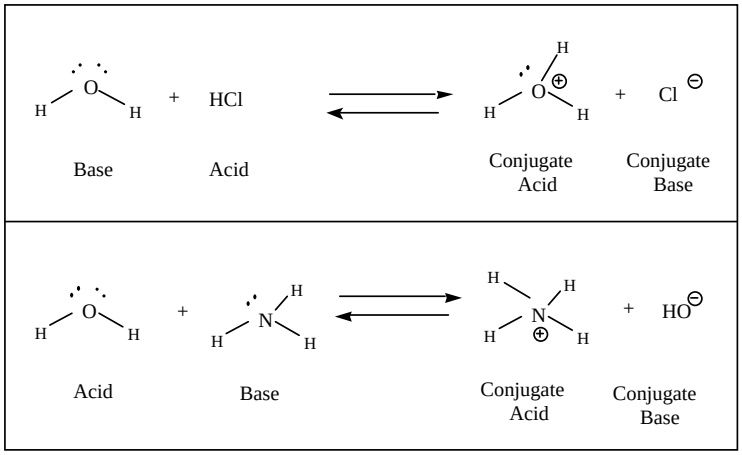
BRONSTED LOWRY ACIDS & BASES

- A Bronsted Lowry Acid DONATES A PROTON
- A Bronsted Lowry Base ACCEPTS A PROTON

Example:



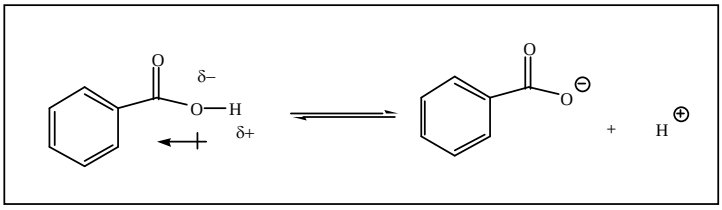
CONJUGATE ACIDS AND BASES

- A conjugate acid results after a Bronsted Lowry base has accepted a proton.
- A conjugate base results after a Bronsted Lowry acid has donated a proton.
- The ionic bond between a conjugate acid and conjugate base forms a salt.

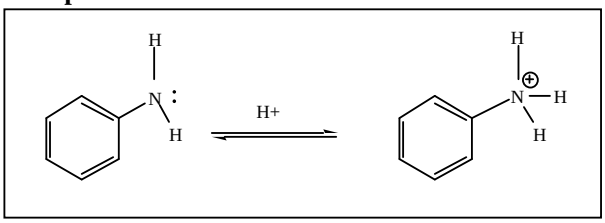
IDENTIFYING ACIDS AND BASES IN A REACTION

- The acid and the base in an acid-base reaction can be identified by "following the proton". Determine where the proton (H+) is going to and where it is coming from. The proton comes from the *acid* and goes to the *base*.
- Functional groups types in organic chemistry can be classified as acidic, basic or neutral.
- Acidic functional groups donate protons. They are neutral in their acidic form and are negatively charged in their conjugate base form.
- Basic functional group accept protons. They are neutral in their basic form and charged in their conjugate acid form.

Example Acid:



Example Base:



STRENGTHS OF ACIDS AND BASES

- The strength of an acid is generally reported as pKa. pKa refers to the tendency of a molecule to give up a proton. The lower the pKa, the stronger the acid. Inorganic acids generally have very low pKas. Organic acids are weaker than inorganic acids and have higher pKas.

- The strength of an acid (reported in pKa units) is related to its Ka. Ka is the ionization constant (i.e., equilibrium constant) for an acid in water. The Ka is defined by the ratio:

$$Ka = \frac{[A^-][H_3O^+]}{[HA][H_2O]} \quad \frac{\text{(Products)}}{\text{(Reactants)}}$$

where the acid/base reaction is represented by the general scheme...

$$H\text{-}A + H_2O \rightleftharpoons A^- + H_3O^+$$

- A large value for Ka (i.e., greater than 1), indicates a strong acid. (i.e., HCl). A small value for Ka (i.e., less than 1), indicates a weak acid (phenol). When Ka is equal to 1, the acidity is "medium" (carboxylic acid). Stronger acids are more ionized in water than weaker acids.

  Acid strength is reported as pKas, so the relationship between pKa and Ka must be established. The pKa is the negative log of the Ka.

  pKa = -log Ka

  Therefore, a strong acid has a large Ka, but a small pKa. A weak acid has a small Ka and a large pKa.

- The strength of a base is NOT reported as a pKa of the base, it is reported as a pKb. pKbs are generally not used in medicinal chemistry, pharmaceutics or pharmacy. pKbs (specifically for amines) are converted to pKas. The strength of a base can be determined from the pKa of the base's ***conjugate acid***. Stronger bases have a larger Kb and a smaller pKb. Stronger bases are more ionized in water than weaker bases.

- pKas ALWAYS refer to acid strength. The magnitude of the pKa determines acid strength not whether the compound is acidic or basic. A high pKa indicates a weaker acid (NOT A BASE!!) and a low pKa indicates a stronger acid.

- Amines and imines are bases. The pKas associated with amines DO NOT refer to the amine's tendency to give up a proton bonded to a nitrogen atom. The pKa associated with an amine refers to the tendency of the CONJUGATE ACID of the amine to donate a proton.

- A strong acid has a weak conjugate base and a strong base has a weak conjugate acid. The mathematical relationship between Ka and Kb (and therefore pKa and pKb can be described.

$$Ka = \frac{[A^-][H_3O^+]}{[HA][H_2O]} \qquad Kb = \frac{[HA][H_2O]}{[A^-][H_3O^+]}$$

$$Ka \times Kb = 1 \times 10^{-14} \qquad pKa + pKb = 14$$

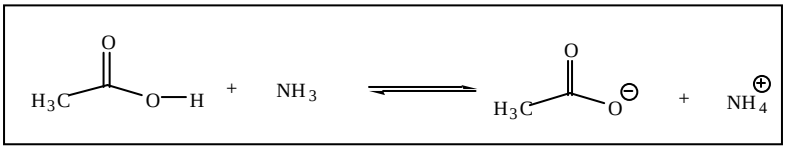
So if either the pKa (or Ka) or pKb (or Kb) is known, then the other can be calculated.

$$H\text{-}A + H_2O \underset{Kb}{\overset{Ka}{\rightleftharpoons}} A^- + H_3O^+$$

if a strong acid, then equilibrium favors "products"and Ka is large

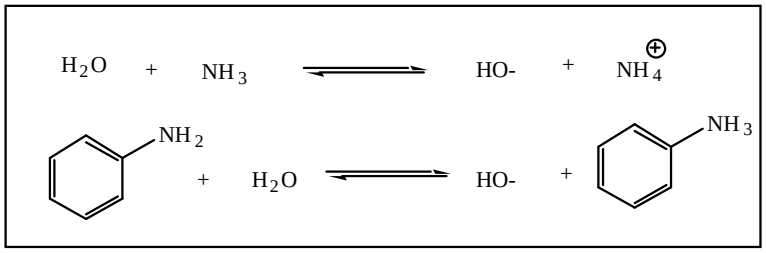
if HA is strong, then A- is a weak base and Kb is small; reverse rxn not favorable

Example:



The pKa of acetic acid is 4.75. The pKa of ammonia is 9.3. The pKb of acetic acid is 9.25. The pKb of ammonia is 4.7. Acetic acid is a strong acid than the conjugate base of ammonia. Ammonia is a stronger base than the conjugate base of acetic acid. The forward reaction is favored since the Ka for acetic acid is larger than the Ka for the ammonium ion. Relative base strengths can be determined from their pKas. A base with a high pKa (low pKb) is a stronger base than a base with a low pKa and a high pKb.

Ammonia has a pKa = 9.3. Aniline has a pKa = 4.3. The pKb of ammonia is 4.7 and the pKb of aniline is 9.7. Ammonia is a stronger base.



IONIZATION OF ACIDS AND BASES AND SOLUBILITY

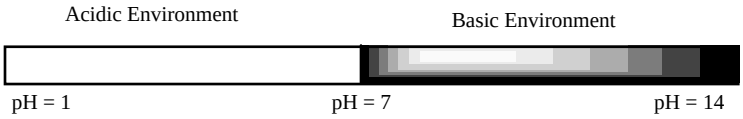
- Weak acids ionize in basic, aqueous solutions.
- Weak bases ionize in aqueous acidic solution.
- When acids and bases ionize they become polar and dissolve in polar solvents (like dissolves like)

- Compounds of like or similar polarity dissolve in each other. Polar compounds dissolve in polar solvents. Non-polar compounds dissolve in non-polar solvents. Water is the most polar solvent and is the major constituent of blood. Polar drugs dissolve in water and therefore in blood. Non-polar solvents are compounds made up predominantly of only C and H atoms, i.e., hydrocarbons. Membranes in the body are made up of fatty acids and other non-polar, hydrocarbon-like substances. Non-polar compounds dissolve in membranes. Fat and other tissues (lipids) in the body are often non-polar but may contain polar regions or pockets.

- Any compound with a charge associated with it has, at least a part of the molecule, that is polar. There may be other parts of the same molecule that are not polar. Solubility is determined by the overall polarity of the molecule.

- *pKa is not the same as pH*
  An acidic compound or drug that is ionized is polar. An acidic drug will be ionized in a basic environment. A basic drug that is ionized is polar. A basic drug will be ionized in an acidic environment. Both acidic and basic compounds may be ionized to some extent (depending on their acid/base strength, i.e., pKa or pKb) in a neutral environment. Compounds which contain neutral functional groups are not ionizable. Compounds or drugs that are ionized are soluble in polar solvents especially water (hydrophilic/lipophobic). Unionized compounds or drugs are not soluble in water (hydrophobic/lipophilic).

- The acidity or basicity of the environment is described by pH. pH is a measure of the concentration of H+ ions in an aqueous medium. If the H+ concentration is high, the pH is low. A high concentration of H+ ions is a very acidic environment. If the H+ concentration is low, the pH is high and the environment is basic. A pH = 7 is neutral. Above 7 is basic, below 7 is acidic.



HENDERSOHN-HASSELBACH EQUATION: pH and pKa

The Hendersohn-Hasselbach equation describes the mathematical relationship between pH and pKa. It allows for the calculation of exactly how much of an acidic or basic compound is ionized at equilibrium.

$$pH = pKa + \log \frac{[Base]}{[Acid]}$$

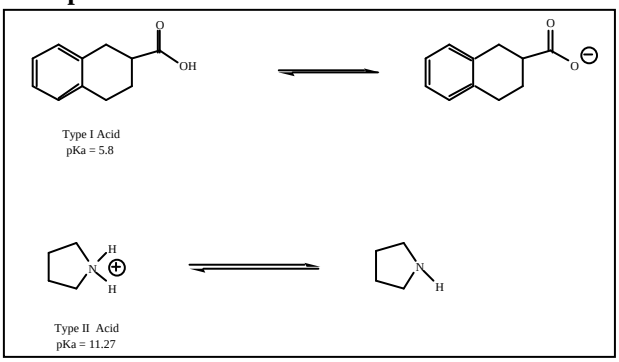
<----------could also be conjugate base
<----------could also be conjugate acid

or

$$pH = pKa + \log Ka$$

So at a given pH, the Ka can be determined as long as the pKa of the acid or the base is known.

Example:



At a pH = 7.4 (physiological pH), how much of each of these compounds is ionized?
For the carboxylic acid, the Hendersohn Haselbach equation is:
7.4 = 5.8 + log Ka
1.6 = log Ka
39.8 = Ka (large number, >1)
The donation of the proton is favored. (The carboxylc acid is a strong acid)
The ionized form of the acid is favored at this pH.

For the conjugate acid of the amine, Hendersohn Hasselbach equation is:
7.4 = 11.27 + log Ka
-3.87 = log Ka
0.00013 = Ka (small number, <1)
The donation of the proton is not favored. (The amine is a strong base.)
The ionized form of the amine is favored at this pH.
How much, in percentages (%) of each form (i.e., acid vs. conjugate base) is present at equilibrium in each of these cases?

For the carboxylic acid....
39.8 = Ka

$$39.8 = \frac{[A-]}{[HA]}$$

[HA] + [A-] = 100%
100 - [HA] = [A-]

39.8[HA] = 100 - [HA]
[HA] = 2.45% (unionized)
[A-] = 97.5% (ionized)

For the amine....

$$0.00013 = \frac{[B]}{[HB+]}$$

[HB+] + [B] = 100%
100- [HB+] = [B]

0.00013[HB+] = [B]
100- [HB+] = 0.00013[HB+]
[HB+] = 99.98% (ionized)
[B] = 0.13% (unionized)

Both of these compounds would be soluble at this pH.

NOTE: The **ionized form of an acidic functional group is its conjugate base** (or basic form) that appears in the numerator of the H-H equation. The **ionized form of a base is the conjugate acid** that appears in the denominator of the H-H equation. The ionized form is water soluble. The unionized form is not water soluble.

In general,
For Acids:
If the pH is 2 units or more higher than the pKa, then the acid will be almost 100% ionized. If the pH is 2 units or more lower than the pKa, then the acid will be almost 100% unionized.

For Bases:
If the pH is 2 units or more higher than the pKa (of the conjugate acid), then the base will be almost 100% unionized. If the pH is 2 units or more lower than the pKa, then the base will be almost 100% ionized.

Fluid	pH
Aqueous humor	7.2
Blood, arterial	7.4
Blood, venous	7.4
Blood, maternal umbilical	7.3
Cerebrospinal fluid	7.4
Duodenum	5.5
Feces	7.12 (4.6-8.8)
Ileum, distal	8.0
Intestine, microsurface	5.3
Lacrimal fluid (tears)	7.4
Breast milk	7.0
Skeletal muscle	6.0
Nasal secretions	6.0
Prostatic fluid	6.5
Saliva	6.4
Semen	7.2
Stomach	1.0-3.5
Sweat	5.4
Urine	5.8 (5.5-7.0)
Vaginal secretions, premenopausal	4.5
Vaginal secretions, post menopausal	7.0

Table 1: pH Values for Tissue Fluids
(Taken from Foye, "Principles of Medicinal Chemistry", 4th Ed., p. 961)