# Organic Chemistry



$C_8H_{10}N_4O_2$
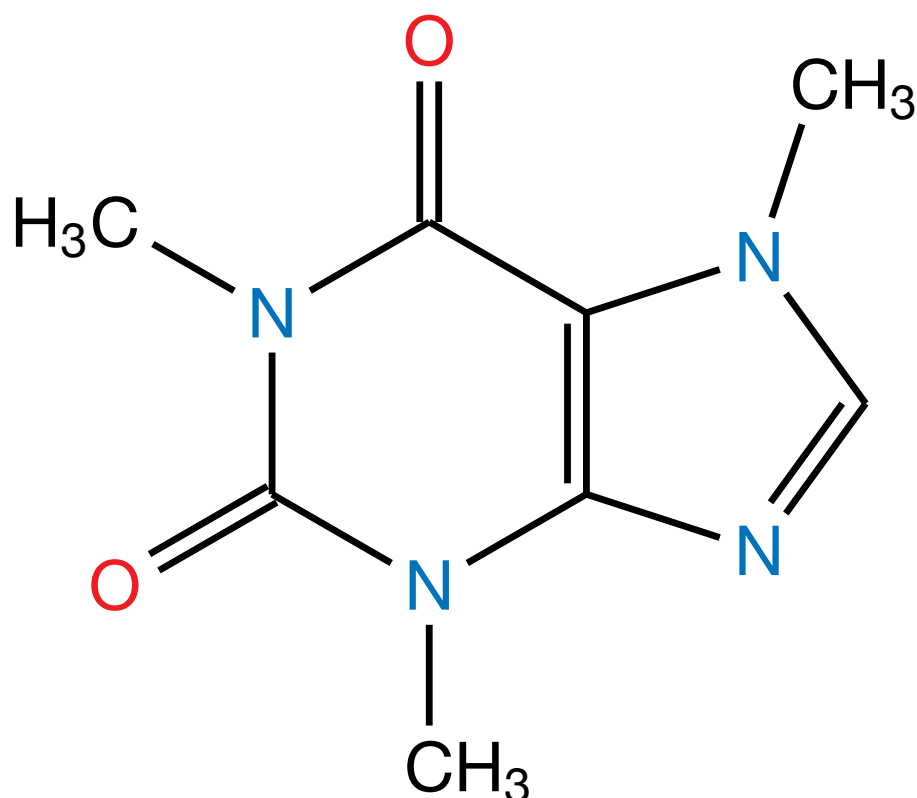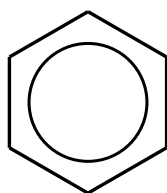
1,3,7-trimethylpurine-2,6-dione

-

Caffeine

Chapters 8 to 12

# 1 Arenes

## 1.1 Benzene

Benzene is simplest possible aromatic compound, or arene. The first known and isolated arene compounds had pleasant smells, such as benzaldehyde. Unfortunately, even though most known arenes now smell terrible and are carcinogenic, the name stuck.



The structural representation of benzene.

The most common form of arene is the benzene ring, or phenyl functional group. Note that aromatic rings with other configurations and structures can also form, such as with nitrogen.

Its basic structure consists of 6 carbon atoms, arranged in a hexagonal fashion. However, unlike cyclohexane, benzene is a flat, planar molecule. All 6 carbon atoms are sp$^2$ hybridised, forming the following structure:
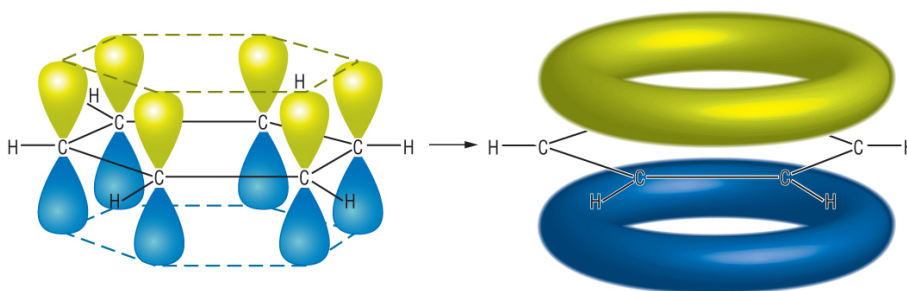


The trigonal structure of the sp$^2$ hybrid orbitals dictates this structure, since the angle between each orbital is 120°, which is the internal angle of a regular hexagon. Note that there is one H atom bonded to each carbon, making the molecular formula of benzene $C_6H_6$.

The carbon atoms are bonded to each other through π-bonds with their unhybridised p-orbitals, while the bonds with the hydrogen atoms (or other substituents if substituted) are done with the sp$^2$ orbitals.

Furthermore, the 6 π-bond electrons are delocalised, and move freely within the ring. This increases the stability of the benzene ring, which increases the amount of energy needed to modify it by fiddling with bonds.

### 1.1.1   Physical Properties

Since benzene is a regular hexagon, each C=C bond is the same length. However, it shorter than a C−C bond, but longer than a C≡C bond.

Benzene is a volatile, flammable and carcinogenic. Don't drink it. Don't eat it. Don't touch it. It also happens to be colourless, with a distinct "aromatic" odour.

As a non-polar molecule, it has relatively low melting and boiling points ($5.5\,°C$ and $80.1\,°C$), as well as low solubility in water. Of course, it is soluble in non-polar solvents, and in fact can be used as a solvent in its own right.

### 1.1.2   Chemical Reactions

Benzene undergoes substitution reactions rather than addition reactions, since adding atoms to the ring would destroy the delocalised π-system of the ring, which is energetically unfavourable. Instead, the H atoms on the ring are substituted.

The main mechanism for this is electrophilic substitution, as seen below.

# Electrophilic Substitution

The delocalised π-system of benzene has a very high electron density, and thus is a prime target for electrophiles, which will substitute the H atoms on the ring. Thus, the most common form of reaction involving benzenes is electrophilic substitution, barring special conditions and requirements.

## Step 1

In the first, rate-determining step, the aromaticity of the benzene ring is partially and temporarily broken, disrupted by the attacking electrophile.
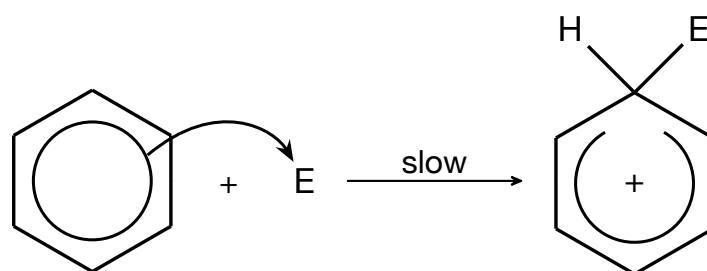


Note that the '+' is drawn in the centre of the ring, not on any one carbon.

Two electrons out of six from the delocalised π-system are used to form the bond between the electrophile, E, and the carbon. Thus, there is a positive charge on the carbon; due to the delocalised nature of the π-system however, this positive charge is delocalised across *all 6 carbons*, making it much more stable than a simple carbocation.

However, the activation energy for this step is still large, and only strong electrophiles are able to attack the benzene ring without catalysts.

## Step 2

Next, a nucleophile ($\colon\!Nu^-$ in this example) attacks the hydrogen attached to the hydrogen on the carbon atom, restoring the aromaticity of the benzene ring. The new substituent is now in place, and the two electrons in the C−H bond are returned to the π-system. Note that the arenium ion (which is the partially delocalised benzene) has 5 $sp^2$ carbons, and one $sp^3$ carbon. This results in a disruption of the planar structure of benzene — it is restored once the substitution is completed.

# Nitration of Benzene

The nitration of benzene involves the substitution of one of the H atoms on the benzene with a nitro ($-NO_2$) group. It has a number of specific requirements:
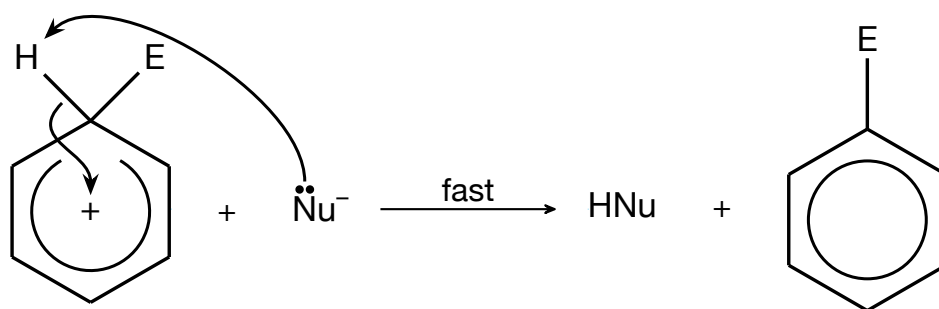
**Conditions:**   Concentrated $HNO_3$, concentrated $H_2SO_4$ catalyst.
*Constant* temperature of $50\,°C$.

**Observations:**   *Pale yellow* oily liquid, nitrobenzene.

## IV.  A New Electrophile

Since $H_2SO_4$ is a stronger acid than $HNO_3$, it donates a proton to $HNO_3$, forming $H_2O$, $HSO_4^-$, and $NO_2^+$, the electrophile. Next, another molecule of $H_2SO_4$ then forms $H^+_{(aq)}$, or $H_3O^+$. The overall equation is as such:

$$2\,H_2SO_4 \;+\; HNO_3 \longrightarrow NO_2^+ \;+\; H_3O^+ \;+\; 2\,HSO_4^-$$
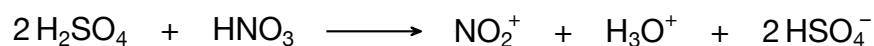
The catalyst $H_2SO_4$ is restored in a later step.

## V.  The π-Electrons Strike Back

Now that the electrophile $NO_2^+$ has been formed, it is attacked by the π-system. As with all electrophilic substitutions, this involves the breaking of the aromatic system, and is the slow step. The mechanism follows the general mechanism outlined above.
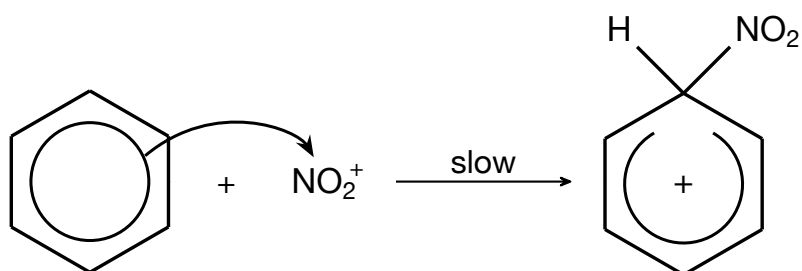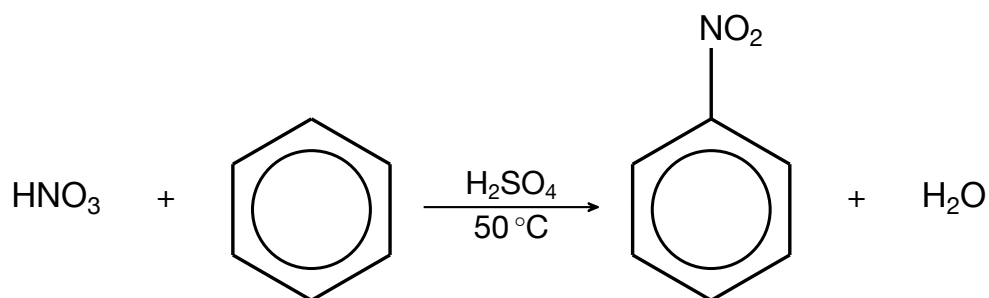
## VI. Return of the Aromaticity

The $HSO_4^-$ intermediate acts as a nucleophile and attacks the H atom bonded to the benzene intermediate. This restores both the π-system of the benzene ring, as well as the catalyst, $H_2SO_4$.
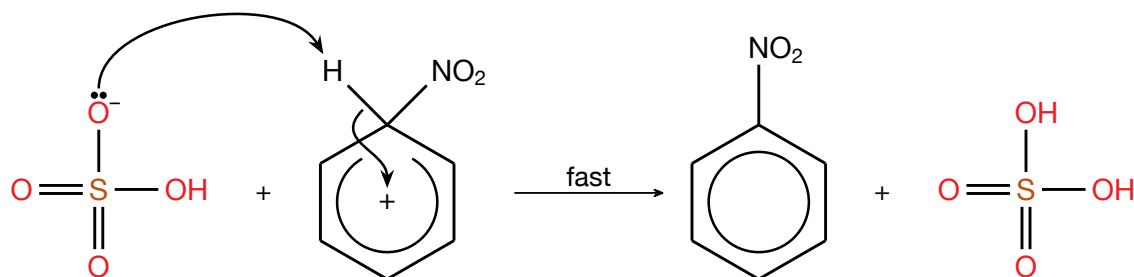
## VII. Overall Reaction

## 1.4    Halogenation of Benzene

Halogenation of benzene requires rather specific conditions, such as anhydrous $FeBr_3$ or $FeCl_2$ (for a reaction with bromine and chlorine respectively), and a warm environment.

Aluminium-based analogues of these catalysts ($AlBr_3$, $AlCl_3$) can also be used, as can pure filings of the metal, in which case the catalyst will be generated *in-situ* ($2\,Fe_{(s)} + 3\,Br_{2(l)} \longrightarrow 2\,FeBr_3$).

**Conditions:**    Warm, Anhydrous $FeBr_3$, $AlBr_3$, or Fe / Al filings (for bromine),
Anhydrous $FeCl_3$, $AlCl_3$, or Fe / Al filings (for chlorine)

**Observations:**    *reddish-brown* $Br_2$ / *yellowish-green* $Cl_2$ decolourises.
Formation of white fumes of Hydrogen Halide gas.

## 1.4.1    Conditions for Reaction

Lewis acid catalysts must be used, since the $Br-Br$ and $Cl-Cl$ are only instantaneously polar (instantaneous dipole moments). As such, they are nowhere near strong enough to attack the benzene system on their own.

Indeed, this can be used to distinguish between alkenes and benzenes, since the former does not require a catalyst for addition of halogens.

Furthermore, the entire reaction must be conducted in the absence of water; the reaction mechanism for the lewis-acid catalyst involves accepting a lone pair, the lone pair on water can, and will, in sufficient concentrations, destroy the catalyst.

## 1.4.2    Reaction Mechanism

### Generation of Electrophile

The reaction below uses Iron (III) chlorine ($FeCl_3$) as an example, adding $Cl$ to benzene, and this reaction mechanism applies to aluminium-based catalysts as well.

$$FeBr_3 \;+\; Br_2 \longrightarrow Br^+ \;+\; FeBr_4^-$$
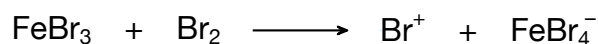
The catalyst is $FeBr_4^-$ — the *electrophile* is $Br^+$

# Formation of Benzene Intermediate

Again, this mechanism is similar in nature to electrophilic substitution in general. Now, the electrophile ($Br^+$) attacks the π-system, forming the arenium ion.
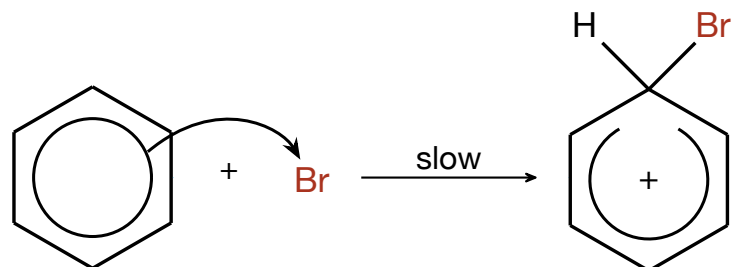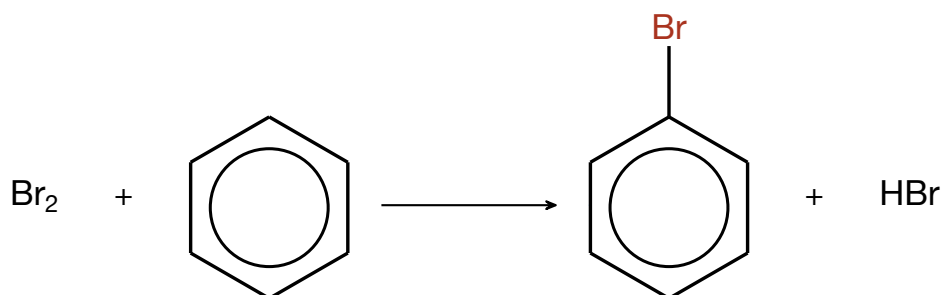


# Restoration of π-system and Aromaticity

In the final step, the $FeBr_4^-$ acts as a nucleophile, attacking the H atom attached to the benzene intermediate. This regenerates the catalyst $FeBr_3$, and also forms HBr.
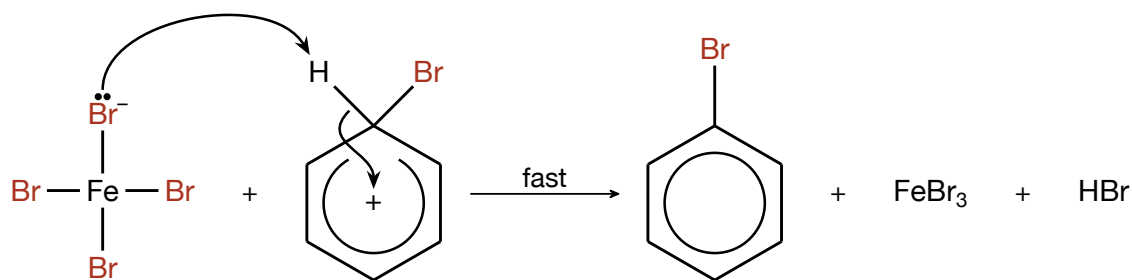


# Overall Reaction

# 1.5   Substituted Benzenes

The primary reaction mechanism of benzenes is electrophilic substitution, which involves the electrophiles attacking the electron-rich π-system of the benzene ring. As mentioned in Chapter 4 on Induction and Resonance, certain groups and atoms have the ability to withdraw or donate electrons, which affects the characteristics of the benzene ring.

## 1.5.1   Effect of Reactivity

If a benzene has electron-donating substituents, (such as $CH_3$) it will be more reactive, since it would increase the electron density of the π-system, making it a more appealing target for electrophiles. Thus, the ring is said to be *activated*. Conversely, electron-withdrawing substituents (such as $-NO_2$ or $-CO_2H$) *deactivate* the benzene, which decreases the reactivity of the benzene ring by making it less susceptible to electrophilic attacks.

Importantly, it *must be noted* that for the nitration of benzene, when the benzene ring is *activated*, the required temperature for reaction is only **30 °C**, whereas for *deactivated* rings, the required temperature is **above 50 °C**.

## 1.5.2   Effect on Positions of Further Substituents

Since the main way substituents affect the benzene ring is through the distortion of its π-system electrons, naturally this distortion can affect the positions of additional substituents on the ring.

For instance, an electrophilic substitution, of an electrophile R on methylbenzene can produce 3 possible products:



|  2-directed | 4-directed | 3-directed |
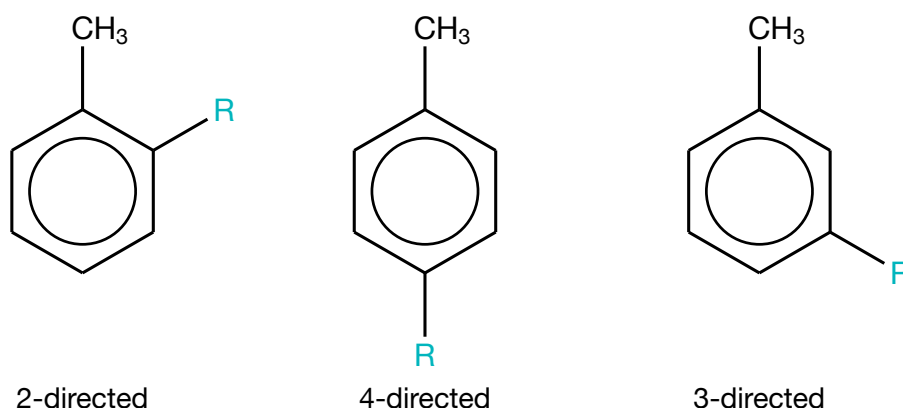
In this case, the $CH_3$ is considered to be attached to carbon 1.

The exact reasoning for this directing behaviour is complex, and has to deal with the resonance structures of the intermediate benzene, and the distribution of electrons within the π-system. Furthermore, there are only two types of substituents: *2,4-directing*

and *3-directing*. Also note that this is similar in concept to major and minor products; both will be produced, except one in much larger quantities.

The directing effects of various groups are summarised below.

| Substituent | Electron Effect | Directing Effect |
|---|---|---|
| Alkyl/aryl groups (eg. $-CH_3$) | Weakly Activating | 2,4-directing |
| $-OH$, $-NH_2$, $-OCH_3$ | Strongly Activating | 2,4-directing |
| $-Cl$, $-Br$ | Weakly Deactivating | 2,4-directing |
| $-CHO$, $-NO_2$, $-CN$, $-CO_2H$ | Strongly Deactivating | 3-directing |

## 1.5.3   Directing Mechanism

The exact mechanism behind the directing effects of substituents can be explored through the resonance structure of the substituted ring. Technically, the 2, 3, and 4 positions are called *ortho*, *meta*, and *para* respectively. It's just a naming thing.

## Electron-withdrawing Groups

Taking nitrobenzene as an example, the attached $NO_2$ group is electron-withdrawing. As such, based on the resonance structure of the $\pi$-system below, there will be three points with a partial positive charge ($\delta^+$). Since the substitution requires the attack of an *electrophile*, these positions are *less favourable*. Hence, the electrophile will tend to target the meta (or 3-directed) position, and the $NO_2$ group is said to be meta-directing, or 3-directing.
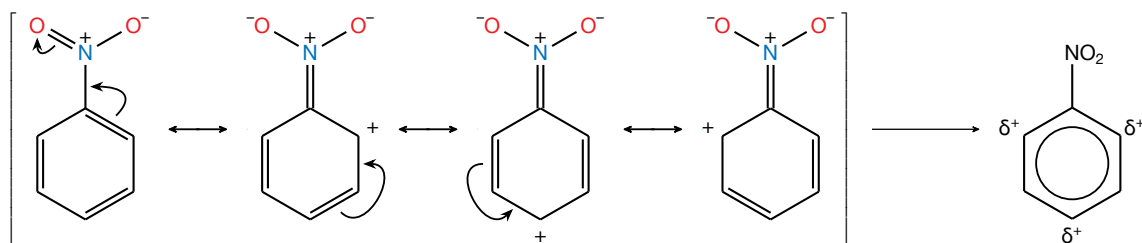


The $\delta^+$ positions represent areas of low electron density.

# Electron-donating Groups

On the other hand, for an electron-donating group such as $NH_2$, the reverse is true; there will be 3 areas of *high electron density* (actually the same 3 positions), which *attracts* electrophiles, and as such favours substituting further groups on the ortho/para positions, or 2,4 positions. Thus, $NH_2$ is said to be ortho/para-directing, or 2,4-directing.
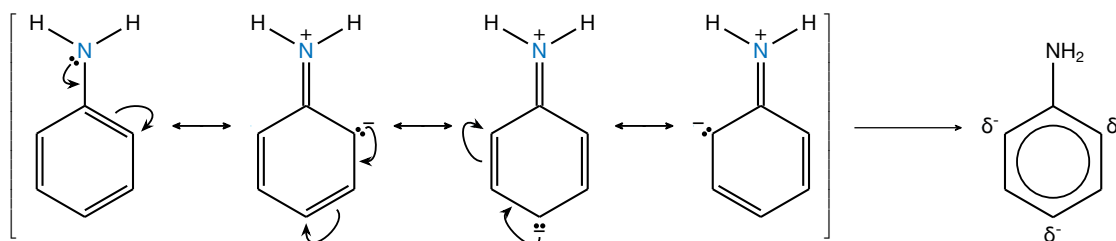


The δ⁻ positions represent areas of high electron density.
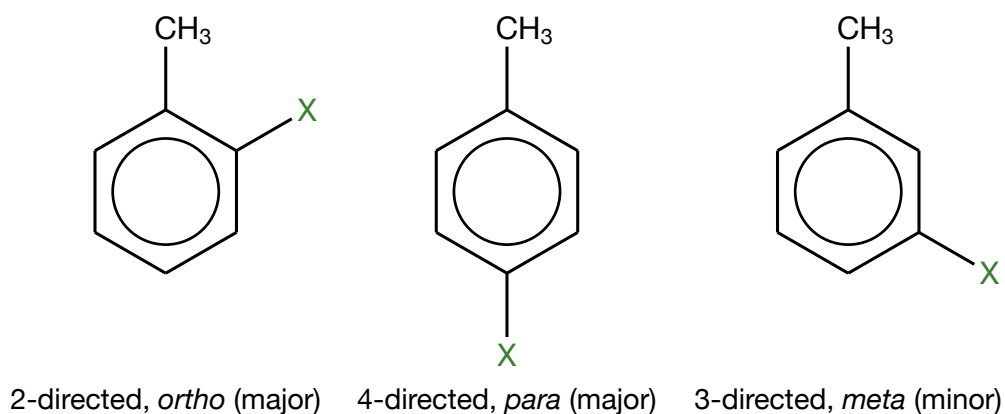
# Halogen Substituents

Halogens are a special case, since they can donate electrons through induction, but can also withdraw electrons through the resonance effect due to their substantial electronegativity difference, compared to carbon.

The overall effect is that halogens are *ortho/para* directors.

# 1.6  Alkylbenzene Reactions

## 1.6.1  Halogenation

The reagents and conditions for the halogenation of alkylbenzenes is similar to that of normal, unsubstituted benzenes. This time, however, there are two major products, and one minor product, due to the 2,4-directing nature of alkyl groups.



2-directed, *ortho* (major)    4-directed, *para* (major)    3-directed, *meta* (minor)

## 1.6.2  Nitration

Similarly, the nitration of alkylbenzenes also gives two major products, and one minor product.



2-directed, *ortho* (major)    4-directed, *para* (major)    3-directed, *meta* (minor)
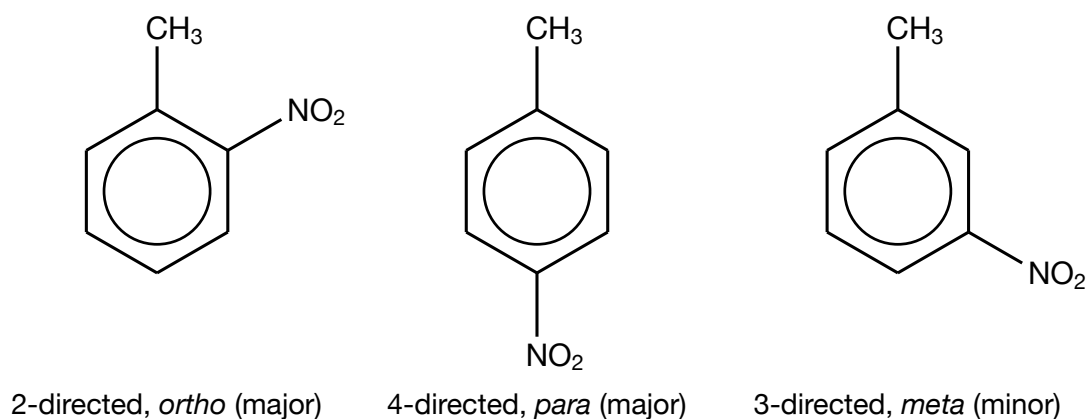
### 1.6.3   Free Radical Substitution

In the absence of Lewis-acid catalysts, halogens will not react with the benzene ring, due to the high unfavourability of that reaction. However, remember that reactants can, and will, react with *any* functional group on the molecule. In this case, the halogens will react with the alkyl side-chain of the alkylbenzene. The conditions are identical to that of regular free radical substitution.

**Conditions:**     UV Light, $Br_2$ / $Cl_2$ gas
**Observations:**   *Reddish-brown* $Br_2$ / *yellowish-green* $Cl_2$ decolourises.
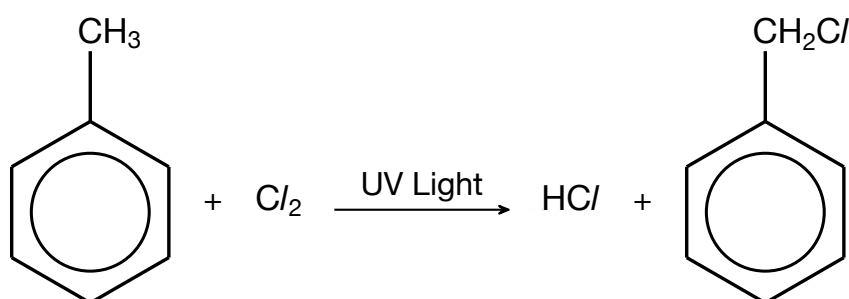


Naturally, the alkyl side-chain can also undergo multiple substitutions, giving a mix of products and isomers.

### 1.6.4   Side-chain Oxidation

When reacted with the strong oxidising agent, $KMnO_4$, and heated, the alkyl chain attached to the benzene will be oxidised. Regardless of the length of the chain, benzoic acid is always formed.
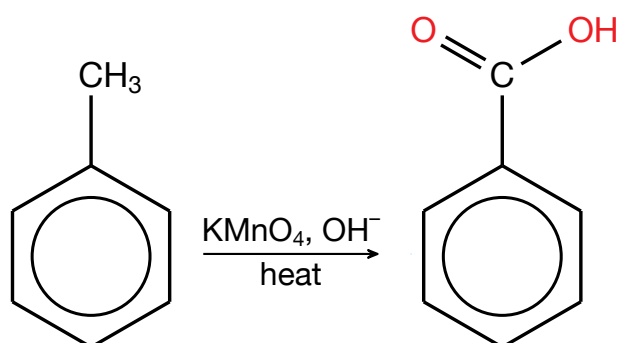
**Conditions:**     Heat, $KMnO_4$, dilute acid or alkali.

**Observations:**   *Purple* $KMnO_4$ decolourises (*acid*), or
                    *Brown* precipitate of $MnO_2$ (*alkali*).
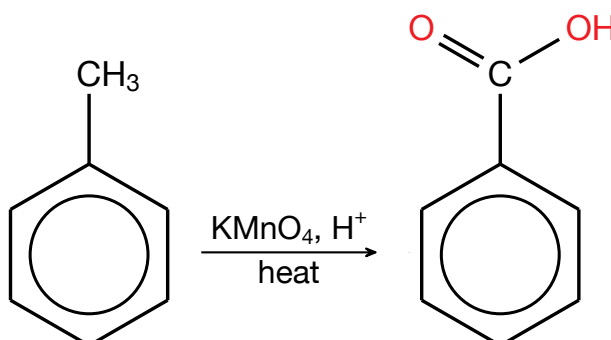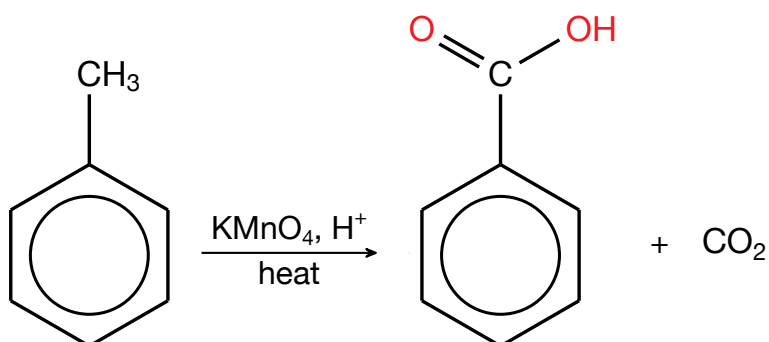


In this case, an acidic medium is used, hence $H^+$.

Alternatively, an alkali medium can be used, for instance with $NaOH_{(aq)}$. Instead of forming benzoic acid however, the benzoate ion is formed, which would form an ionic bond with Na.



If the alkyl chain is 2-long, (ie. ethylbenzene), then $CO_2$ will be formed from the oxidation of the second carbon, in addition to benzoic acid.



If the chain is 3 or longer, then the rest of the chain (apart from the first) will be oxidised to form a carboxylic acid.