# Electrophilic Aromatic Substitution for Substituted Benzenes (see handout)

Substituents already present on the benzene ring determine:

the position of reaction and

the reactivity of the system

# **Resonance and Inductive Effects**

A substituent can **donate** or **withdraw** electrons from the aromatic ring in 2 ways: by inductive effects and by resonance effects

## **Resonance Effect:**

- \* Through pi (double bond) system (due to conjugation)
- \* Strong effect
- \* Can be e-donating (ortho-para directing) or withdrawing (meta directing)

#### Inductive Effect:

- \* Through sigma (single bond) system (due to electronegativity of atoms)
- \* Weaker effect
- \* Can be e-donating (ortho-para directing) or withdrawing (meta directing)

# How to determine position & reactivity

Substituents already present on the benzene ring determine:

the position of reaction and the reactivity of the system



**Example:** 

(-SCH3)



product

product

**Example:** 



## **Electrophilic Aromatic Substitution for Substituted Benzenes**

Substituents already present on the benzene ring determine: The <u>position</u> of the reaction. The <u>reactivity</u> of the system.

#### **Resonance and Inductive Effects**

A substituent can **donate** or **withdraw** electrons from the aromatic ring in 2 ways: Inductive effects 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 though conjugation by donating or withdrawing electrons through pi ( $\pi$ ) 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 strong compared to inductive effects.

**Example:** 



Alkyl groups direct ortho and para

Aromatic compound with a heteroatom attached (has lone pair of electrons) is considered a resonance donating system and will direct the reaction to the *ortho* or *para* positions because they have higher electron density as seen through the resonance structures



Aromatic compounds with a conjugated double bond conjugated to the aromatic ring are generally resonance withdrawing (especially if Z is electronegative) and will direct aromatic substitution to the *meta* position, where there is no partial positive charge.



# **Example:**



**Example:** 



**Resonance Donation** 

## How to determine position and reactivity: Examples

# The strongest donating group wins:



This reactivity can be explained by the following resonance forms:



# **Meta-director example:**



This reactivity can be explained by the following resonance forms:



The electrophile is positive and reacts at sites that are not positive (ortho para) but at those that are more negative (meta) as shown below





In this reaction, chlorobenzene has a chloro (-Cl) group attached on the benzene ring. When we perform nitration, only *ortho* and *para* substitution occurs. The chloro group is an electron withdrawing group **inductively**, however, the lone pairs of electrons are conjugated to the benzene ring through **resonance** as an electron donating group. As a result, resonance beats inductive effect, which gives *ortho* and *para* substitution products. However, chlorbenze is less reactive than benzene

## **Example:**

Acetophenone is meta directing



When the electrophile attacks, it avoids the partial positive charges on the *ortho* and *para* positions:



Aromatic compounds with an alkyl chain are considered inductively donating (weak) and will direct substitution to the *ortho* or *para* positions.



The reaction occurs at the para position instead of the ortho position due to sterics.

Notice how the order that reactions are done affect the following two examples:



The products of the above two reactions are structural (or constitutional) isomers.

Aromatic compounds that have an electron-withdrawing group attached but that do not fall into the above categories (e.g.  $CF_3$ ) are inductively withdrawing and direct substitution to the *meta* position.



**Example:** 



If ortho:



disfavored (not observed)

 $-CF_3$  is electron-withdrawing and does not want to withdraw electrons from a carbon that is already positively-charged.

### Multiple Substitution

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

An example is the dialkylation of methoxybenzene with methyl iodide by Friedel-Crafts alkylation. Since the methoxy group is an electron-donating group (resonance donator), 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 donator) than the methyl group (inductive donator). The second alkylation will go *ortho* to the methoxy rather than *ortho* to the methyl.



Similarly, nitration occurs at the *ortho* position for the following example:



In the following case the nitro group is an electron-withdrawing group, so the methyl group is the strongest donating group and takes precedence in directing where the acetyl group will go.



In this last example, the position between the two *meta* substituents is too sterically hindered. Therefore, substitution in that position is not observed.

Follow-up: How do you synthesize the starting material in the previous reaction?

Answer:  $HNO_3$   $H_2SO_4$   $HO_2$   $HO_2$ 

If alkylation was done first, followed by nitration, the *meta*-substituted aromatic compound could not be obtained, since the methyl group is an *ortho/para*-directing group.

Synthesis Example: The sequence of steps is critical

How to make versalide, shown below, from benzene?



The answer is below. Be able to rationalize this sequence.



If you start to add ethyl group first, polyalkylation happens:



Alkylation must also be last because the acetyl group will direct to the meta position.