Protein Structure

College of medicine
Second stage

By
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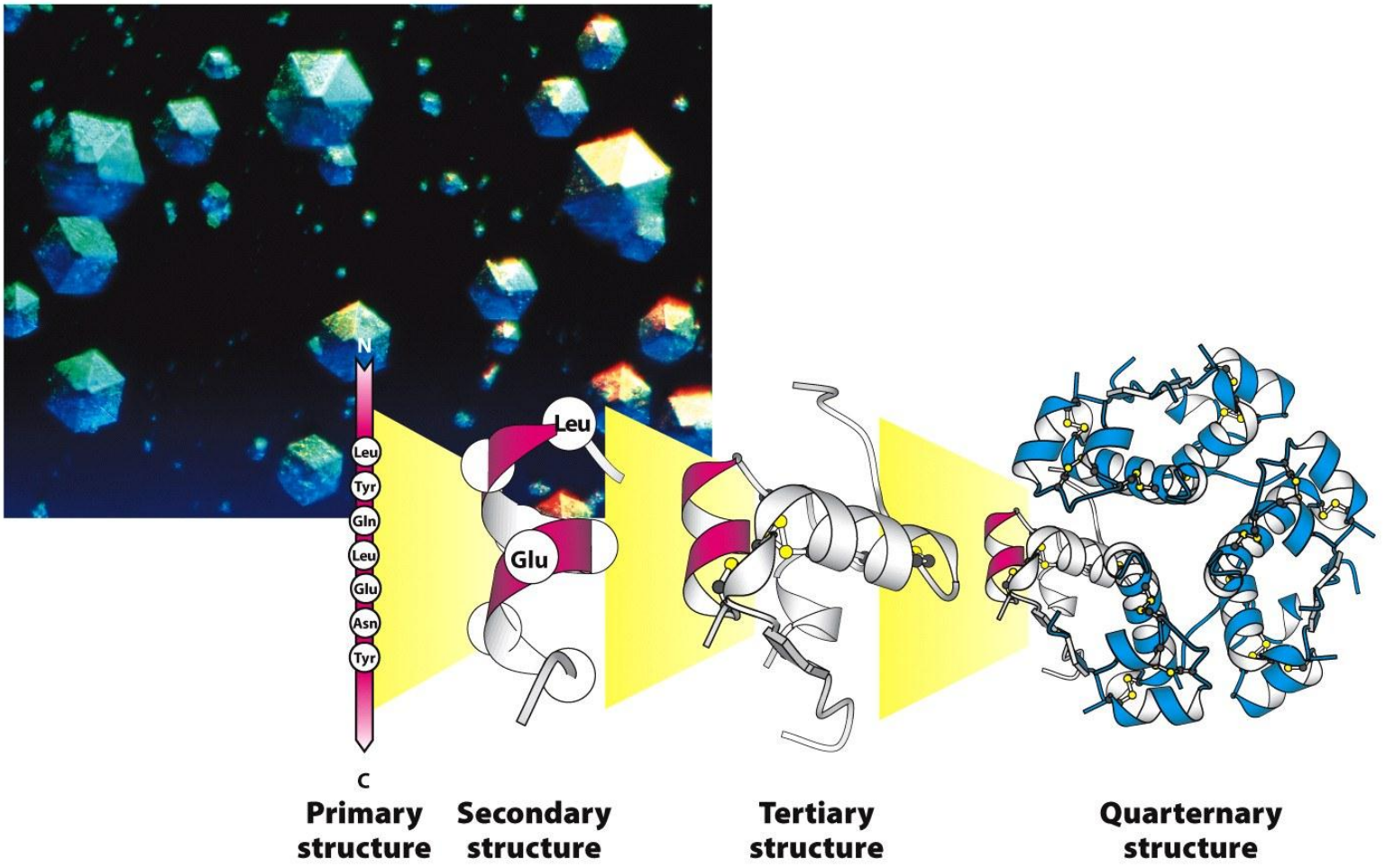
Protein Structure



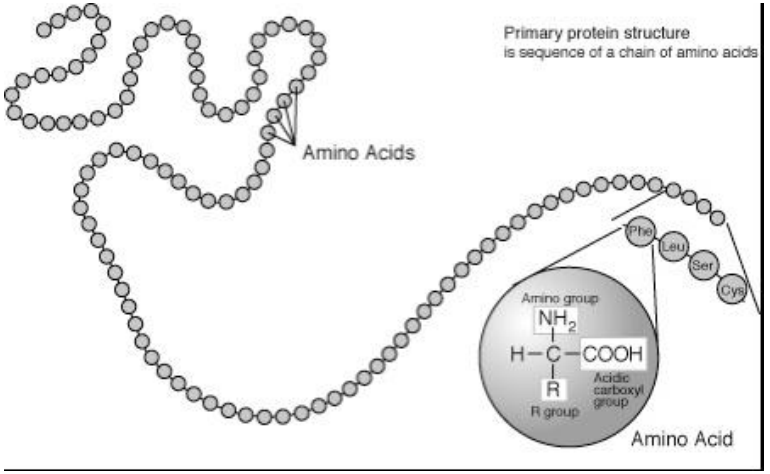
Chapter 2 Opener
***Biochemistry*, Seventh Edition**

Protein Structure

1. Proteins are amino acid polymers.

2. The functional groups of amino acids account for the large variety in protein function:

    - Structure
    - Catalysis (enzymes)
    - Regulation: interaction with other proteins and macromolecules (DNA, RNA, carbohydrates)



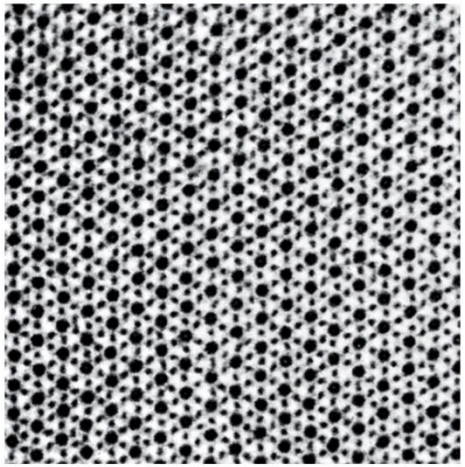


Figure 2.2
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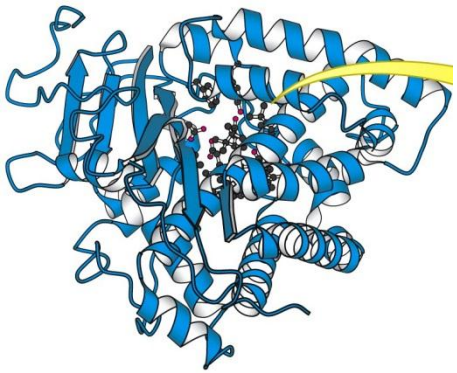

Figure 8.5
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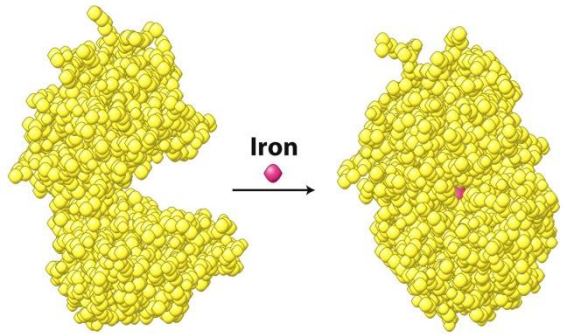

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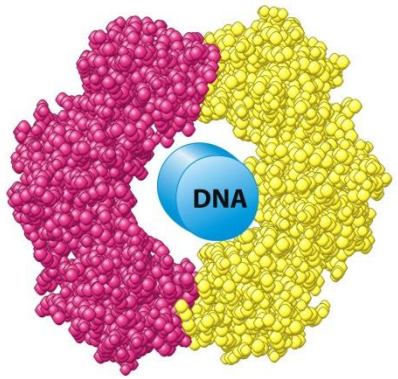

Figure 2.1
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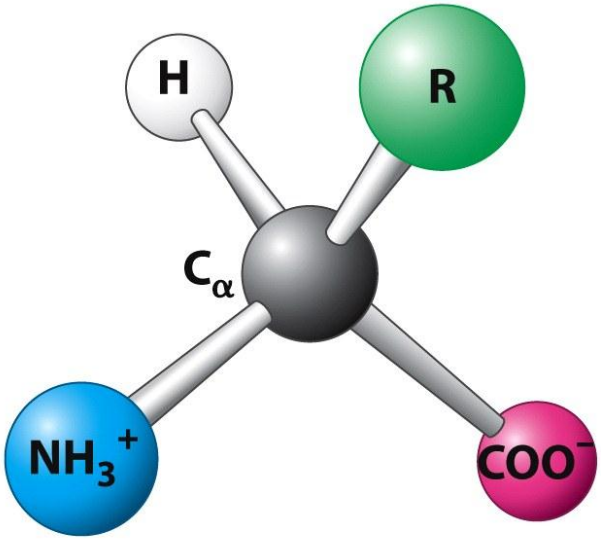
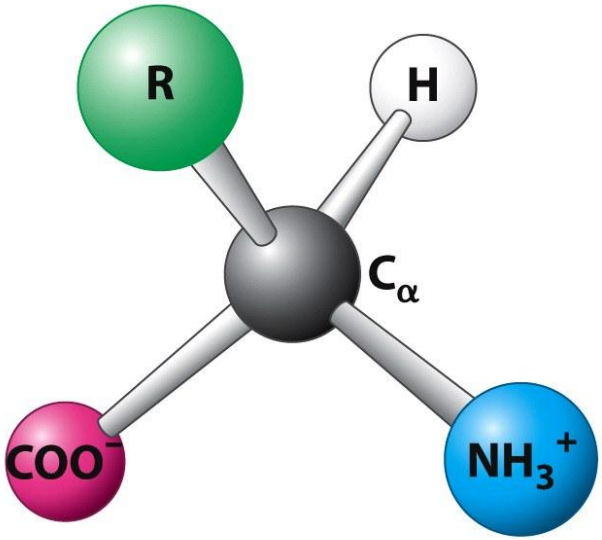
https://sites.google.com/site/mrsebiology97/cell-chemistry-objective-1d-1e

Amino Acids



L isomer



D isomer

Figure 2.4
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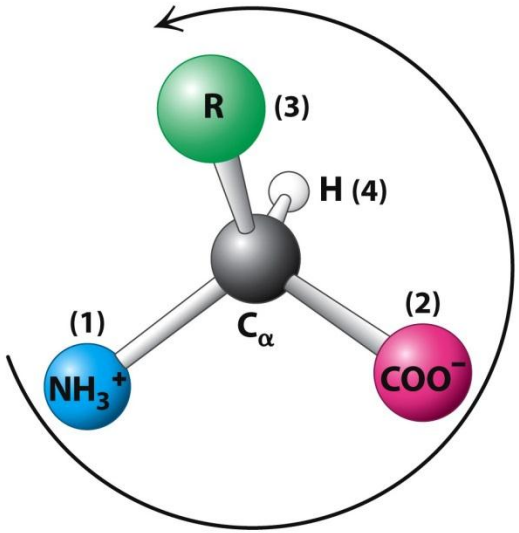

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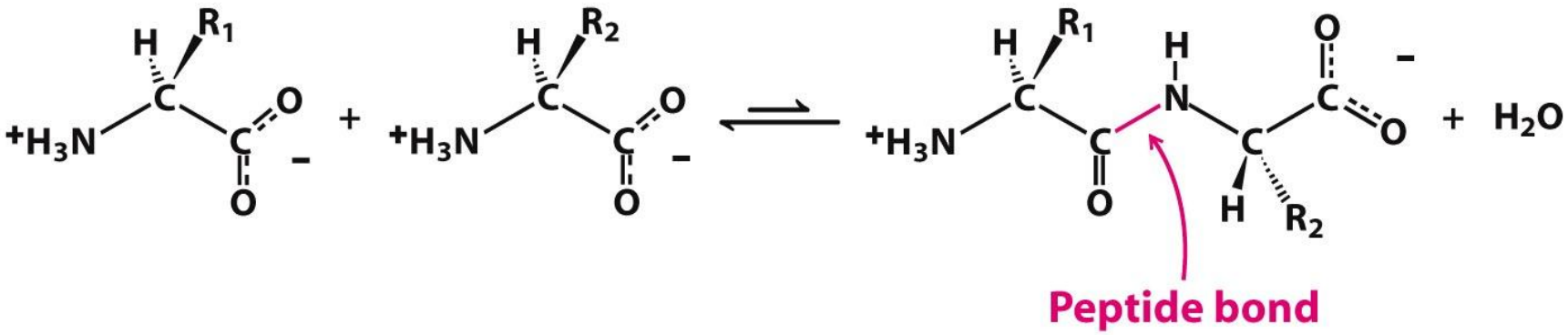
Peptide Bonds



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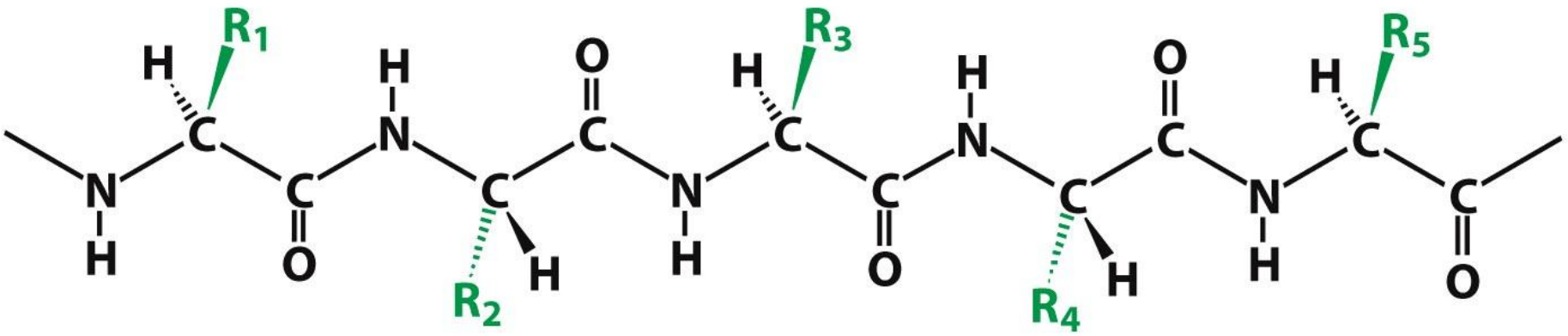
The Polypeptide Chain



Primary structure: the amino acid polymer

The Polypeptide Chain

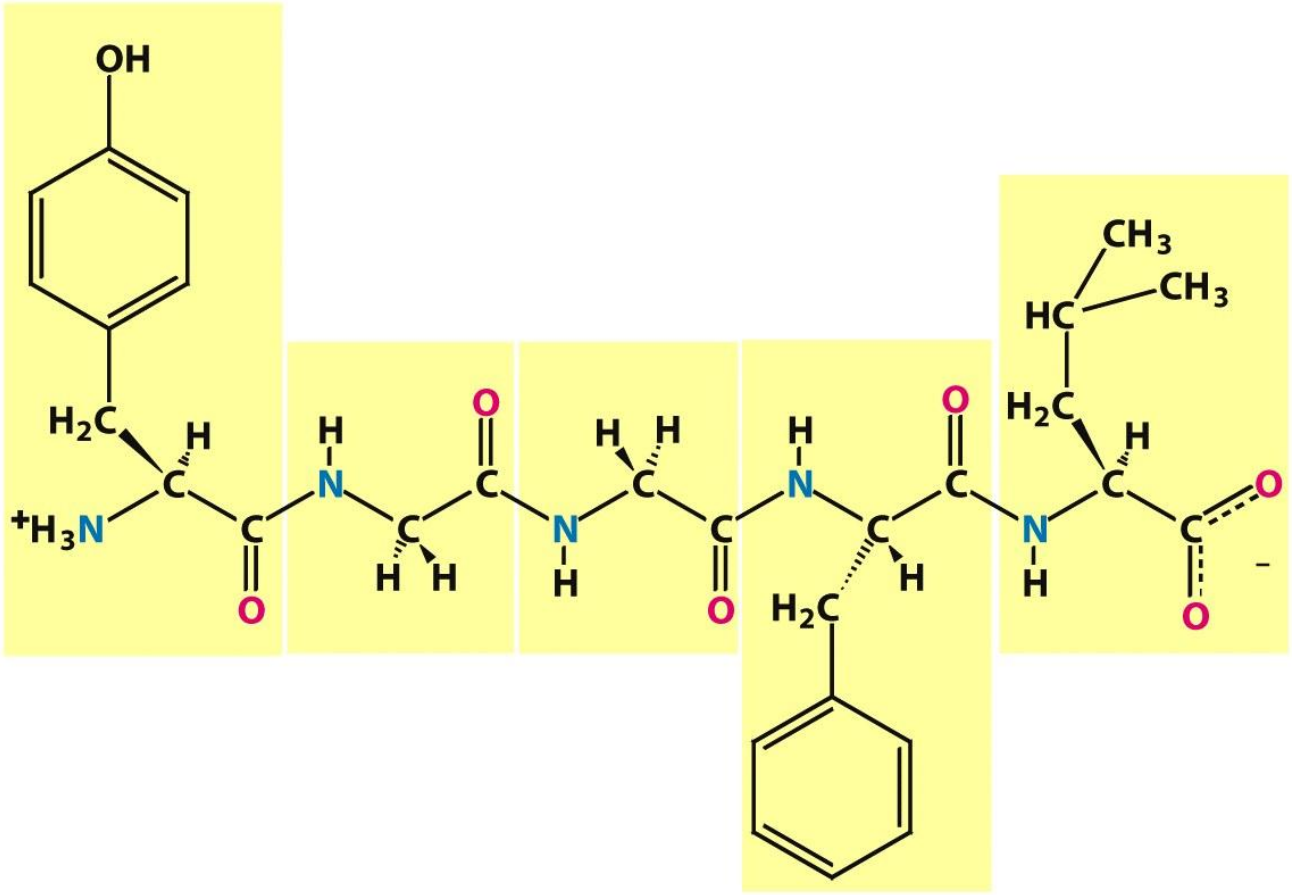


Figure 2.14
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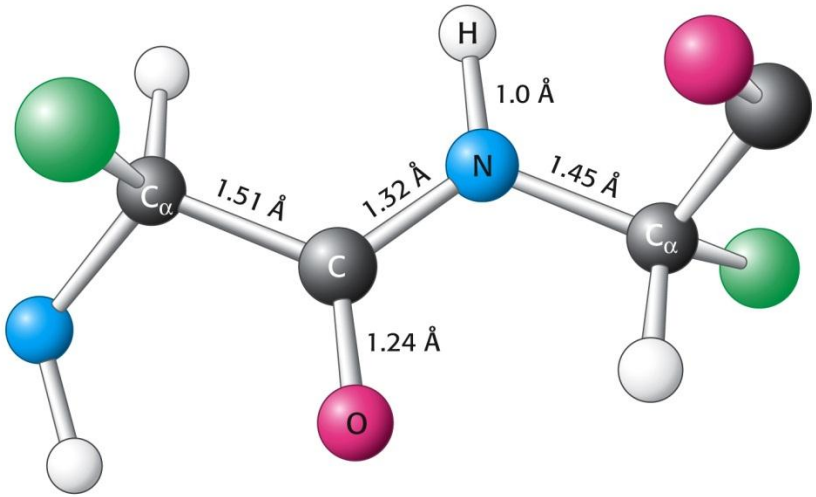
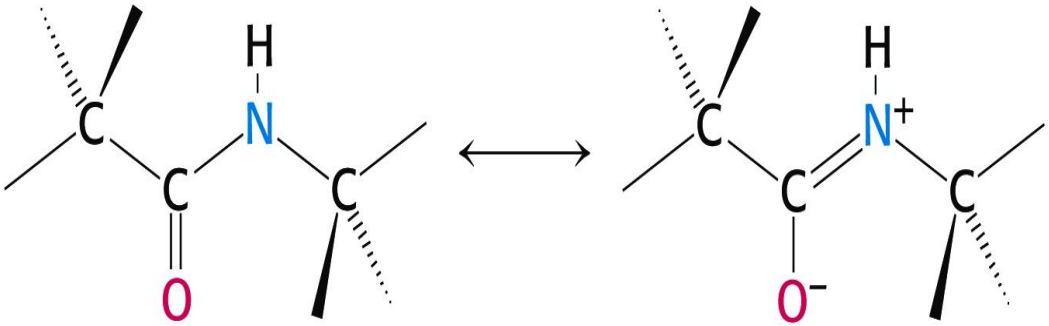
The Peptide Bond

- is usually found in the *trans* conformation
- has partial (40%) double bond character
- N partially positive; O partially negative
- has a length of about 0.133 nm - shorter than a typical single bond but longer than a double bond
- Due to the double-bond character of the peptide bond, the six atoms of the peptide bond group define a plane – the amide plane



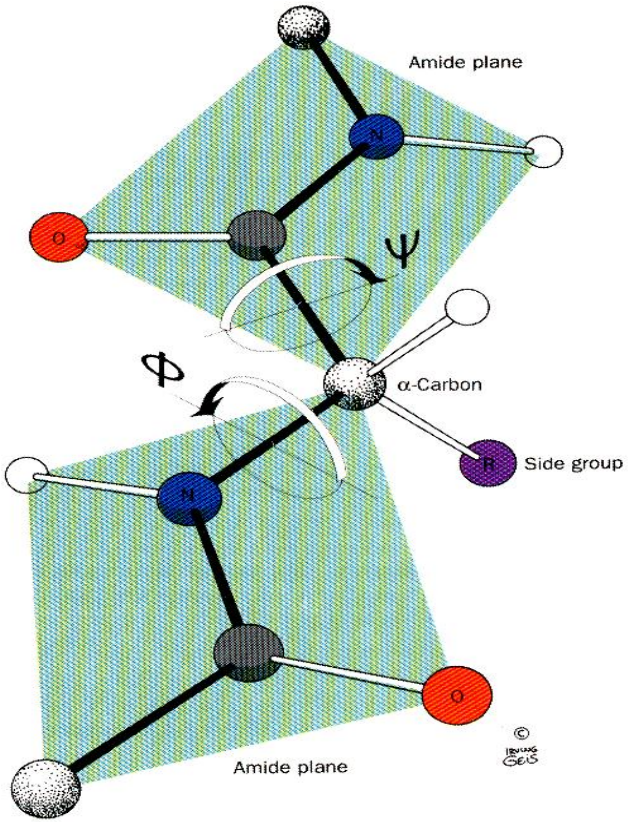
Due to the double bond character, the six atoms of the peptide bond group are always planar!



Peptide bond resonance structures

The six atoms of the peptide bond group define a plane – the amide plane

The Cα-N and Cα-C sigma bonds are single bonds, can rotate



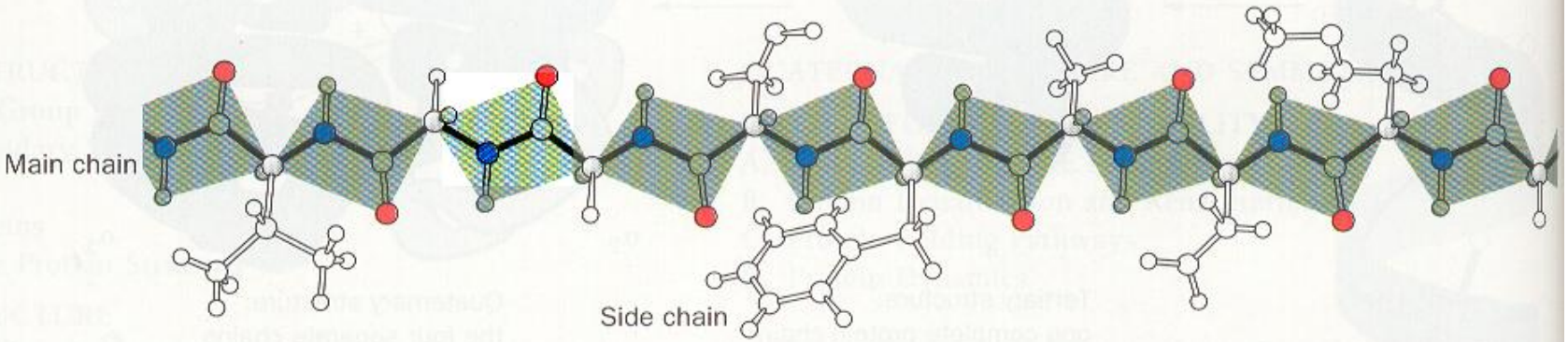


Figure 6-3. **Extended conformation of a polypeptide.** The backbone is shown as a series of planar peptide groups. [Figure copyrighted © by Irving Geis.]

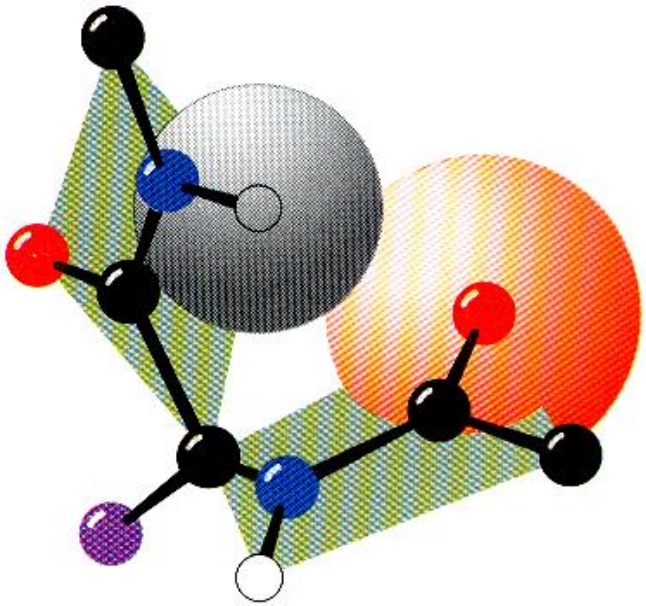


Figure 6-5. **Steric interference between adjacent peptide groups.** Rotation can result in a conformation in which the amide hydrogen of one residue and the carbonyl oxygen of the next are closer than their van der Waals distance. [Figure copyrighted © by Irving Geis.]

- **All amino acids side chains are in a trans configuration to minimize steric hindrance**

- **The Cα -N (φ, phi) and Cα –C (Ψ, psi) bonds can rotate. But only certain conformations are sterically stable**

The Polypeptide Chain

Steric hindrance between the chemical groups attached to the α-carbon strongly favors the trans conformation.

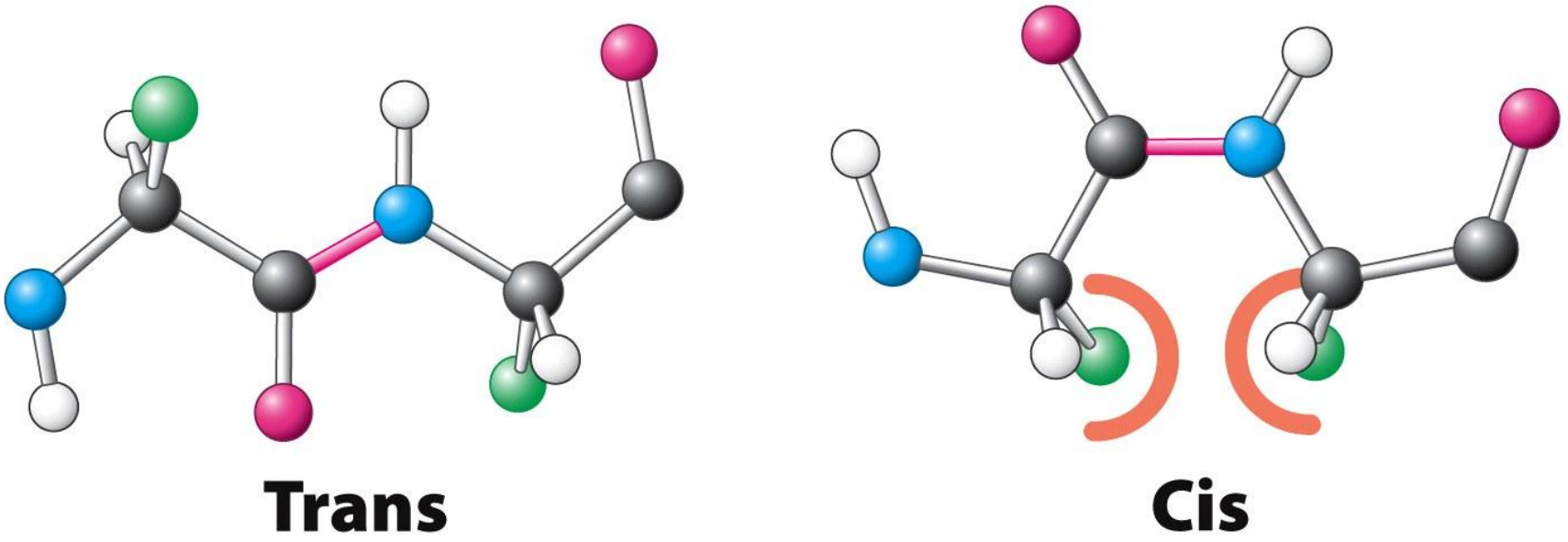


Figure 2.20
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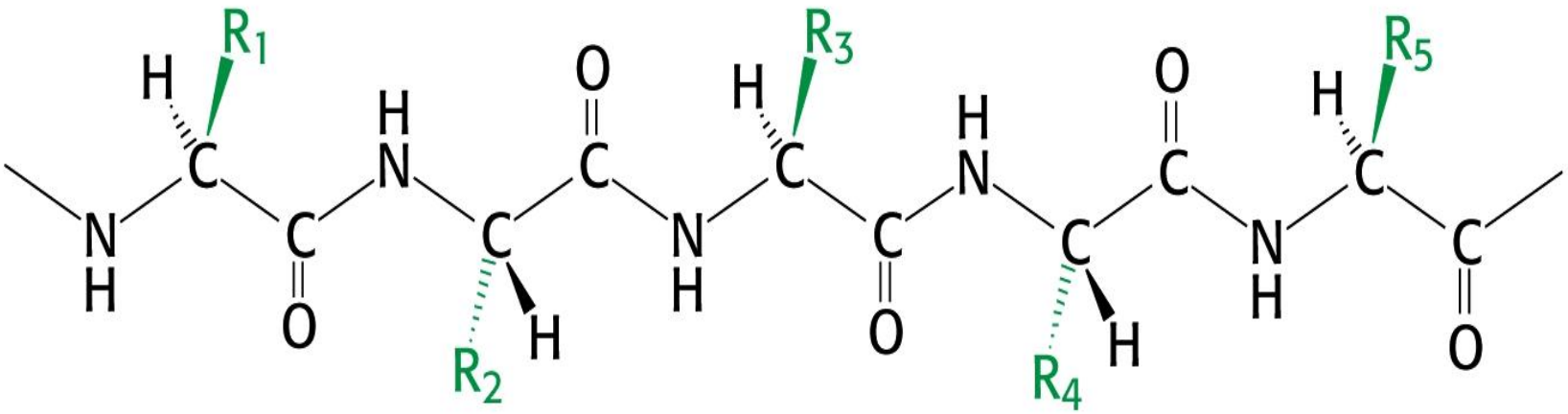
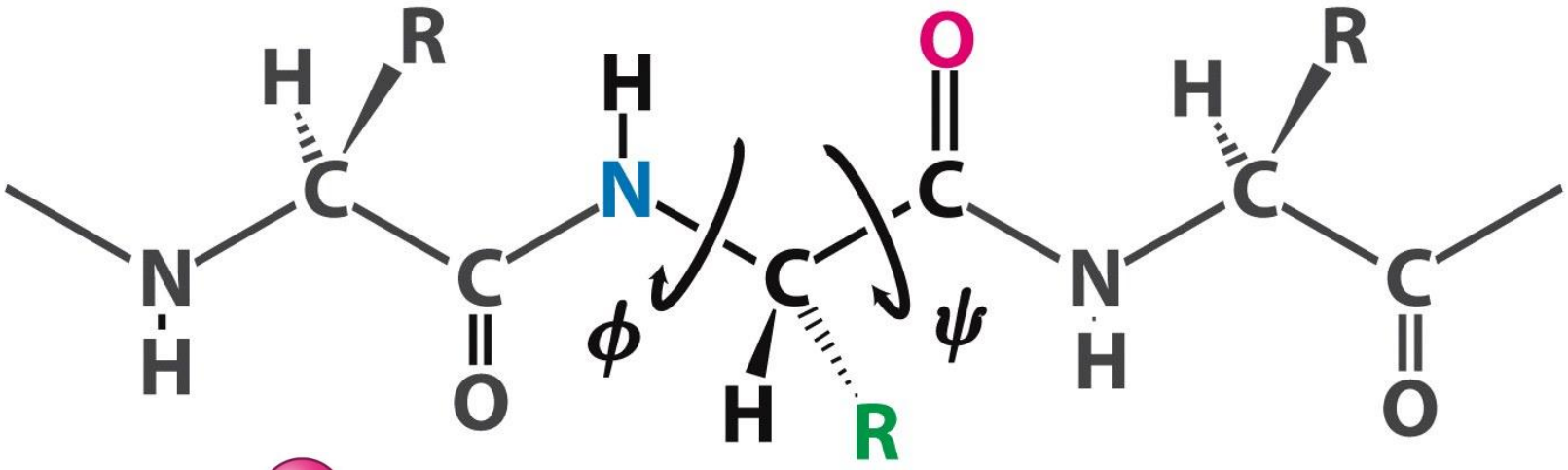
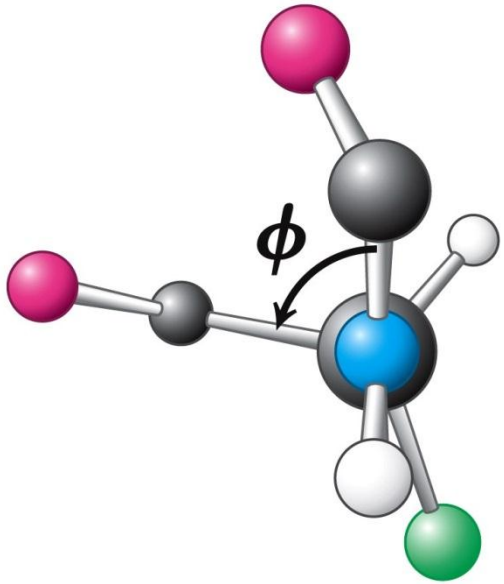
A polypeptide consists of a regularly repeating main chain and variable side chains

- The repeat pattern (–N-C_α-C_o-), called the main chain or backbone, starting from the N-terminal amino acid and ended at c-terminus (from N → C)
- is usually found in the *trans* conformation, which means R_1 and R_2, R_2 and R_3, R_3 and R_4, R_4 and R_5 are on different side along the peptide backbone



Rotation Around Bonds





$\phi = -80°$

Figure 2.22b
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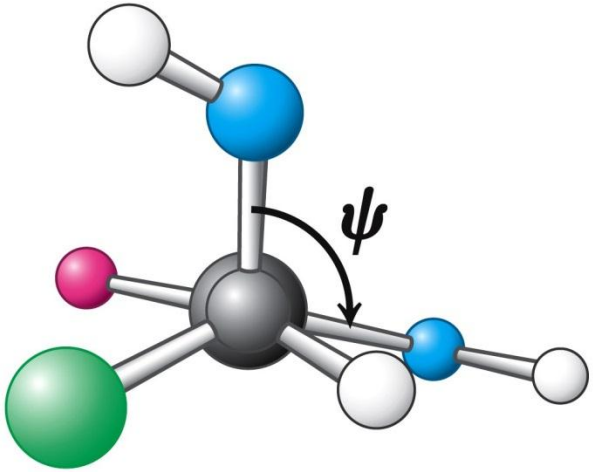

$\psi = +85°$

Figure 2.22c
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The Ramachandran Plot

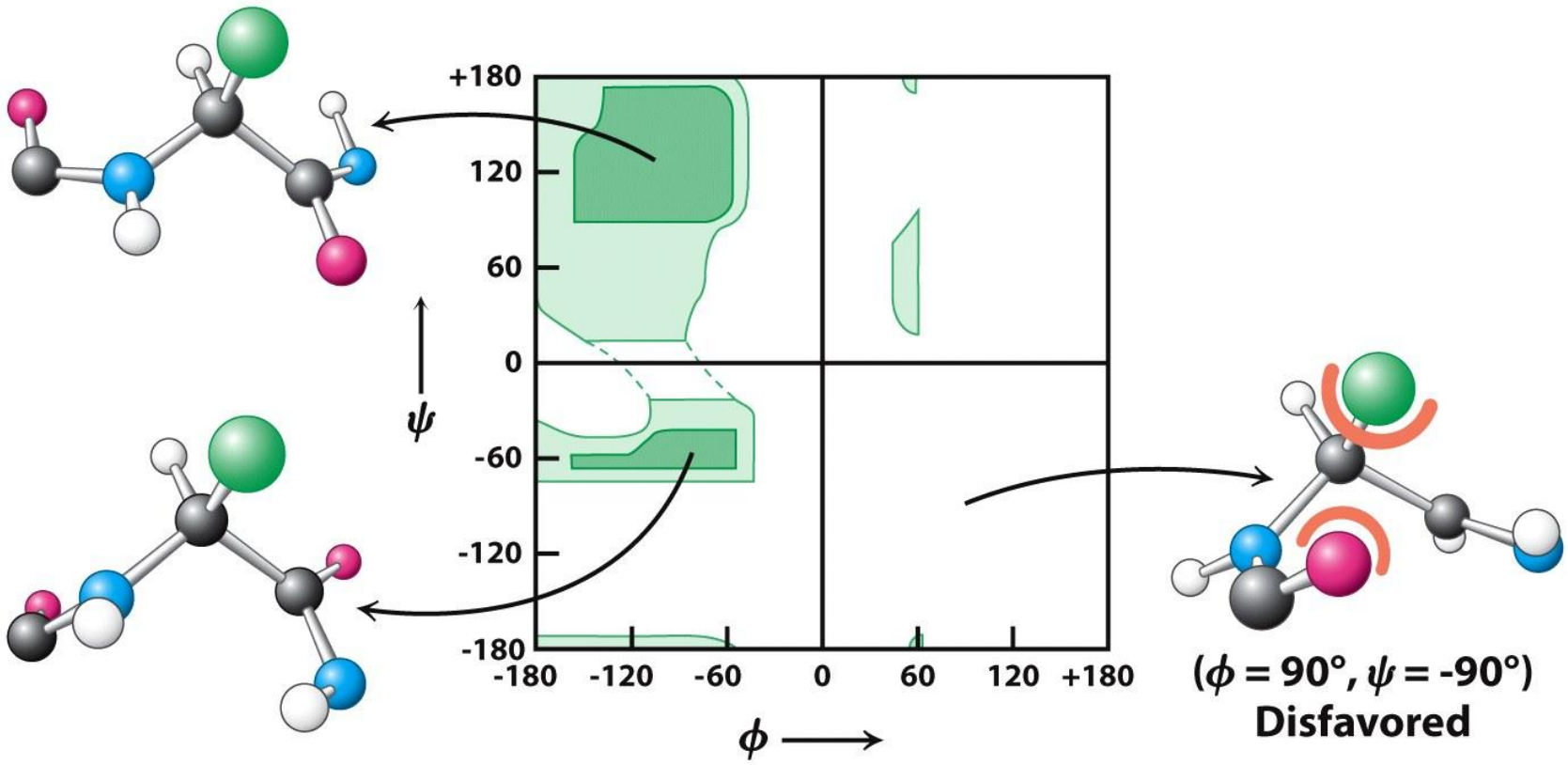

Figure 2.23
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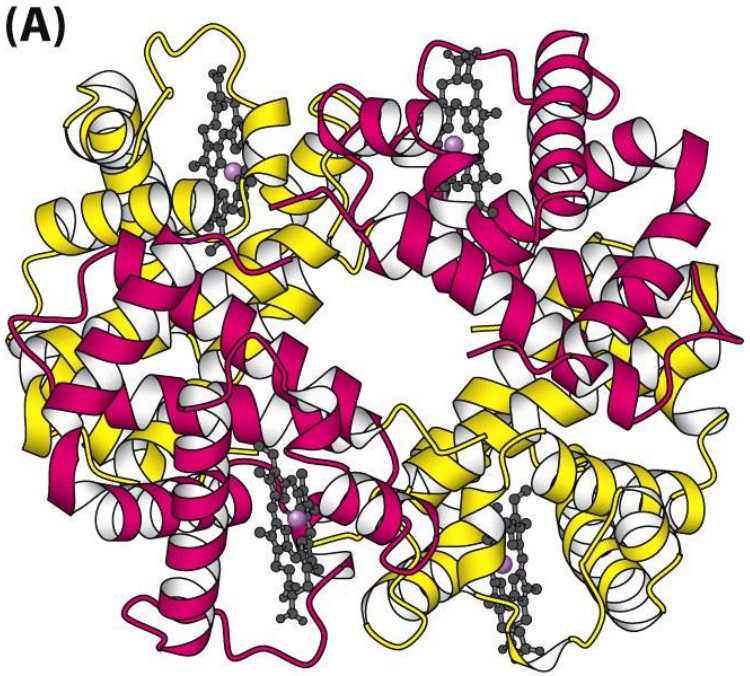
Proteins

One or more polypeptide chains

- One polypeptide chain - a monomeric protein.
- More than one - multimeric protein
  - Homomultimer: one kind of chain
  - Heteromultimer: two or more different chains

Hemoglobin, for example, is a heterotetramer. It has two alpha chains and two beta chains.



Proteins - Large and Small

TABLE 4.2 Size of Protein Molecules*

Protein	M_r	Number of Residues per Chain	Subunit Organization
Insulin (bovine)	5,733	21 (A) 30 (B)	$\alpha\beta$
Cytochrome *c* (equine)	12,500	104	α_1
Ribonuclease A (bovine pancreas)	12,640	124	α_1
Lysozyme (egg white)	13,930	129	α_1
Myoglobin (horse)	16,980	153	α_1
Chymotrypsin (bovine pancreas)	22,600	13 (α) 132 (β) 97 (γ)	$\alpha\beta\gamma$
Hemoglobin (human)	64,500	141 (α) 146 (β)	$\alpha_2\beta_2$
Serum albumin (human)	68,500	550	α_1
Hexokinase (yeast)	96,000	200	α_4
γ-Globulin (horse)	149,900	214 (α) 446 (β)	$\alpha_2\beta_2$
Glutamate dehydrogenase (liver)	332,694	500	α_6
Myosin (rabbit)	470,000	2,000 (heavy, *h*) 190 (α) 149 (α') 160 (β)	$h_2\alpha_1\alpha'_1\beta_2$
Ribulose bisphosphate carboxylase (spinach)	560,000	475 (α) 123 (β)	$\alpha_8\beta_8$
Glutamine synthetase *(E. coli)*	600,000	468	α_{12}

Biological Functions of Proteins

Proteins are the agents of biological function

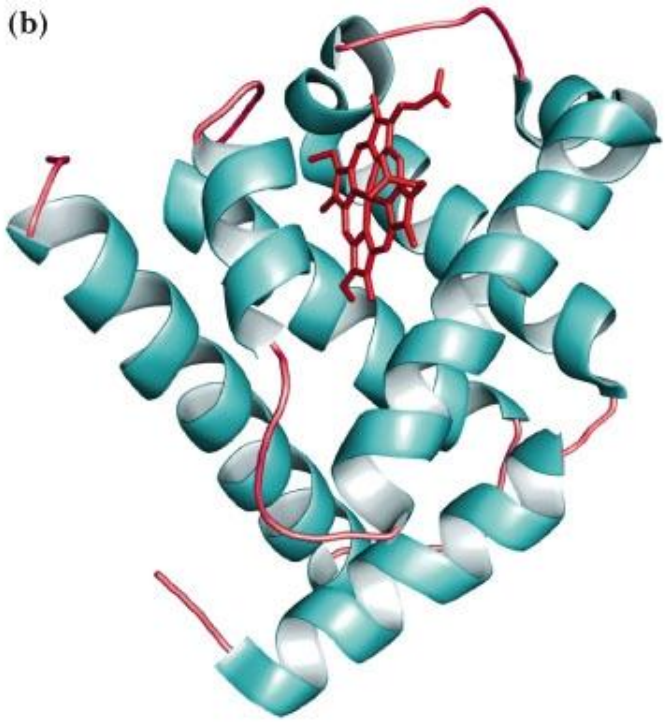
- **Enzymes - Ribonuclease**
- **Regulatory proteins - Insulin**
- **Transport proteins - Hemoglobin**
- **Structural proteins - Collagen**
- **Contractile proteins - Actin, Myosin**
- **Exotic proteins - Antifreeze proteins in fish**

Protein Structure

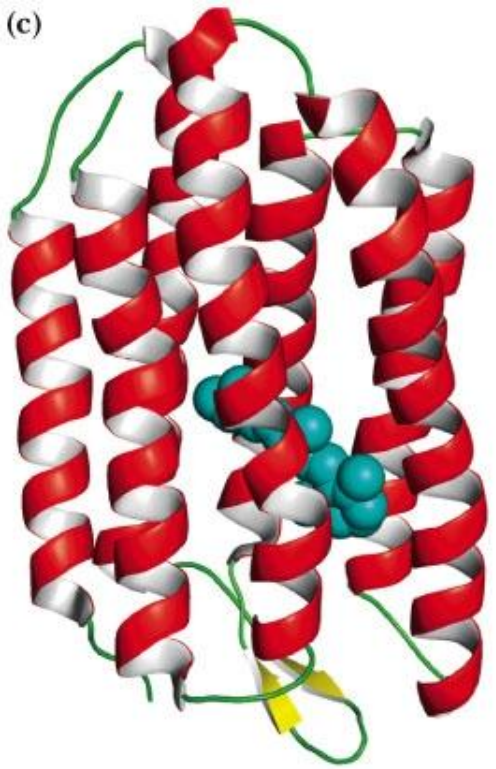
- **Proteins are classed according to shape and solubility**
- **Shape - globular or fibrous**
- **The four levels of protein structure are:**
  - **Primary (1°) – amino acid sequence**
  - **Secondary (2°) - local structures - H-bonds**
  - **Tertiary (3°) - overall 3-dimensional shape**
  - **Quaternary (4°) - subunit organization**

Protein Structure

Collagen,
a fibrous protein



Myoglobin, a globular protein

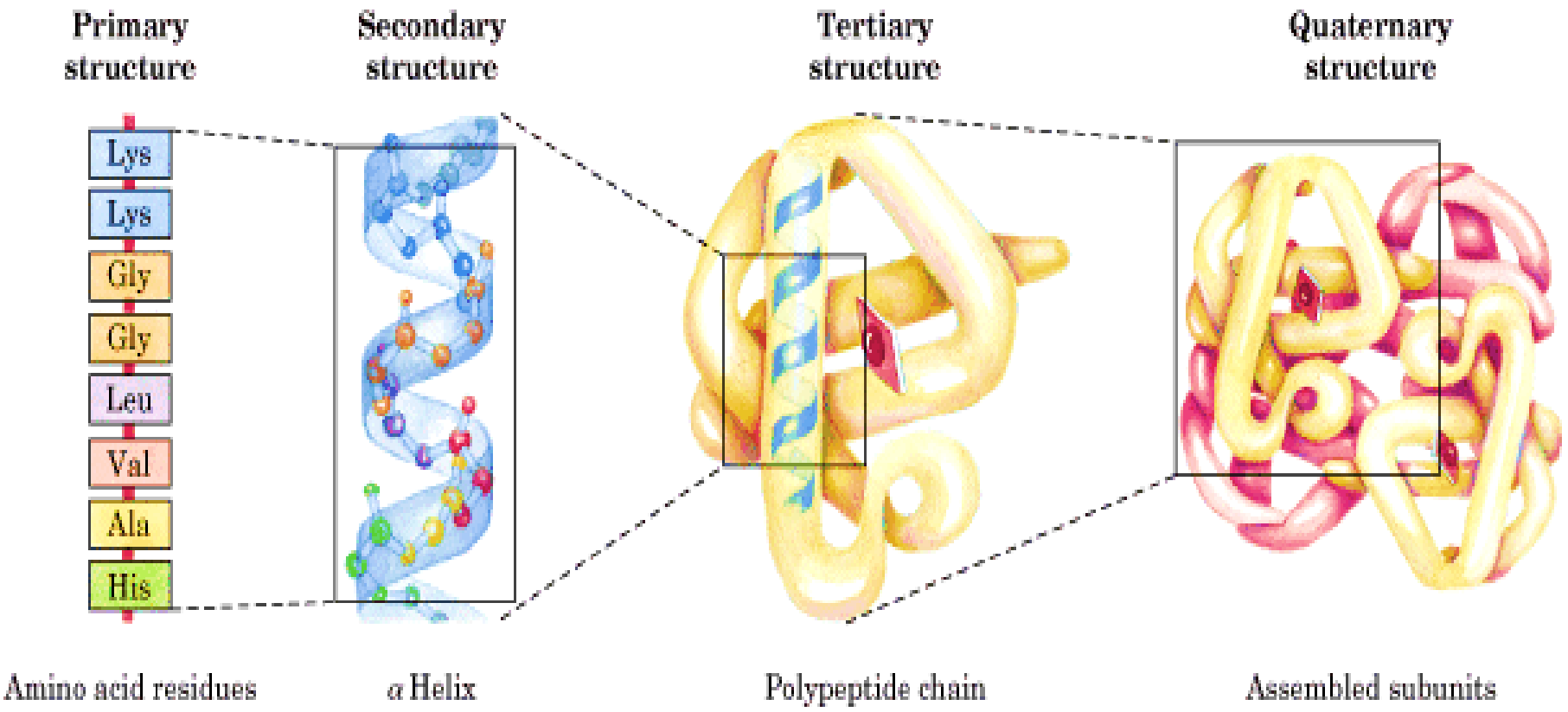


Bacteriorhodopsin, a membrane protein

(a) Fibrous proteins tend to have relatively simple, regular linear structures. They often serve structural roles in cells. Typically, they are insoluble in water or in dilute salt solutions. (b) Myoglobin is a globular protein. (c) Membrane proteins fold so that hydrophobic amino acid side chains are exposed in their membrane-associated regions.

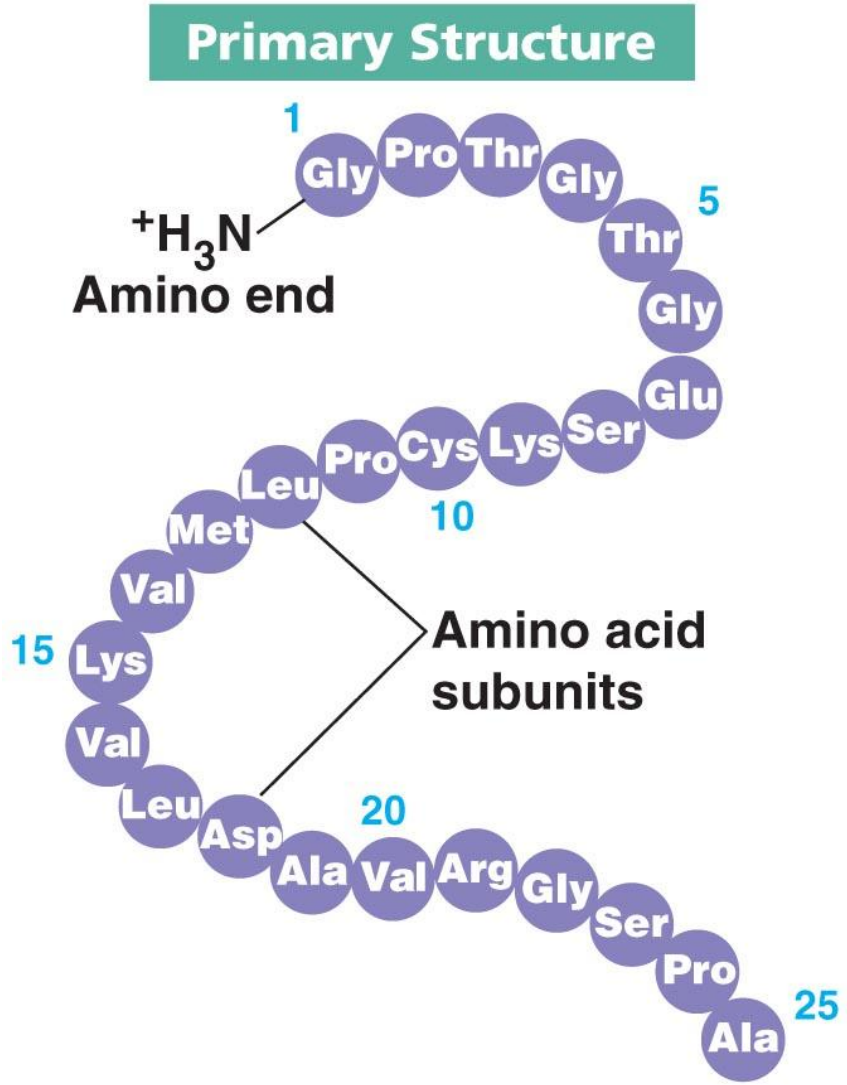
Biochemistry by Garret and Grisham, 5th ed.

Levels of Protein Structure



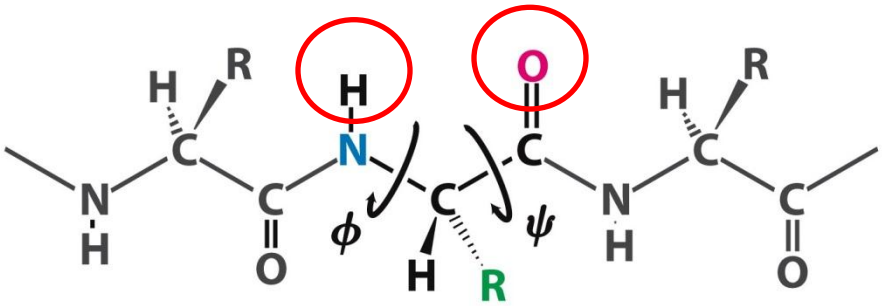
Primary Structure

- The amino acid sequence of a protein.
- Is a unique characteristic of every protein.
- Is encoded by the nucleotide sequence of DNA.
- Is thus a form of genetic information.
- Is read from the amino terminus to the carboxyl terminus.

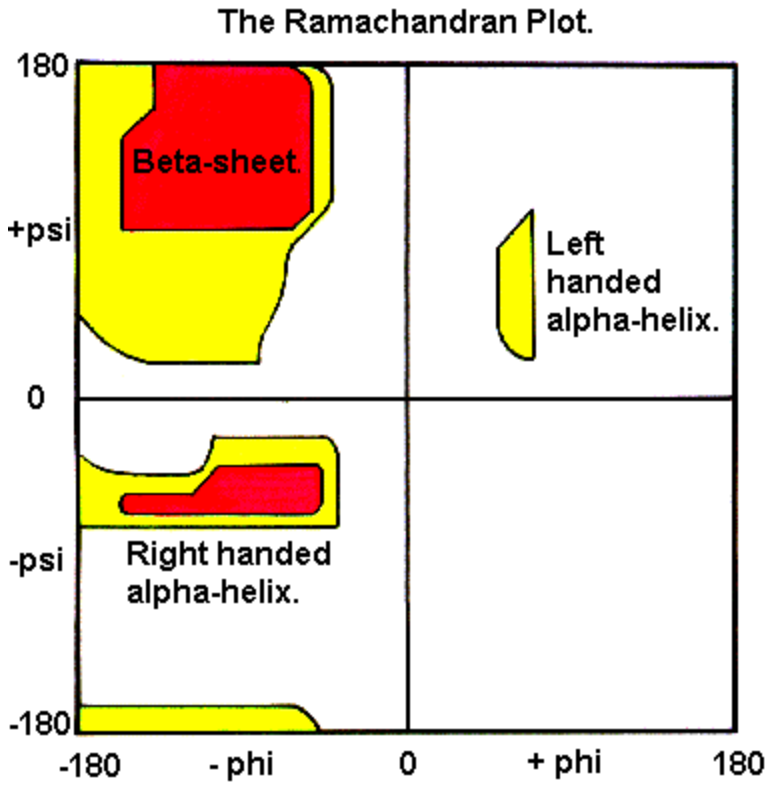


The Ramachandran Plot

- **Restrictions of the ϕ- and ψ-angles result in a limited set of secondary structures.**
  - **Alpha-helices**
  - **Beta-sheets**
  - **Turns**
  - **Loops**
- **Secondary structures are formed by hydrogen bonds between the peptide N—H and C=O groups.**



- **Near one another in the linear sequence**



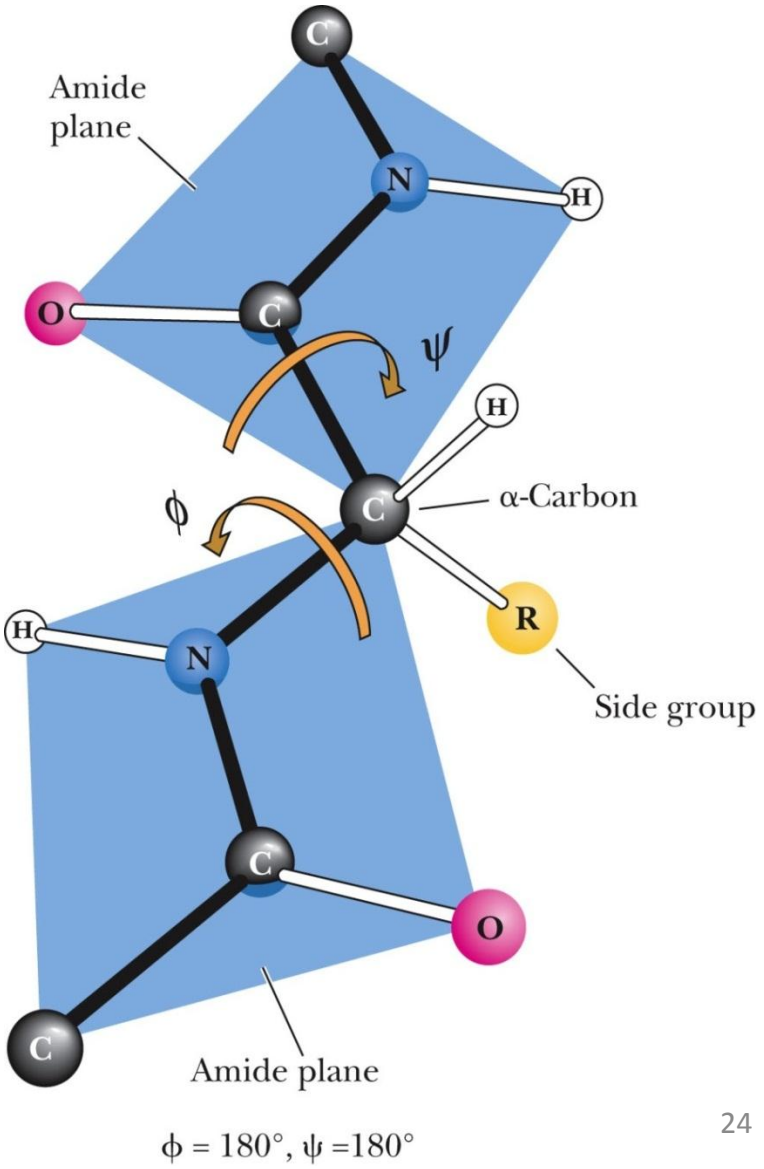
http://www.cryst.bbk.ac.uk/PPS95/course/3_geometry/rama.html

What Are the Elements of Secondary Structure in Proteins, and How Are They Formed?

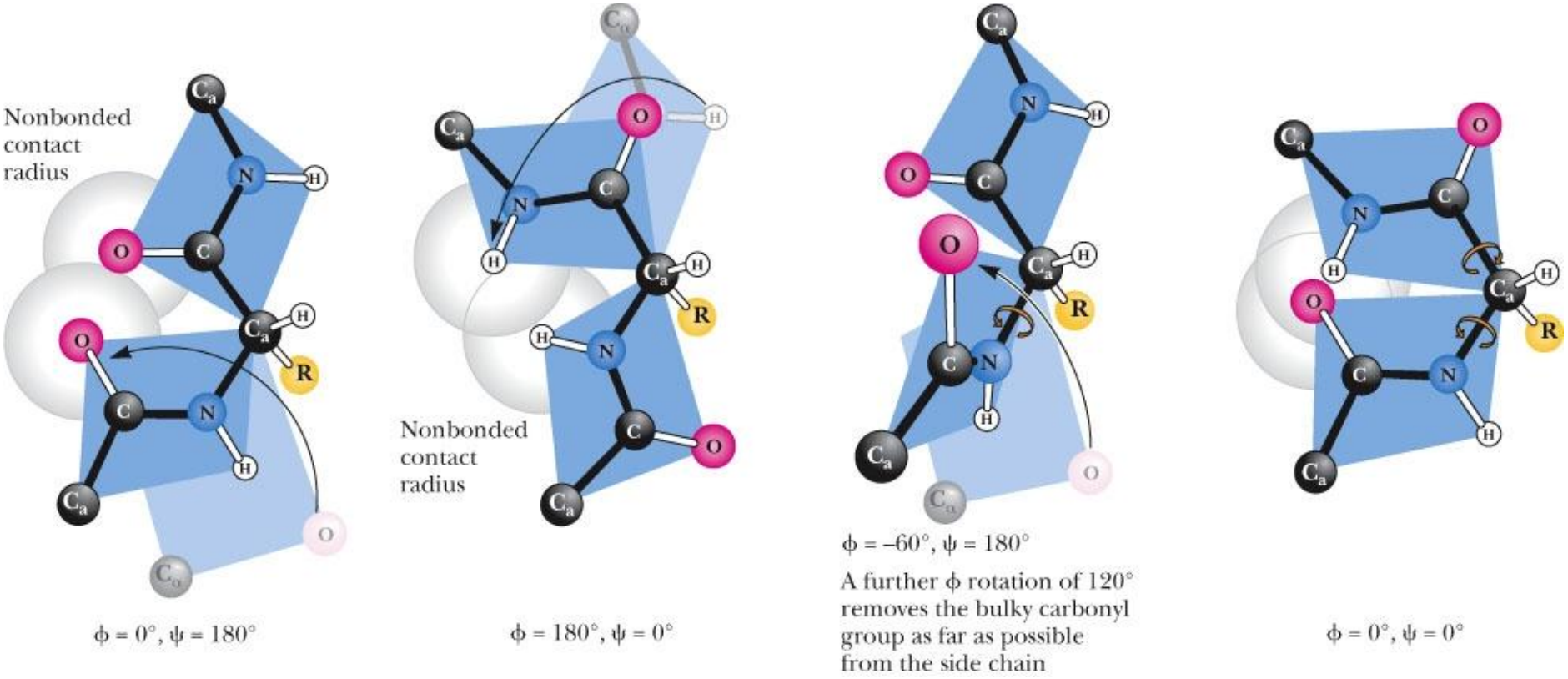
- The atoms of the peptide bond lie in a plane.
- All protein structure is based on the amide plane.
- Peptide bonds are rigid with no rotational freedom.
- Rotation can occur about either of the bonds linking the alpha carbon to the other atoms of the peptide backbone.

What Are the Elements of Secondary Structure in Proteins, and How Are They Formed?

The rotation parameters are φ (phi) and ψ (psi). The conformations shown corresponds to φ= 180˚ and ψ= 180˚ .



Some Values of φ and ψ Are Not Allowed



$\phi = 0°, \psi = 180°$

$\phi = 180°, \psi = 0°$

$\phi = -60°, \psi = 180°$

A further ϕ rotation of 120° removes the bulky carbonyl group as far as possible from the side chain

$\phi = 0°, \psi = 0°$

Many of the possible conformations about an α-carbon between two peptide planes are forbidden because of steric crowding.

Steric Constraints on φ & ψ

Unfavorable orbital overlap/steric crowding precludes some combinations of φ and ψ.

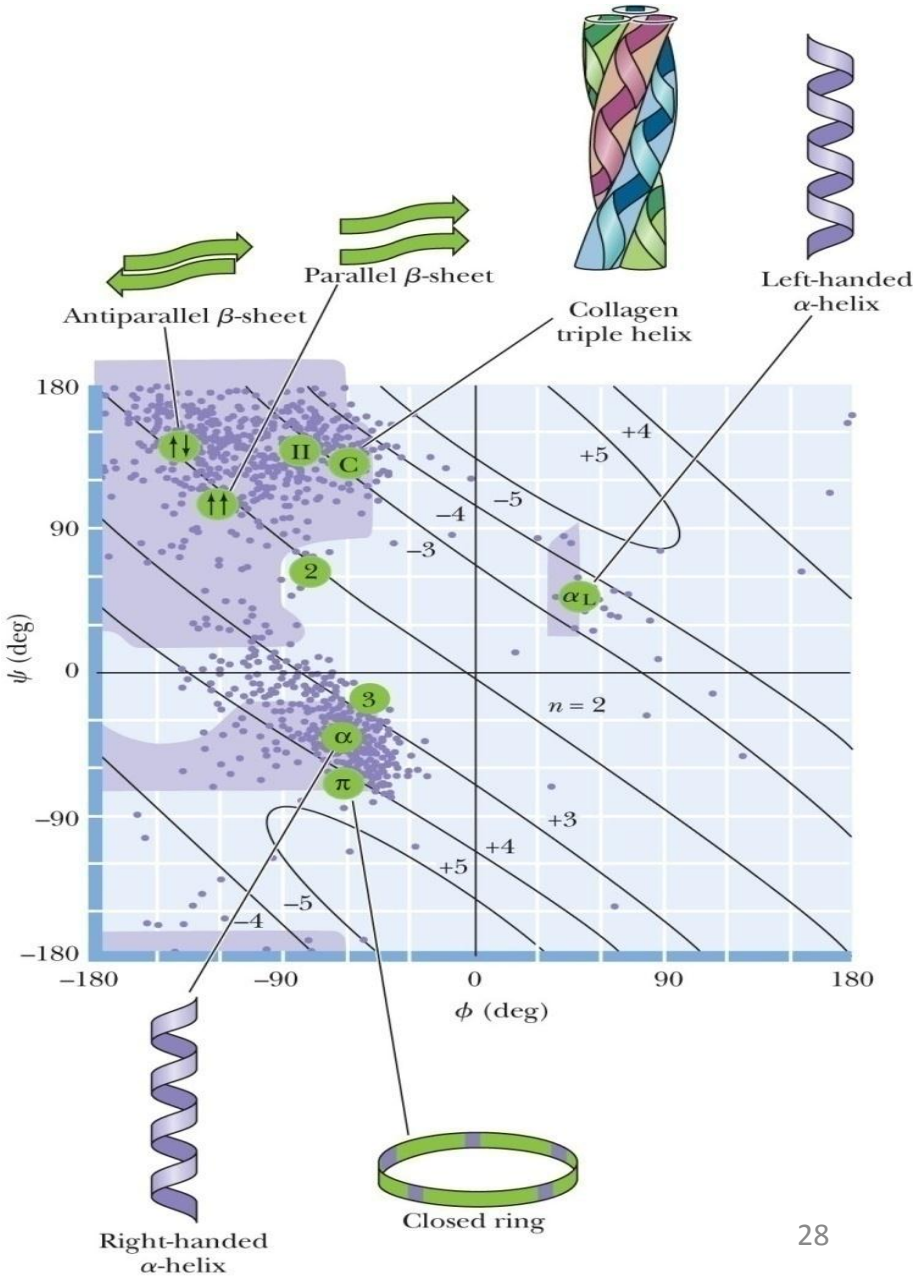
ϕ = 0°, ψ = 180° is unfavorable.
ϕ = 180°, ψ = 0° is unfavorable.
ϕ = 0°, ψ = 0° is unfavorable.

Steric Constraints on φ & ψ

- G. N. Ramachandran was the first to demonstrate the convenience of plotting phi, psi combinations from known protein structures
- The sterically favorable combinations are the basis for preferred secondary structures

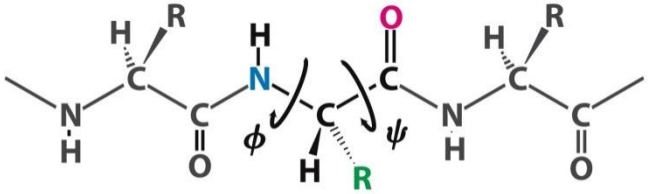
Steric Constraints on φ & ψ

Ramachandran diagram showing the sterically reasonable values of the angles ϕ & ψ. The shaded regions indicate favorable values of these angles. Dots in purple indicate actual angles measured for 1000 residues (excluding glycine, for which a wider range of angles is permitted) in eight proteins.



The Alpha Helix

- **Linus Pauling and Robert Corey explored which conformations of peptides are sterically allowed.**



- **Proposed the structure of the α helix:**
  - **Rodlike structure.**
  - **Tightly coiled backbone forms the inner part of the rod and the.**
  - **Side chains extend outward in a helical array.**

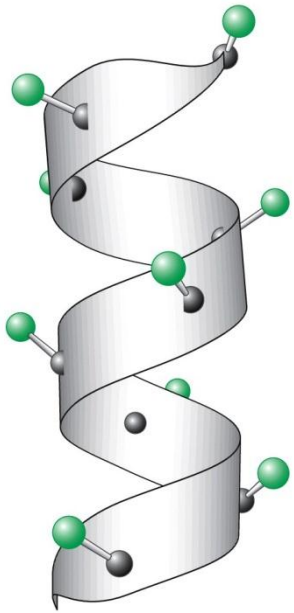


Figure 2.24a
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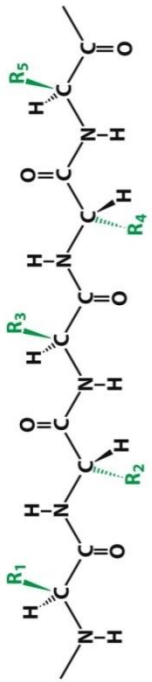

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The Alpha Helix

- **Rodlike structure.**
- **Tightly coiled backbone.**
- **Side chains extend outward.**

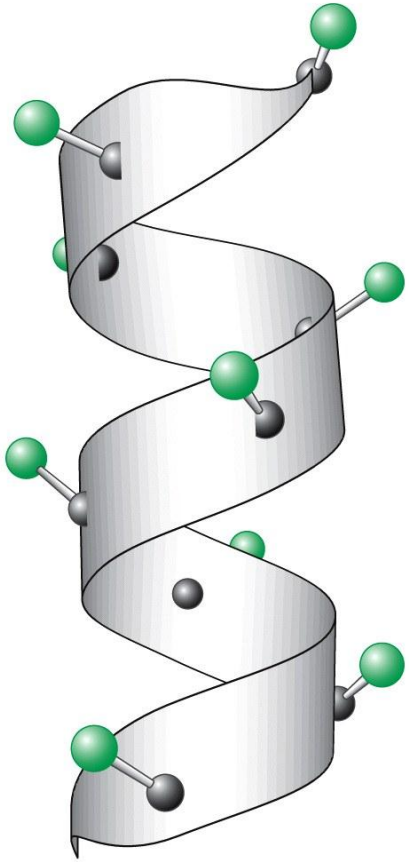

Figure 2.24a
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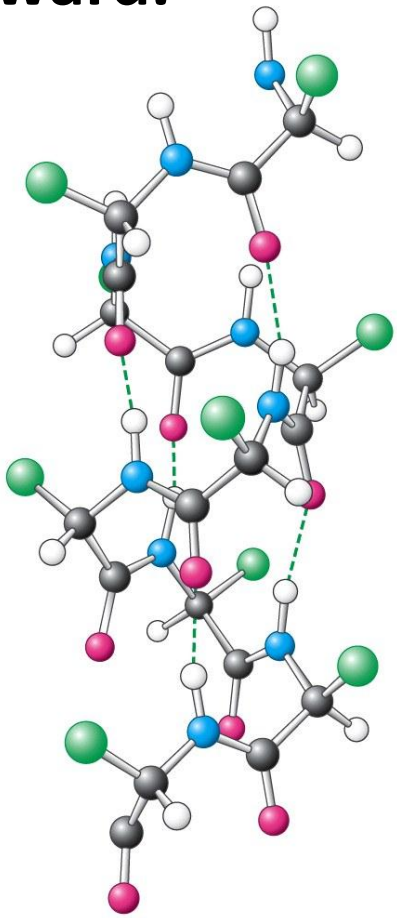

Figure 2.24b
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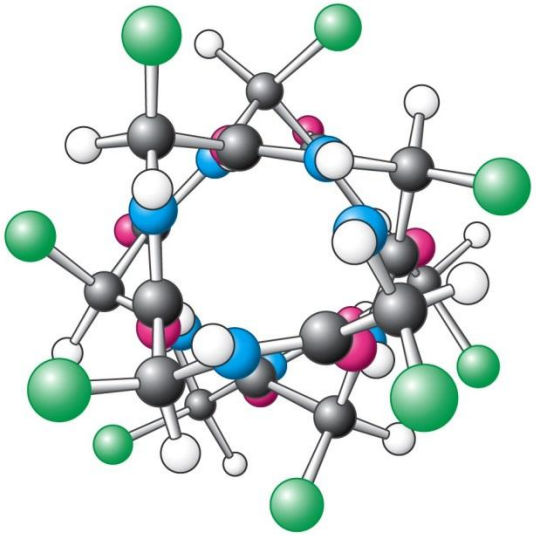


Figure 2.24c
***Biochemistry*, Seventh Edition**

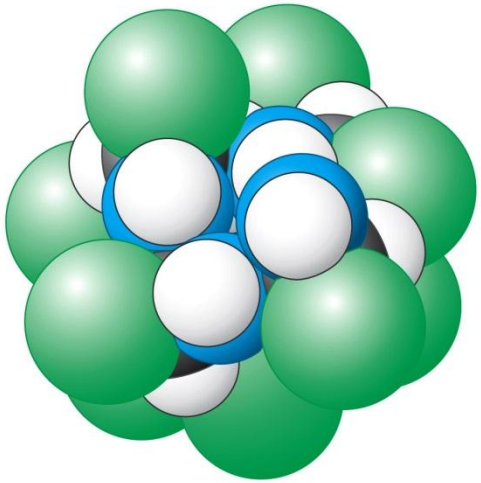


Figure 2.24d
***Biochemistry*, Seventh Edition**

The Alpha Helix

- **The α helix is stabilized by hydrogen bonds between the N-H and C=O groups.**
  - **C=O group of each amino acid forms a hydrogen bond with the N-H group of the amino acid that is situated four residues ahead in the sequence.**

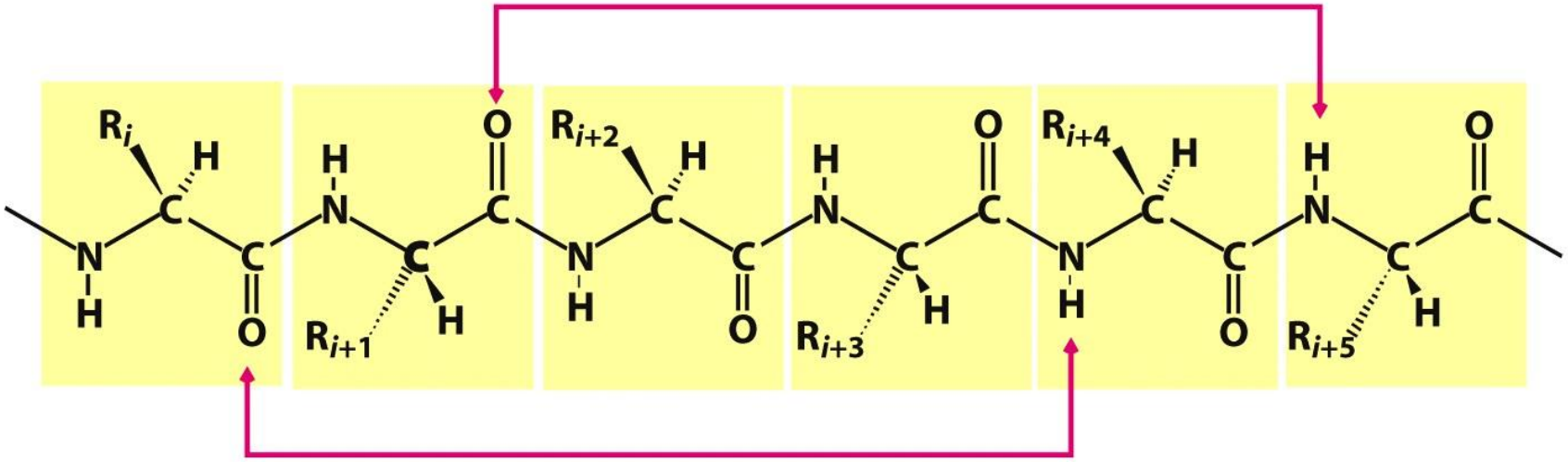


Figure 2.25
***Biochemistry*, Seventh Edition**

The Alpha Helix

- **All the C=O and N-H groups in the amino acids of the α-helix chain are hydrogen bonded.**
  - ***Except the terminal amino acids.***
- **Each amino acid residue is related to the next one by a rise (translation) of 1.5 Ångstrom (Å).**
- **Each amino acid make up a rotation of 100°.**
- **3.6 amino acid residues per turn of the helix.**

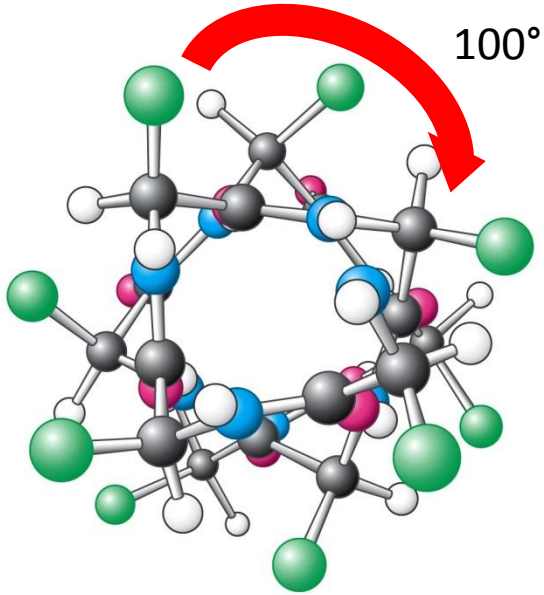
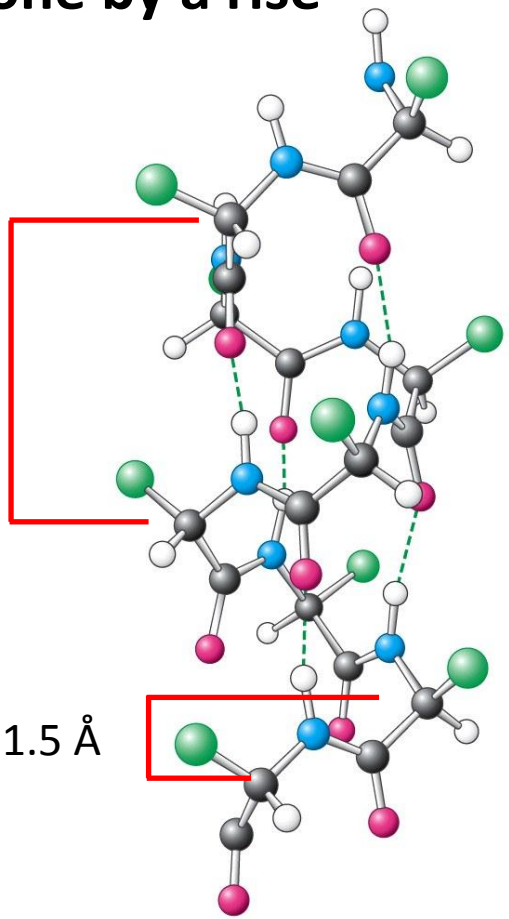
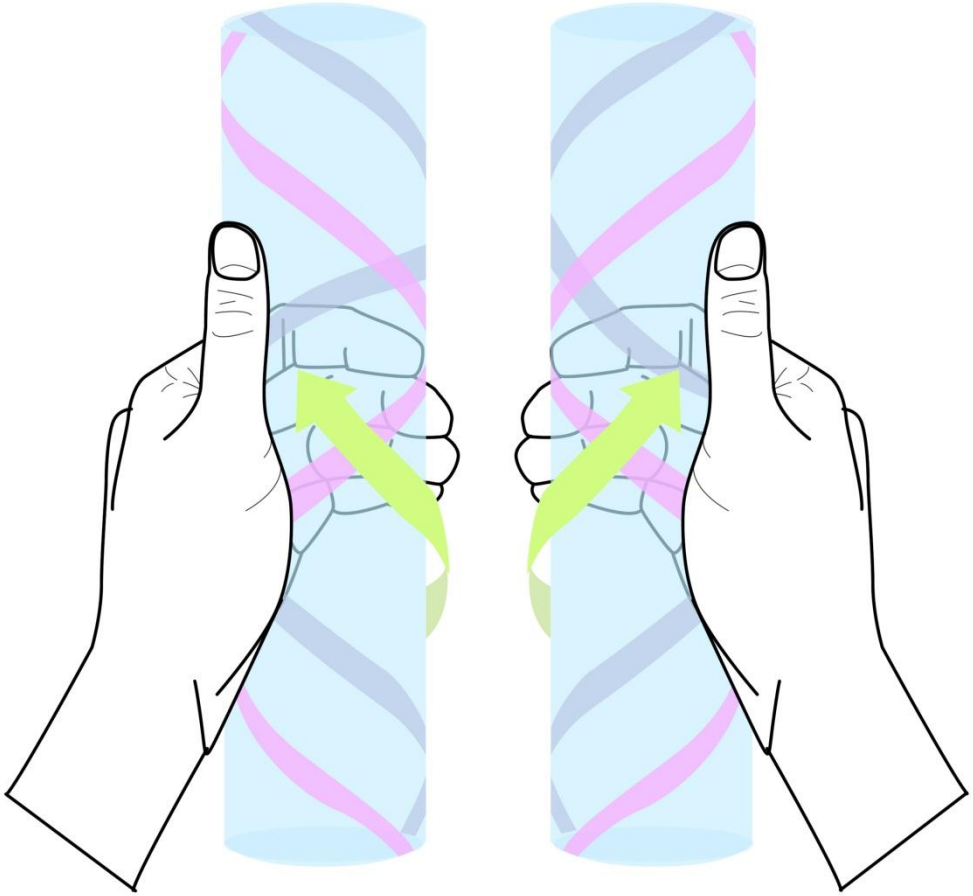


Figure 2.24c



The Alpha Helix

- **Alpha-helixes can be “right-handed” or “left-handed”.**
  - **Left-handed helices are *VERY* rare.**
  - **Basically ALL naturally found α-helices are right-handed.**



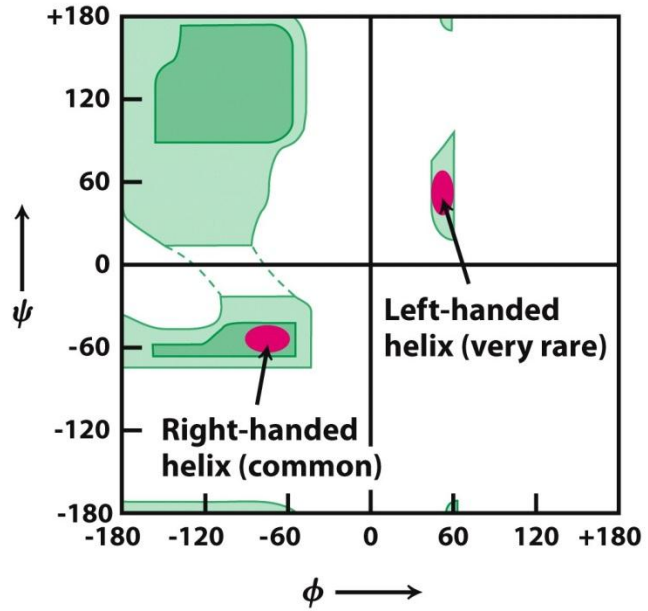


Figure 2.26
Biochemistry, Seventh Edition

The right-handed helix is energetically more favorable, due to more steric hindrance in the left-handed helix.

The Alpha Helix

- **When thinking about the structure of an α-helix, it's important to think about steric hindrance or "clashes".**
- **Are all amino acids equally likely to be found in an α-helix?**
  - **Branched amino acids: valine, threonine, and isoleucine.**
  - **Amino acids that can form hydrogen bonds on their side chains : serine, aspartate, and asparagine.**
  - **Amino acids without an N-H-group: Proline.**
  - **The ring group of proline prevents it from "fitting" into an α-helix.**
- **Do we know any proteins that consists mostly of α-helices?**

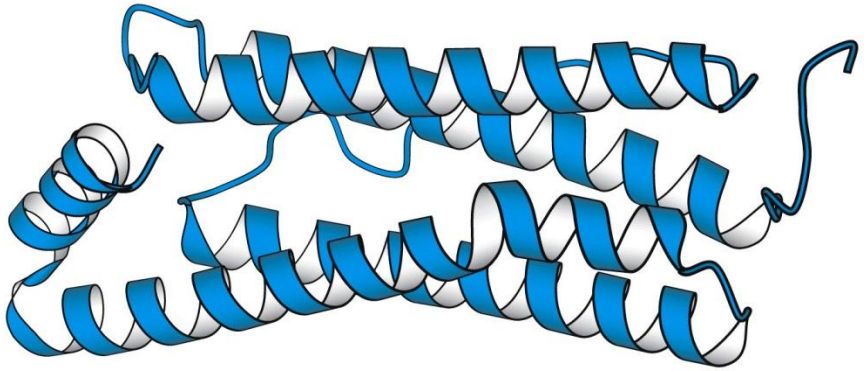
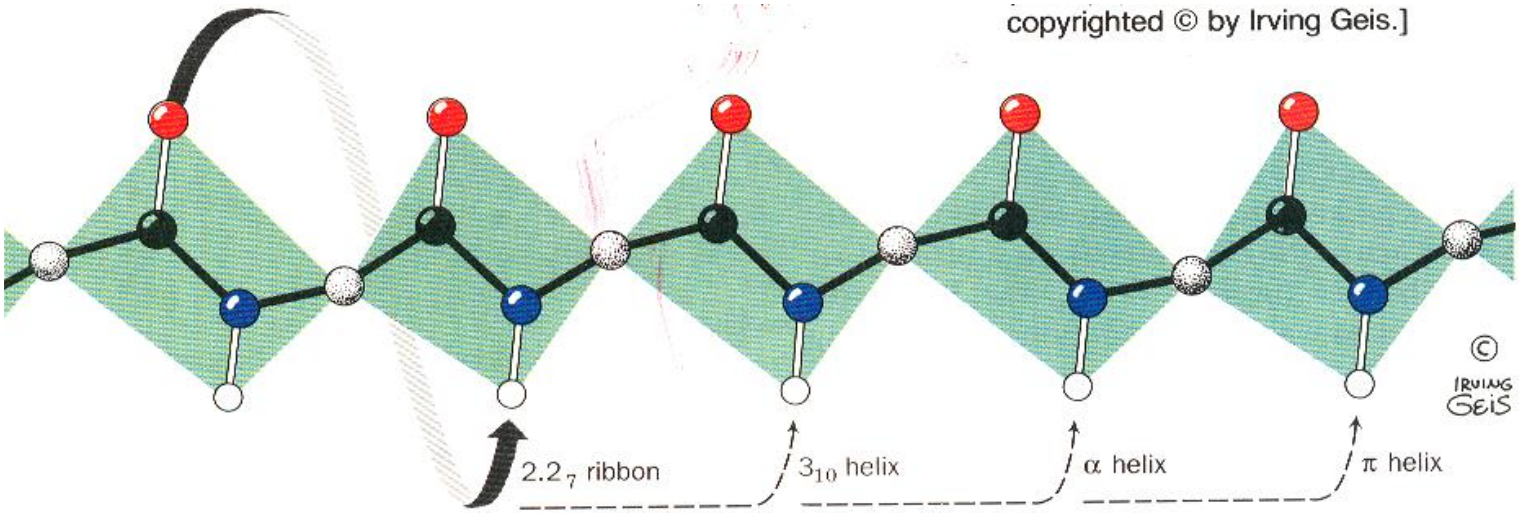


Figure 2.28
Biochemistry, Seventh Edition

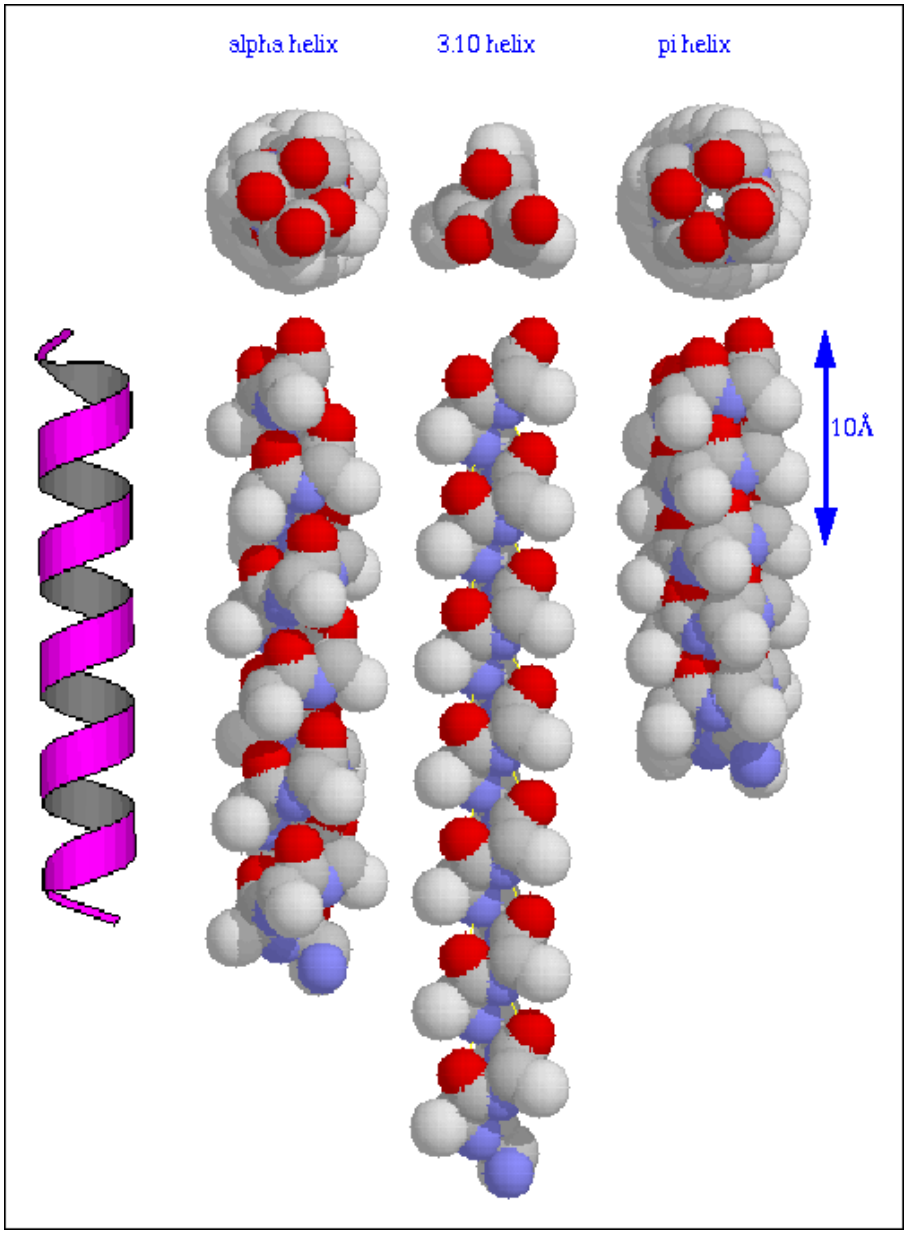
Ferritin

The H-bonding pattern of several existing helices



- **Indication of how hydrogen bonded polypeptide helices may be constructed.**

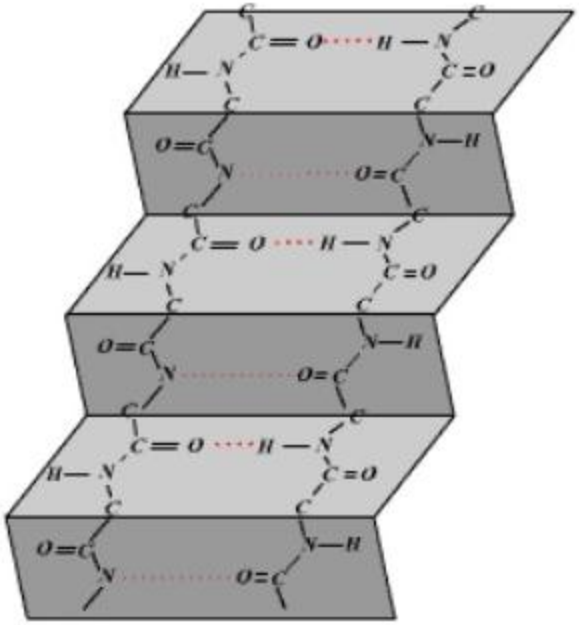
- In the cases shown, the peptide chain curls around such that the C=O group on residue n, forms a H-bond with the N-H groups on residues as indicated (2.2$_7$, 3$_{10}$, α-helix and π-helix).

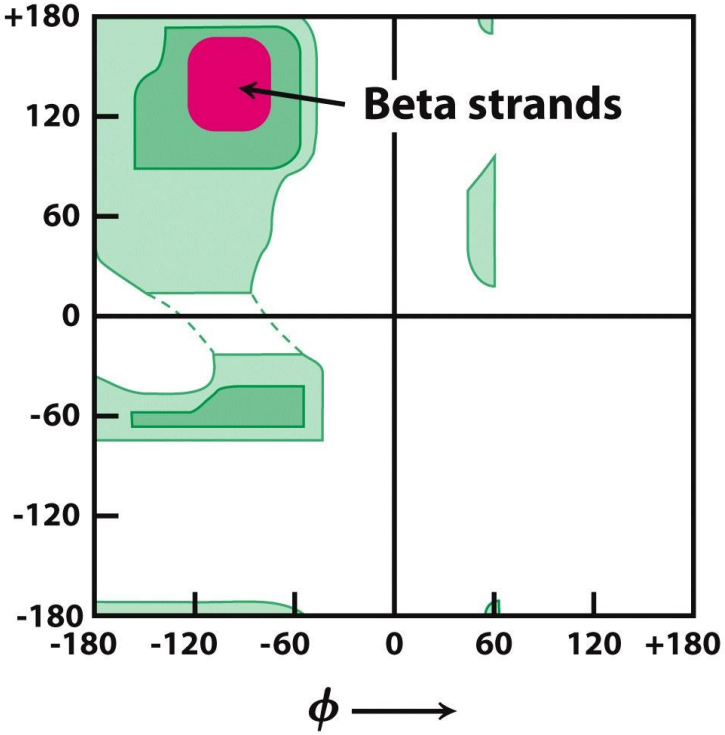


http://www.cryst.bbk.ac.uk/PPS2/course/section8/ss-960531_5.html

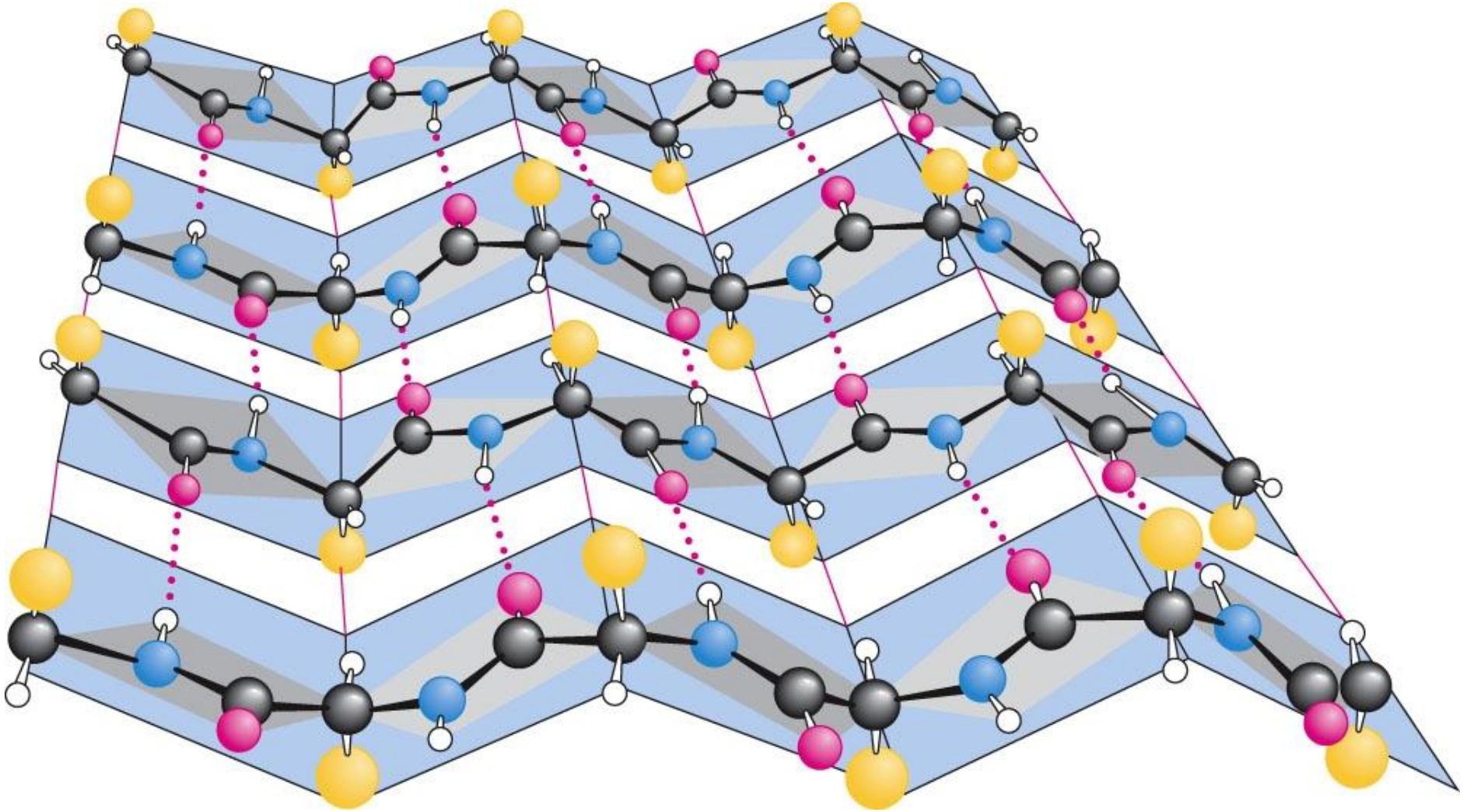
The Beta Sheet

- **Beta sheet is pleated (think a pleated skirt or a lamp-shade).**
- **Consist of two or more polypeptide chains.**
  - **Each known as a β-strand.**
- **The β-strands are more extended than an α-helix. A larger range of extended structures are sterically allowed (Ramachandran plot).**





The Beta Sheet



A “pleated sheet” of paper with an antiparallel β-sheet drawn on it.

The Beta Sheet

A β-strand:

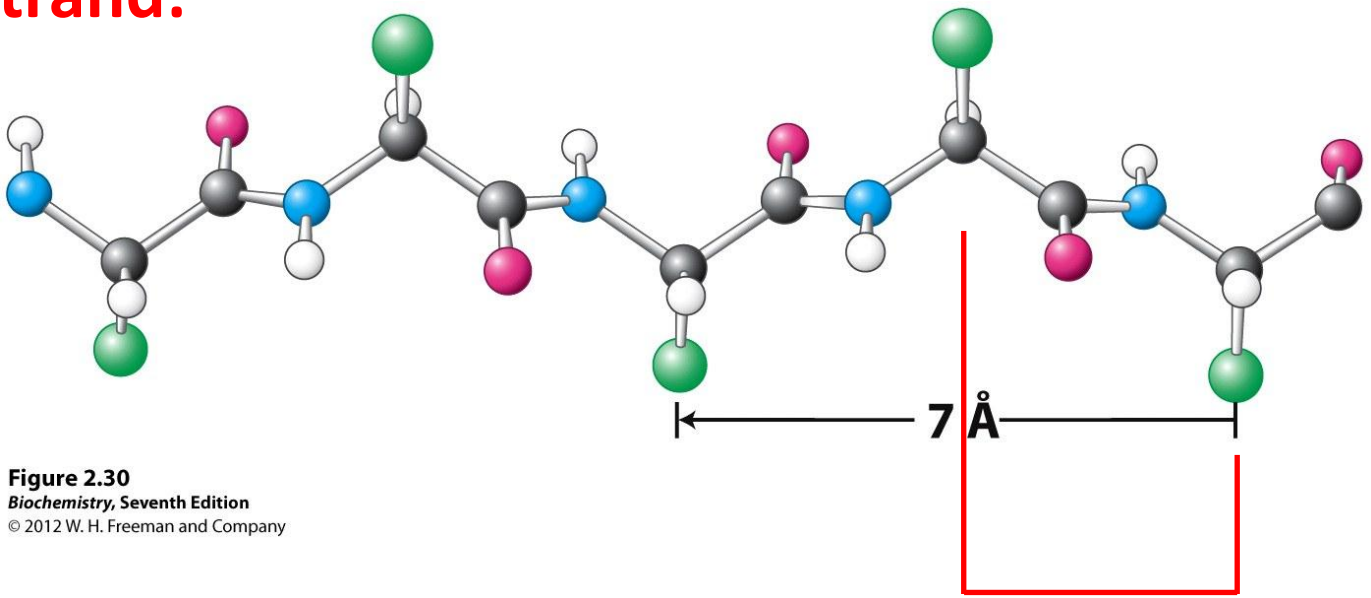


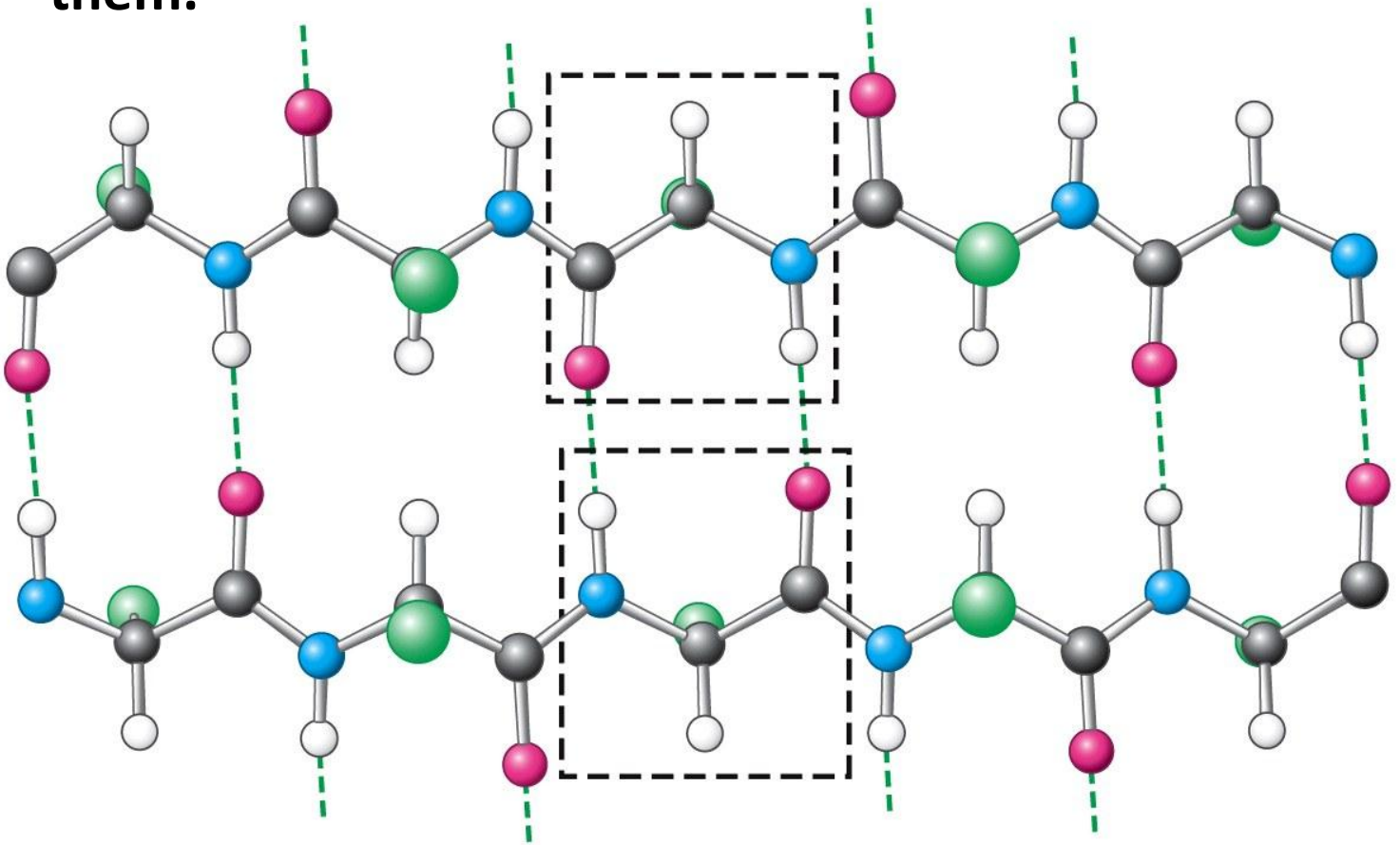
Figure 2.30
Biochemistry, Seventh Edition

3.5 Å
between adjacent amino acids

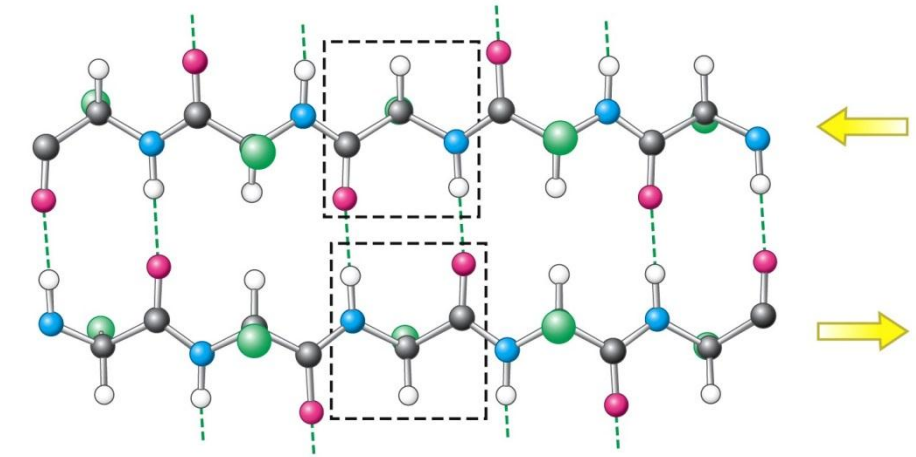
- **More spread out compared to an α-helix (1.5 Å between adjacent amino acids).**

The Beta Sheet

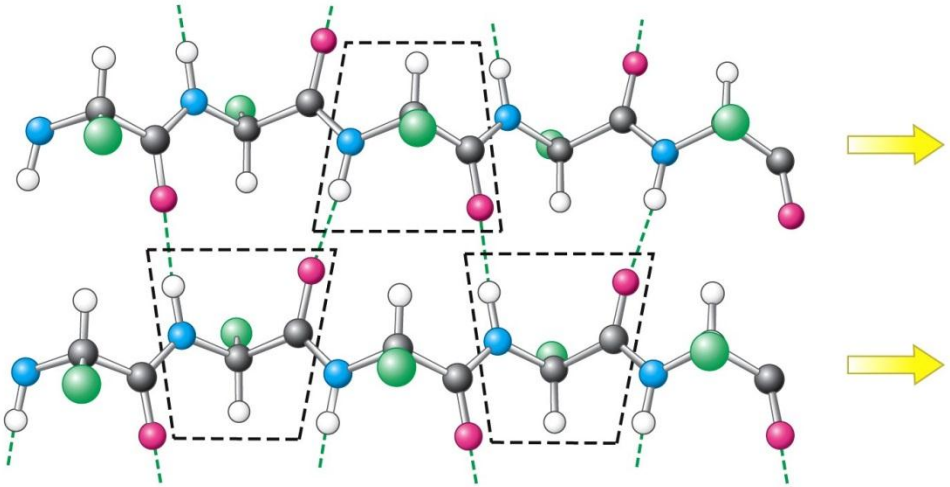
- **A β-sheet consists of two or more β-strands (or polypeptide chains).**
  - **Hydrogen bonds form between the strands NOT within them.**



- **β-strands within a β-sheet can run in parallel or anti-parallel directions.**
  - **Anti-parallel: β-strands run in the *opposite* direction.**
  - **Parallel: β-strands run in the *same* direction.**



Anti-parallel
"The opposite direction".



Parallel
"The same direction".

Anti-parallel β-sheets

Hydrogen bonds between the N-H group and the C=O group of one amino acid to the C=O and N-H groups of the partner amino acid on the adjacent chain.

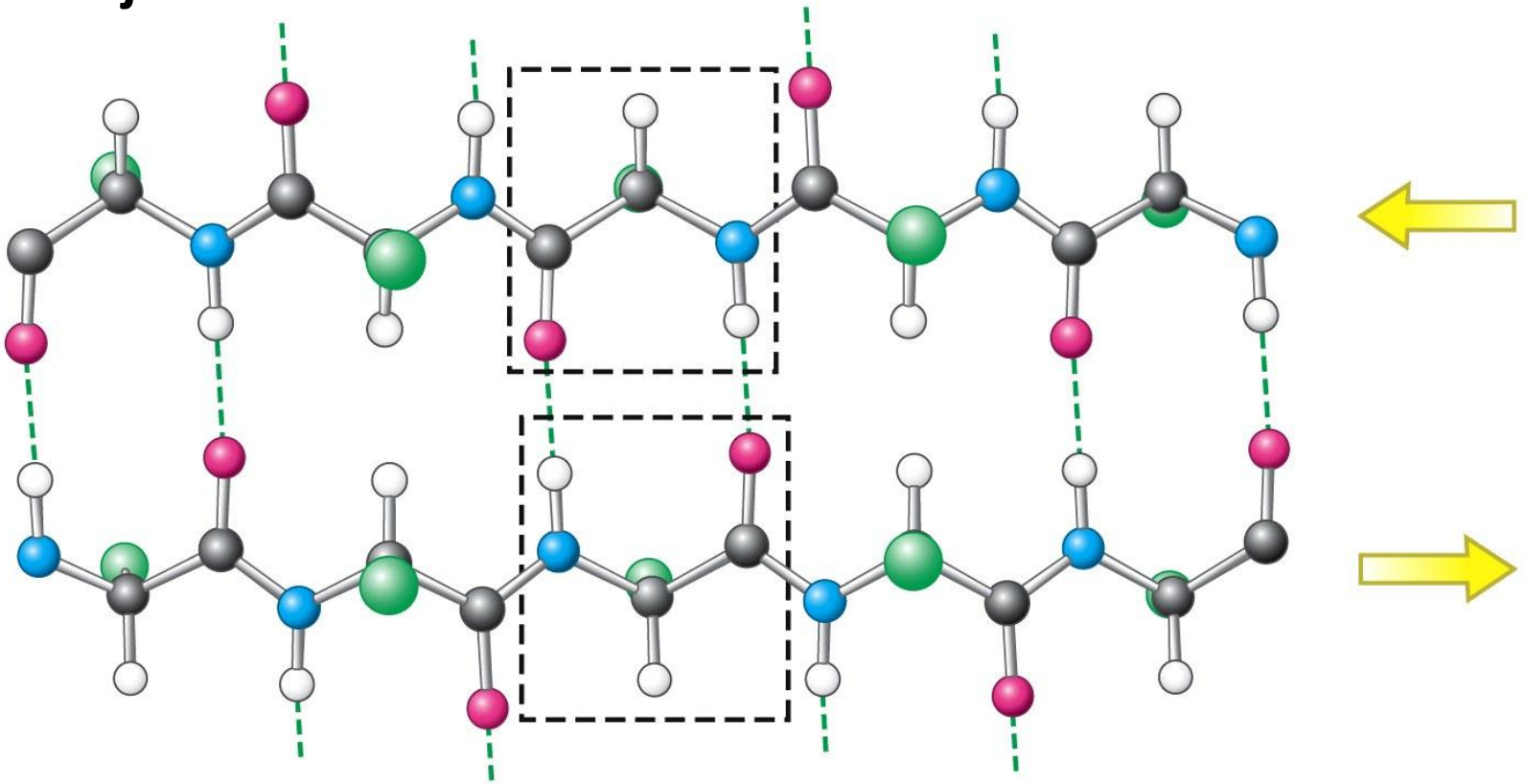
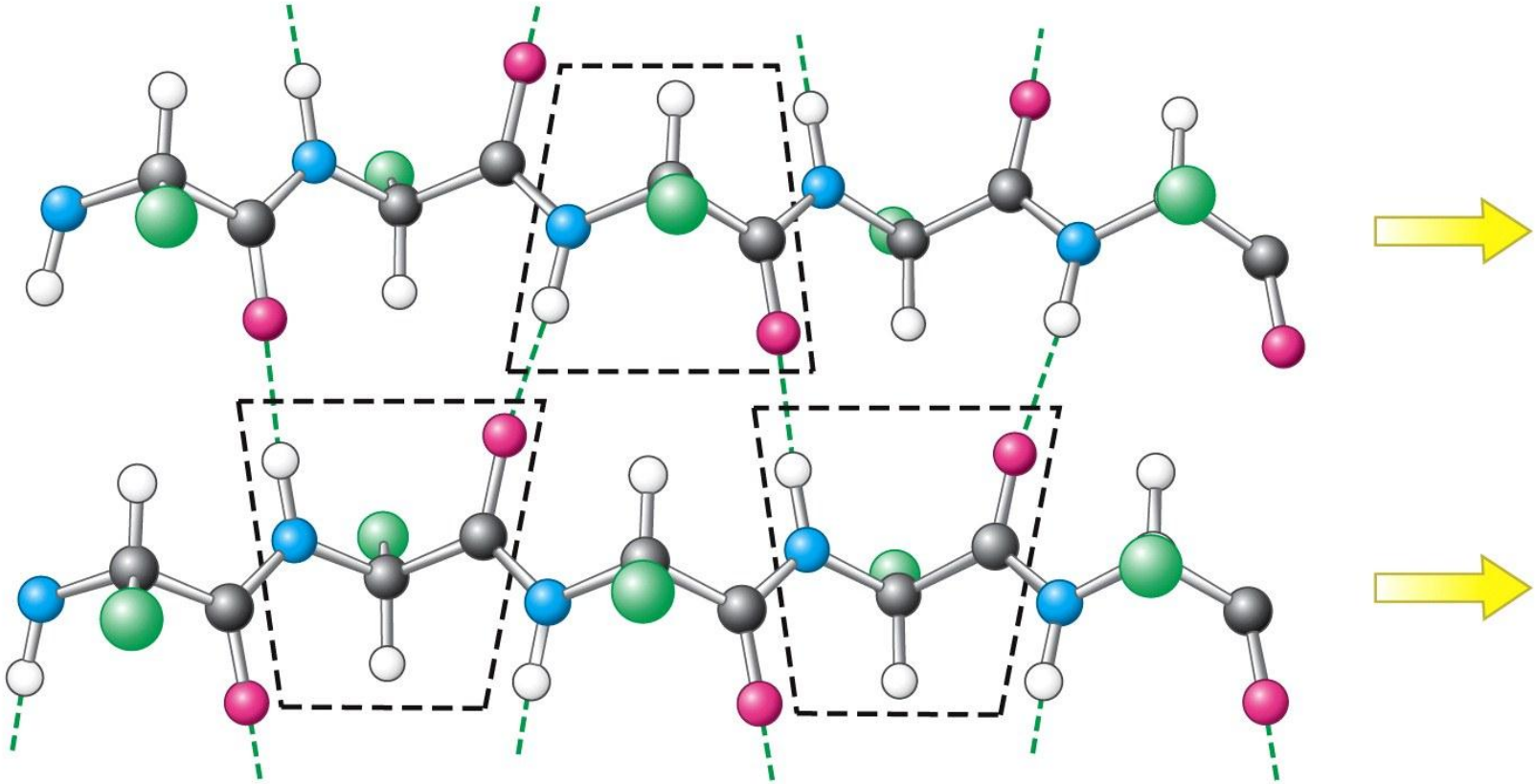


Figure 2.31
***Biochemistry*, Seventh Edition**

Parallel β-sheets

Hydrogen-bonding in the parallel β-sheets are a bit more complicated:

- **For each amino acid, the N-H group is h-bonded to the C=O group of anamino acid on the adjacent strand.**
- **The C=O group is h-bonded to the N-H group on the amino acid *two* residues down the chain**



Mixed β-sheets

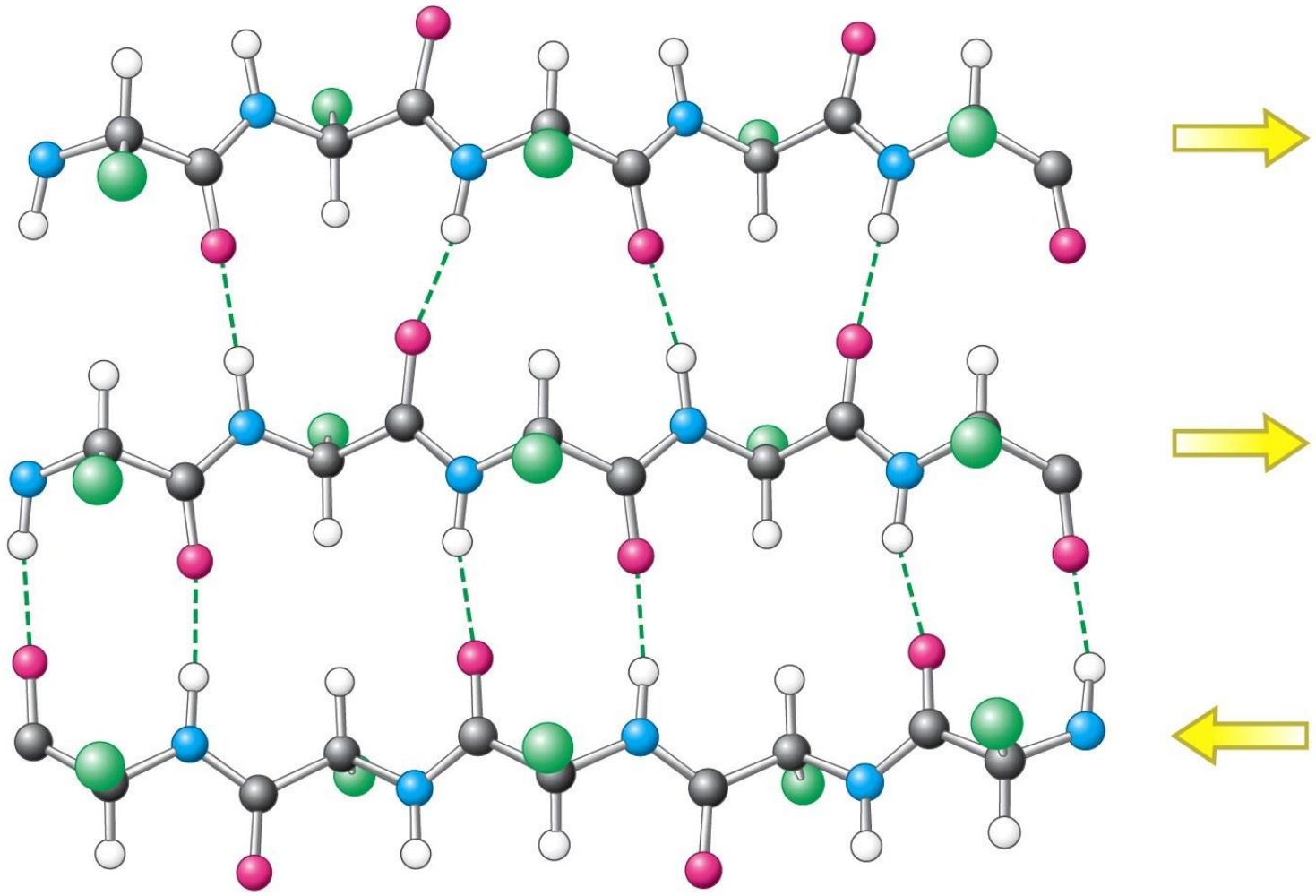
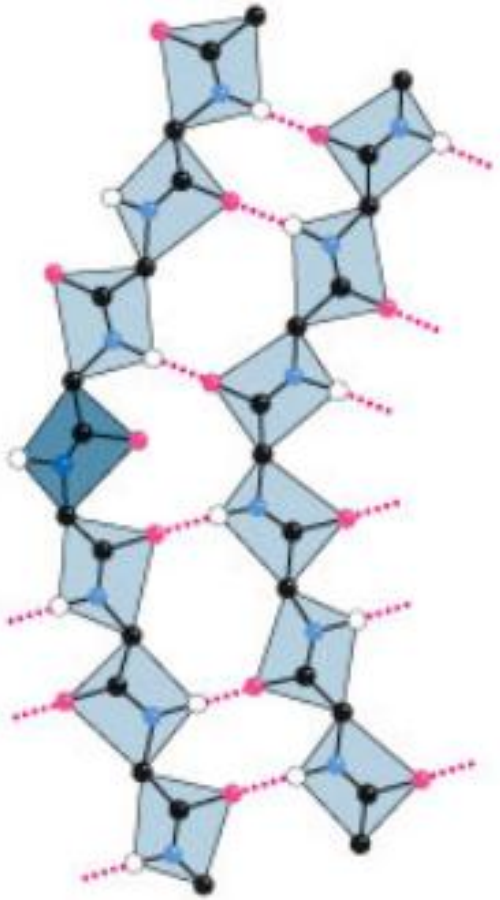


Figure 2.33
***Biochemistry*, Seventh Edition**

The Beta Bulge

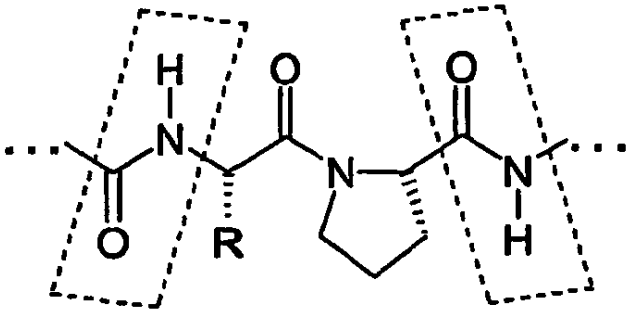
- The β-bulge most often occurs as an irregularity in antiparallel β-structures.
- A β-bulge occurs between two normal β-structure H bonds and comprises two residues on one strand and one residue on the opposite strand.
- The extra residue on the longer side causes additional backbone length. This is accommodated partially by creating a bulge in the longer strand and partially by forcing a slight bend in the β-sheet.



Classic bulge

The Beta Sheet

- Are all amino acids equally likely to be found in a β-sheet?
  - Proline is not favored in β-sheets, since it cannot form a hydrogen bond to another amino acid.
- So where is proline found?
  - Turns and loops.



http://www.google.com/patents/EP1725580B1?cl=en

Turns and Loops

Reverse turn (β-turn, hairpin turn):

- A turn is an element of secondary structure in proteins where the polypeptide chain reverses its overall direction.
- Often found on the surface of proteins.
- The C=O group of residue *i* in a polypeptide is h-bonded to the N-H group of residue *i* + 3.

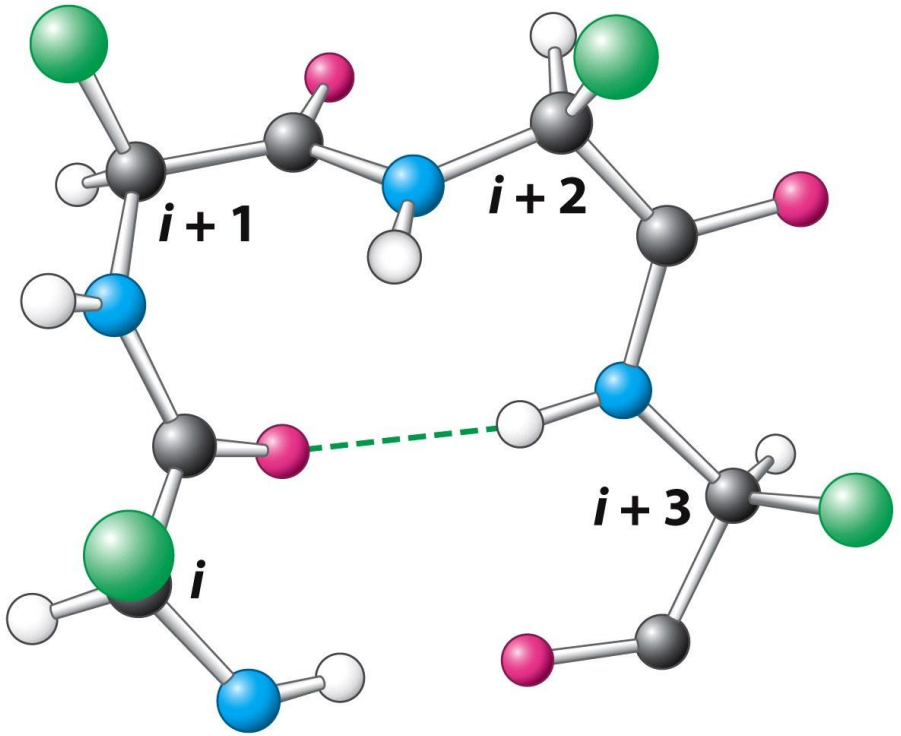


Figure 2.36
***Biochemistry*, Seventh Edition**

http://www.google.com/patents/EP1725580B1?cl=en

Turns and Loops

Omega loops:

- The Ω-loops are generally longer than turns and less structured.
- Lack rigid backbone angles and regular patterns of hydrogen bonds.

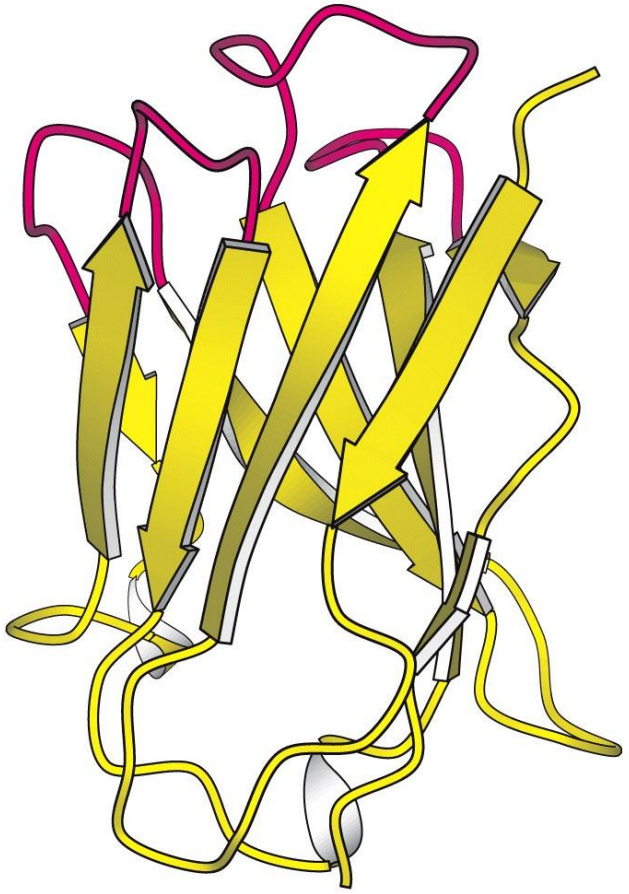
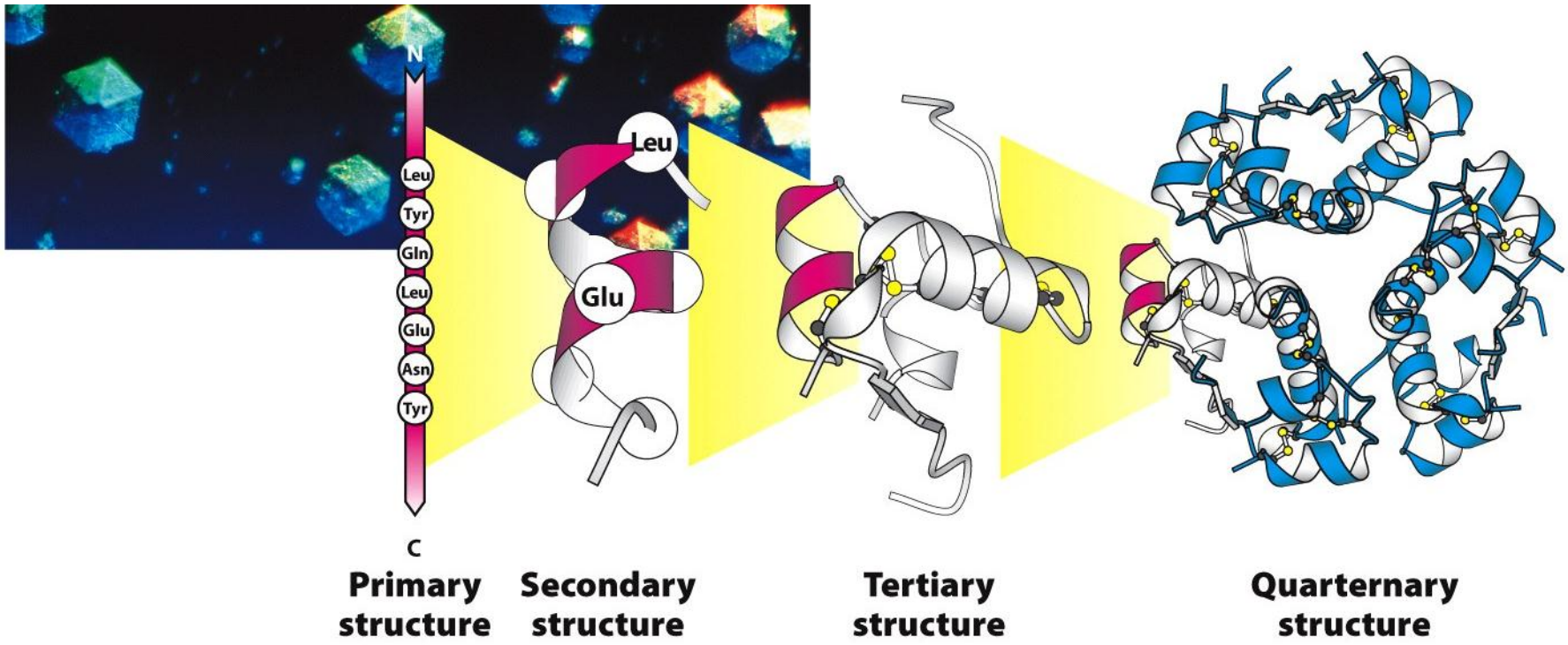


Figure 2.37
***Biochemistry*, Seventh Edition**

http://www.google.com/patents/EP1725580B1?cl=en

Tertiary Structure

- *Tertiary structure* refers to the spatial arrangement of amino acid residues that are far apart in the sequence and to the pattern of disulfide bonds. What does this mean?
- Assembly of secondary structures into a whole protein (or protein subunit).
- Backbone angles and hydrogen bonding determine secondary structures. What determines tertiary structures?



Tertiary Structure

What determines tertiary structure?

- **The chemical properties of the amino acids:**
  - **The distribution of polar and nonpolar residues.**
  - **In an aqueous environment, protein folding is driven by the strong tendency of hydrophobic residues to be excluded from water.**
  - **The protein is more thermodynamically stable when hydrophobic amino acids are clustered together rather than extended into the aqueous surroundings.**
  - **As a result, the polypeptide chain folds so that the hydrophobic side chains are buried on the inside and its polar, charged chains are on the surface.**

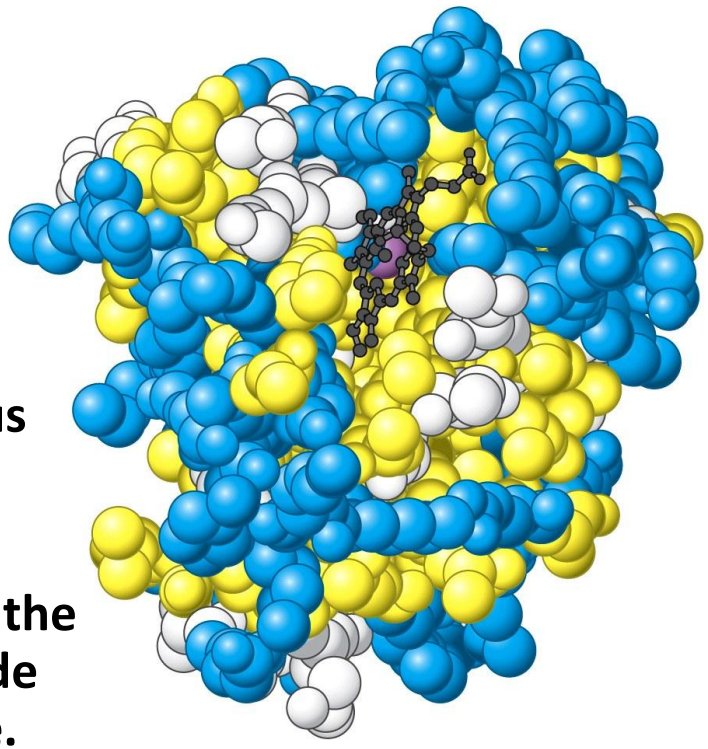
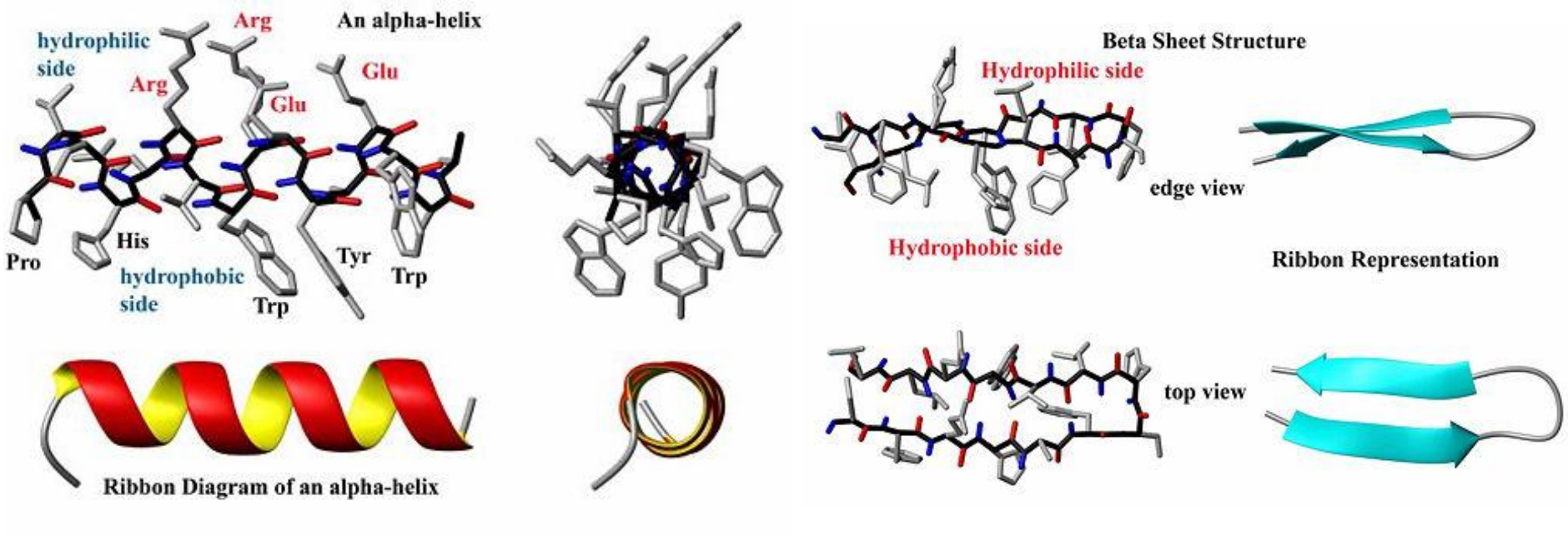


Figure 2.44a
***Biochemistry*, Seventh Edition**

What determines tertiary structure?

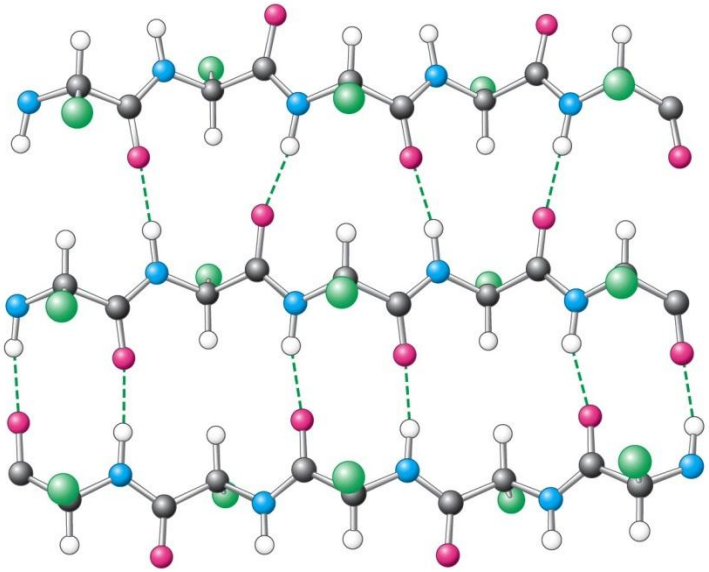
- **Alpha helices and β strands are often amphipathic (a hydrophobic and a polar side).**
  - **The hydrophobic side will point to the interior of the protein.**
  - **The polar side will point to the outside (aqueous environment) of the protein.**

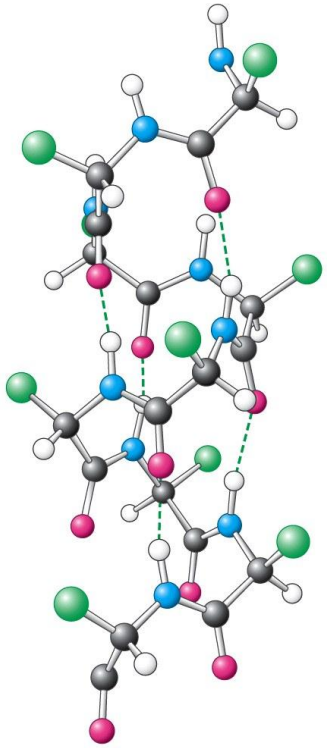


http://en.citizendium.org/wiki/Protein_structure

What determines tertiary structure?

- The main chain backbone is important too.
  - Unpaired (no hydrogen bonds) N-H and C=O group prefers an aqueous environment.
  - Therefore all the main chain N-H and C=O must be hydrogen bonded to be buried in the hydrophobic environment inside the protein.
  - How is that accomplished? Do we know any structures that “use” all the H-bonds?
  - Alpha helices and β sheets!

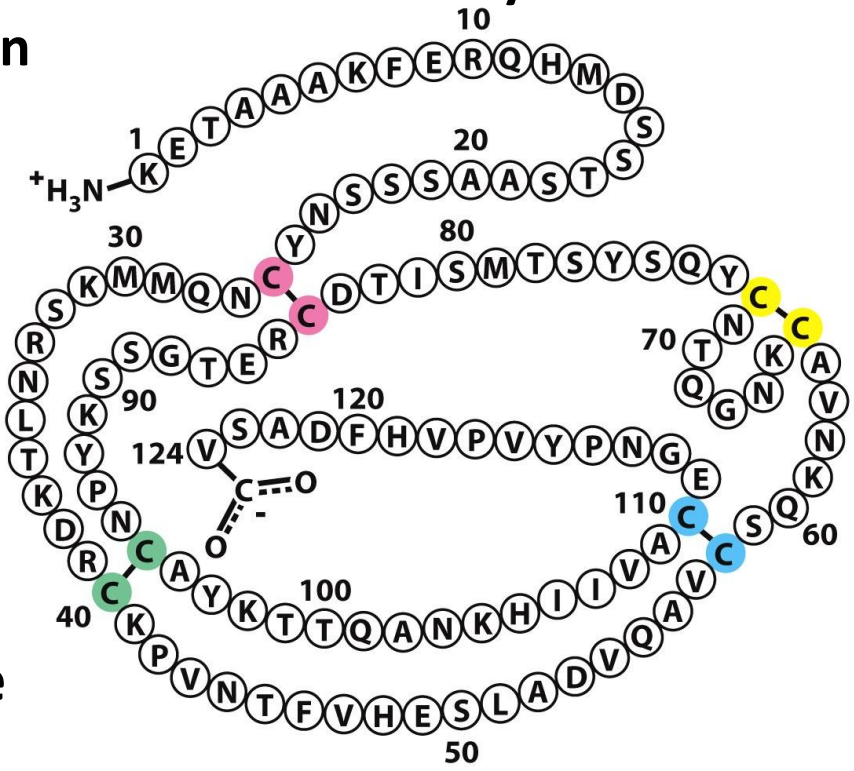




Tertiary Structure

What determines tertiary structure?

- **Hydrophobic interactions (van der Waals) contribute to the stability of proteins. Especially to the hydrophobic interior of the protein.**
- **Disulfide bonds form between to cysteine residues that may be far apart in sequence, but close together in spatial arrangement.**
  - **Stabilize proteins.**
  - **Contribute to the overall structure.**



Bovine ribonuclease

Tertiary Structure

What determines tertiary structure?

- **Hydrophobic interactions (van der Waals) contribute to the stability of proteins. Especially to the hydrophobic interior of the protein.**

- **Now we know why nature has chosen 20 different amino acids with many different sizes, shapes and chemical properties (charged, uncharged, polar, hydrophobic etc.).**
  - **The 20 aa are like a palette from which you can choose to fill the interior and exterior of a protein.**

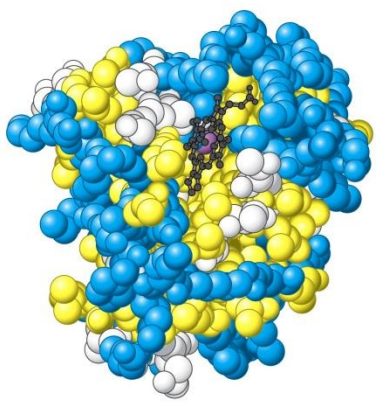


Figure 2.44a
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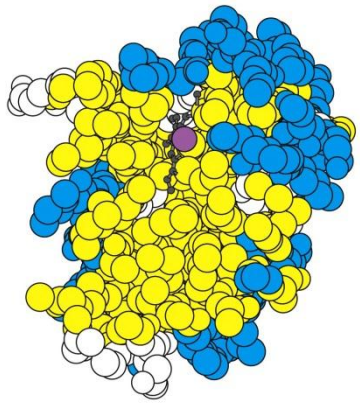

Figure 2.44b
Biochemistry, Seventh Edition
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http://pixshark.com/artist-palette-and-brush.htm

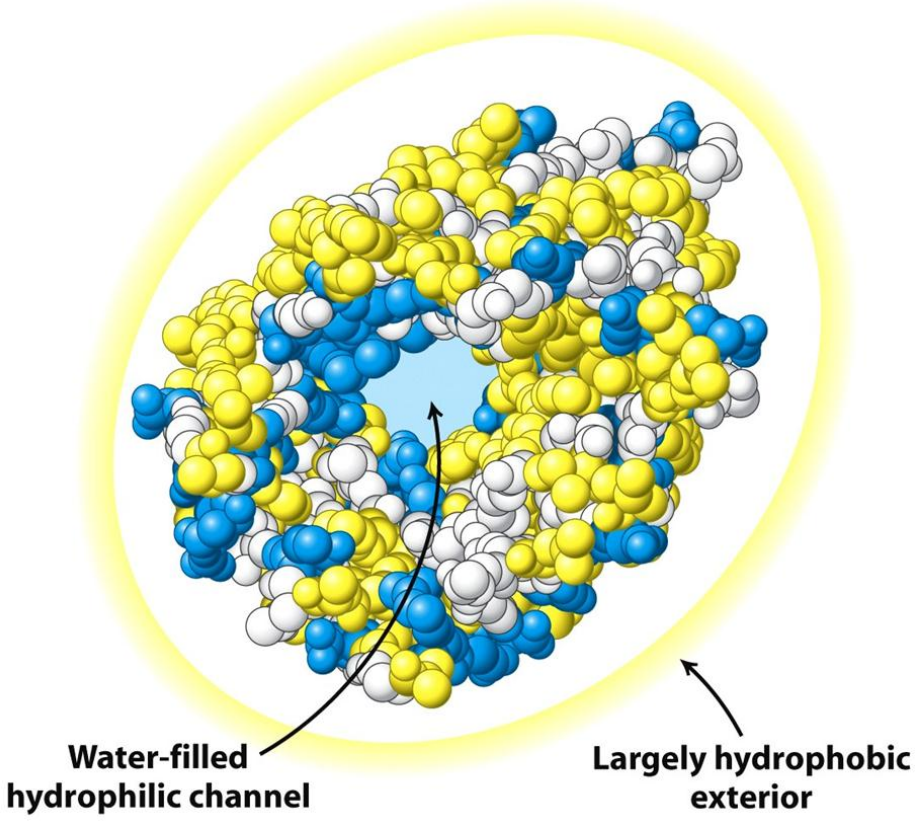
Tertiary Structure

- **Is the protein interior always hydrophobic? And the exterior always polar?**
- **No! Of course there are exceptions to every rule.**

Membrane proteins have the reverse distribution of amino acids. Their exteriors are hydrophobic and their interiors are polar. Why?

-They are located in the membrane, which is made out of lipids (hydrophobic).

One example is the porins, proteins found in the outer membranes of many bacteria.



Which Noncovalent Interactions Stabilize the Higher Levels of Protein Structure?

What are these "weak forces"?

What are the relevant numbers?

- van der Waals: 0.4 - 4 kJ/mol.
- Hydrogen bonds: 12-30 kJ/mol.
- Ionic bonds: 20 kJ/mol.
- Hydrophobic interactions: <40 kJ/mol.

Which Noncovalent Interactions Stabilize the Higher Levels of Protein Structure?

- Secondary, tertiary, and quaternary structure of proteins is formed and stabilized by weak forces
- Hydrogen bonds are formed wherever possible
- Hydrophobic interactions drive protein folding
- Ionic interactions usually occur on the protein surface
- van der Waals interactions are ubiquitous

Tertiary Structure

- **Certain combinations of secondary structure are present in the tertiary structure of proteins: *Motifs.***

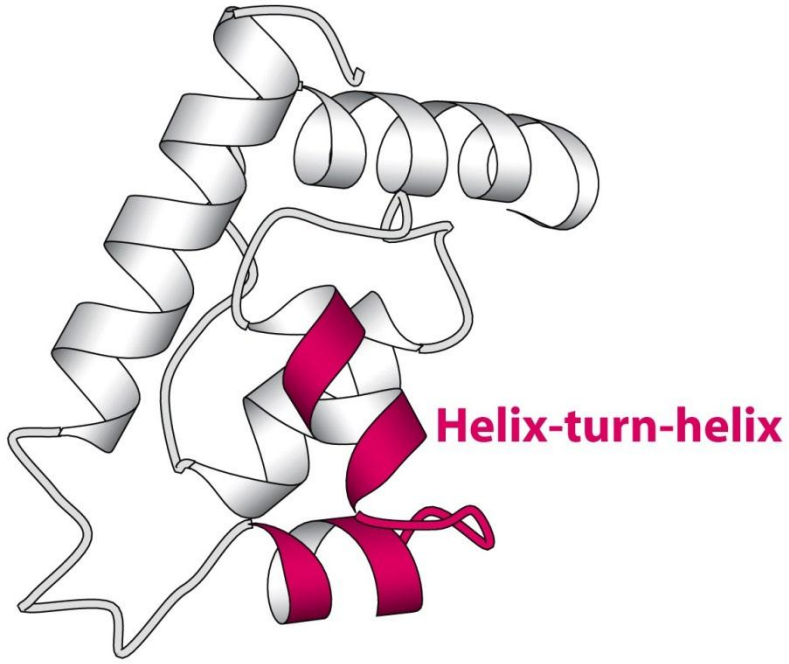


Figure 2.46
***Biochemistry*, Seventh Edition**

Motifs

Motifs are known as *super secondary structures*, and involve the association of secondary structures in a particular geometric arrangement.

Motifs are sometimes referred to as “super secondary structures”, since they contain more than one secondary structural element (combination of alpha-helix, beta-sheet, turn and/or loop).

If we think of each secondary structure (alpha-helix, beta-strand etc.) as a 'unit', then a *motif* would be comprised of at least two 'units' of secondary structure.

Some super secondary structures are known to have a specific biological or structural role, but for others their role is unknown. Secondary structures are grouped to form geometric arrangements (*motifs*).

To avoid confusion, we will refer to motifs as being a part of a protein’s *tertiary structure*.

Motifs

Alpha-helix motifs:

1. **Helix-turn-helix**
2. **Helix-loop-helix**
3. **EF hand**
4. **Leucine zipper**

Beta-sheet motifs:

1. **Beta hairpins**
2. **Greek key**

Mixed motifs:

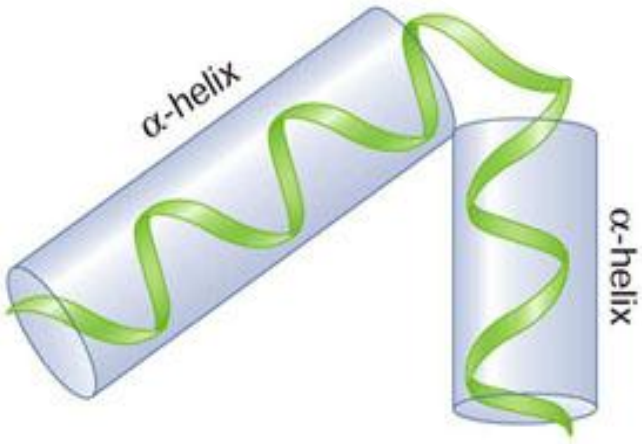
1. **Beta-alpha-beta**
2. **Rossmann fold**
3. **Zinc finger**

Alpha-helix Motifs

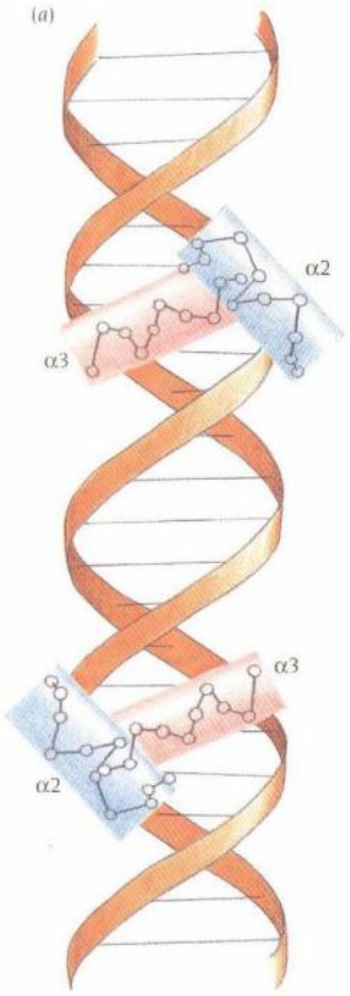
1. **Helix-turn-helix: two alpha-helices connected by a turn.**

– **A major structural motif observed in proteins capable of binding DNA.**

– **One helix contributes to DNA recognition ("recognition helix") and second helix stabilizes the interaction between protein and DNA.**



Alpha-helix-turn-alpha-helix



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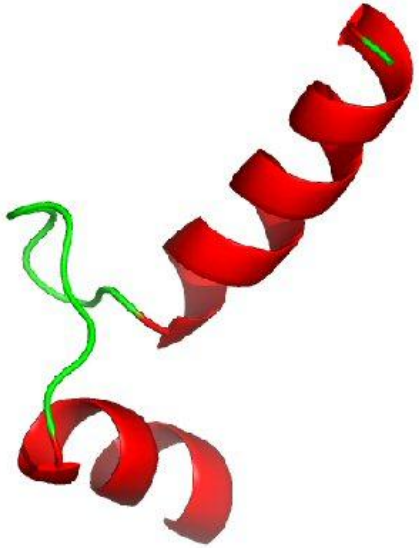
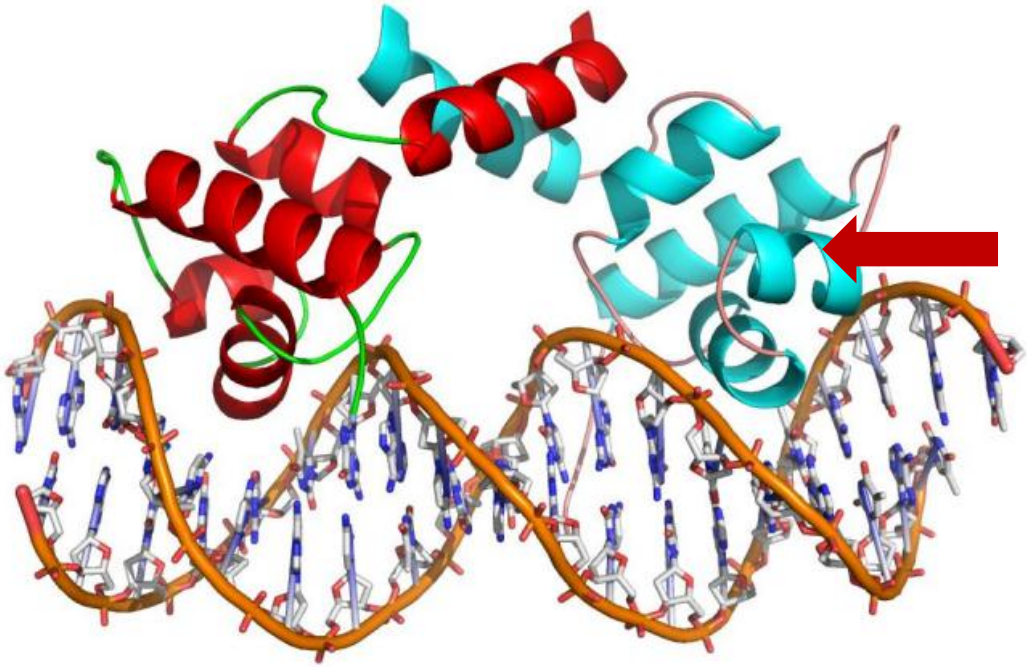
Alpha-helix Motifs

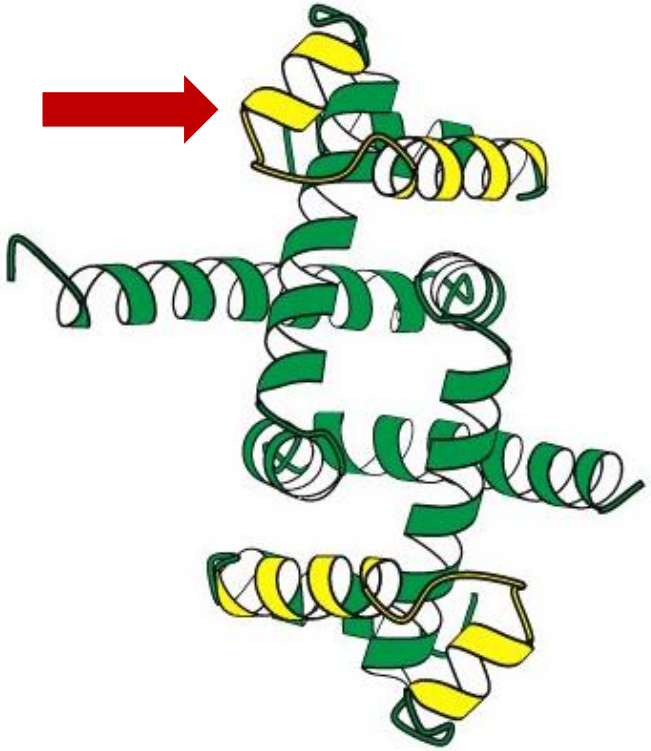


1. **Helix-turn-helix: two alpha-helices connected by a turn.**

– **Proteins having this motifs are generally involved in bacterial operons (Trp repressor, Lambda Cro) and initiation of transcription, cell proliferation, developmental regulation.**



Lambda Cro

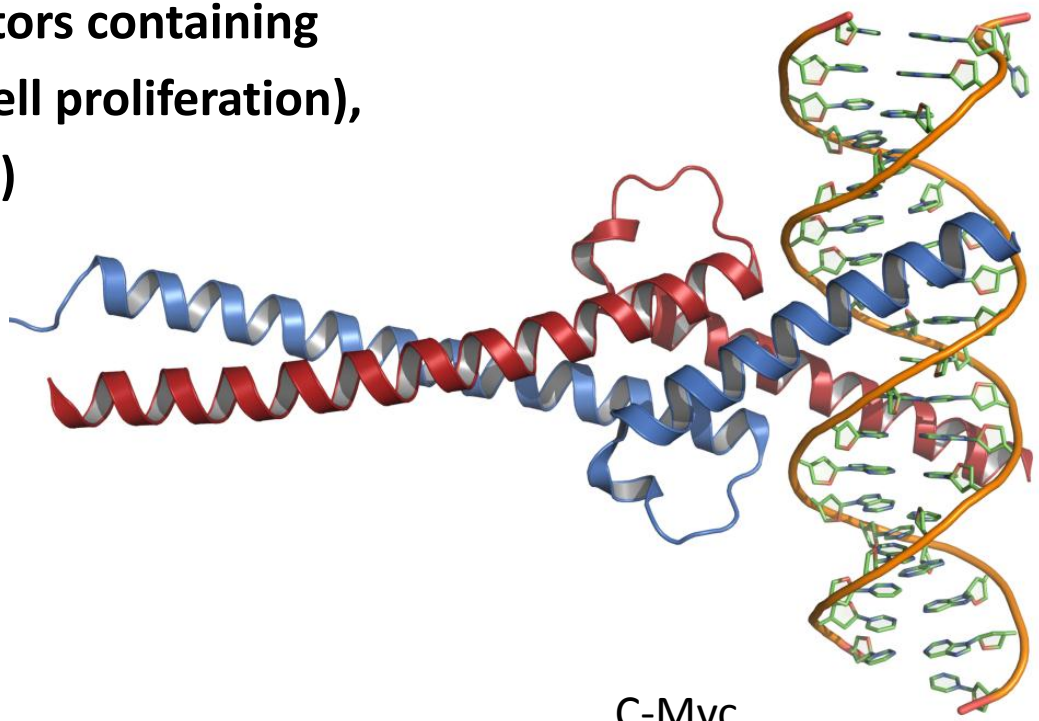


Trp repressor

Alpha-helix Motifs

2. Helix-loop-helix: two alpha-helices connected by a loop.

- **A protein structural motif that characterizes a family of transcription factors.**
- **In general, one helix is smaller.**
- **The loop is flexible and allows dimerization by folding and packing against another helix.**
- **The larger helix typically contains the DNA-binding regions.**
- **Examples of transcription factors containing helix-loop-helix are C-Myc (cell proliferation), MyoD (muscle differentiation) and HIF (oxygen response).**



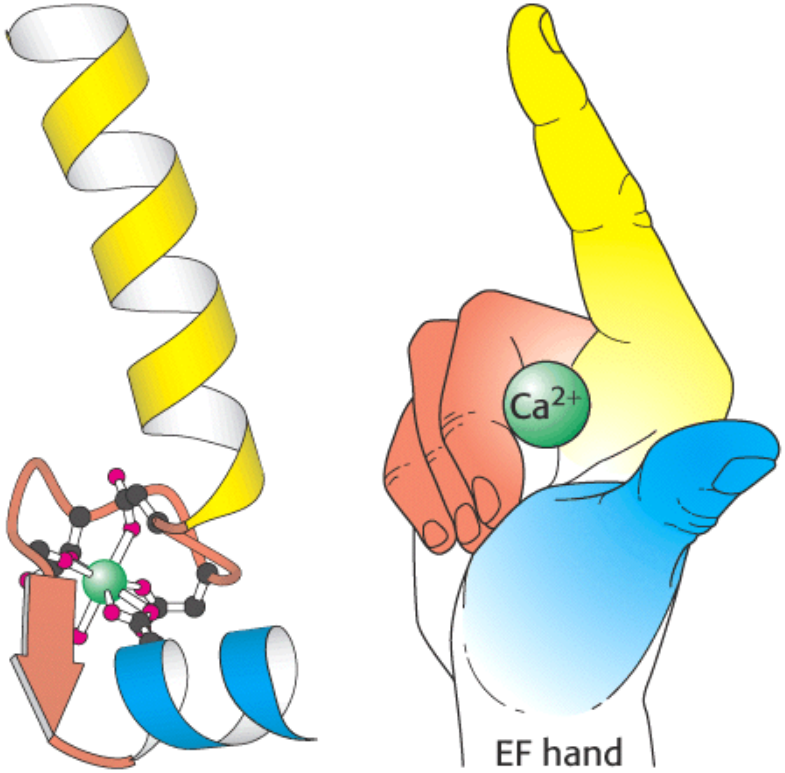
C-Myc

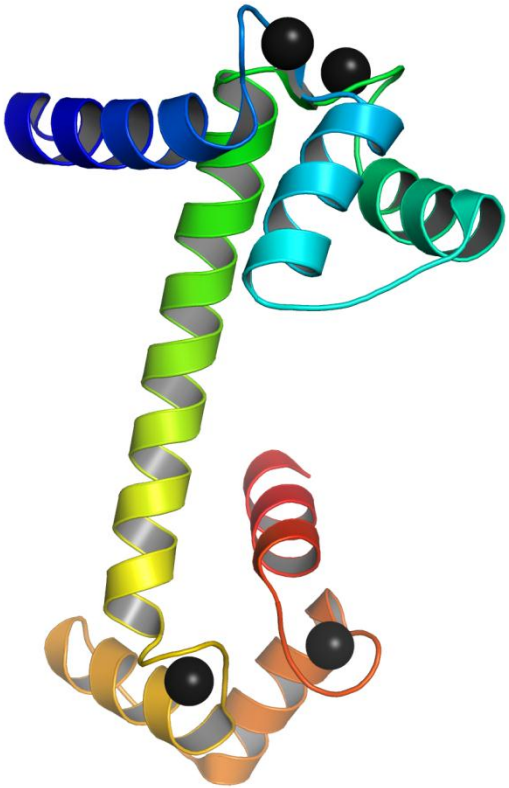
https://en.wikipedia.org/wiki/Myc

Alpha-helix Motifs

3. EF hand: two α-helices connected by a loop that contains residues to coordinate a calcium ion (Ca2+).

– **Present in calcium binding proteins such as parvalbumin and calmodulin.**



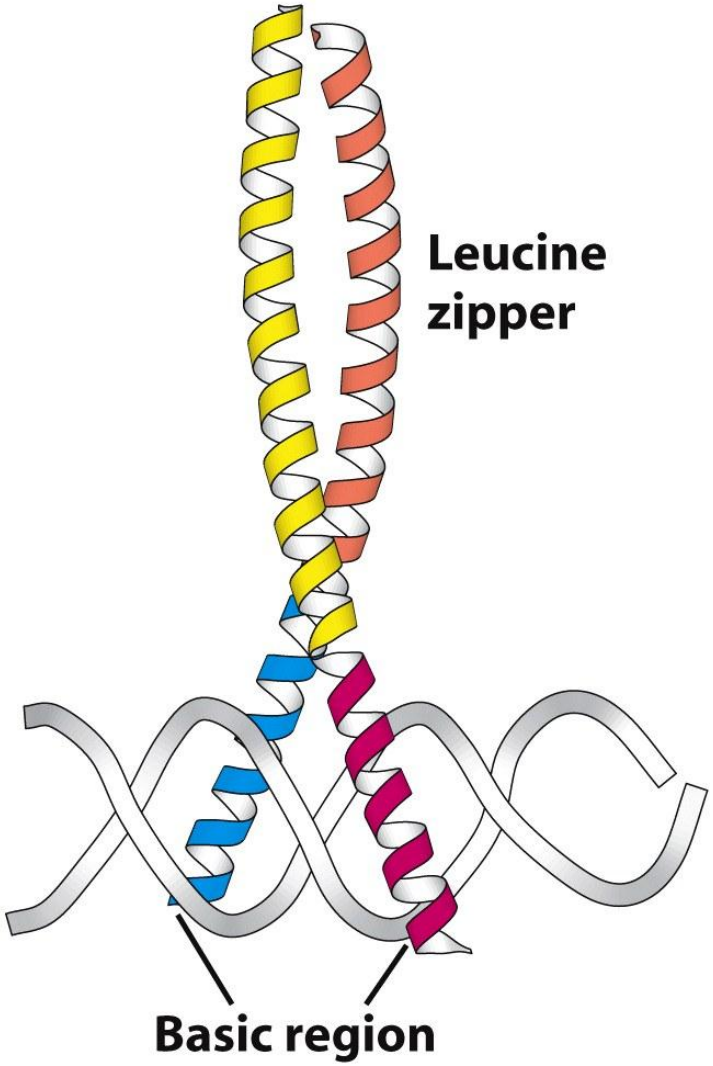


Calmodulin: calcium sensor and signal transducer.

Alpha-helix Motifs

3. Leucine Zipper: Two alpha-helices (one from each monomer of a protein) form a coiled-coil structure at one end.

- **The two helices dimerize due to the leucines present on each helix (the hydrophobic leucines are buried between the two helices).**
- **Beyond the dimerization interface the alpha helices diverge, allowing them to fit into the major groove of the DNA double helix.**
- **The dimerization partner determines DNA binding affinity and specificity.**
- **Found in fibrinogen (essential in blood coagulation), DNA binding proteins (c-Fos-c-Jun), muscle protein myosin.**

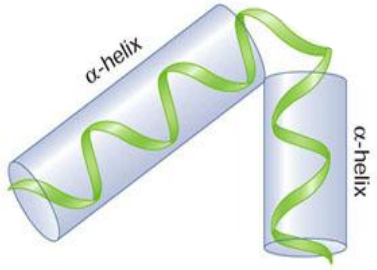


Transcription factor c-Fos-c-Jun

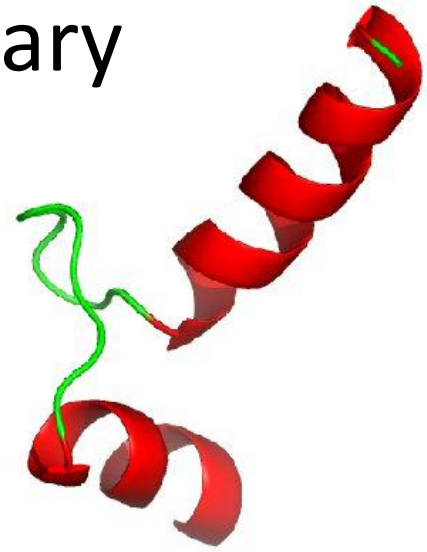
Alpha-helix-Motifs Summary

Alpha-helix motifs:

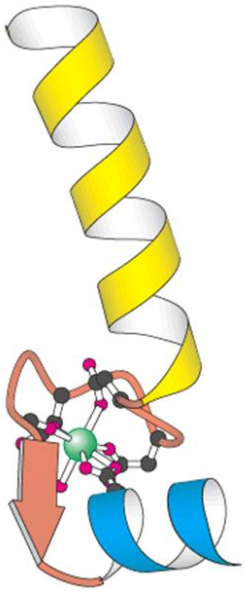
1. **Helix-turn-helix**
2. **Helix-loop-helix**
3. **EF hand**
4. **Leucine zipper**

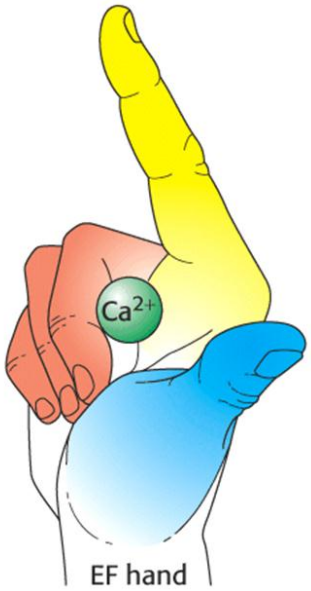


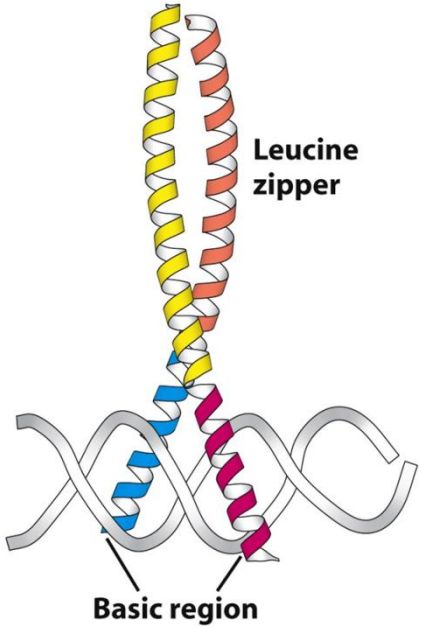
Helix-turn-helix



Helix-loop-helix





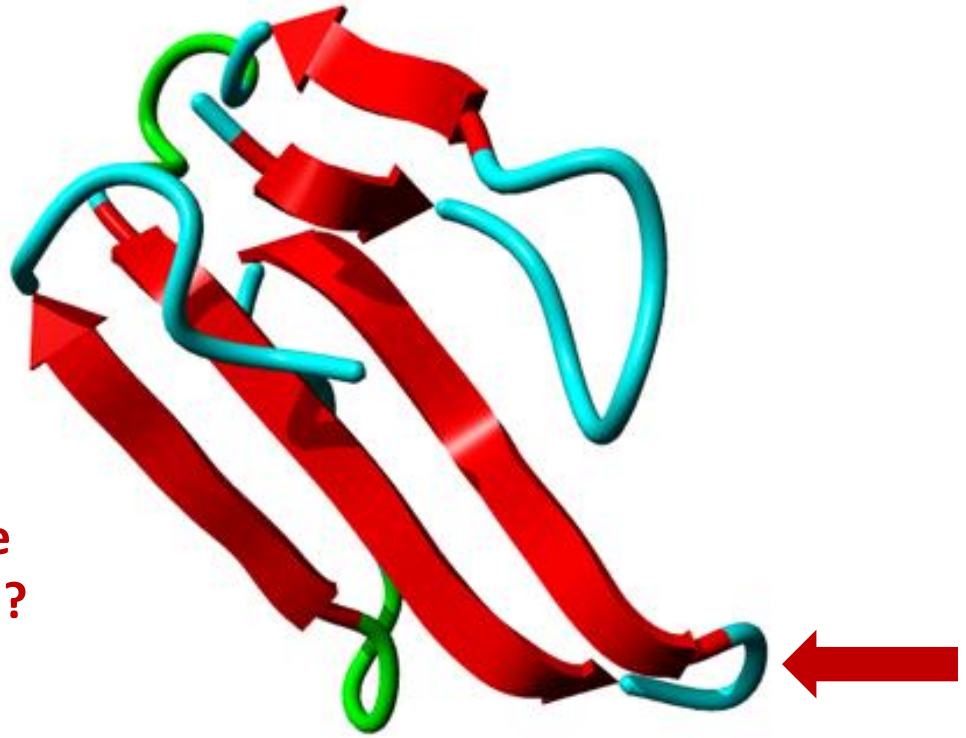


Beta-Sheet Motifs

1. Beta-hairpin: two antiparallel beta-strands connected by a "hairpin" turn (reverse turn).

Two anti-parallel β-strands connected by a reverse turn.

Where is the beta-hairpin?



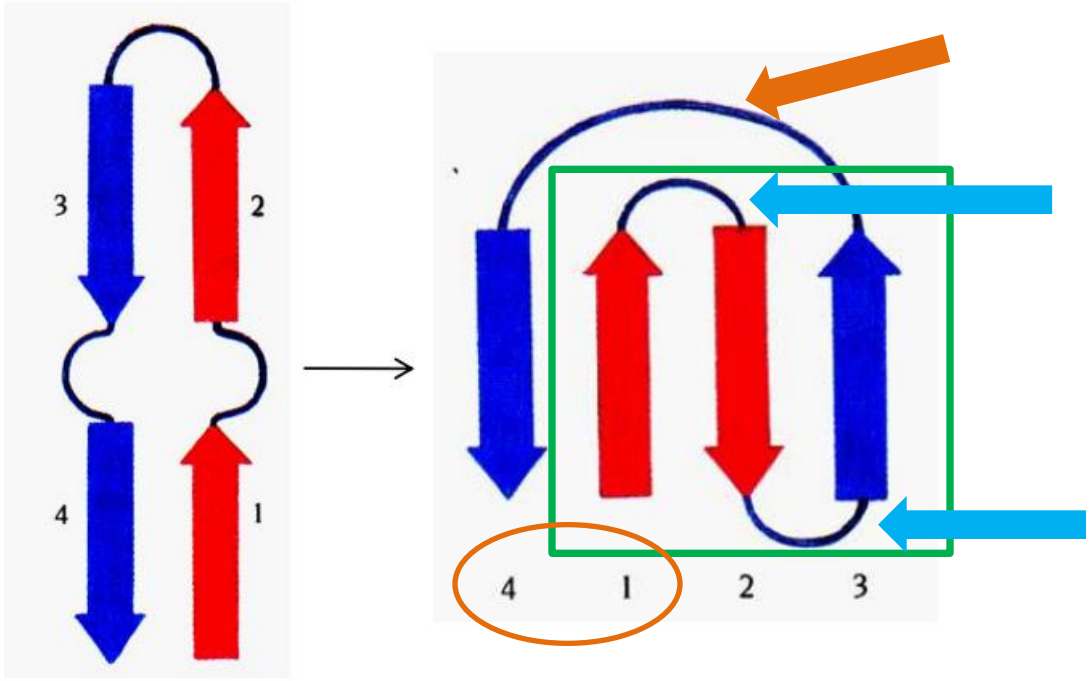
Erabutoxin (snake venom)

http://curser.science.ru.nl/content-e/pub_NWI/Bioinformatics%20Summerschool%202006%20light%2003092006/documents/do_4271.htm

Beta-Sheet Motifs

2. Greek key: four adjacent antiparallel beta strands with linking loops that fold upon themselves.

- **The Greek key motif consists of four adjacent antiparallel strands and their linking loops.**
- **It consists of three antiparallel strands connected by hairpins, while the fourth is adjacent to the first and linked to the third by a longer loop.**



Three anti-parallel strands

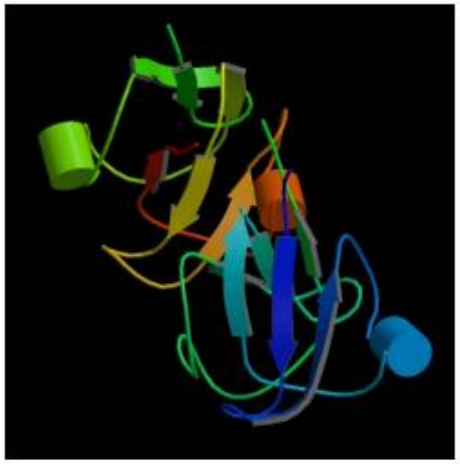
Connected by two hairpins

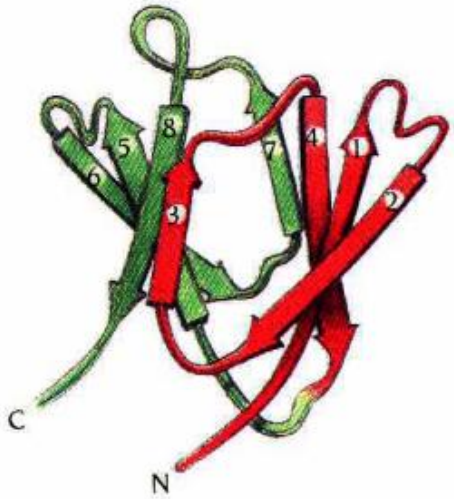
The first and fourth beta-strands are adjacent and connected by a loop

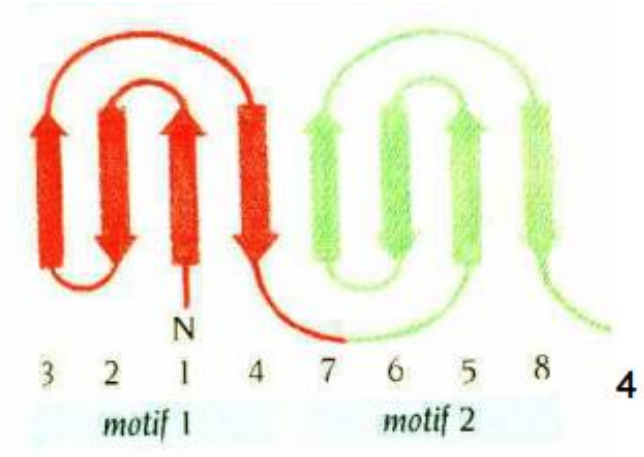
Beta-Sheet Motifs

2. Greek key: four adjacent antiparallel beta strands with linking loops that fold upon themselves.

– **Example of protein with Greek key motif: gamma crystallin.**







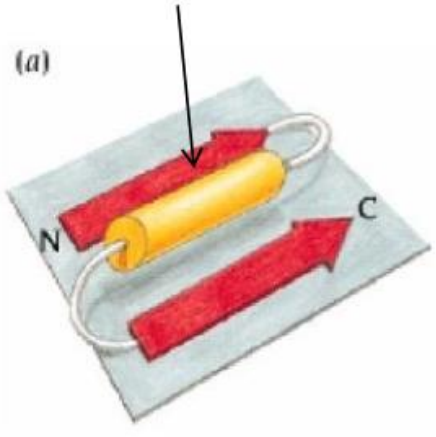
Gamma crystallin is found in the eye lens of vertebrate animals, where it maintains the refractive index of the lens. The crystallins are made during development and are kept throughout life, making them very stable proteins.

Mixed Motifs

1. **Beta-alpha-beta (βαβ) motif: two parallel beta strands connected by an alpha-helix.**

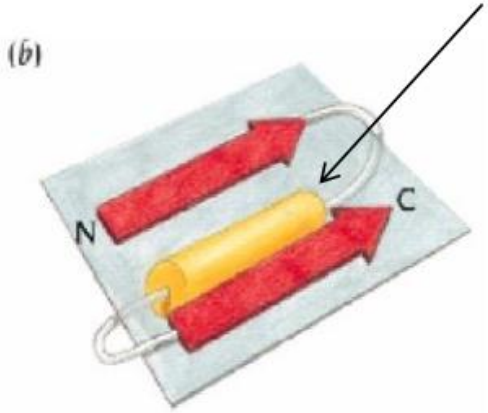
- **Two types of beta-alpha-beta: right-handed and left-handed.**
- **In the right-handed motif the helix is above the plane.**
- **In the left-handed motif the helix is below the plane.**

Helix above the plane

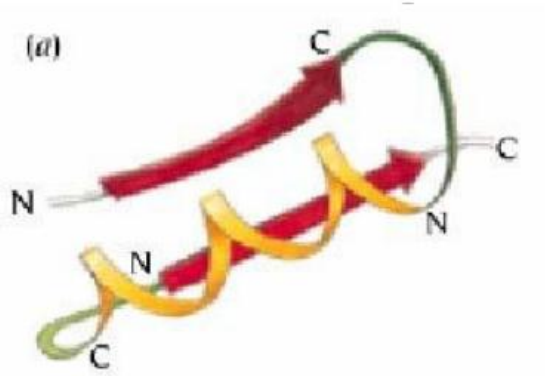


Right-handed
> 95%

Helix below the plane



Left-handed

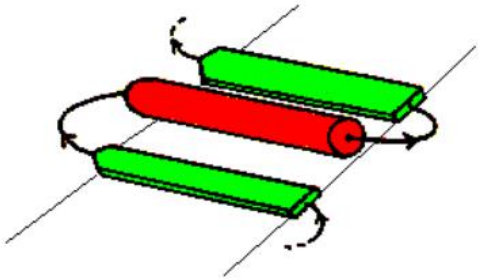


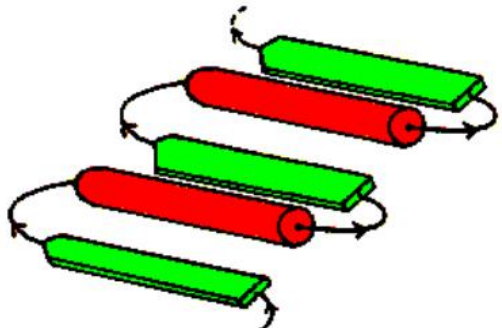
The first loop is often evolutionarily conserved, and often binds or "recognizes" other proteins.

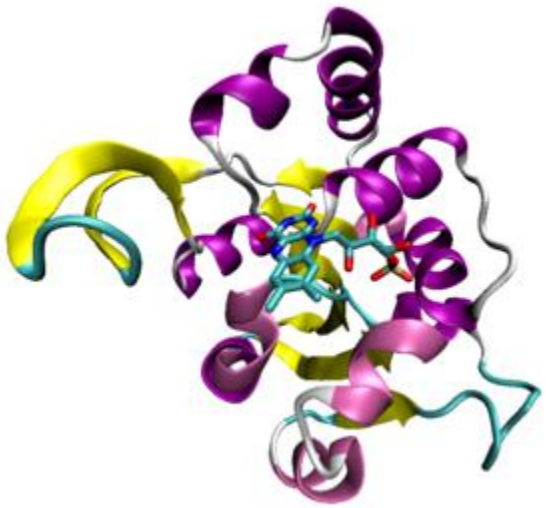
Mixed Motifs

2. Rossmann Fold: 2x Beta-alpha-beta motif.

- **Two Beta-alpha-beta motifs combine to form the Rossmann fold.**
- **The middle β-strand is often shared between the two units.**
- **This type of motif is often found in proteins that bind nucleotides as co-factors.**







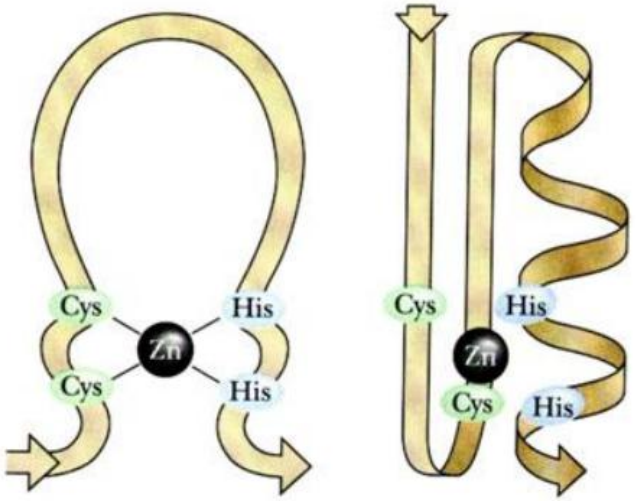
Decarboxylase with bound flavin mononucleotide cofactor.

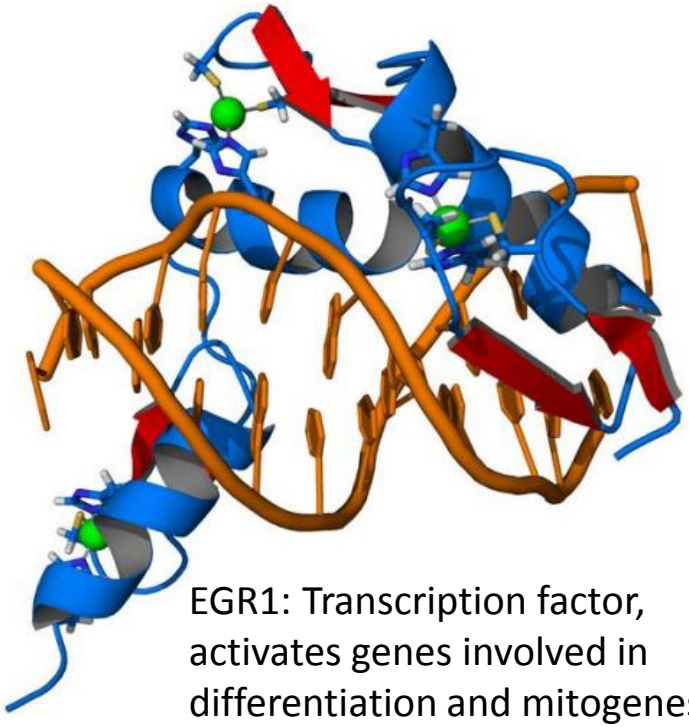
https://en.wikipedia.org/wiki/Rossmann_fold

Mixed Motifs

3. Zinc finger: An alpha helix bound to a loop by a zinc ion.

- **The zinc ion is held in place by two cysteines and two histidines.**
- **Proteins with zinc fingers bind to DNA.**
- **The alpha helix lies in the major groove of the DNA double helix.**
- **Zinc finger motifs are often repeated in clusters.**





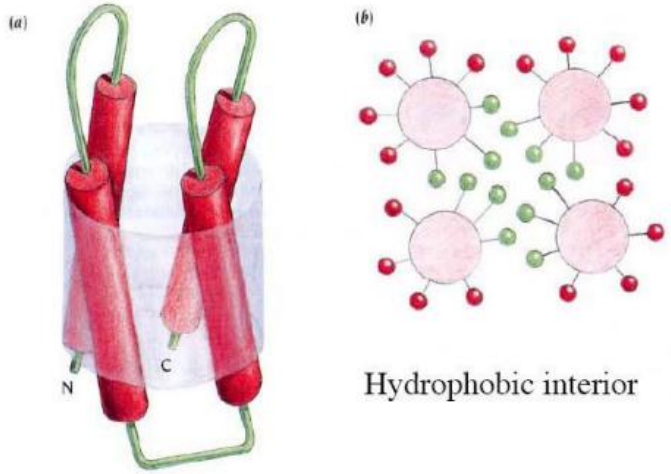
EGR1: Transcription factor, activates genes involved in differentiation and mitogenesis.

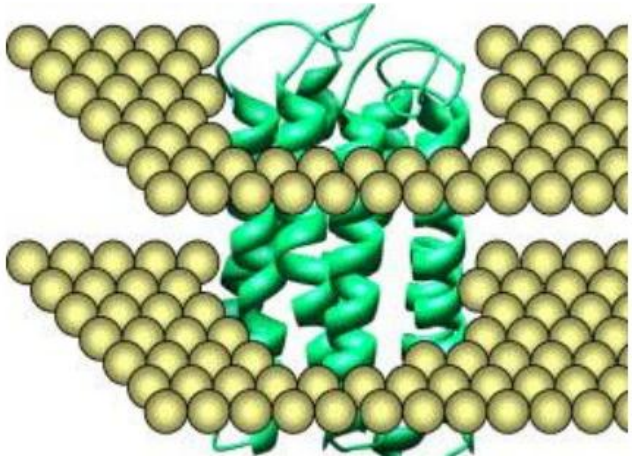
Motifs

Motifs can go together to form larger structures:

Helix bundle (two helix-turn-helix):

- **Long stretches of hydrophobic amino acids.**
- **Transmembrane alpha-helices.**
- **Exception to the rule (hydrophobic amino acids on the exterior**
- **Examples: Cell surface receptors, ion channels and transporters.**



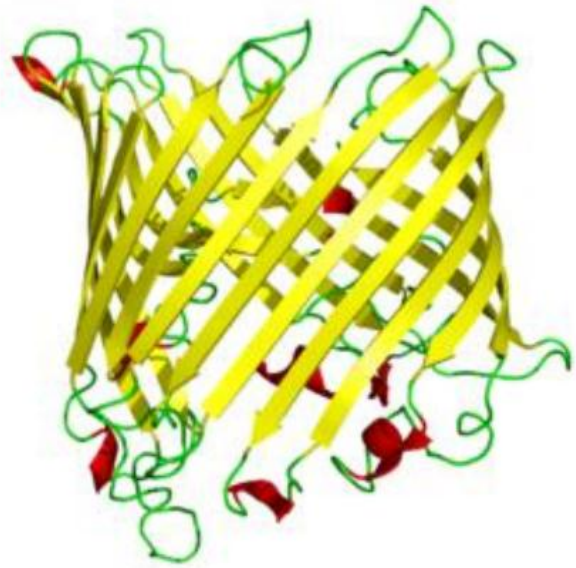


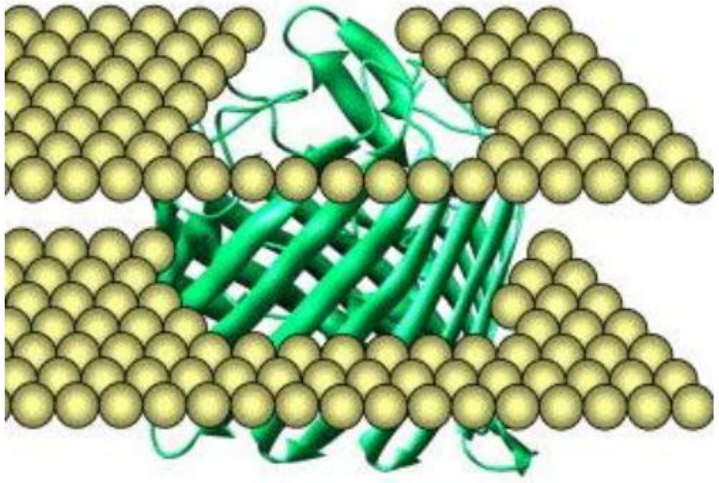
Motifs

Motifs can go together to form larger structures:

Beta barrel (several beta-hairpins):

- **Anti-parallel sheets rolled into cylinder.**
- **Membrane proteins.**
- **Again exception to the rule (interior is polar, exterior is hydrophobic).**
- **Examples: Outer membrane of Gram negative bacteria, porins (diffusion of small molecules).**

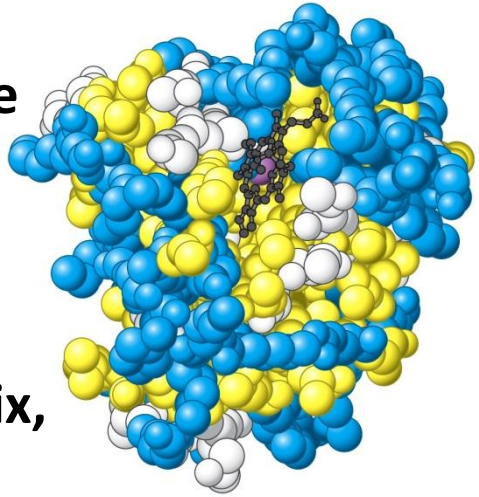




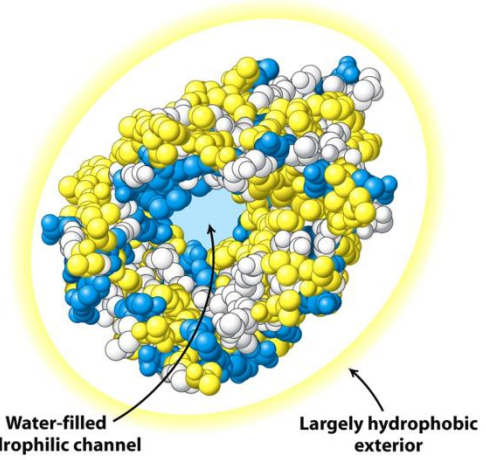
Tertiary Structure Summary

What determines tertiary structure? **The chemical properties of the amino acids (The distribution of polar and nonpolar residues).**

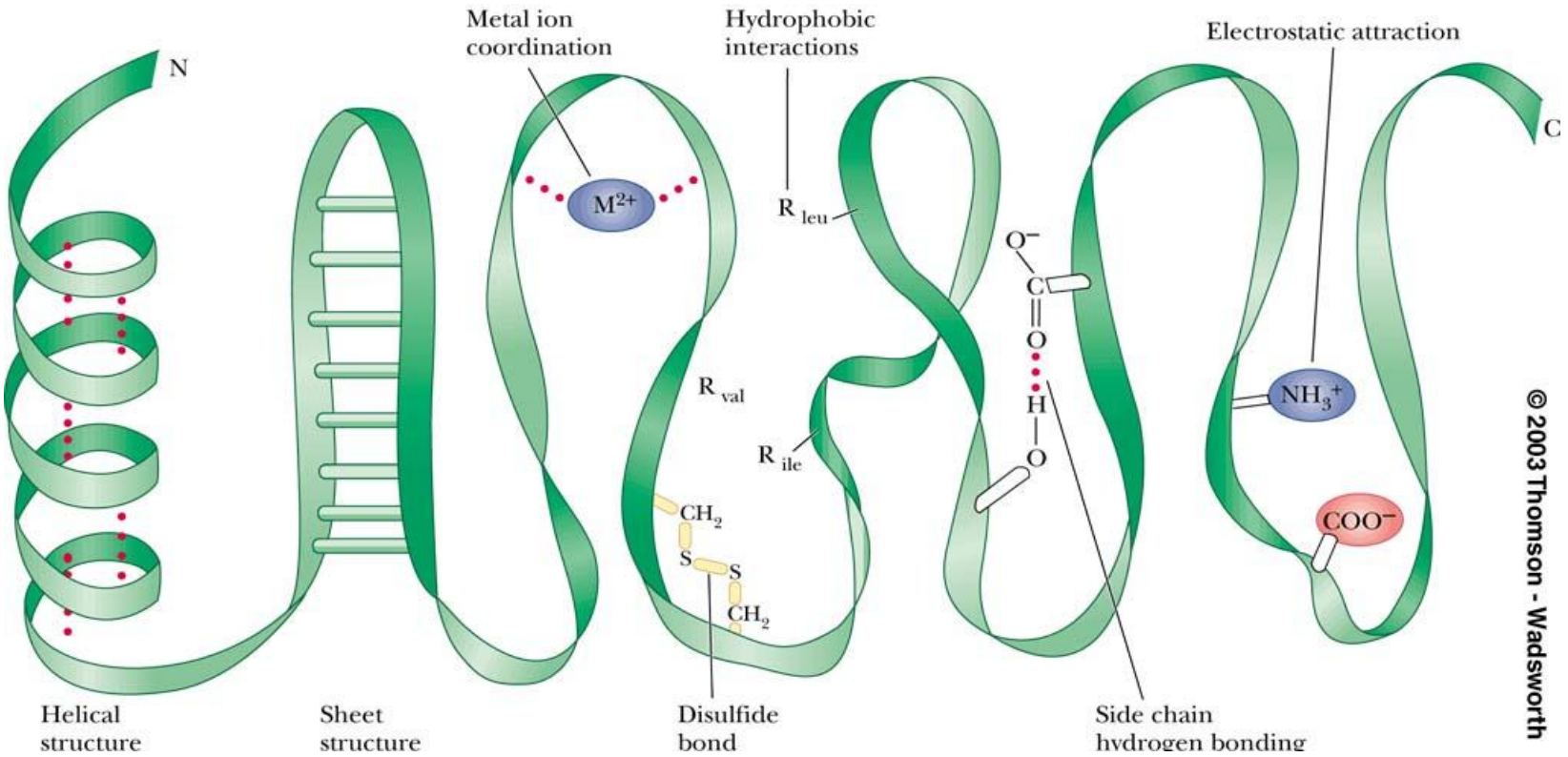
Polar amino acid on the exterior of the protein facing the aqueous environment. Exception to the rule: membrane Proteins (hydrophobic amino acids are on the exterior).



Secondary structures arrange into motifs. **Helix-turn-helix, helix-loop-helix, EF hand, leucine zipper, beta-hairpin, Greek key, Beta-alpha-beta, Rossman fold, zinc finger, helix bundle, beta barrel.**



Forces that stabilize the tertiary structure of proteins

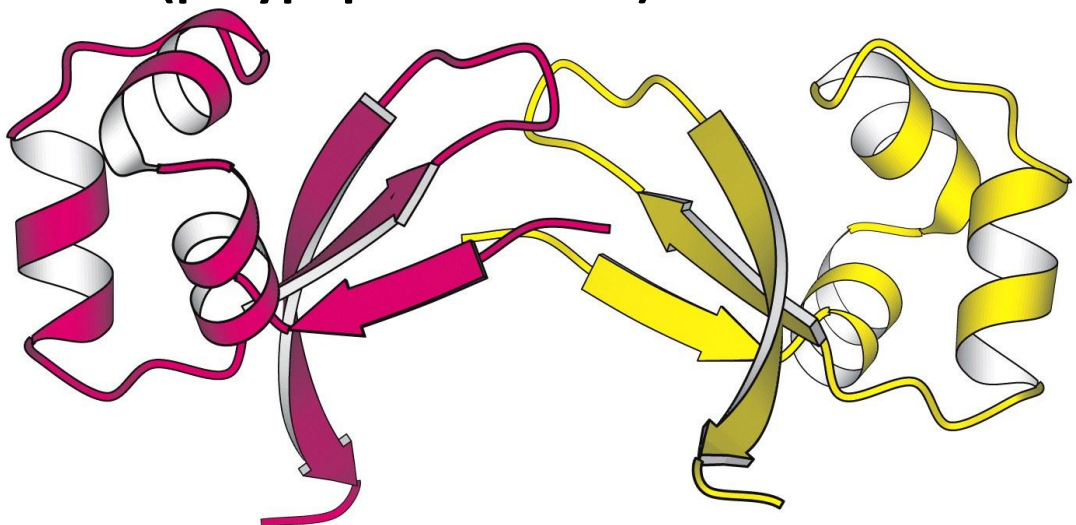


Quaternary Structure

So far, we have looked at p*rimary structure* (the amino acid sequence), s*econdary structure* (the spatial arrangement of amino acids residues that are nearby in the sequence) and t*ertiary structure (*the spatial arrangement of amino acid residues that are far apart in sequence and disulfide bonds).

Quaternary structure describes proteins with *more than one* polypeptide chain.

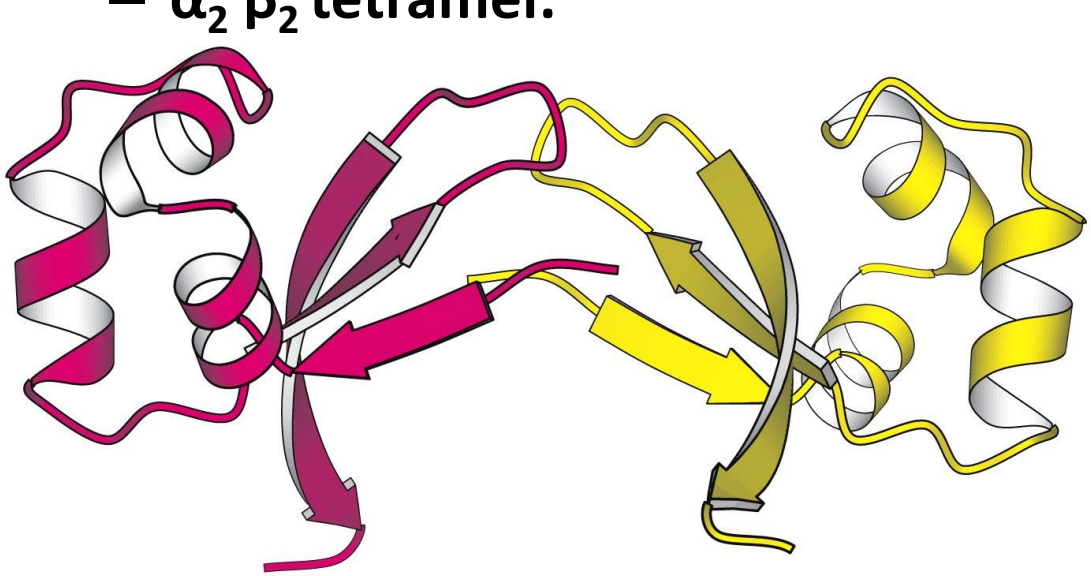
- **Each folded three-dimensional polypeptide chain is referred to as a *subunit*.**
- **A protein consisting of two subunits (polypeptide chains) is known as a dimer.**
- **Three subunits is a trimer.**
- **Four subunits a tetramer etc.**



Bacteriophage Cro protein.

Quaternary Structure

- **More than one type of subunit can be present in a protein.**
  - **Homomeric (one type of subunit), heteromeric (more than one type of subunit).**
- **One example is hemoglobin that contains two α subunits and two β subunits.**
  - **α_2 β_2 tetramer.**



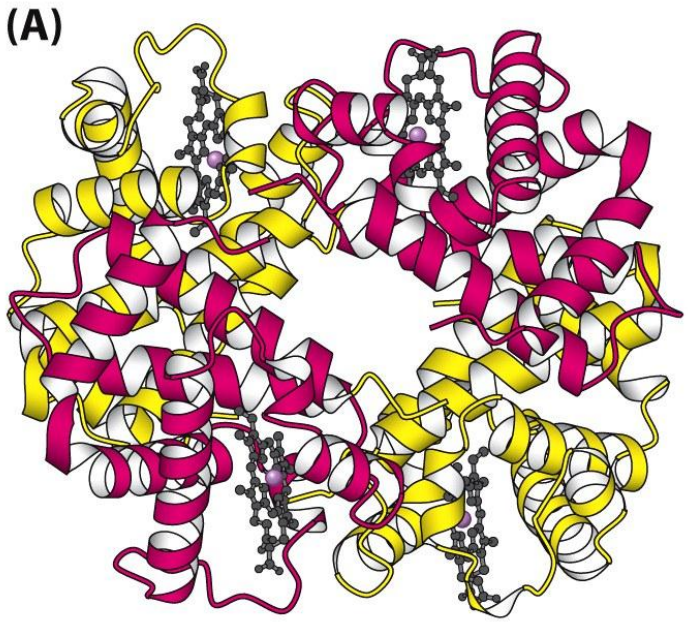


Figure 2.48
***Biochemistry*, Seventh Edition**

Bacteriophage Cro protein: homomeric dimer.

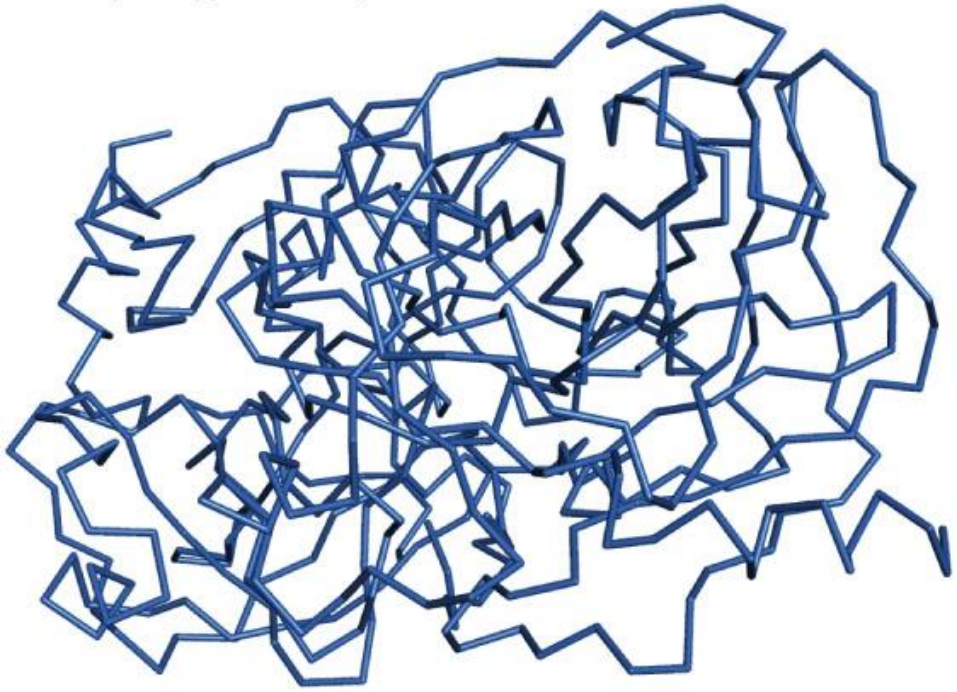
Hemoglobin: heteromeric tetramer.

How to view a protein?

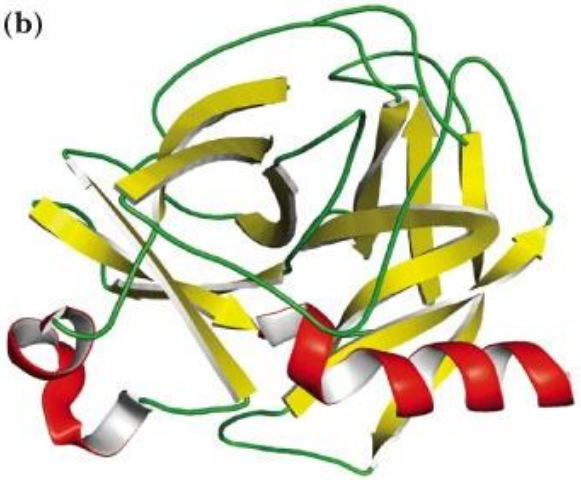
- The tertiary structure of a protein may be viewed in several ways:
  - Backbone only
  - Backbone plus side chains
  - Ribbon structure
  - Space-filling structure
- Each of these is an abstraction.

How to view a protein?

(a) Chymotrypsin tertiary structure

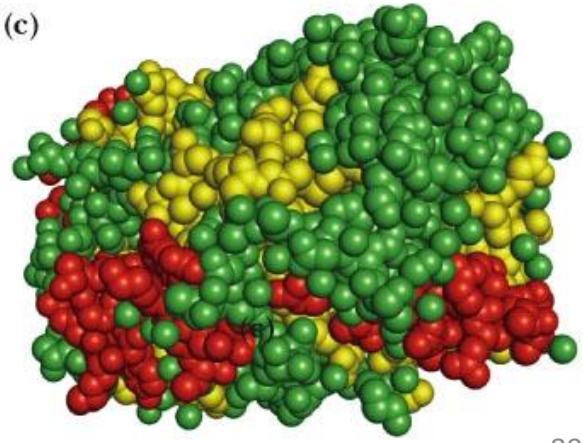


(b)



Chymotrypsin ribbon

(c)



Chymotrypsin space-filling model

Folding of the polypeptide into a compact, roughly spherical conformation creates the tertiary structure.

Biochemistry by Garret and Grisham, 5th ed.

Do Proteins Have Chemical Groups Other Than Amino Acids?

Proteins may be "conjugated" with other chemical groups

- **If the non-amino acid part of the protein is important to its function, it is called a prosthetic group.**
- **Be familiar with the terms: glycoprotein, lipoprotein, nucleoprotein, phosphoprotein, metalloprotein, hemoprotein, flavoprotein.**

Do Proteins Have Chemical Groups Other Than Amino Acids?

TABLE 5.5 Some Prominent Post-Translational Modifications Found in Proteins

Name	Nonprotein Part	Amino Acid Side Chain Modified	Examples
Phosphorylation	$-PO_3^{2-}$	S, T, Y	Hormone receptors, regulatory enzymes
Acetylation	$-CH_2COO^-$	K	Histones, metabolic enzymes
Methylation	$-CH_3$	K, R	Histones
Acylation	Palmitic acid	C	G-protein-coupled receptors
Prenylation	Prenyl group	C	Ras p21
ADP-ribosylation	ADP-ribose	H, R	G proteins, eukaryotic elongation factors
Adenylylation	AMP	Y	Glutamine synthetase

Biochemistry by Garret and Grisham, 5th ed.

Do Proteins Have Chemical Groups Other Than Amino Acids?

TABLE 5.6 Some Common Conjugated Proteins

Name	Nonprotein Part	Association	Examples
Lipoproteins	Lipids	Noncovalent	Blood lipoprotein complexes (HDL, LDL)
Nucleoproteins	RNA, DNA	Noncovalent	Ribosomes, chromosomes
Glycoproteins	Carbohydrate groups	Covalent	Immunoglobulins, LDL receptor
Metalloproteins and metal-activated proteins	Ca^{2+}, K^{+}, Fe^{2+}, Zn^{2+}, Co^{2+}, others	Covalent to noncovalent	Metabolic enzymes, kinases, phosphatases, among others
Hemoproteins	Heme group	Covalent or noncovalent	Hemoglobin, cytochromes
Flavoproteins	FMN, FAD	Covalent or noncovalent	Electron transfer enzymes

Biochemistry by Garret and Grisham, 5th ed.