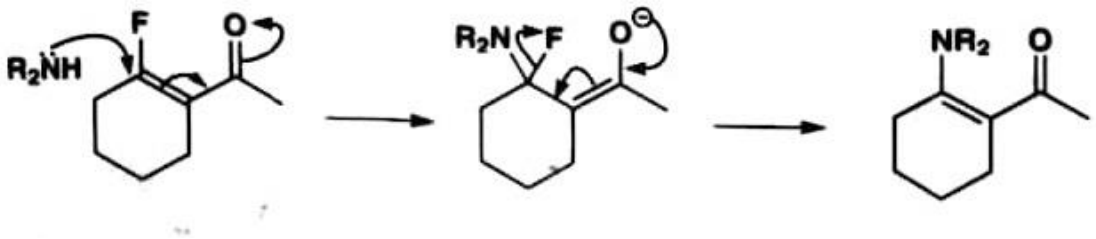
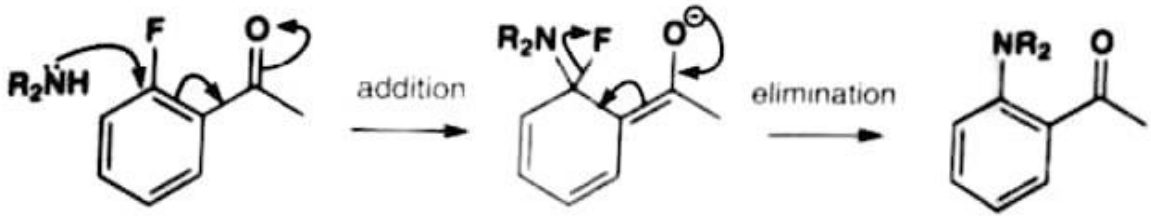
The addition-elimination mechanism

Imagine a cyclic B-fluoro-enone reacting with a secondary amine in a conjugate substitution reaction. The normal addition to form the enolate followed by return of the negative charge to expel the fluoride ion gives the product.

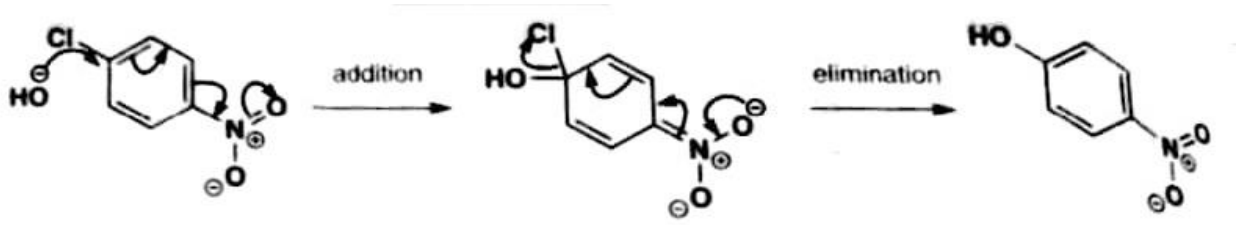


Now imagine just the same reaction with two extra double bonds in the ring. These play no part in our mechanism; they just make what was an aliphatic ring into an aromatic one. Conjugate substitution has become nucleophilic aromatic substitution.



The mechanism involves addition of the nucleophile followed by elimination of the leaving

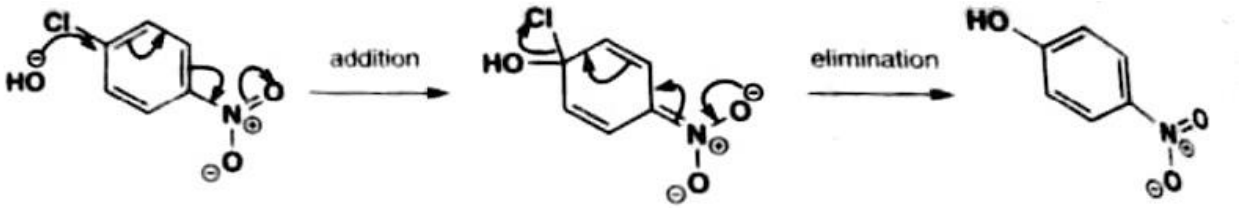
group-the addition-elimination mechanism.



Everything is different about this example-the nucleophile (HO'), the leaving group (Chats the anion-stabilizing group (NO2), and its position (para) -but the reaction still works. The nucleophile is a good one, the negative charge can be pushed through on to the oxygen atom(s) of the nitro group, and chloride is a better leaving group than OH.

A typical nucleophilic aromatic substitution has:

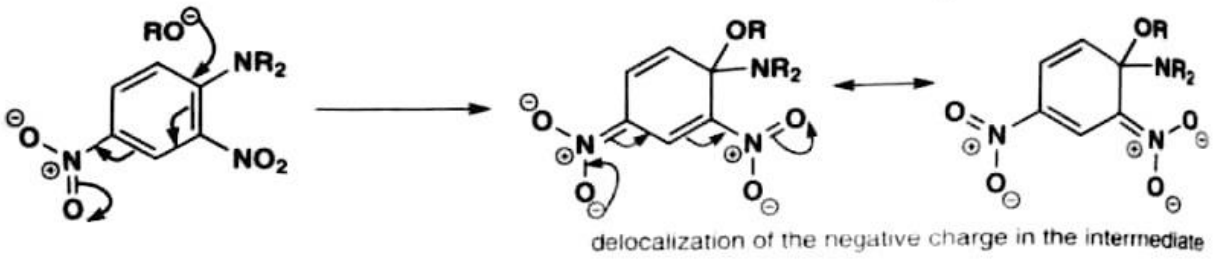
- **an oxygen, nitrogen, or cyanide nucleophile**
- **a halide for a leaving group**
- **a carbonyl, nitro, or cyanide group ortho and/or para to the leaving group**.



Everything is different about this example-the nucleophile (HO), the leaving group (C1 the anion-stabilizing group (NO_2), and its position (para) -but the reaction still works. The nucleophile is a good one, the negative charge can be pushed through on to the oxygen atom(s) of the nitro group, and chloride is a better leaving group than OH.

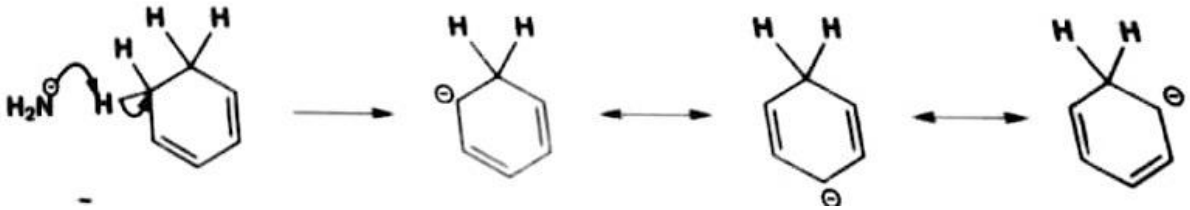
The intermediate in the addition elimination mechanism

What evidence is there for intermediates like the ones we have been using in this section When reactions like this last example are carried out, a purple colour often appears the reaction mixture and then fades away. In some cases the colour is persisten thought to be due to the intermediate. Here is an example with RO attacking a nitrated aniline. This intermediate is persistent because neither potential leaving group (NR, R2 OR) is very good.



delocalization of the negative charge in the intermediate

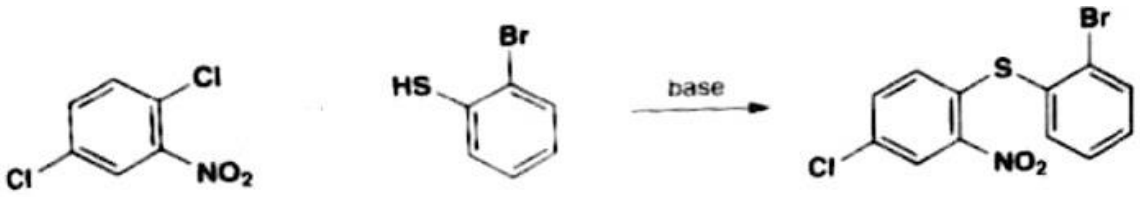
What is the nature of this intermediate? Well, in essence it is an anion delocalized over five sp? hybridized carbons of a six-membered ring (the sixth, the point at which the nucleophile attacked, is sp' hybridized). It's possible to make a simple homologue of such a species by deprotonating yclohexadiene. Delocalizing the anion generates the three structures below.



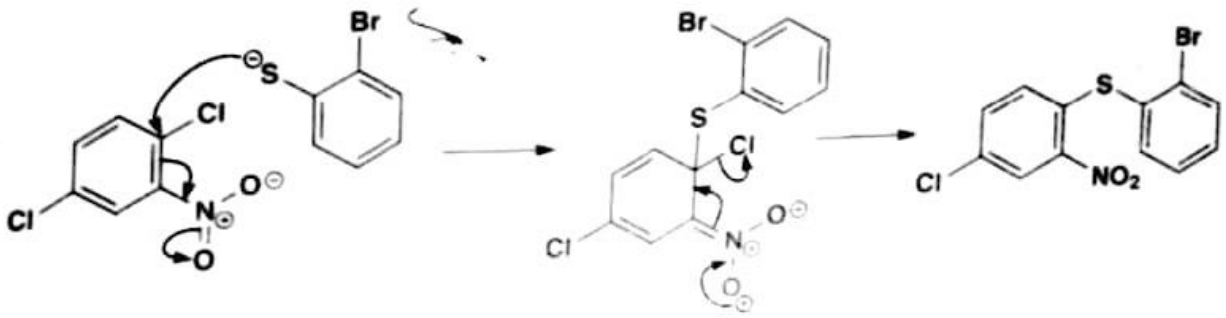
These results are very striking. The shifts of the meta cartons in both ions are very slightly different from those of benzene itself (about 130 ppm). But the ortho and para carbons in the anion have gone upfield to much sinaller shifts, indicating greater electron density. By contrast, ortho and para carbons in the cation have gone downfield to much larger shifts.

The differences are very great- about 1000 ppm between the cation and the anion! It is very clear from these spectra that the ionic charge is delocalized almost exclusively to the ortho and para carbons in both cases. The alternative structures in the margin show this delocalization. on.

This means that stabilizing groups, such as nitro or carbonyl in the case of the anion, canmonly have an effect if they are on carbons ortho or p-ra to the position being attacked by the nucleophile. A good illustration of this is the selective displacement of one chlorine atom out of these two. The chlorine ortho to the nitro group is lost; the one meta is retained.

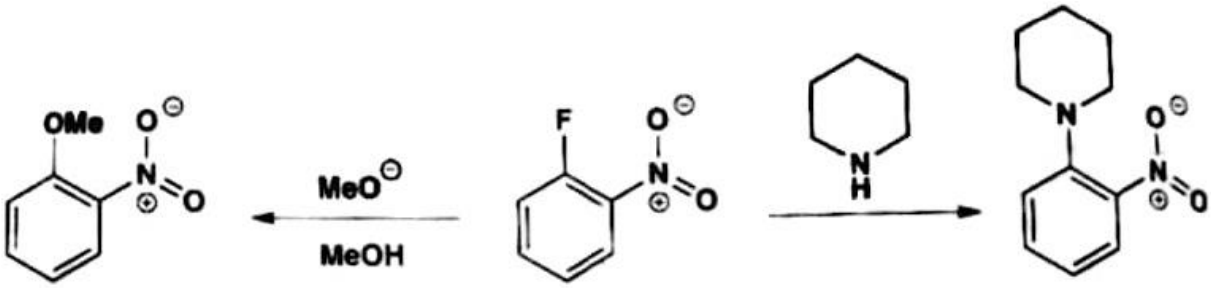


The mechanism works well if the nucleophile (the anion derived from the thiol) attacks the carbon bearing the chlorine ortho to the nitro group as the negative charge can then be pushed into the nitro group. Satisfy yourself that you cannot do this if you attack the other chlorine position. This is a very practical reaction and is used in the manufacture of a tranquillizing drug.

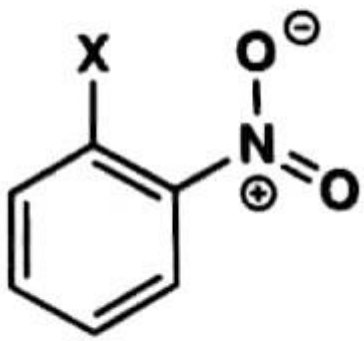


The leaving group and the mechanism

In the first nucleophilic aromatic substitution that we showed you, we used fluoride ion a leaving group. Fluoride works very well in these reactions and even such a simple com. pound as 2-halo-l-nitrophenyl fluoride reacts efficiently with a variety of nucleophiles, as in these examples.



reactivity of 2-halo-1-nitrobenzenes in nucleophilic aromatic substitution



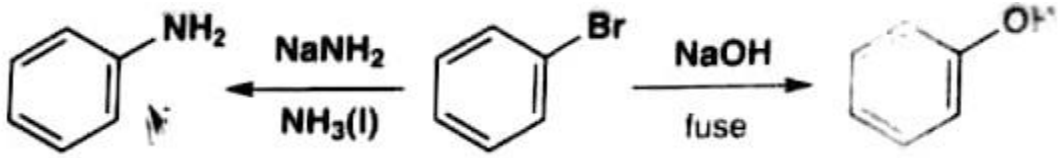
F >> Cl ~ Br >> I

The benzyne mechanism

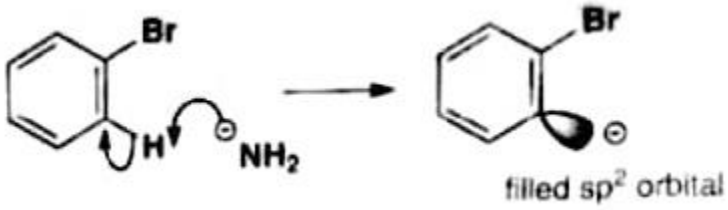
We now need to introduce you to one last mechanism for aromatic nucleophilic substitution and you may well feel that this is the weirdest mechanism you have yet seen with the most unlikely intermediate ver! For our part, we hope to convince you that this mechanism is not only possible but also useful.

Earlier in this chapter we said that the displacement by nucleophiles of bromide from bromobenzene does not occur. In fact substitution reactions of bromobenzene can occur but only under the most vigorous conditions, such as when bromobenzene and NaOH are melted together (fused) at very high temperature. A similar reaction

with the very powerful reagent NaNH, (which supplies NH, ion) also happens, at a rather lower temperature.

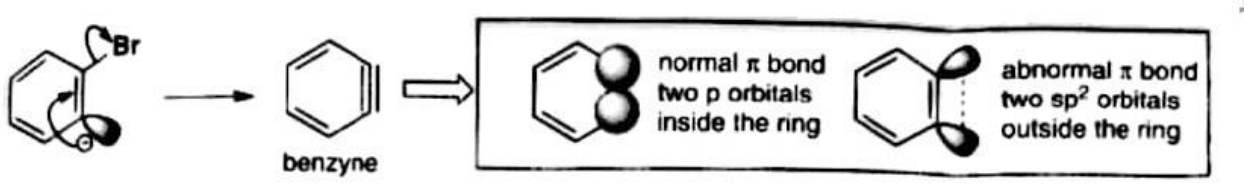


These reactions were known for a long time before anyone saw what was happening. They do not happen by an S, 2 mechanism, as we explained earlier, and they can't happen by the addition-elimination mechanism because there is nothing to stabilize the negative charge in the intermediate. The first clue to the true mechanism is that all the nucleophiles that react in this way are very basic, They start the reaction off by removing a proton ortho to the leaving group.

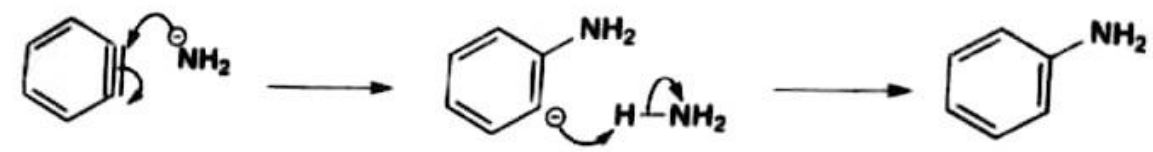


The carbanion is in an sp2 orbital in the plane of the ring. Indeed, this intermediate is very similar to the aryl cation intermediate in the Syl mechanism from diazonium salts. That had no electrons in the sp' orbital; the carbanion has two. should this proton be removed rather than any other? The bromine atom is electronegative and the C Br bond is in the plane of the sp' orbital and removes electrons from it. The stablization is nonetheless weak and only exceptionally strong bases will do this reaction.

The next step is the loss of bromide ion in an elimination reaction. This is the step that is dif- ficult to believe as the intermediate we are proposing looks impossible. The orbitals are bad for the elimination too-it is a sun- rather than an anti-periplanar elimination. But it happens.

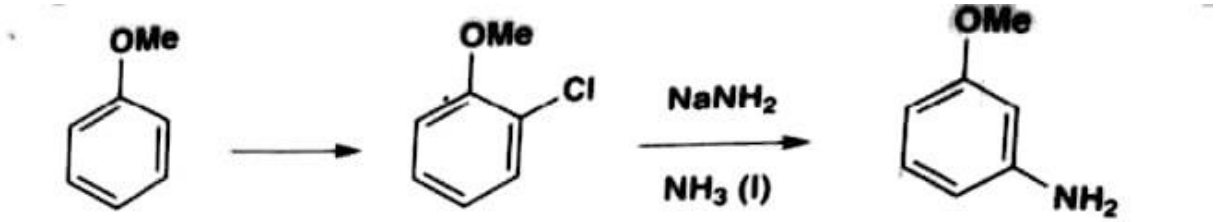


The intermediate is called benzyne as it is an alkyne with a triple bond in a benzene ring. But what does this triple bond mean? It certainly isn't a normal alkyne as these are linear. In fact one bond is normal-it is just part of the aromatic system. One n bond -the newone-is abnormal and is formed by overlap of two sp- orbitals outside the ring. This external bond is very weak and benzyne is a very unstable intermediate. Indeed, when the structure was proposed few chemists believed it and some pretty solid evidence was needed before they did We shall come to that shortly, but let us first finish the mechanism. Unlike normal alkynes benzyne is electrophilic as the weak third bond can be attacked by

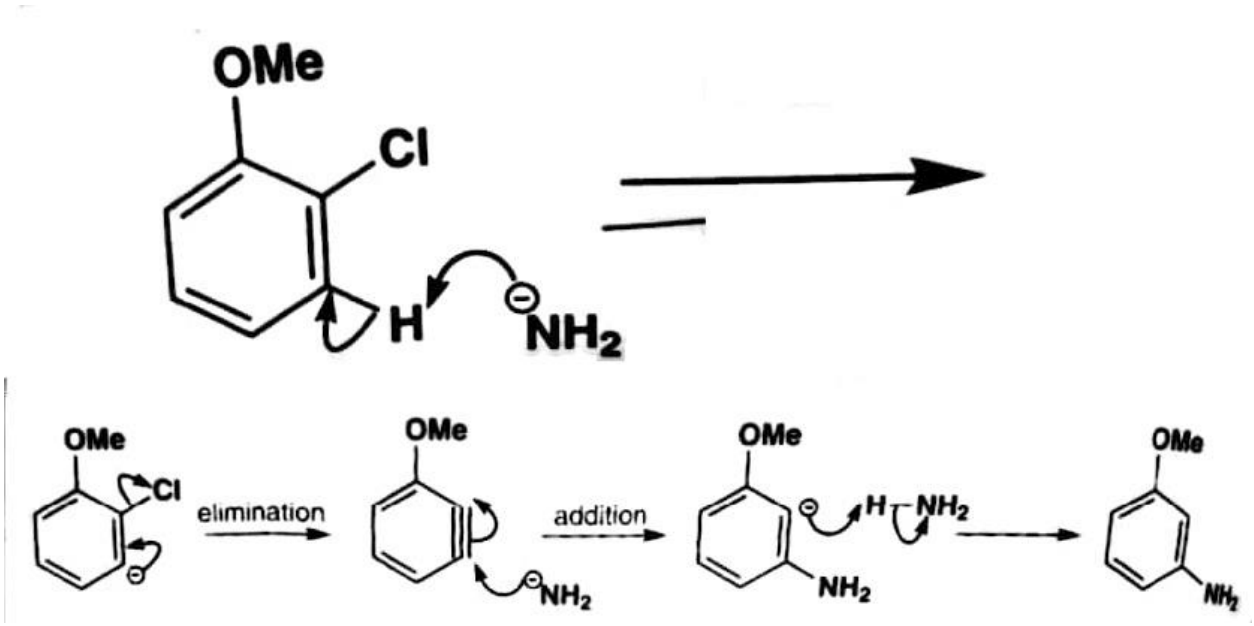


The whole mechanism from bromobenzene to aniline involves an elimination to give benzyne followed by an addition of the nucleophile to the triple bond of benzyne. In many ways, this mechanism is the reverse of the normal addition-elimination mechanism for nucleophilic aromatic substitution and it is sometimes called the elimination-addition mechanism.

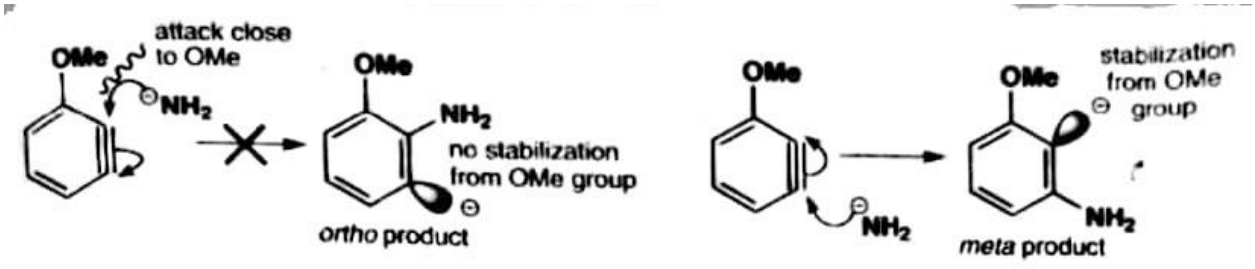
Any nucleophile basic enough to remove the ortho proton can carry out this reaction. Known examples include oxyanions, amide anions (R,N"), and carbanions. The rather basic alkoxide t-butoxide will do the reaction on bromoberzene if the potassium salt is used in the dipolar aprotic solvent DMSO to maximize reactivity.



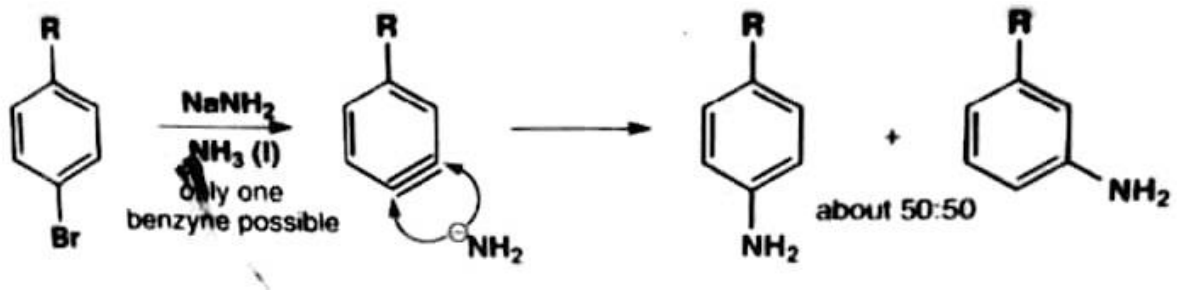
The new amino group finds itself in the meta position even though the chlorine was at the the ortho position. It would be very difficult to explain this other than by the benzyne mechan. ism. Using the same elimination-addition sequence, this must be the mechanism:



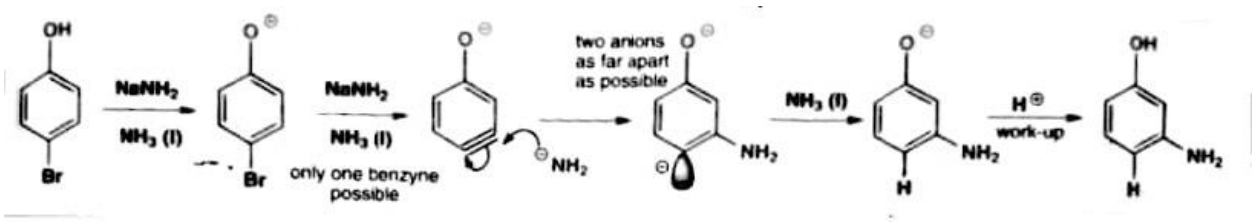
That shows how the meta product might be formed, but why should it be formed? Attack could also occur at the ortho position, so why is there no ortho product? There are two reasons: electronic and steric. Electronically, the anion next to the electronegative oxygen atom is preferred because oxygen is inductively edectron-withdrawing. The same factor facilitates deprotonation next to Cl in the formation of the benzyne. Sterically, it is better for the amide anion to attack away from the OMe group rather than come in alongside it. attack on a benzyne has to occur in the plane of the benzene ring because that is where the orbitals are. This reaction is therefore very sensitive to steric hindrance as the nucleophie must attack in tne plane of the substituent as well



This is a useful way to make amino ethers with a meta relationship as both groups are ortho para-directing and so the meta compounds cannot be made by electrophilic substitution para-Disubstituted halides can again give only one benzyne and most of them give mixtures of products. A simple alkyl substituent is too far from the triple bond to have much steric effect.



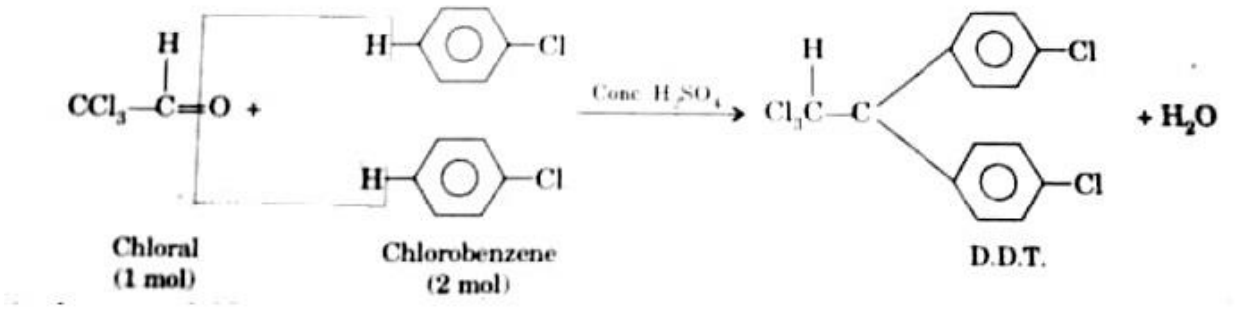
If the substituent is an electron-repelling anion, then the meta product is formed exclusively because this puts the product anion as far as possible from the anion already there. This again is useful as it creates a meta relationship between two ortho, para-directing groups,



D. D. T.

p, p'-Dichlorodiphenyltrichloroethane

It in synthesised by heating a mixture of chloral (I mol) will hlorobenzene (2 mol) in the presence of concentrated

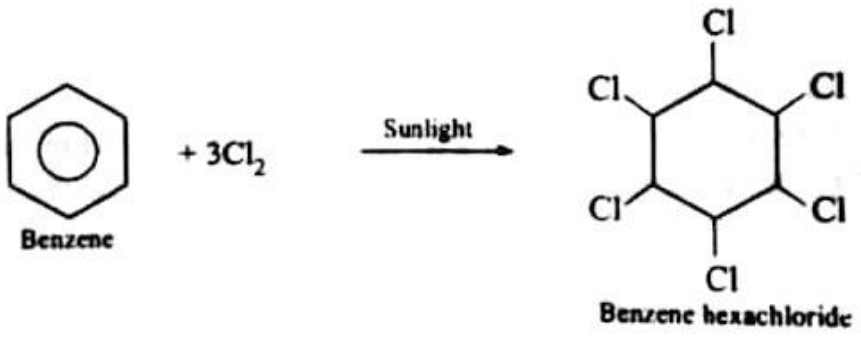


D. D. T. is almost insoluble in water but it is moderately soluble in polar solvents. D. D. T. is a powerful insecticide. It is widely used as an insecticide for killing mosquitoes and other inяects. d. D. T.

Side Effects of D. D. T. D. D. T. is one of the most powerful and effective insecticides. The use of D. D. T. increased after world War II because ofits effectiveness against the mosquito that spreads malaria and lice that carry typhus. However, it was realised that exessive use of D. D. T. leads to many problems. Many species ofineects developed resistance to D. D. T. and also D. D. T. was formed to have high toxicity towards fish. The chemical stability of D. D. T. and its fat solubility further increased the problem. D. D. T. is not biodegradable. Its residues accumulate in environment and ita long term effects could be highly dangerous. D D. T. is not metabolised very repidly by animals rather it gets deposited and stored in fatty tissues. This raised alarming dangers. Therefore, its use has been banned in U. S. A. in J973. However, inspite of its dangerous side effects, DDT is still being widely used in India and other Asian countries due to non- availability of other cheaper insecticides.

BHC (benzene hexachloride).

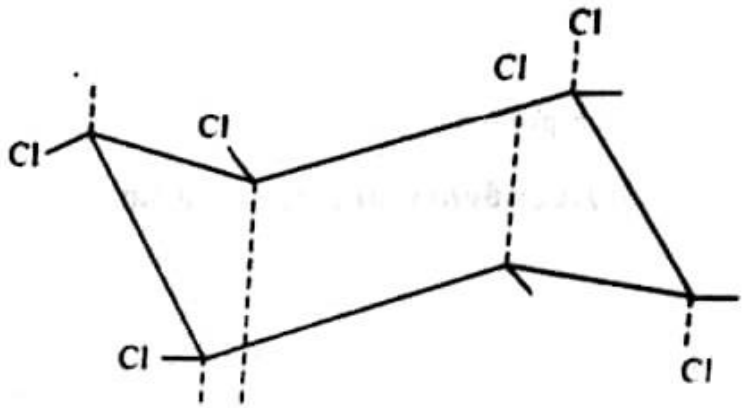
Preparation. It is prepared by the action of chlorine on benzene. Action takes place in the presence of sunlight by free-radical mechanism. A mixture of products containing isomers of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane (or benzene hexachloride) is obtained. This mixture is called BHC or 666.



Benzene

Benzene hexachloride

There is one hydrogen atom linked at every corner which has not been shown. There are 9 possible stereoisomers of BHC, out of which 8 have been identified. The toxic properties of BHC are attributed to r-isomer which constitutes 10-18% of the mixture. It is known as gammaxene or lindane. It has the ollowing chair-form structure:



Structure formula of lindane

Uses. It is used as a potent insecticide.