Biochemistry

Macromolecules, Proteins, Amino Acids

Introduction to Biochemistry

Most biologically important macromolecules are polymers, called biopolymers.

Biopolymers fall into three classes:

- proteins,
- polysaccharides (carbohydrates), and
- nucleic acids.

Proteins

Amino Acids

Proteins are large molecules present in all cells.

They are made up of α-amino acids.

There are two forms of an amino acid: one that is neutral (with $-NH_2$ and -COOH groups) and one that is zwitterionic (with $-NH_3^+$ and $-COO^-$ groups).

A zwitterion has both positive and negative charge in one molecule.

There are about 20 amino acids found in most proteins.

Amino Acids

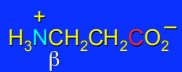
Fundamentals

While their name implies that amino acids are compounds that contain an $—NH_2$ group and a $—CO_2H$ group, these groups are actually present as $—NH_3^+$ and $—CO_2^-$ respectively.

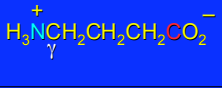
They are classified as α, β, γ, *etc*. amino acids according the carbon that bears the nitrogen.

Amino Acids

an α-amino acid that is an intermediate in the biosynthesis of ethylene



a β-amino acid that is one of the structural units present in coenzyme A



a γ-amino acid involved in the transmission of nerve impulses

The 20 (22) Key Amino Acids

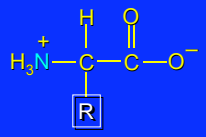
More than 700 amino acids occur naturally, but 20 (22?)of them are especially important.

These 22 amino acids are the building blocks of proteins. All are α-amino acids.

They differ in respect to the group attached to the α carbon.

See Handout.

Amino Acids

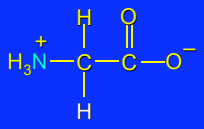


The amino acids obtained by hydrolysis of proteins differ in respect to R (the side chain).

The properties of the amino acid vary as the structure of R varies.

Amino Acids

Glycine
(Gly or G)



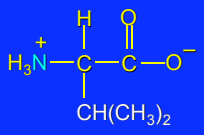
Glycine is the simplest amino acid. It is the only one in the table that is achiral.

In all of the other amino acids in the table the α carbon is a stereogenic center.

Amino Acids

Alanine
(Ala or A)

Amino Acids

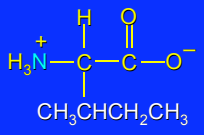


Valine
(Val or V)

Amino Acids

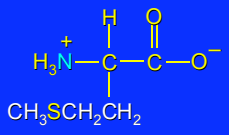
Leucine
(Leu or L)

Amino Acids



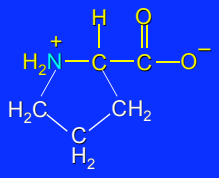
Isoleucine
(Ile or I)

Amino Acids



Methionine
(Met or M)

Amino Acids



Proline
(Pro or P)

Amino Acids

Phenylalanine
(Phe or F)

Amino Acids

Tryptophan
(Trp or W)

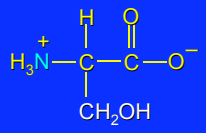
Amino Acids

Asparagine
(Asn or N)

Amino Acids

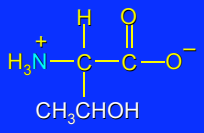
Glutamine
(Gln or Q)

Amino Acids



Serine
(Ser or S)

Amino Acids



Threonine
(Thr or T)

Amino Acids

Aspartic Acid
(Asp or D)

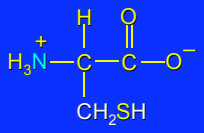
Amino Acids

Glutamic Acid
(Glu or E)

Amino Acids

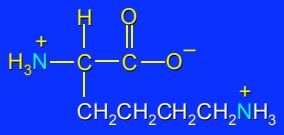
Tyrosine
(Tyr or Y)

Amino Acids



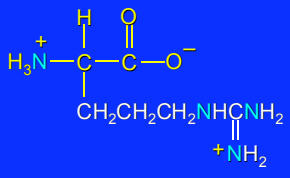
Cysteine
(Cys or C)

Amino Acids



Lysine
(Lys or K)

Amino Acids

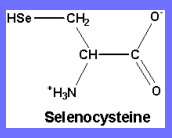


Arginine
(Arg or R)

Amino Acids

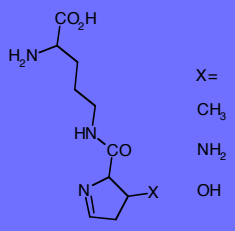
Histidine
(His or H)

Amino Acids: #21
(2001)



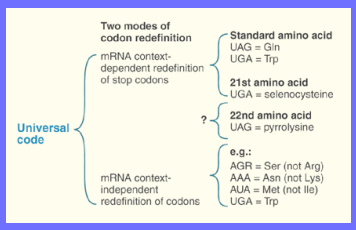
Selenocysteine

Amino Acids: #22
(2002)



Pyrrolysine (4 R, 5 R)

Amino Acids: #22 (2002)



Pyrrolysine

Acid-Base Behavior of Amino Acids

Amino Acids

While their name implies that amino acids are compounds that contain an —NH_2 group and a —CO_2H group, these groups are actually present as —NH_3^+ and —CO_2^- respectively.

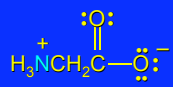
How do we know this?

Properties of Glycine

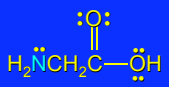
The properties of glycine:

high melting point (when heated to 233°C it decomposes before it melts)
solubility: soluble in water; not soluble in nonpolar solvent

more consistent with this



than this



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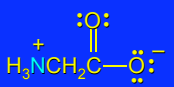

called a *zwitterion* or *dipolar ion*

Acid-Base Properties of Glycine

The zwitterionic structure of glycine also follows from considering its acid-base properties.

A good way to think about this is to start with the structure of glycine in strongly acidic solution, say pH = 1.

At pH = 1, glycine exists in its protonated form (a monocation).

Acid-Base Properties of Glycine

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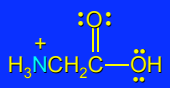
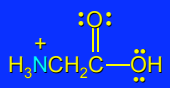


Acid-Base Properties of Glycine

Now ask yourself "As the pH is raised, which is the first proton to be removed? Is it the proton attached to the positively charged nitrogen, or is it the proton of the carboxyl group?"

You can choose between them by estimating their respective pK_as.



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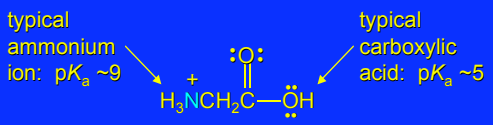
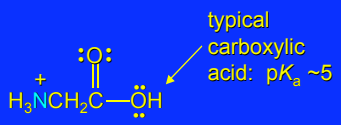


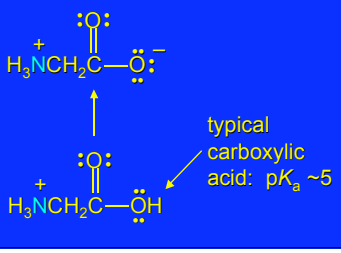
Acid-Base Properties of Glycine

The more acidic proton belongs to the CO_2H group. It is the first one removed as the pH is raised.



Acid-Base Properties of Glycine

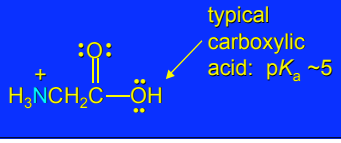
Therefore, the more stable neutral form of glycine is the zwitterion.



Acid-Base Properties of Glycine

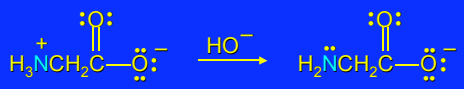
The measured pK_a of glycine is 2.34.

Glycine is stronger than a typical carboxylic acid because the positively charged N acts as an electron-withdrawing, acid-strengthening substituent on the α carbon.



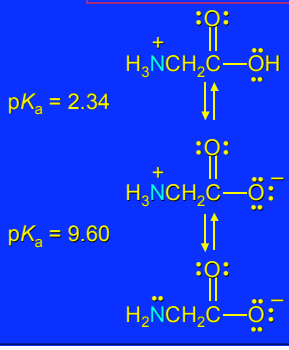
Acid-Base Properties of Glycine

A proton attached to N in the zwitterionic form of nitrogen can be removed as the pH is increased further.



The pK_a for removal of this proton is 9.60. This value is about the same as that for NH_4^+

Isoelectric Point pI



The pH at which the concentration of the zwitterion is a maximum is called the *isoelectric point*. Its numerical value is the average of the two pK_as.

The p*I* of glycine is 5.97.

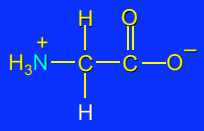
Acid-Base Properties of Amino Acids

One way in which amino acids differ is in respect to their acid-base properties. This is the basis for certain experimental methods for separating and identifying them.

Just as important, the difference in acid-base properties among various side chains affects the properties of the proteins that contain them.

Amino Acids with Neutral Side Chains

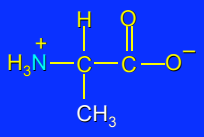
Glycine



pK_{a1} = 2.34
pK_{a2} = 9.60
p*I* = 5.97

Amino Acids with Neutral Side Chains

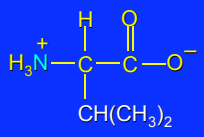
Alanine



pK_{a1} = 2.34
pK_{a2} = 9.69
p*I* = 6.00

Amino Acids with Neutral Side Chains

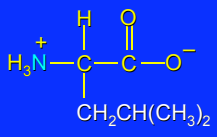
Valine



pK_{a1} = 2.32
pK_{a2} = 9.62
p*I* = 5.96

Amino Acids with Neutral Side Chains

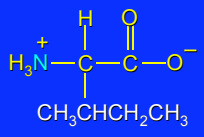
Leucine



pK_{a1} = 2.36
pK_{a2} = 9.60
p*I* = 5.98

Amino Acids with Neutral Side Chains

Isoleucine



pK_{a1} = 2.36
pK_{a2} = 9.60
p*I* = 5.98

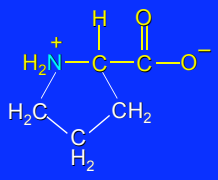
Amino Acids with Neutral Side Chains

Methionine

pK_{a1} = 2.28
pK_{a2} = 9.21
p*I* = 5.74

Amino Acids with Neutral Side Chains

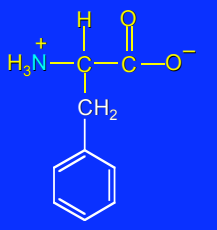
Proline



pK_{a1} = 1.99
pK_{a2} = 10.60
p*I* = 6.30

Side Chains

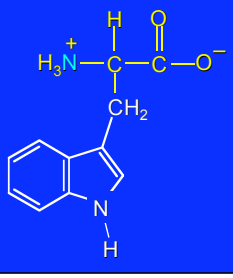
Phenylalanine



pK_{a1} = 1.83
pK_{a2} = 9.13
p*I* = 5.48

Amino Acids with Neutral Side Chains

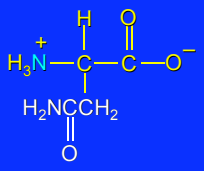
Tryptophan



pK_{a1} = 2.83
pK_{a2} = 9.39
p*I* = 5.89

Amino Acids with Neutral Side Chains

Asparagine



pK_{a1} = 2.02
pK_{a2} = 8.80
p*I* = 5.41

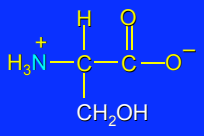
Amino Acids with Neutral Side Chains

Glutamine

pK_{a1} = 2.17
pK_{a2} = 9.13
p*I* = 5.65

Amino Acids with Neutral Side Chains

Serine



pK_{a1} = 2.21
pK_{a2} = 9.15
p*I* = 5.68

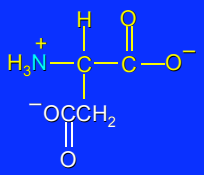
Amino Acids with Neutral Side Chains

Threonine

pK_{a1} = 2.09
pK_{a2} = 9.10
p*I* = 5.60

Amino Acids with Ionizable Side Chains

Aspartic acid



pK_{a1} = 1.88
pK_{a2} = 3.65
pK_{a3} = 9.60
p*I* = 2.77

For amino acids with acidic side chains, pI is the average of pK_{a1} and pK_{a2}.

Amino Acids with Ionizable Side Chains

Glutamic acid

pK_{a1} = 2.19
pK_{a2} = 4.25
pK_{a3} = 9.67
p*I* = 3.22

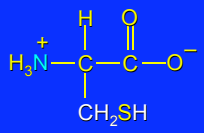
Amino Acids with Ionizable Side Chains

Tyrosine

pK_{a1} = 2.20
pK_{a2} = 9.11
pK_{a3} = 10.07
p*I* = 5.66

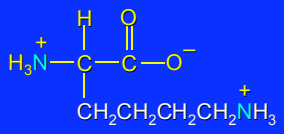
Amino Acids with Ionizable Side Chains

Cysteine



pK_{a1} = 1.96
pK_{a2} = 8.18
pK_{a3} = 10.28
p*I* = 5.07

Amino Acids with Ionizable Side Chains

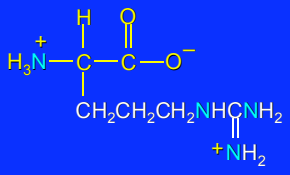


Lysine

pK_{a1} = 2.18
pK_{a2} = 8.95
pK_{a3} = 10.53
p*I* = 9.74

For amino acids with basic side chains, pI is the average of pK_{a2} and pK_{a3}.

Amino Acids with Ionizable Side Chains



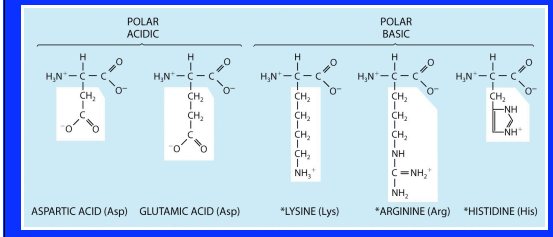
Arginine

pK_{a1} = 2.17
pK_{a2} = 9.04
pK_{a3} = 12.48
p*I* = 10.76

Amino Acids with Ionizable Side Chains

Histidine

pK_{a1} = 1.82
pK_{a2} = 6.00
pK_{a3} = 9.17
p*I* = 7.59

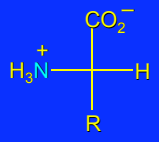


Proteins and Amino Acids

Stereochemistry of Amino Acids

Configuration of α-Amino Acids

Glycine is achiral. All of the other amino acids in proteins have the L-configuration at their α carbon.



Proteins
Amino Acids

Our bodies can synthesize about 10 amino acids.

Essential amino acids are the other 10 amino acids, which have to be ingested.

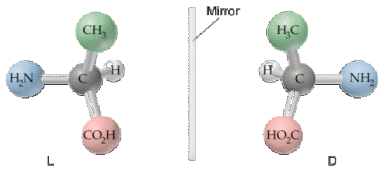
The α-carbon in all amino acids except glycine is chiral (has 4 different groups attached to it).

Chiral molecules exist as two non-superimposable mirror images.

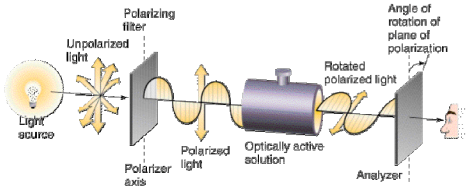
The two mirror images are called enantiomers.

Chiral molecules can rotate the plane of polarized light.

Proteins
Amino Acids



Proteins
Amino Acids



Proteins
Amino Acids

The enantiomer that rotates the plane of polarized light to the left is called L- (*laevus* = "left") and the other enantiomer is called D- (*dexter* = right).

Enantiomers have identical physical and chemical properties. They only differ in their interaction with other enantiomers.

Most amino acids in proteins exist in the L-form.

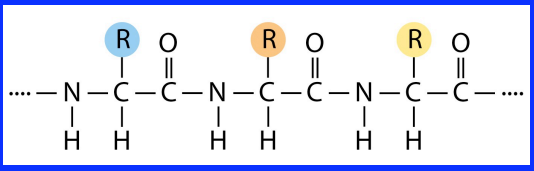
Proteins
Polypeptides and Proteins

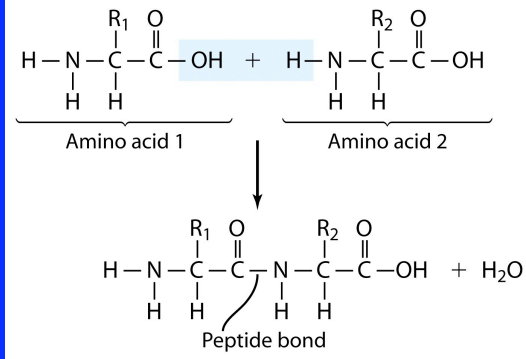
Proteins are polyamides.

When formed by amino acids, each amide group is called a peptide bond.

Peptides are formed by condensation of the -COOH group of one amino acid and the NH group of another amino acid.

The acid forming the peptide bond is named first. Example: if a dipeptide is formed from alanine and glycine so that the COOH group of glycine reacts with the NH group of alanine, then the dipeptide is called glycylalanine.





Proteins
Polypeptides and Proteins

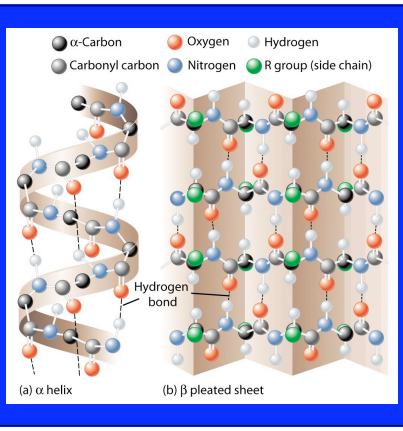
Glycylalanine is abbreviated gly-ala or GA.

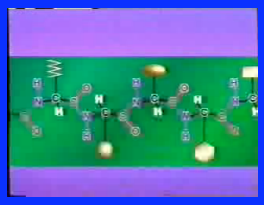
Polypeptides are formed with a large number of amino acids (usually result in proteins with molecular weights between 6000 and 50 million amu).

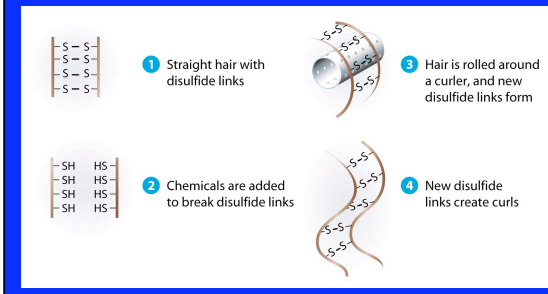
Protein Structure

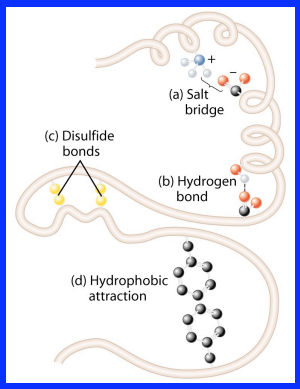
Primary structure is the sequence of the amino acids in the protein.

A change in one amino acid can alter the biochemical behavior of the protein.









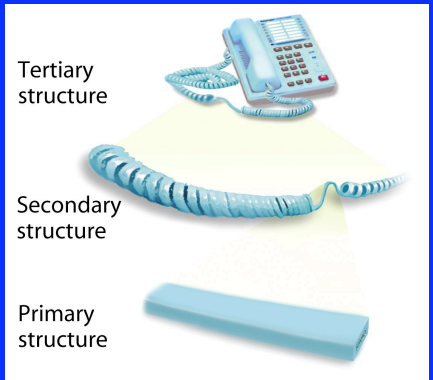
Protein Structure

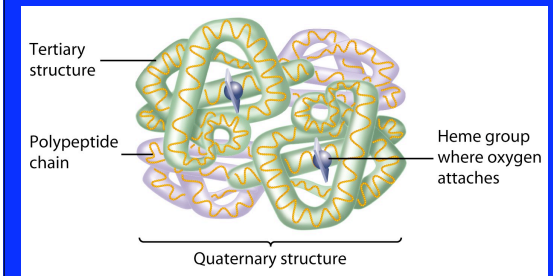
1º : The linear sequence of amino acids and disulfide bonds eg. ARDV:Ala·Arg·Asp·Val.

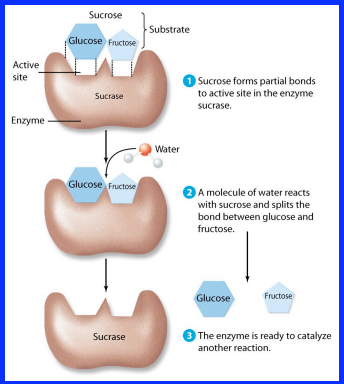
2º : Local structures which include, folds, turns, ∝-helices and β -sheets held in place by hydrogen bonds.

3º : *3-D* arrangement of all atoms in a single polypeptide chain.

4º : Arrangement of polypeptide chains into a functional protein, eg. hemoglobin.







Enzymes

Enzymes are proteins which act as biological catalysts.

Over 1500 have been isolated.

Human genome project scientists estimate that there are about 30,000 (~~>100,000~~) enzymes in a human.

Active (catalytic) site is a crevice which binds a substrate. Lock & key metaphore ....but, protein can change conformation.

The active site is evolutionarily conserved.

Enzyme Inhibitors / Effectors

Michaelis-Minton Kinetics

$$E + S \rightleftharpoons [ES] \rightarrow E + \text{Product}$$

E = Enzyme; S = Substrate

Enzyme Activity is reduced by inhibitors.

Four types of inhibitors:

Reversible, Irreversible, Competitive, Non-competitive

Equilibrium Constant & Free Energy

$K_{[ES]eq} = 10^{-2}$ to 10^{-6}; Free Energies -3 to -12 kcal/mol

vs. covalent bonds -50 to -110 kcal/mol

Effectors increase enzyme activity.