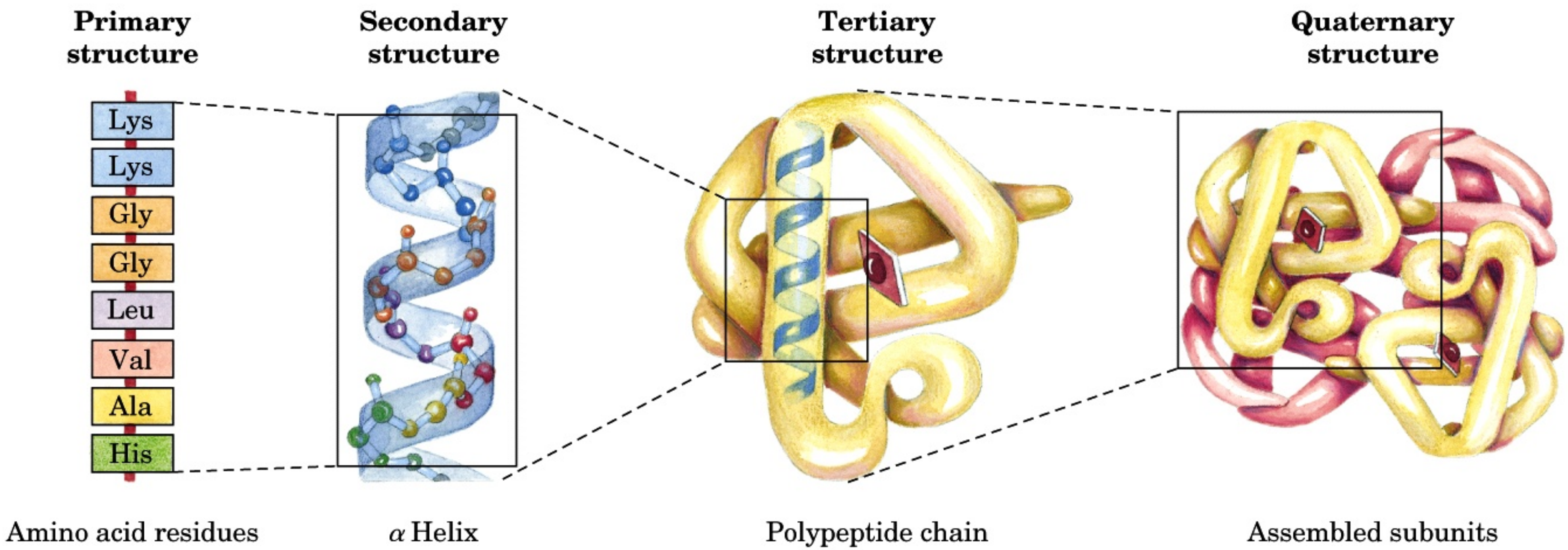
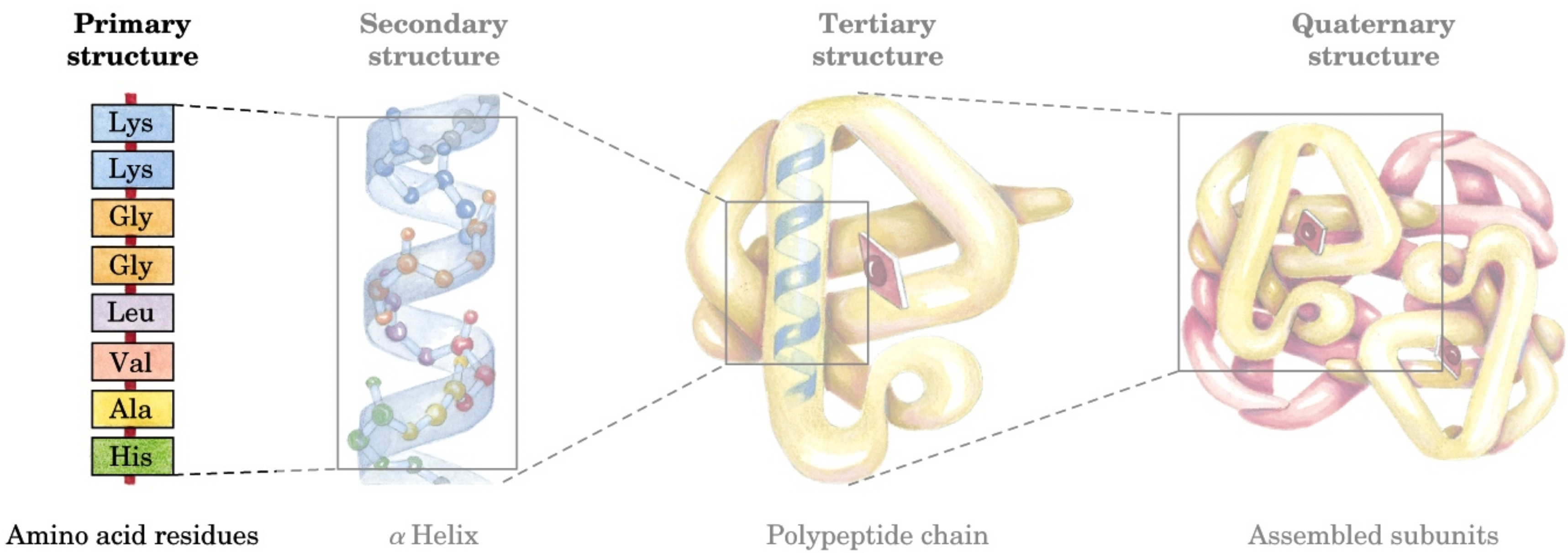
# Protein Chemistry & Structure

# Levels of Protein Structure

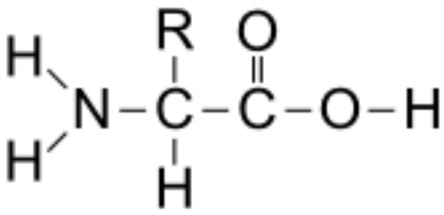


# Primary structure = order of amino acids in the protein chain

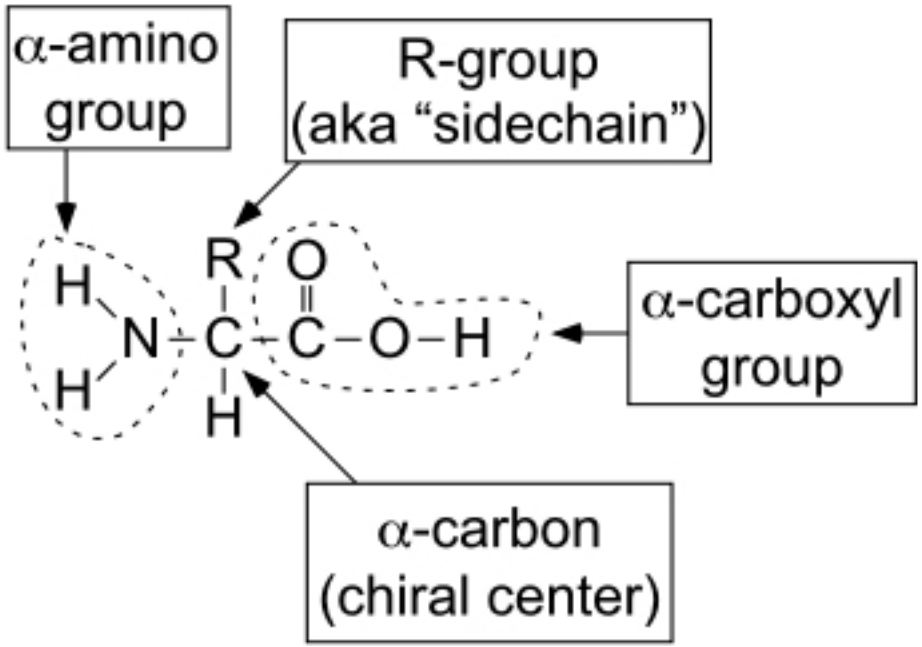


# Anatomy of an amino acid

General amino acid structure

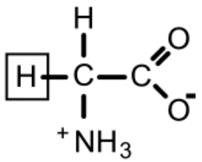



Chemical anatomy of an amino acid

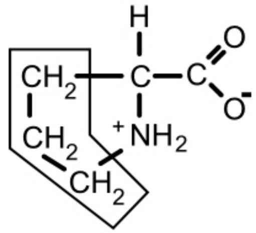


# Non-polar amino acids

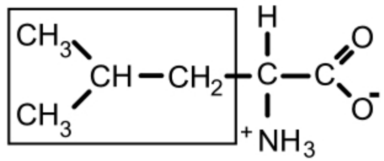
Glycine (Gly, G)



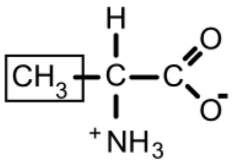
Proline (Pro, P)



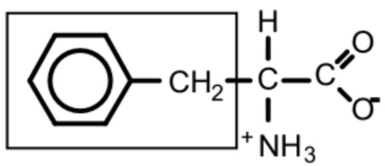
Leucine (Leu, L)



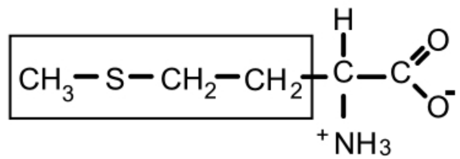
Alanine (Ala, A)



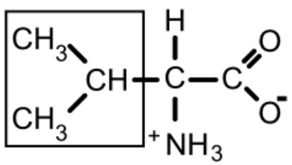
Phenylalanine (Phe, F)



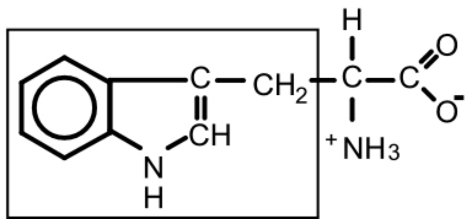
Methionine (Met, M)



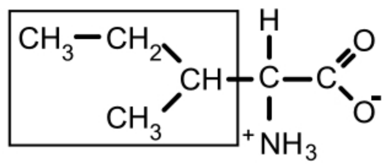
Valine (Val, V)



Tryptophan (Trp, W)

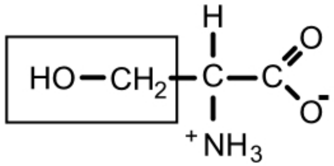


Isoleucine (Ile, I)

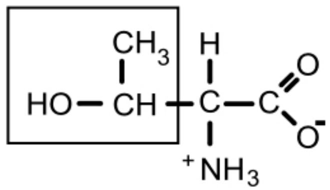


# Polar, non-charged amino acids

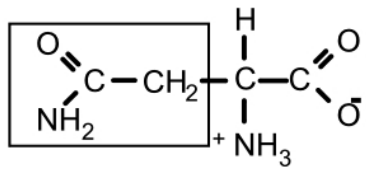
Serine (Ser, S)



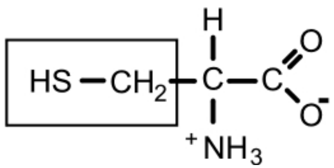
Threonine (Thr, T)



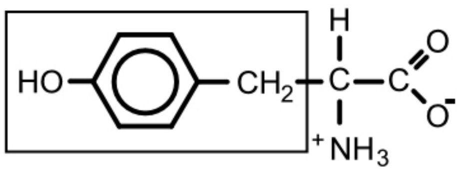
Asparagine (Asn, N)



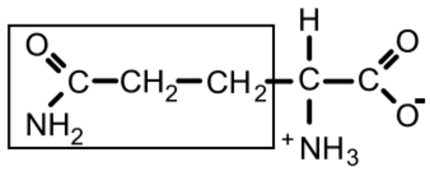
Cysteine (Cys, C)



Tyrosine (Tyr, Y)

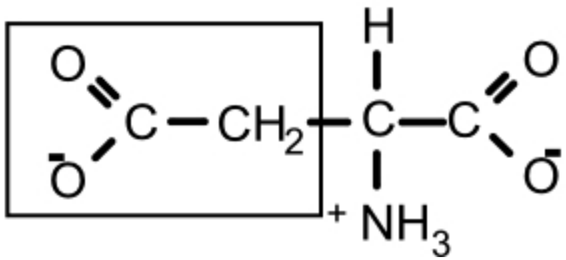


Glutamine (Gln, Q)

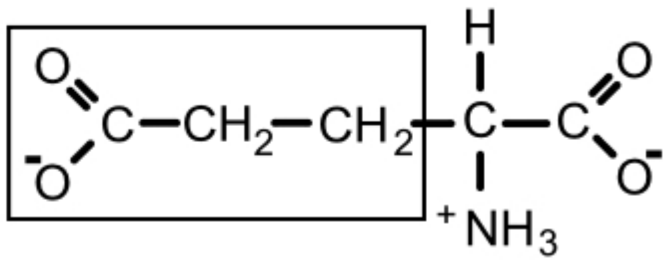


# Negatively-charged amino acids

Aspartate (Asp, D)

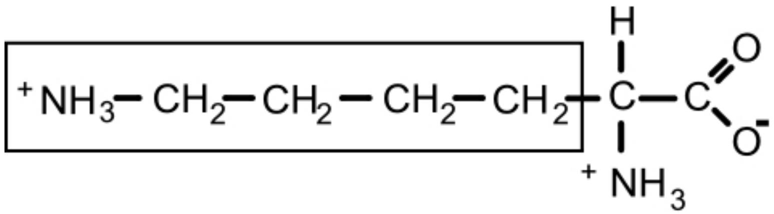


Glutamate (Glu, E)

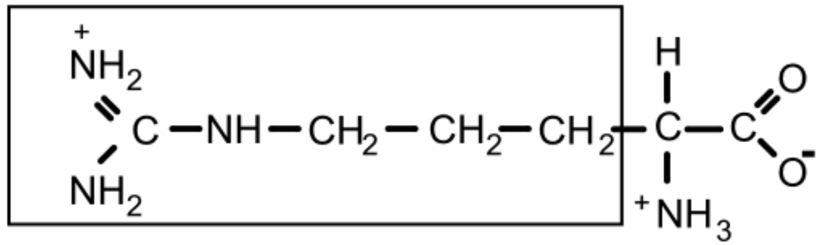


# Positively-charged amino acids

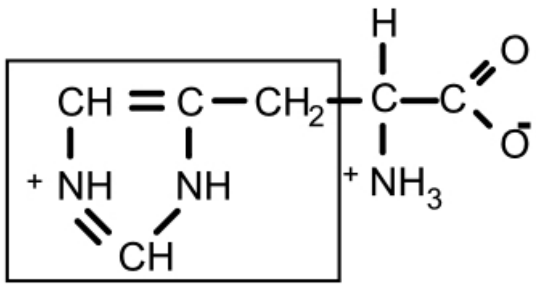
Lysine (Lys, K)



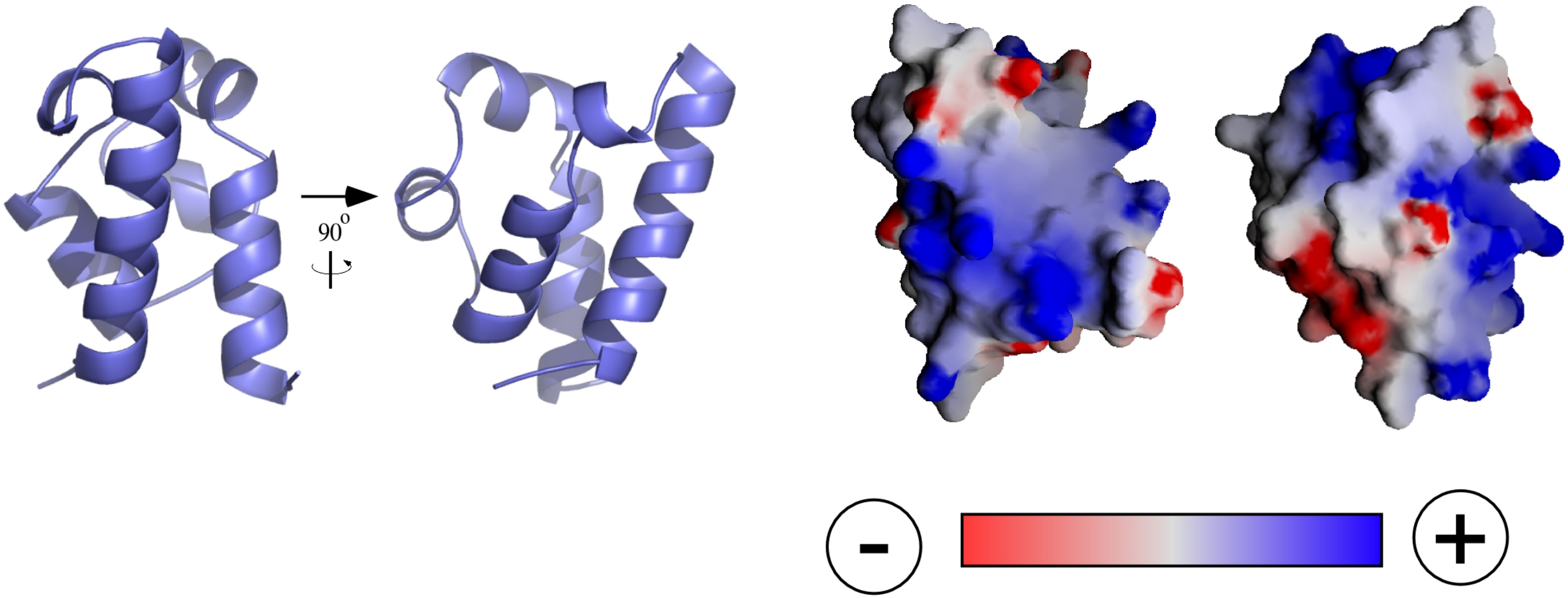

Arginine (Arg, R)



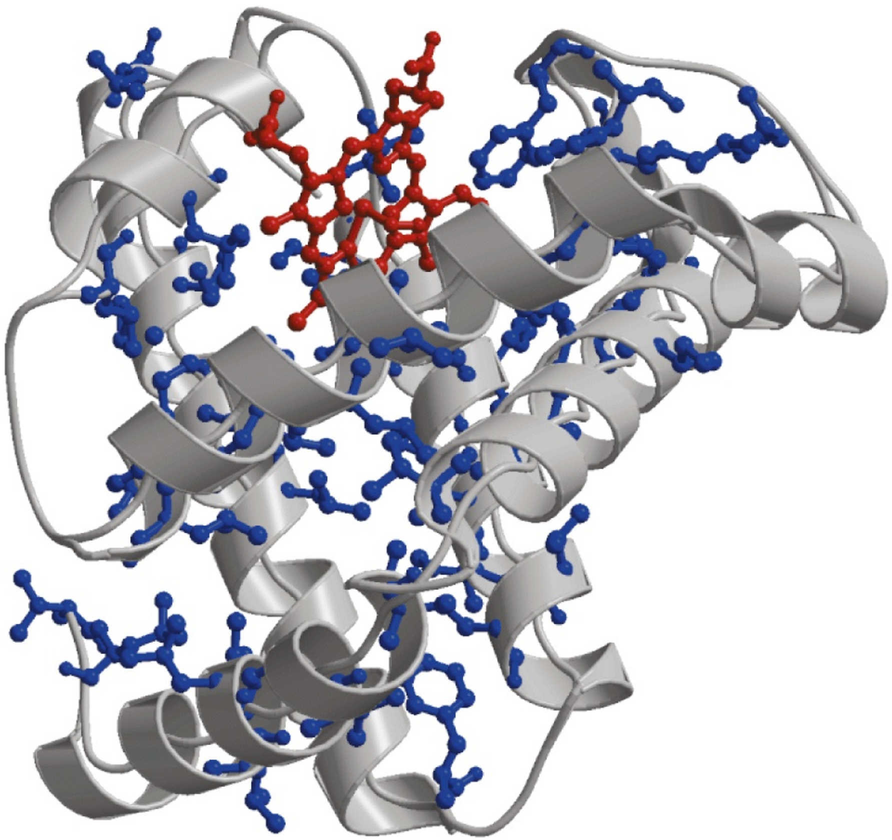

Histidine (His, H)
(protonated form)



# Charged and polar R-groups tend to map to protein surfaces



# Non-polar R-groups tend to be buried in the cores of proteins



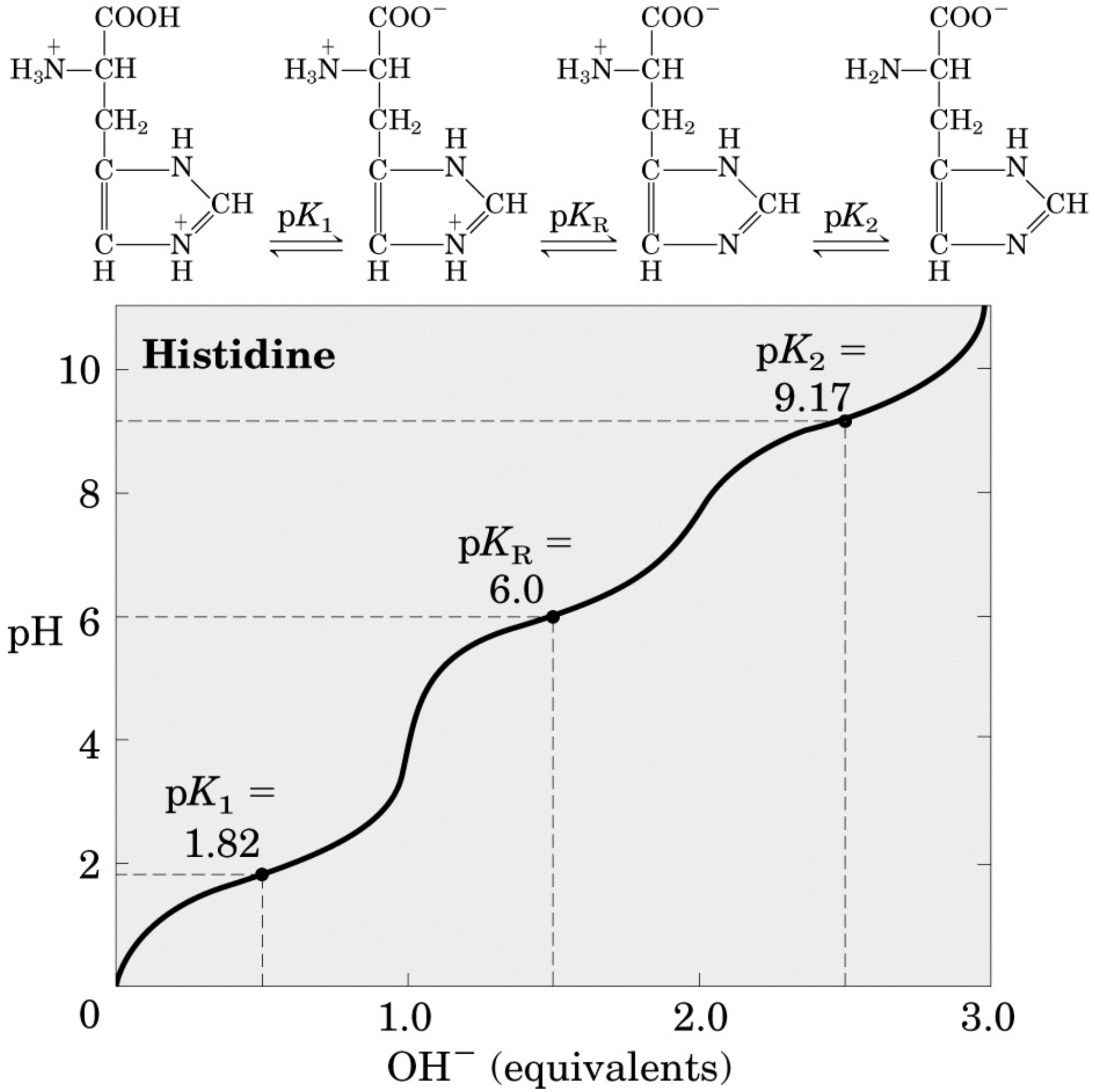
(d)

<u>Myoglobin</u>

Blue = non-polar R-group

Red = Heme

# Some R-groups can be ionized



(b)

The Henderson-Hasselbalch equation allows calculation of the ratio of a weak acid and its conjugate base at any pH

Henderson-Hasselbalch

$$pH = pK' - \log \frac{[HB]}{[B^-]}$$

# General protein pK’ values

| Group | Approximate pK' In a “Typical” Protein |
|---|---|
| α-carboxyl (free) | 3 (C-terminal only) |
| β-carboxyl (Asp) | 4 |
| γ-carboxyl (Glu) | 4 |
| imidazole (His) | 6 |
| sulfhydryl (Cys) | 8 |
| 1˚α-amino (free) | 8 (N-terminal only) |
| ε-amino (Lys) | 10 |
| hydroxyl (Tyr) | 10 |
| 2˚α-amino (Pro)(free) | 9 (N-terminal only) |
| guanido (Arg) | 12 |

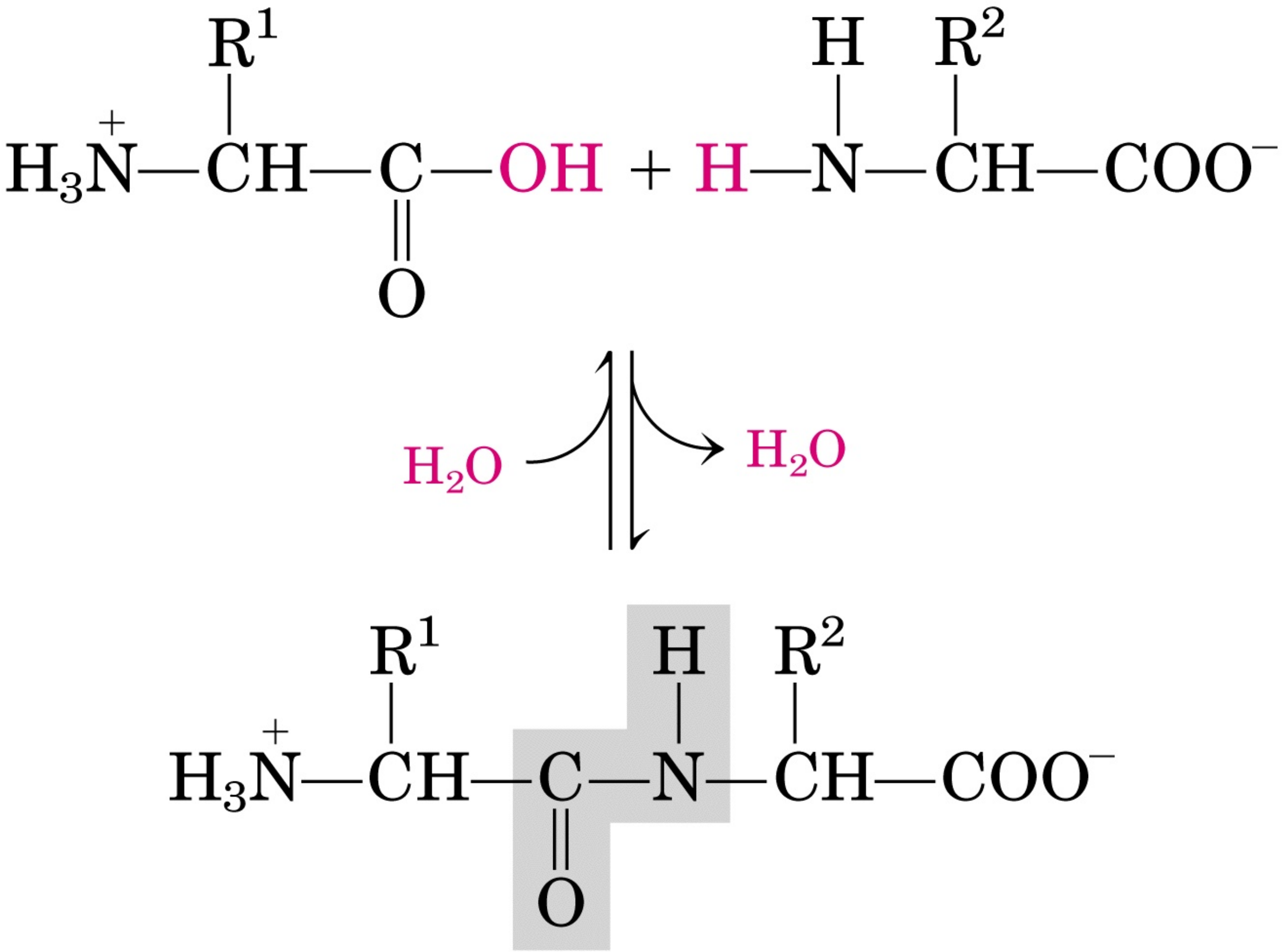
# Some R-groups can modified

| Modification | Chemistry | Common sites of attachment |
| --- | --- | --- |
| Phosphorylation | R-OH + $HPO_4^{2-}$ → R-O-$PO_3^{2-}$ + $H_2O$ | Residues with hydroxyl groups (Ser, Thr, Tyr) |
| N-Glycosylation | R-NH-sugar | Asn |
| O-Glycosylation | R-O-sugar | Ser, Thr, and modified residues |
| Hydroxylation | hydroxyl group (OH) added to R group | Pro, Lys |
| Carboxylation | carboxyl group (COOH) added to R group | Glu |

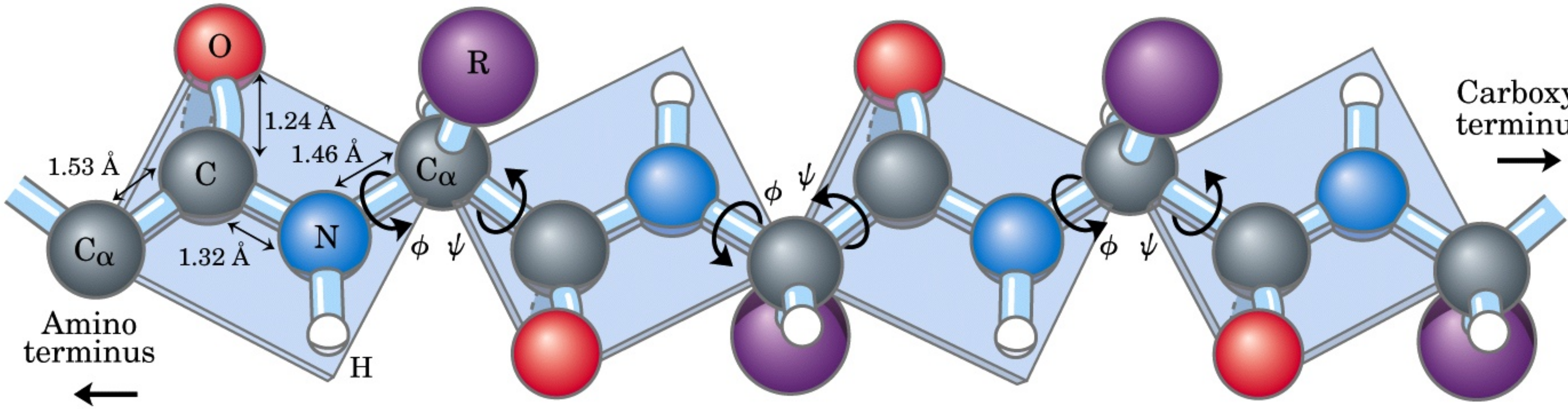
# Amino Acids Are Joined By Peptide Bonds In Peptides

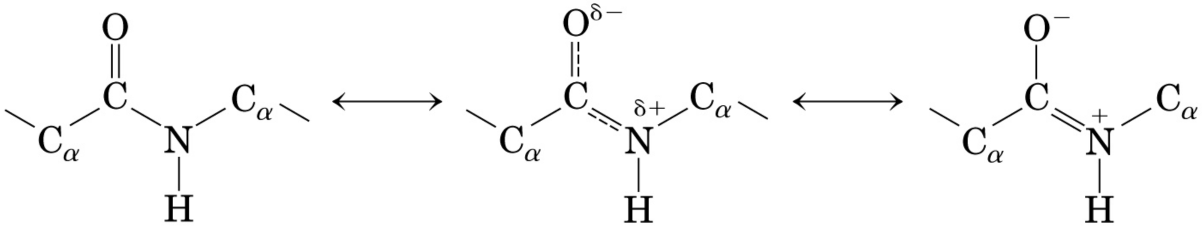
- $\alpha$-carboxyl of one amino acid is joined to $\alpha$-amino of a second amino acid (with removal of water)
- only $\alpha$-carboxyl and $\alpha$-amino groups are used, not R-group carboxyl or amino groups

# Chemistry of peptide bond formation



# The peptide bond is planar



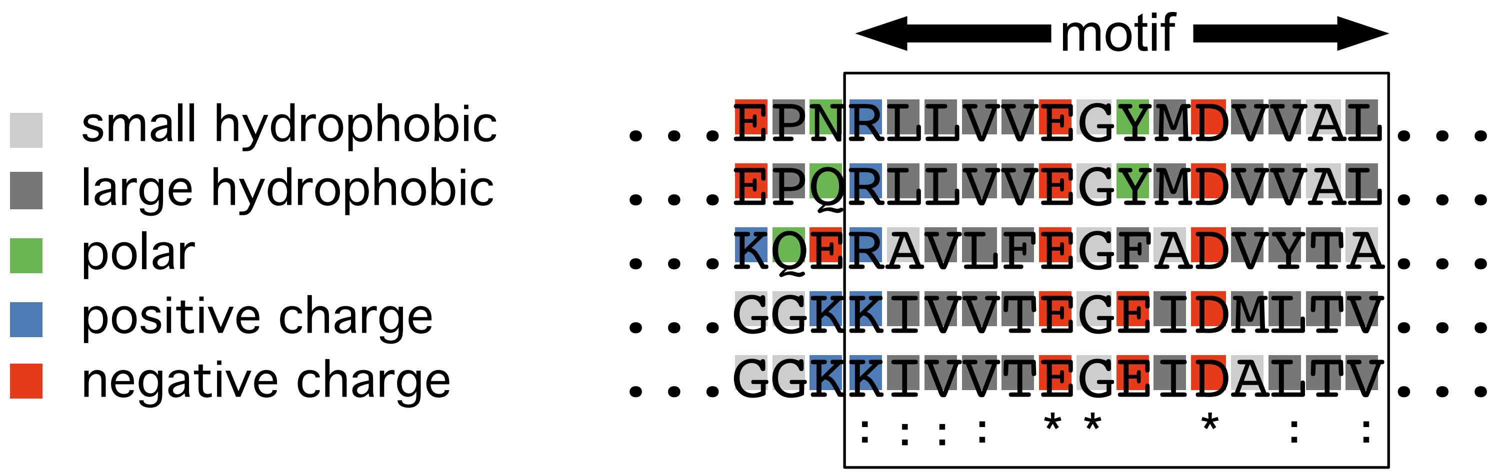




This resonance restricts the number of conformations in proteins -- main chain rotations are restricted to ϕ and ψ.

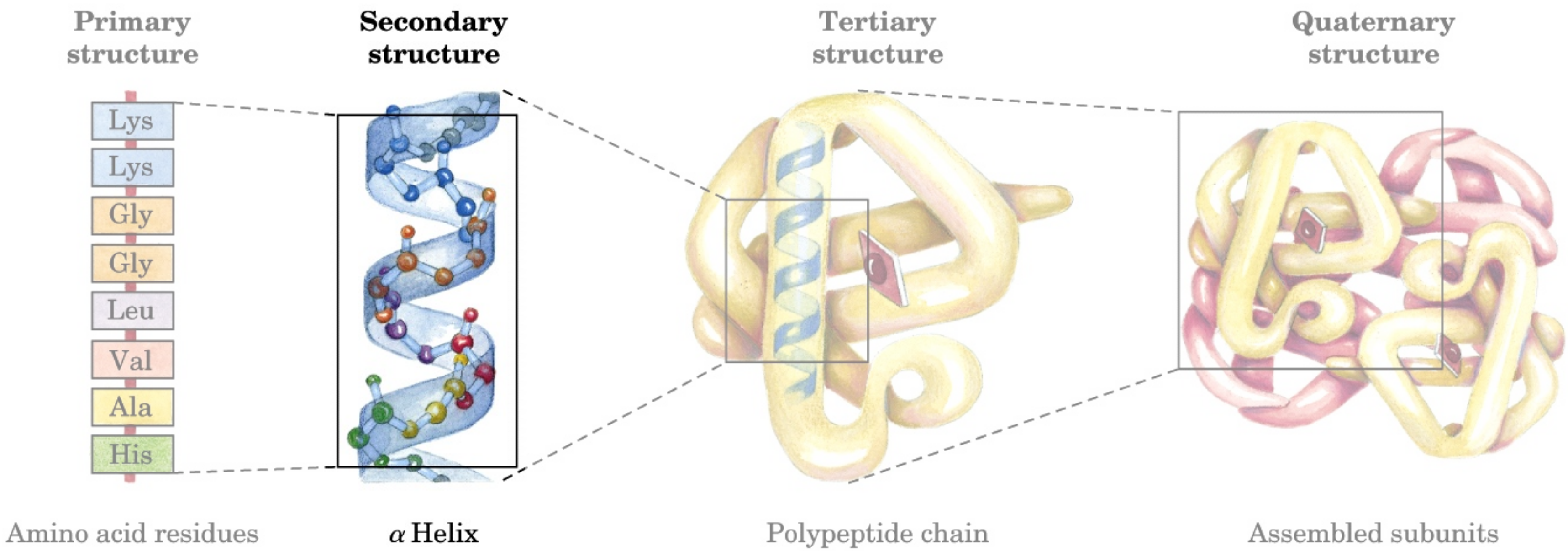
# Primary sequence reveals important clues about a protein

• Evolution conserves amino acids that are important to protein structure and function across species. Sequence comparison of multiple “homologs” of a particular protein reveals highly conserved regions that are important for function.

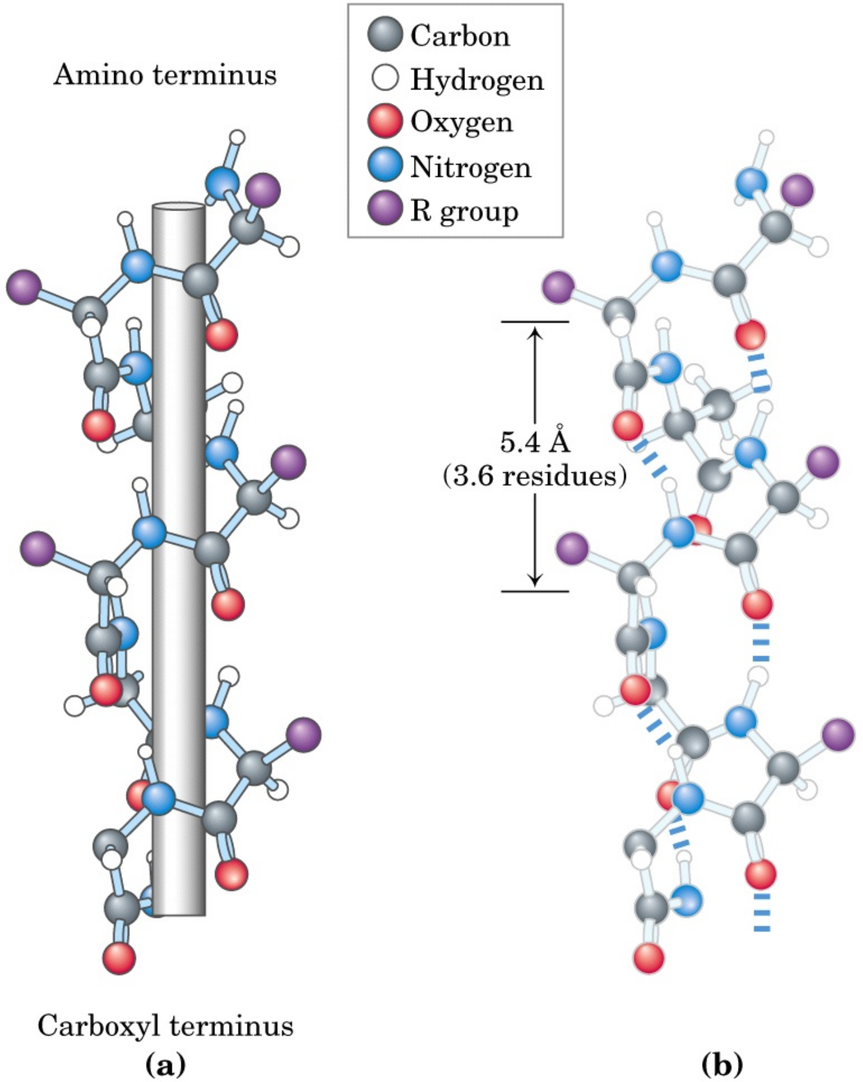
• Clusters of conserved residues are called “motifs” -- motifs carry out a particular function or form a particular structure that is important for the conserved protein.



# Secondary structure = local folding of residues into regular patterns



# The α-helix

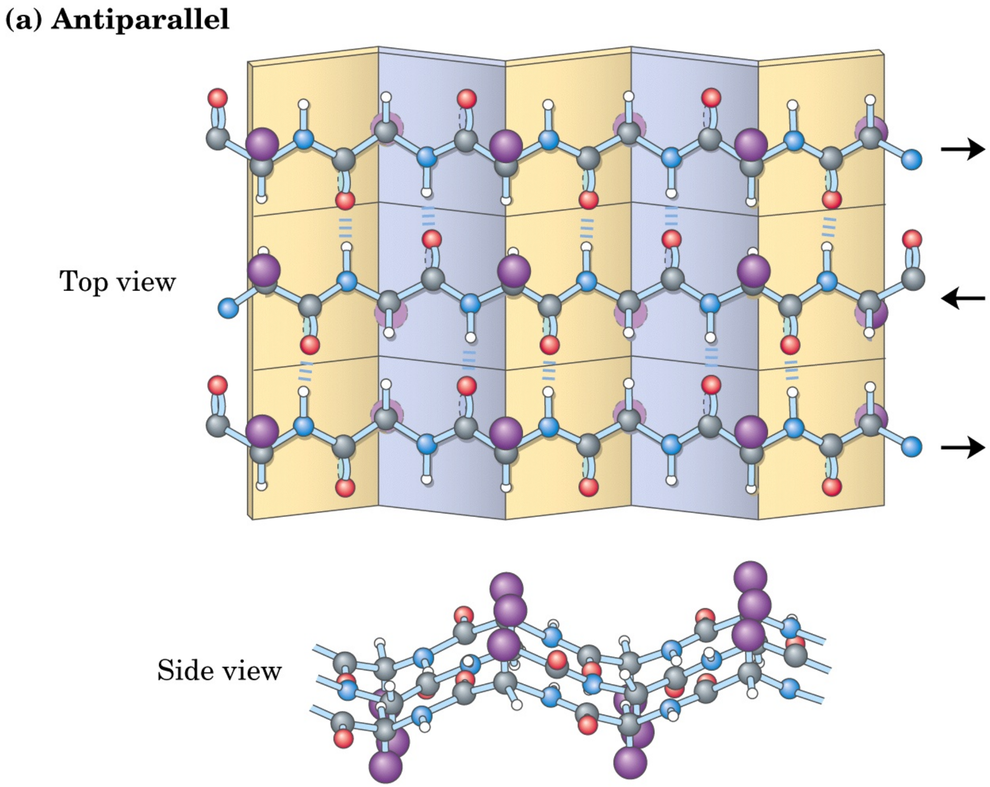



- In the α-helix, the carbonyl oxygen of residue “i” forms a hydrogen bond with the amide of residue “i+4”.

- Although each hydrogen bond is relatively weak in isolation, the sum of the hydrogen bonds in a helix makes it quite stable.

- The propensity of a peptide for forming an α-helix also depends on its sequence.

# The β-sheet

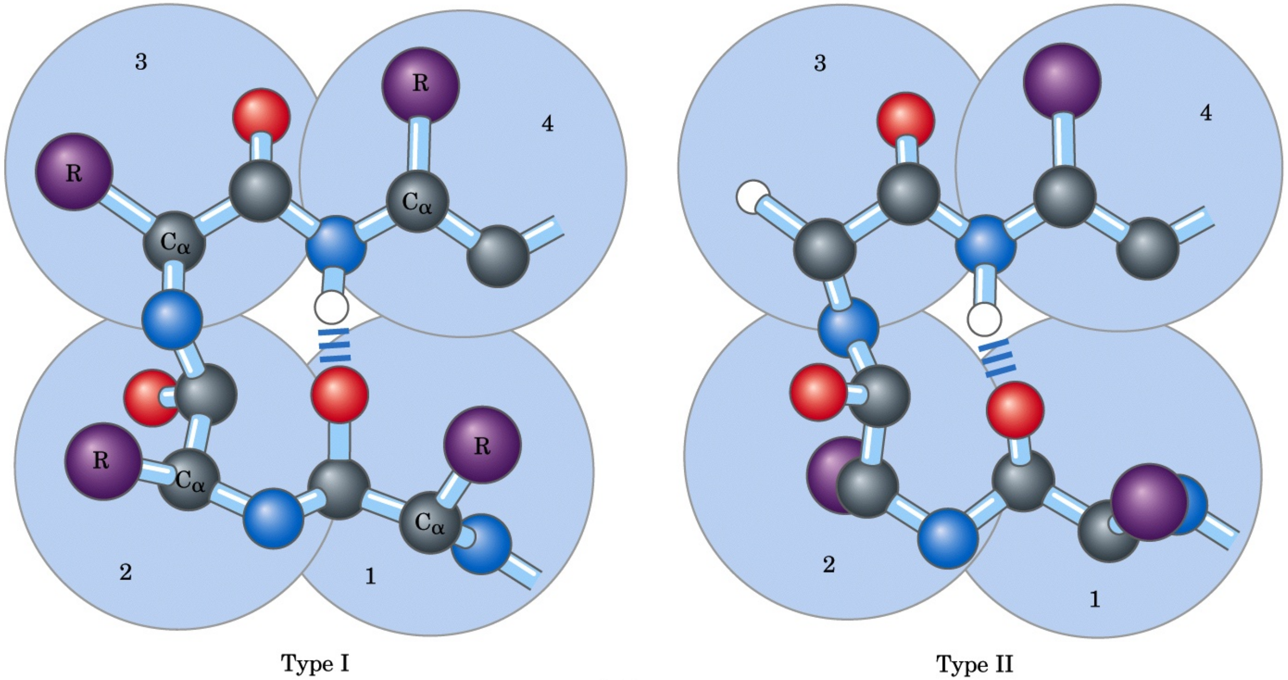



- In a β-sheet, carbonyl oxygens and amides form hydrogen bonds.

- These secondary structures can be either antiparallel (as shown) or parallel and need not be planar (as shown) but can be twisted.

- The propensity of a peptide for forming β-sheet also depends on its sequence.

# β turns

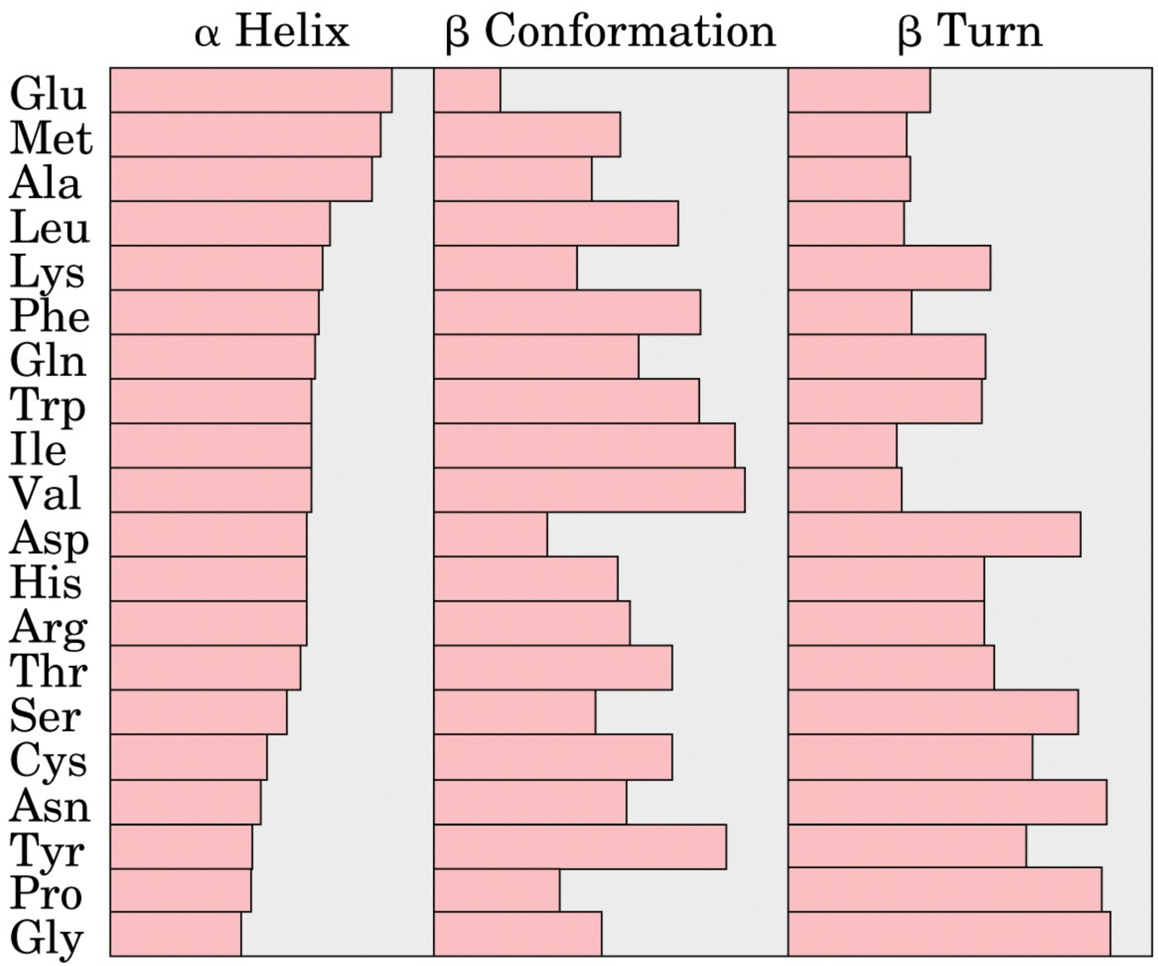



β **Turns**
**(a)**

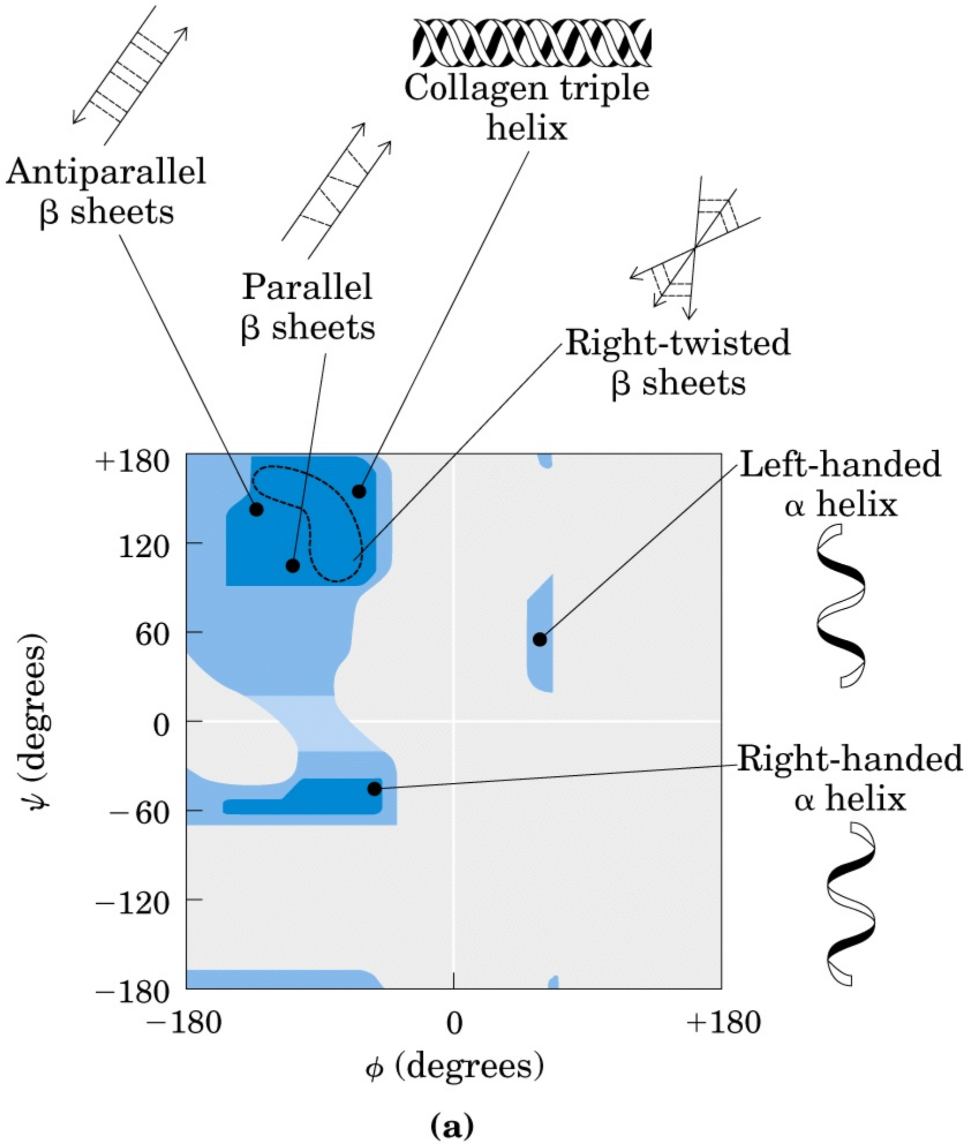
- β-turns allow the protein backbone to make abrupt turns.

- Again, the propensity of a peptide for forming β-turns depends on its sequence.

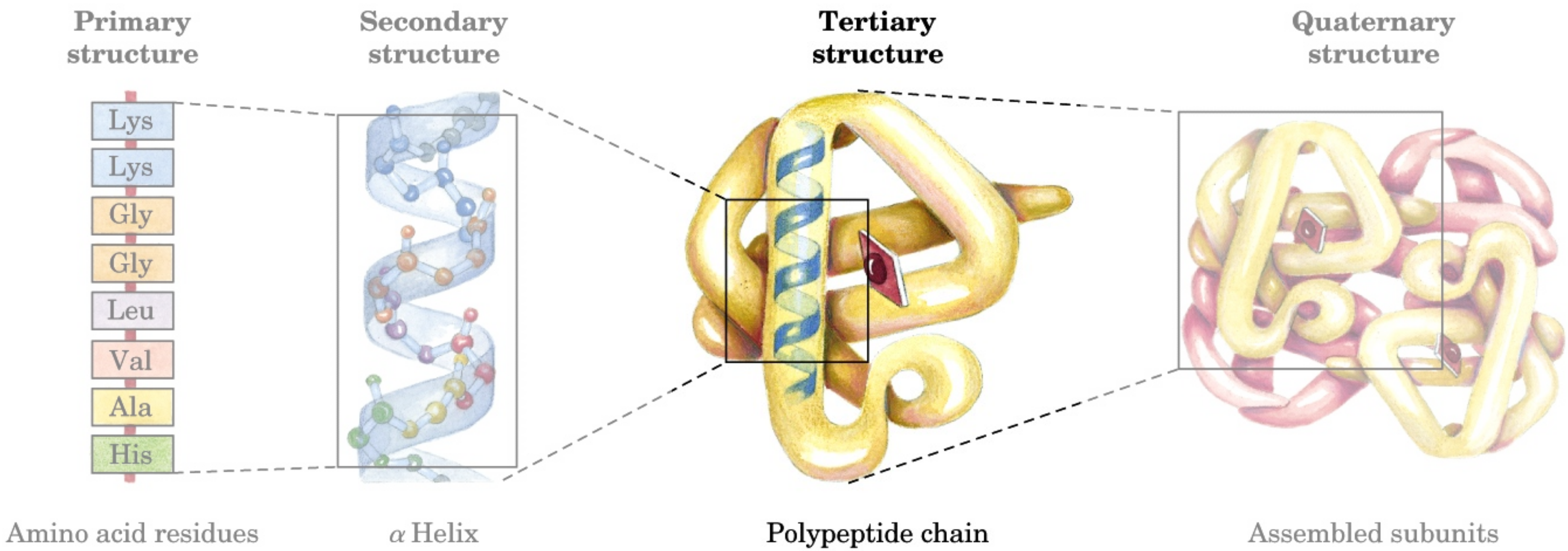
# Which residues are common for α-helix, β-sheet, and β-turn elements?



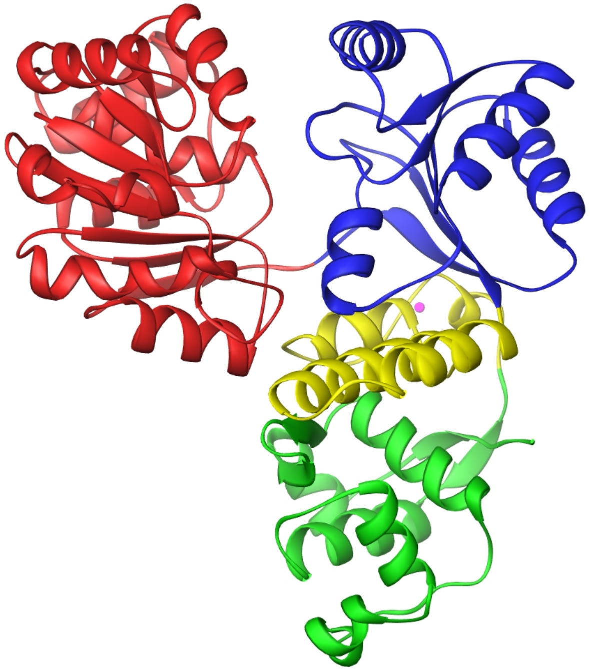
# Ramachandran plot -- shows $\phi$ and $\psi$ angles for secondary structures

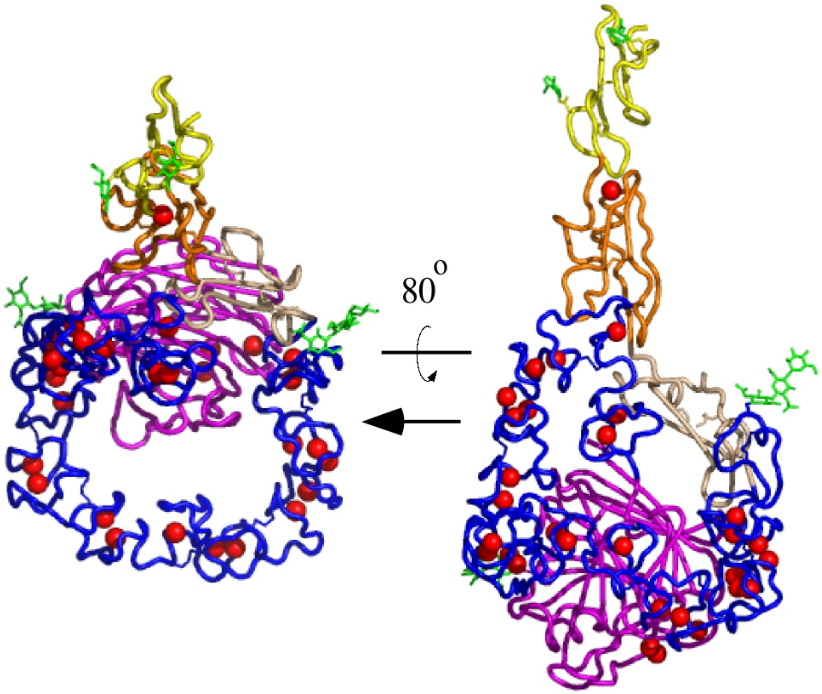


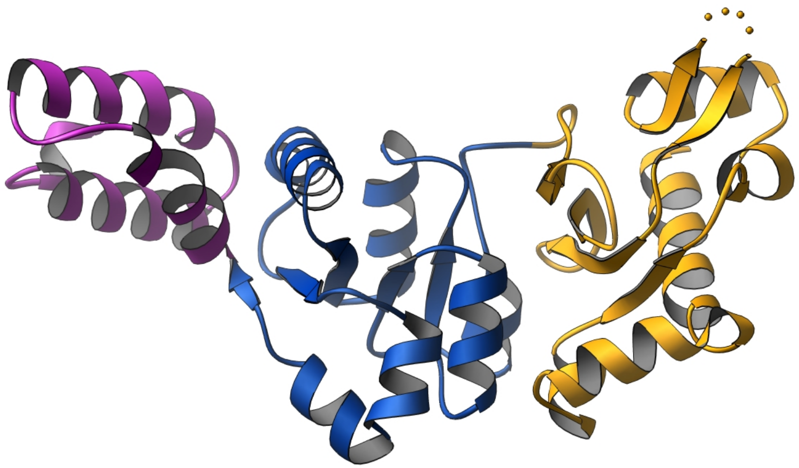
# Tertiary structure = global folding of a protein chain

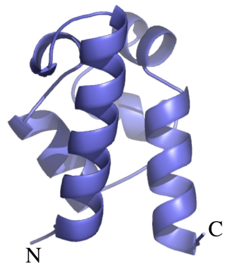


# Tertiary structures are quite varied

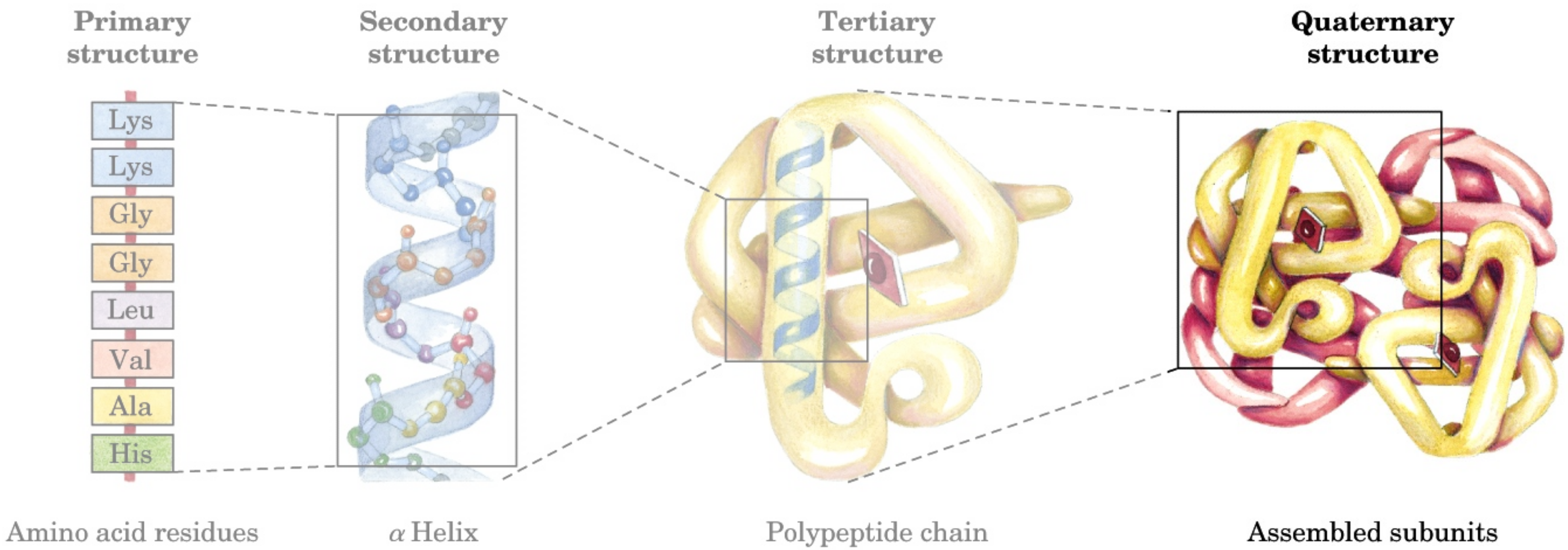




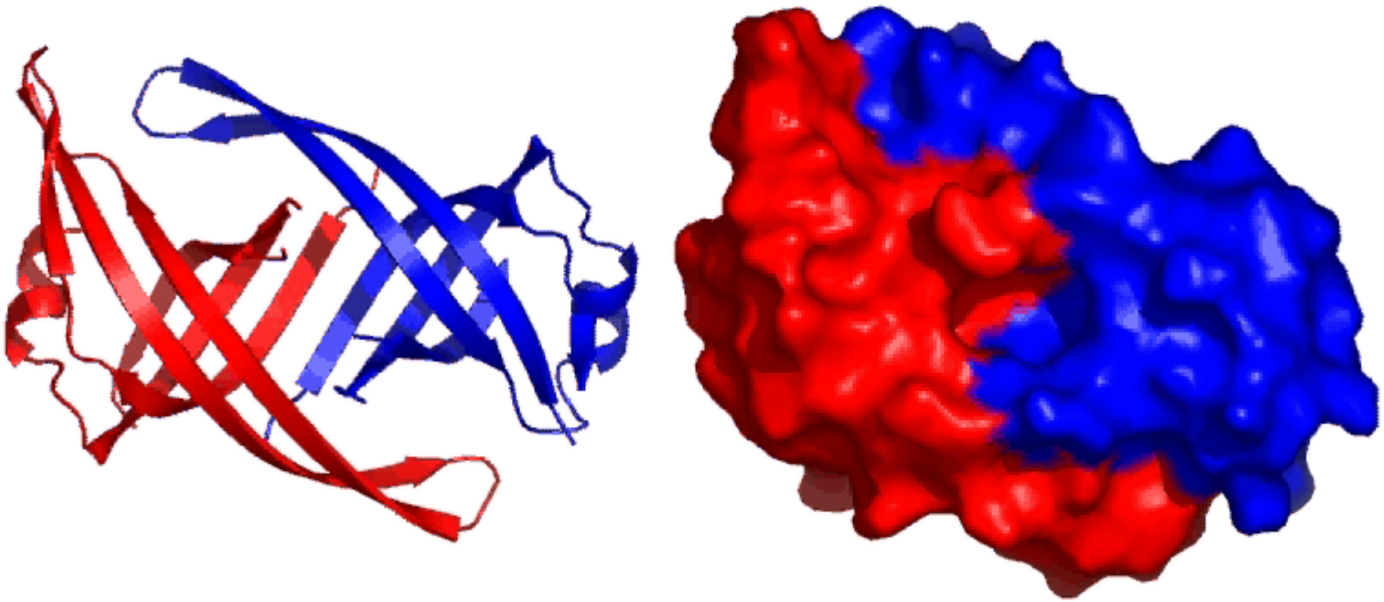





# Quaternary structure = Higher-order assembly of proteins

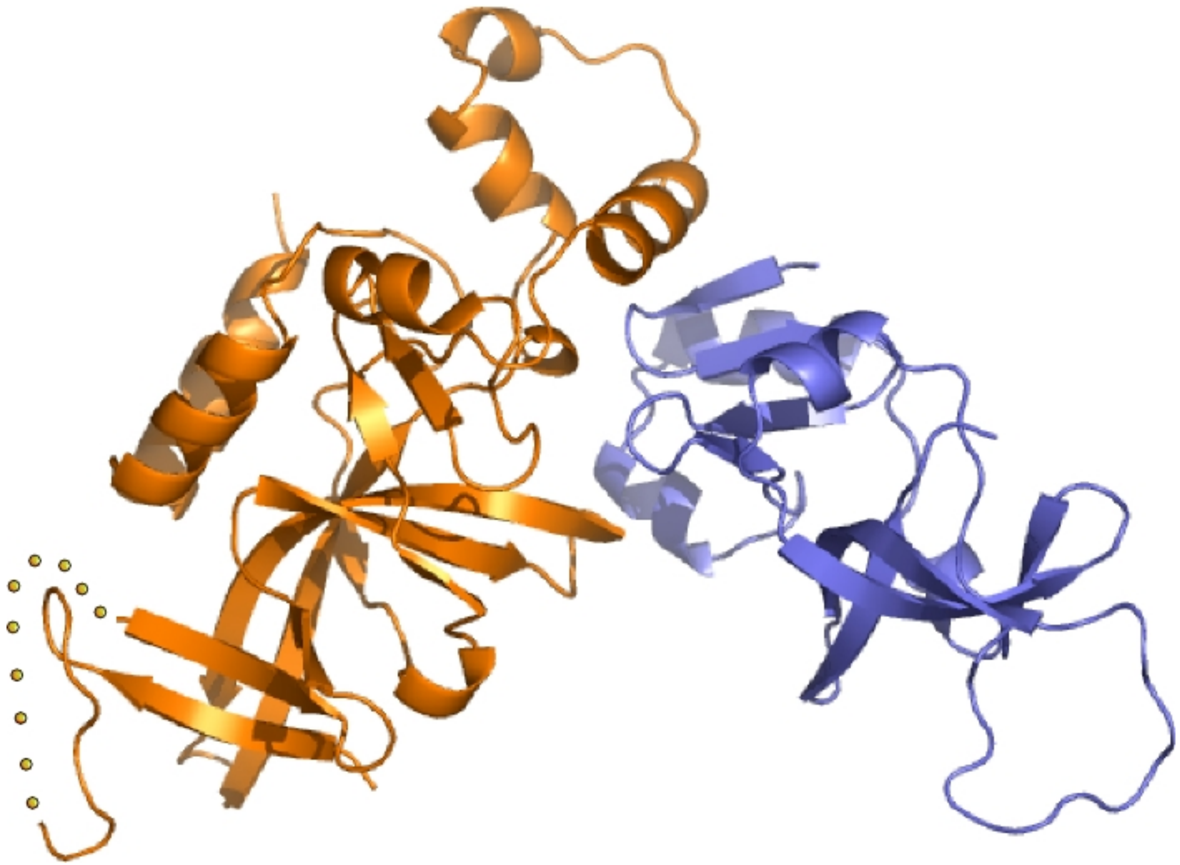


# Example of tertiary and quaternary structure - PriB homodimer



Example is PriB replication protein solved at UW: Lopper, Holton, and Keck (2004) *Structure* **12**, 1967-75.

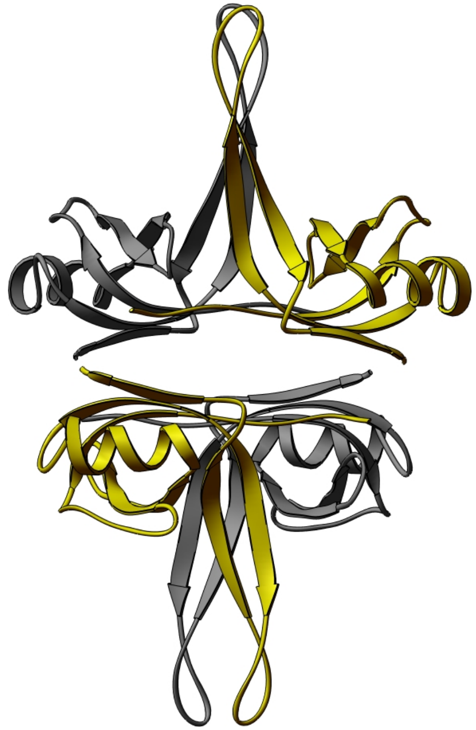
# Example of tertiary and quaternary structure - Sir1/Orc1 heterodimer

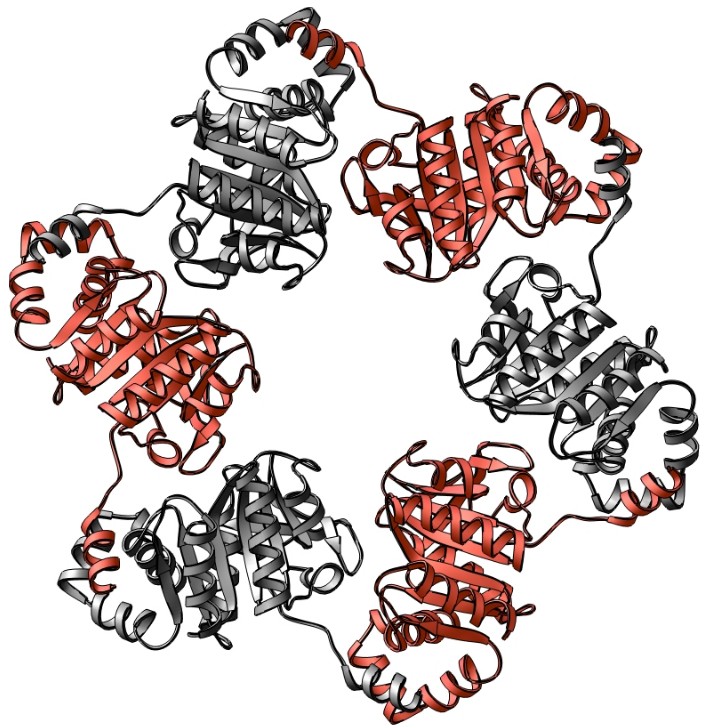


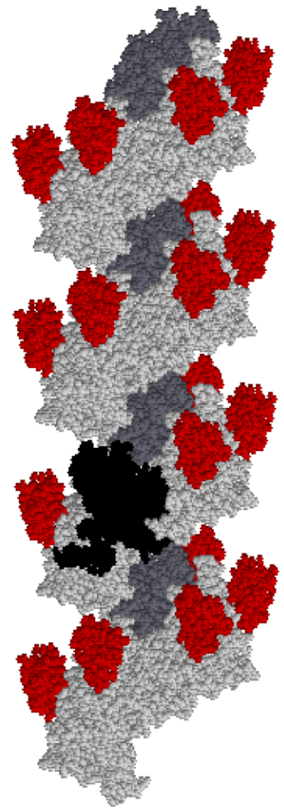
Example is Sir1/Orc1 complex solved at UW: Hou, Bernstein, Fox, and Keck (2005) *Proc. Natl. Acad. Sci.* **102**, 8489-94.

# Examples of other quaternary structures

<u>Tetramer</u> | <u>Hexamer</u> | Filament







<u>SSB</u>
Allows coordinated DNA binding

<u>DNA helicase</u>
Allows coordinated DNA binding and ATP hydrolysis

<u>Recombinase</u>
Allows complete coverage of an extended molecule

# Classes of proteins

Functional definition:

| | |
|---|---|
| Enzymes: | Accelerate biochemical reactions |
| Structural: | Form biological structures |
| Transport: | Carry biochemically important substances |
| Defense: | Protect the body from foreign invaders |

Structural definition:

| | |
|---|---|
| Globular: | Complex folds, irregularly shaped tertiary structures |
| Fibrous: | Extended, simple folds -- generally structural proteins |

Cellular localization definition:

| | |
|---|---|
| Membrane: | In direct physical contact with a membrane; generally water insoluble. |
| Soluble: | Water soluble; can be anywhere in the cell. |