16. Electrophilic Aromatic Substitution

A. Introduction

Aromatic compounds are especially stable and despite having π-bonds do not react like typical alkenes. For example, the π-bond in 1-hexene undergoes bromination to give 1,2-dibromohexane, while benzene does not react under similar conditions (figure 1).

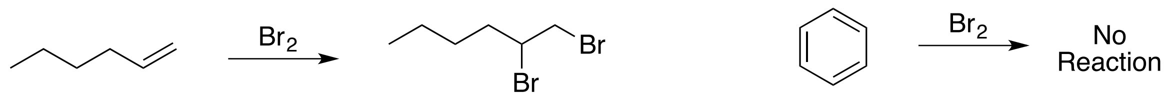
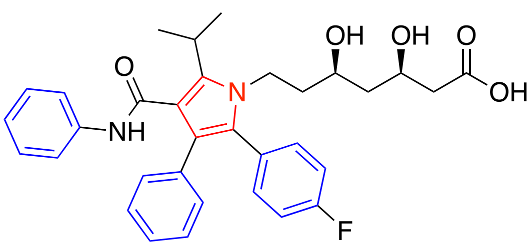
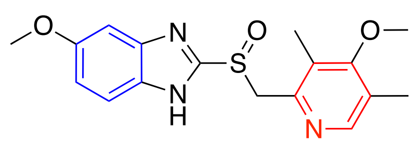


Figure 1. Bromination of Alkenes

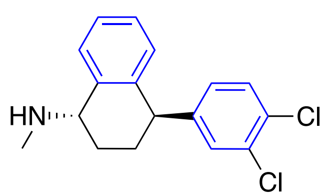
Aromatic compounds are extremely important for their industrial and pharmaceutical use. A few prescription drugs containing one or more aromatic rings are shown in figure 2. With their immense value as synthetic targets, it is important to understand both the properties and the reactivity of aromatic rings. By tapping into the reactions of aromatic rings, a simple benzene ring can be highly functionalized to provide complex organic molecules. The focus of this experiment is on electrophilic substitution of benzene rings (shown in blue in figure 2), however, a variety of other aromatic rings (shown in red in figure 2) do exist, and bring an entirely different breadth of properties to these molecules.



Lipitor
used for treating high cholesterol



Nexium
a proton pump inhibitor used to treat acid reflux



Zoloft
used for treating depression

Figure 2. Pharmaceutical Compounds Containing Aromatic Functionality

Although benzene does not react with bromine alone, it was found that by adding a Lewis acid ($FeBr_3$) to the reaction mixture, benzene could be mono-brominated in relatively high yield. Addition of the Lewis acid enhances the electrophilicity of the bromine to such a degree that one can overcome the low reactivity inherent to benzene. The reaction mechanism first involves generation of the active electrophile by coordination of bromine with iron tribromide. This Lewis acid-base adduct provides a source for the highly electrophilic bromonium ion ($Br^{\oplus}$). The second part of the mechanism involves reaction of the benzene π-bond with either the Lewis acid-base adduct (shown) or simply with $Br^{\oplus}$ to provide a carbocation intermediate. This step temporarily breaks the aromaticity in the ring. Bromide ($Br^{\ominus}$), from $FeBr_4^-$ then acts as a base removing a proton from the ring to form a π-bond and reestablishing aromaticity. This overall process is referred to as an electrophilic aromatic substitution (EAS) because a hydrogen on the aromatic ring is substituted with an electrophile, such as Br. (Figure 3)

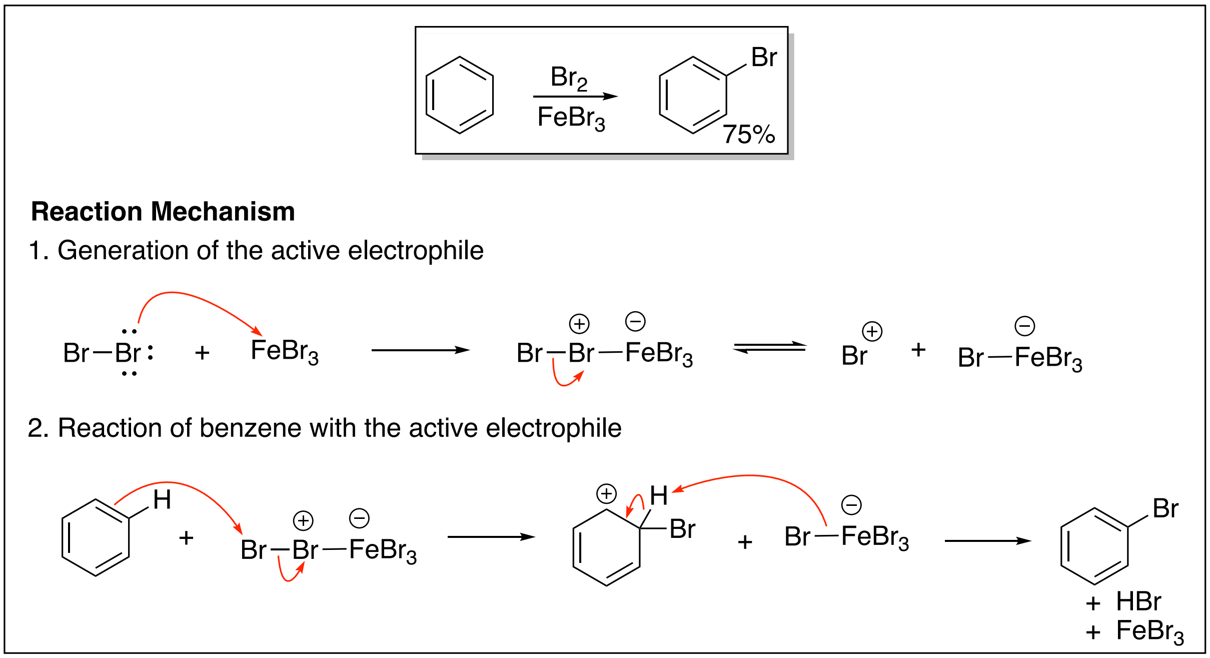


Figure 3. Electrophilic Bromination of Benzene

A variety of conditions can be employed to obtain severed different mono-substituted benzene rings. Table 1 lists the five most common electrophilic aromatic substitution reactions.

	Conditions	Product	Active Electrophile
Ph—H	$\xrightarrow[FeBr_3]{Br_2}$	Ph—Br	$Br^{\oplus}$
Ph—H	$\xrightarrow[FeCl_3]{Cl_2}$	Ph—Cl	$Cl^{\oplus}$
Ph—H	$\xrightarrow[H_2SO_4]{HNO_3}$	Ph—NO_2	$\overset{\oplus}{N}O_2$
Ph—H	$\xrightarrow[H_2SO_4]{SO_3}$	Ph—SO_3H	$\overset{\oplus}{S}O_3H$
Ph—H	$\xrightarrow[AlCl_3]{R\text{-}Cl}$	Ph—R	$R^{\oplus}$

Table 1. Typical Conditions for Electrophilic Aromatic Substitution

Disubstituted Benzene Terminology

The terms *ortho*, *meta*, and *para* are frequently used to describe the locational relationship between two substituents on an aromatic ring. Two substituents in a 1,2 relationship are said to be *ortho*, two substituents in a 1,3 relationship are said to be *meta*, and two substituents in a 1,4 relationship are said to be *para*. (Figure 4)

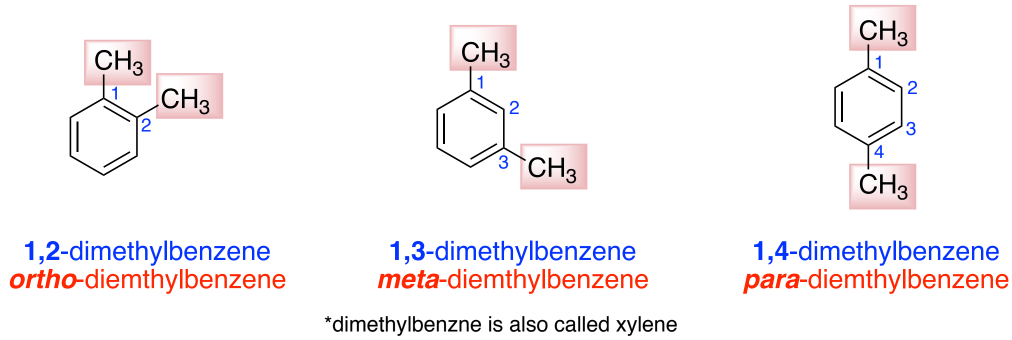


Figure 4. Ortho, Meta, and Para Terminology

Directing Group Effects

When an aromatic ring contains a substituent, that substituent affects the nucleophilicity and therefore reactivity of the aromatic ring. Some substituents activate the ring, making it more reactive than benzene alone, while other substituents deactivate the ring, making it less reactive than benzene. Figure 5 lists some common activating and deactivating groups. These groups can be generalized in the following way: Activating groups typically contain a lone pair on the atom that is directly attached to the aromatic ring. Alkyl groups are one exception, however, and are only weakly activating. Deactivating groups on the other hand have a halogen or electron withdrawing group, such as C=O, directly attached to the aromatic ring.

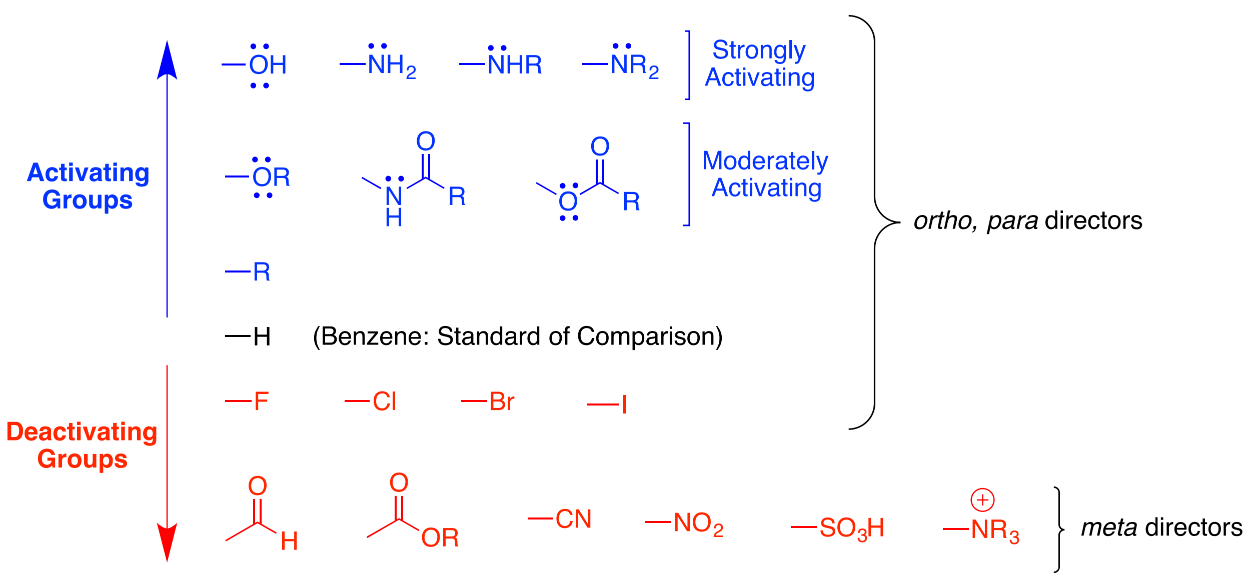


Figure 5. Common Activating and Deactivating Groups

Activating groups enhance the nucleophilicity and reactivity of the ring by resonance donation as shown in figure 6a. Deactivating groups on the other hand, decrease the nucleophilicity and reactivity of the ring by resonance and/or inductive withdraw of electron density from the aromatic ring as shown in figure 6b.

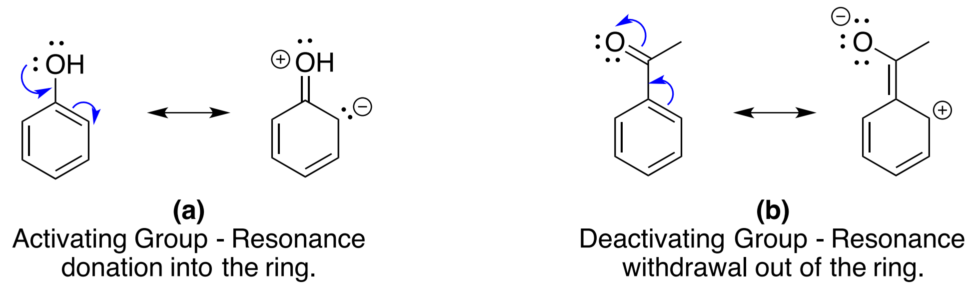


Figure 6. Resonance Effect of Activating and Deactivating Groups

It is also important to note that when an electrophilic aromatic substitution reaction is performed on a mono-substituted benzene ring containing an activating group, the new electrophile will add to the *ortho* and the *para* positions of the ring (figure 7a). In the case of most deactivating groups on the ring, the electrophile will add to the *meta* position (figure 7b). The origin of this selectivity will be discussed in the next section.

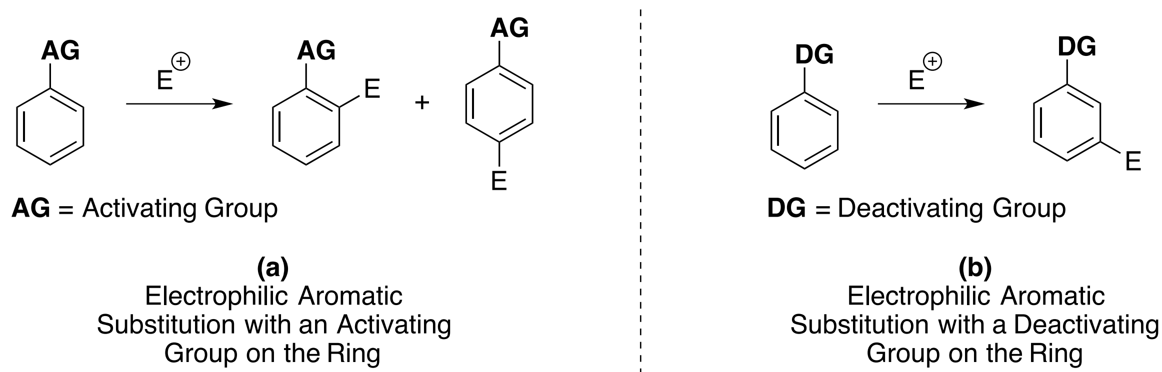


Figure 7. Directing Group Effects in Electrophilic Aromatic Substitution

Aromatic rings containing very strongly activating groups such as –OH (phenol) and $–NH_2$ (aniline) can actually be halogenated in the absence of a Lewis acid catalyst. In fact, these strongly activated aromatic rings are so highly activated that it is difficult to stop at mono-halogenation. When three equivalents of bromine are used, the compound is tri-halogenated at both *ortho* positions and the *para* position as shown in figure 8. In the first part of this laboratory experiment, you will brominate phenol to produce tribromophenol.

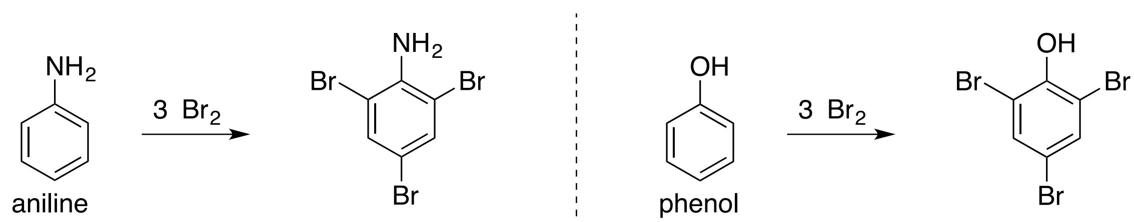


Figure 8. Halogenation of a Strongly Activated Aromatic Ring

In the second part of the laboratory experiment you will perform an electrophilic nitration on two substituted benzene derivatives. Like bromination, the first step of nitration involves generation of the active electrophile, which is a nitronium ion ($NO_2^{\oplus}$). The aromatic compound then reacts with this electrophile. You will investigate the relative reactivities of methyl benzoate and acetanilide under electrophilic nitration conditions to determine experimentally which of the two substrates is more reactive. (Figure 9)

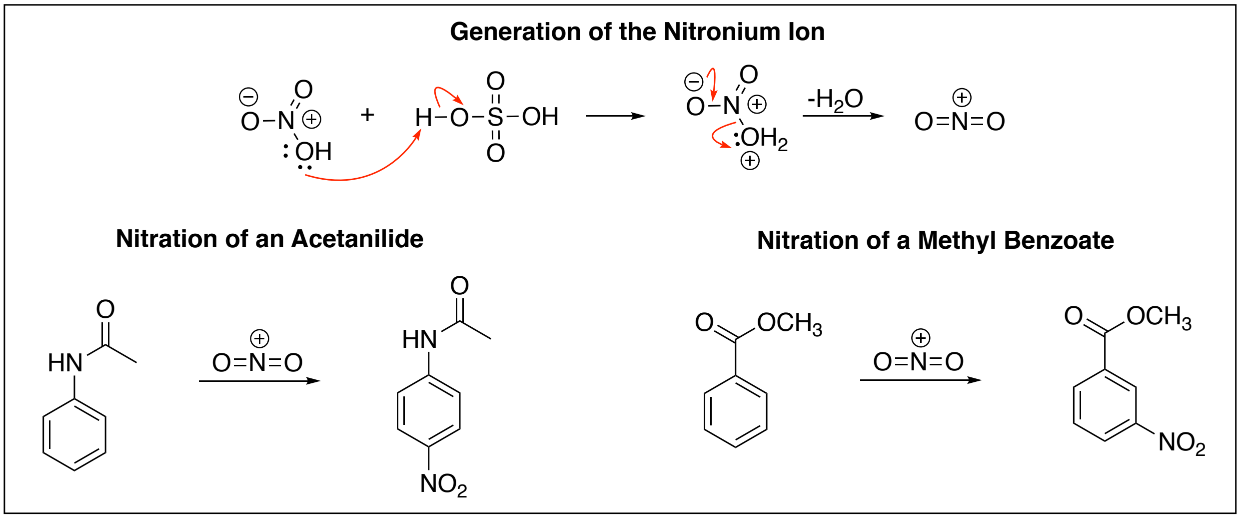


Figure 9. Nitration of an Aromatic Ring

Ortho/Para Selectivity with an Activating Group

When an activating group is present on the benzene ring, electrophilic aromatic substitution occurs such that the new group adds *ortho* and/or *para* to the activating group. This selectivity can be understood by investigating the reaction mechanism. In both *ortho* and *para* additions of the electrophile, aromaticity is temporarily broken and a carbocation resides on the ring. This carbocation can be delocalized over the ring's π-system (blue arrows, figure 10). Additionally, the lone pair on the activating group is delocalized (green arrows, figure 10) giving a fourth resonance structure which is a major contributor to the resonance hybrid due to all atoms in this resonance structure having an octet of electrons. *Para* addition is analogous, giving four similar resonance structures. You will explore the mechanism for para addition in pre-lab question 3.

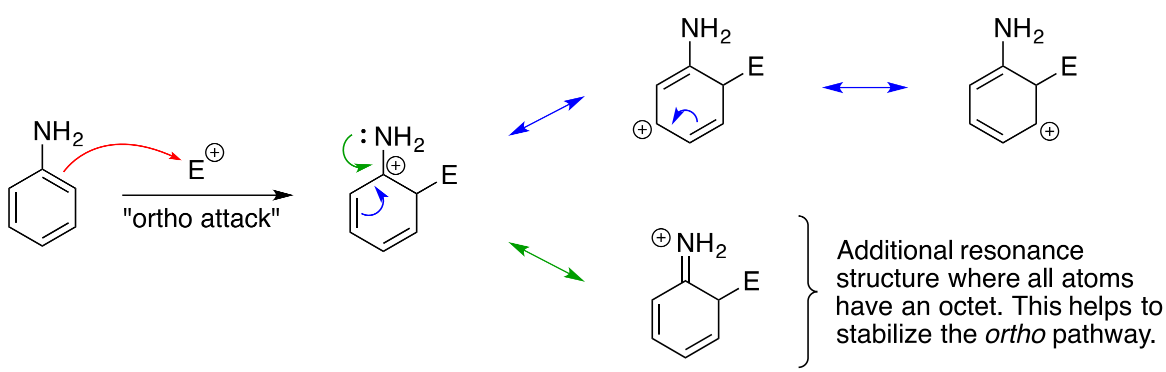


Figure 10. Ortho Addition of an Electrophile to an Activated Aromatic Ring

While there is nothing especially bad about *meta* addition to an activated aromatic ring, it is simply a much slower process due to the mechanistic pathway being higher in energy than *ortho/para* addition pathway. The *meta* addition pathway (figure 11), has only three resonance structures stabilizing the intermediate carbocation. In comparison, the *ortho/para* pathway has four resonance structures.

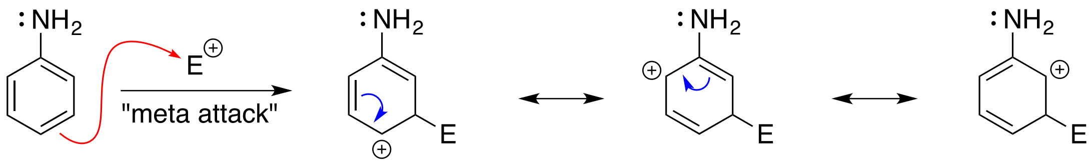


Figure 11. Meta Addition of an Electrophile to an Activated Aromatic Ring

Mechanistically, the pathways for both *ortho* and *para* nitration of acetanilide are essentially equivalent, yet when the reaction is performed, the *para* product is obtained selectively. This selectivity is due to the substrate's large/bulky activating group which sterically hinders (blocks) the *ortho* sites, making *para* addition preferred. (Figure 12)

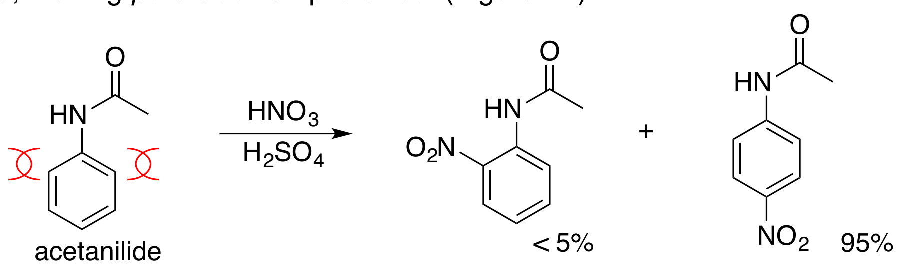


Figure 12. Electrophilic Nitration of Acetanilide

***Meta* Selectivity with a Deactivating Group**

When a deactivating group is present on the aromatic ring, the electrophilic aromatic substitution takes place at a much slower rate than with an activating group. Additionally, most deactivating groups direct the incoming electrophile to the *meta* position. While there is nothing especially stabilizing about the *meta* pathway, it is lower in energy than the *ortho/para* pathways. As shown in figure 13, *ortho/para* addition will give a resonance structure that puts the carbocation adjacent to a partially positive charged atom. This is a high-energy structure that is not favored. *Meta* addition does not give this high-energy resonance structure, resulting in it being the preferred pathway when a deactivating group is on the ring.

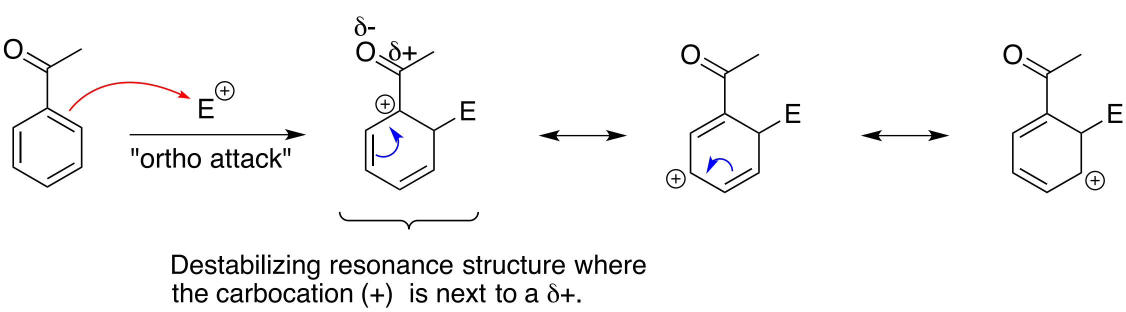


Figure 13. Ortho Addition of an Electrophile to a Deactivated Aromatic Ring

B. Experimental Procedure

1. Tribromination of Phenol

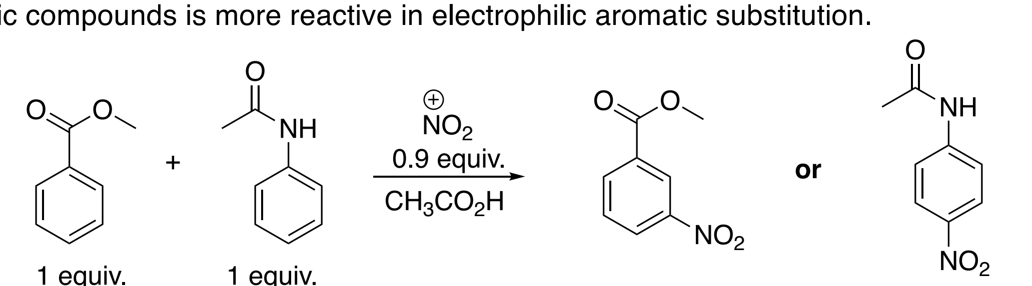
Reaction: Measure 50. mg of phenol into a a small test tube supported in a 100-mL beaker. Add 5 mL of water to dissolve the phenol. Next add 20% bromine in acetic acid solution dropwise mixing thoroughly throughout the addition. Bromine addition should be ceased once a permanent red/brown color persists. At this point, bromination is complete. Add 5-10 drops of aqueous $NaHSO_3$ with thorough mixing to destroy the excess bromine. Collect the solid product via Hirsch filtration, washing the solid with 2-3 mL of cold water.

Recrystalization[1]: After briefly air drying the solid, transfer it to a Craig tube and dissolve it in a minimum amount of hot ethanol. This is achieved by placing the Craig tube in a 100-mL beaker half-filled with water, heated to boiling. Ethanol can then be added a few drops at a time until the solid all dissolves. Remove the Craig tube from the hot water bath and allow the solution to cool slowly to room temperature at which time crystals should begin to form. Finally, place the mixture in an ice bath to complete crystallization. Collect the solid product by centrifugation. *While waiting for crystallization, you can begin experiment 2.*

Data Collection: Determine the yield, measure the melting point, and record an IR spectrum of the final product.

2. Competitive Nitration

In this experiment, you will investigate the relative reactivities of acetanilide and methyl benzoate toward electrophilic nitration. Based on the experimental results, you will be able to provide experimental evidence to support your theoretical hypothesis as to which one of the two aromatic compounds is more reactive in electrophilic aromatic substitution.



The actual product will come from the more reactive aromatic starting material (methyl benzoate or acetanilide)

When performing this experiment, it is imperative that a deficiency of nitric acid be used. Otherwise, once the more reactive aromatic compound has reacted away, the less reactive one will begin to react, skewing your results. The reagent table below is based on 50. mg of nitric acid, however, once you weigh out the nitric acid for the experiment, you will need to adjust the requires masses of acetanilide and methyl benzoate based on the actual amount of nitric acid.

				Sample Data		Actual Data	
Reagent	**Mol. Wt.**	**Equiv.**	**Density**	**Mass**	**Mmol**	**Mass**	**Mmol**
Methyl Benzoate	136 g/mol	1	--	83.9 mg	0.617		
Acetanilide	135 g/mol	1	--	83.3 mg	0.617		
HNO_3 (70%)	63 g/mol	0.9	1.5 g/mL	50.0 mg	0.556[2]		

[1] See Chem 235 Experiment 3 to review the microscale recrystallization technique.

[2] When calculating the moles of nitric acid, the mass must first be multiplied by 0.7 to account for the 70% HNO_3 solution.

Generation of the Electrophile: Measure approximately 50 mg of concentrated HNO_3 (70% aqueous solution) into a pre-weighed 3-mL conical reaction vial. Weigh the vial containing the acid to get the exact mass of HNO_3 used. *Note: Two drops of HNO_3 is approximately 50 mg*. Next, add 10 drops of glacial acetic acid followed by 20 drops of concentrated H_2SO_4. Mix the solution thoroughly to generate the active electrophile (nitronium ion) *in situ*.
EAS Reaction: To a 5-mL conical reaction vial, add methyl benzoate and acetanilide (masses should come from your calculations). Add 10 drops of glacial acetic acid and 20 drops of sulfuric acid. Insert a spin vane into the vial and mix until a clear, but not colorless solution is obtained. Place this vial into a cold-water bath (~10 °C) prepared in a small beaker. With rapid stirring, add the nitronium ion solution dropwise via pipet over 5 min. Once addition is complete, remove the water bath and allow the mixture to stir at room temperature for 5 min. To the resulting solution, slowly add water with mixing to bring the total volume in the vial to 4 mL. Collect the solid precipitate via Hirsch filtration and wash the solid well with small volumes of ice-cold water. Transfer the solid to the Craig tube and recrystallize from hot ethanol.
Data Collection: Once the crystals have dried, determine the yield, measure the melting point, and record an IR spectrum, and NMR spectrum. You will be able to identify the nitration product based on this data.

C. Pre-Lab Questions

1. Compare the reactivity of $PhNH_3^{\oplus}$ and $PhNH_2$ under bromination conditions. Classify each as an activating or deactivating group and explain your reasoning. *Hint: draw out the complete structure of each showing all lone pairs.*

2. Show all aniline resonance structures involving donation of the $–NH_2$ lone pair into the aromatic ring. Using these resonance structures, explain why $–NH_2$ is an *ortho, para* directing group.

3. The mechanism for the *ortho* substitution of aniline is shown in figure 10. Using acetanilide, which is an activating group like aniline, show the mechanism for *para* addition. Include all resonance structures. Explain why *para* addition, like *ortho* addition, is favored when an activating group is on the ring.

4. Based on the discussion of reactivity in the introduction, what do you hypothesize will be the major product of the competitive nitration reaction?

D. Post-Lab Questions

1. Had you performed the bromination of phenol with only one equivalent of Br_2, which product (*ortho* or *para*) do you think would predominate? *Hint: think about probability and statistics.*

2. What product did you obtain from the competitive nitration?
   a. Which particular IR absorptions led you to this conclusion?
   b. How can the NMR signals in the aromatic region be used to confirm the identity of your product?
   c. Look up the literature melting points for 4-nitroacetanilide and methyl 3-nitrobenzoate at www.sigmaaldrich.com. How does your experimental melting point compare?

3. Explain why the $–NHCOCH_3$ in acetanilide is only moderately activating while the $–NH_2$ group in aniline is strongly activating.