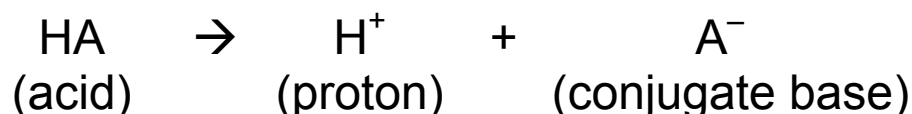


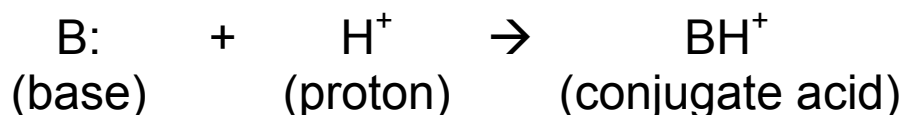
## 2. Acids and Bases (text 2.1 – 2.6)

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- Acid-base reactions are one of the most important reaction types in organic chemistry and biology, *e.g.*:
  - Enzyme-catalyzed reactions
  - Control of blood pH by  $\text{CO}_2$  ( $\text{H}_2\text{CO}_3$ ,  $\text{HCO}_3^-$ ,  $\text{CO}_3^{2-}$ )
- Of special relevance is proton exchange, which fits into the Bronsted-Lowry definition of acids and bases:
  - An acid is a proton donor



- A base is a proton acceptor



- Every acid-base reaction must have both an acid and a base (to supply and accept the proton, respectively). Such reactions often occur in water, so we more properly write:
  - For an acid HA:



- For a base B:



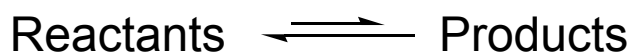
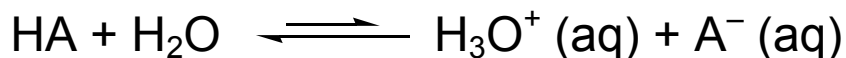
- In first-year chem, we measured  $[H^+]$  in the form of pH for strong and weak acids:  **$pH = -\log_{10} [H^+]$**
- Recall that strong acids are those that dissociate completely in water, and strong bases are those that become fully protonated in water. These are usually inorganic compounds, e.g. HCl and NaOH.
- On the contrary, organic compounds act as weak acids or bases: they do not dissociate or protonate completely.
- For the general weak acid (HA), we can write:
  1. The equilibrium:  $HA + H_2O \rightleftharpoons H_3O^+ (aq) + A^- (aq)$
  2. The equilibrium constant:  $K_{eq} = \frac{[H_3O^+][A^-]}{[HA][H_2O]}$
  3. Define the acid dissociation constant as  $K_a = K_{eq}[H_2O]$ 

$$K_a = \frac{[H_3O^+][A^-]}{[HA]}$$
    - $K_a$  increases as the acid becomes stronger, but for organic weak acids,  $K_a$  usually  $\ll 1$ .
    - Why? Charges are bad... they are high in energy.
  4. Like pH, we can define:  **$pK_a = -\log_{10} K_a$**
- Therefore, as acids get stronger, their  $K_a$  \_\_\_\_\_ and their  $pK_a$  \_\_\_\_\_.

*K<sub>a</sub> and pK<sub>a</sub> values of selected acids*

| Acid                            | Name              | K <sub>a</sub>        | pK <sub>a</sub> |
|---------------------------------|-------------------|-----------------------|-----------------|
| HF                              | hydrofluoric acid | $6.9 \times 10^{-4}$  | 3.16            |
| CH <sub>3</sub> COOH            | acetic acid       | $1.8 \times 10^{-5}$  | 4.76            |
| H <sub>2</sub> O                | water             | $2.0 \times 10^{-16}$ | 15.7            |
| NH <sub>3</sub>                 | ammonia           | $1.0 \times 10^{-38}$ | 38.0            |
| CH <sub>3</sub> CH <sub>3</sub> | ethane            | $1.0 \times 10^{-51}$ | 51.0            |

- Organic chemists concentrate on *structural features* of molecules that influence acid or base strength.
- Consider again the equilibrium:

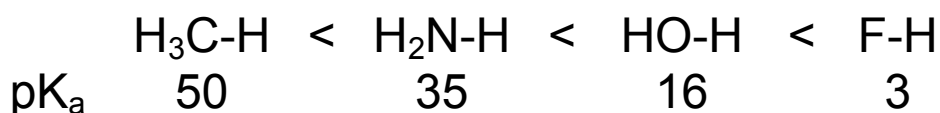


- As seen in first-year chemistry, K<sub>eq</sub> is related to the Gibbs free energy of the reaction by  $\Delta G = -RT(\ln K_{eq})$ .
- So, when  $\Delta G$  is more negative, the reaction is more favourable, K<sub>eq</sub> is larger, and the products are thermodynamically more stable.

- The strength of an acid is primarily dependent on the stability of the products. If we assume that the reaction is happening in water, then one of the products is  $\text{H}_3\text{O}^+$ , but this is always formed regardless of what the acid HA is.
- **The only product that differs from one acid to another is the identity of  $\text{A}^-$ .** It is the relative thermodynamic stabilities of different conjugate bases ( $\text{A}^-$ ) that allow us to assess the relative strength of different acids.
- Six features affecting the stability of  $\text{A}^-$  are:
  1. Electronegativity of the atom bearing the “-” charge
  2. Atomic size of the atom bearing the “-” charge
  3. Hybridization of the atom bearing the “-” charge
  4. Inductive effect of other atoms/groups present in  $\text{A}^-$ .
  5. Resonance stabilization of  $\text{A}^-$  relative to resonance stabilization of HA.
  6. Solvation of  $\text{A}^-$ .
- What is the order of importance of these features? This is not possible to answer, since one feature can sometimes be more important than another. Electronegativity is usually the most important, but not always!
- That said, on exams, we will only give you questions where the choices that can be logically deduced.

## 1. Electronegativity

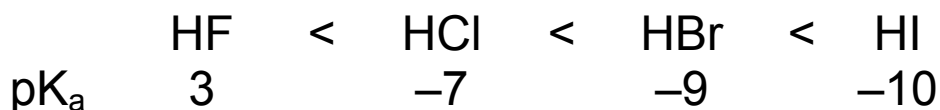
- Acidity increases from left to right:



- Stabilities of conjugate bases:  $\text{H}_3\text{C}^- < \text{H}_2\text{N}^- < \text{HO}^- < \text{F}^-$
- When the atom bearing the hydrogen becomes more electronegative, the hydrogen becomes more acidic. (more electronegative = more stable conjugate base)
- Every molecule that bears an H atom can act as an acid, and will have a  $\text{pK}_a$  value for the acidity of each H atom, even  $\text{NH}_3$  (which also functions as a base).

## 2. Atomic Size

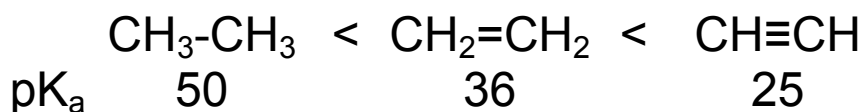
- Acidity increases going down a column:



- Also compare  $\text{H}_2\text{O}$  to  $\text{H}_2\text{S}$  ( $\text{pK}_a$  16 and 7, respectively)
- The larger the atom bearing the hydrogen, the more acidic that hydrogen becomes. This is because the resulting negative charge is more spread out over the surface of a larger atom.
- When going down a column in the periodic table the size effect is greater than that of electronegativity.

### 3. Hybridization

- The *effective electronegativity* of an atom depends on the identity of the atom as well as its hybridization.
- s orbitals are lower in energy and are closer to the nucleus. They can bind electrons more strongly, and this occurs when a hybrid orbital has more s character. This has a major effect on acidity.
- $sp^3$  has 25% s character,  $sp^2$  33%, and  $sp$  50%.



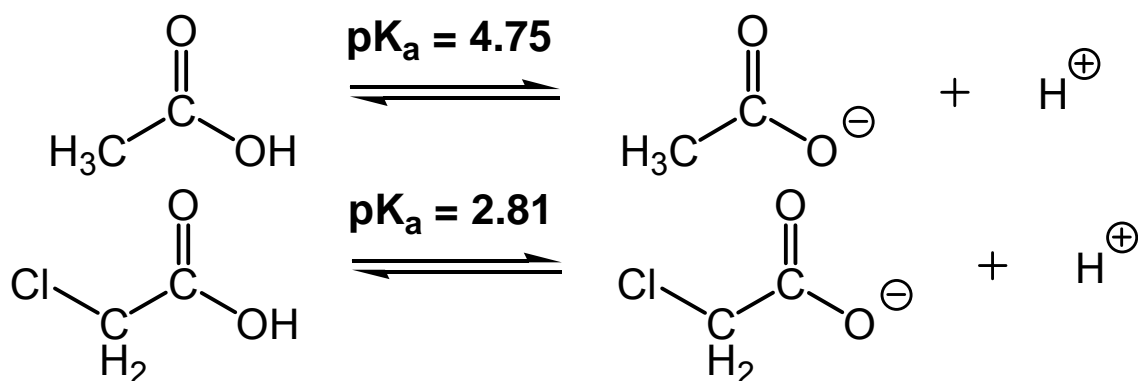
Essentially  
not an acid

Not acidic

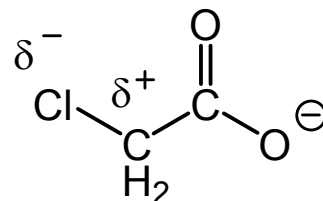
Acidic enough to  
react with strong  
bases (e.g. NaNH<sub>2</sub>)

### 4. Inductive Effects

- The stabilization (or destabilization) of charges by through-bond effects is called the **inductive effect**.



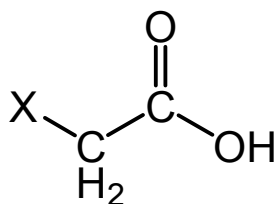
- The replacement of H with Cl results in an acid that is about 100-fold stronger. In chloroacetate, the  $\delta^+$   $\text{CH}_2$  that is two bonds away from the negative oxygen stabilizes it by drawing electrons away from the  $\text{O}^-$  through sigma bonds.



- Here, the inductive effect is caused by the an electronegative atom. The Cl is an **electron-withdrawing group (EWG)**.
- Groups differ in their electron-withdrawing ability:  
 $\text{CH}_3 < \text{H} < (\text{CH}_2=\text{CH} \text{ or } \text{Ph}) < (\text{HO} \text{ or } \text{CH}_3\text{O}) < \text{halogen} < [\text{NO}_2 \text{ or } (\text{CH}_3)_3\text{N}^+]$
- So in general terms, the EWG order is:  
 $\text{alkyl} < \text{H} < sp^2 < \text{O} < \text{halogen} < \text{positive charge}$

Structure of nitro group:

- EWG ability is roughly based on electronegativity:



$$\text{CH}_3 = 4.87$$

$$\text{H} = 4.75$$

$$\text{CH}_2=\text{CH} = 4.35$$

$$\text{Ph} = 4.31$$

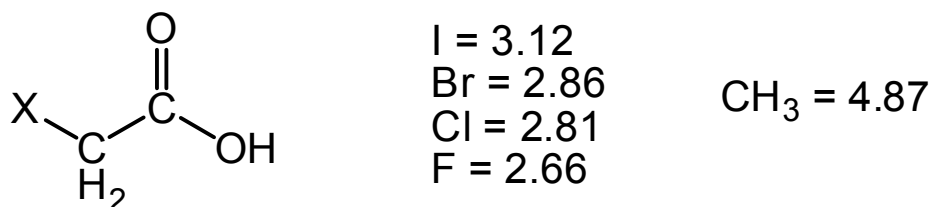
$$\text{HO} = 3.87$$

$$\text{Cl} = 2.87$$

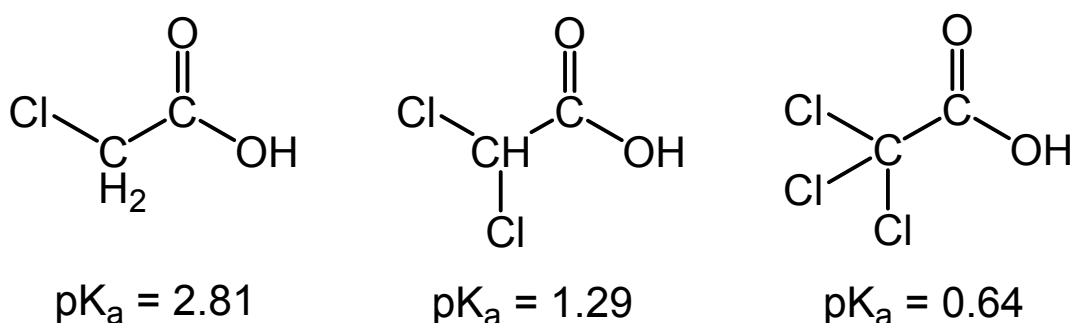
$$(\text{CH}_3)\text{N}^+ = 1.83$$

$$\text{NO}_2 = 1.68$$

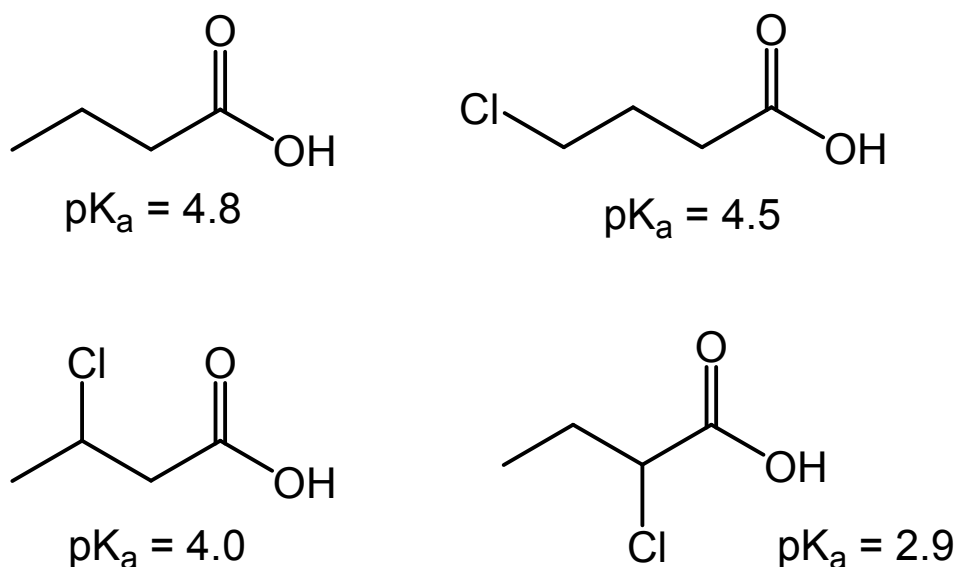
- And for these haloacetic acids:



- EWG effects are cumulative:



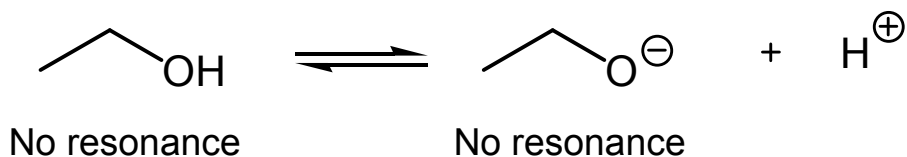
- EWG effects fall off with distance. Inductive effects become insignificant after about four or more bonds, as shown by these chlorobutanoic acids:



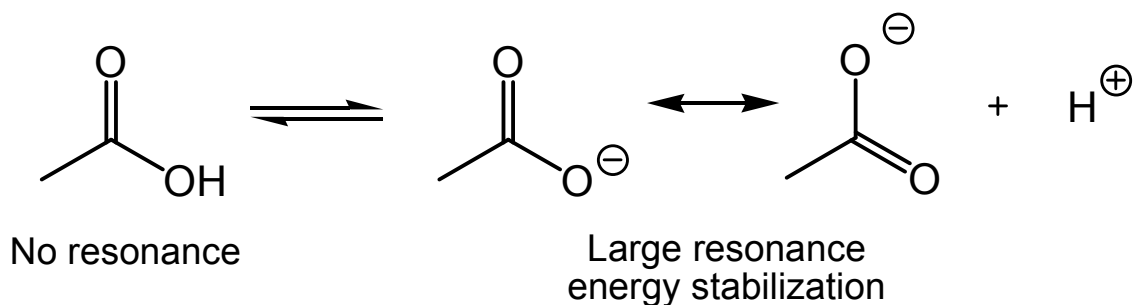


## 5. Resonance Effects

- Resonance can act to increase acid strength or (less commonly) decrease it, depending on which species is stabilized by resonance. The species stabilized will be present in greater amount in the acid equilibrium.
- For instance, the pKa of ethanol is about 16



- Whereas, the pKa of acetic acid is near 4.8



- Acetate is resonance-stabilized, so acetic acid is a much stronger acid than ethanol.

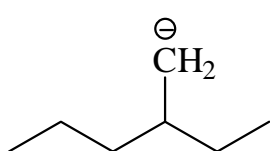
## 6. Solvation Effects

- Solvation plays an enormous role in acidity. For example, HCl does not easily dissociate in the gas phase, because it's bonded form is much more stable than separate  $\text{H}^+$  and  $\text{Cl}^-$ . Yet, in water, it is totally dissociated into these ions.

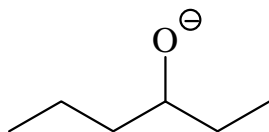
- This is because water is a polar solvent, and the charged regions of water can surround and stabilize both  $\text{H}^+$  and  $\text{Cl}^-$ . Non-polar solvents (or no solvent in the case of gas-phase) cannot do this.
- Two extreme solvents:
  1. Water  $\rightarrow$  Polar  $\rightarrow$  Good solvent for ions
  2. Alkanes  $\rightarrow$  Non-polar  $\rightarrow$  Poor solvents for ions
- Since organic solvents are non-polar, acids will dissociate less in these solvents. Therefore, they are weaker when dissolved in solvents compared to water.
- However, the *relative order* of acidity in organic solvents is almost identical to the relative order in water, e.g. chloroacetic acid is always more acidic than acetic acid, provided they're in the same solvent!
- Unless otherwise stated, assume that all compounds are dissolved in the same solvent.

## Sample Acid-Strength Questions

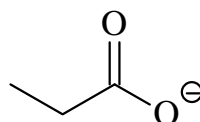
Easy question: Arrange the following in decreasing order of anion stability, *i.e.* from most stable to least stable.



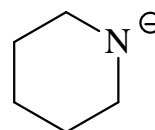
1



2

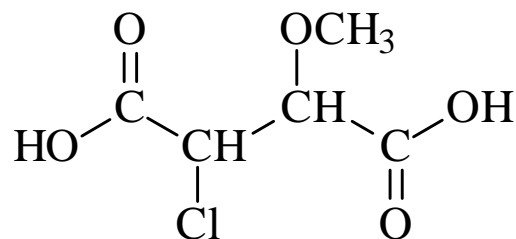


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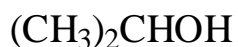


4

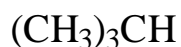
Medium question: Which is the most acidic hydrogen?



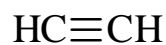
Difficult question: Arrange the following compounds in order of their  $pK_a$  values, from lowest  $pK_a$  to highest  $pK_a$ .



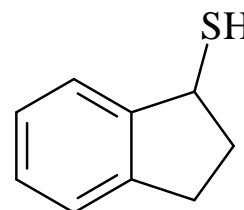
1



2



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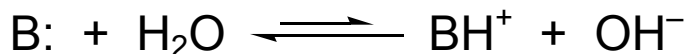


4

Impossible question: compare acetic acid and 2,2,2-trifluoroethanol (cannot be logically deduced).

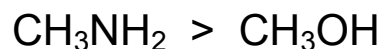
## Base Strength

- All factors previously discussed for acid strength also apply to base strength in similar ways. Consider the following:

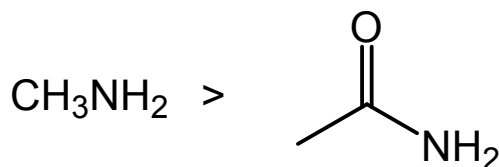


- Any feature that makes the lone pair on the basic atom B (any atom with a lone pair, such as N) more stable will shift the equilibrium to the left. Thus, stabilization of the lone pair will decrease basicity.
- Examples of base strength:

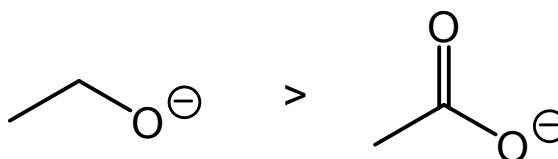
- The lone pair on O is more stable than on N, because of electronegativity



- The lone pair on N next to the carbonyl is more stable because of resonance.



- The carboxylate is more stable than the oxide due to resonance.

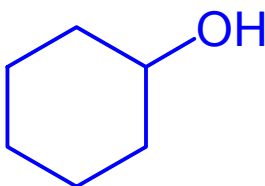
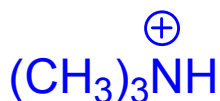
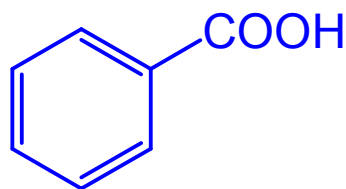
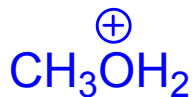


- Helpful hints...

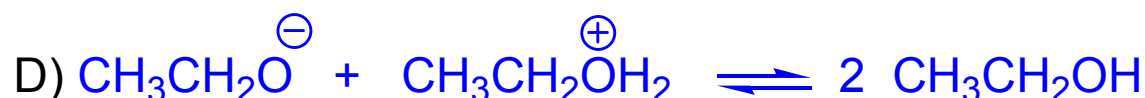
- When determining the strengths of acids, compare the conjugate base stabilities. More stable CB = stronger acid = weaker CB.
- When determining the strengths of bases, look at the bases themselves. More stable base = weaker base.

Summary:

- Textbook pages: Chapter 2, 41-52 (plus extra concepts)
- Text problems: 10, 11, 13, 14, 15, 18, 29, 30
- Old midterm problems:  
2005: 6-9; 2006, 2007, and 2008: 7-10
- Past test question: Which one of the following is the strongest acid?



- Past test question: For which one of the following acid/base reactions will the equilibrium lie furthest to the right?



- MCAT question: Why does  $\text{ClCH}_2\text{CH}_2\text{CH}_2\text{COOH}$  (M1) have a greater  $\text{pK}_a$  than  $\text{ClCH}_2\text{COOH}$  (M2)?
  - M1 has a higher molecular weight than M2
  - M1 has a lower molecular weight than M2
  - M1 has an electron-withdrawing group on the 3<sup>rd</sup> carbon from the  $\text{COOH}$  while M2 has an electron-withdrawing group on the 1<sup>st</sup> carbon from the  $\text{COOH}$
  - M1 is a longer chain than M2