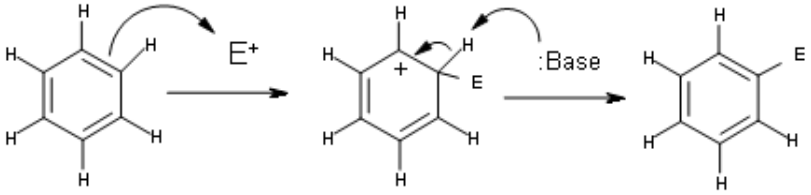
Ch 16 Electrophilic Aromatic Substitution



Mechanism

- Aromatic rings typically undergo substitution, where an H is replaced with an electrophile (E+).
- The rings do not typically undergo addition across the Π bonds.
- Basic mechanism for all of the substitutions is the same.
- An electrophile (E+) adds to a C on the ring using the two e^{-1}'s from it Π bond.
- This C becomes sp^3 when the bond to E+ is created.
- The other C that lost the bond remains sp^2, however it becomes cationic (+1).
- The sp^3 C then loses H^{+1}, and uses the two e^{-1}'s to recreate the Π bond with the C^{+1}.
- This loss of H^{+1} restores the aromatic ring structure.
- The energy diagram of the reaction has two humps (like alkene additions), where the non-aromatic carbocation intermediate is between the two humps (see Fig 16.3).

Bromination

- The electrophile (Br^{+1}) is created with Br_2 and $FeBr_3$ (catalyst):

$$Br_2 + FeBr_3 \rightarrow Br^{+1} + FeBr_4^{-1}$$

- H^{+1} is removed from the ring by $FeBr_4^{-1}$, and this regenerates the catalyst:

$$H^{+1} + FeBr_4^{-1} \rightarrow HBr + FeBr_3$$

Chlorination

- The electrophile (Cl^{+1}) is created similarly, with Cl_2 and $FeCl_3$ (catalyst):

$$Cl_2 + FeCl_3 \rightarrow Cl^{+1} + FeCl_4^{-1}$$

Iodination

- The electrophile (I^{+1}) is created with I_2 and an oxidizing agent such as $CuCl_2$:

$$I_2 + 2Cu^{+2} \rightarrow 2I^{+1} + 2Cu^{+1}$$

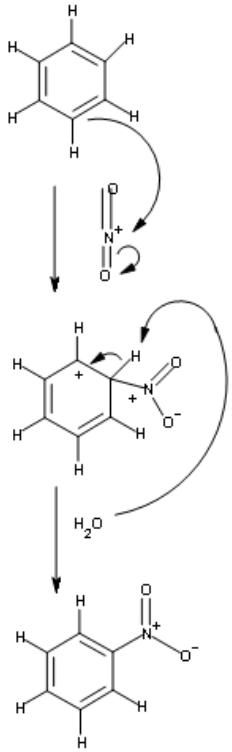
Nitration

- The electrophile is a nitronium cation ($O{=}N^{+1}{=}O$).
- The cation is created from conc. HNO_3 and conc. H_2SO_4:

$$H_2SO_4 + HONO_2 \rightarrow HSO_4^{-1} + H_2ONO_2^{+1}$$

$$H_2ONO_2^{+1} \rightarrow H_2O + O{=}N^{+1}{=}O$$

- The positive N is electrophilic, and accepts two e^{-1}'s from a C on the ring.
- However, the N keeps the positive (+1) charge, as it also gives up two shared e^{-1}'s from a Π bond to one of the two O's.
- This gives that O a negative (−1) charge in the nitro group.



Sulfonation

- The electrophile ($HOSO_2^{+1}$) is created with fuming sulfuric acid (SO_3 in conc. H_2SO_4):

$$H_2SO_4 + SO_3 \rightarrow HSO_4^{-1} + HOSO_2^{+1}$$

- The S on $HOSO_2^{+1}$ is positive and electrophilic. It accepts two e^{-1}'s from a C on the ring. However, the S keeps the +1 charge as it gives up two e^{-1}'s (from a bond) to one of the O's. This gives that O a negative (−1) charge in the sulfonate group.

Hydroxylation

- Direct addition of OH to a ring is not easily done is a laboratory.
- A method for converting an alkylbenzene ($ArCHR_2$) to a phenol (ArOH) is covered in chapter 17 (alcohols and phenols).

Friedel-Crafts Alkylation

- Adds an alkyl group to an aromatic ring, where the electrophile is a carbocation (R^{+1})
- The carbocation is created from an alkyl chloride (RCl) and aluminum chloride ($AlCl_3$), where $AlCl_3$ catalyzes the reaction by accepting Cl^{-1} from RCl:

$$RCl + AlCl_3 \rightarrow R^{+1} + AlCl_4^{-1}$$

  Notice how the Al atom gains e^{-1}'s in order to fulfill its octet, rather than losing e^{-1}'s as it typically does to become a metal cation.
- There are limitations on the types of alkyl chlorides and aromatic rings that will work.
- First the chloride must be alkyl (Cl is attached to an sp^3 C), and not vinylic or aromatic.
- Secondly, the carbocation will rearrange by an alkyl or hydride shift if that will increase its stability (see section 7.11). A 1^o carbocation will rearrange to a 2^o or 3^o where possible, and a 2^o will rearrange to a 3^o. For instance, an n-propyl cation (1^o) will shift an H atom from the middle C to become an isopropyl cation (2^o). So, a reaction between benzene and 1-chloropropane will create more isopropylbenzene than n-propylbenzene.
- Next, more than one alkyl group will often add to a ring unless an excess of the aromatic compound is used. This occurs because an alkylbenzene is more reactive than benzene.
- Also, there are limitations on the aromatic rings that will work. The ring may not possess an electron-withdrawing substituent (have δ+ atom attached to ring), such as nitro, nitriles, and carbonyls. The ring also may not possess basic substituents like amines (reacts with E+).

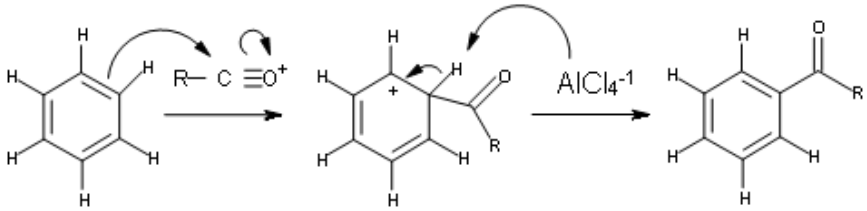
Friedel-Crafts Acylation

- Adds an acyl group (RC=O) to an aromatic ring, where the electrophile is an acyl cation (RC^{+1}=O).
- The cation is created from an acid chloride (RC=OCl) and aluminum trichloride ($AlCl_3$) at 80 ^oC, where $AlCl_3$ catalyzes the reaction by accepting Cl^{-1} from RC=OCl:

$$RC{=}OCl + AlCl_3 \rightarrow RC{=}O^{+1} + AlCl_4^{-1}$$

- The acyl cation is stabilized by resonance because the O can share the positive charge by donating a lone pair to create a second Π bond:

$$RC^{+1}{=}O \leftrightarrow RC{\equiv}O^{+1}$$



Types of Substituents Effects (creating disubstituted benzenes)

- A substituent already on the ring will affect both the reactivity and orientation of the next substitution reaction.
- Substituents that increase reactivity are called activators. Substituents that decrease reactivity are called deactivators.
- Substituents that cause 1,2 and 1,4 disubstituted products to form are called ortho/para directors.
- Substituents that cause 1,3 disubstituted products to form are called meta directors.
- There are three general types of effects:
  ortho/para activators: alkyls (R), amines (NR_2), hydroxy (OH), and alkoxy (OR)
  ortho/para deactivators: halogens (F, Cl, Br, and I)
  meta deactivators: carbonyls (C=O), nitro (NO_2), and nitrile (C≡N)

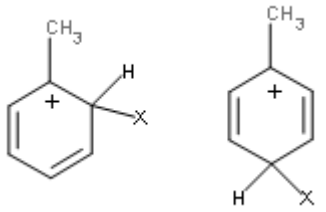
Electronic Effects of Substituents

- Substituents have two types of electronic effects.
  Induction effects are caused by σ bond polarity and electronegativity differences.
  Resonance effects are caused by Π bond delocalization between resonance forms.
- Both induction and resonance will be either e^{-1} donating or e^{-1} withdrawing.
- An e^{-1} donating effect increases ring reactivity (activating), and an e^{-1} withdrawing effect decreases ring reactivity (deactivating).
  This occurs because donating e^{-1}'s will stabilize the + cation intermediate.
- All substituents possess induction effects.
  However, only those with a Π bond or lone pair have resonance effects.

Substituent Categories

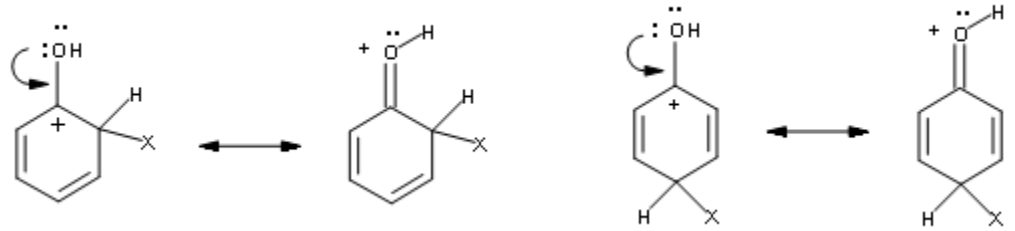
Refer to Figures 16.13 through 16.16, as well as Table 16.2, for pictures and diagrams.

1. Alkyl groups possess only e^{-1} donating induction.
   Essentially, they allow the intermediate cation to be 3^o (and more stable) if the 2^{nd} substituent is added to ortho or para.
   So, alkyl groups are ortho/para activators.



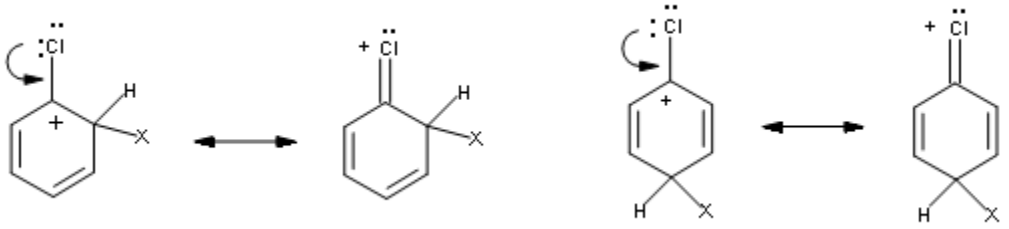
Stable Ortho and Para Cation Intermediates

2. Hydroxyl (OH), alkoxyl (OR), and amino (NH_2) groups each have lone pairs that can be donated. They donate two e^{-1}'s to form a Π bond with the cationic C. In effect, the O and N stabilize the cation by sharing the positive charge, and this is how e^{-1} donating resonance activates the ring for ortho and para substitution. This effect is stronger than the e^{-1} withdrawing induction caused by the electronegativity of O and N. **So, OH, OR, and NH_2 are strong ortho/para activators.**



Resonance Stabilized Ortho and Para Cation Intermediates

3. Like OH and NH_2, all four halogens (F, Cl, Br, and I) also exhibit e^{-1} donating resonance and e^{-1} withdrawing induction. However, their donating effect is weaker, and their withdrawing effect is stronger. **The net result is that all four halogens are ortho/para deactivators.**



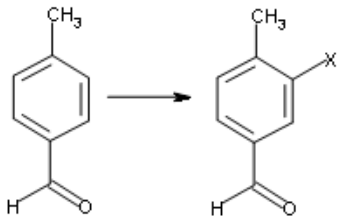
Resonance Stabilized Ortho and Para Cation Intermediates

4. Carbonyl (C=O), nitro (NO_2), nitrile (C≡N), and sulfonate (SO_3H) groups have e^{-1} withdrawing resonance due to the δ+ (or +1) atoms attached to the ring. This destabilizes the cation so that ortho and para substitution becomes unfavorable. Since meta substitution does not put the + charge on the C with the e^{-1} withdrawing substituent, it is the least destabilized. **So, C=O, NO_2, C≡N, and SO_3H are meta deactivators.**

Least Destabilized (Meta) Very Unstable

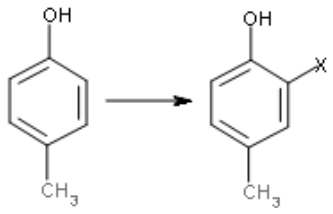
Cumulative Effects (creating trisubstituted benzenes)

- If there are two substituents on a ring, both will affect where the third is added.

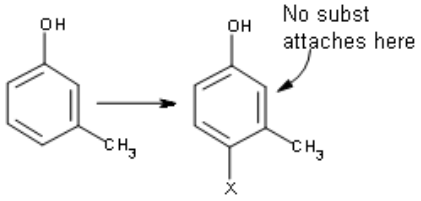


- Sometimes they reinforce each other, such as an o/p activator that is para (1,4) to a meta deactivator.

- Sometimes, they oppose each other.
  Here, the general rule is that effect of the more strongly activating substituent will predominate.
  For instance, OH is more strongly activating than CH_3, and will direct formation of the major product.

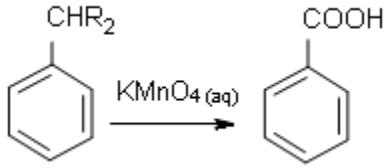


- Steric hindrance prevents a substituent from attaching between two substituents that are meta to each other.



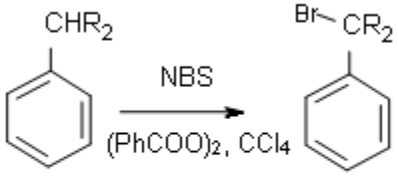
Oxidation of Alkylbenzenes

- In the laboratory, an alkylbenzene can be oxidized to benzoic acid (ArCOOH) with $KMnO_{4(aq)}$ if it possesses a benzylic H, that is on the alkyl C that is attached to the ring.
- The reaction occurs by a free-radical mechanism when the benzylic H• is removed.



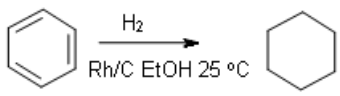
Bromination of Alkylbenzenes

- Adding a Br to the benzylic C can also be done by a free-radical mechanism if there is a benzylic H• that can be removed.
- This reaction can be done with NBS and benzoyl peroxide $(PhCOO)_2$ in CCl_4.
  NBS, n-bromosuccinimide, is a stable source of Br_2.
  Benzoyl peroxide is a radical initiator, where PhCOO• allows formation of Br• radicals.

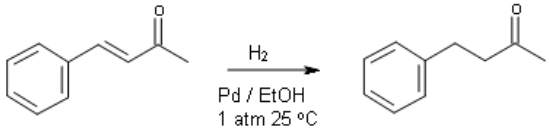


Catalytic Hydrogenation

- A very strong catalyst is required to hydrogenate the benzene ring to a cyclohexane ring.
  H_2 can be added using Pt as the catalyst with ethanol at 130 atm (at 25 ^oC).
  More effectively, H_2 can be added using rhodium supported on carbon (Rh/C) with ethanol at ambient conditions (1 atm and 25 ^oC).

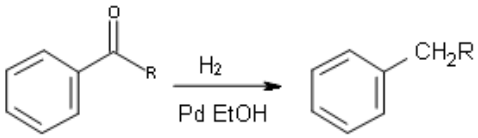


- A weaker catalyst can be used to hydrogenate only alkenyl substituents, while leaving the ring structure as well as carbonyls intact.
  This can be done by adding H_2 using a palladium (Pd) catalyst in ethanol at 1 atm and 25 ^oC.



Reduction of Benzylic Carbonyls

- A benzylic carbonyl (attached directly to the ring) is more reactive to hydrogenation.
- So, an aromatic ketone (ArC=OR) can be reduced to an alkylbenzene ($ArCH_2R$) by adding H_2 using a palladium catalyst on carbon (Pd/C) in ethanol.



Synthesis Problems (trisubstituted benzenes)

- Ex 16.4 shows how to create 4-bromo-2-nitrotoluene from benzene.
- Essentially, the CH_3 must go before the NO_2 in order for the Friedel-Crafts alkylation to work.
- In general, the NO_2 should go on last if possible, because it is a deactivator and slows down the reactions.
- So, the molecule can be made by bromination and alkylation, in either order, along with removal the ortho isomer, which is the side product. At that point, the p-bromotoluene can be nitrated to make the desired product.

- Ex 16.5 shows how to create 4-chloro-2-propylbenzenesulfonic acid from benzene.
- The alkyl group must go before the SO_3H (sulfonate) in order for the Friedel-Crafts alkylation to work.
- Sulfonates are also strongly deactivating meta-directors because of the two S=O Π bonds. So, the alkyl and the sulfonate would both reinforce each other. But, this would put the Cl in the wrong places.
- So, the sulfonate must go on last.
- But, we still need to have the alkyl and Cl meta to each other, and they are both o/p directors!
- There is a solution, though. We can add a propanoyl acyl group ($O=CCH_2CH_3$) first. This can be done by Friedel-Crafts acylation with propanoyl chloride and $AlCl_3$. The carbonyl a meta director, and it can be reduced to a propyl group after the Cl is added. (see Reduction of Benzylic Carbonyls on previous page)
- Once we have m-chloropropylbenzene, we can proceed with sulfonation to make the desired product.