Objectives

After completing this section, you should be able to

1. account for the basicity and nucleophilicity of amines.
2. explain why amines are more basic than amides, and better nucleophiles.
3. describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
4. explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids, and illustrate the synthetic usefulness of the strong bases that can be formed from these weak acids.

Key Terms

Make certain that you can define, and use in context, the key term below.

• amide

Study Notes

The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles. Indeed, we have seen in past chapters that amines react with electrophiles in several polar reactions (see for example the nucleophilic addition of amines in the formation of imines and enamines in Section 19.8).

The ammonium ions of most simple aliphatic amines have a \( pK_a \) of about 10 or 11. However, these simple amines are all more basic (i.e., have a higher \( pK_a \)) than ammonia. Why? Remember that, relative to hydrogen, alkyl groups are electron releasing, and that the presence of an electron-releasing group stabilizes ions carrying a positive charge. Thus, the free energy difference between an alkylamine and an alkylammonium ion is less than the free energy difference between ammonia and an ammonium ion; consequently, an alkylamine is more easily protonated than ammonia, and therefore the former has a higher \( pK_a \) than the latter.

Basicity of nitrogen groups

In this section we consider the relative basicity of several nitrogen-containing functional groups: amines, amides, anilines, imines, and nitriles. When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen?
Comparing the basicity of alkyl amines to ammonia

Because alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine’s nitrogen greater than the nitrogen of ammonium. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.

Comparing the basicity of alkylamines to amides

With an alkyl amine the lone pair electron is localized on the nitrogen. However, the lone pair electron on an amide are delocalized between the nitrogen and the oxygen through resonance. This makes amides much less basic compared to alkylamines.

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{H} & \quad \text{H} & \quad \text{C} & \quad \text{N}^+ \\
\text{H}_3\text{C} & \quad \text{H} & \quad \text{O}^- & \quad \text{H} \\
\end{align*}
\]

In fact, when an amide is reacted with an acid, the protonation occurs at the carbonyl oxygen and not the nitrogen. This is because the cation resulting from oxygen protonation is resonance stabilized. The cation resulting for the protonation of nitrogen is not resonance stabilized.

Basicity of heterocyclic amines

When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context. In a pyridine ring, for example, the nitrogen lone pair occupies an \( sp^2 \)-hybrid orbital, and is \textit{not} part of the aromatic sextet - it is essentially an imine nitrogen. Its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.

In a pyrrole ring, in contrast, the nitrogen lone pair \textit{is} part of the aromatic sextet. This means that these electrons are very stable right where they are (in the aromatic system), and are much less available for bonding to a proton (and if they \textit{do} pick up a proton, the aromatic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic.
The aniline, pyridine, and pyrrole examples are good models for predicting the reactivity of nitrogen atoms in more complex ring systems (a huge diversity of which are found in nature). The tryptophan side chain, for example, contains a non-basic ‘pyrrole-like’ nitrogen, while adenine (a DNA/RNA base) contains all three types.

The lone pair electrons on the nitrogen of a nitrile are contained in a sp hybrid orbital. The 50% s character of an sp hybrid orbital means that the electrons are close to the nucleus and therefore not significantly basic.

A review of basic acid-base concepts should be helpful to the following discussion. Like ammonia, most amines are Brønsted and Lewis bases, but their base strength can be changed enormously by substituents. It is common to compare basicity’s quantitatively by using the pKₐ’s of their conjugate acids rather than their pKₓ’s. Since pKₐ + pKₓ = 14, the higher the pKₐ the stronger the base, in contrast to the usual inverse relationship of pKₐ with acidity. Most simple alkyl amines have pKₐ’s in the range 9.5 to 11.0, and their water solutions are basic (have a pH of 11 to 12, depending on concentration). The first four compounds in the following table, including ammonia, fall into that category.

The last five compounds (colored cells) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In pyridine the nitrogen is sp² hybridized, and in nitriles (last entry) an sp hybrid nitrogen is part of the triple bond. In each of these compounds (shaded red) the non-bonding electron pair is localized on the nitrogen atom, but increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton.
Finally, the very low basicity of pyrrole (shaded blue) reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic ring. Indole (pK\textsubscript{a} = -2) and imidazole (pK\textsubscript{a} = 7.0), see above, also have similar heterocyclic aromatic rings. Imidazole is over a million times more basic than pyrrole because the sp\textsuperscript{2} nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.

Although resonance delocalization generally reduces the basicity of amines, a dramatic example of the reverse effect is found in the compound guanidine (pK\textsubscript{a} = 13.6). Here, as shown below, resonance stabilization of the base is small, due to charge separation, while the conjugate acid is stabilized strongly by charge delocalization. Consequently, aqueous solutions of guanidine are nearly as basic as are solutions of sodium hydroxide.

The relationship of amine basicity to the acidity of the corresponding conjugate acids may be summarized in a fashion analogous to that noted earlier for acids:

\begin{center}
\begin{itemize}
\item Strong bases have weak conjugate acids,
\item weak bases have strong conjugate acids.
\end{itemize}
\end{center}

\section*{Amine Extraction in the Laboratory}

Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids are dissolved, and (2) the extracting solvent. The two immiscible liquids are then easily separated using a separatory funnel. For amines one can take advantage of their basicity by forming the protonated salt (RNH\textsubscript{2}\textsuperscript{+},Cl\textsuperscript{-}), which is soluble in water. The salt will extract into the aqueous phase leaving behind neutral compounds in the non-aqueous phase. The aqueous layer is then treated with a base (NaOH) to regenerate the amine and NaCl. A second extraction-separation is then done to isolate the amine in the non-aqueous layer and leave behind NaCl in the aqueous layer.

\begin{center}
\begin{itemize}
\item First extraction
\item Second extraction
\end{itemize}
\end{center}
Acidity of Amines

We normally think of amines as bases, but it must be remembered that 1º and 2º-amines (not 3º-amines which have no N-H protons) are also very weak acids (ammonia has a $pK_a = 34$). In this respect it should be noted that $pK_a$ is being used as a measure of the acidity of the amine itself rather than its conjugate acid, as in the previous section. For ammonia this is expressed by the following hypothetical equation:

$$\text{NH}_3 + \text{H}_2\text{O} \rightleftharpoons \text{NH}_2(\text{-}) + \text{H}_2\text{O-H}(\text{+})$$

The same factors that decreased the basicity of amines increase their acidity. This is illustrated by the following examples, which are shown in order of increasing acidity. It should be noted that the first four examples have the same order and degree of increased acidity as they exhibited decreased basicity in the previous table. The first compound is a typical 2º-amine, and the three next to it are characterized by varying degrees of nitrogen electron pair delocalization. The last two compounds (shaded blue) show the influence of adjacent sulfonyl and carbonyl groups on N-H acidity. From previous discussion it should be clear that the basicity of these nitrogens is correspondingly reduced.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$</td>
<td>33</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5\text{NH}_2$</td>
<td>27</td>
</tr>
<tr>
<td>$\text{O}_2\text{N-} - \text{NH}_2$</td>
<td>19</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_4\text{NH}$</td>
<td>15</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$</td>
<td>10</td>
</tr>
<tr>
<td>$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2$</td>
<td>9.6</td>
</tr>
</tbody>
</table>

The acids shown here may be converted to their conjugate bases by reaction with bases derived from weaker acids (stronger bases). Three examples of such reactions are shown below, with the acidic hydrogen colored red in each case. For complete conversion to the conjugate base, as shown, a reagent base roughly a million times stronger is required.

$\text{C}_6\text{H}_5\text{SO}_2\text{NH}_2 + \text{KOH}$ a sulfonamide base
Important Reagent Bases

The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amide bases, and fill the gap in base strength between amines and amide salts. In the following table, $pK_a$ again refers to the conjugate acid of the base drawn above it.

<table>
<thead>
<tr>
<th>Base Name</th>
<th>Pyridine</th>
<th>Triethyl Amine</th>
<th>Hünig's Base</th>
<th>Barton's Base</th>
<th>Potassium t-Butoxide</th>
<th>Sodium HMDS</th>
<th>LDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td><img src="image" alt="Pyridine" /></td>
<td>(C$_2$H$_5$)$_3$N</td>
<td><img src="image" alt="Hünig's Base" /></td>
<td><img src="image" alt="Barton's Base" /></td>
<td>(CH$_3$)$_3$CO$^-$ K$^+$</td>
<td><img src="image" alt="Sodium HMDS" /></td>
<td><img src="image" alt="LDA" /></td>
</tr>
<tr>
<td>$pK_a$</td>
<td>5.3</td>
<td>10.7</td>
<td>11.4</td>
<td>14</td>
<td>19</td>
<td>26</td>
<td>35.7</td>
</tr>
</tbody>
</table>

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine ($pK_a$=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine ($pK_a$=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and like DBU is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of DBU or other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

Exercises
Questions

Q24.3.1

Select the more basic amine from each of the following pairs of compounds.

(a)

\[ \text{NH} \quad \text{or} \quad \text{O} \text{NH}_2 \]

(b)

\[ \text{NH} \quad \text{or} \quad \text{NaOH} \]

(c)

\[ \text{or} \]

Q24.3.2

The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

Solutions

S24.3.1

(a)

\[ \text{NH} \]

(b)
The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

Contributors

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

Objectives

After completing this section, you should be able to

1. use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
2. arrange a given series of arylamines in order of increasing or decreasing basicity.
3. discuss, in terms of inductive and resonance effects, why a given arylamine is more or less basic than aniline.

Study Notes

With reference to the discussion of base strength, the traditional explanation for the base-strengthening effect of electron-releasing (I) substituents is that such substituents help to stabilize the positive charge on an arylammonium ion more than they stabilize the unprotonated compound, thereby lowering ΔG°.

The electron-withdrawing (i.e., deactivating) substituents decrease the stability of a positively charged arylammonium ion.

Note that the arylammonium ion derived from aniline, PhNH₃⁺, is commonly referred to as the anilinium ion.
Basicity of aniline

Aniline is substantially less basic than methylamine, as is evident by looking at the pK$_a$ values for their respective ammonium conjugate acids (remember that the lower the pK$_a$ of the conjugate acid, the weaker the base).

This difference in basicity can be explained by the observation that, in aniline, the basic lone pair on the nitrogen is to some extent tied up in – and stabilized by – the aromatic p system.

This effect is accentuated by the addition of an electron-withdrawing group such as a carbonyl, and reversed to some extent by the addition of an electron-donating group such as methoxide.

In the case of 4-methoxy aniline (the molecule on the left side of the figure above), the lone pair on the methoxy group
donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the lone pair of the nitrogen more reactive. In effect, the methoxy group is ‘pushing’ electron density towards the nitrogen. Conversely, the aldehyde group on the right-side molecule is ‘pulling’ electron density away from the nitrogen, decreasing its basicity.

At this point, you should draw resonance structures to convince yourself that these resonance effects are possible when the substituent in question (methoxy or carbonyl) is located at the ortho or para position, but not at the meta position. An imine functional group is characterized by an sp²-hybridized nitrogen double-bonded to a carbon. Imines are somewhat basic, with pKₐ values for the protonated forms ranging around 7. Notice that this is significantly less basic than amine groups (eg. pKₐ = 10.6 for methylammonium), in which the nitrogen is sp³-hybridized. This phenomenon can be explained using orbital theory and the inductive effect: the sp² orbitals of an imine nitrogen are one part s and two parts p, meaning that they have about 67% s character. The sp³ orbitals of an amine nitrogen, conversely, are only 25% s character (one part s, three parts p). Because the s atomic orbital holds electrons in a spherical shape, closer to the nucleus than a p orbital, sp² hybridization implies greater electronegative than sp³ hybridization. Finally, recall the inductive effect from section 7.3C: more electronegative atoms absorb electron density more easily, and thus are more acidic. Moral of the story: protonated imine nitrogens are more acidic than protonated amines, thus imines are less basic than amines.

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**Contributors**

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**Acidity of Amines**

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\text{(CH}_3\text{)}_3\text{COH} + \text{NaH} & \rightarrow \text{(CH}_3\text{)}_3\text{CO}^-(\text{Na}^+) + \text{H}_2 \\
\text{(C}_2\text{H}_5\text{)}_2\text{NH} + \text{C}_4\text{H}_9\text{Li} & \rightarrow \text{(C}_2\text{H}_5\text{)}_2\text{N}^-(\text{Li}^+) + \text{C}_4\text{H}_{10} \\
\end{align*}
\]

a sulfonamide base
an alkoxide base
an amide base