\textbf{\textit{\(\alpha\)-Amino Acids}}

\[ \text{\(\alpha\)-Amino Acids:} \quad \text{H} \quad \xleftarrow{\text{pk}_a = 2-3} \quad \text{\(\text{NH}_2\)} \quad \text{\(\alpha\)} \quad \text{\(\text{C}^\text{\(\alpha\)}\)} \quad \text{\(\text{CO}_2\text{H}\)} \]

\[ \text{\(\text{Zwitterion}\)} \quad \text{Form} \quad \text{(pH 4-8)} \]

20 Common Natural Amino Acids.

\underline{Stereochemistry of \(\text{\(\alpha\)}\) Carbon}

\[
\begin{align*}
\text{\(\text{NH}_2\)} & \quad \text{CO}_2\text{H} & \quad \text{R} & \quad \text{CO}_2\text{H} \\
\text{R} & \quad \text{H} & \quad \text{NH}_2 & \quad \text{H}
\end{align*}
\]

\underline{Chiral Center}

\underline{Enantiomers}

\text{\textit{\(\alpha\)}-Amino acids in patients are always L-}

\text{\textit{\(\alpha\)}-Amino acids in patients are always L-}
2.2 AMINO ACIDS - THE BUILDING BLOCKS

![Structures of L- and D-amino acids](image)

FIG. 2.1 The structures of (a) an L-amino acid and (b) a D-amino acid.

PROTEIN ANATOMY

![Protein structure](image)

FIG. 6. The "central". Antimetric for the handedness of amino positions around the asymmetric carbon in naturally occurring L-amino acids. Looking down on the α-carbon from the direction of the hydrogen atom, the other branches should be CO—R—N, reading clockwise (i.e., carboxy, side-chain R, main-chain N).
The Peptide Bond Joins Two Amino Acid Residues
Peptides and Proteins

Polymers of Amino Acids.

Peptides 2-50

Proteins 50-1500

\[
\begin{align*}
\text{NH}_3^- & \quad \text{C} \quad \text{C} \quad \text{C} \quad \text{O}^- \\
& \quad \text{R}_1 \\
\text{H} & \quad \text{O} & \quad \text{H} \\
\text{NH}_3^- & \quad \text{C} \quad \text{C} \quad \text{O}^- \\
& \quad \text{R}_2 \\
\rightarrow & \quad \text{NH}_3^- \quad \text{C} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{C} \quad \text{O}^- \\
& \quad \text{R}_1 \quad \text{R}_2 \\
\text{peptide bond} & \quad + \quad \text{H}_2\text{O}
\end{align*}
\]
PRIMARY STRUCTURE OF tPA

KRINGLE-1

KRINGLE-2

"ACTIVATION SITE"

FINGER

EGF

SERINE PROTEASE

COOH
Basic Biophysical Chemistry

- Electrostatic Interactions
- Van der Waals Interactions
- Hydrogen-bonded Interactions
- Hydrophobic Interactions

\[ \Delta G_{ab} = \Delta H - T \Delta S \]
\[ \Delta G_{ab} = -RT \ln K_{ab} \]
Planarity of Peptide Bond.

\[ \text{Co} \quad \text{C} \quad \text{N} \quad \text{C} \quad \Theta \quad \text{C} \quad \text{C} \quad \text{H} \quad \leftrightarrow \quad \text{C} = \text{N}^+ \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{Ca} \]

\[ \text{C} \quad \text{C} \quad \text{N} \quad \text{C} \quad \text{H} \quad \Theta \quad \text{C} \quad \text{C} \quad \text{H} \quad \text{Ca} \]

\[ \text{Trans} \quad \leftrightarrow \quad \text{Cis} \]

\[ \Delta G = 5 \text{ kcal/mol} \]

\[ 180 \quad \omega \quad 0 \]
X-Pro Peptide Bonds.

Trans

Cis

$\Delta 6 N O.$
Dihedral Angles in Polypeptides

\[
\begin{align*}
\phi & \quad \psi & \quad \chi_1 & \quad \chi_2 & \quad \chi_3 \\
C^\alpha & \quad N & \quad C & \quad N-C^\alpha \\
C^\alpha & \quad \cdot & \quad \cdot & \quad \cdot & \quad \cdot \\
H & \quad \cdot & \quad \cdot & \quad \cdot & \quad \cdot \\
N & \quad C^\alpha & \quad \cdot & \quad \cdot & \quad \cdot \\
\end{align*}
\]
Amide plane

\[ \phi = 180^\circ, \psi = 180^\circ \]

\[ \alpha - \text{Carbon} \]

Side group

Overhead transparencies to accompany Garrett/Grisham: Biochemistry page 140
Transparency 15 Figure 5.3 ©1998 Saunders College Publishing
Figure 2.5. The planar characteristics of the peptide bond, and rotation of the peptide backbone about the $C_\alpha$ atom. Note the two planar peptide bonds about a central alpha carbon, shown here as a ball-and-stick model. Rotation is only possible about the $\Phi$ ($C_\alpha-N$) and $\Psi$ ($C_\alpha-C$) angles. Arrows about the two angles show the direction that is considered positive rotation. In this figure, both angles are approximately 180°. From R.E. Dickerson and I. Geis. The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
Ramachandran Plot of Polypeptide Conformation

$n = \# \text{ residues} / \text{ turn}$
Ac-L-Ala-NHMe

FIG. 7. Plot of main chain dihedral angles \( \phi \) and \( \psi \) (see Fig. 2 for definitions) experimentally determined for approximately 1000 N-acetyl glycine residues in eight proteins whose structures have been refined at high resolution (chosen to be representative of all categories of tertiary structure).

Ac-Gly-NHMe

FIG. 8. Plot of main chain dihedral angles \( \phi \) and \( \psi \) experimentally determined for the glycines in 20 high-resolution protein structures.

Figure 1. Conformational energy contour map of N-acetyl-N'-methylglycineamide. Locations of minima are indicated by the filled circles (also see Table II). The contour lines are labeled with energy in kcal/mol above the minimum-energy point at \( \phi = 104^\circ, 78^\circ \).

Figure 2. Conformational energy contour map of N-acetyl-N'-methyl-\( \alpha \)-aminoamide. Locations of minima are indicated by the filled circles (also see Table II). The contour lines are labeled with energy in kcal/mol above the minimum-energy point at \( \phi = 135^\circ, 78^\circ \).
\[ p = \frac{\text{Rise}}{\text{turn}} = \frac{\Delta Z}{\text{turn}} \]

\[ \text{Rise} (h) = \frac{\Delta Z}{\text{Residue residue}} \]

\[ \text{Pitch} (p) = \frac{\Delta Z}{\text{turn}} = \frac{\text{Rise}}{\text{turn}} \]
The hydrogen bonding patterns of different helical secondary structures. The peptide backbone is shown in an extended conformation, noting the hydrogen bonding pairings that would occur in each type of helix. The common α helix, depicted in Figure 2.7, forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 4 residues ahead in the helix. The $3_{10}$ helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 3 residues ahead, forming a more narrow and elongated helix. The $\pi$ helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue five residues ahead, forming a wider helix. Regular secondary structure, but is shown here to demonstrate all possible hydrogen bond pairings. From R. E. Dickerson and I. Geis. The Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
The Right-Handed Alpha Helix (\(3.6_{13}\) Helix)

- Alpha helix
- 3.6 residues / turn
- 5.4 Ang / turn
- 13 atoms / H-bond loop

Figure 2.8. The hydrogen bonding patterns of different helical secondary structures. The peptide backbone is shown in an extended conformation, with an arrow denoting the hydrogen bonding pairings that would occur in each type of helix. The common \(\alpha\) helix, depicted in Figure 2.7, forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 4 residues ahead in the helix. The \(3_{10}\) helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 3 residues ahead, forming a more narrow and elongated helix. The \(\pi\) helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue five residues ahead, forming a wider helix. The \(2_{1}\) ribbon is not a regular secondary structure, but is shown here to demonstrate all possible hydrogen bond pairings. From R. E. Dickerson and I. Geis. The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
Figure 2.7. Diagram of an α helix using a ball-and-stick model. The bonds forming the backbone of the polypeptide are darkly shaded. The α helix is stabilized by internal hydrogen bonds formed between the carbonyl oxygen of each residue and the amide proton of the residue 4 residues ahead in the helix, shown here as dashed lines. Note that the polypeptide backbone curves towards the right, and as such the α helix is a right-handed helix. From R.E. Dickerson and J. Geis. The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Geis Archives.
Alpha Helix
3.6 residues / turn
13 atoms / H-bonded loop
Figure 2.4. The backbone of a protein shows different structural arrangements. The bumps indicate an extended conformation, with an increasing number of hydrogen bonds between the main chain atoms and the backbone atoms. This results in a more packed and rigid structure. The diagram illustrates the arrangement of the backbone atoms in a protein molecule, showing the hydrogen bonds that contribute to the stability of the structure.
Helix Dipole
Amphipathic Helices - every 3-4 residues is hydrophobic
Four Helical Bundle
With Antiparallel Helices

Amphipathic Helices forming a Hydrophobic Core
Beta-Sheets

Top - antiparallel

Bottom - parallel
Ramachandran Plot of Polypeptide Conformation

$n = \# \text{ residues} / \text{ turn}$
Beta-Turns (tight turns)

Antigen binding sites from a known antibody sequence is thus essentially a problem of modeling the three-dimensional structures of loop regions since the core structures of all antibodies are very similar. Such model building has been
Beta-Turns
(tight turns)

Fig. 30. The two major types of tight turn (I and II). In type II (bottom), R₂ is generally glycine.
Principal Classes of Proteins

- Globular
- Membrane
- Fiberous
Representations of Protein Structures

a - full atom

b,c - strands / helices

d - Topology diagrams
Storing Protein Structure Information

**Cartesian Coordinates**
- x,y,z coordinate for each atom
- 3 per atom / 30 - 100 per residue

**Dihedral Angles**
- assumes fixed bond lengths and fixed bond angles
- 3 - 8 per residue

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Principal Protein Fold Classes

- All alpha
- All beta
- alpha + beta
- alpha / beta
Classification of Protein Folds

- SCOP
- CATH
- DALI / FSSP
Protein Domains

“Independent Folding Units”

50 - 350 residues
Mean size - 125 residues

Alpha folds; Beta Folds;
Alpha+Beta Folds; Alpha/Beta Folds
Most proteins in biology have been produced by the duplication, divergence and recombination of the members of a small number of protein domain families.
Domain Combinations in Genome Sequences

In bacteria close to
1/3 of proteins consist of one domain and
2/3 consist of two or more domains.

In eukaryotes close to
1/4 of proteins consist of one domain and
3/4 consist of two or more domains.

courtesy of C. Chothia