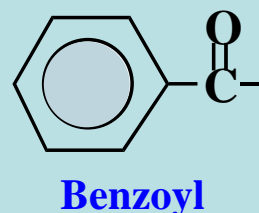
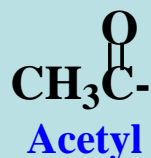
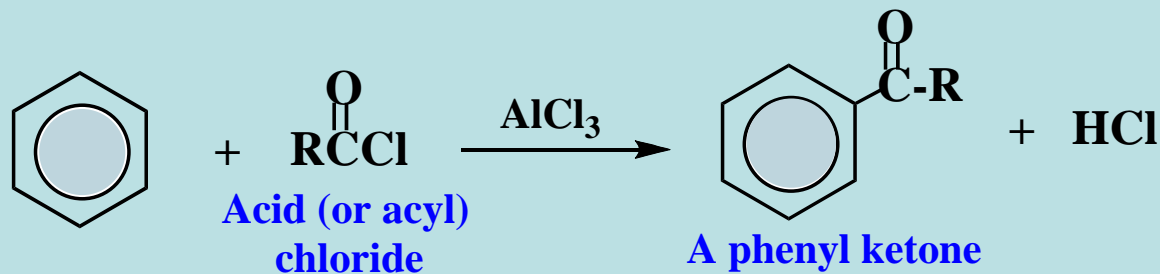


Friedel-Crafts Acylation

Acylation is the introduction of an acyl group, $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-$, into a structure. Two important acyl groups are:

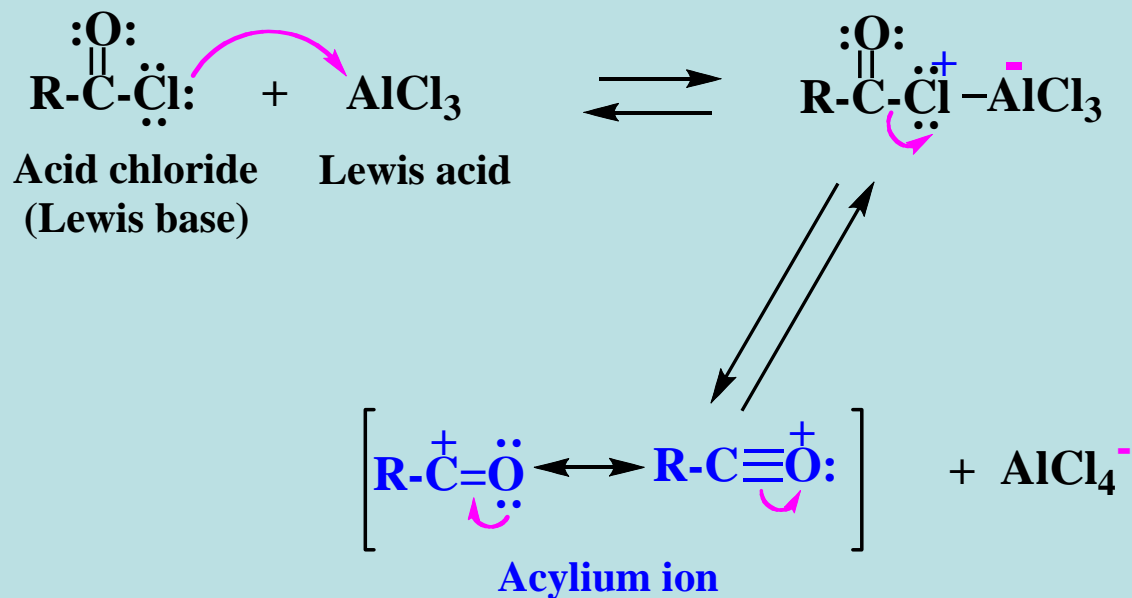


The Friedel-Crafts acylation reaction attaches an acyl group to an arene. A **Lewis acid catalyst** is required to generate the electrophile from an **acyl halide** reactant.



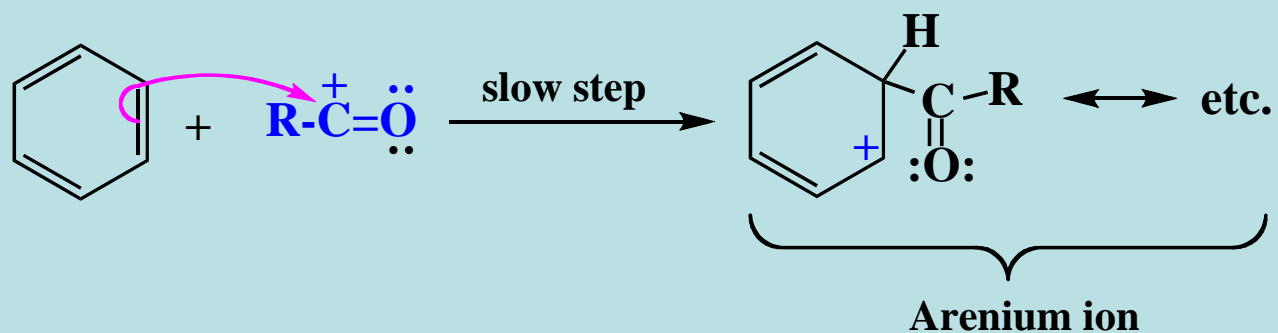
A Mechanism for Friedel-Crafts Acylation

(1) Generation of the Electrophile

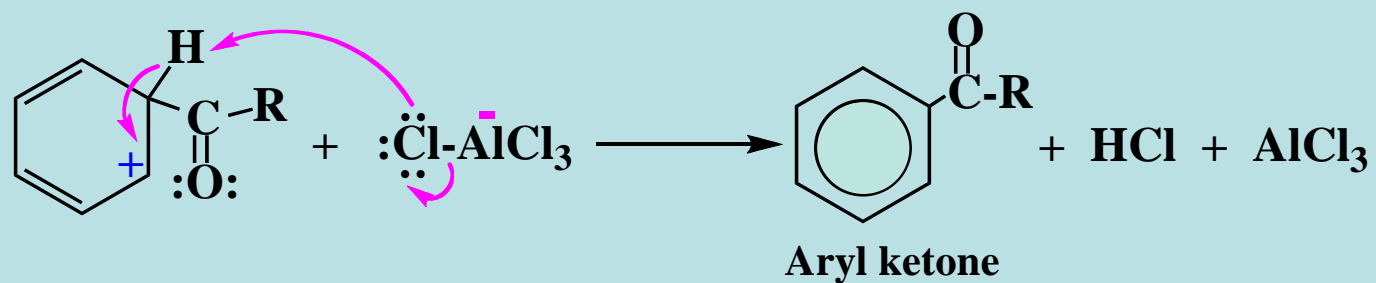


Acylium ions are generally thought to be the electrophilic intermediates in Friedel-Crafts acylation reactions. As shown, these ions have two contributing resonance structures.

(2) Electrophilic Attack



(3) Deprotonation and Re-aromatization

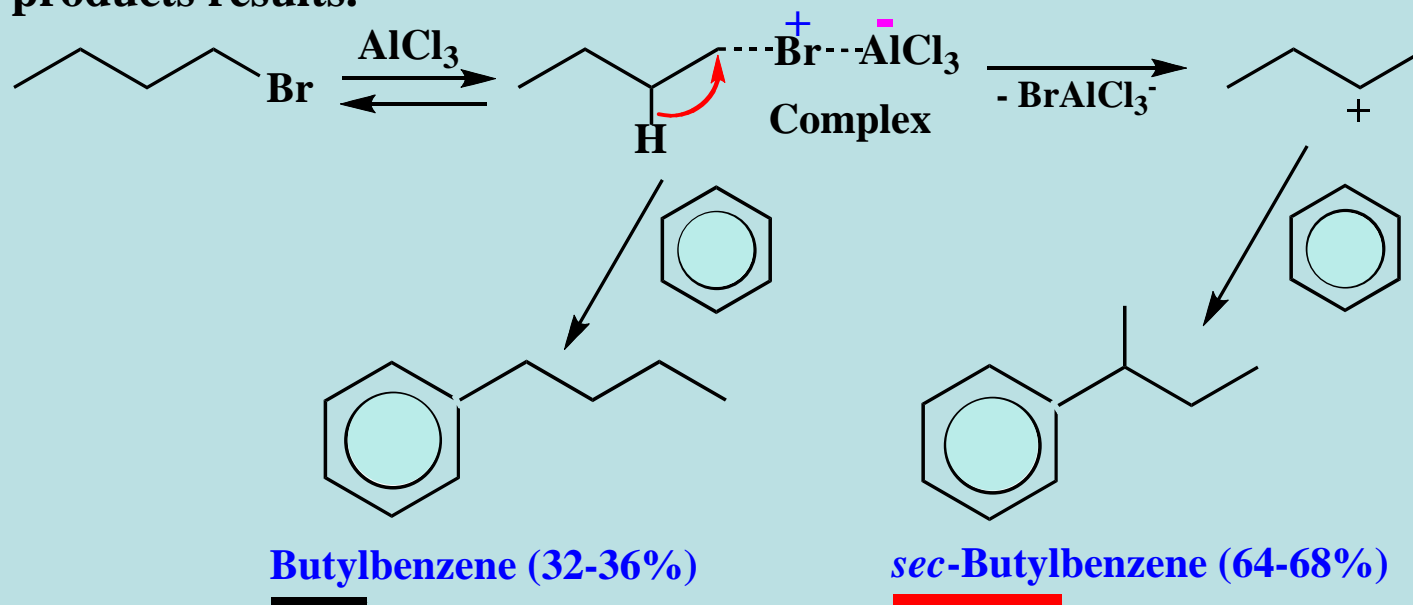


Limitations of the Friedel-Crafts Reactions

(1) Rearrangements during Alkylations

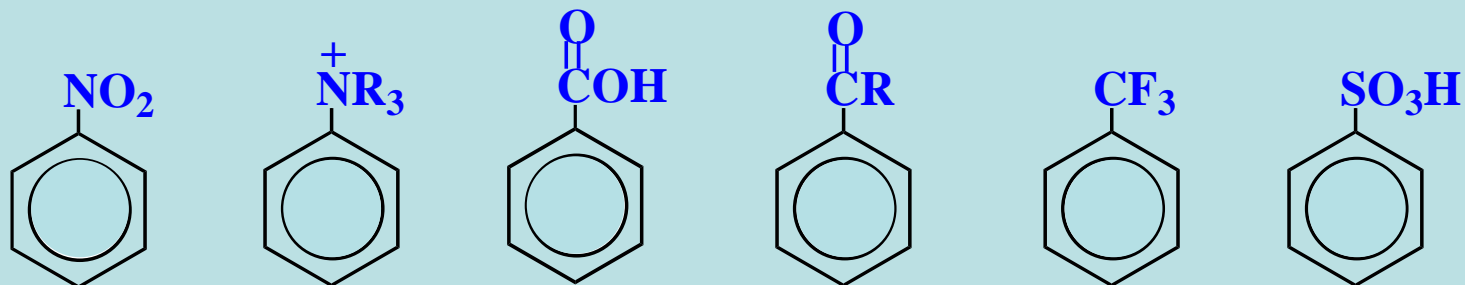
Whenever **carbocation intermediates** are formed, they are subject to **rearrangements** that produce more stable species.

Example: During the Friedel-Crafts reaction of benzene with butyl bromide a **1,2-hydride shift**, possibly concurrent with dissociation, produces some of the more stable *sec*-butyl carbocation. A mixture of products results.



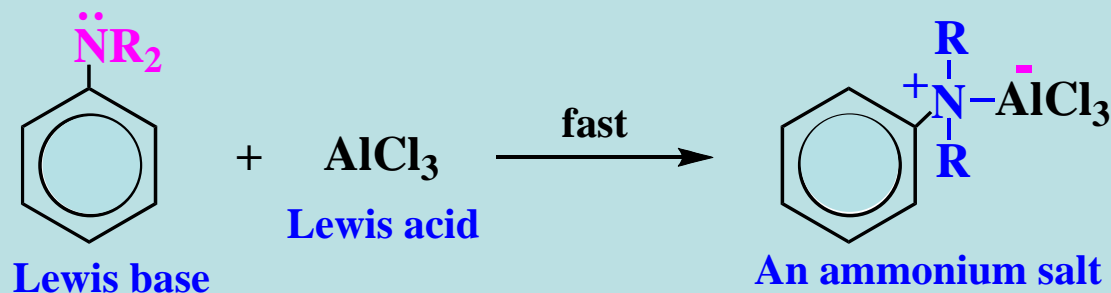
(2) Friedel-Crafts reactions do not proceed well with electron-deficient benzenes, or with aromatics that have amino groups.

The following **electron-withdrawing substituents** lead to electron-deficient π -systems that react slowly with electrophiles.

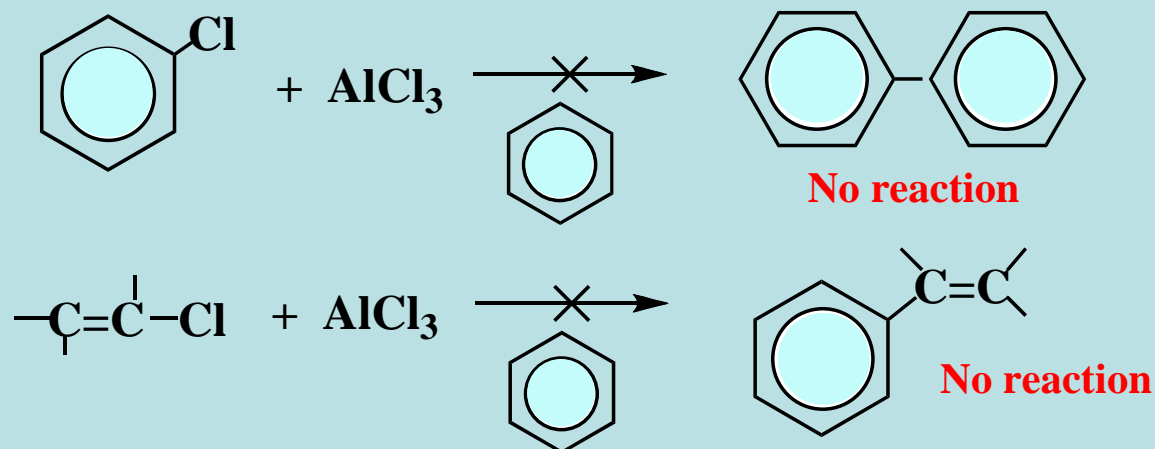


In general, Friedel-Crafts reactions do not proceed with benzenes that have these substituent groups (which are **meta-directing**; discussed later).

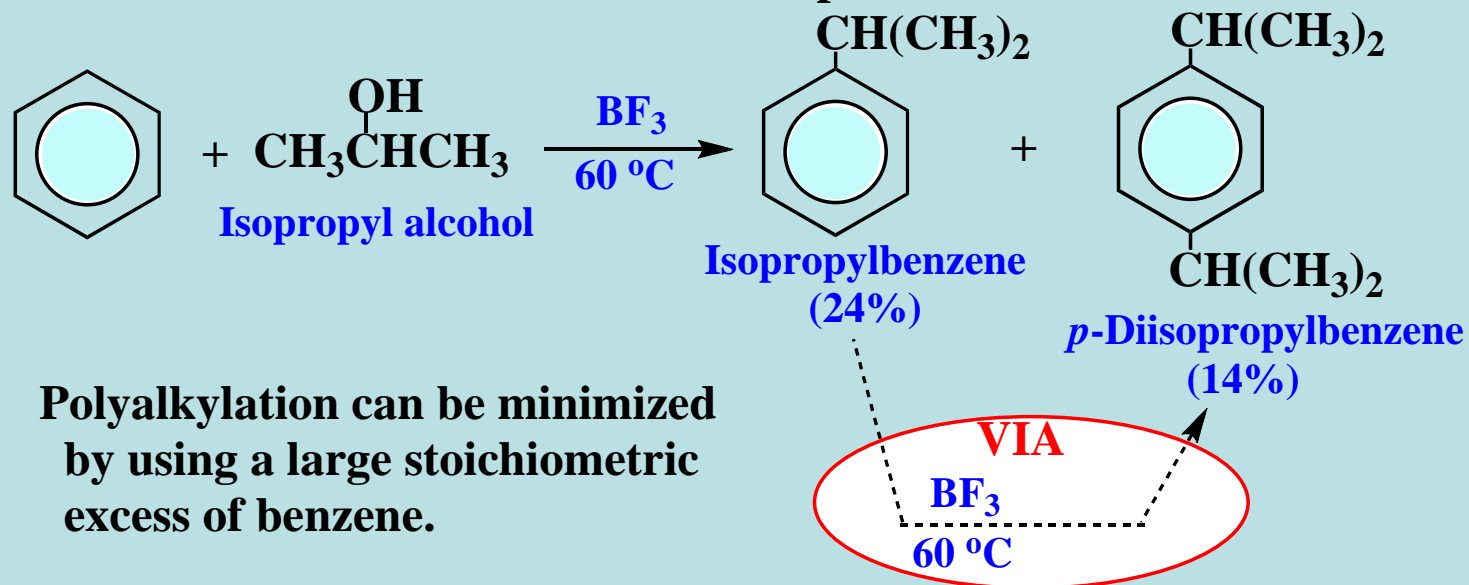
Benzenes with **amino functions** ($-\ddot{\text{N}}\text{R}_2$) do not undergo Friedel-Crafts reactions because they rapidly react with the Lewis acid catalysts to produce an **unreactive complex salt**.



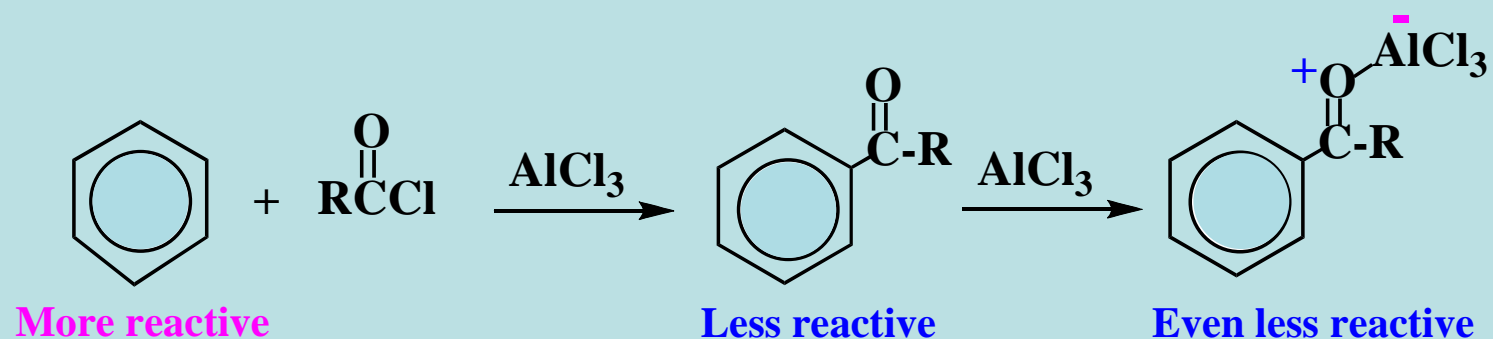
(3) Aryl and vinylic halides cannot be used as the halide because they do not form **carbocations** readily.



(4) **Polyalkylations** often occur because the alkylbenzene products are **more reactive than benzene** in electrophilic substitution reactions.

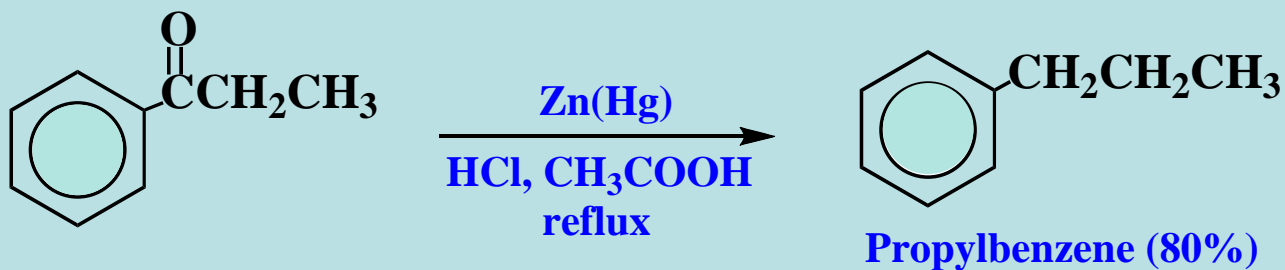


Polyacylation is not a problem because the acyl group ($\overset{\text{O}}{\parallel}{\text{RC}}-$) is electron-withdrawing, which deactivates the aromatic ring towards further electrophilic addition. Complexing of the carbonyl with AlCl_3 further reduces π -electron density in the ring.



The Clemmensen Reduction

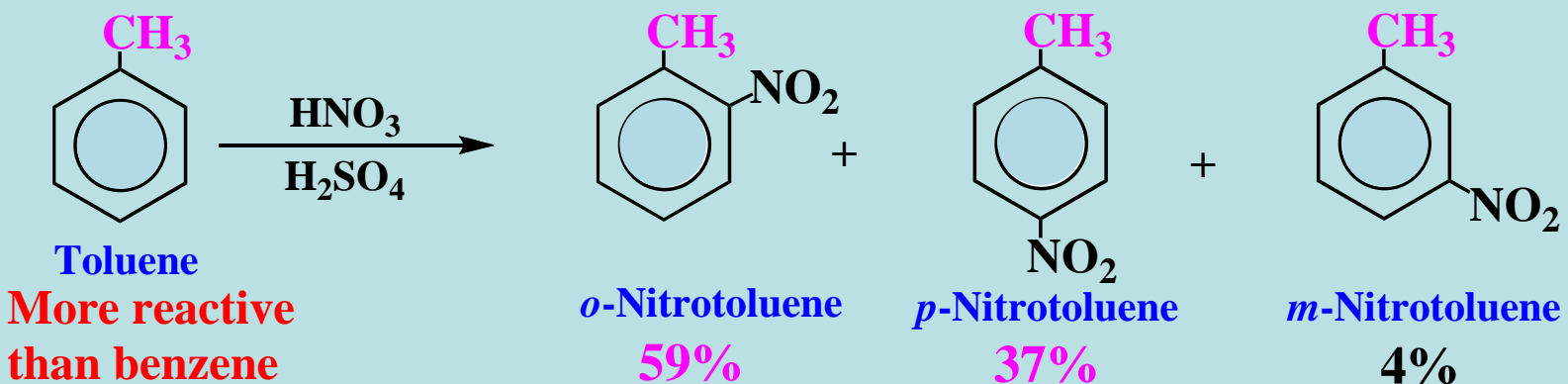
In 1913, E. Clemmensen developed a standard reduction that involves refluxing the ketone in a heterogeneous mixture of amalgamated zinc and hydrochloric acid. Often, acetic acid is added to improve the solubility of the ketone. Good yields of the alkylbenzene are typically obtained.



Activating Groups: *Ortho-Para* Directors

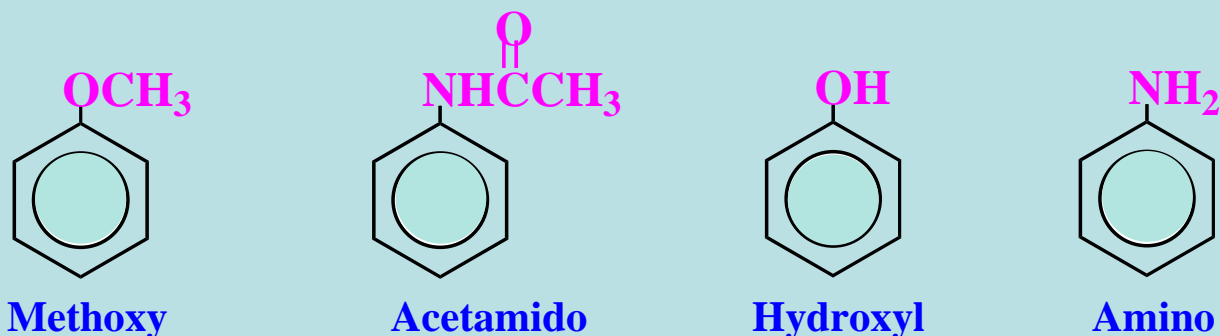
The methyl and other alkyl groups are in this category.

Example: Nitration of toluene proceeds **faster** than that of benzene and gives predominantly *ortho* and *para* nitrotoluene products.



Alkyl groups are also **activating** and *ortho/para* directing in other electrophilic aromatic substitutions.

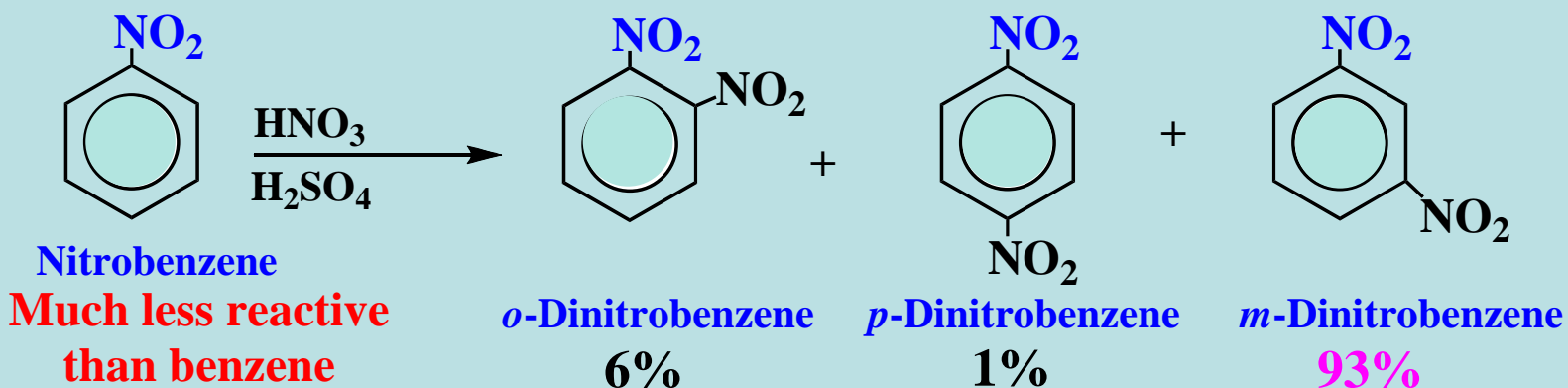
Additional Activating and *Ortho/Para* Directing Groups



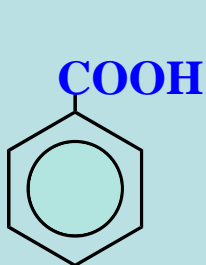
Deactivating Groups: *Meta* Directors

The nitro group, $-\text{NO}_2$, is an example.

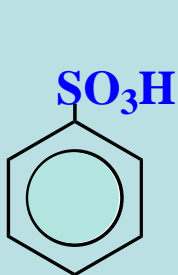
Nitration of nitrobenzene proceeds at a rate approximately 10^{-8} times the rate of nitration of benzene, and the major product is *m*-dinitrobenzene.



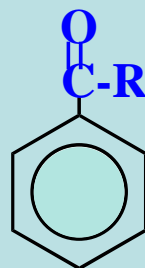
Other deactivating and *meta*-directing groups are:



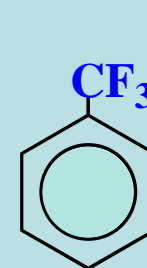
Carboxyl



Sulfonic acid



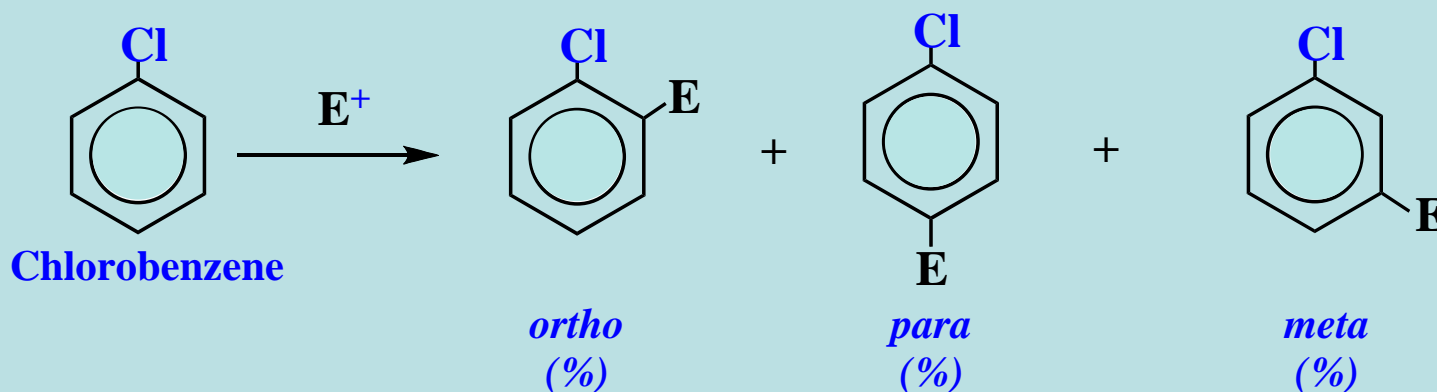
Acyl



Trifluoromethyl

Halogen Substituents: Deactivating but *Ortho/Para* Directing

Chloro and **bromo** substituents are unique in decreasing reactivity in electrophilic aromatic substitution but producing mostly *ortho* and *para* products.



Reaction:

Chlorination	39	55	6
Bromination	11	87	2
Nitration	30	70	--
Sulfonation	--	100	--

Summary of Substituent Effects on Electrophilic Aromatic Substitution

<i>Ortho/para directing and activating</i>	<i>Ortho/para directing and deactivating</i>	<i>Meta directing and very deactivating</i>
$-\ddot{\text{N}}\text{R}_2$	$-\ddot{\text{F}}:$	$-\text{NO}_2$
$-\ddot{\text{O}}-\text{H}$	$-\ddot{\text{Cl}}:$	$-\overset{+}{\text{N}}\text{R}_3$
$-\ddot{\text{O}}-\text{R}$	$-\ddot{\text{Br}}:$	$-\text{CF}_3, -\text{CCl}_3$
$-\ddot{\text{N}}\overset{\text{O}}{\parallel}\text{CR}$	$-\ddot{\text{I}}:$	$-\text{COOR}$
$-\text{R}$		$\overset{\text{O}}{\parallel}-\text{CR}$
$-\text{Ar}$		$-\text{C}\equiv\text{N}$
		$-\text{SO}_3\text{H}$

The **reactivity order** of substituted benzenes in electrophilic aromatic substitution reactions is:



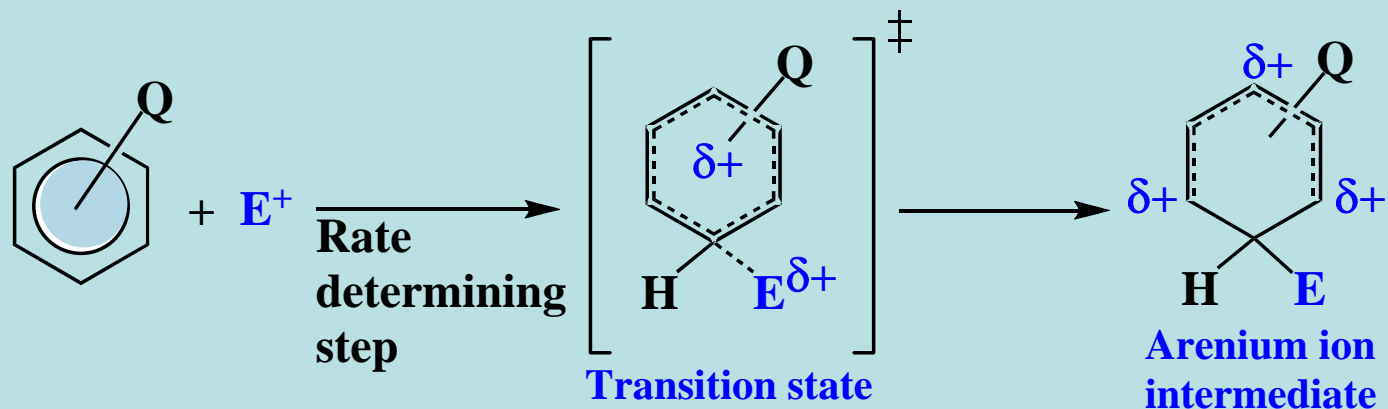
Among the *meta* directors, the reactivity order is:



Theory of Substituent Effects

The **reactivity** of substituted benzenes in electrophilic aromatic substitution is determined by the **electronic influence** of the substituent on the developing carbocation intermediate, the **arenium ion**.

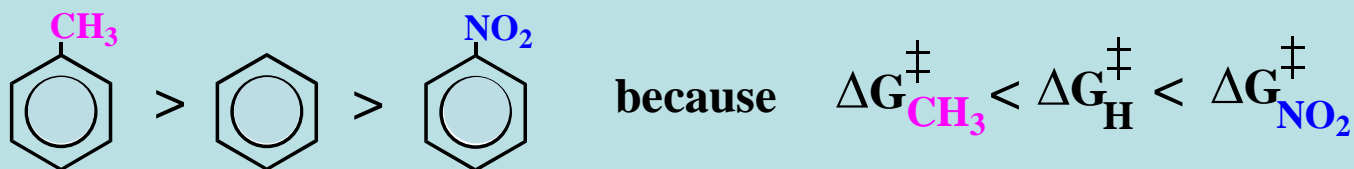
Illustration: An electrophile attacks *o*, *m*, or *p* to a substituent, Q.



When Q is **electron-releasing**, it stabilizes the arenium ion intermediate, **decreasing** the energy of the transition state relative to that from benzene.

When Q is **electron-withdrawing**, it destabilizes the arenium ion intermediate, **increasing** the energy of the transition state relative to that from benzene.

Since the addition of the electrophile is the rate determining step (RDS), the **reactivities of the arenes are in the order:**



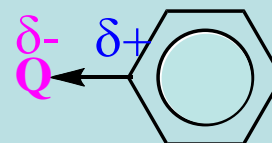
Electronic Influences of Substituent Groups: Inductive and Resonance Effects

The electronic influences of substituent groups that operate on the transition state leading to the arenium ion (and on the arenium ion) include both **inductive and resonance effects**.

The Inductive Effect

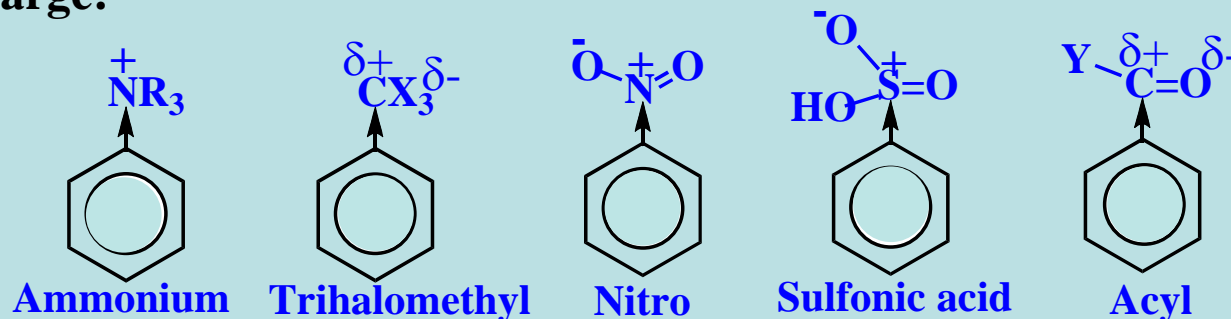
The inductive effect of a substituent Q arises from electrostatic interactions transmitted through polarized sigma bonds.

In a covalent bond where Q is more electronegative than C, there is a **permanent polarization** of the sigma electrons toward the more electronegative atom (e.g., a halogen atom):

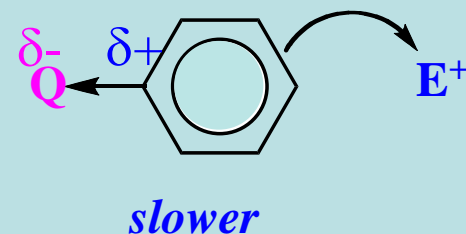


Thus the ring carbon with the substituent is more electropositive than the other carbons in the ring.

Other examples of electron withdrawing substituents are these, in which an atom attached to the ring has a full or partial positive charge:

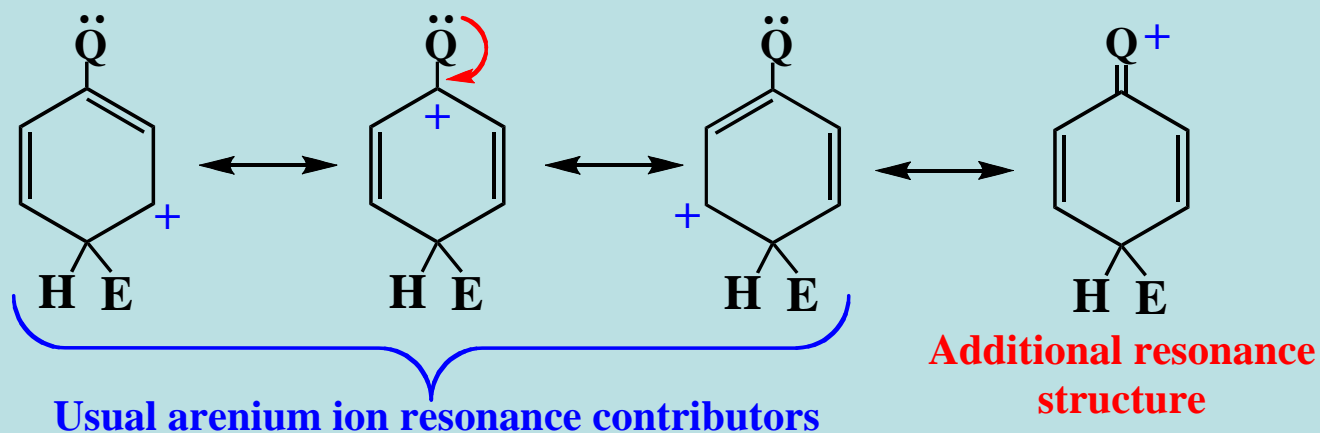


Addition of an electrophile E^+ to such a substituted benzene will be **slower** than addition to benzene because of the buildup of additional positive charge in the ring as the arenium ion is formed.

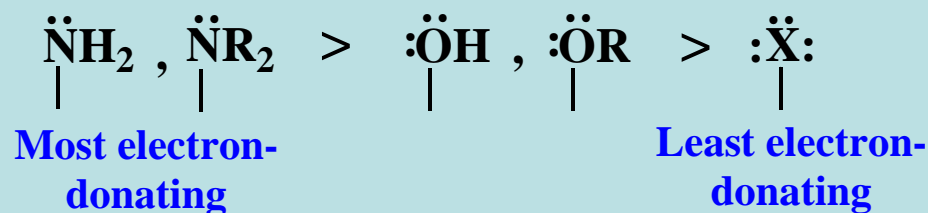


The Resonance Effect

The resonance effect of a substituent Q arises from any **additional resonance structures** that are possible because of the electronic features present in Q. For example, **nonbonding electron pairs** on Q help **stabilize** the arenium ion through an additional resonance structure.



The **stabilizing influencing** of a nonbonding electron pair on Q is in the order:

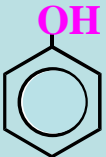
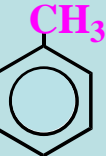

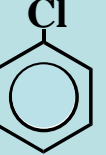
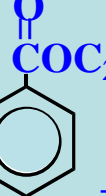
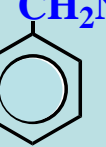
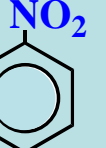
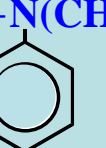


The Resonance Effect of the Halogens

With the halogens, the resonance effect (electron-donating ability) of **Cl, Br, and I is poor** because the p-orbitals containing the nonbonding electron pairs (3p, 4p, or 5p, respectively) do not match up well spatially with the 2p orbital on the ring carbon. There is better overlap of a nonbonding electron pair on F, which utilizes the 2p orbital.

Nevertheless, the ***ortho/para* directing ability of the halogens** in electrophilic aromatic substitution is explained by the resonance effect of the nonbonding electron pairs, as presented later.

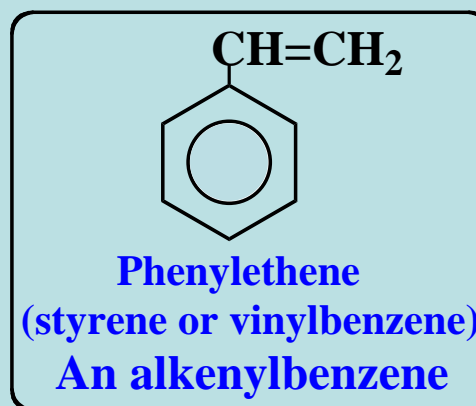
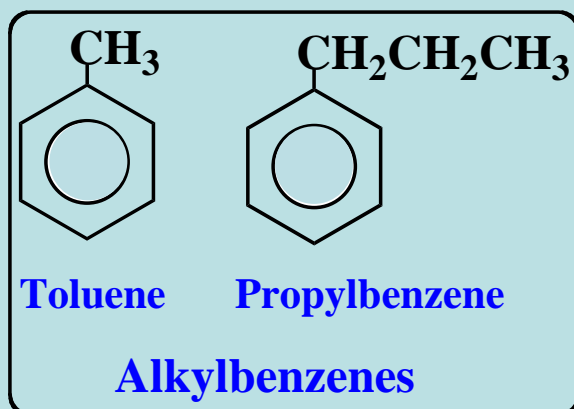
Relative Rates of Nitration of Substituted Benzenes

Compound	Major product(s)	Relative rate
	<i>ortho/para</i>	1000
	<i>ortho/para</i>	25
	mono	1
	<i>ortho/para</i>	0.03
	<i>meta</i>	0.004
	<i>meta</i>	2.6×10^{-5}
	<i>meta</i>	6×10^{-8}
	<i>meta</i>	1.2×10^{-8}

A reactivity range of 10^{11} !

Reactions of the Side Chain of Alkyl Benzenes

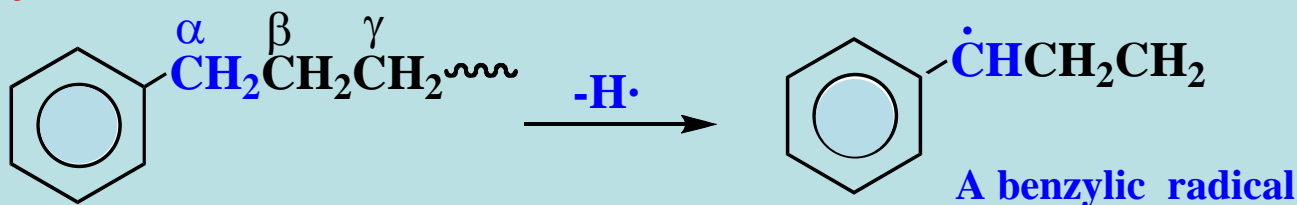
Hydrocarbons containing both aromatic and aliphatic groups are also called **arenes**. Some examples are shown below.



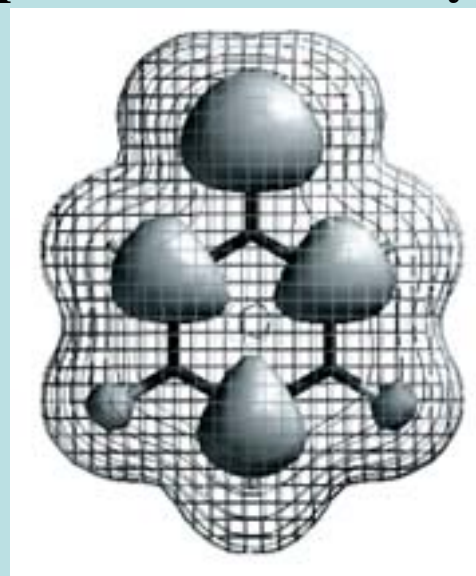
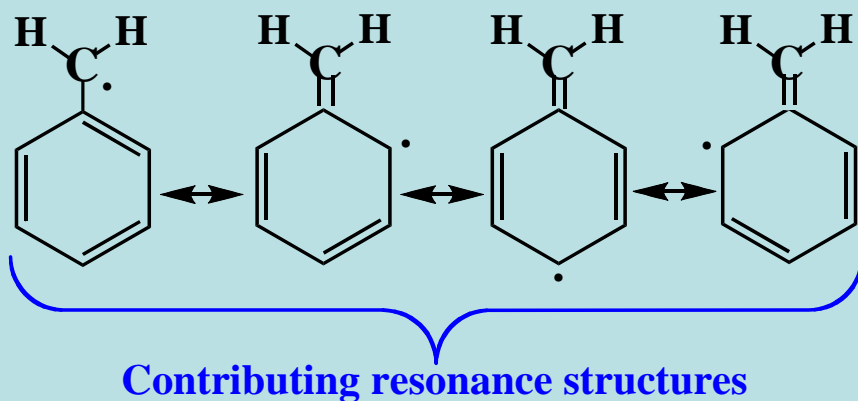
Alkylbenzenes and alkenylbenzenes have characteristic reactivities because of the presence of the aromatic ring.

Benzylic Radicals

Removal of a hydrogen atom ($\text{H}\cdot$) from an α -carbon of an alkylbenzene produces a **benzylic radical** (the simplest, **that from toluene, is the benzyl radical**).

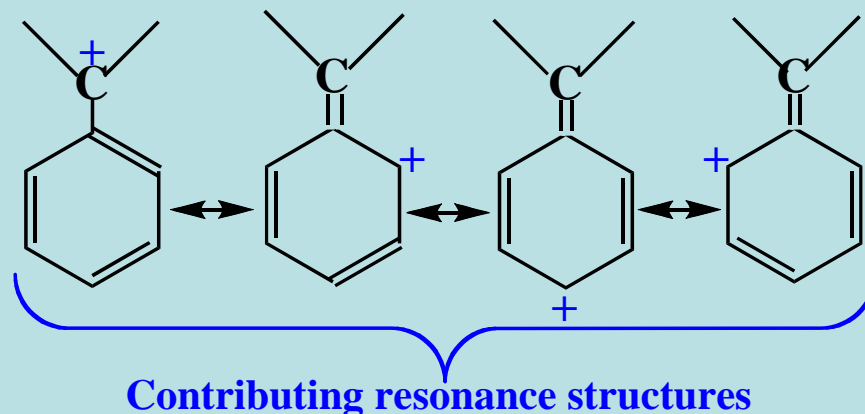


Benzylic radicals are more stable than simple alkyl radicals because their unpaired electron is **delocalized** through interaction with the aromatic π -system. This interaction is described below for the **benzyl radical** by use of resonance structures, or by the calculated structure, whose gray areas show the distribution of unpaired electron density.



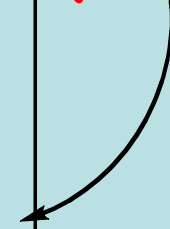
The Benzyl Cation

Because of π -delocalization, the **benzyl cation** also shows enhanced stability, comparable to that of a 2° carbocation (see below). This delocalization may be illustrated using resonance structures.



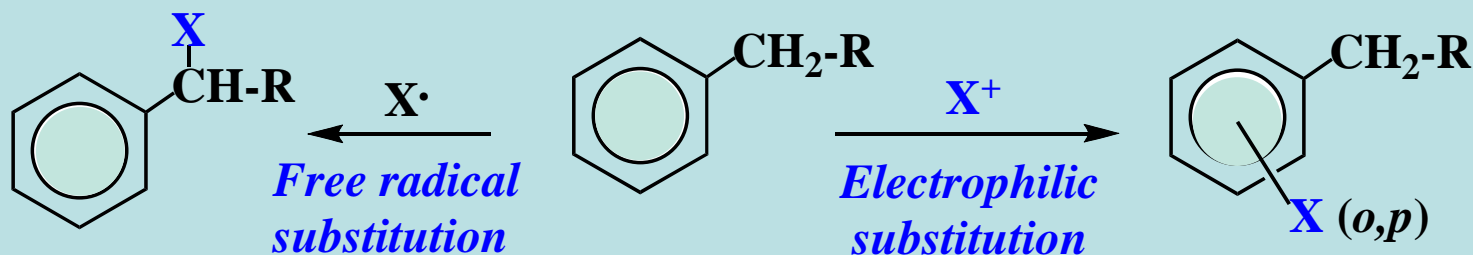
Energetics of Some Heterolytic Bond Dissociations

			ΔH
$\text{C}_6\text{H}_5\text{CH}_2\text{-Cl}$	\longrightarrow	$\text{C}_6\text{H}_5\overset{+}{\text{C}}\text{H}_2 + \text{Cl}^-$	+695 kJ/mol
$\text{CH}_3\text{-Cl}$	\longrightarrow	$\overset{+}{\text{C}}\text{H}_3 + \text{Cl}^-$	+950 kJ/mol
$\text{CH}_3\text{CH}_2\text{-Cl}$	\longrightarrow	$\text{CH}_3\overset{+}{\text{C}}\text{H}_2 + \text{Cl}^-$	+799 kJ/mol
$(\text{CH}_3)_2\text{CH-Cl}$	\longrightarrow	$(\text{CH}_3)_2\overset{+}{\text{C}}\text{H} + \text{Cl}^-$	+711 kJ/mol
$(\text{CH}_3)_3\text{C-Cl}$	\longrightarrow	$(\text{CH}_3)_3\overset{+}{\text{C}} + \text{Cl}^-$	+657 kJ/mol



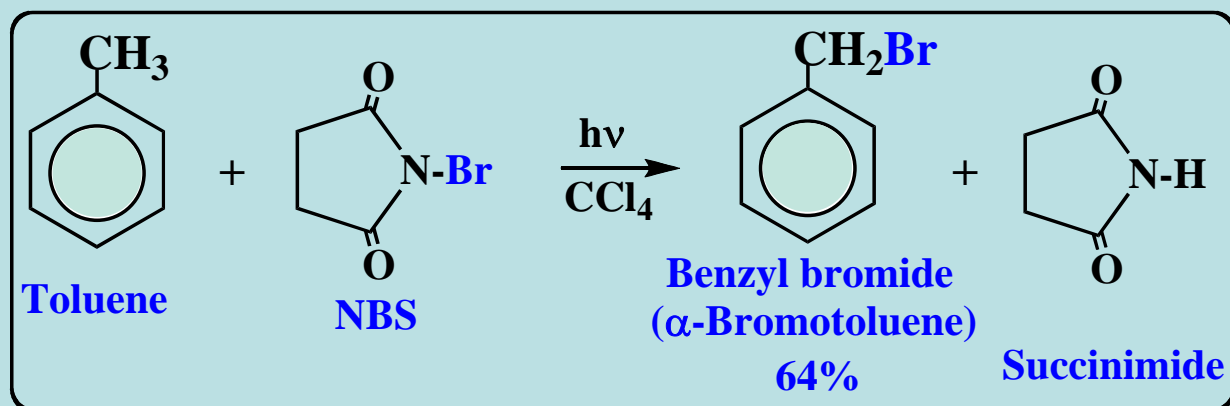
Halogenation of Arene Side Chains: Role of Benzylic Radicals

Halogenation of the α -position of an alkyl side chain in an arene occurs under **free radical conditions**. In contrast, substitution of the ring positions by halogen requires electrophilic conditions.



Side Chain Bromination with NBS

N-Bromosuccinimide (NBS) is the reagent of choice for selectively substituting bromine into the α -position. The free radical, photo induced chain reaction involves Br_2 being maintained at a low concentration during the reaction.

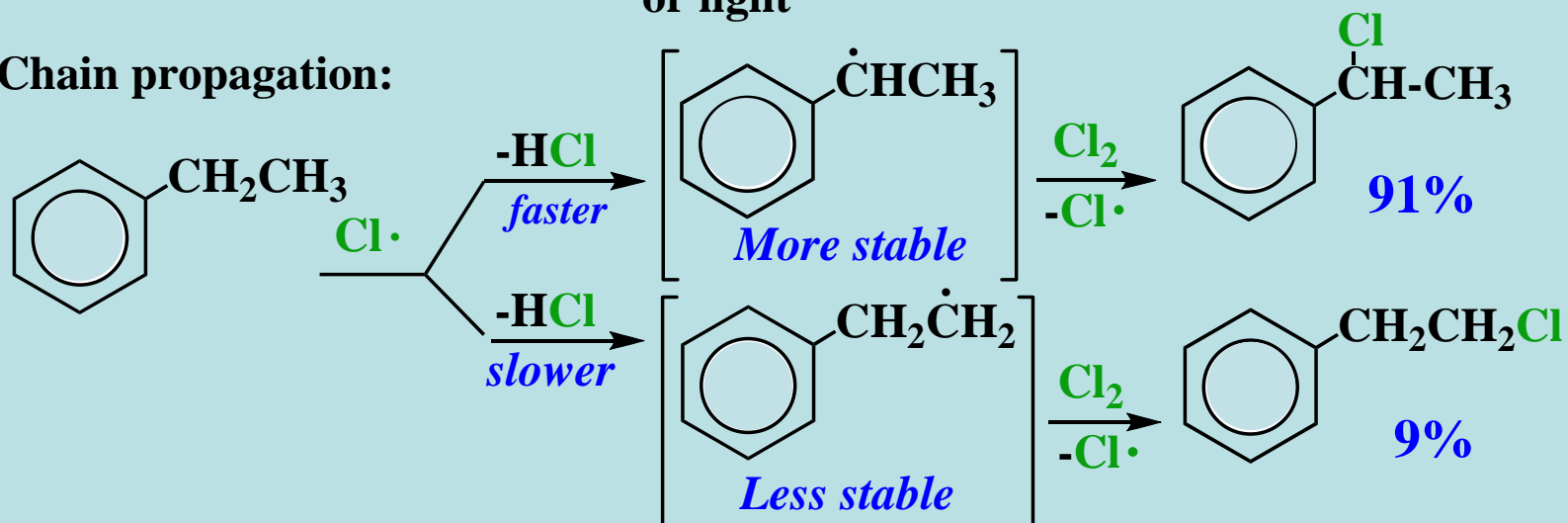


Photochlorination

Photochlorination of alkyl benzenes introduces **chlorine** into the side chain, with predominant reaction at α carbons.

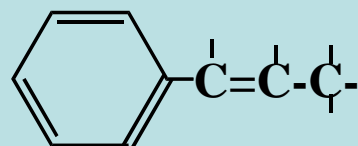


Chain propagation:



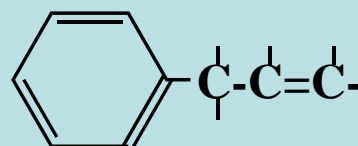
Alkenylbenzenes

Alkenylbenzenes with a side chain double bond conjugated with the aromatic ring are more stable than nonconjugated systems.



Conjugated system

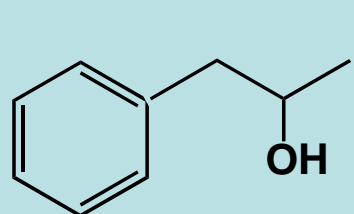
more stable



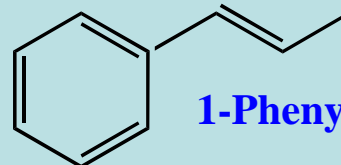
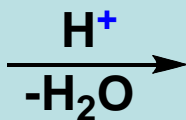
Nonconjugated system

less stable

In acid-catalyzed dehydration reactions, the more stable conjugated alkenylbenzene is preferentially formed. For example:



1-Phenyl-2-propanol

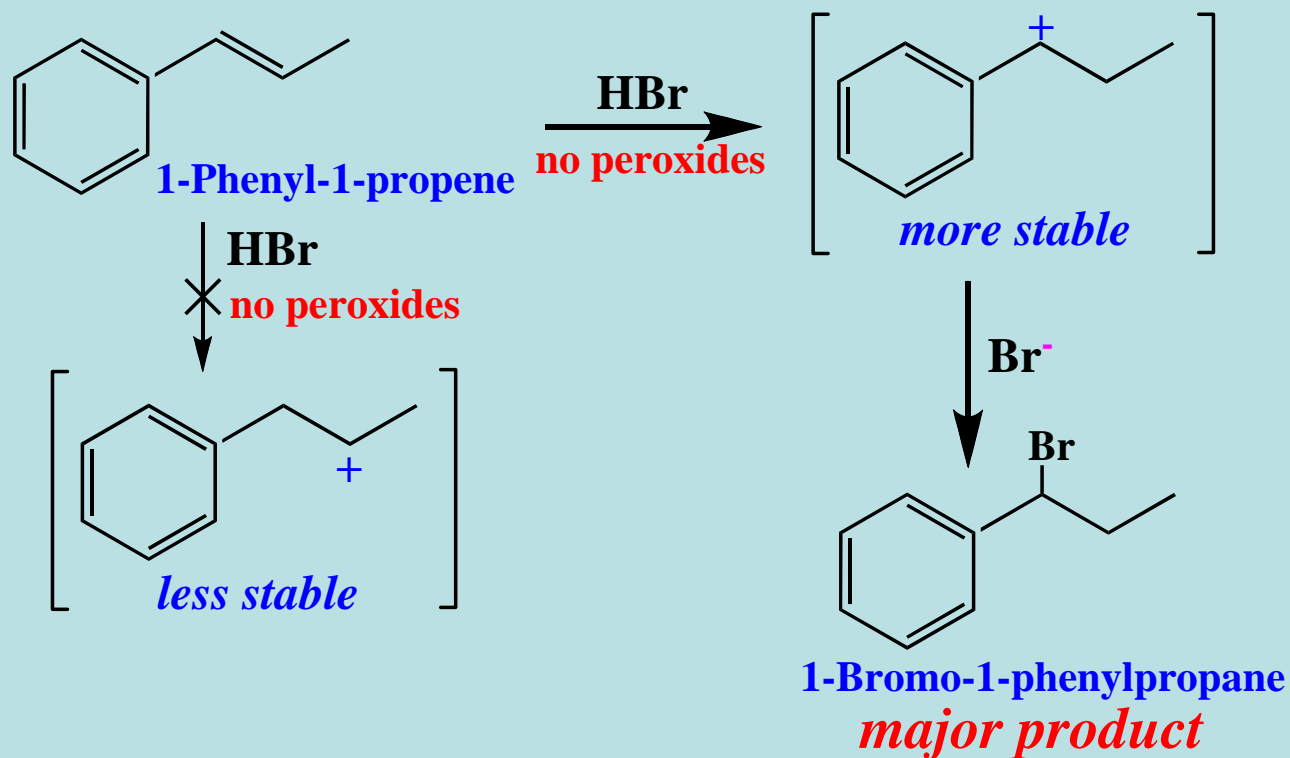


1-Phenyl-1-propene

major product

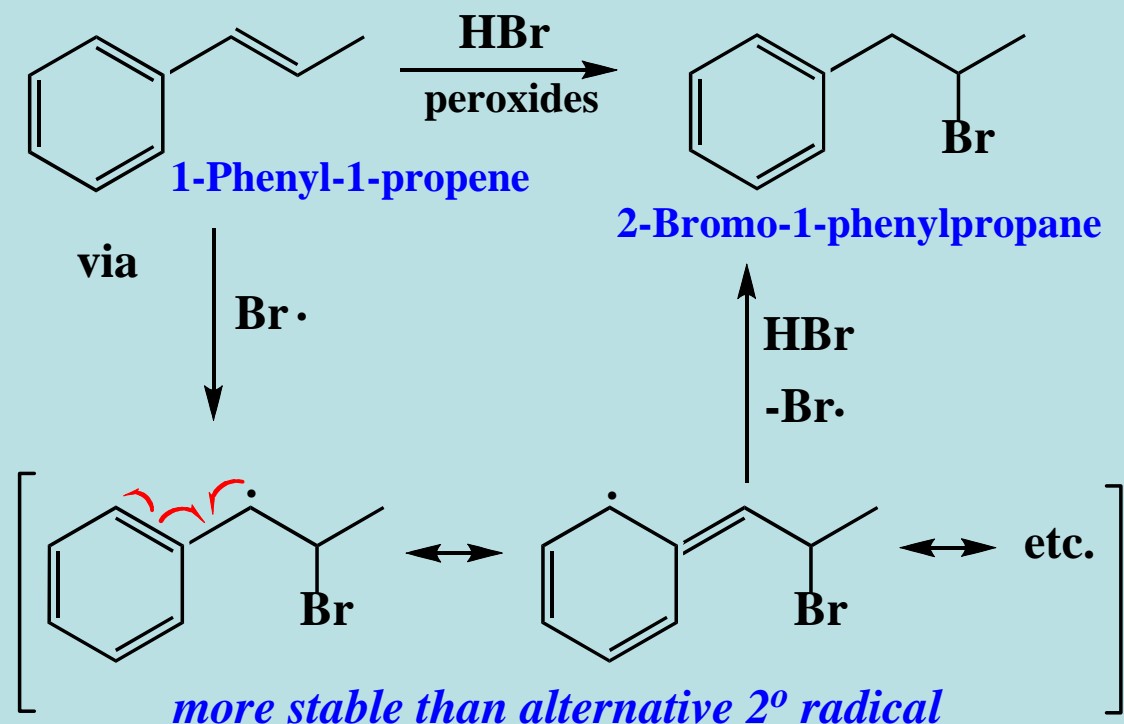
Additions to Alkenylbenzenes

Addition reactions of alkenylbenzenes are like those of simple alkenes and proceed through the **more stable intermediate**.



Free Radical Addition of HBr

As expected, free radical addition reactions to conjugated alkenylbenzenes proceed via the **more stable radical intermediate**.

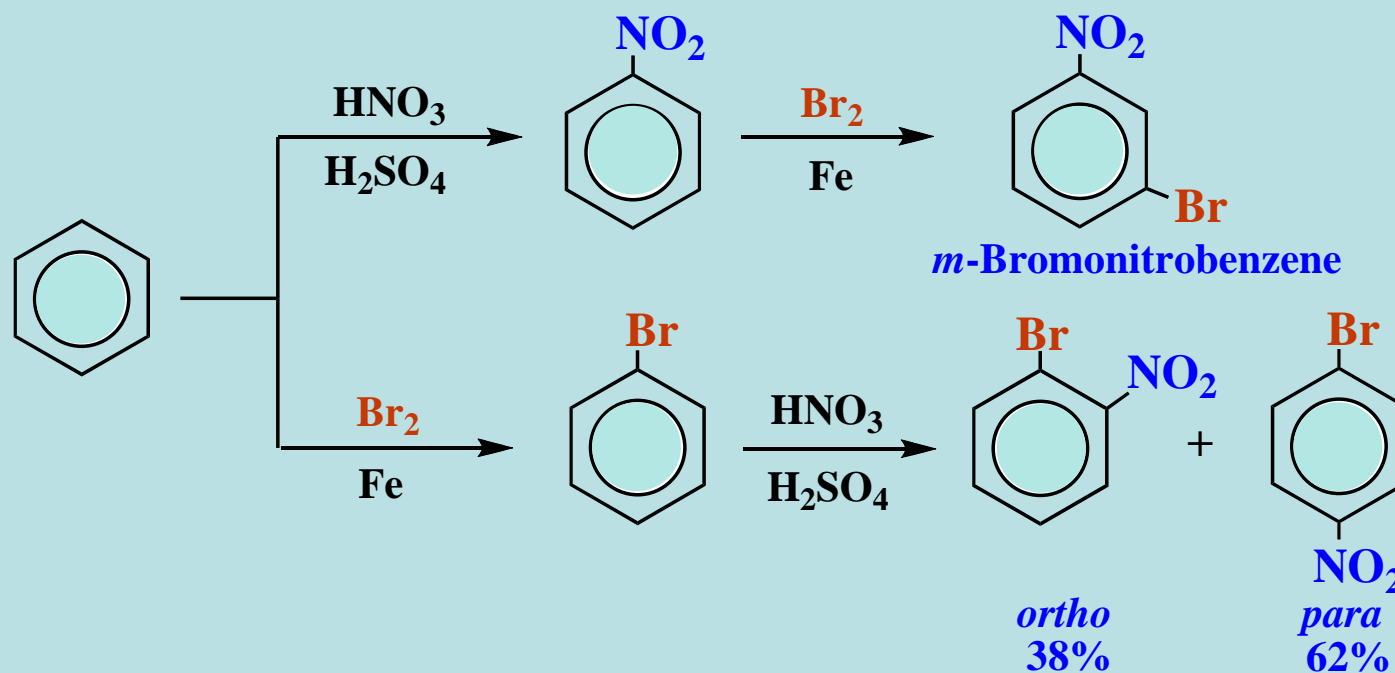


The **regiochemistry** of radical additions to conjugated alkenylbenzenes is explained by preferential formation of the **resonance stabilized benzylic intermediate**.

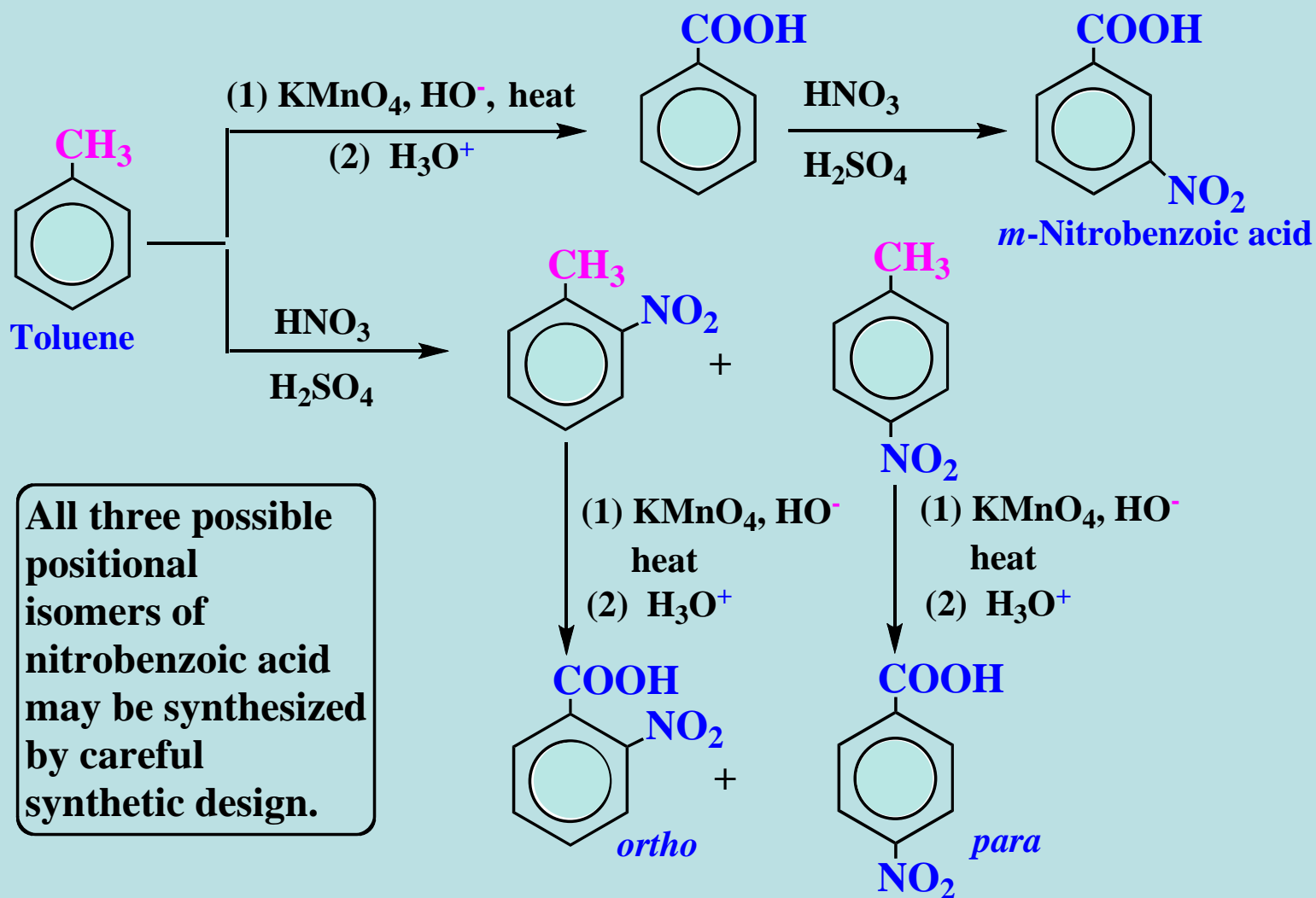
Synthetic Applications and Strategies

The influence of substituents on electrophilic aromatic substitution requires special attention to the **order** in which they are introduced into a benzene ring when synthesizing multiply substituted benzenes.

Example: The nitration and bromination of benzene.



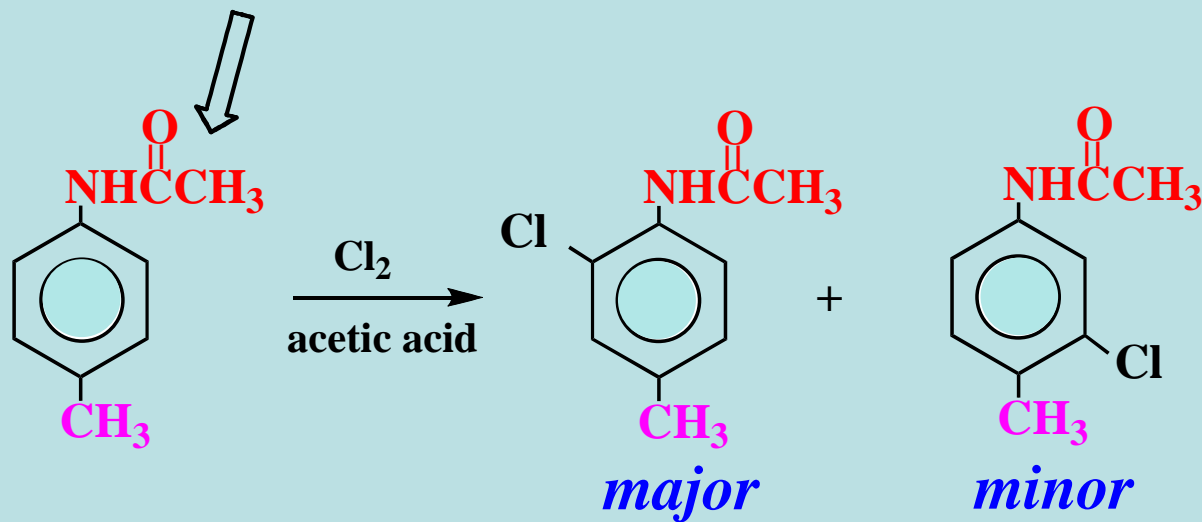
Example: The nitration and side-chain oxidation of toluene

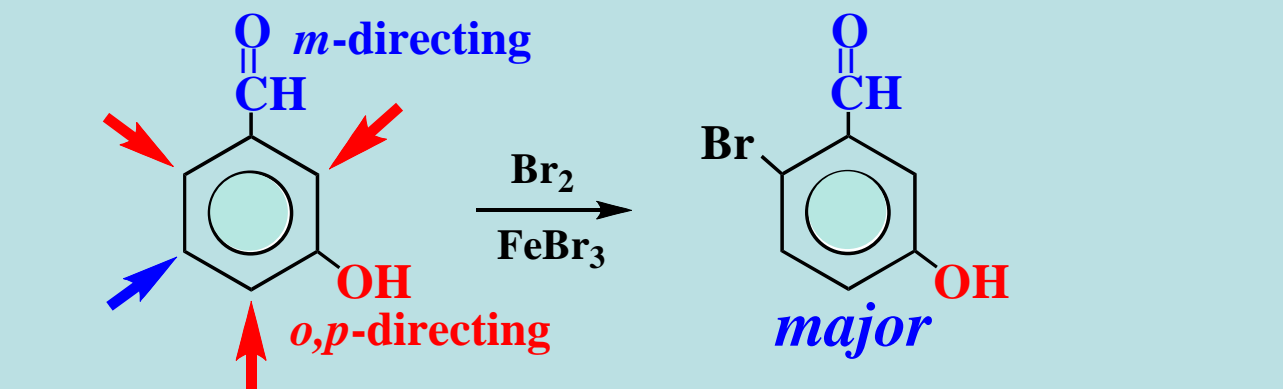


All three possible positional isomers of nitrobenzoic acid may be synthesized by careful synthetic design.

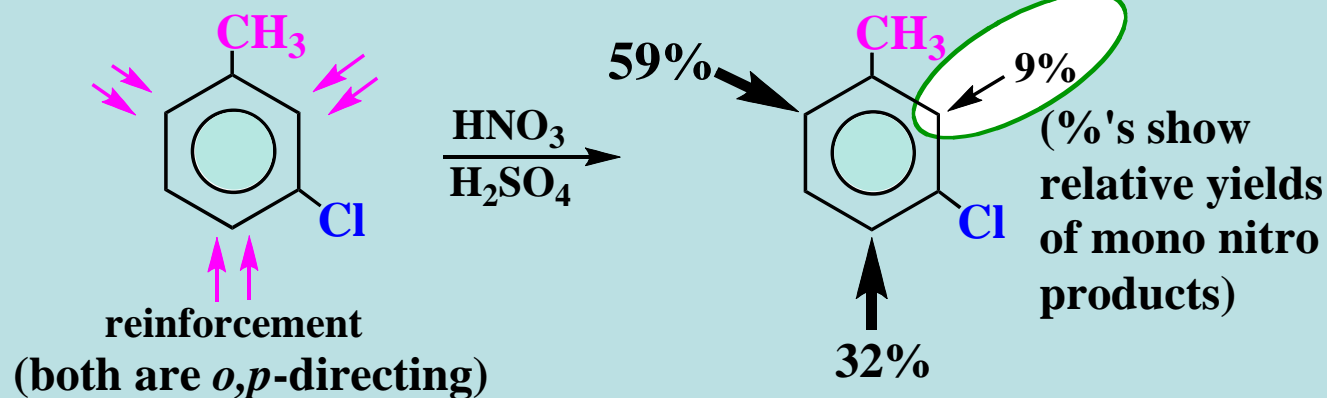
Orientation of Substitution in Disubstituted Benzenes

When two or more substituents are present in a benzene, the **most powerful activating group** controls the product formation.



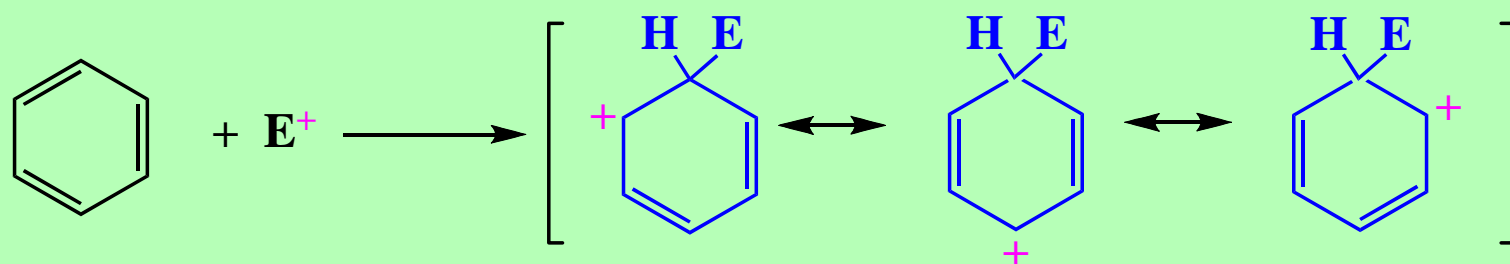


Position between two groups is hindered.



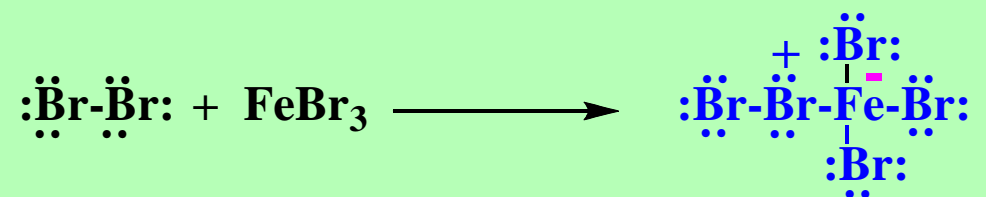
Quiz 15.01

Draw the three contributing resonance structures of the arenium ion intermediate produced in the addition of an electrophile, E^+ , to benzene.



Quiz 15.02

Draw the complex formed between bromine (Br_2) and FeBr_3 that is believed to be involved in the electrophilic bromination of benzene and other aromatics. Show the polarization of charge in the complex.

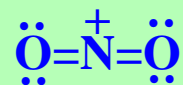


Quiz 15.03a

Draw the Lewis structure of the nitronium ion, NO_2^+ , a strong electrophile.

Solution

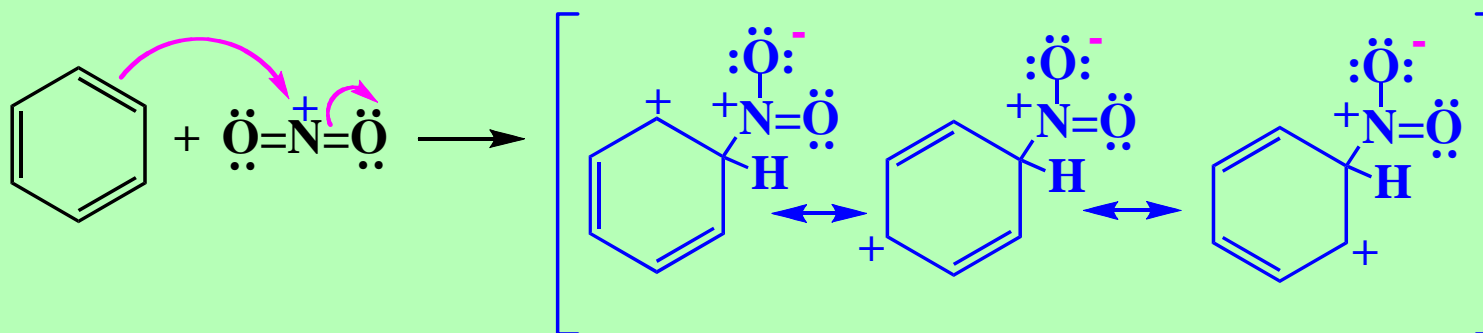
NO_2^+ is a 16 valence electron system. The proper Lewis structure must conform to the *Octet Rule* and have *formal charge(s)* indicated, so the answer is:



Quiz 15.03b

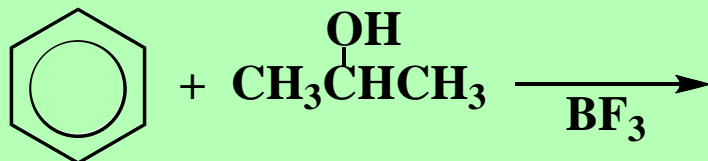
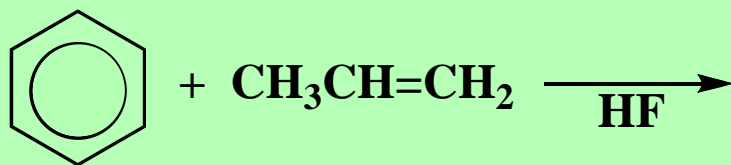
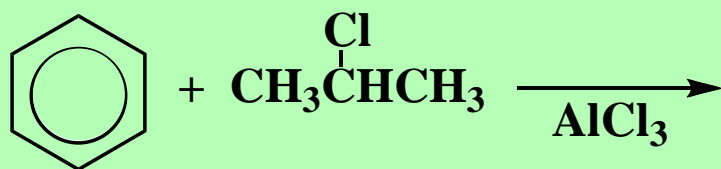
Draw the resonance structures of the arenium ion intermediate formed from electrophilic attack of the nitronium ion on benzene.

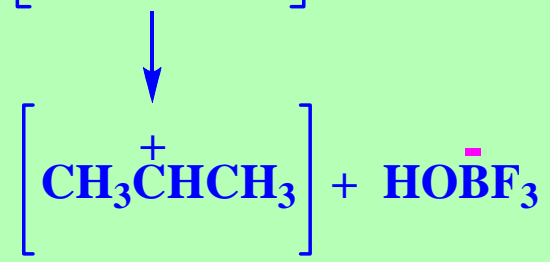
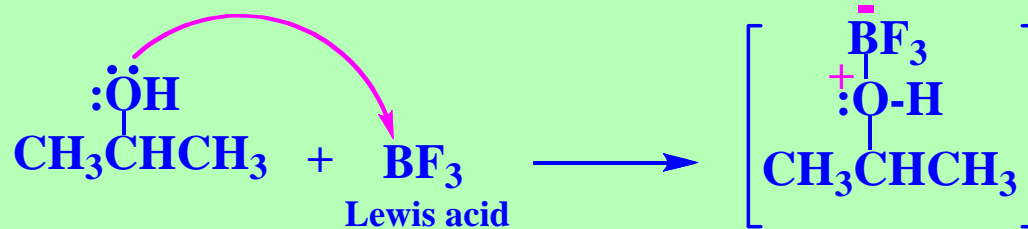
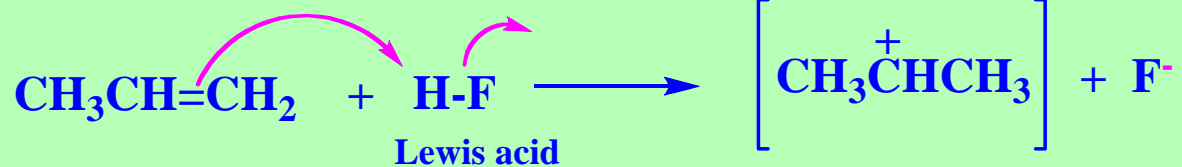
Note: Disregard resonance structures of the nitro group.



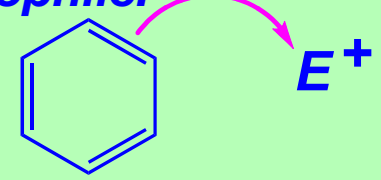
Quiz 15.04

Isopropylbenzene $\left(\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)_2 \right)$ may be prepared from benzene by any of the three methods below. In each case, show how the "effective" electrophile is formed.



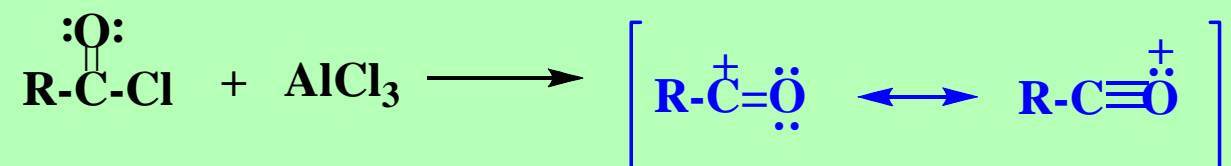


Benzene acts as a Lewis base (nucleophile) in reacting with the "effective" electrophile.



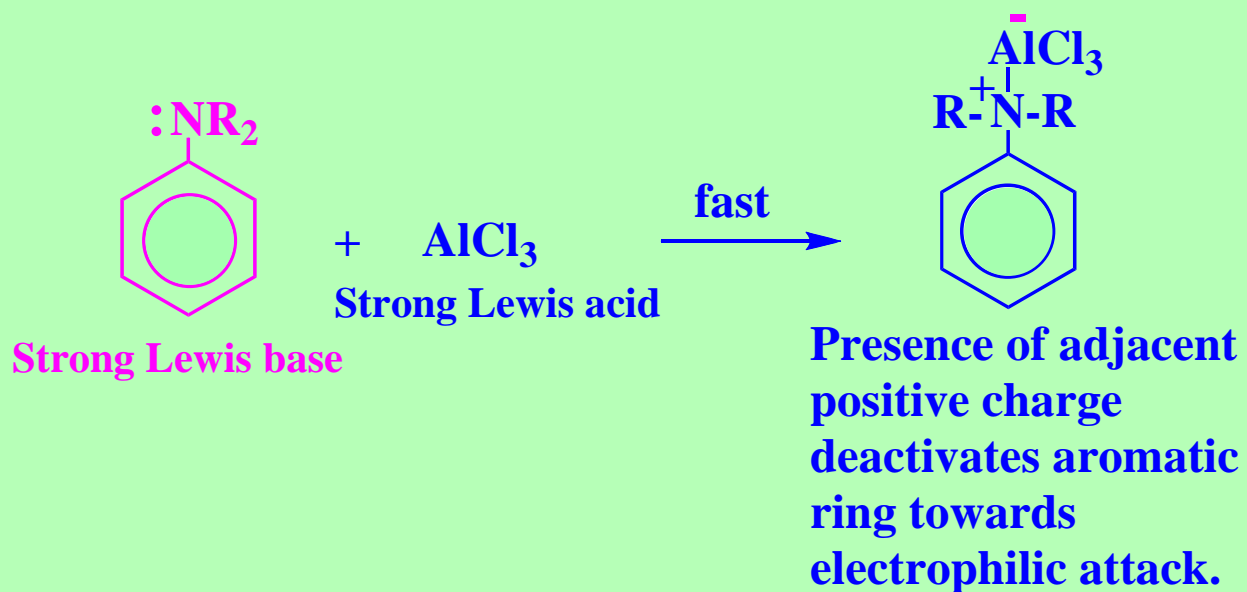
Quiz 15.05

Draw the contributing resonance structures of the acylium ion produced in the reaction below.



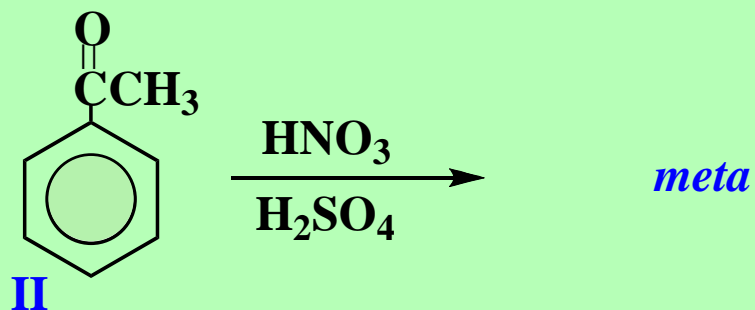
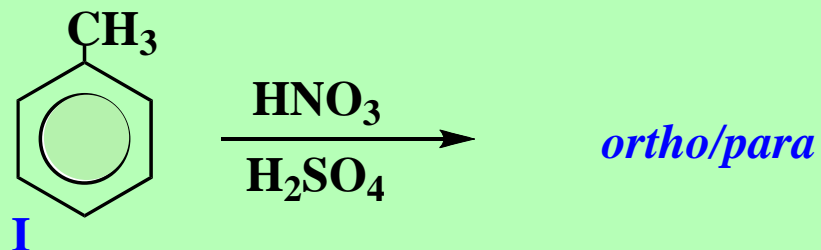
Quiz 15.06

Explain why aniline (aminobenzene) does not undergo Friedel-Crafts reactions.



Quiz 15.07

Predict the major products (*ortho/para* or *meta*) from the nitration of the following substituted benzenes.

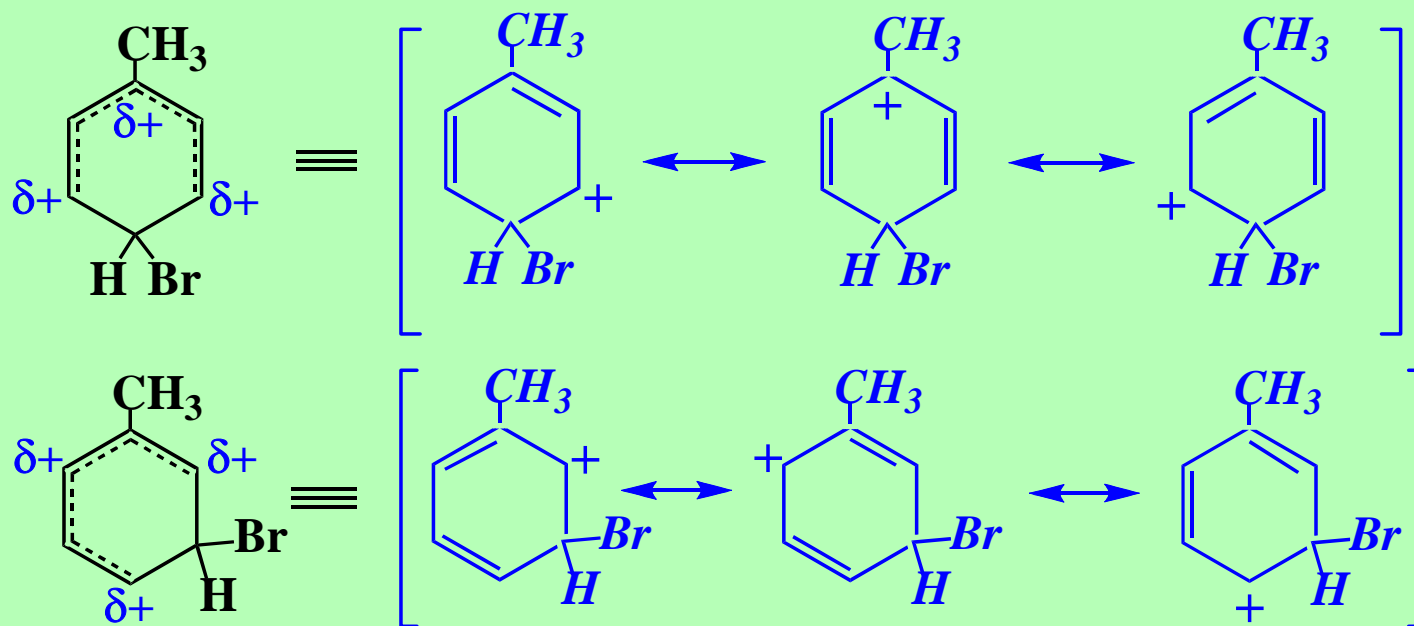


What is the order of reactivity of the three substituted benzenes in the nitration reaction?



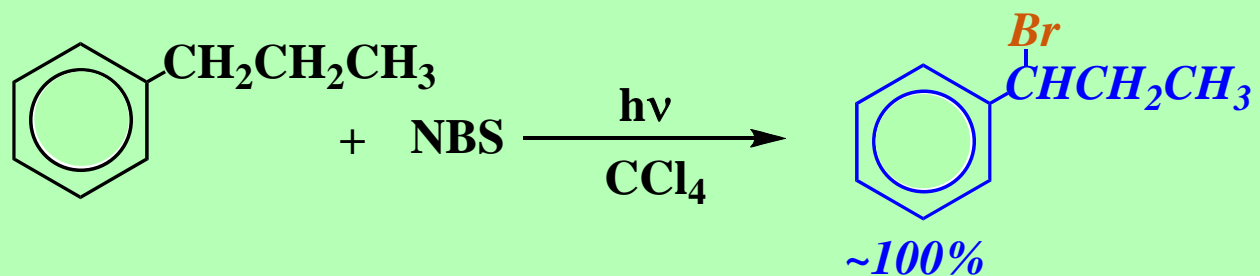
Quiz 15.08

Draw the contributing resonance structures for the arenium ion intermediates formed from *para* and *meta* addition of Br^+ to toluene.



Quiz 15.09

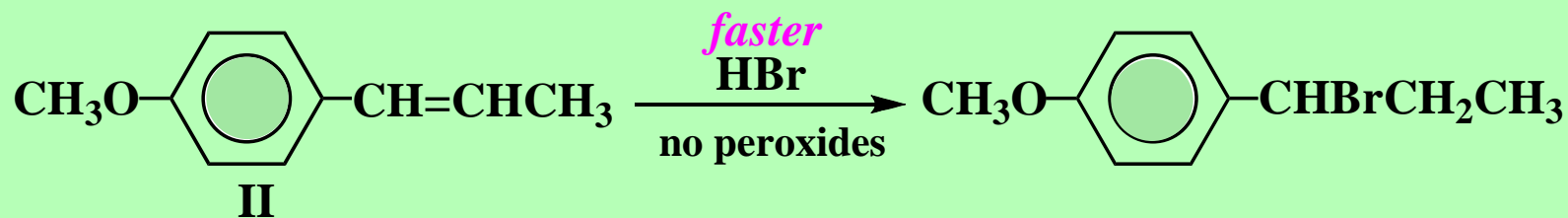
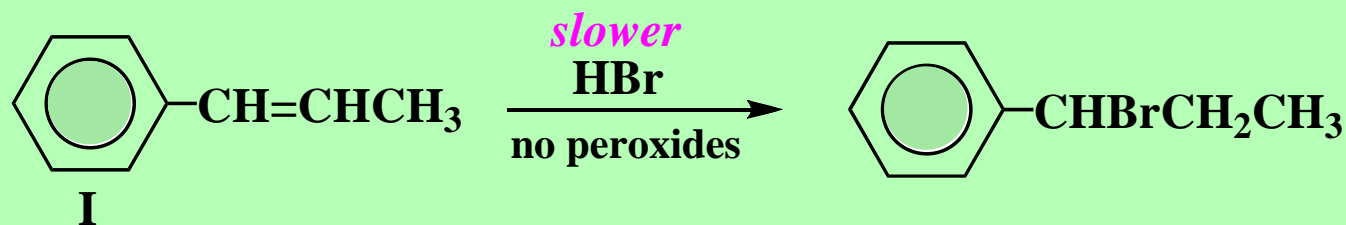
Draw the structure of the product of the following reaction.



Free radical bromination is a highly site selective reaction.

Quiz 15.10

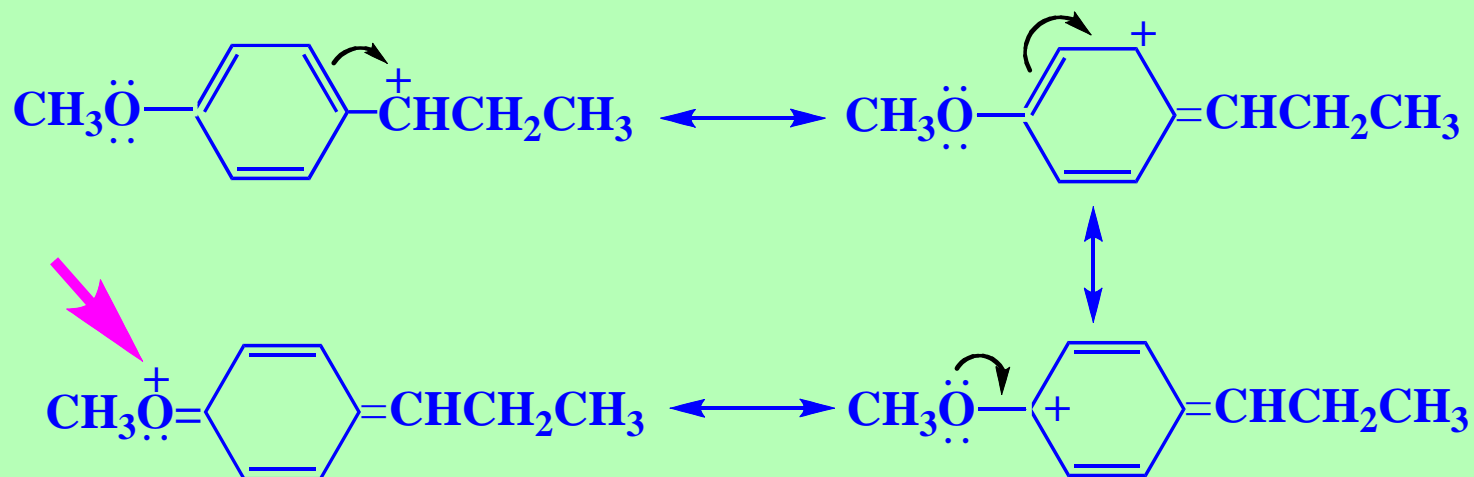
In the following addition reactions, explain why the indicated products are predominant and also why there is the reactivity difference between I and II.



SOLUTION:

These are ionic additions where formation of the carbocation intermediate is the rate determining step. The orientation of the addition reaction follows from the greater stability of the benzylic type carbocation compared with a simple secondary carbocation, resulting in a lower transition state energy for formation of the benzylic type carbocation and subsequent formation of the observed products.

The faster reaction rate for II reflects the stabilizing influence of the *p*-methoxy group on the developing benzylic type carbocation, as shown in the resonance structures below for the intermediate ion.



Quiz 15.11

Draw the structure of the major monosubstitution product from each of these reactions.

