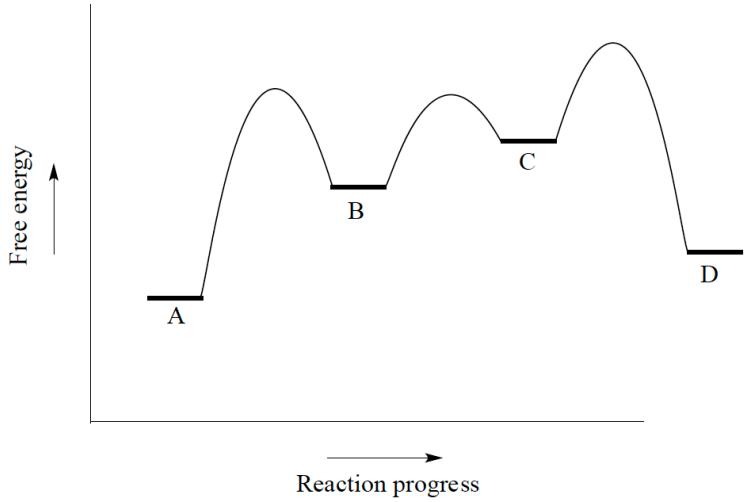
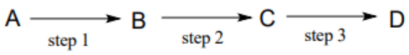
5.1 Organic reactivity

a) Use the reaction coordinate diagram below to answer the questions

- Is the overall reaction endergonic or exergonic in the forward (A to D) direction?
- How many steps does the reaction mechanism have
- How many intermediates does the reaction mechanism have?
  Which one is the rate-determining step of the forward reaction?
- What is the fastest reaction step, considering both the forward and reverse directions?



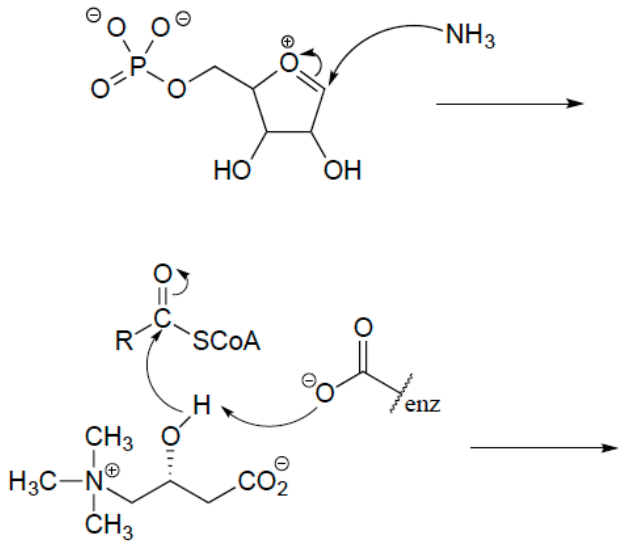
b) Below is a diagram of a hypothetical reaction.



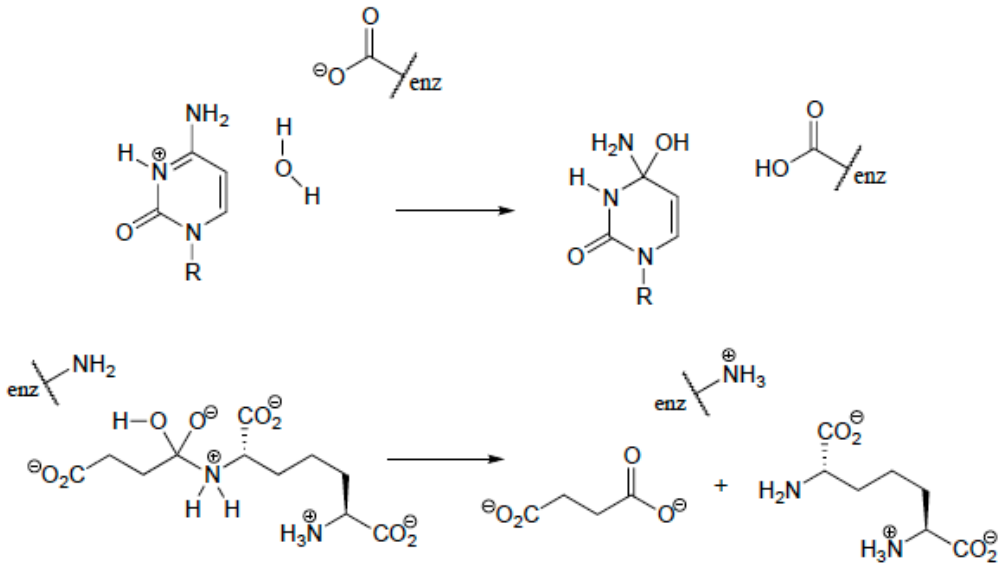
Step 2 is the rate-determining step, C is the least stable species, B is higher energy than D, and the overall reaction has an equilibrium constant Keq = 0.33.

Draw a diagram that corresponds to all of this information.

c) For each step illustrated below, draw the products or intermediate species that would form according to the electron-movement arrows given. Be sure to include all formal charges. You do not need to show stereochemistry.)As context: Illustrated below are individual steps in some biochemical reaction mechanisms, that we will be studying later.)

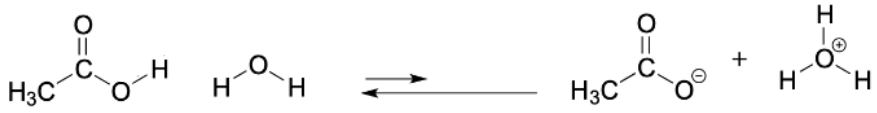


d) For each step illustrated below, draw curved arrows showing the electron movement taking place.



5.2 Acidity and Basicity – Definition and important conepts

a) In the reaction below, draw curved arrows showing the electron movement taking place and mark which compound are condisered to be the Acid, Base, Conjugate base and Conjugat acid.



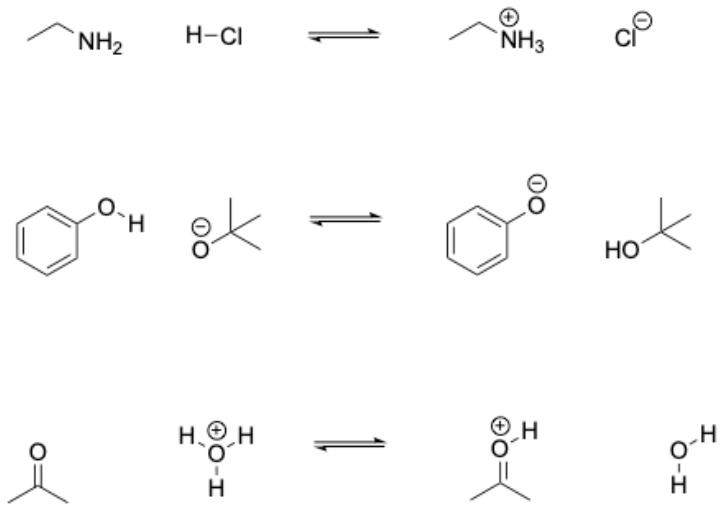
b) Remind yourself of the relationship between strong acids, weak bases and pKa and answer following questions as true (T) or false (F)

An acid base reaction will be favored when a weaker base and a weaker acid combine to form a stronger acid and stronger base.	**T F**
Generally, strong acids have weak conjugate bases	**T F**
Strong acid have high pKa values	**T F**
A weak base is less stable than a strong base	**T F**

c) Draw the mentioned functional groups below and order them from most acidic to least acidic. For each functional group indicate its approximate pKa value. Hint: Consult lecture materials and/or literature to find good pKa estimates.

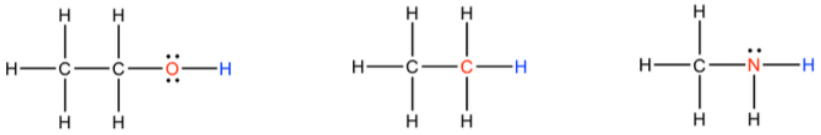
- *thiol*
- *protonated carboyl(ketone)*
- *alcohol*
- *carboxylic acid*
- *phenol*
- *amide*
- *protonated alcohol*

d) In the acid base reactions below draw curved arrows showing the electron movement taking place.

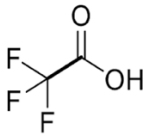


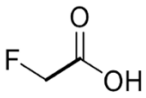
5.3 Acidity and Basicity – Trends in Acidity

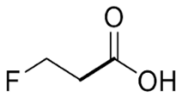
a) Order the following compounds according to their acidity and justify your answer. What is the trend that you can observe here?



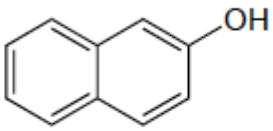
b) Classify the following carboxylic acids according to their acidity and justify your answer. How is the effect called that we observe here? *Bonus:* Are alkyl groups electron withdrawing or donating?



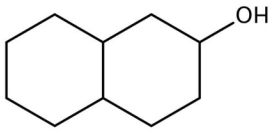




c) Draw the conjugate base of (the major resonance contributor), and on your drawing indicate with arrows all of the atoms to which the negative charge can be delocalized by resonance. Why is 2-Naphthol a stronger acid than Decahydro-2-naphthol?



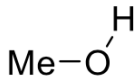
2-naphthol



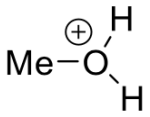
Decahydro-2-naphthol

5.4 Acidity and Basicity – Determine Acidity

a) Which of the following two compounds is the stronger acid? Give reasons for your answer.

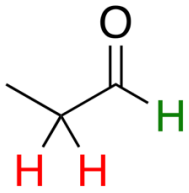


Methanol

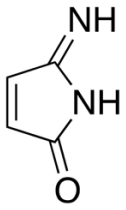


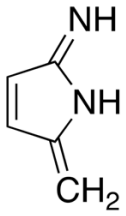
Methyloxonium

b) Compare the acidity of the labeled protons and decide which one is more acidic. Give reasons for your choice.

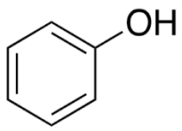


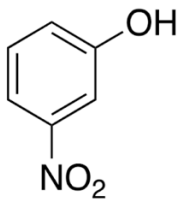
c) Which is the most acidic proton in the molecules shown below? Which compound of the two is the stronger acid? Give reasons with the help of resonance structures.

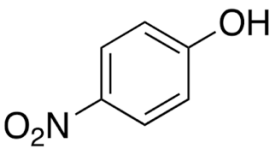




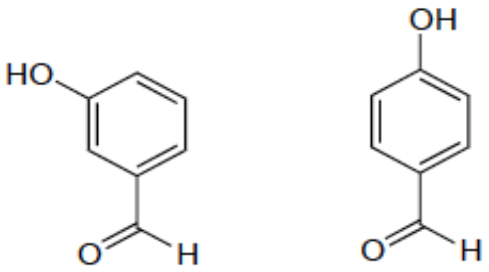
d) Classify the following compounds according to their acidity and give reasons for your answer.



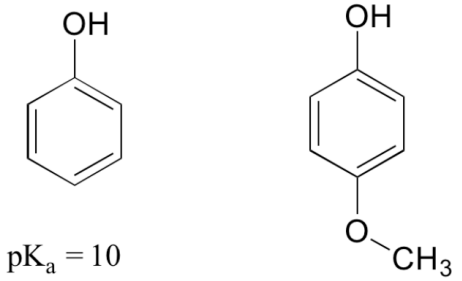




e) The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



f) *Challenging:* Consider the acidity of 4-methoxyphenol, compared to phenol. Notice that the methoxy group (OCH3) increases the pKa of the phenol group - it makes it *less* acidic. Why is this? *Hint: look at unfavorable resonance structures.*



$pK_a = 10$

$pK_a = 10.6$

5.5 Acidity and Basicity – Calculations

a) What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pKa of acetic acid is 4.8. (Tip: use Henderson-Hasselbalch equation introduced in the lecture).

b) What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid (pKa = 4.8) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

c) What is the approximate net charge on a tetrapeptide Cys-Asp-Lys-Glu in pH 7 buffer?