Biomolecules

- Proteins: Amino acid polymers; amino acids are often called residues; oligopeptide = very small chain of amino acids; polypeptide = longer chain of amino acids.
  - General Amino Acid Characteristics
    - Alpha-carbon Stereocenter: All human amino acids, except one, are chiral at the \( \alpha \) carbon because the \( \alpha \) carbon contains four different substituents: an \(-R\) group, a hydrogen, a carboxylic acid, and an amine.
    - Absolute Configuration: All amino acids are designated as either L- or D-, depending on the side on which the amine group is located in a Fischer Projection (L = Left; D = Right). All native human amino acids are L-amino acids. L- and D- do NOT correlate directly with R and S and should be considered as separate stereochemical designations. Most L-amino acids are S, but some L-amino acids are R (e.g., cysteine).
  - Q1. Draw a Fischer projection of the amino acid alanine in both its L- and D- forms.
  - Q2. While true that L- and D- do not correlate directly with R and S, among all 20 of the common amino acids there are only two cases in which an amino acid cannot be said to be BOTH L- and S. Name the two exceptions and explain why, specifically, they are exceptions.
  - \(-R\) Groups DETERMINE Chemistry: Amino acid \(-R\) groups largely DETERMINE the chemistry of the amino acid, and the combination of \(-R\) groups in a protein almost exclusively DETERMINES its chemistry and folding pattern.
    - Will a substrate bind in an active site? The answer depends on the existence of complementary charges on the \(-R\) groups, and/or the hydrophilicity or hydrophobicity of the \(-R\) groups.
    - How will a protein fold? Hydrophobic \(-R\) groups fold INTO the protein core (hydrophobic environment), and hydrophilic \(-R\) groups are more common on the surface of the protein (hydrophilic environment). Proteins with low hydrophobicity do not fold into a stable structure, but can retain function (e.g., Intrinsically Disordered Proteins).
    - Reaction mechanisms in the enzyme pocket? They are entirely a function of the chemistry of the \(-R\) groups found in that pocket. You can usually predict accurately the amino acids present in a protein ligand or in an enzyme active site, just by knowing how the protein is functioning (At the very least, you can narrow it down to a select group of possibilities).
    - When you see PROTEIN or ENZYME THINK: What amino acids are present and what is the chemistry of their \(-R\) groups?
  - The 20 Common Amino Acids: FOR MCAT-2015 YOU MUST KNOW YOUR AMINO ACIDS!
    - The pre-released MCAT-2015 materials from the AAMC contained multiple questions that required specific knowledge of amino acid structure, including:
      - \(-R\) group structure
      - \(-R\) group chemistry
      - \(-R\) group hydrophilicity vs. hydrophobicity (polar vs. non-polar)
      - \(-R\) groups with charges (negative = acidic; positive = basic)
      - \(-R\) groups that are aromatic
      - amino acid names
      - amino acid three-letter abbreviations
      - amino acid single-letter abbreviations.
IMPORTANT NOTE

This is an excellent time to revisit the concept of semantic processing. If you only make rote notecards about these amino acid details, or re-copy the chart mindlessly over and over again, you are engaging in SHALLOW functional or phonemic processing, NOT semantic processing. In addition to basic rehearsal, go further by looking for commonalities or relatedness. Here is one extremely powerful thing you can do: Learn one real-life function for each amino acid – R group. Is it part of a catalytic triad? Where is it usually found in proteins? If you know WHAT it does, or HOW it works, you will more easily remember its structure.

Sample MCAT Question

1) 5HTT is a monoamine transport protein responsible for the reuptake of serotonin from synapses in the central nervous system. 5HTT also has a high affinity for which amino acid?

![Serotonin]

A) Arg  
B) Trp  
C) Val  
D) Glu

Solution: The stem states that 5HTT transports serotonin. It is logical to assume that it will also transport, and therefore have high affinity for, something very similar to serotonin in structure and polarity. Answer B, tryptophan, is certainly a possibility given that the aromatic portion of serotonin is nearly identical to that of Trp. Answer A, arginine, would not be a good candidate because it has a positively-charged side chain and no aromatic group. Answer C, valine, is a much smaller non-polar amino acid. Answer D also has a negatively charged side chain. This leaves Answer B as the best answer.
- **Order of Deprotonation:** There are multiple cases wherein you will benefit from knowing approximate pK\(_a\) values for the side chains. There are not that many, and they predict the order in which the acidic functional groups of a protein or amino acid will be deprotonated.
  
  - **Proceeding from acidic to basic** (low to high pH):
    1. \(\alpha\)-COOH Group \(pK_a \approx 2\)
    2. -R Group, ACIDIC \(pK_a \approx 4\) \([\text{Asp} = 3.7; \text{Glu} = 4.5]\)
    3. -R Group, His \(pK_a \approx 6\)
    4. \(\alpha\)-NH\(_3^+\) Group \(pK_a \approx 9\)
    5. -R Group, BASIC \(pK_a \approx 11-12\) \([\text{Lys} = 10.7; \text{Arg} = 12]\)

- **Q4.** Which amino acids are most likely to be part of an enzyme active site where the first step of the catalyzed reaction involves abstraction of a proton from the substrate? What if the first step is protonation of a functional group on the substrate?

- **Essential vs. Non-Essential Amino Acids:**
  
  - ESSENTIAL = Your body cannot synthesize this amino acid. You must ingest it.
  - NON-ESSENTIAL = Your body can synthesize this amino acid on its own.

- **Zwitterion:**
  
  - A dipolar version of an amino acid wherein positively and negatively charged functional groups cancel one another out, resulting in a neutral ion.
  - **Q5.** Draw isoleucine and glutamic acid in their Zwitterion forms.

- **Acid-Base Functionality of Amino Acids:** *Amino ACIDS are weak ACIDS.* Therefore, **amino acids exhibit the same general acid-base functionality covered in the General Chemistry 2 chapter.**
  
  - Each amino acid has a MINIMUM of two acidic protons: \(-\text{COOH}\) and \(-\text{NH}_3^+\)
  - Some amino acids (discussed below) have acidic side chains, and therefore three acidic protons.
  - Per the above statements, each amino acid has either two or three pK\(_a\) values.
    
    - The amino acid acts as a buffer when the pH is near the pKa of one of the acidic protons.

- **Isoelectric Point:**
  
  - **Q6.** Provide a conceptual definition for isoelectric point. To which acid-base titration term is the isoelectric point most similar? a) half-equivalence point, b) equivalence point, c) end point, or d) buffer region? Why?
  
  - **Estimating Isoelectric Point:** acidic, basic and neutral amino acids
    
    - \(pI_{\text{neutral}}\) = average of \(pK_a\)-amine group and \(pK_a\)-carboxyl group.
    - \(pI_{\text{acidic}}\) = average of \(pK_a\)-acidic R group and \(pK_a\)-carboxyl group.
    - \(pI_{\text{basic}}\) = average of \(pK_a\)-amine group and \(pK_a\)-basic R group.

  - **Q7.** Draw a titration curve for the titration of a solution of phenylalanine with sodium hydroxide. Label the following: half-equivalence point, equivalence point, end point, \(pI\), and buffer region (Hint: Some terms may apply more than once). Describe the relative concentrations of each species at each of the above-stated points along the curve. Draw a similar titration curve for aspartic acid titrated with sodium hydroxide. In what ways does this titration curve differ?
Amino Acid Reactions

- Peptide Bond Formation:
  - Reaction Type: Dehydration Synthesis and Acyl Substitution
    - The amine group nitrogen (nucleophile) from the NEW amino acid attacks the carbonyl carbon (electrophile) on the C-TERMINUS of the growing peptide chain (aided by the enzymatic function of the ribosome).
  - Peptide Chain Conventions
    - Peptides are Written, Read, AND Synthesized from N-terminus \(\rightarrow\) C-terminus
  - Resonance
    - Resonance between the pi electrons of the C=O bond, and the nitrogen lone pair of the C-N bond, yield two resonance structures for any peptide bond. The actual structure is a hybrid of the two, and therefore: BOTH the C=O bond and the C-N bond in a peptide bond have DOUBLE BOND character.
      - Q8. Draw both resonance structures for a peptide bond.
    - Double bond character \(\Rightarrow\) RIGID peptide bond with limited rotation.

- Protein Hydrolysis: Trypsin and chymotrypsin cleave proteins on the CARBOXYL SIDE of specific amino acid residues:
  - Trypsin = arginine, lysine
  - Chymotrypsin = phenylalanine, tryptophan, tyrosine

- Sulfur Linkage
- Strecker Synthesis
- Gabriel Synthesis

Sample MCAT Question

2) If the pH of a solution is below the pKₐ of the \(\alpha\) carboxylic acid of isoleucine, what will be the charge on the majority of isoleucine molecules in that solution?

A) 2+
B) 1+
C) 0
D) 1-

Solution: Isoleucine has a non-polar aliphatic side chain. The side chain will never have a charge because it has no acidic or basic properties. The answer to this question would be different if the amino acid in question were, say glutamine. For isoleucine, when the pH is below the pKₐ of the \(\alpha\) carboxylic acid group, that group will be protonated. In other words, it will be a neutral –COOH with no charge. At that same pH the amino group will be fully protonated, existing as the positively-charged –NH₃⁺ group (pKₐ ~ 9). Adding these together gives a net charge of 1⁺, so Answer B is correct. Note that with a very small increase in pH, to above the pKₐ of the \(\alpha\) COOH group of isoleucine (about 2) the carboxyl group will be deprotonated and isoleucine will then exist as the neutral Zwitterion—as it does at physiological pH.
Q9. Draw a mechanism for each of the reactions outlined on the previous page: 
a) oxidation/sulfur-linkage of two cysteine residues, b) formation of a peptide bond, c) 
hydrolysis of a peptide bond, d) Strecker Synthesis and e) Gabriel Synthesis. Use real amino 
acid species and show electron flow wherever possible.

Protein Structure:

- **Primary**: The amino acid sequence.
- **Secondary**:
  - **Alpha-Helices**: Hydrogen bonding between the carbonyl oxygens and the amide hydrogens 
    that are exactly FOUR residues apart, including the residues involved in the hydrogen bond 
    (i.e., A-B-B-A arrangement where A and A share a hydrogen bond).
  - Each amino acid forms a hydrogen bond with the fourth amino following it in the chain.
  - **R groups are directed exactly away from the alpha helix cylinder** (i.e., perpendicular 
    to a plane tangent to the surface of the alpha helix).
  - **Beta Sheets**: Hydrogen bonding between ALL of the carbonyl oxygens in one row and the 
    amide hydrogens in the adjacent row.
    - ALL residues involved in hydrogen bonding!
    - R groups are directed perpendicular to the plane of the beta sheet, on **both** sides.
    - Beta sheets assume a **pleated** conformation. This is necessary for the carboxyl and 
      amide moieties to line up properly so that every residue is participating in two hydrogen 
      bonds.
  - **PROLINE**: Usually the first residue at the very end of an alpha helix, but rarely found inside 
    the helix because it introduces a KINK/TURN. This same KINK/TURN is desirable at the end 
    of beta-sheets because the chain must make a 180 degree turn to align as a neighboring 
    row in the beta sheet.
  - Common Applications of Secondary Structures:
    - **Keratin**, found in hair and nails = alpha helices.
    - **Fibroin**, the molecule that makes up silk = beta sheets.
  - **Tertiary**: Geometric, three-dimensional folding of the alpha helices, beta sheets, and other 
    moieties to form a functional globular or structural protein.
  - **Quaternary**: Association of multiple folded proteins into a multi-subunit complex.
    - **Hemoglobin** = Classic example of quaternary structure.
      - Consists of four protein chains, two alpha subunits and two beta subunits.
      - Each subunit contains one heme capable of binding one O₂ molecule.
      - **Positive Cooperativity** = **Ligand affinity increases with the binding of each 
        subsequent ligand**. In the case of hemoglobin, affinity for the first oxygen is relatively 
        low, but increases for the second, third, and fourth oxygen to bind. This affinity remains 
        in effect during offloading of oxygen at the tissues. Therefore, the first oxygen (highest 
        cooperative affinity) dissociates at the slowest rate, but each subsequent oxygen is 
        released more easily.
Charged side chains will be found on the surface of globular proteins if they are NOT paired with a complementary molecule. However, they CAN be found inside the hydrophobic core if they are paired up with a complementary side chain of opposite charge. A similar complementarity exists between acid and base side chains because they can undergo an acid-base neutralization reaction. Finally, none of these rules of thumb are absolutes. One will occasionally find hydrophobic residues on the surface (i.e., proline is relatively common), but the majority of hydrophobic –R groups will be internal and the majority of hydrophilic –R groups will be on the surface. This is a perfectly safe generalization for the MCAT.

**Protein Folding:** A translated protein assumes secondary structure almost instantly, and then folds into its globular or structural tertiary state, driven by the interactions described below. You may see proteins in various states of folding referred to as a **globule** (fully folded), **molten globule** (partially folded) or as **molten** (fully unfolded; a.k.a. **denatured**).

- **Hydrophobic Core:** Hydrophobic –R groups fold into the **interior** of a globular protein to escape water. They often bring some smaller polar groups with them, which interact in a complementary way to stabilize the folded protein further.

- **Hydrophilic Surface:** The majority of the –R groups on the surface of a globular protein are either polar or charged.

- **Electrostatic Interactions:** Interactions between charged –R groups both encourage the act of folding itself, and stabilize the protein in its folded state.

- **Hydrogen Bonds:** Hydrogen bonding between –R groups also encourages folding and stabilizes the folded protein.

- **Disulfide Bonds:** Two oxidized cysteine residues form a disulfide (R-S-S-R) bond. This is the strongest type of protein folding interaction. Disulfide bonds between keratin alpha helices are what make hair more or less curly.

- **Salt Bridges:** Formed when acidic and basic –R groups undergo a neutralization reaction resulting in a salt.

- **Proline Turns:** Can be considered as either disrupting 2\(^\circ\) structure or as contributing to 3\(^\circ\) structure. **Neither α-helices, nor β-sheets can contain proline internally without disruption of the 2\(^\circ\) structure.** However, proline residues are often found at the beginning of α-helices and are very common (along with glycine) in the sharp turns at the end of two adjacent rows in a β-sheet.

- **Solvation Layer:** A layer of water that surrounds a dissolved protein. The water molecules in this layer interact closely with each other and with the protein’s surface. The water in the hydration layer is more ordered that the bulk water in the general area and is considered not to participate with the bulk (a.k.a., unstructured) water when considering colligative properties.

- **Entropy and Protein Folding:** Even when water interacts with a dissolved polar solute, this interaction is less entropically favorable than the same water molecules interacting with only other water molecules. However, the driving thermodynamic force that favors protein folding results from the fact that non-polar regions require a much GREATER ordering of water molecules to accomplish solvation. Therefore, transitioning from solvation of non-polar regions to solvation of a mostly polar or charged globular protein surface, represents a net increase in entropy. In fact, it is enough to overcome the decreased entropy associated with the protein being in a folded rather than an unfolded state. **This favorable increase in entropy is a major contributor to the overall conformational stability of the folded protein.**

- Q11. What aspect of a protein is primarily responsible the manner in which it folds?
o Protein Denaturing Agents:
  • Acid
  • Heat
  • Urea
  • Mercaptoethanol

  Q12. What steps are necessary to cause a simple denatured protein to re-fold? Will this process work, unaided, for all proteins?

o Protein Separation Techniques:
  • Isoelectric Point
  • Electrophoresis

  Q13. Explain conceptually, including drawings or figures, the process of separating proteins via a) isoelectric point, and b) electrophoresis. Propose at least two AAMC-style questions you could be asked on the MCAT about these two protein separation techniques. (Hint: It is very likely the MCAT will ask you to make a prediction, such as relative distance traveled in electrophoresis, based off of the structure of the protein or amino acid.)

o Major Non-Enzymatic Protein Functions: KEEP IT SIMPLE! We believe MCAT-2015 will only require that you be generally familiar with these “other important” functions of proteins.

  • RECOGNIZING PROTEINS: The central dogma is certainly important, as are enzymes, but students often miss questions when they fail to recognize proteins in other circumstances. Many MCAT-2015 questions reward the examinee for a simple recognition such as this: STEM = “In what part of the cell is calmodulin synthesized?” The unsophisticated student will think this requires specific prior knowledge about the biochemistry of calmodulin. All it really requires is recognizing that calmodulin is a protein. Remember that ANY protein in the cell must have been coded for by DNA. Alternate splicing and post-transcriptional processing allows for a greater variety of proteins, but ultimately all proteins are still gene products.

    • Binding Proteins = hemoglobin, calmodulin, troponin, tropomyosin, histones, transcription factors, cell adhesion molecules

    • Immune System = antigens, antibodies

    • Structural Proteins = actin (thin filaments, microfilaments), tubulin (microtubules), keratin (hair and nails, intermediate filaments), elastin (connective tissue, extracellular matrix).

    • Motors = myosin (power stroke, cellular transport), kinesins and dyneins (vesicles, cellular transport, cell division, cilia, flagella).

      • Kinesins = Move along microtubules from (−) to (+) end [center of cell to periphery; nerve cell body → dendrite]

      • Dyneins = Move along microtubules from (+) to (−) end [periphery to center of the cell; nerve cell dendrite → cell body]
**Enzymes**: Biological Catalysts

- **WHEN YOU SEE ENZYME THINK**: **Enzyme** = **Protein**. (For the MCAT, assume all enzymes are proteins, unless told otherwise. There are a few rare exceptions. Ribosomes, for example, are made primarily of rRNA, and yet they catalyze the polymerization of amino acids.)

  - Q14. Describe the differences between a catalyst and an enzyme.
  - Q15. How do enzymes affect each of the following? a) reaction rate, b) energy of activation, c) equilibrium, d) $K_{eq}$, e) yield, and f) percent yield.

- **Effects of Local Conditions on Enzyme Activity** (pH, temperature, etc.)

  - Q16. How do each of the following affect reaction rate for an enzyme-catalyzed reaction? a) pH, b) temperature, c) substrate concentration and d) enzyme concentration. Draw a graph of RXN rate vs. each of the variables listed above.

- **Enzyme Classification by Reaction Type**:

  - Some enzymes fit into multiple categories.
    - **Oxidoreductases** = REDOX reactions
    - **Transferases** = Transfer of a functional group (e.g., kinases, aminotransferases)
    - **Hydrolases** = Hydrolysis
    - **Isomerasers** = Rearrangements (e.g., phosphoglucose isomerase [G6P $\rightarrow$ F6P], epimerases)
    - **Lyases** = AB $\rightarrow$ A + B [cleavage/synthesis; NO H2O, NOT hydrolysis]
    - **Ligases** = Addition or synthesis of LARGE molecules, usually ATP-dependent (e.g., DNA Ligase)
      - MNEMONIC: **Enzymes help reactions Over The HILL** (i.e., the Energy of Activation)

- **Substrate-Enzyme Specificity**

  - Q17. Provide a conceptual explanation for: substrate, active site, and enzyme-substrate complex.
  - Q18. Two theories of enzyme specificity are: ____________ and ______ & ______. Which of these two theories has been largely dismissed by scientists? Why has it been dismissed?

- **Mechanism of Catalysis**: **Cofactors, Coenzymes, and Prosthetic Groups**

  - **Cofactors**: A general term for any species required by an enzyme to function; coenzymes and prosthetic groups are both examples of cofactors.
  - **Coenzymes**: Non-protein species NOT permanently attached to the enzyme but required by the enzyme to function.
  - **Prosthetic Groups**: Non-protein species that ARE permanently attached to the enzyme and are required by the enzyme to function.
    - Q19. Provide a real-life human body example of a reaction that requires a) a coenzyme, and b) a prosthetic group. Draw and describe the function/role of the cofactor in the reaction.

- **Simple vs. Conjugated Proteins**

  - Simple Protein = Protein that contains only amino acids and no non-protein cofactors or prosthetic groups. If it is a simple protein that is an enzyme, it is called an apoenzyme.
  - Conjugated Protein = Protein that is associated with its cofactors, either covalently or via intermolecular attractions. Hemoglobin is a conjugated protein because it contains the non-protein heme group. If it is a conjugated protein that is an enzyme, together with its cofactors it is called a holoenzyme.
Vitamins & Minerals

- Vitamin
  - Fat Soluble = A, D, E, and K
  - Water Soluble = All the rest.
  - Q20. Can a person more easily overdose on fat-soluble vitamins or water-soluble vitamins? Why?

- Minerals
  - Q21. What are the differences between vitamins and minerals? What key biological functions involve or require vitamins and minerals?

Michaelis-Menten (M-M) Kinetics

- M-M Saturation Curve: A graph of reaction velocity vs. substrate concentration [S]. This graph reveals the relationship between \( \frac{1}{2}v_{\text{max}} \) and \( K_m \), as well as the overall concept of "saturation kinetics."
  - Q22. Draw a graph of Reaction Rate vs. [Substrate] and label the axes. Label and describe \( v_{\text{max}} \). Label and describe \( K_m \). Describe the meaning of the term "saturation kinetics" in terms of your graph.

- M-M Equation: The relationship between reaction velocity, \( K_m \) and substrate concentration.
  - \( v = v_{\text{max}}[S]/(K_m + [S]) \)
  - Q23. Use a derivation of the Michaelis-Menten Equation to prove that at one-half the maximum velocity \( K_m \) is equal to the substrate concentration, \([S]\).

- Michaelis Constant: \( (K_m) \)
  - \( K_m = \text{Relative measure of an enzyme's affinity for its substrate. The magnitude of } K_m \text{ is INVERSELY proportional to substrate-enzyme binding affinity. The lower the } K_m, \text{ the stronger the binding affinity.} \)
  - \( K_m = [S] @ \frac{1}{2}v_{\text{max}} \)

- Lineweaver-Burk Plots: A double-inverse graph of the Reaction Rate (\( v \) inverted to \( 1/v \)) and substrate concentration ([S] inverted to \( 1/[S] \)) graph described above.
  - Y-Intercept = \( 1/v_{\text{max}} \)
  - X-Intercept = \( -1/K_m \)
  - Applications:
    - Used to calculate \( v_{\text{max}} \) and \( K_m \) experimentally.
    - Used to identify Enzyme Inhibition: We will cover enzyme inhibition in the following section. Each type of inhibition has a characteristic impact on \( K_m \) and \( v_{\text{max}} \). Because these two values can be easily calculated from the x- and y-intercepts of a Lineweaver-Burk plot, the type of enzyme inhibition can be easily deduced. To do so, you must have two trials, one with, and one without, the inhibitor. By comparing these two results you can observe the IMPACT of the inhibitor on \( K_m \) and \( v_{\text{max}} \), and therefore deduce the type of inhibitor.
Enzyme Inhibition:

- **REVERSIBLE INHIBITION**: Inhibitor is not permanently bound; enzyme is not completely disabled.
  - **Competitive**: *Inhibitor binds at the active site*: The inhibitor resembles the substrate in shape; the inhibitory effect can be overcome by increasing the concentration of the substrate.
    - $V_{\text{max}} = \text{NO CHANGE}$
    - $K_{\text{m}} = \text{INCREASES}$
  - **Uncompetitive**: *Inhibitor binds ONLY with the enzyme-substrate complex*.
    - $V_{\text{max}} = \text{DECREASES}$
    - $K_{\text{m}} = \text{DECREASES}$
  - **Non-Competitive**: *Inhibitor binds away from the active site* and changes the shape of the enzyme. The inhibitor has an equal affinity for both the enzyme-substrate complex (E-S) and the enzyme (E).
    - $V_{\text{max}} = \text{DECREASES}$
    - $K_{\text{m}} = \text{NO CHANGE}$
  - **Mixed**: Inhibitor has unequal affinity for the E-S and the E, favoring one over the other.
    - $V_{\text{max}} = \text{DECREASES}$
    - $K_{\text{m}} = \text{INCREASES if inhibitor = } \uparrow \text{affinity for E-S over E}$
    - $K_{\text{m}} = \text{INCREASES if inhibitor = } \uparrow \text{affinity for E over E-S}$

- **IRREVERSIBLE INHIBITION**: Inhibitor binds covalently to the enzyme and/or the active site, disabling the enzyme for either a prolonged period of time, or permanently.
  - **Q24.** Identify one real-life (preferably human-body) example of each of the following kinds of enzyme inhibition: Competitive, Uncompetitive, Non-Competitive, Mixed, and Irreversible.
  - **Q25.** Draw a Lineweaver-Burk plot showing three trials for a hypothetical enzyme-catalyzed reaction with: a) no inhibitor, b) a competitive inhibitor, and c) a noncompetitive inhibitor.
  - **Q26.** Draw a graph of Reaction Rate vs. Substrate Concentration [$S$] for a hypothetical enzyme-catalyzed reaction with a) no inhibitor, b) a competitive inhibitor, and c) a noncompetitive inhibitor, and d) an irreversible inhibitor.
Feedback Inhibition (a.k.a., Negative Feedback): A specific type of non-competitive or allosteric inhibition that applies to multi-step reactions, synthetic pathways, or cascades. One of the products of a reaction later in the chain acts as an inhibitor for one of the enzymes earlier in the chain.

- **Sample MCAT Question**

3) The graph below depicts reaction velocity for an enzyme-catalyzed reaction with and without a competitive inhibitor. If a third trial is added to the graph for a noncompetitive inhibitor, the new saturation curve will be oriented:

![Graph with reaction velocity](image)

- A) between the existing curves, with a higher $V_{max}$.
- B) above the existing curves, with a lower $V_{max}$.
- C) below the existing curves, with a lower $V_{max}$.
- D) below the existing curves, with the same $V_{max}$.

**Solution:** Noncompetitive inhibitors decrease $V_{max}$ while having no effect on $K_m$. This eliminates answers A and D because reaction velocity will be decreased. Answer B is impossible because for the curve to exist on the coordinate system “above” the existing curves would require increased reaction velocity. Answer C is therefore correct.

- **Feedback Inhibition** (a.k.a., Negative Feedback): A specific type of non-competitive or allosteric inhibition that applies to multi-step reactions, synthetic pathways, or cascades. One of the products of a reaction later in the chain acts as an inhibitor for one of the enzymes earlier in the chain.

- **Q27.** Provide a conceptual definition for each of the following and provide real-life human body examples: a) positive feedback, b) zymogens, c) allosteric enzymes.
**Carbohydrates**: Empirical formula of all monosaccharides = \((\text{CH}_2\text{O})_n\); polysaccharides = \(C_n(\text{H}_2\text{O})_x\)

- **Nomenclature and Classification**
  - "-ose" ending is given to all sugars.
  - "deoxy-" prefix is used if the normal location of an –OH group is replaced with hydrogen.
  - Aldose vs. Ketose (aldehyde vs. ketone)

- **Common-Named Sugars for MCAT-2015**
  - Common Monosaccharides
    - glyceraldehyde
    - dihydroxyacetone
    - ribose
    - deoxyribose
    - glucose
    - fructose
    - galactose
    - mannose
  - Common Disaccharides
    - lactose = galactose + glucose (β-linked)
    - maltose = glucose + glucose
    - sucrose = glucose + fructose

- **Cyclic Structure and Conformation of Hexoses**
  - Pyranose vs. Furanose (6-member ring vs. 5-member ring)
  - Hemiacetals vs. Hemiketals (cyclical aldehydes vs. cyclical ketones)

- **Stereochemistry**: Absolute Configuration, Epimers & Anomers
  - **R/S ≠ D-/L-**: For non-mathematical types, R and S are NOT the same as D- and L-.
    - D-sugars = all human body sugars; **L-sugars do NOT occur naturally in humans.**
  - **D-glucose vs. L-glucose** = ENANTIONMERS (same molecule, different stereochemistry)
    - L = furthest –OH group from the carbonyl is to the LEFT in Fischer projection.
    - D = furthest –OH group from the carbonyl is to the RIGHT in Fischer projection.
    - SAME molecule; different stereochemistry at the last chiral carbon.
  - **α-glucose vs. β-glucose** = ANOMERS
    - SAME molecule; different stereochemistry @ the anomeric carbon
  - **glucose vs. galactose** = EPIMERS
    - DIFFERENT molecules; an example of diastereomers
    - NOTICE that the enantiomers and anomers have the SAME name (glucose in all of these examples), whereas the epimers have DIFFERENT names (glucose/galactose)

**IMPORTANT NOTE**

Your safest bet is to ignore those occasions when the R/S and D/L conventions happen to correlate. Treat them as entirely different concepts. If asked to determine R/S, rank the substituents and assign R or S. If asked for D- or L-, DRAW A FISCHER PROJECTION! If the hydroxyl group attached to the highest-numbered chiral carbon is on the right in the Fischer projection it is D-, if it is on the left, it is L-.
Carbohydrate Reactions

- **Ring-Closing:**
  - **Intramolecular Nucleophilic Substitution:** The –OH group on the chiral carbon that is furthest from the carbonyl carbon (the same one used to determine D/L) acts as the nucleophile, attacking the carbonyl carbon (electrophile). The carbonyl oxygen is protonated to form a hydroxyl group.
  - **Q28.** Draw each of the following: a) glucose and fructose in both "ring" and "chain" forms, b) the electron flow for the ring-closing reaction of both glucose and fructose, c) the alpha & beta anomers of glucose, and d) ribose and deoxyribose (IMPORTANT: because they form the sugar backbone of RNA & DNA, respectively). Which of the molecules just drawn are ketones? Which ones are aldehydes?
  - **Q29.** Differentiate between a reducing sugar and a non-reducing sugar.

- **Hydrolysis of the Glycoside Linkage:** Polymer(n) + H₂O → Polymer(n-1) + monomer

- **Keto-enol Tautomerism of Monosaccharides:** Like other ketones and aldehydes, sugars can alternate between keto and enol forms.

- **Polymerization:** Monosaccharide → Disaccharides → Polysaccharides
  - α-linkage = linked through an oxygen that is on the OPPOSITE SIDE of the plane from the CH₂OH group (i.e., trans).
  - β-linkage = linked through an oxygen that is on the SAME SIDE of the plane as the CH₂OH group (i.e., cis).

- **Glucose Polysaccharides:**
  - **Glycogen:** Branched, α-linked glucose polymer, used for energy storage in animals
  - **Starch:** Branched, α-linked glucose polymer, used for energy storage in plants
  - **Cellulose:** β-linked glucose polymer, used for energy storage in plants, indigestible to animals without help from symbiotic bacteria.

Lipids:

- **Definition:** Lipids are a class of biomolecules with a rather inexact definition. Many sources define the term "lipid" by giving a list of the biomolecules classified as such. These include fats, oils, waxes, sterols, fat-soluble vitamins, glycerides (mono-, di-, and tri-), phospholipids, and terpenes.

  - **For MCAT-2015 focus on the two major identifying characteristics of lipids:**
    1) Lipids are biomolecules
    2) Lipids are hydrophobic.

- **Lipids to Know for MCAT-2015:** Be generally familiar with each structure, be able to draw it in line-bond form, recognize each functional group it contains, and predict where it is likely to be found or used in the human body.

  - **Fatty Acids**
  - **Triacylglycerols** (a.k.a., triglycerides)
    - Glycerol backbone (HOCH₂CH(OH)CH₂OH) with three fatty acids attached via ester linkages.
    - Saturated vs. Unsaturated Fats
      - **Q30.** Differentiate between saturated and unsaturated fats. Which one is more healthy in terms of human consumption and why?
  - **Phospholipids**
    - Phosphatid = The most basic phospholipid, with two fatty acid moieties and ONLY a phosphate group—which is attached directly to the glycerol backbone. Most phospholipids in biological membranes have other functional groups attached to the phosphate head. You may also see this term as part of a named phospholipid, as in phosphatidylcholine.
- **Saponification**: The hydrolysis of an ester (e.g., triglycerides, phospholipids, etc.)
  - *Triacylglycerols and phospholipids are both ESTERS.* Fatty acids are the only lipids that have a –COOH group. Students often refer to triacylglycerols as “fatty acids attached to glycerol,” and many books even call them “fatty acid tails.” This has led some students to be confused. Once a fatty acid attaches to glycerol, it is an ester.

- **Steroids**
  - Q31. All steroids are ______-member ring structures. Identify the A, B, C, D ring-naming convention for steroids.

- **Terpenes** (Terpenoids)

- **Sphingolipids**

- **Waxes**

- **Glycolipids**
  - Q32. Draw each of the lipids described above in line-bond form (fatty acids, triacylglycerols, phospholipids, steroids, terpenes, sphingolipids, waxes, and glycolipids).

- **Prostaglandins**
  - Lipid mediators that have **autocrine** (self-target) and **paracrine** (target = cell in immediate vicinity) functions throughout the body.
  - **UNLIKE endocrine hormones:**
    - Produced and released throughout the body; NOT only in specialized glands.
    - Act locally, rather than traveling to a distant target via the bloodstream.
  - Q33. Which of the above lipids (fatty acids, triglycerides, phospholipids, steroids, terpenes, sphingolipids, waxes, glycolipids, and prostaglandins) are amphipathic?
Sample MCAT Question

4) Given four amino acids, Glycine, Phenylalanine, Glutamine and Aspartamine, how many unique proteins can be formed without using any amino acid more than once in any protein?

A) 8
B) 16
C) 24
D) 256

Solution: The safest way to approach this question is to write out all of the chains you can create starting with one of the four amino acids. This is the more conceptual approach. For example, starting with Gly you could form: Gly-Phe-Glu-Asp, Gly-Phe-Asp-Glu, Gly-Glu-Phe-Asp, Gly-Glu-Asp-Phe, Gly-Asp-Glu-Phe and Gly-Asp-Phe-Glu. That is six unique chains by starting with Gly. This could be done once for each of the four amino acids, so there are 6 times 4, or 24 possible proteins. Answer C is thus correct. Using n! (n factorial) will also work in this case, only because each item can only be used once. The n represents the number of items and the math becomes: 4 x 3 x 2 x 1 = 24. Be careful, however, using the factorial method. We have seen many students who rely on this method use it when each item could be used more than once—in which case it gives an incorrect answer. Had this question allowed you to use each item multiple times (i.e., proteins such as Gly-Gly-Gly-Gly and Phe-Phe-Phe-Phe would have been possible), you could obtain the answer using x^y where x is the number of possible values for each position, and y is the number of positions. This only works, however, if any position can use any of the available values (i.e., license plates). It is also pertinent to this question to remember that proteins are not reversible. Peptide A-B-C is not the same as C-B-A because in the first case A is the N-terminus and in the second case A is the C-terminus. Nucleotides are also non-reversible, one side being 5’ and the other 3’.
Amino Acid Chart:

Use the following chart as a reference while committing to memory the various attributes of the 20 common amino acids. Selenocysteine, the 21st acid in this chart, is an interesting case. It is proteinogenic, but is NOT coded for by the DNA. Instead, the DNA codes for a translation factor which causes the ribosome to insert selenocysteine for a codon that is otherwise a STOP codon. This kind of unique circumstance is something the MCAT-2015 authors might highlight in a passage, but it would not be required previous knowledge.
Amino Acid Chart:

Make multiple copies of the following chart and use them for practice. The structures, three-letter abbreviations, one-letter abbreviations, and pKₐ values have all been removed.