Nuggets of Knowledge for Chapter 18 – Aromatic Compounds II Chem 2320

I. Electrophilic Aromatic Substitution

Introduction

- When an alkene reacts with bromine, an addition product is formed in which bromine atoms are added to the compound without any atoms being lost. However, a benzene ring does not react with bromine in this way because if an addition product were formed, it would lose its aromaticity.
- A benzene ring will react with bromine in the presence of FeBr3 as a catalyst, but a substituted product is formed, in which a hydrogen atom is lost and a bromine atom is gained. This product is still aromatic.
- These results imply that aromatic rings will undergo substitution rather than addition in order to preserve their special stability. They also require different reagents than addition reactions.

<u>Mechanism</u>

- In the addition reacts of alkenes, the C=C reacts as a weak nucleophile (or as a base), and a carbocation is formed. The electrophile that they attack has to fairly reactive in order for the reaction to go. The carbocation will then react as either a strong electrophile or a strong acid, forming either a substitution or an addition product.
- Benzene rings also act as weak nucleophiles, but they are even weaker than alkenes because their aromaticity makes them more stable. Therefore, the electrophile that they attack must be even more reactive than in the reaction with an alkene. The activation energy of this step will be much higher than in the addition reaction of alkenes.
 - The carbocation which is formed is no longer aromatic, since it has an sp3 hybridized carbon where the electrophile attached, but it is stabilized by resonance. Three carbon atoms in the ring share the positive charge. This is sometimes called the sigma complex.
 - The carbocation is a very strong acid, since when the hydrogen is removed, the electrons go back into the ring and restore aromaticity. Therefore the base in this step can be very weak.
- The two steps of the reaction can be summarized as follows:
 - 1) A pair of electrons in the ring attacks the electrophile, forming a nonaromatic but resonance-stabilized carbocation.

- 2) A weak base removes a hydrogen from the same carbon as the electrophile was added, restoring aromaticity.
- By looking at this mechanism, we can see why the reaction is called electrophilic aromatic substitution:
 - electrophilic: the reagent is an electrophile
 - the starting material must be aromatic, or a different mechanism would occur
 - the end result is a substitution, as the electrophile is added and a hydrogen removed
- This reaction differs from nucleophilic aromatic substitution is several ways:
 - 1) in nucleophilic aromatic substitution, the reagent is a nucleophile that attacks the benzene ring, while in electrophilic aromatic substitution, the reagent is an electrophile that is attacked by the benzene ring.
 - 2) Nucleophilic aromatic substitution only works on aryl halides, while electrophilic aromatic substitution works for benzene rings with no substituents.

Reagents and Products

- There are several common variations of electrophilic aromatic substitution. They differ in what the electrophile is that is attacked by the aromatic ring and what the product is. You must memorize these reagents and products and be able to reproduce them!
 - Chlorination uses Cl₂ and AlCl₃, and puts a chlorine on the ring.
 - \circ Bromination uses Br₂ and FeBr₃, and puts a bromine on the ring. Br₂ and Fe may also be used, since Fe reacts with Br₂ to form FeBr₃ in the reaction.
 - \circ Iodination uses I₂ and HNO₃, and puts an iodine on the ring.
 - Nitration uses H₂SO₄ and HNO₃, and puts a nitro group (NO₂) on the ring.
 - Sulfonation uses H₂SO₄ and SO₃, and puts a sulfonic acid group (SO₃H) on the ring.
 - Freidel-Crafts alkylation uses AlCl₃ and RCl (an alkyl chloride), and puts an alkyl group on the ring.
 - Freidel-Crafts acylation uses AlCl₃ and RCOCl (an acid chloride), and puts a ketone group on the ring.

Electrophiles

- Each set of reagents reacts to create an electrophile. The base that takes the H in the second step will depend on what is present in those reactions.
 - Chlorination: A chlorine atom in Cl₂ attacks the aluminum atom in AlCl₃ to form a complex. This electrophile is attacked by the benzene ring at the furthest chlorine atom, pushing the electrons back onto the other chlorine atom and giving an AlCl₄⁻ ion. AlCl₄⁻ is the base; it reacts with the carbocation to form HCl and AlCl₃.
 - Note that the Cl₂ is used up by the reaction, while the AlCl₃ is catalytic.
 - Bromination: A bromine atom in Br_2 attacks the iron atom in $FeBr_3$ to form a complex. This electrophile is attacked by the benzene ring at the furthest bromine atom, pushing the electrons back onto the other bromine atom and giving an $FeBr_4^-$ ion. $FeBr_4^-$ is the base; it reacts with the carbocation to form HBr and $FeBr_3$.
 - Note that the Br₂ is used up by the reaction, while the FeBr₃ is catalytic.
 - \circ Iodination: Iodine reacts with nitric acid and excess acid in a redox reaction to form an I⁺ ion, NO₂, and water. The I⁺ ion is attacked by the benzene ring. Water is the base, forming H₃O⁺.
 - Sulfonation: SO₃ serves as the electrophile; it is attacked by the benzene ring and attaches to it. Sulfuric acid (H₂SO₄) is the solvent; SO₃ is the anhydride of sulfuric acid, and together they form "fuming sulfuric acid" (so called because clouds of sulfuric acid form from water vapor in the air when the container is opened). The base is the SO₃⁻ ion itself it takes a H from the benzene ring and forms a sulfonic acid group (SO₃H).
 - $^{\circ}$ Nitration: Sulfuric acid (H₂SO₄) gives a hydrogen to nitric acid (HNO₃), which then loses a water molecule to form a nitronium ion. This electrophile is attacked by the benzene ring at the nitrogen. The water molecule that was created earlier is the base, and forms H₃O⁺.

Effects of Substituents

- If electrophilic aromatic substitution takes place on a benzene ring which has a substituent, this will affect both the rate of the reaction and the proportion of the three possible products (ortho, meta, and para).
- These effects depend on the substituent, not on the reaction since they all share the same mechanism, all electrophilic aromatic substitution reactions show the same effects for a give substituent.
- Substituents may be grouped into 3 categories:

- Alkyl substituents and substituents with an atom with a lone pair directly attached to the ring.
 - All of these are activating (make the reaction go faster). Alkyl substituents are mildly activating (a methyl group speeds up the reaction 25 times) while substituents with an atom with a lone pair directly attached to the ring are strongly activation (a methoxy group speeds up the reaction 10,000 times).
 - All of these are ortho/para directing (give mostly ortho and para products).
- Substituents with a positive or partially positive atom attached directly to the ring.
 - All of these are deactivating (make the reaction go slower). (Nitrobenzene reacts 100,000 times more slowly than benzene).
 - All of these are meta directing (give mostly meta products).
- Halogens.
 - Halogens are mildly deactivating (chlorobenzene reacts 10 times slower than benzene).
 - Halogens are ortho/para directing (give mostly ortho and para products).
- These observations can be explained by looking at the effects of the substituent on the resonance-stabilized carbocation, since its formation is the rate-limiting step of the reaction.
 - In the ortho and para products, the carbon with the substituent shares some of the positive charge. Therefore, substituents which stabilize a carbocation will make these products form faster, while substituents which destabilize a carbocation will make these products form slower.
 - In the meta products, the carbon with the substituent does not share any of the positive charge. Therefore, substituents will not have as much of an effect on the rate of formation of the meta product.
- In summary:
 - Alkyl substituents will cause ortho and para carbocation intermediates to be 3°, which will lower their activation energy and speed up the reaction, while meta products will be only slightly faster. Overall, the reaction will be faster, and give ortho and para products.

- Substituents with atoms having lone electron pairs on them greatly stabilize ortho and para intermediates by forming a 4th resonance structure with a double bond between the atom and the ring. This will greatly speed up the reaction of ortho and para products, but meta products will actually be slower because they will not have the extra resonance structure and the electronegativity of the atom will destabilize the carbocation. Overall, the reaction will be much faster, and give ortho and para products.
- Substituents with positive or partially positive atoms directly attached to the ring will destabilize ortho and para intermediates. This will slow down the formation of ortho and para products even more than meta products. Overall, the reaction will be slower, and give meta products.
- Halogen substituents will stabilize ortho and para intermediates by forming an additional resonance structure. However, the electronegativity of these atoms will also reduce the stabilization of all intermediates. Overall, the reaction will be slower, but give ortho and para products.
- When more than one substituent is already present on a ring, their directing effects may be either reinforcing or conflicting.
 - If both substituents stabilize the carbocation intermediate in the same positions on the ring, this is said to be reinforcing.
 - If the substituents stabilize the carbocation intermediate in different positions on the ring, this is said to be conflicting.
 - When a conflict occurs, certain types of substituents take priority: 1) strong ortho/para directing groups; 2) mild ortho/para directing groups; 3) all meta direction groups.
 - Whichever group has highest priority will dictate where the new substituent is added. If both groups have the same priority, a mixture will result.

Freidel-Crafts Alkylation and Acylation

- Freidel-Crafts alkylation requires AlCl3 and an alkyl chloride, and results in an alkyl group being added to the ring.
- Freidel-Crafts acylation requires AlCl3 and an acid chloride, and results in a ketone group being added to the ring.
 - However, because of steric hindrance, ortho/para directing groups give only para products.
- AlCl3 reacts with the alkyl chloride to form a complex similar to the one formed in chlorination; the complex is attacked at the carbon next to the chlorine atom.

- AlCl3 reaction with the acid chloride to form a similar complex, but this complex them dissociates to form an acylium ion, which has two resonance structures. The acylium ion is attacked at the carbon atom.
- AlCl4- is the base in both reactions.
- Freidel-Crafts alkylation has 3 major limitations:
 - Primary alkyl halides always give rearranged products.
 - The product of the reaction has an alkyl group, which is an activating group. Therefore, the product is more reactive than the starting material, and products with multiple alkyl substitutions will form.
 - If the ring contains a strong deactivating group, the reaction will not proceed.
- Freidel-Crafts acylation overcomes two of these limitations:
 - Acylium ions are stabilized by resonance, so no rearrangements occur.
 - A ketone group is a deactivating group, so no multiple substitutions occur.
 - However, the reaction still fails if there is a strong deactivating group on the ring.
- An alkyl substituent may be added to a benzene ring using Freidel-Crafts acylation followed by a Clemmensen reduction.
 - Clemmensen reduction uses a Zn/Hg amalgam and HCl to remove the =O entirely and replace it with two H's, making the ketone into an alkyl group.

Synthesis using Electrophilic Aromatic Substitution

- The directing effect of substituents must be taken into account when planning multi-step syntheses using electrophilic aromatic substitution.
 - If two substituents are ortho or para to each other, then an ortho/para directing substituent must be attached first.
 - If two substituents are meta to each other, then a meta directing substituent must be attached first.
 - If this is not possible, then the compound cannot be synthesized using this reaction.

- Multiple products from ortho/para directing substituents usually cannot be avoided, but are not as detrimental as in most syntheses, because these isomers can often be separated.
- When using Freidel-Crafts acylation, strong deactivating groups must be avoided.
- When using Freidel-Crafts alkylation together with a Clemmensen reduction to attach an alkyl group to a ring, the substituent will be meta directing if the reduction has not yet been accomplished and it is still a ketone, or ortho/para directing if it has been reduced to an alkyl group.
- Nucleophilic aromatic substitution may be used in conjunction with electrophilic aromatic substitution to form phenols, aryl ethers, or anilines from aryl halides; strong electron-withdrawing groups are needed if the nucleophile is hydroxide or an alkoxide.