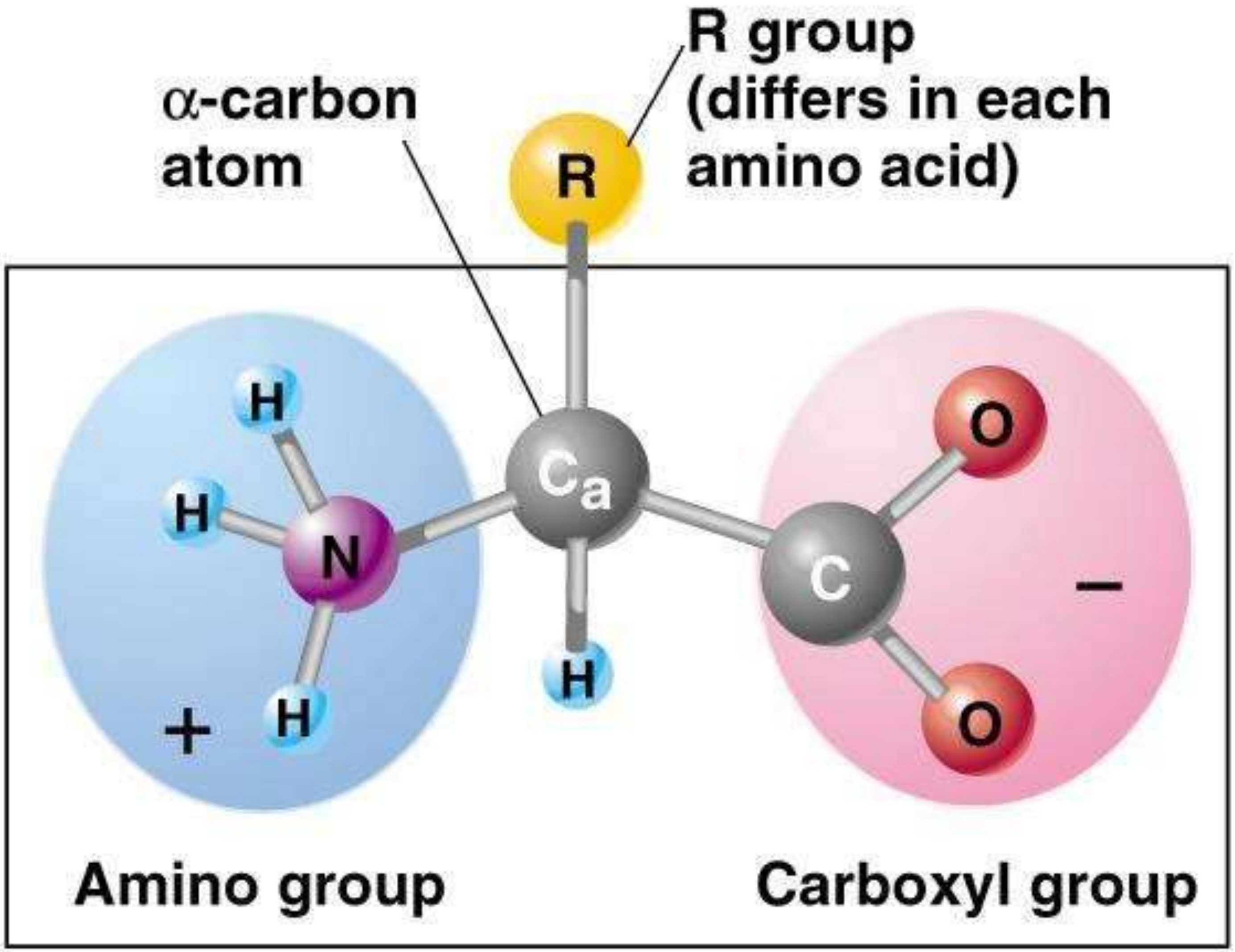
Fig. 6.1



Structures common to all amino acids

Fig. 6.2. Acidic and basic amino acids.

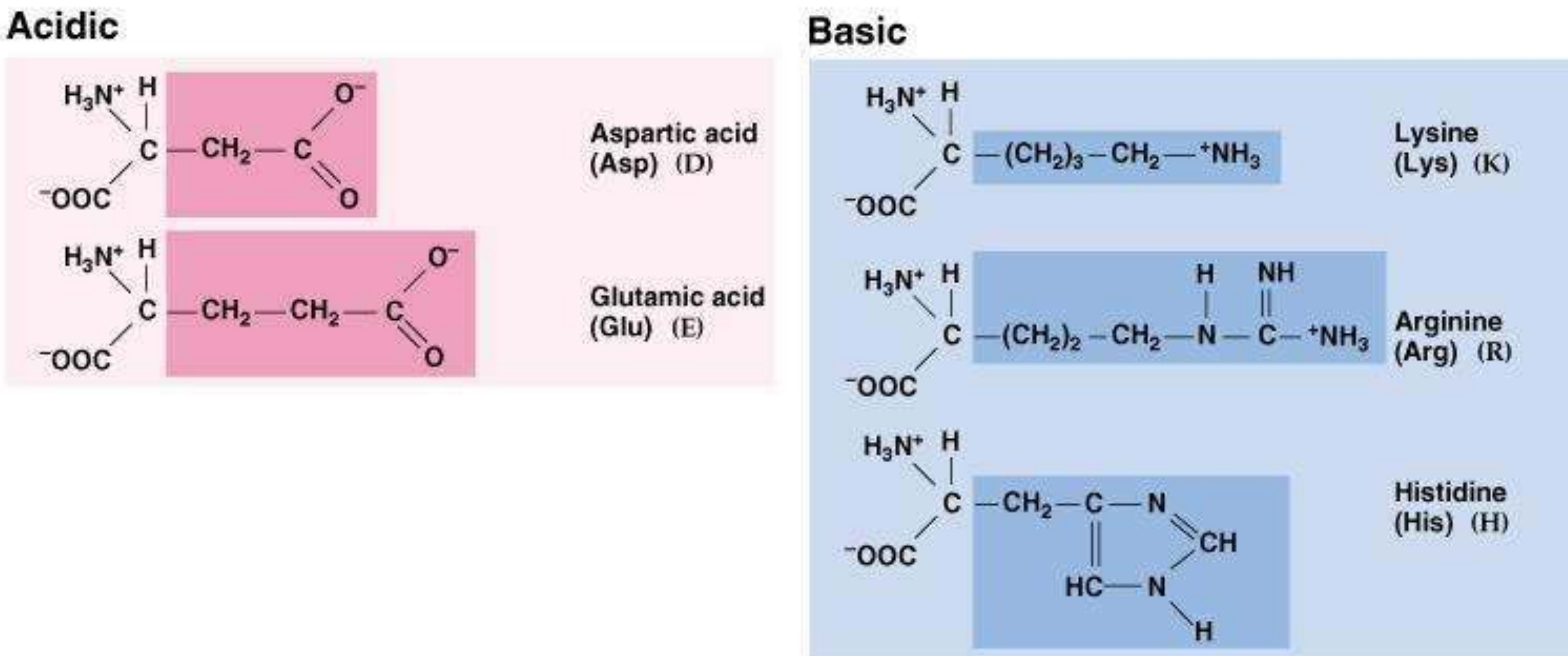


Fig. 6.2. <u>Neutral, non-polar (hydrophobic) amino acids</u>.

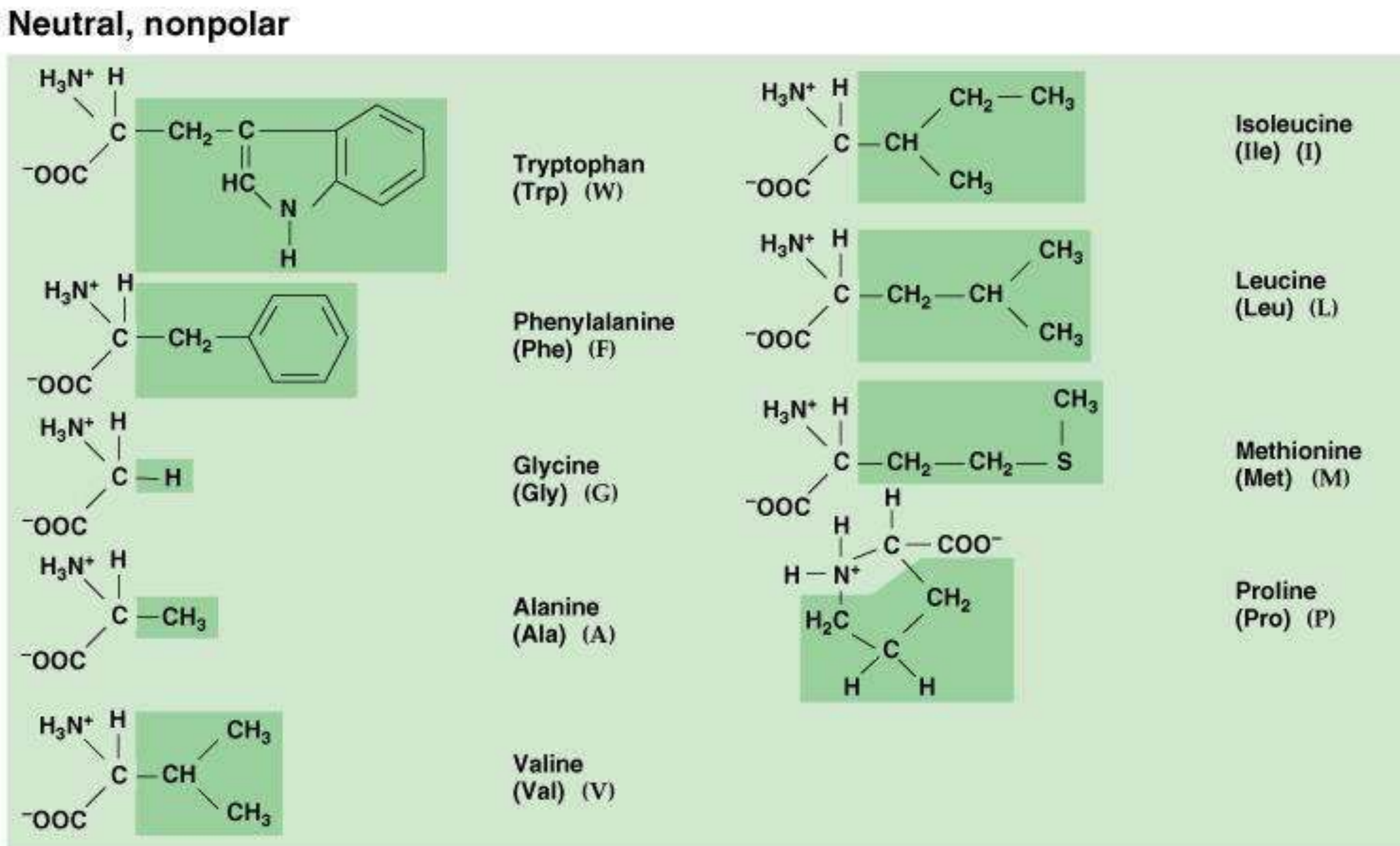
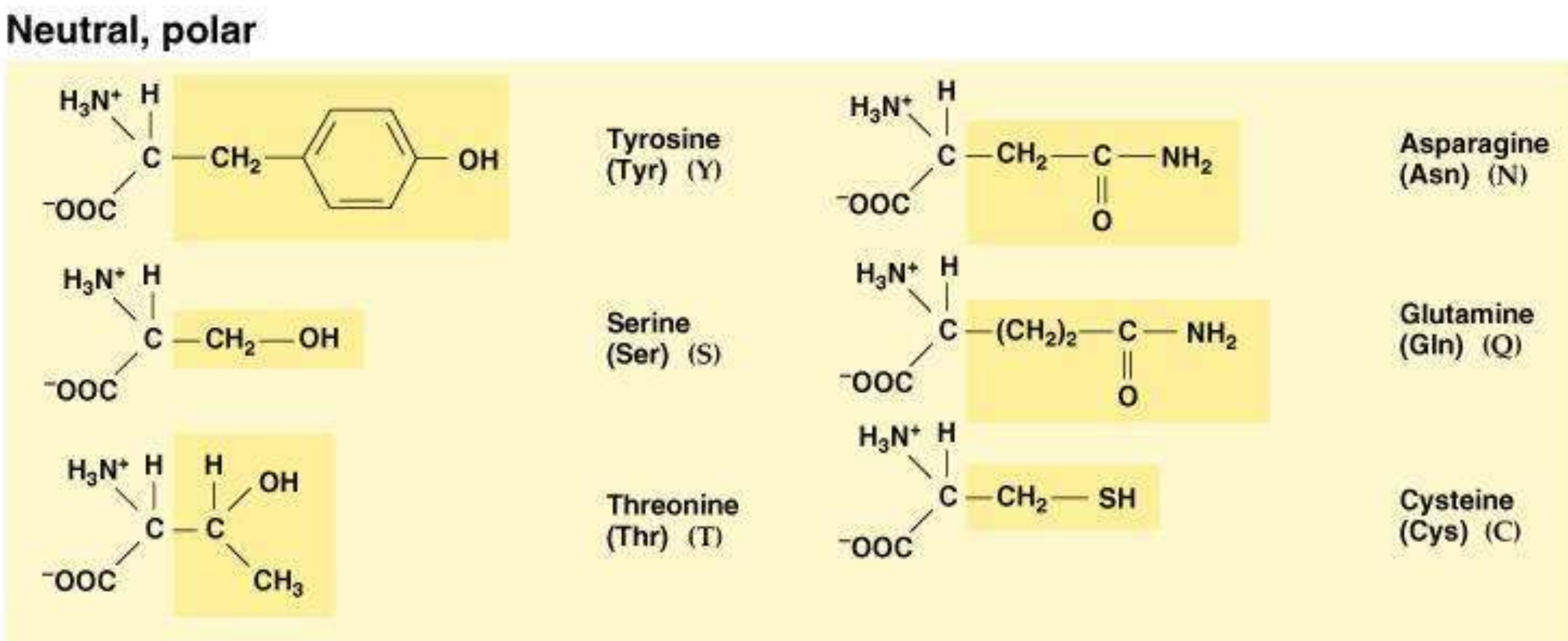


Fig. 6.2. <u>Neutral, polar (hydrophilic) amino acids</u>.



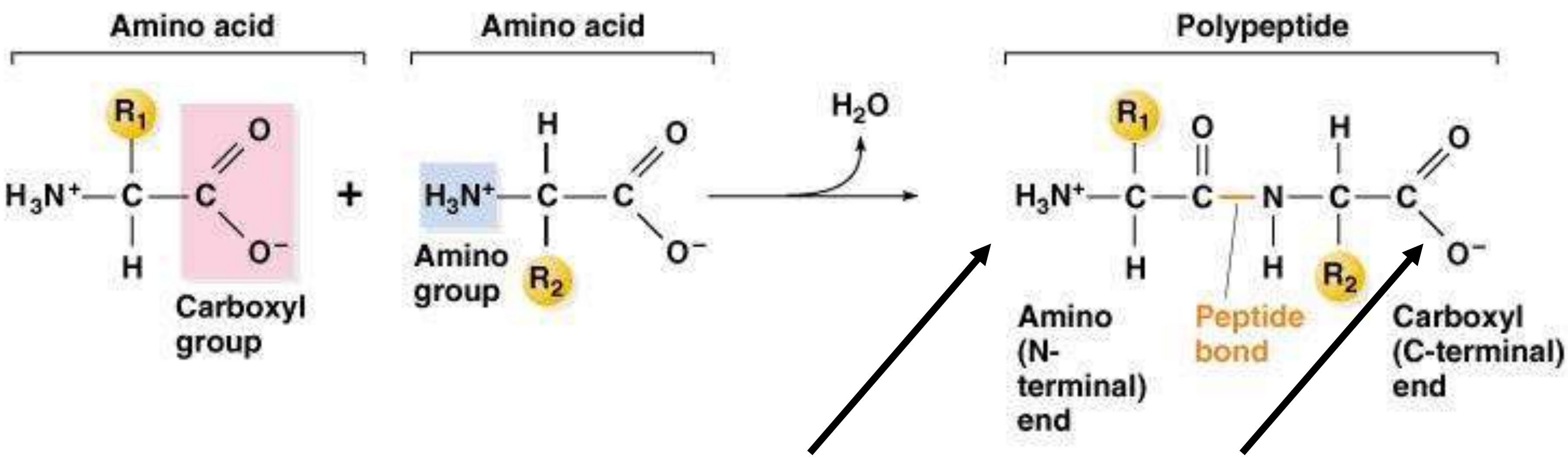
Proteins

$$\begin{array}{ccccc} & R & & & R \\ & | & & & | \\ H_2N-- & C & --COOH & H_2N-- & C & --COOH \\ & | & & & | \\ & H & & & H \end{array}$$

Amino acids are joined to form unbranched polypeptides by a **<u>peptide bond</u>**.

✓ **Covalent bond between the carboxyl group of one amino acid and amino group of the next amino acid.**

Fig. 6.3



N-terminus **C-terminus**

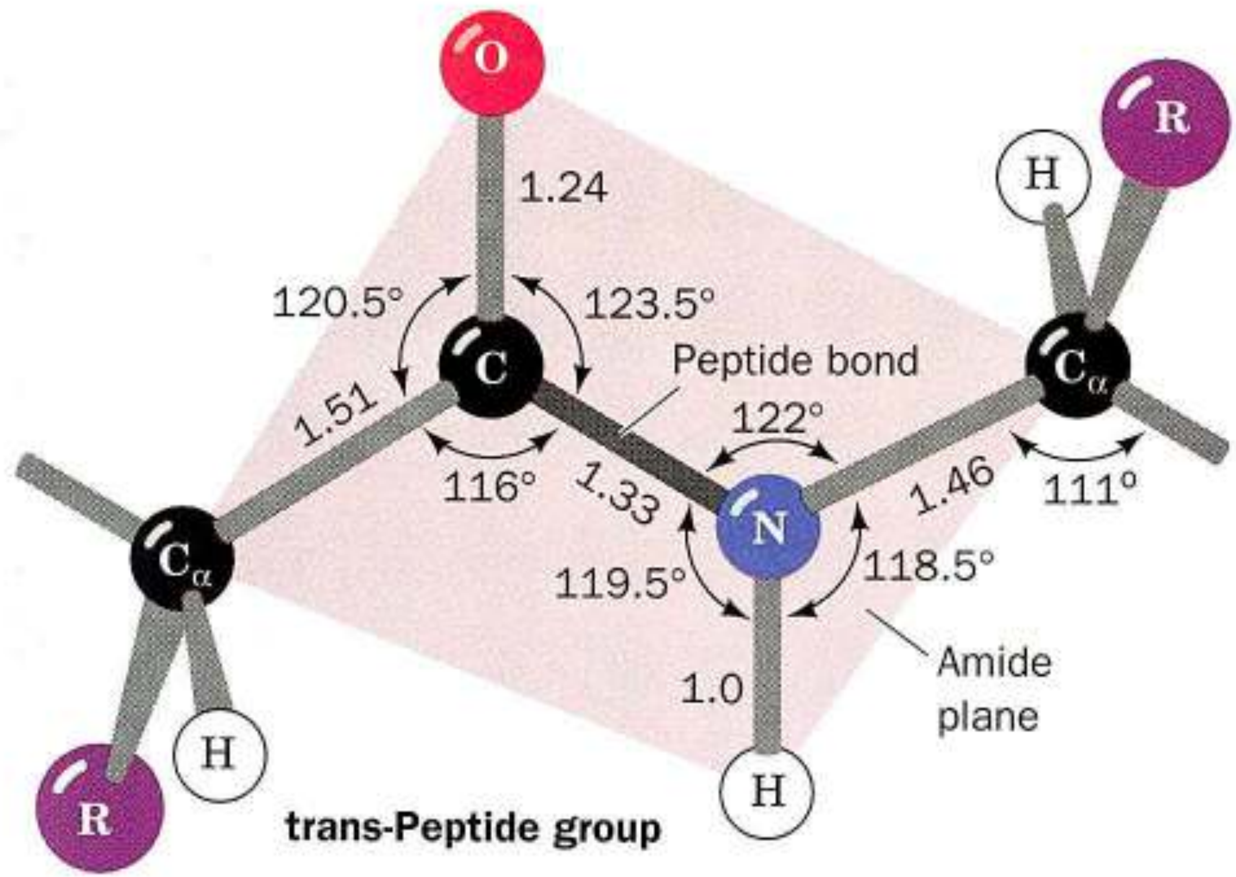
5′ (DNA) **3′ (DNA)**

Dipeptide

This is a peptide bond

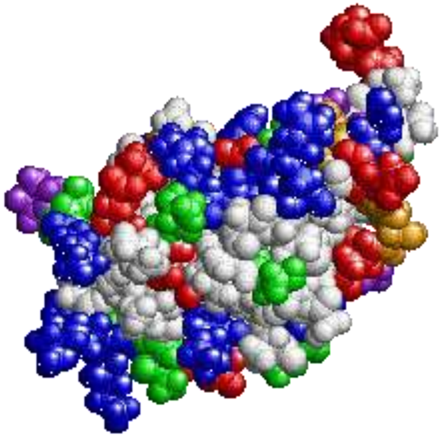
```
       R   O        R
       |   ||       |
H2N--C--C--NH--C--COOH
       |            |
       H            H
```

Peptide bond



Protein structure

- Linear sequence of amino acids folds to form a complex 3-D structure.
- The structure of a protein is intimately connected to its function.



Proteins show four hierarchical levels of structural organization:

1. **Primary structure** = amino acid sequence

   - ✓ **Determined by the genetic code of the mRNA.**

2. **Secondary structure** = folding and twisting of a single polypeptide chain.

   - ✓ **Result of weak H-bonds and electrostatic interactions**

   - ✓ **e.g., α-helix (coiled) and β-pleated sheet (zig-zag).**

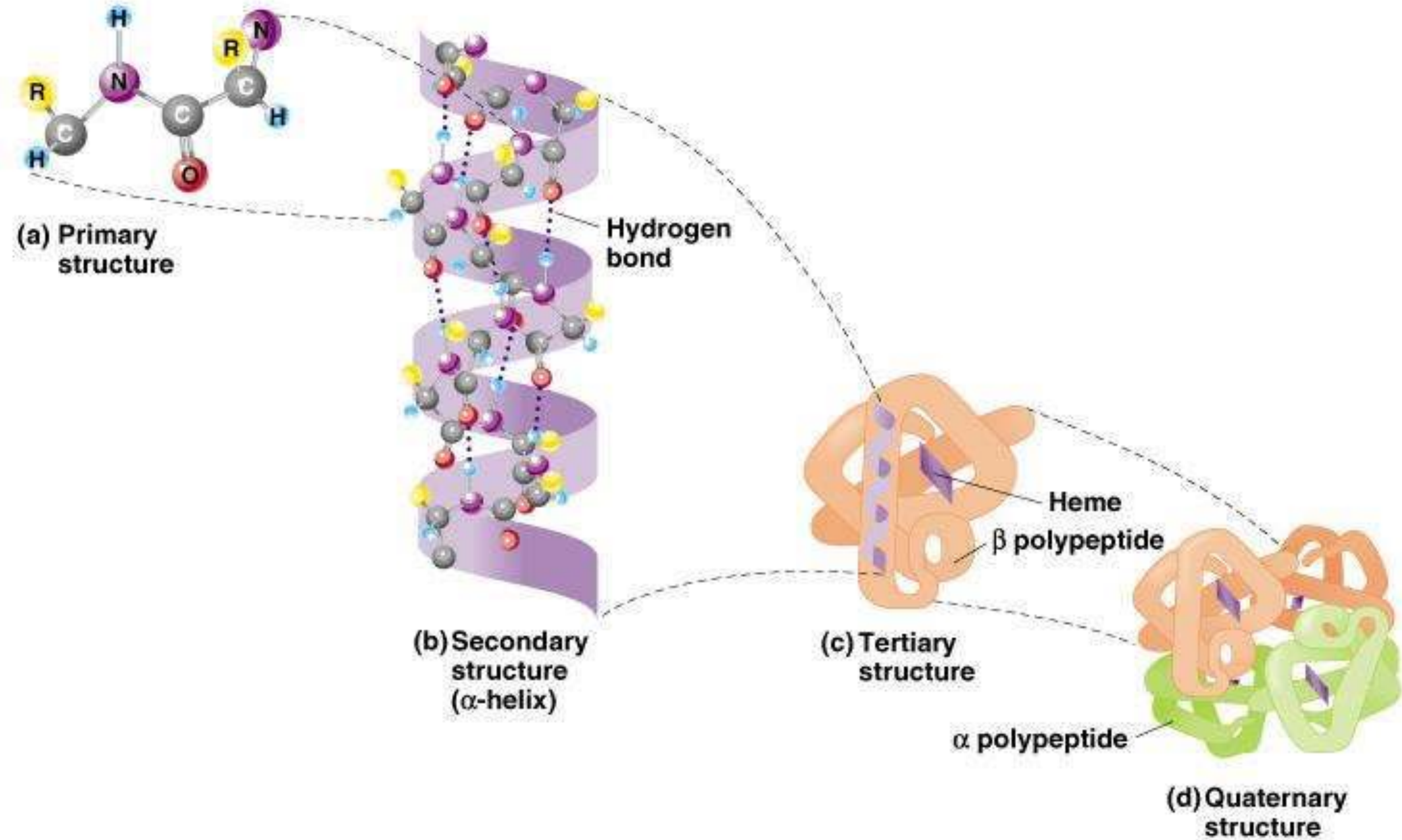
3. **Tertiary structure** = three dimensional shape (or conformation) of a polypeptide chain.

   - ✓ **Function of R groups contained in the polypeptide.**

4. **Quaternary structure** = association between polypeptides in multi-subunit proteins (e.g., hemoglobin).

   - ✓ **Occurs only with two or more polypeptides.**

Fig. 6.4



H
R
N
R
C
C
C
H
H
O
(a) Primary structure
Hydrogen bond
(b) Secondary structure (α-helix)
Heme
β polypeptide
(c) Tertiary structure
α polypeptide
(d) Quaternary structure

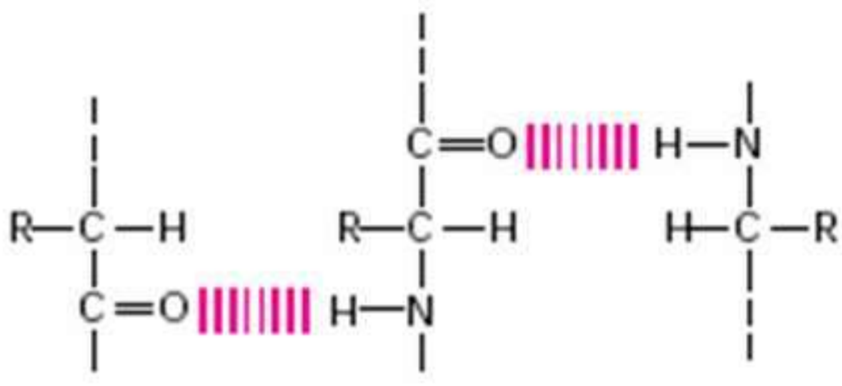
HYDROGEN BONDS

As already described for water (see Panel 2–2, pp. 50–51) hydrogen bonds form when a hydrogen atom is "sandwiched" between two electron-attracting atoms (usually oxygen or nitrogen).

Hydrogen bonds are strongest when the three atoms are in a straight line:

Examples in macromolecules:

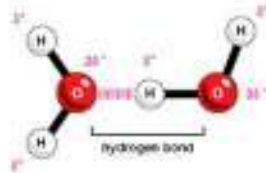
Amino acids in polypeptide chains hydrogen-bonded together.

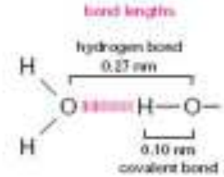


HYDROGEN BONDS

Because they are polarized, two adjacent H_2O molecules can form a linkage known as a hydrogen bond. Hydrogen bonds have only about 1/20 the strength of a covalent bond.

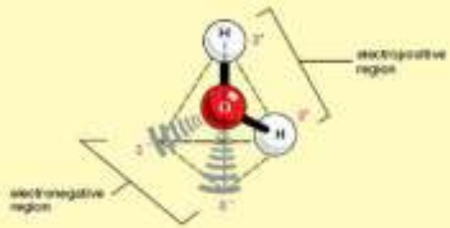
Hydrogen bonds are strongest when the three atoms lie in a straight line.





WATER

Two atoms, connected by a covalent bond, may exert different attractions for the electrons of the bond. In such cases the bond is polar, with one end slightly negatively charged (δ^-) and the other slightly positively charged (δ^+).



Although a water molecule has an overall neutral charge (having the same number of electrons and protons), the electrons are asymmetrically distributed, which makes the molecule polar. The oxygen nucleus draws electrons away from the hydrogen nuclei, leaving these nuclei with a small net positive charge. The excess of electron density on the oxygen atom creates weakly negative regions at the other two corners of an imaginary tetrahedron.

WATER STRUCTURE

Molecules of water join together transiently in a hydrogen-bonded lattice. Even at 37°C, 15% of the water molecules are joined to four others in a short-lived assembly known as a "flickering cluster."

The cohesive nature of water is responsible for many of its unusual properties, such as high surface tension, specific heat, and heat of vaporization.

HYDROPHILIC MOLECULES

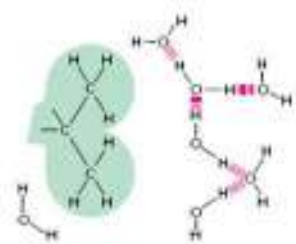
Substances that dissolve readily in water are termed hydrophilic. They are composed of ions or polar molecules that attract water molecules through electrical charge effects. Water molecules surround each ion or polar molecule on the surface of a solid substance and carry it into solution.

Ionic substances such as sodium chloride dissolve because water molecules are attracted to the positive (Na^+) or negative (Cl^-) charge of each ion.

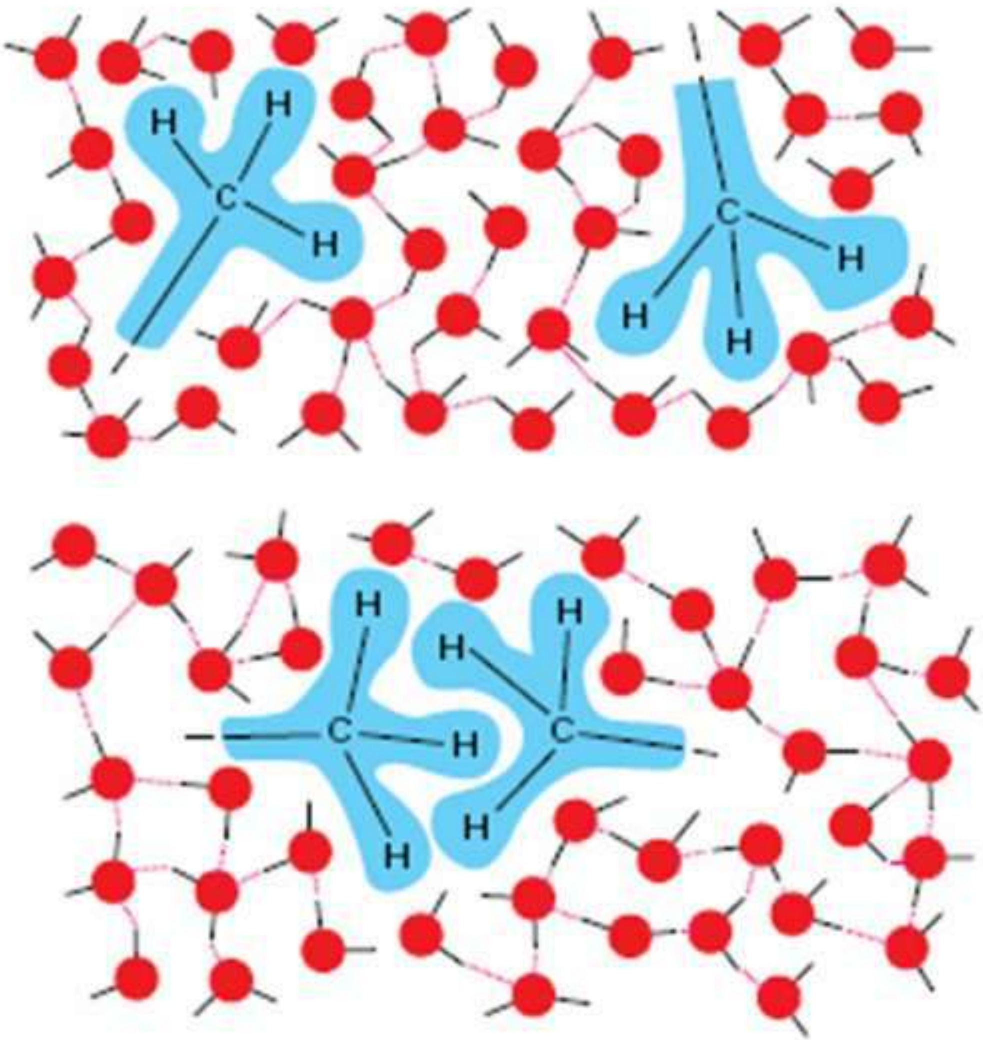
Polar substances such as urea dissolve because their molecules form hydrogen bonds with the surrounding water molecules.

HYDROPHOBIC MOLECULES

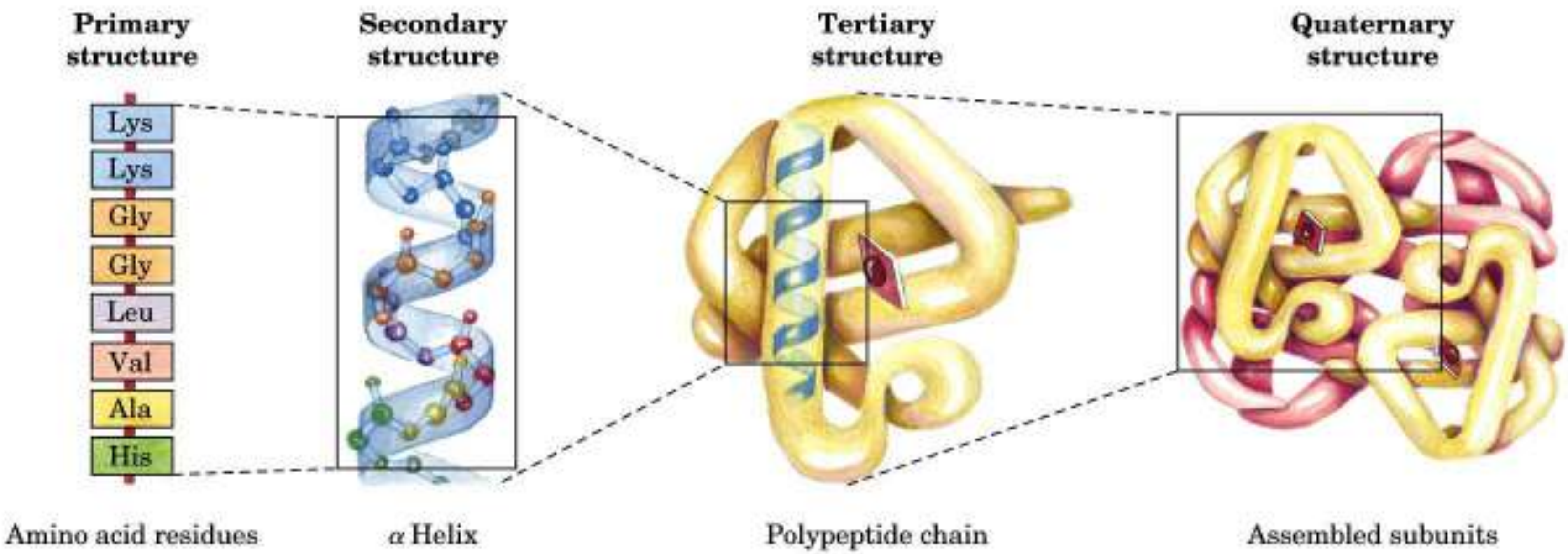
Molecules that contain a preponderance of nonpolar bonds are usually insoluble in water and are termed hydrophobic. This is true, especially, of hydrocarbons, which contain many C–H bonds. Water molecules are not attracted to such molecules and so have little tendency to surround them and carry them into solution.



HYDROPHOBIC FORCES



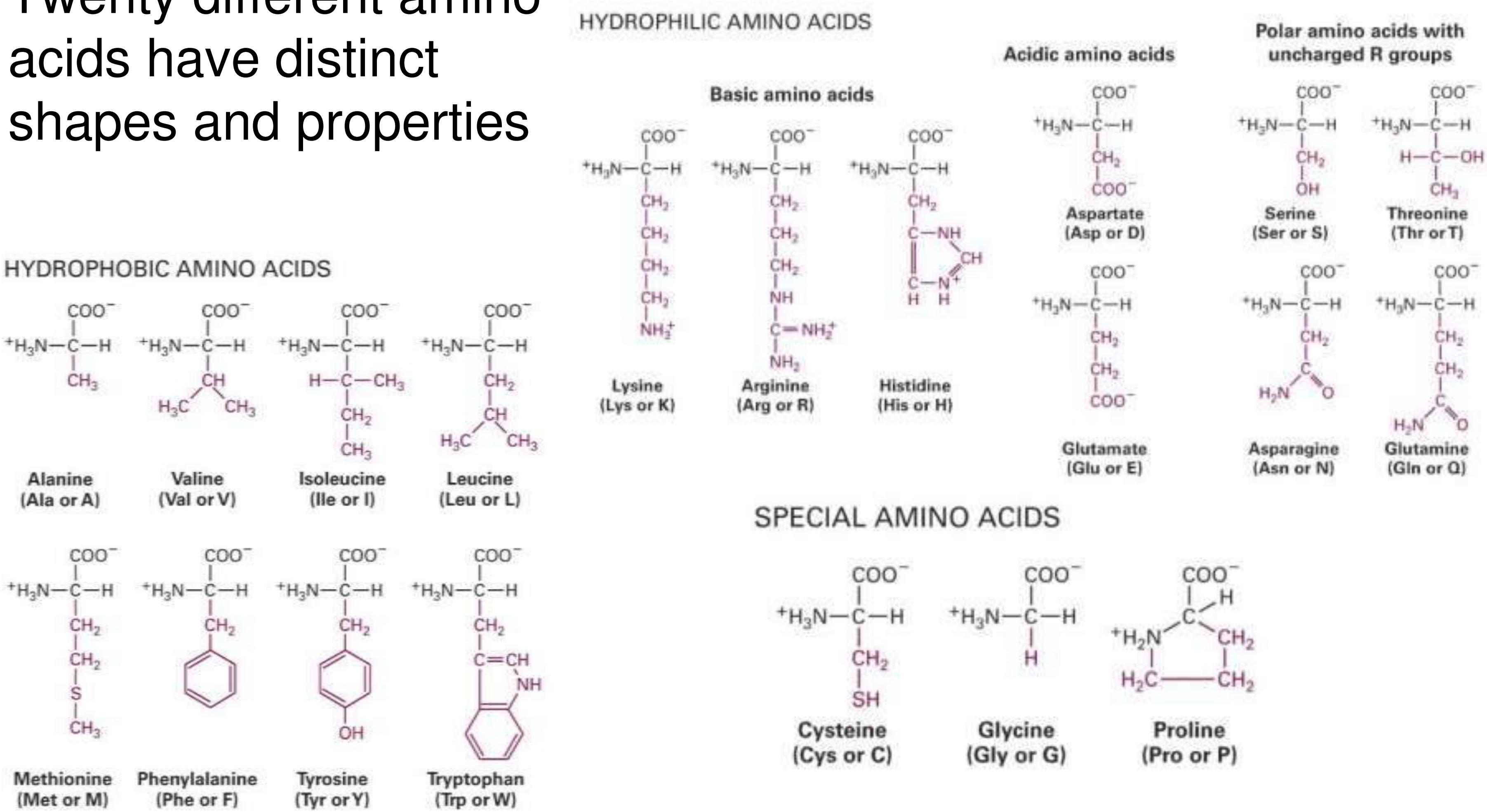
Levels of Protein Structure



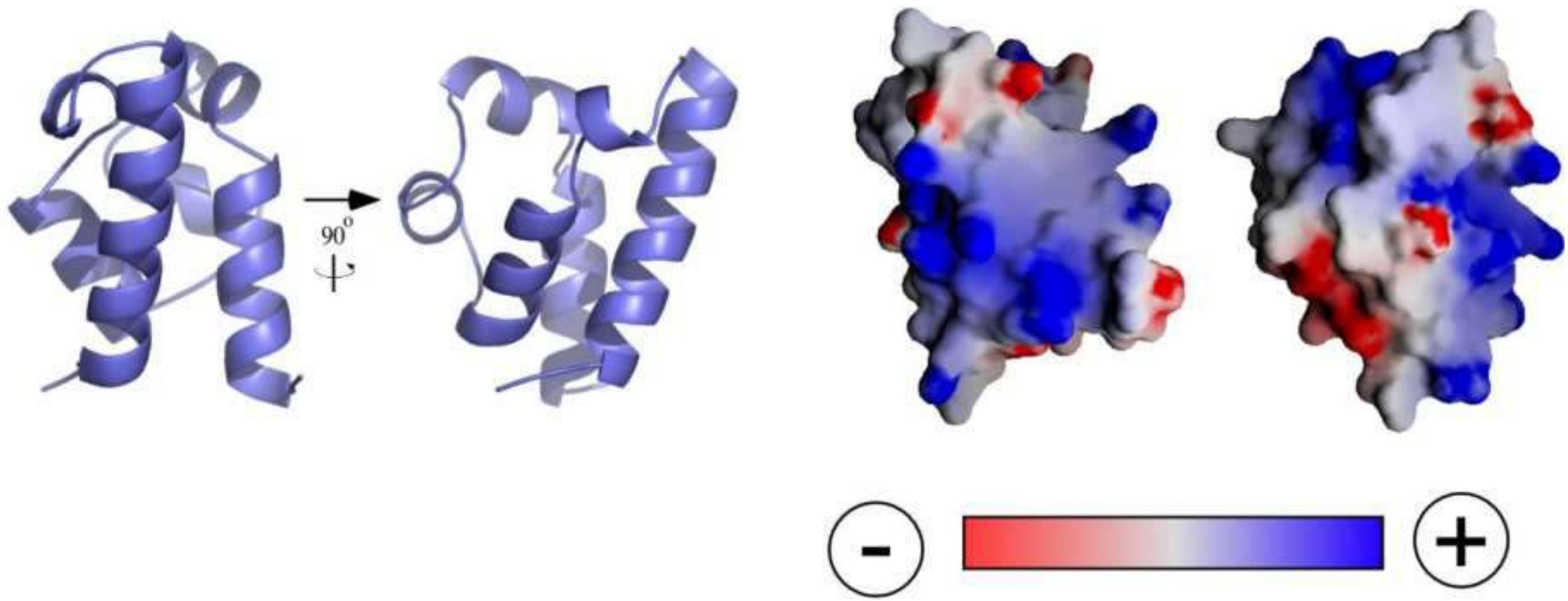
Primary structure =
order of amino acids
in the protein chain

Primary Structure: Sequence

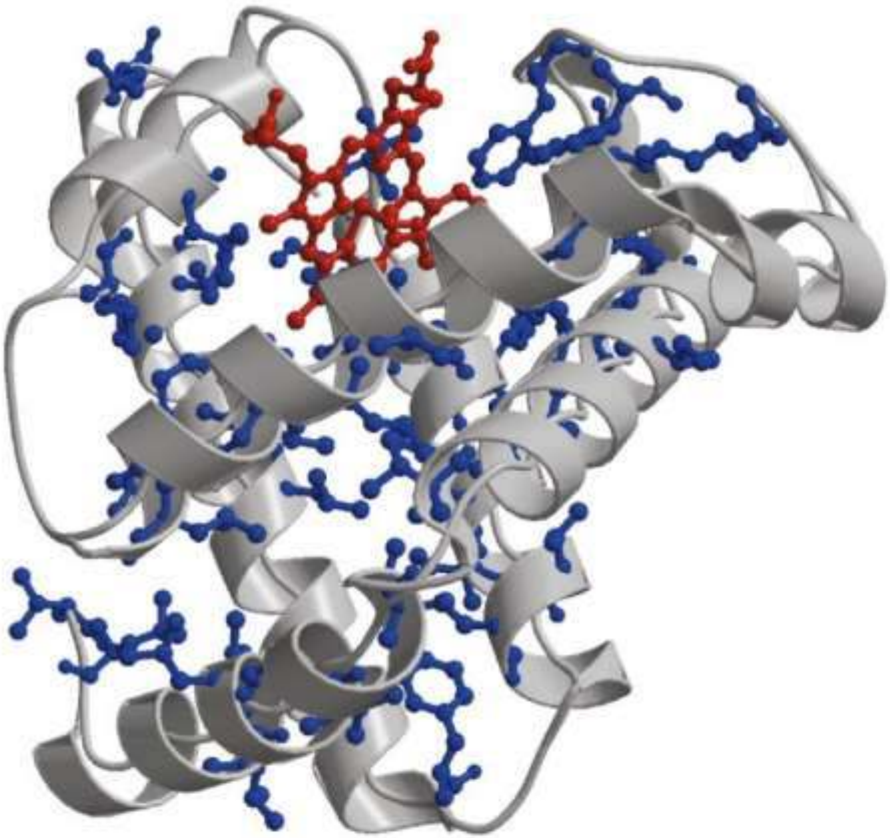
- Twenty different amino acids have distinct shapes and properties



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



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

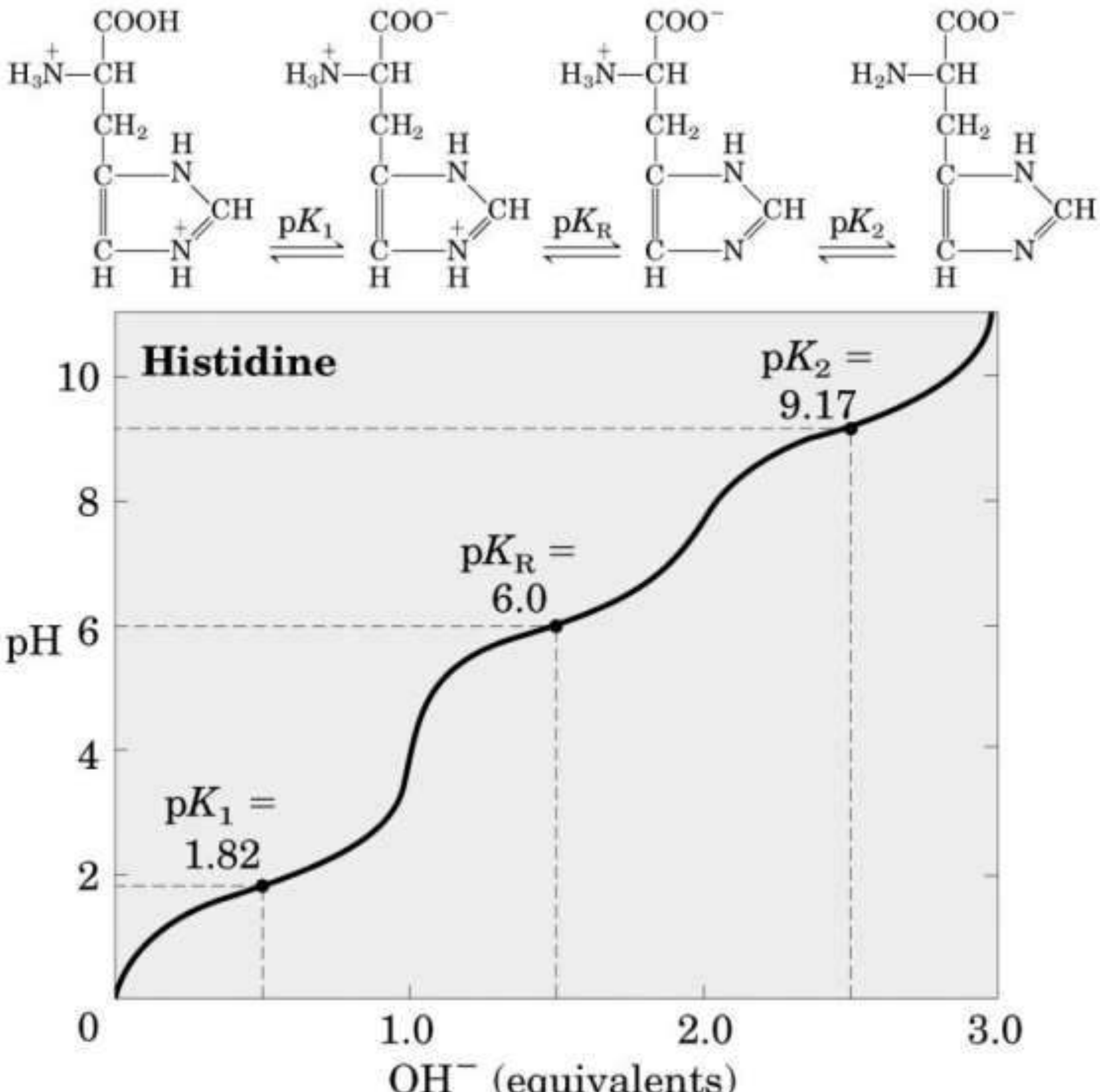


(d)

Myoglobin
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

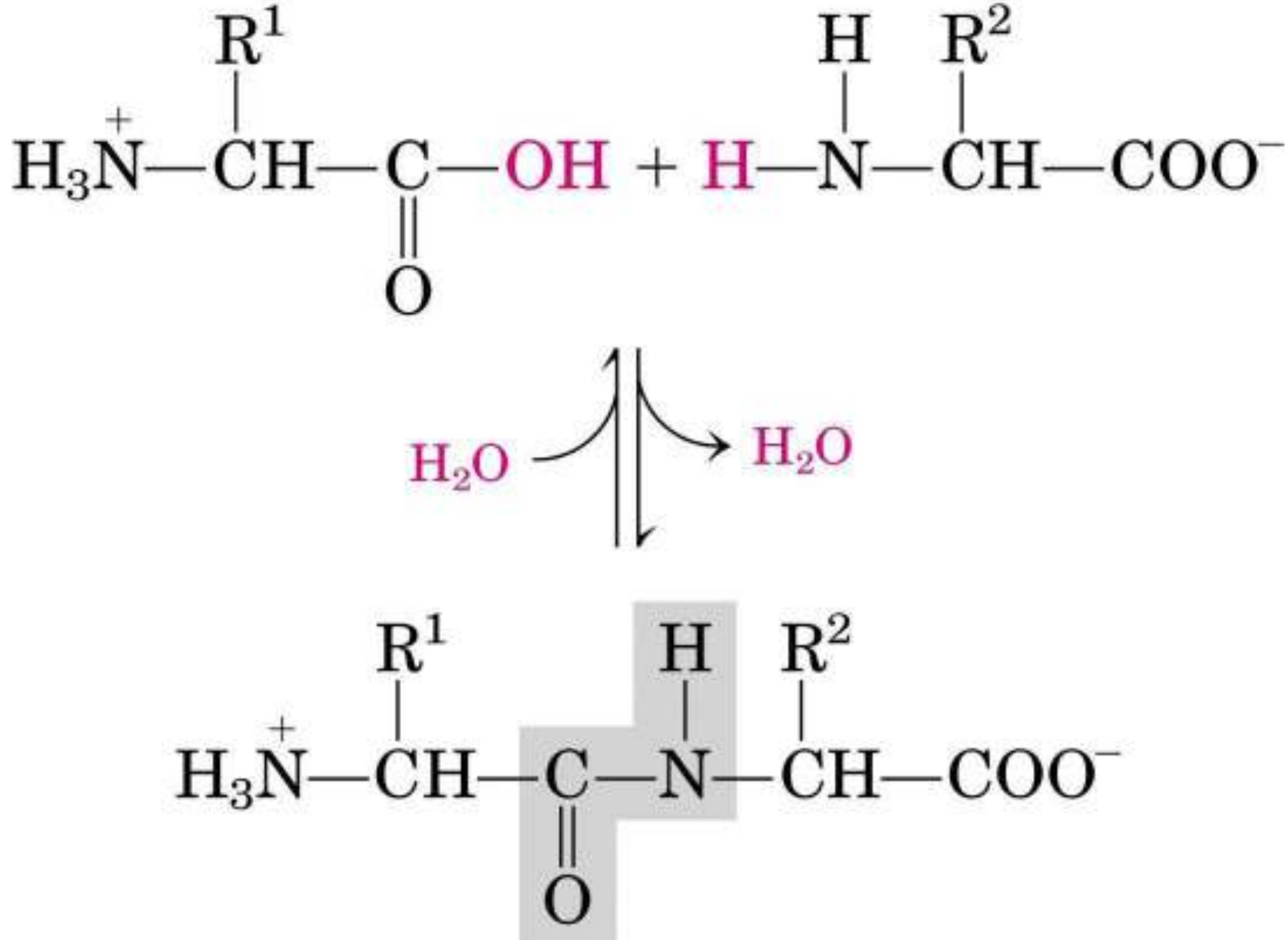
Henderson-Hasselbalch

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

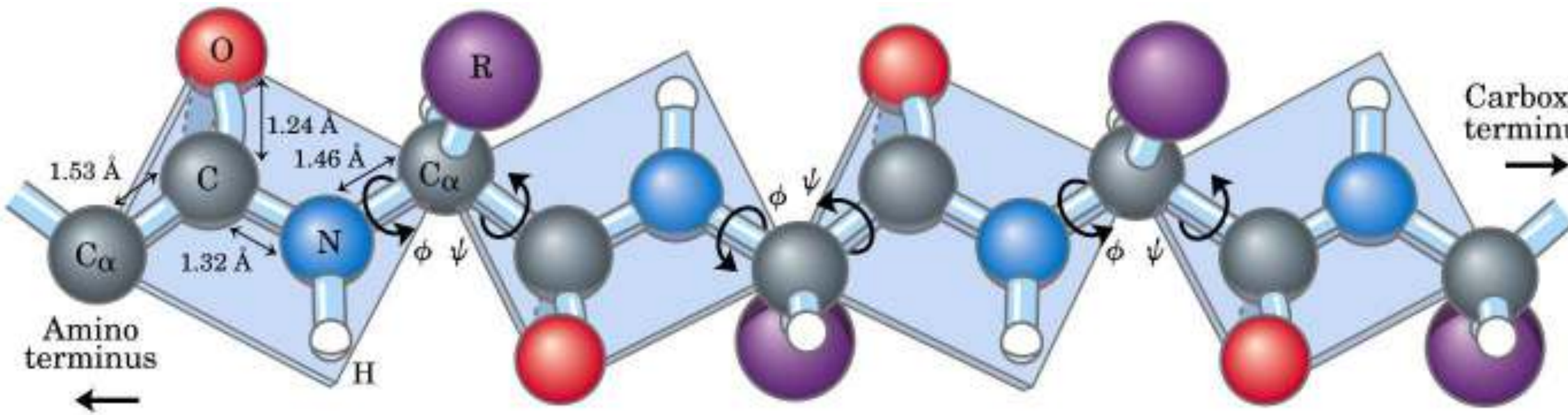
Some R-groups can modified

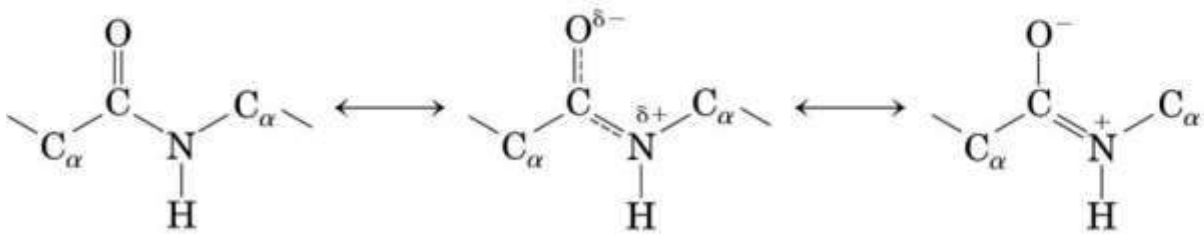
Modification	Chemistry	Common sites of attachment
Phosphorylation	R-OH + HPO_4^{2-} $\rightarrow$ R-O-PO_3^{2-} + H_2O	Residues with hydroxyl groups (Ser, Thr, Tyr)
N-Glycosylation	R-NH-sugar	Asn
O-Glycosylation	R-O-sugar	Ser, Thr, and modified residues
Hydroxylation	hydroxyl group (OH) added to R group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

Chemistry of peptide bond formation



The peptide bond is planar



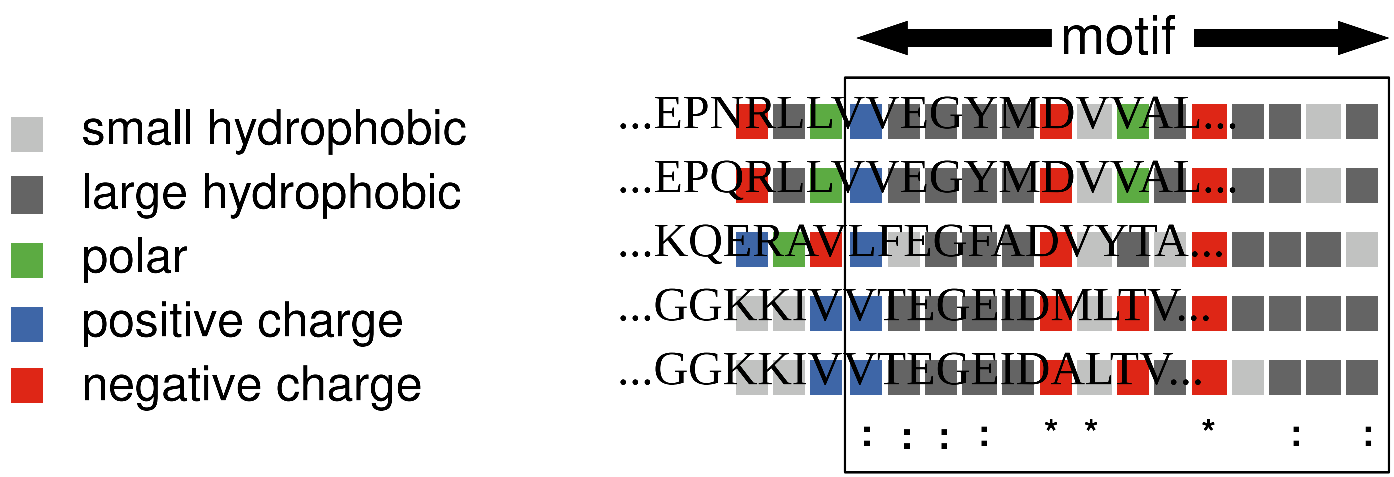


This resonance restricts the number of conformations in proteins -- main chain rotations are restricted to ϕ and ψ.

Primary sequence reveals important clues about a protein

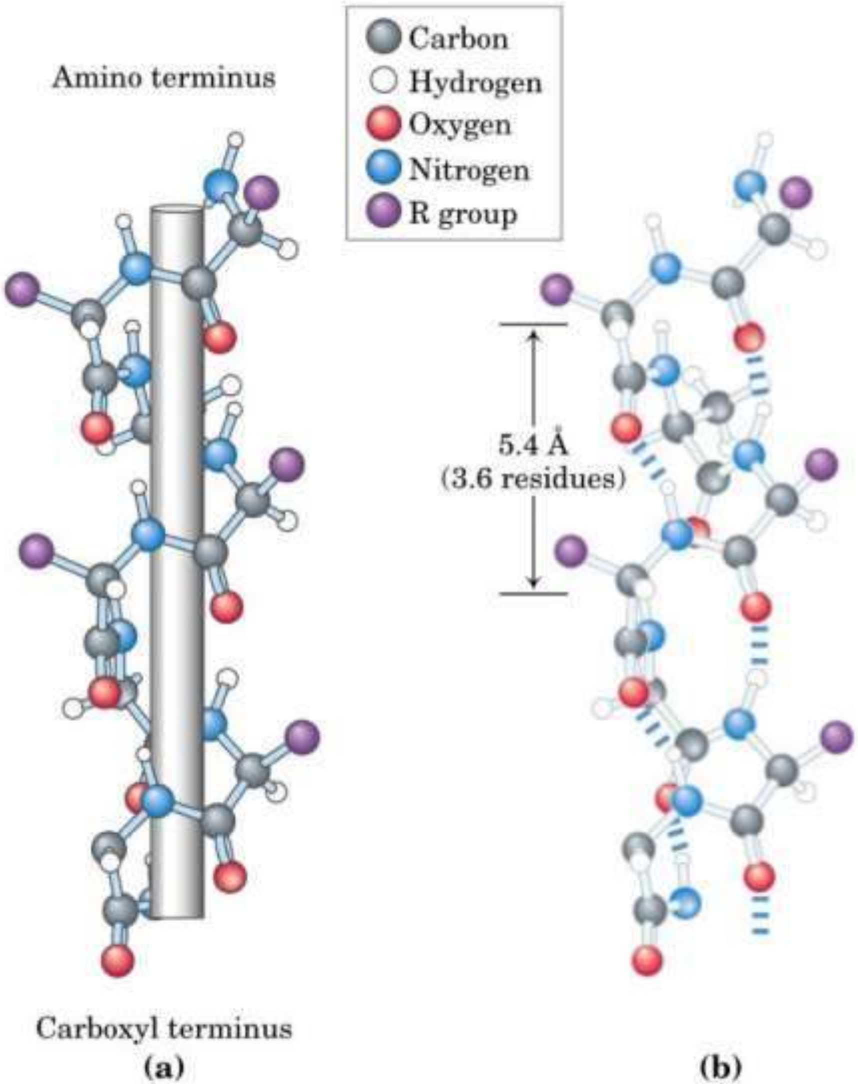
• Evolution conserves amino acids that are important to protein structure and function across species. Sequence comparison of multiple “homologs” of a particular protein reveals highly conserved regions that are important for function.

• 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 =
<u>local</u> folding of residues
into regular patterns

The α-helix

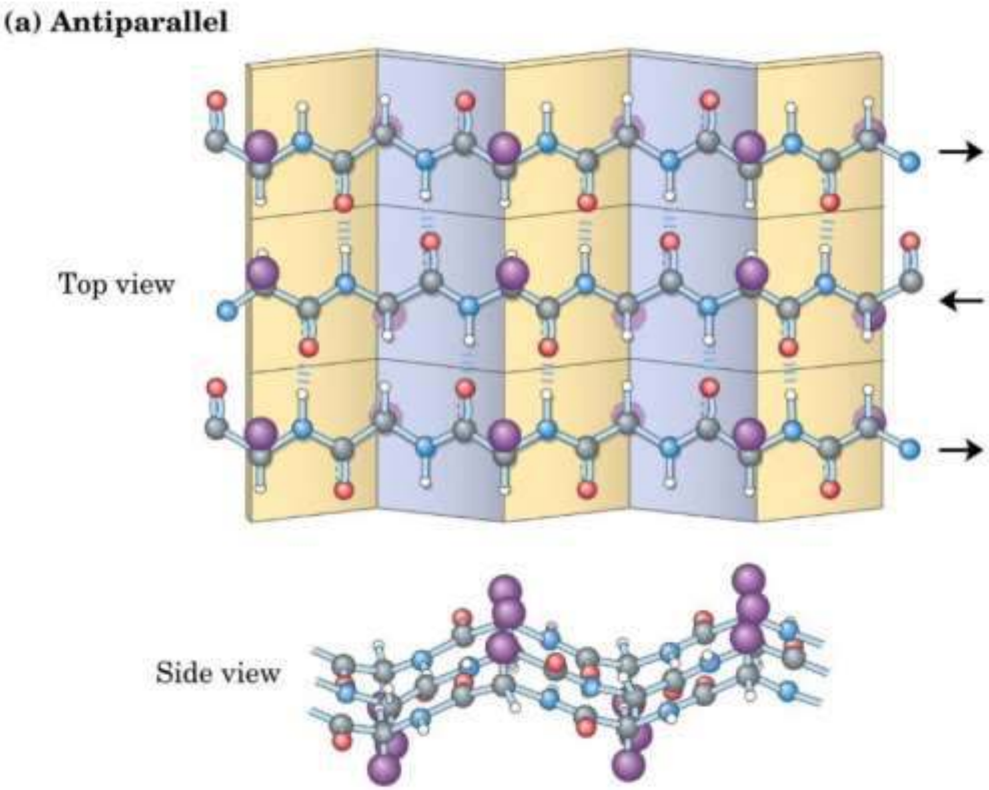


- In the α-helix, the carbonyl oxygen of residue “i” forms a hydrogen bond with the amide of residue “i+4”.

- 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

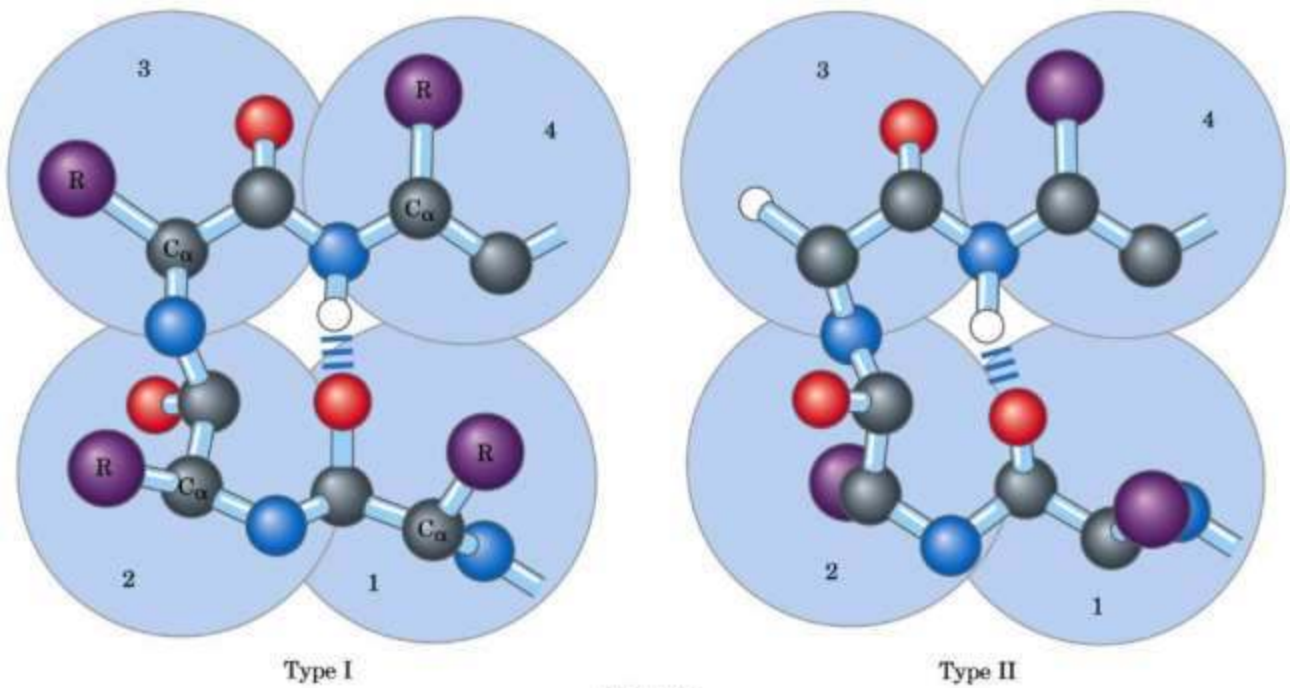


• In a β-sheet, carbonyl oxygens and amides form hydrogen bonds.

• 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.

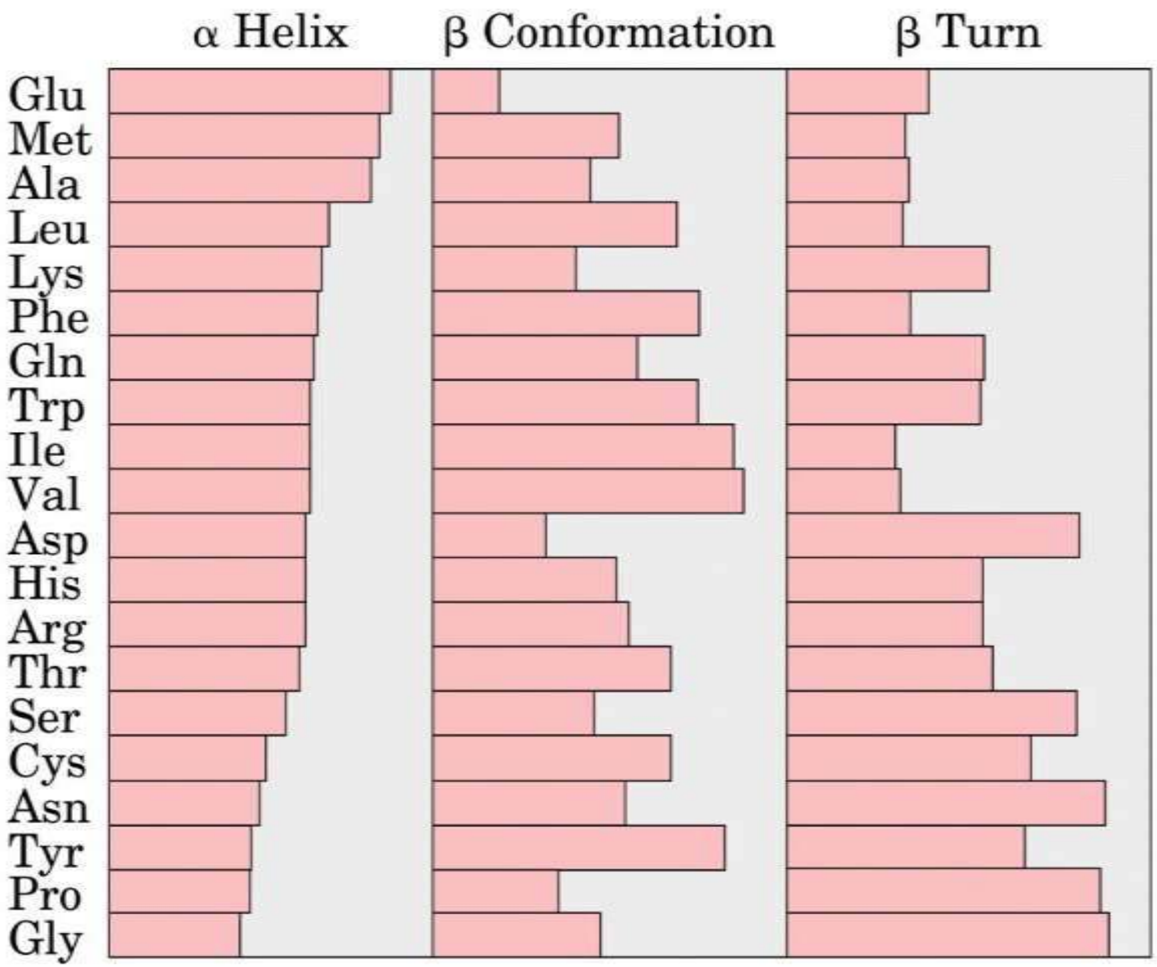
β turns



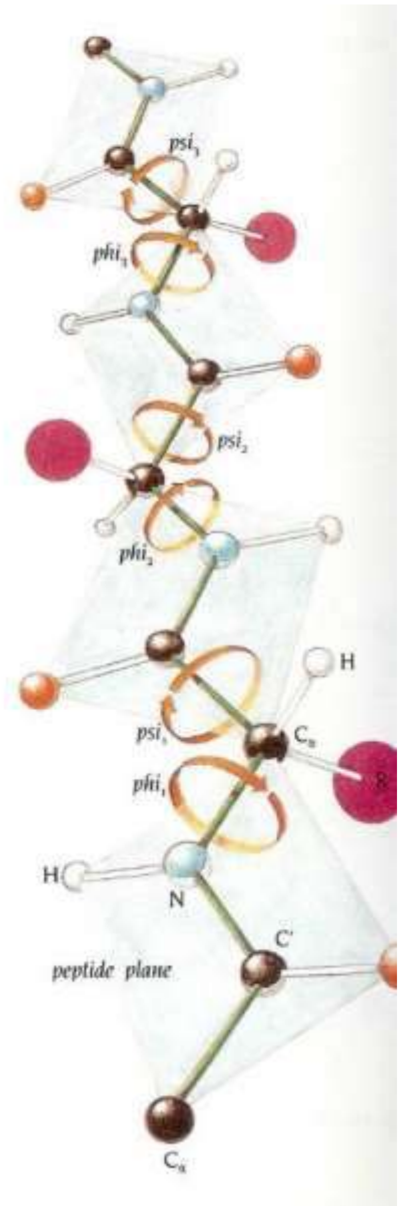
β **Turns**
(a)

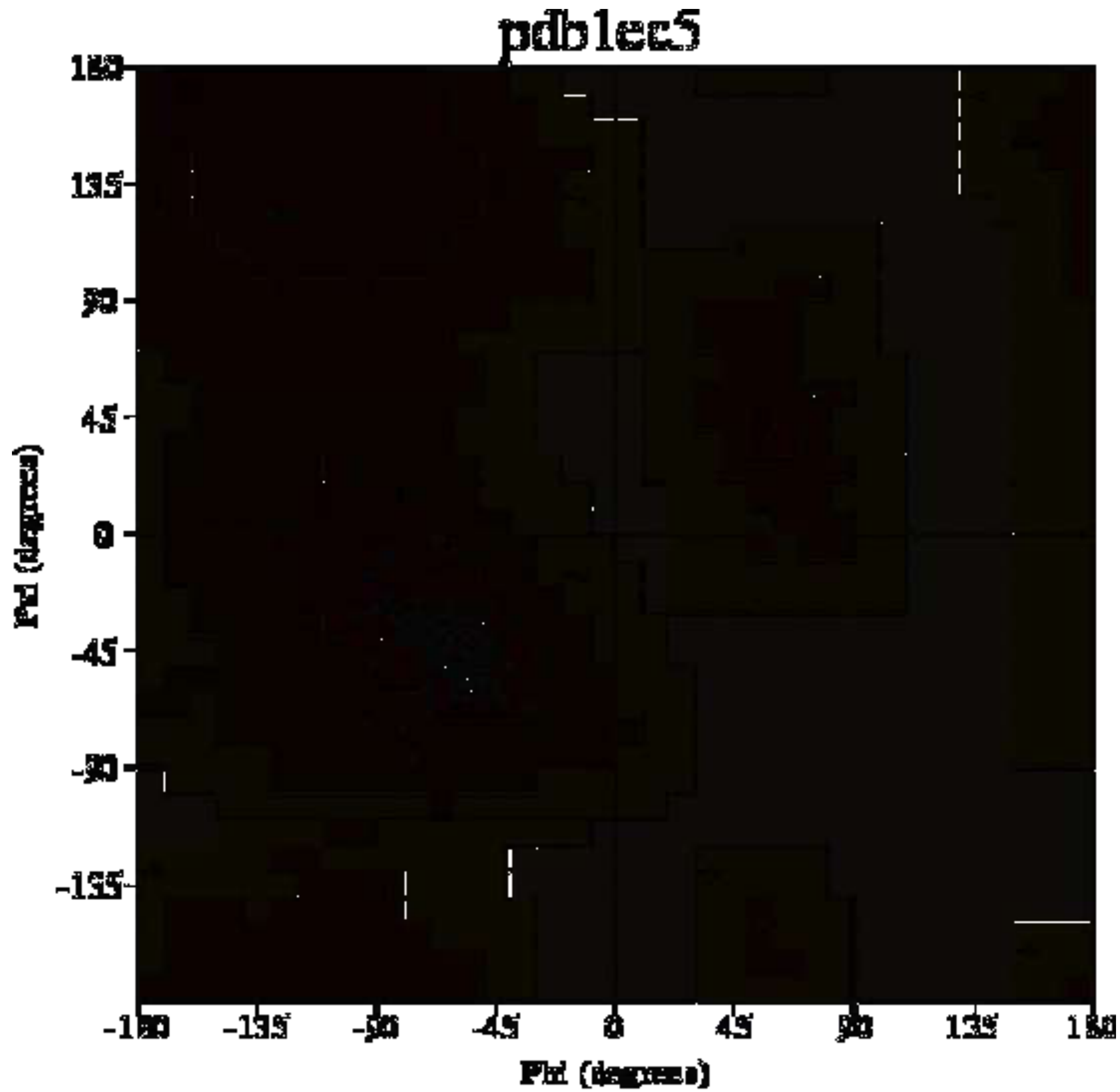
- β-turns allow the protein backbone to make abrupt turns.
- Again, the propensity of a peptide for forming β-turns depends on its sequence.

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



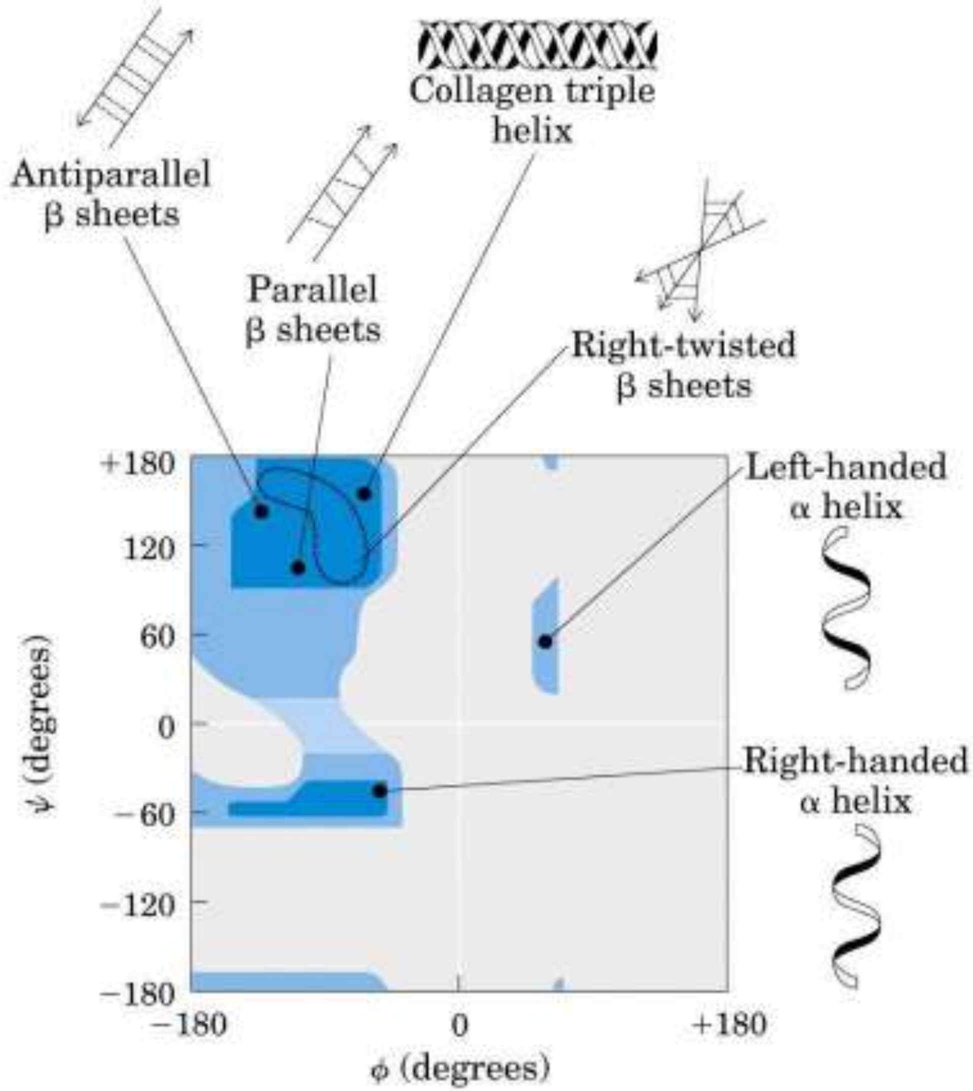
Geometry of the Chain





From Brandon and Tooze

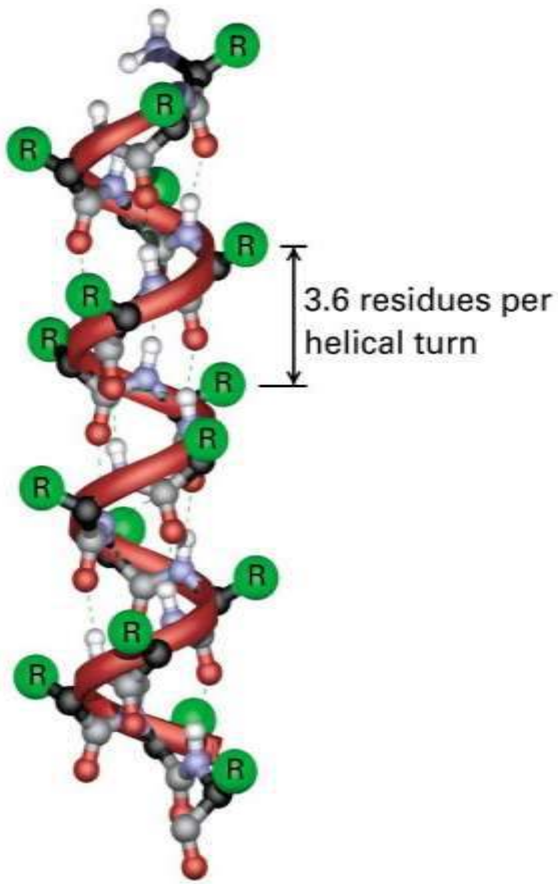
Ramachandran plot -- shows ϕ and ψ angles for secondary structures

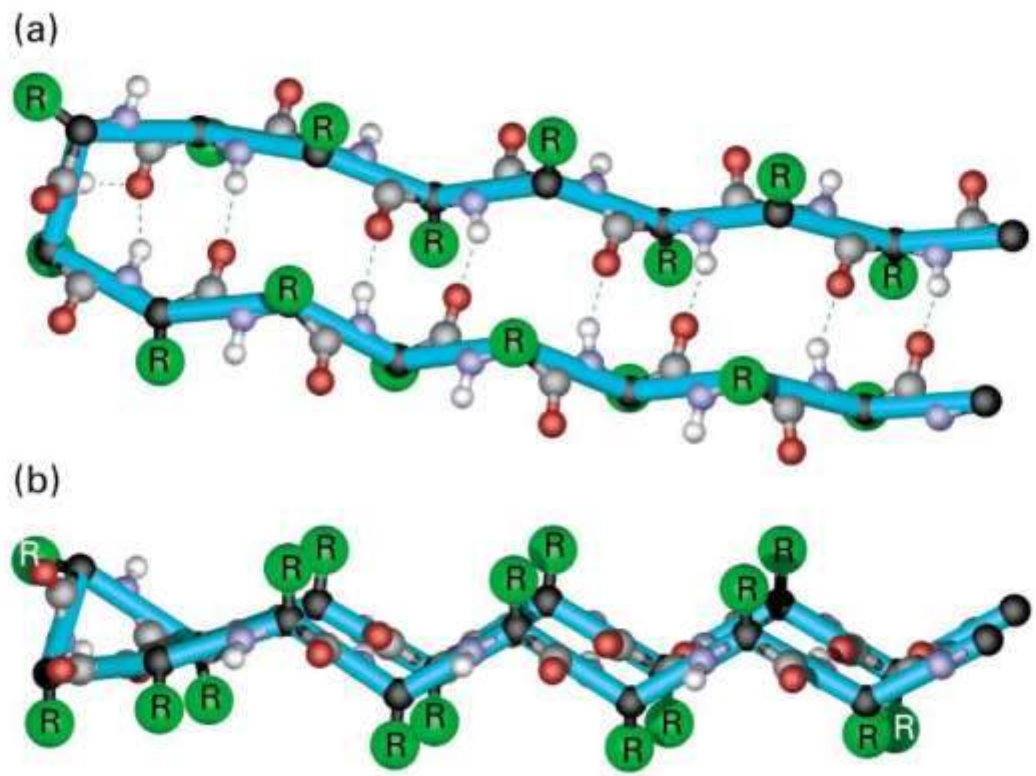


(a)

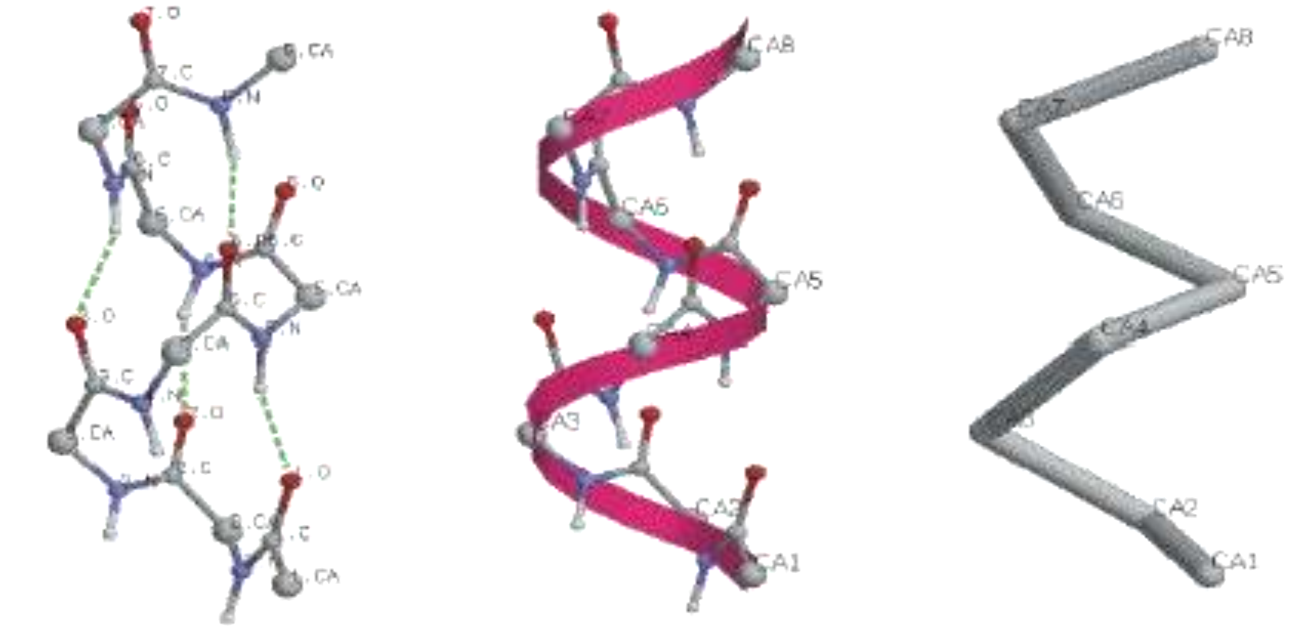
Secondary Structure: α, β, & loops

- α helices and β sheets are stabilized by hydrogen bonds between backbone oxygen and hydrogen atoms





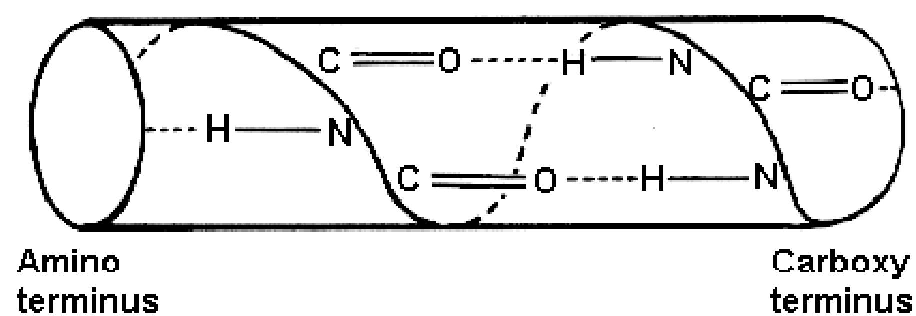
Secondary Structure: α helix



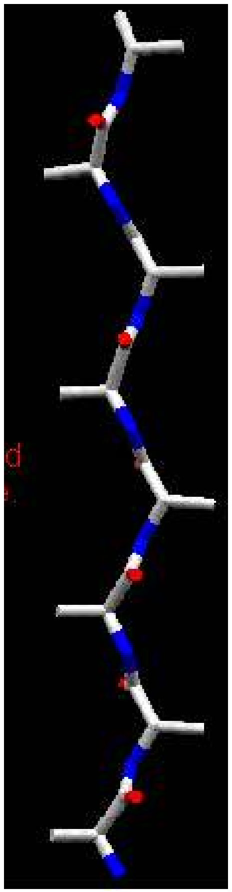
Atoms of the backbone

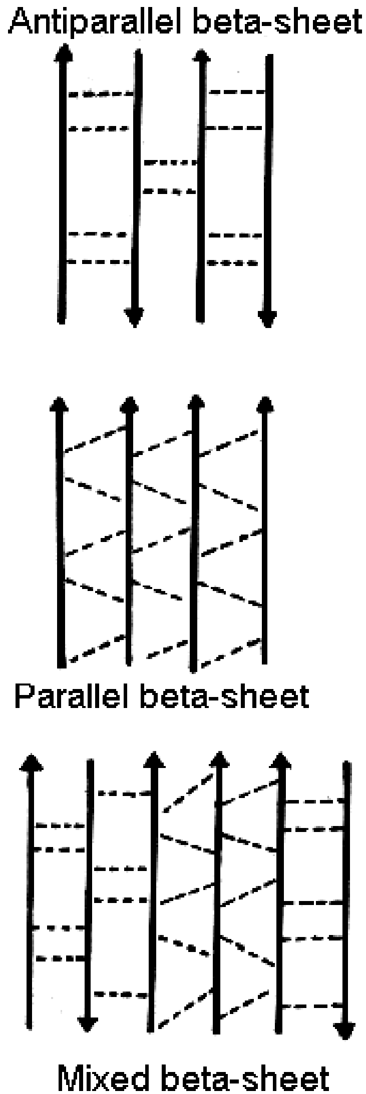
"Ribbon"/ "Cartoon"

"Backbone"

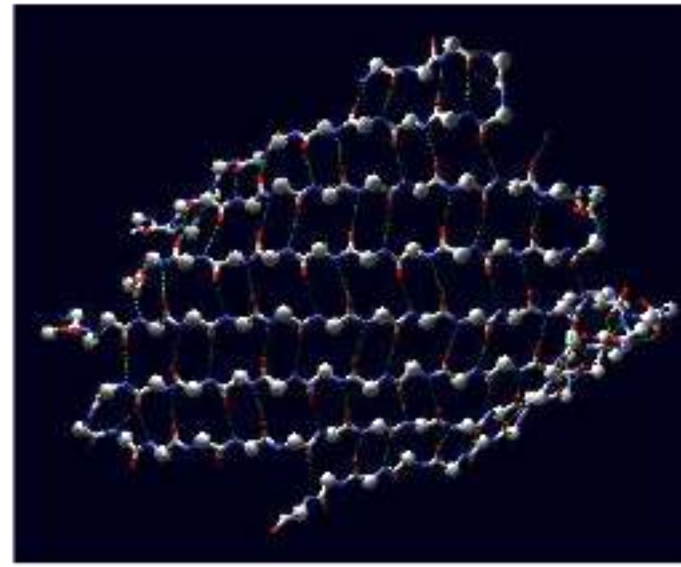


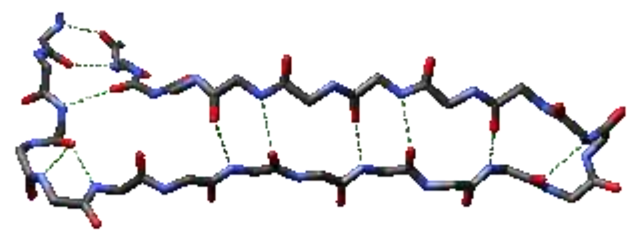
Secondary Structure: β sheet



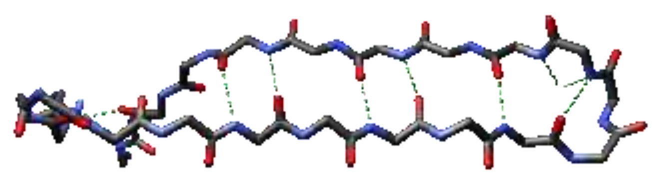


β sheet



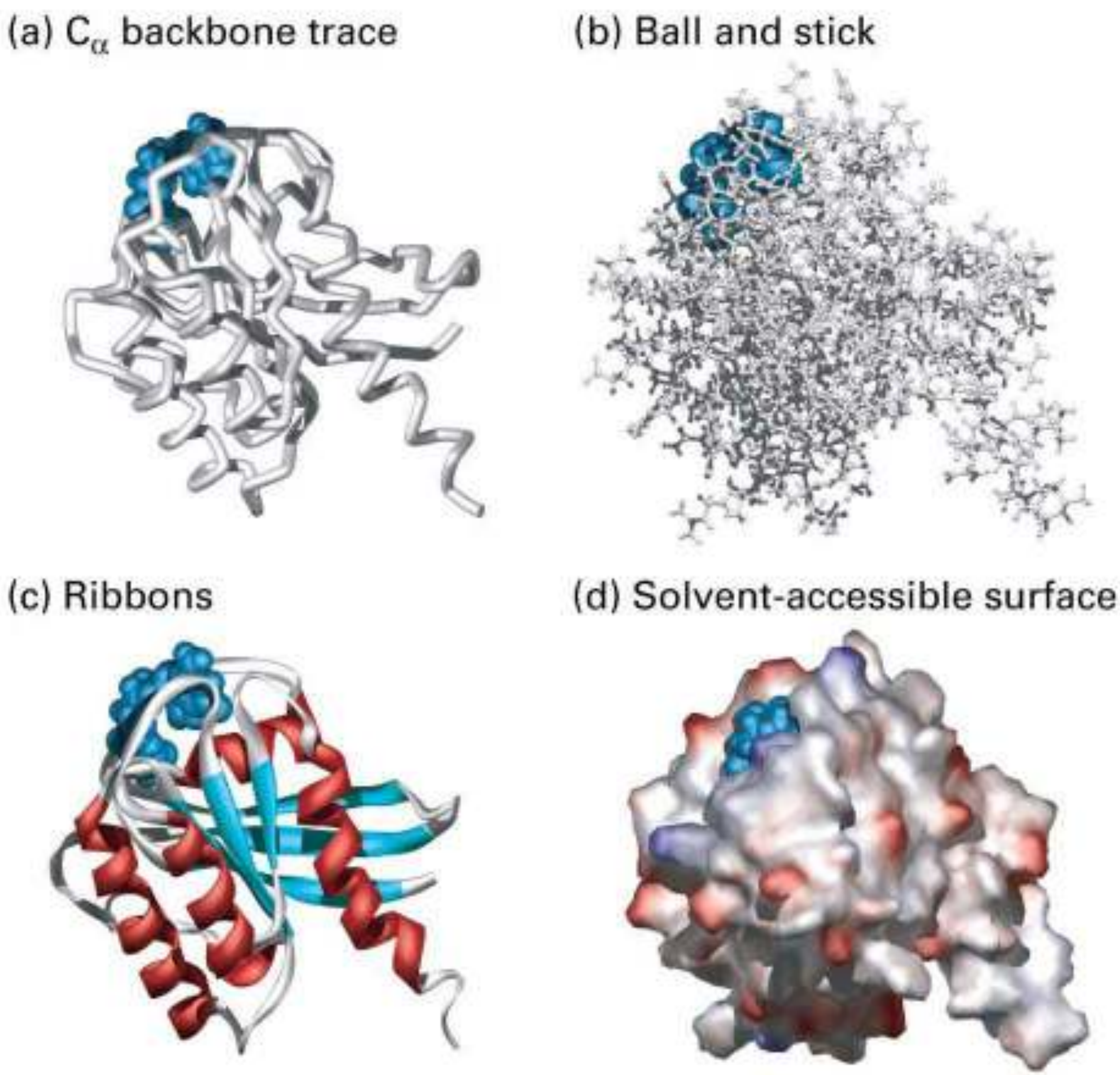


β buldge



Tertiary structure =
<u>global</u> folding
of a protein chain

Tertiary Structure: A Protein Fold



Protein Data Bank (PDB)

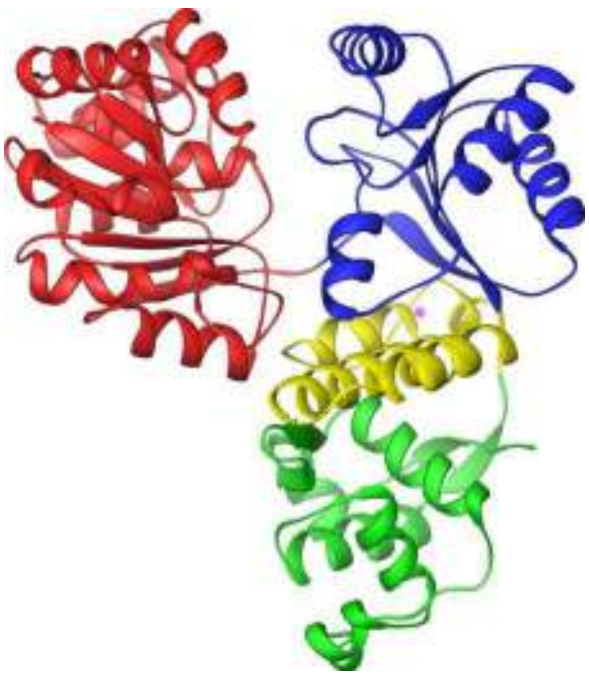
– http://www.rcsb.org/pdb/

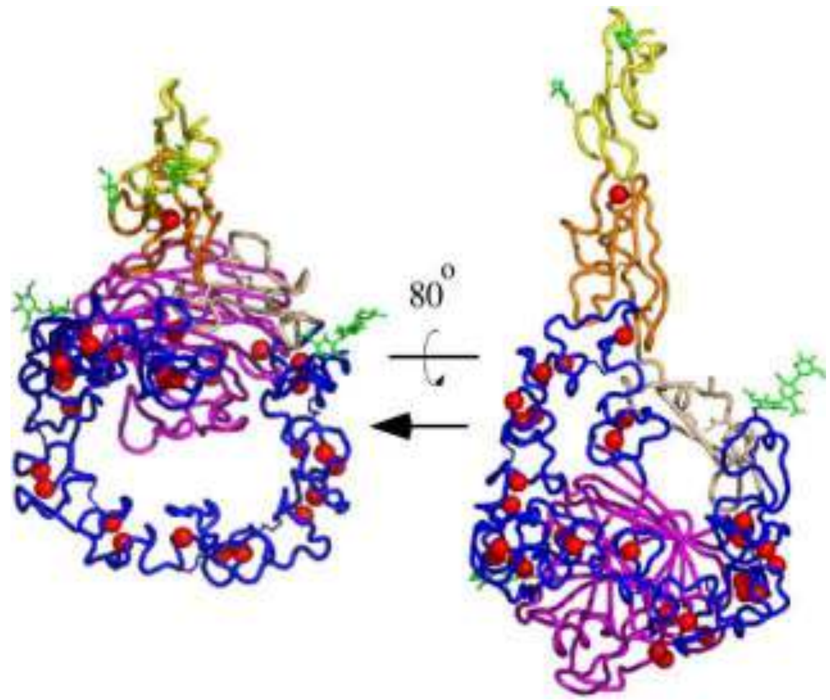
- File Format

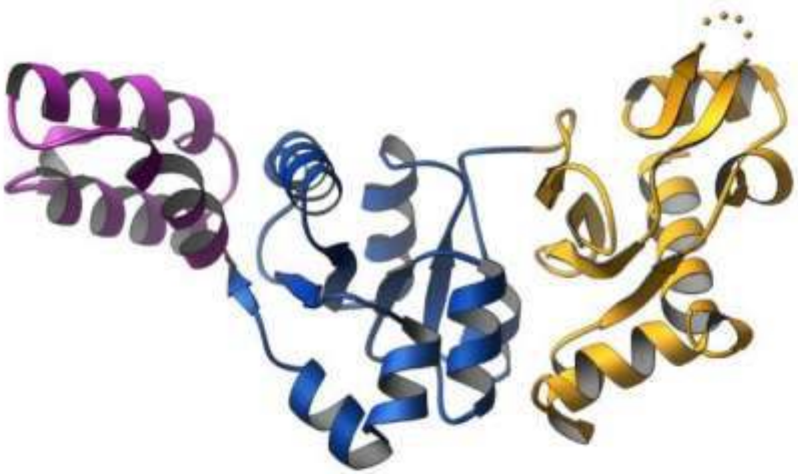
	ATOM number	ATOM name	Residue name	Chain id	Residue number	Atomic coordinates x	y	z
ATOM	1	N	PRO	A	1	-27.582	31.362	-2.081
ATOM	2	CA	PRO	A	1	-28.062	31.417	-0.726
ATOM	3	C	PRO	A	1	-26.791	31.512	0.110

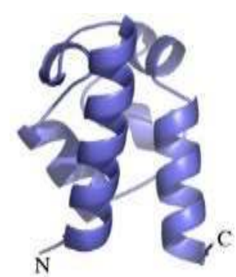
.
.
.

Tertiary structures are quite varied



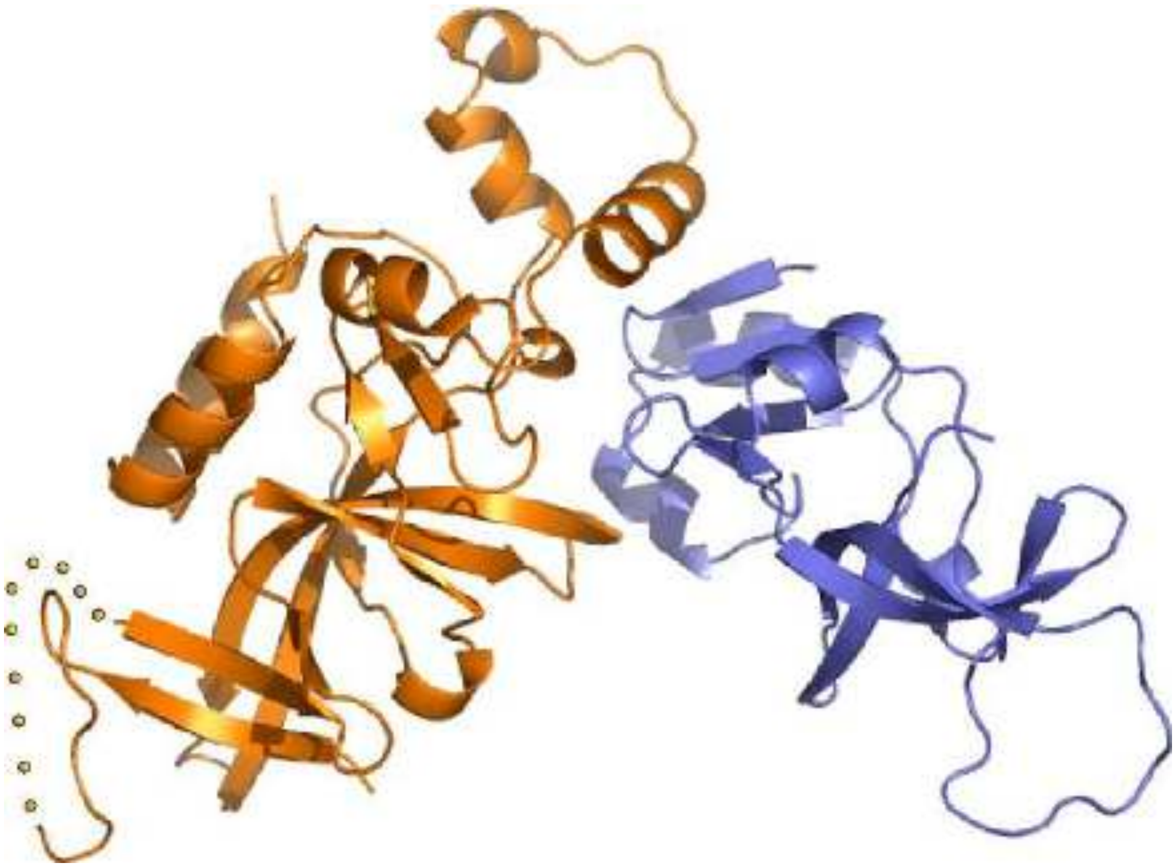






Quaternary structure =
Higher-order assembly of proteins

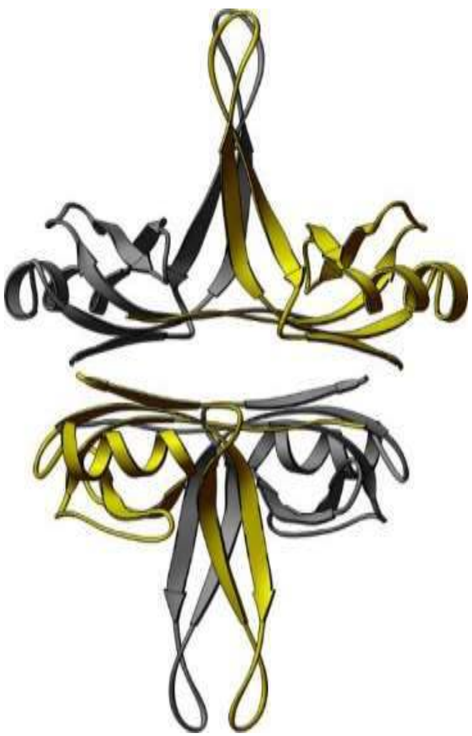
Example of tertiary and quaternary structure - Sir1/Orc1 heterodimer



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

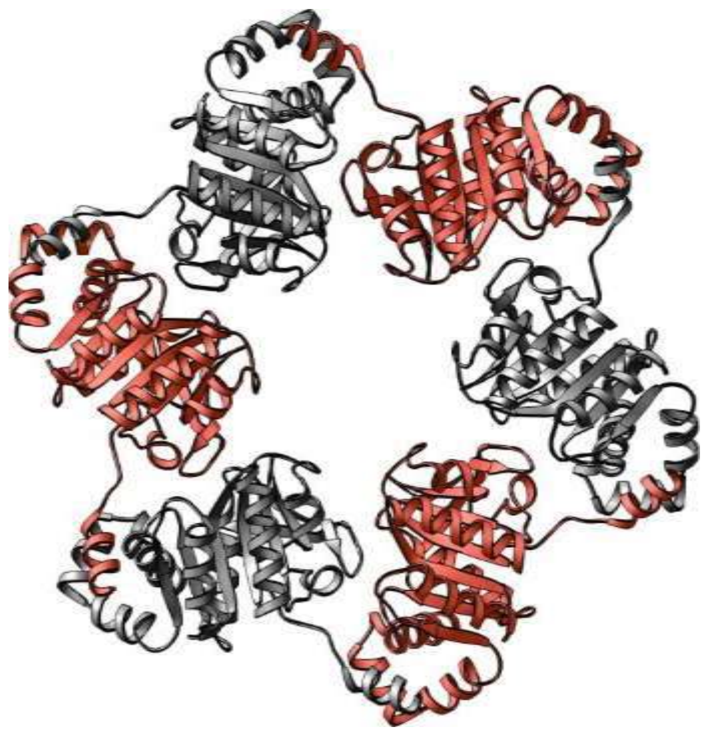
<u>Tetramer</u>



<u>SSB</u>

Allows coordinated DNA binding

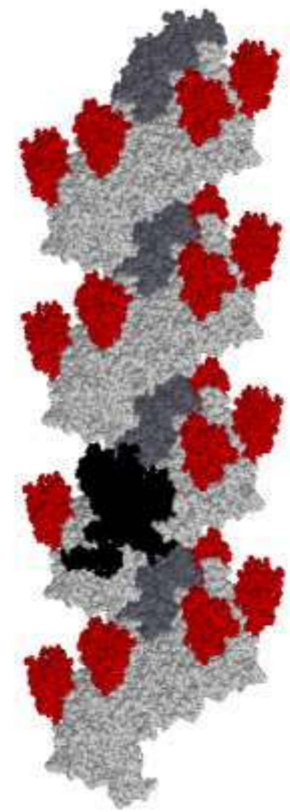
<u>Hexamer</u>



<u>DNA helicase</u>

Allows coordinated DNA binding and ATP hydrolysis

Filament



<u>Recombinase</u>

Allows complete coverage of an extended molecule

Classes of proteins

<u>Functional definition:</u>

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

<u>Structural definition:</u>

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

<u>Cellular localization definition:</u>

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