12.9
Rate and Regioselectivity in Electrophilic Aromatic Substitution

A substituent already present on the ring can affect both the rate and regioselectivity of electrophilic aromatic substitution.
Effect on Rate

Activating substituents increase the rate of EAS compared to that of benzene.

Deactivating substituents decrease the rate of EAS compared to benzene.
Toluene undergoes nitration 20-25 times faster than benzene.

A methyl group is an activating substituent.
(Trifluoromethyl)benzene undergoes nitration 40,000 times more slowly than benzene. A trifluoromethyl group is a deactivating substituent.
Ortho-para directors direct an incoming electrophile to positions ortho and/or para to themselves.

Meta directors direct an incoming electrophile to positions meta to themselves.
Nitration of Toluene

\[
\text{CH}_3\text{C}_6\text{H}_4\text{CH}_3 + \text{HNO}_3 + \text{acetic anhydride} \rightarrow \text{CH}_3\text{C}_6\text{H}_4\text{NO}_2\text{CH}_3 + \text{CH}_3\text{C}_6\text{H}_4\text{NO}_2\text{CH}_3 + \text{C}_6\text{H}_4\text{NO}_2\text{CH}_3
\]

63%  3%  34%

\(\sigma\)- and \(\rho\)-nitrotoluene together comprise 97% of the product

A methyl group is an ortho-para director
Nitration of (Trifluoromethyl)benzene

\[
\begin{align*}
\text{CF}_3 & \quad \stackrel{HNO_3}{\longrightarrow} \quad \text{CF}_3 \quad \text{NO}_2 + \quad \text{CF}_3 \quad \text{NO}_2 \\
\text{H}_2\text{SO}_4 & \quad \text{H}_2\text{SO}_4 \\
6\% & \quad 91\% \quad 3\%
\end{align*}
\]

\textit{m-nitro(trifluoromethyl)benzene comprises 91\% of the product}

\textit{a trifluoromethyl group is a meta director}
12.10 Rate and Regioselectivity in the Nitration of Toluene
Carbocation Stability Controls Regioselectivity

- The left structure gives ortho.
- The middle structure gives para.
- The right structure gives meta.
Carbocation Stability Controls Regioselectivity

- More stable
- Less stable

- Gives ortho
- Gives para
- Gives meta
ortho Nitration of Toluene
ortho Nitration of Toluene
ortho Nitration of Toluene

This resonance form is a tertiary carbocation.
ortho Nitration of Toluene

The rate-determining intermediate in the ortho nitration of toluene has tertiary carbocation character.
para Nitration of Toluene
para Nitration of Toluene

This resonance form is a tertiary carbocation.
para Nitration of Toluene

This resonance form is a tertiary carbocation.
The rate-determining intermediate in the para nitration of toluene has tertiary carbocation character.
meta Nitration of Toluene

\[
\begin{align*}
&\text{CH}_3 \\
&\text{H} \\
&\text{H} \\
&\text{H} \\
&\text{H} \\
&\text{NO}_2
\end{align*}
\]
meta Nitration of Toluene

\[
\begin{align*}
\text{CH}_3 & \quad \text{H} & \quad \text{H} & \quad \text{NO}_2 \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} & \quad \text{H} & \quad \text{H}
\end{align*}
\]
all the resonance forms of the rate-determining intermediate in the meta nitration of toluene have their positive charge on a secondary carbon
Nitration of Toluene: Interpretation

- The rate-determining intermediates for ortho and para nitration each have a resonance form that is a tertiary carbocation. All of the resonance forms for the rate-determining intermediate in meta nitration are secondary carbocations.
- Tertiary carbocations, being more stable, are formed faster than secondary ones. Therefore, the intermediates for attack at the ortho and para positions are formed faster than the intermediate for attack at the meta position. This explains why the major products are o- and p-nitrotoluene.
Nitration of Toluene: Partial Rate Factors

- The experimentally determined reaction rate can be combined with the ortho/meta/para distribution to give partial rate factors for substitution at the various ring positions.
- Expressed as a numerical value, a partial rate factor tells you by how much the rate of substitution at a particular position is faster (or slower) than at a single position of benzene.
Nitration of Toluene: Partial Rate Factors

All of the available ring positions in toluene are more reactive than a single position of benzene.

A methyl group activates all of the ring positions but the effect is greatest at the ortho and para positions.

Steric hindrance by the methyl group makes each ortho position slightly less reactive than para.
Nitration of Toluene vs. tert-Butylbenzene

$t$-Butyl is activating and ortho-para directing.
$t$-Butyl crowds the ortho positions and decreases the rate of attack at those positions.
all alkyl groups are activating and ortho-para directing
12.11 Rate and Regioselectivity in the Nitration of (Trifluoromethyl)benzene
A methyl group is electron-donating and stabilizes a carbocation.

Because F is so electronegative, a CF$_3$ group destabilizes a carbocation.
Carbocation Stability Controls Regioselectivity

gives ortho

gives para

gives meta
Carbocation Stability Controls Regioselectivity

- CF$_3$NO$_2$ gives ortho and is less stable.
- CF$_3$ gives para and is more stable.
- CF$_3$NO$_2$ gives meta and is more stable.
ortho Nitration of (Trifluoromethyl)benzene
ortho Nitration of (Trifluoromethyl)benzene
ortho Nitration of (Trifluoromethyl)benzene

this resonance form is destabilized
one of the resonance forms of the rate-determining intermediate in the ortho nitration of (trifluoromethyl)benzene is strongly destabilized
para Nitration of (Trifluoromethyl)benzene
para Nitration of (Trifluoromethyl)benzene

This resonance form is destabilized.
para Nitration of (Trifluoromethyl)benzene

this resonance form is destabilized
one of the resonance forms of the rate-determining intermediate in the para nitration of (trifluoromethyl)benzene is strongly destabilized
meta Nitration of (Trifluoromethyl)benzene
meta Nitration of (Trifluoromethyl)benzene
none of the resonance forms of the rate-determining intermediate in the meta nitration of (trifluoromethyl)benzene have their positive charge on the carbon that bears the CF$_3$ group.
Nitration of (Trifluoromethyl)benzene: Interpretation

The rate-determining intermediates for ortho and para nitration each have a resonance form in which the positive charge is on a carbon that bears a CF$_3$ group. Such a resonance structure is strongly destabilized. The intermediate in meta nitration avoids such a structure. It is the least unstable of three unstable intermediates and is the one from which most of the product is formed.
Nitration of (Trifluoromethyl)benzene: Partial Rate Factors

All of the available ring positions in (trifluoromethyl)benzene are much less reactive than a single position of benzene.

A CF$_3$ group deactivates all of the ring positions but the degree of deactivation is greatest at the ortho and para positions.