

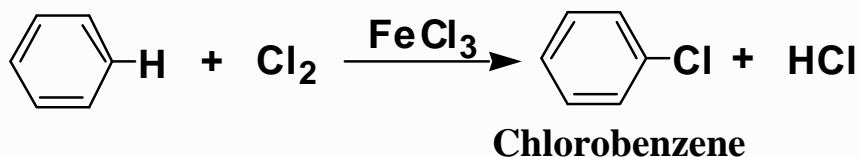
Reactions of Benzene & Its Derivatives

Chapter 22 1

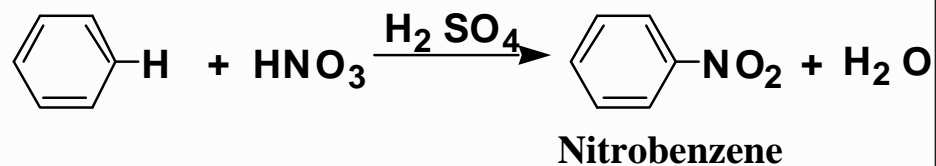
Reactions of Benzene

The most characteristic reaction of aromatic compounds is substitution at a ring carbon:

Halogenation:

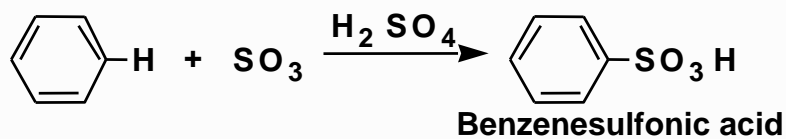


Nitration:

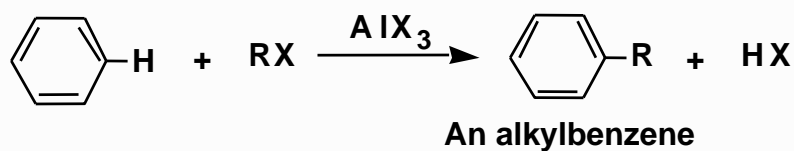


Reactions of Benzene

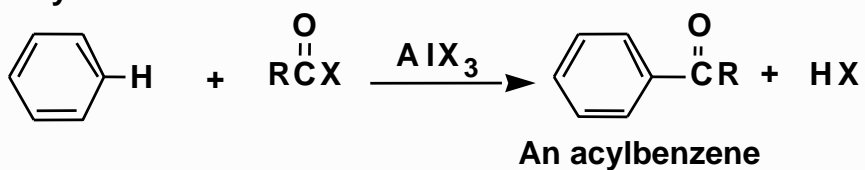
Sulfonation:



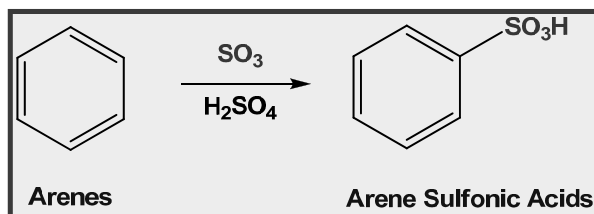
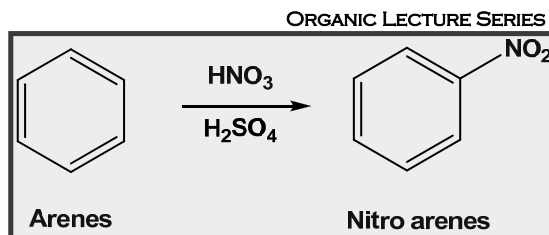
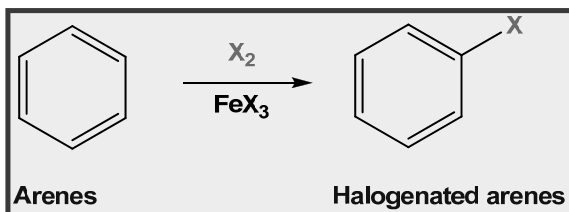
Alkylation:



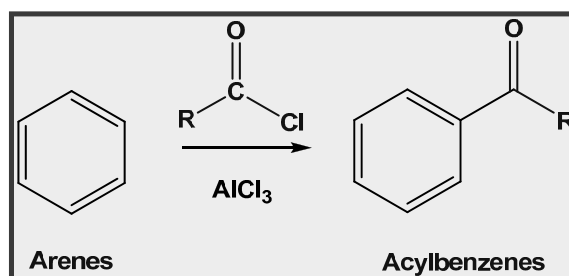
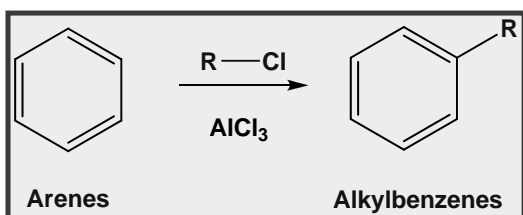
Acylation:



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Carbon-Carbon Bond Formations:



Electrophilic Aromatic Substitution

- Electrophilic aromatic substitution: a reaction in which a hydrogen atom of an aromatic ring is replaced by an electrophile

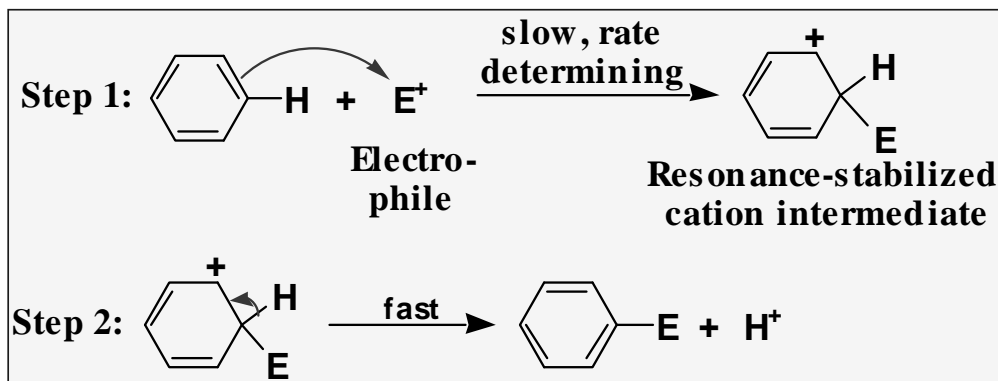


- In this section:
 - several common types of electrophiles
 - how each is generated
 - the mechanism by which each replaces hydrogen

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EAS: General Mechanism

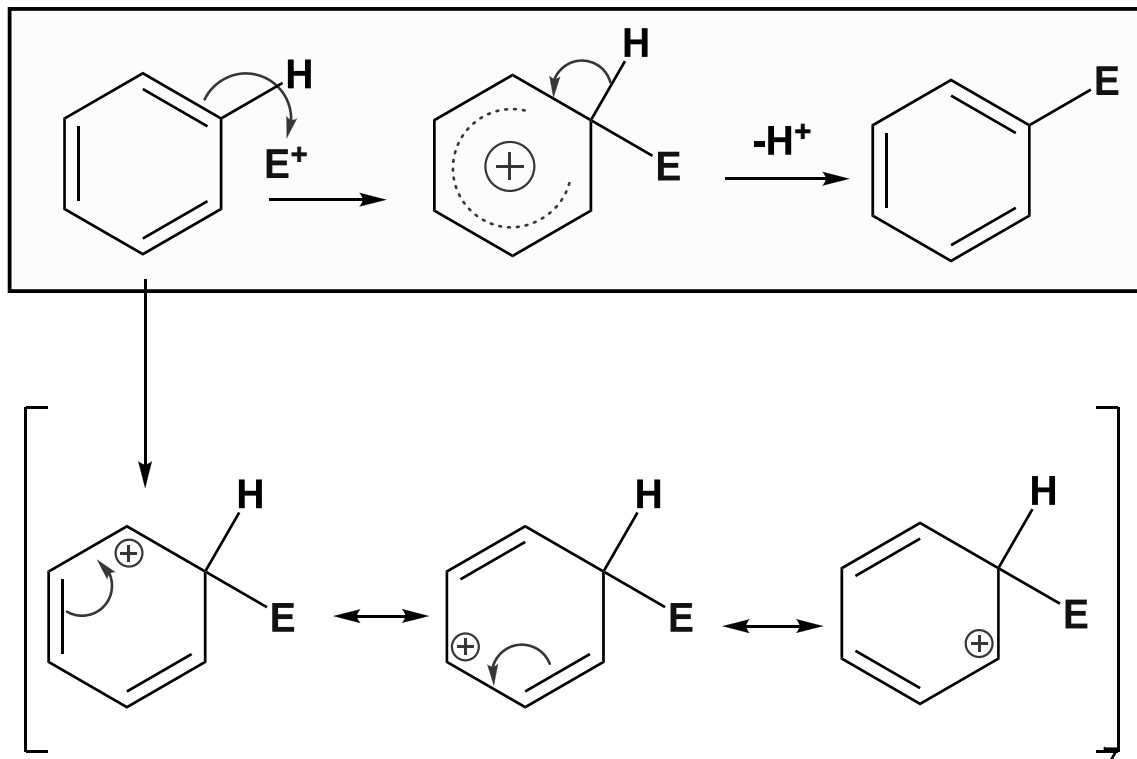
- A general mechanism



- Key question: What is the electrophile and how is it generated?

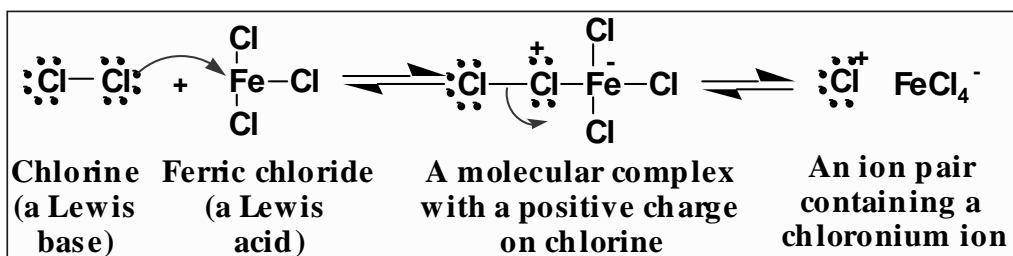
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Electrophilic Aromatic Substitution (EAS)

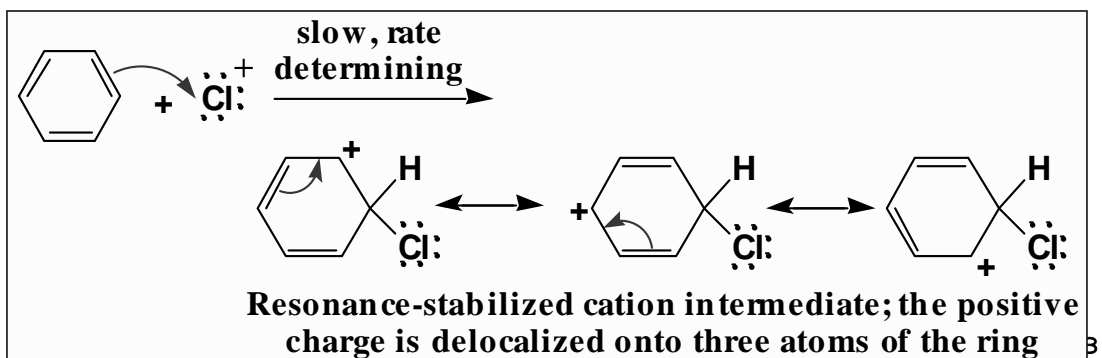


Chlorination

Step 1: formation of a chloronium ion

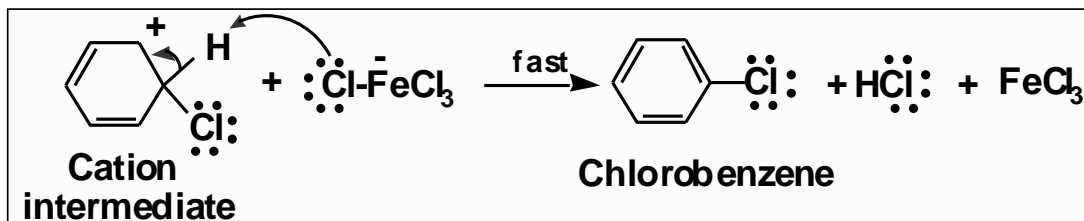


Step 2: attack of the chloronium ion on the ring



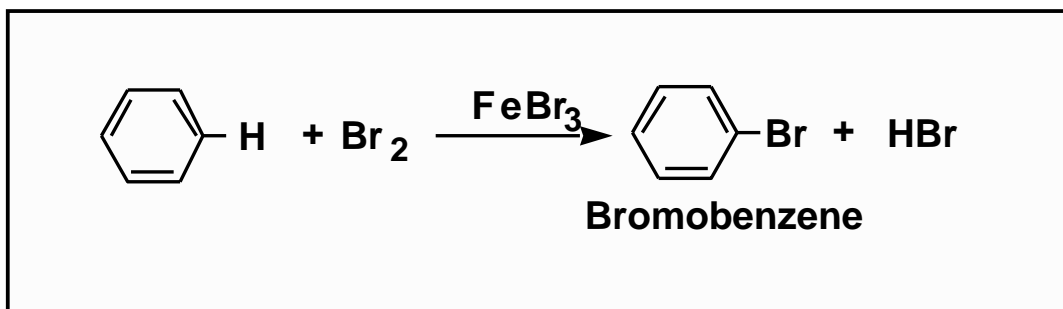
Chlorination

Step 3: proton transfer regenerates the aromatic character of the ring



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Bromination

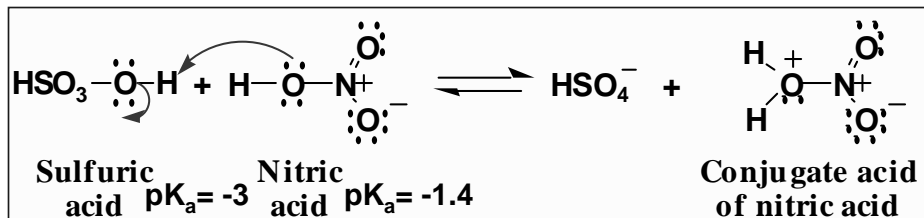


This is the general method for
Substitution of halogen onto a benzene ring
 (CANNOT be halogenated by Free Radical Mechanism)

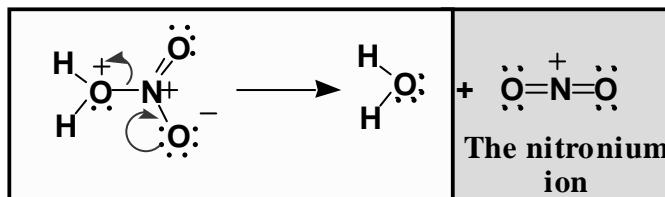
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Nitration

- Generation of the nitronium ion, NO_2^+
 - Step 1: proton transfer to nitric acid



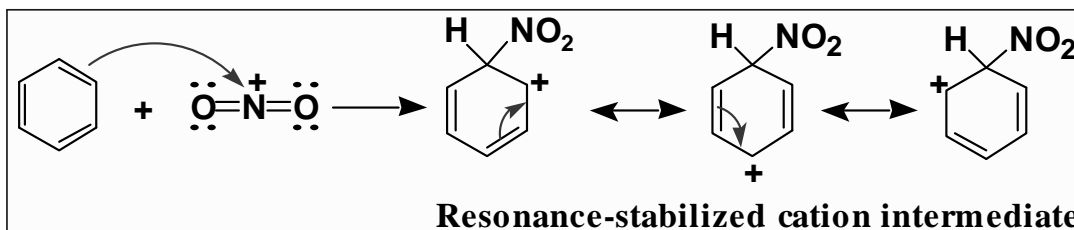
- Step 2: loss of H_2O gives the nitronium ion, a very strong electrophile



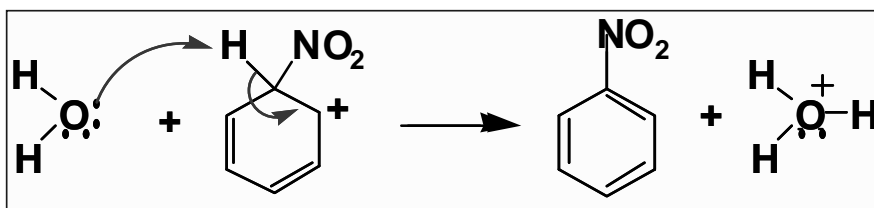
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Nitration

- Step 1: attack of the nitronium ion (an electrophile) on the aromatic ring (a nucleophile)



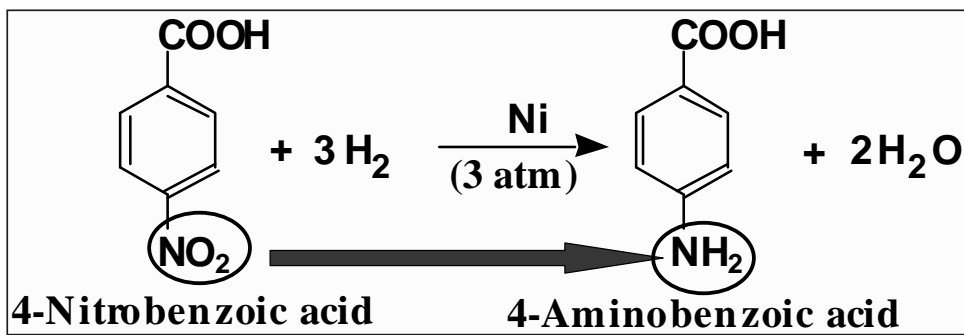
- Step 2: proton transfer regenerates the aromatic ring



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Nitration

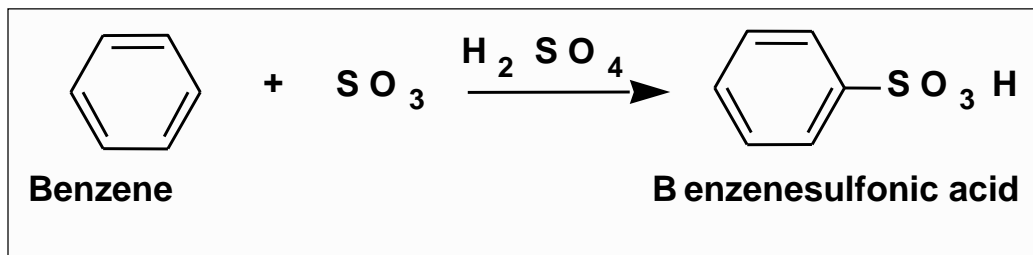
- A particular value of nitration is that the nitro group can be reduced to a 1° amino group



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Sulfonation

- Carried out using concentrated sulfuric acid containing dissolved sulfur trioxide

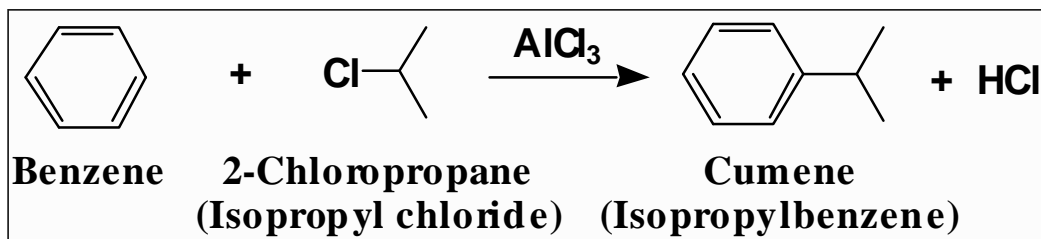


(SO₃ in H₂SO₄ is sometimes called “fuming” sulfuric acid.)

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Friedel-Crafts Alkylation

- Friedel-Crafts alkylation forms a new C-C bond between an aromatic ring and an alkyl group

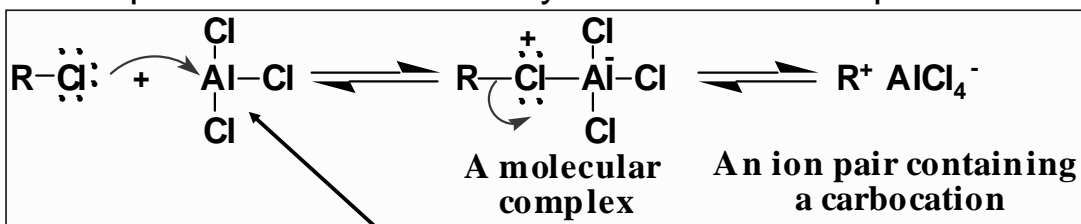


The electrophilic partner is a carbocation;
it will arrange to the most stable ion: allylic > 3° > 2° > 1°

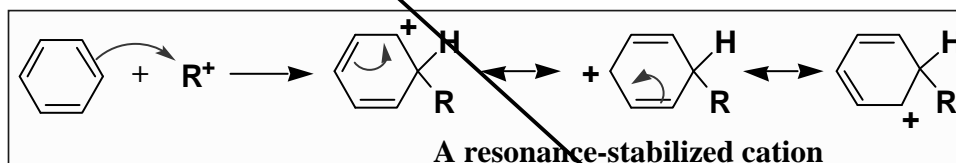
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Friedel-Crafts Alkylation

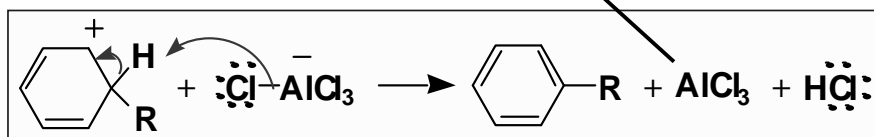
Step 1: formation of an alkyl cation as an ion pair



Step 2: attack of the alkyl cation on the aromatic ring



Step 3: proton transfer regenerates the aromatic ring

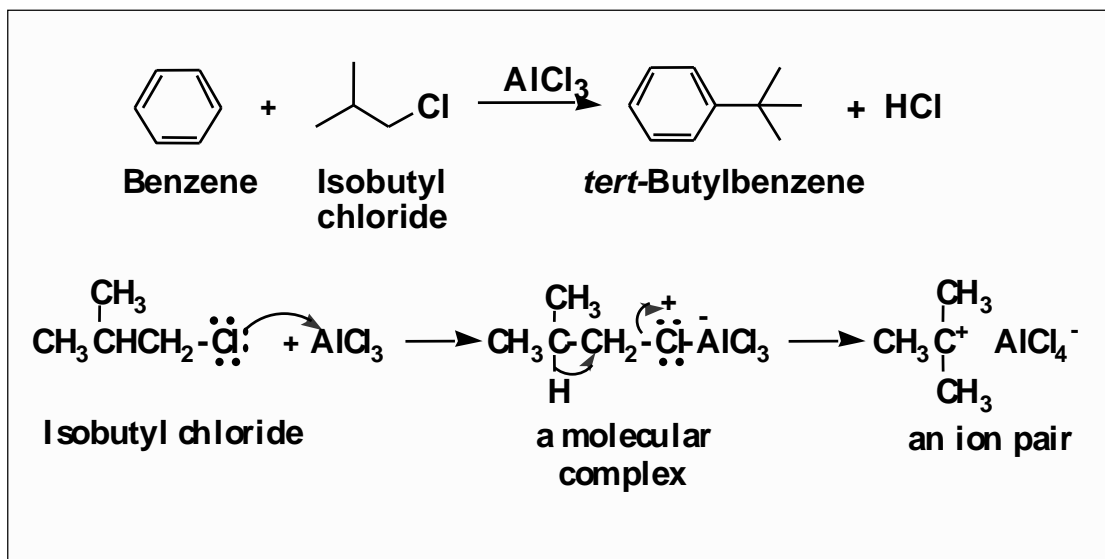


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Friedel-Crafts Alkylation

There are two major limitations on Friedel-Crafts alkylations:

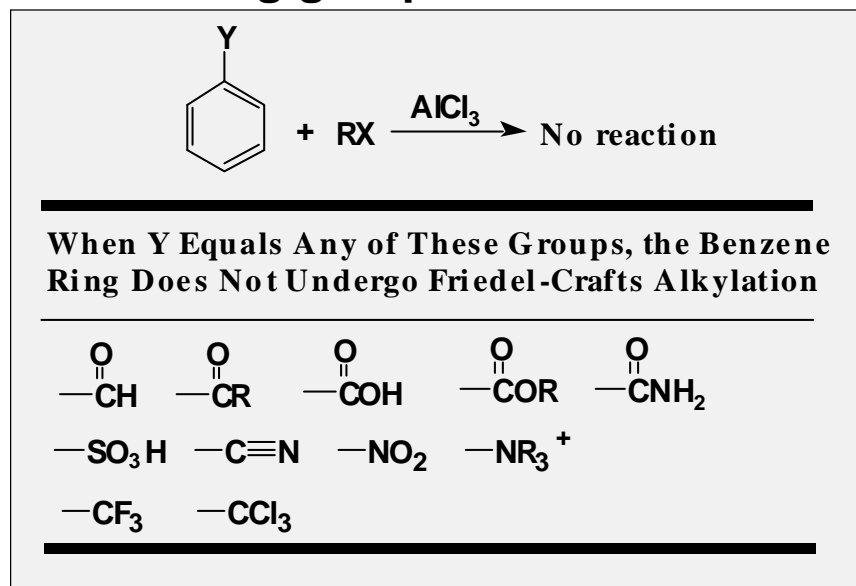
1. carbocation rearrangements are common:



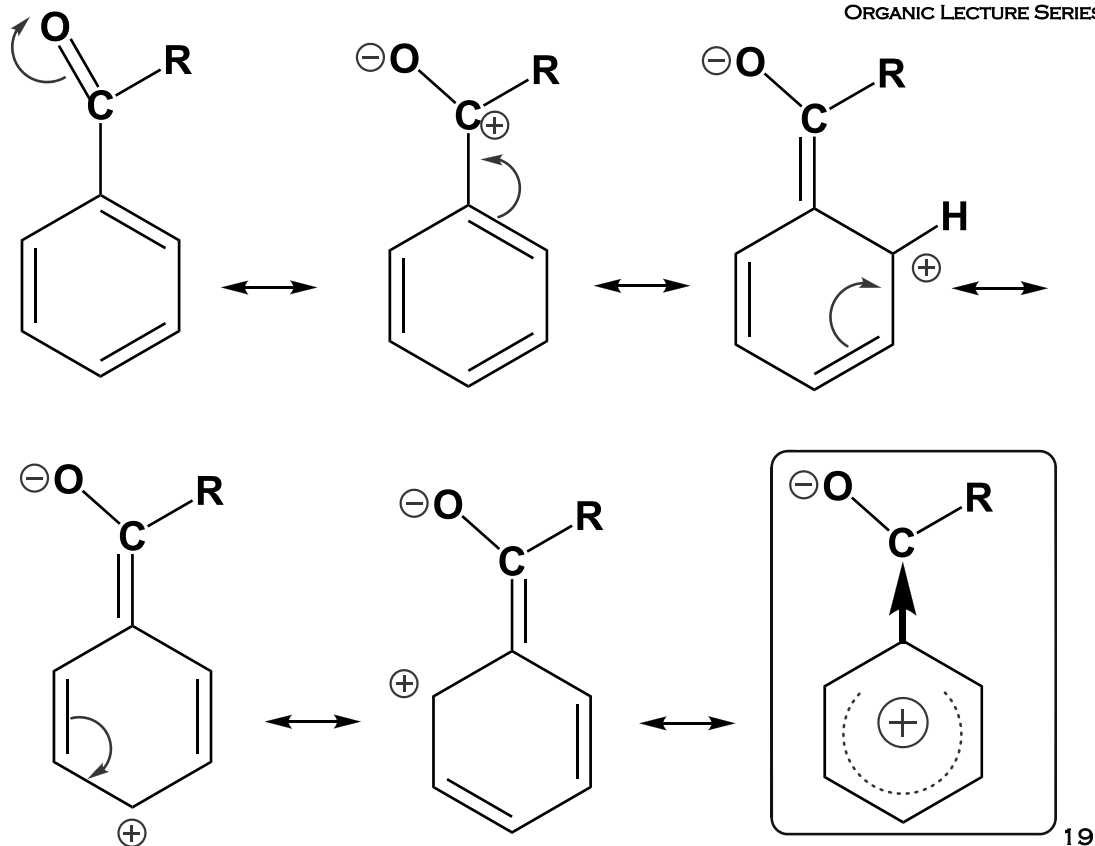
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Friedel-Crafts Alkylation

2. F-C alkylation fails on benzene rings bearing one or more of these strongly **electron-withdrawing groups**

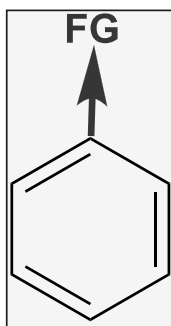


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The "De-activation" of Aromatic Systems

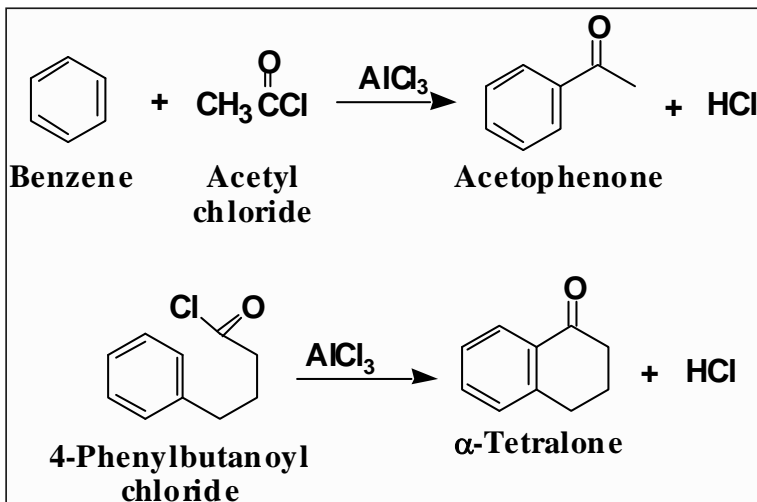


If the FG is an e^- withdrawing substituent, then the ring system becomes more electron poor and is said to be "deactivated" towards electrophilic aromatic substitution. EAS occurs at a slower rate.

Note: deactivation refers to the **rate** of EAS

Friedel-Crafts Acylation

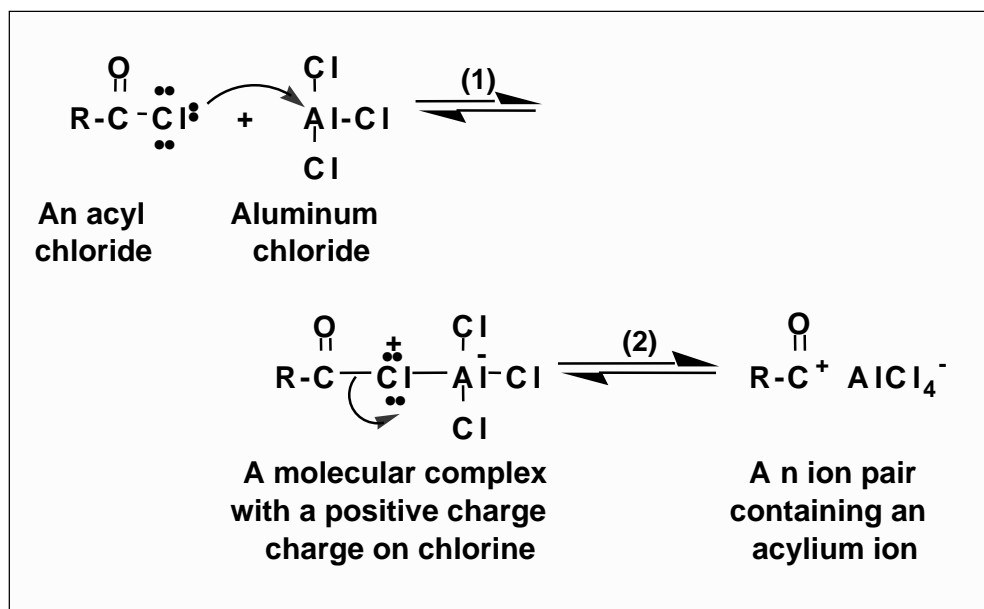
- Friedel-Crafts **acylation** forms a new C-C bond between a benzene ring and an acyl group:



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Friedel-Crafts Acylation

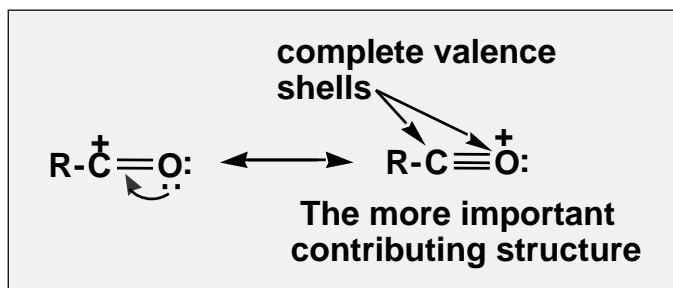
- The electrophile is an **acylium ion**



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Friedel-Crafts Acylation

– an acylium ion is a resonance hybrid of two major contributing structures

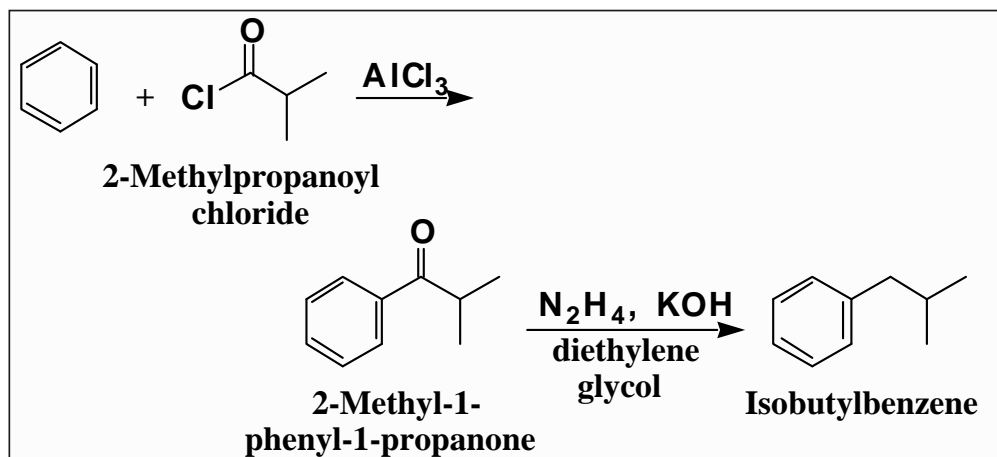


- F-C acylations are free of a major limitation of F-C alkylations; **acylium ions do not rearrange.**

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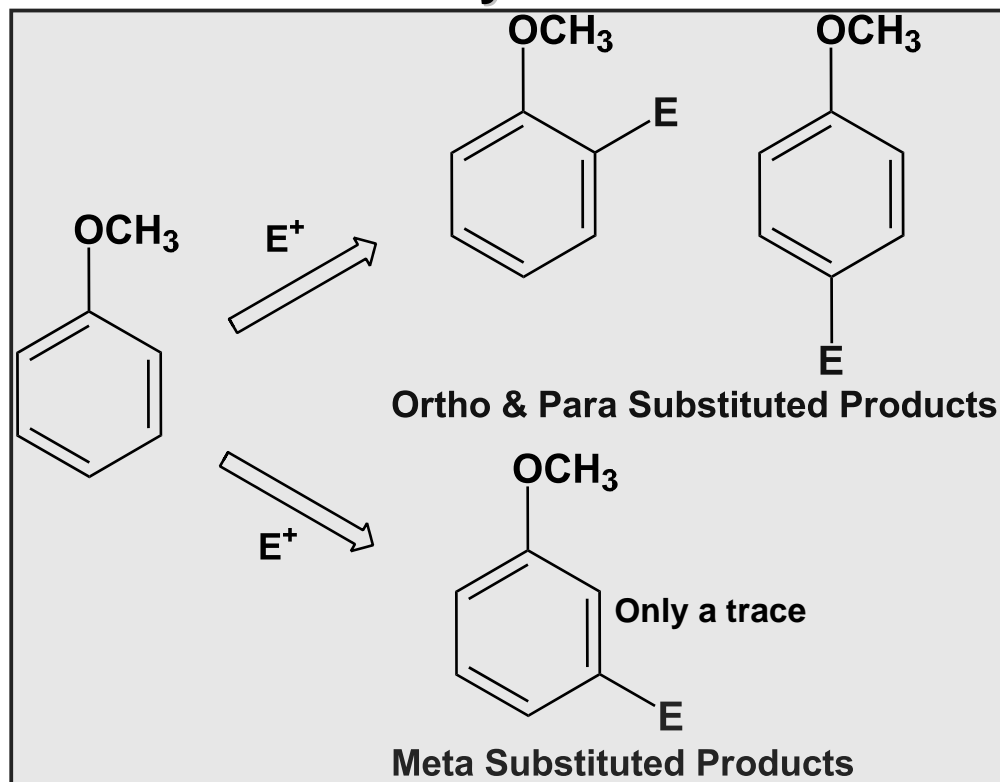
Friedel-Crafts Acylation

A special value of F-C acylations is preparation of **unrearranged** alkylbenzenes:



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Di- and Polysubstitution



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Di- and Polysubstitution

Orientation on nitration of monosubstituted benzenes:

Substituent	ortho	meta	para	ortho + para	meta
—OCH ₃	44	-	55	99	trace
—CH ₃	58	4	38	96	4
—Cl	70	-	30	100	trace
—Br	37	1	62	99	1
—COOH	18	80	2	20	80
—CN	19	80	1	20	80
—NO ₂	6.4	93.2	0.3	6.7	93.2

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Di- and Polysubstitution

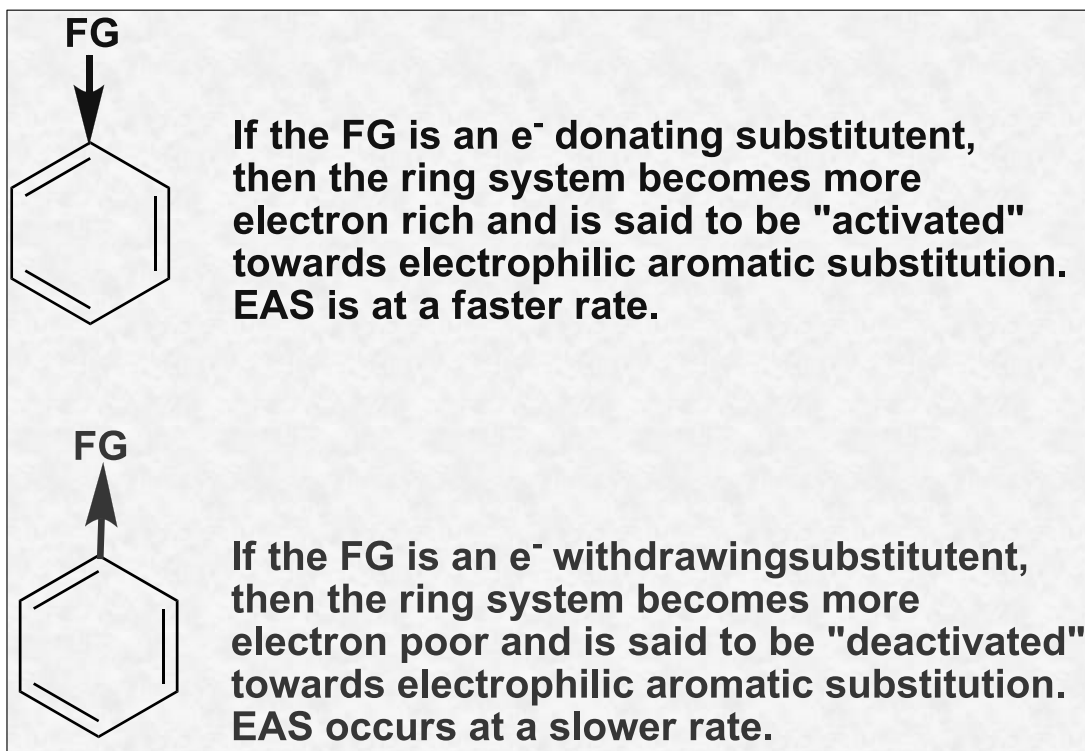
- **Orientation:**
 - certain substituents direct preferentially to ortho & para positions; others to meta positions
 - substituents are classified as either **ortho-para directing** or **meta directing** toward further substitution

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Di- and Polysubstitution

- **Rate**
 - certain substituents cause the rate of a second substitution to be greater than that for benzene itself; others cause the rate to be lower
 - substituents are classified as **activating** or **deactivating** toward further substitution

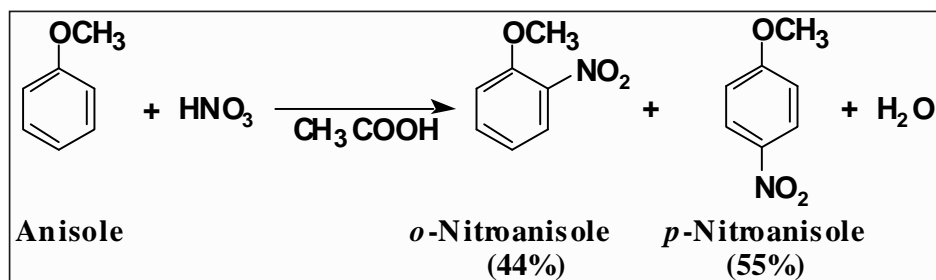
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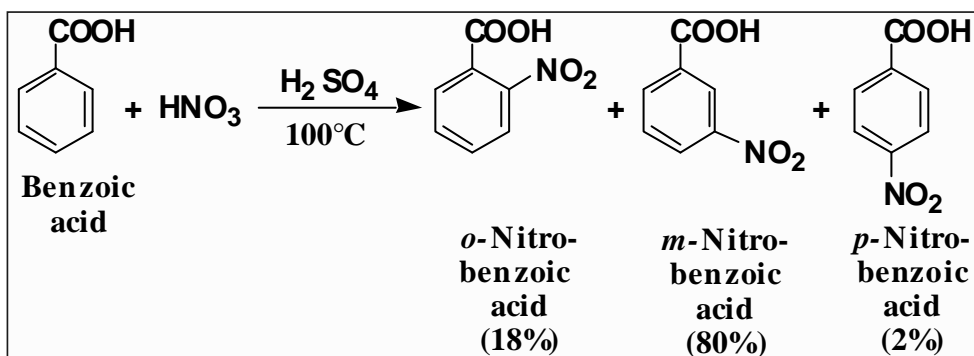
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Di- and Polysubstitution

– -OCH₃ is ortho-para directing:

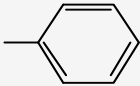


– -CO₂H is meta directing



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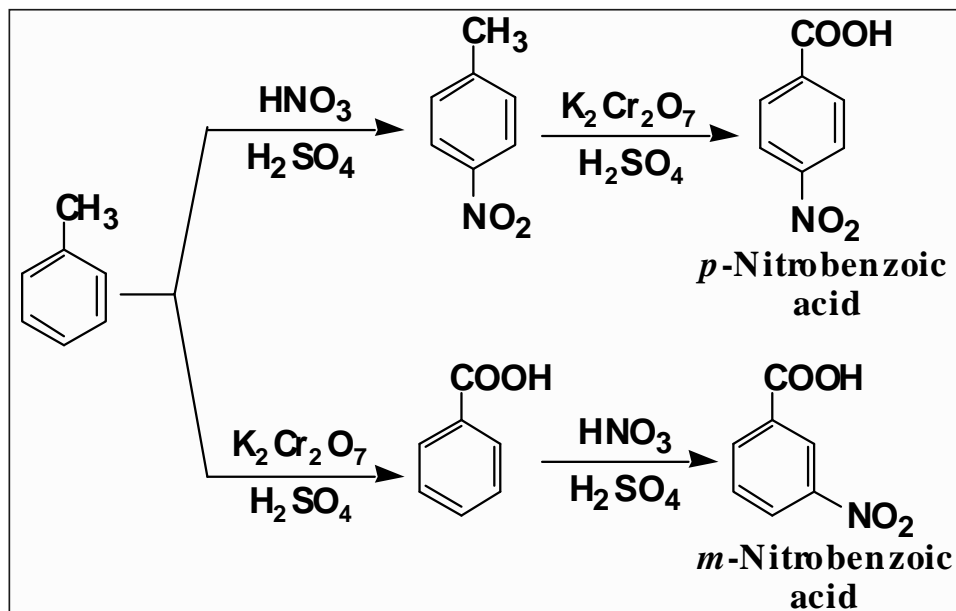
Di- and Polysubstitution

Ortho-para Directing	Strongly activating	$-\ddot{\text{N}}\text{H}_2$	$-\ddot{\text{N}}\text{HR}$	$-\ddot{\text{N}}\text{R}_2$	$-\ddot{\text{O}}\text{H}$	$-\ddot{\text{O}}\text{R}$
	Moderately activating	$-\ddot{\text{N}}\overset{\text{O}}{\parallel}\text{CR}$	$-\ddot{\text{N}}\overset{\text{O}}{\parallel}\text{CAr}$	$-\ddot{\text{O}}\overset{\text{O}}{\parallel}\text{CR}$	$-\ddot{\text{O}}\overset{\text{O}}{\parallel}\text{CAr}$	
	Weakly activating	$-\text{R}$				
	Weakly deactivating	$-\ddot{\text{F}}:$	$-\ddot{\text{Cl}}:$	$-\ddot{\text{Br}}:$	$-\ddot{\text{I}}:$	
Meta Directing	Moderately deactivating	$-\overset{\text{O}}{\parallel}\text{CH}$	$-\overset{\text{O}}{\parallel}\text{CR}$	$-\overset{\text{O}}{\parallel}\text{COH}$	$-\overset{\text{O}}{\parallel}\text{COR}$	
	Strongly deactivating	$-\overset{\text{O}}{\parallel}\text{CNH}_2$	$-\text{SO}_3\text{H}$	$-\text{C}\equiv\text{N}$		
		$-\text{NO}_2$	$-\text{NH}_3^+$	$-\text{CF}_3$	$-\text{CCl}_3$	

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Di- and Polysubstitution

the order of steps is important:



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Theory of Directing Effects

- The rate of EAS is limited by the slowest step in the reaction
- For almost every EAS, **the rate-determining step is attack of E^+** on the aromatic ring to give a resonance-stabilized cation intermediate
- **The more stable this cation intermediate, the faster the rate-determining step** and the faster the overall reaction

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Theory of Directing Effects

- For ortho-para directors, ortho-para attack forms a more stable cation than meta attack
 - ortho-para products are formed faster than meta products
- For meta directors, meta attack forms a more stable cation than ortho-para attack
 - meta products are formed faster than ortho-para products

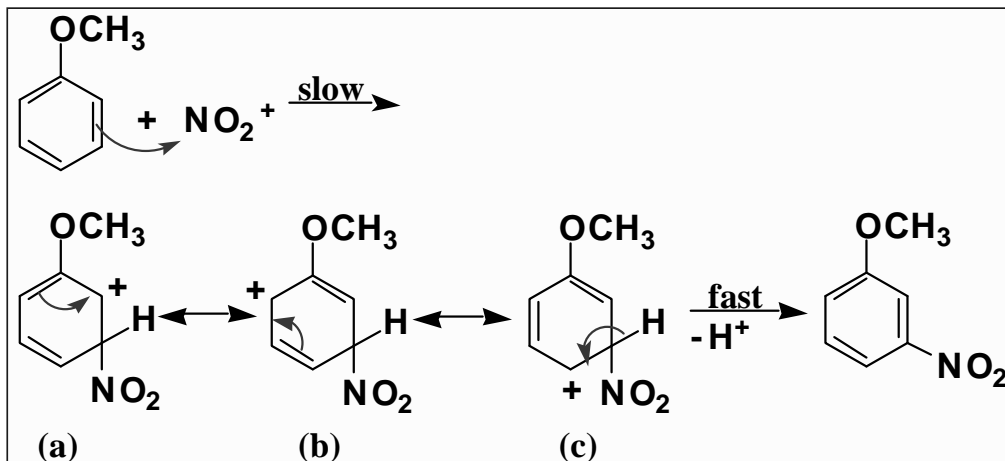
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Theory of Directing Effects

ORGANIC LECTURE SERIES

Nitration of anisole

-OCH₃; examine the meta attack:

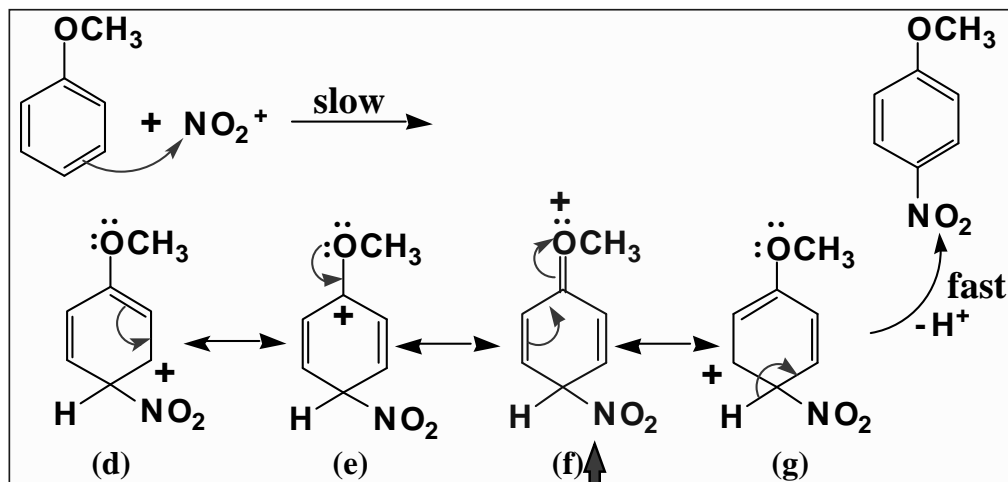


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ORGANIC LECTURE SERIES

Nitration of anisole

-OCH₃: examine the ortho-para attack:



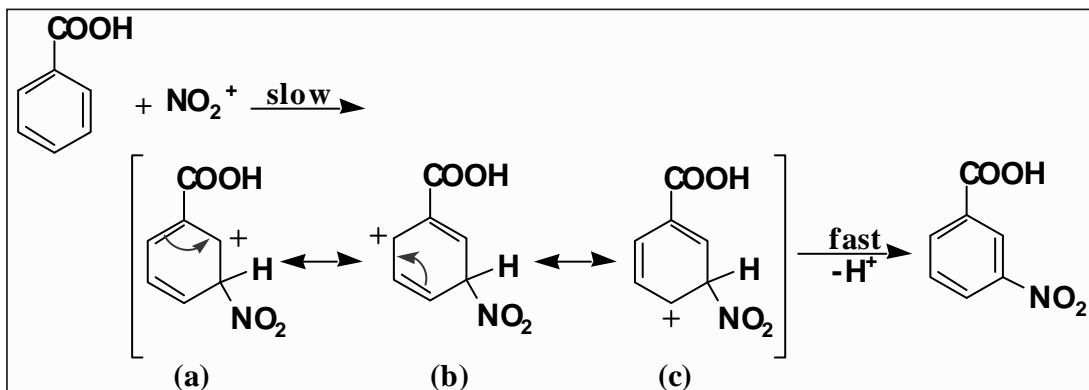
This resonance structure accounts for the selectivity

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Theory of Directing Effects

Nitration of benzoic acid

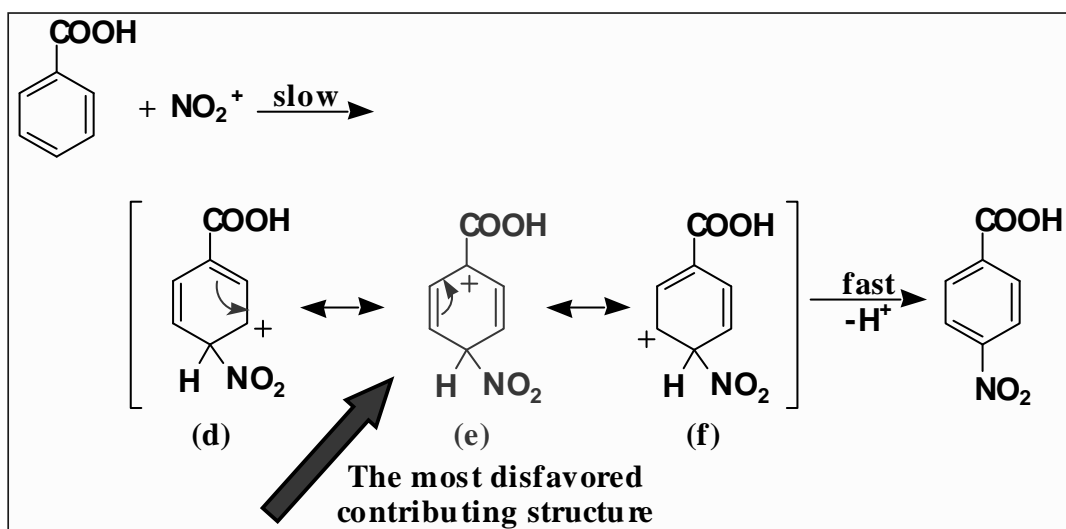
-NO₂; examine the meta attack:



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Nitration of benzoic acid

-NO₂: assume ortho-para attack:



This resonance structure accounts for the selectivity

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Activating-Deactivating

- Any resonance effect, such as that of -NH₂, -OH, and -OR, that delocalizes the positive charge on the cation intermediate lowers the activation energy for its formation, and has an **activating** effect toward further EAS
- Any resonance effect, such as that of -NO₂, -CN, -CO, and -SO₃H, that decreases electron density on the ring **deactivates** the ring toward further EAS

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Activating-Deactivating

- Any inductive effect, such as that of -CH₃ or other alkyl group, that releases electron density toward the ring **activates** the ring toward further EAS
- Any inductive effect, such as that of halogen, -NR₃⁺, -CCl₃, or -CF₃, that decreases electron density on the ring **deactivates** the ring toward further EAS

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Di- and Polysubstitution

ORGANIC LECTURE SERIES

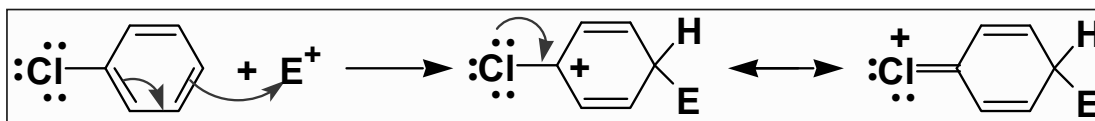
- **Generalizations:**
 - alkyl, phenyl, and all other substituents in which the atom bonded to the ring has an unshared pair of electrons are ortho-para directing; all other substituents are meta directing
 - all ortho-para directing groups except the halogens are activating toward further substitution;
 - the halogens are weakly deactivating

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ORGANIC LECTURE SERIES

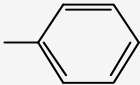
Activating-Deactivating

- for the **halogens**, the inductive and resonance effects run counter to each other, but the former is somewhat stronger
- **the net effect is that halogens are deactivating but ortho-para directing**



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Di- and Polysubstitution

Ortho-para Directing	Strongly activating	$-\ddot{\text{N}}\text{H}_2$	$-\ddot{\text{N}}\text{HR}$	$-\ddot{\text{N}}\text{R}_2$	$-\ddot{\text{O}}\text{H}$	$-\ddot{\text{O}}\text{R}$
	Moderately activating	$-\ddot{\text{N}}\overset{\text{O}}{\parallel}\text{CR}$	$-\ddot{\text{N}}\overset{\text{O}}{\parallel}\text{CAr}$	$-\ddot{\text{O}}\overset{\text{O}}{\parallel}\text{CR}$	$-\ddot{\text{O}}\overset{\text{O}}{\parallel}\text{CAr}$	
	Weakly activating	$-\text{R}$				
	Weakly deactivating	$-\ddot{\text{F}}:$	$-\ddot{\text{Cl}}:$	$-\ddot{\text{Br}}:$	$-\ddot{\text{I}}:$	
Meta Directing	Moderately deactivating	$-\overset{\text{O}}{\parallel}\text{CH}$	$-\overset{\text{O}}{\parallel}\text{CR}$	$-\overset{\text{O}}{\parallel}\text{COH}$	$-\overset{\text{O}}{\parallel}\text{COR}$	
	Strongly deactivating	$-\overset{\text{O}}{\parallel}\text{CNH}_2$	$-\text{SO}_3\text{H}$	$-\text{C}\equiv\text{N}$		
		$-\text{NO}_2$	$-\text{NH}_3^+$	$-\text{CF}_3$	$-\text{CCl}_3$	