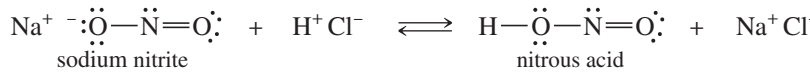
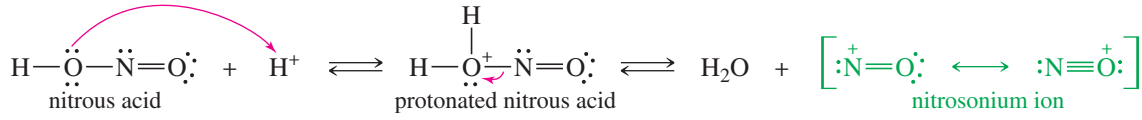
19-16 Reactions of Amines with Nitrous Acid

Reactions of amines with nitrous acid (H—O—N=O) are particularly useful for synthesis. Because nitrous acid is unstable, it is generated *in situ* (in the reaction mixture) by mixing sodium nitrite ($NaNO_2$) with cold, dilute hydrochloric acid.



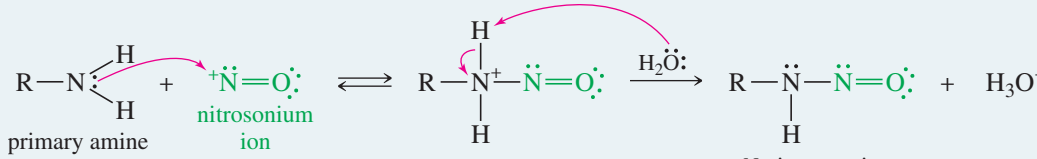
In an acidic solution, nitrous acid may protonate and lose water to give the nitrosonium ion, $^{+}N{=}O$. The nitrosonium ion appears to be the reactive intermediate in most reactions of amines with nitrous acid.



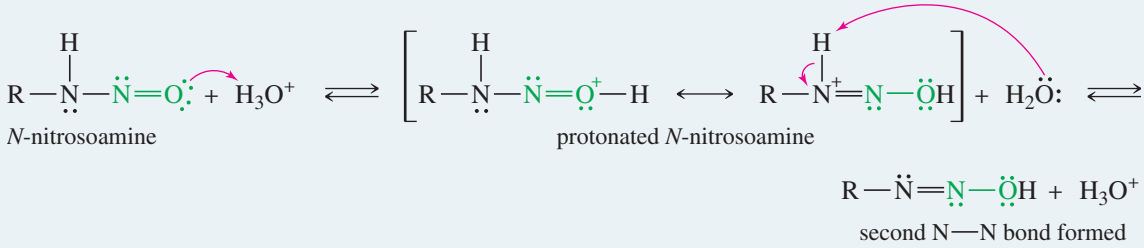
Reaction with Primary Amines: Formation of Diazonium Salts Primary amines react with nitrous acid, via the nitrosonium ion, to give diazonium cations of the form $R{-}\overset{+}{N}{\equiv}N$. This procedure is called **diazotization** of an amine. Diazonium salts are the most useful products obtained from the reactions of amines with nitrous acid. The mechanism for diazonium salt formation begins with a nucleophilic attack on the nitrosonium ion to form an *N*-nitrosoamine.

MECHANISM 19-6 Diazotization of an Amine

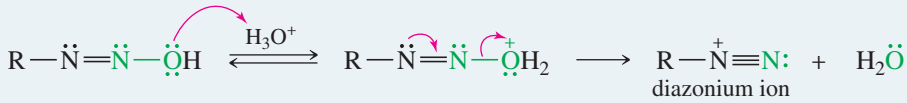
Part 1: Attack on the nitrosonium ion (a strong electrophile), followed by deprotonation, gives an *N*-nitrosoamine.



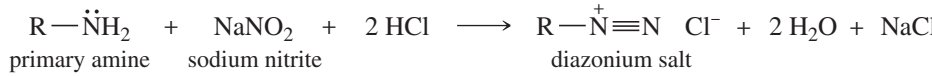
Part 2: A proton transfer (a tautomerism) from nitrogen to oxygen forms a hydroxyl group and a second N—N bond.



Part 3: Protonation of the hydroxyl group, followed by loss of water, gives the diazonium ion.



The overall diazotization reaction is

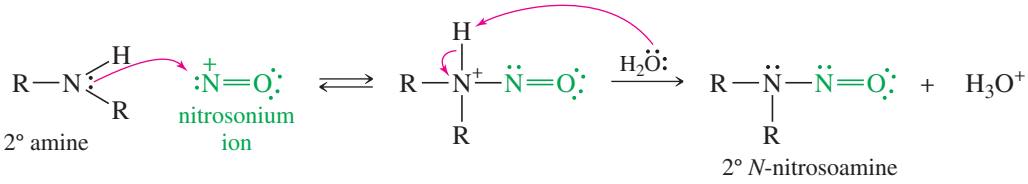


Alkanediazonium salts are unstable. They decompose to give nitrogen and carbocations.

The driving force for this reaction is the formation of N_2, an exceptionally stable molecule. The carbocations generated in this manner react like others we have seen: by nucleophilic attack to give substitution, by proton loss to give elimination, and by rearrangement. Because of the many competing reaction pathways, alkanediazonium salts usually decompose to give complex mixtures of products. Therefore, the diazotization of primary alkylamines is not widely used for synthesis.

Arenediazonium salts (formed from arylamines) are relatively stable, however, and they serve as intermediates in a variety of important synthetic reactions. These reactions are discussed in Section 19-17.

Reaction with Secondary Amines: Formation of *N*-Nitrosoamines Secondary amines react with the nitrosonium ion to form secondary ***N*-nitrosoamines,** sometimes called *nitrosamines*.



Secondary *N*-nitrosoamines are stable under the reaction conditions because they do not have the N—H proton needed for the tautomerism (shown in Mechanism 19-6 with a primary amine) to form a diazonium ion. The secondary *N*-nitrosoamine usually separates from the reaction mixture as an oily liquid.

Small quantities of *N*-nitrosoamines have been shown to cause cancer in laboratory animals. These findings have generated concern about the common practice of using sodium nitrite to preserve meats such as bacon, ham, and hot dogs. When the meat is eaten, sodium nitrite combines with stomach acid to form nitrous acid, which can convert amines in the food to *N*-nitrosoamines. Because nitrites are naturally present in many other foods, it is unclear just how much additional risk is involved in using sodium nitrite to preserve meats. More research is being done in this area to evaluate the risk.

The most useful reaction of amines with nitrous acid is the reaction of arylamines to form arenediazonium salts. We consider next how these diazonium salts may be used as synthetic intermediates.

PROBLEM 19-23

Predict the products from the reactions of the following amines with sodium nitrite in dilute HCl.
(a) cyclohexanamine **(b)** *N*-ethylhexan-2-amine **(c)** piperidine **(d)** aniline

19-17 Reactions of Arenediazonium Salts

In contrast to alkanediazonium salts, arenediazonium salts are relatively stable in aqueous solutions around 0–10 °C. Above these temperatures, they decompose, and they may explode if they are isolated and allowed to dry. The diazonium ($-\overset{+}{N}\equiv N$) group can be replaced by many different functional groups, including —H, —OH, —CN, and halogens.

Arenediazonium salts are formed by diazotizing a primary aromatic amine. Primary aromatic amines are commonly prepared by nitrating an aromatic ring, then reducing the nitro group to an amino ($-NH_2$) group. In effect, by forming and diazotizing an