Electrophilic Aromatic Substitution

Electrophilic substitution is the typical reaction type for aromatic rings.

Generalized electrophilic aromatic substitution:

$$E^{+} + H^{+}$$

$$Electrophile- Nucleophile- Lewis acid: Lewis base. may be \oplus Shorthand: or neutral. Ar-H
$$Electrophile- Nucleophile- Product: neutral if electrophile i \oplus ; \\ \ominus if electrophile is neutral. Shorthand: Ar-E$$$$

Nitration —

$$Ar-H + HNO_3 \xrightarrow{H_2SO_4} Ar-NO_2 + H_2O$$

(1)
$$HONO_2 + 2 H_2SO_4$$
 \longrightarrow $H_3O + 2 HSO_4 + NO_2$

a nitronium ion, $cf. NO_2^+ BF_4^-$

(2) $O=N=O+$
 $Slow$
 $Slow$
 $O=N=O+$
 $O=$

Addition of a basic group, eg HSO₄, to the σ complex would result in formation of a non-aromatic compound, whereas expulsion of H⁺ results in an aromatic product.

(3)
$$HSO_3$$
 $+$ HO_2 $+$ H_2SO_4

Since the nitro group can often be reduced to the amine group (tin or iron and HCl are frequently used to effect this reduction), ArNO₂ —> Ar-NH₂, nitration is often used to ultimately make an aryl amine.

Sulfonation —

$$Ar-H + H_2SO_4 \xrightarrow{SO_3} ArSO_3H + H_2O$$

Mechanism

(1)
$$2 \text{ H}_2\text{SO}_4 \longrightarrow \text{H}_3\text{O}^+ + \text{HSO}_4^- + \text{SO}_3$$

(2) $O_3\text{S} \longrightarrow \text{H}$
(3) $O_3\text{S} \longrightarrow \text{H}$
(4) $O_3\text{S} \longrightarrow \text{H}$
(5) $O_3\text{S} \longrightarrow \text{H}$
(6) $O_3\text{S} \longrightarrow \text{H}$
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(12) $O_3\text{S} \longrightarrow \text{H}$
(23) $O_3\text{S} \longrightarrow \text{H}$
(34) $O_3\text{S} \longrightarrow \text{H}$
(45) $O_3\text{S} \longrightarrow \text{H}$
(46) $O_3\text{S} \longrightarrow \text{H}$
(50) $O_3\text{S} \longrightarrow \text{H}$
(67) $O_3\text{S} \longrightarrow \text{H}$
(7) $O_3\text{S} \longrightarrow \text{H}$
(88) $O_3\text{S} \longrightarrow \text{H}$
(99) $O_3\text{S} \longrightarrow \text{H}$
(90) $O_3\text{S} \longrightarrow \text{H}$
(11) $O_3\text{S} \longrightarrow \text{H}$
(12) $O_3\text{S} \longrightarrow \text{H}$
(13) $O_3\text{S} \longrightarrow \text{H}$
(14) $O_3\text{S} \longrightarrow \text{H}$
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(15) $O_3\text{S} \longrightarrow \text{H}$
(16) $O_3\text{S} \longrightarrow \text{H}$
(17) $O_3\text{S} \longrightarrow \text{H}$
(18) $O_3\text{S} \longrightarrow \text{H}$
(19) $O_3\text{S} \longrightarrow \text{H}$

Note the following —

- Sulfonic acids (eg, ArSO₃H), derivatives of sulfuric acid, are strong acids and are highly ionized in water.
- Each step in the sulfonation mechanism is an equilibrium; therefore, the entire reaction is an equilibrium. Thus, Ar-H can be sulfonated using fuming sulfuric acid, H₂SO₄CSO₃, and Ar-SO₃H can be desulfonated (to Ar-H) by boiling it in a dilute solution of sulfuric acid.
- Sulfonation of an aromatic ring can provide a route to a *phenol*, Ar-OH. If a sulfonic acid is *fused* with solid KOH, the -SO₃H group is replaced by -OH. [Owing to the vigorous reaction conditions, there are limitations with regard to which substituents may be present on the ring.]
- Sulfonation of an aromatic ring provides a highly polar site capable of hydrogen bonding; this gives rise to water solubility. Dyes are sometimes made water soluble in this way.
- Some synthetic detergents have the structure

R—SO₃ Na⁺, where R is a long-chain alkyl group. The ionic "head" is *hydrophilic* and the long "tail" is *hydrophobic*. This combination enables this material to disperse oily material in water.

3. Halogenation —

$$Ar-H + X_2 \longrightarrow Ar-X + HX$$

Mechanism

$$2 \text{ Fe } + 3 \text{ Cl}_2 \longrightarrow 2 \text{ FeCl}_3$$

$$(1) \text{ Cl}_2 + \text{ FeCl}_3 \longrightarrow \begin{bmatrix} \text{FeCl}_4 & \text{Cl}^+ \end{bmatrix} \text{ complex}$$

$$(2) \text{ FeCl}_4 & \text{Cl}^+ + \\ \text{electrophile} & \text{electrophile} & \text{FeCl}_4 & \text{Cl}^+ \end{bmatrix}$$

$$(3) \text{ } \oplus \text{ } + \text{ FeCl}_4 & \text{ } + \text{ }$$

Friedel-Crafts Alkylation —

Ar-H + R-X
$$\frac{\text{anhydrous AlCl}_3}{\text{or HF}}$$
 Ar-R + HX

 $X = \text{halogen}, R = \text{alkyl}, \text{NOT vinyl}, \text{NOT aryl}$

Ar-H + R-OH $\frac{\text{Bronsted-Lowry}}{\text{acid}, eg \text{ HF}}$ Ar-R + H₂O

 $Ar\text{-H} + C = C$
 $\frac{\text{Bronsted-Lowry}}{\text{acid}, eg \text{ HF}}$ Ar-C-CH

 eg
 $Ar\text{-H} + C = C$
 Cl
 eg
 $Ar\text{-C-CH}$
 Cl

NOT

 Cl

Mechanism

Since a carbocation can be the electrophile in this mechanism, a variety of carbocation *precursors* could be used: alkenes, for example. Since aryl and vinyl carbocations are unstable, Ar-X and vinyl-X cannot be used as precursors for these species.

Friedel-Crafts Acylation —

Mechanism

Limitations —

Any group which deactivates an aromatic ring more than the halogens (vide infra) cannot be present on the ring prior to F-C acylation, nor can -NH₂, -NHR, or -NR₂.

However, the acylium ion does *not* rearrange and polyacylation is not a problem because the acyl group *deactivates* the ring toward further electrophilic substitution.

Effect of Substituents Already on the Ring

Reactivity: Activating or Deactivating —

If we allow toluene and benzene to react with mixtures of nitric and sulfuric acids under the same conditions and the toluene reacts 25 times faster than the benzene, we say it is 25 times more reactive. We would also say that the methyl group activates the aromatic ring toward nitration. Since the other electrophilic aromatic substitutions have mechanisms similar to nitration, we might expect the methyl group to activate the aromatic ring toward these reactions; usually, it does.

If we nitrate toluene, we find that the major products are *p*-nitrotoluene and *o*-nitrotoluene; only a small amount of *m*-nitrotoluene is formed.

We say the methyl group is an *ortho*, *para* director for electrophilic substitutions.

The table below shows the effect of some common aromatic ring substituents on electrophilic substitution —

Activating; Ortho, Para Directing

Strongly activating: -NH2, -NHR, -NR2, -OH.

Moderately activating: -OR, -NH-CO-R.

Weakly activating: -C₆H₅, -R.

Deactivating; Meta Directing

-NO₂, -N⁺R₃, -C/N, -COOH, -SO₃H, -CHO, -CRO.

Deactivating; Ortho, Para Directing Weakly deactivating: -F, -Cl, -Br, -l.

Except for the halogens, activating groups activate all positions of the ring, but have greater effect on o & p; deactivating groups deactivate all positions of the ring, but have greater effect on o & p.

The rate of formation of o, m or p isomers depends on the rate of formation of the precursor carbocations (σ complexes).

Boxed resonance structures make an especially large contribution if X is electron *releasing*; they make an especially small contribution if X is electron *withdrawing*.

Note: ortho and para attack form carbocations with one boxed structure; the carbocation resulting from meta attack has no boxed structures.

OK. Electron withdrawing groups on the ring destabilize the transition state leading to the s-complex, and electron donating ones stabilize the transition state, so reaction occurs faster with electron donating groups. And the effect is greatest at the ortho and para positions so an electron withdrawing group is meta directing because it deactivates the o and p positions.

BUT, two questions.

- Why are some groups which appear to be electron withdrawing, -NO₂ for example, deactivating and meta directing as expected, while others, -NH₂ for example, are activating and o, p directing?
- Why are the halogens deactivating and o, p directing?
 OK.
- Note that all the groups which would seem to be deactivating meta directors and turn out to be activating o, p directors, -OH and -NH₂, for example, carry at least one pair of unshared electrons. These unshared electrons are delocalized into the ring as the σ-complex intermediate forms if attack is at the ortho or para position.

The red resonance structure makes a minor contribution: there is an electronegative element attached to the positively charged carbon; the positive charge is intensified by inductive electron withdrawal.

The boxed resonance structure makes a major contribution. Although positive charge resides on an electronegative element, every atom (except hydrogens) has an octet of electrons.

 When halogen is the ring substituent it seems that its ability to donate electrons via resonance determines

the preferred orientation of attack by the electrophile, while reactivity is controlled by its inductive electron withdrawing effect.

Position of Electrophilic Attack for Disubstituted Benzenes

 Where two groups reinforce each other, the outcome is obvious.

In cases of opposing effects prediction is more difficult and mixtures may result.

 Strongly activating groups usually win out over deactivating or weakly activating groups.

The is usually little substitution between two groups which are meta to each other.