Molecular Cell Biology A

“Protein structure and pathways”

BIOX24ZL
Tuesdays 9-10:30
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THE AMINO ACID

The general formula of an amino acid is

\[
\text{H}_2\text{N} \quad \text{C} \quad \text{COOH}
\]

\- \text{amino group}
\- \text{\(\alpha\)-carbon atom}
\- \text{carboxyl group}
\- \text{side-chain group}

\(R\) is commonly one of 20 different side chains. At pH 7 both the amino and carboxyl groups are ionized.

Panel 1: (Part 2) Molecular Biology at the Grid (c)©-Garland Science 2015
**PEPTIDE BONDS**

Amino acids are commonly joined together by an amide linkage, called a peptide bond.

**Peptide bond:** The four atoms in each gray box form a rigid planar unit. There is no rotation around the C-N bond.

Proteins are long polymers of amino acids linked by peptide bonds, and they are always written with the N-terminus toward the left. The sequence of this tripeptide is histidine-cysteine-valine.

These two single bonds allow rotation, so that long chains of amino acids are very flexible.
Proteins are specified by their amino acid sequence.

- Polypeptide backbone with AA side chains
- Bond angle restricted, weak noncovalent bond: H+, electrostatic, van der Waals determine final 3D shape
- Nonpolar (hydrophobic) side chains (Leu Phe Trp Val) cluster together interior to H+ water
- Polar (hydrophilic) side chains (Asp- Arg+ His+ Gln polar) H+ bond outside, backbone interact
OPTICAL ISOMERS

The α-carbon atom is asymmetric, which allows for two mirror images (or stereo-) isomers, L and D.

Proteins consist exclusively of L-amino acids.

Figure 3.4: Molecular Biology of the Cell (© Garland Science 2013)
FAMILIES OF AMINO ACIDS

The common amino acids are grouped according to whether their side chains are

- acidic
- basic
- uncharged polar
- nonpolar

These 20 amino acids are given both three-letter and one-letter abbreviations.

Thus: alanine = Ala = A
BASIC SIDE CHAINS

**lysine**
(Lys, or K)

**arginine**
(Arg, or R)

**histidine**
(His, or H)

This group is very basic because its positive charge is stabilized by resonance.

These nitrogens have a relatively weak affinity for an H⁺ and are only partly positive at neutral pH.

ACIDIC SIDE CHAINS

**aspartic acid**
(Asp, or D)

**glutamic acid**
(Glu, or E)
NONPOLAR SIDE CHAINS

- Alanine
  (Ala, or A)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_3
  \end{array}
  \]
- Valine
  (Val, or V)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_3 \\
  \text{CH}_2
  \end{array}
  \]
- Methionine
  (Met, or M)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_3 \\
  \text{CH}_2
  \end{array}
  \]
- Tryptophan
  (Trp, or W)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_3 \\
  \text{H}
  \end{array}
  \]
- Leucine
  (Leu, or L)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_3 \\
  \text{CH}_2
  \end{array}
  \]
- Isoleucine
  (Ile, or I)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_3 \\
  \text{CH}_2
  \end{array}
  \]
- Glycine
  (Gly, or G)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_2
  \end{array}
  \]
- Cysteine
  (Cys, or C)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{S} \\
  \text{CH}_2
  \end{array}
  \]

Disulfide bonds can form between two cysteine side chains in proteins.

\[ \text{S-S} \]

UNCHARGED POLAR SIDE CHAINS

- Asparagine
  (Asn, or N)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_2
  \end{array} \text{O} \text{NH}_2
  \]
- Glutamine
  (Gln, or Q)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_2
  \end{array} \text{O} \text{NH}_2
  \]

Although the amide N is not charged at neutral pH, it is polar.

- Serine
  (Ser, or S)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_2
  \end{array} \text{OH}
  \]
- Threonine
  (Thr, or T)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_2
  \end{array} \text{OH}
  \]
- Tyrosine
  (Tyr, or Y)
  \[
  \begin{array}{c}
  \text{H} \\
  \text{H} \\
  \text{CH}_2
  \end{array} \text{OH}
  \]

The -OH group is polar.
Proteins fold into unique 3D conformations of lowest energy.

- Study by denaturing noncovalent bonds (urea), allow to renature from flexible chain
- Conformation altered if interact with cell mol
- Chaperones: prevent hydrophobic aggregates making folding more reliable, assist folding
- SH2 (GTGA domains) 100AA backbone, ribbon, wire, space-filling models

Figure 3-1 Molecular Biology of the Cell (© Garland Science 2013)
Team work.

Which of the following pairs of amino acid residues would you expect to form ionic bonds?
• A. Glutamic acid and glutamine
• B. Arginine and lysine
• C. Tryptophan and tyrosine
• D. Tyrosine and glutamine
• E. Lysine and glutamic acid

Which of the following stretches of amino acid residues would you expect to find in the interior of protein molecules?
• A. Ala-Val-Leu-Ile-Trp
• B. Ala-Asp-Asp-Tyr-Arg
• C. Phe-Glu-Gln-Glu-Asn
• D. Gly-Tyr-His-Arg-His
• E. Gly-Lys-Ser-Pro-Thr
Proteins form common patterns (alpha helix, beta sheet) by backbone H bond.

- Alpha helix: keratin in skin hair, N-H (up) H bond to C=O (down) 4 away, turn every 3.6, C end part neg, N part pos, membrane proteins inside H bond each other, outside nonpolar
- Beta sheet: fibroin in silk, H bond between diff chains, R alternate up down, protein core rigid
- Beta sheet run in parallel (same orientation) or anti-parallel (fold back on itself) directions
- Coiled coil alpha helix 2-3 chains, nonpolar on one side inward so twist around each other
Figure 3B: Watermelon Bacteria of the Cell (C) - Guerard Skane 2013

Figure 3C: Watermelon Biology of the Cell (C) - Guerard Skane 2013
Proteins are characterized by four (plus one) levels of structure.

- Primary structure: AA sequence
- Secondary structure: alpha helix, beta sheet
- Tertiary structure: 3D peptide organization
- Quaternary structure: multiple peptide chains
- Domains: part of chain into stable modules, e.g. Src Kinase SH2 SH3 regulate C-term kinase
- $20^n$ possible seq but evolution selects for only 1 in a billion for its stable structure
Protein diversity result from reuse of same modules as homologs.

- Families of protein from duplicated mutations
- Diff AA seq (25% same) still similar structure due to small number of characteristic shapes
- Pattern matches in signature seq allow identification with proteins of known function
- Domain shuffling forms new proteins from existing motifs, binding sites mutated for diff ligands, N-C terms at opposite or same ends
Only green are identical AAs.
Diversity of protein structures allow for adaptability.

- Half of domains shared between all organisms only 5% of 2-domain combos shared ev recent
- Humans: similar genes vastly shuffled domains
- Binding sites noncovalent interactions with other polypeptides lead to multi-chain proteins
- Repeat helical filaments common, e.g. actin
- Fibrous proteins span large distance in extracellular matrix, e.g. collagen triple helix
- Unstructured chains allow stretch, e.g. elastin
Protein assemblies are formed by various means.

- Disulfide bonds (SH cysteine) cross-links proteins together in extracellular environ only, reducing (provide electrons) to separate
- Protein subunits assemblies, e.g. icosohedral viral capsid
- Self assembly: tobacco mosaic virus, ribosome
- Irreversibility: cannot self assemble after proteolytic cleavage, mitochondria
Team work.

Protein secondary structure elements such as α helices and β sheets constitute the major regular folding patterns in proteins. With regard to these elements, ...

• A. the folding patterns result from hydrogen-bonding between the N–H and C=O groups in the polypeptide backbone.
• B. a certain short amino acid sequence always adopts the same secondary structure.
• C. hydrogen-bonding between the amino acid side chains defines the type of secondary structure.
• D. only a few specific amino acid sequences can adopt these repetitive structures.
• E. All of the above.

You have purified a multisubunit extracellular protein that has several interchain disulfide bonds. Which of the following chemicals would you add to your purified protein mixture if you wanted to eliminate the disulfide bonds?

• A. NaCl, a salt
• B. DTT, a reducing agent
• C. \( \text{H}_2\text{O}_2 \), an oxidizing reagent
• D. SDS, an ionic detergent and denaturing agent
• E. Tris, a buffering agent