

CFQ & PP: Electrophilic Aromatic Substitution

Reading

Brown and Foote: 20.1 – 20.3, 21.1, 21.2

Lecture Handout

Substituent Directing Effects and Summary of EAS Reactions

Suggested Text Exercises

Brown and Foote Chapter 21: 1 – 5, 7 – 9, 14 – 25

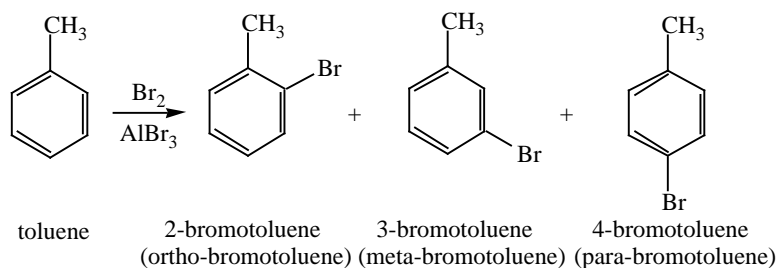
Optional Interactive Organic Chemistry CD and Workbook

Mechanism Overview: Electrophilic Aromatic Substitution (p. 71), Aromatic Nitration (p. 20), Electrophilic Aromatic Substitution with Cl (p. 25), Friedel-Crafts Acylation (p. 26), Friedel-Crafts Alkylation (p. 27)

Concept Focus Questions

1. Provide clear and concise definition of "electrophilic aromatic substitution."
2. Write a generic mechanism for the electrophilic aromatic substitution reaction.

Questions 3 - 7 refer to this reaction:



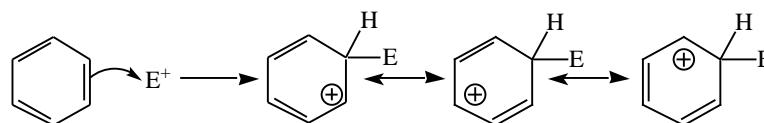
3. Provide a mechanism for the formation of the major product of this reaction. Include all important resonance contributors.
4. Briefly explain your choice of major product.
5. What is the purpose of the AlBr_3 in the reaction?
6. What is the rate-determining step in this reaction?
7. Draw a potential energy diagram for formation of the ortho product. Label all the important parts of the diagram.
8. Explain why the reaction gives substitution and not addition products.

- Define "activating substituent" and "deactivating substituent." Give at least two examples of each.
- As a general rule, are electron withdrawing substituents ortho, meta, or para directors and are they activating or deactivating? Briefly explain why.
- As a general rule, are electron donating substituents ortho, meta, or para directors and are they activating or deactivating? Briefly explain why.
- Briefly explain why the halogens are ortho/para directors, but deactivating.

Concept Focus Questions Solutions

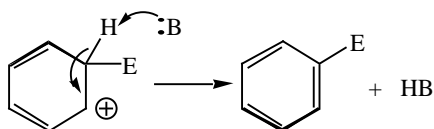
- Electrophilic aromatic substitution is a reaction in which there is substitution of an electrophile for a hydrogen atom on an aromatic ring.
- The reaction proceeds in two basic steps:

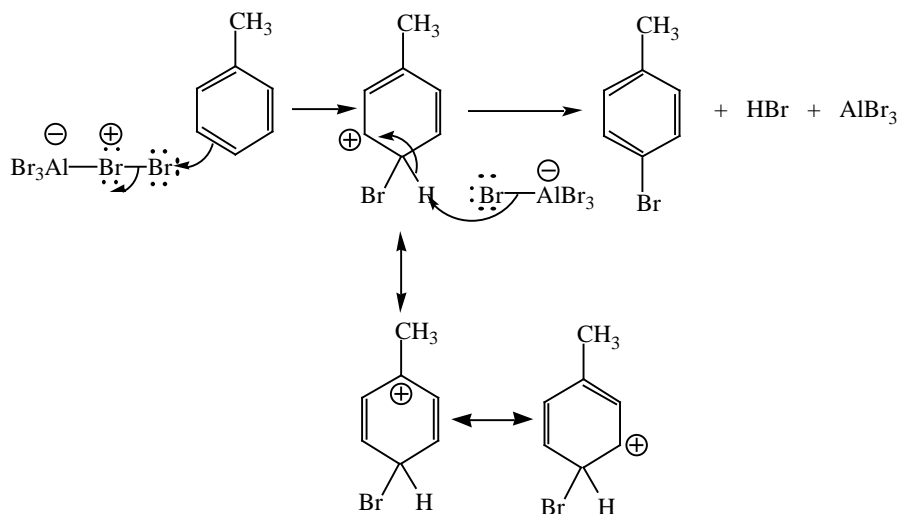
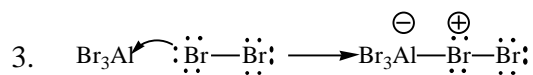
Step 1: Attack of the electrophile (E^+) upon the aromatic ring affording a resonance-stabilized carbocation called an arenium ion. The energy of activation for this step is high because aromaticity is lost.



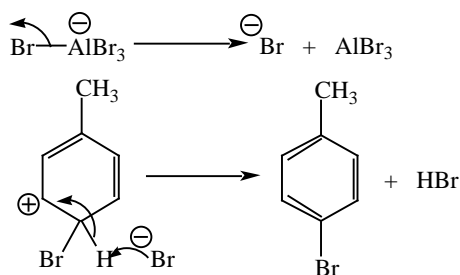
Arenium ion resonance contributors

Step 2: The arenium ion is deprotonated (one of the three fundamental carbocation fates) by a weak base ($:B$). The energy of activation for this deprotonation is exceptionally low as aromaticity is regained.

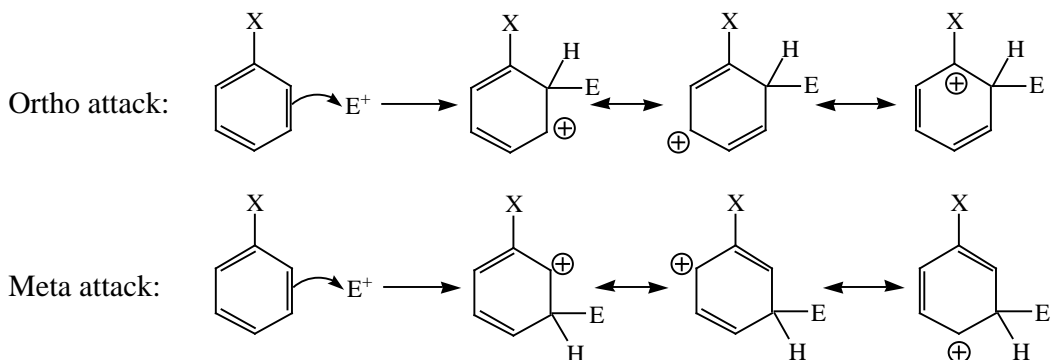


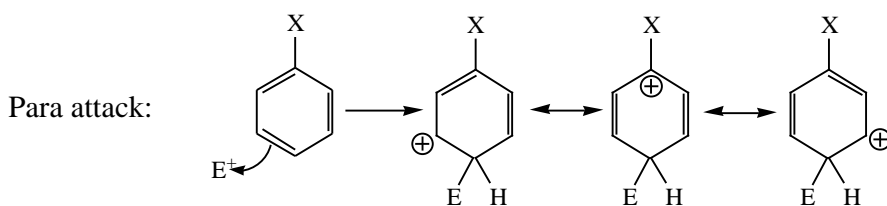


It is also acceptable to ionize the tetrabromoaluminate anion prior to deprotonation:



4. Which isomer of the product is formed is controlled by the position of attack of the electrophile on the benzene ring. Two major factors influence this. As in all other mechanisms, a mechanism step proceeds to give the most stable product if there are no other overriding factors. (An example of an overriding factor would be the C-H/C-LG periplanar requirement for the E2 reaction.) Since the electrophilic attack affords a carbocation, the attack leading to the most stable carbocation is favored.





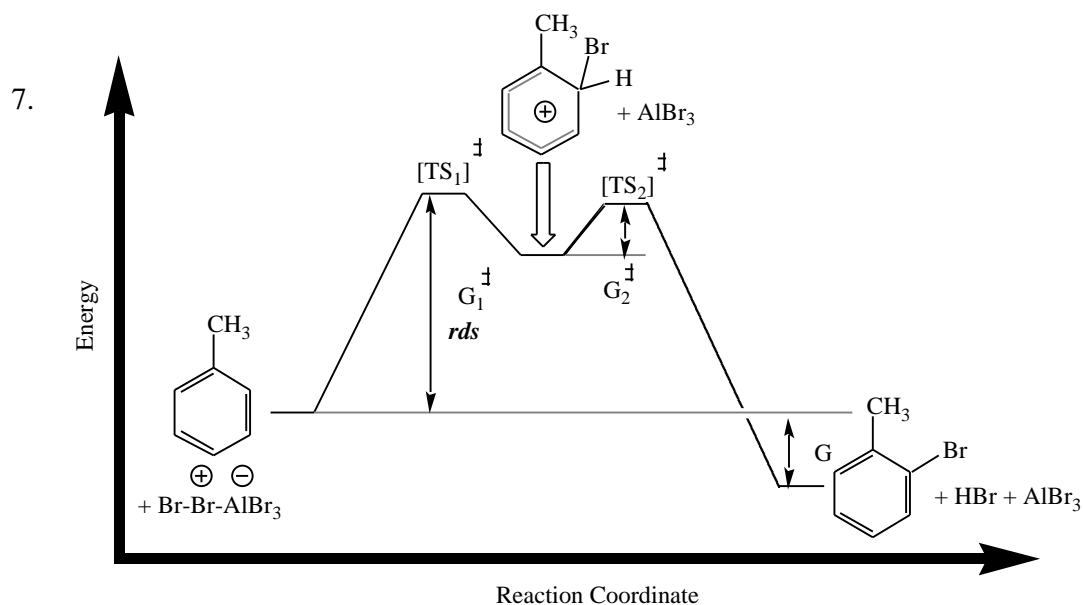
Attack at any position leads to a carbocation with at least three resonance contributors. In the specific example of this question, $X = \text{CH}_3$, an electron-donating group. The best carbocation in the ortho and para cases is tertiary, while the best carbocation in the meta case is secondary. Based on carbocation stability, we predict attack at the ortho and para positions to be favored over meta attack. (If the X group can share lone pairs through resonance then the ortho and para carbocations can have a fourth resonance contributor, further improving their stability over the meta carbocation.)

The X group disfavors attack at the ortho position because it is more crowded than the meta or para positions.

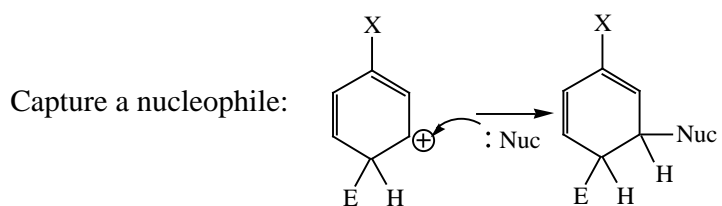
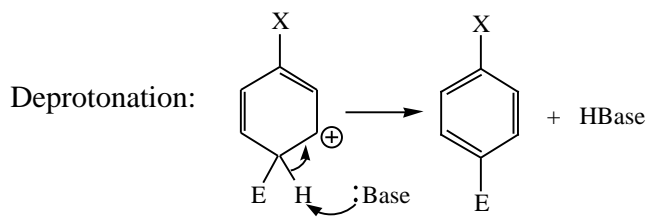
Resonance generally dominates, so the carbocation stability issue is more important than the steric effect. Thus the order of attack when $X = \text{CH}_3$ or any other electron-donating group is para (most) > ortho > meta (least). Electron-donating groups are therefore termed ortho/para directors.

When X is an electron-withdrawing group, it destabilizes an adjacent carbocation by increasing the net positive charge on that carbon. This occurs in the carbocations resulting from ortho and para attack, but not from meta attack. In this case the order of attack is meta > para > ortho. Electron-withdrawing groups are termed meta directors.

- Electrophilic attack on the benzene ring disrupts aromaticity and forms a carbocation, and thus requires a powerful electrophile. Molecular bromine is not sufficiently electrophilic to overcome aromaticity, so a more powerful electrophile is needed. The AlBr_3 serves to increase the electrophilicity of the bromine by strongly polarizing the Al-Br bond, thus increasing the amount of positive charge on the bromine. This is the first step of the mechanism shown above. (In cases where an arenium ion with a full octet resonance contributor is produced, the bromine may be sufficiently electrophilic by itself.)
- As seen in the mechanism for this reaction, attack of the electrophile on the benzene ring sacrifices aromaticity. Aromaticity is recovered when the arenium ion is deprotonated. Based in this, we conclude the electrophilic attack step to be much slower than the deprotonation step. Thus the electrophilic attack step is the rate-determining step.



8. Whether the reaction affords a substitution or addition product is determined by the mechanistic fate of the arenium carbocation. Recall the three fundamental mechanistic fates of a carbocation. Deprotonation results in a recovery of aromaticity, affording a product in which a hydrogen has been replaced by the electrophile. If the arenium carbocation captures a nucleophile, the product is not aromatic, and the net effect is addition.



Aromaticity is worth about 36 kcal mol^{-1} of extra stability, and thus deprotonation is favored over capture of a nucleophile. The net product is one of substitution, not addition.

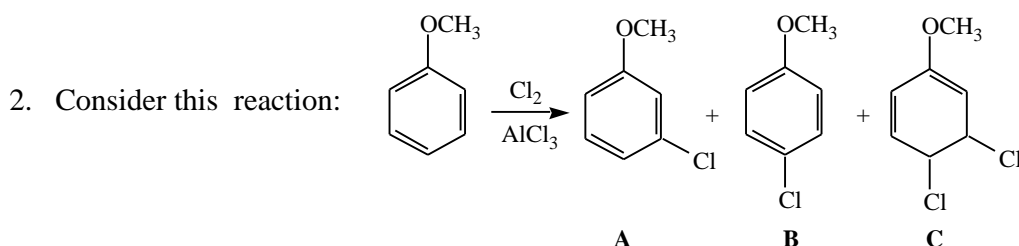
9. Activating substituent: An atom or group of atoms that increases the rate of electrophilic aromatic substitution by increasing the nucleophilicity of the aromatic ring and stabilizing the arenium ion. Examples: alkyl, aryl, vinyl, alkynyl, hydroxyl, ether, and amine.

Deactivating substituent: An atom or group of atoms that decreases the rate of electrophilic aromatic substitution by decreasing the nucleophilicity of the aromatic ring and destabilizing the arenium ion. Examples: nitro, carbonyl, trifluoromethyl, ammonium.

10. Electron withdrawing groups destabilize an adjacent carbocation as discussed in the answer to question 4. In this case, the most stable carbocations result from meta attack. Thus we conclude that electron-withdrawing substituents are generally meta directors. Electron withdrawing substituents remove electron density from the aromatic ring, reducing nucleophilicity and slowing the rate of electrophilic attack. Thus we conclude that electron-withdrawing substituents are deactivators.
11. Electron donating groups stabilize an adjacent carbocation as discussed in the answer to question 4. In this case, the most stable carbocations result from ortho or para attack. Thus we conclude that electron-donating substituents generally are ortho/para directors. Electron donating substituents release electron density into the aromatic ring, increasing nucleophilicity and accelerating the rate of electrophilic attack. Thus we conclude that electron donating substituents are activators.
12. The halogens are ortho/para directors due to a small resonance contribution. (This small resonance contribution is a combination of high electronegativity and poor overlap with carbon p orbitals by elements not in the same period as carbon.) When the electrophile attacks either ortho or para to the halogen, the carbocation can be stabilized to a small extent by a resonance contributor which places the positive charge on the halogen. The electronegativity of the halogens deactivates the aromatic ring due to an inductive effect, since they are more electronegative than carbon. The two effects counter each other, but the inductive effect is more significant in this case. (This is an uncommon example of another effect overwhelming a resonance effect.) Therefore halogens deactivate the aromatic ring, but cause ortho and para substitution.

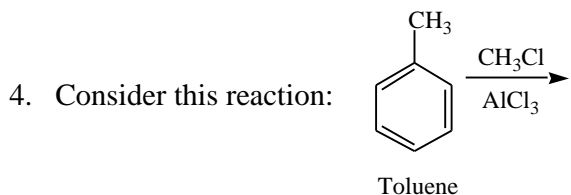
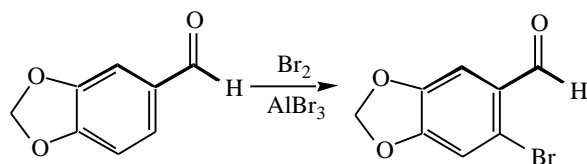
Practice Problems

1. The methoxy group (OCH_3) is an ortho/para director. Give an example that clearly illustrates what this means. Why is the OCH_3 group an ortho/para director? Be specific.

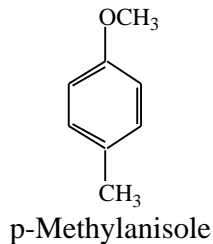


- (a) Draw a curved arrow mechanism that shows how this major product is formed.
- (b) Briefly explain why the other products are formed in lesser amounts.

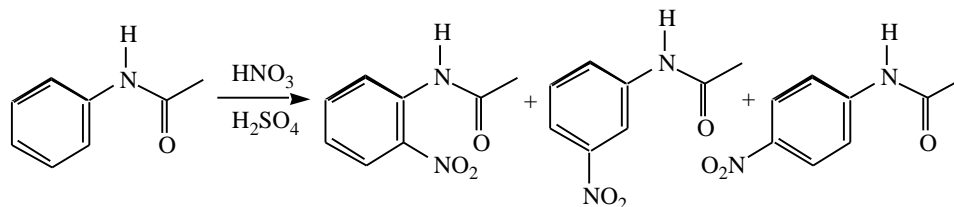
3. Provide a detailed curved-arrow mechanism for this reaction:



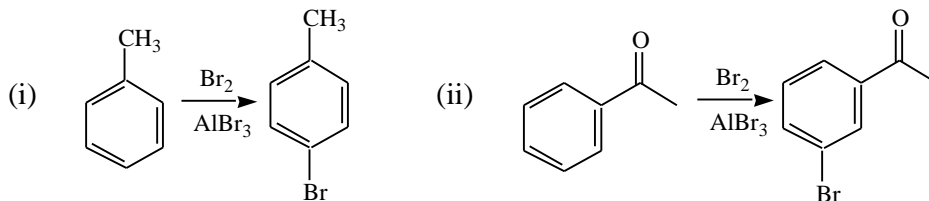
- Predict the major product of this reaction.
- Write a mechanism showing how the major product is formed. Include all important resonance contributors.
- Give two reasons why this is the major product.
- Would the reaction of p-methylanisole with $\text{CH}_3\text{Cl}/\text{AlCl}_3$ be faster or slower than the reaction with toluene? Briefly explain.



5. What is the major product of this reaction? Briefly explain.



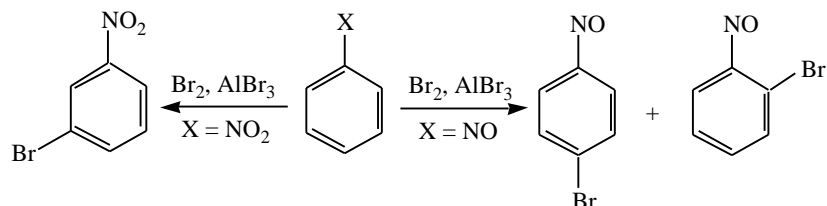
6. Consider these reactions:



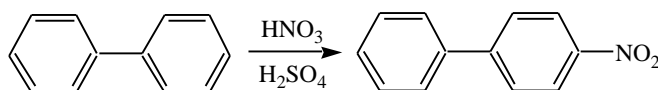
(a) Which reaction is slower?

- (b) Provide a complete curved arrow mechanism for the faster reaction. Include all important resonance contributors. Label the rate-determining step of this mechanism as "rds."
 (c) Briefly explain your choice of the rate-determining step.

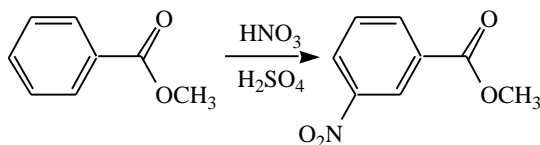
7. The nitro group (NO_2) is a meta director but the nitroso group (NO) is an ortho-para director. Explain.



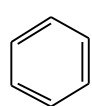
8. Electrophilic aromatic substitution on a benzene ring containing a functional group with a carbon-carbon bond conjugated with the benzene ring give mostly ortho and para products. Among these functional groups are phenyl (Ph), vinyl ($-\text{CH}=\text{CH}_2$) and ethynyl ($-\text{C}\equiv\text{CH}$). For example:



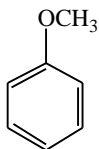
Conversely, similar reactions on benzene rings bearing functional groups with a carbonyl group directly attached to the ring such as ketones and esters give mostly the meta product. Explain.



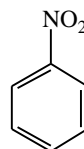
9. Rank the following compounds in order of relative rate of electrophilic aromatic substitution. Very briefly explain your answer.



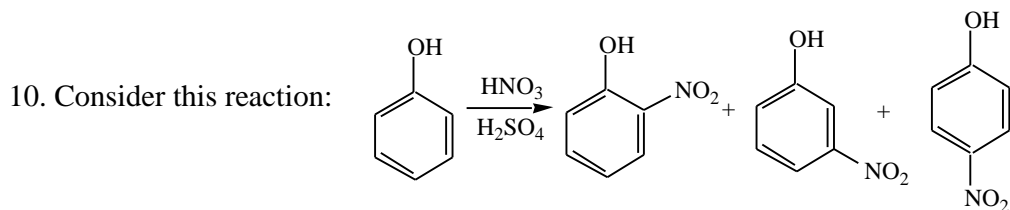
Benzene



Anisole

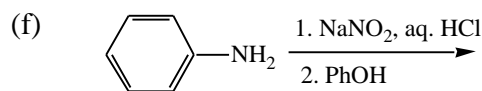
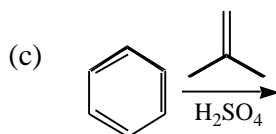
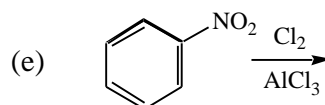
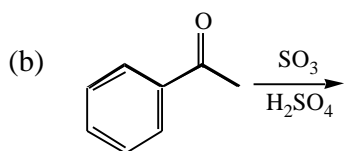
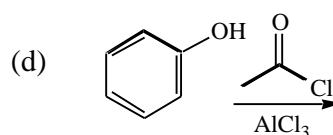
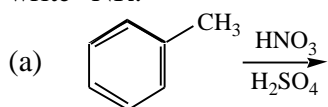


Nitrobenzene



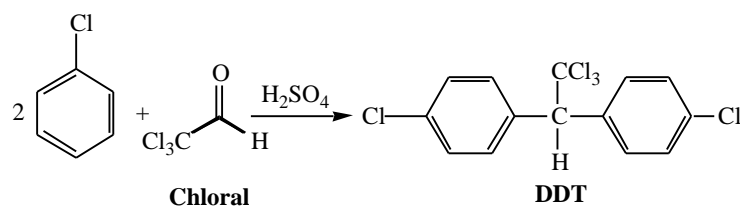
- Write a complete mechanism showing how the major product is formed. It is not necessary to draw all resonance contributors.
- Explain why the other two products are not major.
- Write a reaction that is similar to, but clearly faster than the reaction shown above.

11. Provide the organic product(s) of the following reactions. If more than one product is formed, indicate which product (if any) is the major product. If no reaction occurs, write "NR."

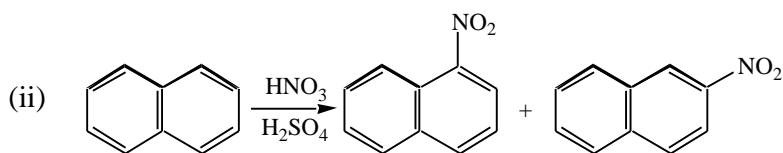
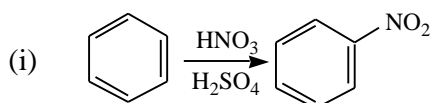


12. Provide a complete mechanism for the major product formed in each reaction of the previous question.

13. The insecticide DDT was widely used after World War II as an inexpensive and effective way to suppress reproduction of the *Anopheles* mosquito, chief carrier of the parasite that transmits malaria. The use of DDT in the United States was banned in 1972, after it had been shown that this material was responsible for the declining populations of certain birds that depended heavily on fish for their diets. It was also shown that DDT accumulates in lipids and fatty tissues of higher mammals. Although it appears human resist any significant short-term toxicity from DDT or DDE (an enzymatic degradation product), the long-term effects are unknown. Millions of pounds of DDT were synthesized from the reaction of chlorobenzene with chloral (trichloroacetaldehyde) in the presence of sulfuric acid. Write a mechanism for this reaction.



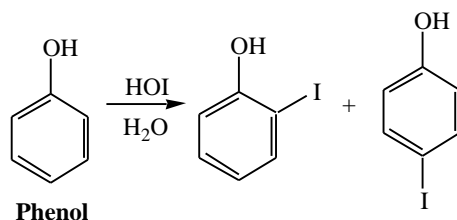
14. Consider these two reactions.



(a) What is the major product of reaction (ii)?

(b) Reaction (i) is slower than reaction (ii). Briefly explain why this is so.

15. Consider the biosynthesis of thyroxine, an iodinated amino acid hormone found only in thyroglobulin, a protein produced in the thyroid gland. It has been suggested that the iodine atom is added by electrophilic aromatic substitution with HOI, which is produced by the reaction of I_2 and H_2O_2 under the influence of the enzyme iodoperoxidase. In a lab test of this process, phenol was reacted with HOI to afford a mixture of ortho and para-iodophenol.



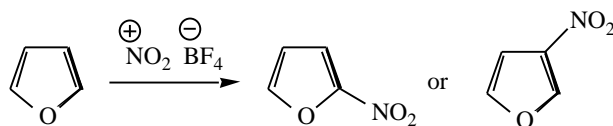
(a) Provide a mechanism for the formation of the major product of this reaction.

(Normally the HO group would be considered a very poor leaving group, but the weakness of the I-O bond overcomes this.)

(b) Briefly explain why hydroxyl (HO) is an ortho/para director.

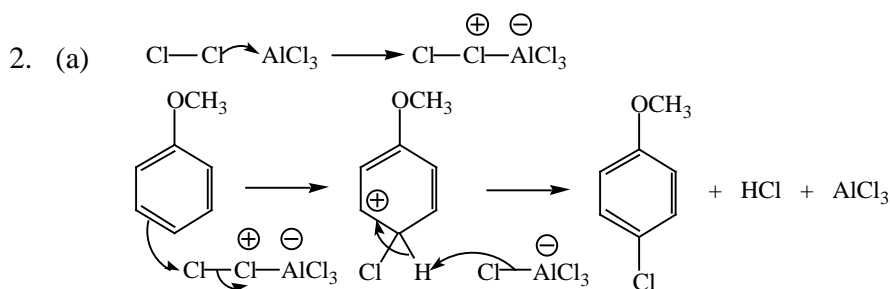
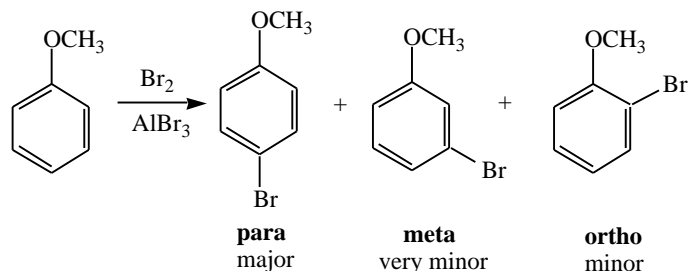
(c) Briefly explain why HOI is an electrophilic source of iodine.

16. Select the major product of this reaction, briefly explain why it is the major product, and draw a mechanism for its formation.



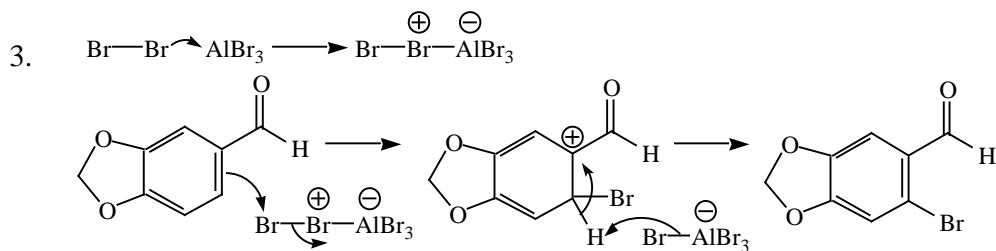
Practice Problems Solutions

- In the example shown below, the OCH_3 group is an ortho/para director because intermediate carbocations that result from electrophilic attack ortho or para to the OCH_3 group can assume four resonance contributors, one of which has a complete octet on every atom. Attack meta to the OCH_3 results in only three resonance contributors, none of which has a complete octet on every atom. Because the carbocations formed from ortho or para attack are more stable than those formed from meta attack (full octets; four versus three resonance contributors), ortho and para attack are favored over meta attack.

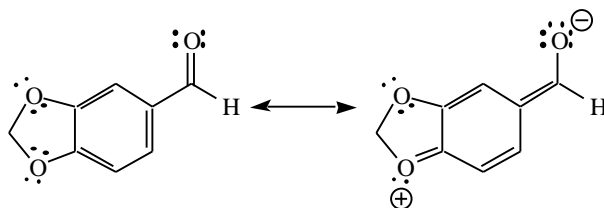


- Product A:** Para product **B** is favored over meta product **A** because the methoxy group can provide resonance stabilization to carbocation intermediates resulting from ortho or para attack of the electrophile, but not from meta attack.

Product C: This product would be formed when the carbocation intermediate captures a nucleophile (chloride ion) instead of losing a proton to form para product **B**. Capture of a nucleophile does not restore aromaticity, whereas deprotonation does. This provides a significant driving force for deprotonation over capture of chloride ion.

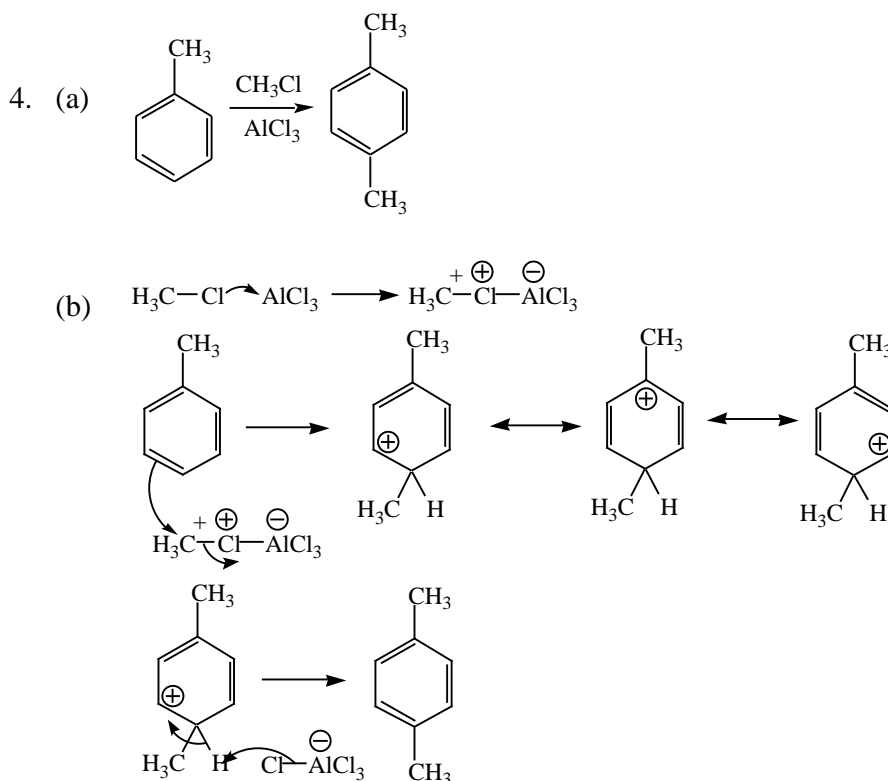


Many students have asked if the given product of this reaction is in error. Given that ether groups are ortho/para directors and the aldehyde group is a meta director, you might predict the major product to have the new C-Br bond meta to the aldehyde group. However, the given product is correct. So what is special about this case? The answer is our old friend resonance. Consider the following resonance contributors:



This resonance ties up some of the electron lone pair density on the ether oxygen, reducing its ability to stabilize an adjacent carbocation and thus weakening its influence as an ortho/para director. This same resonance adds electron density to the aldehyde group, decrease its electron withdrawing destabilization of an adjacent carbocation, and thus weakening its influence as a meta director. This leaves the other ether oxygen as the dominant directing group. The net effect is EAS para to this strongest group (ortho to the aldehyde, as shown in the given product).

Resonance interaction of an electron donating group para or ortho to an electron withdrawing group influence many aspects of aromatic ring chemistry.



- (c) Reason #1: The methyl group disfavors ortho attack due to steric repulsion of the incoming electrophile. This repulsion is not a factor in meta or para attack.

Reason #2: Ortho and para attack are favored because both have an intermediate carbocation with three resonance contributors. Two of these resonance contributors are 2° carbocations and the other is 3°. Meta attack yields an intermediate that also has three resonance contributors, each of which is a 2° carbocation. The resonance hybrids resulting from ortho or para attack are more stable than the resonance hybrid from meta attack, so meta attack will be disfavored.

- (d) Whenever we consider effects on reaction rates, we need to examine the rate-determining step (rds) of the reaction mechanism. In electrophilic aromatic substitution the rds is the initial attack of the electrophile on the benzene ring. Factors which make the benzene ring a better nucleophile will increase the rate of this reaction. The OCH₃ group is a strong electron donating group (resonance). This increases the electron density of the benzene ring, making it a better nucleophile. A methyl group is a weak electron donating group, so p-methylanisole is better nucleophile than toluene. Therefore the reaction of p-methylanisole will be faster than the reaction of toluene.

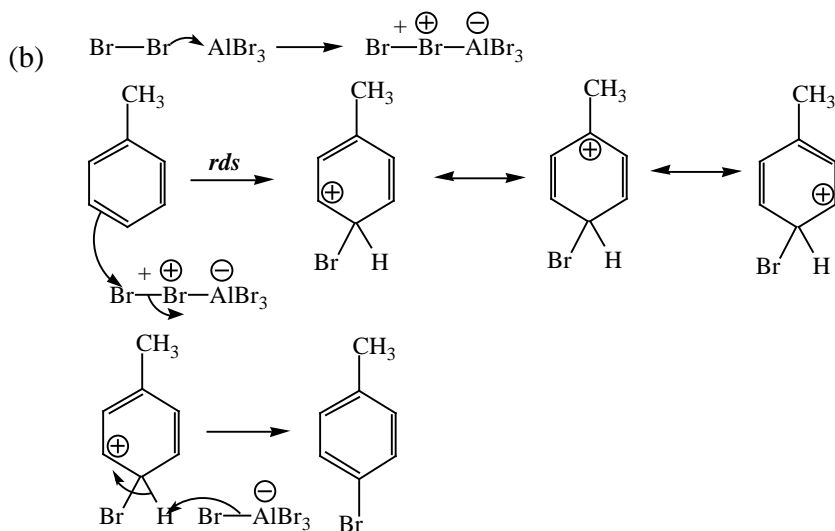
Alternate answer: Because the OCH₃ group can stabilize a carbocation more effectively than CH₃, adding this group to the ring will increase the rate of the reaction.

5. The major product of this reaction is the para isomer. There are two major factors that influence which product is formed.

Stability of carbocation intermediate. Initial electrophilic attack on the benzene ring occurs so as to afford the most stable carbocation. Attack at the ortho or para positions affords a carbocation that has four resonance contributors. In one of these contributors all atoms have a complete octet. This is due to the lone pair in the nitrogen atom, adjacent to the benzene ring. Attack at the meta position affords a carbocation that is less stable, as it only has three resonance contributors, and none of these three have a complete octet on all atoms. Thus attack at the ortho and para positions is favored over attack at the meta position.

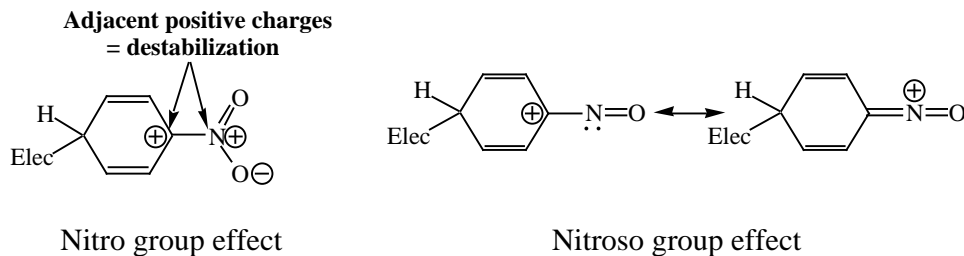
Steric effects. The amide hinders the incoming electrophile when attack occurs at the ortho position. There is significantly less hindrance to electrophilic attack at the para position. Thus, steric effects favor para attack over ortho attack.

6. (a) Reaction (ii) is slower.



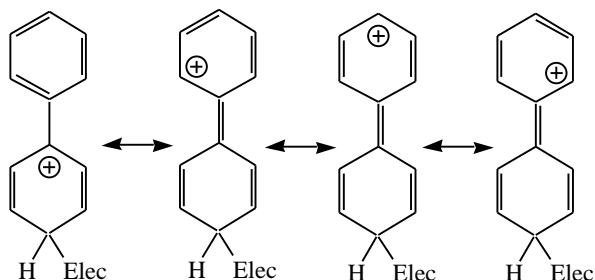
(c) The rate-determining step is the step with the greatest energy of activation. In the step labeled "rds," aromaticity is lost. This raises the energy of activation by 36 kcal mol⁻¹. In the deprotonation step, aromaticity is regained, so the energy of activation is lowered by 36 kcal mol⁻¹. Thus we predict the step in which aromaticity is lost to have the highest energy of activation.

7. Whether a substituent is an ortho/para or meta director is a function of how it influences the stability of the arenium ion intermediate. If the group stabilizes a carbocation by resonance or inductive electron release, then it enhances ortho or para attack because this forms an arenium ion whose positive charge may be stabilized. If the group destabilizes an adjacent positive charge by inductive electron withdrawing effects then it inhibits ortho or para attack but not meta attack, so meta attack is preferred. (Note that a meta director does not enhance meta attack, but instead exerts its directing influence by inhibiting ortho and para attack.) A nitro group bears a positively charged nitrogen atom and therefore destabilizes an adjacent open octet (with positive charge) on carbon. The nitroso group bears a nitrogen lone pair, so it can stabilize an adjacent open octet through resonance. The nitroso group is thus an ortho/para director.

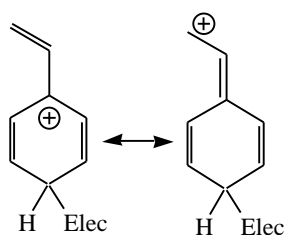


8. As discussed in the previous answer, functional groups containing bonds adjacent to the arenium ion positive charge will delocalize the positive charge by resonance and therefore function as ortho/para directors. Their propensity to function in this

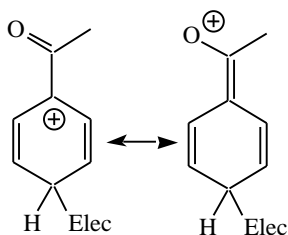
way is controlled by the degree of extra stabilization imparted. A phenyl substituent provides three additional resonance contributors (at the expense of aromaticity), so it is expected to be a moderately good ortho/para director.



An alkene or alkyne group adds but one additional resonance contributor. In the case of a monosubstituted vinyl group, the addition resonance contributor is a lowly primary carbocation.



A carbonyl substituent also has a π bond adjacent to the arenium ion, and resonance is a possibility. However, in the extra resonance contributor the positive charge resides on an oxygen atom with an open octet. This provides less stabilization than a carbon atom with an open octet. To rationalize why the carbonyl group is a meta director, then, we must assume the resonance contribution is minor and is overwhelmed by the oxygen's inductive effect.

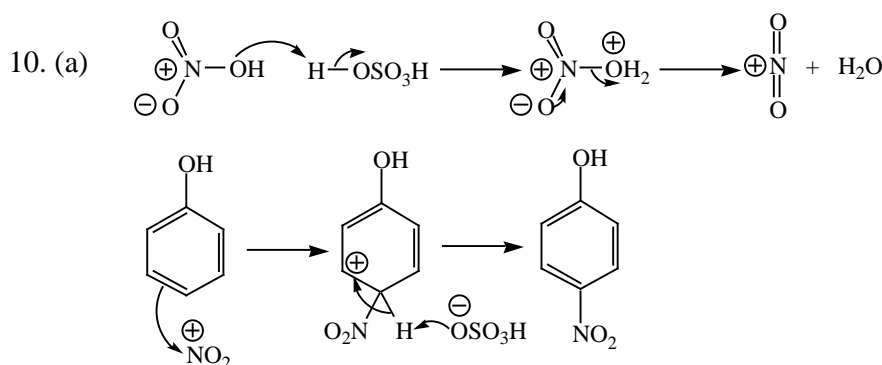


- In the rate-determining step of EAS, the benzene ring acts as a nucleophile and aromaticity is disrupted. The more electron-rich benzene ring is a stronger nucleophile. An OCH_3 group is electron donating, so anisole is a stronger nucleophile than benzene. The NO_2 group is electron withdrawing, so nitrobenzene is a poorer nucleophile than benzene.

Also, recall that formation of a more stable carbocation results in a faster reaction. Electrophilic attack on anisole affords an arenium ion with four resonance

contributors, one of which has a full octet on each atom. Similar electrophilic attack on benzene affords an arenium with three resonance contributors, none of which has a full octet on every atom. Because the arenium ion derived from anisole is more stable than the arenium ion derived from benzene, the rate of attack on anisole is faster than the rate of attack on benzene. In the nitrobenzene case, electrophilic attack affords an arenium ion with three resonance contributors, none of which have a full octet on every atom. The electron withdrawing effects of the nitro group further destabilizes this arenium ion. Because the arenium ion derived from nitrobenzene is less stable than the arenium ion derived from benzene, the rate of attack on nitrobenzene is less than the rate of attack on benzene.

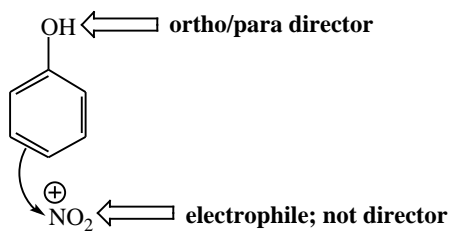
The combination of these effects suggest the order of EAS is anisole (fastest) > benzene > nitrobenzene (slowest).



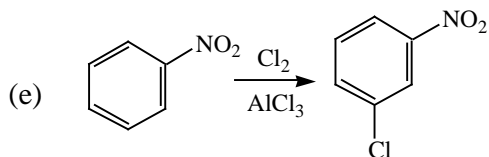
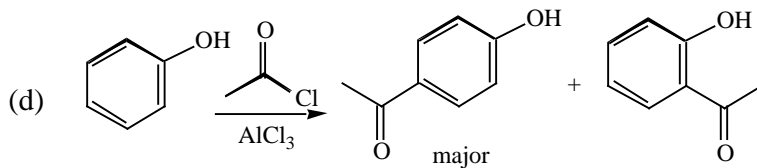
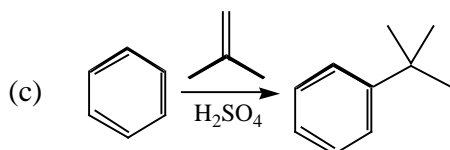
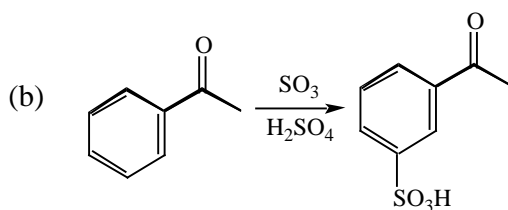
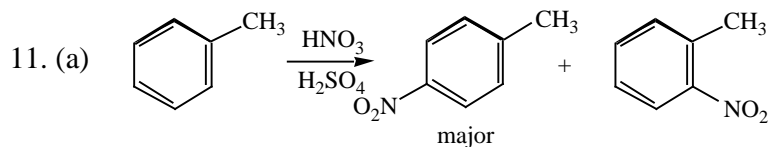
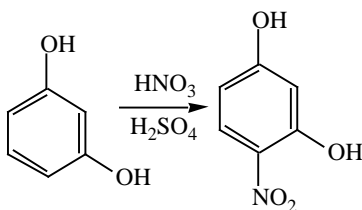
In the deprotonation step, bisulfate ion (HSO_3H) is shown as the base instead of water. Although water is a stronger base than bisulfate ion, any water present would be protonated by the excess of H_2SO_4 used in this reaction and thus unavailable to function as a base.

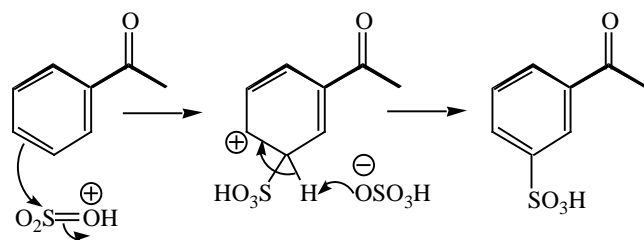
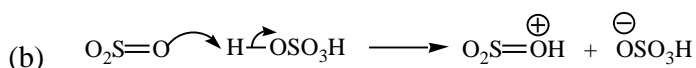
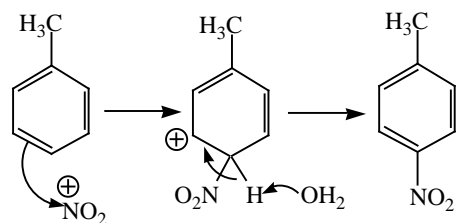
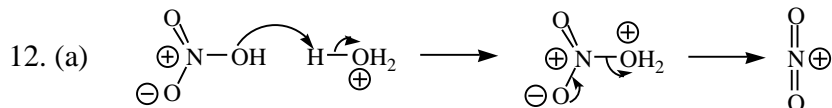
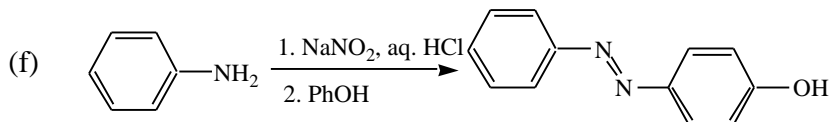
- (b) Ortho: Attack at the ortho site is sterically inhibited. Meta: Attack at the ortho and para sites yields a carbocation with a full octet on all atoms. Carbocations resultant from meta attack do not have a complete octet on all atoms, are therefore less stable, and thus not formed as readily.

It is the group already attached to the benzene ring and not the incoming electrophile controls the site of electrophilic attack. For example, if phenol is being nitrated (the mechanism shown in part (a) of this answer), the OH group directs the attack ortho/para. The nitronium ion (NO_2^+) has no influence on the site of attack because it does not influence the arenium ion stability in the same way as the OH group does.

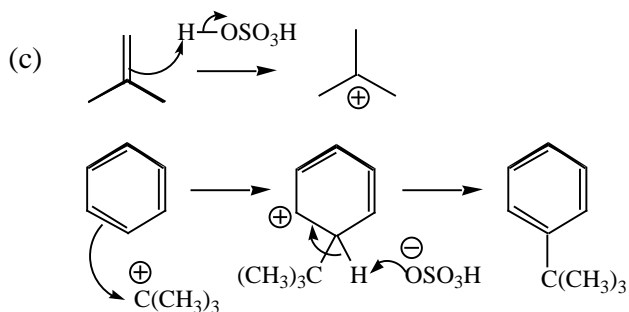


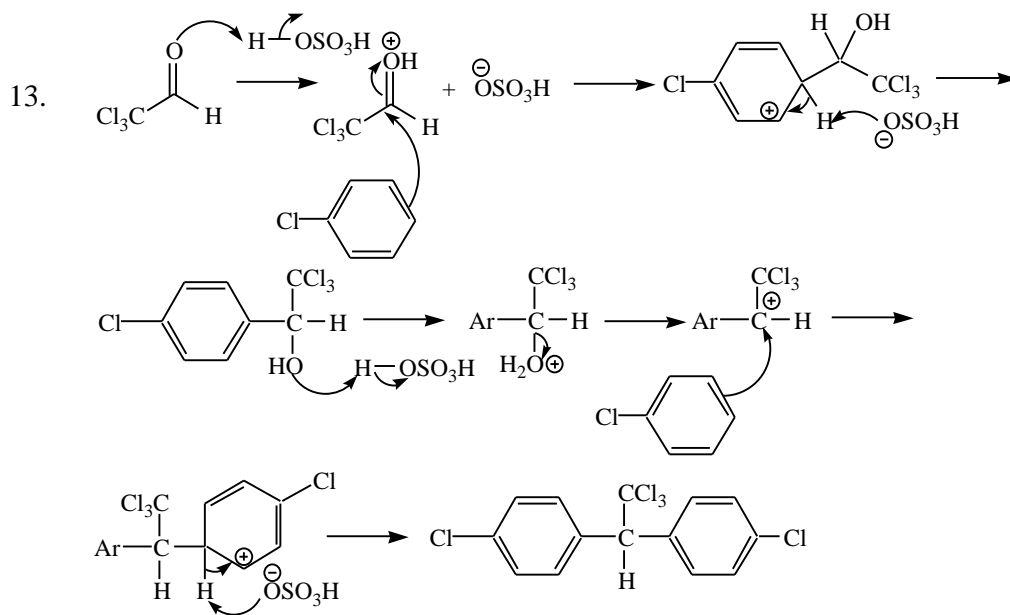
(c) The reaction will be faster if the aromatic ring is more electron-rich. This makes the ring more nucleophilic, and the carbocation intermediates more stable. The example shown below has two electron-donating OH groups.



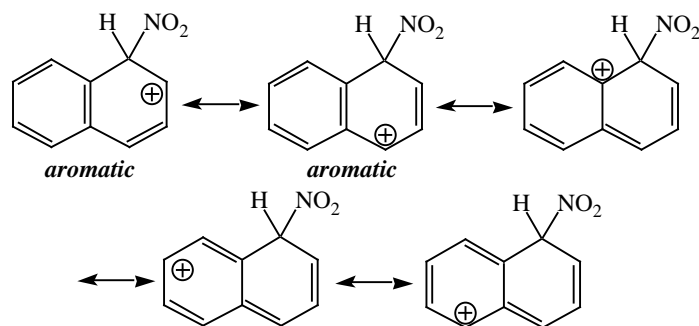


Laboratory studies of electrophilic aromatic sulfonation with $\text{SO}_3/\text{H}_2\text{SO}_4$ have suggested that the exact structure of the electrophile depends on the reaction conditions. For Chem 30C, the electrophile may be SO_3 , SO_3H^+ or H_3SO_4^+ . Work out the mechanism with each of these electrophiles to see the similarities and differences.

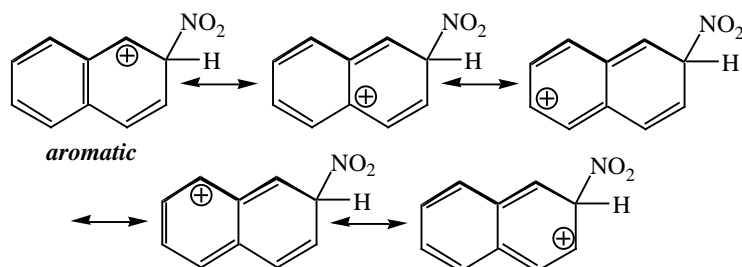




14. (a) The major product of any EAS is reaction is controlled principally by the resonance stabilization of the arenium ion intermediate. The more stable arenium ion is formed faster and thus leads to the major product. The arenium ions leading to 1-nitronaphthalene:

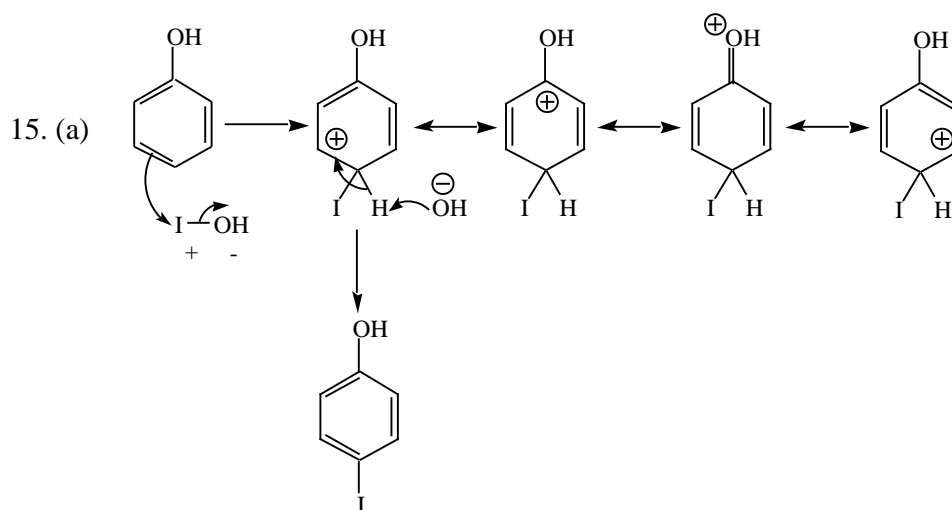


Of these five resonance contributors, two retain an aromatic ring. The arenium ions leading to 2-nitronaphthalene:



Of these five resonance contributors, only one retains an aromatic ring. Thus the arenium ion leading to 1-nitronaphthalene is more stable, so 1-nitronaphthalene is the major product.

- (b) Reaction rate is controlled by the rate-determining step (rds) of the mechanism. For electrophilic aromatic substitution, this step is attack of the electrophile on the aromatic ring. This is the rds because aromaticity is sacrificed. In reaction (i), all aromaticity is lost. In reaction (ii), the intermediate carbocation still has aromaticity (one benzene ring is left in tact). In addition, the arenium ion intermediate in reaction (ii) has more resonance contributors (and is therefore easier to form) than the arenium ion intermediate in reaction (i).

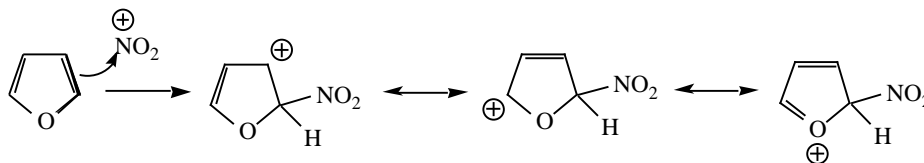


- (b) As can be seen in the mechanism above, electrophilic attack at the para position leads to an arenium ion with four resonance contributors, one of which has a full octet on all atoms. Ortho attack also leads to four resonance contributors. Meta attack leads to an arenium ion with only three resonance contributors. Everything else being equal, a carbocation with more resonance contributors is more stable and therefore more readily formed.

- (c) Iodine is significantly less electronegative than oxygen, so the I-O bond is polarized. The iodine end has a + charge and therefore IOH can serve as an electrophilic source of iodine.

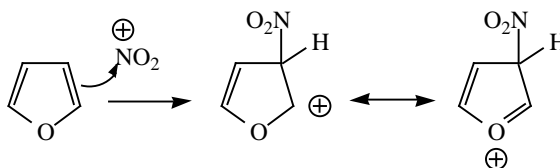
16. Furan is aromatic, and one of its hydrogen atoms is being replaced by NO_2^+ . (NO_2^+ is the nitronium cation. We have encountered it before.) Therefore this appears to be an electrophilic aromatic substitution reaction. The major product of an EAS reaction is derived from the more stable carbocation intermediate.

Attack at the 2 carbon:



This attack leads to a carbocation with three significant resonance contributors, one of which features a full octet on every atom.

Attack at the 3 carbon:



This attack leads to a carbocation with two significant resonance contributors, one of which features a full octet on every atom.

Because a carbocation with three resonance contributors is generally more stable than a carbocation with two contributors, attack at the 2 carbon is favored. The mechanism ends the same way as other EAS examples: the carbocation is deprotonated.

