

## Aromatic Electrophilic Substitution

### Substituted Benzene Rings

Only one monosubstituted product can result when electrophilic substitution occurs on benzene, but what happens if we do the reaction on a ring that already has a substituent present? Substituents already present on the ring have two effects:

- 1) Substituents affect the reactivity of the aromatic ring. Some substituents make the ring more reactive than benzene and some make it less reactive than benzene.
- 2) Substituents affect the orientation of the reaction. Three possible disubstituted products can result: ortho, meta and para. The nature of the substituents already present on the benzene ring determines the position of the second substituent.

### Resonance and Inductive Effects

A substituent can donate or withdraw electrons from the aromatic ring in two ways: by inductive effects and by resonance effects.

Inductive effects are due to the intrinsic electronegativity of the atoms and to bond polarity in functional groups. These effects operate by donating or withdrawing electrons through the sigma ( $\sigma$ ) bonds. An electron donating group will direct to the ortho/para position while an electron withdrawing group will direct to the meta position. This effect is considered weak compared to resonance effects.

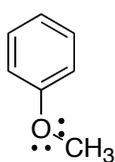
Resonance effects operate by donating or withdrawing electrons through the pi ( $\pi$ ) bonds by overlap of the p atomic orbital on the substituent with the p atomic orbitals ( $\pi$  molecular orbital system) on the aromatic ring. An electron donating group will direct to the ortho/para position while an electron withdrawing group will direct to the meta position. This effect is considered strong compared to inductive effects.

## Resonance Donating Effect

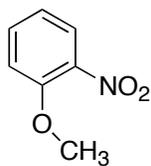
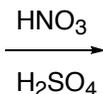
The general way to determine if a substituted aromatic ring is an electron donor is the presence of an electron pair on the substituent (halogen, phenol, ether, amine etc.), where Y = an atom with an electron pair.



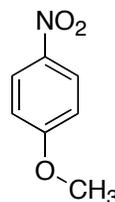
An example of this effect is the nitration of methoxybenzene (anisole) in which the aromatic ring is substituted in the ortho and para positions. The para disubstituted product is formed in higher yield due to steric effects with the ortho product.



methoxybenzene



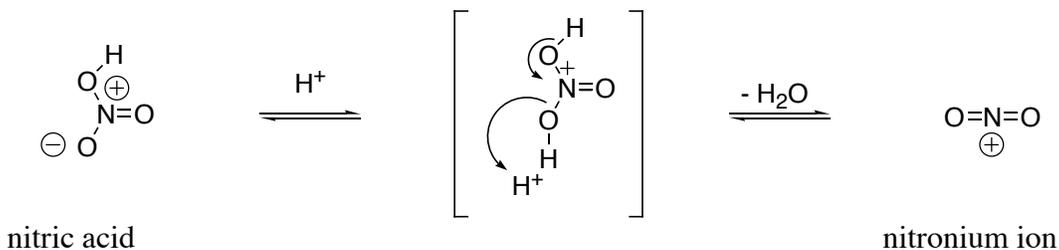
o-nitromethoxybenzene



p-nitromethoxybenzene

## Mechanism

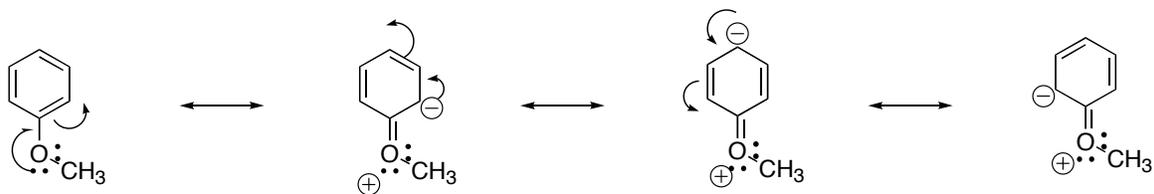
The first step of the reaction mechanism is the formation of the electrophile, the nitronium ion, from nitric acid. Nitric acid is protonated in the presence of sulfuric acid and with the loss of water, the nitronium ion is formed.



nitric acid

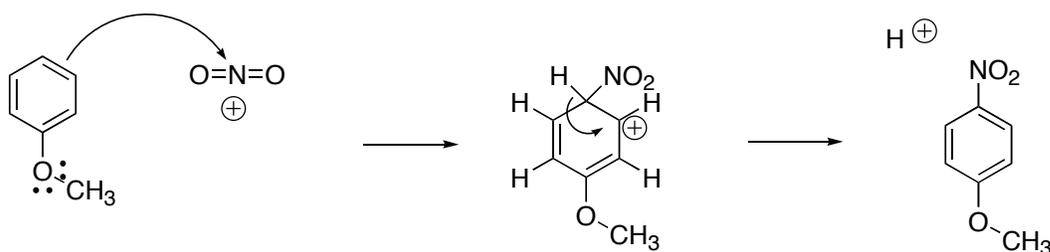
nitronium ion

The lone pair electrons from the oxygen are conjugated to the aromatic ring as shown by the below resonance structures. This electron donation places negative charge at the ortho and para positions. The anion in each case is conjugated and stabilized by resonance.



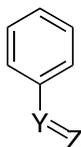
methoxybenzene (anisole)

The anion then attacks the electrophile, and with loss of a proton, para-nitromethoxybenzene is formed along with ortho-nitromethoxybenzene. Shown is the formation of the para derivative. The ortho derivative forms analogously.

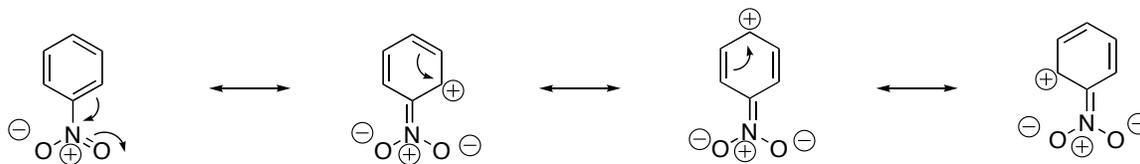


### Resonance Withdrawing Effects

The general way to determine if a substituted aromatic ring is an electron withdrawer is the presence of a conjugated double bond to a heteroatom (nitro, carbonyl, cyano, etc.). The general structure is  $-Y=Z$  where the Z atom is usually more electronegative than Y.

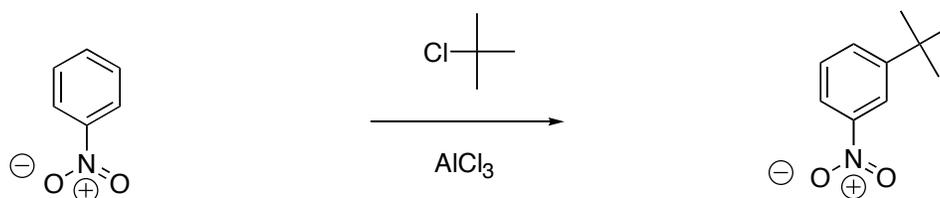


The resonance forms for nitrobenzene are shown below to produce positive charge within the aromatic ring at the ortho and para positions. In the previous case with a methoxy substituent, negative charge was produced at those positions. The electrophile will then react where there is the least amount of positive charge, therefore at the meta position.



nitrobenzene

An example is the alkylation of nitrobenzene with t-butyl chloride, in which meta-t-butylnitrobenzene is formed.

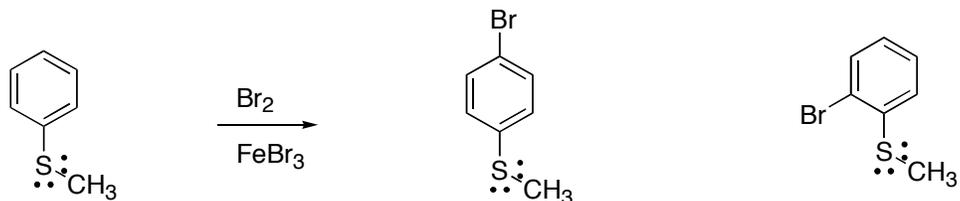


nitrobenzene

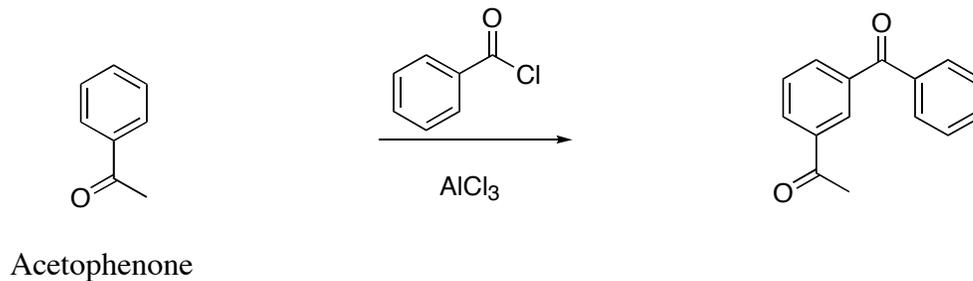
m-t-butylnitrobenzene

## Examples

An example is the bromination of the sulfur containing compound below. Since there is a lone pair of electrons on sulfur, it will direct the bromination to the ortho and para positions.

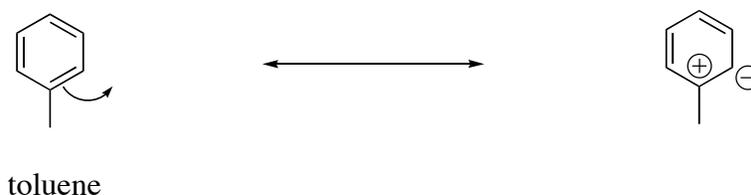


Another example is the Friedel-Crafts acylation of acetophenone shown below. The conjugated ketone in acetophenone directs the acylation to the meta position.

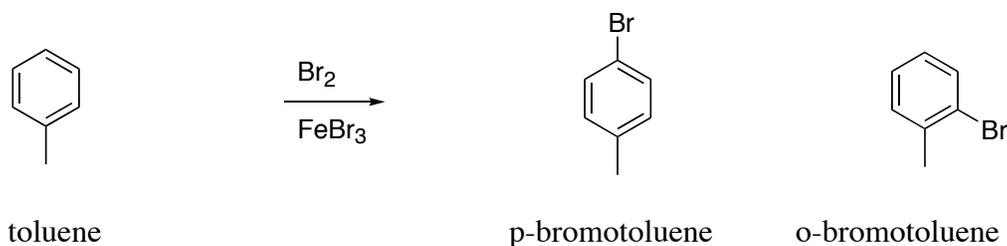


## Inductive Effects

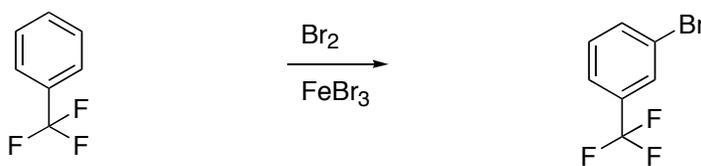
Inductive effects are weak and operate by donating or withdrawing electrons through the sigma bonds. If there is no conjugated double bond or lone pair on the substituent, there is no resonance effect. For example, alkyl groups are inductively electron donating and therefore activate the aromatic ring towards ortho and para substitution. The alkyl substituent is able to stabilize the positive charge (cation) that is formed through inductive effects as shown below.



An example is the bromination of toluene where only the ortho and para products are formed.



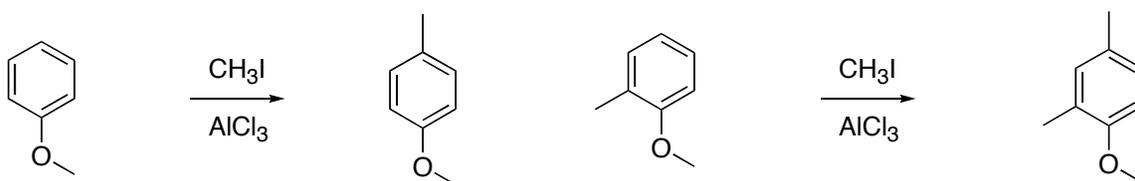
A few special groups (e.g.  $\text{CF}_3$ ) are inductively electron withdrawing and therefore direct substitution to the meta position. An example is the bromination of trifluorotoluene where the meta product is formed.



### Additional Substitution.

If there is more than one group on an aromatic ring, electrophilic aromatic substitution is controlled by the strongest donating group.

This is governed by the same resonance and inductive effects discussed before but it is necessary to consider the effects of the two groups. An example is the di alkylation of methoxybenzene with methyl iodide by a Friedel-Crafts alkylation. Since the methoxy group is an electron donating group (resonance donor), it will direct the first alkylation to the ortho and para positions. The second alkylation is also directed to the ortho and para positions relative to the methoxy group because it is a stronger director (resonance donor) than the methyl group (inductive donor). The second alkylation will go ortho to the methoxy rather than ortho to the methyl. As demonstrated, the strongest donating group always determines the site of substitution.



An interesting example is the chlorination of chlorobenzene. In this case, the inductive effects of the chlorine could suggest the substitution should go meta, but chlorine also displays a resonance effect which directs substitution to the ortho and para positions. In general, a resonance effect always is a stronger director than an inductive effect.

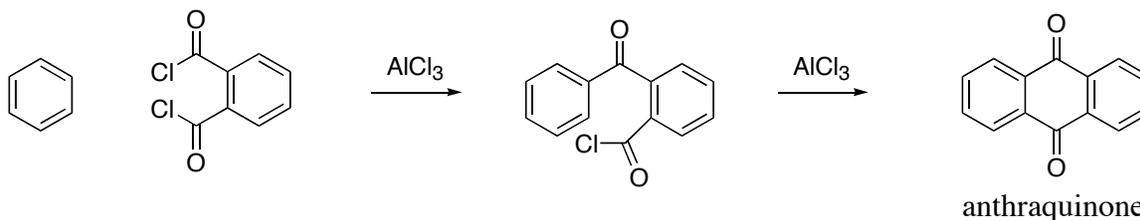


chlorobenzene

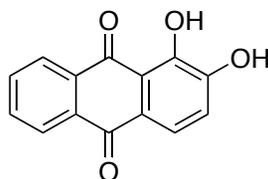
p-dichlorobenzene

o-dichlorobenzene

An unexpected example (“exception”) is the Friedel-Crafts acylation of benzene with the bis acyl chloride (phthaloyl chloride) shown below. After the standard first acylation, the substituent (a ketone) would normally direct the second acylation to the meta position as a resonance withdrawer. This does not occur as this would produce a very strained structure. In this example, the second acylation goes to the ortho position to relieve the strain to produce anthraquinone.



An example of an anthraquinone type structure is Alizarin, shown below. This compound is a dye from the madder root (*Rubia tinctorum*) that is red in color.

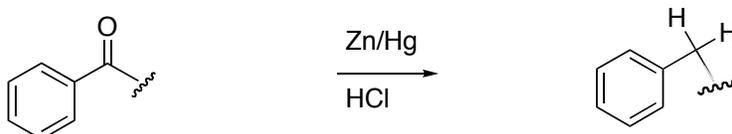


Alizarin

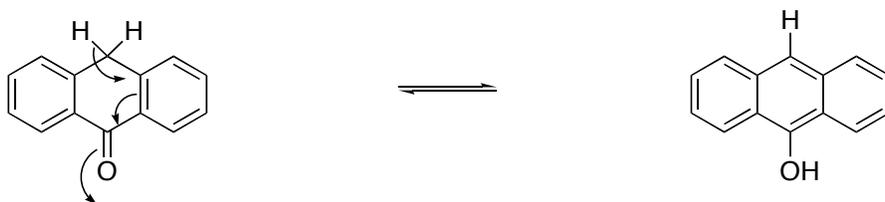
### Reactions of Side Chains of Aromatic Compounds (3 to be discussed)

#### Clemmensen Side Chain Reduction Reaction

The Clemmensen reduction is an example of a reduction of a conjugated ketone to the alkyl chain using a zinc/mercury and an acid as shown below.



This reaction could in principle be used to reduce anthraquinone to anthrone. Anthrone then undergoes a keto to enol isomerization to anthrol which is a fluorescent dye that absorbs UV light and emits in the visible (remember the demo in class).



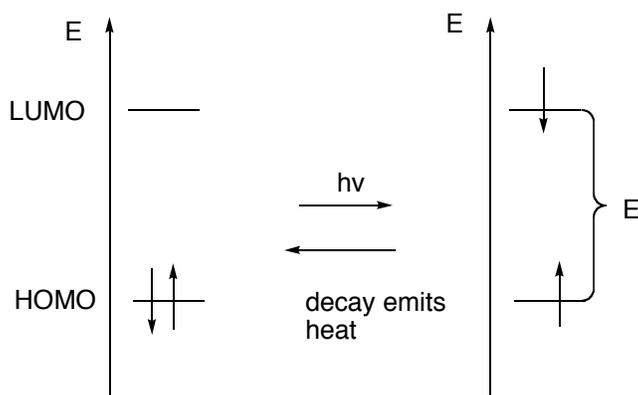
Anthrone (keto form)

Anthrol (enol form)

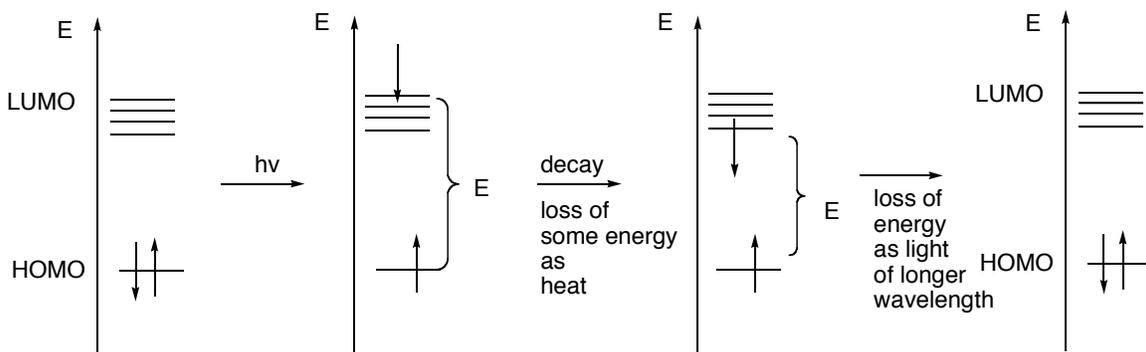
## Fluorescence

Fluorescence is the emission of electromagnetic energy from an excited state (obtained by irradiation, normally in the ultraviolet) as light (often visible wavelengths).

Commonly, electromagnetic radiation (light) is absorbed if it matches the difference between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO). The promoted electron in the LUMO then decays back to the HOMO with loss of the energy as heat (molecular motion, collision with other molecules).



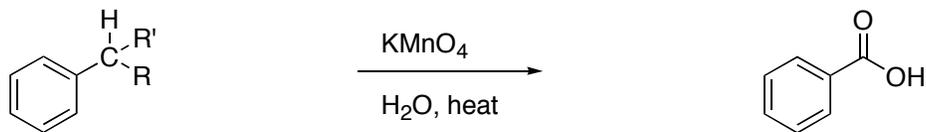
However, if a conjugated molecule absorbs a high-energy photon into a higher vibrational state of the LUMO and the electron energy decays to the lowest vibrational excited state of the LUMO (loss of energy as heat), the remaining energy to return to the ground state can be emitted as a lower-energy photon with a longer wavelength (visible).



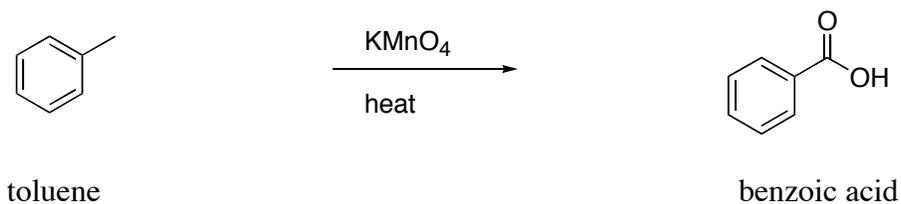
Ground State

## Alkyl Side Chain Oxidation Reaction

If the carbon directly attached to the aromatic ring has  $\geq 1$  hydrogen attached to it, it can be oxidized to the carboxylic acid with hot aqueous potassium permanganate ( $\text{KMnO}_4$ ) as shown below.



An example is the oxidation of toluene to benzoic acid.



In the below example 2-methyl-3-propyl-6-t-butyl-1-bromobenzene is oxidized using potassium permanganate. Note that only the propyl and methyl side chains have one hydrogen on the adjacent carbon to the aromatic ring and therefore are the only ones that are oxidized.

