Chapter 6

Amines and Amides
Bonding Characteristics of Nitrogen Atoms in Organic Compounds

Nitrogen (Group VA)
- 5 valence electrons
- forms 3 covalent bonds to complete octet

Structure and Classification of Amines

amine
- organic derivative of ammonia (NH₃) in which one or more alkyl, cycloalkyl or aryl groups are attached to nitrogen atom

amino group (functional group)
- the –NH₂ functional group
Classification of Amines

Primary amine (1º)
- amine in which nitrogen atom is bonded to one hydrocarbon group and two H atoms
- general formula: RNH₂

Secondary amine (2º)
- amine in which nitrogen atom is bonded to two hydrocarbon groups and one H atom
- general formula: R₂NH

Tertiary amine (3º)
- amine in which nitrogen atom is bonded to three hydrocarbon group and no H atoms
- general formula: R₃N
Classification of Amines

<table>
<thead>
<tr>
<th>Class</th>
<th>Molecular Structure</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMMONIA</td>
<td><img src="image" alt="NH₃" /></td>
<td>NH₃</td>
</tr>
<tr>
<td>PRIMARY AMINE</td>
<td><img src="image" alt="CH₃-NH₂" /></td>
<td>CH₃-NH₂</td>
</tr>
<tr>
<td>SECONDARY AMINE</td>
<td><img src="image" alt="CH₃-NH-CH₃" /></td>
<td>CH₃-NH-CH₃</td>
</tr>
<tr>
<td>TERTIARY AMINE</td>
<td><img src="image" alt="CH₃-N-CH₃" /></td>
<td>CH₃-N-CH₃</td>
</tr>
</tbody>
</table>

Fig. 6.1 (p.182)
Classification of amines is related to the number of R groups attached to the nitrogen atom.
Note: this classification differs from that for alcohols:
  1) for alcohols we look at how many R groups are on a C atom, 
     the hydroxyl-bearing C atom 
  2) for amines, we look at how many R groups are on the N atom 

Cyclic amines 
  - always either 2° or 3° 
  - are heterocyclic cmpds
Nomenclature for Amines

Common Names
- named by listing alkyl group or groups attached to nitrogen atom in alphabetical order and adding suffix – amine
- all one word
- prefixes di- and tr- when identical groups are bonded to the N atom

Summary of some common names:

<table>
<thead>
<tr>
<th>one word</th>
<th>two words</th>
<th>two or three words</th>
</tr>
</thead>
<tbody>
<tr>
<td>amines</td>
<td>alcohols</td>
<td>ethers</td>
</tr>
<tr>
<td>aldehydes</td>
<td>esters</td>
<td>ketones</td>
</tr>
</tbody>
</table>
IUPAC Naming
- similar to naming alcohols
- where alcohols are names as alkanols, amines are names as alkanamines

Rules for naming 1º amines:
1) select parent carbon chain as longest chain to which N atom is attached
2) name parent chain by changing –e ending of corresponding alkane name to –amine
3) number parent chain from end nearest the N atom
4) position of attachment of N atom is indicated by # in front of parent chain name
5) Identity and location of any substituents are appended to front of parent chain name
Note: in diamines the –e of the carbon chain name is retained
2° and 3° amines
- names as substituted 1° amines
- largest carbon group bonded to nitrogen is used as parent amine name
- names of other groups attached to nitrogen are appended to front of base name with N- or N, N- prefixes used to indicate these groups are attached to N atom rather than base carbon chain

Note: in amines where additional functional groups are present, the amine group is a substituent known as the amino group (NH₂)
### IUPAC nomenclature priority list:

<table>
<thead>
<tr>
<th>Increasing Priority</th>
<th>Carboxylic Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aldehyde</td>
</tr>
<tr>
<td></td>
<td>Ketone</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Amine</td>
</tr>
</tbody>
</table>

**Aromatic Amines**

- **Aniline**
  - simplest amino group bearing benzene ring based cmpd
  - simple aromatic amines names based on aniline

**Note:** 2º and 3º aromatic amines

- additional group or groups attached to N atom are located using capital N

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Fig. 6.2 (p.185)
Aniline, the simplest aromatic amine. Aromatic amines are generally toxic.
<table>
<thead>
<tr>
<th>IUPAC</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;o&lt;/sup&gt; (one word)</td>
<td>(one word)</td>
</tr>
<tr>
<td>alkananine</td>
<td>alkylamine</td>
</tr>
<tr>
<td>2&lt;sup&gt;o&lt;/sup&gt; (one word)</td>
<td>(one word)</td>
</tr>
<tr>
<td>N-alkylalkanamine</td>
<td>alkylalkylamine</td>
</tr>
<tr>
<td>3&lt;sup&gt;o&lt;/sup&gt; (one word)</td>
<td>(one word)</td>
</tr>
<tr>
<td>N-alkyl-N-alkylalkanamine</td>
<td>alkylalkylalkylamine</td>
</tr>
</tbody>
</table>
Isomerism for Amines

- constitutional isomerism in amines from several causes:
  1) different C atom arrangements produce isomers
  2) different positioning of N atom on carbon chain

Note: for 2° and 3° amines, different partitioning of C atoms among carbon chains present produces constitutional isomers
# Physical Properties of Amines

**Physical states**
- methyl- and ethyl-amines
  - gases at room temperature with ammonia-like odor
- most other amines
  - liquids with odors resembling raw fish
- some diamines
  - strong, disagreeable odors
- simpler amines
  - irritating to eyes, skin and mucous membranes
  - toxic by ingestion
- aromatic amines
  - generally toxic
  - readily absorbed through skin
  - affect blood and nervous system
Physical Properties

<table>
<thead>
<tr>
<th></th>
<th>C_1</th>
<th>C_3</th>
<th>C_5</th>
<th>C_7</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_2</td>
<td></td>
<td>C_4</td>
<td>C_6</td>
<td>C_8</td>
</tr>
</tbody>
</table>

Gas  Liquid

Fig. 6.3 (p.186)
Unbranched primary amines at room temperature and pressure.
**Boiling Points**
- intermediate btw alkanes and alcohols of similar molecular mass
  1) higher than alkanes
    - H-bonding possible btw amine molecules with this bonding involving H atoms and N atoms of amino groups
  2) lower than alcohols
    - N--H H-bonds are weaker than O--H H-bonds

**Solubility**
- amines with fewer than 6 carbons – infinitely soluble
- even 3º amines
  - water-soluble b/c amine N atom has nonbonding e⁻ pair that can form bond with H atom of water
Physical Properties

Fig. 6.4 (p.186)  
Amine-amine hydrogen bonding.

← Fig. 6.5 (p.186)  
Comparison of boiling points of unbranched primary amines and unbranched primary alcohols.
Physical Properties

Fig. 6.6 (p. 186)
Low-molecular amines are soluble in water because of amine-water hydrogen bonding interactions.
Basicity of Amines

Amines are weak bases
- accepts proton (H\(^+\)) from water to produce ammonium ion (NH\(_4^+\)) and hydroxide ion (OH\(^-\))

Substituted ammonium ion
- an ammonium ion in which one or more alkyl, cycloalkyl or aryl groups have been substituted for H atoms

3 generalizations apply
1) substituted ammonium ions are charged species rather than neutral molecules
2) N atom in ammonium ion or substituted ammonium ion participates in four bonds
3) substituted ammonium ions have common names derived from names of “parent amines”
   - replacement of word amine in name of “parent” amine with words ammonium ion
aromatic amines
- exhibit basic behavior in water with positive ion formed being called a substituted anilinium ion

Amine Salts
- rxn of acid with base to produce a salt
- b/c amines are bases, rxn with acid produces amine salt

amine salt
- an ionic cmpd in which the positive ion is a mono-, di- or trisubstituted ammonium ion (RNH$_3^+$, R$_2$NH$_2^+$ or R$_3$NH$^+$) and the negative ion comes from the acid
- named using standard nomenclature procedures for ionic cmpds
  i) positive ion (substituted ammonium or anilinium ion)
  ii) separate word for name of negative ion
- virtually all amine salts are water-soluble so formation of amine salt provides means for higher molecular mass amines to become water-soluble cmpds
- many drugs with amine functionalities are administered to patients as amine salts due to increased solubility in water
- reversible process
  - treating amine salt with strong base (NaOH) regenerates “parent” amine
Preparation of Amines and Quaternary Ammonium Salts

Preparation
- alkylation in presence of base
- two step process:
  Step 1: $1^\circ$ amine (as eg.) reacts with alkyl halide to form an amine salt
  Step 2: rxn of amine salt from step 1 with base (NaOH) to convert amine salt to free amine

Note: general and specific equation involving $1^\circ$, $2^\circ$ and $3^\circ$ amines will be presented in class
**quaternary ammonium salt**

- an ammonium salt in which all four groups attached to the nitrogen atom of the ammonium ion are hydrocarbon groups
- differ from amine salts in that addition of strong base does not convert quaternary ammonium salts back to “parent” amines
- colorless, odorless crystalline solids with high m.p. and are usually water-soluble
- named in same way as amine salts taking into account that four organic groups are attached to the nitrogen atom rather than a lesser number of groups
Heterocyclic Amines

**heterocyclic amine**
- an organic cmpd of which N atoms of amine groups are part of either an aromatic or a nonaromatic ring system
- several points to note:
  1) ring systems may be saturated, unsaturated or aromatic
  2) more than one N atom may be present in a given ring
  3) fused ring systems often occur

**Note:** heterocyclic amines often have strong odors, some agreeable and some disagreeable

eg. i) odor of popped popcorn
   ii) odor of roasted peanuts
- two most widely used central nervous system stimulants
  i) caffeine
  ii) nicotine
Heterocyclic Amines

Heterocyclic amines serve as “parent” molecules for more complex amine derivatives.

Fig. 6.8 (p.192)
**porphyrin**
- large cyclic structure built on four pyrrole rings
- important in chemistry of living organisms
- form metal ion complexes in which metal ion is located in middle of large ring structure

**heme**
- an iron-porphyrin complex in red blood pigment hemoglobin
  and responsible of oxygen transport in human body
**Biologically Important Amines**

**Neurotransmitter** (Fig.6.9, p.192)
- a chemical substance that is released at the end of a nerve, travels across the synaptic gap btw the nerve and another nerve, and then bonds to a receptor site on the other nerve, triggering a nerve impulse
- most important:
  i) acetylcholine
  ii) norepinephrine
    - maintains muscle tone in blood vessels
  iii) dopamine
    - in brain with a deficiency resulting in Parkinson’s disease (degenerative neurological disease)
  iv) serotonin
    - brain chemical involved in sleep perception and regulation of body temperature
    - deficiency has been implicated in mental illness
histamine
- heterocyclic amine
- responsible for unpleasant effects felt by individuals susceptible to hay fever and various pollen allergies
- natural in human body in “stored” form; in complex molecules
- there are triggers to release “stored” histamine (p.194)

antihistamines
- counteract the effects of histamine
- similar structural feature to histamine which allows it to block receptor site in nerves which may be occupied by histamine resulting in symptoms
Alkaloids

alkaloid
- a nitrogen-containing organic cmpd extracted from plant material
- 3 well-known alkaloids:
  1) nicotine – tobacco plant
  2) caffeine – coffee beans and tea leaves
  3) cocaine – coca plant
- alkaloids in medicine
  1) quinine – cinchona bark
     - used in treatment of malaria
  2) atropine – isolated for belladonna plant
     - used to dilate pupil of eye patients for examination
     - preoperative drup to relax muscles and reduce secretion of saliva in surgical patients
narcotic painkillers
  - class of drgs derived from resin (opium) of oriental poppy plant
  - important drugs: morphine and codeine
  - synthetic modification of morphine yields heroin

morphine
  - one of most effective painkillers (100X greater potency than aspirin
  - major drawback: addictive

codeine (methylmorphine)
  - less potent than morphine (potency 1/6 that of morphine)

heroin (diacetyl ester of morphine)
  - more than 3X painkilling effect of morphine
  - very addictive and not medically used in U.S.
Structure and Classification of Amides

**Amide**
- carboxylic acid derivative in which the carboxyl –OH group has been replaced with an amino or a substituted amino group

**Classification of amides**

1º amide
- amide in which two H atoms are bonded to the amide N atom (referred to as unsubstituted amide)
  - RC(O)NH₂

2º amide
- amide in which an alkyl (or aryl) group and a H atom are bonded to the amide N atom (referred to a monosubstituted amide)
  - RC(O)NHR
3° amide
- amide in which two alkyl (or aryl) groups and no H atoms are bonded to the amide N atom (referred to as disubstituted amides)
- RC(O)NR₂
- simplest amide
  - H atom attached to unsubstituted amide functional group
- simplest aromatic amide
  - benzene ring to which unsubstituted amide functional group is attached
- cyclic amide structures are possible
  - called lactams (parallel to term lactones used for cyclic esters)
Classification of Amides

Fig. 6.12 (p.198)
Primary, secondary, and tertiary amines and amides and the “H v. R” relationship.
Nomenclature for Amides

- for both IUPAC and common naming, amides are considered as derivatives of carboxylic acids and are named based on name of parent carboxylic acid

Rules:

1) ending of name of carboxylic acid is changed from –ic acid (common) or –oic acid (IUPAC) to –amide

2) names of groups attached to nitrogen (2° and 3° amides) are appended to front of base name, using an N- prefix a a locator

IUPAC vs. Common Names for Amides

<table>
<thead>
<tr>
<th>IUPAC</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>(one word)</td>
<td>(one word)</td>
</tr>
<tr>
<td>alkanamide</td>
<td>(prefix)amide</td>
</tr>
<tr>
<td>eg. ethanamide</td>
<td>eg. acetamide</td>
</tr>
</tbody>
</table>
Naming aromatic amides

- benzene ring with unsubstituted amide group is called benzamide
- other aromatic amides are named as benzamide derivatives
Selected Amides and Their Uses

1) urea – simplest naturally occurring amide
   - a water-soluble, white solid produced in the human body from CO₂ and NH₃ through complex series of metabolic rxns
   - formation of urea – human body’s primary method for eliminating waste “waste” nitrogen

2) melatonin (polyfunctional amide)
   - hormone that regulates sleep-wake cycle in humans
   - levels increase in evening and decrease close to morning
   - higher levels associated with longer and more sound sleep
   - concentration in blood decrease with age
   - as prescription drug, used to treat insomnia and jet lag
3) synthetic amides with physiological activity
   a) acetaminophen
      - replaced Aspirin in 1992 as over-the-counter pain reliever
      - derived from acetamide (Chemical Connections, p.203)
   b) barbituates
      - cyclic amide cmpds
      - group of prescription drugs that cause:
         relaxation (tranquilizers)
         sleep (sedatives)
         death (overdoses)
      - all are derivatives of barbuturic acid, a cyclic amide first
derived from urea and malonic acid
**Properties of Amides**

- do not exhibit basic properties in sol’n as amines do
- although N atom present in amides has nonbonding pair of electrons, these electrons are not available for bonding to H+ ion (due to polarity of C=O of amide)

**Physical States**

- methanamide, N-methyl and N,N-methyl derivatives
  - liquids at room temperature
- all other unbranched primary amides
  - solids at room temperature

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Fig. 6.14 (p.202)
Unbranched primary amines at room temperature and pressure.
melting point

1° amides

- even higher than corresponding carboxylic acid due to numerous intermolecular H-bonding possibilities btw amide H atoms and carbonyl O atoms

Fig. 6.15 (p.202)
The high boiling point of amides are related to the numerous amide-amide hydrogen bonding possibilities that exist.
2° amides
- fewer H-bonding possibilities since N atom has only one H atom and as a rule m.p. is lower

3° amides
- lower m.p. then 2° amides since no H-bonding possible

Solubility
- low molecular mass amides (up to 5-6 C atoms) are soluble in water (numerous H-bonding possibilities btw amide and water
- even disubstituted amides can participate in H-bonding
**Preparation of Amides**

- least reactive of common carboxylic acid derivatives
- can be synthesized from an acid chlorides, an acid anhydride, an ester, the carboxylic acid itself

**Amidification reaction**

- rxn of carboxylic acid with NH₃, 1º or 2º amine to give amide
- rxn conditions: - elevated temp. (greater than 100ºC)
  - dehydrating agent

**Note:** this rxn is similar to rxn of carboxylic acid with alcohol

- in both cases, H₂O is formed as by-product
Hydrolysis of Amides

amide hydrolysis
- most imp. rxn of amides
- bond btw carbonyl C atom and N atom is broken, and free acid and free amine are produced
- catalyzed by acids, bases and certain enzymes
- sustained heating is also often required

i) acidic conditions
- convert product amine to amine salt

ii) basic conditions (amide saponification)
- convert product carboxylic acid to acid salt
Reaxion Summary of Amines and Amides

**Alkylation of Amines**
- Reaction with an alkyl halide
- Basic condition (NaOH) required

  - Anmonia → 1° amine
  - 1° amine → 2° amine
  - 2° amine → 3° amine
  - 3° amine → quaternary ammonium salt

**Amination of Amines**
- Reaction with an amine
- Temperature of 180°C or greater
- No hydrazine as a catalyst

  - Anmonia → 1° amine
  - 1° amine → 2° amine
  - 2° amine → 3° amine

**Reversible Amine Salt Formation**

  - Acidic Conditions
    - Reaction of amine with a strong acid
    - Formation of amine salt

  - Basic Conditions
    - Reaction of amine salt with a strong base
    - Depoamination of amine salt occurs

**Hydrolysis of Amides**
- Heating is often required.

  - Acidic Hydrolysis
    - Hydrolysis with an acid (HCl)

  - Basic Hydrolysis (Saponification)
    - Hydrolysis with a base (NaOH)

  - Anlile → acid + amine salt
  - Anlile → acid salt + amine