Topic/ Objective:

Chapter 23: Aromatic Substitution 2

Reactions of substituted Benzenes

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Class: Organic Chemistry II

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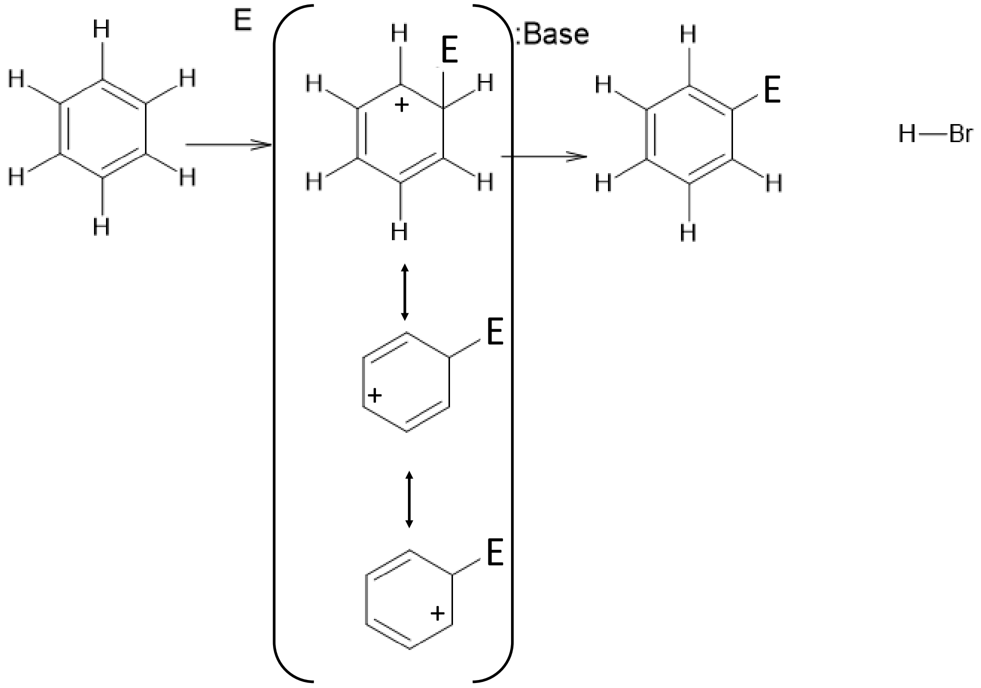
Essential Questions and Themes:

Regiochemistry (defining Ortho/Para and Meta directors), Inductive and resonance effects from substituents, Deactivating Vs Activating Groups , and impacts of substituent on the outcome of EAS reactions

Subheadings -> Questions

Notes:

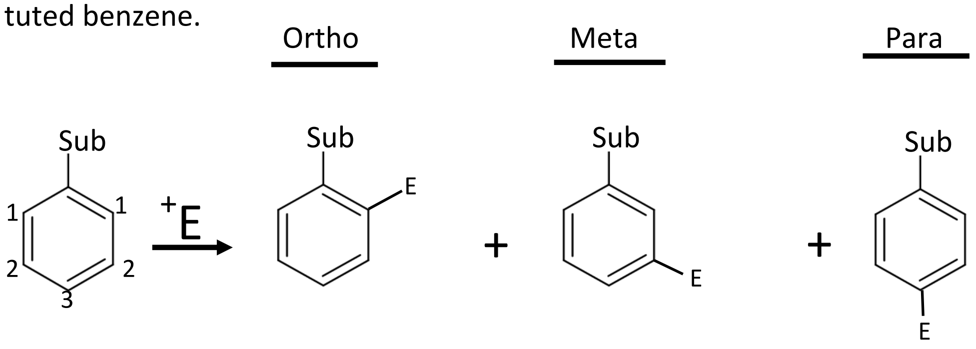
Review the general reaction of electrophilic aromatic substitution to get a monosubstituted benzene



Disubstituted benzene regiochemistry:

Ortho-, Meta-, and Para– structures

A monosubstituted benzene has three chemically distinct hydrogens that can lead to three different possible products: Ortho-, Meta-, and Para– disubstituted benzene.



In order to determine the regiochemistry (or where disubstitution will occur), we need to consider the inductive and resonance effects of the substituent on the benzene ring

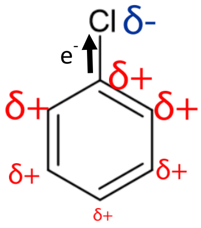
Inductive effect on benzene substituent groups

What is the inductive effect? the push/pull of electrons across a sigma bond that arises due to a difference in electronegativity (EN) of surrounding atoms

Electronegativity by Pauling Scale

H	C	S	I	Br	N	Cl	O	F
2.20	2.55	2.58	2.66	2.96	3.04	3.16	3.44	3.98

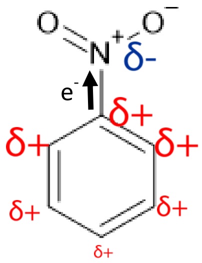
Negative inductive effect (- I) examples:



Chlorine is highly electronegative (EN) and LOVES electrons! **Carbon EN < Chlorine EN**

Halogens **pull** electrons across the sigma bond towards it, inducing a partial positive charge on the benzene ring and decreasing the electron density of the system.

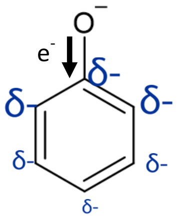
"Electron Withdrawing Group (EWG)"



Also, if the substituent bond connecting to the benzene ring is fully or partially positive, the substituent will withdraw electrons from the ring.

Ex: nitro(-NO$_2$), carbonyl (-CO), and cyano (-CN) groups

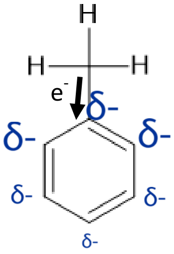
Positive inductive effect (+ I) examples:



O^- has a negative charge and DOES NOT want any more electrons!

Anions **push** electrons across the sigma bond away from it, inducing a partial negative charge on the benzene ring and increasing the electron density of the system.

"Electron Donating Group (EDG)"



Also, if the substituent bond connecting to the benzene ring is fully or partially negative, the substituent will donate electrons to the ring.

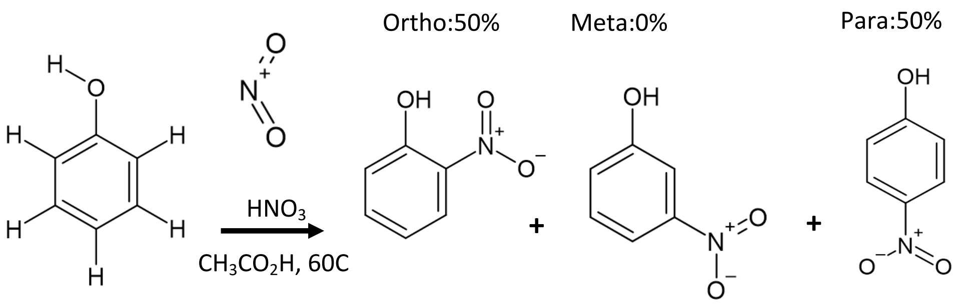
Ex: alkyl(-R), alkoxy(-OR), and amine(-CNHR) groups

Important Takeaways! The inductive effect is negative (-I) when the substituent is an electron withdrawing group (halogen or adjacent positive charge). The inductive effect is positive (+I) when the substituent is an electron donating group (anion or adjacent negative charge). The inductive effect is distance dependent, decreasing rapidly with distance, so it has a stronger influence on the Ortho and Meta positions.

Questions:

Resonance stability from the lone pair of electrons on the hydroxyl group make phenol groups ortho and para directing

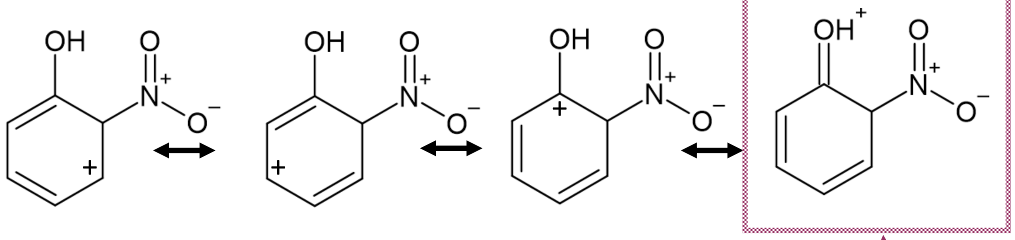
Topic:



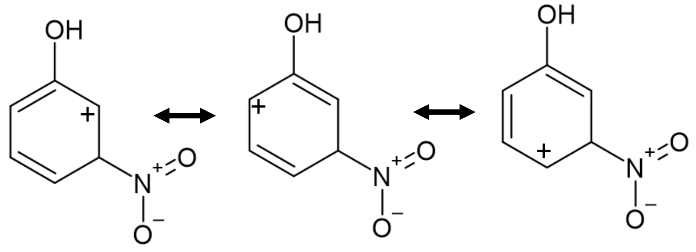
2-nitrophenol | 3-nitrophenol | 4-nitrophenol

o-Nitrophenol | *m*-Nitrophenol | *p*-Nitrophenol

Ortho Intermediate: 4 resonance structures

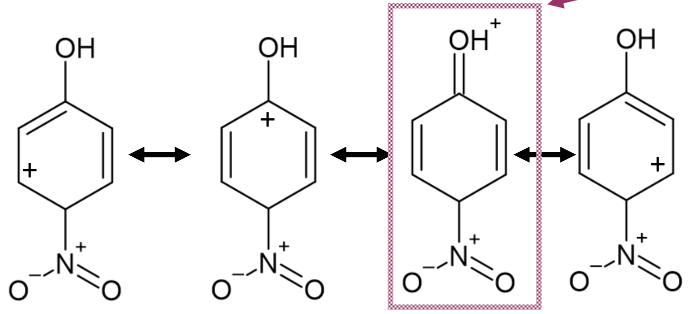


Meta Intermediate: 3 resonance structures



All non– hydrogen atoms have octets, making these resonance structures especially stable.

Para Intermediate: 4 resonance structures



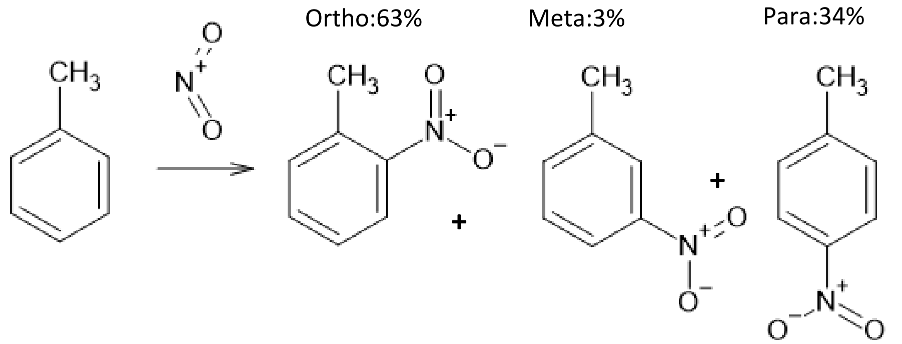
"Positive Resonance (+ R) effect"

Important Take away! If the first substituent is attached by an atom with at least one lone pair of electrons (ex. –OH, -O$^-$, -OR, halogens) the disubstituted atom/group will have one additional stable resonance structure in the ortho and para position and favor ortho/para disubstituent. **This substituent groups have a positive resonance (+ R) effect.**

Questions:

Topic:

Show how the methyl substituent on benzene is Orth-/Para– directing using resonance structures



2-nitrotoluene

o-Nitrotoluene

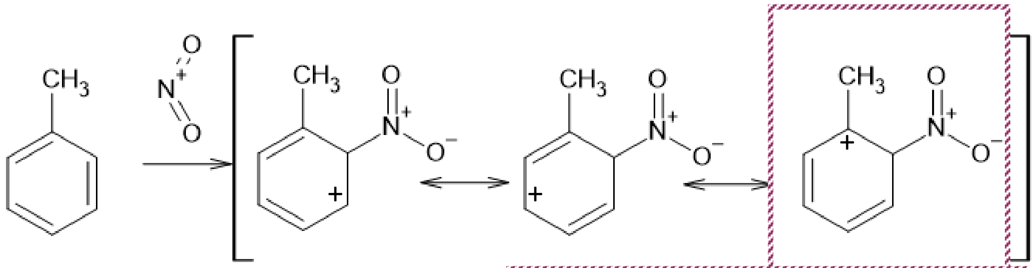
3-nitrotoluene

m-Nitrotoluene

4-nitrotoluene

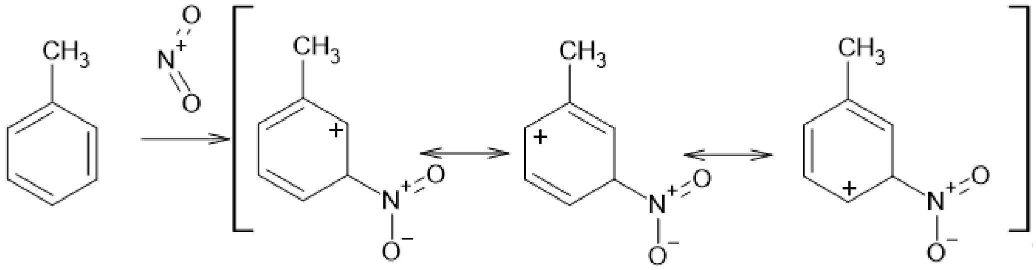
p-Nitrotoluene

Ortho Intermediate: 3 resonance structures



Especially stable structure because CH_3 group can act as an electron donating group (EDG) and stabilizes the adjacent positive charge

Meta Intermediate: 3 resonance structures ***"Positive Inductive (+ I) effect"***



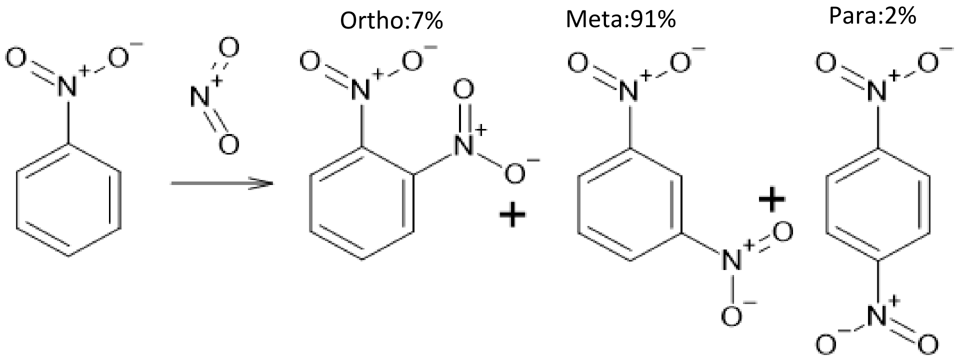
Para Intermediate: 3 resonance structures similar to ortho resonance

Important Take away! In addition to considering the number of resonance structures formed in the intermediate step, you need to consider the stability of structure and the substituents inductive effect on stability. **EDGs will help stabilize an adjacent positive charge and act as ortho/para directors, because of the methyl groups positive inductive (+ I) effect.**

Questions:

Topic:

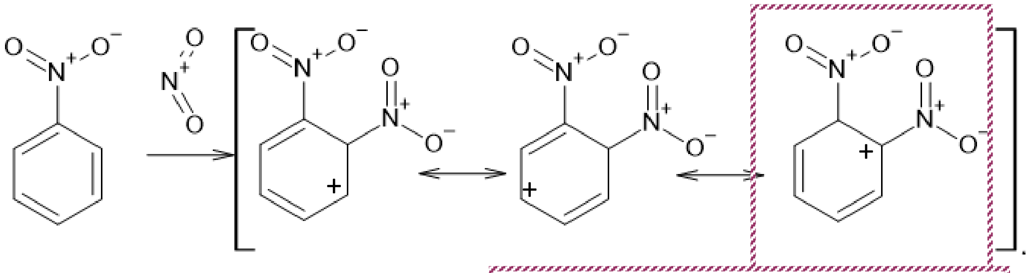
Show how the nitro group (-NO_2) on benzene is Meta– directing using resonance structures



2-nitrotoluene 3-nitrotoluene 4-nitrotoluene

O-Nitroluene m-Nitrotoluene p-Nitrotoluene

Ortho Intermediate: 3 resonance structures

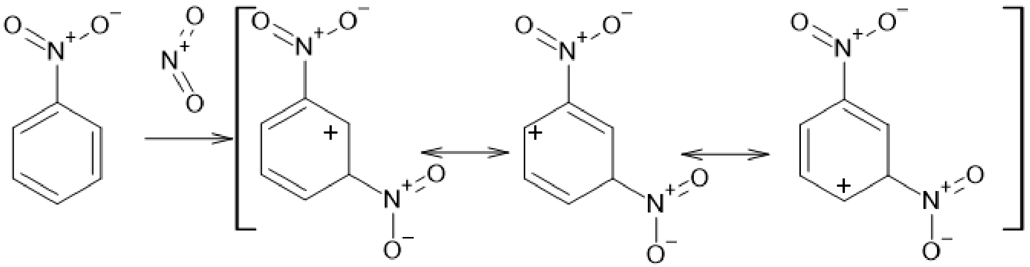


Negative Inductive (- I) effect

Negative Resonance (-R) effect

NO_2 group is an electron withdrawing-group (EWG) and significantly destabilizes the adjacent positive charge

Meta Intermediate: 3 resonance structures



Para Intermediate: 3 resonance structures similar to ortho resonance

Important Take away! EWGs will destabilize an adjacent positive charge and act as meta directors due to their negative inductive effect. Nitro groups are strongly electron withdrawing

Questions:

Topic:

Simple guide to determining disubstitution regiochemistry

1. Substituents attached by an atom with at least one lone pair of electrons are **ortho/para director** (Ex: OH,F,Cl,Br), which means the ortho/para intermediate will have one additional stable resonance structures.

2. Substituents attached by an atom with no lone pair of electrons are:

- **Ortho/para directors** if they are alkyl groups (CH_3, CH_2CH_3,etc). There is not an extra resonance structure, but the alkyl group is electron-donating and stabilizes the adjacent positive charge.

- **Mets directors** if the atom at the point of attachment is electronegative or if it is bonded to highly electronegative atoms (Ex: NO2, CN,$N(CH_3)_3$,CO_2H). There is no extra resonance structure AND the electron withdrawing group attached makes the resonance structure with the adjacent positive charge destabilized

Key takeaway! The major product of EAS is the one with the most stable (lower in energy) arenium intermediate state. To determine this, one most consider: (1) The substituents inductive effect (EDG or EWG) (2) Resonance structure amount and stability (3) how fast the reaction is formed

Activating and Deactivating groups determine the rate of EAS reaction

Activating groups are substituent groups that *activate the benzene ring* towards electrophilic aromatic substitution (EAS). Activating groups make EAS occurs faster relative to unsubstituted benzene.

Deactivating groups are substituent groups that *deactivate the benzene ring* towards electrophilic aromatic substitution (EAS), so EAS occurs slower relative to unsubstituted benzene.

Substituent	Resonance (+/-R) effect	Inductive (+/- I) effect	Activating or Deactivating	Ortho/Para or Meta
$-O^-$	+R	+I (EDG)	Str. Activating	o/p
-OH	+R	-I (EWG)	Str. Activating	o/p
-Cl	+R	-I (EWG)	W. Deactivating	o/p
-NO2	-R	-I (EWG)	Str. Deactivating	m
CO-OR (ester)		-I (EWG)	Deactivating	m

Questions:

Topic:

Important Take aways!

1) Activating (fast) and Deactivating (slow) groups determine speed of reaction

2) Activating Groups are generally ortho/para directors and Deactivating groups are generally meta directors (except for halogens)

3) If resonance and inductive effect are completing: resonance effect tends to have a greater impact.

Textbook table references for activating and deactivating group relative reaction rates

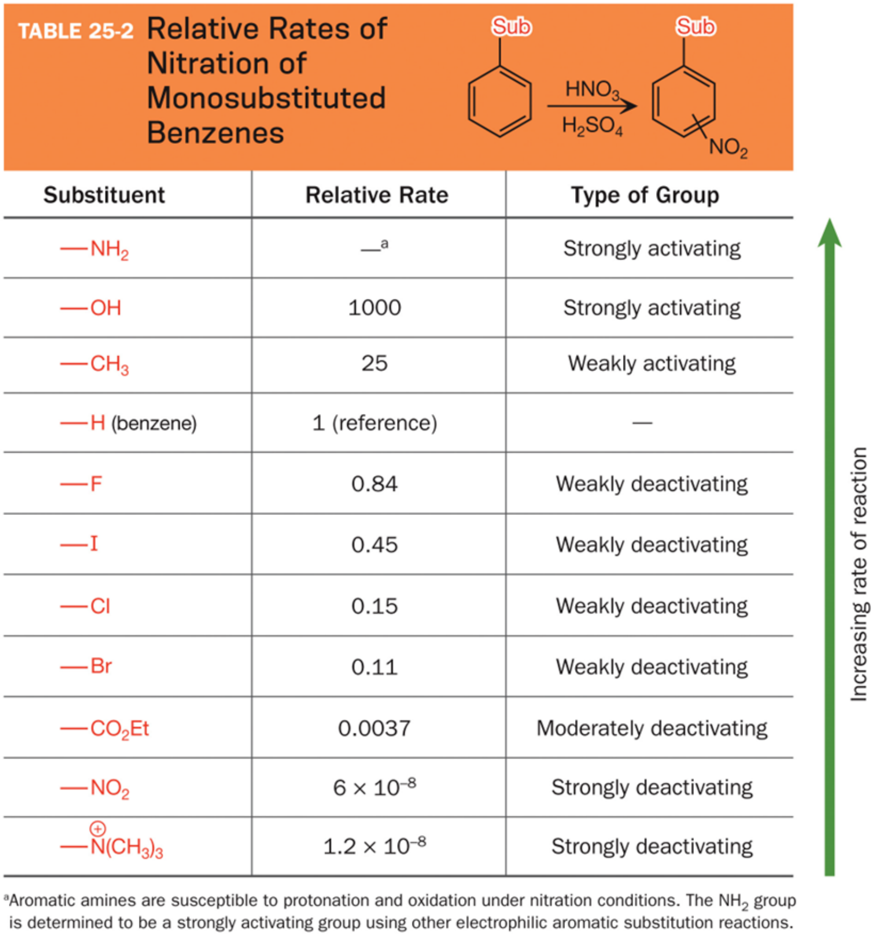


TABLE 25-2 Relative Rates of Nitration of Monosubstituted Benzenes

Substituent	Relative Rate	Type of Group
$—NH_2$	—[a]	Strongly activating
—OH	1000	Strongly activating
$—CH_3$	25	Weakly activating
—H (benzene)	1 (reference)	—
—F	0.84	Weakly deactivating
—I	0.45	Weakly deactivating
—Cl	0.15	Weakly deactivating
—Br	0.11	Weakly deactivating
$—CO_2Et$	0.0037	Moderately deactivating
$—NO_2$	6×10^{-8}	Strongly deactivating
$—\overset{\oplus}{N}(CH_3)_3$	1.2×10^{-8}	Strongly deactivating

[a] Aromatic amines are susceptible to protonation and oxidation under nitration conditions. The NH_2 group is determined to be a strongly activating group using other electrophilic aromatic substitution reactions.

Strongly Activating Groups: $-O^-$, $-NH_2$, $-NR_2$, -OH, -OR

Moderately Strong Activating Groups: amide (-NHCOR/-NHCOH)

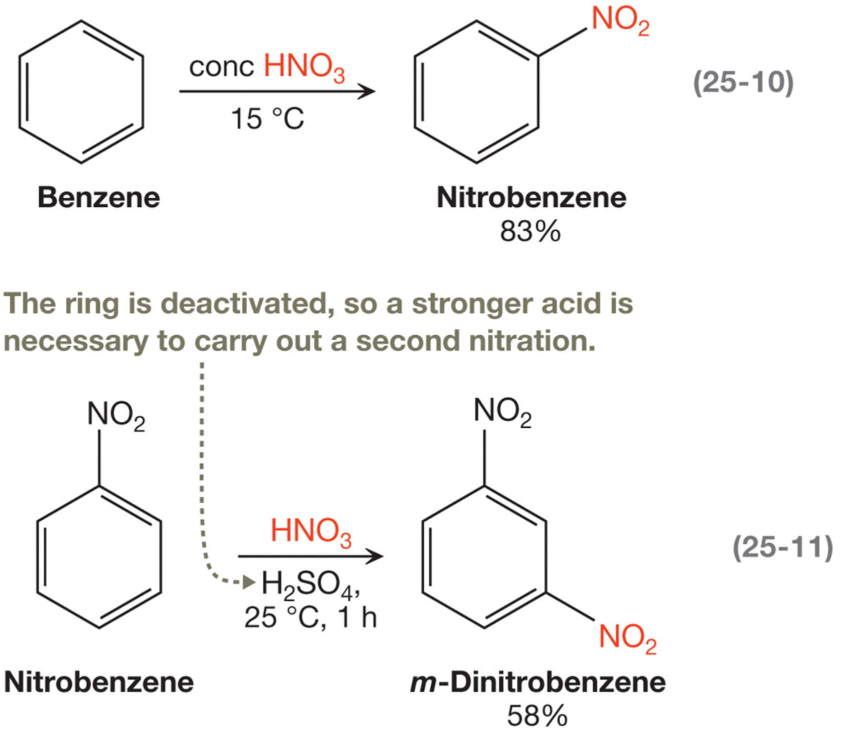
Weakly Activating Group: Alkyl groups (-R)

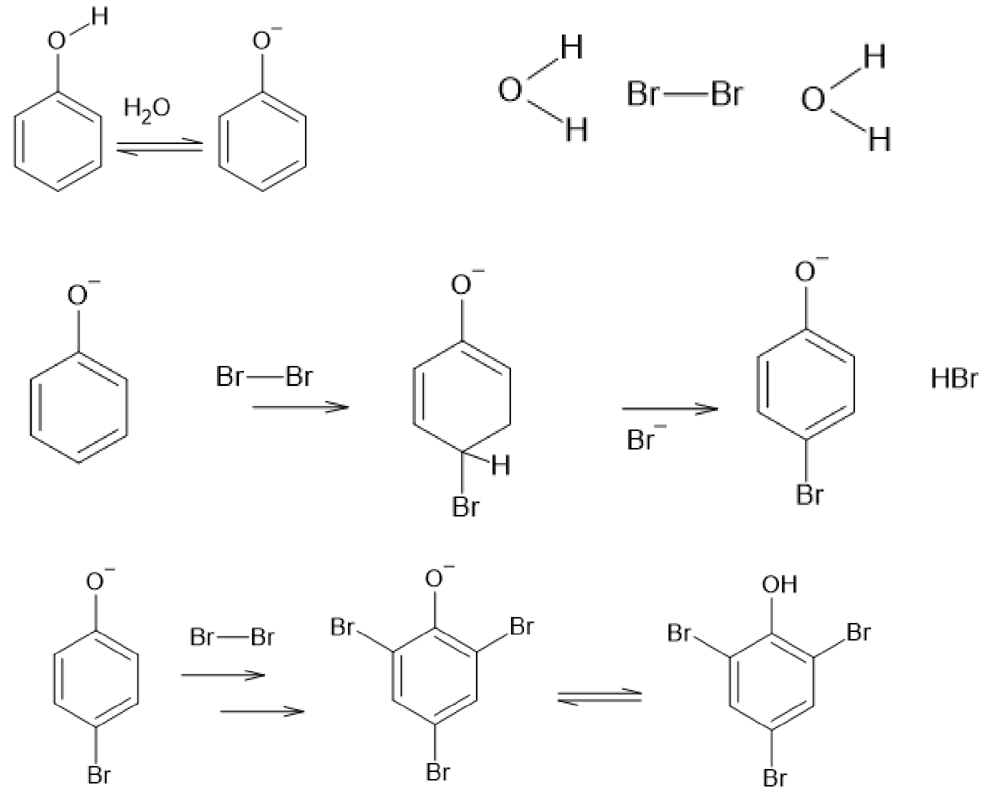
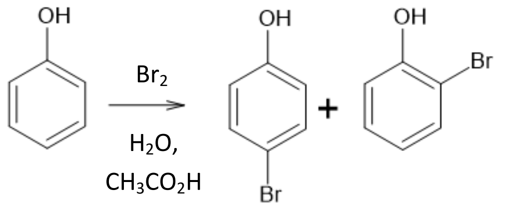
——————— Reference **Benzene** (-H)————————-

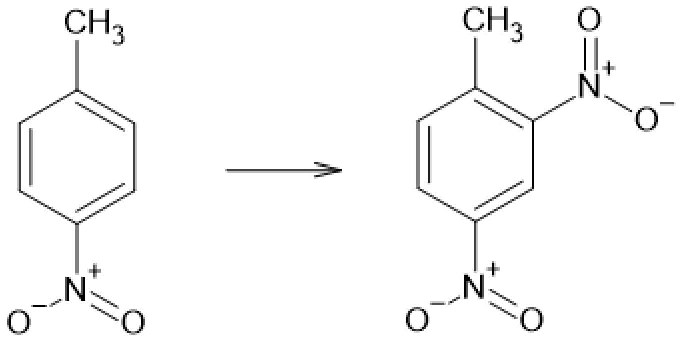
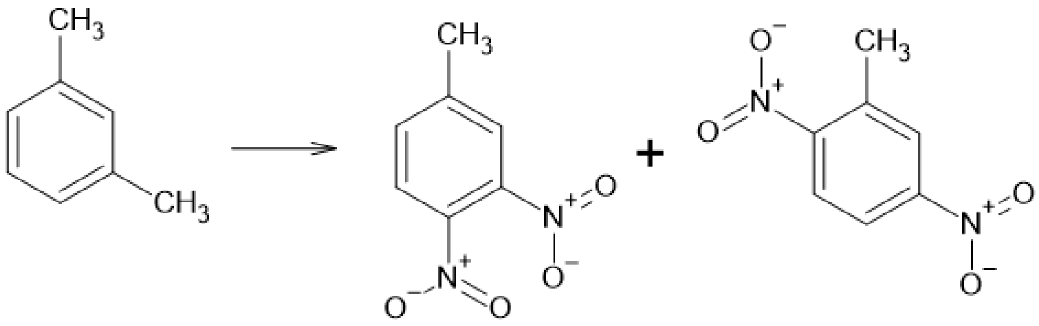
Weakly Deactivating: halogens (-Cl, -Br, -I)

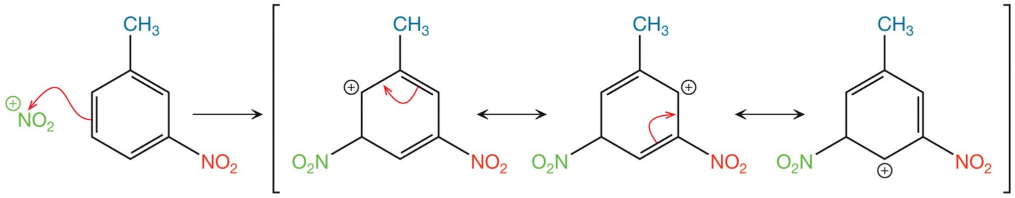
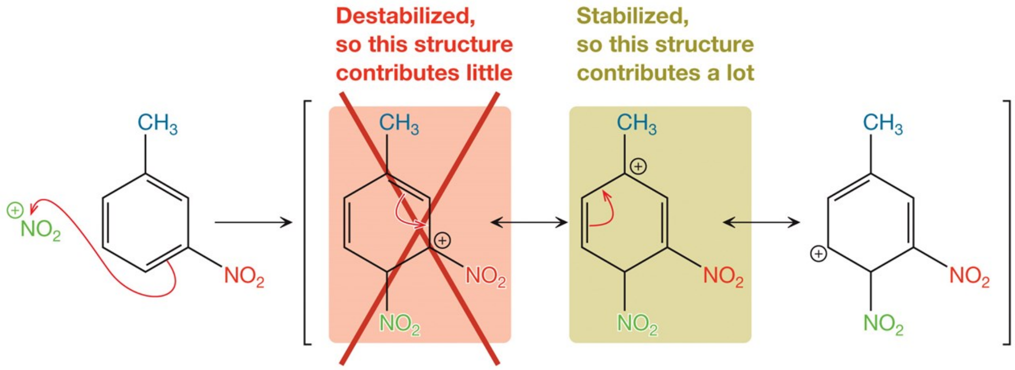
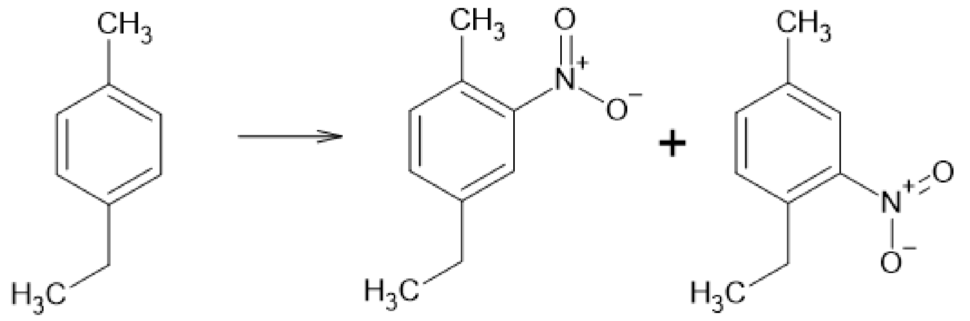
Moderately Deactivating: Esters(-COOR), carboxylic acid (-COOH) , Ketones (-COR), aldehydes (-CHO)

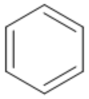
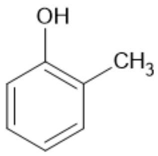
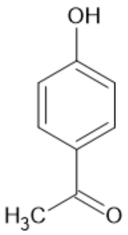
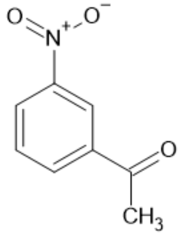
Strongly Deactivating: nitrile (-CN), nitro (-NO2), sulfonic acid ($-SO_2OH$), amine ($-NH_3^+$), trimethyl amine($-N(CH_3)_3^+$)

Questions:	**Topic:**
If substituent group is deactivating, disubstitution is slower and more difficult	If the substituent group is a deactivating group, the second substitution will be slower and more difficult requiring a stronger acid to increase the electrophile. Ex.  (25-10) The ring is deactivated, so a stronger acid is necessary to carry out a second nitration. (25-11)
Substituent impacts on Friedel-Crafts reactions	1. Friedel-Crafts reactions do not readily take place on moderately or strongly deactivating groups. Why? Deactivation groups slow the reaction and the cation electrophile from Friedel crafts reactions will degrade or polymerize before the ring attacks it. 2. Friedel-Crafts alkylations are subject to polyalkylation Why? Because alkyl groups are activating and each alkyl group added will increase the overall reaction rate and make subsequent alkylations faster. Solution! First add an acyl group (moderately deactivating) to the ring, then reduce C=O to CH_2 with an acid.

Questions:	**Topic:**
Impact of reaction conditions on substituent effects	The substituents effect on regiochemistry (ie. orth-, meta-, and para-) and reaction rate is not always absolute. For some substituents, the reaction conditions play a role 
There are two ways to slow this reaction down and induce single bromination	**1.** Add a weak acid to make the substituent less activating Acetic acid will decrease the pH of the solution resulting in an increased concentration of H^+ substantially decreasing the concentration of phenoxide anion (a very powerful activating group). The only route available is through phenol which is slower and easier to stop after a single Bromo nation  2. Decreasing the temperature and adding a nonpolar solvent instead of water A nonpolar solvent, such as CS_2, will not aid in the separation of Br_2 and will reduce the amount of bromines available for the reaction, making it difficult to form two bromine additions. Similarly, if the substituent is a strong Lewis Base and is likely to bond with a H and gain a positive charge (ex. Amino group) . Increasing the pH can lead to a meta-directing, deactivated group that avoids Friedel– Crafts reaction.

Questions:	**Topic:**
Consider regiochemistry with multi-substitutions	If you have a disubstituted benzene and you want to determine where the next substitution will occur you need to consider 3 things: 1. Where each existing group is directing 2. The Activating/Deactivating strength of each group 3. Steric hindrance
Ideal scenario! Both groups direct the same way ***p*-Nitrotoluene**	 *p*-Nitrotoluene *2,4*-Dinitrotoluene
Directing group disagreement	 *m*-Nitrotoluene *3,4*-Dinitrotoluene *2,5*-Dinitrotoluene 1. Where each existing group is directing? CH$_3$= ortho/para, NO$_2$=meta 2. The Activating/Deactivating strength of each group? CH$_3$ =weakly activating, NO$_2$=strongly deactivating. The most activating group is usually favored because it usually offers more resonance stsbility 3. Steric hindrance: EAS is disfavored in the position ortho to two different substituents

Questions:	**Topic:**
High activation groups offer more resonance stability	 (25-24)  (25-25) Para intermediates have one destabilizing and one stabilizing resonance intermediate structure. Its tempting to think these will “cancel each other out”, however the contribution to the resonance hybrid increases with increasing stability. Thus, 3,4-Dinitrotoluene is favored
What if directing groups disagree and activating groups have the same ability	 *p*-Ethyltoluene *4*-Ethyl-*2*-Nitrotoluene **(56%)** *4*-Ethyl-*3*-Nitrotoluene **(44%)** **Nearly equal influence!**
How does multiple substitutions impact overall rate of EAS?	Substituent effects on overall rate are ~ Additive meaning, each activating group increases reaction rate and each deactivating group decreases the reaction rate by how strongly activating or deactivating the group is.

Questions:	**Topic:**
Now you try: rank these groups from fastest to slowest reaction	 A  B  C  D A: Neutral Activation B: Strongly Activating Group + Weakly Activating Group C: Strongly Activating Group + Moderately Deactivating Group D: Strongly Deactivating Group + Moderately Deactivating Group **B (fastest) > C > A > D (slowest)**
	Link to completed Notes: https://www2.atmos.umd.edu/~hmdaley/EMU_OCch23_blanks.pdf Link to blank Notes: https://www2.atmos.umd.edu/~hmdaley/EMU_OCch23_blanks.pdf