بسم الله الرحمن الرحيم

BIOCHEMISTRY

Lecture 13

Peptides

سَيُفْتَحُ بَابٌ إِذَا سُدَّ بَـابُ نَعَمْ، وَتـهُونُ الأُمُورُ الصِّعَابُ

وَيتَّسِعُ الحَالُ مِنْ بَعْدِ مَا تَضِيقُ المَذَاهِبُ فِيهَا الرِّحَابُ

الإمام الشافعي - رحمه الله

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Definitions and concepts

As we discussed in the previous lecture, amino acids on their own (without being part of a polypeptide) can also have biological functions.

The professor mentioned that oligopeptides usually consist of 3 to 10 units, similar to how "oligo" is used in carbohydrates. However, oligopeptides typically contain between 20 and 30 amino acids.

- A residue: each amino acid in a (poly)peptide
- Dipeptide, tripeptide, tetrapeptide, etc.
- Oligopeptide (peptide): a short chain of 20-30 amino acids (Up to)
- Polypeptide: a longer peptide with no particular structure
- Protein: a polypeptide chains with an organized 3D structures
- The average molecular weight of an amino acid residue is about 110
  - The molecular weights of most proteins are between 5500 and 220,000 (calculate how many amino acids)
- We refer to the mass of a polypeptide in units of Daltons
  - A 10,000-MW protein has a mass of 10,000 Daltons (Da) or 10 kilodaltons (kDa)

Average MW of an amino acid is 110 (with variation of course between amino acids)
we can use this formula to calculate the number of amino acids in a protein:
#of amino acids = protein MW / 110 (approximately)

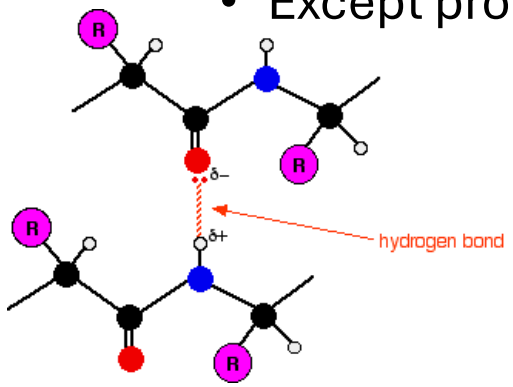
Medical knowledge (NOT FOR MEMORIZATION):
A change in a protein's 3D structure can result in a non-functional protein or one with a different, potentially harmful function. For example, in the 1990s, research was conducted on the B503 gene, which is normally an oncosuppressor (tumor suppressor) gene. A mutation in this gene led to the production of a protein with an altered 3D structure, turning the gene into an oncogene (cancer-causing).

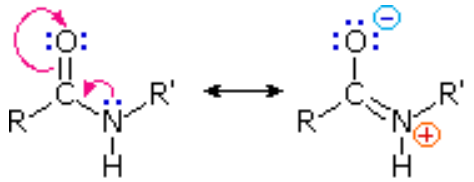
Peptide bond

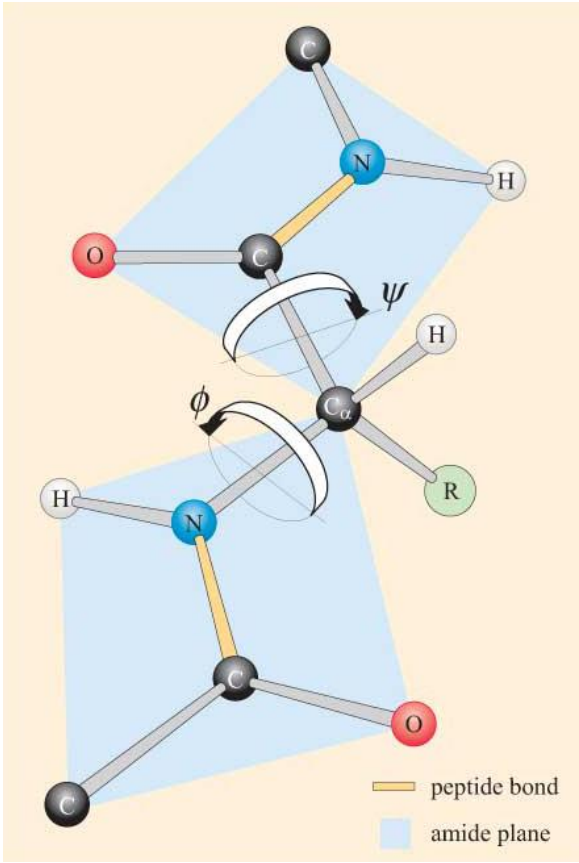
- It is called an amide bond formed via a condensation reaction.
- Features
  - It has a resonance structure
  - Zigzag structure
  - Double bond
    - Planar, charged, Rigid, Un-rotatable
  - Hydrogen bonding
    - Except proline

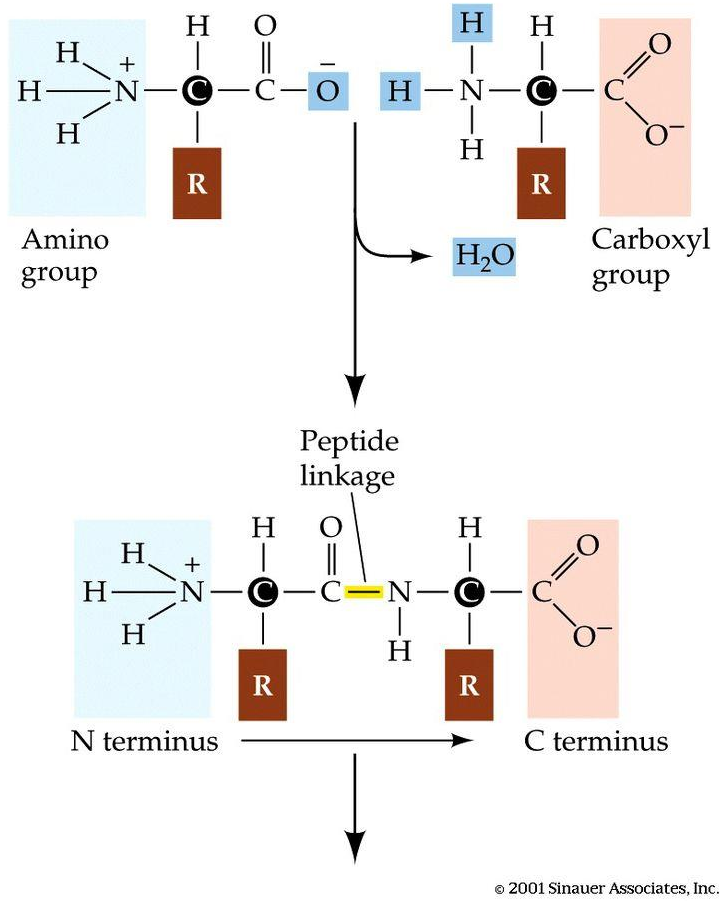
Condensation reaction (Dehydration reaction): a reaction where an H2O molecule is removed.

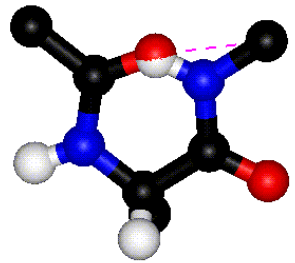
It can have a double bond character due to resonance

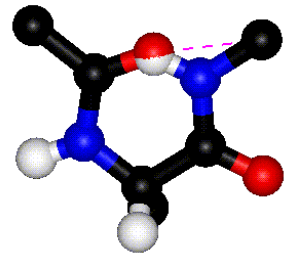












When is the peptide bond a double bond?

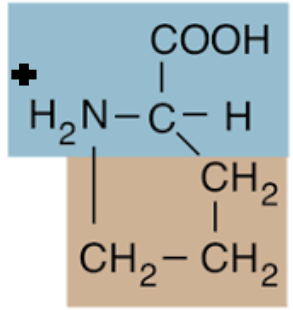
Remember, the actual structure isn't exactly any of the resonance structures but rather a hybrid of them, so the peptide bond will always have partial double bond character, as a result:

1. The peptide group that forms the link between the two amino acids is **planar**.

2. The peptide bond is stronger than an ordinary single bond because of this resonance stabilization.

3. There is no significant rotation around the peptide bond. However, there is free rotation around the bonds between the α-carbon of an amino acid residue and the amino nitrogen and carbonyl carbon of that residue.

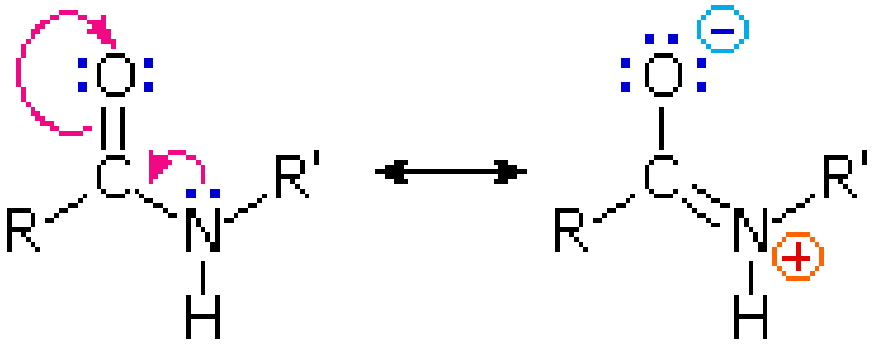
4. The nitrogen in the peptide bond becomes positively charged, and the oxygen becomes negatively charged, enabling hydrogen bonding.
(NH is the hydrogen bond donor)
(O is the hydrogen bond acceptor)
exception : proline

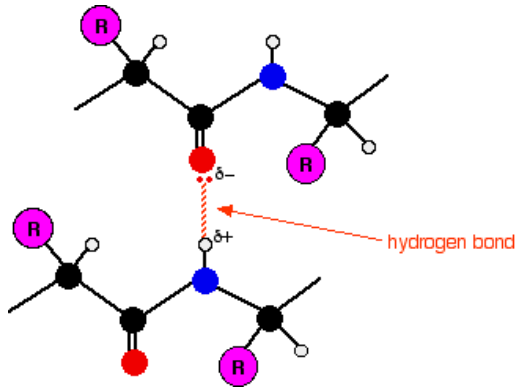


Proline (pro)

Why is proline an exception, and why can't it form hydrogen bonds?

Looking at its structure, proline is cyclic, and its nitrogen is secondary. After forming a peptide bond and becoming a residue, the nitrogen in proline becomes tertiary, meaning it no longer has a hydrogen atom. As a result, it can't act as a hydrogen bond donor anymore. However, the oxygen in the carboxyl group can still function as a hydrogen bond acceptor.

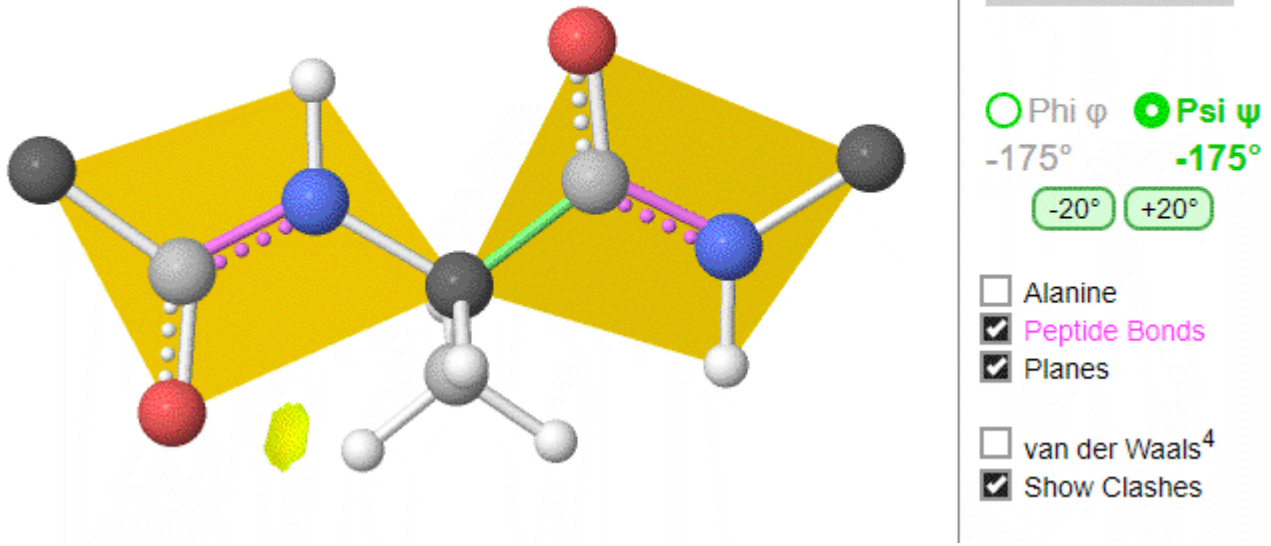


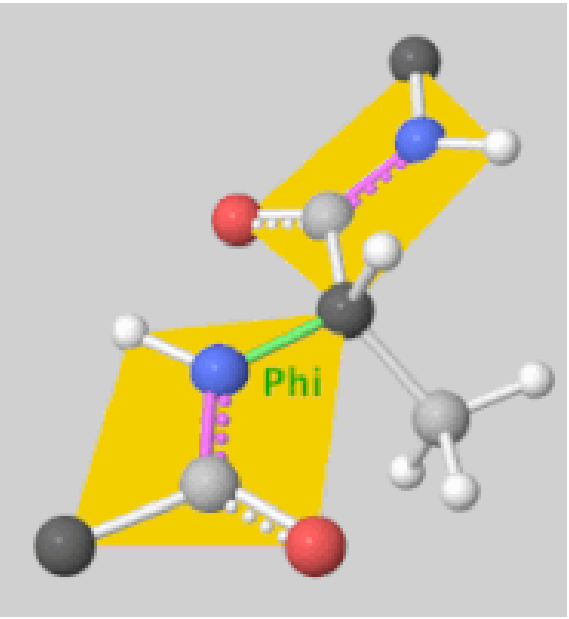


Peptide bond **remain rigid**
while
phi (i.e. Angle of the bond between C_α and N from amino group)
psi (i.e. Angle of the bond between C_α and C from carboxyl group)
can rotate freely

*Knowing phi and psi is not required

watch it, it may be helpful : https://youtu.be/JUxhEdMOgTQ?si=ryka5k48h1yTQqjT

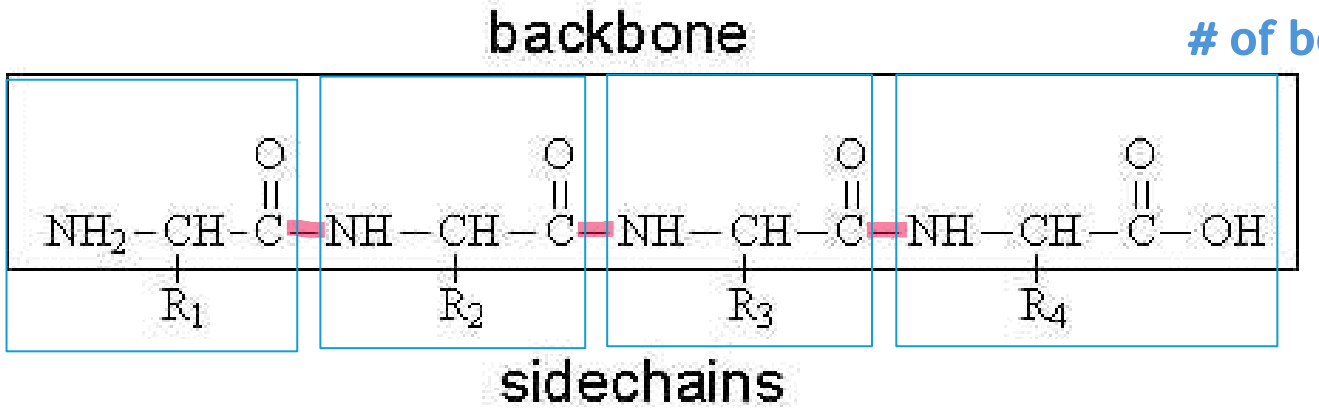




Backbone, orientation and directionality

α-amide N, the α-C, and the α carbonyl C atom

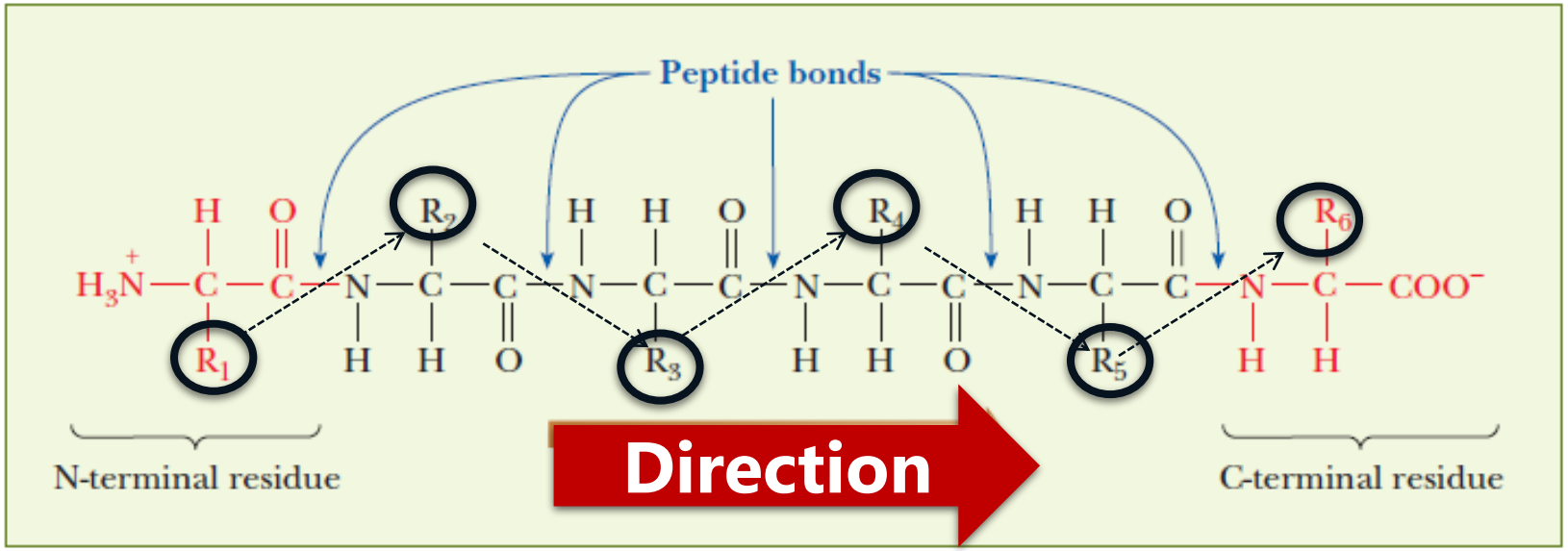
4 amino acids → 3 peptide bonds
# of bonds = # of amino acids – 1



Like all amide linkages, the –C=O and –NH groups of the peptide bond are uncharged and do not accept or release protons across the pH range of 2–12.

However, the peptide bond can become charged in different resonance structures, as shown on slide 5.

Therefore, the charged groups in polypeptides are limited to the N-terminal (α-amino) group, the C-terminal (α-carboxyl) group, and any ionized side chain groups of the amino acids.



R groups follow a pattern of alternating between up and down positions sequentially (trans configuration). This arrangement is primarily due to repulsion from van der Waals forces.

The starting point is the N-terminus

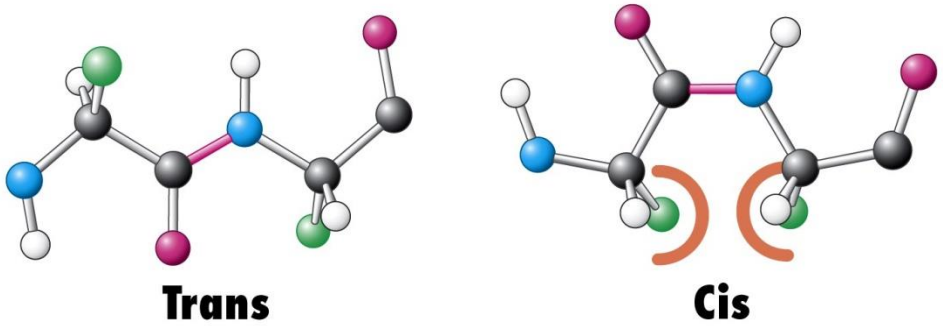
Adding amino acids occurs exclusively at the C-terminus of a polypeptide chain. This is mainly because there is no enzyme that adds amino acids to the N-terminus.

Except for proline

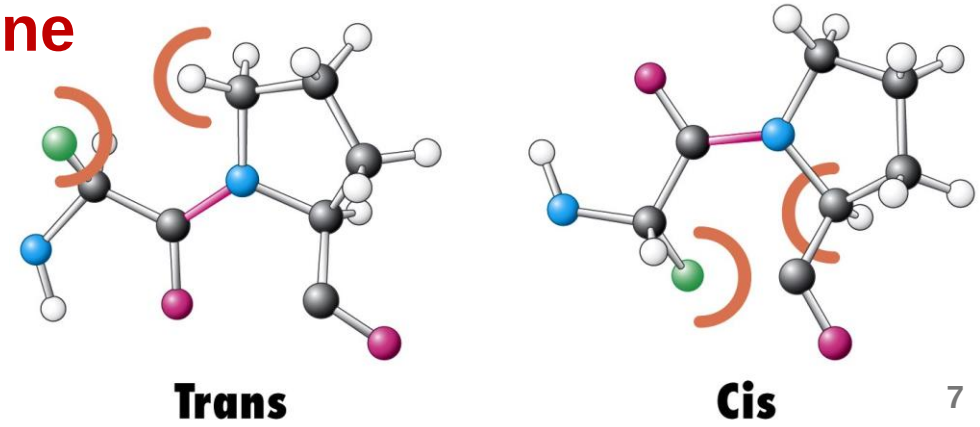
Advice from the doctor regarding exams:
Do not treat slides as individual data,
Instead, try to understand and comprehend the course as a whole to sneak out from "evil" questions.

- Steric hindrance between the functional groups attached to the Cα atoms will be greater in the cis configuration.
- In proline, both cis and trans conformations have about equivalent energies. (repulsion occur in both configurations of proline).
- Proline is thus found in the cis configuration more frequently than other amino acid residues. (Since there is no difference in stability between its 2 configurations)

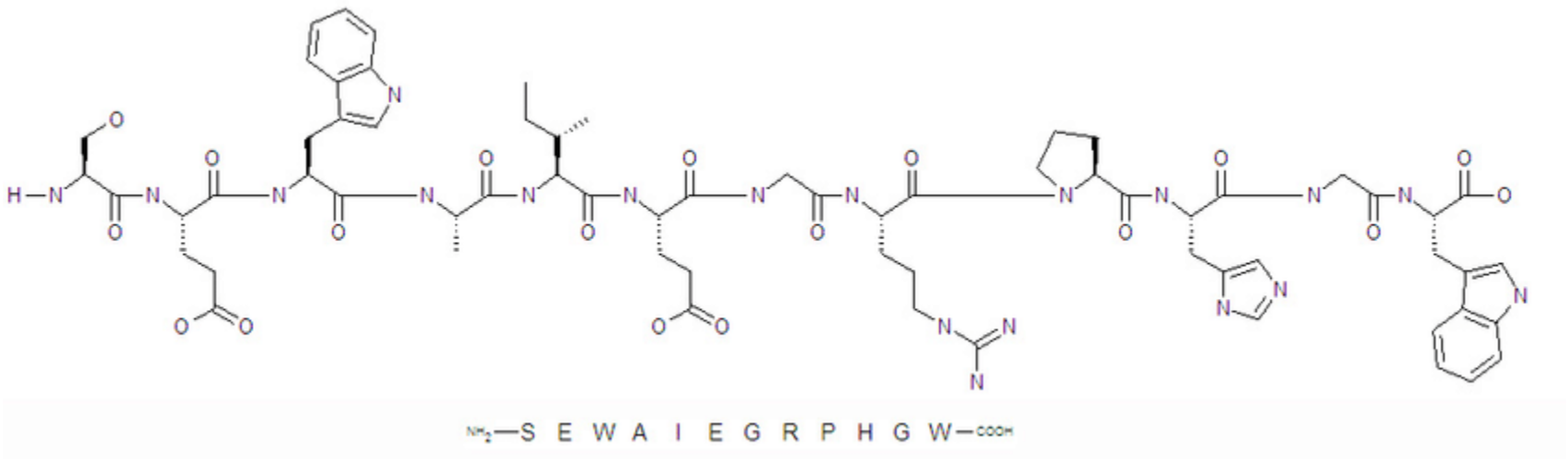
All other amino acids



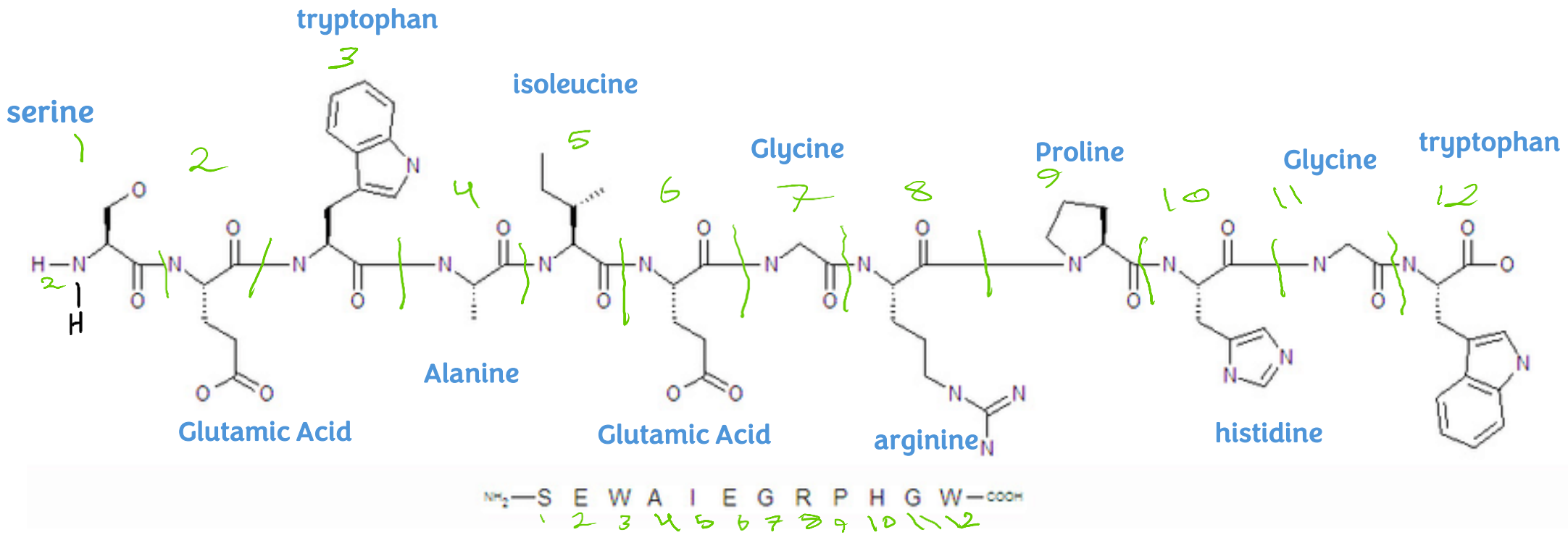
Proline



Practice: *name the amino acid residues*



Solution for slide 9

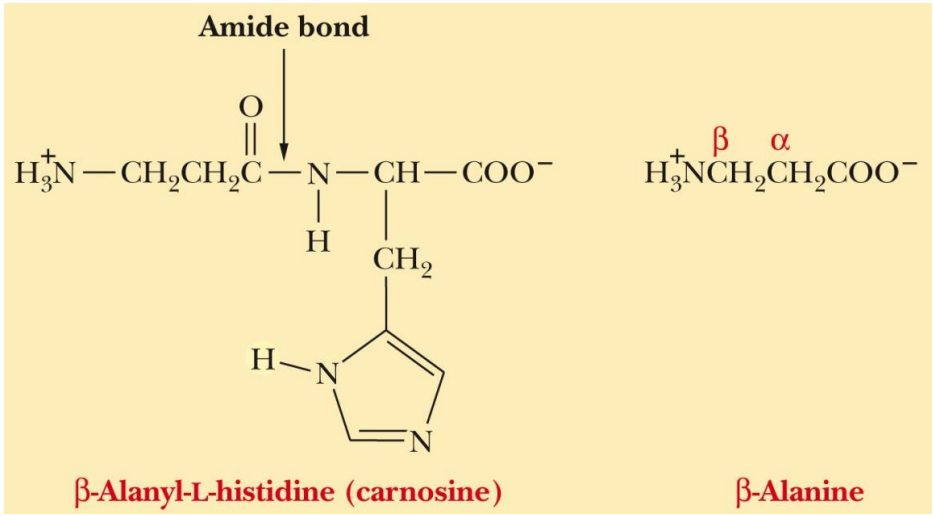


Examples of
Functional and Exceptional peptides

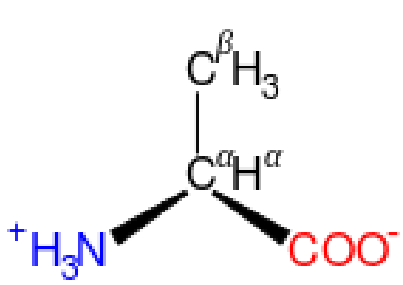
Carnosine (β-alanyl-L-histidine)

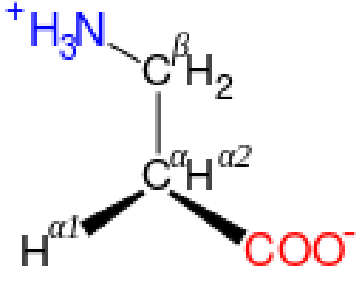
When a polypeptide is named, all amino acid residues have their suffixes (-ine, -an, -ic, or -ate) changed to -yl, except for the C-terminal amino acid which remains as it is.

- A dipeptide of β-alanine and histidine
- The amino group is bonded to the β -carbon of alanine
- It is highly concentrated in muscle and brain tissues
  - Protection of cells from ROS (radical oxygen species) and peroxides
  - Contraction of muscle



Radicals:
Highly reactive species with an odd number of electrons, which can react with stable molecules giving them an electron (reducing agent) or taking from them an electron (oxidizing agent)





→ Because the amino group is attached to the C_β instead of C_α

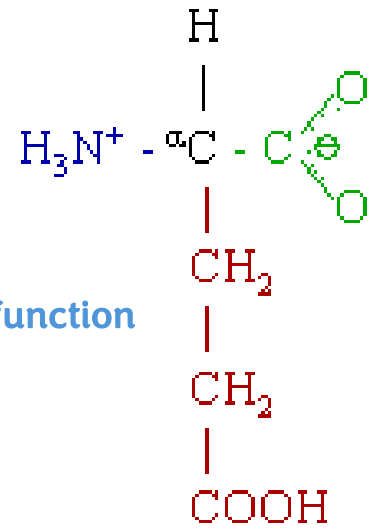
Glutathione

(γ-glutamyl-L-cysteinylglycine)

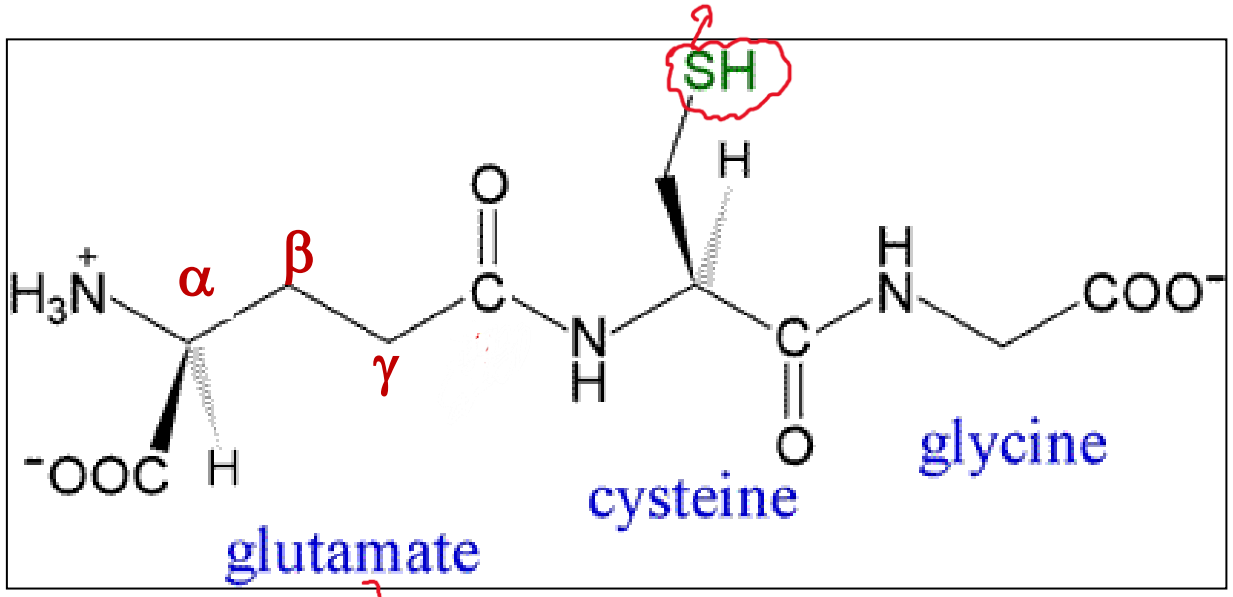
Glutathione–> tripeptide
Consists of:
1. Glutamate
2. Cysteine
3. Glycine

Thiol group is the functional group

Important because of its function



Glutamic Acid
(Glu / E)

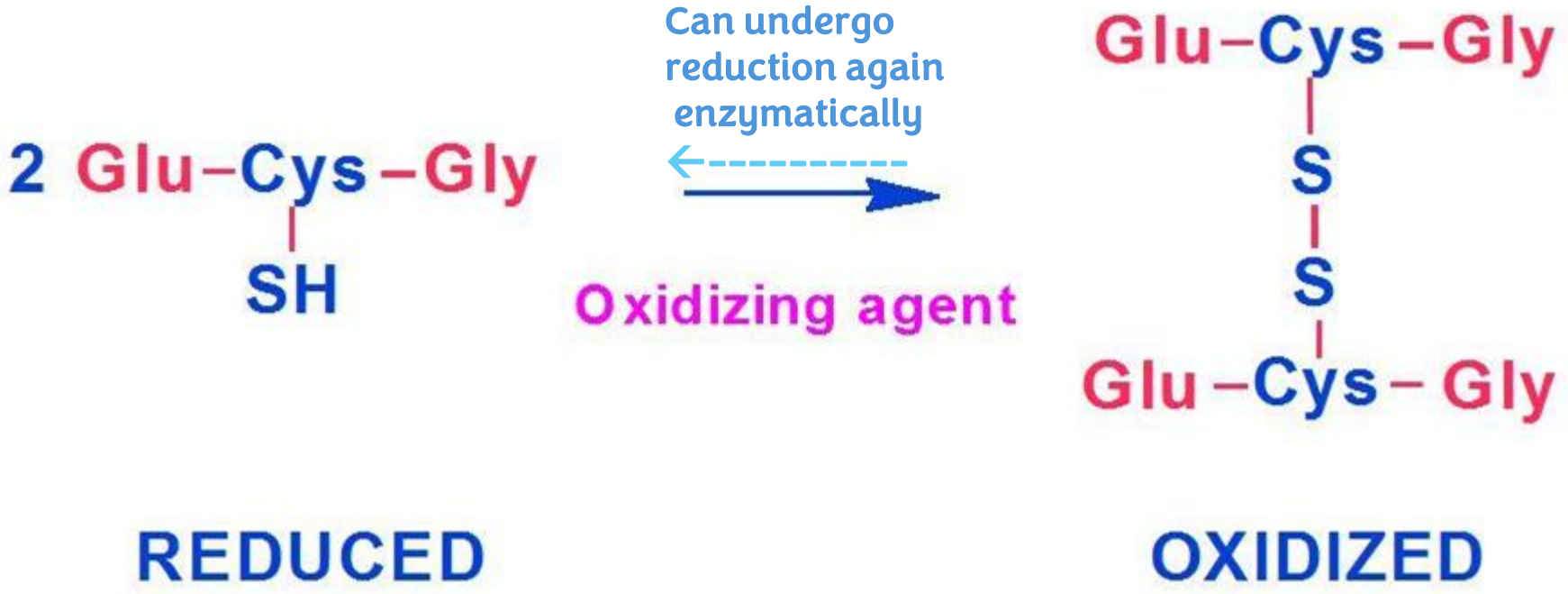


it is called γ –Glutamate because the carboxylic group in the R group (which is attached to the carbon designated as C_γ) makes the peptide bond with the amino group of cysteine rather than the carboxyl group attached to Cα.

Function of glutathione

It has a protective role: it removes reactive oxygen species

- It scavenges oxidizing agents by reacting with them.
- Two molecules of the reduced glutathione molecules form the oxidized form of glutathione by forming a disulfide bond between



It is oxidized → the other substance which needs electrons is reduced.

Enkephalins

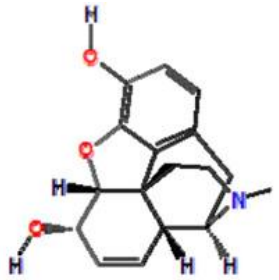
Knowing the full order of amino acids in enkephalins is not required;
focus on the difference in the last amino acid, and on the presence of Tyr and Phe

- Two pentapeptides found in the brain known as enkephalins, and function as analgesics (pain relievers).
  - They differ only in their C-terminal amino acids.
    - Met-enkephalin: Tyr-Gly-Gly-Phe-Met
    - Leu-enkephalin: Tyr-Gly-Gly-Phe-Leu

One of them ends with methionine
& the other one with leucine

  - The aromatic side chains of tyrosine and phenylalanine play a role in their activities.
- There are similarities between the three-dimensional structures of opiates (المواد الأفيونية), such as morphine, and enkephalins.

Morphine :(مخدر) addictive anesthetic
It is given for patients with calculated doses to avoid the addictive effect.

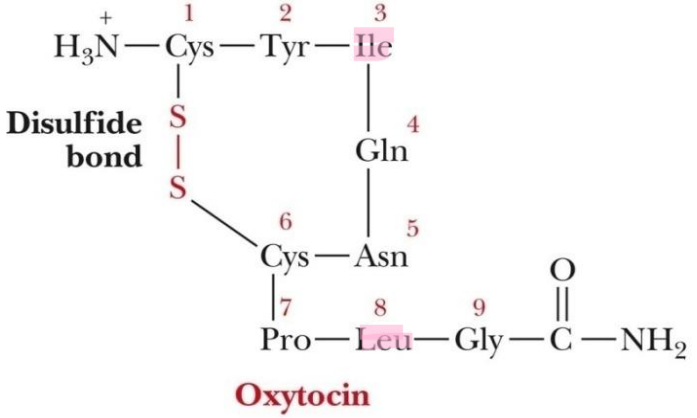


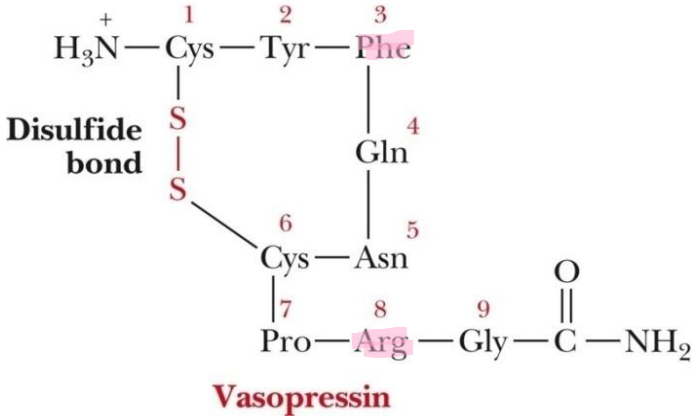
Morphine

Enkephalins

Oxytocin and vasopressin

- Hormones with cyclic structures due to S-S link between Cys.
- Both have amide group at the C-terminus.
- Both contain nine residues, but different in two:
  - Oxytocin has isoleucine and leucine.
  - Vasopressin has phenylalanine and arginine .
- Oxytocin regulates contraction of uterine muscle (labor contraction).
- Vasopressin regulates contraction of smooth muscle, increases water retention, and increases blood pressure.

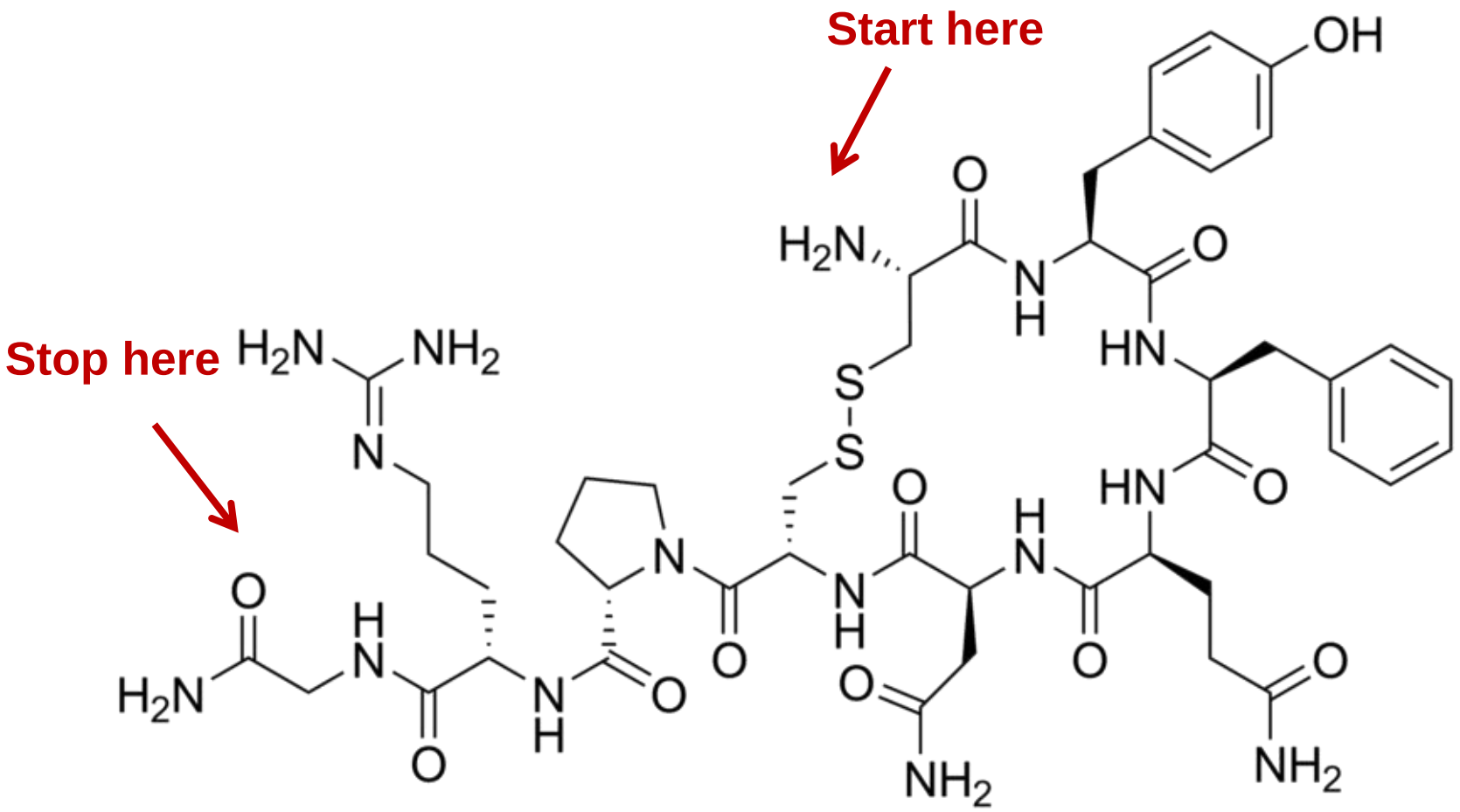




They are cyclic because they contain 2 cysteine residues which form a disulfide bond (which is covalent)

Vasopressin

Practice: what is the primary structure?

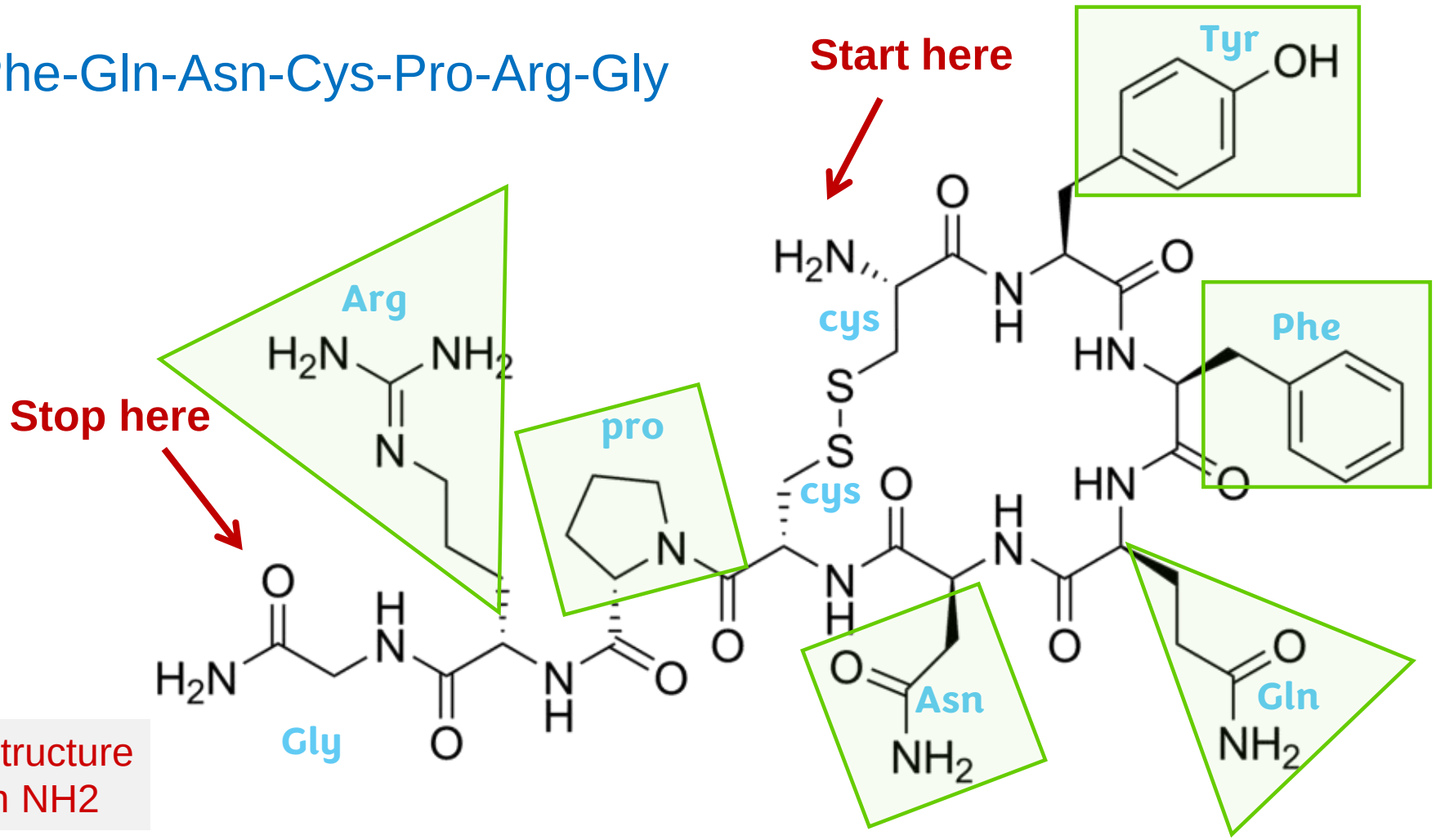


Vasopressin

Practice: what is the primary structure?

Ans:

Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly



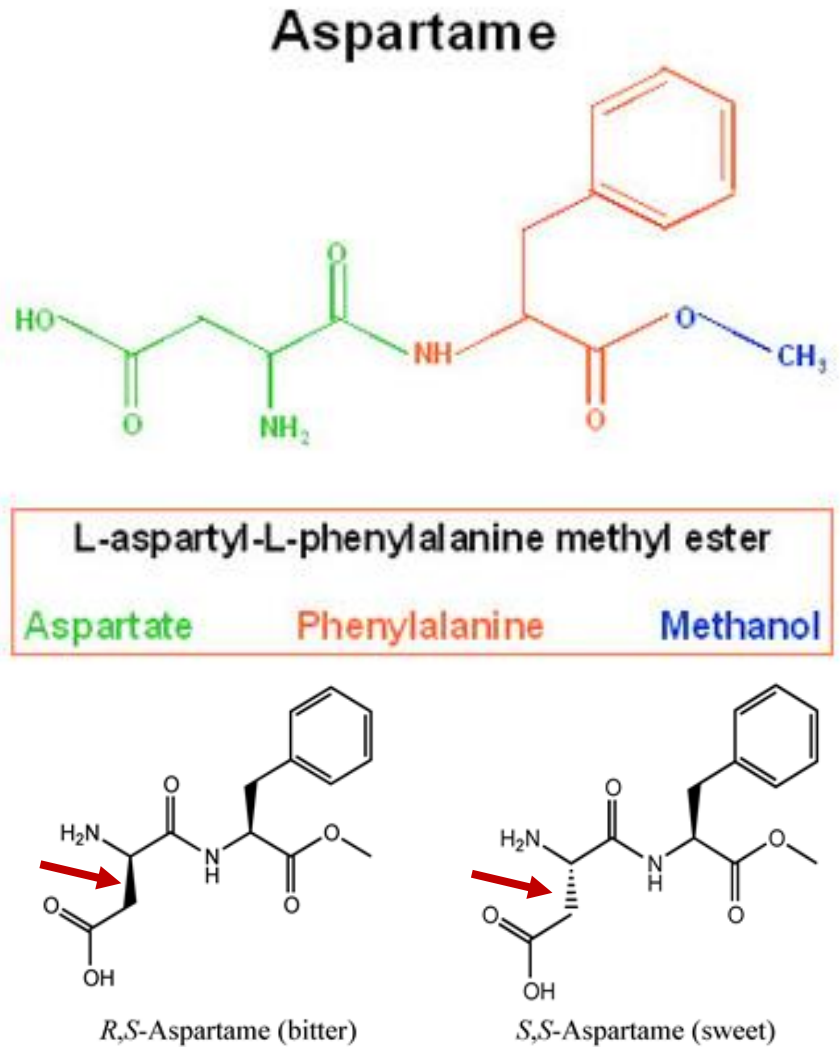
Note: the structure ends with NH2

Aspartame

L-Aspartyl-L-phenylalanine (methyl ester)

- A dipeptide that is 200 times sweeter than sugar. **(It is used as a sweeter)**
- If a D-amino acid is substituted for either amino acid or for both, the resulting derivative is bitter (مرّ) rather than sweet!!

L and D structures are completely different; here is an illustrative example.



Aspartame and cancer

REUTERS® World Business Markets Sustainability Legal Breakingviews Technology Invest

Government Health Policy

Exclusive: WHO's cancer research agency to say aspartame sweetener a possible carcinogen -sources

By **Jennifer Rigby** and **Richa Naidu**

June 29, 2023 10:17 PM GMT+3 · Updated 7 days ago

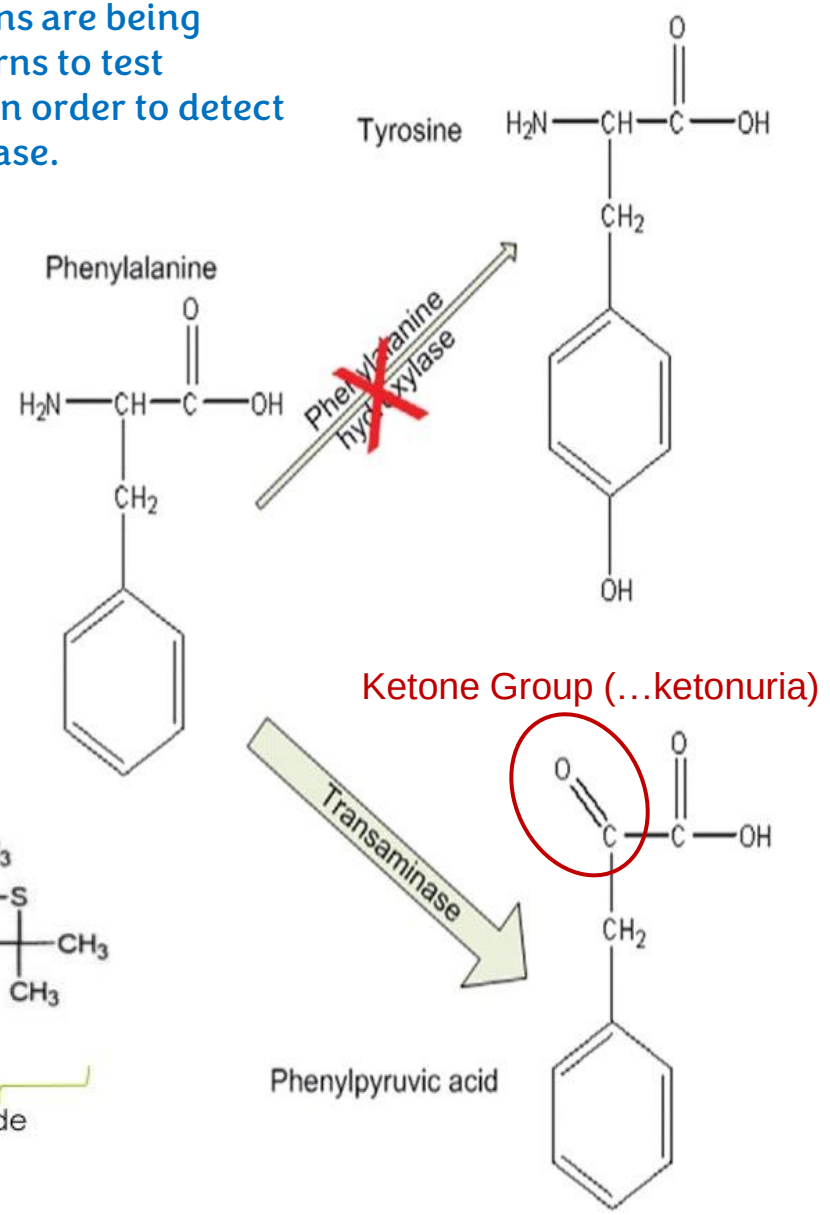
The link

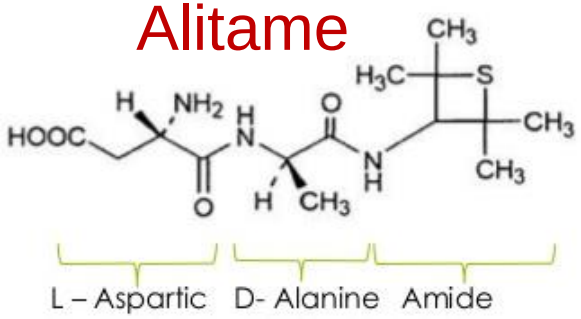
Just to know

Phenylketonuria (PKU)

- PKU is a hereditary “inborn error of metabolism” caused by defective enzyme, phenylalanine hydroxylase.
- It causes accumulation of phenylpyruvate, which causes mental retardation.
- Sources of phenylalanine such as aspartame must be limited.
- A substitute for aspartame, known as alitame, contains alanine rather than phenylalanine.

Recently, examinations are being conducted on newborns to test phenylalanine levels in order to detect and address this disease.





Patients suffering of PKU must not take aspartame because it is a source of Phe

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V1 → V2	2; bottom right 6; right (zigzag of R) 14; bottom left 18; bottom right red arrow 20; top right 20	----- ----- ----- Wrong pointing Laterally, … -----	Purple text rephrased Made more concise Text rephrased Correct pointing Recently, … Added the texts with Dark Red
V2 → V3	General Rephrasing تزبيط بعض الجمل بشكل عام		

Additional Resources Used:

رسالة من الفريق العلمي:

1. **Lippincott’s Illustrated Reviews page 14**
   2.Marry Cambell biochem page 70 & 71

إِذا أَنا لَم أُعْطِ الْمَكارِمَ حَقَّها
فَلا عَزَّنِي خالٌ وَلا ضَمَّنِي أَبُ

محمود سامي البارودي