Chemical Properties of Amino Acids
Protein Function

Make up about 15% of the cell and have many functions in the cell

1. Catalysis: enzymes
2. Structure: muscle proteins
3. Movement: myosin, actin
4. Defense: antibody
5. Regulation: enzymes, hormones
6. Transport: globins
7. Storage: Mb, ferritin
8. Stress Response: hormones
The polymeric Nature of Protein

• Peptides: A short chain of residues with a defined sequence
  – No max number of residues in a peptide
  – Its physical properties are those expected from the sum of its amino acid residues
  – No fixed 3D conformation

• Polypeptide: A longer chain with a defined sequence and length

• Polyamino acids: Nonspecific polymerization of one or a few amino acids

• Protein:
  – Polypeptides that occur naturally
  – Have a definite 3D structure under physiological conditions
Amino acid composition

• Basic Amino Acid Structure:
  – The side chain, R, varies for each of the 20 amino acids
  – In aqueous solution,
    – the amino and carboxylic acid groups will ionize to give the \textbf{zwitterionic} form:

\[ ^{+}\text{H}_3\text{N}-\text{CHR}-\text{CO}_2\text{^-} \]
General Amino Acid Structure
At pH 7.0

\[
\begin{array}{c}
+H_3N \quad C^\alpha \quad COO^- \\
H \\
R
\end{array}
\]
H₂N−C−C−OH
Glycine (Gly) G

H₂N−C−C−OH
Alanine (Ala) A

H₂N−C−C−OH
Valine (Val) V

H₂N−C−OH
Leucine (Leu) L

H₂N−C−C−OH
Isoleucine (Ile) I

H₃N−C−C−OC−OH
Proline (Pro) P

H₂N−C−C−OH
Methionine (Met) M

H₂N−C−C−OH
Cysteine (Cys) C

H₂N−C−C−OH
Serine (Ser) S

H₂N−C−C−OH
Threonine (Thr) T

H₂N−C−C−OH
Aspartic acid (Asp) D

H₂N−C−C−OH
Glutamic acid (Glu) E

H₂N−C−C−OH
Asparagine (Asn) N

H₂N−C−C−OH
Glutamine (Glu) Q

H₂N−C−C−OH
Lysine (Lys) K

H₂N−C−C−OH
Arginine (Arg) R

H₂N−C−C−OH
Histidine (His) H

H₂N−C−C−OH
Phenylalanine (Phe) F

H₂N−C−C−OH
Tyrosine (Tyr) Y

H₂N−C−C−OH
Tryptophan (Trp) W

~50% at pH 7

+1

+1
Stereochemistry

- Note that the R group means that the $\alpha$-carbon is a chiral center.
- All natural amino acids are L-amino acids.
- This means that almost all have the S configuration.
- Rules for assigning R/S configuration:
  Configuration is assigned by "looking" down the bond to the lowest priority substituent and assigning R to the configuration where the remaining substituents are arranged clockwise in decreasing priority
  Group Priorities: SH > OH > NH$_2$ > COOH > CHO > CH$_2$OH > C$_6$H$_5$ > CH$_3$ > H
  Clockwise: R, counterclockwise: S configuration

(Exceptions: glycine and cysteine –R configuration)
(a) L-Alanine

(b) L-Alanine

(c) L-Alanine
# Amino acid abbreviations

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Three-letter abbreviation</th>
<th>One-letter abbreviation</th>
<th>Amino acid</th>
<th>Three-letter abbreviation</th>
<th>One-letter abbreviation</th>
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<tbody>
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<td>Alanine</td>
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<td>A</td>
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<td>M</td>
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<td>Pro</td>
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<td>Gln</td>
<td>Q</td>
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<td>Trp</td>
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<td>V</td>
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<td>H</td>
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<td>Asx</td>
<td>B</td>
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<td>Isoleucine</td>
<td>Ile</td>
<td>I</td>
<td>Glutamine or glutamic acid</td>
<td>Glx</td>
<td>Z</td>
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<td>Leucine</td>
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<td>L</td>
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<td>Lysine</td>
<td>Lys</td>
<td>K</td>
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</table>
Numbering (lettering) amino acids

α-carbon

α-carboxyl (attached to the α-carbon)

α-amino

ε-amino group

lysine

α-carbon
Side chain nomenclature:

- Numbered according to the Greek $\alpha\lambda\phi\alpha\beta\varepsilon\tau$!
- Branches:
  - Same alphabetic subscript.
  - "Heavier" atom = 1.
- Computer storage: no Greek alpha’s/subscripts
  - E.g. OE2 means $O_{\varepsilon2}$. 
Aromatic ring numbering/naming (IUPAC)

IUPAC nomenclature:
http://www.chem.qmw.ac.uk/iupac/AminoAcid/index.html
Amino Acid Groups 1

Based on chemical characteristics of R groups

1. Polar and negative charge (aspartic acid and glutamic acid)
2. Polar and positive charge (arginine, lysine, histidine)
3. Polar and uncharged (asparagine, glutamine, serine, threonine, tyrosine)
4. Nonpolar (alanine, glycine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan, cysteine)
Character of amino acid side chains

- Amino acids don’t fall neatly into classes--they are different combinations of small/large, charged/uncharged, polar/nonpolar properties
- How we casually speak of them can affect the way we think about their behavior.
- The properties of a residue type can also vary with conditions/environment
Nonpolar, aliphatic R groups

Glycine

Alanine

Proline

Valine

Leucine

Isoleucine

Methionine
Aromatic R groups

- Phenylalanine
- Tyrosine
- Tryptophan
Absorption spectra of Trp & Tyr

Beer’s law: $A = \varepsilon cl$. Used to estimate protein concentration
Polar, uncharged R groups

- **Serine**: \( \text{H}_3\text{N}^+ - \text{C} - \text{H} - \text{CH}_2\text{OH} \)
- **Threonine**: \( \text{H}_3\text{N}^+ - \text{C} - \text{H} - \text{H} - \text{C} - \text{OH} - \text{CH}_3 \)
- **Cysteine**: \( \text{H}_3\text{N}^+ - \text{C} - \text{H} - \text{CH}_2 - \text{SH} \)
- **Asparagine**: \( \text{H}_3\text{N}^+ - \text{C} - \text{H} - \text{CH}_2 - \text{C} - \text{O} - \text{H}_2\text{N} \)
- **Glutamine**: \( \text{H}_3\text{N}^+ - \text{C} - \text{H} - \text{CH}_2 - \text{C} - \text{O} - \text{H}_2\text{N} \)
Negatively charged R groups

Aspartate

Glutamate
Grouping of Amino Acids 2

• By side chain properties
  – Size
  – Charge
  – Polarity

• Gly, Cyclic imino acid, Aliphatic, Hydroxyl, Acidic, Amide, Basic, His (imidazole), Aromatic, Sulfur-containing
Glycine

No D- and L-isomer
Cyclic Imino Acid - Proline
Aliphatic Amino Acids

V

CH₃

H₂N

C

COOH

H

CH₃

I

CH₃

H₂N

C

COOH

H

CH₃

A

CH₃

H₂N

C

COOH

H

CH₃

L

CH₃

CH₃

H₂N

C

COOH

H
Hydroxylic Amino Acids

- Thr
- Ser
Acidic Amino Acids

Asp

Glu
Amide Group

Asn

Gln
Basic Amino Acids

Lys

Arg
Imidazole Side Chain - Histidine
Aromatic Amino Acids

- Trp
- Tyr
- F
- Phe
Sulfo-Amino Acids

\[
\text{C} \quad \text{SH} \quad \text{C} \quad \text{CH}_3 \\
\text{C} \quad \text{COOH} \quad \text{C} \quad \text{COOH} \\
\text{H}_2N \quad \text{H} \quad \text{H}_2N \quad \text{C} \\
\]

\[
\text{M} \\
\]
Cysteine and cystine

Pairs of cysteines frequently undergo oxidation to a disulfide bonded form called “cystine”

\[ 2 \text{CH}_2\text{SH} + \frac{1}{2}\text{O}_2 \rightarrow \text{CH}_2\text{S}--\text{SCH}_2 \quad + \text{H}_2\text{O} \]

2 cysteines

cystine

more hydrophobic than cysteine

disulfide exchange

\[ \text{R}_1\text{S}^{\ominus} + \text{R}_2\text{S}--\text{SR}_2 \rightarrow \text{R}_2\text{S}^{\ominus} + \text{R}_1\text{S}--\text{SR}_2 \]

disulfide exchange occurs through the thiolate anion at neutral to basic pH

Basis of Ellman assay – assay of thiol group. Use dithionitrobenzoic acid (DTNB) results in formation of nitrobenzoic acid (yellow aromatic thiol).
Sizes of amino acids

<table>
<thead>
<tr>
<th>a.a</th>
<th>mass (dalton)</th>
<th>Van der Waals Volume (A³)</th>
<th>a.a</th>
<th>mass (dalton)</th>
<th>Van der Waals Volume (A³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>71.09</td>
<td>67</td>
<td>L</td>
<td>113.16</td>
<td>124</td>
</tr>
<tr>
<td>R</td>
<td>156.19</td>
<td>148</td>
<td>K</td>
<td>128.17</td>
<td>135</td>
</tr>
<tr>
<td>D</td>
<td>115.09</td>
<td>96</td>
<td>M</td>
<td>131.19</td>
<td>124</td>
</tr>
<tr>
<td>N</td>
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<td>C</td>
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<tr>
<td>E</td>
<td>129.12</td>
<td>109</td>
<td>S</td>
<td>87.08</td>
<td>73</td>
</tr>
<tr>
<td>Q</td>
<td>128.14</td>
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<td>T</td>
<td>101.11</td>
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</tr>
<tr>
<td>G</td>
<td>57.05</td>
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<td>W</td>
<td>186.21</td>
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<tr>
<td>H</td>
<td>137.14</td>
<td>118</td>
<td>Y</td>
<td>163.18</td>
<td>141</td>
</tr>
<tr>
<td>I</td>
<td>113.16</td>
<td>124</td>
<td>V</td>
<td>99.14</td>
<td>105</td>
</tr>
</tbody>
</table>

Weighted Avg 119.40 161
Can group into several categories:

1) alkanes: A V I L (P)
2) aromatics: F W Y (H)
3) carboxylates: D E
4) corresponding amides: N Q
5) positively charged: K R (H)
6) Sulfur-containing: C M
7) hydroxyls: S T Y
Can group into several categories:

8)  $\beta$-branched: V T I
9)  small: G A S C (V T...)
10) large: W R Y F (M...)
11) H-bond donors: S T Y N Q K R H W
    (D & E, if protonated)
12) H-bond acceptors: S T Y N Q D E R H W
Grouping the amino acids by properties

from http://www.russell.embl-heidelberg.de/aas/

which adapted it from Livingstone & Barton, CABIOS, 9, 745-756, 1993.
Acid-Base Properties of Amino Acids

• Amino acids form zwitterions (dipolar ions) at neutral pH

• Therefore, amino acids can act as acids (proton donor) and bases (proton acceptor), often called ampholytes.

• Hence a simple amino acid, like Alanine below, can yield two protons.
Ionization state as a function of pH

Physiological pH (measure of \([H^+]\))
Shifting of side chain titration curves

![Diagram showing the shift of side chain titration curves with pH values ranging from 3 to 14. The curve for Histidine (His+) is shown with eq. OH⁻ added at pH 7, indicating the physiological pH range. The pKₐ is marked at pH 8. The chemical structure of Histidine is also shown.]
pK$_a$ of ionizable side chains

**TABLE 3.1** Typical pK$_a$ values of ionizable groups in proteins

<table>
<thead>
<tr>
<th>Group</th>
<th>Acid</th>
<th>Base</th>
<th>Typical pK$_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal α-carboxyl group</td>
<td></td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Aspartic acid</td>
<td></td>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>Glutamic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histidine</td>
<td></td>
<td></td>
<td>6.0</td>
</tr>
<tr>
<td>Terminal α-amino group</td>
<td></td>
<td></td>
<td>8.0</td>
</tr>
<tr>
<td>Cysteine</td>
<td></td>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td>Tyrosine</td>
<td></td>
<td></td>
<td>10.9</td>
</tr>
<tr>
<td>Lysine</td>
<td></td>
<td></td>
<td>10.8</td>
</tr>
<tr>
<td>Arginine</td>
<td></td>
<td></td>
<td>12.5</td>
</tr>
</tbody>
</table>

*pK$_a$ values depend on temperature, ionic strength, and the microenvironment of the ionizable group.*
Titration Curves of Amino Acids with Ionizing Side Chain

Figure 5-12, p. 125: Lehninger Principles of Biochemistry
Ionization of Amino Acids

Equilibrium dissociation constant;

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

Henderson-Hasselbolch Equation;

$$-\log[H^+] = -\log K_a + \log \frac{[A^-]}{[HA]}$$

$$\text{pH} = pK_a + \log \frac{[A^-]}{[HA]}$$

$$\text{pH} = pK_a \quad @ \quad [A^-] = [HA]$$
How to calculate pI

• The isoelectric point (pI) of an amino acid or peptide is the pH at which the charge of the molecule = 0.

• It can be calculated simply as the arithmetic mean of the 2 pKₐ's corresponding to the transitions generating the +1 and -1 forms.
How to calculate pI

1. Identify all ionizable groups
2. Assign pK$_a$’s to each ionizable group
3. Start with each ionizable group in protonated form (very low pH – maybe 0 or 1) and calculate its net charge
4. Slowly move up in pH to the first ionizable group’s pK$_a$ and deprotonate it (reduce charge by 1)
5. Do this until each group is deprotonated. Now you have identified all charged forms and at which pH each transition occurs.
6. Identify the form with net charge = 0
7. Take the pK$_a$ on either side of the electrically neutral form and take their average. This is the pI.
The diagram represents the pH titration curve of glycine. The pK values are indicated as follows:

- pK₁ = 2.34
- pK₂ = 9.60

The isoelectric point (pI) of glycine is pI = 5.97.
How to calculate pI

Take **Glycine** as an example – it has only 2 ionizable groups. The transition (from low to high pH) would be:

\[
\text{Gly}^{+1} \rightarrow \text{Gly}^0 \rightarrow \text{Gly}^{-1}
\]

\[
\text{pK}_a (-\text{CO}_2\text{H}) = 2.34; \text{ pK}_a (-\text{NH}_3^+) = 9.60
\]

\[
pI = (2.34 + 9.60)/2 = 11.94/2 = 5.97
\]
The molecule shown is glutamate. It has three pK values, pK₁, pKᵣ, and pK₂. The pK values are as follows:

- pK₁ = 2.19
- pKᵣ = 4.25
- pK₂ = 9.67

These pK values indicate the pH at which the molecule is in the form of glutamate (COO⁻) and glutamate (CH₂COO⁻) respectively.
How to calculate pI

Glutamate has an ionizable group (-CO₂H; pKₐ = 4.25) that generates a negative charge when deprotonated. Its transitions would be:
Glu⁺¹ → Glu⁰ → Glu⁻¹ → Glu⁻²

The relevant pKₐ 's are
pKₐ(-CO₂H) = 2.19; pKₐ(R) = 4.25

pl = (2.19 + 4.25)/2 = 6.44/2 = 3.22
How to calculate pI

**Histidine** has an ionizable group (imidazole; \(pK_a = 6.00\)) that is positively charged when protonated. Its transitions would be:

\[ \text{His}^{+2} \rightarrow \text{His}^{+1} \rightarrow \text{His}^0 \rightarrow \text{His}^{-1} \]

The relevant \(pK_a\)'s are

\[ pK_a(R) = 6.00; \quad pK_a(-\text{NH}_3^+) = 9.17 \]

\[ \text{pI} = (6.00 + 9.17)/2 = 15.17/2 = 7.59 \]
### TABLE 3-1  Properties and Conventions Associated with the Common Amino Acids Found in Proteins

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>Abbreviation/symbol</th>
<th>$M_r$</th>
<th>$pK_a$ values</th>
<th>$pK_{1a}$ (–COOH)</th>
<th>$pK_{2a}$ (–NH$_3^+$)</th>
<th>$pK_{R}$ (R group)</th>
<th>$pI$</th>
<th>Hydropathy index*</th>
<th>Occurrence in proteins (%)$^\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polar, uncharged</strong></td>
<td></td>
<td></td>
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<td></td>
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<td>Serine</td>
<td>Ser S</td>
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</tbody>
</table>

* A scale combining hydrophobicity and hydrophilicity of R groups; it can be used to measure the tendency of an amino acid to seek an aqueous environment (− values) or a hydrophobic environment (+ values). See Chapter 11. From Kyte, J. & Doolittle, R.F. (1982) A simple method for displaying the hydropathic character of a protein. J. Mol. Biol. 157, 105-132.

Peptide bond

Primary structure of protein: Between AAs

α-carboxyl group of one AA & α-amino group of another

2 amino acids → Dipeptide → Loss of H₂O

Peptide bond
Making dipeptides

\[ ^+\text{H}_3\text{N-CHR-CO}_2^- + ^+\text{H}_3\text{N-CHR-CO}_2^- \rightarrow \]
\[ ^+\text{H}_3\text{N-CHR-CONH-CHR-CO}_2^- + \text{H}_2\text{O} \]

This process can be repeated to make a tripeptide and so on:

\[ ^+\text{H}_3\text{N-CHR-CONH-CHR-CO}_2^- + ^+\text{H}_3\text{N-CHR-CO}_2^- \rightarrow \]
\[ ^+\text{H}_3\text{N-CHR-CONH-CHR-CONH-CHR-CO}_2^- \]
Making dipeptides

The C-N bond has partial double bond character, making the -CONH- moiety planar.

This limits the orientations available to the polypeptide
Peptide bond

Double bond character
Prevents rotation about this bond

Bond length:
- C-N peptide = 1.32 Å
- C-N single bond = 1.49 Å
- C-N double bond = 1.27 Å

Two configurations (cis & trans) possible. Only trans used
Consequences of double bond character in the peptide bond

The peptide C-N bond is 0.12 Å shorter than the Calpha-N bond, and the C=O is 0.02 Å longer than that of aldehydes and ketones.

All six of the atoms highlighted at left lie in the same plane, and as with carbon-carbon double bonds there are two configurations—cis and trans (trans shown at left).
...and that means that the dihedral angle describing rotation around the peptide bond, defined by the four atoms $C\alpha(i)-C-N-C\alpha(i+1)$, will generally be close to $180^\circ$. This angle is known by the greek symbol $\omega$.

So the properties of the peptide bond place a strong restriction on the backbone conformation or main-chain conformation of proteins, that is to say, the spatial configuration of the non side-chain atoms.
Consequences of double bond character in the peptide bond

*trans* peptide bond

Still another consequence: in the *cis* form, the R groups in adjacent residues tend to clash. Hence almost all peptide bonds in proteins are in the *trans* configuration.
Main chain or backbone

Constant backbone: regularly repeating part

Distinctive side chains (R-groups): variable part

AA unit in a polypeptide is called a residue, which contains, a carbonyl group; good hydrogen-bond acceptor, an NH group (except Pro); good hydrogen-bond donor
Polypeptide chain has direction

Tyr   Gly   Gly   Phe   Leu

Amino terminal residue → Carboxyl terminal residue
Proteins are chains of amino acids

- **Polymer** – a molecule composed of repeating units