

## Amines

**Reading:** Wade chapter 19, sections 19-1-19-19

**Study Problems:** 19-37, 19-39, 19-40, 19-41, 19-44, 19-46, 19-47, 19-48, 19-51, 19-54

### **Key Concepts and Skills:**

- Explain how the basicity of amines varies with hybridization and aromaticity
- Predict the products of reactions of amines with ketones and aldehyde, alkyl halides and tosylates, acid chlorides, sulfonyl chlorides, nitrous acid, and oxidizing agents, and arylamines with electrophiles.
- Give examples of the use of arenediazonium salts in diazo coupling reactions and in the synthesis of aryl halides and nitriles..
- Illustrate the uses and mechanisms of the Hoffmann and Cope eliminations, predicting major products.
- Show how to synthesize amines from other amines, ketones, aldehydes, acid chlorides, nitro compounds, alkyl halides, nitriles, and amides

### **Lecture Topics:**

#### **I. Amines: structure and nomenclature**

Amines are derivatives of ammonia with one or more alkyl groups attached to nitrogen. Primary amines have one alkyl group on nitrogen; secondary amines have two alkyl groups on nitrogen; tertiary amines have three alkyl groups on nitrogen; quaternary ammonium salts have four alkyl groups on nitrogen.

### **A. Structure of Amines**

Amines have  $sp^3$  hybridization at nitrogen and tetrahedral geometry. Rapid inversion at nitrogen means that chiral amines cannot be resolved.

However, chiral quaternary ammonium salts can be resolved and isolated; also, amines that are constrained in small rings and thus have a high energy barrier for attaining the planar  $sp^2$  hybridized nitrogen of the transition state for interconversion can also be resolved and isolated.

## **II. Physical Properties of Amines**

Primary and secondary amines can form hydrogen bonds with themselves and protic solvents. Amine-amine hydrogen bonds are weaker than those present in alcohol solvents, since the NH bond is less polar (due to the lower electronegativity of N relative to O) than the OH bond. All amines, including tertiary amines, are soluble in water to to hydrogen bonding. Since tertiary amines cannot hydrogen bond with themselves, they have lower boiling points than primary and secondary amines, which have lower boiling points than alcohols of the same molecular weight.

### **III. Amine Basicity**

Amines are both nucleophilic and basic:

Aqueous solutions of amines are basic; stronger bases have smaller values of  $pK_b$ :

#### **Structural Effects on basicity**

Addition of alkyl groups is expected to increase the basicity of amines by inductive stabilization of the cationic (ammonium ion) conjugate acid; indeed in the gas phase, trialkyl amines are more basic than secondary amines, which are more basic than primary amines. In solution, however, differential solvation effects level the basicities of 1°, 2°, and 3° amines; increasing number of alkyl groups decreases the ability of the solvent to stabilize the positively charged ammonium cation. Thus, the basicities of 1°, 2°, and 3° amines are about equal.

### **Resonance Effects on Basicity**

Aromatic amines are weaker bases than aliphatic amines because of N lone pair resonance delocalization into the aromatic pi system. Such charge delocalization is broken up upon protonation:

### **Hybridization Effects on Amine Basicity**

Nitrogen lone pairs in sp orbitals are closest to the nucleus and are thus the most stable and least basic. Nitrogen lone pairs in sp<sup>3</sup> orbitals are furthest from the nucleus, least stable, and most basic.

## **IV. Ammonium Salts**

Protonation of amines by acids results in the formation of ammonium salts. While amines have strong odors, ammonium salts are odorless. Ammonium salts are also more stable than amines (amines are prone to oxidation in air); they are more soluble in water and tend to be insoluble in organic solvents. Acidifying an amine present in an organic solvent results in transfer of the ammonium salt to the aqueous phase; basicifying an aqueous phase deprotonates the ammonium salt, resulting in an organic-soluble amine. One can take advantage of this process to purify amines by acid-base extraction.

Quaternary ammonium salts are used as phase-transfer catalysts to make insoluble reagents soluble in organic media. A common application is phase transfer of hydroxides or alkoxides into organic phase where reactions such as deprotonation and/or alkylation may take place.

## **V. Spectroscopy**

In infrared spectra, the N-H stretch is observable from  $3200\text{-}3500\text{ cm}^{-1}$ .  $1^\circ$  amines, with two N-H bonds, display 2 spikes in the  $3200\text{-}3500\text{ cm}^{-1}$  absorption.  $2^\circ$  amines show only one spike, and  $3^\circ$  amines show no NH absorption.

## **VI. Reactions of Amines**

### **A. Formation imines, enamines, oximes and hydrazones**

These reactions occur under slightly acidic conditions (pH 4.5) and usually involve the loss of water. The reactions are condensations of amines with aldehydes and ketones.

## **B. Aryl amines**

Aryl amines are activated for electrophilic aromatic substitution; the amino group is a strong ortho-para director. The reactivity of the amino group is attenuated by acylation to form the aryl amide. In contrast, acidic reagents tend to protonate aryl amines, forming ammonium ions that are strongly deactivating and meta directing.

## **C. Reactions of Pyridine**

Pyridine is deactivated toward electrophilic aromatic substitution because of the presence of the electron-withdrawing nitrogen atom in the ring. Because the pyridine lone pair is perpendicular to the pi system of the ring, there is no stabilization of neighboring positive charges on the ring. As a result, 2-substitution is not observed, and in general 3-substituted pyridines are favored. An additional problem is that the basic/nucleophilic nitrogen atom of the ring may directly react with the electrophile.

Nucleophilic aromatic substitution of pyridine occurs readily with electron rich nucleophiles. Nucleophilic aromatic substitution occurs at the 2 position, because placing a negative charge on nitrogen is favorable:

