Learning Guide for Chapter 23: Amines

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I. Introduction to amines

Amines are considered to be organic derivatives of ammonia. They are classified as primary, secondary, or tertiary depending on how many alkyl or aryl groups are attached to the N. Quaternary ammonium salts have four alkyl groups and bear a positive charge. Amines may also be part of heterocyclic rings.



The nitrogen in an amine is sp³hybridized (unless it can contribute to the pi system of an aromatic ring). Amines with three different groups attached to the nitrogen are chiral, but the enantiomers cannot be isolated because they quickly racemize. The electron pair briefly goes into a p orbital and back again, inverting the stereocenter.



Quaternary ammonium salts are also sp^{3} hybridized, but since they have no lone pair of electrons, they cannot invert, and enantiomers can be isolated.



Amines are quite polar because of the N-H bonds. Primary and secondary amines are also capable of hydrogen bonding with neighboring molecules. Tertiary amines can only form hydrogen bonds with compounds containing partially positive hydrogens (such as alcohols or water).



Amines and alcohols are soluble in each other, and amines with up to 6 carbons are soluble in water. The boiling points of primary and secondary amines are lower than alcohols because nitrogen is not as electronegative as oxygen, but higher than ethers. Tertiary amines are lower than ethers.



Small molecular weight amines have strong, unpleasant odors.



rotting fish

cadaverine

Alkaloids are complex organic compounds containing nitrogen which are bitter in taste and usually obtained from seed plants. Many are used as drugs or medicines because of their high degree of biological activity.



nicotine



ephedrine an adrenal hormone



niacin a vitamin



methamphetamine an addictive stimulant



histamine dilates blood vessels



II. Nomenclature of amines

Common names are often used for simple amines. They are similar to common names for alkyl halides and alcohols.



Amines are a principle group, but they have lower priority than any other group. When they are the principle group, the name ends in "amine". When named as a substituent, they are called amino groups.

aldehydes > ketones > alcohols > amines

















III. Spectroscopy of Amines

IR: N-H bonds occur at 3200-3400 cm⁻¹

primary (NH_2) have two bands, secondary (NH) have one band, tertiary (N) have no bands primary amines may also show an NH_2 scissor band at 1600 cm⁻¹



NMR: amine H's often give broad peaks. The chemical shift varies, but is usually found between 1 and 5 ppm. Amine H's exchange with D_2O . H's on neighboring C's appear around 2.5-3.0 ppm.

2.6 ppm (2H, t) 1.7 ppm (2H, broad s) 1.4 ppm (2H, hextet) 0.9 ppm (3H, t)

/// NH₂

IV. Acid/base properties of amines

The lone pair of electrons on an amine can act as a nucleophile or a base. Amines are the most common organic bases. The pK_a of the ammonium ion is 9.4; pK_a 's of alkyl amine salts are around 10.



Any acid with a pK_a lower than 10 can protonate an amine. Amines are readily protonated by dilute mineral acids, or by carboxylic acids, which have pK_a 's around 5.



Aniline is much less basic than alkyl amines. The pK_a of its conjugate acid is 4.62. The electrons on N are in conjugation with the pi system of the ring, and are less available for bonding to H's. Electron withdrawing groups make aniline even less basic, while electron-donating groups make it somewhat more so.



Pyridine is also less basic than alkyl amines; its conjugate acid has a pK_a of 5.25. This is because the electrons on N are in an sp²hybridized orbital rather than an sp³hybridized orbital. This analogy follows what happens with carbon anions - an alkyl anion is much more basic than an alkyne anion.



Any amine in which the lone pair is involved in an aromatic pi system is very weakly basic, because once the compound is protonated it loses aromaticity. The amine salt of pyrrole has a pK_a of approximately -1, similar to hydronium ion.



Once an amine has been protonated, it is an ionic compound. Amine salts are solids, and are usually soluble in water but insoluble in organic solvents. Most biologically active amines are used as their amine salts, which dissolve to make injectable or drinkable water solutions, and are also less prone to oxidation and decomposition.

This property can be used to separate amines from other organic chemicals. They mixture is extracted with dilute aqueous acid, which converts the amine to the amine salt which is soluble in the water layer. After the separation, treatment with dilute base restores the amine.



Amines are amphoteric, meaning that they can be both acids and bases. However, they are very weak acids. Sodium metal or an organolithium agent is required to form the conjugate base. These bases can be very useful once formed.



Unlike amine salts, quaternary ammonium salts are soluble in organic solvents because of the large proportion of hydrocarbon in the molecule. They are often used as phase transfer catalysts because they can form an ionic bond with an nucleophile and carry it into the organic layer, then carry the ionic byproduct back to the water layer.



V. Reactions with alkyl halides and tosylates

Alkylation of amines by alkyl halides

Amines act as nucleophiles in S_N^2 reactions. However, once the product is formed it continues to react, and a mixture of products is usually obtained.

Overalkylation can sometimes be avoided by using ammonia as the solvent, so that it is in a large excess.



Or, taking the reverse strategy, if an excess of the alkyl halide is used, this reaction can be useful for making quaternary ammonium salts. When methyl halides are used, it is called exhaustive methylation.

The Hofmann elimination

Quaternary ammonium salts with small alkyl groups can serve as leaving groups in E2 reactions. After exhaustive methylation, the salt is treated with Ag_2O and water, which react together to form a hydroxide ion, which exchanges with the halide ion. Heating this salt causes an E2 reaction to occur.



The regioselectivity of this reaction is opposite from what we have encountered with alkyl halides. The least substituted alkene is formed. The reasoning for this is that the leaving group is unusually bulky, and the more substituted H's have a more difficult time achieving the anti conformation needed for the E2 reaction to occur.



Gabriel synthesis of primary amines

An excellent synthesis of primary amines makes use of a compound called phthalimide. It is like a double amide, and the NH has a pK_a of 8.3. When deprotonated by NaOH, it becomes a good nucleophile in S_N2 reactions with primary alkyl halides or tosylates.



Once the alkyl group has been added, the free amine is obtained either treatment with hydrazine or by hydrolysis of the amide groups using acid, water, and heat, followed by mild base to deprotonate the amine.



Synthesize the following amines using the Gabriel synthesis.





VII. Reactions with aldehydes and ketones

Formation of imines and enamines

Recall from our study of aldehydes and ketones that they react with ammonia, primary, and secondary amines under mildly acidic conditions to form imines or enamines.

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

$$\overrightarrow{H^{+}}$$

Reductive amination

Primary, secondary, and tertiary amines can be formed by reacting ammonia, a primary amine, or a secondary amine with an aldehyde or ketone to form an imine or enamine, then reducing it to form the amine.

$$\bigcup = \dddot{i} + \checkmark \dddot{i} H_2 \xrightarrow{H^+} \xrightarrow{H_2, Pd/C}$$

Both of these reactions can be performed in the same reaction vessel by a process called reductive amination. A reducing agent is used which will react with the imine or enamine, but not with the original aldehyde or ketone. Reagents which accomplish this are catalytic hydrogenation, sodium cyanoborohydride, and pyridine-borane.



VII. Reactions with acid chlorides

Amides are formed when acid chlorides react with ammonia, primary or secondary amines. The amine attacks the carbonyl carbon, pushing the electrons onto the oxygen. The electrons then come down, pushing off the chloride.

In order to deprotonate the amide, two equivalents of the amine must be used, or a nonnucleophilic amine such as triethyl amine or pyridine must be included.





Amides can be reduced by lithium aluminum hydride, a strong reducing agent. Formation of an amide followed by reduction to the amine gives a more substituted amine.



How could the following amines be formed by reduction of an amide?







VIII. Reduction of other groups to form amines

Nitro groups

Nitro groups are easily reduced to amines. This is most commonly used to make aryl amines, since nitro groups are added to benzene rings by nitration. Catalytic hydrogenation or acid and an active metal (Fe, Sn, Zn) may be used; in this case a base is needed in the second step to deprotonate the ammonium ion.



<u>Azides</u>

Sodium azide is an anion with three nitrogens. It can act as a nucleophile in S_N^2 reactions with primary alkyl halides or tosylates to form azides.



Azides can be reduced with catalytic hydrogenation or lithium aluminum hydride to form primary amines.



<u>Nitriles</u>

Nitriles are formed by the reaction of cyanide with primary alkyl halides or tosylates. Cyanohydrins are made by reacting cyanide with aldehydes or ketones. We will also see a way to make aryl cyanides later in this chapter.



Nitriles and cyanohydrins are also reduced to primary amines by catalytic hydrogenation or lithium aluminum hydride.



In what ways could the following amines be synthesized?









IX. Reactivity of anilines

Aromatic substitution

An amino group is strongly activating in the electrophilic aromatic substitution reaction. Less strenuous conditions are needed, and often all ortho and para positions are substituted.

However, care must be taken to avoid acidic conditions. Once the amine has been protonated, it has a positive charge and is a deactivating, meta directing group.

This problem may be avoided by converting the amine to an amide. Amides are not basic, but are still activating and ortho/para directing when the nitrogen is attached to the ring. The amine may be recovered by hydrolysis of the amide.



Formation and reactions of diazonium ions

Amines react with nitrous acid (HNO_2) to form diazonium ions. Nitrous acid is unstable, so it is formed *in situ* by combining sodium nitrite to dilute aqueous HCl.



The neutral N_2 molecule is the world's best leaving group. Alkyl diazonium ions are so reactive that they immediately undergo a mixture of S_N1 and E1 reactions, which aren't very useful except as a test for alkyl amines.



Aryl diazonium ions are stable because carbocations do not form on benzene rings. They are not usually isolated because they are explosive when dry. They react with Cu^{+1} salts and other reagents to give a variety of useful products.





These reactions greatly enhance our toolbox for constructing substituted benzene rings.

