Alkyl halides

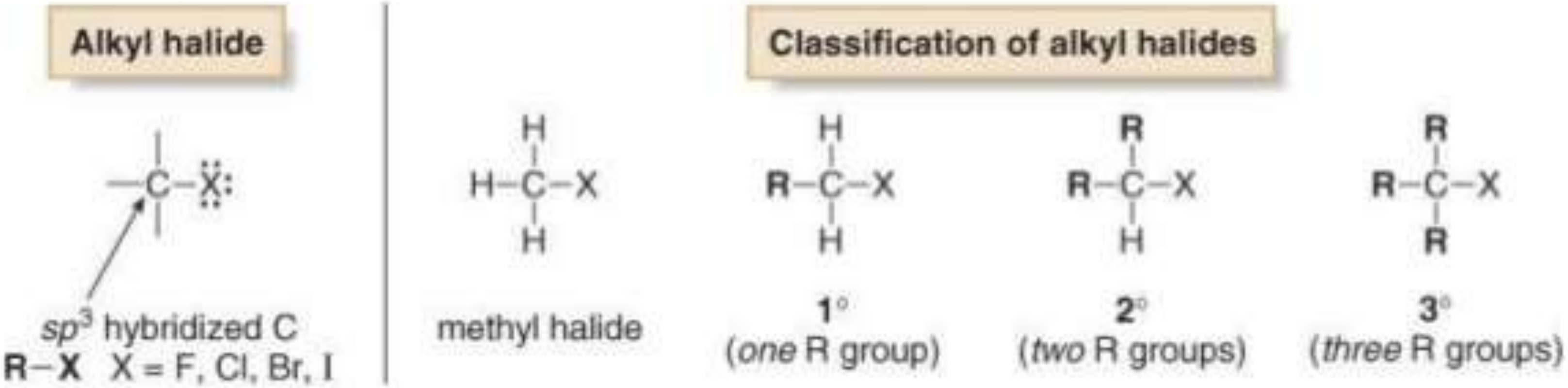
By
Mr. Y Pradeep Kumar
Associate Professor
Dept of Pharmaceutical Chemistry

ANNAMACHARYA COLLEGE OF PHARMACY
AUTONOMOUS
New Boyanapalli, Rajampet - 516126, Annamayya District. A.P., India

Degree Awarding University: JNTUA, Approved by PCI, New Delhi & Govt. of A.P.
Recognised u/s 2-f & 12-B of the UGC Act, 1956, Recognised Research Centre under JNTUA,
Accredited by NBA (UG Program), New Delhi, and NAAC, Bangalore with "A" Grade
ISO 9001:2015 Certified Institution

Introduction to Alkyl Halides

- Alkyl halides are organic molecules containing a halogen atom bonded to an sp^3 hybridized carbon atom.
- Carbon-halogen bond of alkyl halides is polarized.
- Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of carbons bonded to the carbon with the halogen atom.
- The halogen atom in halides is often denoted by the symbol "X".



Types of organic halides

Vinyl halides

- have a halogen atom (X) bonded to a C=C double bond.

Aryl halides

- have a halogen atom bonded to a benzene ring.

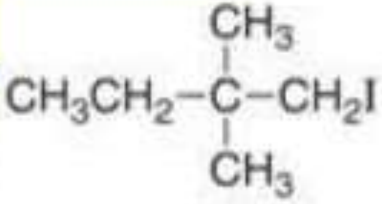
Allylic halides

- have X bonded to the carbon atom adjacent to a C=C double bond.

Benzylic halides

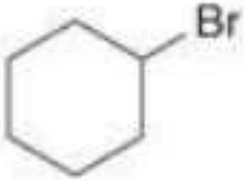
- have X bonded to the carbon atom adjacent to a benzene ring.

Examples of 1 , 2 , and 3 alkyl halides:

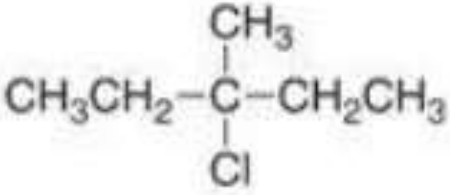


$$CH_3CH_2-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-CH_2I$$

1° iodide



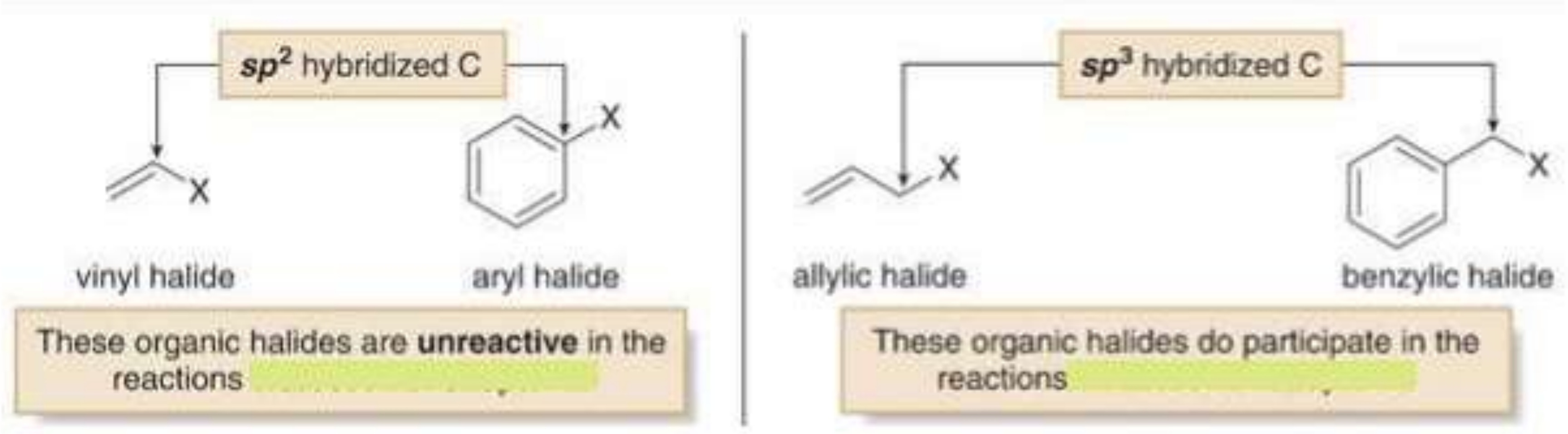
2° bromide



$$CH_3CH_2-\overset{\displaystyle CH_3}{\underset{\displaystyle Cl}{C}}-CH_2CH_3$$

3° chloride

Four types of organic halides (RX) having X near a π bond:

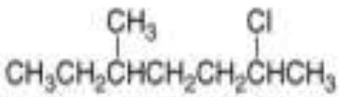


These organic halides are **unreactive** in the reactions [redacted]

These organic halides do participate in the reactions [redacted]

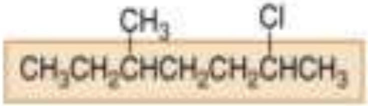
How To Name an Alkyl Halide Using the IUPAC System

Example Give the IUPAC name of the following alkyl halide:



$CH_3CH_2\overset{CH_3}{C}HCH_2CH_2\overset{Cl}{C}HCH_3$

Step [1] Find the parent carbon chain containing the halogen.



$CH_3CH_2\overset{CH_3}{C}HCH_2CH_2\overset{Cl}{C}HCH_3$

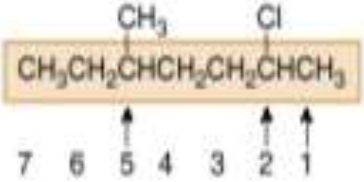
7 C's in the longest chain

7 C's ---→ heptane

- Name the parent chain as an ***alkane,*** with the halogen as a substituent bonded to the longest chain.

Step [2] Apply all other rules of nomenclature.

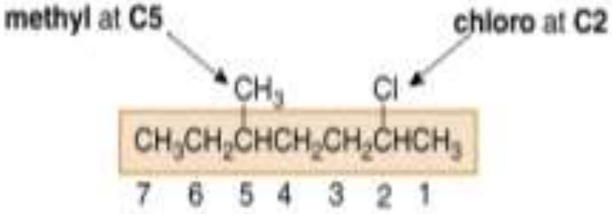
a. **Number** the chain.



$CH_3CH_2\overset{CH_3}{C}HCH_2CH_2\overset{Cl}{C}HCH_3$

- Begin at the end nearest the first substituent, either alkyl or halogen.

b. **Name** and **number** the substituents.



methyl at **C5**

chloro at **C2**

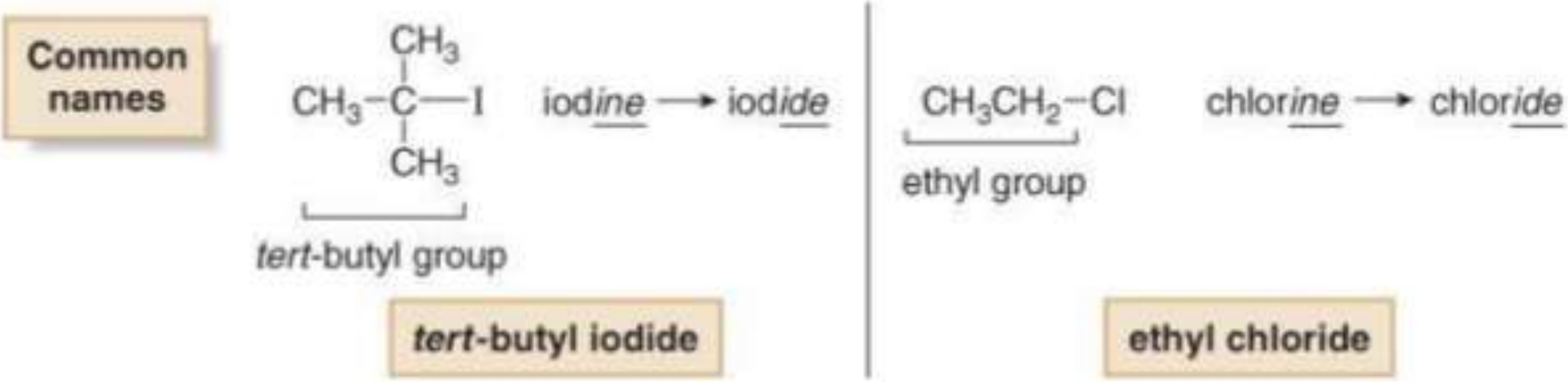
$CH_3CH_2\overset{CH_3}{C}HCH_2CH_2\overset{Cl}{C}HCH_3$

c. **Alphabetize: c** for **c**hloro, then **m** for **m**ethyl.

ANSWER: 2-chloro-5-methylheptane

Nomenclature:

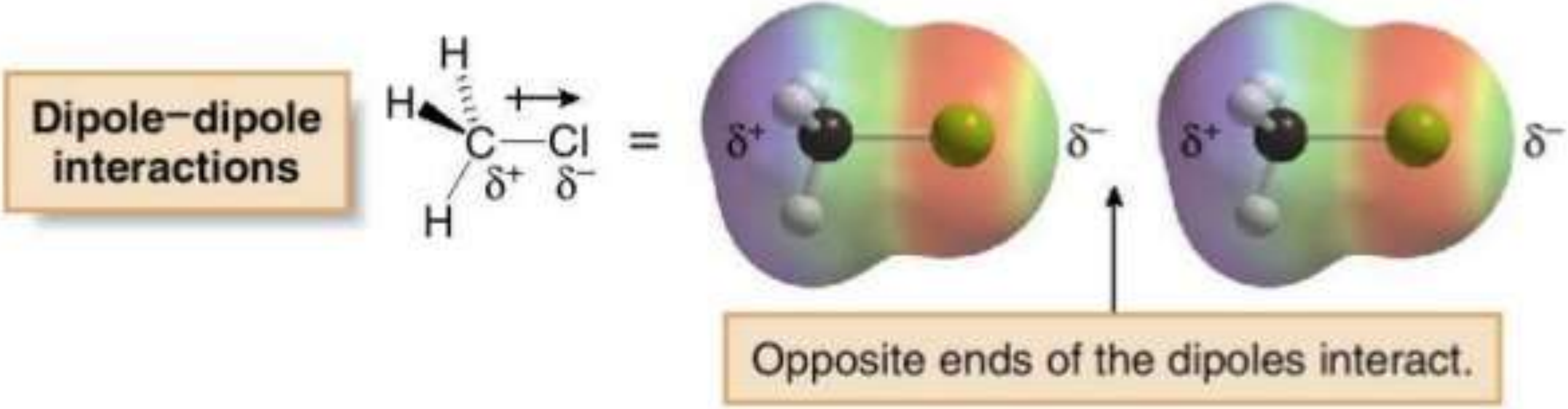
- Common names are often used for simple alkyl halides. To assign a common name:
    - Name all the carbon atoms of the molecule as a single alkyl group.
    - Name the halogen bonded to the alkyl group.
    - Combine the names of the alkyl group and halide, separating the words with a space.



Physical Properties:

- Alkyl halides are weak polar molecules. They exhibit dipole-dipole interactions because of their polar C—X bond, but because the rest of the molecule contains only C—C and C—H bonds, they are incapable of intermolecular hydrogen bonding.
- Density correspond to the molecular weight.

  F < Cl < Br < I



Opposite ends of the dipoles interact.

Physical Properties:

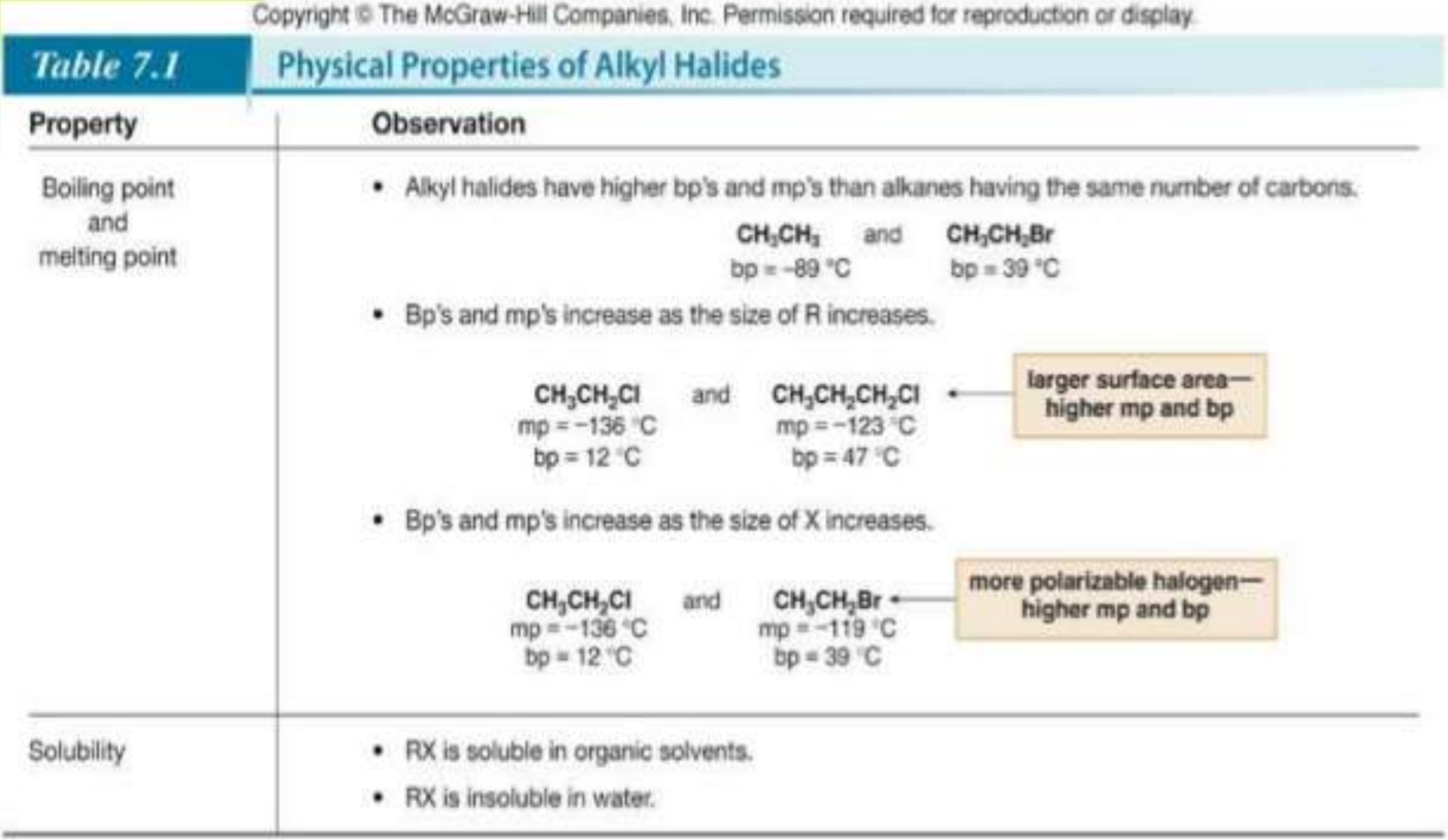
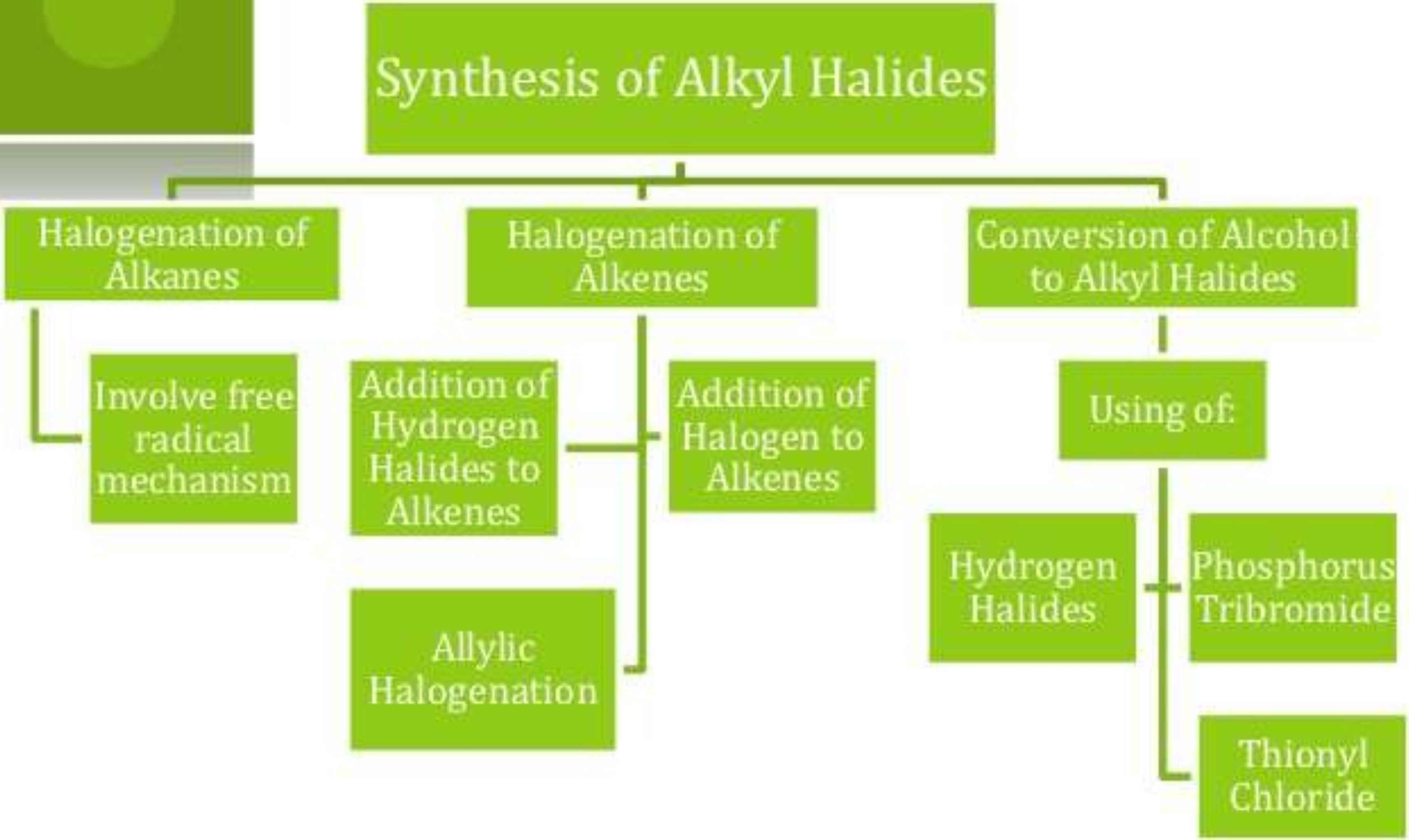


Table 7.1 Physical Properties of Alkyl Halides

Property	Observation
Boiling point and melting point	• Alkyl halides have higher bp's and mp's than alkanes having the same number of carbons. CH_3CH_3 bp = −89 °C and CH_3CH_2Br bp = 39 °C • Bp's and mp's increase as the size of R increases. CH_3CH_2Cl mp = −136 °C, bp = 12 °C and $CH_3CH_2CH_2Cl$ mp = −123 °C, bp = 47 °C **larger surface area—higher mp and bp** • Bp's and mp's increase as the size of X increases. CH_3CH_2Cl mp = −136 °C, bp = 12 °C and CH_3CH_2Br mp = −119 °C, bp = 39 °C **more polarizable halogen—higher mp and bp**
Solubility	• RX is soluble in organic solvents. • RX is insoluble in water.



Synthesis of Alkyl Halides

- Halogenation of Alkanes
  - Involve free radical mechanism
- Halogenation of Alkenes
  - Addition of Hydrogen Halides to Alkenes
  - Addition of Halogen to Alkenes
  - Allylic Halogenation
- Conversion of Alcohol to Alkyl Halides
  - Using of:
    - Hydrogen Halides
    - Phosphorus Tribromide
    - Thionyl Chloride

A)HALOGENATION OF ALKANES

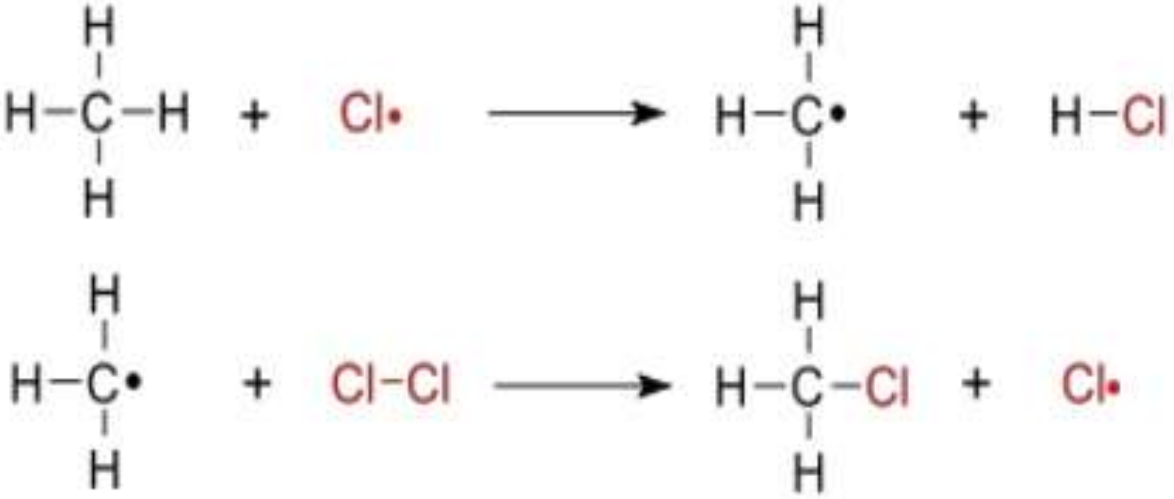
1. <u>Initiation</u>

- ✓ Splitting of a chlorine molecule to form two chlorine atoms, initiated by ultraviolet radiation or sunlight.
- ✓ A chlorine atom has an unpaired electron and acts as a free radical.

2. Chain propagation (two steps):

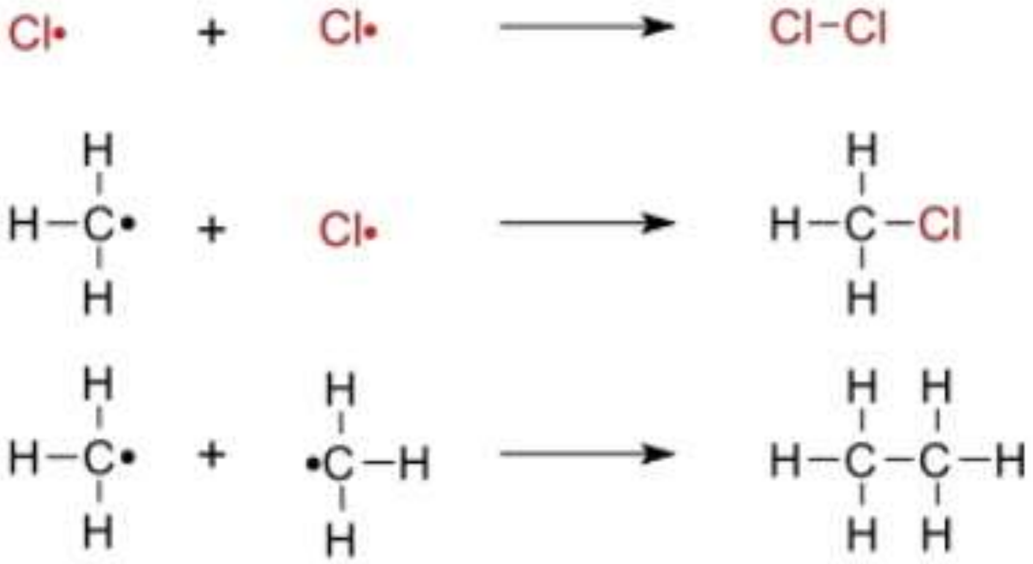
✓ A hydrogen atom is pulled off from methane leaving a 1° methyl radical.

✓ The methyl radical then pulls a Cl· from Cl2.

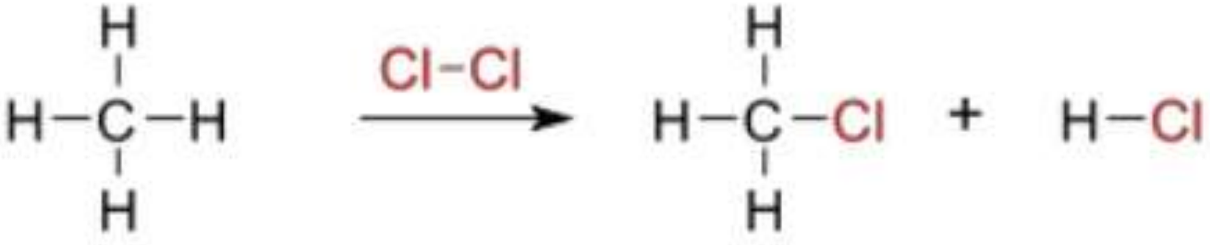


3. **Chain termination**:

- ✓ recombination of two free radicals:



The net reaction :



B) HALOGENATION OF ALKENES

There is 3 types of halogenation of alkenes which are:

I. Addition of Hydrogen Halides to Alkenes
II. Addition of Halogen to Alkenes
III. Allylic Halogenation

1)ADDITION OF HYDROGEN HALIDES TO ALKENES

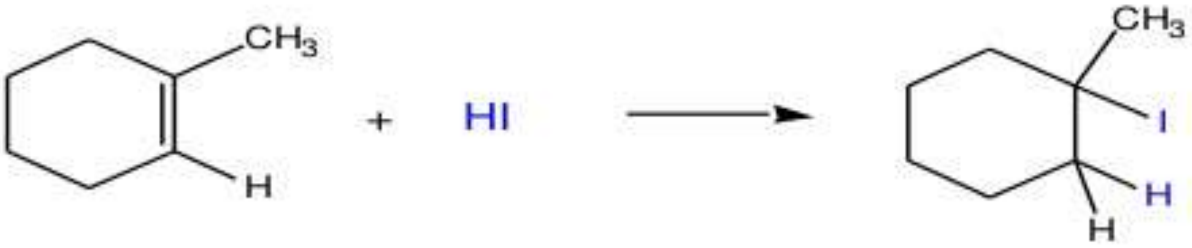
- All alkenes undergo addition reactions with the hydrogen halides.
- Reactions are controlled by Markonikov rule:

  In the addition of HX to an alkene, the H atom adds to the carbon atom of the double bond that already has the greater number of hydrogen, and a halogen atom to the other.

- **Anti Markonikov rule: with the presence of Hydrogen peroxide, H_2O_2, the halogen atom will be added to the carbon atom of the double bond that has the greater number of hydrogen**.

EXAMPLE OF ADDITION OF HYDROGEN HALIDES TO ALKENES

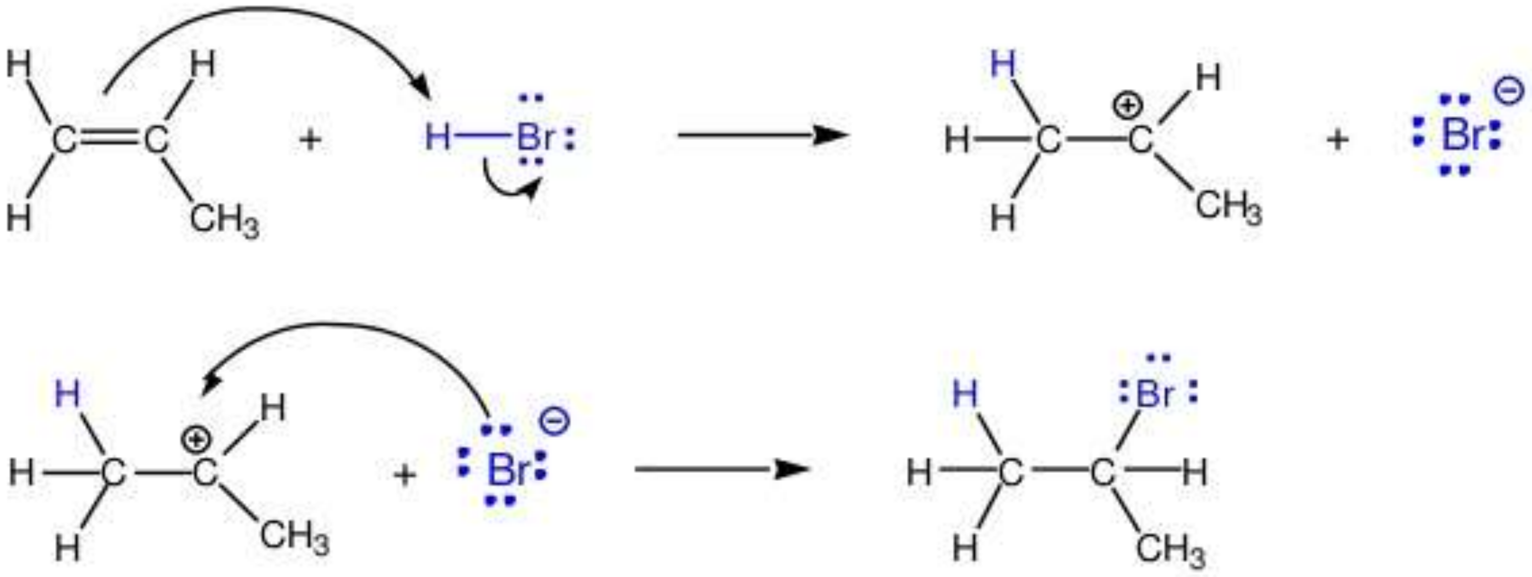
Examples:



MECHANISM OF HALOGENATION

- Halogenation takes place in two steps
- In the first step, H^+ is transferred from HBr to the alkene to form a carbocation and bromide ion
- Second, Br^- reacts with the carbocation to form a bromoalkane

Example:



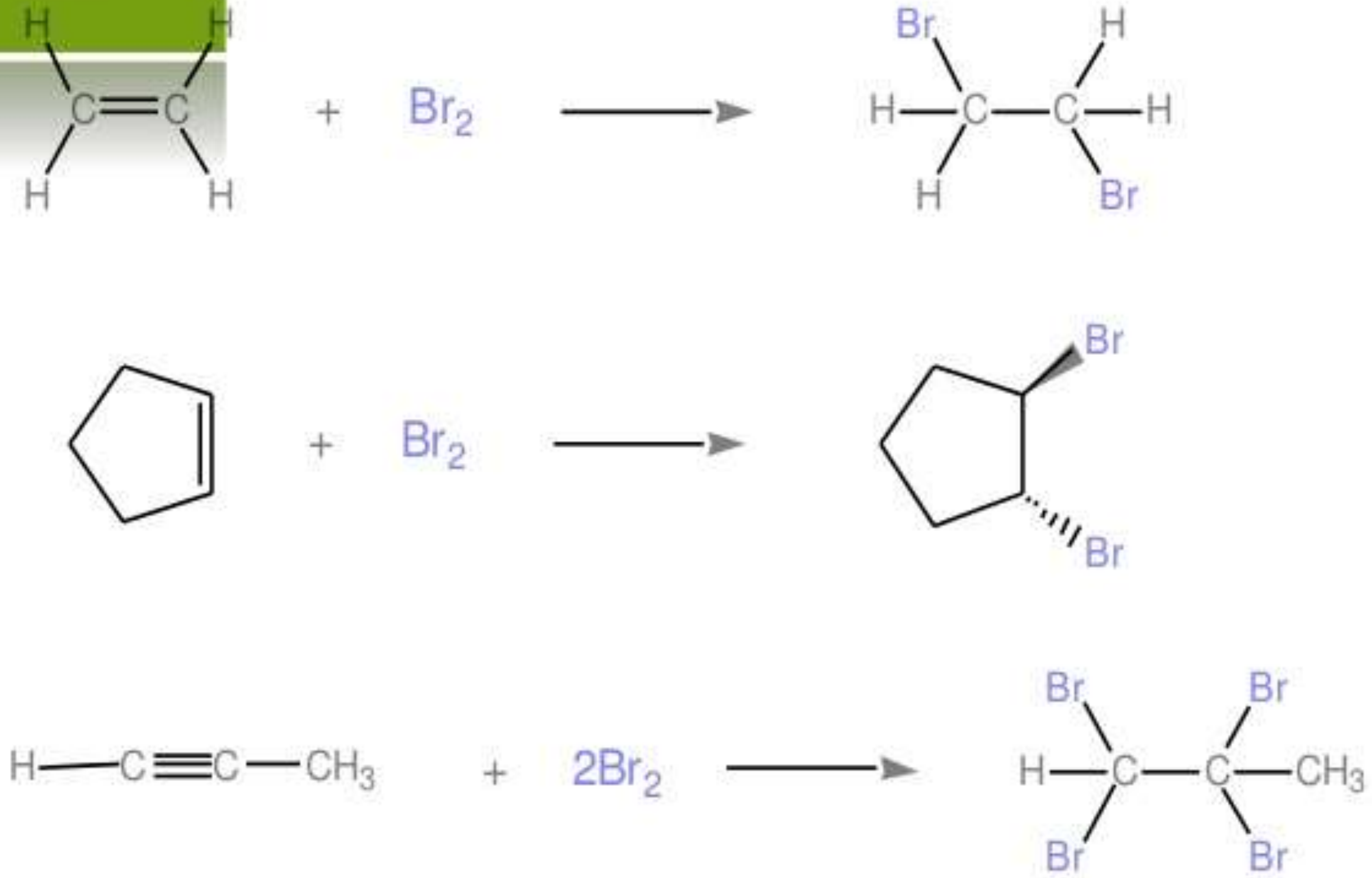
2)ADDITION OF HALOGEN TO ALKENES

- This type of reaction is called halogenation and an electrophilic addition.
- The general chemical formula of the halogen addition reaction is:

$C=C + X2 \longrightarrow X-C-C-X$

(X represents the halogens bromide or chlorine, and in this case, a solvent could be CH2CI2 or CCI4). The product is a vicinal alkyl halides.

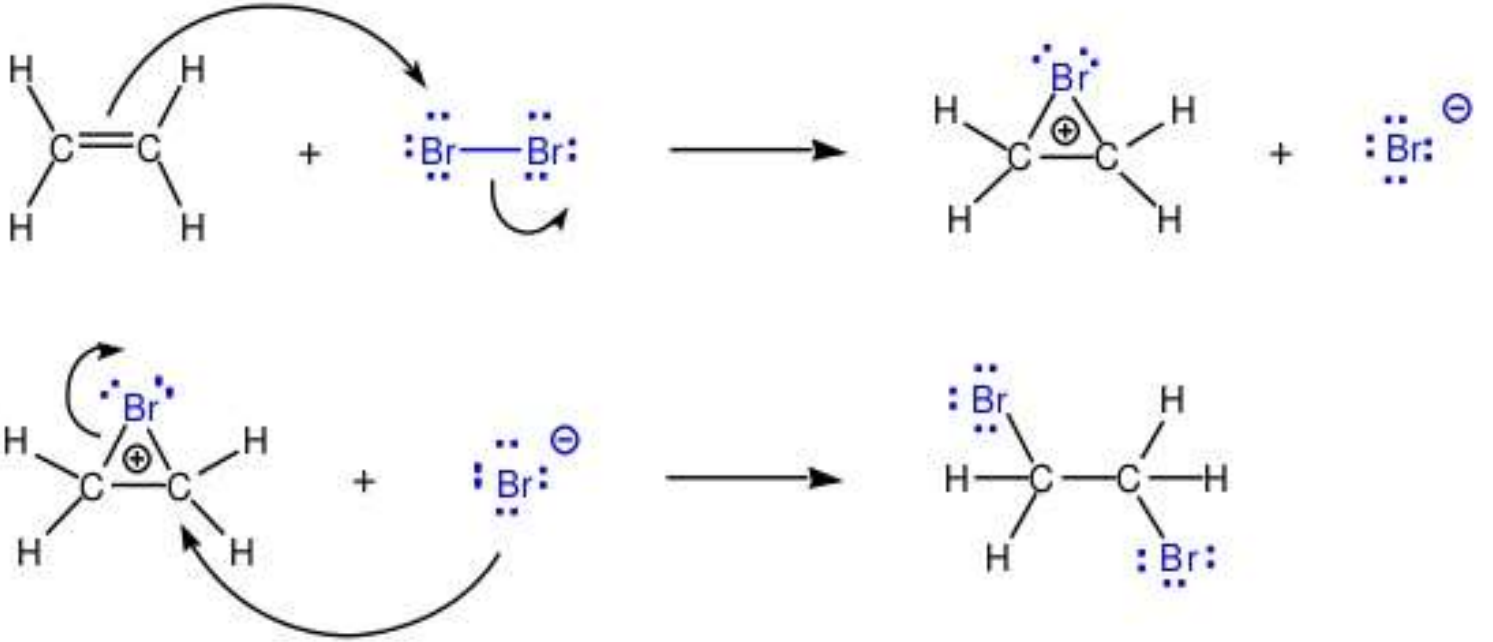
Examples:



H
H
C
C
H
H
+
Br2
Br
H
H
C
C
H
H
Br
+
Br2
Br
Br
H
C
C
CH3
+
2Br2
Br
Br
H
C
C
CH3
Br
Br

MECHANISM OF BROMINATION OF ETHENE

- First, a Br^+ is transferred from Br_2 to the alkene to form a bromonium ion and a bromide ion
- Next, the bromide ion reacts with the bromonium ion to form the product



3) ALLYLIC HALOGENATION

- Alkenes can be directly halogenated in the allylic position. High temperature and lower concentration of halogen used to prevent reaction at double bond.

- Example: N-bromosuccinimide (NBS) selectively brominates allylic positions.

Cyclohexene

3-Bromocyclohexene (85%)

B) CONVERSION OF ALCOHOL

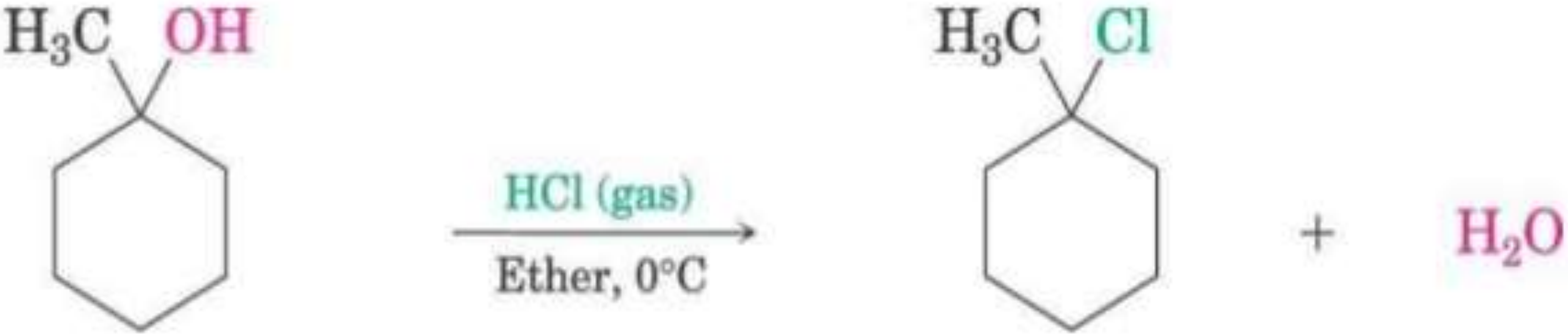
- Hydrogen halides(HCl, HBr, Hl)
- Phosphorus tribomide(PBr_3)
- Thionyl chloride($SOCl_2$)

- Alcohol react with a variety of reagents to yield alkyl halides.
- The most commonly used reagent are:

a) Hydrogen Halides (HCl, HBr, HI)

- Only tertiary alcohol actively react with hydrogen halide. Reactivity followed the sequences: tertiary > secondary > primary alcohol
- $R\text{-}OH \quad HX\text{ , }H_2SO_4 \longrightarrow R\text{-}X + H_2O$

- Reaction of tertiary C-OH with HX is fast and effective.
- Add HCI or HBr gas into ether solution of tertiary alcohol.
- Primary and secondary alcohols react very slowly and often rearrange, so alternative methods are used.



1-Methylcyclohexanol

1-Chloro-1-methylcyclohexane (90%)

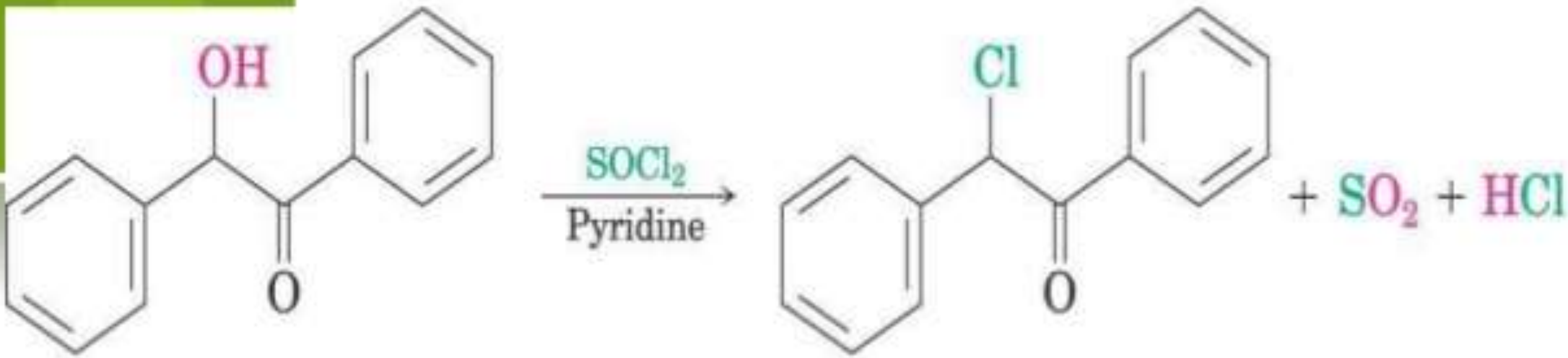
Primary and secondary alkyl halides are normally prepared from alcohols using either

b) Thionyl chloride (SOCI2)

$SOCl_2$: ROH → RCl

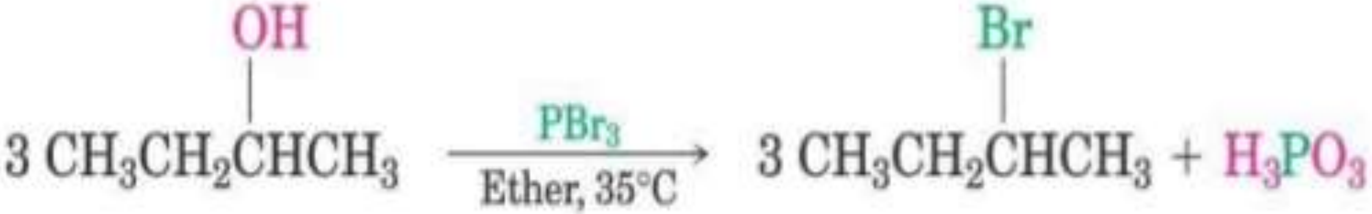
c) Phosphorus Tribromide (PBr3)

PBr_3 : ROH → RBr



Benzoin

Desyl chloride (86%)



$$3\ \mathrm{CH_3CH_2\overset{\overset{\displaystyle OH}{|}}{C}HCH_3} \xrightarrow[\text{Ether, 35°C}]{\mathrm{PBr_3}} 3\ \mathrm{CH_3CH_2\overset{\overset{\displaystyle Br}{|}}{C}HCH_3} + \mathrm{H_3PO_3}$$

2-Butanol

2-Bromobutane
(86%)

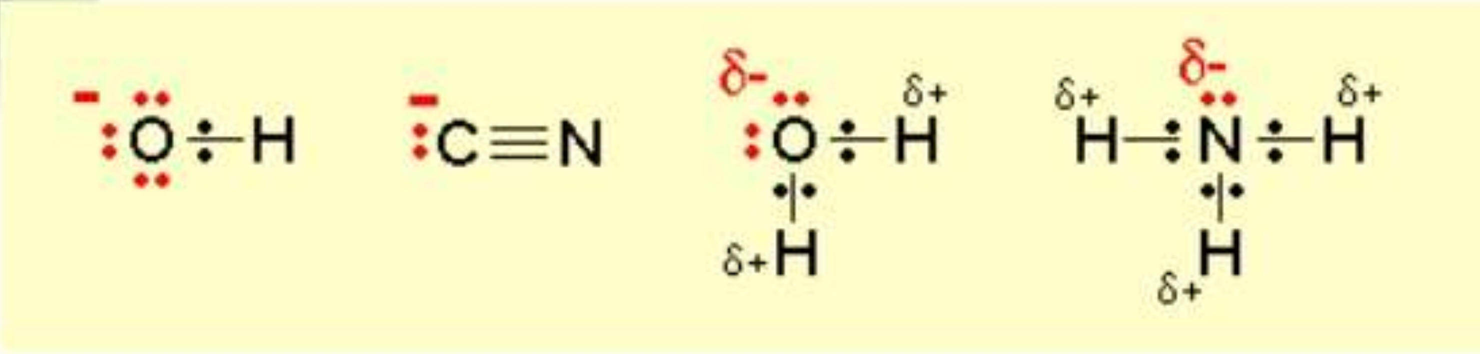
Reaction of alkyl halides

- Nucleophilic substitution reaction
  - -nucleophile
    -leaving group
  - -types :
    > S_N2
    > S_N1
- Elimination Reaction
  - E_1
  - E_2
- Organohalides Reaction
  - Grignard Reagents
  - Reduction of Alkyl Halides

Nucleophile

- Species with lone pairs(fully or slightly negative).
- Strongly attracted to a region of positive charge(nucleus).
- Weak nucleophile does not contain negative charge. Eg : H_2o, and undergo S_N1 pathway.
- Strong nucleophile contain negative charge(when in ionic form). Eg : I^- and undergo S_N2.
- Due to heterolysis of carbon-halogen bond, nucleophile form new bond with carbon atom(replace halogen).
- Examples of nucleophiles are: H_2O, NH_3, OH^-, Cl^-, Br^-, CN^-.

Examples of nucleophiles :

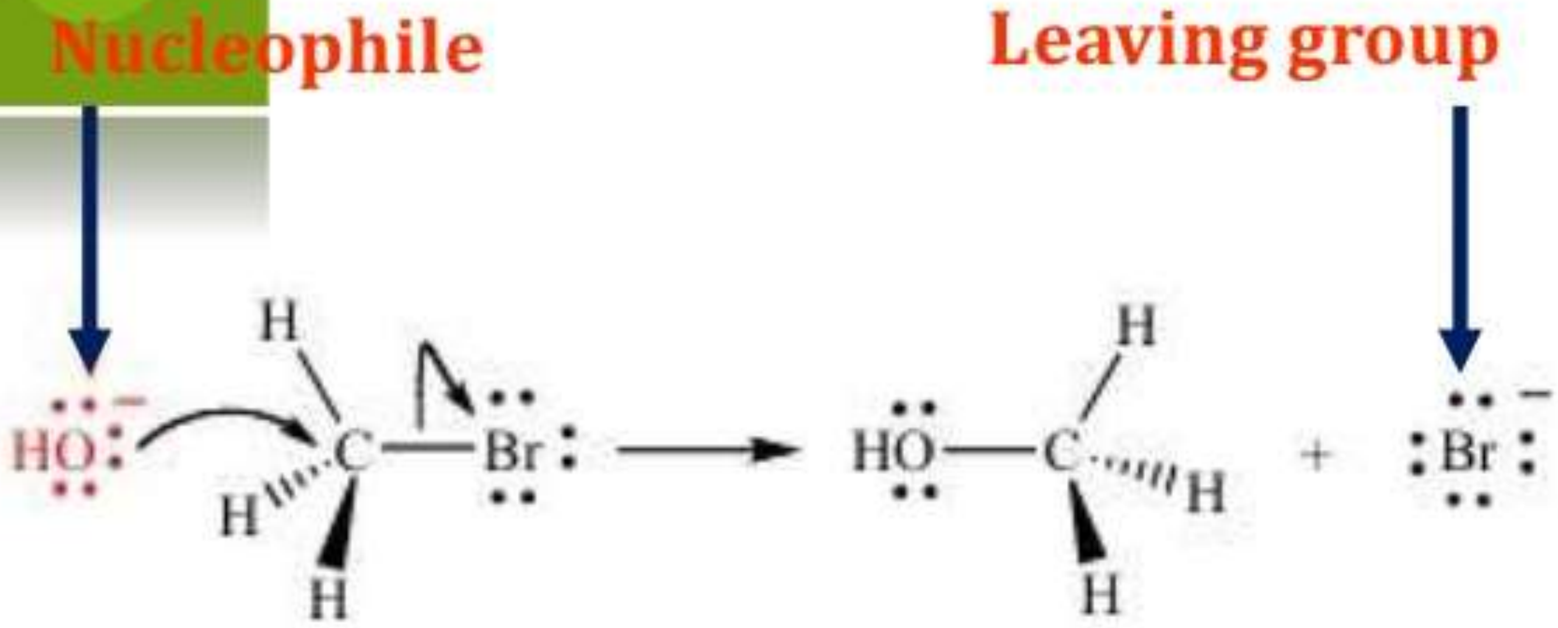


OH^- CN^- H_2O NH_3

Leaving group

- Substituent that leave substrate.
- Good substituent
  - Leave in stable condition
  - Weak molecule
- Example(s) :
  - F(strong base)
  - Br
  - Cl
  - I

(weak base)

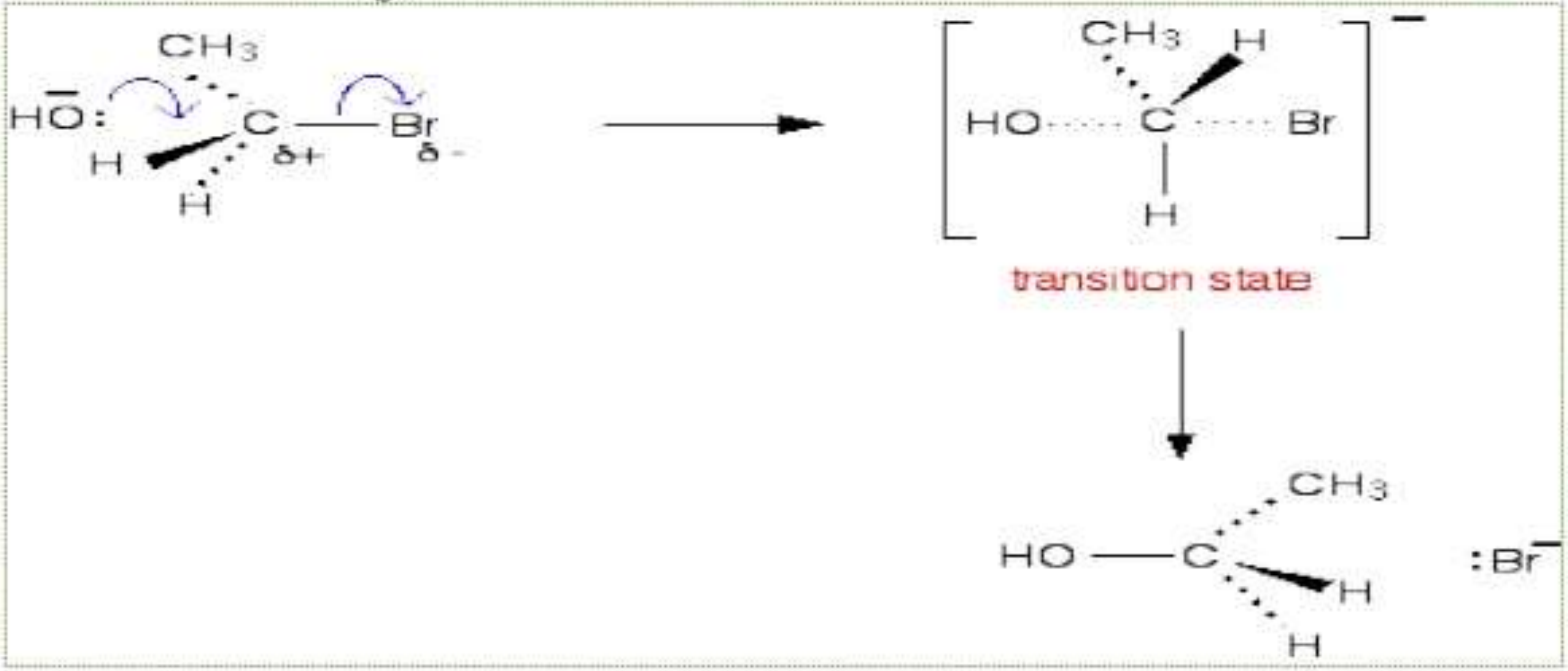


Nucleophile

Leaving group

NUCLEOPHILIC SUBSTITUTION BIMOLECULAR REACTION, S_N2

- Single step mechanism on 1° carbon.
- No intermediates, only transition state.
- Rate of reaction : *k* x [RX] x [Nu:]
- Inversion of configuration.
- Eg :

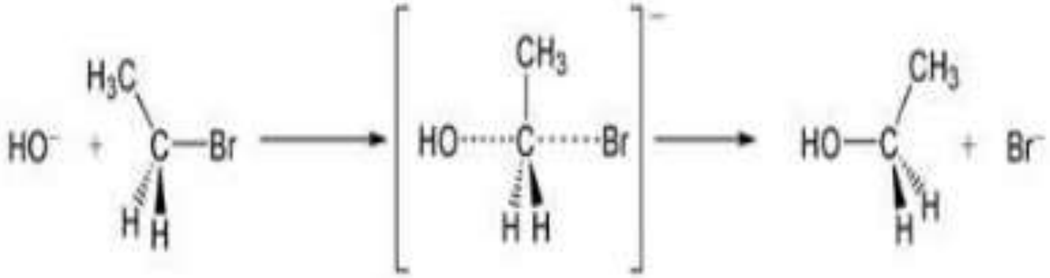


FACTOR THAT EFFECT S_N2 REACTION

- S_N2 Stereochemistry
- Steric Effect
- Nucleophile
- Solvent Effect
- Leaving Group

S_N2 STEREOCHEMISTRY

- Changes in the configuration of the carbon atom of target molecules.



- Causes the inversion of configuration at a stereocenter.

  - R or S configuration

  - cis or trans configuration

STERIC EFFECT

- Reactivity order in S_N2 : CH3 > 1 > 2 > 3
- Steric hindrance to attack by the nucleophile slows the rate
  n-Br > iso-Br > sec-Br > tert-Br

NUCLEOPHILE

- Negative charge is a stronger nucleophile than an analogous neutral species

$(OH^- > H_2O)$ & $(NH_2^- > NH_3)$

- Nucleophilicity increase from left to right across the periodic chart

$(OH^- > F^-)$

- Nucleophilicity increase down the periodic table

$(I^- > Br^- > Cl^- > F^-)$

SOLVENT EFFECT

- Protic solvent

(–OH or NH groups)

- decrease the rate of S_N2 reaction

- Aprotic solvent

(H_3COCH_3, CH_3CN , $(CH_3)_2NCHO$)

- increase the rate of S_N2 reaction

Protic solvent

Aprotic solvent

LEAVING GROUP

- The weakest bases (from strong acid) is the best leaving group

ANION	RELATIVE REACTIVITY
OH^-, NH_2^-	<< 1
F^-	1
Cl^-	200
Br^-	10,000
I^-	30,000

NUCLEOPHILIC SUBSTITUTION UNIMOLECULAR REACTION (S_N 1)

- "SN" stands for nucleophilic substitution and the "1" represents the fact that the rate-determining step is unimolecular

- The reaction show a second-order kinetics, with the rate law:

  Rate: k x[RX]

STEPS OF S_N 1 REACTION

Formation of carbocation

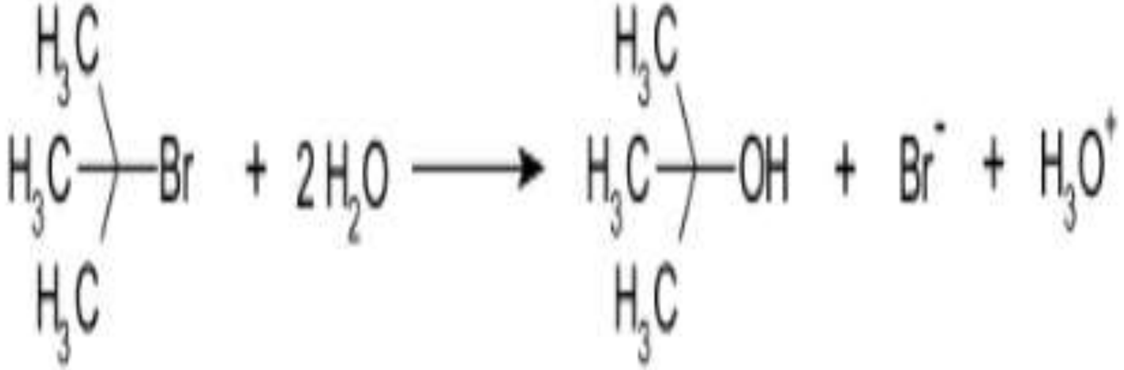
Nucleophilic attack

Deprotonation

* Only occur if nucleophili is neutral molecule

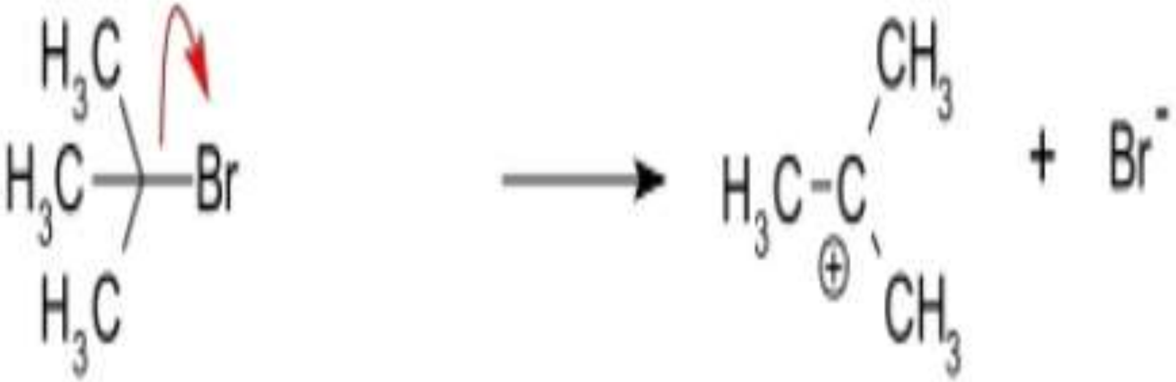
EXAMPLE

- The hydrolysis of tert-butyl bromide with water forming tert-butyl alcohol



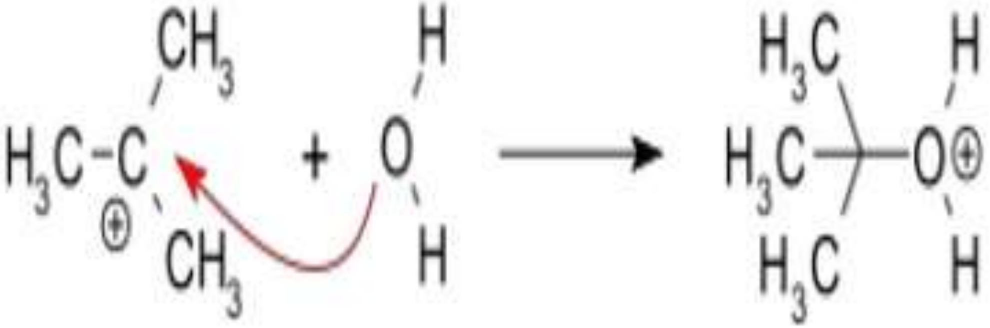
FORMATION OF A TERT-BUTYL CARBOCATION

- Separation of a leaving group (a bromide anion) from the carbon atom



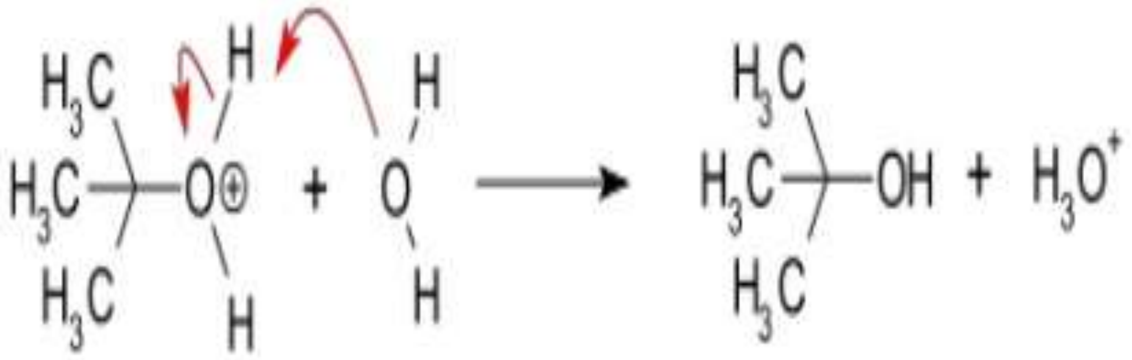
NUCLEOPHILIC ATTACK

- The carbocation reacts with the nucleophile
- When the solvent is water, the intermediate is an oxonium ion



DEPROTONATION

- Removal of a proton of the protonated nucleophile by water acting as a base forming the alcohol and a hydronium ion



S_N1

Unimolecular nucleophilic substitution

Rate determining step involves only 1 reactant.

Two steps in mechanism.

Rate = k [RX]

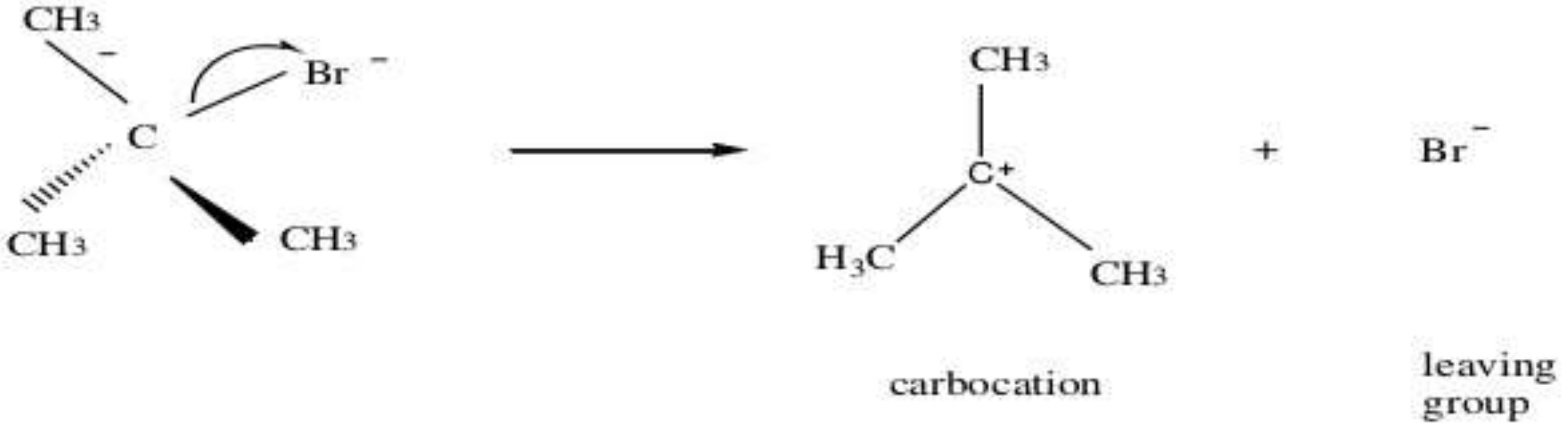
MECHANISM OF SN1

- Heterolysis of C-X bond.

  - slow reaction

  - form carbocation

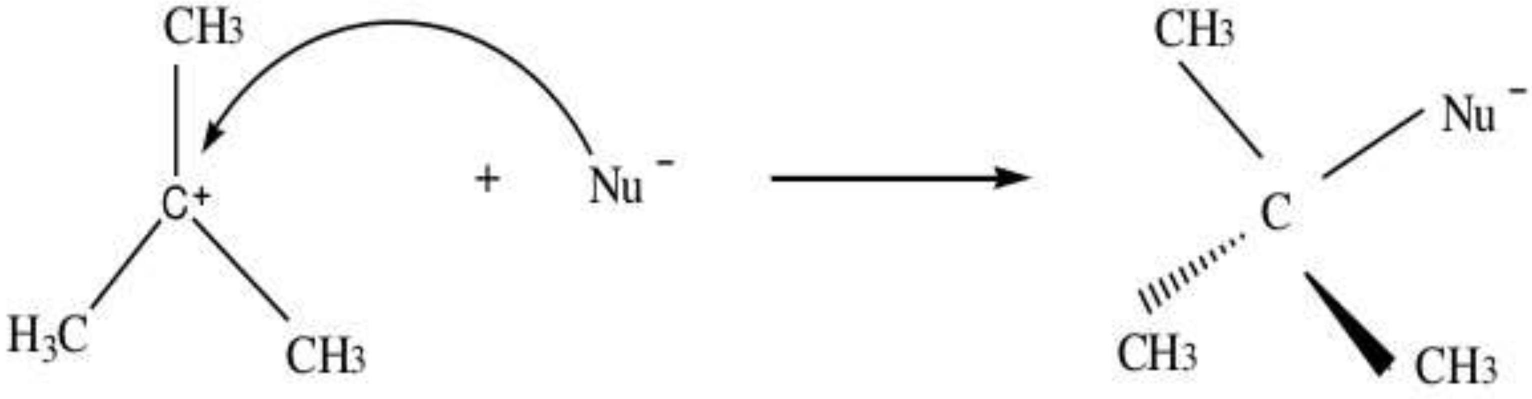
  - step for rate determining



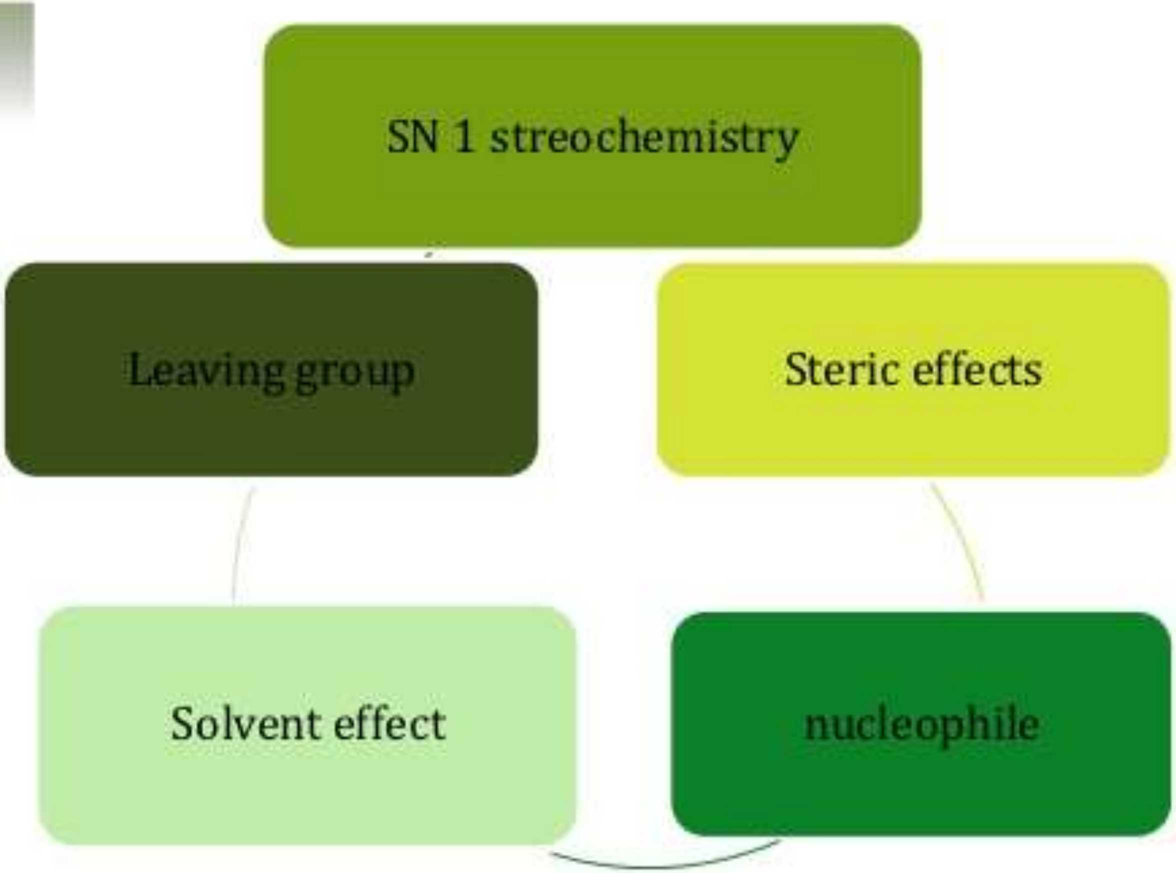
- Nucleophilic attack

  - carbocation form new bond in product.

  - fast reaction



FACTORS THAT EFFECT SN1 REACTION



SN 1 streochemistry

Leaving group

Steric effects

Solvent effect

nucleophile

FACTORS THAT AFFECT SN1 REACTION

- Carbocation formation
- Displacement from (in front, back side)
- Racemization

STREOCHEMISTRY

STERIC EFFECT

- Stability order of carbocation benzyl>3>2>1

- Nucleophile did not affect the rate of reaction of SN1
- Weak nucleophile

NUCLEOPHILE

SOLVENT EFFECT

- Protic solvent increase rate of reaction of SN1 reaction
- Protic solvent encourage solvation of carbocation
- Eg: EtOH, MeOH

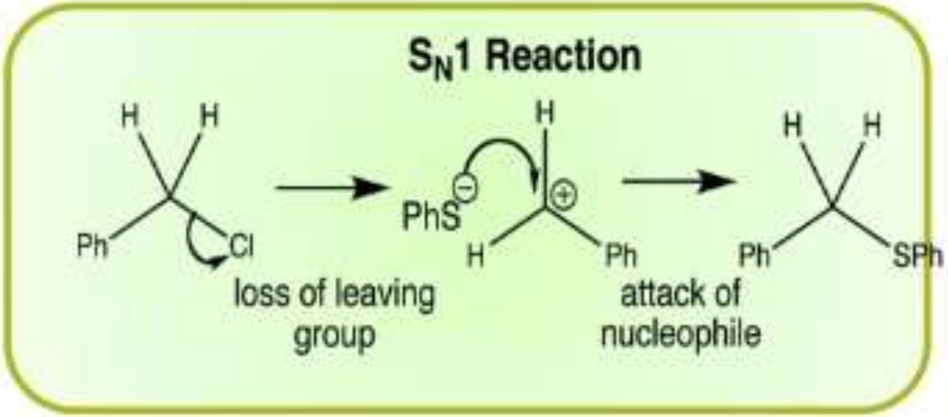
LEAVING GROUP

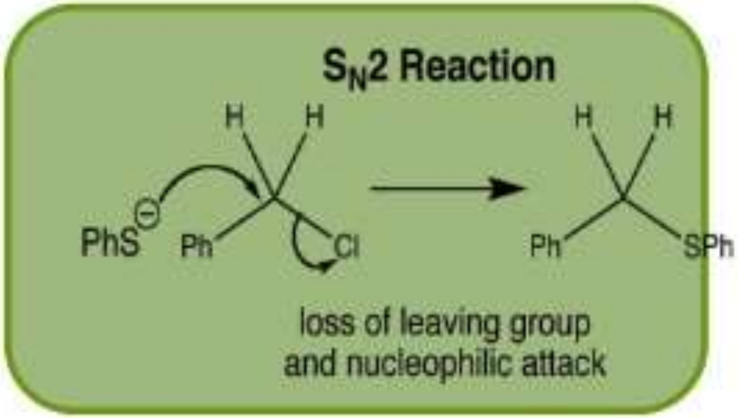
- Best leaving group
- Weakest bases from strong acid
- Stability of anion correlated to basicity

COMPARISON BETWEEN SN1 AND SN2 REACTION

PARAMETER	SN1	SN2
KINETIC	First order *k*[RX]	Second order *k*[RX][Nu:]
ALKYL HALIDE	3 > 2 > 1	CH3X > 1 > 2
LEAVING GROUP	Need good leaving group	Need good leaving group
NUCLEOPHILE	Weak nucleophile	Strong nucleophile

COMPARISON OF MECHANISM OF REACTION BETWEEN S_N1 AND S_N2 REACTION





ELIMINATION REACTION, E

Bimolecular
Elimination
Reaction, E2

Unimolecular
Elimination
Reaction, E1

E_2

Alkyl halide treated with strong base

Second order kinetics

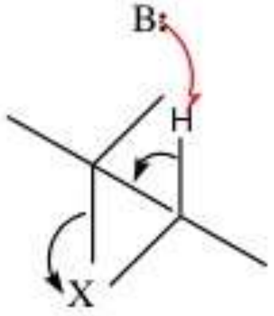
Rate = k [RX]

Occur with periplanar geometry

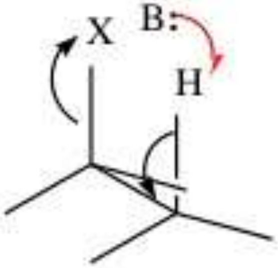
(1 hydrogen atom, 2 carbon atom, leaving group)

Possible geometry

- Syn planar geometry
- Anti planar geometry



ANTI PERIPLANAR



SYN PERIPLANAR

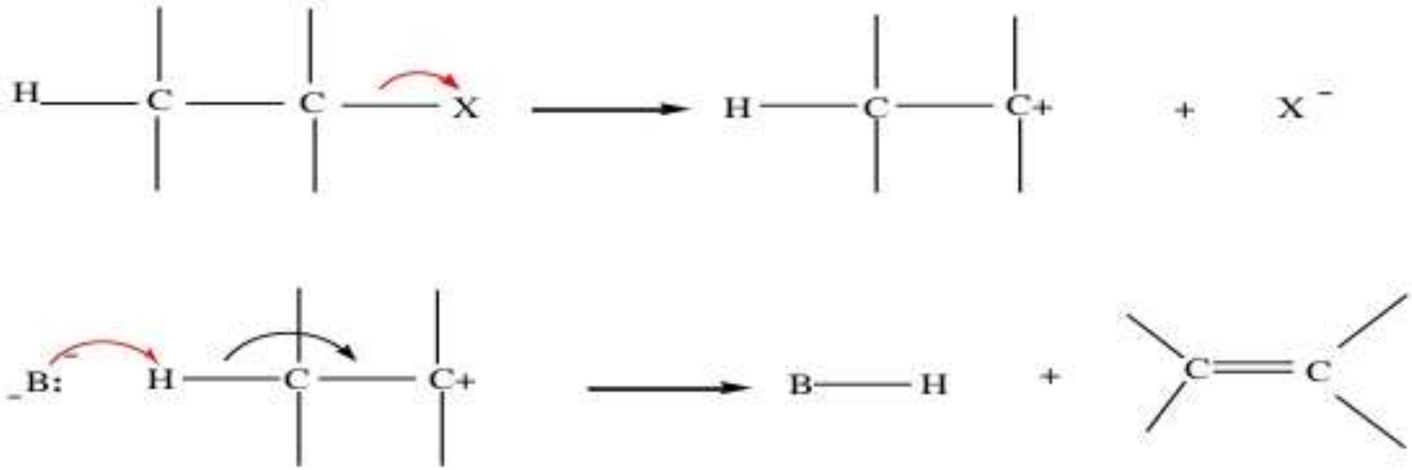
E1

- Begin with loss of leaving group to generate carbocation intermediate

Followed by loss of a proton H+ from carbocation to form double bond

- First order kinetics

  Rate = k[RX]



Grignard reagent

Reduction of alkyl halide

REACTION OF ORGANO HALIDE

GRIGNARD REAGENTS	REDUCTIONS OF ALKYL HALIDE
RX react with magnesium metal in ether or tetrahydrofuran (THF) solvent to organomagnesium halides, RMgX- grignards reagents	Reaction which alkyl halide transform to alkane