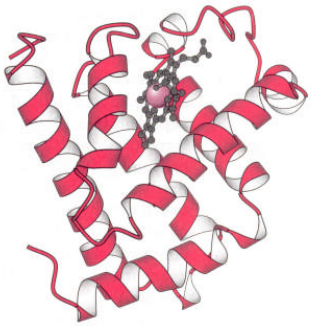
Protein Structure



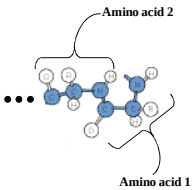
Hierarchy of Protein Structure

	Structural element	Description
1°	Primary structure	amino acid sequence of protein
2°	Secondary structure	helices, sheets, turns and loops
	Super-secondary structure	association of secondary structures
	Domain	independently stable structural unit
3°	Tertiary structure	folded structure of whole polypeptide • includes disulfide bonds
4°	Quaternary structure	assembled complex (oligomer) • homo-oligomeric (1 protein type) • hetero-oligomeric (>1 type)

Primary Structure

Linear amino acid sequence

-Can be chemically sequenced
Sanger – insulin 1955
-Can usually be 'translated' from gene
NB - inteins



Equine hemoglobin primary structure

VLSAADKTNVKAAWSKVGGHAGEYGAEALERMF
LGFPTTKTYFPHFDLSHGSAQVKAHGKKVADGL
TLAVGHLDDLPGALSDLSNLHAHKLRVDPVNFK
LLSHCLLSTLAVHLPNDFTPAVHASLDKFLSSV
STVLTSKYR

Secondary Structure

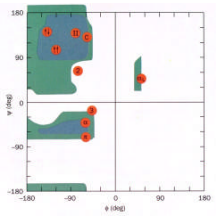
Defined by main chain angles

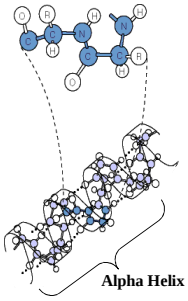
- **Helix**
- **Sheet**
- **Turn**

} **Distinct hydrogen bonding patterns**

- **Loop (or coil)**

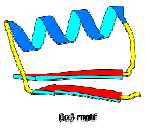
Ramachandran Plot



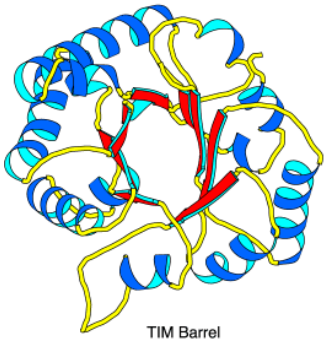


Alpha Helix

Super-Secondary Structure



TIM barrel composed of strand-helix-strand motifs



TIM Barrel
(7TIM)

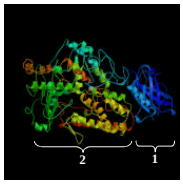
Tertiary Structure

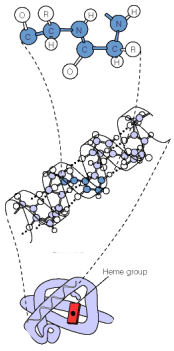
Three main categories:

- **all alpha**
- **all beta**
- **alpha/beta**

May contain one or more domains

Lipoxygenase

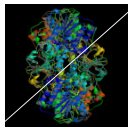




Quaternary Structure

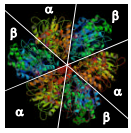
Homodimer

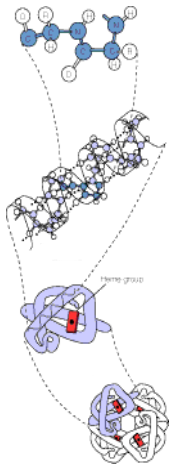
S-adenosyl homocysteine hydrolase



Homotrimer of heterodimers

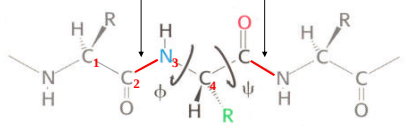
F_0F_1 ATPase



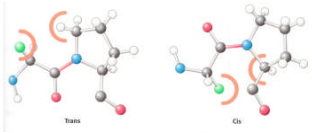


Main Chain Angles (Review)

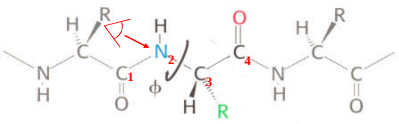
Omega (peptide bond) is ~180°
and can be 0° for proline



Omega is angle between two planes:
-Plane made by atoms 1,2,3
-Plane made by atoms 2,3,4



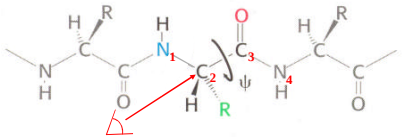
Main Chain Angles (Phi)



Phi is angle between two planes:
-Plane made by atoms 1,2,3
-Plane made by atoms 2,3,4

No Phi for proline

Main Chain Angles (Psi)



Psi is angle between two planes:
-Plane made by atoms 1,2,3
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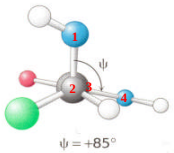
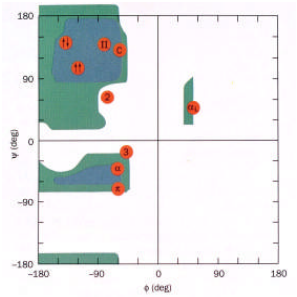
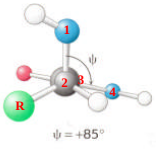


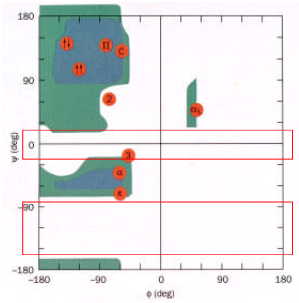
Ramachandran Plot



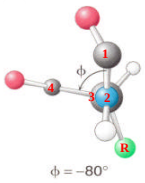
Describes allowable areas for 18 amino acids (not G and P)

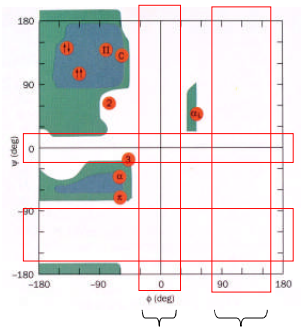
Psi Restrictions





Phi Restrictions

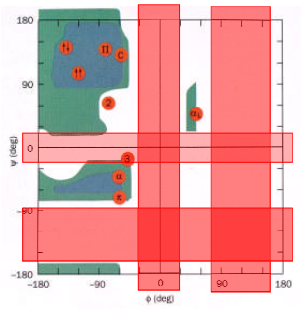




Clash between C1 and C4

Clash between C1 and R

1,4 Interactions Limit Main Chain Conformational Space



Secondary Structure Elements

alpha-helix

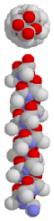
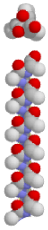
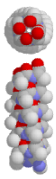
beta-sheet

- Helices (310, alpha, pi)
- Sheets (parallel, anti-parallel)
- Turns (beta, gamma)
- Loop/Coil (everything else)

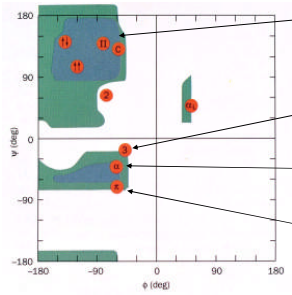
ribonuclease A

coil
(usually exposed on
the surface of proteins)

Helices

	alpha	3.10	pi
			
amino acids per turn:	3.6	3.0	4.4
frequency	~97%	~3%	rare
H-bonding	*i*, *i*+4	*i*, *i*+3	*i*, *i*+5

Helical Main Chain Angles



Collagen, PolyProline

3_{10} Helix

Alpha Helix

Pi Helix

α-helices

-Local interactions

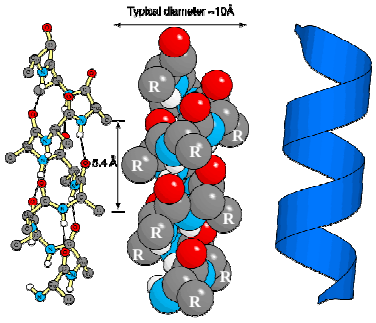
-Right handed
rise per residue, 1.5 Å

-Residue per turn, 3.5Å

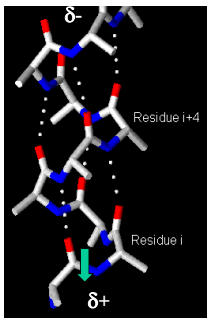
-Alpha helices are about 10 residues on average

-Side chains staggered

-Linus Pauling (Nobel Prize in Chemistry, 1954) figured out the structure of alpha-keratin helix.



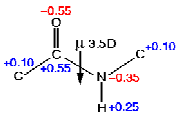
α-helix Dipole Moment

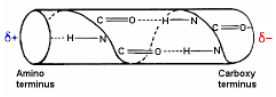


Dipole moment

-Hydrogen bond between C=O(i).....H-N(i+4)

-Dipole moment arises due to the orientation of peptide bond (3.5 Debye)





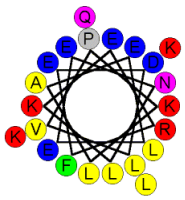
Helical Wheels

Helical Wheel

- a tool to visualize the position of amino acids around an alpha-helix

- allows for quick visualization of whether a side of a helix posses specific chemical properties

- example shown is a helix that forms a **Leucine-Zipper**



Hydrophobic residues on one side interact with helix displaying same pattern

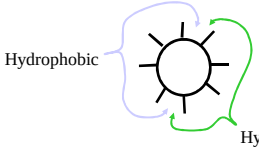
http://cti.itc.virginia.edu/~cmg/Demo/wheel/wheelApp.html

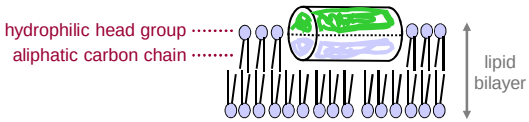
Amphipathic Helices

***Amphipathic**: hydrophilic & hydrophobic*

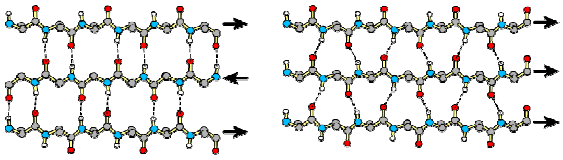
- these helices posses hydrophilic amino acids on one side and hydrophobic residues on the other.

-these α-helices can interact with membrane





β-sheets

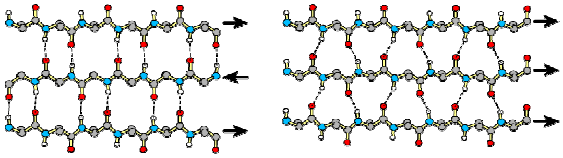


Antiparallel β-sheet

Parallel β-sheet

β-sheets fulfill the hydrogen bonding potential of the main-chain atoms, except at the edges.
Sheet are composed of individual beta strands.
Adjacent strands are usually close in sequence.

β-sheets



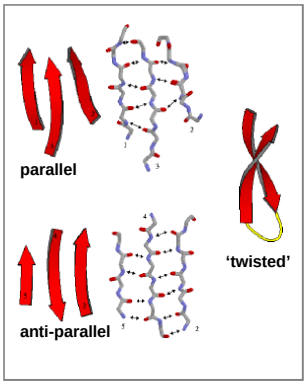
Antiparallel β-sheet

Parallel β-sheet

Properties:

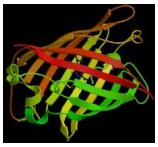
-Parallel beta-strands (3.25 Å between adjacent Ca's)
-Anti-parallel beta-strands (3.47 Å between adjacent Ca's)
-Distance between strands ~4.6 Å
-No significant net dipole moment
-Strands are not flat. They have a characteristic right-handed twist

Right Handed Twist



- beta-sheets can form various higher-level structures, such as a beta-barrel

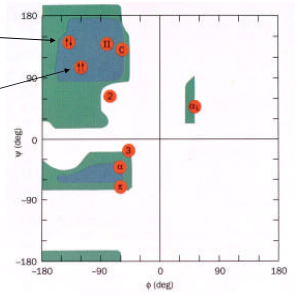
Green Fluorescent Protein (GFP)



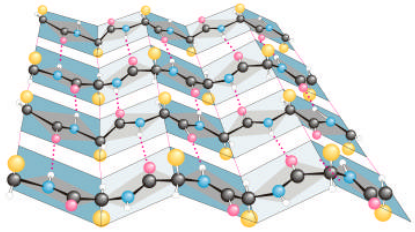
Beta Strand Main Chain Angles

Antiparallel

Parallel



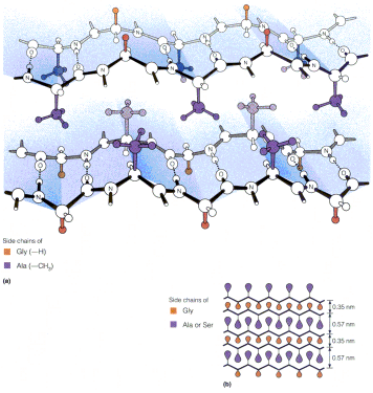
Side Chains Extend Above and Below Beta-Sheets



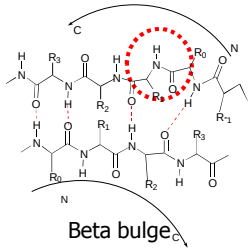
Silk

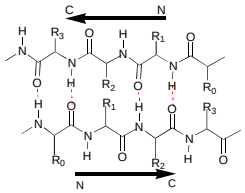
An example of complex beta-sheets: ***Silk Fibroin***

- multiple pleated sheets provide toughness & rigidity to many structural proteins.



Beta Bulge





-Beta bulges occur on the last strand (edge) of an anti-parallel beta sheet
-An additional amino acid is present in the last strand
-Bulges cause bending of otherwise straight anti-parallel beta strands

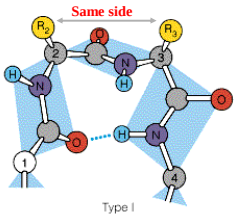
Beta - Turns

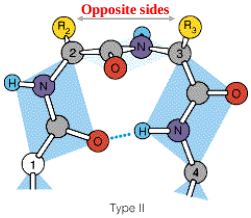
There are two classes of beta-turns:
- type I
- type II

Type I turns have the amino acids on the **same side**

Type II turns have the amino acids on the **opposite sides**

Hydrogen-bonding between backbones of residue 1 and 4

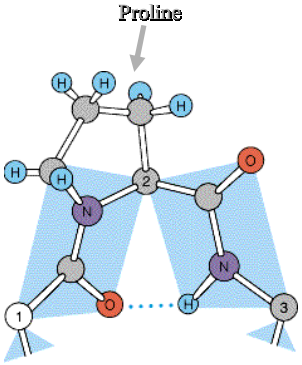




Gamma-Turns

A 3 amino acid turn utilizing proline at the turn.

Hydrogen-bonding with C=O of residue 1 and N-H of residue 2



Conformational Preferences of the Amino Acids

Amino acid	Preference α-helix	β-strand	Reverse turn
Glu	**1.59**	0.52	1.01
Ala	**1.41**	0.72	0.82
Leu	**1.34**	1.22	0.57
Met	**1.30**	1.14	0.52
Gln	**1.27**	0.98	0.84
Lys	**1.23**	0.69	1.07
Arg	**1.21**	0.84	0.90
His	**1.05**	0.80	0.81
Val	0.90	**1.87**	0.41
Ile	1.09	**1.67**	0.47
Tyr	0.74	**1.45**	0.76
Cys	0.66	**1.40**	0.54
Trp	1.02	**1.35**	0.65
Phe	1.16	**1.33**	0.59
Thr	0.76	**1.17**	0.90
Gly	0.43	0.58	**1.77**
Asn	0.76	0.48	**1.34**
Pro	0.34	0.31	**1.32**
Ser	0.57	0.96	**1.22**
Asp	0.99	0.39	**1.24**

Helical Preference

Strand Preference

Turn Preference

Williams, RW et al., Biochim. Biophys. Acta 1987, 916: 200-4

Conformational Preferences of the Amino Acids

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Lys	**1.23**	0.69	1.07
Arg	**1.21**	0.84	0.90
His	**1.05**	0.80	0.81
Val	0.90	**1.87**	0.41
Ile	1.09	**1.67**	0.47
Tyr	0.74	**1.45**	0.76
Cys	0.66	**1.40**	0.54
Trp	1.02	**1.35**	0.65
Phe	1.16	**1.33**	0.59
Thr	0.76	**1.17**	0.90
Gly	0.43	0.58	**1.77**
Asn	0.76	0.48	**1.34**
Pro	0.34	0.31	**1.32**
Ser	0.57	0.96	**1.22**
Asp	0.99	0.39	**1.24**

Extended flexible side chains

Bulky side chains, beta-branched

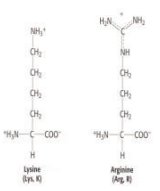
Restricted conformations, side Chain – main chain interactions

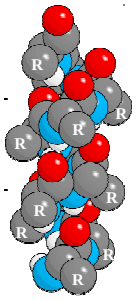
Williams, RW et al., Biochim. Biophys. Acta 1987, 916: 200-4

Helical Preference

Amino acid	Preference α-helix	β-strand	Reverse turn
Glu	**1.59**	0.52	1.01
Ala	**1.41**	0.72	0.82
Leu	**1.34**	1.22	0.57
Met	**1.30**	1.14	0.52
Gln	**1.27**	0.98	0.84
Lys	**1.23**	0.69	1.07
Arg	**1.21**	0.84	0.90
His	**1.05**	0.80	0.81

Extended flexible side chains

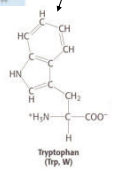




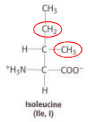
Strand Preference

Amino acid	Preference α-helix	Preference β-strand	Preference Reverse turn
B Val	0.90	1.87	0.41
B Ile	1.09	1.67	0.47
Tyr	0.74	1.45	0.76
Cys	0.66	1.40	0.54
Trp	1.02	1.26	0.65
Phe	1.16	1.33	0.59
B Thr	0.76	1.17	0.90

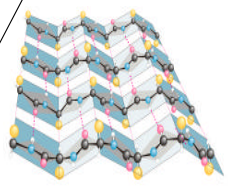
Bulky side chains, beta-branched



Tryptophan (Trp, W)



Isoleucine (Ile, I)

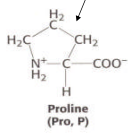


Bulky residues better tolerated above and below sheet

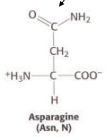
Turn Preference

Amino acid	Preference α-helix	Preference β-strand	Preference Reverse turn
Gly	0.43	0.58	1.77
Asn	0.76	0.48	1.34
Pro	0.34	0.31	1.32
Ser	0.57	0.96	1.22
Asp	0.99	0.39	1.24

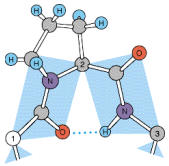
Restricted conformations, side chain – main chain interactions



Proline (Pro, P)



Asparagine (Asn, N)

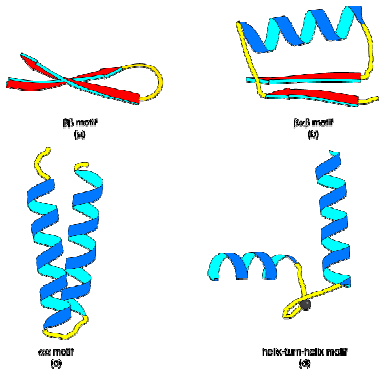


End of Secondary Structure

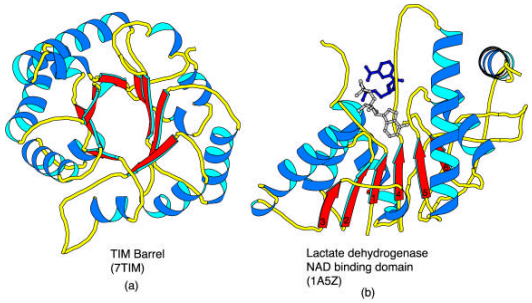
Super Secondary Structure Motifs

These simple arrangements of secondary structural elements account for most protein domains. In all cases the stabilizing interactions occur within a local area of the sequence (this is convenient for evolution).

Note also that all of these motifs are chiral and are observed almost exclusively in these arrangements



Tertiary Structure

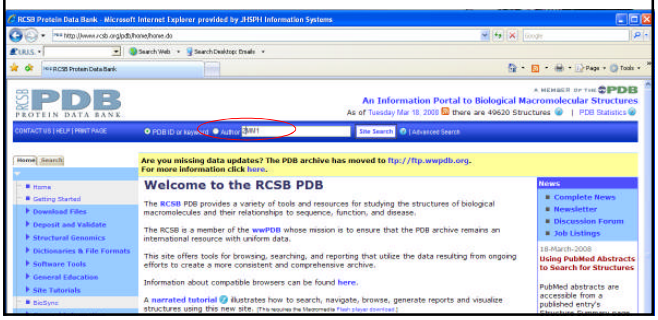


TIM Barrel
(7TIM)
(a)

Lactate dehydrogenase
NAD binding domain
(1A5Z)
(b)

PDB

http://www.rcsb.org/pdb/home/home.do

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2mm1
DOI 10.2210/pdb2mm1/pdb
Title X-RAY CRYSTAL STRUCTURE OF A RECOMBINANT HUMAN MYOGLOBIN MUTANT AT 2.8 ANGSTROMS RESOLUTION
Authors Hubbard, S.R., Hendrickson, W.A., Lambright, D.G., Boxer, S.G.
Primary Citation Hubbard, S.R., Hendrickson, W.A., Lambright, D.G., Boxer, S.G. (1990) X-ray crystal structure of a recombinant human myoglobin mutant at 2.8 A resolution. J.Mol.Biol. 213: 215-218 [Abstract]
History Deposition 1991-02-19 Release 1993-01-15
Experimental Method Type X-RAY DIFFRACTION Data
Parameters Resolution(A) 2.80 R-Value 0.158 (obs.) R-Free n/a Space Group P 3 2 1
Unit Cell Length (A) a 86.20 b 86.20 c 35.60 Angles (°) alpha 90.00 beta 90.00 gamma 120.00
Molecular Description Polymer: 1 Molecule: MYOGLOBIN Chains: A
Images and Visualization
Biological Molecule
Display Options
KiNG
Jmol
WebMol
MBT SimpleViewer*
MBT Protein Workshop
QuickPDB
All Images
* Capable of displaying biological molecules
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