Electrophilic Aromatic Substitution Reactions

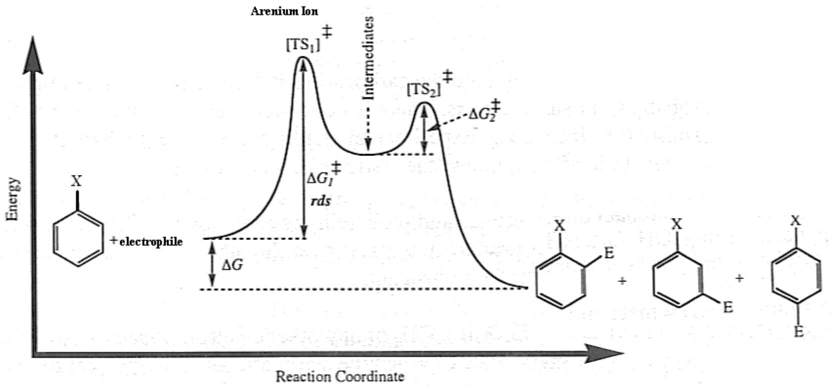
An organic reaction in which an electrophile substitutes a hydrogen atom in an aromatic compound.

*** Always think about **RESONANCE** ***
- Do I have resonance?
- How can I regain resonance?
- How does resonance influence the rate of this reaction?

Aromaticity is VERY important and nice to have. Benzene rings are very stable, aromatic molecules. Therefore, the electrophile must be VERY strong in order to disrupt aromaticity.

When doing EAS reactions, consider a few important things:
- *How can I make my electrophile stronger?*
    - Strong electrophiles REALLY need electrons, therefore, electrophiles are stronger when they are MORE POSITIVE (+, _+). Use a STRONG ACID to protonate a weak electrophile!
- *How can I make my nucleophile (benzene ring) stronger?*
    - Strong nucleophiles REALLY want to donate electrons, therefore, nucleophiles are stronger when they are MORE NEGATIVE (-, _-, lone pair electrons, pi-bond). Does your benzene ring have electron donating substituents with resonance?
- *How can I make my reaction FASTER?*
    - Reaction rate depends on the rate determining step (slowest step)
    - The rate determining step is the step which leads to the formation of the arenium ion (carbocation)
    - Therefore, you can make your reaction faster by **increasing the stability of the arenium ion**:
        - resonance electron delocalization
        - and/or better electron donating groups (substituents) on the benzene

Two-step mechanism of all EAS reactions:



(with adjustments, *Thinkbook*, P. 164 CFQ#7)

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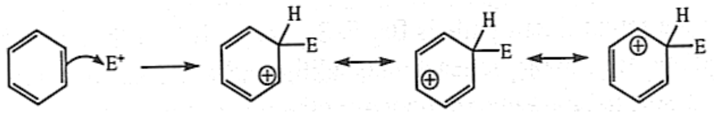
Bruice, P. *Organic Chemistry*. Pearsons Prentice Hall, 2004.
Hardinger, S. *Chemistry 14D Thinkbook*. Steven A. Hardinger, 2005.
Hardinger, S. *EAS*

1. **ELECTROPHILIC ATTACK**:
    - Electrophile (+E) attacks the aromatic ring
    - *THE rate determining step*: Requires a high energy of activation because **aromaticity is lost**.
    - Leads to the formation of a resonance stabilized carbocation known as an ***arenium ion***.

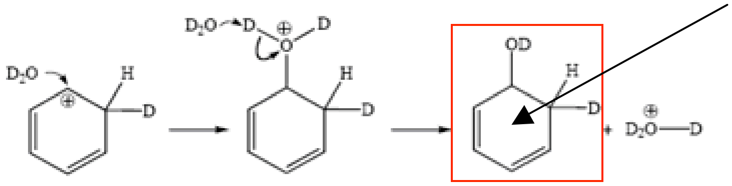


(Hardinger *Thinkbook*, P. 161, CFQ#2)

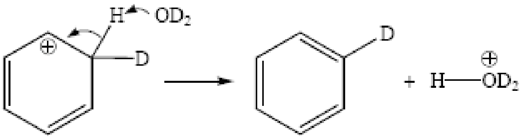
An **Arenium Ion** IS a carbocation. It has <u>resonance</u>!

Think of the 3 Fates (**Hardinger Textbook Chapter on *EAS*, P. 4)**

1) Capture a nucleophile – addition reaction; **won't restore aromaticity.**

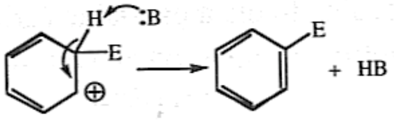


2) **Lose a proton**, gain a pi-bond – **restores aromaticity**! ← This occurs



3) Rearrangement – won't accomplish much

2. **DEPROTONATION:**



(Hardinger *Thinkbook*, P. 161, CFQ#2)

- The arenium ion is deprotonated by a weak base (:B)
- Requires a lower energy of activation because **aromaticity is regained**.

* * *

Two ways in which substituents donate or withdraw electrons:

What makes the substituent UNIQUE compared to the other hydrogen atoms attached to the benzene ring? (resonance, higher electronegativity…)

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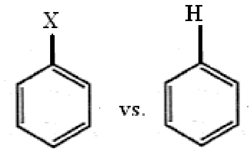
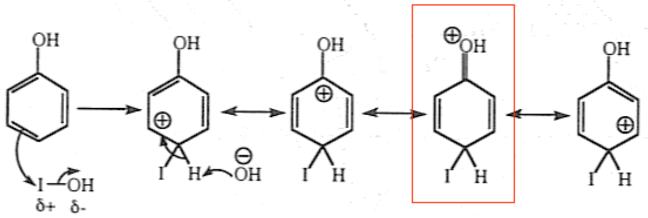


Inductive Effect

Electron Withdrawing	**Electron Donating**
• If the substituent is more electronegative than the other hydrogen atoms attached to the benzene ring, the substituent has a greater electron *withdrawing* ability • SLOWER REACTION	• If electrons on the sigma-bond of substituent move more readily towards the benzene ring, the substituent has a greater electron *donating* ability • FASTER REACTION

Resonance Effect

- delocalized lone pairs on the substituent can donate electron density to the benzene ring
- at the same time, the substituent is more electronegative than hydrogen and may inductively withdraw electrons (but has a lesser effect)
- Example: **Hardinger *Thinkbook* Practice Problem, P. 178 #15a:**



1 2 **3** 4 (resonance contributors)

*important resonance contributor: full octet for all atoms

Characteristics of Electron-donating Substituents:

- lone pairs (except alkyl, aryl, and CH=CHR groups)
- resonance: delocalizes positive charge of a carbocation, which increases carbocation stability

Characteristics of Electron-withdrawing Substituents:

- positive charge or partial positive charge
- high electronegativity ("electron greedy")

Substituent Directing Effect

The electrophile attacks the nucleophilic pi-bond on the benzene ring, but the **substituent on the benzene influences WHERE THE ELECTROPHILE ATTACHES** in order to have the FASTEST RATE.

Ortho/Para and Meta

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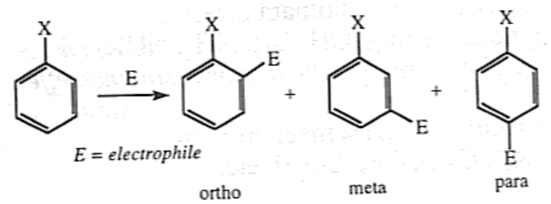
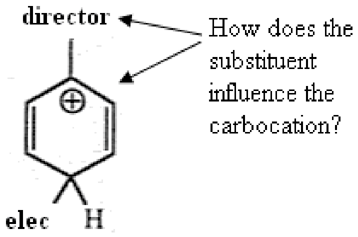


Important Qualities of Substituent (in order of importance):

1) *MECHANISM: How do resonance and the degree of substitution on the arenium ion influence the reaction rate?*

RESONANCE: Increases the stability of the carbocation!

- There are always at least 3 resonance contributors for ortho, para, and meta:
    - Think of the resonance contributor where the positive formal charged carbon is directly attached to the substituent/director:

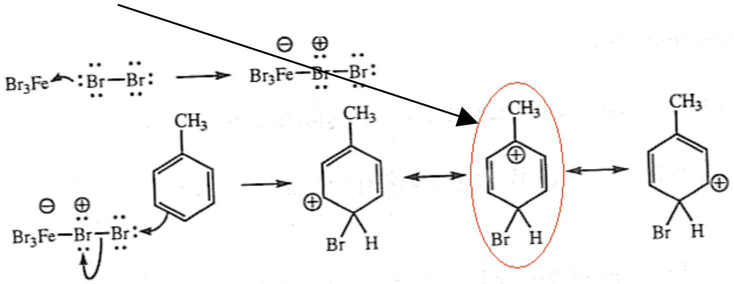


-
    - If the substituent is an electron donating substituent, it now can donate electrons to stabilize the electron-deficient carbocation.

Resonance Contributors (Hardinger *Thinkbook,* Lecture Supplement P. 17)

DEGREE OF SUBSTITUTION: increases the stability of the carbocation!

Tertiary > Secondary > Primary



(Hardinger *Thinkbook*, P. 162CFQ #3)

Ortho, para > meta

2) *Probability* – 2 ortho, 1 para, and 2 meta positions

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Hardinger, S. *Chemistry 14D Thinkbook*. Steven A. Hardinger, 2005.
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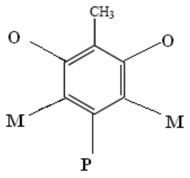
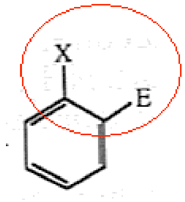


meta, ortho > para

3) *Steric Effects*: Electrophile attaches where there is the least amount of steric hindrance.



Para, meta > ortho

Activators: Substituents that make benzene MORE REACTIVE <u>donate electrons</u> into the benzene ring

- Increase benzene nucleophilicity (more reactive towards electrophiles)
- stabilizes carbocation intermediate
- stabilizes transition state leading to carbocation formation
- faster reaction rate for electrophilic attack

Deactivators: Substituents that make benzene LESS REACTIVE <u>withdraw electrons</u> from the benzene ring

- decrease benzene nucleophilicity (less reactive towards electrophiles)
- destabilize carbocation intermediate (increases the net positive charge on the carbocation)
- destabilize transition state leading to carbocation formation
- slower rate of electrophilic attack

All **ortho/para directors** are activators, *except for halides*.
All **meta directors** are deactivators, no exceptions.

(P. 632, Bruice *Organic Chemistry* – Contains a table of many more Ortho/para and Meta directors)

Ortho-Para Directors: all substituents that donate by resonance and/or inductive effects, are ortho-para directors

Common Ortho/Para Directors

- -- alkyl groups (electron donors)
- -- Ph (adjacent pi bond = resonance)
- -- :X (provides more resonance)

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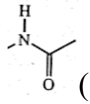
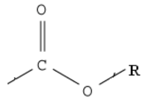
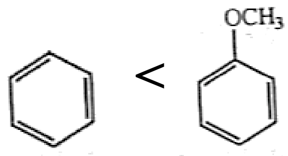
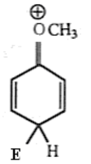
-  (amine)
-  (ester)
- --OH
- --O--R (ether)
- --NR2
- Halides: --Cl, --Br, --I (remember, they're also deactivators!)

Influence on Rate?
Which reaction is faster?



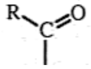
- Has 4 resonance contributors. The most important resonance contributor has a full octet on all atoms:



- Increased stability
- Decreased activation energy
- **Faster rate!**

Meta Directors: all substituents that withdraw electrons by resonance and/or inductive effects (EXCEPT halogens, which donate electrons by resonance, but withdraw electrons inductively)

Common Meta Directors

- --NO2
- --CF3
- --+NR3
- 
- --C_N

Why are electron withdrawing groups meta directors?
If you have a substituent, which removes electron density from the benzene ring, you want to make the most stable carbocation possible.

Compare the relative stability of resonance contributors for carbocations with a strongly electron withdrawing substituent like nitro (NO2):

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Hardinger, S. *Chemistry 14D Thinkbook*. Steven A. Hardinger, 2005.
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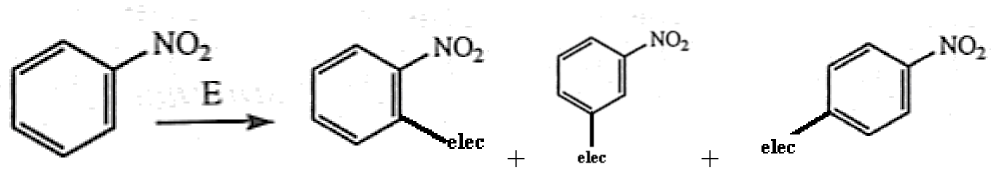
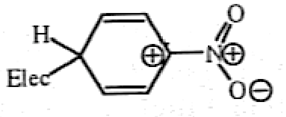


Ortho **Meta** **Para**

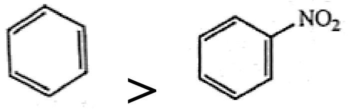
Ortho and Para will form one resonance contributor that looks like this:



This resonance contributor does not make a significant contribution to the stability of the arenium ion. In fact, the adjacent positively charged N **destabilizes** the carbon's open octet.

Therefore, **Ortho and Para positions** have TWO resonance contributors, while the **Meta position** has THREE resonance contributors, none of which forms this destabilizing resonance contributor. Thus, you can conclude that **meta directors** are **ortho-para inhibitors**.

Influence on Rate?
Which reaction is faster?



- Fewer resonance contributors (none of which has a full octet on all atoms)
- Less stable
- Increase activation energy
- **Slower Rate!**

Regioselectivity or Major Product:

Rule: the *most stable mechanism intermediate* will have the lowest energy of activation and the fastest rate, and therefore, be the major product.

Why a substituent on the benzene directs an electrophile to a certain position, depends on the stability of the carbocation intermediate.

Some Conditions Required in Order to Carry out a Reaction:

- Friedel-Crafts reactions won't happen with meta directors because the rings are too unreactive
- The order of a reaction is important in order to achieve the desired product. (Bruice, *Organic Chemistry,* P. 643)
- A STRONG ELECTROPHILE is necessary in order to overcome benzene's aromaticity

Important EAS reactions:

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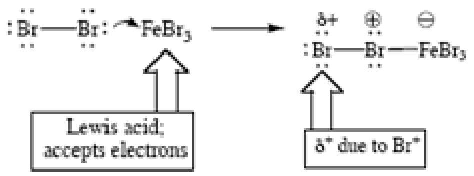
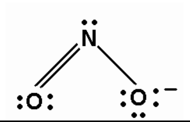
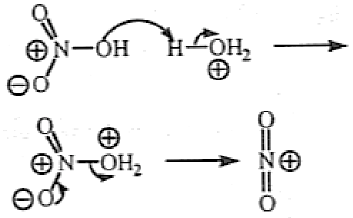
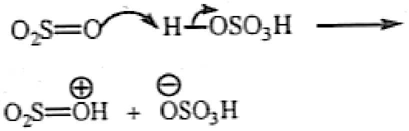
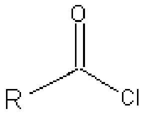
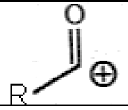
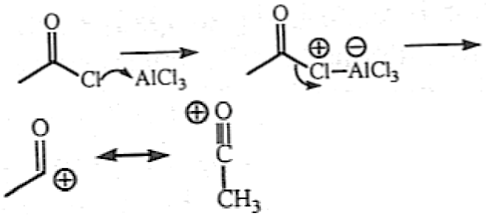
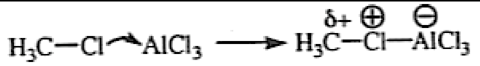
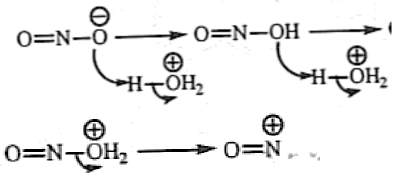
Hardinger, S. *EAS*.

Lewis Acid: electron-deficient; may react with an electrophile to increase its electrophilicity (increase _+)

Important EAS Reaction	**Original Electrophile** **Better Electrophile-** Electron deficient	**Catalyst: Strong Lewis Acid-** increases electrophilicity	**Mechanism to make a better electrophile:**
Halogenation	Br2 Cl2 I2 Br _+ Cl _+ I _+ F is too reactive	FeBr3 FeCl3 HgO or HNO3 for I	
Nitration	HNO3 NO2- 	H2SO4	
Sulfonation	SO3 SO3H+	H2SO4	
Friedel-Crafts acylation	 	AlCl3	
Friedel-Crafts alkylation	R – Cl _+ ⊕ ⊖ R—Cl—AlCl3	AlCl3	
Diazo Coupling	NO2 NO+	H3O+	

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