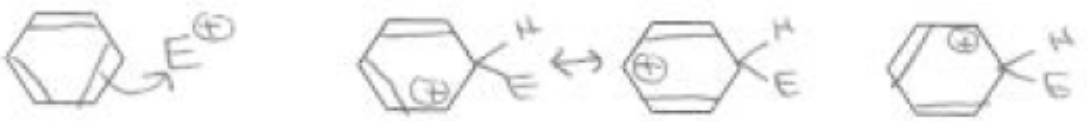
Electrophilic Aromatic Substitution

Electrophilic Aromatic Substitution: a reaction in which the hydrogen atom of an aromatic ring is replaced as a result of an electrophilic attack on the aromatic ring

Here are three general steps to an electrophilic aromatic substitution:

1. Attack of the electrophile on the aromatic ring, creating a resonance-stabilized carbocation called an arenium ion. *We lose aromaticity in this step, so the energy of activation is high. Furthermore, this is the rate-determining step of the reaction because of the disruption of aromaticity.*

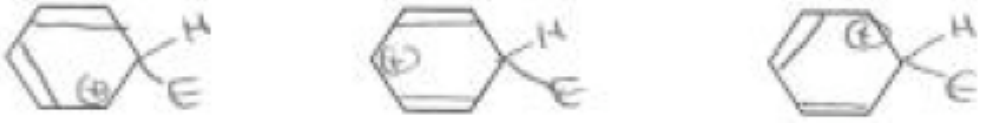


2. Deprotonation of the arenium ion by a weak base to regain aromaticity

Arenium ion: an ion that is the result of an electrophilic attack on a benzene ring

General structure of an arenium ion:

The arenium ion is a hybrid resonance structure. Here are three general resonance contributors of an arenium ion:

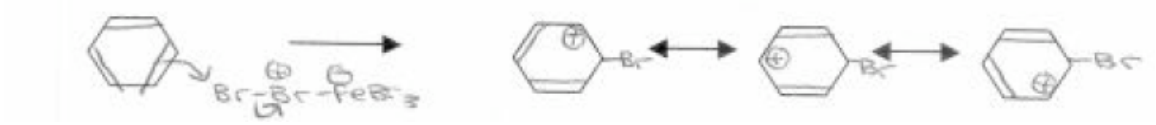


Try writing a mechanism for this reaction using the two steps outlined above. Include all resonance contributors of the arenium ion:

Solution:
This is a bromination reaction, which means that we must first generate the electrophile by adding a strong Lewis acid to the Br_2.

1. Generation of the nucleophile:

2. Attack of the elctrophile on the aromatic ring



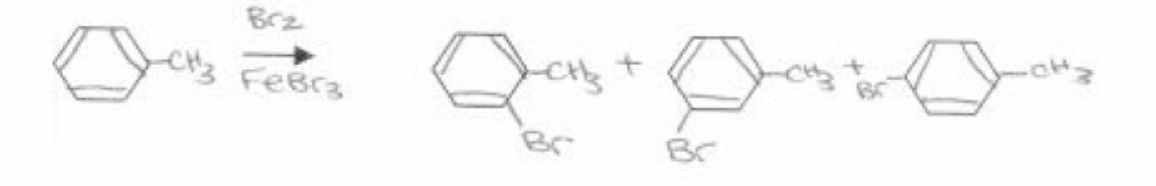
note: There are arenium ion resonance contributors, and aromaticity is lost in this step.

3. Deprotonation of the arenium ion by a weak base to regain aromaticity:

Directing effects of Elecrophilic Aromatic Substitution:

What happens if there is a substituent on the aromatic ring? How do we determine which isomer of the product is formed?

Example: (14D Thinkbook, CFQ #3)



3 Factors that determine where the electrophile attacks (in decreasing order of importance)

1. Resonance
2. Probability
3. Steric hinderance

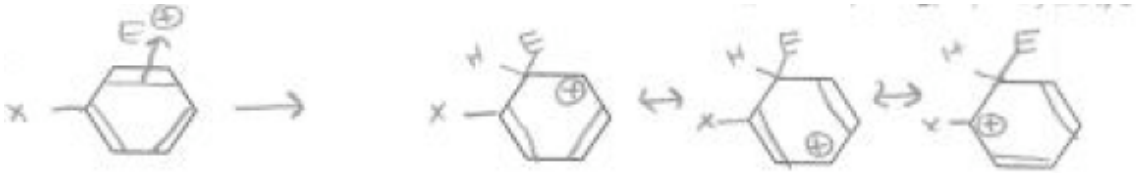
First, we will talk about resonance…

There are two types of substituent directors:

Note: we want to choose the most likely attack, which creates the most resonance-stabilized carbocation. Furthermore, full octets are highly favored over open octets.

1. Ortho/Para directors-groups that donate electron density to the ring. These groups are referred to as "activating groups" because they speed up the reaction.
    a. Three types of ortho/para directors
        i. Alkyl groups stabilize the aromatic ring by providing electron density through inductive effects
        ii. Pi bonds stabilize the aromatic ring by providing electron density through resonance
        iii. Lone pairs stabilize the aromatic ring by providing resonance
    b. Some examples of ortho/para directors
        i. Alkyl group, benzene ring, OH, OR, NH_2, NHR, NR_2, F, CL, BR, I

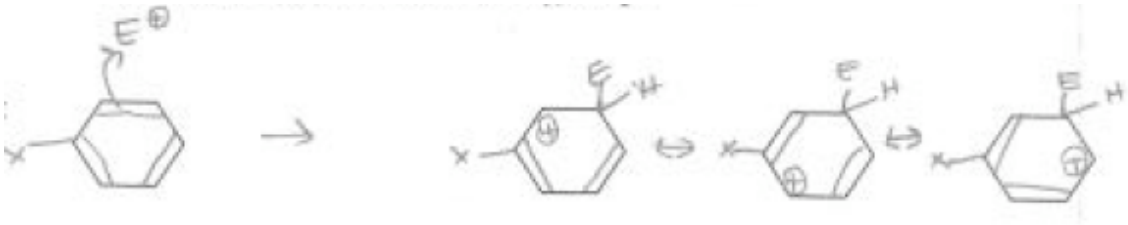
Ortho attack:



Para attack:

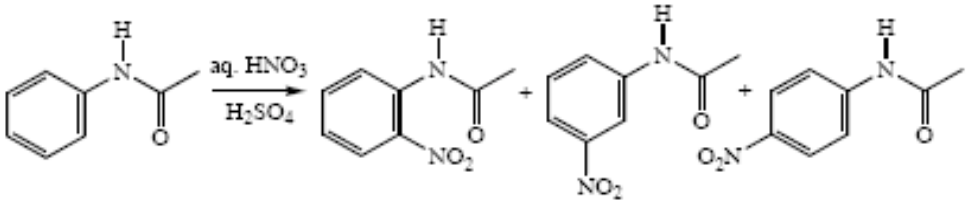
2. Meta directors-usually groups that withdraw electron density from the ring. These groups are often referred to as "deactivating groups" because they slow down the reaction.
    a. Some examples of meta directors
        i. NO_2, CN, NR_3^+, C=O, CF_3, SO_3H

Meta attack:



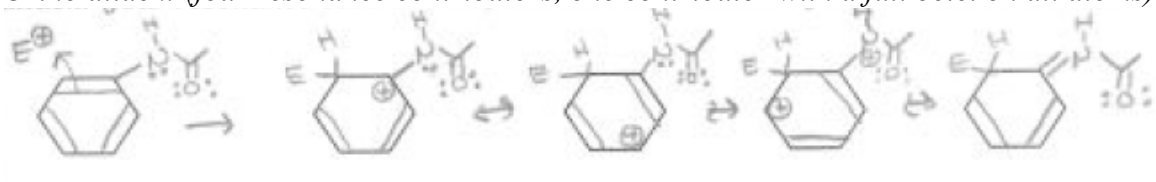
Try this problem: (From 14D Thinkbook, PP#3)

Determine which products dominate: the ortho and para product, or the meta product?

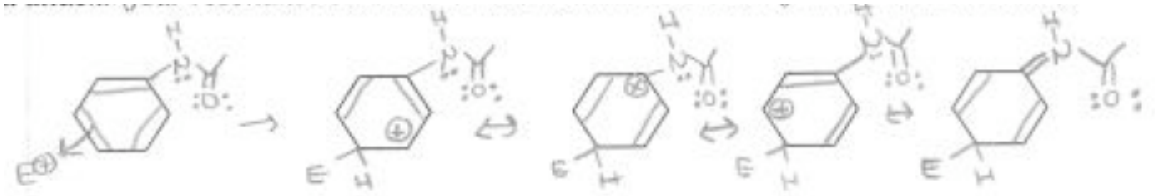


Solution: To determine which products dominate, we need to look at the resonance contributors of each of the arenium ion intermediates.

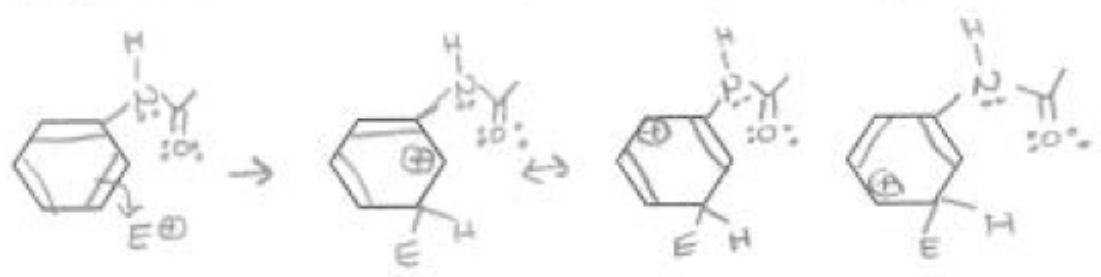
Ortho attack: (four resonance contributors, one contributor with a full octet on all atoms)



Para attack: (four resonance contributors one contributor with a full octet on all atoms)



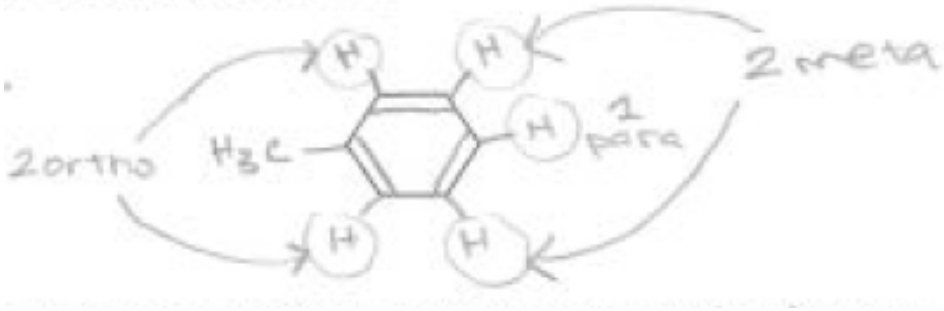
Meta attack: (three resonance contributors, no contributors have a full octet on all atoms)



Because the ortho/para attack results in more resonance contributors with full octets than the meta attack, the ortho/para attack is favored and ortho/para positions are favored for the substituent.

Other factors that determine where the electrophile attacks:

Next, we will talk about probability…



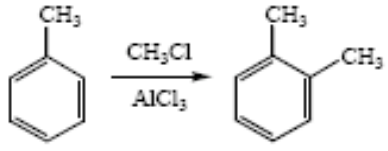
Note that there are two locations for ortho and meta attack but only one position for para attack. Therefore, in terms of probability, ortho and meta attacks are favored over para attack.

Next, we will talk about steric hinderance…

Usually, steric hinderance doesn't affect where the electrophile attacks. (When the electrophile is relatively small. However, if the electrophile is larger, then para attack is favored over ortho attack to reduce steric hinderance between the substituent and the electrophilic group.

Try this problem: (From 14D Thinkbook, PP#9)

Determine whether this reaction has ortho, para, or meta attack based on arenium ion stability, probability, and steric effects.



Solution:

Based on arenium ion stability, we see that ortho and para attack are favored because the arenium ion has three resonance contributors (two of the contributors have secondary carbocations and the other has a tertiary carbocation). However, meta attack

results in three resonance contributors (but all three contributors have secondary carbocations).

Based on probability, we see that there are two ortho and meta positions, but only one para position, so probability favors attack at the ortho and para positions.

Based on steric effects, we see that there is steric hinderance of the methyl group, (however this is not significant steric hinderance), so ortho attack is still favored over para. If the group had been large, para attack would have been favored over ortho attack.

Special Case—Substituent effects of Halogens:

Halogens are generally ortho/para directors because they provide a small amount of resonance stabilization due to their high electronegativity and small overlap with carbon p orbitals by elements not in the same period as carbon. However, halogens are deactivators because they are electron withdrawing (due to the inductive effect—they are highly electronegative)

If there is more than one substituent director:

Activators dominate deactivators while stronger activators dominate over weaker activators and weaker deactivators dominate over stronger deactivators.

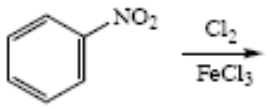
<u>Six Common Electrophilic Aromatic Substitution Reactions:</u>

Reminder: in electrophilic aromatic substitution reactions, a hydrogen on an aromatic ring is replaced by an electrophile.
You should practice these mechanisms and be able to determine the products and mechanisms when the reactants are given. You should also be able to recognize the missing reactants when given the product.

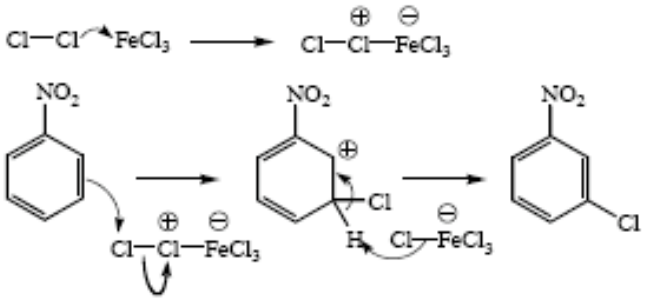
1. Halogenation: replacing hydrogen with a bromine or chlorine. Bromonation and chloronation require a Lewis acid, which accepts a pair of electrons to create a permanent bond dipole of the Br-Br bond or the Cl-Cl bond. This dipole allows the bromine or chloride to have a formal positive charge and therefore allows the group to be electrophilic enough to overcome the activation energy caused by the loss of aromaticity of the benzene ring.

    a. Bromonation (see example on page 1 for a bromination reaction)
    b. Chloronation

    Try this chloronation problem (Problem from 14D Thinkbook, PP#12e)
    Hint: it is very similar to the bromonation example given on page 1



Solution:

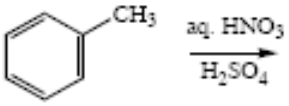


Notice the three general steps of electrophilic aromatic substitution as given on page 1.

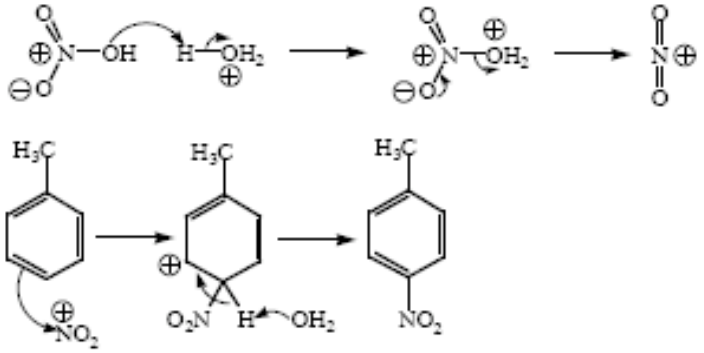
In this problem, the $FeCl_3$ is the Lewis acid, which has accepted a pair of electrons from the Cl-Cl bond. Note the formal positive charge that results on the Cl which is bonded to the $FeCl_3$. This formal positive charge increases the electrophilicity of the group and the electrophile can now attack the aromatic ring. In the final step, a proton is lost to restore aromaticity. Notice that NO_2 is a meta director.

2. Nitration: replacing a hydrogen with a nitro (NO_2) group. Nitration requires the presence of sulfuric acid (H_2SO_4) as a catalyst. Just like we had to take extra steps to create the electrophile in bromonation and chloronation (with the help of a Lewis acid), we must use the sulfuric acid to protonate the nitric acid, resulting in the formation of a nitronium ion. The nitronium ion can then proceed as a general electrophlic aromatic substitution.

   Try this nitration problem (Problem from 14D Thinkbook, PP#12a)
   Hint: Use H_3O^+ instead of H_2SO_4 *in this problem because mixing* H_2SO_4 *with* HNO_3 *produces several different products, including H_3O^+.*



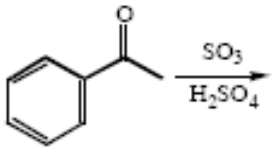
Solution:



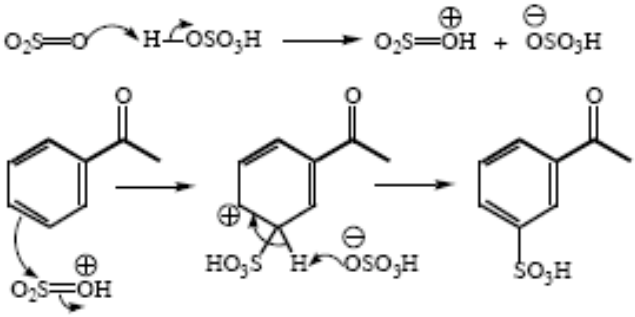
In this problem, we generated the electrophile using the H_3O^+ to protonate the nitric acid. Water leaves, and the result is a nitronium ion, which is the electrophile required for this mechanism. Notice that the nitrogen has a positive charge and electrophilic attack to the benzene ring occurs. Notice that in this reaction, the methyl group is a para director.

3. Sulfonation: replacing a hydrogen with a sulfonic acid (SO_3). Sulfonation is similar to nitration because in general, we create the electrophile by protonating the SO_3 with H_2SO_4 to make a stronger electrophile. The mechanism can then proceed as an electrophilic aromatic substitution reaction.

   Try this sulfunation problem (Problem from 14D Thinkbook, PP#12b)



   Solution:

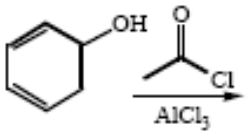


   In this problem, we used the H_2SO_4 to protonate the sulfonic acid to generate the electrophile. $^-OSO_3$ leaves and is used again to remove the proton to restore the aromatic ring structure. Note that sulfonation reactions are easily reversible and depending on reaction conditions, SO_3, SO_3H^+, or $H_3SO_4^+$ can be used as the

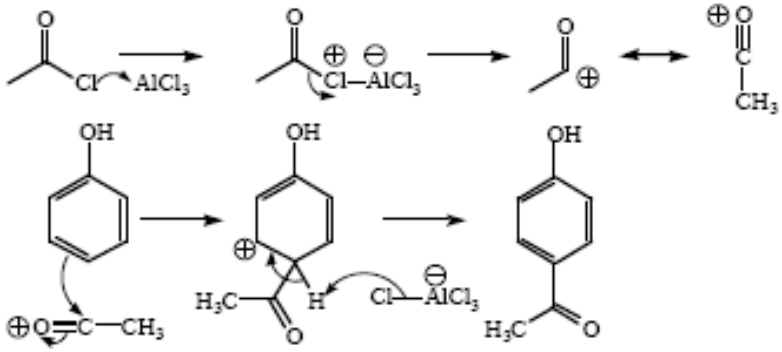
electrophile depending on reaction conditions. Note that $COCH_3$ is a meta director.

4. Friedel-Crafts Acylation: replacing a hydrogen with an acyl group (RC=O). In Friedel-Crafts Acylation, we form the acylium ion (the electrophile in the reaction) by using a lone pair from the chlorine (of the H_3COCl) to fill the open octet of the alunimum (of the $AlCl_3$). As a result, the chlorine carbon bond is weakened and Cl^+-Al^-Cl_3 leaves. The acylium ion acts as an electrophile in the electrophilic aromatic substitution mechanism.

   Try this problem (14D Thinkbook, PP#12d)



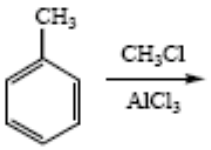
   Solution:



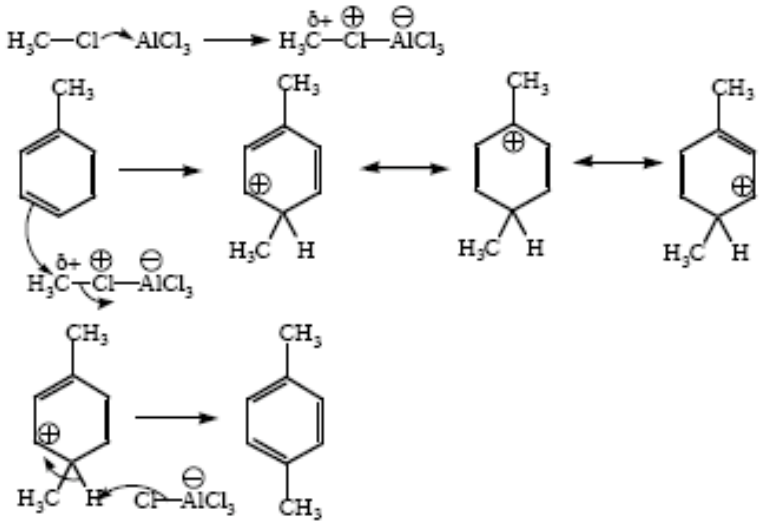
   In this Friedel-Crafts Acylation, we use the acylium ion for electrophilic attack on the aromatic ring. We use the Cl^+-Al^-Cl_3 to remove the proton to restore the aromaticity of the aromatic ring. Notice that ^-OH is a para director in this reaction.

5. Friedel-Crafts Alkylation: replacing a hydrogen with an alkyl group (R). In Friedel-Crafts Alkylation, we use the lone pair of the chlorine (of the CH_3Cl) to fill the open octet of aluminum (of the $AlCl_3$). As a result, the $ClAl^-Cl_3$ leaves. The $(CH_3)_3C^+$ acts as the electrophile in the electrophilic aromatic substitution mechanism.

   Try this problem (From Chem 14D Thinkbook, PP#9)



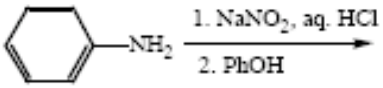
Solution:



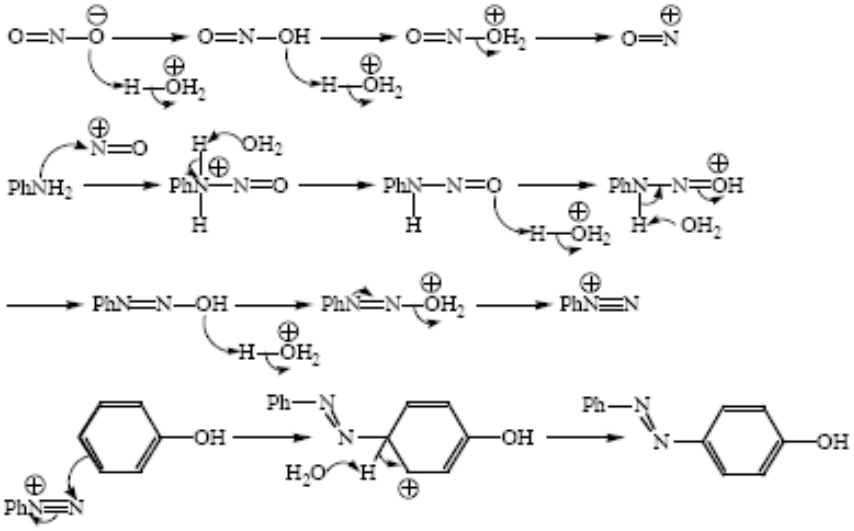
This mechanism follows the general mechanism for Friedel-Crafts Alkylation. I have discussed the directing effects of the CH_3 for this problem on page 5.

6. Diazonization of a Primary Amine: In this reaction, we react an acid (like H_3O^+) with NO_2^- to form a nitrosonium cation ($O{=}N^+$) which acts as the electrophile. Then, we form the N-N bond with the electrophilic attack of the nitrosonium cation to the Ph-NH_2. Then, through a series of protonation and deprotonation steps by water (the proton shuttle) we form a diazonium cation. In 14D, we did a specific reaction which was diazo coupling.

Try this problem (Chem 14D Thinkbook, PP#12f)



Solution:



This mechanism might look intimidating, but it the trickiest part is the formation of the nitrosonium cation and the formation of the N-N bond. Through a series of protonation and deprotonation steps, we get a product of $PhN^{+} \equiv N$, which is used as the electrophile to the PhOh. The rest of the mechanism proceeds as a general electrophilic aromatic substitution reaction.

Note: All the above information and example problems are taken from lecture, Chemistry 14D Thinkbook by Steven Hardinger for Winter 2006, *Organic Chemistry* by Paula Yurkanis Bruice, 4th edition, and the Electrophilic Aromatic Substitution chapter of Professor Hardinger's textbook in progress