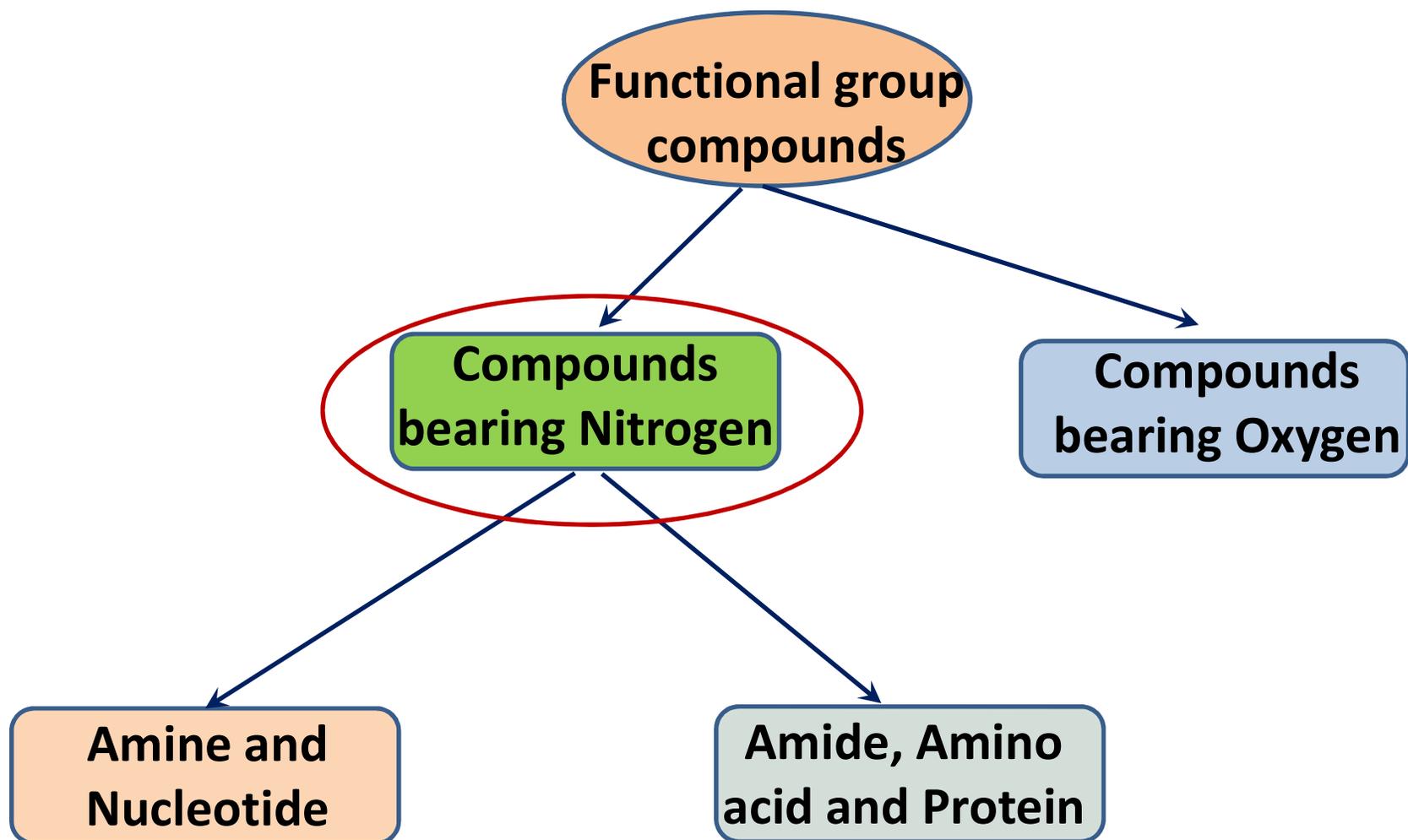
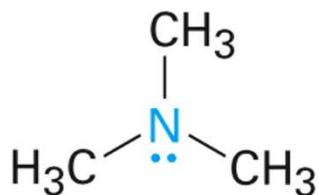


Chapter 5: Compounds bearing Nitrogen

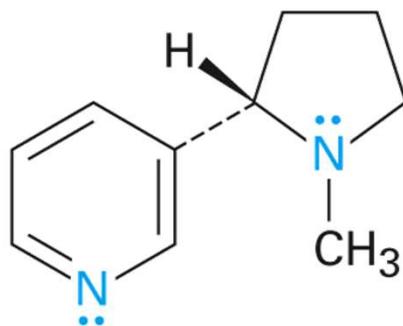


1. Amines

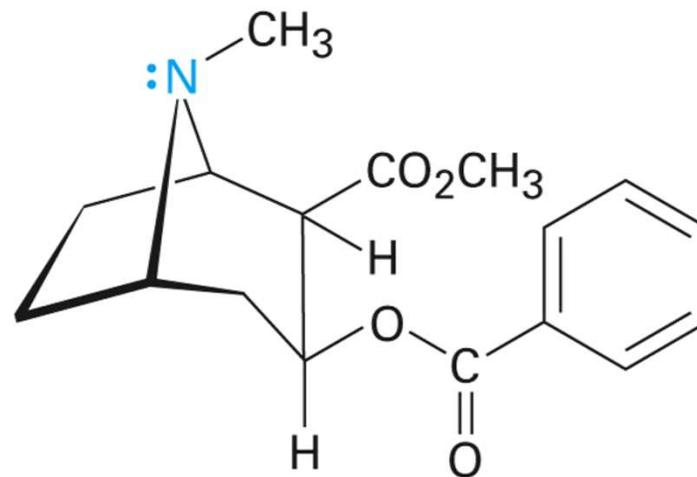
- ❑ Organic **derivatives** of ammonia, NH_3
- ❑ Nitrogen atom with **a lone pair** of electrons, making amines both **basic** and **nucleophilic**.
- ❑ Occur in plants and animals



Trimethylamine



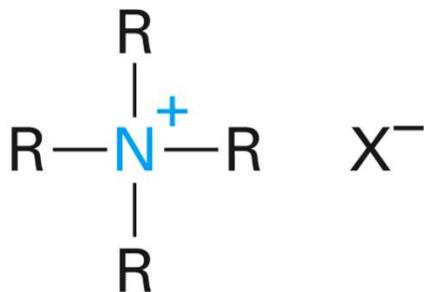
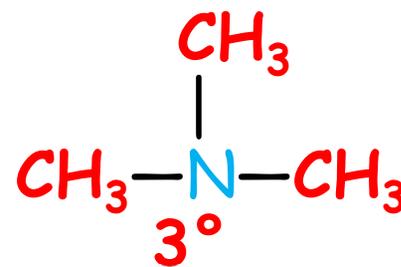
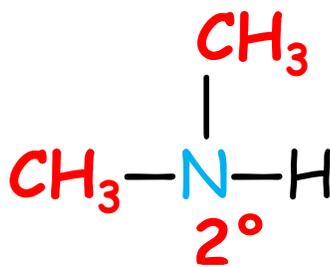
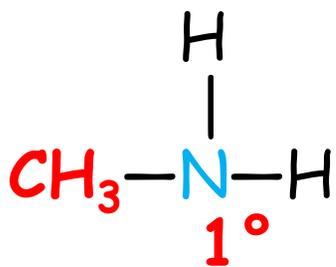
Nicotine



Cocaine

Classification of Amines

- **Primary** (1°) amine: one carbon group bonded to the nitrogen atom.
- **Secondary** (2°) amine: two carbon groups bonded to the nitrogen atom.
- **Tertiary** (3°) amine: three carbon groups bonded to the nitrogen atom.
- **Quaternary** ammonium salts: A nitrogen atom with four attached groups is positively charged



A quaternary ammonium salt

Common Nomenclature

For Simple Amines,

- Simple **1°** amines are named as "alkylamine"

examples

methylamine



ethylamine



butylamine



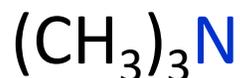
- Symmetrical **2°** or **3°** amines are named as "dialkylamine" or "trialkylamine"

examples

Diethylamine



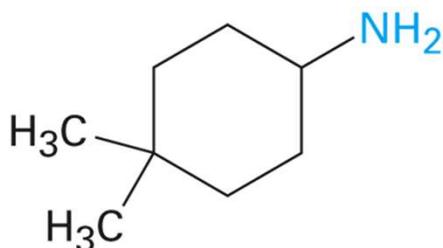
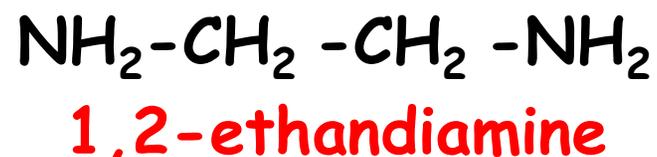
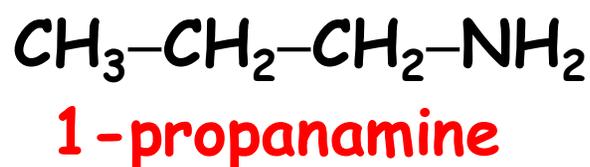
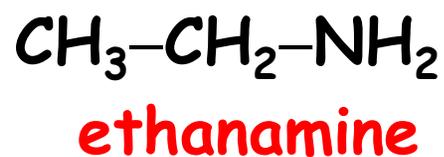
Trimethylamine



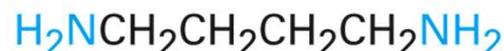
IUPAC Nomenclature

For 1° Amines,

- ❑ Find name of basic hydrocarbon
- ❑ Drop the “-e” from the alkane name; add “**amine**”.
- ❑ In front of name gives **location** of amino group
- ❑ Number and name of all substituents and write them in **alphabetical** order.



4,4-Dimethylcyclohexanamine



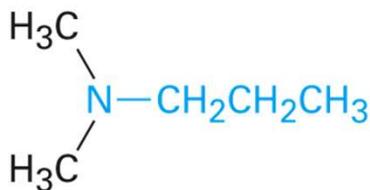
1,4-Butanediamine

Common and IUPAC Nomenclature: multiple

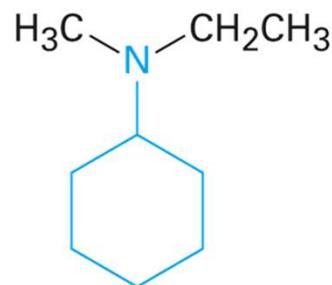
For Multiple, Different Alkyl Groups

□ Common Name:

- Named as *N*-substituted primary amines
- The largest alkyl group is the parent name, and other alkyl groups are considered *N*-substituents

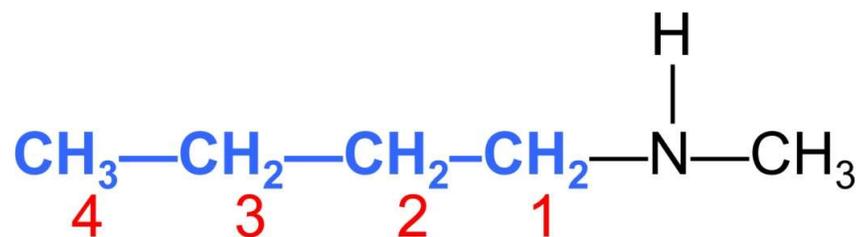


N,N-Dimethylpropylamine



N-Ethyl-*N*-methylcyclohexylamine

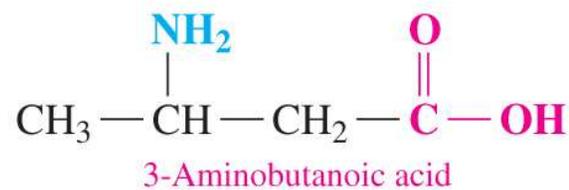
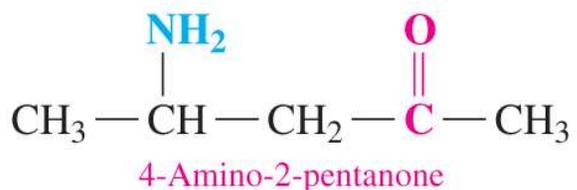
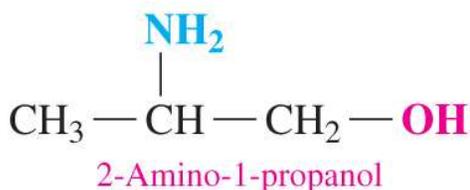
- ### □ (IUPAC) Name the longest carbon chain bonded to the N atom by replacing the *e* of its alkane name with *amine*.



N-methyl-1-butanamine.

Naming Compounds with Two Functional Groups

- When a compound contains **more than one** functional group, we need to identify which group is used as the name of the **compound** and which group is named as the **substituent**.
 - According to the IUPAC rules, an oxygen-containing group will have **priority over** an -NH_2 group.
- ➔ As a result, the -NH_2 group is named as the substituent, **amino**.



Aromatic Amines

The amine of benzene

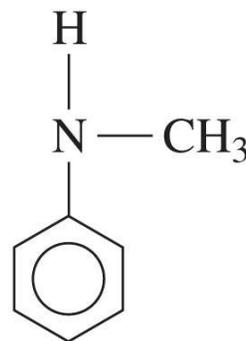
- is called **aniline**.
- may have alkyl groups attached to N that use the prefix **N-** and **the alkyl** name.



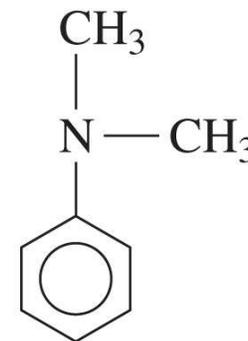
Aniline



4-Bromoaniline
(*p*-bromoaniline)



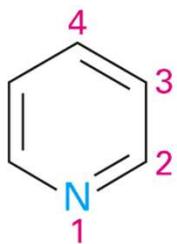
N-Methylaniline



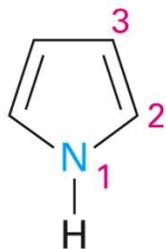
N,N-Dimethylaniline

Common Names of Heterocyclic Amines

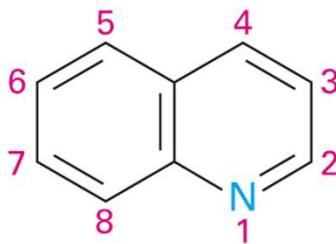
- If the nitrogen atom occurs as part of **a ring**, the compound is designated as being **heterocyclic**
- Each ring system has **its own parent name**



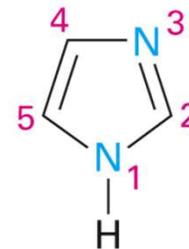
Pyridine



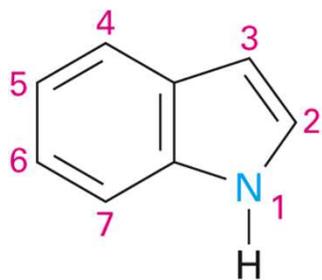
Pyrrole



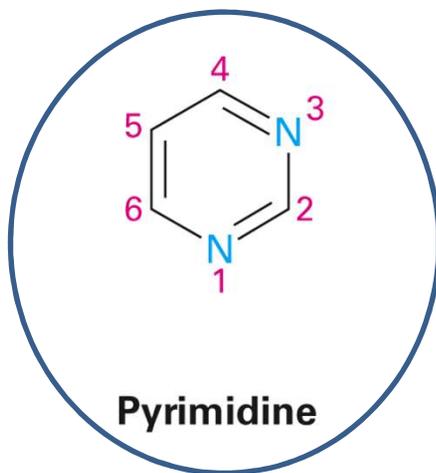
Quinoline



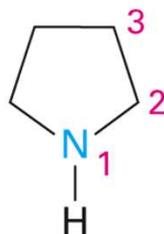
Imidazole



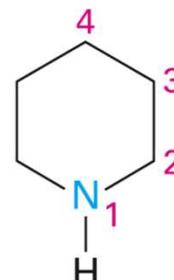
Indole



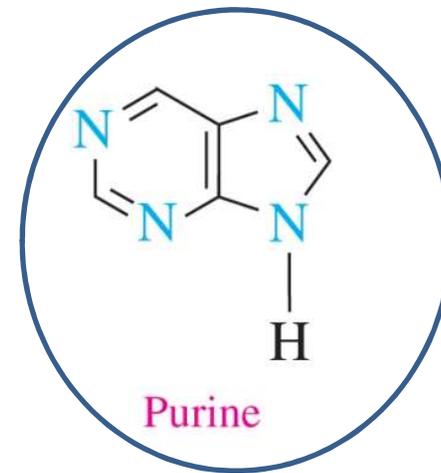
Pyrimidine



Pyrrolidine

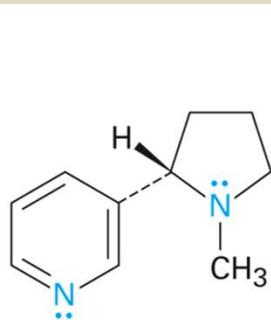


Piperidine

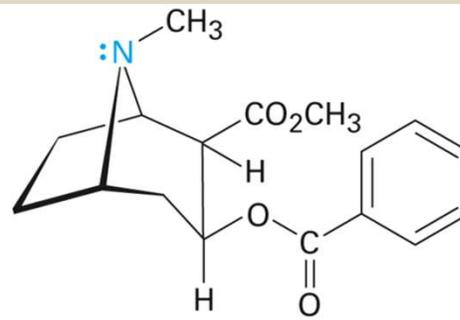


Purine

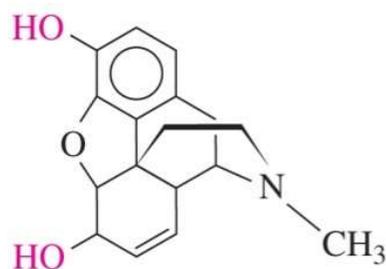
Natural Amines



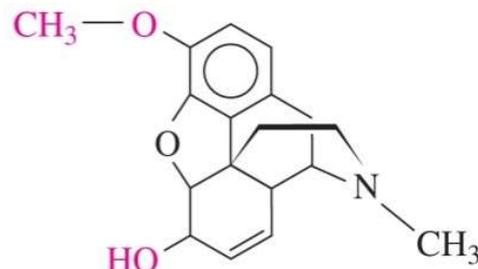
Nicotine



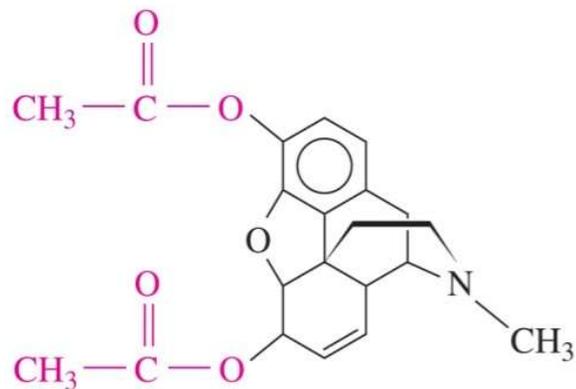
Cocaine



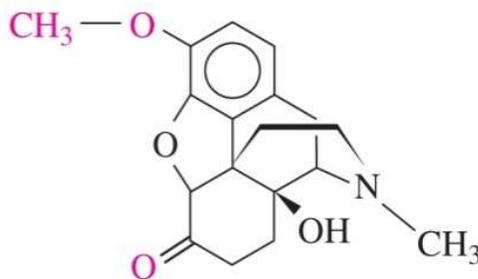
Morphine



Codeine



Heroin



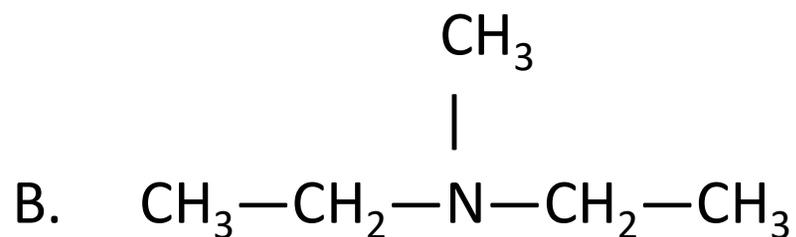
OxyContin®

Examples

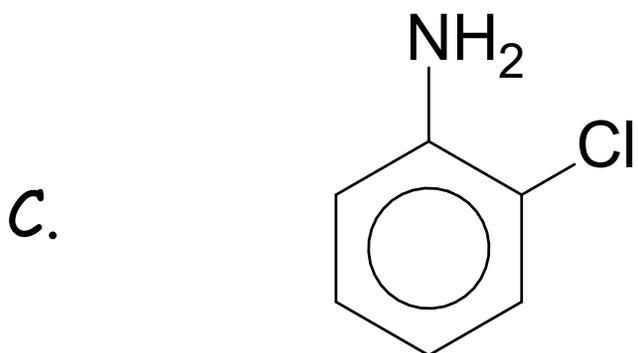
Give the common name of each compound.



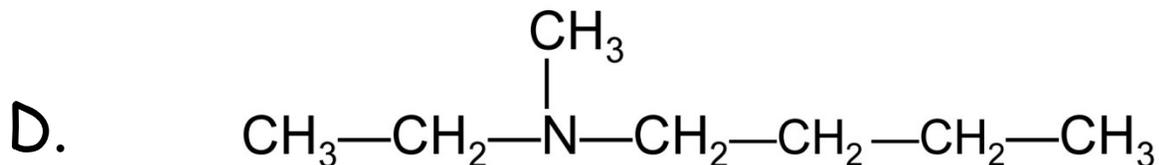
N-ethylmethanamine



N,N-diethylmethanamine



2-chloroaniline



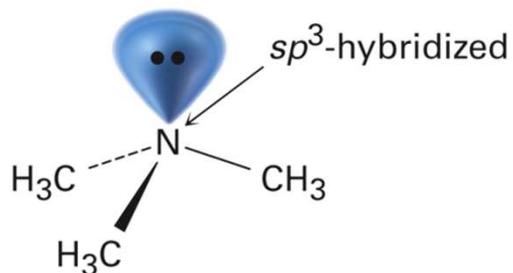
N-ethyl-N-methylbutanamine (common)

N-ethyl-N-methyl-1-butanamine

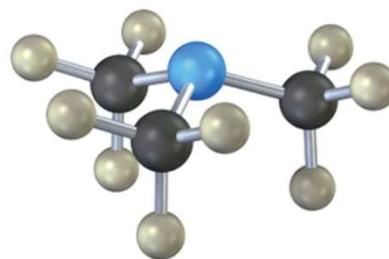
Properties of Amines

Bonding to N is similar to that in ammonia

- N is sp^3 -hybridized
- C–N–C bond angles are close to 109° tetrahedral value

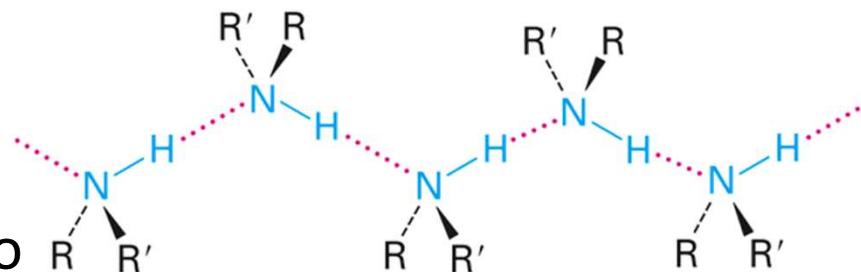


Trimethylamine



- Amines contain polar N—H bonds, which allow **primary** and **secondary** amines to form **hydrogen** bonds

- Nitrogen is **NOT** as electronegative as oxygen, which results in **weaker** hydrogen bonds as compared to those found in alcohols.



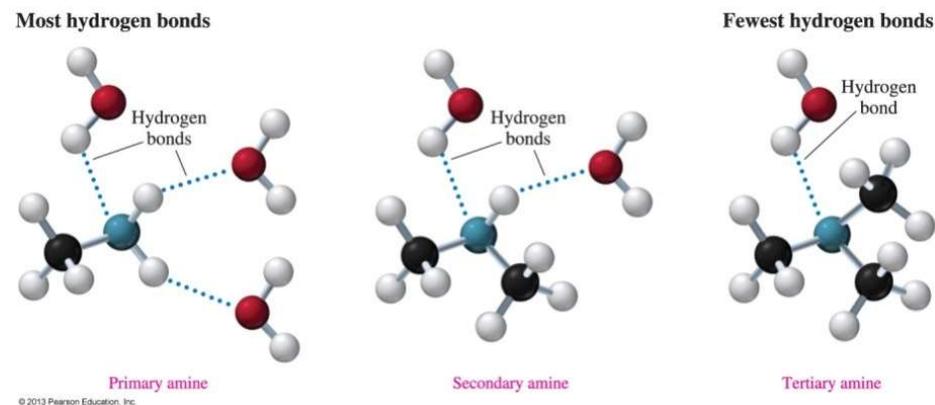
Solubility in Water

- Amines are soluble in water if they have 1 to 6 carbon atoms.
- Generally, 1° amines are most **soluble** while 3° amines are **least** soluble because the N atom in smaller amines forms hydrogen bonds with the polar O—H bond in water.

Examples

Consider following compounds:

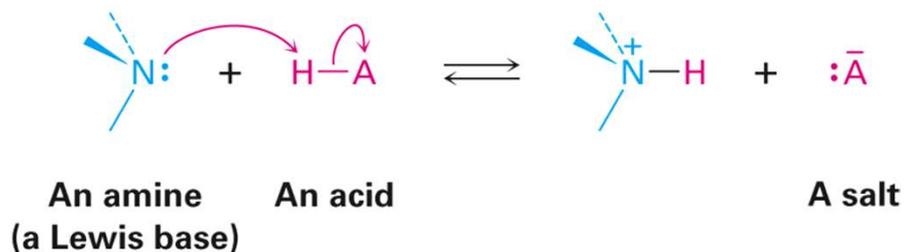
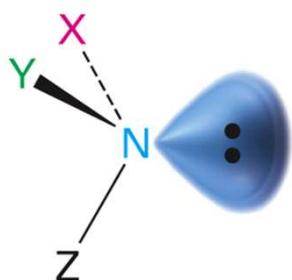
- 1) $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—NH}_2$
- 2) $\text{CH}_3\text{—CH}_2\text{—NH—CH}_3$
- 3) $\text{CH}_3\text{—CH}_2\text{—CH}_2\text{—CH}_3$



- A. Which compound has the highest boiling point?
- B. Which compound(s) is/are soluble in water?

Basicity of Amines

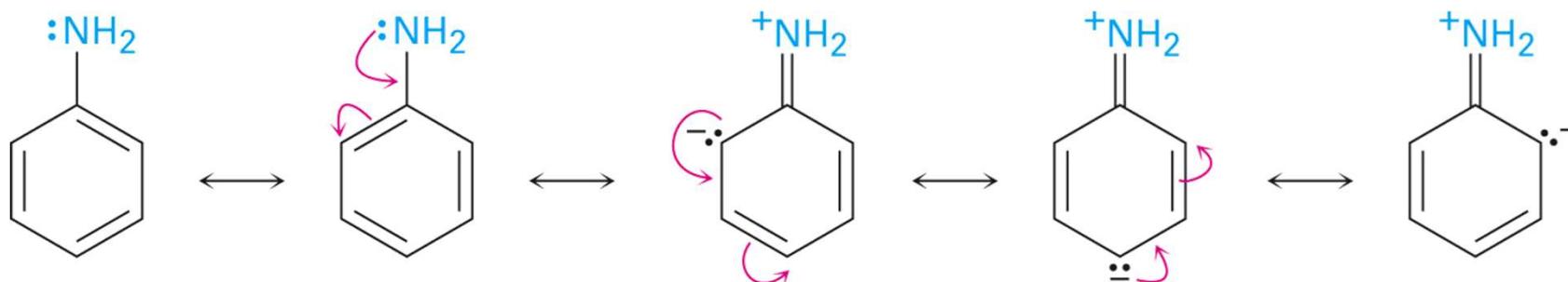
- The **lone pair** of electrons on nitrogen makes amines **basic** and **nucleophilic**



- They react with **acids** to form acid-base salts and they react with **electrophiles**
 - Amines are **stronger** bases than alcohols, ethers, or water
- Basic ability: Amin (NH_2) > Alcohol (OH), ether (-O-), H_2O

Basicity of Arylamines

- Arylamines and heterocyclic aromatic amines are **less basic** than alkylamines
- The **N lone-pair electrons** in arylamines are **delocalized** by interaction with the aromatic ring π electron system and are **less able** to accept H^+ than are alkylamines

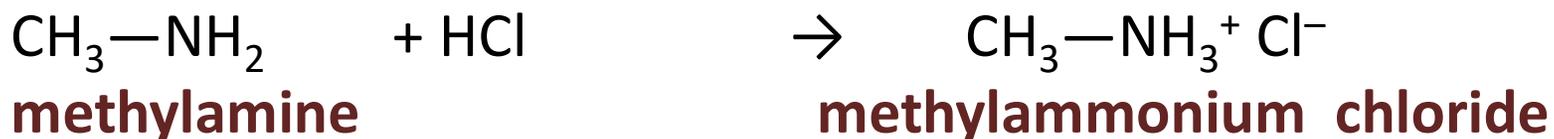


- Substituted Aniline Can be more basic or less basic than **aniline**
 - Electron-**donating** substituents (such as $-CH_3$, $-NH_2$, $-OCH_3$) **increase** the basicity of the corresponding arylamine
 - Electron-**withdrawing** substituents (such as $-Cl$, $-NO_2$, $-CN$) **decrease** arylamine basicity

Reactions of Amines

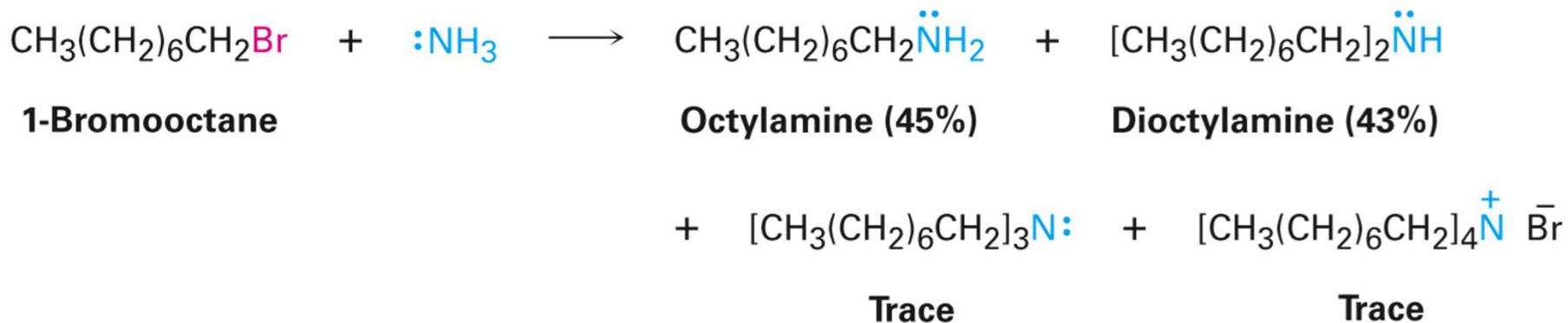
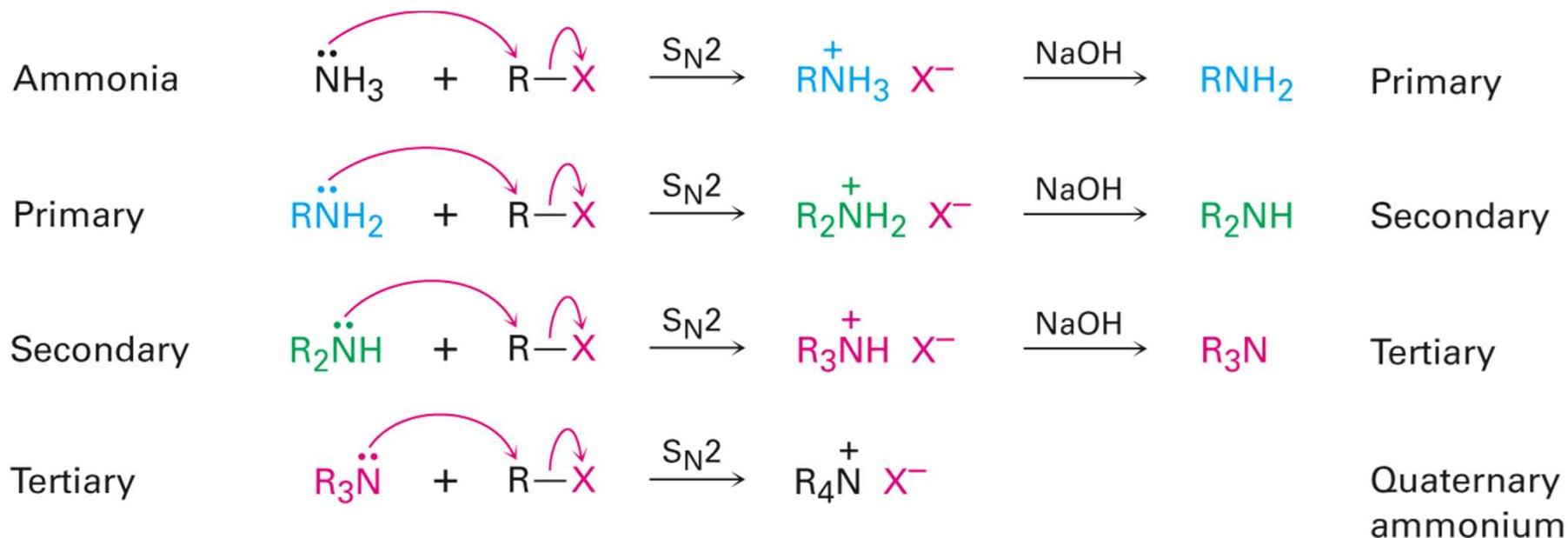
□ Neutralization Forms Amine Salts

- An **amine salt** forms when an amine is neutralized by acid.
- amine salt is named by **replacing** the **amine** part of the name with **ammonium**, followed by the name of the negative ion.



Reactions of Amines

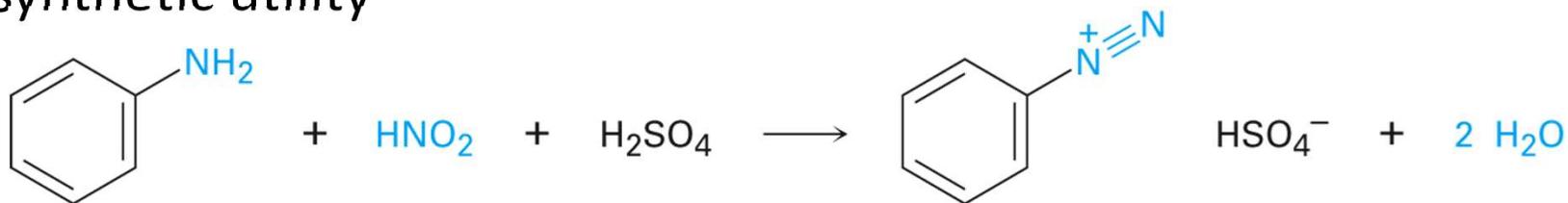
Reactions with Alkyl Halides: Ammonia and other amines are good nucleophiles.



Reactions of Amines

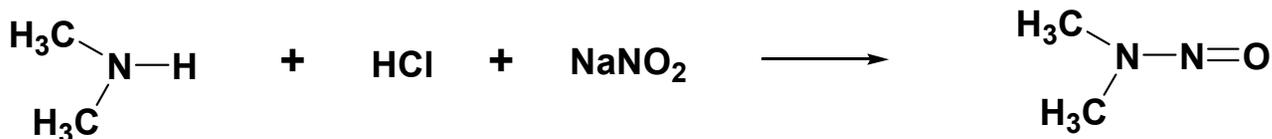
□ Amines with Nitrous Acid (HNO_2)

- **1° aliphatic** amines form very **unstable** diazonium salts
- **1° aromatic** amines form **stable** diazonium salts at 0°C of great synthetic utility

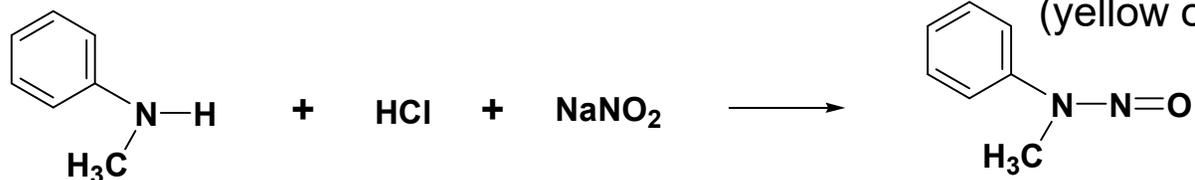


➤ 2° Amines with nitrous acid

N-Nitrosoamines



N-Nitrosodimethylamine
(yellow oil)



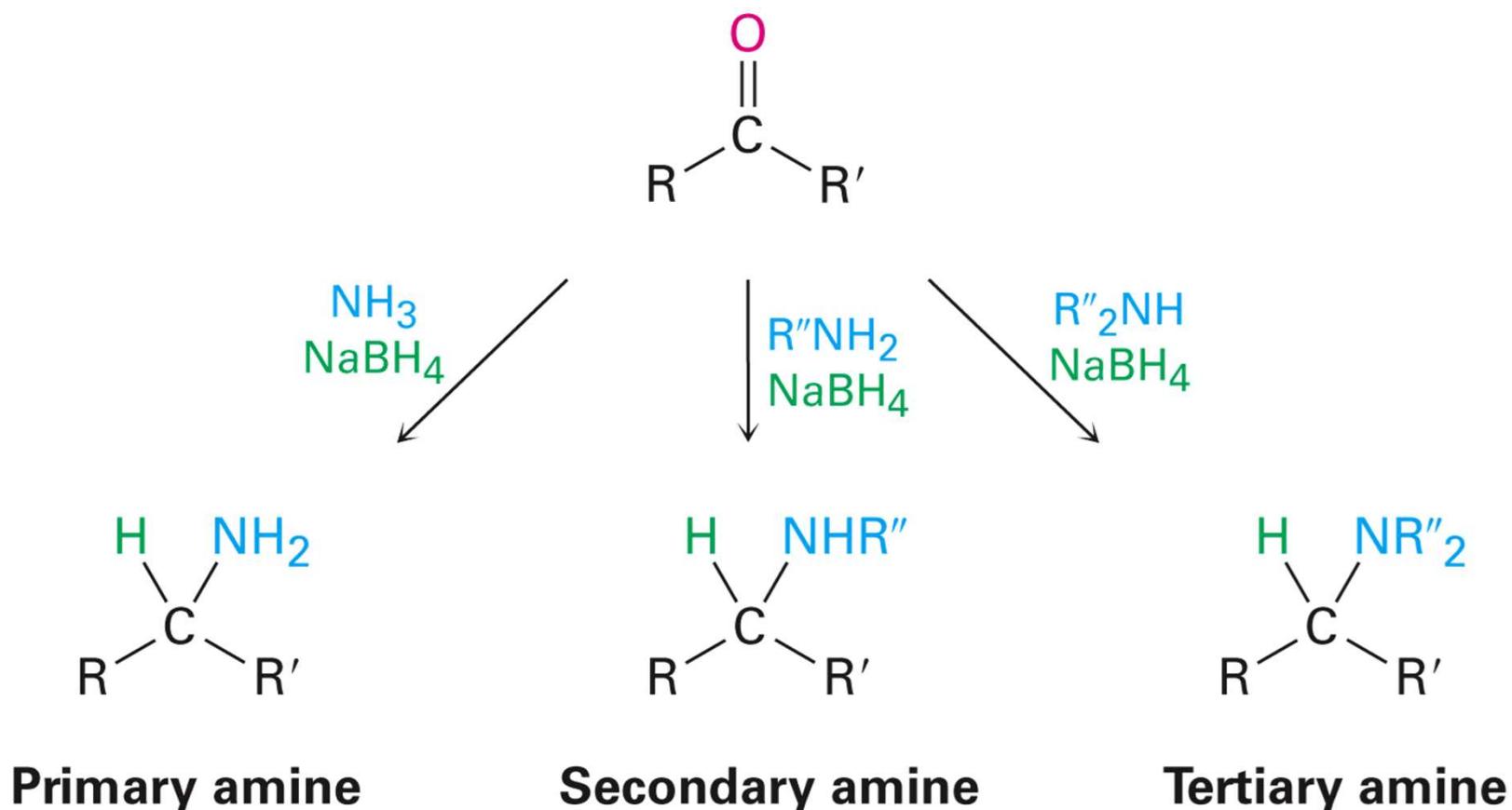
N-Nitroso-N-methylaniline
(yellow oil)

➤ 3° Amines with nitrous acid: NOT forms N-Nitrosoamine

Reactions of Amines

□ Reductive Amination of Aldehydes and Ketones

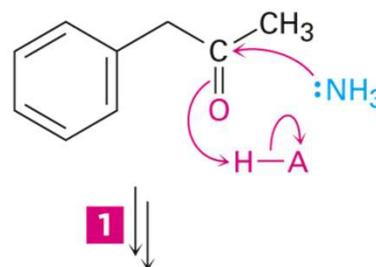
- Treatment of an aldehyde or ketone with ammonia or an amine in the presence of a reducing agent



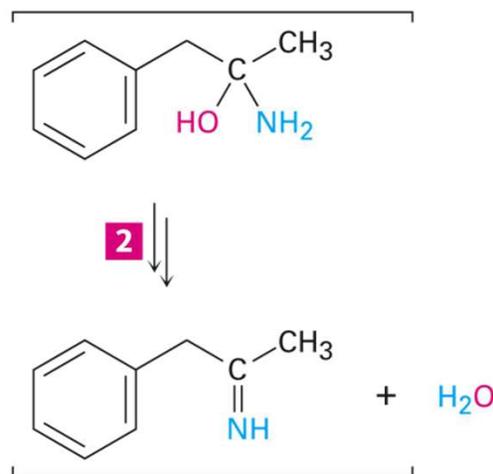
Reactions of Amines

□ Reductive Amination of Aldehydes and Ketones

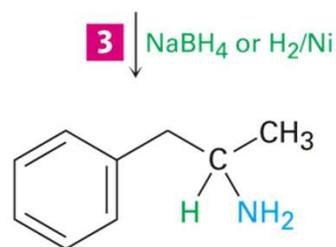
1 Ammonia adds to the ketone carbonyl group in a nucleophilic addition reaction to yield an intermediate carbinolamine.



2 The carbinolamine loses water to give an imine.

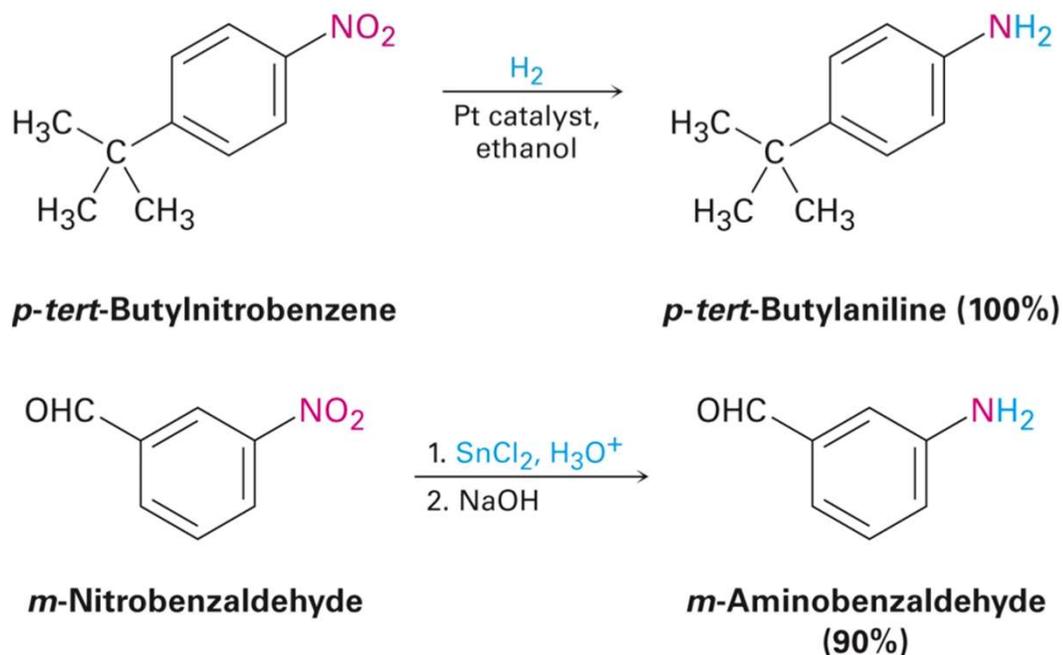


3 The imine is reduced by NaBH_4 or H_2/Ni to yield the amine product.



Preparation of Aryl Amines

- Arylamines are prepared from **nitration** of an aromatic compound and **reduction** of the **nitro** group
- Reduction by catalytic **hydrogenation** over **platinum** is suitable if no other groups can be reduced
- Iron, zinc, tin, and tin(II) chloride are **effective** in acidic solution



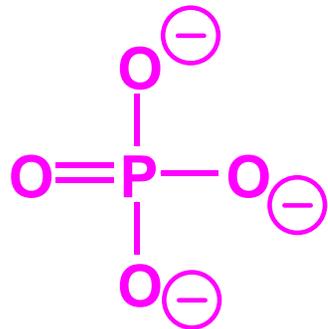
2. Nucleotides

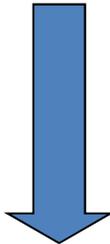
- ❑ **Two Nucleic Acids (Polymers)** - deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)
- ❑ **Mild degradation yields monomeric units Nucleotides**
- ❑ **Complete degradation yields**

1. **A Heterocyclic Base**  **Purine or Pyrimidine**

2. **A five Membered Monosaccharide**

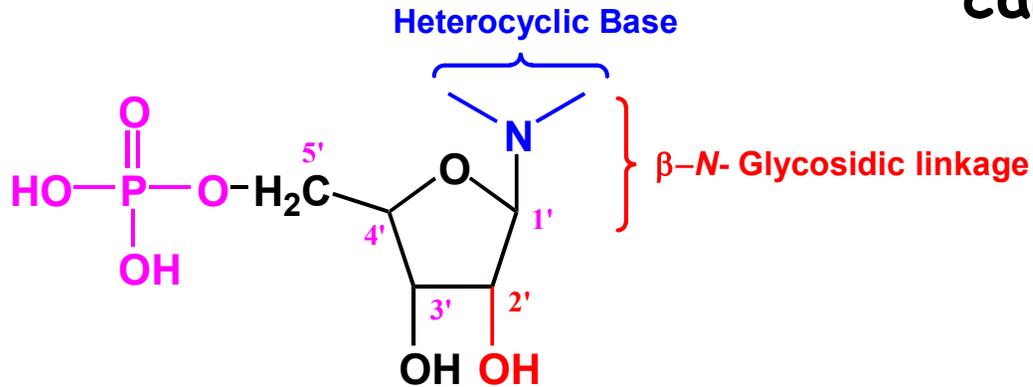
3. **A Phosphate ion**



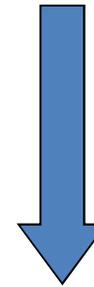

**D-Ribose or
2-deoxy-D-ribose**

Nucleotides

RNA - Nucleotide



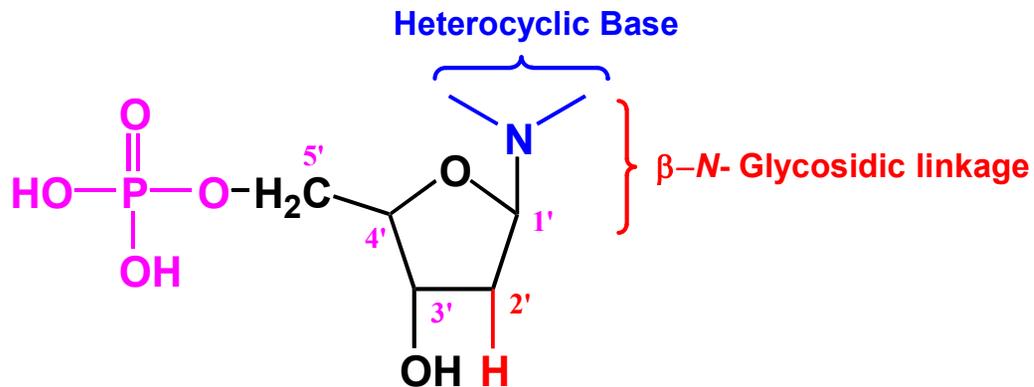
The Phosphate ester
can be at C-5' or C-3'



Hydolysis of
Phosphate

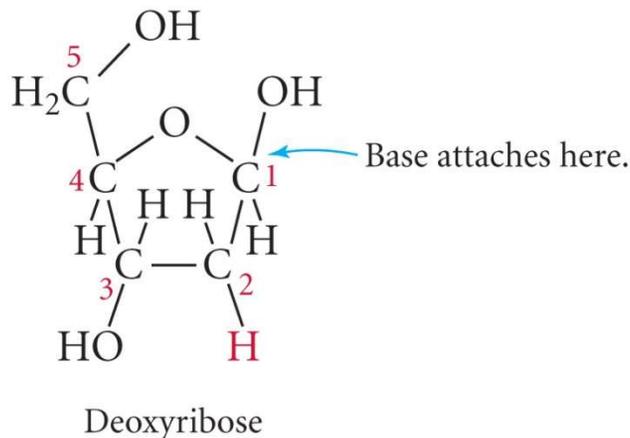
Nucleoside

DNA - Nucleotide

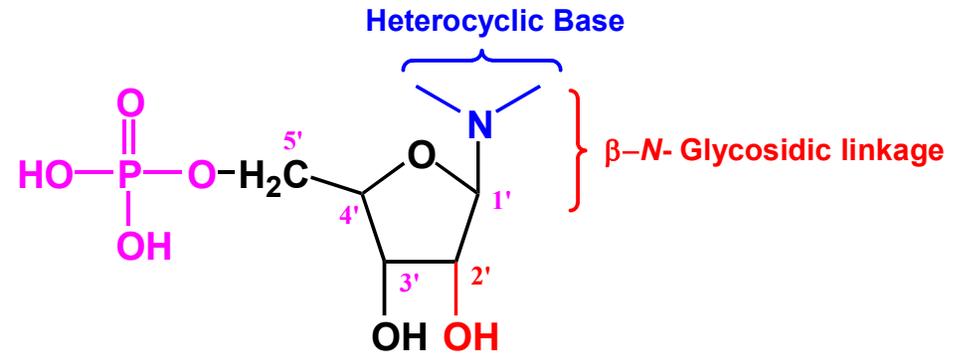


Nucleotide Structure

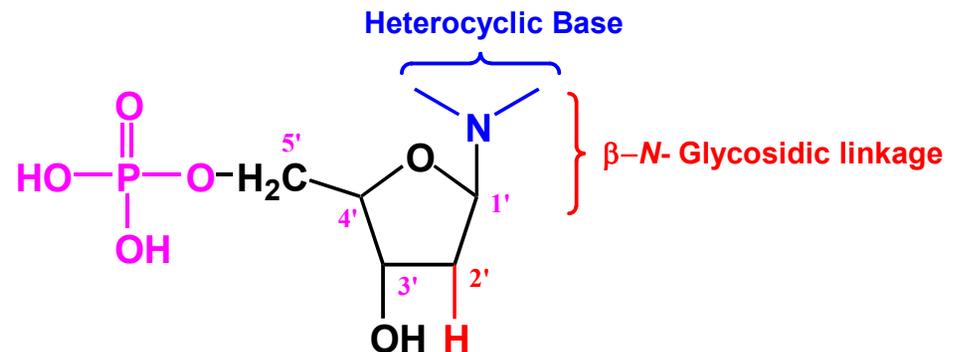
- Each nucleotide has **3 parts** - a cyclic **pentose**, a **phosphate** group, and an organic **aromatic base**
- The pentoses are **ribose** or **deoxyribose**
- The pentoses are the **central** backbone of the nucleotide
- The pentose is attached to the organic base at **C1** and to the phosphate group at **C5**



RNA - Nucleotide



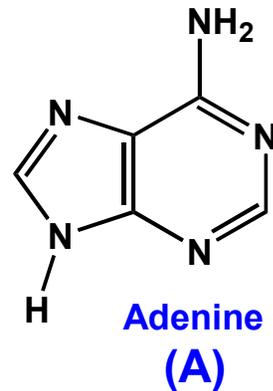
DNA - Nucleotide



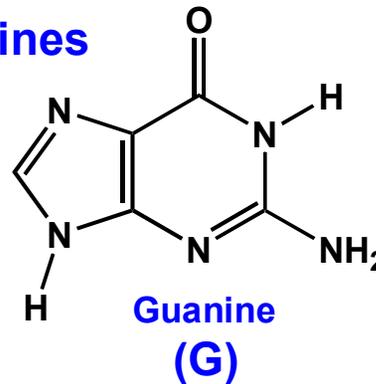
Nucleotide Structure

Bases

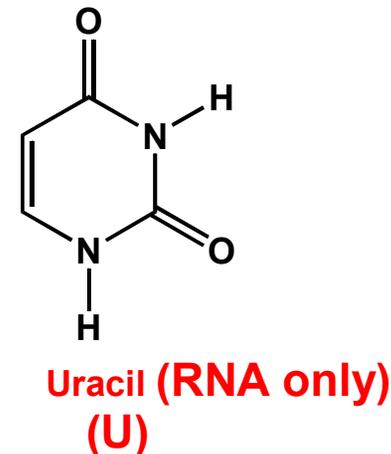
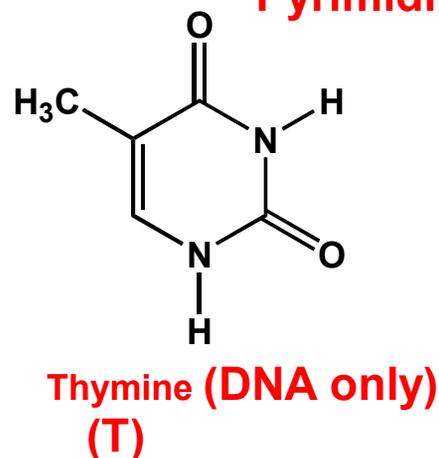
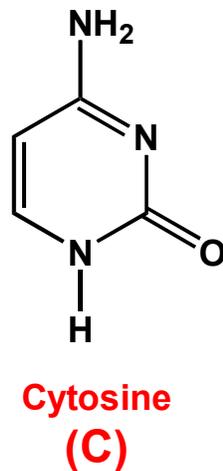
- two general structures: two of the bases are similar in structure to the organic base **purine**; the other two bases are similar in structure to the organic base **pyrimidine**



Purines

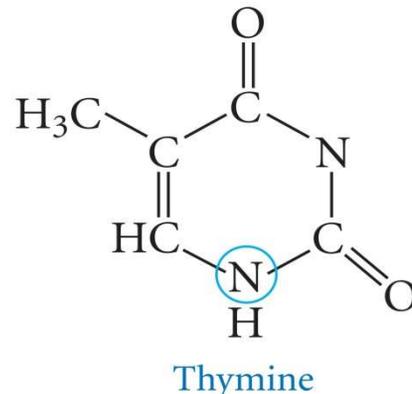
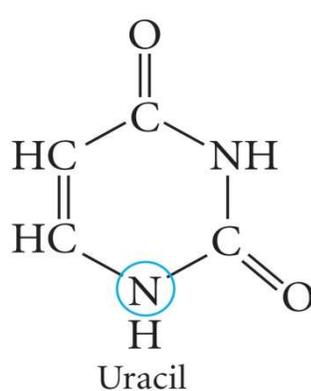
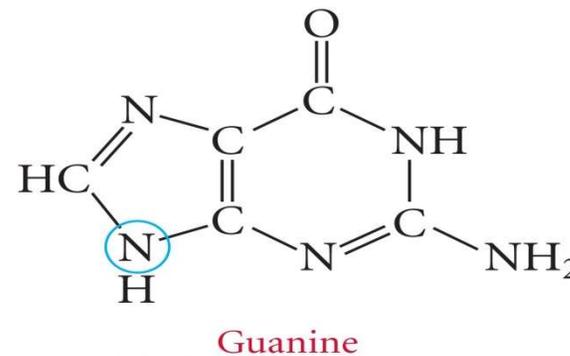
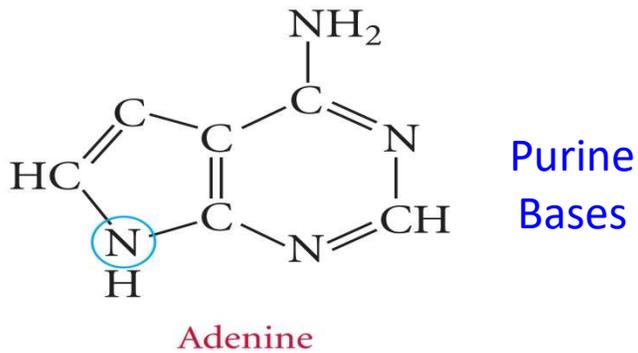


Pyrimidines

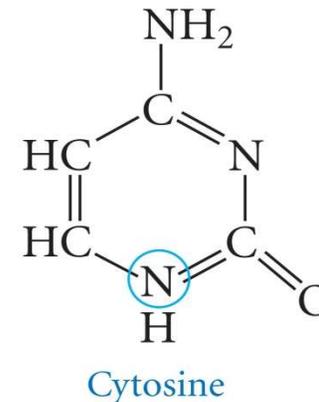


Bases

- The structures of the base are **complementary**, meaning that a purine and pyrimidine will precisely align to **H-bond** with each other
 - Adenine matches Thymine or Uracil
 - Guanine matches Cytosine
- Attach to **sugar** at **C1** of the sugar through circled N

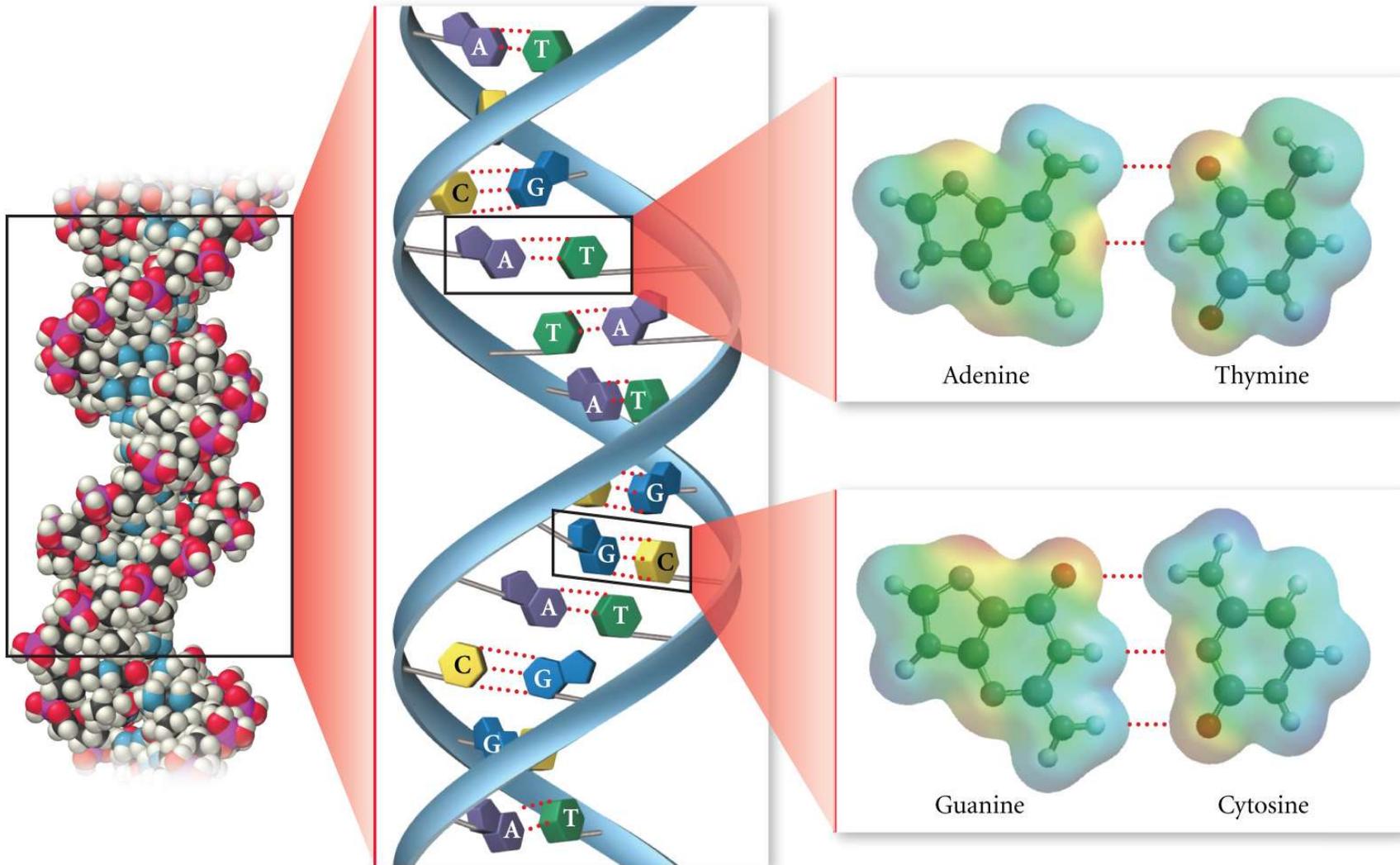


Pyrimidine Bases

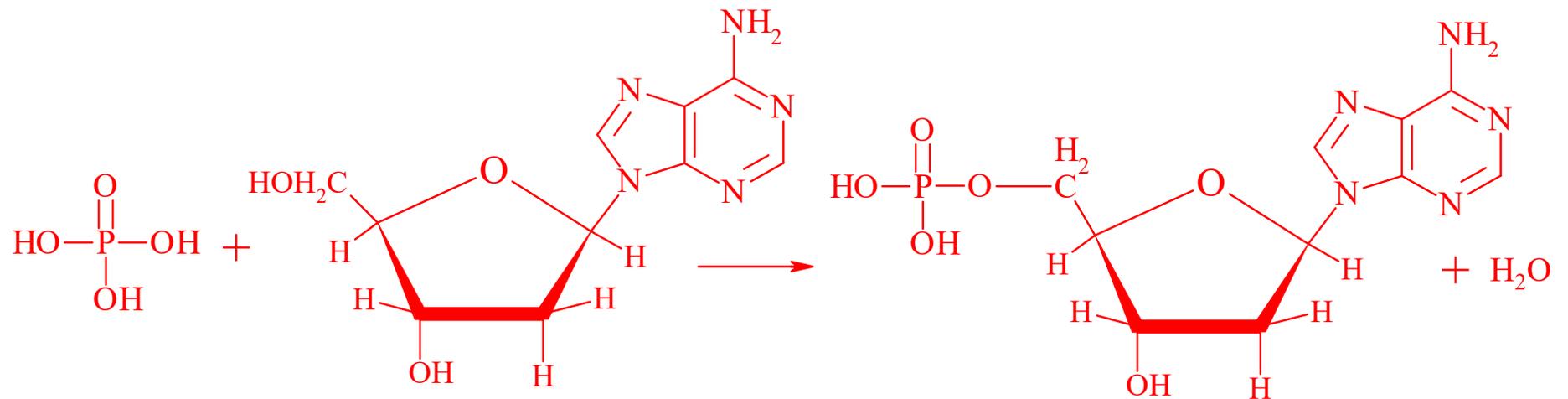
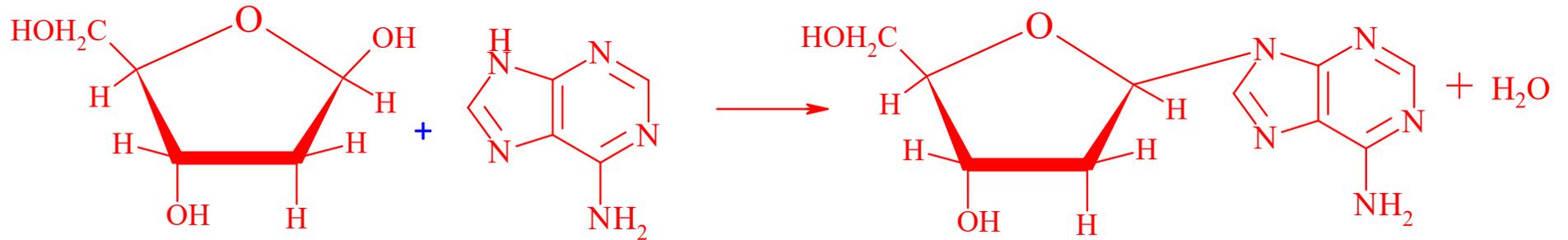


Bases: H-Bond

Base-pairing in DNA

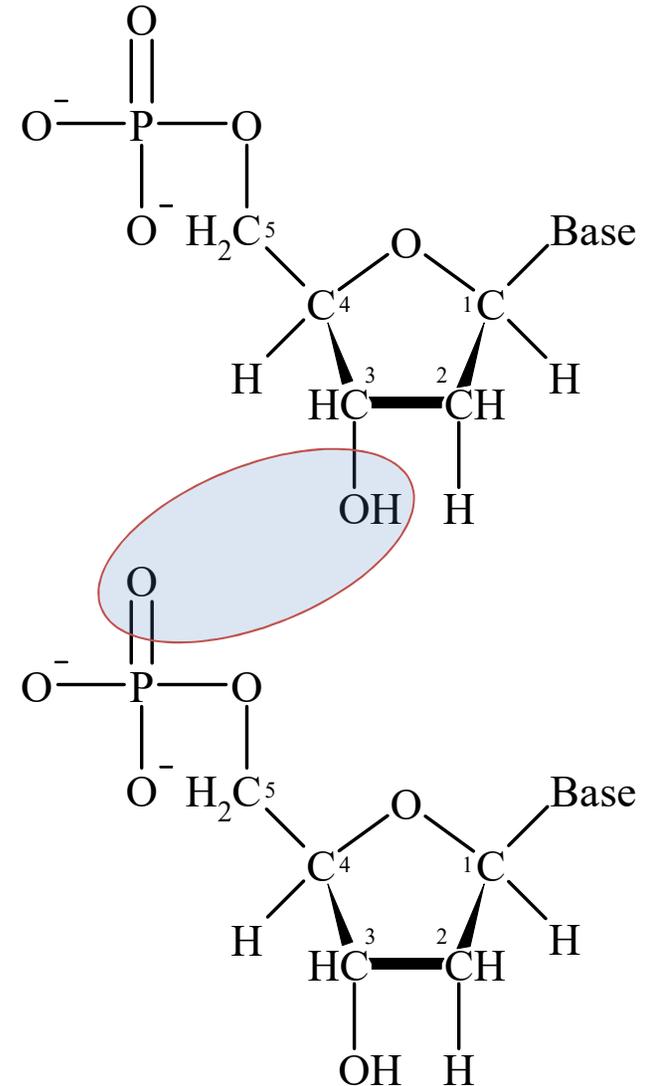


Nucleotide Formation

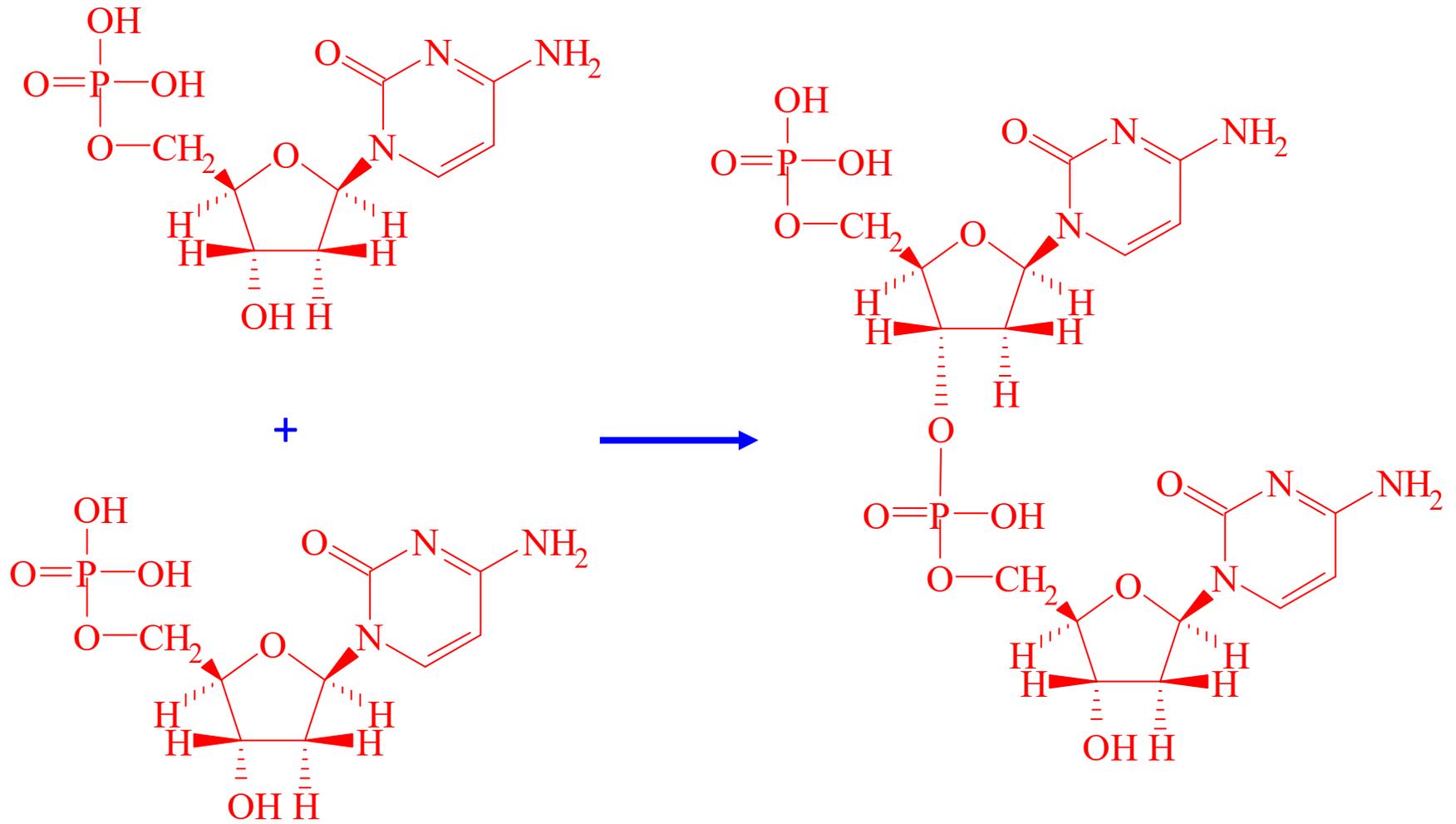


Primary Structure of Nucleic Acids

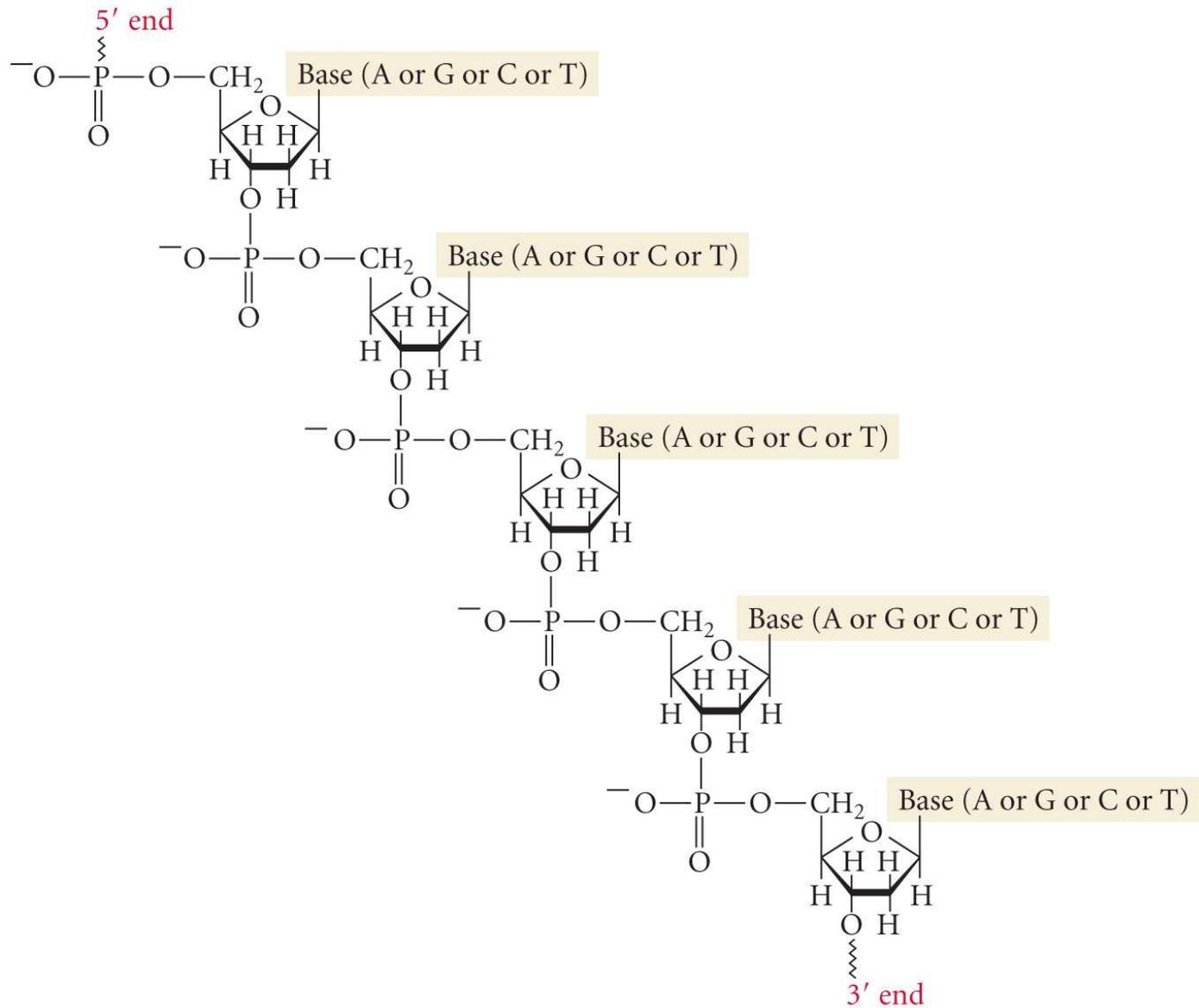
- ☐ Nucleotides are linked together by attaching the **phosphate** group of one to the **sugar** of another at the O of **C3**
- ☐ The attachment is called an **phosphate ester bond**
- ☐ The phosphate group attaches to C3 of the sugar on **the next nucleotide**



Primary Structure of Nucleic Acids

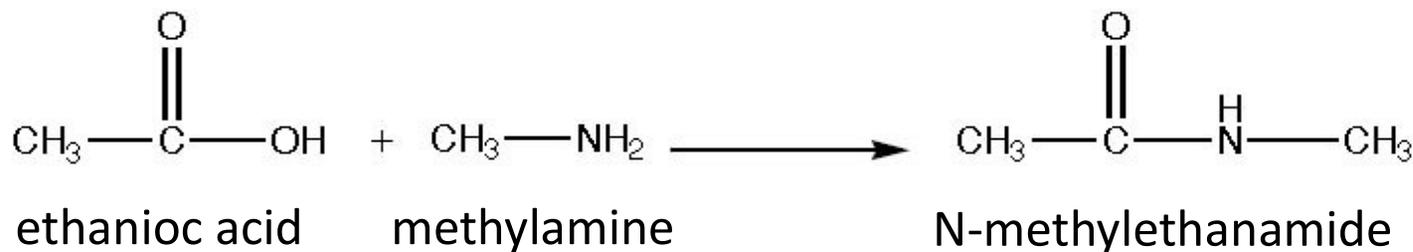
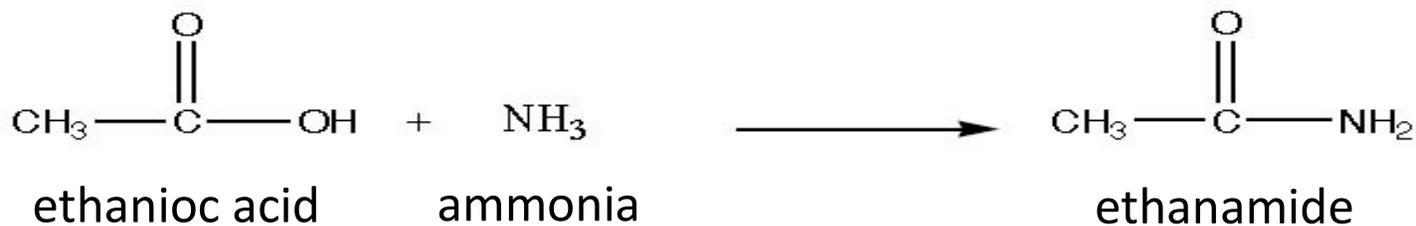
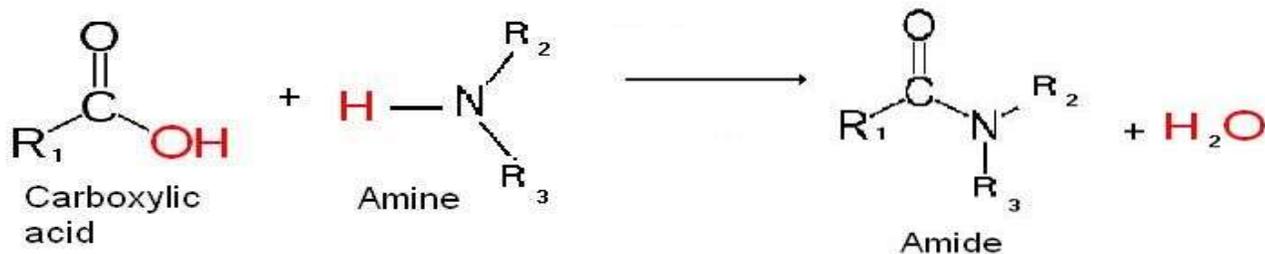


Primary Structure of Nucleic Acids



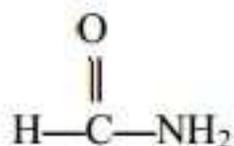
3. Amides

- Amides are made when an **amino** group (-NH₂) replaces the **hydroxyl** group (-OH) of a carboxylic acid
- Amide functional group is an **internal** group like an ester group

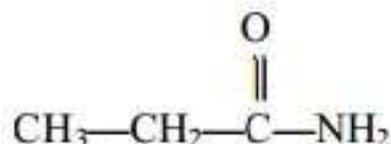
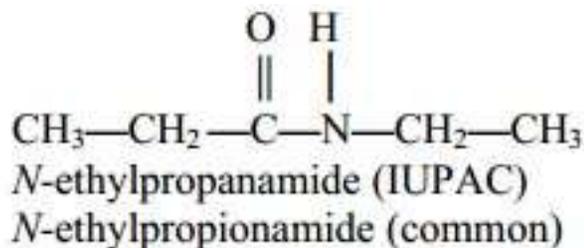
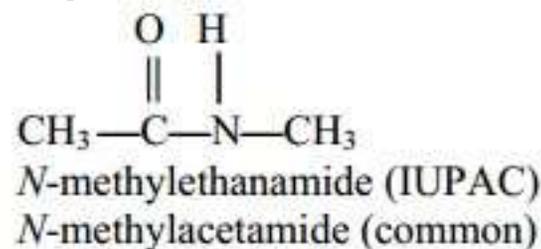


Naming Amides (simple)

- ❑ IUPAC: Carboxylic acid replaces **-oic** acid with **-amide**
- ❑ Common name: replaces **-ic** acid with **-amide**
- ❑ An alkyl group attached to the Nitrogen of an amide adds the prefix **N-** followed by the alkyl name



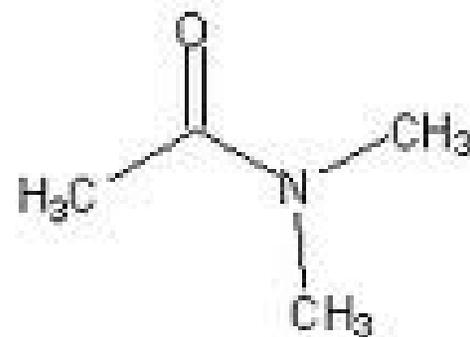
Methanamide (IUPAC)
Formamide (common)



Propanamide (IUPAC)
Propionamide (common)

❑ Subclasses of Amides

- 1° Amides: 2 H/no alkyl on amine part
- 2° Amides: 1 H/1 alkyl on amine part
- 3° Amides: no H/2 alkyls on amine part

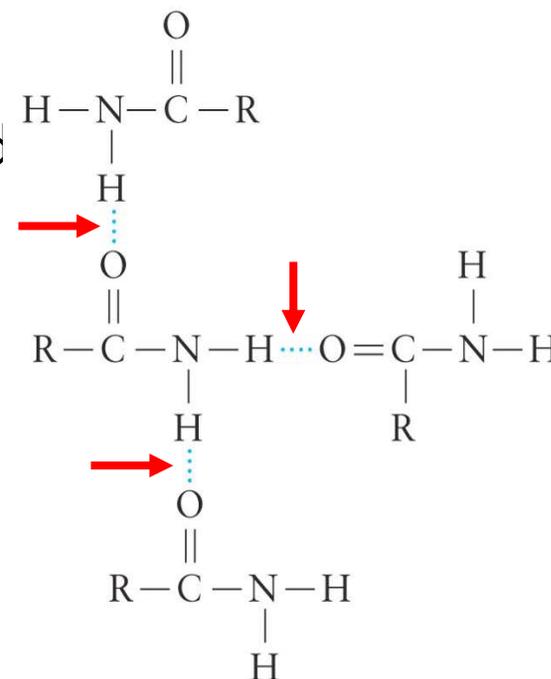


N,N-dimethylethanamide

Physical Properties

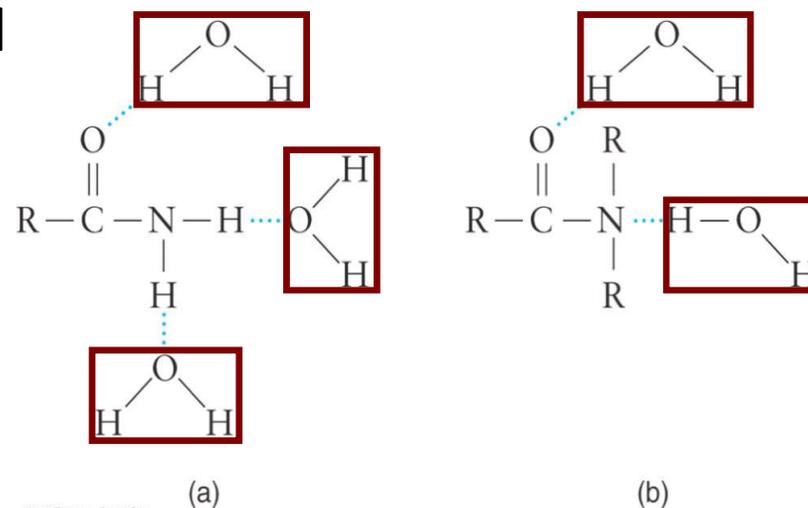
□ Melting Point

- **Highest** for **1°** amides ($-\text{NH}_2$) can form 2 H-bonds
- **Lower** in **2°** amides ($-\text{NH}$) can form 1 H-bond
- **Lowest** in **3°** amides (no H) no H bond



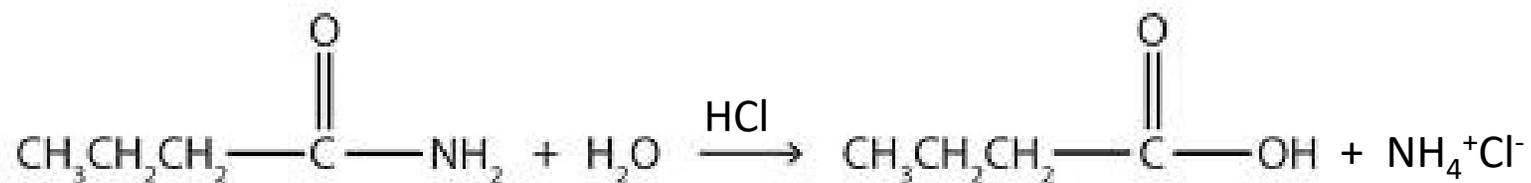
□ Solubility

- All amides form **hydrogen** bonds with water – even 3° over carbonyl dipole
- Amides with 1-5 carbons are **soluble**

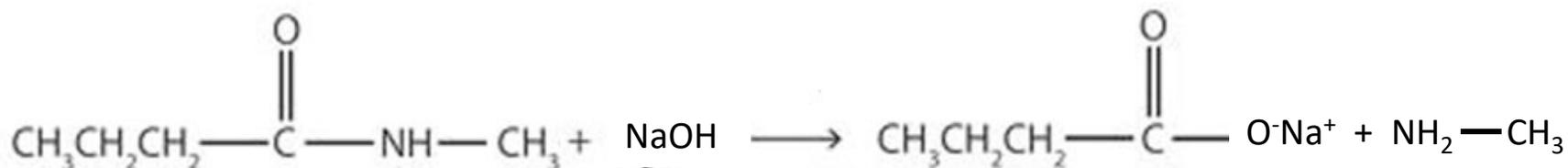


Hydrolysis of Amides

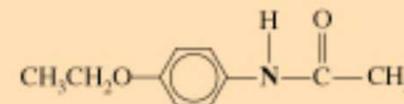
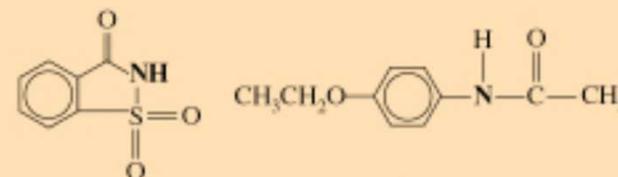
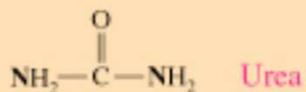
- **Acid hydrolysis of amides:** Produces **carboxylic acid** & **ammonium salt**



- **Base hydrolysis of amides:** Produces **carboxylate** salt & ammonia or amine

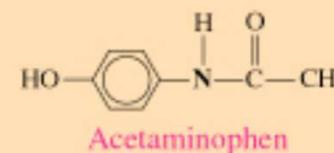


Amides in Everyday Life

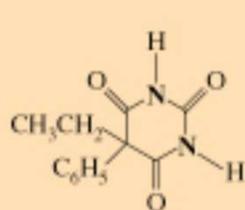


Saccharin

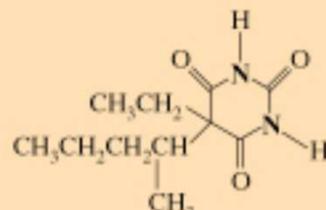
Phenacetin



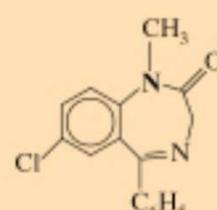
Acetaminophen



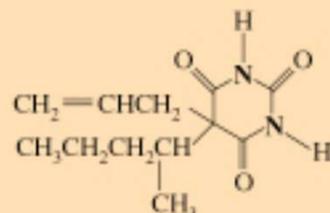
Luminal (phenobarbital)



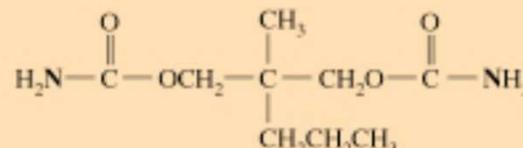
Nembutal (pentobarbital)



Valium (diazepam)



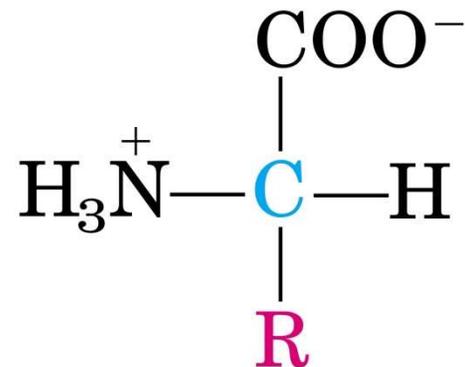
Seconal (secobarbital)



Equanil (meprobamate)

4. Amino acids

- ❑ Amino acids are the building block of proteins
- ❑ There are **20** naturally occurring amino acids
- ❑ All amino acids have an **amino group** ($-\text{NH}_3^+$), a **carboxylate** ($-\text{COO}^-$) group and a **hydrogen** bonded to the same carbon atom
- ❑ They differ from each other in their side chain called **R** group.
- ❑ R groups vary in **structure**, **size** and **electric charges** and influence the solubility of amino acids in water.



Classification of natural Amino Acids

Amino Acids

```
graph TD; A[Amino Acids] --> B[Nutritional]; A --> C[Based on R group];
```

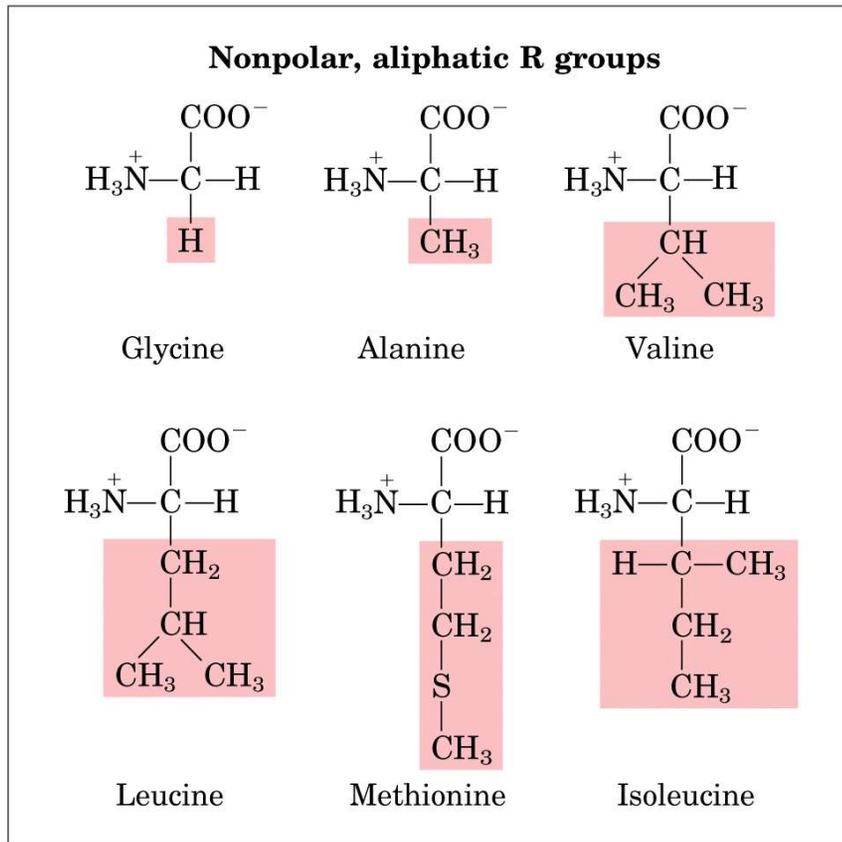
- Nutritional

- Essential
- Non-essential

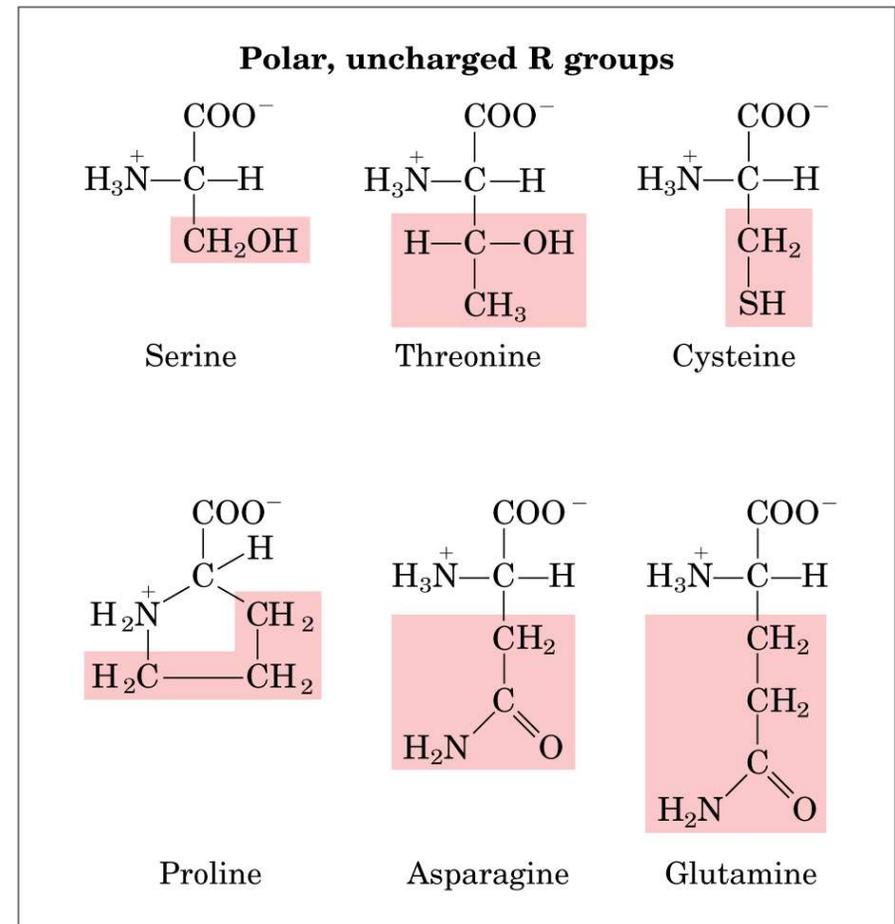
Based on R group

- Non polar aliphatic R group
- Polar uncharged R group
- Aromatic R group
- Positively charged R group
- Negatively charged R group

Classification of natural Amino Acids



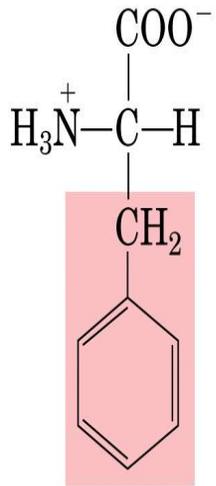
The **bulky** side chain of valine, isoleucine and leucine are important in promoting hydrophobic interactions within protein structures



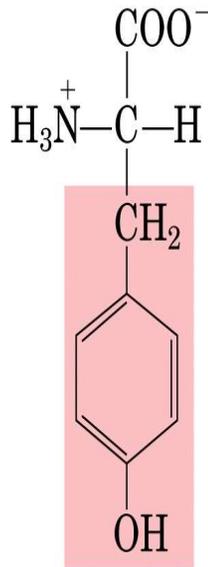
The R group of these amino acids is **more soluble** in water, or **hydrophilic** than those of non polar amino acids, because they contain functional groups that form **hydrogen** bond with water

Classification of natural Amino Acids

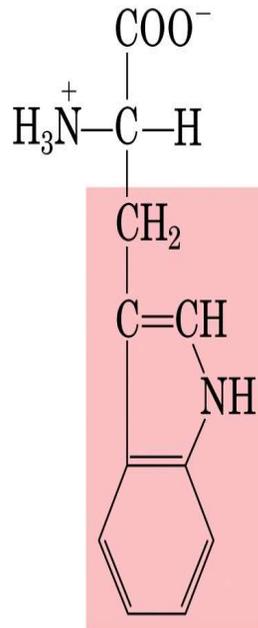
Aromatic R groups



Phenylalanine



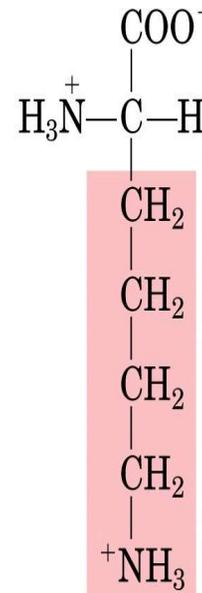
Tyrosine



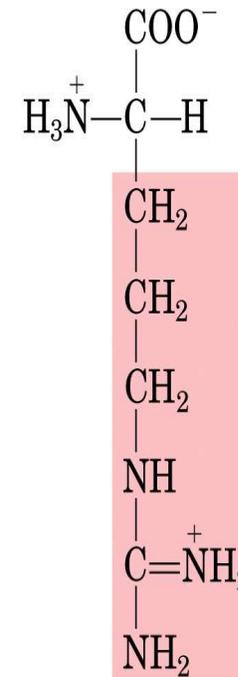
Tryptophan

Their aromatic side chains are relatively **nonpolar**

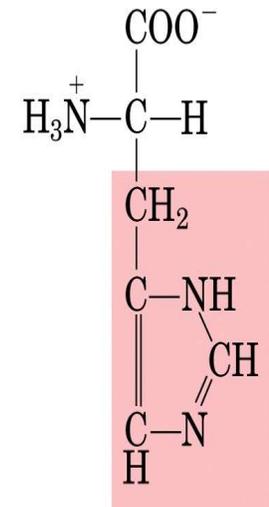
Positively charged R groups



Lysine



Arginine

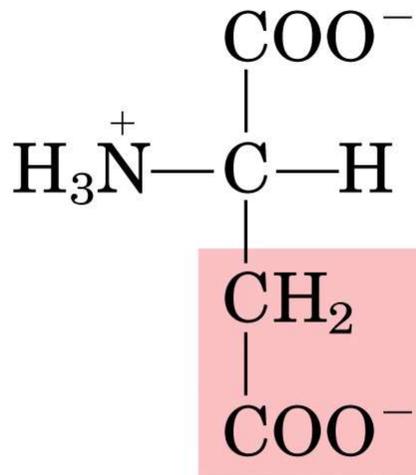


Histidine

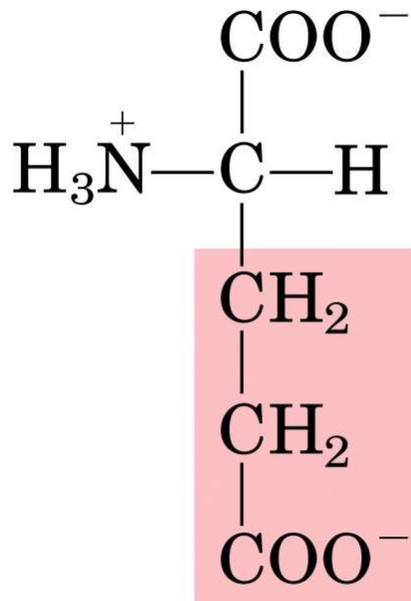
The amino acids in which the R group have a net **positive** charge at pH 7.0

Classification of natural Amino Acids

Negatively charged R groups



Aspartate

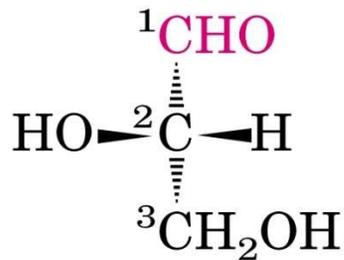


Glutamate

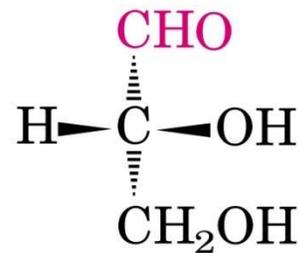
Amino acids having R group with a net **negative** charge at pH 7.0, with a second carboxyl group

Structures of amino acids

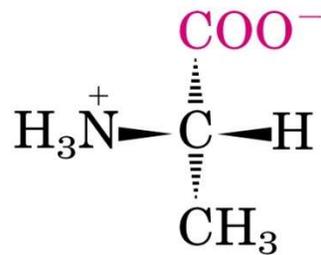
- All the amino acids except glycine have handedness (**chiral**)
- Amino acids exist as **D** or **L** form that are nonsuperimposable mirror image of one another
- **L-form** naturally occurs in proteins



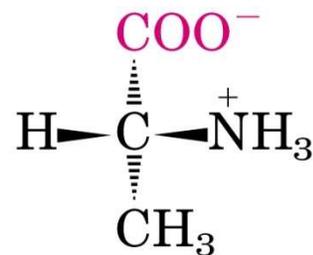
L-Glyceraldehyde



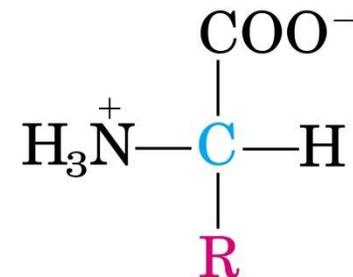
D-Glyceraldehyde



L-Alanine



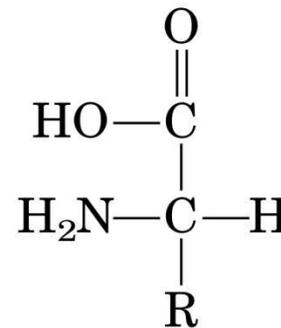
D-Alanine



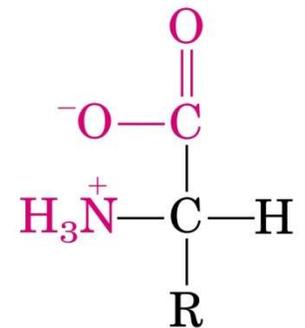
Structures of amino acids

- Amino acids form internal salts called **zwitterions**
- In the pure **solid** state and in **aqueous** solution near neutral pH, amino acids exist almost completely as zwitterions

- At **low** pH, proton concentration $[H^+]$ is high. Therefore, both amines and carboxylic acids are **protonated**. ($-NH_3^+$ & $-COOH$)



Nonionic
form

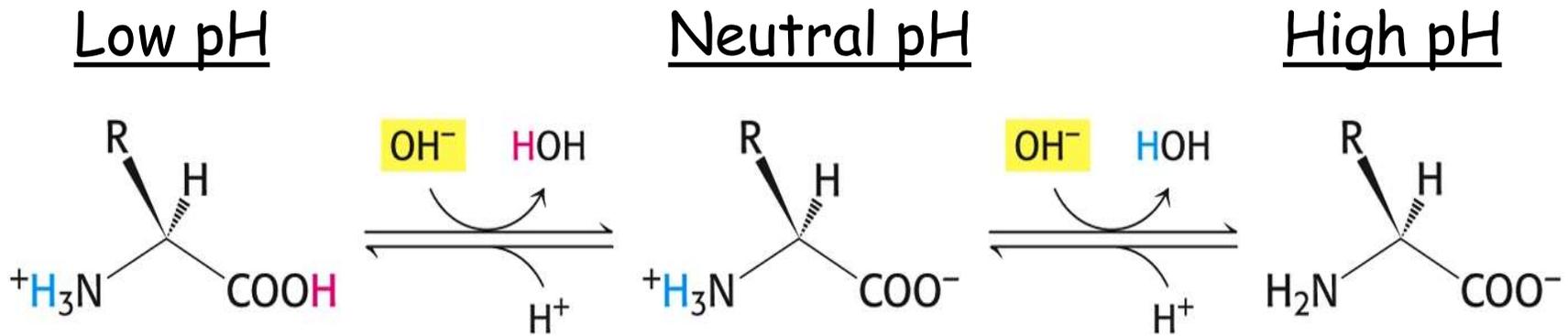


Zwitterionic
form

- At **high** pH, proton concentration is low. Therefore, both amines and carboxylic acids are **deprotonated**. ($-NH_2$ & $-COO^-$)

- At **neutral** pH, amines are protonated ($-NH_3^+$) and carboxylates are deprotonated ($-COO^-$)

Structures of amino acids

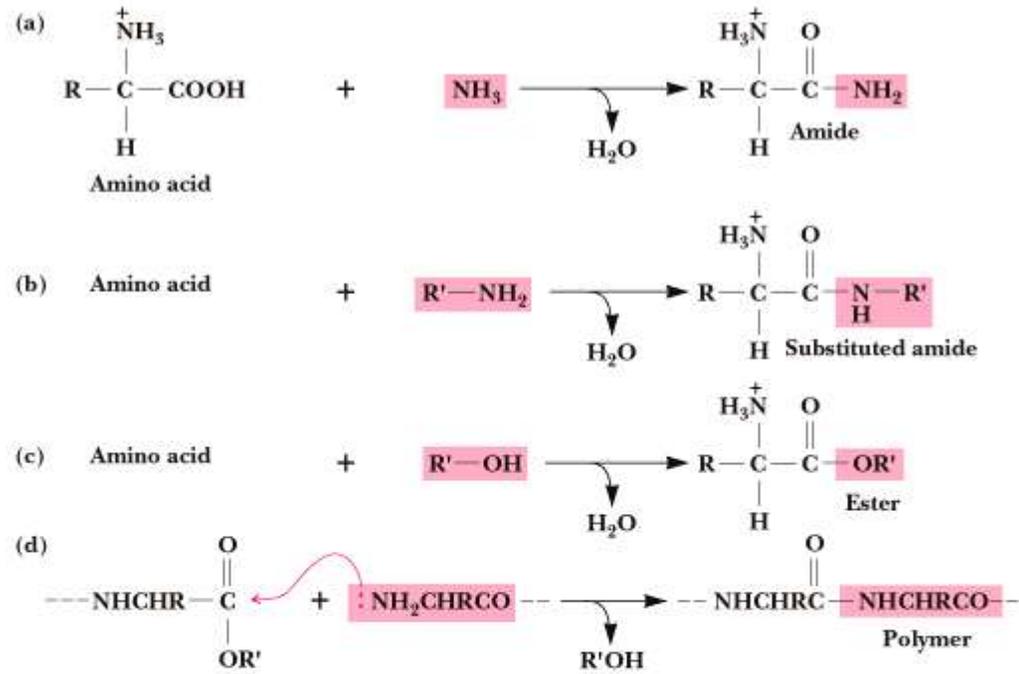


Example: Draw the following chemical structures for glycine:
(*Non-existent form:*) **H₂N – CH₂ – COOH**

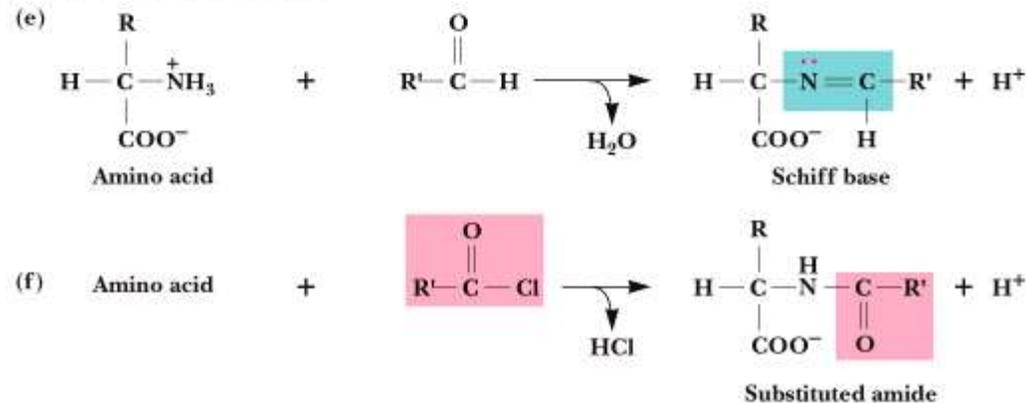


Properties of amino acids

CARBOXYL GROUP REACTIONS

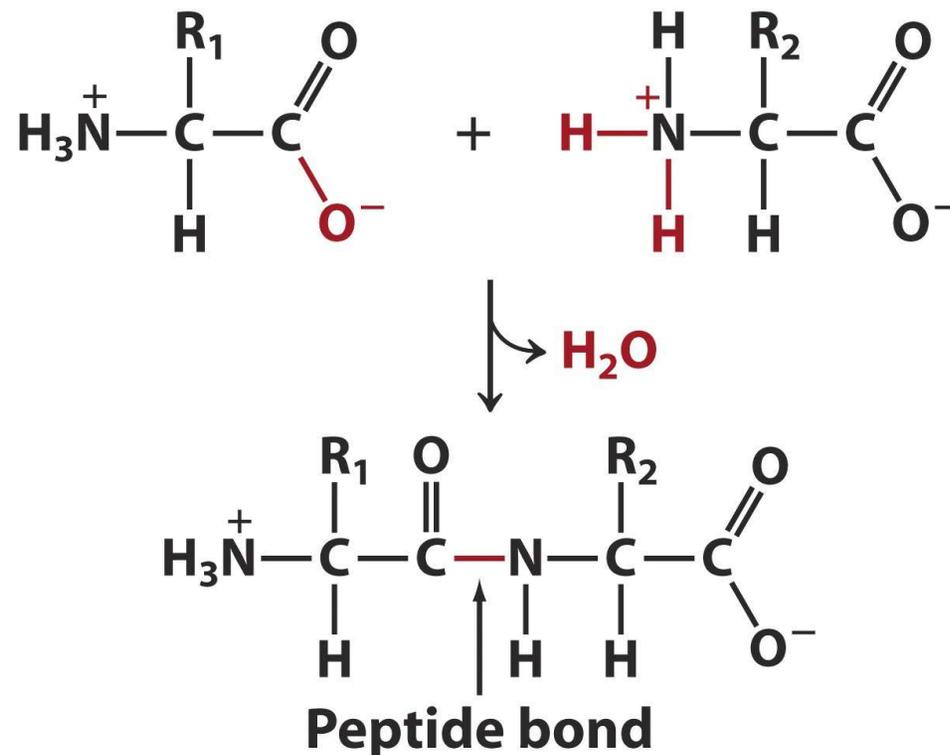


AMINO GROUP REACTIONS



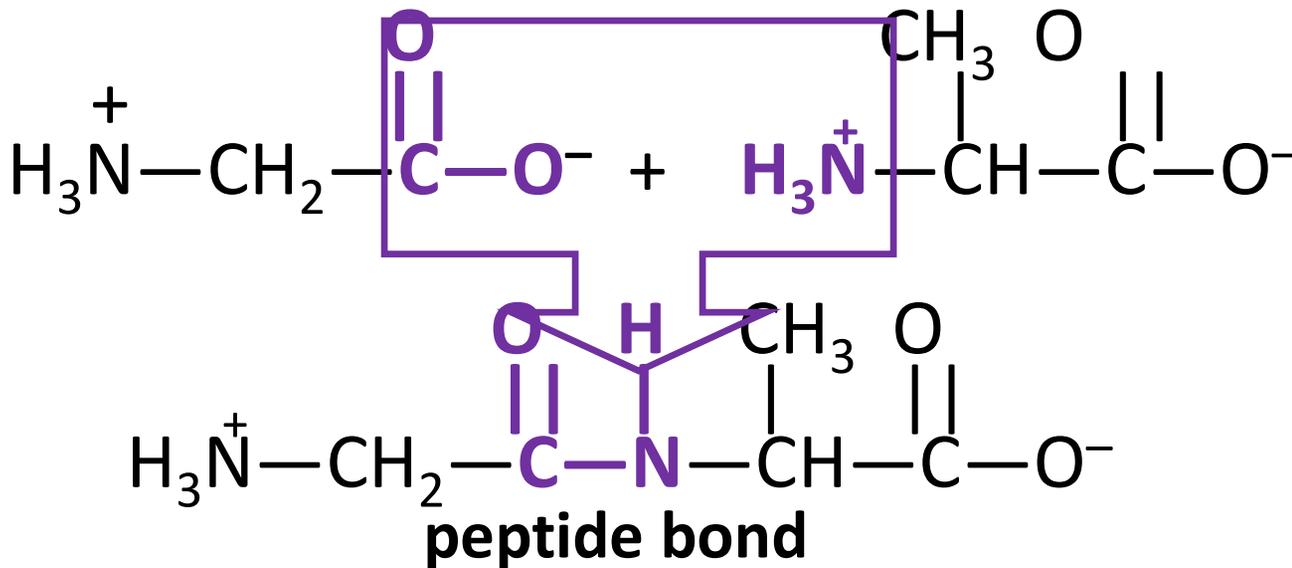
Properties of amino acids

- Amino Acids are linked to form amide or **peptide**
- The condensation of the carboxylic group of one amino acid with the amino group of another amino acid releases a water molecule and forms a **peptide bond** or **peptide link**



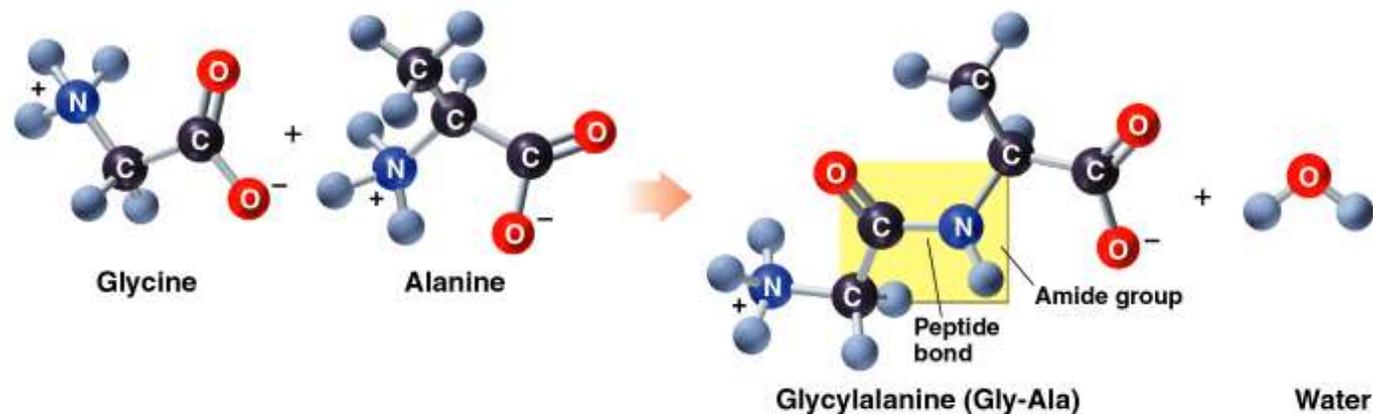
5. Peptides and Proteins

- A **dipeptide bond**
 - is an **amide bond**.
 - forms between the **carboxyl** group of one **amino** acid and the amino group of the next amino acid.



Naming Peptides

- A **dipeptide** is named from the free amine (NH_3^+) using **-yl** ending for the name.
- Names the **last** amino acid with the **free** carboxyl group (COO^-) by its amino acid name.



Timberlake, *General, Organic, and Biological Chemistry*. Copyright © Pearson Education Inc., publishing as Benjamin Cummings

Examples

1. Write the three-letter abbreviations and names of the tripeptides that could form from two glycine and one alanine.

Glycylglycylalanine

Glycylalanylglycine

Alanylglycylglycine

Gly-Gly-Ala

Gly-Ala-Gly

Ala-Gly-Gly

2. What are the possible tripeptides formed from one each of leucine, glycine, and alanine?

Leu-Gly-Ala

Leu-Ala-Gly

Ala-Gly-Leu

Ala-Leu-Gly

Gly-Ala-Leu

Gly-Leu-Ala

Secondary Structures of proteins

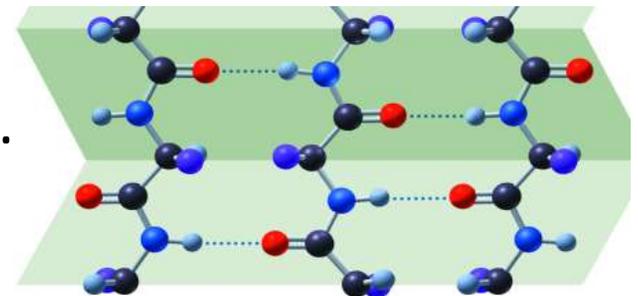
□ The secondary structure of an alpha helix is

- a **three-dimensional** spatial arrangement of amino acids in a polypeptide chain.
- held by **H bonds** between the H of $-N-H$ group and the O of $C=O$ of the **fourth** amino acid down the chain.
- a **corkscrew** shape that looks like a coiled “telephone cord”.



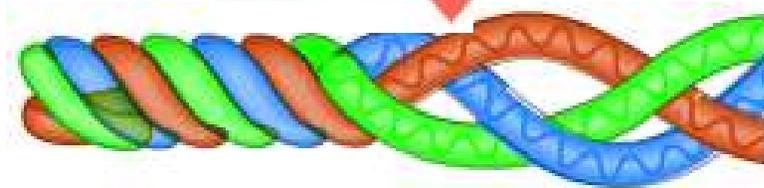
□ The secondary structure a beta pleated sheet

- consists of polypeptide chains arranged **side by side**.
- has hydrogen bonds **between** chains.
- has R groups **above** and **below** the sheet.
- is typical of **fibrous proteins** such as silk.



Secondary structures of proteins

- The secondary structure of a triple helix is
 - three **polypeptide chains** woven together.
 - typical of **collagen**, connective **tissue**, **skin**, **tendons**, and **cartilage**.



Triple helix

3 α -Helix peptide chains

Examples

Indicate the type of protein structure.

- 1) primary 2) alpha helix
3) beta pleated sheet 4) triple helix

- A. Polypeptide chains held side by side by H bonds 3
B. Sequence of amino acids in a polypeptide chain 1
C. Corkscrew shape with H bonds between amino acids 2
D. Three peptide chains woven like a rope 4