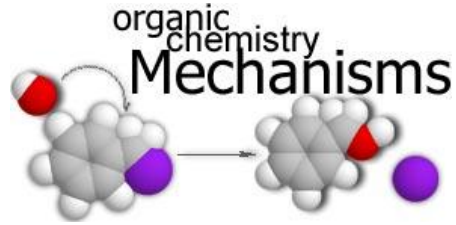
CHEM 344

ORGANIC REACTION MECHANISM



FOR CHEMISTRY' STUDENTS, COLLEGE OF SCIENCE

PRE-REQUISITES COURSE; CHEM 241

CREDIT HOURS; 2 (2+0+0)

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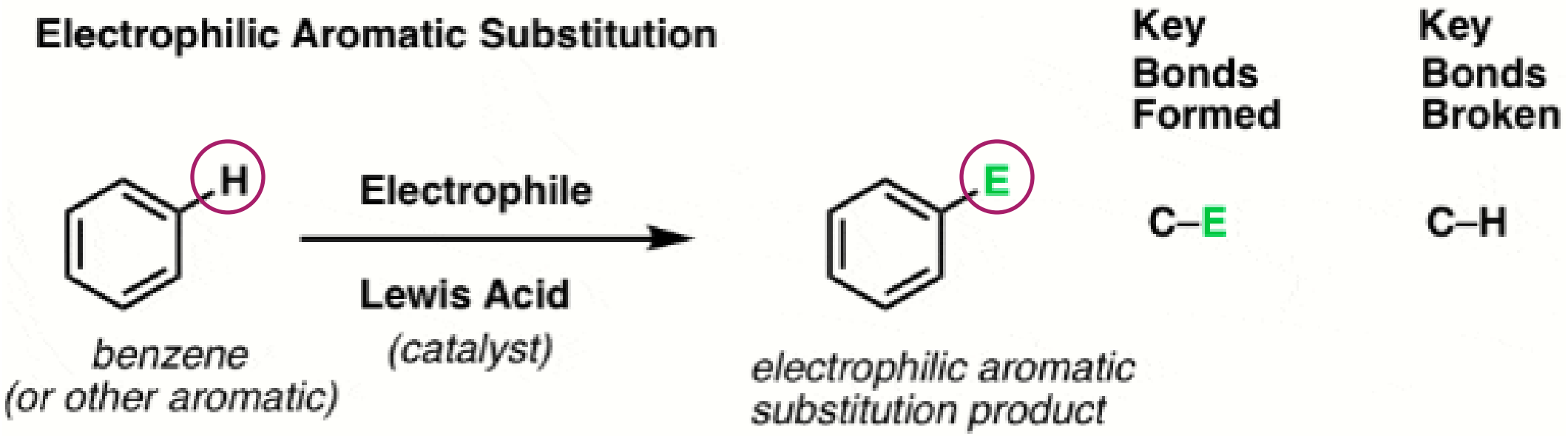
AROMATIC SUBSTITUTION REACTIONS

1) Electrophilic Aromatic Substitution Reactions

2) Nucleophilic Aromatic Substitution Reactions of Aryl halides

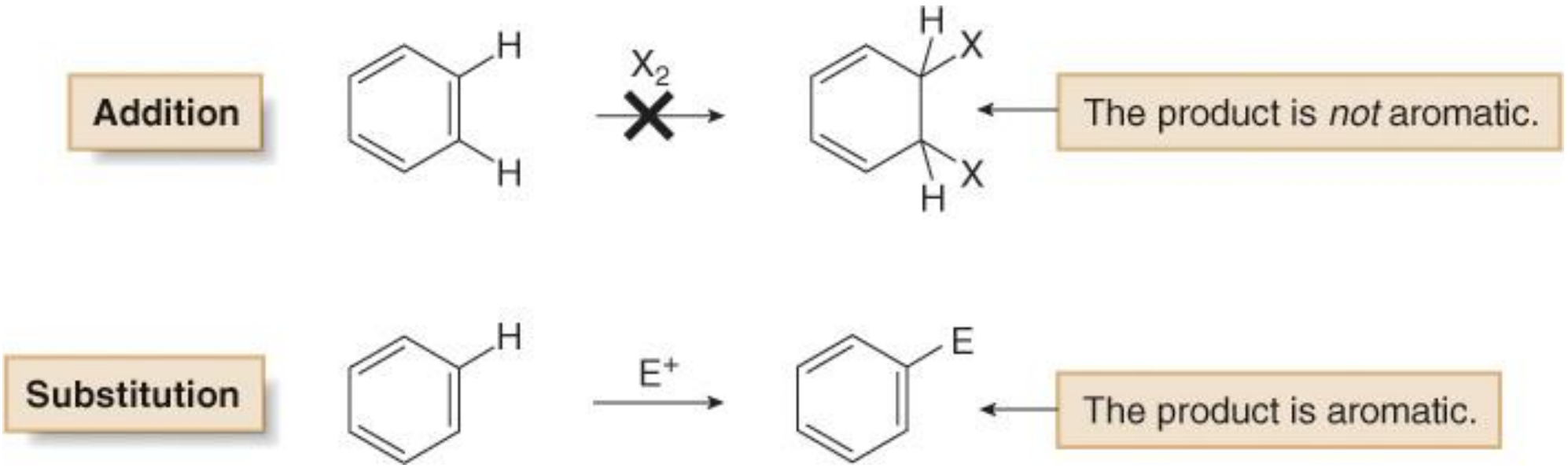
ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

- **Electrophilic aromatic substitution** *is an organic reaction in which an atom that is attached to an aromatic system (usually hydrogen) is replaced by an electrophile.*



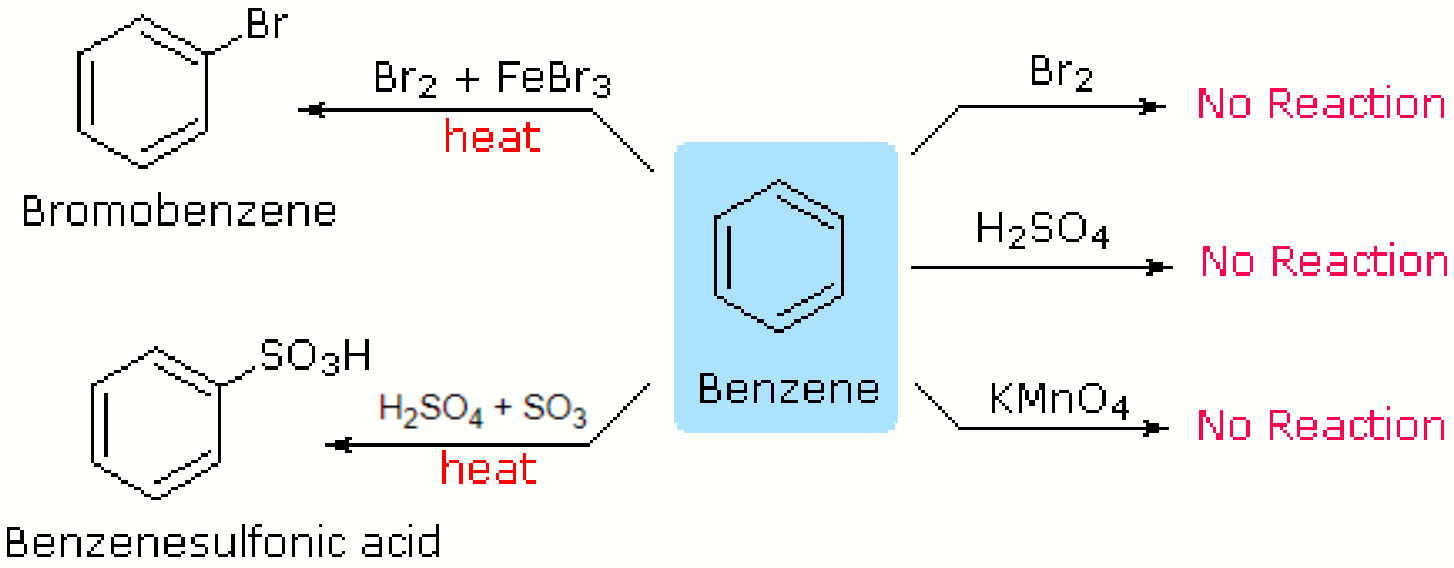
ELECTROPHILIC AROMATIC SUBSTITUTION

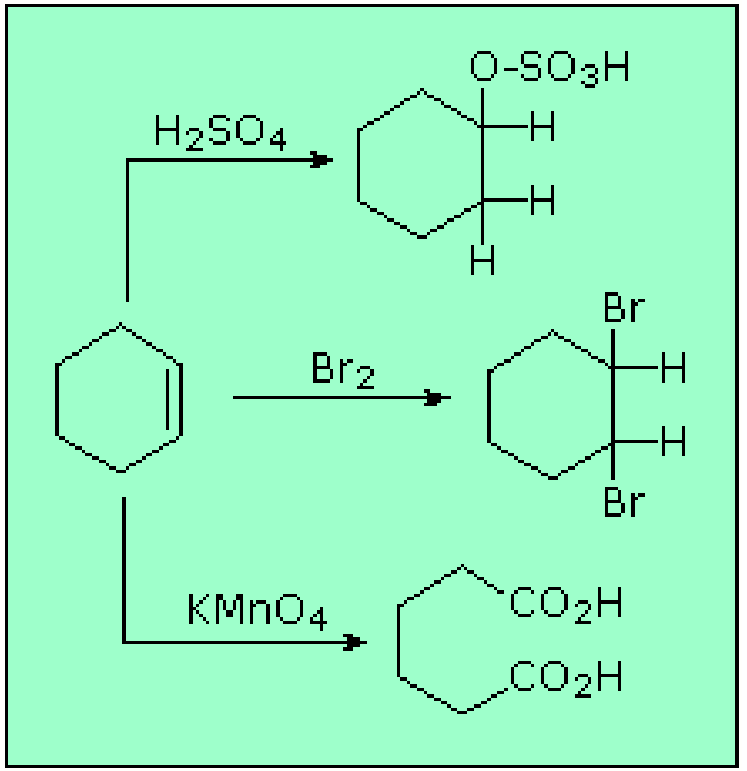
- Benzene *does not undergo addition reactions* like other unsaturated hydrocarbons, because addition would yield a product that is not aromatic.
- Substitution of a hydrogen keeps the aromatic ring intact.



TYPICAL REACTIONS

- The chemical reactivity of benzene contrasts with that of the alkenes in that *substitution reactions occur in preference to addition reactions*.





TYPICAL REACTIONS

- **Common Electrophilic Aromatic Substitution;**

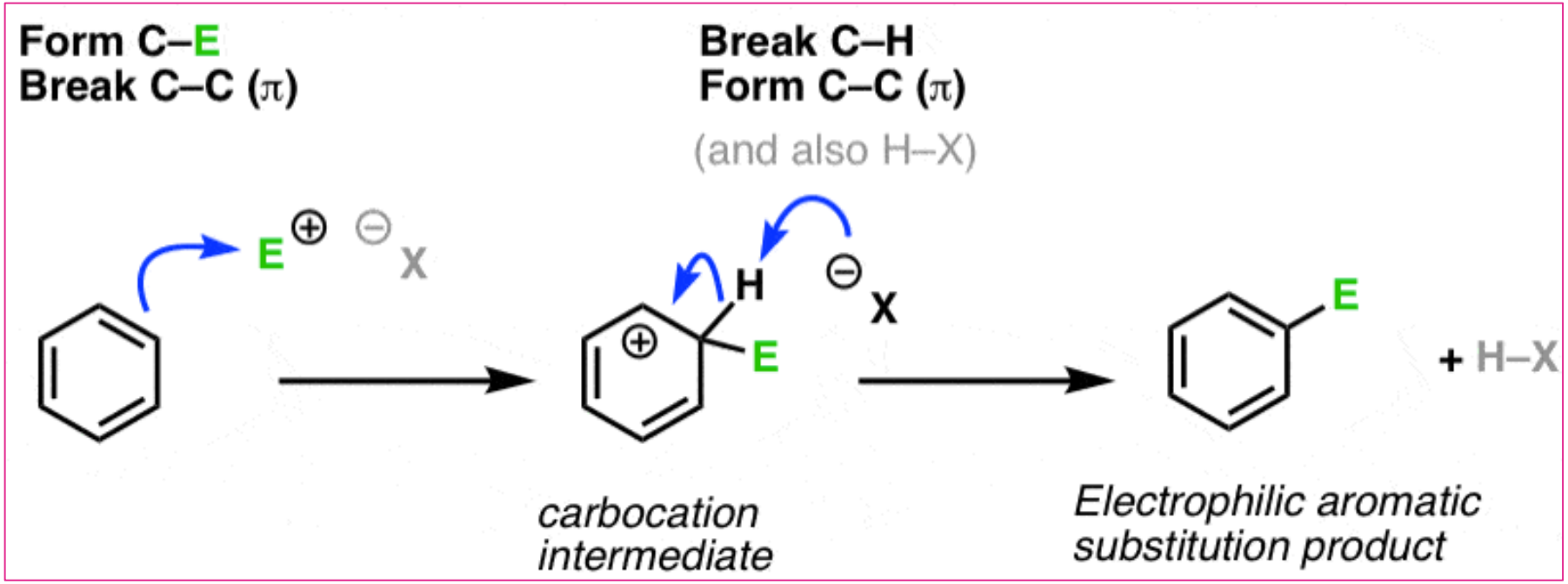
  The catalysts and co-reagents serve to generate the strong electrophilic species needed to effect the initial step of the substitution.

Reaction Type	Typical Equation	Electrophile $E^{(+)}$
Halogenation:	C_6H_6 + Cl_2 & heat, $FeCl_3$ catalyst ⟶ C_6H_5Cl + HCl (Chlorobenzene)	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6 + HNO_3 & heat, H_2SO_4 catalyst ⟶ $C_6H_5NO_2$ + H_2O (Nitrobenzene)	$NO_2^{(+)}$
Sulfonation:	C_6H_6 + H_2SO_4 + SO_3 & heat ⟶ $C_6H_5SO_3H$ + H_2O (Benzenesulfonic acid)	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6 + R-Cl & heat, $AlCl_3$ catalyst ⟶ C_6H_5-R + HCl (An Arene)	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6 + RCOCl & heat, $AlCl_3$ catalyst ⟶ C_6H_5COR + HCl (An Aryl Ketone)	$RCO^{(+)}$

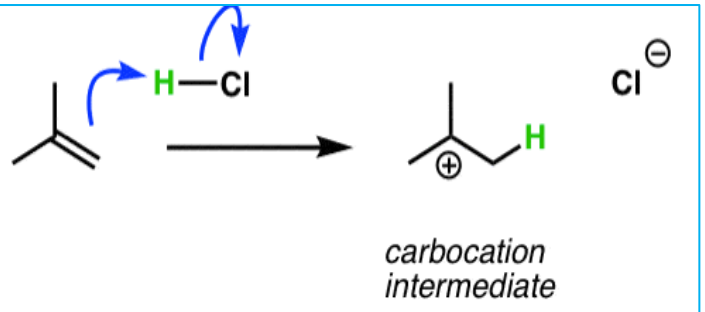
GENERAL MECHANISM

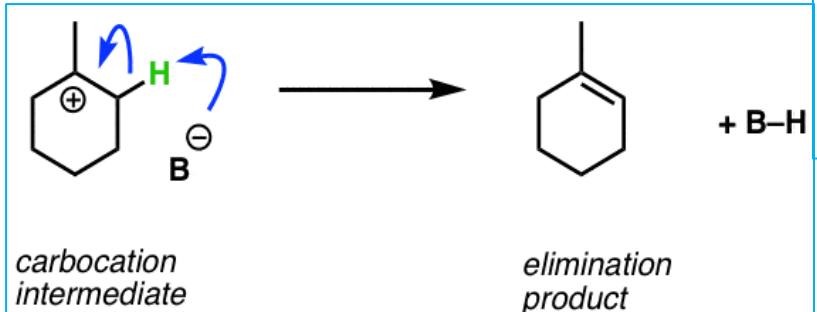
Step 1: *Attack of the electrophile (E^+) by aromatic π-bond results in formation of a carbocation intermediate*

Step 2: *Deprotonation of the tetrahedral carbon restoring aromaticity*



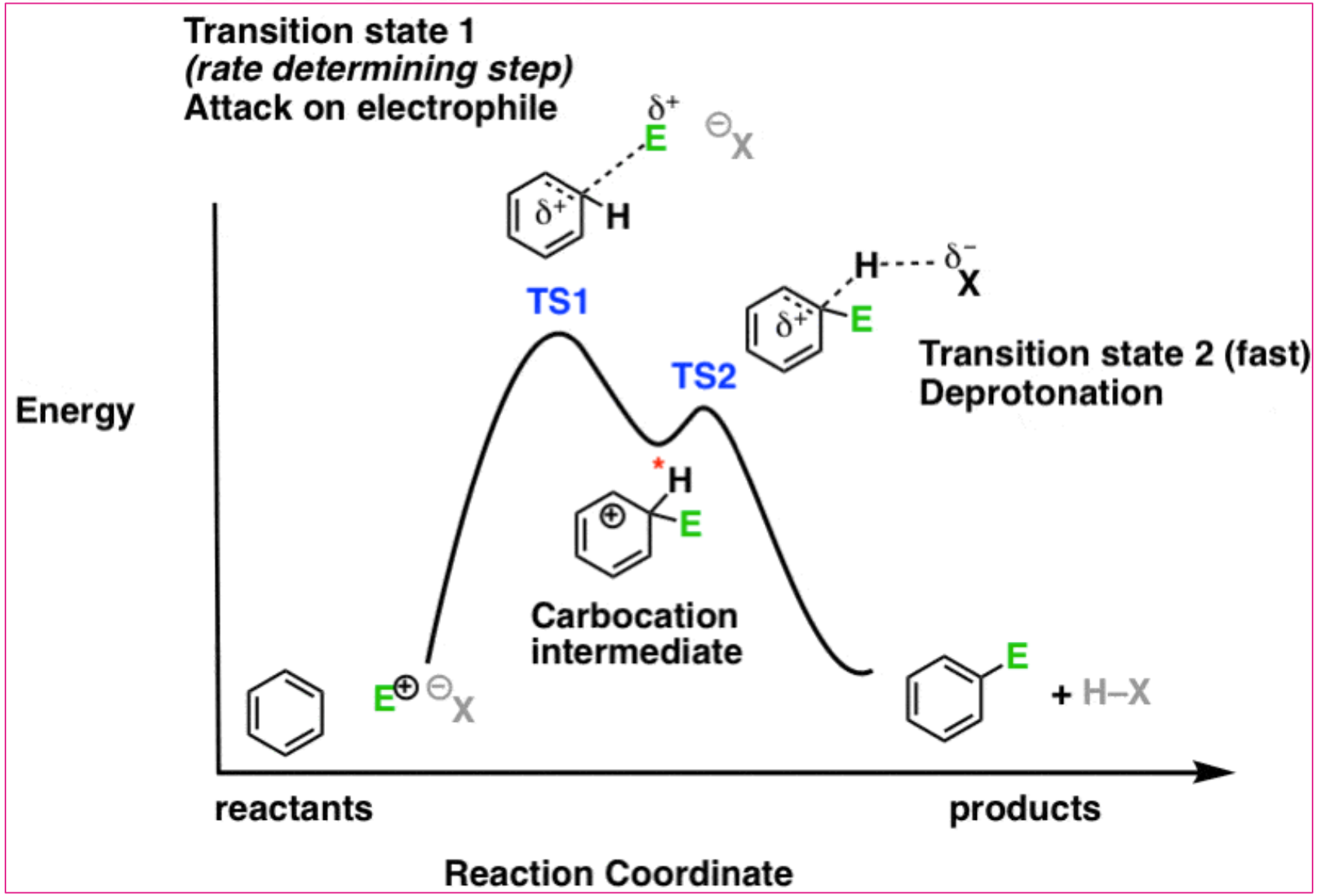
This resemble to the first step of the electrophilic addition to alkenes





This resemble to the second stem of the E1 reaction.

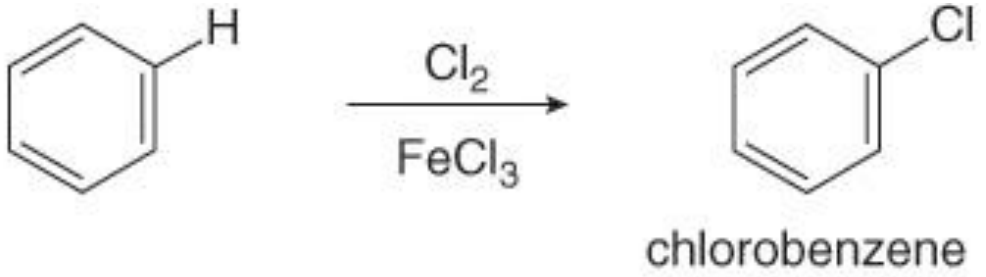
REACTION ENERGY DIAGRAM



HALOGENATION

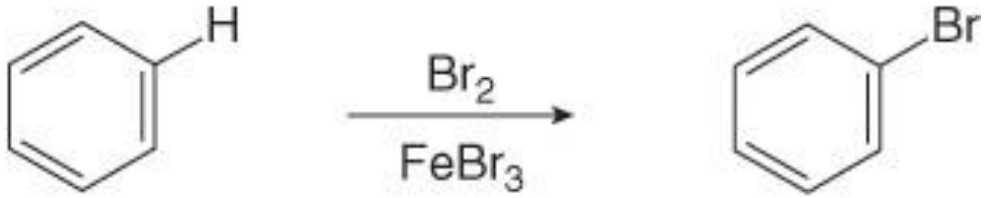
- In **halogenation**, benzene reacts with *Cl_2* or *Br_2* in the presence of a *Lewis acid catalyst*, such as $FeCl_3$ or $FeBr_3$, to give the aryl halides (chlorobenzene or bromobenzene), respectively.
- Analogous reactions with I_2 and F_2 are not synthetically useful because
  - I_2 is too unreactive and
  - F_2 reacts too violently.

Chlorination



chlorobenzene

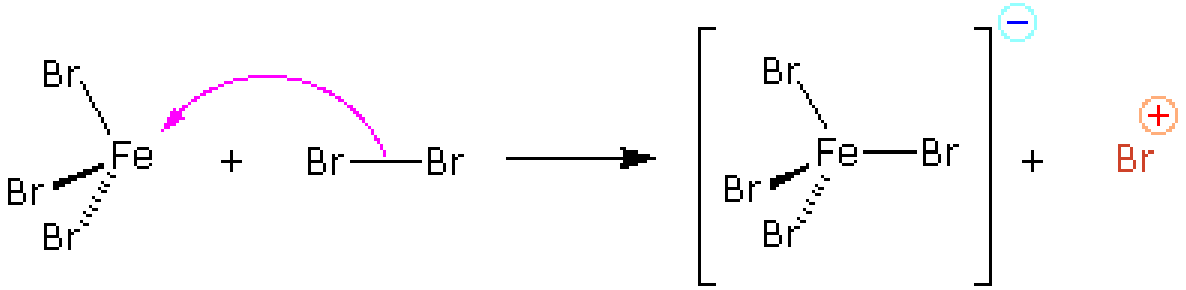
Bromination



bromobenzene

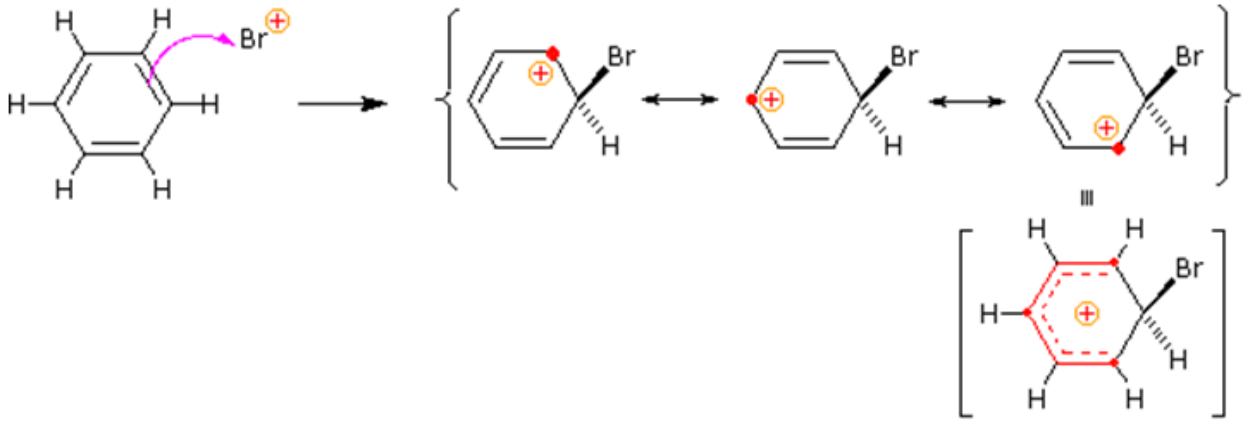
HALOGENATION: MECHANISM

- A two-step mechanism has been proposed for these electrophilic substitution reactions.
  - **Preliminary step:** *Formation of the strongly electrophilic bromine cation*



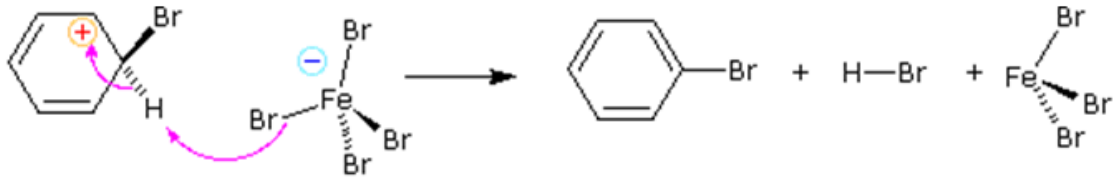
- **Step 1:** slow or rate-determining step

  The electrophile forms a sigma-bond to the benzene ring, generating a positively charged benzenonium intermediate.

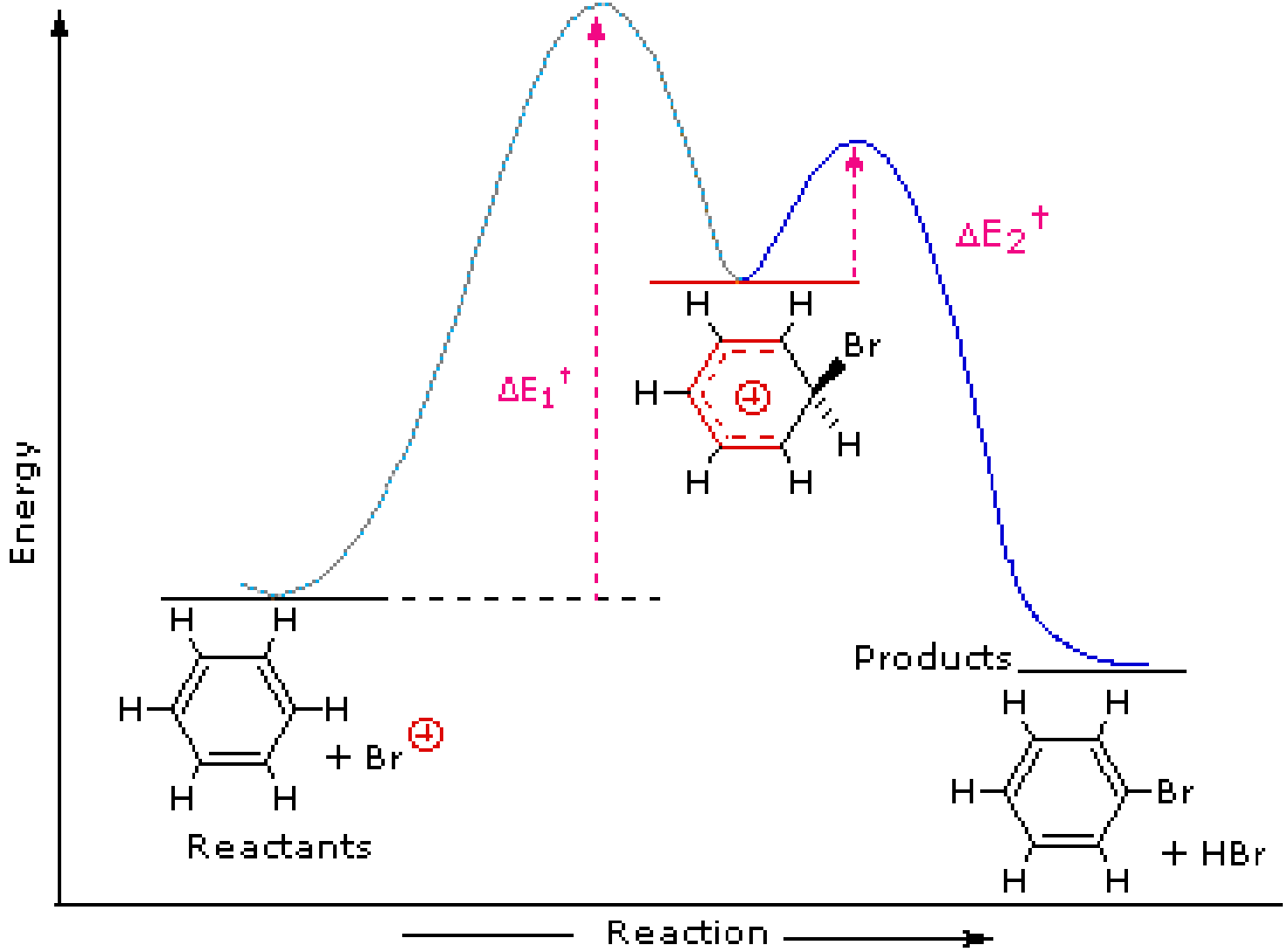


- **Step 2:** fast step

  A proton is removed from this intermediate, yielding a substituted benzene ring

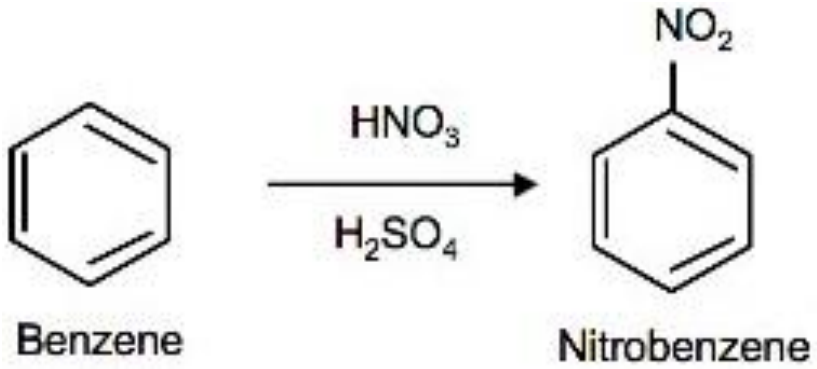


HALOGENATION: REACTION ENERGY DIAGRAM



NITRATION

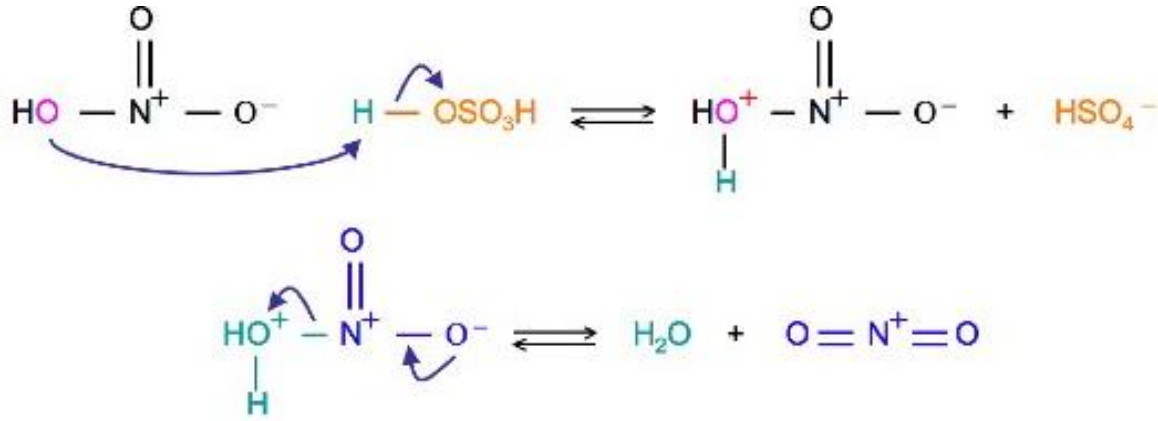
- The source of the *nitronium ion* is through the *protonation of nitric acid by sulfuric acid*, which causes the loss of a water molecule and formation of a nitronium ion.



NITRATION: MECHANISM

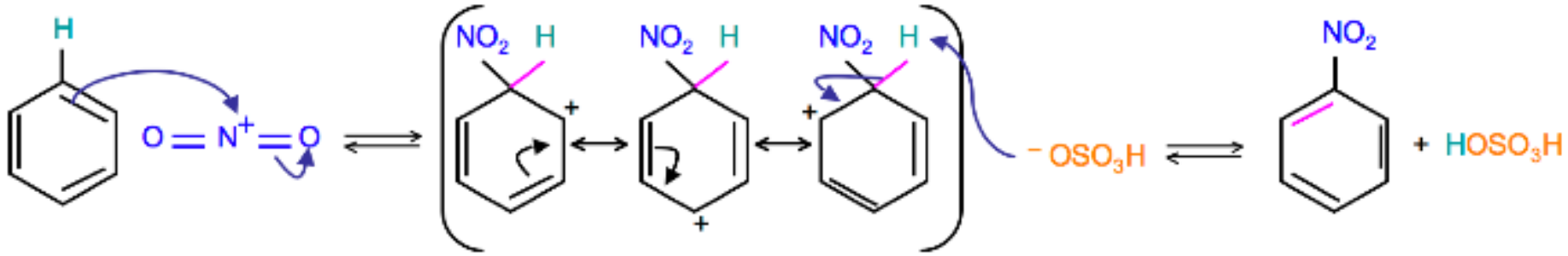
- **Sulfuric Acid Activation of Nitric Acid**

  The first step in the nitration of benzene is to activate HNO_3 with sulfuric acid to produce a stronger electrophile, the nitronium ion.



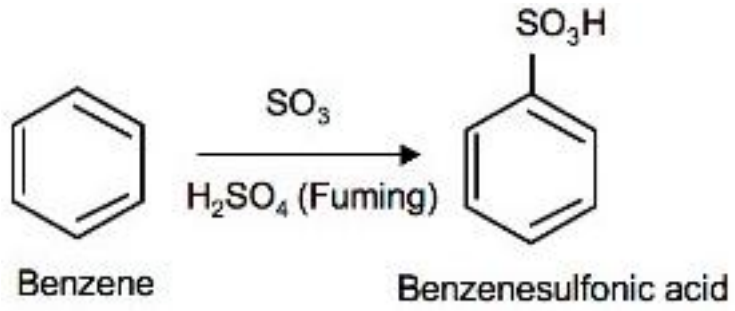
- **Mechanism**

  Because the nitronium ion is a good electrophile, it is attacked by benzene to produce Nitrobenzene.

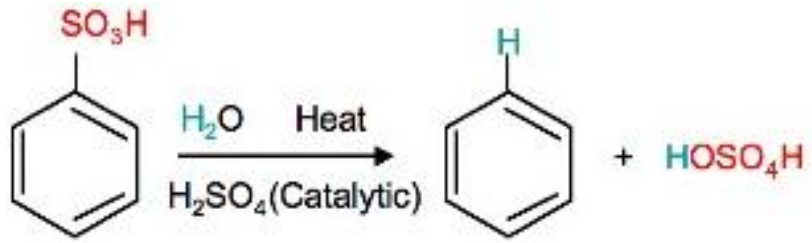


SULFONATION

- **Sulfonation** is a reversible reaction that produces *benzenesulfonic acid* by adding *sulfur trioxide and fuming sulfuric acid*.

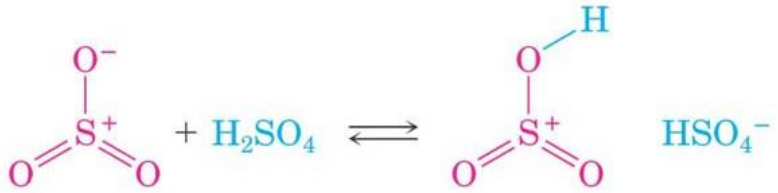


- The *reaction is reversed* by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



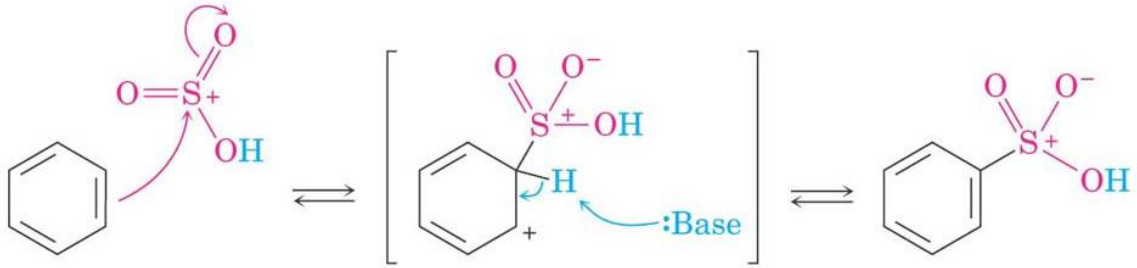
SULFONATION: MECHANISM

- Reaction with a mixture of sulfuric acid and SO_3
  - *Fuming sulfuric acid (oleum), is a concentrated solution of dissolved sulfur trioxide in sulfuric acid.*
  - *The sulfur in sulfur trioxide is electrophilic because the oxygen's pull electrons away from it because oxygen is very electronegative.*



Sulfur trioxide

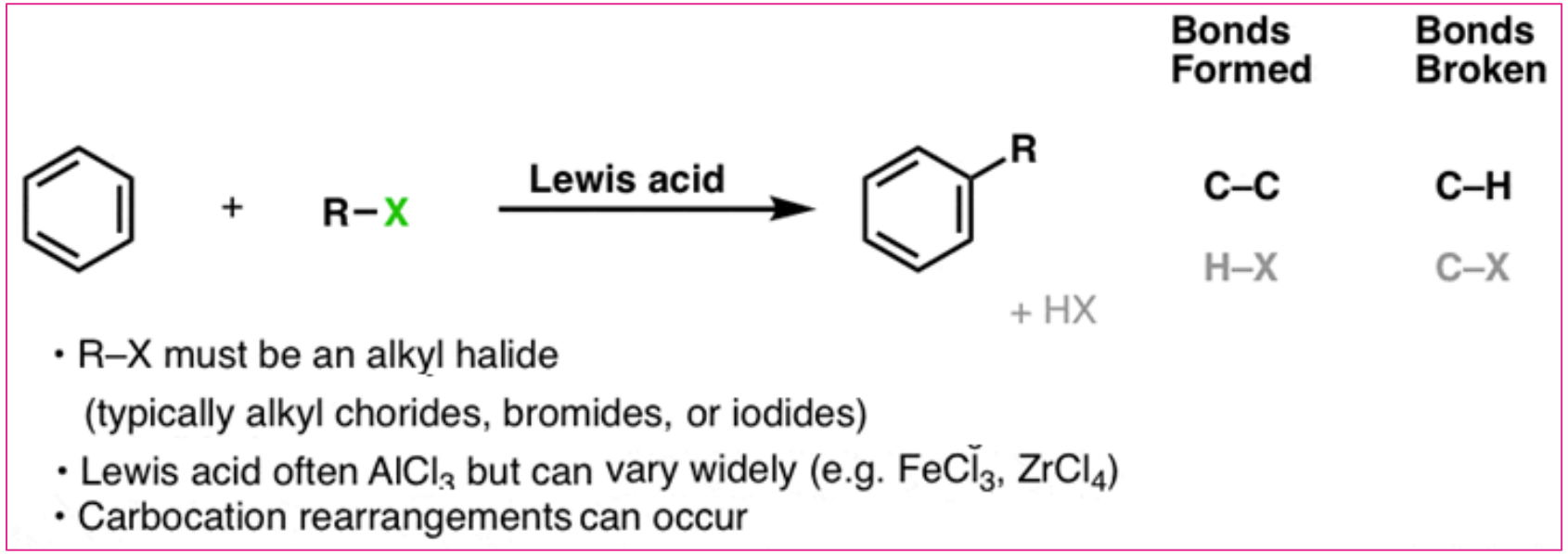
- Mechanism
  - *The benzene attacks the sulfur (and subsequent proton transfers occur) to produce benzenesulfonic acid.*

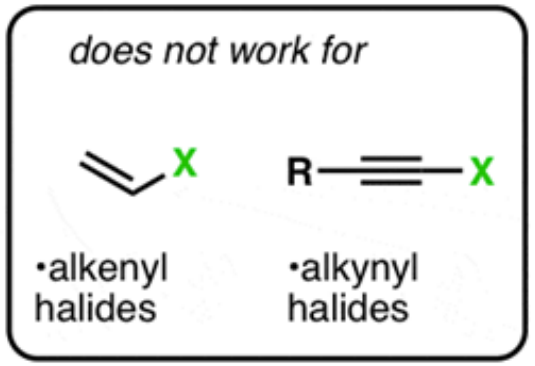


Benzenesulfonic acid

FRIEDEL-CRAFTS REACTION: ALKYLATION

- Friedel-Crafts Alkylation was first discovered by French scientist Charles Friedel and his partner, American scientist James Crafts, in 1877.
- This reaction allowed for the formation of *alkyl benzenes* from alkyl halides.



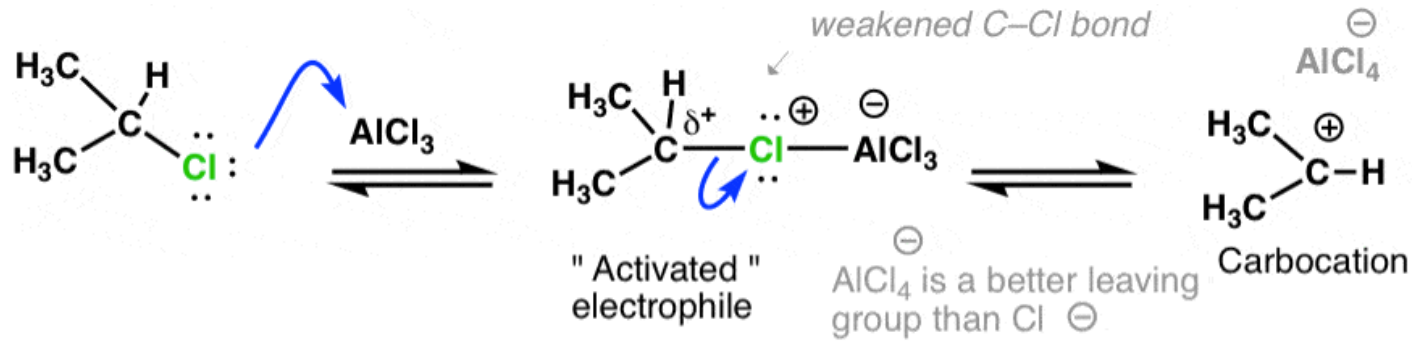


The *reactivity of haloalkanes* increases as you move up the periodic table and increase polarity.

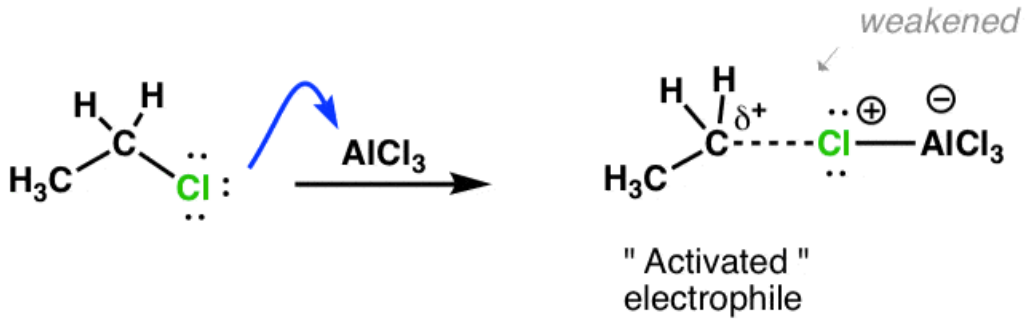
e.g. RF haloalkane is most reactive followed by RCl then RBr and finally RI.

FRIEDEL-CRAFTS REACTION: ALKYLATION

- Mechanism
  - Activation of Electrophile with Lewis Acid
    - *This steps activates the haloalkane and creates a carbocation that acts as the electrophile.*
    - *Secondary and tertiary halides only form the free carbocation in this step.*

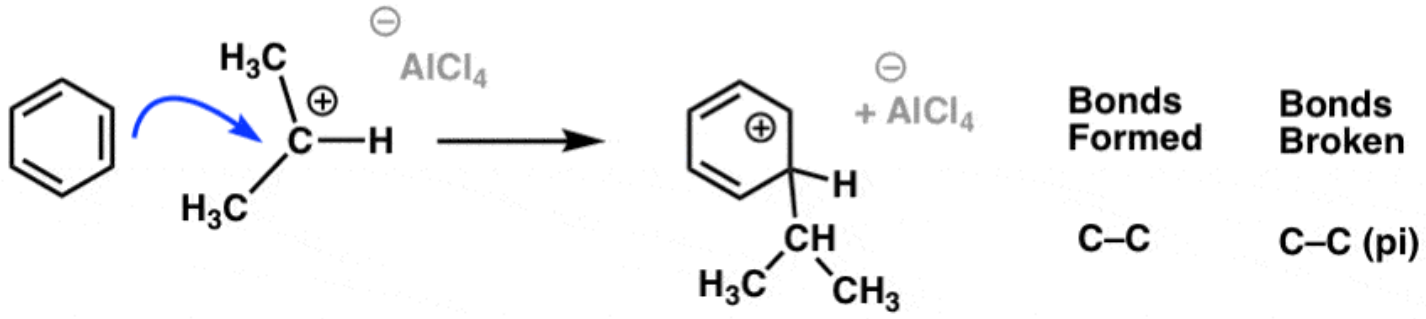


- *For primary (and methyl alkyl halides, it is unlikely that a "free" carbocation is present.*

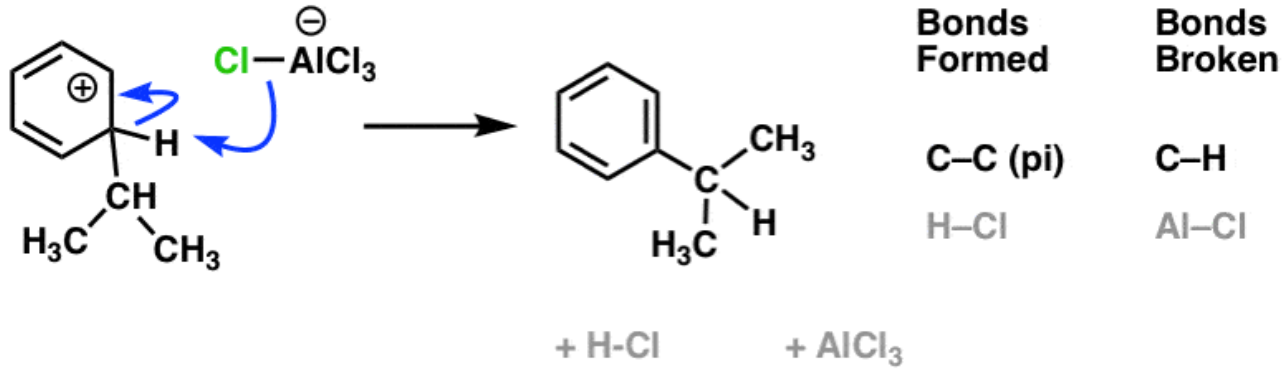


FRIEDEL-CRAFTS REACTION: ALKYLATION

- Mechanism
  - Step 1: Attack of activated electrophile by aromatic ring (rate-determining step)



  - Step 2: Deprotonation at carbon to regenerate aromatic ring



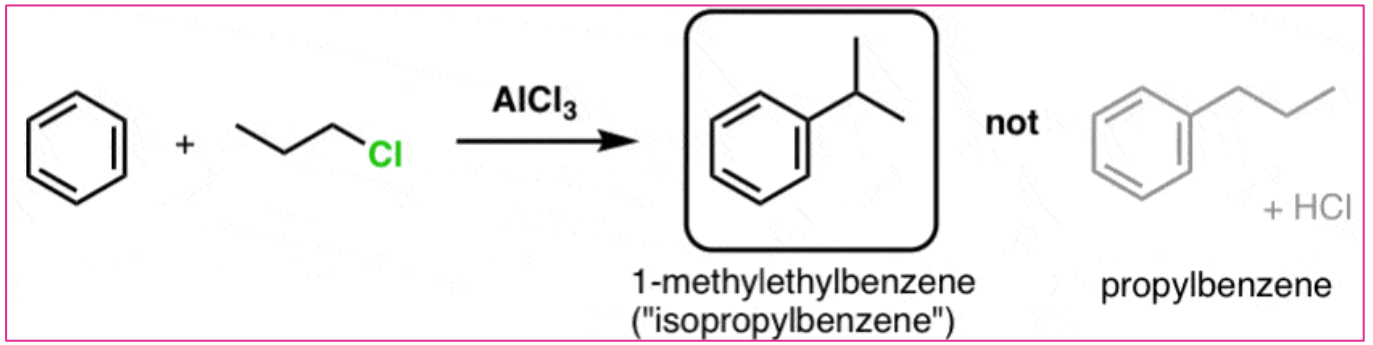
NOTE: This step regenerates $AlCl_3$, which can react with more alkyl halide starting material.

FRIEDEL-CRAFTS REACTION: ALKYLATION

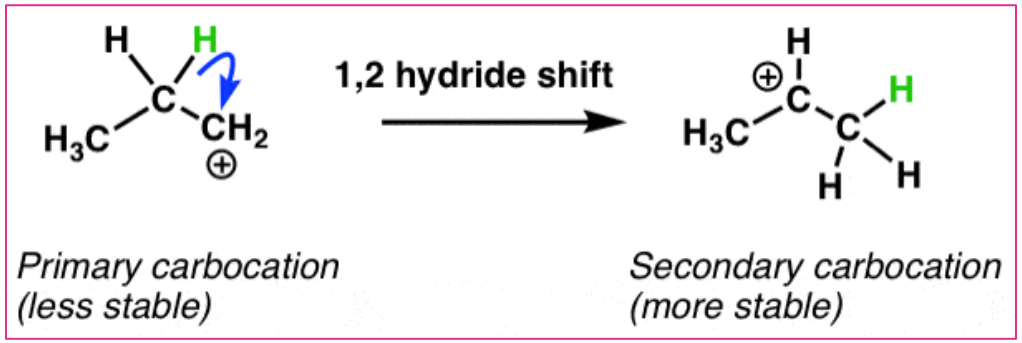
○ Some limitations of Friedel-Crafts Alkylation

▪ Carbocation rearrangements:

- *The Friedel-Crafts alkylation reaction between propyl chloride and benzene does not give propylbenzene, but isopropyl benzene.*

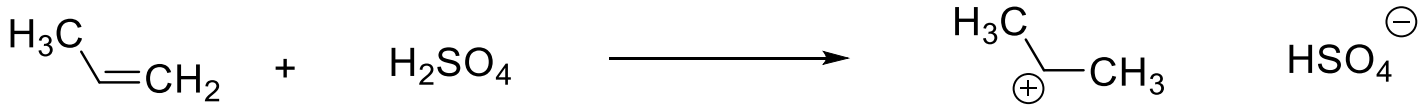


- *Carbocations can rearrange via hydride and alkyl shifts and a less stable carbocation is transformed into a more stable carbocation.*

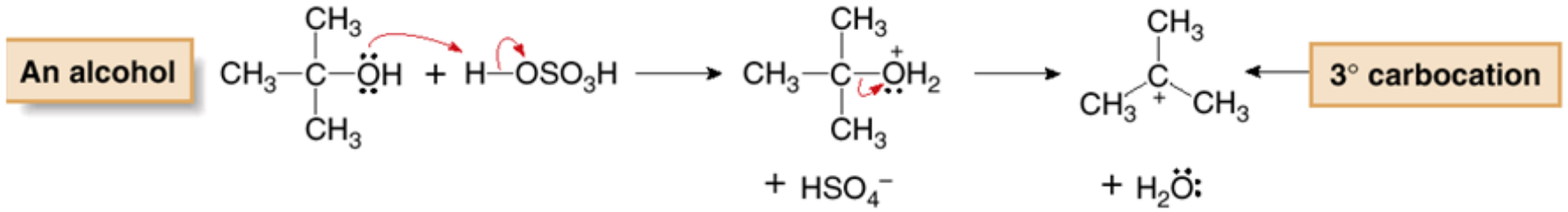


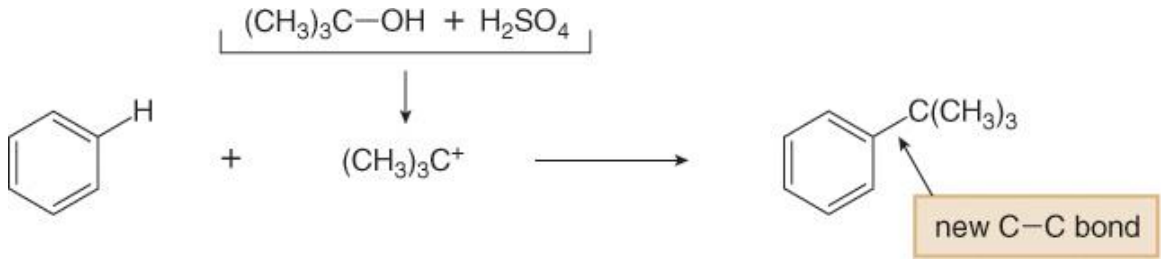
FRIEDEL-CRAFTS REACTION: ALKYLATION

- Some limitations of Friedel-Crafts Alkylation
  - Other functional groups that form carbocations can also be used as starting materials:
    - *Protonation of an alkene forms a carbocation, which can then serve as an electrophile in a Friedel-Crafts alkylation*



    - *Protonation of an alcohol, followed by loss of water, likewise forms a carbocation*



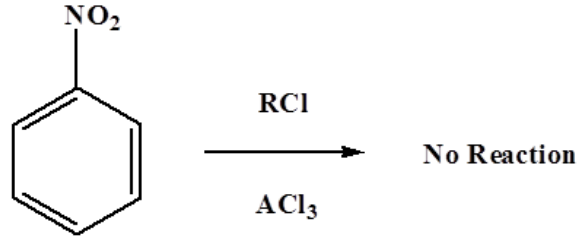


FRIEDEL-CRAFTS REACTION: ALKYLATION

Some limitations of Friedel-Crafts Alkylation

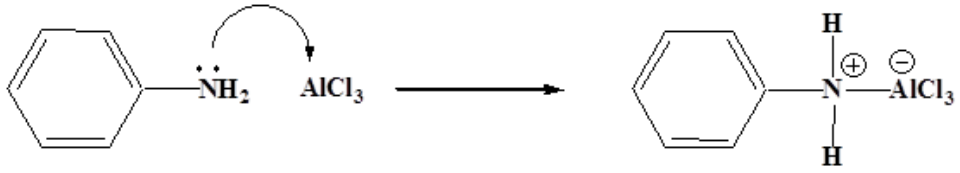
Alkylation of deactivating Systems:

- *Friedel-Crafts fails with compounds such as nitrobenzene and other strong deactivating systems.*



Friedel-Crafts reactions cannot be preformed with aromatic ring contains a NH_2, NHR, or NR_2 substituent.

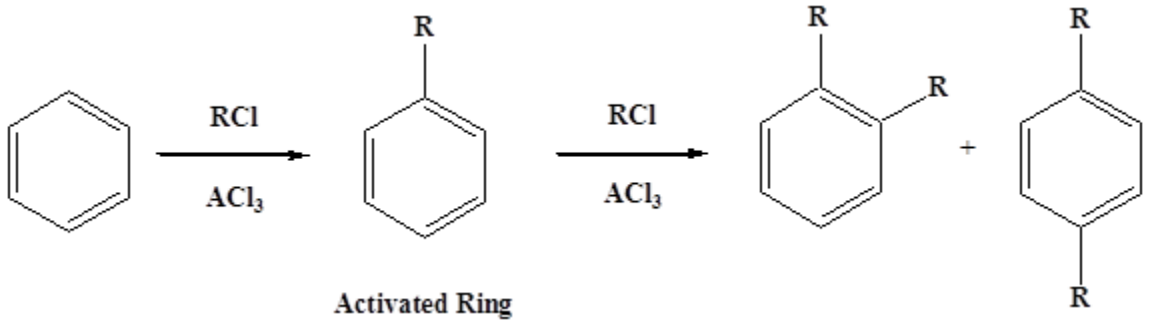
- *The lone pair electrons on the amines react with the Lewis acid $AlCl_3$.*
- *This places a positive charge next to the benzene ring, which is so strongly deactivate the Friedel-Crafts reaction.*



The positive charge strongly deactivates the benzene ring

FRIEDEL-CRAFTS REACTION: ALKYLATION

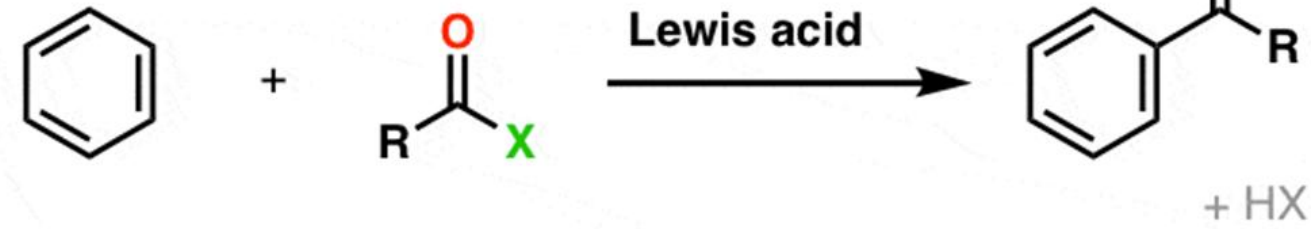
- Some limitations of Friedel-Crafts Alkylation
  - Friedel-Crafts alkylation can undergo polyalkylation:
    - *The reaction adds an electron-donating alkyl group, which activates the benzene ring to further alkylation.*



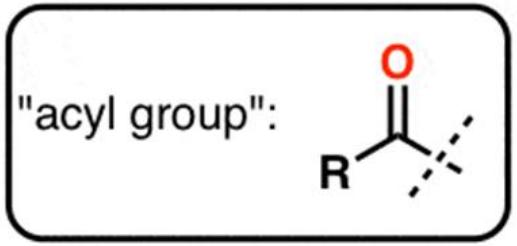
Activated Ring

FRIEDEL-CRAFTS REACTION: ACYLATION

- The Friedel–Crafts acylation is the *reaction of an arene with acyl chlorides* using a strong Lewis acid catalyst.



Bonds Formed	Bonds Broken
C–C	C–H
H–X	C–X

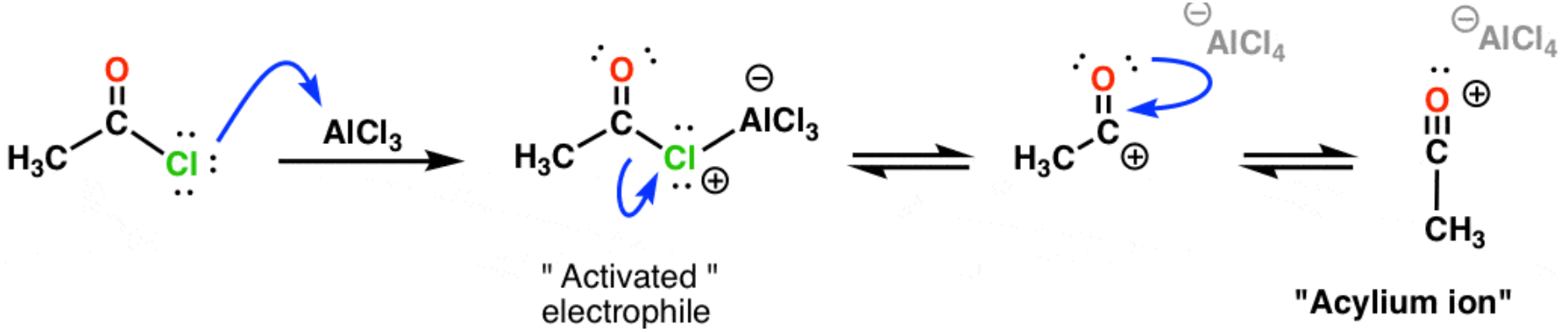


X is usually a halogen
e.g. Cl, Br, I

FRIEDEL-CRAFTS REACTION: ACYLATION

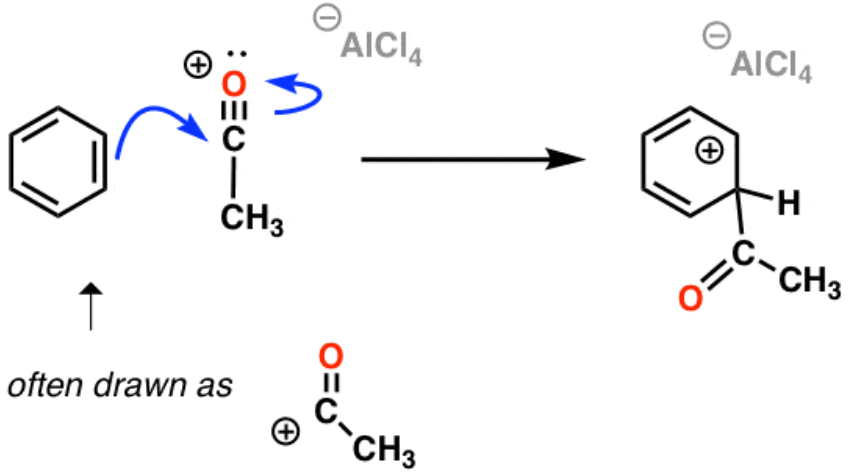
- Mechanism
  - Activation of Electrophile with Lewis Acid

Lewis acid coordinates to the halogen, and departure of the halogen (as $AlCl_4^-$) results in a fairly stable, resonance-stabilized carbocation know as the "acylium ion".



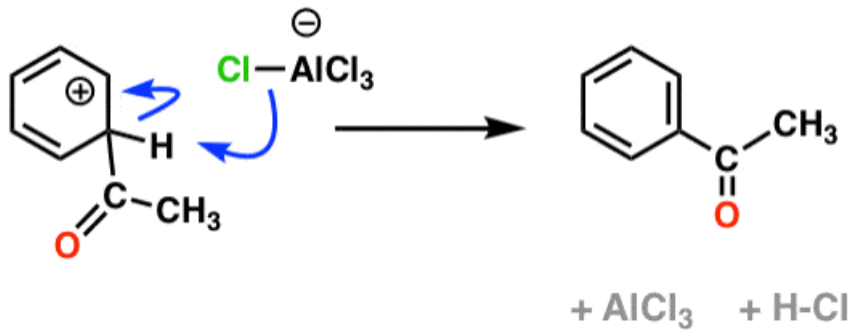
FRIEDEL-CRAFTS REACTION: ACYLATION

- Mechanism
  - Step 1: Attack of activated electrophile by aromatic ring (rate-determining step)



Bonds Formed	Bonds Broken
C–C	C–C (π)
	C–O (π)

  - Step 2: Deprotonation at carbon to regenerate aromatic ring



Bonds Formed	Bonds Broken
C–C (π)	C–H
H–Cl	Al–Cl

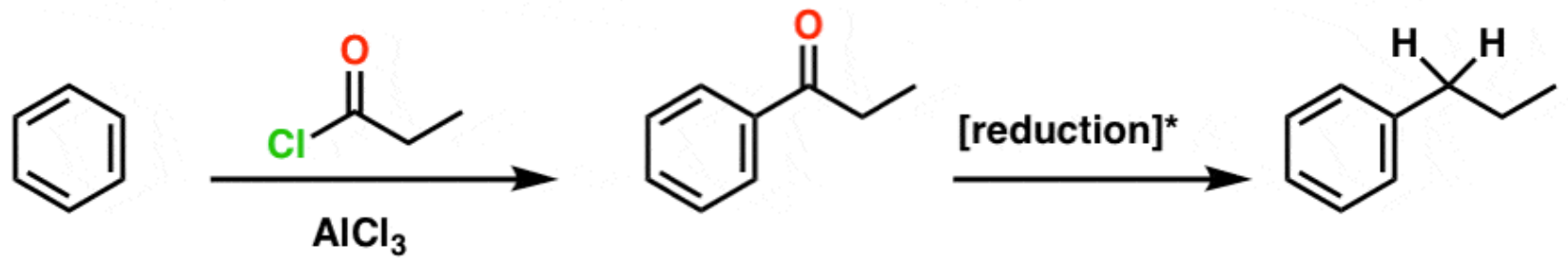
FRIEDEL-CRAFTS REACTION: ACYLATION

- Unlike the Friedel-Crafts alkylation, *no rearrangement occurs* with the Friedel-Crafts acylation.

  This opens up a "workaround" to use the Friedel-Crafts acylation to obtain products that are otherwise difficult to obtain through the Friedel-Crafts alkylation due to carbocation rearrangements.

  Example: *A rearrangement "workaround"*

  The Friedel-Crafts acylation in combination with reduction can be used as a workaround for situations where a Friedel-Crafts alkylation reaction would lead to rearrangement.



Propylbenzene

* one of at least three methods can be used:
- $Pd\text{-}C/H_2$ (hydrogenation)
- $Zn(Hg), H^+$ (Clemmensen reduction)
- NH_2NH_2, KOH, heat (Wolff-Kishner reduction)

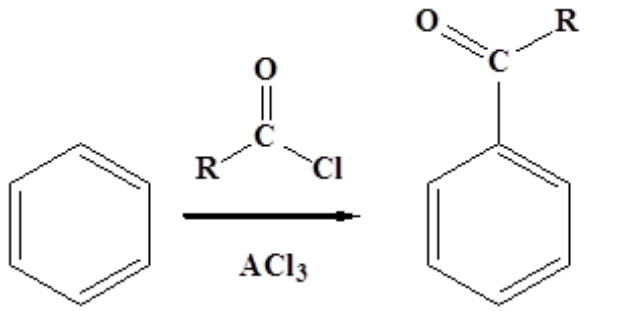
FRIEDEL-CRAFTS REACTION: ACYLATION

- Some limitations of Friedel-Crafts Acylation
  - Friedel-Crafts acylation tends to fail on aromatic rings with strongly deactivating groups.

    Similarly to alkylation, such as nitro, CF_3, sulfonyl and so on.

  - Friedel-Crafts alkylation cannot undergo further acylation:

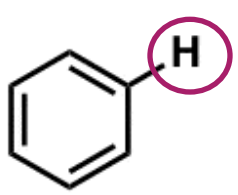
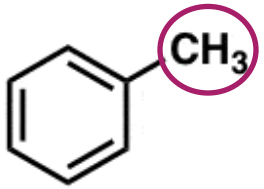
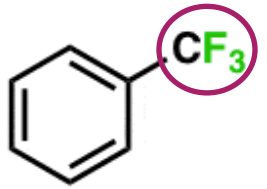
    This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating, thus prevents further acylation.



Dectivated Ring

SUBSTITUTED BENZENE

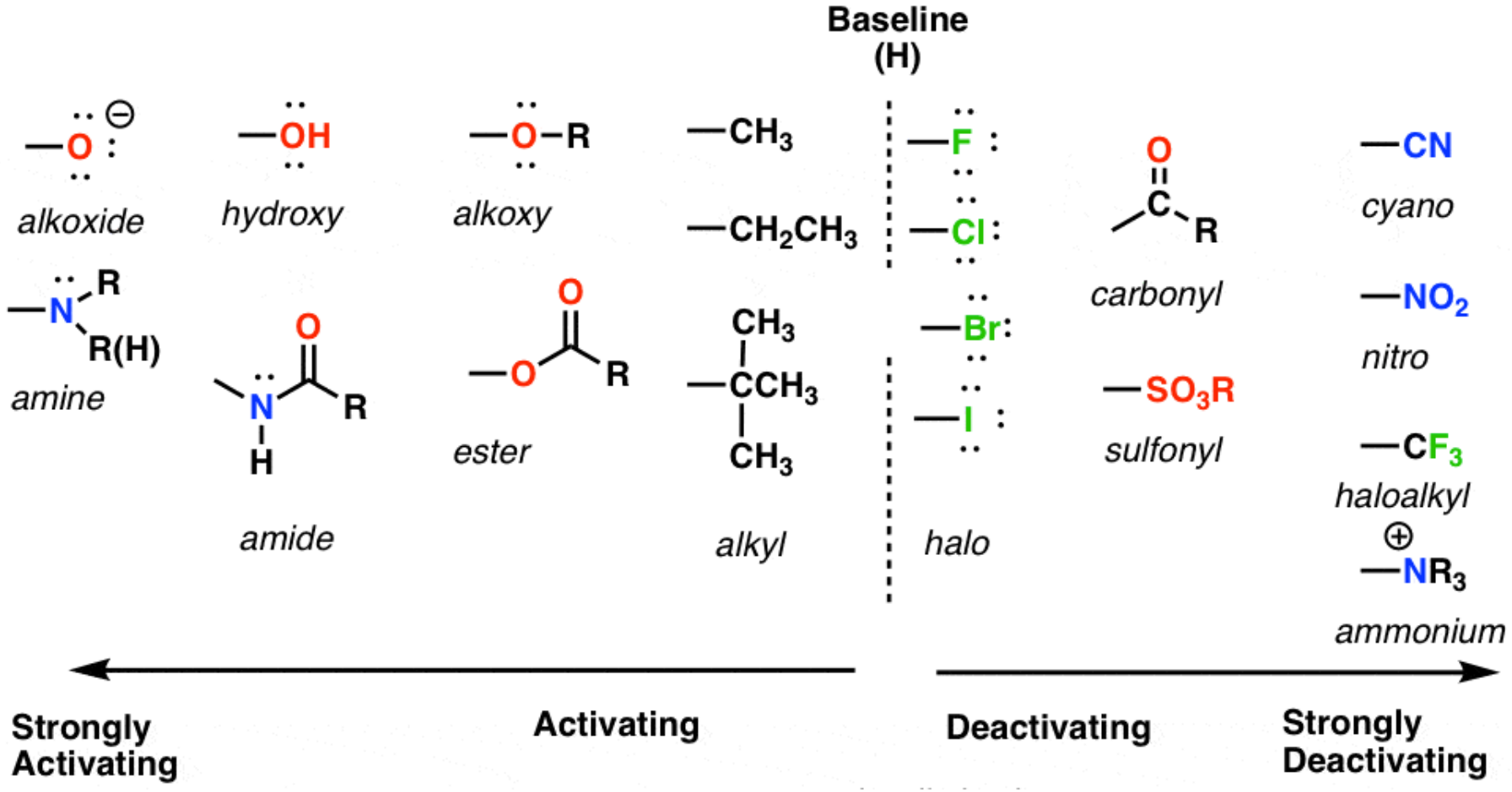
- What happens to the reaction rate if a substituent is added?

	Benzene	Methylbenzene	Trifluoromethylbenzene
			
Relative rate:	**1**	**23**	**2.5×10^{-5}**
	(baseline)	**(faster)**	**(slower)**

- An electron-donating group (CH_3) results in a *faster* reaction than benzene itself
- An electron-withdrawing group (CF_3) results in a *slower* reaction than benzene itself

SUBSTITUTED BENZENE

- Table of activating and deactivating groups



SUBSTITUTED BENZENE

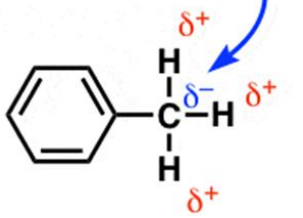
- When substituted benzene compounds undergo electrophilic substitution reactions, the following features must be considered:

(1) Inductive Effect *(2) Resonance Effect.*

(1) Inductive Effect; *"Sigma" (σ) donors and acceptors*

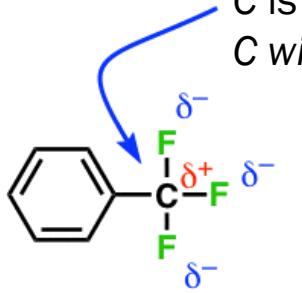
Electron-donating group (e.g. Alkyl group)

C is relatively electron-rich (δ-)
C donates electron density to the ring



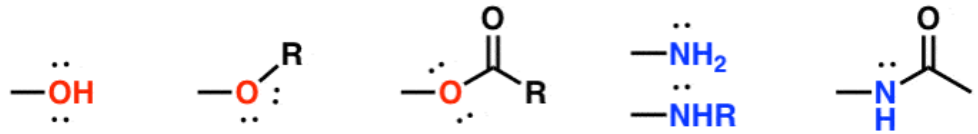
Electron-withdrawing group (e.g. CF_3)

C is relatively electron-donor (δ+)
C withdraws electron density from the ring



(2) Resonance Effect; *Pi (π) donors and acceptors*

Functional groups with lone pairs on oxygen and nitrogen are activating, dramatically increasing the rate of electrophilic aromatic substitution relative to H.

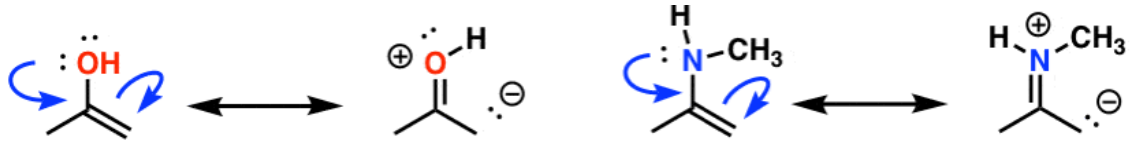


Hydroxyl Ether O-Acyl Amine *N*-Acyl

SUBSTITUTED BENZENE

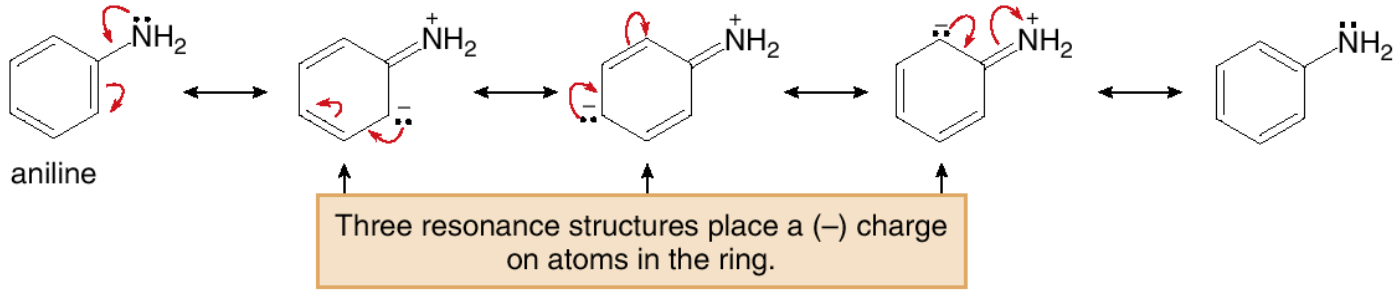
- ***π-donors groups are strongly activating***
  - *Inductive effect "σ-acceptors" withdraws electron density; Oxygen and nitrogen are more electronegative than carbon.*

  - *π-donor; oxygen and nitrogen bearing lone pairs and can form π–bond with adjacent p-orbital.*



In this case; σ-acceptors < π-donor.

Example: *An electron-donating resonance effect is observed whenever an atom having a lone pair of electrons is directly bonded to a benzene ring.*

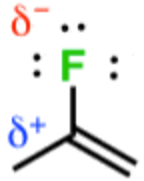


SUBSTITUTED BENZENE

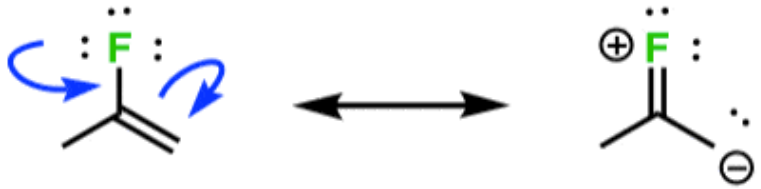
- **Halogens (F, Cl, Br, I) are deactivating**

Halobenzenes react more slowly towards electrophilic aromatic substitution than benzene itself.

- *Inductive effect "σ-acceptors"; Fluorine much more electronegative than carbon.*



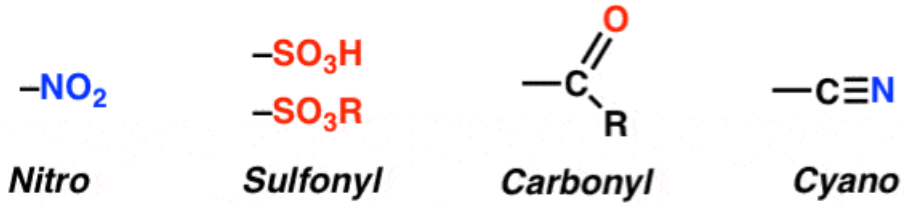
- *π-donor; Fluorine can donate a lone pair to form π–bond with adjacent p-orbital.*



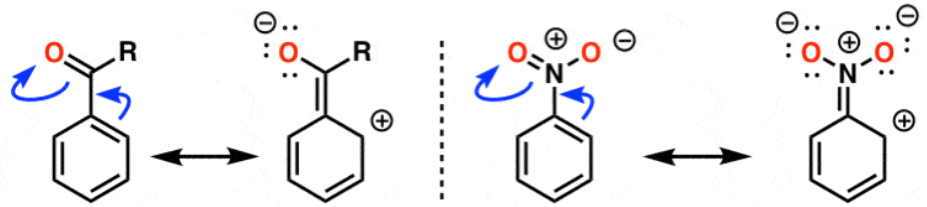
In this case; σ-acceptors > π-donor.

SUBSTITUTED BENZENE

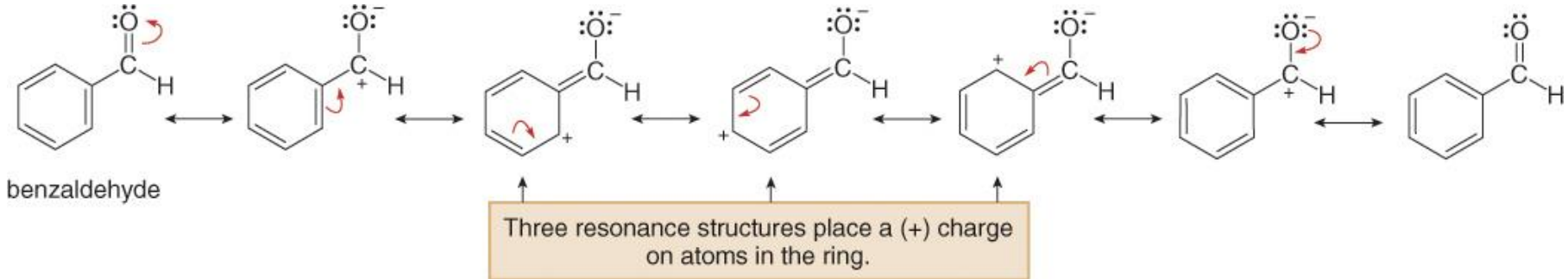
- ***π-acceptors groups are strongly deactivating***
  - *π-donor groups are strongly deactivating.*



The rate of electrophilic aromatic substitution are lower than benzene itself.



Example: *An electron-withdrawing resonance effect is observed in substituted benzenes having the general structure C_6H_5-Y=Z, where Z is more electronegative than Y.*

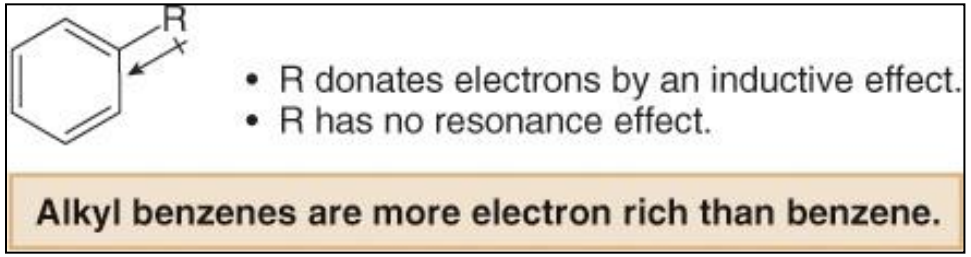


SUBSTITUTED BENZENE

- We must consider the net balance of both the *inductive* and *resonance effects*.

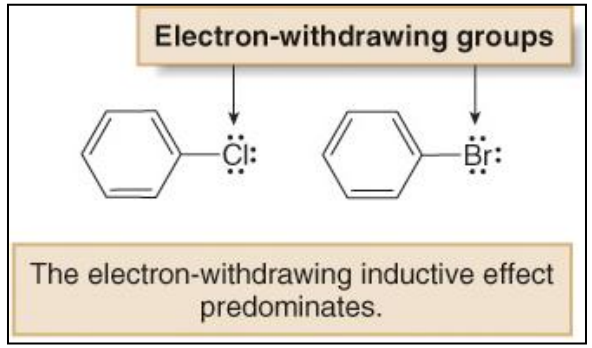
Electron-donating groups

Activating groups-with no lone pairs, e.g. alkyl groups)

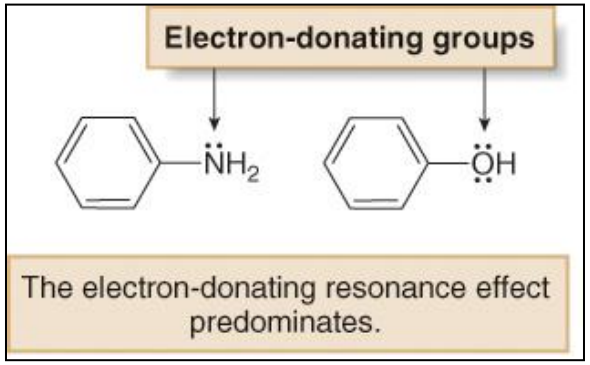


Electron-withdrawing groups

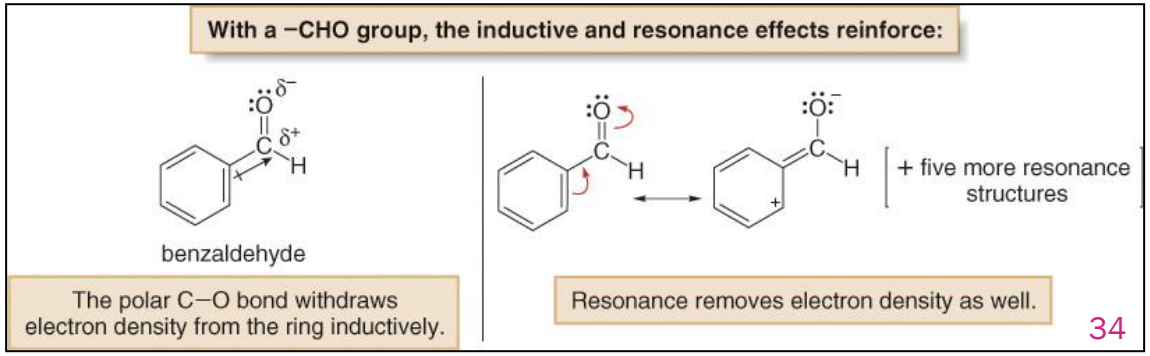
Deactivating groups-with lone pairs, e.g. halogens)



Activating groups-with lone pairs, e.g. OH, NH_2, ...etc)



Deactivating groups-with lone pairs, e.g. general structure C_6H_5-Y=Z (with Z more electronegative than Y)



SUBSTITUTED BENZENE

- A substituent affects two aspects of the electrophilic aromatic substitution reaction:

1) The rate of the reaction

A substituted benzene reacts faster or slower than benzene itself.

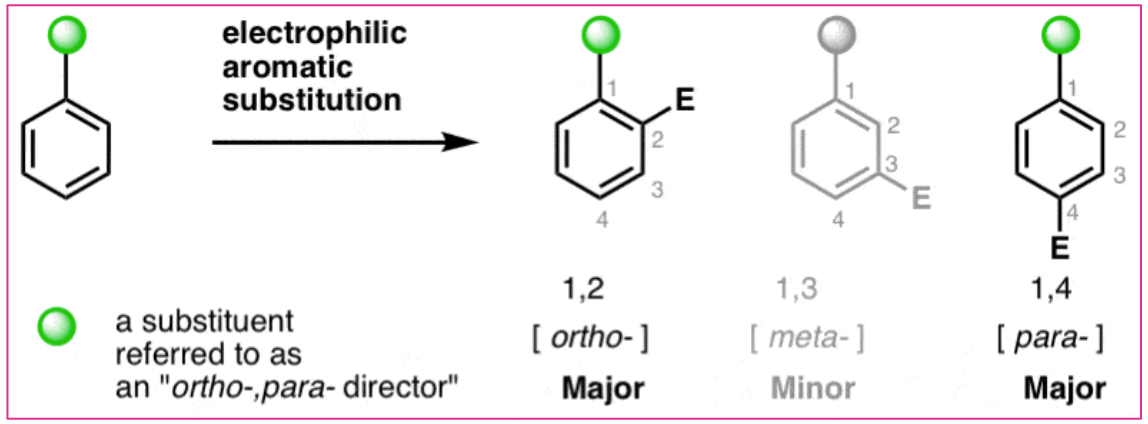
Activating groups *increase the rate of electrophilic aromatic substitution, relative to hydrogen.*

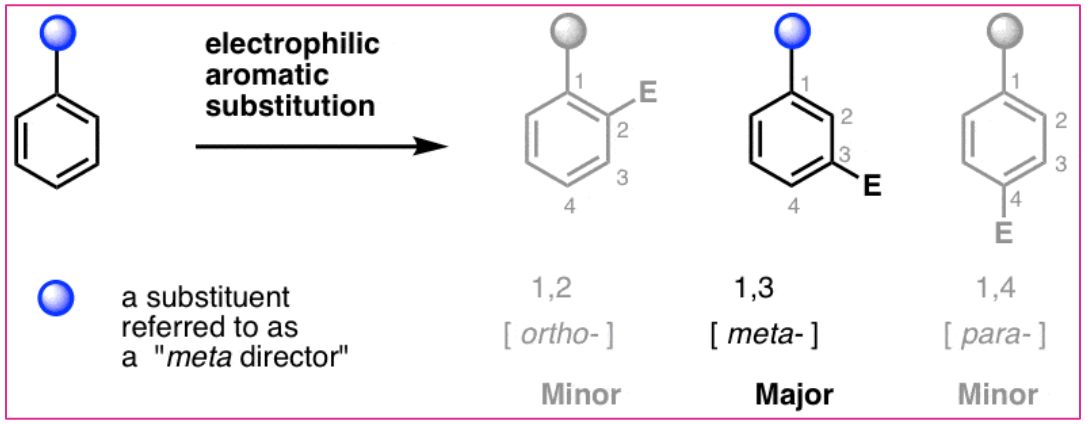
Deactivating groups *decrease the rate of electrophilic aromatic substitution, relative to hydrogen.*

2) Orientation

The new group is located either *ortho*, *meta*, or *para* to the existing substituent.

The identity of the first substituent determines the position of the second incoming substituent.



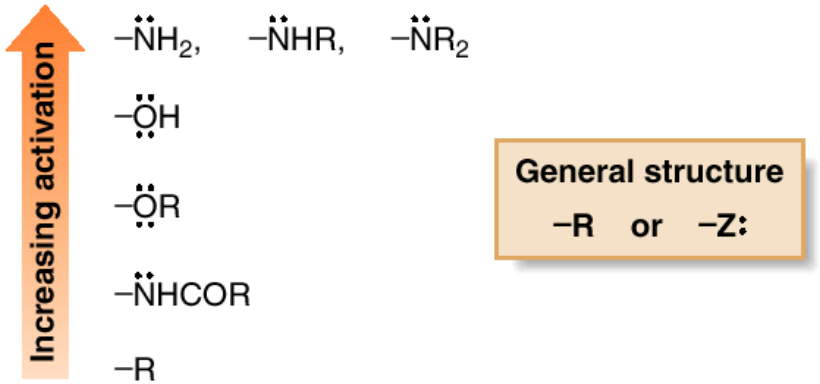


SUBSTITUTED BENZENE

- All substituents can be divided into three general types:

1) ortho, para directors and activators

Substituents that activate a benzene ring and direct substitution ortho and para

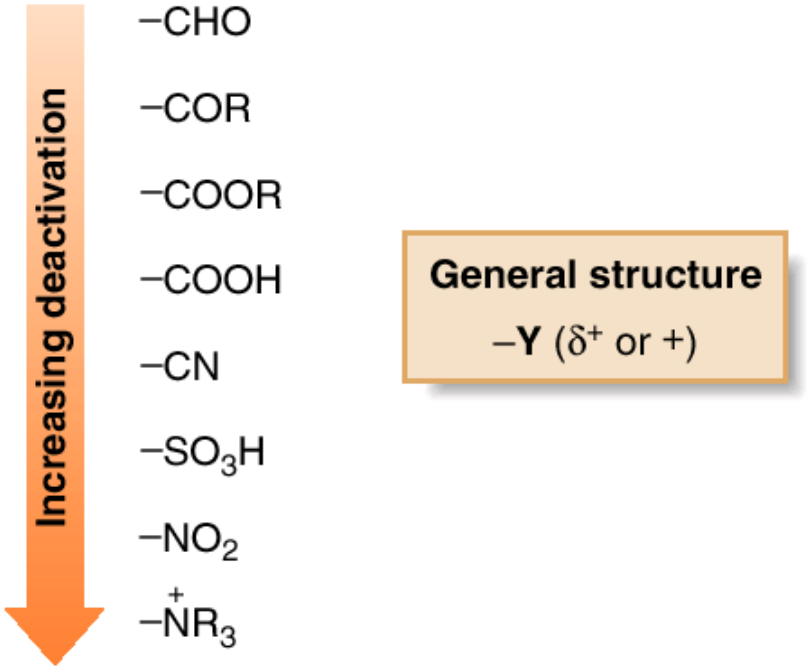


2) ortho, para deactivators

Substituents that deactivate a benzene ring and direct substitution ortho and para

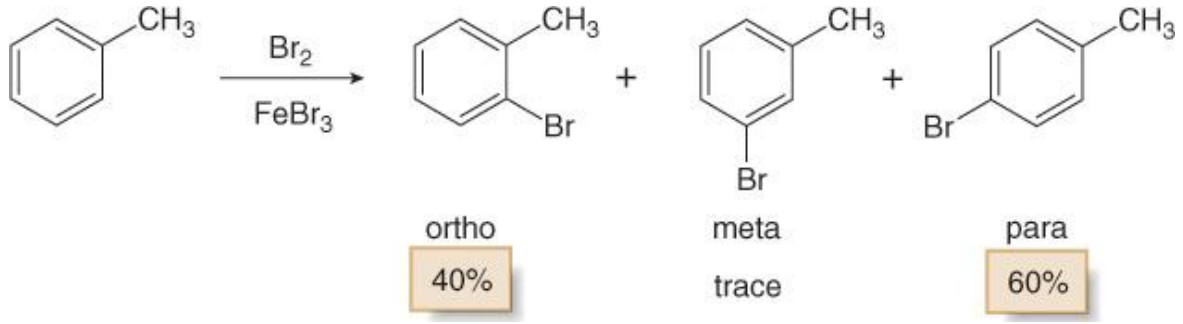
3) meta directors

Substituents that direct substitution meta. All meta directors deactivate the ring

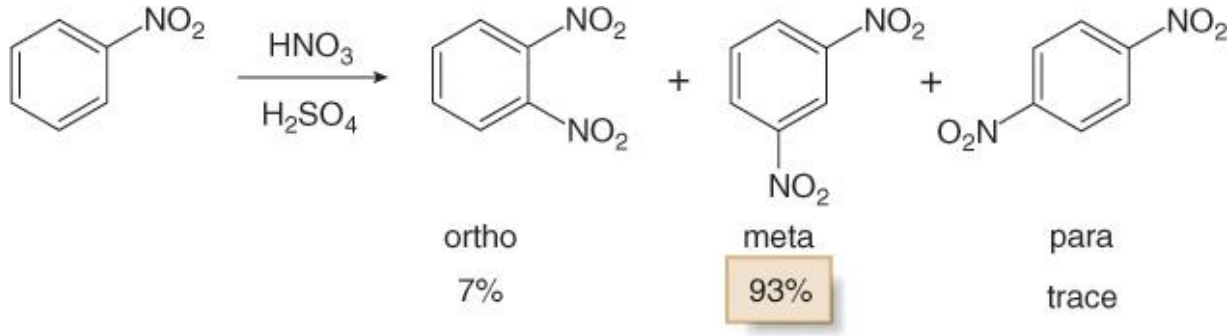


SUBSTITUTED BENZENE

- Examples:
  - Bromination of Toluene
    - Toluene reacts faster than benzene.
    - The electron-donating CH_3 group activates the benzene ring.
    - The CH_3 group is called an ortho, para director.



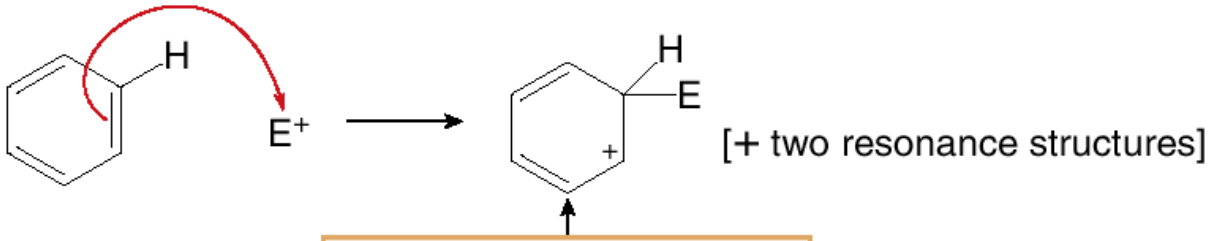
  - Nitration of nitrobenzene
    - It reacts more slowly than benzene.
    - The electron-withdrawing NO_2 group deactivates the benzene attack.
    - The NO_2 group is called a meta director.



SUBSTITUTED BENZENE

How substituents activate or deactivate the ring?

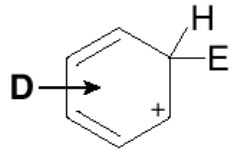
- The first step involves addition of the electrophile (E^+) to form a resonance stabilized carbocation.



The more stable the carbocation, the lower the energy of the transition state and the faster the reaction

- The principles of *inductive effects* and *resonance effects* can now be used to predict carbocation stability.

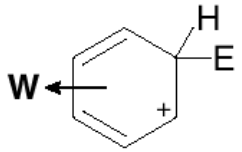
D = electron-donor group



more stable carbocation

Substitution is **faster**.
The ring is **activated.**

W = electron-withdrawing group

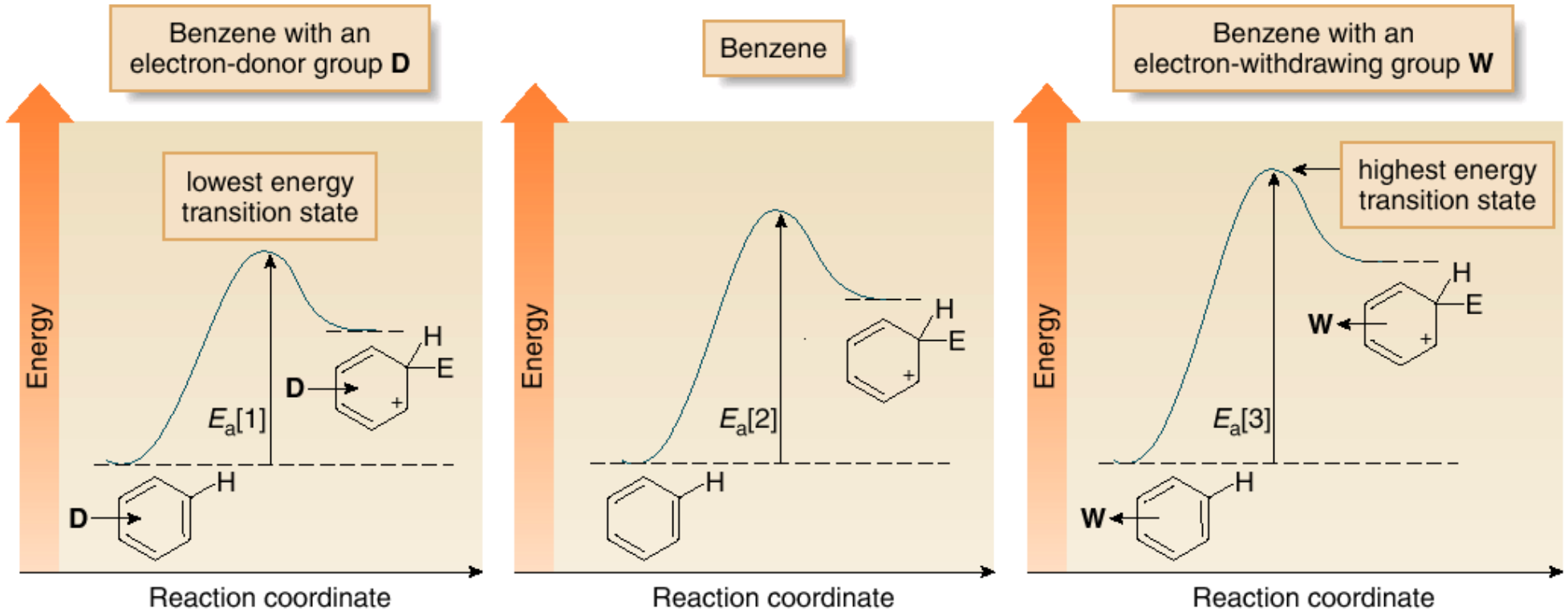


less stable carbocation

Substitution is **slower.**
The ring is **deactivated.**

SUBSTITUTED BENZENE

- The energy diagrams



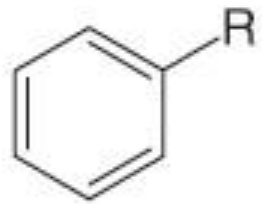
- Electron-donor groups **D** stabilize the carbocation intermediate, lower the energy of the transition state, and increase the rate of reaction.
- Electron-withdrawing groups **W** destabilize the carbocation intermediate, raise the energy of the transition state, and decrease the rate of reaction.

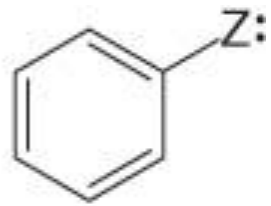
SUBSTITUTED BENZENE

Orientation Effects in Substituted Benzenes

- There are two general types of ortho, para directors and one general type of meta director.
- All ortho, para directors are R groups or have a non-bonded electron pair on the atom bonded to the benzene ring.
- All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.

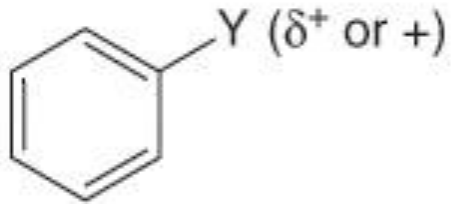
Ortho, para directors





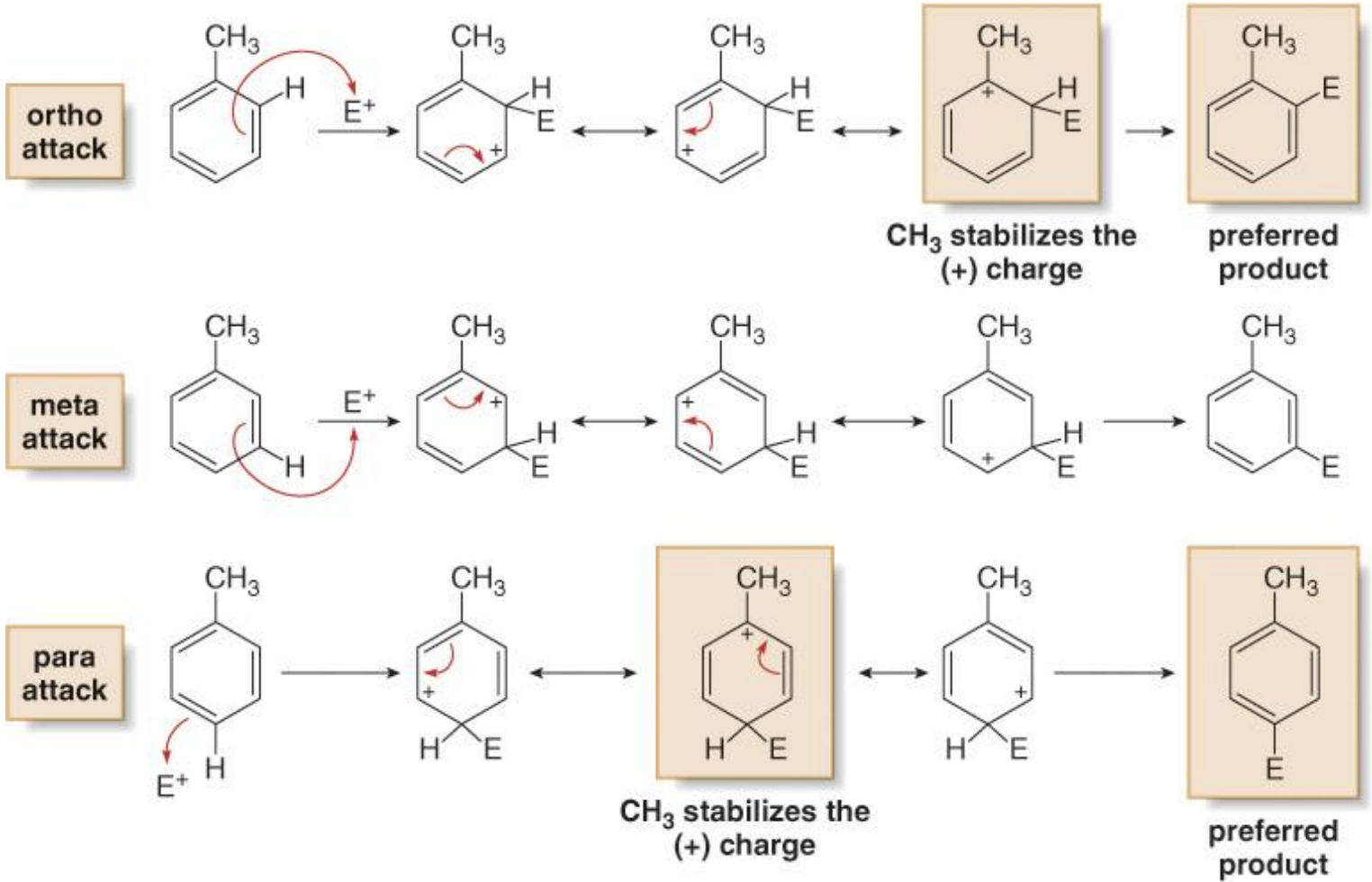
Z = N, O, or X

Meta directors



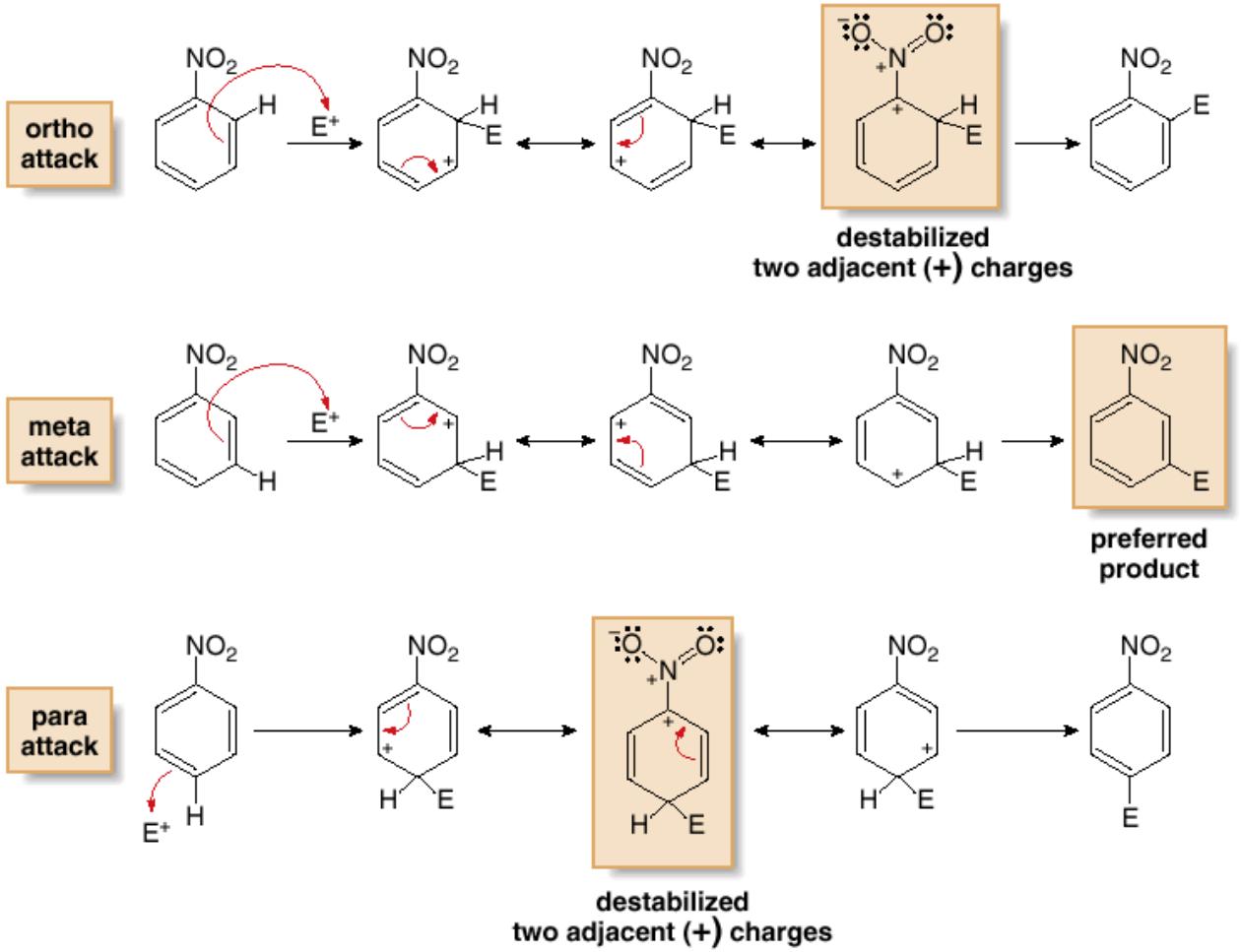
SUBSTITUTED BENZENE

- A CH_3 group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.



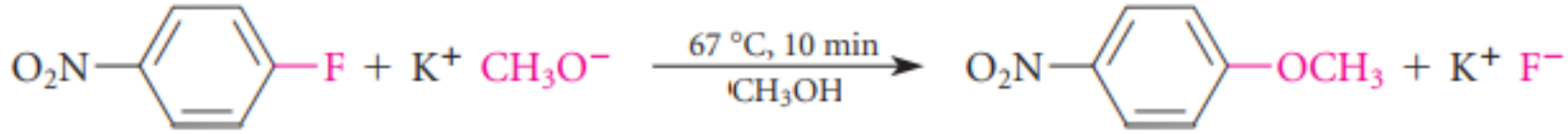
SUBSTITUTED BENZENE

- With the NO_2 group (and all meta directors) meta attack occurs because attack at the ortho and para position gives a destabilized carbocation intermediate.

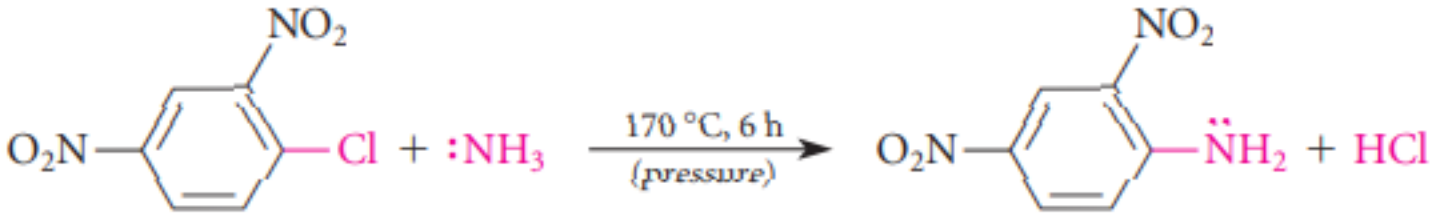


NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF ARYL HALIDES

- The **carbon-halogen bonds of aryl halides** are being much *shorter* and *stronger* than those of alkyl halides.
- Aryl halides are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions.
- **Aryl halides** that have one or more nitro groups *ortho* or *para* to the halogen undergo *nucleophilic substitution reactions* under relatively mild conditions.



***p*-fluoronitrobenzene** — ***p*-nitroanisole** (93% yield)

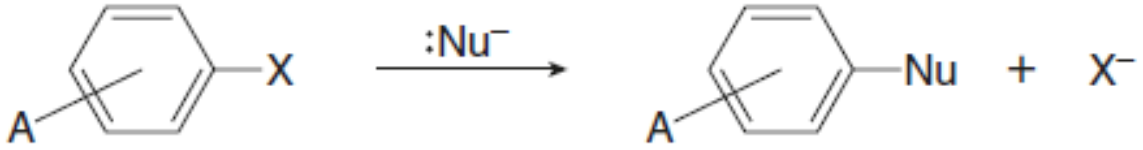


1-chloro-2,4-dinitrobenzene — **2,4-dinitroaniline** (70% yield)

NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF ARYL HALIDES

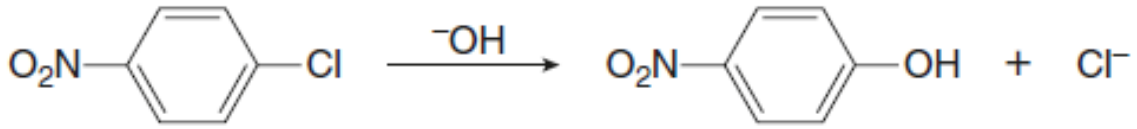
- **Nucleophilic aromatic substitution reactions become quite rapid**
  - when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2,
  - when very strongly basic nucleophilic reagents are used.

- **General reaction:**



X = F, Cl, Br, I
A = H or electron-withdrawing group

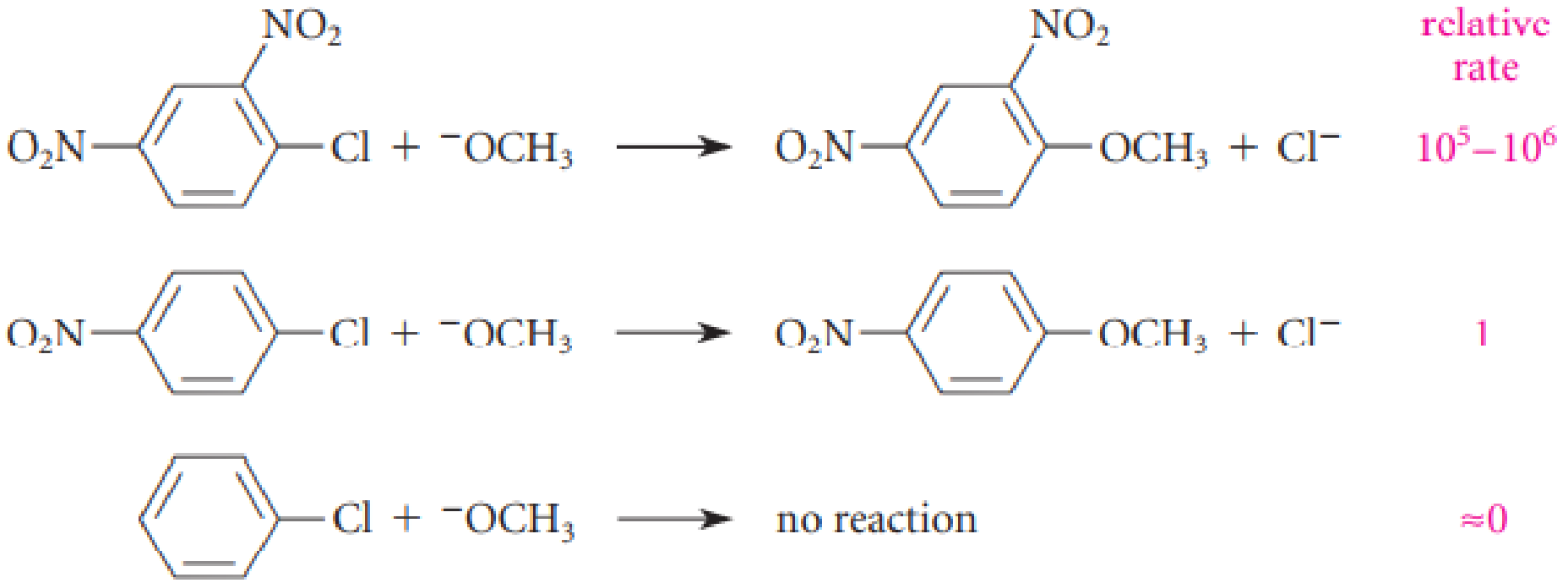
- **Example:**



p-chloronitrobenzene *p*-nitrophenol

NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF ARYL HALIDES

- The reaction is *faster* when there are more nitro groups *ortho* and *para* to the halogen leaving group

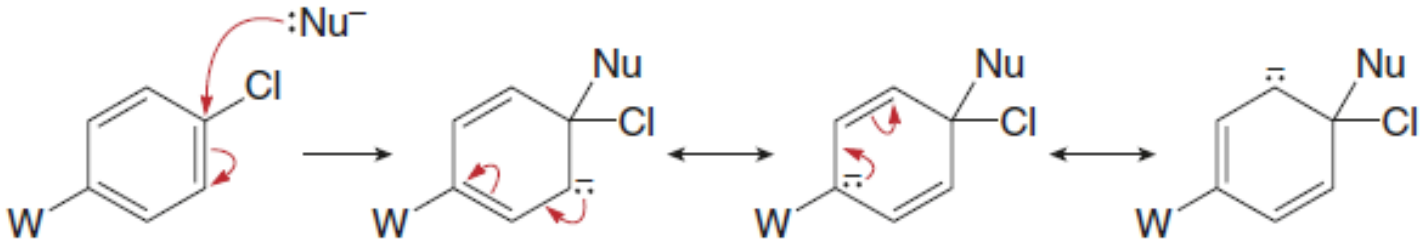


GENERAL MECHANISM

Addition-Elimination Mechanism of Nucleophilic Substitution of Aryl Halides

- **Step 1: rate-determining step**

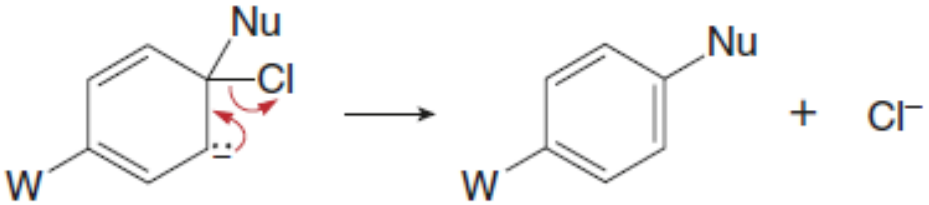
  The nucleophile reacts at the halide-bearing carbon to yield a resonance stabilized anion called a Meisenheimer complex.



resonance-stabilized carbanion

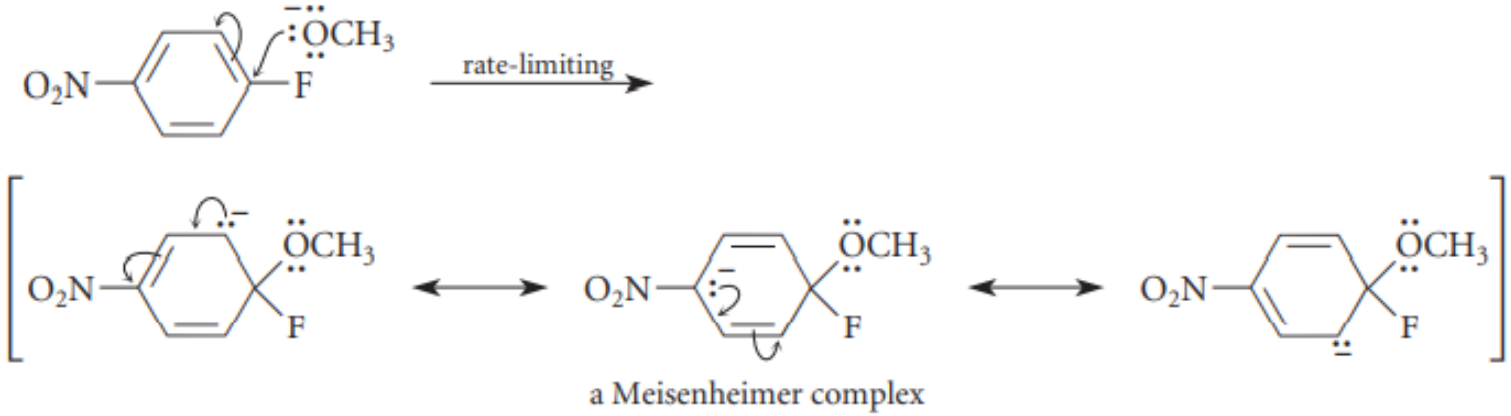
- **Step 2:**

  Loss of the leaving group to reform the aromatic ring.



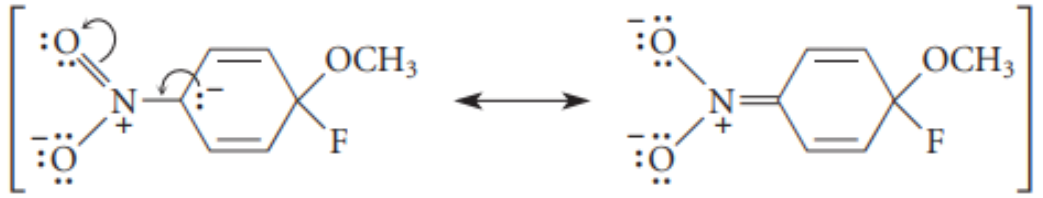
EXAMPLE

- The nucleophile reacts at the halide-bearing carbon to yield a *resonance stabilized anion called a Meisenheimer complex*.

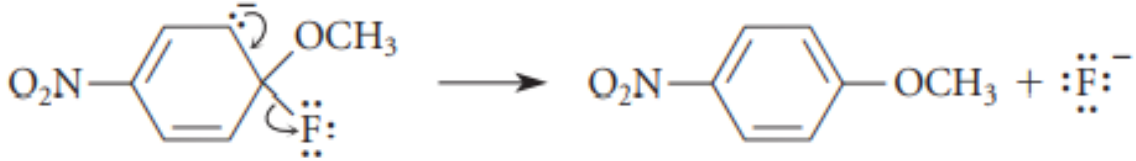


a Meisenheimer complex

- The negative charge in this complex is also delocalized into the nitro group.



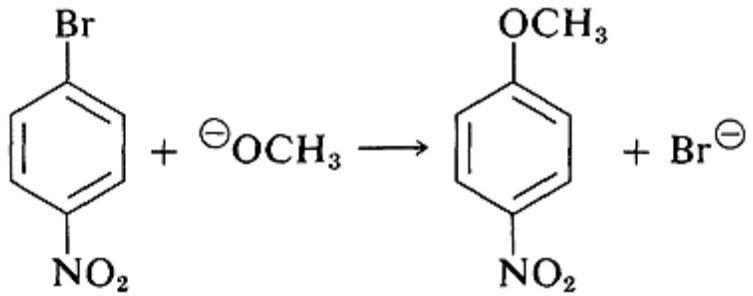
- The Meisenheimer complex breaks down to products by loss of the halide ion.



NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF ARYL HALIDES

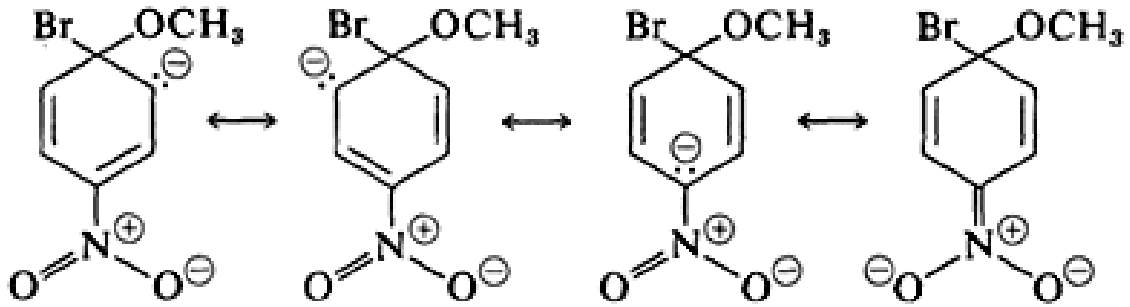
- *Ortho* and *para* nitro groups accelerate the reaction as they stabilize the intermediate by resonance (but not meta nitro groups).

Example: consider the displacement of bromine by methoxid (OCH_3) in the reaction of 4-bromonitrobenzene and methoxide ion:



4-nitromethoxybenzene

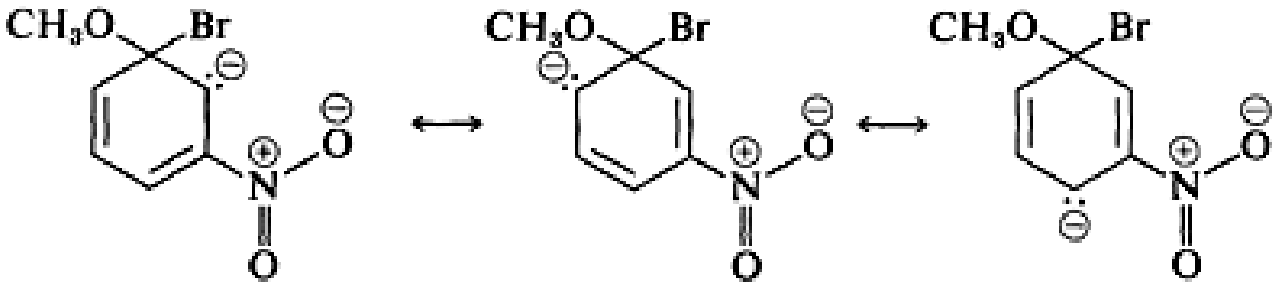
The anionic intermediate formed by addition of methoxide ion to the aryl halide



The negative charges are both on atoms next to positive nitrogen  *and*  ,

NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF ARYL HALIDES

- **Substituents in the meta positions** have much *less effect on the reactivity of an aryl halide* because delocalization of electrons to the substituent is not possible.



NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS OF ARYL HALIDES

NUCLEOPHILIC AROMATIC SUBSTITUTION REACTION *vs.* S_N2 REACTIONS OF ALKYL HALIDES;

	Nucleophilic aromatic substitution reaction of aryl halides	*S_N2 reactions of alkyl halides*
Intermediate	There is an actual intermediate: Meisenheimer complex.	There is no evidence for an intermediate
Configuration	Frontside substitution (it requires no inversion of configuration.	Backside substitution with inversion of configuration.
Effect of the halogen on the reaction rate	Aryl fluorides react most rapidly	Alkyl fluorides react most slowly
Reagents	involve nucleophiles and leaving groups.	
Rate of reaction	obey second-order rate laws. rate = k[aryl halide][nucleophile]	

- Polar effect of F, is greater than the other halogens.
- Loss of halide is not rate-limiting, the basicity of the halide is not important in determining the reaction rate.