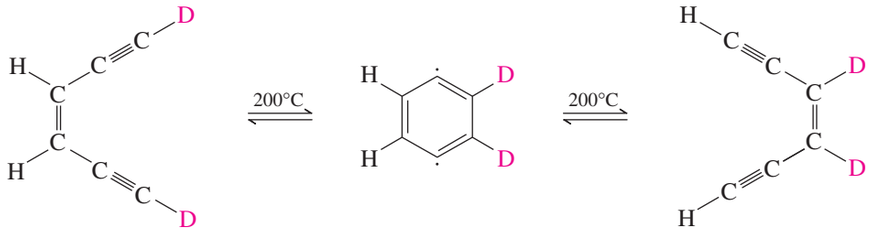
The first evidence that 1,4-dehydrobenzene could be generated as a reactive intermediate came in 1972 from studies of the thermal isomerization of the deuterium-labeled enediyne shown:

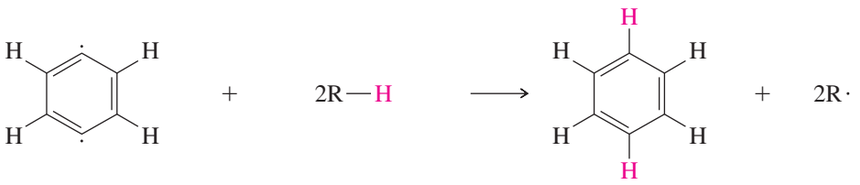


1,6-Dideuterio isomer 3,4-Dideuterio isomer

When the enediyne labeled with deuterium at each end of the chain was heated, it produced a mixture of it and the isomer having deuteriums on the double bond. Moreover, the isomer having a trans double bond did not undergo a comparable rearrangement. The most reasonable interpretation of these observations is the formation of 1,4-dehydrobenzene as a reactive intermediate.

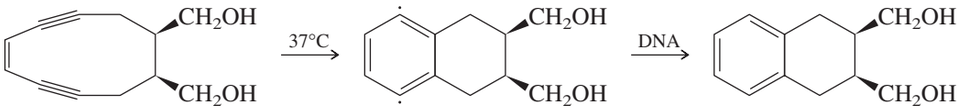
The conversion of enediynes to 1,4-dehydrobenzene is called the *Bergman cyclization* after Robert G. Bergman of the University of California at Berkeley who discovered it.

Further evidence for the formation and diradical structure of 1,4-dehydrobenzene comes from similar cyclizations carried out in a hydrocarbon solvent. Under these conditions benzene was formed, most likely by a reaction in which 1,4-dehydrobenzene abstracts hydrogen atoms from the solvent.



1,4-Dehydrobenzene Hydrocarbon solvent Benzene Alkyl radicals

Subsequent to this work, which demonstrated the formation of 1,4-dehydrobenzene in novel chemical reactions, similar intermediates were implicated in biological processes. Several potent anticancer drugs are characterized by the presence of a conjugated enediyne unit in a ten-membered ring (Section 9.1). Their mode of action is believed to involve binding of the drug to DNA followed by Bergman cyclization of the enediyne unit. This produces a 1,4-dehydrobenzene, which then abstracts hydrogen atoms from the 2-deoxyribose portion of DNA and results in DNA cleavage and cell death. This biological reactivity was modeled in a simple 10-membered cyclic enediyne, which, when incubated with DNA in water, not only underwent Bergman cyclization but also cleaved the DNA.



One wonders whether the unique mode of action of the enediyne antibiotics would have been unraveled so readily had the experiments designed to look for dehydrobenzene intermediates in purely chemical processes not been carried out.

23.11 SUMMARY

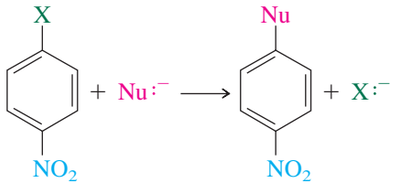
Section 23.1 Aryl halides are compounds of the type Ar—X where X = F, Cl, Br, or I. The carbon–halogen bond is stronger in ArX than in an alkyl halide (RX).

Section 23.2 Some aryl halides occur naturally, but most are the products of organic synthesis. The methods by which aryl halides are prepared were recalled in Table 23.2.

Section 23.3 Aryl halides are less polar than alkyl halides.

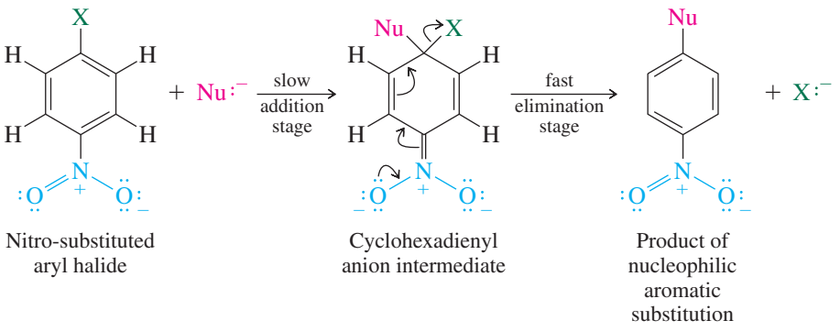
Section 23.4 Aryl halides are less reactive than alkyl halides in reactions in which C—X bond breaking is rate-determining, especially in nucleophilic substitution reactions.

Section 23.5 Nucleophilic substitution in ArX is facilitated by the presence of a strong electron-withdrawing group, such as NO_2, ortho or para to the halogen.



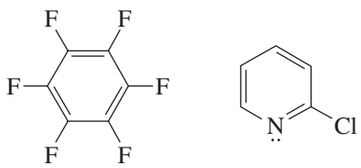
In reactions of this type, fluoride is the best leaving group of the halogens and iodide the poorest.

Section 23.6 Nucleophilic aromatic substitutions of the type just shown follow an **addition–elimination mechanism.**

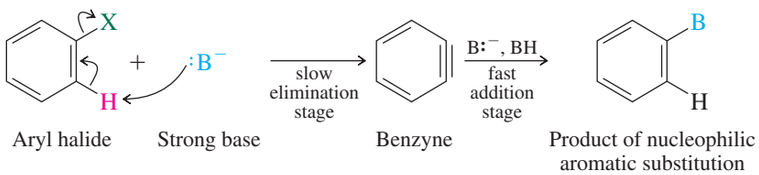


The rate-determining intermediate is a cyclohexadienyl anion and is stabilized by electron-withdrawing substituents.

Section 23.7 Other aryl halides that give stabilized anions can undergo nucleophilic aromatic substitution by the addition–elimination mechanism. Two examples are hexafluorobenzene and 2-chloropyridine.



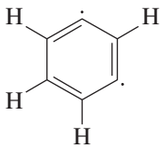
Section 23.8 Nucleophilic aromatic substitution can also occur by an **elimination–addition mechanism.** This pathway is followed when the nucleophile is an exceptionally strong base such as amide ion in the form of sodium amide ($NaNH_2$) or potassium amide (KNH_2). **Benzyne** and related **arynes** are intermediates in nucleophilic aromatic substitutions that proceed by the elimination–addition mechanism.



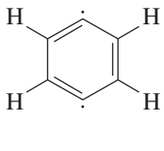
Nucleophilic aromatic substitution by the elimination–addition mechanism can lead to substitution on the same carbon that bore the leaving group or on an adjacent carbon.

Section 23.9 Benzyne is a reactive dienophile and gives Diels–Alder products when generated in the presence of dienes. In these cases it is convenient to form benzyne by dissociation of the Grignard reagent of *o*-bromofluorobenzene.

Section 23.10 Benzyne is a reactive intermediate and capable of being studied only at low temperatures. Two isomers of benzyne, 1,3-dehydrobenzene and 1,4-dehydrobenzene, are diradicals and are even less stable.



1,3-Dehydrobenzene



1,4-Dehydrobenzene

1,4-Dehydrobenzene and compounds related to it are formed from enediynes by the Bergman cyclization.

An analogous process appears responsible for the DNA cleaving properties of the antitumor enediyne antibiotics.

PROBLEMS

23.11 Write a structural formula for each of the following:

(a) *m*-Chlorotoluene
(b) 2,6-Dibromoanisole
(c) *p*-Fluorostyrene
(d) 4,4′-Diiodobiphenyl
(e) 2-Bromo-1-chloro-4-nitrobenzene
(f) 1-Chloro-1-phenylethane
(g) *p*-Bromobenzyl chloride
(h) 2-Chloronaphthalene
(i) 1,8-Dichloronaphthalene
(j) 9-Fluorophenanthrene

23.12 Identify the major organic product of each of the following reactions. If two regioisomers are formed in appreciable amounts, show them both.

(a) Chlorobenzene + acetyl chloride $\xrightarrow{AlCl_3}$
(b) Bromobenzene + magnesium $\xrightarrow{\text{diethyl ether}}$
(c) Product of part (b) + dilute hydrochloric acid $\longrightarrow$
(d) Iodobenzene + lithium $\xrightarrow{\text{diethyl ether}}$
(e) Bromobenzene + sodium amide $\xrightarrow{\text{liquid ammonia, } -33^\circ C}$
(f) *p*-Bromotoluene + sodium amide $\xrightarrow{\text{liquid ammonia, } -33^\circ C}$
(g) 1-Bromo-4-nitrobenzene + ammonia $\longrightarrow$
(h) *p*-Bromobenzyl bromide + sodium cyanide $\longrightarrow$
(i) *p*-Chlorobenzenediazonium chloride + *N*,*N*-dimethylaniline $\longrightarrow$
(j) Hexafluorobenzene + sodium hydrogen sulfide $\longrightarrow$

23.13 Potassium *tert*-butoxide reacts with halobenzenes on heating in dimethyl sulfoxide to give *tert*-butyl phenyl ether.

(a) *o*-Fluorotoluene yields *tert*-butyl *o*-methylphenyl ether almost exclusively under these conditions. By which mechanism (addition–elimination or elimination–addition) do aryl fluorides react with potassium *tert*-butoxide in dimethyl sulfoxide?