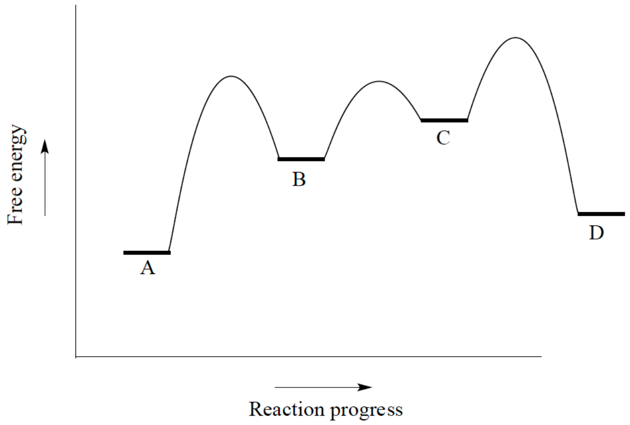
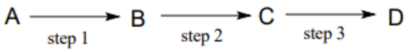
5.1 Organic reactivity

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?
  Endergonic (D is higher in energy than A)
- How many steps does the reaction mechanism have? 3 steps
- How many intermediates does the reaction mechanism have?
  Two intermediates (B and C)
  Which one is the rate-determining step of the forward reaction? Step 1
- What is the fastest reaction step, considering both the forward and reverse directions?
  C to B in the reverse direction (activation energy from C to middle transition state is lowest of the six possible activation energies).

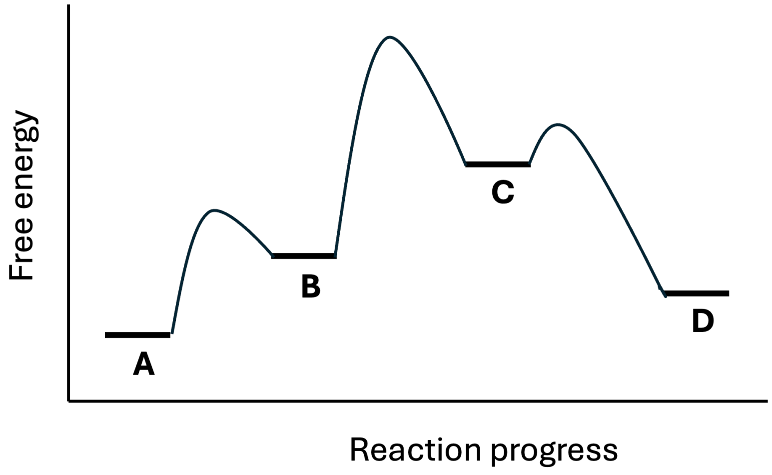


b) Below is a diagram of a hypothetical reaction.

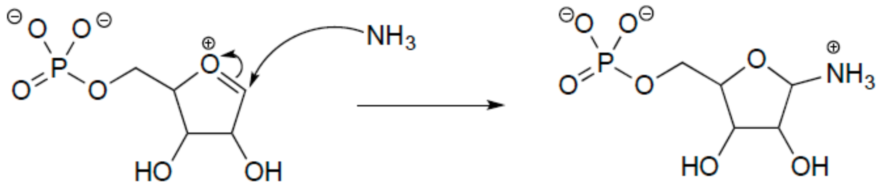


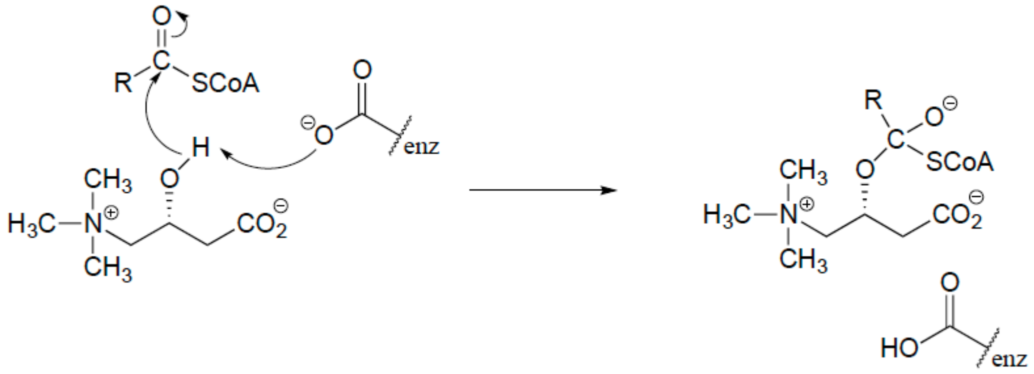
Step 2 is the rate-determining step, C is the least stable species, B is higher energy than D, and the overall reaction has an equilibrium constant Keq = 0.33.

Draw a diagram that corresponds to all of this information.

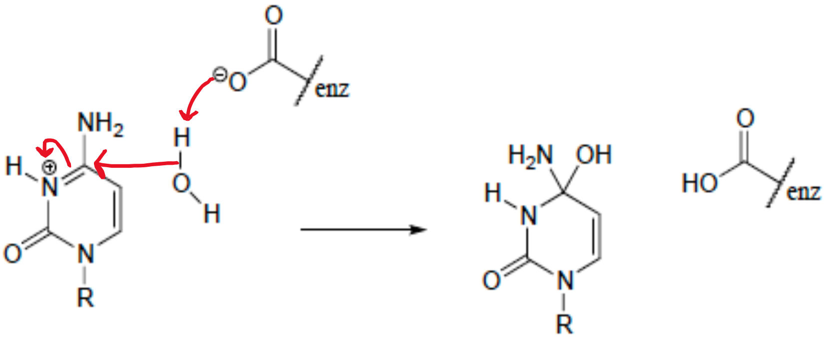


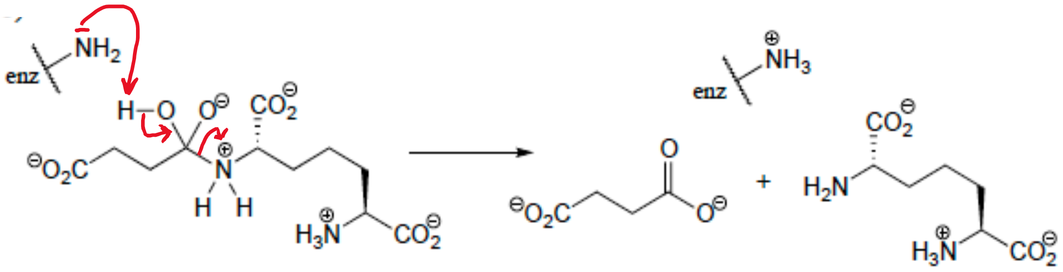
c) For each step illustrated below, draw the products or intermediate species that would form according to the electron-movement arrows given. Be sure to include all formal charges. You do not need to show stereochemistry. *(As context: Illustrated below are individual steps in some biochemical reaction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





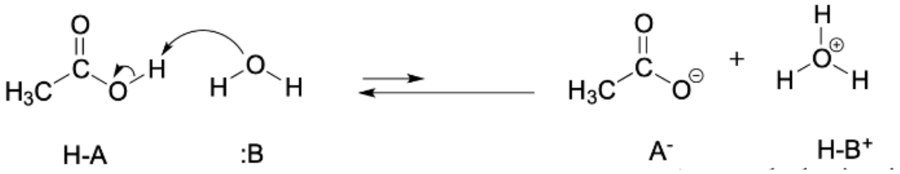
d) For each, draw curved arrows showing the electron movement taking place.





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.



ACID BASE Conjugate BASE Conjugate ACID

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

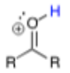
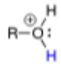
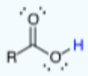
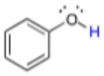
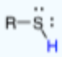
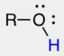
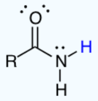
An acid base reaction will be favored when a weaker base and a weaker acid combine to form a stronger acid and stronger base.	**T** [✓ **F**]
Generally, strong acids have weak conjugate bases	[✓ **T**] **F**
Strong acid have high pKa values	**T** [✓ **F**]
A weak base is less stable than a strong base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

General concept to know:

A strong acid has a weak conjugate base that can stabalize the accepted electrons (negative charge) well and a low pKa.

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.

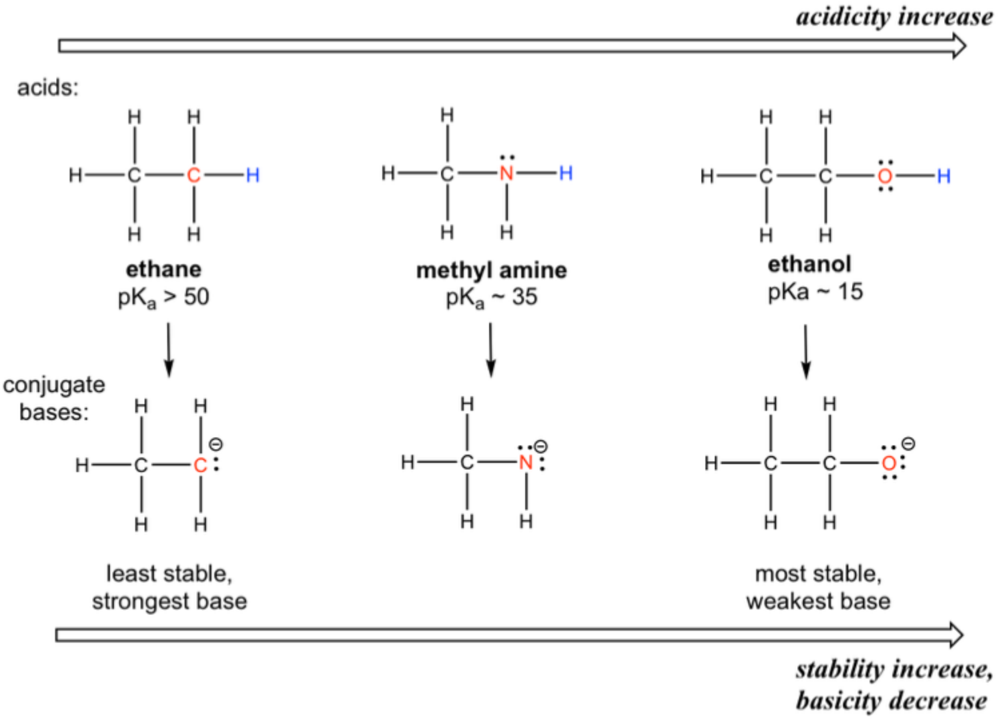
- *thiol*
- *protonated carboyl(ketone)*
- *alcohol*
- *carboxylic acid*
- *phenol*
- *amide*
- *protonated alcohol*

							
	protonated ketone	protonated alcohol	carboxylic acid	phenol	thiol	alcohol	amide
pKa	< 0	< 0	5	10	10	15	20

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

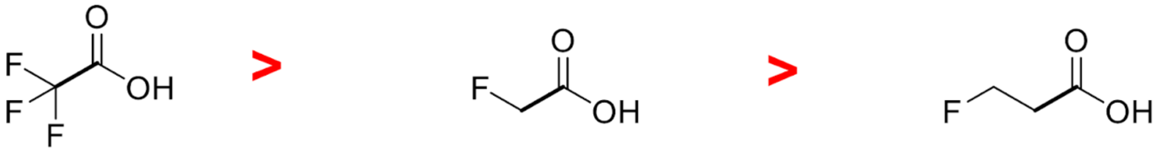
5.3 Acidity and Basicity – Trends in Acidity

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



Trend: The more **electornegative** the atom where the hydrogen is connected, the lower its pKa/stronger acid it is (O>N>C). The connection between electronegativity and acidity can be explained as the atom with a higher electronegativity being able to better accommodatethe negative charge of the conjugate base, therefore stabilizing the conjugate base in a better way. Therefore, *the more stable conjugate base, the weaker the conjugate base is, and the stronger the acid is*.

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?



It is called the **Inductive effect**

The inductive effect describes the electrostatic influence of a covalently bonded substituent (in this case fluorine) on the change in charge distribution in a molecule. Substituents with a high electronegativity or a positive charge attract electrons particularly strongly. Trifluoroacetic acid has the greatest inductive effect with 3 fluorine in the α-position and is therefore the strongest acid. The inductive effect depends strongly on the distance between the neighboring functional groups. Therefore, fluoroacetic acid is the stronger acid compared to 3-fluoropropanoic acid, which has the fluorine in the β-position.

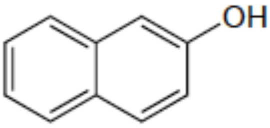
Bonus: Akyl groups are condisered weakly electron-donating.

This is due to the difference in electronegativity between carbon and hydrogen. Because carbon is more electronegative, it pulls electron density slightly towards itself away from the hydrogen atoms. This gives the carbon a small negative charge and the hydrogens each get a small positive charge.

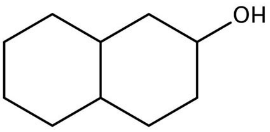
The additional electron density aquired by the carbon atom allows it to "donate" additional charge to other carbon atoms to which it is bonded.

(To be very precise the explanation for the electron donating nature of alkyl groups are due to an effect called Hyperconjugation, which refers to the delocalization of electrons over sigma bonds. The concept of Hyperconjugation however exceeds the scope of this course and is not exam relevant.)

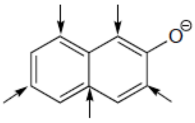
c) Draw the conjugate base of (the major resonance contributor), and on your drawing indicate with arrows all of the atoms to which the negative charge can be delocalized by resonance. Why is 2-Naphthol a stronger acid than Decahydro-2-naphthol?



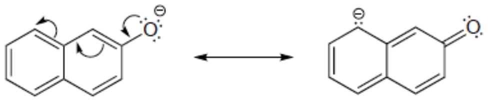
2-naphthol



Decahydro-2-naphthol



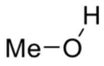
for example:



2-Naphthol is a stronger acid due to the **Resonance effect,** meaning that the electron density in the conjugated base is stabilized by resonance delocalization.

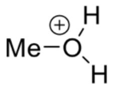
5.4 Acidity and Basicity – Determine Acidity

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



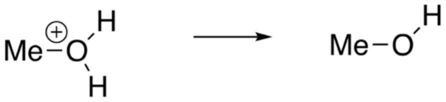
Methanol

$<$



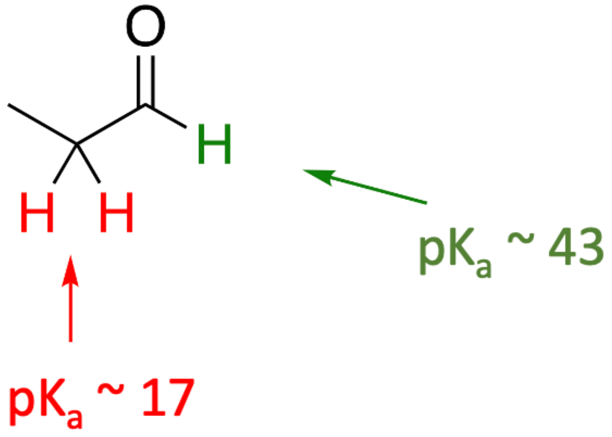
Methyloxonium

- Methyloxonium is positively charged, which is energetically unfavorable. ($\mathrm{p}K_a$ ~ -3). (The positive charge is on an electronegative atom!)

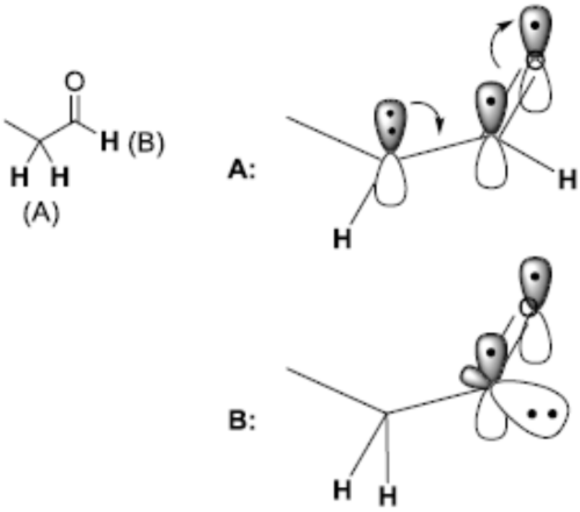


- Methanol is not a strong acid ($\mathrm{p}K_a$ ~ 15.5). The deprotonation of methanol produces the corresponding methanolate (conjugate base) which carries a non-resonance-stabilized negative charge. This in turn is energetically unfavorable.

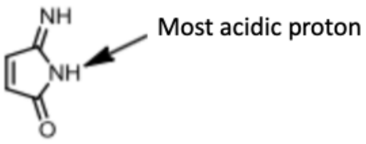
b) Compare the acidity of the labeled protons and decide which one is more acidic. Give reasons for your choice.

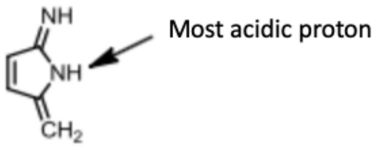


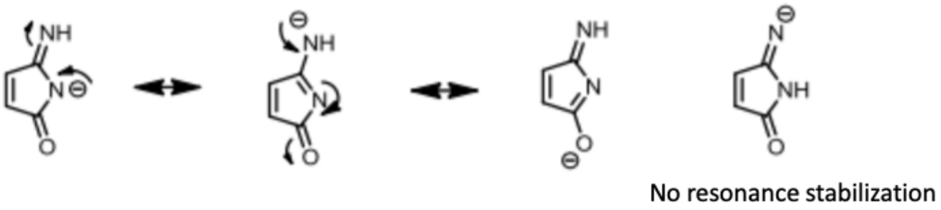
The major difference in the acidity of the protons lies in the geometric arrangement of the resulting non-bonding electron pair. In the case of proton A (red), the electrons are located in a p-orbital, which is oriented parallel to the p-orbitals of the carbonyl group (this parallel arrangement enables resonance stabilization with the carbonyl group). In contrast, the non-bonding electrons in case B (green) are located in an sp2 hybrid orbital perpendicular to the p-plane of the carbonyl group, which means that resonance stabilization is not possible:

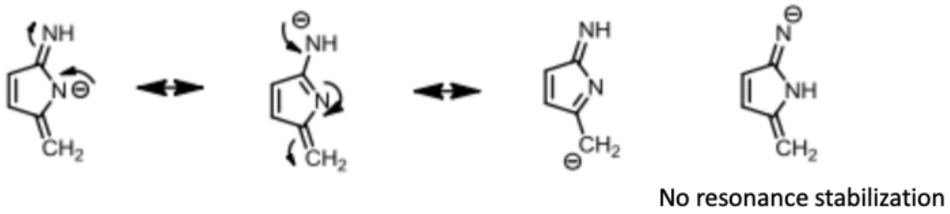


c) Which is the most acidic proton in the molecules shown below? Which compound of the two is the stronger acid? Give reasons with the help of resonance structures.



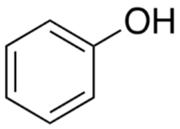


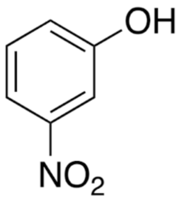


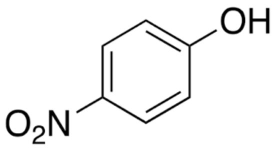


Both deprotonated molecules each have three resonance structures. However, the left molecule (5-imino-1,5-dihydro-2H-pyrrol-2-one) has a resonance structure in which the negative charge lies on the electronegative oxygen, while the negative charge of the right molecule (5-methylene-1,5-dihydro-2H-pyrrol-2-imine) lies on the less electronegative carbon. Therefore, the negative charge of the left molecule is better stabilized (delocalized) and thus acidic. The pK_a of pyrroles is in the range of 20.

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

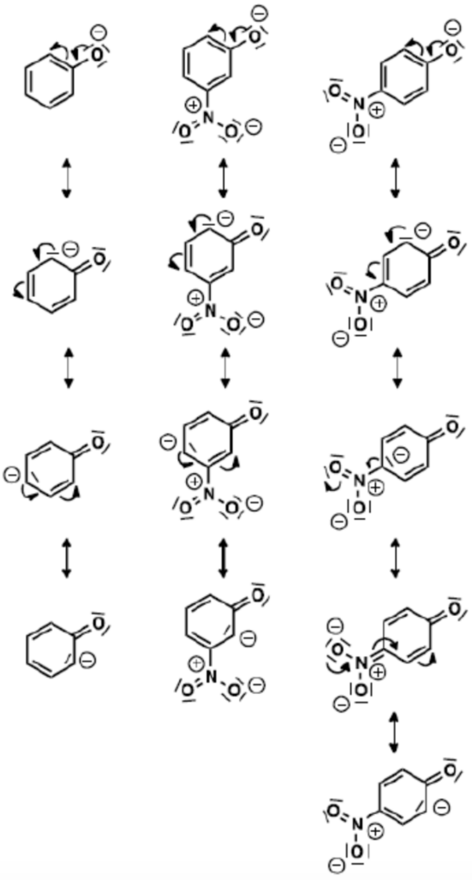




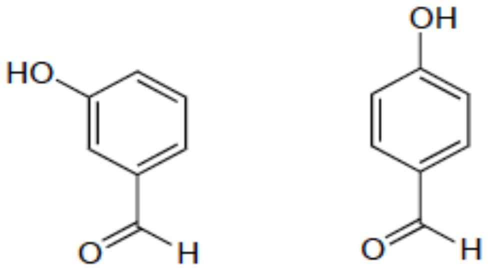


4-Nitrophenol is the strongest acid because the conjugate base has the most resonance structures and is therefore more stable than the conjugate base of 3-nitrophenol. 3-Nitrophenol and phenol have the same number of resonance structures. 3-Nitrophenol is the stronger acid compared to phenol because the electron-withdrawing nitro group in 3-nitrophenol exerts a negative inductive effect and can therefore stabilize the negative charge of the conjugate base.

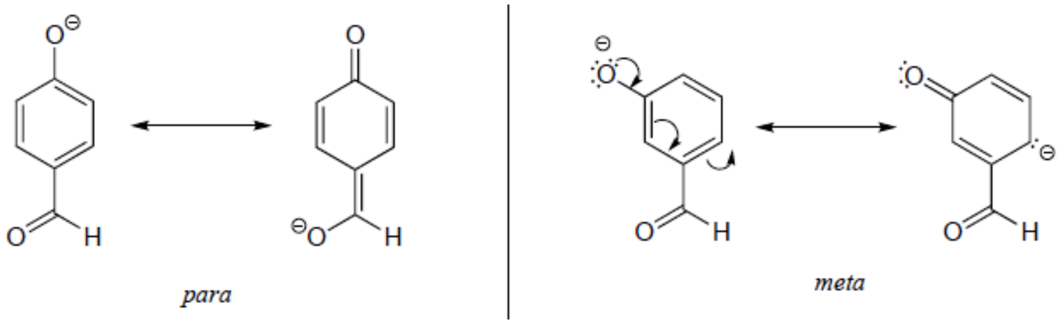
Phenol: pK_a value (in DMSO) = 18.0; 4-nitrophenol: pK_a value (in DMSO) = 10.8; 3-nitrophenol: pK_a value (in DMSO) = 14.4.



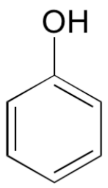
e) The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



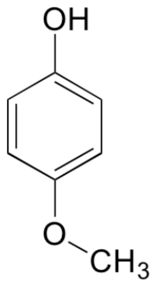
The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position (try drawing curved arrows to convince yourself of this - the negative charge can be delocalized to ring carbons, but not the aldehyde oxygen).



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.*

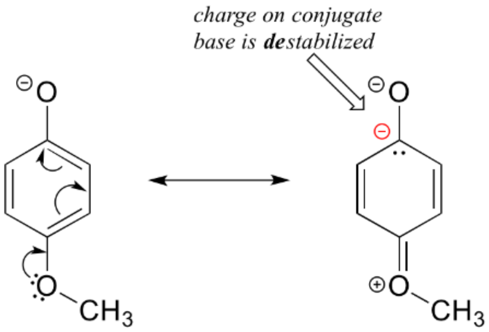


$pK_a = 10$



$pK_a = 10.6$

At first inspection, you might assume that the methoxy substituent, with its electronegative oxygen, would be an electron-withdrawing group by induction. That is correct, but only to a point. The oxygen atom does indeed exert an electron-withdrawing inductive effect, but the lone pairs on the oxygen cause the exact opposite effect – *the methoxy group is an* ***electron-donating group by resonance****.* A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.



charge on conjugate base is ***de****stabilized*

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).

This is a direct application of the **Henderson-Hasselbalch** equation

$pH = pK_a$ + log([concentration of conjugate base / [concentration of weak acid])

The ratio of base to acid is 40mM/30mM, or 1.33.

Therefore, substituting these values and the pK_a results in

$$
\begin{aligned}
pH &= 4.8 + \log(40\text{mM}/30\text{mM}) \\
&= 4.8 + \log 1.33 \\
&= 4.8 + 0.125 \\
&= 4.9
\end{aligned}
$$

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?

We again use the Henderson-Hasselbalch equation and let the base to acid ratio

be X.

For pH = 2.8:

2.8 = 4.8 + log X

X = 0.01 to 1

pH 3.8, the ratio is 0.10 to 1

pH 4.8, the ratio is 1.0 to 1

pH 5.8, the ratio is 10 to 1

pH 6.8, the ratio is 100 to 1

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

We must consider the protonation state/charge of all ionizable groups on the peptide - including the terminal amino and carboxylic acid groups - at pH 7.

terminal amino: +1

Cys: thiol, 0

Asp: carboxylate, -1

Lys: ammonium, +1

Glu: carboxylate, -1

terminal carboxylate: -1

Net charge is therefore approximately -1.