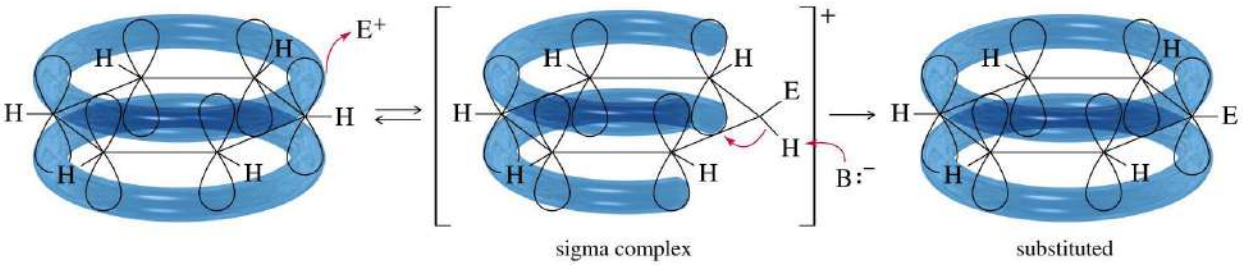
Reactions of Aromatic Compounds

Just like an alkene, benzene has clouds of π electrons above and below its sigma bond framework.



Although the π electrons are in a stable aromatic system, they are still available for reaction with **strong** electrophiles.

This generates a carbocation which is resonance stabilized (but not aromatic).

This cation is called a **sigma complex** because the electrophile is joined to the benzene ring through a new sigma bond.

The sigma complex (also called an arenium ion) is **not** aromatic since it contains an sp^3 carbon (which disrupts the required loop of p orbitals).

The loss of aromaticity required to form the sigma complex explains the highly endothermic nature of the first step. (That is why we require strong electrophiles for reaction).

The sigma complex wishes to regain its aromaticity, and it may do so by either by a reversal of the first step (i.e. regenerate the starting material) or by loss of the proton <u>on the sp^3 carbon</u> (leading to a **substitution** product).

When a reaction proceeds this way, it is **electrophilic aromatic substitution**.

There are a wide variety of electrophiles that can be introduced into a benzene ring in this way, and so electrophilic aromatic substitution is a very important method for the synthesis of substituted aromatic compounds.

I) <u>Substitution of Benzene</u>

A) <u>Halogenation of Benzene</u>

<u>1) Bromination of Benzene</u>

Bromination follows the same general mechanism for the electrophilic aromatic substitution (EAS).

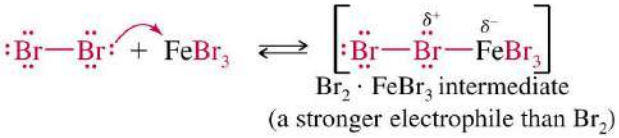
Bromine itself is **not** electrophilic enough to react with benzene.

But the addition of a strong **Lewis acid** (electron pair acceptor), such as $FeBr_3$, catalyses the reaction, and leads to the **substitution** product.

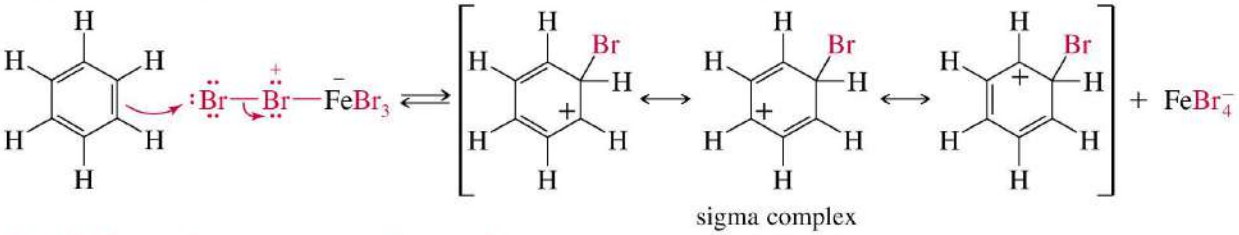
The bromine molecule reacts with $FeBr_3$ by donating a pair of its electrons to the Lewis acid, which creates a more polar Br-Br bond, and thus a more **reactive** electrophile.

Benzene will now attack this electrophile to generate the sigma complex.

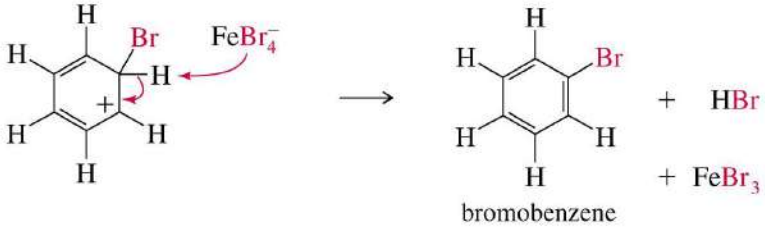
Step 1: Formation of a stronger electrophile.



Step 2: Electrophilic attack and formation of the sigma complex.



Step 3: Loss of a proton gives the products

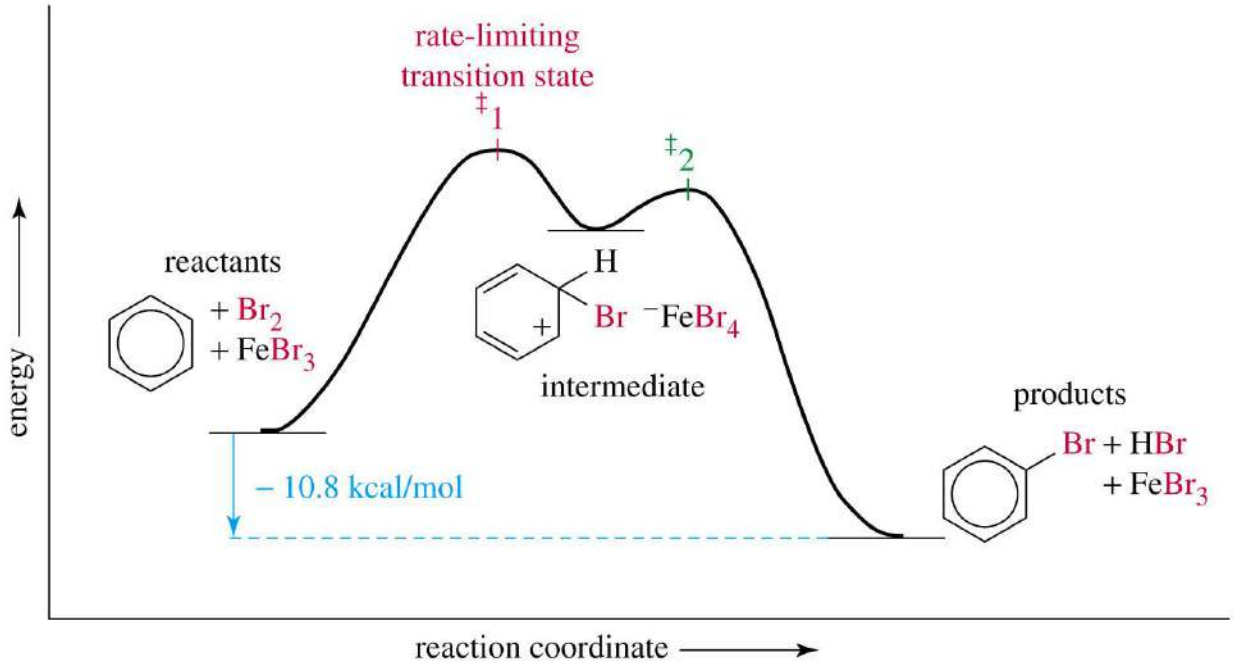


Bromide ion from the $FeBr_4^-$ can act as a weak base to remove the proton, thus generating the aromatic product, H-Br, and regenerating the catalyst ($FeBr_3$).

The formation of the sigma complex is an endothermic and energetically unfavorable process - it is therefore the **rate determining step**.

The second step is exothermic since it regenerates the aromatic π system.

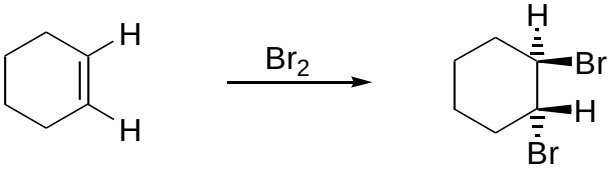
The overall reaction is exothermic by about 11 kcal/mol.



Comparison with Alkenes

Alkenes react spontaneously with bromine to give addition products.

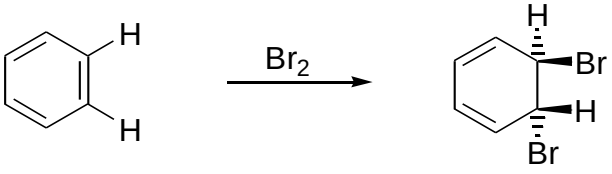
E.g.



ΔH^o = -29kcal

This reaction is exothermic by 29kcal/mol.

An analogous addition reaction between benzene and bromine would be endothermic by 2kcal.



ΔH^o = +2kcal

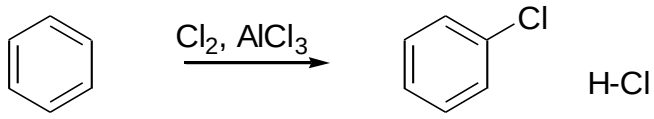
The destruction of the **aromatic** sextet causes this endothermicity.

This reaction is <u>not</u> observed under normal reaction conditions.

The substitution of bromine for hydrogen is an overall exothermic process, but requires a catalyst to convert the bromine molecule into a more reactive electrophile.

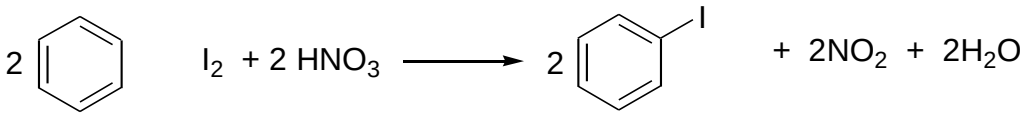
2) <u>Chlorination of Benzene</u>

The chlorination proceeds analogously to the bromination except this time the Lewis acid catalyst used is $AlCl_3$.



3) <u>Iodination of Benzene</u>

The iodination procedure requires an acidic oxidizing agent, such as nitric acid.



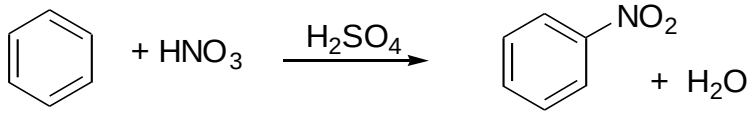
The nitric acid is a strong **oxidizer** (i.e. removes electrons, converts iodine into I^+), this makes the iodine a much <u>stronger</u> electrophile.

$$2H^+ + 2HNO_3 + I_2 \rightarrow 2I^+ + 2NO_2 + 2H_2O$$

The nitric acid is consumed in the reaction, it is therefore a **reagent**, not a catalyst.

B) <u>Nitration of Benzene</u>

Benzene will react with hot concentrated nitric acid to produce nitrobenzene.

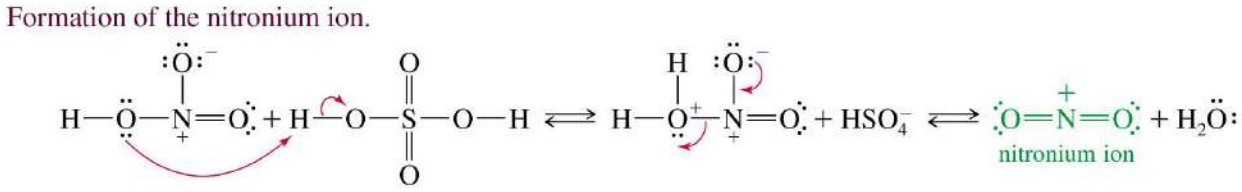


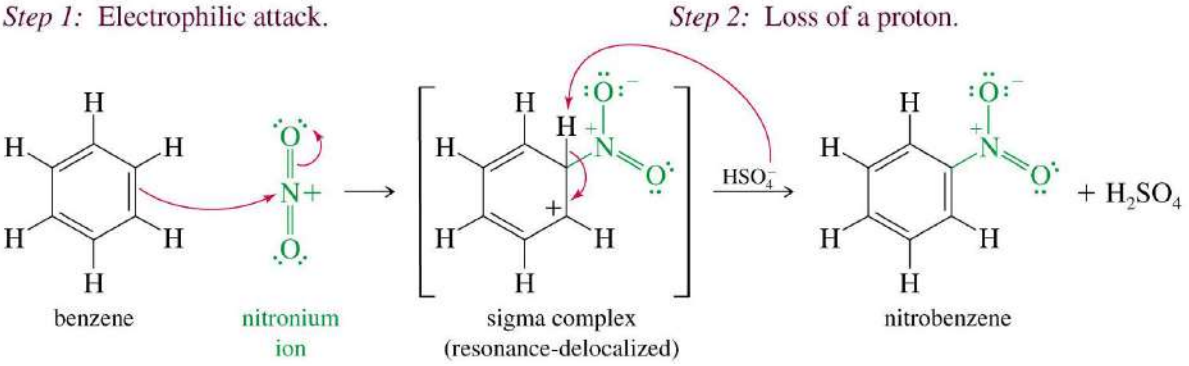
However, this reaction proceeds slowly, which is inconvenient (dangerous) since hot, conc. nitric acid is a powerful oxidizer, and organic compounds are easily oxidizable. (i.e. potential for BOOM!)

A safer reaction involves a mixture of nitric and sulfuric acid.

The sulfuric acid behaves as a catalyst, and allows this nitration reaction to proceed at a lower temperature and more quickly (i.e. safer).

Sulfuric acid reacts with nitric acid to generate a nitronium ion (NO_2^+), which is a very powerful electrophile.



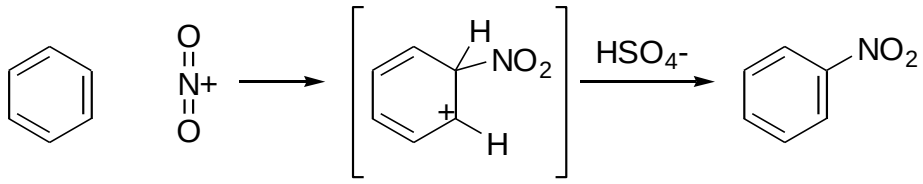


The reaction mechanism is similar to an acid catalyzed dehydration.

Sulfuric acid is a stronger acid than nitric acid, so sulfuric acid protonates nitric acid.

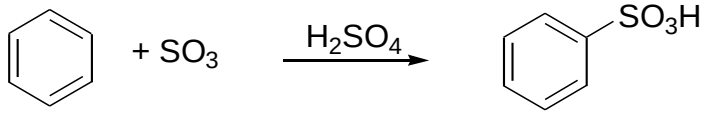
After protonation, water is eliminated (good leaving group), and the nitronium ion is generated.

The nitronium ion reacts with benzene to form the sigma complex, which then loses a proton to generate the aromatic product.



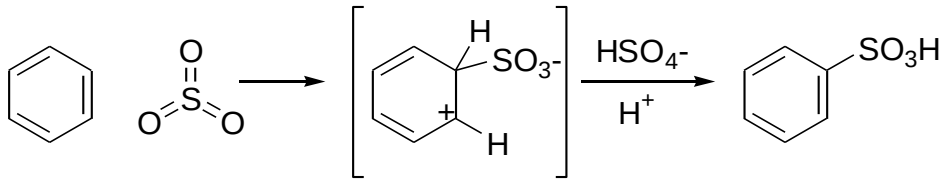
C) <u>Sulfonation of Benzene</u>

1) Benzene will react with sulfur trioxide, and in the presence of an acid, arylsulfonic acids are produced.



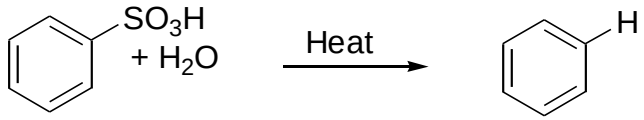
Sulfur trioxide is very reactive electrophile which will sulfonate benzene.

The sigma complex loses a proton to regain its aromaticity, and then the oxyanion becomes protonated.



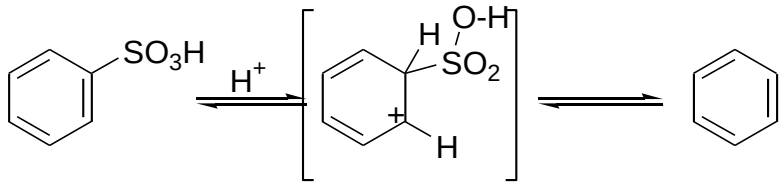
2) <u>Desulfonation</u>

The sulfonation reaction is reversible, and a sulfonic acid group may be removed (i.e. replaced by hydrogen) from the aromatic ring by heating in dilute sulfuric acid.



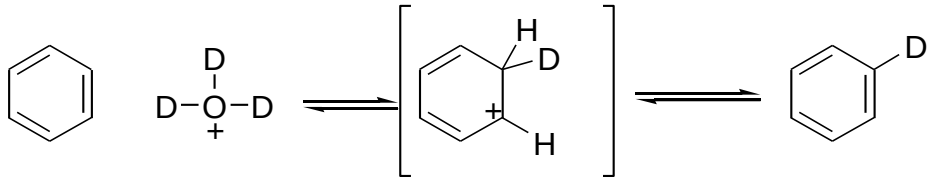
(Often just steam is used for this reaction).

The mechanism for desulfonation is identical to the sulfonation mechanism, except in the reverse order.



D) Hydrogen-Deuterium Exchange

Protonation of the benzene ring may also occur by this mechanism.



After protonation has occurred, the sigma complex can lose either of the hydrogens from the sp^3 carbon to regain its aromaticity.

To prove that reaction has actually occurred, deuterated sulfuric acid can be used.

The products will have deuterium substituted for hydrogen.

If a large excess of deuterated reagent is used, hexadeuteriobenzene can be produced from this equilibrium reaction.

II) Substitution of Mono-substituted Benzenes

A) Nitration of Toluene

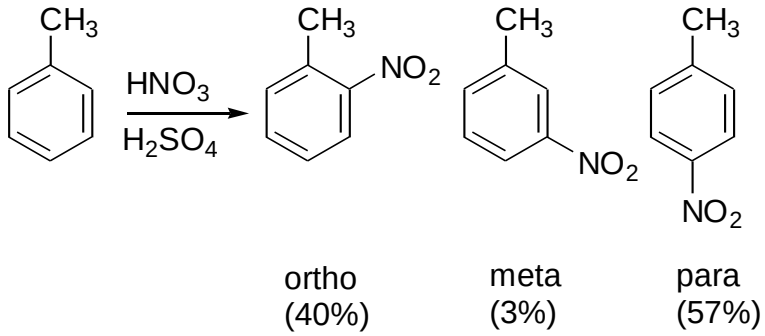
Previously we have concentrated on the reactions of benzene.

Benzene derivatives in a general sense react in the same way that benzene does, although there are some interesting differences.

i) Toluene reacts about 25 times faster than benzene under identical conditions. (We say toluene is **activated** toward electrophilic

aromatic substitution, and that the methyl group is an activating group).

ii) Nitration of toluene generates a **mixture** of products. The major products are those with substitution at the ortho and para positions. (This preference for o/p substitution makes the methyl group an ortho/para director).



The product ratios imply that substitution at each position is not equally likely or energetically favorable).

The distribution is not random, since if it were, there would be 40% ortho, 40% meta and 20% para.

We have already seen that the RDS for EAS is the first step, which requires the loss of aromaticity to generate the sigma complex.

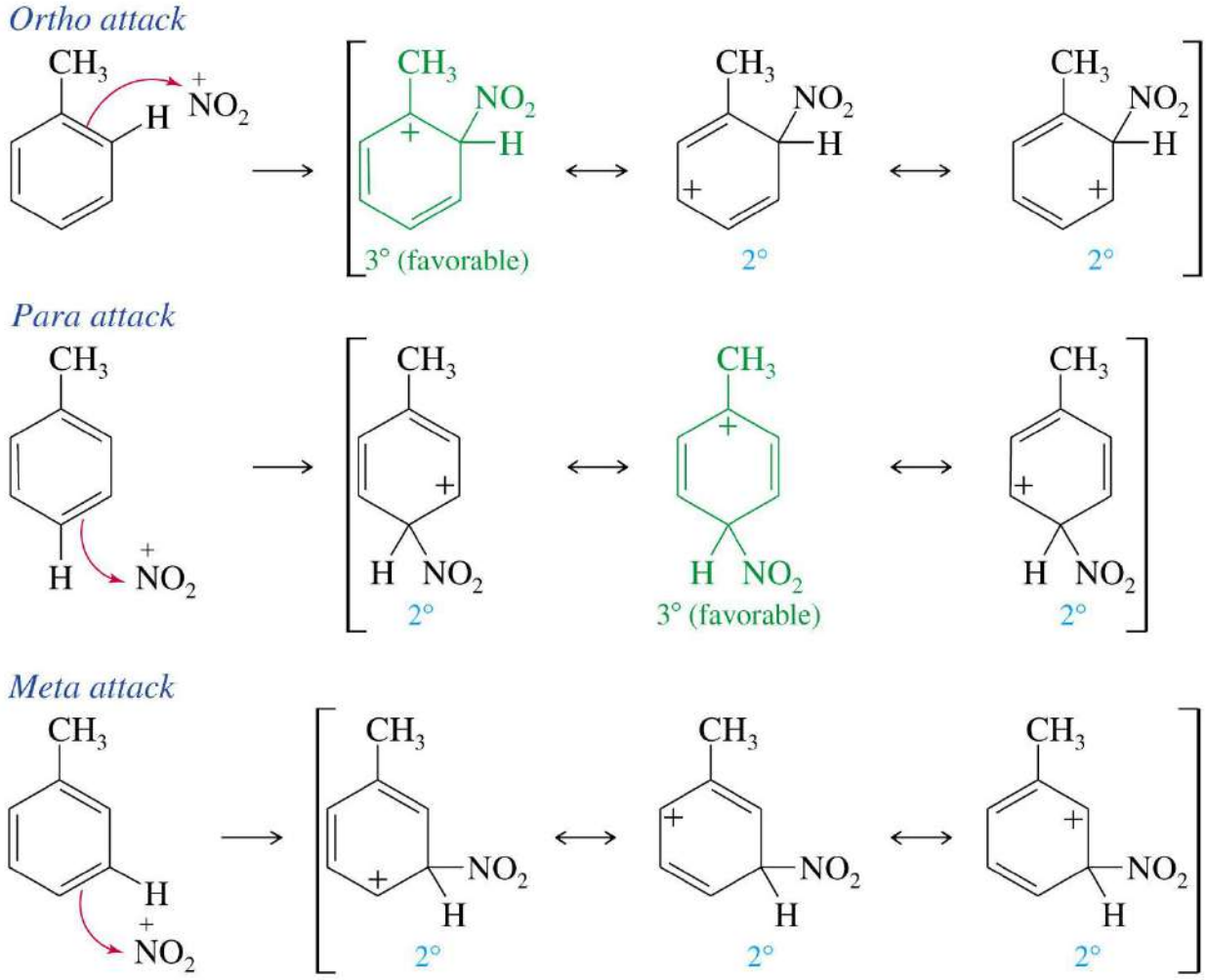
This step is also when the electrophile binds to the ring (i.e. governs the location of substitution).

The enhanced rate and substitution pattern for toluene can be explained by considering the structures of the intermediate sigma complexes for substitution at each of the different positions.

The RDS is *highly* endothermic, therefore according to Hammond's postulate (Ch 4), the energy of the TS should resemble the energy of the product (in this case the product is actually an intermediate, the sigma complex).

Thus it is reasonable to discuss the energies of the TS in terms of the stabilities of the sigma complexes (i.e. cation stabilities).

When benzene reacts with the nitronium ion,. The resulting sigma complex has the positive charge equally distributed over three secondary carbon atoms.



In the case of toluene, ortho (and para) attack result in the positive charge being spread over two secondary carbons and one tertiary carbon atom (the one bearing the CH_3 group).

Since the sigma complexes for ortho (and para) attack have resonance forms with tertiary carbons, they are more **stable** that the corresponding resonance forms for benzene's reaction with nitronium ion.

Thus toluene reacts **faster** than benzene at the ortho and para positions.

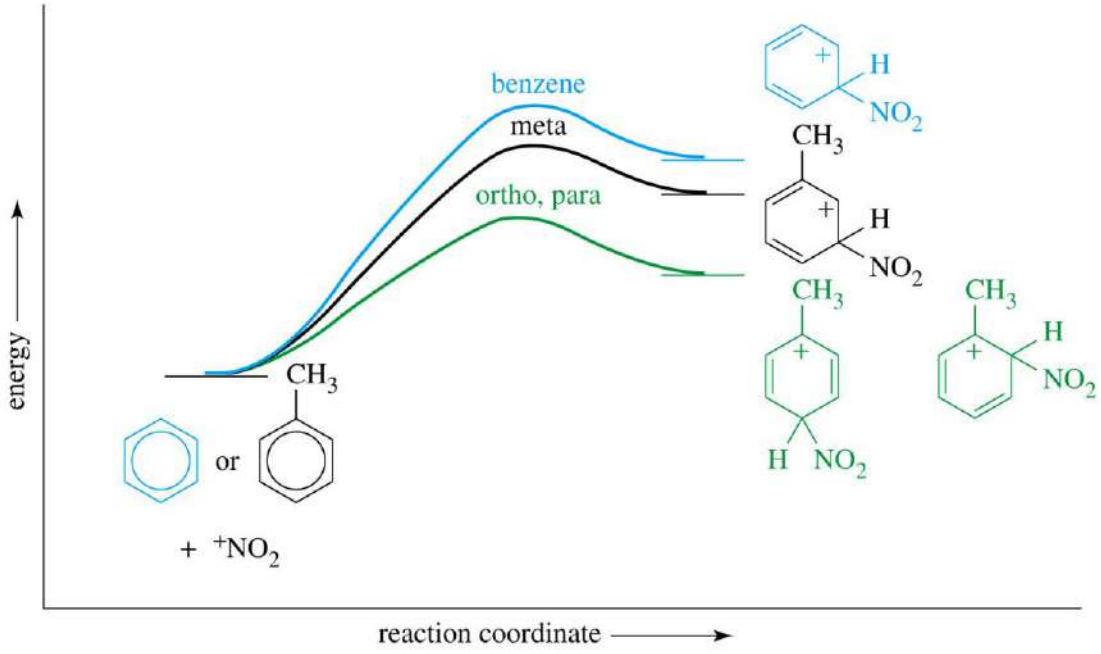
When reaction of toluene occurs at the meta position, then the resonance forms of the sigma complex put positive charge over 3 secondary carbons - the same as for benzene.

Therefore meta substitution of toluene does not show any (significant) enhancement of rate relative to benzene.

The methyl group is slightly electron donating (not by resonance or conjugation but by another effect we shall see later), and so stabilizes the intermediate sigma complex, and therefore the TS leading to it.

This effect is pronounced in ortho and para attack since these give rise to resonance structures which contain tertiary carbons, and are therefore more stable.

Meta substitution does not show these huge stabilizations, and is only slightly more stable then the unsubstituted benzene case.



B) Substitution with other Activating Ortho/Para Directing Substituents

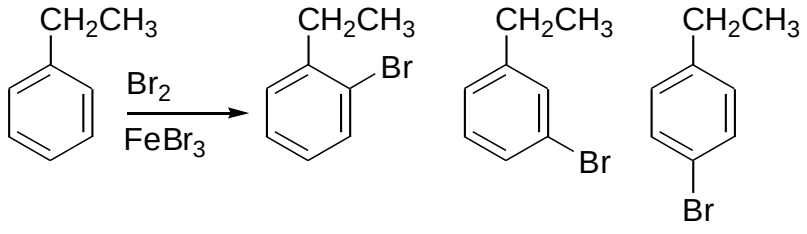
The results found with toluene are general for any alkyl substituted benzene undergoing EAS.

Any alkyl benzene will under EAS faster than benzene itself, and will generate products that are primarily ortho and para.

The alkyl group is an **activating** group, and is ortho and para directing.

This is called **inductive stabilization**, since the alkyl group donates electron density through the σ bond which attaches it to the benzene ring.

The $FeBr_3$ catalyzed reaction of ethyl benzene with bromine gives the following ratio of products.



ortho (38%) meta (<1%) para (62%)

The ortho and para isomers are the two major ones, whereas the meta isomer is only present in a small amount.

C) Substituents with Nonbonding electrons

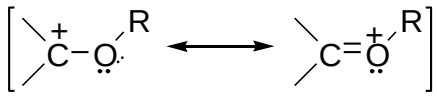
1) The methoxyl group:

Methoxybenzene (anisole) undergoes nitration around 10,000 times faster than benzene, and about 400 times faster than toluene.

Since oxygen is more electronegative than carbon, it may seem strange that methoxyl is a better activating group than methyl for EAS.

However, the difference is that the methoxyl group has **lone pairs**.

The lone pair can be used to stabilize adjacent positive charges through **resonance**.

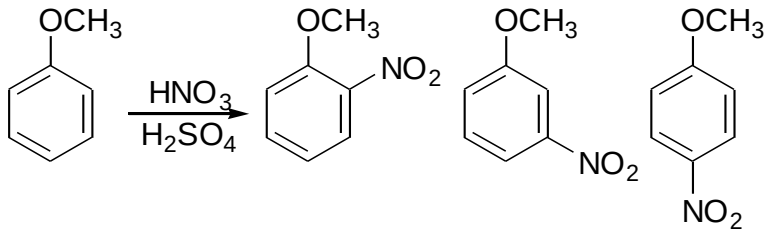


The second resonance structure is still a significant one since despite putting the positive charge on a more electronegative element (bad) since it has **more bonds** than the previous structure (good) and also carbon now has a full octet (good).

This type of stabilization is called **resonance stabilization**.

The oxygen atom is said to be resonance donating, or pi donating since it is donating electron density through a π bond in one of the resonance structures.

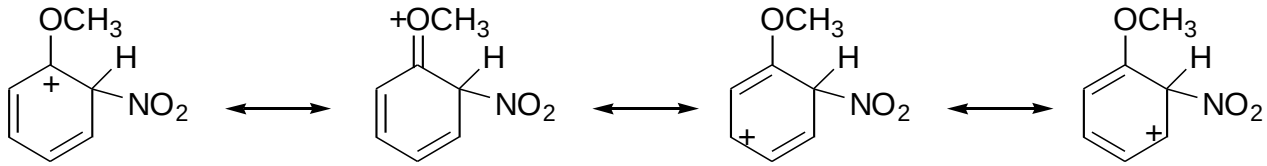
Just like the activating alkyl groups, anisole preferentially activates the ortho and para positions.



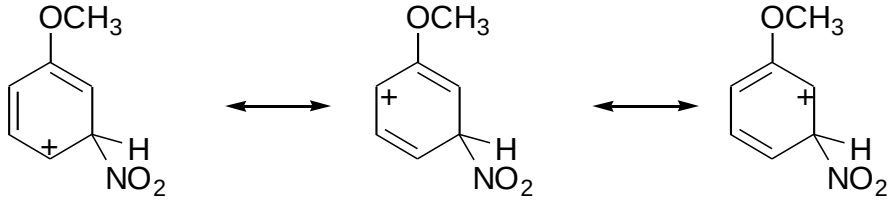
ortho (45%) meta (<0.1%) para (55%)

Resonance forms show that the methoxyl group effectively stabilizes the sigma complex for ortho and para substitution, but not if it is meta.

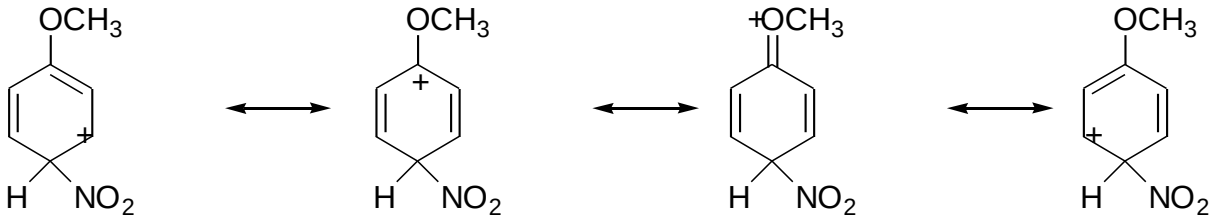
ortho attack



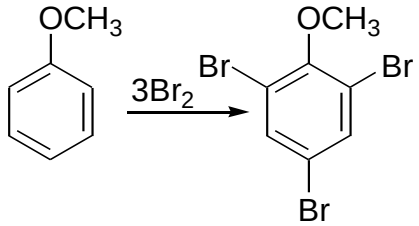
meta attack



para attack



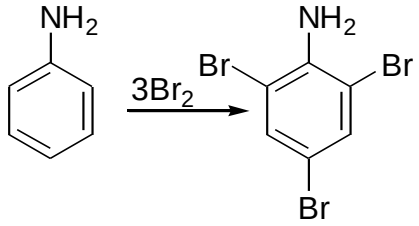
The methoxyl group is so activating that anisole will react with bromine itself, and if excess bromine is used, the tribromide is readily generated.



2) The Amino Group

In a similar fashion, the lone pair of electrons on the nitrogen in an amino group causes the -NH_2 substituent to be a powerful **activating** group with strong ortho and para directing effects.

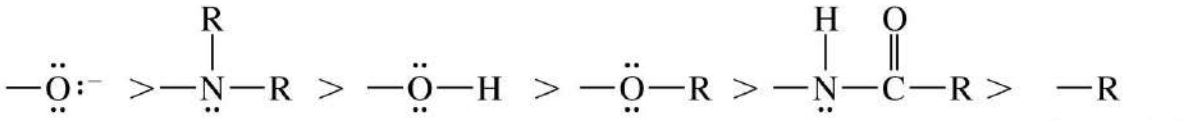
Aniline will react with bromine without a catalyst to generate tribromoaniline.



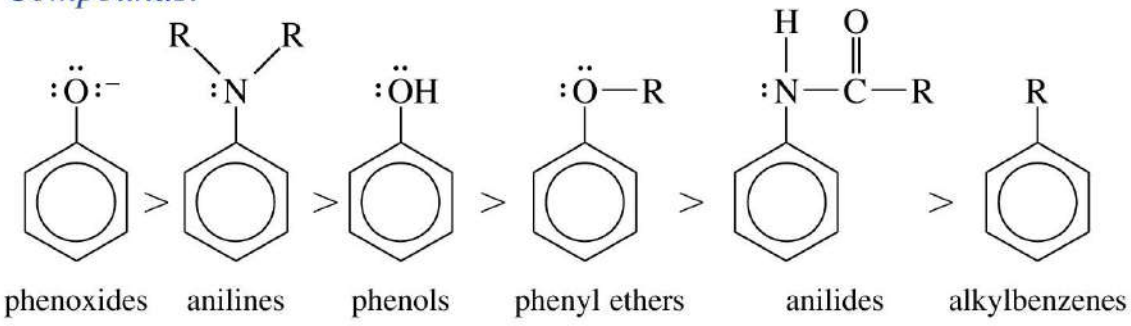
Again it is the non bonding electrons that provide resonance stabilization of the sigma complex when the attack is ortho and para.

Therefore any substituent with a lone pair of electrons on the **atom directly bonded** to the benzene ring can provide this resonance stabilization of the sigma complex for ortho and para attack.

Groups:



Compounds:

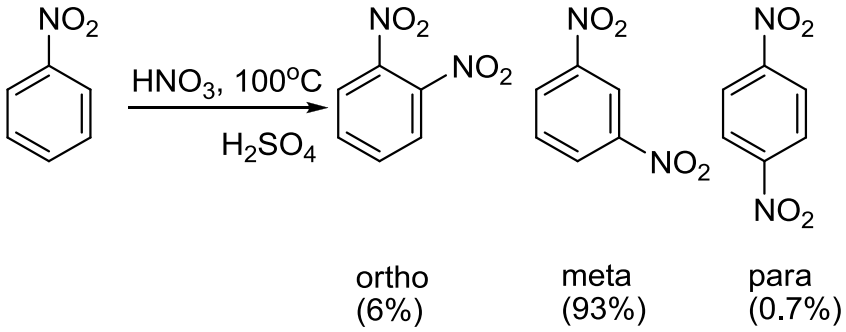


D) Deactivating, Meta Directing Substituents

Nitrobenzene is about 100,000 times **less** reactive than benzene towards EAS.

Nitration of nitrobenzene requires concentrated nitric and sulfuric acids at temperatures above 100°C.

This proceeds slowly, and the dinitrobenzene product produces three isomers, with the meta isomer being the major one.

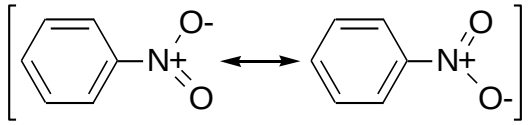


In the same way that electron donating groups activate the ortho and para positions, an electron withdrawing group deactivates the ortho and para positions.

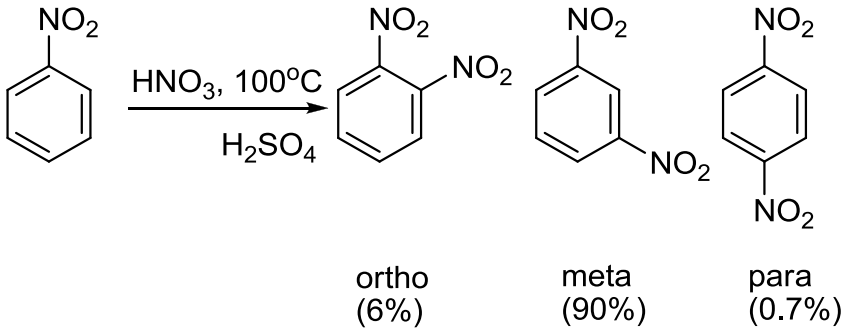
This selective deactivation leaves the meta position as the most reactive site for attack.

Meta directors deactivate the meta position much less than they deactivate the ortho and para positions.

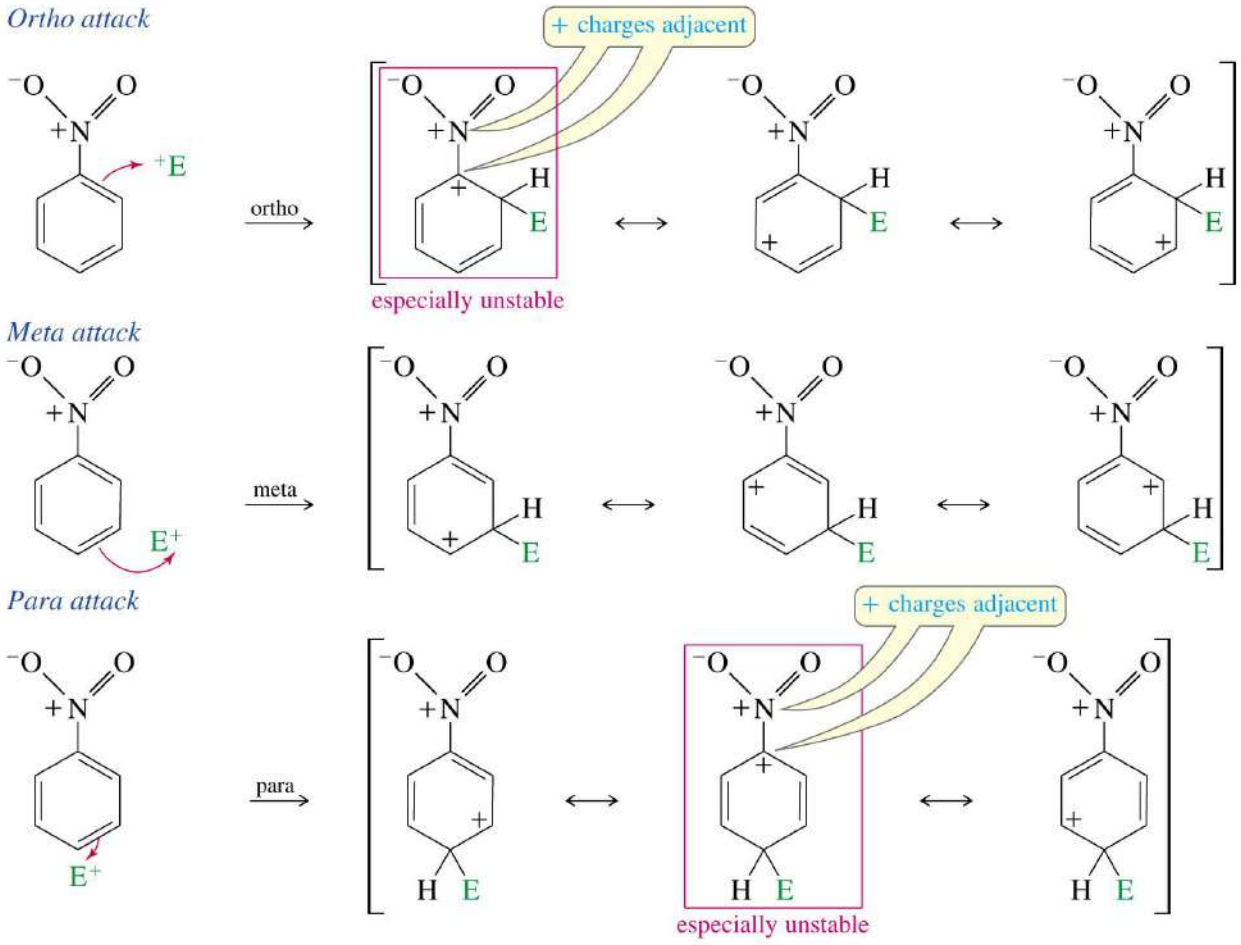
The nitro group is deactivating since the nitrogen is positively charged in both resonance forms, and this inductively withdraws electron density from the ring.



This removal of electron density makes the benzene ring a worse nucleophile, therefore the nitro group is deactivating for EAS.

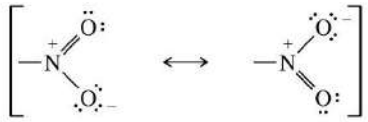
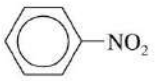
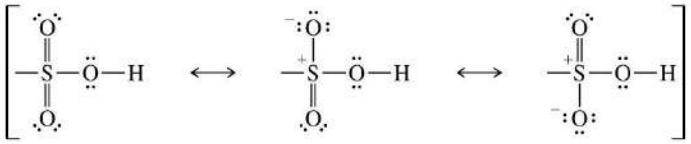
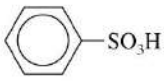
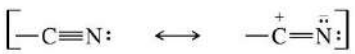
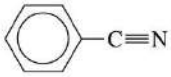
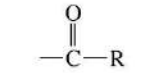
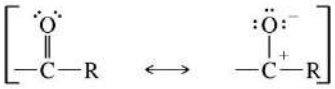
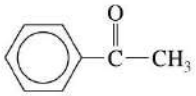
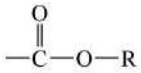
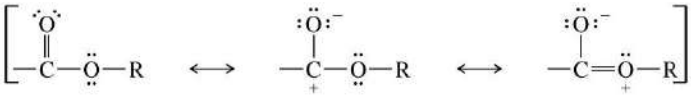
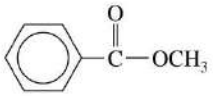


The deactivation is strongest for attack at the ortho and para positions since these orientations place positive charge adjacent to the nitro group, and having identical charges on adjacent carbons is very unfavorable due to the repulsion of like charges.

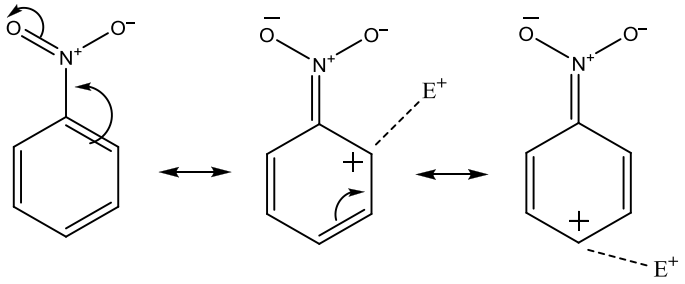


-For meta attack, the positive charges are never on adjacent carbons, therefore this is relatively the most stable site for attack.

-Attack even at the meta position for nitrobenzene is a higher energy situation than attack on benzene.
-All activating groups are ortho and para directors, and ALMOST all deactivating groups are meta directing.
-Deactivating groups have either full or partial positive charges on the atom bound directly to the ring.

Group	*Resonance Forms*	*Example*
—NO_2 nitro		 nitrobenzene
—SO_3H sulfonic acid		 benzenesulfonic acid
—C≡N: cyano		 benzonitrile
 ketone or aldehyde		 acetophenone
 ester		 methyl benzoate
$-\overset{+}{N}R_3$ quaternary ammonium		 trimethylanilinium iodide

Instead of looking at the charges in the σ-complex, look at the approach of the electrophile E^+. Resonance structures put a + charge in the ortho and para positions. The + charge hinders the approach of the positively charged E^+.



E) Exceptions to the Rule, or New rule: Halogens)

Halogen substituents are the exception to these rules.

Halogen substituents are deactivating, yet are ortho and para directors.

Halogens are unusual (special/interesting) since they show an interesting dichotomy of features:

1) The halogens are very electronegative. They can powerfully withdraw electron density from the ring inductively through the sigma bond (therefore **deactivating**).

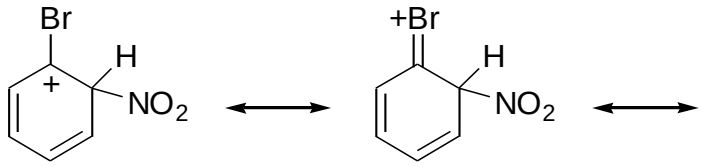
2) The halogens have lone pairs of electrons that can donate electron density (resonance donation) through π bonding (therefore ortho and para directors).

These effects oppose one another and make the halogens the exceptions to the previous generalizations.

Attack at the ortho (or para) position generates a sigma complex that can put the positive charge adjacent to a halogen substituent. The halogen uses its lone pair to stabilize this charge, generating a halonium ion structure.

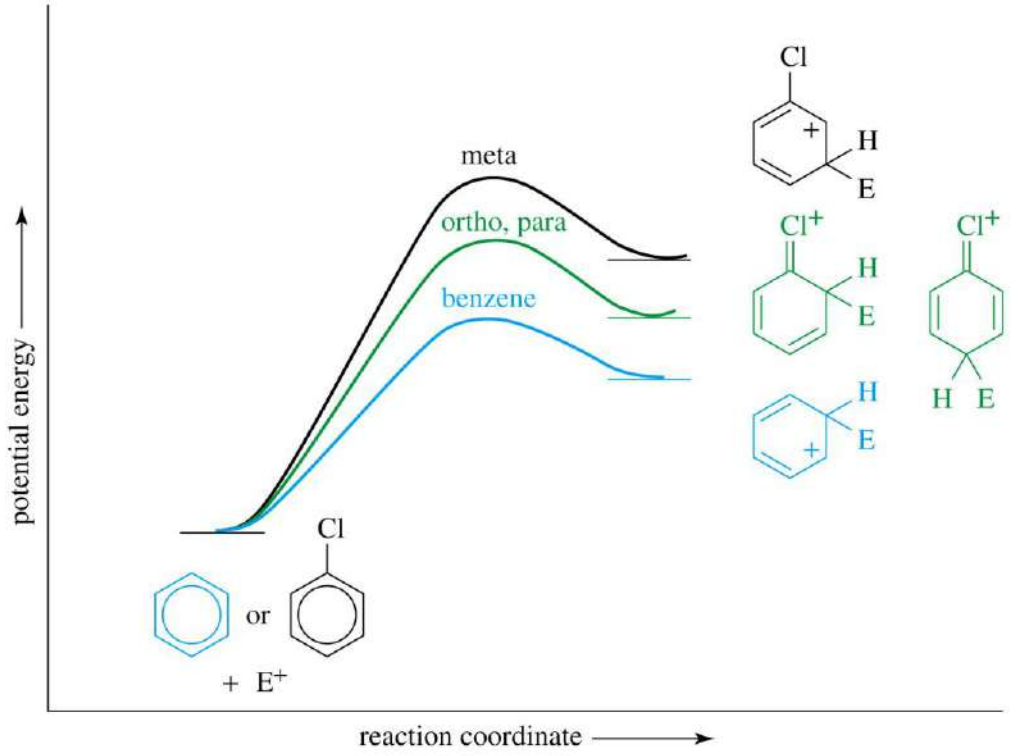
The sigma withdrawing substituent is also pi donating.

ortho attack



Reaction at the meta position does not allow for the positive charge to be placed adjacent to the halogen, and therefore does not result in any stabilization.

Halogens are **deactivating** because of the inductive withdrawal of electron density from the ring , yet are ortho para directors since they can use resonance donation to stabilize adjacent carbocations.



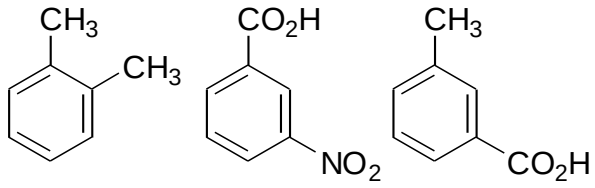
Summary of (De)Activators and Directors

π Donors	*σ Donors*	*Halogens*	*Carbonyls*	*Other*
—$\ddot{N}H_2$	—R (alkyl)	—F	O ‖ —C—R	—SO_3H
—$\ddot{O}H$	 (aryl)	—Cl	O ‖ —C—OH	—C≡N
—$\ddot{O}R$		—Br	O ‖ —C—OR	—NO_2
—$\ddot{N}HCOCH_3$		—I		—$\overset{+}{N}R_3$
ortho, para-directing			meta-directing	
ACTIVATING		DEACTIVATING		

III) Effects of More than One Substituent

Two or more substituents produce a combined effect on the reactivity of an aromatic ring.

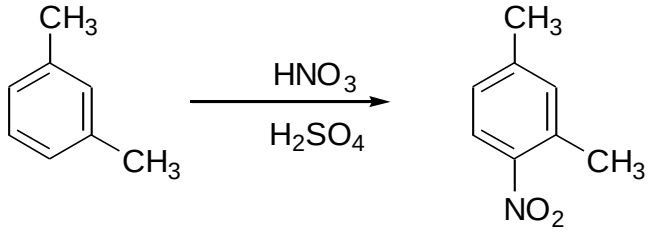
For example we can predict that xylenes (dimethyl benzenes) will be activated to EAS, and that a nitrobenzoic acid will be deactivated to EAS (relative to benzene).



However, the relative reactivity (and directing effect) of toluic acid is less obvious.

In some cases the orientation of addition is easy to predict (directing effects are complementary).

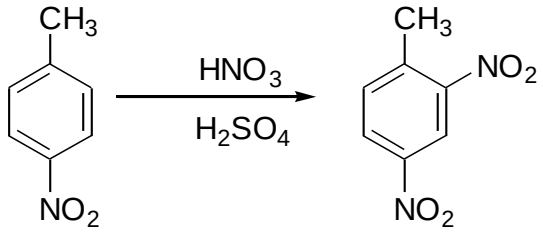
For meta xylene, there are two sites which are ortho to one methyl group and para to the other (double reinforcement).



Therefore, EAS would be directed preferentially to those sites.

Another site is doubly reinforced, yet since it is between the two methyl groups, it is sterically hindered, and is therefore of reduced reactivity.

For p-nitrotoluene, the methyl group directs ortho and para, but since the para position is blocked, it only directs the attack at the ortho position.



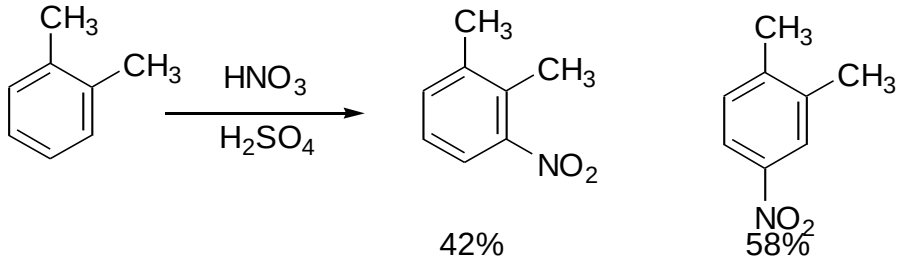
The nitro group also directs to this position since it is a meta director.

Both groups direct to the same site, and this reaction is very site selective.

It is more complicated if the directing effects conflict with each other.

Often in these cases, mixtures of products are produced.

E.g. o-xylene is activated at all positions, and so mixtures of nitrated products are observed.



When there is a conflict between an activating group and a deactivating group, usually the activating group dominates the orientation of substitution.

Generally, activating groups are stronger directors than deactivating groups.

Substituents can be divided into three groups, differing in the strength of their directing abilities.

1) Powerful o/p directing groups with lone pairs (resonance stabilizers)
2) Moderate o/p directors such as alkyl groups and halogens

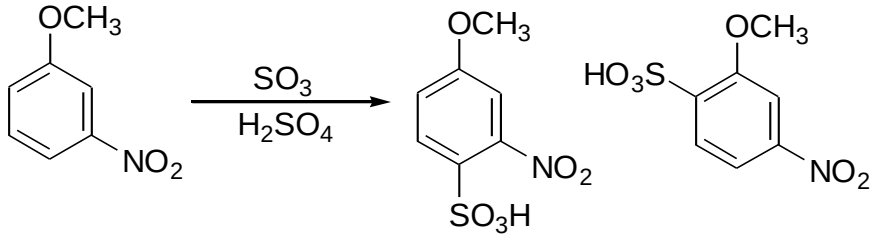
3) Meta directors

(From strongest to weakest).

If two substituents are in conflict of directing abilities, the stronger one will win.

If they are in the same class, then mixtures will be produced.

E.g. Sulfonation of m-nitroanisole is directed by the methoxyl group.

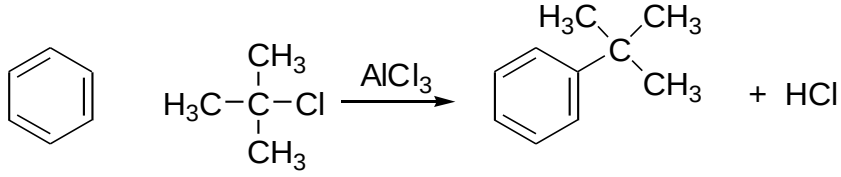


Friedal-Crafts Alkylation

Carbocations are electrophiles, and can therefore be useful reagents for forming new C-C bonds in EAS processes.

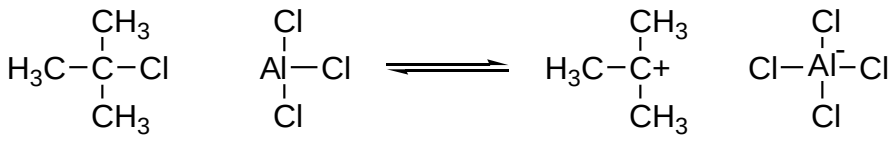
Friedal and Craft demonstrated that benzene would react with alkyl halides in the presence of a Lewis acid (e.g. $AlCl_3$) to produce alkyl benzenes.

This reaction became known as **Friedal-Crafts alkylation**.
E.g.

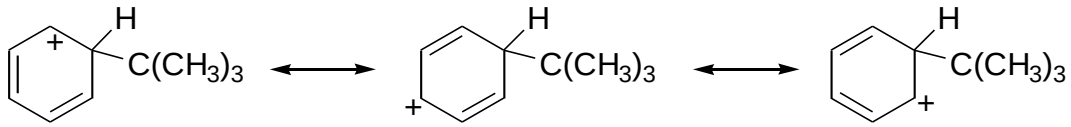


This alkylation is a typical EAS type reaction.

The ^{t}butylchloride reacts with the Lewis acid to generate the tbutyl carbocation.



The ^{t}butyl carbocation acts as the electrophile, and forms a sigma complex.



This is followed by loss of a proton, giving tbutyl benzene as the product.

The Lewis acid catalyst is regenerated in the last step.

Friedal-crafts reactions work with a variety of alkyl halides, and so is a very versatile reaction.

For secondary and tertiary halides, the reactive species probably is the free carbocation.

Whereas for primary alkyl halides (which cannot form stable carbocations) the electrophilic species is a <u>complex</u> of the Lewis acid and the alkyl halide.

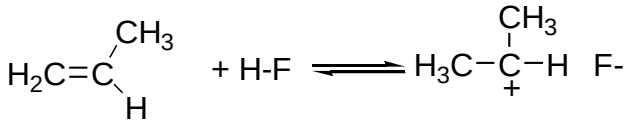
In this complex, the C-X bond is weakened (dashed line), and there is considerable positive charge on the carbon (but not a free carbocation).

$$CH_3\text{-}CH_2\text{-}Cl \; + \; AlCl_3 \; \rightarrow \; CH_3\text{-}CH_2\text{----}Cl\text{----}AlCl_3$$

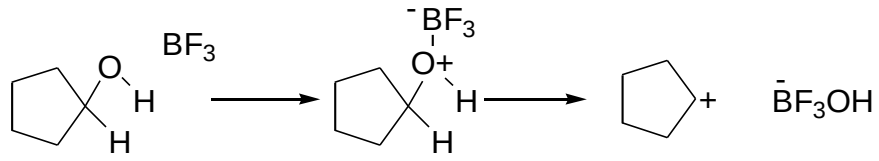
Other Friedal-Crafts Reactions

Other carbocation sources can be employed in these type of reactions.

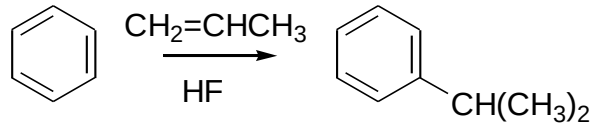
Carbocations can be formed by protonation of alkenes, and also through reaction of alcohols with boron trifluoride (a good Lewis acid).



The BF_3 is consumed in this reaction, therefore it is a **reagent**, not a catalyst.



E.g.



Limitations of the Friedal-Crafts Reaction

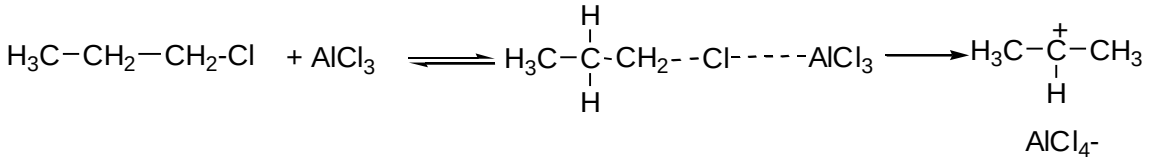
There are (unfortunately) some drawbacks or limitations to these Friedal-crafts reactions:

1) They only work with activated benzenes, benzene itself and halobenzenes. Strongly deactivated aromatics cannot be used in these reactions.

Systems such as nitrobenzene, benzenesulfonic acids and phenyl ketones all fail to react.

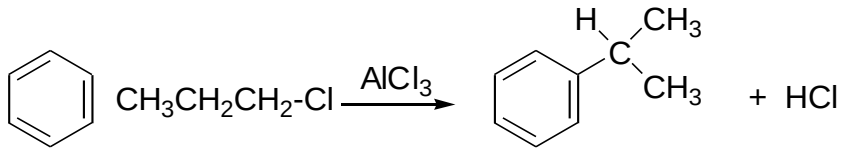
2) Since these reactions involve carbocations (or carbocation like) species, there is the possibility of carbocation rearrangements.

Certain alkyl groups can be introduced with out rearrangement (tbutyl-, isopropyl-, ethyl-) but consider what happens when we try to introduce an n-propyl group.



The carbocation-like intermediate can **rearrange** into a more stable carbocation.

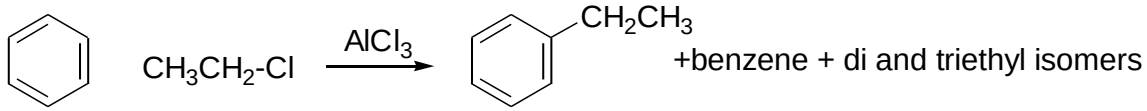
In trying to introduce an n-propyl group, we end up introducing an isopropyl group.



3) Alkyl groups are activating for EAS processes. Therefore the product of a Friedal-Craft reaction is more reactive than the starting material.

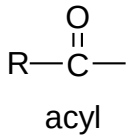
This means that multiple alkylations are difficult to avoid.

Even if only 1 equivalent of alkylating agent is added, a mixture of polysubstituted products is recovered along with unreacted benzene.



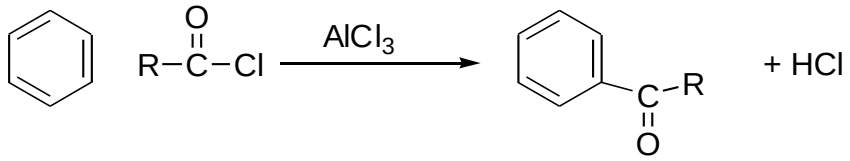
The Friedal-Crafts Acylation

An acyl group is a substituent which contains an alkyl group bound to a carbonyl group.



An acyl chloride is the same as an acid chloride.

In the presence of a Lewis acid, an acyl chloride reacts with benzene to produce a phenyl ketone (or acylbenzene).

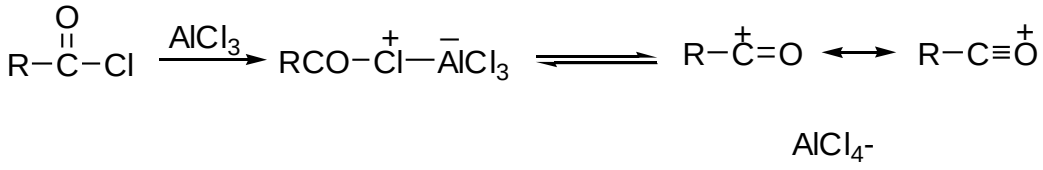


This Friedal-Crafts **acylation** is the same as the alkylation except that an acyl chloride is used instead of an alkyl chloride, and that an acyl group is incorporated instead of an alkyl group.

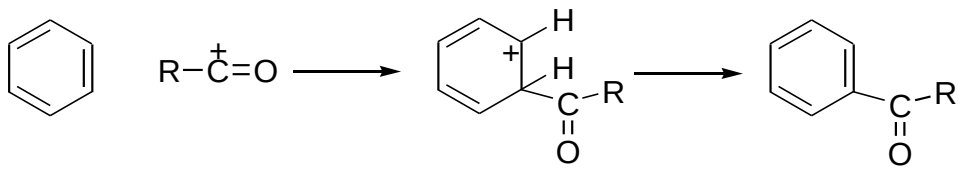
Mechanism of Acylation

The mechanism is very similar to before except the carbonyl group helps to stabilize the cationic intermediate.

The acyl halide reacts with the Lewis acid, and loss of $AlCl_4^-$ generates a resonance stabilized acylium ion.

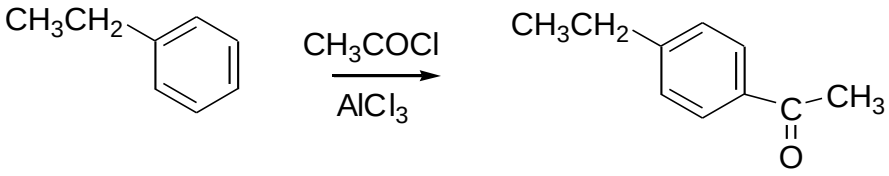


The acylium ion is a strong electrophile, and reacts with benzene generating an acylbenzene.



The product is a ketone, and since this is a deactivating group, poly-substitution does not occur. (Advantage over alkylation).

The acylation reaction actually involves a bulky electrophilic complex (not a free acylium ion) since para substitution tends to dominate.

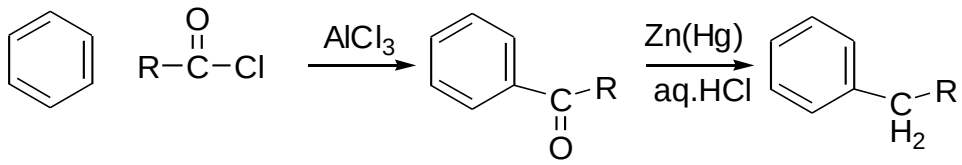


The acylium ion is resonance stabilized, and therefore will tend not to rearrange.

The Friedal-Crafts acylation however also still does not work with strongly deactivated systems.

<u>The Clemmensen Reduction</u>
We can use the acylation procedure to produce alkyl benzenes that otherwise **cannot** be prepared directly by alkylation

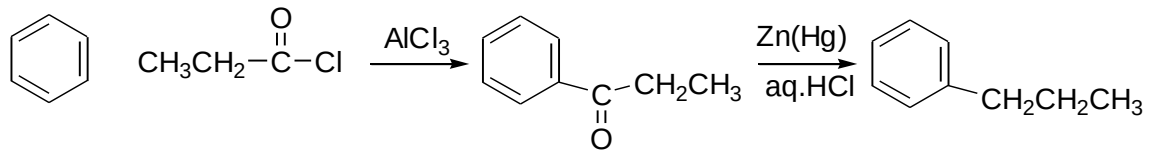
All that is required is the <u>reduction</u> of the acyl carbonyl group to a CH_2.



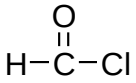
This is achieved by Clemmensen Reduction.

The reagents used are a zinc/mercury amalgam and aqueous hydrochloric acid.

Therefore to synthesize n-propyl benzene (which we could not do via direct FC alkylation), we can acylate using propanoyl chloride, and then reduce the phenyl ketone product which gives our final product.

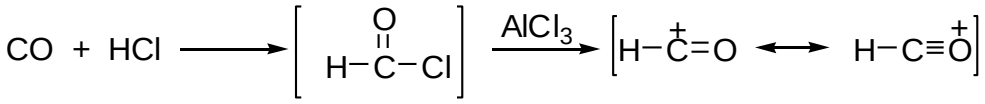


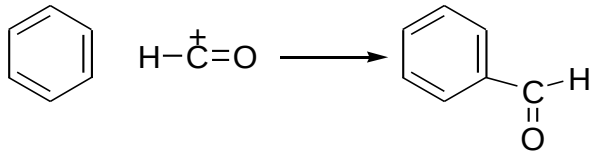
Synthesis of Benzenealdehydes (Gatterman-Koch Formylation)
The addition of a formyl group to benzene cannot be achieved by FC acylation since the required formyl chloride is not stable.



An alternative which overcomes this problem is the Gatterman-Koch reaction.

A high pressure mixture of carbon monoxide and HCl together with a catalyst can generate a formyl cation, which can then react with benzene to produce formyl benzene (more often called benzaldehyde).





This is a widely used industrial reaction.

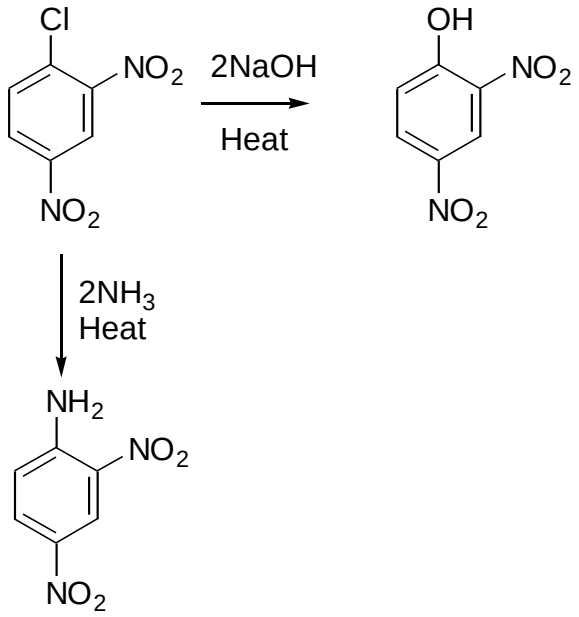
Nucleophilic Aromatic Substitution

Normally **electrophilic** aromatic substitution is the type of reaction mechanism we associate most commonly with benzene derivatives.

However, it is also possible for nucleophiles to displace halides ions (i.e. good leaving groups) from aryl halides if there are strong electron withdrawing electron groups bound to the ring (and especially if they are located ortho and para to the halide).

Since a nucleophile substitutes for the leaving group on the benzene ring, this is called nucleophilic aromatic substitution.

For example 2,4-dinitrochclorobenzene will undergo reaction with nucleophiles such as ammonia and hydroxide, where the chlorine becomes displaced.



The mechanism of this nucleophilic substitution is interesting since it **cannot** proceed by the S_N2 mechanism because the aryl halide cannot provide a suitable geometry for back side attack of the nucleophile (aryl ring blocks the attack of the nucleophile).

Yet the S_N1 mechanism also cannot operate since the reaction is not found to be unimolecular, and strong nucleophiles are required. (Also we would not expect ionization of the aryl halogen bond to give an aryl cation to proceed easily).

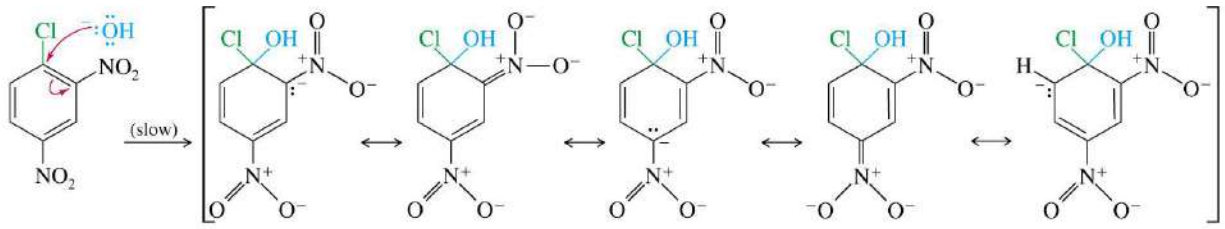
There are two different possible reaction mechanisms for NAS.

1) Addition Elimination Mechanism
2) Elimination Addition Mechanism (The Benzyne mechanism)

<u>The Addition Elimination Mechanism</u>

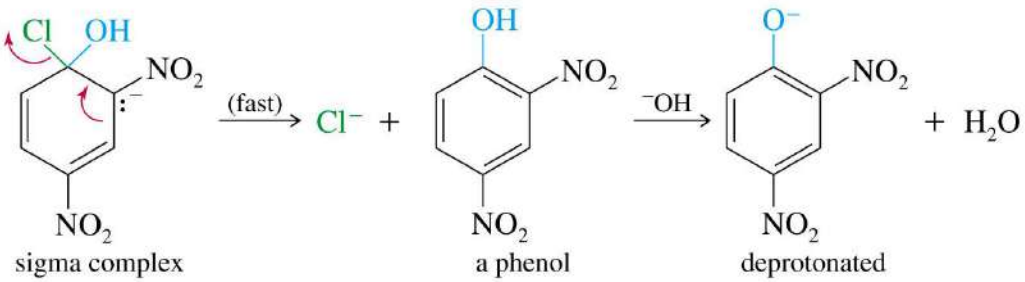
Consider the reaction of hydroxide ion with 2,4-dinitrochlorobenzene.

Step 1: Attack by hydroxide gives a resonance-stabilized sigma complex.



Step 2: Loss of chloride gives the product.

Step 3: Excess base deprotonates the product.



When the nucleophile attacks the carbon bearing the chlorine, a negatively charged sigma complex is generated.

The negative charge is delocalized over the ortho and para positions, and further delocalized into the electron withdrawing groups (conveniently located at these positions).

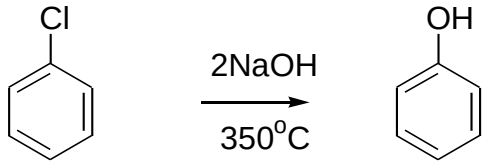
Loss of chloride from the sigma complex generates 2,4-dinitrophenol.

(This is like the mechanism for EAS, but with the benzene reacting with a **nucleophile** instead of an electrophile).

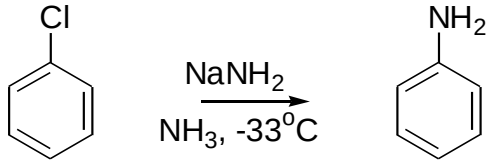
<u>The Benzyne Mechanism (Elimination Addition Mechanism).</u>
The previous addition elimination reaction mechanism required powerfully electron withdrawing groups on the benzene ring.

However, under forcing conditions, unactivated halobenzenes can react with strong bases.

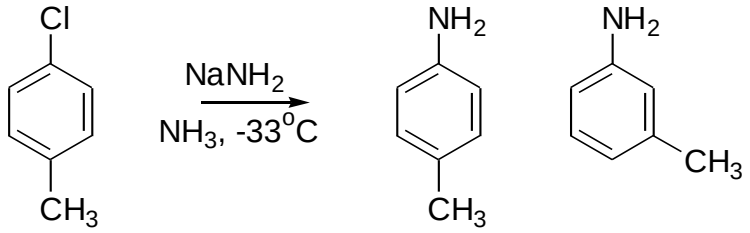
For example, phenol is produced commercially via the reaction of sodium hydroxide with chlorobenzene.



Analogously, aniline is produced via reaction of chlorobenzene with sodium amide.

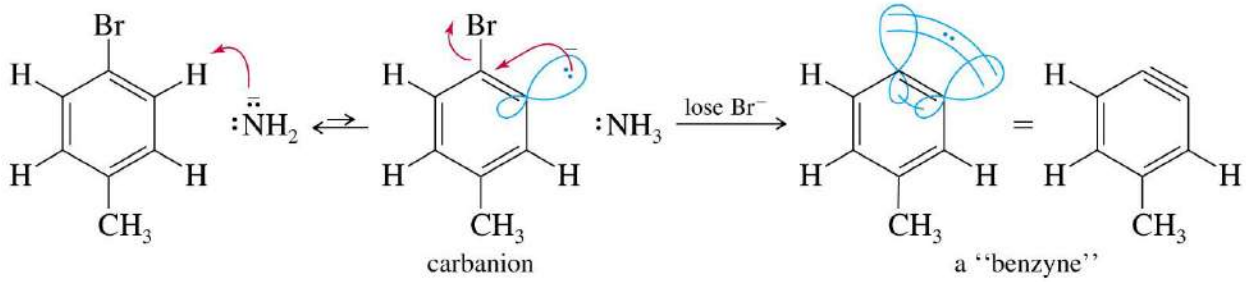


A clue to the mechanism of this type of reaction was provided by the below reaction:

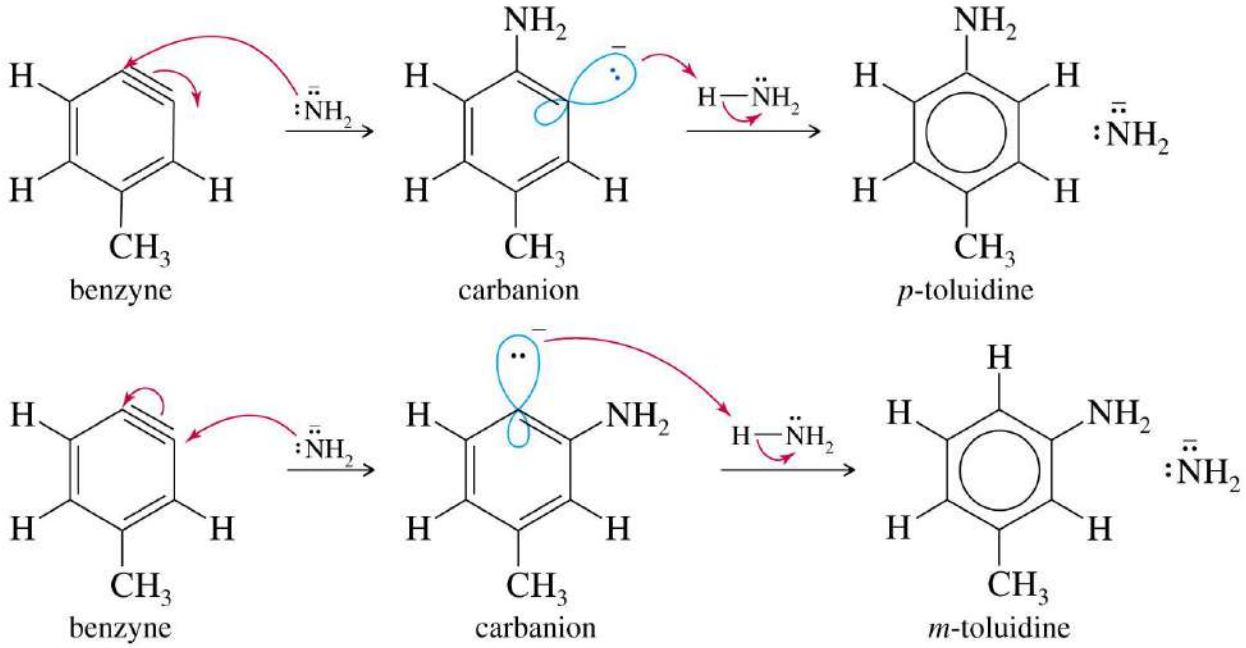


The products were found to be a 50:50 mixture of meta and para substituted compounds.

These two isomers can be explained as coming from the same intermediate, a **Benzyne**.



Then the NH_2^- anion attacks either side of the benzyne:



The reagent used acts as a strong base, and abstracts the proton adjacent to the leaving group.

The anion can expel the leaving group, thus generating a neutral species and another π bond (making a triple bond).

This is called a benzyne (benzene + alkyne).

The benzyne is a reactive intermediate.

The triple bond is reactive since it is very strained (should be linear).

The amide nucleophile attacks the triple bond, generating a carbanion, which then gets protonated to give the product.

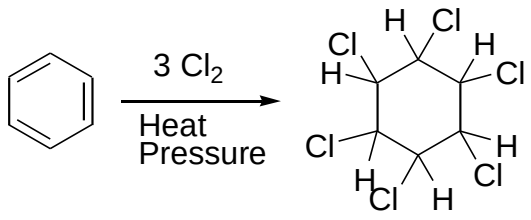
The attack on the triple bond may occur with equal probability (and energy) at either end, and thus the 50:50 mixture results.

Addition reactions of benzene

Although **substitution** is by far the most common reaction type of benzene and it derivatives, addition reactions can occur if forcing conditions are employed.

Chlorination

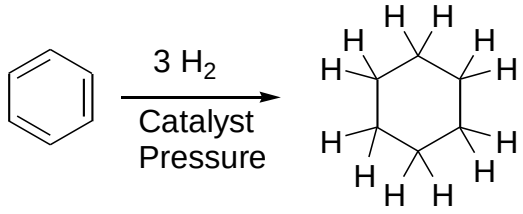
For example, if benzene is treated with an excess of chlorine under conditions of heat and pressure, then 6 chlorine atoms will add, generating 1,2,3,4,5,6-hexachlorocyclohexane.



This is believed to proceed through free radical intermediates, but the mechanism is not relevant here.

Catalytic Hydrogenation

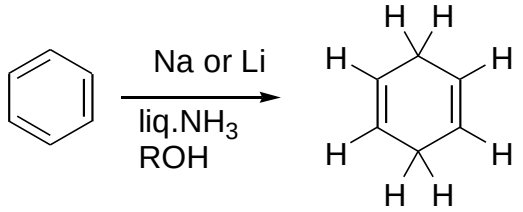
The addition of hydrogen to benzene occurs at elevated temperatures and pressures, and requires a catalyst.



Intermediate unsaturated compounds like cyclohexene or dienes cannot be prepared because of the high pressures involved.

Birch Reduction

However, Birch (1944) discovered a way to prepare 1,4-cyclohexadienes from benzene.



The use of sodium (or lithium) in a mixture of alcohol and liquid ammonia is called the **Birch reduction**.

The mechanism is very similar to the sodium/liquid ammonia reduction of alkynes to trans alkenes (Ch 9).

An electron adds to the benzene, producing a radical anion, and the anion quickly abstracts a proton from the solvent.

The cyclohexadienyl radical receives another electron to produce a cyclohexadienyl anion, that in turn gets protonated to give the reduced product.

Substituent Effects

Since the two carbons that are reduced go through carbanionic intermediates, then electron withdrawing substituents stabilize them whilst electron donating substituents destabilize them.

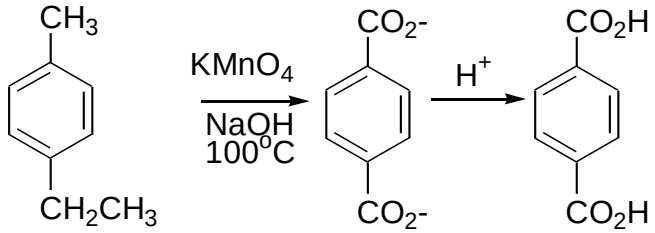
Therefore reduction occurs on the carbon atoms bound to electron withdrawing groups, and not at carbons bearing electron donating groups.

IV) Reactions of the Side Chains in Benzene Derivatives

Permanganate Oxidation

An aromatic ring imparts extra stability to the carbon atoms **directly** bonded to it.

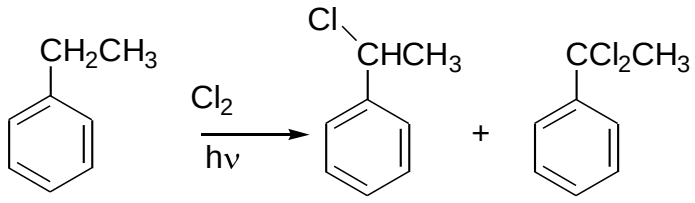
Therefore when an alkyl benzene is oxidized with permanganate, the product is the carboxylate salt of benzoic acid.



Side Chain Halogenation

Alkyl benzenes undergo free radical halogenation very easily at the benzylic position, since the required intermediate radical is a benzylic radical, and is therefore resonance stabilized.

For example, ethylbenzene reacts with chlorine under UV irradiation to give (1-chloroethyl)benzene and (1,1-dichloroethyl)benzene.

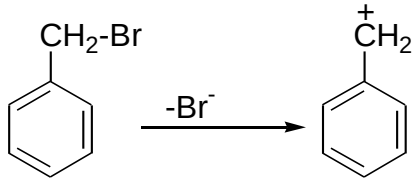


Nucleophilic Substitution at the Benzylic Position

In the same way that allylic halides are more reactive than normal alkyl halides in both S_N1 and S_N2 reaction, benzylic halides are even more reactive.

First Order Reactions

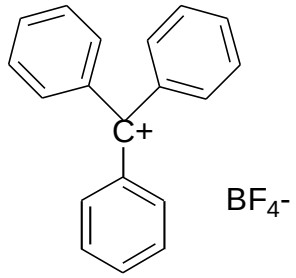
First order nucleophilic substitutions require ionization of the substrate to generate the carbocation, and benzylic cations are resonance stabilized.



Therefore benzylic halides undergo S_N1 reactions very easily.

If a benzylic cation has more than one phenyl group as a substituent then the stabilizing effects are additive, and these are very stable systems.

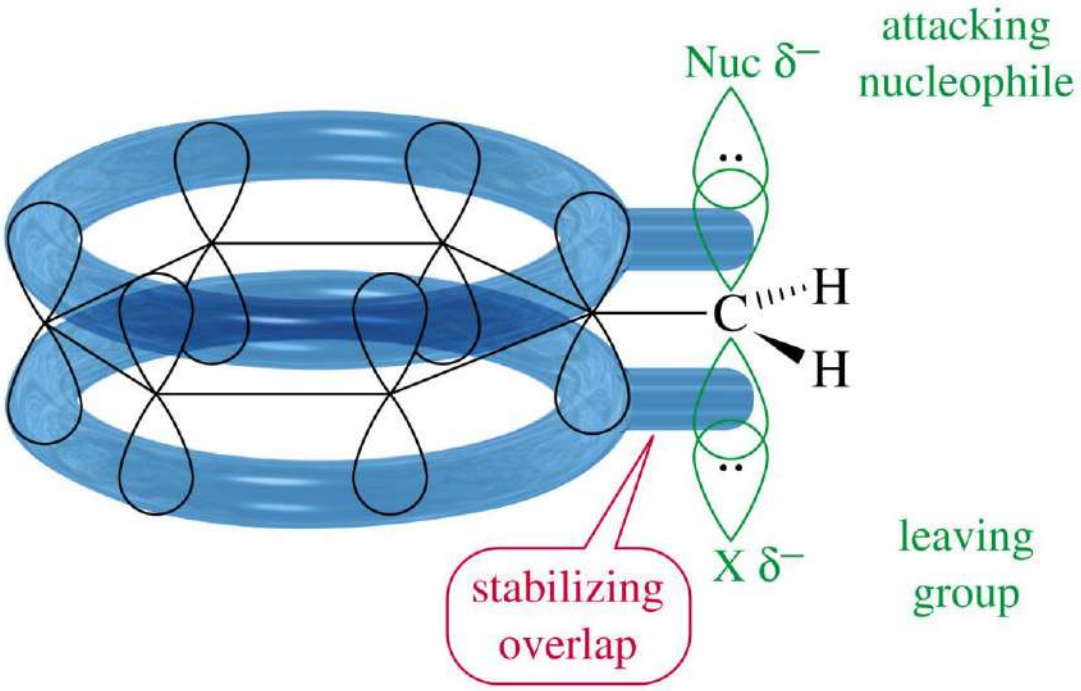
E.g. the triphenylmethyl tetrafluoroborate salt is a **stable** ionic solid.



Second Order Reactions

Just like allylic halides, benzylic halides are around 100 times more reactive than primary alkyl halides in S_N2 reactions.

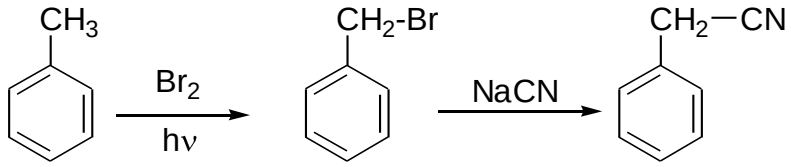
During the displacement, the p orbital that partially bonds to the nucleophile and leaving group also overlaps with the π electrons of the aromatic ring.



This conjugation lowers the energy of the TS and so enhances reaction rate.

S_N2 reactions of benzyl halides are good methods for converting aromatic methyl groups into different functional groups, via halogenation, followed by S_N2 substitution.

E.g.



Reactions of Phenols

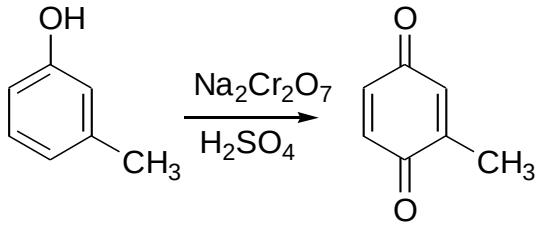
Phenols behave very similarly to aliphatic alcohols (Ch 11), with the exceptions that (a) they form more stable phenoxide ions (vs. alkoxide ions), and (b) they do not undergo either acid catalyzed reactions or back side attack (e.g. no reaction with HBr).

The aromatic ring in phenol also gives rise to some unique phenol reactions.

Oxidation of Phenols to Quinones

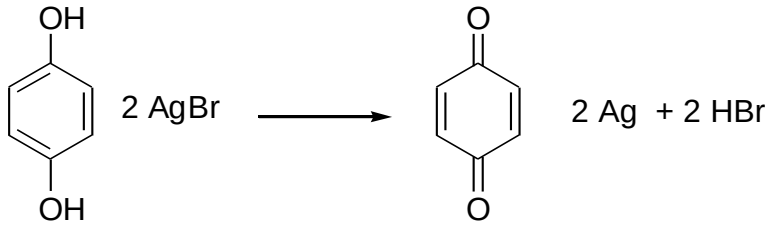
Oxidation of normal alcohols gives either carbonyl products (aldehydes/ketones) or carboxylic acids.

However, oxidation of phenols gives conjugated 1,4-diketone products, which are called quinones.



Most commonly this is achieved with chromic acid, although some phenols will auto-oxidize in the presence of air (oxygen).

Hydroquinone is very easily oxidized since it already contains the two oxygen atoms bonded to the ring.

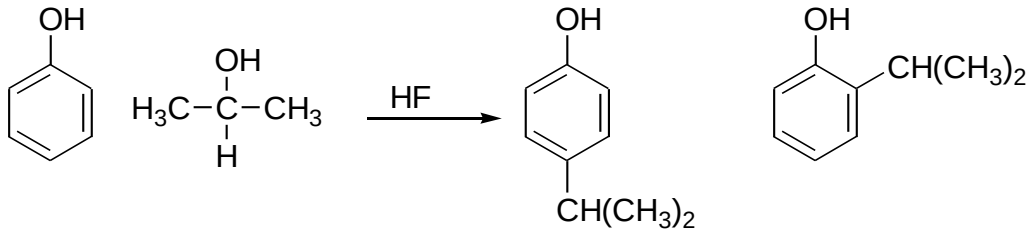


Even silver bromide (weak oxidant) can accomplish this transformation. (The basis of black and white photography).

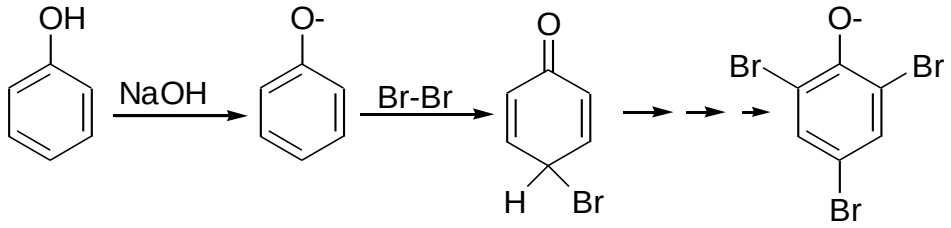
Electrophilic Aromatic Substitution

Phenol is a very reactive substrate for EAS since the non-bonding electrons stabilize the sigma complex from attack at the ortho and para positions.

The high reactivity of phenol allows the use of **weak** Lewis acid catalysts (e.g. HF) in alkyl-or acyl-ations which helps prevent the possibility of over reaction.

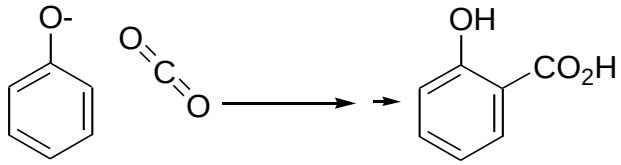


Phenoxide anions are even more reactive towards EAS, and the neutral sigma complexes that are formed resemble quinone type structures.



Phenoxide anions are so strongly activated that they even undergo EAS with carbon dioxide (a weak electrophile).

E.g.



salicylic acid

This is a useful and common industrial process (aspirin synthesis).