Chemistry for Physicians: Amino Acids and Proteins

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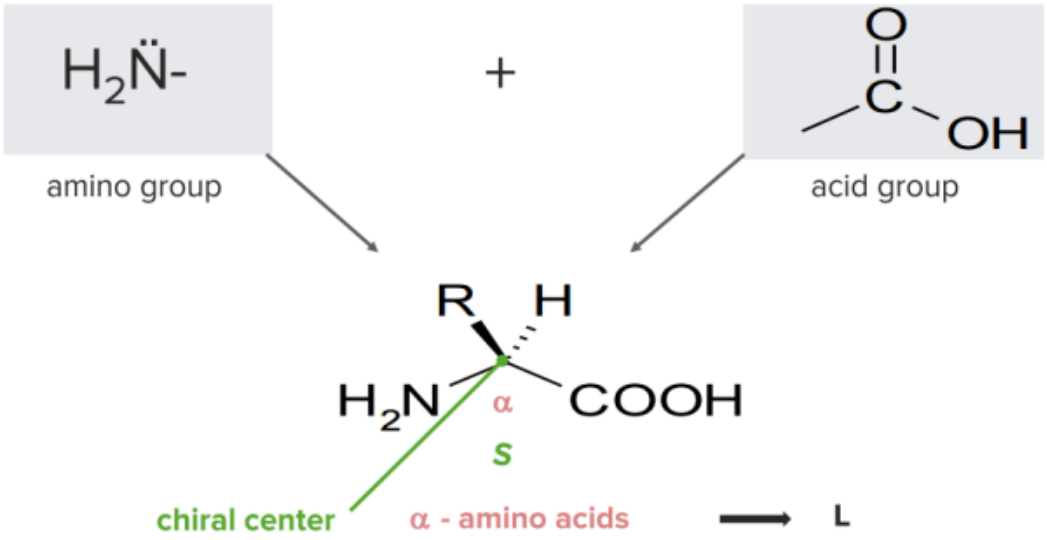
In the human organism, proteins undertake multiple and vital functions. Structural proteins are found in each and every cellular compartment. Intracellularly, motor proteins power the energy-dependent transportation of vesicles. Signal proteins receive and transmit information. Transport and storage proteins bind, for example, oxygen, and carry it to a location where it is needed. Of equally great significance are enzyme proteins as, without these biocatalysts, a smooth and "frictionless" exchange of energy and nutrients would be practically impossible. This article illustrates the role of amino acids as building blocks in the structure of proteins, their chemical properties and also presents the ways in which amino acids fulfil their multiple duties.

General Structure of Amino Acids: The "Residue" Makes the Difference

One can safely deduce the components of an amino acid from its name: they include a **carboxylic acid part**, namely a part that contains a carboxylic functional group.

Then comes an **amine group** on **the left side of the α-C-atom**, which is the second carbon atom to the carbon atom with the highest oxidation state. In this case, it is the C-

atom of the carboxylic group. In a strict sense, this is a α-L-amino acid. Next to the carboxylic and amine group, a **hydrogen atom and an R-side chain ("R"** is used to convey the meaning of "residue" or "root") are substituents attached to the α-C-atom. Each amino acid contains a different side chain, which defines their specific properties.

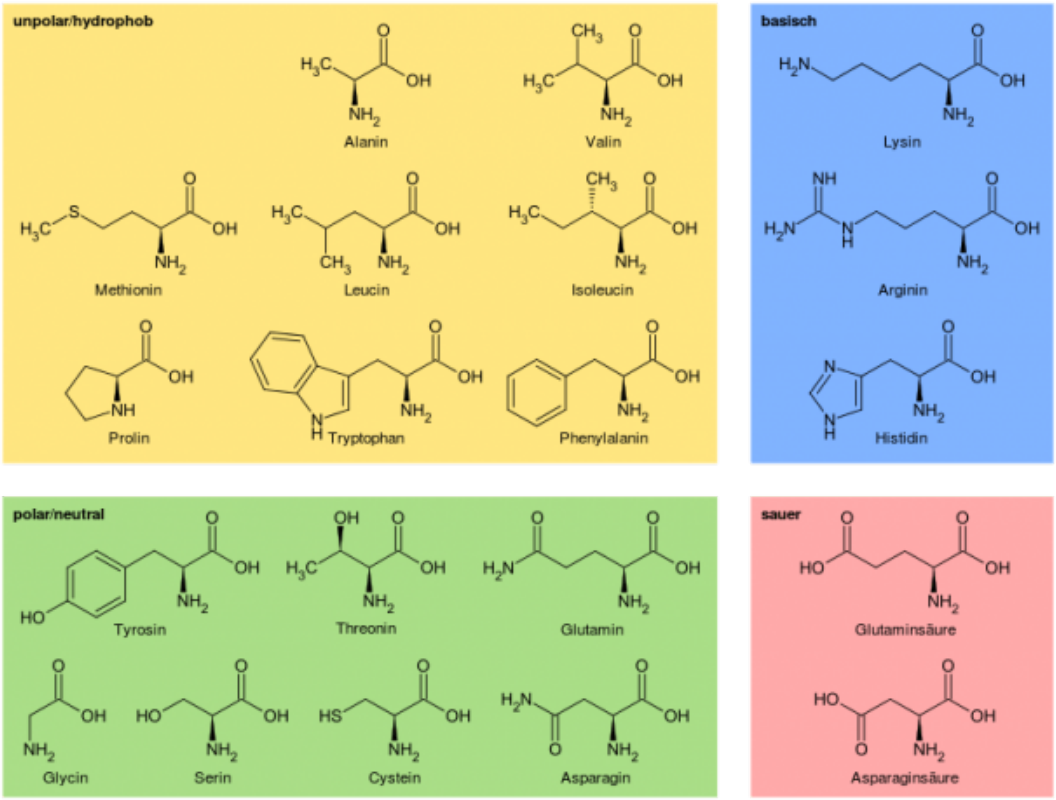


Proteinogenic amino acids are those that can be found in human proteins. Currently, the scientific community is familiar with **21 different amino acids,** which can be divided as follows:

- **Nonpolar side chains:** Glycine, Alanine, Valine, Leucine, Isoleucine, Methionine, Proline, Phenylalanine and Tryptophan
- **Non-charged, polar side chains:** Tyrosine, Serine, Threonine, Cysteine, Selenocysteine, Asparagine and Glutamine
- **Acidic side chains:** Aspartate and Glutamate
- **Basic side chains:** Lysine, Arginine and Histidine

The **essential,** or **indispensable amino acids,** are those that have to be supplied to the human organism through the diet since they cannot be synthesized by it. Those include Methionine, Threonine, Valine, Histidine, Tryptophan, Phenylalanine, Isoleucine, Leucine and Lysine.

Essential Amino Acids: Amino acids which can´t be synthesized in the body. These amino acids are required in the diet.

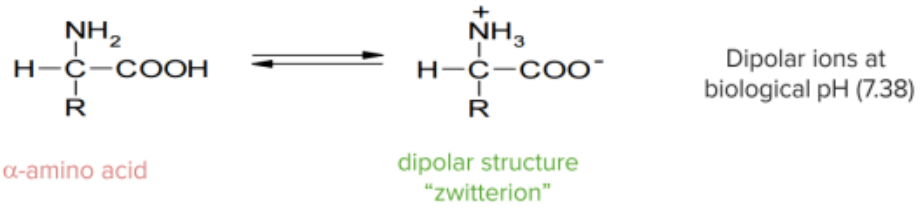


Overview proteinogenic amino acids

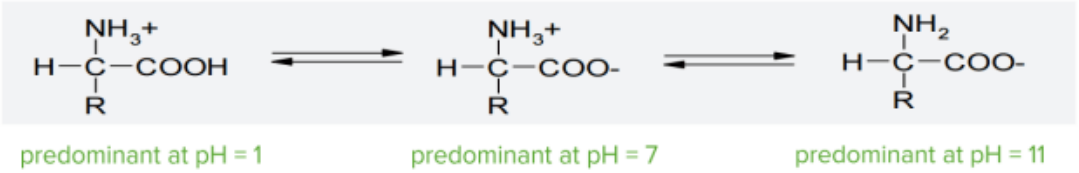
Chemical Properties of Amino Acids

Amino acids are **amphoteric** molecules. This means that they possess both basic, as well as acidic properties, and therefore constitute very good **buffer systems.** Their functional groups are the reason for this: the amino group has a **free unbound pair of electrons** on the N-atom and so it can function in a **basic way:** it can accept a proton. On the other hand, the carboxylic group releases a proton due to its positive electrical charge of the H-atom, thus functioning in an **acidic way.** In this way, an individual molecule can, at the same time, assume both the role of the proton donor and the proton acceptor.

This **intracellular protolytic reaction** leads to the formation of **zwitterions**, namely compounds containing a carboxylate and an ammonium group, which are firmly bound together in a crystal lattice. They are distinguishable by their high melting temperatures and good water solubility (analogically to ionic bonds). Zwitterions take their name from the German **“Zwitter”,** meaning hermaphrodite or hybrid.



pI = isoelectric point = Ph at which the aminoacid is in the zwitterion form



In a water solution, the **pH value** is of vital importance. When the pH value is that of the **isoelectric point** (IEP= specific pH value), amino acids are present in the form of zwitterions.

If the **pH value** of a solution is **below the IEP** (acidic solution), amino acids gain a proton and become **cations.** The proton is gained by the N-atom of the amine group, which, as a result, becomes an ammonium group. Respectively, they form **anions,** when the solution's **pH value is greater than that of the IEP.** In this case, the greatly available hydroxide ions take a proton away from the carboxylic group. This leads to deprotonated **carboxylate groups.**

The graphic depiction of this pH-dependent behavior results in the **titration curve** of an amino acid:

- In **very low pH values,** amino acids exist in protonated form: ammonium form/conjugated acid/**cation.**
- **As the pH value rises,** even more, carboxylic groups dispose of their protons. When pH reaches **pKs1 value,** the concentration of the cationic forms equals that of the zwitterionic forms.
- If the pH value rises **above the pKs1-value,** the zwitterions predominate in concentration. When **pH=IEP,** only zwitterions are found.
- With the further rise of pH-value, the ammonium group also disposes of its proton. The concentration of the anionic form builds up until the **pKs2-value** is reached. Then, again, the concentration of zwitterions matches that of the anions.
- In cases of **very high pH-values,** only the carboxylates/conjugated bases/**anions** are to be found in a solution. This is the highest, deprotonated form of amino acids.

The pks- and IEP-values are characteristic in each case. If even more protonatable or deprotonate side chains are present, PKS3 and PKS4 values can additionally be described.

4 Typical Reactions of Amino Acids

The **decarboxylation** of an amino acid leads to the formation of **biogenic, primary amines** and CO_2. These undertake vital transport functions, e.g.: Catecholamines, like adrenaline and noradrenaline, are built from tyrosine and phenylalanine. The vital, inhibitory transmitter GABA, results from glutamate. A further example is a histidine, from which histamine is built. Histamine is a hormone produced in the body's tissues and is

responsible, amongst others, for immediate hypersensitivity reactions.

The **transamination** is a reaction through which an **amino acid 1** reacts with an **a-keto acid 2,** catalyzed by the enzyme aminotransferase. As we can understand from its name, **the amine group is exchanged:** the amino acid 1 (original amino acid) converts to a **α-keto acid 1,** and the α-keto acid 2 converts to **amino acid 2.**

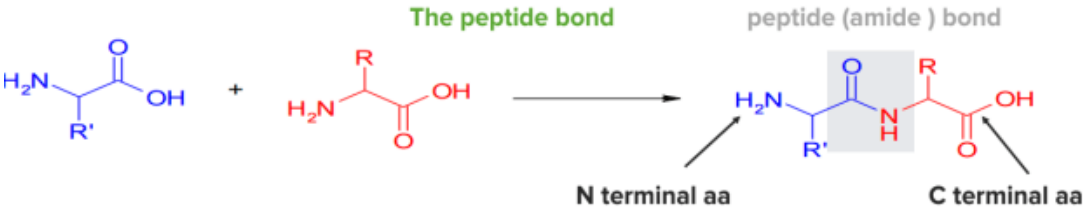
Non-oxidative deamination (or also eliminating deamination) involves the **removal of water** from certain amino acids. The formation of an unstable intermediate product leads to a **α-keto acid** and **ammonia.**

The three aforementioned reactions always require **PLP as a co-factor.** On the other hand, the fourth typical reaction that amino acids engage in, the **oxidative deamination,** requires **water and NAD+** instead. The latter is downscaled to $NADPH/H^+$.

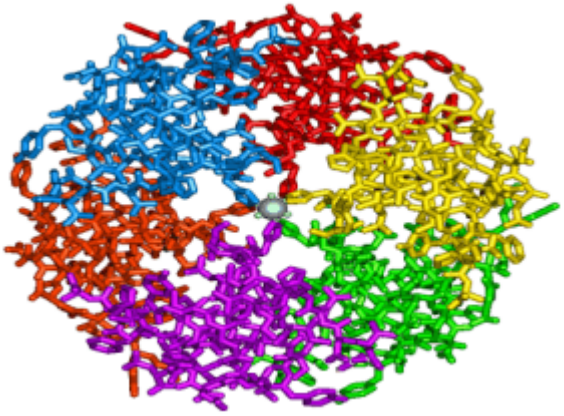
Just like in eliminating deamination, the final product here is **ammonia** and the corresponding **α-keto acid.**

Amino Acids to Protein

Many amino acids, joined by peptide bonds, form a polypeptide chain. An amino acid unit in a polypeptide is called a residue.



Longer chain peptides (polypeptides) are called proteins (the boundary of these definitions is a bit blurred!).



Human Insulin (a protein)

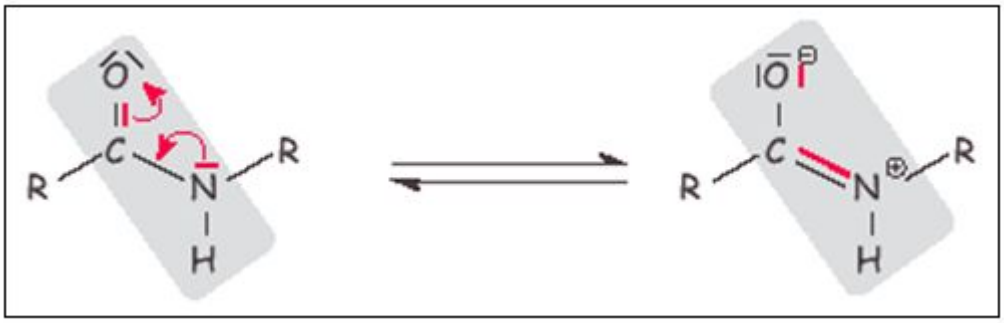
Proteins can be formed in thousands of amino acids residues.

The properties of the substituents are responsible, not only for the intramolecular, but also for the **intermolecular** interactions. When two amino acids are bound together in a so-called **peptide bond,** dipeptides are formed and, should another one be added, a tripeptide.

Oligopeptides consist of up to 10 amino acids, whereas **polypeptides** of over 10 amino acids. At the stage when polypeptides congregate or fold, a protein is produced, with hundreds to thousands of amino acids. The biggest known protein of the human organism is titin, with 30,000 amino acids.

The peptide bond is an **amine linkage**, in which the **nucleophile amine** group of amino acid 1 “attacks” the carboxylic group of amino acid 2and, as a result, they bind together. Water is released from the bond formation, which is why the reaction is called a condensation reaction.

The groups taking part in the bond are on a **planar level** and are characterized by **mesomerism.** This actually explains why hydrogen bonds are possible between the amino acids of a protein, which constitutes a vital prerequisite for protein folding.



mesomeric structures of the peptide bond

The end of a polypeptide, or protein, which has a free amine group, goes by the name **N-terminus.** Respectively, the end with the free carboxylic group is called **C-terminus.** In nomenclature, correct molecular names are produced when one reads from the N-terminus to the C-terminus, so that, if the sequence is altered, a different molecule is represented. The virtually endless number of possible combinations is calculated according to:

$$x^n$$

where x = the number of different amino acids
and n = the number of amino acids in the chain (chain length)

Protein Structural Principles

The overall structure of a protein can be a very complex issue. In order to facilitate the visualization, 4 levels are taken into consideration, which illustrates a gradual “zoom out” from primary to quaternary structure.

Primary structure – looking deeply into the protein

The primary structure of a protein includes its amino acid sequence, namely the **type and succession** of amino acids in the polypeptide chain.

Example: glycin-alanine-tryptophan-glutamine

Secondary structure – sectionally viewed

Neighboring sections of the peptide can actually interact with each other. Their spatial array is described in the secondary structure, where there are many different shapes. The most important include that of a **α-helix structure,** where the chain is **right hand-coiled** (or simply right-handed). A coil contains **3,6 amino acids.**

The inner part is formed by the main chain, whereas the **side** chains protrude **externally** in a spike-like manner. The helix structure is stabilized by **intra**molecular hydrogen bonds between the NH-group of a peptide bond and the CO-group of the 4th subsequent peptide bond (they are opposite each other in the coil). To that cause, charged side chains function rather unfavorably. Multiple helices can congregate in tangled bunches or merge in so-called **coiled-coil structures**.

Another type of common secondary protein structure is the **β-pleated sheet,** where the peptide bond is always planar and the chain follows a front-and-back **zig-zag pattern.** The **side chains** protrude interchangeably from the sheet in a downwards or upward direction, which is the reason why they must be relatively short. The distinction between **parallel and anti-parallel** pleated sheets is based on the direction of the N- and C-terminal ends. The anti-parallel array, in which an N-terminus is opposite a C-terminus, is definitely more stable. In contradistinction to the helix structure, **inter**molecular hydrogen bonds are developed here.

Peptide chains are always folded in the way that allows for the **maximum number** of hydrogen bonds to form.

Tertiary structure – the whole chain

The tertiary structure depicts the spatial structure of a complete peptide chain. We can distinguish various shapes, e.g. helix structures, pleated sheet structures, loops or unclassified/irregular sections. They are formed as a result of interactions and bonds, which are mostly developed between the side chains:

- **Van-der-Waals'-Forces** as hydrophobic interaction, e.g between unpolar side chains
- **Hydrogen bonds** between specific a polar side chain
- **Ionic bonds**, e.g. between the amine group of a basic amino acid and the carboxylic group of an acidic amino acid
- Particularly stable, covalent **disulfide bonds** between two cysteine residues (-SH), through which the so-called "loops" are formed
- **Ester bonds**

During the denaturation of proteins, their **tertiary structure is always lost**. The existing bonds are destroyed and new ones are formed, causing the initial protein structure to (possibly) lose its properties and functions.

Quaternary structure – big functional units

Big proteins are composed, not only of a polypeptide chain, but also by **various subunits:** altogether they form a functional unit. Additionally, they can also form bonds with **carbohydrates, heterocyclic compounds and other molecules**, a fact that underlines the variety of their functions. The interactions, that have already been explained in the section for tertiary structure, occur again here, and, this time, between the individual subunits.

References

Hay, R. W., &Nolan, K. B. (n.d.). Metal complexes of amino-acids, peptides, and proteins. *Amino-Acids Peptides and Proteins Amino Acids, Peptides And Proteins,*414-464. doi:10.1039/9781847552693-00414.

Hughes, A. B. (2009). *Amino acids, peptides and proteins in organic chemistry: Modified amino acids, organocatalysis and enzymes*.

In Folkers, K. (1960). *Amino acids, peptides, and proteins*. New York: New York Academy of Sciences.

Lubec, G., & Rosenthal, G. A. (1992). *Amino Acids: Chemistry, Biology and Medicine*. Dordrecht: Springer Netherlands.

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