

I. ELECTROPHILIC AROMATIC SUBSTITUTION (EAS)

- A. There are five general types of electrophilic aromatic substitution reactions.
1. Halogenation of benzene with Br_2 , Cl_2 or I_2 occurs through the same mechanism.
 - a. Bromination of benzene occurs upon treatment with Br_2 and FeBr_3 .
 - b. Chlorination of benzene occurs upon treatment with Cl_2 and FeCl_3 .
 - c. Iodination of benzene occurs upon treatment with I_2 and CuCl_2 .
 2. Nitration of benzene occurs through treatment with a nitronium ion, $^+\text{NO}_2$.
 - a. The nitronium ion can be generated from nitric acid and sulfuric acid.
 - b. The nitronium ion can be generated from nitronium tetrafluoroborate.
 - c. Nitration of benzene occurs through the same mechanism as halogenation.
 3. Sulfonation of benzene occurs through treatment with fuming sulfuric acid. The reaction is reversible and products depend on the reaction conditions.
 - a. In strong acid, sulfonation is favored.
 - b. In hot, dilute acid, desulfonation is favored.
 - c. Sulfonation of benzene occurs through the same mechanism as halogenation & nitration.
 4. Alkylation (Friedel-Crafts Alkylation) of benzene involves substituting a hydrogen atom on a benzene ring with an alkyl group. This reaction occurs by treatment of benzene with a stable carbocation and aluminum trichloride. There are a number of problems with alkylation of an aromatic ring using the Friedel-Crafts reaction.
 - a. Only alkyl halides can be used to generate the carbocation.
 - b. Benzene rings substituted with electron-withdrawing groups are not reactive.
 - c. The monosubstituted product initially formed is more reactive than the starting material
 - d. Rearrangements can occur with unstable carbocations.
 - e. Amino substituted benzenes do not undergo Friedel-Crafts reactions.
 5. Acylation (Friedel-Crafts Acylation) of benzene involves substitution of a hydrogen atom on the benzene ring with an acyl group. This reaction occurs by treatment of benzene with an acid chloride and aluminum trichloride.
 - a. Acylation of aromatic rings occurs through the same mechanism as alkylation, sulfonation, nitration and halogenation.
 - b. Amino substituted benzenes do not undergo Friedel-Crafts reactions.

B. REACTIVITY OF SUBSTITUTED AROMATIC RINGS IN ELECTROPHILIC AROMATIC SUBSTITUTIONS

1. There are two types of substituents that affect the reactivity of aromatic rings in electrophilic aromatic substitutions.
 - a. Activating groups make the ring more electron rich and thus more reactive. (Electron-donating groups)
 - b. Deactivating groups make the ring electron poor and thus less reactive. (Electron-withdrawing groups)
2. The activating or deactivating ability of a substituent can be described in two ways.
 - a. The inductive effect of a substituent depends on the polarity of the substituent relative to the benzene ring.
 - b. The resonance effect of a substituent depends on the group's ability to delocalize electrons.
3. Reaction on a monosubstituted aromatic ring can occur in three possible positions on the ring relative the initial substituent, i.e., ortho-, meta- and/or para-. Different substituents can direct the reaction to specific positions on the ring and can be classified according to their directing ability.
 - a. Ortho-/para-directing activators direct reaction to ortho- and para positions.
 - b. Ortho-/para-directing deactivators direct reaction to ortho- and para positions.
 - c. Meta-directing deactivators direct reaction to the meta position.
4. To predict the reactivity of a di- or trisubstituted benzene refer to the following rules.
 - a. If substituents direct the reaction to the same position then reaction will occur at that position.
 - b. If substituents direct reactivity to different positions then the more powerful director will dominate.
 - c. In a meta-disubstituted benzene, reaction at the site ortho to both substituents does not occur due to steric hindrance.

C. SUBSTITUENT EFFECTS ON pKa of IONIZABLE FUNCTIONAL GROUPS OF AROMATIC RINGS

1. The Hammett Equation

- The Hammett equation is a mathematical formula which relates substituent effects (electron donating/electron-withdrawing ability), ionization of carboxylic acids and rates of related reactions. Hammett noted there was a linear relationship between the equilibrium constant associated with the ionization of acids (acid strengths) and the rate of related reactions (directly proportional; faster rate, lower pKa)
- The equation involves two values, σ and ρ . The ρ value is dependent on the parent structure of the acid and is equal to 1 for benzoic acid and its derivatives. The σ value is dependent on the electron donating/electron withdrawing ability of para- and meta- substituents, *not ortho*-.

2. Substituent Effects on pKa of Substituted Benzoic Acids

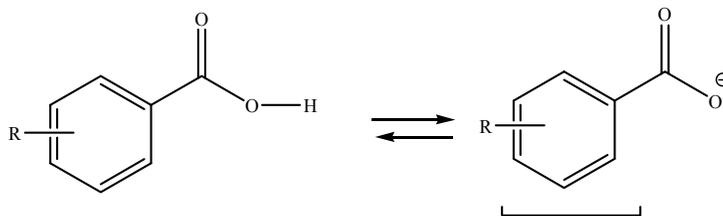
- There is a logarithmic relationship between the σ value and the ionization constants of benzoic acid and substituted benzoic acids (Ka).
- Substituents which have a positive σ value, increase Ka and favor ionization (i.e., have a low pKa). Substituents with a negative σ value have a smaller Ka and higher pKa.
- Substituents with positive σ values stabilize the conjugate base of the benzoic acid while substituents with negative σ values destabilize the conjugate base. EWG stabilize the conjugate base because they pull electron density away from the developing negative charge of the conjugate base. EDG groups destabilize the conjugate base by increasing electron density around the developing negative charge.

Substituent	Abbreviation	σ meta	σ para
acetamido-	AcNH-	0.21	-0.01
acetoxy-	AcO-	0.39	0.31
acetyl-	Ac-	0.38	0.50
amino-	NH ₂ -	-0.16	-0.66
bromo-	Br-	0.39	0.23
tert-butyl-	(CH ₃) ₃ C-	-0.10	-0.20
chloro-	Cl-	0.37	0.23
cyano-	NC-	0.56	0.66
ethoxy-	EtO-	0.10	-0.24
ethyl-	Et-	-0.07	-0.15
fluoro-	F-	0.34	0.06
hydrogen	H-	0.00	0.00
hydroxy-	HO-	0.12	-0.37
methoxy-	MeO-	0.12	-0.27
methyl-	Me-	-0.07	-0.17
nitro-	NO ₂ -	0.71	0.78
phenyl-	Ph-	0.06	-0.01
trifluoromethyl	F ₃ C-	0.43	0.54
trimethylamino-	(CH ₃) ₃ N ⁺ -	0.88	0.82

Table 1: σ values for Various Substituents

$$\frac{\log K_a (\text{substituted benzoic acid})}{\log K_a (\text{benzoic acid})} = \sigma \rho$$

$$\rho = 1$$



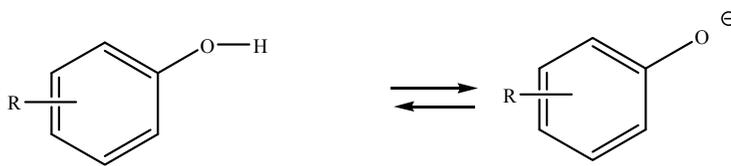
R = meta -NO₂

R σ is +: a ring with "positive character" will stabilize the conjugate base ↑K_a, ↓pK_a STRONGER ACID

R = para -OCH₃

R σ is -: a ring with "negative character" will destabilize the conjugate base ↓K_a, ↑pK_a WEAKER ACID

3. Substituent Effects on pK_a of Substituted Phenols
 Phenols are acidic functional groups and substituents of phenols can also influence the pK_a of phenolic compounds



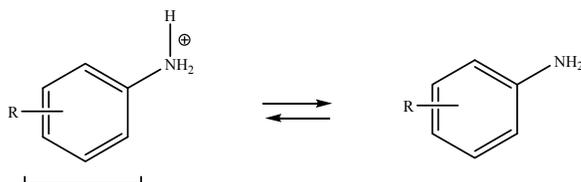
R = meta -NO₂

R σ is +: a ring with "positive character" will stabilize the conjugate base ↑K_a, ↓pK_a STRONGER ACID

R = para -OCH₃

R σ is -: a ring with "negative character" will destabilize the conjugate base ↓K_a, ↑pK_a WEAKER ACID

4. Substituent Effects on pK_a of Substituted Anilines
 This concept can be applied to substituted anilines as well. The substituent can either stabilize or destabilize the conjugate acid of aniline (as opposed to the conjugate base of phenols and benzoic acids) via the electron-donating or electron-withdrawing ability of substituents.



R = meta -NO₂

R σ is +: a ring with "positive character" will destabilize the conjugate acid ↑K_a, ↓pK_a STRONGER CONJUGATE ACID, WEAKER BASE

Base strength is expressed as the pK_a of the base's conjugate acid. pK_a is a measure of acid strength. pK_b is a measure of base strength.

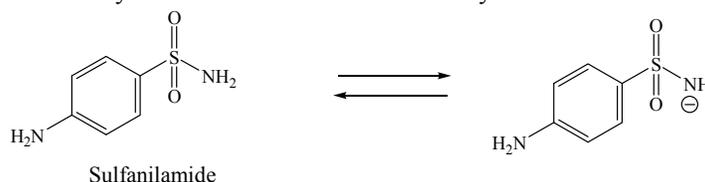
$$pK_a + pK_b = 14.$$

R = para -OCH₃

R σ is -: a ring with "negative character" will stabilize the conjugate acid ↓K_a, ↑pK_a WEAKER CONJUGATE ACID, STRONGER BASE

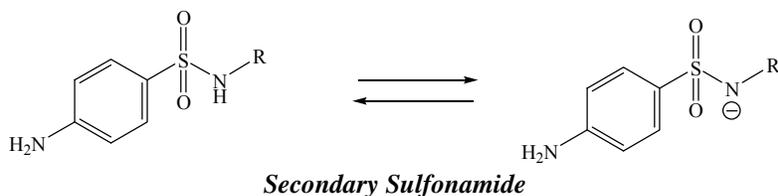
If pK_a is small, the conjugate acid is a strong acid and the pK_b is large and a weak base. Conversely, if the pK_a is large the pK_b is small and is a strong base.

5. Substituent Effects on pK_a of Substituted Sulfonamides
 a. Primary and secondary sulfonamides are acidic. Tertiary sulfonamides are NOT ACIDIC.



Sulfanilamide

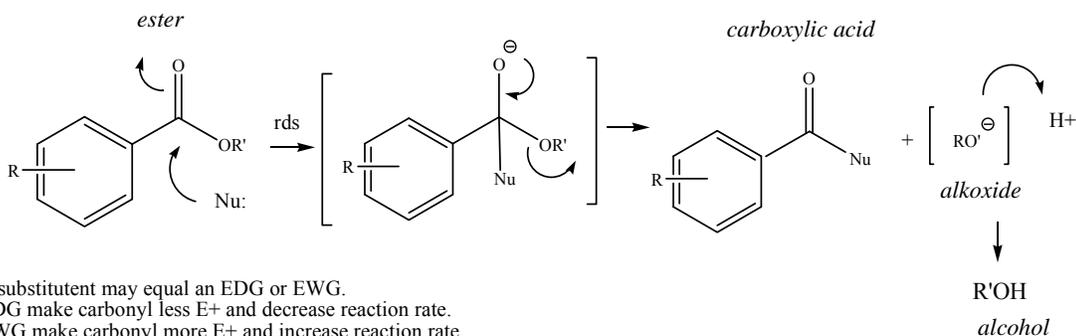
Primary Sulfonamide



- b. Substituents on the sulfonamide benzene ring or on the N atom of the sulfonamide can influence the pKa of sulfonamides.

D. SUBSTITUENT EFFECTS ON RATES OF HYDROLYSIS OF BENZOATE ESTERS

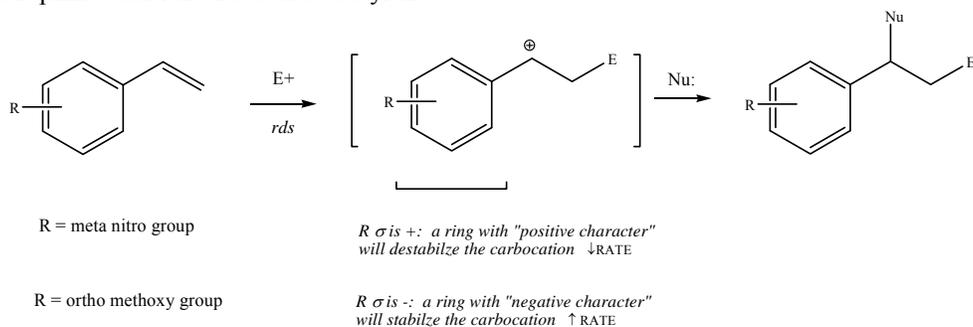
The σ values for substituents which affect ionization constants can be used to predict relative rates of hydrolysis of substituted benzoate esters.



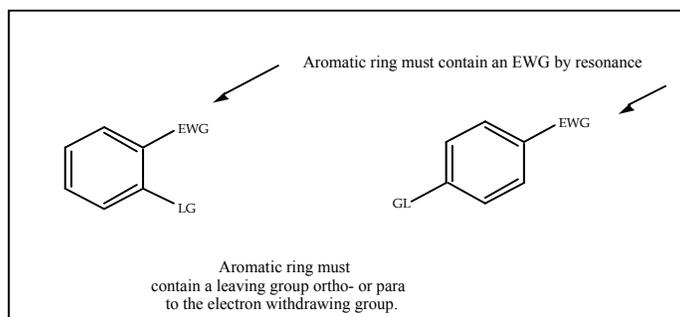
R substituent may equal an EDG or EWG.
 EDG make carbonyl less E⁺ and decrease reaction rate.
 EWG make carbonyl more E⁺ and increase reaction rate

E. SUBSTITUENT EFFECTS ON RATES OF ELECTROPHILIC ADDITION OF SUBSTITUTED STYRENES

The σ values for substituents which affect ionization constants can be used to predict relative rates of electrophilic addition of substituted styrenes.

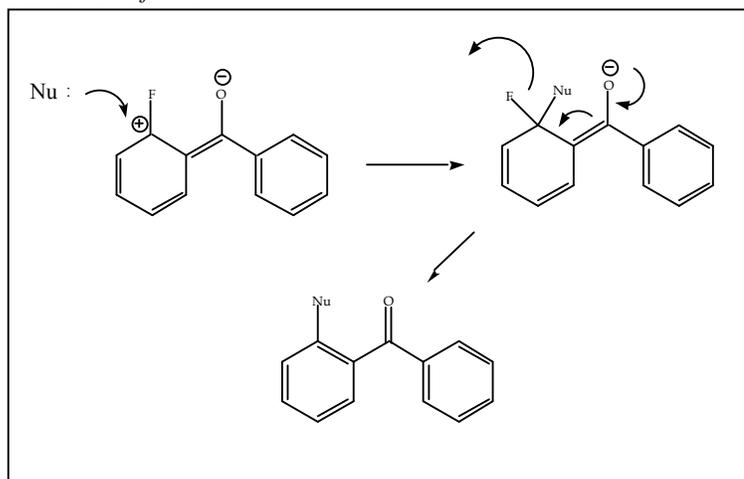


II. NUCLEOPHILIC AROMATIC SUBSTITUTION (NAS)

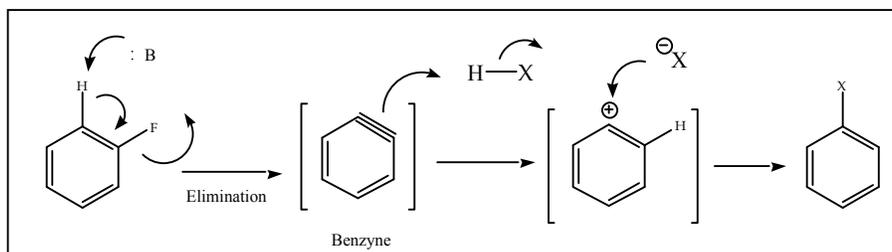


- A. Nucleophilic aromatic substitution involves attack of a nucleophilic reagent on an aromatic ring that contains an EWG group.
- B. Nucleophilic aromatic substitution occurs only if the EWG is ortho or para to the leaving group.
- C. There are three basic differences between EAS and NAS.
 - a. EAS displaces a hydrogen atom; NAS displaces a leaving group.
 - b. EWG's deactivate aromatic rings for EAS and activate aromatic rings for NAS.

Mechanism of NAS



III. BENZYNE



- A. Benzyne is a very reactive intermediate formed upon treatment of a substituted aryl group with base.
- B. Benzyne is formed through an elimination. The leaving group is usually a fluorine atom.
- C. Benzyne reacts like any other alkyne.
- D. The overall sequence of the benzyne reaction is called an elimination-addition reaction.

IV. OXIDATION

- A. Oxidation of benzene rings occurs on substituents of the ring not on the ring itself. KMnO_4 is generally used for this oxidation.
- B. Oxidation occurs only on the benzylic position of the substituent.
- C. The benzylic carbon atom must bear a hydrogen in order for this reaction to proceed.

- D. Bromination (which is a type of oxidation) also can occur on the benzylic position of a substituted benzene ring using NBS.

V. REDUCTION

- A. Catalytic hydrogenation (H_2 , catalyst) can be used to reduce substituents of benzene rings without reducing the aromatic ring itself.
- B. Under extremely vigorous conditions benzene can be reduced to cyclohexane using catalytic hydrogenation.
- C. Clemmensen Reduction uses Zn and HCl to reduce ketones to alkyl substituents.
- D. The Wolff-Kishner reduction uses hydrazine and KOH to reduce ketones to alkyl substituents.