Lecture : 3

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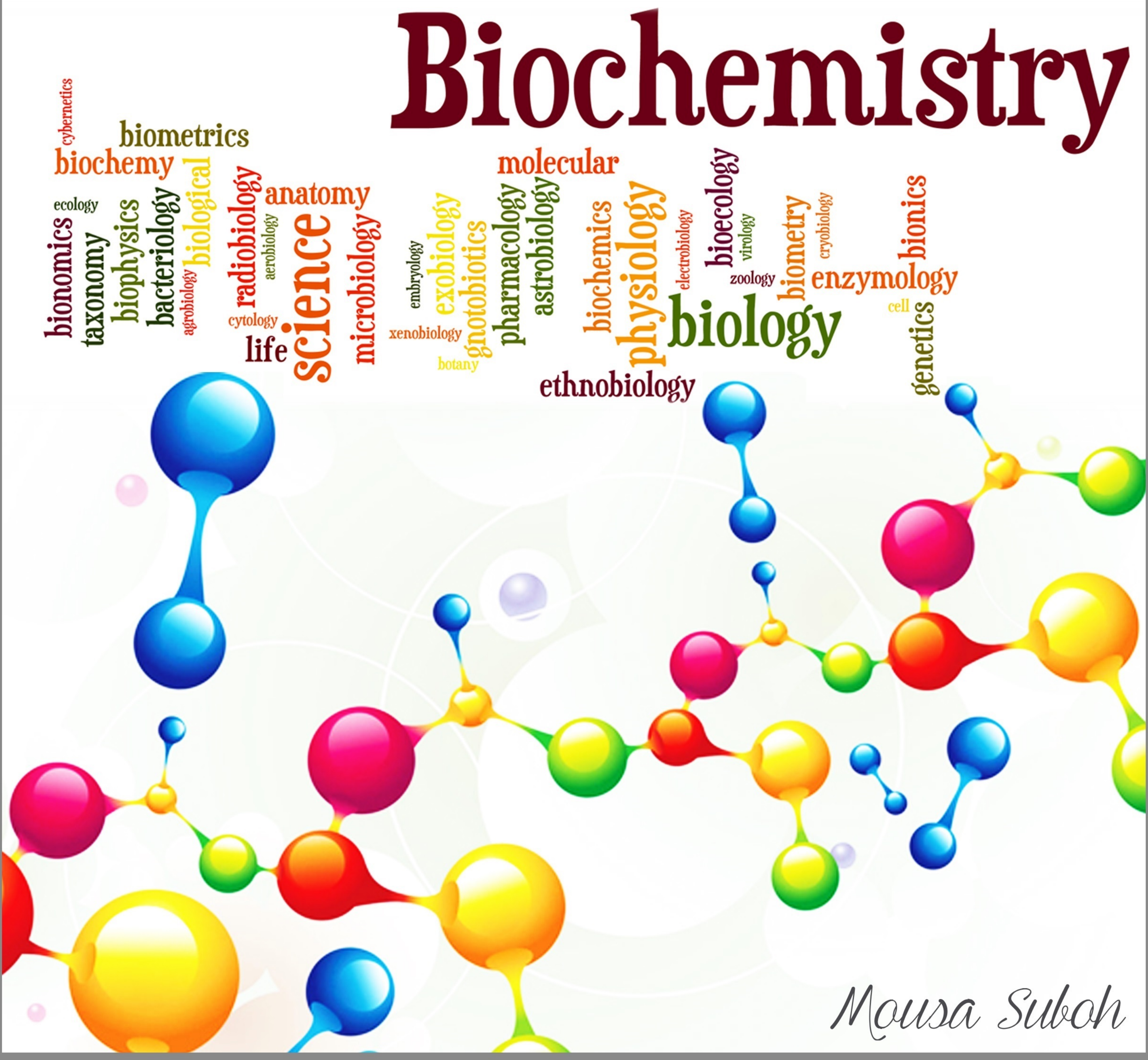
Medical Committee
The University of Jordan



Peptide Bonds

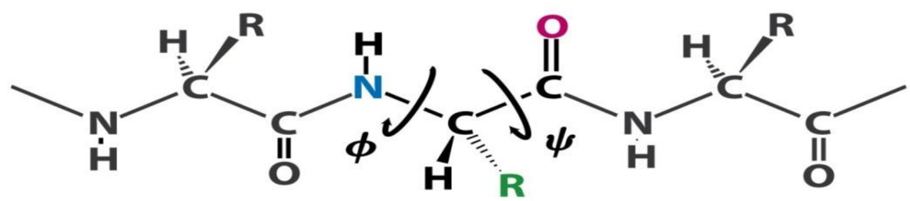
Features of peptide bond:

- **Zigzag structure** : when you look at it you notice that it's going up ,down ,up …… Notice the figure below

A structure that consumes the least amount of energy to form and to keep it stable. (The most stable structure)

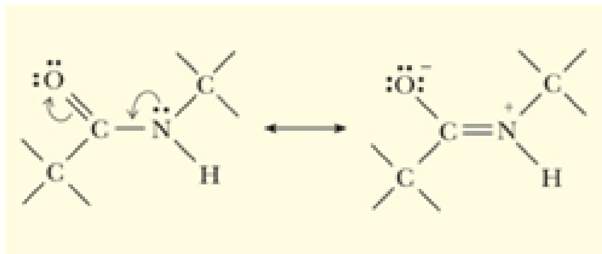
In order to have the least amount of energy to keep as is ,the most stable structure.

- **Planar** : it's flat because it has a double bond feature.
- **Rigid (double bond)**: also because of double bond
- **Un-rotatable** : because of double bond(كلو مربوط ببعضو)



*We have a C=O (carbonyl group) which can make resonance by switching from the C=O to C=N in the peptide bond and flipping back and forth. This make it rigid and hard to rotate so it is flat.

- (un)charged : its (un)charged but could be charged because of the resonance structure, when the double bond is formed between C and N the OXYGEN atom will have a negative charge and the NITROGEN atom will have a positive charge.



*Now the question is: Why does it have a zigzag structure?

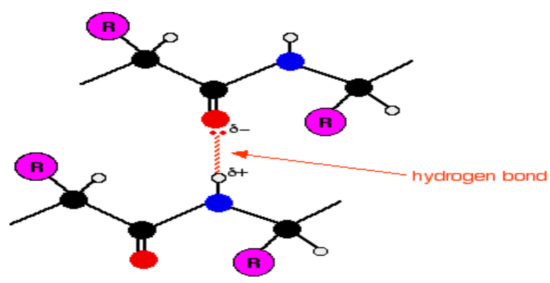
Whenever you think about biochemistry as a definition, it is definitely the understanding of the structure, function, organization and distribution of molecules in biological systems, in other words you are studying basically everything about molecules in biological systems (if you are talking about molecules in test tube, then you are not talking about Biochemistry. But if you are studying them in a biological system, then you are talking about Biochemistry). Biochemistry deals with something very important that is the core of life, it is one word "Energy" and what Biochemistry does is to try to explain to us the flow of energy (without energy there is no life, there is no biological systems and there is no Biochemistry) that's what is the Biochemistry all about. **So when we are talking about a structure of a molecule we need a structure that consumes the least amount of energy to form and to keep it stable.**

- A peptide bond can form a hydrogen bond between H-bond donor (the hydrogen in the amino group, partial positive) and H-bond acceptor (the oxygen in the carbonyl group, partial negative) in another molecule.

- These donors and acceptors have partial positive or negative charges not real because one of the atoms ,involved in the covalent bond, is more electronegative and attracts electrons from the other atom towards it, so these electrons would revolve around the electronegative atom more often than around the other one so it will have a partial negative charge and the other atom will have a partial positive charge.

- A peptide bond has both a H-bond donor and a H-bond acceptor
  * The acceptor is the oxygen in the carbonyl (C=O):
  Oxygen atom is more electronegative, attracts electrons from the carbon atom, and it will have a partial negative charge, so it's ready to accept hydrogens or protons from another molecules.

- Another example is the amide group (which contains H and N), the nitrogen is more electronegative than hydrogen, so it attracts electrons, and the hydrogen will have a partial positive charge as a result, and this bond is the H-bond donor, "it's the one that will donate a proton to the other group.

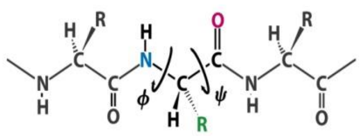


Blue: nitrogen
Blank: hydrogen (δ+)
Black: carbon

Red: oxygen (δ-)

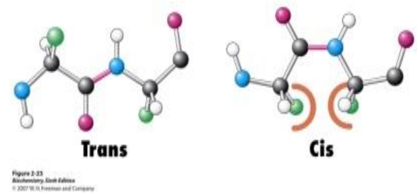
H-bond is not only formed in peptide bond it can be formed between water and a peptide bond .
As an exception proline can't form H-bond ; it has an electron acceptor (carbonyl group) nut no H-bong donor here nitrogen does not have hydrogen (because nitrogen is bonded to the side chain it has nothing to donate)

Organic molecule that are made of chains carbon, carbon ....or a series of repeated unit as a backbone (nitrogen of the amide ,alpha carbon and carbonyl group , branching out of the backbone hydrogen and R-group) R-group is arranged up then down then up....
We said before that the peptide bond is un-rotatable but the bond around the alpha carbon can rotate : phi (فاي) , psi (ساي)

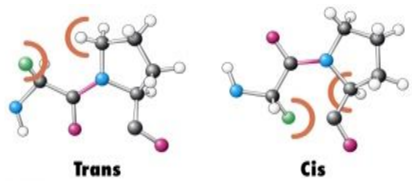


Each molecule want to have the least energy and the most stable structure so that the R-groups are in peptide chain are in opposite direction (up,down) ;they are always trans.

This is the most stable structure. If they were in the same direction (cis), the R-groups of the two neighboring amino acids would be close to each other and the electron valences would overlap and that makes a repulsion, which will cause a steric clash or a steric hindrance (steric in space, clash = تصادم), so we want them to be far not too close to each other nor far away from each other (we don't want them to clash causing repulsion and don't want them to be far away from each other causing no attraction to occur). So they are in the trans orientation that they are at a distance that attraction occurs with causing repulsion.



There is one exception whic is Proiline; whether it iss in the cis or trans orientation it will cause a clash



Meaning that in a certain solution or in a peptide there will be 95% of amino acids in the Trans orientation and 5% in the Cis orientation except for Proline; it has 50% of amino acids in the Trans orientation and 50% in the Cis orientation so it does not have a favorable structure .

Uncommon peptides:

1) Carnosine (β-alanyl-L-histidine):

A dipeptide made of two amino acids : β-alanine and regular histidine.

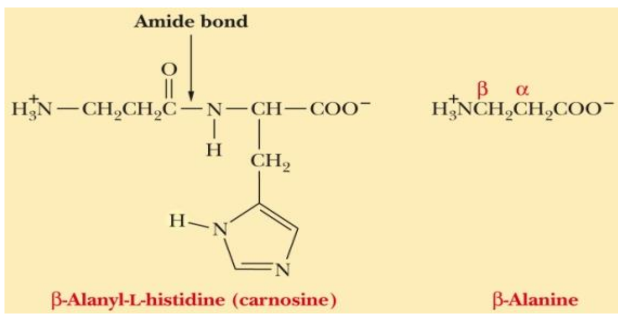
β-alanine is different from α-alanine; the α-carbon in the α-alanine has a methyl group (R group), a Hydrogen, an amino group and a carboxyl group with all of them attached to it, but in β-alanine the amino group is bonded to the third or β -carbon of alanine (R group not to the α-carbon).

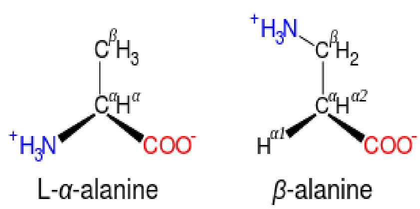
It's very important in removal of reactive oxygen species, It is highly concentrated in muscle and brain tissues

- Protection of cells from ROS (radical oxygen species) like peroxides and supraoxides.

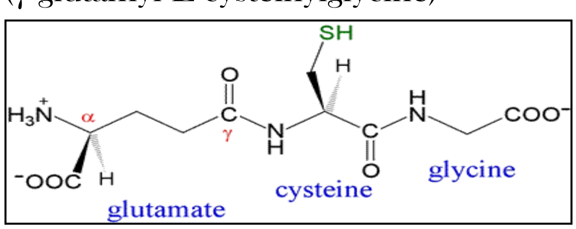
-Contraction of muscle (muscle has a lot o metabolism reaction which can produce reactive oxygen) so it need protection.

What does reactive oxygen do? these atoms either have an extra electron or need an electron so they attack other molecules common in cells such as DNA , RNA , carbohydrates and lipids especially lipids that are present in the membrain. Whenever these oxygen atoms attack these molecules, these molecules will be damaged. As a result, we have these peptides like carnosine and what they do is to scarify themselves, they jump infront of the reactive Oxygen does species and tell them: attack me. And this is why they are present in muscles (there is a lot of oxygen metabolism of muscles that results with reactive Oxygen species produced like peroxides and so on) and brain (To protect brain cells).





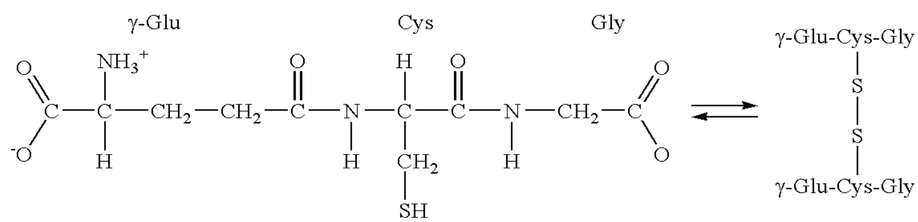
2) **Glutathione:** it's a tripeptide (glutamic acid ,cysteine and glycine) (γ-glutamyl-L-cysteinylglycine)



Why γ? Here the peptide bond between glutamate and cysteine is formed between the carboxyl group of the side chain of glutamate that is linked to γ-carbon (not the carboxyl attached to alpha group) and the amino group of cysteine.

Functions:

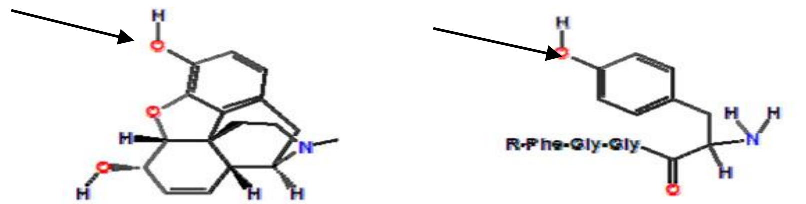
- Like carnosine protecting cells from free radicals , It scavenges oxidizing agents by reacting with them, jumping in front of them telling them: hit me, do not hit DNA or carbohydrates!
- The molecule that does the work is Cysteine (exactly the thiol group -SH). Two molecules of the reduced glutathione molecules form the oxidized form of glutathione by forming a disulfide bond between the –SH groups of the two cysteine residues donating electrons to other groups that need them , enzymaticly what cells do is that they take this oxidized form and reduce it and now they are ready to protect cells against reactive oxygen .



enkephalins:

There are other Two pentapeptides (5 amino acids) know as enkephalins found in the brain known as enkephalins, and they are pain relievers ,they are released from cells in the central nervous system functioning as an analgesics ,they reduce the sensation of pain.
The two pentapeptides differ in the last amino acid and that's why they are called:
Met-enkephalin: Tyr-Gly-Gly-Phe-**Met**
Leu-enkephalin: Tyr-Gly-Gly-Phe-**Leu**
The fuctional amino acids are the tyrosine and phenylalanine .
You don't have to memorize the sequence but you have to understand the important features .

What is interesting in enkephalins is that they have a similar structure to morphine (a pain reliever, analgesic)



Morphine **Enkephalins**

They seems different but they have one point of similarity which is the point above.

Sometimes what drug companies do when they manufacture drugs is that they look at the structure of protein and they look at a specific point where the protein is active at (exact point), it can be a small amino acid or two amino acid closed to each other and they design a small drug that can fit into that protein (all what they have to do is to make a small drug that looks like a small part of the functional part of the protein).

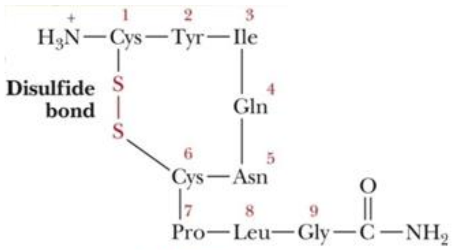
Oxytocin and vasopressin:

They have similar structures: They are cyclic (the cyclic structure is formed by disulfide link between two cysteines) and they are decapeptide (10 amino acids). Both have similar structure in having the carboxy terminus aminlated (they have the attachment of amino group to the carboxylic group in both of them).

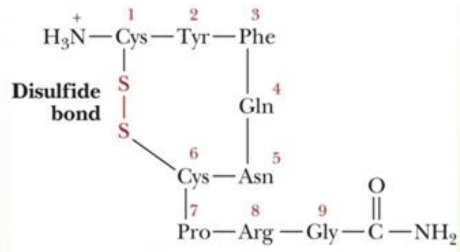
- Both contain nine residues, but they differ in two positions :
    - Oxytocin has isoleucine and leucine.
    - Vasopressin has phenylalanine and arginine .

  Both regulate contraction of muscle but They also differ :
- Oxytocin regulates contraction of uterine muscle (labor contraction)الطلق

  In hospitals during labor they give injection of Oxytocin.
- Vasopressin regulates contraction of smooth muscle (blood vessel, gut, abdominal organs), increases water retention, and increases blood pressure.



Oxytocin

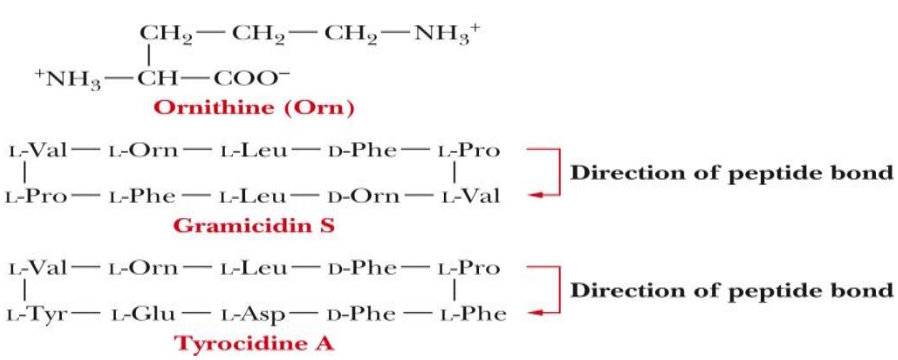


Vasopressin

Gramicidin S and tyrocidine A

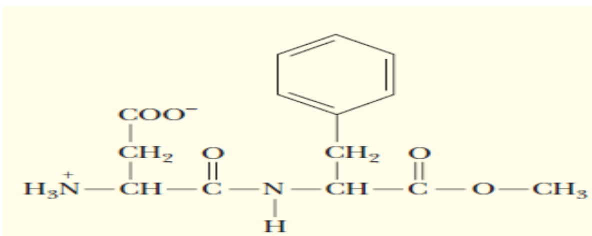
They are cyclic decapeptides, the cylclic structure occurs between the carboxylic end and the amino end of the peptide so it loops around and forms a peptide bond.

- They are produced by the certain bacteria (bacterium Bacillus brevis) and act as antibiotics.
- They are made of a combination of D and L-amino acids which is an **exception because L-amino acids occur naturally in biological systems** and D ones don't
- Both contain the **amino acid ornithine (Orn),** which does not occur naturally in proteins.



Aspartame :
it's the sweeter used for the caffeine tee
L-Aspartyl-L-phenylalanine (methyl ester) , its dipeptide made of twe amino acid aspartic acid and phenylalanine.
The phenylalanine is capped by a methyl group so they have the formation of a methyl ester at the end of phenylalanine.

- This **dipeptide** is about 200 times sweeter than sugar.
- They both occur in L- formation, if the a D-amino acid is substituted for either amino acid or for both of them, the resulting derivative is bitter taste rather than sweet.



L-Aspartyl-L-phenylalanine (methyl ester)

Phenylketonuria (PKU)

Some people have this disease, it is a disease that results from a metabolic defect in the conversion of phenylalanine to tyrosine (which only differ in a hydroxyl group). people have a defective enzyme so there will be accumulation of phenylalanine in their systems which will be converted to another molecule known as phenylpyruvate which accumulate in the central nervous system to cause mental retardation .

In new born babies PKU is one of the first tests done by taking a small amount of blood from their foot to see if there is a defect in this enzyme

- A substitute for aspartame, known as alatame, contains alanine rather than phenylalanine because people who is infected with PKU can't handle aspartame because it has phenylalanine so the take alatame.

Proteins:

A cell weight is made mainly of water and 30% other chemical like DNA ,RNA ,proteins and carbohydrates . A subunit is basically the precursor or the building block of large molecules (macromolecules, the opposite is micromolecules)

So by having the amino acid as a subunit and adding it to second amino acid, second amino acid and so on that will build up a protein (macromolecule)

- Carbohydrates ,proteins , nucleic acids ,lipids are macromolecules. Except for lipids, these macromolecules are also considered polymers.

Carbohydrates , proteins and nucleic acids are polymers but lipids are not because they do not have repeated units. Polymers are made of repeated units (like protein as it is made of repeated units of amino acids: amino acid ,aminoacid ,amino acid ….). They are made by dehydration reaction (Condensation) and can be broken to smaller subunit by hydrolysis.

Different proteins have different structures; some of them are elongated, others are globular they have also different branches .

A protein may have gazillion (10^{21}) possibilities of structures, but a few would be active maybe one,two, three…etc
These active structures are known as the **native conformations**.

There are different levels of protein structure they are known as primary ,secondary , tertiary and quaternary .