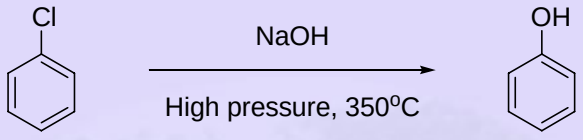
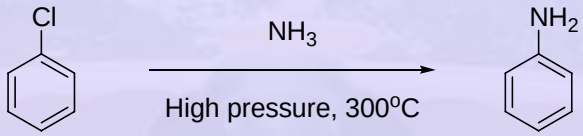
Nucleophilic Aromatic Substitution

In our discussion so far, we focused on elctrophilic aromatic substitution. Even though the electophilic substitution is by far the most common mode of substitution in aromatic systems, the nucleophilic substitution is indeed possible and is a useful tool in certain cases. The early industrial syntheses of phenols and anilines in fact were based on the nucleophilic aromatic substitution reaction.



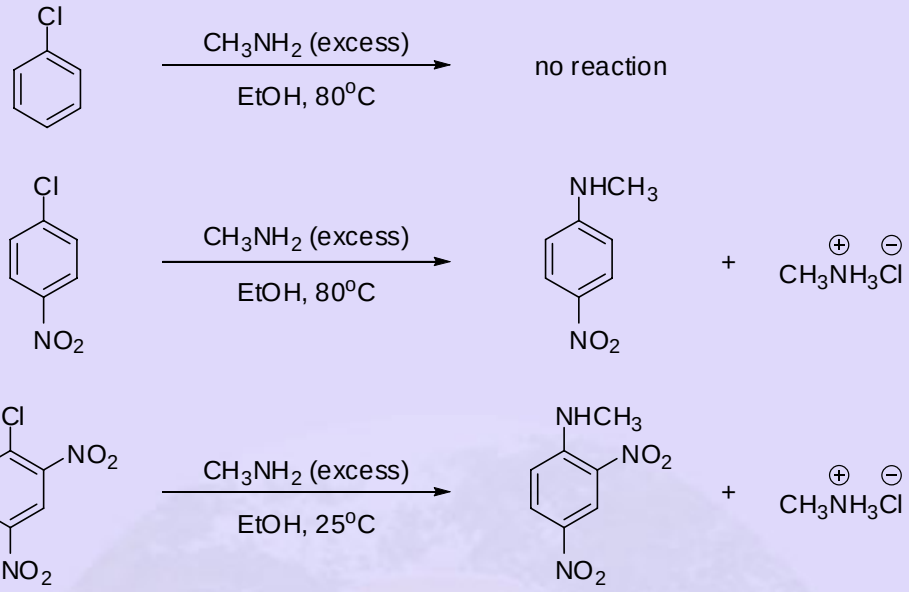


If we try and draw parallels between nucleophilic substitution in aliphatic systems and that in aromatic systems, we would quickly realize that the typical S_N1 and S_N2 mechanisms are not feasible in aromatic systems. One of the major reasons is that the p-electrons in aromatic systems are in conjugation. More over, back side attack (as in S_N2) and inversion is precluded by the geometry of the ring. On the other hand, S_N1 type of substitution would require formation of the phenyl cation which is less stable than a primary carbocation. Obviously, the reaction has to proceed with a totally different type of mechanisms. There are two mechanisms which are possible and they are:

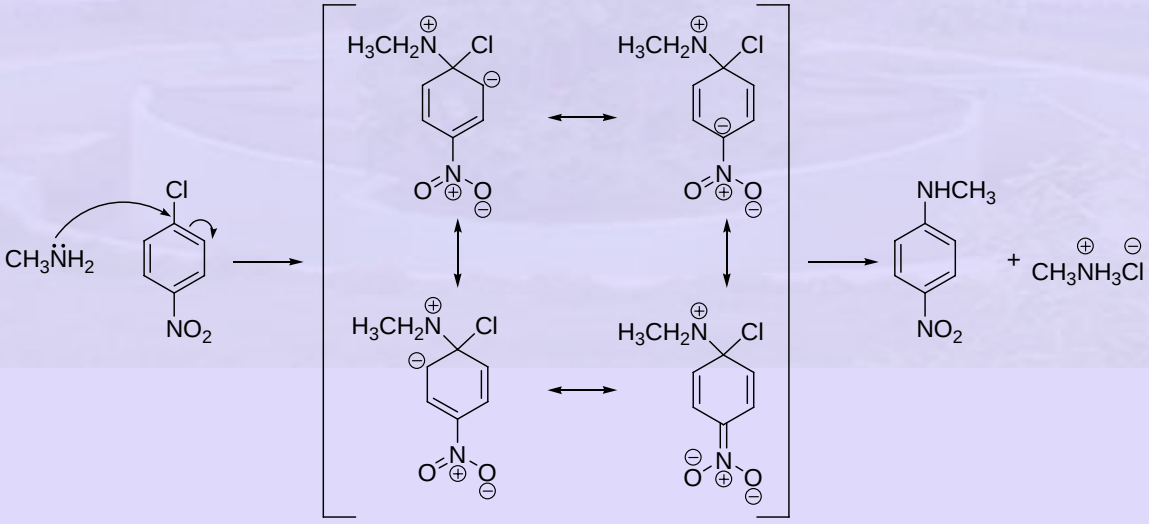
a) Addition-Elimination Mechanism
b) Elimination-Addition Mechanism

Addition-Elimination Mechanism:

Consider the reaction of an amine with chlorobenzene or nitro-substituted chlorobenzenes. Here, the reaction takes place with substituted chlorobenzene readily whereas under similar conditions, the chlorobenzene itself is unreactive. The nitro group clearly influences the rate of the reaction. In a similar manner, it was observed that the electron withdrawing groups such as –CN, -CO- etc. facilitated the substitution reaction.

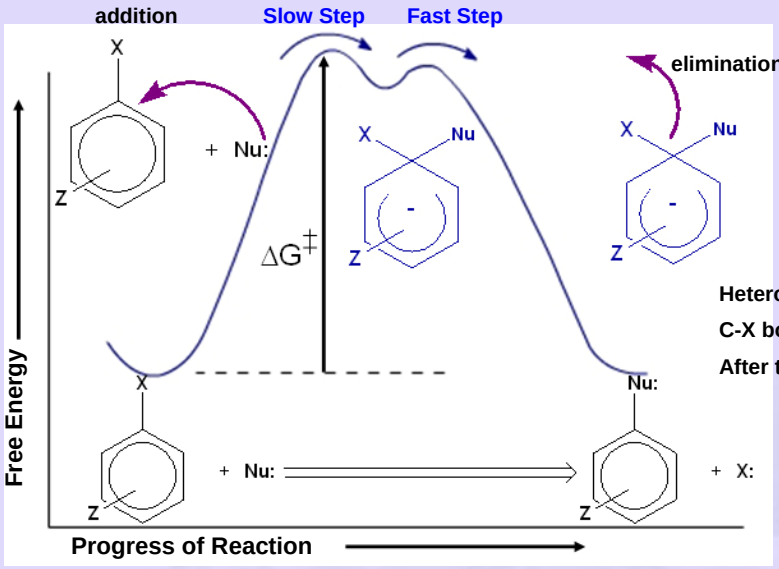


These observations suggest that electron withdrawing groups lower the energy of activation by stabilizing the negative charge developed as the nucleophile adds to aromatic ring. One can write a series of resonating structures for the cyclohexadienyl anion generated after the addition of the nucleophile to the aromatic system. Finally, loss of chlorine completes the substitution process. This mechanism is parallel to the one which we studied for the electrophilic aromatic substitution reaction.



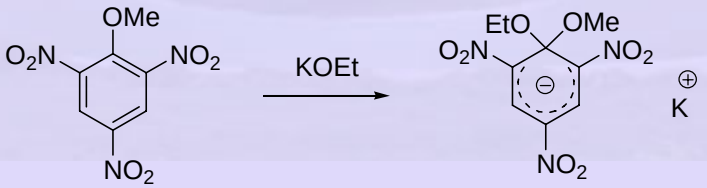
Kinetic studies demonstrate that these reactions are second-order – first order in nucleophile and first-order in the aromatic substrate. The formation of the addition intermediate is the rate determining step (r.d.s.) in these reactions.

Energy profile for S_NAr



A further proof for this argument comes from the fact that the order of reactivity for halogens is F > Cl > Br > I (and not the reverse of this i.e. I > Br > Cl > F based on their leaving group ability). This order clearly suggests that stronger bond dipoles associated with the more electronegative atom favor the addition step thus lowering the energy of activation of the nucleophilic addition step (which is r.d.s.).

The most convincing evidence that nucleophilic addition is a reasonable initial step was provided by the isolation of a stable adduct from potassium ethoxide and the methyl ether of 2,4,6-trinitrophenol (picric acid) which is called as Meisenheimer complex.



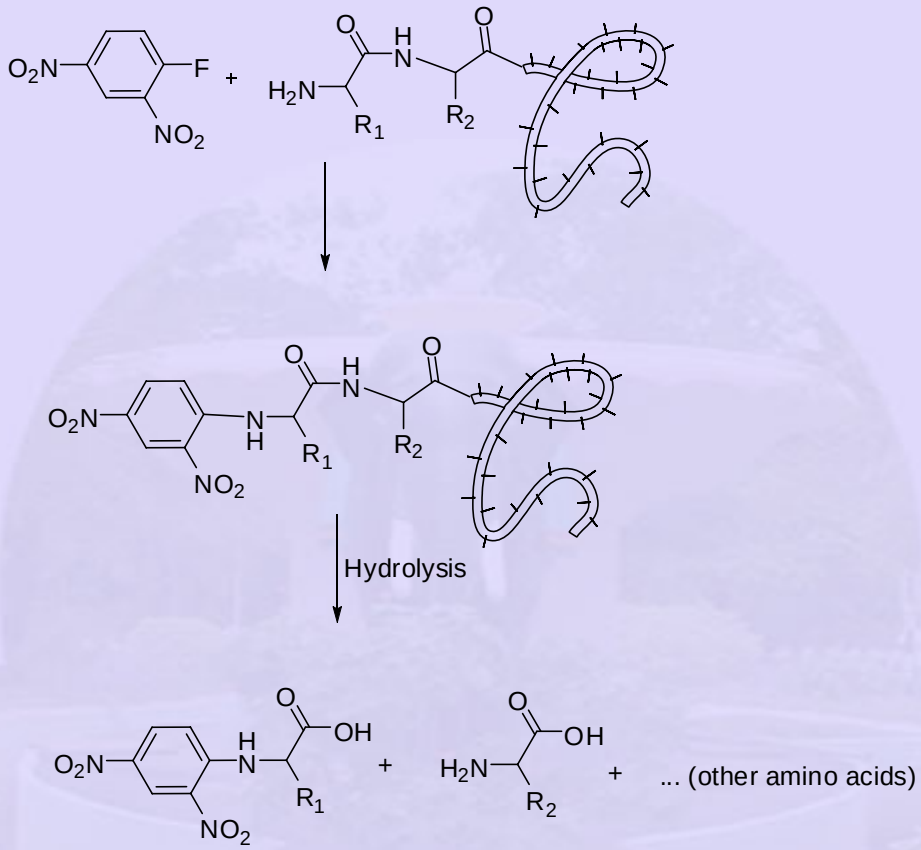
1-Methoxy-2,4,6-trinitrobenzene (Methyl picrate)

Meisenheimer complex

Sanger's Method of N-terminal Amino acid determination in proteins:

One of the most important applications of the nucleophilic aromatic susbstitution could be seen in Sanger's method for determining the primary structure of protein – particularly determination of the N-terminal amino acid in proteins. In Sanger's protocol, the 2,4-

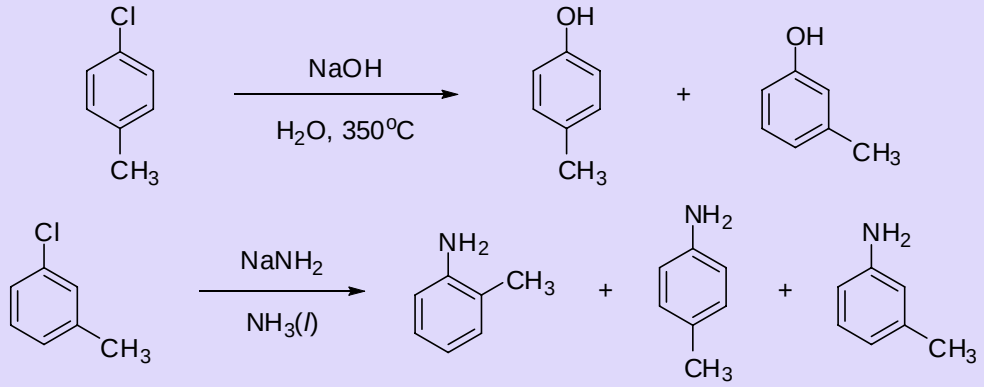
dinitrofluorobenzene is treated with the protein of interest under mild alkaline conditions (this doesn't cause cleavage of peptide bonds). The 2,4-dinitrofluorobenzene – protein adduct is then subjected to acid hydrolysis which leads to the cleavage of peptide bonds, leaving the N-terminal residue in the form of its 2,4-dinitrofluorobenzene – derivative. This derivative can be then be identified by chromatographic methods.



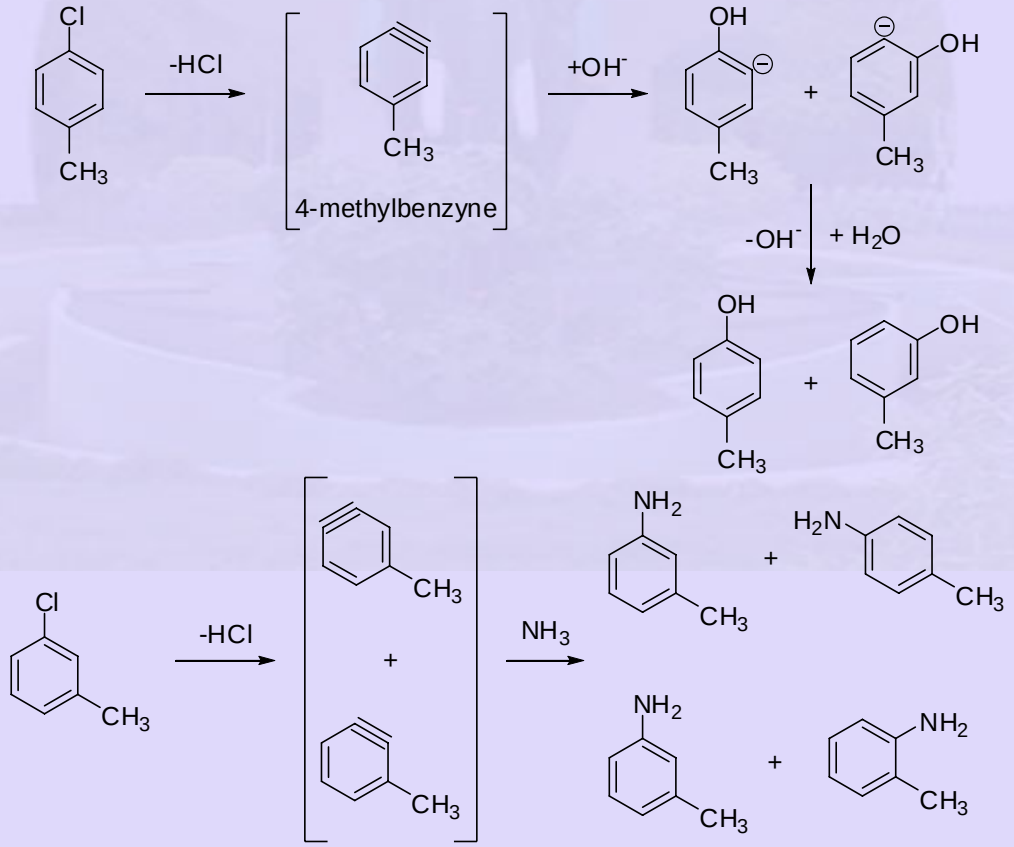
This method was introduced in 1945 and used in the structural elucidation of insulin, reported in 1955. Sanger was awarded Nobel prize for chemistry in 1958 for those contributions.

Elimination-Addition Mechanism – Benzyne:

As we have seen earlier, substituted halobenzenes on treatment with strong bases under harsh conditions lead to products formed by nuclephilic aromatic substitution reaction. But products could spring some surprises i.e. position of substitution does not necessarily correspond to the carbon atom from which the leaving group departs. In other words, in cases, we see formation of regioisomeric products.

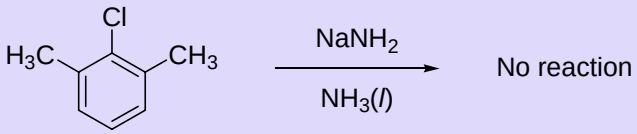


These reactions cannot be adequately explained by addition-elimination mechanism. After several studies, it was proposed that these reactions involve initial elimination of HX by the strong base. The intermediate thus formed contains a triple bond within the benzene and is called **benzyne**. This is a very unstable intermediate and readil undergoes addition of nucleophile (base) in a second step. This addition can take place at either end f the triple bond and after subsequent protonation, leads to product mixtures observed

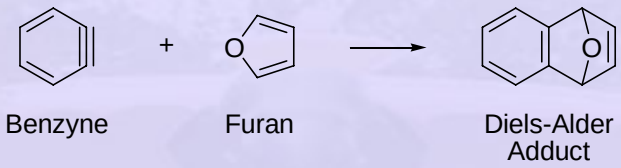


Even though, the formation of benzyne seems quite surprising, there is strong evidence for its formation apart from the product distribution that we have seen above. Unlike addition-elimination, the order of halogen reactivity in these reactions is I > Br > Cl > F.

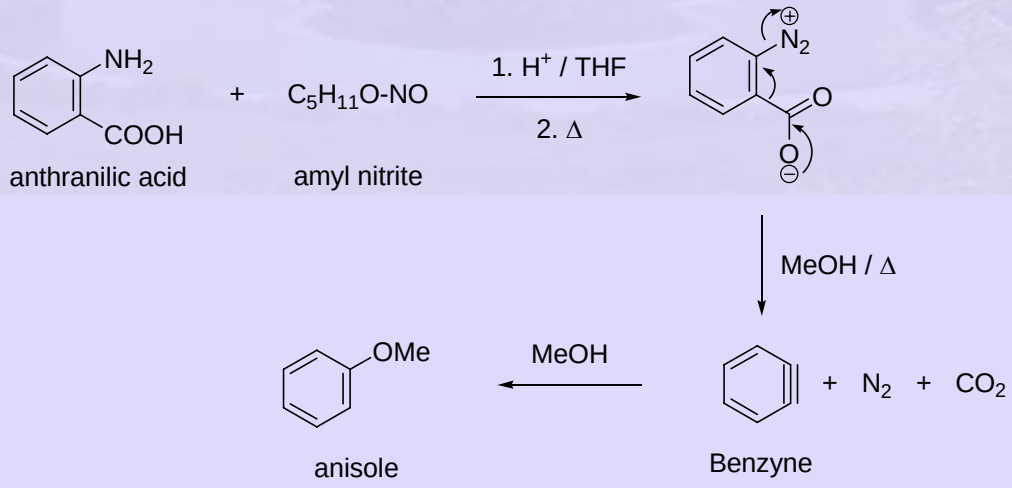
This is in line with what we would expect if elimination was to be the rate controlling step. Another evidence for this mechanism is reaction of 2,6-dimethylchlorobenzene with sodium amide in liquid ammonia. No substitution is observed in this reaction – obviously because there are no hydrogen atoms beta to the chlorine for the initial elimination step.



Further support was obtained by trapping the benzyne intermediate in a Diels-Alder reaction. (For a detailed discussion of Diels-Alder reaction see notes on Pericyclic reactions)



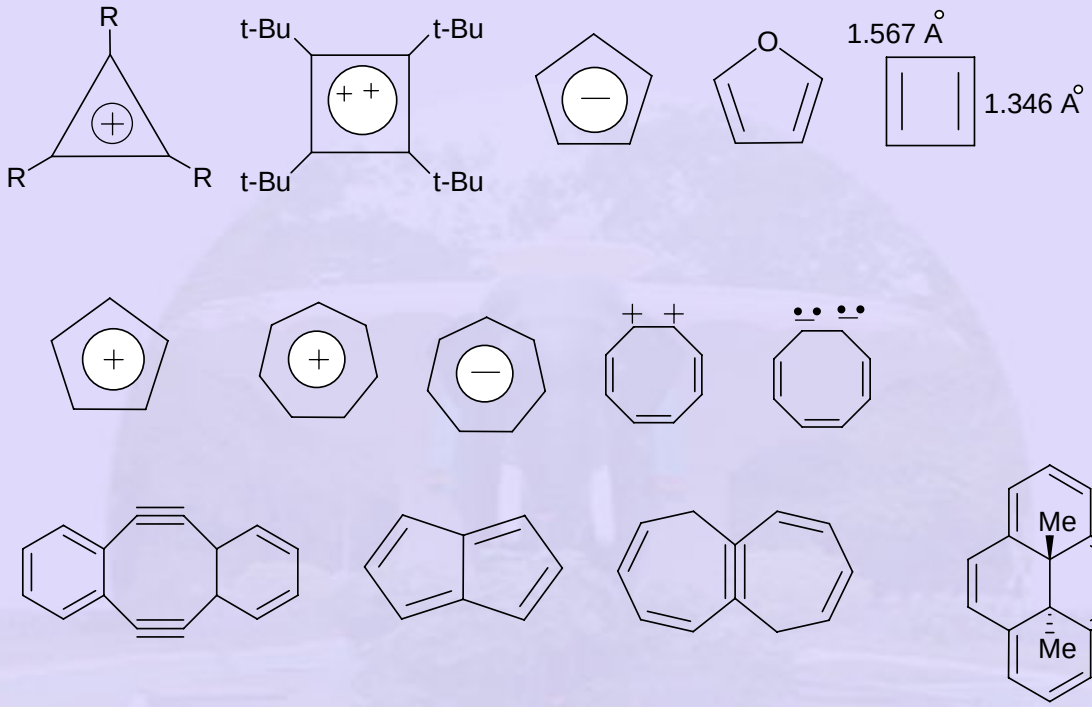
The reaction conditions that we looked at so far involved use of strong bases which could also act as nucleophiles and add to benzyne forming substitution products. One can generated benzynes without having to resort to strong bases. This allows us to use non-basic nucleophile to be added to the intermediate benzyne. E.g. the thermal decomposition of the diazonium salt derived from 2-aminobenzoic acid (anthranilic acid) leads to the formation of benzyne which undergoes addition of methanol to form anisole. In this reaction pentyl nitrite (amyl nitrite) is used to prepare the diazonium slat.



AROMATICITY AND AROMATIC SUBSTITUTION REACTIONS

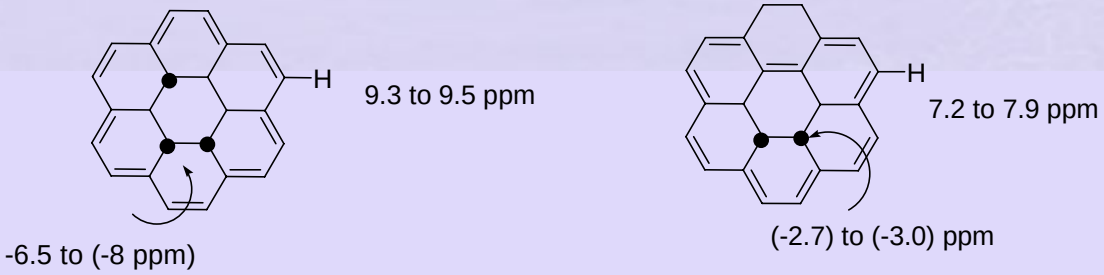
Assignment 1

1. State whether the following are aromatic/ non aromatic/ anti aromatic/ in nature. Count the number of electron in each case. You can assume that the molecules are Plannar?



The dianion of the compound **11** to **14**.

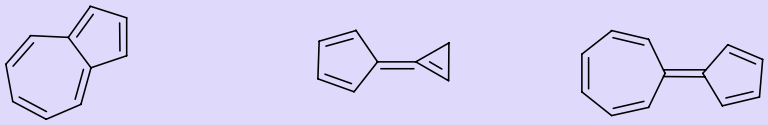
2. Explain the chemical shifts given in the following two isomeric structures based on ring current effect. Based on chemical shift which one is more aromatic ? Then thick dot on the structure indicate that the hydrogen is above the plane of the ring.



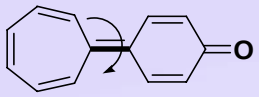
3.Explain the following observations.
(a) Compound A is a non-aromatic whereas compound B shows aromatic character

A **B**

(b) The following hydrocarbons shows unusually high dipole moment



(C) barrier for the rotation of the middle double bond(in thick line) is unusually very low (only about 14 k/Cal



(d) NMR spectra of the following indicates that there is a ring current effect (diamagnetic anisotropy)

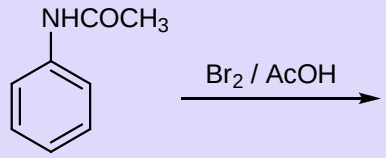
AROMATICITY AND AROMATIC SUBSTITUTION REACTIONS

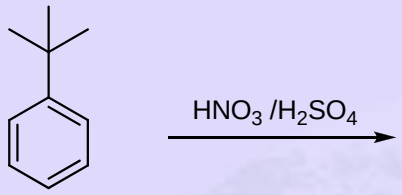
Assignment 2

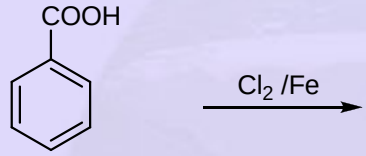
1. Draw an energy profile diagram for a typical electrophilic substitution of benzene and its deuterated derivative. From the diagram explain why is kinetic isotope effect not observed for this reaction. Is your explanation applicable to aromatic sulfonation reaction which is a reversible process?

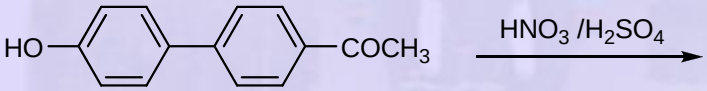
2. The dipole moment of chlorobenzene is 1.6D and it is directed towards chlorine atom. Although nitrogen and oxygen atoms are more electronegative than carbon atom, the dipole moment in aniline and phenol are directed towards the aromatic ring. Explain these experimental observations.

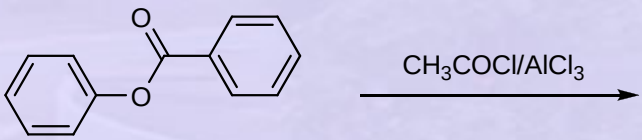
3. Write the structure of the products (indicate major/minor products) formed in the following reactions.

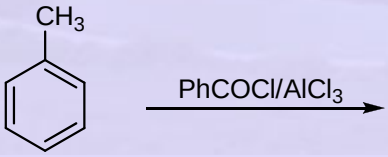
a) 

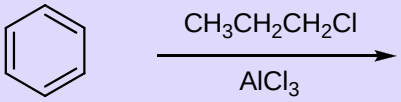
b) 

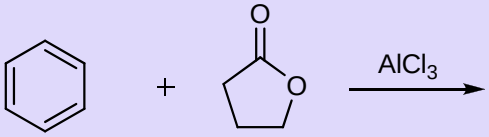
c) 

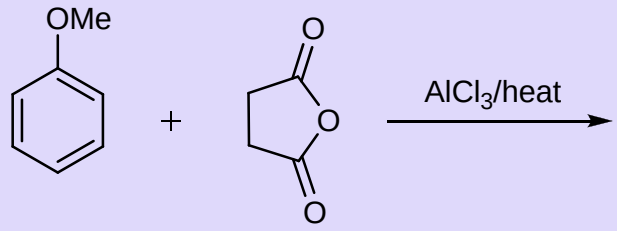
d) 

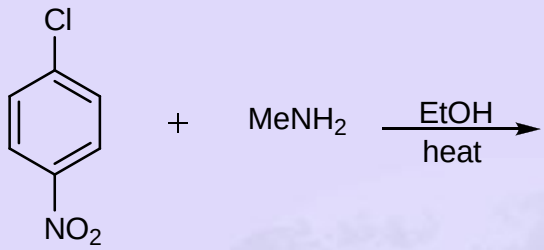
e) 

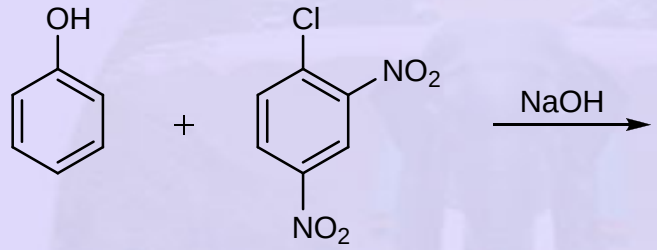
f) 

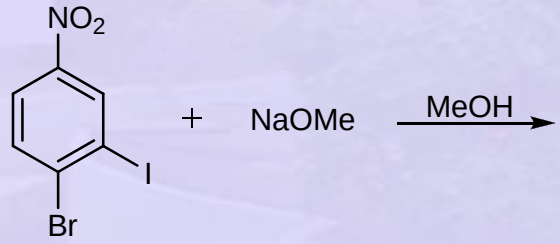
g) 

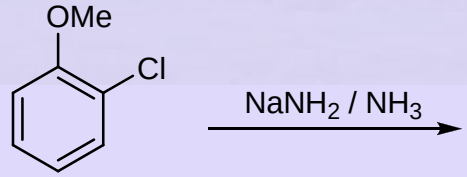
h) 

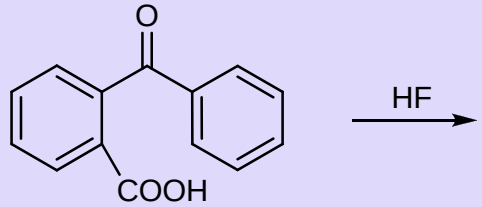
i) 
OMe
O
O
O
AlCl3/heat

j) 
Cl
NO2
MeNH2
EtOH
heat

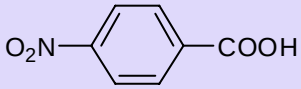
k) 
OH
Cl
NO2
NO2
NaOH

l) 
NO2
I
Br
NaOMe
MeOH

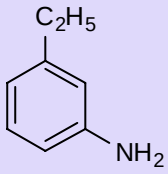
m) 
OMe
Cl
NaNH2 / NH3

n) 
O
COOH
HF

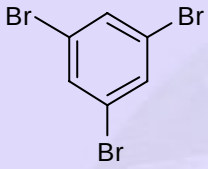
4. Suggest a synthetic sequence for each of the following transformations:

(a) 

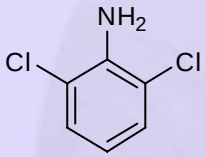
from toluene

(b) 

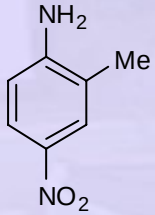
from acetophenone

(c) 

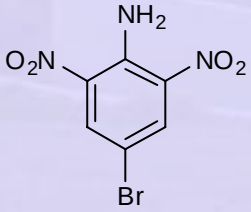
from benzene

(d) 

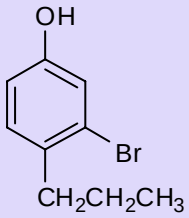
from benzene

(e) 

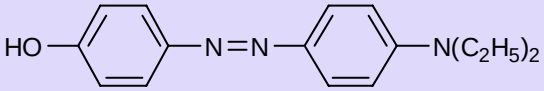
from nitrobenzene

(f) 

from aniline

(g) 

from benzene

(i) 

from aniline