Amino Acids

INTRODUCTION

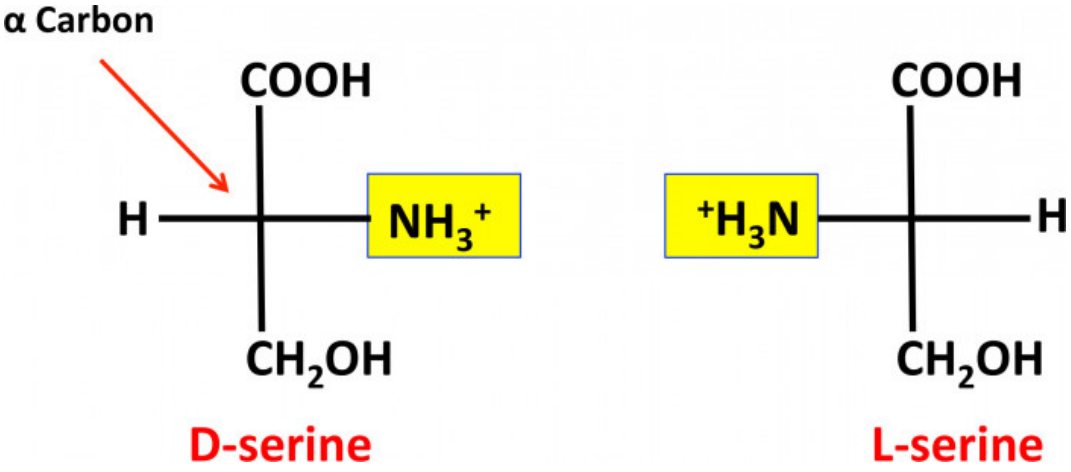
The vast majority of pharmaceutical drugs target cellular proteins, ranging from enzyme inhibition to targeting receptors as agonists and antagonists. As proteins are composed of linear chains of amino acids that fold into a functional 3D conformation, understanding amino acid structure, particularly in the context of protein function, is a central objective in biochemistry. We know the MCAT loves this topic.

Further, amino acids and their derivatives play important roles outside of protein structure and function in diverse processes. This is because many amino acids are converted into important biomolecules ranging from serotonin (neurotransmission) to histamine (allergic response, vasodilation). It is therefore clear to see why amino acid/protein structure and function formulates a very widely covered topic on the MCAT. Every MCAT exam will cover amino acids.

Absolute configuration at the α carbon

Each of canonical proteinogenic amino acids, with the exception of glycine, is chiral. That is, they display optical activity based upon the presence of an asymmetric carbon center (α carbon). For amino acids, there are two possible stereogenic states L and D that are related to each other as non-superimposable mirror images. Only the L-isomer is incorporated into proteins in humans, but bacteria use D amino acids in their peptidoglycan walls.

Amino acids are often represented as Fischer projections as shown below with serine. In a Fischer projection, the D isomer has the amino function on the right and its L enantiomer has the amino group on the left.



Acid/Base chemistry

➢ Amino acids are either di or triprotic Bronsted-Lowry acids because they dissociate protons.

➢ Bronsted-Lowry acids dissociate protons as shown below in the equilibrium dissociation with a generic acid designated as HA.

➢ The amino and carboxyl protons are considered weak acids because the protons do not completely dissociate under equilibrium conditions.

$$HA \longleftrightarrow H^+ + A^- \qquad K_a = \frac{[A^-][H^+]}{[HA]}$$

$$pK_a = -\log[K_a]$$

➢ The extent of proton (H^+) ionization can be measured by determining the equilibrium constant K_A, which is defined in this case as equal to the ratio of $[A^-][H^+]/[HA]$.

- K_A depends on various factors including the ionic strength of the buffer and the temperature.
- High K_a values signify the formation of more product(s) than reactant(s) at equilibrium.
- As K_a values can be very large or small, a more convenient and useful method of describing equilibrium is the "pK_a". By definition:

$pK_a = -\log[K_A]$

- The pK_a of typical carboxyl and amino groups is ~2.4 and 9.5, respectively and are typically reported as whole numbers. However, keep in mind that the true pK_A value is governed by the local environment and can change as a function of environment (interior or exterior of protein).

- The pK_A value quantifies the strength of a Bronsted-Lowry acid in solution and is often applied to the Henderson Hasselbach equation:

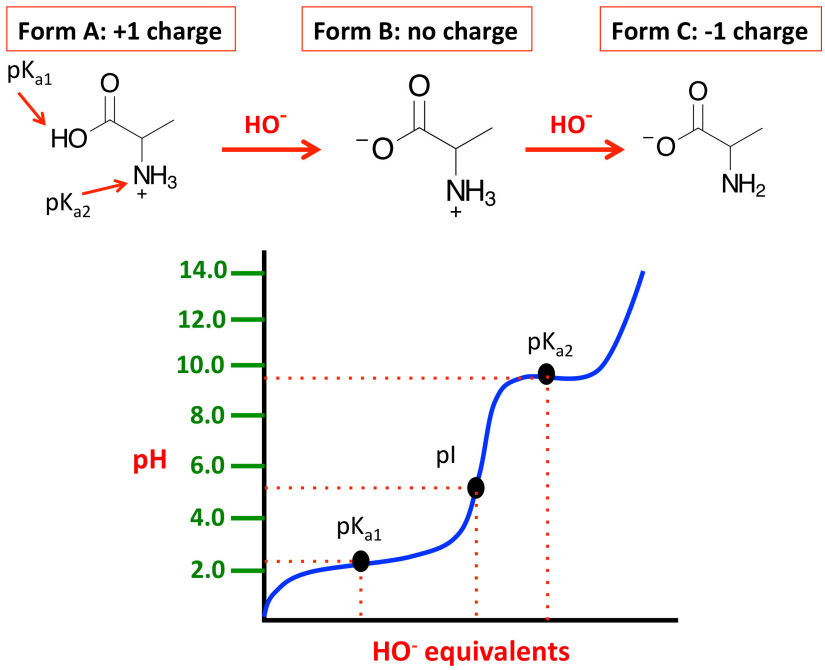
$pH = pK_a + \log[A^-]/[HA]$ **or**

$pH = pK_a + \log[BASE]/[ACID]$

Titration of Alanine

- Diprotic amino acids such as alanine exists in three ionization states (Forms A, B, and C), each with a distinct charge as shown below.

Alanine Titration Curve



➢ Low pH: Carboxyl and Amino groups are both protonated (Form A, +1 net charge).

➢ As more HO^- is added to the solution, the pH rises until it reaches a value equal to pK_{A1}, the point where ½ of the carboxyl groups are protonated and the other half are ionized. This is the ½ equivalence point.

➢ When pH = pK_A, [HA] = [A^-] or the concentration of an acid is equivalent to that of its conjugate base.

➢ Form B is generated when the carboxyl group becomes completely titrated to COO^-, the conjugate base.

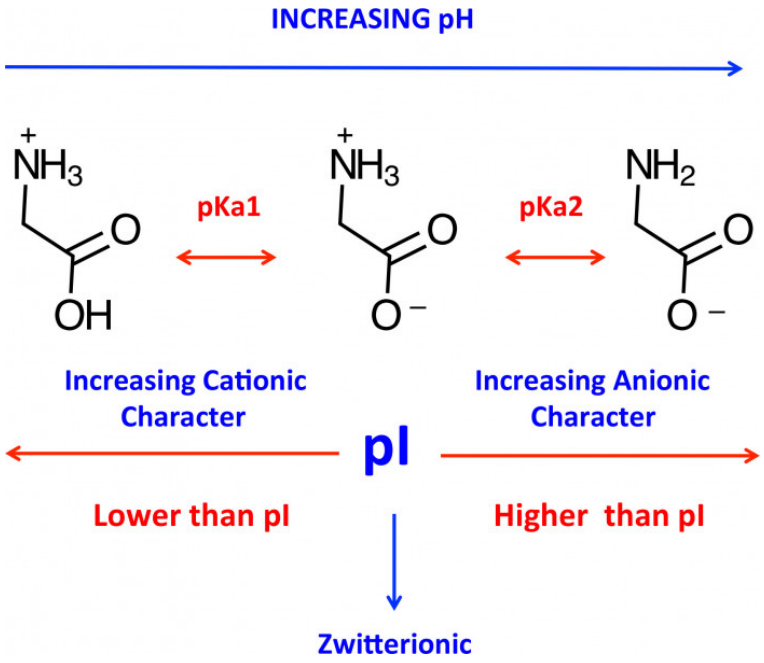
➢ This pH represents the isoelectric point (pI), the point at which the net charge on the molecule is zero.

➢ The pI for a diprotic amino acid = $pK_{A1} + pK_{A2}/2$

The pI for a triprotic amino acid = average of the two "like" pK_A values (i.e. both carboxyl groups for Asp and both amino groups for Lysine)

- Form C is generated through the addition of more HO^-, the pH will become equal to pK_{A2}. This is the pH at which ½ of the amino protons are titrated.

- The relationship between the overall charge of a diprotic amino acid (glycine) as a function of the pH and the pI are shown below. Note that when the pI > pH, the overall charge is positive, but when the pH > pI, the overall charge is negative.



Amino Acid Structure/Chemistry

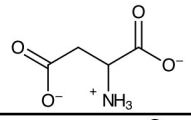
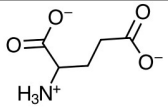
You will be dealing with amino acids forever. So, do you have to memorize the structures of the amino acids? Perhaps, but at the minimum you should be able to recognize a given amino acid and immediately associate its structure with function, particularly with respect to its general classification as acidic/basic, hydrophobic/hydrophilic, sulfur containing, posttranslational modifications etc. That is, you must understand the chemistry of the amino acid side chains.

Amino acids are usually classified by the structure and function of their side chains. The various categories are examined below.

Acidic Amino Acids

Aspartic Acid and Glutamic Acid are the proteinogenic acidic amino acids as they have side chains with carboxyl groups. They are also known as Aspartate and Glutamate when they are in the ionized state.

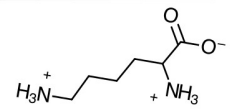
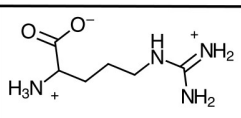
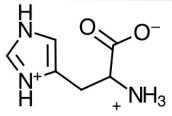
ACIDIC

Name	Abbrev	Structure	Key Features
Aspartic Acid	Asp; D		• Transaminated to Oxaloacetate • Donates Nitrogen in Urea Cycle
Glutamic Acid	Glu; E		• Excitatory Neurotransmitter • Generated from Glutamate or α-ketoglutarate

Basic Amino Acids

There are three basic amino acids as shown below. The pK_a values for the side chains of lysine and arginine are usually reported to be around 11-12. Because the pK_a value of the imidazole side chain for histidine is usually reported in the 6.0-6.8 range, histidine will be mostly neutral and in the unprotonated at the physiological pH of 7.4.

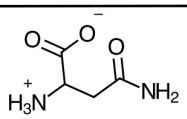
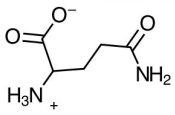
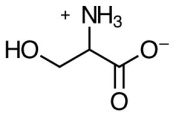
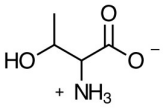
BASIC

Name	Abbrev	Structure	Key Features
Lysine	Lys; K		• Primary Amine • Major component of Histones; Undergoes Epigenetic modification
Arginine	Arg; R		• Synthesized in Urea Cycle • Used to generate Nitric Oxide and Creatinine
Histidine	His; H		• pK_a is close to Biological pH • Decarboxylated to Histamine

Polar Uncharged

The four polar, uncharged amino acids fall into two chemical classes of side chains: amides and alcohols. Therefore, these side chains often participate in hydrogen bonding.

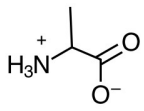
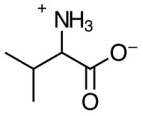
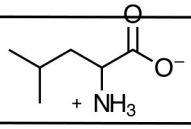
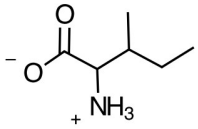
Polar Uncharged

Name	Abbrev	Structure	Key Features
Asparagine	Asn; N		· Site for N-linked Glycosylation · Generated from Aspartate
Glutamine	Gln; Q		· Major Nitrogen Carrier · Converted into Glutamate
Serine	Ser; S		· Site for O-linked Glycosylation · Commonly Phosphorylated · Precursor to Nucleic Acids, Amino Acids, Lipids
Threonine	Thr; T		· Commonly Phosphorylated · Essential

Aliphatic Amino Acids

The aliphatic amino acids consist of alanine as well as the branched chain amino acids, commonly known as "BCAA" amino acids. As these amino acids comprise up to 40% of muscle tissue, BCAAs are commonly marketed as a supplement to build muscle strength.

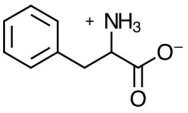
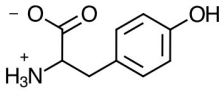
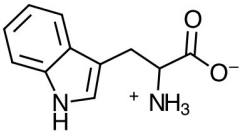
Aliphatic

Name	Abbrev	Structure	Key Features
Alanine	Ala; A		• Transaminated to Pyruvate • Provides Energy to Tissues Via Glucose-Ala Cycle
Valine	Val; V		• Hydrophobic, Aliphatic • Glu → Val in Hb causal for Sickle Cell Disease
Leucine	Leu; L		• Hydrophobic, Aliphatic • Contains "Iso" Group
Isoleucine	Ile; I		• Hydrophobic, Aliphatic • Structural Isomer of Leu

Aromatic Amino Acids

There are three aromatic amino acids, each of which serve as important precursors to neurotransmitters.

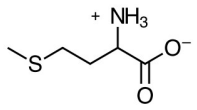
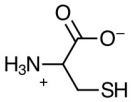
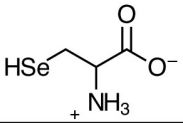
Aromatic

Name	Abbrev	Structure	Key Features
Phenylalanine	Phe; F		• Forms toxic products in Phenylketonuria • Precursor to Tyrosine
Tyrosine	Tyr; Y		• Precursor to Dopamine, Catecholamines (i.e. Epinephrine) • Precursor to Thyroid hormones T3 and T4
Tryptophan	Trp; W		• Responsible for most absorbance by Proteins at 280 nm • Precursor to Serotonin

Sulfur Containing and Selenocysteine

Two amino acids contain sulfur in their side chains, and a third one, selenocysteine, is derived from the replacement of selenium for cysteine and is a constituent in "selenoproteins".

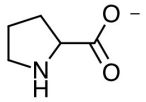
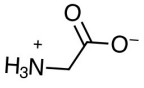
Sulfur Containing & Selenocysteine

Name	Abbrev	Structure	Key Features
Methionine	Met; M		• Generated from Homocysteine In Vit B_{12} dependent manner • N-terminal AA in most proteins
Cysteine	Cys; C		• Forms Disulfide Bridges • Strong Nucleophilic −SH group
Seleno-cysteine	Sec; U		• Proteinogenic Amino Acid • No free pools exist; synthesized on specialized tRNA

Proline and Glycine

These two amino acids are grouped together due to their unusual structures. Glycine is achiral and proline isn't really an amino acid as it is a secondary amine. Rather, proline is an imino acid. Although its side chain is aliphatic in nature, we have classified it separately due to its secondary amine structure.

Proline & Glycine

Name	Abbrev	Structure	Key Features
Proline	Pro; P		• 2° amine = "Imino" Acid • Absent from α helices • Hydroxylated in collagen • Exists in cis-peptide bonds
Glycine	Gly; G		• Achiral • Inhibitory Neurotransmitter • Used to make Heme