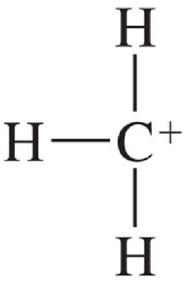
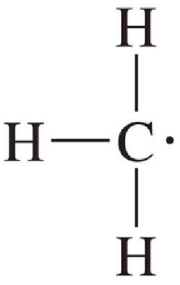
## Intermediates in organic reactions



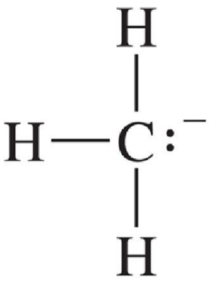
$$\begin{array}{ccc} & & \mathrm{H} \\ & & | \\ \mathrm{H} & - & \mathrm{C}^{+} \\ & & | \\ & & \mathrm{H} \end{array}$$

carbocation



$$\begin{array}{ccc} & & \mathrm{H} \\ & & | \\ \mathrm{H} & - & \mathrm{C}\cdot \\ & & | \\ & & \mathrm{H} \end{array}$$

radical

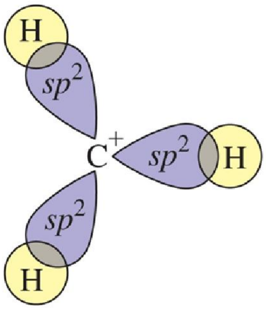


$$\begin{array}{ccc} & & \mathrm{H} \\ & & | \\ \mathrm{H} & - & \mathrm{C}:^{-} \\ & & | \\ & & \mathrm{H} \end{array}$$

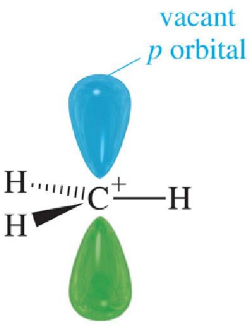
carbanion

# Intermediates in organic reactions

## Carbocations structure



top view

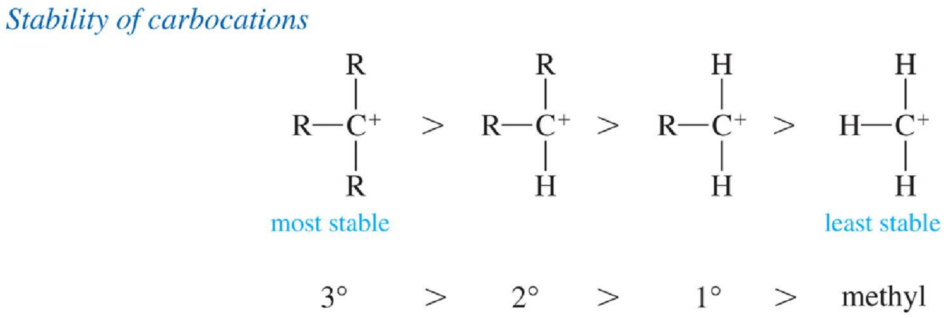


side view

- Carbon has 6 electrons, positively charged.
- Carbon is $sp^2$ hybridized with vacant *p* orbital.

# Intermediates in organic reactions

## Stability of carbocations

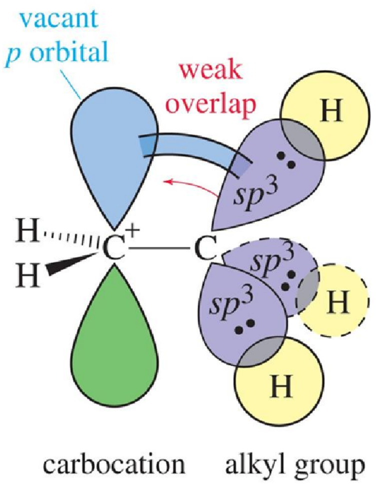


# Intermediates in organic reactions

## Stability of carbocations

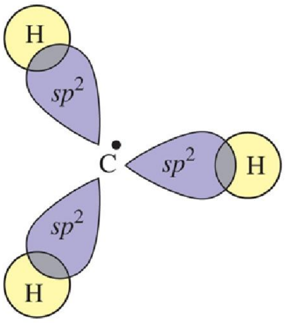
Stabilized by alkyl substituents in two ways:

1. ***Inductive effect***: Donation of electron density along the sigma bonds.
2. ***Hyperconjugation***: Overlap of sigma bonding orbitals with empty *p* orbital.

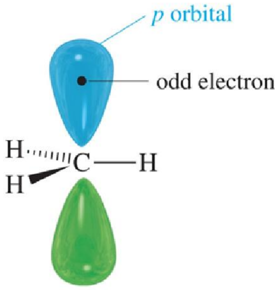


# Intermediates in organic reactions

## Carbon radicals



top view



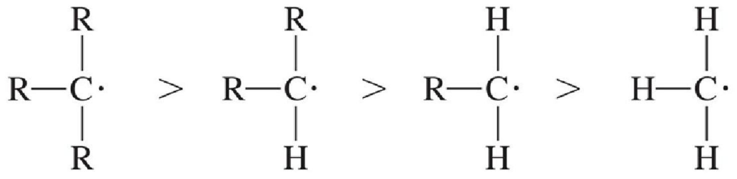
side view

- Also electron-deficient.
- Stabilized by alkyl substituents.
- Order of stability:
  3° > 2° > 1° > methyl

# Intermediates in organic reactions

## Stability of carbon radicals

*Stability of radicals*



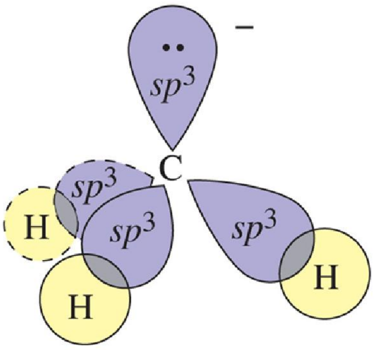
most stable  least stable

3° > 2° > 1° > methyl

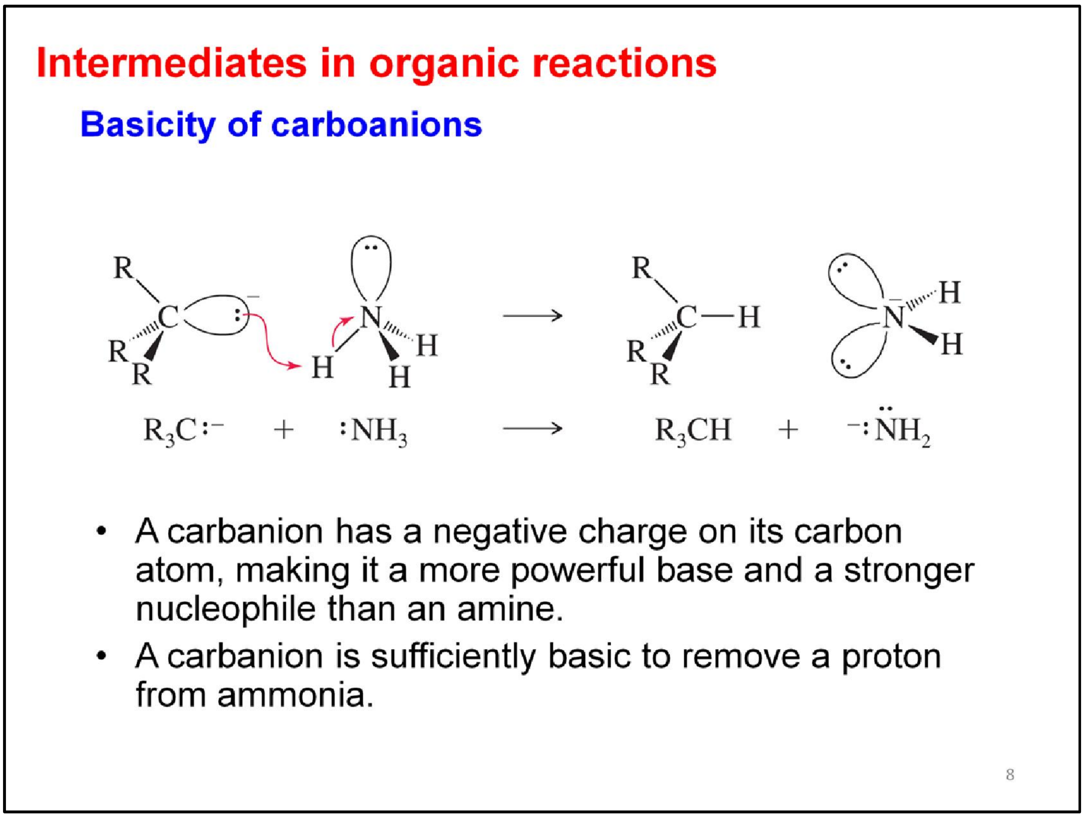
## Intermediates in organic reactions

### Carboanions structure

- Eight electrons on carbon: 6 bonding plus one lone pair.
- Carbon has a negative charge.
- Destabilized by alkyl substituents.
- Methyl >1° > 2 ° > 3 °



methyl anion



## Intermediates in organic reactions

### Basicity of carboanions

$$R_3C:^- \quad + \quad :NH_3 \quad \longrightarrow \quad R_3CH \quad + \quad ^-:\ddot{N}H_2$$

- A carbanion has a negative charge on its carbon atom, making it a more powerful base and a stronger nucleophile than an amine.
- A carbanion is sufficiently basic to remove a proton from ammonia.

Figure: 04_16-02UN.jpg

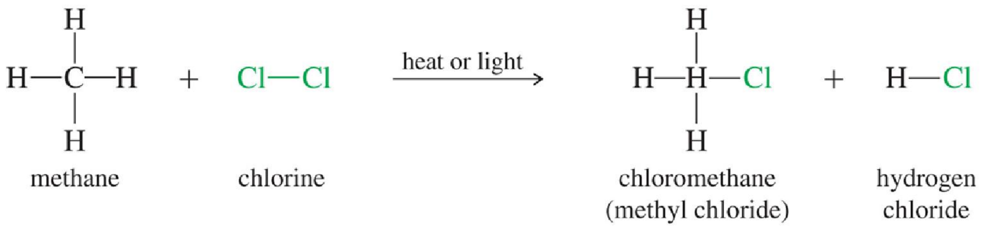
Title:
Reactivity of a Carbanion

Caption:
Like amines, carbanions are nucleophilic and basic. A carbanion has a negative charge on its carbon atom, however, making it a more powerful base and a stronger nucleophile than an amine. For example, a carbanion is sufficiently basic to remove a proton from ammonia.

Notes:
Carbanions are a stronger base than amines, so they can deprotonate amines easily.

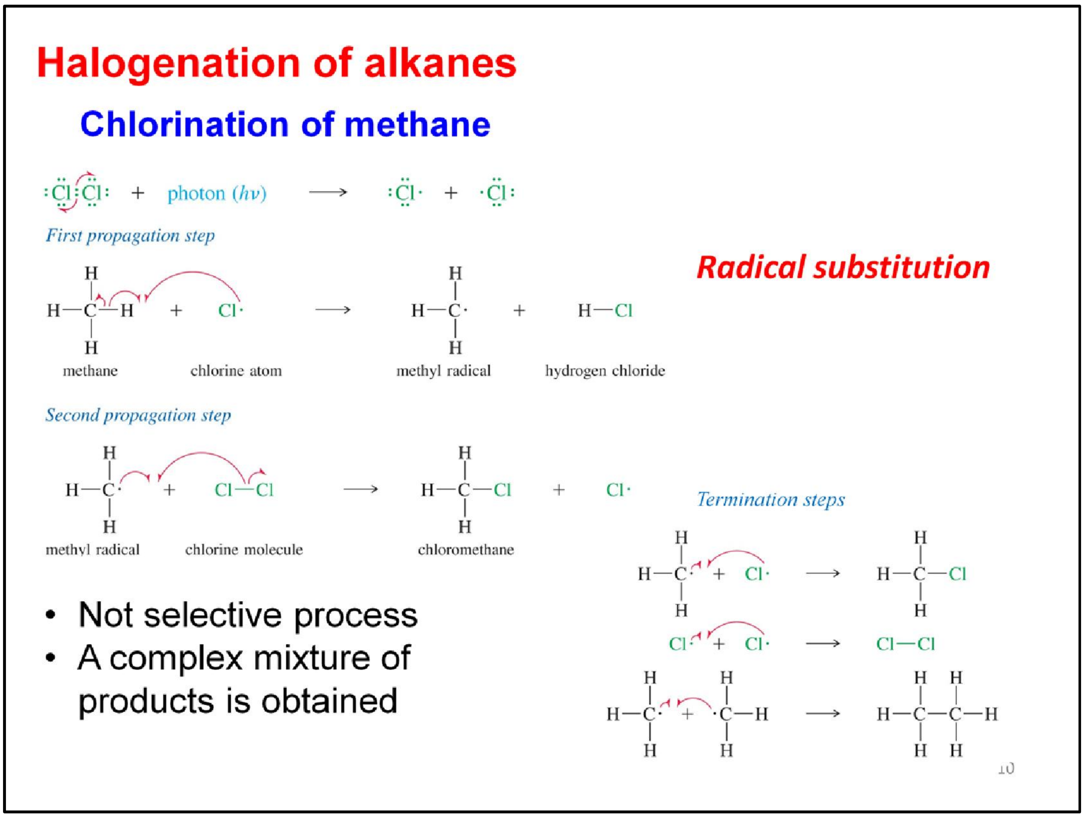
# Halogenation of alkanes

## Chlorination of methane



$$CH_4 + Cl_2 \xrightarrow{\text{heat or light}} CH_3Cl + HCl$$

- Requires heat or light for initiation.
- The most effective wavelength is blue, which is absorbed by chlorine gas.
- Many molecules of product are formed from absorption of only one photon of light (chain reaction).



# Halogenation of alkanes

## Chlorination of methane

**Radical substitution**

- Not selective process
- A complex mixture of products is obtained

Figure: 03_04.jpg

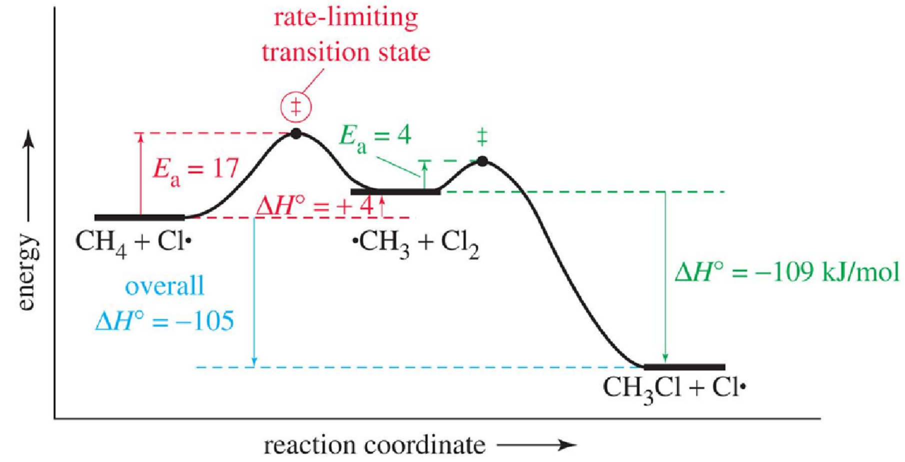
Title:
Melting Points of Alkanes

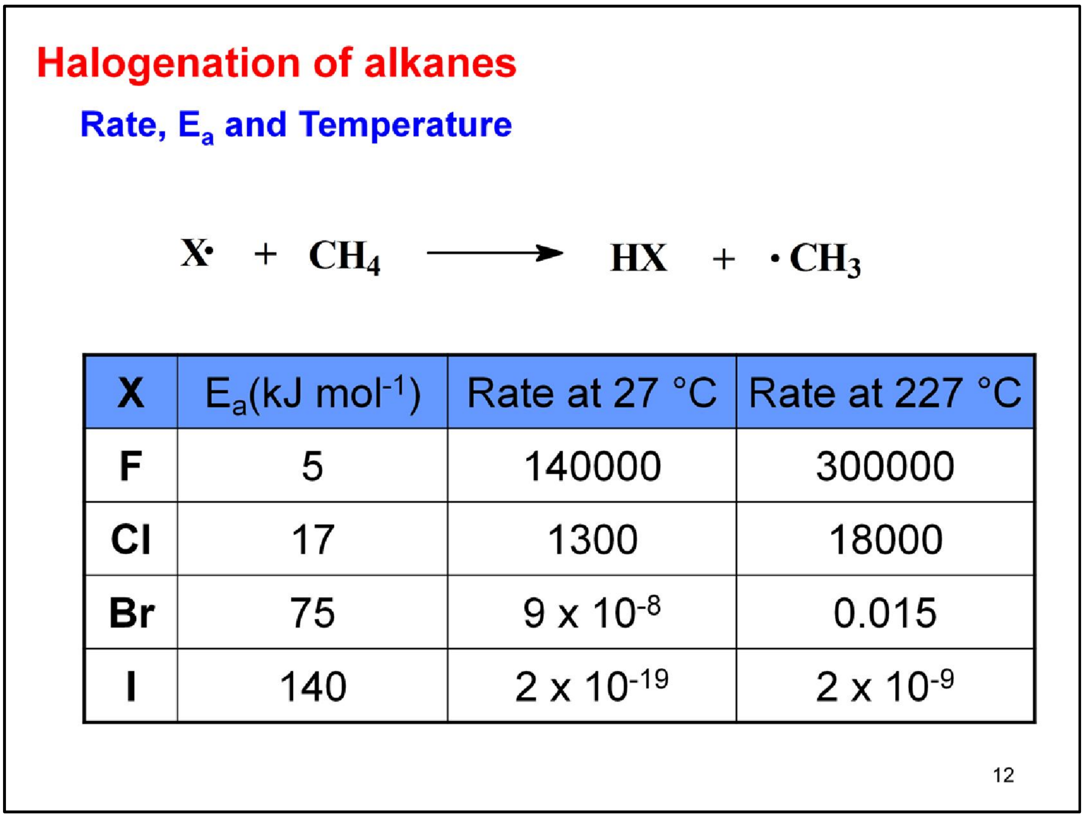
Caption:
Alkane melting points. The melting point curve for *n*-alkanes with even numbers of carbon atoms is slightly higher than that for alkanes with odd numbers of carbons.

Notes:
In solids, the packing of the molecules into a three dimensional structure affects the melting point. When molecules can pack in neat order avoiding empty pockets the melting point will be higher than when the packing is not ordered. Alkanes with an even number of carbons pack better than those with an odd number of carbons.

# Halogenation of alkanes

## Energy Diagram for the Chlorination of Methane



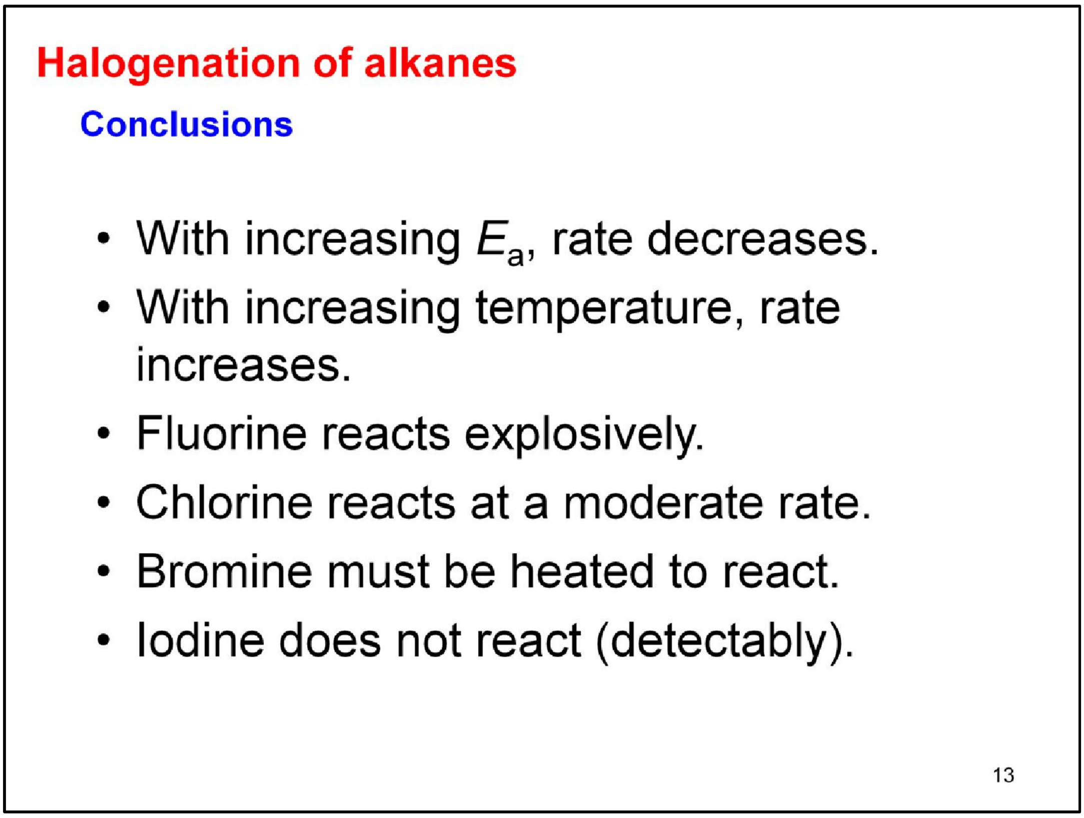


# Halogenation of alkanes

## Rate, $E_a$ and Temperature

$$X\cdot + CH_4 \longrightarrow HX + \cdot CH_3$$

| X | $E_a$(kJ $mol^{-1}$) | Rate at 27 °C | Rate at 227 °C |
|---|---|---|---|
| F | 5 | 140000 | 300000 |
| Cl | 17 | 1300 | 18000 |
| Br | 75 | $9 \times 10^{-8}$ | 0.015 |
| I | 140 | $2 \times 10^{-19}$ | $2 \times 10^{-9}$ |



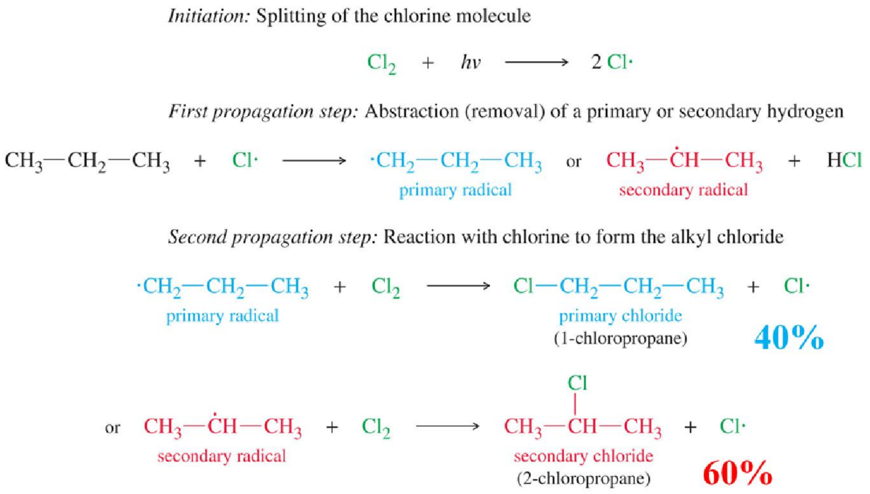
## Halogenation of alkanes

### Conclusions

- With increasing $E_a$, rate decreases.
- With increasing temperature, rate increases.
- Fluorine reacts explosively.
- Chlorine reacts at a moderate rate.
- Bromine must be heated to react.
- Iodine does not react (detectably).

# Halogenation of alkanes

## Chlorination of propane



*Initiation:* Splitting of the chlorine molecule

$$Cl_2 + h\nu \longrightarrow 2\,Cl\cdot$$

*First propagation step:* Abstraction (removal) of a primary or secondary hydrogen

$$CH_3{-}CH_2{-}CH_3 + Cl\cdot \longrightarrow \underset{\text{primary radical}}{\cdot CH_2{-}CH_2{-}CH_3} \text{ or } \underset{\text{secondary radical}}{CH_3{-}\dot{C}H{-}CH_3} + HCl$$

*Second propagation step:* Reaction with chlorine to form the alkyl chloride

$$\underset{\text{primary radical}}{\cdot CH_2{-}CH_2{-}CH_3} + Cl_2 \longrightarrow \underset{\text{primary chloride}}{Cl{-}CH_2{-}CH_2{-}CH_3} + Cl\cdot$$

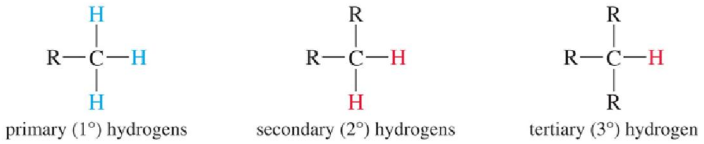
(1-chloropropane) **40%**

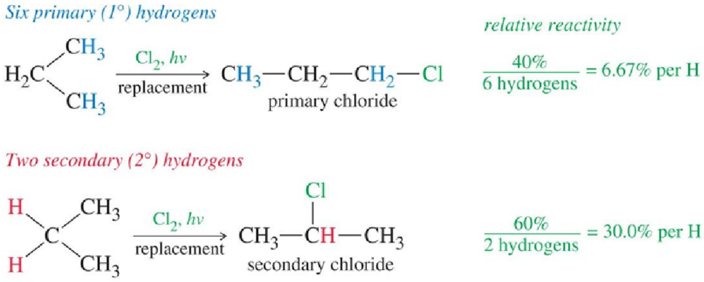
$$\text{or } \underset{\text{secondary radical}}{CH_3{-}\dot{C}H{-}CH_3} + Cl_2 \longrightarrow \underset{\text{secondary chloride}}{CH_3{-}\overset{\overset{Cl}{|}}{C}H{-}CH_3} + Cl\cdot$$

(2-chloropropane) **60%**

# Halogenation of alkanes

## Primary, Secondary and Tertiary Hydrogens

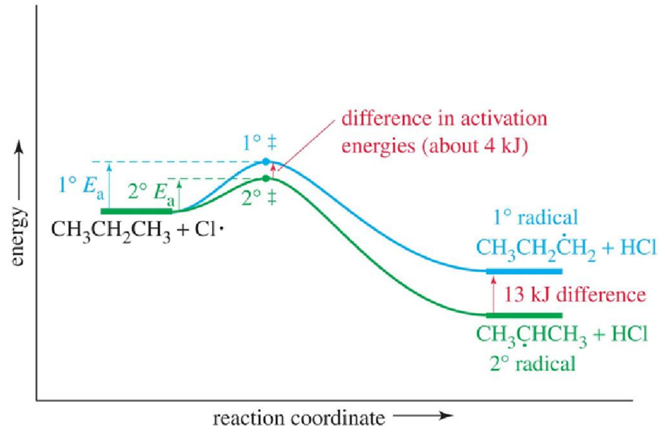




The 2° hydrogens are $\frac{30.0}{6.67} = 4.5$ times as reactive as the 1° hydrogens.

# Halogenation of alkanes

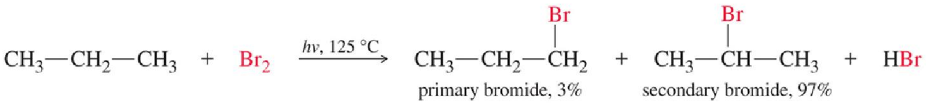
## Chlorination Energy Diagram



Lower $E_a$, faster rate, so more stable intermediate is formed faster.

# Halogenation of alkanes

## Bromination of Propane



$$CH_3-CH_2-CH_3 + Br_2 \xrightarrow{h\nu,\ 125\ ^\circ C} CH_3-CH_2-\overset{Br}{\overset{|}{CH_2}} + CH_3-\overset{Br}{\overset{|}{CH}}-CH_3 + HBr$$

primary bromide, 3%

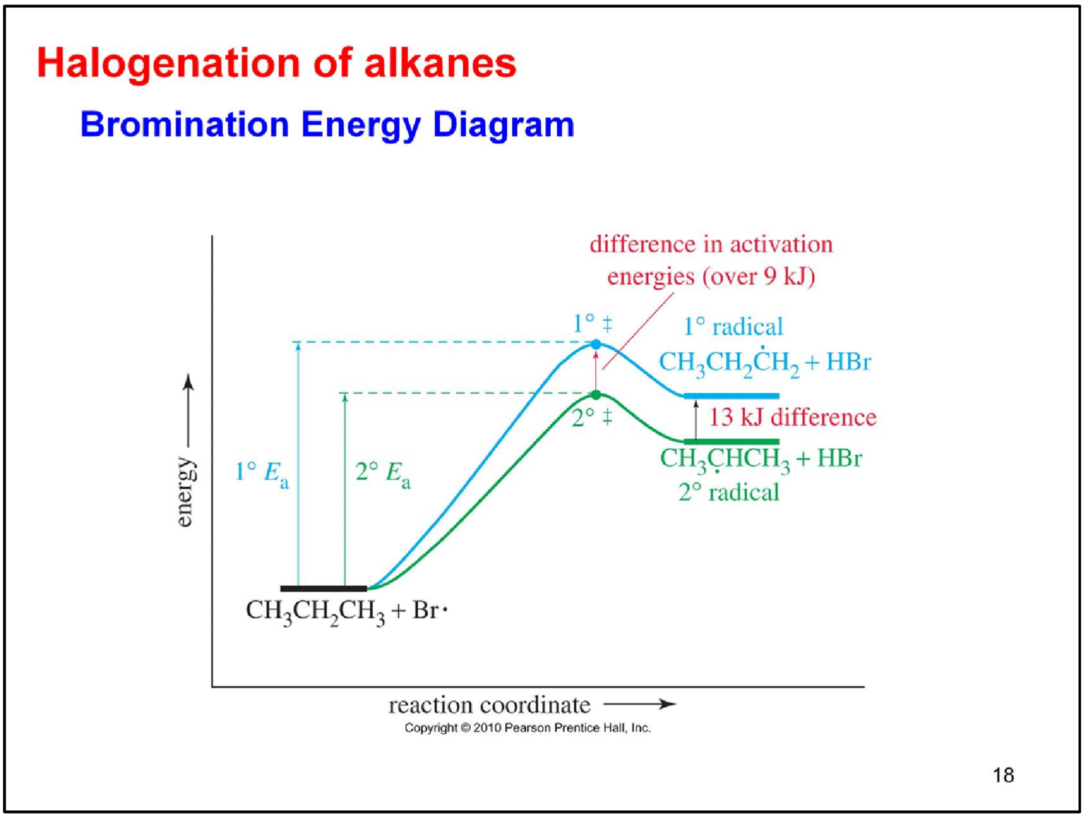
secondary bromide, 97%

*Relative reactivity*

six primary hydrogens $\frac{3\%}{6} = 0.5\%$ per H

two secondary hydrogens $\frac{97\%}{2} = 48.5\%$ per H

The 2° hydrogens are $\frac{48.5}{0.5} = 97$ times as reactive as the 1° hydrogens.



## Halogenation of alkanes

### Bromination Energy Diagram

Figure: 04_10.jpg

Title:
Energy Diagram for the Bromination of Propane

Caption:
Reaction-energy diagram for the first propagation step in the bromination of propane. The energy difference in the transition states is nearly as large as the energy difference in the products.

Notes:

## Halogenation of alkanes

### Hammond postulate

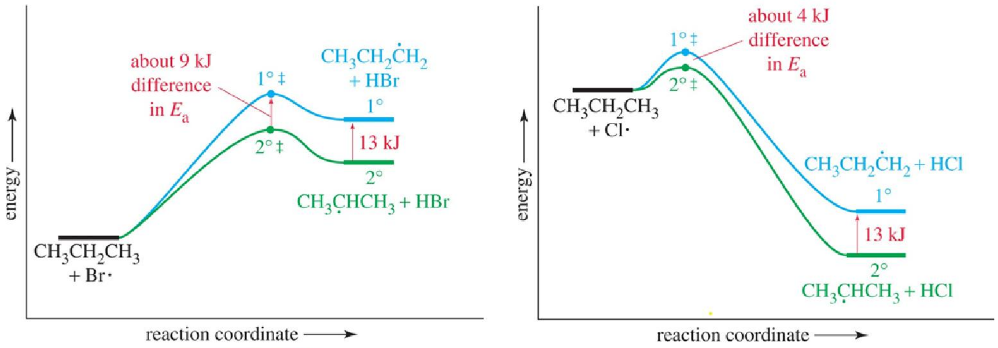
- Related species that are similar in energy are also similar in structure.
- The structure of the transition state resembles the structure of the closest stable species.

- ***Endothermic reaction***: Transition state is product-like.

- ***Exothermic reaction***: Transition state is reactant-like.

# Halogenation of alkanes

## Energy Diagrams: Chlorination Versus Bromination

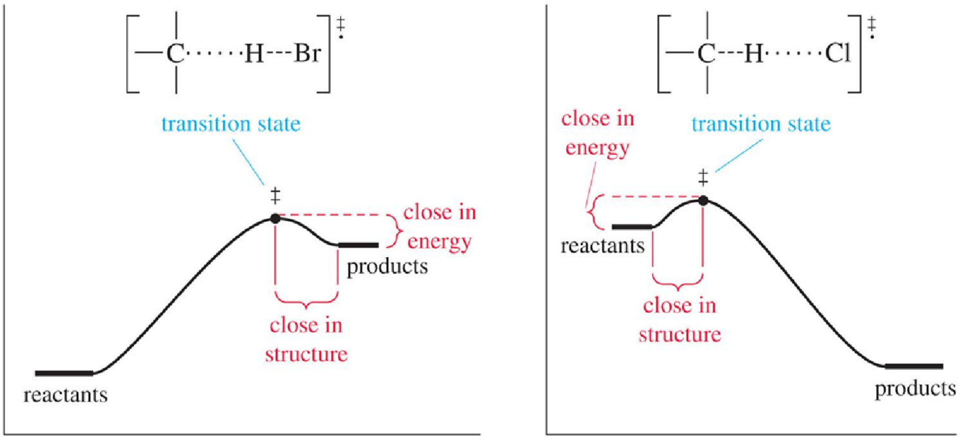


(a) BROMINATION
endothermic
TS close to products
large difference in $E_a$

(b) CHLORINATION
exothermic
TS close to reactants
small difference in $E_a$

# Halogenation of alkanes

## Endothermic and Exothermic Diagrams



# Electrophilic addition

## Types of additions

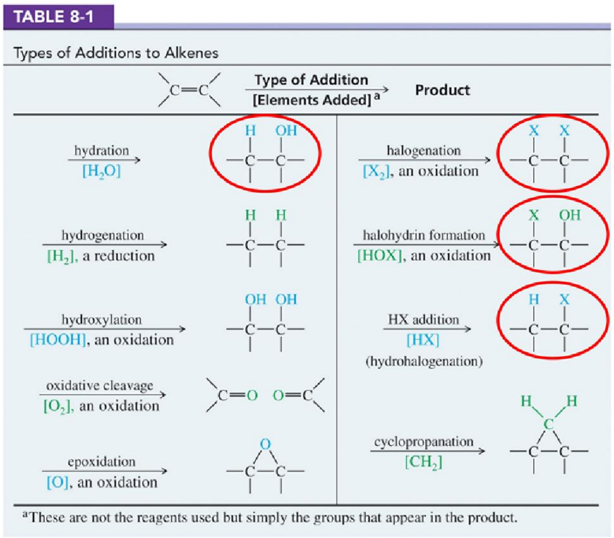


**TABLE 8-1**

Types of Additions to Alkenes

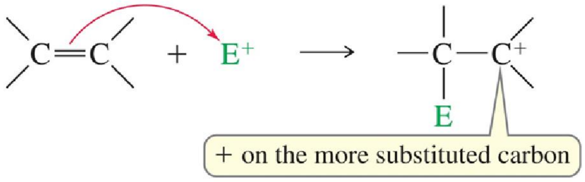
| Type of Addition | [Elements Added]$^a$ | Product |
|---|---|---|
| hydration | $[H_2O]$ | H, OH |
| hydrogenation | $[H_2]$, a reduction | H, H |
| hydroxylation | [HOOH], an oxidation | OH, OH |
| oxidative cleavage | $[O_2]$, an oxidation | C=O O=C |
| epoxidation | [O], an oxidation | O |
| halogenation | $[X_2]$, an oxidation | X, X |
| halohydrin formation | [HOX], an oxidation | X, OH |
| HX addition (hydrohalogenation) | [HX] | H, X |
| cyclopropanation | $[CH_2]$ | H, H, C |

$^a$These are not the reagents used but simply the groups that appear in the product.

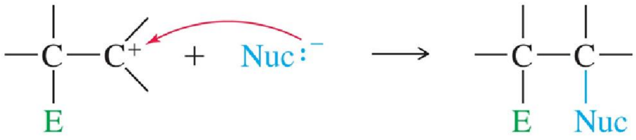
# Electrophilic addition

## General mechanism

- Step 1: Pi electrons attack the electrophile.



- Step 2: Nucleophile attacks the carbocation.



# Electrophilic addition

## Regioselectivity

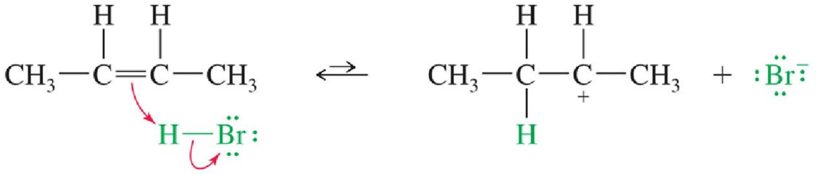
### Markovnikov's Rule (extended)

In an electrophilic addition to the alkene, the electrophile adds in such a way that it generates the most stable intermediate.

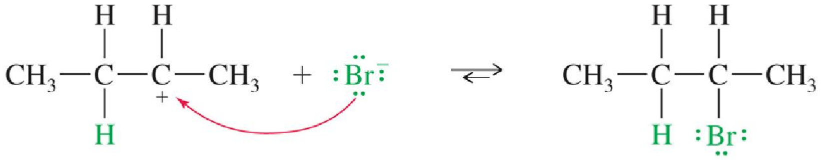
# Electrophilic addition

## Mechanism of addition of HX

Step 1: Protonation of the double bond.

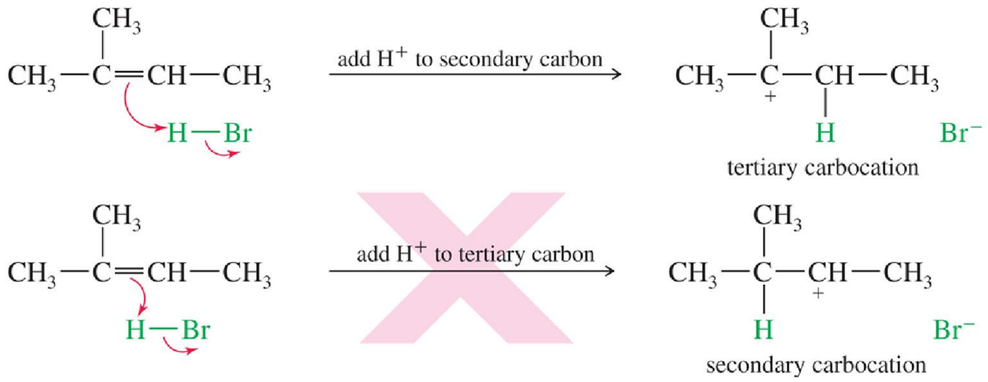


Step 2: Nucleophilic attack of the halide on the carbocation.



## Electrophilic addition

### Markovnikov's rule



The acid proton will bond to carbon 3 in order to produce the most stable carbocation possible.

## Electrophilic addition

### Free-radical addition of HBr

- In the presence of peroxides, HBr adds to an alkene to form the “anti-Markovnikov” product.
- Peroxides produce free radicals.
- Only HBr has the right bond energy.
- The HCl bond is too strong, so it will add according to Markovnikov’s rule, even in the presence of peroxide.
- The HI bond tends to break heterolytically to form ions, it too will add according to Markovnikov’s rule.

## Electrophilic addition

### Free-radical initiation

- The peroxide bond breaks homolytically to form the first radical:

$$R{-}O{-}O{-}R \xrightarrow{\text{heat}} R{-}O\cdot + \cdot O{-}R$$

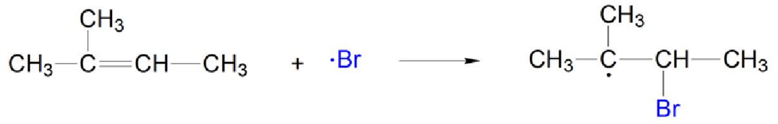
$$R{-}O\cdot + H{-}Br \longrightarrow R{-}O{-}H + Br\cdot$$

- Hydrogen is abstracted from HBr.

# Electrophilic addition

## Propagation steps

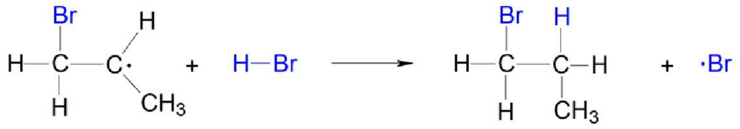
- Bromine adds to the double bond forming the most stable radical possible:



$CH_3-C(CH_3)=CH-CH_3 + \cdot Br \longrightarrow CH_3-\dot{C}(CH_3)-CH(Br)-CH_3$

tertiary radical (more stable)

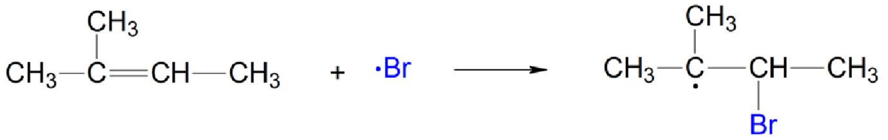
- Hydrogen is abstracted from HBr:



$H_2C(Br)-\dot{C}H(CH_3) + H-Br \longrightarrow H_2C(Br)-CH_2(CH_3) + \cdot Br$

# Electrophilic addition

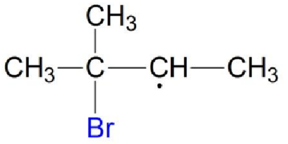
## Anti-Markovnikov stereochemistry



$$CH_3-\overset{CH_3}{C}=CH-CH_3 + \cdot Br \longrightarrow CH_3-\overset{CH_3}{\underset{\bullet}{C}}-\underset{Br}{CH}-CH_3$$

tertiary radical (more stable)

- The intermediate tertiary radical forms faster because it is more stable.



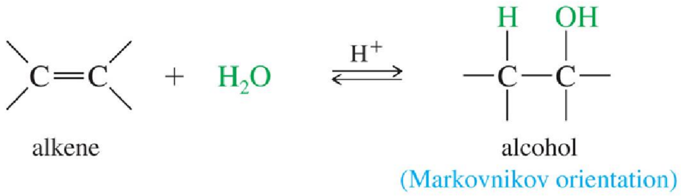
$$CH_3-\overset{CH_3}{\underset{Br}{C}}-\underset{\bullet}{CH}-CH_3$$

secondary radical (less stable)
**not formed**

# Electrophilic addition

## Hydration of alkenes

*Hydration of an alkene*

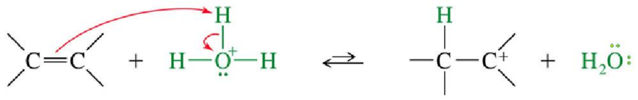


- The Markovnikov addition of water to the double bond forms an alcohol.
- Uses dilute solutions of $H_2SO_4$ or $H_3PO_4$ to drive equilibrium toward hydration.

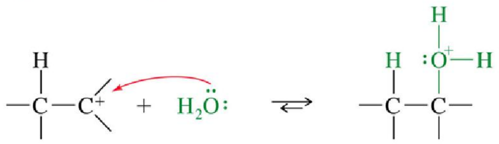
# Electrophilic addition

## Mechanism for hydration

*Step 1:* Protonation of the double bond forms a carbocation.



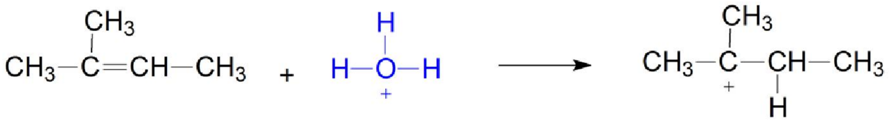
*Step 2:* Nucleophilic attack by water.



*Step 3:* Deprotonation to the alcohol.

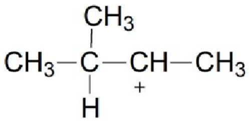
# Electrophilic addition

## Orientation of hydration



3°, more stable

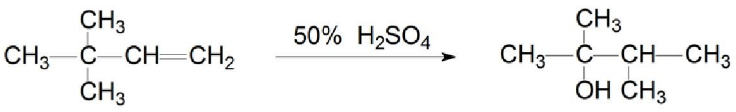
The protonation follows Markovnikov's rule: The hydrogen is added to the less substituted carbon in order to form the most stable carbocation.



2° less stable, not formed

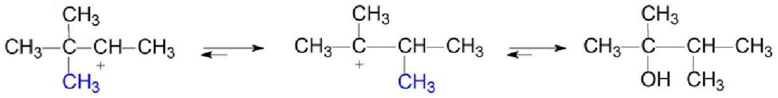
# Electrophilic addition

## Rearrangements



$CH_3-C(CH_3)_2-CH=CH_2 \xrightarrow{50\%\ H_2SO_4} CH_3-C(CH_3)(OH)-CH(CH_3)-CH_3$

*Rearrangement:*



2°, less stable

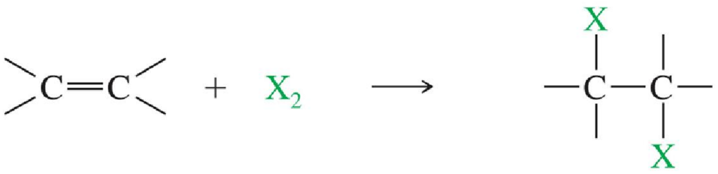
3°, more stable

2,3-dimethyl-2-butanol
(major product)

- Rearrangements can occur when there are carbocation intermediates.
- A methyl shift after protonation will produce the more stable tertiary carbocation.

# Electrophilic addition

## Addition of halogens



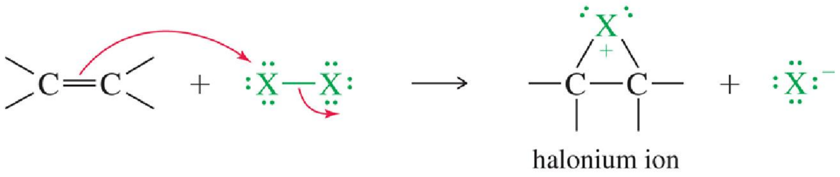
($X_2$ = $Cl_2$, $Br_2$, sometimes $I_2$)

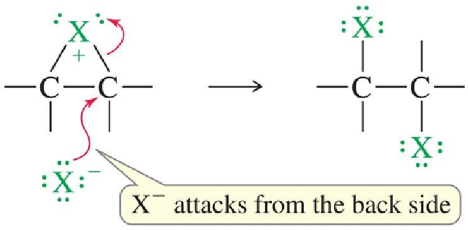
usually anti addition

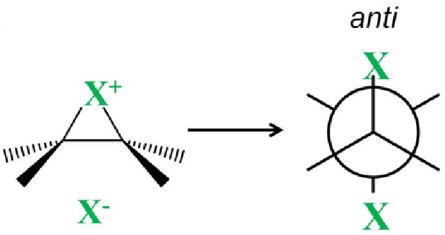
$Cl_2$, $Br_2$, and sometimes $I_2$ add to a double bond to form a vicinal dibromide.

# Electrophilic addition

## Mechanism of addition of halogens

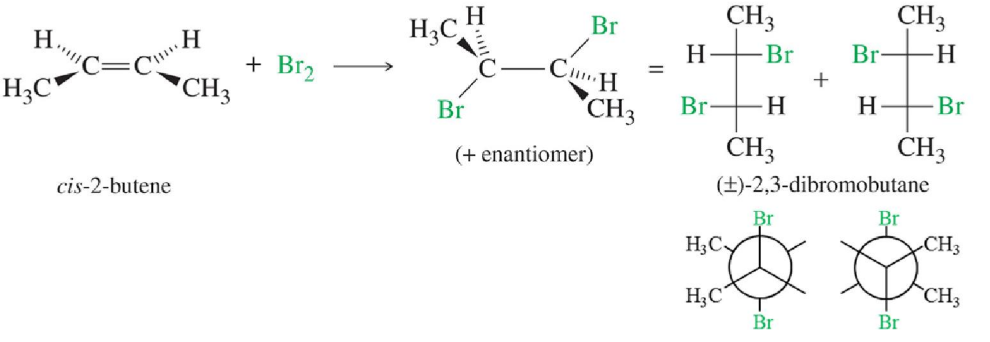



X⁻ attacks from the back side



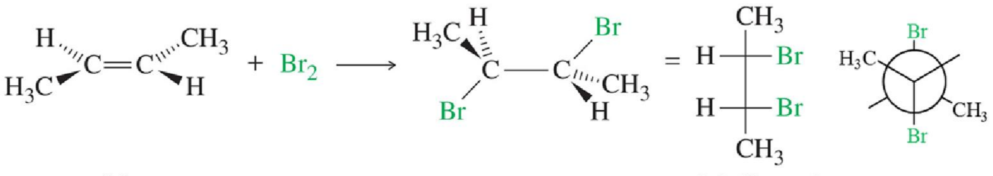
# Electrophilic addition

## Examples of stereospecificity



*cis*-2-butene

(±)-2,3-dibromobutane

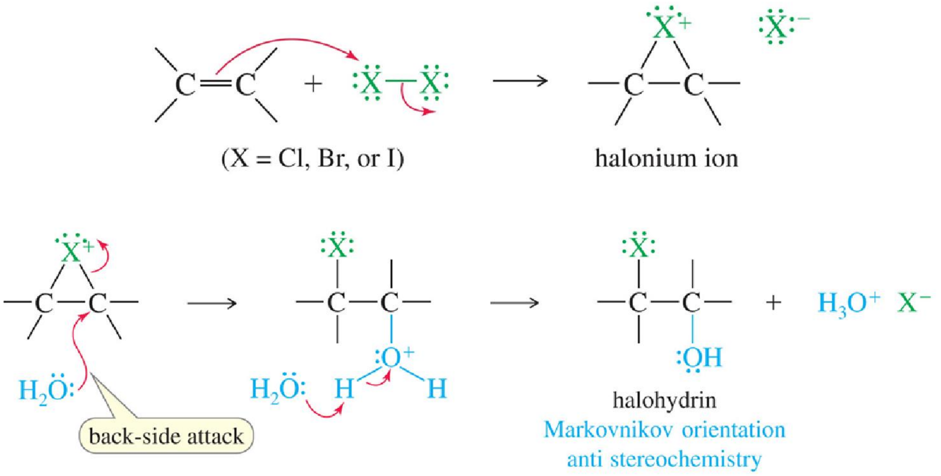


*trans*-2-butene

*meso*-2,3-dibromobutane

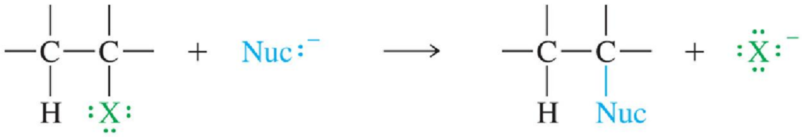
## Electrophilic addition

### Mechanism of halohydrin formation



# Nucleophilic substitution

## General reaction



- The halogen atom on the alkyl halide is replaced with a nucleophile (Nuc$^-$).
- Since the halogen is more electronegative than carbon, the C—X bond breaks heterolytically and X$^-$ leaves.

# Nucleophilic substitution

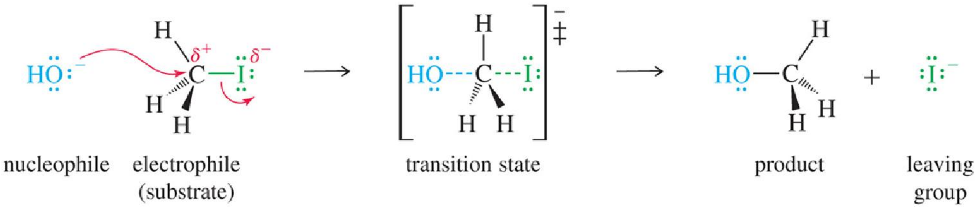
## Possible reactions

$$\text{Nuc}{:}^{-} + \text{R—X} \longrightarrow \text{Nuc—R} + \text{X}^{-}$$

| *Nucleophile* | | | | *Product* | *Class of Product* |
|---|---|---|---|---|---|
| R—X | + | $^{-}{:}\ddot{\underset{\cdot\cdot}{\text{I}}}{:}$ | $\longrightarrow$ | $\text{R—}\ddot{\underset{\cdot\cdot}{\text{I}}}{:}$ | alkyl halide |
| R—X | + | $^{-}{:}\ddot{\underset{\cdot\cdot}{\text{O}}}\text{H}$ | $\longrightarrow$ | $\text{R—}\ddot{\underset{\cdot\cdot}{\text{O}}}\text{H}$ | alcohol |
| R—X | + | $^{-}{:}\ddot{\underset{\cdot\cdot}{\text{O}}}\text{R}'$ | $\longrightarrow$ | $\text{R—}\ddot{\underset{\cdot\cdot}{\text{O}}}\text{R}'$ | ether |
| R—X | + | $^{-}{:}\ddot{\underset{\cdot\cdot}{\text{S}}}\text{H}$ | $\longrightarrow$ | $\text{R—}\ddot{\underset{\cdot\cdot}{\text{S}}}\text{H}$ | thiol (mercaptan) |
| R—X | + | $^{-}{:}\ddot{\underset{\cdot\cdot}{\text{S}}}\text{R}'$ | $\longrightarrow$ | $\text{R—}\ddot{\underset{\cdot\cdot}{\text{S}}}\text{R}'$ | thioether (sulfide) |
| R—X | + | ${:}\text{NH}_3$ | $\longrightarrow$ | $\text{R—NH}_3^{+}\ \text{X}^{-}$ | amine salt |
| R—X | + | $^{-}{:}\ddot{\text{N}}\text{=}\overset{+}{\text{N}}\text{=}\ddot{\text{N}}{:}^{-}$ | $\longrightarrow$ | $\text{R—}\ddot{\text{N}}\text{=}\overset{+}{\text{N}}\text{=}\ddot{\text{N}}{:}^{-}$ | azide |
| R—X | + | $^{-}{:}\text{C}\equiv\text{C—R}'$ | $\longrightarrow$ | $\text{R—C}\equiv\text{C—R}'$ | alkyne |
| R—X | + | $^{-}{:}\text{C}\equiv\text{N}{:}$ | $\longrightarrow$ | $\text{R—C}\equiv\text{N}{:}$ | nitrile |
| R—X | + | $\text{R}'\text{—CO}\ddot{\underset{\cdot\cdot}{\text{O}}}{:}^{-}$ | $\longrightarrow$ | $\text{R}'\text{—COO—R}$ | ester |
| R—X | + | ${:}\text{PPh}_3$ | $\longrightarrow$ | $[\text{R—PPh}_3]^{+}\ {}^{-}\text{X}$ | phosphonium salt |

## Nucleophilic substitution

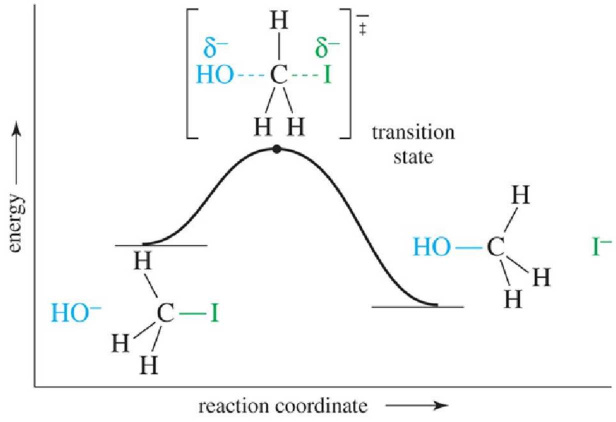
### $S_N2$ Mechanism



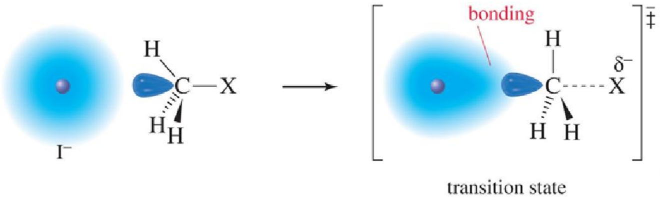
- Bimolecular nucleophilic substitution.
- Concerted reaction: new bond forming and old bond breaking at same time.
- Rate is first order in each reactant.

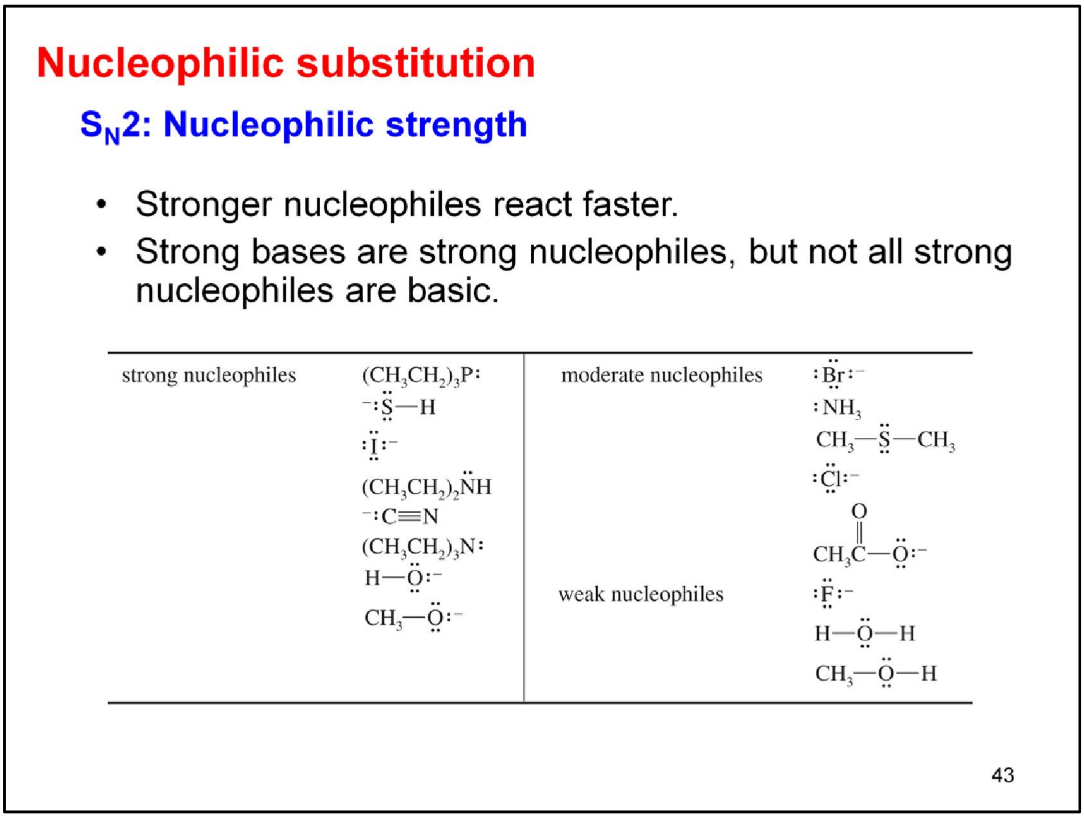
# Nucleophilic substitution

## $S_N2$ Energy diagram



- The $S_N2$ reaction is a one-step reaction.
- Transition state is highest in energy.





# Nucleophilic substitution

## $S_N2$: Nucleophilic strength

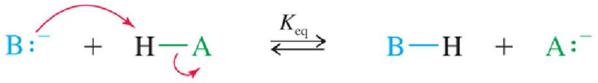
- Stronger nucleophiles react faster.
- Strong bases are strong nucleophiles, but not all strong nucleophiles are basic.

| | | | |
|---|---|---|---|
| strong nucleophiles | $(CH_3CH_2)_3P\colon$ | moderate nucleophiles | $\colon\ddot{Br}\colon^-$ |
| | $^-\colon\ddot{S}-H$ | | $\colon NH_3$ |
| | $\colon\ddot{I}\colon^-$ | | $CH_3-\ddot{S}-CH_3$ |
| | $(CH_3CH_2)_2\ddot{N}H$ | | $\colon\ddot{Cl}\colon^-$ |
| | $^-\colon C\equiv N$ | | $CH_3C(=O)-\ddot{O}\colon^-$ |
| | $(CH_3CH_2)_3N\colon$ | weak nucleophiles | $\colon\ddot{F}\colon^-$ |
| | $H-\ddot{O}\colon^-$ | | $H-\ddot{O}-H$ |
| | $CH_3-\ddot{O}\colon^-$ | | $CH_3-\ddot{O}-H$ |

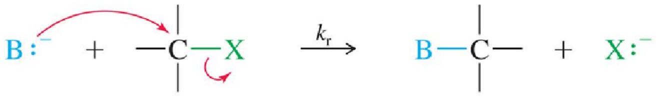
# Nucleophilic substitution

## Basicity vs Nucleophilicity

*Basicity*



*Nucleophilicity*



- Basicity is defined by the equilibrium constant for abstracting a proton.
- Nucleophilicity is defined by the rate of attack on the electrophilic carbon atom

## Nucleophilic substitution

### Trends in Nucleophilicity

- A negatively charged nucleophile is stronger than its neutral counterpart:

$OH^- > H_2O$ $HS^- > H_2S$ $NH_2^- > NH_3$

- Nucleophilicity decreases from left to right:

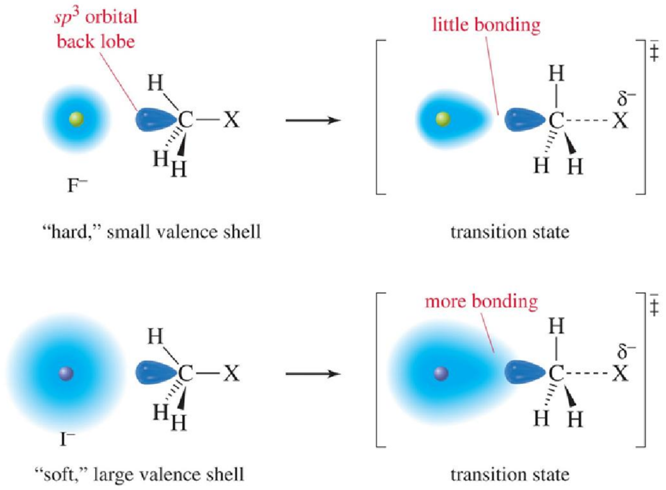
$OH^- > F^-$ $NH_3 > H_2O$

- Increases down Periodic Table, as size and polarizability increase:

$I^- > Br^- > Cl^-$

# Nucleophilic substitution

## Polarizability effect

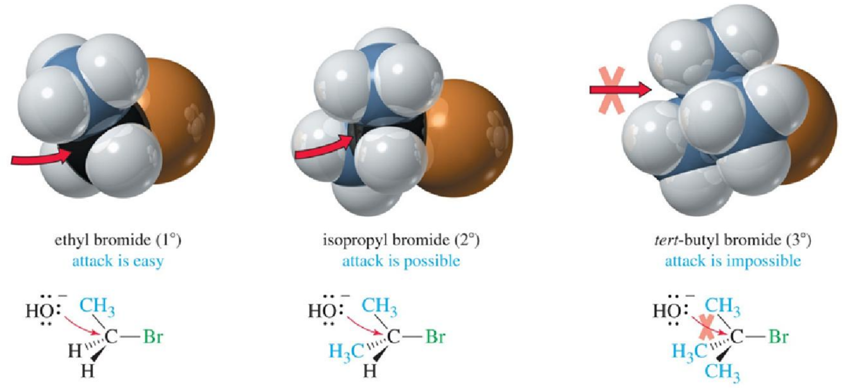


Bigger atoms have a soft shell which can start to overlap the carbon atom from a farther distance.

# Nucleophilic substitution

## $S_N2$: Structure of substrate

- Nucleophile approaches from the back side.
- It must overlap the back lobe of the C—X $sp^3$ orbital.



ethyl bromide (1°)
attack is easy

isopropyl bromide (2°)
attack is possible

*tert*-butyl bromide (3°)
attack is impossible

## Nucleophilic substitution

### $S_N2$: Structure of substrate

- Relative rates for $S_N2$:

  $CH_3X > 1° > 2° >> 3°$

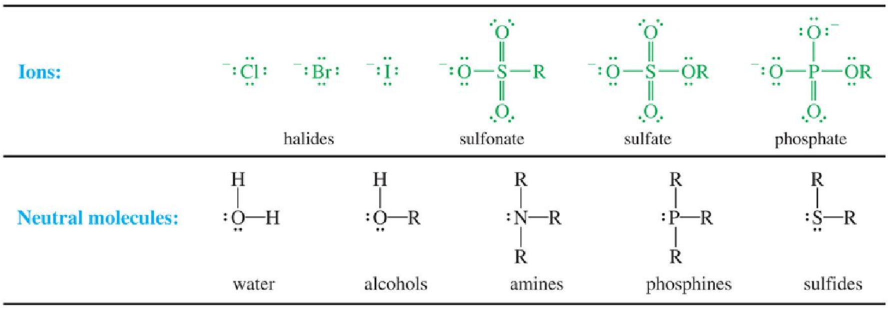
- Tertiary halides do not react via the $S_N2$ mechanism, due to steric hindrance.

# Nucleophilic substitution

## $S_N2$: Leaving group ability

The best leaving groups are:

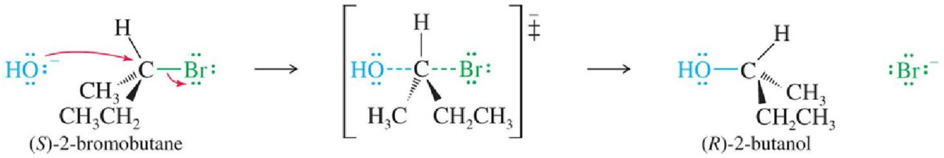
- Electron-withdrawing, to polarize the carbon atom.
- Stable (<u>not</u> a strong base) once it has left.
- Polarizable, to stabilize the transition state.

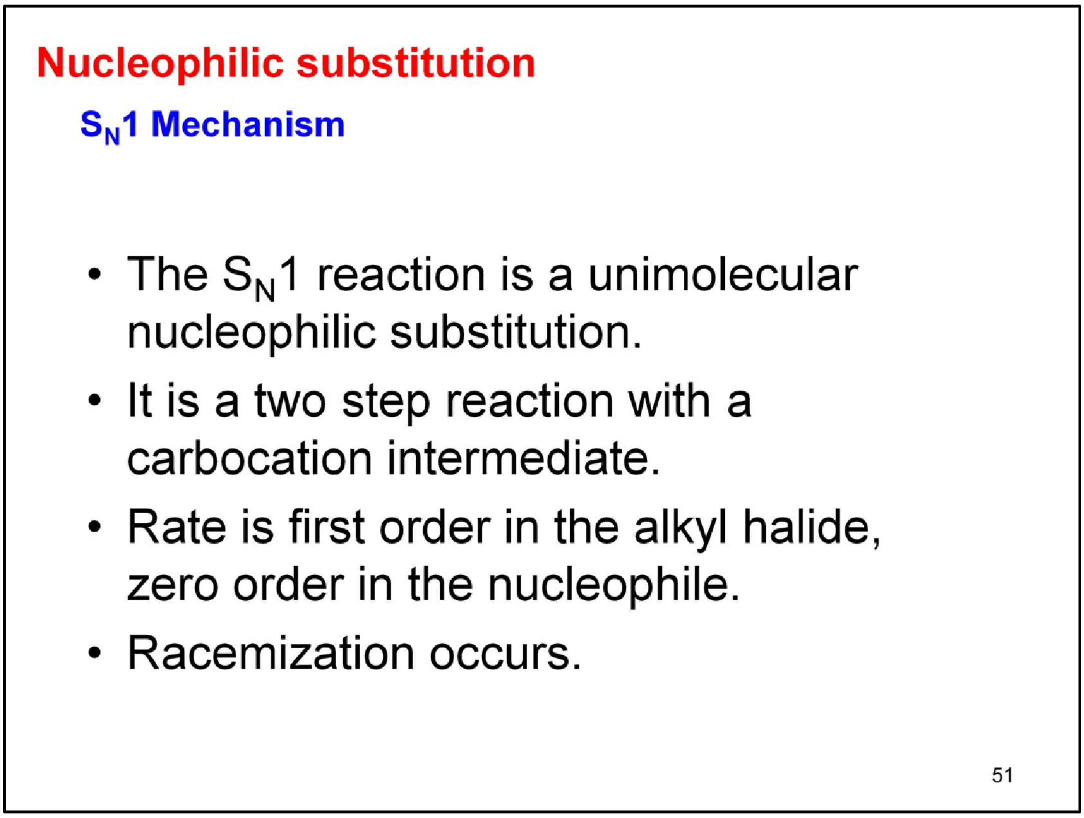


# Nucleophilic substitution

## $S_N2$: Stereochemistry

$S_N2$ reactions will result in an inversion of configuration.





## Nucleophilic substitution

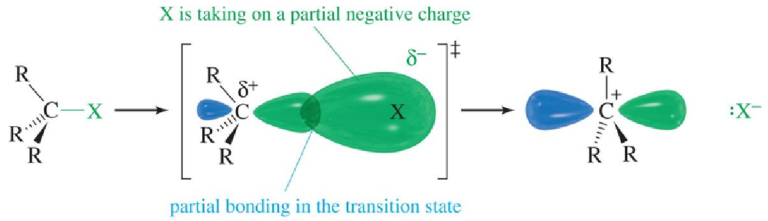
### $S_N1$ Mechanism

- The $S_N1$ reaction is a unimolecular nucleophilic substitution.
- It is a two step reaction with a carbocation intermediate.
- Rate is first order in the alkyl halide, zero order in the nucleophile.
- Racemization occurs.

# Nucleophilic substitution

## $S_N1$ Mechanism

1. Formation of carbocation (rate determining step)



X is taking on a partial negative charge

partial bonding in the transition state

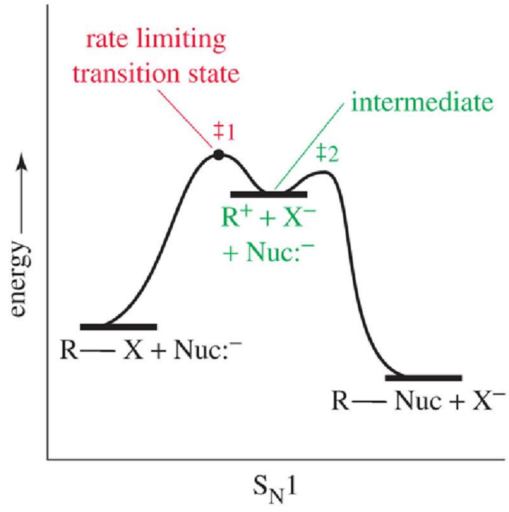
2. The nucleophile attacks the carbocation, forming the product. If the nucleophile was neutral, a third step (deprotonation) will be needed.

$$R^+ + Nuc:^- \longrightarrow R{-}Nuc$$

## Nucleophilic substitution

### $S_N1$ Energy diagram

- Forming the carbocation is an endothermic step.
- Step 2 is fast with a low activation energy.



# Nucleophilic substitution

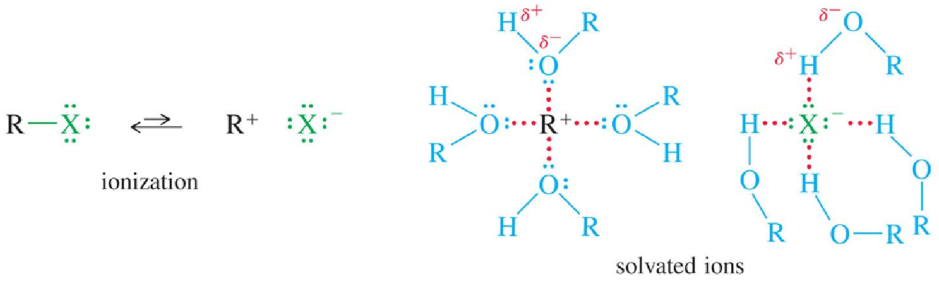
## $S_N1$: Reaction rates

- Order of reactivity follows stability of carbocations (opposite to $S_N2$)
  - 3° > 2° > 1° >> $CH_3X$
  - More stable carbocation requires less energy to form.
- A better leaving group will increase the rate of the reaction.

# Nucleophilic substitution

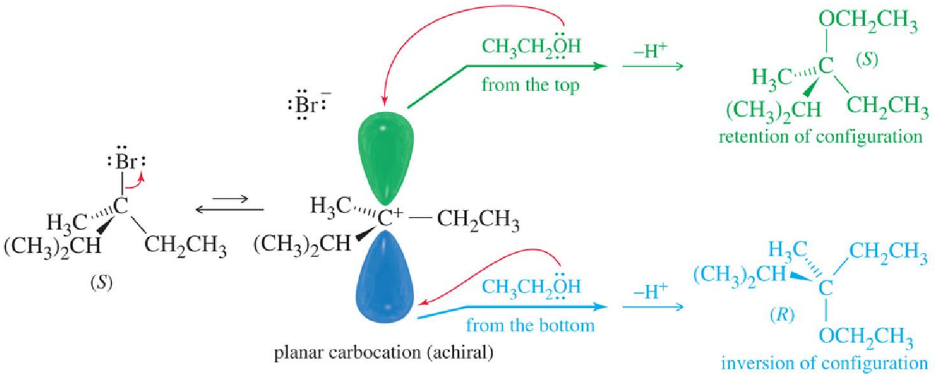
## $S_N1$: Solvation effect

Polar protic solvent are the best choice because it can solvate both ions strongly through hydrogen bonding.



# Nucleophilic substitution

## $S_N1$: Stereochemistry

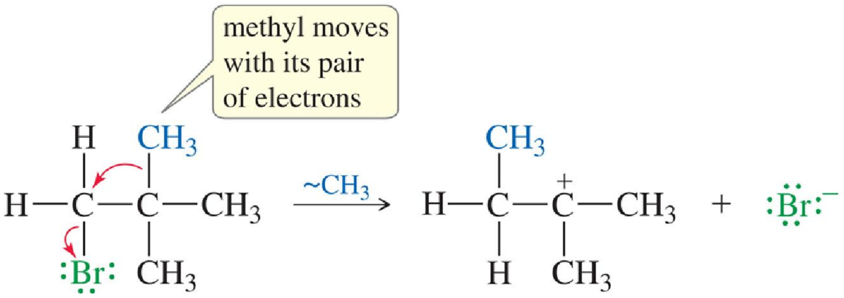


The $S_N1$ reaction produces mixtures of enantiomers. There is usually more inversion than retention of configuration.

# Nucleophilic substitution

## $S_N1$: Rearrangements

- Carbocations can rearrange to form a more stable carbocation.
- Hydride shift: $H^-$ on adjacent carbon bonds with $C^+$.
- Methyl shift: $CH_3^-$ moves from adjacent carbon <u>if</u> no hydrogens are available.

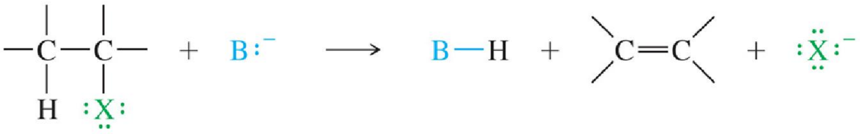


# Nucleophilic substitution

## $S_N1$ or $S_N2$ mechanism?

| **$S_N2$** | **$S_N1$** |
|---|---|
| $CH_3X$ > 1º > 2º | 3º > 2º |
| Strong nucleophile | Weak nucleophile (may also be solvent) |
| Polar aprotic solvent | Polar protic solvent. |
| Rate = *k*[alkyl halide][Nuc] | Rate = *k*[alkyl halide] |
| Inversion at chiral carbon | Racemization |
| No rearrangements | Rearranged products |

## Elimination reactions



- Elimination reactions produce double bonds.
- The alkyl halides loses a hydrogen and the halide.
- Also called dehydrohalogenation (-HX).

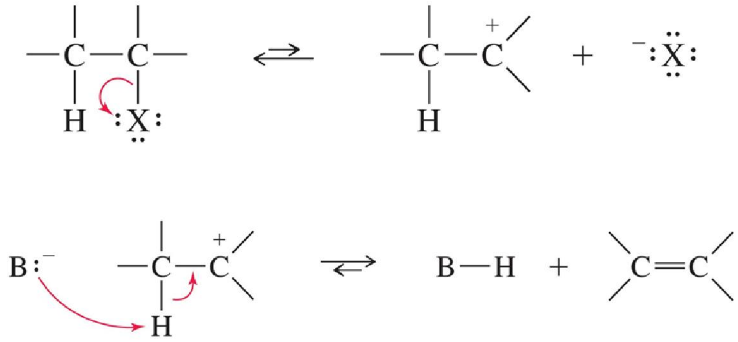
# Elimination reactions

## E1 Mechanism

- Unimolecular elimination.
- Two groups lost: a hydrogen and the halide.
- Nucleophile acts as base.
- The E1 and $S_N1$ reactions have the same conditions so a mixture of products will be obtained.

# Elimination reactions

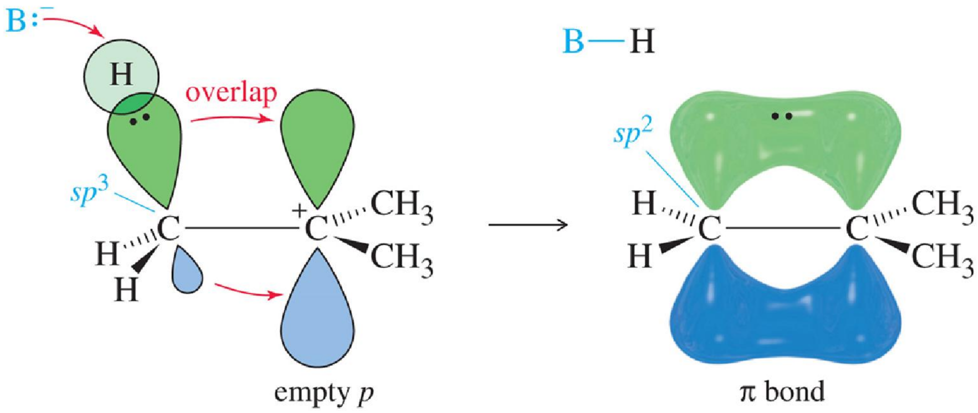
## E1 Mechanism



- Step 1: halide ion leaves, forming a carbocation.
- Step 2: Base abstracts $H^+$ from adjacent carbon forming the double bond.

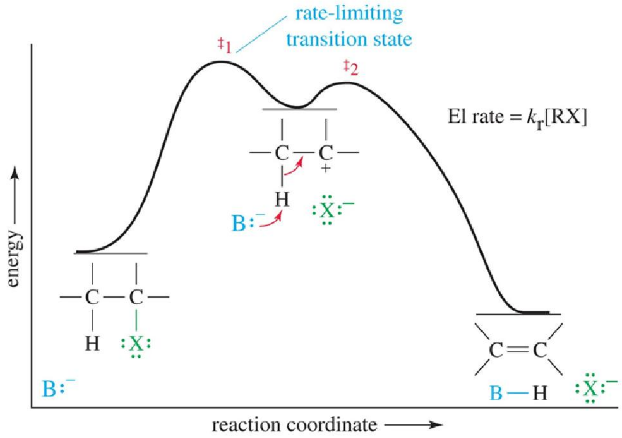
## Elimination reactions

### E1 Mechanism



# Elimination reactions

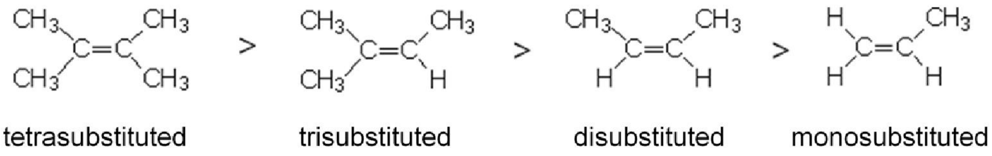
## E1 Energy diagram



The E1 and the $S_N1$ reactions have the same first step: carbocation formation is the rate determining step for both mechanisms.

## Elimination reactions

### Double bond substitution patterns



- The more substituted double bond is more stable.
- If more than one elimination product is possible, the most-substituted alkene is the major product (most stable).

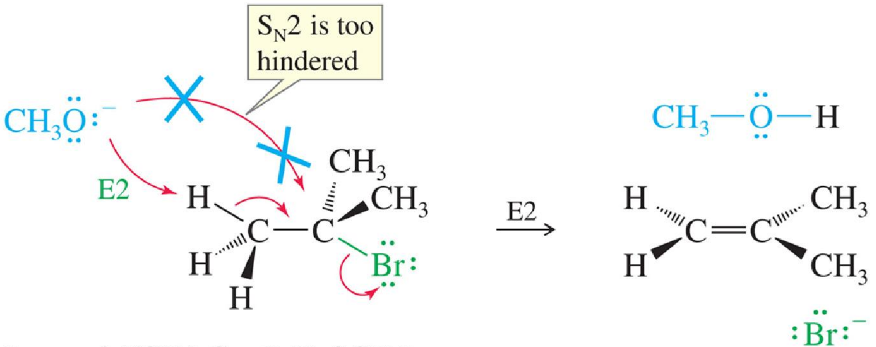
## Elimination reactions

### E2 Mechanism

- Elimination, bimolecular
- Requires a strong base
- This is a concerted reaction: the proton is abstracted, the double bond forms and the leaving group leaves, all in one step.

# Elimination reactions

## E2 Mechanism



Rate $= k_r[(CH_3)_3C-Br][^-OCH_3]$

- Order of reactivity for alkyl halides:
  3° > 2 ° > 1°
- Mixture may form, but Zaitsev product predominates.

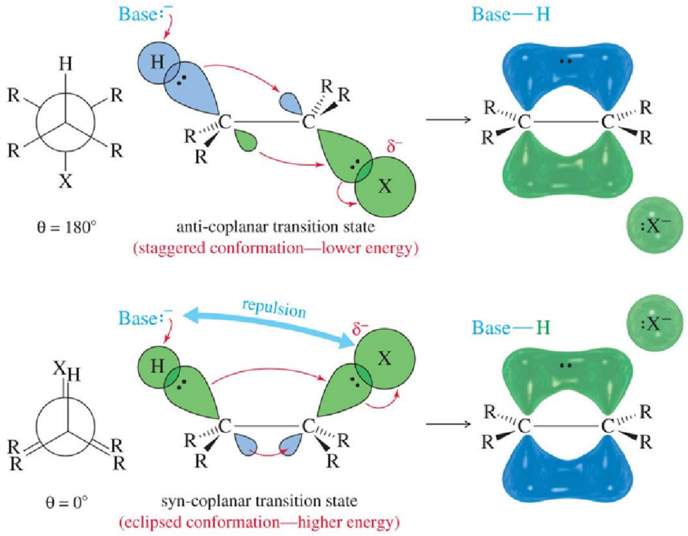
# Elimination reactions

## E2 stereochemistry

- The halide and the proton to be abstracted must be anti-coplanar ($\theta$=180º) to each other for the elimination to occur.
- The orbitals of the hydrogen atom and the halide must be aligned so they can begin to form a pi bond in the transition state.
- The anti-coplanar arrangement minimizes any steric hindrance between the base and the leaving group.

# Elimination reactions

## E2 stereochemistry



# Elimination reactions

## E1 or E2 Mechanism?

| | |
|---|---|
| Tertiary > Secondary | Tertiary > Secondary |
| Base strength unimportant (usually weak) | Strong base required |
| Good ionizing solvent | Solvent polarity not important. |
| Rate = $k$[alkyl halide] | Rate = $k$[alkylhalide][base] |
| More substituted product | More substituted product |
| No required geometry | Coplanar leaving groups (usually anti) |
| Rearranged products | No rearrangements |

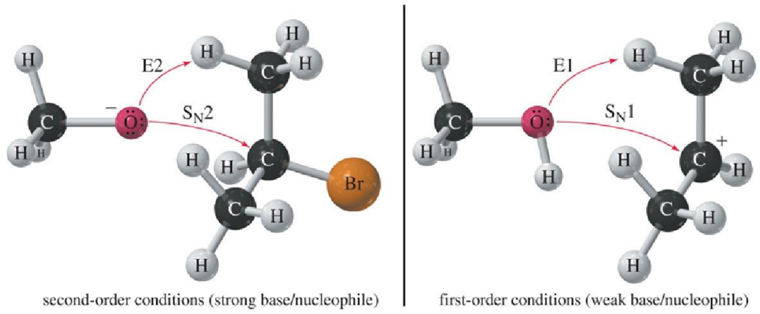
## Elimination or substitution?

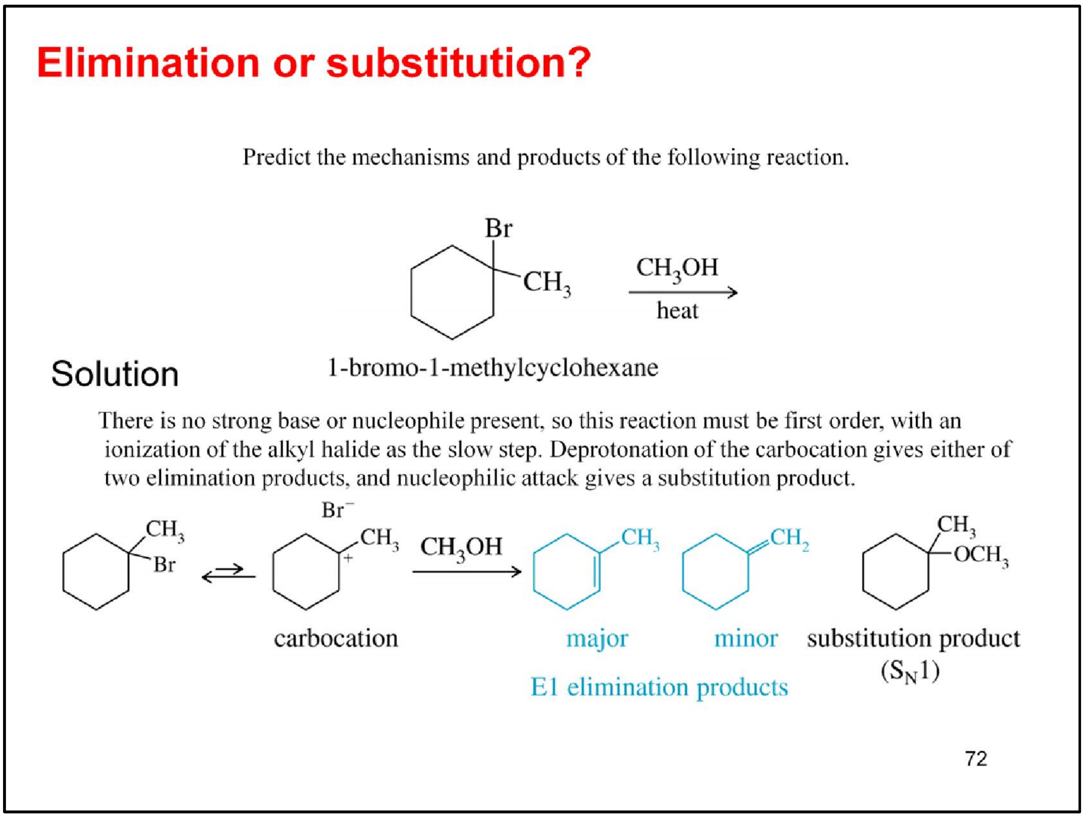
- Strength of the nucleophile determines order: Strong nucleophiles or bases promote bimolecular reactions.
- Primary halide usually undergo $S_N2$.
- Tertiary halide mixture of $S_N1$, E1 or E2. They cannot undergo $S_N2$.
- High temperature favors elimination.
- Bulky bases favor elimination.

# Elimination or substitution?

## Secondary Alkyl Halides

- Secondary alkyl halides are more challenging:
  - Strong nucleophiles will promote $S_N2$/E2
  - Weak nucleophiles promote $S_N1$/E1
- Strong nucleophiles with limited basicity favor $S_N2$. Bromide and iodide are good examples of these.





# Elimination or substitution?

Predict the mechanisms and products of the following reaction.

1-bromo-1-methylcyclohexane

## Solution

There is no strong base or nucleophile present, so this reaction must be first order, with an ionization of the alkyl halide as the slow step. Deprotonation of the carbocation gives either of two elimination products, and nucleophilic attack gives a substitution product.

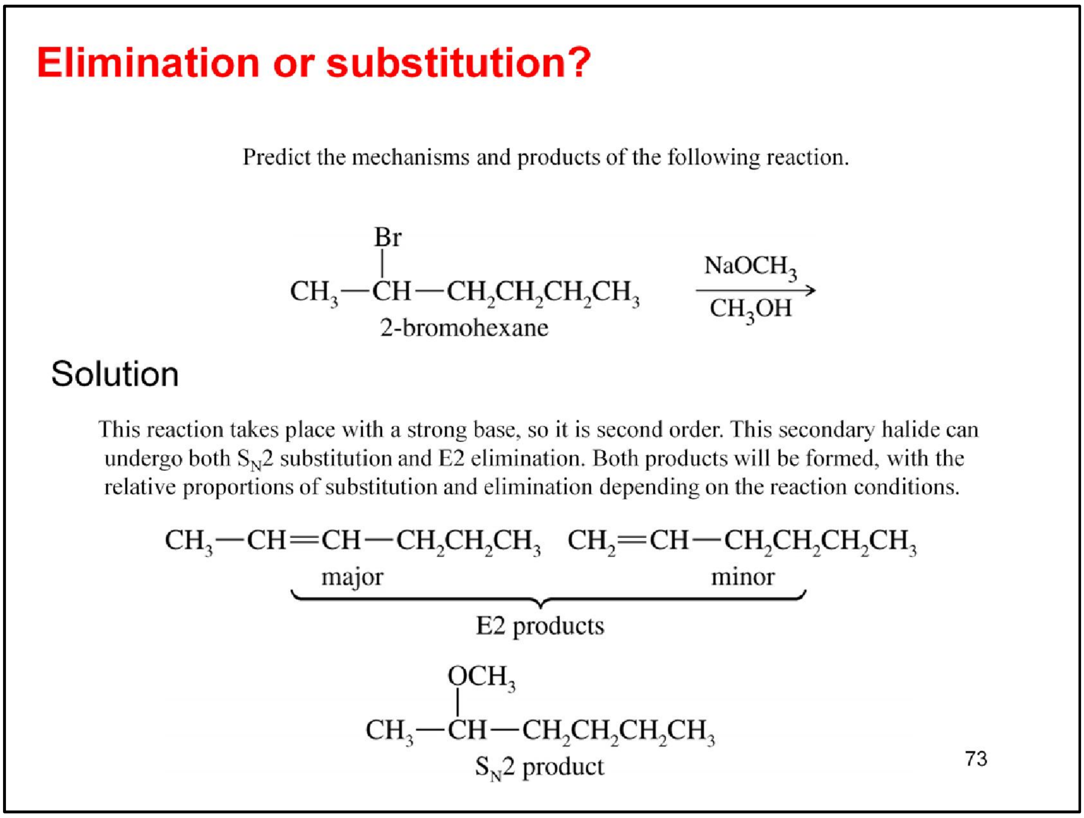
carbocation

major

minor

E1 elimination products

substitution product
(S$_N$1)



## Elimination or substitution?

Predict the mechanisms and products of the following reaction.

$$\underset{\text{2-bromohexane}}{CH_3-\overset{Br}{\overset{|}{CH}}-CH_2CH_2CH_2CH_3} \xrightarrow[CH_3OH]{NaOCH_3}$$

### Solution

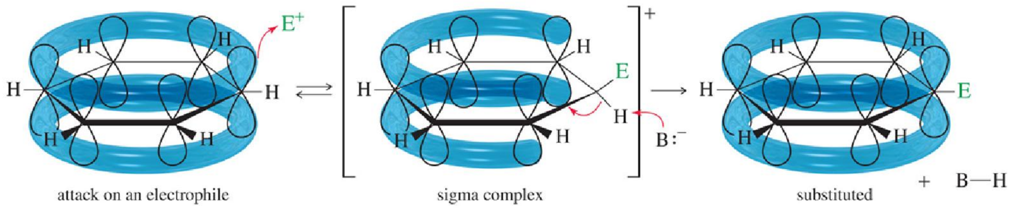
This reaction takes place with a strong base, so it is second order. This secondary halide can undergo both $S_N2$ substitution and E2 elimination. Both products will be formed, with the relative proportions of substitution and elimination depending on the reaction conditions.

$$\underbrace{\underset{\text{major}}{CH_3-CH=CH-CH_2CH_2CH_3} \quad \underset{\text{minor}}{CH_2=CH-CH_2CH_2CH_2CH_3}}_{\text{E2 products}}$$

$$\underset{S_N2\text{ product}}{CH_3-\overset{OCH_3}{\overset{|}{CH}}-CH_2CH_2CH_2CH_3}$$

# Electrophilic aromatic substitution

## General mechanism

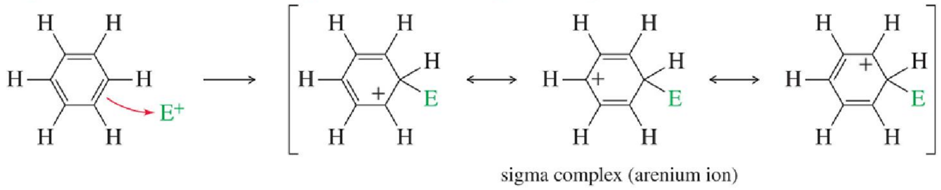


- Although benzene's pi electrons are in a stable aromatic system, they are available to attack a strong electrophile to give a carbocation.
- This resonance-stabilized carbocation is called a ***sigma complex*** because the electrophile is joined to the benzene ring by a new sigma bond.
- Aromaticity is regained by loss of a proton.

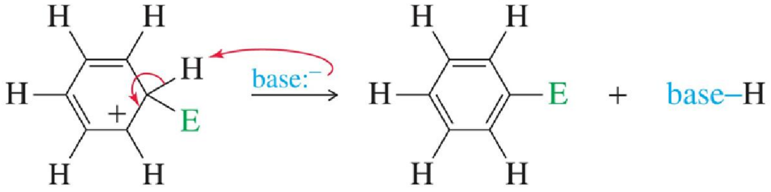
# Electrophilic aromatic substitution

## General mechanism

*Step 1:* Attack on the electrophile forms the sigma complex.

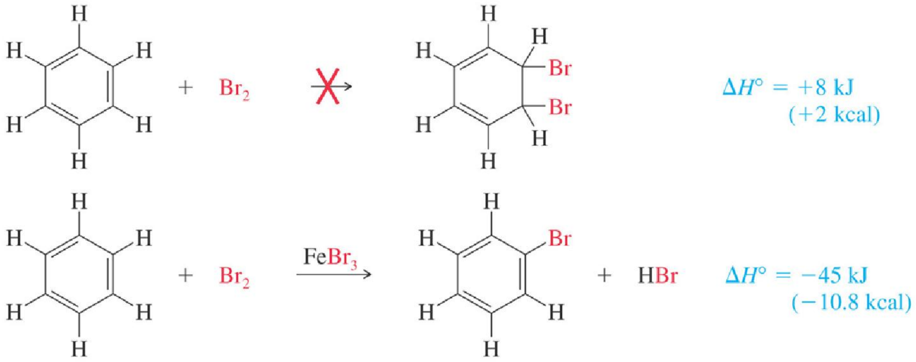


*Step 2:* Loss of a proton gives the substitution product.



# Electrophilic aromatic substitution

## Bromination of benzene



bromobenzene
(80%)

# Electrophilic aromatic substitution

## Bromination of benzene: Step 1

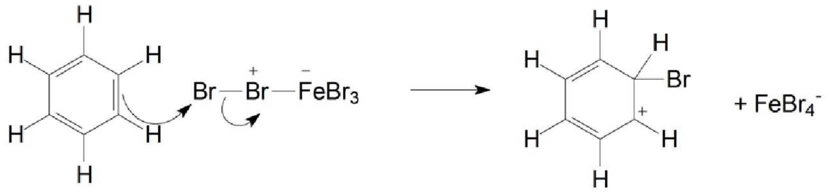
(stronger electrophile than $Br_2$)

- Before the electrophilic aromatic substitution can take place, the electrophile must be activated.
- A strong Lewis acid catalyst, such as $FeBr_3$, should be used.

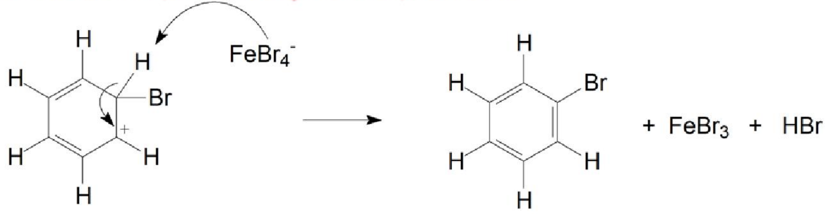
# Electrophilic aromatic substitution

## Bromination of benzene: Steps 2 & 3

Step 2: Electrophilic attack and formation of the sigma complex.

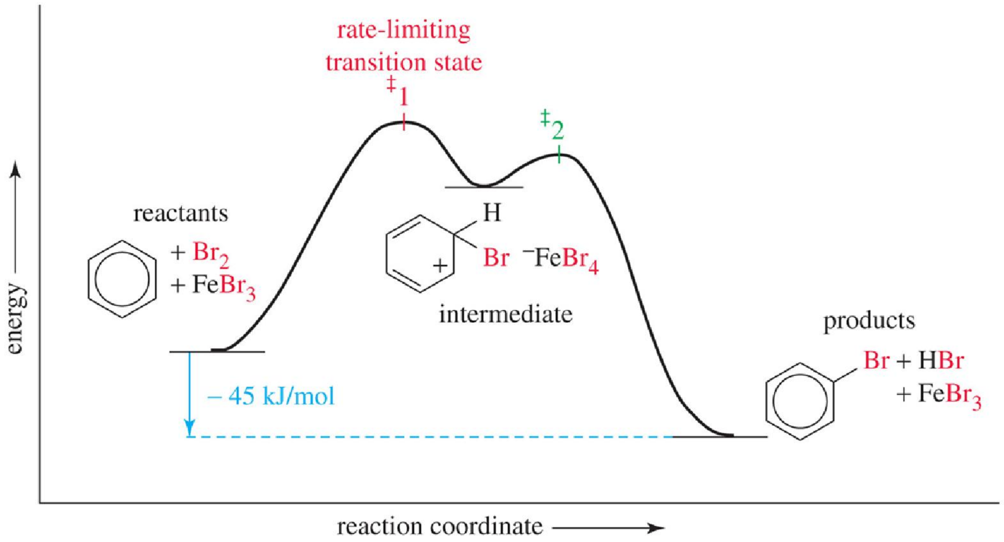


Step 3: Loss of a proton to give the products.



# Electrophilic aromatic substitution

## Bromination of benzene: Energy diagram



# Electrophilic aromatic substitution

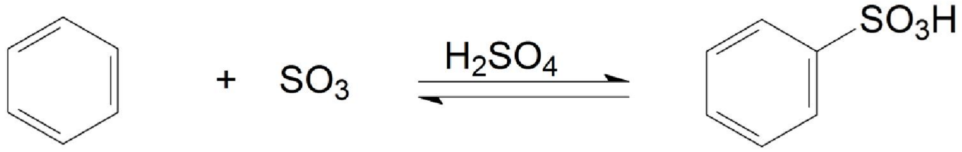
## Chlorination and Iodination

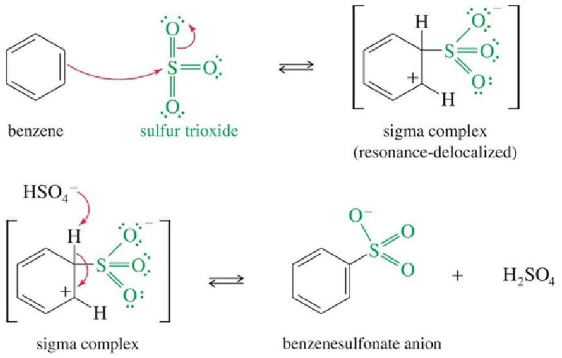
- Chlorination is similar to bromination. $AlCl_3$ is most often used as catalyst, but $FeCl_3$ will also work.
- Iodination requires an acidic oxidizing agent, like nitric acid, to produce iodide cation.

$$H^+ + HNO_3 + \tfrac{1}{2} I_2 \longrightarrow I^+ + NO_2 + H_2O$$

# Electrophilic aromatic substitution

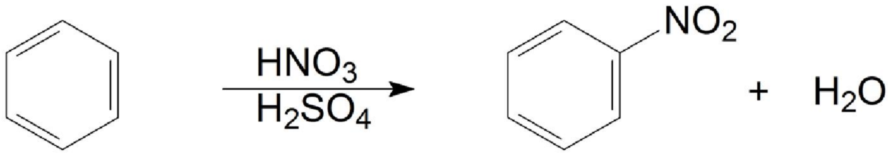
## Sulfonation of benzene

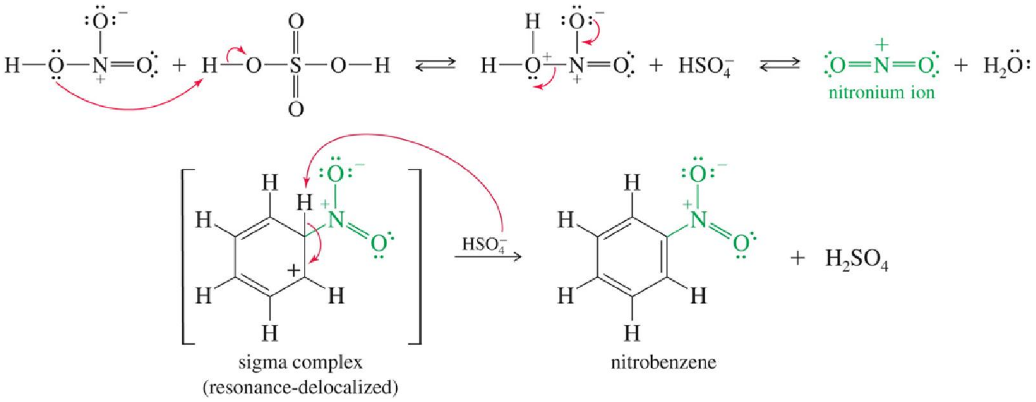




# Electrophilic aromatic substitution

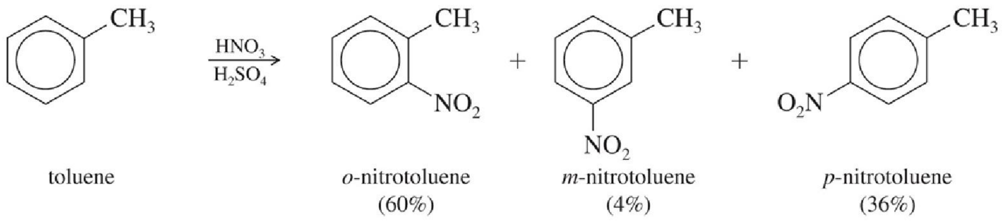
## Nitration of benzene





# Electrophilic aromatic substitution

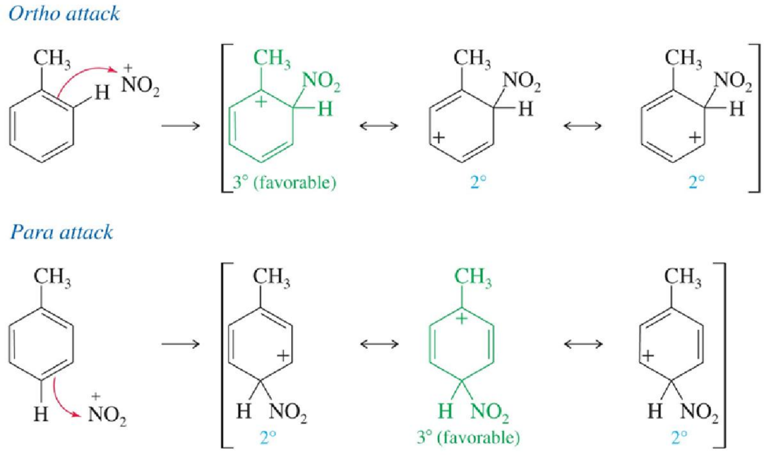
## Nitration of toluene



- Toluene reacts 25 times faster than benzene.
- The methyl group is an activator.
- The product mix contains mostly *ortho* and *para* substituted molecules.

# Electrophilic aromatic substitution

## Ortho and Para Substitution

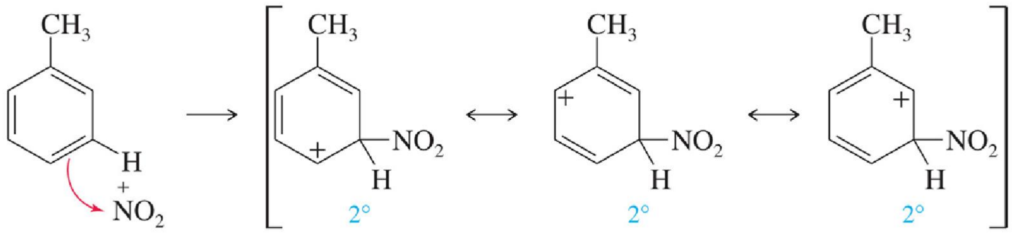


*Ortho* and *para* attacks are preferred because their resonance structures include one tertiary carbocation.

# Electrophilic aromatic substitution

## Meta Substitution

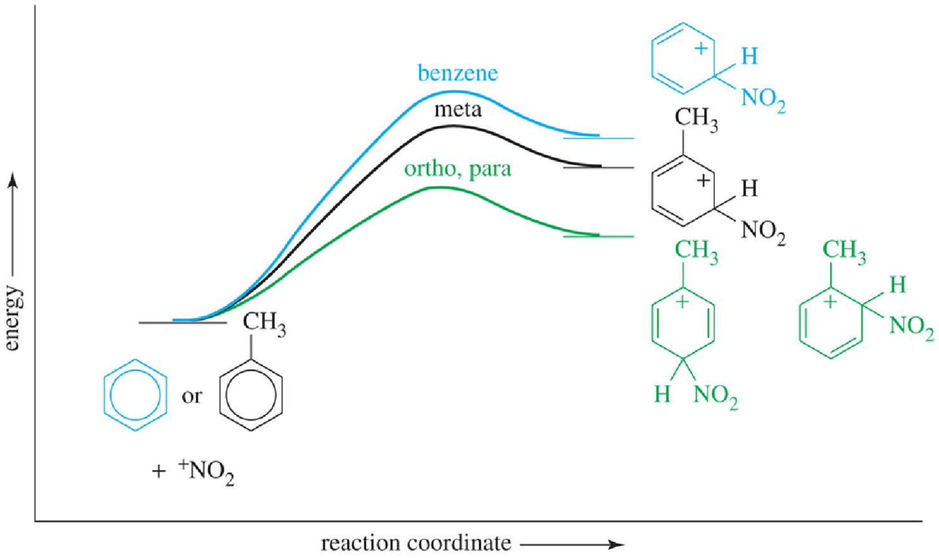
*Meta attack*



When substitution occurs at the meta position, the positive charge is not delocalized onto the tertiary carbon, and the methyl groups has a smaller effect on the stability of the sigma complex.

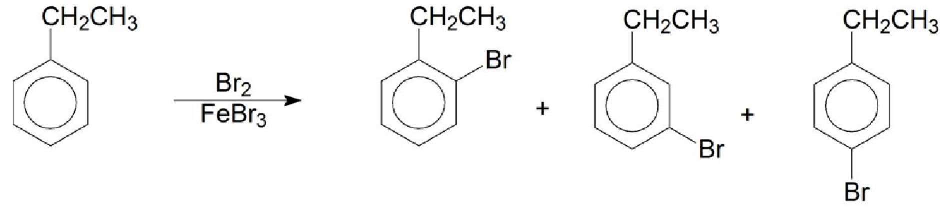
# Electrophilic aromatic substitution

## Energy diagram



# Electrophilic aromatic substitution

## Alkyl Group Stabilization



*o*-bromo (38%)

*m*-bromo (< 1%)

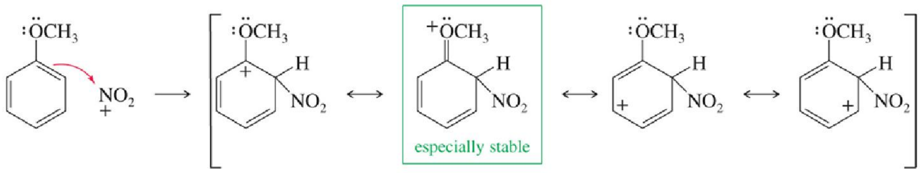
*p*-bromo (62%)

- Alkyl groups are **activating** substituents and ortho, para-directors.
- This effect is called the ***inductive effect*** because alkyl groups can donate electron density to the ring through the sigma bond, making them more active.

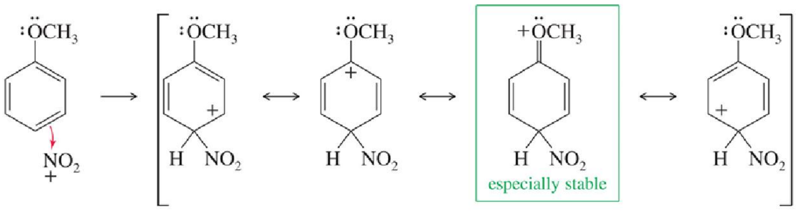
# Electrophilic aromatic substitution

## Substituents with Non Bonding Electrons

*Ortho attack*



*Para attack*

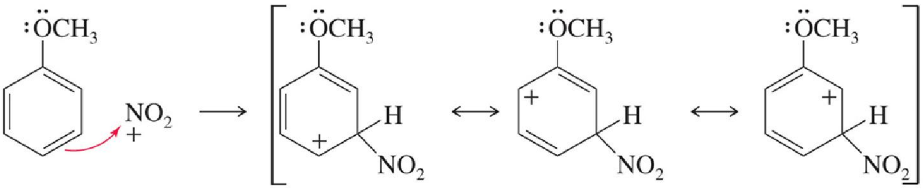


Resonance stabilization is provided by a pi bond between the —$OCH_3$ substituent and the ring.

# Electrophilic aromatic substitution

## Substituents with Non Bonding Electrons

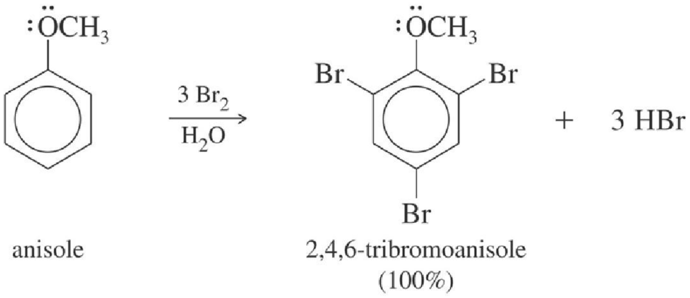
*Meta attack*



Resonance forms show that the methoxy group cannot stabilize the sigma complex in the meta substitution.

## Electrophilic aromatic substitution

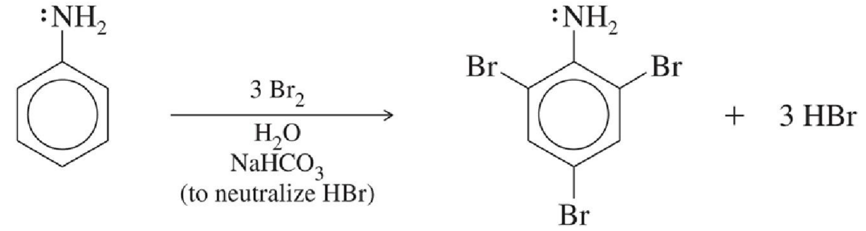
### Bromination of anisole



A methoxy group is so strongly activating that anisole is quickly tribrominated without a catalyst.

# Electrophilic aromatic substitution

## Bromination of aniline



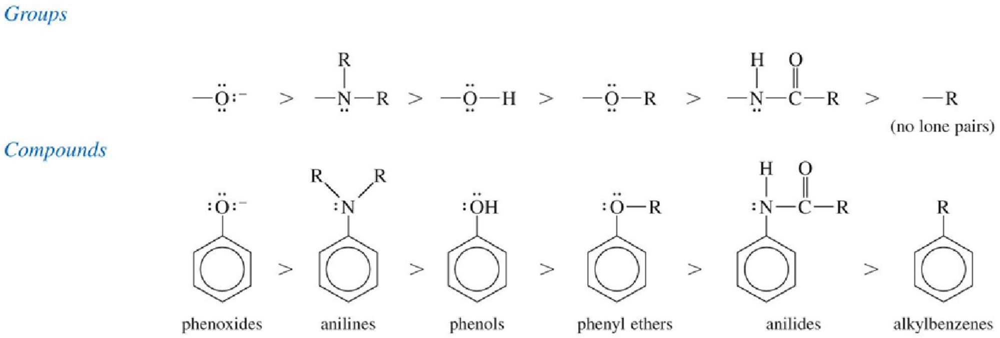
aniline

2,4,6-tribromoaniline
(100%)

- Aniline reacts with bromine water (without a catalyst) to yield the tribromoaniline.
- Sodium bicarbonate is added to neutralize the HBr that is also formed.

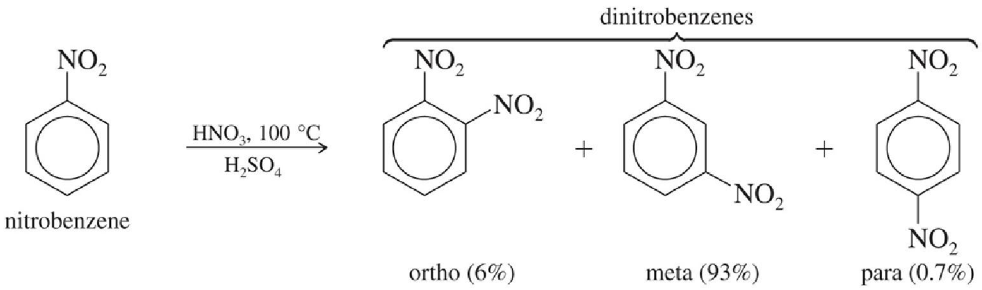
## Electrophilic aromatic substitution

### Summary of activators



# Electrophilic aromatic substitution

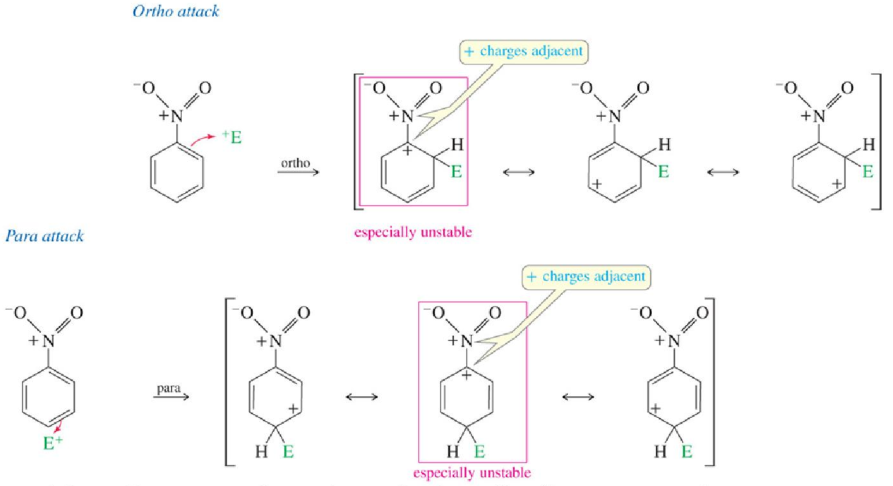
## Nitration of nitrobenzene



- Electrophilic substitution reactions for nitrobenzene are 100,000 times slower than for benzene.
- The product mix contains mostly the meta isomer, only small amounts of the ortho and para isomers.

# Electrophilic aromatic substitution

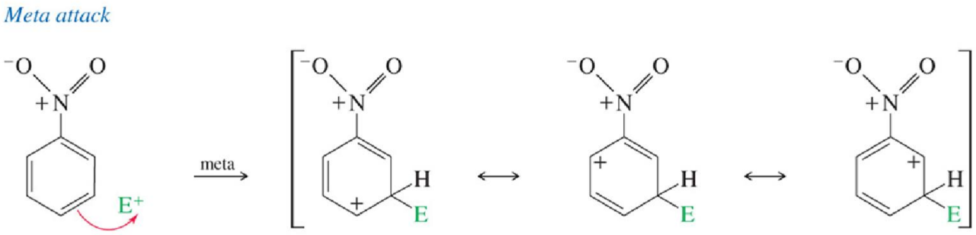
## Ortho and Para Substitution



- The nitro group is a strongly deactivating group when considering its resonance forms. The nitrogen always has a formal positive charge.
- Ortho or para addition will create an especially unstable intermediate.

# Electrophilic aromatic substitution

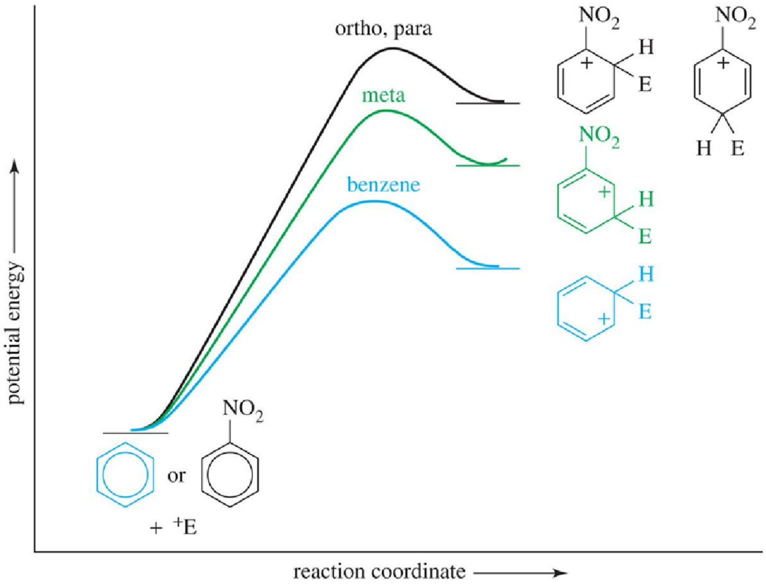
## Meta Substitution



- Meta substitution will not put the positive charge on the same carbon that bears the nitro group.

# Electrophilic aromatic substitution

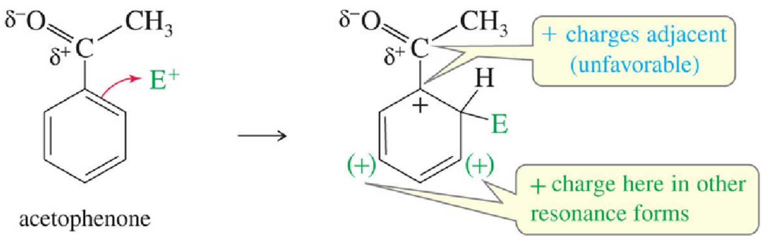
## Energy Diagram



## Electrophilic aromatic substitution

### Ortho attack of acetophenone

*Ortho attack*

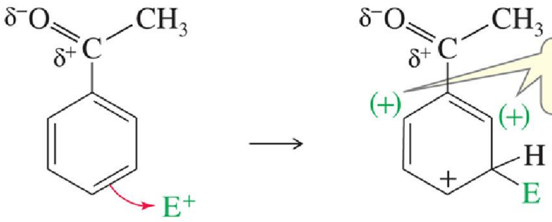


- In ortho and para substitution of acetophenone, one of the carbon atoms bearing the positive charge is the carbon attached to the partial positive carbonyl carbon.
- Since like charges repel, this close proximity of the two positive charges is especially unstable.

# Electrophilic aromatic substitution

## Meta attack of acetophenone

*Meta attack*



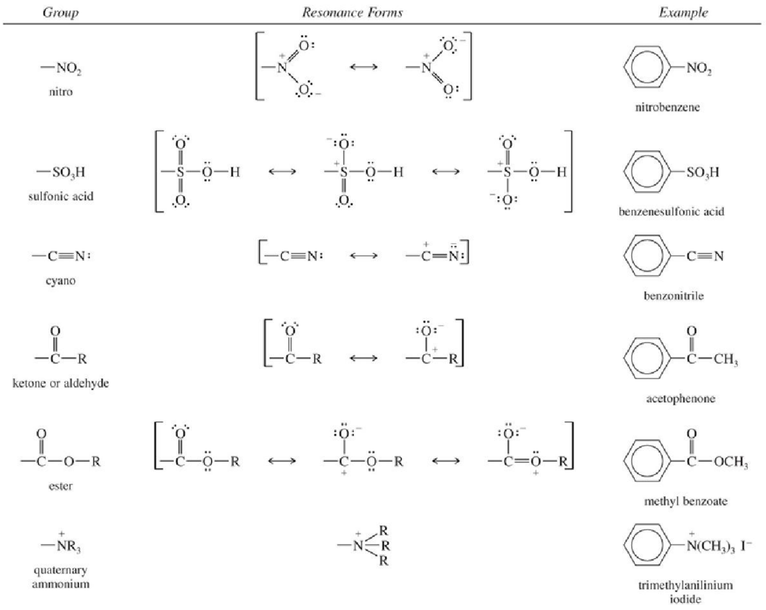
+ charge here in other resonance forms

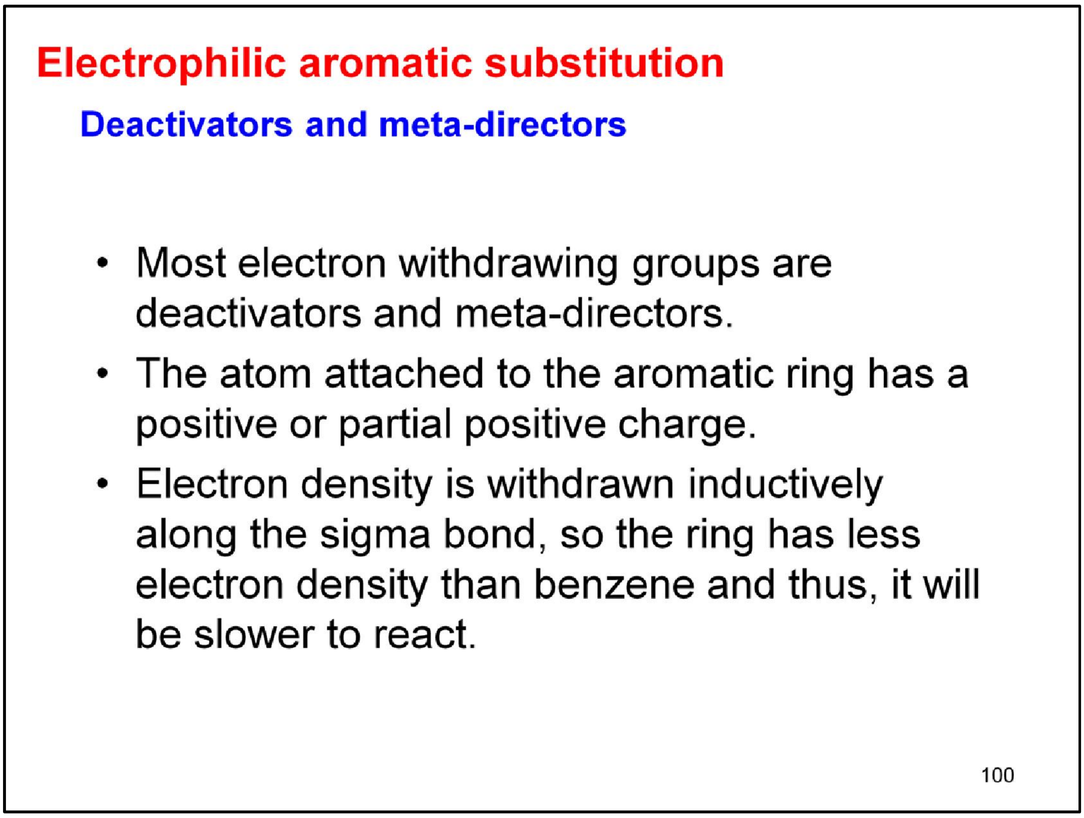
This sigma complex does not place the positive charge on the ring carbon bearing the carbonyl group.

- The meta attack on acetophenone avoids bearing the positive charge on the carbon attached to the partial positive carbonyl.

# Electrophilic aromatic substitution

## Other deactivators





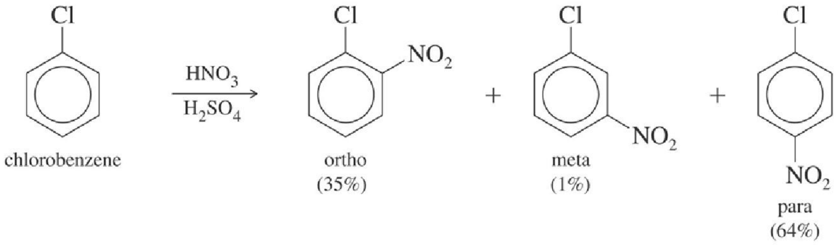
## Electrophilic aromatic substitution

### Deactivators and meta-directors

- Most electron withdrawing groups are deactivators and meta-directors.
- The atom attached to the aromatic ring has a positive or partial positive charge.
- Electron density is withdrawn inductively along the sigma bond, so the ring has less electron density than benzene and thus, it will be slower to react.

# Electrophilic aromatic substitution

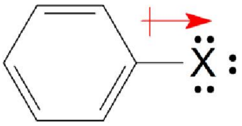
## Nitration of chlorobenzene



- When chlorobenzene is nitrated the main substitution products are ortho and para. The meta substitution product is only obtained in 1% yield.

## Electrophilic aromatic substitution

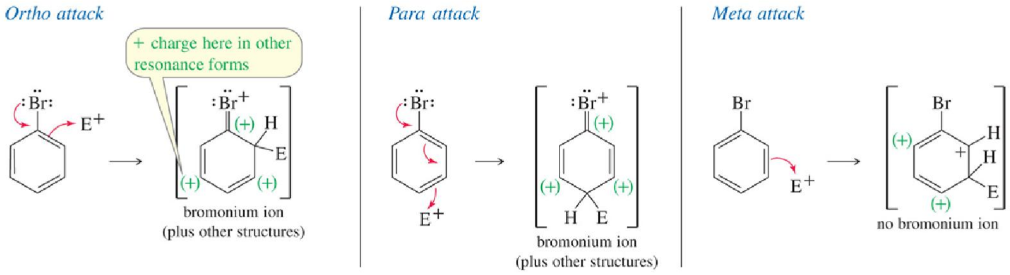
### Halogens are deactivators



- ***Inductive Effect***: Halogens are deactivating because they are electronegative and can withdraw electron density from the ring along the sigma bond.

# Electrophilic aromatic substitution

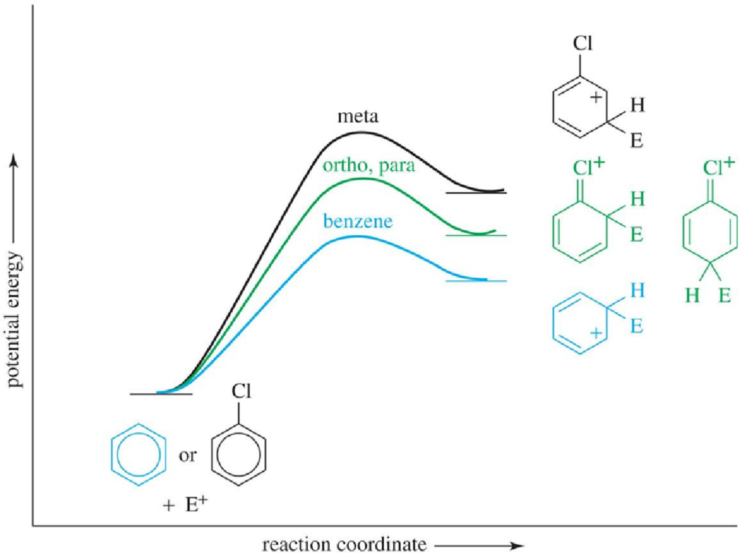
## Halogens are ortho, para-directors



- ***Resonance Effect***: The lone pairs on the halogen can be used to stabilize the sigma complex by resonance.

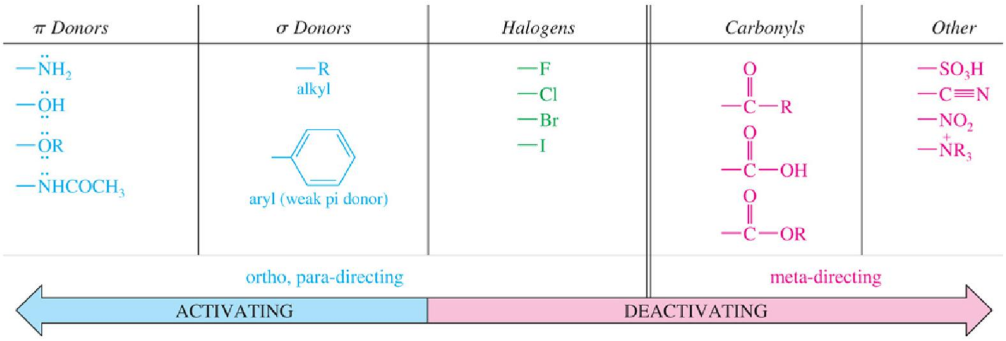
# Electrophilic aromatic substitution

## Energy diagram



# Electrophilic aromatic substitution

## Summary od directing effects



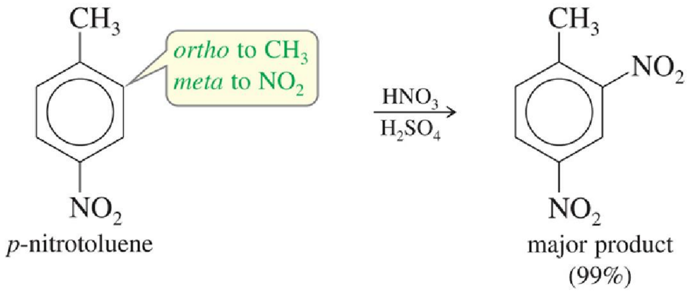
| *π Donors* | *σ Donors* | *Halogens* | *Carbonyls* | *Other* |
|---|---|---|---|---|
| $-\ddot{N}H_2$ | $-R$<br>alkyl | $-F$ | $-\overset{O}{\overset{\Vert}{C}}-R$ | $-SO_3H$ |
| $-\ddot{\underset{..}{O}}H$ | aryl (weak pi donor) | $-Cl$ | $-\overset{O}{\overset{\Vert}{C}}-OH$ | $-C\equiv N$ |
| $-\ddot{\underset{..}{O}}R$ |  | $-Br$ | $-\overset{O}{\overset{\Vert}{C}}-OR$ | $-NO_2$ |
| $-\ddot{N}HCOCH_3$ |  | $-I$ |  | $-\overset{+}{N}R_3$ |

ortho, para-directing

meta-directing

# Electrophilic aromatic substitution

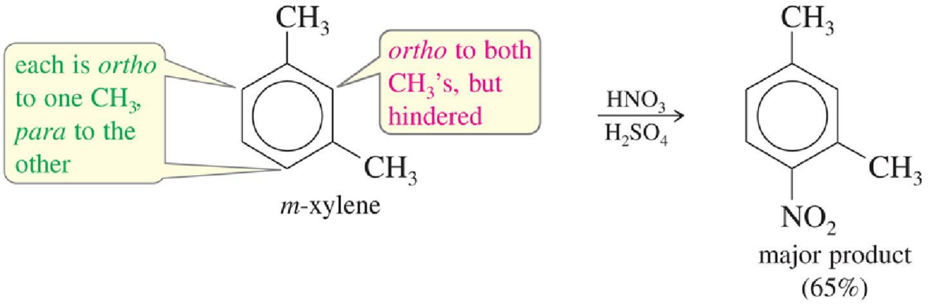
## Effect of multiple substituents



The directing effect of the two (or more) groups may reinforce each other.

## Electrophilic aromatic substitution

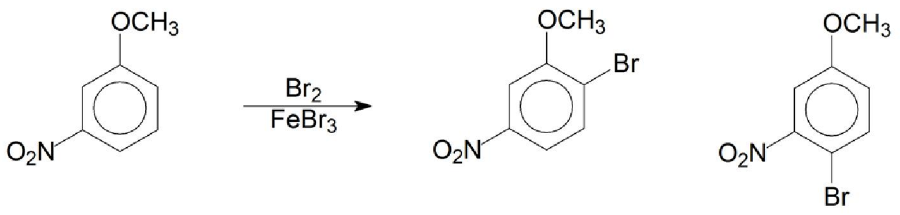
### Effect of multiple substituents



The position in between two groups in Positions 1 and 3 is hindered for substitution, and it is less reactive.

# Electrophilic aromatic substitution

## Effect of multiple substituents



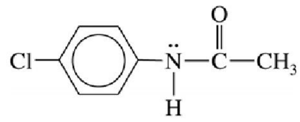
**major products obtained**

If directing effects oppose each other, the most powerful activating group has the dominant influence.

## Electrophilic aromatic substitution

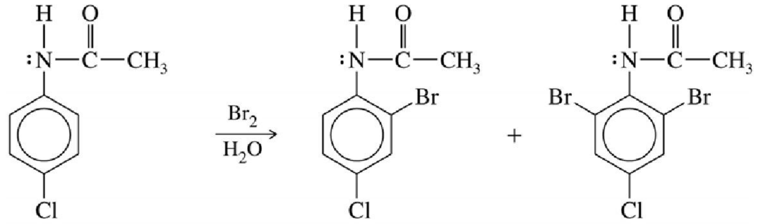
### Problem 1

Predict the major product(s) of bromination of *p*-chloroacetanilide.



### Solution

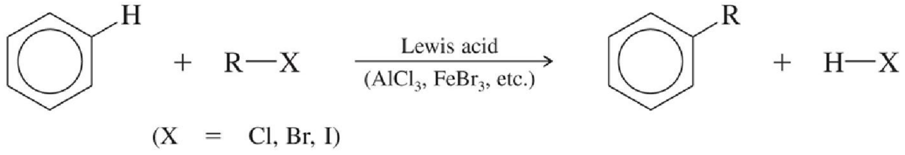
The amide group (–NHCOCH$_3$) is a strong activating and directing group because the nitrogen atom with its nonbonding pair of electrons is bonded to the aromatic ring. The amide group is a stronger director than the chlorine atom, and substitution occurs mostly at the positions ortho to the amide. Like an alkoxyl group, the amide is a particularly strong activating group, and the reaction gives some of the dibrominated product.



*p*-chloroacetanilide

# Electrophilic aromatic substitution

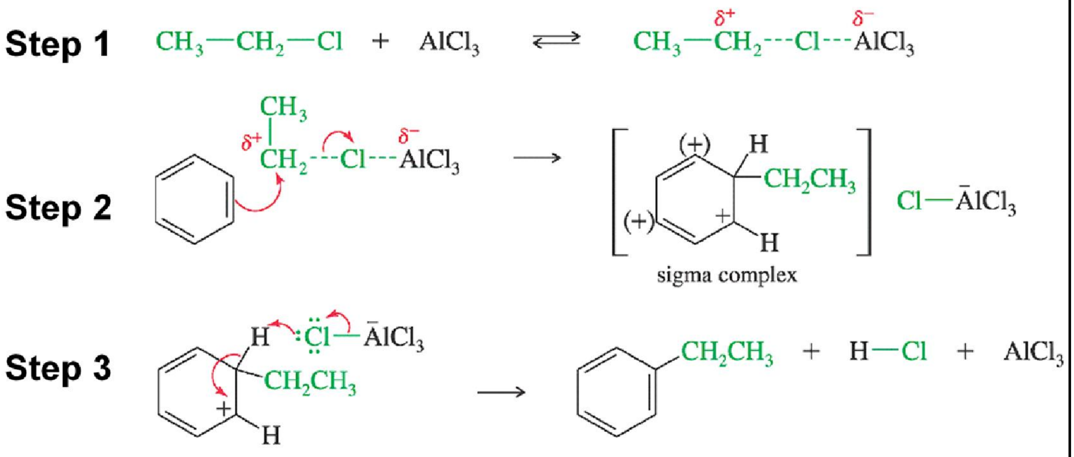
## Friedel-Crafts alkylation



- Synthesis of alkyl benzenes from alkyl halides and a Lewis acid, usually $AlCl_3$.
- Reactions of alkyl halide with Lewis acid produces a carbocation, which is the electrophile.

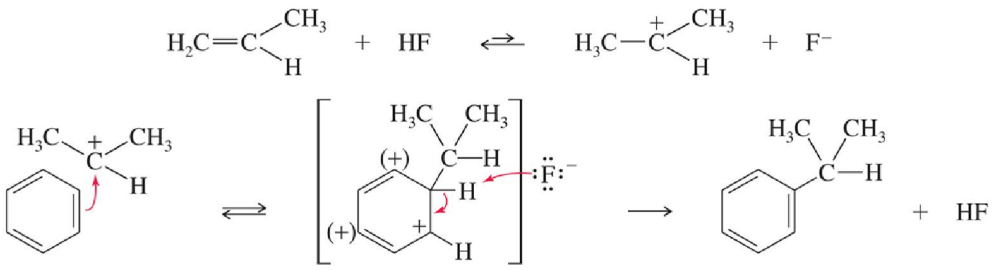
# Electrophilic aromatic substitution

## Mechanism of Friedel-Crafts alkylation



# Electrophilic aromatic substitution

## Friedel-Crafts alkylation: protonation of alkenes

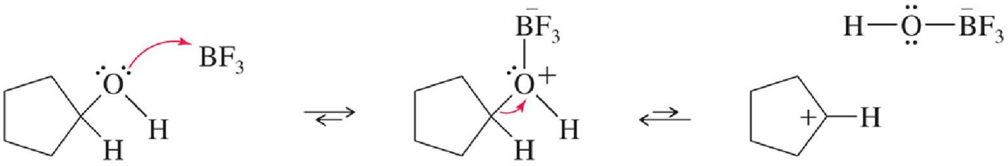


- An alkene can be protonated by HF.
- This weak acid is preferred because the fluoride ion is a weak nucleophile and will not attack the carbocation.

# Electrophilic aromatic substitution

## Friedel-Crafts alkylation: alcohols and Lewis acids

*Formation of the cation*



Alcohols can be treated with BF$_3$ to form the carbocation.

## Electrophilic aromatic substitution

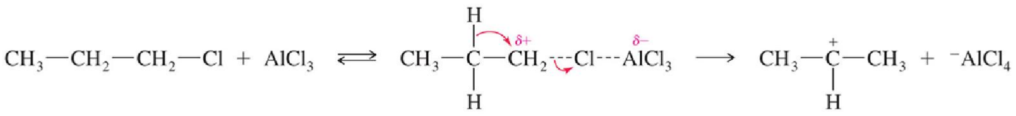
### Friedel-Crafts alkylation: limitations

- Reaction fails if benzene has a substituent that is more deactivating than halogens.
- Rearrangements are possible.
- The alkylbenzene product is more reactive than benzene, so polyalkylation occurs.

# Electrophilic aromatic substitution

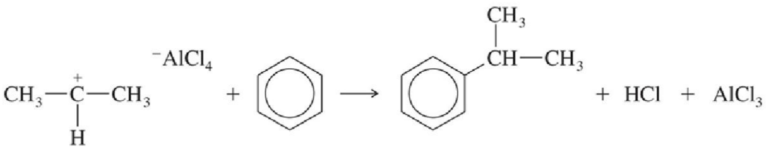
## Friedel-Crafts alkylation: rearrangements

*Ionization with rearrangement gives isopropyl cation*



$$CH_3{-}CH_2{-}CH_2{-}Cl + AlCl_3 \rightleftharpoons CH_3{-}\underset{H}{\overset{H}{C}}{-}\overset{\delta+}{CH_2}\cdots Cl\cdots\overset{\delta-}{AlCl_3} \longrightarrow CH_3{-}\underset{H}{\overset{+}{C}}{-}CH_3 + {}^{-}AlCl_4$$

*Reaction with benzene gives isopropylbenzene*



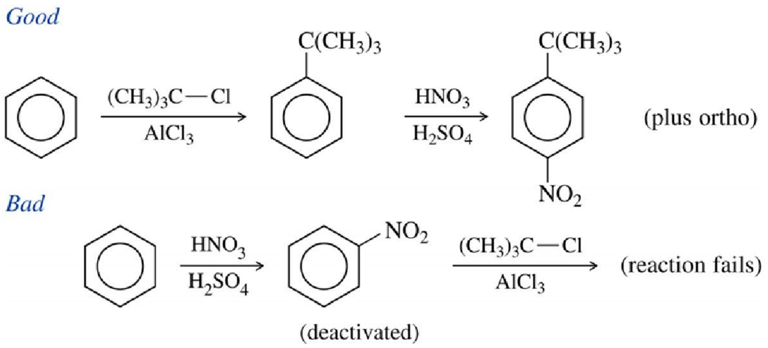
# Electrophilic aromatic substitution

## Problem 2

Devise a synthesis of *p*-nitro-*t*-butylbenzene from benzene.

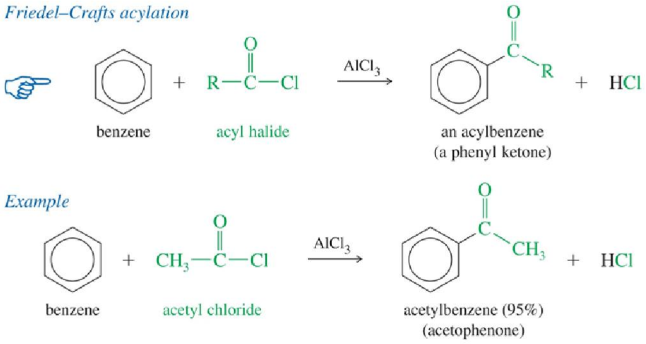
## Solution

To make *p*-nitro-*t*-butylbenzene, we would first use a Friedel–Crafts reaction to make *t*-butylbenzene. Nitration gives the correct product. If we were to make nitrobenzene first, the Friedel–Crafts reaction to add the *t*-butyl group would fail.



# Electrophilic aromatic substitution

## Friedel-Crafts acylation

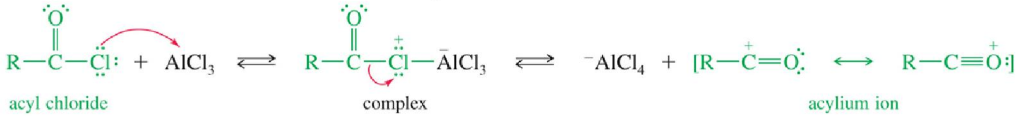


- Acyl chloride is used in place of alkyl chloride.
- The product is a phenyl ketone that is less reactive than benzene.

## Electrophilic aromatic substitution

### Friedel-Crafts alkylation: mechanism

Step 1: Formation of the acylium ion.



Step 2: Electrophilic attack to form the sigma complex.