<table>
<thead>
<tr>
<th>Lecture</th>
<th>Assignment</th>
<th>Due*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>McMurry &amp; Begley (M&amp;B) Chapter 1 #1-8</td>
<td>Week 2</td>
</tr>
<tr>
<td>2</td>
<td>M&amp;B Chapter 1 # 12,14</td>
<td>4/9</td>
</tr>
<tr>
<td>3</td>
<td>M&amp;B Chapter 1 # 1.9-11, 13, 15</td>
<td>Week 3</td>
</tr>
<tr>
<td>4</td>
<td>Draw the ionic species for full pH range (1-14) for acidic &amp; basic</td>
<td>4/16</td>
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<tr>
<td></td>
<td>amino acids. *No posted key for L4 HW. Check your solutions with your TA</td>
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<tr>
<td></td>
<td>in office hours or discussion</td>
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<tr>
<td>5</td>
<td>See HW Set on p. HW-2</td>
<td>Week 2</td>
</tr>
<tr>
<td>6</td>
<td>McMurry 8th Ed. Chapter 26 #38a, 44 (provide your answers at pH 3, 7.4,</td>
<td>4/23</td>
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<tr>
<td></td>
<td>and 10)</td>
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<tr>
<td></td>
<td>Design an enzyme active site for each reaction in the synthesis of</td>
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<td></td>
<td>glutamine from glutamate (Lecture 5). Try to keep the number of</td>
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<td></td>
<td>intermediates to a minimum, although it may not be possible to do each</td>
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<td>reaction in one step. Use appropriate amino acid residues as acids and</td>
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<tr>
<td></td>
<td>bases as needed, as well was Mg$^{2+}$ to stabilize the negatively</td>
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<td></td>
<td>charged phosphates.</td>
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<tr>
<td>7</td>
<td>McMurry 8th ed. Chapter 26 #16, 17;</td>
<td>Week 5</td>
</tr>
<tr>
<td></td>
<td>Carbohydrate Activity #1-4 (p HW-3)</td>
<td>4/30</td>
</tr>
<tr>
<td>8</td>
<td>Carbohydrate Activity #5-8 (p. HW-4)</td>
<td>Week 6</td>
</tr>
<tr>
<td>9</td>
<td>M&amp;B 4.6-4.9 (p. HW-5)</td>
<td>5/7</td>
</tr>
<tr>
<td>10</td>
<td>Print out a blank Lecture 10 and re-do without looking at your notes.</td>
<td>Week 7</td>
</tr>
<tr>
<td></td>
<td>It's ok to use different amino acid residues, as long as they're</td>
<td>5/14</td>
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<tr>
<td></td>
<td>reasonable. No key posted for this HW (refer to webcast).</td>
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<tr>
<td>11</td>
<td>See p. HW-6-7</td>
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<tr>
<td>12</td>
<td>See p. HW-7-8</td>
<td>Week 8</td>
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<td>5/21</td>
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<tr>
<td>Lecture</td>
<td>Assignment</td>
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<tr>
<td>13</td>
<td>See p. HW-9-10</td>
<td>Week 9</td>
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<tr>
<td>14</td>
<td>See p. HW-11</td>
<td>5/28</td>
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<tr>
<td>15</td>
<td>See p. HW-12</td>
<td>Week 10</td>
</tr>
<tr>
<td>16</td>
<td>See p. HW-13</td>
<td>6/4</td>
</tr>
<tr>
<td>17</td>
<td>Carry out the 9 starred mechanisms from the Lecture 17 notes using</td>
<td>Finals Week</td>
</tr>
<tr>
<td></td>
<td>acids (H$^+$) and bases (:B) – not for credit, but for exam prep!</td>
<td></td>
</tr>
</tbody>
</table>

*HW is not checked for credit. HW should be completed as soon as possible after lecture, but to keep you on track, plan on having your HW done by Monday the following week. Monday dates are given in the table for clarity. Unannounced quizzes are given in section and are directly from the HW “due” that week. Students may use their own HW notebook during quizzes.
Lecture 5 Homework

You are not expected to memorize the schemes in the notes and HW for the exams! You are expected to be able to work through the mechanisms given the starting materials, intermediates, products, and/or reaction names. This is more about understanding reactions than memorizing the complex reaction schemes.

**Biological Mechanisms:** Assume that the reactions are taking place at physiological pH (7.4). Take that into account when determining charges and proton movement. Use acids (H⁺) and bases (:B) freely when needed.

1. On page L5-2, we covered the biosynthesis of asparagine from aspartate. The biosynthesis of glutamine from glutamate is strikingly similar! Show the mechanisms for each of the three steps in the synthesis of glutamine from glutamate: (1) hydrolysis of glutamine, (2) phosphate transfer with ATP, and (3) amide formation. The ammonia needed to make glutamine does actually come from the hydrolysis of glutamine. It is not uncommon for the degradation products of metabolic intermediates to be used to make the same molecule again!

   ![Glutamine synthesis](image)

2. The final phase in the biosynthesis of proline is the reductive amination of glutamate 5-semialdehyde. Without looking at your notes, draw the arrow-pushing mechanism for both steps. Check your mechanism with what was covered in lecture 5.

   ![Glutamate reductive amination](image)

3. Go through your lecture 5 notes and make a list of the different types of mechanisms using terms in the mechanism review from lectures 1-3.

4. Explain the difference between glutamate and glutamic acid. Do the same for aspartate and aspartic acid. When is each name more appropriate?
Lecture 7 HW - CARBOHYDRATE ACTIVITY

A. Define the following terms on a separate sheet while you complete Part B. Include formulas or structures, where appropriate.

<table>
<thead>
<tr>
<th>Carbohydrate</th>
<th>Triose</th>
<th>Hemiacetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosaccharide</td>
<td>Tetrose</td>
<td>Anomeric Carbon</td>
</tr>
<tr>
<td>Disaccharide</td>
<td>Pentose</td>
<td>Anomers</td>
</tr>
<tr>
<td>Trisaccharide</td>
<td>Hexose</td>
<td>Epimers</td>
</tr>
<tr>
<td>Polysaccharide</td>
<td>Penultimate Carbon</td>
<td>Furanose</td>
</tr>
<tr>
<td>Aldose</td>
<td>d-Monosaccharide</td>
<td>Pyranose</td>
</tr>
<tr>
<td>Ketose</td>
<td>L-Monosaccharide</td>
<td>Glycosidic Bond</td>
</tr>
</tbody>
</table>

B. Structural Conventions

1. Draw one example of each of the following types of monosaccharides (there may be several correct answers) and indicate the number of possible stereoisomers (while keeping the same D/L configuration).
   a. D-Aldotriose
   b. L-Ketotetrose
   c. L-Aldopentose
   d. D-Ketohexose
   e. L-Aldohexose

2. Draw Fischer projections of the following:
   a. The C2 epimer of D-Glucose
   b. The C3 epimer of D-Glucose
   c. The C4 epimer of D-Glucose

#3-6. Use the following templates when drawing sugars in Haworth projections and chair conformations.

3. Draw Haworth projections for the following (consult Fig 25.3 of McMurry; memorize the structure of D-Glucose for the second exam). What is the relationship between a & b; between a & c?
   a. α-D-Allopyranose
   b. β-D-Allopyranose
   c. α-D-Glucopyranose
   d. β-D-Mannopyranose
   e. α-D-Gulopyranose
   f. β-D-Idopyranose
   g. α-D-Galactopyranose
   h. β-D-Talopyranose

Lecture 8 HW – Carbohydrate Activity, Part 2 - Disaccharides

1. There are at least eight common ways for two glucose units to be linked together to form eight different disaccharides. Show the mechanism for the linking of D-glucose units to make a disaccharide with loss of water. Use any glycosidic linkage or try a few!

2. Draw the Haworth projection for \( \beta\text{-D-idopyranosyl-(1} \rightarrow 6\text{)}\alpha\text{-D-allopyranoside} \), disaccharide formed between D-Idose and D-Allose linked by a \( \beta\text{-1,6-glycosidic bond} \) (consult Fig 25.3 of McMurry).

3. Draw the Haworth projection for milk sugar (lactose). 
\( \beta\text{-D-galactopyranosyl-(1} \rightarrow 4\text{)}\beta\text{-D-glucopyranoside} \) - disaccharide formed from D-galactose and D-glucose linked by a \( \beta\text{-1,4-glycosidic bond} \) (consult Fig 25.3 of McMurry).

4. Draw the Haworth projection for table sugar (sucrose).
\( \alpha\text{-D-glucopyranosyl-(1} \rightarrow 2\text{)}\beta\text{-D-fructofuranoside} \) – disaccharide formed between D-glucose and D-fructose by a \( \alpha\text{-1,2-glycosidic bond} \) (consult Fig 25.3 of McMurry and the structure below).

![β-D-fructofuranose](image)

5. Show the mechanism for the hydrolysis (addition of water) to a disaccharide into two D-monosaccharides.
Lecture 9 HW - use amino acid residues as acids and bases.

4.6 Mannose, a component of dietary glycoproteins, is metabolized by an initial phosphorylation and isomerization to fructose 6-phosphate. Propose a mechanism for the isomerization.

4.7 Plants, but not animals, are able to synthesize glucose from acetyl CoA by a pathway that begins with the glyoxalate cycle. One of the steps in the cycle is the conversion of isocitrate to glyoxalate plus succinate, a process catalyzed by isocitrate lyase. Propose a mechanism for the reaction.

4.8 Galactose, a constituent of the disaccharide lactose found in dairy products, is metabolized by a pathway that includes the epimerization of UDP-galactose to UDP-glucose, where UDP = uridylyl diphosphate. The epimerase enzyme uses NAD$^+$ as cofactor. Propose a mechanism for the reaction.

4.9 Propose a mechanism for the conversion of 6-phosphogluconate to 2-keto-3-deoxy-6-phosphogluconate, a step in the Entner–Doudoroff bacterial pathway for glucose catabolism.
Lecture 11 HW – Read all instructions carefully before attempting! Refer to Lecture 10 notes to learn reactivity patterns in these new cofactors.

1. Show the mechanism for Step 4 of the citric acid cycle, conversion of $\alpha$–ketoglutarate into succinyl CoA. The reaction involves...

1. an initial nucleophilic addition reaction to $\alpha$–ketoglutarate by TPP ylid,
2. decarboxylation,
3. reaction with lipoamide,
4. elimination of TPP ylid, and finally
5. a transesterification of the dihydrolipoamide thioester with coenzyme A.

Use the structures below to complete this transformation, plus amino acid residues as acids and bases where appropriate.

![Diagram of $\alpha$-Ketoglutarate to Succinyl CoA]

2. Show the mechanism for Step 7 of the reductive pentose phosphate (RPP) pathway. This is a transketolase-catalyzed reaction that involves...

1. an initial nucleophilic addition reaction to fructose-6-phosphate by TPP ylid,
2. C-C cleavage to release erythrose-4-phosphate,
3. nucleophilic addition of the TPP adduct to glyceraldehyde-3-phosphate, and
4. elimination of TPP ylid with release of xylulose-5-phosphate.

Use the structures below and descriptions above to complete this transformation, plus amino acid residues as acids and bases where appropriate.

![Diagram of Fructose-6-phosphate to Erythrose-4-phosphate]
Lecture 11 HW (cont’d)

3. Show the mechanism for Step 10 of the reductive pentose phosphate (RPP) pathway. This is a transketolase-catalyzed reaction that involves…

(1) an initial nucleophilic addition reaction to sedoheptulose-7-phosphate by TPP ylid,
(2) C-C cleavage to release ribose-5-phosphate,
(3) nucleophilic addition of the TPP adduct to glyceraldehyde-3-phosphate, and
(4) elimination of TPP ylid with release of xylulose-5-phosphate.

Use the structures below and descriptions above to complete this transformation, plus amino acid residues as acids and bases where appropriate. Number. Your. Carbons.

Lecture 12 HW

1. Refer to the mevalonate pathway in your notes or the textbook when determining the final positions of the carbon-14 labeled carbon atoms from Acetyl CoA into IPP, DMAPP, GPP, and Limonene. You are you not expected to memorize the pathways, but given the outline of the process, you should be able to follow a labeled atom. Indicate the positions with a star (*)

\[ \text{Acetyl CoA} \rightarrow \text{Isopentenyl Diphosphate} \rightarrow \text{Dimethylallyl diphosphate (DMAPP)} \rightarrow \text{Limonene} \]
Lecture 12 HW (cont’d)

2. The biosynthesis of terpenes often involves complex skeletal rearrangements, including hydride and methyl shifts. Add the arrows to complete the mechanism for the synthesis of **trichodiene** from **FPP**. Note that the last step requires base involvement, similar to the second step of an E1 mechanism.

3. Propose a mechanistic pathway for the synthesis of **borneol** from **GPP** and **water**. The first step should be to carefully number the carbons in the starting material to align with the product. You will find a somewhat similar addition of water to alkenes in your lecture 1 notes!
Lectures 13 Homework Set – Heterocycles & Nucleotides

1. **Build the Nucleosides and Nucleotides.** You are responsible for knowing how to build RNA and DNA bases in their nucleoside & nucleotide form, given the structures of the nucleobases. You are expected to know the structure of ribose, 2-deoxyribose, and of course a phosphate.

<table>
<thead>
<tr>
<th>Nucleobase</th>
<th>Nucleoside (DNA)</th>
<th>Nucleotide (RNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Adenine" /></td>
<td><img src="image" alt="Adenine" /></td>
<td><img src="image" alt="Adenine" /></td>
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<tr>
<td><img src="image" alt="Guanine" /></td>
<td><img src="image" alt="Guanine" /></td>
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<tr>
<td><img src="image" alt="Cytosine" /></td>
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<td><img src="image" alt="Thymine" /></td>
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<tr>
<td><img src="image" alt="Uracil" /></td>
<td><img src="image" alt="Uracil" /></td>
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</tbody>
</table>
2. Look up the structures of the following pharmaceuticals online used in common-brand medicines (trade names and conditions they are used for in parenthesis). Rewrite them, and circle and name any heterocyclic substructure present in them. We are not looking for the actual IUPAC name of the pharmaceutical, just the name of the heterocycles present in them (such as pyridine, piperidine, etc.). This is more for application of material to everyday life. You will not need to memorize the structures and names of heterocycles for the exam.

a) Loratadine (Claritin; allergies)

b) Rosuvastatin (Crestor; hypercholesterolemia)

c) Atorvastatin (Lipitor; hypercholesterolemia)

d) Cimetidine (Tagamet; heartburn)

e) Ciprofloxacin (Cipro; antibiotic)

f) Tioconazole (Vagistat-1; antifungal)

3. Check the structures of the heterocycles mentioned below and explain why...

a) Pyrrole (pK_a = 17.5) is more acidic than pyrrolidine (pK_a ≈ 35)

b) The conjugate acid of pyrrole (pK_a = 0.4) is more acidic than the conjugate acid of pyrrolidine (pK_a = 11.3)

c) Pyrimidine (pK_a conj. acid = 1.3) is less basic than pyridine (pK_a conj. acid = 5.25)

d) Pyridine (pK_a conj. acid = 5.25) is less basic than piperidine (pK_a conj. acid = 11.2)

e) N7 in purine (pK_a conj. acid = 2.4) is less basic than N3 in imidazole (pK_a conj. acid = 6.95)

f) H on purine’s N9 (pK_a = 8.9) is more acidic than H on imidazole’s N1 (pK_a = 14.2)

g) Imidazole (pK_a conj. acid = 6.95) is more basic than pyrimidine (pK_a conj. acid = 1.3)

4. Consider Risperidone, a drug used to treat schizophrenia and bipolar disorder, shown below; pK_a (B^+H) = 7.91. Circle the most basic nitrogen.
Lecture 14 HW

1. Draw structures for four different enol forms of uracil.

2. Propose a mechanism for the deamination of cytosine catalyzed by acid. I hope you’ve realized by now that you’re not expected to memorize each new mechanism! Instead, you should be gaining an understanding of reasonable electron flow to lead to the observed product. With this, you can predict the mechanism of almost any reaction, regardless of whether you’ve seen it before! That being said, parts of this mechanism should be familiar!

3. One of the drawbacks of eating nitrite-cured meats is potential for nucleobase mutation, although at low concentration the risk is low. Everything in moderation! Several intermediates are given for such a mutation. Propose reasonable mechanisms for each step, using :B and H⁺ for bases and acids, respectively. This is a more involved version of problem #2.

4. The pKₐ's for H₃PO₄ are pKₐ₁ = 2.12; pKₐ₂ = 7.21 and pKₐ₃ = 12.7. What are the main species in equilibrium in blood, pH 7.4?

5. Use the structures of the nucleobases on p. 1 and practice drawing the H-bonding patterns in DNA base pairing.

6. Draw the full structures of the ribonucleotides A & G, then draw the mechanism for the reaction between the two, leading to the formation of the A-G dinucleotide. Include the pentacoordinate phosphate intermediate. It is definitely OK to abbreviate the nucleobases in the intermediate and product!

7. Show the mechanism for the hydrolysis (cleavage) of the A-G dinucleotide.
Medicinal Chemistry HW, Lecture 15

1. Associate each one of the following terms with one of the three phases: pharmaceutical, pharmacokinetic, pharmacodynamic
   (a) absorption
   (b) dosage form
   (c) receptor
   (d) metabolism
   (e) binding site
   (f) elimination
   (g) excipient
   (h) oral administration

2. Classify each method of drug administration as enteral or parenteral:
   (a) Inhalation
   (b) Subcutaneous
   (c) Rectal
   (d) Intravenous
   (e) Oral
   (f) Topical
   (g) Intramuscular
   (h) Sublingual

3. Consider the following local anesthetic agents and find the pharmacophore.

   ![Etidocaine](image1)
   ![Ropivacaine](image2)
   ![Mepivacaine](image3)
   ![Prilocaine](image4)
   ![Lignocaine](image5)

4. Consider the following local anesthetic agents and find the pharmacophore.

   ![Methyclothiazine](image6)
   ![Benzthiazide](image7)
   ![Chlorothiazide](image8)
   ![Hydroflumethiazide](image9)
Lecture 16 HW

5. Calculate the therapeutic index of a drug that produces a toxic effect in 50% of the test population at a dose of 85 mg/kg and has a therapeutic effect in 50% of the test population at a dose of 100 μg/kg. Is this a better drug than a similar one with a therapeutic index of 100? Justify your answer.

6. Look up the structures of the following drugs and predict if they are soluble in water. If not, what would you do to increase its solubility? Does pH affect the solubility potential?
   (a) Ropivacaine (see #3)
   (b) Mephophenobarbital (or mephobarbital)
   (c) Indomethacin

7. The pKa's of Butorphanol, a potent analgesic in the morphine family, are 7.97 and 10.26.
   (a) Keeping in mind that the structure provided is at physiological pH, identify the acidic protons and indicate which pKa goes with which proton.
   (b) What is the charge of butorphanol at pH 2? pH 5? pH 11?

8. Propose a structure for the active metabolite of Famciclovir, an antiviral agent. In other words, which bonds are likely to be metabolized and what would be the resultant structure?

![Famciclovir](image)

9. Calculate the solubility potential of Penicillin G and Isopenicillin N using the solubility potential table from lecture 16.

![Isopenicillin N](image)  ![Penicillin G](image)