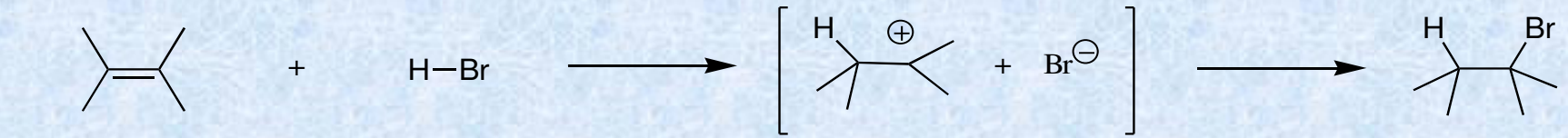
Electrophilic Aromatic Substitution

Dr. Mishu Singh
Department of chemistry
Maharana Pratap Govt.P.G.College
Hardoi

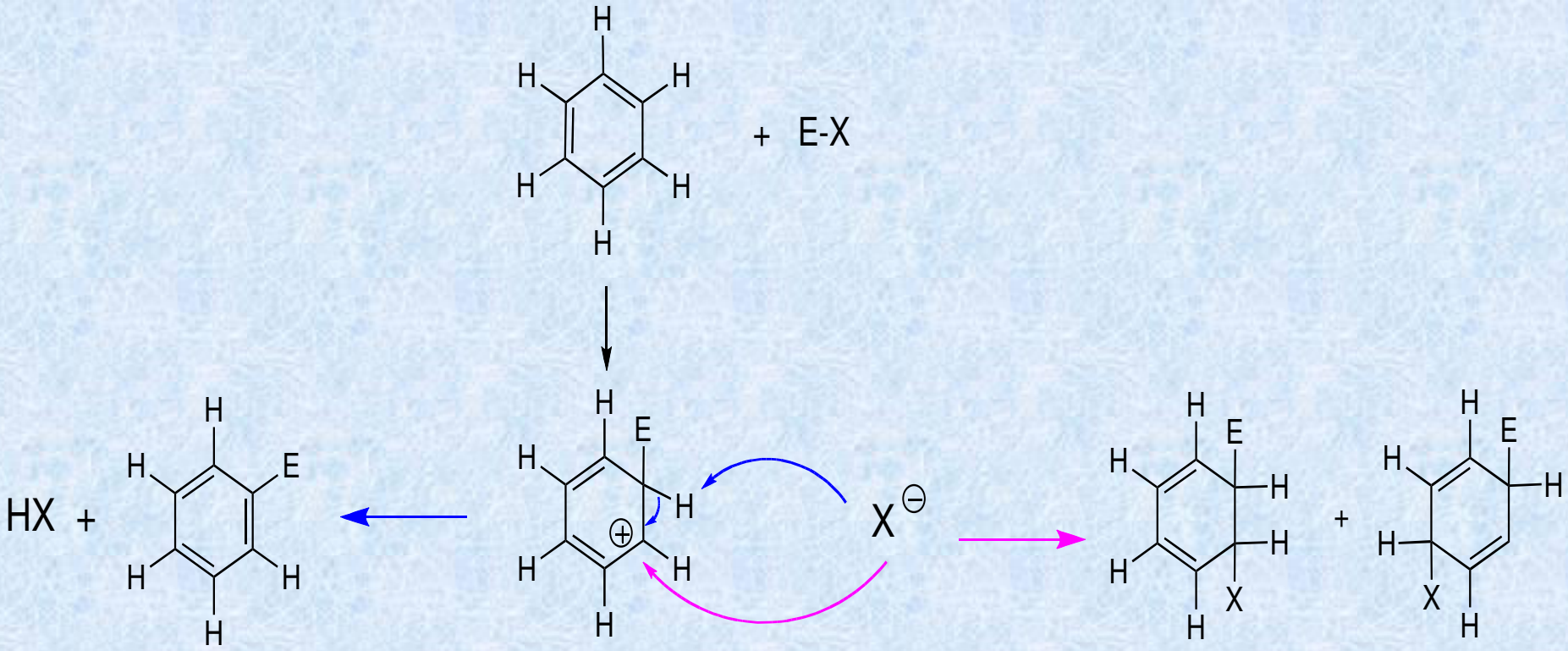
Recall the electophilic addition of HBr (or Br_2) to alkenes



nucleophile electrophile

Most aromatic rings (benzene) are not sufficiently nucleophilic to react with electrophiles. Catalysts are often needed to increase the reactivity of the electrophiles.

Mechanism: a π-bond of benzene acts as a nucleophile and "attacks" the electrophile leading to a resonance stabilized cyclohexadienyl carbocation. Loss of a proton gives the substitution product and restores aromaticity.



Electrophilic substitution: product regains aromatic stabilization

Resonance stabilized cyclohexadienyl cation intermediate

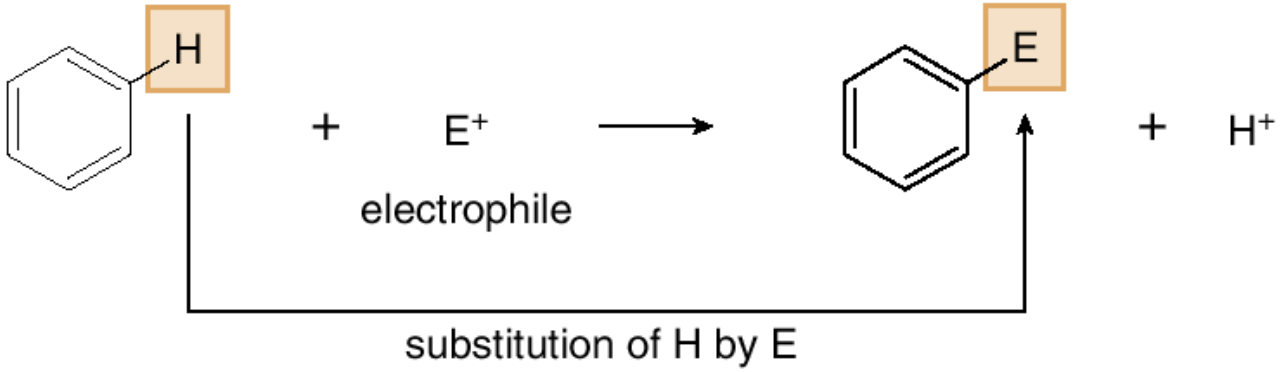
Electrophilic addition: products lose aromatic stabilization

Aromaticity is worth ~ 130-150 kJ/mol

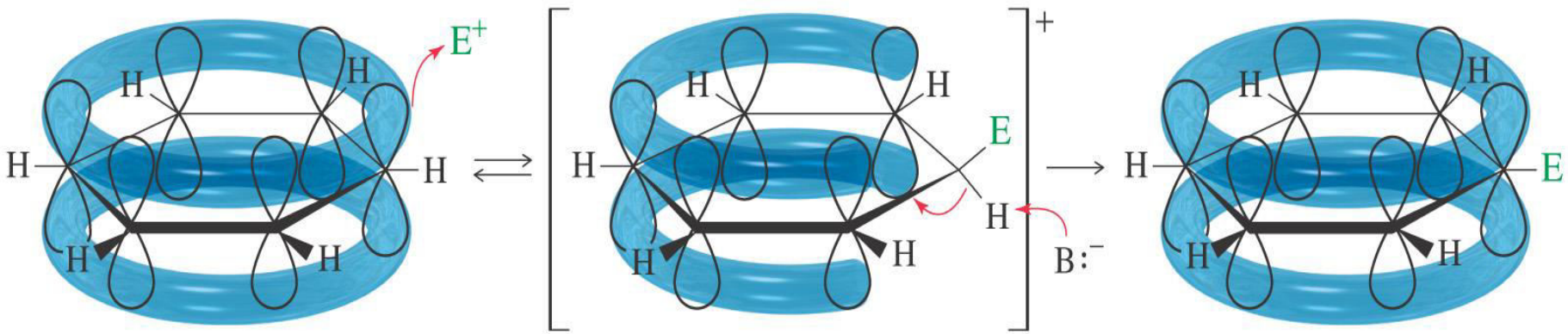
- **The characteristic reaction of benzene is electrophilic aromatic substitution—a hydrogen atom is replaced by an electrophile.**

- Benzene has six π electrons delocalized in six *p* orbitals that overlap above and below the plane of the ring. These loosely held π electrons make the benzene ring electron rich, and so it reacts with electrophiles.
- Because benzene's six π electrons satisfy Hückel's rule, benzene is especially stable. Reactions that keep the aromatic ring intact are therefore favored.

Electrophilic aromatic substitution



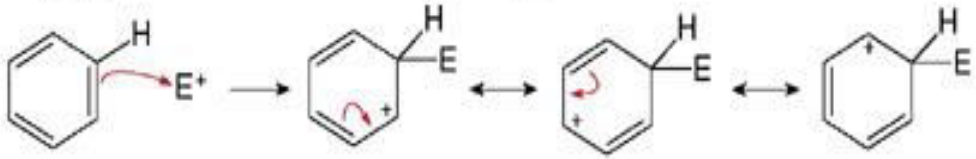
REACTIONS OF AROMATIC COMPOUNDS



- **Regardless of the electrophile used, all electrophilic aromatic substitution reactions occur by the same two-step mechanism—addition of the electrophile E^+ to form a resonance-stabilized carbocation, followed by deprotonation with base, as shown below:**

Mechanism 18.1 General Mechanism—Electrophilic Aromatic Substitution

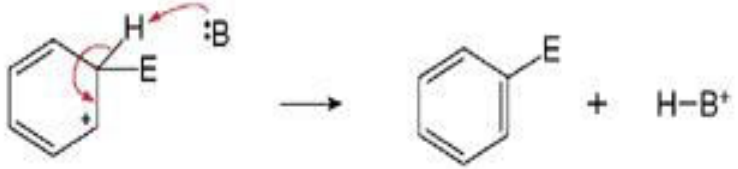
Step [1] Addition of the electrophile (E^+) to form a carbocation



resonance-stabilized carbocation

- Addition of the electrophile (E^+) forms a new C–E bond using two π electrons from the benzene ring, and generating a carbocation. This carbocation intermediate is not aromatic, but it is resonance stabilized—**three resonance structures can be drawn.**
- Step [1] is rate-determining because the aromaticity of the benzene ring is lost.

Step [2] Loss of a proton to re-form the aromatic ring

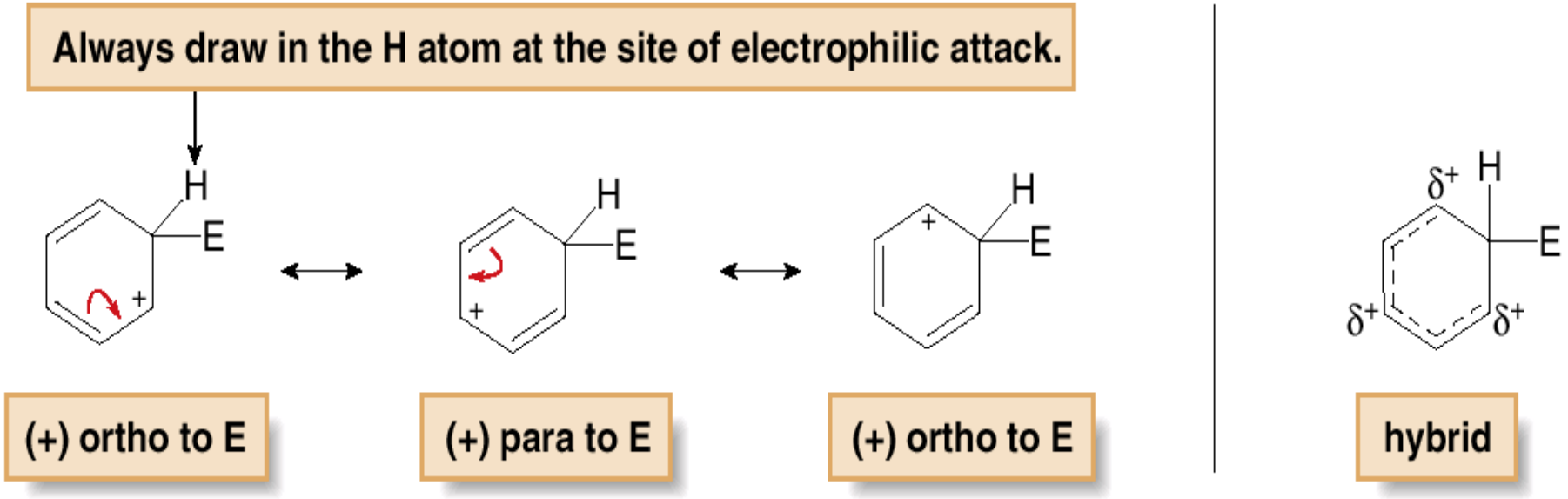


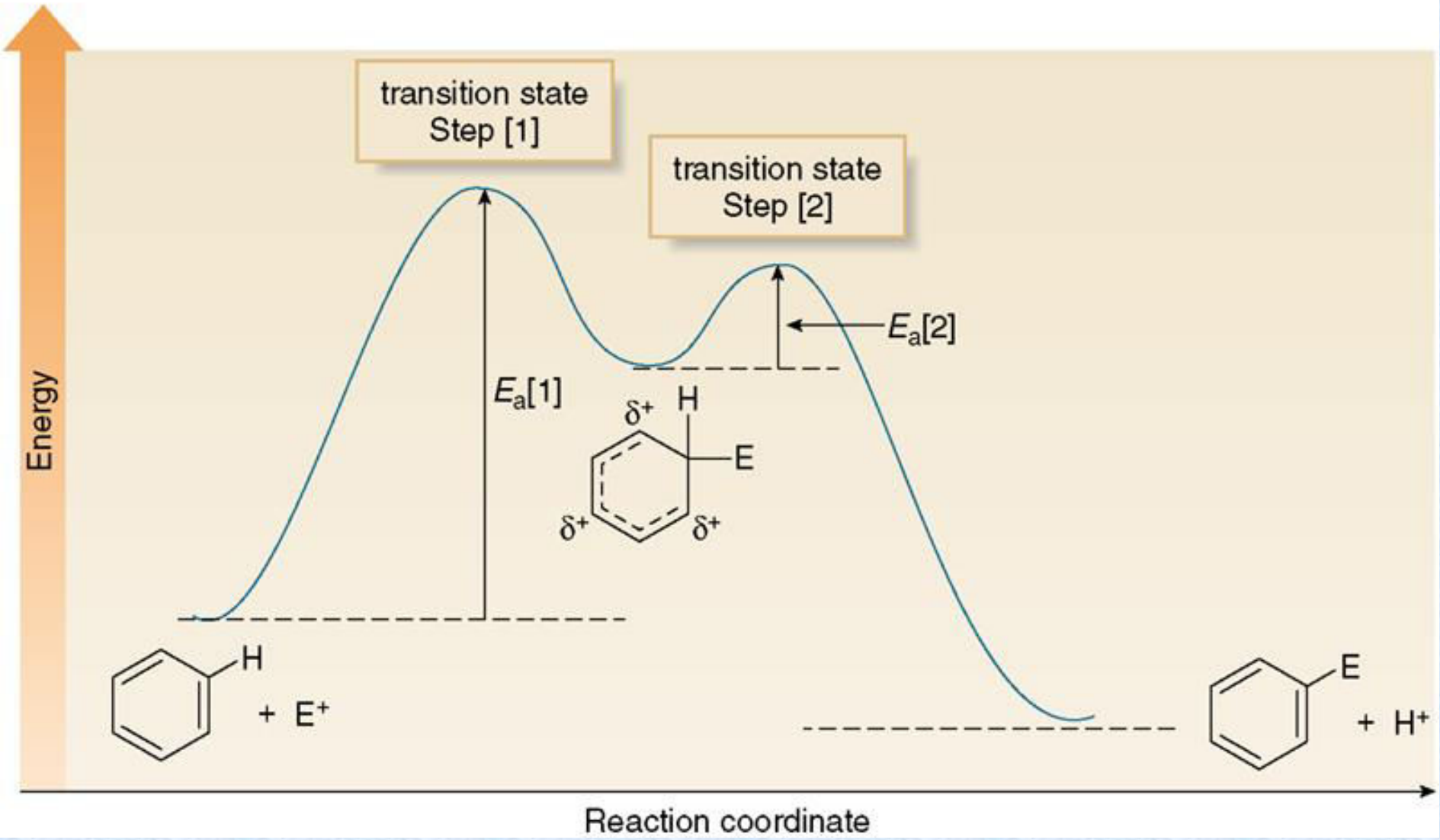
- In Step [2], a base (B:) removes the proton from the carbon bearing the electrophile, thus re-forming the aromatic ring. This step is fast because the aromaticity of the benzene ring is restored.
- Any of the three resonance structures of the carbocation intermediate can be used to draw the product. The choice of resonance structure affects how curved arrows are drawn, but not the identity of the product.

- **The first step in electrophilic aromatic substitution forms a carbocation, for which three resonance structures can be drawn.**

- Always draw in the H atom on the carbon bonded to E. This serves as a reminder that it is the only sp^3 hybridized carbon in the carbocation intermediate.

- Notice that the positive charge in a given resonance structure is always located ortho or para to the new C–E bond. In the hybrid, therefore, the charge is delocalized over three atoms of the ring.

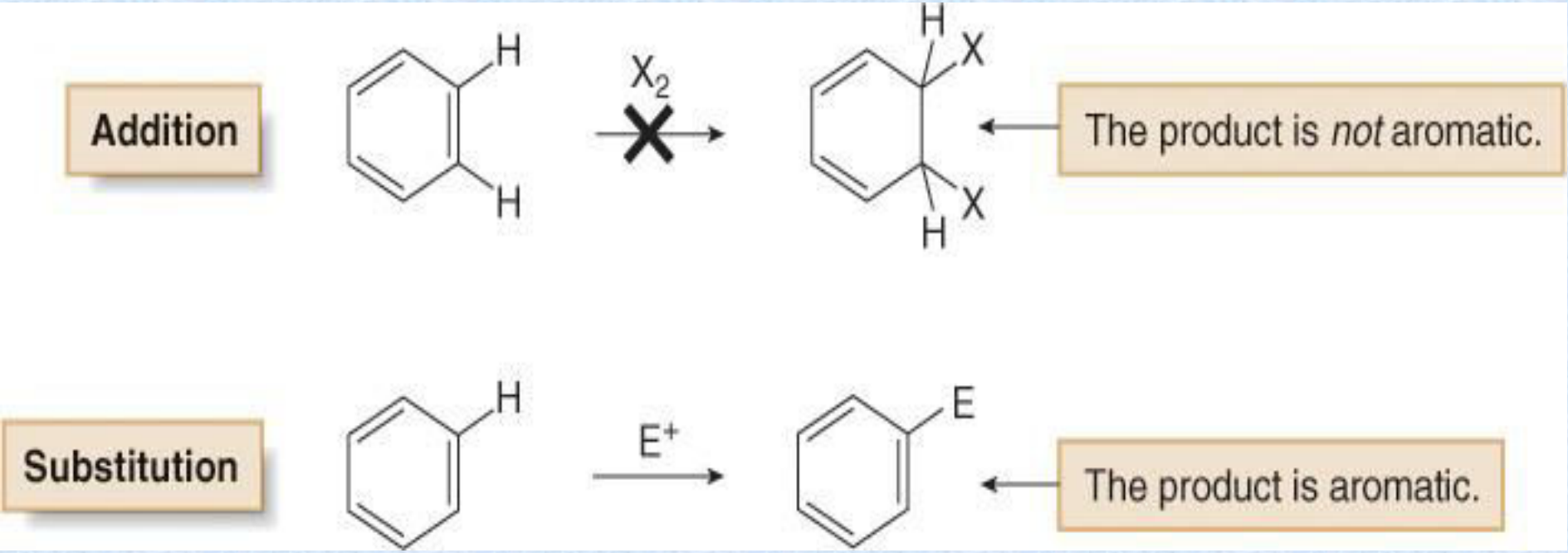


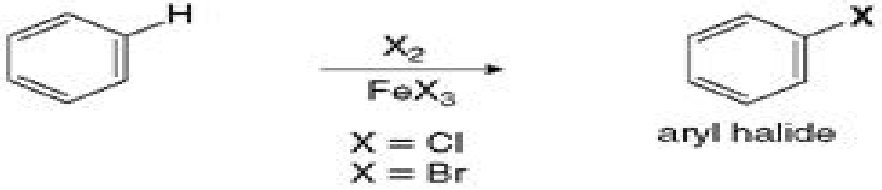


Energy diagram for electrophilic aromatic substitution:

$PhH + E^+ \rightarrow PhE + H^+$

- **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. (retention of the aromatic core).**

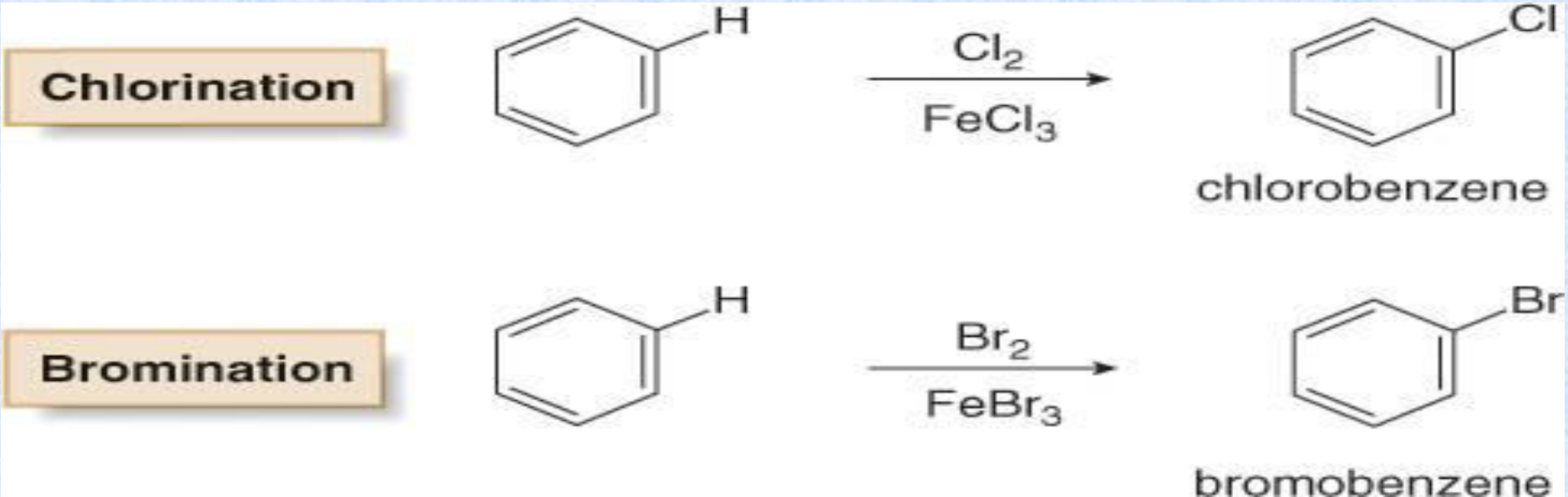


Reaction	Electrophile
[1] Halogenation—Replacement of H by X (Cl or Br)	
	$E^+ = Cl^+$ or Br^+
[2] Nitration—Replacement of H by NO_2	
	$E^+ = \overset{+}{N}O_2$
[3] Sulfonation—Replacement of H by SO_3H	
	$E^+ = \overset{+}{S}O_3H$
[4] Friedel–Crafts alkylation—Replacement of H by R	
	$E^+ = R^+$
[5] Friedel–Crafts acylation—Replacement of H by RCO	
	$E^+ = R\overset{+}{C}O$

Examples of electrophilic aromatic substitution

HALOGENATION

- In halogenation, Benzene's π electrons participate as a Lewis base in reactions with Lewis acids
- 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.



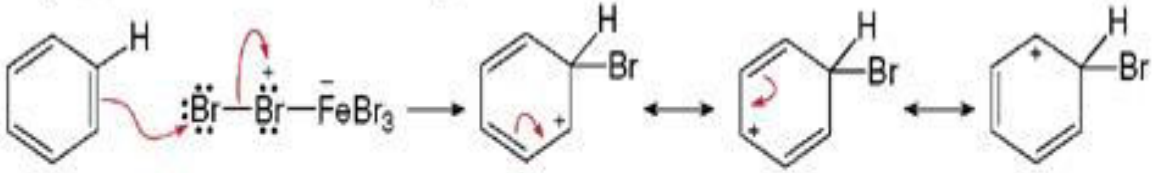
Mechanism 18.2 Bromination of Benzene

Step [1] Generation of the electrophile

Lewis base Lewis acid — electrophile (serves as a source of Br^+)

- Lewis acid–base reaction of Br_2 with $FeBr_3$ forms a species with a weakened and polarized Br – Br bond. This adduct serves as a source of Br^+ in the next step.

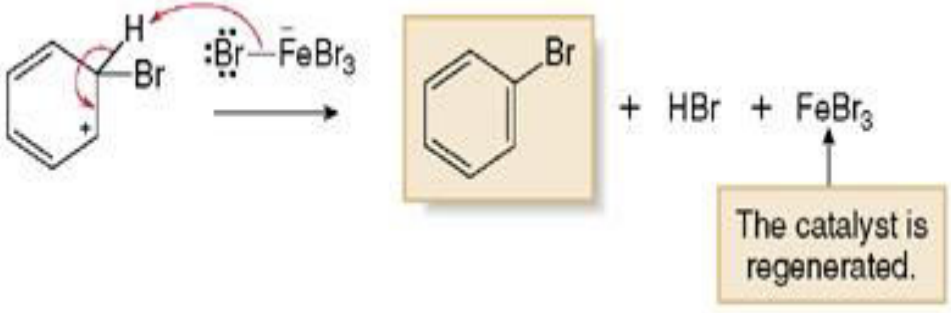
Step [2] Addition of the electrophile to form a carbocation



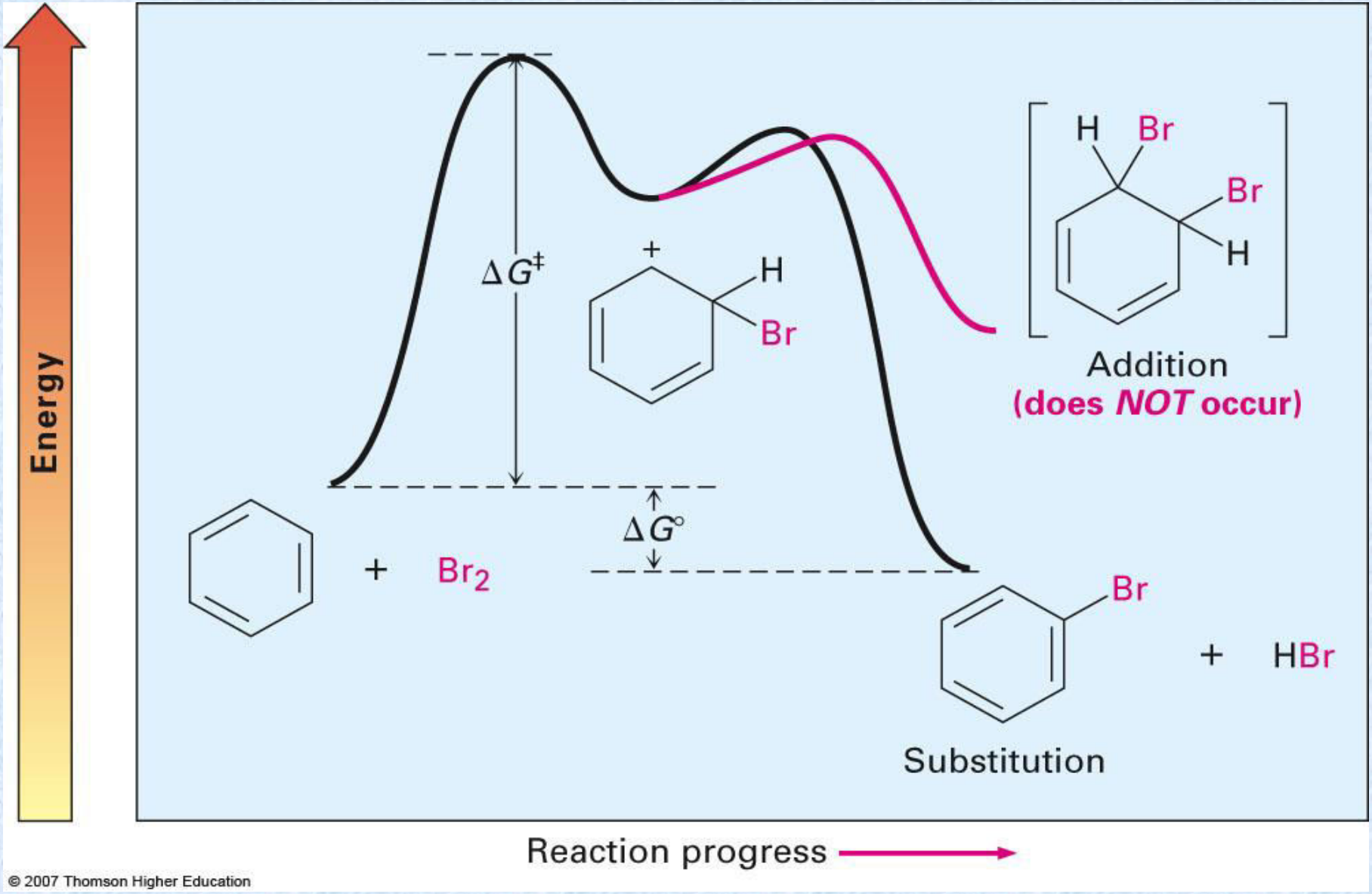
resonance-stabilized carbocation + $FeBr_4^-$

- Addition of the electrophile forms a new C – Br bond and generates a carbocation. This carbocation intermediate is resonance stabilized—**three resonance structures can be drawn.**
- The $FeBr_4^-$ also formed in this reaction is the base used in Step [3].

Step [3] Loss of a proton to re-form the aromatic ring

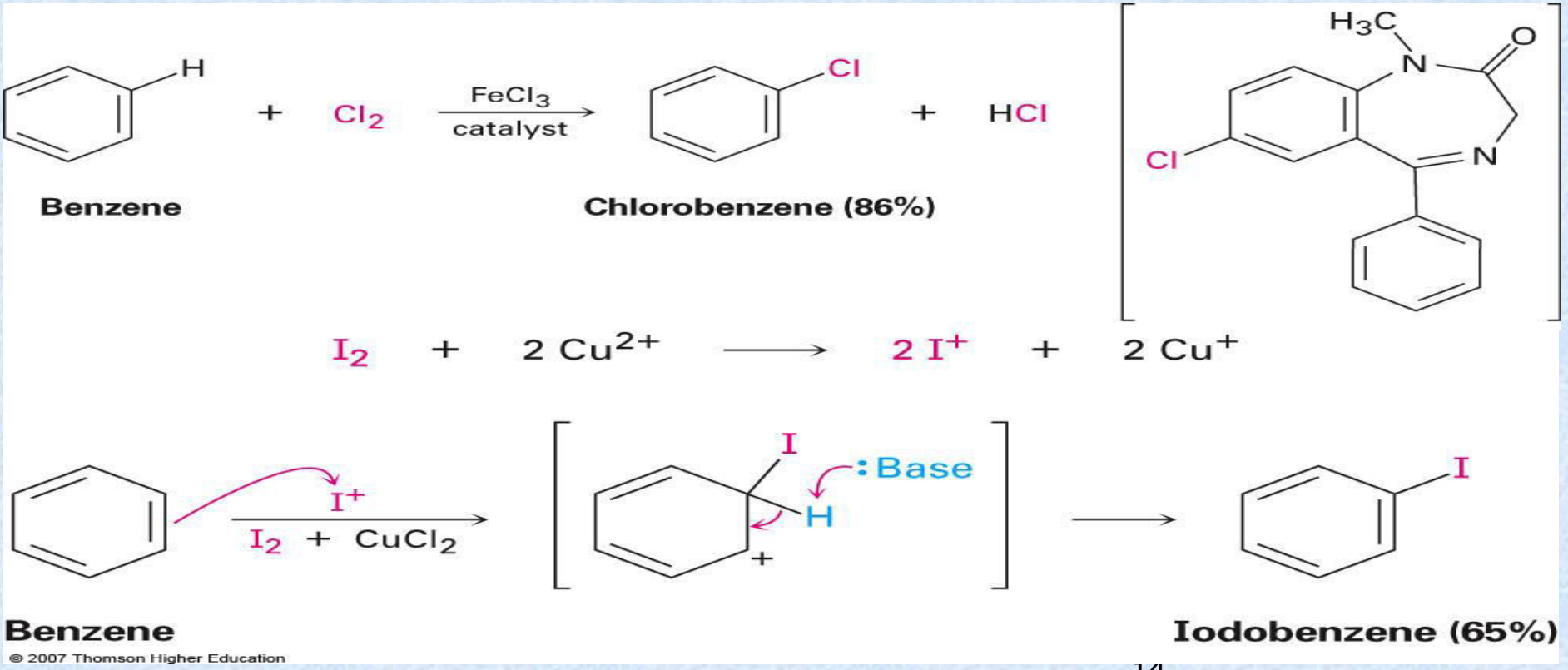


- $FeBr_4^-$ removes the proton from the carbon bearing the Br, thus re-forming the aromatic ring.
- $FeBr_3$, a catalyst, is also regenerated for another reaction cycle.



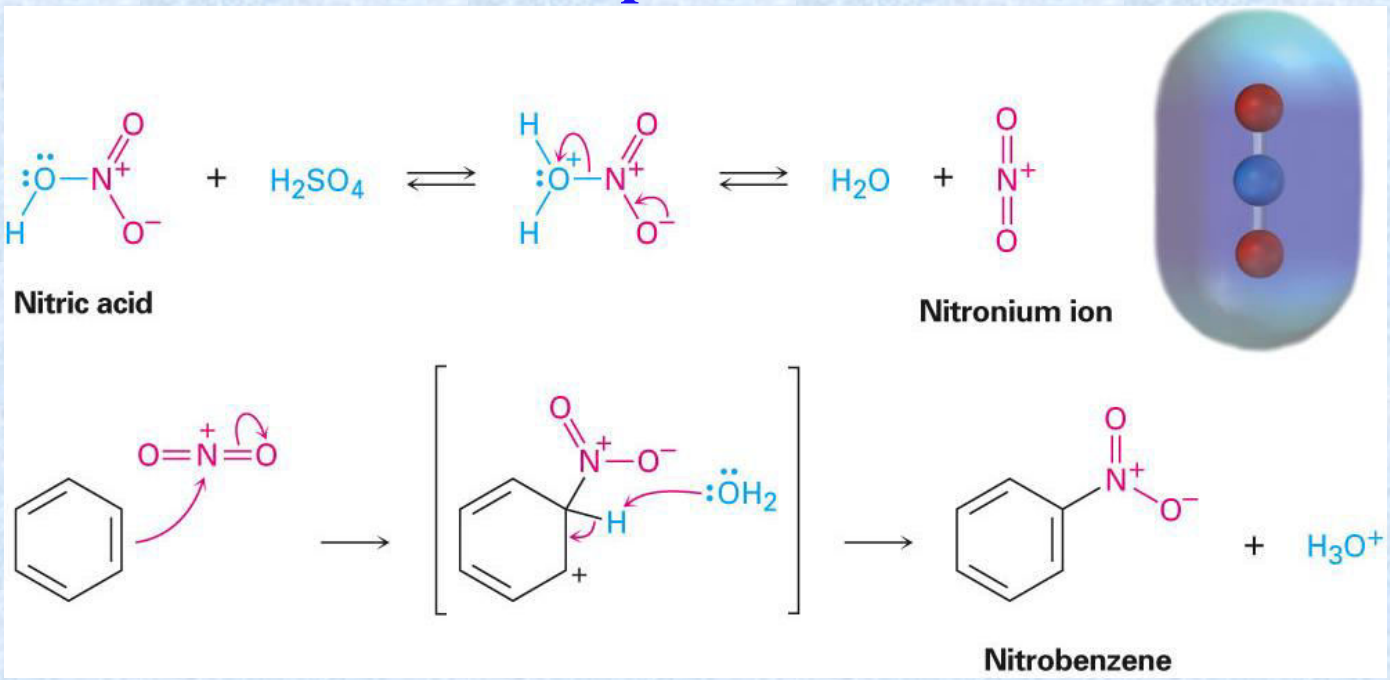
Energy diagram for bromination

- Chlorine and iodine (but not fluorine, which is too reactive) can produce aromatic substitution with the addition of other reagents to promote the reaction
- Chlorination requires $FeCl_3$
- Iodine must be oxidized to form a more powerful I^+ species (with Cu^{2+} from $CuCl_2$)

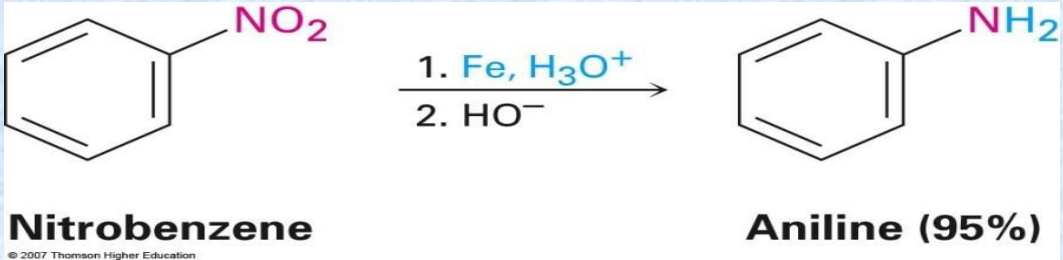


NITRATION

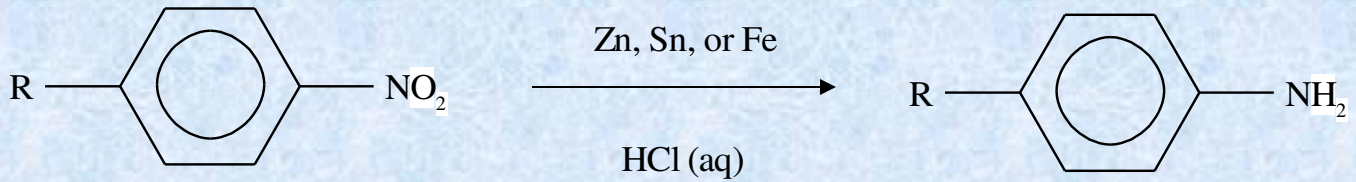
- The combination of nitric acid and sulfuric acid the electrophile, NO_2^+ (nitronium ion)
- Its reaction with benzene produces nitrobenzene



- The Nitro group can be reduced to an Amino group if needed



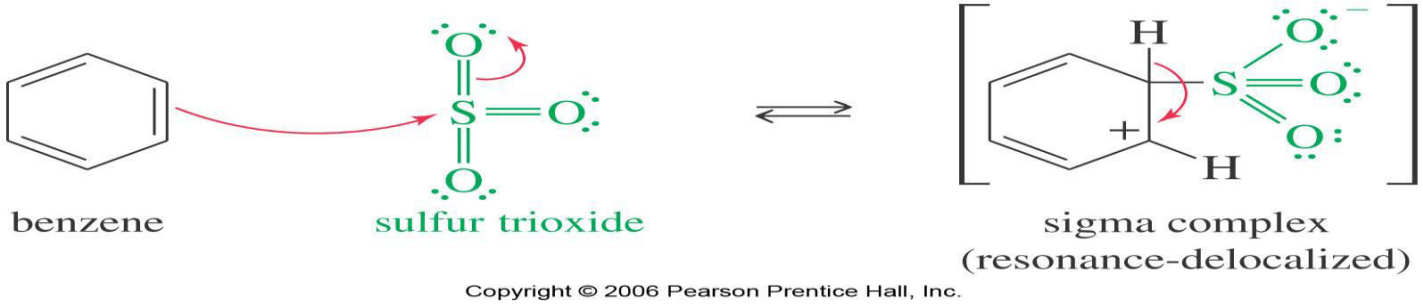
Nitration of an aromatic ring is often the first step in a two step process that is used to add an amine group to an aromatic ring. The reduction of the nitro group is easily accomplished by treatment with a metal and dilute acid.

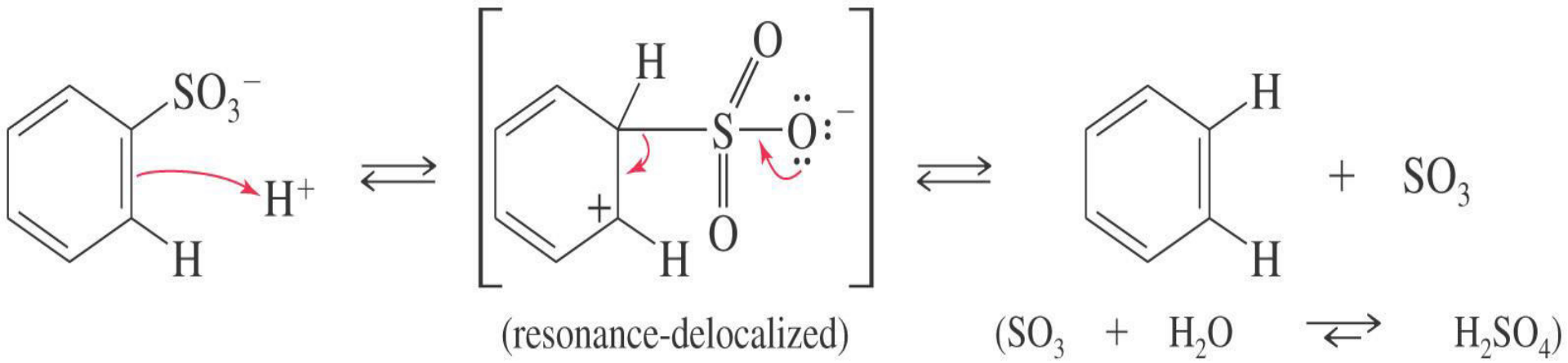


It is common in organic synthesis to add a functional group to a substrate and then to convert the group to the desired group.

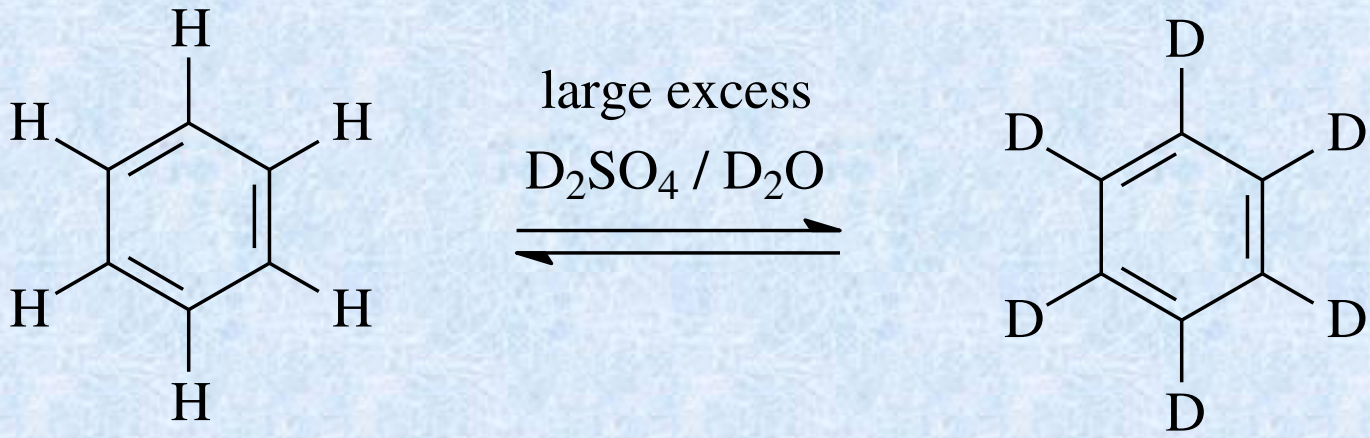
SULPHONATION

- Substitution of H by SO_3 (sulphonation)
- Reaction with a mixture of sulfuric acid and SO_3 ("Fuming H_2SO_4, 7% SO_3 in H_2SO_4.)
- Reactive species is sulfur trioxide or its conjugate acid





PROTONATION

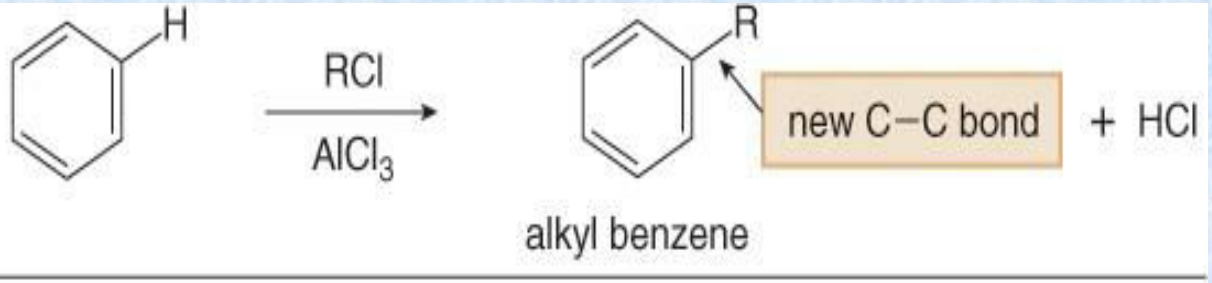


FRIEDEL-CRAFTS ALKYLATION &

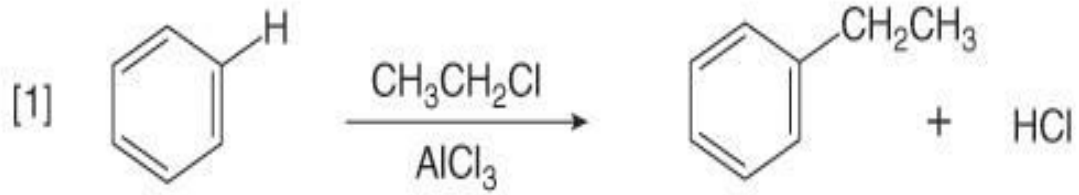
FRIEDEL-CRAFTS ACYLATION

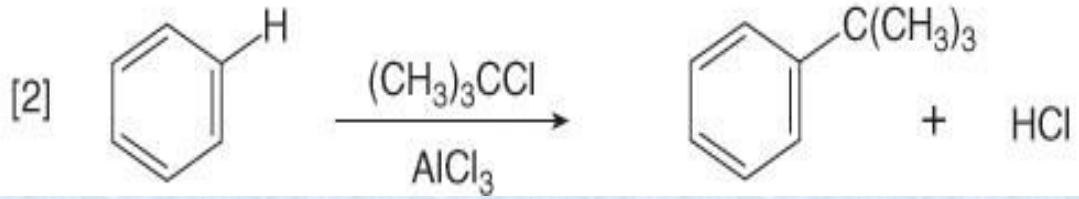
- **In Friedel-Crafts alkylation, treatment of benzene with an alkyl halide and a Lewis acid ($AlCl_3$) forms an alkyl benzene.**

Friedel–Crafts alkylation—General reaction

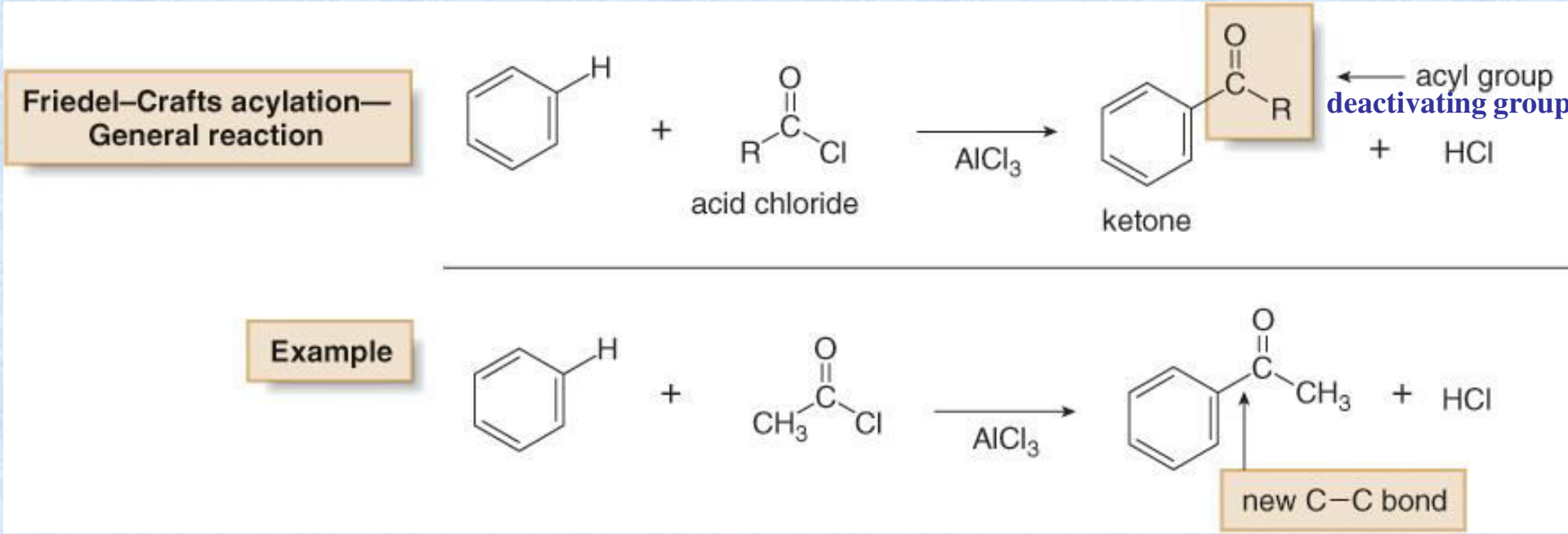


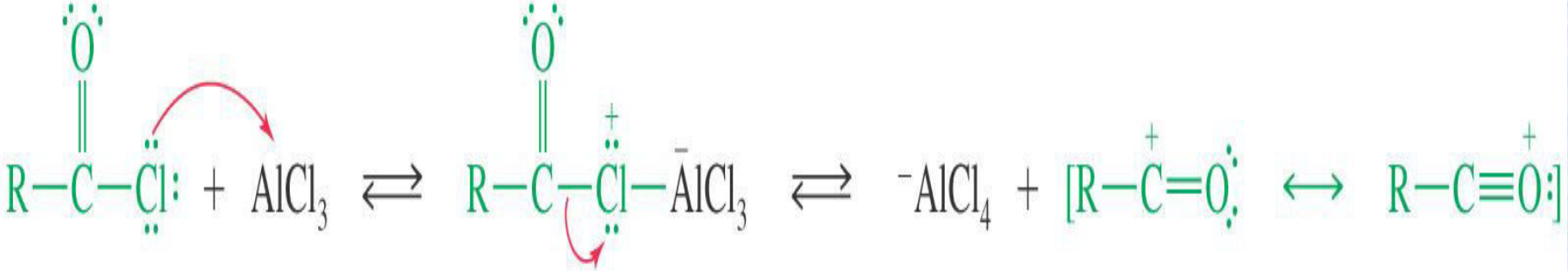
Examples





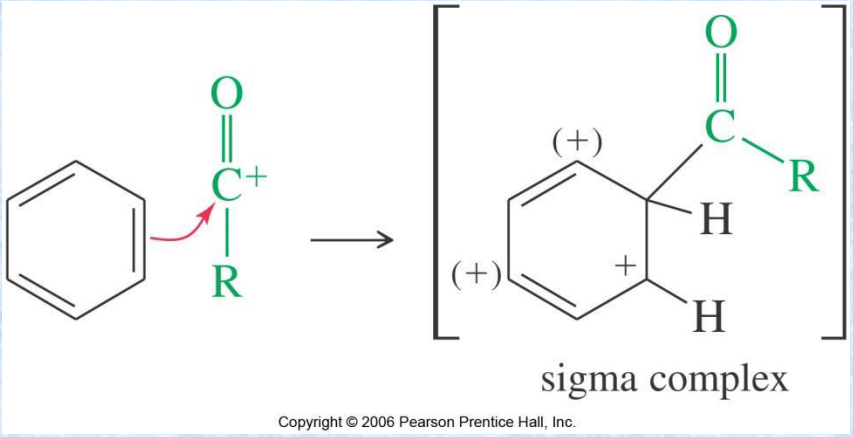
- In **Friedel-Crafts Acylation**, a benzene ring is treated with an acid chloride (RCOCl) and $AlCl_3$ to form a ketone.
- Because the new group bonded to the benzene ring is called an acyl group, the transfer of an acyl group from one atom to another is an acylation.





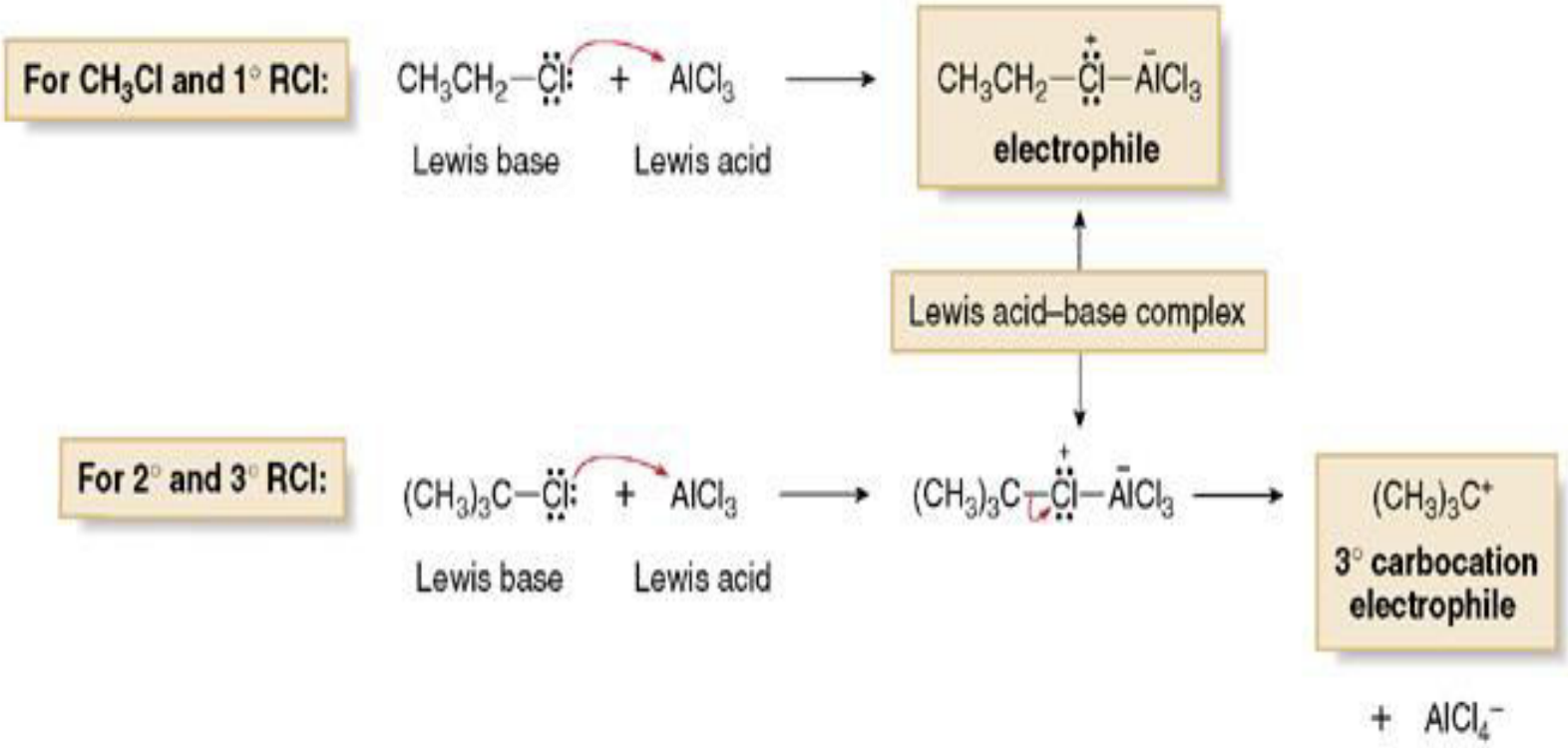
electrophile -I

electrophile -II



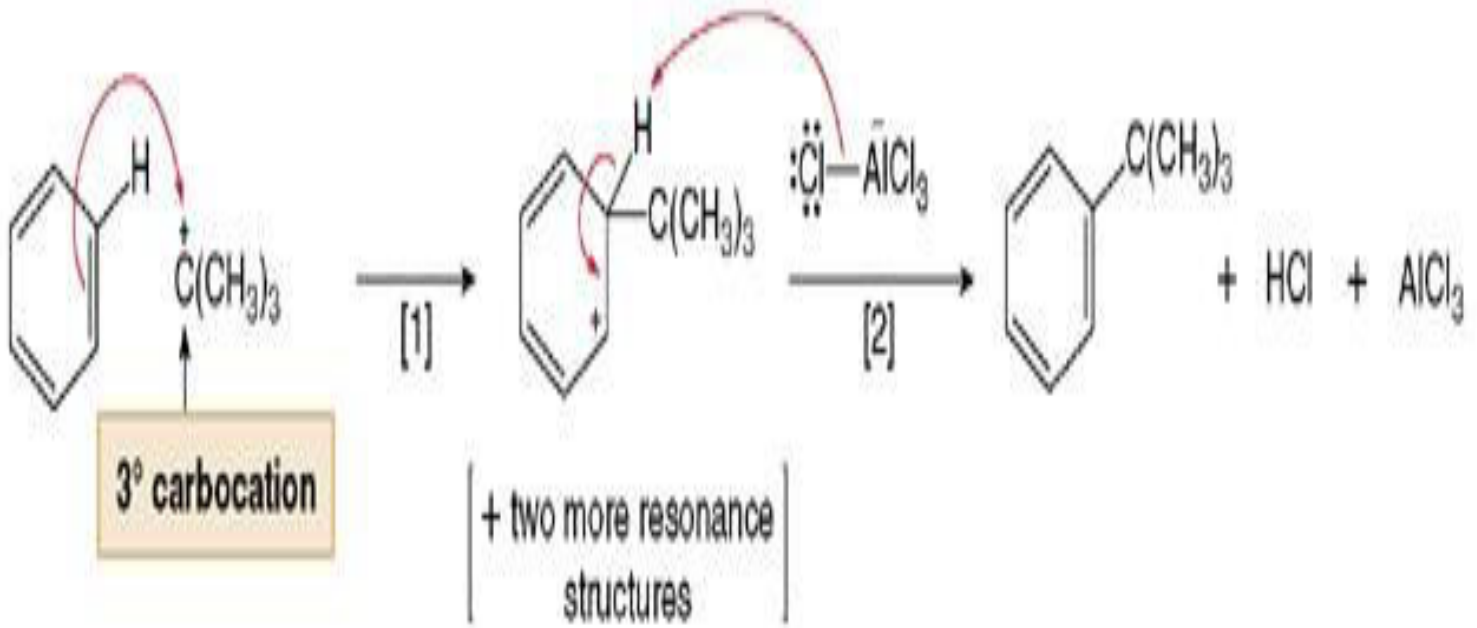
1. The reaction require a full equivalent of Lewis acid, because the ketone product of the reaction will complex the Lewis acid.
2. The actual electrophilic species is thought to be a bulky complex, such as R-C^{+}=O -$AlCl_4^{-}$. As a result of the size of the electrophile, para substitution is predominate when the substrate contains an ortho/para director.
3. There are basically two electrophiles involved: the oxygen bound complex and the acylium ion. Formation of acylium ion dominates when –R is aromatic, since the positive charge is delocalized to aromatic ring.
4. The addition of the acyl group deactivates the ring toward additional substitution reactions.

Mechanism 18.5 Formation of the Electrophile in Friedel–Crafts Alkylation—Two Possibilities



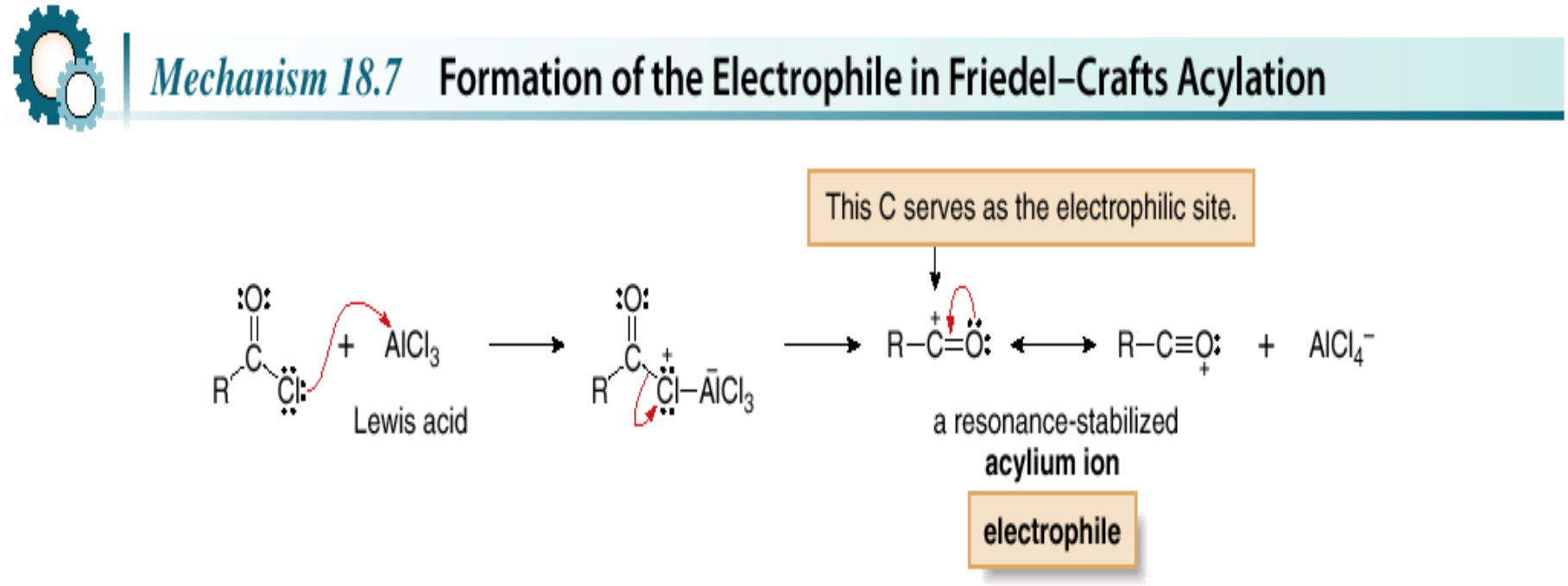
- For CH_3Cl and 1° RCl, the Lewis acid–base complex itself serves as the electrophile for electrophilic aromatic substitution.
- With 2° and 3° RCl, the Lewis acid–base complex reacts further to give a 2° or 3° carbocation, which serves as the electrophile. Carbocation formation occurs only with 2° and 3° alkyl chlorides, because they afford more stable carbocations.

Mechanism 18.6 Friedel–Crafts Alkylation Using a 3° Carbocation



- Addition of the electrophile (a 3° carbocation) forms a new carbon–carbon bond in Step [1].
- $AlCl_4^-$ removes a proton on the carbon bearing the new substituent, thus re-forming the aromatic ring in Step [2].

- In **Friedel-Crafts acylation**, the Lewis acid $AlCl_3$ ionizes the carbon-halogen bond of the acid chloride, thus forming a positively charged carbon **electrophile** called an **acylium ion**, which is **resonance stabilized**.
- The positively charged carbon atom of the acylium ion then goes on to react with benzene in the two step mechanism of electrophilic aromatic substitution.



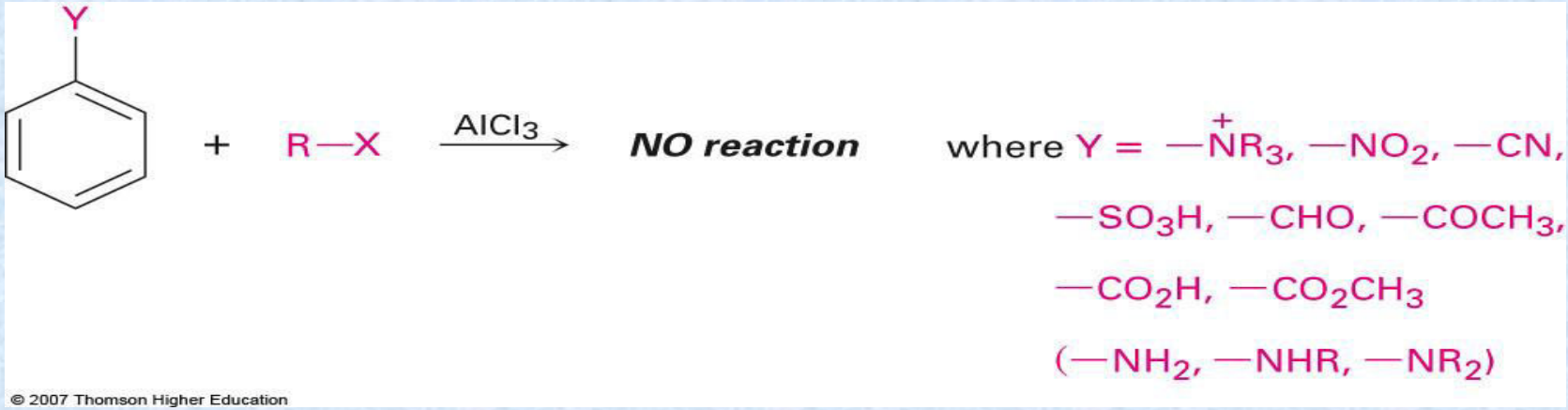
Limitations of the Friedel-Crafts Alkylation

Few facts about Friedel-Crafts alkylation should be kept in mind.

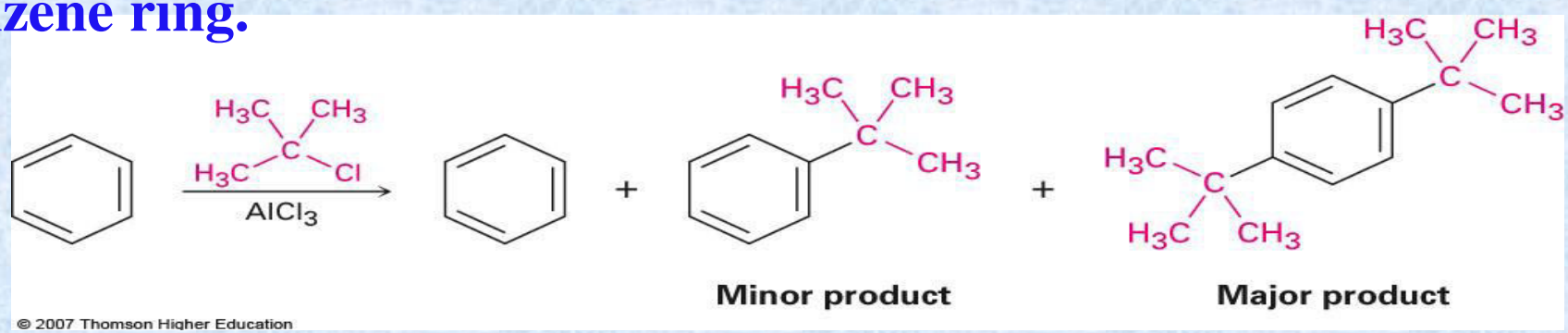
[1] Vinyl halides and aryl halides do not react in Friedel-Crafts alkylation (their carbocations are too hard to form).

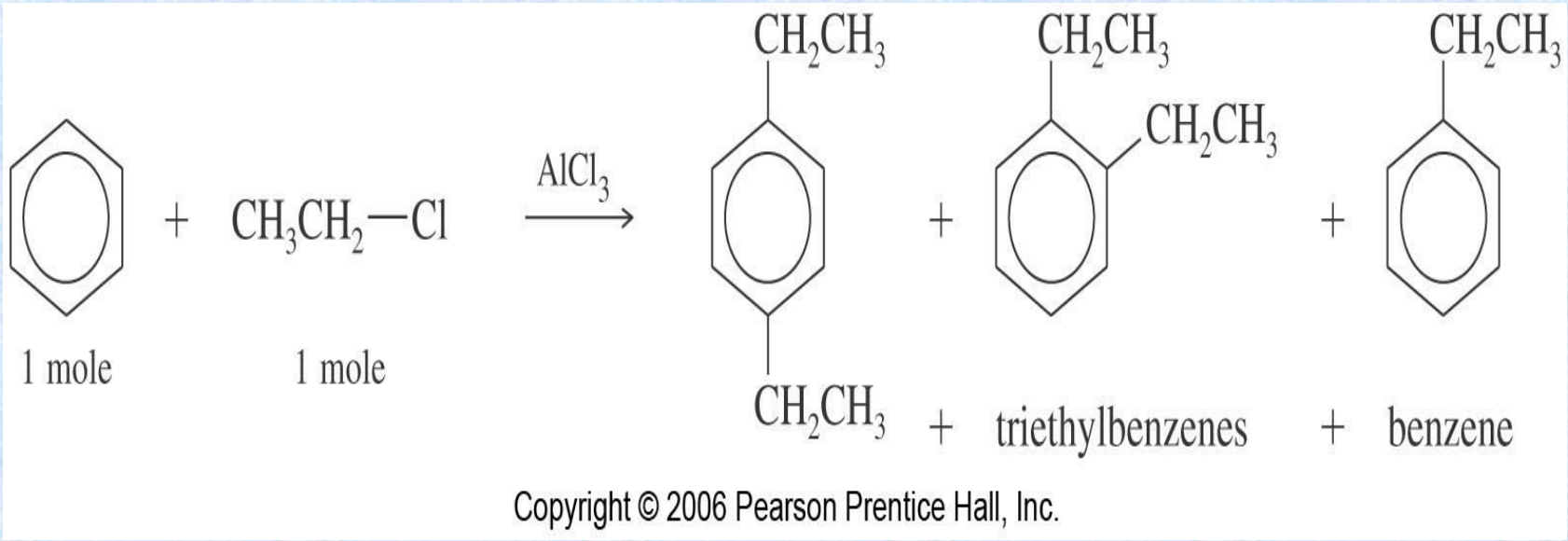
Unreactive halides in the Friedel–Crafts alkylation

[2].Will not work with rings containing an amino group substituent or a strongly electron-withdrawing group. Gps like –OH , -OR , -NH_2 coordinate with the catalyst and don't facilitate FCA



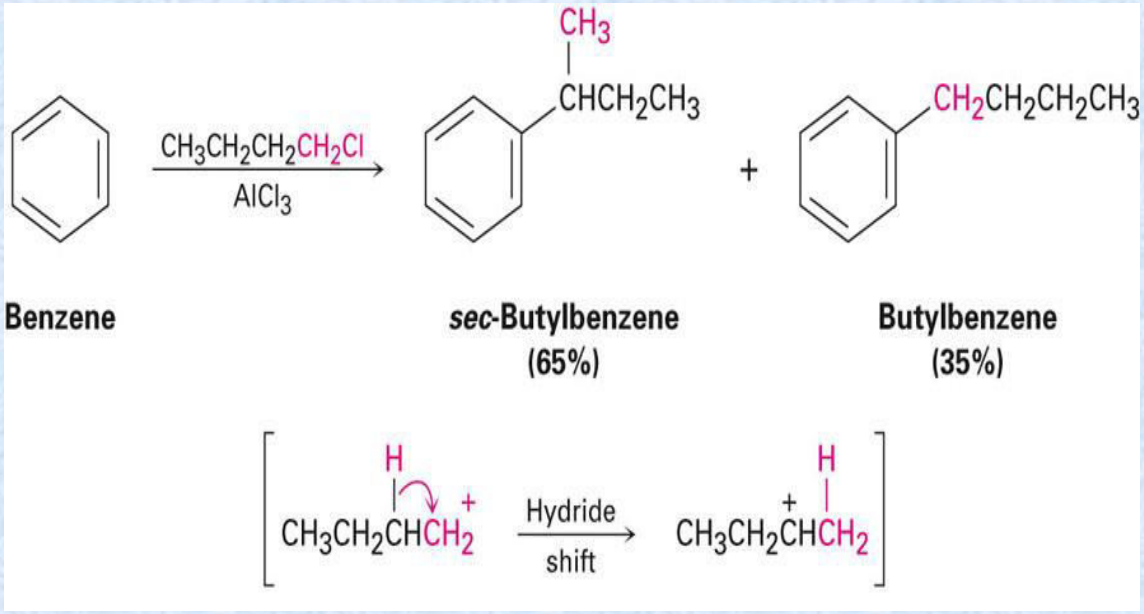
[3]. Multiple alkylations can occur because the first alkylation is activating (e- donating nature of R- assists electrophilic attack on benzene ring.

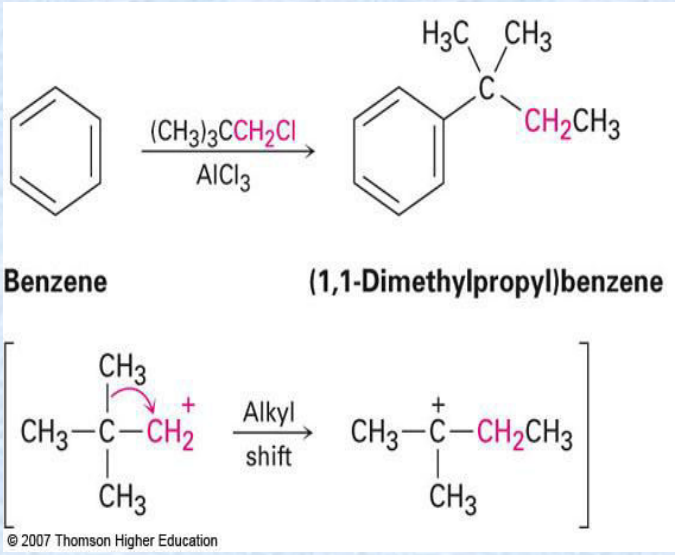




Multiple alkylation is a limitation and as a result mixtures of products are common.

[4] Carbocation rearrangements occur during alkylation Similar to those occuring during electrophilic additions to alkene or can involve H or alkyl shifts

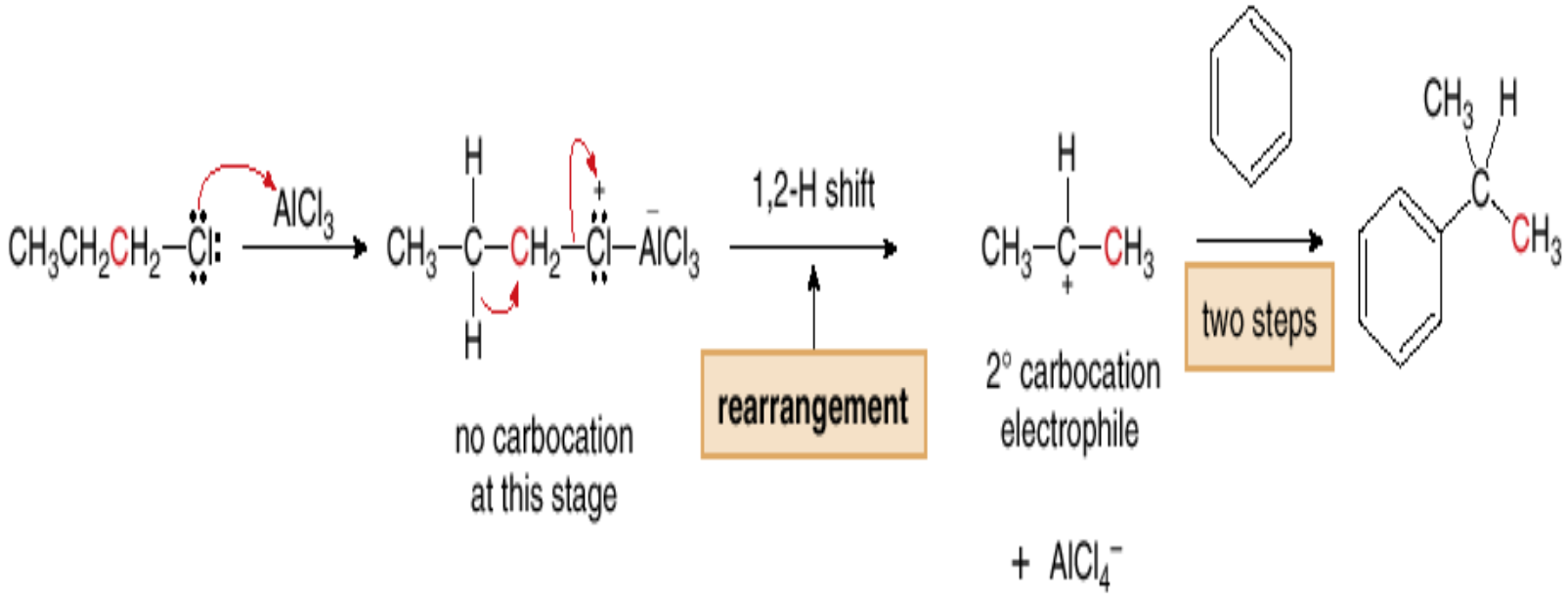




As a result, only certain alkylbenzenes can be made using the Friedel-Crafts alkylation.

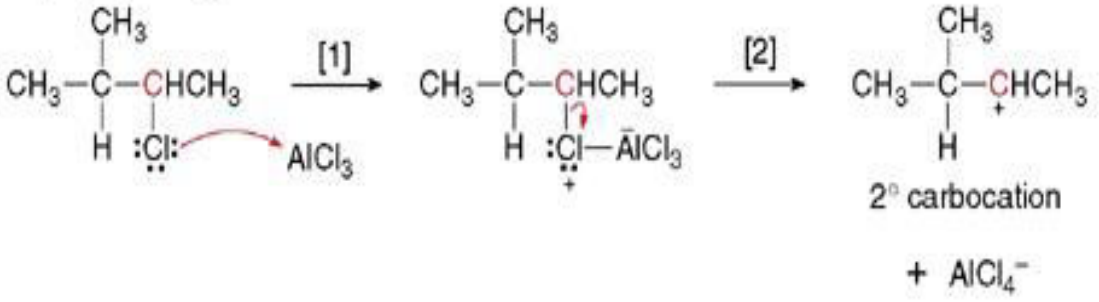
These results can be explained by carbocation rearrangements.

Mechanism 18.9 A Rearrangement Reaction Beginning with a 1° Alkyl Chloride



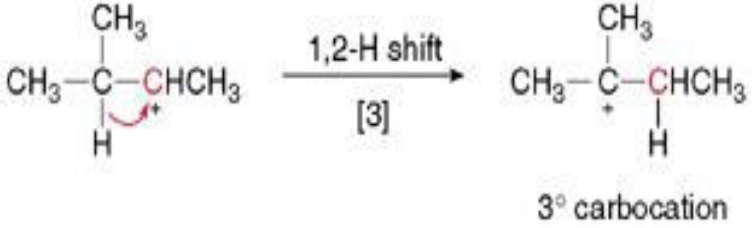
Mechanism 18.8 Friedel–Crafts Alkylation Involving Carbocation Rearrangement

Steps [1] and [2] Formation of a 2° carbocation



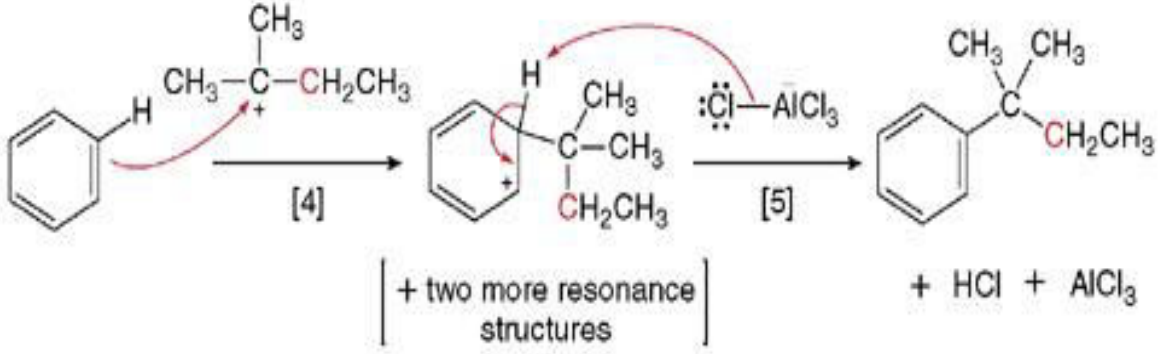
- Reaction of the alkyl chloride with $AlCl_3$ forms a complex that decomposes in Step [2] to form a **2° carbocation.**

Step [3] Carbocation rearrangement



- **1,2-Hydride shift** converts the less stable 2° carbocation to a more stable 3° carbocation.

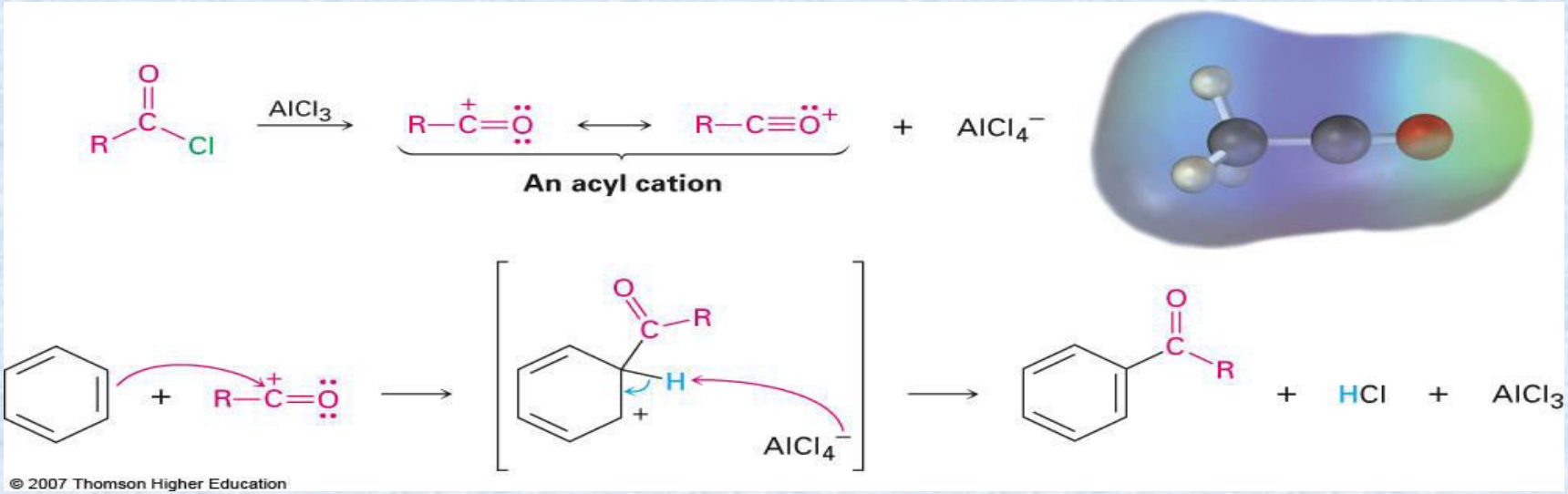
Steps [4] and [5] Addition of the carbocation and loss of a proton

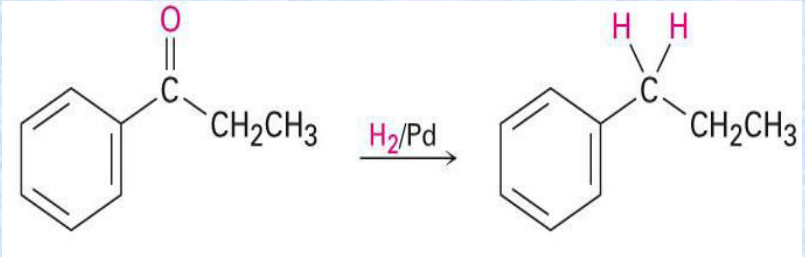


- Friedel–Crafts alkylation occurs by the usual two-step process: **addition of the carbocation** followed by **loss of a proton** to form the alkylated product.

However, acylation avoids many of the problems of alkylation.

1.Only substitutes once, because acyl group is deactivating.
2. No rearrangement takes place because of resonance stabilized acyl cation.
3. An acyl cation does not rearrange
4. The acylation product can be reduced to get alkyl product

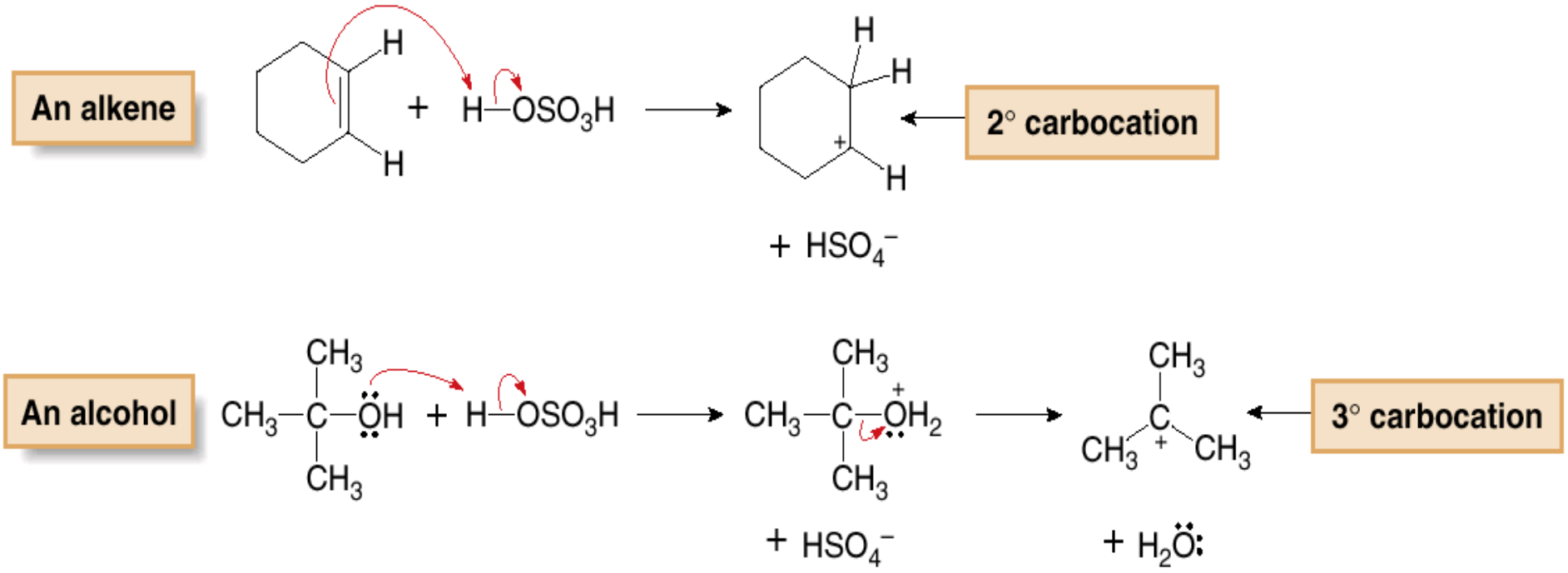




Other functional groups that form carbocations can also be used as starting materials.

- Protonation of an alkene forms a carbocation, which can then serve as an electrophile in a Friedel–Crafts alkylation.

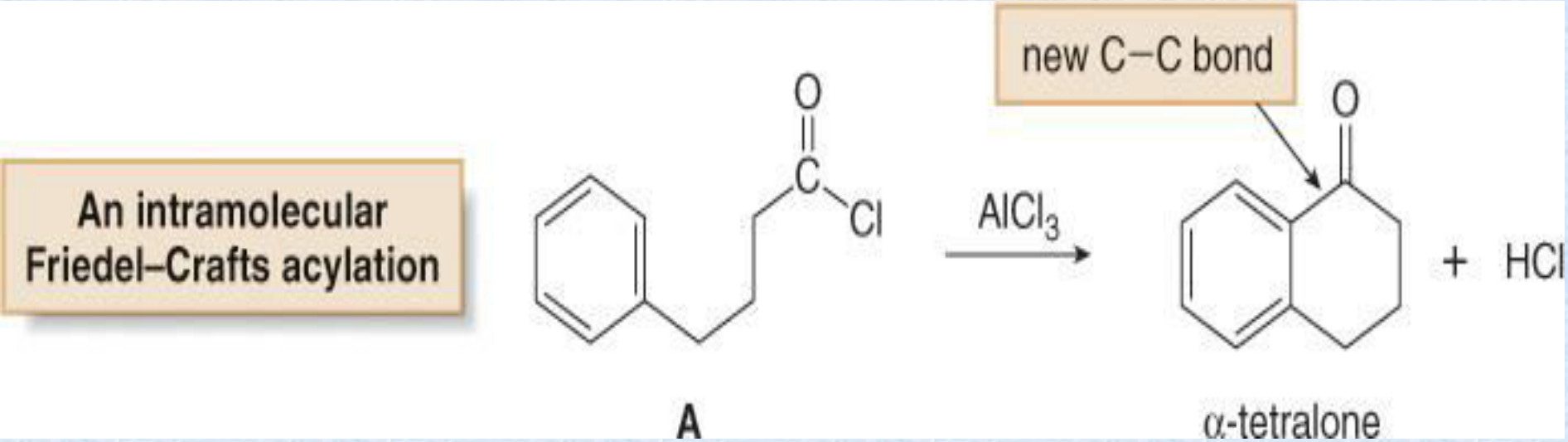
- Protonation of an alcohol, followed by loss of water, likewise forms a carbocation.



Each carbocation can then go on to react with benzene to form a product of electrophilic aromatic substitution.

INTRAMOLECULAR FRIEDEL-CRAFTS REACTIONS.

❖**Starting materials that contain both a benzene ring and an electrophile are capable of intramolecular Friedel-Crafts reactions.**



SUBSTITUTED BENZENES

Many substituted benzene rings undergo electrophilic aromatic substitution.

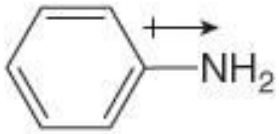
Each substituent either increases or decreases the electron density in the benzene ring, and this affects the course of electrophilic aromatic substitution.

- Donation of electron density to the ring makes benzene more electron rich.
- Withdrawal of electron density from the ring makes benzene less electron rich.

- Atoms more electronegative than carbon—including N, O, and X—pull electron density away from carbon and thus exhibit an electron-withdrawing inductive effect.
- Polarizable alkyl groups donate electron density, and thus exhibit an electron-donating inductive effect.

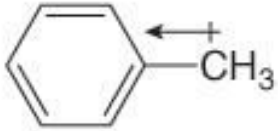
Considering inductive effects only, the NH_2 group withdraws electron density and CH_3 donates electron density.

Electron-withdrawing inductive effect



- N is **more electronegative** than C.
- N inductively withdraws electron density.

Electron-donating inductive effect

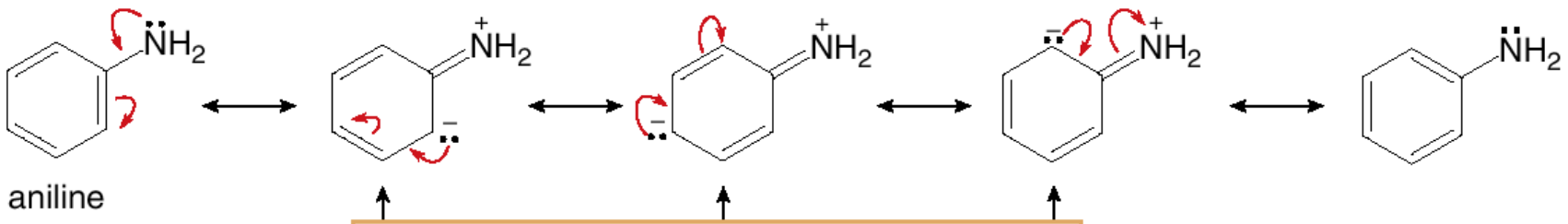


- Alkyl groups are **polarizable**, making them electron-donating groups.

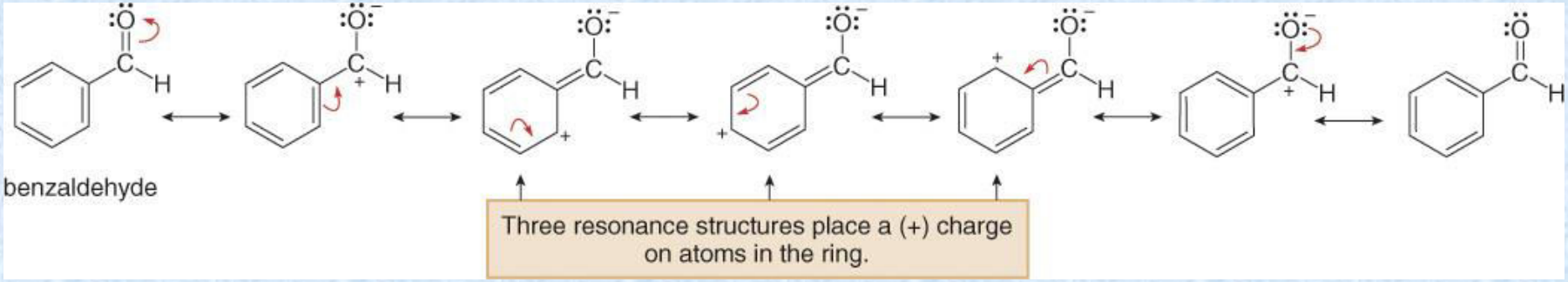
Resonance effects are only observed with substituents containing lone pairs or π bonds.

- A resonance effect is electron donating when resonance structures place a negative charge on carbons of the benzene ring.
- A resonance effect is electron withdrawing when resonance structures place a positive charge on carbons of the benzene ring.

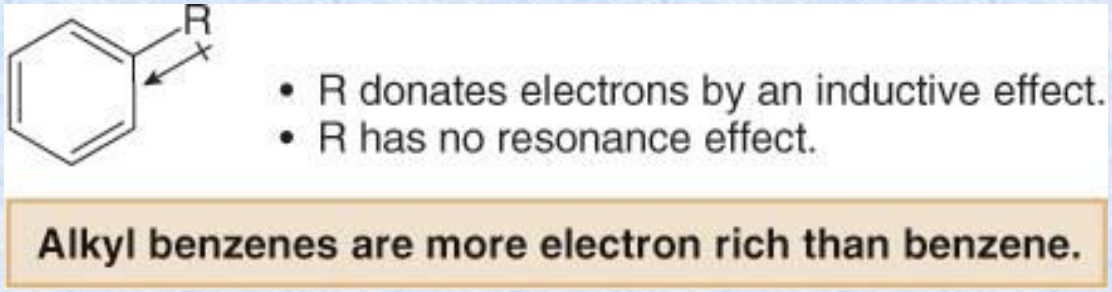
An electron-donating resonance effect is observed whenever an atom Z having a lone pair of electrons is directly bonded to a benzene ring.

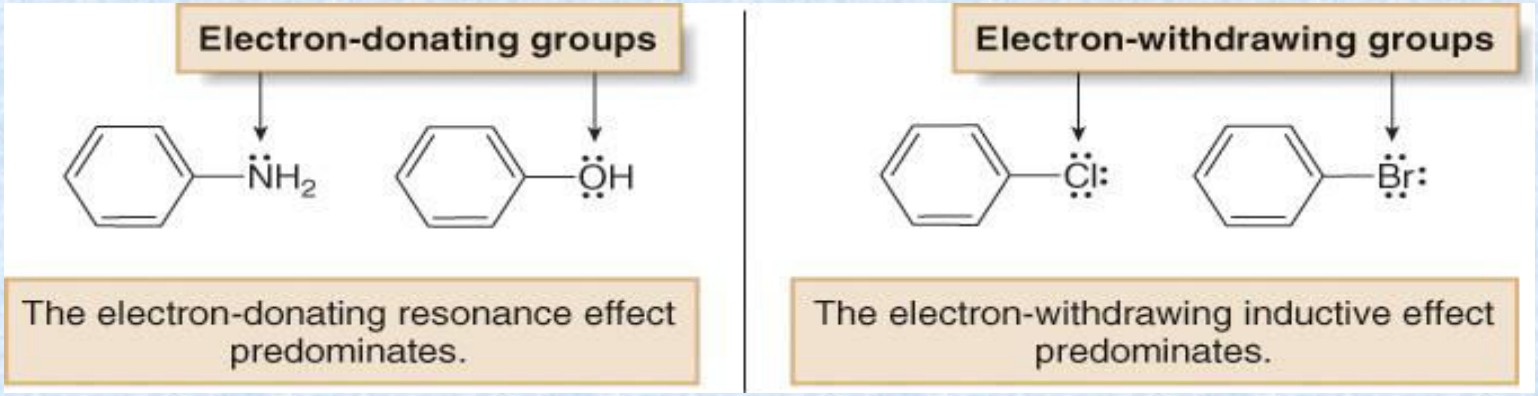


- **An electron-withdrawing resonance effect is observed in substituted benzenes having the general structure C_6H_5-Y=Z, where Z is more electronegative than Y.**
- **Seven resonance structures can be drawn for benzaldehyde (C_6H_5CHO). Because three of them place a positive charge on a carbon atom of the benzene ring, the CHO group withdraws electrons from the benzene ring by a resonance effect.**

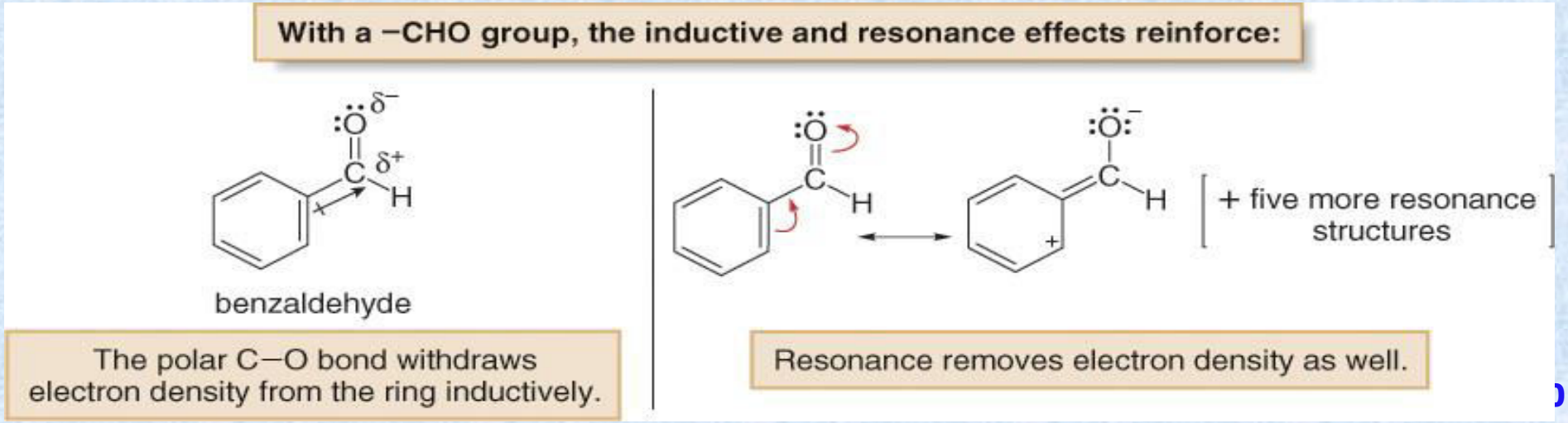


- **To predict whether a substituted benzene is more or less electron rich than benzene itself, we must consider the net balance of both the inductive and resonance effects.**
- **For example, alkyl groups donate electrons by an inductive effect, but they have no resonance effect because they lack nonbonded electron pairs or π bonds.**
- **Thus, any alkyl-substituted benzene is more electron rich than benzene itself.**

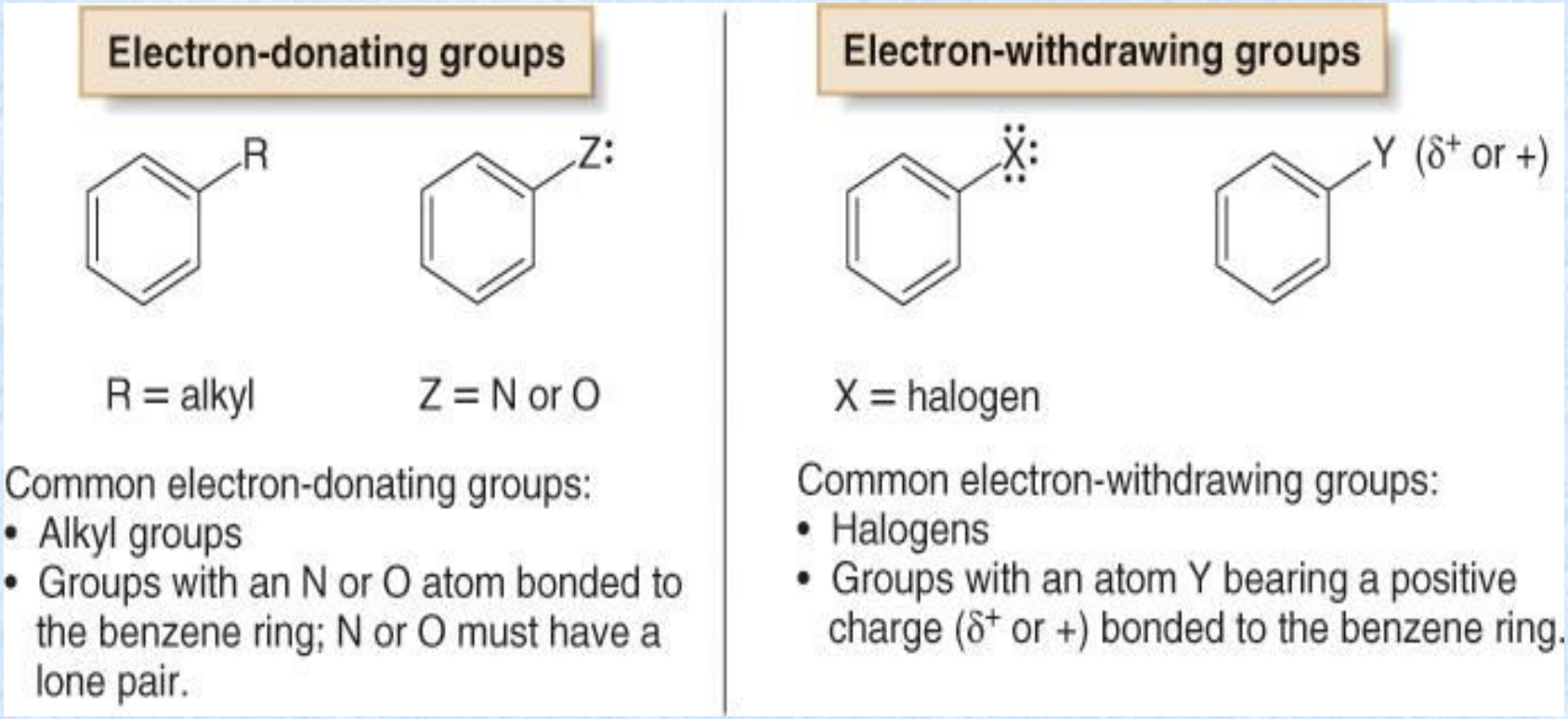




- **The inductive and resonance effects in compounds having the general structure C_6H_5-Y=Z (with Z more electronegative than Y) are both electron withdrawing.**



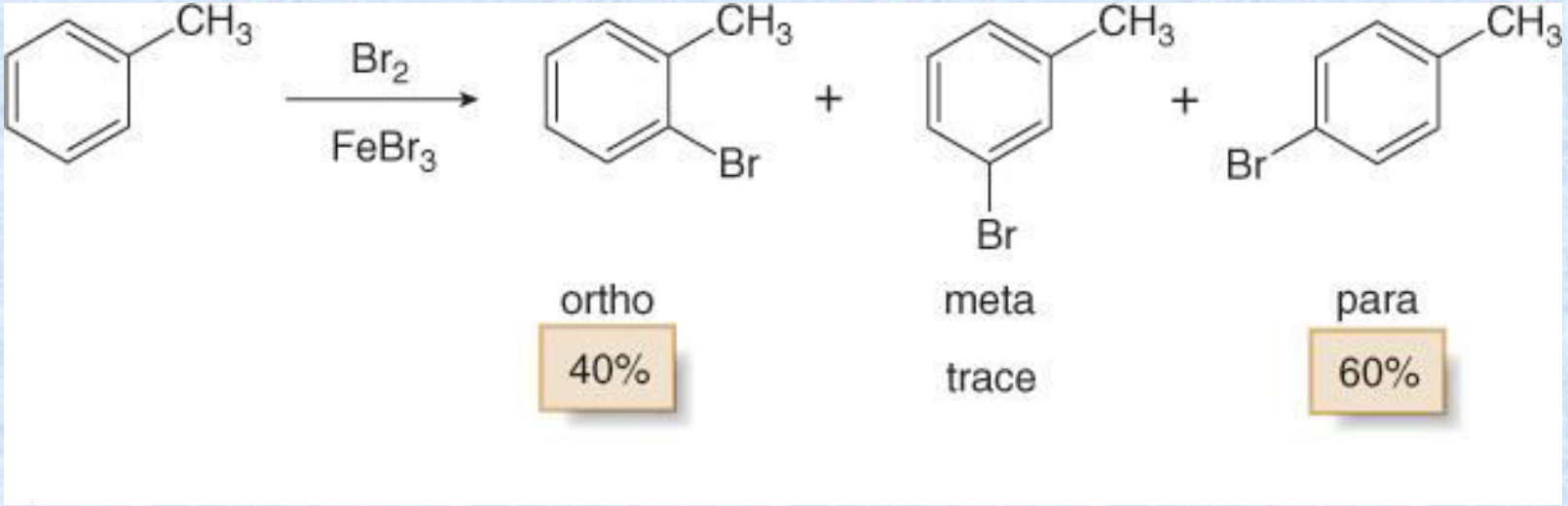
- **These compounds represent examples of the general structural features in electron-donating and electron withdrawing substituents.**



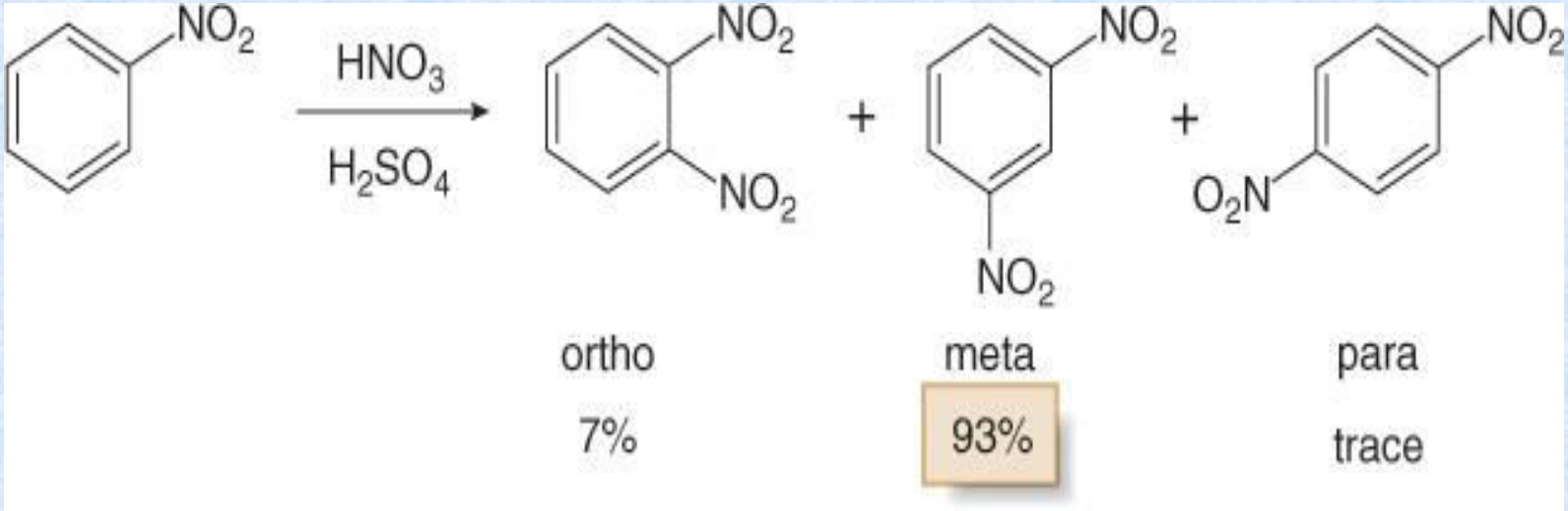
Electrophilic Aromatic Substitution and Substituted Benzenes.

- **Electrophilic aromatic substitution is a general reaction of all aromatic compounds, including polycyclic aromatic hydrocarbons, heterocycles, and substituted benzene derivatives.**
- **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.**
    2. **The 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.**

- **Consider Toluene—Toluene reacts faster than benzene in all substitution reactions. Reaction rate for toluene is ~25 times faster then benzene..**
- **The electron-donating CH_3 group activates the benzene ring to electrophilic attack.**
- **Ortho and para products predominate.**
- **The CH_3 group is called an ortho, para director.**



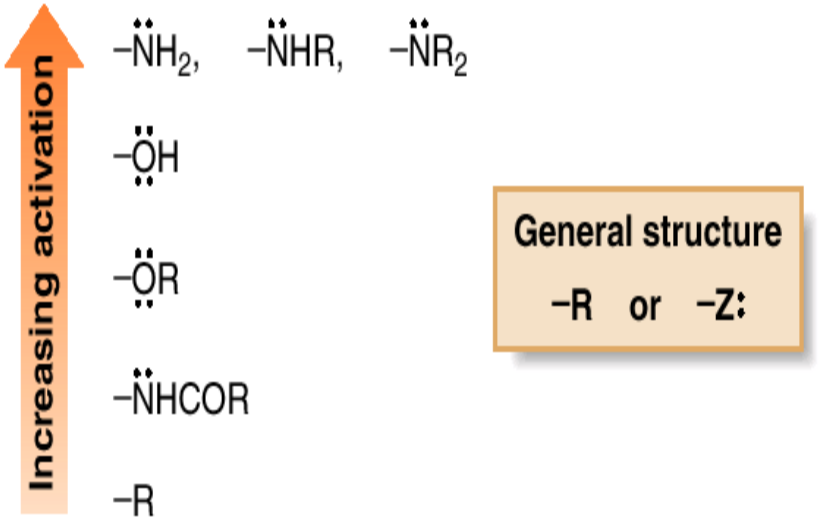
- Consider **Nitrobenzene**—It reacts more slowly than benzene in all substitution reactions.
- The electron-withdrawing NO_2 group deactivates the benzene ring to electrophilic attack.
- The meta product predominates.
- The NO_2 group is called a meta director.



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.

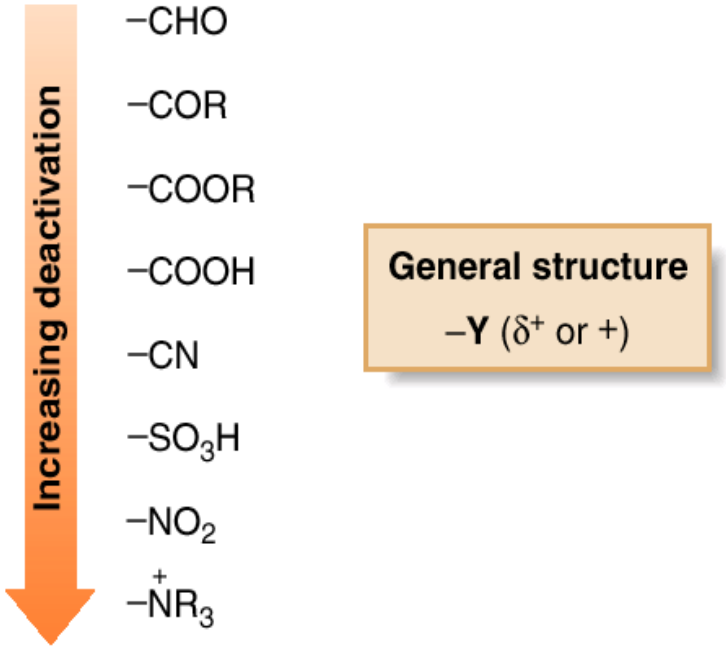


[2] ortho, para deactivators

- **Substituents that *deactivate* a benzene ring and direct substitution ortho and para.**

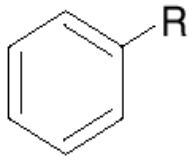
[3] meta directors

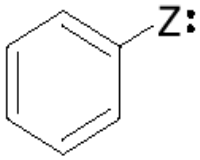
- **Substituents that direct substitution meta.**
- **All meta directors *deactivate* the ring.**



- **Keep in mind that halogens are in a class by themselves.**
- **Also note that:**

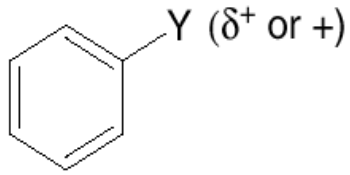
- All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.



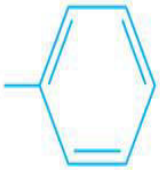


Z = N or O ⟶ The ring is **activated.**
Z = halogen ⟶ The ring is **deactivated.**

- All meta directors have a full or partial positive charge on the atom bonded to the benzene ring.



Summary of substituent effects

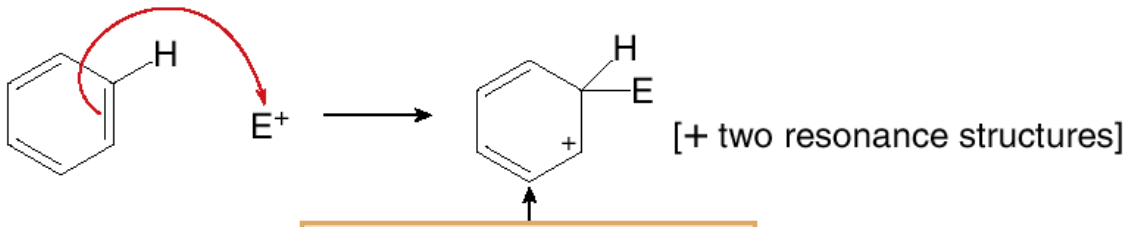
π Donors	σ Donors	Halogens	Carbonyls	Other
$-\ddot{N}H_2$ $-\ddot{O}H$ $-\ddot{O}R$ $-\ddot{N}HCOCH_3$	$-R$ alkyl  aryl (weak pi donor)	$-F$ $-Cl$ $-Br$ $-I$	$-\overset{O}{\overset{\|\|}{C}}-R$ $-\overset{O}{\overset{\|\|}{C}}-OH$ $-\overset{O}{\overset{\|\|}{C}}-OR$	$-SO_3H$ $-C\equiv N$ $-NO_2$ $-\overset{+}{N}R_3$

ortho, para-directing — meta-directing

ACTIVATING — DEACTIVATING

- **To understand how substituents activate or deactivate the ring, we must consider the first step in electrophilic aromatic substitution.**
- **The first step involves addition of the electrophile (E^+) to form a resonance stabilized carbocation.**
- **The Hammond postulate makes it possible to predict the relative rate of the reaction by looking at the stability of the carbocation intermediate.**

- The more stable the carbocation, the lower in energy the transition state that forms it, and the faster the reaction.

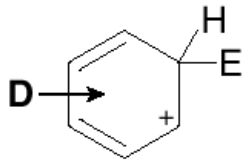


Stabilizing the carbocation makes the reaction faster.

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

- Electron-donating groups stabilize the carbocation, making the reaction faster.
- Electron-withdrawing groups destabilize the carbocation, making the reaction slower.

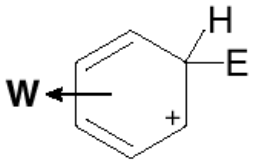
D = electron-donor group



more stable carbocation

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

W = electron-withdrawing group

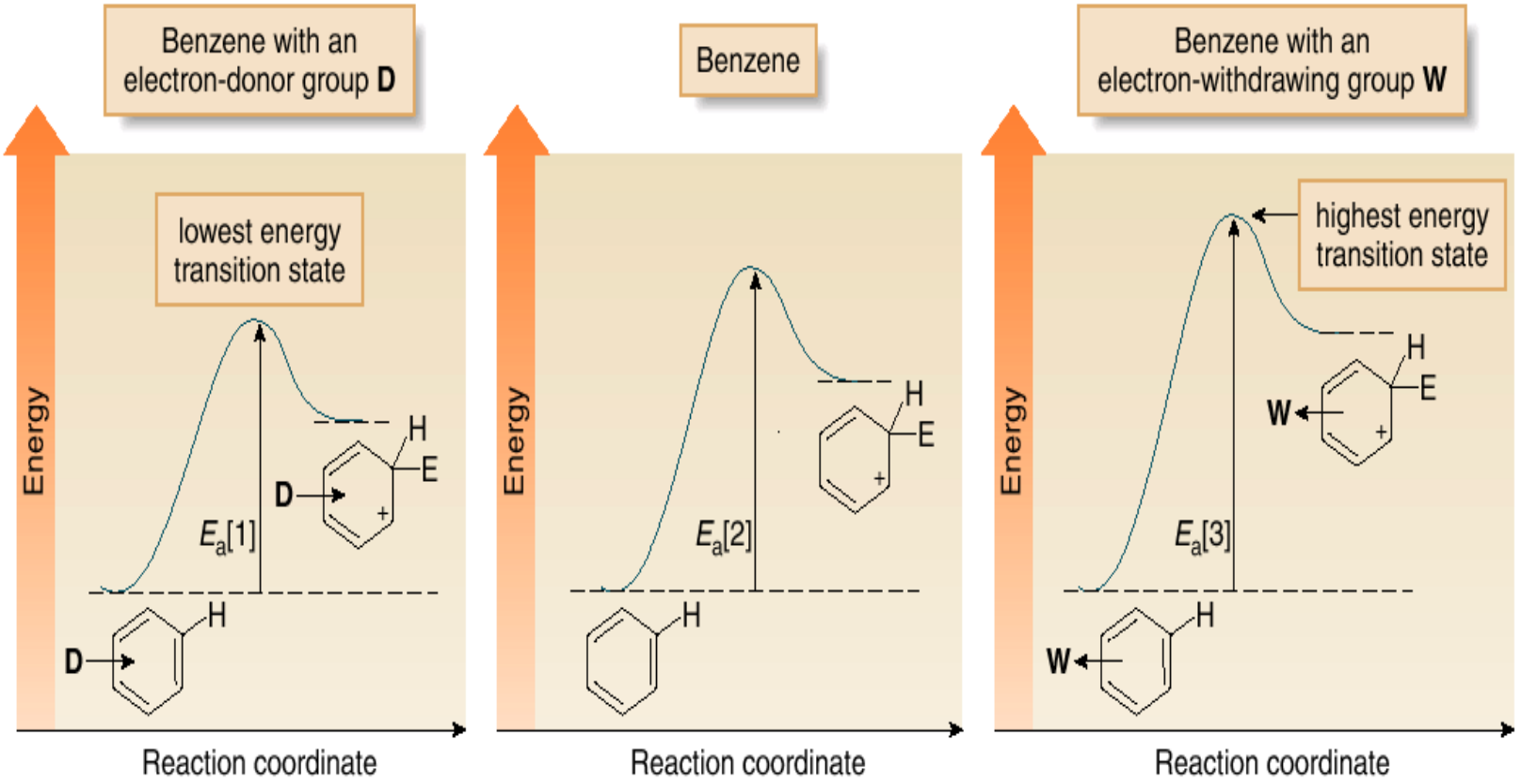


less stable carbocation

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

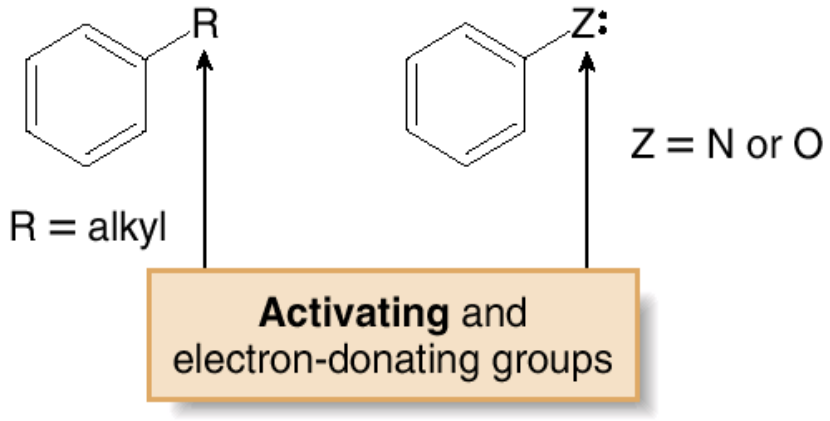
- In other words, electron-donating groups activate a benzene ring and electron-withdrawing groups deactivate a benzene ring towards electrophilic attack.

The energy diagrams below illustrate the effect of electron-withdrawing and electron-donating groups on the transition state energy of the rate-determining step.



- 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.

- All activators are either R groups or they have an N or O atom with a lone pair directly bonded to the benzene ring. These are the electron-donor groups of Section 18.6.



For example:

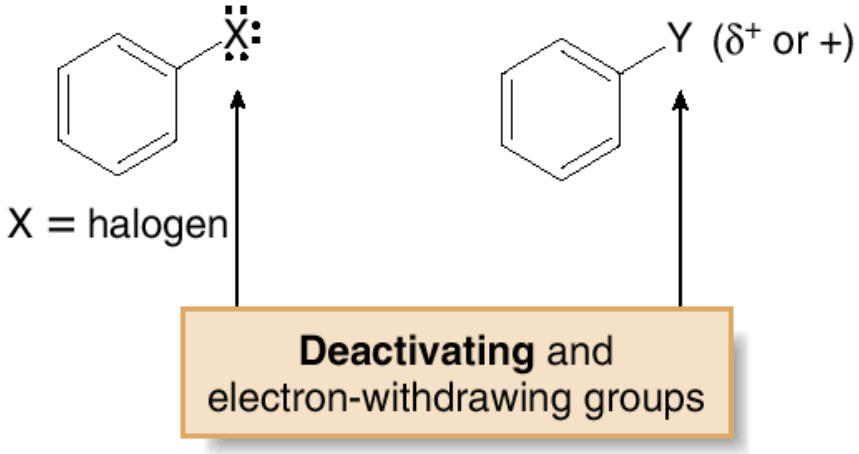
$-\ddot{N}H_2$ $-\ddot{N}HR$ $-\ddot{N}R_2$

$-\ddot{O}H$ $-\ddot{O}R$

$-\ddot{N}HCOR$

$-R$

- All deactivators are either halogens or they have an atom with a partial or full positive charge bonded directly to the benzene ring. These are the electron-withdrawing groups of Section 18.6.



For example:

$-\ddot{F}:$ $-\ddot{Cl}:$ $-\ddot{Br}:$ $-\ddot{I}:$

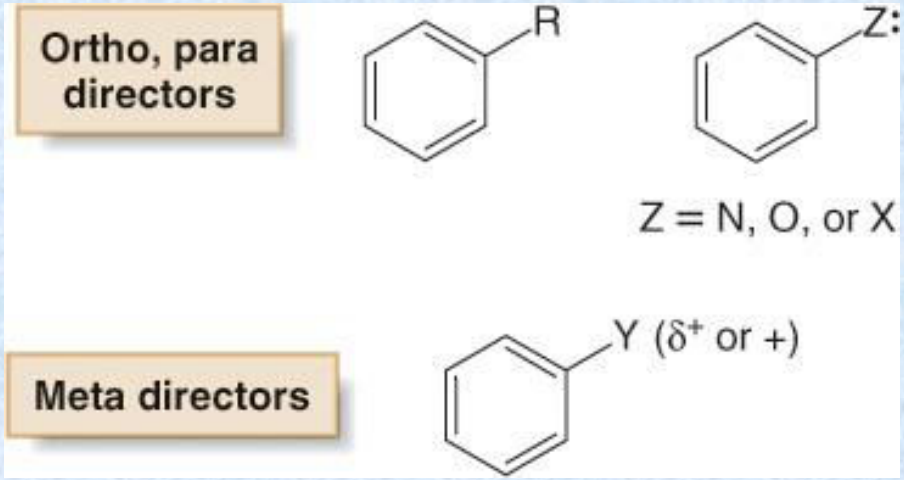
$-CHO$ $-COR$

$-COOR$ $-COOH$

$-CN$ $-SO_3H$ $-NO_2$ $-\overset{+}{N}R_3$

Orientation Effects in Substituted Benzenes

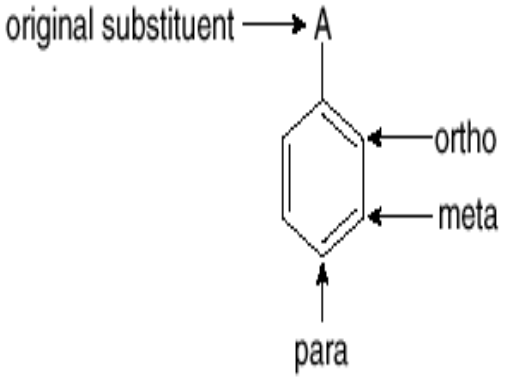
- There are two general types of ortho, para directors and one general type of meta director.
- All ortho, para directors are R groups or have a nonbonded electron pair on the atom bonded to the benzene ring.
- All meta directors have a full or partial positive charge on the atom bonded to the benzene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



To evaluate the effects of a given substituent, we can use the following stepwise procedure:

How To Determine the Directing Effects of a Particular Substituent

Step [1] Draw all resonance structures for the carbocation formed from attack of an electrophile E^+ at the ortho, meta, and para positions of a substituted benzene (C_6H_5-A).



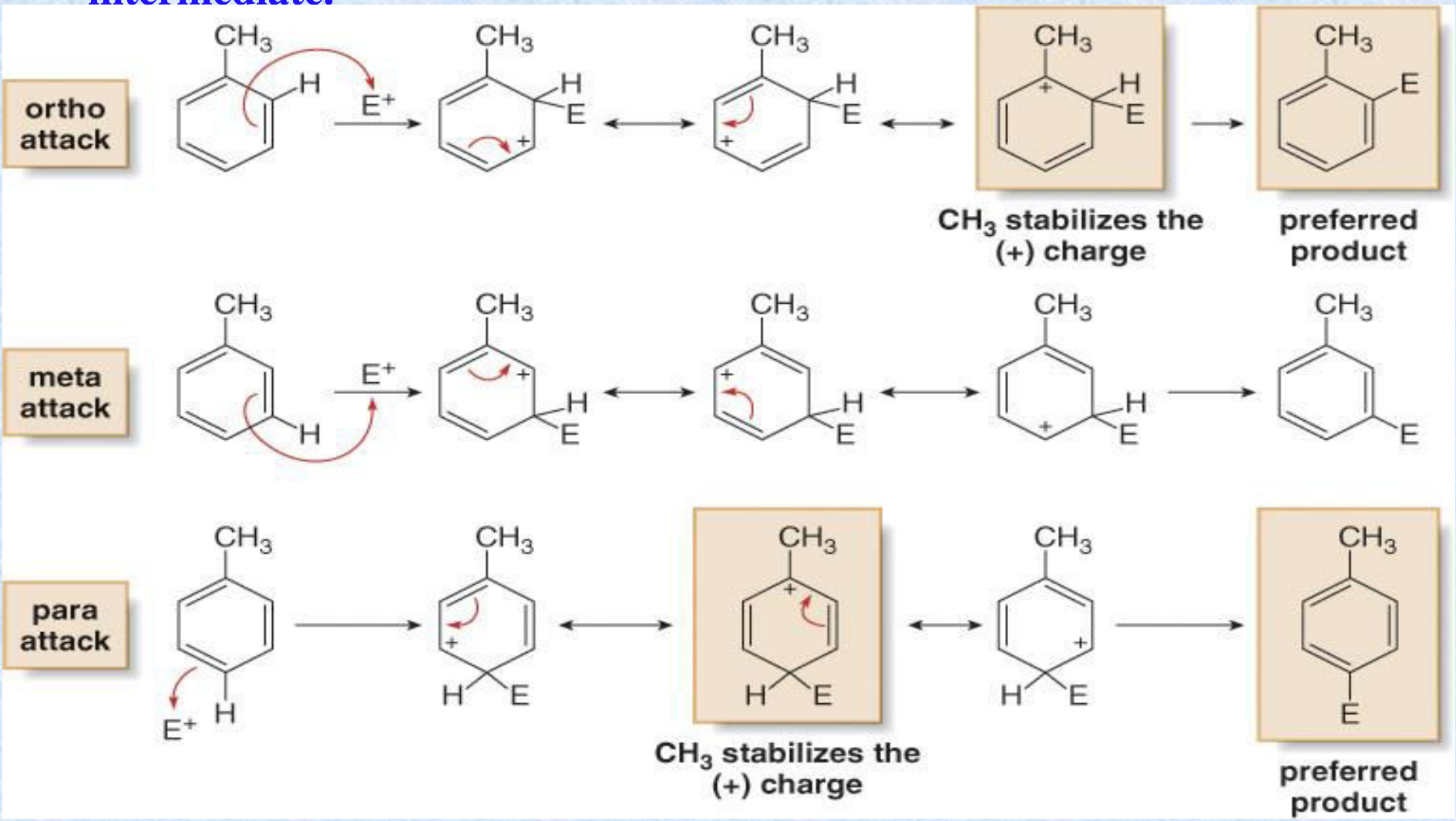
- There are at least three resonance structures for each site of reaction.
- Each resonance structure places a positive charge ortho or para to the new C–E bond.

Step [2] Evaluate the stability of the intermediate resonance structures. The electrophile attacks at those positions that give the most stable carbocation.

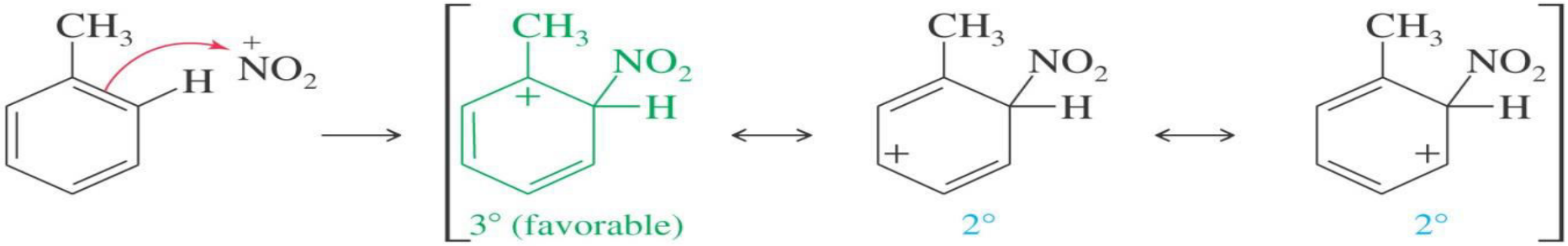
EFFECT
OF
RING SUBSTITUENTS

ORTHO-PARA DIRECTING SUBSTITUENTS

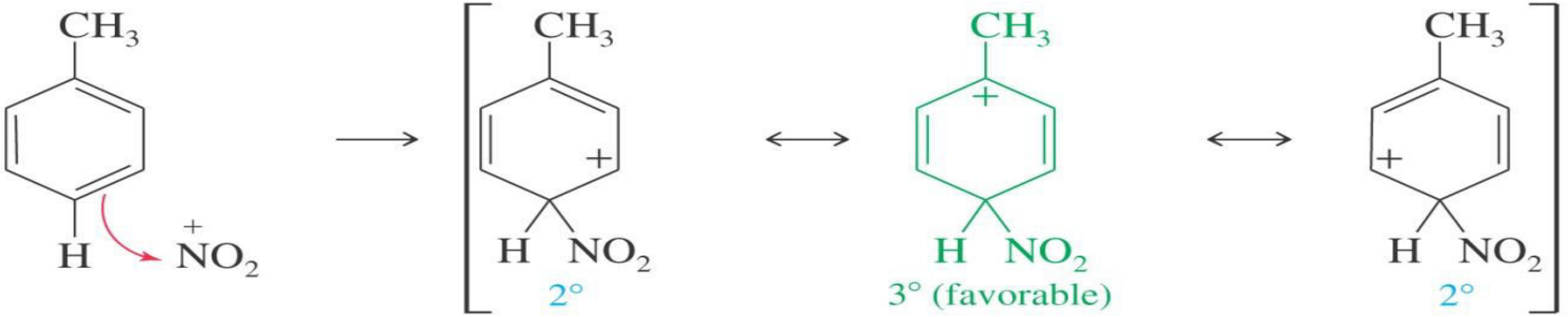
- A CH_3 group directs electrophilic attack ortho and para to itself because an electron-donating inductive effect stabilizes the carbocation intermediate.



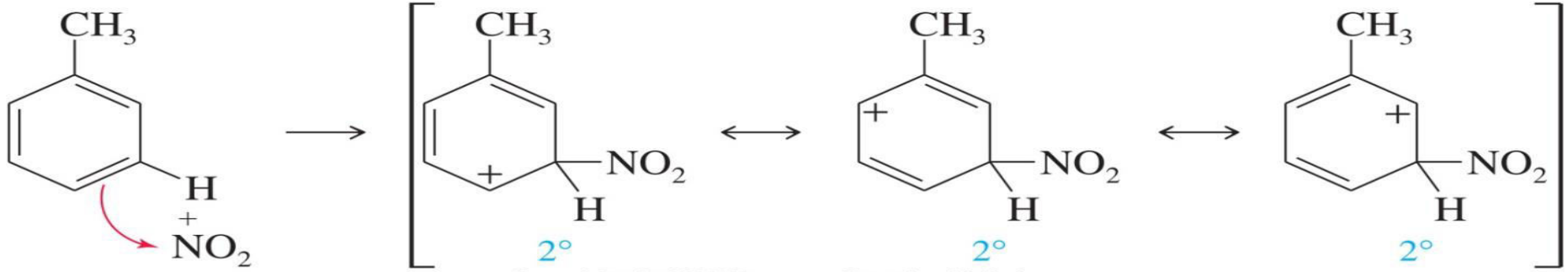
Ortho attack



Para attack

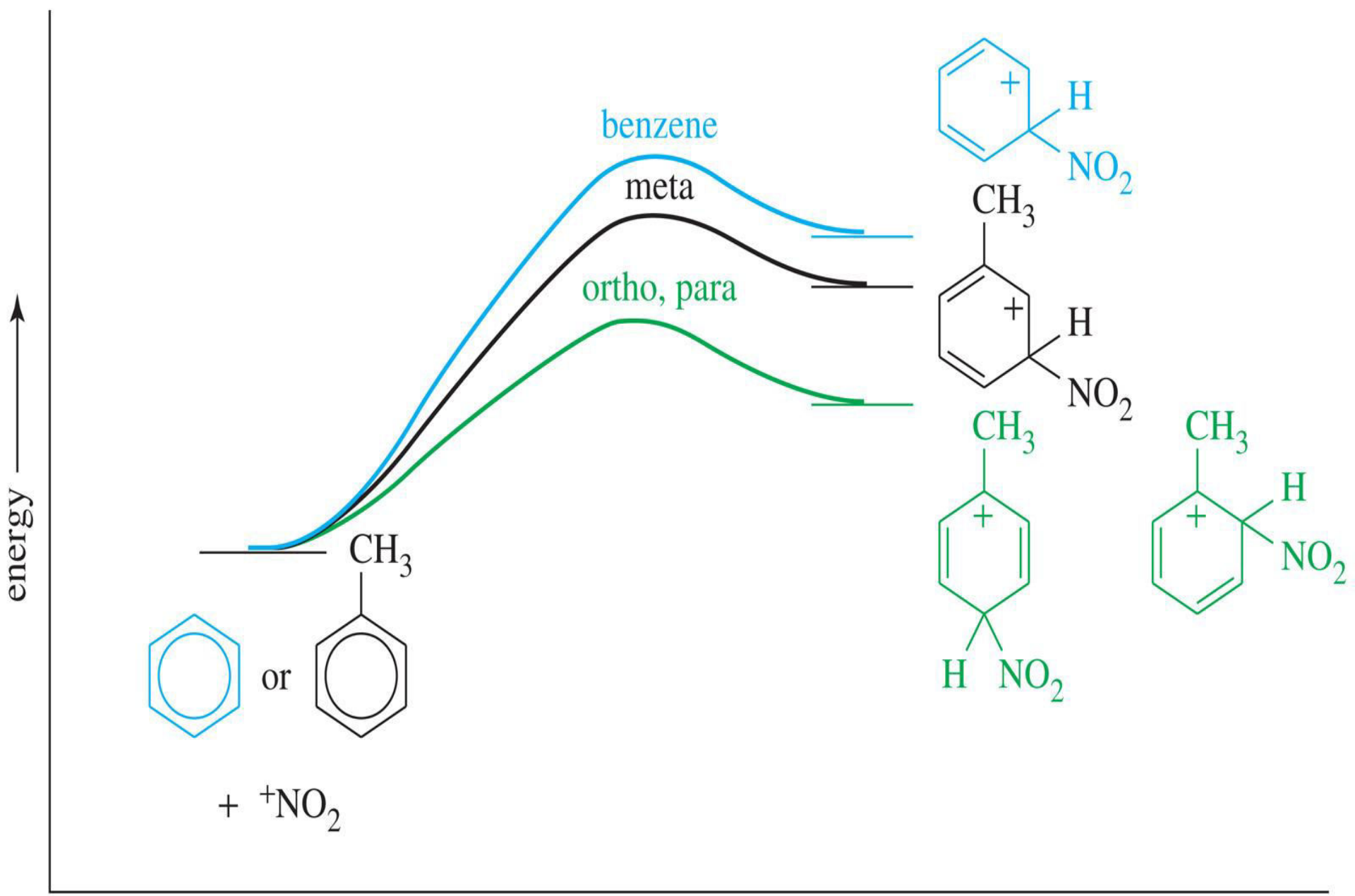


Meta attack



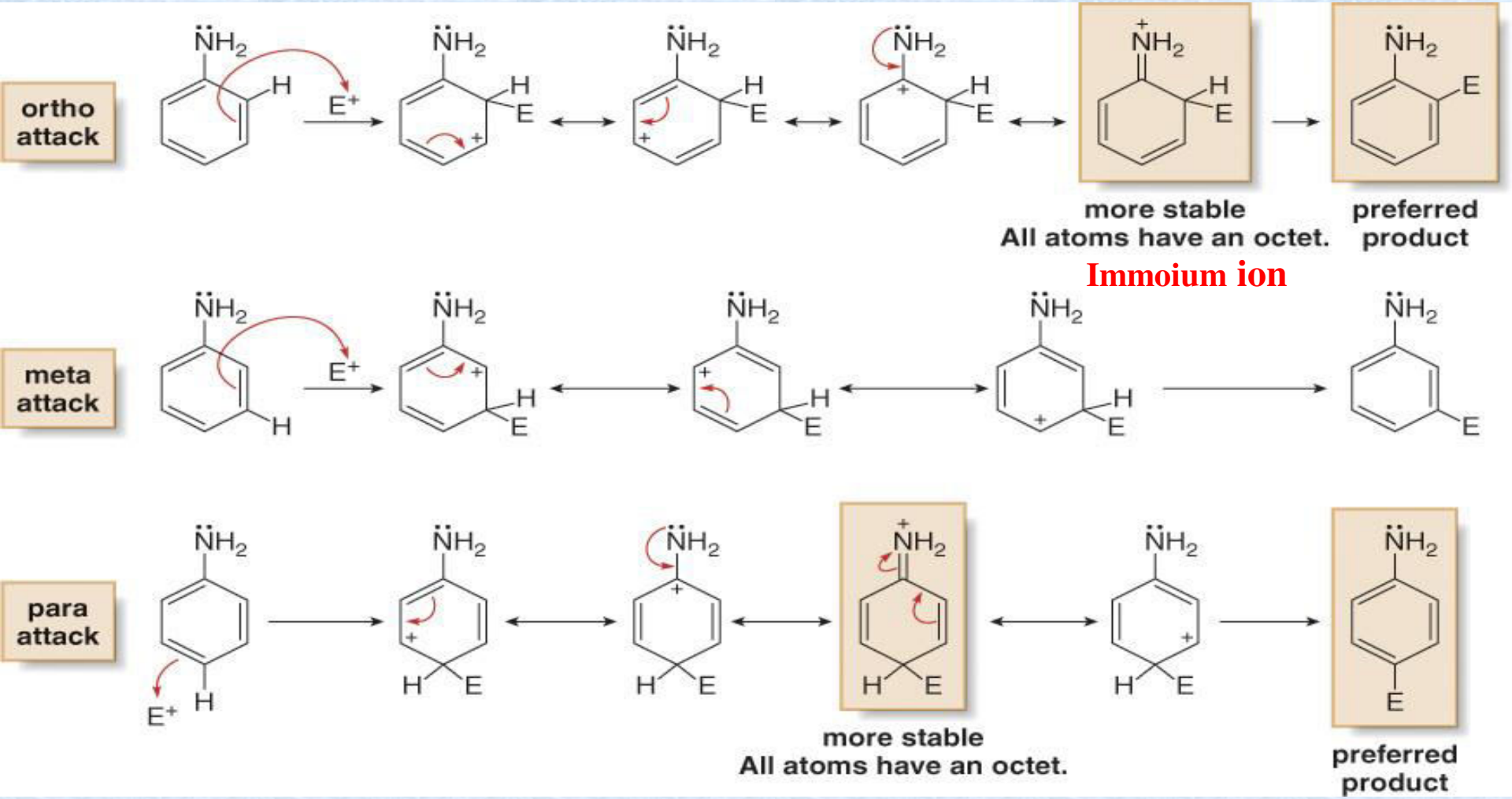
The results seen here for toluene (methylbenzene) are general for all mono-alkylbenzenes when undergoing electrophilic aromatic substitution reactions.

The sigma complexes formed ortho and para to the alkyl group are more stable then the meta complex because the ortho and para complex have resonance forms with tertiary carbocations. This effect is called *inductive stabilization* because the alkyl group is donating electron density to the intermediate through the sigma bond.

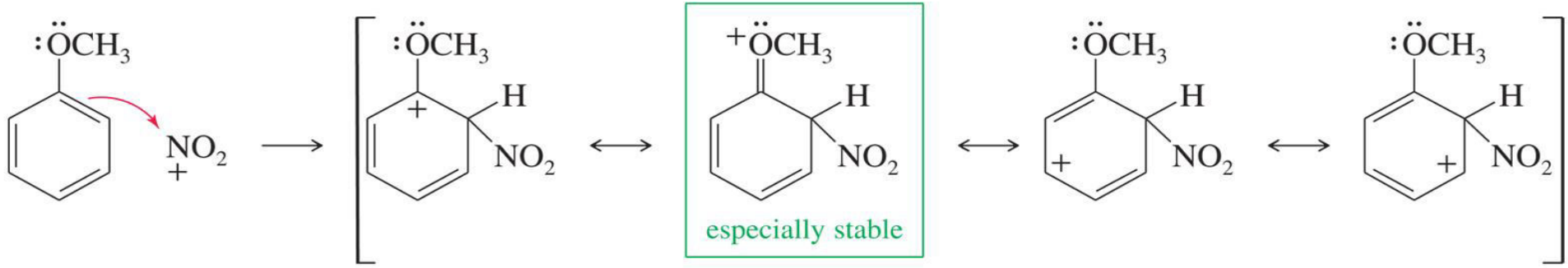


EFFECT OF SUBSTITUENTS WITH NON-BONDING ELECTRONS (O, P- DIRECTING, RING ACTIVATING)

- An NH_2 group directs electrophilic attack ortho and para to itself because the carbocation intermediate has additional resonance stabilization.

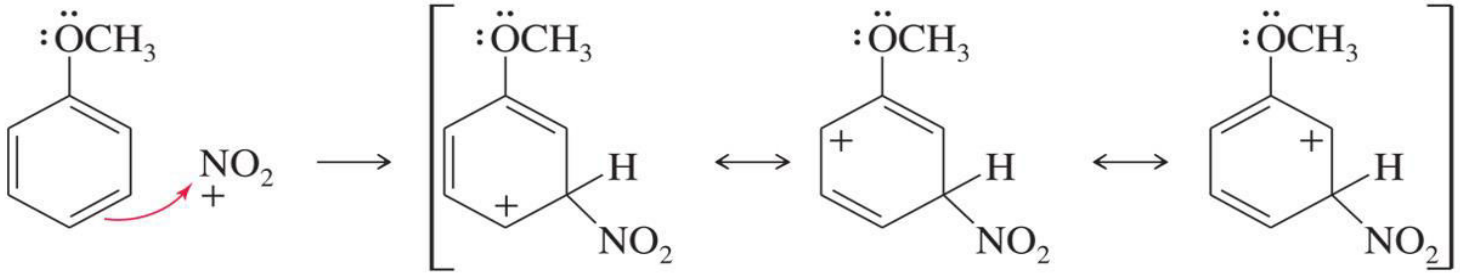


Ortho attack

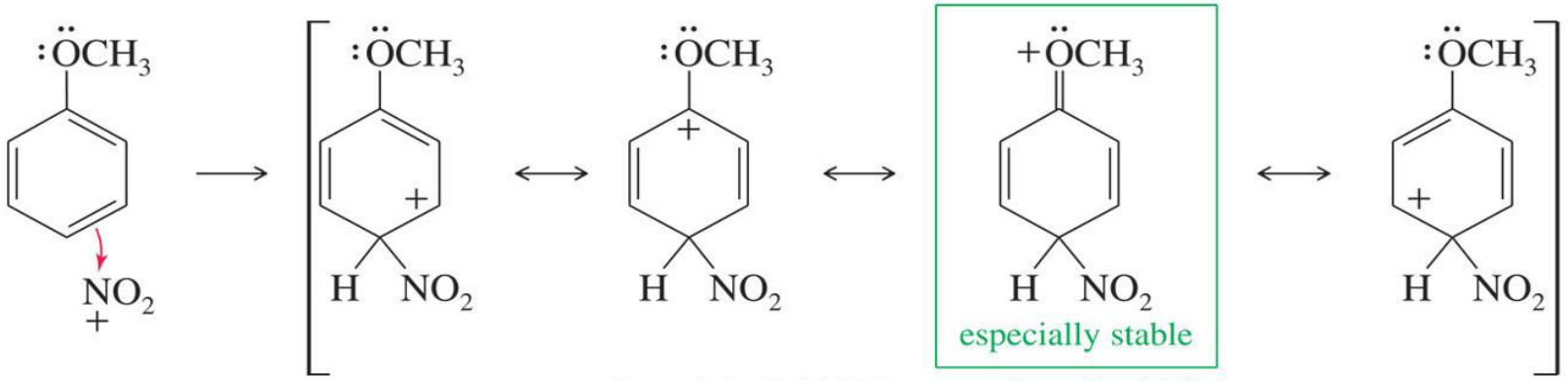


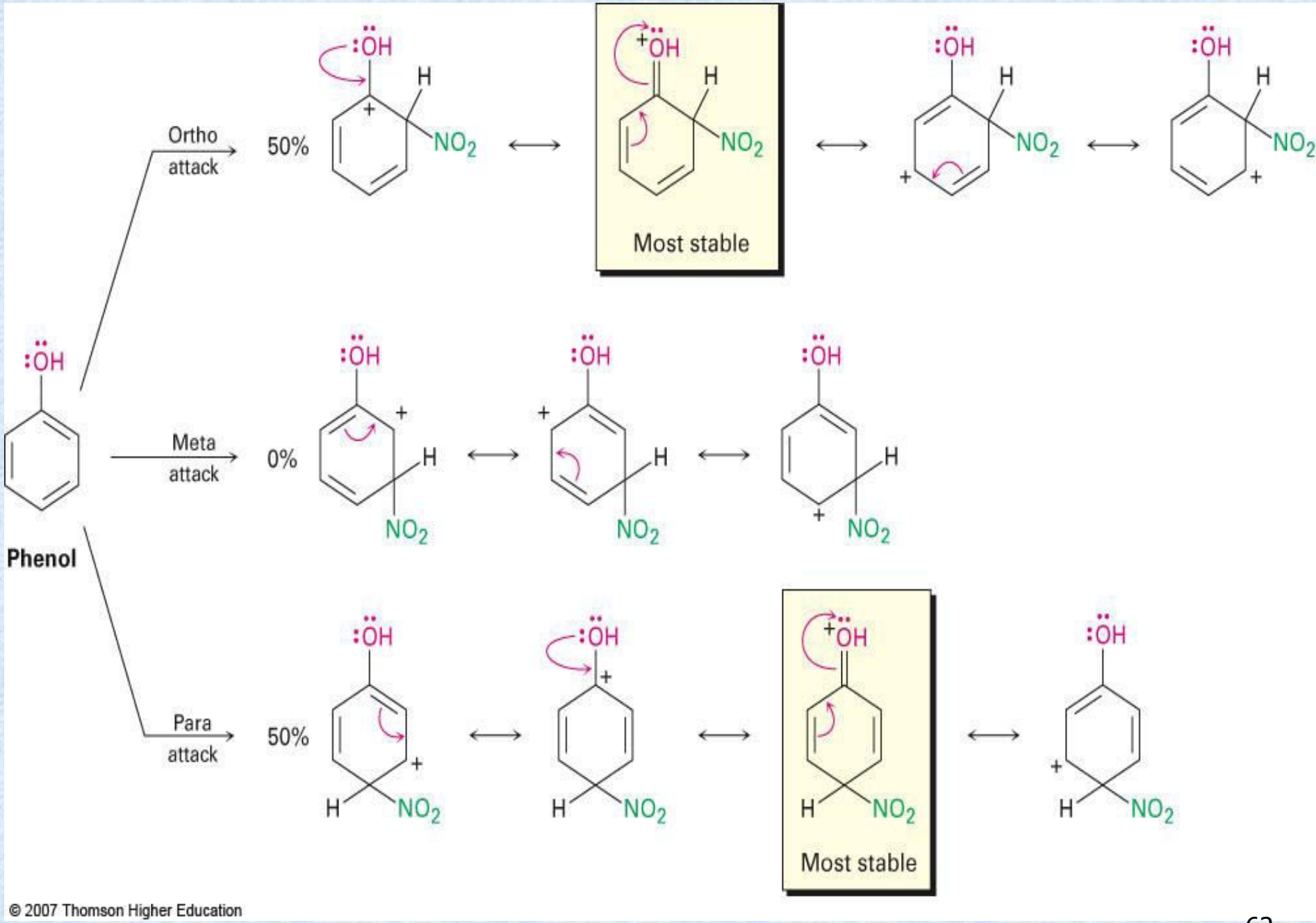
Oxonium ion

Meta attack



Para attack





- **The affect of *resonance stabilization* by substituents with non-bonding electrons on reaction rates can be very large. In the case of anisole the rate of nitration is ~10,000 time faster than benzene and ~ 400 times faster then toluene. This type of stabilization is also called *resonance donating and pi-donating*.**

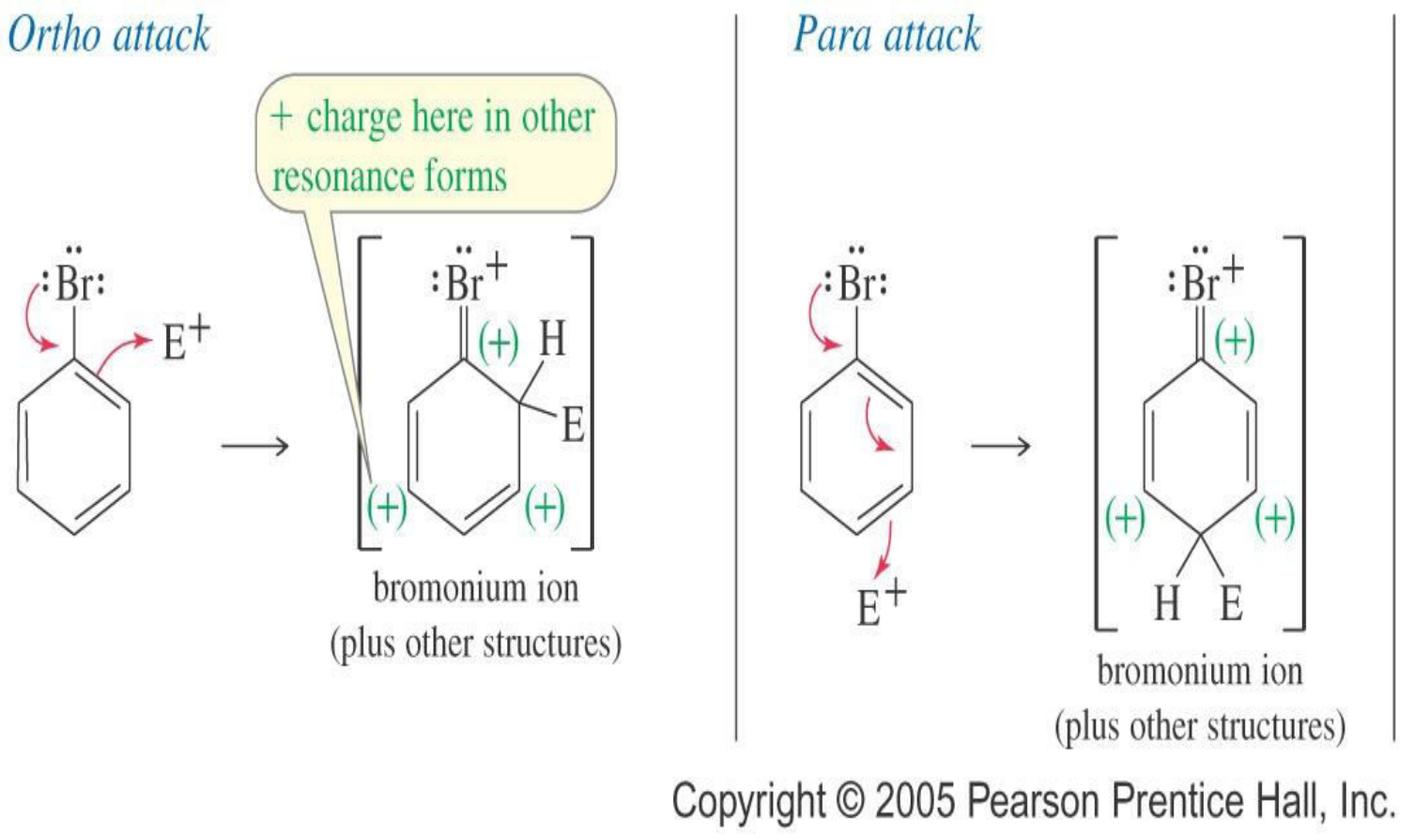
- **Substituents with non-bonding electrons are ortho/para directors. They may be either activating or deactivating.**

EFFECT OF SUBSTITUENTS WITH NON-BONDING ELECTRONS (O, P- DIRECTING, RING DECTIVATING)

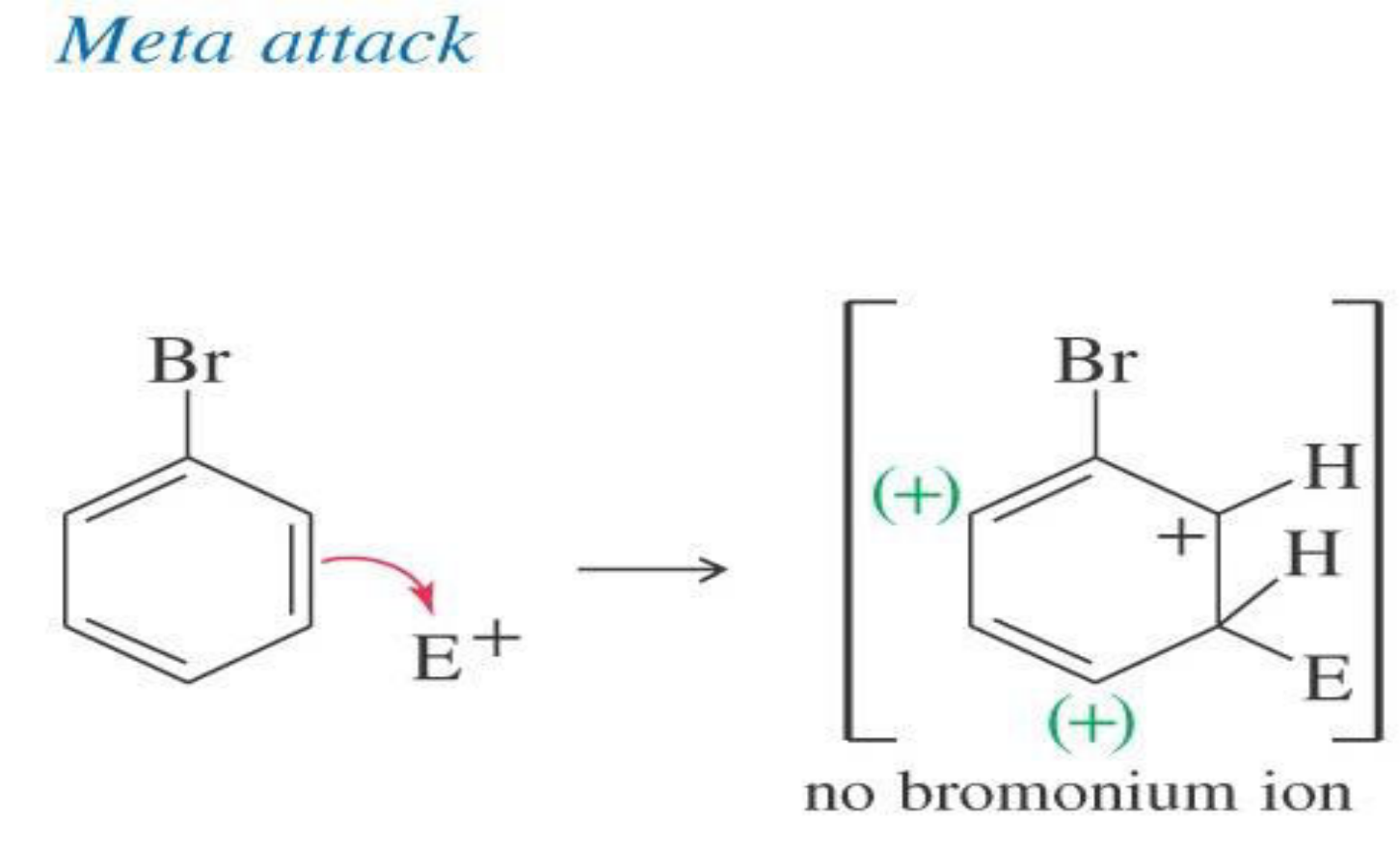
Halogenated aromatic compounds under go electrophile substitution ortho and para to the halogen. This is an expected result since halogens have non-bonding electrons that can resonance stabilize the intermediate sigma complex .

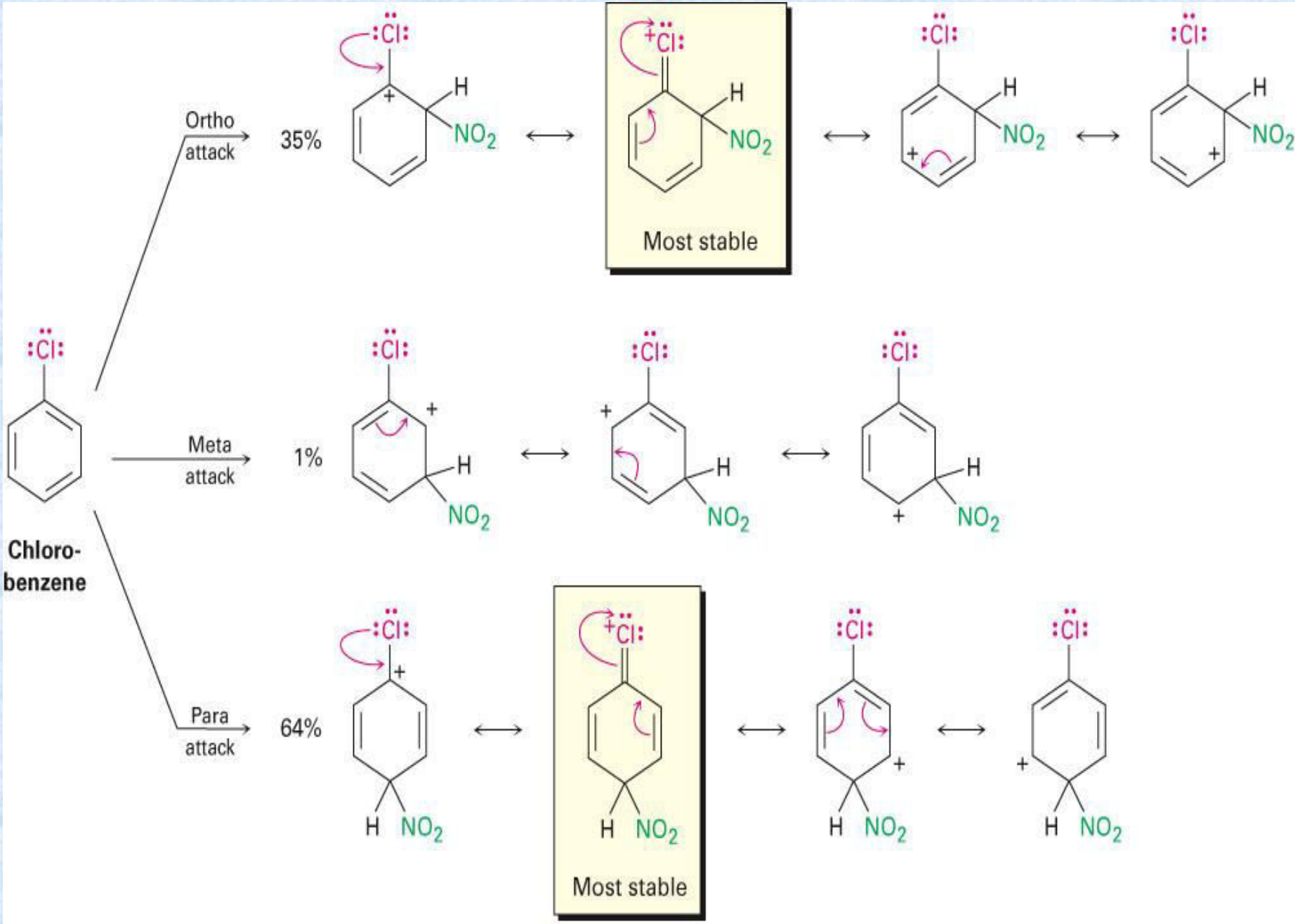
Halogens are orhto/para directors but unlike other ortho/para directors, halogens deactivate the aromatic ring toward electrophilic substitution reactions. ***Why are halogens deactivators?`***

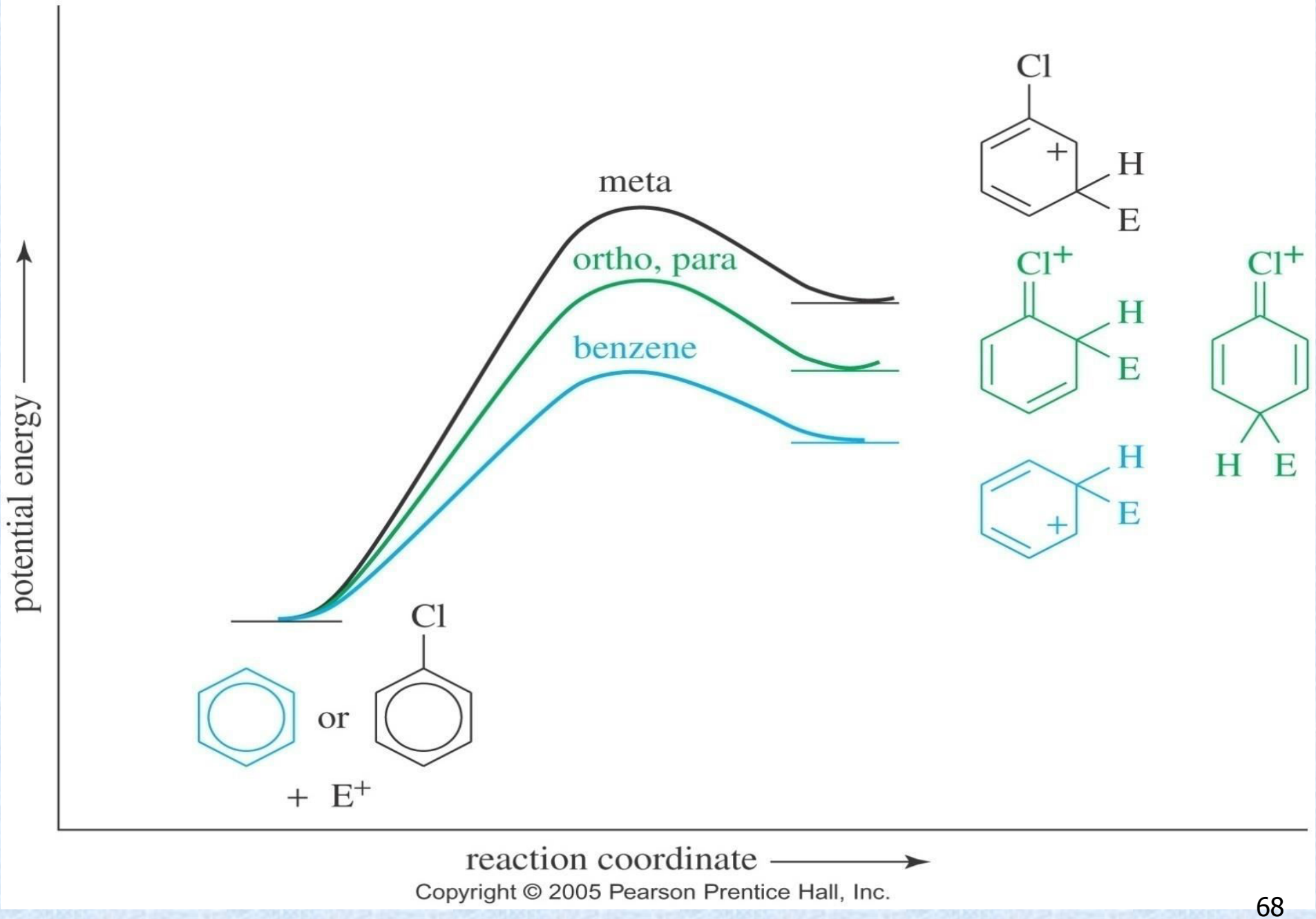
Ortho and para attacks produce a bromonium ion and other resonance structures.



In the meta position there is no stabilization of the sigma complex.

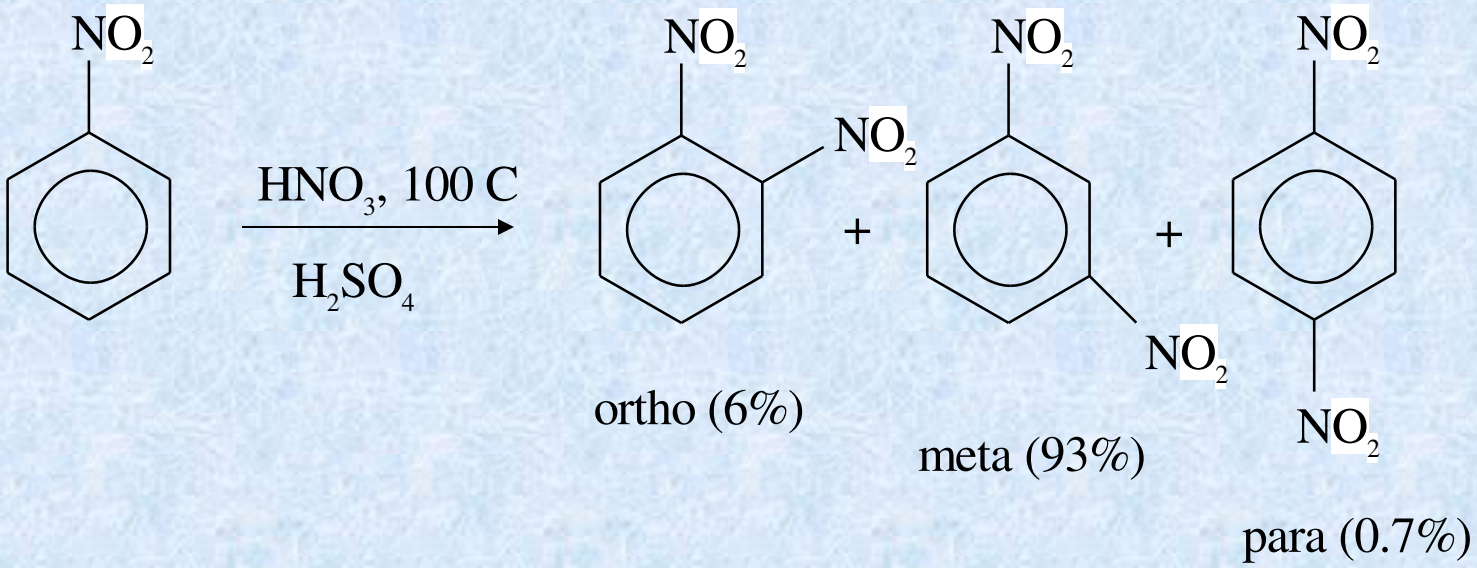






META DIRECTING SUBSTITUENTS

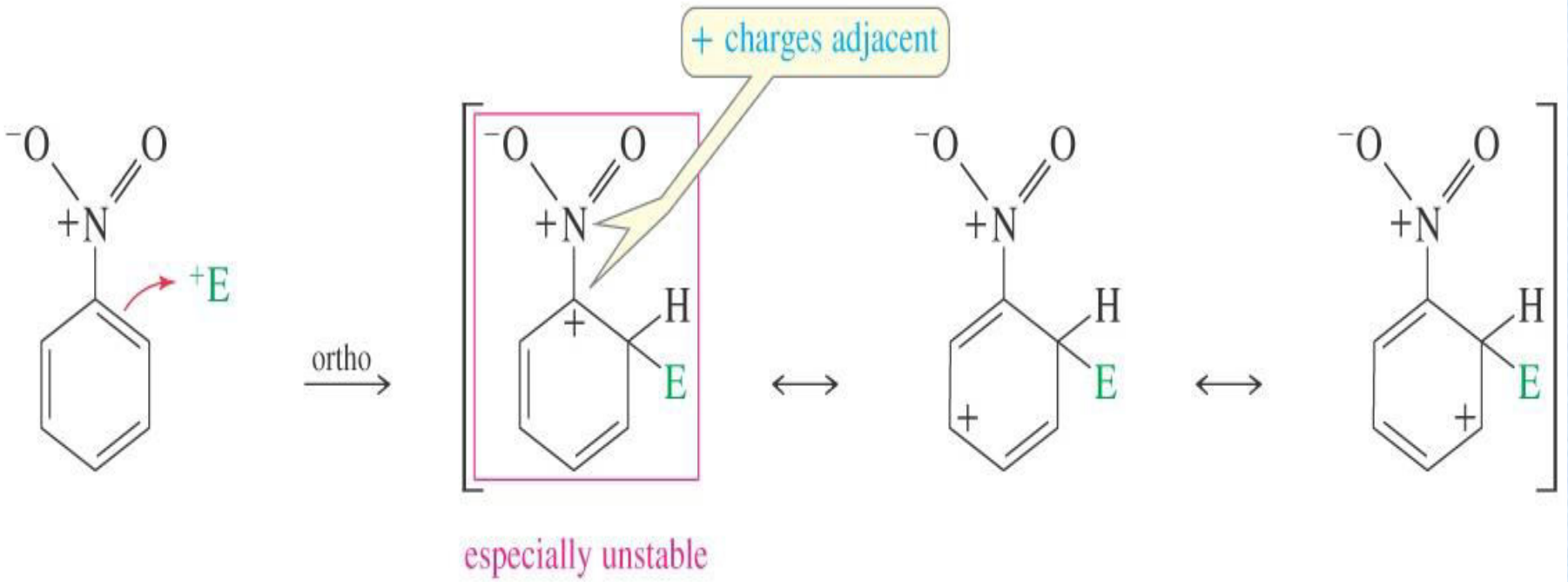
In electrophilic aromatic substitution reactions nitrobenzene is ~100,000 less reactive than benzene. In addition to deactivation of the ring the substitution occurs at the meta position.



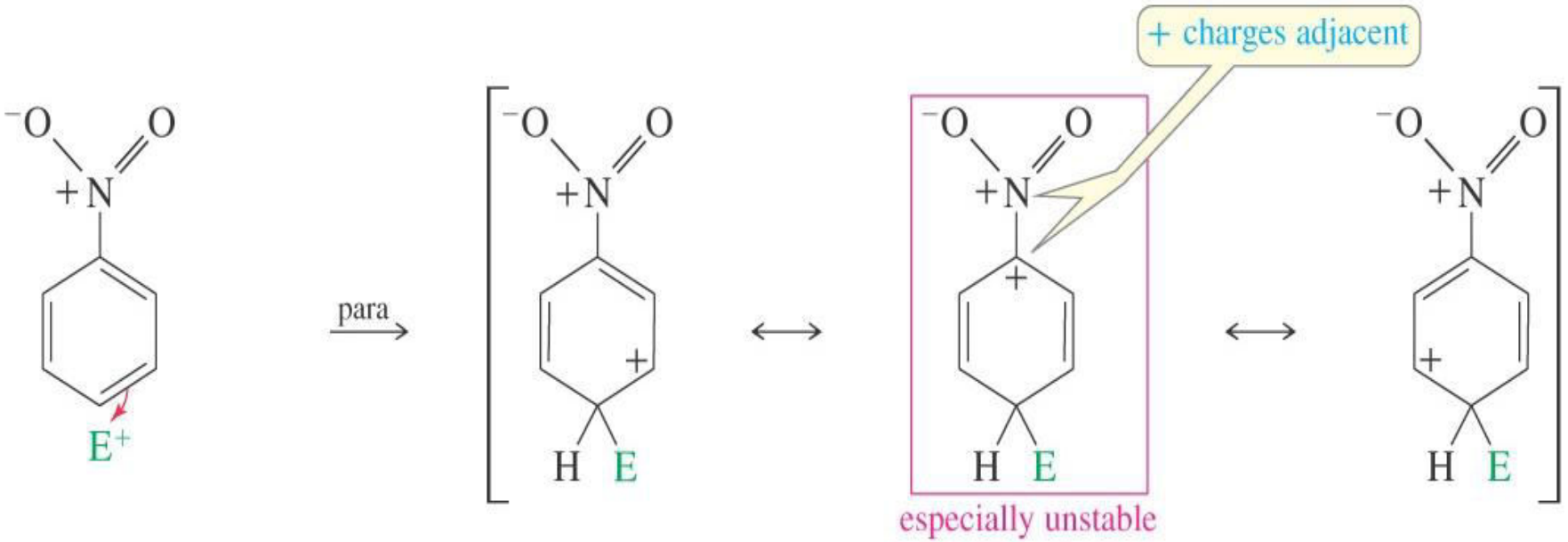
Why does the nitro group deactivate the ring in electrophilic aromatic substitution reactions? Why is the nitro group a meta director?

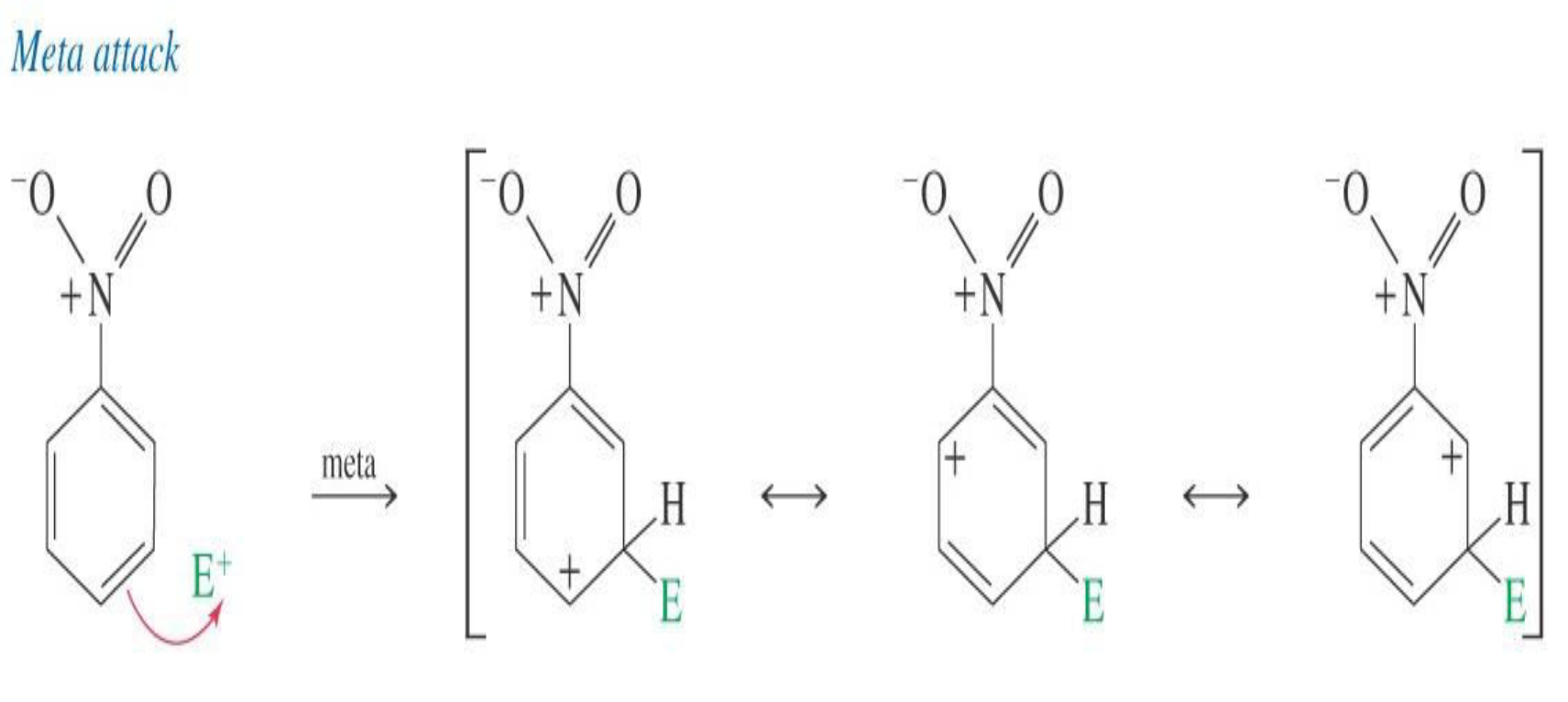
To answer these questions we need to look at the intermediates that are formed during the reaction.

Ortho attack

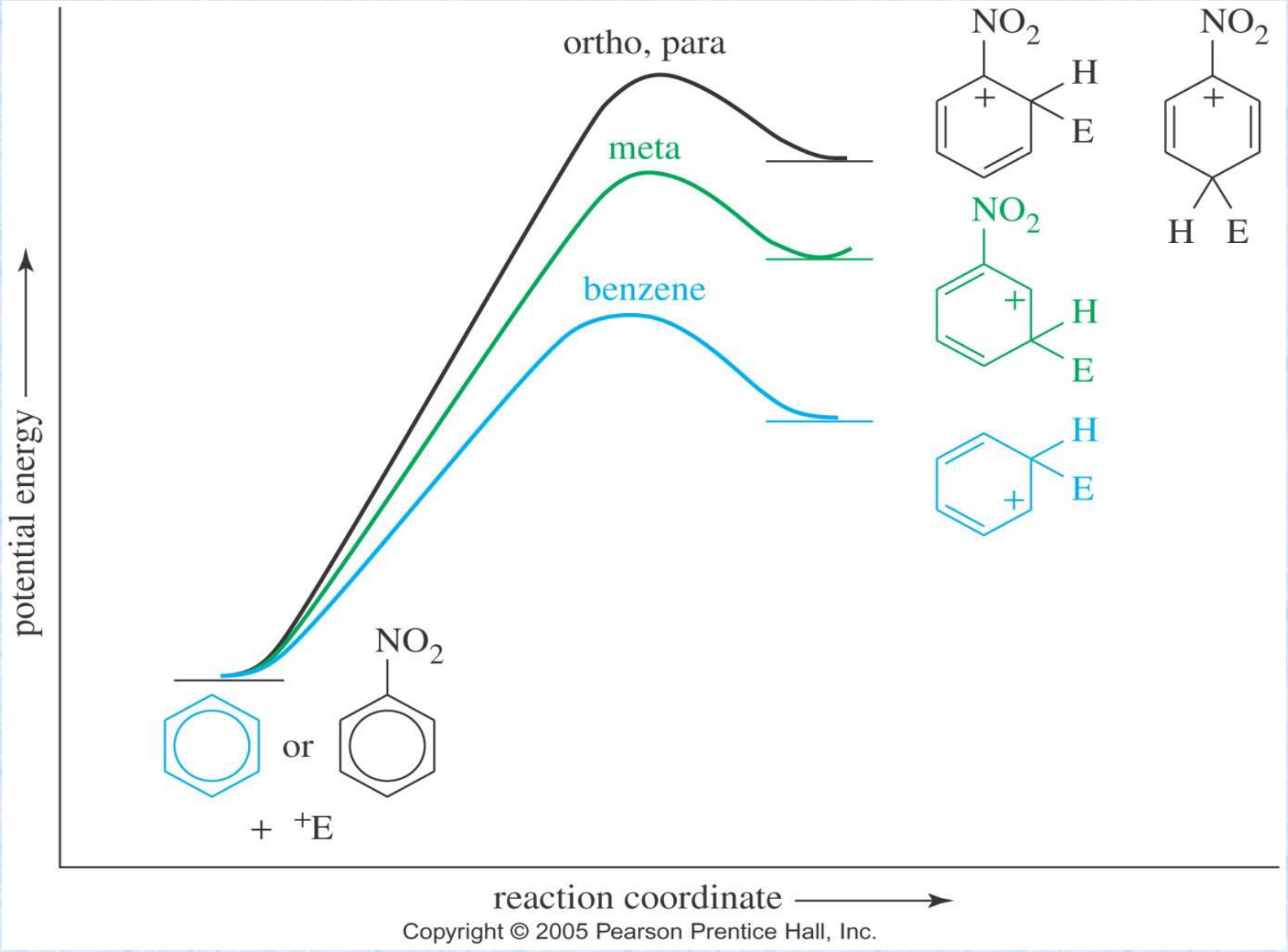


Para attack

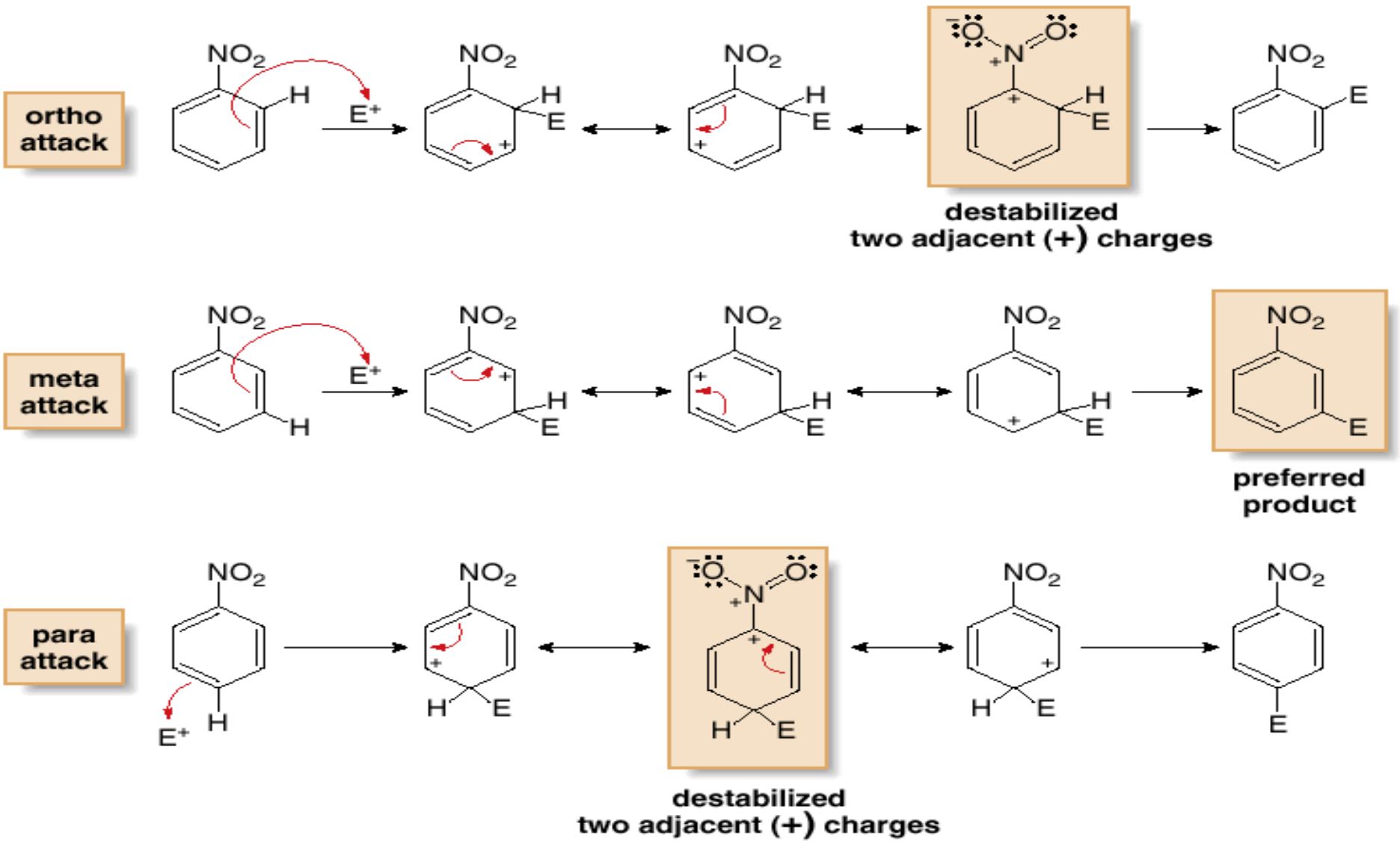


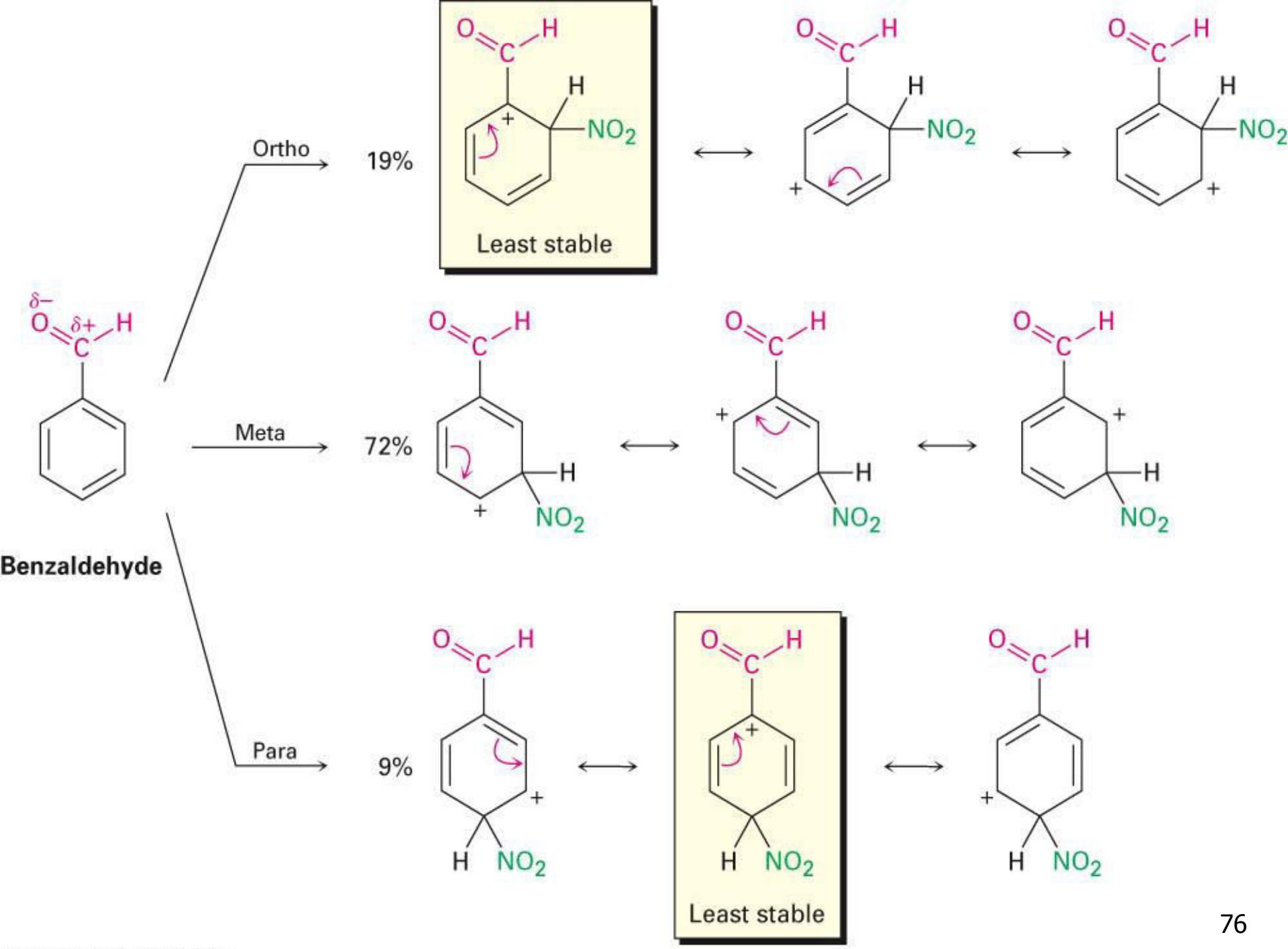


Stable carbocation



- 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.

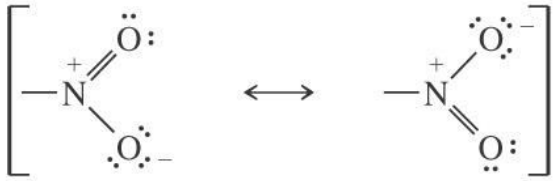
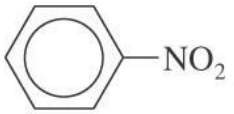
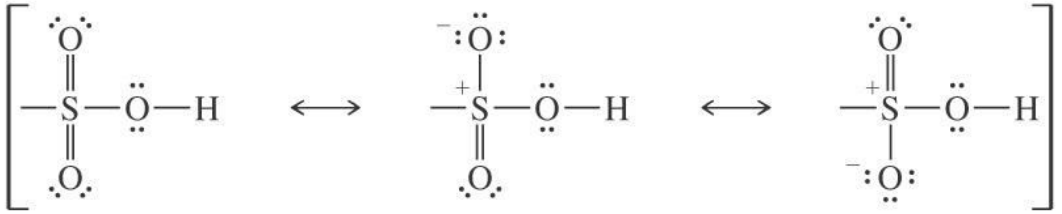
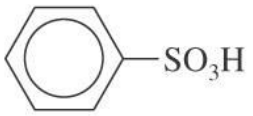
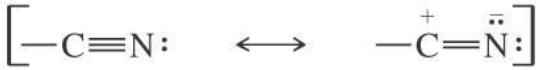
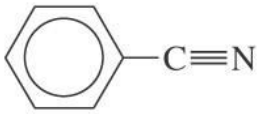
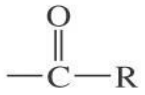
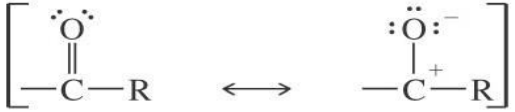
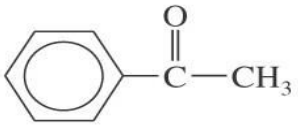
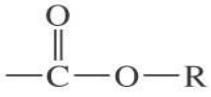
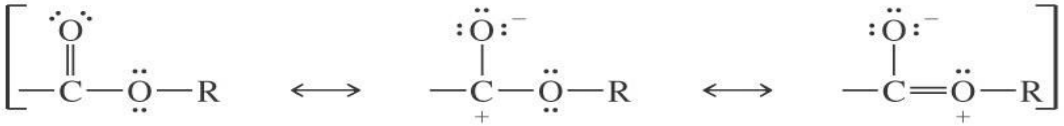
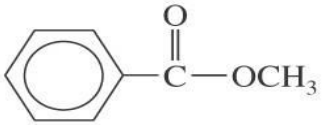
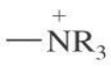
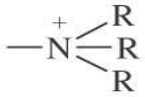
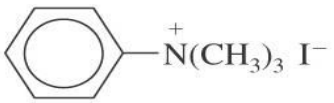




STRUCTURAL CHARACTERISTICS OF META-DIRECTING DEACTIVATORS

1. **The atom attached to the aromatic ring will have a formal positive charge or a partial positive charge.**

2. **Electron density is withdrawn inductively along the sigma bond, so the ring is less electron-rich than benzene. Destabilizes the sigma complex.**

Group	Resonance Forms	Example
—NO_2 nitro		 nitrobenzene
—SO_3H sulfonic acid		 benzenesulfonic acid
—C≡N: cyano		 benzonitrile
 ketone or aldehyde		 acetophenone
 ester		 methyl benzoate
 quaternary ammonium		 trimethylanilinium iodide

EFFECTS OF MULTIPLE SUBSTITUENTS

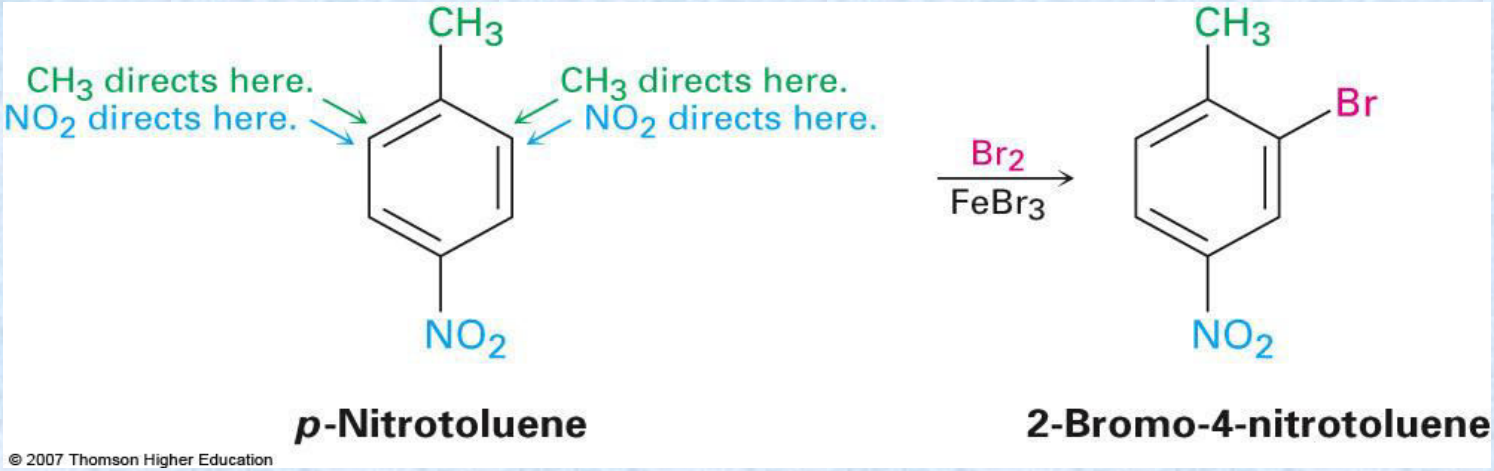
1. When two or more substituents are present on an aromatic ring a combined effect is observed in subsequent reactions.
2. In many cases it is easy to predict the effects of multiple substituent groups because the individual effects are mutually supporting of each other.
3. In cases were there is a conflict in the directing effects of the substituent groups it can more difficult to predict what products will be produced. When dealing with multiple substituents activating groups are generally stronger directors than deactivating groups.

a. Strong activating ortho, para-directors that stabilize the transition state through resonance. i.e. –OH, –OR

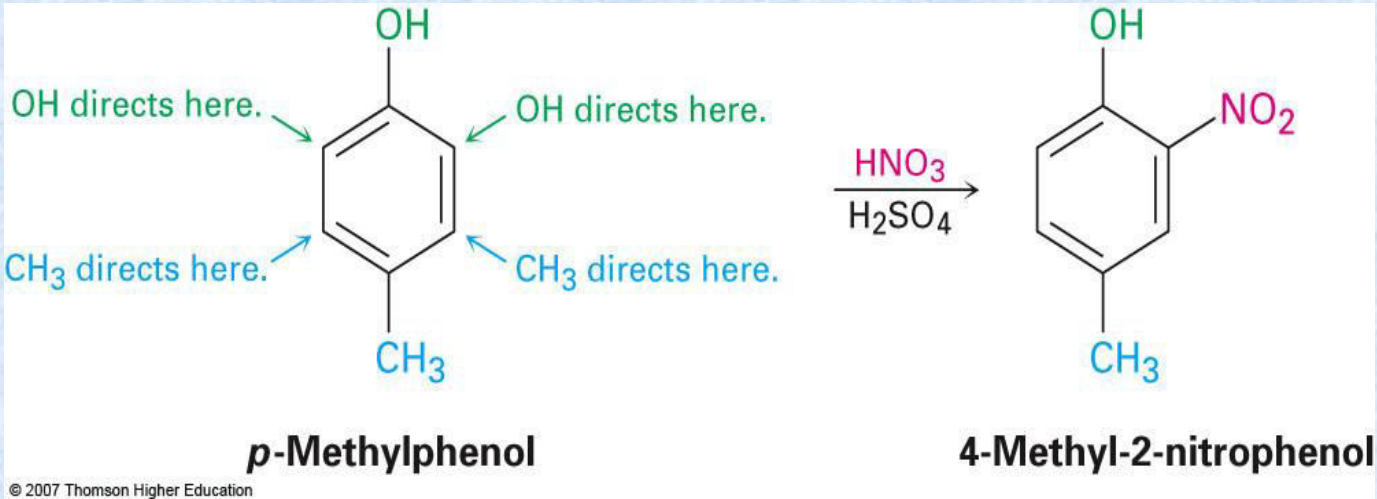
b. Activating ortho, para-directors. i.e. alkyl groups and halogens

c. Deactivating meta directors.

- **If the directing effects of the two groups are the same, the result is additive**

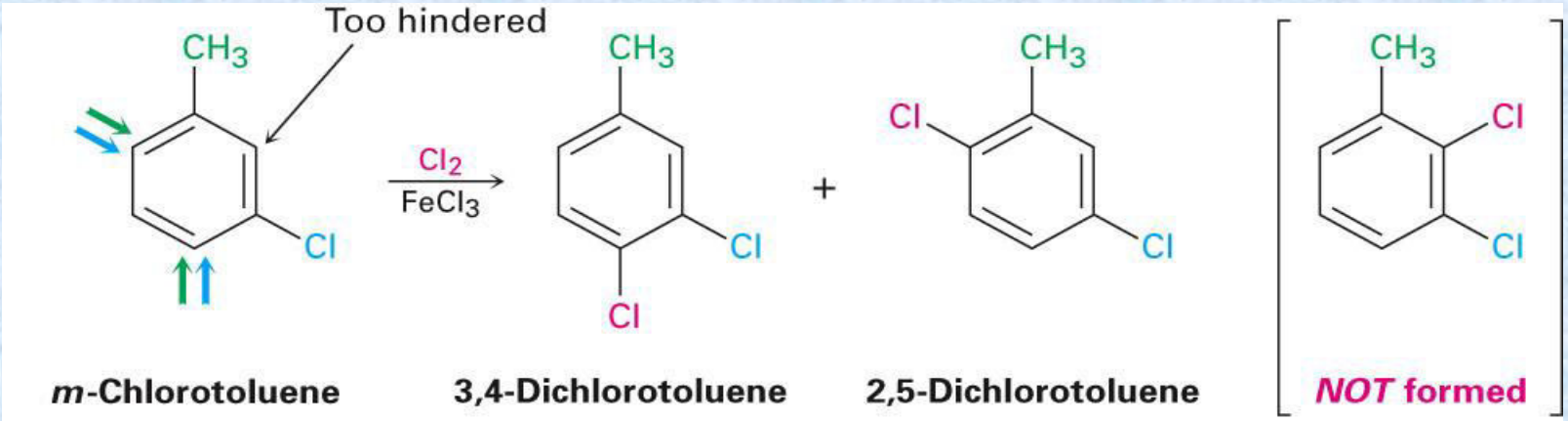


- **If the directing effects of two groups oppose each other, the more powerful activating group decides the principal outcome usually gives mixtures of products**

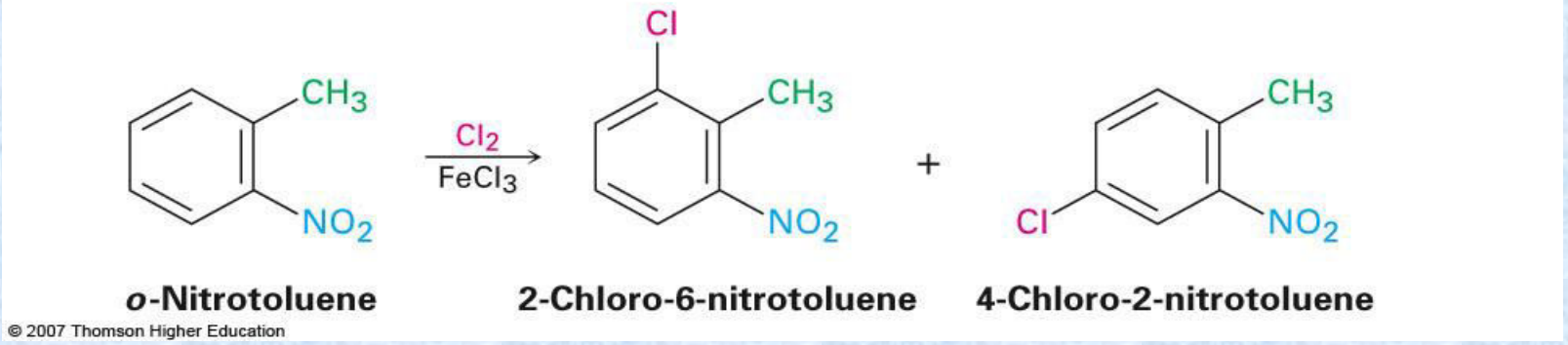


Meta-Disubstituted Compounds

- The reaction site is too hindered
- To make aromatic rings with three adjacent substituents, it is best to start with an ortho-disubstituted compound



But:



THANK YOU