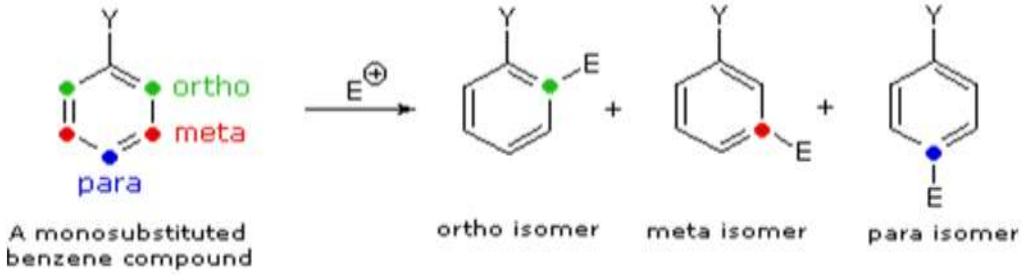
Reactions of Benzene Derivatives

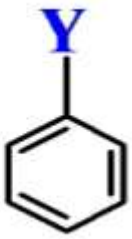


A monosubstituted benzene compound

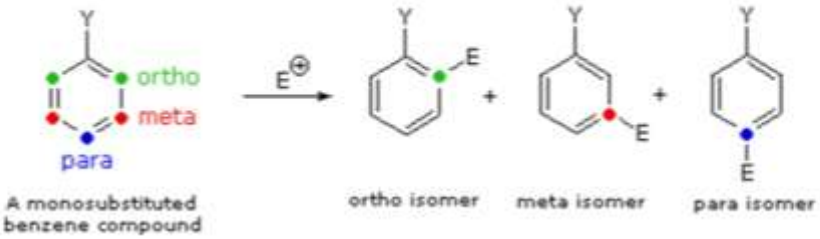
Substituent Effects in Substituted Aromatic Rings

A substituent present on an aromatic ring affects:

1- The reactivity of the aromatic ring



2- The orientation (regioselectivily) of the reaction



A monosubstituted benzene compound

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

Origins of Substituent Effects

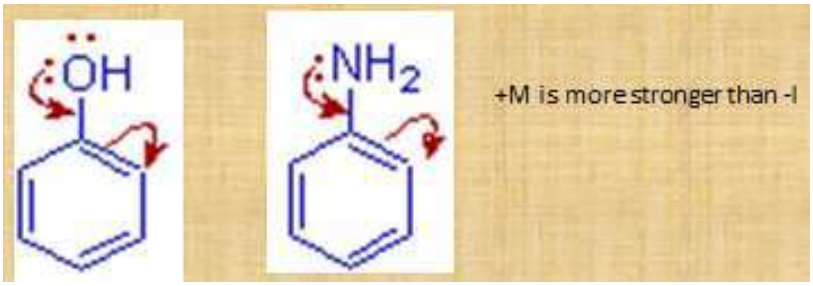
- An interplay of ***inductive effects*** and ***resonance effects***.

1. **Inductive effect** – withdrawal (-I) or donation (+I) of electrons through a s bond.
2. **Resonance effect** (Mesomeric effect)- withdrawal (-M) or donation (+M) of electronsthrough a □ bond due to the overlap of a *p* orbital on the substituent with a *p* orbital on the aromatic ring.

A-Any resonance (Mesomeric) and inductive effect (+M,-I)):

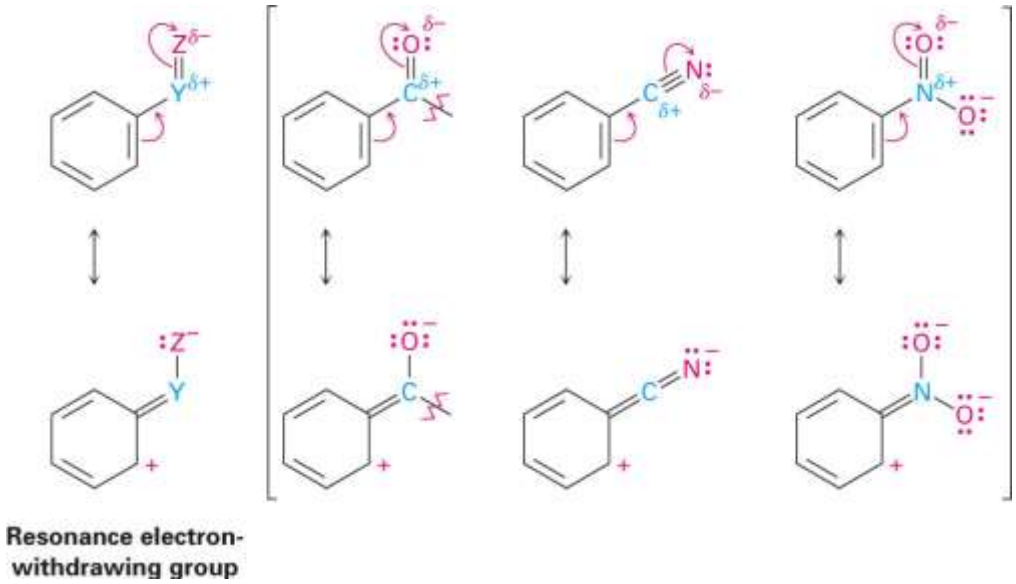
such as that of -NH2, -OH, and -OR, that delocalizes of electrons through a □ bond, and has an ***activating*** **the ring**.

For example, In phenol and aniline



B-Any resonance and inductive effect (-M, -I):

such as that of -NO_2, -CN, -CO, and -SO_3H, that **decreases electron density** on the ring and then **deactivates the ring.**



Resonance electron-withdrawing group

C-Any iinductiive effect (+I):

such as that of -CH_3 or other alkyl group, that **releases electron density** on the ring and then **activates the ring.**

The examples of groups in the decreasing order of +I effect.

$$C(CH_3)_3 > CH(CH_3)_2 > CH_2CH_3 > CH_3 > H$$

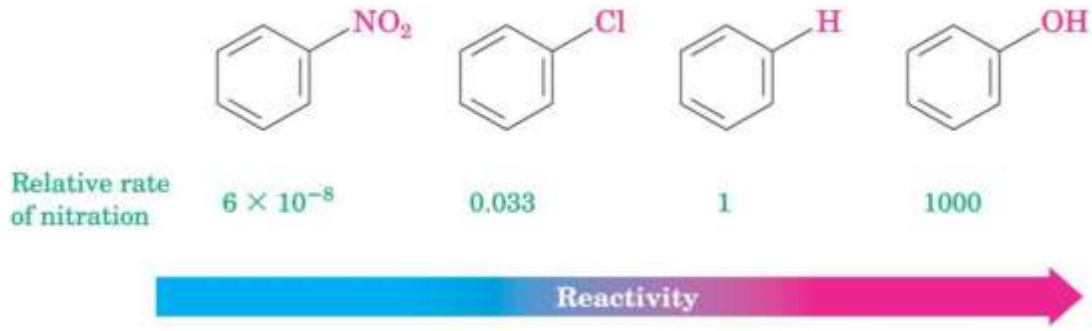
D-Any inductive effect (-I),

such as that of halogen, -NR_3^+, -CCl_3, or -CF_3, that decreases electron density (-I) on the ring deactivates the ring toward further EAS.

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

Substituents may

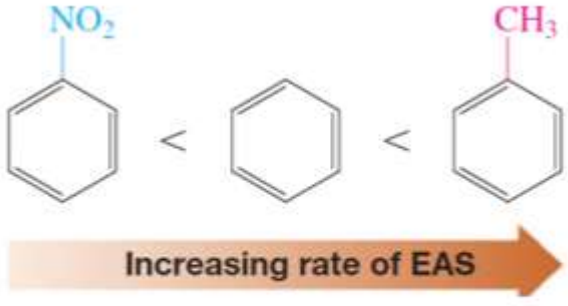
- **activators (electron donors) group, which** activate the ring, make it (much) more reactive than benzene. or
- **deactivators (electron acceptors) group, which** deactivate the ring, make it (much) less reactive than benzene.



1- Effect of Substituents on reactivity Benzene Ring

Q/What effect of substitunts on the rate of electrophilic aromatic substitution?

A1//any substitutuent increases **electron density** on benzene ring, increase *activating* of ring toward further EAS.



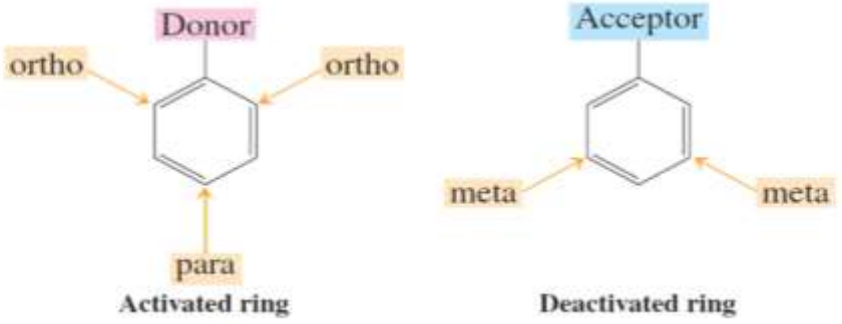
depending on:
1-induction and 2-resonance.

2- Effect of Substituents on the Orientation (regioselectivily) of electrophilic aromatic substitution

Q/what effect of substituents on the regioselectivily Orientation (regioselectivily) of electrophilic aromatic substitution?

A. **activators (electron donors) group**, which generally direct a second electrophilic attack to the ortho and para positions.

B. **deactivators (electron acceptors) group,** which generally direct electrophiles to the meta positions.

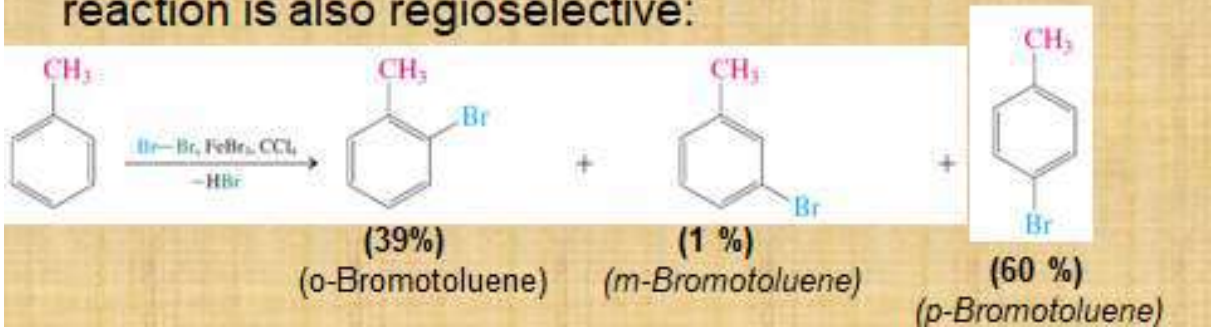


1-Electrophilic Aromatic Substitution

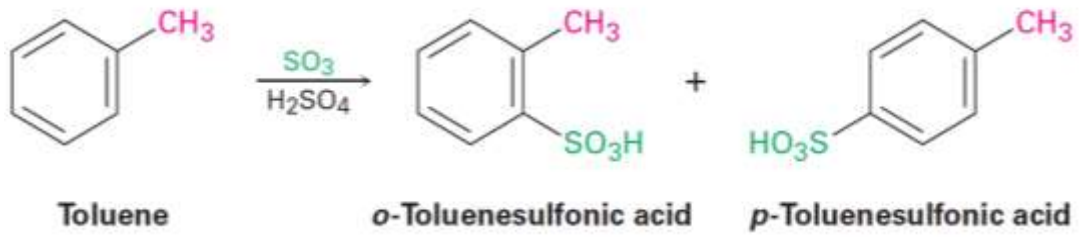
Q//What controls the position along the benzene ring at which an electrophile will attack?

1.1-Groups that donate electrons by induction are activating and direct ortho and para.

- Electrophilic bromination of toluene is considerably faster than the bromination of benzene itself. The reaction is also regioselective:



- Is bromination a special case? The answer is no; nitration, sulfonation, and Friedel-Craftsreactions of the alkylbenzene give similar results—mainly ortho and para substitutions.
- Can we explain this selectivity by a mechanism?



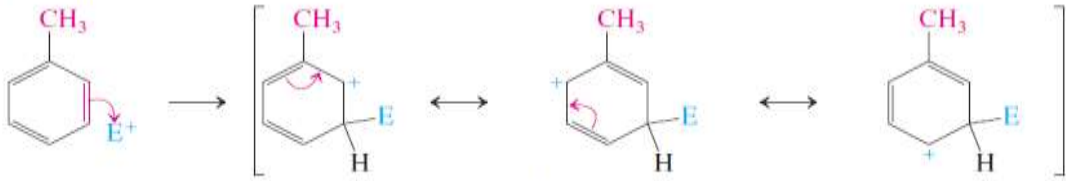
Toluene ***o*-Toluenesulfonic acid** ***p*-Toluenesulfonic acid**

Ortho, Meta, and Para Attack on Methylbenzene (Toluene)

Ortho attack (E^+ = electrophile)

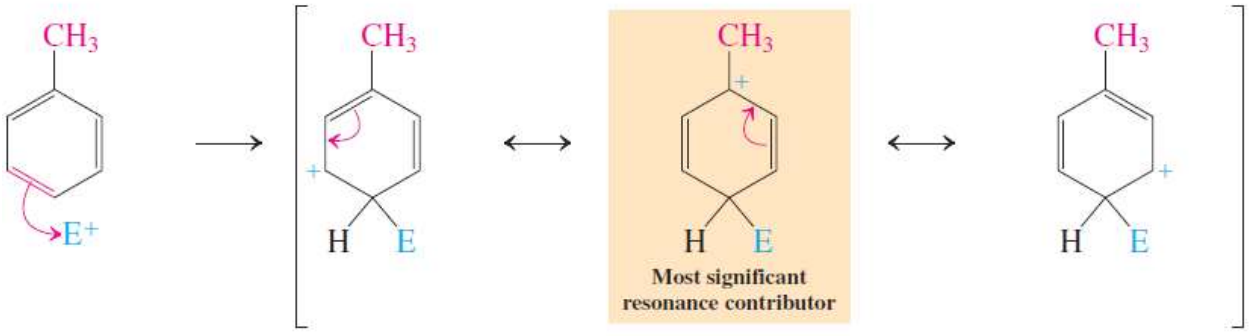
More stable cation

Meta attack



Less stable cation

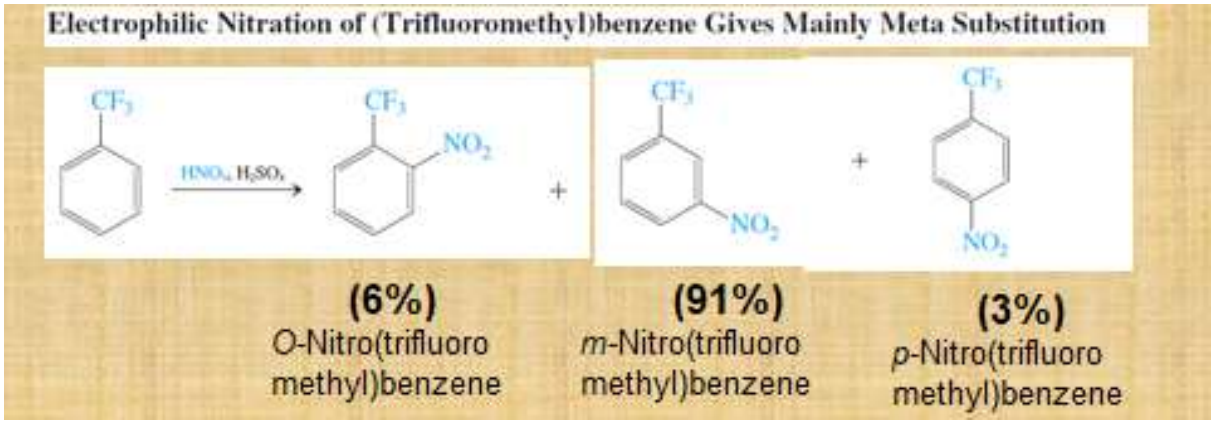
Para attack



More stable cation

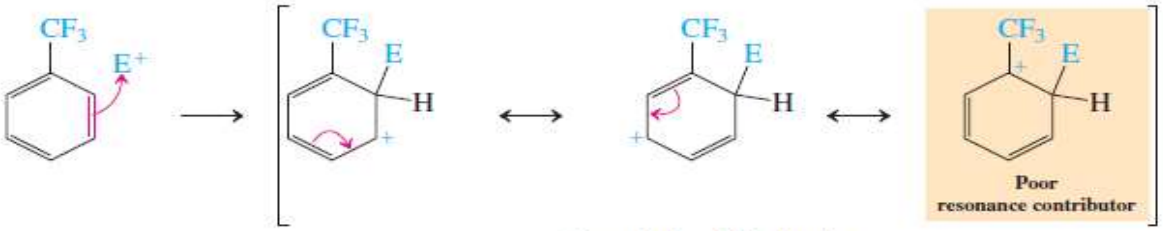
1.2-Groups that withdraw electrons inductively are deactivating and meta directing.

The strongly electronegative fluorine atoms in (trifluoromethyl) benzene make the trifluoromethyl group inductively electron withdrawing. the benzene ring becomes deactivated.



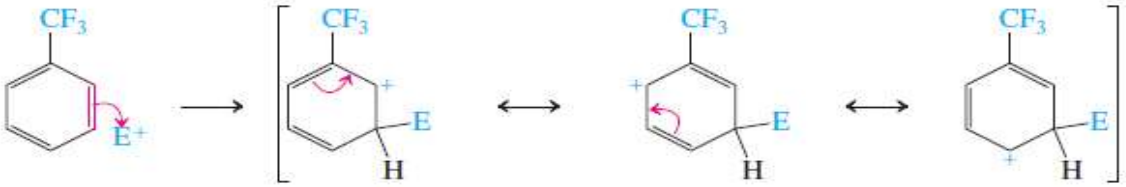
Ortho, Meta, and Para Attack on (Trifluoromethyl)benzene

Ortho attack



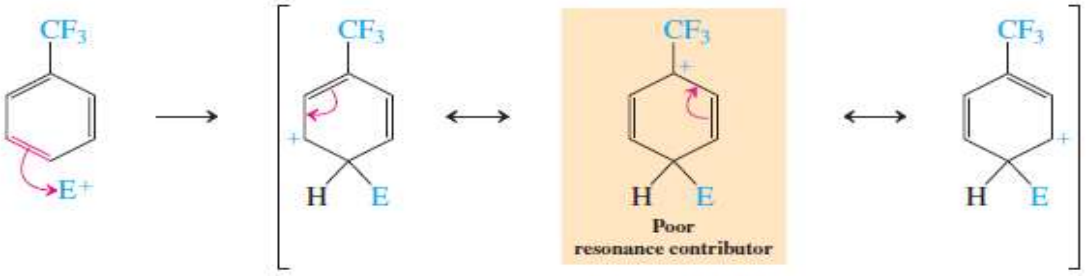
Strongly destabilized cation

Meta attack



Less destabilized cation

Para attack

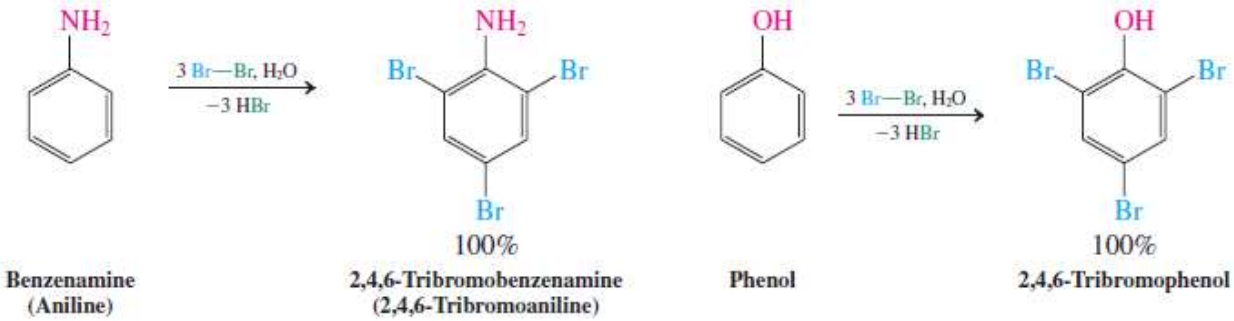


Strongly destabilized cation

1.3-Groups that donate electrons by resonance activate and direct ortho and para.

Benzene rings bearing the groups $–NH_2$ and –OH are strongly activated. For example,halogenations of benzenamine (aniline) and phenol not only take place in the absence ofcatalysts but also are difficult to stop at single substitution.

Electrophilic Brominations of Benzenamine (Aniline) and Phenol Give Ortho and Para Substitution

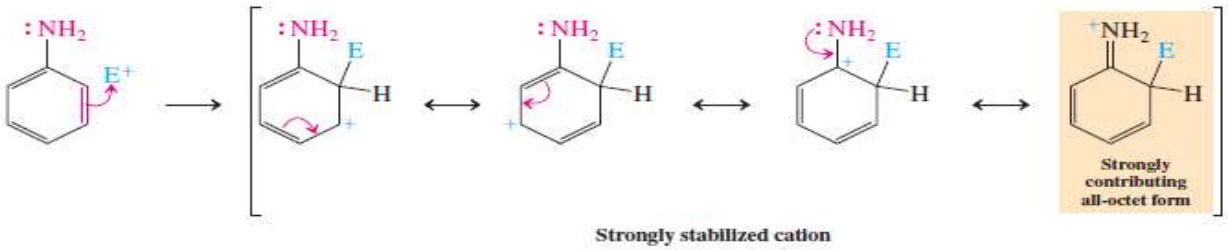


Benzenamine (Aniline) | **2,4,6-Tribromobenzenamine (2,4,6-Tribromoaniline)** | **Phenol** | **2,4,6-Tribromophenol**

The observed regioselectivity on electrophilic substitution can be explained by writing resonance forms for the various intermediate cations.

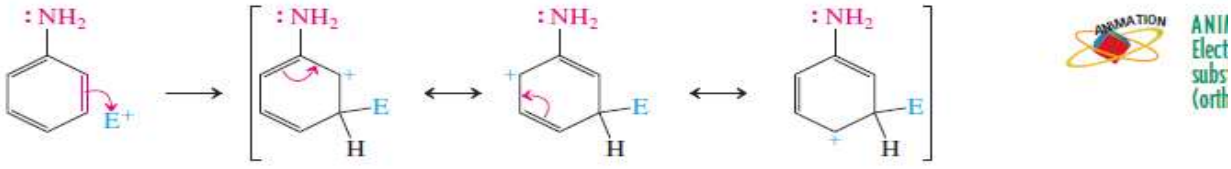
Ortho, Meta, and Para Attack on Benzenamine (Aniline)

Ortho attack

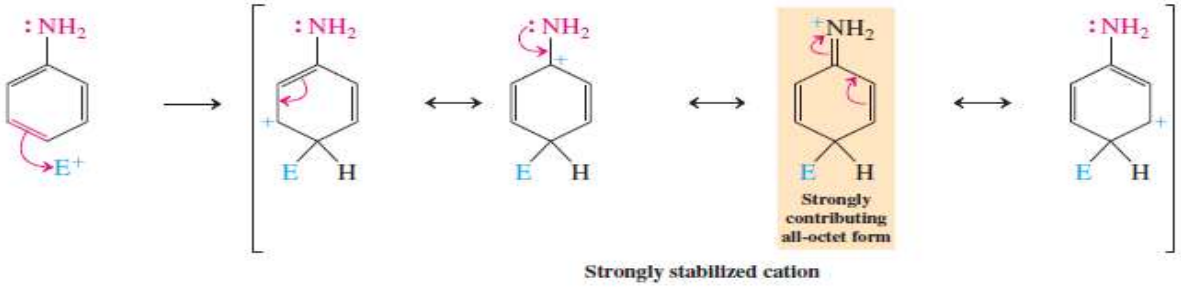


Strongly stabilized cation

Meta attack

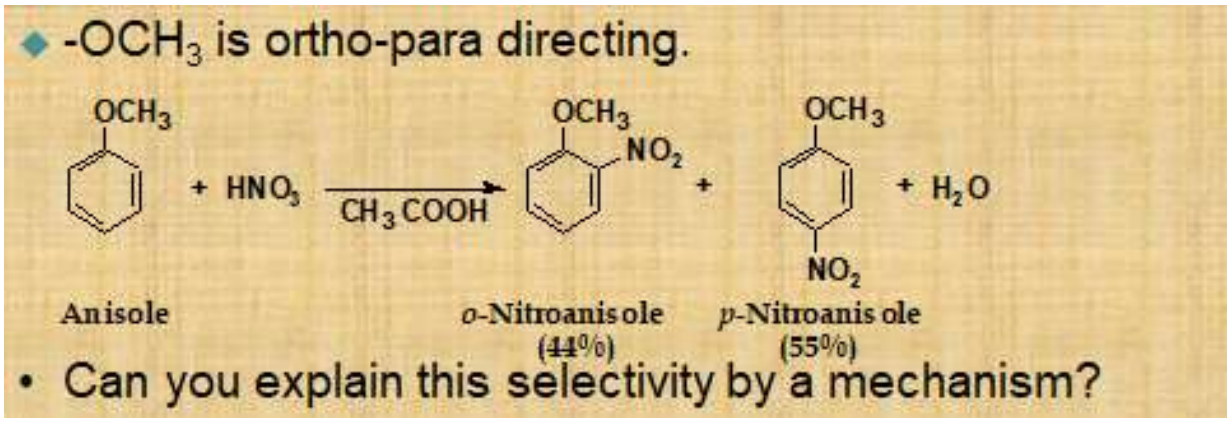


Para attack

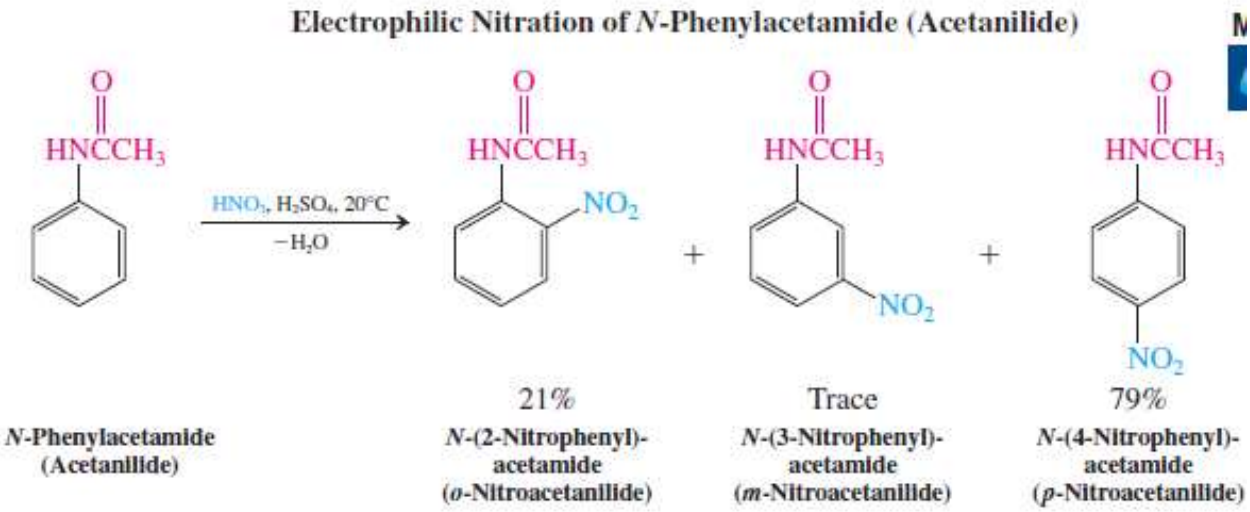


Strongly stabilized cation

Because **nitrogen** is more electronegative than **carbon**, the amino group in aniline is inductively electron withdrawing. However, the lone electron pair on the **nitrogen** atom may participate in resonance, thereby stabilizing the intermediate cations resulting from **ortho and para** substitutions.



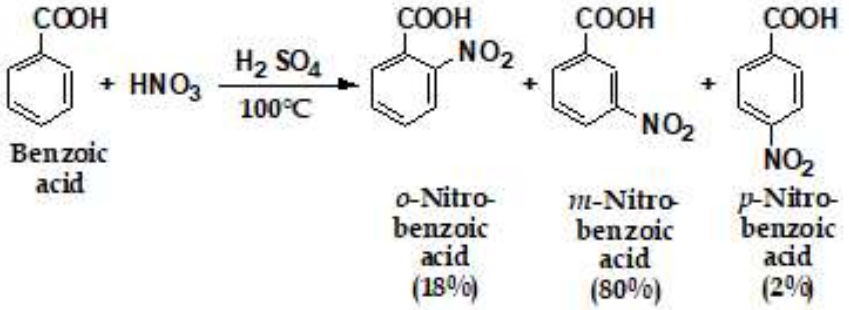
Better control of monosubstitution is attained with modified **amino and hydroxyl** substituents, such as in ***N-phenylacetamide and methoxybenzene***. These groups are **ortho and para** directing but less strongly activating.



1.4-Groups that withdraw electrons by resonance deactivate and direct meta

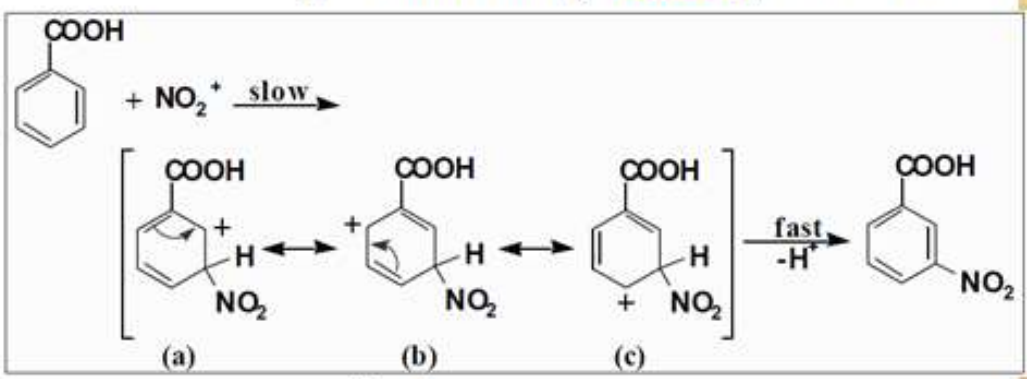
- Several groups **deactivate** *the benzene* ring by resonance.
- For example: Nitration of benzoic acid and give meta substitution.

Electrophilic Meta Nitration of Benzoic Acid



- how conjugation with the CO_2H function affects the resonance forms of the cations resulting from electrophilic attack on benzoic acid.

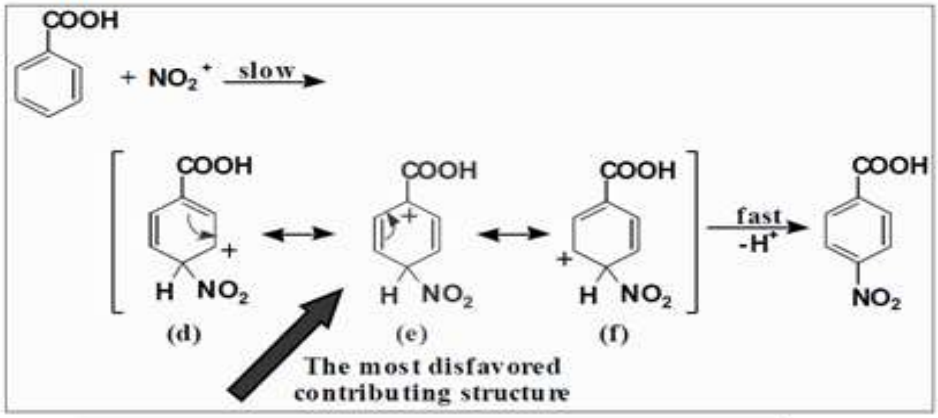
Meta attack -CO_2H : events during a favored meta attack.



None is poor
Less destabilized cation

The cation never appears adjacent to the (+) carbon of C=O.

-CO_2H : events during an unfavored ortho-para attack.



This resonance structure accounts for the selectivity

Strongly destabilized cation

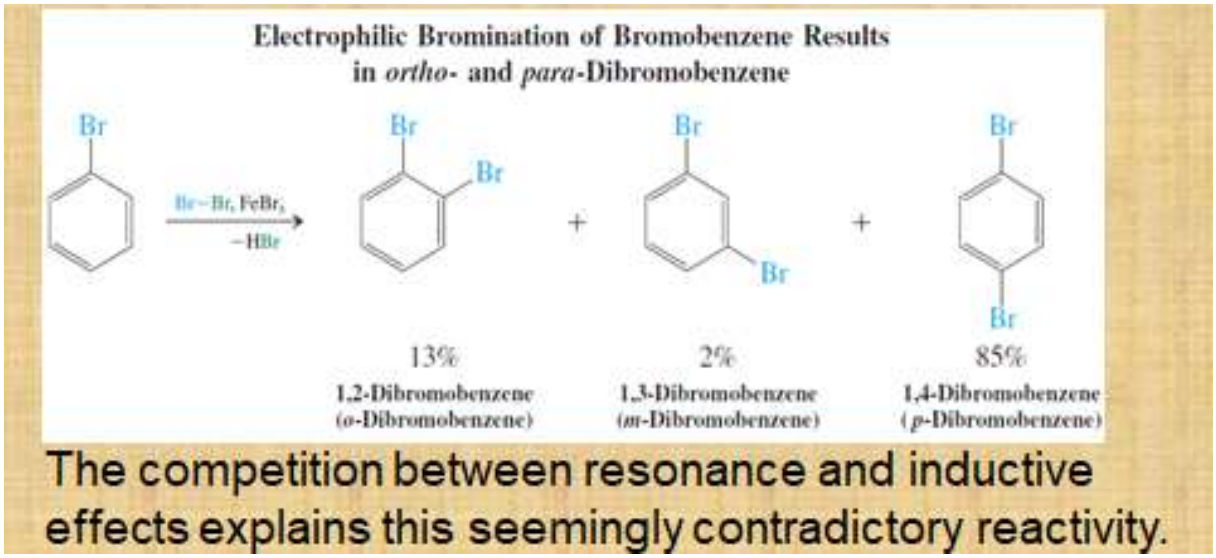
The cation appears adjacent to a (+) carbon of C=O.

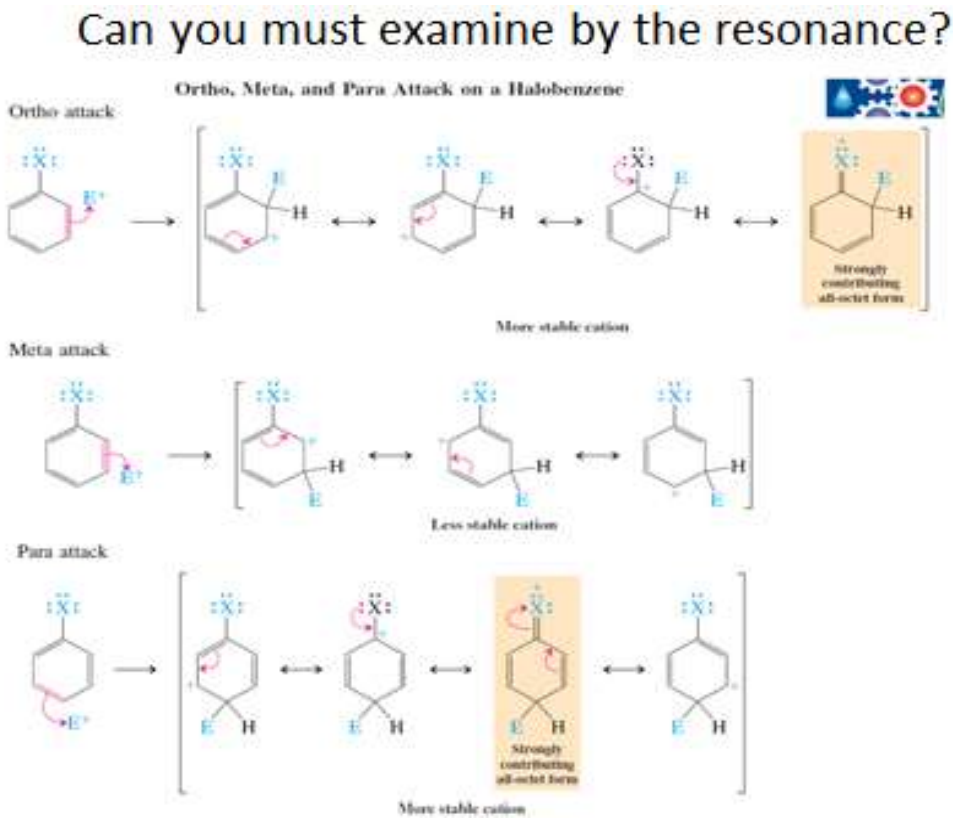
- Attack at the meta position avoids placing the positive charge next to the electronwithdrawing carboxy group, whereas ortho and para attacks necessitate the formulation of poor resonance contributors.

1.5-There is always an exception: halogen substituents, although deactivating, direct ortho and para.

Halogen substituents inductively withdraw electron density, however, they are donors by resonance.

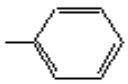
On balance, the inductive effect wins out.





- Note that **ortho and para attack** lead to resonance forms in which the **positive charge is placed next to the halogen substituent**. Although this might be expected to be **unfavorable**, because the halogen is inductively electron withdrawing, resonance with the lone electron pairs allows the charge to be delocalized. Therefore, ortho and para substitutions become the preferred modes of reaction.

B-Di- and Polysubstitution

Ortho-para Directing	Strongly activating	$-NH_2$ $-NHR$ $-NR_2$ $-OH$ $-OR$
	Moderately activating	$-NHCR$ $-NHCAr$ $-OCR$ $-OCAr$
	Weakly activating	$-R$ 
	Weakly deactivating	$-F:$ $-Cl:$ $-Br:$ $-I:$
Meta Directing	Moderately deactivating	$-CH$ $-CR$ $-COH$ $-COR$ $-CNH_2$ $-SO_3H$ $-C\equiv N$
	Strongly deactivating	$-NO_2$ $-NH_3^+$ $-CF_3$ $-CCl_3$

- we can make these generalizations:

1-alkyl, phenyl, and all other substituents in which the atom bonded to the ring has an **unshared pair** of electrons are **ortho-para** directing;

2-all other substituents are **meta directing**.

3-all **ortho-para directing** groups except the **halogens are activating** toward further substitution; the halogens are weakly deactivating.

Substituents affect the *orientation* of the reaction

Substituents present on the ring determine the position of the 2nd substitution: ortho, meta, and para

TABLE 16.1 Orientation of Nitration in Substituted Benzenes

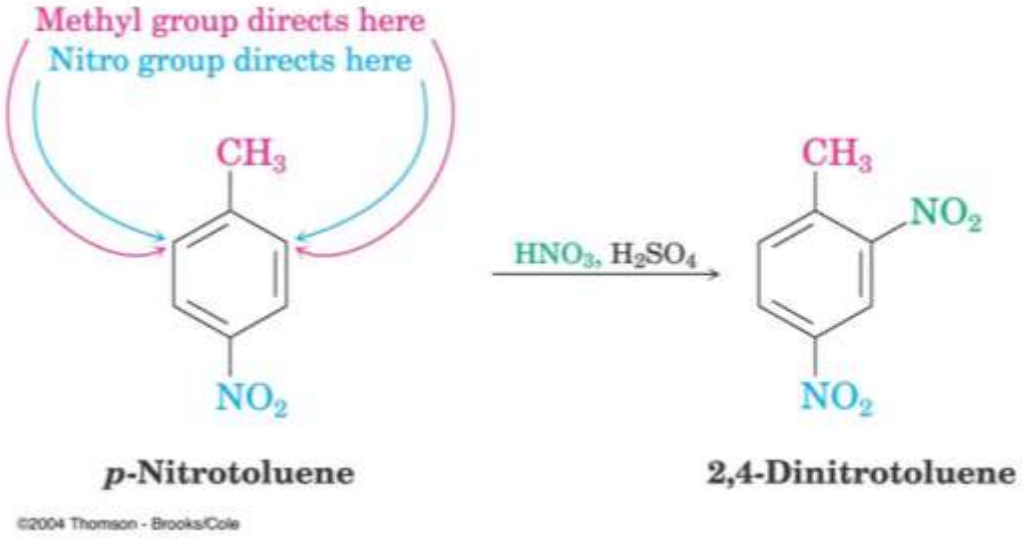
	Product (%)		
	Ortho	Meta	Para
Meta-directing deactivators			
$-\overset{+}{N}(CH_3)_3$	2	87	11
$-NO_2$	7	91	2
$-CO_2H$	22	76	2
$-CN$	17	81	2
$-CO_2CH_2CH_3$	28	66	6
$-COCH_3$	26	72	2
$-CHO$	19	72	9

	Product (%)		
	Ortho	Meta	Para
Ortho- and para-directing deactivators			
$-F$	13	1	86
$-Cl$	35	1	64
$-Br$	43	1	56
$-I$	45	1	54
Ortho- and para-directing activators			
$-CH_3$	63	3	34
$-\ddot{O}H$	50	0	50
$-\ddot{N}HCOCH_3$	19	2	79

C-Others Reactions of Di- and Polysubstitution

1. If the directing effects of the two groups are the same, the result is additive

   – It gives a single product



***p*-Nitrotoluene** **2,4-Dinitrotoluene**

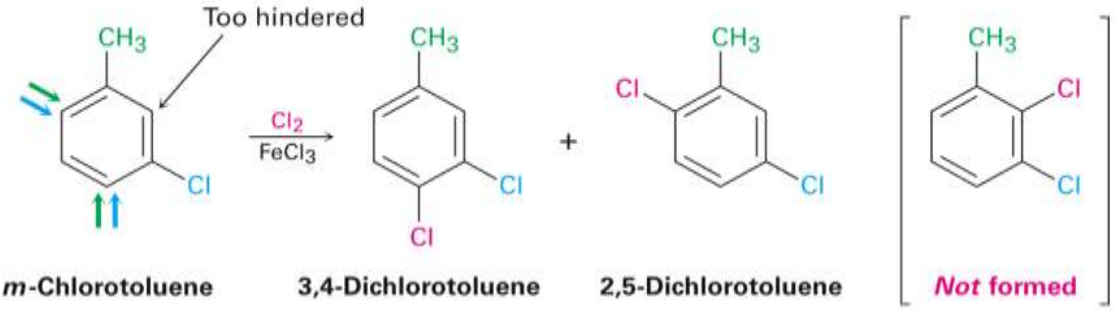
2. If the directing effects of two groups oppose each other, the more powerful activating group determines the principal outcome

   – It usually gives mixtures of products

***p*-Methylphenol (*p*-Cresol)** **2-Bromo-4-methylphenol (major product)**

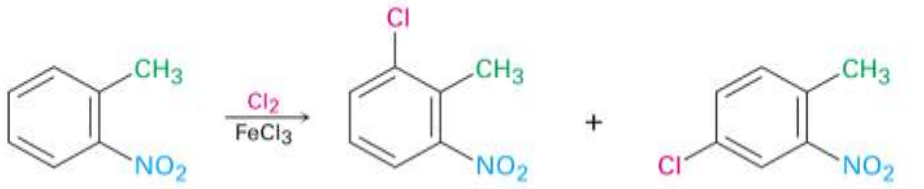
3. The position between the two groups in meta-disubstituted compounds is unreactive

- The reaction site is too hindered
- To make aromatic rings with three adjacent substituents, it is best to start with an ortho-disubstituted compound .

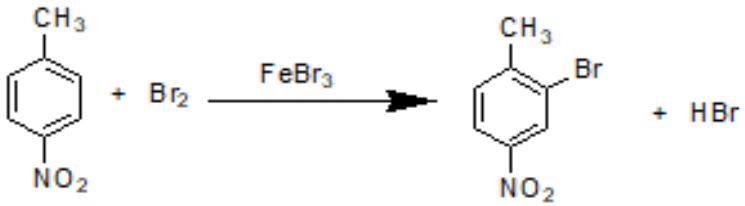


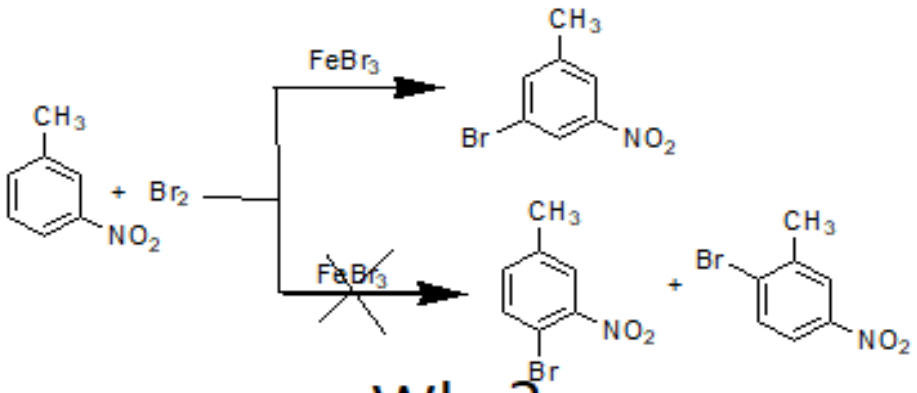
m-Chlorotoluene 3,4-Dichlorotoluene 2,5-Dichlorotoluene ***Not* formed**

But:



***o*-Nitrotoluene** **2-Chloro-6-nitrotoluene** **4-Chloro-2-nitrotoluene**





Why?

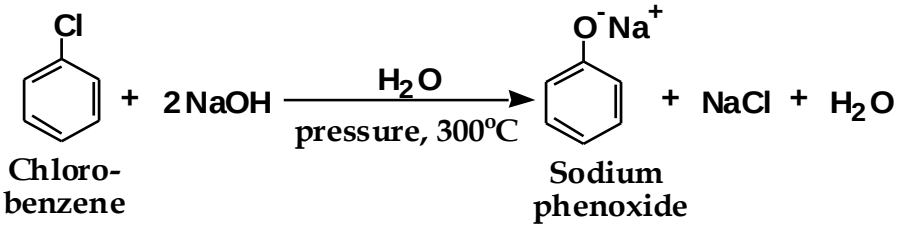
2. Nucleophilic Aromatic Substitution

- Aryl halides do not undergo nucleophilic aromatic substitution by either S_N1 or S_N2.
- They do undergo nucleophilic substitutions, but by benzyne mechanism.
- Nucleophilic aromatic substitutions are far less common than electrophilic aromatic substitutions.

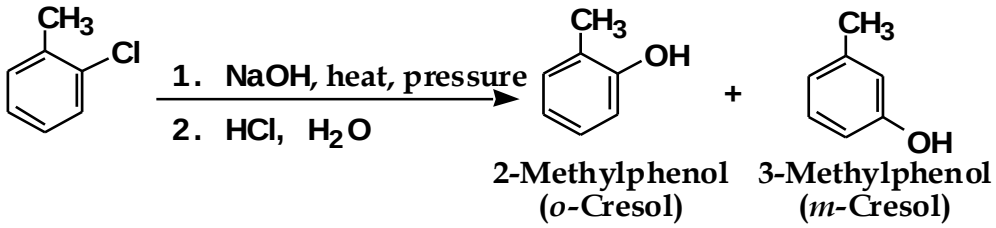
Benzyne Intermediates

1-Chlorobenzene is converted to sodium phenoxide.

– neutralization with HCl gives phenol.

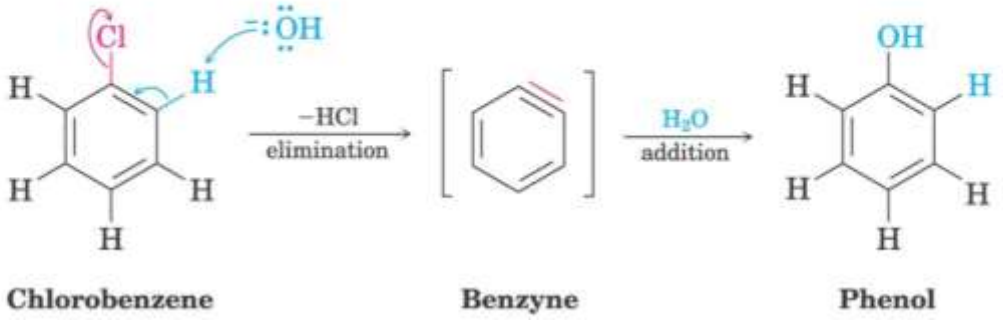


The same reaction with 2-chlorotoluene gives a mixture of ortho- and meta-cresol.



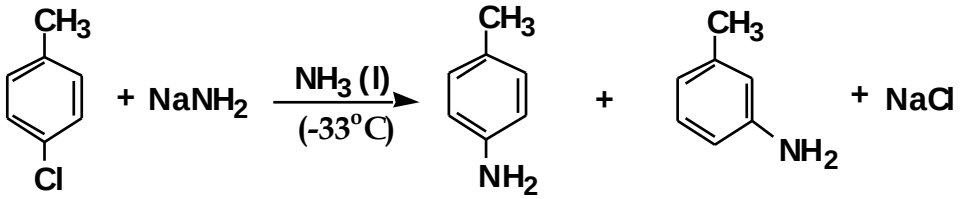
Mechanism of nucleophilic Aromatic substitutions by benzyne mechanism.

- The synthesis of phenol occurs in two steps by the elimination/addition mechanism rather than addition/elimination:
  - Step 1: Elimination of a HX from halobenzene in an E2 reaction catalyzed by a strong base, forming a highly reactive benzyne intermediate
  - Step 2: Addition of a nucleophile (Nu^-) to the benzyne intemediate



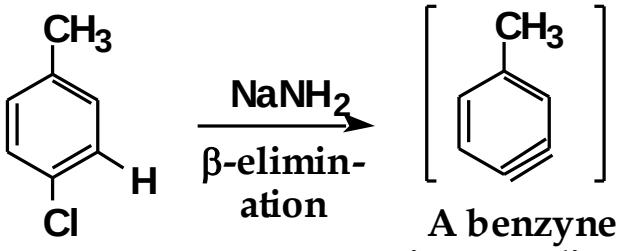
Chlorobenzene Benzyne Phenol

2-the same type of reaction can be brought about using of sodium amide in liquid ammonia.



4-Methylaniline (*p*-Toluidine) 3-Methylaniline (*m*-Toluidine)

β-elimination of HX gives a benzyne intermediate, that then adds the nucleophile to give products.



A benzyne intermediate

Benzyne is unstable due to poor orbital overlap, brackets mean that this is a transient intermediate.