

TEXT BOOK

- **Menger, Goldsmith and Mandell, Organic Chemistry: A Concise Approach**
- **Reference**
- **T.W.G. Solomons**

CHAPTER 1

ORGANIC MOLECULES

ORGANIC CHEMISTRY I (BY TAKKELE R

Energy levels and atomic orbitals

Electrons are moving continuously around nucleus.

electrons have

kinetic energy, and this energy is what counters the attractive force of the positively charged protons inside the nucleus while the negatively charged electrons are pulled into the nucleus.

For a long time, electrons were perceived to be particles—infinitesimal “planets” orbiting the nucleus of an atom.

The solutions to the Schrödinger equation are called wave functions or orbitals.

Orbital means the region where electrons mostly spend their time. Wave functions tell us the energy of the electron and the volume of space around the nucleus where an electron is most likely to be found

electron in an atom is associated with a set of four quantum numbers

These are: n , l , m_l , and m_s Each energy sub level corresponds to an orbital of a different shape, which describes where the electron is likely to be found

Principle quantum number (n):
This has the largest role in determining the energy of the electron, and it is also the main factor in determining how far the electron is, on average, from the nucleus.

Angular momentum quantum number (l)

It determines the shape of the volume of space that the electron can occupy.

Magnetic quantum number (m_l):
It determines the orientation in space (x, y, z direction) of the volume that can contain the electron

Spin quantum number (m_s): This gives the orientation of the magnetic field associated

	Permitted value	Example
n	Any positive integer	1, 2, 3, 4.....
l	Any integer from 0 to (n-1)	0,...,(n-1)
ml	Any integer from -l to +l	-l.....0.....+l
ms	-1/2 or +1/2	-1/2 or +1/2

ENERGY LEVELS, TYPES OF SUB LEVEL AND MAXIMUM NUMBER OF ELECTRONS IN THE SHELL

Principal energy level	No of sub levels (l)	Types of sub level	Max. no of electrons
$n = 1$	$l = 0$	1s	2
$n = 2$	$l = 0, 1$	2s, 2p	8
$n = 3$	$l = 0, 1, 2$	3s, 3p, 3d	18
$n = 4$	$l = 0, 1, 2, 3$	4s, 4p, 4d, 4f	32

BONDING

- **Forces that hold atoms together.**
- **In Organic Compounds covalent bond is the most important type of bond.**
- **Covalent bond is formed when two atoms share electron pair(s), usually each bringing one electron to the bond.**
- **There are various ways of representing a covalent bond such as two dots between the atoms, a line etc.**

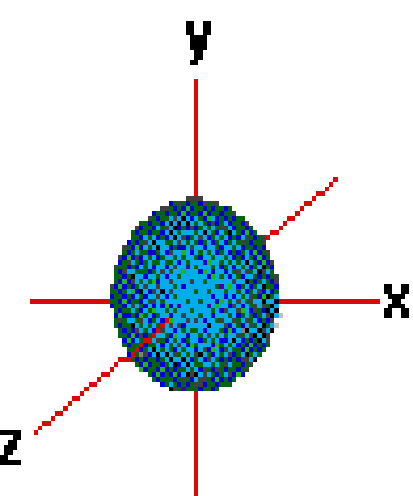
ATOMIC ORBITALS

A more detailed model of covalent bonding requires a consideration of *valence shell atomic orbitals (AO)*.

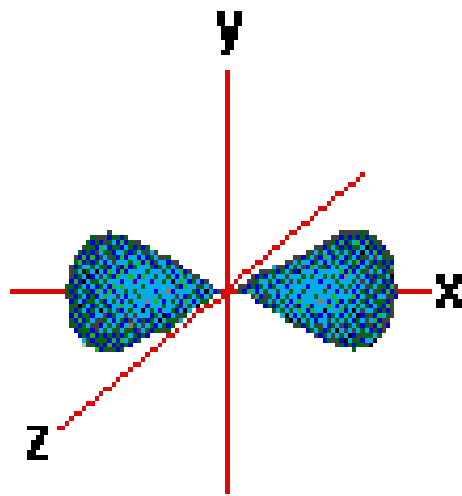
For second period elements such as carbon, nitrogen and oxygen, these orbitals are the $2s$, $2p_x$, $2p_y$ & $2p_z$.

The spatial distribution of electrons occupying each of these orbitals is as shown in the diagram.

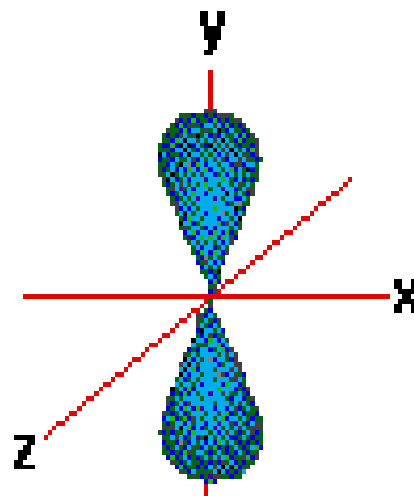
SHAPES AND SPATIAL ORIENTATIONS OF AO OF 2ND ROW ELEMENTS



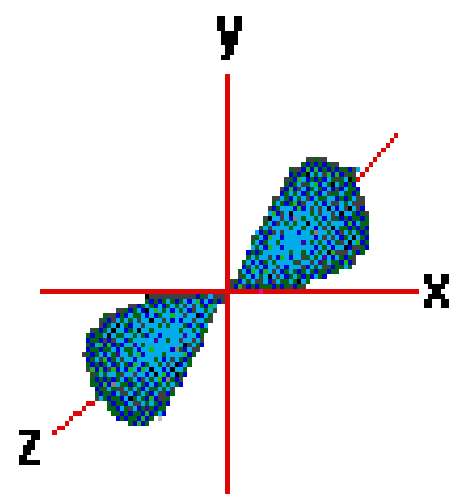
2s atomic orbital



p_x



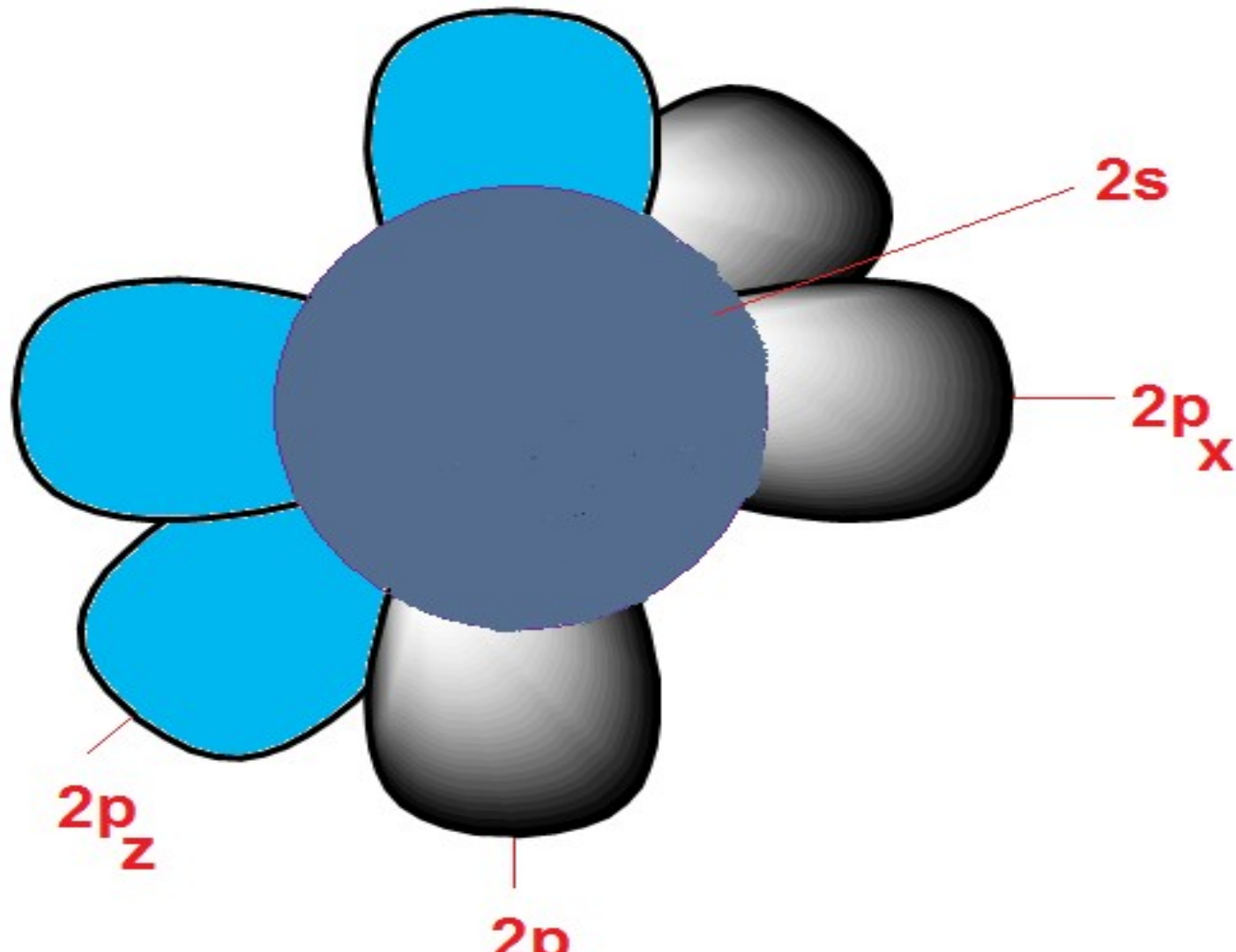
p_y



p_z

2p atomic orbitals

VALENCE ORBITALS OF 2ND RAW ELEMENTS



CARBON: COVALENT BOND FORMATION

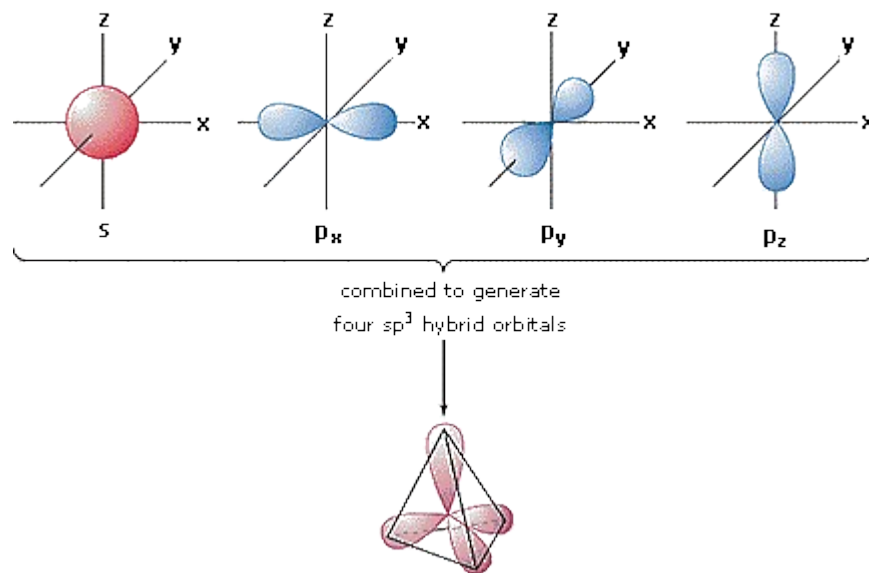
- **The valence shell electron configuration of carbon is $2s^2$, $2p_x^1$, $2p_y^1$ & $2p_z^0$.**
- **With this configuration, carbon would only be able to form two covalent bonds by using its singly occupied $2p_x$ and $2p_y$ AO.**
- **The bond angle of such a compound would be expected to be 90° .**
- **However, in most of its highly stable compounds, such as methane, carbon forms four covalent bonds with bond angle of 109° , in contradiction with its electronic configuration.**

HYBRIDIZATION

In order to explain the structure of methane (CH_4), the 2s and three 2p orbitals must be converted to four equivalent hybrid atomic orbitals, each having 25% s and 75% p character, and designated sp^3 .

These hybrid orbitals have a specific orientation, and the four are oriented in a tetrahedral fashion.

SP³ HYBRID ORBITALS



TYPES OF COVALENT BONDS

The sigma (σ) bond

The pi (π) bond

THE SIGMA BOND

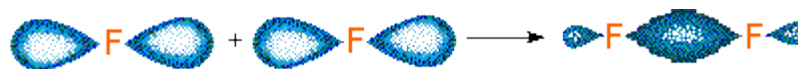
Formed by head-on overlap of AO or hybrid orbitals.

Have a cylindrical symmetry and encompass two (or more) nuclei.

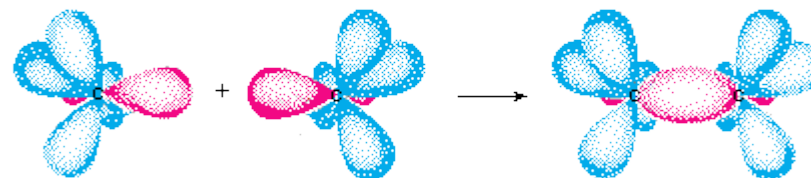
For example, the sigma MO that serves to bond two fluorine atoms together is generated by the head-on overlap of two p-orbitals.

Two sp^3 hybrid orbitals of carbon may combine to give a similar σ orbital.

SIGMA BOND FORMATION



A σ -orbital formation from two p-orbitals



sp^3 carbon atom sp^3 carbon atom
in each case one sp^3 orbital is colored red a sigma molecular orbital
the six remaining sp^3 orbitals are blue

B σ -orbital formation from two sp^3 orbitals

THE PI (Π) BOND

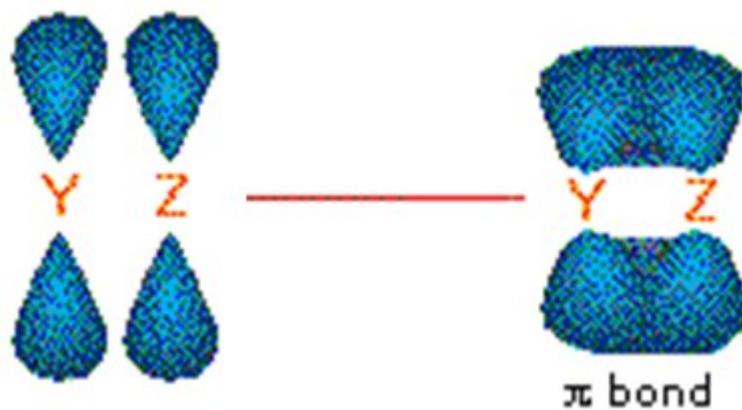
Formed from two p-orbitals by a lateral (side ways) overlap.

Thus pi-bonds are weaker than sigma bonds.

Pi-bonding between two atoms occurs only when a sigma bond has already been established.

Thus, pi-bonding is generally found only as a component of double and triple covalent bonds.

PI (Π) BOND FORMATION



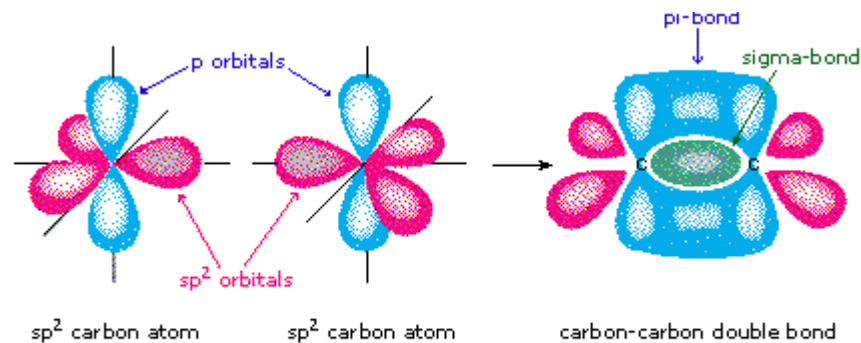
DOUBLE BOND FORMATION

Carbon atoms involved in double bonds have only three bonding partners, and require only three hybrid orbitals to contribute to three sigma bonds.

A mixing of the 2s-orbital with two of the 2p orbitals gives three sp^2 hybrid orbitals, leaving one of the p-orbitals unused.

Two sp^2 hybridized carbon atoms are then joined together by sigma and pi-bonds (a double bond).

DOUBLE BOND FORMATION



B Formation of σ - and π - molecular orbitals
from two sp^2 hybridized carbon atoms

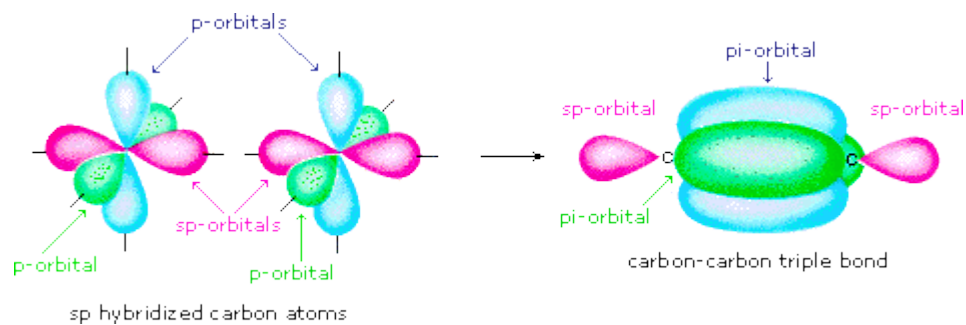
TRIPLE BOND FORMATION

Carbon atoms with only two bonding partners require only two hybrid orbitals for the sigma bonds formations.

These sp hybrid orbitals are directed 180° from each other.

Two p-orbitals remain unused on each sp hybridized atom, and these overlap to give two pi-bonds following the formation of a sigma bond (a triple bond), as shown.

TRIPLE BOND FORMATION



POLAR COVALENT BONDS

When two different atoms are bonded covalently, the shared electrons are attracted to the more electronegative atom of the bond, resulting in a shift of electron density toward the more electronegative atom.

Such a covalent bond is polar, and will have a dipole (one end is positive and the other end negative).

The degree of polarity and the magnitude of the bond dipole will be proportional to the difference in electronegativity of the bonded atoms.

ELECTRONEGATIVITY

The ability of an element to attract or hold onto electrons.

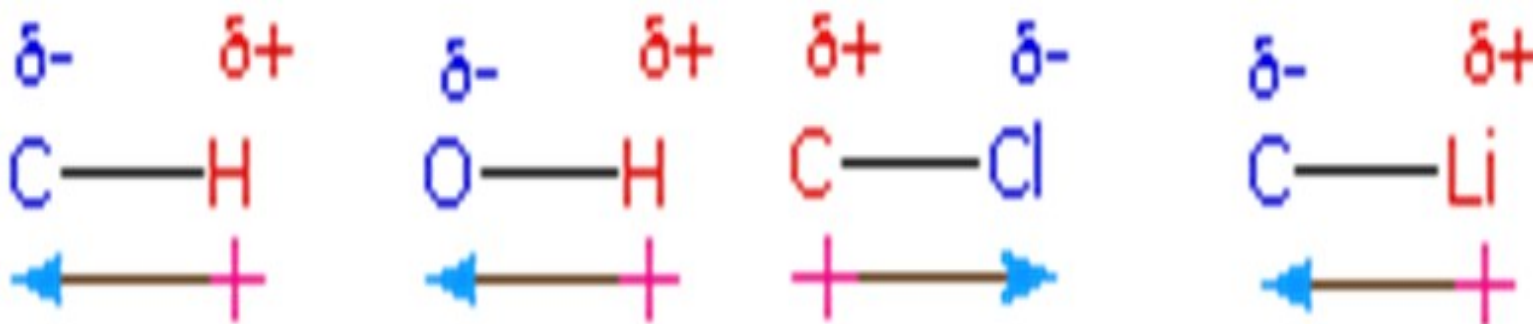
**Carbon is about in the middle of the electronegativity range,
and is slightly more electronegative than hydrogen.**

QUANTITATIVE SCALE OF ELECTRONEGATIVITY VALUES BY LINUS PAULING

H 2.20 Electronegativity Values for Some Elements						
Li 0.98	Be 1.57	B 2.04	C 2.55	N 3.04	O 3.44	F 3.98
Na 0.90	Mg 1.31	Al 1.61	Si 1.90	P 2.19	S 2.58	Cl 3.16
K 0.82	Ca 1.00	Ga 1.81	Ge 2.01	As 2.18	Se 2.55	Br 2.96

REPRESENTATION OF BOND POLARITY

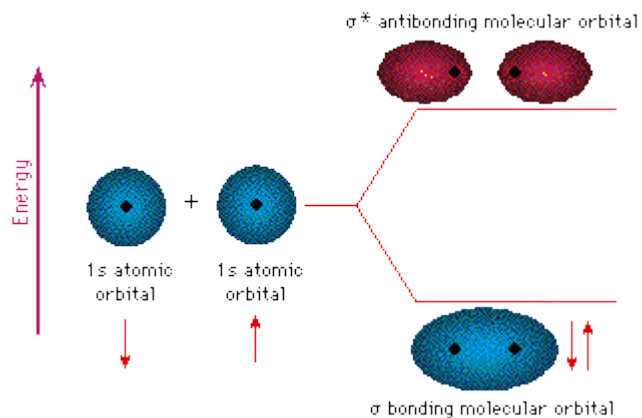
The dipolar nature of covalent bonds is indicated by a partial charge notation ($\delta+/-$) or by an arrow pointing to the negative end of the bond.



MOLECULAR ORBITALS (MO)

- **Electrons of molecules may be thought of as occupying Molecular Orbitals (MO) the way electrons of atoms occupy atomic orbitals (AO).**
- **Molecular orbitals are formed by mixing two or more atomic orbitals.**
- **In general, mixing of n atomic orbitals generates n molecular orbitals.**
- **The hydrogen molecule provides a simple example of MO formation.**
- **The two $1s$ atomic orbitals combine to give a σ bonding (low energy) MO and a σ^* (higher energy) MO referred to as an antibonding molecular orbital.**
- **The bonding MO is occupied by two electrons of opposite spin, the result being a covalent bond.**

MOLECULAR ORBITAL FORMATION IN H₂ MOLECULE



REPRESENTATION OF MOLECULES

The three dimensional shape of a molecules is known as configuration.

Configuration is dependent on the preferred spatial orientation of covalent bonds to atoms having two or more bonding partners.

Representation of three dimensional structures on a two dimensional surfaces such as a white board or paper is difficult.

Thus the so called perspective drawings are used to overcome such problems.

PERSPECTIVE DRAWINGS

Are often used to represent configurations on a two-dimensional surfaces (paper, blackboard or screen).

In such drawings the direction of a bond is specified by the line connecting the bonded atoms.

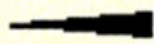
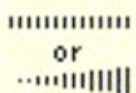
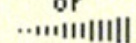
A simple straight line represents a bond lying approximately in the surface plane.

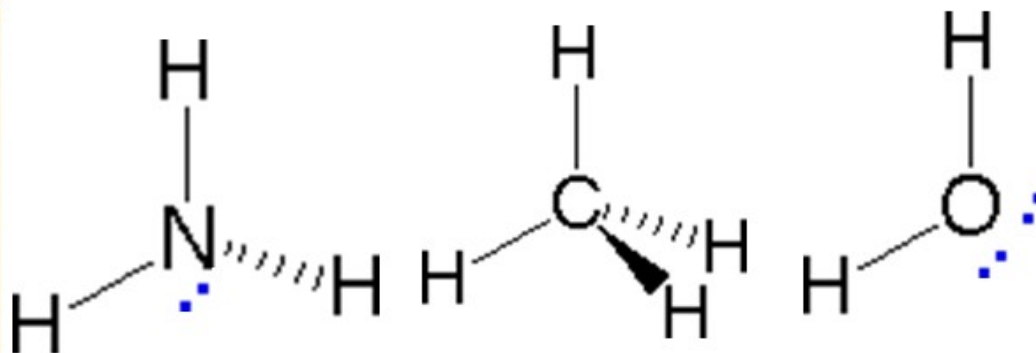
A wedge shaped bond is directed in front of the plane (toward the viewer).

A hatched bond is directed in back of the plane (away from the viewer).

It is important to include non-bonding valence shell electron pairs when drawing configurations .

REPRESENTATION OF BONDS

	normal bond
	wedge bond
 or 	hatched bond
	dashed bond



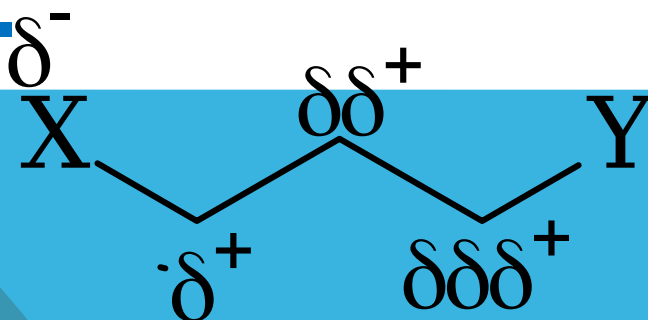
INDUCTIVE AND RESONANCE EFFECTS

INDUCTIVE EFFECT

Electronegativity differences can be transmitted through bonds and leads to successive polarization of the bonds.

This is known as inductive effect.

The polarization diminishes rapidly as the number of intervening bonds increases.



INDUCTIVE EFFECT CONTINUED

Replacing one of the hydrogens of water by a more electronegative atom increases the acidity of the remaining O-H bond.

Thus hydrogen peroxide, HO-O-H, is 10^4 times more acidic than water.

Hypochlorous acid, Cl-O-H, is 10^8 times more acidic than water.

Presence of more than one electronegative atom has a cumulative effect.

For example, trifluoro ethanol, $\text{CF}_3\text{CH}_2\text{-O-H}$ is about 10^4 times more acidic than ethanol, $\text{CH}_3\text{CH}_2\text{-O-H}$.

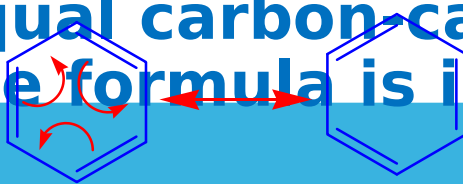
RESONANCE

Structures of some compounds and ions cannot be represented by a single Kekulé formula.

For example, benzene is represented by two equivalent formulas.

If only one formula for benzene was correct and accurate, then the double bonds would be shorter and stronger than the single bonds.

Since experimental evidence indicates that benzene has equal carbon-carbon bond lengths, a single formula is inadequate.



RESONANCE, CONTINUED

Thus an average of the two formulas is used to represent the actual structure.

This averaging of electron distribution over two or more hypothetical contributing structures (*canonical or resonance forms*) to produce a hybrid structure that resembles the actual structure is called resonance.

The electron delocalization described by resonance enhances the stability of the molecules.

Compounds or ions composed of such structures often show exceptional stability.

BASIC PRINCIPLES OF RESONANCE

- **All contributors must have precisely the same molecular structure and geometry.**
- **Positive charge is best accommodated on atoms of low electronegativity, and negative charge on atoms of higher electronegativity.**
- **Charge separation or less than a full octet of outer electrons decreases the stability and importance of the contributor.**
- **No C, O, N, or other 2nd row atom may contain more than eight electrons in its outer shell.**
- **Maximum resonance stabilization is achieved when there are two or more equivalent, low energy contributors.**

FUNCTIONALITY

CLASSES OF ORGANIC COMPOUNDS & FUNCTIONALITY

A functional group is a particular combination of atoms in a molecule that undergoes a characteristic set of reactions no matter what other atoms may be near the reactive center.

The surroundings may affect the rates of reaction, but the essentials of the reaction remain the same.

Example:



Sodium hydroxide



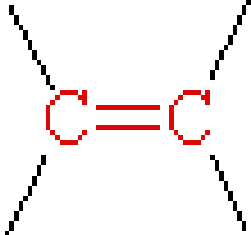
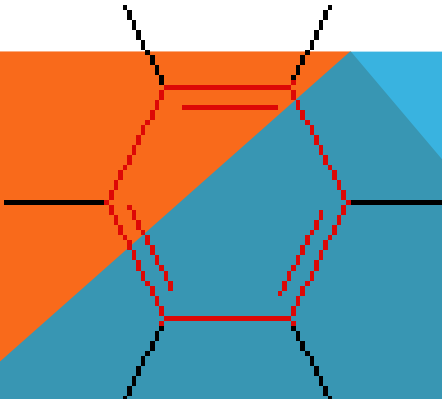
Sodium methoxide



Sodium ethoxide

Although water reacts faster with sodium than methanol or ethanol, the actual reactions are analogous.

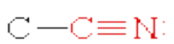
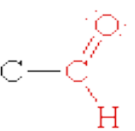
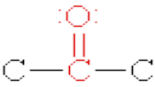
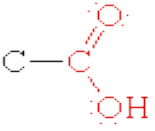
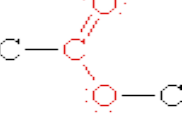
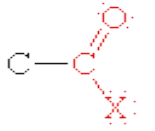
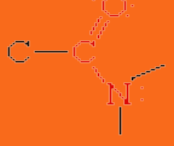
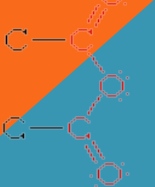
EXCLUSIVELY CARBON FUNCTIONAL GROUPS

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	Alkene	$\text{H}_2\text{C}=\text{CH}_2$	Ethene	Ethylene
	Alkyne	$\text{HC}\equiv\text{CH}$	Ethyne	Acetylene
	Arene	C_6H_6	Benzene	Benzene

FUNCTIONAL GROUPS WITH SINGLE BONDS TO HETEROOATOMS

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
$\text{C}-\ddot{\text{X}}$	Halide	$\text{H}_3\text{C}-\text{I}$	Iodomethane	Methyl iodide
$\text{C}-\ddot{\text{O}}\text{H}$	Alcohol	$\text{CH}_3\text{CH}_2\text{OH}$	Ethanol	Ethyl alcohol
$\text{C}-\ddot{\text{O}}-\text{C}$	Ether	$\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$	Diethyl ether	Ether
$\text{C}-\ddot{\text{N}}:$	Amine	$\text{H}_3\text{C}-\text{NH}_2$	Aminomethane	Methylamine
$\text{C}-\overset{\oplus}{\text{N}}(\text{O}^-)=\text{O}$	Nitro Compound	$\text{H}_3\text{C}-\text{NO}_2$	Nitromethane	
$\text{C}-\ddot{\text{S}}\text{H}$	Thiol	$\text{H}_3\text{C}-\text{SH}$	Methanethiol	Methyl mercaptan
$\text{C}-\ddot{\text{S}}-\text{C}$			Dimethyl	

FUNCTIONAL GROUPS WITH MULTIPLE BONDS TO HETEROATOMS

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	Nitrile	$\text{H}_3\text{C-CN}$	Ethanenitrile	Acetonitrile
	Aldehyde	H_3CCHO	Ethanal	Acetaldehyde
	Ketone	H_3CCOCH_3	Propanone	Acetone
	Carboxylic Acid	$\text{H}_3\text{CCO}_2\text{H}$	Ethanoic Acid	Acetic acid
	Ester	$\text{H}_3\text{CCO}_2\text{CH}_2\text{CH}_3$	Ethyl ethanoate	Ethyl acetate
	Acid Halide	H_3CCOCl	Ethanoyl chloride	Acetyl chloride
	Amide	$\text{H}_3\text{CCON}(\text{CH}_3)_2$	N,N-Dimethylethanamide	N,N-Dimethylacetamide
	Acid Anhydride	$(\text{H}_3\text{CCO})_2\text{O}$	Ethanoic anhydride	Acetic anhydride

ALKANES: STRUCTURE, REACTIVITY AND SYNTHESIS

The simplest organic compounds composed of C and H atoms linked by single bonds.

Open chain compounds: *aliphatic* hydrocarbons.

Cyclic or ring structures: cycloalkanes (cycloalkanes)

Also known as *alicyclic* compounds.

the smallest ring contains three carbon atoms (cyclopropane).

Melting points, boiling points and specific gravity increase with increasing molecular masses.

REACTIVITY

Alkanes are comprised of σ -bonds which are unpolarized due to the nearly equal electronegativities of C and H.

Therefore, alkanes are relatively unreactive.

All the members of the series do not react readily at ordinary temperatures with such reagents as acids, bases, or oxidizers.

One viable way bonds break in alkanes is by homolysis mechanism which triggers generation of free radicals.

However, homolysis in alkanes require so much energy that it is difficult to control the reaction and mixtures of products result.

Therefore, a typical reaction of alkanes is *free radical substitution*.

Radical reactions proceed by chain reaction,

AN EXAMPLE OF HALOGENATION: CHLORINATION OF METHANE

Methane, the simplest alkane, has four carbon-hydrogen bonds that could potentially react in a halogenation reaction.

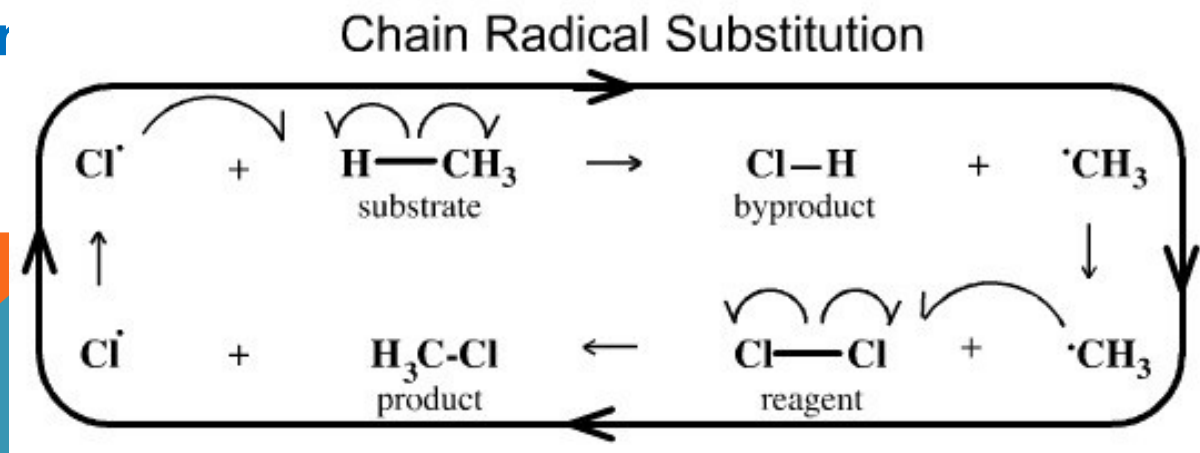
Thus free radical halogenation of alkanes gives mixture of products that are difficult to separate and is of little synthetic importance.

							IUPAC Name	Common Name
CH ₄	+	Cl ₂	————→	CH ₃ Cl	+	HCl	Chloromethane	Methyl chloride
CH ₃ Cl	+	Cl ₂	————→	CH ₂ Cl ₂	+	HCl	Dichloromethane	Methylene chloride
CH ₂ Cl ₂	+	Cl ₂	————→	CHCl ₃	+	HCl	Trichloromethane	Chloroform
CHCl ₃	+	Cl ₂	————→	CCl ₄	+	HCl	Tetrachloromethane	Carbontetrachloride

CHAIN RADICAL SUBSTITUTION

The reaction proceeds as a chain, radical, substitution mechanism:

A chlorine radical abstracts a hydrogen from methane to give hydrogen chloride and a methyl radical. The methyl radical then abstracts a chlorine atom (a chlorine radical) from Cl_2 to give methyl chloride and a chlorine radical... which abstracts a hydrogen



THE CHAIN REACTION

Three steps are involved in the process: initiation, propagation and termination:

Initiation



Propagation



Termination



INITIATION, PROPAGATION AND TERMINATION

Initiation is used to form the low concentration of radical required to start the chain reaction.

A peroxide, perester or azo compound which undergoes homolytic bond fission on heating is usually used as initiator.

In the case of chlorination, chlorine may be used as the initiator.

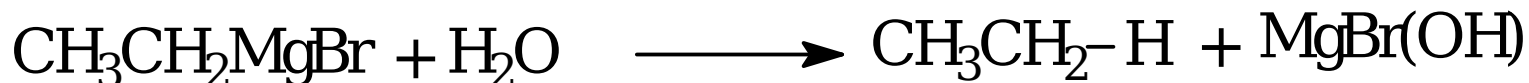
Propagation describes the chain reaction itself. There may be thousands of identical propagation steps.

Termination is the process by which radical centres are quenched.

Termination occurs when two radical centres come into contact and couple together.

SYNTHESIS OF ALKANES

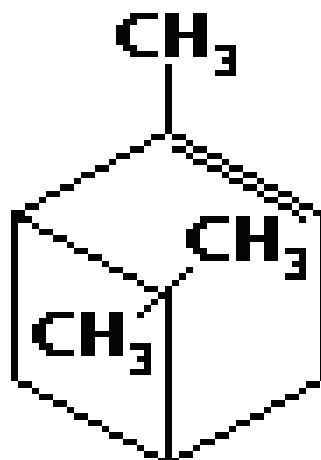
Alkanes can be prepared by reduction of alkyl halides, using *Grignard reagent* or *lithium aluminum hydride*, LiAlH_4 .



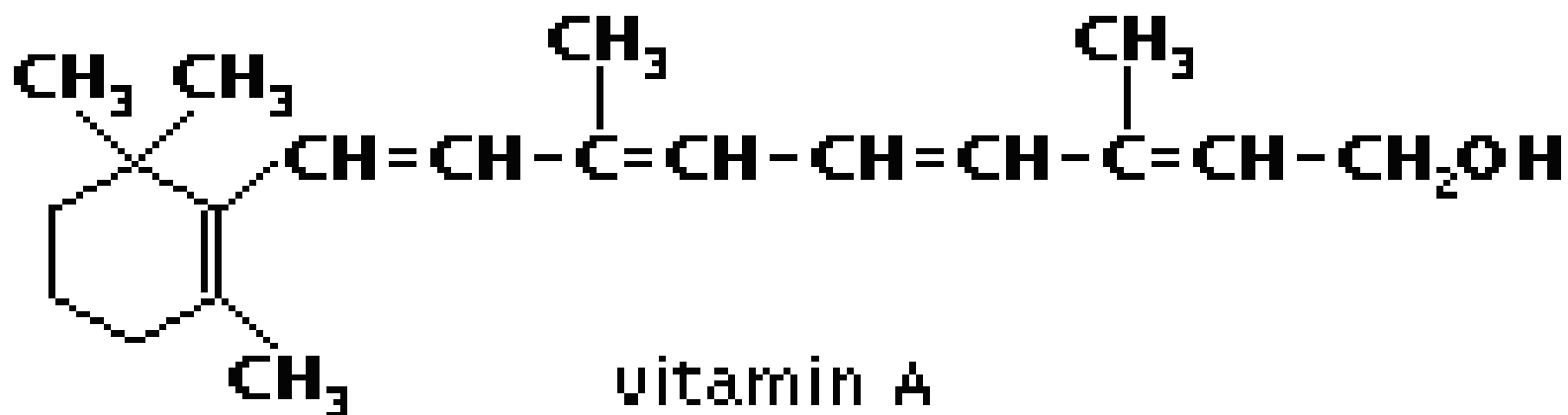
ALKENES OR OLEFINS

Alkenes or olefins are hydrocarbon compounds characterized by at least one double bond between carbon atoms, and referred to as *unsaturated* hydrocarbons.

SOME EXAMPLES OF ALKENES



α - pinene



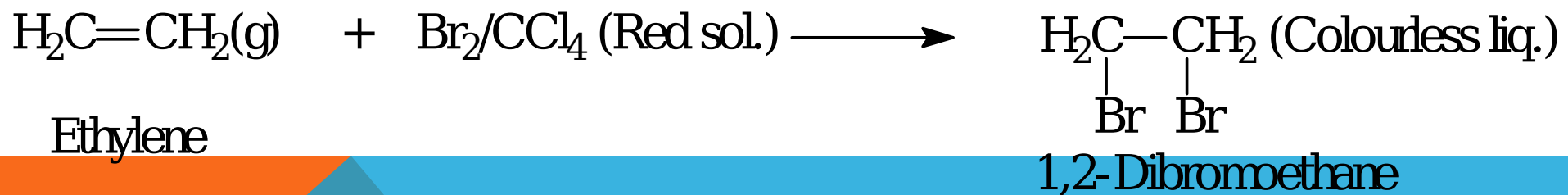
vitamin A

REACTIVITY

Double bonds are composed of a σ bond a π bond

π bonds are much weaker and more reactive than σ bonds.

For example if ethylene gas is bubbled through a solution of bromine in carbon tetrachloride (CCl_4) the characteristic red color of the solution disappears indicating the consumption of the bromine in the formation of 1,2-dibromoethane:



This reaction is known as *electrophilic addition reaction* which is a characteristic reaction of alkenes.

SYNTHESIS OF ALKENES

Alkenes are generally prepared by *elimination* reactions.

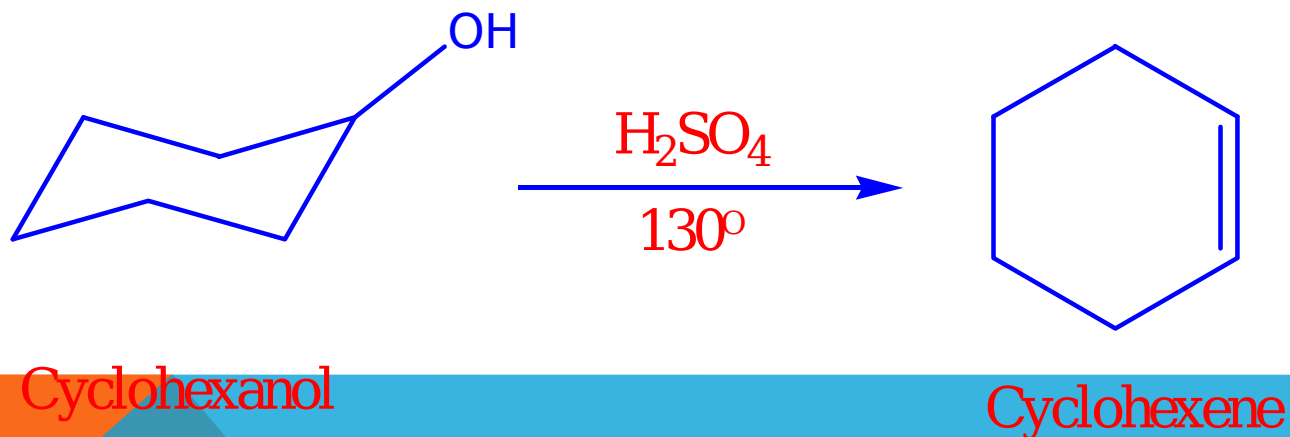
Elimination involves ejection of a small fragment from a molecule leading to introduction of a double bond.

The most commonly used elimination reactions to prepare alkenes are *dehydration of alcohols* and *dehydrohalogenation of alkyl halides*.

***Elimination of vicinal dihalides* and *catalytic dehydrogenations* can also yield alkenes.**

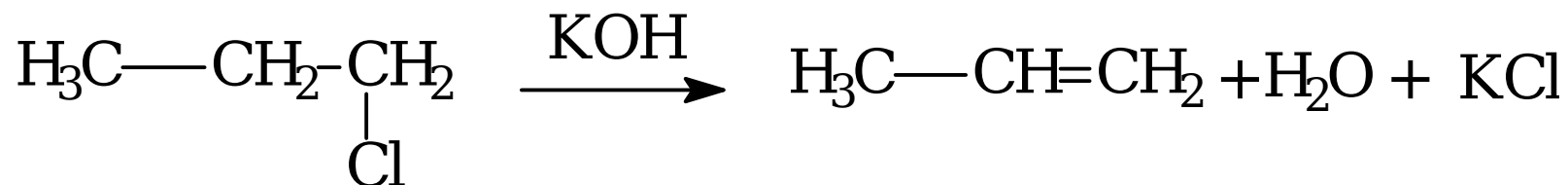
ALCOHOL DEHYDRATION

Alcohol dehydration is an acid catalyzed removal of elements of water from an alcohol to produce an alkene.



DEHYDROHALOGENATION OF ALKYL HALIDES

This reaction is a base promoted removal of elements of hydrogen halide (HX, X = Cl, Br or I) from alkyl halides to produce alkenes.



ALKYNES

Hydrocarbons having at least one carbon-carbon triple bond.

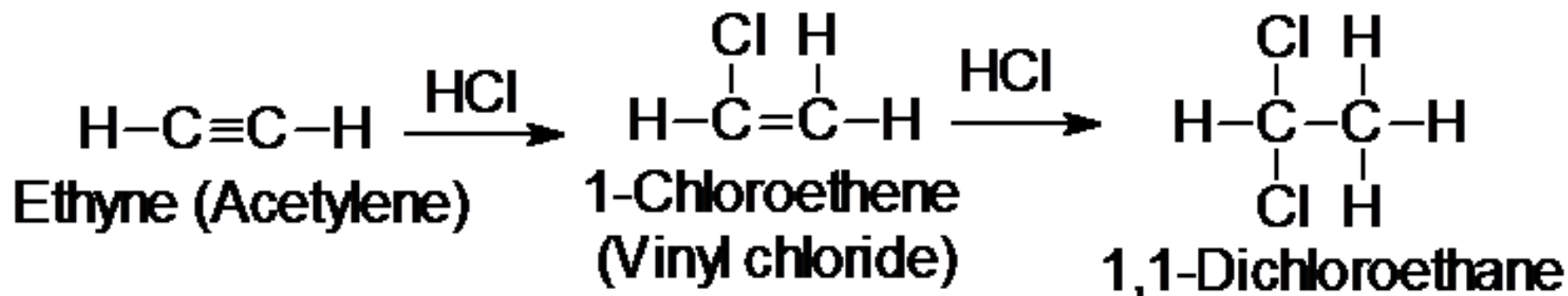
E.g. acetylene, C_2H_2



Ethyne (Acetylene)

CHARACTERISTIC REACTION

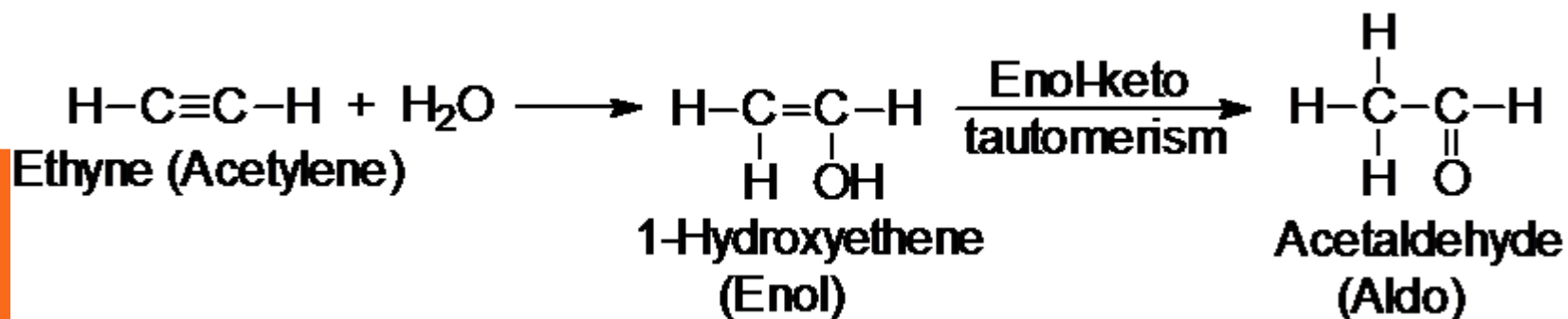
- electrophilic addition reactions
- add up to two moles of electrophiles



HYDRATION OF ALKYNES

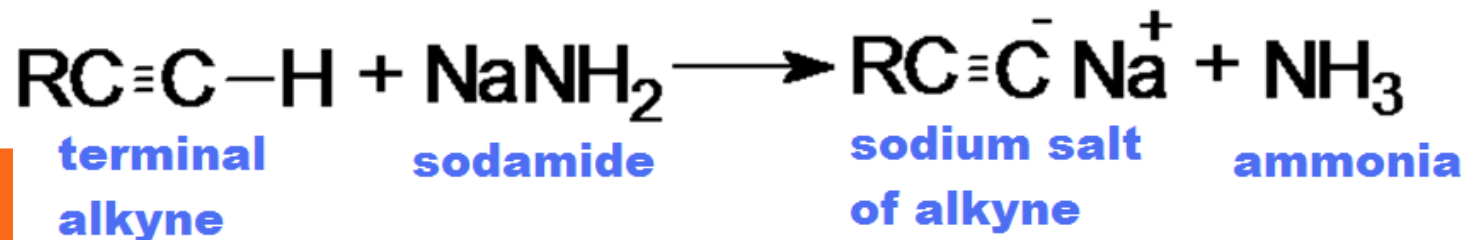
Addition of water to an alkyne forms an unstable intermediate known as *enol*.

Enols rearrange (*enol-keto tautomerism*) to either aldehydes or ketones.



ACIDITY OF TERMINAL ALKYNES

- Terminal alkynes, in which the triple bond is at the end of a carbon chain, are very weak carbon acids.
- They react with strong bases such as sodium amide, NaNH_2 , to form sodium salts of the alkyne.



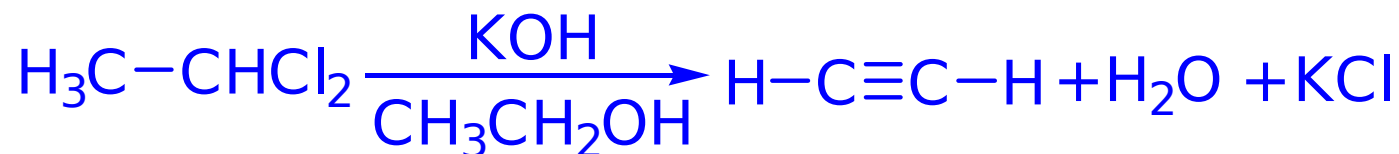
SYNTHESIS OF ALKYNES

Prepared by *elimination* reactions such as *dehydrohalogenation of alkyl halides*.

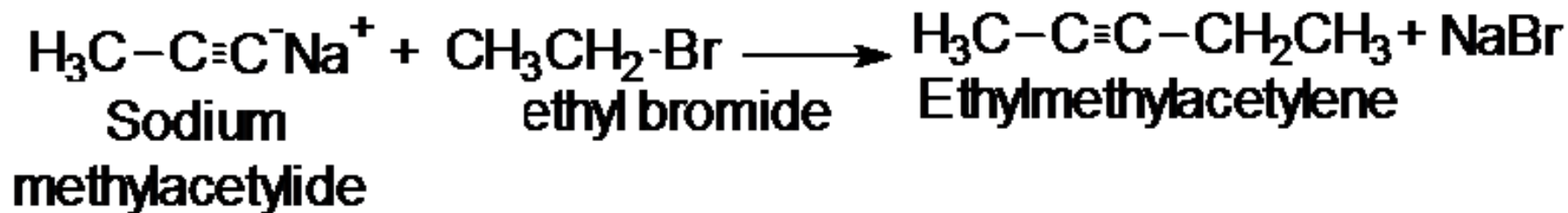
Higher alkynes can be prepared from lower ones by alkylation of sodium salts of alkynes with alkyl halides.

ELIMINATION

- *Dehydrohalogenation of Alkyl halides*



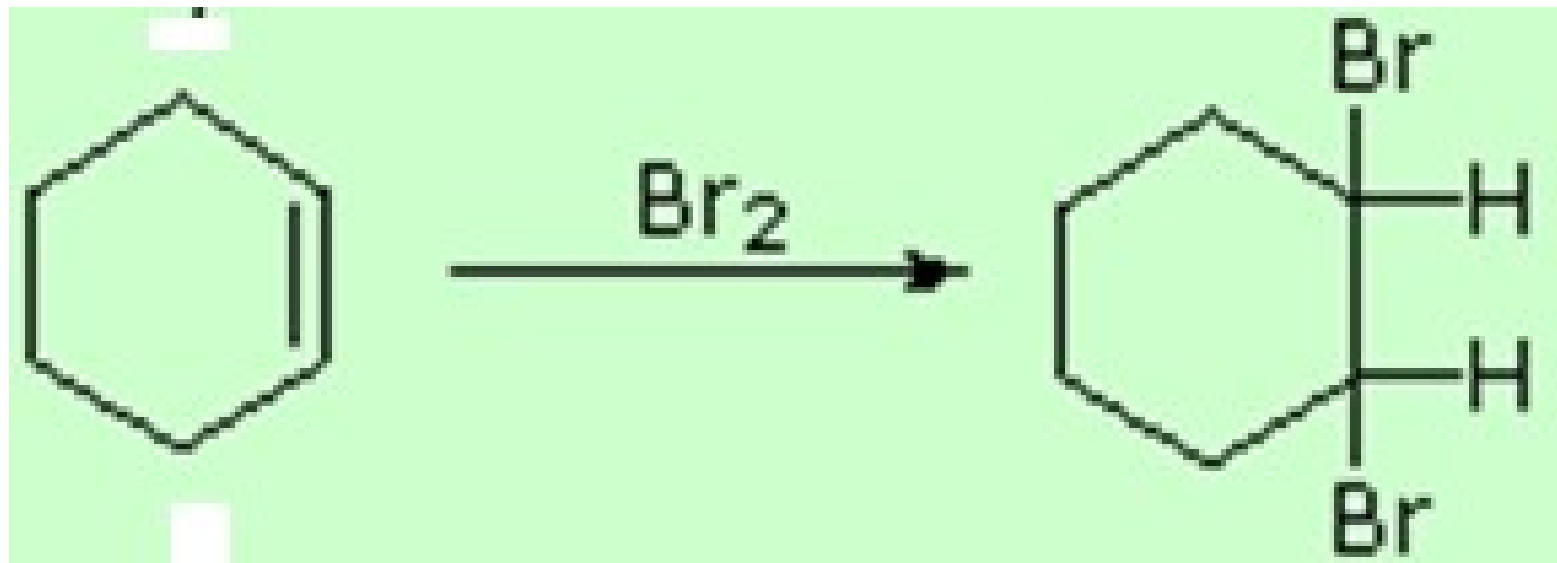
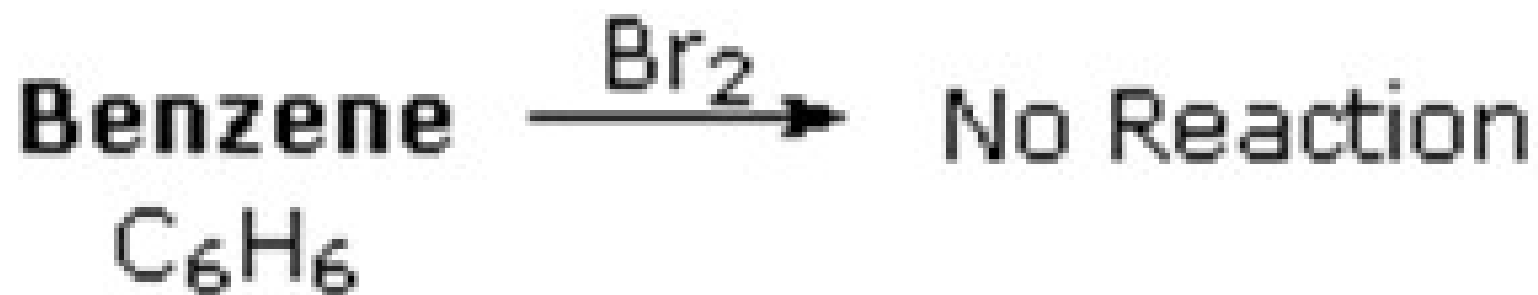
ALKYLATION OF SODIUM SALTS OF ALKYNES WITH ALKYL HALIDES



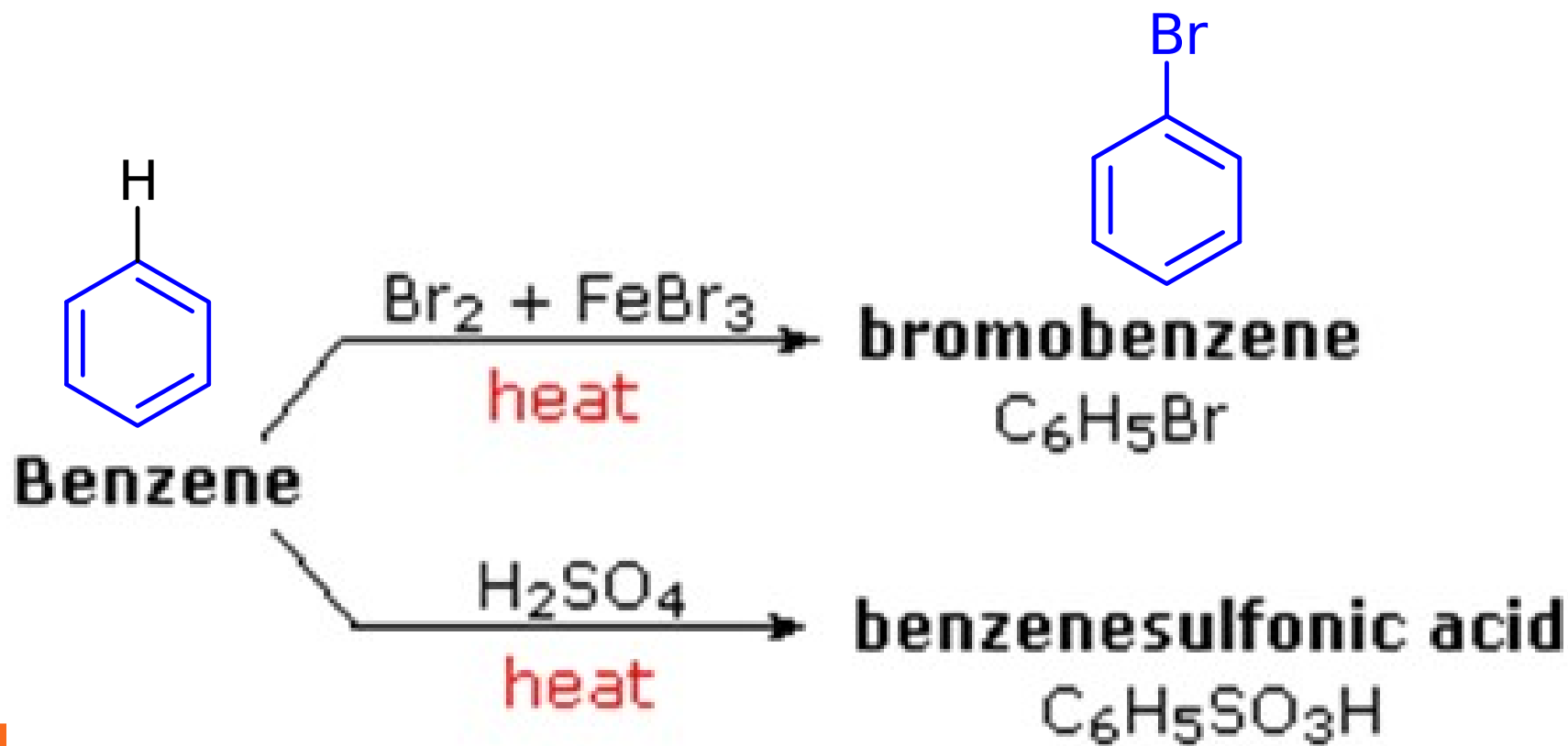
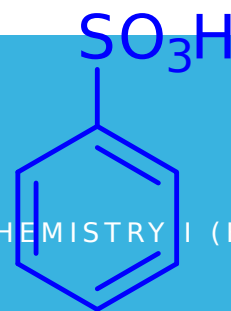
AROMATIC COMPOUNDS

**Benzene and its derivatives.
Show high stability
compared with alkenes.**

REACTION OF ALKENES: ADDITION REACTIONS



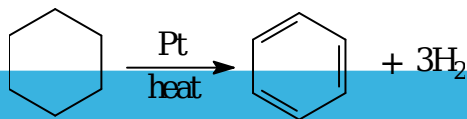
TYPICAL REACTIONS



SYNTHESIS

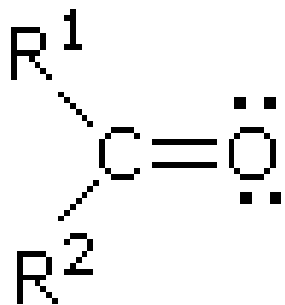
Can be synthesized by modifications of already existing ring systems.

The driving force for the transformation is the high thermodynamic stability of benzene.



CARBONYL GROUP: ALDEHYDES AND KETONES

Compounds which incorporate a carbonyl functional group, $C=O$.

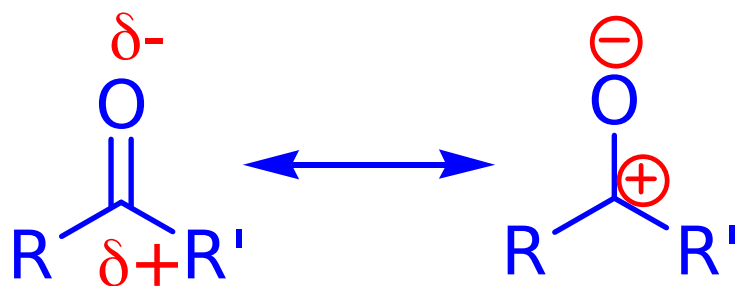
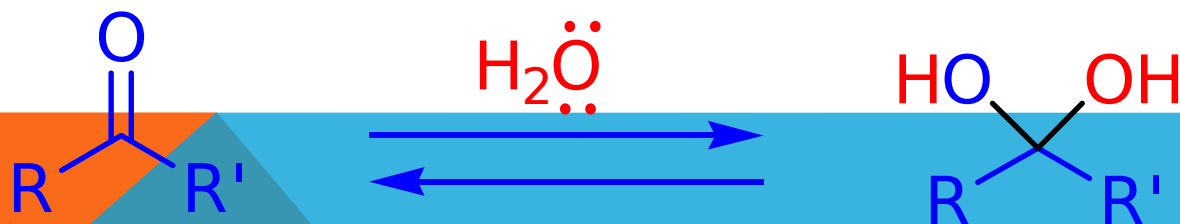


Aldehyde: R^1 and/or $R^2 = H$

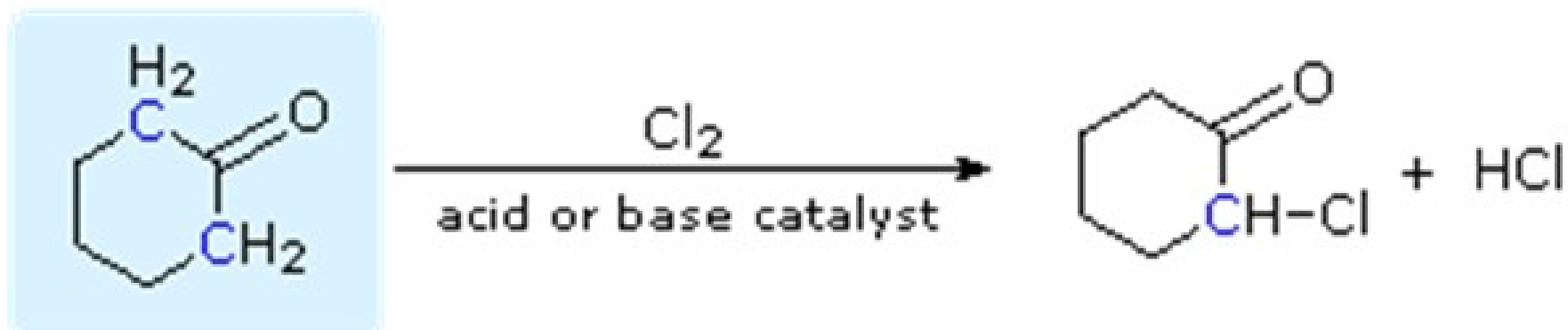
Ketone: R^1 and $R^2 = \text{alkyl or aryl}$

REACTIVITY

Nucleophilic addition:

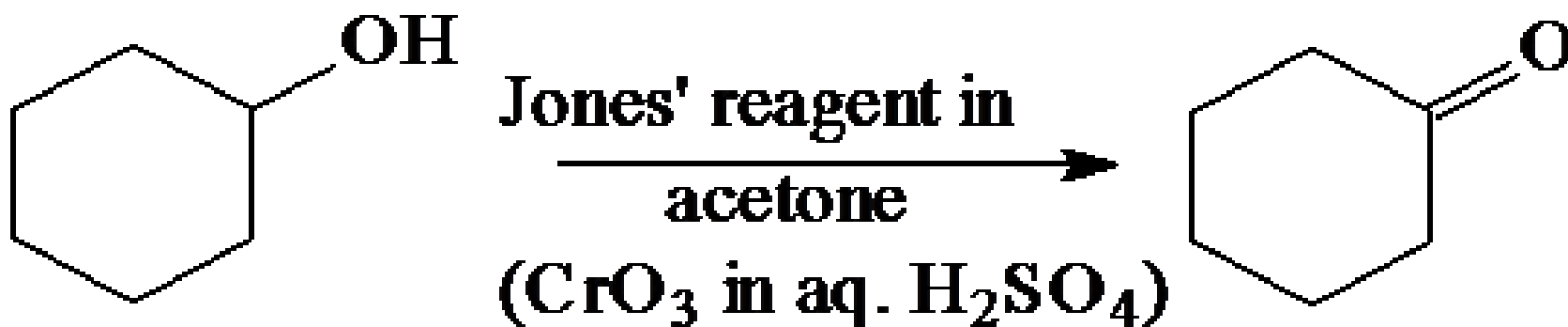


REACTIONS AT THE α -CARBON



SYNTHESIS OF CARBONYL GROUP

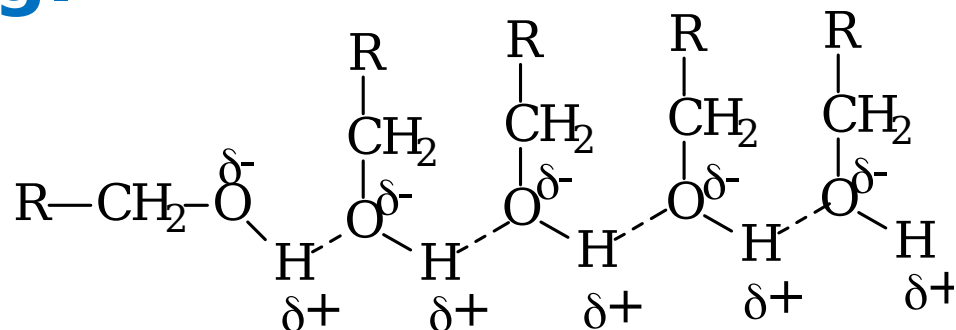
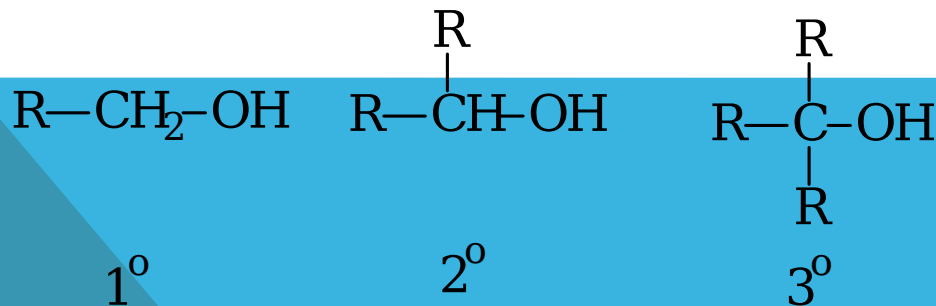
Oxidation of alcohols



ALCOHOLS

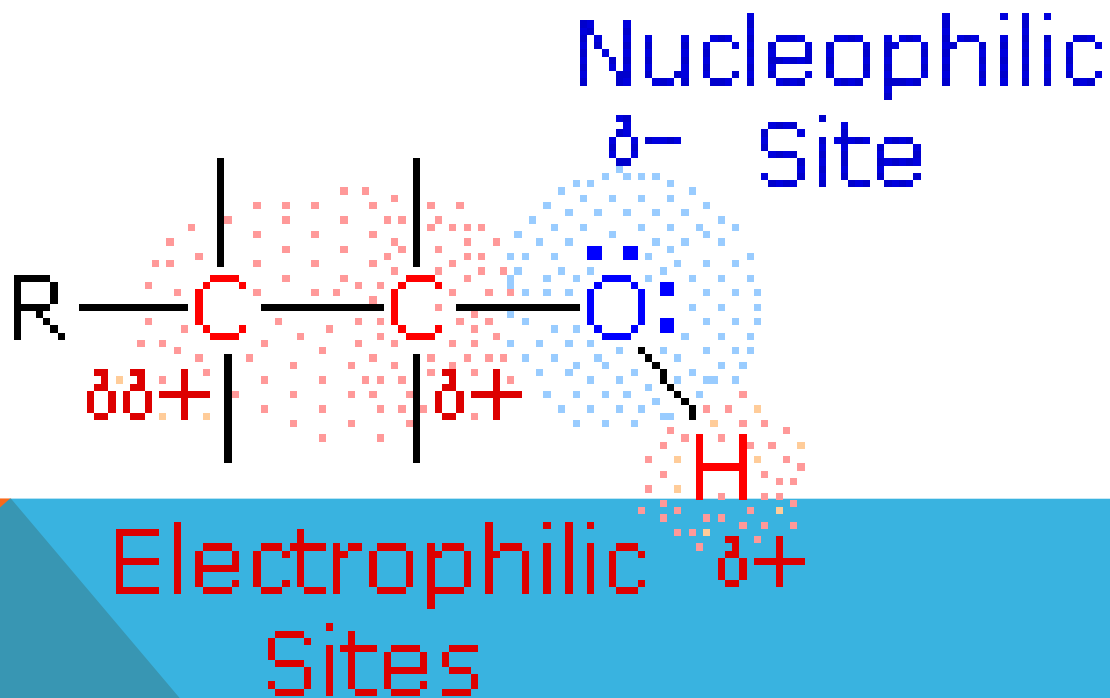
Classified as 1°, 2° & 3°.

Show high boiling points due to H-bonding.



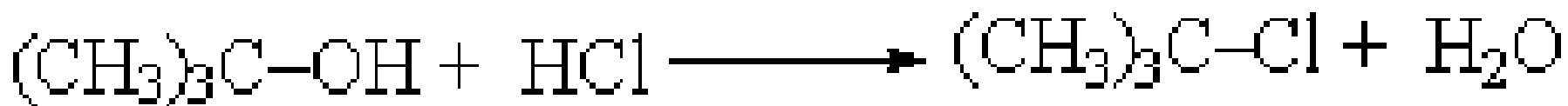
REACTIVITY

- has two reactive centers: the C-O and the O-H bonds.



TYPICAL REACTIONS

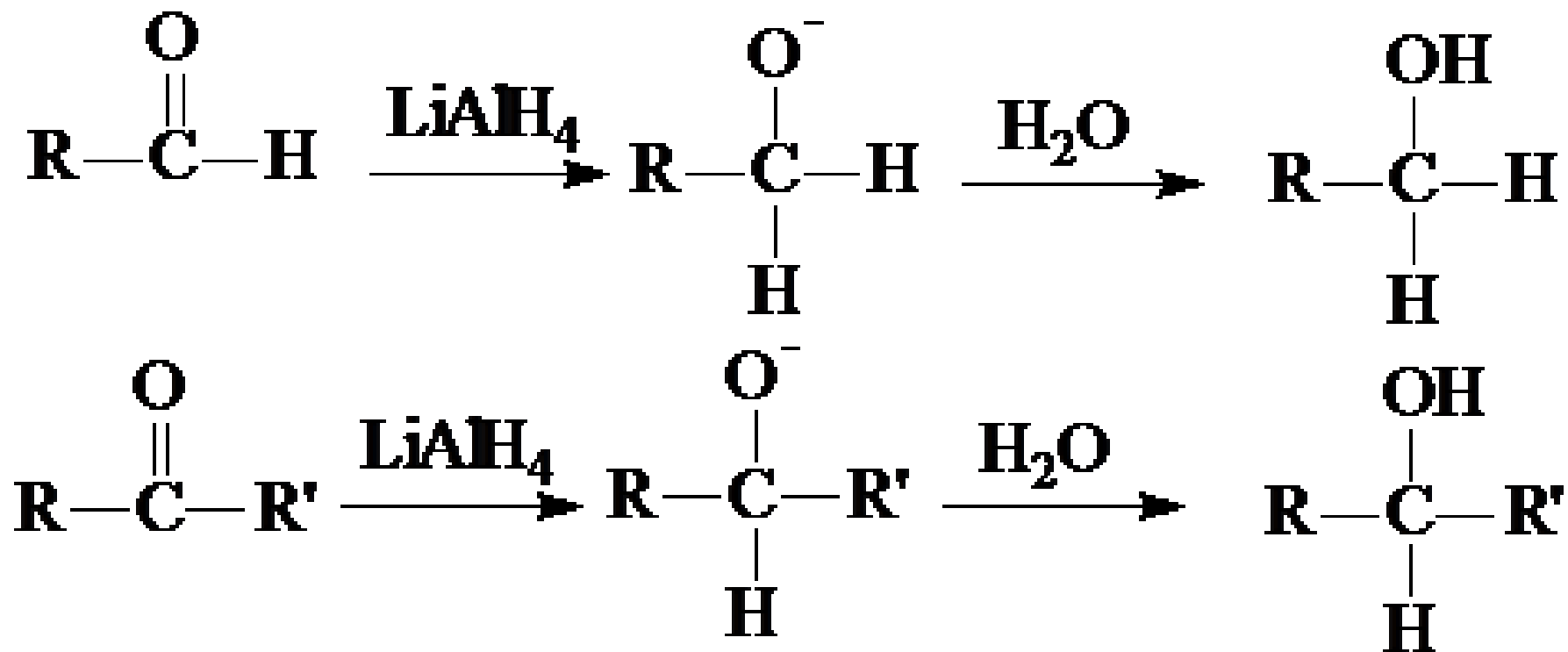
- *Formation of Alkyl Halides:*



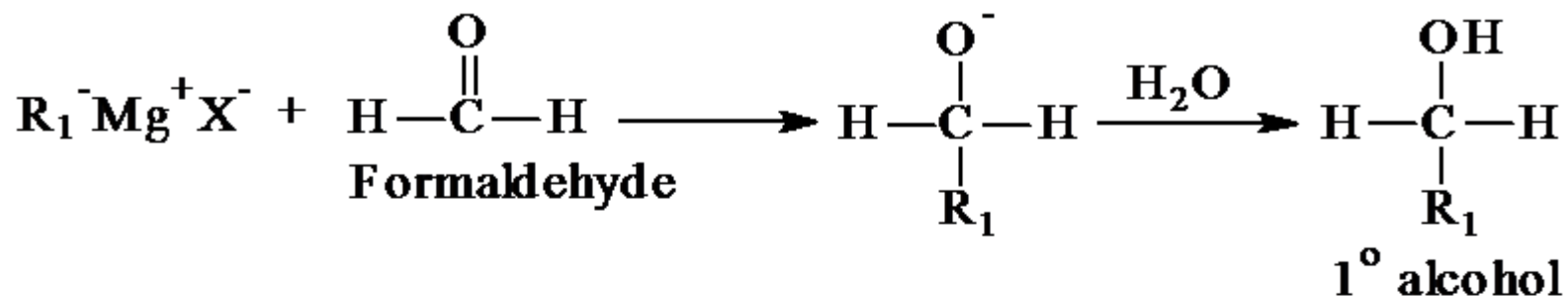
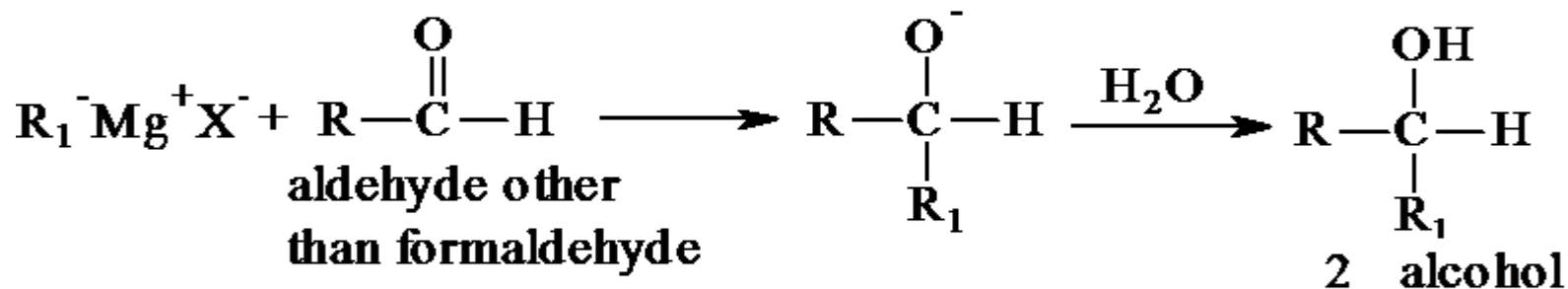
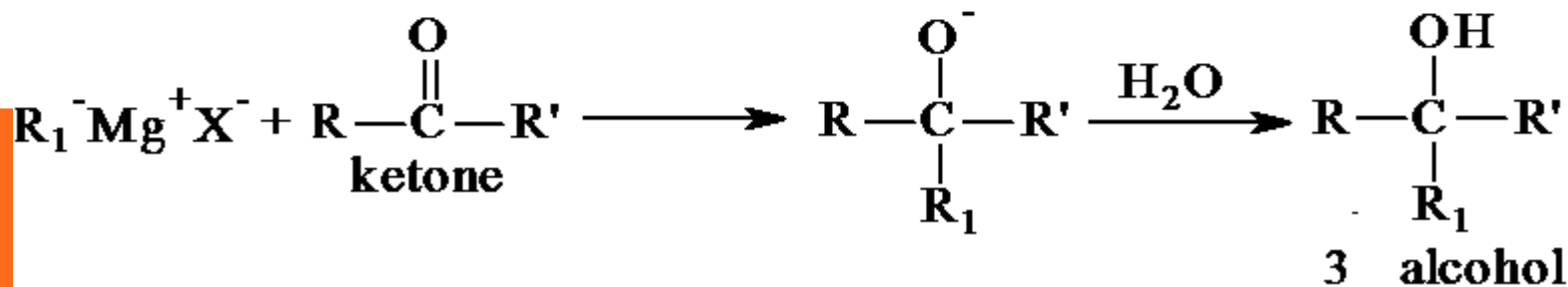
SYNTHESIS OF ALCOHOLS

- 1.Reduction of carbonyl compounds with LiAlH_4
- 2.Reaction of Grignard reagent with aldehydes or ketones.

REDUCTION OF CARBONYL COMPOUNDS WITH LiAlH_4

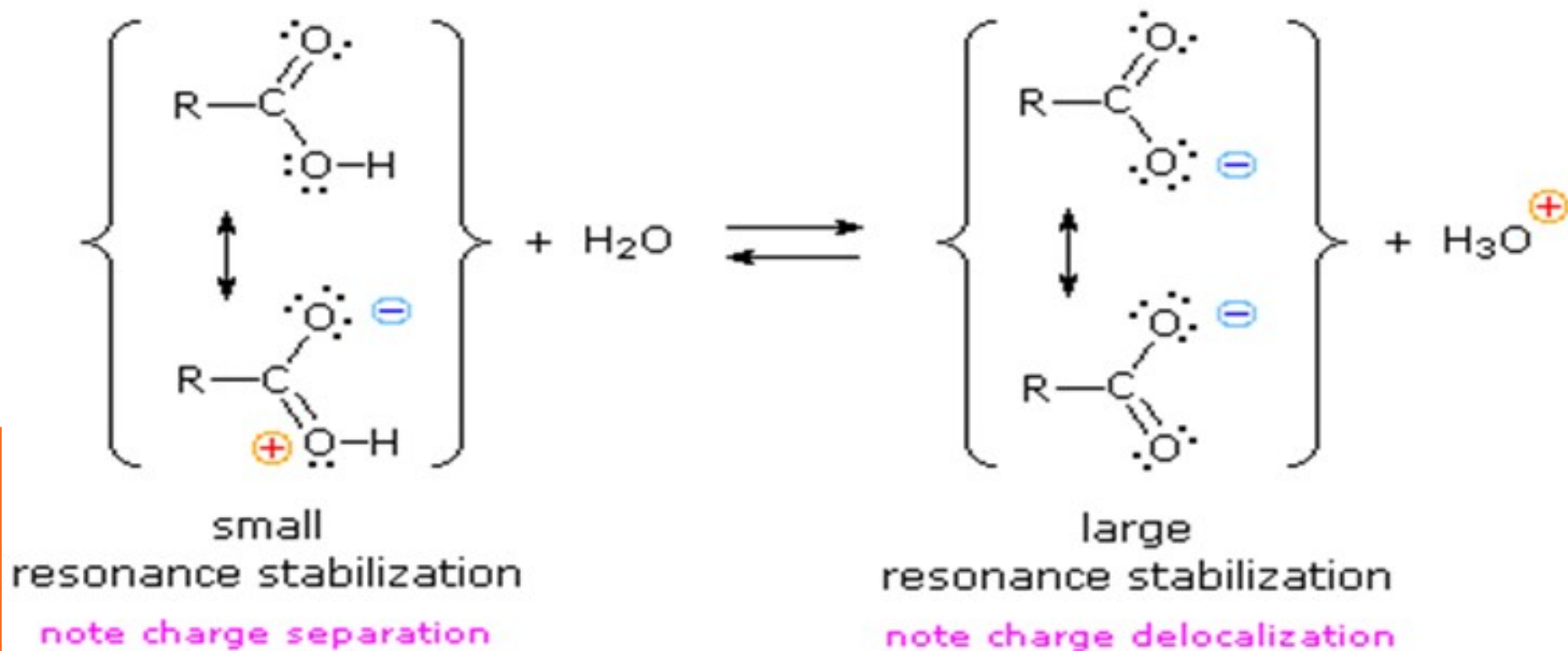


REACTION OF GRIGNARD REAGENTS WITH ALDEHYDES OR KETONES



CARBOXYL GROUP: RCOOH

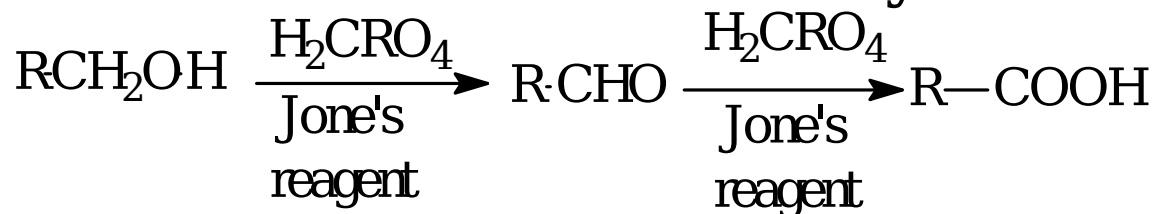
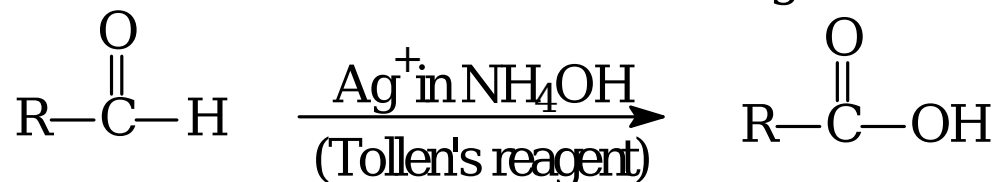
- Weakly acidic, because carboxylate anions are resonance stabilized.



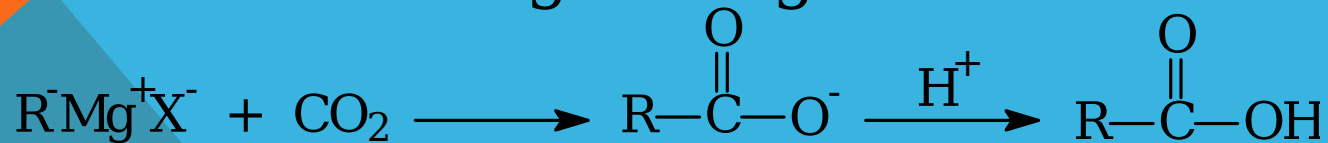
PREPARATION OF CARBOXYLIC ACIDS

Mainly prepared by oxidations.

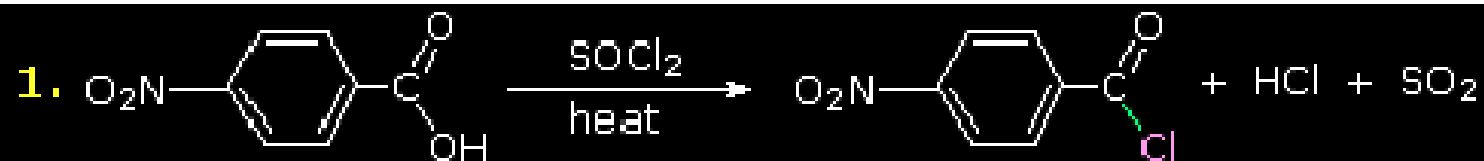
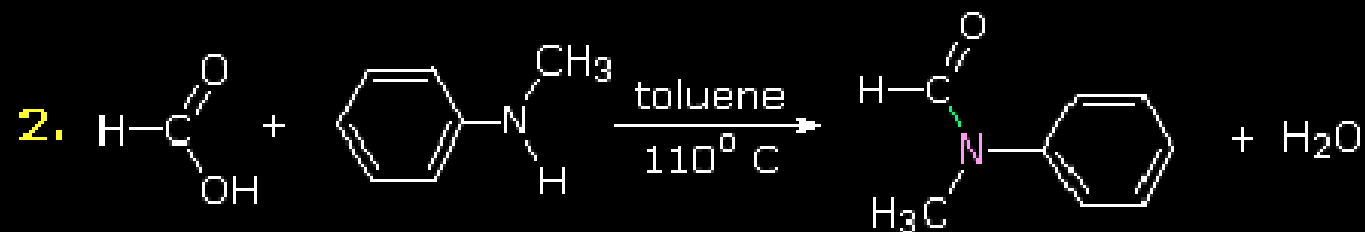
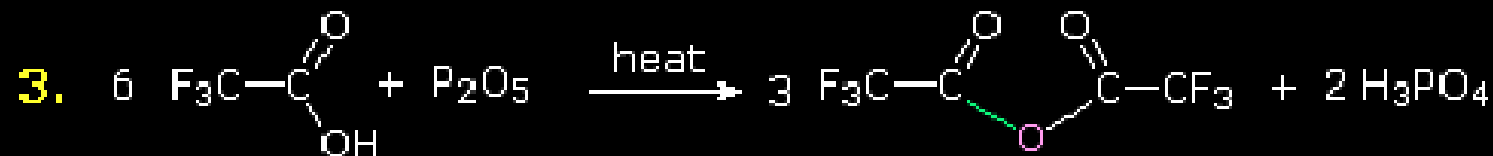
1. Oxidation of 1° alcohols & aldehydes



2. Carbonation of Grignard reagents

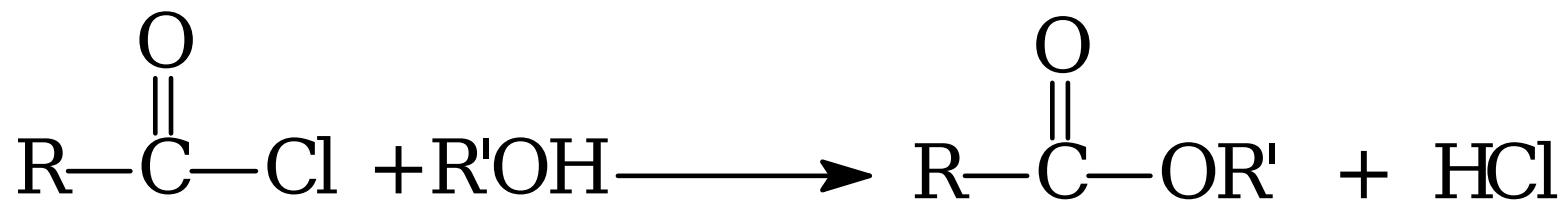
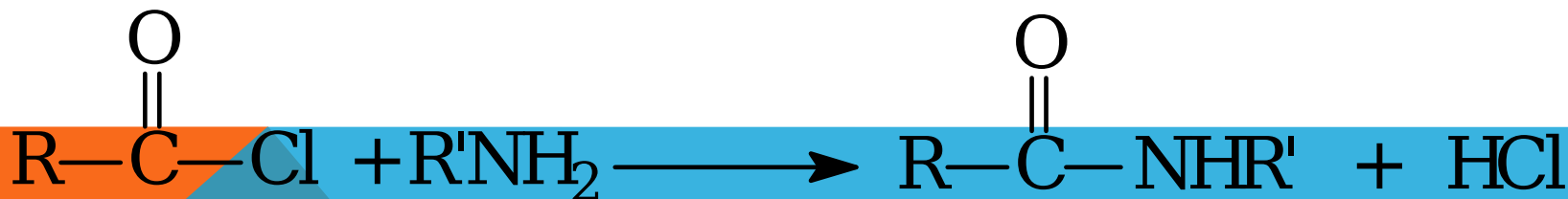


DERIVATIVES OF CARBOXYLIC ACIDS



ACID CHLORIDES

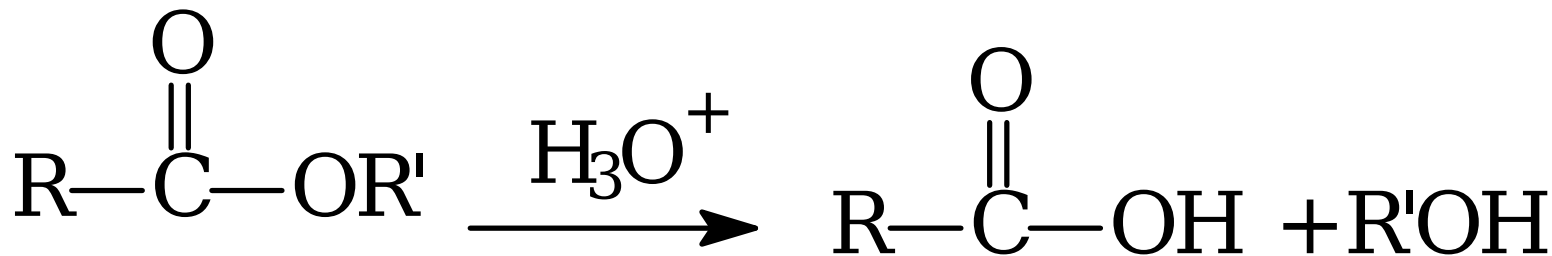
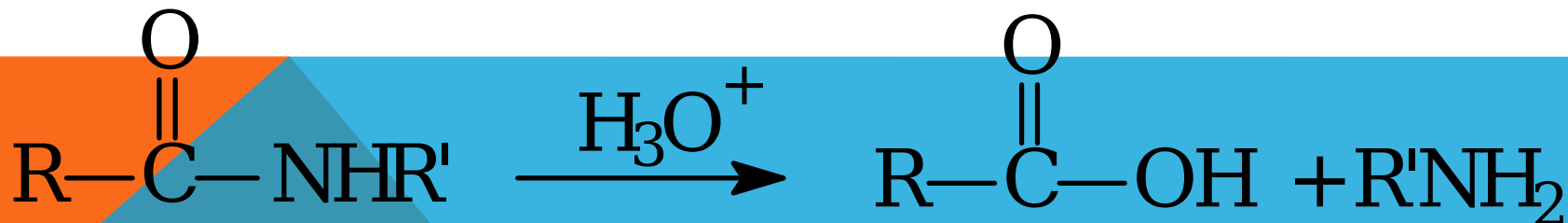
Are useful reagents in that the chloride is easily displaced by an alcohol or amine to give an ester or amide, respectively.



HYDROLYSIS OF ESTERS AND AMIDES

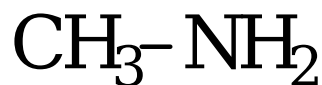
Esters and amides can be converted back to the parent acid by hydrolysis reaction.

Hydrolysis reaction is a reaction with water under acid or base catalysis.



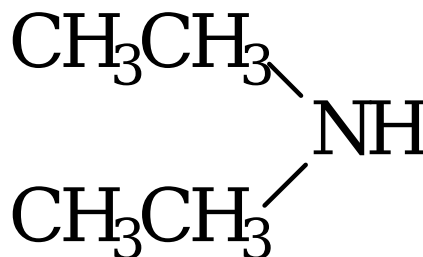
AMINO GROUP (AMINES)

- Classified as primary (1°), secondary (2°) & tertiary (3°).
- Basic because of the presence of lone pair of electrons on nitrogen (Brønsted and Lewis bases).



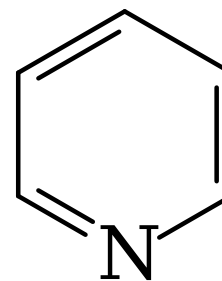
methylamine

1° amine



diethylamine

2° amine



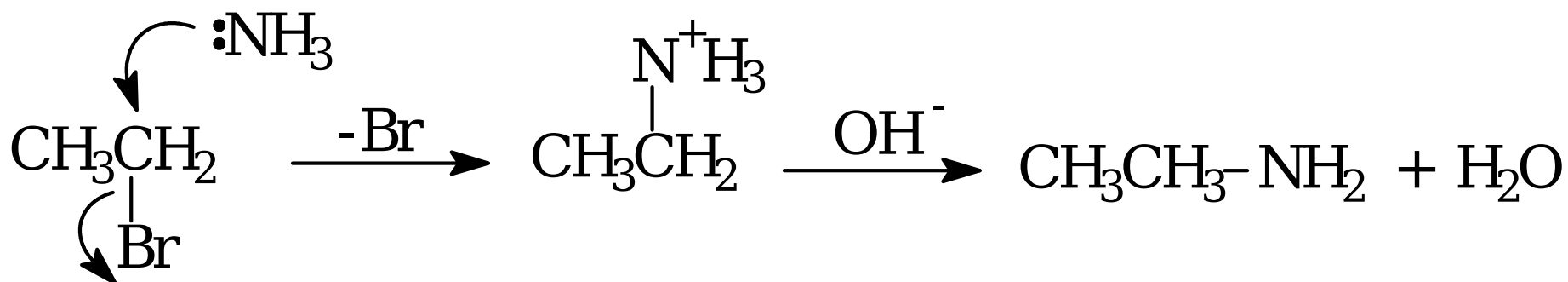
pyridine

3° amine



SYNTHESIS OF AMINES

Can be prepared by alkylation of ammonia by alkyl halides:



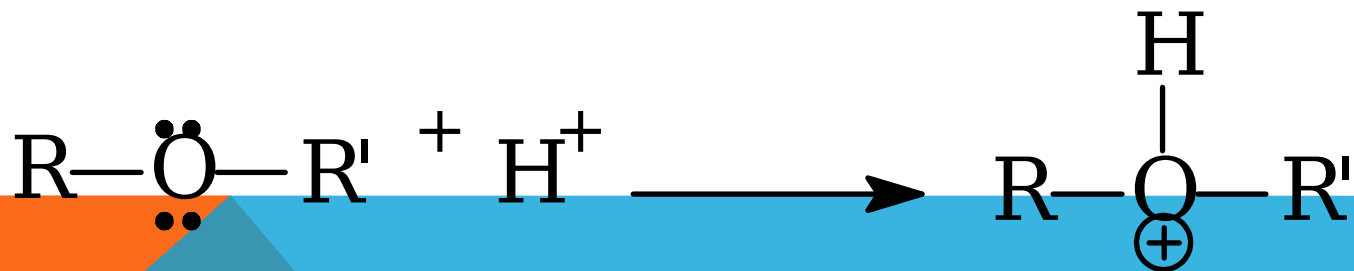
ETHERS

Compounds having two alkyl or aryl groups bonded to an oxygen atom, as in the formula R_1-O-R_2 .

organic solvents

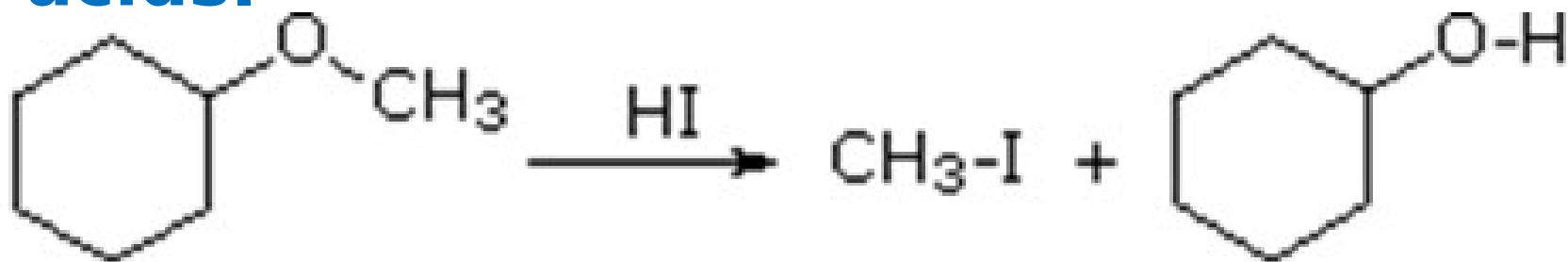
relatively inert.

May display very weak basicity.

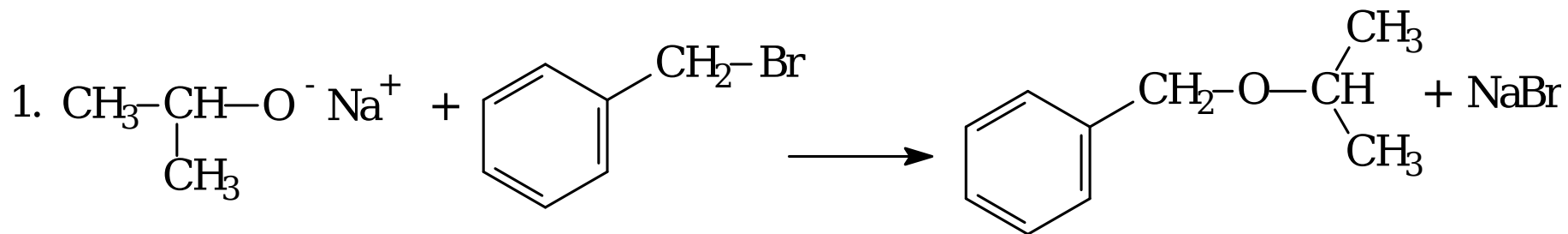
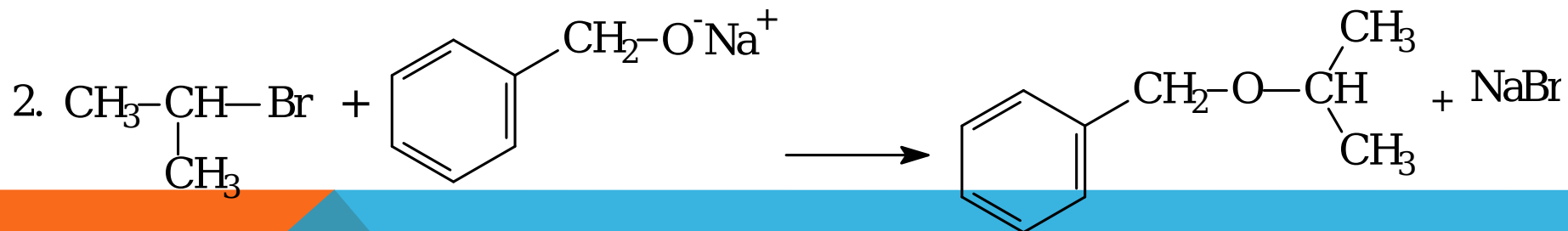


REACTIONS OF ETHERS

The most common reaction of ethers is cleavage of the C-O bond by strong acids.



SYNTHESIS OF ETHERS



CHAPTER 3

STEREOCHEMISTRY

STEREOCHEMISTRY

Stereochemistry: deals with properties of molecules resulting from the spatial relationships of their constituent groups.

SYMMETRY AND DISSYMMETRY

Molecules are either symmetric or dissymmetric.

Symmetric molecule is superimposable on its mirror image.

Dissymmetric molecule is non-superimposable on its mirror image.

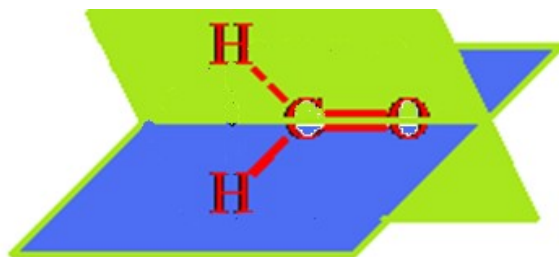
Dissymmetric molecules are chiral, or exhibit handedness.

ELEMENTS OF SYMMETRY

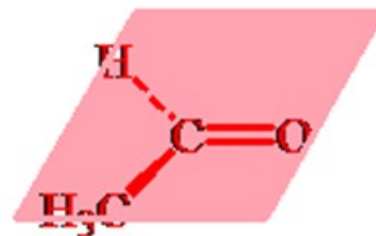
Plane of Symmetry (Mirror Plane):

A plane that bisects a molecule into halves which are exact mirror reflections of each other.

The molecule of formaldehyde has two mirror planes while acetaldehyde molecule has only one mirror plane.



formaldehyde
two mirror planes



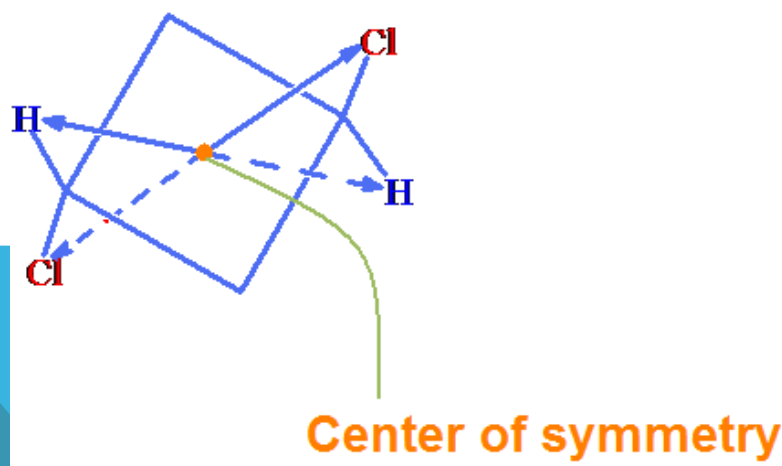
acetaldehyde
one mirror plane

CENTRE OF SYMMETRY

A central point in a structure of a molecule from which lines extended equally in opposite direction meet groups that are exact reflections of each other through that central point.

A molecule of trans-1,3-dichlorocyclobutane has centre of symmetry.

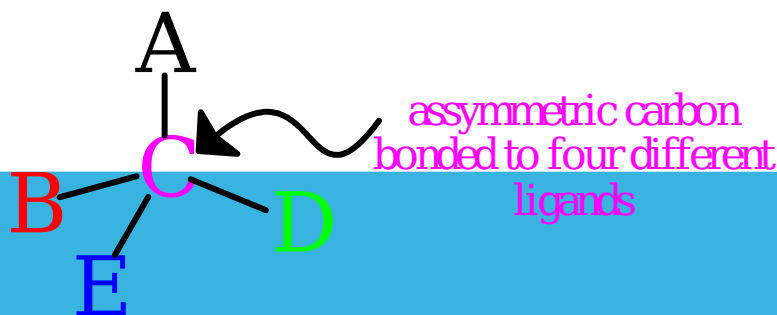
N.B. the molecule also has a plane of symmetry.



THE ASYMMETRIC CARBON

The most common form of dissymmetry in organic molecules is caused by presence of an asymmetric (chiral, stereogenic) carbon, asymmetric (chiral, stereogenic) centre.

A carbon atom is asymmetric when it is coordinated with four non-equivalent ligands.



ENANTIOMERS OR OPTICAL ANTIPODES

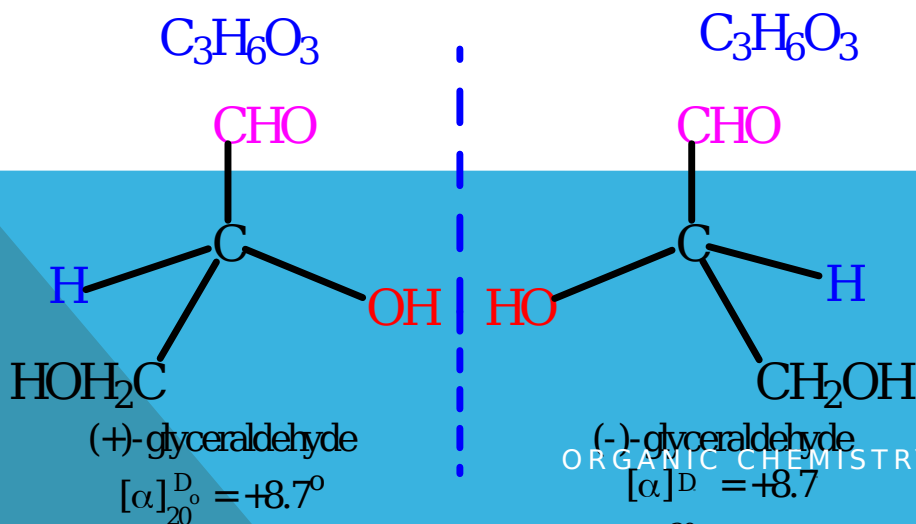
Non-superimposable mirror image compounds.

have identical melting and boiling points, identical solubilities in symmetrical solvents, identical chemical reactivities with symmetric reagents.

display differing reactivities with dissymmetrical reagents.

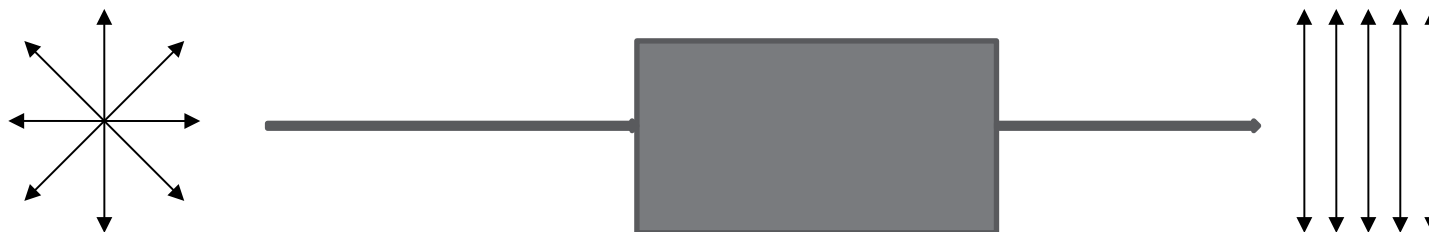
rotate plane of polarized light differently.

manifestation of optical isomerism, a class of *stereoisomerism*.



PLANE POLARIZED LIGHT

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

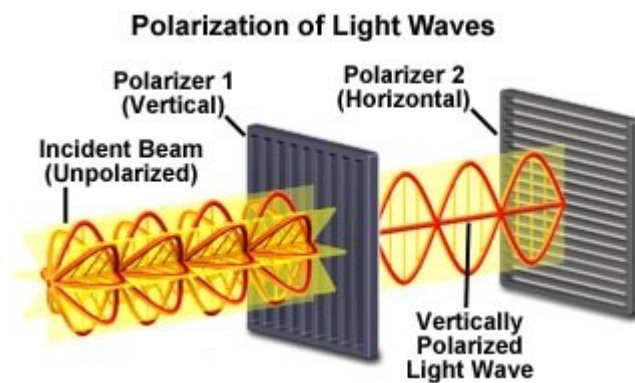


Ordinary light

Polarizer

Plane Polarized Light
PPL

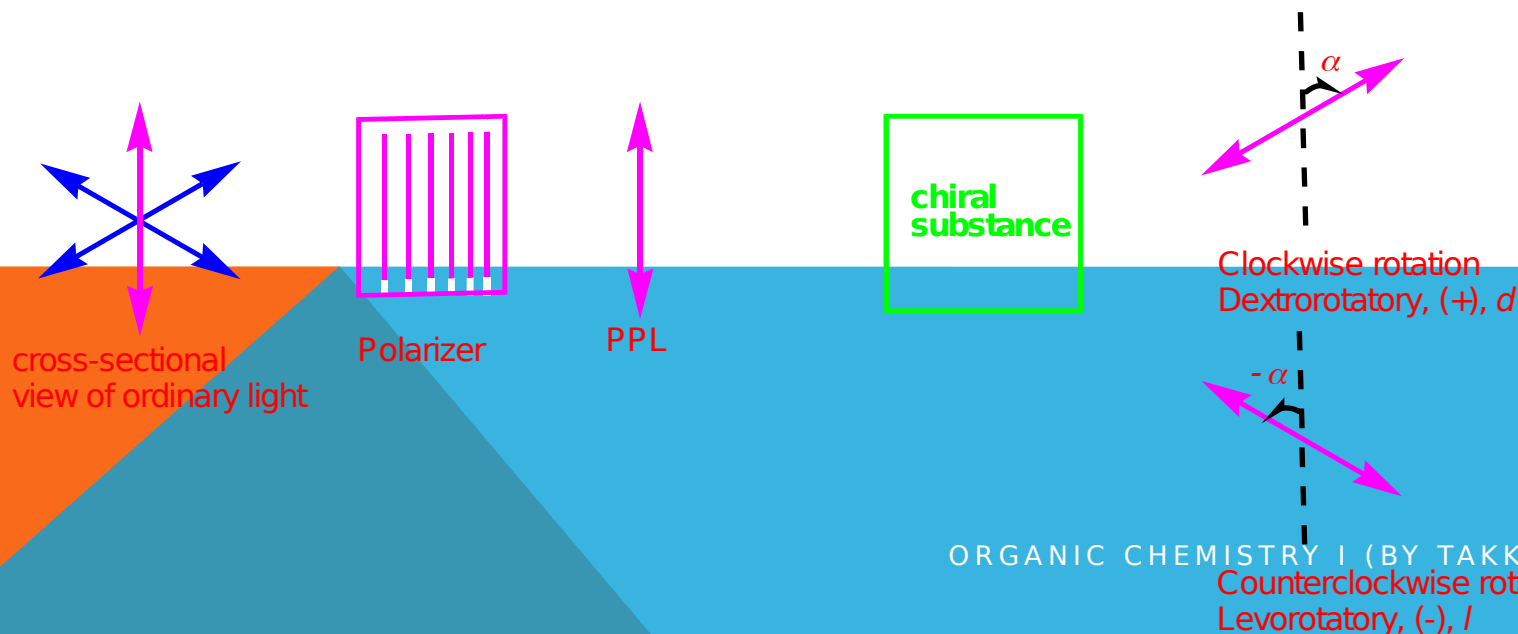
PLANE POLARIZED LIGHT



OPTICAL ACTIVITY

The phenomenon of rotating the plane of plane polarized light by some substances. (1815 by Biot)

Compounds that are capable of rotating plane of PPL are said to be *optically active*.



OPTICAL ISOMERISM

Is a form of isomerism in which stereoisomers rotate plane of polarized light differently.

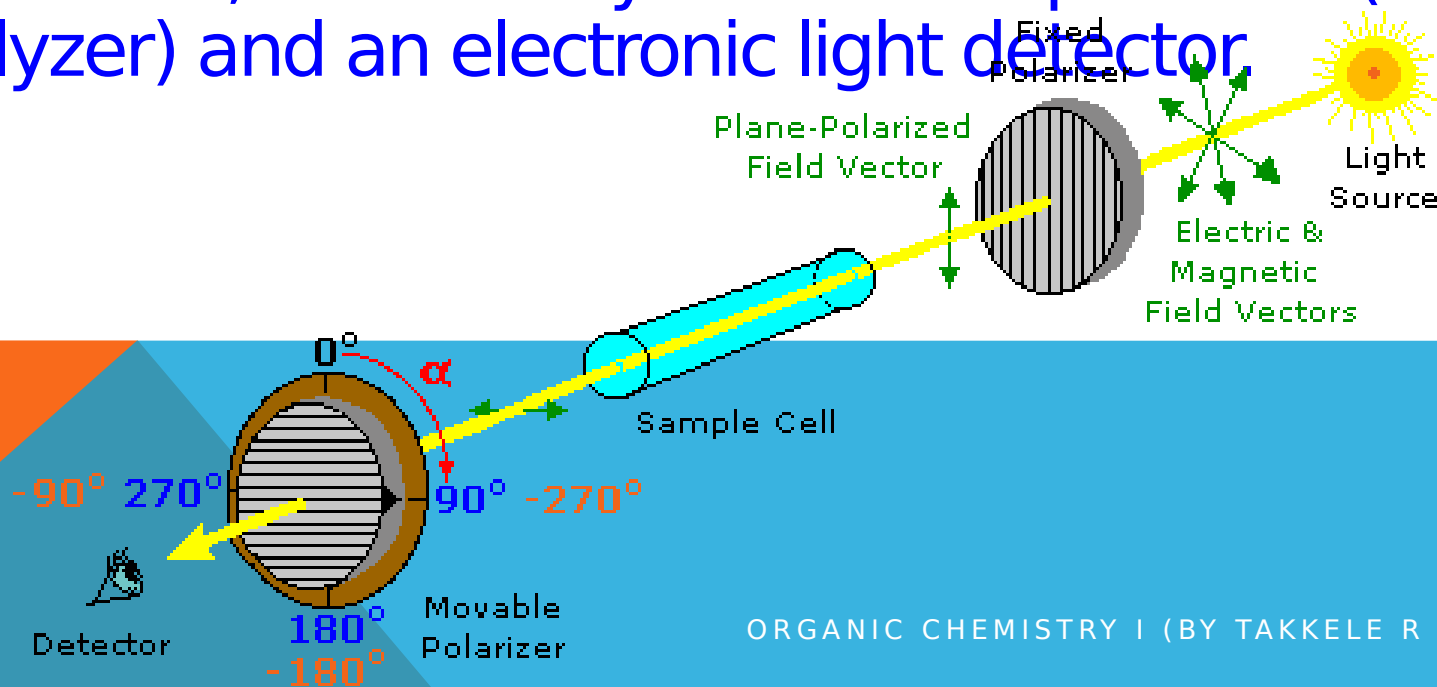
For example enantiomers rotate PPL by equal amount in opposite directions.

ENANTIOMERS AND OPTICAL ISOMERISM

- Enantiomers can be distinguished from each other by their differing rotation of a plane polarized light,
- If the plane of the PPL is rotated in the clockwise direction by an angle α , the enantiomer is known as *dextrorotatory*, (+), or *d*.
- If it is in the opposite direction, the enantiomer is *levorotatory*, (-), or *l*.
- Equimolar mixture of two enantiomers produce no discernible rotation of plane of PPL (zero net rotation) and is called *racemic mixture* or *racemate*.
- Instrument for measuring optical rotation is known as a *polarimeter*.

Polarimeter

- Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source.
- A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an electronic light detector.



SPECIFIC ROTATION

The magnitude of optical rotation (α) for a given chiral compound is dependent on the concentration of the solution used to measure it.

Specific rotation is the optical rotation value measured at a specific wavelength (λ) & temperature (T) and is characteristic of a particular compound.

It is defined as:

$$[\alpha]_T^\lambda = [\alpha]/l \times c$$

- Where T is the absolute temperature, λ is the wavelength of sodium lamp, usually the sodium D line which is 589 nm.
[α] is the observed rotation, l is the length of the sample tube in decimetres and c is the concentration of the sample in grams per millilitre.

CONFIGURATION

the arrangement in space of the four different groups about a chiral center, the assignment of a unique configuration to each "right-handed" and "left-handed" molecule is done by using a convention devised by three chemists: **R. S. Cahn, C.K. Ingold and V. Prelog.**

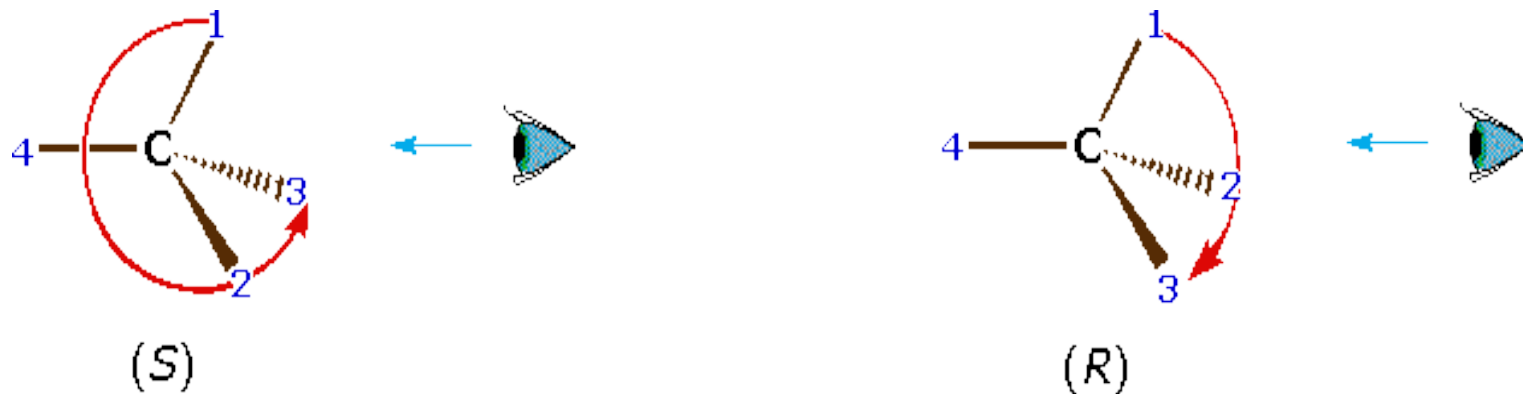
called the **Cahn-Ingold-Prelog (the CIP)** system or the **R-S (Rectus, Sinister)** system.

each chiral center in a molecule is assigned a prefix (R or S), based on "The Sequence Rule" and "The Viewing Rule".

THE SEQUENCE RULE

- 1. The higher the atomic number of the immediate substituent atom, the higher the priority.**
For example, $\text{H-} < \text{C-} < \text{N-} < \text{O-} < \text{Cl-}$.
(Different isotopes of the same element are assigned a priority according to their atomic mass.)
- 2. If two substituents have the same immediate substituent atom, evaluate atoms progressively further away from the chiral center until a difference is found.**
For example, $\text{CH}_3\text{-} < \text{C}_2\text{H}_5\text{-} < \text{ClCH}_2\text{-} < \text{BrCH}_2\text{-} < \text{CH}_3\text{O-}$. Reading ass.
- 3. If double or triple bonded groups are encountered as substituents, they are treated as an equivalent set of single-bonded atoms. For example, $\text{C}_2\text{H}_5\text{-} < \text{CH}_2=\text{CH-} < \text{HC}\equiv\text{C-}$**

THE VIEWING RULE



The chiral center must be viewed from the side opposite the lowest priority group.

an observer (the eye) notes whether a curved arrow drawn from the # 1 position to the # 2 location and then to the # 3 position turns in a clockwise or counter-clockwise manner.

If the turn is clockwise, the configuration is classified R.

If it is counter-clockwise, as in the left illustration, the configuration is S.

If any two substituent groups on a stereogenic carbon are exchanged, the configuration changes to its mirror image.

FISHER PROJECTIONS

Are used only for chiral centers!

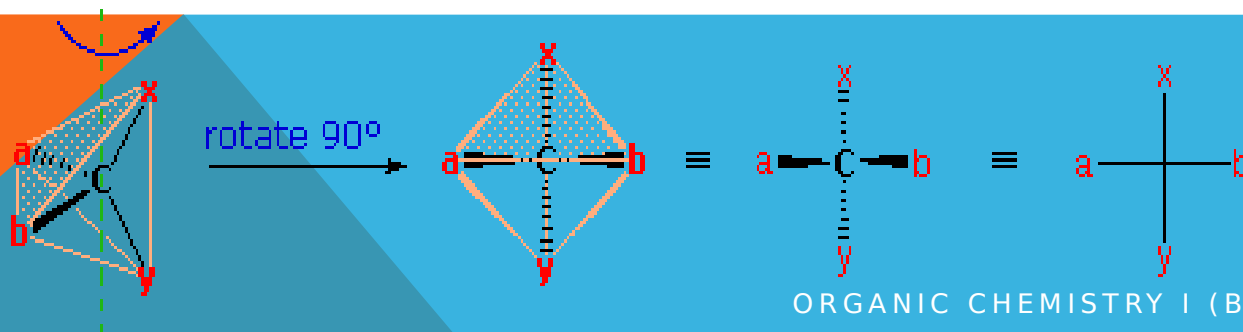
Representation of a 3D structure on a 2D surface.

The four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines.

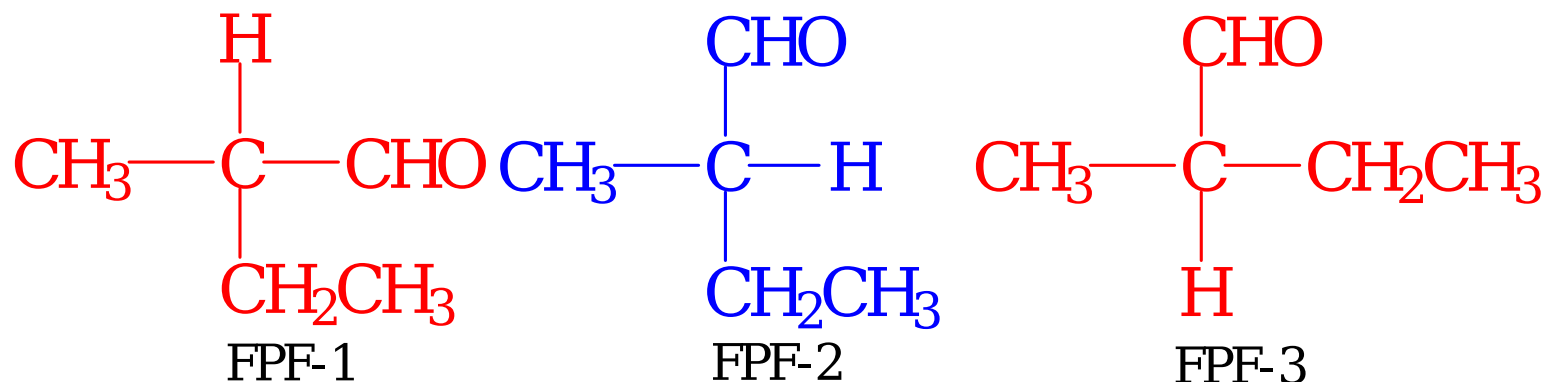
The two horizontal bonds are directed toward the viewer and the two vertical bonds are directed away from the viewer.

Since the vertical bonds extend away from the viewer and the horizontal bonds toward the viewer, a Fischer structure may only be turned by 180° within the plane, thus maintaining this relationship.

The structure must not be flipped over or rotated by 90° .



EQUIVALENCE OF FISHER PROJECTION FORMULAS



- FPF-1, 2, 3 represent 2-methylbutyraldehyde. Are they equivalent?
- This can be confirmed by exchange of groups until one is changed to the other.
- If the total number of exchange is *even*, the two represent equivalent FPFs.
- Otherwise, the two represent enantiomers.
- In this example, exchange of H and CHO groups of 1 generates 2
- Exchange of H with CH₂CH₃ in FPF-2 gives FPF-3.
- The total number of exchanges is even and the two must be equivalent.

MULTIPLE ASYMMETRIC CENTERS: DIASTEREOMERS

n chiral centers $\Rightarrow$ 2^n maximum stereoisomers

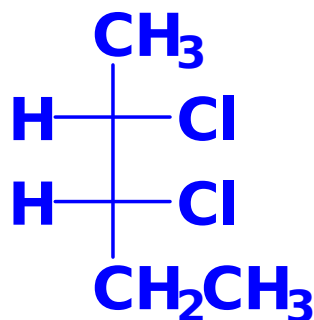
n = 2 $\Rightarrow$ $2^2 = 4$ stereoisomers

Example: 2,3-dichloropentane

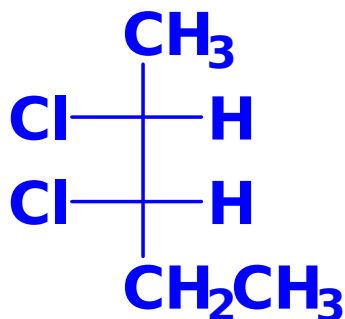


DIASTEREOMERS

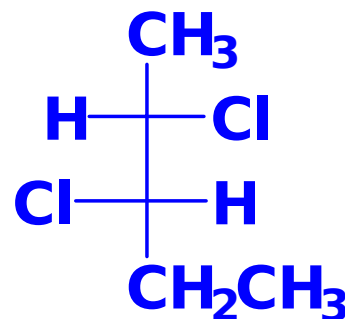
The four stereoisomer are the following:



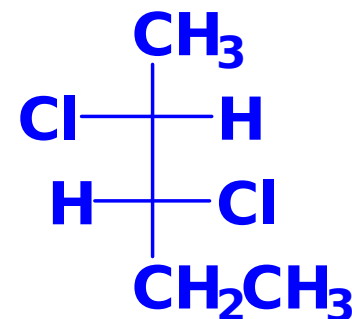
I



II



III



IV

I & II, III & IV are each pairs of enantiomers; I & III, I & IV, II & III, II & IV, are diastereomers;

Definition: Diastereomers are stereoisomers which are not enantiomers.

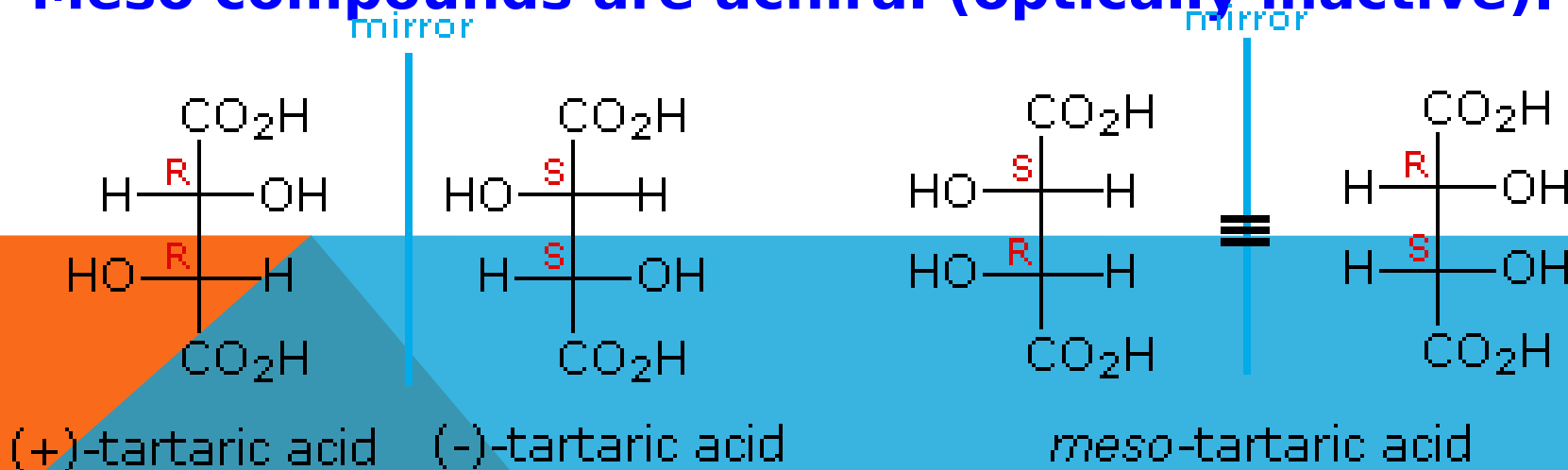
ACHIRAL DIASTEREOMERS (MESO-COMPOUNDS)

The two chiral centers of tartaric acid have the same substituents.

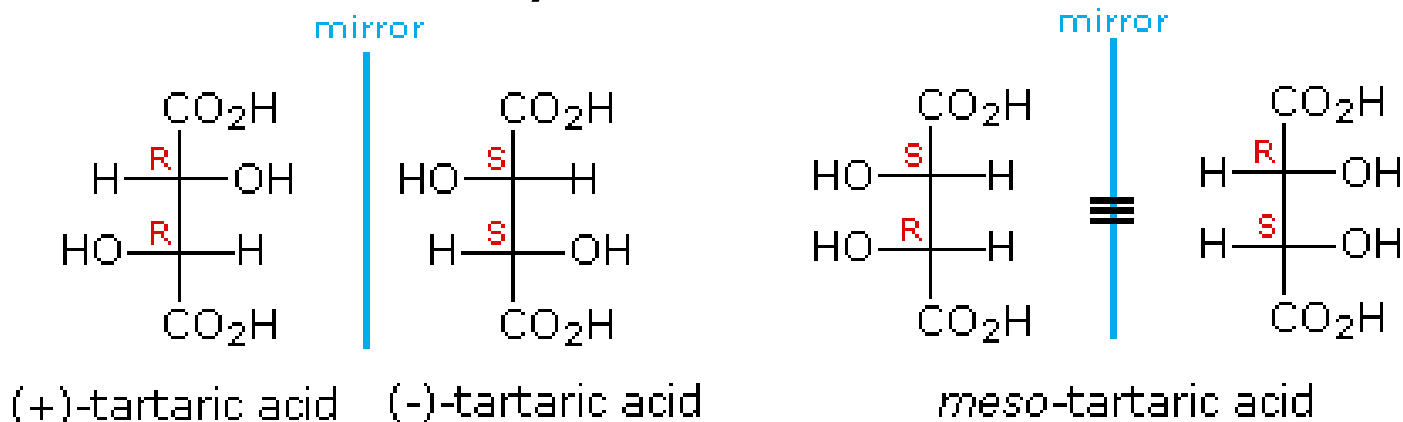
As a result, two of the stereoisomers are identical and is called a meso compound.

so there are only three stereoisomeric tartaric acids.

Meso compounds are achiral (optically inactive).



ACHIRAL DIASTEREOMERS (MESO-COMPOUNDS)



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As a result, two of the stereoisomers are identical and is called a meso compound.

so there are only three stereoisomeric tartaric acids.

Meso compounds are achiral (optically inactive).

CONFORMATION

The various spatial orientation of substituents in a molecule (conformers).

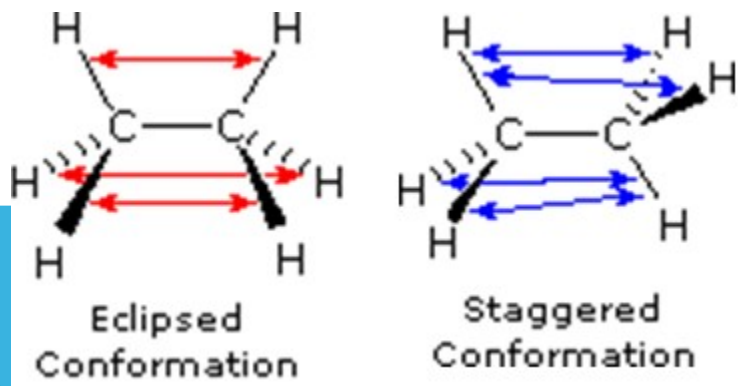
Arises from facile rotation across single bonds.

Usually conformers are in thermal equilibrium and can't be separated.

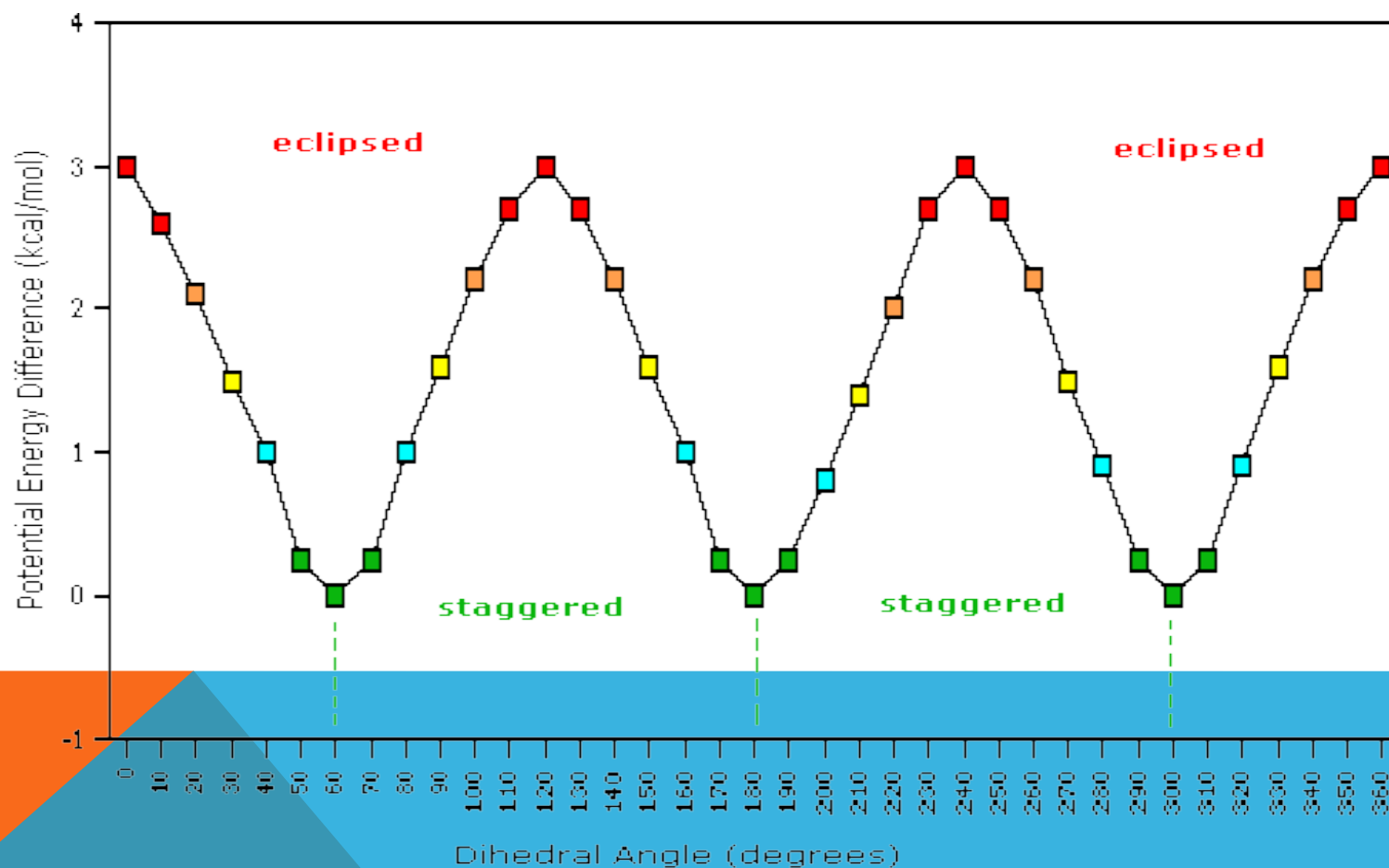
ETHANE CONFORMATIONS

Provides a good introduction to conformational analysis.

The conformers (rotamers) that it may assume fall between two extremes, eclipsed & staggered.



POTENTIAL ENERGY PROFILE OF ETHANE CONFORMERS



EXTREME CONFORMATIONS OF ETHANE

Three different representations of ethane extreme conformers are known.

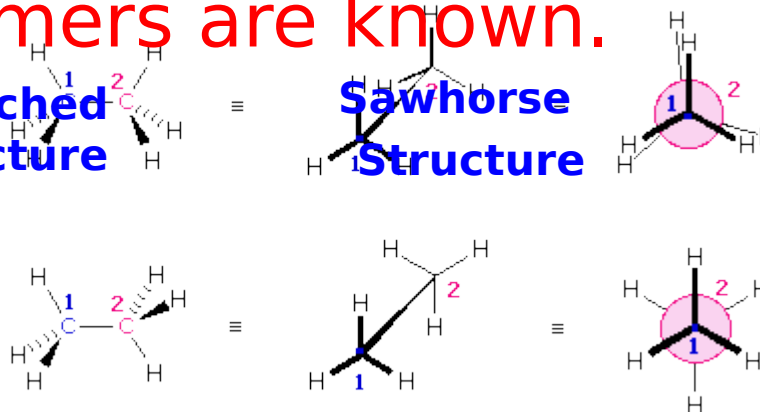
**Name of
Conformer**

**Wedge-Hatched
Bond Structure**

**Sawhorse
Structure**

**Newman
Projection**

Staggered
Conformation

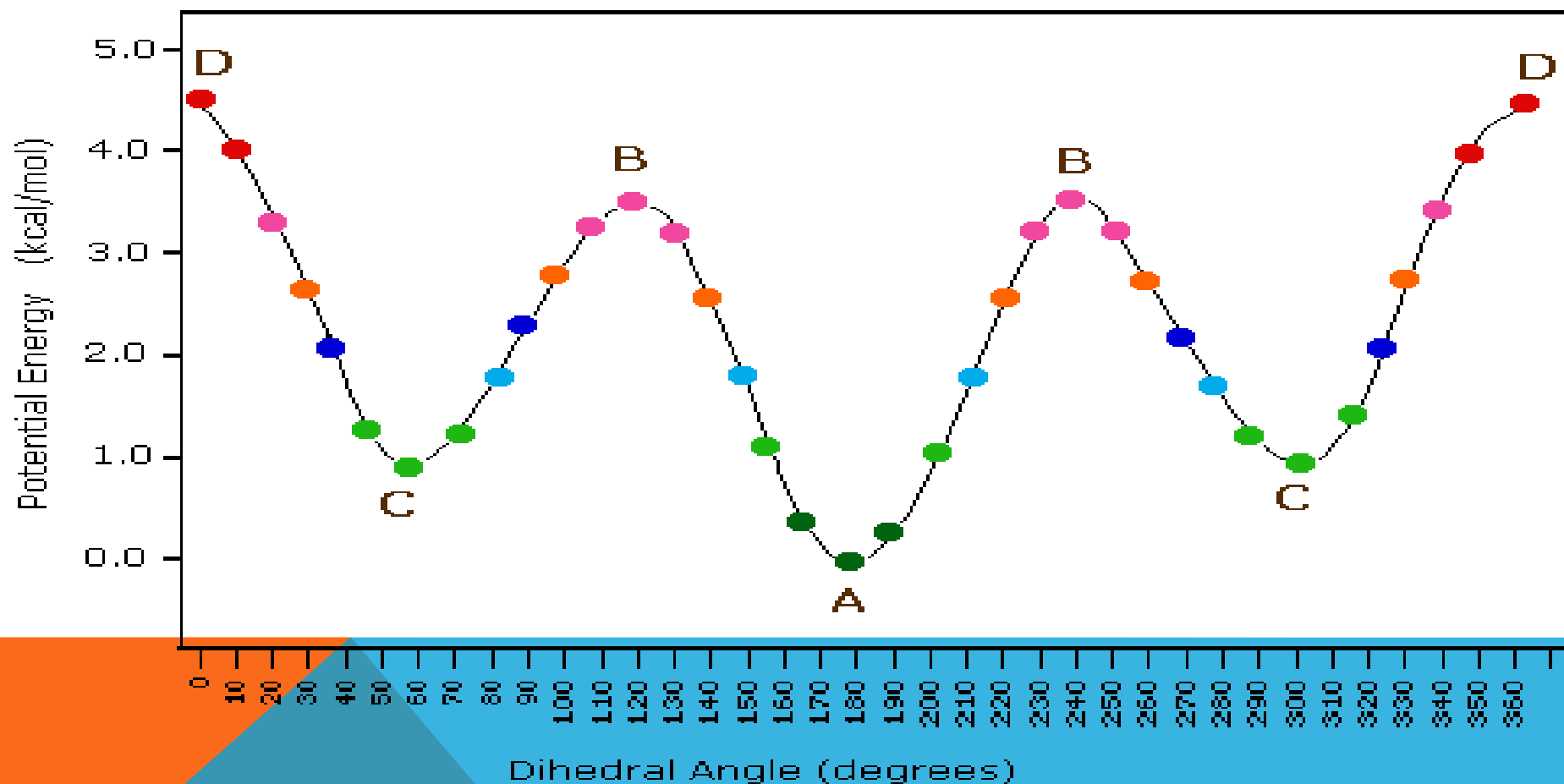


STABILITY OF THE CONFORMERS

Due to bond-electron repulsions, the eclipsed conformation is less stable than the staggered conformation by roughly 3 kcal/mol (*eclipsing strain*).

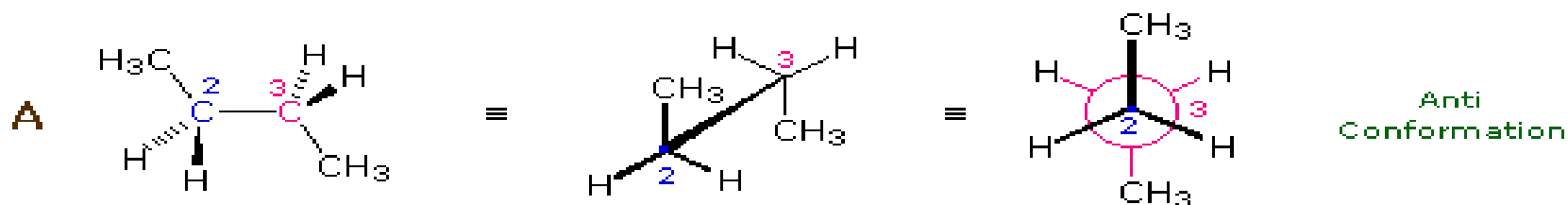
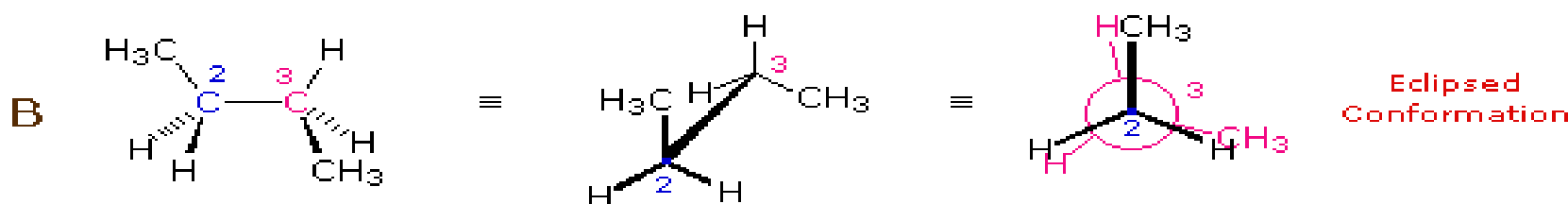
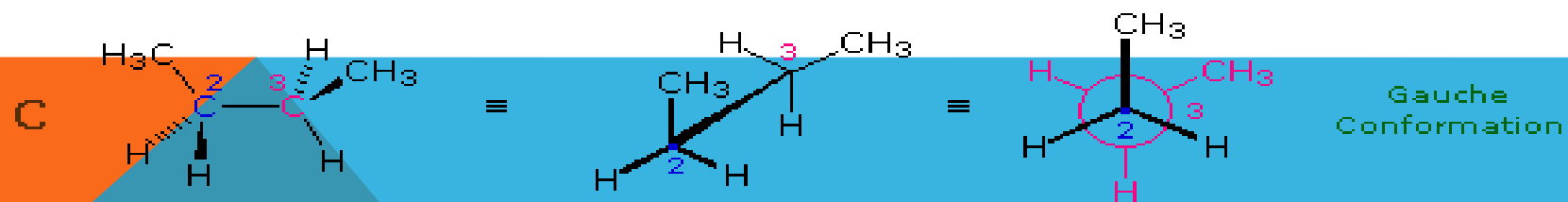
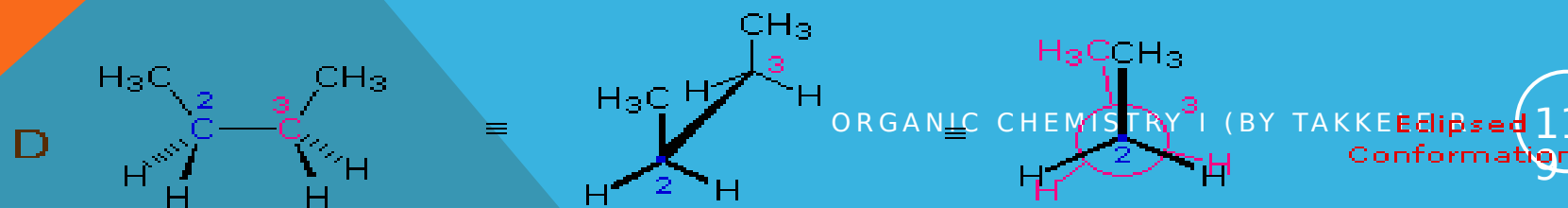
The conformers are in rapid equilibrium with each other, but the 3 kcal/mol energy difference leads to a 99.9% of staggered conformers at any given time.

BUTANE CONFORMERS & THEIR POTENTIAL ENERGY PROFILE



BUTANE CONFORMATIONS

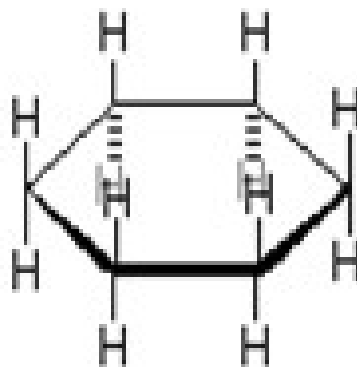
The staggered conformers are more stable than the eclipsed by 2.8 to 4.5 kcal/mol and designated anti (A) and gauche (C).



CYCLOHEXANE: PLANAR

A planar structure for cyclohexane is improbable.

Angle and eclipsing strains would severely destabilize such a structure.



Planar Structure

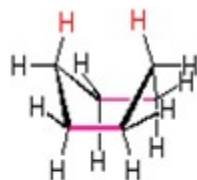
severe angle strain (120°)

severe eclipsing strain (all bonds)

small steric strain

CYCLOHEXANE: BOAT

- In boat structure much of the angle strain can be eliminated.
- Still has 2 eclipsed bonds and severe steric crowding of 2 hydrogen atoms on the "bow" and "stern" of the boat.
- This steric crowding is often called steric hindrance.

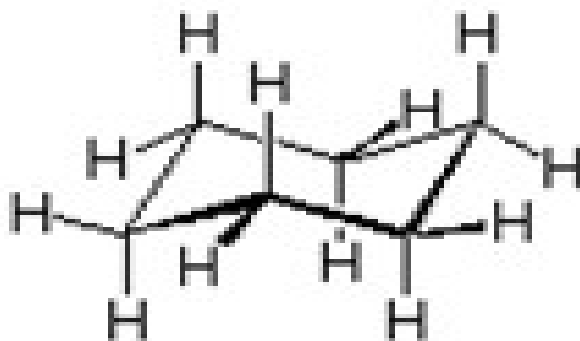


Boat Conformation

slight angle strain
eclipsing strain at **two bonds**
steric crowding of **two hydrogens**

CYCLOHEXANE: CHAIR

A relatively strain-free conformer, thus predominant.



Chair Conformation

no angle strain

no eclipsing strain

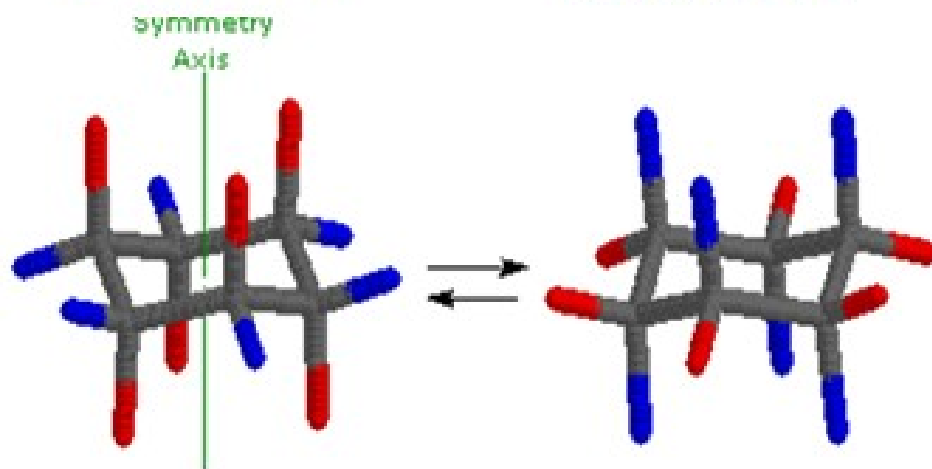
small steric strain

CHAIR CONFORMATION

Two equivalent chair conformations of cyclohexane in rapid equilibrium.

The 12 hydrogens of a chair cyclohexane are not equivalent: 6 are equatorial and the other 6 are axial.

All axial bonds are in chair-1
All equatorial bonds are in chair-2



Cyclohexane Chair Conformations

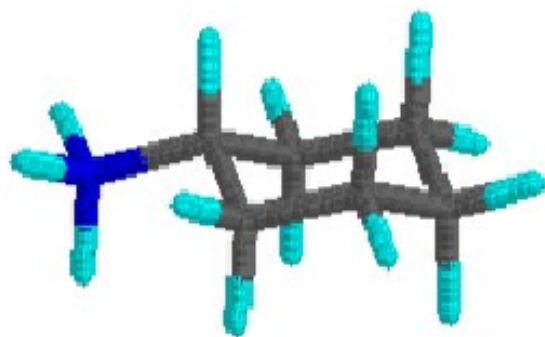
Axial Hydrogens
Equatorial Hydrogens

Axial Hydrogens
Equatorial Hydrogens

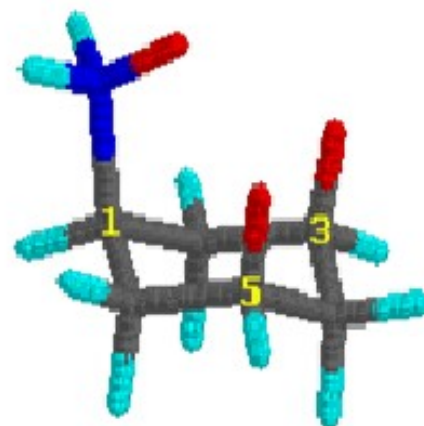
(BY TAKKELE R

METHYLCYCLOHEXANE

Bulky axial substituents suffer high steric crowding.
preferentially adopt equatorial orientation.



Methyl Cyclohexane
Equatorial Conformer

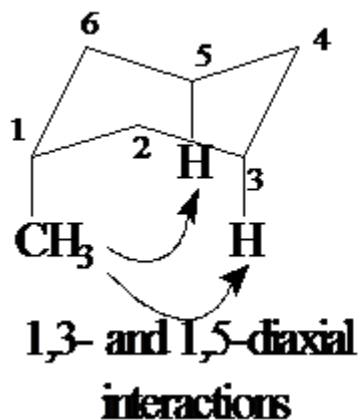
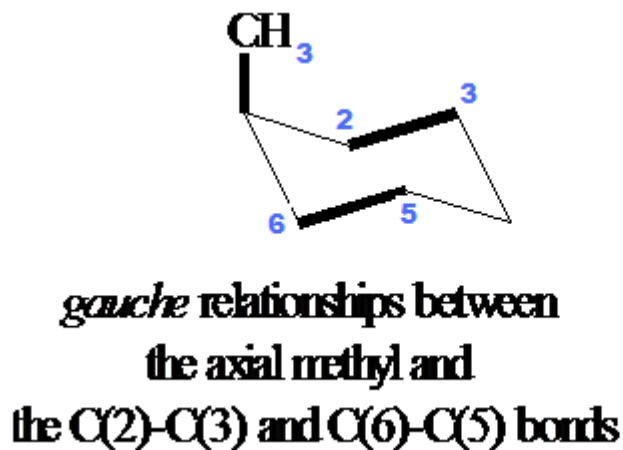
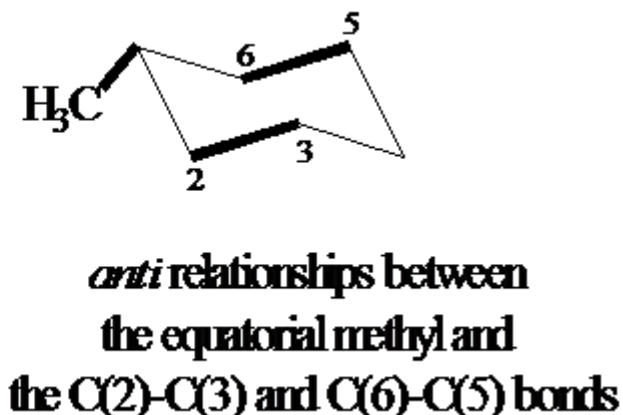


Methyl Cyclohexane
Axial Conformer
Severe Hydrogen Crowding

METHYLCYCLOHEXANE

Suffers 1,3 & 1,5-diaxial interactions.

Suffers steric hindrance due to two *gauche*-like orientations of the methyl group with ring carbons 3 and 5.



DIMETHYLCYCLOHEXANE

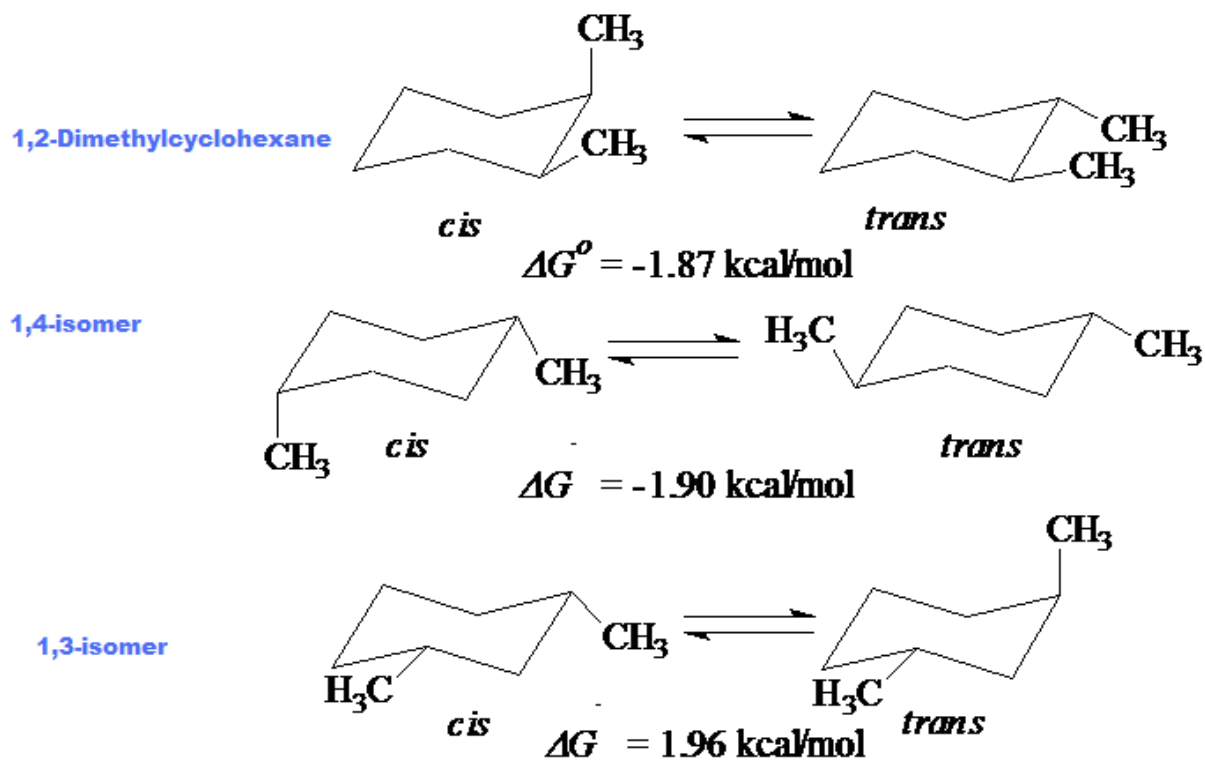
1,2-, 1,3- and 1,4-disubstituted compounds can have both groups equatorial, but this requires a *cis*-or a *trans*-relationship depending on the relative location of the substituents.

In *cis*-1,2-disubstitution, one must be equatorial and the other axial; in the *trans*-isomer both may be equatorial.

In 1,3-disubstituted *cis* is all equatorial, *trans* is equatorial/axial.

1,4-disubstitution reverts to the 1,2-pattern.

DIMETHYLCYCLOHEXANE



CHAPTER 5

SUBSTITUTION REACTIONS

CLASSES OF ORGANIC REACTIONS

All heterolytic organic reactions fall into one of four reaction categories:

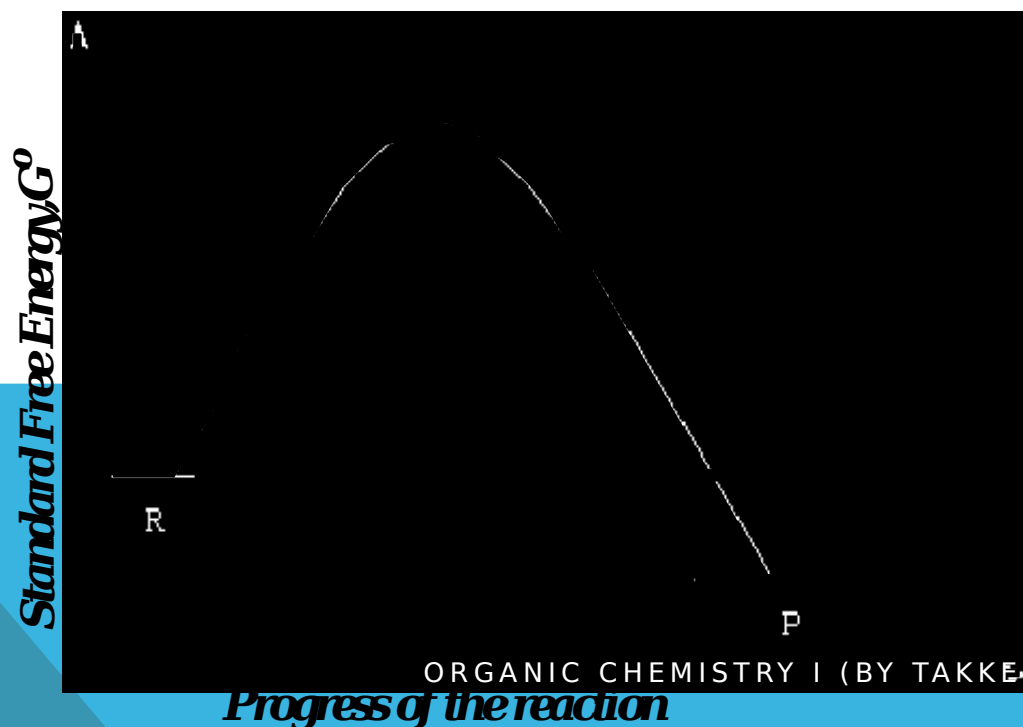
- Substitution
- Eliminations
- Additions
- Rearrangements

ENERGY DIAGRAM OF A REACTION

A plot of standard free energy, G° , of a reaction (y-axis) as a function of the progress of the reaction.

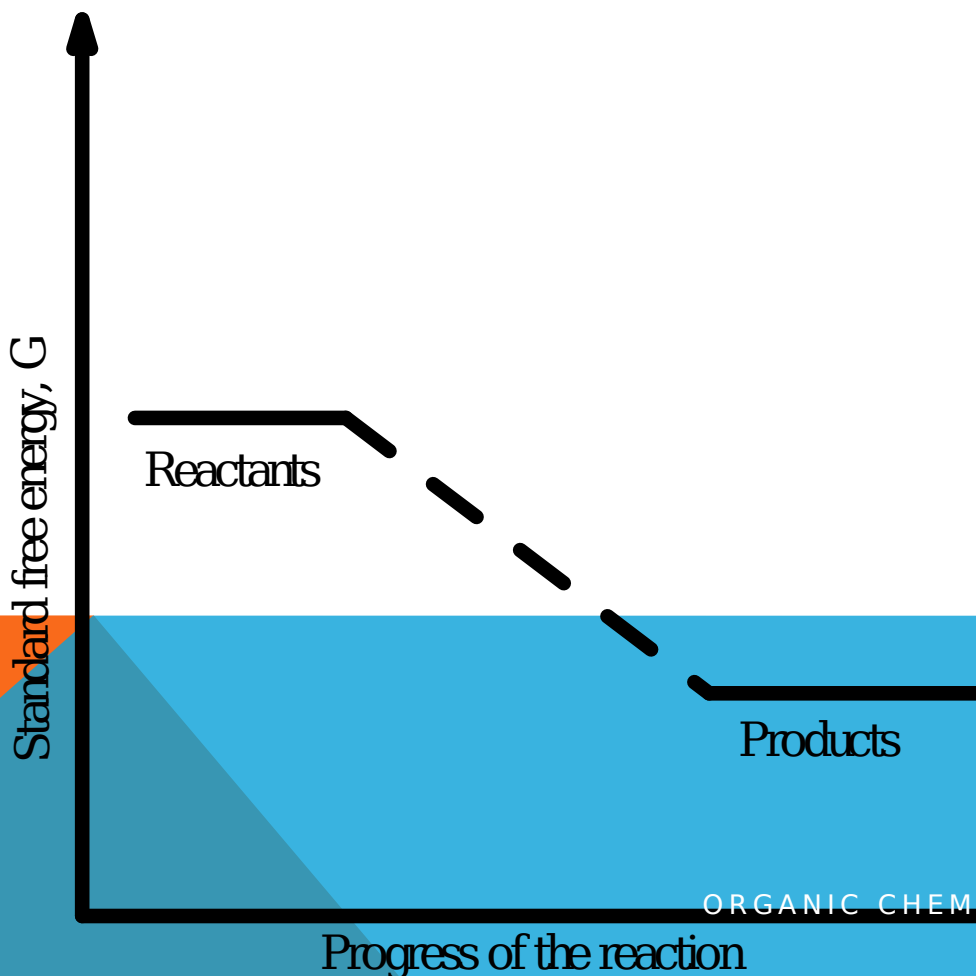
In a diagram shown below, the product predominates at equilibrium due to its smaller free energy.

Relative stability alone dictates the equilibrium composition.

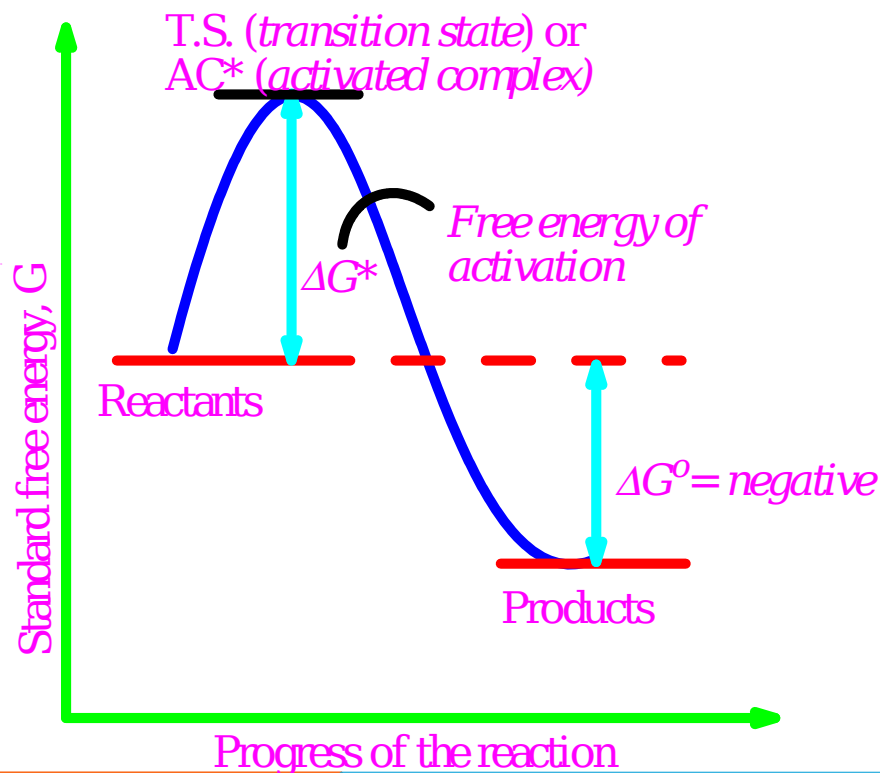


DIFFUSION CONTROLLED REACTIONS

Reactions in which the rate of the reaction depends only on the rate of diffusion of the reactants towards each other.



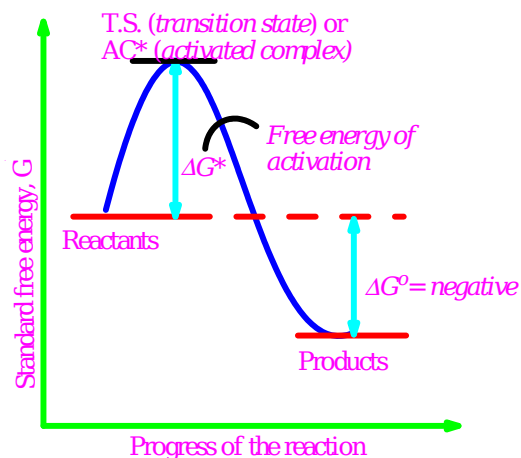
REACTIONS WITH FREE ENERGY OF ACTIVATION: TRANSITION STATES AND MOLECULARITY



The species formed at the maximum energy is known as the transition state or activated complex.

The number of species coming together to form the activated complex is the molecularity of a reaction.

REACTIONS WITH FREE ENERGY OF ACTIVATION: TRANSITION STATES AND MOLECULARITY

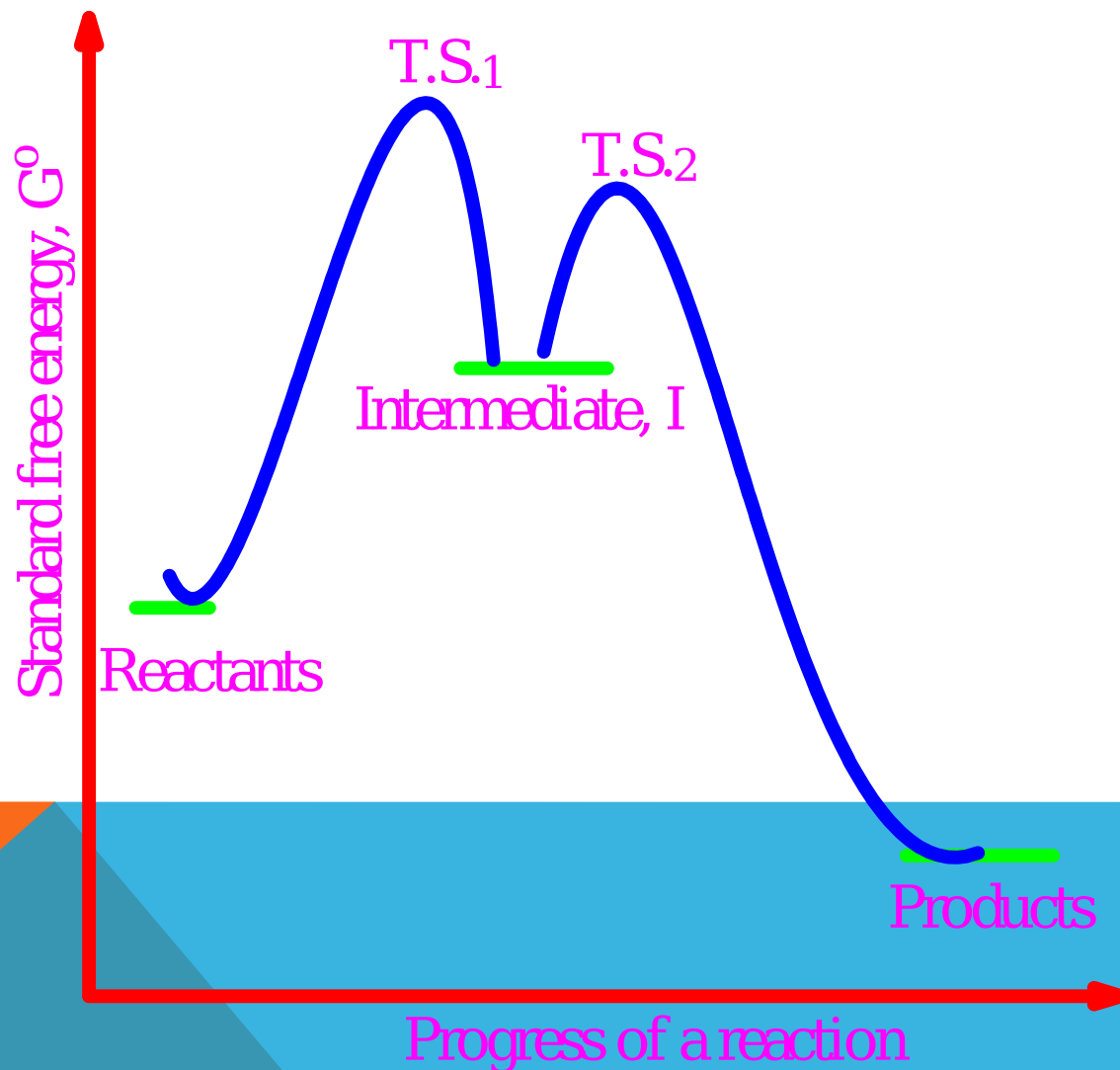


Free Energy of Activation:
The minimum amount of energy required to begin a reaction

The species formed at the maximum energy is known as the transition state or activated complex.

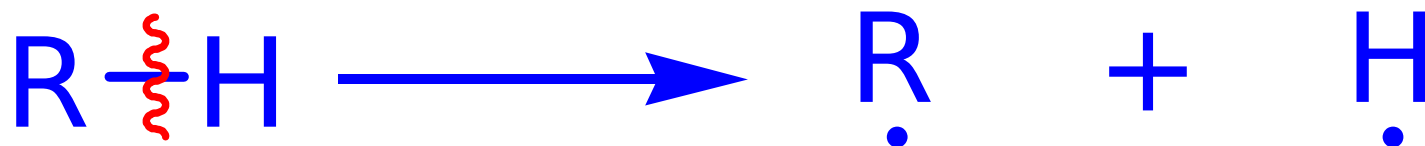
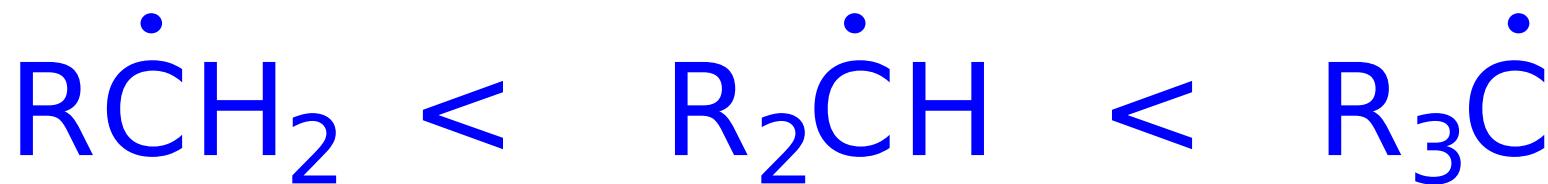
The number of species coming together to form the activated complex is the molecularity of a reaction.

REACTIVE INTERMEDIATES



MAJOR TYPES OF INTERMEDIATES

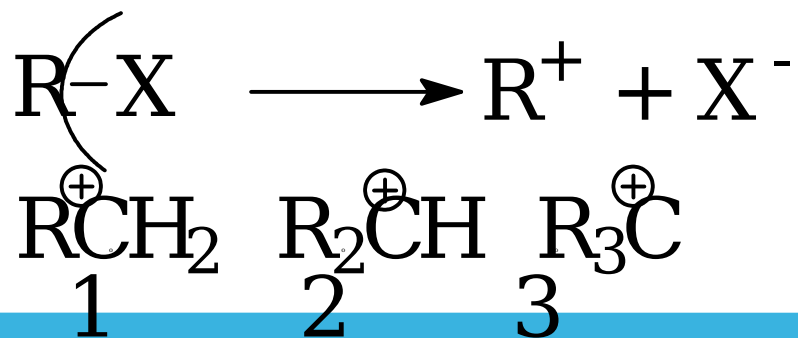
Free Radicals: generated by homolysis.
Stability order: $3^\circ > 2^\circ > 1^\circ$



CARBOCATIONS

Generated by heterolysis of bond between carbon and a more electronegative atom.

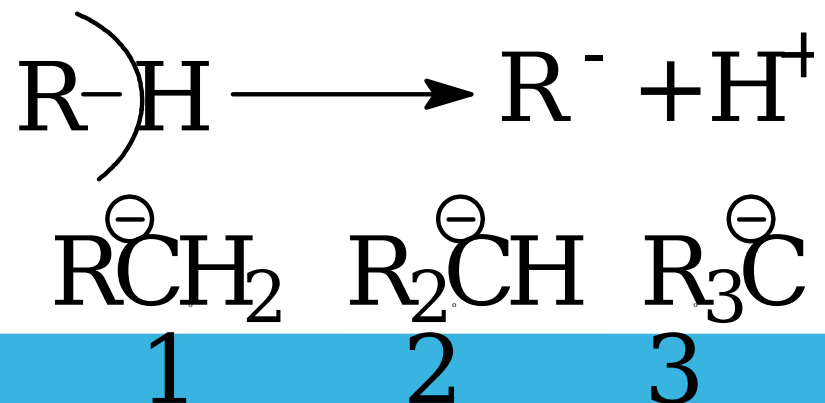
Stability order: $3^\circ > 2^\circ > 1^\circ$



CARBANIONS

Generated by hetrolysis of a covalent bond between carbon and a less electronegative atom.

Stability order: $3^\circ < 2^\circ < 1^\circ$.



NUCLEOPHILIC SUBSTITUTION AT A SATURATED CARBON ATOM

- A reaction in which an electron pair donor (a nucleophile, Nu:) reacts with an electron pair acceptor (an electrophile).
- The nucleophile can be negatively charged or neutral.
- An sp^3 -hybridized electrophile must have a leaving group (X).
- Display general principles that lead to understanding of other reactions as well.



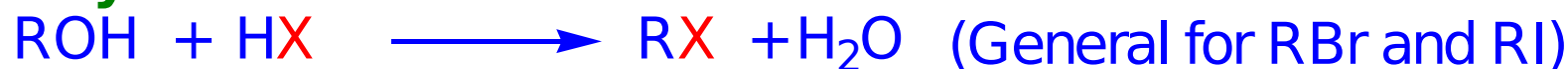
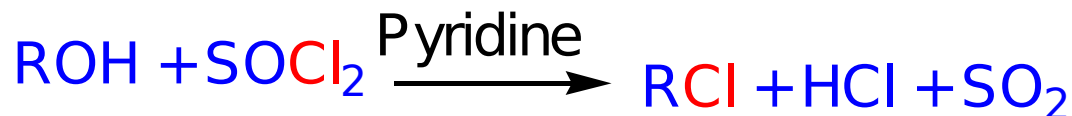
R = alkyl group
X = leaving group
Nu: = nucleophile

EXAMPLES

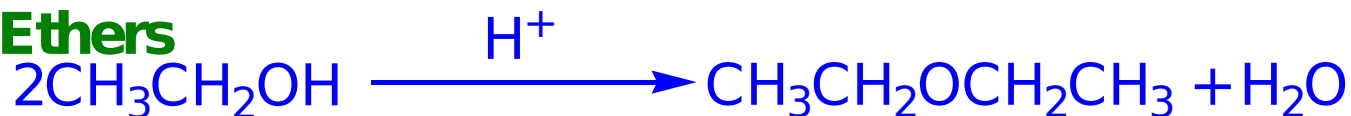
Alcohols



Alkyl halides



Ethers



Nitriles

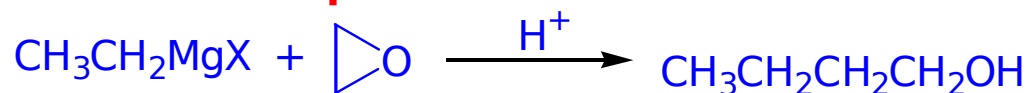


Alkynes

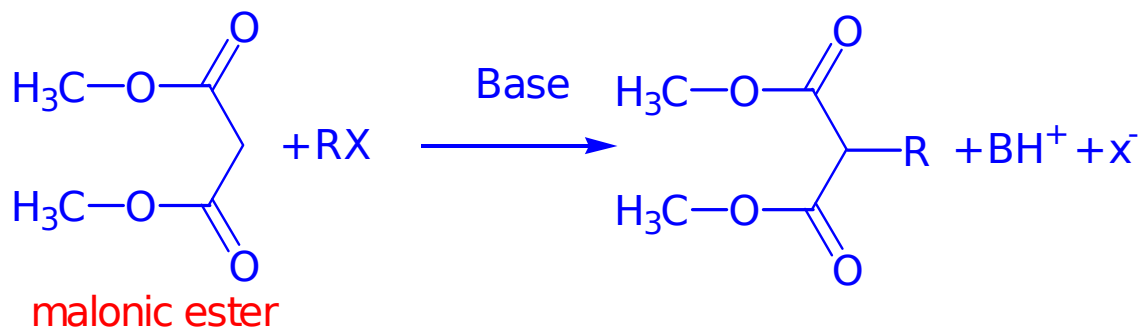
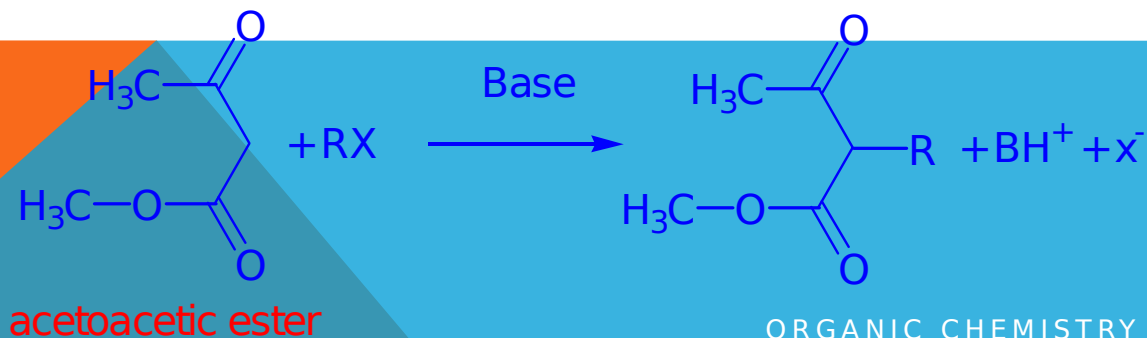


MORE EXAMPLES

Alcohols from epoxides

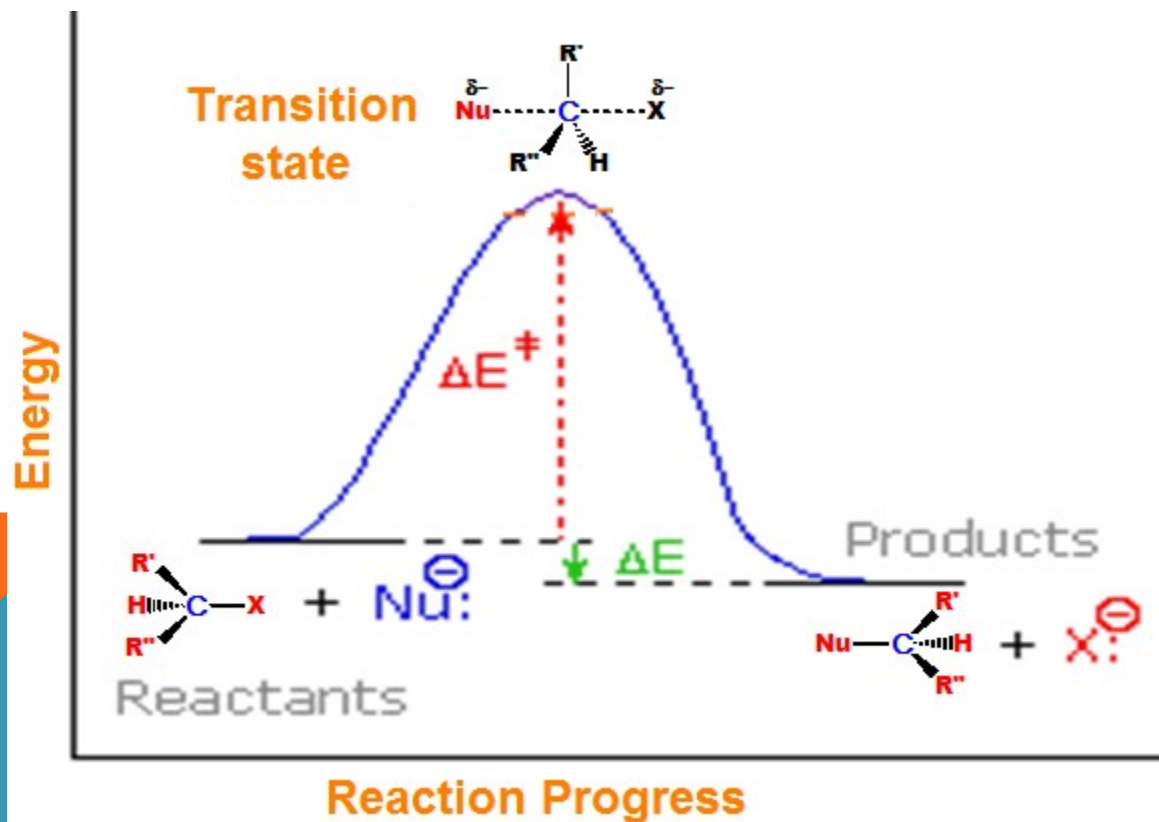


Malonic ester and acetoacetic ester synthesis



MECHANISMS: THE S_N2 MECHANISM

S stands for Substitution, **N** for Nucleophilic and **2** for bimolecular



DESCRIPTION OF THE DIAGRAM FOR AN ANIONIC NUCLEOPHILE

The nucleophile approaches the electrophilic carbon from the side opposite the x.

As the nucleophile begins to bond, the carbon-x bond weakens and stretches, the x eventually leaving as an anion.

In the T.S. the carbon is sp^2 hybridized with the partial bonds to the nucleophile and the x having largely p-character.

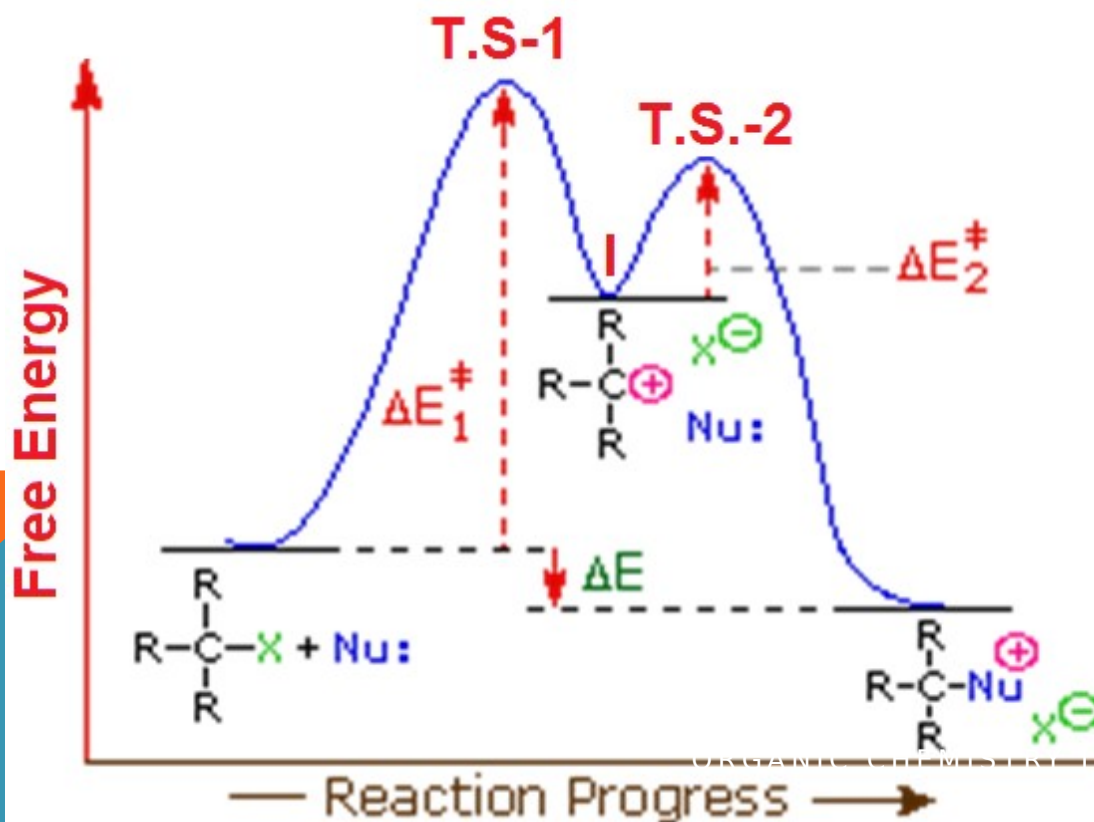
Both the nucleophile and the x bear a δ^- , the full charge being transferred to the x in the products.

The consequence of rear-side bonding by the nucleophile is an *inversion of configuration* about the carbon.

Neutral nucleophiles react by a similar mechanism, with a different charge distribution in the T.S.

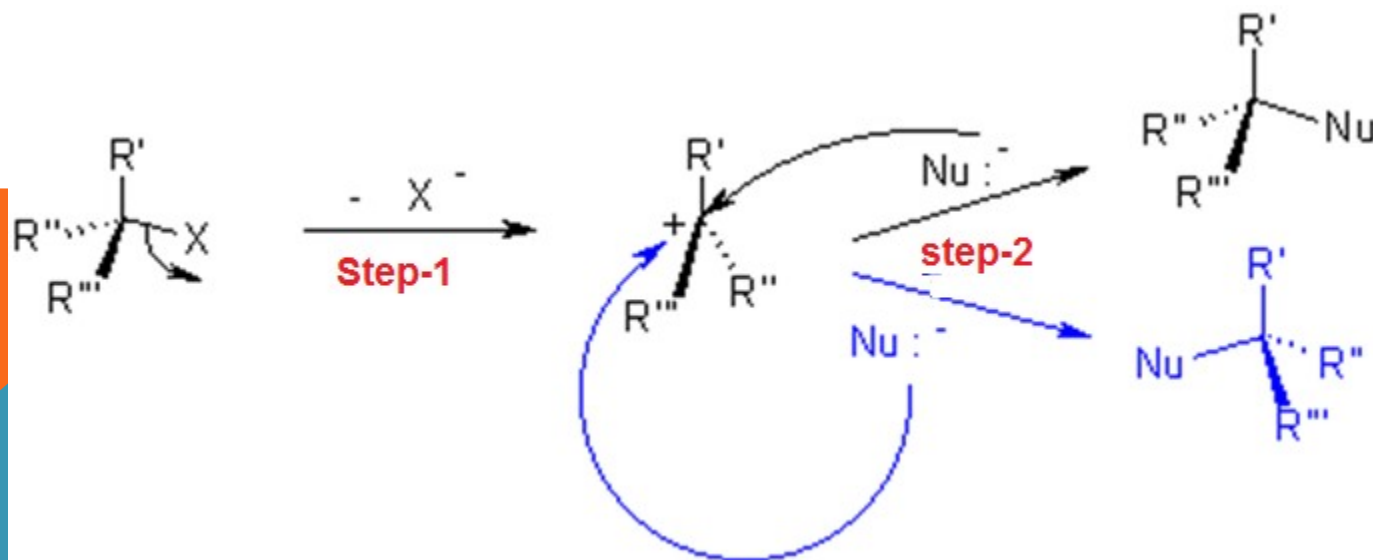
THE S_N1 MECHANISM

S stands for substitution N for nucleophilic
1 for unimolecular



DESCRIPTION OF S_N1 MECHANISM

- This is a two step process:
- **Step 1: Formation of a planar carbenium ion intermediate (I) by ionization,**
- **Step 2: Combination of the carbenium ion intermediate (I) with the nucleophile.**
- **Since the nucleophile is free to attack from either side, the reaction leads to racemization in cases of optically active substrates.**



DOES A GIVEN SUBSTITUTION PROCEED BY S_N1 OR S_N2 ?

Experimental Evidences for Determination of the Mechanisms of Nucleophilic Substitution Reactions

KINETIC EVIDENCE

First order kinetics (rate law):

Rate = k [substrate]

Indicative of S_N1 mechanism.

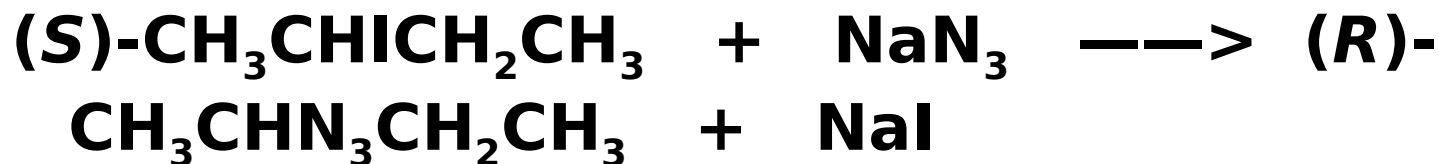
Second order kinetics (rate law):

Rate = k [substrate] [Nu:] (bimolecular)

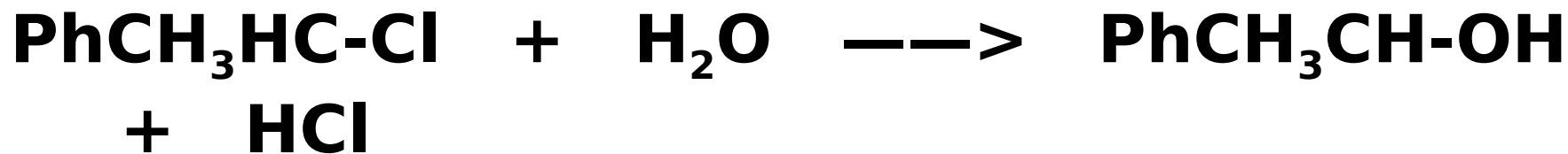
Indicative of S_N2 mechanism.

STEREOCHEMICAL EVIDENCE

Inversion of configuration of the product is indicative of S_N2 mechanism:



racemization of the configuration of the product is indicative of S_N1 mechanism.



EVIDENCES FROM STERIC EFFECTS

- In S_N2 substitution, CH_3Br reacts 20-30 times faster than 1° -alkyl bromides, which in turn react about 20 times faster than 2° -alkyl bromides, and 3° -alkyl bromides are essentially unreactive or undergo elimination.
- β -alkyl substitution decreases the rate of substitution, as witnessed by the failure of neopentyl bromide, $(\text{CH}_3)_3\text{CCH}_2\text{Br}$ (a 1° -bromide), to react.
- This shows bulky substrates are sterically hindered to react by S_N2 mechanisms.

S_N1 OR S_N2

Weak nucleophile favors an S_N1 pathway.

Polar solvents favor an S_N1 pathway (e.g. polar protic solvents such as water/acetone).

Highly substituted substrate will follow an S_N1 pathway.

Very good leaving groups, such as triflate, tosylate and mesylate, favor S_N1 .

APPLICATIONS OF SUBSTITUTION REACTIONS

- **Alcohol synthesis**
- **Alkyl halide synthesis**
- **Ether synthesis**
- **Carboxylic acids synthesis**
- **Alkynes, Alkenes and Alkanes synthesis**
- **Amines synthesis**
- **Alcohol synthesis (Epoxide ring opening)**
- **Carboxylic acid and ketone synthesis (Malonic and acetoacetic ester synthesis)**

ALCOHOL SYNTHESIS: REACTION OF ALKYL HALIDES WITH DILUTE AQUEOUS BASE

1°- and 2°-alkyl halides react with dilute aqueous base to form alcohols in a nucleophilic substitution reaction.

In 3°-alkyl halides, elimination would predominate over substitution and alkene would be a major product.



ALKYL HALIDE SYNTHESIS FROM ALCOHOLS

Despite the fact that alkyl halides can be converted into alcohols as described above, the more usual practice is to produce alkyl halides from alcohols via nucleophilic substitution reaction as indicated below.

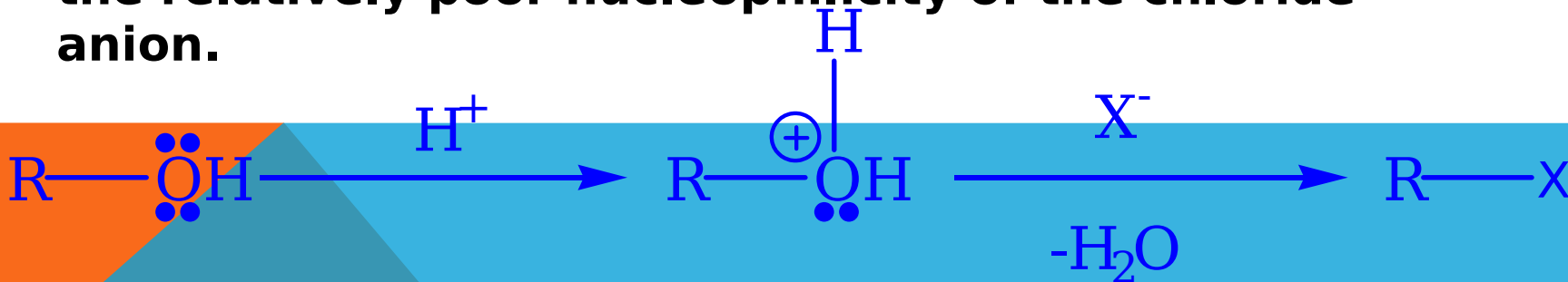


ALKYL HALIDE SYNTHESIS CONTINUED

The displacement of a hydroxyl group requires prior protonation of the oxygen, which facilitates heterolytic cleavage of the carbon-oxygen bond by converting the hydroxyl group, which is a poor leaving group in to oxonium cation, which is a good leaving group:

This method is commonly used to synthesize alkyl bromides and iodides.

Chlorides are not synthesized by this method because of the relatively poor nucleophilicity of the chloride anion.



SUMMARY OF REACTION OF ALCOHOLS WITH HYDROGEN HALIDES

Reaction type: Nucleophilic Substitution (S_N1 or S_N2)

When treated with HBr or HCl alcohols typically undergo a nucleophilic substitution reaction to generate an alkyl halide and water.

Alcohol relative reactivity order : $3^\circ > 2^\circ > 1^\circ > \text{methyl}$.

Hydrogen halide reactivity order : $\text{HI} > \text{HBr} > \text{HCl} > \text{HF}$ (paralleling acidity order).

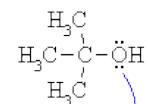
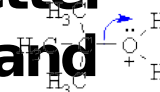
Reaction usually proceeds via an S_N1 mechanism.

Methanol and primary alcohols will proceed via an S_N2 mechanism since these have highly unfavorable carbocations.

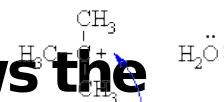
The reaction of alcohols with HCl in the presence of ZnCl_2 (catalyst) forms the basis of the Lucas test for alcohols.

S_N1 MECHANISM FOR REACTION OF ALCOHOLS WITH HBR

Step 1: An acid/base reaction. Protonation of the alcoholic oxygen to make a better leaving group. This step is very fast and reversible. The lone pairs on the oxygen make it a Lewis base.



Step 2: Cleavage of the C-O bond allows the loss of the good *leaving group*, a neutral water molecule, to give a carbocation intermediate. This is the rate determining step (bond breaking is endothermic)



Step 3: Attack of the nucleophilic bromide ion on the electrophilic carbocation creates the alkyl bromide.



PROBLEMS

- (a) Alcohols react with HBr to give alkyl bromides, whereas there is no reaction with NaBr. Why ?**
- (b) If an alcohol is reacted with NaBr / H_2SO_4 then the alkyl bromides form. Why ?**

ALKYL CHLORIDES

Alkyl chlorides are synthesized by using phosphorous trichloride or thionyl chloride in pyridine as solvent:

Thionyl chloride is a particularly convenient reagent to use since the by products can easily be removed.

HCl can be neutralized by the pyridine and the SO₂ is expelled as a gas.



MECHANISM

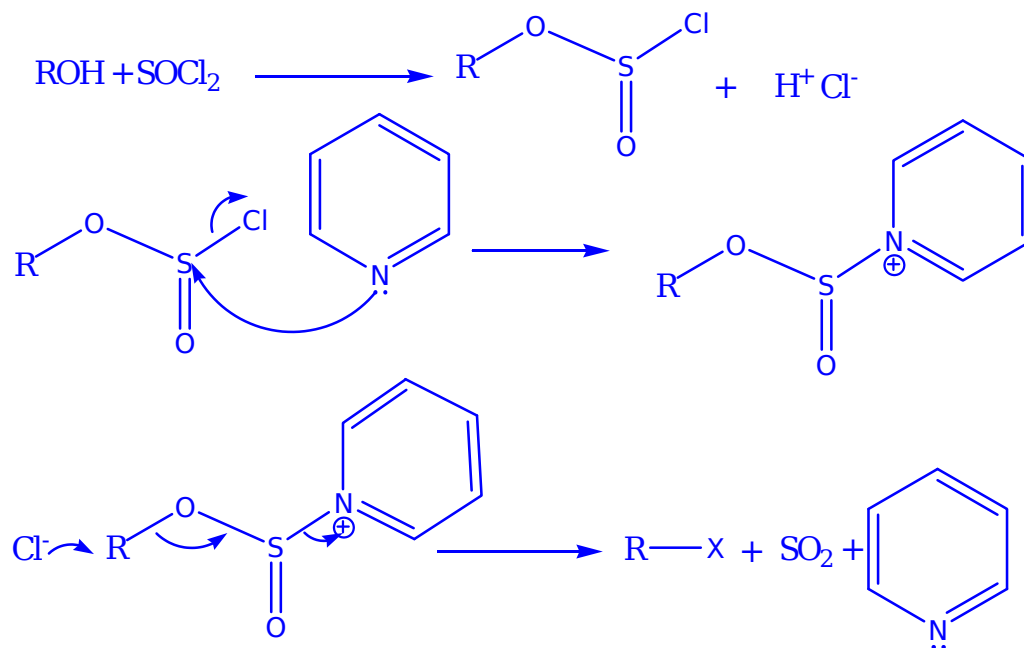
The mechanism is a three step process:

In the first step, the hydroxyl group is converted into a good leaving group, a chlorosulfite group forming HCl as byproduct, which is subsequently neutralized by the pyridine

In a second step, pyridine displaces the chloride from the chlorosulphite generating even a better leaving group , a quaternary ammonium ion.

The third step is a S_N2 nucleophilic substitution with chloride as the nucleophile leading to inversion of configuration.

THE MECHANISM



ETHER SYNTHESIS

Depending on the nature of the alkyl groups bonded to the oxygen, ethers can be classified as symmetrical or unsymmetrical.



symmetrical

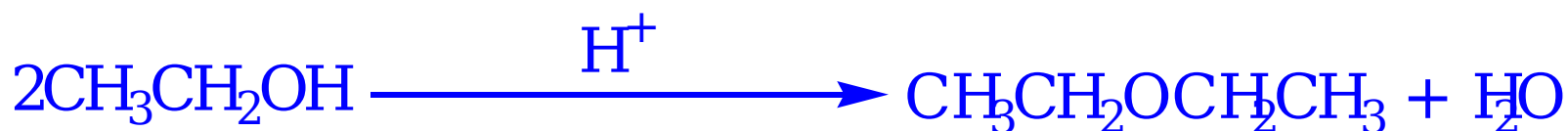
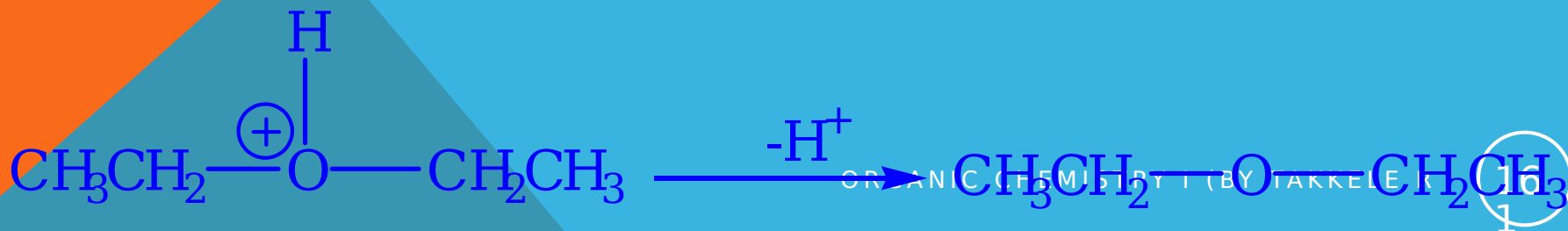


unsymmetrical

Symmetrical ethers can be prepared from alcohol under acidic condition via nucleophilic substitution reaction as described for synthesis of diethyl ether from ethanol:

SYMMETRICAL ETHER SYNTHESIS

Symmetrical ethers can be prepared from alcohol under acidic condition via nucleophilic substitution reaction as described for synthesis of diethyl ether from ethanol:

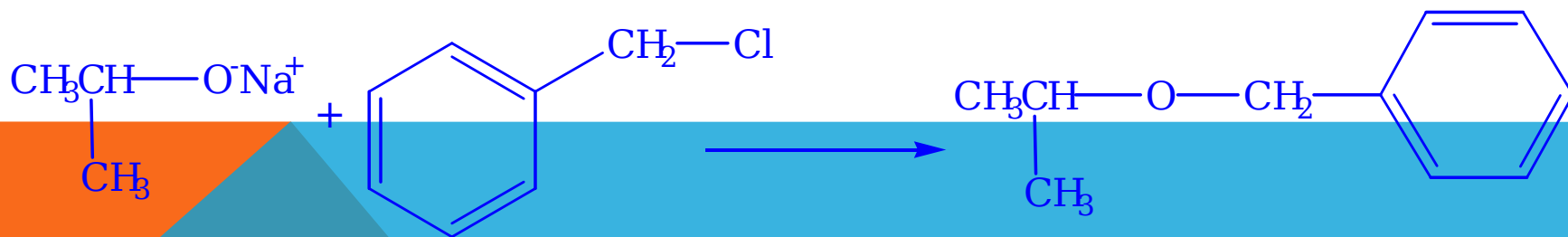


The acid used for this reaction is sulphuric acid.

HCl or HBr which would give the corresponding alkyl halides as described earlier can not be used

WILLIAMSON SYNTHESIS

Williamson synthesis as described in chapter 3 can be used for the synthesis of unsymmetrical ethers as illustrated below for preparation of isopropyl 1-phenyl methyl ether:



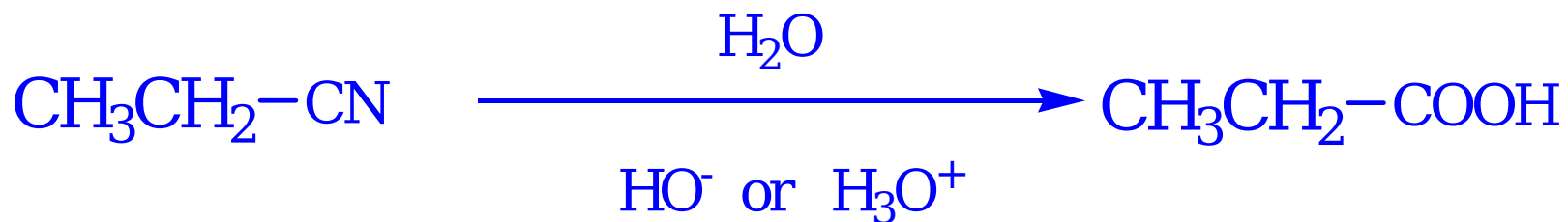
CARBOXYLIC ACIDS SYNTHESIS

Carboxylic acids cannot be prepared directly by nucleophilic substitution at a saturated carbon.

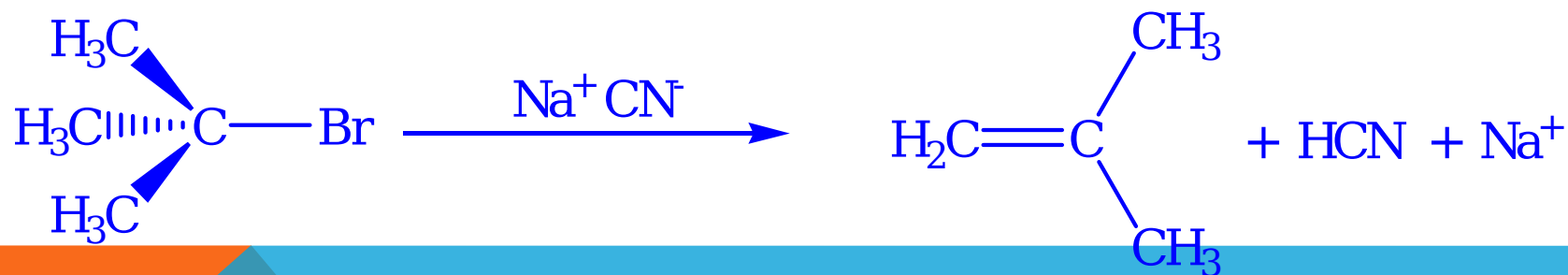
However, alkyl *nitriles* can be prepared by an S_N2 reaction between a primary or secondary halide and sodium cyanide:



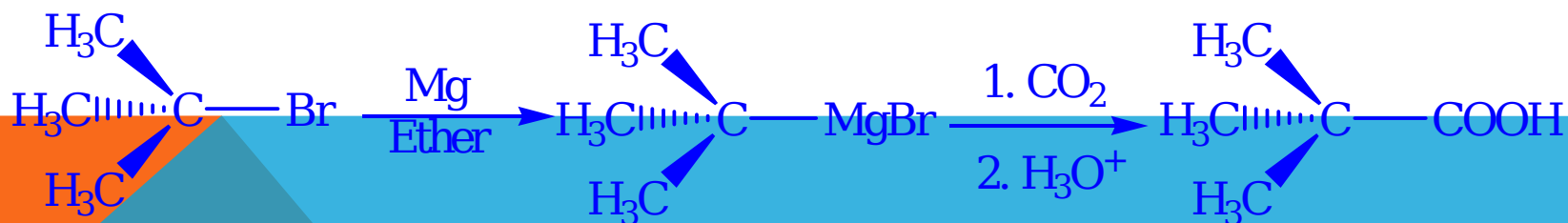
The nitrile group can then be hydrolyzed to a carboxylic acid in either strong acid or strong base:



Tertiary halides give too much elimination if treated with sodium cyanide and cannot be used to prepare carboxylic acids by this method:



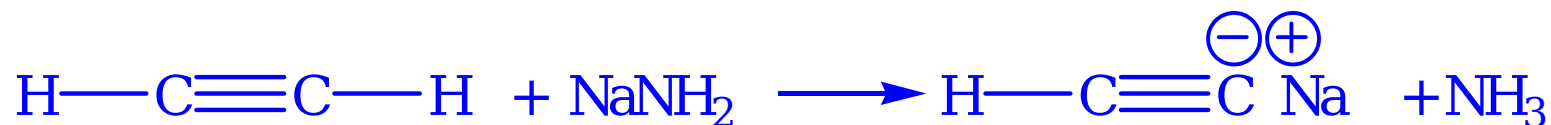
An alternative and preferable method of converting alkyl halides into carboxylic acids is carbonation of Grignard reagent as described in Chapter 3. This method works well even with tertiary halides:



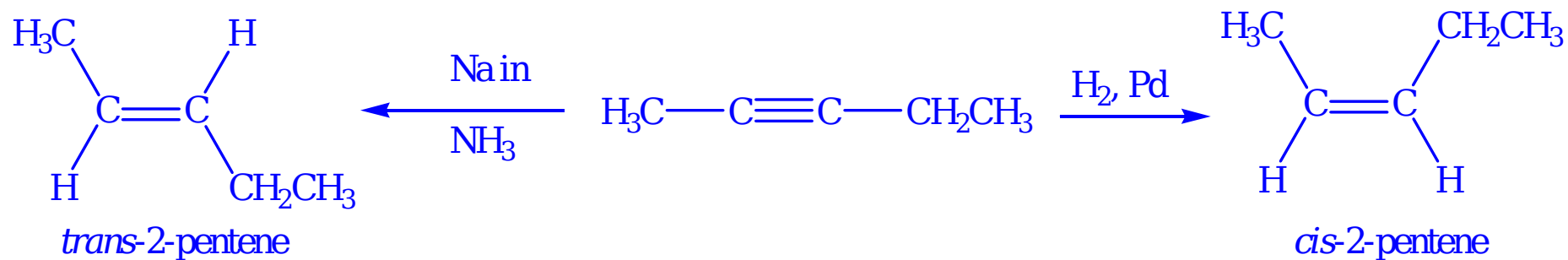
ALKYNES, ALKENES AND ALKANES

Alkynes can be prepared by nucleophilic substitution reaction in which the nucleophile is the acetylide anion and the substrate is an alkyl halide as described in Chapter 3.

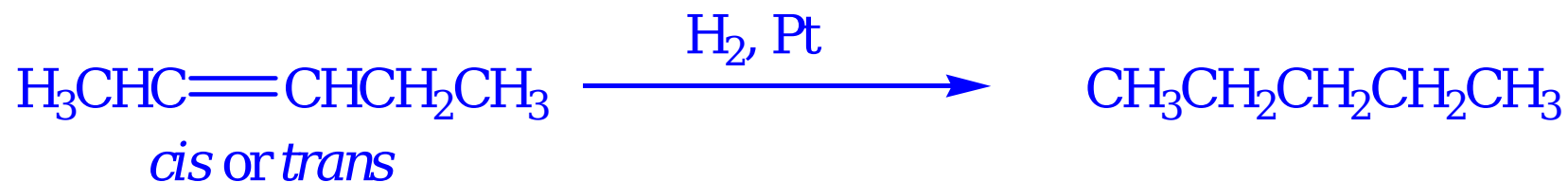
The reaction is known as alkylation of acetylide.



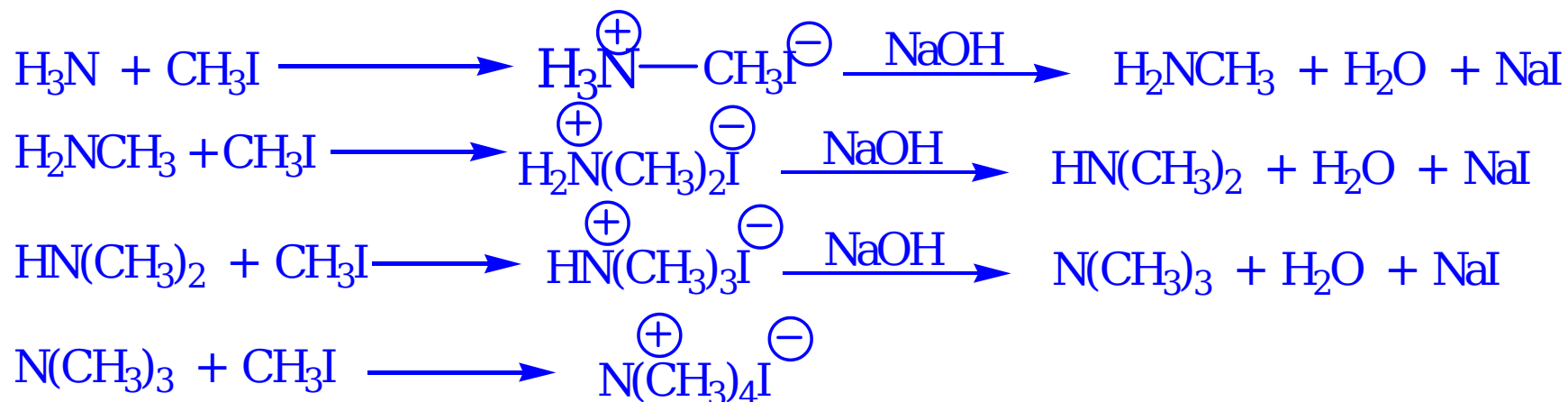
ALKENES FROM ALKYNES: REDUCTION



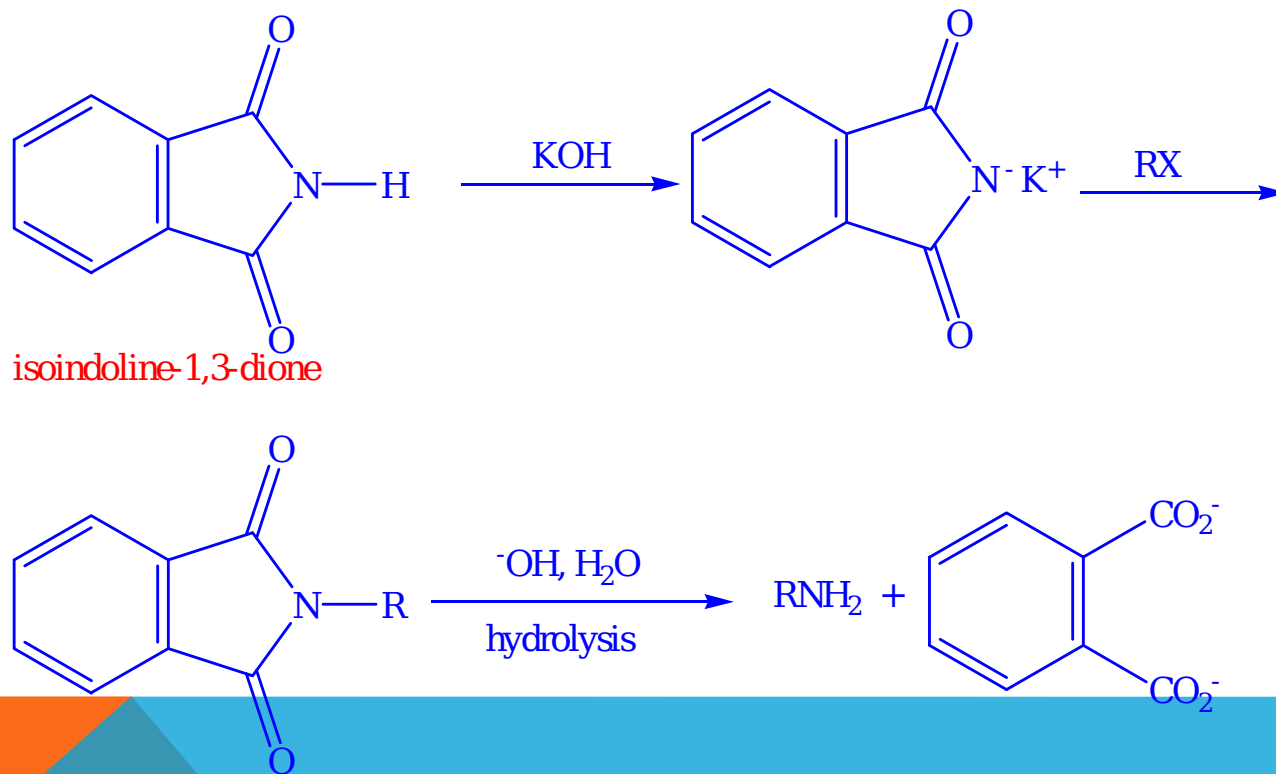
ALKANES FROM ALKENES: REDUCTION



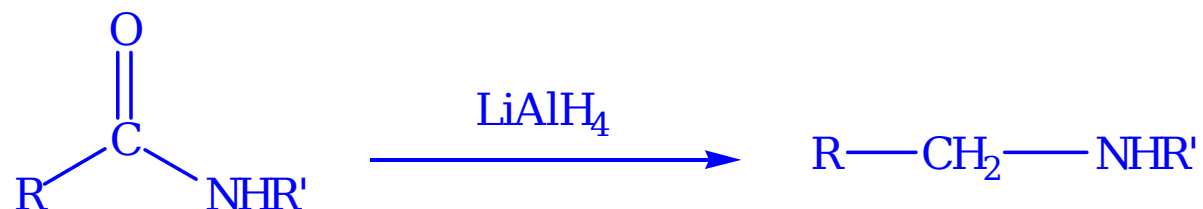
AMINES SYNTHESIS: ALKYLATION OF AMMONIA



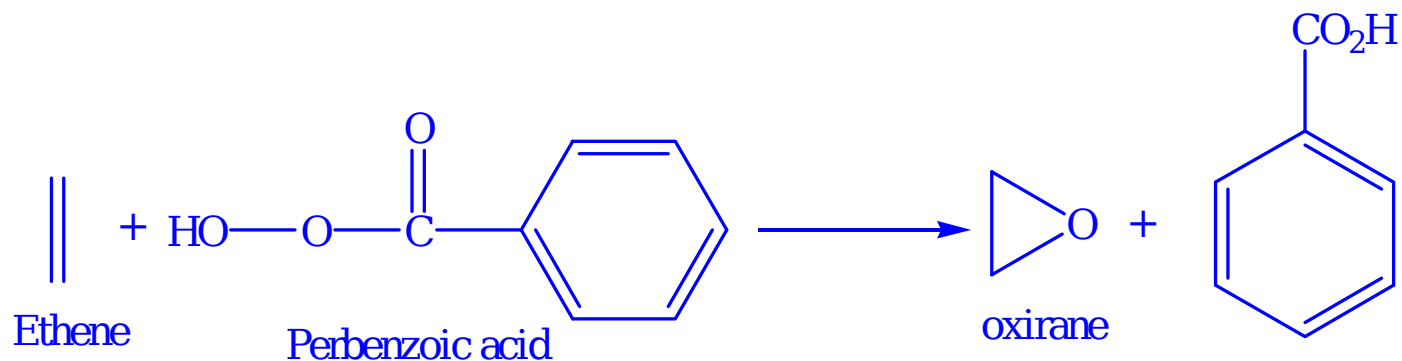
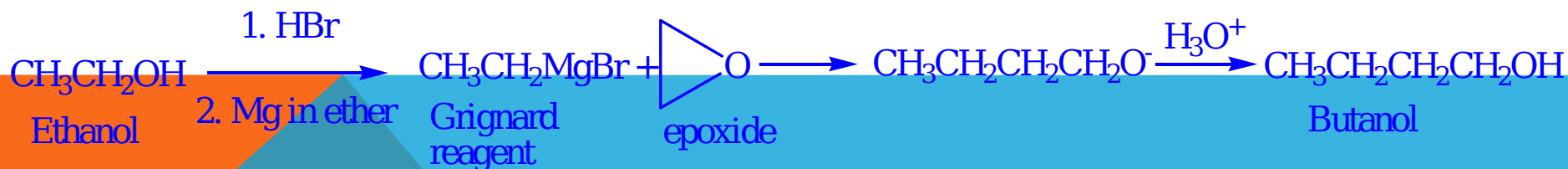
GABRIEL SYNTHESIS: (1° AMINE): ALKYLATION



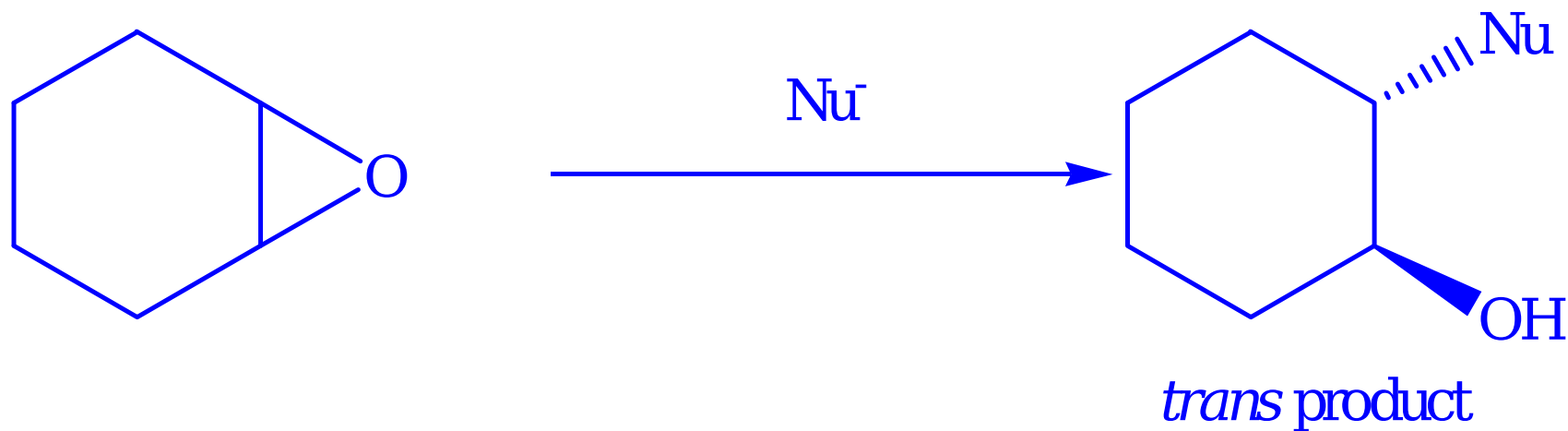
REDUCTION OF AMIDES



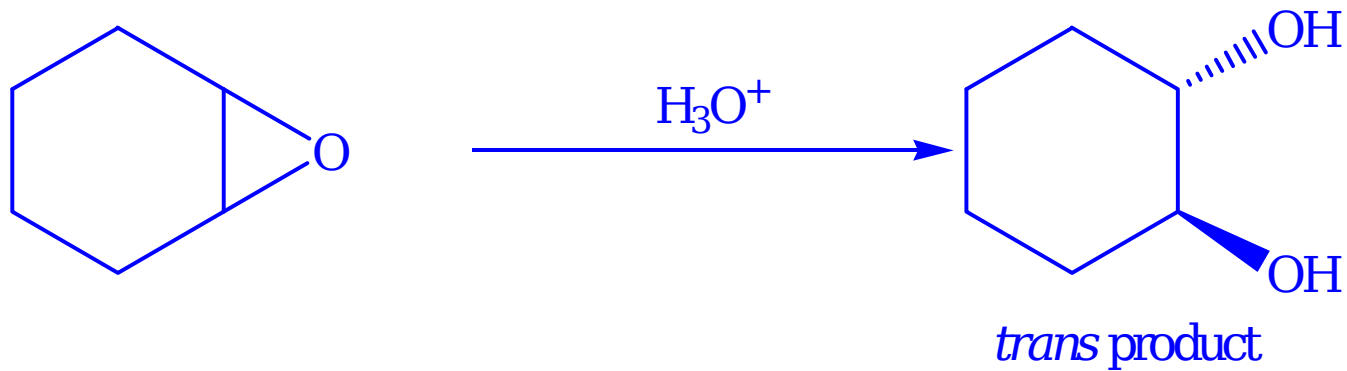
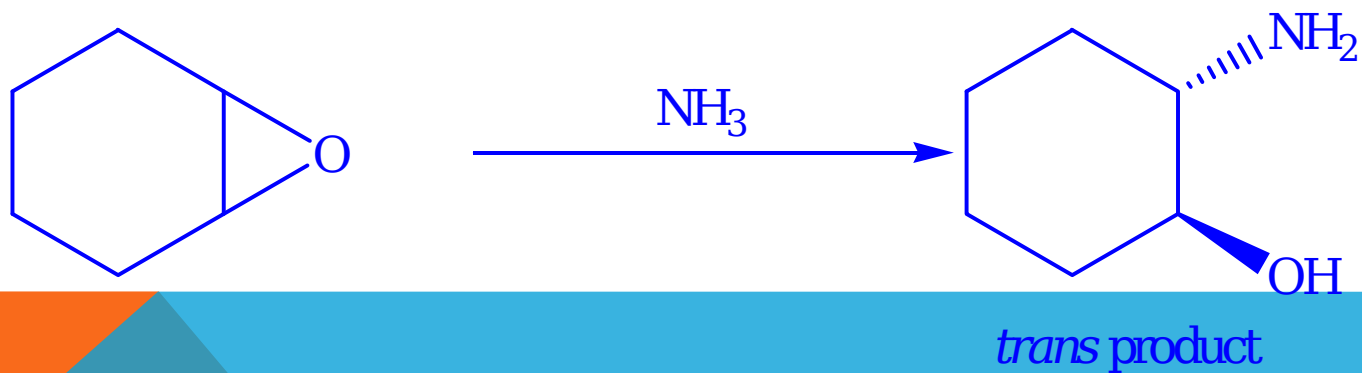
ALCOHOL SYNTHESIS BY EPOXIDE RING OPENING



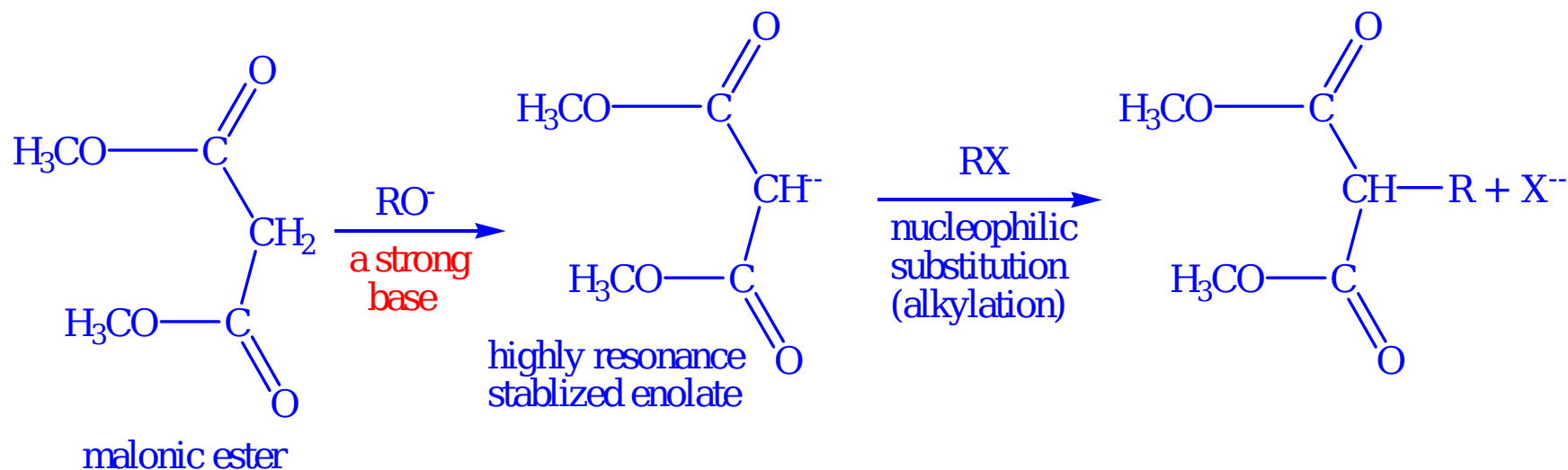
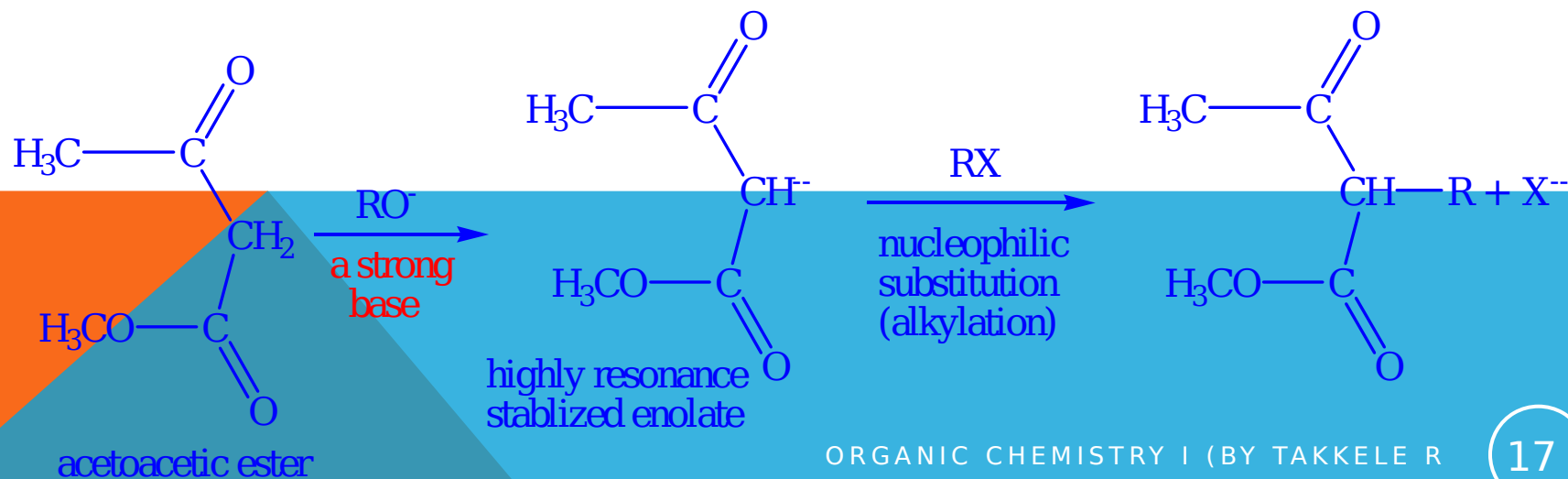
RING EPOXIDES



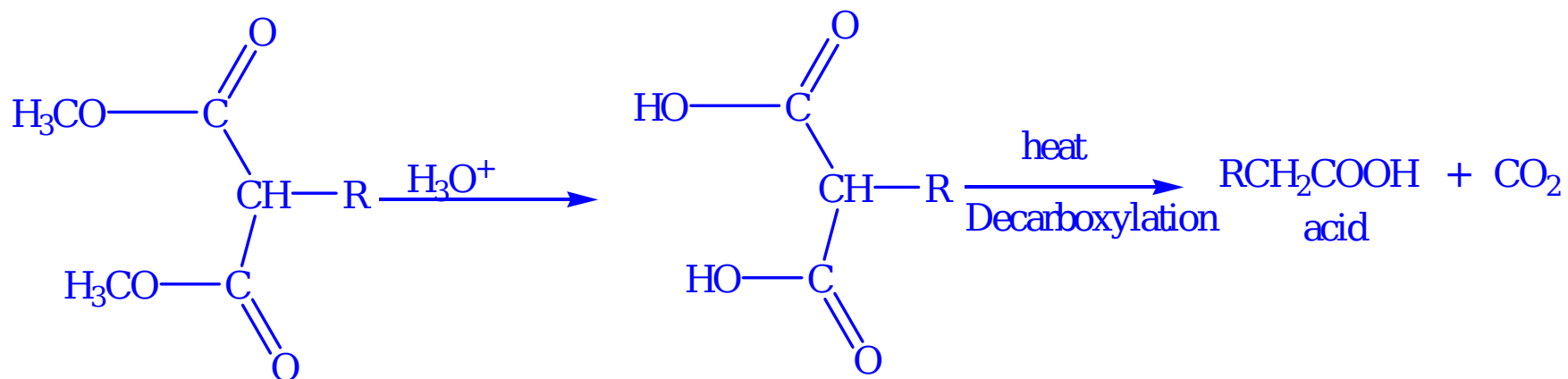
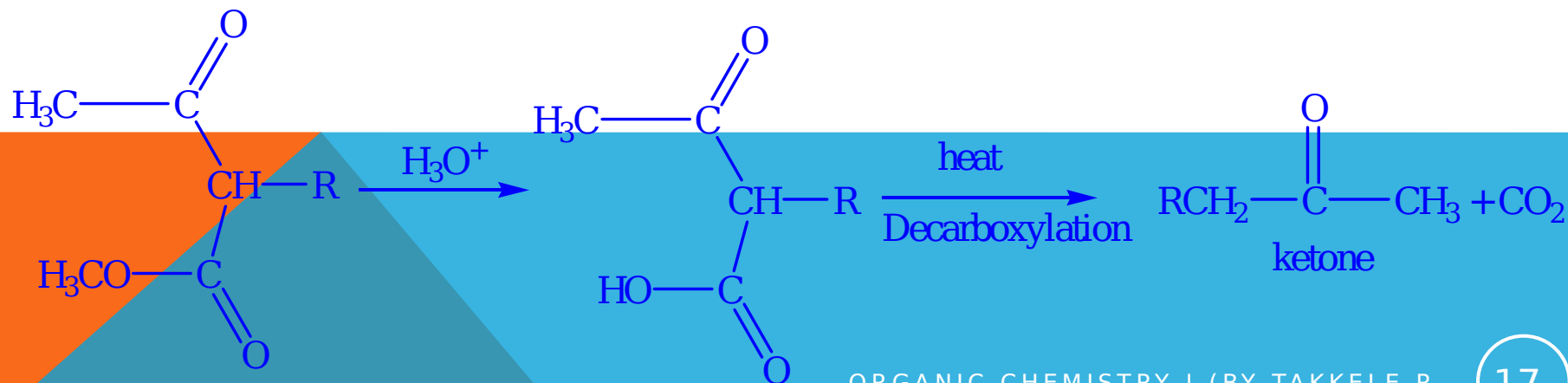
EXAMPLES



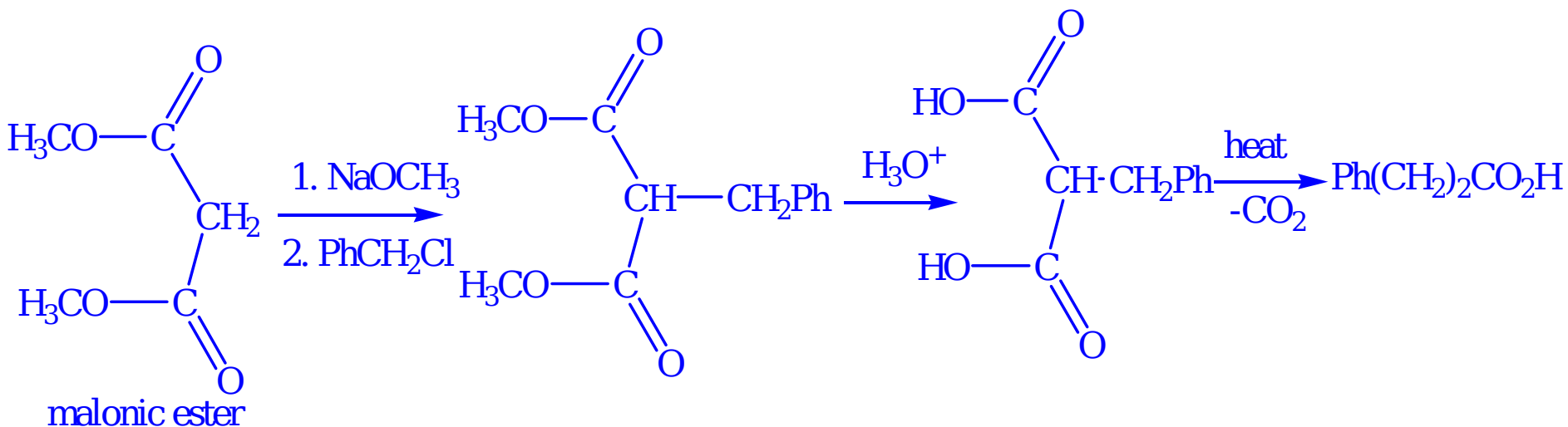
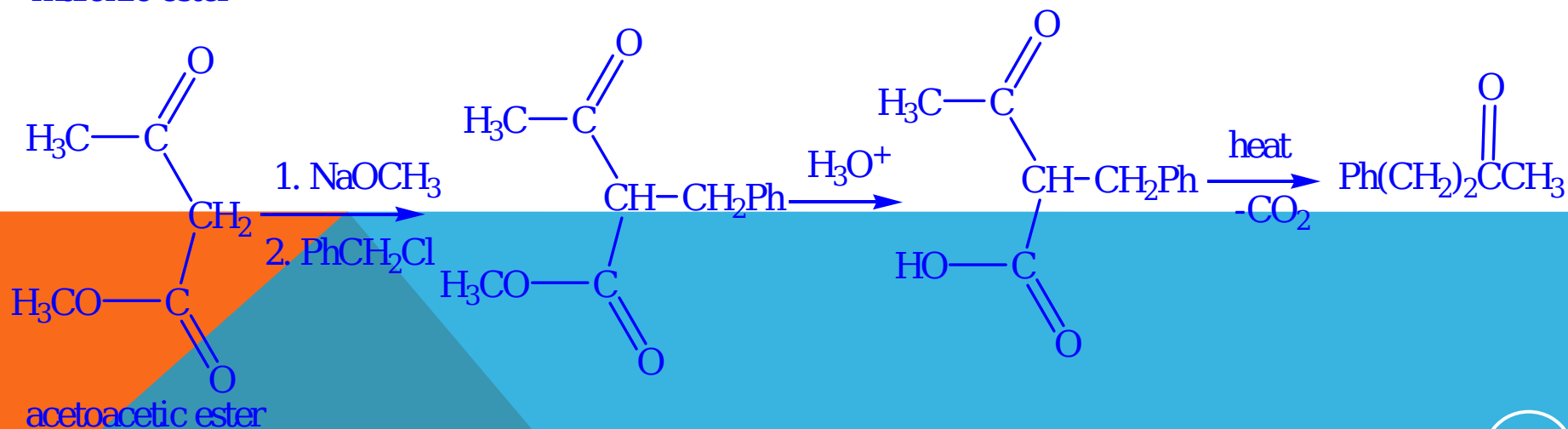
MALONIC & ACETOACETIC ESTERS: ALKYLATIONS



DECARBOXYLATION: LOSS OF CO₂ BY B-DIKETOACIDS



SPECIFIC EXAMPLES



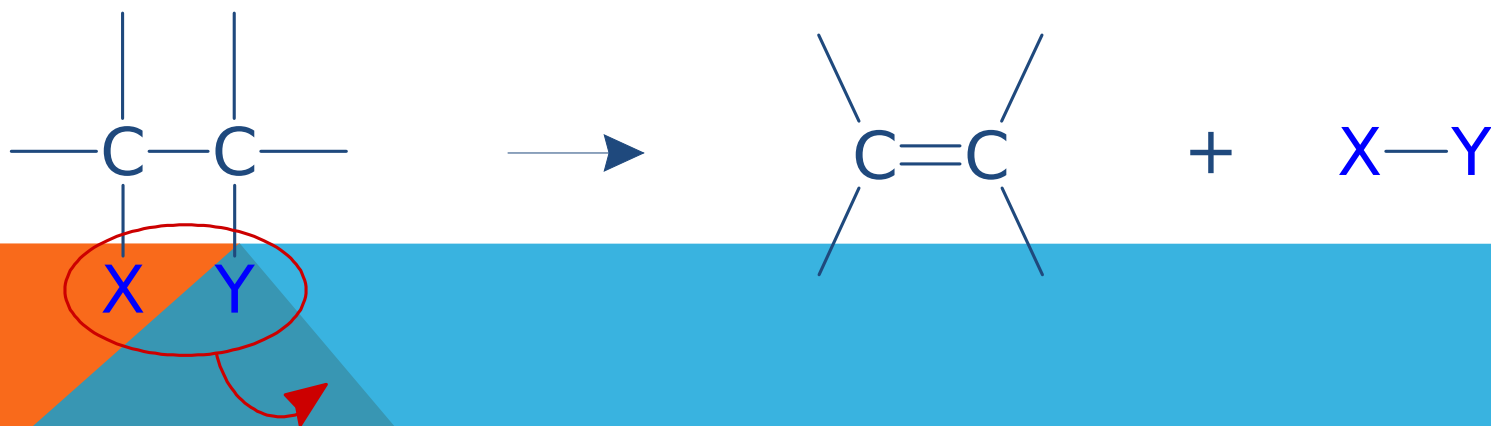
CHAPTER 5

ELIMINATION REACTIONS

ELIMINATION REACTIONS

2nd of the fundamental heterolytic organic reactions.

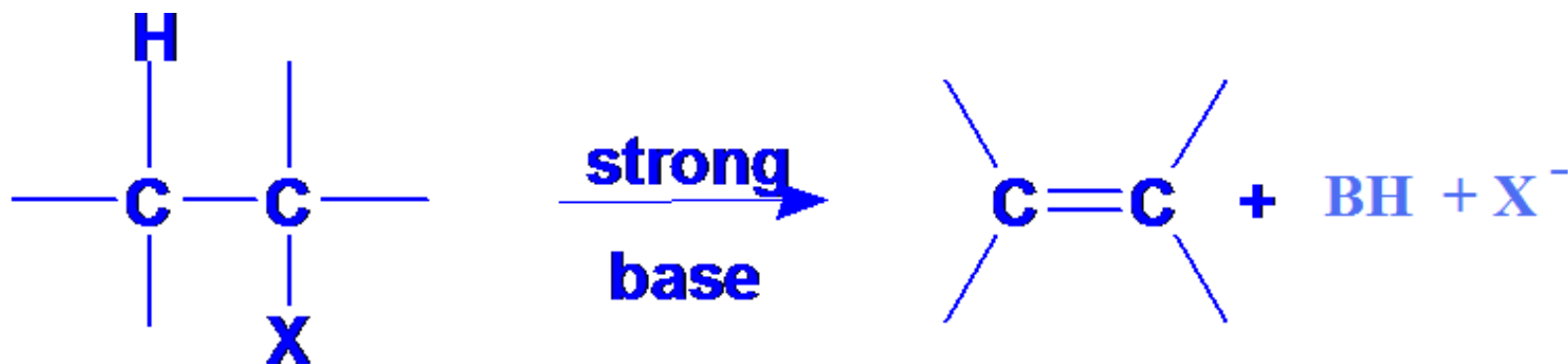
A small fragment is ejected resulting in formation of unsaturation.



MAIN TYPES OF ELIMINATION REACTIONS

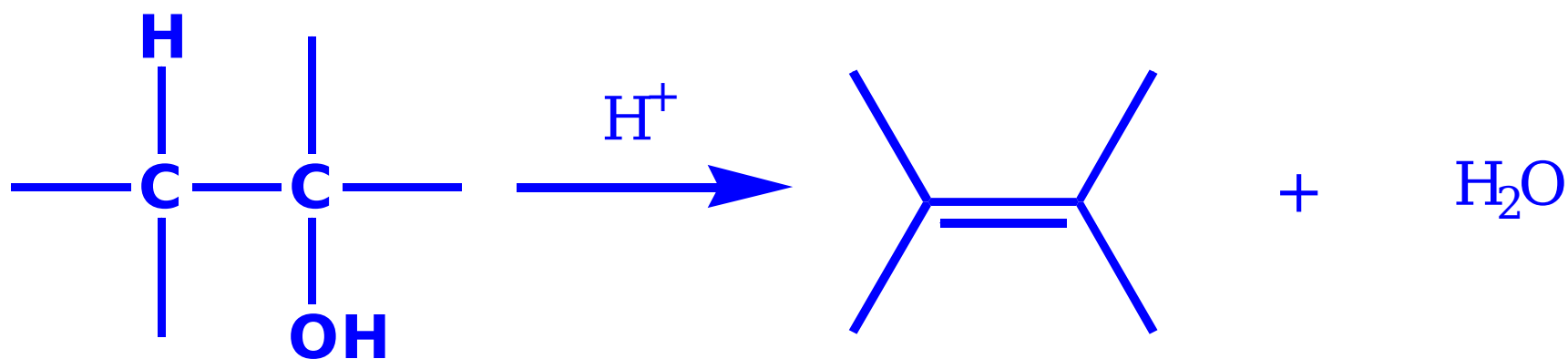
- **Base promoted dehydrohalogenation (-HX) of alkylhalides**
- **Acid catalyzed dehydration (-H₂O) of alcohols**
- **Elimination of vicinal dihalides**
- **Intramolecular eliminations such as**
 - elimination from quaternary ammonium hydroxides,
 - cope elimination and
 - ester pyrolysis

DEHYDROHALOGENATION (-HX)

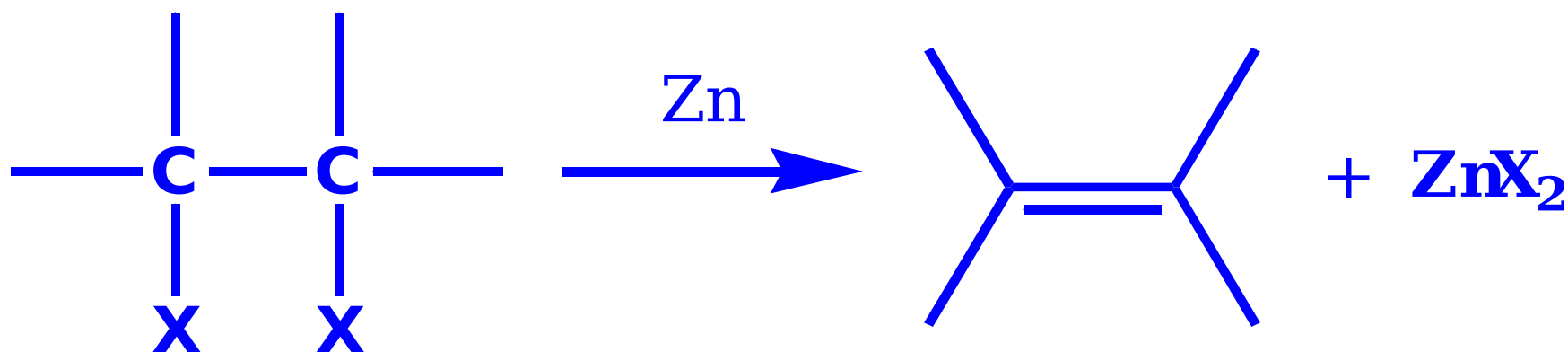


X = Cl, Br, I

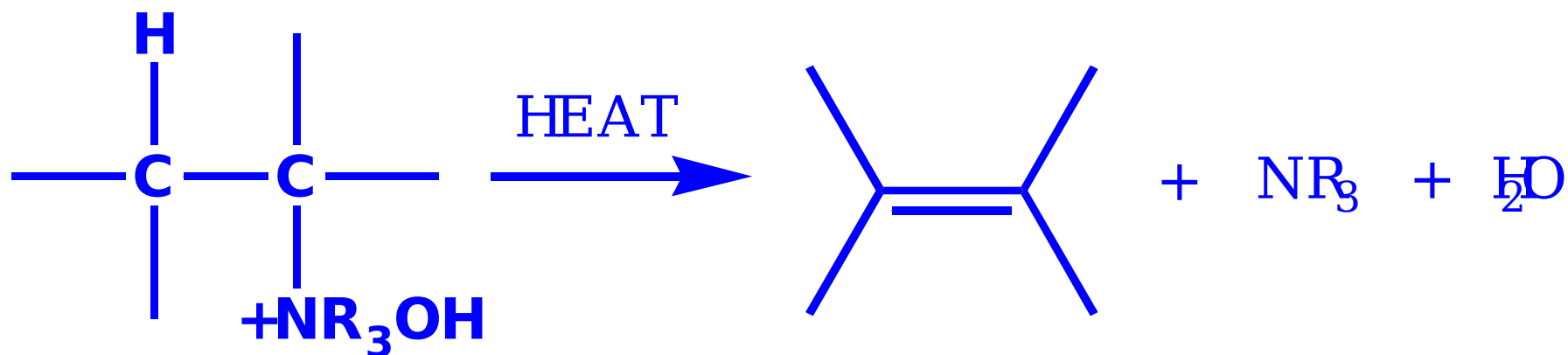
DEHYDRATION (-H₂O)



VICINAL DIHALIDES ELIMINATION(-X₂)



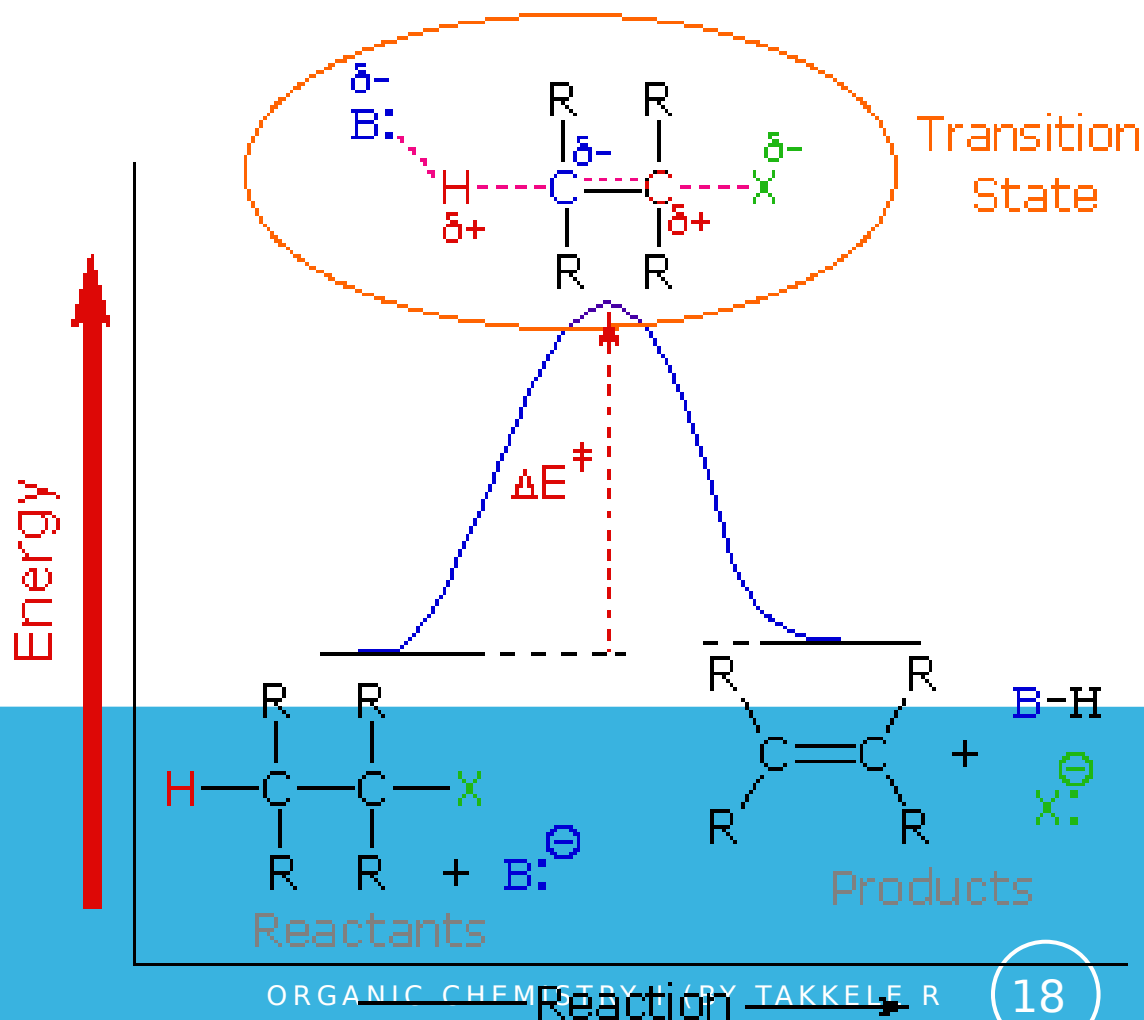
ELIMINATION FROM QUATERNARY AMMONIUM HYDROXIDES



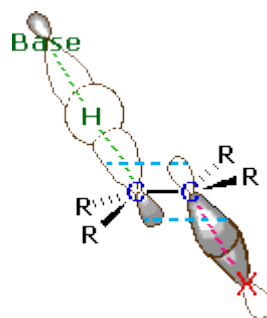
MECHANISMS OF ELIMINATIONS:

THE E2, ELIMINATION BIMOLECULAR MECHANISM

- **E2** a single-step bimolecular mechanism ,
- **Simultaneous bond breaking and making,**
- **Regioselectivity due to *trans coplanar* arrangement of the base and the two groups being eliminated**

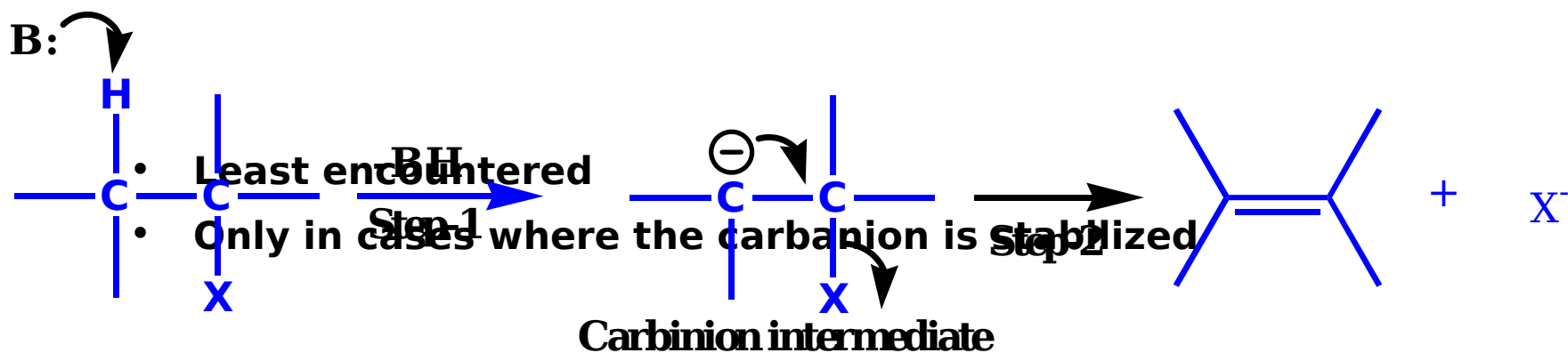


STEREOCHEMISTRY OF E2 ELIMINATIONS



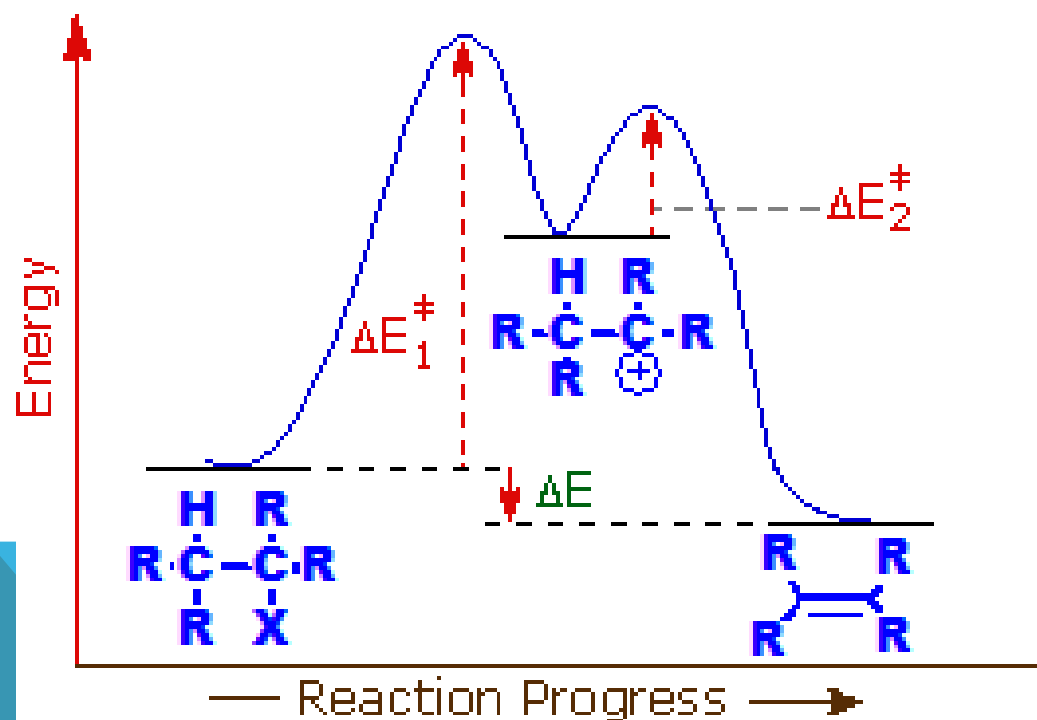
THE E1CB MECHANISM:
ELIMINATION FROM A CARBANION

- **Elimination from a carbanion**
- **A two step process**



THE E1 MECHANISM

A two step mechanism involving a carbenium ion intermediate like S_N1 mechanism



E1 OR E2?

EXPERIMENTAL EVIDENCES FOR A MECHANISM

Kinetic Evidences

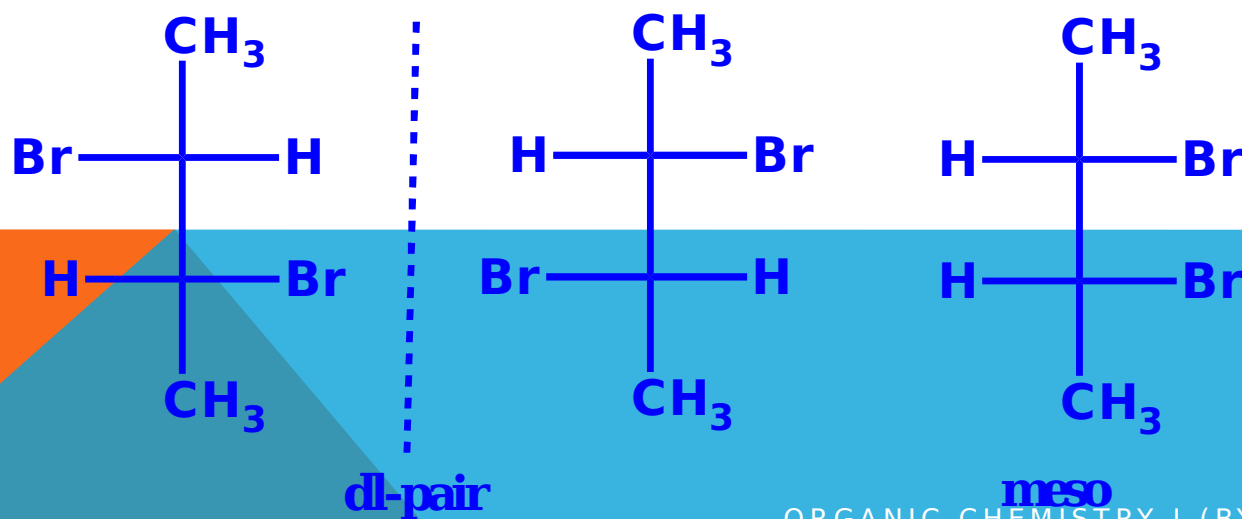
- If second order, bimolecular E2
- If first order, unimolecular E1

Stereochemical Evidences

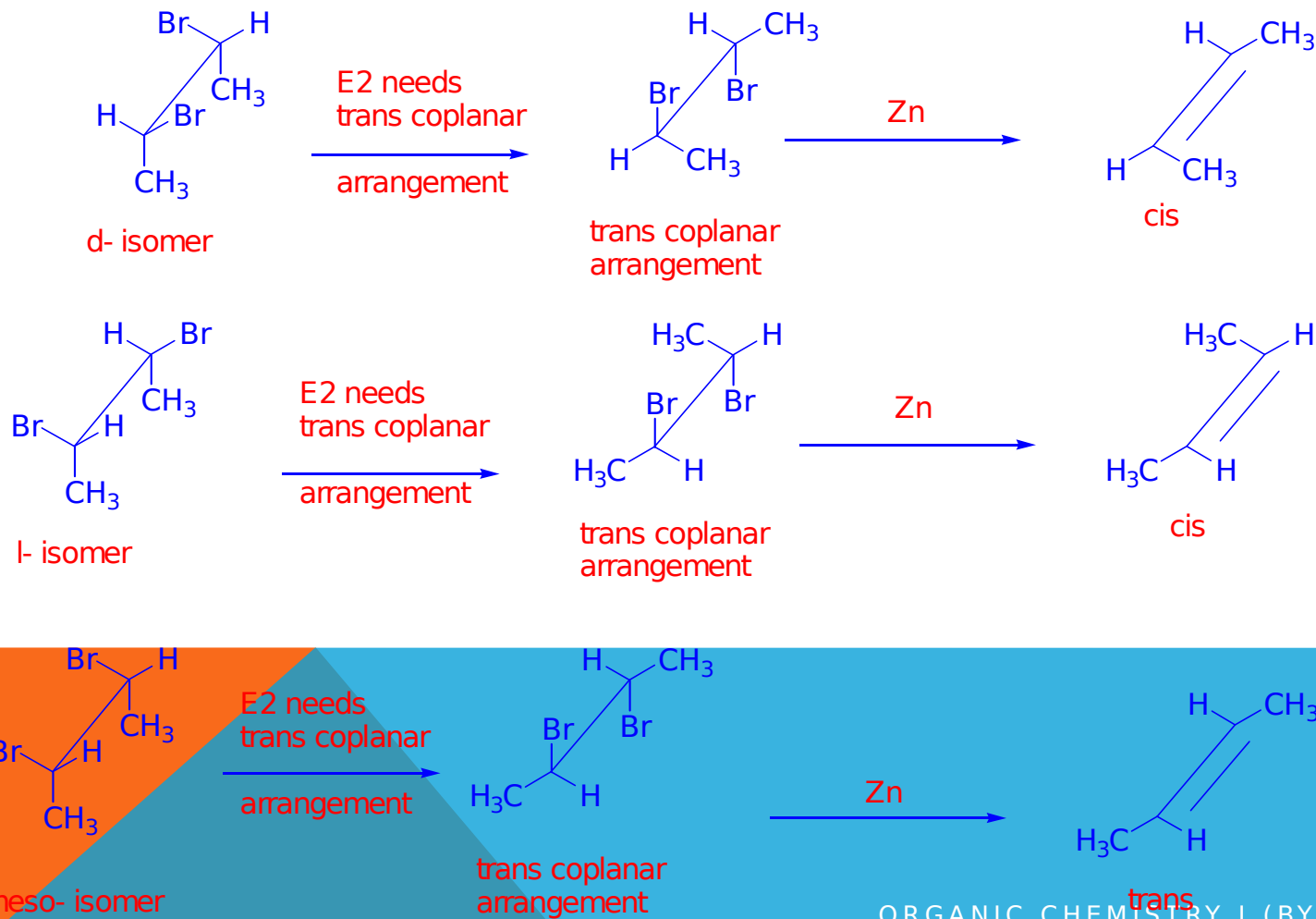
- If an elimination reaction proceeds by trans coplanar geometry, then it is E2

ELIMINATION FROM 2,3-DIBROMOBUTANE: E2

- Exists in diastereomeric forms: the **dl-pair** and **meso**.
- Can undergo vicinal dihalide elimination to give 2-butene.
- The **dl-pairs** always give *cis*-2-butene
- The **meso** gives *trans*-2-butene
- This is a clear evidence for a **trans coplanar arrangement** and an E2 mechanism.



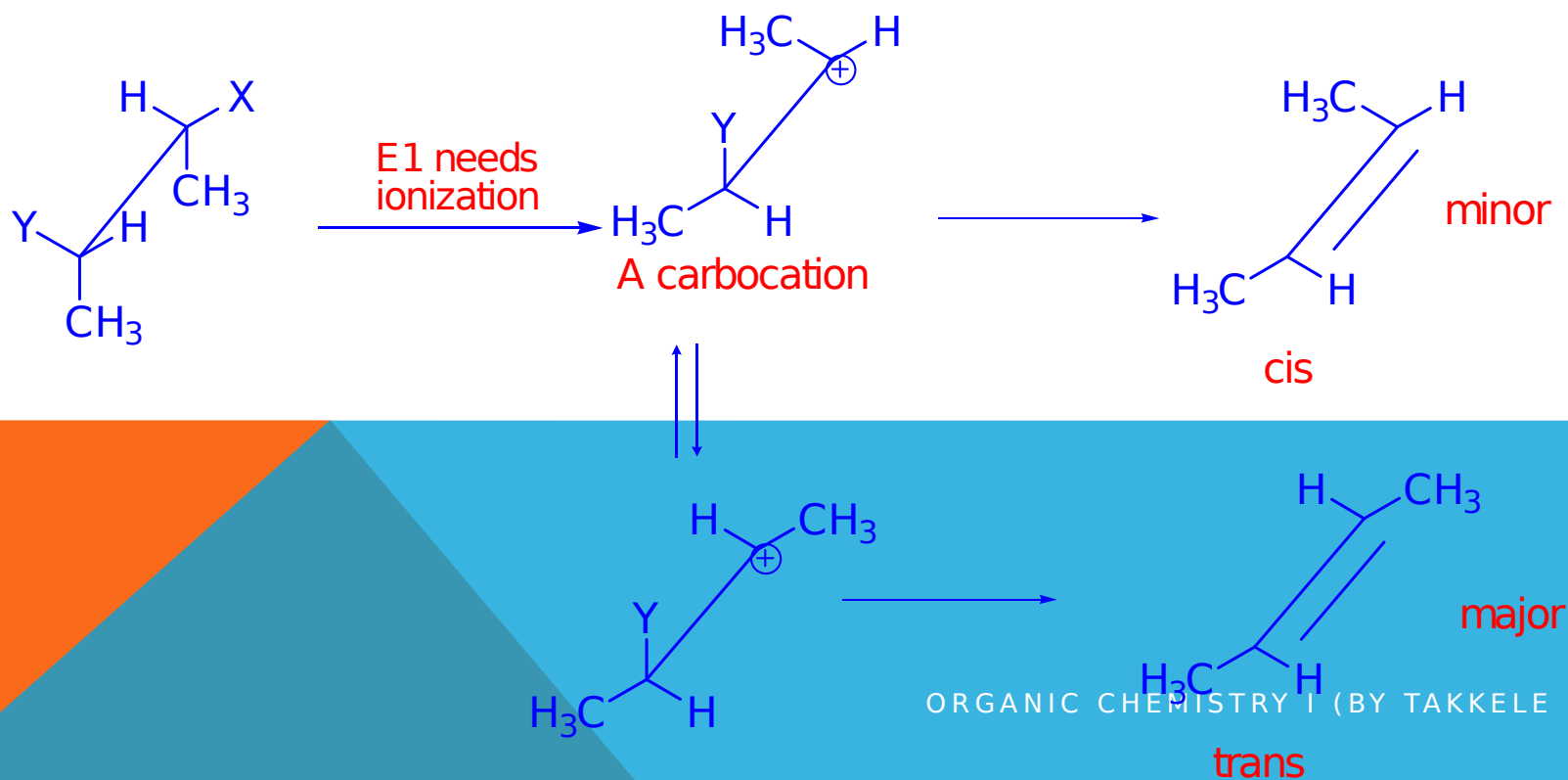
ELIMINATION FROM 2,3-DIBROMOBUTANE: E2



STEREOCHEMISTRY OF E1

Need not display stereospecificity.

Forms the more stable *trans* isomer; the *cis* would be destabilized by steric interaction of the bulky methyl groups.



E1 VERSUS E2

Strong bases such as OH^- , NH_2^- favor E2, but their absence favor E1.

Substrates that can form stable carbenium ion favor E1

Good leaving groups favor E1

Polar solvents favor E1

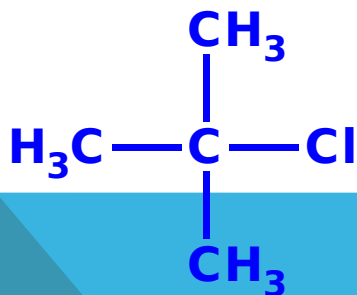
ELIMINATION VERSUS SUBSTITUTION

Bimolecular reactions

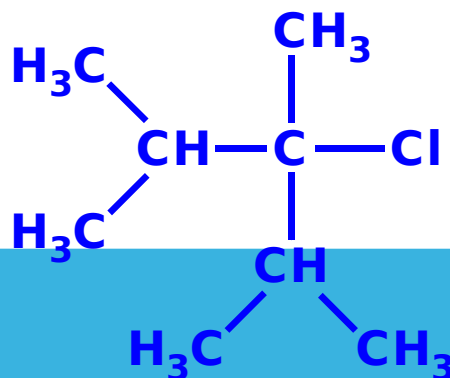
- Strong base favors elimination

Unimolecular reactions

- Bulky substrates favor elimination.

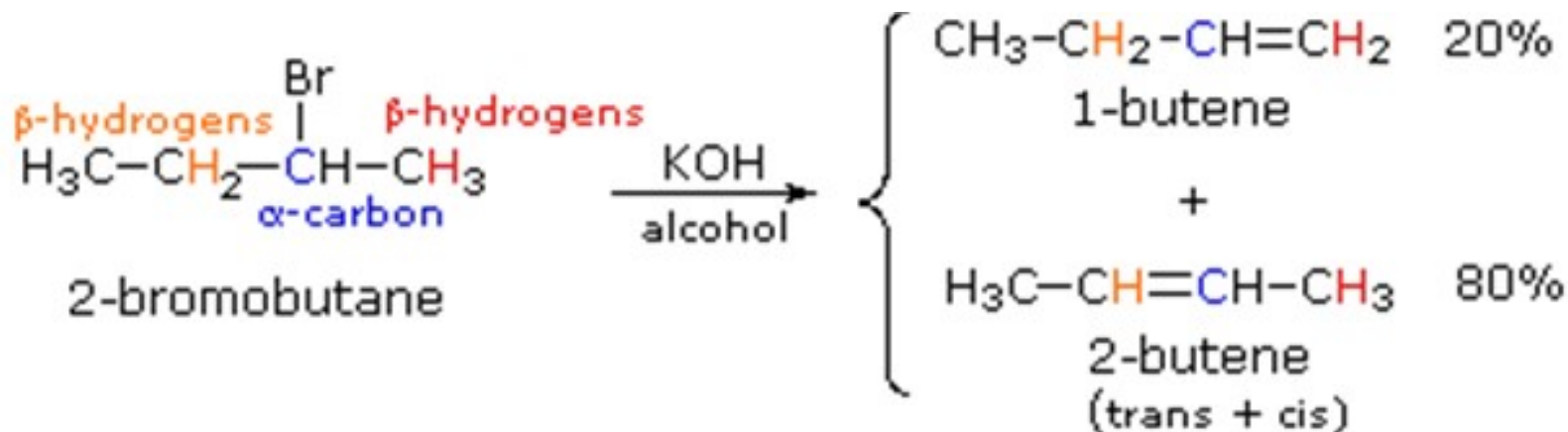


16% elimination



78% elimination

ZAITSEV'S (SAYTZEFF'S) RULE



If two or more different β -hydrogens are present, isomeric alkenes may be formed, as in 2-bromobutane.

Shows a strong **regioselectivity** favoring the more **highly substituted product** double bond, an empirical statement generally called the Zaitsev Rule.

Most bimolecular eliminations will follow Saytzeff's Rule

HOFMANN'S RULE

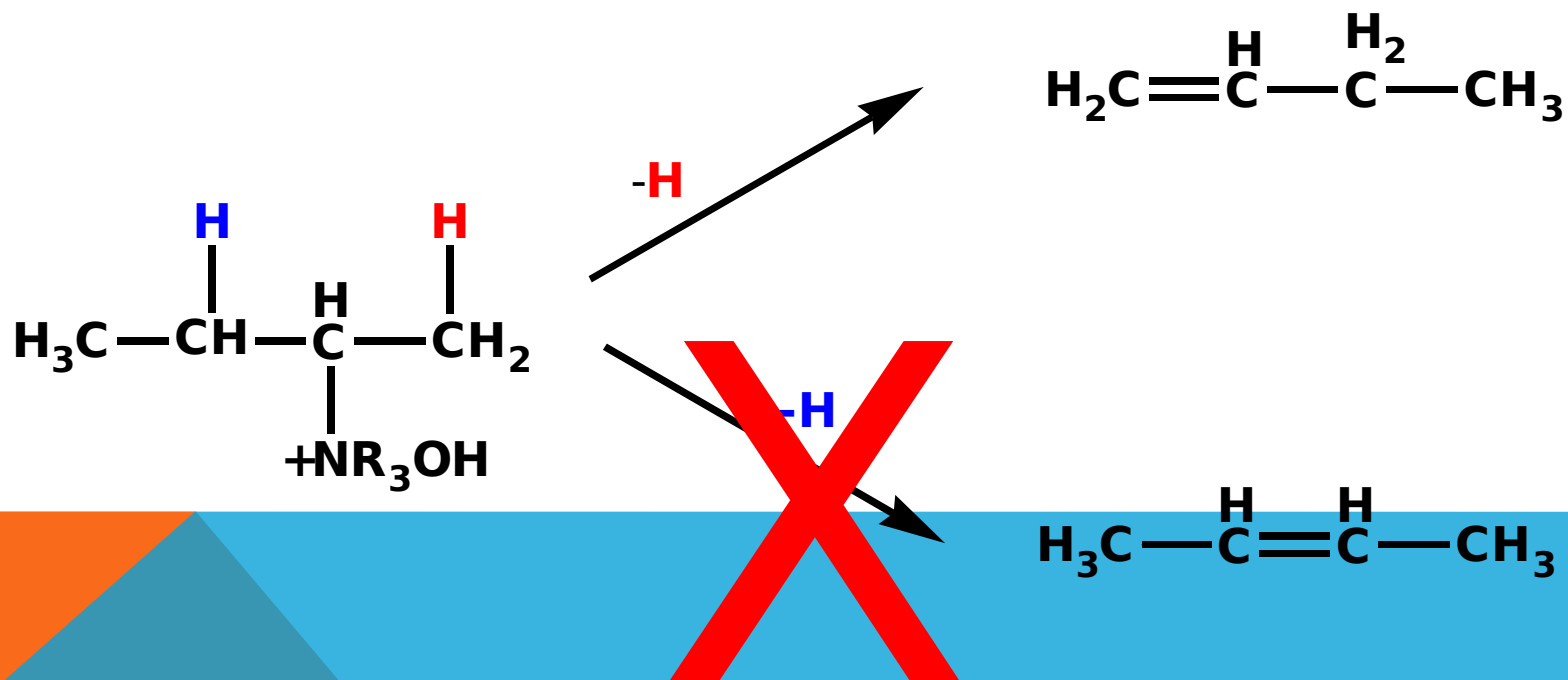
The loss of the β -hydrogen occurs preferably from the least substituted position [$-\text{CH}_3 > -\text{CH}_2-\text{R} > -\text{CH}(\text{R}_2)$].

The product alkene with fewer substituents will predominate.

Valid for all **intra-molecular** eliminations.

HOFFMAN ELIMINATION

Quaternary ammonium hydroxide undergo elimination to give a less substituted alkene.



APPLICATIONS OF ELIMINATION REACTIONS

Alcohol dehydrations (Acid catalyzed)

Dehydrohalogenation of alkyl halides: complement dehydrations

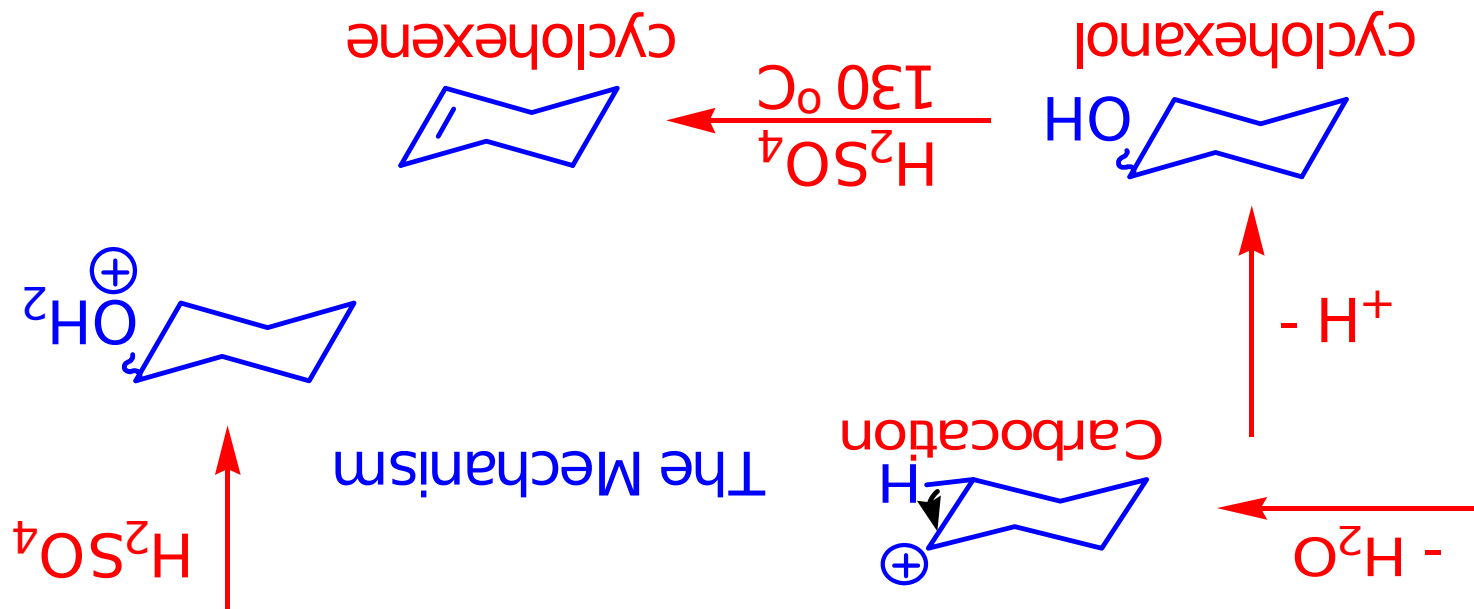
Eliminations of vicinal dihalides

Hofmann eliminations

Acetate pyrolysis

Cope reaction

ACID CATALYZED ALCOHOL DEHYDRATIONS



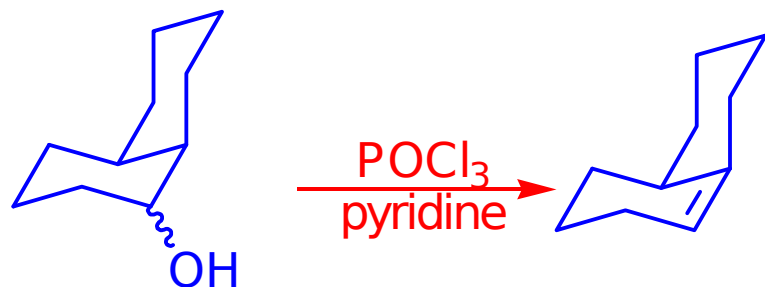
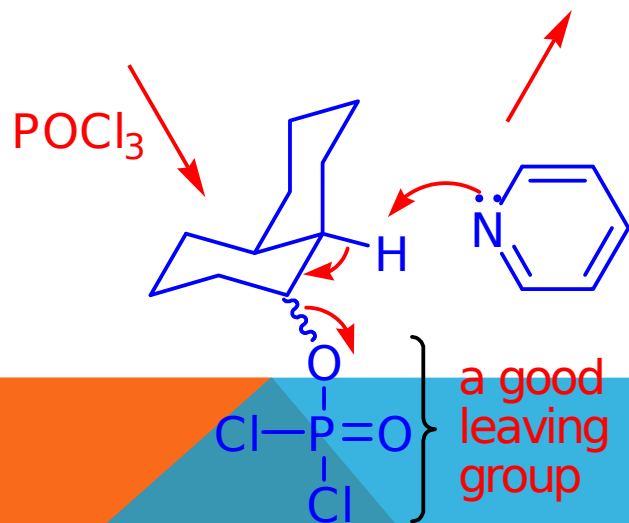
3° Alcohols dehydrate better than 2° or 1° in this method.

This follows the stability order of simple alkyl carbocations.

In practice, only small molecular weight alcohols can be dehydrated by this method. (Why?)

This is because they can be removed as soon as they form by distillation precluding any polymerization.

PHOSPHOROUS OXYCHLORIDE OR THIONYL CHLORIDE DEHYDRATION



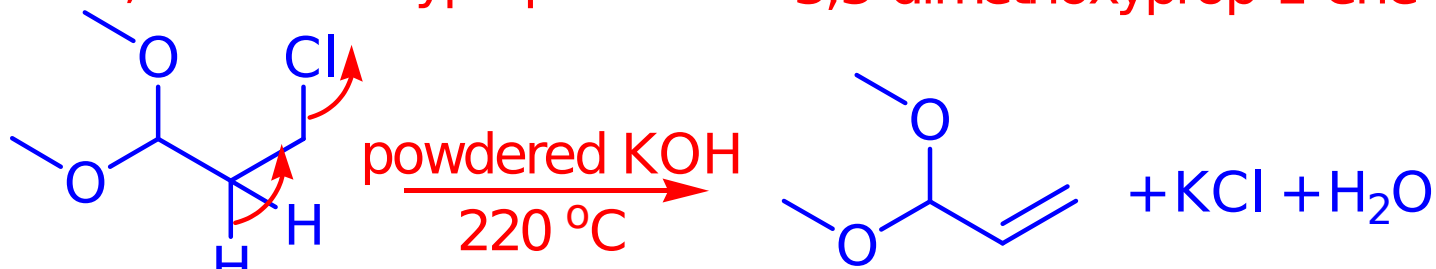
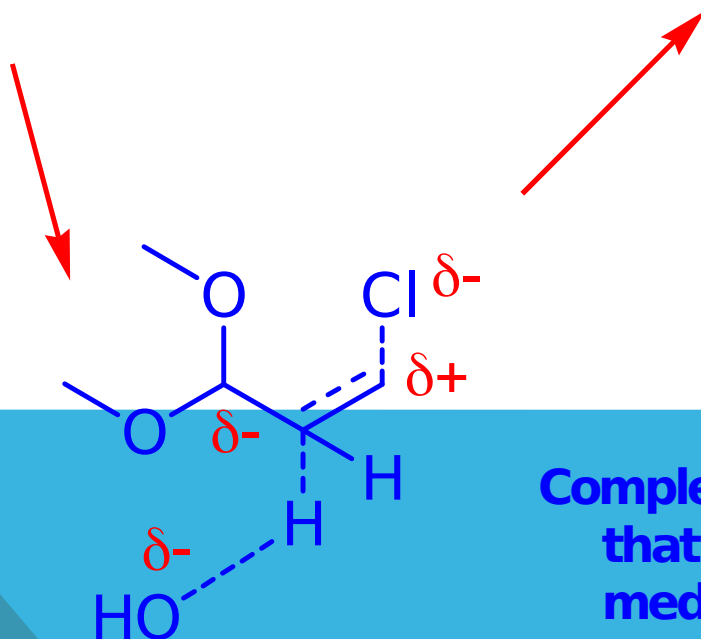
This method is used for high molecular weight alcohols, because the product alkenes would polymerize under acidic conditions.

This is because the alkene products, being high molecular weight product, are non-volatile and can't be distilled off as soon as they form.

DEHYDROHALOGENATION OF ALKYL HALIDES

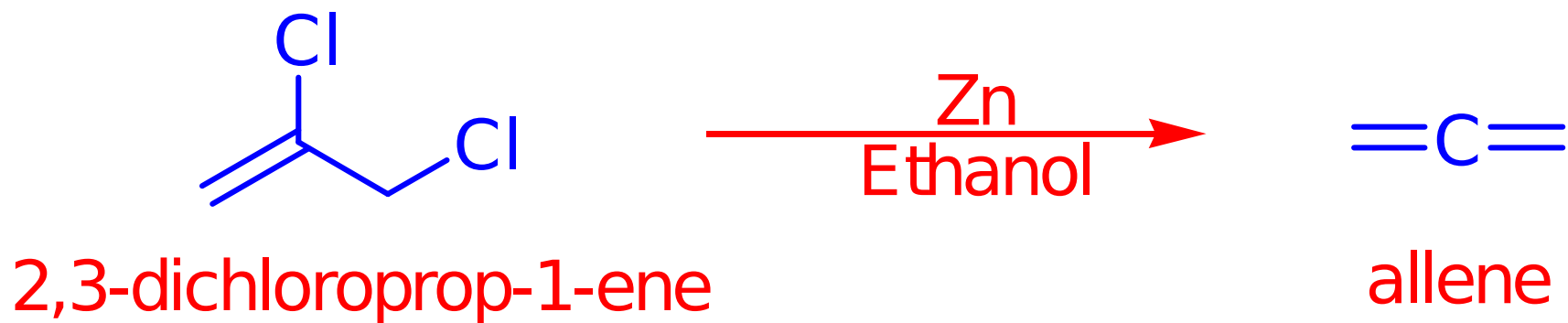
3-chloro-1,1-dimethoxypropane

3,3-dimethoxyprop-1-ene

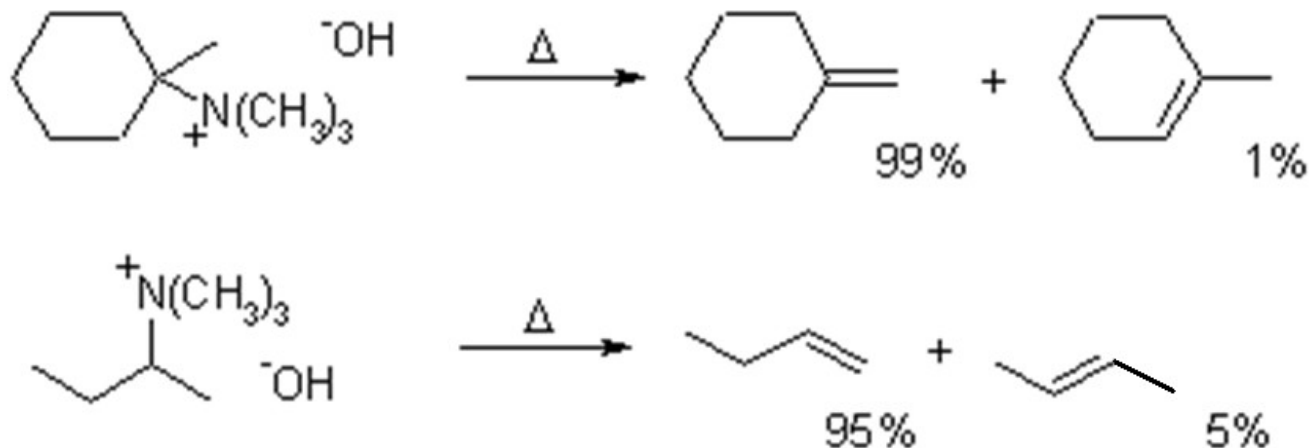


Complements dehydrations in that it takes place in basic media.

ELIMINATIONS OF VICINAL DIHALIDES



HOFMANN ELIMINATION

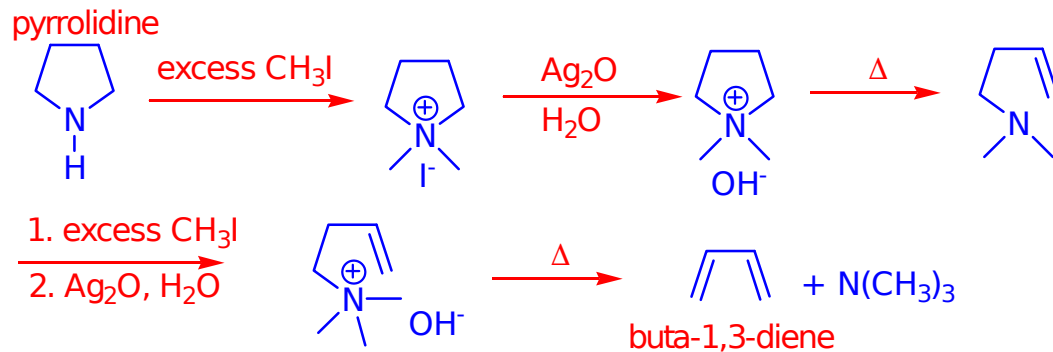


Eliminations from quaternary ammonium hydroxide upon heating (intramolecular)

Gives the least substituted olefin as the major product.

Used to degrade naturally occurring amines into simpler compounds.

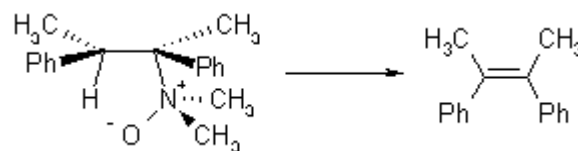
CONVERSION OF PYRROLIDINE INTO BUTADIENE



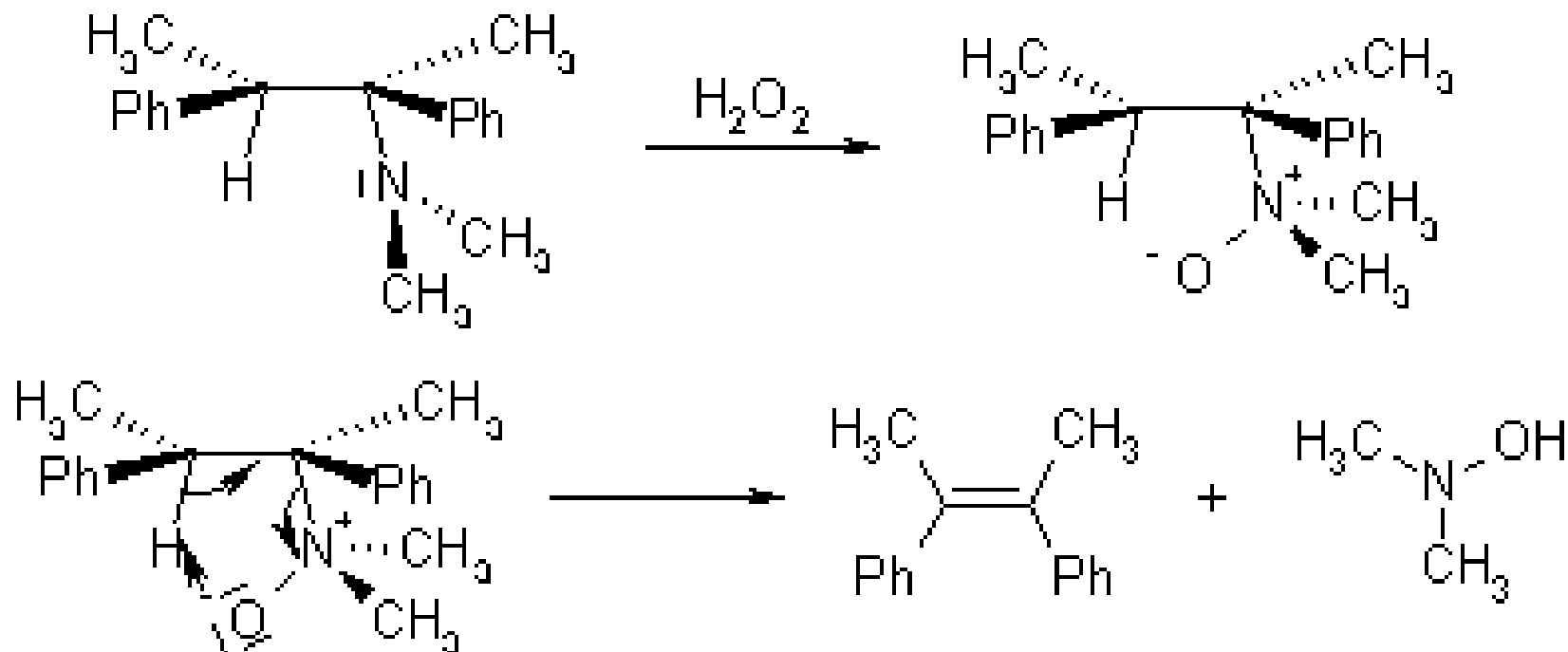
COPE ELIMINATION

***N*-Oxides give alkenes via a *syn*-elimination under heating.
This reaction obeys Hofmann's Rule**

COPE ELIMINATION



MECHANISM OF THE COPE ELIMINATION

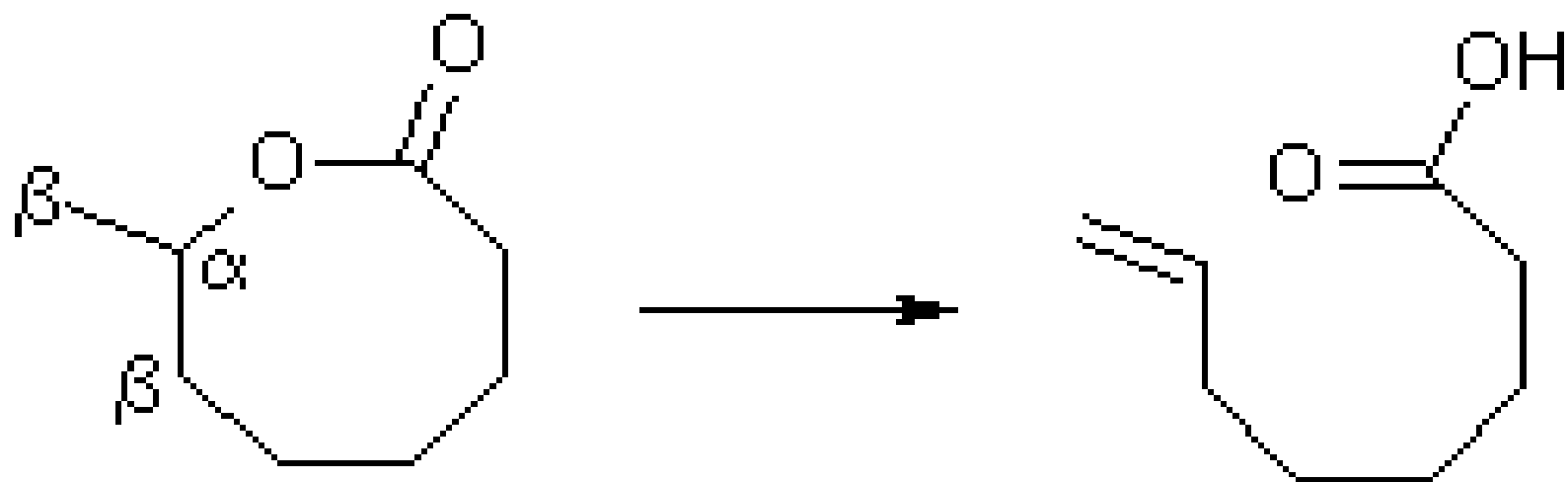


ESTER PYROLYSIS

Obeys the Hofmann Rule

is generally followed whenever a reaction passes through a cyclic transition state.

ESTER PYROLYSIS (CONTINUED)



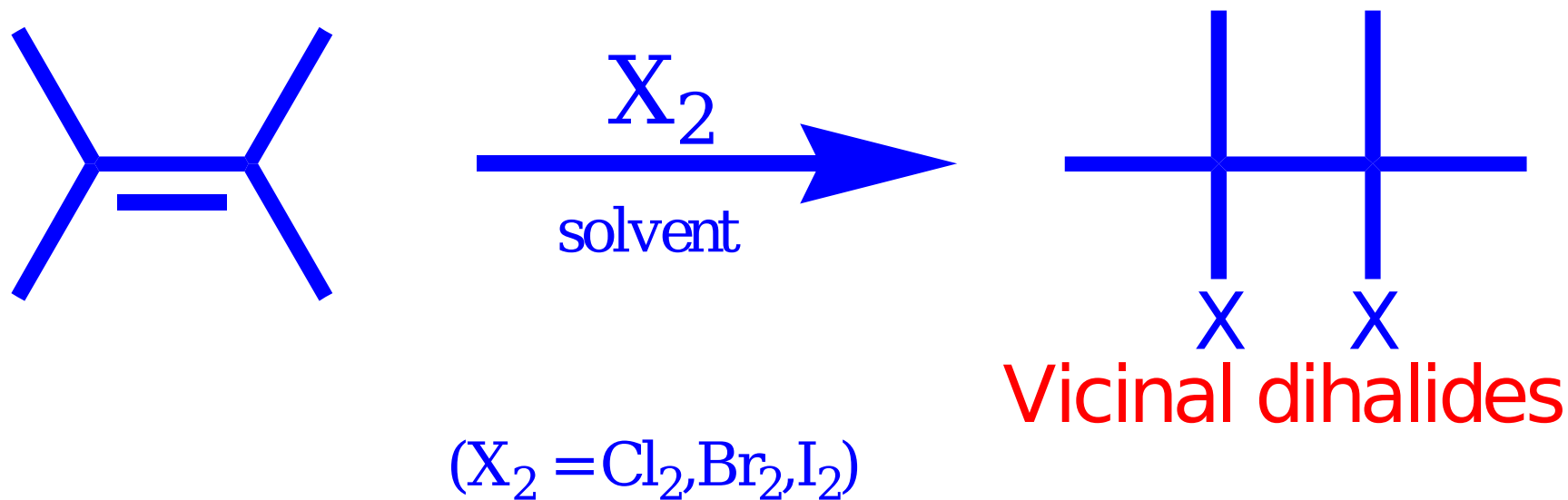
CHAPTER 6

ADDITION REACTIONS

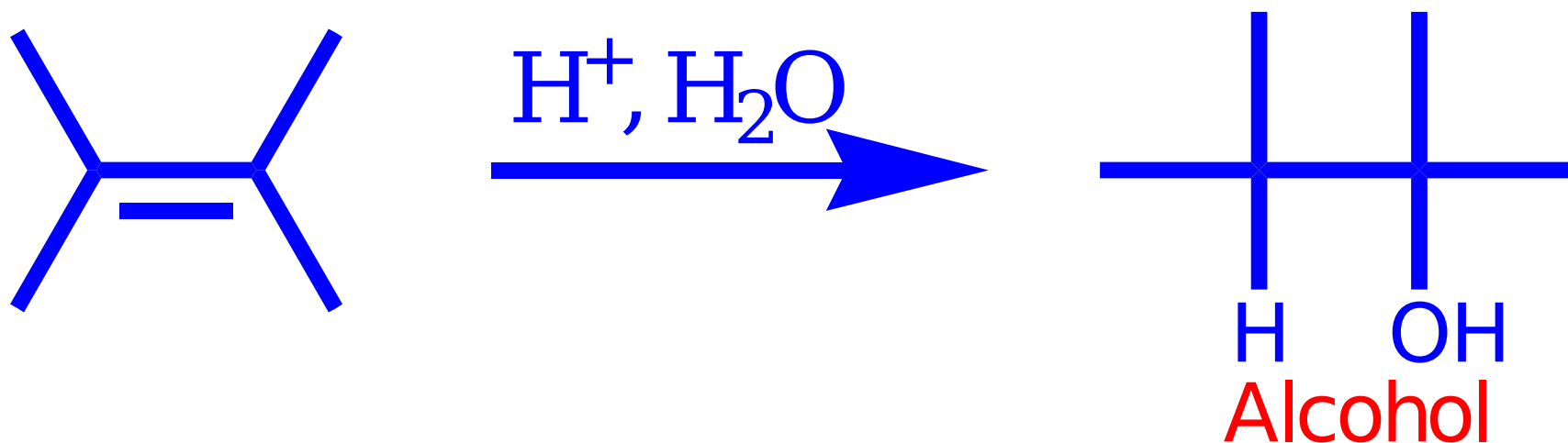
ADDITION REACTIONS

- **Addition of electrophiles to sites of unsaturations (c-c double or triple bonds)**
- **Major Addition reactions include:**
 - Halogenation: forms vicinal dihalides
 - Hydration: yields water
 - Hydrohalogenation: gives alkyl halides
 - Addition of mercaptanes: produces sulfides
 - Hydroborations: results in alcohols formation
 - Catalytic hydrogenations: yields alkanes

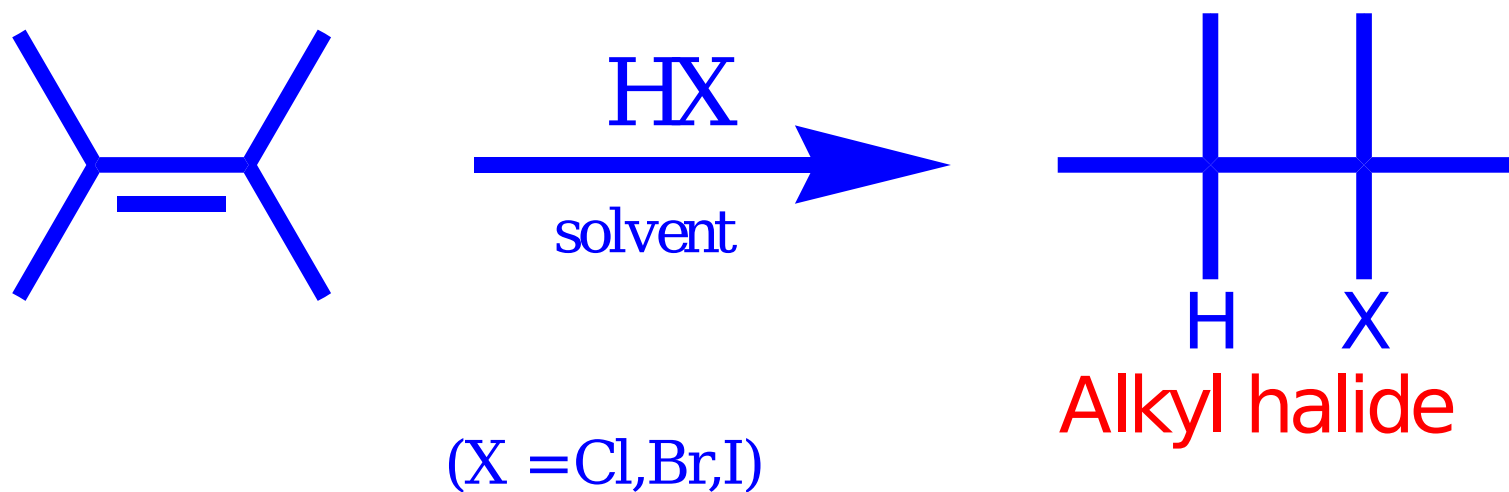
HALOGENATION: VICINAL DIHALIDE FORMATION



HYDRATION: ALCOHOL FORMATION



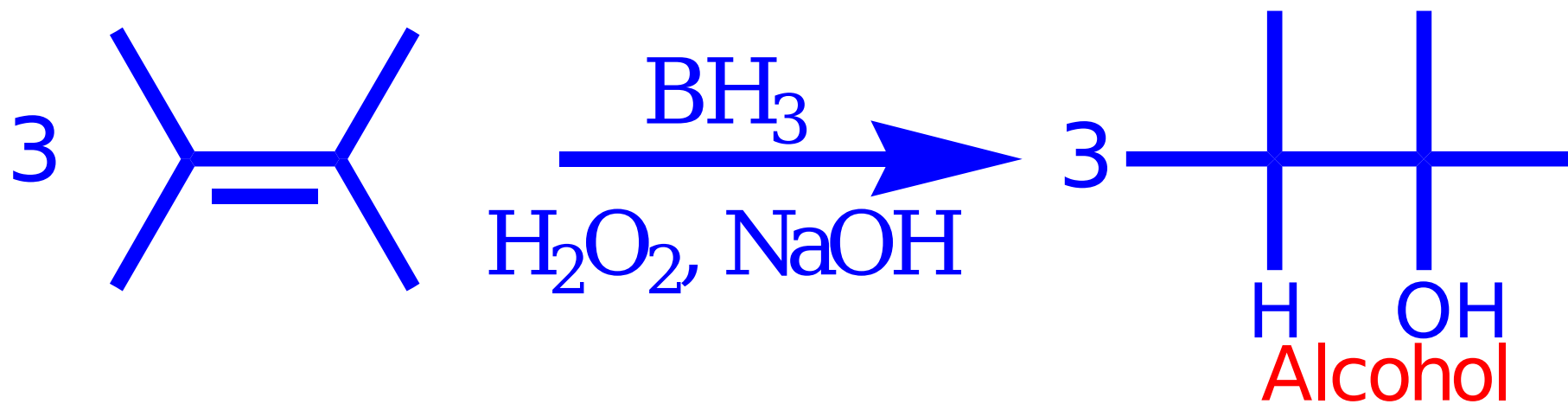
ADDITION OF HYDROGEN HALIDES:
FORMATION OF ALKYL HALIDES



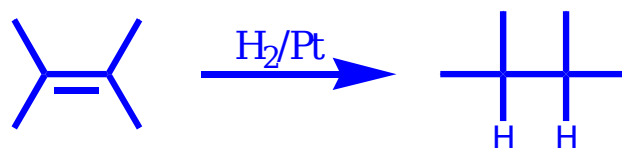
ADDITION OF MERCAPTANES:
FORMATION OF DISULFIDES



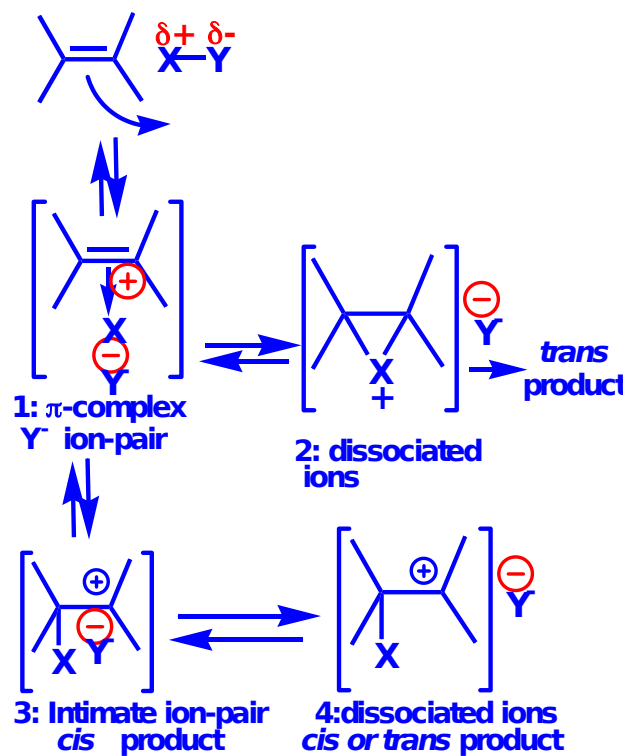
HYDROBORATION:
ALCOHOL FORMATION



CATALYTIC HYDROGENATION

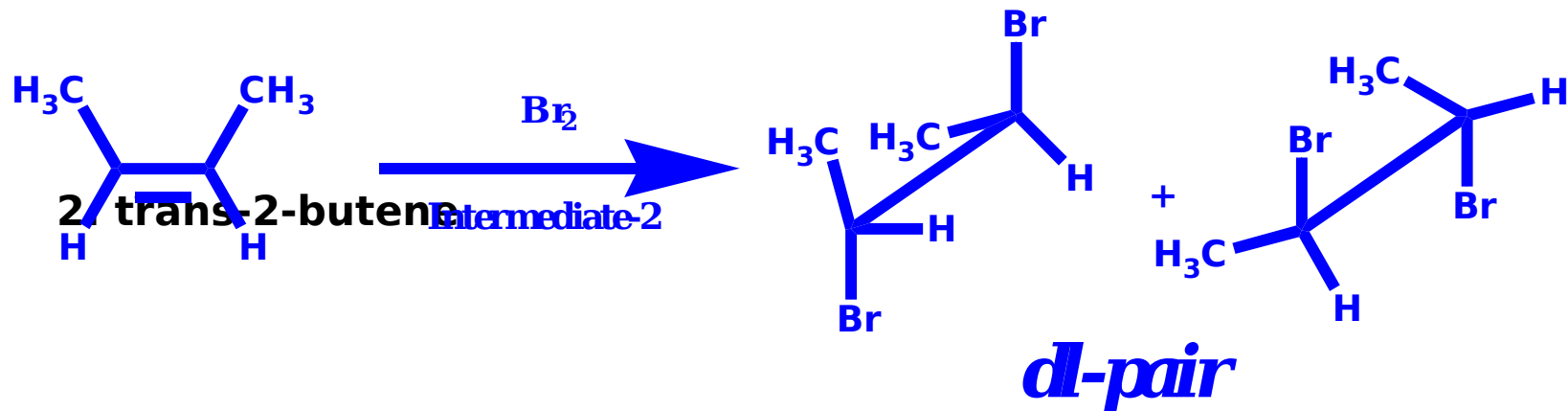
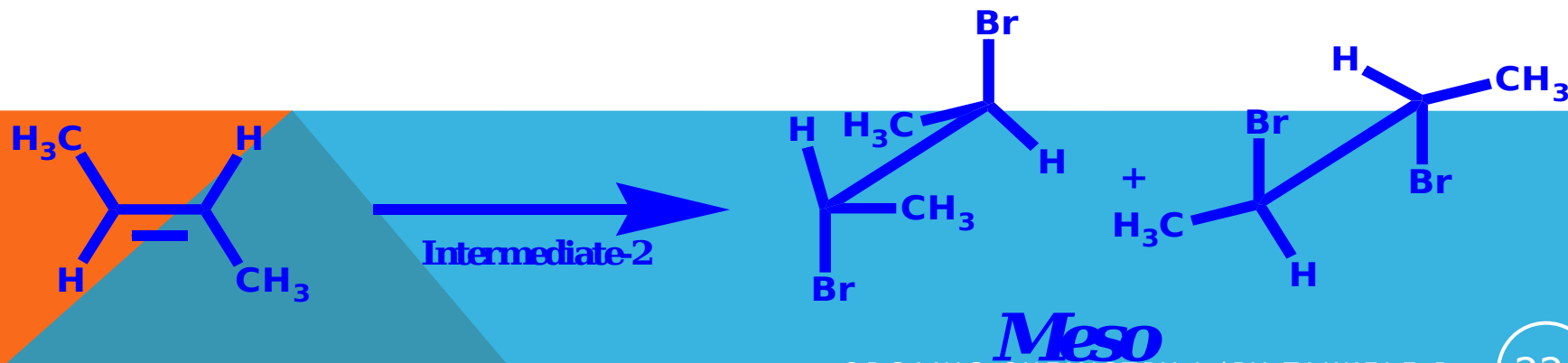


MECHANISMS



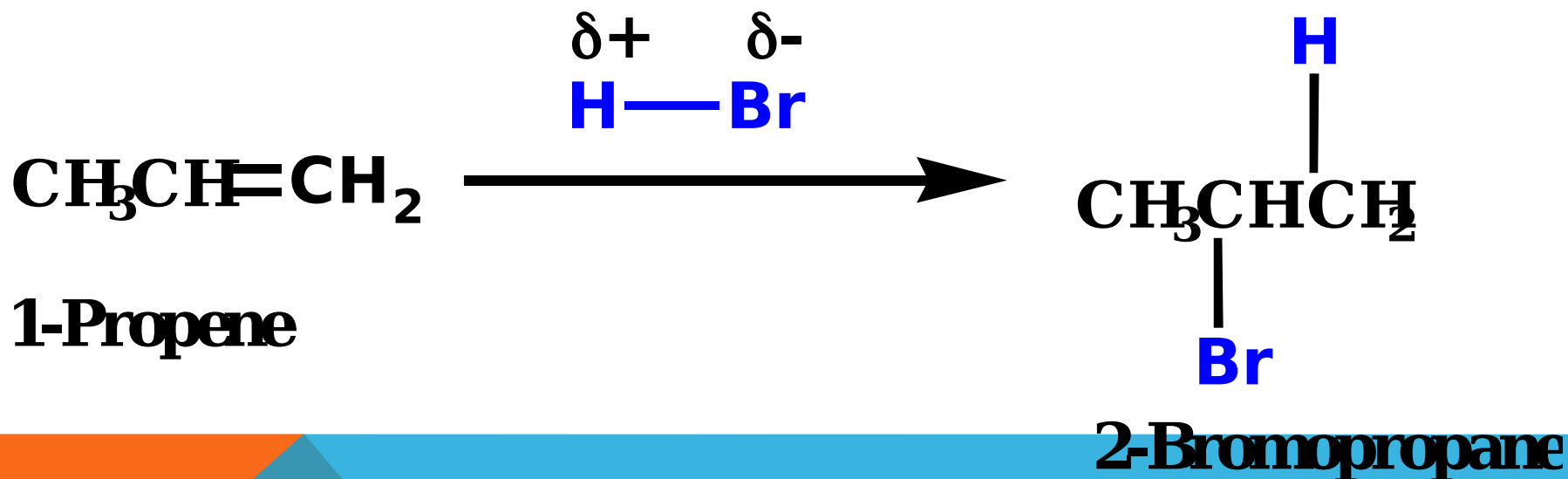
BROMINATION OF 2-BUTENE

1. cis-2-butene



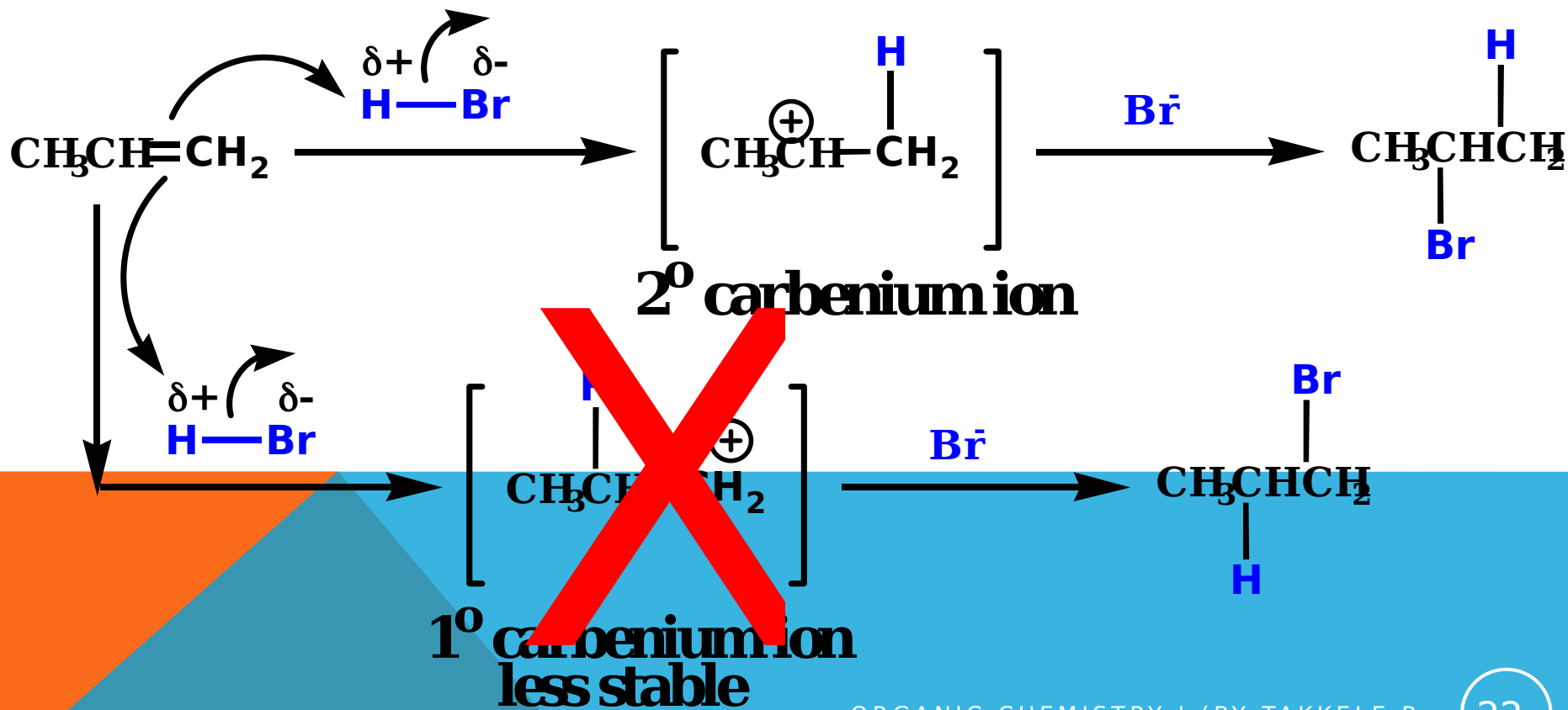
MARKOVNIKOV'S RULE

- Adding an unsymmetrical reagent to an unsymmetrical olefin bonds the negative portion of the reagent to the MORE substituted carbon.



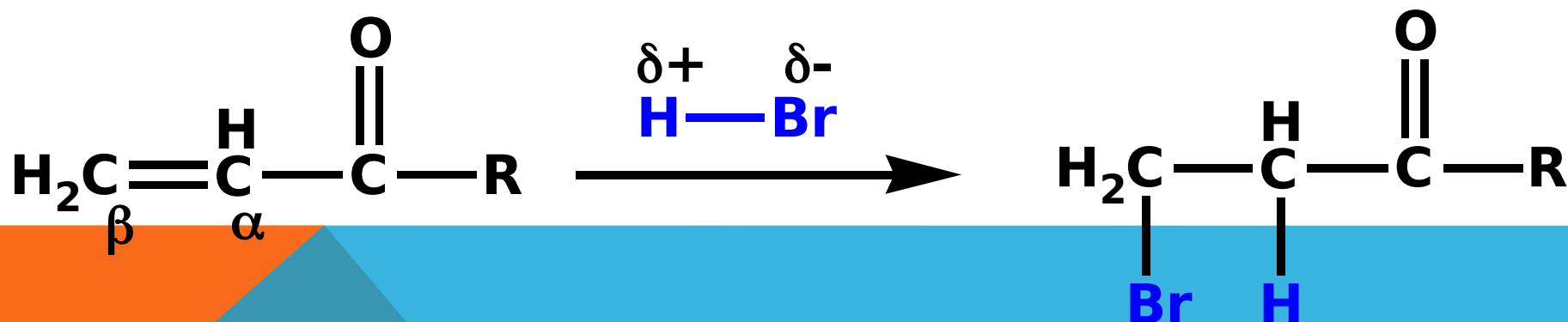
BASIS FOR MARKOVNIKOV'S RULE

- Preference for the more stable secondary carbenium ion:



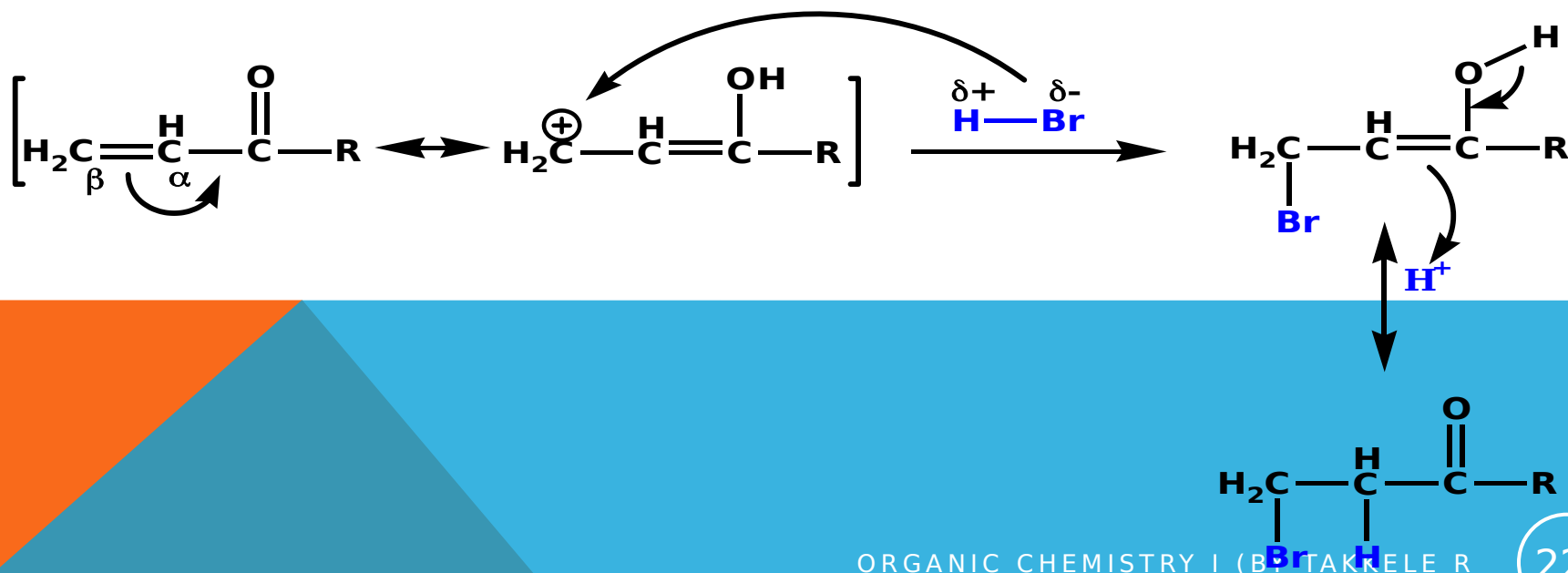
ADDITION TO α,β -UNSATURATED CARBONYL COMPOUNDS

Addition of polarized electrophiles to α,β -unsaturated carbonyl compounds adds the negative portion always to the β -carbon.



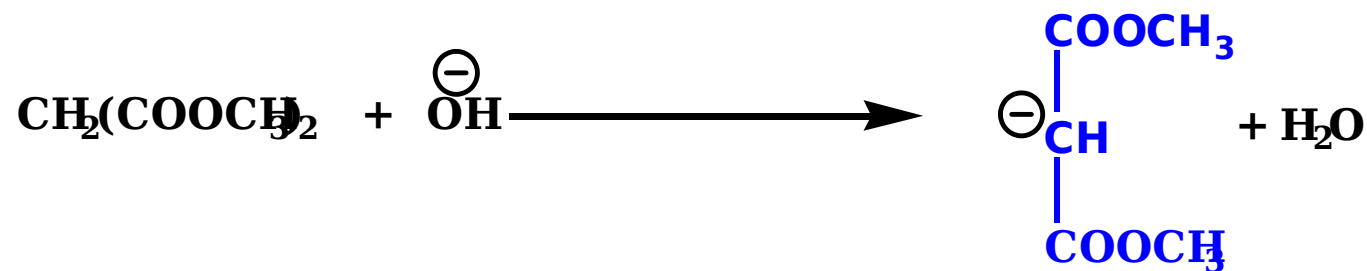
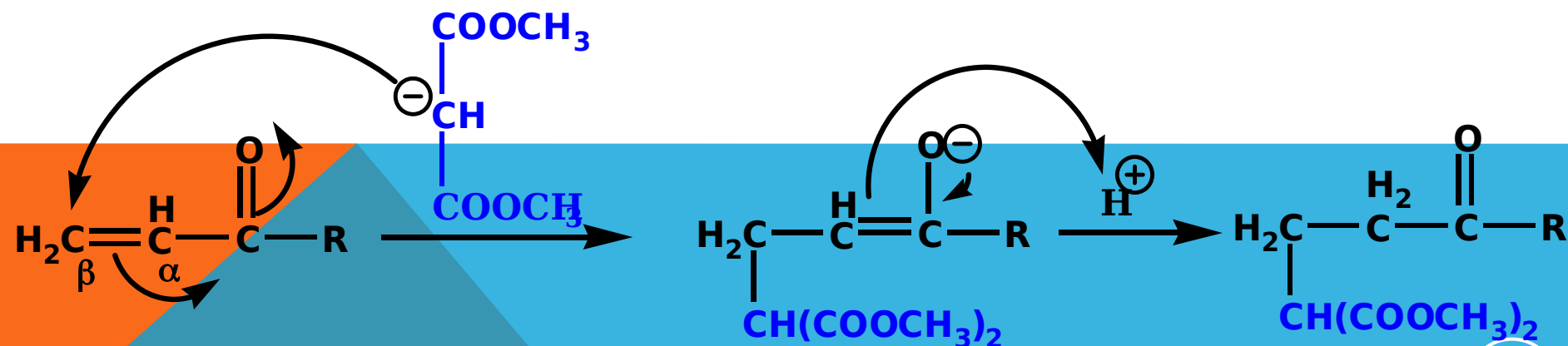
MECHANISM

- The negative part adds to the β -carbon.
- The β -carbon carbon is deshielded by the electron withdrawing carbonyl group.
- The carbonyl group withdraws electrons of the alkene by resonance.
- Otherwise **no nucleophile** can attack isolated c-c double bonds.



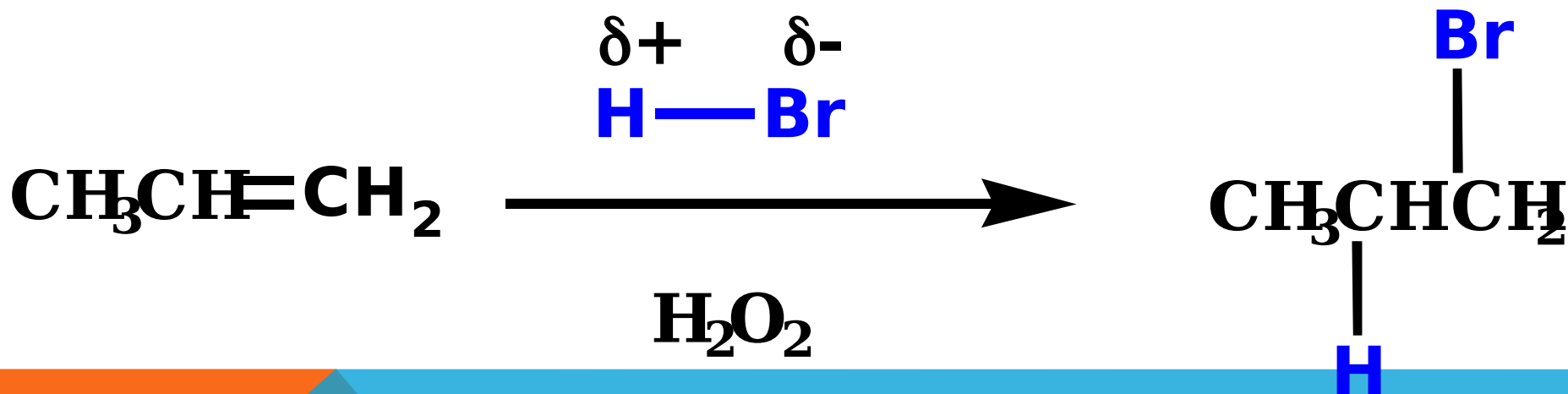
MICHAEL ADDITION

Addition to an α,β -unsaturated carbonyl compounds under **basic condition**.



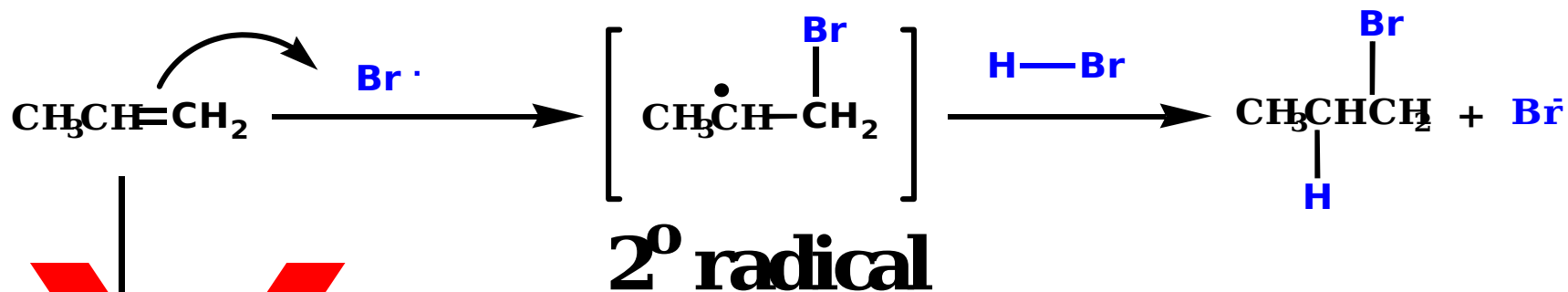
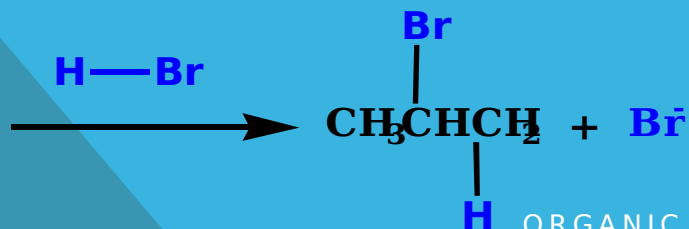
RADICAL ADDITION (ANTI-MARKOVNIKOV'S ADDITION)

- Adding an unsymmetrical reagent to an unsymmetrical olefin in the presence of **radical initiators** bonds the negative portion of the reagent to the **LESS** substituted carbon.



BASIS FOR THE ANTI-MARKOVNIKOV'S RULE

The reaction proceeds by homolytic (radical) mechanism NOT heterolytic
Preference for the more stable secondary radical.



WHICH REAGENTS REACT BY RADICAL MECHANISM?

- **Mercaptanes (RSH) react by radical mechanism only.**
- **HBr react by both heterolytic as well as radical mechanism.**
- **HCl and HI do not undergo free radical addition.**
- **For HCl, the bond doesn't break easily.**
- **For HI, the I radical prefers to combine with itself to form I_2 .**

CHAPTER 8

REARRANGEMENT REACTIONS

REARRANGEMENT REACTIONS

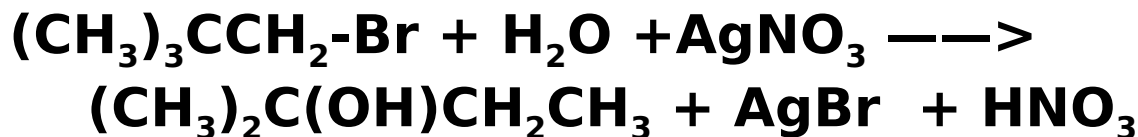
Structural rearrangement due to migration of groups such as H or alkyl.

Triggered by intermediates incorporating *positively charged* or *electron deficient* atoms,

In the case of carbon, these are *carbocations*.

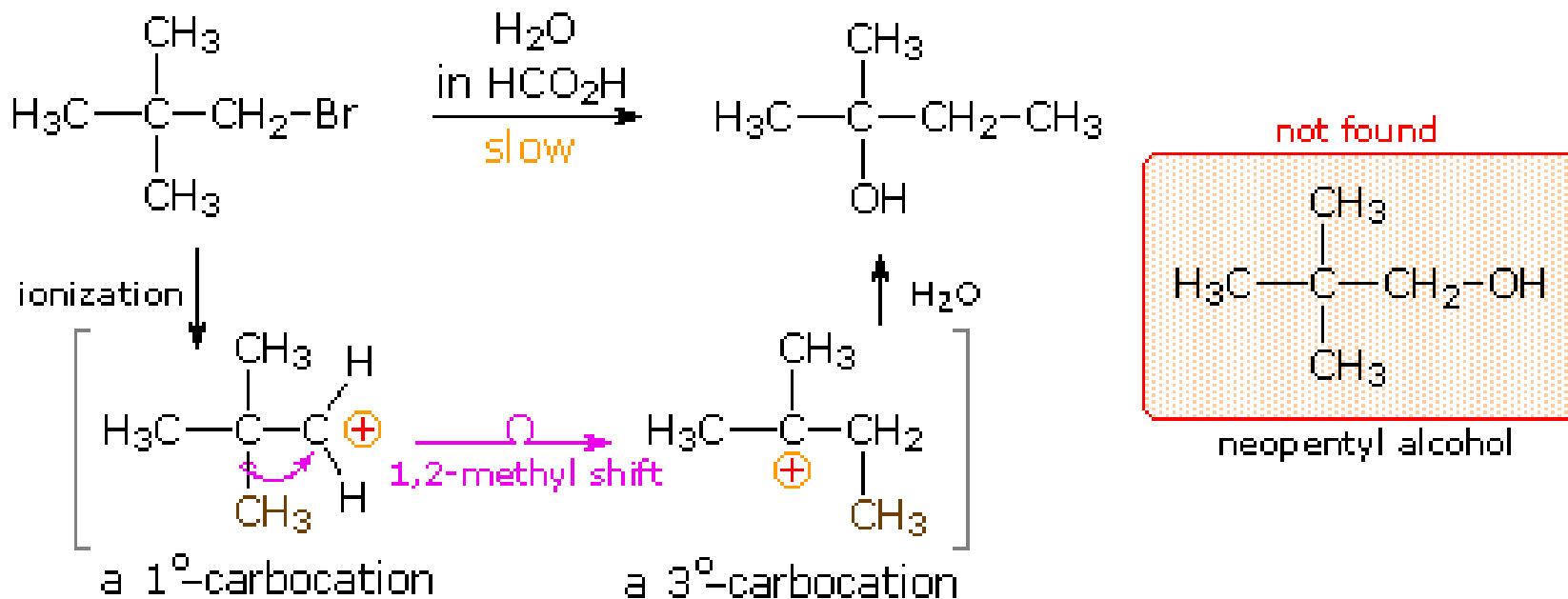
An example is hydrolysis of neopentyl bromide.

HYDROLYSIS OF NEOPENTYL BROMIDE

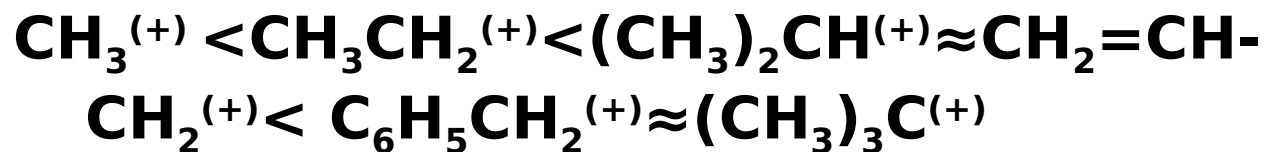


Product is not the expected *neopentyl alcohol* rather *2-methyl-2-butanol*.

Product is a result of structural rearrangement.



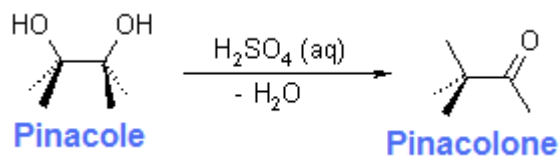
CARBOCATION STABILITY



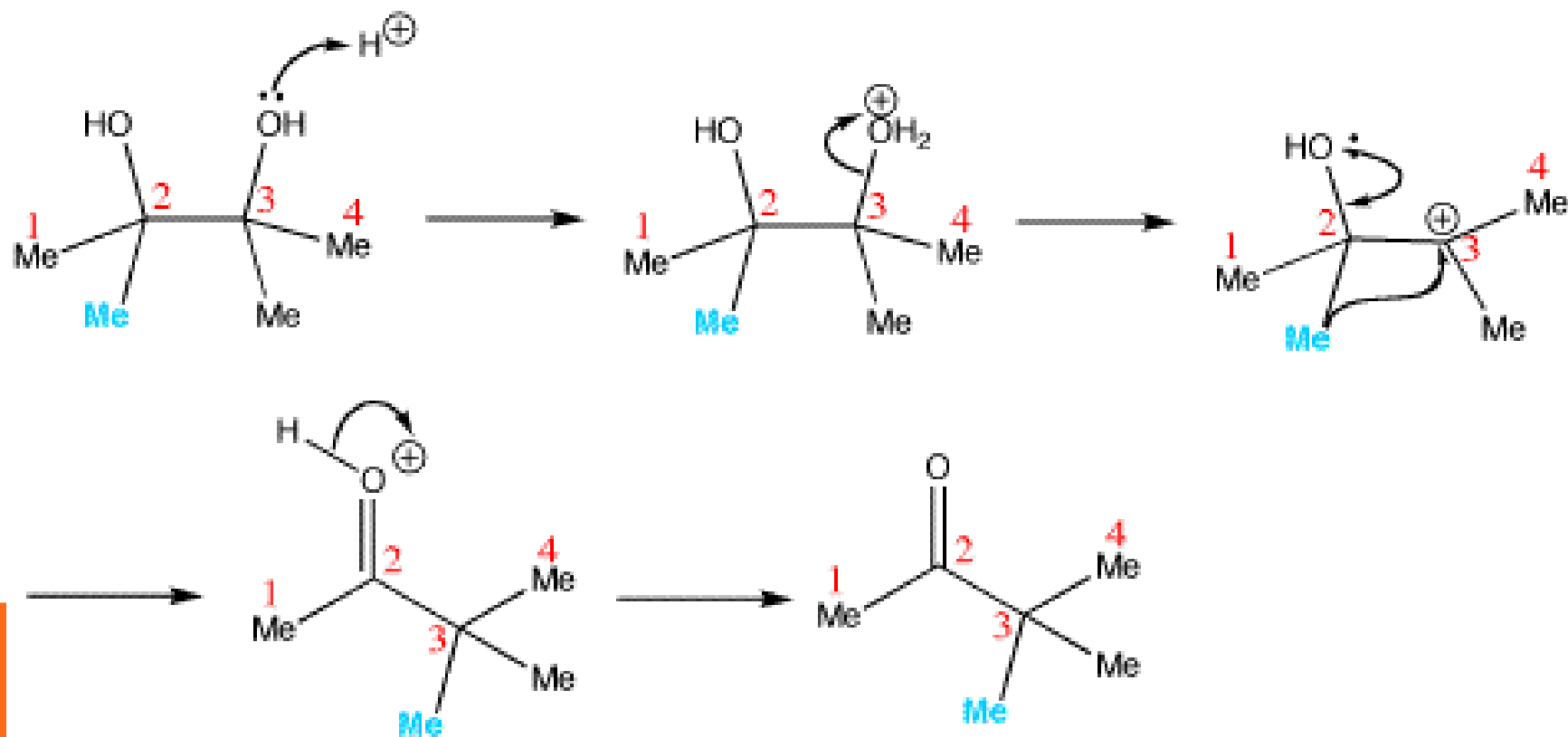
WAGNER-MEERWEIN REARRANGEMENT

- Such rearrangements are called Wagner-Meerwein rearrangement.
- They involve migration of an alkyl group to a cationic centre.
- In the example, the first-formed carbocation is the unstable 1° .
- But, migration of a methyl group forms a more stable 3° cation.
- Migratory aptitude in such rearrangements is:
- 3° alkyl > cyclohexyl > 2° alkyl > phenyl > 1° alkyl > CH_3 .

PINACOL-PINACOLONE REARRANGEMENT



MECHANISM



DESCRIPTION OF THE MECHANISM

involve the formation of a carbenium ion intermediate that subsequently undergoes a rearrangement.

The first generated intermediate, an α -hydroxy carbenium ion, rearranges through a 1,2-alkyl shift to produce the carbonyl compound.

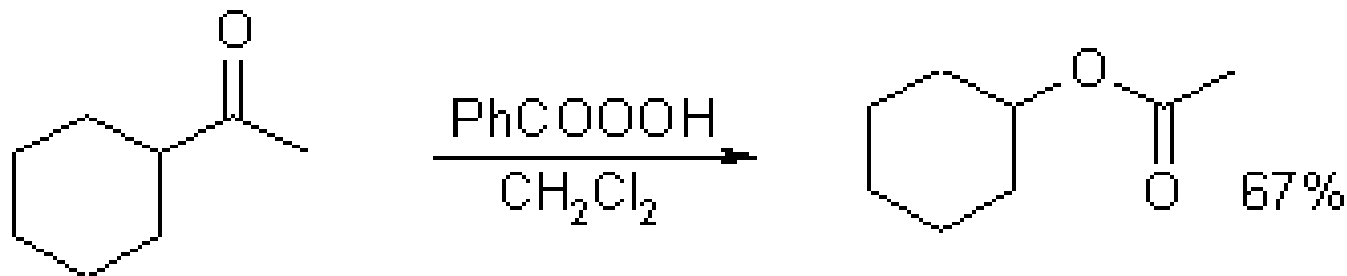
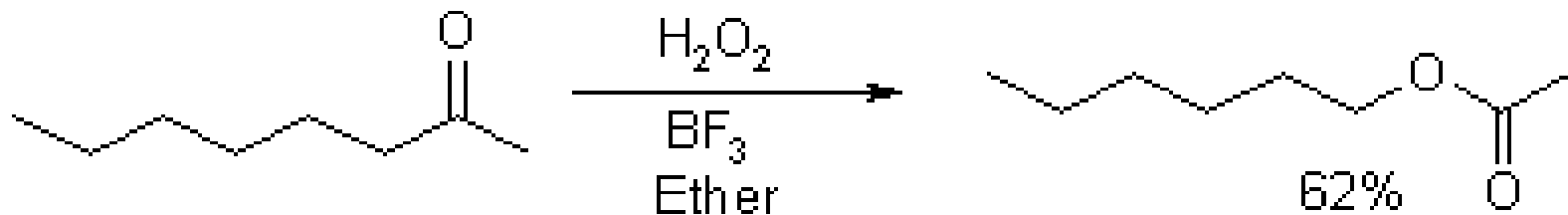
BAEYER-VILLIGER OXIDATION

is the oxidative cleavage of a carbon-carbon bond adjacent to a carbonyl.

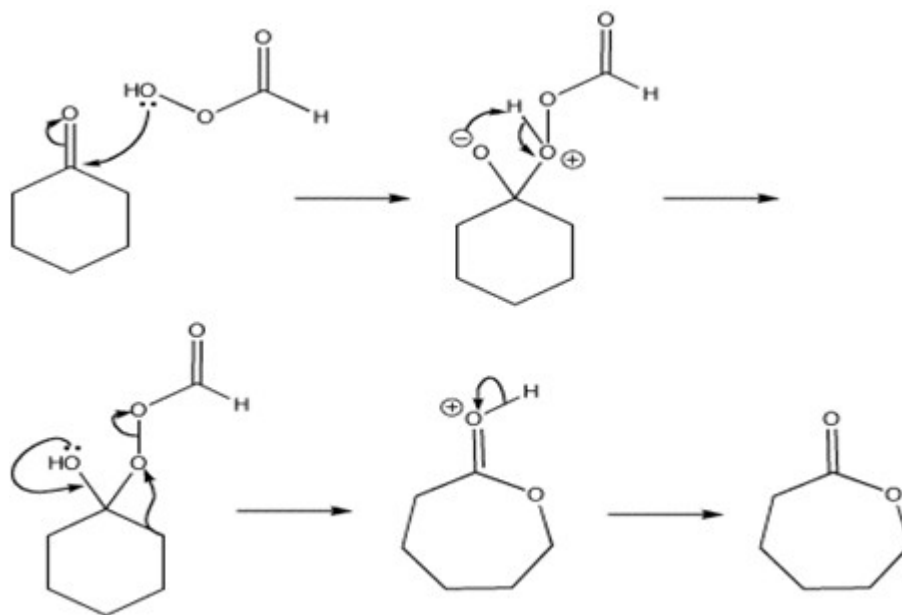
converts ketones to esters and cyclic ketones to lactones.

carried out with peracids.

CONTINUED

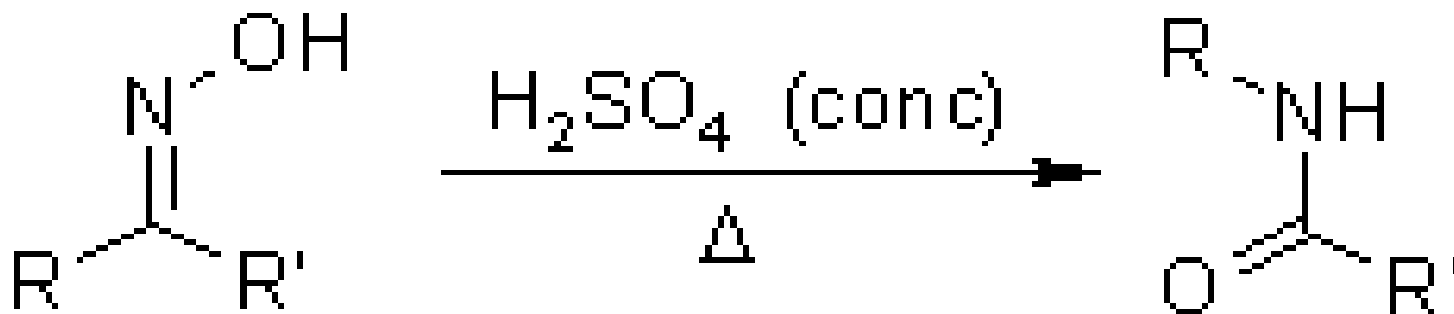


MECHANISM OF THE BAEYER-VILLIGER OXIDATION



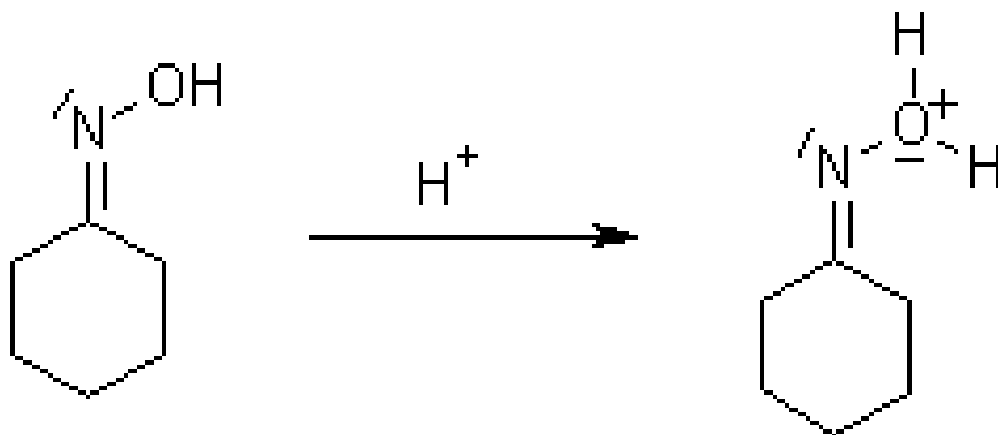
BECKMANN REARRANGEMENT

An acid-induced rearrangement of **oximes** to give **amides**.
an electropositive nitrogen is formed that initiates an alkyl migration.

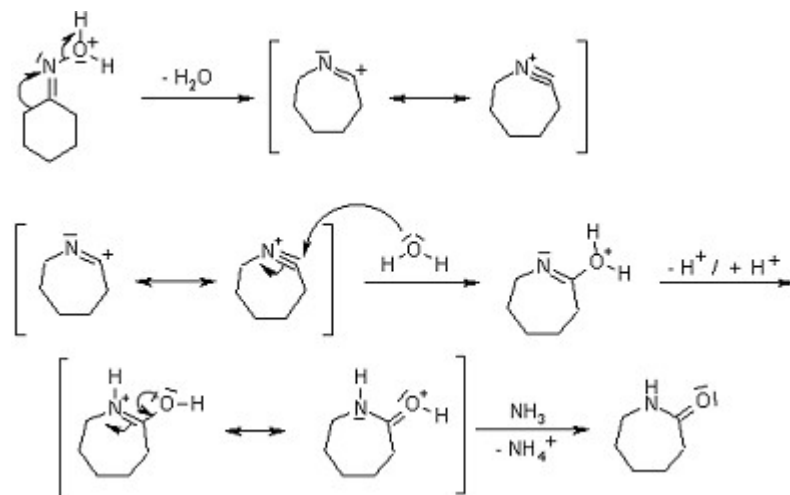


MECHANISM OF THE BECKMANN REARRANGEMENT

- Proceeds by protonation of the oxime hydroxyl, followed by migration of the alkyl substituent "*trans*" to nitrogen.
- The N-O bond is simultaneously cleaved with the expulsion of water.



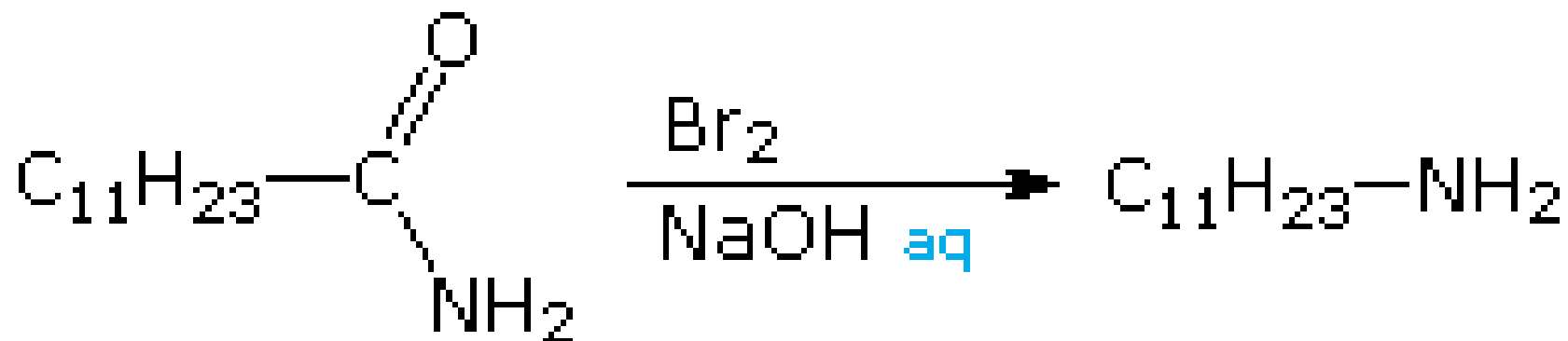
MECHANISM (CONTINUED)



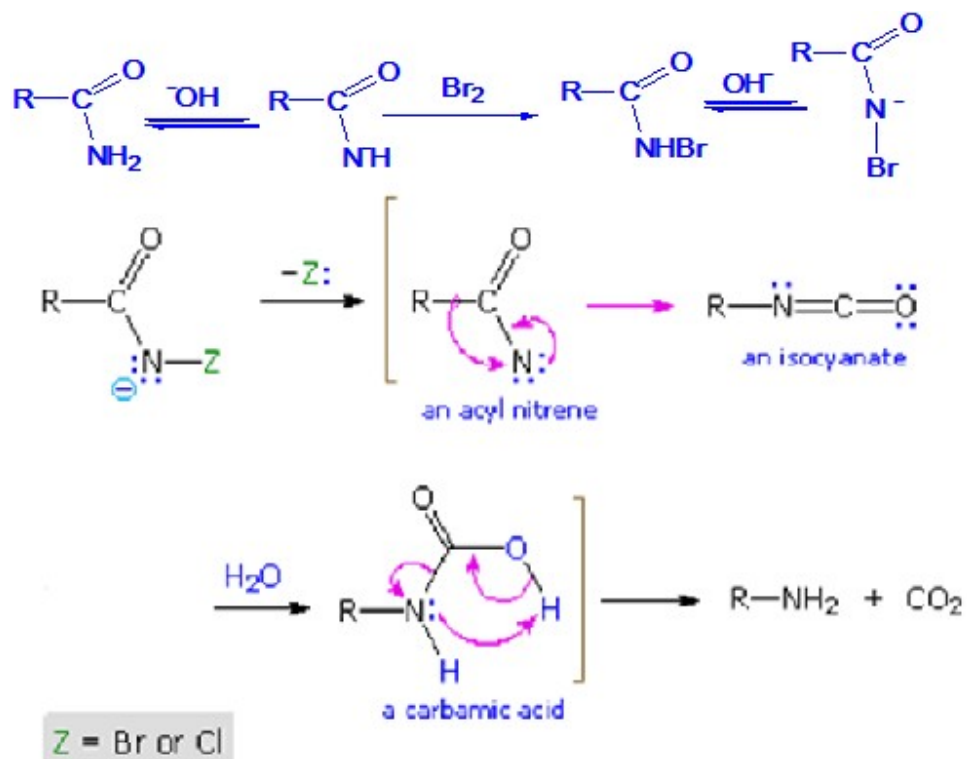
HOFMANN REARRANGEMENT

Rearrangement of 1° amides to 1° amines one carbon less than the amide in basic media.

Involves rearrangement towards electron poor nitrogen.



MECHANISM OF HOFMANN REARRANGEMENT



OTHER CAUSES FOR SKELETAL REARRANGEMENTS

relieve of angle strain , torsional strain or steric crowding in the reactant structure by an alkyl or aryl shift to a carbocation site.

WAGNER MEERWIEN REARRANGEMENT

