Organic Chemistry
Aromatic Compounds

Arenes:

compounds containing both aliphatic and aromatic parts.

Alkylbenzenes

Alkenylbenzenes

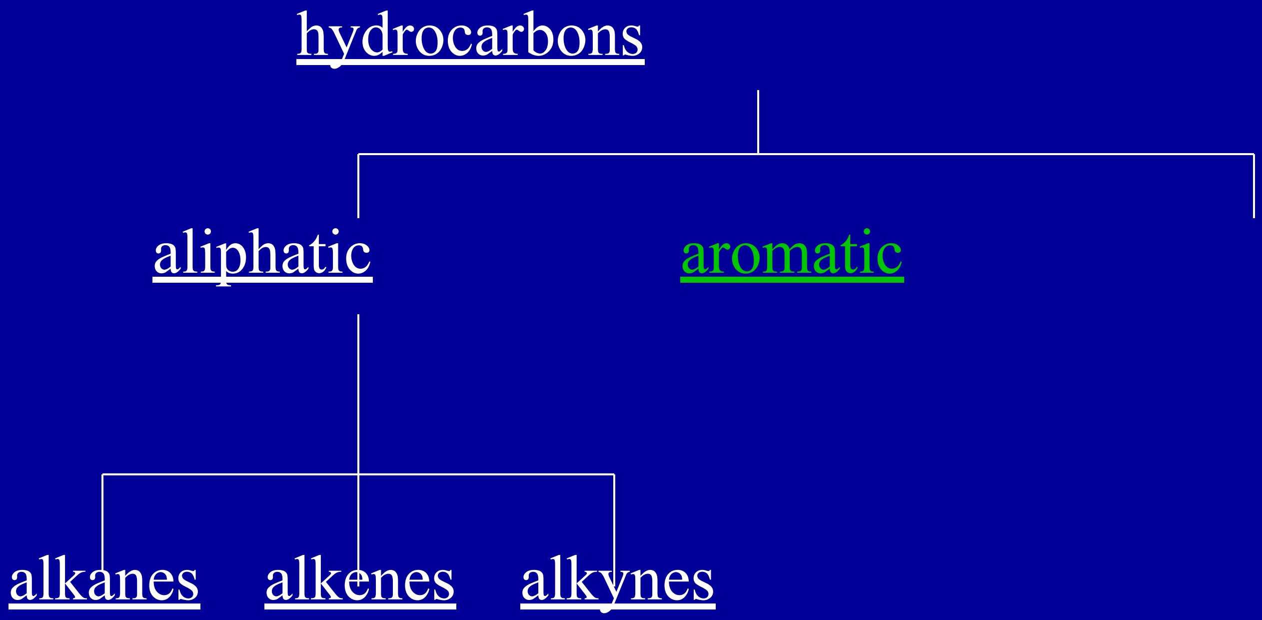
Alkynylbenzenes

Etc.

Emphasis on the effect that one part has on the chemistry of the other half.

Reactivity & orientation

Aromatic Hydrocarbons



hydrocarbons

aliphatic

aromatic

alkanes

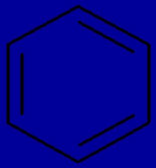
alkenes

alkynes

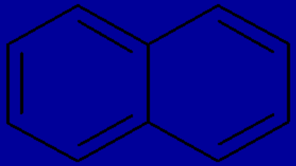
Aliphatic compounds: open-chain compounds and ring compounds that are chemically similar to open-chain compounds. Alkanes, alkenes, alkynes, dienes, alicyclics, etc.

Aromatic compounds: unsaturated ring compounds that are far more stable than they should be and resist the addition reactions typical of unsaturated aliphatic compounds. Benzene and related compounds.

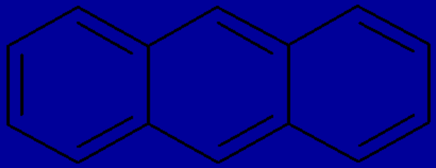
Nomenclature – common names



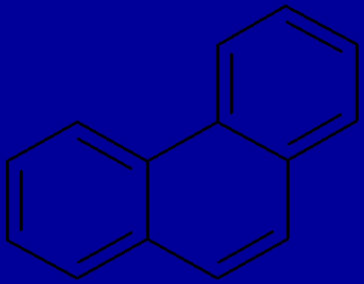
benzene



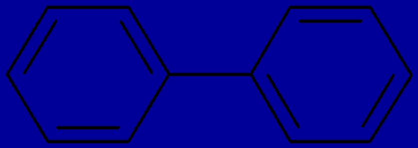
naphthalene



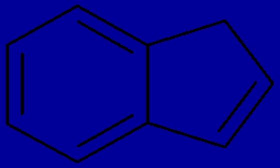
anthracene



phenanthrene

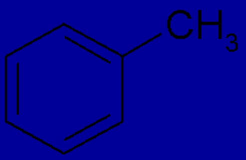


biphenyl

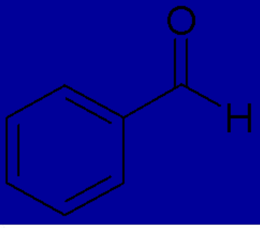


indene

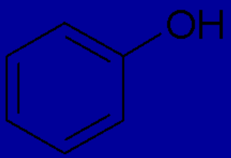
Nomenclature – common names



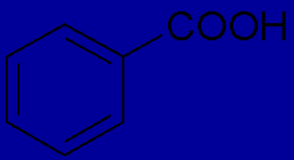
toluene



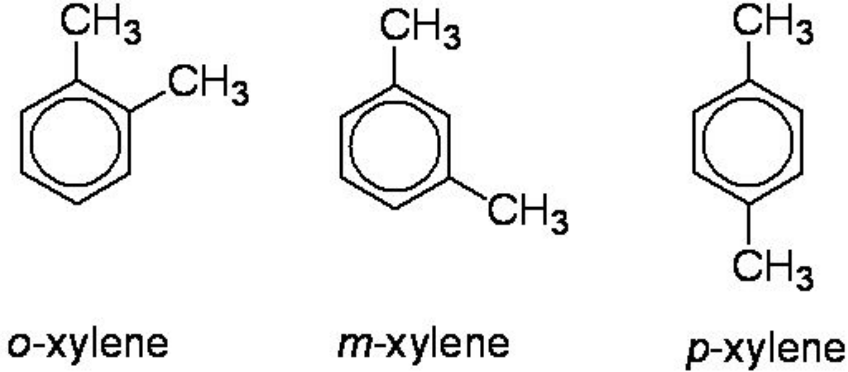
benzaldehyde



phenol



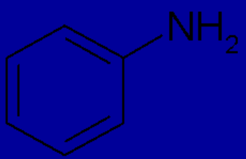
benzoic acid



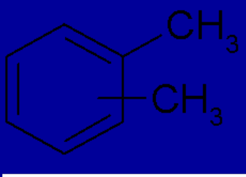
o-xylene

m-xylene

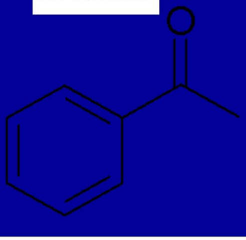
p-xylene



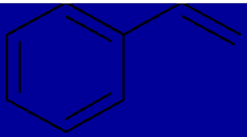
aniline



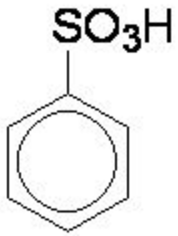
xylenes (ortho, metal, and para)



acetophenone



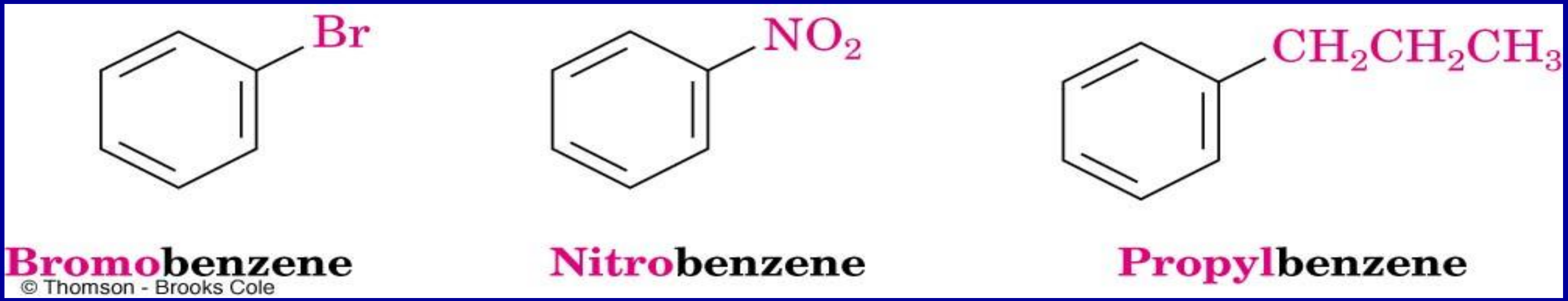
styrene



benzenesulfonic acid

Systematic Nomenclature

- Monosubstituted benzenes
- Hydrocarbon with *benzene* as parent
- C_6H_5Br = bromobenzene
- $C_6H_5NO_2$ = nitrobenzene
- $C_6H_5CH_2CH_2CH_3$ = propylbenzene



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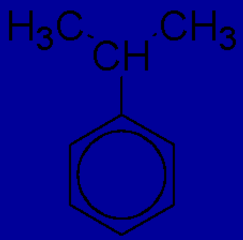
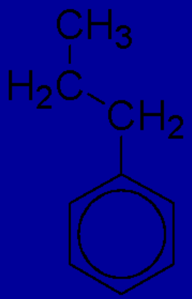
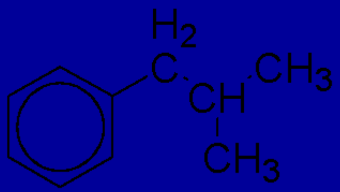
others named as “alkylbenzenes”:



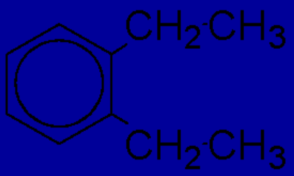
isopropylbenzene



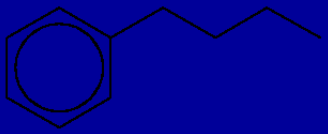
n-propylbenzene



isobutylbenzene



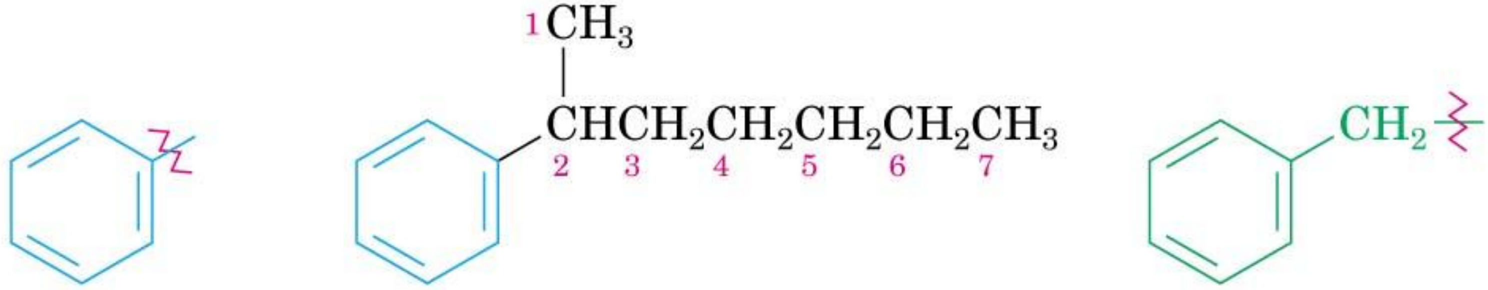
o-diethylbenzene



n-butylbenzene

The Phenyl Group

- When a benzene ring is a substituent, the term **phenyl** is used (for $C_6H_5^{\text{羊}}$)
- You may also see “Ph” or “φ” in place of “C_6H_5”
- “**Benzyl**” refers to “$C_6H_5CH_2^{\text{羊}}$”

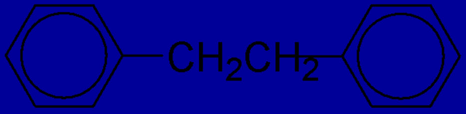


A phenyl group | **2-Phenylheptane** | **A benzyl group**

Use of phenyl

C_6H_5- = “phenyl”

2-methyl-3-phenylheptane



1,2-diphenylethane

do not confuse phenyl (C_6H_5-) with benzyl ($C_6H_5CH_2$-)

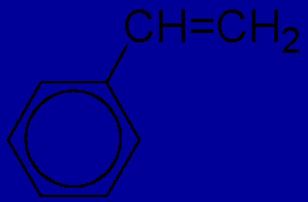
Nomenclature: Side Chains

- If side chain has < 6 carbons
  - Alkyl benzene

- If side chain has > 6 carbons
  - Phenyl alkane

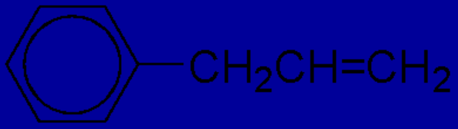
Alkenylbenzenes, nomenclature:

Special name

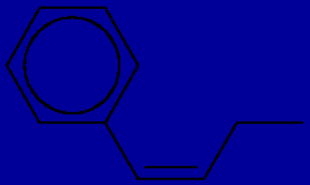


styrene

Rest are named as substituted alkenes

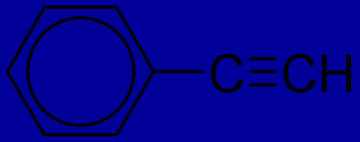


3-phenylpropene
(allylbenzene)



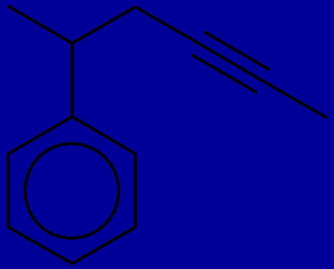
(*Z*)-1-phenyl-1-butene

Alkynylbenzenes, nomenclature:



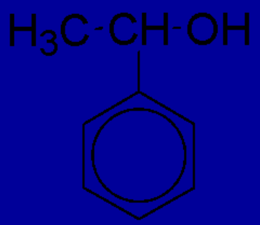
phenylacetylene

phenylethyne



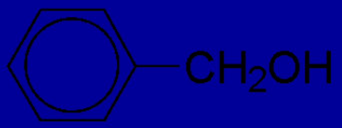
5-phenyl-2-hexyne

Alcohols, etc., nomenclature:

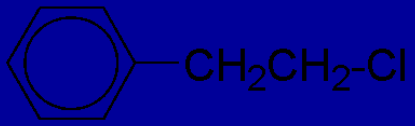


1-phenylethanol

α–phenylethyl alcohol

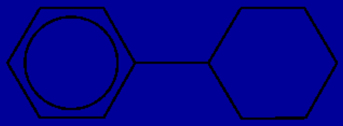


benzyl alcohol



1-chloro-2-phenylethane

β-phenylethyl chloride

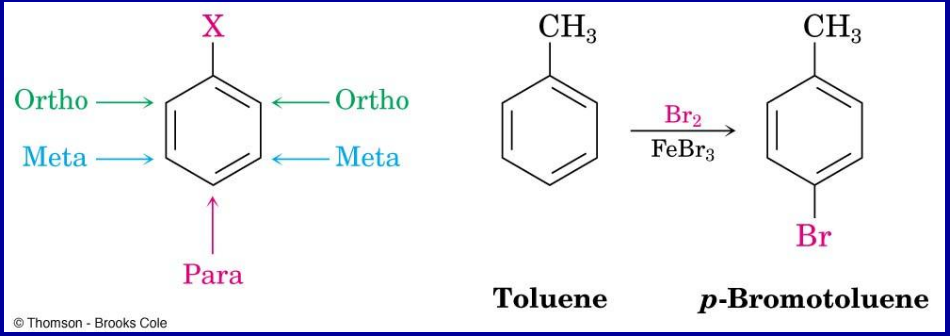


cyclohexylbenzene

phenylcyclohexane

Nomenclature Disubstituted Benzene

- Relative positions on a benzene ring
  - ***ortho- (o)*** on adjacent carbons (1,2)
  - ***meta- (m)*** separated by one carbon (1,3)
  - ***para- (p)*** separated by two carbons (1,4)
- Describes reaction patterns ("occurs at the para position")



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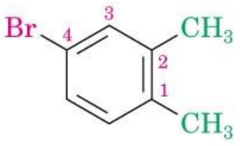
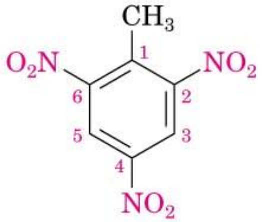
Nomenclature More Than Two Substituents

- Choose numbers to get lowest possible values
- List substituents alphabetically with hyphenated numbers
- Common names, such as “toluene” can serve as root name (as in TNT)



4-Bromo-1,2-dimethylbenzene

2-Chloro-1,4-dinitrobenzene



2,4,6-Trinitrotoluene (TNT)

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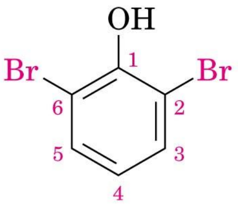
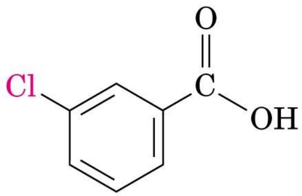


2,6-Dibromophenol



m-Chlorobenzoic acid

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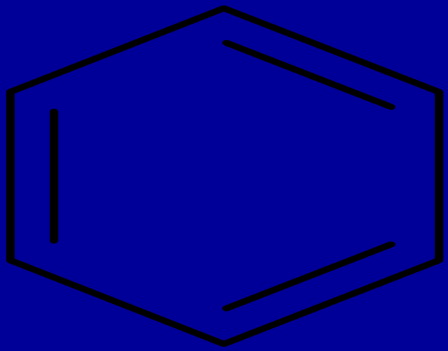
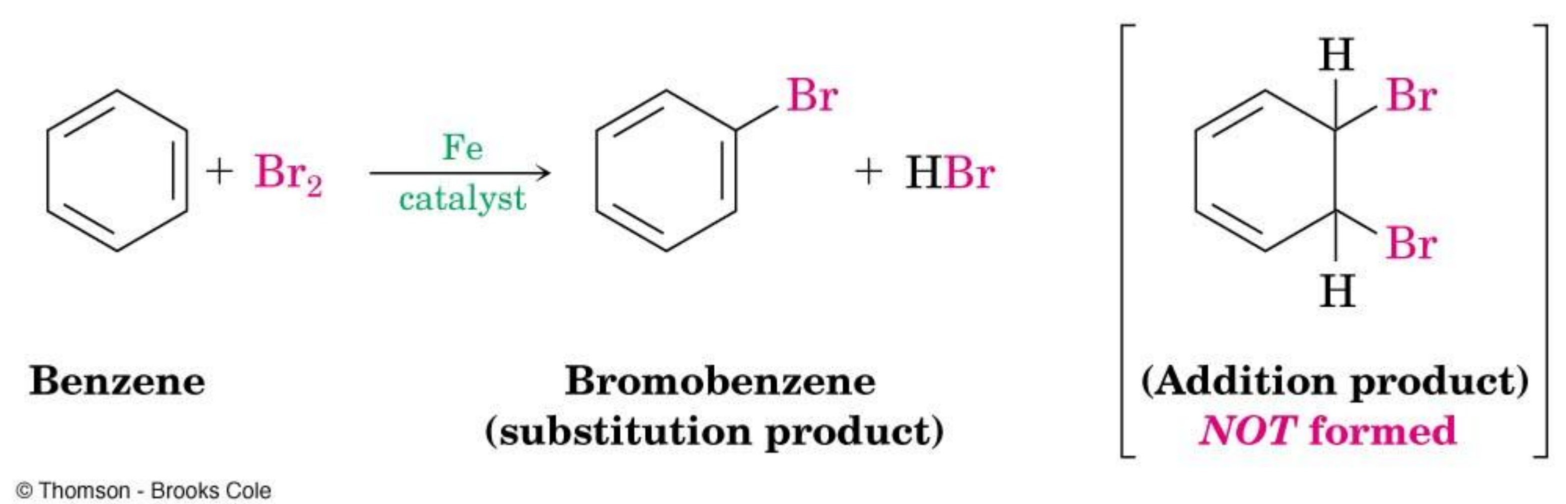
Benzene



- Three double bonds
- Unreactive towards normal reagents (compare to alkenes)
- Very stable
- Why?
- How can we get benzene to react?
- Can we control these reactions?

Observations: Reactions of Benzene

- Benzene reacts slowly with Br_2
- Product is bromobenzene
- Substitution Product
- Addition products are not observed.

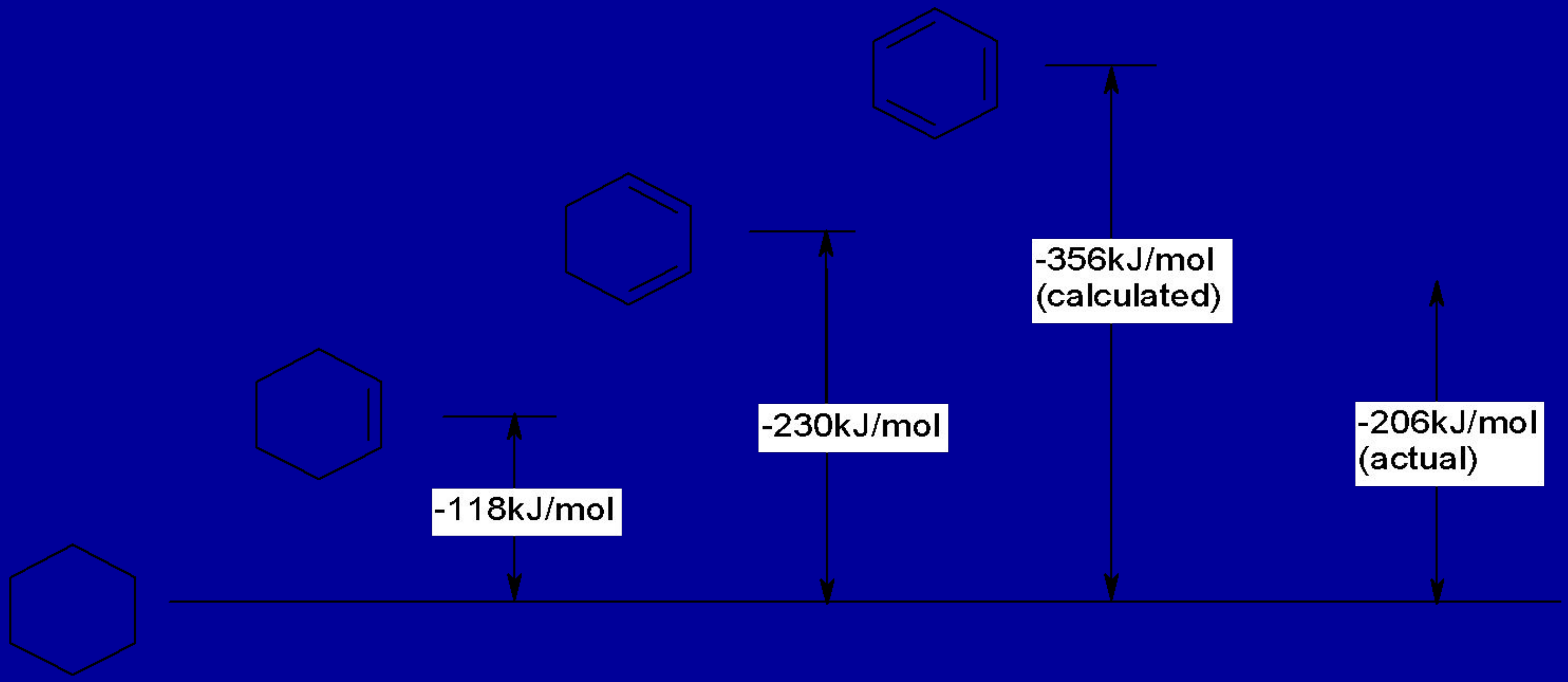


Stability of Benzene

- $KMnO_4$
  - Reacts with alkenes
  - No reaction with benzene
- HCl
  - Reacts with alkenes
  - No reaction with benzene
- HBr
  - Reacts with alkenes
  - No reaction with benzene

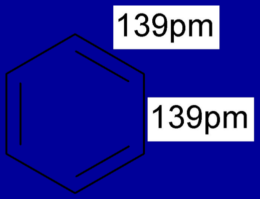
Stability of Benzene

- Heat of Hydrogenation data



Structure of Benzene

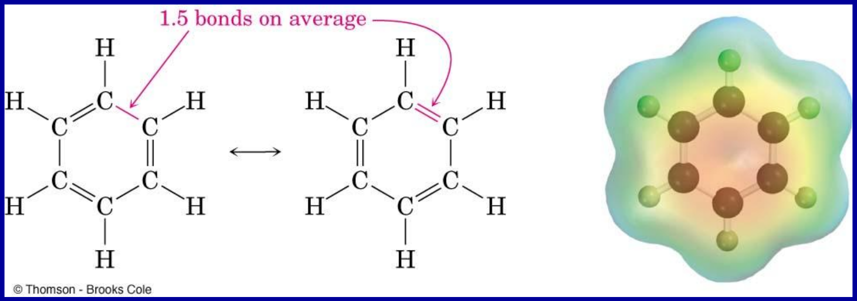
- C-C bond length



C-C: 154pm

C=C: 134pm

- Electrostatic potential
- Electron density at C is the same
- planar



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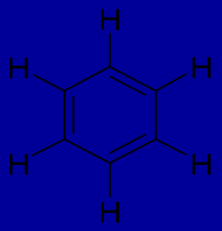
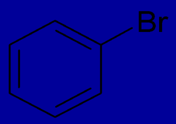
Structure of Benzene

- August Kekule proposed:

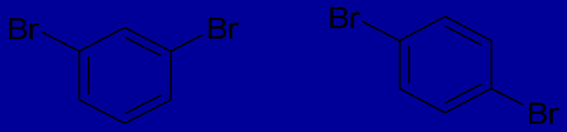




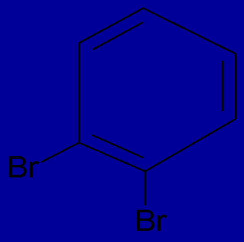
- 1,3,5-cyclohexatriene structure
- Explained single monobromo product

Structure of Benzene

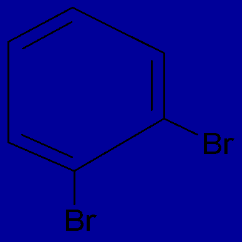
- Dibromobenzene



but



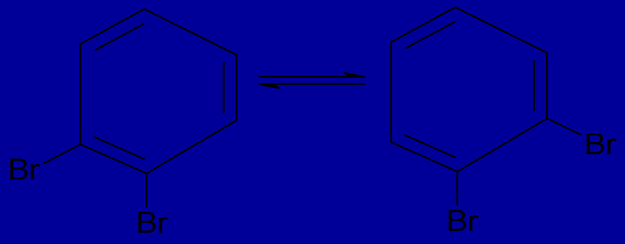
1,2-dibromo



1,6-dibromo

Structure of Benzene

- Issue was resolved by Kekule



1,2-dibromo

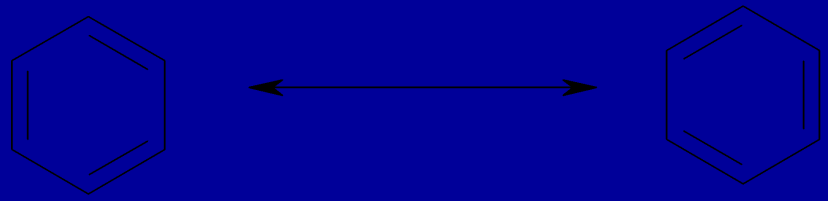
1,6-dibromo

Structure of Benzene

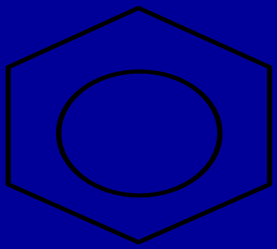
- Explains the observed products
- Does not explain
  - Unreactive nature of benzene
  - Observation of only substitution products
- A triene
  - As reactive as any alkene
  - Would give addition products
  - Not expected to be more stable

Structure of Benzene

- Resonance Hybrid

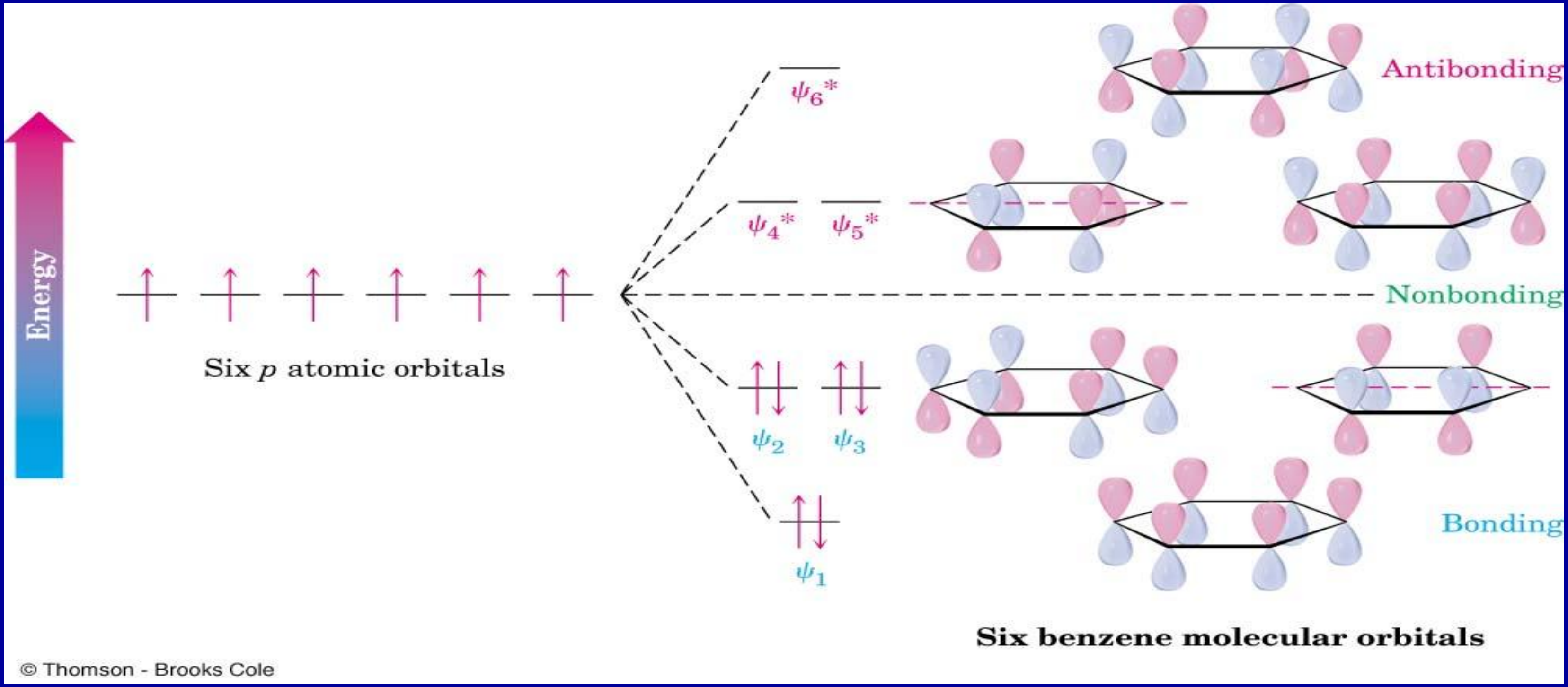


- Not
- Never
- -6.023×10^{23} points



Stability of Benzene

- MO Description
- 6 p atomic orbitals combine in cyclic manner
- Generate 6 molecular orbitals



Key Ideas on Benzene

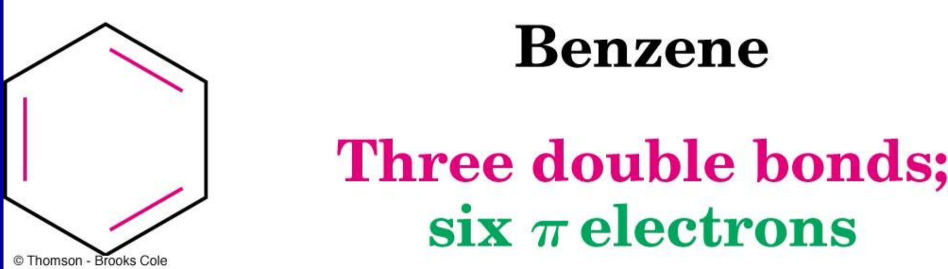
- Unusually stable
- heat of hydrogenation 150 kJ/mol lower than a cyclic triene
- Planar hexagon:
- bond angles are 120°
- carbon–carbon bond lengths 139 pm
- Undergoes substitution not addition
- Resonance hybrid
- One more important factor is the number of electrons in the cyclic orbital

Aromaticity

- E Huckel (1931)
  - Aromaticity is a property of certain molecules
  - Chemistry would be similar to benzene
  - Meet the following criteria
    - Planar
    - Mono cyclic system
    - Conjugated pi system
    - Contains 4n + 2 *π electrons*
- Can apply rules to variety of compounds and determine aromatic nature.
- Led to wild chase to make compounds
  - Met the rules
  - Violated the rules

Aromaticity and the 4*n* + 2 Rule

- Huckel's rule, based on calculations – a planar cyclic molecule with alternating double and single bonds has aromatic stability if it has ***4n+ 2*** *π electrons (n is 0,1,2,3,4*)
- For n=1: 4n+2 = 6
- **benzene** is stable and the electrons are delocalized



Benzene

Three double bonds; six π electrons

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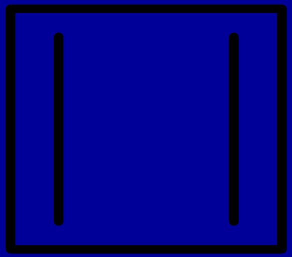
Compounds With 4n π Electrons Are Not Aromatic (May be Anti-aromatic)

- Planar, cyclic molecules with ***4 n π*** electrons are much *less* stable than expected (anti-aromatic)
- They will distort out of plane and behave like ordinary alkenes
- 4- and 8-electron compounds are not delocalized
- Alternating single and double bonds

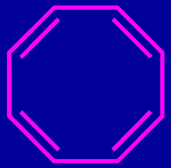
Cyclobutadiene

- Cyclobutadiene is so unstable that it dimerizes by a self-Diels-Alder reaction at low temperature

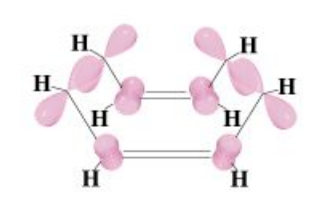


Cyclooctatetraene

- Cyclooctatetraene has four double bonds
- Behaves as if it were 4 separate alkenes
- It reacts with Br_2, $KMnO_4$, and HCl
- Non-planar structure



cyclooctatetraene

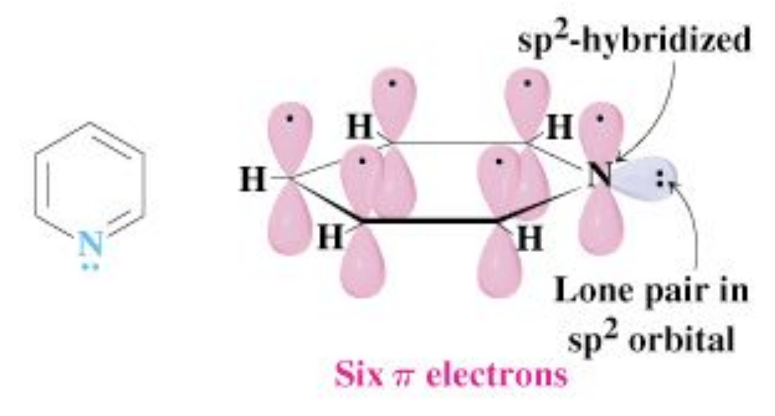


Aromatic Heterocycles

- Heterocyclic compounds contain elements other than carbon in a ring, such as N,S,O,P
- There are many heterocyclic aromatic compounds
- Cyclic compounds that contain only carbon are called carbocycles
- Nomenclature is specialized
- Four are important in biological chemistry

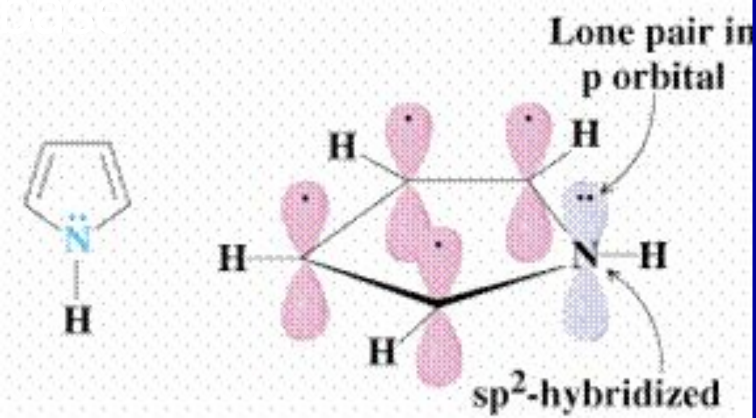
Pyridine

- A six-membered heterocycle with a nitrogen atom in its ring
- π electron structure resembles benzene (6 electrons)
- The nitrogen lone pair electrons are not part of the aromatic system (perpendicular orbital)
- Pyridine is a relatively weak base compared to normal amines but protonation does not affect aromaticity



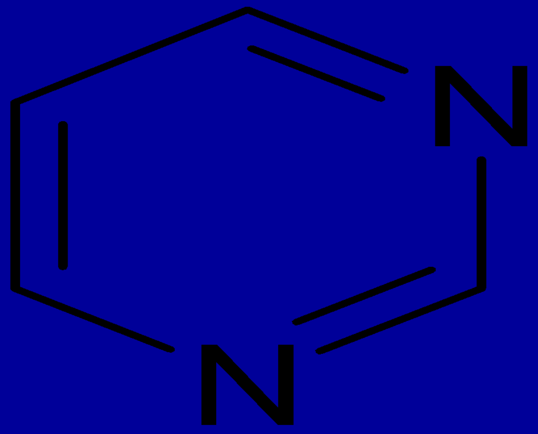
Pyrrole

- A five-membered heterocycle with one nitrogen
- Four *sp*^{2}-hybridized carbons with 4 *p* orbitals perpendicular to the ring and 4 p electrons
- Nitrogen atom is *sp*^{2}-hybridized, and lone pair of electrons occupies a *p* orbital (6 π electrons)
- Since lone pair electrons are in the aromatic ring, protonation destroys aromaticity, making pyrrole a very weak base



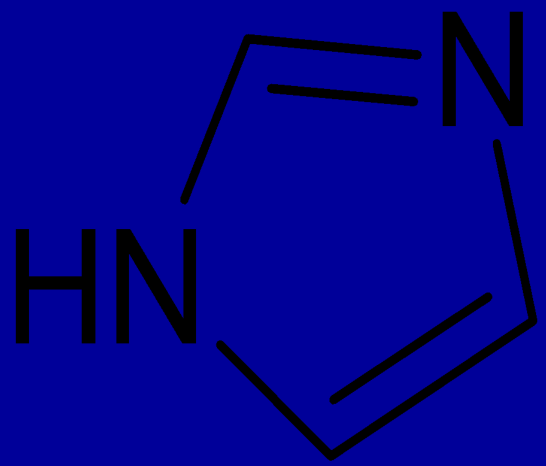
Pyrimidine

- Similar to benzene
- 3 pi bonds
- 4n + 2 pi electrons
- aromatic



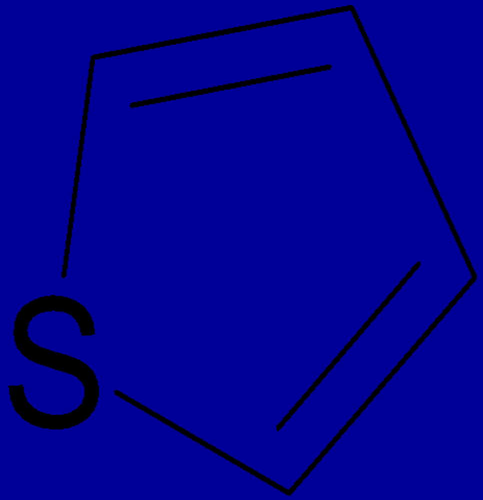
Imidazole

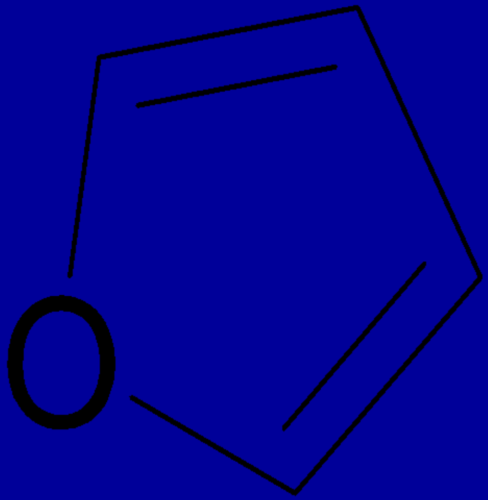
- Similar to pyrrole
- Pair of non-bonding electrons on N used
- 4n + 2 pi electrons



Thiophene and Furan

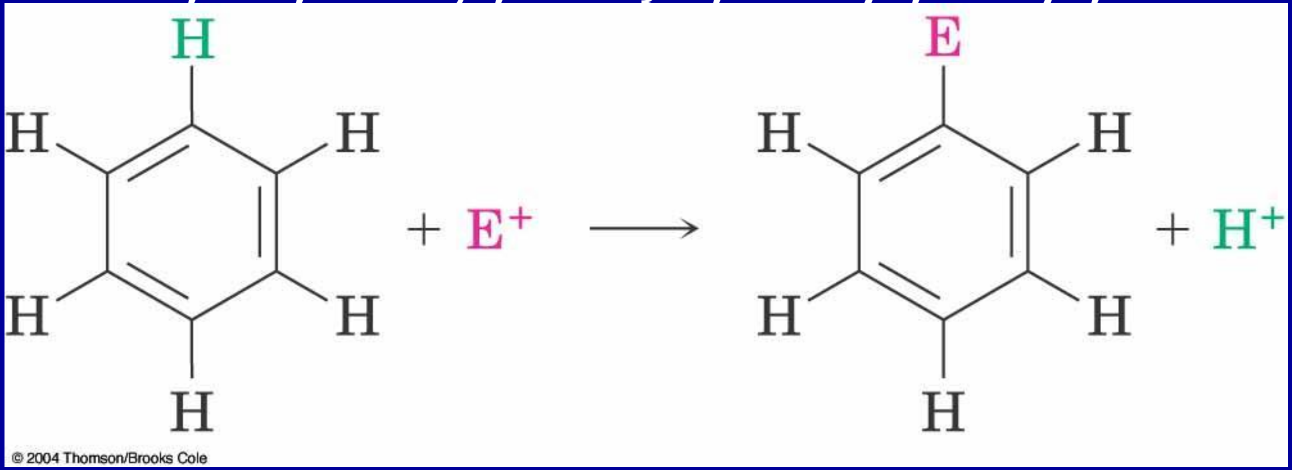
- Non-bonding electrons are used
- 4n + 2 pi electrons





Substitution Reactions of Benzene

- Benzene is aromatic: a cyclic conjugated compound with 6 π electrons
- Reaction with E^+ Leads to Substitution
- Aromaticity of Benzene is retained
- E^+ = Br, Cl, NO_2 , SO_3H, Alkyl, Acyl, etc



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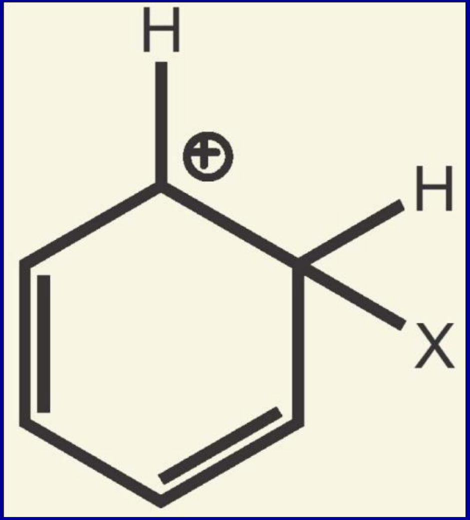
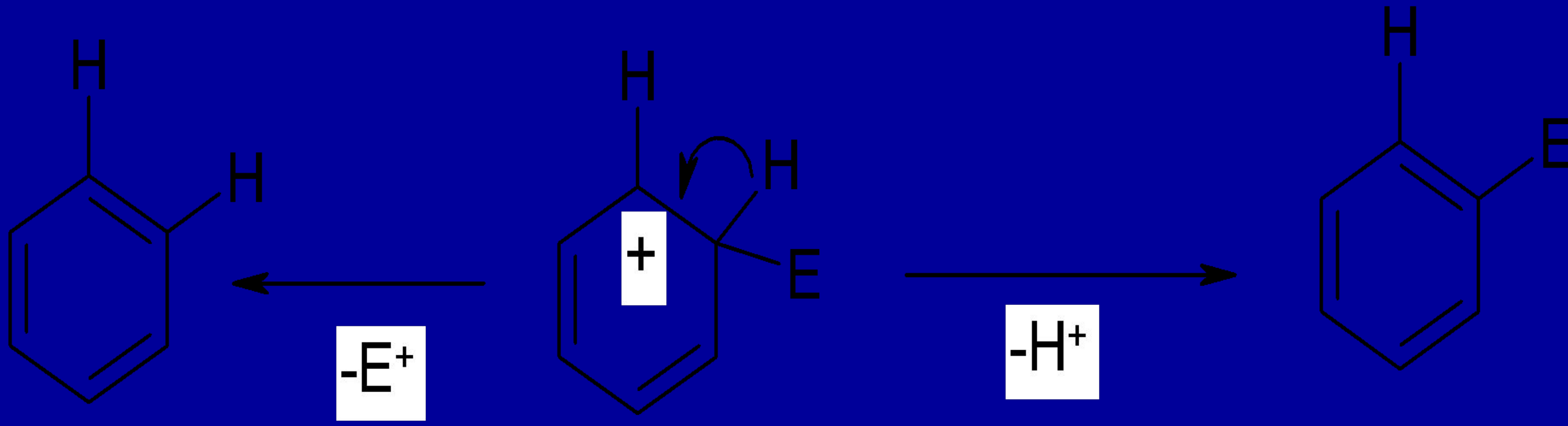
Aromatic Substitutions

- The proposed mechanism for the reaction of benzene with electrophiles involves a cationic intermediate
- first proposed by G. W. Wheland of the University of Chicago
- Often called the Wheland intermediate



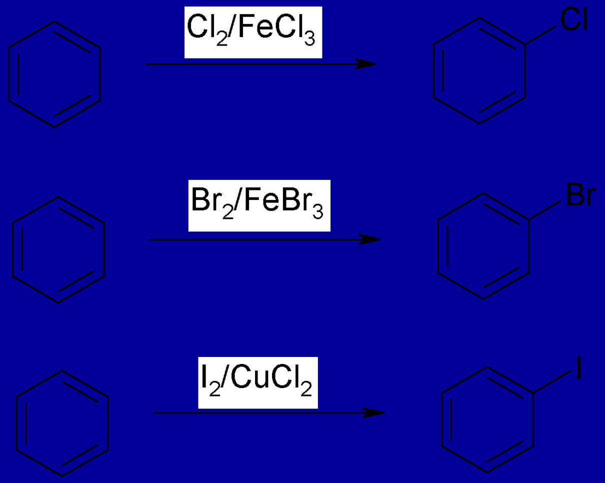
Chemistry of the Intermediate

- Loss of a proton leads to rearomatization and substitution
- Loss of E^+ returns to starting material



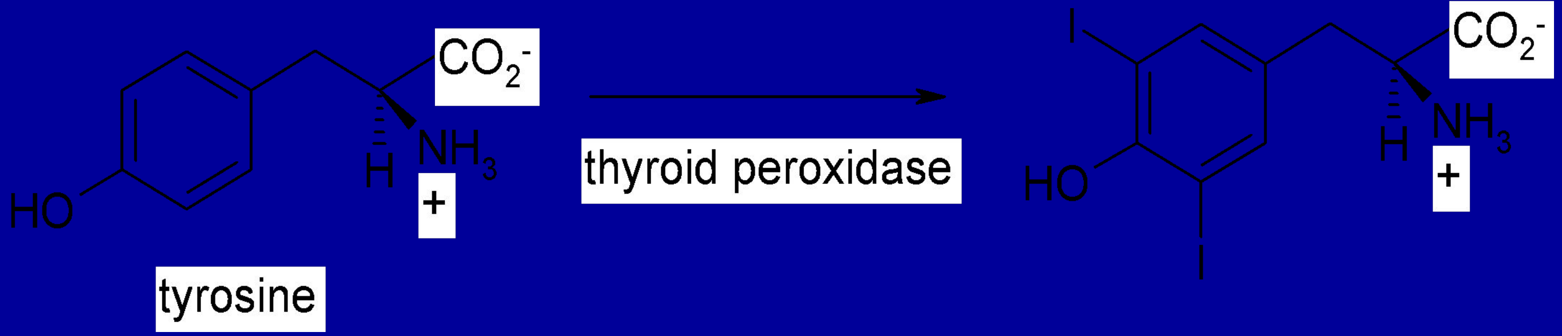
Halogenation

- Add Cl, Br, and I
- Must use Lewis acid catalyst
- F is too reactive and gives very low yields



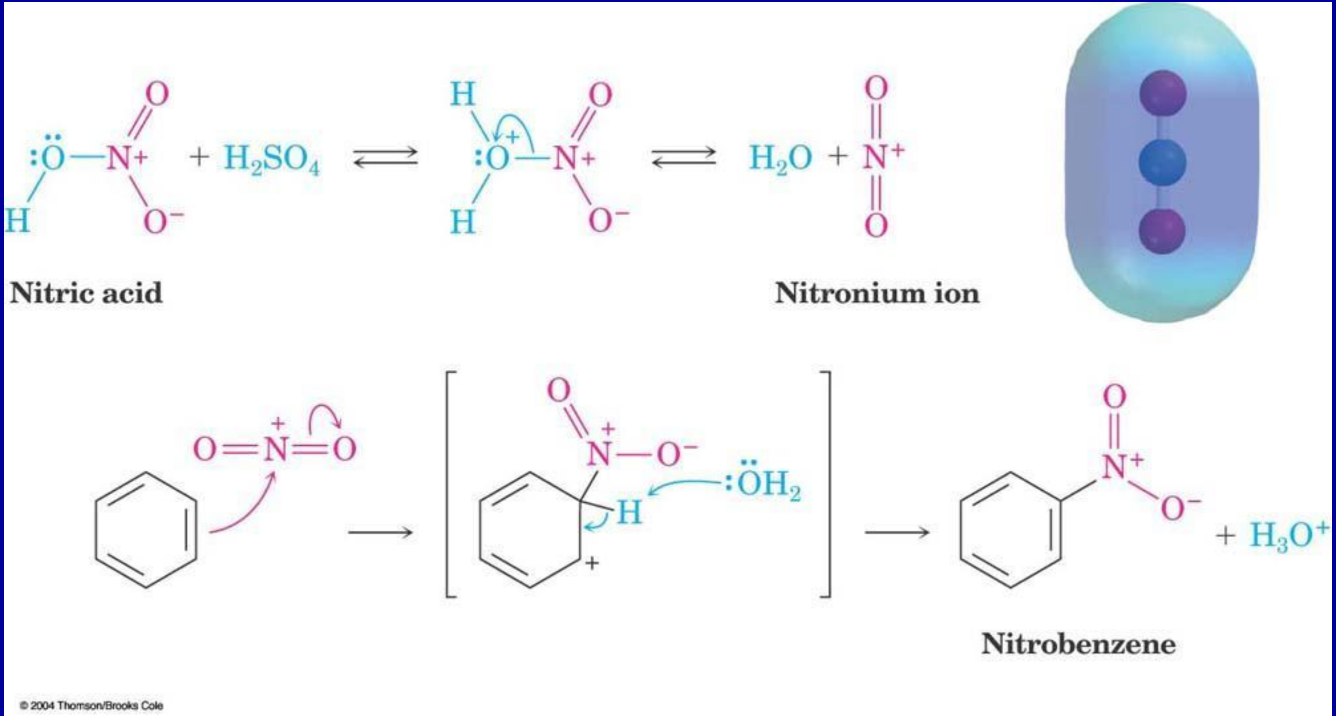
Biological Halogenation

- Accomplished during biosynthesis of
- thyroxine



Aromatic Nitration

- The combination of nitric acid and sulfuric acid produces NO_2^+ (nitronium ion)
- The reaction with benzene produces nitrobenzene



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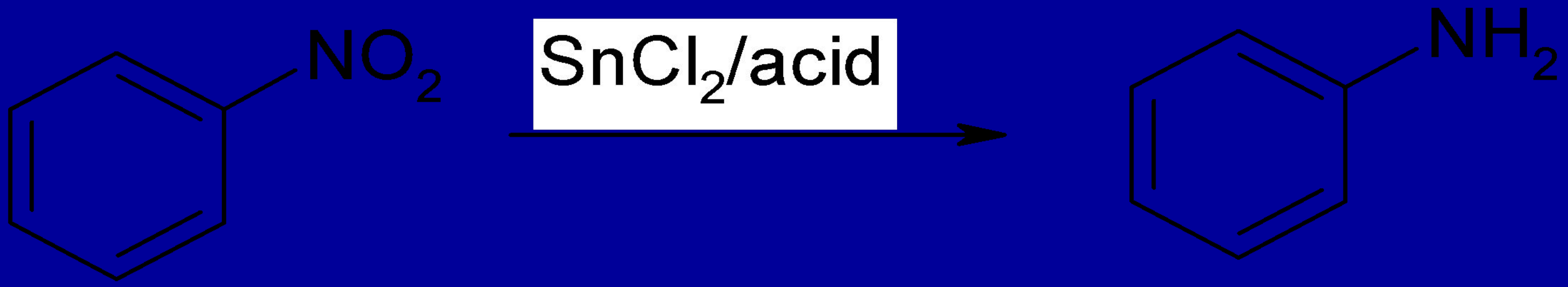
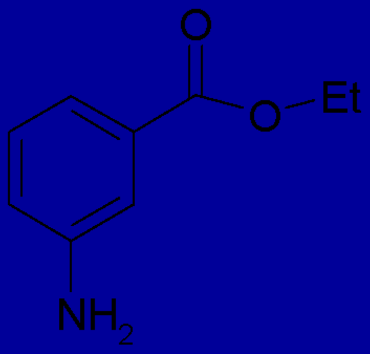
Nitrobenzenes: Precursors to Anilines

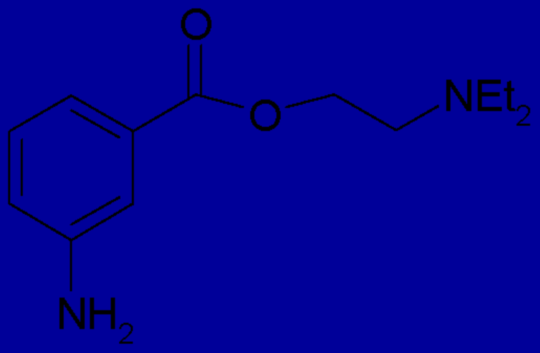
- Nitric acid destroys alkenes through [O]
- In sulfuric acid reacts with benzene giving nitrobenzene
- Nitrobenzene may be reduced to aniline
- Aniline useful precursors to many industrially important organic compounds



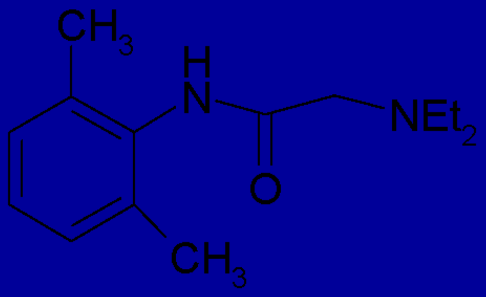
Important Anilines



benzocaine



procaine



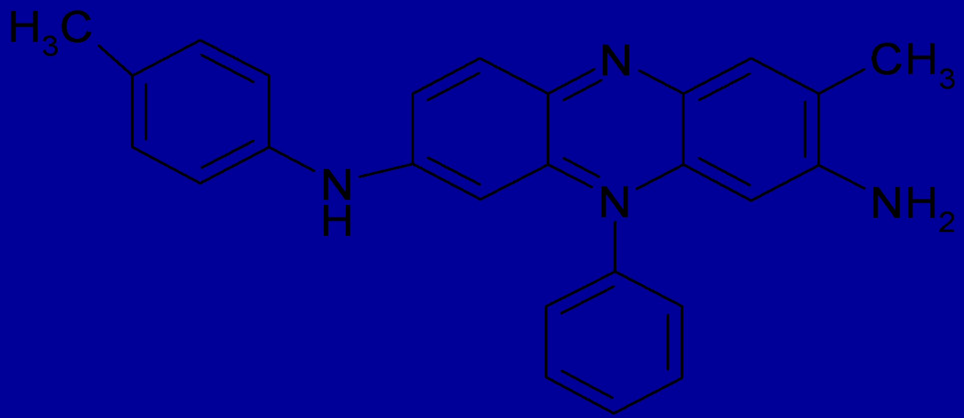
lidocaine

Aromatic Dyes

- William Henry Perkin
- Age 17 (1856)
- Undergraduate student in medicine
- Reacted aniline with potassium dichromate
- Tarry mess

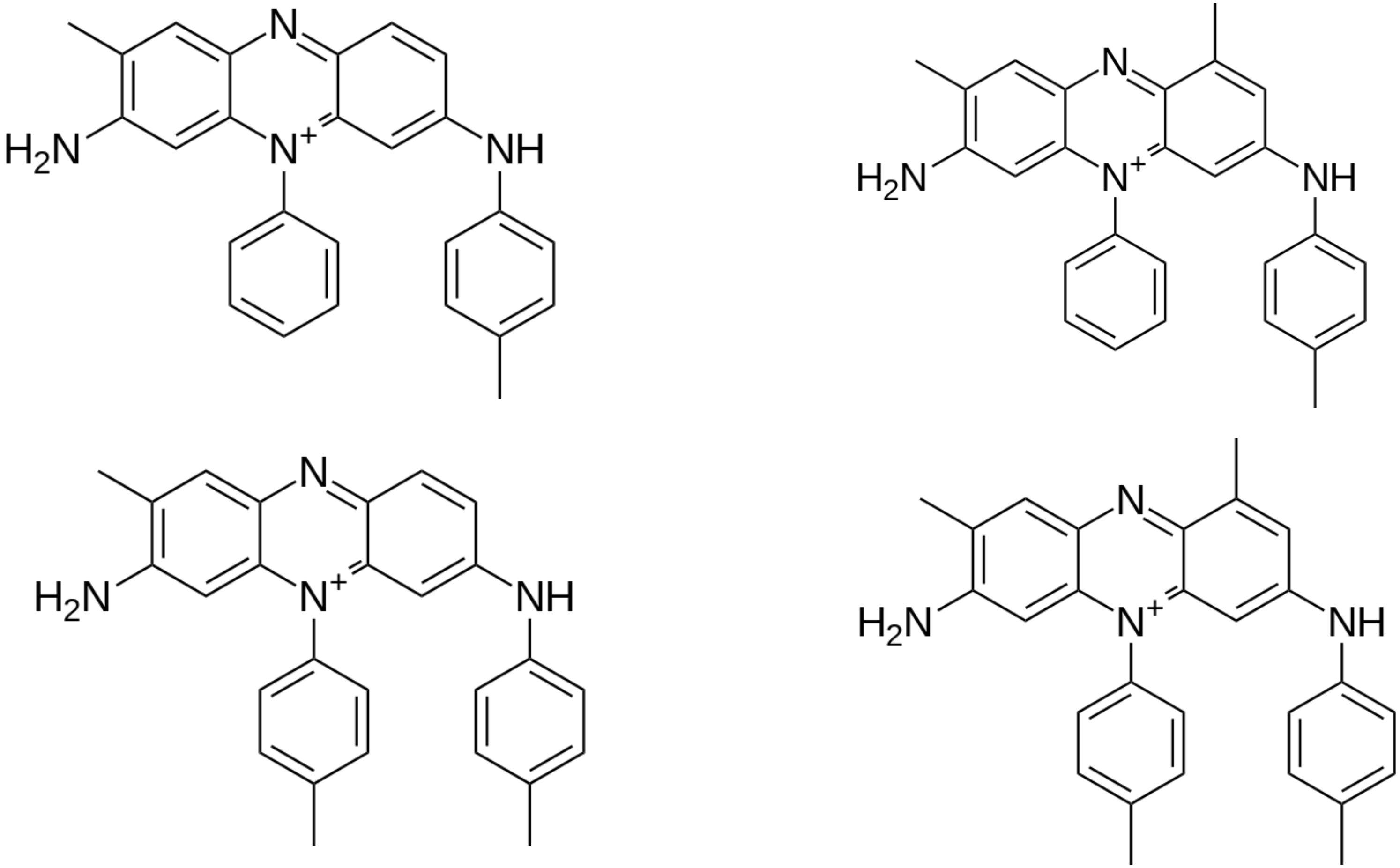
Aromatic Dyes

- Isolated



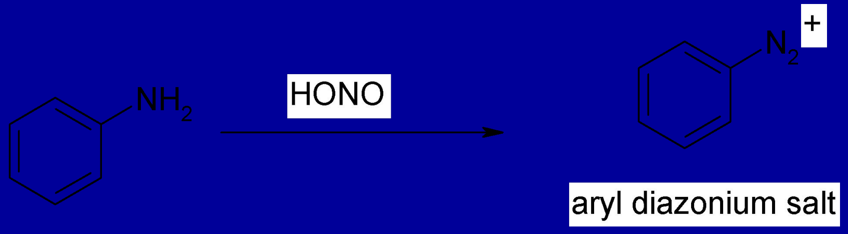
- Mauve - a purple color
- Dyed white cloth
- Patented material and process
- First chemical company

Mauveines -> 1994 !

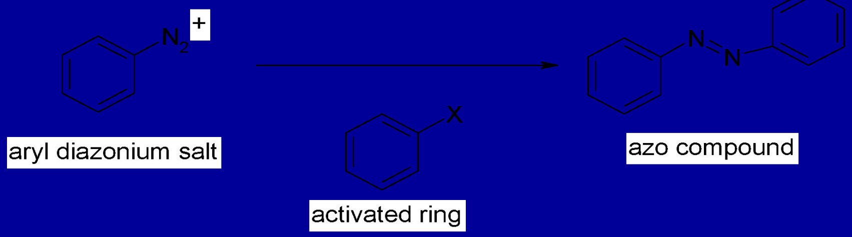


Some Aniline Chemistry

- Anilines readily react with nitrous acid

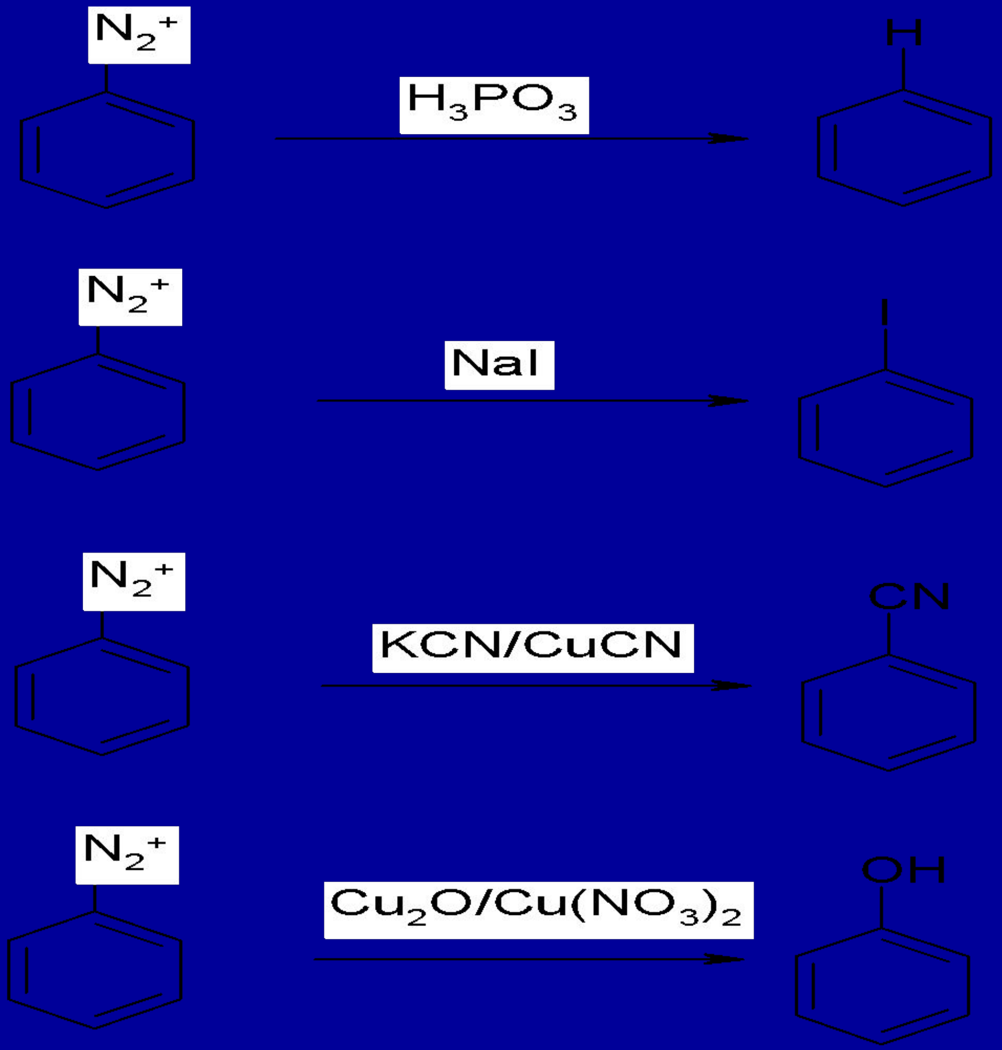


- Diazonium salts
  - Coupling reaction giving an azo compound



- Dyes and sulfa drugs

Aniline Chemistry

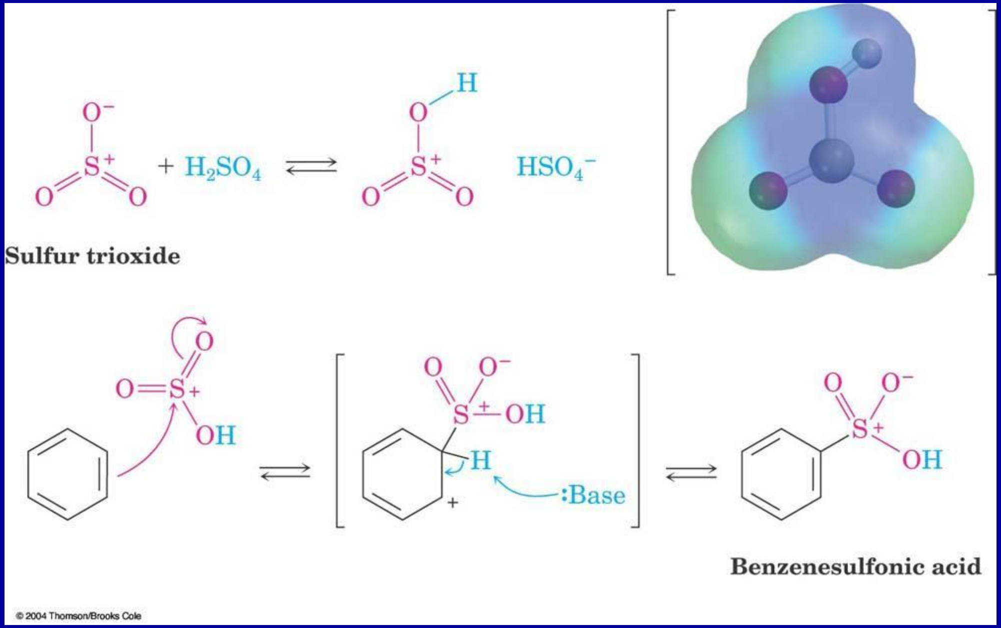


How do we make sulfuric acid?

- H_2SO_4 – least expensive manufactured chemical
- S (mined pure) + O_2 $\longrightarrow$ SO_3
- $SO_3 + H_2O \longrightarrow H_2SO_4$
- Continue adding SO_3 gives
- Fuming sulfuric acid: H_2SO_4/ SO_3

Aromatic Sulfonation

- Substitution of H by SO_3 (sulfonation)
- Reaction with a mixture of sulfuric acid and SO_3
- Reactive species is sulfur trioxide or its conjugate acid
- Reaction occurs via Wheland intermediate and is reversible



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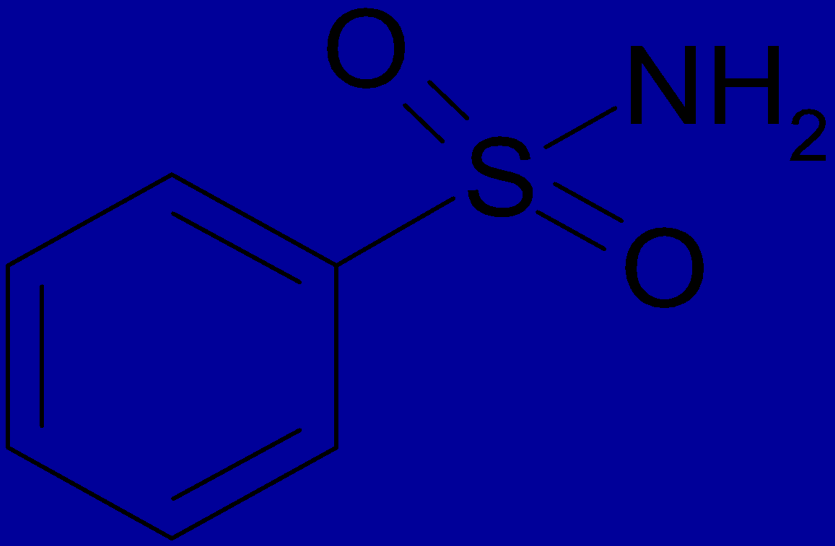
Benzene Sulfonic Acid

- Manufacture of Ion Exchange Resins
  - Water softening
  - Water purification
  - Environmental restoration (removal of toxic metal ions)

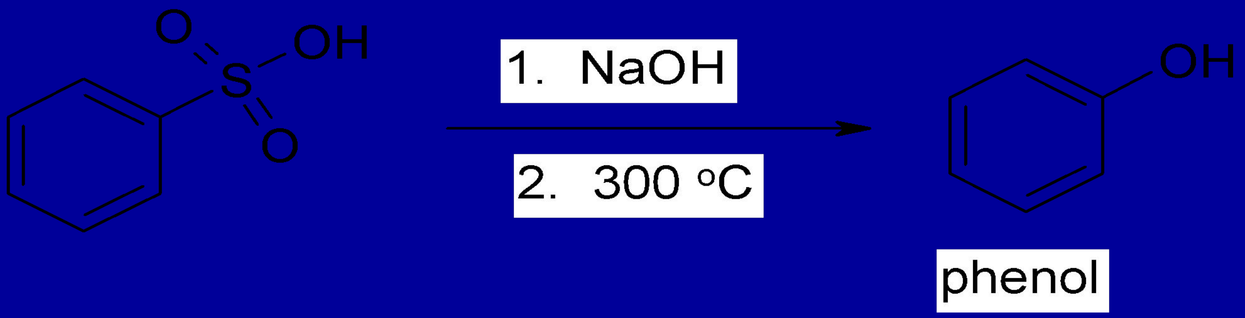
Benzene Sulfonic Acid

- Starting material for Sulfa Drugs
- First useful antibiotics



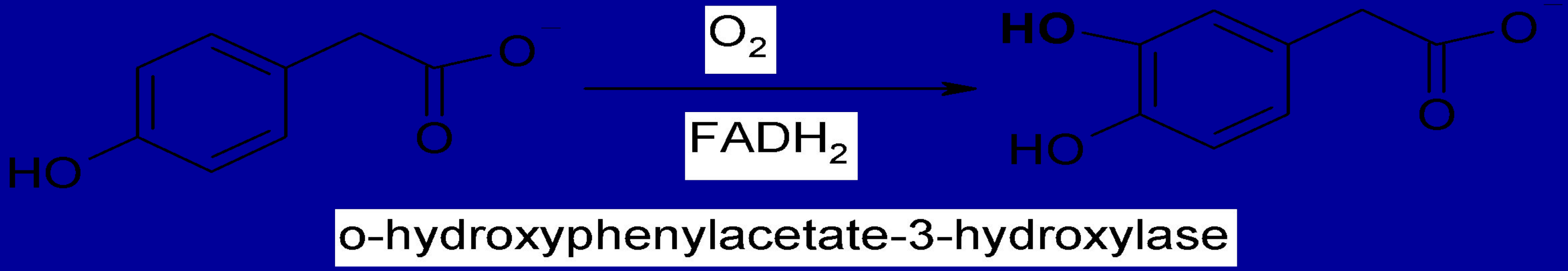
Hydroxylation

- Direct hydroxylation is difficult in lab
- Indirect method uses sulfonic acid



Biological Hydroxylation

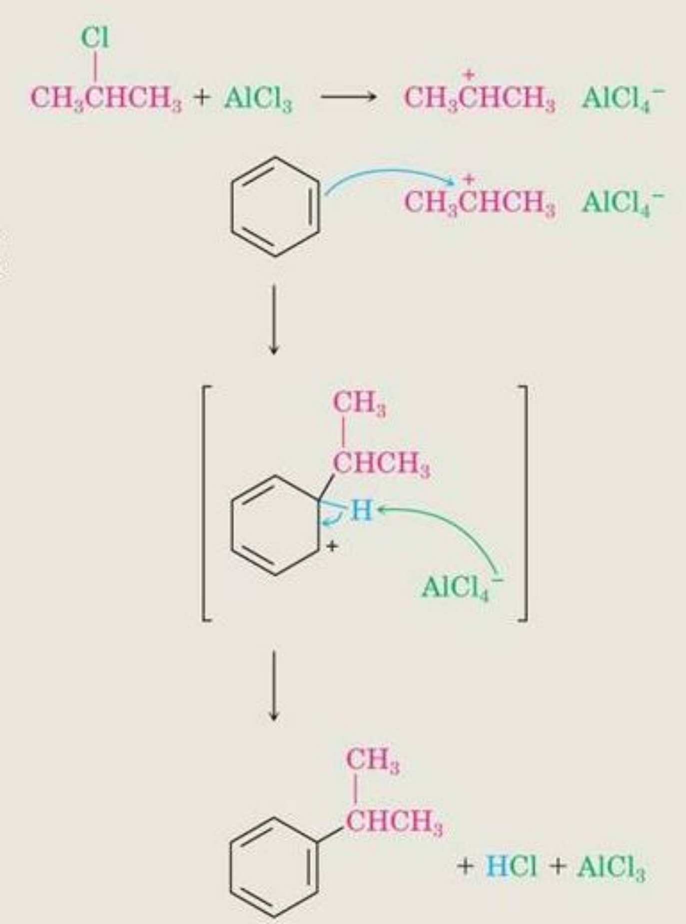
- Frequently conducted
- Example,



- Coenzyme necessary

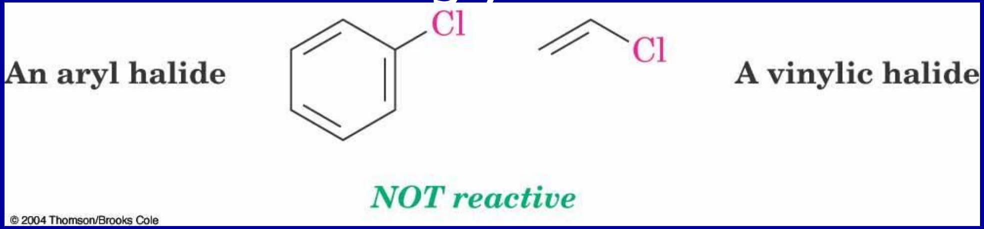
Alkylation of Aromatic Rings The Friedel–Crafts Reaction

- Aromatic substitution of a R^+ for H
- Aluminum chloride promotes the formation of the carbocation
- Wheland intermediate forms



Limitations of the Friedel-Crafts Alkylation

- Only *alkyl* halides can be used (F, Cl, I, Br)
- *Aryl* halides and *vinylic* halides do not react (their carbocations are too hard to form)
- Will not work with rings containing an amino group substituent or a strongly electron-withdrawing group



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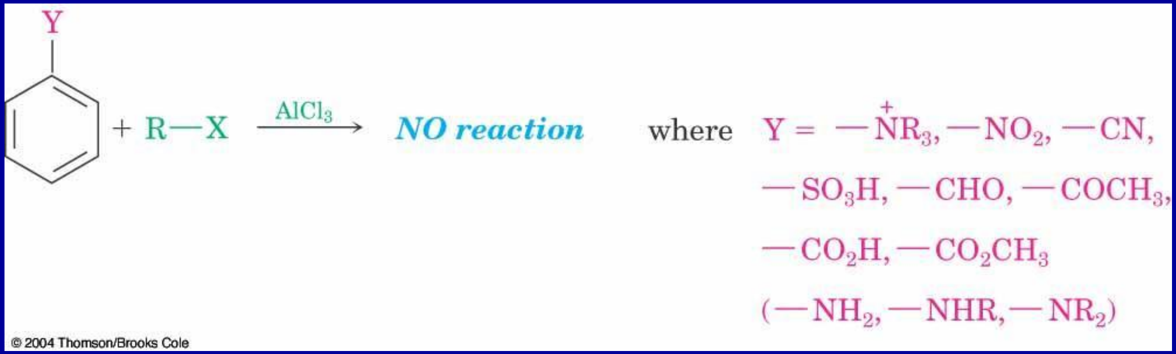

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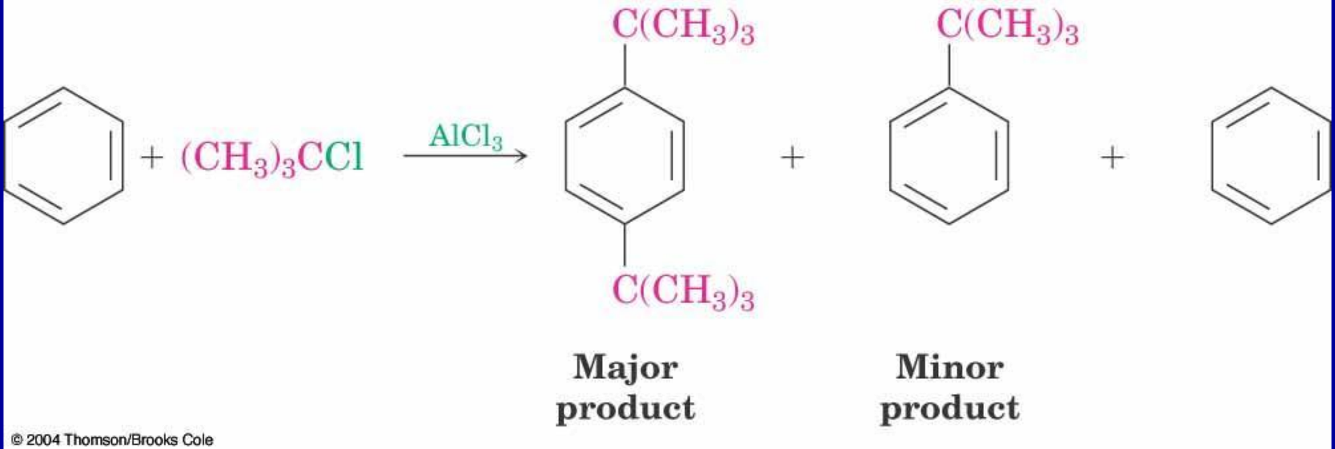
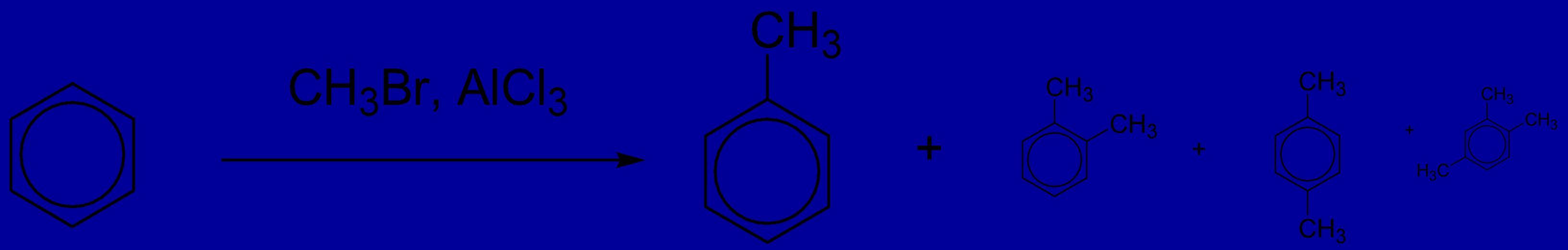
Limitations

- Multiple alkylations occur because the first alkyl group activates the ring



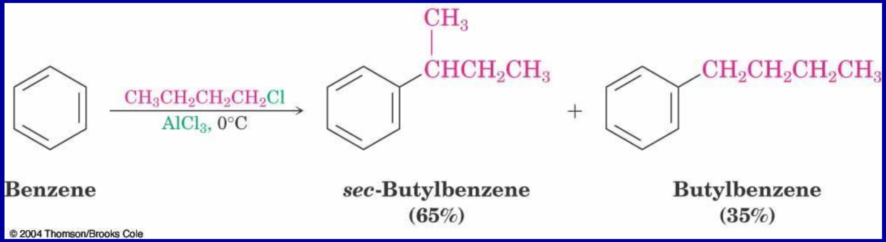
polyalkylation



The alkyl group activates the ring making the products more reactive that the reactants leading to polyalkylation. Use of excess aromatic compound minimizes polyalkylation in the lab.

Limitations

- Carbocation Rearrangements During Alkylation
- Similar to those that occur during electrophilic additions to alkenes
- Can involve H or alkyl shifts



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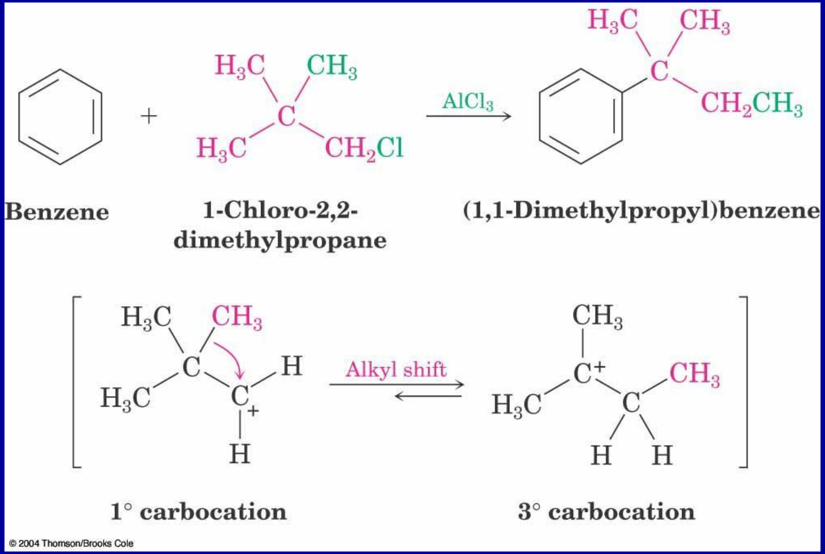

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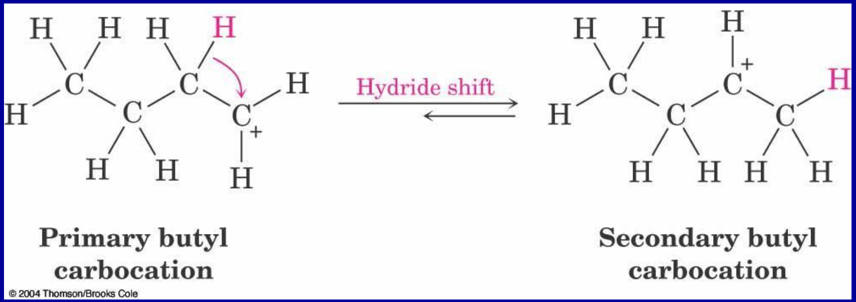

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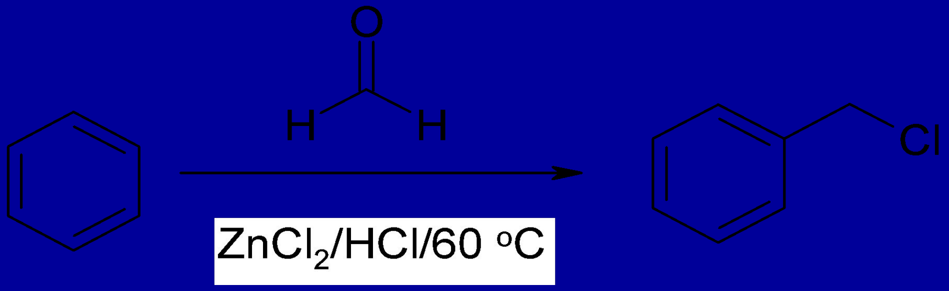
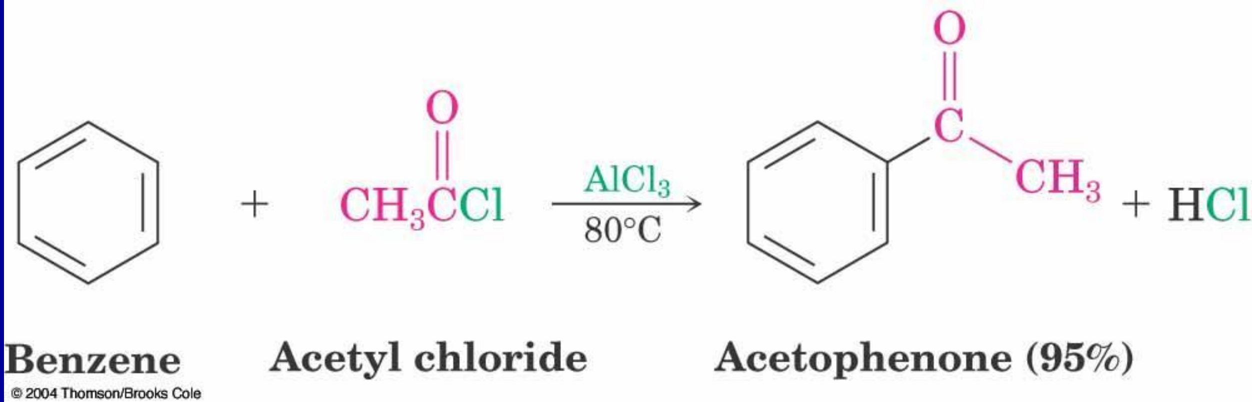
Related Reactions

- Chloromethylation



Related Reaction

- Acylation of Aromatic Rings
- Reaction of an acid chloride (RCOCl) with an aromatic ring in the presence of $AlCl_3$ introduces the **acyl group**,
- —COR
- Benzene with acetyl chloride yields acetophenone
- Acyl group deactivates ring
- Reaction stops after one group is added



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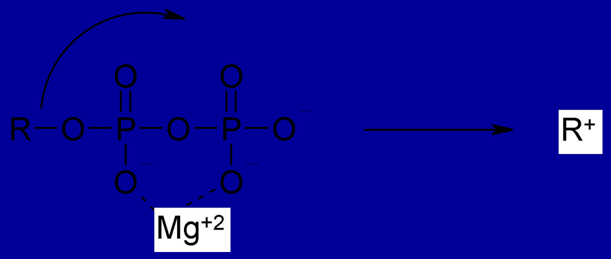
Biological Alkylations

- Common reaction
- No $AlCl_3$ present
- Utilizes an organodiphosphate
- Dissociation is facilitated by Mg^{+2}
- Important reaction in biosynthesis of Vitamin K_1



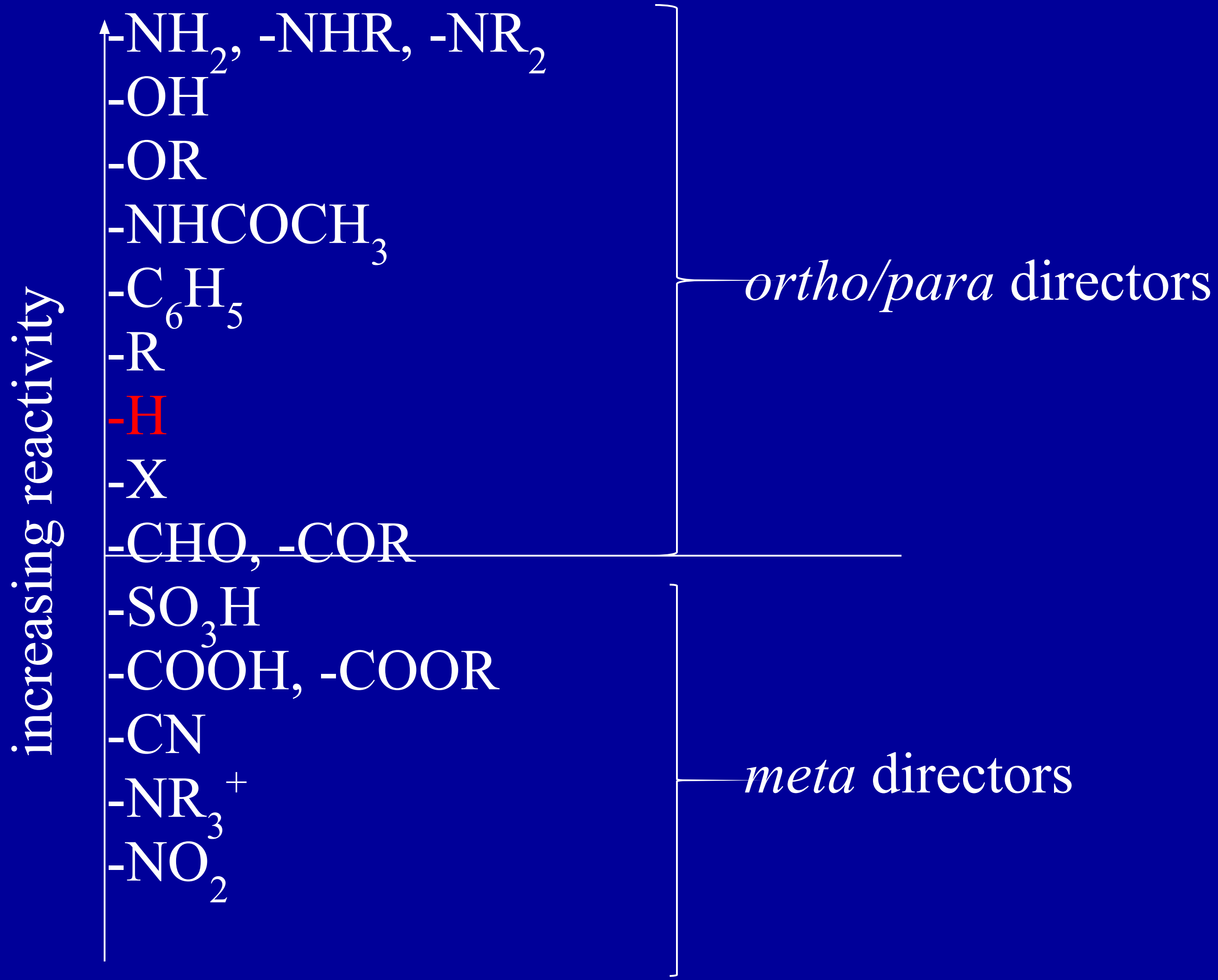
Ring Substitution Effects

- Activation and deactivation of ring
  - Alkyl activates the ring
  - Acyl deactivates the ring
- Activating Groups
  - group promotes substitution faster than benzene
- Deactivating Groups
  - group promotes substitution slower than benzene

Activating and Deactivating Groups

- Activating groups
  - electron donating groups
  - stabilizes the carbocation intermediate
  - activates through induction or resonance
- Deactivating groups
  - electron withdrawing groups
  - destabilizes the carbocation intermediate
  - deactivates through induction or resonance

Common substituent groups and their effect on EAS:



increasing reactivity

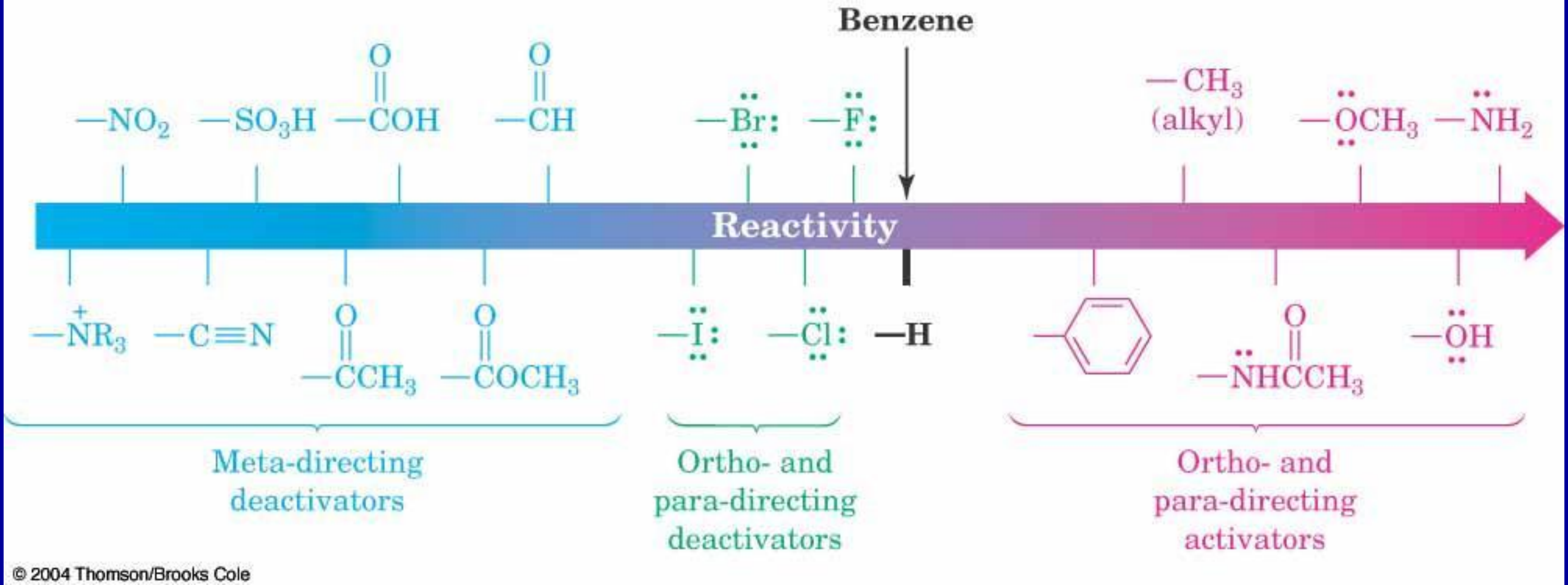
$-NH_2$, $-NHR$, $-NR_2$
-OH
-OR
$-NHCOCH_3$
$-C_6H_5$
-R
-H
-X
-CHO, -COR

ortho/para directors

$-SO_3H$
-COOH, -COOR
-CN
$-NR_3^+$
$-NO_2$

meta directors

Activating and Deactivating Groups

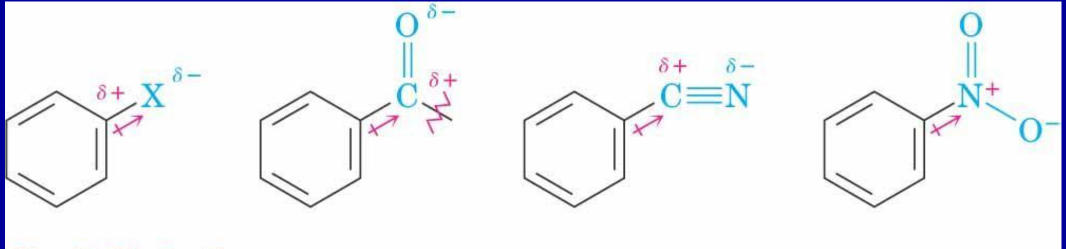


Origins of Substituent Effects

- **Inductive effect** - withdrawal or donation of electrons through a σ bond
- **Resonance effect** - withdrawal or donation of electrons through a π bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring

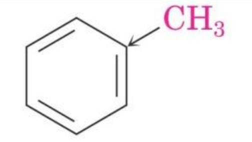
Inductive Effects

- Controlled by electronegativity and the polarity of bonds in functional groups
- Halogens, C=O, CN, and NO_2 *withdraw* electrons through σ bond connected to ring
- Alkyl groups *donate* electrons through σ bond



(X = F, Cl, Br, I)

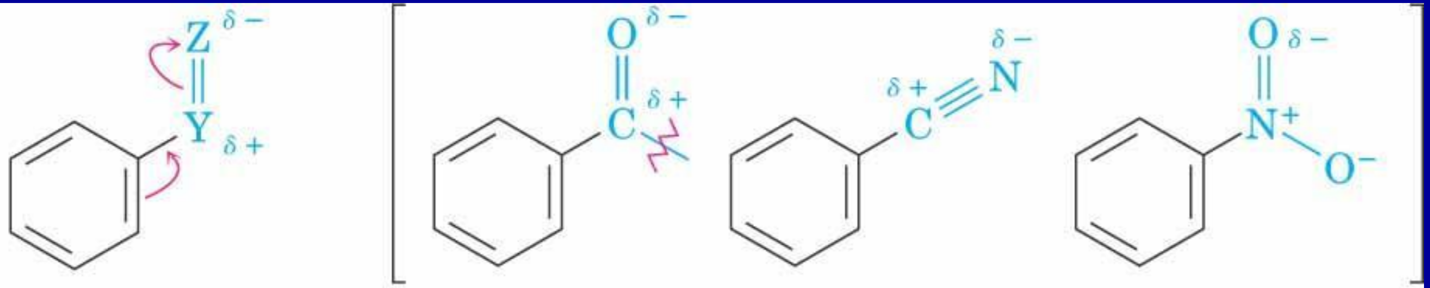
The groups attached to the aromatic rings are inductively electron-withdrawing because of the polarity of their bonds.



Alkyl group; inductively electron-donating

Resonance Effects: Electron Withdrawal

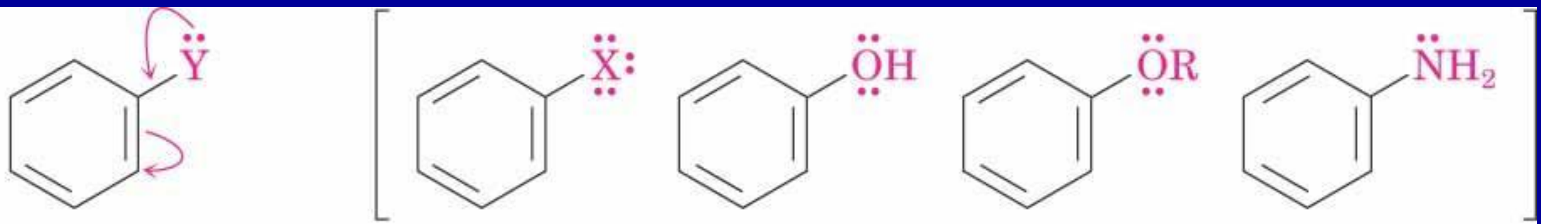
- C=O, CN, NO_2 substituents *withdraw* electrons from the aromatic ring by resonance
- π electrons flow from the rings toward the substituent



Rings substituted by a group with an electron-withdrawing resonance effect have this general structure.

Resonance Effects: Electron Donation

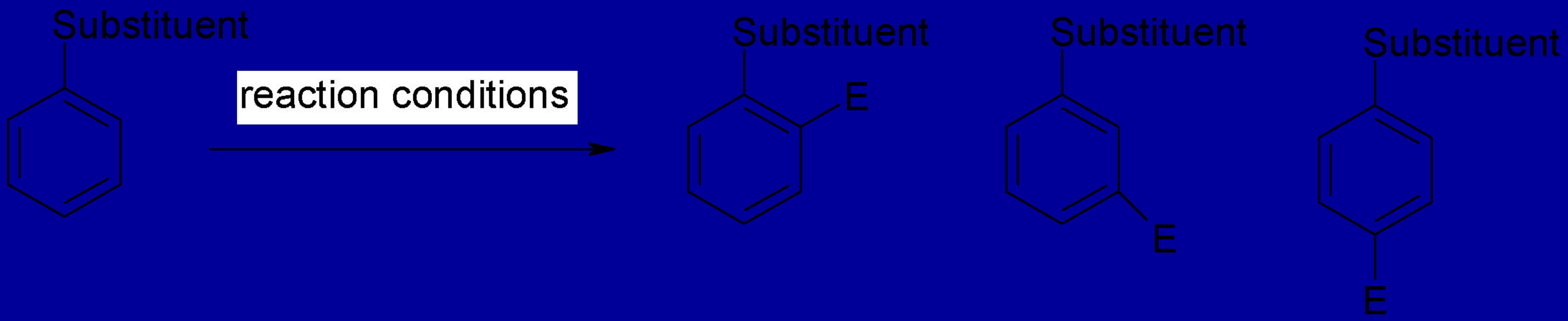
- Halogen, OH, alkoxyl (OR), and amino substituents *donate* electrons through resonance
- π electrons flow from into the ring



Rings substituted by a group with an electron-donating resonance effect have this general structure.

X = Halogen

Consider the following data



Substituent	Conditions	% ortho	% meta	% para
Bromine	$Br_2/FeBr_3$	13	<0.1	87
Methoxy	$Br_2/HOAc$	4	0	96
Methyl	HNO_3/H_2SO_4	62	5	33
Nitro	Br_2/Ag_2SO_4	0	100	0
Carbomethoxy	HNO_3/H_2SO_4	0	100	0

Analysis of Data

- Methoxy and Methyl
- Activating
- Ortho and para products

- Nitro and Carbomethoxy
- Deactivating
- Meta product

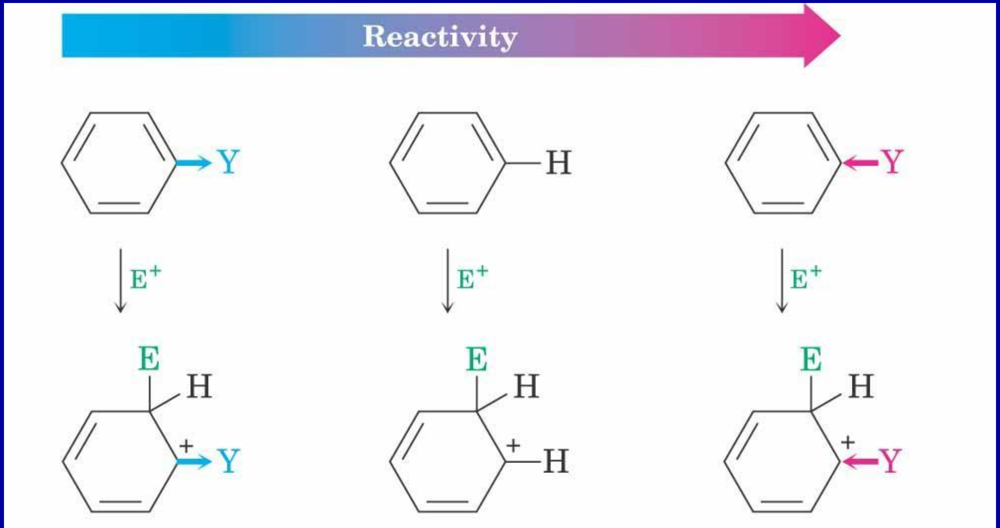
- Bromine
- Deactivating
- Ortho and para products

Ring Effects - Conclusions

- Activating groups
- Substitution is faster than for benzene
- Groups direct substitution to o/p positions
- Deactivating Groups
- Substitution is slower than for benzene
- Groups direct substitution to m position
- Halogens
- Deactivate ring
- Substitution is slower than for benzene
- Groups direct substitution to o/p positions

Ring Effects – The Explanation

- Activating groups donate electrons to the ring, stabilizing the Wheland intermediate (carbocation)
- Deactivating groups withdraw electrons from the ring, destabilizing the Wheland intermediate

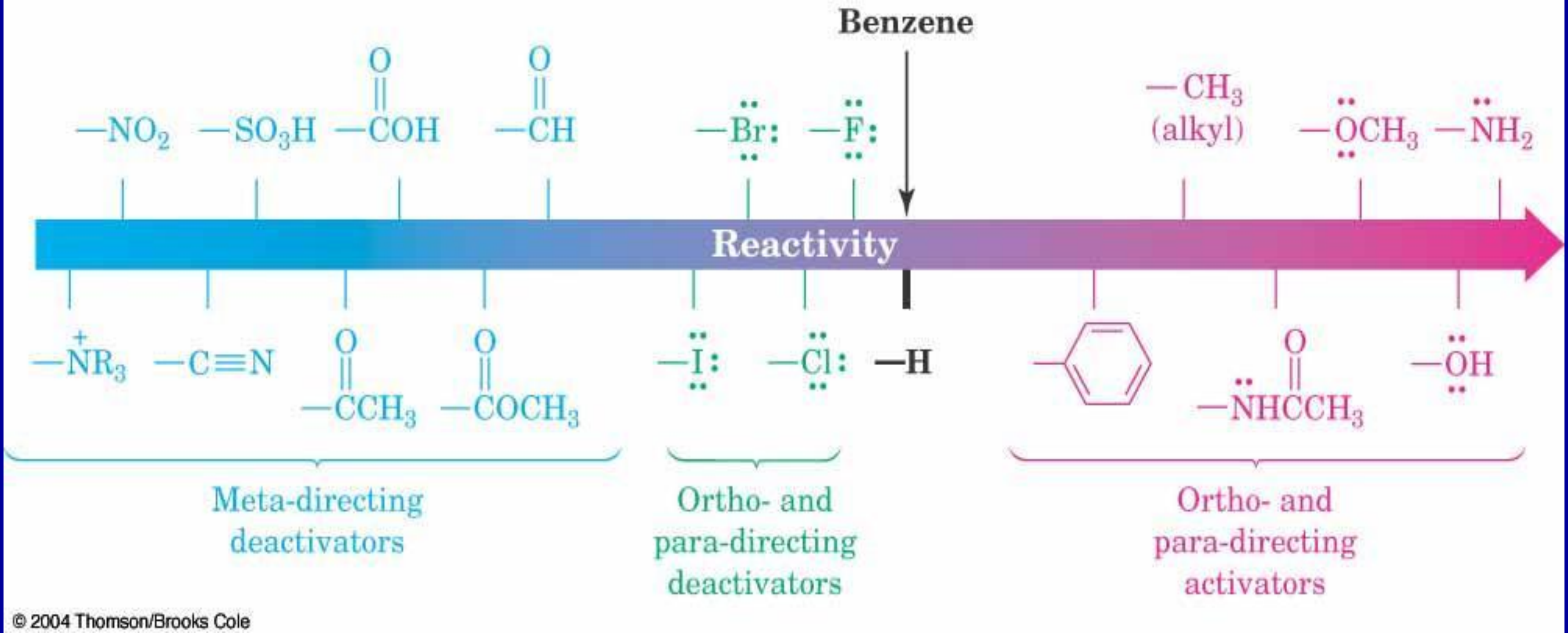


Y withdraws electrons; carbocation intermediate is less stable, and ring is less reactive.

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

Important

- You need to know this:

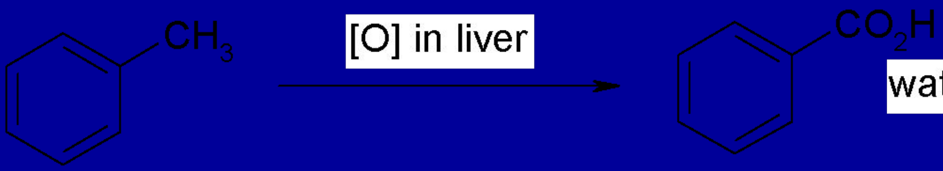


Oxidation of Benzene

- Toluene is readily oxidized by reagents
- Benzene is inert to oxidizing agents
  - Benzene is toxic to humans
  - Benzene is a suspected carcinogen
- Cytochrom P
  - strong oxidant in Liver
  - Primary detoxification process used

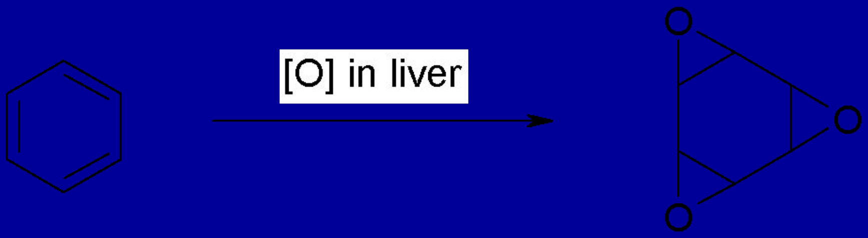
Proposed Chemistry

Toluene is non-toxic



water soluble

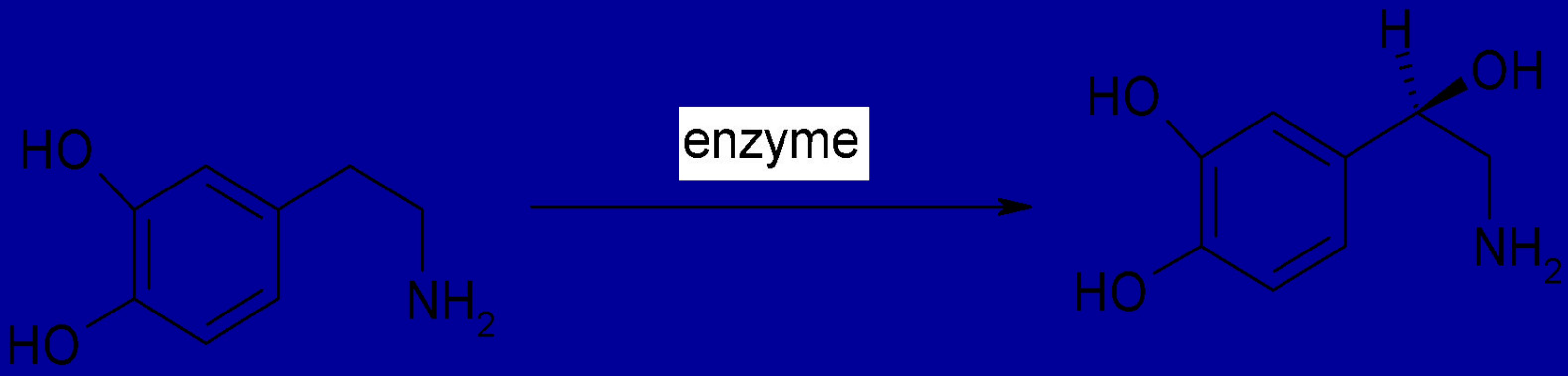
Benzene is toxic



triepoxide
lipid soluble
mutagen

Biological Oxidations of Side Chains

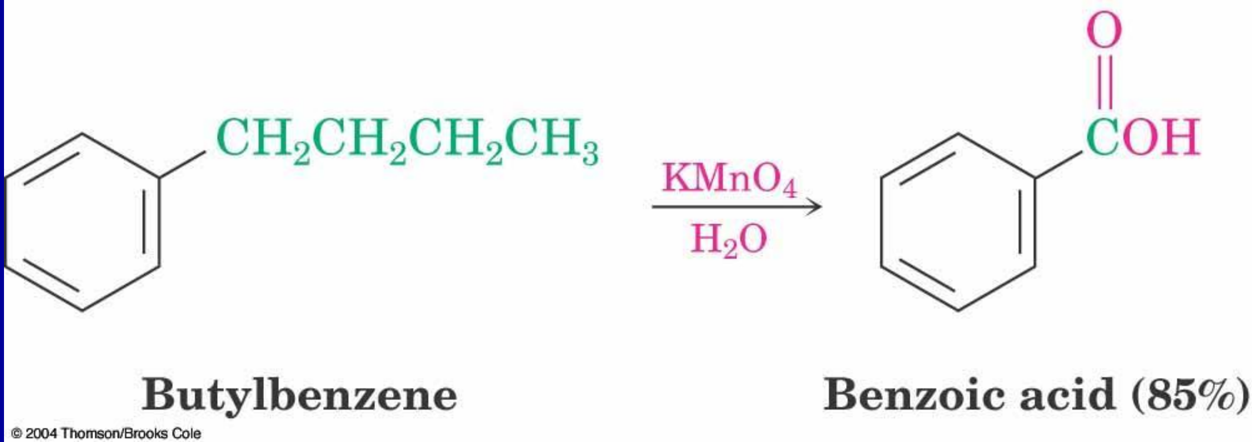
- Biosynthesis of norepinephrine



enzyme = dopamine-beta-monooxygenase

Oxidation of Aromatic Compounds

- Alkyl side chains can be oxidized to $-CO_2H$ by strong reagents such as $KMnO_4$ and $Na_2Cr_2O_7$ if they have a C-H next to the ring
- Converts an alkylbenzene into a benzoic acid, $Ar-R \rightarrow Ar-CO_2H$



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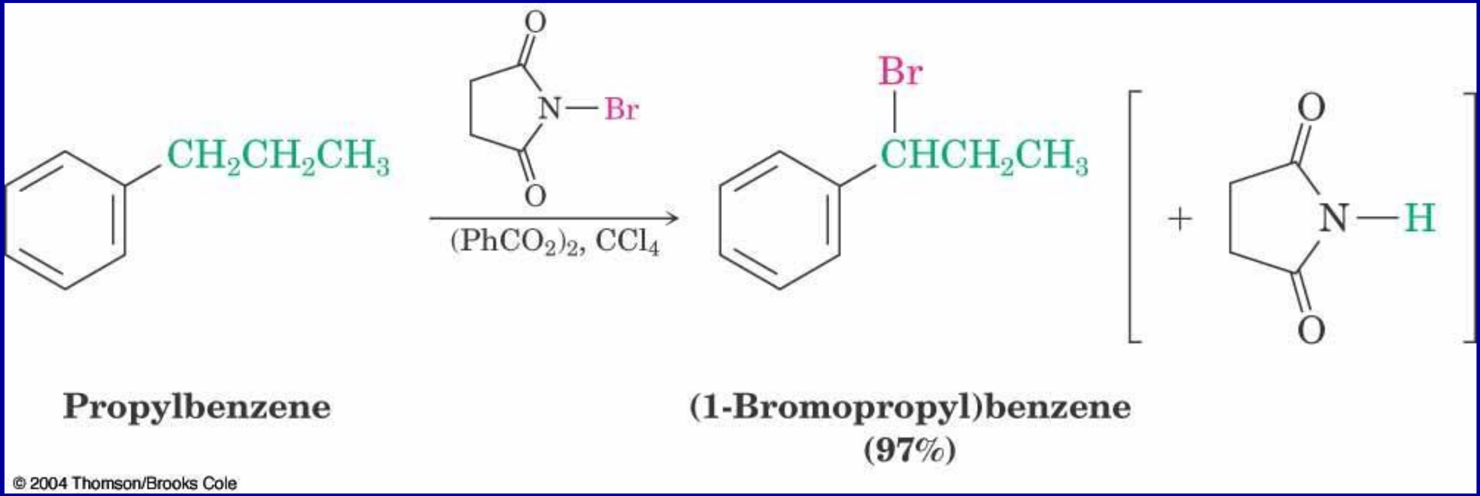
Bromination of Alkylbenzene Side Chains

- Reaction of an alkylbenzene with *N*-bromo-succinimide (NBS) and benzoyl peroxide (radical initiator) introduces Br into the side chain



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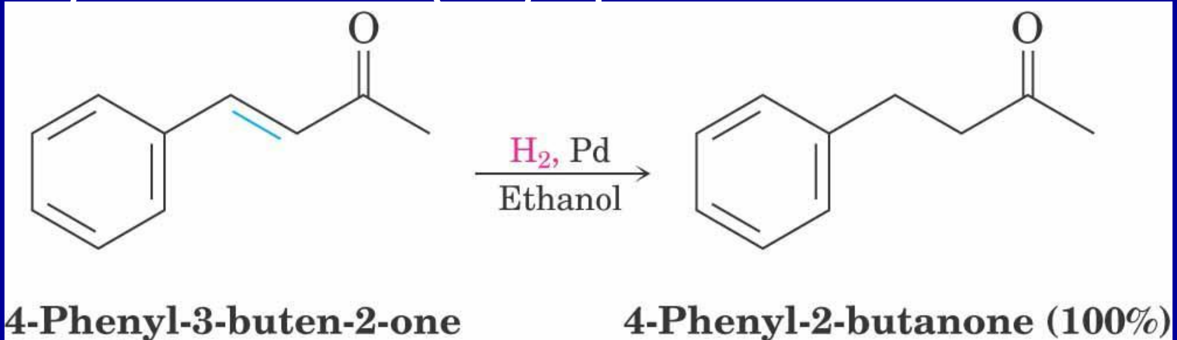
Reduction of Aromatic Compounds

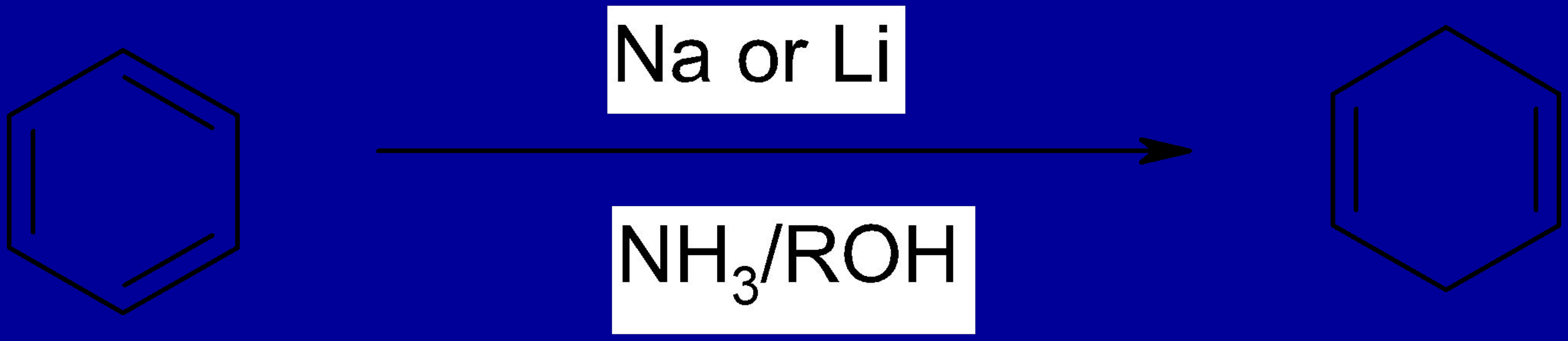
- Aromatic rings are inert to catalytic hydrogenation under conditions that reduce alkene double bonds
- Can selectively reduce an alkene double bond in the presence of an aromatic ring
- Reduction of an aromatic ring requires more powerful reducing conditions (high pressure or rhodium catalysts)



4-Phenyl-3-buten-2-one 4-Phenyl-2-butanone (100%)

Reduction of Aromatic Compounds

- Aromatic Rings can be reduced using Li or Na metal dissolved in liquid ammonia



Reduction of Aryl Alkyl Ketones

- Aromatic ring activates neighboring carbonyl group toward reduction
- Ketone is converted into an alkylbenzene by catalytic hydrogenation over Pd catalyst