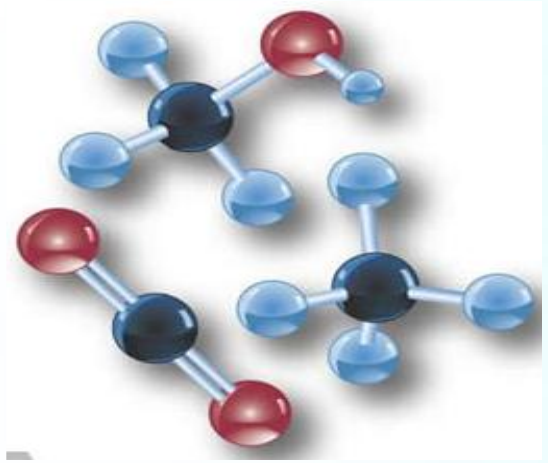
Organic Chemistry



Le Liu

le.liu@xjtu.edu.cn

Chapter 10

Organic Compounds

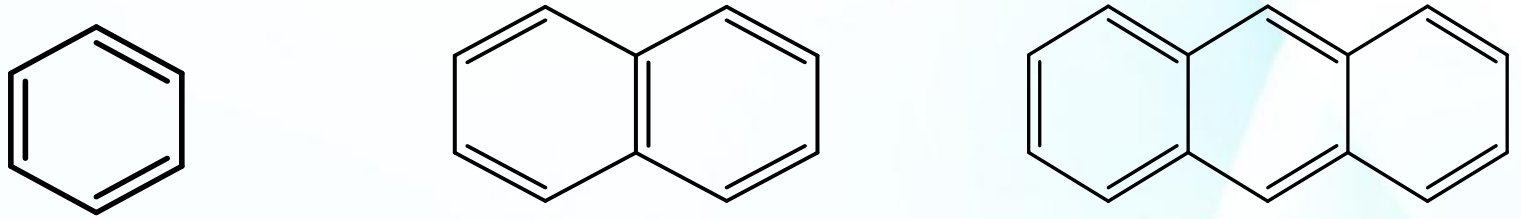
—Aromatic Compounds

Outline:

1. What is the structure of benzene?
2. What is aromaticity?
3. How are benzene compounds named?
4. What is the benzylic position, and how does it contribute to benzene reactivity?
5. What is electrophilic aromatic substitution?
6. How do existing substituents on benzene affect electrophilic aromatic substitution?

Aromaticity

The term aromatic was originally applied to benzene-like structures because of the distinctive aroma of these compounds, but the term now means something different in modern chemistry.

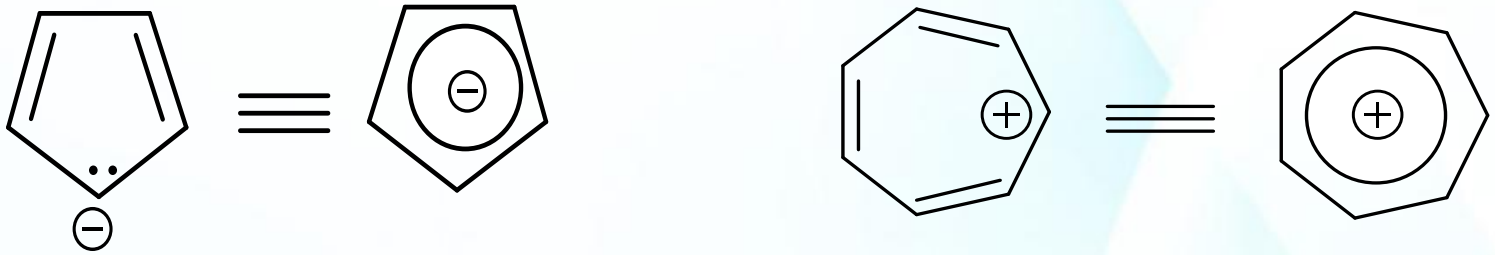


Aromatic compounds are highly unsaturated compounds, but unlike alkenes and alkynes, they are relatively unreactive. They undergo reactions which retain the aromatic ring system, and behave differently from alkenes or polyenes.

Hückel Rule

- Aromatic compounds are cyclic and planar with sp^2 hybridized atoms.

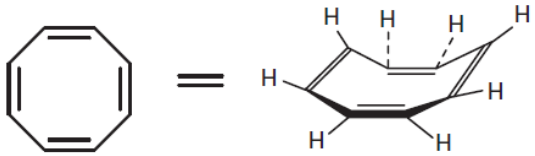
Aromatic systems can be monocyclic or polycyclic, neutral, or charged.



- They also obey the Hückel rule and have 4n+2 π electrons where n=0,1,2,3,…

Therefore, ring systems which have 6,10,14,…π electrons are aromatic.

Cyclooctatetraene

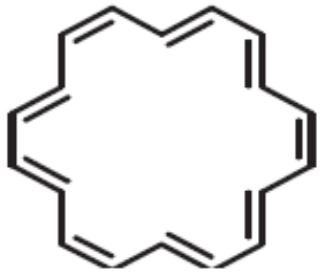


Cyclooctatetraene has eight π electrons and does not obey the Hückel rule.

It is not planar, the π electrons are not delocalized .

Cyclooctatetraene reacts like a conjugated alkene.

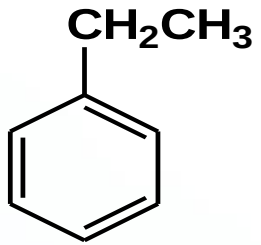
18-membered



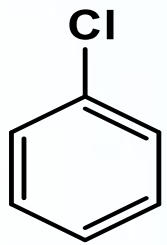
18-membered cyclic system does fit the Hückel rule(n=4) and is a planar molecule with aromatic properties and a delocalized π system.

Nomenclature

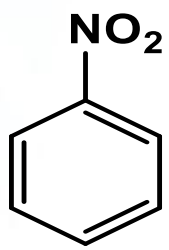
A. Monosubstituted benzenes



Ethylbenzene

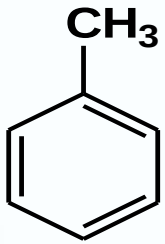


Clorobenzene

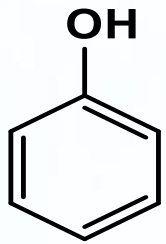


Nitrobenzene

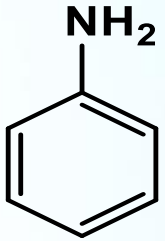
The following are usually considered parent compouds:



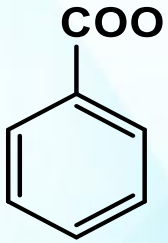
Toluene



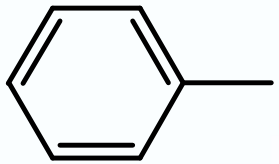
Phenol



Aniline

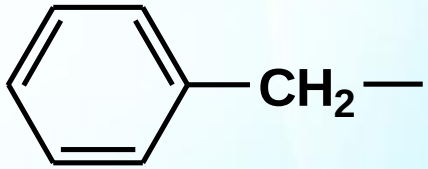


Benzoic acid



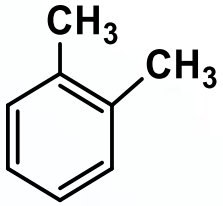
ph-

phenyl

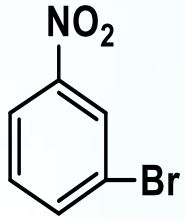


benzyl

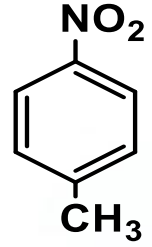
B. Disubstituted benzenes



ortho-Dimethylbenzene

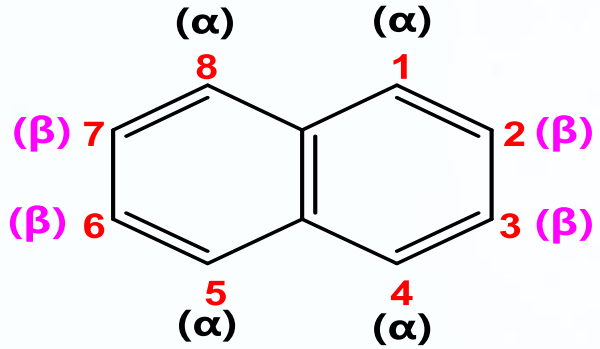


meta-Bromonitrobenzene



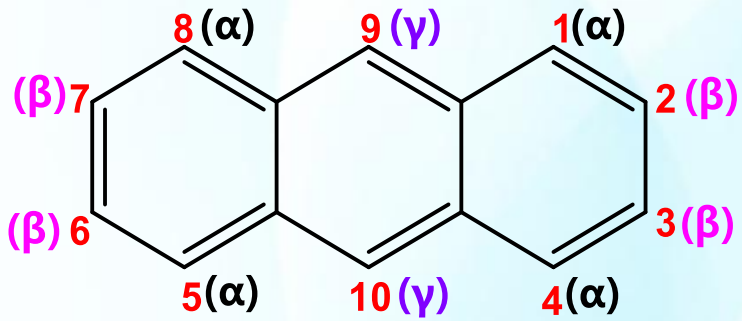
para-Nitrotoluene

C. Polynuclear Aromatic Hydrocarbons



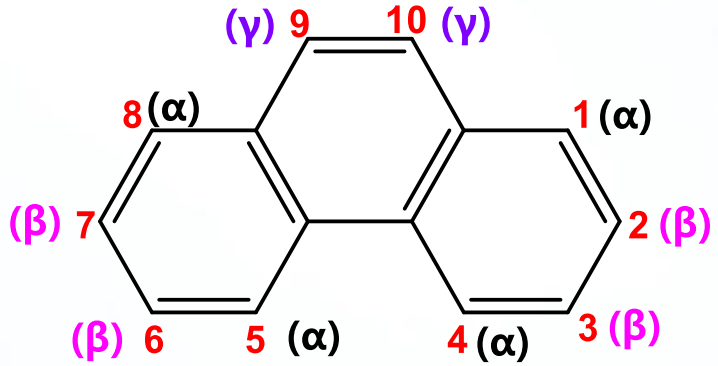
Naphthalene

萘

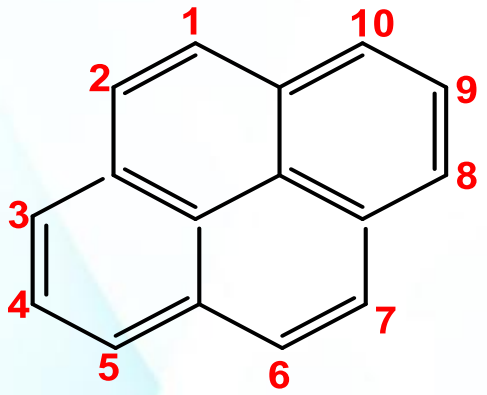


Anthracene

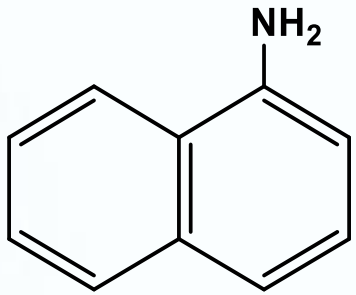
蒽



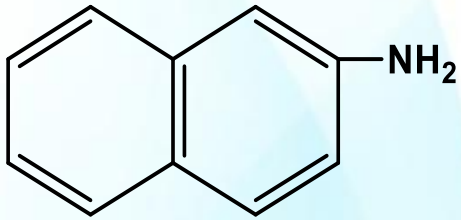
Phenanthrene 菲



Pyrene 芘



α- naphthylamine
A weak carcinogen

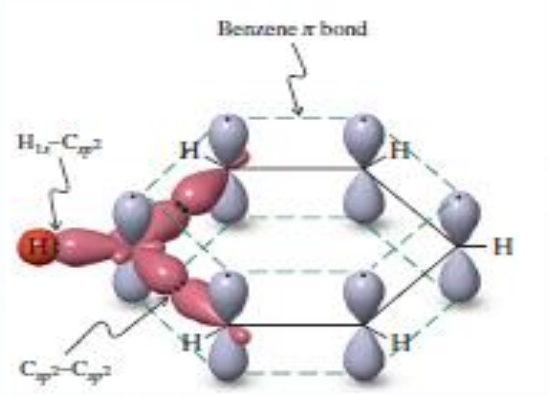


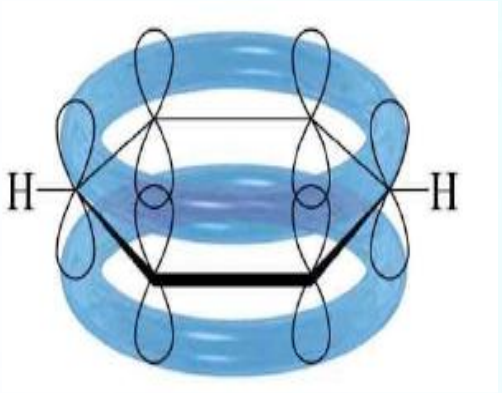
β-Naphthylamine
A strong carcinogen

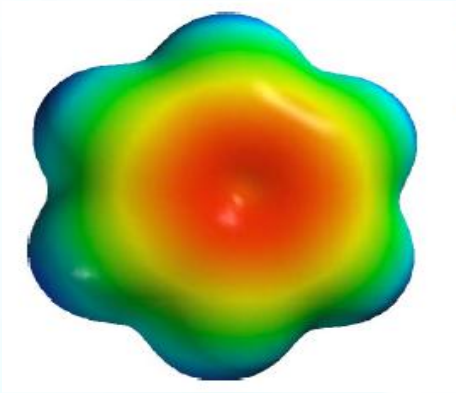
Structure

The structure of benzene is planar, and each carbon is sp^2 hybridization.

In addition to its three sp^2 hybrid orbitals, each carbon has a half-filled *2p* orbital that can participate in π bonding.





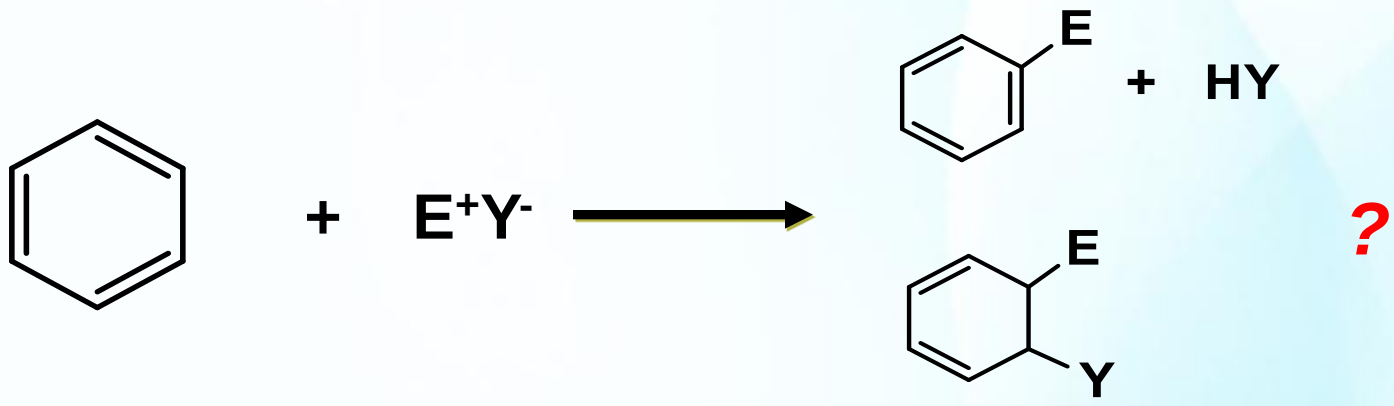


The six π electrons are delocalized around the ring which results in an increased stability.

Question：

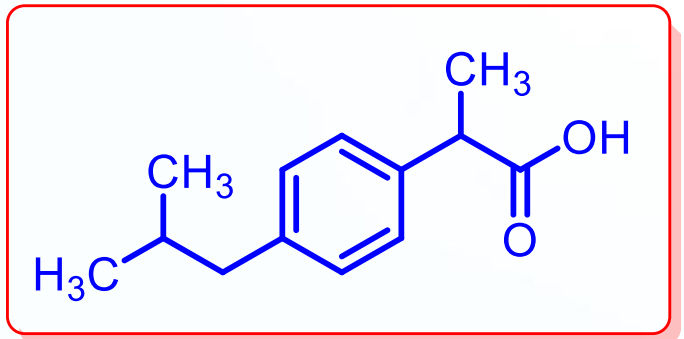
What are the characteristic reactions of benzene?

Reactions which disrupt this delocalization are not favored since it means a loss of stability, so benzene undergoes reactions where the aromatic ring system is retained.



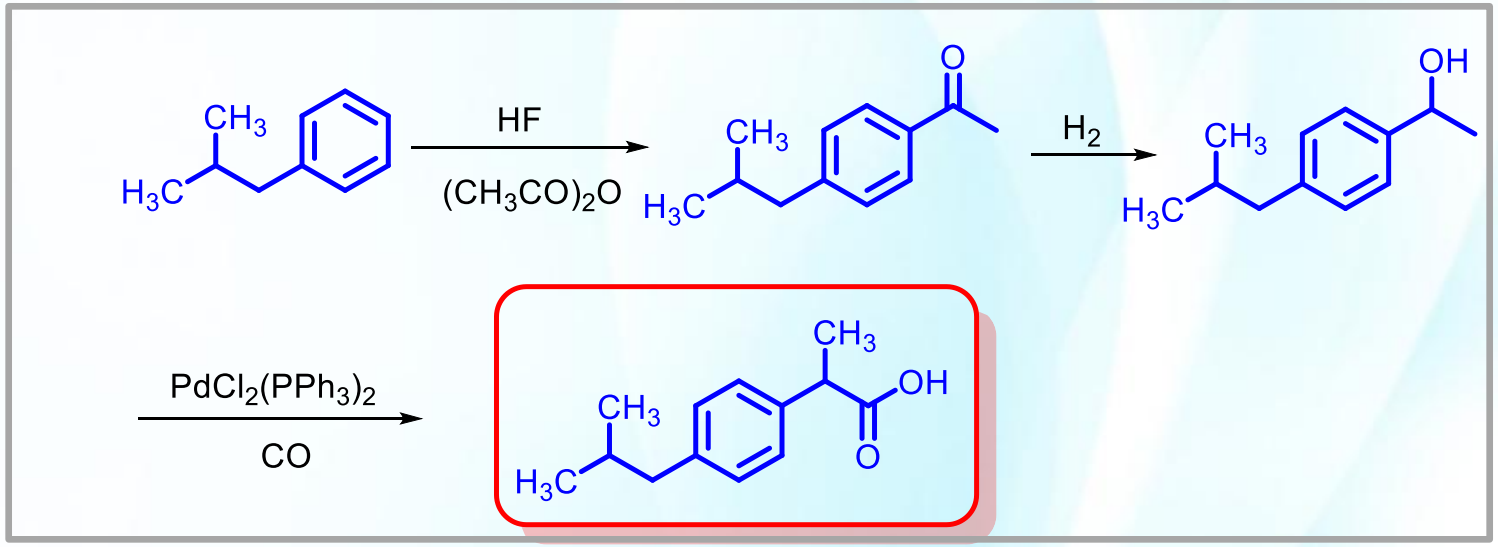
芳烃的亲电取代反应

2023年初，“最火的” 退烧药



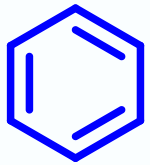
布洛芬

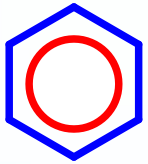
- ✓ **世界卫生组织、美国FDA唯一共同推荐的儿童退烧药**
- ✓ **抗炎、镇痛、解热作用**

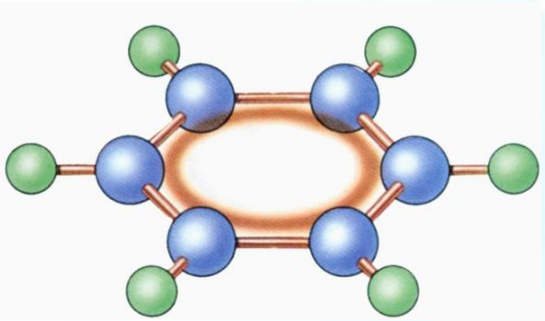


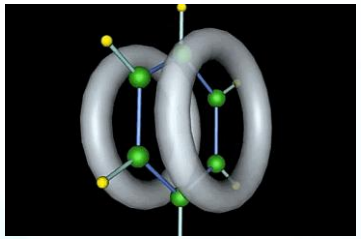
芳烃的亲电取代反应

芳香烃结构特点


苯




芳香六隅体



结构

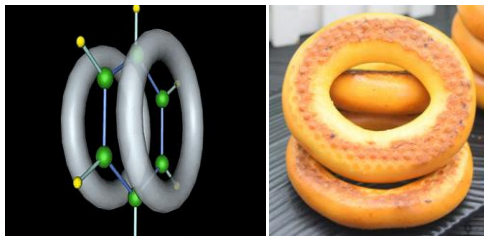
- 平面型分子
- π -电子云均匀分布
- 闭合的共轭体系

性质

- ✓ 环稳定结构：不易发生加成反应
- ✓ π -电子高度离域：易发生取代反应

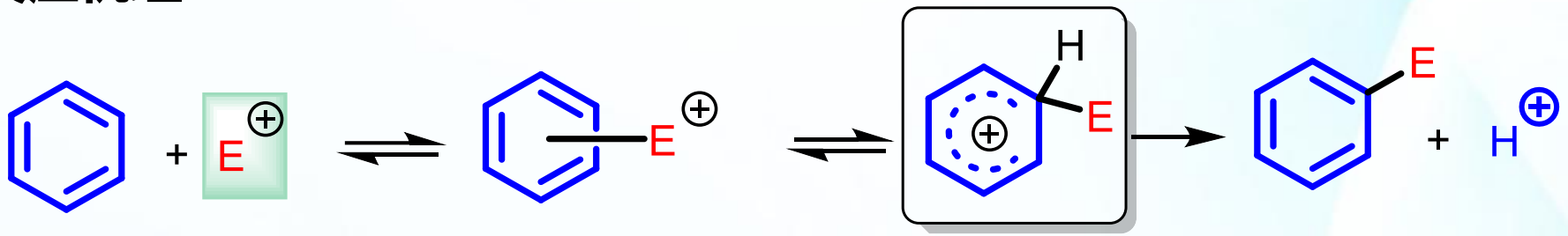
芳烃的亲电取代反应

芳香亲电取代反应：芳环上的氢被亲电试剂取代的化学反应



$$Ar{-}H + E^{+} \longrightarrow Ar{-}E + H^{+}$$

反应机理

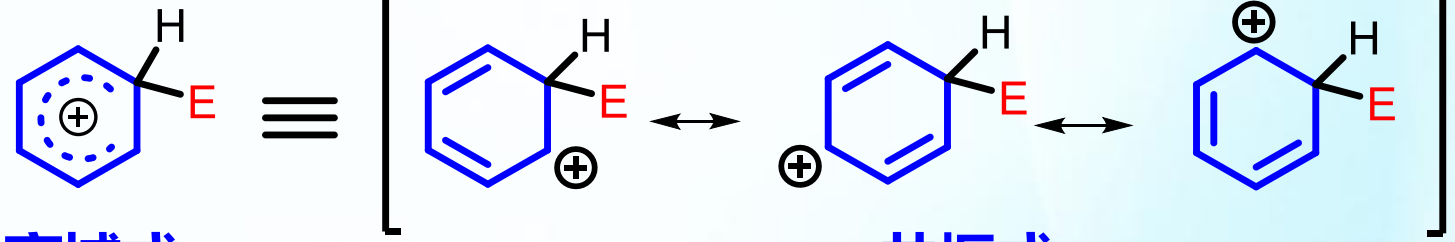


π -络合物　　σ-络合物

“有舍有得”

“将欲取之，必先予之”

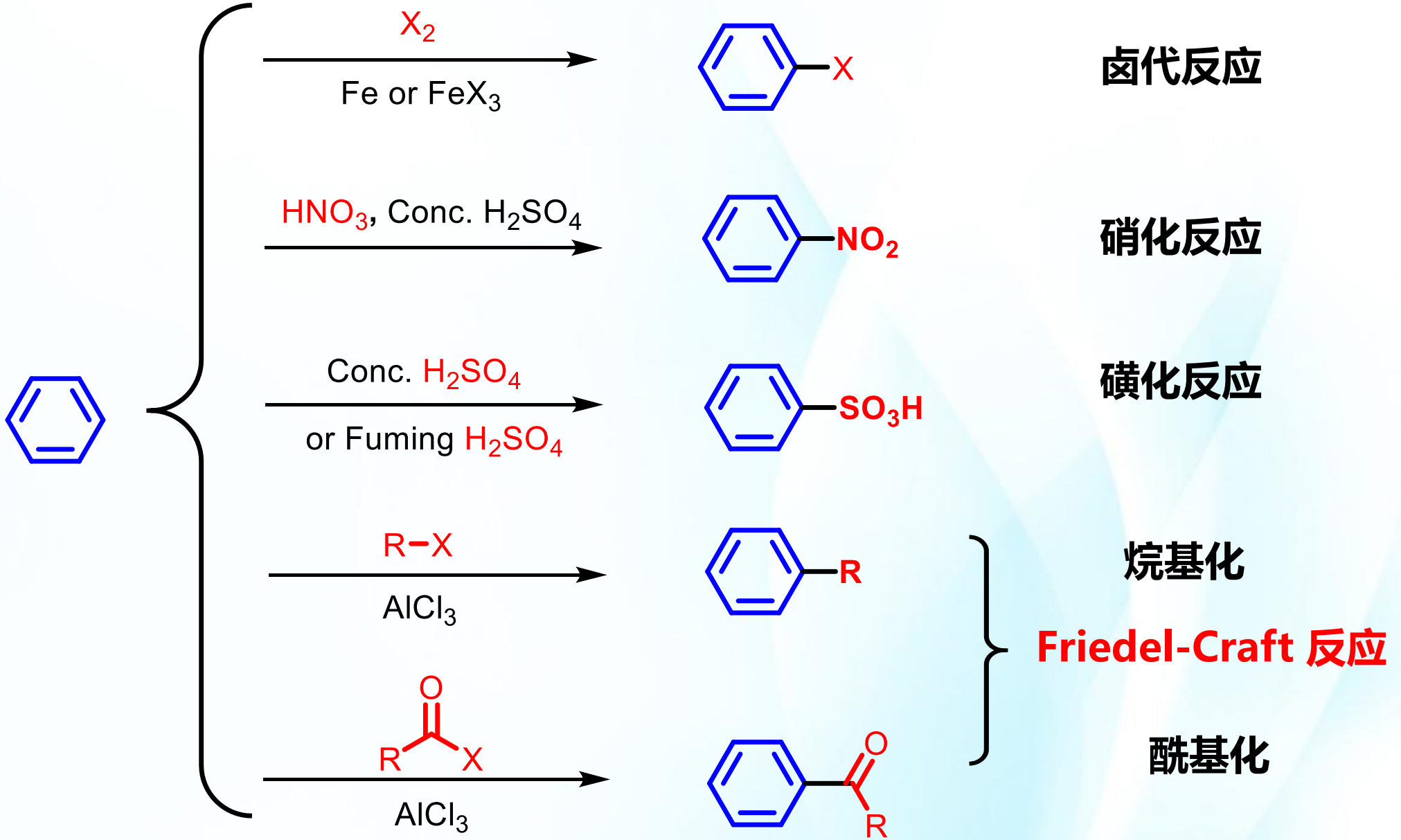
σ-络合物的表达方式



离域式　　共振式

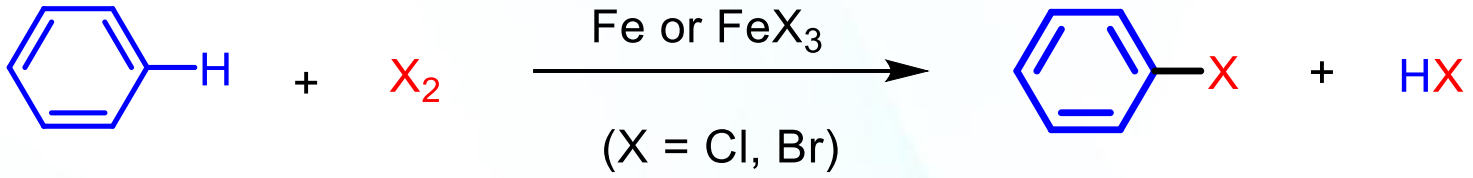
芳烃的亲电取代反应

常见的芳烃亲电取代反应

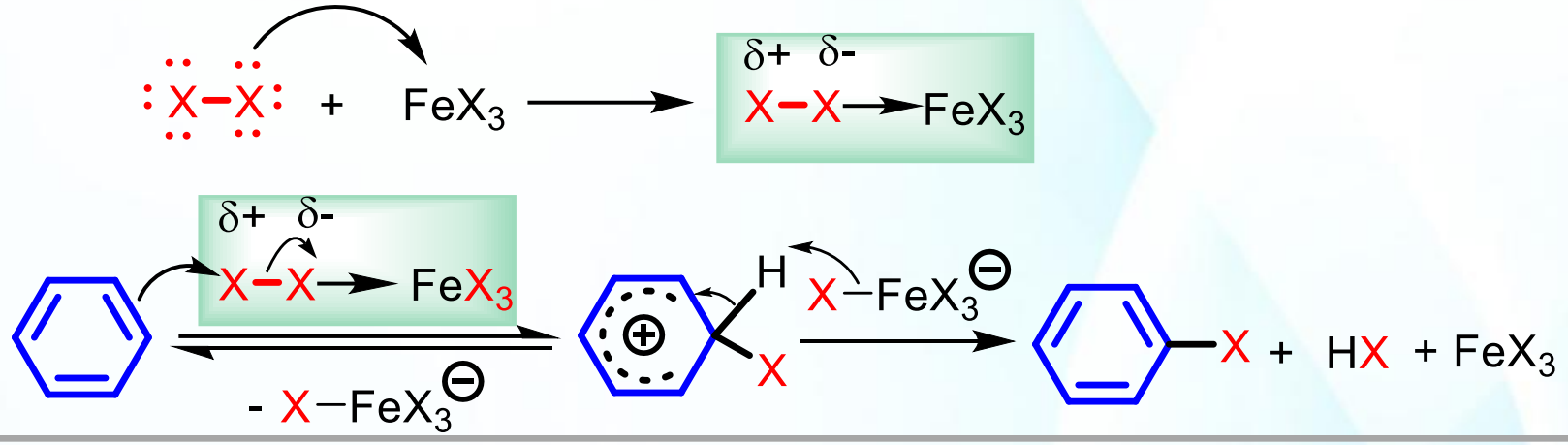


芳烃的亲电取代反应

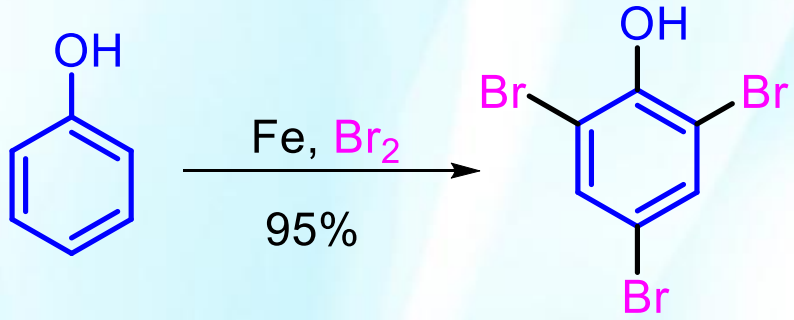
1. 卤代反应



反应机理

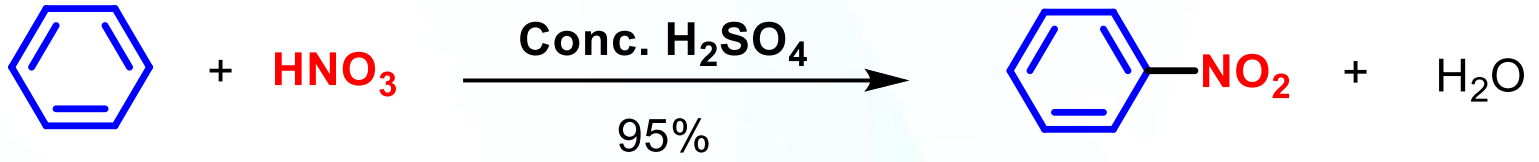


- $FeCl_3$或$FeBr_3$易吸水，铁屑与卤素原位生成催化剂
- Cl, Br, I均可通过卤代反应引入，F需要用间接方法引入
- 催化剂可以极化X-X 键，生成亲电物种

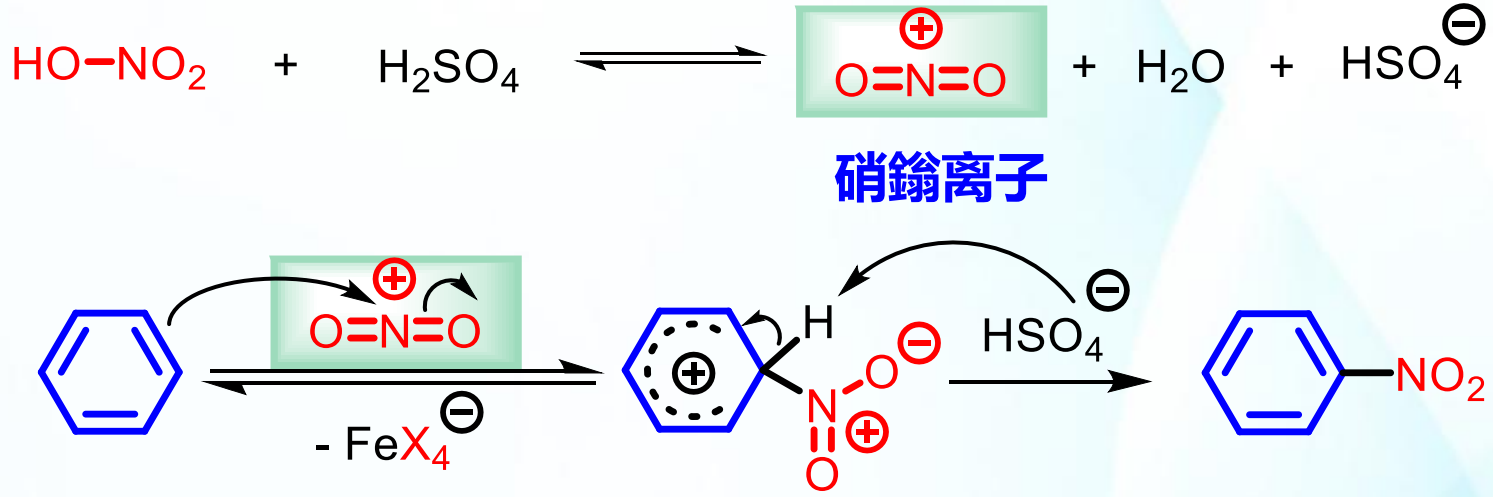


芳烃的亲电取代反应

2. 硝化反应



反应机理



拓展

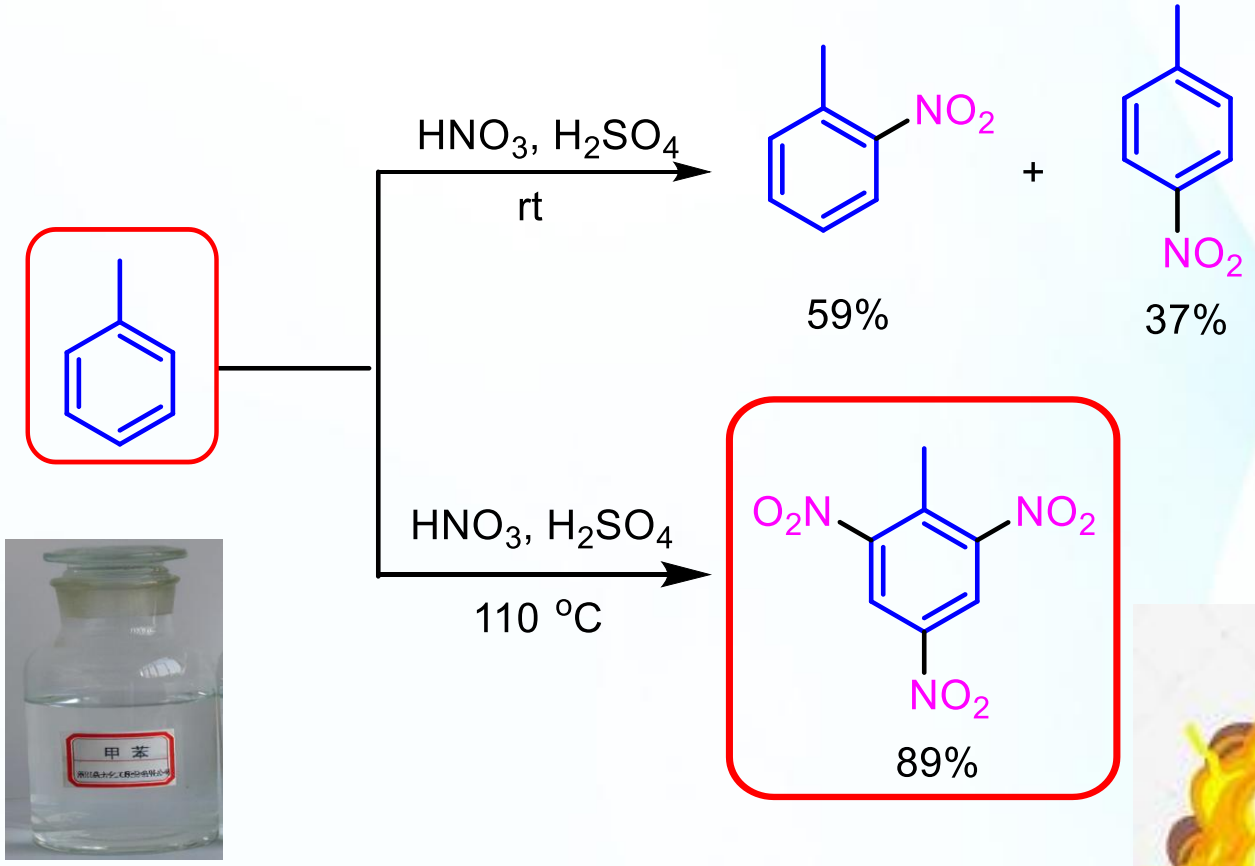
混酸做硝化试剂产生大量废酸，造成环境污染

工业上：酸性白土、离子交换树脂Nafion与硝酸合用

其他硝化试剂：乙酸硝酸混酐（$AcONO_2$）、硝酰盐（NO_2BF_4、NO_2PF_6）

芳烃的亲电取代反应

2. 硝化反应



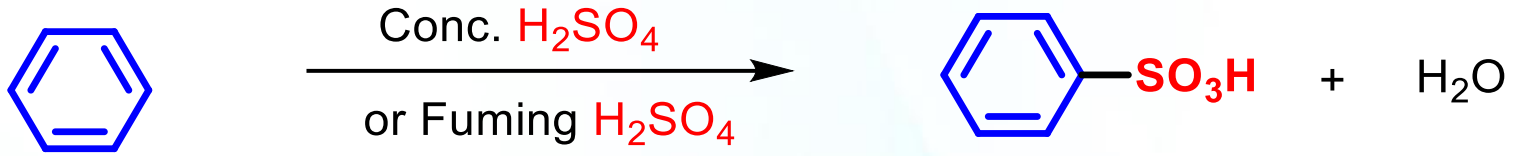
“有舍有得”

“量变与质变”

“磨砺与蜕变”

芳烃的亲电取代反应

3. 磺化反应

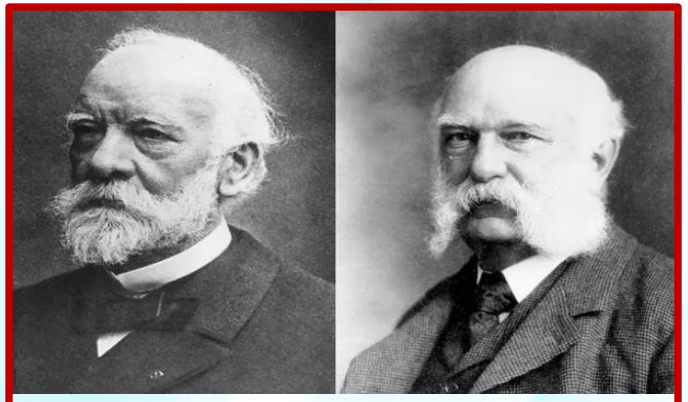


关键亲电物种：

反应机理及磺化反应的用途，课后自学

4. Friedel-Craft反应

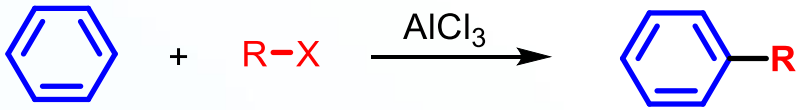
- 源于Friedel对留学生的一次好心帮助
- 好奇心驱使，不断进行试验研究
- 十一年间（1877-1888），发表针对该反应的相关研究论文60余篇
- 应用广泛，被命名为“Friedel-Craft 反应”并载入各国有机化学教科书



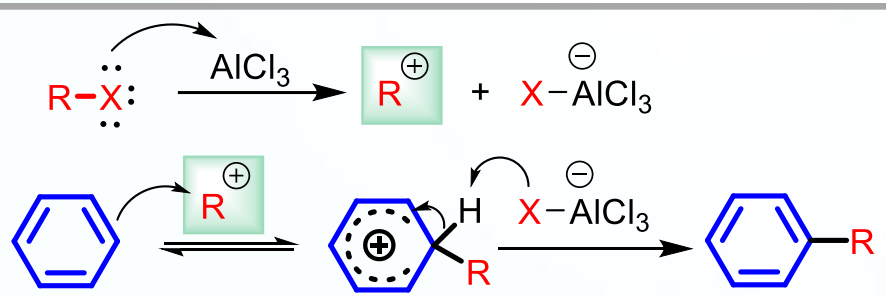
Charles Friedel　James M.Crafts

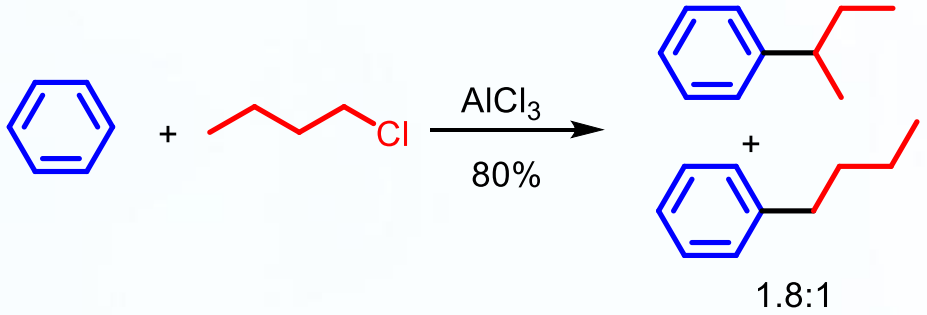
芳烃的亲电取代反应

Friedel-Craft 烷基化反应



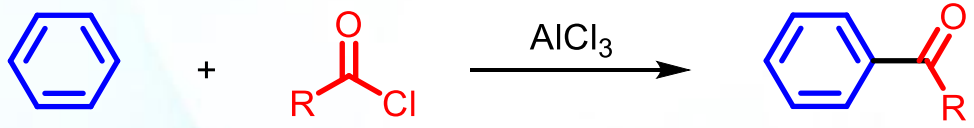
反应机理



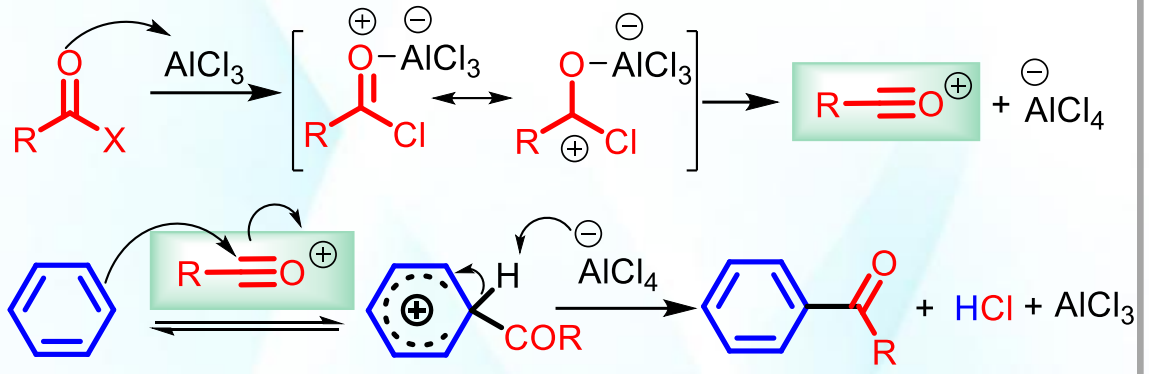


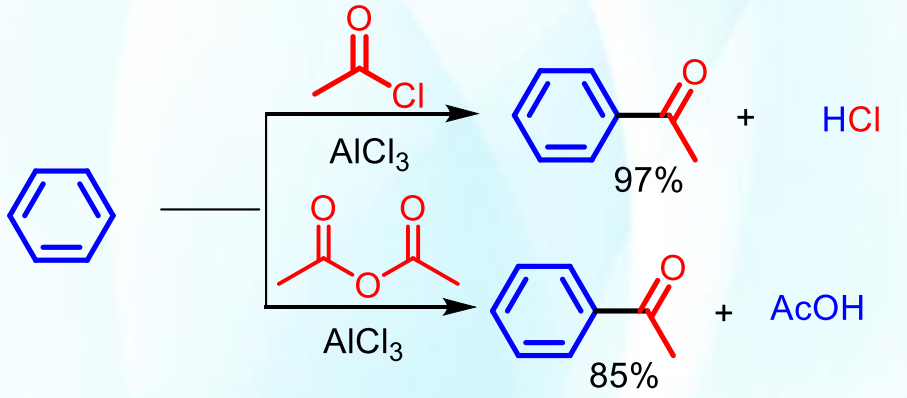
碳正离子易发生重排，产生混合物

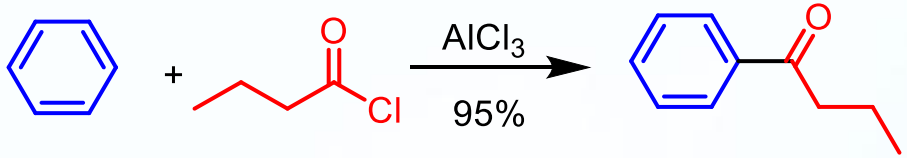
Friedel-Craft 酰基化反应

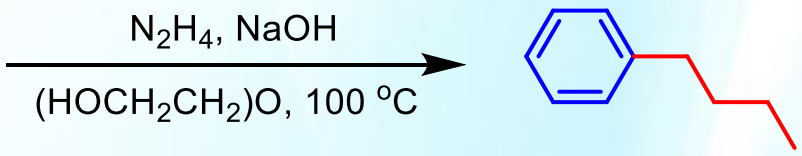


反应机理





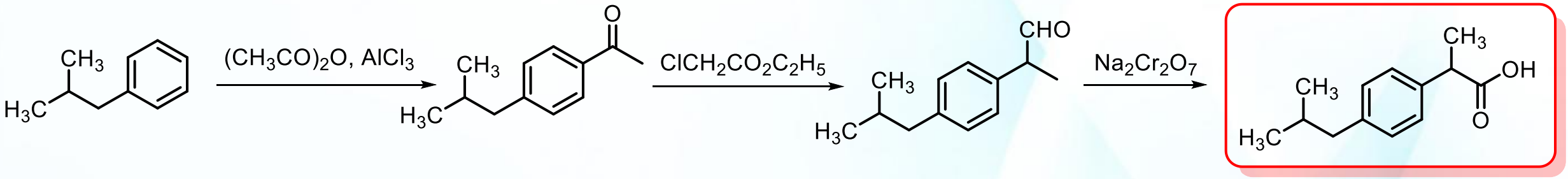




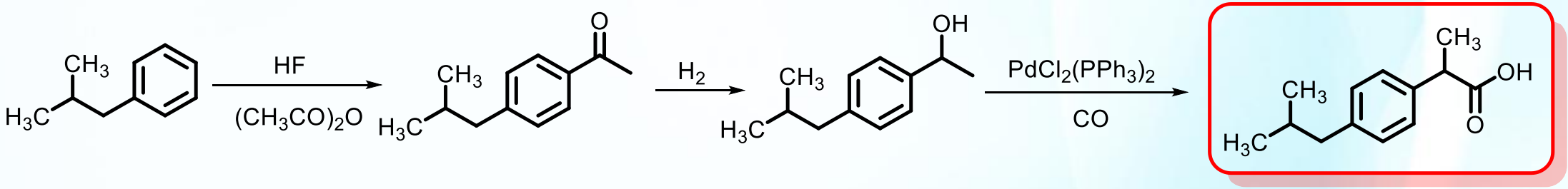
芳烃的亲电取代反应

布洛芬的工业合成路线

路线1

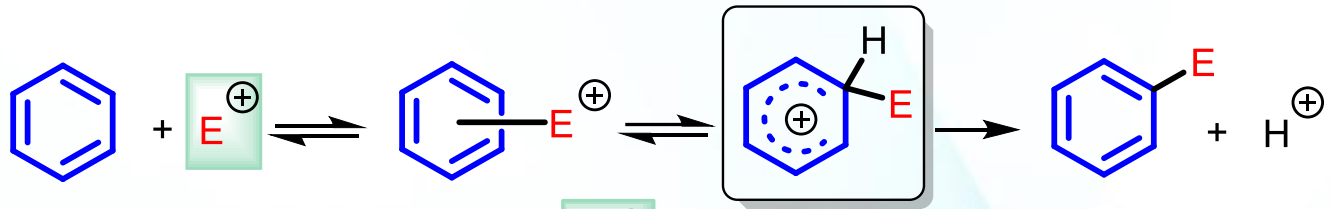


路线2

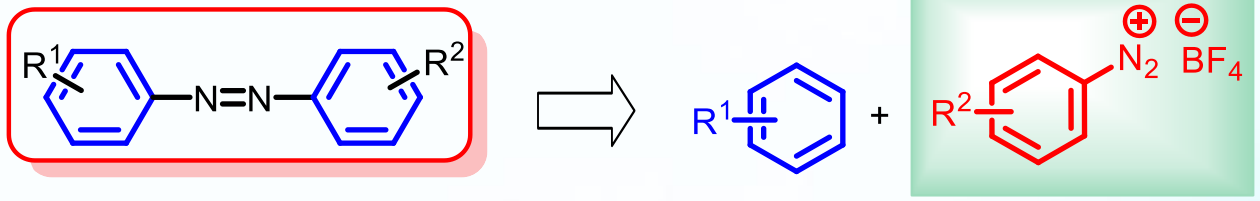


芳烃的亲电取代反应

小结：



X_2/FeX_3	浓H_2SO_4/HNO_3	浓H_2SO_4或发烟硫酸	$AlCl_3$	$AlCl_3$
卤代反应	硝化反应	磺化反应	烷基化	酰基化



如何制备？

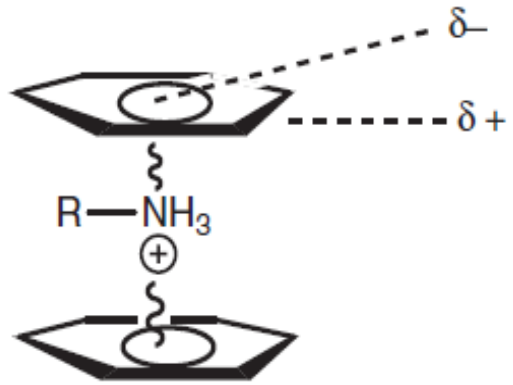
带取代基的芳烃亲电反应位点？

Properties

- Many aromatic compounds have a characteristic aroma and will burn with a smoky flame.
- They are hydrophobic, nonpolar molecules which will dissolve in organic solvents and are poorly soluble in water.
- Aromatic molecules can interact with each other through intermolecular bonding by van der Waals interactions.

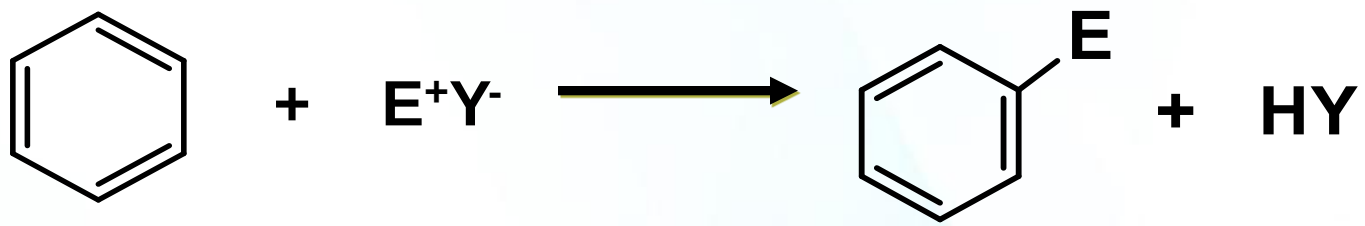
van der Waals interactions

However, induced dipole interactions are also possible with alkyl ammonium ions or metal ions where the positive charge of the cation induces a dipole in the aromatic ring such that the face of the ring is slightly negative and the edges are slightly positive. This results in the cation being sandwiched between two aromatic rings.



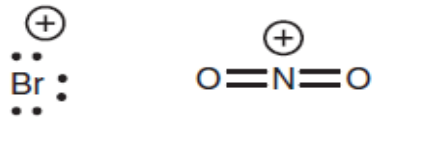
Induced dipole interaction

Electrophilic Substitutions of Benzene



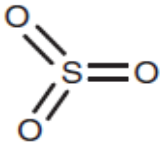
An electrophilic substitution involves the substitution of one electrophile (a proton) from the aromatic ring with another electrophile. The aromatic ring remains intact.

E^+

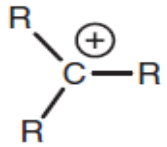


Halogenation

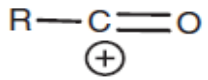
Nitration



Sulfonation



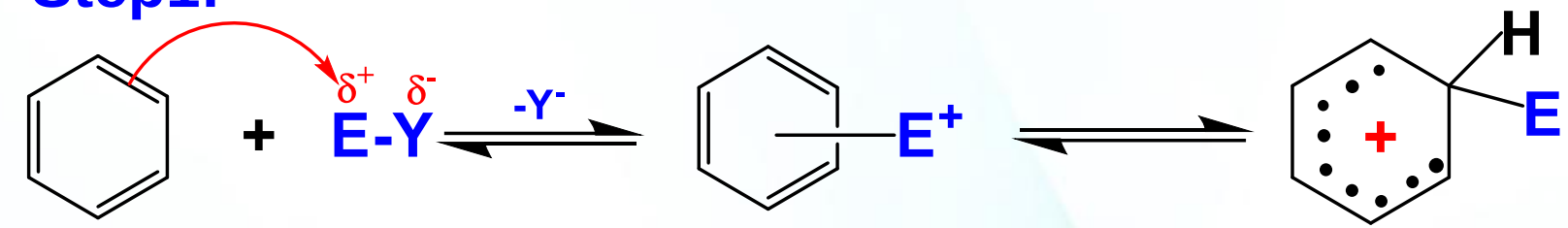
Friedel-Crafts Alkylation



Friedel-Crafts Acylation

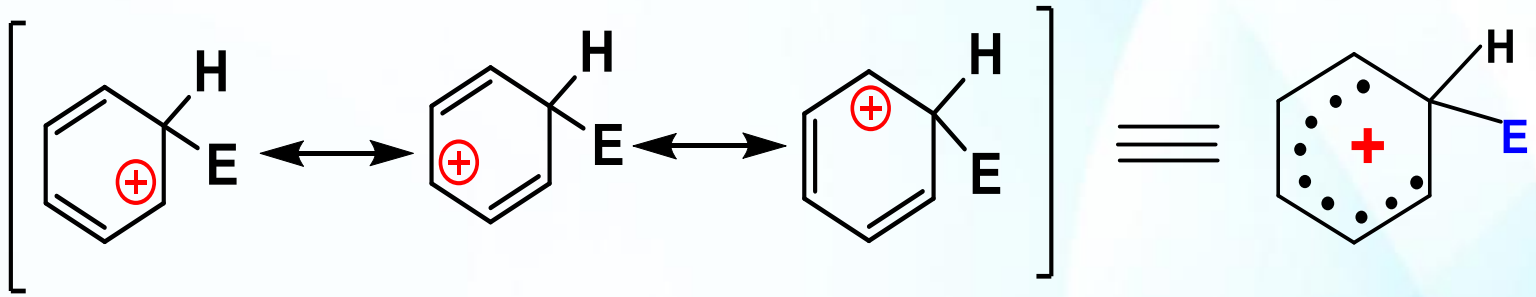
Mechanism

Step1:



Substrate Elictrophlie

intermediate

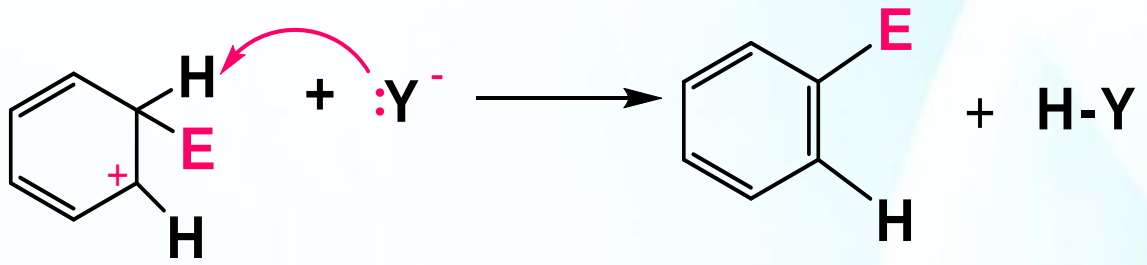


Resonance structure

The aromatic ring uses two of its π electrons to form a bond to the electrophile which results in a positively charged intermediate.

Electrophilic substitution is aided by the fact that the positively charged intermediate is stabilized by resonance, resulting in delocalization of the positive charge.

Step2:



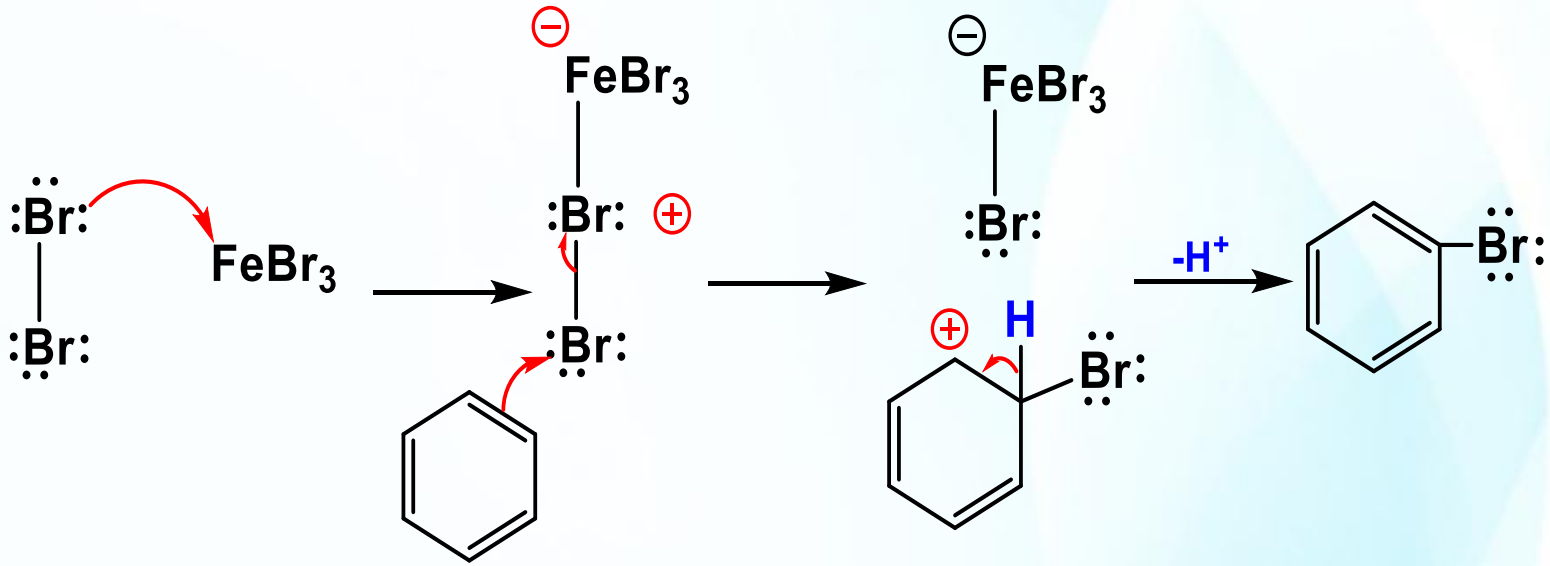
product

A proton is lost from the ring and the electrons of the broken C-H bond are used to reform the π bond and restore aromaticity.

Halogenation

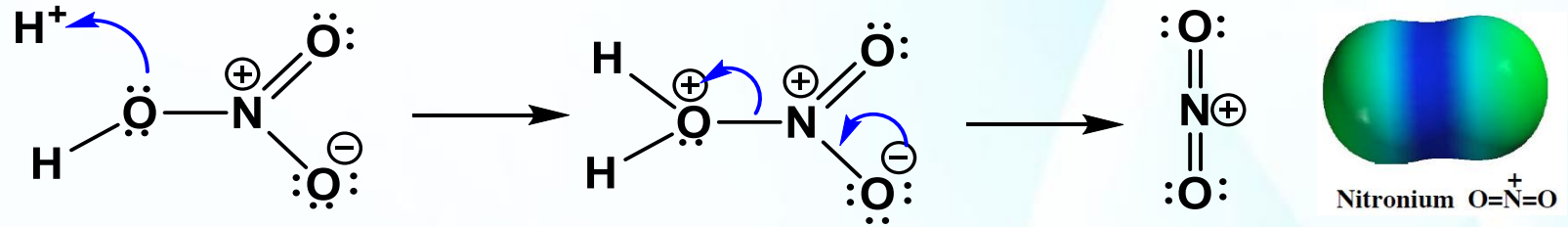
Benzene can be halogenated with chlorine and bromine.

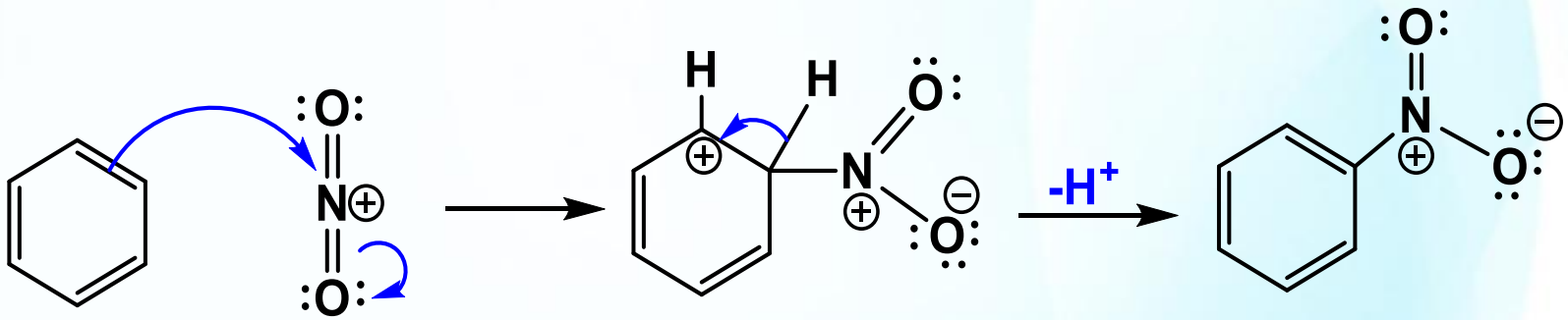
A Lewis acid such as $FeBr_3$ or $FeCl_3$ is required in order to activate the halogen and make it more electrophilic.



Nitration

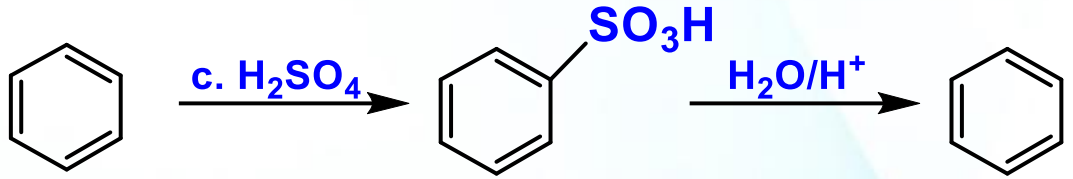
Nitration is carried out using *concentrated nitric acid* and *sulfuric acid*.

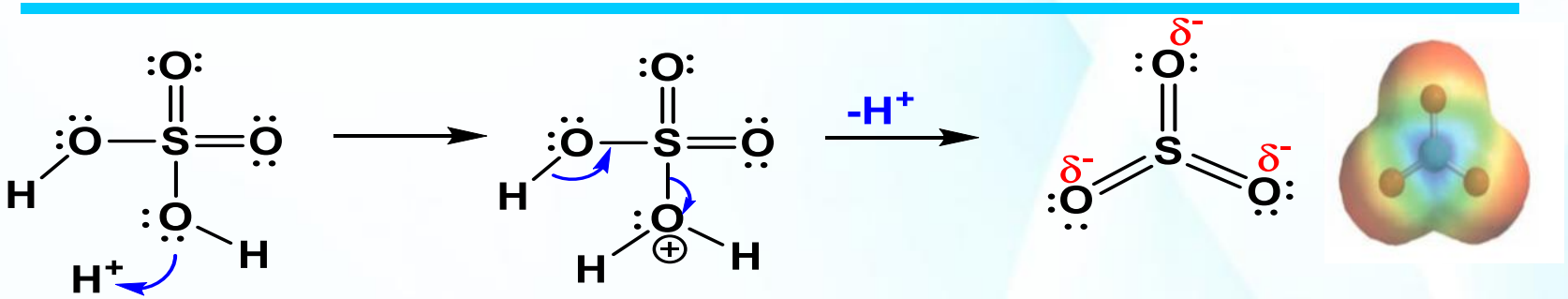




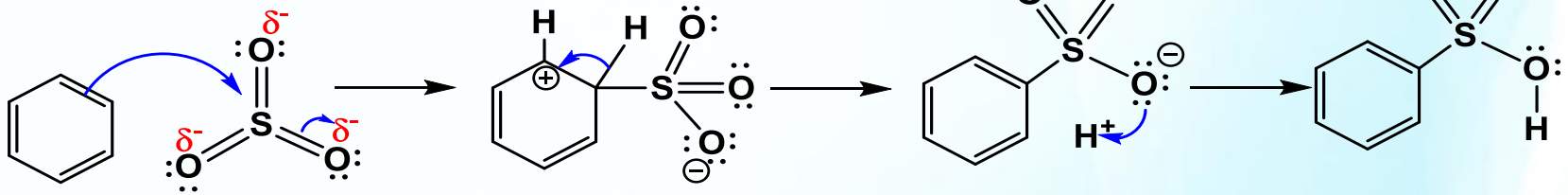
Sulfonation

Benzene is sulfonated with *concentrated sulfuric acid*.

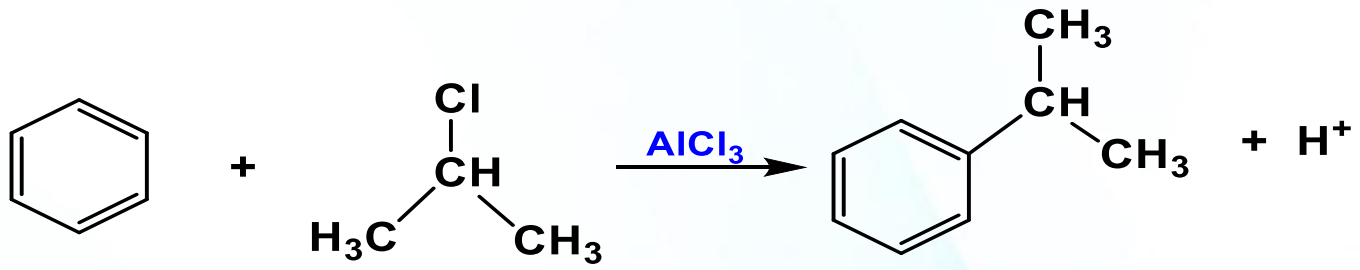


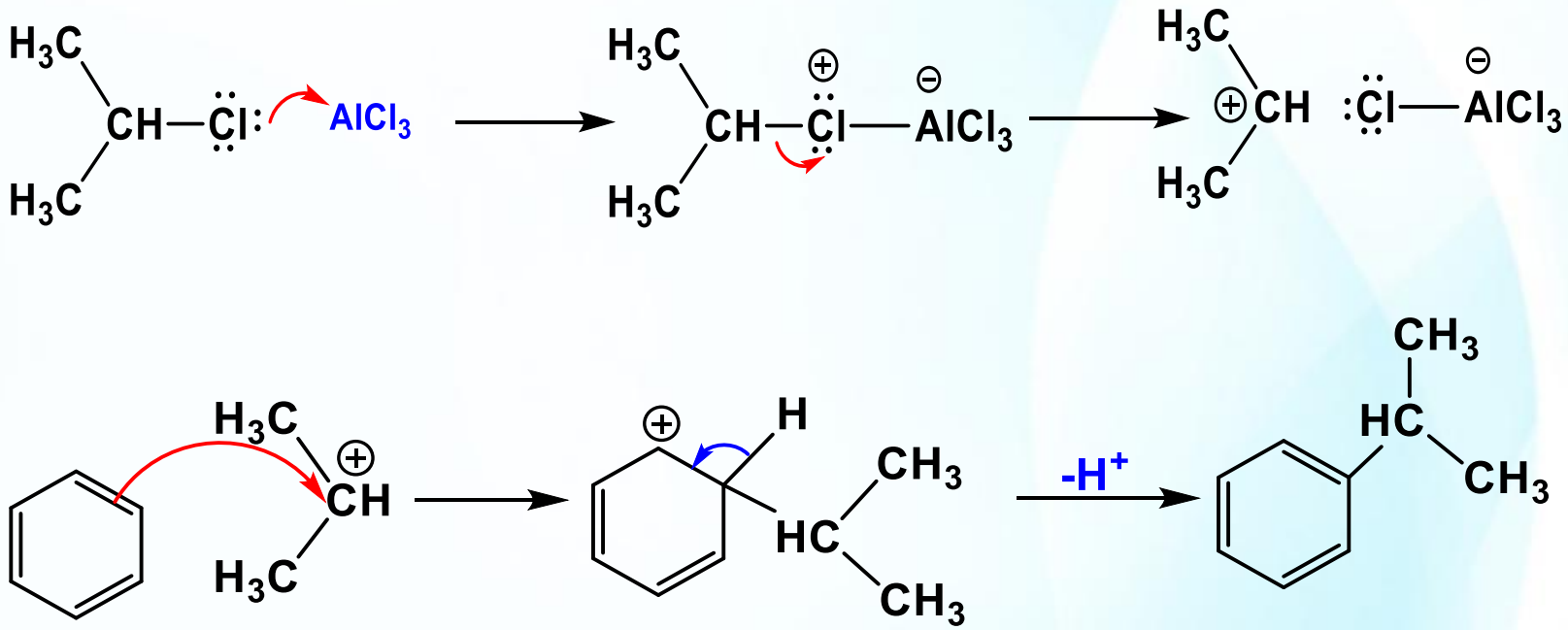


The reaction involves the generation of sulfur trioxide which acts as the electrophile.

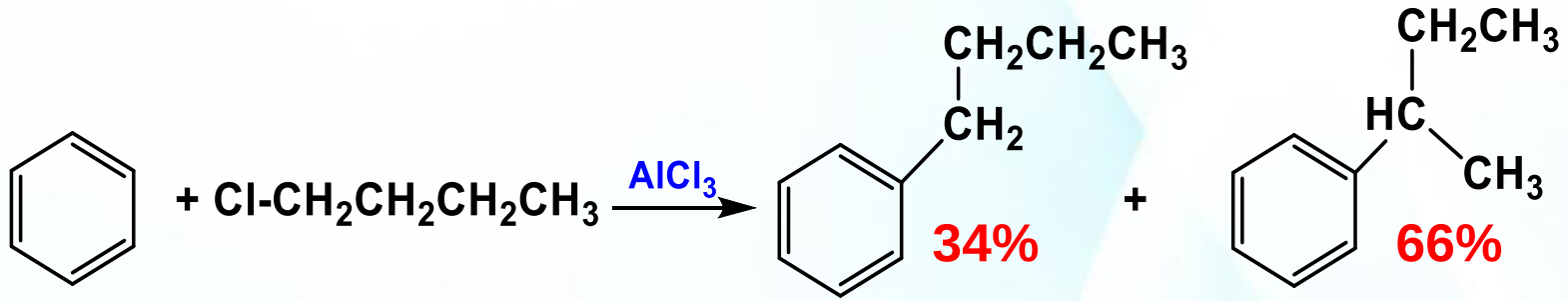


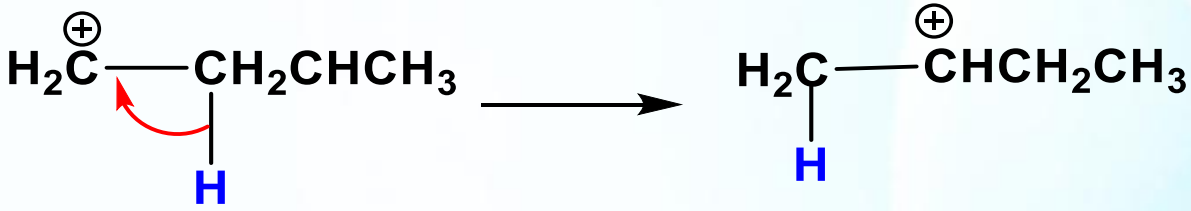
Friedel- Crafts Alkylation

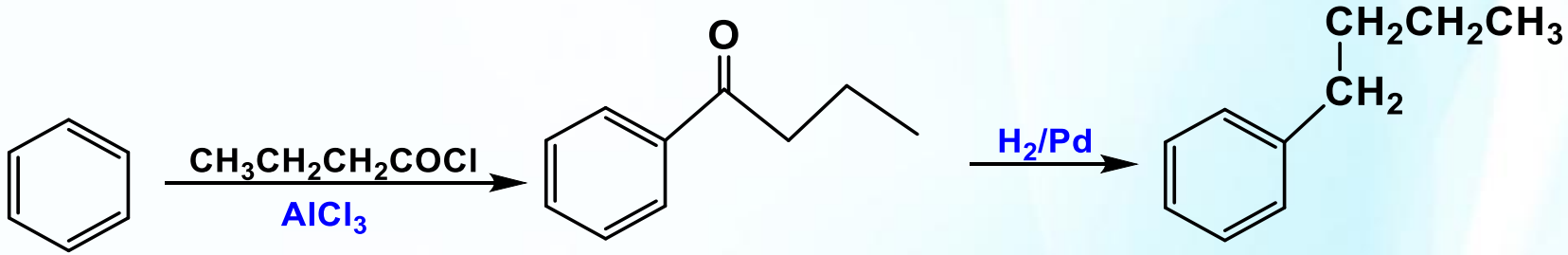




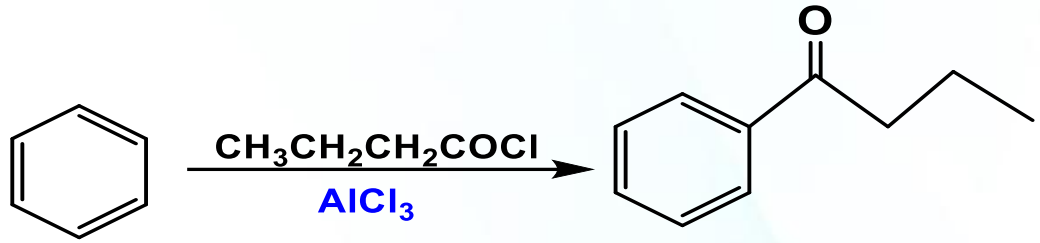
Primary alkyl chlorides are not ideal for the Friedel-Crafts reaction since the primary carbocations generated can rearrange to more stable secondary or tertiary carbocations.



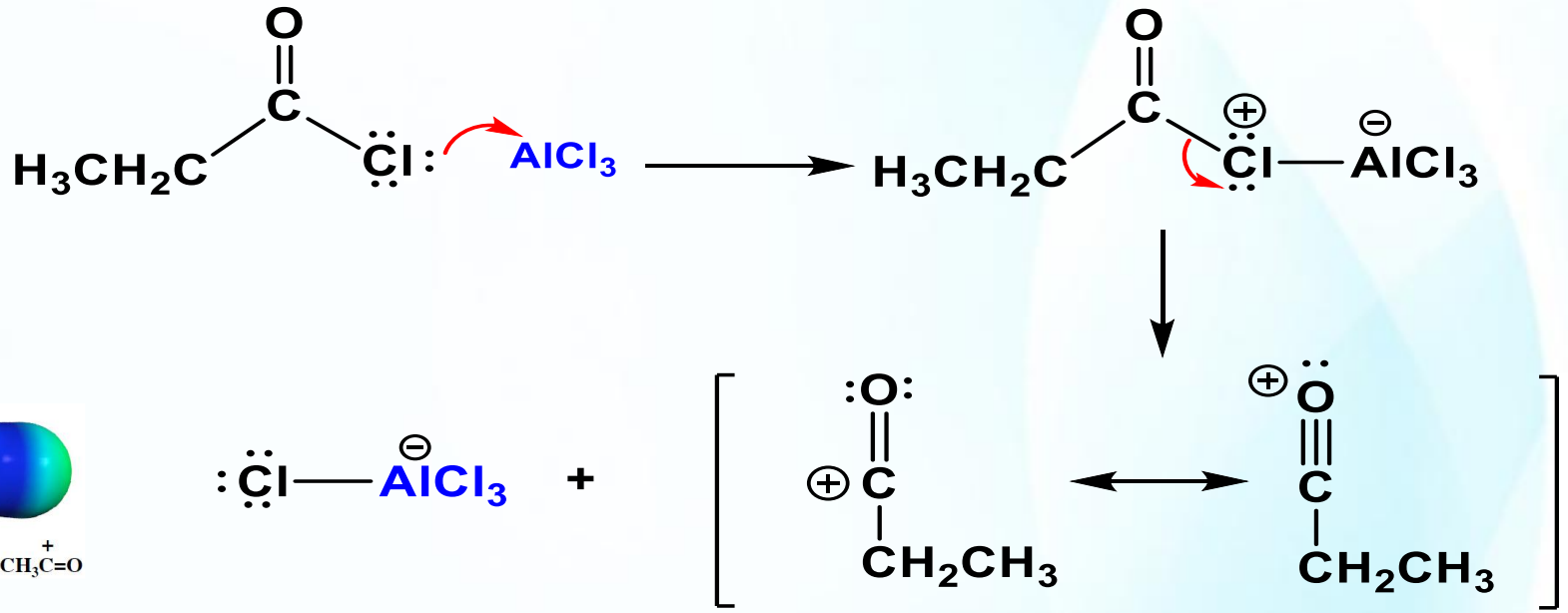




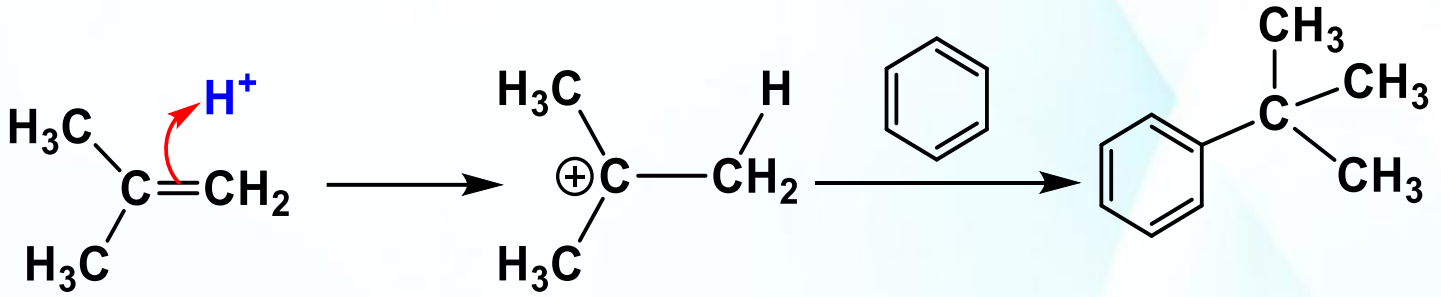
Friedel- Crafts Acylation

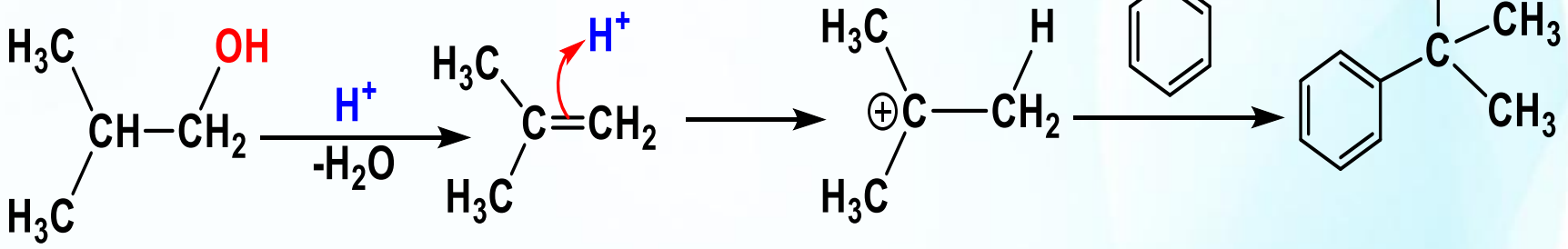


An acylium ion is generated as the electrophile and has the advantage over a carbocation in that it does not rearrange.



The Friedel-Crafts alkylation can also be carried out using an alkene or an alcohol in the presence of a mineral acid.

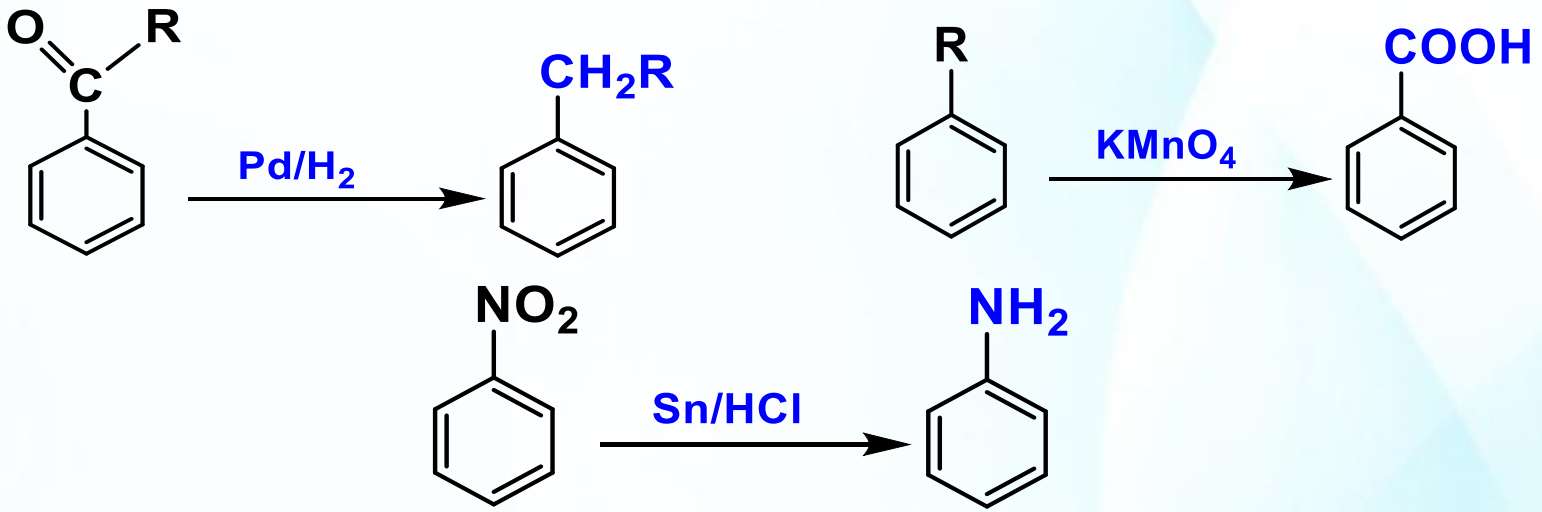




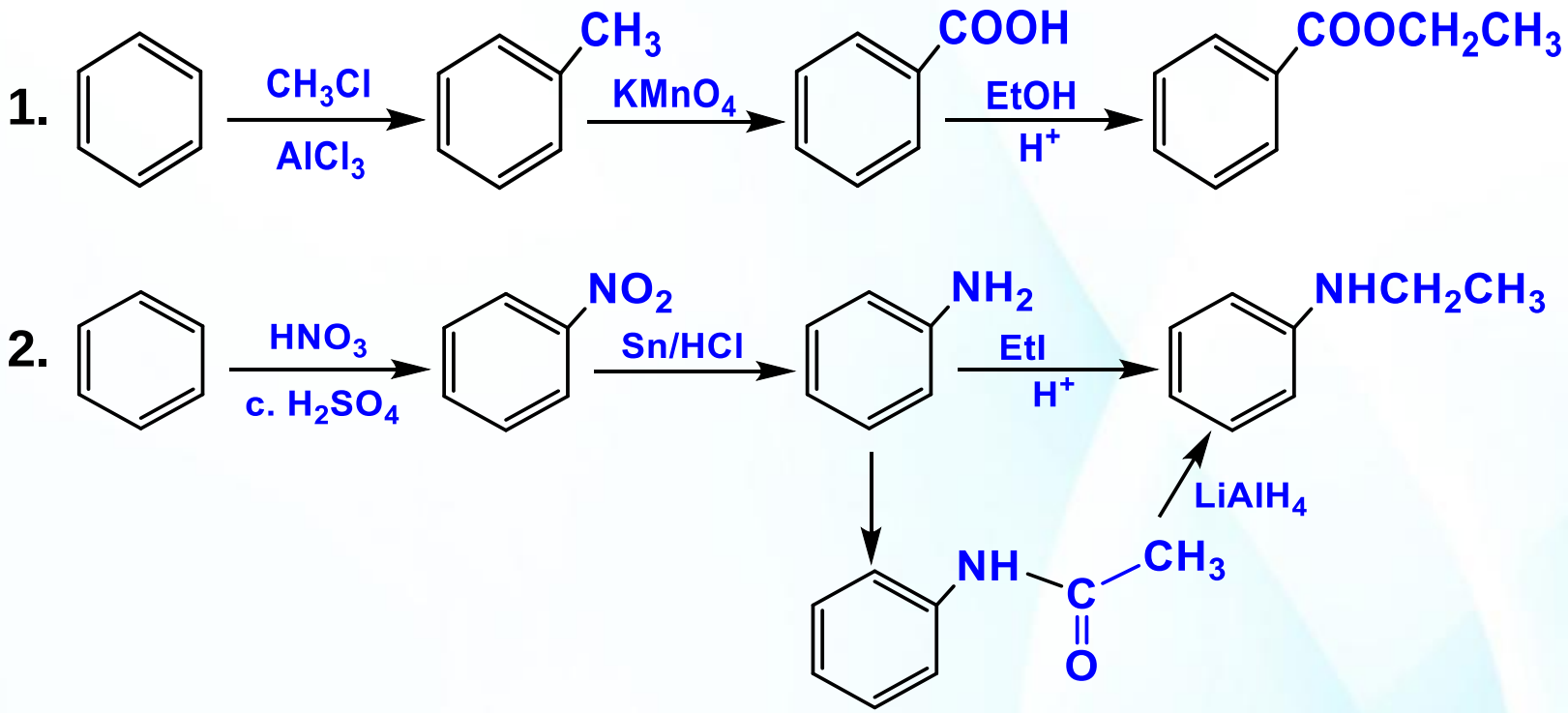
Synthesis of Mono-Substituted Benzenes

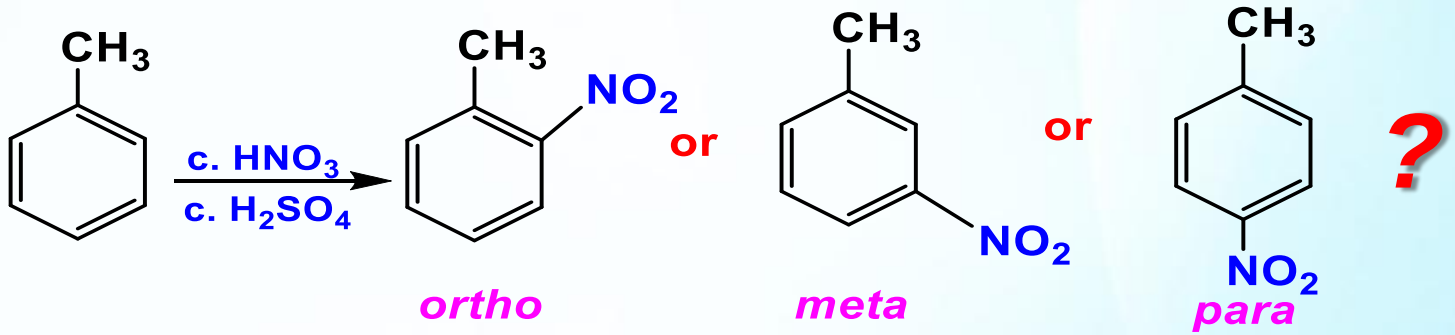
Some substituents cannot be introduced directly onto an aromatic ring by electrophilic substitution.

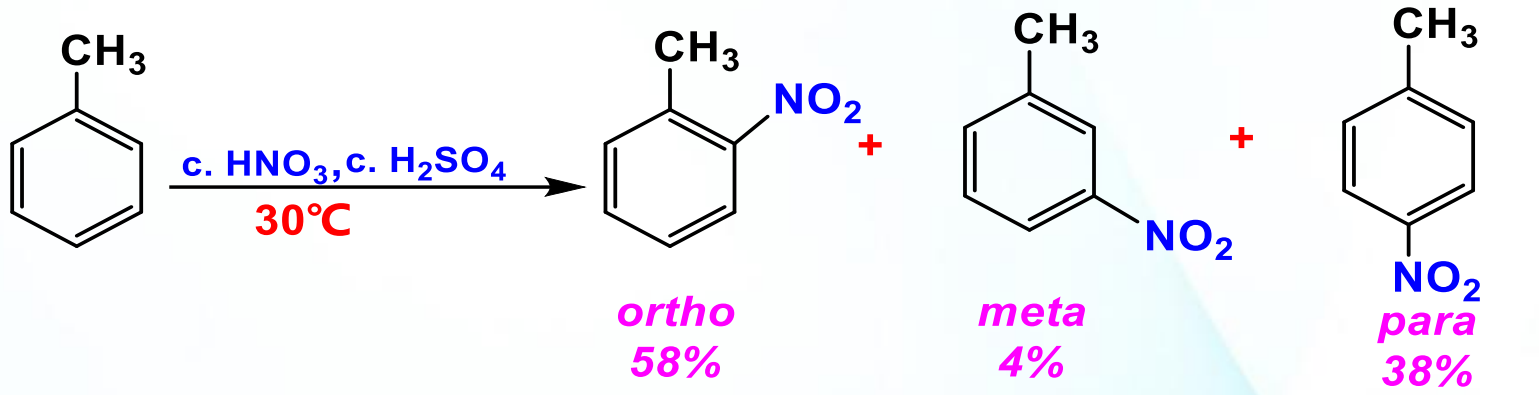
These include the following groups： **-NH_2, -NHR, -NR_2, -$NHCOCH_3$, -COOH,-CN,-OH.**

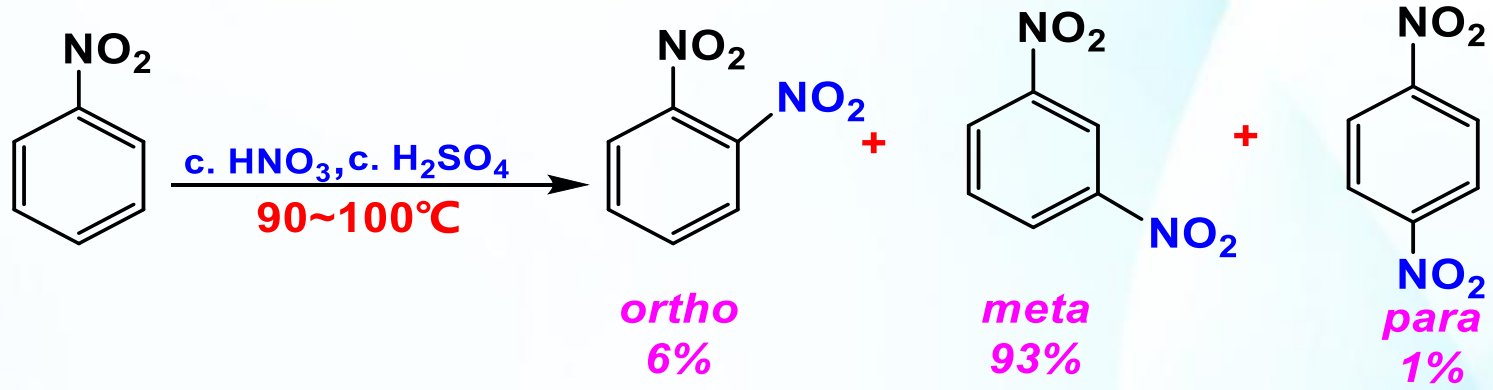


Nitro, alkyl, and acyl groups can readily be added by electrophilic substitution and can then be converted to amino, carboxylic acid, and alkyl groups respectively.


1.
CH3Cl
AlCl3
CH3
KMnO4
COOH
EtOH
H+
COOCH2CH3
2.
HNO3
c. H2SO4
NO2
Sn/HCl
NH2
EtI
H+
NHCH2CH3
LiAlH4
NH
C
O
CH3


CH3
c. HNO3
c. H2SO4
CH3
NO2
or
ortho
CH3
NO2
meta
or
CH3
NO2
para
?





Q1: What is the effect of a substituent on the ***rate*** of electrophilic substitution reaction?

Q2: What is the effect of a substituent on the ***regioselectivity*** of electrophilic substitution reaction?

Substituent Effect

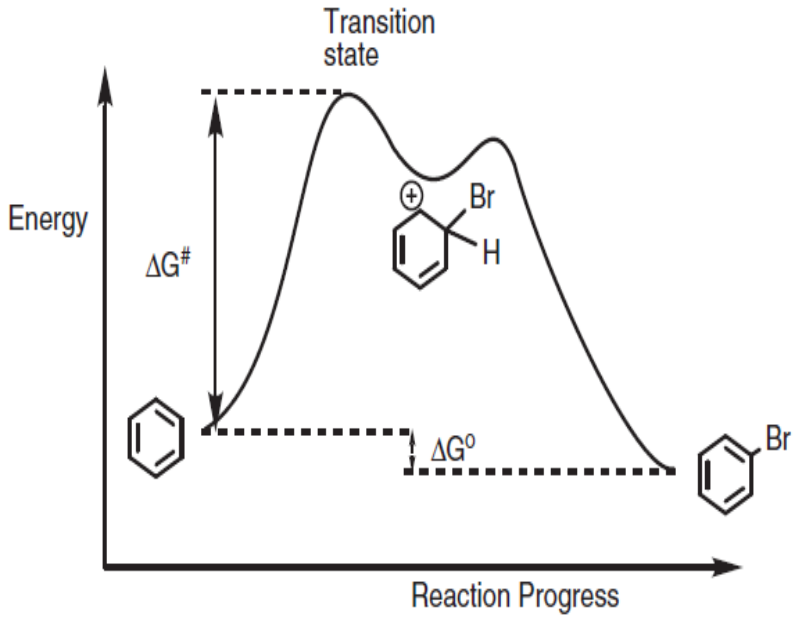
The substituent can affect the rate and the position of further substitution.

- **Activating groups which direct *ortho/para* by inductive effects;**
- **Deactivating groups which direct *meta* by inductive effects;**
- **Activating groups which direct *ortho/para* by resonance effects;**
- **Deactivating groups which direct *ortho/para* by resonance effects.**

There are no substituents which activate the ring and direct meta.

Classification of Substituents

Ortho-para directors	Meta directors
Strongly activating	**Strongly deactivating**
$-NR_2$, NH_2,-OH	$-{}^{+}NR_3$, $-NO_2$
Moderately activating	**Moderately deactivating**
$-OCH_3$, $-NHCOCH_3$	-CN, $-SO_3H$
Weakly activating	**Weakly deactivating**
$-CH_3$, $-C_6H_5$	$-COCH_3$,-COOH, $-COOCH_3$,-CHO
Weakly deactivating*	
-X(Cl, Br, I)	

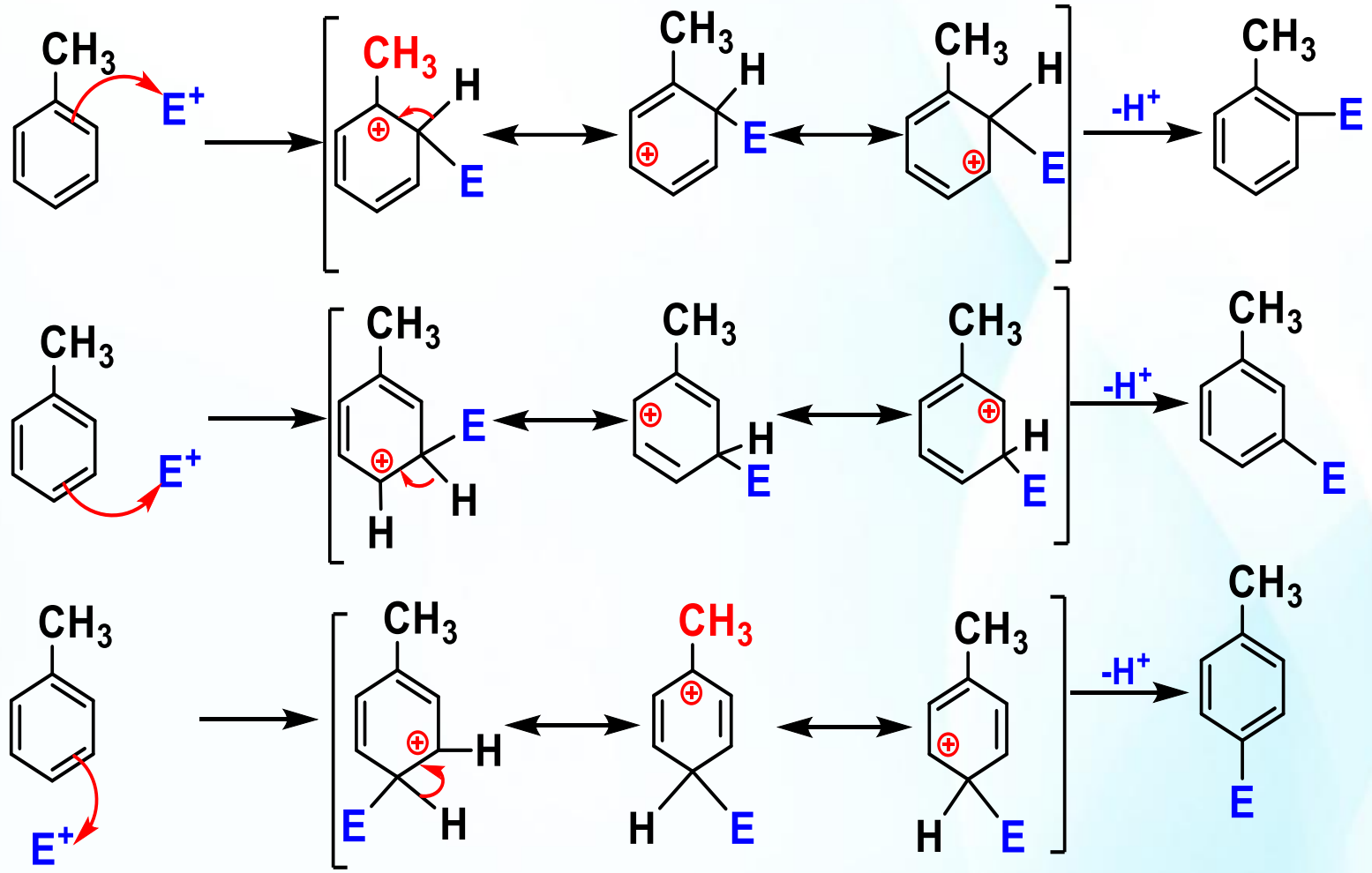


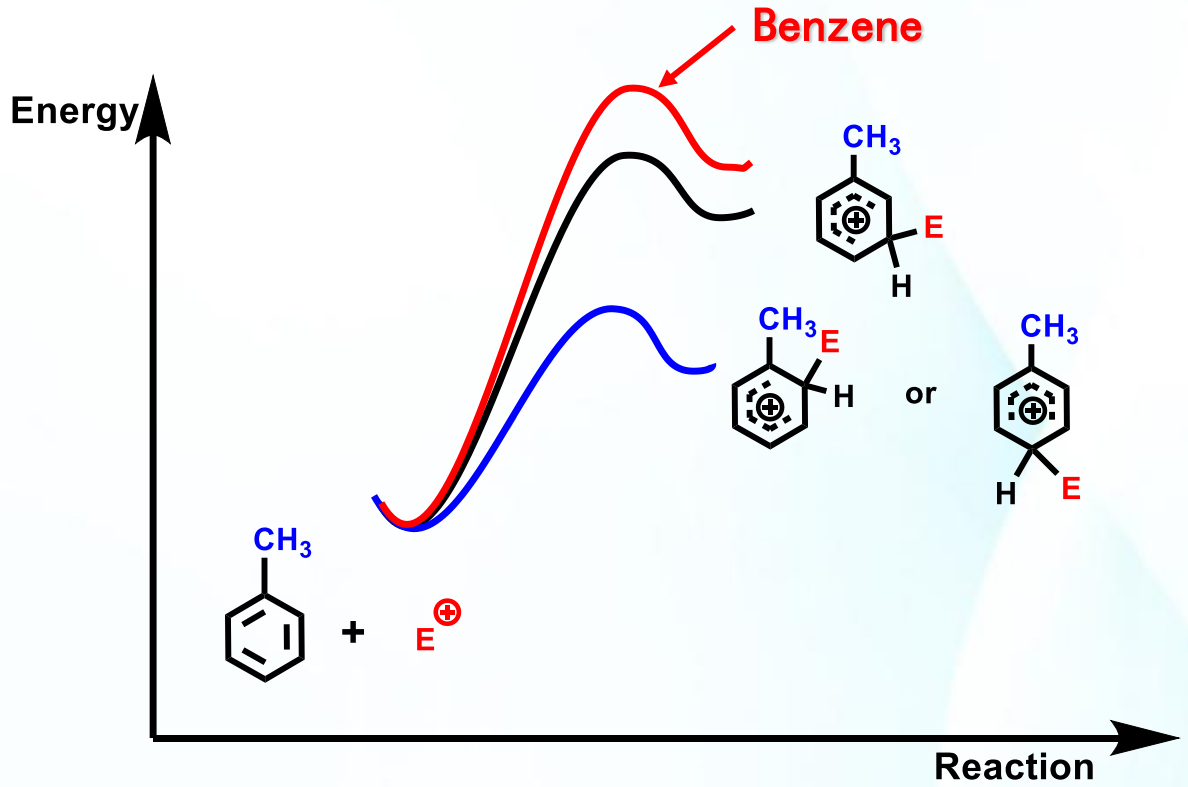
The first step of electrophilic substitution is the rate-determining step.

The ease with which electrophilic substitution takes place is determined by the activation energy of this step, which depends on the stability of the transition state.

The transition state resembles the carbocation intermediate; and so factors stabilizing the carbocation also stabilize the transition state and lower the activation energy.

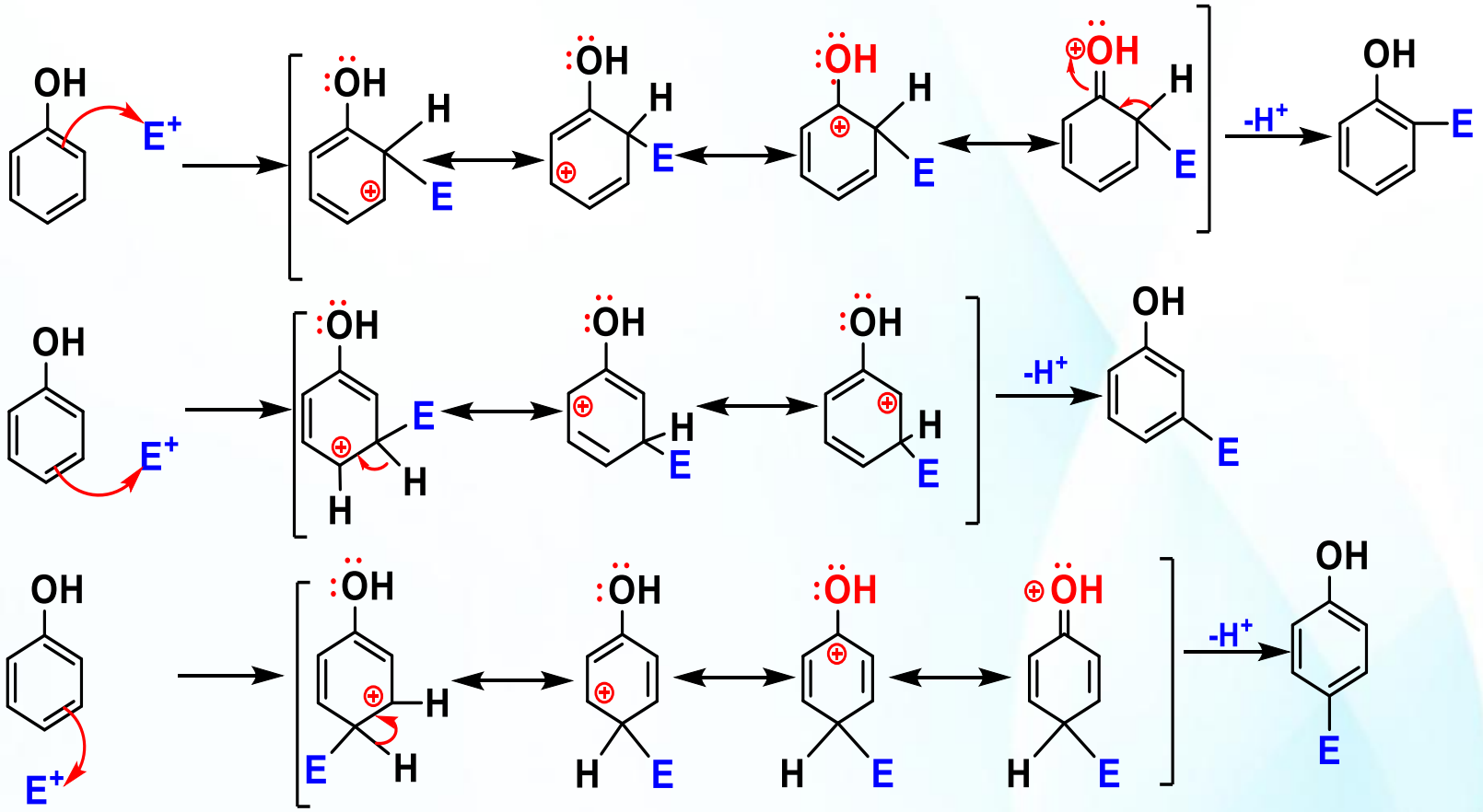
Methyl Benzene





An alkyl group can stabilize a neighboring positive charge by an inductive, electron-donating effect which results in some of the positive charge being spread over the alkyl group.

Phenol

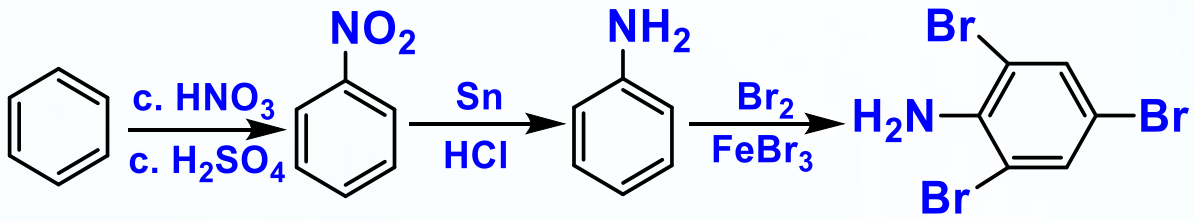


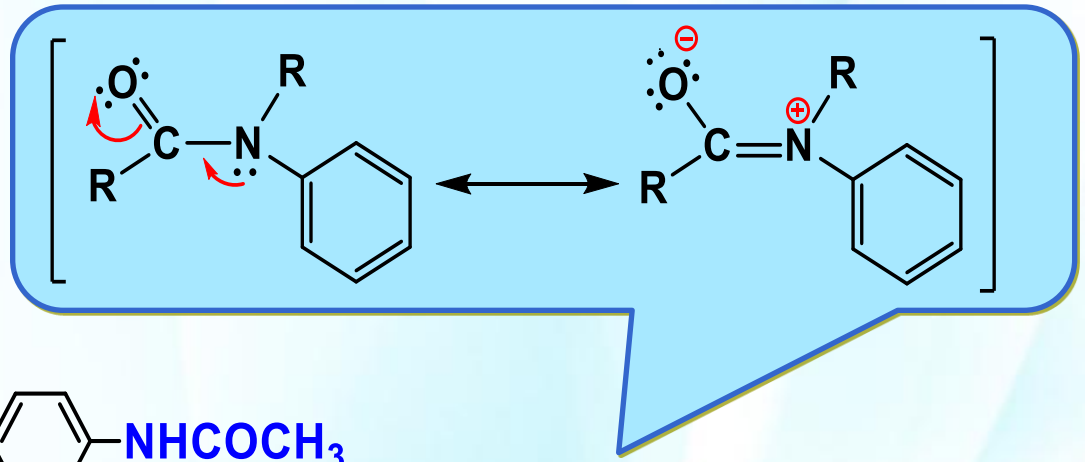
Substituents such as phenols, ethers, amines, and amides activate the aromatic ring and direct substituents to the ortho and para positions.

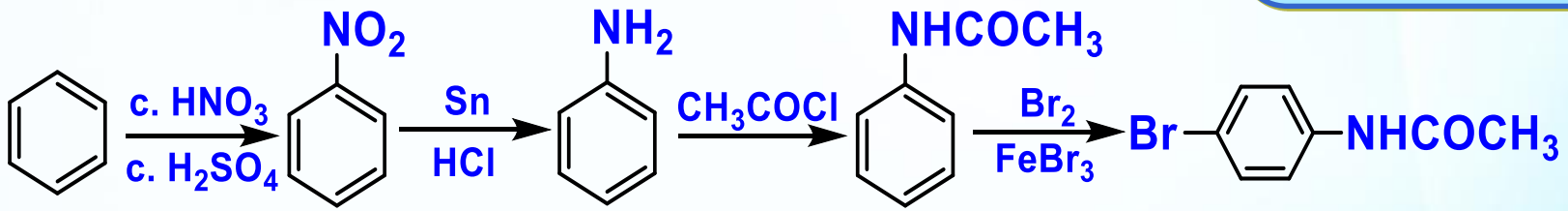
In all these substituents, a nitrogen or an oxygen with a lone pair of electrons is attached directly to the ring.

This resonance effect outweighs any electron-withdrawing effect of the oxygen or nitrogen.

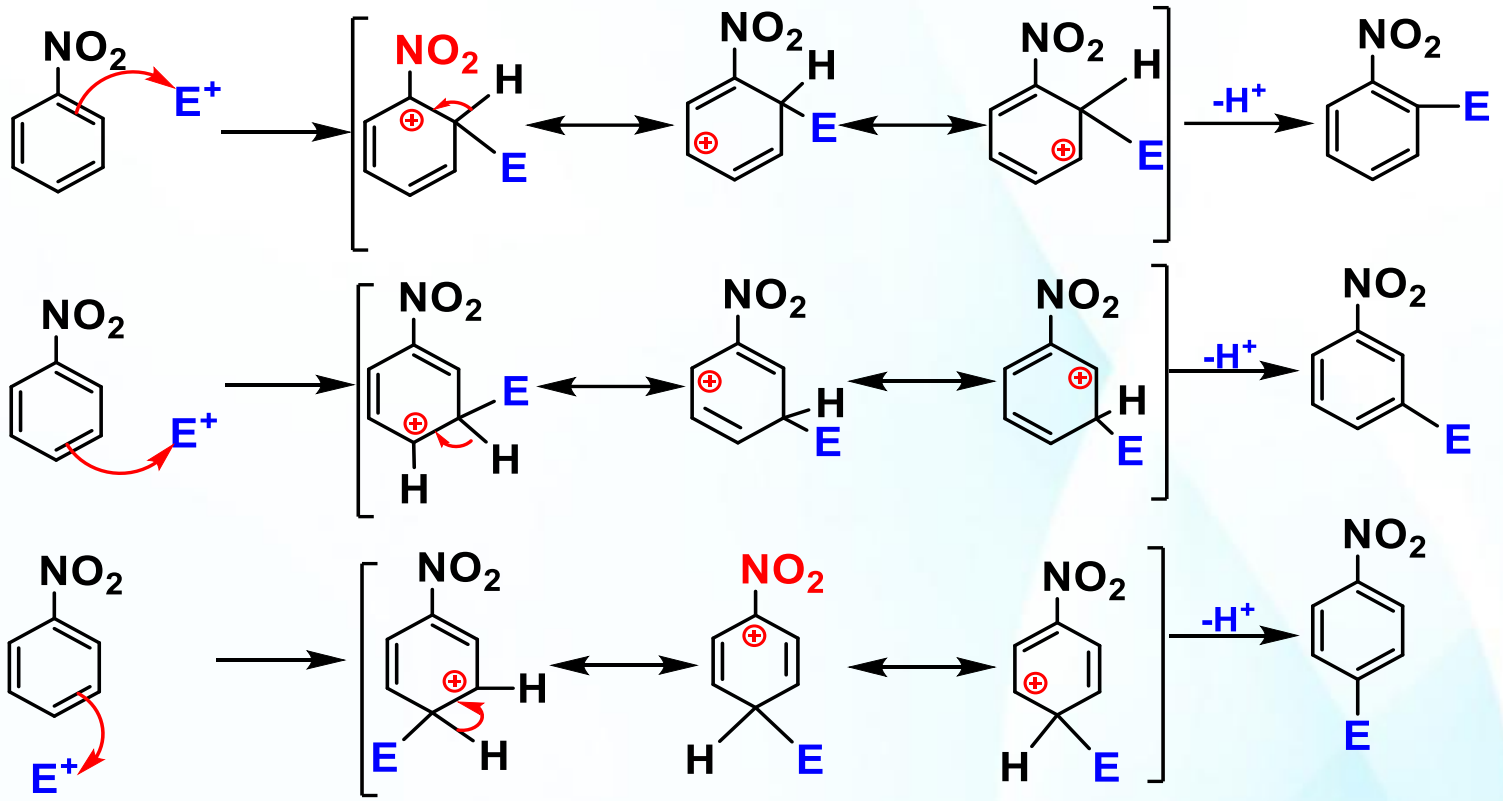
Amides are less activating than amines.



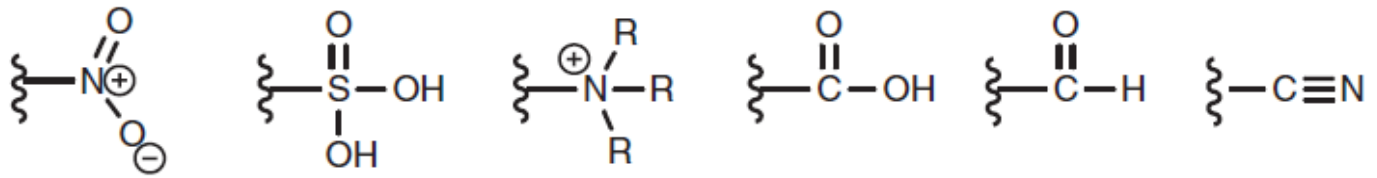




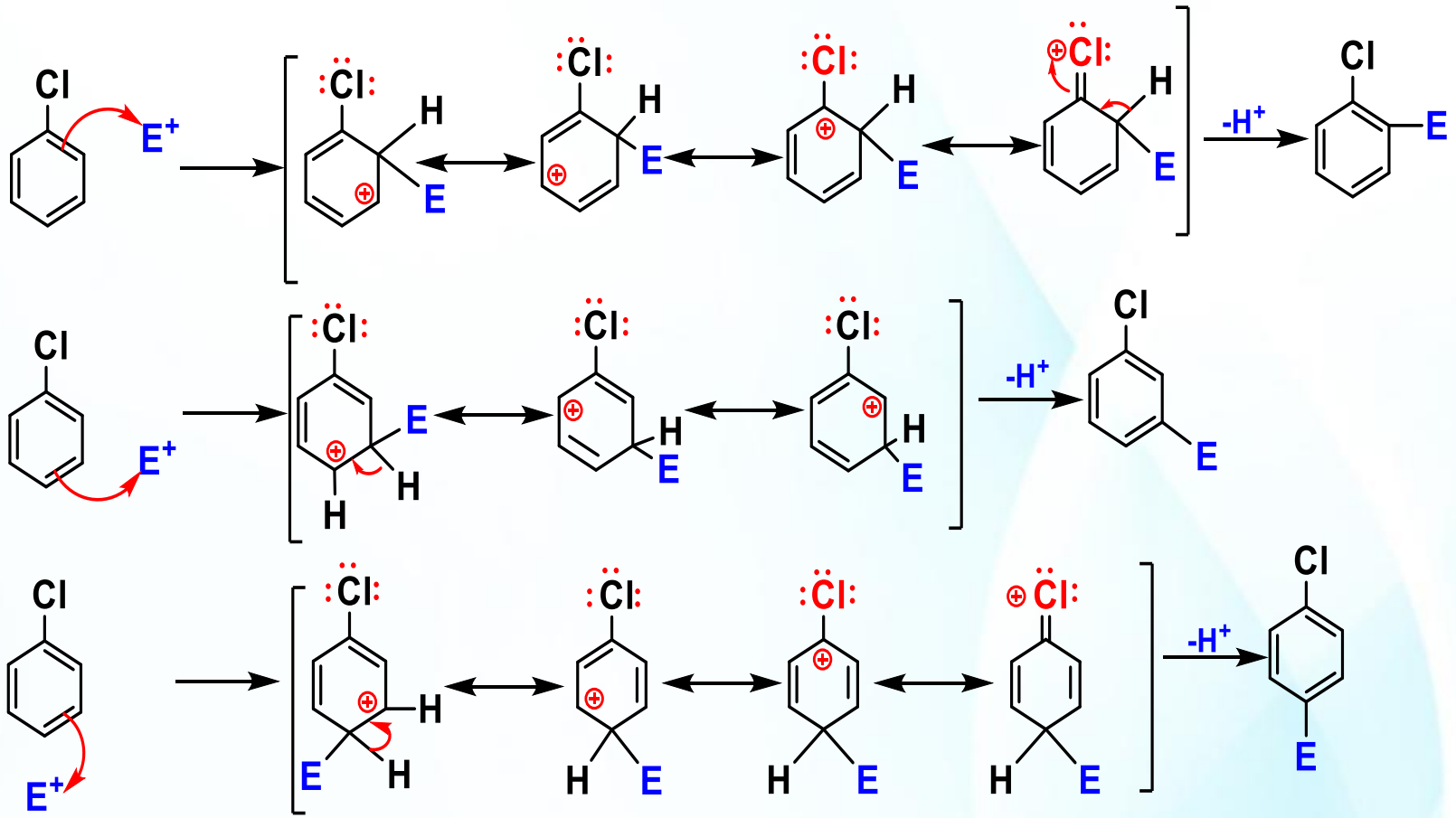
Nitro Benzene



***meta* attack is favored over *ortho/para*.**

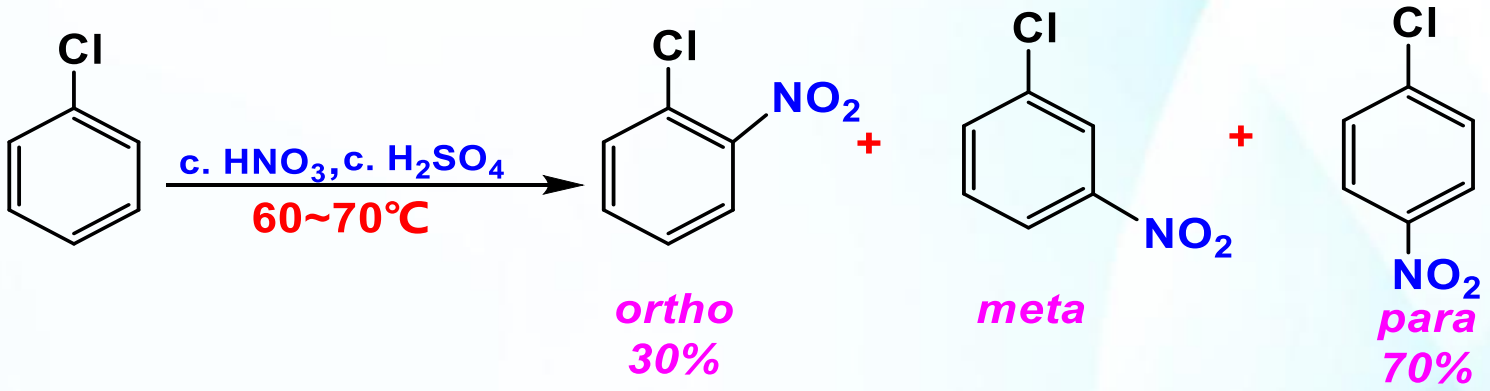


Chloro Benzene



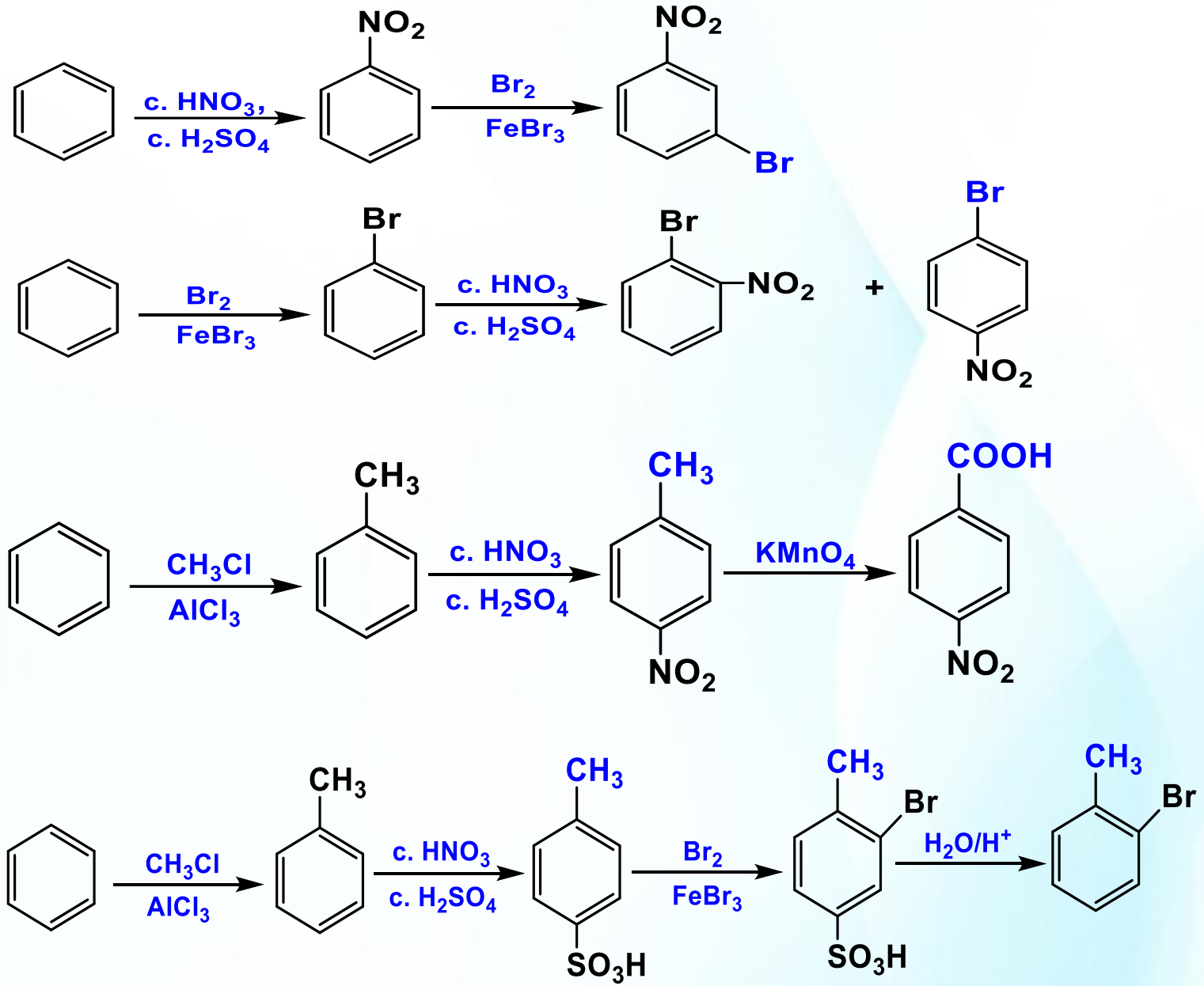
This resonance effect is more important than the inductive effect.

Halogen substituents deactivate aromatic rings towards electrophilic substitution by an inductive effect. These atoms are strongly electronegative and have an electron-withdrawing effect on the ring making it less nucleophilic and less reactive.



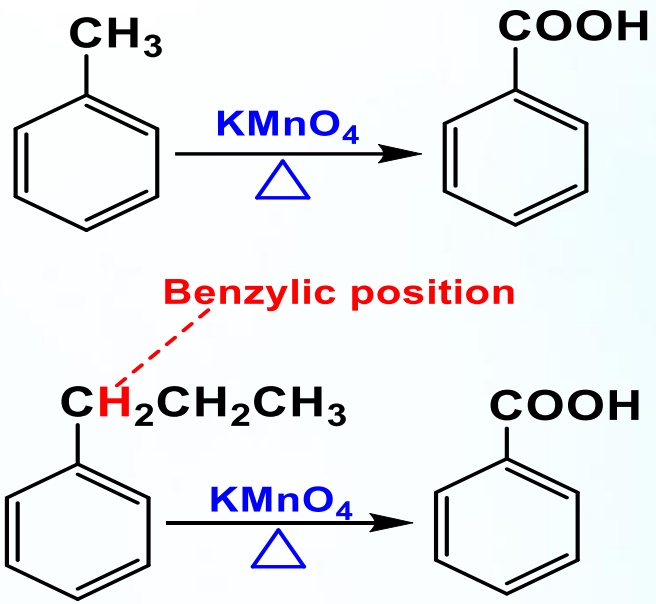
However, once electrophilic substitution does take place, halogens direct to the ortho and para positions due to a resonance effect which helps to delocalize the positive charge onto the halogen atoms.

Synthesis


NO2
c. HNO3,
c. H2SO4
Br2
FeBr3
Br
Br
Br2
FeBr3
c. HNO3
c. H2SO4
NO2
+
Br
NO2
CH3
CH3Cl
AlCl3
c. HNO3
c. H2SO4
CH3
NO2
KMnO4
COOH
NO2
CH3
CH3Cl
AlCl3
c. HNO3
c. H2SO4
CH3
SO3H
Br2
FeBr3
CH3
Br
SO3H
H2O/H+
CH3
Br

Oxidation

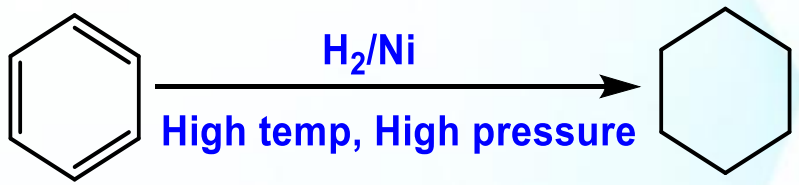
Aromatic rings are resistant to oxidation but alkyl chains attached to the ring are not. Alkyl substituents containing a benzylic hydrogen are oxidized to a carboxylic acid.



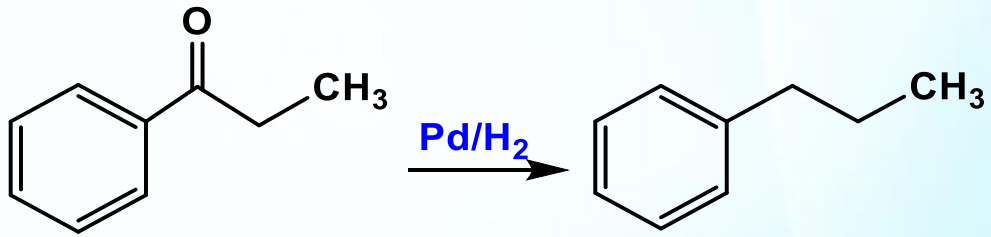
Alkyl groups lacking a benzylic hydrogen are not oxidized.

Reduction

The aromatic ring is difficult to reduce with hydrogen and requires vigorous reaction conditions using high pressure and heat, or strong catalysts such as Ni, Pd, etc.

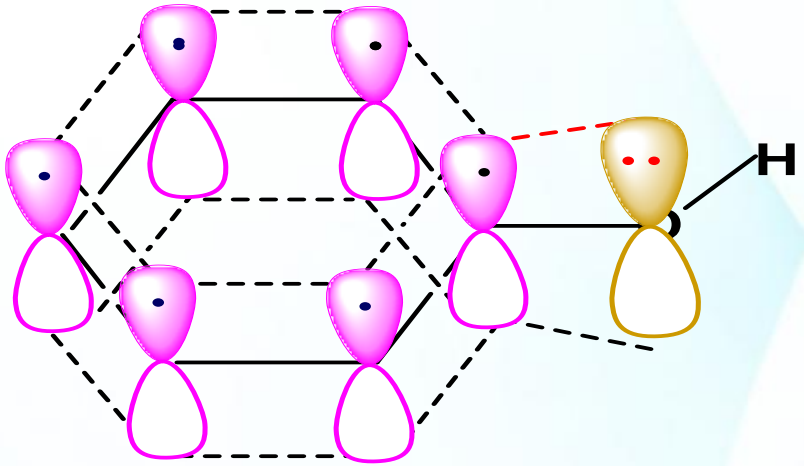


The resistance of the aromatic ring to reduction allows the selective reduction of substituents such as ketones and nitro groups without affecting the aromatic ring itself.



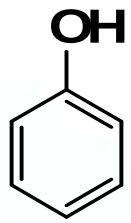
Phenols

The oxygen is sp^3 hybridized and the aryl carbon is sp^2 hybridized.

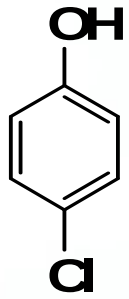


- 苯环上电子云密度增大 ——→ 环上**亲电取代容易**；
- C-O键变牢固 ——→ -OH**不易被取代**；
- O-H键极性增强 ——→ 羟基氢**酸性增强**。

1. Nomenclature

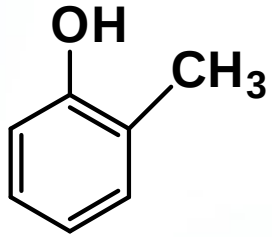


Phenol

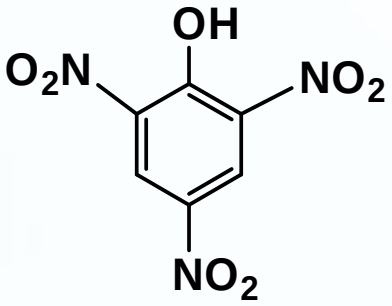


p-Chlorophenol

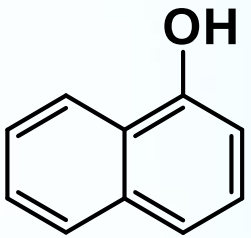
4-Bromo-2-nitrophenol



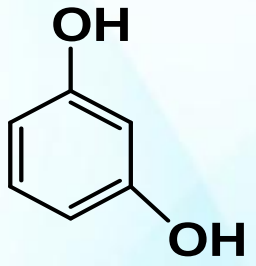
o-Cresol (2-Methylphenol)



2,4,6-trinitro phenol (Picric acid)



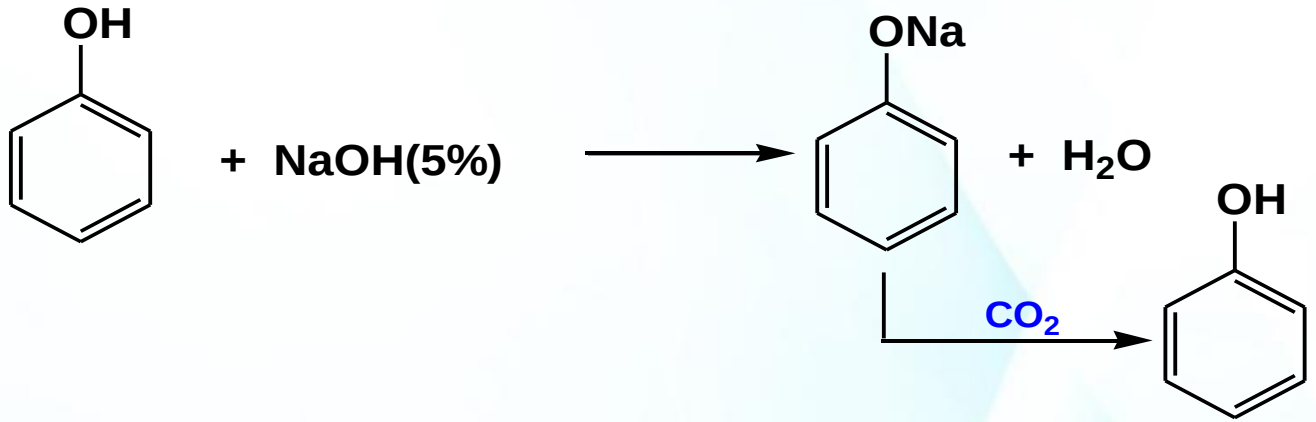
α- Naphthol



Resorcinol (1,3-Benzenediol)

2. Reactions of Phenols

(1) Acidity



问题：酚的酸性到底有多强?

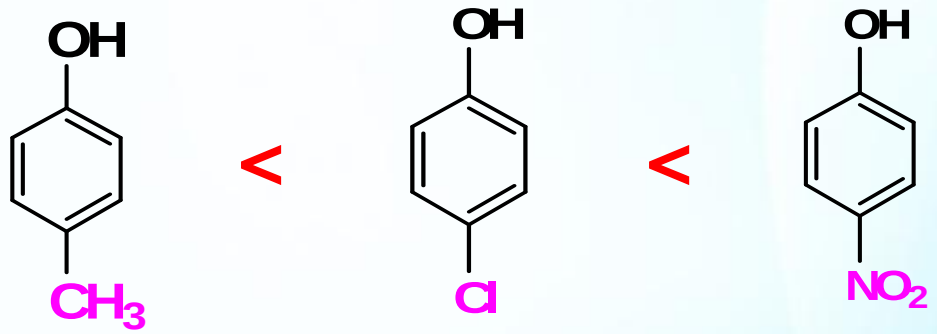
酸性： H_2CO_3 ＞ 酚 ＞ 醇

pKa: ≈6.4 ≈10 ≈18

Why?

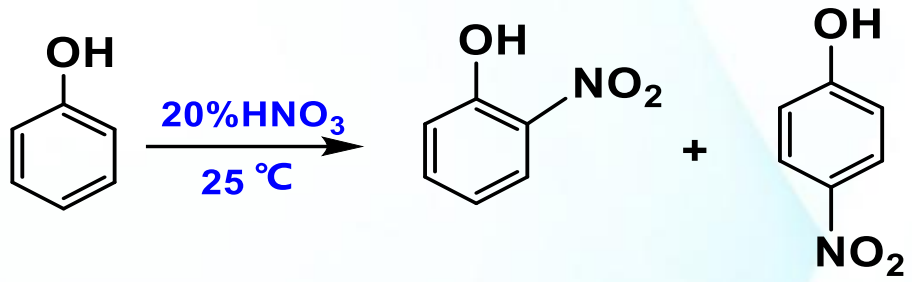
The phenoxide ion is stabilized by resonance and delocalization of the negative charge into the ring, which means that phenoxide ions are weaker bases than alkoxide ions.

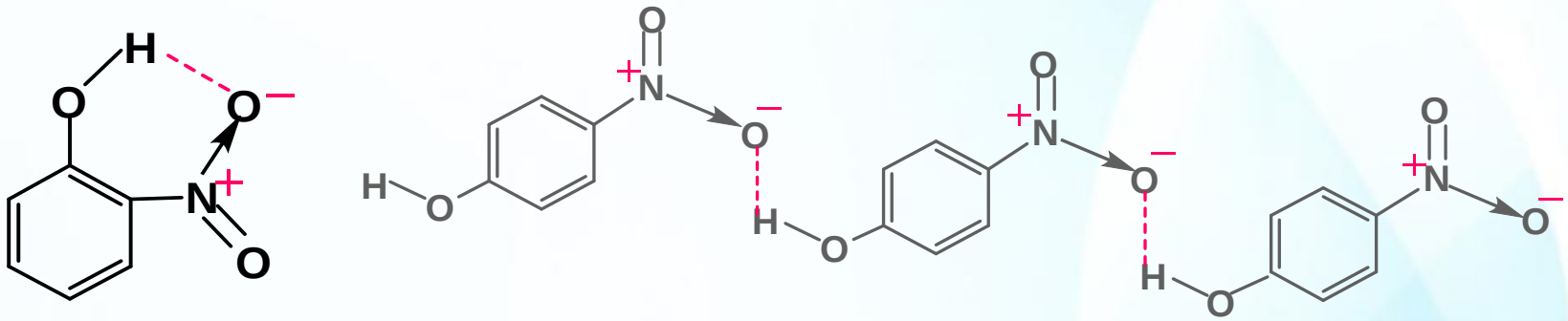
- **Acidity of substituted phenols:**

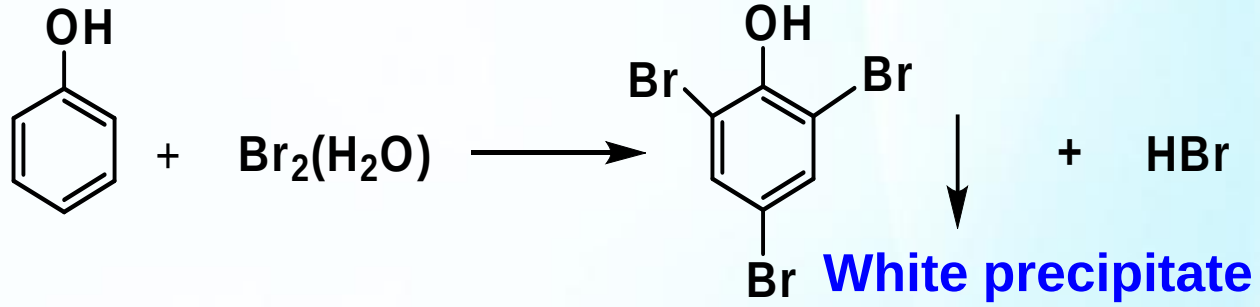


（2）Electrophilic Substitution

Phenols are powerful activating groups which direct electrophilic substitution to the ortho and para positions.

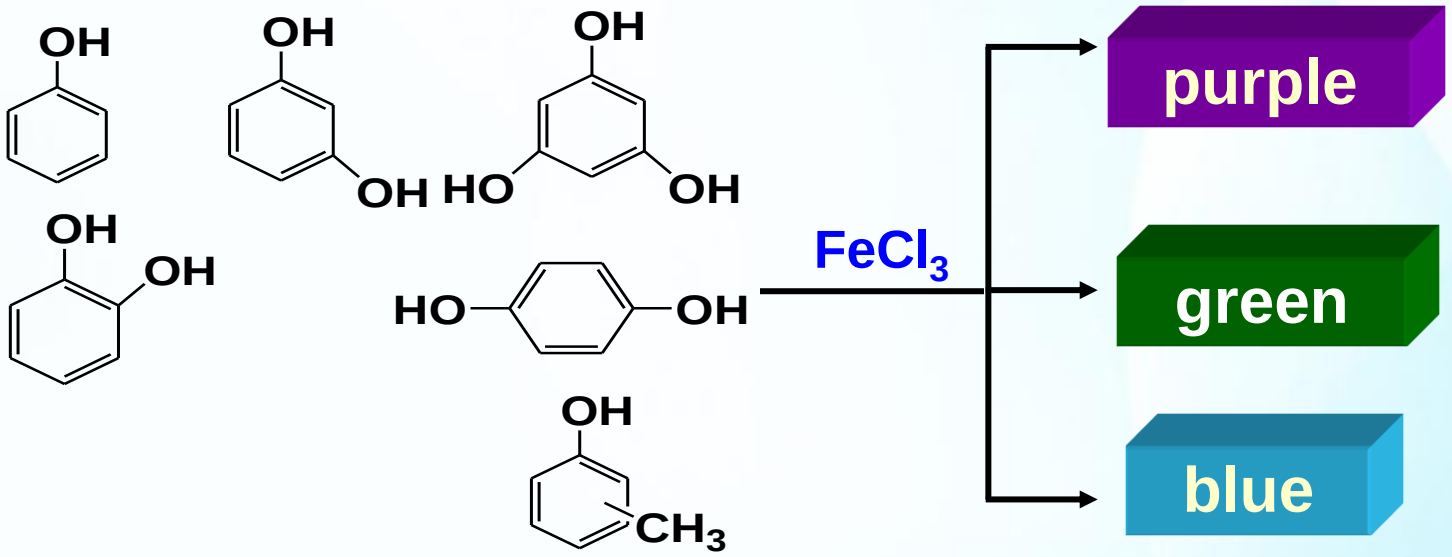




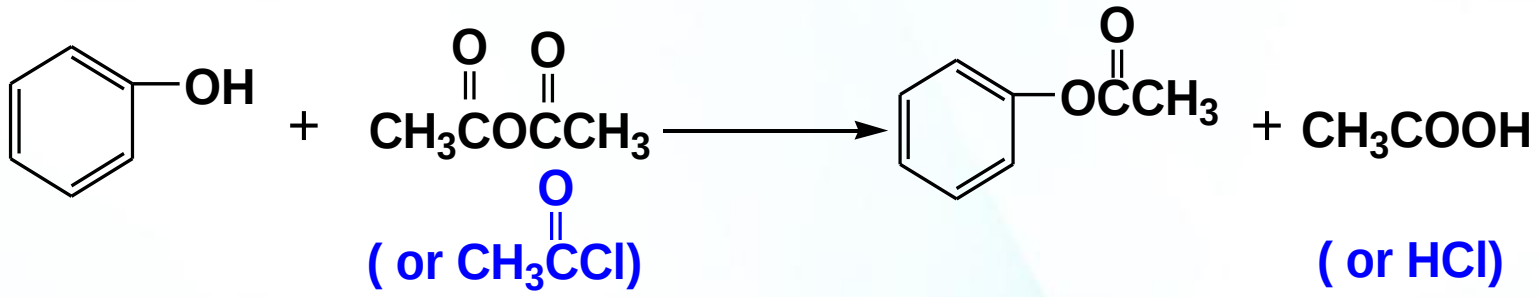


(3) Color reaction

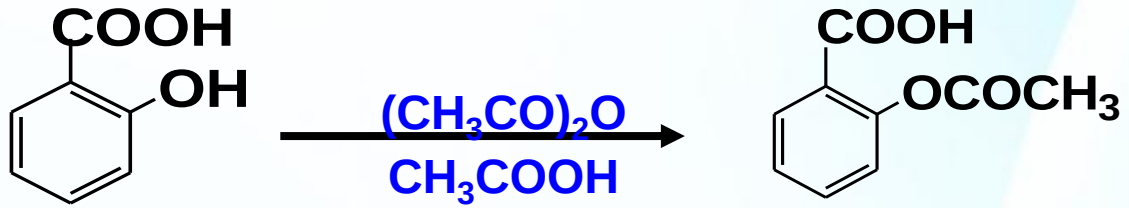
$$6\ C_6H_5OH + FeCl_3 \longrightarrow [\ Fe(OC_6H_5)_6\ ]^{3-} + 3HCl + 3H^+$$



（3）Esterification



Aspirin(阿司匹林)



水杨酸　　乙酰水杨酸

Hippocrates: boiled willow bark to make tea…found that it helped people with fevers

Later….scientists extracted Yellow crystals from willow bark ,

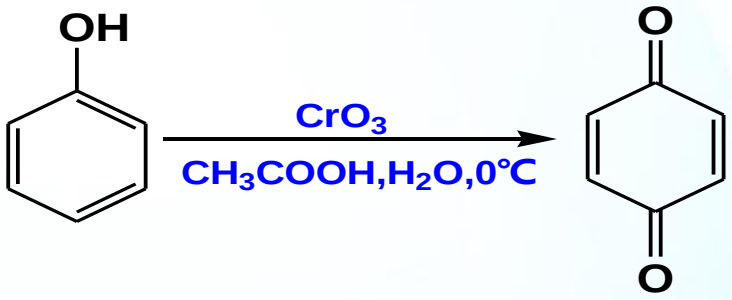
Called it Salicin after (Salix alba), genus species of willow.

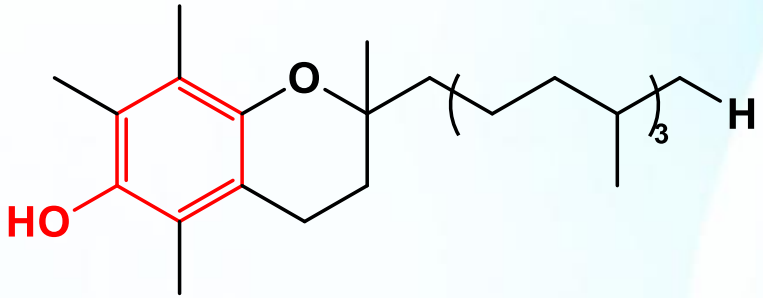
Found that this compond reduced fevers and inflamation

Side effects: stomach irritation and bad taste

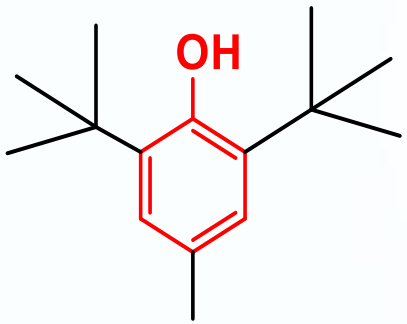
(4) Oxidation

Phenols are susceptible to oxidation to quinones.

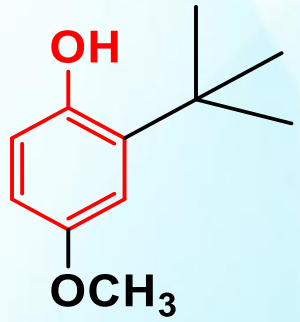




Vitamin E



Butylated hydroxytoluene (BHT)



Butylated hydroxyanisole (BHA)

Summary

1. Small ring cycloalkanes resemble alkene in their properties; big ring cycloalkanes resemble alkane in their properties.
2. The more stable conformations of cyclohexane is *e*-bond substituent.
3. Chemical properties of aromatics
   - Halogenation
   - Nitration
   - Sulfonation
   - Alkylation
   - Acylation
4. Orientation rule
5. Reaction of phenols

作业：

P324 9.13 (a)(b)(c)(d)

P326 9.26(a)(b)(c)(d); 9.28(a)(c)

P327 9.37(a) (c)

P329 9.48(f)

也许有一天，不知不觉，你将渐渐活出写满答案的人生！