CFQ & PP: Aryl Halides and Phenols

Reading

Brown and Foote: Sections 20.5, 20.6 and 21.3

Suggested Text Exercises

Brown and Foote Chapter 20: 6, 7, 32 – 40, 42 - 53
Chapter 21: 6, 28 - 47

Optional Interactive Organic Chemistry CD and Workbook

Kolbe Carboxylation of a Phenol (p. 28), Nucleophilic Aromatic Substitution (p. 29), Reactivity Explorer: Aromatics (p. 44)

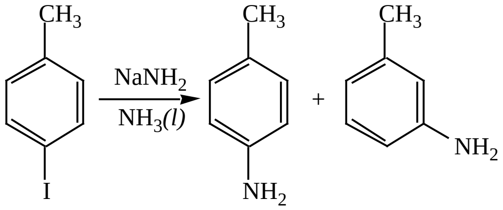
Concept Focus Questions

1. Why do we study aryl halides separately from alkyl halides?

2. The reactions of aryl and alkyl halides are similar in many ways. Give a pair of reactions that clearly illustrate this fact.

3. The reactions of aryl and alkyl halides are different in many ways. Give a pair of reactions that clearly illustrate this fact.

4. Provide a detailed curved-arrow mechanism.



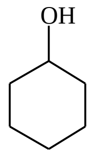
5. Why are S_N2 and S_N1 not viable mechanisms for aromatic substitution?

6. Suggest the two most important requirements for the addition-elimination (ipso) aromatic substitution mechanism.

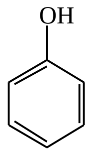
7. Suggest the three most important requirements for the elimination-addition (benzyne) aromatic substitution mechanism.

8. Many reactions involving carbocations, carbanions or radicals occur readily at a benzylic carbon. Explain.

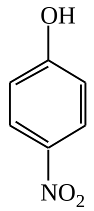
9. Rank the following compounds in order of pK_a. Briefly explain your reasoning.



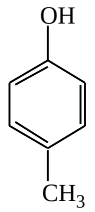
Cyclohexanol



Phenol



p-Nitrophenol

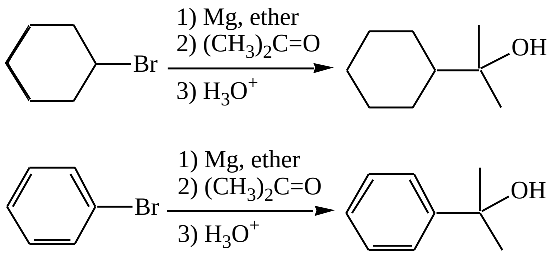


p-Cresol

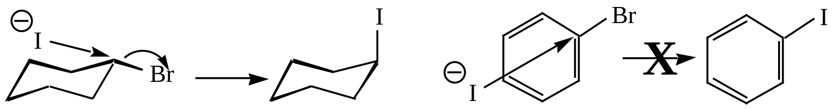
Concept Focus Questions Solutions

1. The presence of a benzene ring can alter the chemistry of the carbon-halogen bond, leading to new reactions and reactivity. Example: Aryl halides cannot undergo a normal S_N2 reaction.

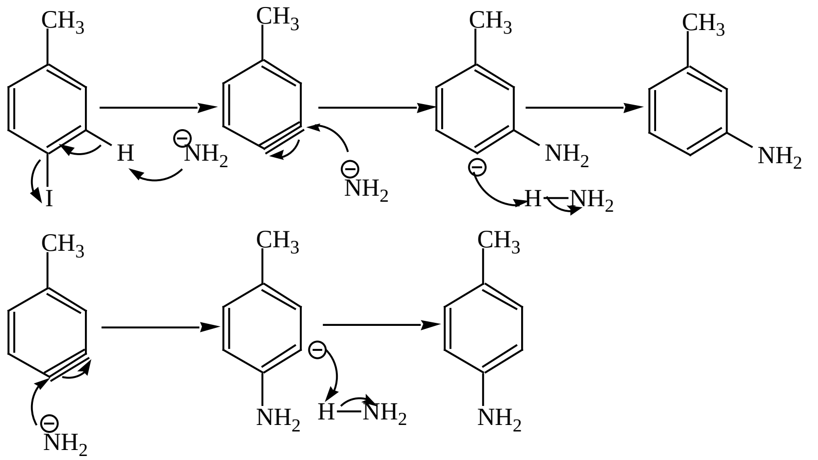
2. Aryl and alkyl halides both undergo the Grignard reaction:



3. Secondary alkyl halides can undergo substitution by the S_N2 mechanism. Aryl halides cannot undergo substitution by this mechanism because the benzene ring prevents attack of a nucleophile along the backside of the carbon-halogen bond.

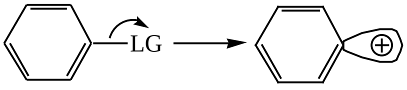


4.



5. S_N2: This mechanism requires the nucleophile to approach along the backside of the carbon-leaving group bond, through the plane of the benzene ring. This approach is much too highly hindered to be feasible (see CFQ #3).

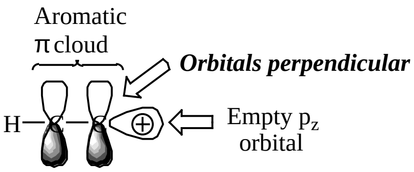
   S_N1: The rate-determining step of the S_N1 reaction is ionization of the carbon-leaving group bond to form a carbocation.



Phenyl carbocation

   A phenyl carbocation is less stable than other typical secondary carbocations, as the carbon bearing the open octet cannot assume the preferred sp hybridization. Thus the energy of activation leading to a phenyl carbocation is high and the S_N1 route to aromatic substitution is unlikely. (Phenyl carbocations do form in some mechanism, but only when the leaving group is exceptionally good and there is no other lower energy pathway available.)

   Many students assume (incorrectly) that because a phenyl carbocation has a benzene ring that it has resonance stabilization. Because this resonance stabilization involves overlap of the empty p_z orbital with an adjacent π system, the p_z orbital and π system must be parallel. In a phenyl carbocation, the empty p_z orbital and π cloud are perpendicular, so there can be no resonance delocalization of the positive charge.

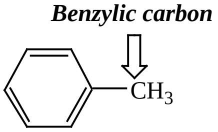


Phenyl carbocation: Side view showing perpendicular orbitals.

6. The two most important requirements for the addition-elimination aromatic substitution mechanism are (i) good nucleophile, and (ii) electron-poor benzene ring. The benzene ring should bear one or more strong electron-withdrawing groups (F, NO_2, CN, etc.), preferably that can also stabilize a negative charge through resonance.

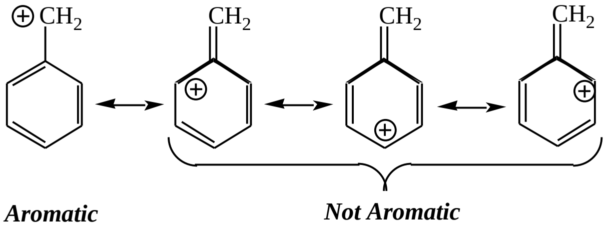
7. The elimination-addition (benzyne) aromatic substitution mechanism is like the E2 mechanism in a number of ways, including fundamental requirements of strong base, good leaving group and hydrogen β to the leaving group.

8. A benzylic carbon is a carbon atom directly bonded to a benzene ring, such as in toluene.

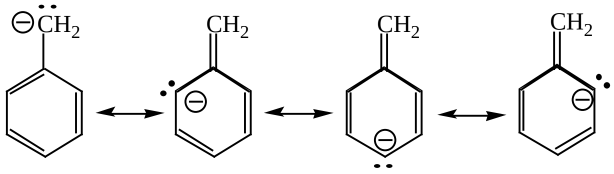


Many reactions involving carbocations, carbanions or radicals occur readily at a benzylic carbon because resonance stabilization by the benzene ring allows these intermediates to form readily.

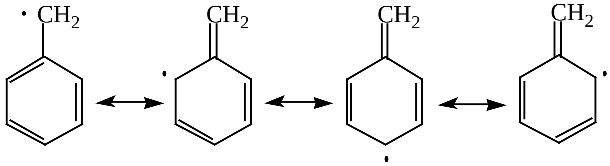
Carbocation:



Carbanion:

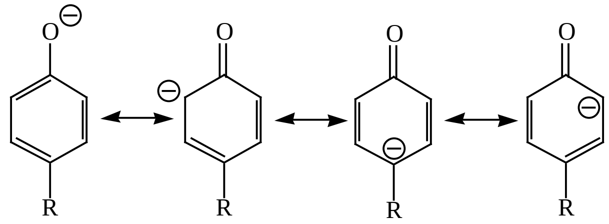


Benzylic radical:

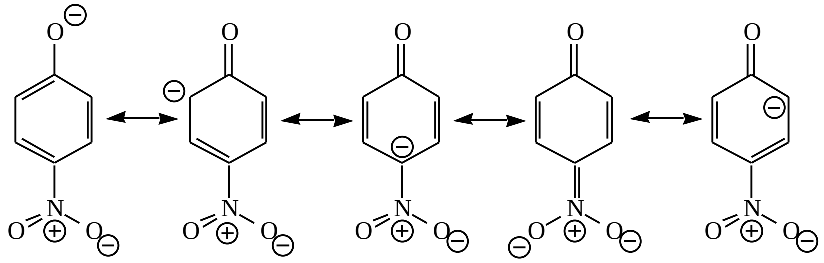


In each set of resonance contributors, only the first retains aromaticity, suggesting the other three contributors are less significant. This is counterbalanced by the presence of four resonance contributors for each intermediate. (Recall that resonance hybrids with more contributors are more stable than hybrids with fewer contributors.) The net effect is that benzene ring resonance is about equal to allylic resonance.

9. Acidity (pK_a) can be viewed as a measure of conjugate base stability. More stable conjugate bases are formed more readily, so the corresponding acids are more acidic (lower pK_a). Recall from the acid/base tutorial (web.chem.ucla.edu/~harding/ tutorials.html) or from Chem 30A that resonance is the most significant structural feature that stabilizes a base. Increasing the number of resonance contributors increases the stability of the base. The conjugate base of cyclohexanol has but a single resonance contributor. The conjugate bases of phenol (R = H) and p-cresol (R = CH_3) both have four resonance contributors.



The conjugate base of p-nitrophenol has five resonance contributors.

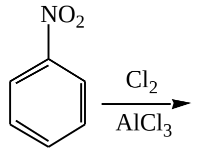


Therefore the conjugate base stability order is p-nitrophenol (most stable) > phenol, p-cresol > cyclohexanol (least stable). Now we compare the conjugate bases of phenol and p-cresol. A methyl group is a weak electron donor, dumping some extra electron density into the benzene ring. This amplifies the charge there and destabilizes the conjugate base. Thus the conjugate base of p-cresol is a bit less stable than the conjugate base of phenol. The final order of conjugate base stability is p-nitrophenol (most stable) > phenol > p-cresol > cyclohexanol (least stable). Since weaker (more stable) conjugate bases come from stronger acids, the order of acidity is p-nitrophenol (most acidic) > phenol > p-cresol > cyclohexanol (least acidic). The observed acidities are p-nitrophenol pK_a 7.15, phenol pK_a 9.99, p-cresol pK_a 10.26 and cyclohexanol pK_a 18.

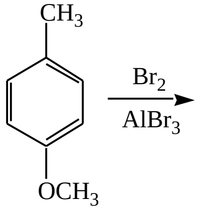
Practice Problems

1. Provide the organic product(s) of the following reactions. If more than one product is formed, indicate which product (if any) is the major one. If no reaction occurs, write "NR." In cases of NR, provide a brief explanation.

(a)



(b)



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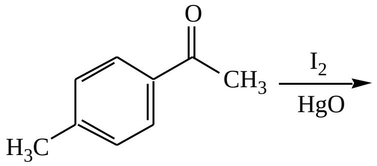

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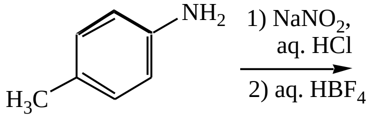

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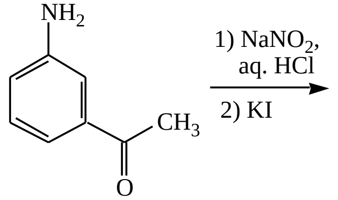

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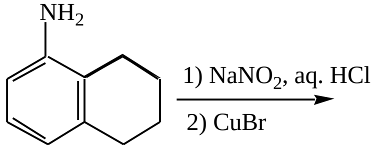

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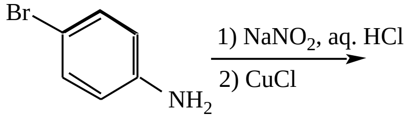

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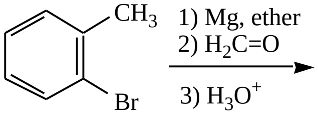
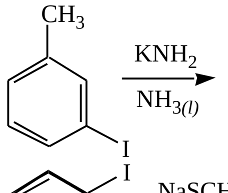
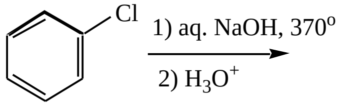
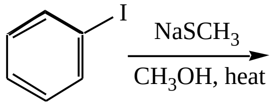
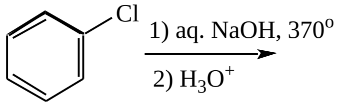
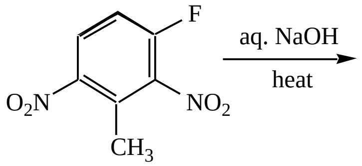


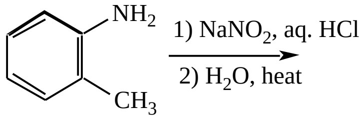
(i) 

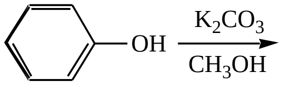
(j) 

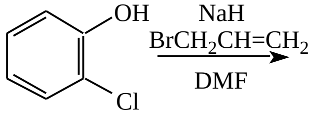
(k) 

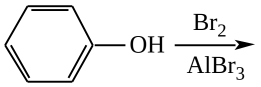
(l) 

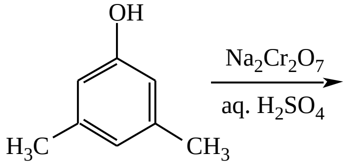
(m) 

(n) 

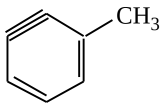
(o) 

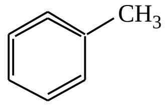
(p) 

(q) 

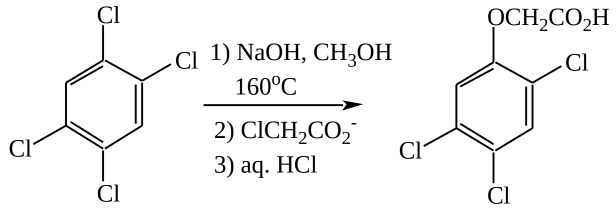
(r) 

2. What is the relationship (if any) between these two benzyne molecules? Given a choice of using either in a reaction mechanism, which would you pick?





3. The aryl ether 2,4,5-T is a component of Agent Orange, the infamous defoliant used during the Vietnam War. The synthesis of 2,4,5-T is shown below.



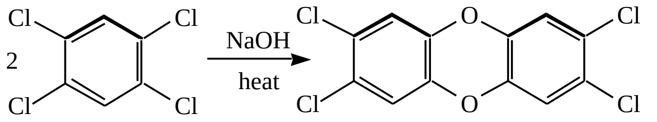
1,2,4,5-Tetrachlorobenzene

2,4,5-T

(a) Write the structures of the intermediates in this synthesis, and include the mechanisms for each step.

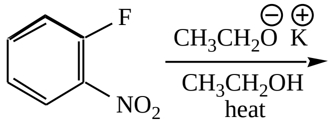
(b) Why can this reaction of tetrachlorobenzene be run at 160°C, whereas similar reaction with chlorobenzene requires 370°C?

(c) A side reaction of this synthesis is 2,3,7,8-tetrachlorodibenzo[b,e][1,4]dioxin (also called dioxin; structure shown below), one of the most toxic and carcinogenic organic compounds known. Write a mechanism for the formation of dioxin.



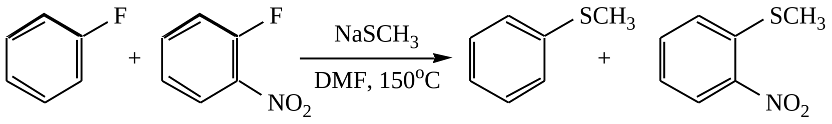
2,3,7,8-tetrachlorodibenzo[b,e][1,4]dioxin

4. Consider this aromatic substitution reaction:

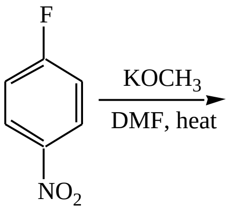


   (a) Write a mechanism that would lead to a single product for this reaction.
   (b) Write a mechanism that would lead to two products for this reaction.

5. Select the product that is formed more rapidly, and briefly explain your choice.



6. The aromatic substitution reaction shown below gives only one product.

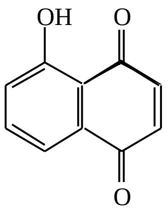


   (a) Considering that only one product was formed what can be concluded about the reaction mechanism?
   (b) Draw the structure of the product and the mechanism for its formation.
   (c) Explain your reasoning for the major product.

7. Fluoride is normally considered to be a poor leaving group, yet it leaves readily in the addition-elimination nucleophilic aromatic substitution mechanism. Why is this?

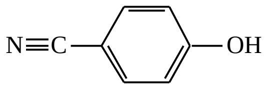
8. Assign pK_a values (7.15, 10.00, 10.46) to these molecules: phenol, 4-aminophenol, 4-nitrophenol. Briefly explain your reasoning.

9. Is juglone more or less acidic than phenol? Explain.



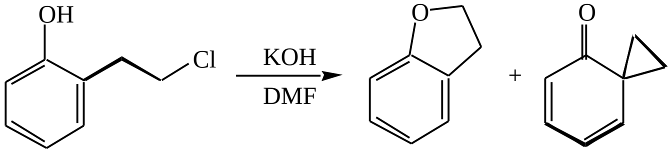
Juglone

10. Give examples of phenols which are more and less acidic than p-cyanophenol. Briefly explain your reasoning.

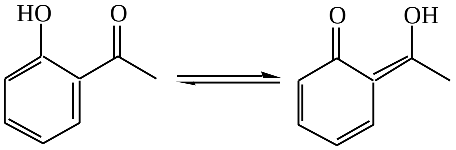


p-Cyanophenol

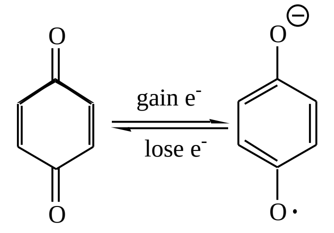
11. Provide a mechanism for both products. Select the major product and explain your reasoning.



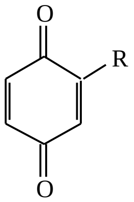
12. Does this equilibrium lie to the left or the right? Briefly explain.



13. Quinones are good electron acceptors (easily reduced), partly because reduction restores aromaticity.



A measure of the ability of a substance to accept electrons is its reduction potential E^o. A more positive E^o indicates a greater thermodynamic preference to accept electrons (to be reduced). Consider this E^o data.



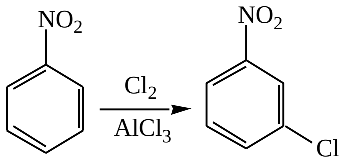
R = H	1,4-Benzoquinone	$E^o = + 0.669V$
R = CH_3	2-Methyl-1,4-benzoquinone	$E^o = +0.645$ V
R = Cl	2-Chloro-1,4-benzoquinone	$E^o = + 0.713V$

(a) Explain the relative order of reduction potentials for these quinones.

(b) Suggest a benzoquinone whose reduction potential is greater than 2-chloro-1,4-benzoquione. Briefly explain your reasoning.

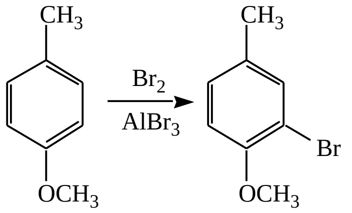
Practice Problem Solutions

1. (a)



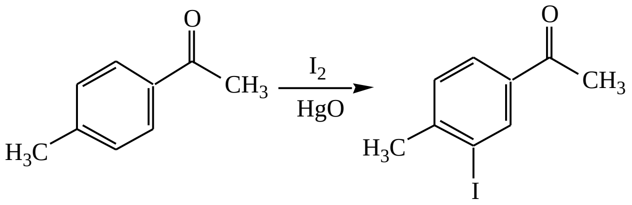
Electrophilic aromatic substitution. NO_2 is meta director.

(b)



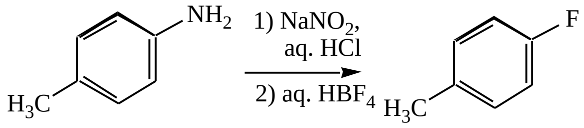
Electrophilic aromatic substitution. CH_3 and CH_3O are both ortho/para directors.

(c)



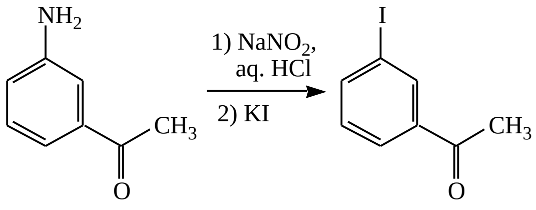
Electrophilic aromatic substitution. $I_2 + HgO \rightarrow I^+$. Ortho/para director ($CH_3$) wins out over meta director (ketone).

(d)



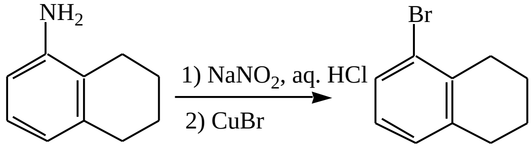
Substitution via diazonium salt.

(e)

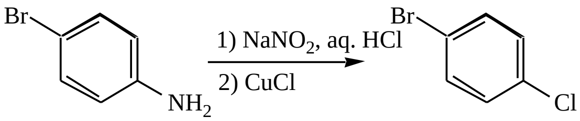


Substitution via diazonium salt.

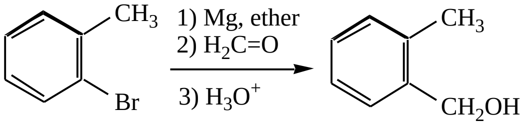
(f)



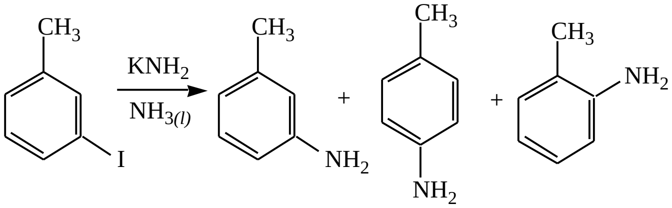
Sandmeyer reaction. Substitution via diazonium salt.

(g) 

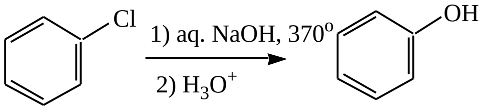
Sandmeyer reaction. Substitution via diazonium salt.

(h) 

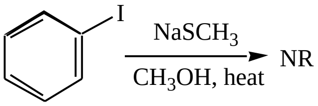
Grignard reaction. Addition of ArMgBr to carbonyl.

(i) 

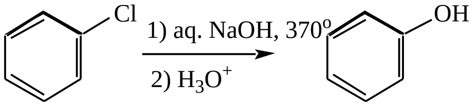
Aromatic substitution via benzyne. The iodine atoms has two β-hydrogens, so two benzyne intermediates are possible.

(j) 

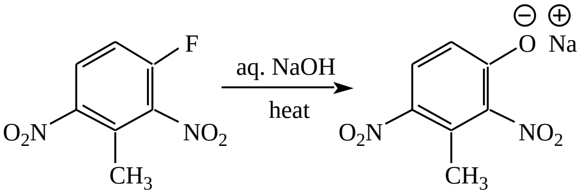
Aromatic substitution via benzyne.

(k) 

Base not strong enough for benzyne formation. Ring not sufficiently electron-poor for nucleophilic aromatic substitution.

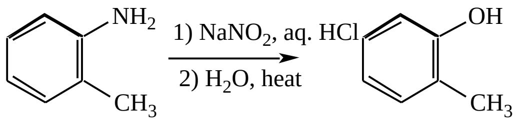
(l) 

Aromatic substitution via benzyne mechanism.

(m) 

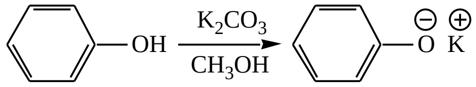
Aromatic substitution via (addition-elimination (ipso) mechanism.

(n)



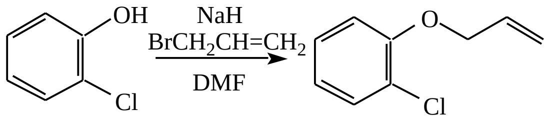
Formation and hydrolysis of diazonium salt.

(o)



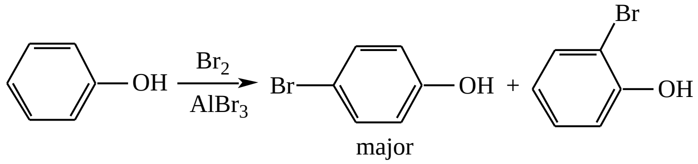
Deprotonation by mild base (CO_3^{2-}).

(p)



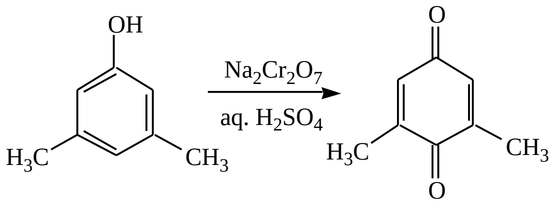
Formation and S_N2 alkylation of phenoxide ion (ArO^-).

(q)



Electrophilic aromatic substitution. HO is ortho/para director.

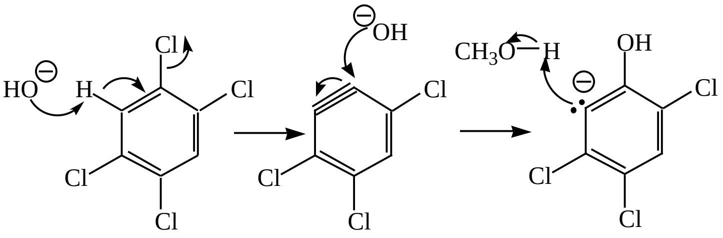
(r)

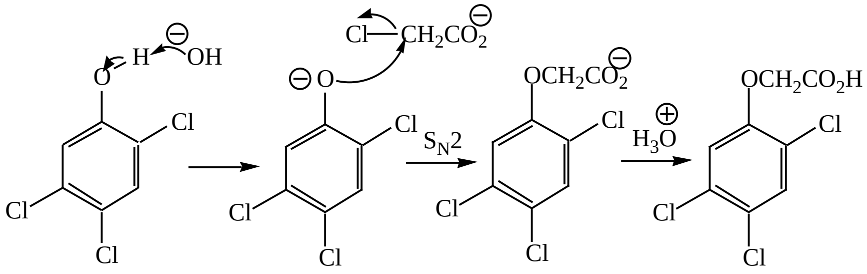


Oxidation of phenol to quinone.

2. These structures are resonance contributors of the same molecule. Because they are resonance contributors, either can be used in a reaction mechanism.

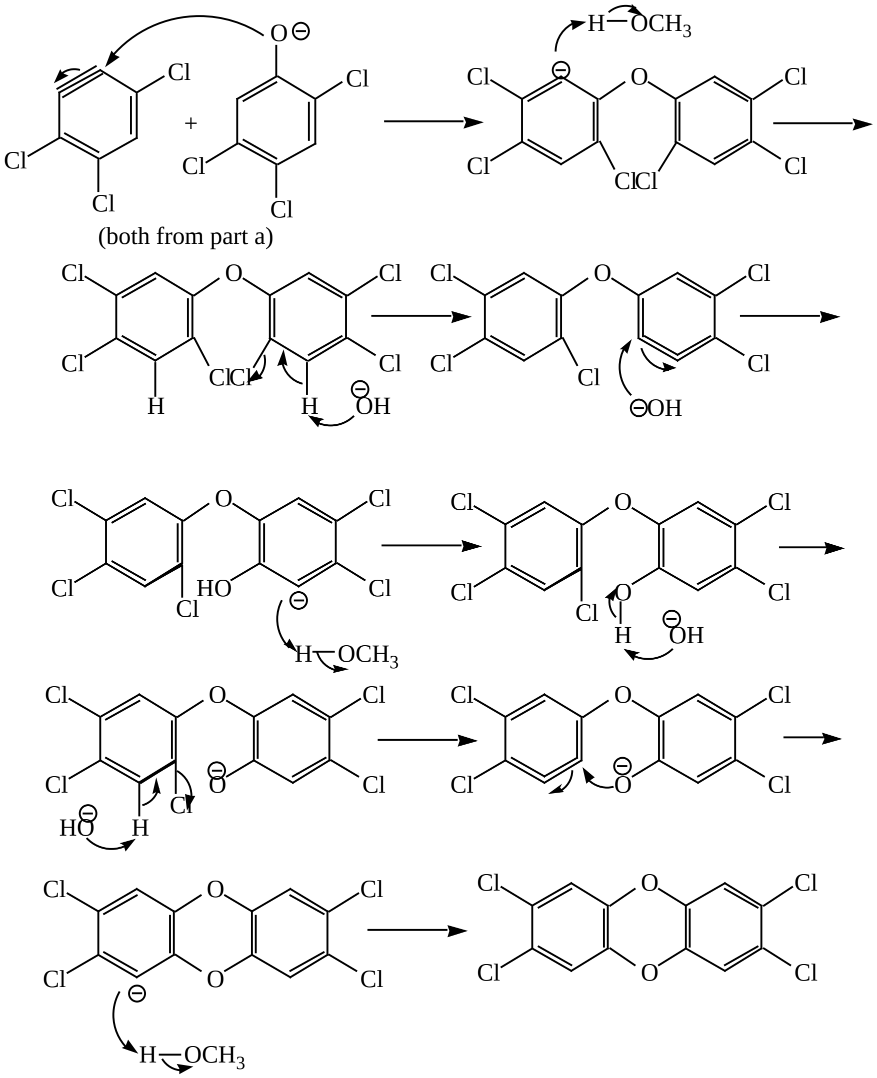
3. (a)





(b) The inductive effect of chlorine gives each phenyl hydrogen atom a δ+, making it slightly acidic. The greater the number of chlorine atoms on the benzene ring, the greater this effect will be. Thus tetrachlorobenzene is more acid than chlorobenzene, so deprotonation of tetrachlorobenzene (and subsequent E2 elimination to form the benzyne intermediate) occurs at a lower temperature.

(c)

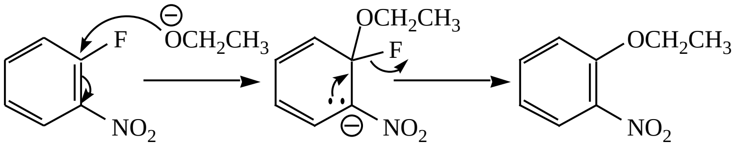


(both from part a)

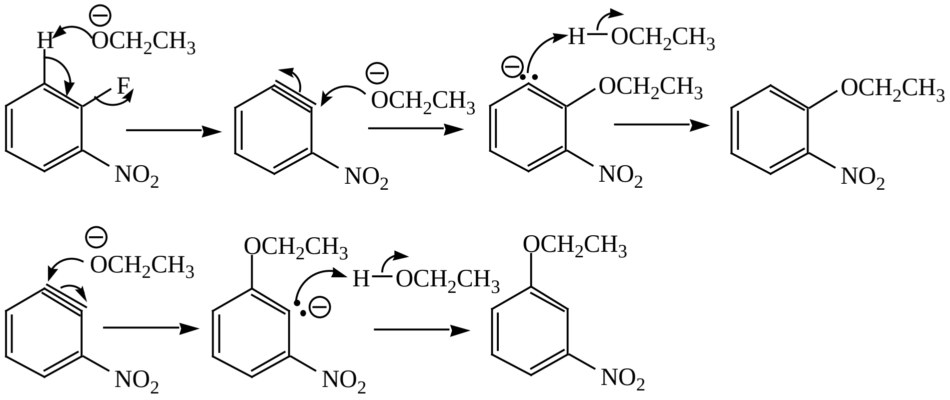
If the benzyne structures used in this mechanism confuse you, review Practice Problem 2.

4. We know of several aromatic substitution mechanisms, but only two occur with strong base: Ipso substitution and the benzyne mechanism. Ipso substitution occurs only at the carbon bearing the leaving group, whereas nucleophilic attack can occur at either sp carbon of the benzyne triple bond, resulting in two products.

   (a) Ipso substitution (also called the addition-elimination mechanism):



   (b) Benzyne mechanism (also called the elimination-addition mechanism):

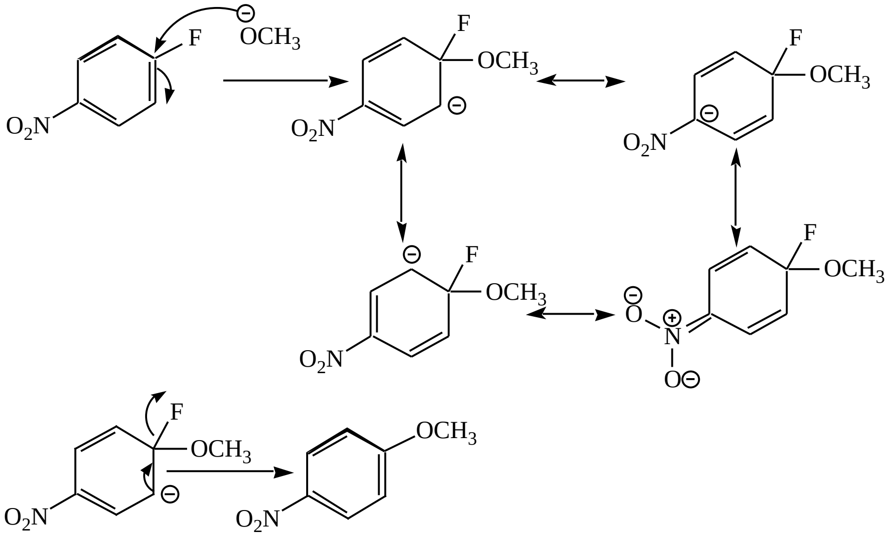


   Fluorine is a poor leaving group, so the benzyne mechanism is disfavored for this reaction.

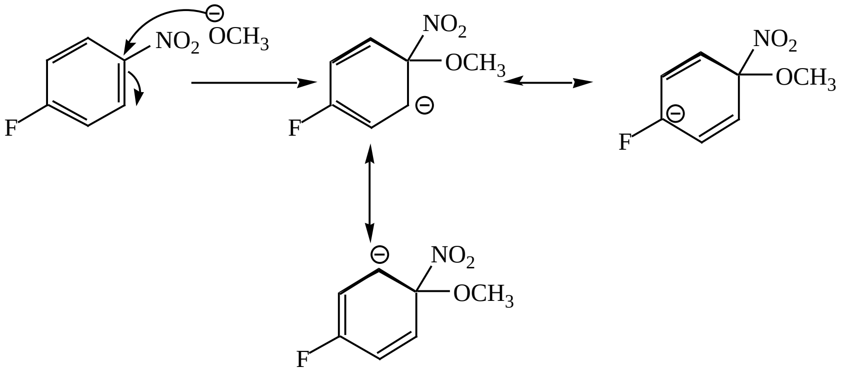
5. The products are clearly formed by an aromatic substitution mechanism of some sort. Methanethiolate (CH_3S^-) is a weak base, ruling out a benzyne mechanism. CH_3S^- is a good nucleophile, so an addition-elimination mechanism is possible. Nucleophilic attack on fluorobenzene is slower than attack on 1-fluoro-2-nitrobenzene as the latter is more electrophilic due to the inductive effect of two electron-withdrawing groups. It also has the nitro group to stabilize the intermediate carbanion. Thus we predict CH_3S^- will react more readily with 1-fluoro-2-nitrobenzene and the major reaction product will be 1-methylthio-2-nitrobenzene.

6. (a) That this aromatic substitution reaction produces a single product suggests the reaction proceeds by the addition-elimination (ipso) substitution mechanism. The elimination-addition (benzyne) mechanism would produce two products.

(b)

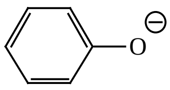


(c) Methoxide addition to the benzene ring will favor the most stable carbanion intermediate. Attack at the fluorine carbon affords a carbanion with four resonance contributors (shown above) whereas attack ipso to the nitro group gives a carbanion with only three resonance contributors (shown below).

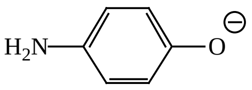


7. In the addition-elimination aromatic substitution mechanism, aromaticity is gained as fluoride leaves. This extra stabilization lowers activation energy for fluoride ion loss enough so that it now occurs at a reasonable rate.

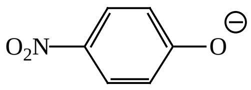
8. Applying the same logic as in CFQ #9, examine the conjugate bases of the three molecules.



Phenoxide



4-Aminophenoxide



4-Nitrophenoxide

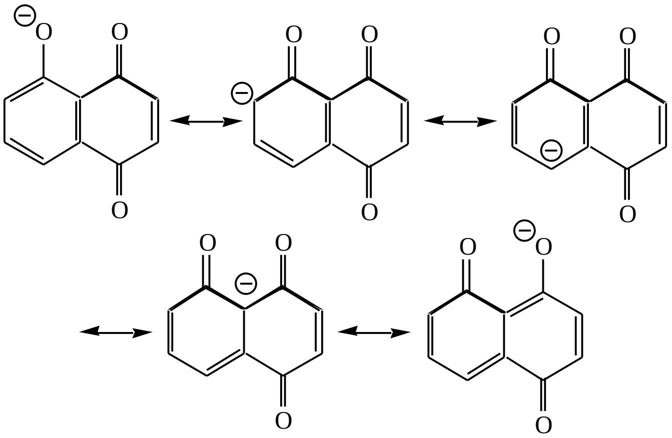
Phenoxide: This conjugate has four significant resonance contributors (CFQ #9).

4-Aminophenoxide: This conjugate base has the same four significant resonance contributors as phenoxide. The amino group is electron donating by resonance due to the nitrogen lone pair. This amplifies the negative charge of the conjugate base, making it less stable than phenoxide.

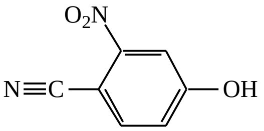
4-Nitrophenoxide: This conjugate base has five significant resonance contributors (CFQ #6) making it more stable than phenoxide.

Thus order of conjugate base stability is 4-aminophenoxide (least stable) < phenoxide < 4-nitrophenoxide (most stable). Since a less stable conjugate base corresponds to weaker acid, the pK_a assignments are 4-aminophenol pK_a 10.46 (weakest acid), phenol pK_a 10.00, and 4-nitrophenol pK_a 7.15 (strongest acid).

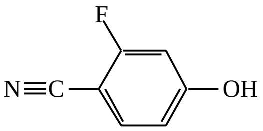
9. Applying the same logic as in CFQ #9, examine the conjugate base of juglone. It has five important resonance contributors, whereas phenoxide has only four. More resonance contributors means the conjugate base of juglone is more stable than the conjugate base of phenol. Thus, juglone is more willing to give up its proton (is more acidic) than is phenol.



10. The conjugate base can be made more stable (and the corresponding phenol more acidic) by increasing the number of resonance contributors. This can be achieved with a nitro group as in 4-cyano-3-nitrophenol. The negative charge can also be stabilized through the inductive effect with an electron-withdrawing group such as a fluorine atom as in 4-cyano-3-fluorophenol.

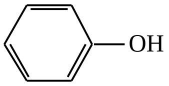


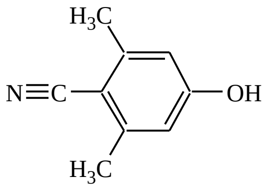
4-Cyano-3-nitrophenol



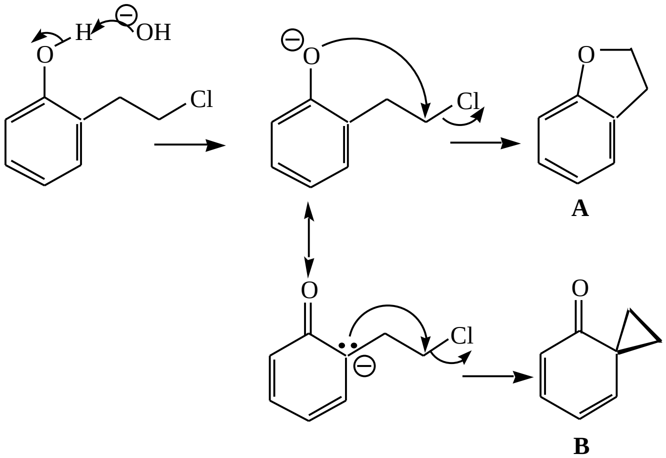
4-Cyano-3-fluorophenol

The opposite effect will make the phenol less acidic. Thus, decreasing number of resonance contributors by removing the nitrile group gives phenol. Increasing the electron density destabilizes the negative charge. This goal can be met by adding electron-donating methyl groups such as in 4-cyano-3,5-dimethylphenol.


Phenol


4-Cyano-3,5-dimethylphenol

11.

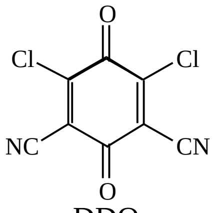


Dihydrobenzofuran **A** is aromatic whereas spirocyclopropane **B** is not. Spirocyclopropane **B** has significant ring strain whereas dihydrobenzofuran **A** does not. Therefore we predict dihydrobenzofuran **A** to be major.

12. Any equilibrium favors the more thermodynamically stable side. The phenol tautomer is aromatic where as the β-hydroxyenone is not. Because the phenol is more stable than the β-hydroxyenone, the equilibrium lies to the left.

13. (a) Judging from the reduction potential data, a quinone which is more electron-poor (the 2-chloro analog) is more easily reduced. This is probably due to better stabilization of the phenoxide ion by electron-withdrawing groups. This is further confirmed by noting that an electron-donating methyl group, which would destabilize the phenoxide ion by adding electron density, results in a decrease in reduction potential, indicating a greater barrier to accept an electron.

(b) A quinone with more electron-withdrawing groups, or more resonance contributors for the reduced form, should be more easily reduced. Adding another chlorine and two nitrile groups achieves both of these goals. The result is 2,6-dichloro-3,5-dicyano-1,4-benzoquinone (DDQ).


DDQ