

Study Question 1: Acid-Base Concepts

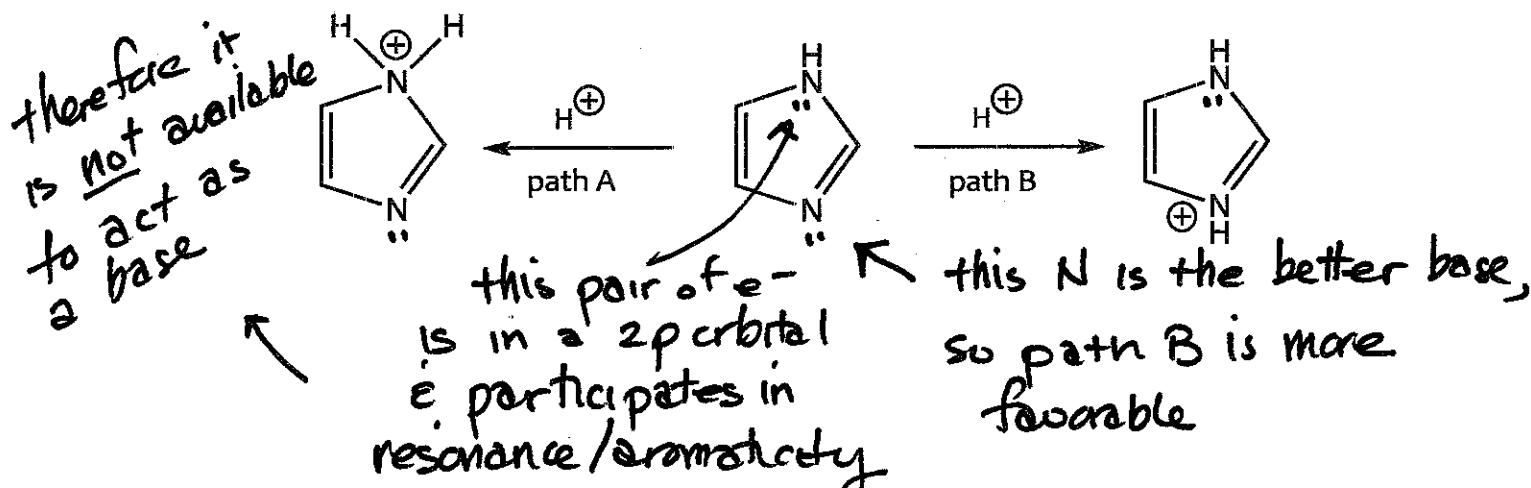
1. For Table 1.2 in McMurry & Begley, draw the structure of the conjugate base produced by each acid. Which conjugate bases are stronger conjugate bases, the ones at the top or the bottom of the table?

see attached copy of table

2. For Table 1.3, which of the conjugate acids shown is the strongest, the one at the top of the table or the bottom?

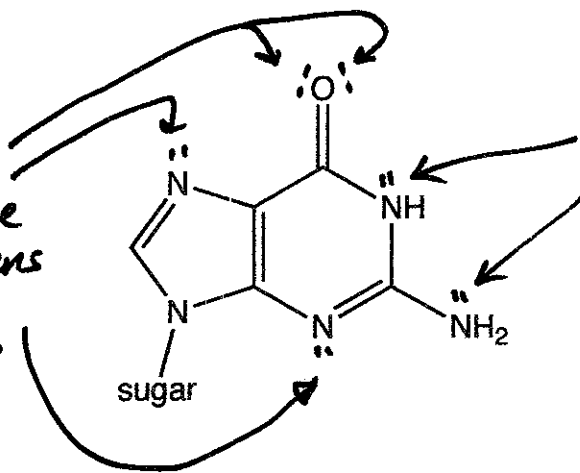
see attached

3. One entry in these tables is imidazole, the ring system in the amino acid histidine, which is a major player at enzyme active sites. There are two nitrogens in imidazole. The scheme below shows each of them acting as a base. Which nitrogen is a better base? Explain your answer.



4. The DNA base guanine is shown below. Which heteroatom on guanine would be the most basic? Explain your choice.

These lone pairs are more basic than the ones on the far side. The nitrogens are the best bases, analogous to the sp² hybridized N in imidazole above.



The oxygen, being more ~~electronegative~~ electronegative, is not as happy to have the (+) charge upon protonation so is less basic than the Ns.

5. If one looks in a biochemistry text book, there is always a chart of pKa's of amino acids (in Nelson & Cox, see Table 3-1 on pg 73). Some interesting trends in this data make good food for thought:

at 15-18, they don't appreciably ionize in H₂O

a. The pKa of the side of tyrosine is 10.07, but no value is given for the other alcohol-containing amino acids, serine and threonine. Why?

Their pKas are around 15-18 as free amino acids - the pKa may be different @ an active site -

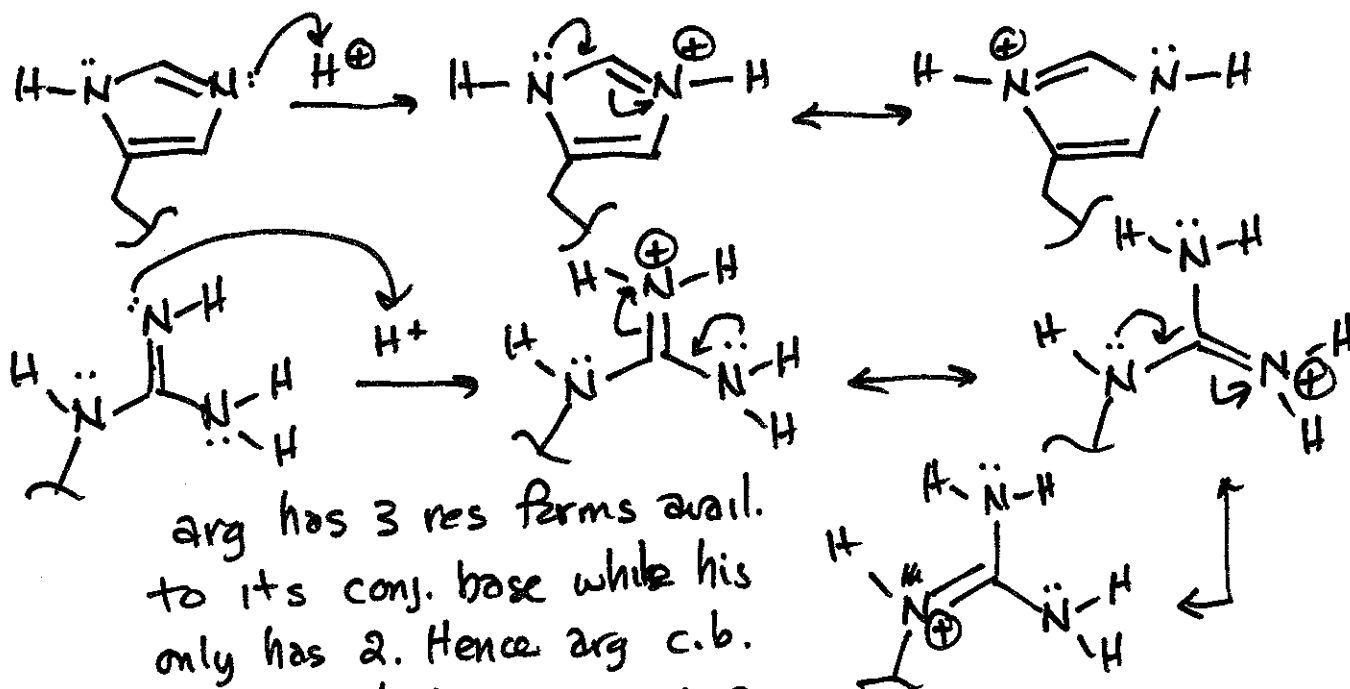
b. What would be an approximate value for the side chain pKa of serine? The side chain of cysteine is identical to that of serine except for the substitution of S for O. Why is the pKa of cysteine so much lower than serine? 15-18

sulfur, which is below O in the PT, uses n=3 orbitals which are larger + more polarizable than n=2 on O. S is happier to be δ^-

c. The three amino acid side chains with a positive charge at physiological pH have rather different structures and pKa's, even though they all involve an N-H bond acting as an acid. Lysine serves as a good reference point, as it is a simple amine and is analogous to all simple amines whose conjugate acids have pKa's in the 9-12 range (lysine's is 10.53). The structural situation regarding histidine was covered in question #3 above; that of arginine is considered in problem 1.6 in the book which was assigned. Histidine's pKa is 6.00, arginine's is 12.48.

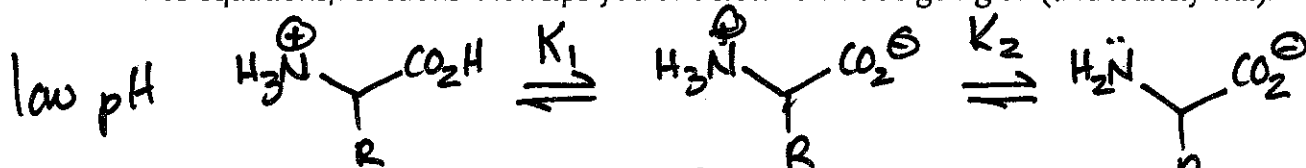
When acting as a base, what do the side chains of histidine and arginine have in common? Why then are their pKa's so different? Explain using structures or reactions.

Both are using a N-sp² orbital containing a lone pair as the base.



arg has 3 res forms avail. to its conj. base while his only has 2. Hence arg c.b. is more stable + arg more basic

6. Another interesting trend from these tables is that for the free amino acids, the pKa of the protonated α -amino group is always within the typical range of 9-12. However, the pKa's of the α -carboxylic acid groups are routinely lower than typical carboxylic acids. Even the two cases where the side chains have carboxylic acids are within the usual range. Explain why the α -carboxylic acids have pKa's lower than typical whereas the protonated α -amino groups are within the usual range. Write equations/reactions if it helps you understand what's going on (and it likely will).



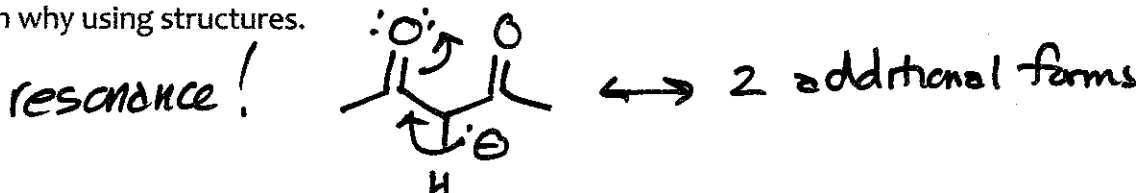
K_1 is larger (pKa1 smaller) for α -amino acids than typical acids because the presence of the $-\text{NH}_3^+$ stabilizes the c.b. due to the proximity of the two charges

7. Table 1.4 of McMurry & Begley gives the pKa's of some carbon acids (where it is the C-H bond that is dissociating).

a. Draw the conjugate base of each acid in this table. Ignoring the entry in brackets, what are these conjugate bases called as group - what is their functional group? *see attached*

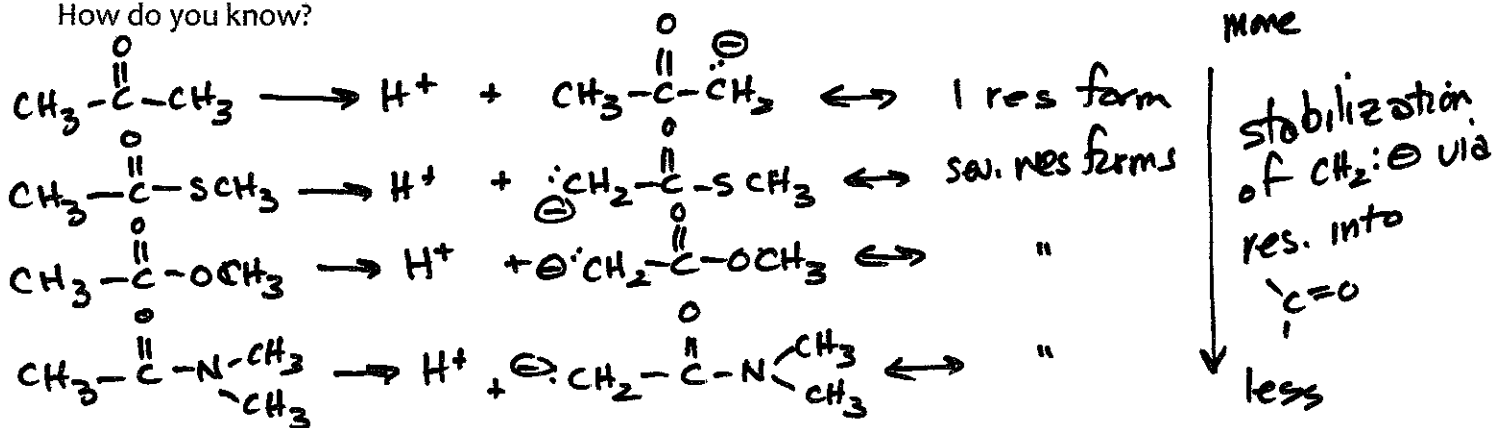
enolates

b. The dicarbonyl compounds all have lower pKa's than compounds with only one carbonyl group. Explain why using structures.



d. Write out the reaction of a ketone, thioester, ester and amide each acting as an acid at the α -carbon. In this series, what is happening to the importance of resonance in the conjugate base?

How do you know?



d. Explain why a ketone is more acidic than an ester.

It's CH_2^- is more stabilized by resonance into the C=O carbonyl because it doesn't have to share the carbonyl with the other resonance forms when S, O or N is present:

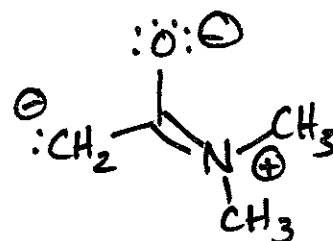
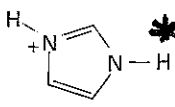


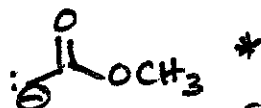
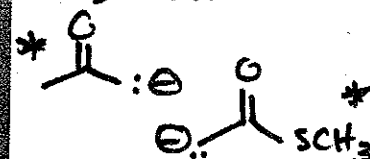
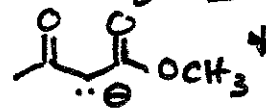
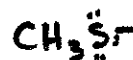
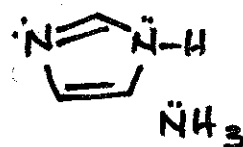
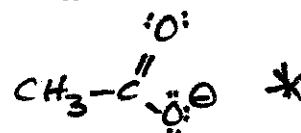
Table 1.2 Relative Strengths of Some Acids

Functional group	Example	pK _a
Carboxylic acid	CH_3COOH	4.76
Imidazolium ion		6.95
Ammonia	NH_4^+	9.26
Thiol	CH_3SH	10.3
Alkylammonium ion	CH_3NH_3^+	10.66
β -Keto ester	$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{OCH}_3$	10.6
Water	H_2O	15.74
Alcohol	$\text{CH}_3\text{CH}_2\text{OH}$	16.00
Ketone	$\text{CH}_3\text{C}(\text{O})\text{CH}_3$	19.3
Thioester	$\text{CH}_3\text{C}(\text{O})\text{SCH}_3$	21
Ester	$\text{CH}_3\text{C}(\text{O})\text{OCH}_3$	25

Stronger acid

Weaker acid

c.b.s

strongest
c.b.s

Just as acids differ in their ability to donate a proton, bases differ in their ability to accept a proton. The strength of a base B in water solution is normally expressed using the *acidity* of its conjugate acid, BH⁺.

For the reaction: $\text{BH}^+ + \text{H}_2\text{O} \rightleftharpoons \text{B} + \text{H}_3\text{O}^+$

$$K_a = \frac{[\text{B}][\text{H}_3\text{O}^+]}{[\text{BH}^+]}$$

so
$$K_a \times K_b = \left(\frac{[\text{B}][\text{H}_3\text{O}^+]}{[\text{BH}^+]} \right) \left(\frac{[\text{BH}^+][\text{OH}^-]}{[\text{B}]} \right)$$

$$= [\text{H}_3\text{O}^+][\text{OH}^-] = K_w = 1.00 \times 10^{-14}$$

* these species have important resonance forms.

be sure you can draw them!

$$\text{Thus } K_a = \frac{K_w}{K_b} \quad \text{and} \quad K_b = \frac{K_w}{K_a}$$

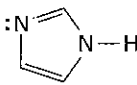
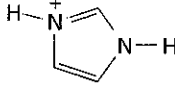
$$\text{so } pK_a + pK_b = 14 \quad \text{and} \quad pK_b = 14 - pK_a$$

Stronger base—larger pK_a for BH^+

Weaker base—smaller pK_a for BH^+

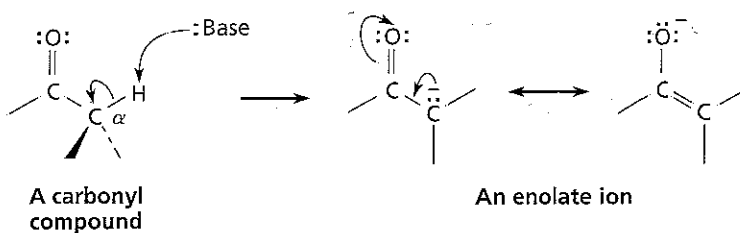
These equations say that we can determine the basicity of a base B by knowing the K_a of its conjugate acid BH^+ . A stronger base holds H^+ more tightly, so it has a weaker conjugate acid (larger pK_a); a weaker base holds H^+ less tightly, so it has a stronger conjugate acid (smaller pK_a). Table 1.3 lists some typical bases found in biochemistry. Note that water can act as either a weak acid or a weak base, depending on whether it donates a proton to give OH^- or accepts a proton to give H_3O^+ . Similarly with imidazole, alcohols, and carbonyl compounds, which can either donate or accept protons depending on the circumstances

Table 1.3 Relative Strengths of Some Bases

Functional group	Example	<i>weakest</i> pK_a of BH^+	
Hydroxide ion	$:\ddot{O}H^-$	H_2O	15.74
Guanidino	$\begin{array}{c} :NH \\ \\ H_2NCNHCH_2CH_3 \end{array}$	$\begin{array}{c} +NH_2 \\ \\ H_2NCNHCH_2CH_3 \end{array}$	12.5
Amine	$CH_3\ddot{N}H_2$	$CH_3\overset{+}{N}H_3$	10.66
Ammonia	$:NH_3$	$^+NH_4$	9.26
Imidazole			6.95
Water	$H_2\ddot{O}:$	H_3O^+	-1.74
Alcohol	$CH_3\ddot{O}H$	$CH_3\overset{+}{O}H_2$	-2.05
Ketone	$\begin{array}{c} :O: \\ \\ CH_3CCH_3 \end{array}$	$\begin{array}{c} +OH \\ \\ CH_3CCH_3 \end{array}$	-7.5

Stronger base ↑

strongest conj. acid



The acidity of carbonyl compounds is due to resonance stabilization of the enolate ion, which allows the negative charge to be shared by the α carbon and the electronegative carbonyl oxygen. As shown in Table 1.4, aldehydes and ketones are the most acidic monocarbonyl compounds, with thioesters, esters,

Table 1.4 Acidity Constants of Some Carbonyl Compounds

Carbonyl compound	Example	$\text{p}K_{\text{a}}$
Carboxylic acid	CH_3COH	4.7
1,3-Diketone	$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{CH}_3$	9.0
β -Keto ester	$\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{COCH}_3$	10.6
1,3-Diester	$\text{CH}_3\text{OC}(\text{O})\text{CH}_2\text{COCH}_3$	12.9
Aldehyde	CH_3CH	17
Ketone	CH_3CCH_3	19.3
Thioester	CH_3CSCH_3	21
Ester	CH_3COCH_3	25
Amide	$\text{CH}_3\text{CN}(\text{CH}_3)_2$	30

Stronger acid



Weaker acid

