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Organic Chemistry with a Biological Emphasis: Solutions to Selected End-of-Chapter Problems

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Organic Chemistry
With a Biological Emphasis

Solutions to selected end-of-chapter problems

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P7.2:

a) The base on the right is stronger: amine vs aniline.
b) The base on the right is stronger: consider conjugate acids: pKa of alcohol is ~16, pKa of ammonium is ~10.
c) The base on the left is stronger: ketone in para position is electron withdrawing by resonance.
e) The base on the left is stronger: positively-charged quaternary amine destabilizes positively charged conjugate acid.
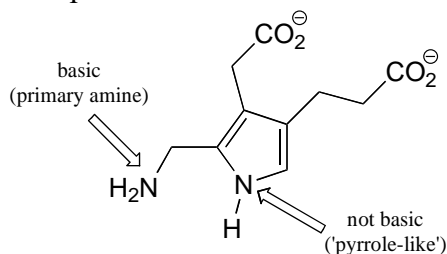h) The base on the right is stronger: amine vs 'pyrrole-like' nitrogen

P7.3:

Lipitor

Zocor
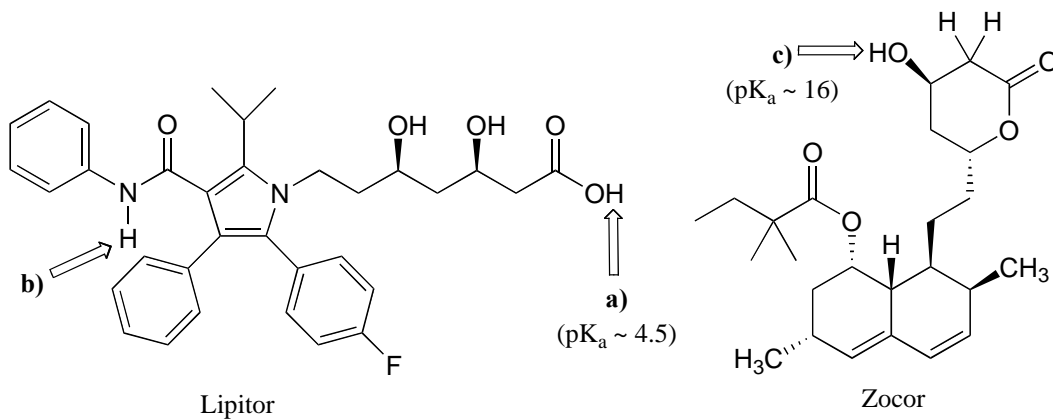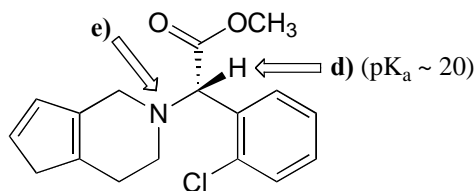
Plavix

P7.4: One nitrogen is simply a primary amine, and as such is basic. The other nitrogen is 'pyrrole-like', meaning that its lone pair is part of an aromatic sextet, and is not available for bonding to another proton.

porphobilinogen

**P7.5:** The alkyl amine nitrogen is most basic, the 'pyrrole-like' nitrogen is least basic.
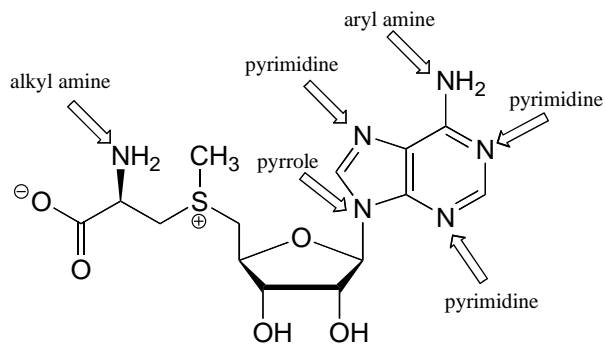
S-adenosylmethionine

P7.6: Of the four protons, H_a is the least acidic. The negative charge that results from abstraction of H_a can be delocalized to only one oxygen atom, whereas the charge resulting from abstraction of either H_b, H_c, and H_d can be delocalized to two oxygens in each case.
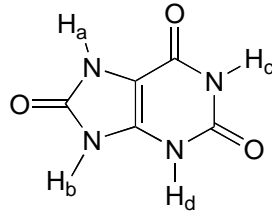
uric acid

P7.7: The total charge will be very close to -3.0. At pH $= 7.3$, the N-terminus proline (pK$_a$ $= 10.6$) will be fully protonated, and will contribute a charge of $+1$. This is balanced, however, by a negative charge on the terminal glutamate (pKa $= 2.2$). Three of the seven amino acids in the peptide have ionizable side chains: an aspartate (D) and two glutamates (E). The pK$_a$ values for these side chains are 3.7 and 4.3, respectively, so at pH 7 all three will be fully ionized, leading to a total peptide charge of -3.

P7.8: There are three ionizable groups on this peptide: the terminal amino group on Asp (pK$_a$ ~ 9.6), the side-chain carboxylate group on Asp (pK$_a$ ~ 3.7) and the terminal carboxylate on Ile (pK$_a$ ~ 2.4). For each buffer, we can use the Henderson-Hasselbalch equation to determine the charged / uncharged ratio for each group.

a) At pH $= 4.0$:

Asp (terminal amino) $[HA^+] / [A] = 10^{(9.6-4.0)} = 10^{5.6} = 4.0 \times 10^5$. At this pH the terminal amino group is essentially 100% protonated and positively charged, so this group contributes a charge of $+1$.

Asp (side chain): $[HA] / [A^-] = 10^{(3.7 - 4.0)} = 10^{(-0.3)} = 0.50$. Approximately 2 out of every 3 side chains is deprotonated and negatively charged, so overall this group contributes a charge of -0.67.

Ile (terminal carboxylate):): $[HA] / [A^-] = 10^{(2.4 - 4.0)} = 10^{(-1.6)} = 0.025$. Most, but not all of the terminal carboxylates are deprotonated and negatively charged. We can calculate the percentage that are protonated:
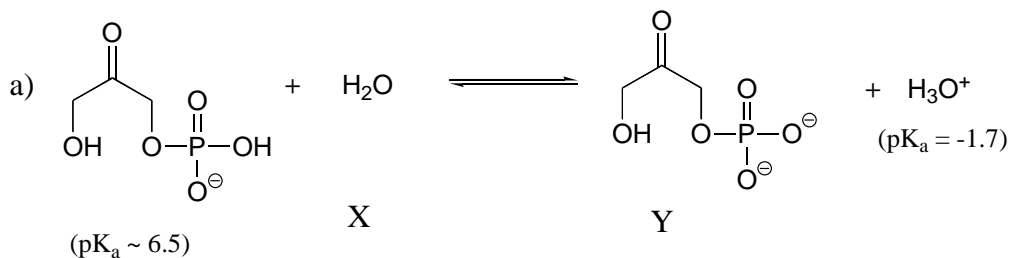
$$\frac{0.025}{(1 + 0.025)} \times 100 = 2.4\,\%$$

. . .thus about 97.6% are deprotonated and negatively charged. This group contributes an overall charge of -0.98.

In a buffer of pH 4.0, the total charge on the dipeptide will be:
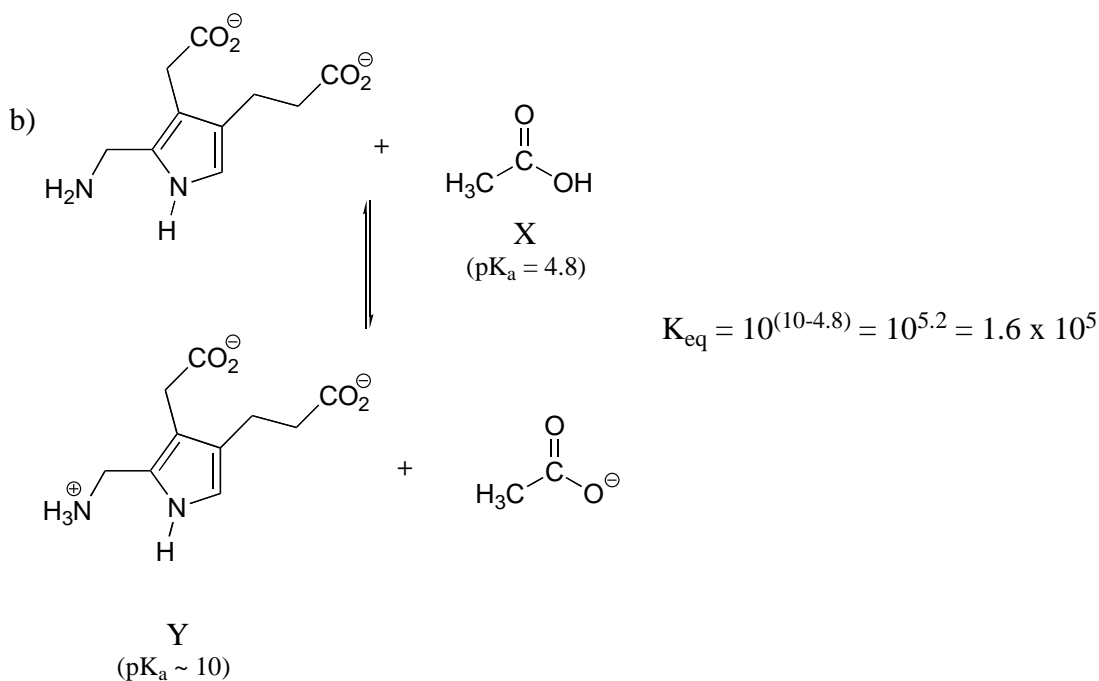$(+1) + (-0.67) + (-0.98) = -0.65$.

b) in a buffer with pH = 7.3, the total charge on the dipeptide will be close to -2 (the terminal amino group is 100% protonated, both carboxylate groups are 100% deprotonated)

c) in a buffer with pH = 9.6, the total charge on the dipeptide will be close to -2.5 (in this basic buffer, the terminal amino group is 50% deprotonated, and so only contributes a charge of +0.5).
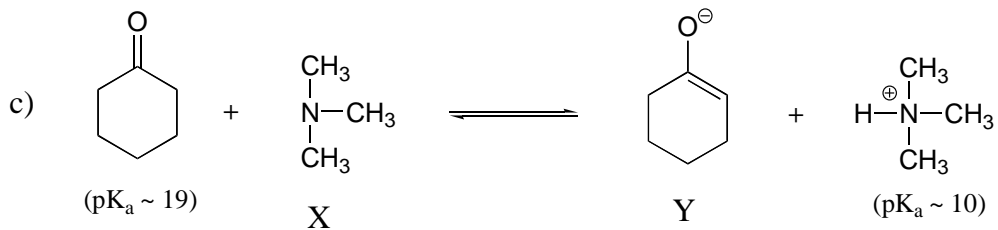
P7.9:

a)

(pK$_a$ ~ 6.5)   X   Y

$$K_{eq} = 10^{-8.2} = 6.3 \times 10^{-9}$$

b)

X
(pK$_a$ = 4.8)

$$K_{eq} = 10^{(10-4.8)} = 10^{5.2} = 1.6 \times 10^5$$
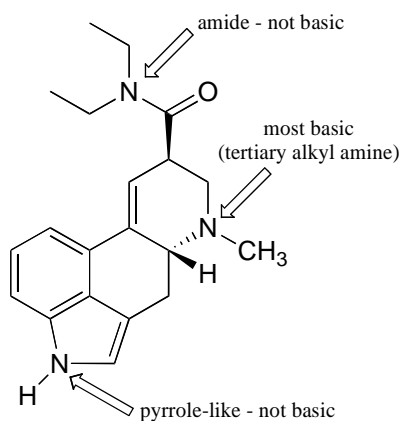
Y
(pK$_a$ ~ 10)

How did we pick the most basic group on the Y species? We have four choices: a primary amine, a 'pyrrole-like' amine, and two carboxylates. We know that pyrrole-like amines are not basic, and we can look at our pK$_a$ table to remind ourselves that primary amines are more basic than carboxylates.

c)

(pK$_a$ ~ 19)   X   Y   (pK$_a$ ~ 10)

$K_{eq} = 10^{(10-19)} = 10^{-9}$

P7.10:

amide - not basic

most basic
(tertiary alkyl amine)

pyrrole-like - not basic
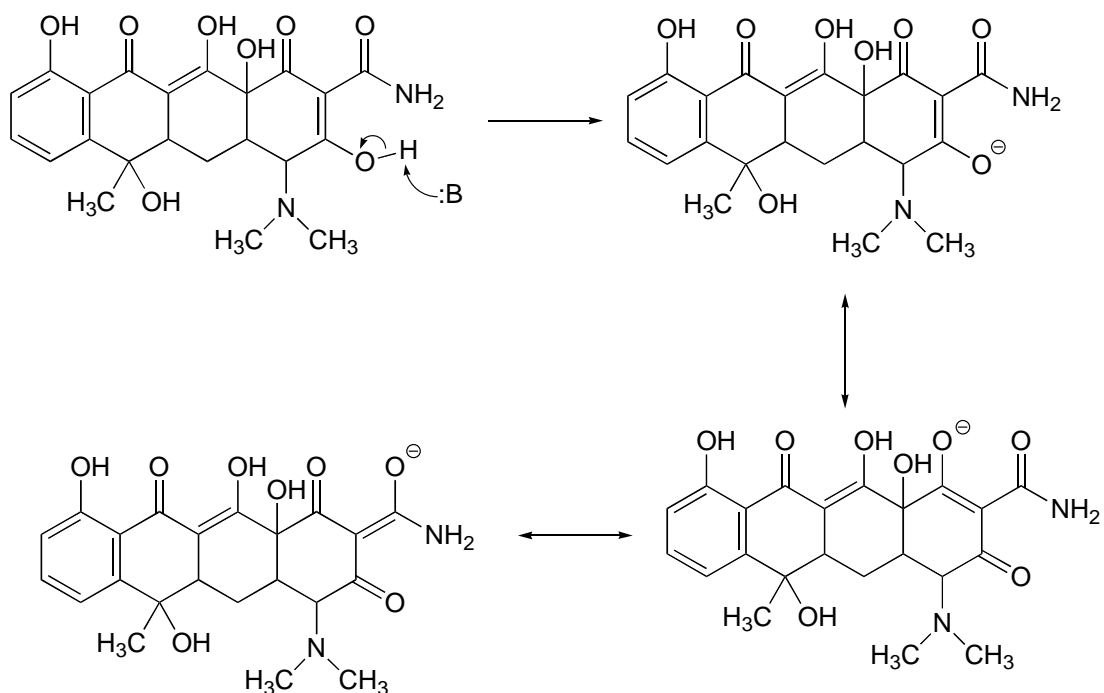
lysergic acid diethylamide
(LSD)

P7.11:

a) The most acidic proton on tetracycline is indicated below. Notice that the negative charge on the conjugate base can be delocalized to *two* carbonyl oxygens.

P7.13: In all cases the pK$_a$ of the amino acid side chain (or of water, for part e) is expected to be *lower* due to the proximity of the cationic magnesium ion. The positive charge on the metal ion is expected to stabilize the negatively-charged conjugate base form of Glu, Tyr, and water, and to destabilize the positively charged, conjugate acid forms of Lys and His.

P7.14: The positive charge on the protonated form of arginine can be delocalized by resonance to all three of the nitrogens – this stabilizes the conjugate acid form (ie. makes it a weaker acid). On the protonated form of lysine, by contrast, the positive charge is 'stuck' on the single nitrogen (see the structure of lysine in chapter 6). Because the positive charge of of lysine is not stabilized by resonance, lysine is more likely to give up a proton and lose the charge.
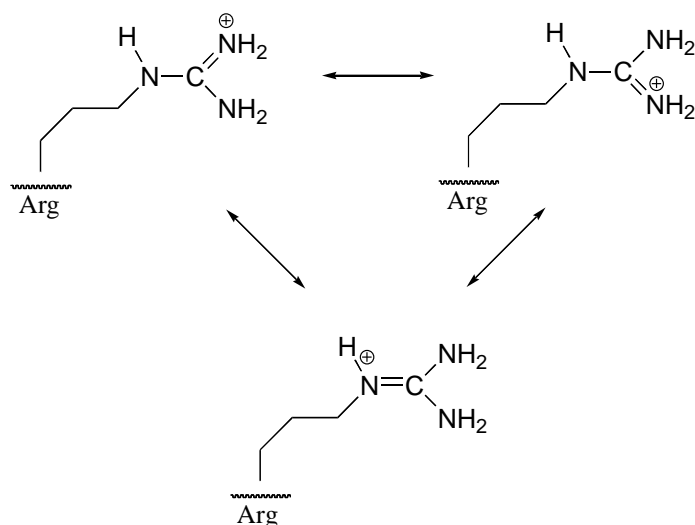
P7.15: The ester oxygen acts as an electron-donating group by resonance. This electron-donating property *destabilizes* the negative charge on the enolate form, making the α-proton *less* acidic. This argument also holds true for thioesters.
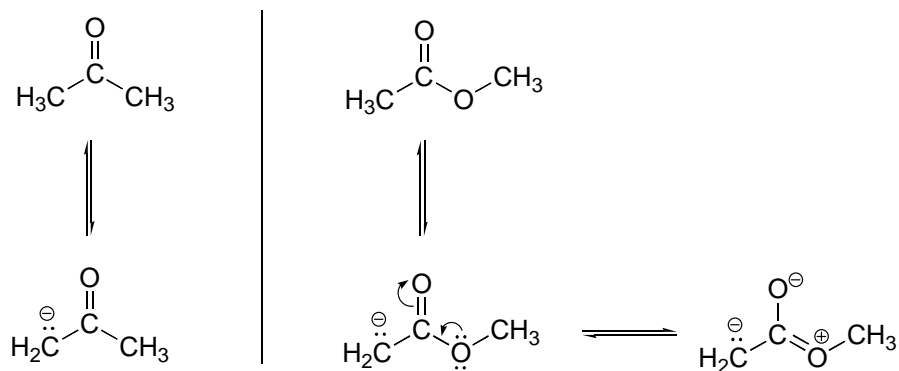
P7.16:

Tris: Using the Henderson-Hasselbalch equation, we find that the ratio $[HA^+] / [A]$ at this pH is $10^{(8.1-7.0)} = 10^{1.1} = 12.6$. The percentage of HA^+ is thus $(12.6/13.6)*100 = 93\%$. The concentration of protonated (positively charged) Tris is $(0.93)(50 \text{ mM}) = 46.5 \text{ mM}$.

Imidazolium: The Henderson-Hasselbalch equation tells us that the buffer is 50% protonated at pH 7 (this is always true when the pH of the solution equals the pKa of the buffer compound), so the concentration of the protonated form (imidazolium) is 25 mM.