$\alpha$-Amino Acids

\[
\begin{align*}
\text{H} & \quad \kappa \quad \text{pK}_a = 2-3 \\
\text{NH}_2 - C^\alpha - \text{COOH} & \\
pK_a = 9-10 & \quad \text{R} \\
\text{Zwitterionic} & \\
\text{Form} & \\
(\text{pH} 4-8)
\end{align*}
\]

20 Common Natural Amino Acids.

**Stereochemistry of C$^\alpha$ Carbon**

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

**Chiral Center**

\[
\text{Amino acids in proteins are always L-}
\]

**Enantiomer**

\[
\text{L-amino acid} \quad \text{D-amino acid}
\]
2.2 AMINO ACIDS - THE BUILDING BLOCKS

![Amino acid structures](image)

**FIG. 3.1** The structures of (a) an L-amino acid and (b) a D-amino acid.

PROTEIN ANATOMY

![Protein structure](image)

**FIG. 4.** The "crown". Anatomical for the handedness of atomic positions around the asymmetric carbon in naturally occurring L-amino acids. Looking down on the carbon from the direction of the hydrogens atoms, 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

\[ \text{NH}_3 - \text{C} - \text{C} - \text{O} + \text{NH}_3 - \text{C} - \text{C} - \text{O} \]

[Diagram of peptide bond formation]

\[ \text{peptide bond} + \text{H}_2\text{O} \]
PRIMARY STRUCTURE OF tPA
Basic Biophysical Chemistry

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

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

\[
\begin{align*}
\text{trans} & \quad \Delta G \approx 5 \text{ kJ/mol} \\
\text{cis} & \quad \Delta G \approx -5 \text{ kJ/mol}
\end{align*}
\]
X-Pro Peptide Bonds.

\[
\begin{align*}
X &\quad \text{Pro} &\quad \text{Peptide Bonds} \\
\text{trans} &\quad \text{cis} &\quad \Delta 6 \text{ NO}
\end{align*}
\]
Dihedral Angles in Polypeptides
Figure 2.5. The planar characteristics of the peptide bond, and rotation of the peptide backbone about the C\text{\textalpha} 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 \( \Phi (\text{C}_{\text{\textalpha}} - \text{N}) \) and \( \Psi (\text{C}_{\text{\textalpha}} - \text{C}) \) 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

\[ n = \# \text{ residues} / \text{ turn} \]
Figure 7. Plot of main chain dihedral angles $\phi$ and $\psi$ (see Fig. 2 for definitions) experimentally determined for approximately 1000 anglycine residues in eight proteins whose structures have been refined at high resolution (chosen to be representative of all categories of tertiary structure).

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

Ac-L-Ala-NHMe

Ac-Gly-NHMe
\[ P = \frac{\text{Rise}}{\text{Rake}} \times \text{TPI} \]

\[ \text{TPI} = \frac{P}{\text{Rake}} \]

\[ \text{N} = \frac{P}{\text{TPI}} \]

\[ \text{Pitch} (\text{P}) = \frac{A_2}{n} \]

\[ \text{Tension} \quad \text{Tension} \]

\[ \text{foot} \]
8. 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 bonds between the carbonyl oxygen of each residue and the amide proton of the residue five residues ahead, forming a wider helix. A 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

(3.6₁₃ 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 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 3₁₀ 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 π helix forms hydrogen bonds between the carbonyl oxygen of each residue and the amide proton of the residue 5 residues ahead, forming a wider helix. The 2₁ ribbon is not a regular secondary structure, but is shown here to demonstrate all possible hydrogen bond pairings. From R. E. Dickerson and J. Gell. The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Gels Archives.
Right-handed alpha helix
Alpha Helix
3.6 residues / turn
13 atoms / H-bonded loop
Figure 26. 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 α helix, depicted in Figure 27, 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 β 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. Dickson and J. Engel, The Structure and Action of Proteins. New York: Harper & Row, 1969. Used with permission from Gels Archives.
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)
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

```
ATOM      1  C   ACE     0       9.401  30.166  60.595  1.00  
ATOM 49.88 1GKY 67
ATOM      2  O   ACE     0      10.432  30.832  60.722  1.00  
ATOM 50.35 1GKY 68
ATOM      3  CH3 ACE     0       8.876  29.767  59.226  1.00  
ATOM 50.04 1GKY 69
ATOM      4  N   SER     1       8.753  29.755  61.685  1.00  
ATOM 49.13 1GKY 70
ATOM      5  CA  SER     1       9.242  30.200  62.974  1.00  
ATOM 46.62 1GKY 71
ATOM      6  C   SER     1      10.453  29.500  63.579  1.00  
ATOM 41.99 1GKY 72
ATOM      7  O   SER     1      10.593  29.607  64.814  1.00  
ATOM 43.24 1GKY 73
ATOM      8  CB  SER     1      10.593  29.607  64.814  1.00  
ATOM 53.00 1GKY 74
ATOM      9  OG  SER     1       7.294  31.409  63.930  1.00  
ATOM 57.79 1GKY 75
ATOM     10  N   ARG     2      11.360  28.819  62.827  1.00  
ATOM 62.94 1GKY1515
```
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.

courtesy of C. Chothia
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