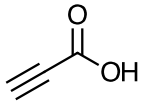
Objective 11. Apply acid-base principles to organic acids.
Skills: Draw structure, ID structural features and reactive sites (alpha C, beta C, LG, etc.), ID Nu^- and E^+, use curved arrows to show bonds breaking and forming, show delocalized electrons with resonance structures.
Key ideas:
Organic acids are weak ($pK_a > 4$)
– charge, pH, and pK (see Chem 1B and biochem)
change group bonded to acid group – explain why one acid is stronger. E.g., sub Cl for H. See pK of different amino acids – why does pK of acid group change?
See stability of conjugate base and resonance structures.
See strongest acid.

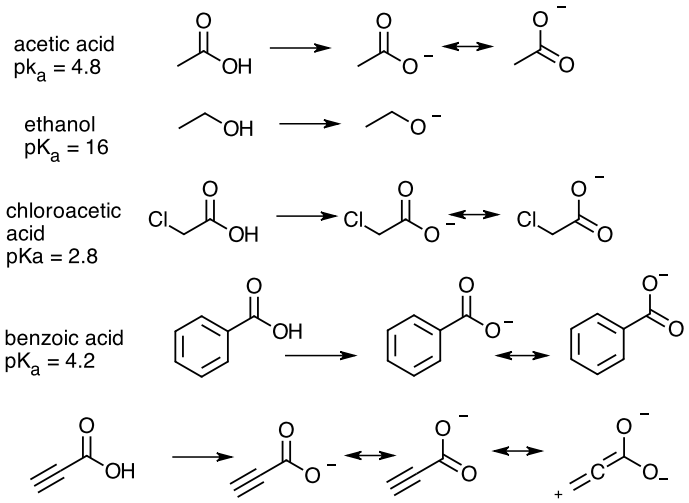
Organic acids are weak acids.
Remember:

- An acid is a H^+ donor and a base is a H^+ acceptor.
- Every acid has a conjugate (partner) base.
- The acid has a higher charge than its conjugate base, e.g., H_2O acid has a charge of 0 and OH^-, its conjugate base, has a charge of -1.
- K_a (or pK_a) determines acid strength: higher K_a (or lower pK_a) means stronger acid.
- A strong acid has a weak conjugate base and a weak acid has a strong conjugate base.
- A weak base is more stable and less reactive (does not want to donate its H^+) than a strong base.
- A strong acid forms a stable (weak) conjugate base. (In other words, you can explain acid strength by looking at the stability of the conjugate base.)
- A weak (stable) base spreads out its charge (inductive or resonance effect) on the basic atom whereas a strong (unstable) base concentrates its charge on the basic atom.

1. a. (i) Draw the structures of acetic acid ($pK_a = 4.8$) and ethanol ($pK_a = 16$) and their conjugate bases.
(ii) Acetate ion is more stable than ethoxide ion because the negative charge on the O is delocalized over three atoms due to ___.
b. (i) Draw the structures of acetic acid and chloroacetic acid ($pK_a = 2.8$) and their conjugate bases.
(ii) How does Cl stabilize the negative charge on chloroacetate better than the H on acetate?
(iii) Compare chloroacetic acid to dichloroacetic acid. Which acid is stronger? Why?
c. (i) Draw the structures of acetic acid and benzoic acid ($pK_a = 4.2$) and their conjugate bases.
(ii) How does the phenyl group stabilize the negative charge on benzoate better than the H on acetate?
d. Compare chloroacetic acid to benzoic acid. How does Cl stabilize the negative charge on chloroacetate better than the phenyl group on benzoate?
e. The acid shown below has a pK_a of approximately 2.



(i) Explain why this acid is a stronger acid than acetic acid. (Hint: see inductive effect of HCC group.)
(ii) You can draw a resonance structure of the conjugate base that involves the pi bond from the triple bond. Draw this resonance structure (hint: more than one atom will have a charge). Is the resonance effect stronger or weaker than the inductive effect?
Answers:
a. (i)

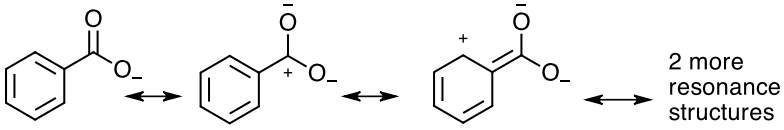


(ii) Acetate ion is more stable than ethoxide ion because the negative charge on the O is delocalized over three atoms due to resonance.

b. (ii) Cl is more electronegative than H. The electronegative Cl withdraws (attracts) electron density from the (-) charge on the O and spreads out the (-) charge ==> more stable.

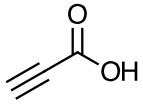
(iii) Dichloroacetic acid is a stronger acid than chloroacetic acid. In the conjugate base of dichloroacetic, two Cl withdraws more electron density from the (-) charge than one Cl. So the conjugate base of dichloroacetic acid is more stable than chloroacetic acid.

c.(ii) The phenyl group stabilizes the negative charge on benzoate better than the H on acetate by delocalizing the charge – see resonance structures.



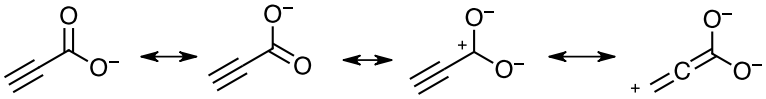
d. Compare chloroacetic acid to benzoic acid. The Cl stabilizes the negative charge on chloroacetate better than the phenyl group on benzoate through an inductive effect (electronegativity) compared to a resonance effect.

e. The acid shown below has a pK$_a$ of approximately 2.

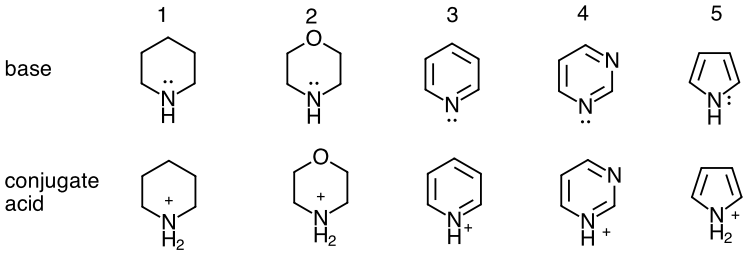


(i) The carbon-carbon triple bond (with sp-hybridized C) attracts electrons through an inductive effect better than H.

(ii) See the resonance structure of the conjugate base that involves the pi bond from the triple bond. The resonance effect is weaker than the inductive effect.



2. The five bases below are ranked from strongest (left) to weakest (right).



a. Explain the ranking. Do you expect the strongest base to have a localized lone pair or not?

b. Which base has the strongest conjugate acid? Draw the structure of this conjugate acid.

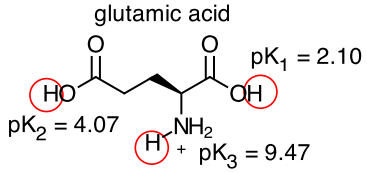
Answers:

a. A Lewis base is an electron pair donor. A strong base easily donates its electron pair whereas a weak base does not easily donate its electron pair. The strongest base has a localized lone pair.
Also, a stronger base has a more stable conjugate acid than a weaker base.
1 = lone pair on N is localized on N – the electron density from the lone pair is "concentrated" on the N.
2 = electronegative O attracts lone pair on N through an inductive effect (or withdraws electron density from the lone pair) – less concentrated electron density from lone pair so weaker base.
3 = Lone pair on N is not part of aromatic ring (see Objective 6). Compare Base 1 to Base 3 and their conjugate acids.
The conjugate acid of Base 1 is a weaker acid than the conjugate acid of Base 3.
The N-H bond in the conjugate acid of Base 1 has sp^3 hybridization.
The N-H bond in the conjugate acid of Base 3 has sp^2 hybridization.
More s orbital character means stronger acid so the conjugate acid of Base 3 is stronger than the conjugate acid of Base 1.
Strong acid means its conjugate base is weak. So stronger conjugate acid of Base 3 means Base 3 is weaker than Base 1.
4 = The 2nd N in the ring replaces a C in Base 3. N is more electronegative than C so the inductive effects of N withdraws electron density from lone pair ==> weaker base.
5 = Lone pair on N is part of aromatic ring so lone pair is delocalized over the 5 atoms in the ring.

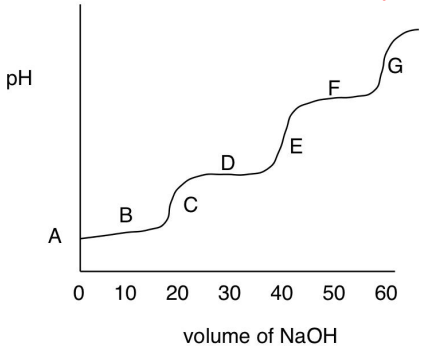
A titration curve is a graph of pH vs. volume. It gives us information about:

- the relative concentrations of acid and conjugate base at different pH's.
- The charge at different pH's.
- The pH at which a buffer can be made.

For the buffer region: Henderson-Hasselbach equation, $pH = pK_a + \log [base]/[acid]$
At half-way point $pH = pK_a$ because [base] = [acid].
For a polyprotic acid, such as an amino acid or protein, use $pH = 0.5(pK_{ai} + pK_{a(i+1)})$.
The isoelectric point (pI) is the pH at which an amino acid or protein has a neutral charge (charge = 0).
3. Glutamic acid is used to make the food flavor enhancer, MSG (monosodium glutamate).



a. (i) Draw a titration curve of glutamic acid if titrated with 0.1 M NaOH. Calculate the pH at each half-way point and the first and second end points. (Answer: at 1st end point, $pH = 0.5(pK_1 + pK_2) = 0.5(2.10 + 4.07) = 3.08$)
(ii) Show the charge of the amino acid at each half-way point and each end point. (Answer: at 1st half-way point, pH = 2.10 and charge is 50% +1 charge and 50% 0 charge; at 2nd end point, $pH = 0.5(pK_2 + pK_3) = 0.5(4.07 + 9.47) = 6.77$ and charge is -1.)
b. MSG: What is the charge on the glutamate ion? At what pH is glutamic acid in the form of glutamate so you can make MSG? Give reasons.
c. What is the isoelectric point of glutamic acid?
Answers: $K_{a1} = 7.9 \times 10^{-3}$ ($pK_{a1} = 2.1$), $K_{a2} = 8.51 \times 10^{-5}$ ($pK_{a2} = 4.07$), $K_{a3} = 3.39 \times 10^{-10}$ ($pK_{a2} = 9.47$)
Titration curve shows three end points.

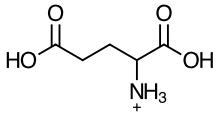


pH at starting point = 1.55 (Point A)
Set up your equilibrium reaction and equilibrium constant equation:

$H_3A \leftrightarrows H^+ + H_2A^-$

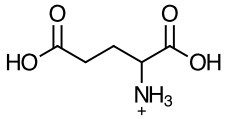
At equilibrium: 0.1-x x x

$K_a = 10^{-pKa} = 7.9x10^{-3} = [x]\,[x]/[\,0.1-x] \approx [x]\,[x]/[\,0.1]$. (REMEMBER: assume 0.1-x = x since K_a is very small.)
Solve for x = $[(7.9x10^{-3})(0.1)]^{0.5} = 0.028 = [H^+]$
pH = - log$[H^+]$ = -log(0.028) = 1.55 (Point A). Charge = +1

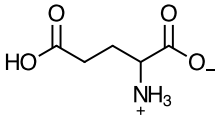


charge = +1

pH at 1st ½ way point = pK_{a1} = 2.1 (Point B). 50% acid (charge = +1) and 50% base (charge = 0)

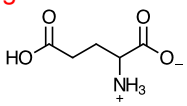


charge = +1



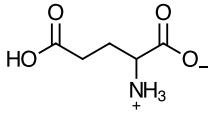
charge = 0

pH at 1st end point = 0.5(pK_{a1} + pK_{a2}) = 0.5(2.1 + 4.07) = 3.08 (Point C). Charge = 0. This is the ISOELECTRIC POINT of glutamic acid = the pH at which the charge = 0.

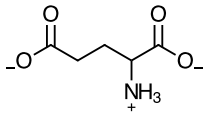


charge = 0

pH at 2nd ½ way point = pK_{a2} = 4.07 (Point D). 50% acid (charge = 0) and 50% base (charge = -1)

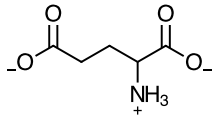


charge = 0



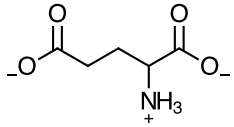
charge = -1

pH at 2nd end point = 0.5(pK_{a2} + pK_{a3}) = 0.5(4.07 + 9.47) = 6.77 (Point E). Charge = -1

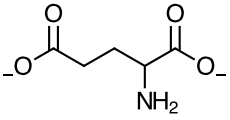


charge = -1

pH at 3rd ½ way point = pK_{a2} = 9.47 (Point F). 50% acid (charge = -1) and 50% base (charge = -2)

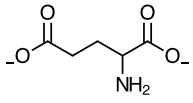


charge = -1



charge = -2

pH at 3rd end point = 10.9 (Point G). Charge = -2



charge = -2

Set up your equilibrium reaction and equilibrium constant equation:

$A^{3-} + H_2O \Longleftrightarrow OH^- + HA^{2-}$

At equilibrium: 0.025-x x x

$K_b = K_w/K_{a2} = 1x10^{-14}/2.95x10^{-5} = 0.020 = [x]\,[x]/[\,0.025-x] \approx [x]\,[x]/[\,0.025]$

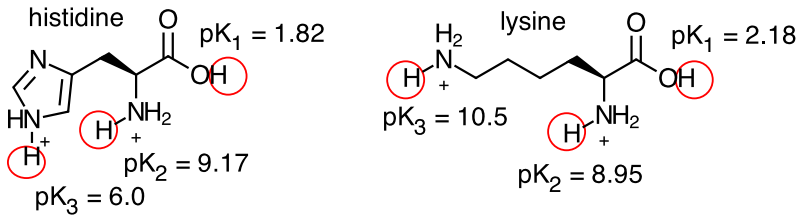
REMEMBER: The volume of solution at the endpoint is 80 ml so using the dilution equation ($C_1V_1 = C_2V_2$), the concentration of A^- is 0.025 M.

Solve for x = $[OH^-] = [(2.95x10^{-5})(0.025)]^{0.5} = 0.00086$

Then, use pOH = - log$[OH^-]$ to calculate pOH. pOH = -log$[OH^-]$ = -log (0.00086) = 3.1

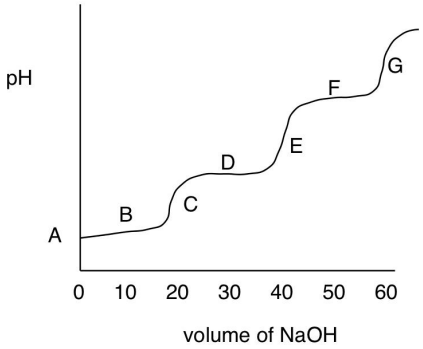
Last, use pH + pOH = 14 to calculate pH. pH = 14 - pOH = 10.9

4. You are given a 0.1 M mixture of two amino acids, histidine and lysine, and want to separate the amino acids by electrophoresis. The Lewis structures of each amino acid, the acidic protons, and pKa's are shown.



a. (i) Draw a titration curve of each amino acid if titrated with 0.1 M NaOH. Calculate the pH at each half-way point and the first and second end points.
(ii) Show the charge of each amino acid at each half-way point and each end point.
b. What is the isoelectric point of histidine? Lysine?
c. What pH would you use in an electrophoresis experiment to separate these two amino acids? Give reasons. (Hint: Choose a pH at which the charge of one amino acid is different than the other amino acid.)
d. Identify the amino acid and salt (conjugate base) combination you would use to make a pH 5 buffer. Describe how you would make this buffer.

Answers: The titration curves for histidine and lysine show three end points.



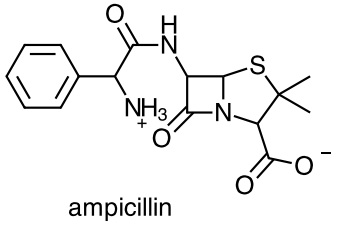
	histidine	lysine
pK_{a1}	1.82	2.18
pK_{a2}	6.0	8.95
pK_{a3}	9.17	10.5
K_b to calculate pH at 3rd endpoint	1.48×10^{-5}	0.00032
pH at starting point / charge	1.41 / +2	1.59 / +2
pH at 1st half-way point / charge	1.82 / +2 and +1	2.18 / +2 and +1
pH at 1st end point / charge	3.91 / +1	5.56 / +1
pH at 2nd half-way point / charge	6.0 / +1 and 0	8.95 / +1 and 0
pH at 2nd end point / charge	7.58 / 0 (ISOELECTRIC POINT)	9.72 / 0 (ISOELECTRIC POINT)
pH at 3rd half-way point / charge	9.17 / 0 and -1	10.5 / 0 and -1
pH at 3rd end point / charge	10.8 / -1	11.4 / -1

c. An electrophoresis experiment uses a difference in charge to separate two amino acids. Choose a pH at which the charge on histidine is different than the charge on lysine.
Example: at pH 3.91, the charge on histidine = +1 and charge on lysine is part +2 and part +1.
At pH 5.56, the charge on histidine is part +1 and part 0 and charge on lysine is +1.
At pH 7.58, the charge on histidine is 0 and charge on lysine is part +1 and part 0.

d. To make pH 5 buffer:
histidine – pH 5 is between the 1st endpoint and 2nd half-way point.
Use histidine with +1 charge as acid and 0 charge as base.
Use Henderson-Hasselbach equation: pH = pK_a + log [base]/[acid]
5 = 6.0 + log [histidine with 0 charge]/[histidine with +1 charge]
[histidine with 0 charge]/[histidine with +1 charge] = 0.1
This means the ratio of histidine with 0 charge to histidine with +1 charge is 0.1:1.
So % histidine with 0 charge = 0.1/(0.1 + 1) = 9.1% histidine with -1 charge
and 100 – 9.1 = 90.9% histidine with +1 charge.
E.g., use 0.91 ml 0.1 M histidine with 0 charge and 9.09 ml of 0.1 M histidine with +1 charge to make a 10 ml of pH 5 buffer.

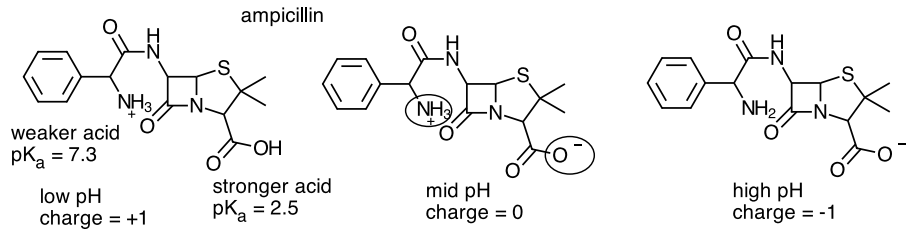
lysine – pH 5 is between the 1st half-way point 1st endpoint.
Use lysine with +2 charge as acid and +1 charge as base.
Use Henderson-Hasselbach equation: pH = pK_a + log [base]/[acid]
5 = 2.18 + log [lysine with +1 charge]/[lysine with +2 charge]
[lysine with +1 charge]/[lysine with +2 charge]= $10^{2.82}$ = 661
This means the ratio of lysine with +1 charge to lysine with +2 charge is 661:1.
So % lysine with +1 charge = 661/(661 + 1) = 99.8% lysine with +1 charge
and 100 – 99.8 = 0.2% lysine with +2 charge.
E.g., use 9.98 ml 0.1 M lysine with +1 charge and 0.02 ml of 0.1 M lysine with +2 charge to make a 10 ml of pH 5 buffer.

5. Ampicillin is a beta-lactam (a beta-lactam is an amide group in a four sided ring) antibiotic. The structure of ampicillin at physiological pH is shown below.



ampicillin

a. Ampicillin is a diprotic acid. The structure above shows one acidic proton and the conjugate base of the other acidic proton. Circle the acidic proton and the conjugate base of the other acidic proton.
b. Which acidic proton has a pK_a below 7? Give reasons.
c. Beta-lactam antibiotics are typically effective at treating bacterial meningitis infections but may have some problems crossing the blood brain barrier, which allows small, lipophilic molecules to cross. Explain why ampicillin has trouble crossing the blood brain barrier.
Answers:
a and b. See acid and amine functional groups and pK_a table for approximate pK_a's.
Or look up pK_a's of ampicillin.
https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Sigma/Product_Information_Sheet/a9393pis.pdf
https://pubchem.ncbi.nlm.nih.gov/compound/ampicillin#section=Optical-Rotation
pK_a of -COOH group = 2.5 (approximate pK_a of acid group = 5).
pK_a of $-NH_3^+$ group = 7.3 (approximate pK_a of amine group = 11).



c. Lipophilic molecules are uncharged (charge = 0).
See pK_a's of ampicillin.
At 1st ½ way point, pH = pK_a of -COOH group = 2.5. Ampicillin charge is 50% +1 and 50% 0.
At 1st end point, pH = 0.5 (pK_{a1} + pK_{a2})= 0.5 (2.5 + 7.3) = 4.9. Ampicillin charge = 0 (isoelectric point).
At 2nd end point, pH = pK_a of - NH_3^+ group = 7.3. Ampicillin charge is 50% 0 and 50% -1.

At blood pH of 7.4, the charge on ampicillin is approximately 50% 0 and 50% -1.
Charge of 0 on ampicillin has a +1 charge on amine group and -1 charge on acid group prevent it from crossing blood-brain barrier.
Charge of -1 on ampicillin prevent it from crossing blood-brain barrier.