

2. Acids and Bases.

2.1 Definitions.

Brønsted acids are proton donors, and Brønsted bases are proton acceptors. Examples of Brønsted acids: HCl, HBr, H₂SO₄, HOH, HOH₂⁺, NH₄⁺, NH₃, CH₃CO₂H, H—CH₂COCH₃, H—C≡CH, H—CH₃. Examples of Brønsted bases: anything with a lone pair. Brønsted acids are generally neutral or cationic, and Brønsted bases are generally neutral or anionic. Some compounds (H₂O, NH₃, acetone) can be either acids or bases.

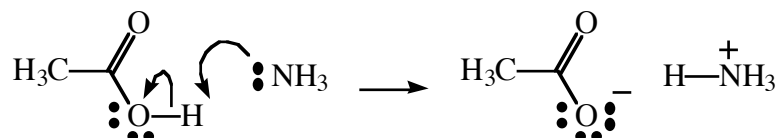
Lewis acids are electron acceptors, and Lewis bases are electron donors. The set of Lewis and Brønsted bases are essentially identical, but many Lewis acids exist that are not proton donors. E.g., BF₃, C⁺Me₃, and many metal salts such as ZnCl₂, TiCl₄, etc. We can also consider the proton, H⁺, a Lewis acid itself. Some books say that all Brønsted acids are Lewis acids also, but we will use the term Lewis acid to denote only those acids to which a bond can be made without breaking another bond. By this definition, H—Cl is not a Lewis acid, because making a bond to H requires breaking the H—Cl bond. Lewis acids are either neutral or cationic.

When we say “acid”, we will mean “Brønsted acid”. If we mean “Lewis acid”, we will say “Lewis acid”. This is the commonly accepted practice among organic chemists.

When an acid HX gives up a proton, the species that is left behind (X⁻) is called the *conjugate base of HX*. Likewise, when a base \ddot{B} accepts a proton, the product ⁺BH is called the *conjugate acid of \ddot{B}* .

2.2 Curved arrows.

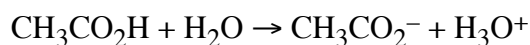
What happens to the electrons in an acid–base reaction? The base uses its pair of electrons to make a new bond to H. In the process, the bond between H and the acidic atom breaks, and the pair of electrons from that bond becomes a lone pair in the conjugate base. We use curved arrows (the same as the ones we use in drawing resonance structures) to show whither the electrons in the starting materials moved to reach the products. The electron pair from NH₃ moves to form a bond *between* N and H; the electrons in the bond between O and H move to become a lone pair on O.



We used curved arrows to keep track of electrons in the course of a reaction. You *must* learn how to use curved arrows correctly. They provide the basic way of communicating in organic chemistry. Any dufus can keep track of nuclei, but only the adept can keep track of electrons. Curved arrows are how we do it.

2.3 Acid–Base Equilibria. K_a s and pK_a s.

When an acid is dissolved in H_2O , it transfers its proton to the solvent to some extent. E.g.,



Note the change in the charges when the proton is transferred. The equilibrium constant for this reaction is:

$$K = \frac{[CH_3CO_2^-][H_3O^+]}{[CH_3CO_2H][H_2O]}$$

Because H_2O is the solvent, we define a new quantity, K_a :

$$K_a = K[H_2O] = \frac{[CH_3CO_2^-][H_3O^+]}{[CH_3CO_2H]} = 1.8 \times 10^{-5} \text{ (for acetic acid).}$$

The larger the value of K_a , the more likely an acid is to ionize, and hence the stronger that acid is.

Because values for K_a vary by up to 60 orders of magnitude, we usually refer to them with a logarithmic (common log, or \log_{10}) scale:

$$pK_a = -\log(K_a) \qquad pK_a(\text{acetic acid}) = -\log(1.8 \times 10^{-5}) = 4.7$$

The smaller the value of pK_a , the stronger that acid is. Common mineral acids such as HCl have pK_a around -10 . The $pK_a(H_2O) = 15$, while $pK_a(H_3N) = 35$, and $pK_a(CH_4) \approx 50$.

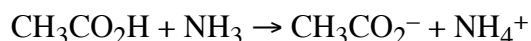
It is important to see the relationship between the strength of an acid/base and the strength of its conjugate base/acid. If an acid is very strong, then when it gives up its proton, the conjugate base will be very unwilling to take that proton back, so it will be a weak conjugate base.

strong acid	weak conjugate base
weak acid	strong conjugate base

strong base	weak conjugate acid
weak base	strong conjugate acid

We arbitrarily define “strong acids” as acids with $pK_a < 0$. Moderately weak acids have $20 > pK_a > 0$. Very weak acids have $35 > pK_a > 20$. Extremely weak acids have $pK_a > 35$.

You should be able to look at an acid–base equilibrium and determine whether the equilibrium lies to the right or left and by how much, given the pK_a s of the two acids. E.g., consider:



The pK_a of acetic acid is 4.7, and the pK_a of NH_4^+ is 10. (Note that even though NH_3 can act as an acid, in this reaction it is acting as a base, so its pK_a is irrelevant.) The equilibrium lies to the right because it lies on the side of the weaker acid. The equilibrium constant is $K_{eq} = 10^{(10 - 4.7)}$. (K_{eq} must be greater than 0 for a reaction that lies towards products. If the reaction had been written in the reverse way, then $K_{eq} = 10^{-(10 - 4.7)}$.)

2.4 Factors affecting pK_a s.

I do not want you to memorize a large number of pK_a s. I do want you to be able to look at two compounds and tell me which compound is more acidic. There are several factors that affect acidity, and we will examine each in turn: electronegativity, size, charge, inductive effects, hybridization, resonance, steric effects. The general rule for determining acidity is: look at the stability (energy) of the conjugate base. The lower in energy the conjugate base, the stronger the acid. This is because acidity is determined by the difference in free energy between the acid and the conjugate base. In most organic acids, the conjugate base is much higher in energy than the acid, so factors that affect energy generally have a much stronger influence on the conjugate base than they do on the acid. (Giving \$10 to a poor man will have much more effect than giving \$10 to a rich man.)

2.4.1 Comparing different elements

2.4.1.1 Size

When comparing two acids in which the protons to be given up are *directly* attached to two elements in the same *column* of the periodic table, the *heavier* element is more acidic than the *lighter* one, all other things being equal. $\text{HI} (-10) > \text{HCl} (-7) \gg \text{HF} (3)$. This trend is *contrary* to electronegativity. The trend is due to the increasingly poor overlap between the tiny H(1s) orbital and the orbital of the acidic

element as you go down the periodic table. *Electronegativity is not the sole determining factor in acidity!!!* Size matters!

2.4.1.2 Electronegativity

When comparing two acids in which the protons to be given up are *directly* attached to two elements in the same row of the periodic table, the more electronegative element is more acidic than the more electropositive one, all other things being equal, because the more electronegative atom is better able to bear a decreased charge in the conjugate base. $\text{HF} (3) > \text{H}_2\text{O} (15) > \text{NH}_3 (35) > \text{CH}_4 (50)$, and $\text{H}_3\text{O}^+ (0) > \text{H}_4\text{N}^+ (10)$. That phrase, “all other things being equal” is important: $\text{NH}_4^+ > \text{H}_2\text{O}$, even though N is more electropositive than O, because here the N has a formal +1 charge.

Conversely, when comparing two bases that are in the same row of the periodic table, the more electronegative atom makes the weaker base. So HO^- is a weaker base than NH_2^- , which is weaker than CH_3^- .

Conversely, when comparing two bases that are in the same column of the periodic table, the heavier atom makes the weaker base. So $\text{CH}_3\text{S}^- (11)$ is a much weaker base than $\text{HO}^- (15.7)$, even though O is more electronegative.

2.4.2 Comparing the same elements

If we are comparing identical atoms, the acronym is CHRIS: charge, hybridization, resonance, inductive effects, steric hindrance.

2.4.2.1 Charge

Given two acids with the same element, the one that has a positive charge is more acidic than the one that is neutral. $\text{NH}_4^+ (10) > \text{NH}_3 (35)$, and $\text{H}_3\text{O}^+ (0) > \text{H}_2\text{O} (15.7)$.

When speaking about the acidity of NH_4^+ and NH_3 , one needs to be careful. The $\text{p}K_a$ of NH_4^+ is 10, and its conjugate base is NH_3 . The $\text{p}K_a$ of NH_3 is 35, and its conjugate base is NH_2^- . If you are talking about the acid–base reactions of NH_3 , you have to be very careful to distinguish whether NH_3 is acting as a base or an acid. Likewise H_2O , and in fact any alcohol ROH and any amine RNH_2 or R_2NH .

2.4.2.2 Hybridization

For any given atom, acidity increases in the order $\text{sp}^3 < \text{sp}^2 < \text{sp}$ hybridization. So $\text{HC}\equiv\text{CH} (25) > \text{H}_2\text{C}=\text{CH}_2 (37) > \text{H}_3\text{C}-\text{CH}_3 (50)$. The reason is that when H^+ is lost, the lone pair left behind in the

conjugate base is lower in energy when it is in an orbital with greater s character (because s orbitals are lower in energy than p orbitals). Because hybrid orbitals are used to make bonds to H, the greater the s character of that hybrid orbital (50% in sp, 33% in sp², 25% in sp³), the more acidic that H.

Conversely, the more s character in the orbital used to hold a lone pair, the less basic that atom is. So H₃N (conjugate acid 10) is more basic than pyridine (conjugate acid 5.2), which is more basic than MeC≡N (conjugate acid -10), and H₂O (conjugate acid 0) is more basic than Me₂C=O (conjugate acid -7).

2.4.2.3 Resonance

The more good resonance structures can be written for the conjugate base of an acid, the more acidic the acid is. *By far the most important resonance stabilizer is the carbonyl group.* So CH₃CO₂H (4.7) >> CH₃CH₂OH (16), and CH₃CONH₂ (17) >> CH₃CH₂NH₂ (35), and CH₃CHO (16.7) >> CH₄ (48). In all cases, a very good resonance structure can be drawn in which the negative charge on the conjugate base is stabilized by resonance into the carbonyl. Two carbonyls have an even more pronounced effect on acidity: so CH₃COCH₂COCH₃ (9) > CH₃COCH₃ (20).

Different carbonyl groups have different acidities, and the differences can be understood by looking at the stability of the $\overset{\ominus}{\text{C}}=\overset{\oplus}{\text{O}}$ resonance structure. The better this resonance structure, the less acidic the compound. So esters, in which this structure is stabilized by resonance donation from O, are less acidic than ketones, which are not. We will return to this point later.

Another important resonance stabilizer is the Ph group. So PhOH (10) > Me₂CHOH (17), and PhNH₂ (27) > EtNH₂ (35). Groups attached to the ortho and para positions of the Ph group can make an acid even more acidic. So 2,4,6-trinitrophenol (1) > PhOH (10).

The nitro and CN groups are also important resonance stabilizers; in fact, CH₃NO₂ (10) > CH₃COCH₃ (20), but CH₃CN (28) < CH₃COCH₃ (20). The effect of resonance stabilization in the nitro group is magnified by the inductive effect of three electronegative atoms near the acidic C.

2.4.2.4 Inductive effects

Electronegative groups near the acidic atom make it a stronger acid. So CF₃CO₂H (0.5) > N≡CCH₂CO₂H (2.5) > CH₃CO₂H (4.7), and CF₃CH₂OH (12.4) > CH₃CH₂OH (16), and CHCl₃ (13.6) > CH₄ (48), and PhSO₃H (-6.5) > PhCH₂OH (16). Note that because the acidic H is not directly bound to the electronegative atoms, size has no influence here, and only electronegativity matters.

Conversely, bases with electronegative groups near the basic atom are less basic than those without. So $\text{C}_6\text{H}_5\text{O}^-$ (10) is more basic than $\text{C}_6\text{F}_5\text{O}^-$ (?).

2.4.2.5 Steric effects

Compounds with more steric bulk are less acidic than compounds with less steric bulk. So Me_3COH (19) < H_3COH (16). The effect is rather small, but significant. These reason is that acidities are measured in solution, and the solvent cannot organize itself to neutralize a bulky conjugate base as well as it can to neutralize a small conjugate base.

2.4.3 Relative importance of different effects

When comparing the acidities of different elements, size and electronegativity (in that order) matter the most. When comparing the acidities of a single element in two different compounds, look at charge first, then hybridization, then resonance, then inductive effects, then steric effects. Follow the scheme below.

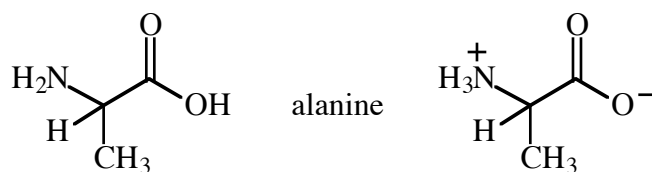
1. Identify the most acidic atom in each compound.
2. The acidic atoms are different.
 - a) If the atoms are in the same column, the compound with the heavier atom is more acidic, all other things (CRHIS) being equal.
 - b) If the atoms are in the same row, the compound with the rightmost atom is more acidic, all other things (CRHIS) being equal.
 - c) If one atom is both to the right and below the other, the compound with that atom is more acidic, all other things (CRHIS) being equal.
 - d) If all other things (CRHIS) are not equal, compare $\text{p}K_a$ s. Memorize the $\text{p}K_a$ s of: HCl , $\text{CH}_3\text{CO}_2\text{H}$, NH_4^+ , ROH , CH_3COCH_3 , $\text{HC}\equiv\text{CH}$, NH_3 , and CH_4 .
3. The acidic atoms are the same.
 - a) If the acidic atoms have different **charges**, the one with the more positive charge is more acidic.
 - b) If the acidic atoms have the same charge but different **hybridizations**, the one with more s character in its hybrid orbitals is more acidic ($\text{sp} > \text{sp}^2 > \text{sp}^3$).
 - c) If the acidic atoms have the same charge and hybridization, *draw the conjugate bases*. The compound whose conjugate base has more **resonance** stabilization is more acidic.
 - d) If the acidic atoms have the same charge, resonance stabilization, and hybridization, the compound with more **inductively** electron-withdrawing groups near the acidic atom is more acidic.
 - e) If the acidic atoms have the same charge, resonance stabilization, hybridization, and inductive effects, the compound with less **steric bulk** near the acidic atom is more acidic.

2.5 Important Organic Acids and Bases

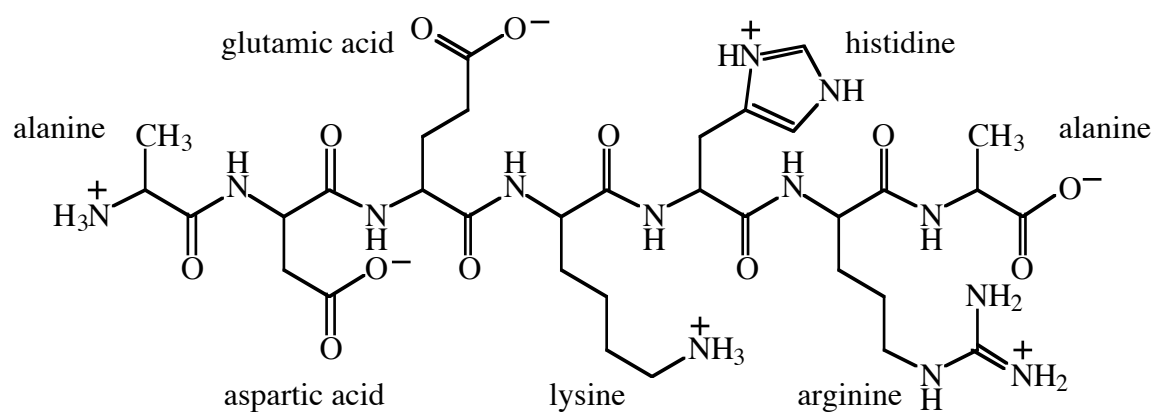
The most important organic acids are the carboxylic acids, RCO_2H . Under physiological conditions (pH 7.4) they are deprotonated and in their ionic form, RCO_2^- . The most important organic bases are amines, RNH_2 . Under physiological conditions (pH 7.4) they are protonated and in their ionic form, RNH_3^+ .



Amino acids, the constituents of proteins, have a free amino group and a carboxylic acid group. They are zwitterionic under physiological conditions: the N is protonated and the carboxylic acid is deprotonated.



Proteins are made up of chains of amino acids joined together by peptide bonds, which are amides. An amino acid in the middle of a protein is not zwitterionic: it no longer has an amino group nor a carboxylic acid group; instead it has two amides. Only the first and last amino acids in the protein are charged: one has a free amine and so is positively charged, and the other has a free carboxylic acid so is negatively charged. However, the side chains of amino acids can be charged. Aspartic acid and glutamic acid have CO_2H groups in the side chain that are deprotonated under physiological conditions. Lysine has a protonated amino group; arginine and histidine have related N-containing groups that are also protonated. Water-soluble proteins have a lot of these charged amino acids on the outside surface, whereas proteins that do not have these groups on the outside tend to be bound to lipids such as are found in cell membranes.



Many drugs, both pharmaceutical and recreational, contain the amine group. For example, cocaine is an amine and hence is basic. The snorted form of cocaine is actually the hydrochloride salt of cocaine. When cocaine is treated with a base such as HO^- , the conjugate base (or “free base”) is obtained, and it can be inhaled — hence the term, “free-basing”. Prozac, an antidepressant drug, and Sudafed, a decongestant, are administered as their hydrochloride salts, whereas dextromethorphan, an antitussive, is administered as its hydrobromide salt. Other salts (acetate, tartrate, succinate, etc.) are used for other amines. The salts of amines are charged and are water-soluble, whereas the free amines are noncharged and are fat-soluble. At physiological pH, amines are largely in their protonated form.

