1. **pH, pKₐ, and all that (25 pts):**

   (a; 9 pts) The imidazole side chain of histidine has a pKₐ of 6.04 (referring to the protonated side chain). **Draw the dominant prototropic forms of histidine at:** (1) pH 4, (2) pH 8, and (3) pH 12.

   ![Chemical Structures]

   +1 for an amino acid
   +2 for histidine side chain
   +2 for each correct protonation state (6)
   +2 for each answer correct at a given pH
(b) (6 pts) Calculate the ratio of neutral to protonated histidine at pH 6.5.

\[
\frac{[H^+]}{[\text{Hist}^-]} = 10^{pK_a - \log \left[ \frac{[H^+]}{[\text{Hist}^-]} \right]}
\]

Here,

\[
6.5 = 6.04 + \log \left[ \frac{[\text{Hist}^-]}{[\text{Hist}^+] + [H^+]} \right] \quad (\text{pH})
\]

\[
\log \left[ \frac{[\text{Hist}^-]}{[\text{Hist}^+] + [H^+]} \right] = 0.46
\]

\[
\frac{[\text{Hist}^-]}{[\text{Hist}^+] + [H^+]} = 10^{0.46} = 2.88
\]

(c) (10 pts) We have mentioned that the pK_a of an amino acid side chain can change substantially in different protein contexts. If a histidine side chain were found buried among isoleucines in the center of a protein, what effect would this have on the actual pK_a of that particular side chain, and why? What if there were a buried aspartate as well?

(3) If the histidine is not near another charged group, the side chain will be almost entirely uncharged in the interior of the protein. In this environment, the pK_a will be shifted to a lower value. The degree of ionization of the histidine will be lower than in water, leading to a lower pK_a value.

2. Amino acid and peptide bond structure and chemistry (26 pts):

(a) (6 pts) Name the two sulfur-containing amino acids, and very briefly list one unique function for each:

- Cysteine
- Methionine

Cysteine: Important in disulfide bonds for protein stabilization.

Methionine: Acts as a thiolase.
(b; 15 pts) Draw the structure of Valine-Proline-Glutamate at pH 7. Make the proline peptide bond cis and the other peptide bond trans. Give the 3- and 1-letter codes for each amino acid below your structure.

Stereochemistry not graded.

Difficult to draw because Pro is non-planar.

Everything but the cis-proline = 13 pts total.
5 pts) The structure below shows two charged tRNA molecules aligned for the process of peptide bond synthesis. Draw the first step of the reaction mechanism.

3. Thermodynamics (25 pts):
(a; 6 pts) What are the two most important functions for lipids?
- **Bioenergetic**
- **Structural**
- **Fuel**
- **Fatty acids**
(b) 9 pts] Briefly describe how cells maintain order in the face of the universal tendency toward increasing entropy.

- Cells take in ordered molecules like glucose.
- They convert the favorable free energy of fuel oxidation (combustion) to the unfavorable decrease in entropy associated with biosynthesis, growth, and reproduction.

- The favorable combustion reactions lead to production of CO₂ gas, with much greater entropy than glucose.
- and also heat (CO₂ is a highly reactive gas as well), which also increases the entropy of the universe. Don't need details.

- Giving off CO₂ just speeds up the overall reaction.

(c) 10 pts] You have discovered an enzyme that converts substance A to substance B without requiring any input of free energy (i.e. the reaction proceeds without high-energy substrates like ATP). The equilibration lies far to the side of B. What then must be true about any process that carries out net conversion of B to A under the same conditions? Also, explain why your discovery either does or does not preclude the possibility that there may be a separate energy-consuming path for going from A to B, and a biological rationale for your answer.

Therefore B → A must be coupled to an exergonic reaction like ATP hydrolysis.

A → B can go via an energy-consuming basic (drive the car downhill under power), would be done for greater speed, specificity, and/or control. 

4. Intermolecular interactions (22 pts):

(a; 12 pts) The structure of the artificial sweetener Aspartame is shown below. Identify potential hydrogen bond donors and acceptors, and electrophilic carbons. Why must phenylketonurics avoid Aspartame? (Memory jogger: would Aspartame absorb UV light?)

- Aspartame is metabolized to give phenylalanine. PKU sufferers cannot convert Phe → Tyr, and toxic by-product accumulates.

- +3 for Asp would absorb UV light marking PKU quinonem
(b) (10 pts) Briefly describe the origin of the hydrophobic effect. Give the signs of $\Delta H^\circ$, $\Delta S^\circ$, and $\Delta G^\circ$ for the process of dissolving a long alkyl chain in water.

- Water forms an ordered cage around hydrophobic solutes. This is unfavorable - aggregation of the solutes (or phase separation)

leads to release of the into more disordered bulk water and is the driving force for the fact that oil and water don’t mix.

\[ \Delta H^\circ < 0 \text{ in the classical cage is entropically favorable!} \]

\[ \Delta S^\circ < 0 \text{ because of ordering of water} \]

\[ \Delta G^\circ = \Delta H^\circ - T \Delta S^\circ > 0 \text{ process is not spontaneous} \]

Score: 1. pH, pK, and all that (25 pts):
2. Amino acid and peptide bond structure and chemistry (26 pts):
3. Thermodynamics (25 pts):
4. Intermolecular interactions (22 pts):

Total: out of 100 (2 pts for Honor Pledge)