Key to Exercises Chapter 8

Exercise 8.1.0.1 Complete the reactions below - in other words, draw structures for the missing conjugate acids and conjugate bases that result from the curved arrows provided.

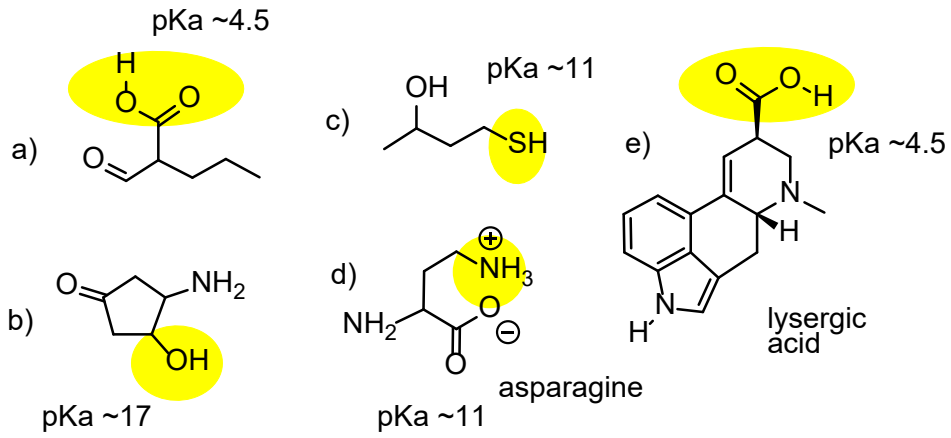
Steps: 1) Form the NH and OH bonds by transferring H+. 2) Calculate formal charge in the new structures. When H+ transfers to a neutral molecule the conjugate acid will be positively charged. Which atom in your new structure has this positive formal charge in the line structure?

Exercise 8.2.0.1 Which is the stronger base, CH_3O^- or CH_3S^-? Acetate ion or ammonia? Hydroxide ion or acetate ion?

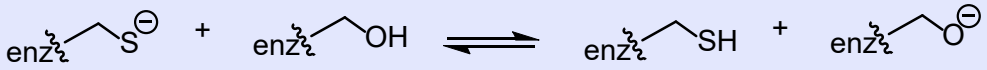
a) CH_3O^-
b) Ammonia
c) Hydroxide

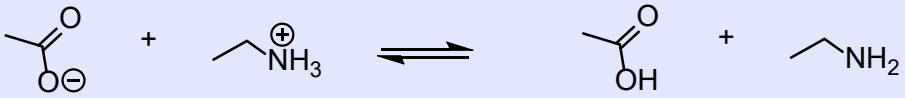
It is more important to know why than it is to know which?

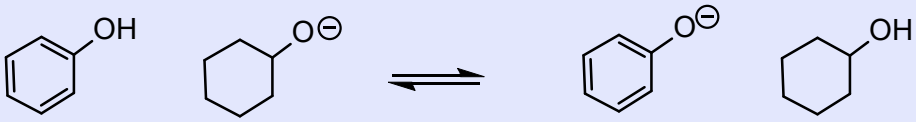
Exercise 8.2.0.2 Identify the most acidic functional group on each of the molecules below, and give its approximate pKa.

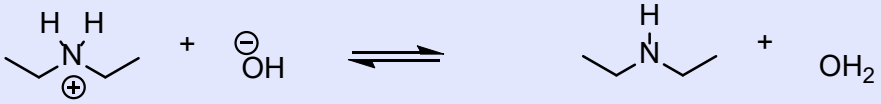


Exercise 8.2.0.3 Show the products of the following acid-base reactions, and roughly estimate the value of Keq.

a) 

b) 

c) 

d) 

a) ΔpKa = ~+8
b) ΔpKa = ~+5.5
c) ΔpKa = ~-8
d) ΔpKa = ~-6.5

Use

$2.30RT\,\Delta pK_a = \Delta G_2 - \Delta G_1 = \Delta G_{rxn}$

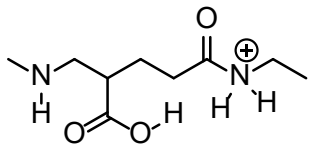
See 5.10.1 pKa is an Energy Unit in Chapter 5 of Organic Chemistry, an Integrated Spectroscopic Approach, ed. 1

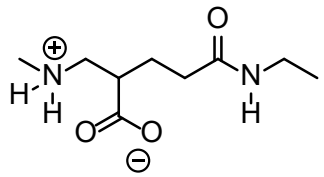
Exercise 8.2.2.1 What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pKa of acetic acid is 4.8.

$$pH = pKa + \log\left(\frac{\text{concentration of conj. base}}{\text{concentration of weak acid}}\right)$$

pH ~ 4.8 + Log (40 / 30) = 4.9

Exercise 8.2.2.2 The molecule below is not drawn in the protonation state that we would expect to see it at physiological pH. Redraw it in the physiologically relevant protonation state.





The amide is not basic enough to be protonated in water at pH ~7

Exercise 8.2.2.3 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?

Answer: Assume that the pH of the solution is 2.8 and remains 2.8 after a small amount of acetic acid is solvated. Use

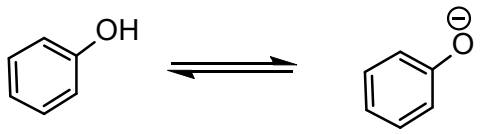
$$\text{pH} = \text{pKa} + \log\left(\frac{\text{concentration of conj. base}}{\text{concentration of weak acid}}\right)$$

2.8 = 4.8 + log (ratio) ; log (ratio) = -2

Ratio = 0.01

Exercise 8.2.2.4 Would you expect phenol to be soluble in an aqueous solution buffered to pH 2? pH 7? pH 12? Explain your answer.

pH 2 no, pH 7 no, pH = 12 yes. At pH 12 the phenolate is the primary species in aqueous solution. It is an anion and water-soluble.



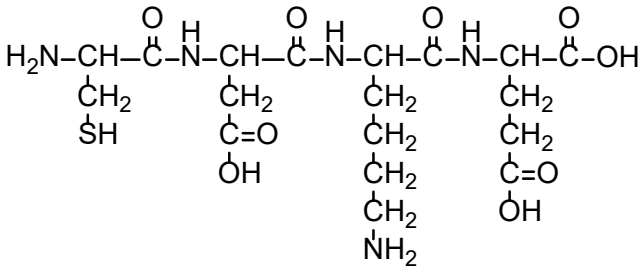
Exercise 8.2.2.5 Methylamine is dissolved in a pH 9.0 buffer. What percent of the solute molecules are charged? What is the average charge on solute molecules?

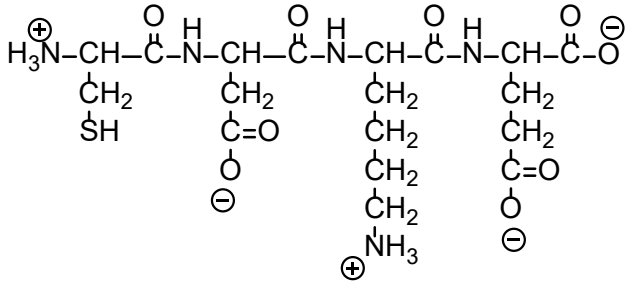
pKa of $MeNH_3^+$ = 10.6

Use the Henderson–Hasselbalch equation. The equilibrium will favor the protonated cationic species since the pH is below the pKa of the protonated cationic species. When pKa is quoted, always realize that the pKa refers to the species that donates H+. The pKa does not refer to neutral $MeNH_2$.

Exercise 8.2.2.3 What is the approximate net charge on a tetrapeptide Cys-Asp-Lys-Glu in pH 7 buffer?

Step 1) Realize that peptides are written out in the N-to-C direction



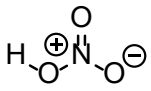


Step 2) Appreciate where the C-to-N connections are and what this means for the structure by writing the structure out in long form.

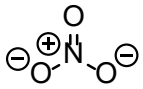
Step 3) Think about which functional groups will ionize at pH ~7 and add or subtract protons and charges to show the average aqueous species.

Step 4) Add the formal charges. Answer = -1.

Exercise 8.3.2.1 a) Draw the Lewis structure of nitric acid, HNO_3.

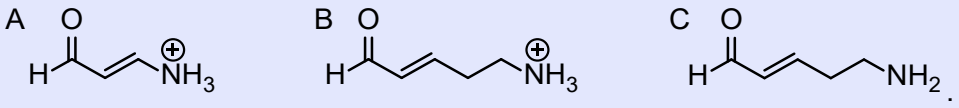


b) Nitric acid is a strong acid - it has a pKa of -1.4. Make a structural argument to account for its strength. Your answer should involve the structure of the conjugate base of nitric acid.



Nitric acid liberates an sp^2 lone pair when it deprotonates. The O atoms is more acidic than the O atom in acetic acid (that does the same) because it is bound directly to an N atom (more electronegative than the C atom in acetic acid) and the N atom is bound to two O atoms.

Exercise 8.3.2.2 Rank the compounds below from most acidic to least acidic, and explain your reasoning

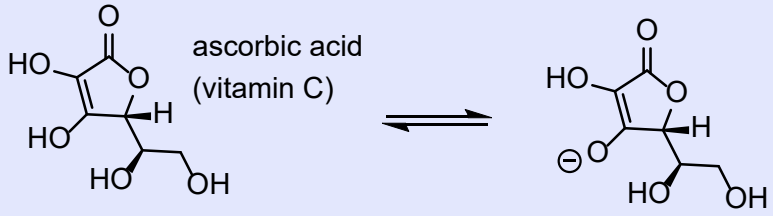


A > B > C

A and B are protonated. C is the deprotonated (conjugate base of B). By definition, the conjugate base of any acid is less acidic than the corresponding acid.

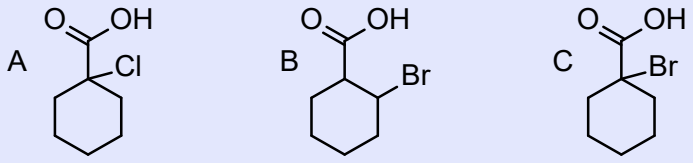
A is more acidic than B because the liberated lone pair in A is π bound which decreases the electronic energy.

Exercise 8.3.2.3 (challenging): Often it requires some careful thought to predict the most acidic proton on a molecule. Ascorbic acid, also known as Vitamin C, has a pKa of 4.1 - the fact that this is in the range of carboxylic acids suggest to us that the negative charge on the conjugate base can be delocalized by resonance to *two* oxygen atoms. Which if the four OH protons on the molecule is most acidic? Draw the structure of ascorbate, the conjugate base of ascorbic acid, then draw a second resonance contributor showing how the negative charge is delocalized to a second oxygen atom. Hint - try deprotonating each OH group in turn, then use your resonance drawing skills to figure out whether or not delocalization of charge can occur.



This conjugate base puts electron density on two O atoms. All other choices for deprotonation distribute electron density to C via π bonding or localize electron density on O atoms.

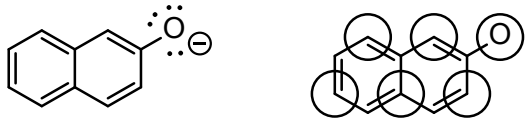
Exercise 8.3.3.1 Rank the compounds below from most acidic to least acidic, and explain your reasoning.



A > C > B

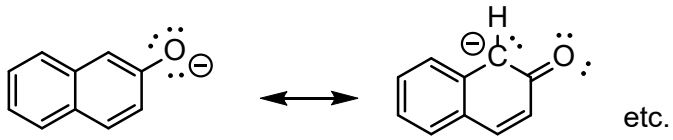
See the text for a discussion of the through-σ-bond inductive effect and the degree to which the inductive effect falls off as the number of σ bonds between the acidic atom and the electronegative atom increases.

Exercise 8.4.0.1 Draw the conjugate base of 2-napthol (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.

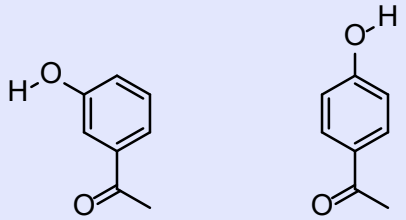


Either realize that it is an odd π system so it's HOMO must be non-bonding. These leads to the nodes at and electron density at the circles above.

Or distribute the electrons into the π system one at a time.

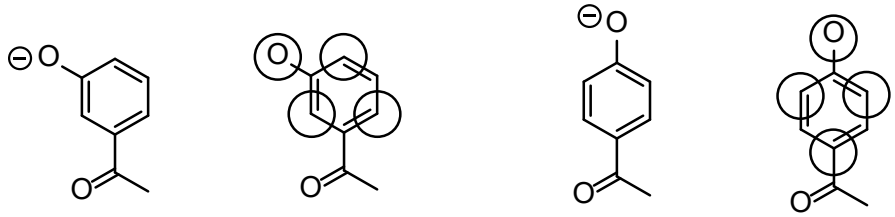


Exercise 8.4.0.2 The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.

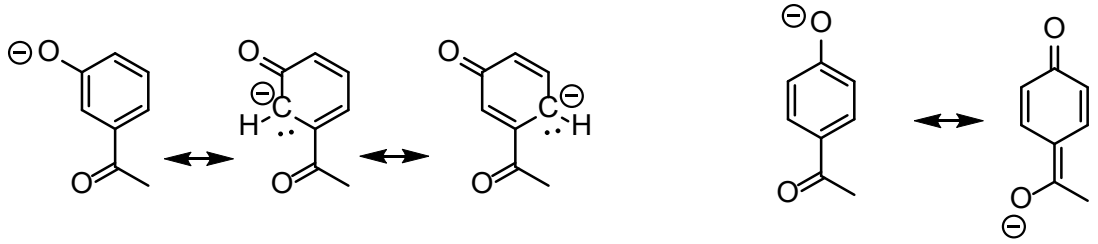


Answer: The 4-hydroxy derivative is more acidic.

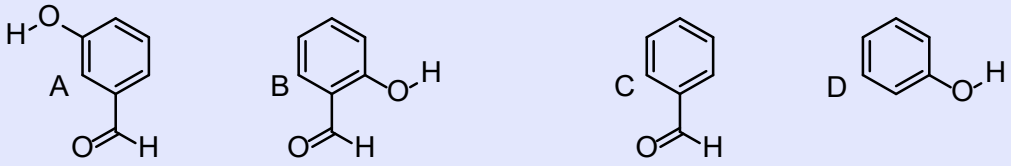
You can use two methods to answer this question. In both methods consider the structure of the conjugate base.



1) Since the substituent occurs at a node in the 3-hydroxy derivative it does not interact in a bonding manner with the π bond in C=O, the effect on the acidity is inductive. The C=O in the 4-derivative does not occur at a node in the π system of phenolate and thus can interact in a bonding manner to stabilize the liberated electron.
2) Realize that the lone pair in the resonance hybrids miss conjugation with the C=O in the 3-hydroxy derivative, but allow conjugation with the C=O in the 4-hydroxy derivative.



Exercise 8.4.0.3 Rank the four compounds below from most acidic to least.



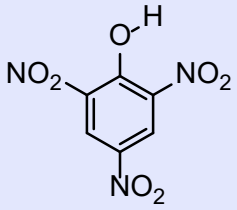
B > A > D > C

C has no protic functionality.

Exercise 8.4.0.4 Nitro groups are very powerful electron-withdrawing groups. The phenol derivative picric acid has a pKa of 0.25, lower than that of trifluoroacetic acid. Use a resonance argument to explain why picric acid has such a low pKa.

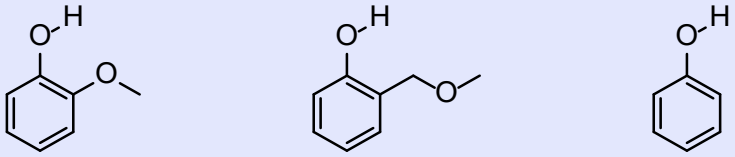
picric acid

pKa = 0.25



Answer: Realize that the N atoms have π structure. See the answer to **Exercise 8.3.2.1** above. Now realize that the answer to **Exercise 8.4.0.3** is analogous to this answer. You can use one of the two methods there to answer this question. Remember to deprotonate picric acid and consider the conjugate base in your answer.

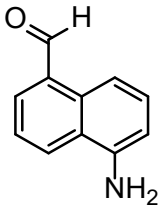
Exercise 8.4.0.5 Rank the three compounds below from lowest pKa to highest, and explain your reasoning. Hint - think about both resonance and inductive effects!

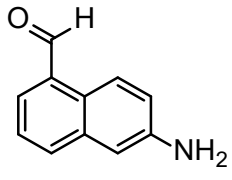


a) b) c)

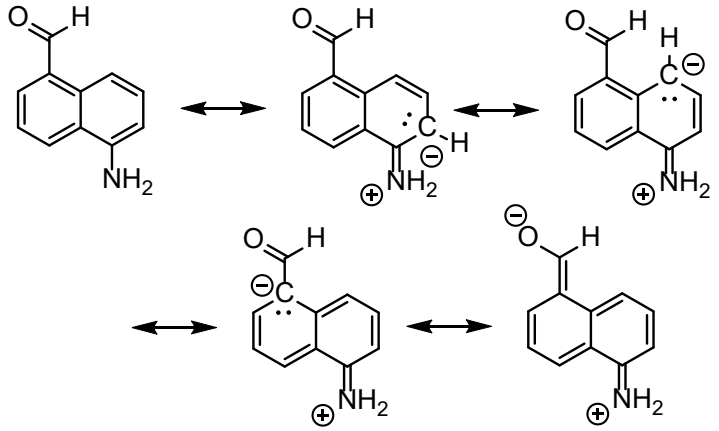
Answer: Here we are asked to rank the molecules from most acidic to least acidic. The effect of the OMe is a π electron-donor which should reduce the acidity. b) is most acidic but only slightly so due to inductive effects. c) is next and a) is least acidic due to the π donor effect.

Exercise 8.5.1.1 With anilines just as with phenols, the resonance effect of the aromatic ring can be accentuated by the addition of an electron-withdrawing group, and diminished by the addition of an electron-donating group. Which of the two compounds below is expected to be more basic? Use resonance drawings to explain your reasoning!

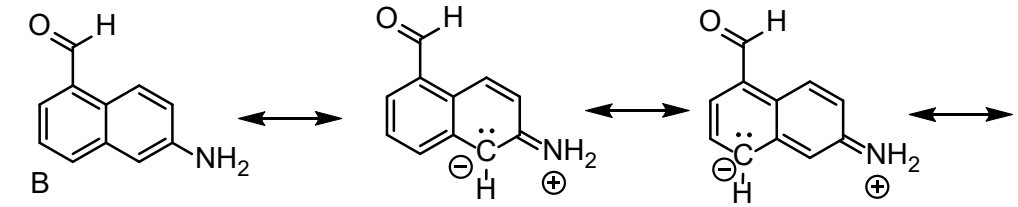
A 

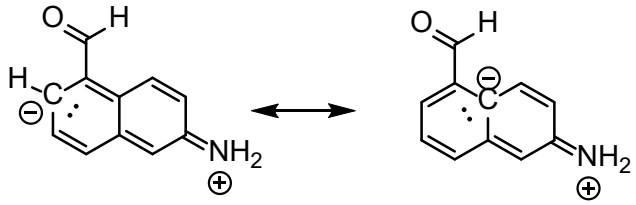
B 

Answer: A is least basic. The carboxaldehyde group is electron-withdrawing and in A the carboxaldehyde group is in conjugation with the N-atom lone pair.



However



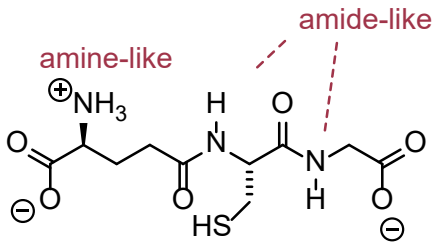


B does not have the carboxaldehyde group in conjugation with the N-atom lone pair.

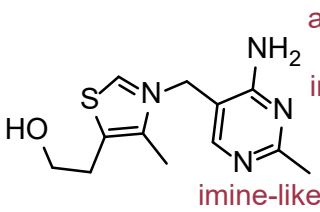
Exercise 8.5.1.2 Below are the structures of four 'coenzyme' molecules necessary for human metabolism […].

a) When appropriate, assign a label to each nitrogen atom using the basicity classifications defined in this section ('pyrrole-like', etc.).

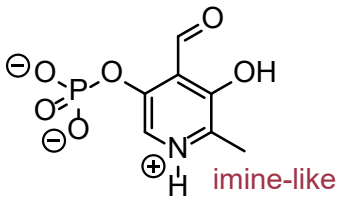
b) There is one nitrogen that does not fall into any of these types - is it basic? Why or why not? What would be a good two-word term to describe the group containing this nitrogen?



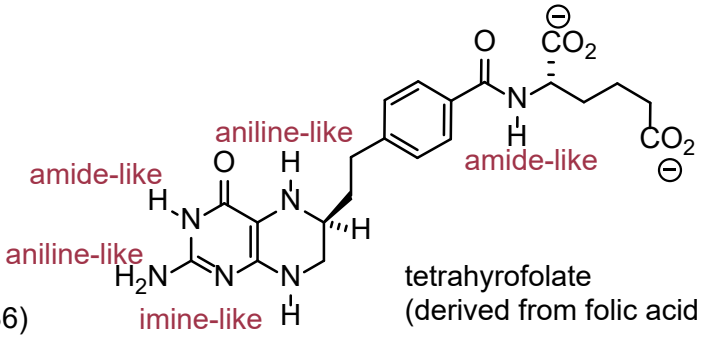
glutathione



thiamine
(vitamine B1)



pyridoxal phosphate
(derived from vitamin B6)



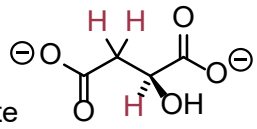
tetrahyrofolate
(derived from folic acid

Exercise 8.6.1.1 For each molecule shown below.

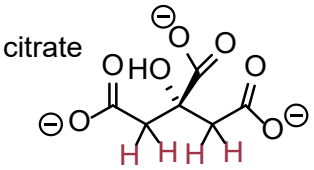
a) Show the location of all α-protons.

b) Draw the structure(s) of all possible enolate conjugate bases.

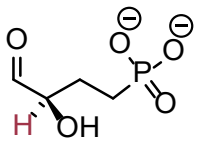
a)



malate

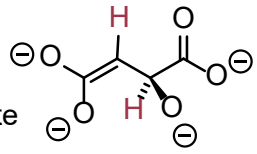


citrate

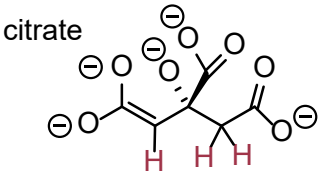


glyceraldehyde-3
-phosphate

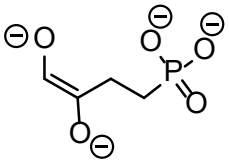
b)



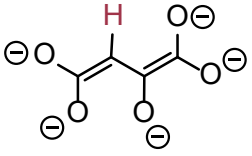
malate

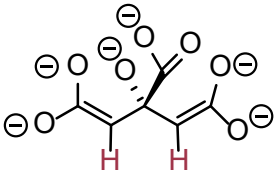


citrate



glyceraldehyde-3
-phosphate

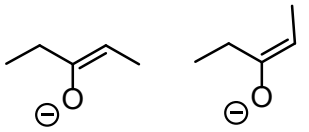




Before you deprotonate the enolate you have to deprotonate the alcohol. The OH groups are more acidic than the C-atom acids at the α-positions.

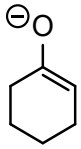
Exercise 8.6.2.1 Draw all of the possible enol forms of the following aldehydes /ketones.

a) 3-pentanone

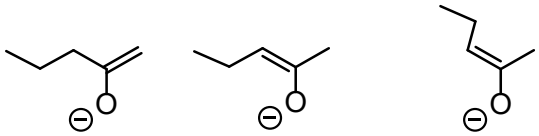


b) acetaldehyde (IUPAC name ethanal)

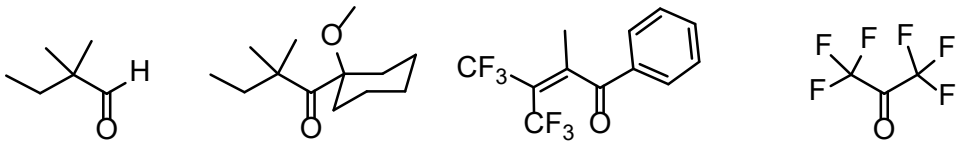
c) cyclohexanone



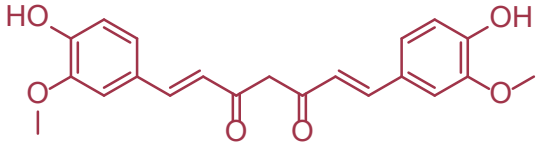
d) 2-pentanone.



Exercise 8.6.2.2 Draw three examples of aldehyde or ketone compounds for which there is no possible enol form.

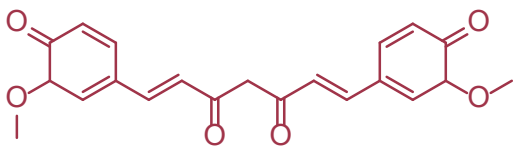


Exercise 8.6.2.3 In some special cases, the enol form of a compound is more stable than the keto form and thus predominates at equilibrium. Curcumin is the compound mainly responsible for the characteristic yellowish color of tumeric, a ubiquitous spice in south/southeast asian cuisine. The extended system of π bonds present in the enol form causes it to be lower in energy than the tautomer in which there are two ketone groups (called the diketo form). Draw the diketo form of curcumin, and explain how the conjugated π system is disrupted.



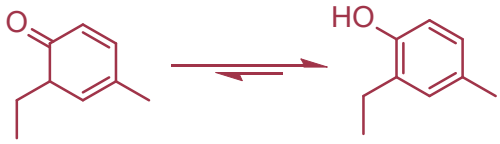
In the diketo tautomer the each of the two π systems is only half as small as the one π system in the enol tautomer.

It can get even worse … same argument applies



Exercise 8.6.2.4 The phenol functional group can also be thought of a kind of enol.

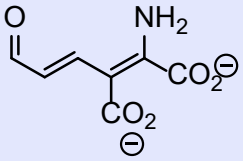
a) Draw the 'keto' form of phenol.

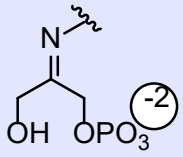


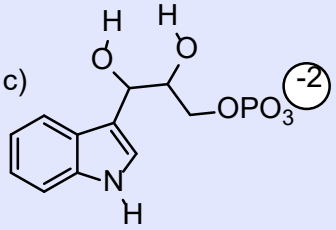
b) The 'keto' form of phenol is highly disfavored compared to the 'enol' form - why?

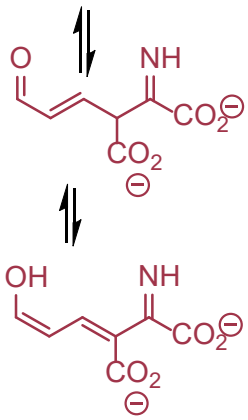
Answer: There is more π bonding in the phenol tautomer than the cyclohexadienone tautomer.

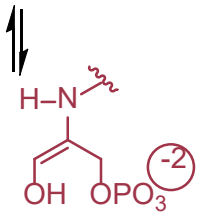
Exercise 8.6.3.1 The structures below all contain either an imine or an enamine group. For each, draw the structure of an alternate tautomer.

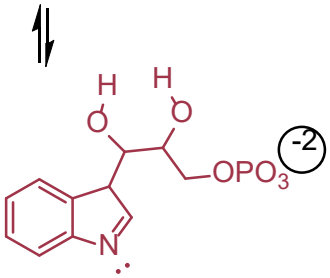
a) 

b) 

c) 

a) 

b) 

c) 

Exercise 8.6.4.1 Hydrogen cyanide, HCN, is another example of a relatively strong carbon acid, with a pKa of 9.2. Suggest a rationale for the acidity of this proton

Answer: Deprotonation liberates an sp hybridized lone pair at C which is bound directly to a relatively electronegative atom.

Exercise 8.7.0.1 In a buffer at physiological pH, what form(s) of phosphoric acid predominate? What is the average net charge?

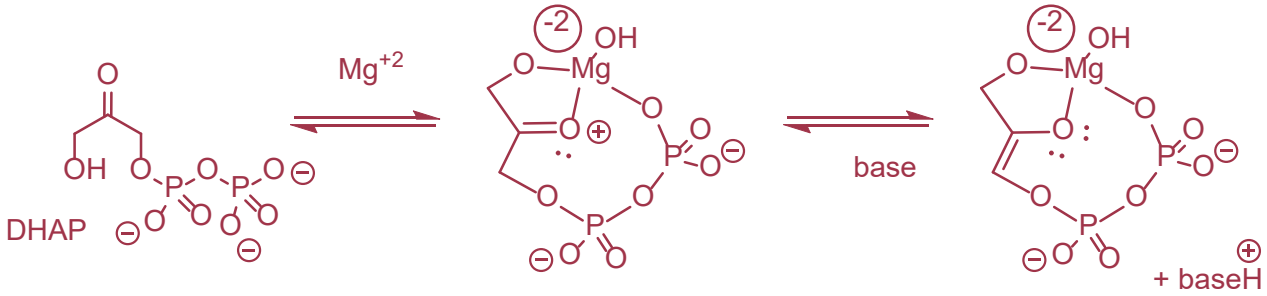
Answer: The mono and dianion predominate. The average charge on the phosphate species is -1.5.

Exercise 8.8.0.1 A lysine residue located deep in the interior of a protein is surrounded by nonpolar residues. In what direction will this alter the 'normal' pKa of the lysine side chain, and why?

Answer: The RNH_3^+ of lysine will be more acidic or equivalently, the RNH_2 of lysine will be less basic in a hydrophobic environment, in the absence of a **salt bridge**.

https://en.wikipedia.org/wiki/Salt_bridge_(protein_and_supramolecular)

Exercise 8.8.0.2 In many biochemical reactions which involve the formation of an enolate intermediate, the carbonyl oxygen of the substrate is coordinated to a divalent metal ion (usually zinc or magnesium) in the active site. Explain, with structural drawings, how this ion-dipole interaction effects the acidity of the α-protons of dihydroxyacetone phosphate (DHAP), an intermediate compound in the glycolysis pathway.



Answer: Chelation promotes α proton acidity by electron-withdrawal.