

# Reactions of Haloalkanes

The reactions of organic halides fall into three categories

**(i) Nucleophilic substitution, or  $S_N$ , reactions.**

*Those in which the halogen is replaced by some other atom or group.*

**(ii) Elimination, or E, reactions.**

*Those that involve the loss of HX from the halide.*

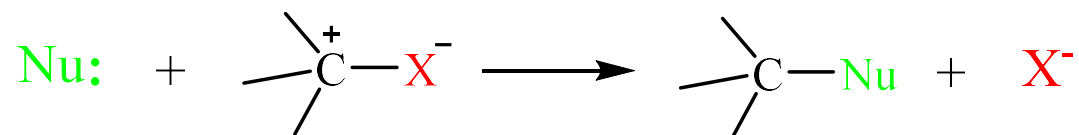
**(iii) Reaction with metals (Formation of organometallic compounds).**

*Those that involve reaction with certain metals.*

# Reactions of Haloalkanes

## Nucleophilic Substitution ( $S_N$ ) Reactions

- A nucleophile reacts with haloalkane (the substrate) having a partial positive charge on the carbon atom bonded to halogen.
- The overall process describing any  $S_N$  reaction is



**Nu:**, is the nucleophile.

*The nucleophile has an unshared electron pair available for bonding.*

**X**, is the leaving group.

*The leaving group is also a nucleophile.*

# Reactions of Haloalkanes

## Nucleophilic Substitution ( $S_N$ ) Reactions

○ The incoming nucleophile must be stronger than the leaving one.

✓ Good leaving groups include  $H_2O$  and *anions* (the conjugate bases) of strong acids, such as Cl, Br, I, and  $HSO_4^-$ .

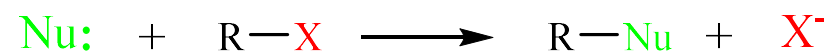
✓ Strong nucleophiles, but poor leaving groups conjugate bases of weak acids;  $HO^-$ ,  $RO^-$ , and  $CN^-$ .

✓ The iodide ion is both a good nucleophilic reagent and a good leaving group.

■ The rates of  $S_N$  reactions for a series of halides always follow the order .

C-X bond dissociation energy (kcal/mole):	R-I	>	R-Br	>	R-Cl	>>	R-F
	55		67		80		107

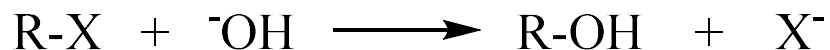
## Nucleophilic Substitution of Alkyl Halides (R-X)



# Reactions of Haloalkanes

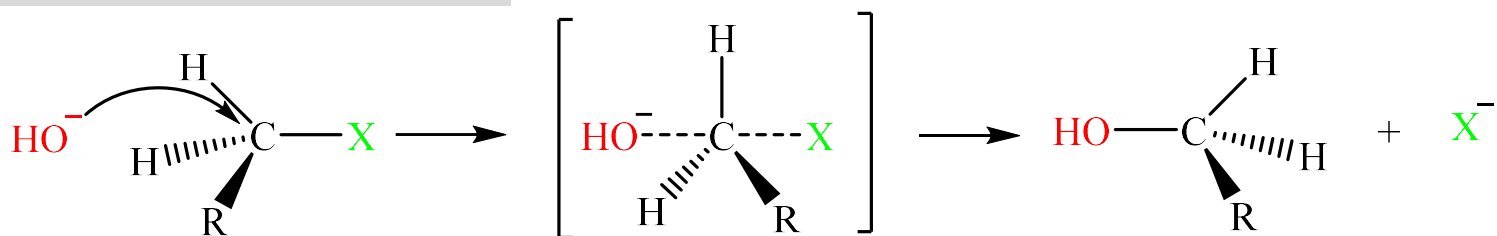
## Mechanism of Nucleophilic Substitution (S<sub>N</sub>) Reactions

- Alkyl halides may undergo nucleophilic substitutions in two different ways:
  - (i) by a one-step mechanism.
  - (ii) by a two-step mechanism.
- Which route is taken depends on
  - (i) The structure of the halide.
  - (ii) The nature of the solvent.
  - (iii) The strength of the nucleophile, Nu:.
- In general;
  - ✓ Primary alkyl halides undergo nucleophilic substitutions by the one-step mechanism.
  - ✓ Tertiary alkyl halides undergo nucleophilic substitutions by the two-step mechanism.
  - ✓ Secondary halides react by **either mechanism**.
- Let us consider the **conversion of an alkyl halide to an alcohol** by hydroxide.



# Reactions of Haloalkanes

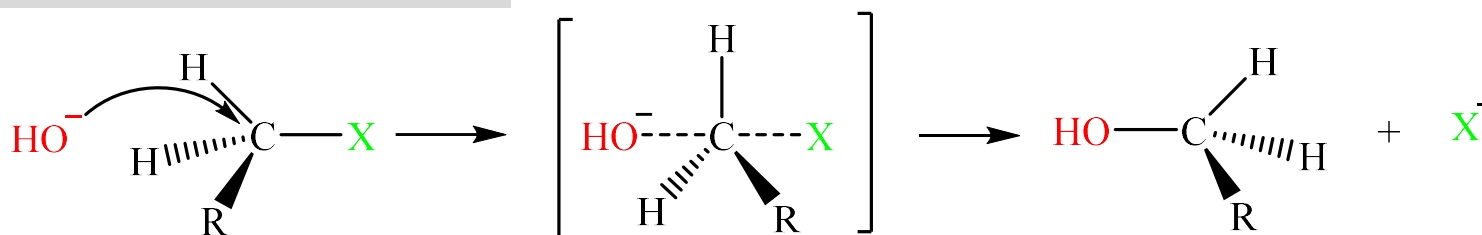
## One-Step Mechanism: S<sub>N</sub><sup>2</sup> Reactions



- The incoming nucleophile interacts with alkyl halide causing; the carbon-halide bond to break while forming a new carbon-OH bond.
- These two processes take place in a **single step** and **no intermediate** is formed.
- The nucleophile attacks the halogen-bearing carbon from the **side opposite the leaving group**; a so-called backside attack.
- **At the same time** that the **nucleophile attacks** from the back side and the **leaving group** departs, the other bonds to the carbon invert (or “flip over”).
- This flipping of the bonds, known as the **Walden inversion**.

# Reactions of Haloalkanes

## One-Step Mechanism: S<sub>N</sub><sup>2</sup> Reactions



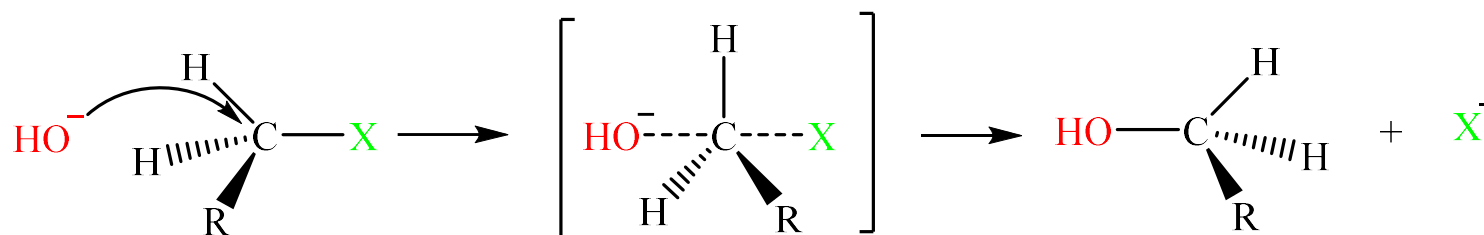
- Bimolecular Nucleophilic Substitution (S<sub>N</sub><sup>2</sup>) reaction.
- The **reaction rate** depends on the concentrations of both reactants, the **alkyl halide** and the **nucleophile**.
- For a given concentration of alkyl halide,

The rate of the reaction increases proportionally with the concentration of hydroxide ion.

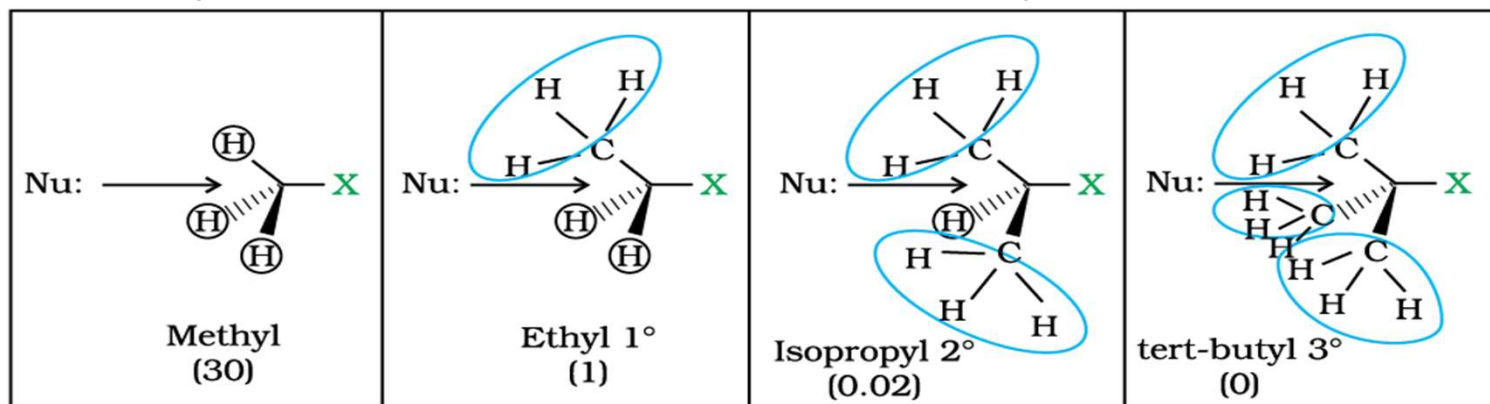
*i.e. This means that if we double the concentration of hydroxide ion, but maintain the same concentration of alkyl halide, the S<sub>N</sub> reaction proceeds twice as fast.*

# Reactions of Haloalkanes

## One-Step Mechanism: S<sub>N</sub><sup>2</sup> Reactions



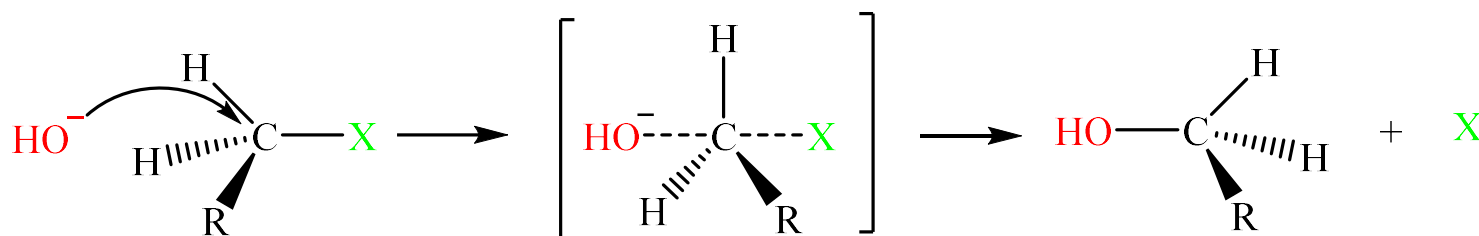
- The rates of hydrolysis follow the order; 1° RX > 2° RX > 3° RX
- Tertiary alkyl halides react slowest by the S<sub>N</sub><sup>2</sup> mechanism because the three alkyl groups on the carbon that bears the halogen hinder the backside approach of the attacking nucleophile.



Steric effects in S<sub>N</sub><sup>2</sup> reaction.

# Reactions of Haloalkanes

## One-Step Mechanism: S<sub>N</sub><sup>2</sup> Reactions



### Summary;

#### 1) S<sub>N</sub><sup>2</sup> reaction

S = substitution;

N = nucleophilic;

2 = bimolecular.

2) The S<sub>N</sub><sup>2</sup> reaction is a single, concerted process.

3) The rate of S<sub>N</sub><sup>2</sup> reaction depends on the concentrations of both the alkyl halide and the nucleophile.

4) The reaction is fastest for primary halides and slowest for tertiary halides.

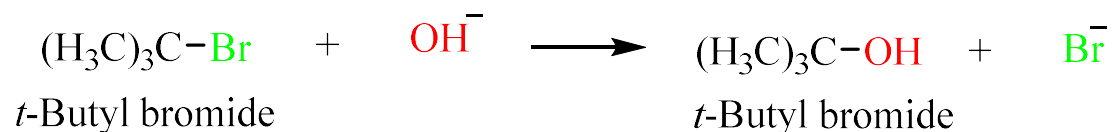
5) All S<sub>N</sub><sup>2</sup> reactions proceed with complete inversion of configuration.



# Reactions of Haloalkanes

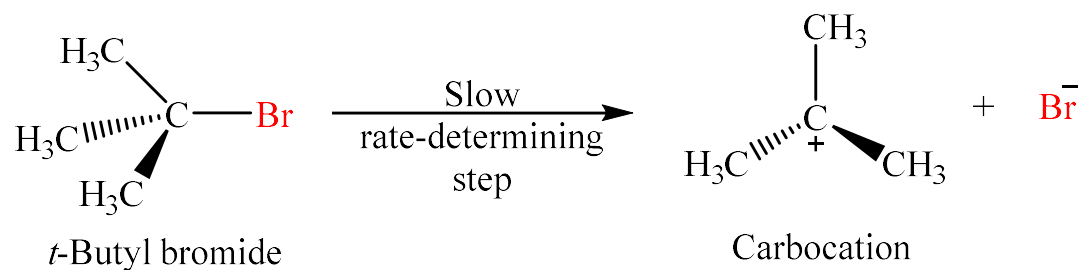
## Two-Step Mechanism: S<sub>N</sub><sup>1</sup> Reactions

- The reaction between *tert*-butyl bromide and hydroxide ion yields *tert*-butyl alcohol and follows the first order kinetics, *i.e.*, the rate of reaction depends upon the concentration of only one reactant, which is *tert*-butyl bromide.



- A mechanism that accounts for these facts involves **two steps**.

**Step 1.** The polarized C—Br bond undergoes slow cleavage to produce a **carbocation** and a bromide ion.  
*This is the slow, rate-determining step.*

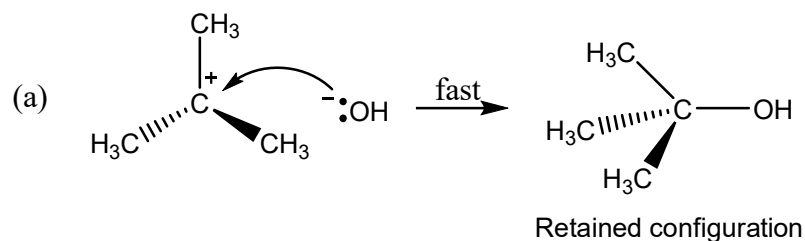


# Reactions of Haloalkanes

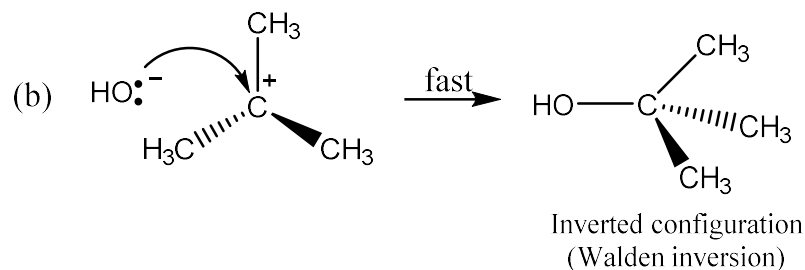
## Two-Step Mechanism: S<sub>N</sub><sup>1</sup> Reactions

**Step 2.** The carbocation thus formed is then attacked by nucleophile to complete the substitution reaction.  
*This step occurs rapidly.*

- The nucleophile has as much chance to bond with the positively charged carbon;
  - on the same side as the departed leaving group (giving *retention* of configuration)



- on the back side (leading to *inversion*).



- If the starting alkyl halide were optically active, the product would be a racemic mixture.

# Reactions of Haloalkanes

## Two-Step Mechanism: S<sub>N</sub><sup>1</sup> Reactions

- The **rate of substitution is independent of the OH<sup>-</sup> ion concentration** and **depends only on the concentration of the alkyl halide**.

The rates of S<sub>N</sub><sup>1</sup> reactions follow the order of stability of carbocation.

Benzylic > allylic = 3° > 2° > 1° halide

- S<sub>N</sub><sup>1</sup> reactions are generally carried out in **polar protic solvents** (like water, alcohol, acetic acid, etc.).
  - *Polar protic solvents have a hydrogen atom attached to an electronegative atom so the hydrogen is highly polarized and help to stabilize the transition state.*
  - Sometimes in an S<sub>N</sub><sup>1</sup> reaction is called a **solvolysis reaction** if the solvent acts as the nucleophile.
- **Weak bases are good leaving groups** as they can leave with both electrons and in order for the leaving group to leave, it needs to be able to accept electrons.
- **Strong bases can't be good leaving groups** as they donate electrons.
- **Halides are an example of a good leaving group.**



Excellent	• TsO <sup>-</sup> • NH <sub>3</sub>
Very Good	• I <sup>-</sup> • H <sub>2</sub> O
Good	• Br <sup>-</sup>
Fair	• Cl <sup>-</sup>
Poor	• F <sup>-</sup>
Very Poor	• OH <sup>-</sup> • NH <sub>2</sub> <sup>-</sup>

# Reactions of Haloalkanes

## Two-Step Mechanism: S<sub>N</sub><sup>1</sup> Reactions

### Summary

#### 1) S<sub>N</sub><sup>1</sup> reaction

S = substitution;      N = nucleophilic;      1 = unimolecular.

2) The S<sub>N</sub><sup>1</sup> reaction is a two-step process.

3) The rate-determining step is the formation of a carbocation.

4) The rates of S<sub>N</sub><sup>1</sup> reactions follow the order of stability of carbocation.

Benzylic > allylic = 3° > 2° > 1° halide

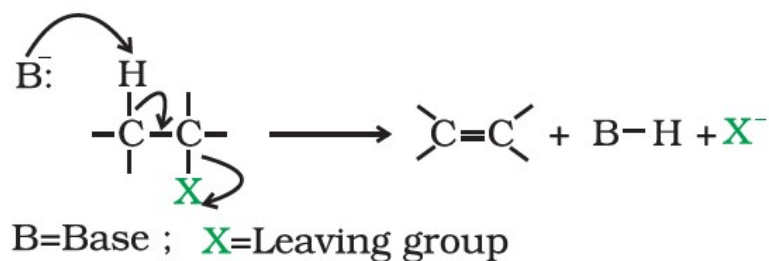
5) S<sub>N</sub><sup>1</sup> reactions proceed with racemization.

# Reactions of Haloalkanes

## Elimination Reactions

### ○ **General consideration**

Alkyl halides can lose H and X from adjacent carbons to form alkenes by an elimination process.



### ○ **Mechanism of Eliminations are of two types:**

- The **E1** (elimination unimolecular) reaction.
- The **E2** (elimination bimolecular) reaction.

### ○ **Generally**

- The **E1** process accompanies the  $S_N1$  reaction.
- The **E2** reaction accompanies the  $S_N2$  reaction.
- **E1** and **E2** eliminations follow **Saytzeff's rule**.



# Reactions of Haloalkanes

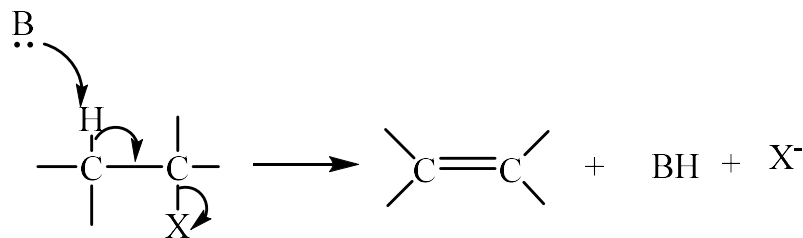
## E2 Mechanism

- **In eliminations;**

The attack by the nucleophile (acting as a base, B:) is on the hydrogen atom attached to the carbon next to the one bearing the halogen (the  $\beta$  hydrogen).

- The **E2 mechanism** involves simultaneous bond breaking and bond formation and *occurs most readily when the  $\beta$  hydrogen and the halogen atom are trans to one another.*

- *The single-step **E2 elimination.***



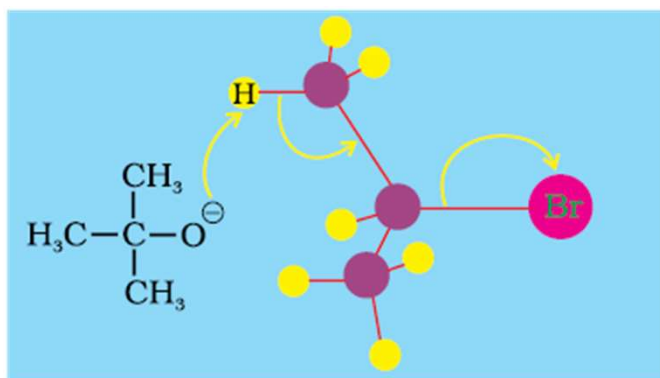
- The order of reactivity of **E2 elimination** is



# Reactions of Haloalkanes

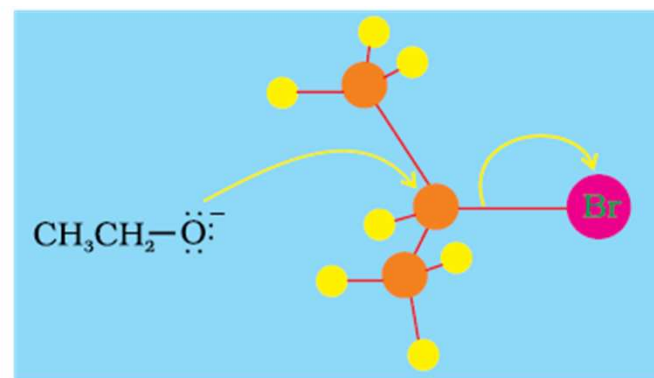
## Elimination versus Substitution

- When an alkyl halide with  $\beta$ -hydrogen atoms reacted with a base or a nucleophile, two competing routes: substitution ( $S_N^1$  and  $S_N^2$ ) and elimination.
- Which route will be taken up depends upon the *nature of alkyl halide*, *strength and size of base/nucleophile* and *reaction conditions*.
  - a **bulkier nucleophile** will prefer to act as a base and abstracts a proton rather than approach a tetravalent carbon atom (steric reasons) and vice versa.
  - a **primary alkyl halide** will prefer a  $S_N^2$  reaction,
  - a **secondary halide-  $S_N^2$  or elimination** depending upon the strength of base/nucleophile.
  - a **tertiary halide-  $S_N^1$  or elimination** depending upon the stability of carbocation or the more substituted alkene.



Elimination

vs



Substitution



# Reactions of Haloalkanes

## Elimination versus Substitution

- The most important being the **structure of the alkyl group** and the **nature of the nucleophilic reactant**.
- **Strong nucleophile favor substitution**, and **strong bases**, especially strong hindered bases (such as *tert*-butoxide) **favor elimination**.
- It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible.
- The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I.
  - In cases where both  $S_N2$  and E2 reactions compete;
    - chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens.
    - Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

# Reactions of Haloalkanes

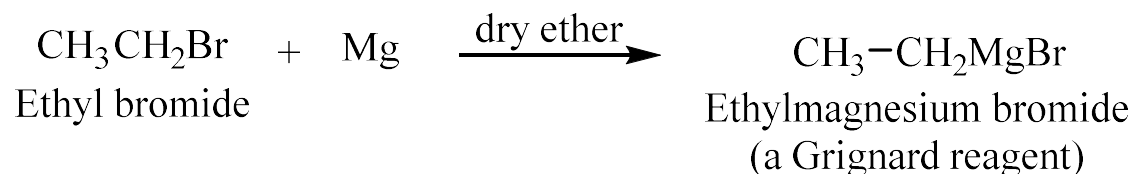
## Elimination versus Substitution

Nucleophile	Anionic Nucleophiles (Weak Bases: I <sup>-</sup> , Br <sup>-</sup> , SCN <sup>-</sup> , N <sub>3</sub> <sup>-</sup> , CH <sub>3</sub> CO <sub>2</sub> <sup>-</sup> , RS <sup>-</sup> , CN <sup>-</sup> etc.) pK <sub>a</sub> 's from -9 to 10 (left to right)	Anionic Nucleophiles (Strong Bases: HO <sup>-</sup> , RO <sup>-</sup> ) pK <sub>a</sub> 's > 15	Neutral Nucleophiles (H <sub>2</sub> O, ROH, RSH, R <sub>3</sub> N) pK <sub>a</sub> 's ranging from -2 to 11
Alkyl Group			
Primary RCH <sub>2</sub> -	Rapid S <sub>N</sub> 2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S <sub>N</sub> 2 substitution. E2 elimination may also occur. e.g. ClCH <sub>2</sub> CH <sub>2</sub> Cl + KOH → CH <sub>2</sub> =CHCl	S <sub>N</sub> 2 substitution. (N ≈ S >> O)
Secondary R <sub>2</sub> CH-	S <sub>N</sub> 2 substitution and / or E2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pK <sub>a</sub> = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β-carbons, and this will increase elimination.	E2 elimination will dominate.	S <sub>N</sub> 2 substitution. (N ≈ S >> O) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S <sub>N</sub> 1 and E1 products may be formed slowly.
Tertiary R <sub>3</sub> C-	E2 elimination will dominate with most nucleophiles (even if they are weak bases). No S <sub>N</sub> 2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S <sub>N</sub> 1 and E1 products may be expected.	E2 elimination will dominate. No S <sub>N</sub> 2 substitution will occur. In high dielectric ionizing solvents S <sub>N</sub> 1 and E1 products may be formed.	E2 elimination with nitrogen nucleophiles (they are bases). No S <sub>N</sub> 2 substitution. In high dielectric ionizing solvents S <sub>N</sub> 1 and E1 products may be formed.

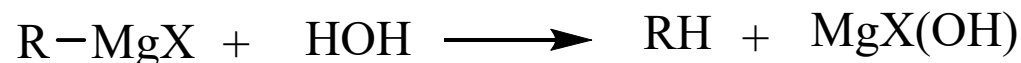
# Reactions of Haloalkanes

## Reaction with Metals

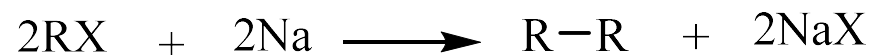
- Most organic chlorides, bromides, and iodides react with certain metals to give **organo-metallic compounds**, molecules with **carbon-metal bonds**.
- Grignard reagents** are obtained by the reaction of alkyl or aryl halides with metallic magnesium in dry ether as the solvent.



- Grignard reagents** react readily with any source of protons to give hydrocarbons.



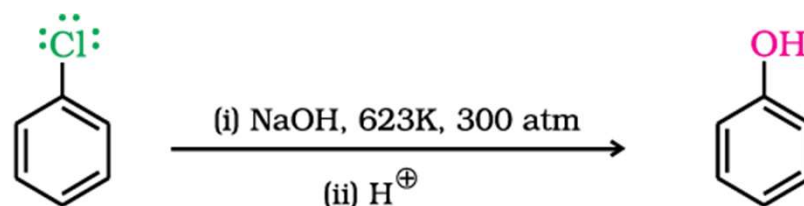
- Wurtz reaction**; Alkyl halides react with sodium in dry ether to give hydrocarbons containing double the number of carbon atoms present in the halide.



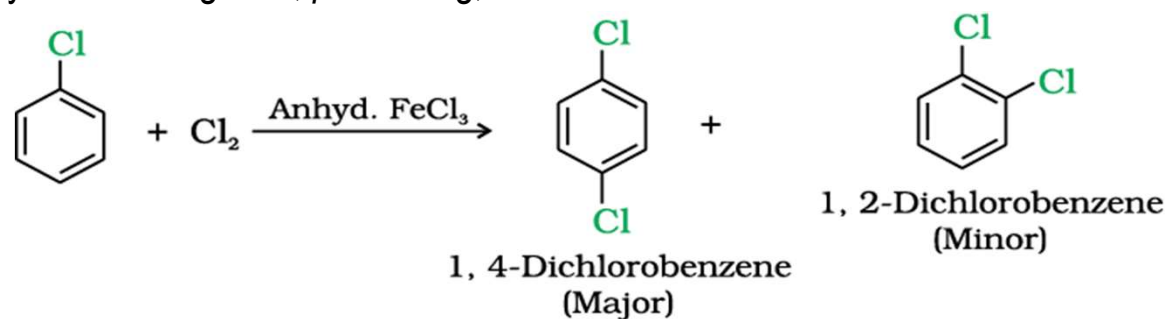
# Reactions of Haloarenes

## Replacement by hydroxyl group

- Chlorobenzene can be converted into phenol by heating in aqueous sodium hydroxide solution at a temperature of 623K and a pressure of 300 atmospheres.



- **Electrophilic substitution reactions;** Haloarenes undergo the usual electrophilic reactions of the benzene ring such as halogenation, nitration, sulphonation and Friedel-Crafts reactions.
- Halogen atom besides being slightly deactivating is *o*-, *p*-directing; .



- **Wurtz reaction;** a mixture of an alkyl halide and aryl halide gives an alkylarene when treated with sodium in dry ether

