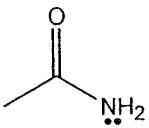
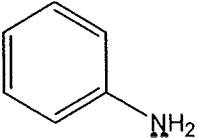
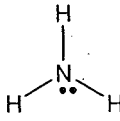
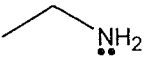



Key F10

ChemActivity 45**Part A: Basicity of Amines**

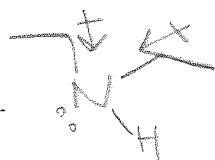
(Why is dimethyl amine a better nucleophile than methyl amine even though it's bulkier?)

Model 1: pK_a Values for Various Nitrogen Compounds

	acetamide (an amide)	aniline (an aromatic amine)	ammonia (the simplest amine)	ethyl amine (a 1° amine)
				
pK _a of conjugate acid	0	4.6	9.3	10.8

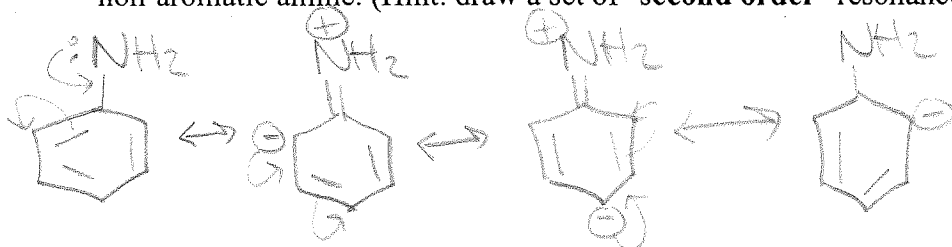
Critical Thinking Questions1. According to the pK_a data in Model 1, which nitrogen compound is most basic? 2. A good way to think about base strength is: The lone pair on an atom is basic if it "wants" to make bond to H⁺. A lone pair "wants" to make a bond to H⁺ if it is **localized** and **high energy**.

a) Construct an explanation for why the lone pair on ethylamine is higher in energy than the lone pair on ammonia.

Inductive e⁻ donation by the R-group increases the e⁻ density of the N lone pair.b) Draw diethyl amine, a secondary (2°) amine, and predict whether the pK_a of its conjugate acid will be higher or lower than 10.8.slightly lower pK_a
see (c) belowc) Diethyl amine is a **stronger base** or weaker base [circle one] than ethyl amine.

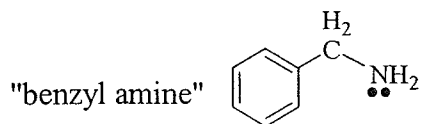
slightly stronger because sterics start to come into effect

3. Construct an explanation for why an aromatic amine is a much weaker base than a non-aromatic amine. (Hint: draw a set of "second order" resonance structures.)



Lone pair on N is delocalized into aromatic ring.

- a) Predict if the pK_a of the conjugate acid of the aromatic compound below is close to 10 or close to 5 [circle one]? Explain your reasoning.

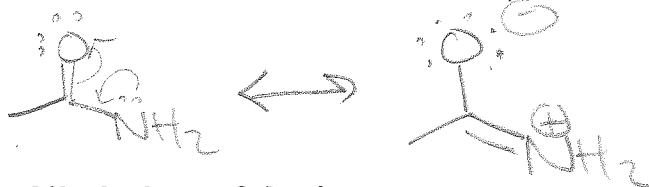


CB is stabilized by aromatic ring.

- b) Explain why the aromatic molecule in part a) is not considered an "aromatic amine."

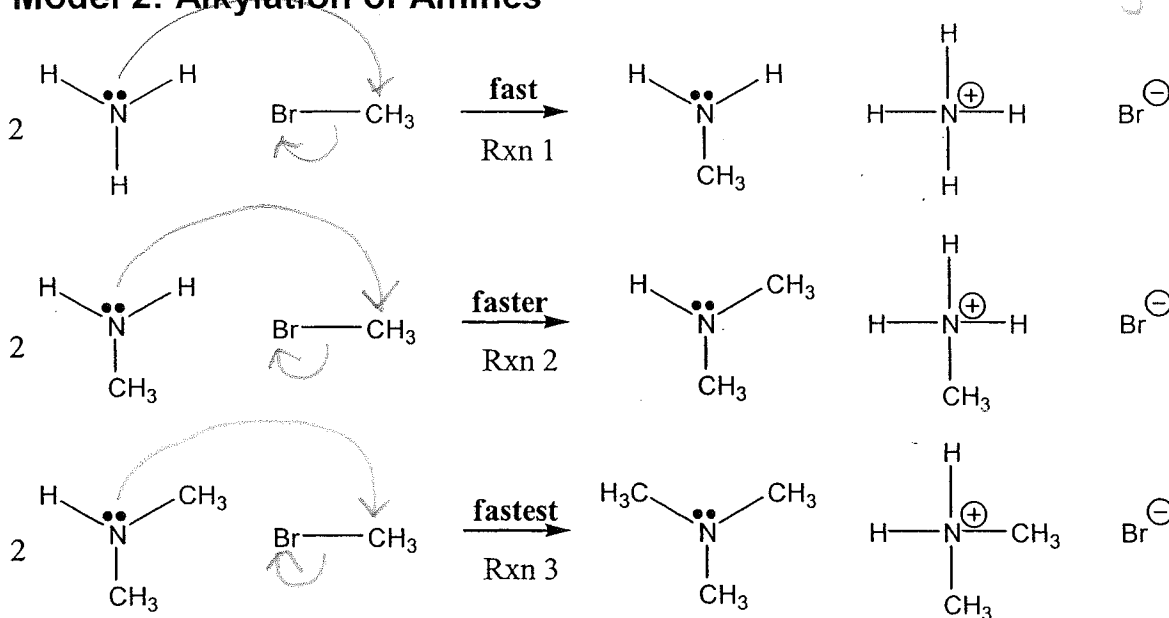
The methylene group (-CH₂-) prevents delocalization of lone pair into aromatic ring.

4. Explain why an amide is an even worse base than an aromatic amine. (Recall that amides are unusual in that they have a 2nd order resonance structure that is nearly equivalent to the 1st order resonance structure.)



Lone pair on N is "tied up" in resonance w/ carbonyl group.

Model 2: Alkylation of Amines



Critical Thinking Questions

5. Use curved arrows to show the mechanism of Rxn 1 in Model 2. What is the general name for this reaction type? *S_N2*
6. Construct an explanation for why the rate of Rxn 3 > rate of Rxn 2 > rate of Rxn 1.

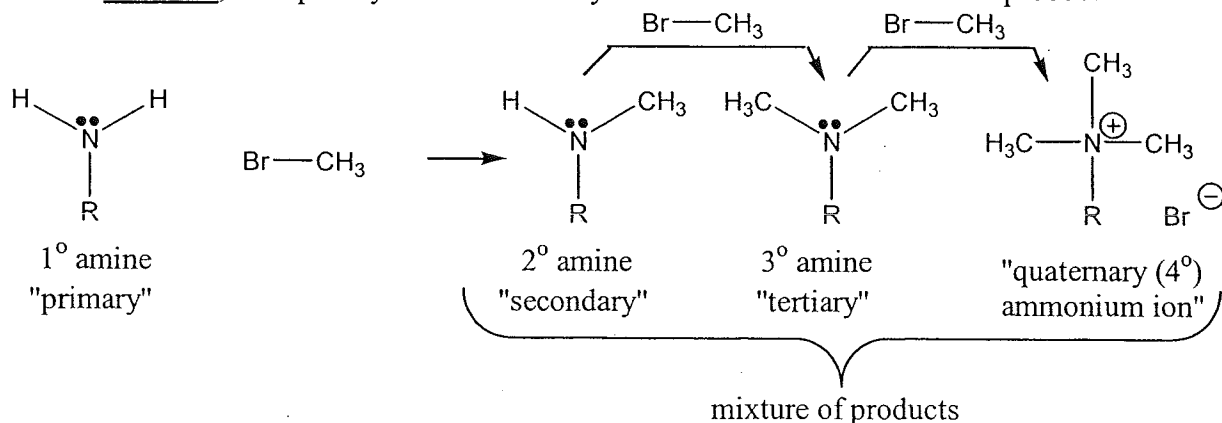
The e^- density of the N increases via inductive e^- donation of R groups.

Part B: Synthesis of Amines/ pK_a of AA's

(How can we add just one alkyl group to an amine?)

Model 3: Messy Alkylation of Amines

- Recall from Part A that a 2° amine is a better nucleophile than a 1° amine.
- This means the reaction below is a messy way to add an alkyl group to an amine.
- Once a little bit of 2° amine product is formed, it will **out-compete the starting material**, and quickly react with methyl bromide to form the 3° amine product.



Critical Thinking Questions

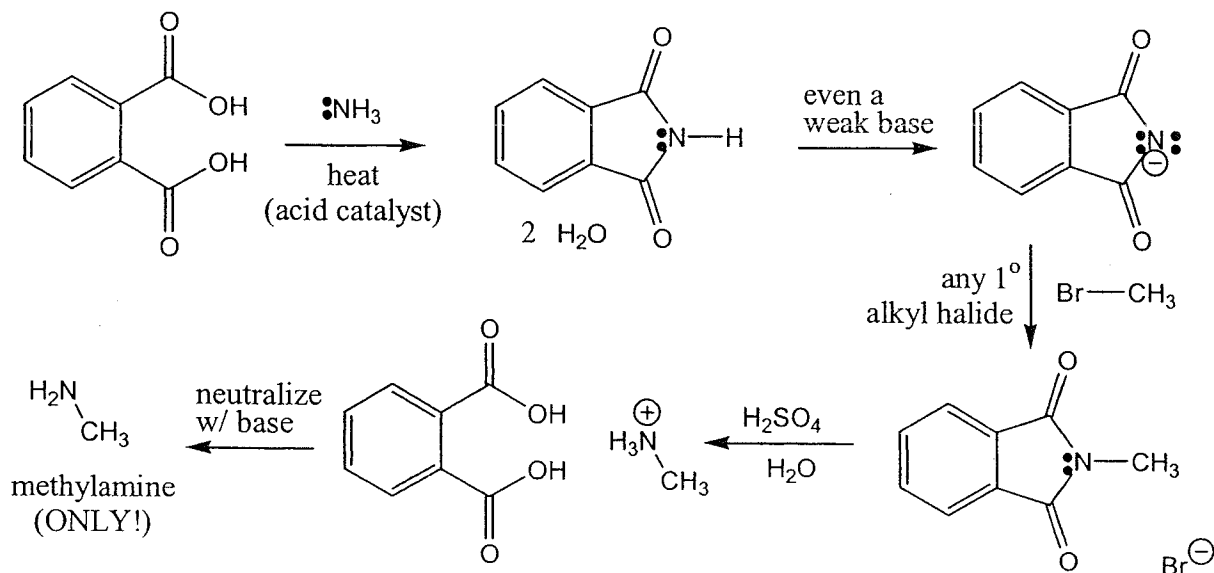
7. Explain why the reaction in Model 3 gives a messy mixture of all the products shown.

The initial product is more reactive than the starting material (1° amine).
(2° amine)

Model 4: Selective Alkylation of Amines

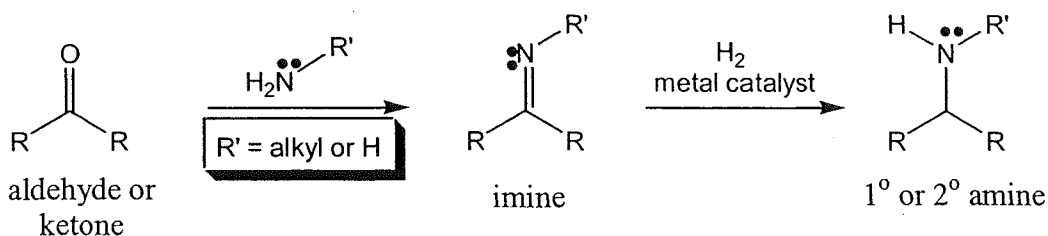
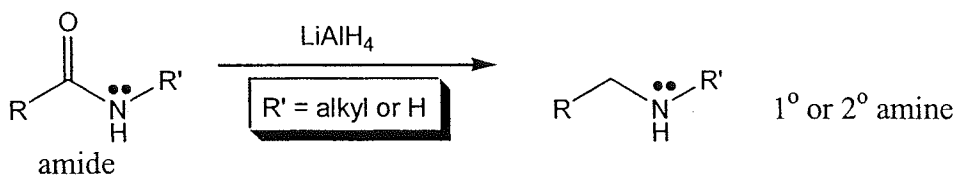
Gabriel Synthesis of Primary Amines:

Named for Prof. Sigmund Gabriel (1851-1924) Univ. of Berlin



Model 4 continued on next page...

Reduction of Amides, Imines and Nitriles to form 1° and 2° Amines:



Critical Thinking Questions

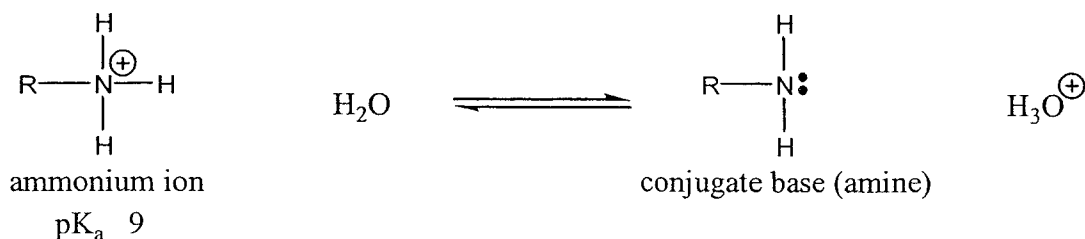
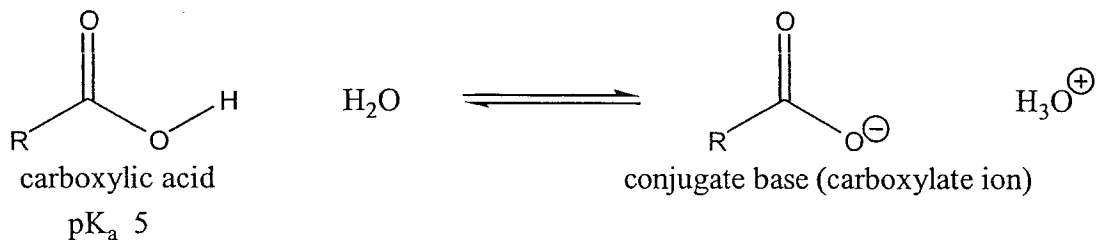
8. What problem plagues direct alkylation of amines (Model 3), but does not plague each of the reactions in Model 4?

2° or 3° alkylations creating 3° and 4° amines,

9. Amines are very weak acids. It takes a huge amount of energy (30+ pKa units) to pull an H off a neutral N (e.g. R₂NH) to make a N with a negative charge (R₂N⁻). Explain why only a weak base (a small amount of energy) is necessary to prepare the N with a negative charge in Step 2 of the Gabriel Synthesis.

Because the CO⁻ is resonance stabilized. The ⊖ on the N can delocalize into both carbonyl groups.

Model 5: pK_a Values for Carboxylic Acids and Amines

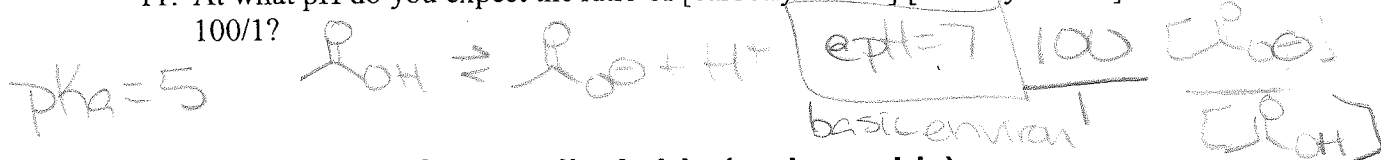


Critical Thinking Questions

10. What form of the nitrogen functional group in Model 5 will be most abundant at biological pH (near pH 7)? ammonium ion or amine [circle one].

$pH < pK_a \therefore$ acidic environment

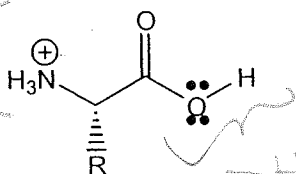
11. At what pH do you expect the ratio of [carboxylate ion]/[carboxylic acid] to be 100/1?



Model 6: Amino Carboxylic Acids (amino acids)

- An **amino acid** is a multi-functional group molecule with an amine end and a carboxylic acid end.
- There are twenty common amino acids found in biological systems.
- Proteins in all living organisms are polymers (long chains) of these amino acids.
- By convention, amino acids are drawn with the amine/ammonium end on the left (as shown below).

$pH < 9$



Each amino acid differs in the identity of the R group.

$pH < 5$

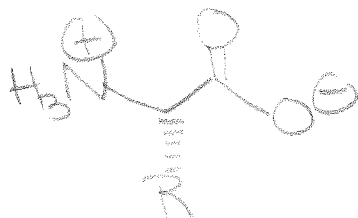
Critical Thinking Questions

12. Water solutions are limited to a pH range of about 0-15. Based on the information in Model 5...

- a) What is the likely pH (give a range) of the aqueous solution containing the amino acid shown in Model 6?

$pH < 5$

- b) Draw the dominant form of an amino acid at pH 7.



$pH 7$ acidic to RNH_2

$pH 7$ basic to $RCOOH$

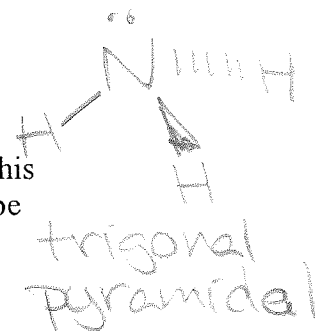
- c) Over what pH range would the form you drew in part b) be dominant?

$pH 5$ to $pH 9$

Exercises for Part A

1. Use wedge and dash bonds to draw a 3-D representation of ammonia.

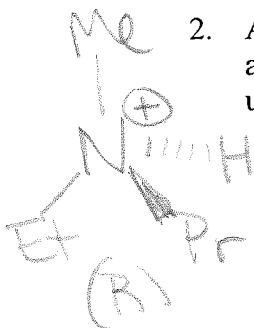
- a) Label your drawing with the word used to describe the shape of this molecule. Note that the shape of a molecule is the geometric shape described by the positions of the nuclei (not the electron pairs).
- b) What is the **hybridization state** of the N in ammonia?



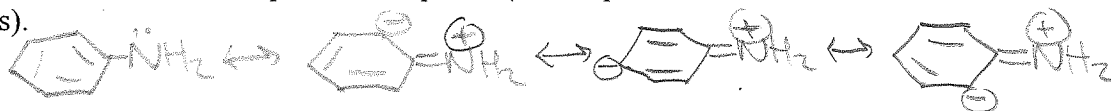
sp³

2. Amines cannot be chiral. This is because the lone pair does not hold a fixed position around the N for very long. An amine is constantly "flipping" back and forth like an umbrella inverting and un-inverting in a strong wind.

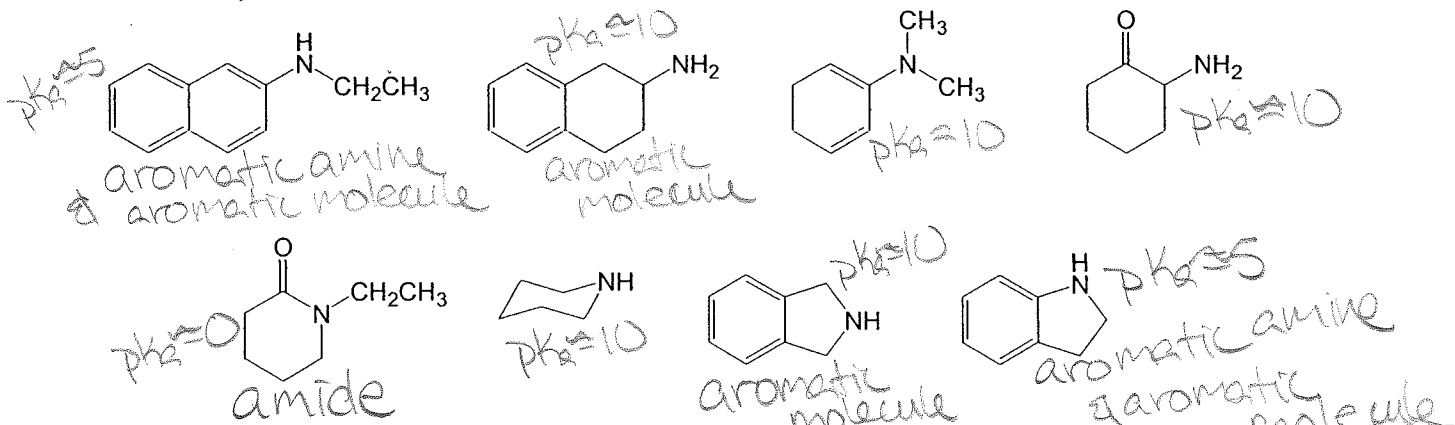
- a) However, ammonium salts can be chiral. Draw a wedge and dash representation of the **R** enantiomer of the conjugate acid of *N*-methyl-*N*-ethyl propylamine (N with 1 methyl, 1 ethyl and 1 propyl group).
- b) Consider the following reaction: If a sample of the pure **R** ammonium salt you drew above is treated with base, and then acid, will the resulting sample be **pure R**, **pure S**, or a **racemic mixture** [circle one]?



3. Draw all three 2nd order resonance structures of aniline and explain why aromatic amines are weak bases and poor nucleophiles (as compared to non-aromatic amines).



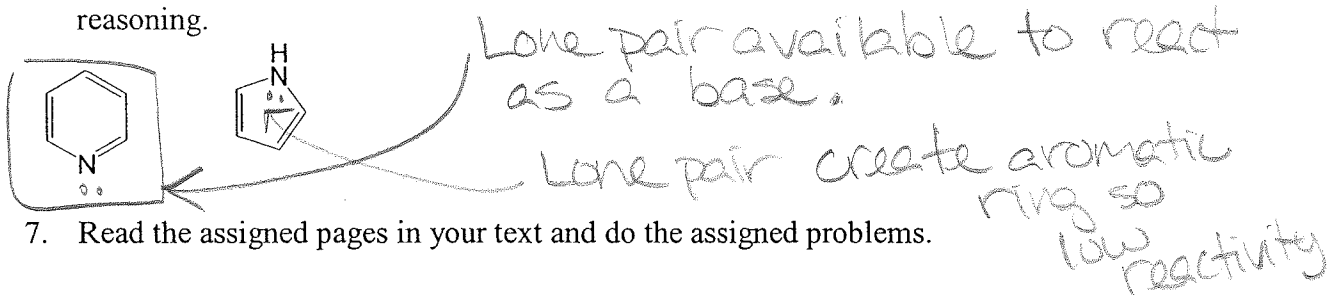
4. Place the following labels on the molecules below. Some will have more than one label, some will have no labels. **Aromatic Molecule** **Aromatic Amine** **Amide**



5. Indicate the approximate pK_a of the conjugate acid of each compound above by writing one of... **pK_a about 0** **pK_a about 5** **pK_a about 10.**

see above

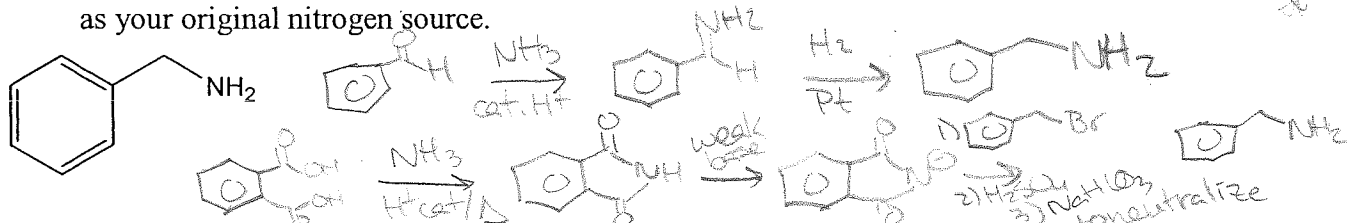
6. Which of the following aromatic compounds is more basic? Explain your reasoning.



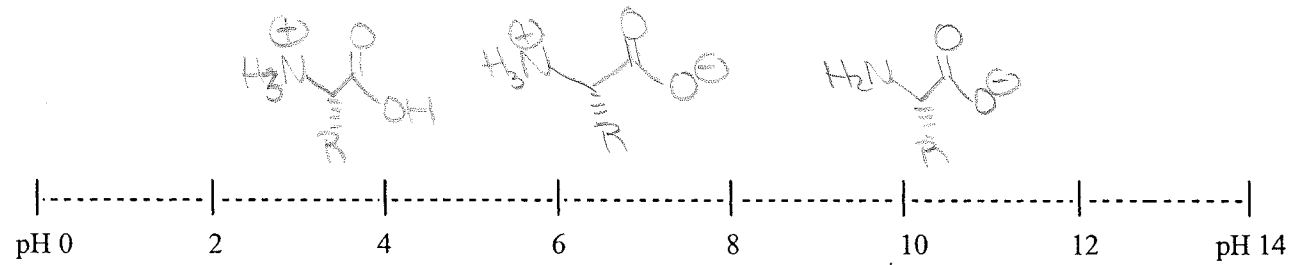
7. Read the assigned pages in your text and do the assigned problems.

Exercises for Part B

8. Show ~~three~~ ^{two} different ways of making benzyl amine (below) using ammonia (NH₃) as your original nitrogen source.



9. On the pH scale below, draw all the possible forms of an amino acid and indicate the pH range through which each form is most likely to be dominant.

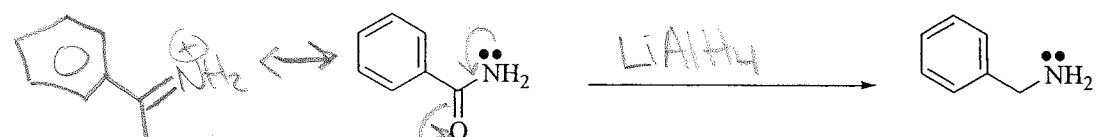


10. In what pH range (if any) is an amino acid likely to...
- have no + or - formal charges on any of its atoms? *none*
 - be overall neutral? *pH near 7*

(Note: A neutral molecule with one + and one - charge is called a **zwitterion**.)

- ~~11. Show the mechanism of Steps 1 and 4 in the Gabriel Synthesis in Model 4.~~

12. Consider the reaction below.



- Write appropriate reagents over the reaction arrow.
- As a result of this reaction, is the N made more nucleophilic or less nucleophilic?
- Draw "second order" resonance structures to support your answer in part b). *see above*

- ~~13. Read the assigned pages in your text and do the assigned problems.~~