ORGANIC CHEMISTRY II

College of Pharmacy

2nd Stage/1st semester



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Friedel–Crafts acylation

The mechanism of the Friedel–Crafts acylation reaction is similar to that of Friedel–Crafts alkylation.

The reactive electrophile is a resonance-stabilized acyl cation, generated by reaction between the acyl chloride and AlCl3.

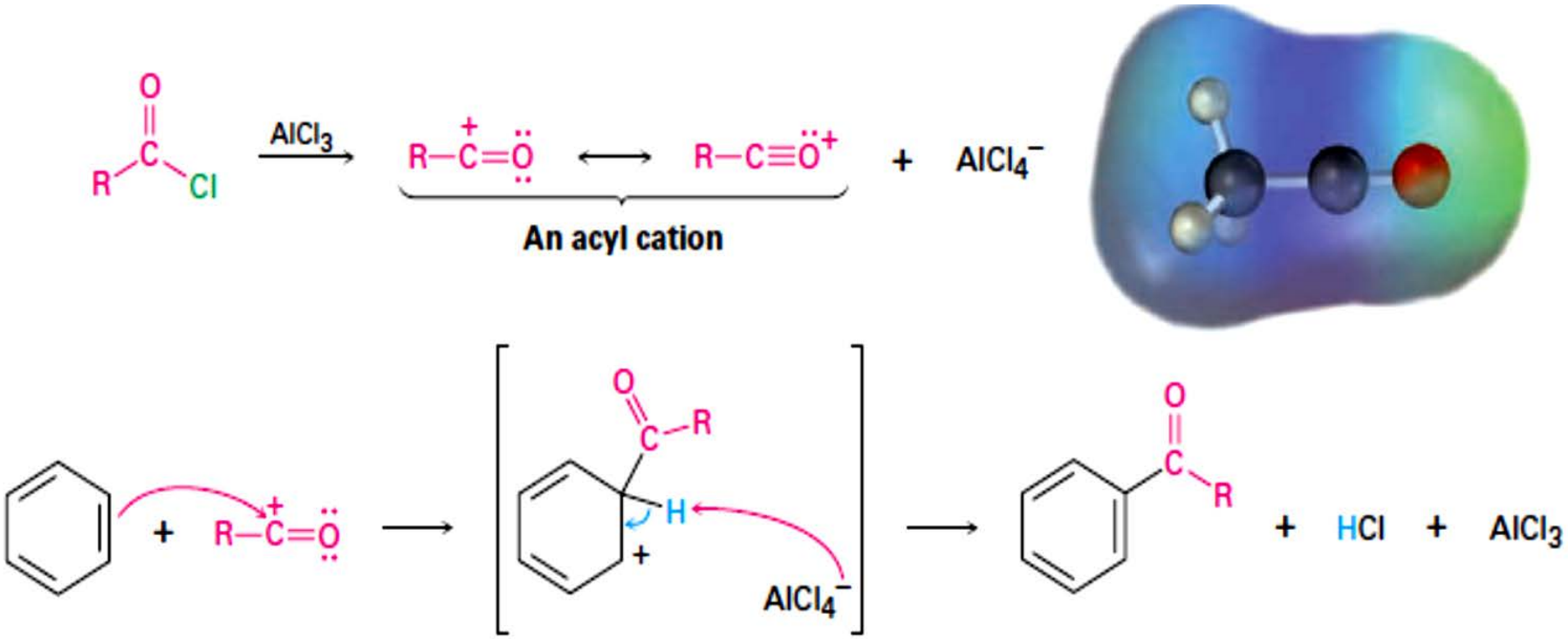
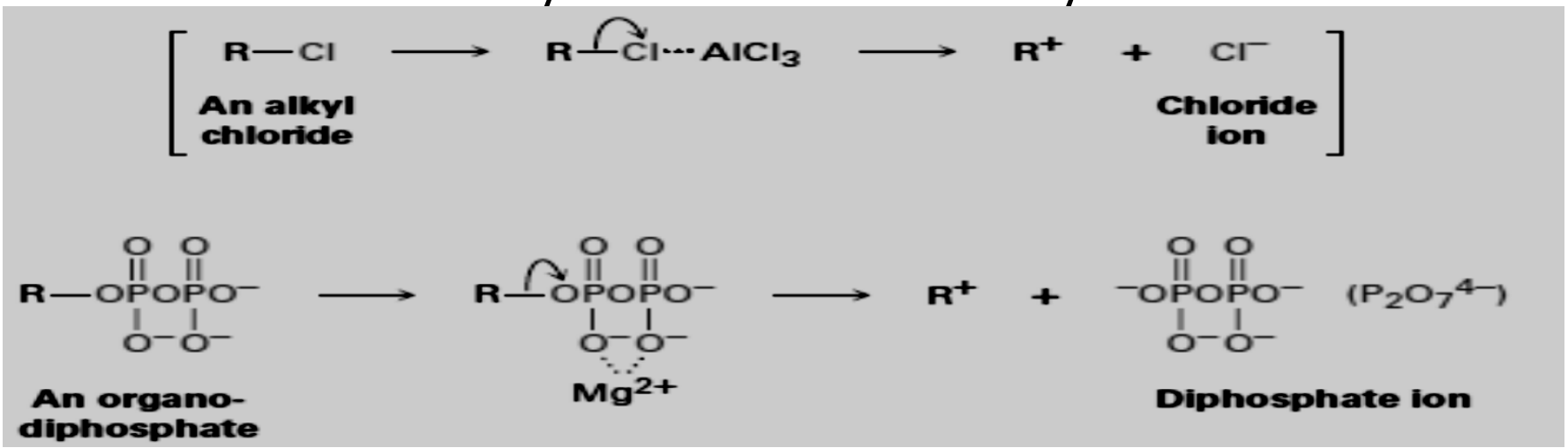


Figure 16.9 Mechanism of the Friedel–Crafts acylation reaction. The electrophile is a resonance-stabilized acyl cation, whose electrostatic potential map indicates that carbon is the most positive atom.

- Unlike the multiple substitutions that often occur in Friedel–Crafts alkylations, acylations never occur more than once on a ring because the product acylbenzene is less reactive than the nonacylated starting material.
- Note: Aromatic alkylations occur in numerous biological pathways, although there is of course no AlCl3 present in living systems to catalyze the reaction. Instead, the carbocation electrophile is typically formed by dissociation of an organodiphosphate. The dissociation is usually assisted by complexation to a divalent metal cation such as (Mg2)1 just as dissociation of an alkyl chloride is assisted by AlCl3.



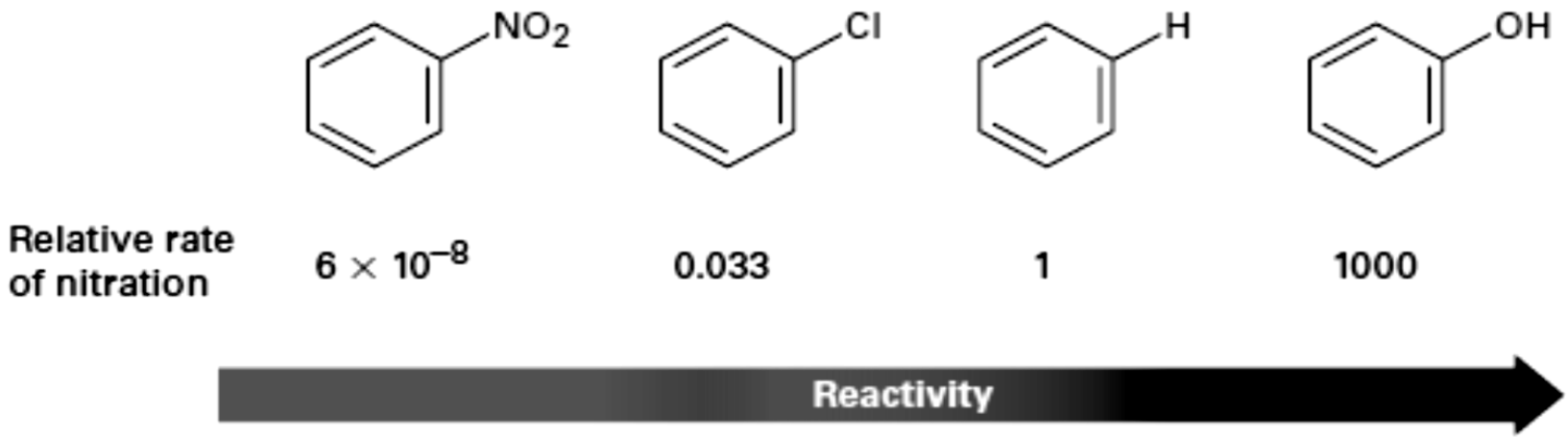
Substituent Effects in Substituted Aromatic Rings

- Only one product can form when an electrophilic substitution occurs on benzene, but what would happen if we were to carry out a reaction on an aromatic ring that already has a substituent? A substituent already present on the ring has two effects.

1. **Substituents affect the reactivity of the aromatic ring**

Some substituents activate the ring, making it more reactive than benzene, and some deactivate the ring, making it less reactive than benzene. In aromatic nitration, for instance, an **OH** substituent makes the ring 1000 times more reactive than benzene, while an **NO2** substituent makes the ring

more than 10 million times less reactive.



2. Substituents affect the orientation of the reaction

The three possible disubstituted products—ortho, meta, and para—are usually not formed in equal amounts. Instead, the nature of the substituent already present on the benzene ring determines the position of the second substitution. An OH group directs substitution toward the ortho and para positions, for instance, while a carbonyl group such as CHO directs substitution primarily toward the meta position.

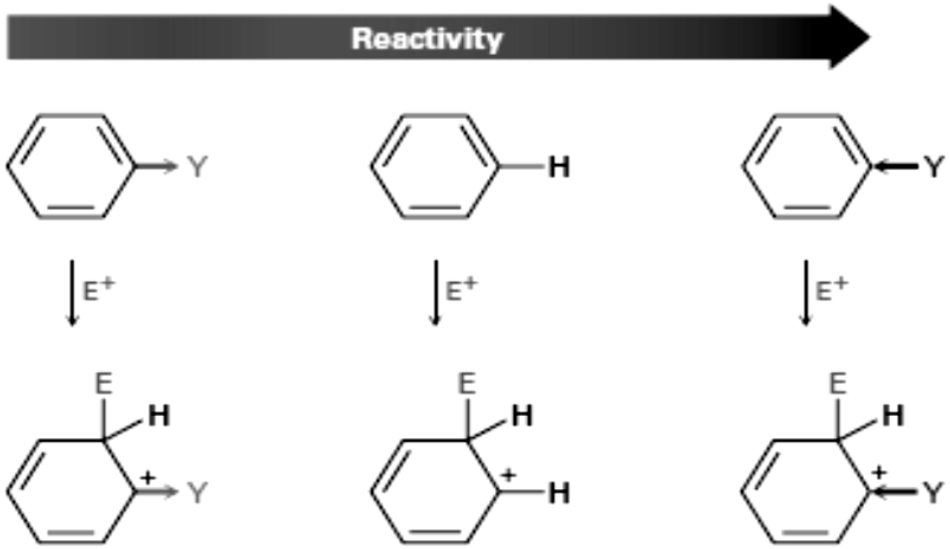
Note:

Substituents can be classified into three groups, ortho- and para-directing activators, ortho- and para-directing deactivators, and meta -directing deactivators. **There are no meta-directing activators**. Notice how the directing effect of a group correlates with its reactivity. All meta-directing groups are strongly deactivating, and most ortho- and para-directing groups are activating. The halogens are unique in being ortho- and para-directing but weakly deactivating.

Activation and Deactivation of Aromatic Rings

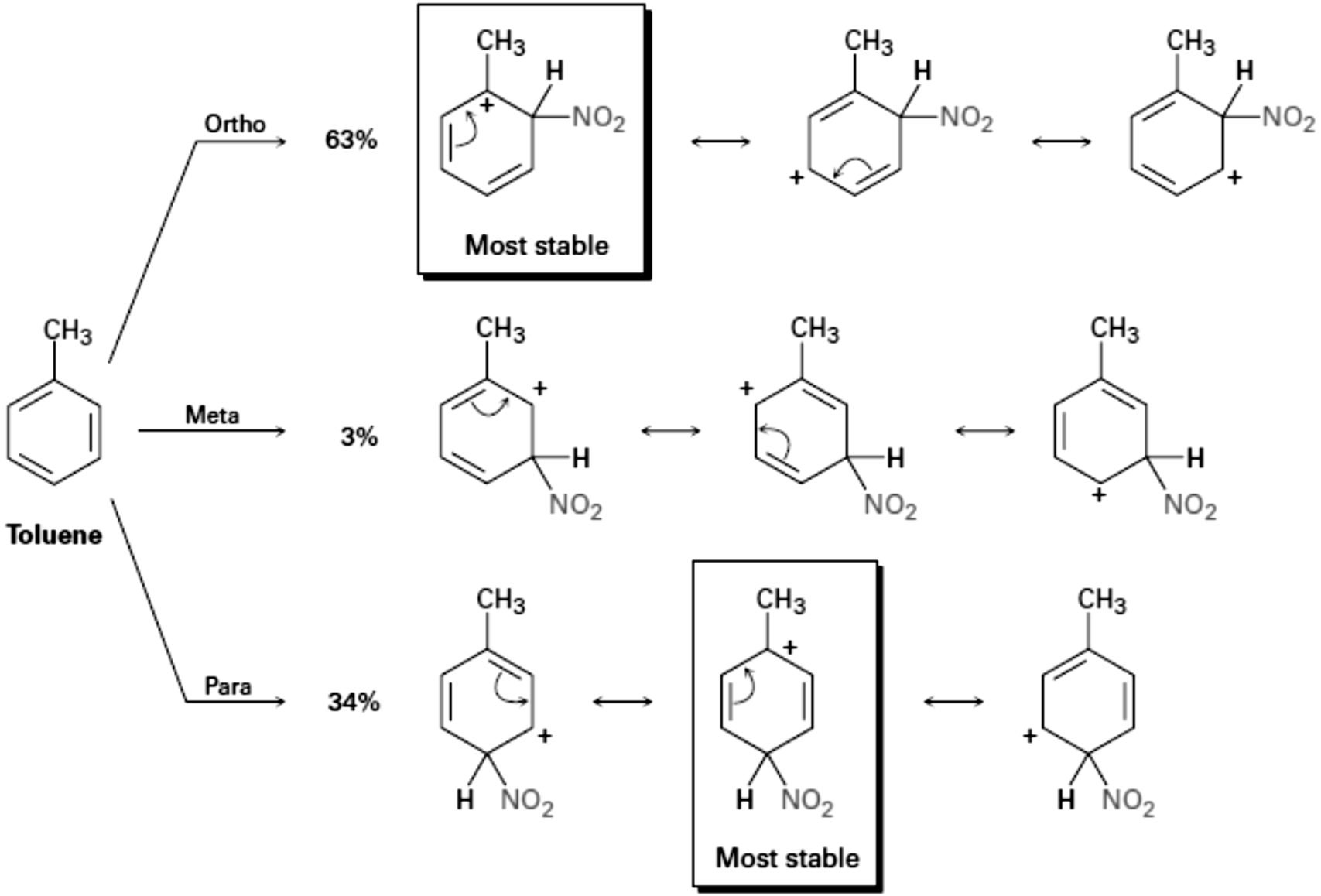
The common characteristic of all activating groups is that they donate electrons to the ring, thereby making the ring more electron-rich, stabilizing the carbocation intermediate, and lowering the activation energy for its formation.

Conversely, the common characteristic of all deactivating groups is that they withdraw electrons from the ring, thereby making the ring more electron-poor, destabilizing the carbocation intermediate, and raising the activation energy for its formation.



Y withdraws electrons; carbocation intermediate is less stable, and ring is less reactive.

Y donates electrons; carbocation intermediate is more stable, and ring is more reactive.



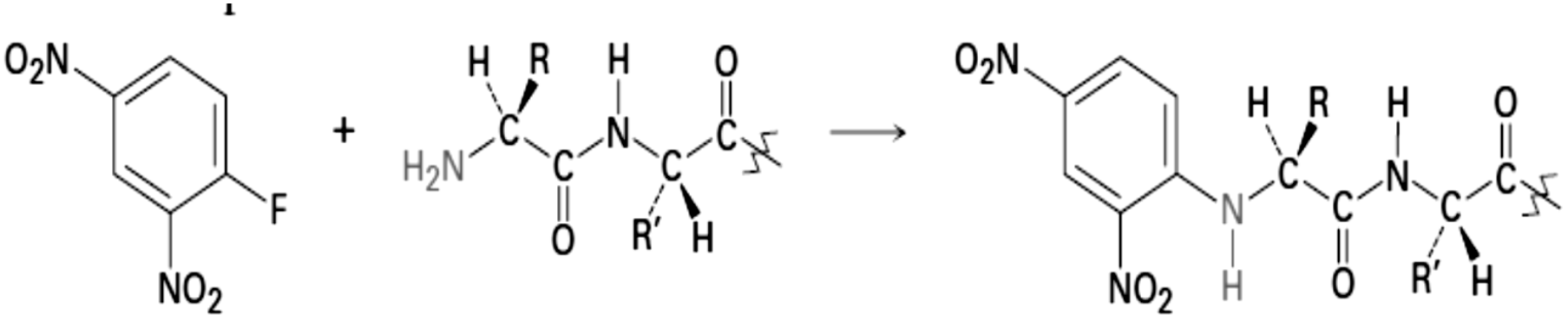
Carbocation intermediates in the nitration of toluene. Ortho and para intermediates are more stable than the meta intermediate because the positive charge is on a tertiary carbon rather than a secondary carbon.

Substituent Effects in Electrophilic Aromatic Substitution

Substituent	Reactivity	Orienting effect	Inductive effect	Resonance effect
$-CH_3$	Activating	Ortho, para	Weak donating	—
$-OH$, $-NH_2$	Activating	Ortho, para	Weak withdrawing	Strong donating
$-F$, $-Cl$ $-Br$, $-I$	Deactivating	Ortho, para	Strong withdrawing	Weak donating
$-NO_2$, $-CN$, $-CHO$, $-CO_2R$ $-COR$, $-CO_2H$	Deactivating	Meta	Strong withdrawing	Strong withdrawing

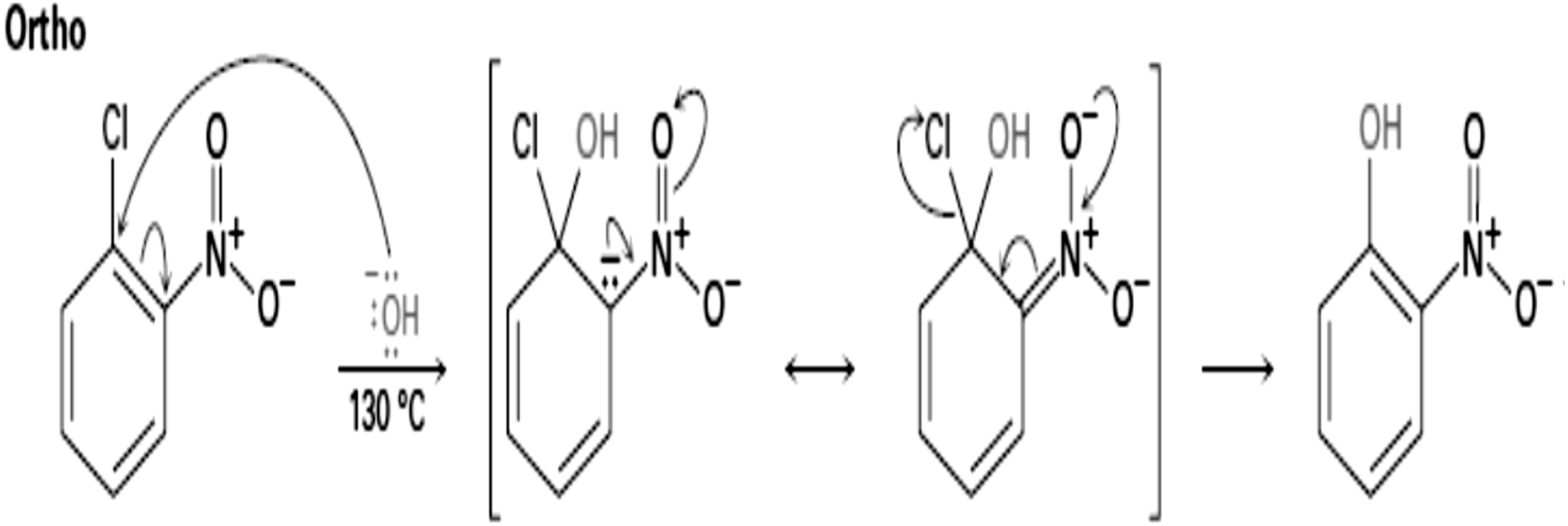
Nucleophilic Aromatic Substitution

Nucleophilic aromatic substitution is much less common than electrophilic substitution but nevertheless does have certain uses. One such use is the reaction of proteins with 2,4-dinitrofluorobenzene, known as Sanger's reagent, to attach a "label" to the terminal NH2 group of the amino acid at one end of the protein chain.

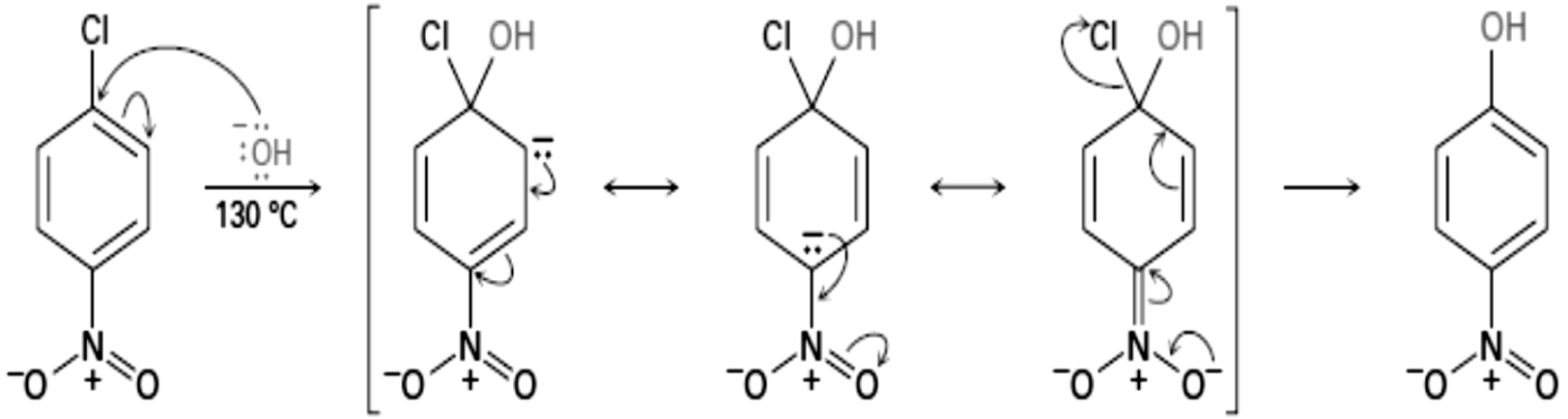


2,4-Dinitro-fluorobenzene **A protein** **A labeled protein**

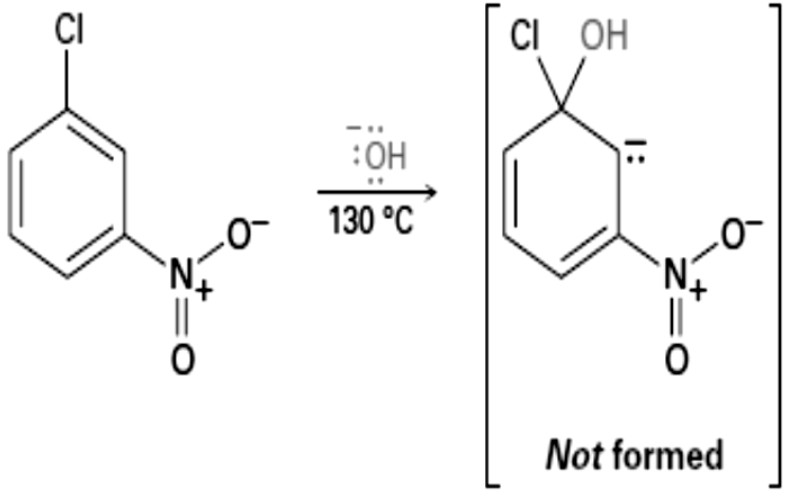
Nucleophilic aromatic substitution occurs only if the aromatic ring has an electron-withdrawing substituent in a position ortho or para to the leaving group to stabilize the anion intermediate through resonance . A meta substituent offers no such resonance stabilization. Thus, p-chloronitrobenzene and o-chloronitrobenzene react with hydroxide ion at 130 °C to yield substitution products, but m-chloronitrobenzene is inert to OH2.



Para



Meta



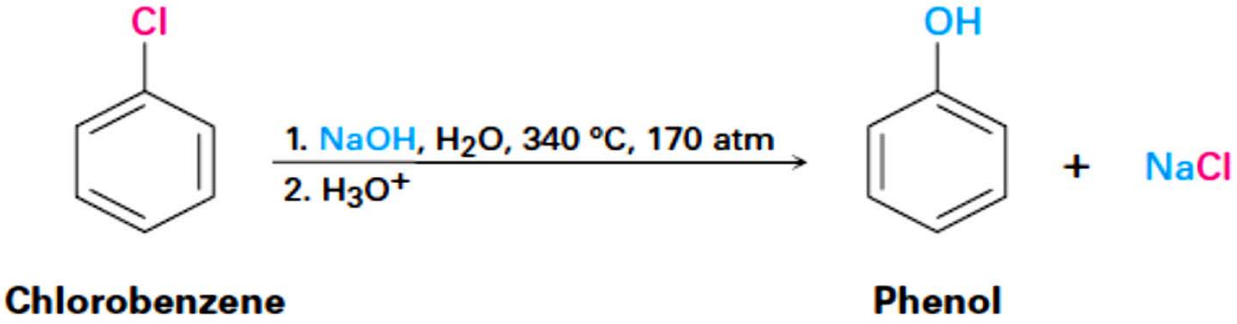
The differences between electrophilic and nucleophilic aromatic substitutions. Electrophilic substitutions are favored by electron-donating substituents, which stabilize a carbocation intermediate, while nucleophilic substitutions are favored by electron-withdrawing substituents, which stabilize a carbanion intermediate.

Thus, the electron-withdrawing groups that deactivate rings for electrophilic substitution (nitro, carbonyl, cyano, and so forth) activate them for nucleophilic substitution. these groups are meta directors in electrophilic substitution but are ortho–para directors in nucleophilic substitution.

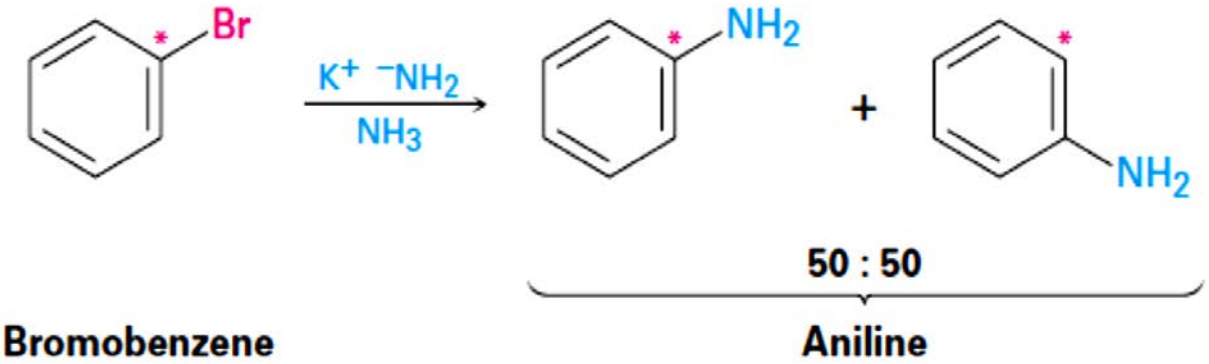
Electrophilic substitutions replace hydrogen on the ring, while nucleophilic substitutions replace a leaving group, usually halide ion.

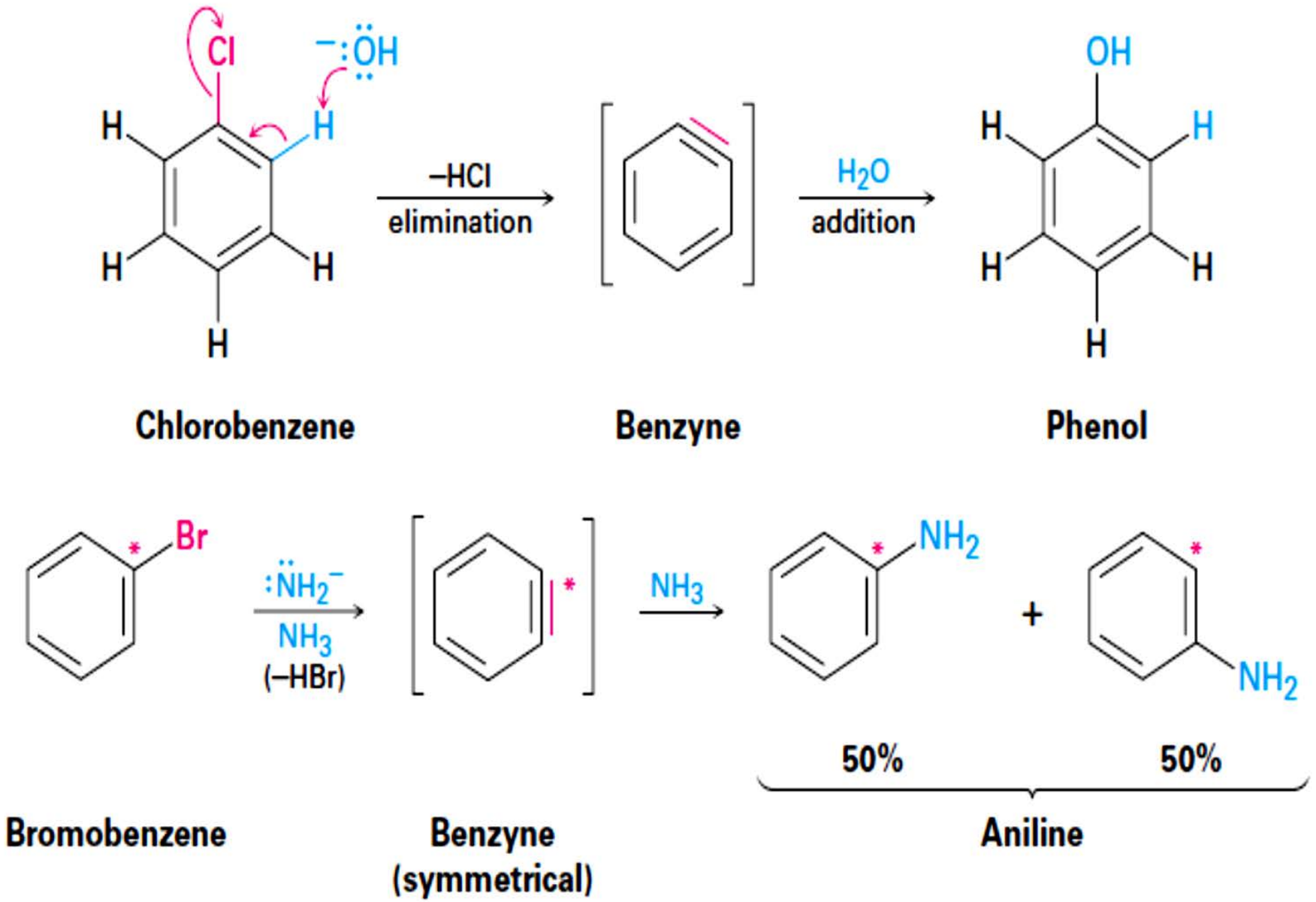
Benzyne

Halobenzenes without electron-withdrawing substituents don't react with nucleophiles under most conditions. At high temperature and pressure, however, even chlorobenzene can be forced to react.



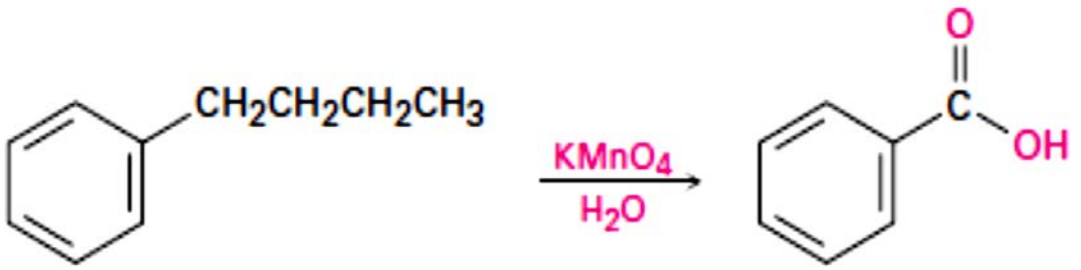
A similar substitution reaction occurs with other strong bases. Treatment of bromobenzene with potassium amide (KNH2) in liquid NH3 solvent, for instance, gives aniline.




Cl
−:ÖH
H
H
H
H
H
–HCl
elimination
H2O
addition
OH
H
H
H
H
H
Chlorobenzene
Benzyne
Phenol
Br
*
:NH2−
NH3
(–HBr)
NH3
NH2
NH2
+
50%
50%
Bromobenzene
Benzyne
(symmetrical)
Aniline

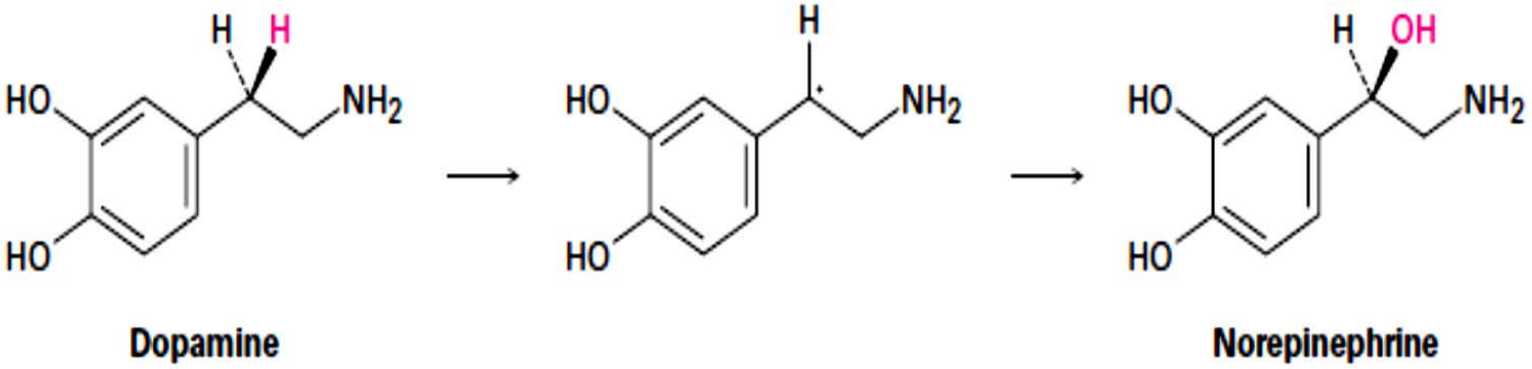
Oxidation of Alkyl Side Chains

Despite its unsaturation, the benzene ring is inert to strong oxidizing agents such as KMnO4 , reagents that will cleave alkene carbon–carbon bonds . It turns out, however, that the presence of the aromatic ring has a dramatic effect on alkyl side chains. Alkyl side chains react rapidly with oxidizing agents and are converted into carboxyl groups, CO2H.The net effect is conversion of an alkylbenzene into a benzoic acid. Butylbenzene is oxidized by aqueous KMnO4 to give benzoic acid, for instance.



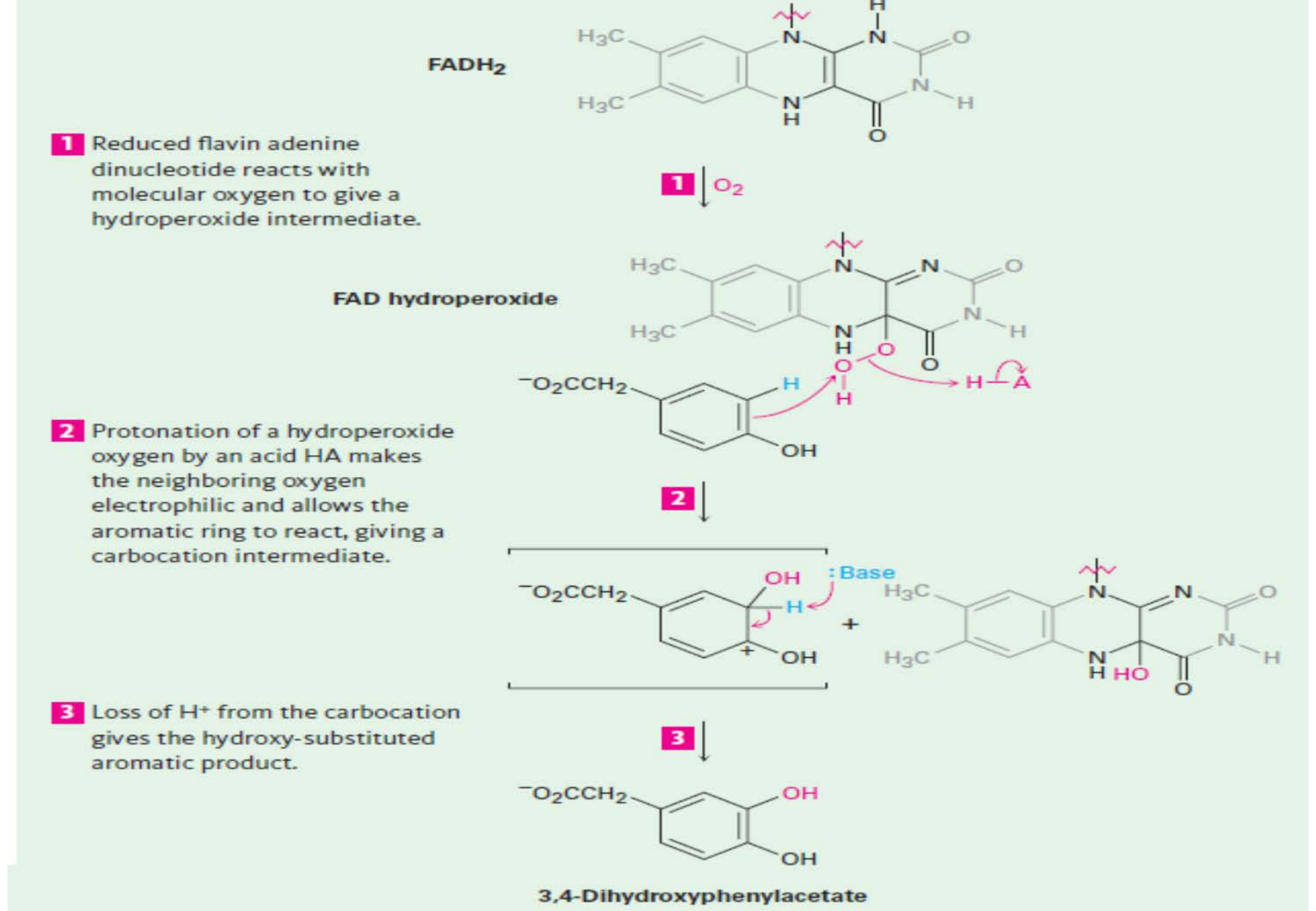
Butylbenzene **Benzoic acid (85%)**

Analogous side-chain oxidations occur in various biosynthetic pathways. The neurotransmitter norepinephrine, for instance, is biosynthesized from dopamine by a benzylic hydroxylation reaction. The process is catalyzed by the copper-containing enzyme dopamine b-monooxygenase and occurs by a radical mechanism. A copper–oxygen species in the enzyme first abstracts the pro-R benzylic hydrogen to give a radical, and a hydroxyl is then transferred from copper to carbon.



Dopamine

Norepinephrine



Mechanism of the electrophilic hydroxylation of *p*-hydroxyphenylacetate, by reaction with FAD hydroperoxide. The hydroxylating species is an "OH^+ equivalent" that arises by protonation of FAD hydroperoxide.