Amino Acids and Peptides

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Protein structure and function

- Greek: proteios, primary (importance)
- 50% of body’s dry weight is protein
- Wide range of different functions

<table>
<thead>
<tr>
<th>TYPE</th>
<th>FUNCTION</th>
<th>EXAMPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymes</td>
<td>Catalysts</td>
<td><em>Amylase</em>—begins digestion of carbohydrates by hydrolysis</td>
</tr>
<tr>
<td>Hormones</td>
<td>Regulate body functions by carrying messages to receptors</td>
<td><em>Insulin</em>—facilitates use of glucose for energy generation</td>
</tr>
<tr>
<td>Storage proteins</td>
<td>Make essential substances available when needed</td>
<td><em>Myoglobin</em>—stores oxygen in muscles</td>
</tr>
<tr>
<td>Transport proteins</td>
<td>Carry substances through body fluids</td>
<td><em>Serum albumin</em>—carries fatty acids in blood</td>
</tr>
<tr>
<td>Structural proteins</td>
<td>Provide mechanical shape and support</td>
<td><em>Collagen</em>—provides structure to tendons and cartilage</td>
</tr>
<tr>
<td>Protective proteins</td>
<td>Defend the body against foreign matter</td>
<td><em>Immunoglobulin</em>—aids in destruction of invading bacteria</td>
</tr>
<tr>
<td>Contractile proteins</td>
<td>Do mechanical work</td>
<td><em>Myosin and actin</em>—govern muscle movement</td>
</tr>
</tbody>
</table>
Structure of the amino acids

- General structure (amino, carboxylic, H, R)
- The basis of their classification
- Two vs. 3-dimensional (handedness, chirality, chiral vs. achiral, left vs. right, L vs. D)
Isomers, stereoisomers, enantiomers

- If two molecules have the same number of atoms, they are isomers.
- If the isomers have the same atomic connectivity, but differ spatially, they are stereoisomers.
- If the stereoisomers are mirror images of each other, they are enantiomers.
What should not be forgotten?

• There are a lot of amino acids in life
• There are 20 encoded by the genetic code
• Naturally occurring amino acids in proteins are all “L”
• Chirality makes a difference
• What follows......

Clockwise vs. counter-clockwise “CO – R – N”
## Names and codes

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>3-letter code</th>
<th>1-letter code</th>
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</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>Ala</td>
<td>A</td>
</tr>
<tr>
<td>Arginine</td>
<td>Arg</td>
<td>R</td>
</tr>
<tr>
<td>Asparagine</td>
<td>Asn</td>
<td>N</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td>Asp</td>
<td>D</td>
</tr>
<tr>
<td>Cysteine</td>
<td>Cys</td>
<td>C</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td>Glu</td>
<td>E</td>
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<tr>
<td>Glutamine</td>
<td>Gln</td>
<td>Q</td>
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<tr>
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<td>G</td>
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<tr>
<td>Histidine</td>
<td>His</td>
<td>H</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Ile</td>
<td>I</td>
</tr>
<tr>
<td>Leucine</td>
<td>Leu</td>
<td>L</td>
</tr>
<tr>
<td>Lysine</td>
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<td>K</td>
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<tr>
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<td>Met</td>
<td>M</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Phe</td>
<td>F</td>
</tr>
<tr>
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<td>Pro</td>
<td>P</td>
</tr>
<tr>
<td>Serine</td>
<td>Ser</td>
<td>S</td>
</tr>
<tr>
<td>Threonine</td>
<td>Thr</td>
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<tr>
<td>Tryptophan</td>
<td>Trp</td>
<td>W</td>
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<tr>
<td>Tyrosine</td>
<td>Tyr</td>
<td>Y</td>
</tr>
<tr>
<td>Valine</td>
<td>Val</td>
<td>V</td>
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</table>
## Classification

<table>
<thead>
<tr>
<th>Non-polar</th>
<th>Polar</th>
<th>Charged (positive)</th>
<th>Charged (negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine</td>
<td>Serine</td>
<td>Lysine</td>
<td>Glutamate</td>
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<tr>
<td>Valine</td>
<td>Threoeine</td>
<td>Arginine</td>
<td>Aspartate</td>
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<tr>
<td>Leucine</td>
<td>Glutamine</td>
<td>Histidine</td>
<td></td>
</tr>
<tr>
<td>Isoleuicine</td>
<td>Asparagine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>Cysteine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Tyrosine</td>
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<tr>
<td>Phenylalanine</td>
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<td></td>
</tr>
<tr>
<td>Proline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Charged

Aspartic acid (Asp, D)

Glutamic acid (Glu, E)

Histidine (His, H)

Arginine (Arg, R)

Lysine (Lys, K)
Polar, Uncharged

Amide group

1. Serine (Ser, S)
2. Threonine (Thr, T)
3. Asparagine (Asn, N)
4. Cysteine (Cys, C)
5. Glutamine (Gln, Q)
6. Tyrosine (Tyr, Y)
Non-polar, Uncharged

Glycine (Gly, G)

Alanine (Ala, A)

Valine (Val, V)

Proline (Pro, P)

Leucine (Leu, L)

Isoleucine (Ile, I)

Methionine (Met, M)

Tryptophan (Trp, W)

Phenylalanine (Phe, F)
Amino acids – general structure

- The amino acids obtained by hydrolysis of proteins differ in respect to $R$ (the side chain)
- The properties of the amino acid vary as the structure of $R$ varies
Glycine is the simplest amino acid. It is the only one that is achiral.

In all of the other amino acids the $\alpha$-carbon is a stereogenic center.
Alanine

$\text{H}_3\text{N}\text{C}^+\text{C}^{\text{O}} \text{CH}_3$
Valine

Valine

Branched

(CH₃)₂CH

(Val or V)
Leucine

\[
\text{H}_3\text{N}\quad \text{C}\quad \text{C}\quad \text{O}
\]

\[
\text{CH}_2\text{CH}(\text{CH}_3)_2
\]

(Leu or L)

Branched
Isoleucine

\[
\begin{align*}
\text{H}_3\text{N} & \quad \text{C} \quad \text{C} \quad \text{O} \\
+ & \quad \text{H} \quad \text{O} \\
\text{CH}_2\text{CHCH}_2\text{CH}_3 & \quad \text{Isoleucine} \\
\end{align*}
\]

Branched

(Ile or I)
Methionine

\[
\text{H}_3\text{N} + \text{C} - \text{C} \rightarrow \text{O}^{-} \\
\text{CH}_3\text{SCH}_2\text{CH}_2
\]

Methionine

(Met or M)
Proline (imino)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{C} \quad \text{C} \quad \text{O} \\
+ & \quad \text{H} \quad \text{O} \\
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{C} & \quad \text{H}_2
\end{align*}
\]

Proline

(Pro or P)
Phenylalanine (aromatic)

Phenylalanine

(Phe or F)
Tryptophan (aromatic)
Asparagine

H\textsubscript{3}N \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{O} \quad +

H\textsubscript{2}NC\text{CH}\textsubscript{2}

\text{Asparagine}

\text{(Asn or N)}
Glutamine

(Gln or Q)
Serine

(Ser or S)

How close?
Threonine

\[
\text{H}_3\text{N} + \text{C} \text{C} \text{C} \text{O} = \text{CH}_3\text{CHOH}
\]

Threonine

(Thr or T)

How close?

Valine

(Val. V)
Aspartic Acid

$\text{Asp or D}$
Glutamic Acid

\[
\text{H}_3\text{N} + \text{C} \quad \text{C} \quad \text{C} \quad \text{O}^- \\
\text{OCCH}_2\text{CH}_2 \\
\text{O}
\]

Glutamic Acid

(Glu or E)
Tyrosine (aromatic)

\[
\begin{align*}
&\text{H}_3\text{N} - \text{C} - \text{C} - \text{O} \\
&\text{CH}_2
\end{align*}
\]

Tyrosine (Tyr or Y)
Cysteine

\[
\begin{array}{c}
\text{H}_3\text{N} \\
\text{C} \\
\text{C} \\
\text{O} \\
\text{CH}_2\text{SH}
\end{array}
\]

\text{Cysteine}

(Cys or C)
Lysine

(Lys or K)
Arginine

\[
\begin{array}{c}
+ \\
H_3N
\end{array}
\quad \text{CH}_2\text{CH}_2\text{CH}_2\text{NHCNHNH}_2
\quad \text{Guanidino group}
\]

**Arginine**

(Arg or R)

Strong base; used in production of plastics & explosives
Histidine (imidazole ring)
Amino Acids & life
Modified Amino Acids
Lysine & Proline

• Both are hydroxylated & are part of collagen structure
Glutamate (Glu) & γ-carboxyglutamate (Gla)

- The glutamate residues of some clotting factors are carboxylated to form γ-carboxyglutamate (Gla) residues
  - Vitamin K is essential for the process
- This carboxylation is essential for the function of the clotting factors

Unnumbered figure pg 214 Principles of Biochemistry, 4/e © 2006 Pearson Prentice Hall, Inc.
Glutamate & GABA

- Is a precursor of γ- aminobutyric acid (GABA)
  - Inhibitory neurotransmitter (CNS)
Glutamate & MSG in food

- Monosodium glutamate, or MSG, is a derivative of glutamic acid used as a flavor enhancer.
- MSG may cause Chinese restaurant syndrome (chills, headaches, & dizziness).
Histidine & Histamine

- Regulates physiological function in the gut
- Acts as a neurotransmitter
- Causes allergic symptoms (a major cause for asthma)
- Contributes to inflammatory response
- Causes constriction of smooth muscle
Tryptophan & Serotonin

- Converted to 5-hydroxytryptamine (serotonin, sedative effect)
- Very low levels are associated with depression, while extremely high levels result in manic state
- Tryptophan, milk & sleep
Tryptophan & Melatonin

- Melatonin is a hormone secreted by the pineal gland in the brain.
- It helps regulate other hormones & maintains the body's circadian rhythm (day-night cycle).
Tyrosine & Catecholamine's

• Converted into catecholamine neurotransmitters
  – L-DOPA
  – Dopamine
  – Norepinephrine
  – Epinephrine
  • flight or fight
Tyrosine & MAOs

- The active products are monoamine derivatives (MA). MAOs
- *A Beautiful Mind*, focused on Dopamine
- $\text{MAO}_i$ makes metabolism slow
Tyrosine & Tyramine

- Tyrosine supplements & morning lift
- Cheese & red wines (tyramine; mimics epinephrine); a cheese omelet is a favorite way to start the day
Tyrosine, Thyroxine & Melanin

- Thyroxine (hormone)
- Melanin (skin color)
Ionization of amino acids
Why do amino acids get ionized?

Is it ionizable?
Why do amino acids get ionized?

- At physiological pH, amino acids (without ionizable groups) are electrically neutral.
- **Zwitterion**: a molecule with a net charge of zero ( Isoelectric point; pI)
Effect of pH

Isoelectric zwitterion

\[
\begin{align*}
H_3N^+ - C - H & \quad pK_a = 2.34 \\
\text{COOH} & \quad \text{R} \\

H_3N^+ - C - H & \quad pK_a = 9.69 \\
\text{COO}^- & \quad \text{R}
\end{align*}
\]
Henderson-Hasselbalch Equation

• We have calculated the ratio of acid to conjugate base for an $\alpha$-carboxyl group and an $\alpha$-amino group at pH 7.0

• We can do this for any weak acid and its conjugate base at any pH using the Henderson-Hasselbalch equation

\[
pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{weak acid}]}
\]
Example 1 (Alanine)

\[ \text{pI} = \frac{pK_{a1} + pK_{a2}}{2} \]
Ionization of side chains

• Nine of the 20 amino acids have ionizable side chains
• These amino acids are:
  – Tyrosine, Cysteine, Serine, Threonyne
  – Arginine, Lysine, Histidine
  – Aspartate, Glutamate
• Each side chain has its own $pK_a$ value for ionization
Let’s consider $pK_a$ of $-\text{NH}_2 = 9$ and $pK_a$ of $-\text{COOH} = 2$ for all amino acids.
Titration of amino acids: what happens?

\[ pI = \frac{pK_{a1} + pK_{a2}}{2} \]
General rules for amino acid ionization

• Alpha carboxylic acids ionize at acidic pH & have pKs < 6; So in titration, alpha carboxylic acids lose the proton first

• Alpha amino groups ionize at basic pH & have pKs > 8; So after acids lose their protons, amino groups lose their proton

• Most of the 20 amino acids are similar to Gly
General rules for amino acid ionization

- Aromatic amines “His” have a pK about pH 6
- On titration: alpha carboxylic acids lose their proton first, then side chain carboxylic acids, then aromatic amine side chains (His), then alpha amino groups, then side chain amino groups
- These rules apply to small peptides, and proteins also
Peptides
The peptide bond, peptides, & proteins

• Amide bond
• Condensation reaction
• Directionality
Definitions and concepts

• A residue: each amino acid in a (poly)peptide
• Dipeptide, tripeptide, tetrapeptide, etc.
• Oligopeptide (peptide): a short chain of 20-30 amino acids
• Polypeptide: a longer peptide with no particular structure
• Protein: a polypeptide chains with an organized 3D structures
• The average molecular weight of an amino acid residue is about 110 Da
  – The molecular weights of most proteins are between 5500 and 220,000 (calculate how many amino acids)
• We refer to the mass of a polypeptide in units of Daltons
  – A 10,000-MW protein has a mass of 10,000 Daltons (Da) or 10 kilodaltons (kDa)
Features of the peptide bond

- Resonance structure makes peptide bond
  - Zigzag structure
  - Planar
  - (Un)charged
  - Rigid (double bond)
  - Un-rotatable
Features of the peptide bond

- Hydrogen bonding (exception: proline)
- Cis vs. trans configurations
- Why is it all trans?
Except for proline

- In proline, both *cis* and *trans* conformations have about equivalent energies
- Proline is thus found in the *cis* configuration more frequently than other amino acid residues
Small Peptides with Physiological Activity

- Carnosine (dipeptide), (β-alanyl-L-histidine)
- It is highly concentrated in muscle & brain tissues
  - Antioxidant; protection of cells from ROS (radical oxygen species)
  - Contraction of muscle
Small Peptides with Physiological Activity

- Glutathione (tripeptide)
- (γ-glutamyl-L-cysteinylglycine)
- A scavenger for oxidizing agents
Small Peptides with Physiological Activity

- Enkephalins (pentapeptides), naturally occurring analgesics
- Found in the brain
  - Tyr—Gly—Gly—Phe—Leu (Leucine enkephalin)
  - Tyr—Gly—Gly—Phe—Met (Methionine enkephalin)
- The aromatic side chains of tyrosine and phenylalanine play a role in their activities
- Similarities of three-dimensional structures to opiates (e.g., morphine)
Small Peptides with Physiological Activity

- Some important peptides have cyclic structures. Two well-known hormone examples, oxytocin & vasopressin.
- S-S linkages between Cys.
- Amide group at the C-terminus.
- Nine residues, but:
  - Oxytocin has Ile & L
  - Vasopressin has Phe & Arg.
- Oxytocin regulates contraction of uterine muscle (labor contraction).
- Vasopressin regulates contraction of smooth muscle, increases water retention, & increases blood pressure.
Peptide Hormones - Small Molecules with Big Effects

Vasopressin stimulates reabsorption of water by the kidney, thus having an antidiuretic effect.
Small Peptides with Physiological Activity

- Gramicidin S & tyrocidine A
- Cyclic decapeptides, act as antibiotics (Bacillus brevis)
- Contain D- & L-amino acids
- Both contain ornithine (Orn), which does not occur in proteins

![Chemical structures of Gramicidin S and Tyrocidine A](image)

- **Ornithine (Orn)**
  \[
  \text{Orn} = \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{NH}_3^+ \\
  ^+\text{NH}_3 - \text{CH} - \text{COO}^-
  \]

- **Gramicidin S**
  \[
  \text{L-Val} \rightarrow \text{L-Orn} \rightarrow \text{L-Leu} \rightarrow \text{d-Phe} \rightarrow \text{L-Pro} \\
  \]

- **Tyrocidine A**
  \[
  \text{L-Tyr} \rightarrow \text{L-Glu} \rightarrow \text{L-Asp} \rightarrow \text{d-Phe} \rightarrow \text{L-Phe} \\
  \]

Direction of peptide bond
Aspartame, the Sweet Peptide

- L-aspartyl-L-phenylalanine, commercial importance
- The methyl ester derivative is called aspartame
- 200 times sweeter than sugar
Phenylketonuria

- Inborn errors of metabolism; errors in enzymes of amino acids metabolism
- May have disastrous consequences (mental retardation)
- Phenylketonuria (PKU) is a well-known example
- PKU can be easily detected and managed in newborns
- Aspartame carry a warning
- Alatame (Ala instead of Phe) is a substituent