Reactions of Aromatic Compounds

Reading: Wade chapter 17, sections 17-1- 17-15
Study Problems: 17-44, 17-46, 17-47, 17-48, 17-51, 17-52, 17-53, 17-59, 17-61

Key Concepts and Skills:

- Predict and propose mechanisms for common electrophilic aromatic substitution reactions
- Draw resonance structures for the sigma complexes resulting from electrophilic attack on substituted aromatic rings. Explain which substitutents are activating or deactivating, and show why they are ortho,para directing or meta-directing.
- Predict the position of electrophilic aromatic substitution on molecules containing multiple substitutents
- Design syntheses that use the influence of substitutents to generate the correct isomers of multisubstituted aromatic compounds.

Lecture Topics:

I. Electrophilic Aromatic Substitution (EAS)

Electrophilic aromatic substitution is the most important mechanism involved in the reactions of aromatic compounds. The electrons of an aromatic system are available to attack by strong electrophiles. Such an attack on an electrophile gives a sigma complex, also referred to as an arenium ion. The sigma complex is a resonance-stabilized carbocation:

In electrophilic aromatic substitution, an H atom is replaced with E.
The first step in this process (formation of the arenium ion) is endothermic because loss of aromaticity is required. The subsequent proton loss, in which aromaticity is regained, is exothermic.

A. Example: the bromination of benzene requires a Lewis acid catalyst to make bromine into a sufficiently good electrophile to be attacked by the benzene ring. $FeBr_3$ is usually the catalyst of choice:

Note that the first step is rate-limiting endothermic reaction with the electrophile which requires breaking aromaticity: a non-aromatic arenium ion is formed.
Chlorination and iodination proceed by the same mechanism.
B. Nitration: the substitution of a nitro group onto a benzene ring.
Mechanism again involves intermediacy of a sigma complex:

Aromatic nitro groups can be reduced to amines, thus providing a practical synthesis of anilines:

C. Sulfonation: addition of a mixture of 7% SO_3 (g) in H_2SO_4 produces "fuming sulfuric acid", which rapidly sulfonates aromatic rings. The reaction is completely reversible, so

that in dilute sulfuric acid benzene sulfonic acid is converted to benzene. The protonation of the aromatic ring during this de-sulfonation process is highlighted when D_2SO_4 is used in place of H_2SO_4:

II. Reactions of Substituted Aromatics

A. -Nitration of methyl benzene (toluene) takes place 25 times faster than benzene, and thus it is said to be "**activated**" toward electrophilic aromatic substitution.

-The substitution products are predominantly 1,2 and 1,4 relative to the methyl group, or ortho, para substituted.. The methyl group is thus said to be an **ortho, para director.**

-The rate-limiting step of substitution is formation of the sigma complex; for an endothermic step, the structure of the rate-limiting transition state must resemble the structure of the intermediate sigma complex (Hammond postulate). Toluene must have a lower energy T.S. than benzene in order to have an enhanced rate; we can gauge T.S. energies by inspecting the sigma complexes formed as intermediates:

The sigma complexes for ortho and para attack are more stable than the sigma complex for meta attack or for attack on benzene. Note that ortho and para attack result in a resonance form with a tertiary carbocation; meta attack does not result in tertiary carbocation formation, and thus meta attack on toluene occurs at only slightly greater rate than electrophilic attack on benzene. **Alkyl groups on aromatic rings are thus ortho, para directing and activating by inductive donation of electron density through sigma bonds!**

B. Other activating, ortho-para directing groups.
Anisole (methoxy benzene) undergoes nitration 10,000 times faster than benzene and 400 times faster than toluene! Oxygen is strongly electronegative and electron-withdrawing, yet it can donate electron density to aromatic rings by resonance. In electrophilic aromatic substitution, aromatic rings act as nucleophiles; more reactive rings have a greater degree of electron density to donate and are thus more nucleophilic. Oxygen can donate its non-bonding pair of electrons to an adjacent carbocation to stabilize that carbocation by resonance. Oxygen is thus a **resonance donor** or a donator of electron density through π bonds.

The methoxy group preferentially activates both ortho and para positions, and indeed there are four resonance forms possible for ortho and para attack, whereas there are only three resonance forms possible for meta attack. Methoxy groups are such strong activators that multiple substitutions are observed in a single operation:

C. The amino group

The amino group has a non-bonding pair of electrons that can participate in resonance donation; thus the amino group serves as a powerful activator for EAS. Indeed, any substitutent with a lone-pair of electrons on the atom bonded to the ring can provide resonance stabilization to the sigma complex. The reactivity of amino groups can be partially attenuated by placing an acyl group (C(=O)R) on the nitrogen atom.

Thus, the reactivity order of the ortho, para directors is as follows:

II. Deactivators

A. Meta-directing deactivators

Nitrobenzene is 100,000 times less reactive than benzene toward EAS. In general, an electron-withdrawing substitutent deactivates the ortho and para positions of the ring,

leaving the meta position the most reactive; thus the meta position is deactivated less than ortho and para. For nitro benzene, the positively charged nitrogen atom inductively withdraws electron density from the aromatic ring:

Note that in the resonance forms for the sigma complex, meta attack avoids placing the positive charge on the carbon right next to the positively charged nitrogen atom:

As a general rule, deactivating groups have a positive charge or partial positive charge on the atom bonded to the aromatic ring:

Deactivating Meta Directors:

B. Ortho,Para-directing Deactivators: Halogens

1. Halogens are strongly electronegative, inductively withdrawing electron-density from the aromatic ring through the sigma bond, thus deactivating the ring.
2. The halogens have non-bonding electrons that can donate electron density through resonance (pi bonding)

The inductive and resonance effects oppose each other for the halogens

Even though halogens are sigma withdrawing, they are pi-donating substitutents, and thus they are ortho, para directing:

Summary of directing effects:

III. Effect of multiple substitutents

Some substituents direct to the same location of the aromatic ring; they reinforce each other, and predicting the products of EAS is easy:

When directing effects conflict, it is often difficult to predict which substitution predominates; mixtures often result

When there is a conflict between an activating and a deactivating group, the activating group directs the substitution.

Directing abilities:

-OH, -OR, -NR_2 > -R, -X > –C(=O)R, -SO_3H, -NO_2

Examples:

IV. Friedel-Crafts Chemistry

A. Friedel-Crafts Alkylation

Carbocations are excellent electrophiles for EAS. In the presence of strong Lewis acid catalysts such as $AlCl_3$ and $FeCl_3$, alkyl halides can alkylate aromatic rings. Carbocations are intermediates only when secondary and tertiary alkyl halides are employed. With primary alkyl halides, free carbocations are too unstable, and direct aromatic attack on an alkyl halide- aluminum chloride complex takes place.

Some alternative means of forming carbocations for EAS involve protonation of alkenes followed by Markovnikov alkylation (promoted by HF) and Lewis-acid promoted ionization of alcohols:

Limitations of Friedel-Crafts Alkylation

1. Works only benzene, halobenzenes, and activated benzene derivatives; does not work with nitrobenzene and other deactivated benzene derivatives.
2. As with SN1 and E1 reactions, the F-C Alkylation is prone to carbocation rearrangements, since carbocations are intermediates. Only t-butyl, isopropyl and ethyl benzene can be prepared by this method. Attempts at making n-propyl benzene by this method result in the production of isopropyl benzene.
3. Since alkyl groups are activating to aromatic rings, the products of Friedel-Crafts alkylation are more reactive than the reactants, and thus multiple alkylations are hard to avoid.

B. Friedel-Crafts Acylation

The acyl group (-C(=O)R) can be placed on an aromatic ring by employing an acyl chloride (RCOCl) in the presence of $AlCl_3$. The acyl chloride can be prepared from the corresponding acid and $SOCl_2$. The acylation reaction proceeds via a highly reactive acylium ion which is resonance stabilized and not prone to rearrangement. Because $AlCl_3$ complexes to the carbonyl oxygen lone pairs of the product, $AlCl_3$ is not a catalyst for the reaction.

The electrophile complex is sterically bulky, and therefore substitution at para positions predominate in most cases:

Features of Friedel-Crafts Acyclation:

1. Acyl substitution deactivates the product toward further substitution, thus multiple substitution is not a problem
2. Resonance stabilization of the acylium ion prevents carbocation rearrangements from occurring during this reaction
3. Acylation fails with deactivated aromatic rings

Combined with the Clemmenson reduction, Friedel-Crafts acylation provides a practical route to mono-alkylated benzene derivatives:

V. Nucleophilic Aromatic Substitution (SN_{Ar})

In this case, the aromatic ring is the electrophile, and an external nucleophile substitutes for a good leaving group.

There are two types of SN_{Ar} reactions, which are distinguished based on mechanism and substrate.

For electron-poor aromatics containing multiple electron-withdrawing groups in addition to a leaving group, an **addition-elimination mechanism** takes place in the presence of a nucleophile:

Note that the electron-withdrawing group must be ortho or para to the leaving group in order for the ring to be activated toward nucleophilic aromatic substitution.

Under extreme conditions, an alternate mechanism maybe operative for non-activated arenes bearing a leaving group: **the benzyne mechanism**. The halobenzene will react only with very strong bases to give substitution products. The base deprotonates the benzene ring next to the leaving group, leaving a carbanion in an sp^2 orbital. This carbanion helps to eject the neighboring leaving group, forming a highly reactive benzyne species, which can undergo nucleophilic attack at either carbon atom of the benzyne intermediate:

The benzyne mechanism is operative under forcing conditions with strong nucleophiles/strong bases. The addition/elimination mechanism is operative when the aromatic ring is substituted with electron-withdrawing groups.

VI. Reduction of Aromatic Rings

A. Hydrogenation of aromatics occurs at high temperatures and pressures in the presence of metal catalysts:

B. A more practical approach to reduction of aromatic rings is the Birch reduction, in which sodium or lithium metal in liquid ammonia/alcohol is used to produce 1,4-cyclohexadienes. Sodium in ammonia produces "solvated" electrons that transfer sequentially to the aromatic ring, first generating a radical anion and then an anion, both of which are protonated by the solvent (ammonia). Note that the reduced carbons proceed through the anionic intermediate, and thus electron-withdrawing groups stabilize the anionic intermediate, while electron donating groups destabilize this intermediate. As a result, reduction will take place preferentially on carbons bearing electron-withdrawing groups. In contrast, rings substituted with electron-donating groups are deactivated for reduction, and the stronger reducing agent Lithium must be used. The carbon atom bearing the electron-donating group is not reduced.

B. Reaction of the side chains on aromatic rings. **Oxidation**
Benzylic positions (the carbon attached directly to the aromatic ring) are activated for oxidation with reagents like $KMnO_4$ and chromic acid. These strong oxidants will convert most carbon fuctional groups to carboxylic acids:

C. Halogenation
Radical halogenation takes place at benzylic positions in a manner similar to allylic radical halogenation. Delocalization of the benzylic radical through the aromatic ring is the source of stability for the benzylic radical

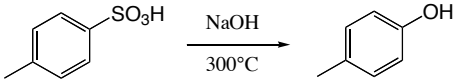
D. SN1 reactions
Solvolysis of benzylic halides occurs in a facile manner because of the intermediacy of bezylic cations, which are resonance stabilized:

E. SN2 reactions

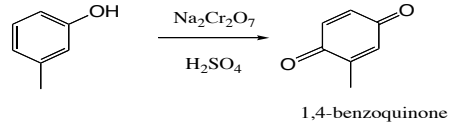
SN2 reactions at benzylic carbon atoms are accelerated in the same way as for allylic halides. Transition state stabilization results from charge delocalization due to overlap of the benzylic p-orbital with the pi system of the aromatic ring:

VII. Phenols

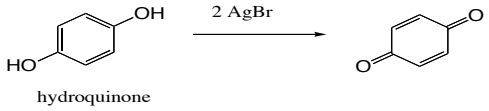
A. Preparation from sulfonic acids: alkali fusion



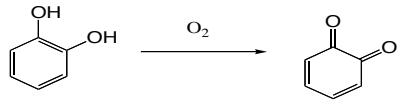
B. Oxidation to benzoquinones:can occur under mild conditions when hydroquinones are employed.



1,4-benzoquinone

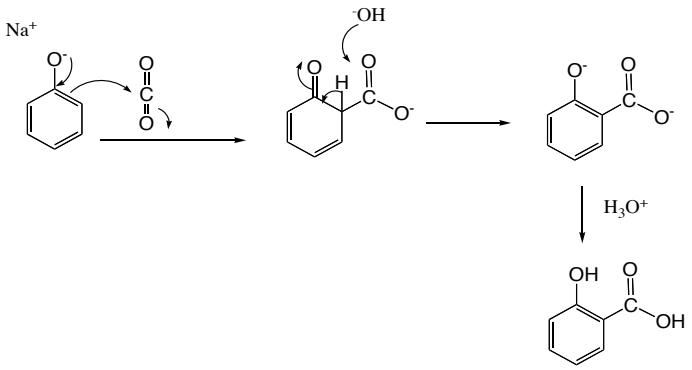


hydroquinone



1,2-benzoquinone

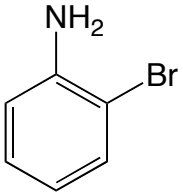
C. Phenoxides are good nucleophiles, and are so highly activated they undergo reaction with weak electrophiles like CO_2:



VIII. Putting it all together: Synthesis of substituted benzenes

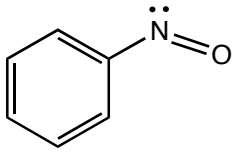
Example:

Prepare the following compound from benzene:



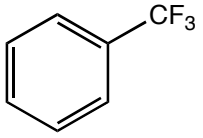
Additional Problems for practice:

1. The nitroso group is one of the very few non-halogens that is an ortho-para directing deactivating group. Draw resonance structures of intermediates in ortho and para electrophilic attack on nitrosobenzene, and explain why they are favored over the intermediate from meta attack:



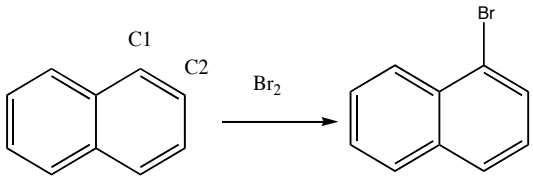
Nitrosobenzene

2. Which compound would you expect to be more reactive toward electrophilic aromatic substitution, toluene or trifluoromethyl benzene? To which position(s) of the aromatic ring does the trifluoromethyl group direct?

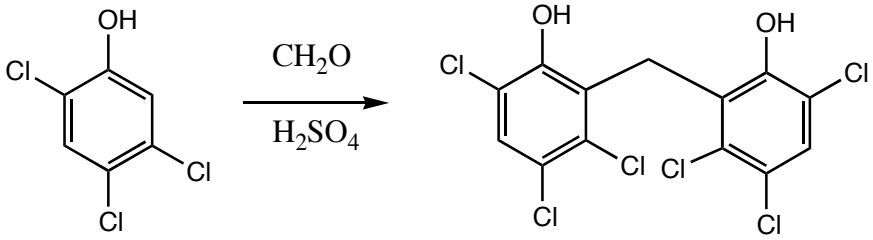


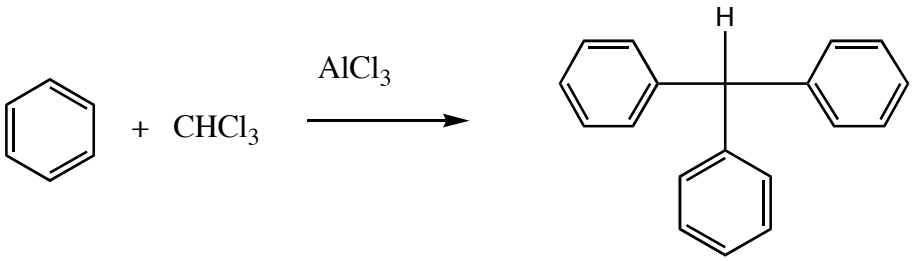
(trifluoromethyl)benzene

3.Draw resonance structures of the intermediate carbocations in the bromination of naphthalene, and account for the fact that naphthalene undergoes electrophilic attack at C1 rather than C2:

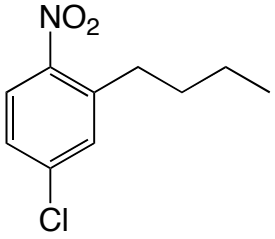


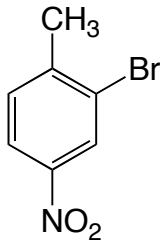
4. Propose mechanisms for the following transformations:

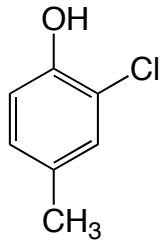
a. 

b. 

5. Propose syntheses of the following substances from benzene or toluene. More than one step is needed:

a. 

b. 

c. 

d.