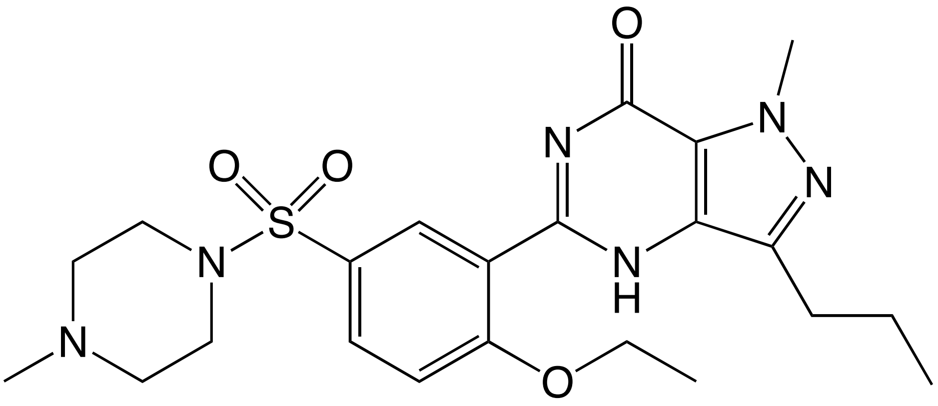
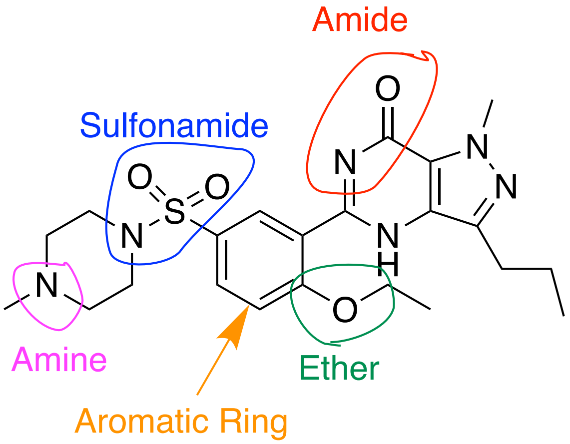
Review:
Some things you should know: Functional groups and structure

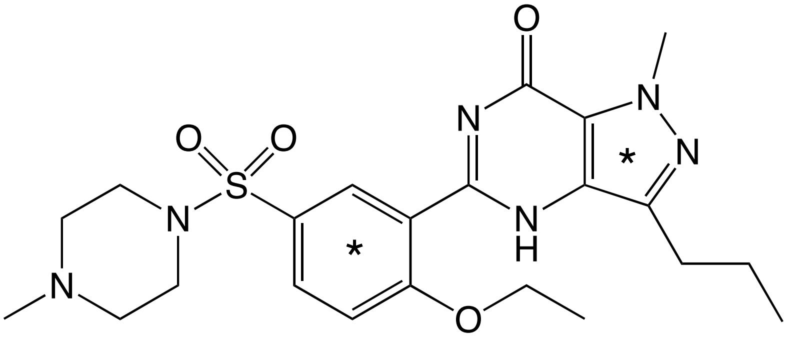


The molecule shown is **Viagra**. It generates more than $ 2.3 billion U.S. per year. Amongst other things, it aids jet lag recovery in hamsters.

Can you recognize its functional groups? **(**ignore sulfonamide)



Are the rings with asterisk aromatic? **YES**



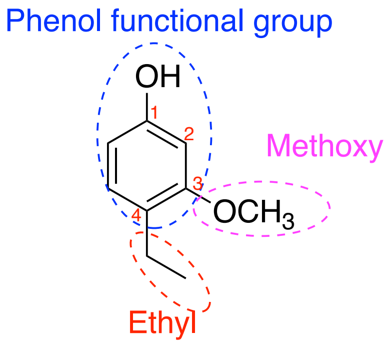
Answer: Yes. The 5-membered ring is cyclic, it has two double bonds (4 pi electrons) that are conjugated and the methyl-substituted nitrogen donates its lone pair into the 5-member ring to fit the 4n+2 rule. The other nitrogen has its lone pair in an sp^2 orbital perpendicular to the pi (π) system.

What is the molecular formula? ($C_{22}H_{30}N_6O_4S$)

Are there any stereogenic centres? (No)

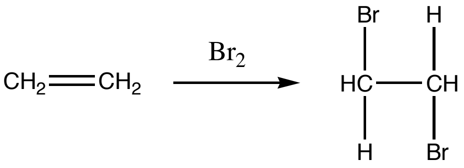
If given a molecule, know how to analyze its parts and functional groups on the exam.

Another Example: 4-ethyl-3-methoxyphenol (a cockroach sex pheromone)



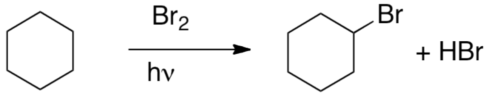
Electrophilic Aromatic Substitution

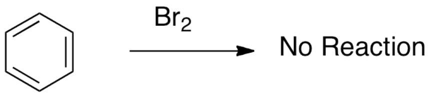
Benzene appears to be a remarkably stable (36 kcal/mole more than expected for cyclohexatriene) and unreactive compared to alkenes, such as cyclohexene or ethylene, or even alkanes, such as cyclohexane or ethane.

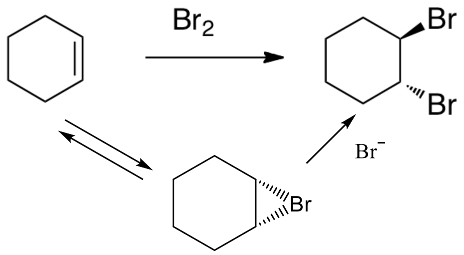


$$CH_2{=}CH_2 \xrightarrow{Br_2} \underset{H}{\overset{Br}{HC}}-\underset{Br}{\overset{H}{CH}}$$

$$CH_3CH_3 \xrightarrow[h\nu]{Br_2} CH_3CH_2Br + HBr$$



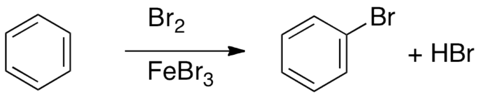




When ethylene or cyclohexene is allowed to react with bromine (an addition reaction), a dibrominated product is formed. However, when benzene is allowed to react with bromine in the absence of catalyst, nothing occurs. It is much less reactive.

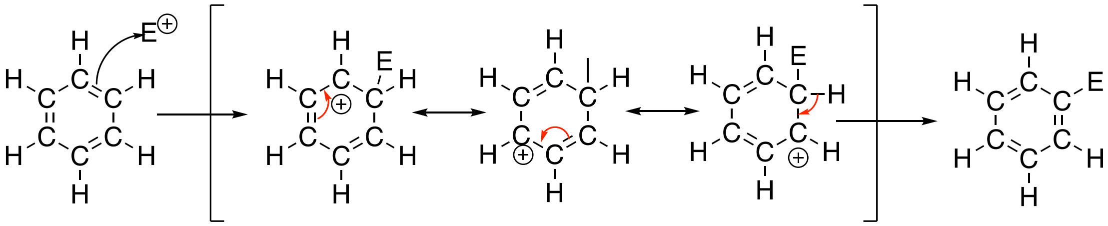
In the case of alkanes such as ethane or cyclohexane, light (h*v*) or heat are required for the bromination to occur (this is a substitution). For benzene, there is still no reaction under these conditions.

However, this is not to say that benzene is completely unreactive. With a Lewis acid catalyst, benzene can be made to react.



This is an <u>Electrophilic Aromatic Substitution</u>.
Electrophiles seek electrons (e^-) or negative charge
Nucleophiles seek positive charge or donate electrons

In electrophilic aromatic substitution, an electrophile (E^+) is substituted for a hydrogen on the aromatic ring.
Aromatic compounds are very stable and unreactive. In this type of reaction, the electrophile must be especially reactive (electron deficient).
The General Mechanism:

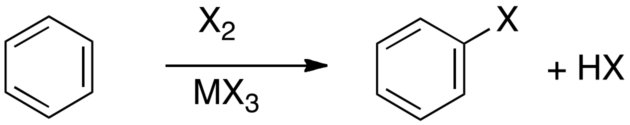


resonance structures

The pi system of the benzene ring acts as the nucleophile.
The cation formed in the reaction is resonance stabilized (conjugated with the two double bonds). However, it is not aromatic.
Note that the positive charge is ortho and para to the electrophile.

Once the aromatic stabilization is lost, it is easily regained (remember that by staying aromatic, the compound becomes more stable). Hence the last step (loss of proton) is fast to regenerate the aromatic system.

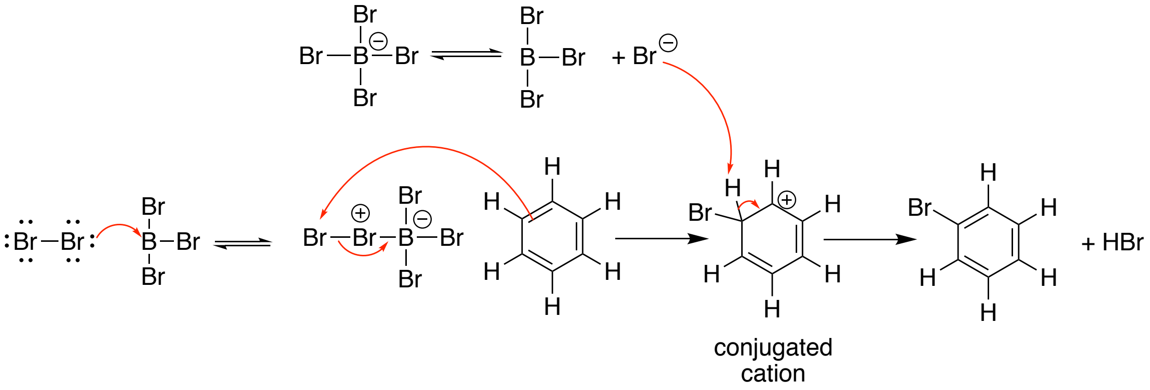
Electrophilic Aromatic Halogenation



Where X = halogen (Cl, Br usually)
M = metal Fe, B, or Al

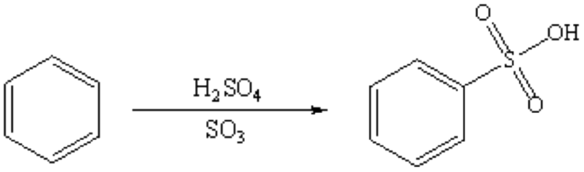
In this reaction, MX_3 ($FeBr_3$, $AlCl_3$, BBr_3) is a Lewis Acid catalyst (a Lewis Acid is a substance that can accept a pair of electrons). MX_3 has an empty orbital to accept a pair of electrons. Chlorine or bromine alone are not strong enough electrophiles to react with the weakly nucleophilic benzene by themselves. The catalyst converts the halogen into a stronger electrophile, which can then react with benzene.

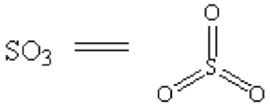
Mechanism:



In halogenation, the Lewis Acid catalyst is regenerated at the end of the reaction.

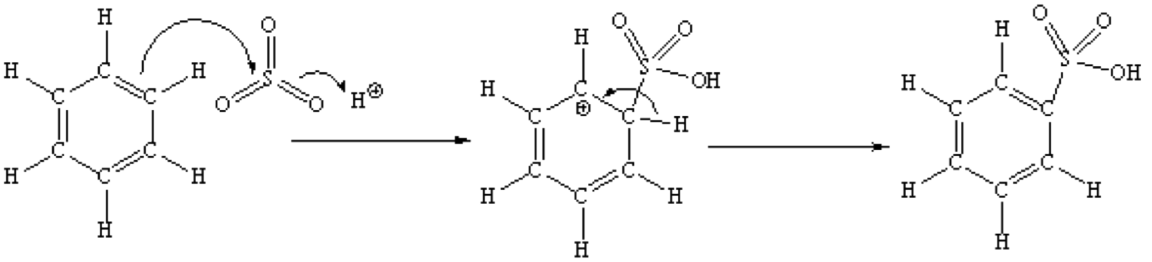
SULFONATION





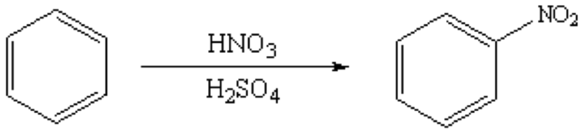
In this reaction, SO_3 is the electrophile.

Mechanism:



This reaction of SO_3 is followed by loss of proton from the conjugated cation intermediate (similar to the one we saw in halogenation).

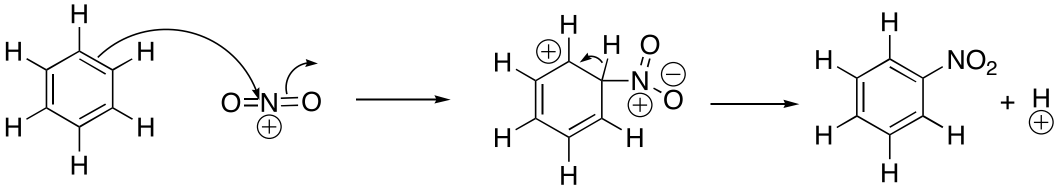
NITRATION



Mechanism:

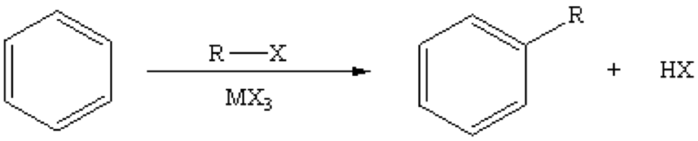
$$HNO_3 + H^{\oplus} \longrightarrow H_2\overset{\oplus}{O}\text{—}NO_2 \rightleftharpoons \underset{\text{nitronium ion}}{{}^{\oplus}NO_2} + H_2O$$

$${}^{\oplus}NO_2 = O{=}\overset{\oplus}{N}{=}O$$



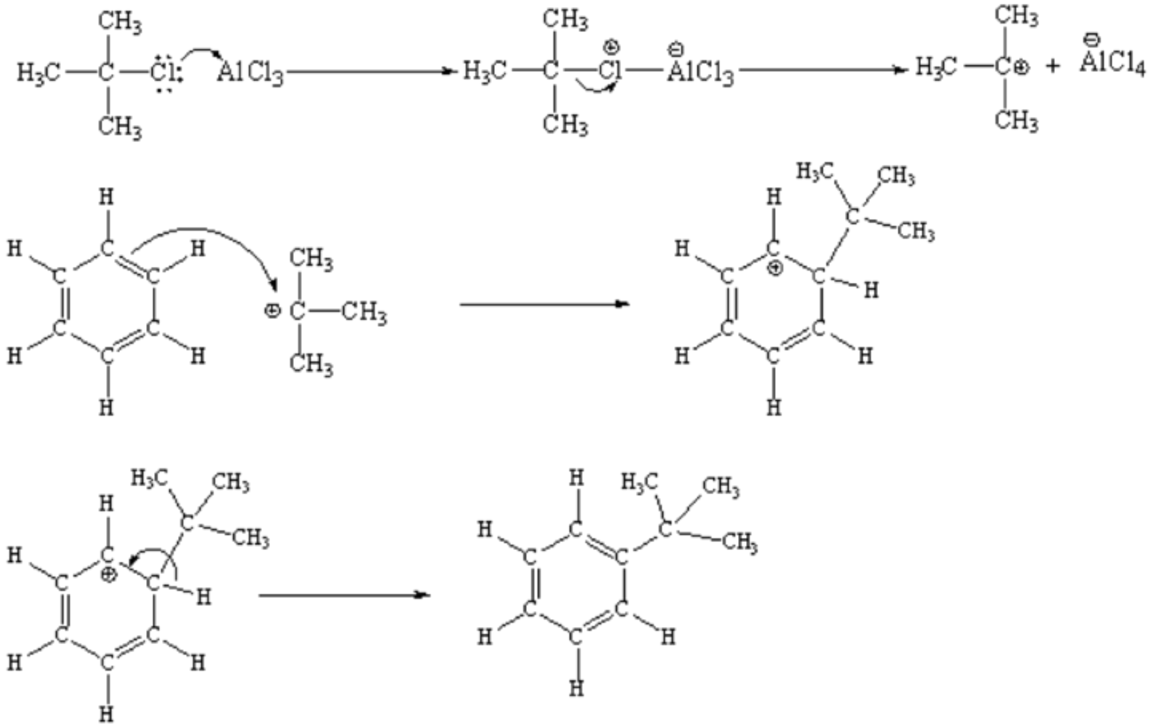
In strong acid (H_2SO_4), nitric acid is protonated to give $H_2NO_3^+$. Loss of water generates the nitronium ion that acts as an electrophile.

FRIEDEL-CRAFTS ALKYLATION



Where R = alkyl (methyl, ethyl, isopropyl, *t*-butyl, etc.)
X = halogen (Cl, Br, and I)
M = metal Fe, B, or Al

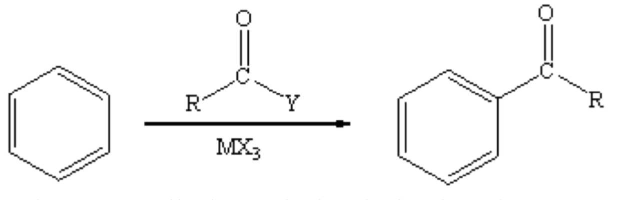
Mechanism:

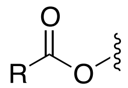


$\overset{\oplus}{H} + \overset{\ominus}{AlCl_4} \longrightarrow HCl + AlCl_3$

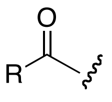
In the Friedel-Crafts alkylation, R^+ is the electrophile

FRIEDEL-CRAFTS ACYLATION

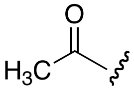


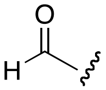


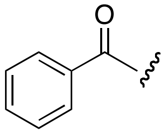
Where R = alkyl (methyl, ethyl, *t*-butyl, etc.)
Y = halogen (Cl, Br, and I), or RC(O)OR (an anhydride functionality)
M = metal Fe, B, or Al
X = halogen

An acyl group = 

The actual shape of the acyl group is linear $R-\overset{\oplus}{C}\equiv O$ (the acylium ion)

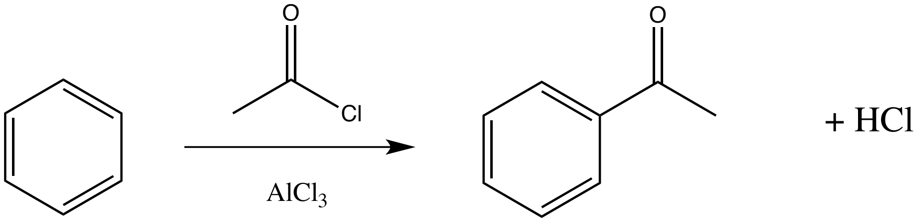
When R=CH_3 the group is called acetyl 

When R=H, the group is called formyl 

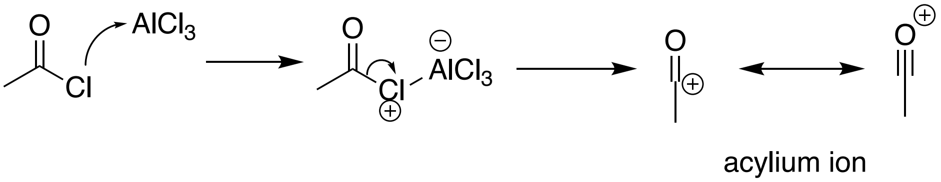
When R=benzene ring, the group is called benzoyl 

In the Friedel-Crafts acylation reaction, RCO^+ is the electrophile.

Example and mechanism:



acetophenone



This reaction proceeds through a resonance stabilized acylium ion