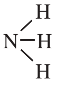
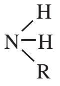
AMINES BY REDUCTION

1. Introduction

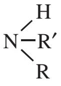
Amines are derivatives of ammonia in which one or more of the hydrogens is replaced with an alkyl, aryl, cycloalkyl, or heterocyclic group. When more than one hydrogen has been replaced, the substituents can either be the same or different. Amines are classified as primary, secondary, or tertiary depending on the number of hydrogens which have been replaced. It is important to note that the designations primary, secondary, and tertiary refer only to the number of substituents and not to the nature of the substituents as in some classes of compounds.



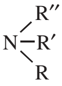
ammonia



primary amine



secondary amine



tertiary amine

Amines can be prepared by a variety of methods including substitution reactions, rearrangements, ammonolysis, and reductions. On a large scale, however, ammonolysis and reductions are usually the most efficient and are generally used in commercial processes. In reductive methods, the nitrogen is already incorporated in the molecule, and the amine is formed by reducing the oxidation state of the compound with the addition of hydrogen. In theory, many different types of nitrogen-containing compounds can be reduced to amines. In practice, however, nitriles or nitro compounds are usually used because they are the most easily obtained starting materials.

There are several commercial processes for reducing nitro or nitrile groups to amines. Most large volume aromatic and aliphatic amines are made by continuous high pressure catalytic hydrogenation. Nitro compounds can also be reduced in good yields with iron and hydrochloric acid in the Béchamp process.

The importance of the Béchamp process has declined over the last few decades, but it is still used in the pigment and dyestuff industry and to make iron oxide pigments; aniline is produced as a by-product. Other more specialized methods used for making amines by reduction include the Zinin reduction, in which sulfides in alkaline media are used to reduce aromatic nitro compounds, bisulfite reductions, electrochemical reductions, and reductions using metal amalgams or hydrides. The special case involving preparation of aliphatic amines by hydrogenation of aromatic amines is also included.

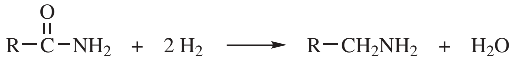
2. Catalytic Hydrogenation

In catalytic hydrogenation, a compound is reduced with molecular hydrogen in the presence of a catalyst. This reaction has found applications in many areas of chemistry including the preparation of amines. Nitro, nitroso, hydroxylamino, azoxy, azo, and hydrazo compounds can all be reduced to amines by catalytic hydrogenation under the right conditions. Nitriles, amides, thioamides, and oximes can also be hydrogenated to give amines (1). Some examples of these reactions follow:

Nitro $R{-}NO_2 + 3\,H_2 \longrightarrow R{-}NH_2 + 2\,H_2O$

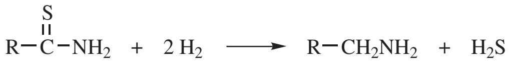
Nitrile $R{-}CN + 2\,H_2 \longrightarrow R{-}CH_2NH_2$

Amide



$$R{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}NH_2 + 2\,H_2 \longrightarrow R{-}CH_2NH_2 + H_2O$$

Thioamide



$$R{-}\overset{\displaystyle S}{\overset{\|}{C}}{-}NH_2 + 2\,H_2 \longrightarrow R{-}CH_2NH_2 + H_2S$$

Azo $R{-}N{=}N{-}R' + 2\,H_2 \longrightarrow R{-}NH_2 + R'{-}NH_2$

Catalytic hydrogenation is the most efficient method for the large scale manufacture of many aromatic and aliphatic amines. Some of the commercially important amines produced by catalytic hydrogenation include aniline (from nitrobenzene), 1,6-hexanediamine (from adiponitrile), isophoronediamine (from 3-nitro-1,5,5-trimethylcyclohexanecarbonitrile), phenylenediamine (from dinitrobenzene), toluenediamine (from dinitrotoluene), toluidine (from nitrotoluene), and xylidine (from nitroxylene). As these examples suggest, aromatic amines are usually made by hydrogenating the corresponding nitro compound, whereas the aliphatic amines generally start with the corresponding nitrile. The main reason for this difference is the availability of the necessary raw materials. Many aromatic hydrocarbons can be easily nitrated to give a variety of aromatic nitro compounds. For aliphatic amines, however, the nitrile precursor is generally easier to obtain than the corresponding aliphatic nitro compound. Nitriles, however, can only yield amines which are located at a primary carbon.

Catalytic hydrogenations can be carried out in the vapor phase or in the liquid phase, either with or without the use of a solvent. The vapor phase reaction is limited to compounds which are thermally stable and relatively volatile. High boiling compounds and those which are thermally unstable must be hydrogenated in the liquid phase.

3. Mechanism and Kinetics of Hydrogenation.

3.1. Reduction of Nitro Compounds. The mechanism for catalytic hydrogenation of nitro compounds has been the subject of many investigations and there is much evidence that this reaction proceeds through several intermediate species. The most widely accepted mechanism for the hydrogenation of nitro compounds was proposed by Haber in 1898 (2) (see Fig. 1).

Haber based this mechanism on the electrochemical reduction of nitrobenzene, but it has since been used by many researchers to explain the results of hydrogenation studies. For example, a mechanistic and kinetic study of the hydrogenation of nitrobenzene to aniline concluded that the reaction proceeds through a number of intermediates including nitrosobenzene, phenylhydroxylamine, azoxybenzene, azobenzene, and hydrazobenzene, even though not all of these intermediates were detected (3). Further evidence of the existence of these intermediates is provided by reports that under certain conditions, catalytic hydrogenation of nitro compounds can yield either hydroxylamines (4,5) or azoxy compounds (6) as the major product.

Many kinetic studies on hydrogenation reactions of nitro compounds have been aimed at determining not only rate equations, but also the effect of various factors on the reaction rate. In one study, the vapor-phase hydrogenation of nitrobenzene to aniline using a copper oxide–chromium oxide catalyst was found to be half order with respect to hydrogen concentration and first order in nitrobenzene (7). Similarly, in a liquid-phase hydrogenation using a homogeneous catalyst, the reaction rate was found to be first order in nitrobenzene concentration and dependent on the hydrogen pressure (8). However, other workers have concluded that the order of the reaction with respect to the nitro compound

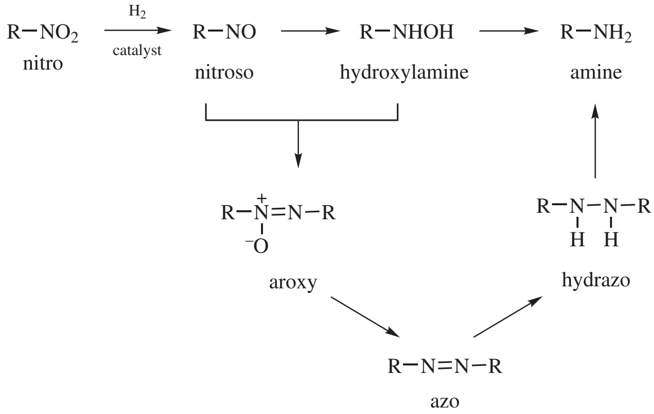


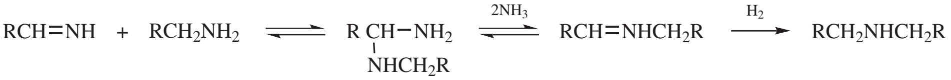
Fig. 1. Mechanism for the hydrogenation of nitro compounds. Functionalities are labeled.

can vary between 0 and 1, depending on factors such as the amount of catalyst and the nature of the solvent (9).

3.2. Reductions of Nitriles. In the reduction of nitriles, hydrogen is added progressively across the carbon−nitrogen triple bond, forming first the imine and then the amine.

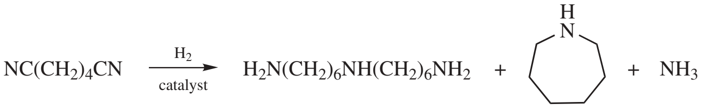
$$R{-}CN \xrightarrow{H_2} R{-}CH{=}NH \xrightarrow{H_2} R{-}CH_2{-}NH_2$$

One characteristic of this reaction that can cause problems is that secondary and tertiary amines are produced in addition to the primary amine. It has been proposed that these side reactions occur through reaction of the imine intermediate with the product amine, followed by the loss ofammonia and further hydrogenation (10).



$$RCH{=}NH + RCH_2NH_2 \rightleftharpoons R\underset{\displaystyle NHCH_2R}{\underset{|}{CH}}{-}NH_2 \overset{2NH_3}{\rightleftharpoons} RCH{=}NHCH_2R \xrightarrow{H_2} RCH_2NHCH_2R$$

The tertiary amine is formed in a similar manner from the imine and a secondary amine. This side reaction can be minimized by carrying out the hydrogenation in the presence of ammonia, which tends to shift the equilibrium back towards the imine. When a compound with two or more nitrile groups is hydrogenated, the formation of both cyclic and acyclic secondary and tertiary amines is possible, depending on whether the side reaction is intramolecular or intermolecular. For example, for the hydrogenation of adiponitrile:



4. Hydrogenation Raw Materials

4.1. Substrates. Many different types of nitrogen-containing compounds can be hydrogenated to amines, but nitro compounds and nitriles are the most commonly used starting materials.

Nitro Compounds. Many aromatic hydrocarbons react with nitric acid in the presence of sulfuric acid to form aromatic nitro compounds. The nitration reaction is an electrophilic aromatic substitution in which the orientation of the nitro group being introduced is controlled by the substituents which are already present (11). Because the nitro group is deactivating, each nitro group becomes progressively more difficult to add, and the reaction conditions can be controlled to give almost exclusively mono-, di- or trinitro compounds. For general reviews of nitration reactions see also references 12 and 13.

Nitriles. Nitriles can be prepared by a number of methods, including (*1*) the reaction of alkyl halides with alkali metal cyanides, (*2*) addition of hydrogen cyanide to a carbon−carbon, carbon− oxygen, or carbon−nitrogen multiple bond, (*3*) reaction of hydrogen cyanide with a carboxylic acid over a dehydration catalyst, and (*4*) ammoxidation of hydrocarbons containing an activated methyl group. For reviews on the preparation of nitriles see references 14 and 15.

4.2. Hydrogenation Catalysts.

The key to catalytic hydrogenation is the catalyst, which promotes a reaction which otherwise would occur too slowly to be useful. Catalysts for the hydrogenation of nitro compounds and nitriles are generally based on one or more of the group VIII metals. The metals most commonly used are cobalt, nickel, palladium, platinum, rhodium, and ruthenium, but others, including copper (16), iron (17), and tellurium (18) have been used. Despite this relatively small list, a wide variety of catalysts and catalyst modifications have been reported in the literature.

4.3. Physical Characteristics.

Heterogeneous catalysts are generally used for both large and small scale hydrogenations, but many homogeneous catalysts have also been used. Homogeneous and heterogeneous catalysts generally contain the same type of metals, but in homogenous catalysts the metals are present in the form of complexes or clusters with various organic and inorganic ligands. Some of the homogeneous catalysts which have been reported include copper triphenylphosphine complexes (19), ruthenium phosphine complexes (20,21), rhodium carbonyl clusters (8), and complexes of palladium with quinoline (22), pyridine (23,24), and phenylisocyano (25) ligands. Despite the high activity (20) and selectivity (21) sometimes claimed for homogeneous catalysts, heterogeneous catalysts are usually preferred because they are easy to use and recover for reuse.

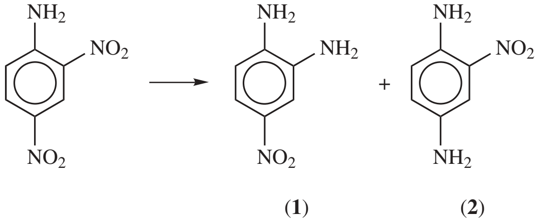
Heterogeneous hydrogenation catalysts can be used in either a supported or an unsupported form. The most common supports are based on alumina, carbon, and silica. Supports are usually used with the more expensive metals and serve several purposes. Most importantly, they increase the efficiency of the catalyst based on the weight of metal used and they aid in the recovery of the catalyst, both of which help to keep costs low. When supported catalysts are employed, they can be used as a fixed bed or as a slurry (liquid phase) or a fluidized bed (vapor phase). In a fixed-bed process, the amine or amine solution flows over the immobile catalyst. This eliminates the need for an elaborate catalyst recovery system and minimizes catalyst loss. When a slurry or fluidized bed is used, the catalyst must be separated from the amine by gravity (settling), filtration, or other means.

The available surface area of the catalyst greatly affects the rate of a hydrogenation reaction. The surface area is dependent on both the amount of catalyst used and the surface characteristics of the catalyst. Generally, a large surface area is desired to minimize the amount of catalyst needed. This can be accomplished by using either a catalyst with a small particle size or one with a porous surface. Catalysts with a small particle size, however, can be difficult to recover from the material being reduced. Therefore, larger particle size catalyst with a porous surface is often preferred. A common example of such a catalyst is Raney nickel.

Because of its relatively low cost, high activity, and long life, Raney nickel is one of the most commonly used hydrogenation catalysts. Raney nickel is composed primarily of nickel and aluminum which has been processed to give it a large surface area. This is done by activating an alloy of nickel and aluminum with aqueous sodium hydroxide under controlled conditions to dissolve most of the aluminum, leaving behind the nickel. The resulting catalyst is extremely porous, having a surface area of up to 100 m^2/g (26). There are several standard types of Raney nickel which are prepared using different activation conditions. These differ both in their physical characteristics and in their activity. Similar activation processes have also been applied to other metals to increase their surface area and catalytic activity.

4.4. Activity and Selectivity.

The activity of a catalyst refers to its ability to promote the desired reaction whereas the selectivity relates to how effective a catalyst is at promoting only a specific reaction. The selectivity which is required in a particular hydrogenation depends on the functional groups present in the material being hydrogenated. Many common functional groups can be reduced by catalytic hydrogenation with varying degrees of difficulty, and often one functional group must be reduced selectively in the presence of other groups which are to be left unchanged. For example, in the reduction of aromatic nitro compounds the catalyst and reaction conditions must be selected so that the nitro group is completely reduced while the aromatic ring is left intact. Since aromatic rings are generally much more difficult to reduce than nitro groups, this reduction can be carried out very selectively. However, other cases exist where it is much harder to selectively reduce one functional group in the presence of another. An impressive example of the selectivity which can be achieved is in the reduction of 2,4-dinitroaniline [97-02-9], ($C_6H_5N_3O_4$). Not only is it possible to reduce one of the nitro groups to an amine while leaving the other unchanged, but through proper choice of catalyst and reaction conditions, either 4-nitro-1,2-benzenediamine [99-56-9] (**1**) ($C_6H_7N_3O_2$) (27) or 2-nitro-1,4-benzenediamine [5307-14-2] (**2**) (28) can be made in good yield.



The subject of catalyst selection for hydrogenation reactions has been summarized in several books (29,30).

Poisoning and Deactivation. Many catalysts can be inhibited or poisoned by the presence of certain materials. Sulfur, phosphorus, arsenic, and bismuth compounds that have unshared electrons are common catalyst poisons. They act by binding to the catalyst surface, thereby preventing the desired reaction from occurring. Catalysts can also be deactivated by other means including pore plugging and physical degradation. However, the effects of poisoning or deactivation are not always permanent, and the catalyst can sometimes be regenerated. For a review of catalyst poisoning, deactivation and regeneration, see reference 31.

4.5. Hydrogen.

Most large scale industrial processes operate with essentially pure hydrogen, but hydrogen mixed with carbon monoxide or inert gases can also be used. Hydrogen can be obtained by any of several known processes (32), but those which simultaneously produce carbon monoxide as a by-product are often favored. The carbon monoxide can react with chlorine to form phosgene, the principal reagent required to convert amines to isocyanates. Methane gas is a convenient starting material for hydrogen generation, and the hydrogen and carbon monoxide produced from methane are generally of a high purity. One common route which produces hydrogen and carbon monoxide from methane is steam reforming, in which methane gas and steam are passed over a nickel– magnesia catalyst at about 800°C under pressure:

$$CH_4 + H_2O \xrightarrow{\text{catalyst}} CO + 3\ H_2$$

4.6. Solvents. A solvent is not always required in catalytic hydrogenations, but the use of a solvent can have several benefits. Using a solvent can make it simpler to hydrogenate solids or materials which are otherwise difficult to handle. A solvent can also act to moderate the heat of reaction, which can be quite large. Finally, a solvent can affect the course of a reaction by influencing the selectivity of the hydrogenation (33). Since hydrogenation processes usually operate under high pressure, the reaction temperature can be significantly above the normal boiling point of the solvent. In practice, low molecular weight alcohols, particularly methanol or ethanol, are the most commonly used hydrogenation solvents. Other solvents which have been used include acetic acid, acetone, ammonia, benzene, glycerol, ethylene glycol, hydrochloric acid, sulfuric acid, and water. When applicable the hydrogenation product itself can act as a solvent (34).

4.7. Additives. Several literature references and patents deal with the use of additives to promote or suppress particular reactions during the preparation of amines by catalytic hydrogenation. For example, the use of triethyl phosphite [122-52-1] (35), phosphoric acid [7664-38-2] (36), and 2,2′-thiodiethanol [111-48-8] $C_4H_{10}O_2S$ (37) has been reported to suppress dehalogenation during the reduction of halogen containing aromatic nitro compounds. Additives have also been reported to be useful both in suppressing the formation of amidines during the hydrogenation of nitriles (38) and promoting the reduction of aromatic nitrosulfonic acids to the corresponding amino derivatives (39). The presence of ammonia as an additive or solvent during the hydrogenation of nitriles helps to inhibit the formation of secondary and tertiary amine by-products.

5. Hydrogenation Reaction Conditions

5.1. Heat of Reaction and Heat Transfer. Catalytic hydrogenation is a very exothermic reaction and, therefore, removal of the heat generated is an important consideration in any hydrogenation process. For example, the heat of reaction for the catalytic hydrogenation of nitroxylene to xylidine is about 488 kJ/mol (117 kcal/mol) at 200°C (40). This value is comparable to the 544 kJ/mol (130 kcal/mol), which is often quoted for the hydrogenation of nitrobenzene to aniline. By comparison, the heat of reaction for the hydrogenation of nitriles is much smaller, about 310 kJ/mol (74 kcal/mol) for the hydrogenation of adiponitrile to 1,6-hexanediamine (41). This difference is, in part, because water is formed in the hydrogenation of nitro compounds, but not in the hydrogenation of nitriles. Nevertheless, any hydrogenation process must be able to remove sufficient heat to keep the reaction mixture at the desired temperature.

5.2. Temperature and Pressure. Temperature and pressure both have large effects on the course of a hydrogenation process. Higher temperatures lead to faster reactions, but excessive temperatures can result in undesirable byproducts and unsafe conditions. A study of the hydrogenation of 3,4-dichloroaniline showed that this reaction involved the initial formation of the hydroxylamine, which at low temperatures disproportionates to give the amine and the nitroso compound. At high temperatures, however, a highly exothermic reaction occurs in which the hydroxylamine and nitroso compounds form the azoxy compound (42).

Increasing hydrogen pressure also increases the rate of reaction by increasing the contact between the hydrogen gas, the catalyst, and the substrate which is needed for the reaction to take place. Usually higher pressures do not cause the problems associated with high temperatures. In fact, increasing the hydrogen pressure may actually serve to suppress side reactions which can occur under hydrogen deficient conditions (43).

5.3. Mixing. Agitation also plays a large role in optimizing a hydrogenation process. The metal catalyst is often much heavier than the rest of the reaction mixture and therefore vigorous mixing is needed to keep the catalyst in contact with the material being reduced and the hydrogen. Various methods have been used to achieve this mixing. With a fixed-bed catalyst system, the reactants flow through the stationary catalyst. In a fluidized-bed reactor the upward vapor flow keeps the catalyst suspended, ensuring good contact. A similar effect is possible with a liquid slurry, where the flow of liquid and gas keeps the catalyst and reactants mixed. It has also been reported that pulsation at frequencies of 30 to 3000 Hz can provide the necessary mixing when the liquid phase hydrogenation is carried out in tube reactors (44). More conventional agitators can also be used in stirred reactors, and in the laboratory the entire reactor is sometimes shaken to provide the necessary mixing.

6. Industrial Hydrogenation Processes

6.1. Liquid-Phase Hydrogenation of Nitro Compounds. Most high boiling aromatic amines are prepared by liquid-phase hydrogenation of the corresponding nitro compound, either with or without the use of a solvent. Early catalytic hydrogenations were performed in stirred batch reactors. More recently these have been replaced by continuous processes which provide better control in terms of heat transfer and mixing of the reactants. A continuous liquid-phase hydrogenation process is illustrated by the process for toluenediamine. Toluene can be readily nitrated by conventional means to give dinitrotoluene (DNT) (methyldinitrobenzene [25321-14-6], $C_7H_6N_2O_4$), consisting primarily of the 2,4- and 2,6-isomers in a ratio of about 4:1 (45). The DNT can be reduced by high pressure liquid-phase catalytic hydrogenation to the corresponding toluenediamine (TDA) (ar-methylbenzenediamine [25376-45-8], $C_7H_{10}N_2$) (see AMINES, AROMATIC, DIAMINOTOLUENES). Most of the TDA produced is phosgenated to give toluenediisocyanate (TDI) (diisocyanatomethylbenzene [26471-62-5], $C_9H_6N_2O_2$), which is used in the manufacture of polyurethanes. A typical industrial process for the reduction of DNT to TDA, as described by patents, is shown in Figure 2 and described in the following (46,47).

A solution containing about 25% DNT in methanol is pumped along with a Raney nickel slurry and enough hydrogen gas to complete the reaction through a series of reactors. There are three high pressure reactors plus an auxiliary reactor, each with a volume of approximately 450 L. The reactors are about 6 m long and 35 cm in diameter and are equipped with water cooling for temperature control. This reaction mixture is fed to the first reactor at a rate of approximately 2000 kg/h. The material from the first reactor is split and fed to the second and third reactors, which are run in parallel. The temperature of the reactors is maintained at about 100°C and the hydrogen pressure at between 15,000 and 20,000 kPa (150 and 200 atm). After the reaction is completed, the pressure is reduced and the excess hydrogen removed in a liquid–gas separator. The hydrogen is recycled to the beginning of the process and the product stream continues on through a series of catalyst removal steps. The recovered catalyst is also recycled with only a small amount, generally 0.1 to 0.3%, being lost in the process. After the catalyst is removed, the product is sent to a methanol column where the solvent is removed and recycled. The water is then removed in the dehydration column. The recovered water from this step contains volatile amines and other by-products and must be processed further before it can be recycled or discharged to the waste treatment plant. The product from the dehydration column can be used directly or taken to a final TDA column where it is distilled to give a product which is more than 99% pure. The residue from the final column can be disposed of by incineration or processed to recover some of the amine, thereby improving the yield and reducing waste-disposal problems.

Numerous modifications to the above process are possible and many variations have been suggested. Inert solvents other than methanol can be used; however, low molecular weight alcohols are usually considered preferable. Part of the reaction product can be recycled back to the front of the process to reduce the amount of solvent required and to eliminate problems associated with DNT solidification. A 76:24 mixture of DNT:TDA has been found to exhibit a minimum freezing point of 26°C, as compared to 50°C for pure DNT (46,47). The temperature at which the reaction is carried out can also be varied. Higher temperatures not only reduce the reaction time needed, but also result in less residue being formed (46). A temperature of 115 to 130°C is considered ideal, whereas temperatures above 170°C are considered unsafe.

6.2. Vapor Phase Hydrogenations of Nitro Compounds. Catalytic hydrogenation of nitro compounds can be carried out in the vapor phase, provided the boiling point of the compound is low enough and the material is thermally stable. These two conditions effectively limit this process to aliphatic and relatively simple aromatic nitro compounds such as nitrobenzene or nitroxylene. Early vapor-phase hydrogenation processes used fixed-bed catalysts. However, fluidized-bed catalytic vapor-phase hydrogenations, such as the one illustrated by the process for aniline, have become more common (see AMINES, AROMATIC, ANILINE AND DERIVATIVES).

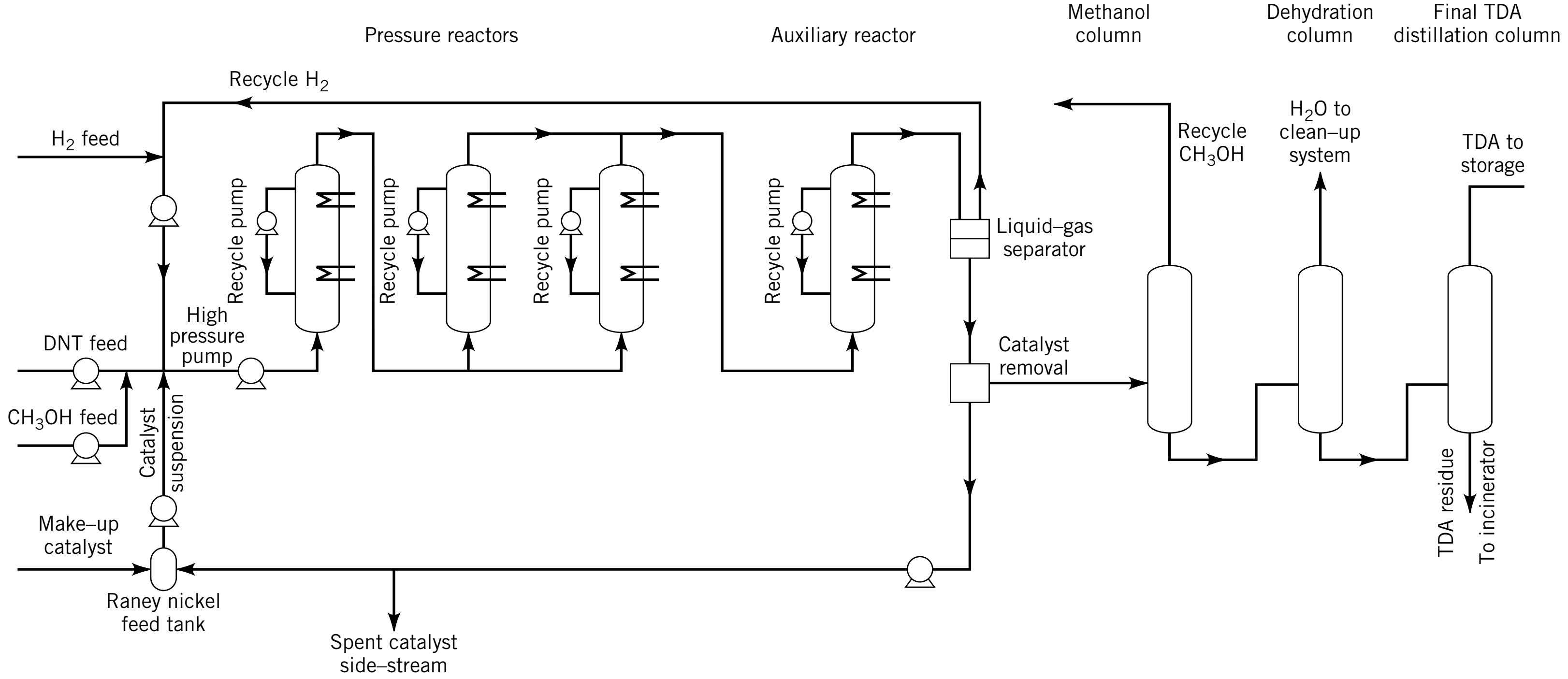


Fig. 2. Continuous liquid phase reduction of dinitrotoluene.

Nitrobenzene [98-95-3], $C_6H_5NO_2$ is produced by the nitration of benzene with a mixture of nitric and sulfuric acid. A process for the manufacture of aniline [62-53-3], C_6H_7N, from nitrobenzene is shown in Figure 3 (16). Nitrobenzene, which contains less than 10 ppm nitrothiophene, a catalyst poison, is fed to a vaporizer where it is vaporized. As the gaseous nitrobenzene leaves the vaporizer, it is mixed with a 200% excess of hydrogen gas. The gaseous mixture then passes upward through a porous distributor plate into the reduction chamber of the fluidized-bed reactor which contains the silica-supported copper catalyst. The catalyst powder is carried upward through the reactor by the vapor flow. The vapor velocity through the reactor is about 30 cm/s. The reaction occurs at 270°C and 234 kPa (2.3 atm) with a very short contact time. The excess heat of reaction is removed by circulating heat transfer fluid through cooling tubes located in the catalyst bed. The upper portion of the reactor is large enough to allow most of the catalyst to fall back into the main catalyst bed. Any catalyst which escapes from the reactor is removed from the product by stainless steel filters.

After leaving the reactor, the reaction mixture consisting of aniline, water, and excess hydrogen is cooled and condensed prior to the purification steps. First, the excess hydrogen is removed and recycled back to the reactor. The rest of the mixture is sent to the decanter where the water and aniline are separated. The crude aniline, which contains less than 0.5% of unreacted nitrobenzene and about 5% water, is distilled in the crude aniline column. The aniline is further dehydrated in the finishing column to yield the purified aniline. Meanwhile, the aqueous layer from the decanter, which contains about 3.5% aniline, is extracted to recover the aniline and clean up the water before it is sent to the waste-water treatment plant.

This process produces aniline with a yield of greater than 99% of theory. The appearance of nitrobenzene in the product is a sign of catalyst deactivation and the catalyst must be regenerated. This is done by stopping the nitrobenzene and hydrogen flow, and passing air through the catalyst at temperatures between 250 and 350°C. With regeneration, each gram of catalyst can produce a minimum of 600 grams of aniline before it must be replaced.

6.3. Aliphatic Amines from the Hydrogenation of Nitriles. One of the most common and economical means of producing aliphatic amines is by the catalytic hydrogenation of nitriles, eg, the process for 1,6-hexanediamine. Adiponitrile (hexanedinitrile [111-69-3], $C_6H_8N_2$), is produced commercially by several routes which are based on different raw materials. It can be made by reaction of adipic acid (qv) with ammonia over a catalyst or by the dimerization of acrylonitrile (qv) at the cathode in an electrolytic cell. Adiponitrile is also made from butadiene, either by direct reaction with hydrogen cyanide or by first chlorinating the butadiene to give 1,4-dichlorobutane, which then reacts with sodium cyanide. A continuous process for the reduction of adiponitrile to 1,6-hexanediamine ([124-09-4], $C_6H_{16}N_2$), is illustrated in Figure 4 and described below (41). This process uses a fixed-bed catalyst with liquid ammonia as a solvent to suppress formation of secondary and tertiary amines.

Adiponitrile, liquid ammonia, and hydrogen gas are introduced together in a molar ratio of approximately 1:25:38 under a pressure of about 60 MPa (600 atm). The mixture passes through a preheater where the temperature is

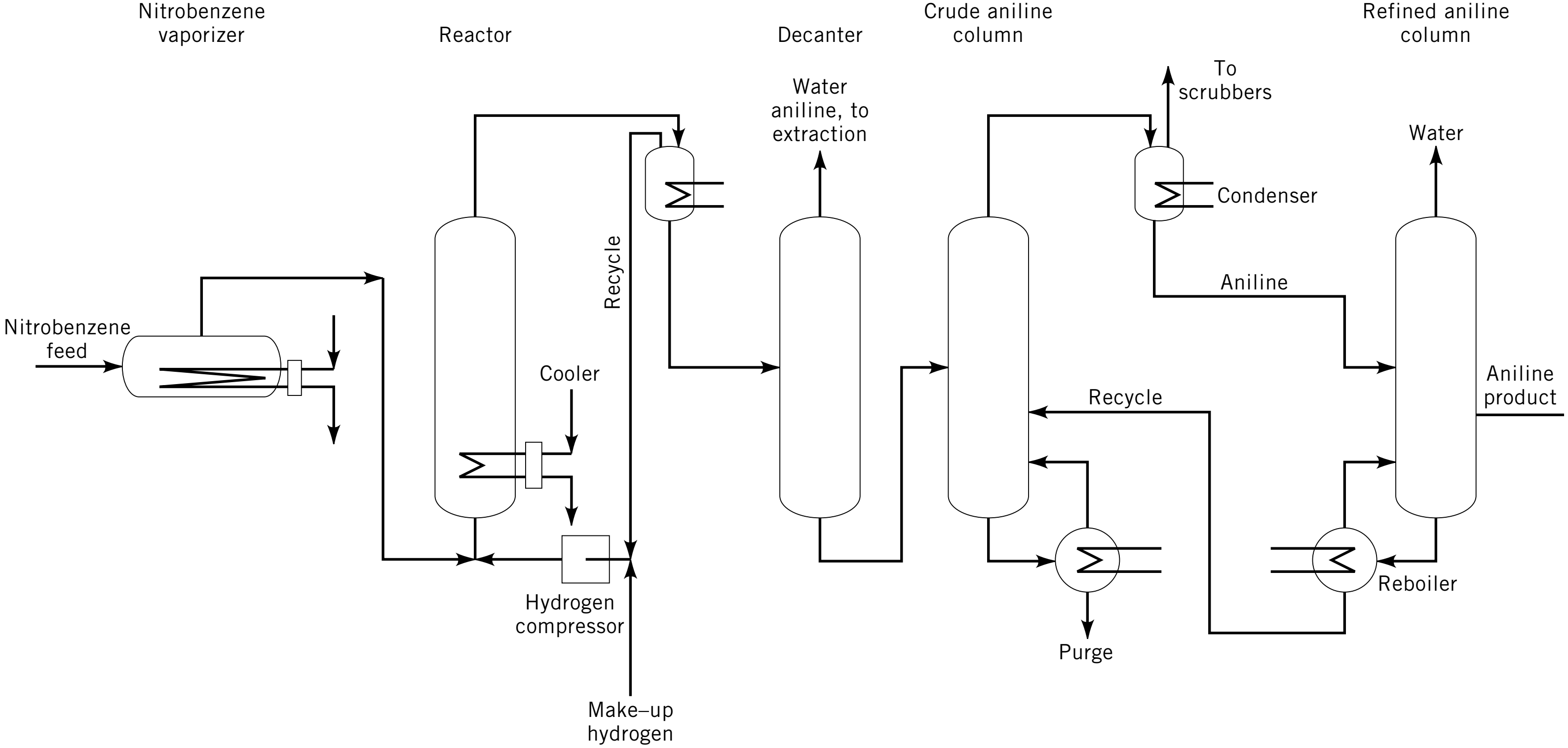


Fig. 3. Continuous fluidized-bed vapor phase reduction of nitrobenzene.

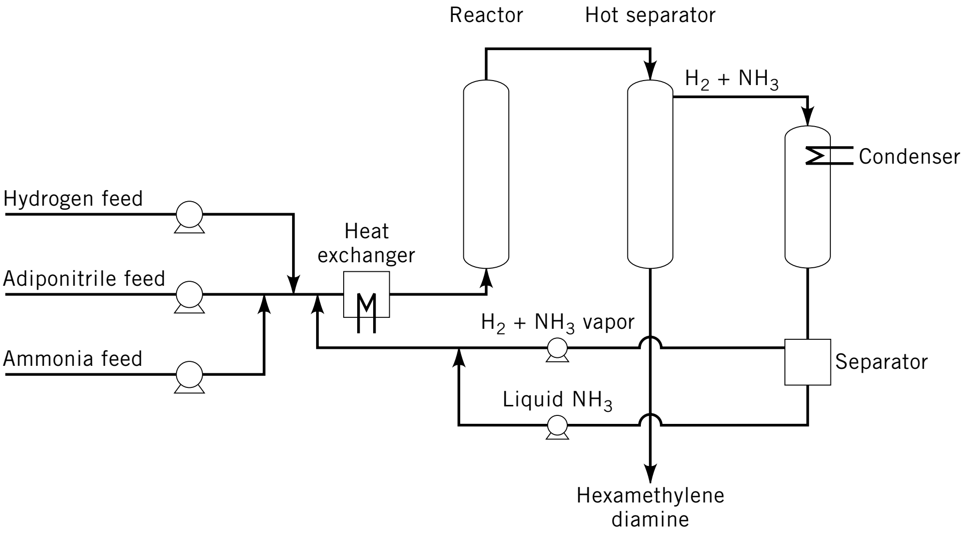


Fig. 4. Continuous fixed-bed reduction of adiponitrile to 1,6-hexanediamine.

raised to about 30°C below the desired reaction temperature. The mixture then enters the reactor which contains the catalyst in the form of a fixed bed. Several different catalysts can be used, including copper–cobalt, cobalt–aluminum, cobalt oxide, and chromium oxide–cobalt oxide. The preferred temperature range is from 110 to 135°C, but any temperature between 100 and 150°C can be used. The adiponitrile is converted to 1,6-hexanediamine in the reactor and transferred to the hot separator where the gaseous hydrogen and ammonia are removed. The hydrogen and ammonia are then taken to a condenser for recycling while the diamine is taken forward for purification.

About 310 kJ/mol (75 kcal/mol) of heat is released during this reaction and the exotherm is controlled by adjusting the recycle streams. Part of the heat is used to raise the temperature of the reaction mixture the final 30°C while a large amount of heat is expended in vaporizing the ammonia.

7. Béchamp Process

In the Béchamp process, nitro compounds are reduced to amines in the presence of iron and an acid. This is the oldest commercial process for preparing amines, but in more recent years it has been largely replaced by catalytic hydrogenation. Nevertheless, the Béchamp reduction is still used in the dyestuff industry for the production of small volume amines and for the manufacture of iron oxide pigments; aniline is produced as a by-product. The Béchamp reduction is generally run as a batch process; however, it can also be run as a continuous (48) or semicontinuous process (49).

7.1. Reaction Mechanism. The overall reaction in the Béchamp process is as follows

$$4\,RNO_2 + 9\,Fe + 4\,H_2O \xrightarrow{FeCl_2} 4\,RNH_2 + 3\,Fe_3O_4$$

However, this is an oversimplification, and the Béchamp reduction is a complex reaction which can be better represented by the following stepwise mechanism (50).

$$2\ R{-\!\!-}NO_2 + FeCl_2 + 6\ Fe + 10\ H_2O \longrightarrow 2\ R{-\!\!-}NH_3Cl + 7\ Fe(OH)_2$$

$$R{-\!\!-}NO_2 + 6\ Fe(OH)_2 + 4\ H_2O \longrightarrow R{-\!\!-}NH_2 + 6\ Fe(OH)_3$$

$$Fe(OH)_2 + 2\ Fe(OH)_3 \longrightarrow Fe_3O_4 + 4\ H_2O$$

In this representation the $FeCl_2$ which takes part in the first step of the reaction is not a true catalyst, but is continuously formed from HCl and iron. This is a highly exothermic process with a heat of reaction of 546 kJ/mol (130 kcal/mol) for the combined charging and reaction steps (50). Despite the complexity of the Béchamp process, yields of 90–98% are often obtained. One of the major advantages of the Béchamp process over catalytic hydrogenation is that it can be run at atmospheric pressure. This eliminates the need for expensive high pressure equipment and makes it practical for use in small batch operations. The Béchamp process can also be used in the laboratory for the synthesis of amines when catalytic hydrogenation cannot be used (51).

Some of the important parameters in the Béchamp process are the physical state of the iron, the amount of water used, the amount and type of acid used, agitation efficiency, reaction temperature, and the use of various catalysts or additives. When these variables are properly controlled, the amine can be obtained in high yields while controlling the color and physical characteristics of the iron oxide pigment which is produced.

7.2. Raw Materials.

Iron. Clean, finely divided, soft, gray cast iron yields the best results. In practice, the iron is often etched by heating it in an acid solution prior to addition of the nitro compound. This ensures a good iron surface and prevents the possibility of a violent delayed reaction. Since the rate of reaction depends in part on the surface area of the iron, finely divided iron leads to a smoother reaction requiring less time. When coarse iron is used, the reaction is slower and a larger excess of iron is required to complete the reaction. For these reasons, iron turnings, shavings, or borings are generally preferred. It has been reported that impurities in the iron can lead to undesirable side reactions in certain cases. For example, when ring-chlorinated aromatic nitro compounds are reduced, dechlorination is possible. Dechlorination is promoted by the presence of nickel in the iron (52), but can be retarded by addition of certain inhibitors including potassium thiocyanate and dicyandiamide (53,54).

Water. Based on the overall balanced equation for this reaction, a minimum of one mole of water per mole of nitro compound is required for the reduction to take place. In practice, however, 4 to 5 moles of water per mole of nitro compound are used to ensure that enough water is present to convert all of the iron to the intermediate ferrous and ferric hydroxides. In some cases, much larger amounts of water are used to dissolve the amino compound and help separate it from the iron oxide sludge after the reaction is complete.

Acid. The reaction requires only enough acid to generate the ferrous ion which is needed to participate in the first step. Alternatively, a ferrous salt can be added directly. Generally 0.05 to 0.2 equivalents of either hydrochloric or sulfuric acid is used, but both acids have their drawbacks. Hydrochloric acid can cause the formation of chlorinated amines and sulfuric acid can cause the rearrangement of intermediate arylhydroxylamines to form hydroxyaryl amines. Occasionally an organic carboxylic acid such as acetic or formic acid is used when there is a danger of hydrolysis products being formed.

7.3. Reaction Conditions.

Mixing. Because of the heterogeneous nature of this system, efficient mixing is essential to ensure the intimate contact of the iron, nitro compound, and water soluble catalyst. An agitator which allows the iron to settle to the bottom and the other materials to separate into layers does not function efficiently. On the other hand, a reaction whose rate is limited by the quality of the iron will not be significantly improved by better mixing.

Amine Recovery. Once the reaction is completed, the amine must be separated from the iron oxide sludge. First, the iron oxide is allowed to settle and the liquid amine layer is removed by siphoning or decanting. A significant amount of amine remains in the iron oxide and this must also be recovered. Several methods have been used to accomplish this (55). Either steam distillation or vacuum distillation of the amine from the iron oxide is possible. In steam distillation, steam is fed into the iron oxide sludge and the condensate is collected. This is an effective but expensive method of recovering the amine. Vacuum distillation is less expensive than steam distillation, but it is difficult to recover all of the amine from the iron oxide using vacuum distillation. Filtration is another way of recovering the amine from the iron oxide. In this method, the iron oxide is first washed with water recovered from the amine purification. This is followed by fresh boiling water and finally, the iron oxide is blown with hot air or steam to remove the remaining liquid.

7.4. Preparation of Aniline by the Béchamp Process.

About 1500 L of a ferrous chloride solution and 1300–1500 L of aniline water are charged to a 20,000-L reactor. Because of the abrasive nature of this reaction mixture, the reactor is often lined with tile or contains a replaceable liner. To this mixture are added 1000 kg of iron filings and 300 L of nitrobenzene. Once the reaction is underway, an additional 4700 kg of nitrobenzene and 5300 kg of iron are added together over a period of 6 to 9 h. After about 12 h, the reaction is complete and the mixture is neutralized. Then the iron sludge is allowed to settle and the aniline is decanted off through an adjustable dip tube. The iron oxide sludge is steam distilled by passing steam through it for 4–5 h and the condensate collected. The condensate is added to the aniline which was decanted and the material is further neutralized and purified by distillation. The aniline water from the distillation is returned to the process or extracted with nitrobenzene to recover the residual aniline (56).

Several modifications to this process are possible (55). Instead of adding ferrous chloride directly, it is more common to generate it by using iron and hydrochloric acid. The order in which the reactants are added can also be altered, and it is even possible to add all of the iron or aniline at the beginning of the reaction. There are also other ways to recover the aniline from the iron oxide sludge.

8. Miscellaneous Reductions

8.1. Zinin Reduction.

The method of reducing aromatic nitro compounds with divalent sulfur is known as the Zinin reduction (57). This reaction can be carried out in a basic media using sulfides, polysulfides, or hydrosulfides as the reducing agent. These reactions can be represented as follows when the counter ion is sodium:

$$4\ ArNO_2 + 6\ Na_2S + 7\ H_2O \longrightarrow 4\ ArNH_2 + 3\ Na_2S_2O_3 + 6\ NaOH$$

$$ArNO_2 + Na_2S_2 + H_2O \longrightarrow ArNH_2 + Na_2S_2O_3$$

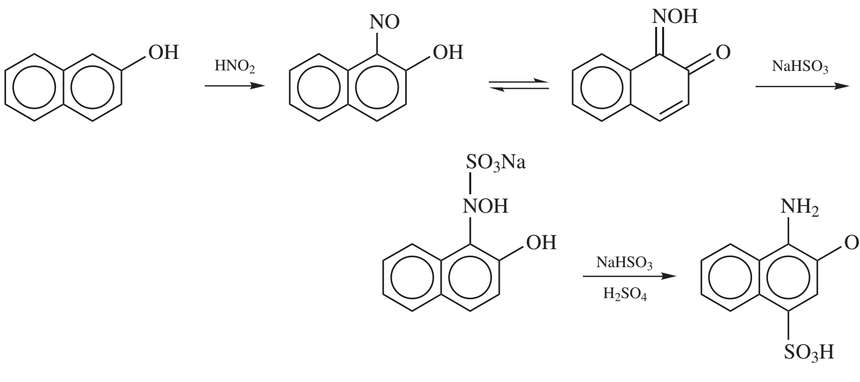
$$4\ ArNO_2 + 6\ NaSH + H_2O \longrightarrow 4\ ArNH_2 + 3\ Na_2S_2O_3$$

Although this reduction is more expensive than the Béchamp reduction, it is used to manufacture aromatic amines which are too sensitive to be made by other methods. Such processes are used extensively where selectivity is required such as in the preparation of nitro amines from dinitro compounds, the reduction of nitrophenol and nitroanthraquinones, and the preparation of aminoazo compounds from the corresponding nitro derivatives. Amines are also formed under the conditions of the Zinin reduction from aromatic nitroso and azo compounds.

The Zinin reduction is also useful for the reduction of aromatic nitro compounds to amines in the laboratory. It requires no special equipment, as is the case with catalytic hydrogenations, and is milder than reductions with iron and acid. Usually ammonium or alkali sulfides, hydrosulfides or polysulfides are used as the reactant with methanol or ethanol as the solvent.

The reduction of *m*-dinitrobenzene [99-65-0] to *m*-nitroaniline [99-09-2] on a laboratory scale offers an example. A solution containing 18 g of sodium sulfide and 6 g of sodium bicarbonate in 50 mL of water is prepared, mixed with 50 mL of methanol, and filtered to remove precipitated sodium carbonate. Next, 6.7 g of *m*-dinitrobenzene, $C_6H_4N_2O_4$, in 50 mL of methanol is added and the mixture refluxed for 20 min. The methanol is removed by distillation and the residue poured into cold water where it solidifies. The material can then be recrystallized from 75% aqueous methanol to give a 69% yield of *m*-nitroaniline, $C_6H_6N_2O_2$, with a melting point of 114°C (58).

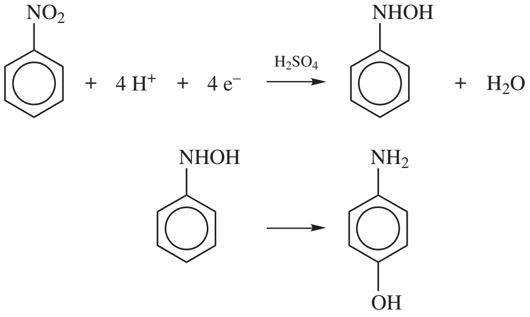
8.2. Sodium Bisulfite. Sodium bisulfite [7631-90-5], $NaHSO_3$, is occasionally used to perform simultaneous reduction of a nitro group to an amine and the addition of a sulfonic acid group. For example, 4-amino-3-hydroxyl-1-naphthalenesulfonic acid [116-63-2], $C_{10}H_9NO_4S$, is manufactured from 2-naphthol in a process which uses sodium bisulfite (59). The process involves nitrosation of 2-naphthol in aqueous medium, followed by addition of sodium bisulfite and acidification with sulfuric acid.



8.3. Electrolytic Reductions. Both nitro compounds and nitriles can be reduced electrochemically. One advantage of electrochemical reduction is the cleanness of the operation. Since there are a minimum of by-products, both waste disposal and purification of the product are greatly simplified. However, unless very cheap electricity is available, these processes are generally too expensive to compete with the traditional chemical methods.

Nitro Compounds. When nitro compounds are reduced by electrochemical methods a number of products are possible depending on such factors as the nature of the electrode, the electrode potential, and the reaction media. For the reduction of nitrobenzene these products include aniline, *p*-aminophenol, *p*-chloroaniline, phenylhydroxylamine, azoxybenzene, azobenzene, and hydrazobenzene (60).

Electrolytic reductions generally cannot compete economically with chemical reductions of nitro compounds to amines, but they have been applied in some specific reactions, such as the preparation of aminophenols (qv) from aromatic nitro compounds. For example, in the presence of sulfuric acid, cathodic reduction of aromatic nitro compounds with a free para-position leads to *p*-aminophenol [123-30-8] by rearrangement of the intermediate *N*-phenyl-hydroxylamine [100-65-2] (61).



Nitriles. The electrolytic reduction of nitriles requires a high negative potential, but can lead to amines in good yields under the right conditions. This reaction occurs in acidic media according to the following equation (62).

$$R{-}CN + 4\,H^+ + 4\,e^- \longrightarrow R{-}CH_2NH_2$$

In general, however, the electrochemical reduction of nitriles offers no significant advantages over traditional chemical methods and has not been widely used.

8.4. Metal Amalgams and Hydrides. Metal hydrides and amalgams are sometimes the preferred method of reducing various functional groups in the laboratory, especially when the necessary equipment for catalytic hydrogenations is unavailable. However, these reagents are usually too expensive to make their use on a large commercial scale feasible.

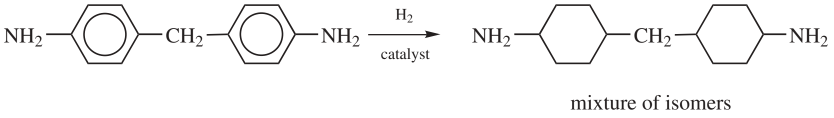
Metal Amalgams. Alkali metal amalgams function in a manner similar to a mercury cathode in an electrochemical reaction (63). However, it is more difficult to control the reducing power of an amalgam. In the reduction of nitro compounds with an $NH_4(Hg)$ amalgam, a variety of products are possible. Aliphatic nitro compounds are reduced to the hydroxylamines, whereas aromatic nitro compounds can give amino, hydrazo, azo, or azoxy compounds.

Metal Hydrides. Metal hydrides can sometimes be used to prepare amines by reduction of various functional groups, but they are seldom the preferred method. Most metal hydrides do not reduce nitro compounds at all (64), although aliphatic nitro compounds can be reduced to amines with lithium aluminum hydride. When aromatic amines are reduced with this reagent, azo compounds are produced. Nitriles, on the other hand, can be reduced to amines with lithium aluminum hydride or sodium borohydride under certain conditions. Other functional groups which can be reduced to amines using metal hydrides include amides, oximes, isocyanates, isothiocyanates, and azides (64).

8.5. Aliphatic Amines from the Ring Reduction of Aromatic Amines.

Certain aliphatic amines can be prepared by reduction of aromatic amines by catalytic hydrogenation. This method is applicable only when a corresponding aromatic amine is available. Nevertheless, it is used for the production of several important amines including cyclohexylamine and bis(4-aminocyclohexyl)-methane. Reduction of an aromatic ring can be carried out using the same types of catalysts that are used for the hydrogenation of nitro compounds and nitriles. The conditions required are much harsher, however, and higher temperatures and pressures are generally required.

Bis(4-aminocyclohexyl)methane. Aniline can react with formaldehyde in the presence of an acid catalyst to give a mixture of polymeric amines. The principal component of this mixture is 4,4′-diaminodiphenylmethane (4,4′-methylenebisbenzenamine [101-77-9], $C_{13}H_{14}N_2$). Most of this material is used in the production of isocyanates for polyurethanes. However, part of the 4,4′-diaminodiphenylmethane is converted to bis(4-aminocyclohexyl)methane (4,4′-methylenebiscyclohexanamine [1761-71-3], $C_{13}H_{26}N_2$) by catalytic hydrogenation, which results in a mixture of cis,cis-, cis,trans-, and trans,trans-stereoisomers. Typically a ruthenium catalyst is used at relatively high temperatures and pressures. For example, one patent describes a process for preparation of bis(4-aminocyclohexyl)methane from 4,4′-diaminodiphenylmethane with excellent yields in short times (65). The reaction is carried out using any of several ruthenium catalysts in the presence of a solvent and ammonia. The preferred temperature range is 225 to 250°C with an initial hydrogen pressure of about 14 to 24 MPa (140–240 atm). Under these conditions, the reaction is completed in less than 30 min with yields of 93 to 97% or higher.



9. Intermediates from the Reduction of Nitro Compounds

In the reduction of nitro compounds to amines, several of the intermediate species are stable and under the right conditions, it is possible to stop the reduction at these intermediate stages and isolate the products (see Figure 1, where

R = C_6H_5). Nitrosobenzene [586-96-9], C_6H_5NO, can be obtained by electrochemical reduction of nitrobenzene [98-95-3]. Phenylhydroxylamine, C_6H_5NHOH, is obtained when nitrobenzene reacts with zinc dust and calcium chloride in an alcoholic solution. When a similar reaction is carried out with iron or zinc in an acidic solution, aniline is the reduction product. Hydrazobenzene [122-66-7], $C_{12}H_{12}N_2$, is formed when nitrobenzene reacts with zinc dust in an alkaline solution. Azoxybenzene [495-48-7], $C_{12}H_{10}N_2O$, is formed from two molecules of nitrobenzene when heated in an alcoholic solution containing a strong base such as sodium hydroxide. Azobenzene [103-33-3], $C_{12}H_{10}N_2$, can be obtained by distilling azoxybenzene in the presence of iron powder or by reaction of nitrobenzene with sodium stannite [12214-41-7], Na_2SnO_2.

10. Environmental and Safety Aspects

Amines, nitro compounds, nitriles, and the various solvents and reagents used in the preparation of amines by reduction vary widely in the hazards they may pose. Some of these materials are acutely toxic by ingestion, inhalation, or absorption through the skin. Others are skin irritants or sensitizers. Still others may cause damage by chronic exposure to organs, such as the liver, or may be carcinogenic. Since amines vary so widely in their potential danger, no general rules can govern their safe use in all cases. The Material Safety Data Sheet (MSDS) for the material in question should be consulted before the chemicals are used.

10.1. Waste Treatment and Effluent Monitoring. Modern chemical plants are closed systems to prevent the emission of pollutants into the environment. Vents are protected by fume scrubbers and process waste water is cleaned up before being discharged. Any unavoidable by-products are collected and disposed of in a manner consistent with government regulations. In the water treatment plant diagrammed in Figure 5, the incoming water is first treated to neutralize the normally acidic stream and the solids are removed in a 4 million liter clarifier. Biological treatment then removes many of the the organic compounds. Aniline and methanol are readily removed at this stage; nitro compounds are much more difficult for the bacteria to digest. An activated carbon system removes final traces of organics and much of the remaining color, providing an effluent which meets state and federal regulations. The carbon is routinely regenerated in a system that incinerates the organics absorbed from the waste stream. Finally, the water leaving the waste water treatment plant is monitored by chemical and biological tests to ensure its quality.

10.2. Air Monitoring. The atmosphere in work areas is monitored for worker safety. Volatile amines and related compounds can be detected at low concentrations in the air by a number of methods. Suitable methods include chemical, chromatographic, and spectroscopic techniques. For example, the NIOSH Manual of Analytical Methods has methods based on gas chromatography which are suitable for common aromatic and aliphatic amines as well as ethanolamines (67). Aromatic amines which diazotize readily can also be detected photometrically using a treated paper which changes color (68). Other methods based on infrared spectroscopy (69) and mass spectroscopy (70) have also been reported.

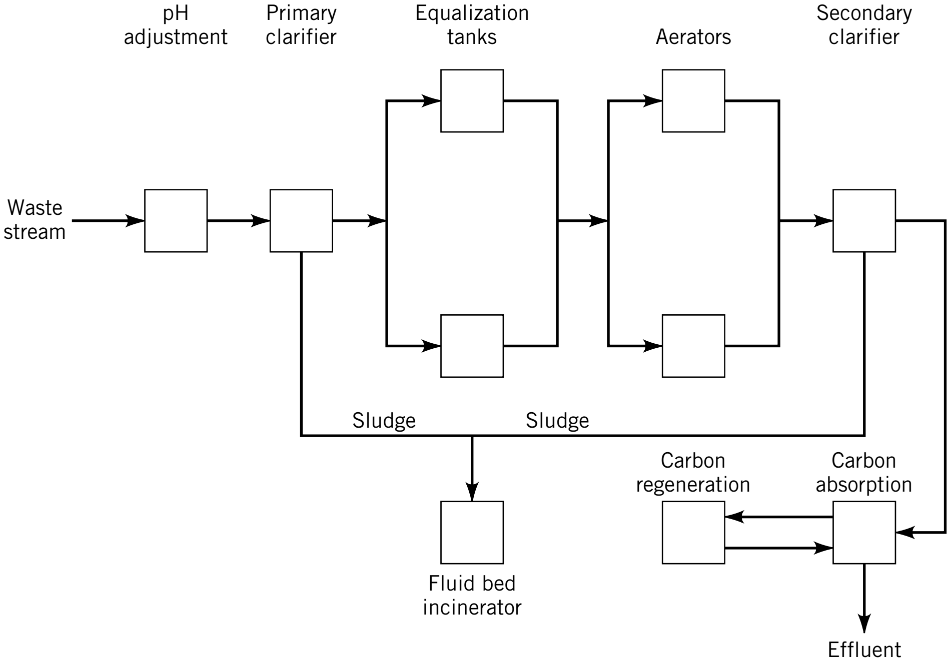


Fig. 5. Typical industrial waste-water treatment plant, eg, 25 × 10^6 L/day, Mobay Corporation plant at New Martinsville, W.V. (66).

10.3. Handling of Amines. Regulations governing the safe handling and shipping of amines in interstate commerce are given in U.S. Department of Transportation publications (71). Specific information on the safe handling and hazards associated with a particular amine can be found in the Material Safety Data Sheet for that material. For further information on the safety of industrial material see also references 72 and 73.

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