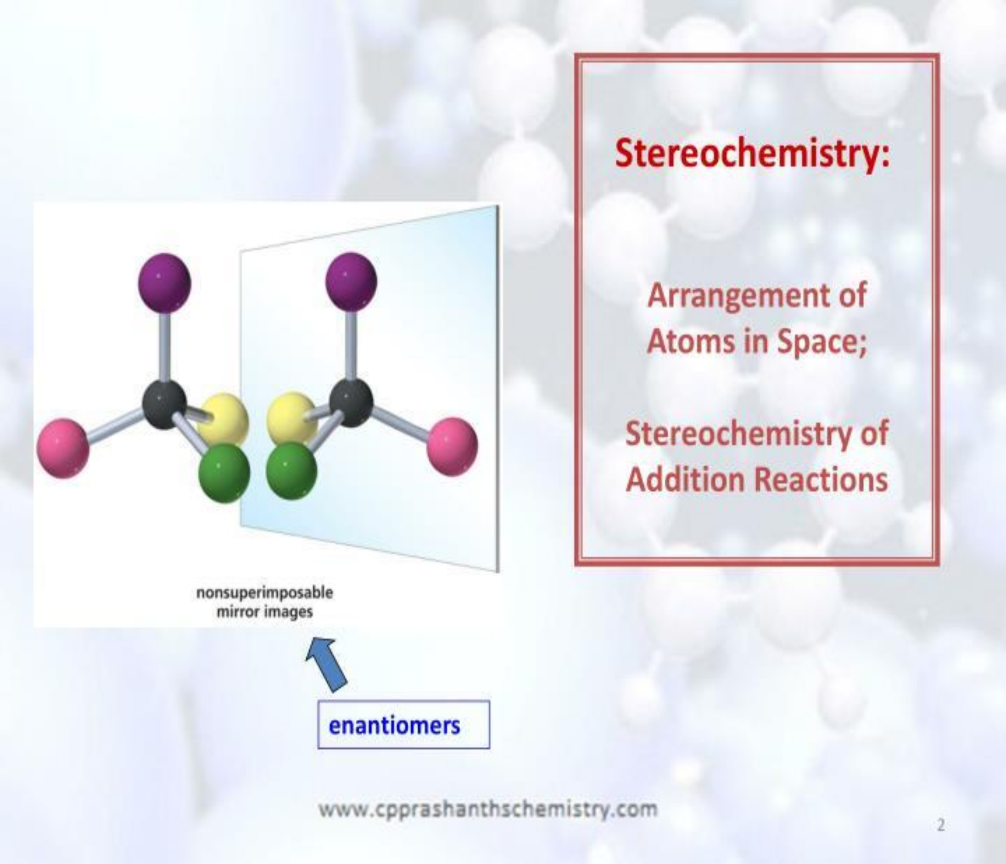

Stereochemistry:

Arrangement of Atoms in Space;

Stereochemistry of Addition Reactions

nonsuperimposable mirror images

enantiomers

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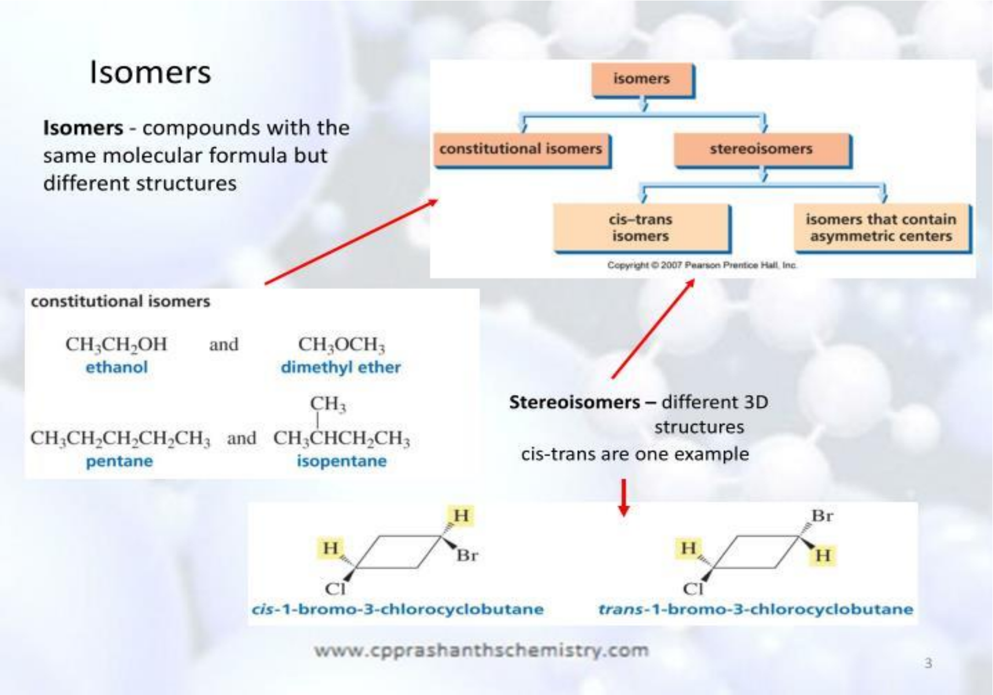

Isomers

Isomers - compounds with the same molecular formula but different structures

isomers

constitutional isomers

stereoisomers

cis–trans isomers

isomers that contain asymmetric centers

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constitutional isomers

CH_3CH_2OH and CH_3OCH_3

ethanol — dimethyl ether

$CH_3CH_2CH_2CH_2CH_3$ and $CH_3\overset{CH_3}{\overset{|}{C}}HCH_2CH_3$

pentane — isopentane

Stereoisomers – different 3D structures

cis-trans are one example

cis-1-bromo-3-chlorocyclobutane

trans-1-bromo-3-chlorocyclobutane

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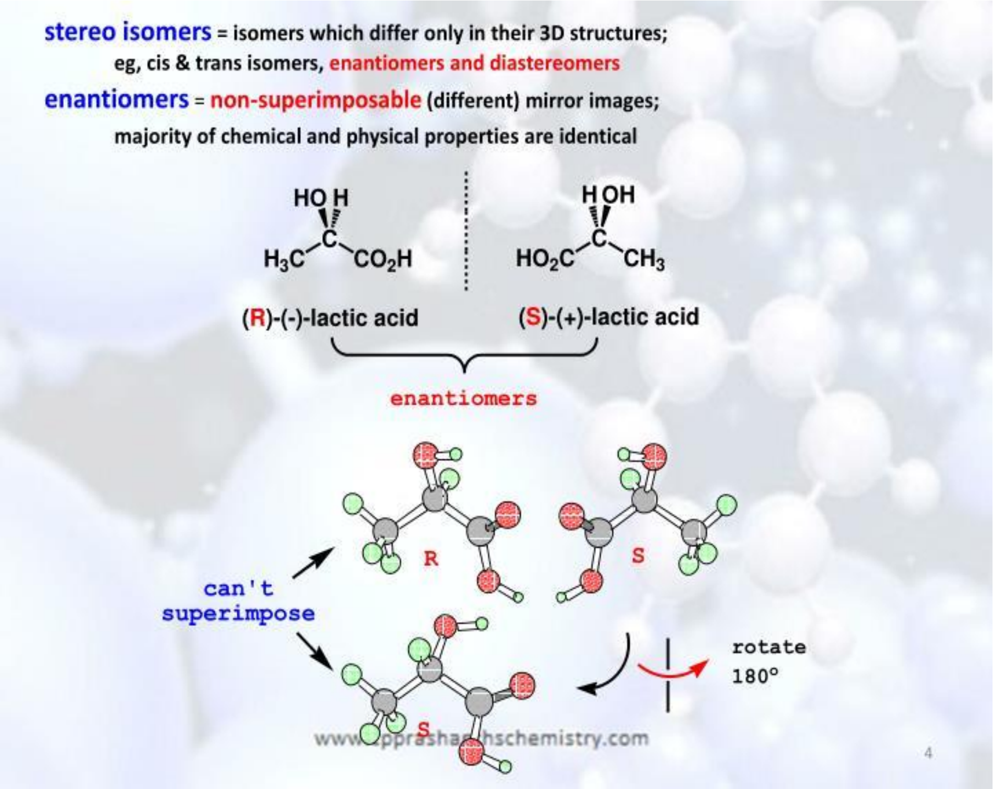
3



stereo isomers = isomers which differ only in their 3D structures; eg, cis & trans isomers, enantiomers and diastereomers

enantiomers = non-superimposable (different) mirror images; majority of chemical and physical properties are identical

(R)-(-)-lactic acid

(S)-(+)-lactic acid

enantiomers

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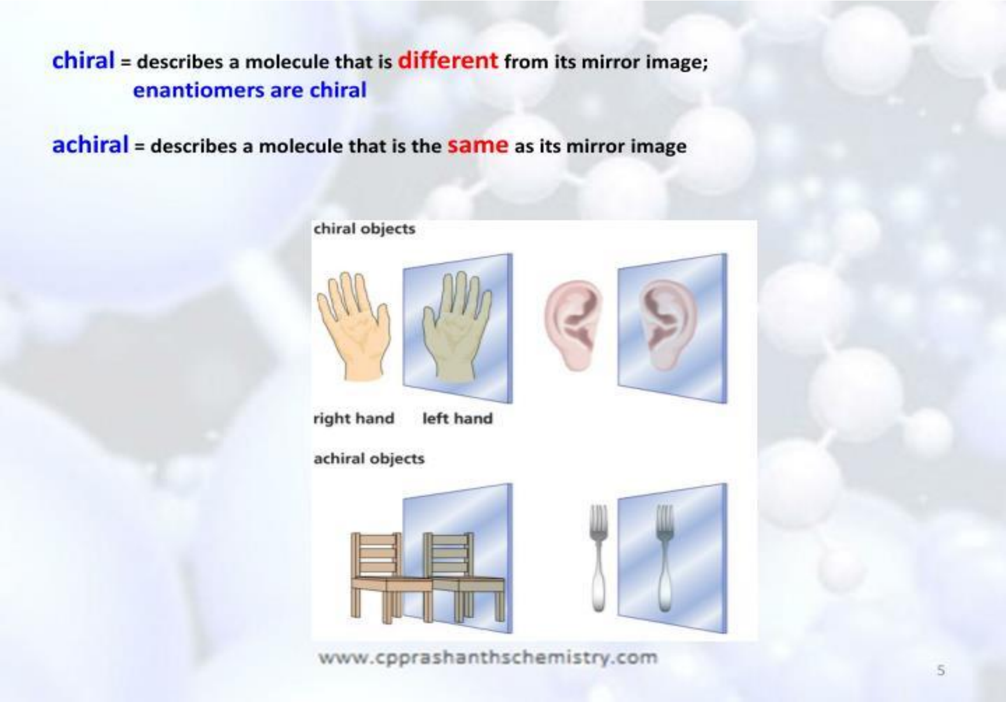

chiral = describes a molecule that is **different** from its mirror image;
enantiomers are chiral

achiral = describes a molecule that is the **same** as its mirror image

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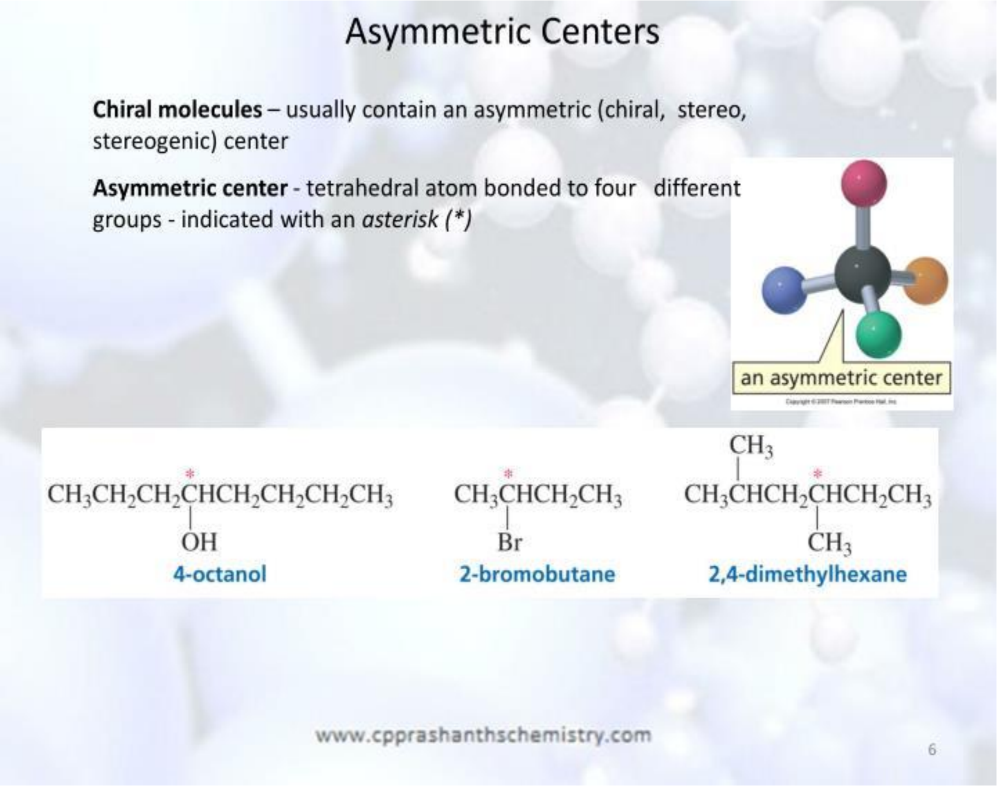

Asymmetric Centers

Chiral molecules – usually contain an asymmetric (chiral, stereo, stereogenic) center

Asymmetric center - tetrahedral atom bonded to four different groups - indicated with an *asterisk (*)*

$$CH_3CH_2CH_2\underset{\substack{|\\ OH}}{\overset{*}{C}}HCH_2CH_2CH_2CH_3$$

4-octanol

$$CH_3\underset{\substack{|\\ Br}}{\overset{*}{C}}HCH_2CH_3$$

2-bromobutane

$$CH_3\overset{\substack{CH_3\\ |}}{C}HCH_2\underset{\substack{|\\ CH_3}}{\overset{*}{C}}HCH_2CH_3$$

2,4-dimethylhexane

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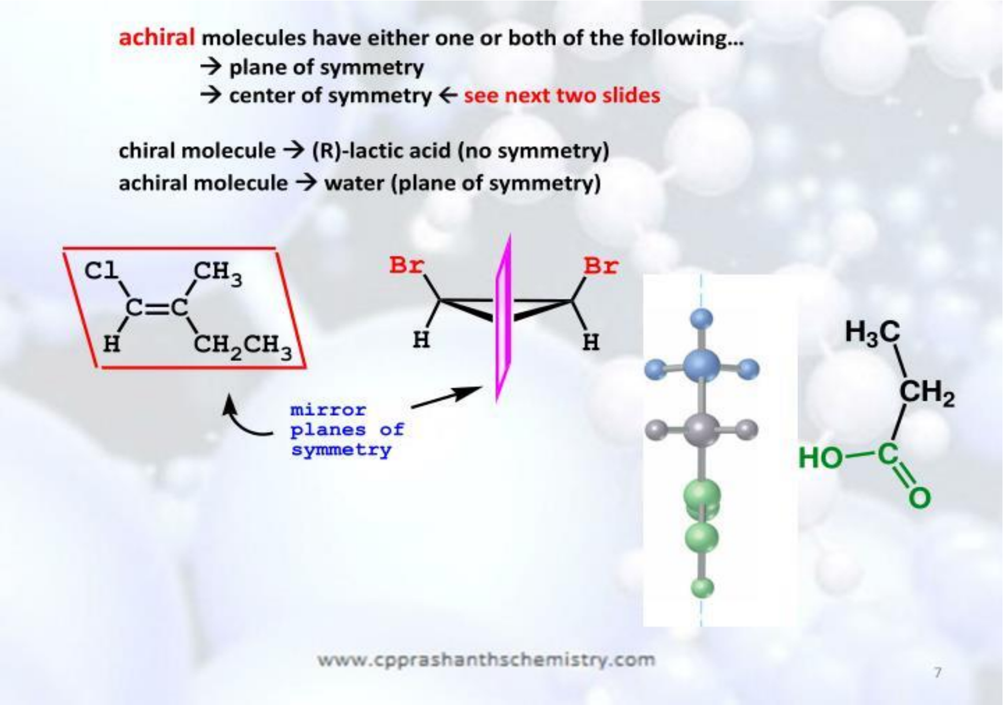

achiral molecules have either one or both of the following…

→ plane of symmetry

→ center of symmetry ← see next two slides

chiral molecule → (R)-lactic acid (no symmetry)

achiral molecule → water (plane of symmetry)

mirror planes of symmetry

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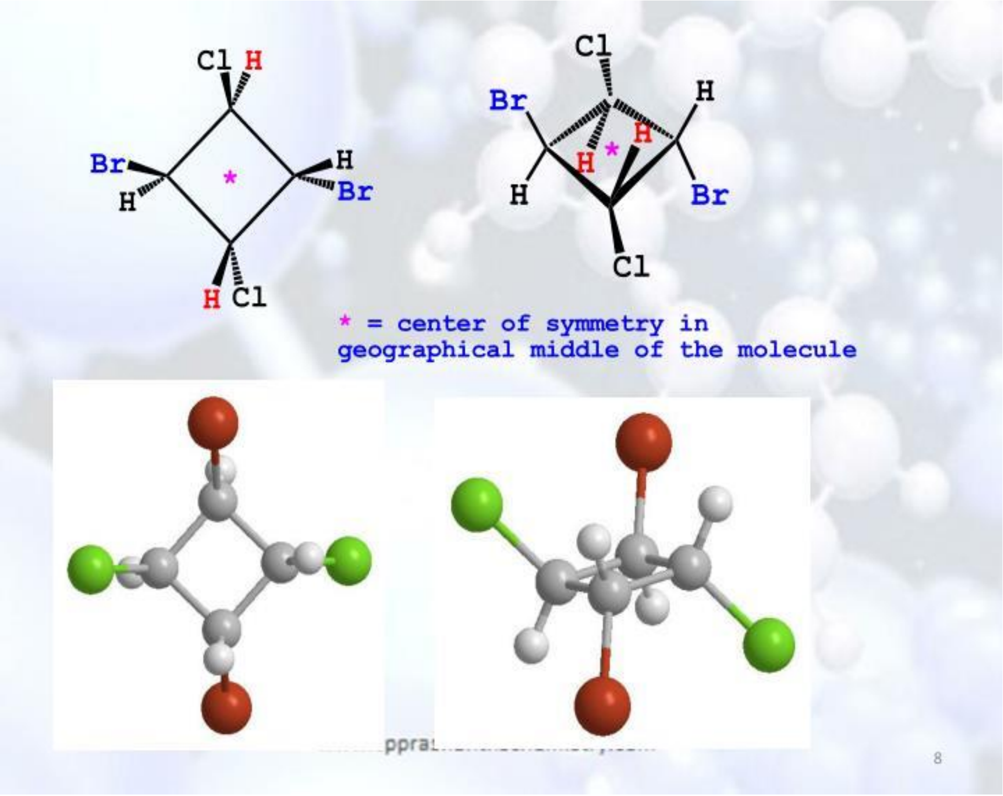
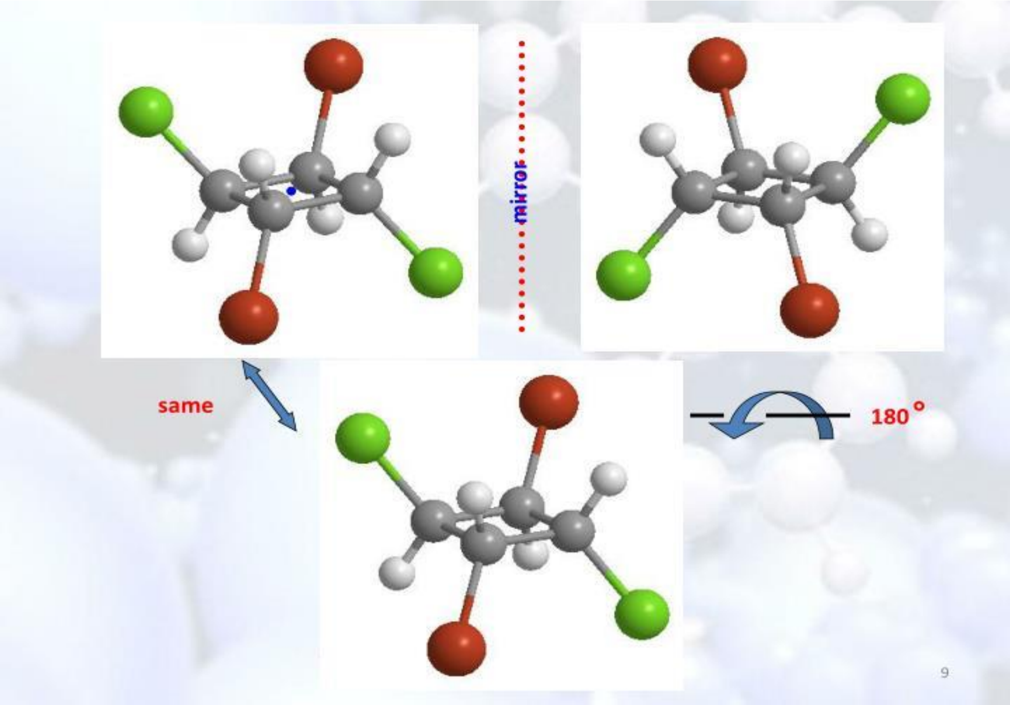
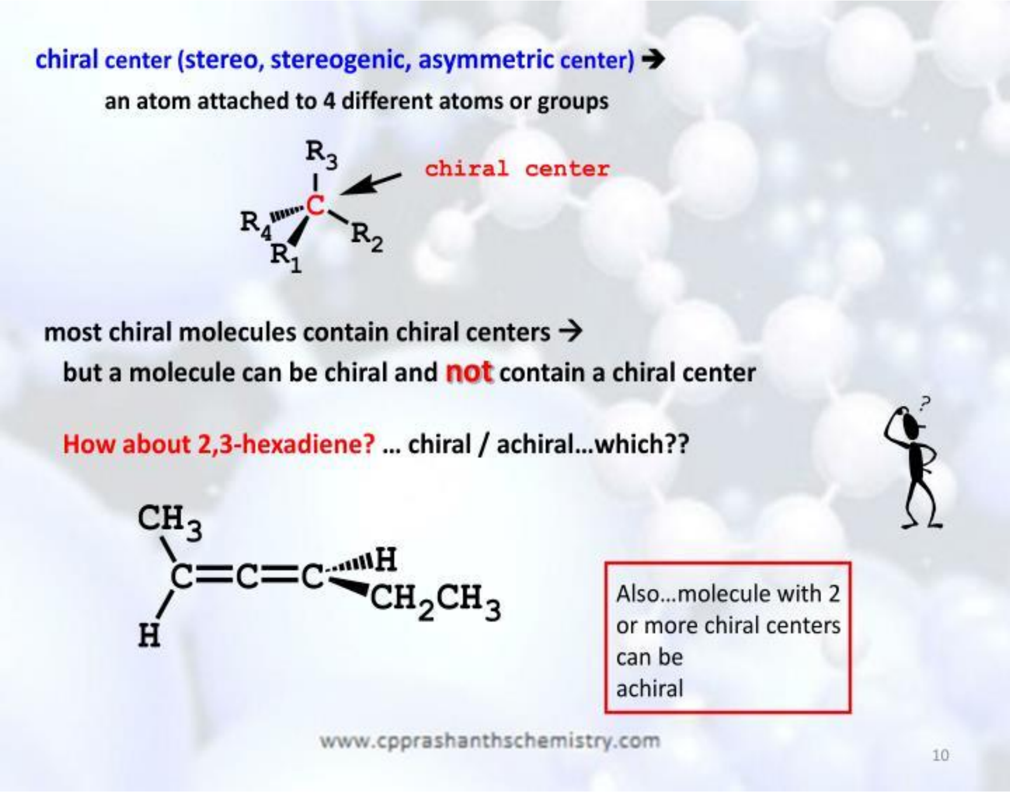


* = center of symmetry in geographical middle of the molecule





chiral center (stereo, stereogenic, asymmetric center) →
an atom attached to 4 different atoms or groups

most chiral molecules contain chiral centers →
but a molecule can be chiral and **not** contain a chiral center

How about 2,3-hexadiene? … chiral / achiral…which??

Also…molecule with 2 or more chiral centers can be achiral

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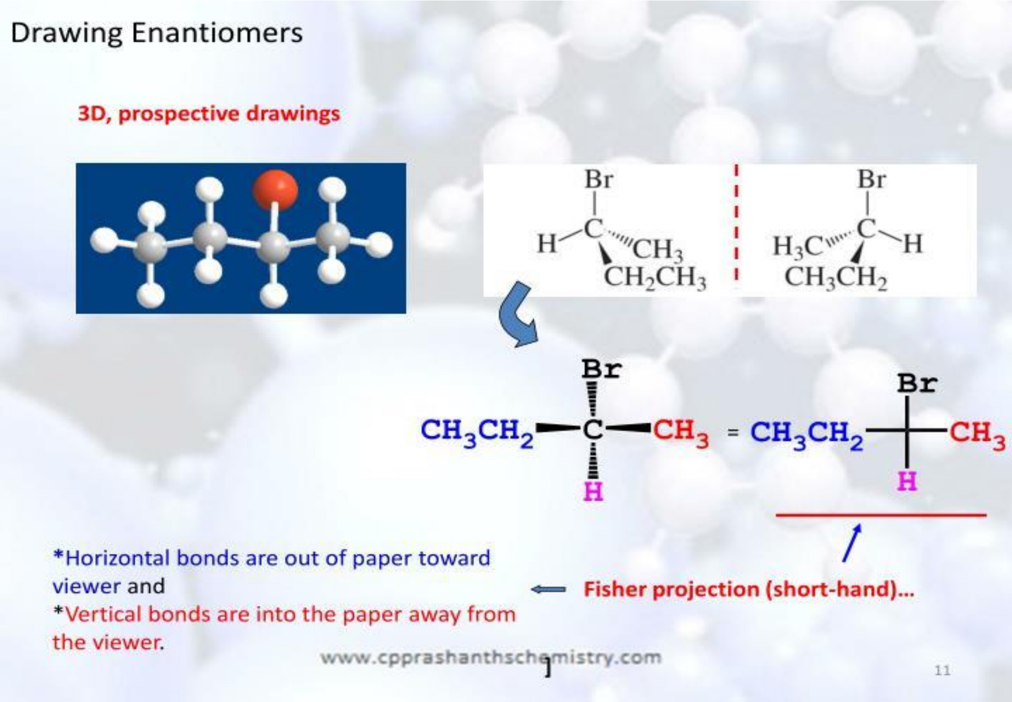

Drawing Enantiomers

3D, prospective drawings

*Horizontal bonds are out of paper toward viewer and
*Vertical bonds are into the paper away from the viewer.

Fisher projection (short-hand)…

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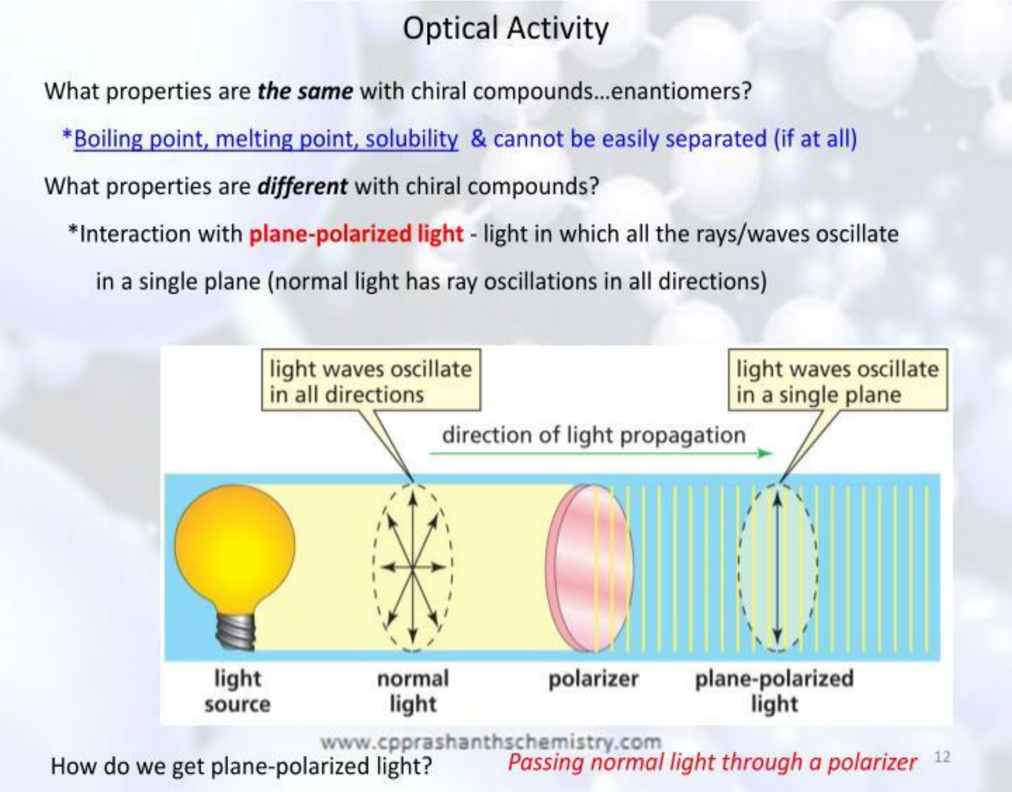

Optical Activity

What properties are ***the same*** with chiral compounds…enantiomers?

*Boiling point, melting point, solubility & cannot be easily separated (if at all)

What properties are ***different*** with chiral compounds?

*Interaction with **plane-polarized light** - light in which all the rays/waves oscillate in a single plane (normal light has ray oscillations in all directions)

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How do we get plane-polarized light? *Passing normal light through a polarizer*

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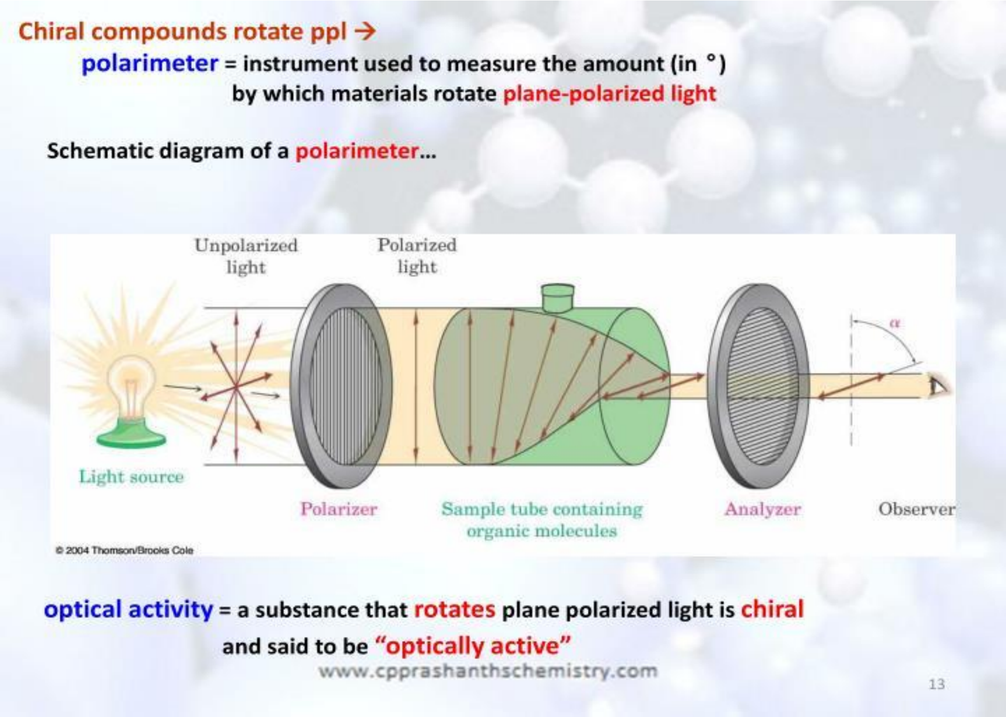
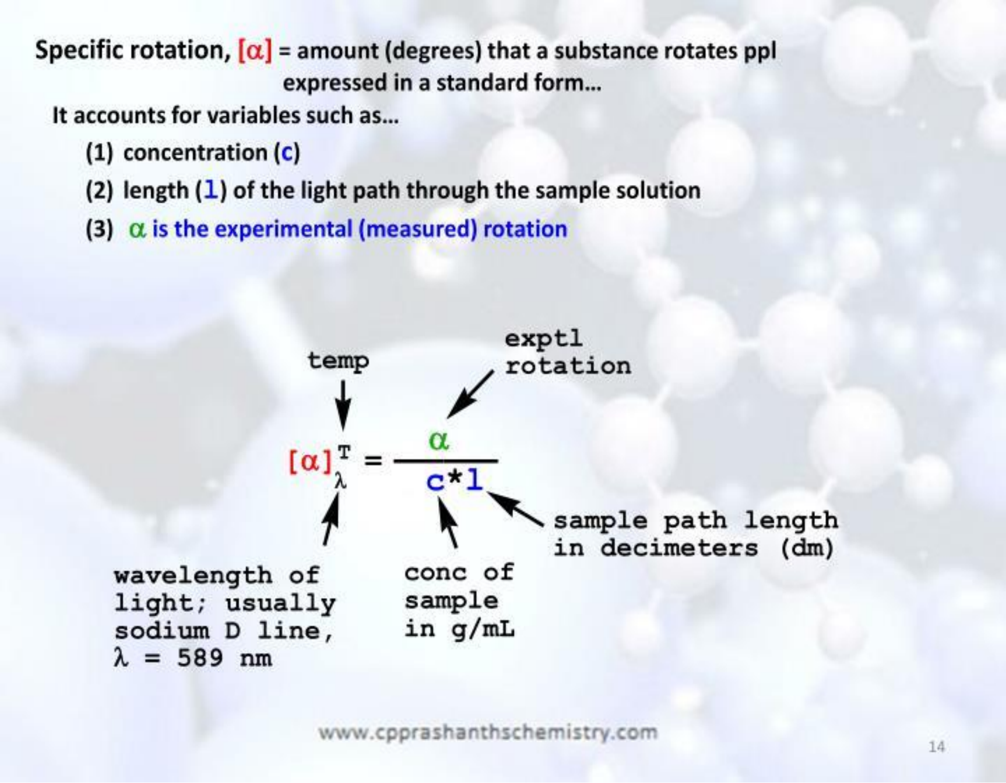


Chiral compounds rotate ppl →

polarimeter = instrument used to measure the amount (in °) by which materials rotate **plane-polarized light**

Schematic diagram of a **polarimeter**…

optical activity = a substance that **rotates** plane polarized light is **chiral** and said to be **"optically active"**



Specific rotation, [α] = amount (degrees) that a substance rotates ppl expressed in a standard form…

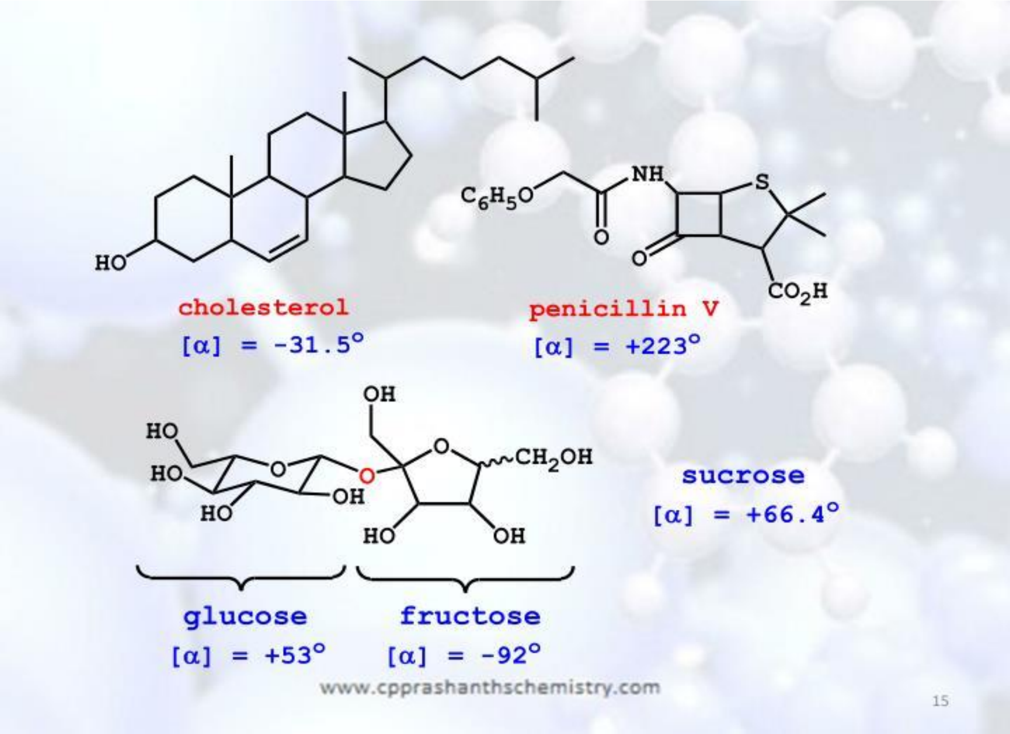
It accounts for variables such as…

(1) concentration (c)

(2) length (l) of the light path through the sample solution

(3) α is the experimental (measured) rotation

$$[\alpha]^{T}_{\lambda} = \frac{\alpha}{c*l}$$



cholesterol
[α] = -31.5°

penicillin V
[α] = +223°

sucrose
[α] = +66.4°

glucose
[α] = +53°

fructose
[α] = -92°

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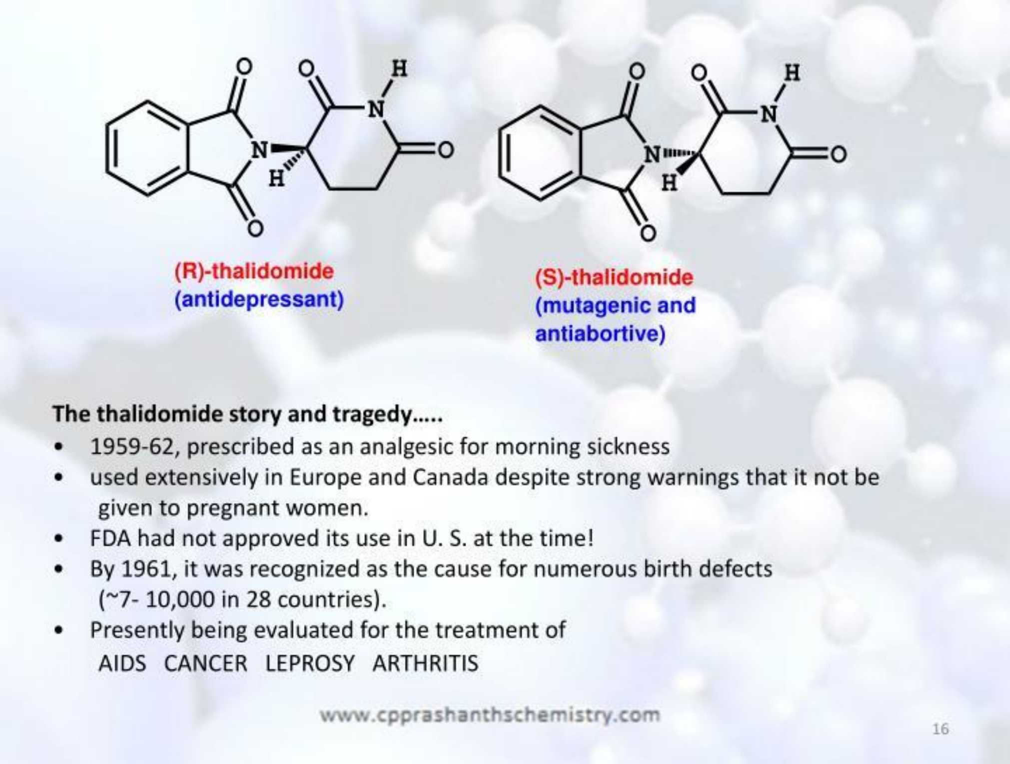

(R)-thalidomide
(antidepressant)

(S)-thalidomide
(mutagenic and
antiabortive)

The thalidomide story and tragedy.....

- 1959-62, prescribed as an analgesic for morning sickness
- used extensively in Europe and Canada despite strong warnings that it not be given to pregnant women.
- FDA had not approved its use in U. S. at the time!
- By 1961, it was recognized as the cause for numerous birth defects (~7- 10,000 in 28 countries).
- Presently being evaluated for the treatment of
  AIDS CANCER LEPROSY ARTHRITIS

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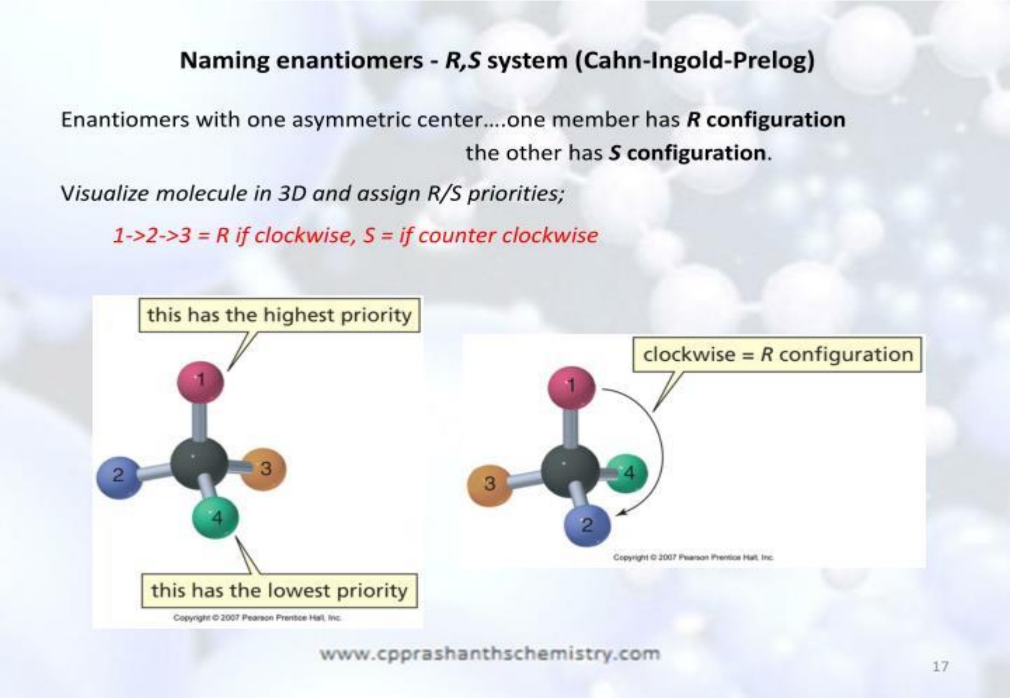


Naming enantiomers - *R,S* system (Cahn-Ingold-Prelog)

Enantiomers with one asymmetric center….one member has ***R* configuration**
the other has ***S* configuration**.

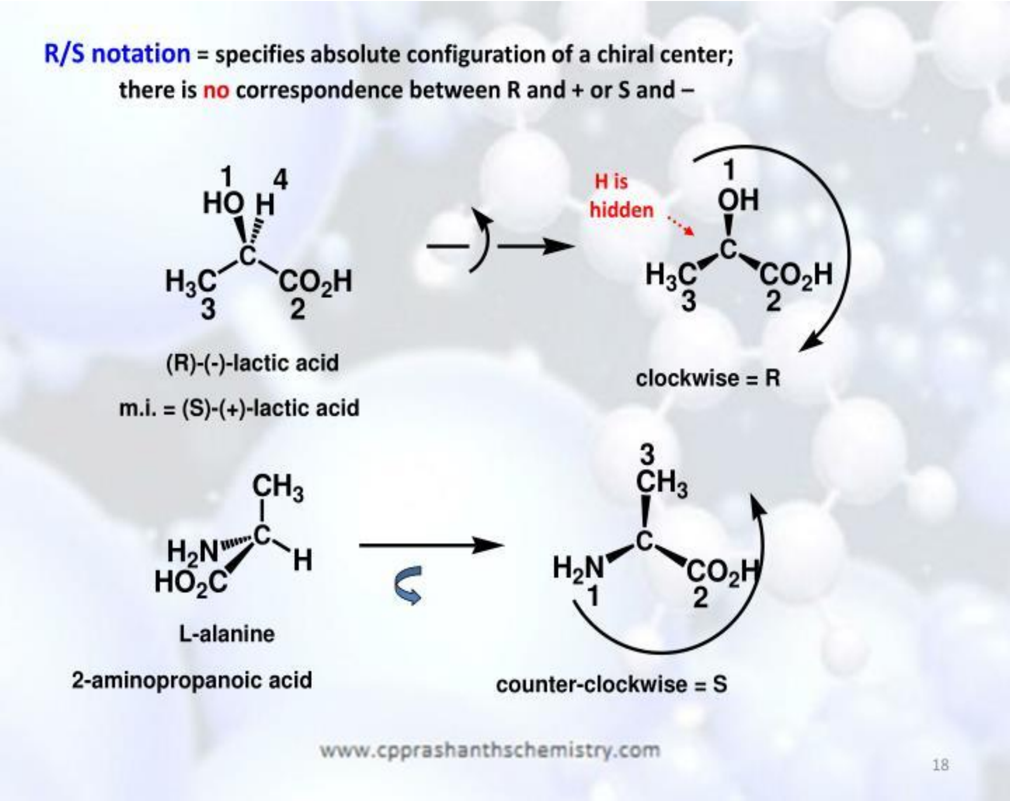
Visualize molecule in 3D and assign R/S priorities;

1->2->3 = R if clockwise, S = if counter clockwise

this has the highest priority

this has the lowest priority

clockwise = *R* configuration



R/S notation = specifies absolute configuration of a chiral center;
there is **no** correspondence between R and + or S and –

(R)-(-)-lactic acid

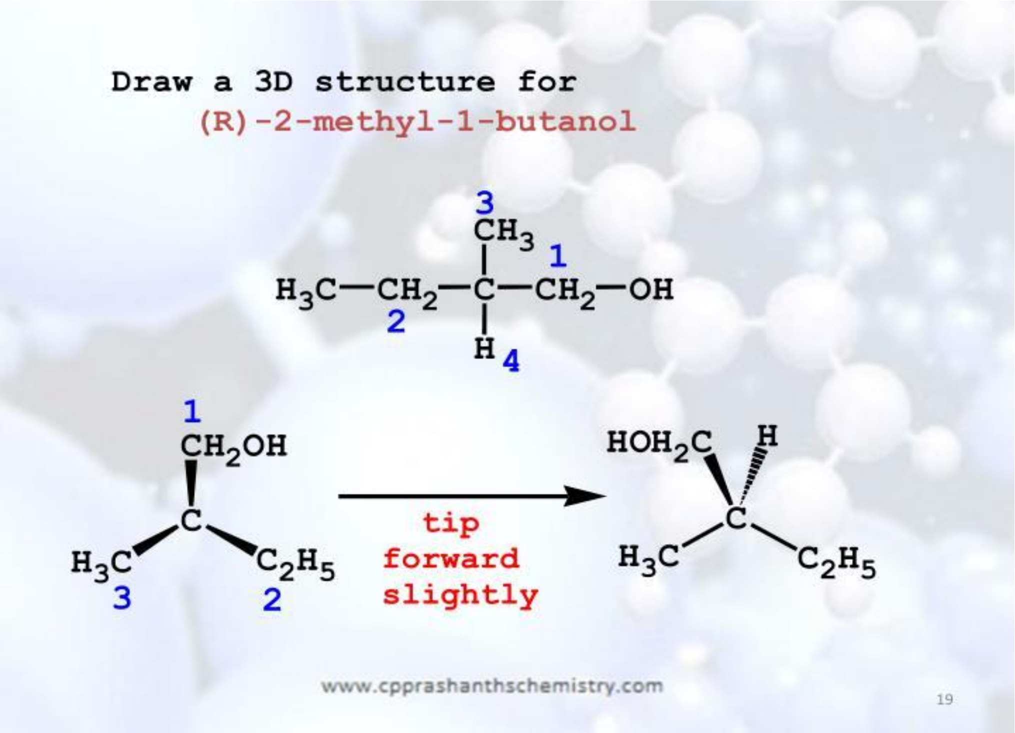
m.i. = (S)-(+)-lactic acid

clockwise = R

L-alanine

2-aminopropanoic acid

counter-clockwise = S



Draw a 3D structure for

(R)-2-methyl-1-butanol

tip forward slightly

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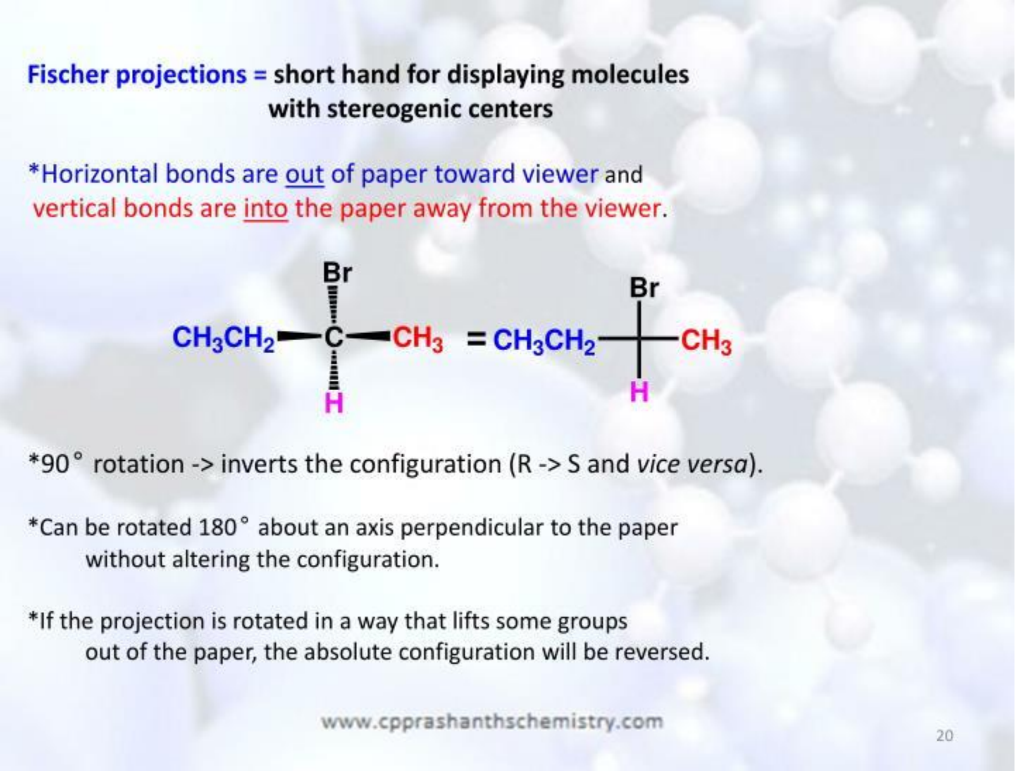

Fischer projections = **short hand for displaying molecules with stereogenic centers**

*Horizontal bonds are out of paper toward viewer and vertical bonds are into the paper away from the viewer.

*90° rotation -> inverts the configuration (R -> S and *vice versa*).

*Can be rotated 180° about an axis perpendicular to the paper without altering the configuration.

*If the projection is rotated in a way that lifts some groups out of the paper, the absolute configuration will be reversed.

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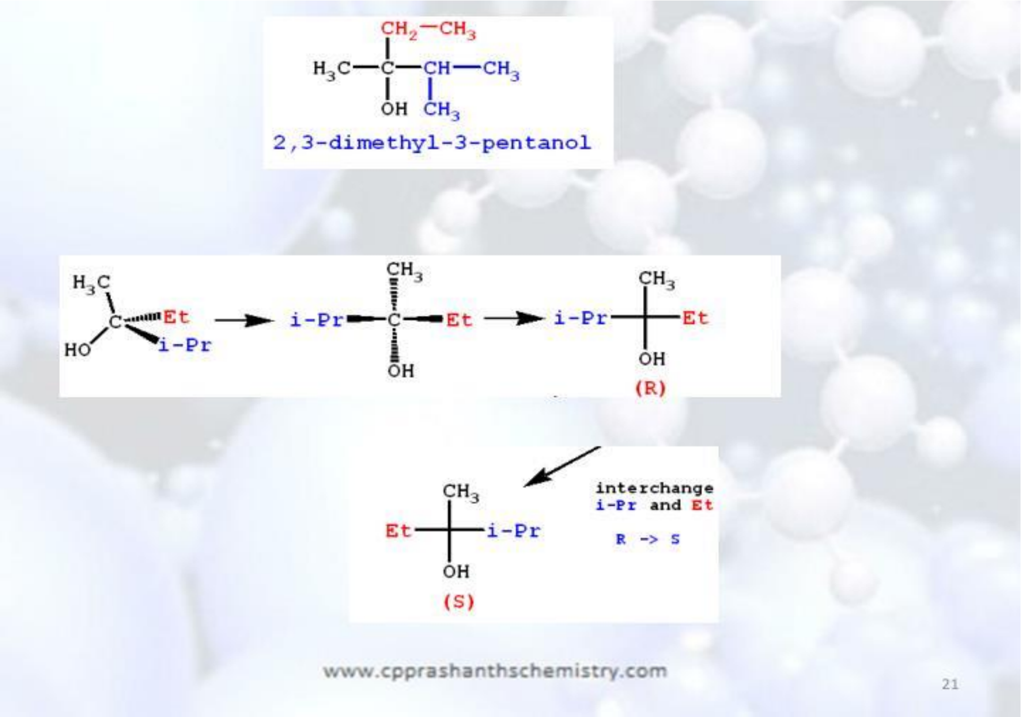

2,3-dimethyl-3-pentanol

interchange i-Pr and Et

R -> S

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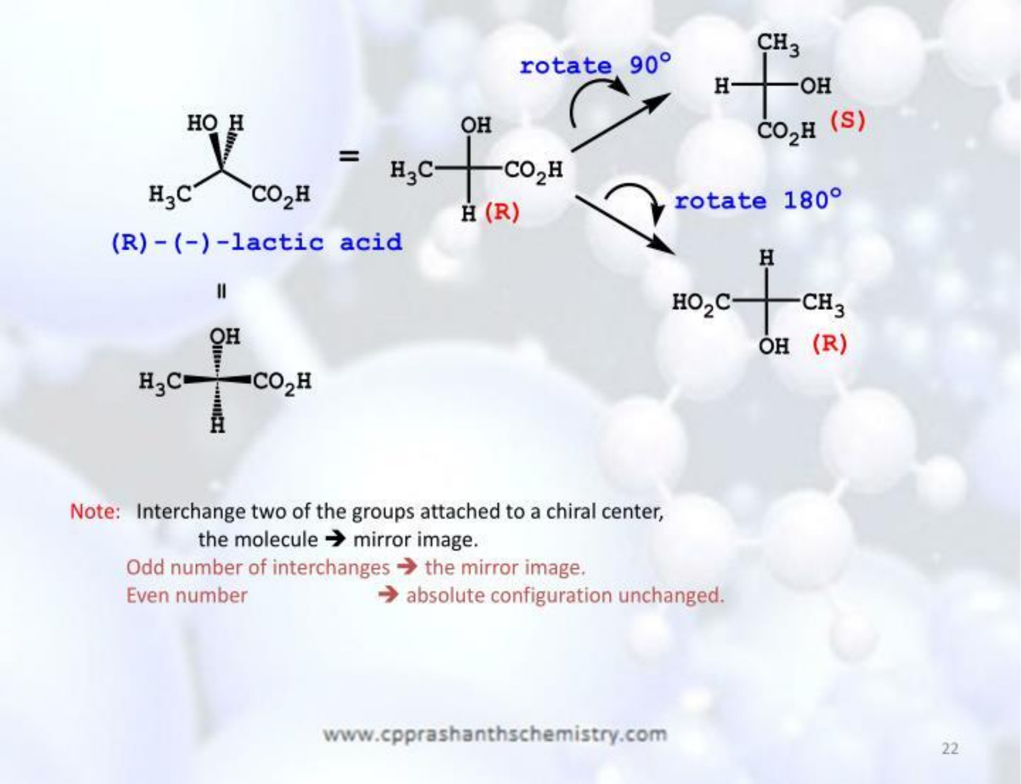

(R)-(-)-lactic acid

rotate 90°

rotate 180°

Note: Interchange two of the groups attached to a chiral center, the molecule → mirror image.

Odd number of interchanges → the mirror image.

Even number → absolute configuration unchanged.

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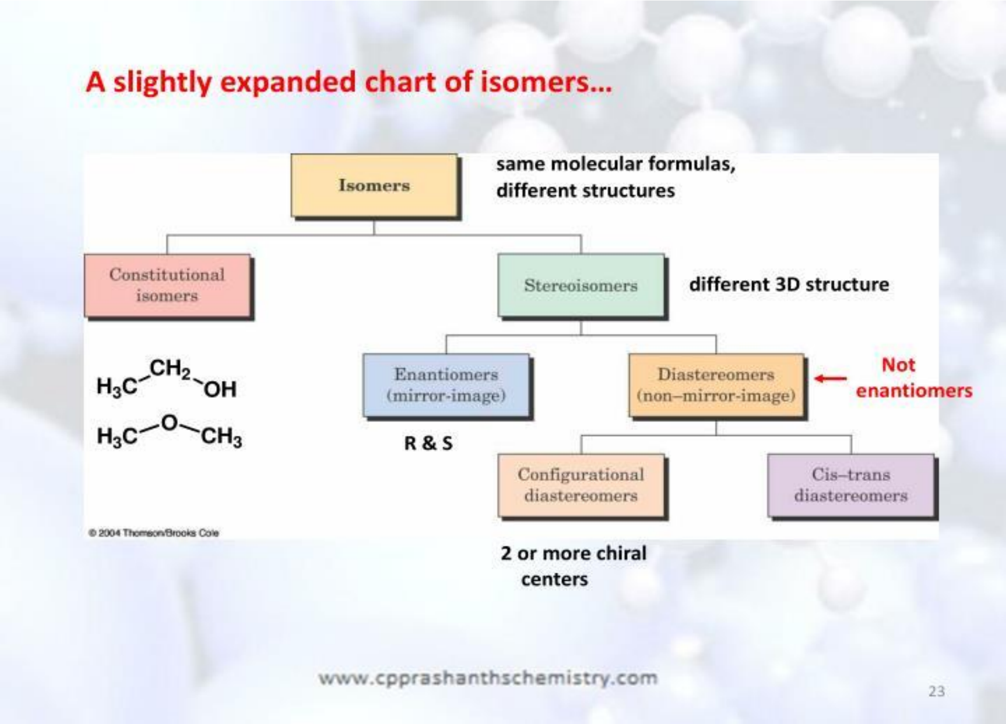

A slightly expanded chart of isomers…

2 or more chiral centers

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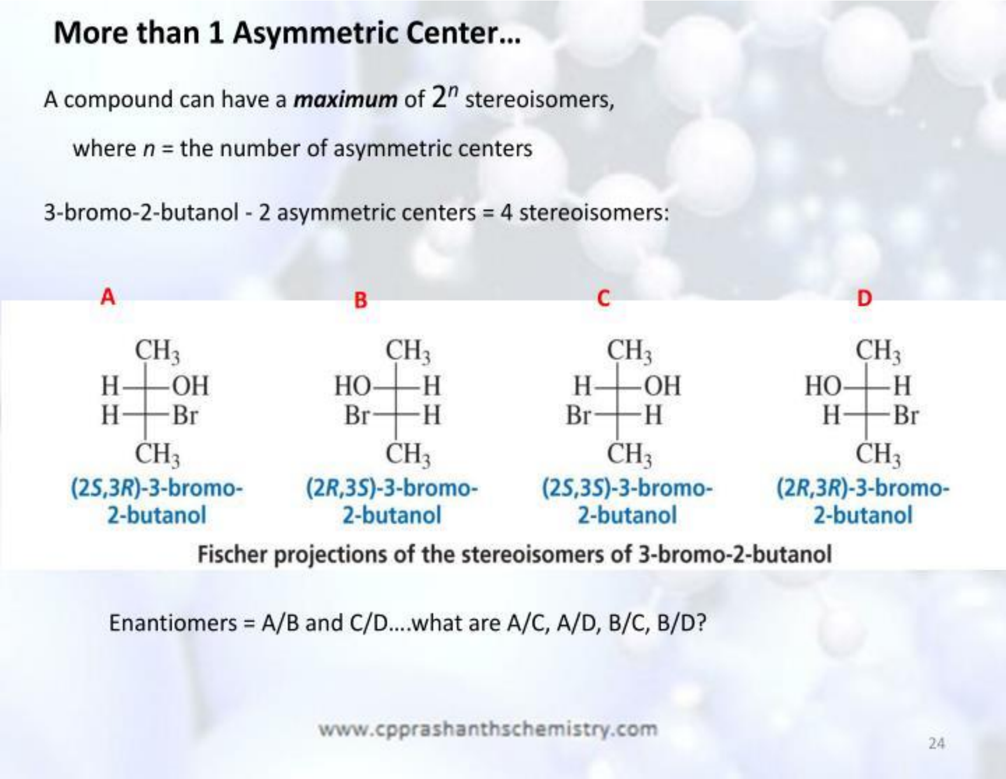

More than 1 Asymmetric Center…

A compound can have a ***maximum*** of 2^n stereoisomers,

where *n* = the number of asymmetric centers

3-bromo-2-butanol - 2 asymmetric centers = 4 stereoisomers:

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

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

(2*S*,3*S*)-3-bromo-2-butanol

(2*R*,3*R*)-3-bromo-2-butanol

Fischer projections of the stereoisomers of 3-bromo-2-butanol

Enantiomers = A/B and C/D….what are A/C, A/D, B/C, B/D?

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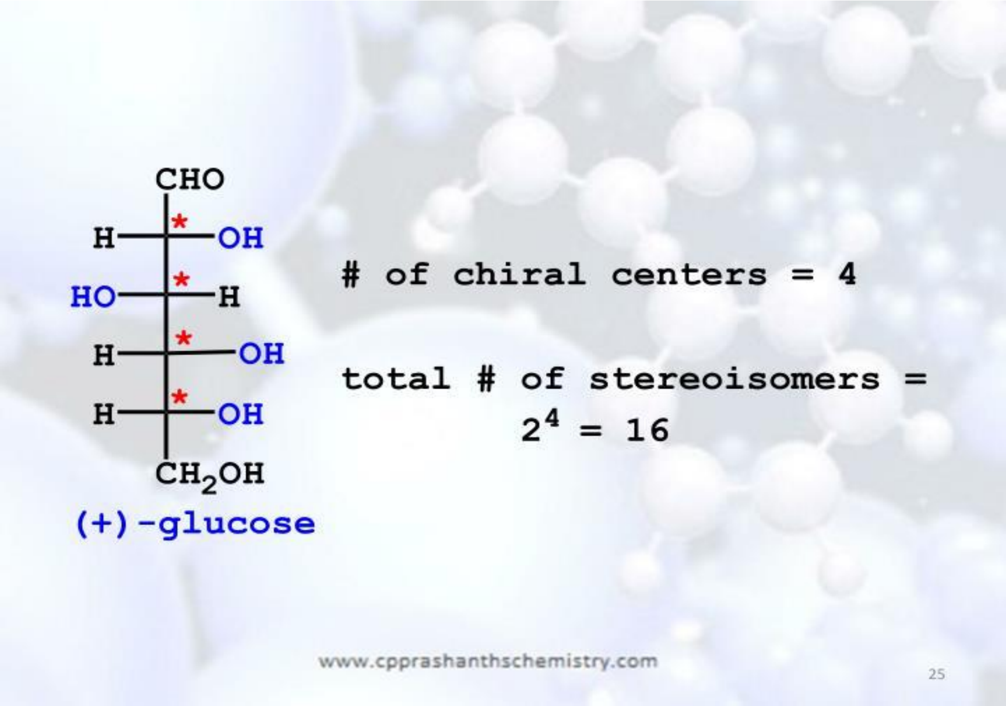

(+)-glucose

# of chiral centers = 4

total # of stereoisomers = $2^4 = 16$

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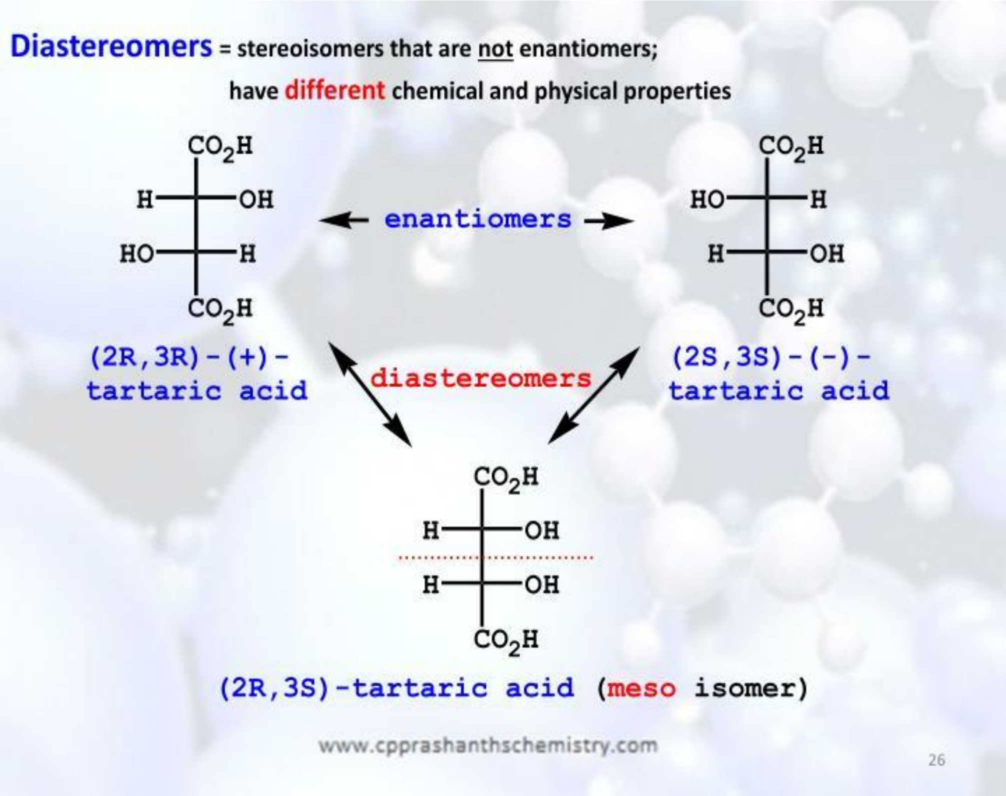
Diastereomers = stereoisomers that are not enantiomers; have different chemical and physical properties

(2R,3R)-(+)-tartaric acid

(2S,3S)-(-)-tartaric acid

(2R,3S)-tartaric acid (meso isomer)

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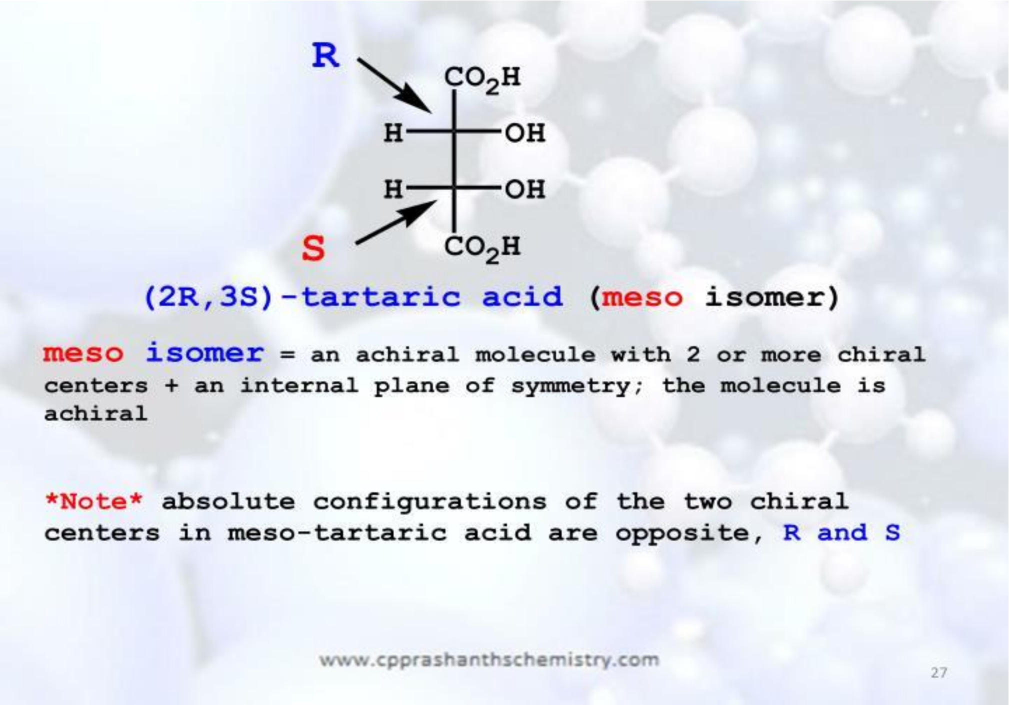
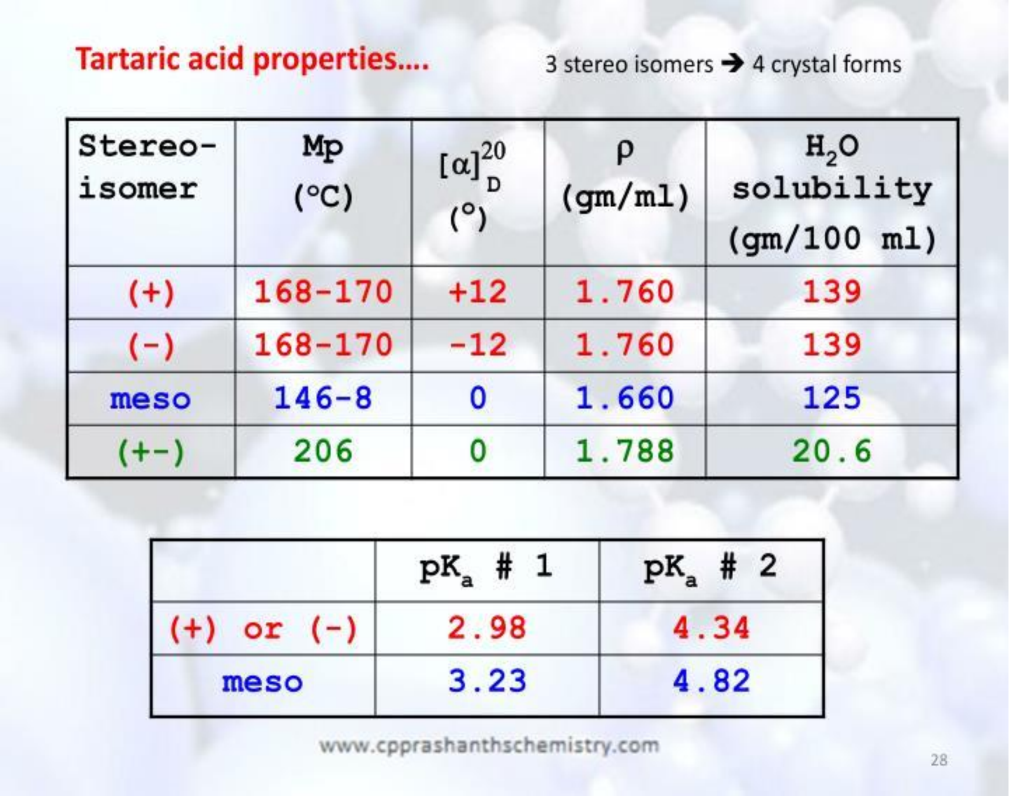


(2R,3S)-tartaric acid (meso isomer)

meso isomer = an achiral molecule with 2 or more chiral centers + an internal plane of symmetry; the molecule is achiral

Note absolute configurations of the two chiral centers in meso-tartaric acid are opposite, R and S

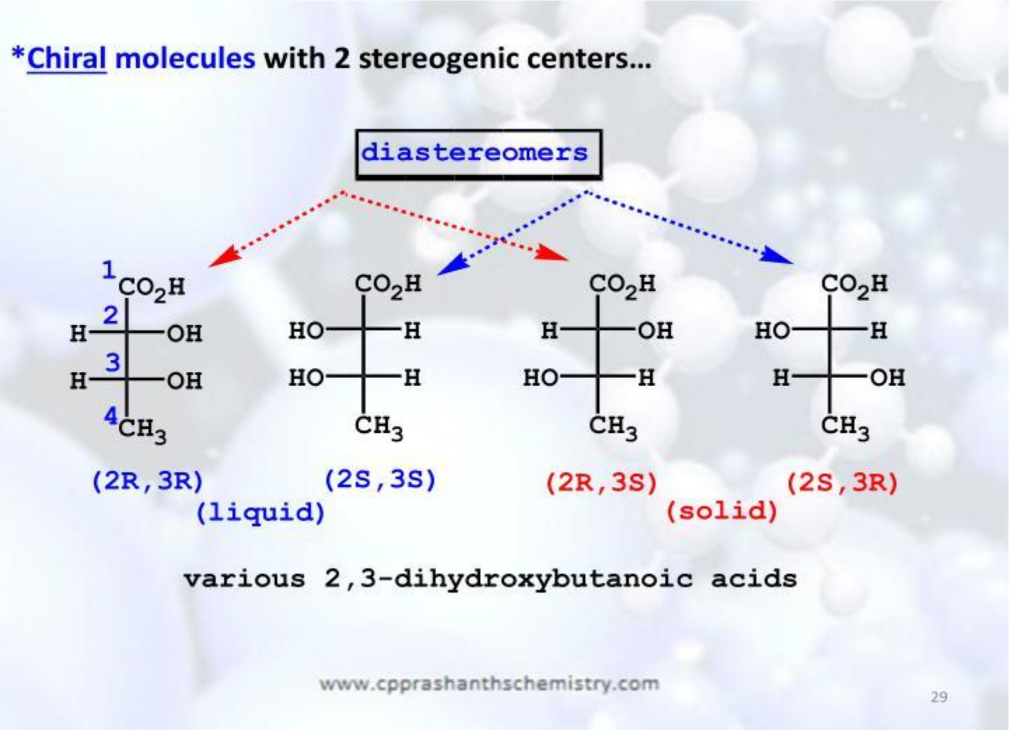


Tartaric acid properties....

3 stereo isomers ➔ 4 crystal forms

Stereo-isomer	Mp (°C)	$[\alpha]^{20}_{D}$ (°)	ρ (gm/ml)	H_2O solubility (gm/100 ml)
(+)	168-170	+12	1.760	139
(-)	168-170	-12	1.760	139
meso	146-8	0	1.660	125
(+-)	206	0	1.788	20.6

	pK_a # 1	pK_a # 2
(+) or (-)	2.98	4.34
meso	3.23	4.82



***Chiral molecules with 2 stereogenic centers…**

diastereomers

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

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

various 2,3-dihydroxybutanoic acids

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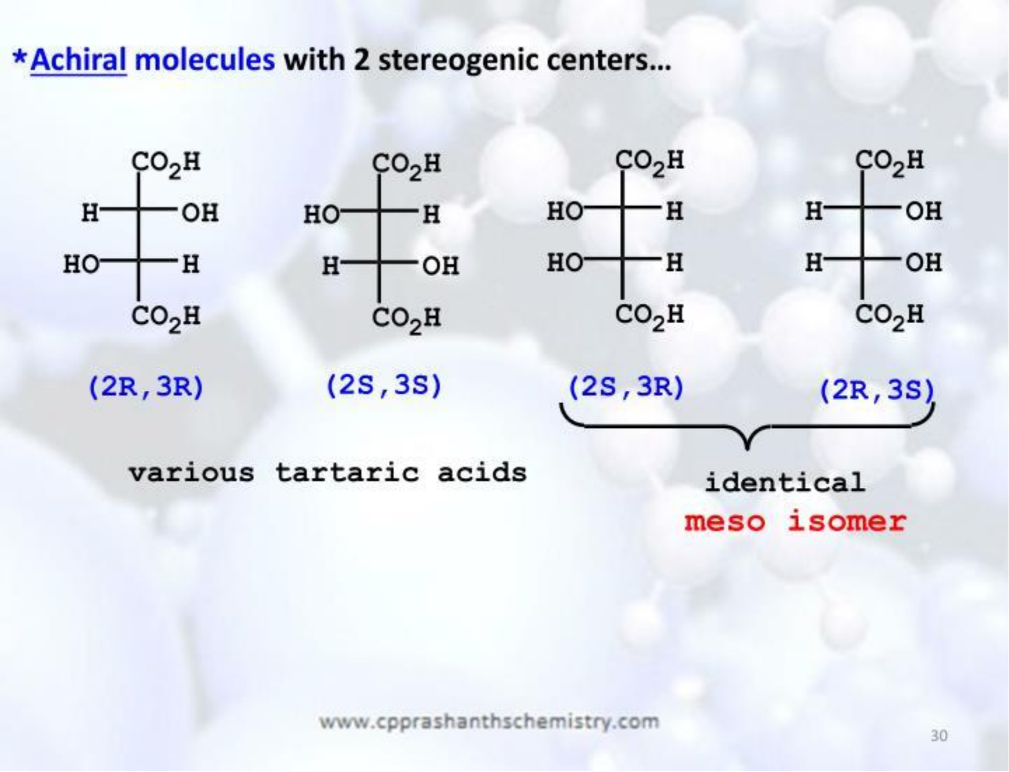

***Achiral molecules with 2 stereogenic centers…**

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

various tartaric acids

identical
meso isomer

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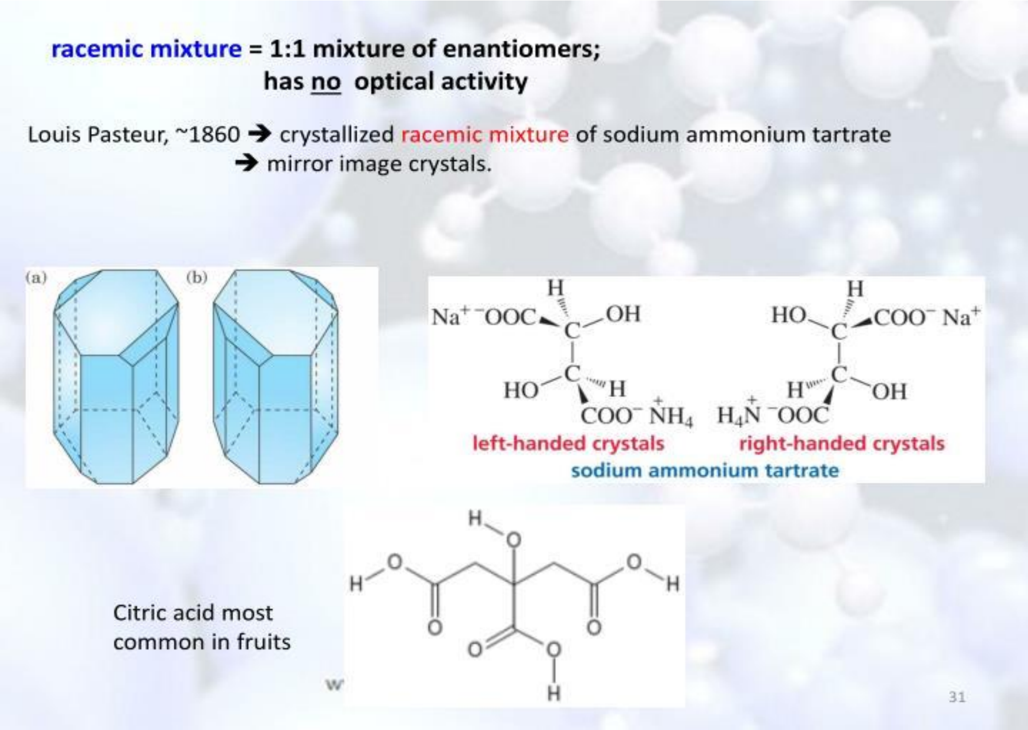


racemic mixture = 1:1 mixture of enantiomers;
has no optical activity

Louis Pasteur, ~1860 ➔ crystallized racemic mixture of sodium ammonium tartrate
➔ mirror image crystals.

left-handed crystals

right-handed crystals

sodium ammonium tartrate

Citric acid most common in fruits

References

1- Organic Stereochemistry, Hua-Jie Zhu (2018)

2- Stereochemistry of organic compounds, Emest L. Eliel, Samuel H. Wilen (2015).

3- Stereochemistry conformation and mechanism, eighth edition, P. S. Kalsi (2020).

4- Stereochemistry of organic compounds principles and applications, D. Nasipure (2019).

5- Guide to stereochemistry, A Detailed Guide, Bishal Bashya, (2014).

Dicarboxylic acids

2nd year students – faculty of education

Chemistry group

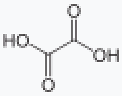
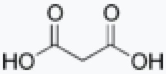
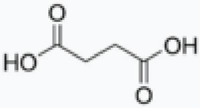
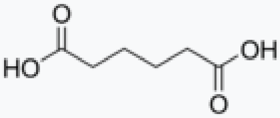
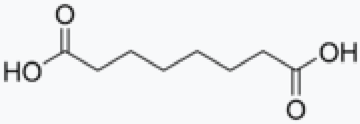
Second term 2022/2023

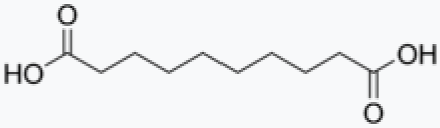
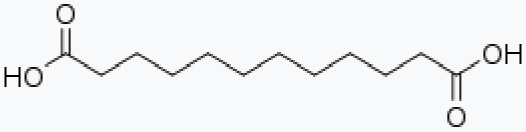
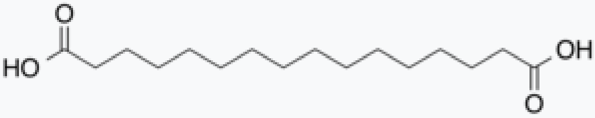
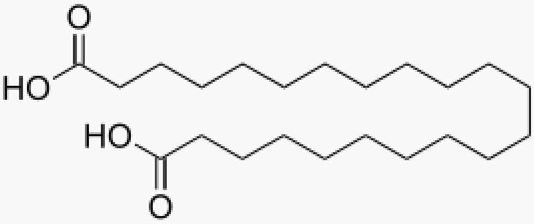
Dr/Ibrahim Abdul-Motaleb mousa

Dicarboxylic acid

In organic chemistry, a dicarboxylic acid is an organic compound containing two carboxyl groups (−COOH). The general molecular formula for dicarboxylic acids can be written as $HO_2C-R-CO_2H$, where R can be aliphatic or aromatic. In general, dicarboxylic acids show similar chemical behavior and reactivity to monocarboxylic acids.

Dicarboxylic acids are used in the preparation of copolymers such as polyamides and polyesters. The most widely used dicarboxylic acid in the industry is adipic acid, which is a precursor in the production of nylon. Other examples of dicarboxylic acids include aspartic acid and glutamic acid, two amino acids in the human body. The name can be abbreviated to diacid.

n	Common name	Systematic IUPAC name	Structure
0	Oxalic acid	ethanedioic acid	
1	Malonic acid	propanedioic acid	
2	Succinic acid	butanedioic acid	
3	Glutaric acid	pentanedioic acid	
4	Adipic acid	hexanedioic acid	
5	Pimelic acid	heptanedioic acid	
6	Suberic acid	octanedioic acid	
7	Azelaic acid	nonanedioic acid	

8	Sebacic acid	decanedioic acid	
9		undecanedioic acid	
10		dodecanedioic acid	
13	Brassylic acid	tridecanedioic acid	
14	Thapsic acid	hexadecanedioic acid	
20	Phellogenic acid	docosanedioic acid	

Occurrence:

Adipic acid, despite its name (in Latin, adipis means fat), is not a normal constituent of natural lipids but is a product of oxidative rancidity. It was first obtained by oxidation of castor oil (ricinoleic acid) with nitric acid. It is now produced industrially by oxidation of cyclohexanol or cyclohexane, mainly for the production of Nylon 6-6. It has several other industrial uses in the production of adhesives, plasticizers, gelatinizing agents, hydraulic fluids, lubricants, emollients, polyurethane foams, leather tanning, urethane and also as an acidulant in foods.

- **Pimelic acid (Greek *pimelh,* fat) was also first isolated from oxidized oil. Derivatives of pimelic acid are involved in the biosynthesis of lysine.**
- **Suberic acid was first produced by nitric acid oxidation of cork (Latin suber). This acid is also**

produced when castor oil is oxidised. Suberic acid is used in the manufacture of alkyd resins and in the synthesis of polyamides (nylon variants).

- **Azelaic acid's name stems from the action of nitric acid (azote, nitrogen, or azotic, nitric) oxidation of oleic acid or elaidic acid. It was detected among products of rancid fats. Its origin explains for its presence in poorly preserved samples of linseed oil and in specimens of ointment removed from Egyptian tombs 5000 years old. Azelaic acid was prepared by oxidation of oleic acid with potassium permanganate, but now by oxidative cleavage of oleic acid with chromic acid or by ozonolysis. Azelaic acid is used, as simple esters or branched-chain esters) in the manufacture of plasticizers (for vinyl chloride resins, rubber), lubricants and greases. Azelaic acid is now used in cosmetics (treatment of acne). It displays bacteriostatic**

and bactericidal properties against a variety of aerobic and anaerobic micro-organisms present on acne-bearing skin. . Azelaic acid was identified as a molecule that accumulated at elevated levels in some parts of plants and was shown to be able to enhance the resistance of plants to infections.

- **Sebacic acid, named from sebum (tallow). Thenard isolated this compound from distillation products of beef tallow in 1802. It is produced industrially by alkali fission of castor oil. Sebacic acid and its derivatives have a variety of industrial uses as plasticizers, lubricants, diffusion pump oils, cosmetics, candles, etc. It is also used in the synthesis of polyamide, as nylon, and of alkyd resins. An isomer, isosebacic acid, has several applications in the manufacture of vinyl resin plasticizers, extrusion plastics, adhesives, ester lubricants, polyesters, polyurethane resins and synthetic rubber.**

- **Brassylic acid can be produced from erucic acid by ozonolysis, but also by microorganisms (*Candida* sp.) from tridecane. This diacid is produced on a small commercial scale in Japan for the manufacture of fragrances.**
- **Dodecanedioic acid is used in the production of nylon (nylon-6,12), polyamides, coatings, adhesives, greases, polyesters, dyestuffs, detergents, flame retardants, and fragrances. It is now produced by fermentation of long-chain alkanes with a specific strain of *Candida tropicalis*. Traumatic acid is its monounsaturated counterpart.**
- **Thapsic acid was isolated from the dried roots of the Mediterranean "deadly carrot", *Thapsia garganica* (Apiaceae).**

Japan wax is a mixture containing triglycerides of C21, C22 and C23 dicarboxylic acids obtained from the sumac tree (*Rhus* sp.).

A large survey of the dicarboxylic acids present in Mediterranean nuts revealed unusual components. A total of 26 minor acids (from 2 in pecan to 8% in peanut) were determined: 8 species derived from succinic acid, likely in relation with photosynthesis, and 18 species with a chain from 5 to 22 carbon atoms. Higher weight acids (>C20) are found in suberin present at vegetal surfaces (outer bark, root epidermis). C16 to C26 a, ω-dioic acids are considered as diagnostic for suberin. With C18:1 and C18:2, their content amount from 24 to 45% of whole suberin. They are present at low levels (< 5%) in plant cutin, except in *Arabidopsis thaliana* where their content can be higher than 50%.

It was shown that hyperthermophilic microorganisms specifically contained a large variety of dicarboxylic acids. This is probably the most important difference between these microorganisms and other marine

bacteria. Dioic fatty acids from C16 to C22 were found in an hyperthermophilic archaeon, *Pyrococcus furiosus*. Short and medium chain (up to 11 carbon atoms) dioic acids have been discovered in Cyanobacteria of the genus *Aphanizomenon*.

Dicarboxylic acids may be produced by ω-oxidation of fatty acids during their catabolism. It was discovered that these compounds appeared in urine after administration of tricaprin and triundecylin. Although the significance of their biosynthesis remains poorly understood, it was demonstrated that ω-oxidation occurs in rat liver but at a low rate, needs oxygen, NADPH and cytochrome P450. It was later shown that this reaction is more important in starving or diabetic animals where 15% of palmitic acid is subjected to ω-oxidation and then tob-oxidation, this generates malonyl-coA which is further used in saturated fatty acid synthesis. The determination of the

dicarboxylic acids generated by permanganate-periodate oxidation of monoenoic fatty acids was useful to study the position of the double bond in the carbon chain.

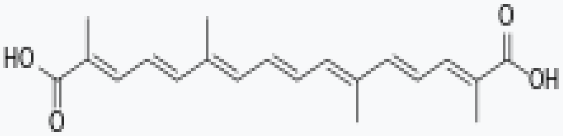
Branched-chain dicarboxylic acids

Long-chain dicarboxylic acids containing vicinal dimethyl branching near the center of the carbon chain have been discovered in the genus *Butyrivibrio*, bacteria which participate in the digestion of cellulose in the rumen. These fatty acids, named diabolic acids, have a chain length depending on the fatty acid used in the culture medium. The most abundant diabolic acid in *Butyrivibrio* had a 32-carbon chain length. Diabolic acids were also detected in the core lipids of the genus *Thermotoga* of the order Thermotogales, bacteria living in solfatara springs, deep-sea marine hydrothermal systems and high-temperature marine and continental oil fields. It

was shown that about 10% of their lipid fraction were symmetrical C30 to C34 diabolic acids. The C30 (13,14-dimethyloctacosanedioic acid) and C32 (15,16-dimethyltriacontanedioic acid) diabolic acids have been described in Thermotoga maritima.

Some parent C29 to C32 diacids but with methyl groups on the carbons C-13 and C-16 have been isolated and characterized from the lipids of thermophilic anaerobic eubacterium Themanaerobacter ethanolicus. The most abundant diacid was the C30 a,ω-13,16-dimethyloctacosanedioic acid.

Biphytanic diacids are present in geological sediments and are considered as tracers of past anaerobic oxidation of methane. Several forms without or with one or two pentacyclic rings have been detected in Cenozoic seep limestones. These lipids may be unrecognized metabolites from Archaea.

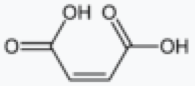
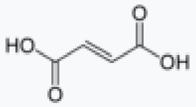
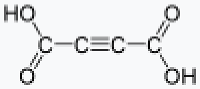
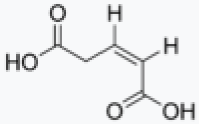
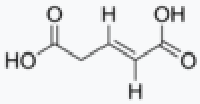


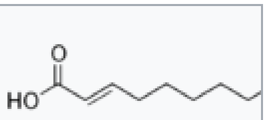
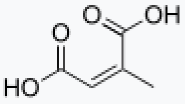
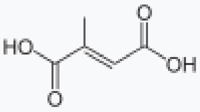
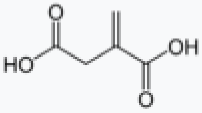
Crocetin

Crocetin is the core compound of crocins (crocetin glycosides) which are the main red pigments of the stigmas of saffron (Crocus sativus) and the fruits of gardenia (Gardenia jasminoides). Crocetin is a 20-carbon chain dicarboxylic acid which is a diterpenenoid and can be considered as a carotenoid. It was the first plant carotenoid to be recognized as early as 1818 while the history of saffron cultivation reaches back more than 3,000 years. The major active ingredient of saffron is the yellow pigment crocin 2 (three other derivatives with different glycosylations are known) containing a gentiobiose (disaccharide) group at each end of the molecule. A simple and specific HPLC-UV method has been developed to quantify the five major biologically

active ingredients of saffron, namely the four crocins and crocetin.

Unsaturated dicarboxylic acids:

Type	Common name	IUPAC name	Isomer	Structural formula
Monounsaturated	Maleic acid	(Z)-Butenedioic acid	cis	
	Fumaric acid	(E)-Butenedioic acid	trans	
	Acetylenedicarboxylic acid	But-2-ynedioic acid	not applicable	
	Glutaconic acid	(Z)-Pent-2-enedioic acid	cis	
		(E)-Pent-2-enedioic acid	trans	
		2-Decenedioic acid	trans	

	Traumatic acid	Dodec-2-enedioic acid	trans	
Diunsaturated	Muconic acid	(2E,4E)-Hexa-2,4-dienedioic acid	trans,trans	
		(2Z,4E)-Hexa-2,4-dienedioic acid	cis,trans	
		(2Z,4Z)-Hexa-2,4-dienedioic acid	cis,cis	
	Glutinic acid (Allene-1,3-dicarboxylic acid)	(RS)-Penta-2,3-dienedioic acid		$HO_2CCH=C=CHCO_2H$
Branched	Citraconic acid	(2Z)-2-Methylbut-2-enedioic acid	cis	
	Mesaconic acid	(2E)-2-Methyl-2-butenedioic acid	trans	
	Itaconic acid	2-Methylidenebutanedioic acid	–	

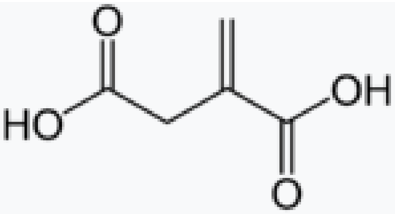
Traumatic acid, was among the first biologically active molecules isolated from plant tissues. This dicarboxylic acid was shown to be a potent wound healing agent in plant that stimulates cell division near a wound site, it derives from 18:2 or 18:3 fatty acid hydro peroxides after conversion into oxo- fatty acids.

***Trans ,trans*-Muconic acid is a metabolite of benzene in humans. The determination of its concentration in urine is therefore used as a biomarker of occupational or environmental exposure to benzene.**

Glutinic acid, a substituted allene, was isolated from *Alnus glutinosa* (Betulaceae).

While polyunsaturated fatty acids are unusual in plant cuticles, a diunsaturated dicarboxylic acid has been reported as a component of the surface waxes or polyesters of some plant species. Thus, octadeca-c6,c9-diene-1,18-dioate, a derivative of linoleic acid, is present in Arabidopsis and Brassica napus cuticle.

Alkylitaconates:

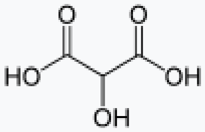
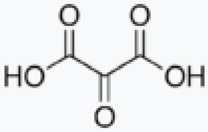
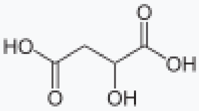
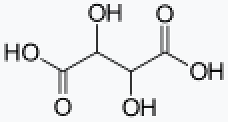


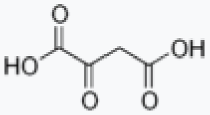
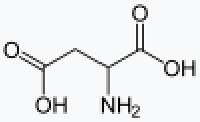
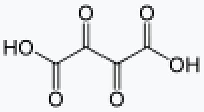
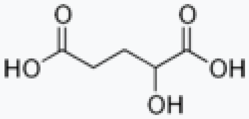
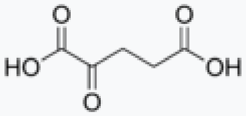
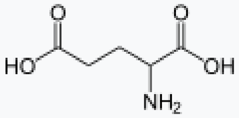
Itaconic acid

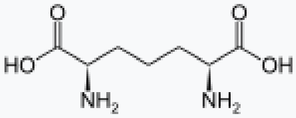
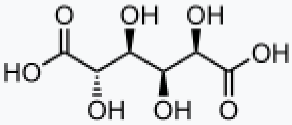
Several dicarboxylic acids having an alkyl side chain and an itaconate core have been isolated from lichens and fungi, itaconic acid (methylenesuccinic acid) being a metabolite produced by filamentous fungi. Among these compounds, several analogues, called chaetomellic acids with different chain lengths and degrees of unsaturation have been isolated from various species of the lichen Chaetomella. These molecules were shown to be valuable as basis for the development of anticancer drugs due to their strong farnesyltransferase inhibitory effects. A series of alkyl- and alkenyl-itaconates, known as ceriporic acids, were found in cultures of a selective lignin-degrading

fungus (white rot fungus), Ceriporiopsis subvermispora. The absolute configuration of ceriporic acids, their stereo selective biosynthetic pathway and the diversity of their metabolites have been discussed in detail.

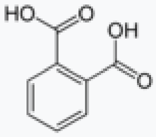
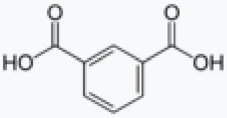
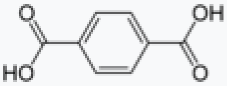
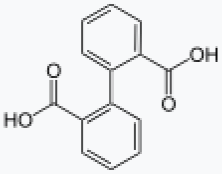
Substituted dicarboxylic acids:

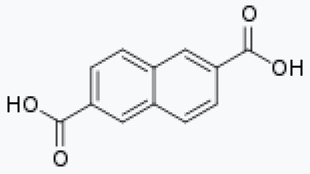
Common name	IUPAC name	Structural formula
Tartronic acid	2-Hydroxypropanedioic acid	
Mesoxalic acid	Oxopropanedioic acid	
Malic acid	Hydroxybutanedioic acid	
Tartaric acid	2,3-Dihydroxybutanedioic acid	

Oxaloacetic acid	Oxobutanedioic acid	
Aspartic acid	2-Aminobutanedioic acid	
dioxosuccinic acid	dioxobutanedioic acid	
α-hydroxyGlutaric acid	2-hydroxypentanedioic acid	
Arabinaric acid	2,3,4-Trihydroxypentanedioic acid	
Acetonedicarboxylic acid	3-Oxopentanedioic acid	
α-Ketoglutaric acid	2-Oxopentanedioic acid	
Glutamic acid	2-Aminopentanedioic acid	

Diaminopimelic acid	(2R,6S)-2,6-Diaminoheptanedioic acid	
Saccharic acid	(2S,3S,4S,5R)-2,3,4,5-Tetrahydroxyhexanedioic acid	

Aromatic dicarboxylic acids:

Common names	**IUPAC name**	**Structure**
Phthalic acid *o*-phthalic acid	Benzene-1,2-dicarboxylic acid	
Isophthalic acid *m*-phthalic acid	Benzene-1,3-dicarboxylic acid	
Terephthalic acid *p*-phthalic acid	Benzene-1,4-dicarboxylic acid	
Diphenic acid Biphenyl-2,2′-dicarboxylic acid	2-(2-Carboxyphenyl)benzoic acid	

2,6-Naphthalenedicarboxylic acid	2,6-Naphthalenedicarboxylic acid	

Terephthalic acid is a commodity chemical used in the manufacture of the polyester known by brand names such as PET, Terylene, Dacron and Lavsan.

<u>Properties</u>:

Dicarboxylic acids are crystalline solids. Solubility in water and melting point of the α,ω- compounds progress in a series as the carbon chains become longer with alternating between odd and even numbers of carbon atoms, so that for even numbers of carbon atoms the melting point is higher than for the next in the series with an odd number. These compounds are weak dibasic acids with pK_a tending towards values of ca. 4.5 and 5.5 as the separation between the two carboxylate groups increases. Thus, in an aqueous

solution at pH about 7, typical of biological systems, the Henderson–Hasselbalch equation indicates they exist predominantly as dicarboxylate anions.

The dicarboxylic acids, especially the small and linear ones, can be used as crosslinking reagents. Dicarboxylic acids where the carboxylic groups are separated by none or one carbon atom decompose when they are heated to give off carbon dioxide and leave behind a monocarboxylic acid.

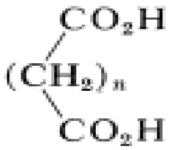
Blanc's Rule says that heating a barium salt of a dicarboxylic acid, or dehydrating it with acetic anhydride will yield a cyclic acid anhydride if the carbon atoms bearing acid groups are in position 1 and (4 or 5). So succinic acid will yield succinic anhydride. For acids with carboxylic groups at position 1 and 6 this dehydration causes loss of carbon dioxide and water to form a cyclic ketone, for example, adipic acid will form cyclopentanone.

Derivatives:

As for monofunctional carboxylic acids, derivatives of the same types exist. However, there is the added complication that either one or two of the carboxylic groups could be altered. If only one is changed then the derivative is termed "acid", and if both ends are altered it is called "normal". These derivatives include salts, chlorides, esters, amides, and anhydrides. In the case of anhydrides or amides, two of the carboxyl groups can come together to form a cyclic compound, for example succinimide.

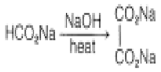
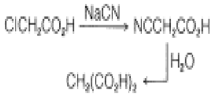
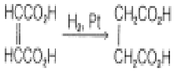
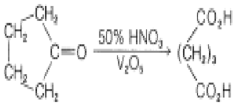
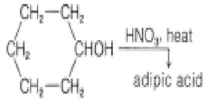
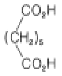
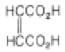
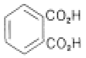
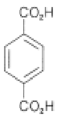
Dicarboxylic Acids

Acids in which there are two carboxyl groups separated by a chain of more than five carbon atoms $(n>5)(n>5)$ for the most part have unexceptional properties, and the carboxyl groups behave more or less independently of one another.



However, when the carboxyl groups are closer together the possibilities for interaction increase; we shall be interested primarily in such acids. A number of important dicarboxylic acids are listed in Table 18-4 together with their physical properties, methods of manufacture, and commercial uses.

Dicarboxylic acids

Acid	Formula	Mp, °C	$K_1 \times 10^5$ at 25°	$K_2 \times 10^5$ at 25°	Commercial preparation	Principal commercial uses
ethanedioic (oxalic)	 CO_2H-CO_2H	189	3500	5.3	 $HCO_2Na \xrightarrow[heat]{NaOH} CO_2Na-CO_2Na$	analytical, reducing, and bleaching agent; rust, paint, varnish, and ink remover
propanedioic (malonic)	 $CO_2H-CH_2-CO_2H$	136 dec.	171	0.22	 $ClCH_2CO_2H \xrightarrow{NaCN} NCCH_2CO_2H \xrightarrow{H_2O} CH_2(CO_2H)_2$	employed as ethyl ester in synthesis of carboxylic acids and manufacture of barbiturates
butanedioic (succinic)	 $CO_2H-(CH_2)_2-CO_2H$	185	6.6	0.25	 $HCCO_2H{=}HCCO_2H \xrightarrow{H_2, Pt} CH_2CO_2H-CH_2CO_2H$	manufacture of lacquers and dyes
pentanedioic (glutaric)	 $CO_2H-(CH_2)_3-CO_2H$	98	4.7	0.29	 $\xrightarrow[V_2O_5]{50\% \ HNO_3} CO_2H-(CH_2)_3-CO_2H$	
hexanedioic (adipic)	 $CO_2H-(CH_2)_4-CO_2H$	152	3.7	0.24	 $\xrightarrow{HNO_3, heat}$ adipic acid	important in condensation polymerization, particularly for manufacture of nylon and urethane foams
heptanedioic (pimelic)	 $CO_2H-(CH_2)_5-CO_2H$	105	3.4	0.26	reverse Claisen condensation of 2-carbethoxycyclohexanone	
cis-butenedioic (maleic)	 $HCCO_2H{=}HCCO_2H$	130	1170	0.026	catalytic oxidation of benzene to the anhydride	mainly used in the form of the anhydride in Diels–Alder diene synthesis; polymers, particularly fiberglass compositions
trans-butenedioic (fumaric)	 $HCCO_2H{=}HO_2CCH$	sub. 200	93	2.9	from glucose by bacterial action	
1,2-benzenedicarboxylic (phthalic)		231	130	0.39[18]	air oxidation of naphthalene and 1,2-dimethylbenzene	used as anhydride in organic synthesis and in manufacture of coating materials such as polyester
1,4-benzenedicarboxylic (terephthalic)		>300	31	1.5	air oxidation of 1,4-dimethylbenzene	polyester fibers such as Dacron

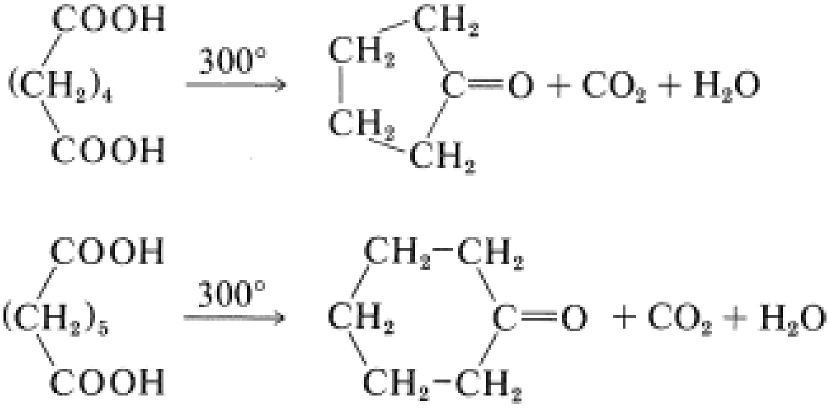
Acidic Properties of Dicarboxylic Acids:

The inductive effect of one carboxyl group is expected to enhance the acidity of the other. In Table 18-4 we see that the acid strength of the dicarboxylic acids, as measured by the first acid-dissociation constant, K1K1, is higher than that of ethanoic acid (Ka=1.5×10−5)(Ka=1.5×10−5) and decreases with increasing number of bonds between the two carboxyl groups. The second acid-dissociation constant, K2K2, is smaller than KaKa for ethanoic acid (with the exception of oxalic acid) because it is more difficult to remove a proton under the electrostatic attraction of the nearby carboxylate anion.

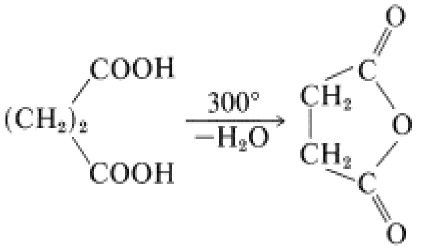
Thermal Behavior of Dicarboxylic Acids:

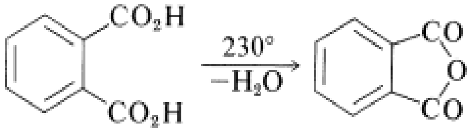
The reactions that occur when dicarboxylic acids are heated depend critically upon the chain length separating the carboxyl groups. Cyclization usually is favored if a strainless five- or six-membered ring can be

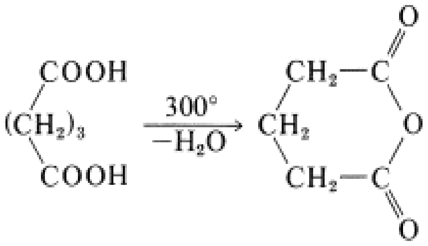
formed. Thus hexanedioic and heptanedioic acids decarboxylate and cyclize to cyclopentanone and cyclohexanone, respectively:

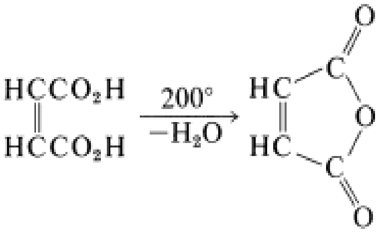


Butanedioic and pentanedioic acids take a different course. Rather than form the strained cyclic ketones, cyclopropanone and cyclobutanone, both acids form cyclic anhydrides that have five- and six-membered rings, respectively. 1,2-Benzenedicarboxylic (phthalic) and *cis*-1,4-butenedicarboxylic (maleic) acids behave similarly:

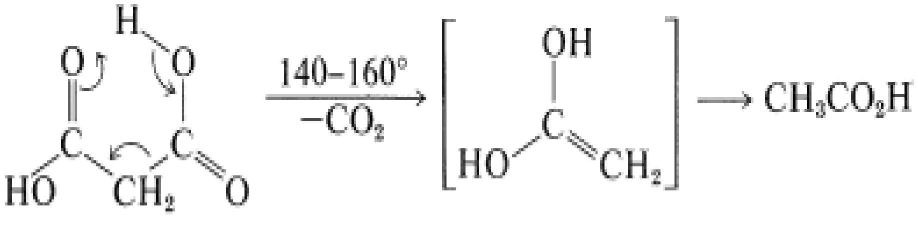


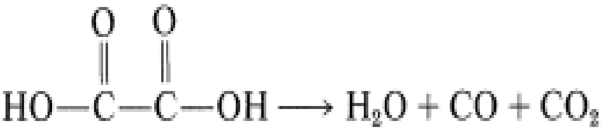






Because of their short chains, propanedioic and ethanedioic acids simply decarboxylate when heated:

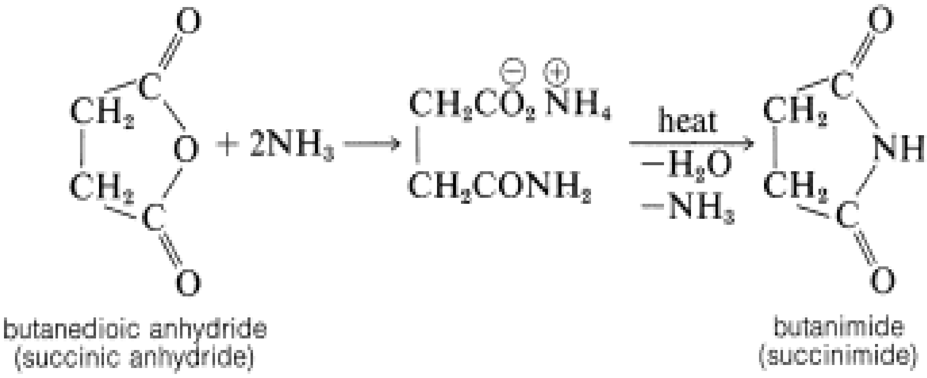




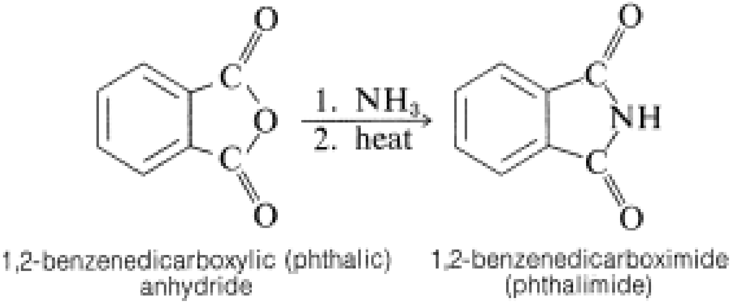
$$HO-\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OH \longrightarrow H_2O + CO + CO_2$$

Imides from Dicarboxylic Acids:

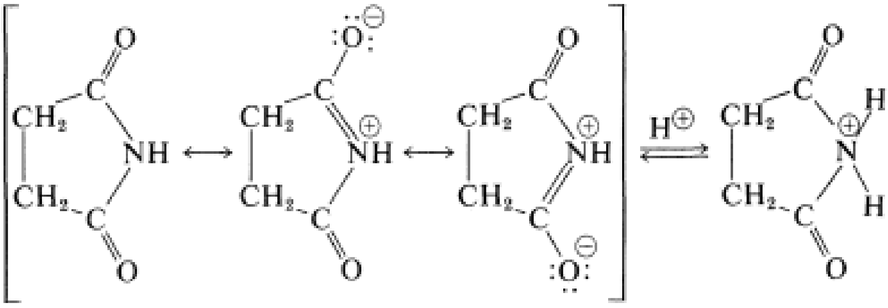
The cyclic anhydride of butanedioic acid reacts with ammonia, as may be expected for a typical anhydride; but the product, when strongly heated, forms a cyclic imide (butanimide):



1,2-Benzenedicarboxylic (phthalic) anhydride behaves similarly, giving 1,2-benzenedicarboximide (phthalimide):



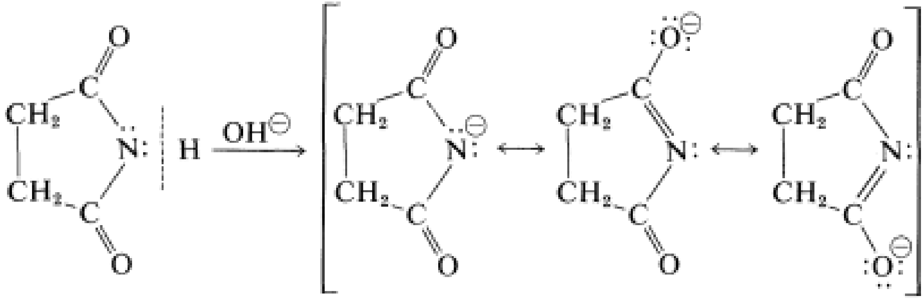
Unlike amines, imides do not have basic properties in water solution; the electron pair of nitrogen is partly delocalized over the carbonyl groups, as indicated by 17a17a to 17c17c. This stabilization is lost if a proton is added to nitrogen to give the conjugate acid, 1818:



17a 17b 17c 18

Imides are, in fact, quite acidic and readily dissolve in alkali-metal hydroxide solutions to give salts. Like carboxylic acids and 1,3-dicarbonyl compounds, imides are acidic primarily because the stabilization of the anion is greater than that of the acid. This can be seen by comparison of the resonance structures that may be written for the imide, 1717, with those of the anion, 1818. Separation of positive and negative charge,

as in Structures 17b17b and 17c17c, increases the energy of such structures. There is no charge separation in the anion; thus 19b19b and 19c19c are more important with respect to their hybrid than are 17b17b and 17c17c to their hybrid. (You may wish to review the corresponding argument for the acidity of carboxylic acids.

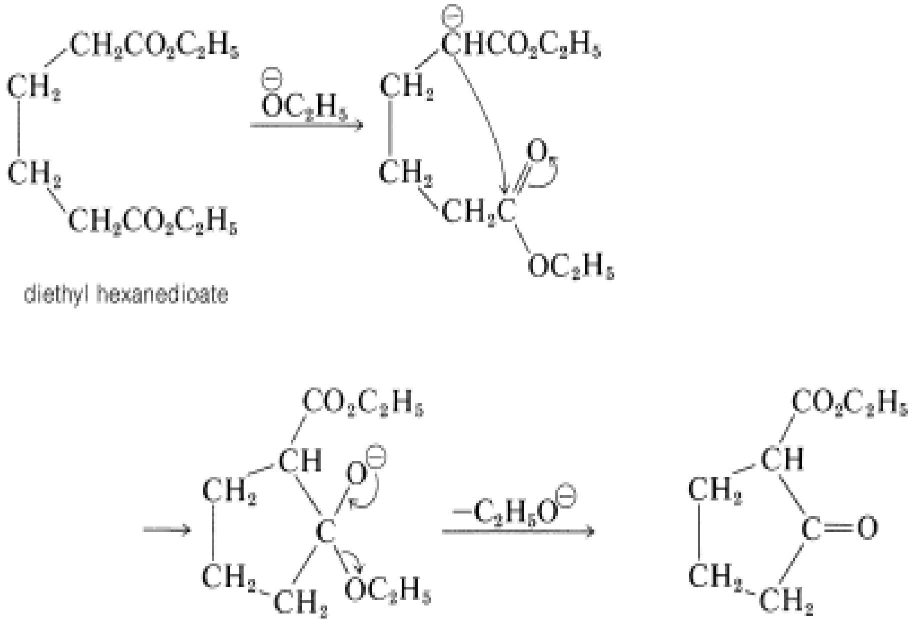


17 19a 19b 19c

The salts of imides are useful in synthesis.

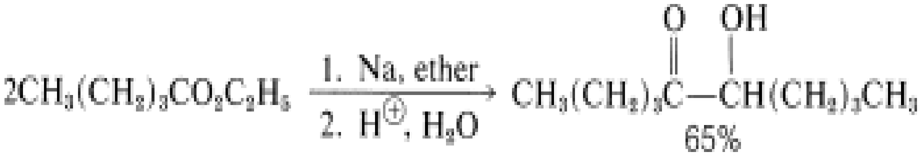
The Dieckmann Condensation

Esters of most dicarboxylic acids, except propanedioic esters, undergo Claisen condensation in much the same way as do esters of monocarboxylic acids (see Section 18-8B). However, when a strainless five- or six-membered ring can be formed, an intramolecular Claisen condensation, called the Dieckmann condensation, may take place which would result in the formation of a cyclic ββ-keto ester:



The Acyloin Reaction

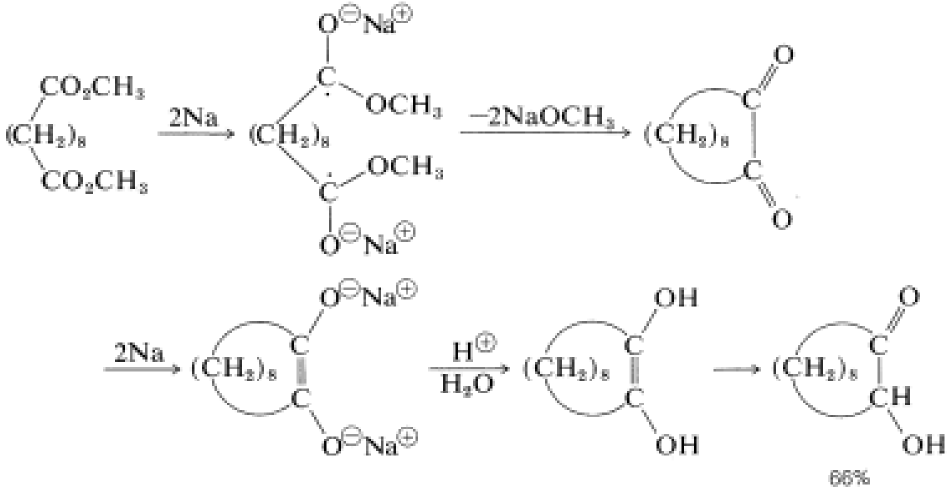
A useful method of forming carbon-carbon bonds involves reduction of esters with sodium metal in aprotic solvents such as ether or benzene and is called the acyloin reaction:



$$2CH_3(CH_2)_3CO_2C_2H_5 \xrightarrow[2.\ H^{\oplus},\ H_2O]{1.\ Na,\ ether} CH_3(CH_2)_3\overset{\overset{O}{\|}}{C}-\overset{\overset{OH}{|}}{C}H(CH_2)_3CH_3$$

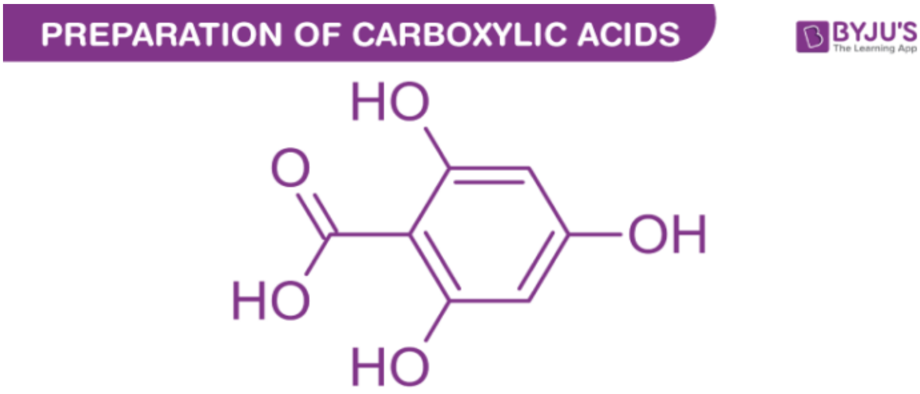
65%

This interesting reaction is especially useful for the synthesis of medium- and large-ring compounds from dicarboxylic esters, and is effective for ring sizes that cannot be made by the Dieckmann condensation or decarboxylation. Radical anions formed by addition of sodium to the ester groups appear to be the key intermediates for carbon-carbon bond formation. Thus, for dimethyl decanedioate:


2Na
−2NaOCH₃
2Na
H⊕
H₂O
66%

How to Prepare Carboxylic acids?

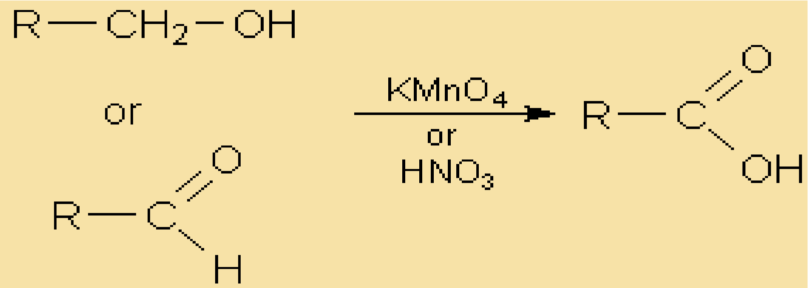
Preparation of Carboxylic Acid?



The compound in which the carbonyl group is attached to hydroxyl then it is called Carboxylic acid. There are various methods that can be used for the preparation of Carboxylic acids.

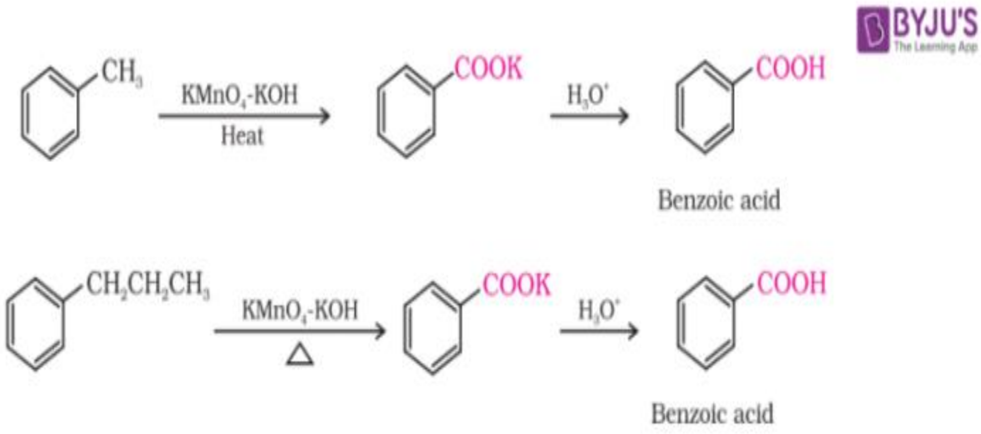
By using primary Alcohols and Aldehyde:

We will notice that the primary alcohol gets oxidised to carboxylic acid when oxidising agents are added, such as potassium permanganate ($KMnO_4$), in an acidic, alkaline or neutral medium. By using a mild oxidising agent, we can get carboxylic acids from aldehydes.



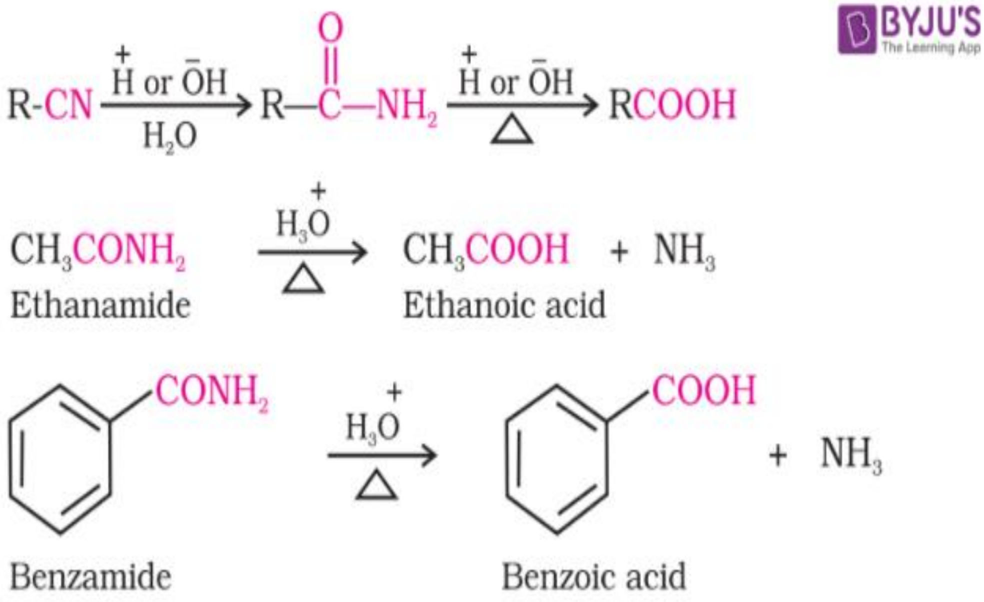
From Alkylbenzenes:

We can get aromatic carboxylic acids after vigorous oxidation of alkylbenzenes with chromic acid. Irrespective of the length of the chain, the whole side chain is oxidised to a carbonyl group. The oxidation of primary and secondary alkyl groups can be done in this manner while the tertiary group is unaffected.



From Nitriles and Amides:

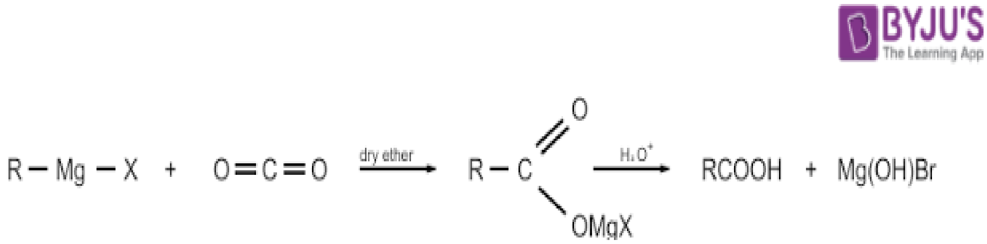
Amides are prepared by the hydrolysis of nitriles and then converted to acids in the presence of catalysts (H^+ or OH^{-1}). In order to stop the reaction at the amide stage, mild reaction conditions are used.



By using Grignard Reagents:

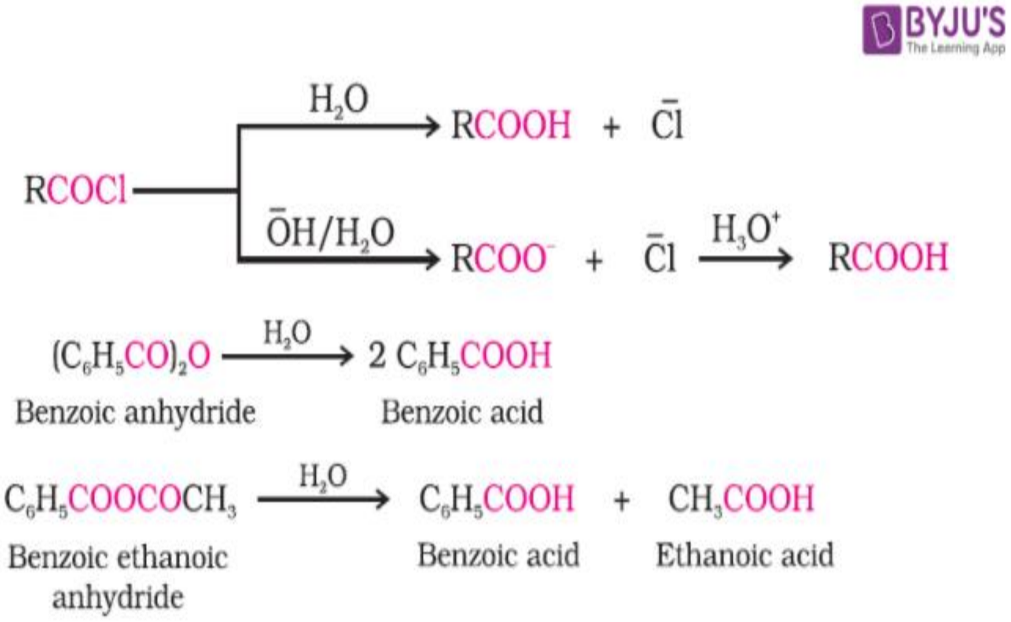
When Grignard reagent reacts with carbon dioxide, it forms salts of carboxylic acids which after some time gives corresponding carboxylic acid after the acidification with any mineral acid. We can prepare

Grignard reagents as well as nitriles from alkyl halides. These methods are very useful for the conversion of alkyl halides into corresponding carboxylic acids which has one carbon atom more than what is present in alkyl halides.



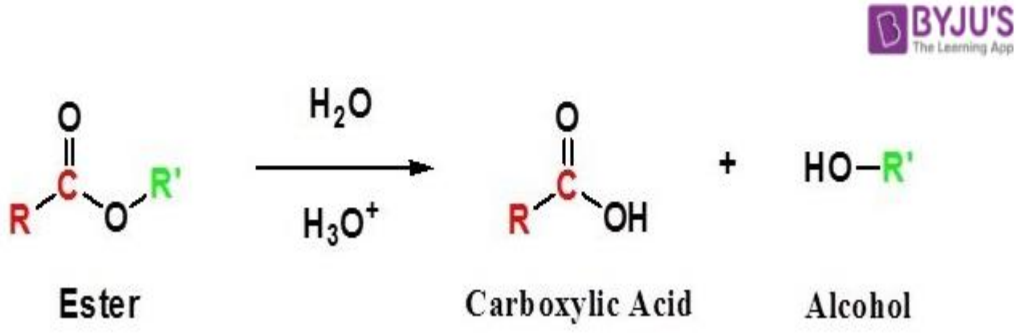
<u>By Acyl Halides and Anhydrides:</u>

When acid chloride is hydrolysed with water then carboxylic acid is produced and it is more readily hydrolysed with an aqueous base and gives corresponding carboxylic ions which on further acidification gives the carboxylic acid.



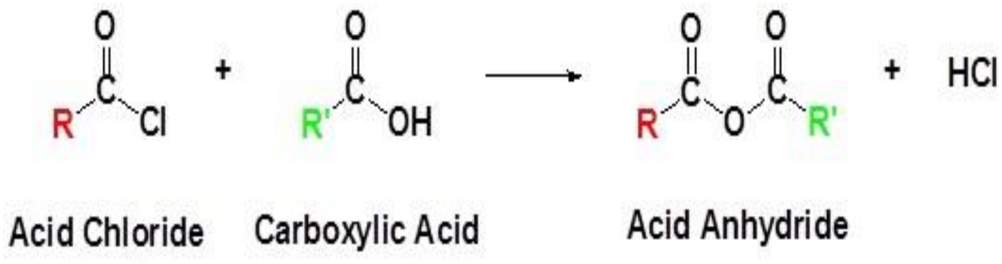
By using Esters:

A carboxylic acid is produced after the acidic hydrolysis of esters and carboxylates are produced after the basic hydrolysis of an ester.



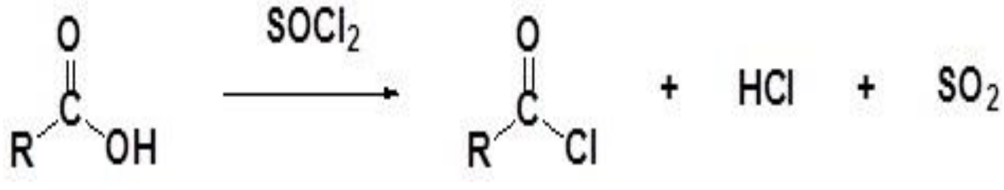
Reactions of Carboxylic Acids

Acid Chlorides react with carboxylic acids to form anhydrides:

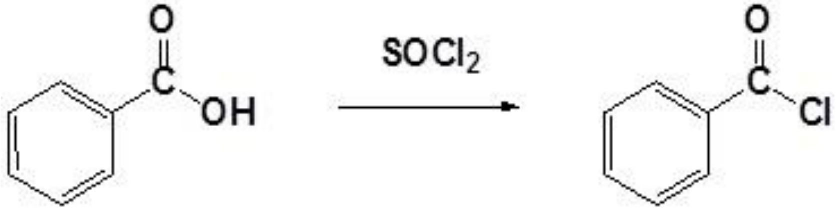


Carboxylic acids react with Thionyl Chloride ($SOCl_2$) to form <u>acid chlorides</u>.

During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

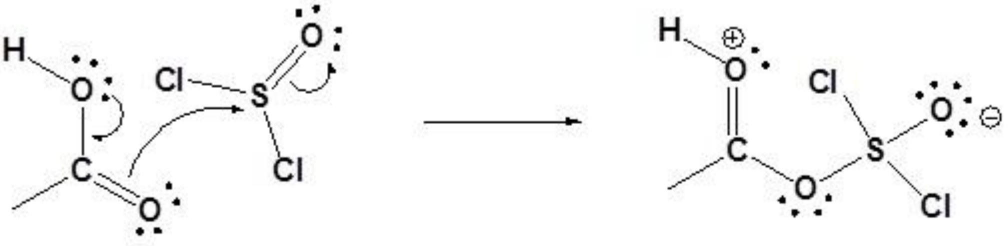


Example:

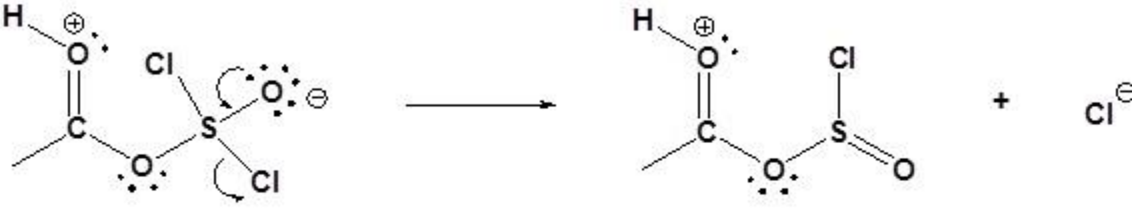


Mechanism:

1) Nucleophilic attack on Thionyl Chloride

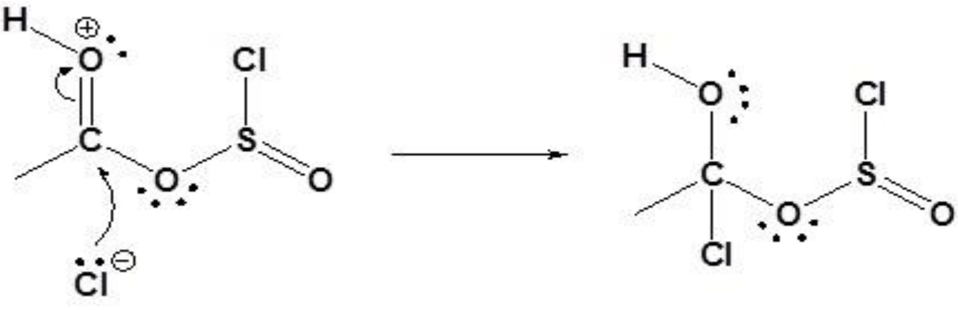


2) Removal of Cl leaving group

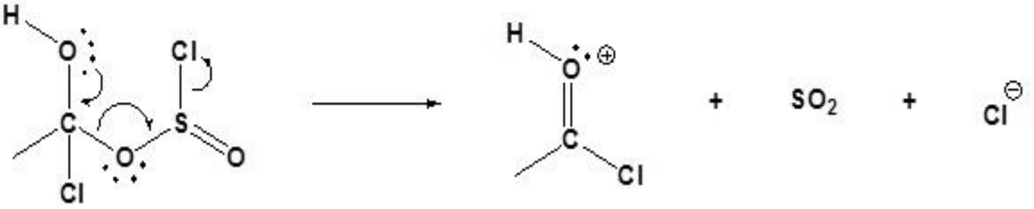


A Chlorosulfite

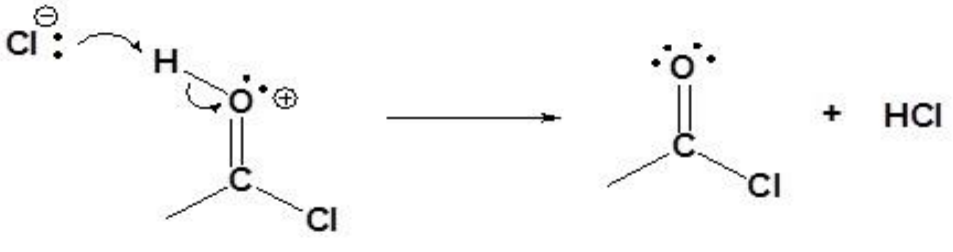
3) Nucleophilic attack on the carbonyl



4) Leaving group removal



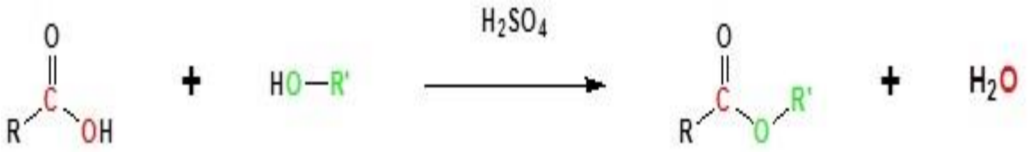
5) Deprotonation



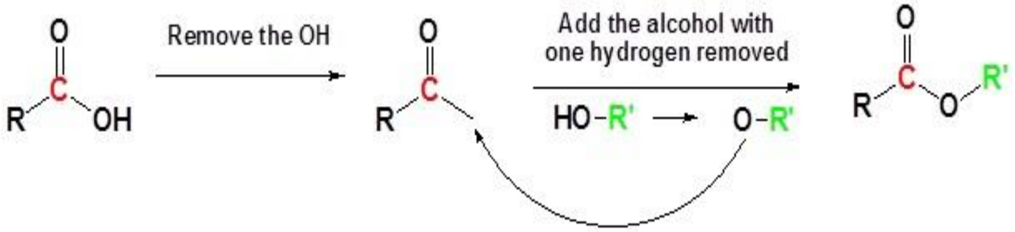
<u>Carboxylic acids</u> can react with alcohols to form esters in a process called Fischer esterification.

Usually the alcohol is used as the reaction solvent. An acid catalyst is required.

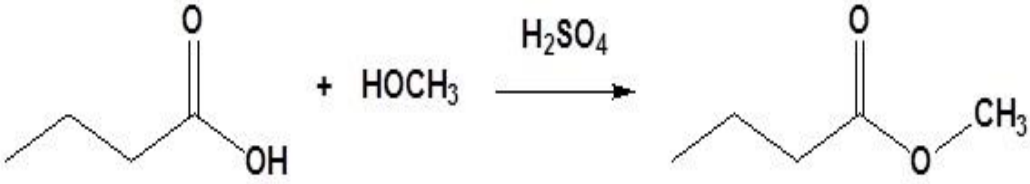
Basic Reaction:



Going from reactants to products simplified:

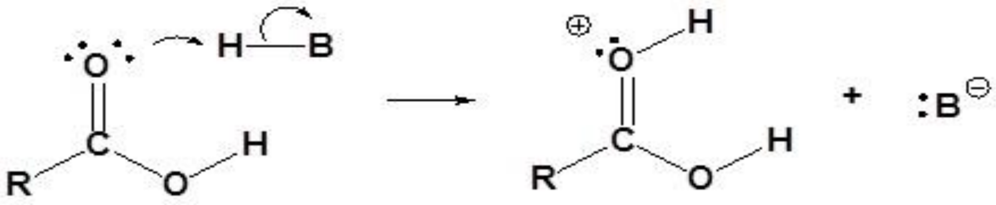


Example:

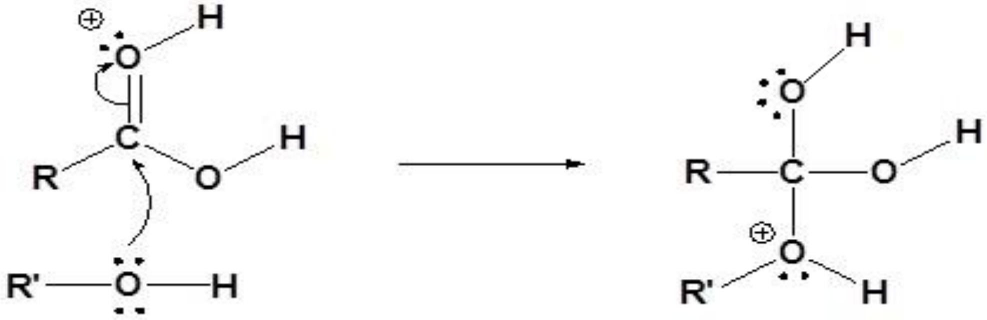


Mechanism:

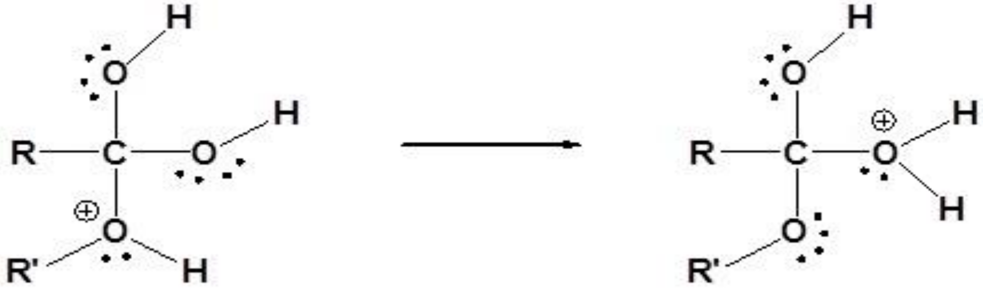
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic attack.



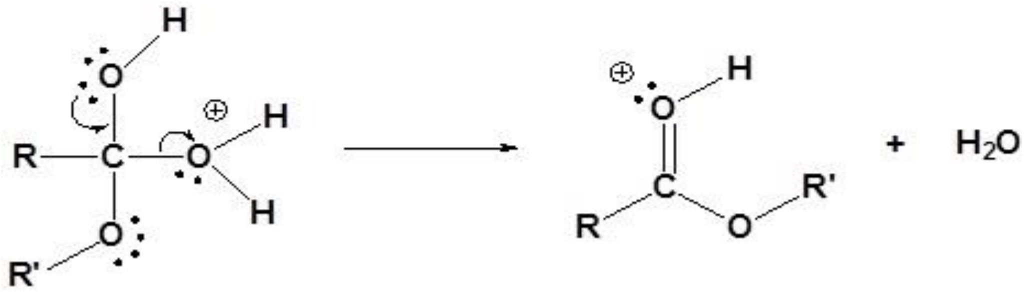
2) Nucleophilic attack on the carbonyl



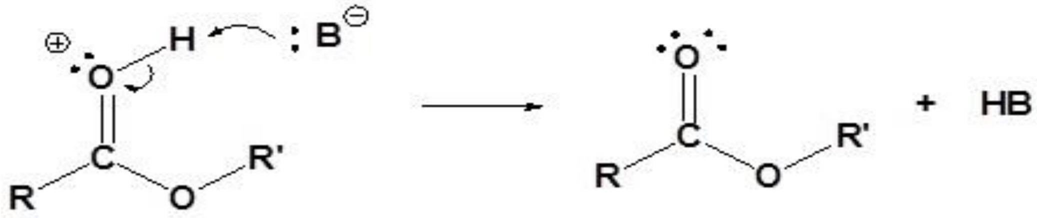
3) Proton transfer



4) Water leaves



5) Deprotonation

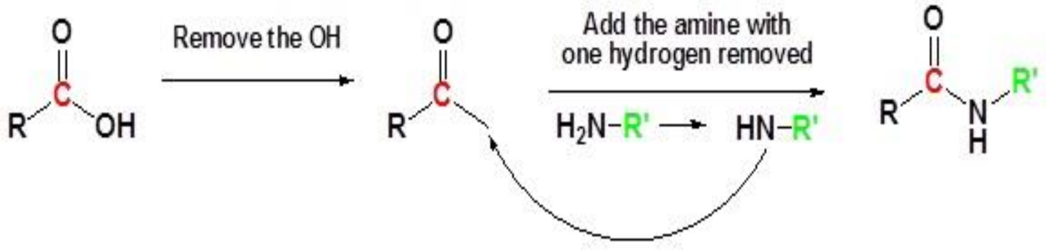


Conversion of Carboxylic Acids to Amides

The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^oC water is driven off and an amide is formed.

General Reaction

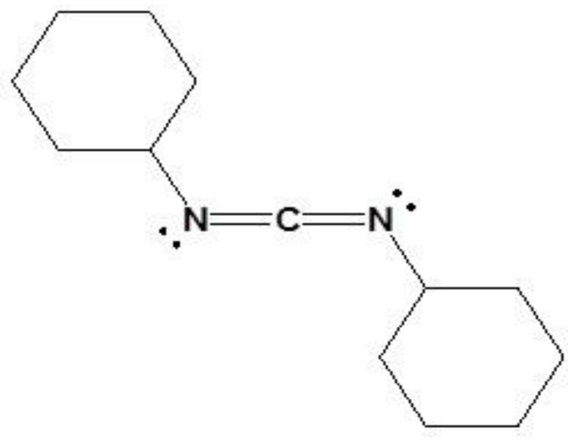
Going from reactants to products simply



Conversion of Carboxylic acids to amide using DCC as an activating agent

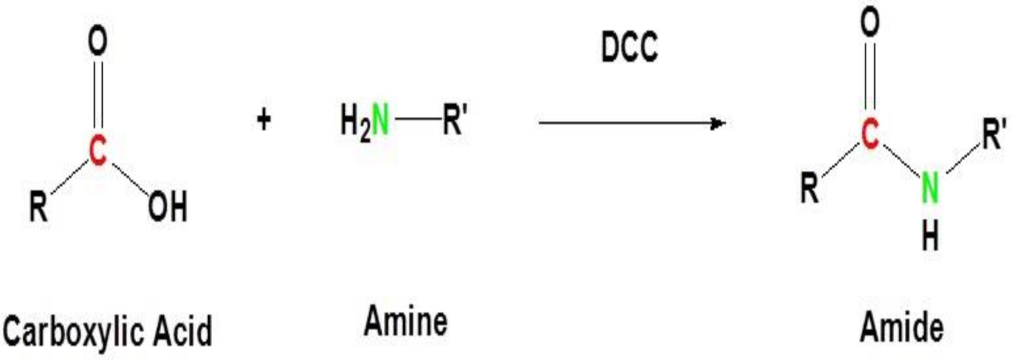
The direct conversion of a carboxylic acid to an amide is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. In this reaction the carboxylic acid adds to the DCC molecule to form a good leaving group which can then

be displaced by an amine during nucleophilic substitution. DCC induced coupling to form an amide linkage is an important reaction in the synthesis of peptides.

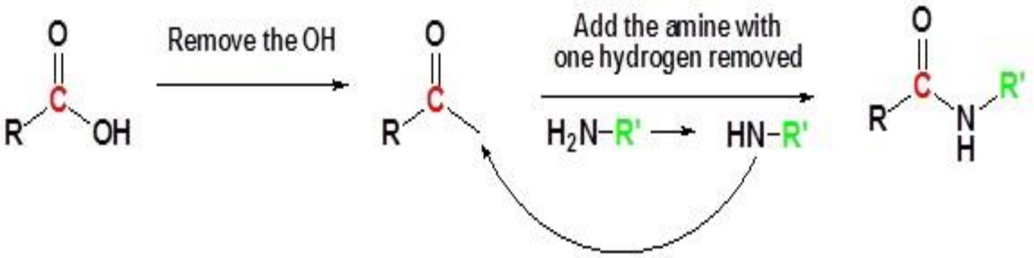


Dicyclohexylcarbodiimide (DCC)

Basic reaction:

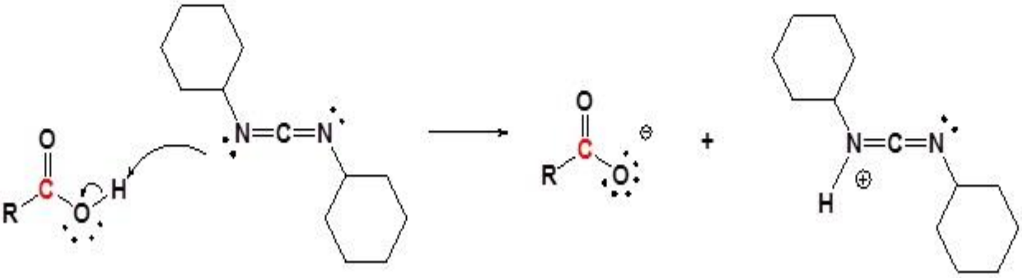


Going from reactants to products simplified

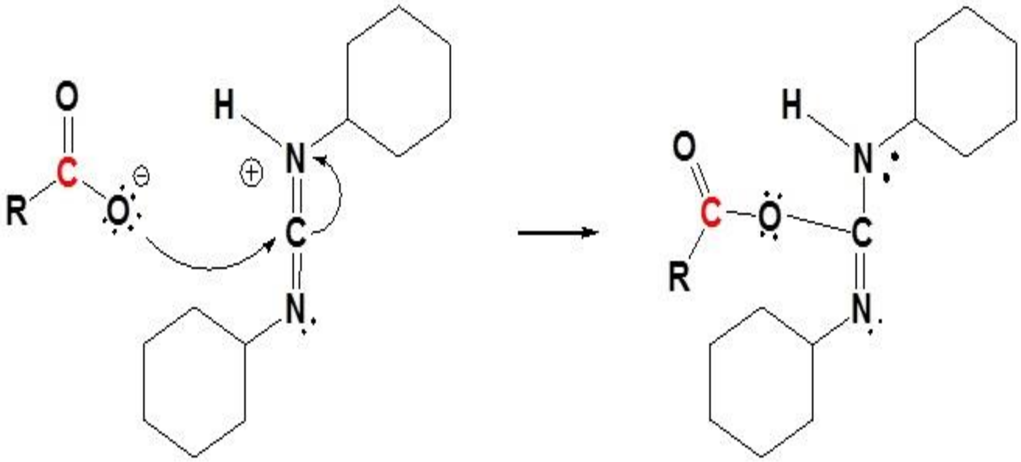


Mechanism

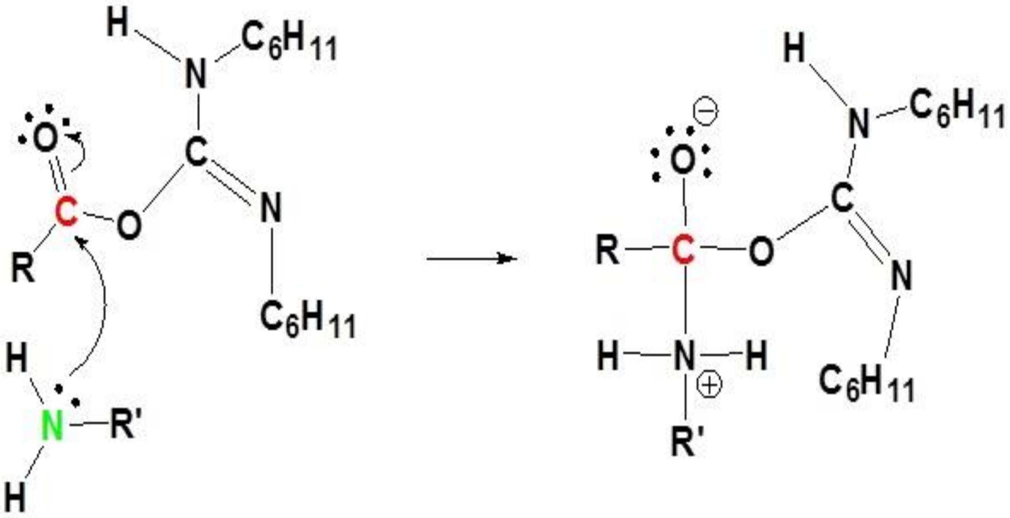
1) Deprotonation



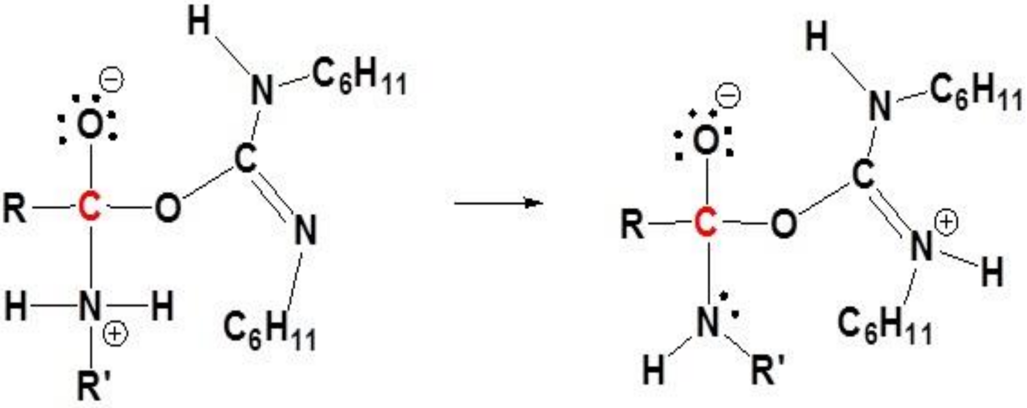
2) Nucleophilic attack by the carboxylate



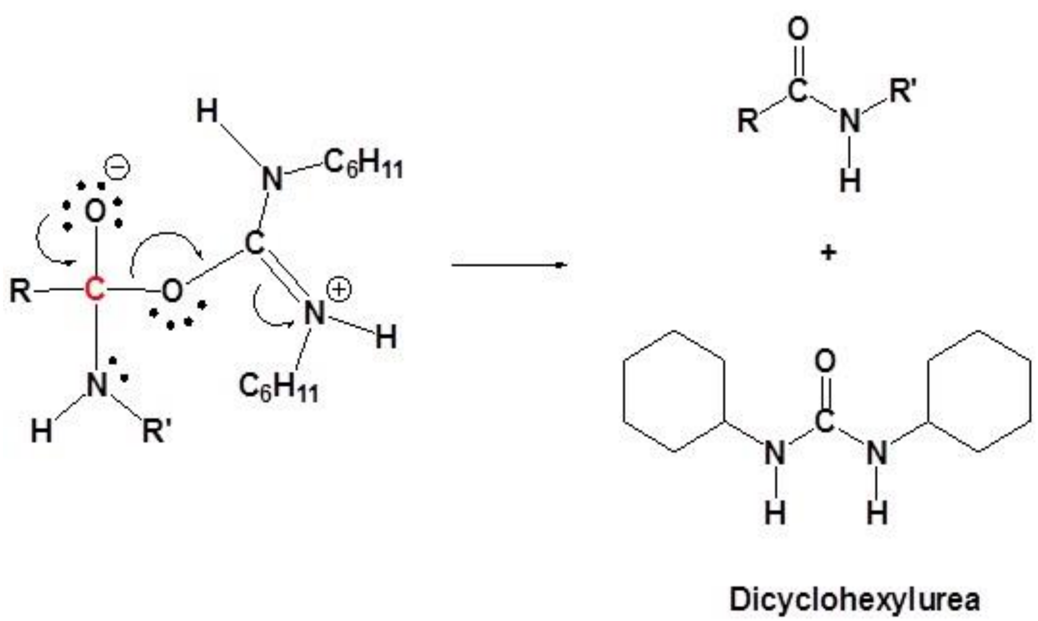
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal


Dicyclohexylurea

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1. **IUPAC, *Compendium of Chemical Terminology,* 2nd ed. (the "Gold Book") (1997). Online corrected version: (2006–) "carboxylic acids". doi:10.1351/goldbook.C00852**
2. **^ Recommendations 1979. Organic Chemistry IUPAC Nomenclature. Rules C-4 Carboxylic Acids and Their Derivatives.**
3. **^ Jump up to:[a] [b] *Morrison, R.T.; Boyd, R.N. (1992). Organic Chemistry (6th ed.). ISBN 0-13-643669-2.***
4. **^ *Haynes, William M., ed. (2011). CRC Handbook of Chemistry and Physics (92nd ed.). CRC Press. pp. 5–94 to 5–98. ISBN 978-1439855119.***
5. **^ *Riemenschneider, Wilhelm (2002). "Carboxylic Acids, Aliphatic". Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH. doi:10.1002/14356007.a05_235. ISBN 35273 06730..***
6. **^ *Perry C. Reeves (1977). "Carboxylation Of Aromatic Compounds: Ferrocenecarboxylic Acid". Org. Synth. 56: 28. doi:10.15227/orgsyn.056.0028.***

7. **^ *Fujisawa, Tamotsu; Sato, Toshio. "Reduction of carboxylic acids to aldehydes: 6-Ooxdecanal". Organic Syntheses. 66: 121. doi:10.15227/orgsyn.066.0121.; Collective Volume, vol. 8, p. 498***
8. **^ *Milligan, D. E.; Jacox, M. E. (1971). "Infrared Spectrum and Structure of Intermediates in Reaction of OH with CO". Journal of Chemical Physics. 54 (3): 927–942. Bibcode:1971JChPh..54..927M. doi:10.1063/1.1675022.***
9. **^ The value is pK_a = −0.2 ± 0.1. *Jeevarajan, A. S.; Carmichael, I.; Fessenden, R. W. (1990). "ESR Measurement of the pK_a of Carboxyl Radical and Ab Initio Calculation of the Carbon-13 Hyperfine Constant". Journal of Physical Chemistry. 94 (4): 1372–1376. doi:10.1021/j100367a033.***