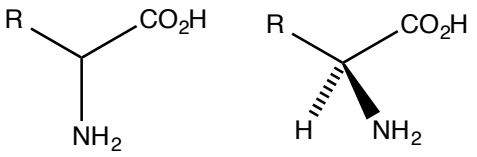
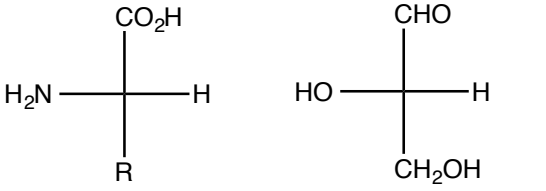
Chapter 25: Amino Acids, Peptides and Proteins

[Sections: 25.1 – 25.8]

1. alpha (α) amino acids





L-amino acids L-Glyceraldehyde

- *amino acids contain an amino group at the α -position relative to the carboxylic acid group*
- *there are 20 naturally-occurring amino acids that vary by the nature of the R group*
- *19 of the amino acids are chiral because of the stereogenic α carbon with the exception of glycine (R=H)*
- *the R groups can be roughly categorized into 4 types: nonpolar, polar, acidic and basic*
- *humans can synthesize 10 of the amino acids from scratch, the other 10 (essential amino acids) must be derived from diet*

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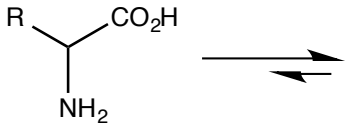
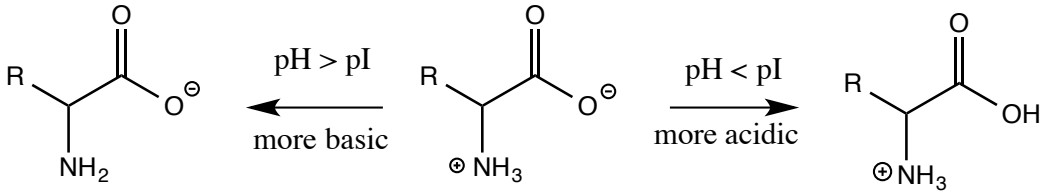
2. Properties of α-amino acids



zwitterionic form



- *pH > IP, the CO2- group remains deprotonated, and the NH_3^+ group becomes deprotonated so that the amino acid is overall negatively charged*

neutral @ isoelectric point (IP =pH of maximum zwitterion content)

- *pH < IP, the CO2- group becomes protonated, and the NH_3^+ group remains protonated so that the amino acid is overall positively charged*

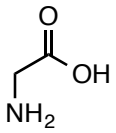
A. What form predominates for lysine (IP = 9.74) in a solution of pH = 6?

B. An amino acid is predominantly negatively charged in a solution of pH = 8.2. What must be true about its IP?

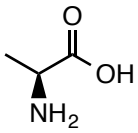
The 20 Common Naturally-Occurring α-Amino Acids found in Proteins

** by the name denotes essential amino acids*

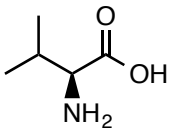
amino acids with non-polar side chains



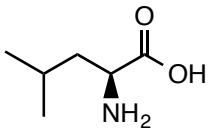
Glycine
Gly or G
IP = 5.97



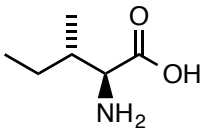
Alanine
Ala or A
IP = 6.01



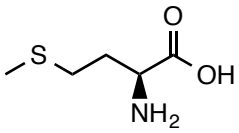
Valine*
Val or V
IP = 5.96



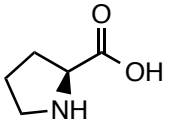
Leucine*
Leu or L
IP = 5.98



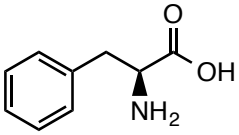
Isoleucine*
Ile or I
IP = 6.02



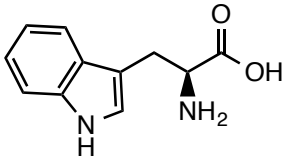
Methionine*
Met or M
IP = 5.74



Proline
Pro or P
IP = 6.30



Phenylalanine*
Phe or F
IP = 5.48



Tryptophan*
Trp or W
IP = 5.89

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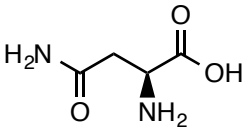
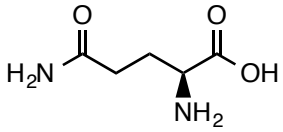
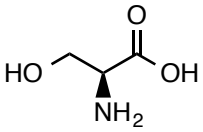
amino acids with polar side chains



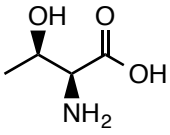
Asparagine
Asn or N
IP = 5.41



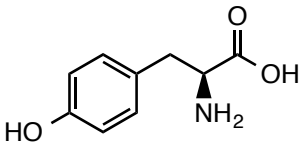
Glutamine
Gln or Q
IP = 5.65



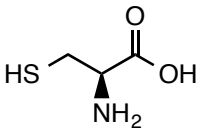
Serine
Ser or S
IP = 5.68



Threonine*
Thr or T
IP = 5.60

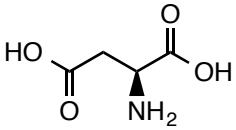


Tyrosine
Tyr or Y
IP = 5.66

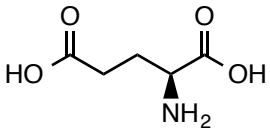


Cysteine
Cys or C
IP = 5.07

amino acids with polar and acidic side chains

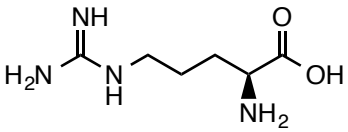


Aspartic Acid
Asp or D
IP = 2.77

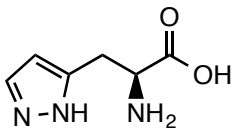


Glutamic Acid
Glu or E
IP =3.22

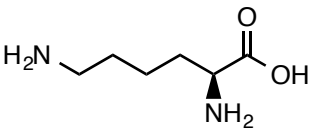
amino acids with polar and basic side chains



Arginine
Arg or R
IP = 10.76

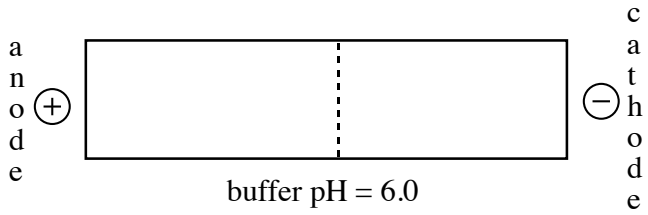


Histidine*
His or H
IP = 7.59



Lysine*
Lys or K
IP = 9.74

3. Analysis of amino acids: electrophoresis

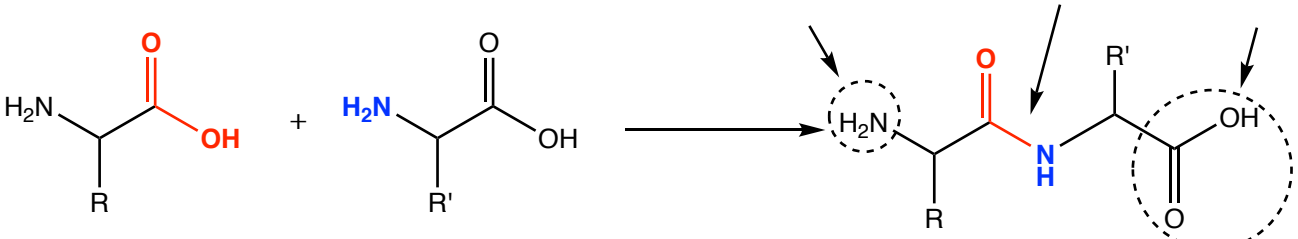


	predominant <u>form</u>	migrates <u>towards</u>
Lysine pI = 9.74		
Alanine pI = 6.02		
Glutamic acid pI = 3.22		
Tyrosine pI =5.66		

- *all 20 amino acids have a unique pI*
- *electrophoresis exploits this difference and the resulting differences in behavior in response to an electric field to separate amino acid mixtures for analysis*
- *in cases where pI's are particularly close (e.g., glycine [MW = 75] pI= 5.97, leucine [MW = 131] pI = 5.98) differences in molecular weight also have an impact on rate/extent of movement*

Problems: 1,2

5. Making peptides

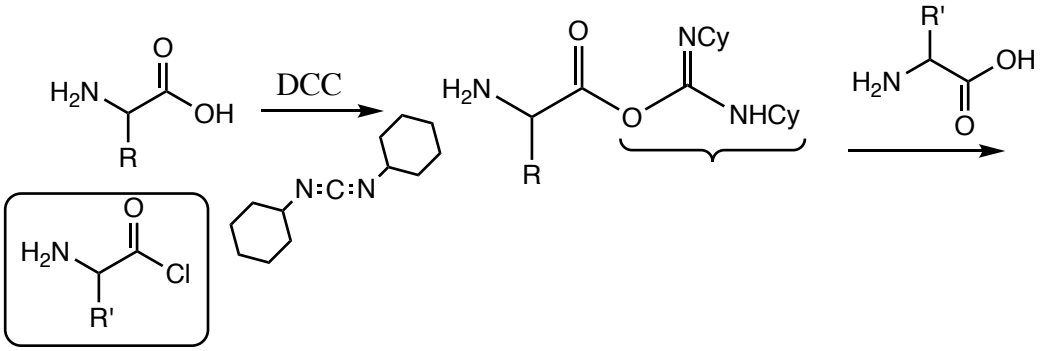


CO_2H group from one α-amino acid

NH_2 group from another α-amino acid

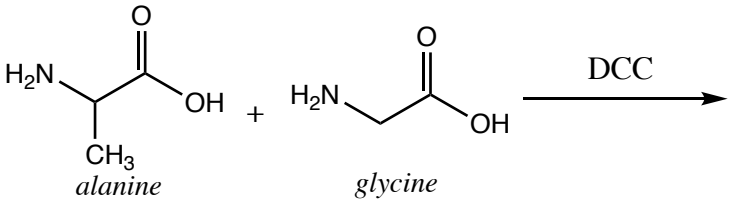
- *amide bond formed: peptide bond*
- *considered to be a "dipeptide"*
- *most often written with amino acid with the "free" NH_2 group at the left (N-terminal residue) and AA with free CO_2H group at the right (C-terminal residue)*

Problem 1: need to convert OH of carboxylic acid group into a leaving group

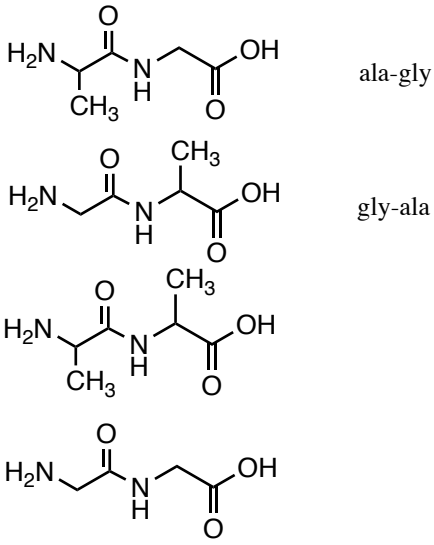


*Problem 2: need to limit reaction to **one** of the CO_2H groups and **one** of the NH_2 groups*

To make a dipeptide from Alanine and Glycine:



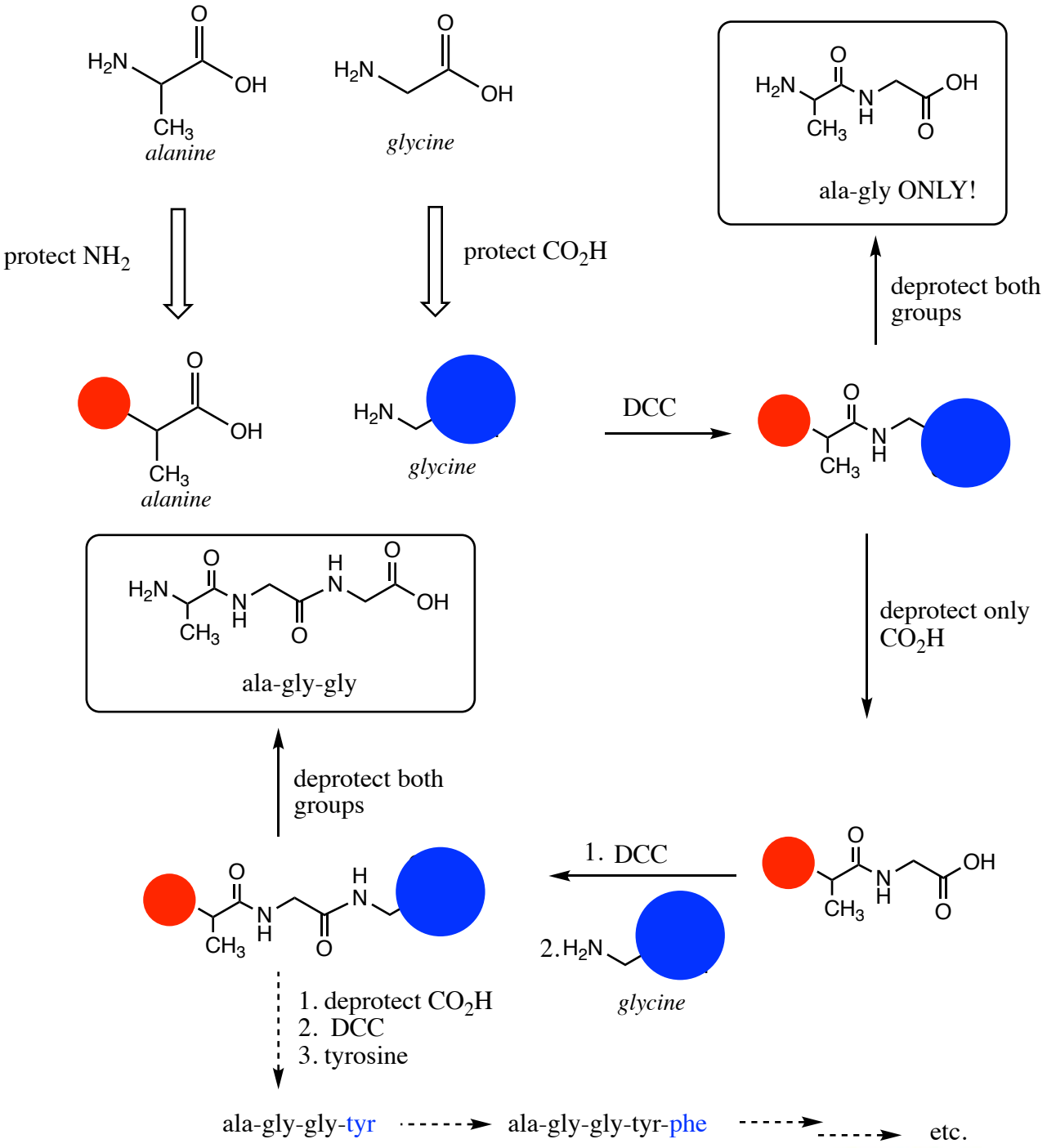
alanine *glycine*



ala-gly

gly-ala

- *in order to ensure that only **one** CO_2H group and **one** NH_2 group react, the other groups must be protected from reaction*

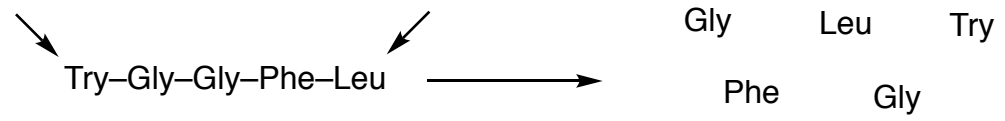


- *using these methods and judicious protection/deprotection, dipeptides, tripeptides, tetra, penta, etc. (i.e., polypeptides) may be constructed sequentially*
- *proteins are polypeptides with ~50 AA residues. Proteins on average have 300 AA residues but can incorporate as many as 30,000*
- *the entire process has been mechanized via the Merrifield synthesis method that makes use of polymer supports*

Determining the primary structure of a peptide

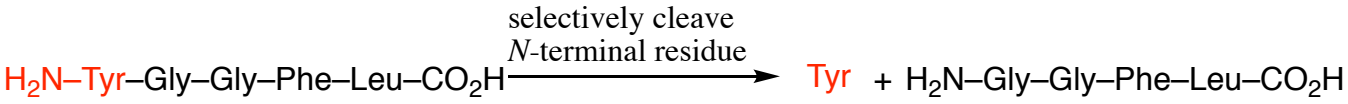
A. Short-chain polypeptides

• *the primary structure of a peptide or protein is the sequence of amino acids (from N-terminal residue to C-terminal residue) that make up the peptide chain*



Leucine enkephalin
found in the brain; interacts with the same receptor as morphine and helps to control pain

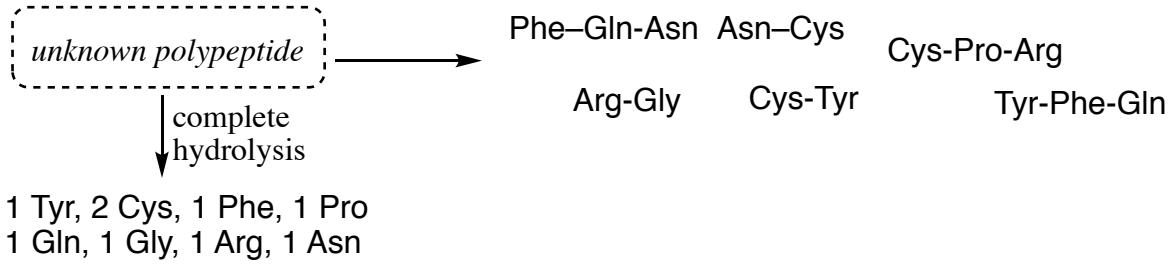
• *complete simultaneous cleavage of all of the peptide bonds is possible*
• *all sequencing information is lost*



• s*equential removal of one AA at a time taking advantage of the free NH_2 group allows for identification of the N-terminal residue specifically*
• *is successful for determining sequence of ~ 50 AA's*
• *similar selective C-terminal residue analysis is also possible*

B. Long-chain polypeptides

• *the primary structure of long chain proteins can be accomplished via partial hydrolysis of the polypeptide into shorter chains (<50 AAs in length) that can be sequenced as above*
• *the individual short chains then need to be stitched together in a logical manner to provide the full sequence*



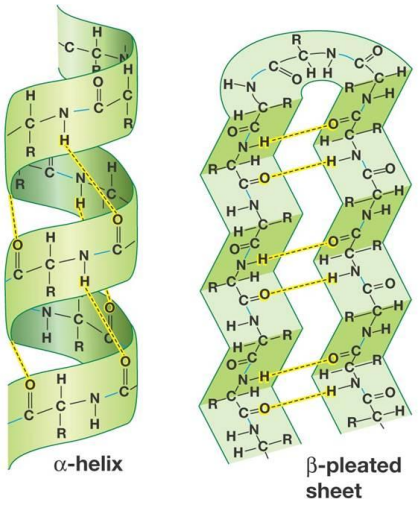
• *polypeptides greater in length than ~ 50 AAs = proteins*

Problems: 5,6

7. Secondary Structures of Proteins

- *Protein secondary structure: general three-dimensional forms of local segments of proteins (e.g., alpha helices and beta sheets)*

- *right-handed*
- *~3.6 AA per turn*
- *NH of each AA is hydrogen bound to the C=O 4 units away*
- *R groups point outward*



- *two or more protein chains line up side by side*
- *hydrogen bonding between NH and C=O of neighboring strand*
- *alkyl groups are generally positioned above and below the sheet*

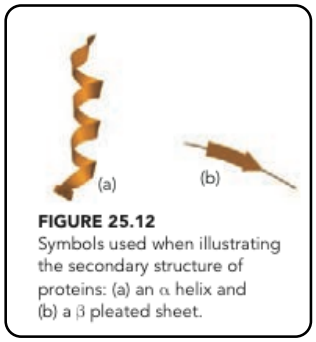


FIGURE 25.12
Symbols used when illustrating the secondary structure of proteins: (a) an α helix and (b) a β pleated sheet.

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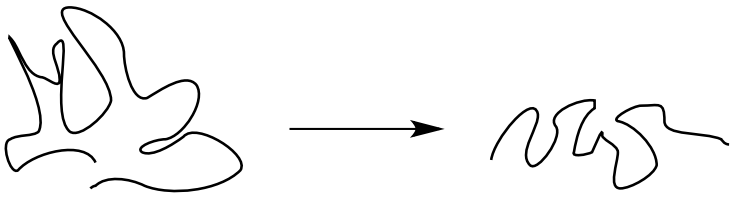
8. Tertiary Structure of Proteins

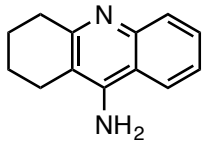
- the protein's overall geometric shape
- *non-regular but not random*
- *most stable arrangement for that sequence of AA residues*
- *hydrogen bonding and S-S [disulfide bonds between cysteine residues] play the major role in structural stability*
- *generally, the structure of enzymes have polar groups directed towards the outside of the structure, and nonpolar groups directed towards the interior which allows for water solubility*
- *change in solvent, pH, or temperature can alter the shape of the protein (unfolding), which is called "denaturization" and is generally irreversible*



- *the tertiary shape of the protein determines its behavior and specificity by creating "pockets" or "active sites" within the structure that recognize specific types of compound*

Example: human cholinesterases in complex with tacrine

- *part of a study to find drugs to aid in the battle against Alzheimer's disease*
- *tacrine was one of the first drugs to be found beneficial in the treatment of Alzheimer's disease, although it has been discontinued since 2013 due to conerns over safety*
- *human cholinesterase (PDB ID 4BDS) is a protein (enzyme) with 529 AA residues*



tacrine