Amines

Amines are organic compounds containing a nitrogen functionality

Depending upon the number of alkyl, or aryl, groups attached to nitrogen
determines its classification, or order

\[
\begin{align*}
\text{primary} & : & \text{secondary} & : & \text{tertiary} & : & \text{quaternary} \\
\text{NH}_2 & & & & & & \text{N}^+ \\
\end{align*}
\]

The order also affects the number of hydrogens attached to nitrogen
(and charge with a quaternary nitrogen)
Alkaloids

Alkaloids refer to amines that are produced by plants

They are often used for medicinal or physiological purposes (the plant makes them to cause an effect when an animal eats them for protection)

morphine  codeine  heroin

Examples of opium alkaloids – compounds bind to receptor sites in the brain
Nomenclature

Common names – name the amine by indicating each alkyl substituent with amine suffix

![Structures](image1)

- ethylamine
- diethylamine
- diethylmethylamine

IUPAC names – similar to alcohol names, find longest continuous chain and name amine as a suffix

![Structures](image2)

- ethylamine
- N-ethylethylamine
- N-ethyl-N-methyl-1-propanamine

Use N-alkyl to name substituents attached to nitrogen
Other Common Names

There are a number of compounds with historic names

\[
\begin{array}{ccc}
\text{aniline} & \text{pyridine} & \text{pyrrolidine} \\
\text{4-methylpyridine} & & \\
\end{array}
\]

These compounds, and others seen in aromatic compounds, use common names.

Substituents are named with the common name as the root.
Structure

With a saturated amine, the lone pair resides in a sp$^3$ hybridized orbital

With conjugation, the lone pair will reside in a p orbital to allow overlap
Nitrogen Inversion

While a saturated amine is sp$^3$ hybridized, the nitrogen atom can undergo a rehybridization to cause an “inversion of configuration”

Any sp$^3$ hybridized center is chiral with four different substituents

With nitrogen inversion, however, we usually cannot isolate stereoisomers

S-N-ethyl-N-methyl-1-propanamine

S configuration  Planar sp$^2$ hybridization  R configuration
Nitrogen Inversion Changes the Chirality

Since this inversion happens at room temperature for nitrogen, cannot isolate pure form of either enantiomer

Can prevent nitrogen inversion by two ways:

1) Create quaternary nitrogen – nitrogen is prevented to invert with four covalent bonds

\[ \text{will invert} \quad \text{cannot invert} \]

2) Strain prevents formation of sp\(^2\) hybridized nitrogen

\[ \text{Strain of ring hinders sp}\(^2\) hybridization \]
Properties of Amines

Amines typically have a relatively high dipole

\[ \text{Net dipole} \]

Have dipole for both from nitrogen to lone pair
and for each carbon-nitrogen bond

In addition, hydrogen bonding causes amines to have a relatively higher boiling point
Basicity

Another major factor with amines is the basicity

The lone pair of electrons on nitrogen can act as an acceptor (hence Brønsted-Lowry base)

\[
\text{R-N}^+ \quad \text{H}_2\text{O} \quad \text{K}_b \quad \text{H}^+ \quad \text{N}^- \quad \text{OH}^-
\]

Can determine pK\textsubscript{b} values (just like pK\textsubscript{a} values for acids)

\[\text{pK}_a + \text{pK}_b = 14\]

Therefore strong bases are weak conjugate acids, and vice versa
Effects of Basicity

The base strength for amines follow many of the same trends as already observed

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H–N} \cdot & \quad \text{R–N} \cdot \\
\text{H} & \quad \text{H}
\end{align*}
\]

\[pK_b = 4.74 \quad pK_b = 3.36\]

Primary amines are more basic than unsubstituted amines, electron donating alkyl groups stabilize ammonium compound after protonation

A difference with amines, however, is that secondary and tertiary amines are approximately the same basicity as primary amines – due to hydration effects
Resonance Effects

Amines in resonance are less basic than saturated amines

\[
\text{HN} \quad \text{pK}_b = 9.40
\]

Protonation prevents the lone pair from conjugation

Also remember resonance considerations for aromatic rings

\[
\text{pK}_b = 15
\]

Protonation makes aromatic compound nonaromatic
Hybridization

As the percent s character increases for the orbital holding the lone pair of electrons, the electrons are held more closely to the positively charged nucleus.

Therefore a \( sp^2 \) hybridized amine have the electrons closer to the nucleus than a \( sp^3 \) hybridized amine.

Thus the \( sp^2 \) hybridized amine is harder to protonate (and form a positive charge) than a \( sp^3 \) hybridized amine (other factors like resonance being equal).

\[
\text{pK}_b = 3.36 \quad \text{pK}_b = 8.75 \quad \text{pK}_b = 24
\]
Amine Salts

There are many advantageous uses of amine salts

First, the salt form of aniline changes the substituent from strongly activating to strongly deactivating, therefore changing the regiochemistry and reactivity

\[
\text{NH}_2 \quad \xrightarrow{\text{H}^+} \quad \text{NH}_3^+ 
\]

Second, the amine salt changes solubility
Amines are soluble in organic phase, salts are soluble in aqueous phase
Phase Transfer Catalysis (PTC)

Amine salts are also used to catalyze a variety of organic reactions that feature two components that are soluble in different liquid phases (e.g. organic and aqueous)

\[
\text{Br} \quad \text{NaCN} \quad \text{Low rate in either organic or aqueous solutions}
\]

High organic solubility  low organic solubility
low aqueous solubility  high aqueous solubility

Adding a phase transfer catalyst will accelerate the rate (often use quaternary amine salts which have solubility in both phases)
Reactions of Amines

Some reactions have already seen in earlier chapters covering ketones and aromatic substitution.

\[
\text{RC} = \text{H} + \text{RNH}_2 \xrightarrow{H^+} \text{RC} = \text{N}^+ - \text{RN} \quad \text{E} + \text{NH}_2 \xrightarrow{E^+} \text{E} - \text{NH}_2
\]
Pyridine

Pyridine is a strongly deactivating ring system

Many reactions do not work with pyridine due to the strongly deactivating system

Those that do react occur with meta substitution

Consider the arenium ion to understand this regiopreference
Nucleophilic Aromatic Substitution

Since pyridine is a strong deactivating group, leaving groups ortho or para to nitrogen will leave in a nucleophilic substitution

\[
\text{Cl} \quad \xrightarrow{\text{NaOCH}_3} \quad \text{OCH}_3
\]

Again consider charged intermediate for this reaction to predict regiopreference

Also remember leaving group ability for these nucleophilic aromatic substitution reactions follow electronegativity trends (\(F > Cl > Br > I\))
Alkylation of Amines

The lone pair of electrons on amines can react in a nucleophilic manner

\[
\begin{align*}
\text{NH}_2 & \quad \text{CH}_3\text{I} \\
\rightarrow & \\
\text{N} & \quad \text{H}
\end{align*}
\]

Yield is best with methyl or primary halide (this is a S\textsubscript{N}2 reaction)

One problem with this reaction is often polyalkylation occurs

\[
\begin{align*}
\text{N} & \quad \text{CH}_3\text{I} \\
\rightarrow & \\
\text{N} & \quad \text{I}
\end{align*}
\]

Will continue until quaternary amine is obtained
To prevent “over alkylation” reaction is run with excess of amine

\[ \text{NH}_2 + \text{CH}_3\text{I} \rightarrow \text{N} \]

10 equivalents

The other option is to run the reaction with excess of alkyl halide

In that case the product will be the quaternary salt where the amine has been fully alkylated
Acylation

The amines can also be reacted with acid chlorides to generate amides

\[
\begin{align*}
\text{CH}_3\text{COOH} & \xrightarrow{\text{SOCl}_2} \text{CH}_3\text{COCl} \\
\text{CH}_3\text{Cl} & \quad \text{CH}_3\text{NH}_2 \\ 
\rightarrow & \quad \text{CH}_3\text{CONHCH}_3
\end{align*}
\]

The amide does not generally react further because the lone pair of electrons is delocalized

\[
\begin{align*}
\text{CH}_3\text{ONHCH}_3 & \leftrightarrow \text{CH}_3\text{NO}^+\text{CH}_3
\end{align*}
\]
Acylation to Modify Aromatic Reactivity

Remember that aniline is highly reactive and the amine is basic

\[
\begin{align*}
\text{NH}_2 \quad \xrightarrow{\text{HNO}_3} \quad \text{NH}_3^+
\end{align*}
\]

With acylation, however, the compound can be reacted under acidic conditions without protonating the amine

\[
\begin{align*}
\text{NH}_2 \quad \xrightarrow{\text{CH}_3\text{Cl}} \quad \text{NH}_2\text{CO} \quad \xrightarrow{\text{HNO}_3} \quad \text{NH}_2\text{CONH}_2
\end{align*}
\]
Hydrolysis of Aryl Acetyl Group

Once used, the acetyl group can be hydrolyzed off in either acidic or basic conditions.

Thus the acetylation of aniline derivatives are quite useful to modify reactivity.
Sulfonamides

Sulfonamides are widely used as antibacterial agents (called “sulfa drugs”)

To synthesize sulfonamides follow similar reactivity as acylation reactions
Use sulfonyl chloride instead of acid chloride
Hofmann Elimination

Remember E2 mechanisms where eliminations occurred with either Saytzeff or Hofmann preference

For these reactions the Saytzeff was generally favored due to the more stable product

Hofmann was observed when the base was too bulky to abstract the hydrogen from the more substituted carbon
The Hofmann product in these E2 reactions is named after amine elimination reactions.

When an amine is alkylated with excess alkyl halide, a quaternary amine is obtained.

\[
\text{NH}_2CH_3 + \text{CH}_3\text{I} \rightarrow \text{N}^+\text{CH}_2\text{CH}_2\text{CH}_3
\]

The amine is now a good leaving group.

When heated with base, the amine can leave to generate an alkene.
When different alkenes can form, the less substituted alkene is preferred

\[ \text{Ag}_2\text{O} \]

A very common base to use in Hofmann eliminations is Ag\(_2\)O, the silver oxide reacts with halide of amine salt to form silver halide (AgI) and hydroxide.

The reason for this preference compared to other E2 reactions is the bulkiness of the quaternary amine leaving group.

E2 reactions must be anticoplanar.
Cope Elimination

Another method to have an amine elimination from a compound is the Cope elimination.

Instead of an E2 base mechanism, the Cope occurs through an oxidation mechanism. A tertiary amine is oxidized to an amine oxide:

\[
\text{oxidation}\quad \overset{\text{N}}{\text{O}}\quad \overset{\text{N}}{\text{O}}(\text{primary amines are oxidized to nitro and secondary amines are oxidized to hydroxylamines})
\]

Amine oxides will eliminate without base:

\[
\overset{\text{N}}{\text{O}}\quad \overset{\text{N}}{\text{O}}\quad \overset{\text{N}}{\text{O}}\quad \overset{\text{N}}{\text{O}}(\text{C}_3\text{H}_2)\quad \overset{\text{N}}{\text{O}}\quad \overset{\text{N}}{\text{O}}\quad \overset{\text{N}}{\text{O}}(\text{HO-N(CH}_3)\text{)}_2
\]
Diazonium Salts

Primary amines will react with nitrous acid to form diazonium salts

\[
\begin{align*}
\text{NaNO}_2 & \quad \text{H}^+ \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{HONO} \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{N}^=\text{O} \quad \text{H}_2\text{O} \\
\text{N}^=\text{O} & \quad \text{RNH}_2 \quad \underset{-\text{H}^+}{\longleftrightarrow} \quad \text{RN}^=\text{N}^=\text{O} \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{RN}^=\text{N}^=\text{N} \quad \text{OH} \\
\text{RN}^=\text{N}^=\text{N} \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{RN}^=\text{N}^=\text{N} \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{RN}^=\text{N}^=\text{N}\quad \text{N}_2
\end{align*}
\]

The key step is that the nitrogen will leave to generate a carbocation

\[
\begin{align*}
\text{RN}^=\text{N}^=\text{N} \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{RN}^=\text{N}^=\text{N} \quad \underset{\text{H}^+}{\longleftrightarrow} \quad \text{RN}^=\text{N}^=\text{N}\quad \text{N}_2
\end{align*}
\]
Arenediazonium Salts

While the generation of alkyl carbocations with this method is unnecessary (there are many other more efficient ways to generate alkyl carbocations), it is a unique method to generate aryl substituted products.

First the arenediazonium salt is generated from an aniline derivative

\[
\text{NH}_2 \quad \xrightleftharpoons{\text{NaNO}_2, \text{HCl}} \quad \text{N}^{+} \equiv \text{N}
\]
The nitrogen leaving group \( (N_2) \) can then be replaced in a second step

**Example of unique potential products:**

\[
\begin{align*}
\text{Convenient method to generate phenol derivatives} \\
\text{(other method is usually a nucleophilic aromatic substitution)} \\
\text{It is difficult to generate an oxygen electrophile} \\
\text{to perform a typical electrophilic aromatic substitution}
\end{align*}
\]
Briefly saw in aromatic substitution chapter that fluorine substituted aromatic rings can be obtained through an arenediazonium pathway.

\[
\begin{align*}
\text{ArN}^+\cdot\text{N}_2 & \xrightarrow{\text{HBF}_4} \text{ArF} \\
\end{align*}
\]

There are few other methods to add fluorine in a preferred regio manner to an aromatic ring.
Arenediazonium salts are often reacted with Cu(I) salts. This reaction is called a Sandmeyer reaction.

- Reaction with CuCl: Arenediazonium salt + CuCl → product with chlorine
- Reaction with CuBr: Arenediazonium salt + CuBr → product with bromine
- Reaction with CuCN: Arenediazonium salt + CuCN → product with cyano

Common substituents to add are chlorine, bromine or cyano with this route.
Replacing Diazonium group with Hydrogen

\[
\begin{align*}
\text{H}_3\text{PO}_2 & \rightarrow \text{H} \\
\end{align*}
\]

Allows an amine to be used as a directing group and then subsequently removed

\[
\begin{align*}
\text{Br}_2 & \rightarrow \text{Br} \quad 1) \text{NaNO}_2, \text{HCl} \\
\text{H}_3\text{PO}_2 & \rightarrow \text{Br} \\
\end{align*}
\]

Would not be able to synthesize bromines meta to each other without this type of method
Synthesis of Amines

Instead of alkylating amines, which lead to overalkylation problems, amines can be created from imine sources

\[
\begin{align*}
\text{O} & \quad \text{NH}_2\text{OH} \quad \text{H}^+ \quad \overset{\text{N-OH}}{\text{N}}
\end{align*}
\]

To synthesize primary amines, react ketone or aldehyde with hydroxylamine to generate an oxime. Once oxime is synthesized, it can be reduced to form an amine.

Use different ketones or aldehydes to add different alkyl groups to amine.
Secondary Amines

Instead of reacting hydroxylamine, react with primary amine to form imine then reduce

Tertiary Amines

React carbonyl with secondary amine to form an imminium salt, the imminium salt is unstable and must be reduced in situ, therefore a weaker reducing agent is used
Another route to substituted amines is to first acylate and then reduce. With the amide functionality, reduction with LAH yields the amine. Can therefore generate either a 1°, 2° or 3° amine depending upon amide used in acylation step.
Gabriel Synthesis

Sometimes is is easier to use an alkyl halide than to obtain the necessary ketone, aldehyde or acid chloride needed in the previous steps.

The problem with using alkyl halides with an amine was the issue of polyalkylation.

Gabriel synthesis uses a phthalimide to prevent overalkylation.

The hydrazine reacts with the phthalimide carbonyls to have the substituted amine as a leaving group.
Another Synthetic Route:
Reduce other Nitrogen Containing Nucleophiles

There are a couple of other strong nucleophile that can be reduced to an amine

**Azides**

\[
\text{Br} \quad \xrightarrow{\text{NaN}_3} \quad \text{N}_3 \quad \xrightarrow{\text{LAH}} \quad \text{NH}_2
\]

**Nitriles**

\[
\text{Br} \quad \xrightarrow{\text{NaCN}} \quad \text{CN} \quad \xrightarrow{\text{LAH}} \quad \text{NH}_2
\]

Both of these routes use a $S_{N}2$ reaction followed by reduction to amine

Realize that cyano (nitrile) route adds one additional carbon to framework
Reduction of Nitro Group

Both alkyl and aryl nitro groups can be reduced to an amine

\[
\begin{align*}
\text{NO}_2 & \quad \text{H}_2, \text{catalyst} \quad \text{NH}_2 \\
\end{align*}
\]

This reduction can occur under a wide variety of conditions

Usually see either \( \text{H}_2 \) and a catalyst (Pt, Pd and Ni are common)

or

Use active metal with \( \text{H}^+ \) source (e.g. Sn, \( \text{H}_2\text{SO}_4 \) or Zn, HCl)
Hofmann Rearrangement

The main advantage of this method is to generate amines on 3° carbons. Realize that with $S_N2$ methods cannot place amine on 3° carbon.

Hofmann rearrangement starts with primary amide that can be generated from the acid chloride.

Upon introduction of basic halide solution ($Br_2$ or $Cl_2$) an amine is obtained.

The reaction is driven by loss of carbon dioxide.
Key is formation of the isocyanate (R-N=C=O structure) which reacts in basic conditions to form carbamic acid, which subsequently decarboxylates to amine