Week 4. There is an exam around the corner! This page, from the Chapter 3 questions 3.34–3.37, give a nice breadth of coverage to Lewis and Brønsted acid-base topics.

3.34 Recalling that ranking Lewis base strengths follows the same trends as ranking Brønsted base strength, predict the product from this highly selective Lewis acid-base complexation reaction.

\[
\text{excess carbonate} \quad \text{products}
\]

3.35 What is the structure of the reaction product between NAAG (one of the most prevalent neurotransmitters in mammals) with excess aqueous sodium carbonate? Give the molecule, derived from NAAG, including any necessary counterions.

\[
\text{bicarbonate}
\]

3.36 It is possible to use pK\textsubscript{a} values to assess an equilibrium constant. Is the value of the equilibrium constant for the 1:1 reaction between conjugate base of phenol and sodium bicarbonate greater than, less than, or equal to 1?

\[
\text{conjugate base of phenol} \quad \text{bicarbonate}
\]

3.37 New pK\textsubscript{a} values can be determined from measuring the equilibrium constant for an acid-base reaction that is carried out with a reaction partner whose pK\textsubscript{a} value is known, and inferring what the pK\textsubscript{a} value of the new compound must have been. Based on the following data, what is the estimated pK\textsubscript{a} value for the conjugate acid of caffeine?

\[
\text{pK}_\text{a} \text{ value for the conjugate acid of caffeine:}
\]

\[
\text{conjugate acid of caffeine}
\]
Acid-base chemistry provides a critical foundation for all of the future studies in organic chemical reactivity.

All of the previously established principles for evaluating molecular structures (closed shell atoms, charges and charge placement, electronegativity difference, delocalization, geometry, atom size difference) are used to explain observed chemical reactivity across a diverse array of experimental results. Nearly all of the examples used to create exam questions are not “made up,” but rather derive from actual published reports in the contemporary chemistry journals.

The Lewis acid-base chemistry of open shell atoms is not surprising: atoms with open shells will react to give their best (most stable) closed-shell arrangement.

The text for part (a) indicates (i) a Lewis acid-base complexation reaction and (ii) that it is highly selective. At this point in CHEM 210, only two reactivities have been introduced: Lewis acid-base complexation reactions and Brønsted acid-base reactions. The text of this problem is doing the identification for you, and so these words are intended to focus your attention on “Lewis acid-base complexation” and what this means. And that is fine, but you need to know what that means, and what you anticipate about what sorts of decisions need to be made, because you cannot figure it out from the information provided. The question, in other words, is testing whether you have figured out two things: (i) what “Lewis acid-base complexation” means, and (ii) how to evaluate a choice (i.e., that something is “highly selective” means that you are about to be presented with a choice.

**Lewis acid-base complexation**

You should be anticipating that there is at least one open shell atom (the Lewis acid, an electron pair acceptor) and a reactive partner that has a non-bonding electron pair that it can share (the Lewis Base, an electron pair donor). The competition could be between a set of different open shell atoms, or the competition could be between a set of different electron pair donors, or both.

- open shell atom: “E” (a Lewis acid, accepts an electron pair, to share, and makes a bond)
- an atom with a nbe pair to share: “LB.” (a Lewis base, donates an electrons pair, to share, and makes a bond)

**Competition and selectivity**

When there are competing reactions, it turns out that there are a number of different ways to predict which pathway is the most likely, and so what is the most likely outcome. These criteria might include relative statistics (there is more of one outcome than another), relative rates (how much faster is one outcome than another), or relative stability (how much more stable is one outcome than another).

Evaluating relative stability is the first type of criterion that is part of CHEM 210.

So, in summary: before you even look at the example, you are anticipating from the text of the question that there are going to be different outcomes from reactions between one open shell atom and at least two different atoms with nbe pairs to share, or between one atom with nbe to share and at least two different open shell atoms, or more than one of each. And you anticipate needing to evaluate the relative stability of the possible outcomes.

Looking at the two molecules, you see three distinctive atoms with nbe pairs (potential Lewis bases) and one atom that has an open shell.

Recalling that ranking Lewis base strengths follows the same trends as ranking Brønsted base strength, predict the product from this highly selective Lewis acid-base complexation reaction.
With only one open shell atom in these two molecules, the one with the boron atom is going to serve as the Lewis acid (with the boron atom being the Lewis acidic atom). That means that competition is between the oxygen atom and the bromine atom, in the other molecule serving as the Lewis base.

All of the previous lessons from the course apply (behavior of well-behaved atoms; curved arrow convention, including using it to predict reactivity; assignment of formal charges) and can be used to predict the two outcomes for comparison.

How to make the choice between these two outcomes?

One of the core lessons from acid-base chemistry relates to science, in general: if you have competing factors with no generalization for ranking them, then you need to rely on experimental results.

As described earlier, all of the usual molecular features apply to evaluating stability: closed shell atoms, charges and charge placement, electronegativity difference, delocalization, geometry, atom size difference. When more than one of these factors are in competition, there is no universal ranking of which is more or less important, and so the experimental results are needed (or, a set of representative experimental results are needed, from which to create an analog).

Lewis acid-base chemistry overlaps with Bronsted acid-base chemistry because all Bronsted bases are Lewis bases, and vice versa. The pK_a table, which summarizes experimental results for Bronsted acid strength, also summarizes Bronsted base strength, and so, too, Lewis base strength. And the evaluation of acid-base strength, at least at this point in the course (and, in fact, in general) is built upon relative stabilities.

So, the only way to make the choice between these two outcomes is to understand how to apply the information from the pK_a table to the evaluation of the two different Lewis basic atoms #1 and #2.
3.34 Recalling that ranking Lewis base strengths follows the same trends as ranking Brønsted base strength, predict the product from this highly selective Lewis acid-base complexation reaction.

The pK_a value
For a given Brønsted acid (H-B; meaning any covalent bond involving a hydrogen atom), the standard acid strength is defined by its ability to protonate water, which is used as the point of reference (the “a” in pK_a).

\[
\begin{align*}
\text{H}_2\text{O} & \rightleftharpoons \text{H}^+ + \text{OH}^- \\
\text{protonation of water} & \text{deprotonation of HB} \\
\text{protonation of conjugate base B} & \text{deprotonation of conjugate acid H}_2\text{O}+ \\
K_a = \frac{[\text{H}_2\text{O}^+][:\text{B}]}{[\text{H}^+][\text{B}]} 
\end{align*}
\]

If you are comparing two Brønsted acids (H-B_1 and H-B_2), you need to understand that being “a stronger acid” means that the reaction with water (shown above) is more likely to happen. In chemistry terms, that means that the reaction of a stronger acid lies more to the right than it does for a weaker acid. If the reaction of H-B_1 lies more to the right (stronger acid) than it does for H-B_2 (weaker acid), then the K_a for H-B_1 (K_a1) will be a greater value than the K_a value for H-B_2 (the weaker acid does not give up its proton as readily, so there will be relatively less “H_2O^+ and B_1^-” formed, compared with “H_2O^+ and B_1^-” and less H-B_1, relative to the concentration of H-B_2).

**ITEM I:** for two acids, H-B_1 and H-B_2
- if H-B_1 is the stronger acid, it has the lower pK_a value

The relative Brønsted base strengths of the conjugate bases can be evaluated, also, because a stronger acid (the H-B_1 bond is more likely to break) and so B_1^- part of H-B_1 releases its proton) creates a corresponding conjugate base (B_1^-) that does not bond with a proton as well, and is classified as the weaker conjugate base (B_1^-) relative to the conjugate base (B_2^-) derived from a weaker acid (H-B_2), which is more inclined to keep its H-B bond intact.

**ITEM II:** for two acids, H-B_1 and H-B_2
- if H-B_1 is the stronger acid, it has the weaker conjugate base B_1^-.

Thus, when you need to compare the relative base strength of two bases, you can use the comparison of the pK_a values of their conjugate acids. For two bases, B_1^- and B_2^- if the pK_a value of their conjugate acids is pK_a1 > pK_a2, then H-B_1 is a stronger acid than H-B_2, and so B_1^- is a weaker base than B_2^-: There is no exception to these relationships, and so every pairing can be assessed exactly the same way. Take any random pair of molecules whose pK_a values are known, you can say something about their relative acidities. For example: the pK_a of ethanol (CH_3CH_2OH) is 17 and the pK_a value of ethanethiol (CH_3CH_2SH) is 10.2.

Ethanethiol is a stronger Bronsted acid than ethanol (10.2 < 17).

You can also compare relative base strengths, but you need to be careful to select the corresponding conjugate acids for doing the evaluation. For example, if you want to compare the relative Bronsted basicity of hydroxide (HO^-) and ethoxide (CH_3CH_2O^-), then you (a) need the pK_a values of their conjugate acids (the conjugate acid of hydroxide is water, H_2O, which has a pK_a value of 15.7; the conjugate acid of ethoxide is ethanol, CH_3CH_2OH, which has a pK_a value of 17).

Because water has a lower pK_a value than ethanol (15.7 < 17), then water is the stronger conjugate Bronsted acid of the pair of bases, therefore hydroxide is a weaker base than ethoxide. The stronger base (ethoxide) has the weaker (higher pK_a) conjugate acid.

**ITEM III:** for two bases, B_1^- and B_2^-.
- if B_1^- is a stronger base, the pK_a of its conjugate acid (H-B_1) will be higher (a weaker acid) than that of H-B_2
The combination of $pK_a$ and a pH value

The $K_a$ relationship is also used in another way: to make an estimate of the $B^-$ to $H-B$ ratio at a given pH (concentration of $H_3O^+$) value. Starting with a duplication of exactly the same relationship and definitions:

$$H_2O \rightarrow H^+ + \text{water}$$
$$H^+ + B \rightarrow HB$$
$$K_a = \frac{[HB]}{[H^+][B]}$$

Experimentally, it is possible to create a solution with a defined pH value (this is a buffer). That means if you know the $K_a$ for a given Bronsted acid, $H-B$, and you know the pH, it will define the $B^-$ to $H-B$ ratio.

Another way to think about this is by the definition of the $pK_a$ value: the $pK_a$ value is the pH where the concentration of $B^-$ is equal to the concentration of $H-B$.

That is: when you know the $pK_a$ value, then at any given pH, you can estimate the ratio of $B^-$ to $H-B$ (and at the pH corresponding to the $pK_a$, that ratio is exactly 1, i.e., $[B^-] = [H-B]$). As you move to the pH values that are in the more acidic direction (lower the pH of the environment), then there is more of the acid form ($H-B$), the ratio increasing by a power of ten for every pH unit. As the pH changes in the more basic direction (higher pH), then the base form ($B^-$) dominates. As an example, Ph-NH$_3^+$ (from the $pK_a$ table) has a $pK_a$ value of 4.6. By definition, in a solution of pH = 4.6, there should be a 1:1 ratio of the acid to its conjugate base. The ratio will change by a power of ten for every pH unit above and below 4.6. This concept is true for any $pK_a$ value. Molecules with more than one acidic proton can be handled as a series of independent cases.

And this is exactly the story that the equation tells:

$$4.6 = \text{pH} - \log \left( \frac{[B^-]}{[HB]} \right) \quad \Rightarrow \quad 4.6 = 2.6 - \log \left( \frac{[B^-]}{[HB]} \right) \quad \Rightarrow \quad 4.6 = 2.6 - \log \left( \frac{1}{100} \right)$$

1. take a molecule with $pK_a$ 4.6
2. put it in a solution of pH 2.6
3. the $[HB] to [B^-]$ ratio is 100:1
Using the \( pK_a \) table for making \( pK_a \) estimates: analogies between structurally similar compounds

With millions of known organic molecules, the examples in any given \( pK_a \) table will always be limited, so learning how to create good analogies and comparisons is critical. In general, molecules with the same functional group will have comparable \( pK_a \) values for that functional group if (and only if) the structural setting of that functional group is as comparable as possible, meaning all of its identifiable structural features, and particularly (a) the identity of the atom, (b) the hybridization, (c) the charge, (d) the directly attached organic structure (including its identity, hybridization, charge, delocalization, and so on).

The only differences that can generally be assumed to be small are the structural effects of a directly attached hydrogen atom relative to simple, saturated hydrocarbon chains (-H, -CH\(_3\), -CH\(_2\)CH\(_3\), -CH(CH\(_3\))\(_2\), -CH\(_2\)CH\(_2\)CH\(_3\), etc, and including rings that are only made up of saturated carbon atoms in the positions nearby to the potential Brønsted acid).

Selecting the proper analogy is critical, because small structural variation can lead to large differences in acidity. There are example of "OH" groups on the CHEM 210 \( pK_a \) table that range from -9 (sulfuric acid) to 17 (ethanol), which is a range of \( 10^{26} \) difference in acid strength. Take just a few of the "OH" examples:

- H\(_3\)C\( \text{O} \) with \( pK_a \) -7.2
- H\(_3\)O\(^+\) with \( pK_a \) -1.7
- sp\(^2\) O\(^+\) with 3H
- sp\(^3\) O\(^+\)

This OH is directly comparable to the ones in the \( pK_a \) 4.2 and 4.8 examples (especially the 4.8 because the C atom directly attached to the C of the C=O is saturated. Estimated \( pK_a \) ~ 4.8

- H\(_2\)Br\(^+\) with \( pK_a \) 10.0
- sp\(^2\) O on C of benzene
- sp\(^3\) O with 2H or H & sp\(^3\)C

This OH is most comparable to the one at \( pK_a \) -1.7 (an sp\(^3\) O\(^+\) with only H and sp\(^3\) hydrocarbon groups attached. Estimated \( pK_a \) ~ 1.7.

And that brings back the original question! Which of the Lewis basic atoms is the stronger Lewis base? The oxygen atom (base #1) or the bromine atom (base #2)? The \( pK_a \) table lacks the most direct comparison for these two as bases. Although an sp\(^3\) O as a base is present twice (water, ethanol), there is no example of an uncharged bromine atom (or any other halogen, for that matter) acting as a base to give a cationic bromine atom. And when you think about the conjugate acids that you might compare: H\(_3\)O\(^+\), \( pK_a \) -1.7 from the water would need to be put up against, for instance H\(_2\)Br\(^+\) as an sp\(^3\) Br\(^+\) reference. And because UNCHARGED HBr (\( pK_a \) -7 to -9) is already more acidic than H\(_3\)O\(^+\), then uncharged sp\(^3\) Br is much less basic than uncharged sp\(^3\) O. The sp\(^3\) O is therefore the stronger Bronsted base, and therefore the stronger Lewis base, and so the answer derived from Lewis base #1 is the best answer.
3.35 What is the structure of the reaction product between NAAG (one of the most prevalent neurotransmitters in mammals) with excess aqueous sodium carbonate? Give the molecule, derived from NAAG, including any necessary counterions.

Predicting Bronsted acid-base reactions

In part (b), a typical “predict the product(s)” question is asked explicitly (and the format is clearly indicating it). The number of possible reactions to select from, at this point in the course, is limited (Lewis acid-base and Brønsted acid-base). The Lewis acid-base (as in part a) can be rapidly excluded because there are no open shell atoms present, and so this is a prediction about a Bronsted acid-base reaction. One of the reagents will be the Brønsted acid (proton donor) and the other will be the Brønsted base (proton acceptor). One of the reagents is indicated as being in excess, and this would generally mean that there is more than one reaction taking place. As in part a, the possible sites for the Brønsted acid-base reactions need to be assessed.

The NAAG molecule has many different atoms whose Brønsted acidity can be assigned. Indeed, the molecule is filled with bonds to hydrogen atoms and, in principle, all of them can be considered. The pK\textsubscript{a} table can be used to assign estimated pK\textsubscript{a} values to these potential Brønsted acids. There are also plenty of atoms with nbe pairs, and every one of them is a potential Brønsted base.

Taking in the landscape of a question rather than just jumping into the details is generally useful.

When you look at sodium carbonate, the question of which partner is going to be the Brønsted acid and which is going to be the Brønsted base is quickly settled, because sodium carbonate has no protons and therefore cannot possibly serve as a Bronsted acid. In addition, there is not even a choice to make about which is the Bronsted basic atom, because all three oxygen atoms are actually identical (recall that being aware of delocalization needs to be an automatic part of considering molecular structures, and carbonate has three equally significant resonance contributors).

The Bronsted acid-base reaction is a single process that can be observed in millions of different molecular combinations. Every covalent bond associated with a hydrogen atom is a potential Brønsted acid, and every atom (or set of atoms) with an electron pair to share, and form a new bond, is a potential Bronsted base.

The degree to which a Bronsted acid-base reaction will take place can be estimated by the relative difference in the pK\textsubscript{a} values. There are constraints on this method of estimating, because there are factors such as relative amounts that can effect an experimental outcome, but the method is a good start for deciding whether a reaction will lie to the left or the right, and by about how much. Because the weaker acid has the stronger bond to hydrogen, the Bronsted acid with the higher pK\textsubscript{a} value is expected to be favored. And because pK\textsubscript{a} values are the exponents associated with the K\textsubscript{a} equilibrium constant, a rough estimate of the equilibrium constant (for the one to one mixture of the reagents) can be made from the difference in the pK\textsubscript{a} values. Keep the math in mind: if the pK\textsubscript{a} of the product acid is higher (weaker), then it will predominate at equilibrium, and the equilibrium constant will be greater than 1. If the starting material’s pKa is higher, on the other hand, the reaction will lie to the left, and the equilibrium constant will be a fraction.
Predicting Brønsted acid-base reactions

For answering this question, the magnitude of the equilibrium constant that qualifies as a completed reaction is needed. The question does not state one, and so there must be a general guideline that is a part of the course. This might come from class; it might appear elsewhere on the exam paper, in a set of general guidelines.

In CHEM 210 and 215, unless the guideline is given, the assumed default for this equilibrium constant is $10^{3}$. Thus, when the Brønsted acid product's $pK_a$ value is $>+3$ $pK_a$ units than the starting acid, the $K_{EQ}$ is estimated to be greater than or equal to $10^{3}$. The definition of “complete reaction” is arbitrary and a guideline needs to be specified.

This guideline is required to answer this question. If carbonate is the Brønsted base, and it is in excess, then you can anticipate what the $pK_a$ value range for a Brønsted acid needs to be to get this $>10^{3}K_{EQ}$.

To answer this question, I need to know which of the potential Brønsted acids in NAAG have $pK_a$ values $<7.2$, which is exactly the same analogy-making exercise from part a.

The C-H bonds are out of consideration, as they all have at least a $pK_a$ of 19. The structural environment for the 3 O-H's are all identical to one another, and the 2 N-H's are also comparable, so two analogies are needed. The best analogy for the O-H's is the uncharged, $sp^2$ O attached to the C of a C=O, which is in turn attached to simple $sp^3$ hydrocarbons groups ($pK_a$ 4.8 from the table). The N-H's have the same description, except they are N-H, and the best comparison is the $pK_a$ 15.0 from the table. By the analysis above, carbonate (whose conjugate acid $pK_a$ is 10.2) can be used to deprotonate anything with a $pK_a$ of 7.2 or below with $K_{EQ} \geq 10^{3}$ - and so all three O-H's can be deprotonated, and will be, because excess carbonate is indicated.
It is possible to use pKₐ values to assess an equilibrium constant. Is the value of the equilibrium constant for the 1:1 reaction between conjugate base of phenol and sodium bicarbonate greater than, less than, or equal to 1?

\[
\text{bicarbonate} \quad \text{conjugate base of phenol}
\]

so, the pKₐ₁ is going to be the bicarbonate, and the pKₐ₂ is phenol (PhOH); both of which can be found on the pKₐ table with no need to estimate.

pKₐ₁ (reactant side) is a higher value than pKₐ₂ (product side), so it is the weaker acid, and so there will be more of it at equilibrium; the \(K_{eq} = [\text{prod}]/[\text{react}]\), [react] > [prod], so \(K_{eq}\) is less than 1.

3.37 New pKₐ values can be determined from measuring the equilibrium constant for an acid-base reaction that is carried out with a reaction partner whose pKₐ value is known, and inferring what the pKₐ value of the new compound must have been. Based on the following data, what is the estimated pKₐ value for the conjugate acid of caffeine?

\[
\text{conjugate acid of caffeine}
\]

\[
\text{phenol}
\]

quantitatively: \(K_{eq}\) would be estimated to be 10\(^{10.0-10.2}\) or 10\(^{-0.2}\) (which is, in fact, < 1)
New pKₐ values can be determined from measuring the equilibrium constant for an acid-base reaction that is carried out with a reaction partner whose pKₐ value is known, and inferring what the pKₐ value of the new compound must have been. Based on the following data, what is the estimated pKₐ value for the conjugate acid of caffeine?

\[
\begin{align*}
\text{conjugate acid of caffeine} & \quad K_{EQ} = 10^{-1.2} & \quad \text{pK}_a = 9.3 \\
\end{align*}
\]

in this reaction, the pKₐ for the acid on the product side is given, and the K_{EQ} is given, and the question asks for the value of the pKₐ of the acid on the left (the reactant side)

quantitatively: \( K_{EQ} \) is given as \( 10^{-1.2} \)
so it would be estimated to be \( 10^{(9.3 - \text{pK}_a \text{ reactant})} \)
therefore, pKₐ of the reactant is 10.5

this number needs to make sense:
- the \( K_{EQ} \) is \( 10^{-1.2} \) (a fraction, [prod]/[react] < 1), so the reaction lies to the left, [react] > [prod]
- the reaction lying to the left means that the reactant is less acidic (higher pKₐ) than the product
- the difference in the values is 1.2, so the reactant's pKₐ needs to be 9.3 + 1.2 = 10.5