Protein synthesis (Primer)

Central Dogma of Molecular Biology states that information flow from DNA $\Rightarrow$ RNA $\Rightarrow$ protein

DNA is made of phosphonucleotides (phosphoate + sugar + base)

Genetic information is encoded in a string of DNA bases (A,C,G,T)

Hydrogen bond mediated base pairing ($A^\bullet\bullet T, C^\bullet\bullet G$) protects DNA bases from chemical damages allows repair using the undamaged strand as template recombination

Three DNA bases are ultimately translated to one amino acid
The first step in protein synthesis is copying the genetic information stored in DNA to messenger RNA in a process called transcription.
mRNA then undergoes editing, including **base insertion, base deletion and base modifications** --Smith et al, RNA 3, 1105 (1997)

mRNA leaves the nucleus and enters the cytoplasm (in eukaryotes), where ribosome, aminoacyl tRNA ("charged" or "loaded" tRNA) come together to synthesizing a polypeptide chain. This process is called **translation**
Synthesis is done, what next?

Once synthesized, proteins must first fold to stable conformations in order to function, ...

although there are also intrinsically disordered proteins


The folding of a peptide chain minimizes the total free energy of the system, which is a combination of

- entropy change in
  » solvent molecules (usually water)
  » protein (both main chain and side chain)
  » disulfide

- enthalpy
  » van der Waals contact (hydrophobic effects)
  » hydrogen bonding interaction (intramolecular as well as protein-water)
  » electrostatic interaction
  » disulfide
van der Waals interaction

- Arise from interactions from transient fluctuating dipole moments
- Attractive at long distances, repulsive at short distances
- Also called London dispersion force, it is usually modeled using 12-6 Lennard-Jones potential

\[ E = \frac{A}{r^{12}} - \frac{B}{r^{6}} = \varepsilon \left[ \left( \frac{r_m}{r} \right)^{12} - 2 \left( \frac{r_m}{r} \right)^{6} \right] \]

for C-C pair, \( \varepsilon \sim 0.05 - 0.2 \) kcal/mol, \( r_m \approx 3.5 - 4 \) ang

Optimal distance between 2 non-interacting atoms is the bottom of the potential energy function.

<table>
<thead>
<tr>
<th>Atom</th>
<th>Radius (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>1.20</td>
</tr>
<tr>
<td>Carbon</td>
<td>1.7</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>1.55</td>
</tr>
<tr>
<td>Oxygen</td>
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</tr>
<tr>
<td>Fluorine</td>
<td>1.35</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.9</td>
</tr>
<tr>
<td>Sulphur</td>
<td>1.85</td>
</tr>
<tr>
<td>Chlorine</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Hydrogen Bond

A sharing of a hydrogen by two electronegative heavy atoms

The hydrogen is covalently attached to one of the two heavy atoms (donor) and interacts electrostatically with the electron lone pair of the other heavy atom (acceptor).

In proteins, hydrogen bonds typically occur as N—H *** O = C (68%), although other combinations are possible and sulfur and carbon atoms can also participate in a hydrogen bond.
Hydrogen bonds are directional and defined by geometry.

stabilization by one hydrogen bond

\[ \Delta G \approx -0.6 \text{ kcal/mol} \]

Pace et al, Faseb J 10, 75 (1996)

McDonald & Thornton, JMB, 238, 777 (1994)

Park & Saven, Proteins, 60, 450 (2005)
Electrostatic interaction

Coulombic interaction between positively and negatively charged side chains
Also called salt bridges, contributes to the stability of protein structure

\[ E_{elec} \propto \frac{q_1 q_2}{\varepsilon r_{12}} \]

where epsilon is the dielectric constant
N.B. this epsilon is different from the epsilon in van der Waals force

Epsilon = 80 in water, whereas epsilon ~ 4 in lipid (or inside the protein core)

Hence, salt bridges exposed to the solvent is not as energetically significant
as salt bridges shielded from the solvent

E.g. salt bridge on barnase
Asp12/Arg110 = 1.25 kcal/mol
Asp8/Arg110 pair = 0.98 kcal/mol

Horovitz, et al JMB 216, 1031 (1990)
Secondary structure

Recurring patterns of main chain conformations stabilized by hydrogen bonds

There are two types of secondary structure, i.e. alpha-helix and beta-sheet, characterized by different hydrogen bonding patterns.

They are each compatible with their characteristic sets of main chain dihedral angles.

The part of a protein without regular secondary structure is often called a random coil and includes turns, loops, and coils, but these don’t necessarily have to be random.

DSSP – 2nd structure determination
Prediction of alpha helix

Pauling and Corey twisted the peptide backbone to create a regular structure consistent with the fiber diffraction pattern of alpha keratin.

They assumed that
i) peptide bond is exactly flat
ii) main chain conformation is independent of sequence

The hydrogen bonding pattern gives rise to a structure that is highly repetitive and stable.

Pauling et al, PNAS 37, 205 (1951)
**Gross anatomy of alpha helix**

Alpha helix consists of a series of main chain hydrogen bonds involving the main chain oxygen of \(i\)th residue (written as O\((i)\)) and the amide nitrogen of \((i+4)th\) residue (written as N\((i+4)\)) : O\((i)\) --- N\((i+4)\)

- e.g. 1\(\rightarrow\)5, 2\(\rightarrow\)6, 3\(\rightarrow\)7, …

Branden & Tooze
• Helices make up ~ 30% of all globular proteins
• Are often found on the surface, and many are bent toward the center

• Helix has a pitch of 5.4 Å (i.e. each turn advances the chain by this amount), 3.6 amino acids per turn (i.e. 100° between adjacent Calpha), giving a rise of 5.4 / 3.6 = 1.5 Å per amino acid

• The residues of a helix occupy a narrow region of the Ramachandran plot
  – typical values of phi = -60°, psi = -50°

• The first residue of a helix is called the N-cap
• The last residue of a helix is called the C-cap
• Side chains point toward N-terminus
Two other less common forms of helix

- $3_{10}$ helix: $O(i) \rightarrow N(i+3)$ (occurs at the ends of alpha-helices)
  » Dipoles do not line up, side chain packing unfavorable
  » The name refers to the number of residues and atoms between hydrogen bonding atoms

- $\pi$ helix: $O(i) \rightarrow N(i+5)$ (not observed in protein)
Heptad repeat

• 3.6 residues per turn give rise to **sided-ness** in a helix—the residues on one side of the helix may be different from the residues on the other side.

• Sequences are often displayed on a “helical wheel” down the axis.

• The characteristic pattern in a helix may repeat itself every seven residues, resulting in a heptad repeat.

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**Glucose transporter**
Helical wheels

Green - hydrophobic
Blue - polar
Red - charged

Buried

Partially buried
“amphipathic” or
“amphiphilic”

Exposed
Distribution of residues along a helix

N-, C-caps: “first and last residues whose alpha carbon lies approximately in the cylinder formed by the helix backbone and approximately along the helical spiral path”

Richardson & Richardson, Science 240, 1648 (1988)
The distribution of different amino acids along the helix is position-dependent

Asn has a strong preference for the N-cap position
Pro has an above average frequency at the beginning of a helix and serves as a helix initiator
Gln cannot replace Asn (incorrect side chain geometry)
C-terminal capping residues terminate a helix
Gly is the most common C-cap residue (34% of the time)
Ala has a smooth and favorable distribution throughout the helix
Positively charged residues (K+R+H) occur more often near the C-terminus
Negatively charged residues (D+E) occur more often near the N-terminus

Ala, Leu, Met are preferred within helix
Branched residues (Val, Ile, Thr) are poor helix formers
Parker and Hefford, Protein Engineering 10, 487, (1997)
Pro disrupt helix

Inclusion of a proline severely disrupts the progression of a helix and destabilizes the structure.

The main chain dihedral angles of Pro (\(\phi=-60^\circ\), \(\psi=-55^\circ\) or \(145^\circ\)) are compatible with an alpha helix.

However, Pro has no amide hydrogen for use as a donor in hydrogen bond.

In the helix center, the cyclic ring of Pro (pyrrolidine) pushes away the preceding (N-terminal) turn of the helix by \(~1\AA\) producing a 30° bend and breaking the next H-bond as well.
Gly is common in membrane proteins

Gly is disruptive as a helix residue in globular proteins but common in integral membrane proteins embedded in the lipid bilayer of the cell

GXXXG motif – Russ & Engelman, JMB 296, 911 (2000)

Transmembrane (TM) domain of membrane proteins often comprises helices TM helices often contain Gly and Pro, which play important functional roles
Helix propensity

• Helix propensity refers to how much an amino acid stabilizes a helix

• Statistically, this information may be inferred by measuring the frequency with which a given amino acid occurs within a helix in known proteins
  – Some amino acids (e.g. Ala) occur in a helix more often than others (e.g. Ser)
  – Thus, we conclude Ala stabilizes the helix more than Ser

• Experimentally, helix propensity can be measured by comparing the stability of helices that are identical in sequence except at one location
  1. constructing short peptides (e.g. Ac-LLLLLXLLLLLL) where L is Leu, X is random residue
  2. measure the helix content of the peptide by CD

Denatured  Structured
Measuring the helix content of a peptide

• When a protein/peptide unfolds, it also loses its secondary structure
• Circular dichroism (CD) spectroscopy can estimate the secondary structure by measuring dichroism in far UV wavelengths (< 250 nm)
• Repeated measurements at progressively elevated temperature can be used to measure the melting temperature (Tm)
• Isolated helices of short peptides are often unstable
• Measurements were made both using peptides and proteins and yield the similar results

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>$\Delta \Delta G_\alpha$ (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ala</td>
<td>-0.77</td>
</tr>
<tr>
<td>Aib</td>
<td>-0.69</td>
</tr>
<tr>
<td>Arg</td>
<td>-0.68*</td>
</tr>
<tr>
<td>Lys</td>
<td>-0.65*</td>
</tr>
<tr>
<td>Leu</td>
<td>-0.62</td>
</tr>
<tr>
<td>Met</td>
<td>-0.50</td>
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<tr>
<td>Trp</td>
<td>-0.45</td>
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<tr>
<td>Phc</td>
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<tr>
<td>Ser</td>
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<tr>
<td>Gln</td>
<td>-0.33</td>
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<tr>
<td>Glu</td>
<td>-0.27*</td>
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<tr>
<td>Cys</td>
<td>-0.23</td>
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<td>Ile</td>
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<tr>
<td>Tyr</td>
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<td>Asp</td>
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<td>Val</td>
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<tr>
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</tr>
<tr>
<td>Pro</td>
<td>$\sim$3</td>
</tr>
</tbody>
</table>


O’Neil and DeGrado, Science 250, 646 (1990)
Origin of helix propensity

• The differing alpha helix propensity derives from the entropic difference between folded and unfolded states
  – Creamer & Rose, PNAS 89, 5937 (1992)

• Two competing effects go into folding an alpha helix
  – enthalpy of hydrogen bonds in a helix wins (~ -1 kcal/mol per residue) when helix contains Ala
  – entropy of unfolded peptide backbone (~ 1.5 – 2 kcal/mol per residue compared to Ala) wins when the peptide contains Gly
  – for all residues other than Gly, the initial main chain entropy is less, and side chain degrees of freedom is also lost upon folding
Additive dipole moment

Helix has a net positive charge near the N-terminus and a net negative charge near C-terminus

Branden & Tooze
Salt bridge stabilizes helix

C-peptide of ribonuclease A forms a weakly stable helix at 1 °C

Helix stability depends strongly on pH

Deprotonated E9, E2 and protonated H12 are required for stability

Salt bridge E9-H12 stabilizes the helix

The salt bridge stabilizes one turn of the alpha-helix, helping to nucleate it

Bierzynski et al, PNAS79, 2470 (1982)
A net +0.5 charge at the N-terminus and a net -0.5 charge at the C-terminus

Idealized Helix

Groupwise free energies of interactions (in 0.15 M NaCl):

- N-cap: 1 to 2 kcal/mol
- C-cap: -0.5 kcal/mol
- Charge-macrodipole electrostatic: -0.5 kcal/mol
- Side chain–side chain electrostatic: -0.5 kcal/mol
- Range of helix propensities: ~1 kcal/mol
- Dehydration of an isobutyl group (Leu): 2 to 5 kcal/mol

Length distribution

- The distribution of helix lengths is periodical.
- The maxima appear with a periodicity of 3-4 amino acids.

Acevedo & Lareo, J Integ Biol 9, 391 (2005)

Penel, et al. JMB 293, 1211 (1999)
• Length periodicity is caused by the amphipathic nature of many helices.
  – Helices are often found on the surface of the proteins and are therefore amphipathic (i.e. amphiphilic).
  – The N-cap usually faces the protein.
  – If there are integer number of turns in the helix, the C-cap will also face the protein, i.e. the same side as the N-cap, which is favorable

Penel, et al. JMB 293, 1211 (1999)
Beta Sheet

Pauling and Corey predicted the beta sheet structure in order to explain the fiber diffraction pattern of beta keratin (e.g. spider silk)

CONFIGURATIONS OF POLYPEPTIDE CHAINS WITH FAVORED ORIENTATIONS AROUND SINGLE BONDS: TWO NEW PLEATED SHEETS

BY LINUS PAULING AND ROBERT B. COREY

GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA, CALIFORNIA

Communicated September 4, 1951

A. Trans-trans Configurations:
1. CH trans to NH, CH trans to CO. Pitch 6.68 Å, 2 residues per turn. Lateral CO and NH suited to forming the two pleated sheets described below.
Not stabilized by hydrogen bond between nearby residues. Rather the hydrogen bonds come from distant parts of a protein. These parts are each called “beta strand”.

The axial distance between adjacent residues is \(~3.4\, \text{Å}\); or equivalently, the beta sheet has a pitch of \(~6.8\, \text{Å}\). This is “extended” compared to helical conformation, where the rise was \(1.5\, \text{Å}\) per residue.
Structural features

- Successive Ca atoms are just above and just below the plane of the sheet, resulting in a “pleated” look.

- Every other side chain is found on the same side of the chain.

- The residues in beta sheet have negative phi values (-140 °) and positive psi values (130 °).
An antiparallel $\beta$-sheet

Hydrogen bonds:
- $N_i \cdots O_j$
- $O_i \cdots N_j$
- $N_{i+2} \cdots O_{j-2}$
- $O_{i+2} \cdots N_{j-2}$

Distances:
- 6.8 Å
- 4.5 Å
Parallel beta sheet

The hydrogen bonds are more evenly spread out but deviate from ideal geometry

Hydrogen bonds

$N_i \text{***} O_j$

$O_i \text{***} N_{j+2}$
Mixed beta sheets are rare (relatively speaking)

Twist in the sheet

When seen from the side, the beta sheet is twisted counter-clockwise (i.e. left-handed) by about 30° per strand (However, if seen from the ends, the twist is twisted clockwise i.e. right-handed)

No satisfactory explanation for this twist has been found

Parallel sheets are usually buried and less twisted than antiparallel sheets, suggesting that it is energetically less stable
Beta sheet propensity

Different amino acids have different beta-sheet propensity


Beta sheet propensity can be measured by substituting a residue on a strand and comparing the stability of the mutant to that of wild type by CD single of minimum at 218 nm
cf. alpha helix has two minima at 208 nm and 222 nm

B1 domain of protein G
no secondary structure

secondary structure

Beta branched side chains favor beta-sheet formation

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>ΔΔG (kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thr</td>
<td>1.1</td>
</tr>
<tr>
<td>Ile</td>
<td>1.0</td>
</tr>
<tr>
<td>Tyr</td>
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</tr>
<tr>
<td>Phe</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Val</strong></td>
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<tr>
<td>Met</td>
<td>0.72</td>
</tr>
<tr>
<td>Ser</td>
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</tr>
<tr>
<td>Trp</td>
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<td>Cys</td>
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<td>Asp</td>
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</tr>
<tr>
<td>Gly</td>
<td>-1.2</td>
</tr>
<tr>
<td>Pro</td>
<td>&lt;-3</td>
</tr>
</tbody>
</table>
Origin of beta sheet propensity

\[ \Delta S = k_B \log \frac{W_B}{W} \]

where \( W \) is the amount of conformation space available to an amino acid when the protein is denatured, and \( W_B \) is the corresponding available conformation space when the protein is folded to a beta sheet

Street and Mayo, PNAS 96, 9074 (1999)
The dominant factor for intrinsic beta sheet propensity is the avoidance of steric clashes between the side chain of an amino acid and its local backbone (i.e. entropic)

Coulombic and solvation effects are less important.

– Street and Mayo, PNAS 96, 9074 (1999)
Context dependent beta sheet propensity

The beta sheet propensity also differs depending on the location of a beta strand within a sheet


Not a good correlation!
There is a correlation with the non-polar solvent accessible surface area.

The interaction with the surrounding beta structure is a dominant force for determining beta sheet propensity—i.e. the tertiary structure is an important determinant of beta sheet propensity.
Turns, loops and bends

- **Nonrepetitive** structural elements include tight turns, bulges, bends and random coils. These are all referred to as residues without secondary structure.

- Turns give proteins their compact appearance.
- Tight turns nearly completely reverse the direction of the peptide chain.

- Loops often play important functional roles—the active sites of many enzymes and receptors are made of loop residues.

- Bends in alpha helix allows the helix to “hug” the protein.
- Bulges in edge beta strands are important negative design elements.
Tight turns

- Tight turns include $\delta$, $\gamma$, $\beta$, $\alpha$, and $\pi$ turns comprising 2 – 6 amino acids.

- Beta turns are most common
  - Four consecutive residues $(i - i+3)$ not present in alpha-helix
    i) in which the distance between Ca$(i)$ and Ca$(i+3)$ is less than 7Å
    ii) in which O$(i)$ hydrogen bonds with N$(i+3)$

Richardson, Adv Protein Chem 34, 167 (1981)
Beta turns usually appear on the surface and are often involved in molecular interaction, catalysis and antigenicity, **protein folding and stability**.

- There are six types of beta turns (I, I', II, II', VIa and VIb)
- Due to potential steric clash with the carbonyl oxygen of the preceding residue, the position i+2 in type II turn is always Gly
• Type I’ and II’ turns are mirror images of I and II, i.e. the signs of phi and psi have been reversed
• I and II are most common, but I’ and II’ are energetically more favorable in beta hairpins (to be discussed later)
• I’ and II’ more compatible with the twist of the beta-sheet

Griffiths-Jones, JMB 292, 1051 (1999)
Beta turn in protein folding

In protein G, the second beta hairpin forms first and the formation of the first hairpin is the rate limiting step in folding.

![Diagram of Protein G with first and second hairpins labeled]

**Table 1 Sequences of designed proteins\(^1\)**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>6-ILNGKTLKGET-16</td>
</tr>
<tr>
<td>NuG1</td>
<td>6-FIVIGDRVVV-16</td>
</tr>
<tr>
<td>NuG2</td>
<td>6-VIVLNGTFFTY-16</td>
</tr>
</tbody>
</table>

\(^1\)Residues 1–5 and 17–57 are identical to wild type protein G. Turn residues are shown in bold. All variants of protein G were made and purified using published methods\(^2\). The identity of the proteins were verified by mass spectrometry.

Increase in stability by \(\sim 3.5 – 4 \text{ kcal/mol}\)

Nauli et al, NSB 8, 602 (2001)
• NuG1/NuG2 fold ~100 times faster than wild type
• Destabilize turn #2 by mutating Asp 46 to Ala (D46A with loss of stability by ~ 1.5 kcal/mol)
• Further mutations in turn #1 and #2 result in different folding kinetics

Nauli et al, NSB 8, 602 (2001)
Beta bulge

The region between two consecutive beta strands joined by hydrogen bonds which include two residues on one strand opposite a single residue on the other strand may affect the direction of the strand.

Extra length in the backbone, causes the strand bend out of the plane and the curvature in the sheet is accentuated.

Chan et al, Protein Sci 2, 1574 (1993)
Classic bulge

bulges are more common in antiparallel beta sheet with more than 50% of them occurring in the “classic +” conformation

NH(1) *** CO(X) (average strength)
NH(2) *** CO(X) (weaker than average)
NH(X) *** CO(2) (average strength)

Res #1 in alpha-R conformation, Res #2 & X in beta conformation

Res #1 & X: large hydrophobic
Res #2: small amino acid gly, ala, ser

![Diagram of antiparallel and C+ (150) conformations]
**G1 bulge (second most common)**

Occurs only in antiparallel beta sheets

Res #1 adopts alpha-L conformation and is usually Gly but can be Asn

Res #2 is often charged and its side chain hydrogen bonds with Res X (D, N)

---

**Wide bulge**

Res #1 and #2 do not participate in hydrogen bond

#1 adopts beta conformation, #2 alpha-L conformation

#2 is often Gly, Asn, Asp, and rarely hydrophobic

---

**Table 6. Amino acid preferences for β-bulges**

<table>
<thead>
<tr>
<th>Class</th>
<th>1</th>
<th>2</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>C+</td>
<td>Ile, Val, Leu</td>
<td>Gly, Ala, Ser</td>
<td>Trp, Val, Arg, Ile</td>
</tr>
<tr>
<td>Gl</td>
<td>Gly, Asn</td>
<td>Arg, Lys, Asp, Asn, Asp, His, Glu, Gln</td>
<td>Cys, Ser</td>
</tr>
<tr>
<td>Wide (anti)</td>
<td>Pro, Asp, Glu</td>
<td>Gln, Asn, Asp</td>
<td>Thr</td>
</tr>
</tbody>
</table>
In general, prolines are not very common in the bulge, although they appear at the position just before Res #1

Creating a bulge is not energetically unfavorable

Bulges may be functionally important since some bulges are conserved in homologous proteins

<table>
<thead>
<tr>
<th>C+ Bulge:</th>
<th>X</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>2RHE</td>
<td>37</td>
<td>NVYQQVPGKAPKLIIYYN</td>
</tr>
<tr>
<td>4FAB</td>
<td>36</td>
<td>TLYQPKQPQKVLYIYKV</td>
</tr>
<tr>
<td>2HFL</td>
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<td>NYMYQKSGTPKRWYDT</td>
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<tr>
<td>2IGF</td>
<td>31</td>
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<tr>
<td>2MCP</td>
<td>37</td>
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<td>1REI</td>
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<td>2FB4</td>
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<td>STVNQQLPGMAPKLIIYRD</td>
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<td>1CD4</td>
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<tr>
<td>1CD8</td>
<td>33</td>
<td>CSQLFQPRGASPTFLLLYS</td>
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immunoglobulin domain
Summary of secondary structure propensity

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>α-Helix</th>
<th>β-Strand</th>
<th>Reverse Turn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu</td>
<td>1.58</td>
<td>0.52</td>
<td>1.01</td>
</tr>
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<td>Ala</td>
<td>1.41</td>
<td>0.72</td>
<td>0.82</td>
</tr>
<tr>
<td>Leu</td>
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<td>1.22</td>
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<tr>
<td>Met</td>
<td>1.30</td>
<td>1.14</td>
<td>0.52</td>
</tr>
<tr>
<td>Gln</td>
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<tr>
<td>His</td>
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<table>
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<th>Amino Acid</th>
<th>α-Helix</th>
<th>β-Strand</th>
<th>Reverse Turn</th>
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<td>Asp</td>
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Figure 1-20 Table of conformational preferences of the amino acids. The normalized frequencies for each conformation were calculated from the fraction of residues of each amino acid that occurred in that conformation, divided by this fraction for all residues. Random occurrence of a particular amino acid in a conformation would give a value of unity. A value greater than unity indicates a preference for a particular type of secondary structure. Adapted, with permission, from Table II of Williams, R.W. et al.: Biochim. Biophys. Acta 1987, 916:200–204.