

Topic/ Objective: Chapter 23: Aromatic Substitution 2 Reactions of substituted Benzenes	Name: Prof. Hannah Daley
	Class: Organic Chemistry II
	Date: 02/16/2024

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:	<p>A monosubstituted benzene has three chemically distinct hydrogens that can lead to three different possible products: _____ disubstituted benzene.</p> <p>In order to determine the regiochemistry (or where disubstitution will occur), we need to consider the _____ and _____ effects of the substituent on the benzene ring</p>
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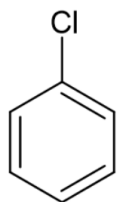
Inductive effect on benzene substituent groups

What is the inductive effect? the _____ across a sigma bond that arises due to a _____ (EN) of surrounding atoms

Electronegativity by Pauling Scale

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

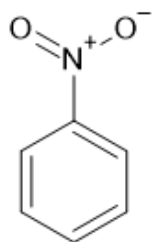
Negative inductive effect (-I) examples:



Chlorine is _____

Halogens _____ electrons across the sigma bond towards it, inducing a _____ charge on the benzene ring and _____ the electron density of the system.

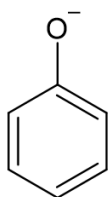
“Electron _____ Group (EWG)”



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

Ex: nitro(-NO₂), carbonyl (-CO), and cyano (-CN) groups

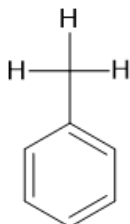
Positive inductive effect (+I) examples:



O⁻ has a _____

Anions _____ electrons across the sigma bond away from it, inducing a _____ charge on the benzene ring and _____ the electron density of the system.

“Electron _____ Group (EDG)”



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

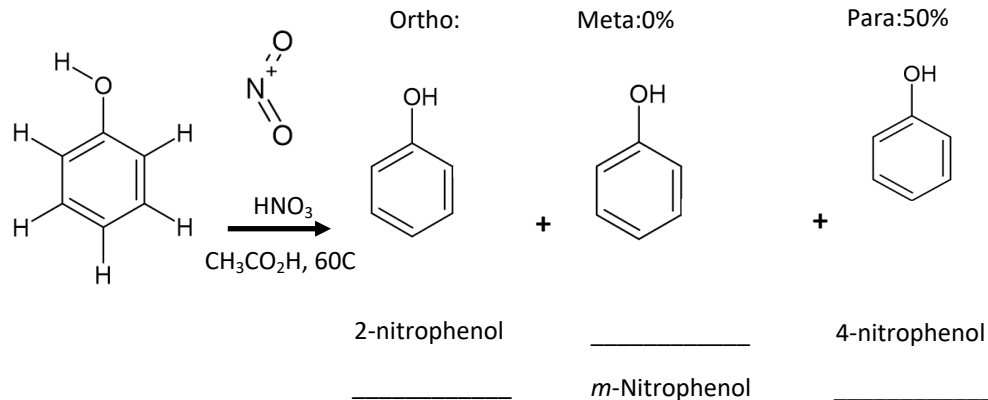
Ex: alkyl(-R), alkoxy(-OR), and amine(-CNHR) groups

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.

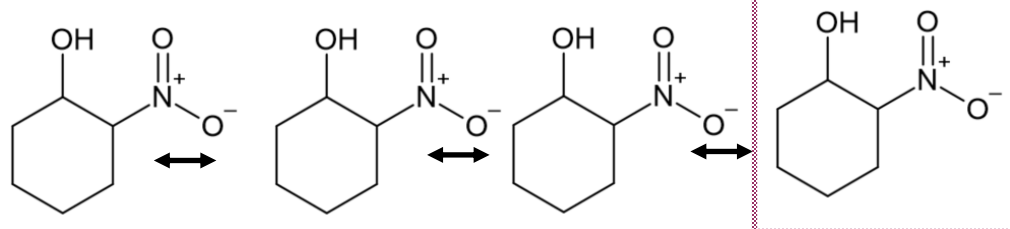
Questions:

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

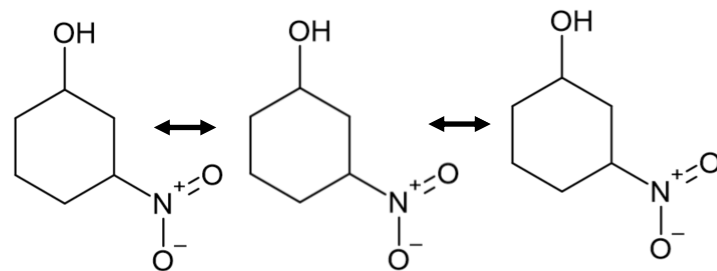
Topic:



Ortho Intermediate: ___ resonance structures

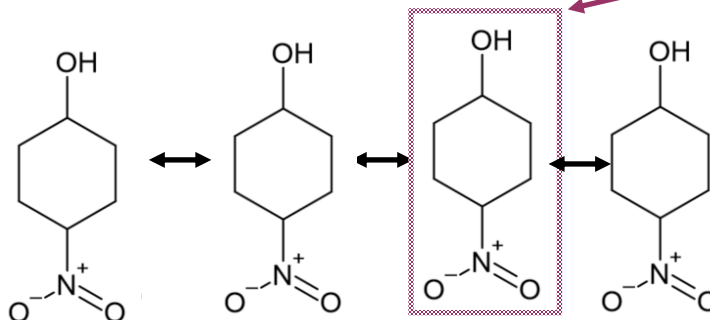


Meta Intermediate: ___ resonance structures



All non-hydrogen atoms have octets, making these resonance structures

Para Intermediate: ___ resonance structures



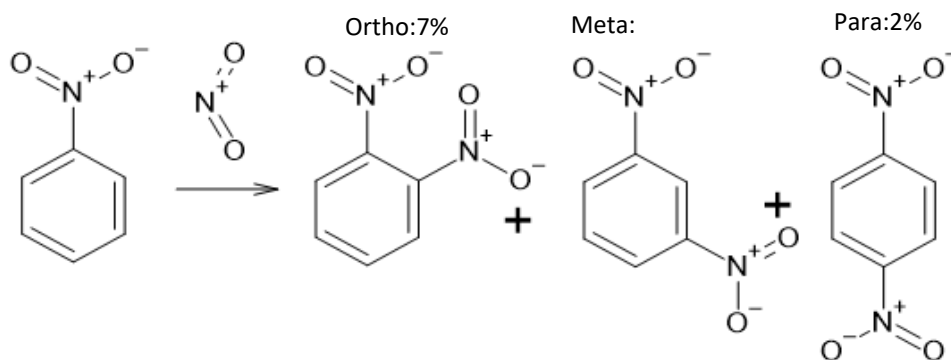
“Positive effect”

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.**

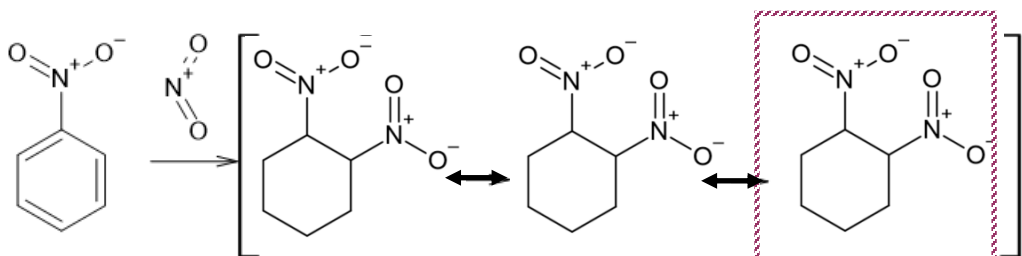
Questions:

Topic:

Show how the nitro group (-NO₂) on benzene is Meta-directing using resonance structures



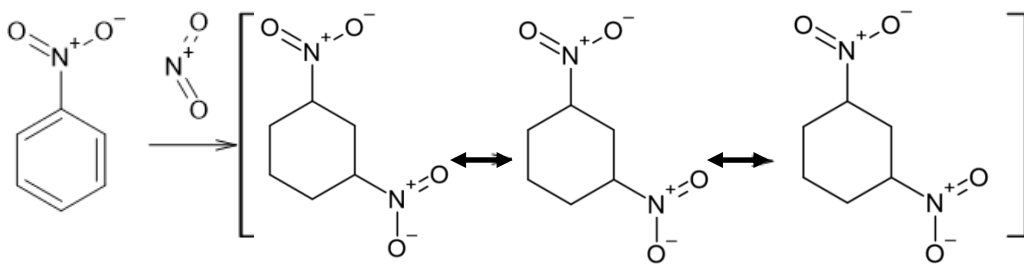
Ortho Intermediate: resonance structures



effect

NO₂ group is an _____
and significantly _____ the
adjacent positive charge

Meta Intermediate: resonance structures



Para Intermediate: resonance structures similar to ortho resonance

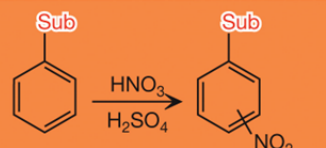
Important Take away! EWGs will destabilize an adjacent positive charge and act as meta directors due to their negative inductive effect. Nitro groups are strongly electron withdrawing

Questions:	Topic:																														
<p>Simple guide to determining disubstitution regiochemistry</p>	<p>1. Substituents attached by an atom with at least one _____ are _____ directors, because the _____ intermediate will have one additional stable resonance structures.</p> <p>2. Substituents attached by an atom with _____ lone pair of electrons are:</p> <ul style="list-style-type: none"> • _____ directors if they are _____. There is not an extra resonance structure, but the alkyl group is _____ and stabilizes the adjacent _____ • Mets directors if the atom at the point of attachment is electronegative or if it is bonded to highly _____. There is no extra resonance structure AND the electron withdrawing group attached makes the resonance structure with the _____ <hr style="border-top: 1px dashed black;"/> <p>Key takeaway! The major product of EAS is the one with the most stable (lower in energy) arenium intermediate state. To determine this, one must consider: (1) The substituents _____. (2) Resonance structure _____ and _____ (3) how _____ the reaction is formed.</p>																														
<p>Activating and Deactivating groups determine the rate of EAS reaction</p>	<p>Activating groups are substituent groups that _____ towards electrophilic aromatic substitution (EAS). Activating groups make EAS occur _____ relative to unsubstituted benzene.</p> <p>Deactivating groups are substituent groups that _____ towards electrophilic aromatic substitution (EAS), so EAS occurs _____ relative to unsubstituted benzene.</p> <table border="1" data-bbox="479 1430 1513 1984"> <thead> <tr> <th>Substituent</th> <th>Resonance (+/-R) effect</th> <th>Inductive (+/- I) effect</th> <th>Activating or Deactivating</th> <th>Ortho/Para or Meta</th> </tr> </thead> <tbody> <tr> <td>-O⁻</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>-OH</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>-Cl</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>-NO₂</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>CO-OR (ester)</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>	Substituent	Resonance (+/-R) effect	Inductive (+/- I) effect	Activating or Deactivating	Ortho/Para or Meta	-O ⁻					-OH					-Cl					-NO ₂					CO-OR (ester)				
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Questions:	Topic:
	<p>Important Take aways!</p> <p>1) Activating /Deactivating groups determine speed of reaction. Activating = _____. Deactivating = _____.</p> <p>2) Activating Groups are generally _____ directors and Deactivating groups are generally _____ directors (except for halogens)</p> <p>3) If resonance and inductive effect are competing: _____ tends to have a greater impact.</p>

Textbook table references for activating and deactivating group relative reaction rates

TABLE 25-2 Relative Rates of Nitration of Monosubstituted Benzenes

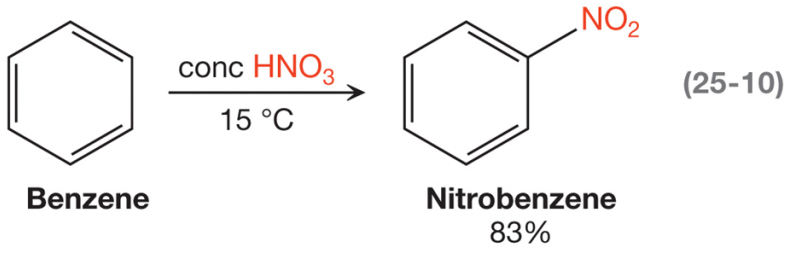
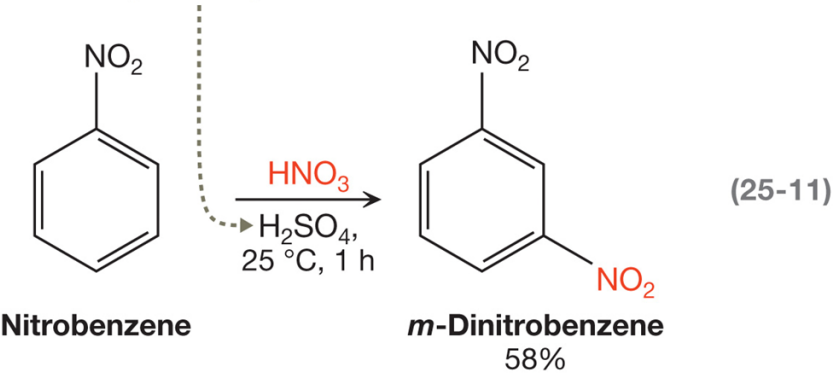


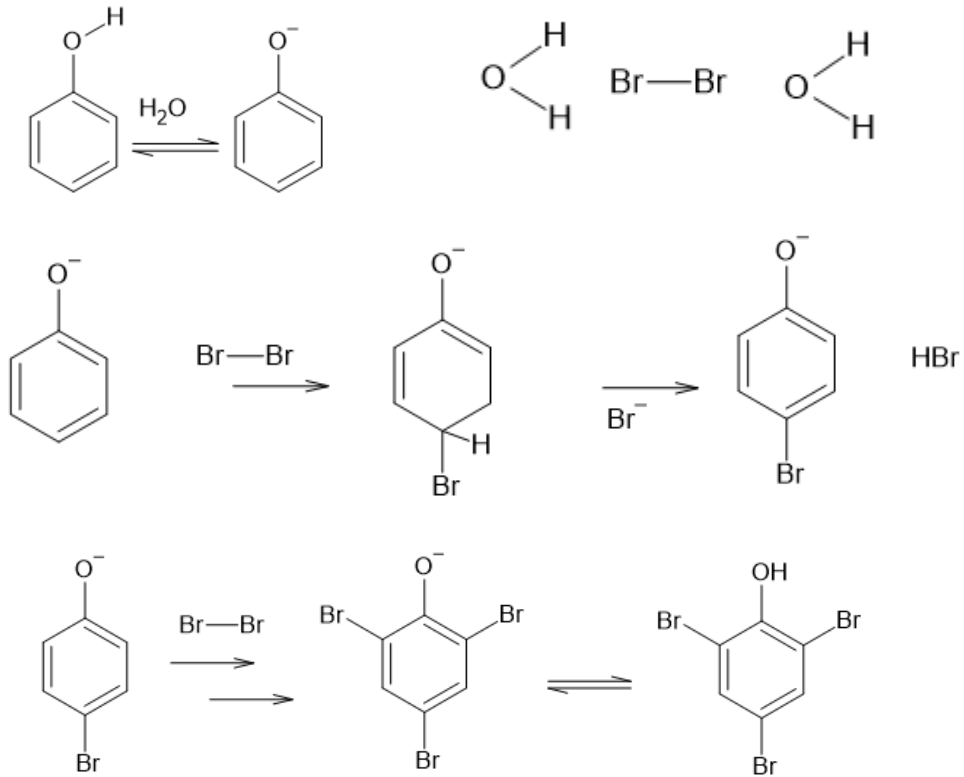
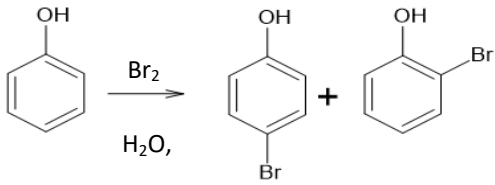
Substituent	Relative Rate	Type of Group
—NH ₂	— ^a	Strongly activating
—OH	1000	Strongly activating
—CH ₃	25	Weakly activating
—H (benzene)	1 (reference)	—
—F	0.84	Weakly deactivating
—I	0.45	Weakly deactivating
—Cl	0.15	Weakly deactivating
—Br	0.11	Weakly deactivating
—CO ₂ Et	0.0037	Moderately deactivating
—NO ₂	6 × 10 ⁻⁸	Strongly deactivating
—N ⁺ (CH ₃) ₃	1.2 × 10 ⁻⁸	Strongly deactivating

Increasing rate of reaction

^aAromatic amines are susceptible to protonation and oxidation under nitration conditions. The NH₂ group is determined to be a strongly activating group using other electrophilic aromatic substitution reactions.

- Strongly Activating Groups:** -O⁻, -NH₂, -NR₂, -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 (-SO₂OH), amine (-NH₃⁺), trimethyl amine(-N(CH₃)₃⁺)

Questions:	Topic:
<p>If substituent group is deactivating, disubstitution is slower and more difficult</p>	<p>If the substituent group is a deactivating group, the second substitution will be _____ difficult requiring a _____ to increase the electrophile.</p> <p>Ex.</p> <div style="text-align: center;">  <p>Benzene Nitrobenzene 83%</p> </div> <p>The ring is deactivated, so a stronger acid is necessary to carry out a second nitration.</p> <div style="text-align: center;">  <p>Nitrobenzene m-Dinitrobenzene 58%</p> </div>
<p>Substituent impacts on Friedel-Crafts reactions</p>	<ol style="list-style-type: none"> Friedel-Crafts reactions do not readily take place _____ groups. Why? Deactivation groups slow the reaction and the cation electrophile from Friedel crafts reactions will _____ before the ring attacks it. Friedel-Crafts alkylations are subject to polyalkylation Why? Because alkyl groups _____ and each alkyl group added will _____ the overall reaction rate and make subsequent alkylations _____. <p>Solution! First add an acyl group (moderately deactivating) to the ring, then reduce C=O to CH₂ with an acid.</p>

Questions:	Topic:
<p>Impact of reaction conditions on substituent effects</p>	<p>The substituents effect on regiochemistry (ie. orth-, meta-, and para-) and reaction rate is not always absolute. The reaction conditions impact the regiochemistry</p> 
<p>There are two ways to slow this reaction down and induce single bromination</p>	<p>1. Add a _____ to make the substituent less activating</p> <p>Acetic acid will _____ of the solution, resulting in an increased concentration of H^+ substantially _____ the concentration of phenoxide anion (a very powerful _____ group). The only route available is through phenol which is slower and _____ after a single bromination</p>  <p>2. Decreasing the _____ and adding a nonpolar solvent instead of water</p> <p>A nonpolar solvent, such as CS_2, will not aid in the separation of Br_2 and will _____ available for the reaction, making it difficult to form two bromine additions.</p> <hr/> <p>Similarly, if the substituent is a _____ and is likely to bond with a H and gain a _____ (ex. Amino group) . Increasing the pH can lead to a _____, _____ group that avoids Friedel– Crafts reaction.</p>

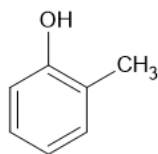
Questions:

Topic:

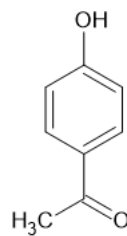
Now you try: rank these groups from fastest to slowest reaction



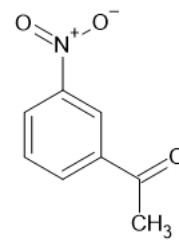
A



B



C



D

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

Summary:

24-72 hours after taking these notes, reread them and summarize what you learned and what you are still confused on. (~3-5 sentences)