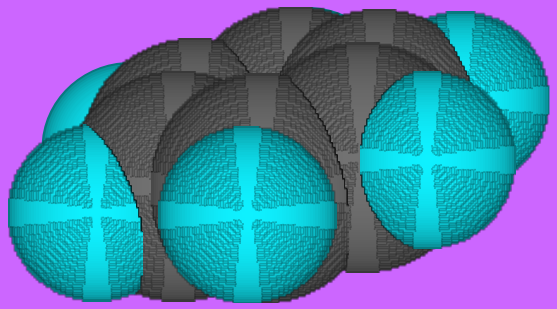
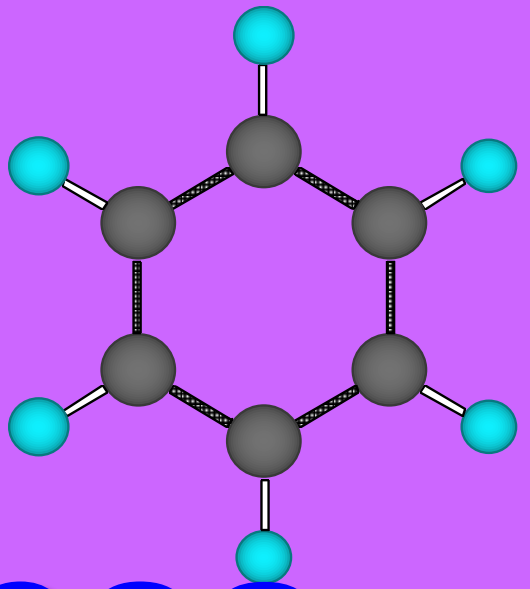
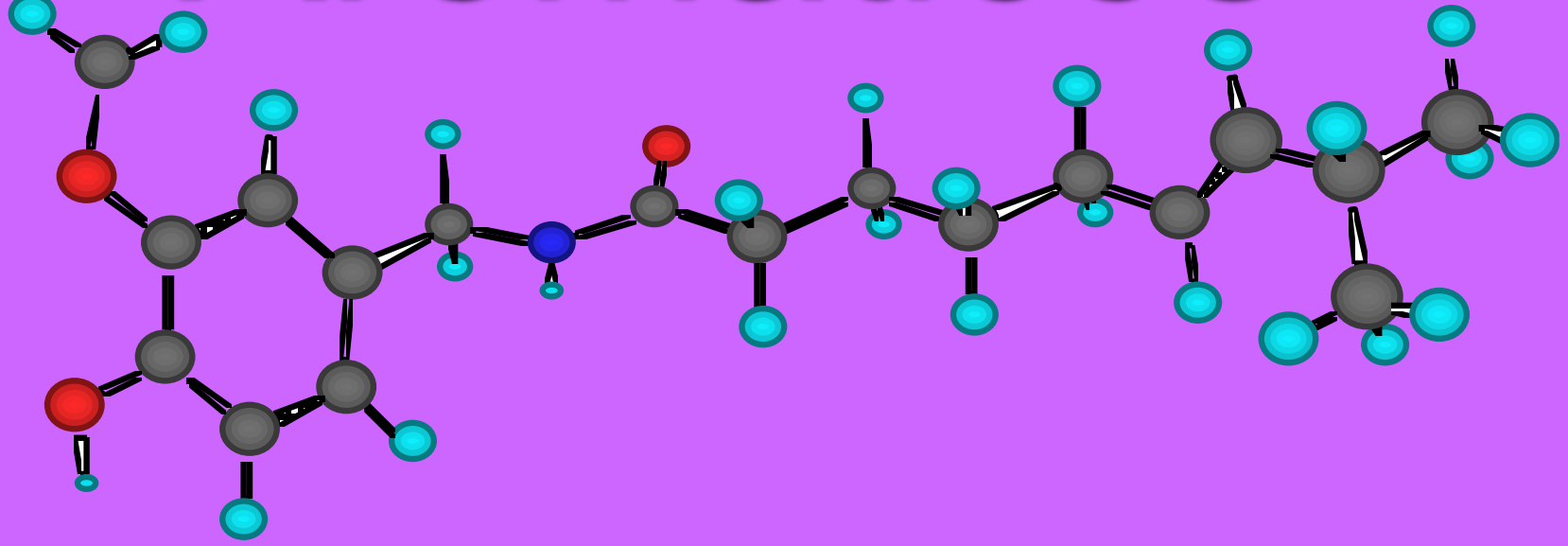


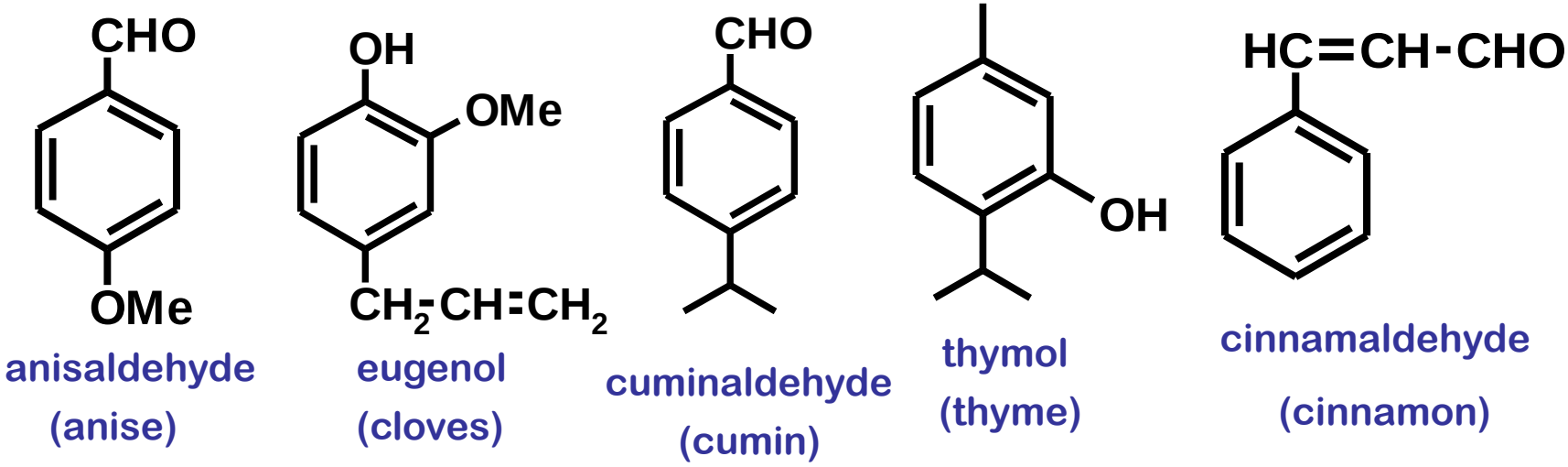


Aromáticos



Aromatic Compounds

- *Aromatic* was used to described some fragrant compounds in early 19th century
  - Not correct: later they are grouped by chemical behaviour



  - Current: distinguished from *aliphatic* compounds by electronic configuration

AROMATICITY

HÜCKEL 4n+2 RULE

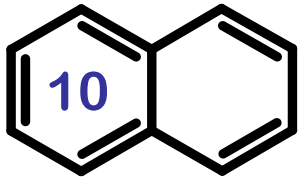
Prediction: Compounds that have 4n+2 pi electrons in a cyclic array will be aromatic.

4n+2 series = 2, 6, 10, 14, 18, 22, 26, 30 …….. etc.

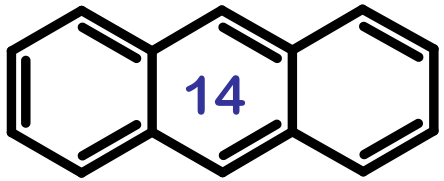
The rule was derived by observation of

POLYCYCLIC AROMATIC COMPOUNDS

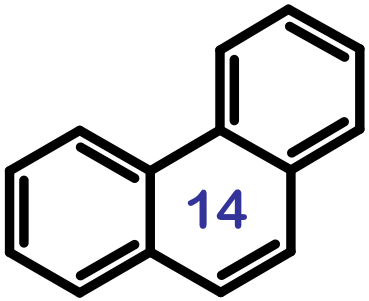
benzene

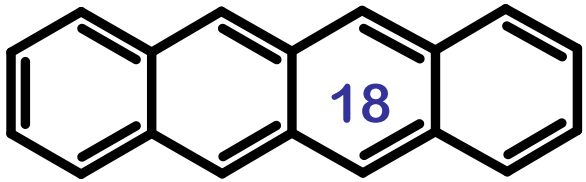


naphthalene

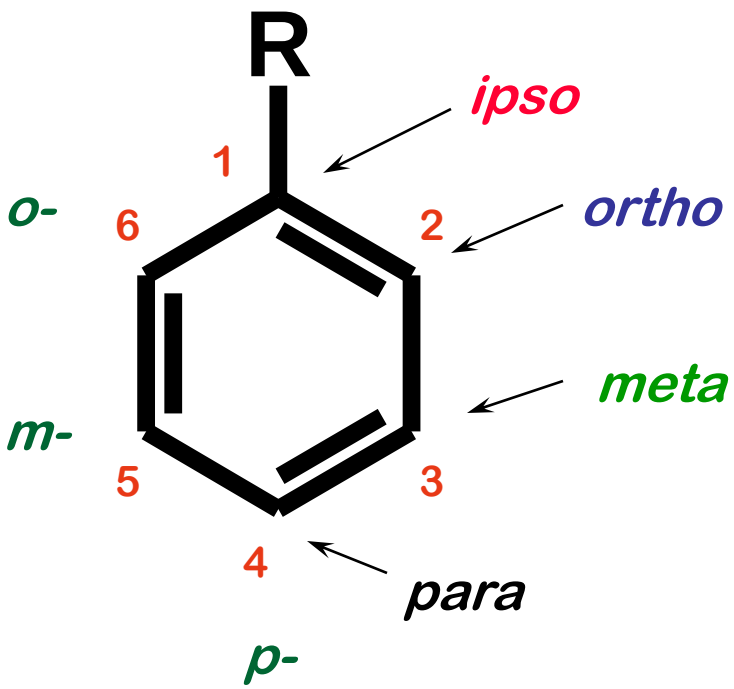


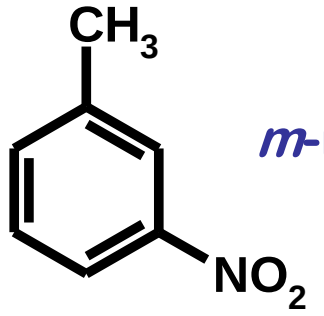
anthracene





Disubstituted Benzenes
ortho, *meta* and *para* Positions

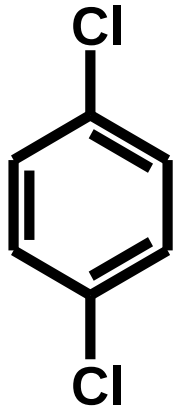




m-nitrotoluene

3-nitrotoluene

1-methyl-3-nitrobenzene



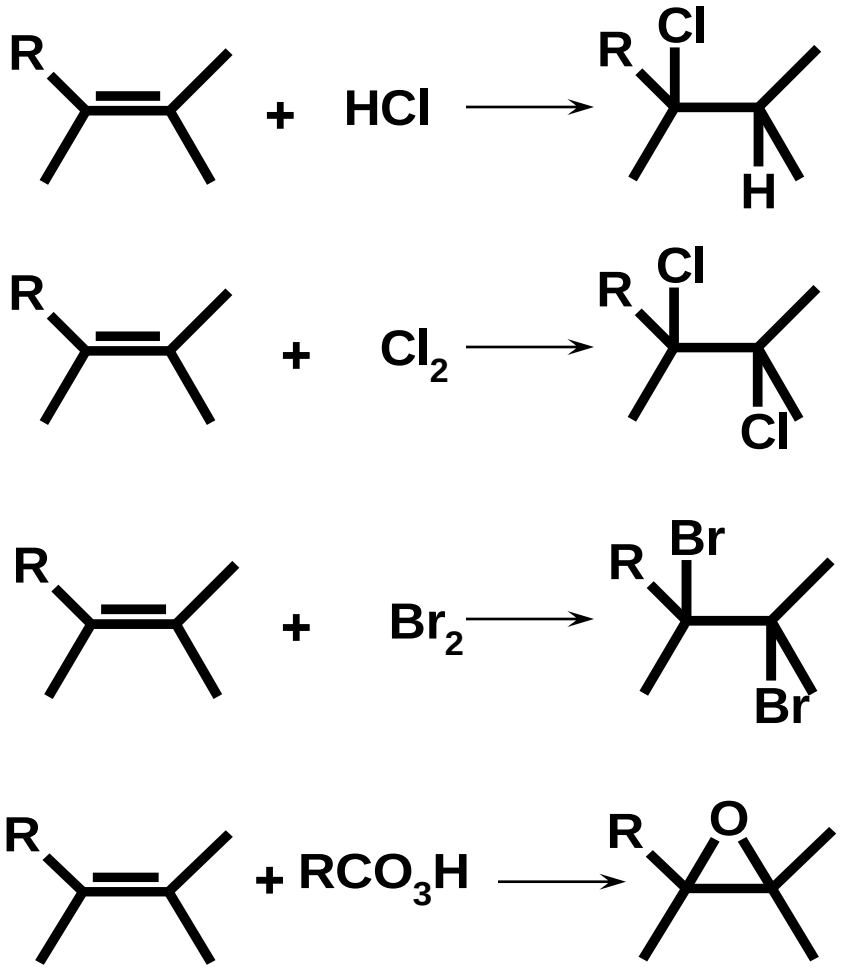
p-dichlorobenzene

1,4-dichlorobenzene

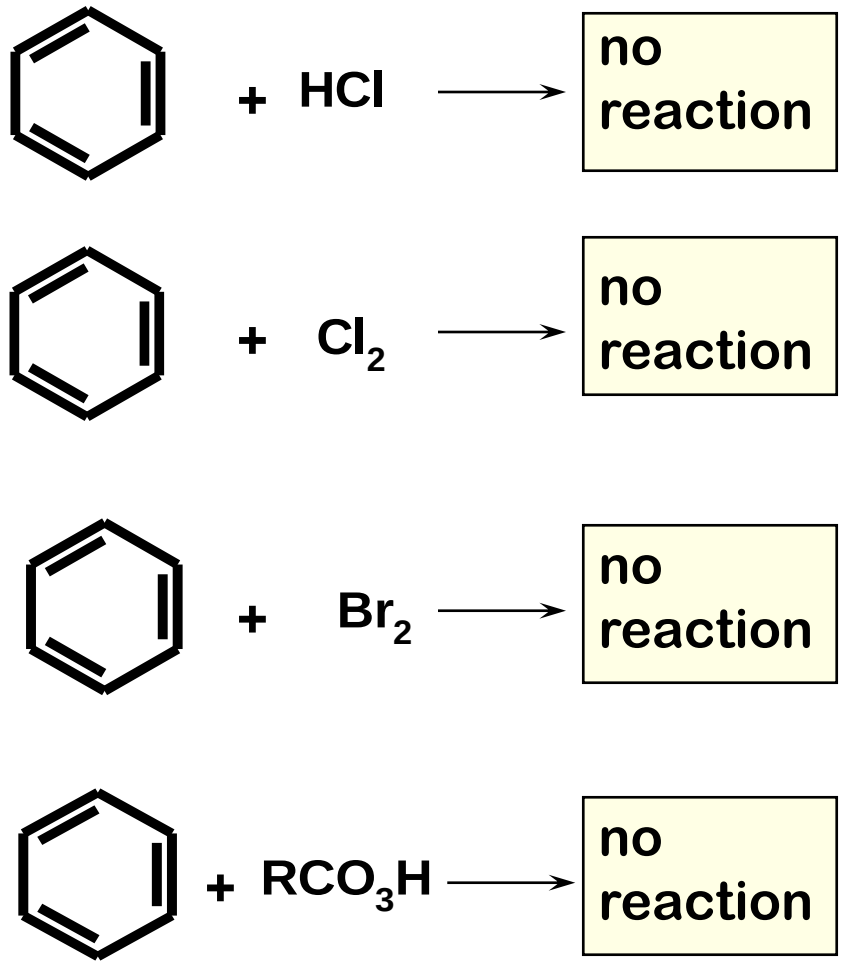

Cyclohexane
Cyclohexene
Benzene

The "Double Bonds" in a Benzene Ring Do Not React Like Others

Alkene

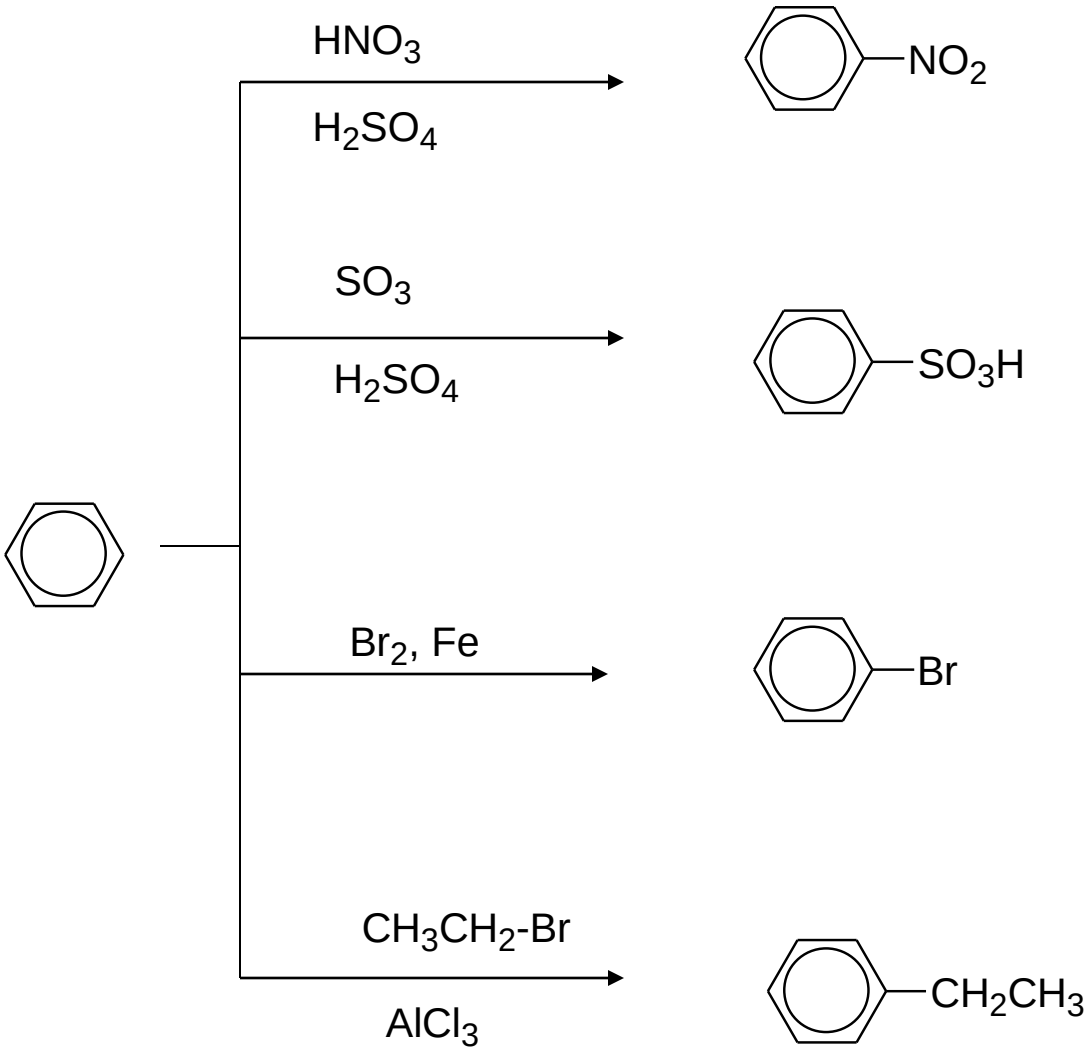


Benzene

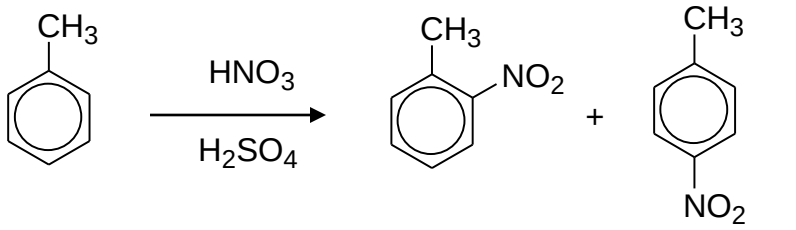


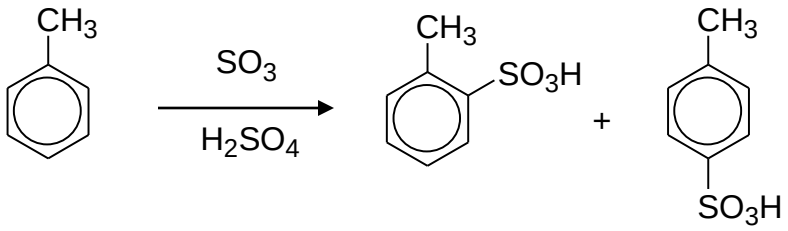
Tipos de Reações Orgânicas

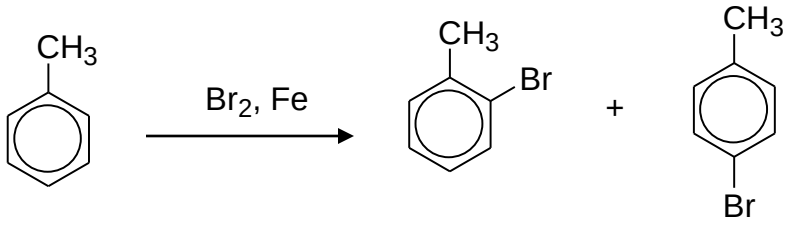
- Reações de :
  - Adição – duas moléculas se combinam
  - Eliminação – uma molécula quebra em duas
  - Substituição – partes de duas moléculas trocam
  - Rearranjo – a molécula sofre mudanças no modo como seus átomos são conectados.


HNO3
H2SO4
NO2
SO3
H2SO4
SO3H
Br2, Fe
Br
CH3CH2-Br
AlCl3
CH2CH3

toluene

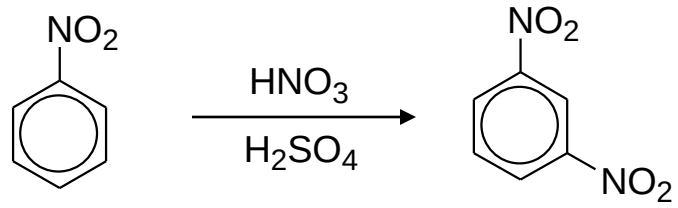


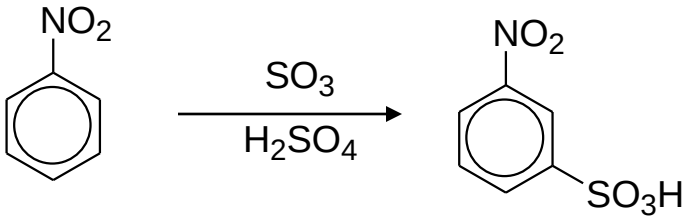


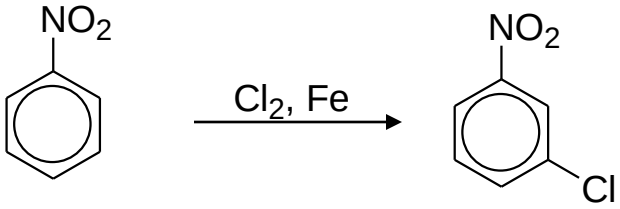


faster than the same reactions with benzene

nitrobenzene



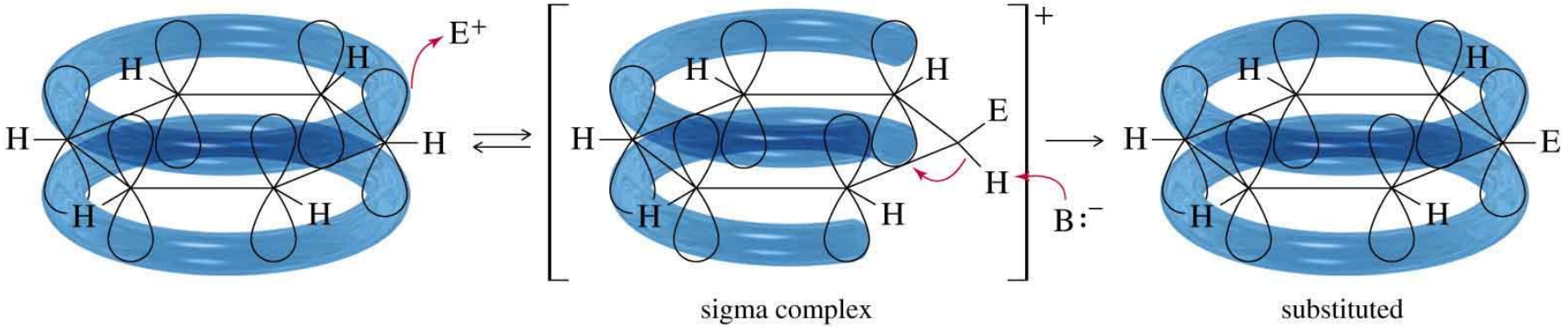




slower than the same reactions with benzene

Electrophilic Aromatic Substitution

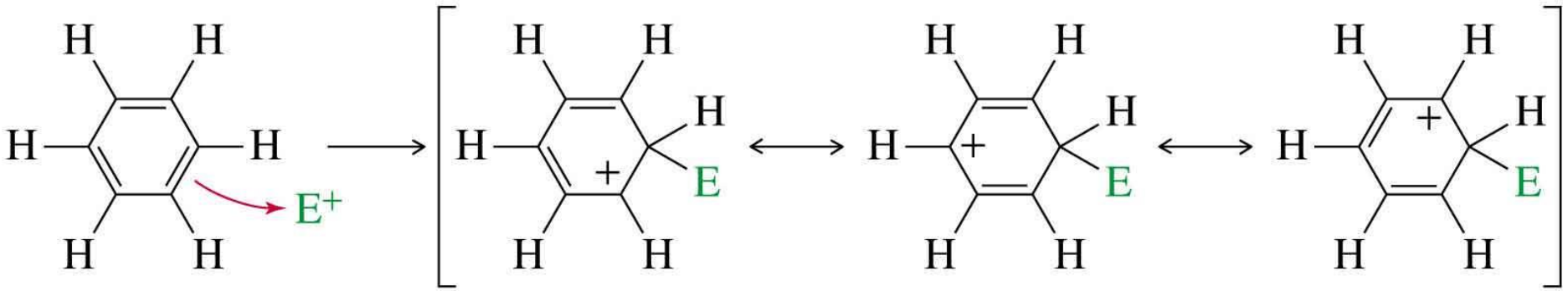
Electrophile substitutes for a hydrogen on the benzene ring.



=>

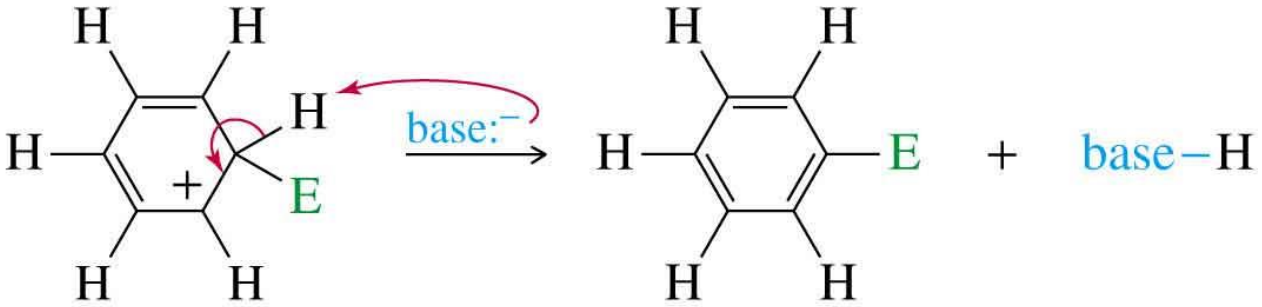
Mechanism

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



sigma complex (arenium ion)

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



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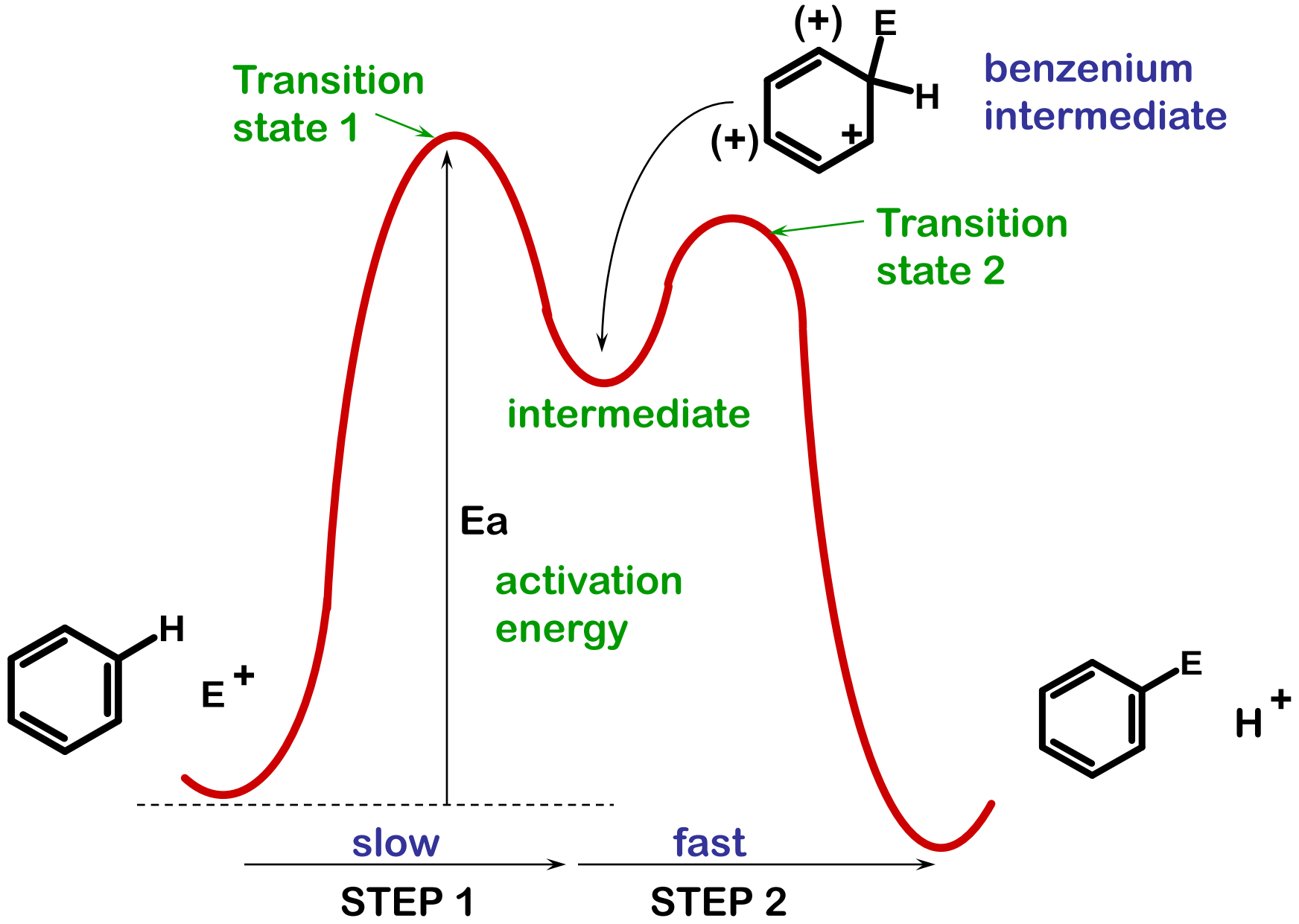
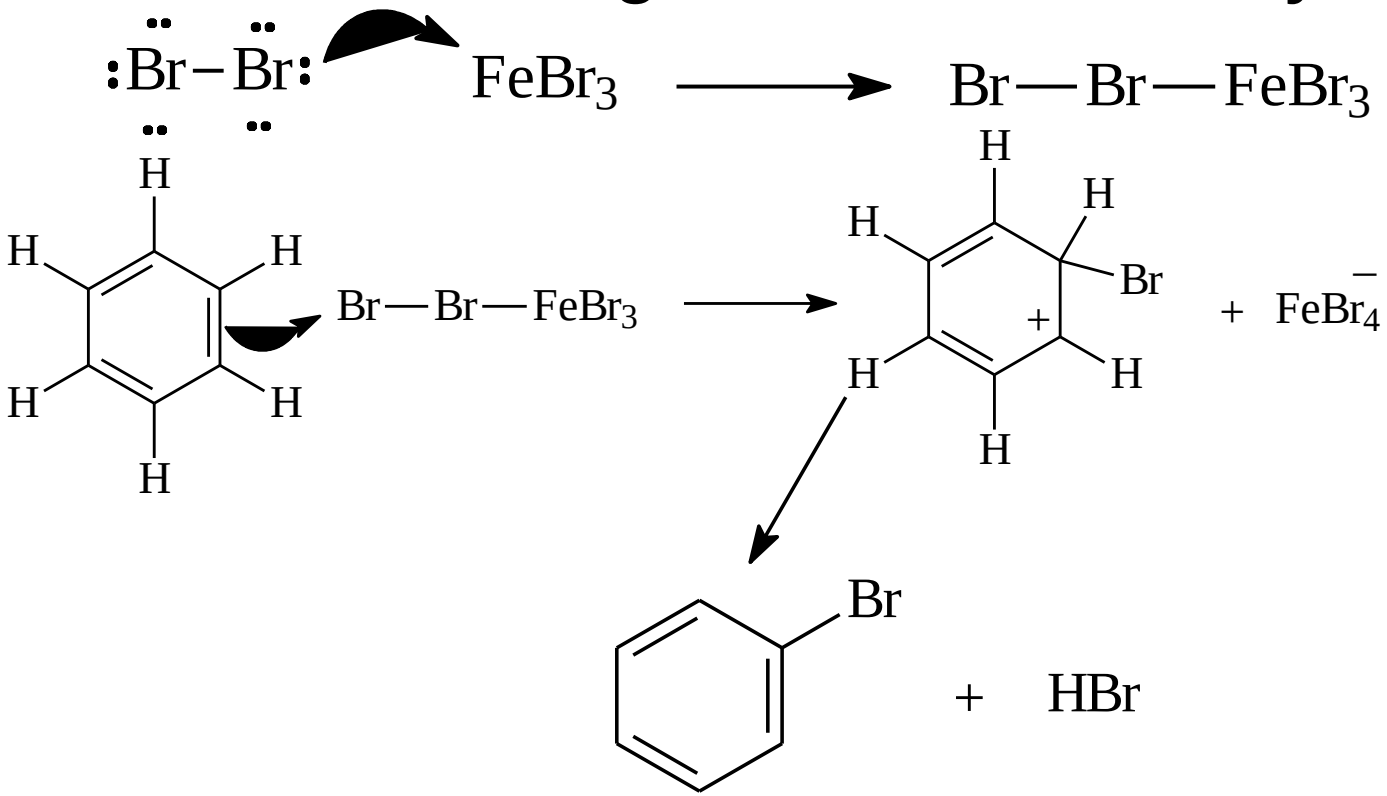
ENERGY PROFILE FOR AROMATIC SUBSTITUTION

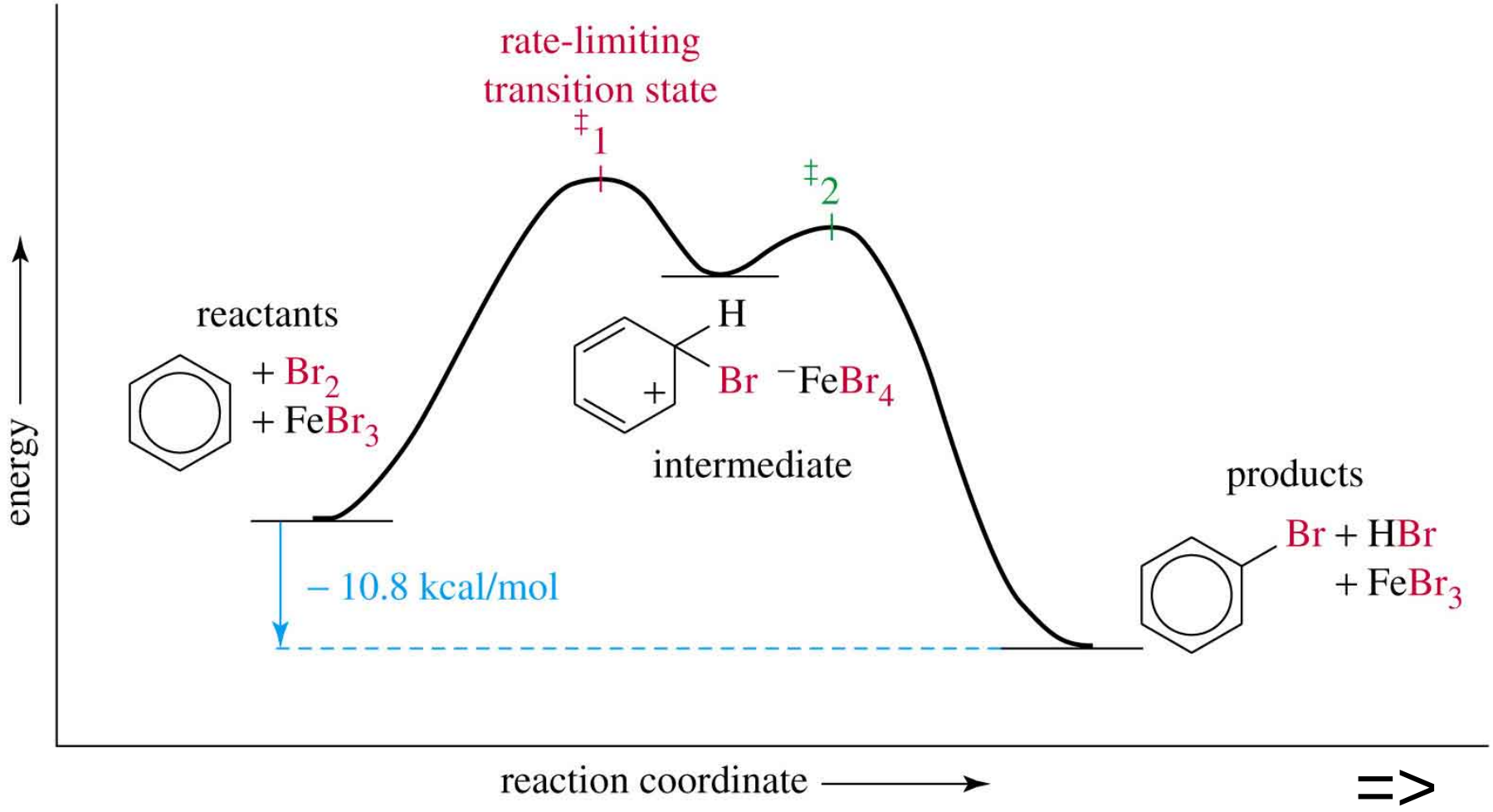


Bromination of Benzene

- Requires a stronger electrophile than Br_2.
- Use a strong Lewis acid catalyst, $FeBr_3$.



Energy Diagram for Bromination



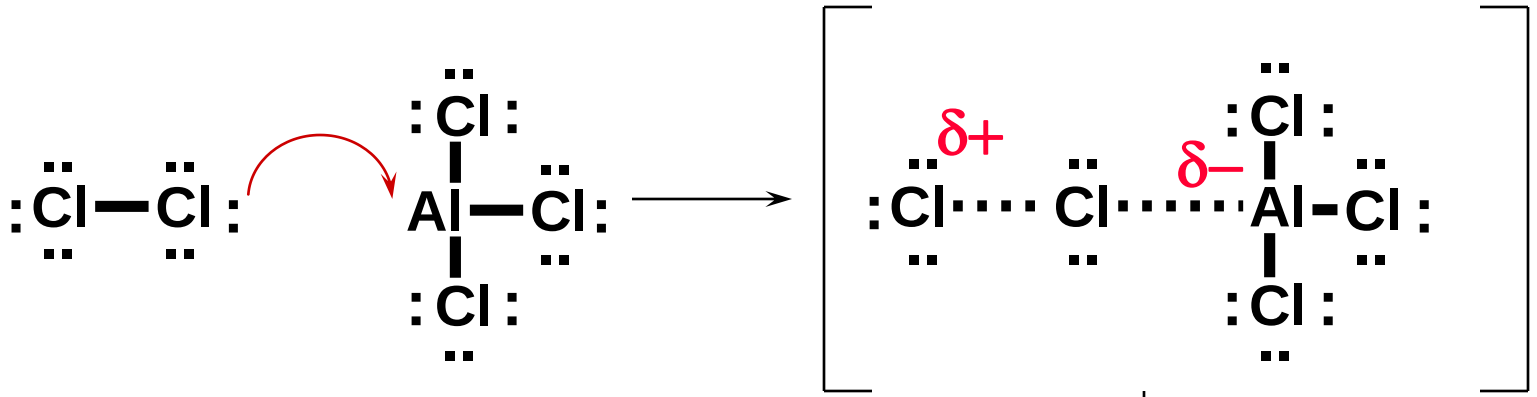
Chlorination and Iodination

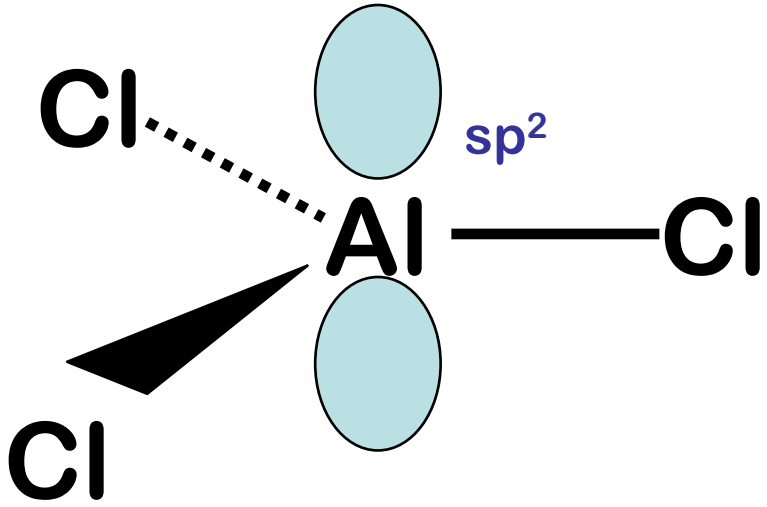
- Chlorination is similar to bromination. Use $AlCl_3$ as the Lewis acid catalyst.
- Iodination requires an acidic oxidizing agent, like nitric acid, which oxidizes the iodine to an iodonium ion.

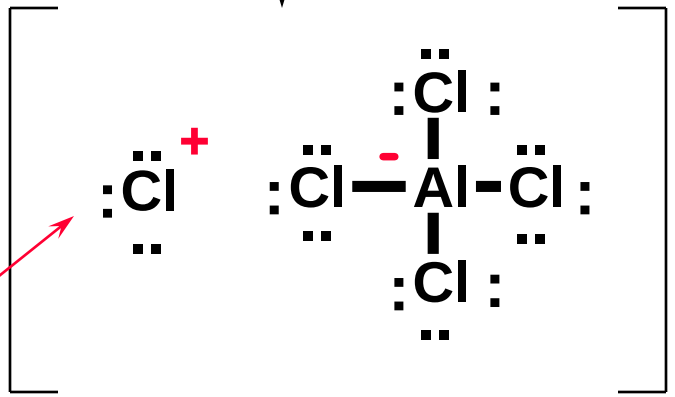
$$H^+ + HNO_3 + {}^1/_2\, I_2 \longrightarrow I^+ + NO_2 + H_2O$$

=>

Formation of the Chloronium Ion Complex

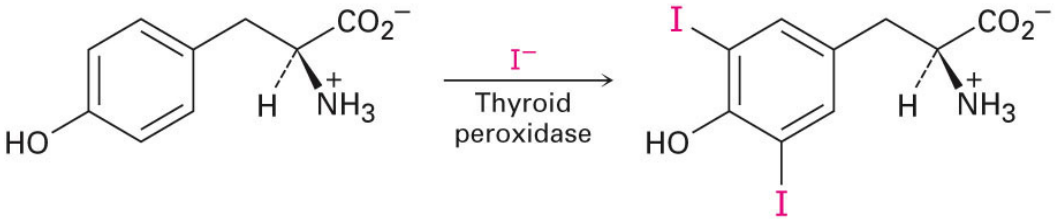






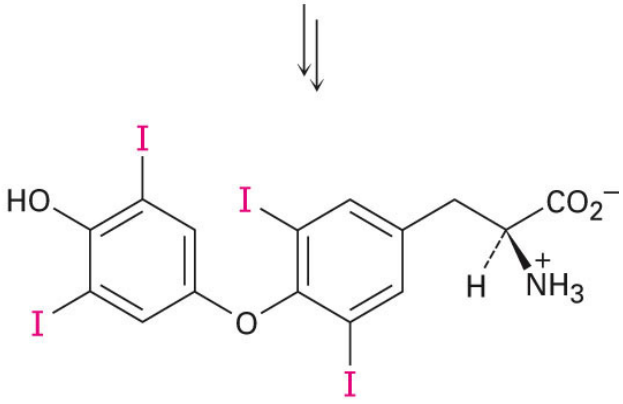
chloronium
ion complex

Electrophilic aromatic halogenations occur in the biosynthesis of numerous naturally occurring molecules, particularly those produced by marine organisms



Tyrosine **3,5-Diiodotyrosine**

– Thyroxine, synthesized in the thyroid gland in humans, is a thyroid hormone involved in regulating growth and metabolism

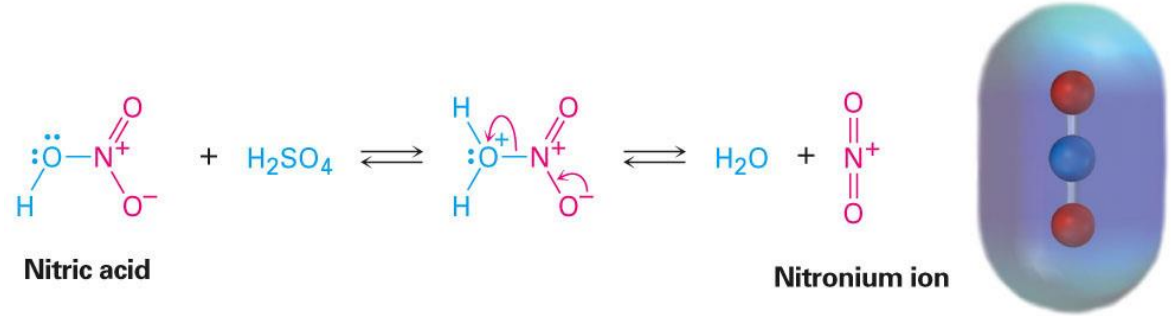


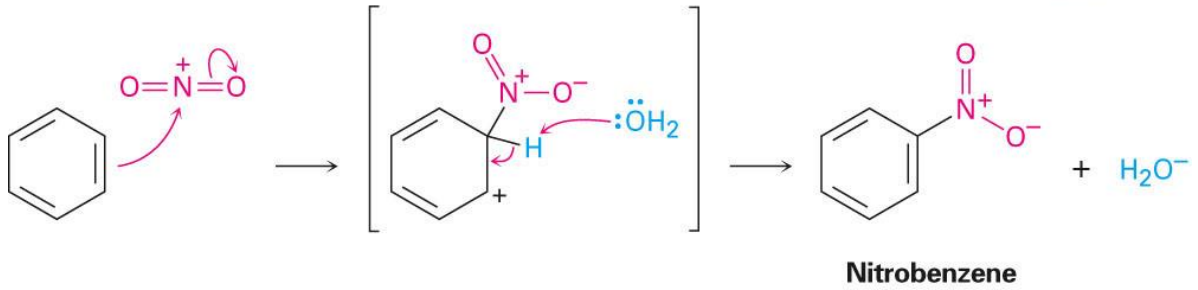
Thyroxine (a thyroid hormone)

Reactions of Aromatic Compounds: Electrophilic Substitution

Aromatic Nitration

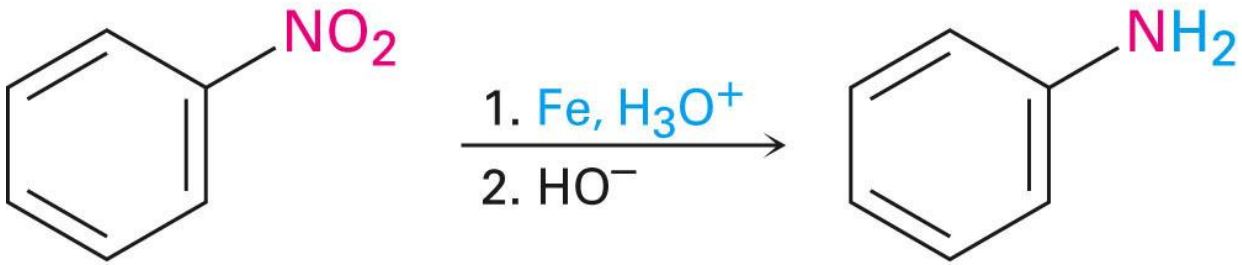
- Aromatic rings can be nitrated with a mixture of concentrated nitric and sulfuric acids
  - The electrophile is the nitronium ion, NO^{2+} which is generated from HNO_3 by protonation and loss of water
  - The nitronium ion reacts with benzene to yield a carbocation intermediate, and loss of H^+
  - The product is a neutral substitution product, nitrobenzene





Aromatic nitration

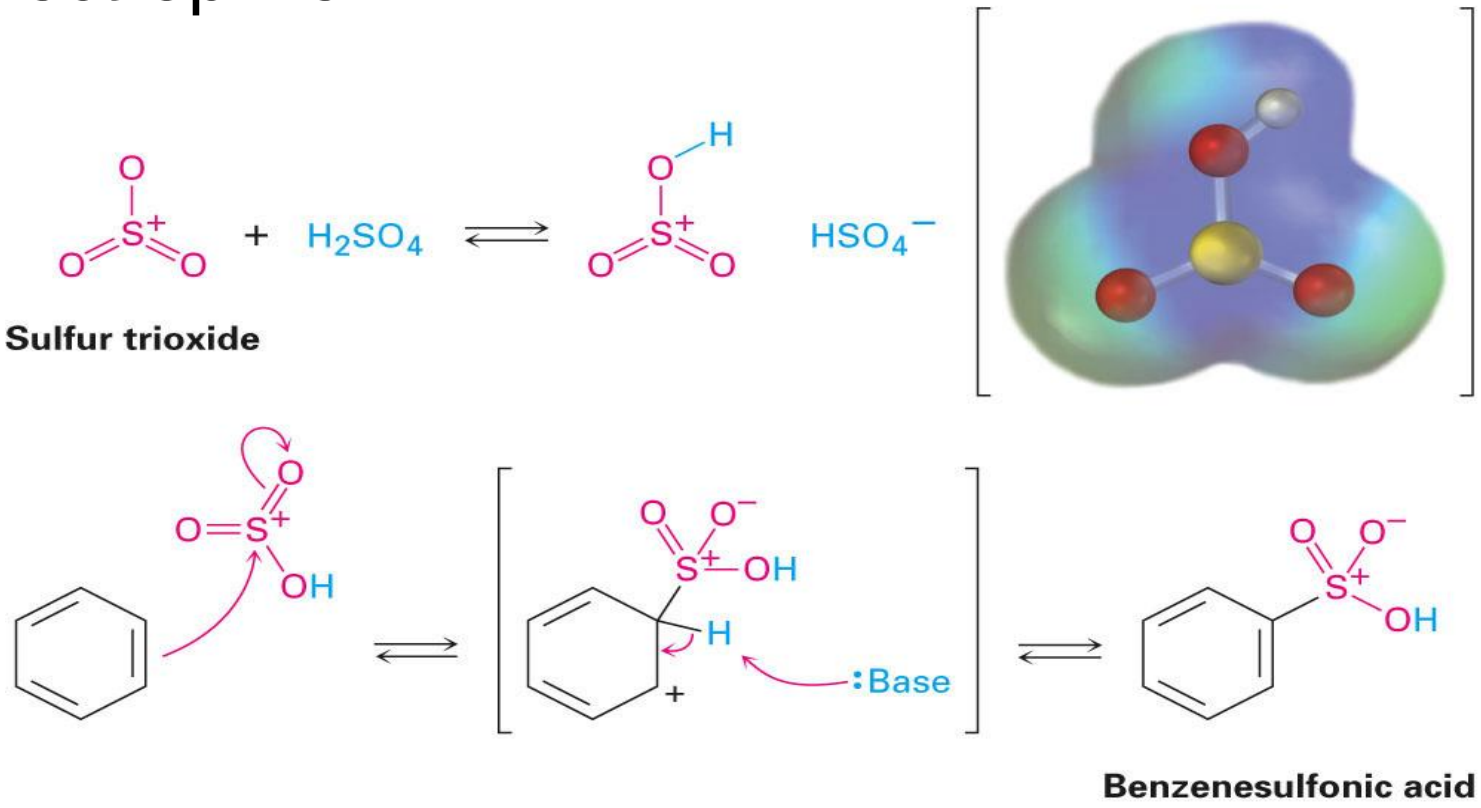
- Does not occur naturally
- Important in the laboratory
  - The nitro-substituted product can be reduced by reagents such as iron or tin metal or to yield an *arylamine*, $ArNH_2$
  - Attachment of an amino group to an aromatic ring by the two-step nitration-reduction sequence is a key part of the industrial synthesis of many dyes and pharmaceutical agents



Nitrobenzene **Aniline (95%)**

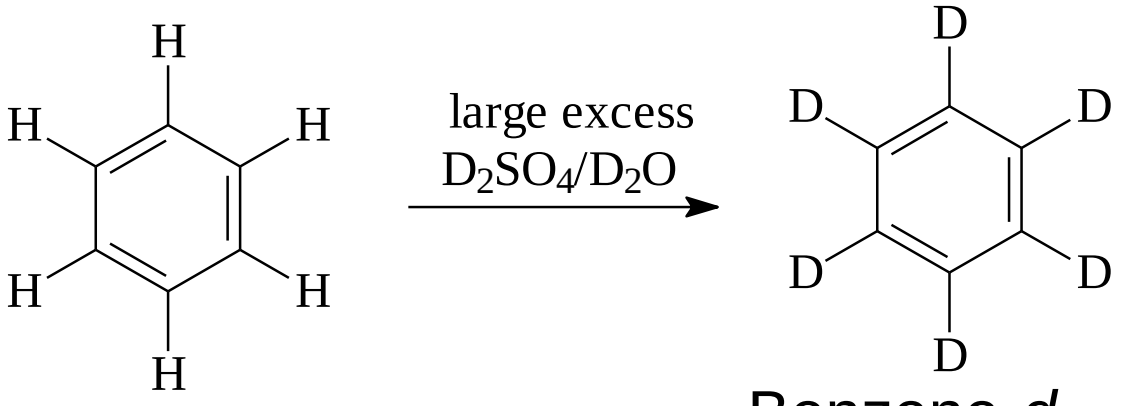
The mechanism of electrophilic sulfonation of an aromatic ring

- Sulfur trioxide, SO_3, in fuming sulfuric acid is the electrophile.



Desulfonation

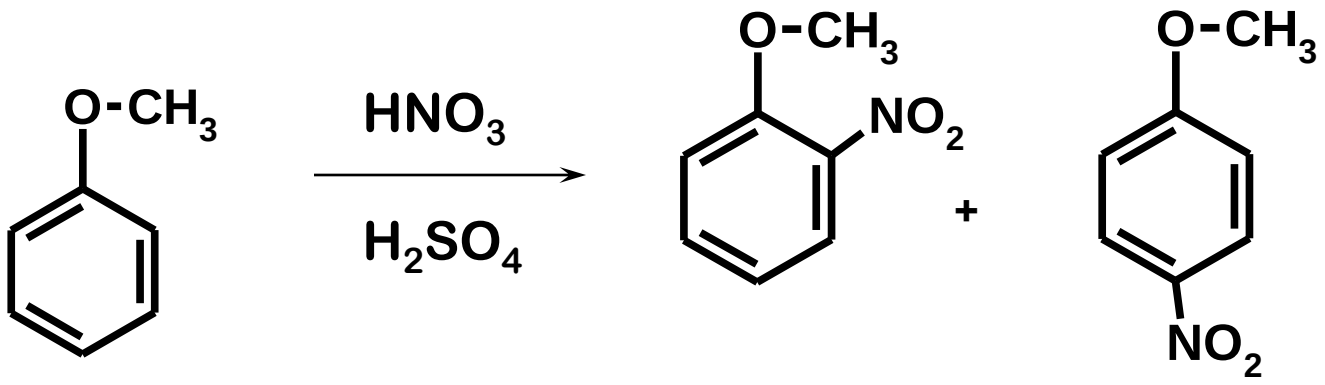
- All steps are reversible, so sulfonic acid group can be removed by heating in dilute sulfuric acid.
- This process is used to place deuterium in place of hydrogen on benzene ring.



Benzene-d_6

=>

Nitration of Anisole



anisole *ortho* *para*

Reacts faster than benzene = "ACTIVATED"

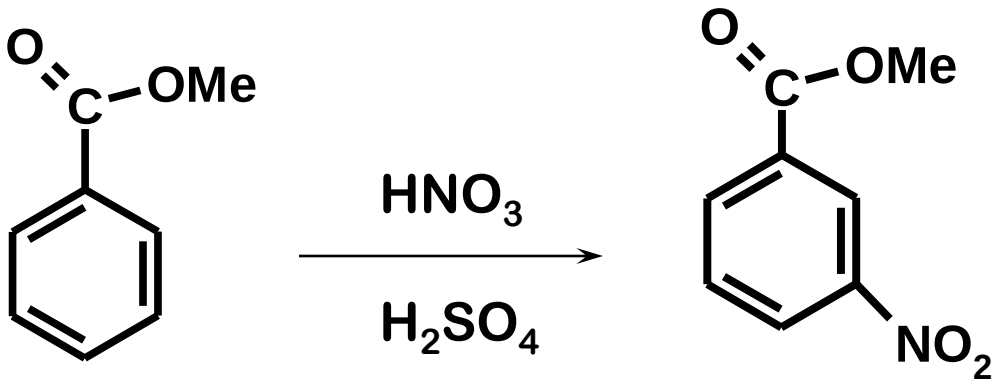
The -OCH_3 group when it preexists on the ring gives only *ortho* and *para* products, and no meta.

Substituents that cause this result are called *o,p* directors

and they usually activate the ring.

DEACTIVATED RING

Nitration of Methyl Benzoate



methyl benzoate

meta

Reacts slower than benzene = "DEACTIVATED"

The -COOMe group when it preexists on the ring gives only *meta*, and no *ortho* or *para* products.

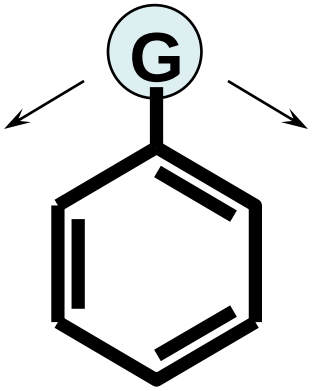
Substituents that cause this result are called *m* directors and they usually deactivate the ring.

SUBSTITUENT CATEGORIES

Most ring substituents fall into one of these two categories:

o,p - directors

activate the ring



m- directors

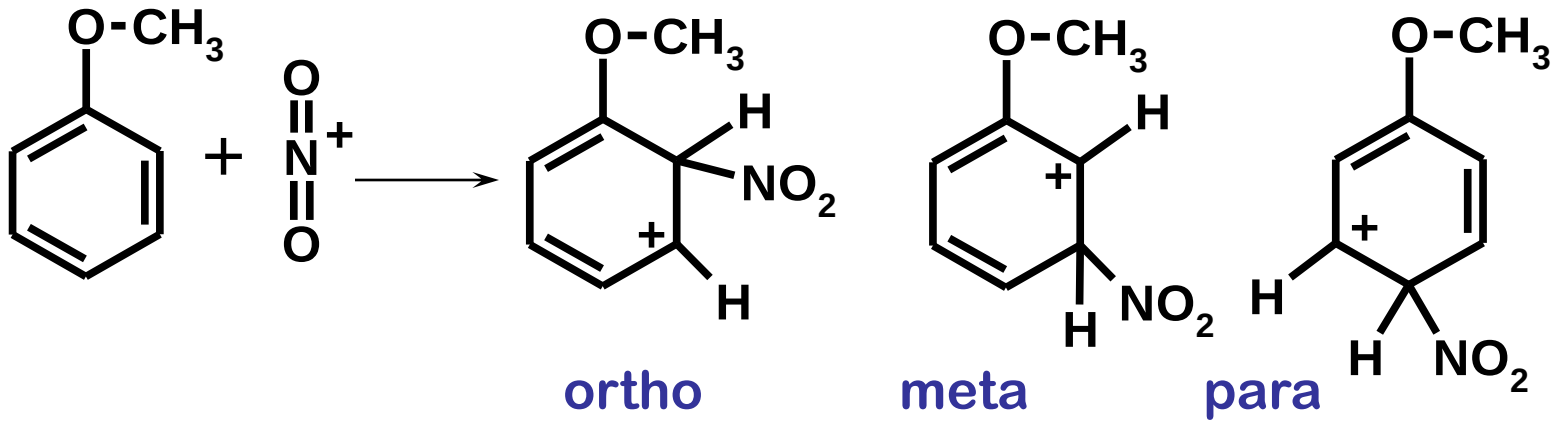
deactivate the ring

We will look at one of each kind in order to understand the difference.....

NITRATION OF ANISOLE

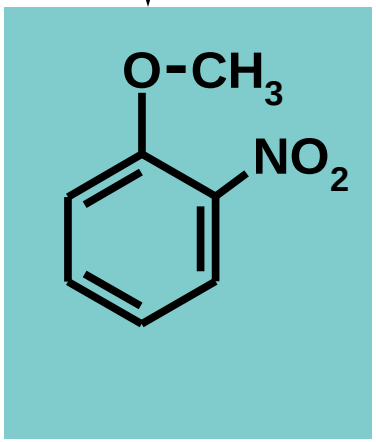
Nitration of Anisole

BENZENIUM ION INTERMEDIATES



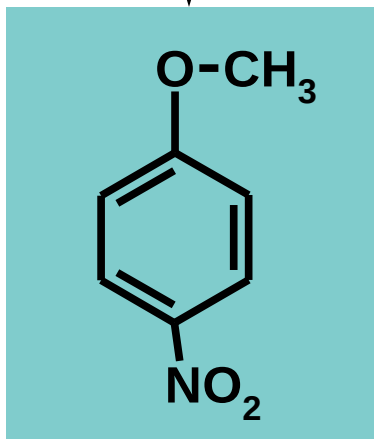
ortho meta para

activated ring

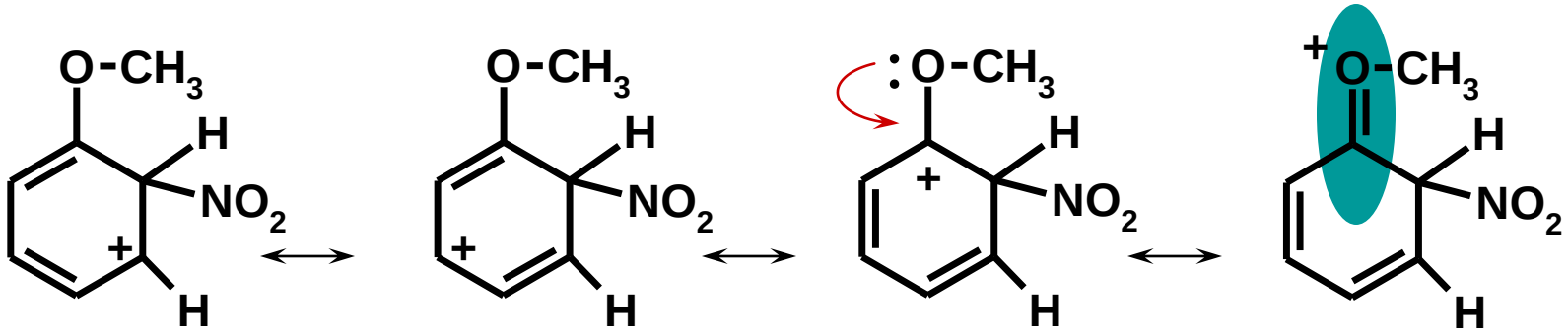


actual products

ortho + para

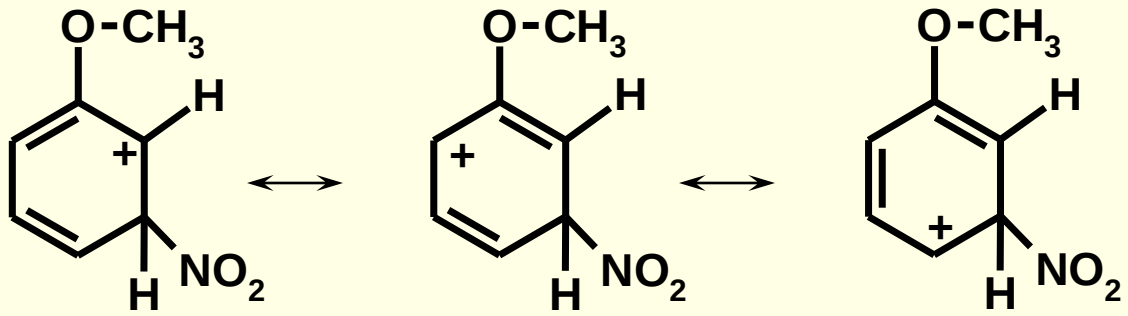


ortho

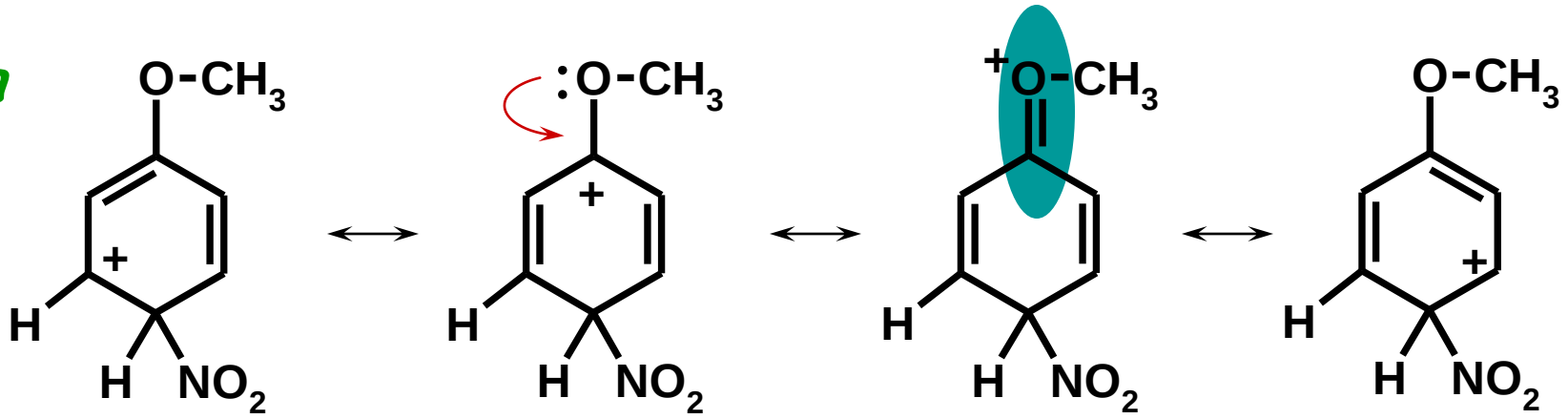


EXTRA!

meta



para

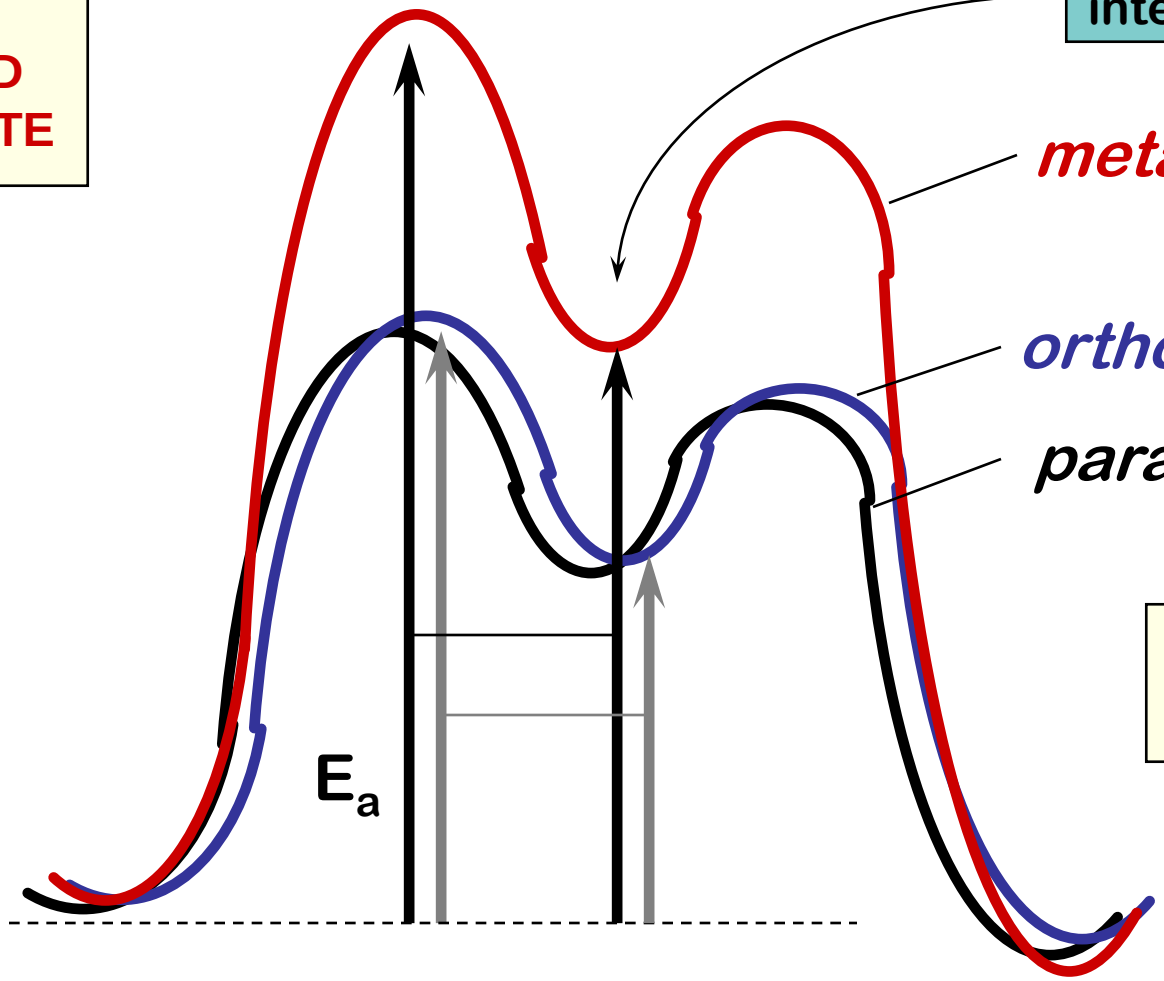


EXTRA!

Energy Profiles

NITRATION OF ANISOLE

RECALL: HAMMOND POSTULATE



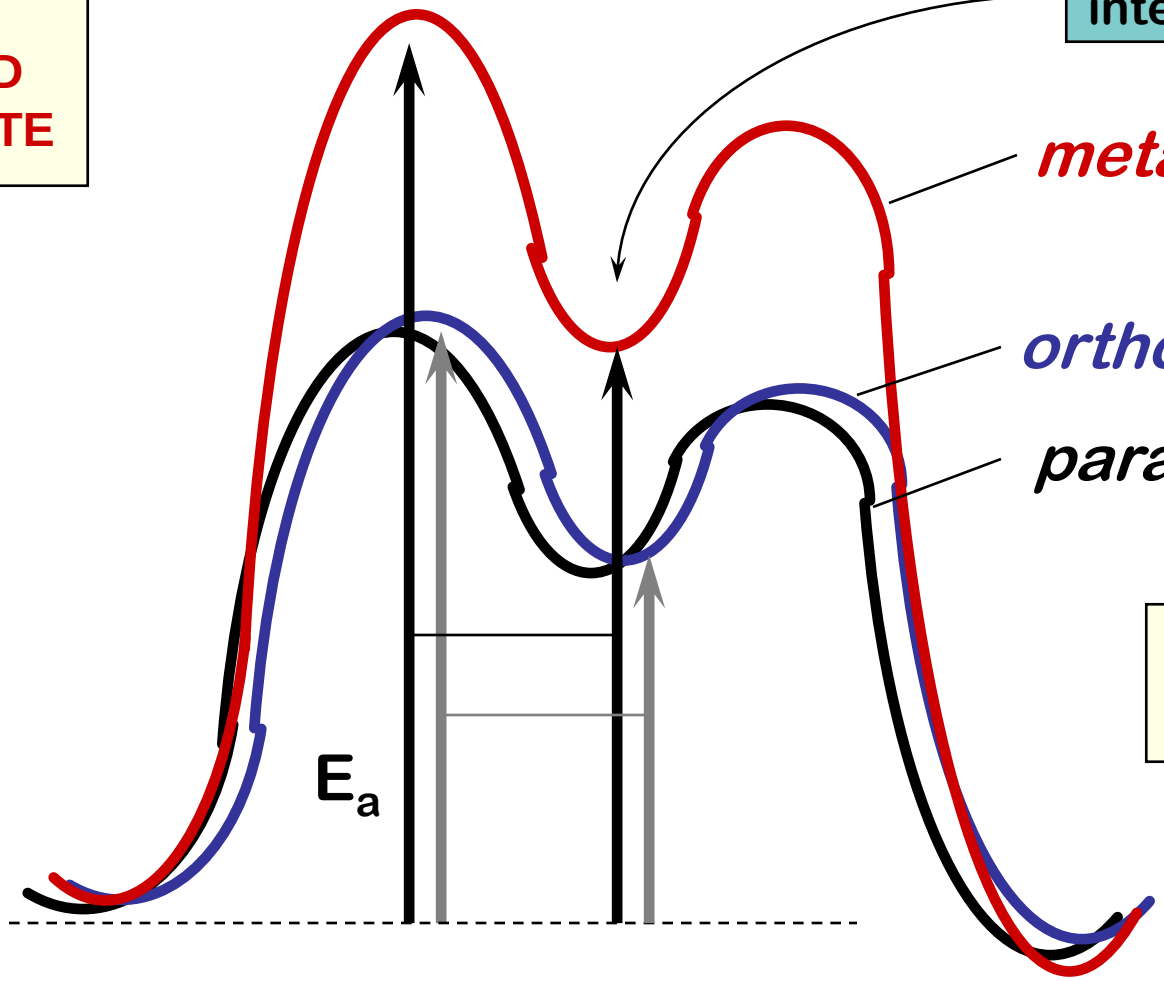
benzenium intermediates have more resonance

ortho-para director

Energy Profiles

NITRATION OF ANISOLE

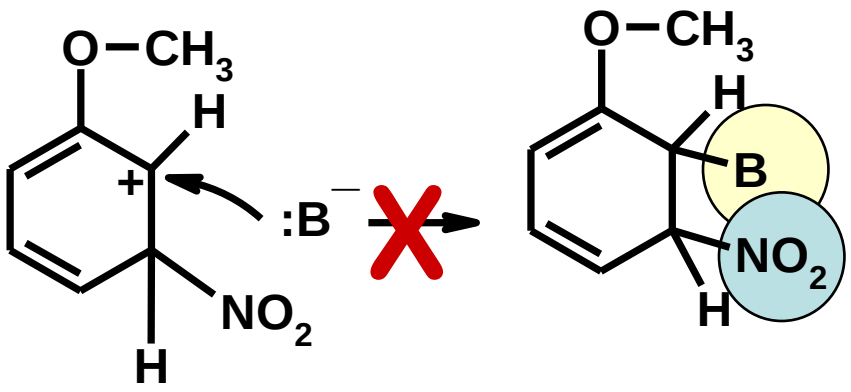
RECALL: HAMMOND POSTULATE



benzenium intermediates have more resonance

ortho-para director

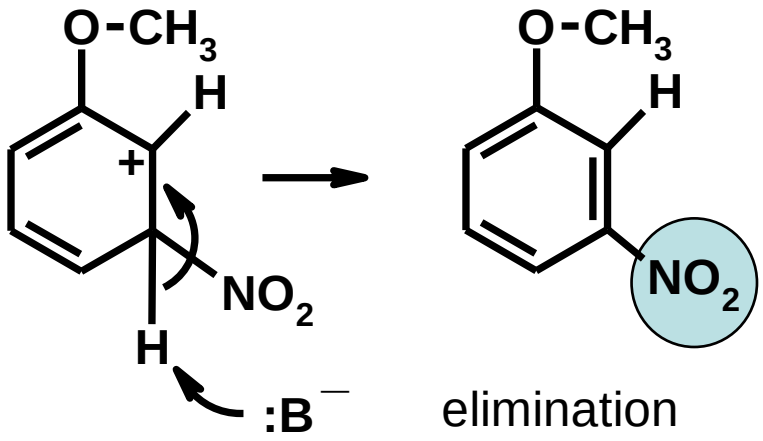
BENZENIUM IONS GIVE ELIMINATION INSTEAD OF ADDITION



addition

ADDITION REACTION

doesn't happen
resonance would be lost



elimination

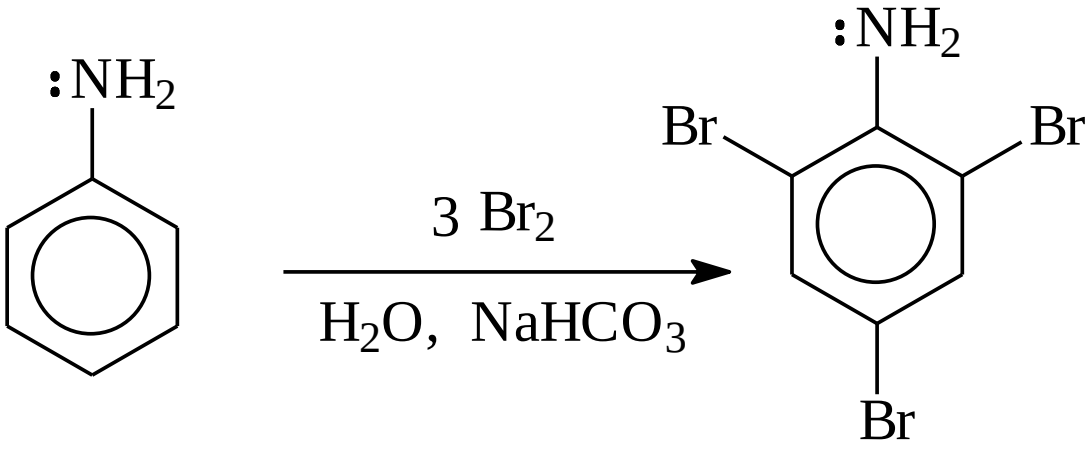
ELIMINATION REACTION

restores aromatic ring resonance

(36 Kcal / mole)

The Amino Group

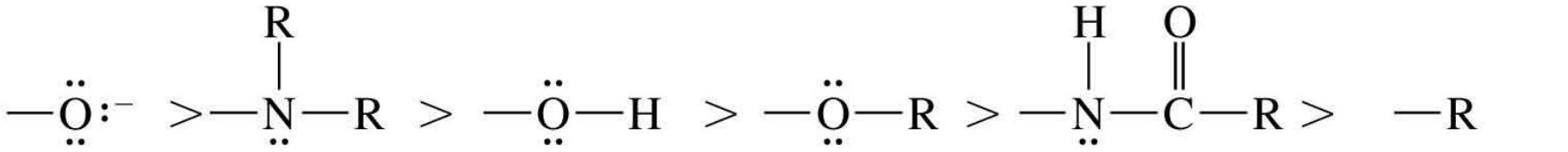
Aniline reacts with bromine water (without a catalyst) to yield the tribromide. Sodium bicarbonate is added to neutralize the HBr that's also formed.



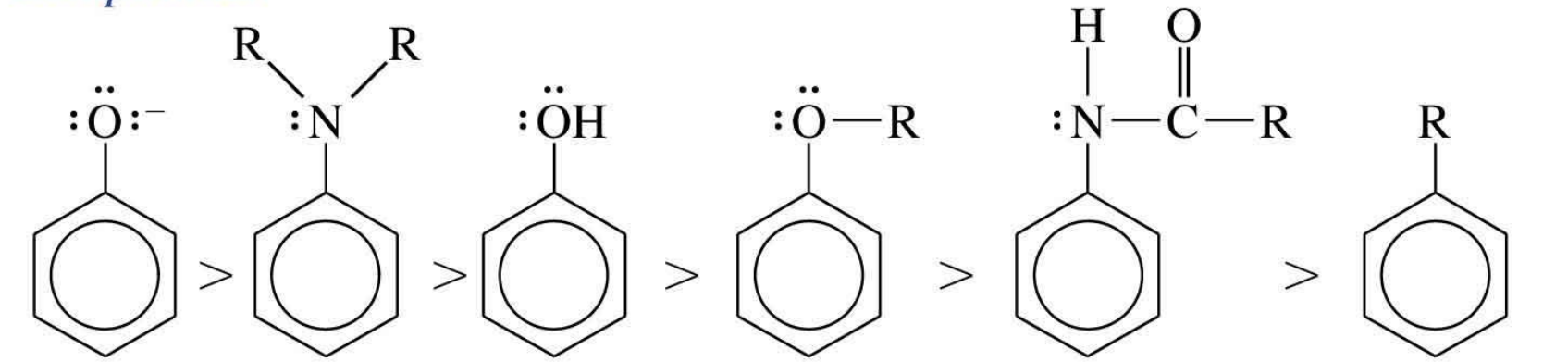
=>

Summary of Activators

Groups:



Compounds:



phenoxides anilines phenols phenyl ethers anilides alkylbenzenes

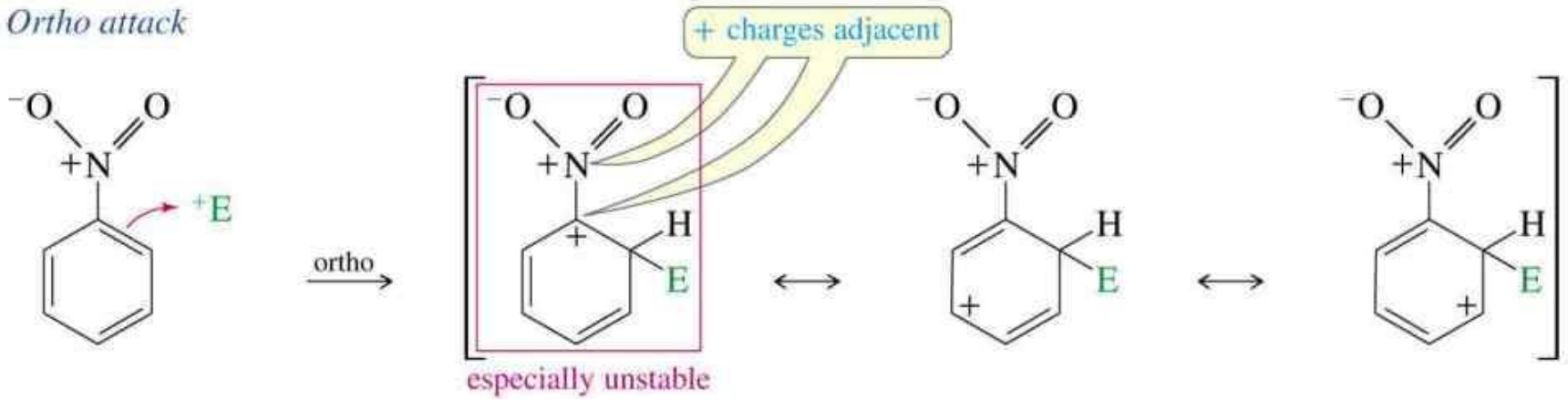
=>

Deactivating Meta-Directing Substituents

- Electrophilic substitution reactions for nitrobenzene are 100,000 times slower than for benzene.
- The product mix contains mostly the meta isomer, only small amounts of the ortho and para isomers.
- Meta-directors deactivate all positions on the ring, but the meta position is less deactivated.

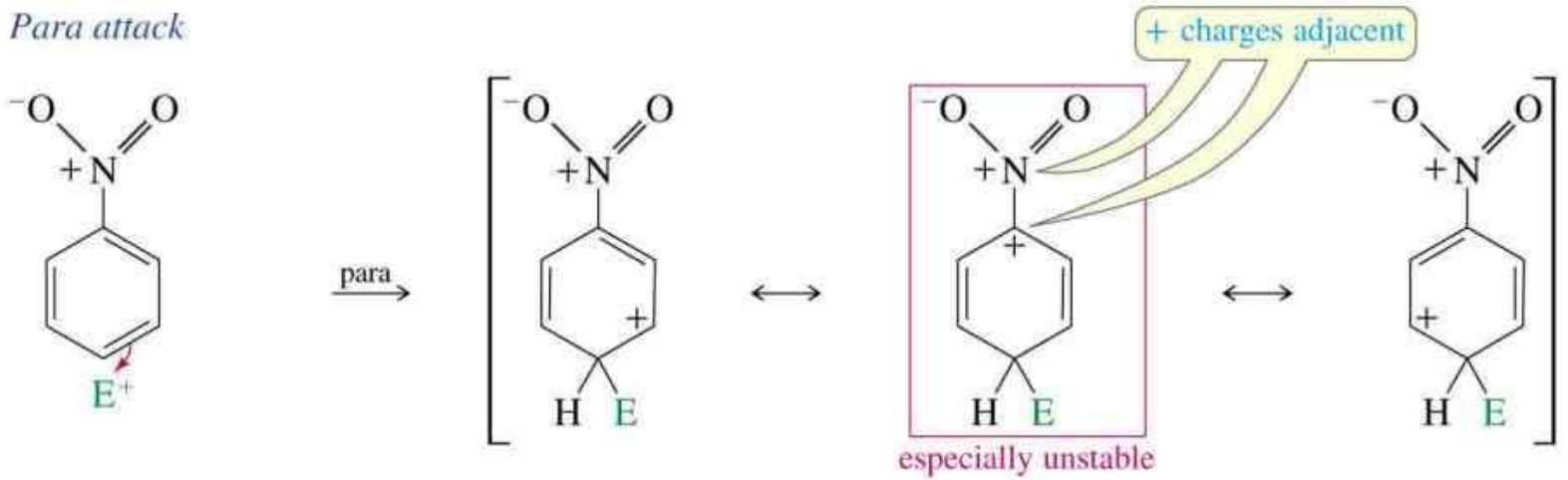
=>

Ortho Substitution on Nitrobenzene



=>

Para Substitution on Nitrobenzene



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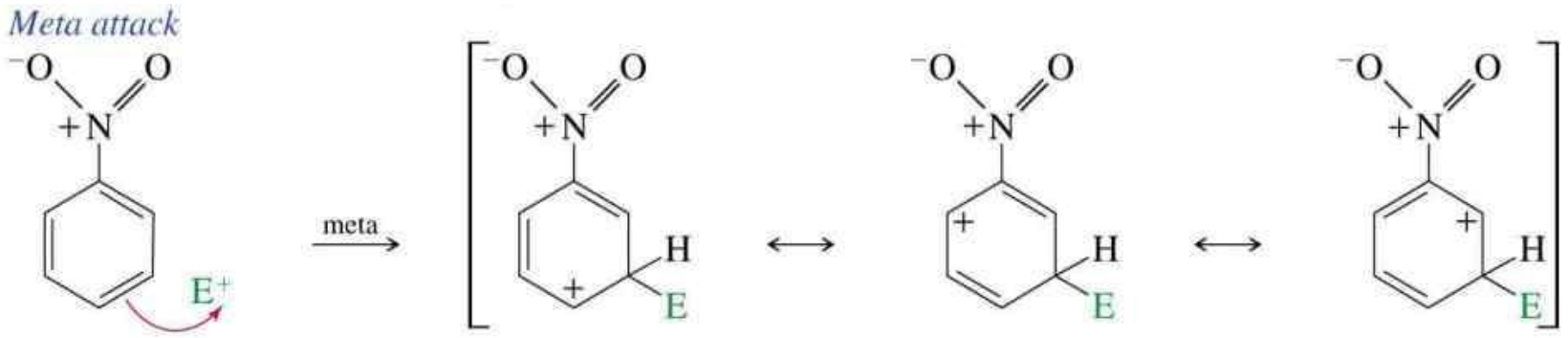
Meta Substitution on Nitrobenzene



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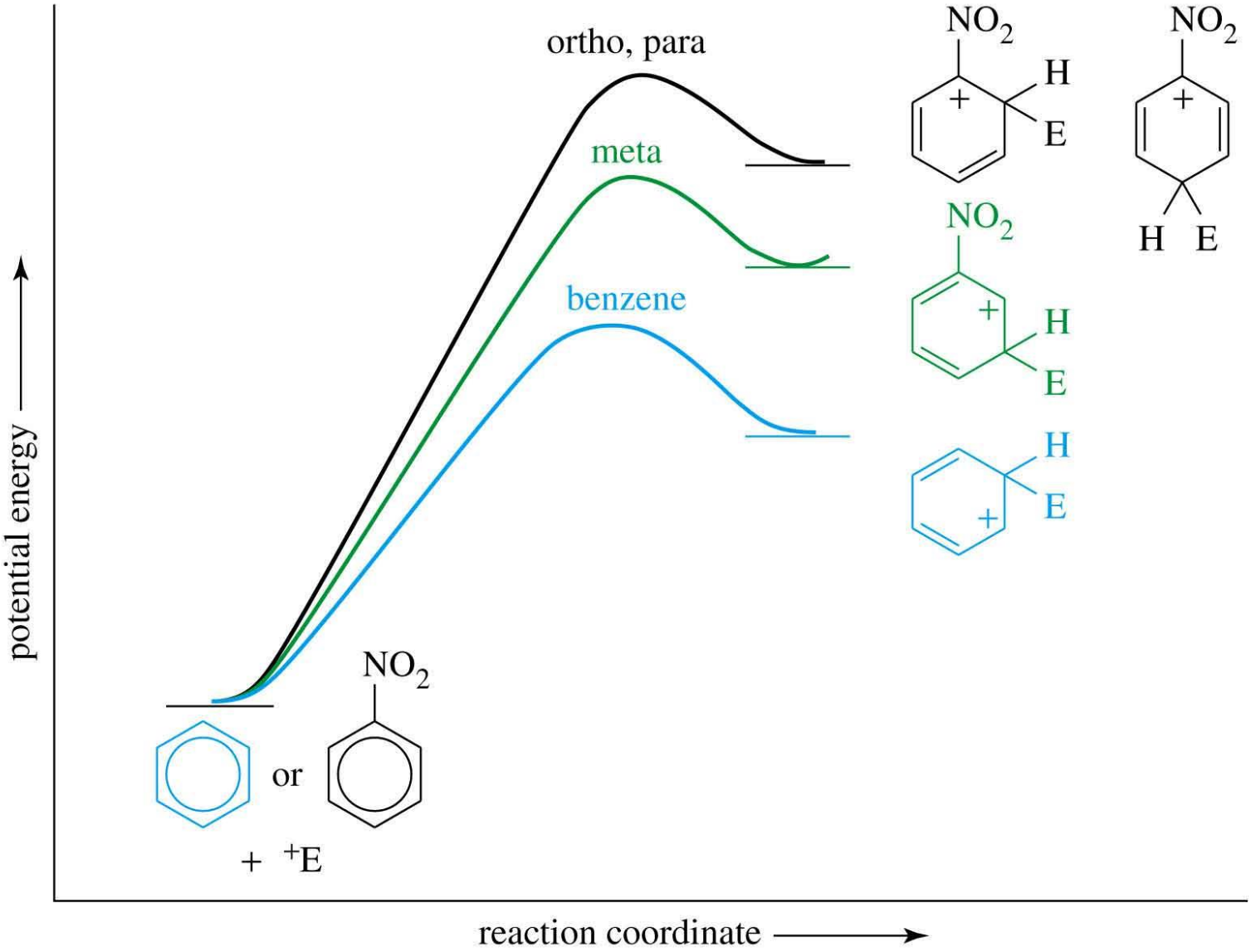
Energy Diagram



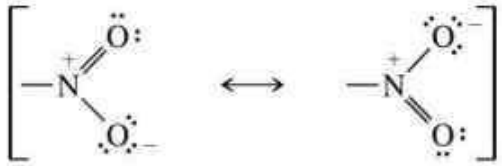
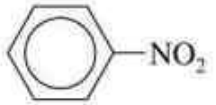
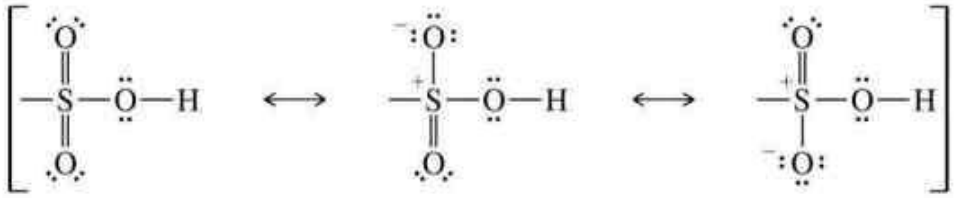
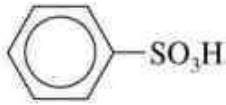
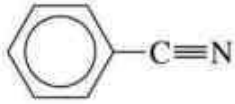
=>

Structure of Meta-Directing Deactivators

- The atom attached to the aromatic ring will have a partial positive charge.
- Electron density is withdrawn inductively along the sigma bond, so the ring is less electron-rich than benzene.

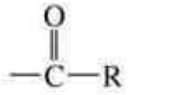
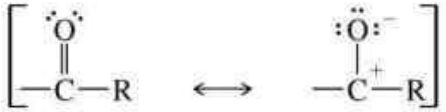
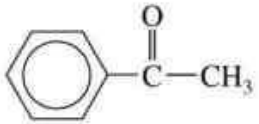
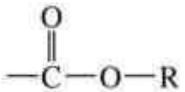
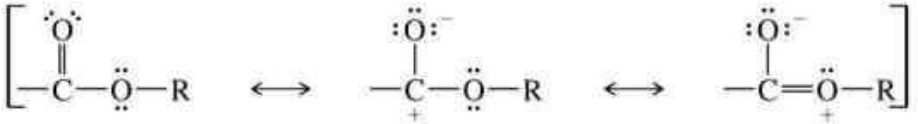
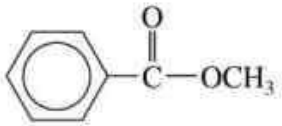
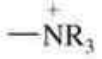
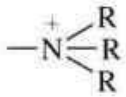
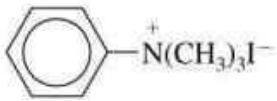
=>

Summary of Deactivators

Group	*Resonance Forms*	*Example*
—NO_2 nitro		 nitrobenzene
—SO_3H sulfonic acid		 benzenesulfonic acid
—C≡N: cyano		 benzonitrile

=>

More Deactivators

Group	*Resonance Forms*	*Example*
 ketone or aldehyde		 acetophenone
 ester		 methyl benzoate
 quaternary ammonium		 trimethylanilinium iodide

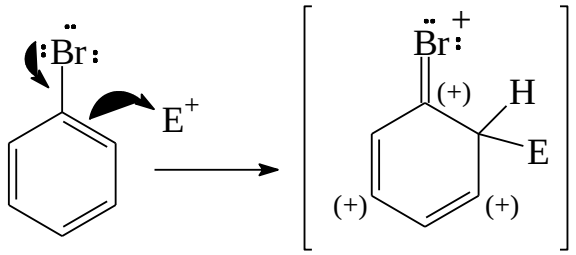
=>

Halobenzenes

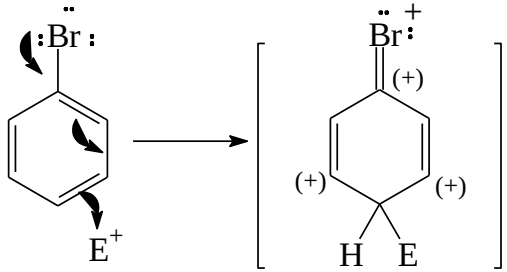
- Halogens are deactivating toward electrophilic substitution, but are ortho, para-directing!
- Since halogens are very electronegative, they withdraw electron density from the ring inductively along the sigma bond.
- But halogens have lone pairs of electrons that can stabilize the sigma complex by resonance. =>

Sigma Complex for Bromobenzene

Ortho attack

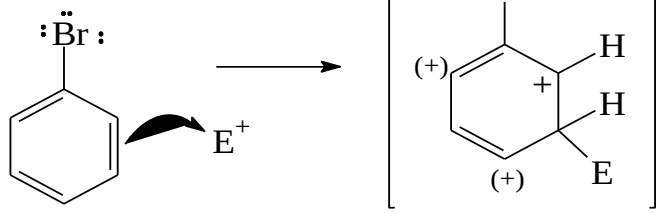


Para attack



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

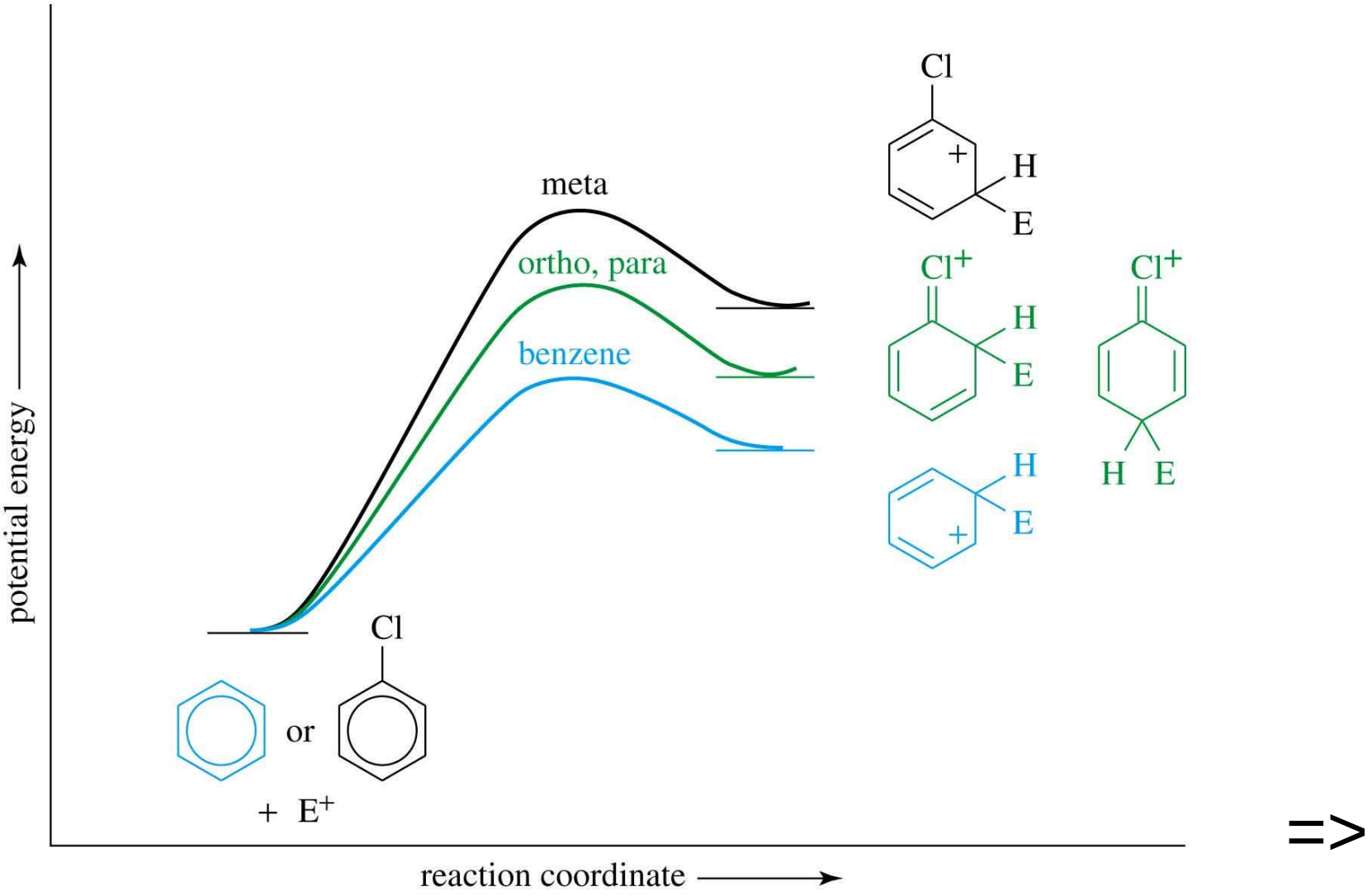
Meta attack



No bromonium ion possible with meta attack.

=>

Energy Diagram



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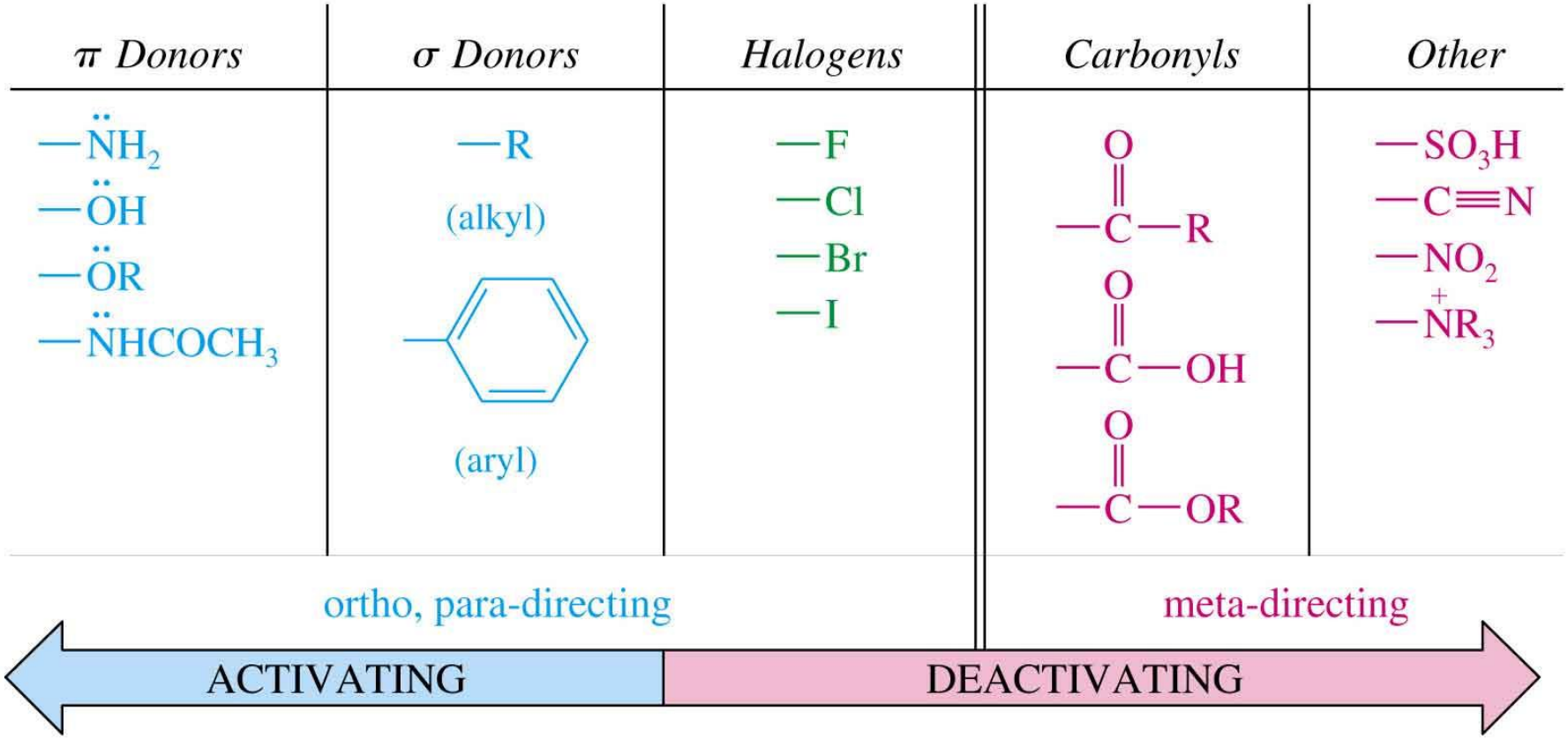
Summary of Directing Effects

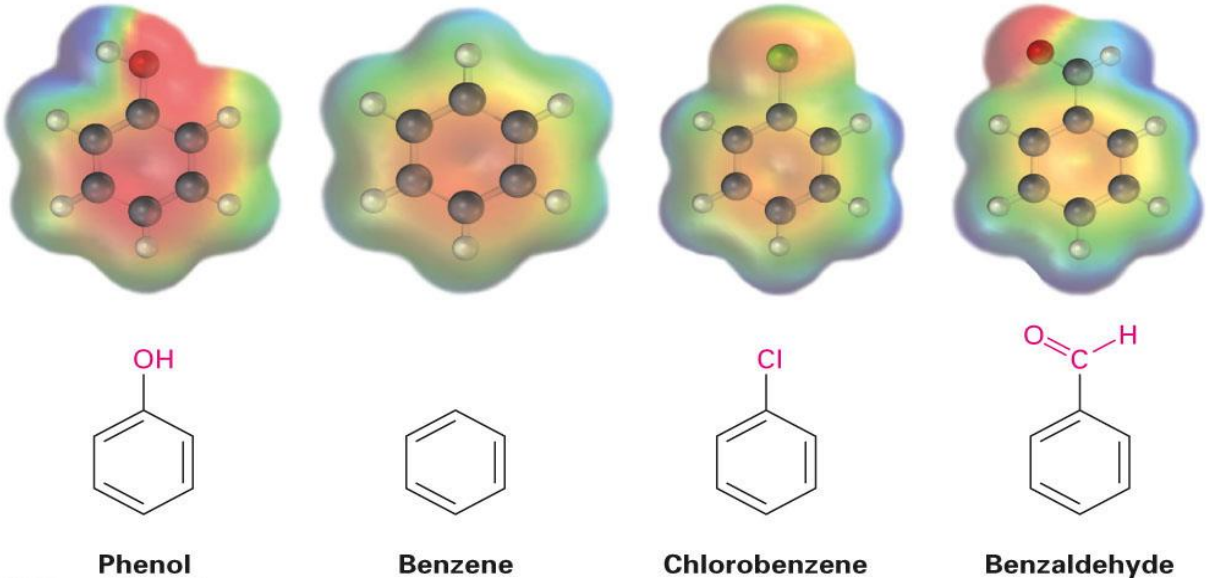


=>

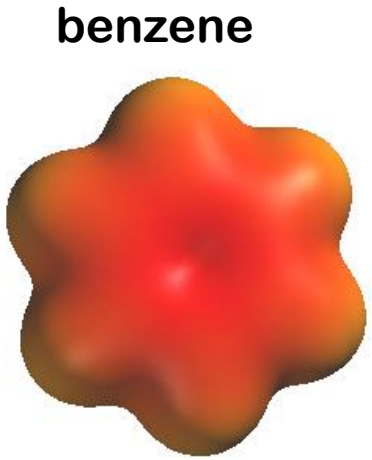
Substituent Effects in Electrophilic Substitutions

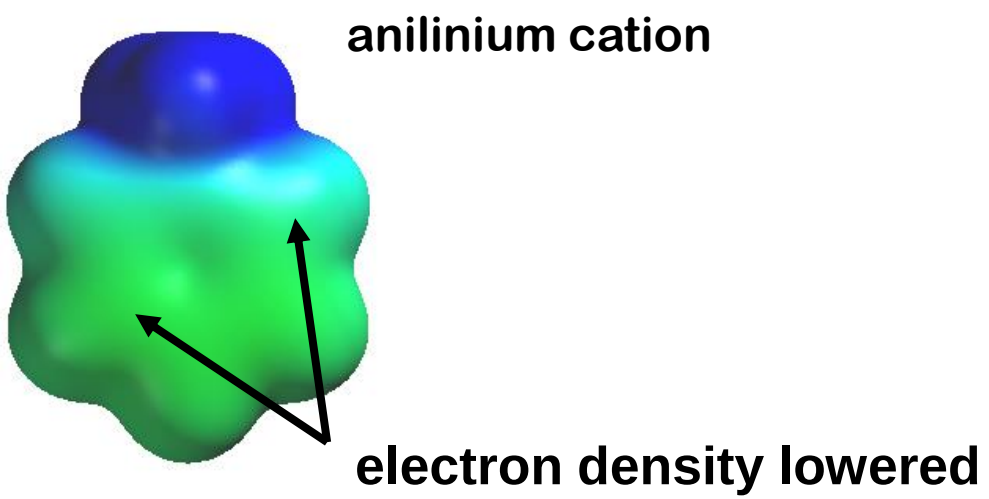
Electrostatic potential maps of benzene, phenol (activated), chlorobenzene (weakly deactivated), and benzaldehyde (more strongly deactivated)

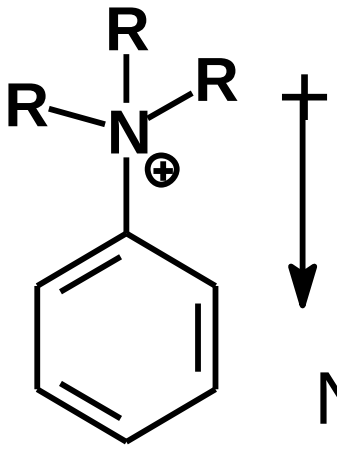
- The –OH substituent makes the ring more negative (red)
- The –Cl makes the ring less negative (orange)
- The –CHO makes the ring still less negative (yellow)



Ammoniumbenzenes







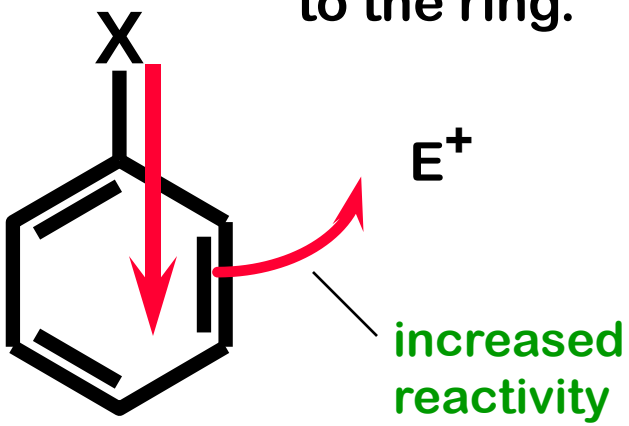
Positively charged nitrogen has strong polarizing effect, lowering electron density in ring system.

Nitrogen lacks lone pair; no resonance effect. Compare to anilines.

DIRECTIVITY OF SINGLE GROUPS

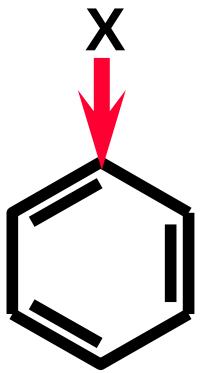
ortho, para - Directing Groups

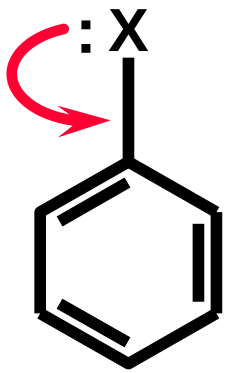
Groups that donate electron density to the ring.



These groups also "activate" the ring, or make it <u>more reactive</u>.

PROFILE:





+I Substituent

CH_3-

R-

+R Substituent

CH_3-Ö-

CH_3-N̈-

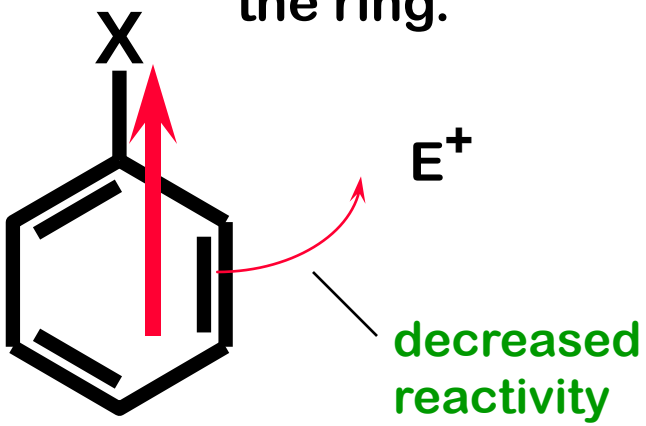
-N̈H_2

-Ö-H

The +R groups activate the ring more strongly than +I groups.

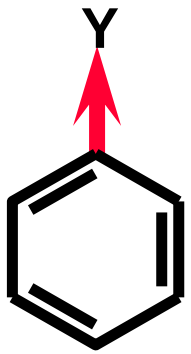
meta - Directing Groups

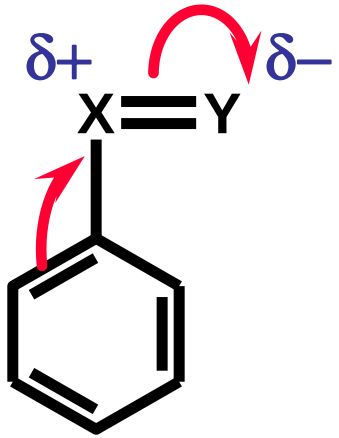
Groups that withdraw electron density from the ring.



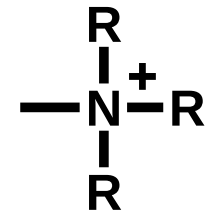
These groups also "deactivate" the ring, or make it less reactive.

PROFILE:

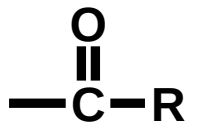


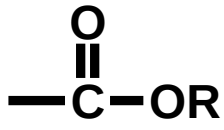


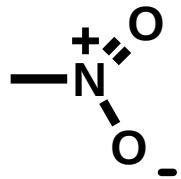
-I Substituent

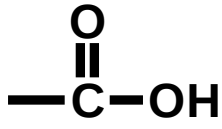


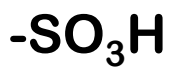
-R Substituent





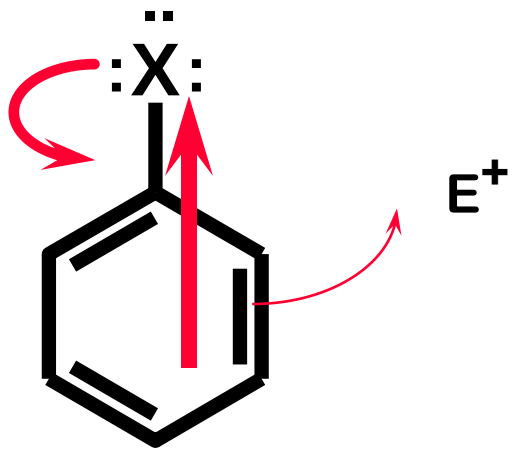






THE EXCEPTION

Halides - *o,p* Directors / Deactivating



+R / -I / *o,p* / deactivating

-F
-Cl
-Br
-I

Halides represent a special case:

They are *o,p* directing groups that are deactivating

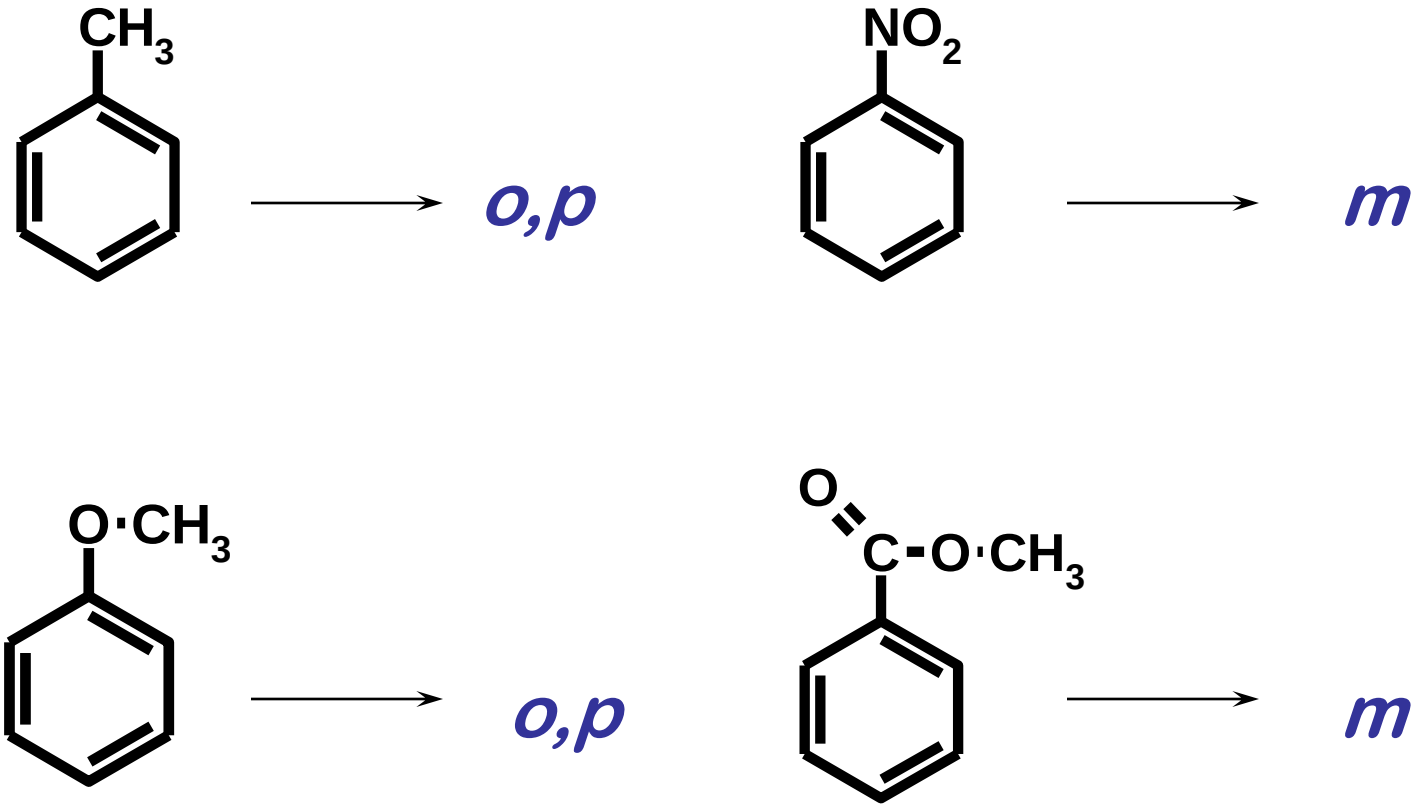
They are *o,p* directors (+R effect)

They are deactivating (-I effect)

Most other other substituents fall into one of these four categories:

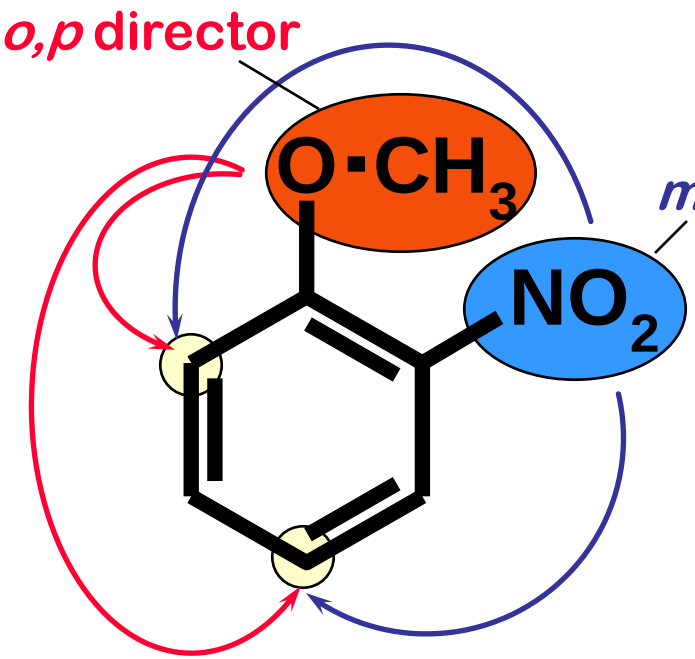
1) +R / *o,p* / activating
2) +I / *o,p* / activating
3) -R / *m* / deactivating
4) -I / *m* / deactivating

PREDICT !

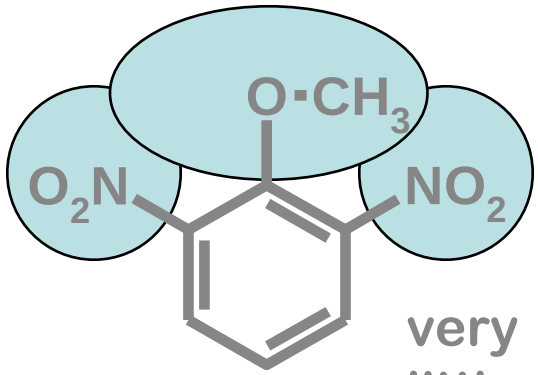


DIRECTIVITY OF MULTIPLE GROUPS

GROUPS ACTING IN CONCERT



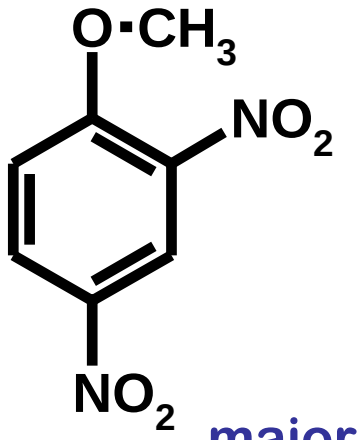
steric crowding



very little formed

HNO_3

H_2SO_4

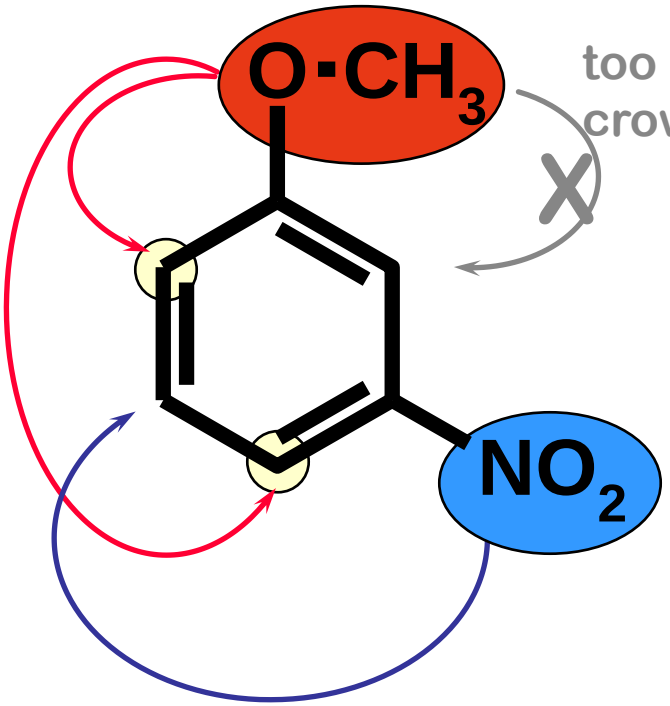


major product

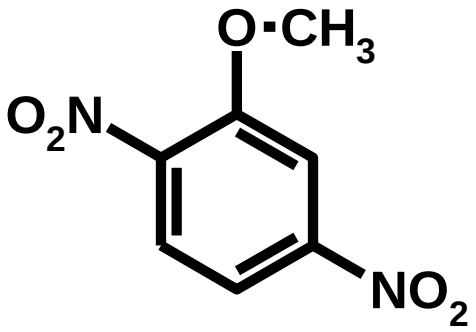
When groups direct to the same positions it is easy to predict the product.

GROUPS COMPETING

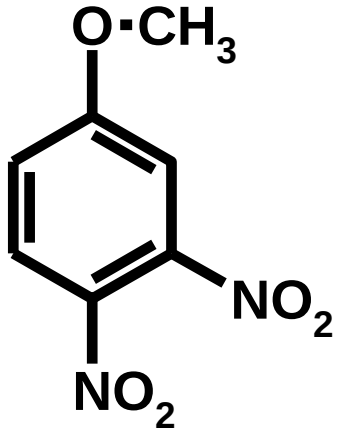
o,p-directing groups win over *m*-directing groups



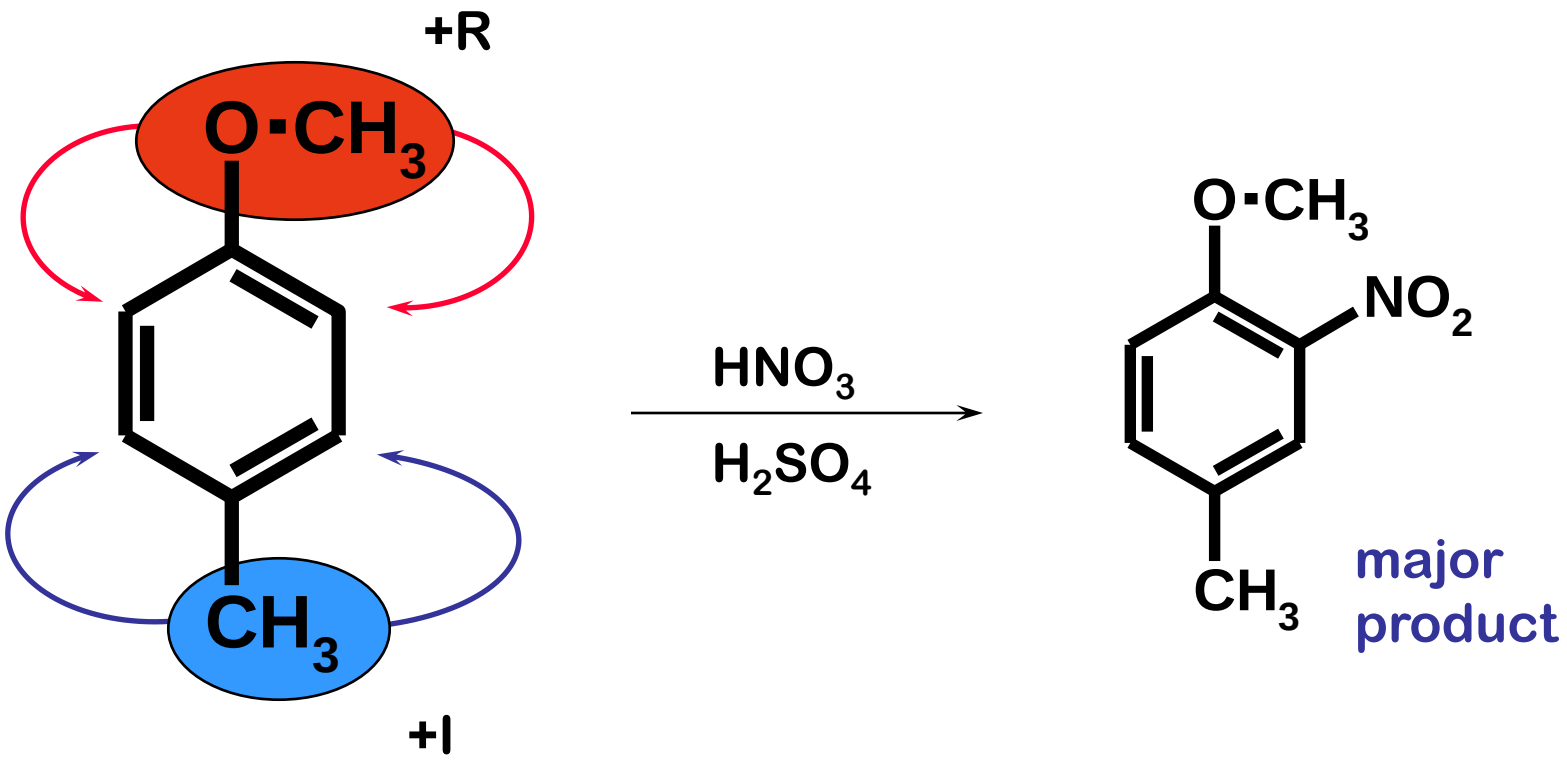
HNO_3 / H_2SO_4



+



RESONANCE VERSUS INDUCTIVE EFFECT



resonance effects are more
important than inductive effects

SOME GENERAL RULES

1) Activating (*o,p*) groups (+R, +I) win over deactivating (*m*) groups (-R,-I).

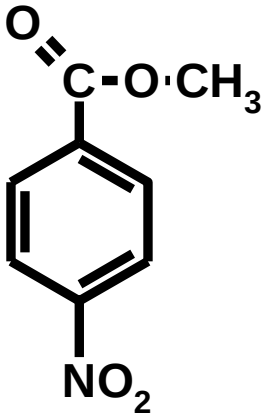
2) Resonance groups (+R) win over inductive (+I) groups.

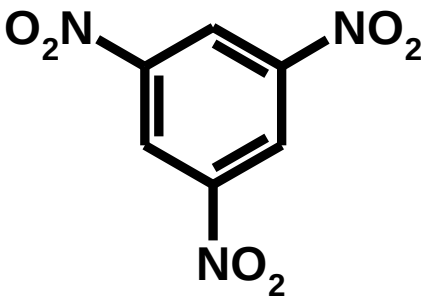
3) 1,2,3-Trisubstituted products rarely form due to excessive steric crowding.

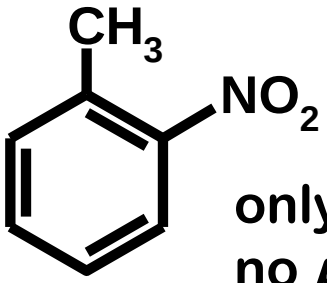
4) With bulky directing groups, there will usually be more *p*-substitution than *o*-substitution.

5) The incoming group replaces a hydrogen, it will not usually displace a substituent already in place.

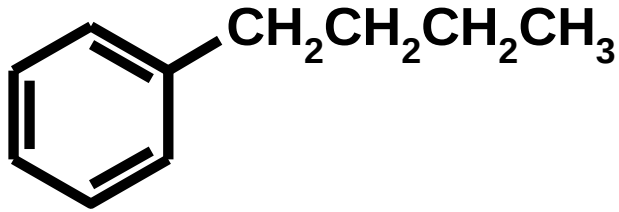
HOW CAN YOU MAKE …







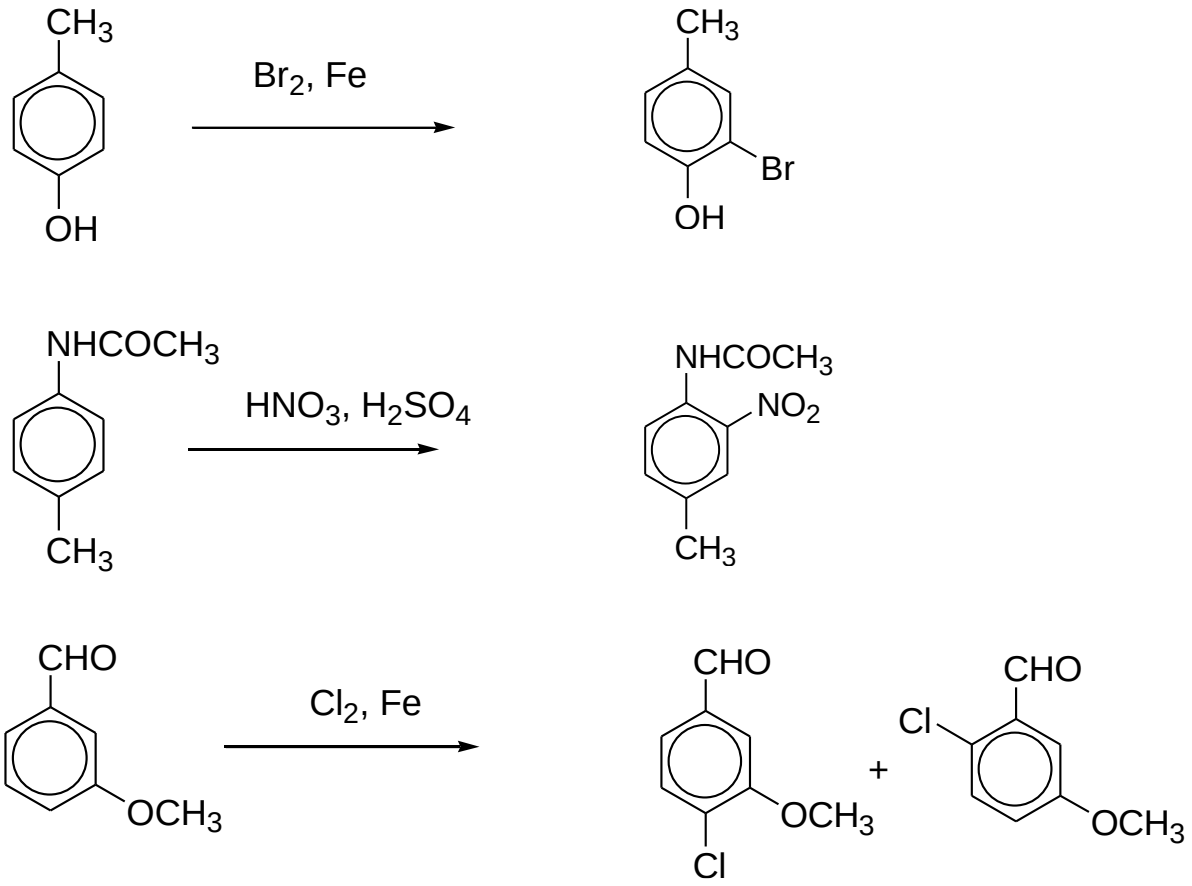
only,
no *para*



Se houver mais de um grupo no anel benzênico:

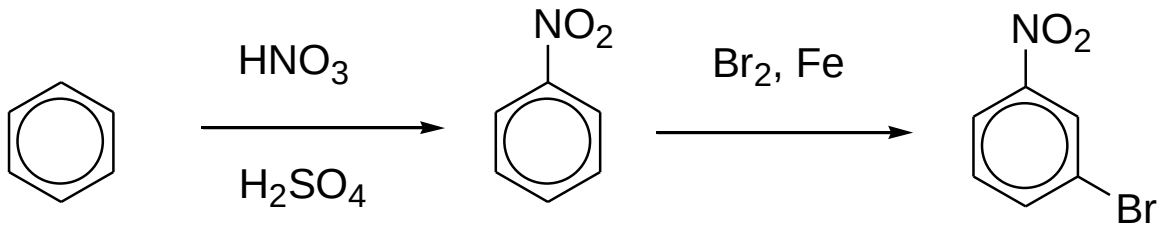
1. O grupo que tiver o maior potencial ativador dirigirá a próxima substituição.

2. Você terá pouca ou nenhuma substituição entre grupos que são *meta*-, em relação entre eles.

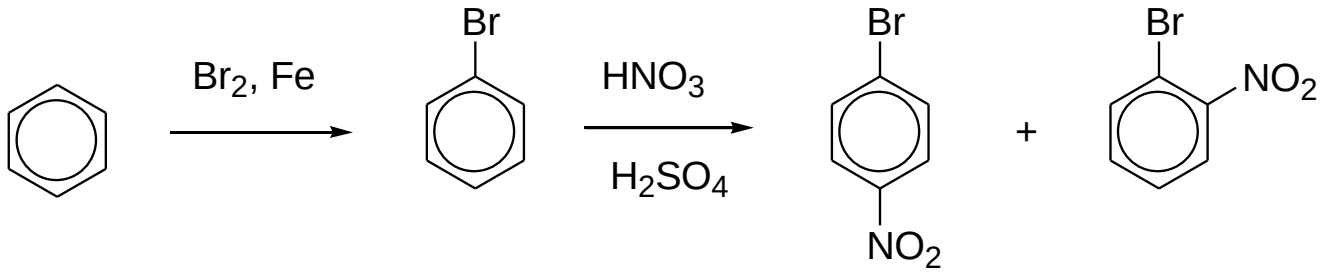

CH3
OH
Br2, Fe
CH3
Br
OH
NHCOCH3
CH3
HNO3, H2SO4
NHCOCH3
NO2
CH3
CHO
OCH3
Cl2, Fe
CHO
OCH3
Cl
+
CHO
Cl
OCH3

Orientation and synthesis. Order is important!

synthesis of *m*-bromonitrobenzene from benzene:



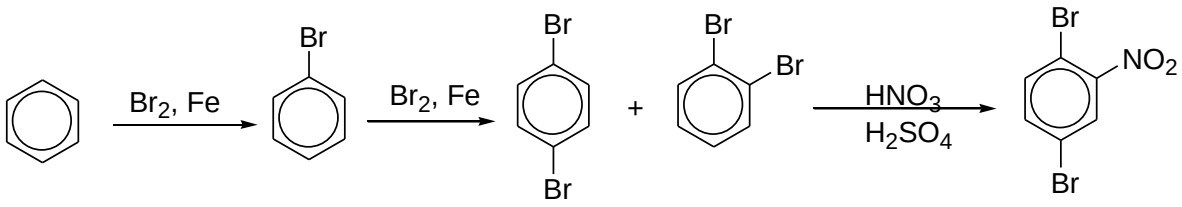
synthesis of *p*-bromonitrobenzene from benzene:



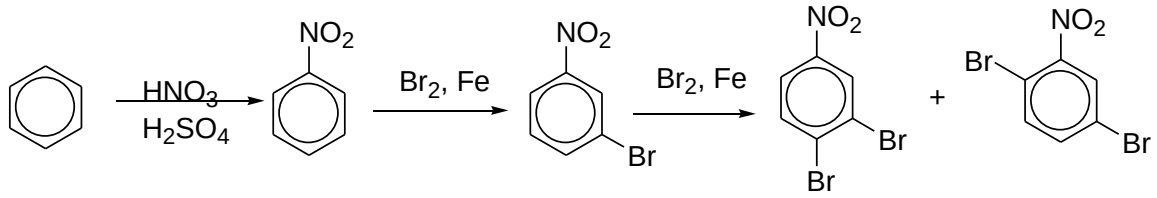
You may assume that you can separate a pure *para*-isomer from an *ortho*-/*para*- mixture.

note: the assumption that you can separate a pure para isomer from an ortho/para mixture does not apply to any other mixtures.

synthesis of 1,4-dibromo-2-nitrobenzene from benzene

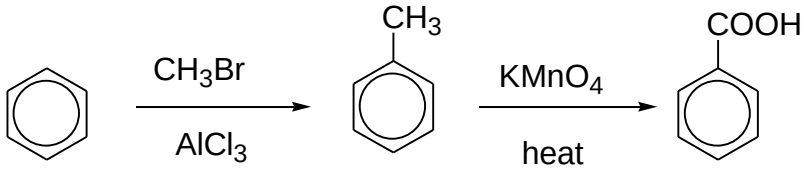


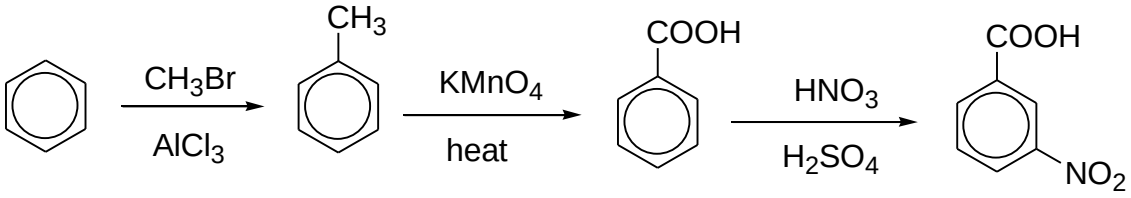
separate pure para isomer from ortho/para mixture

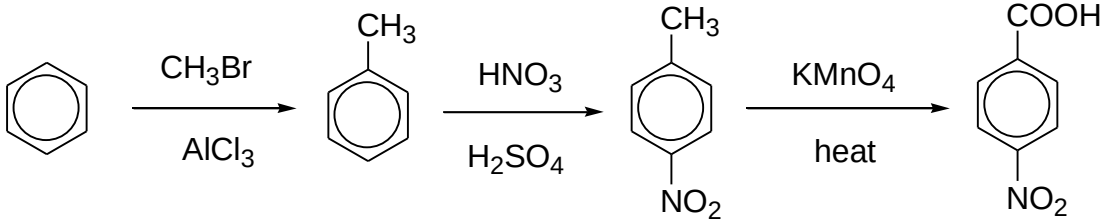


cannot assume that these can be separated!

synthesis of benzoic acids by oxidation of –CH_3







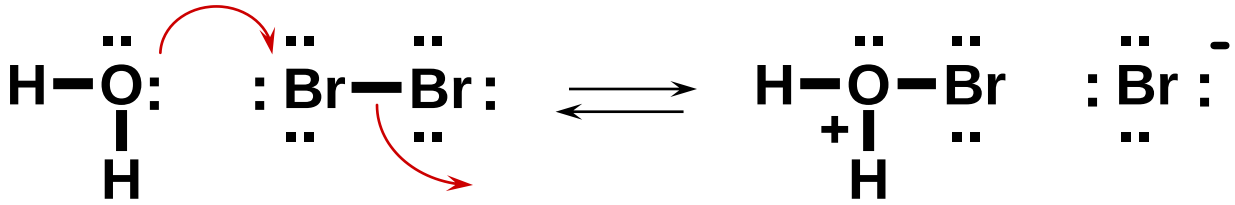
+ ortho-

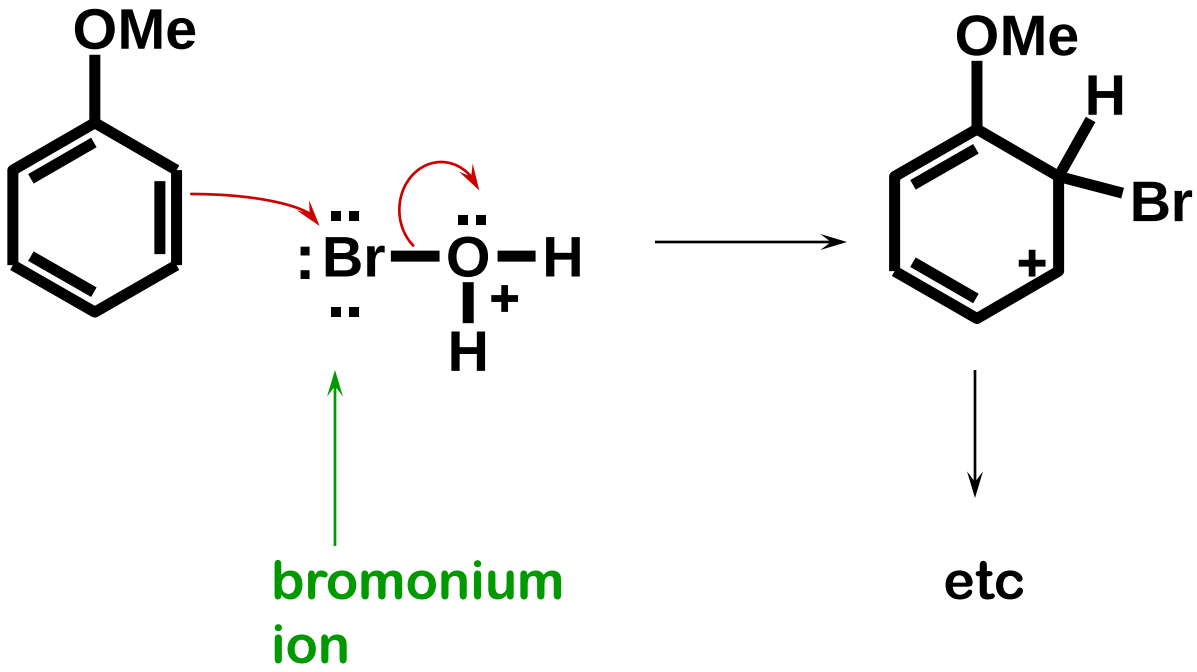
BROMINE - WATER REAGENT

PHENOLS AND ANILINES

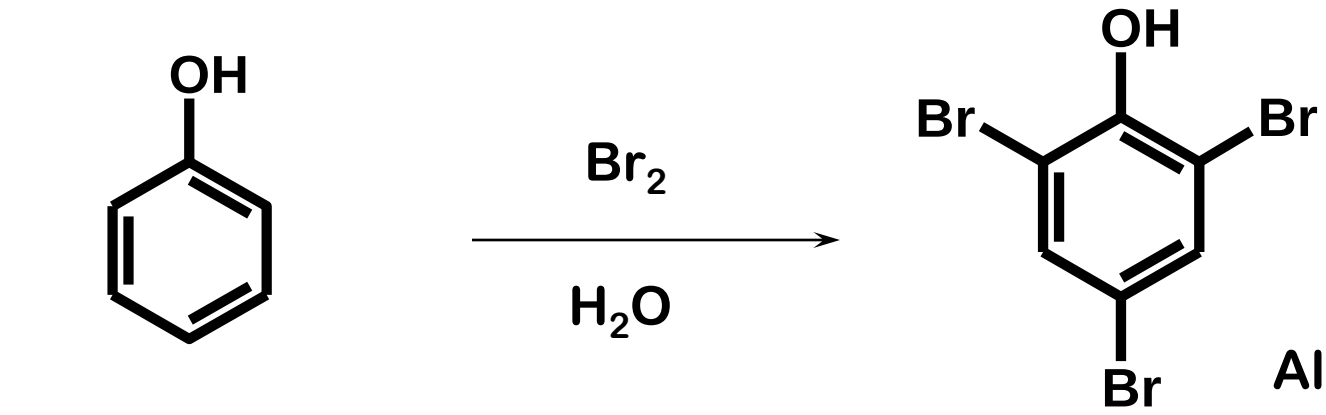
BROMINE IN WATER

This reagent works only with highly-activated rings such as phenols, anisoles and anilines.

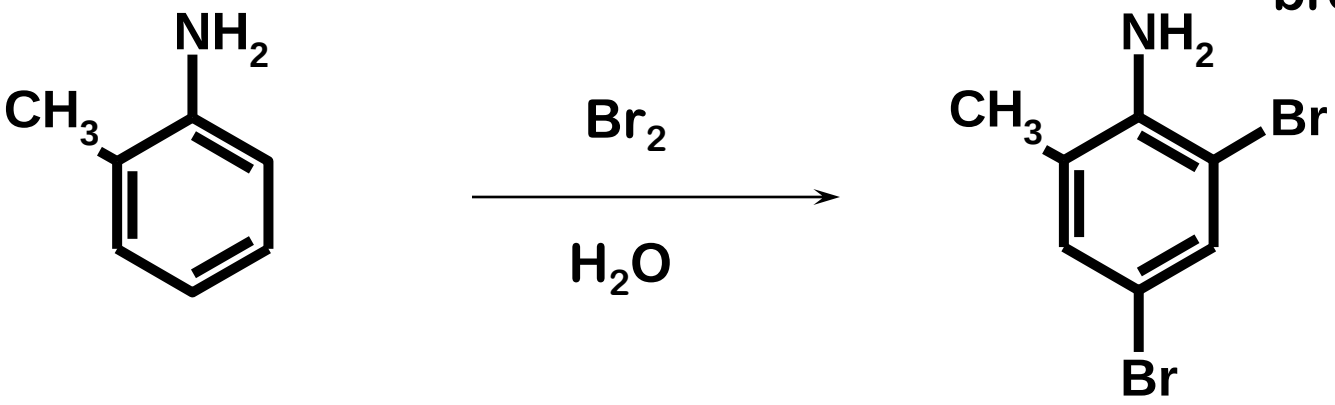




PHENOLS AND ANILINES REACT



All available positions are bromiated.



Friedel-Crafts Alkylation

- Synthesis of alkyl benzenes from alkyl halides and a Lewis acid, usually $AlCl_3$.
- Reactions of alkyl halide with Lewis acid produces a carbocation which is the electrophile.
- Other sources of carbocations: alkenes + HF or alcohols + BF_3.

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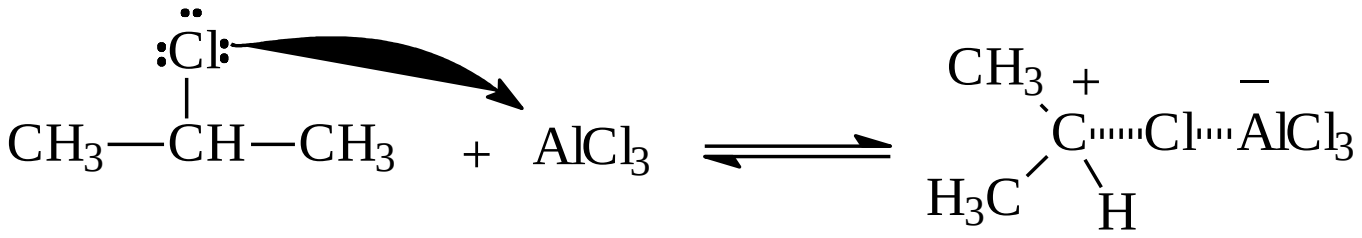
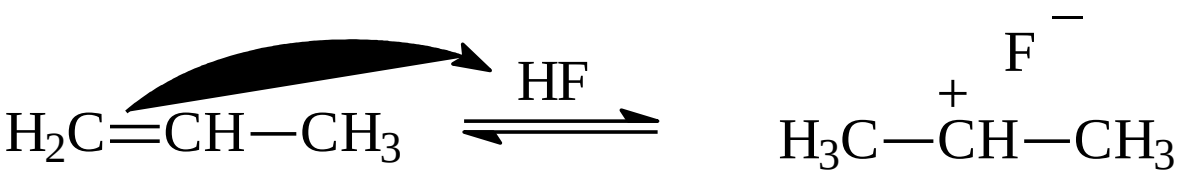
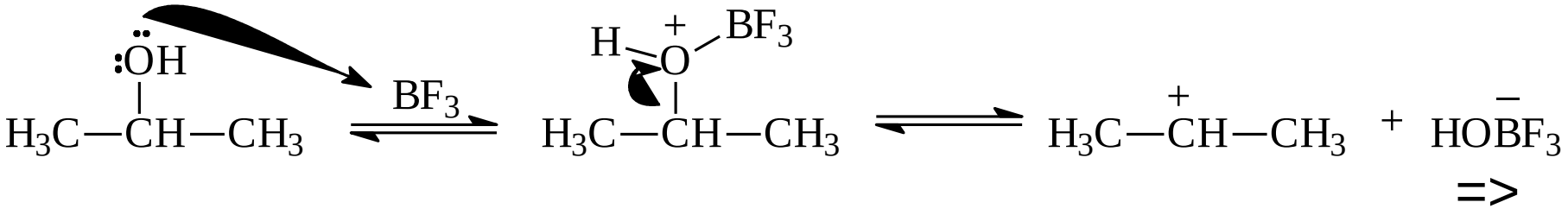
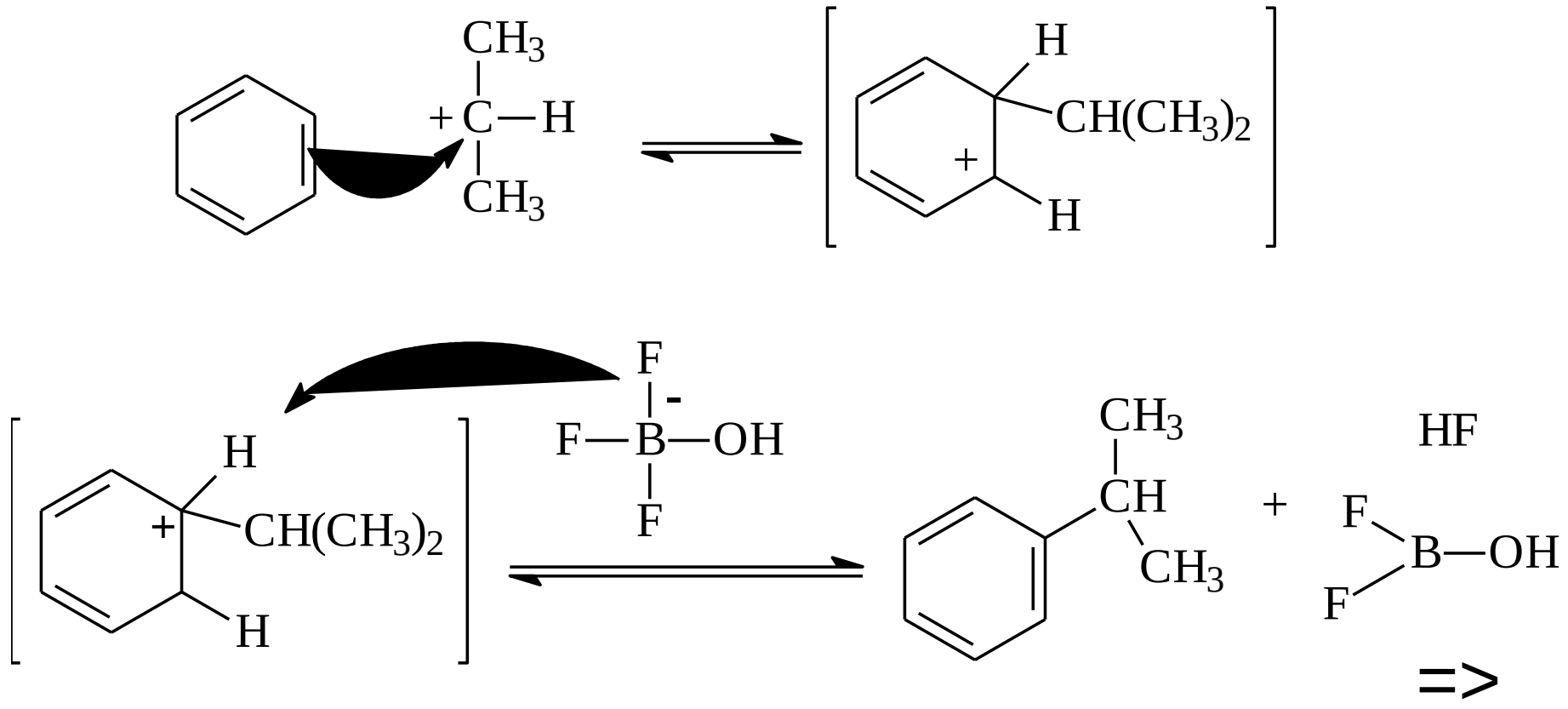
Examples of Carbocation Formation



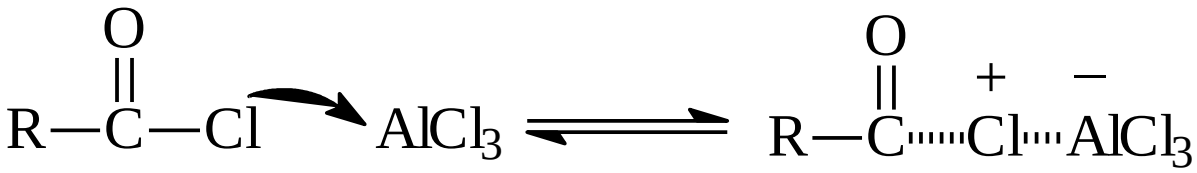


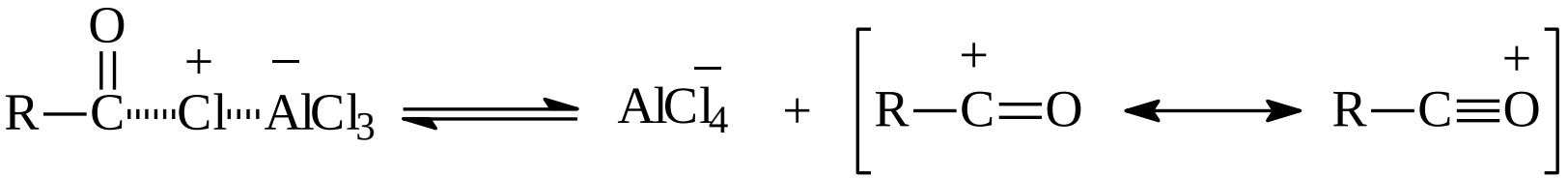


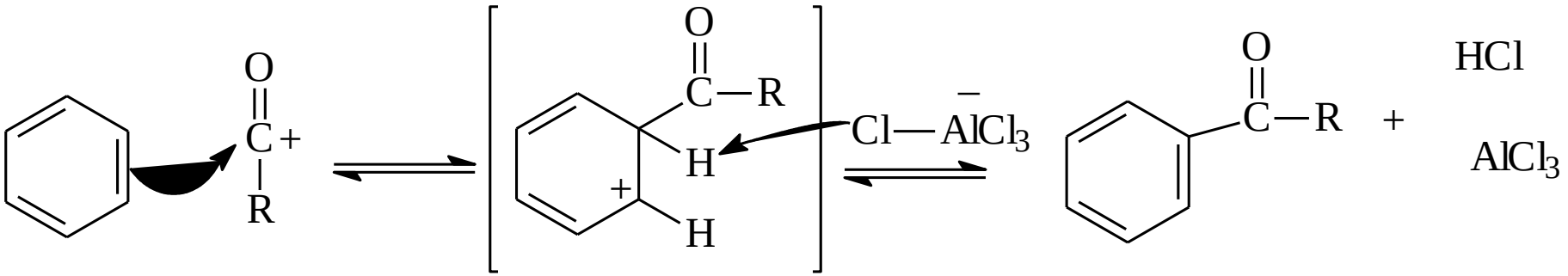
Formation of Alkyl Benzene



Mechanism of Acylation







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Limitations of Friedel-Crafts

- Reaction fails if benzene has a substituent that is more deactivating than halogen.
- Carbocations rearrange. Reaction of benzene with *n*-propyl chloride and $AlCl_3$ produces iso<u></u>propylbenzene.
- The alkylbenzene product is more reactive than benzene, so polyalkylation occurs.

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Friedel-Crafts Acylation

- Acyl chloride is used in place of alkyl chloride.
- The acylium ion intermediate is resonance stabilized and does not rearrange like a carbocation.
- The product is a phenyl ketone that is less reactive than benzene.

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