# Acidity and Basicity

It is useful to begin a discussion of organic chemical reactions with a review of acid-base chemistry and terminology for several reasons. First, acid-base reactions are among the simplest to recognize and understand. Second, some classes of organic compounds have distinctly acidic properties, and some other classes behave as bases, so we need to identify these aspects of their chemistry. Finally, many organic reactions are catalyzed by acids and/or bases, and although such transformations may seem complex, our understanding of how they occur often begins with the functioning of the catalyst.
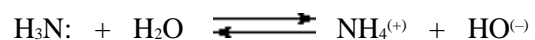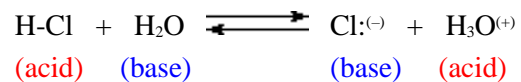
Organic chemists use two acid-base theories for interpreting and planning their work: the *Brønsted theory* and the *Lewis theory*.

Brønsted Theory

According to the Brønsted theory, an acid is a proton donor, and a base is a proton acceptor. In an acid-base reaction, each side of the equilibrium has an acid and a base reactant or product, and these may be neutral species or ions.

$$\text{H-A} + \text{B:}^{(-)} \rightleftharpoons \text{A:}^{(-)} + \text{B-H}$$

(acid¹) (base¹)   (base²) (acid²)
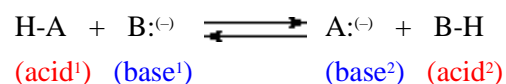
Structurally related acid-base pairs, such as {H-A and A:$^{(-)}$} or {B:$^{(-)}$ and B-H} are called **conjugate pairs**. Substances that can serve as both acids and bases, such as water, are termed **amphoteric**.

$$\text{H-Cl} + \text{H}_2\text{O} \rightleftharpoons \text{Cl:}^{(-)} + \text{H}_3\text{O}^{(+)}$$

(acid)   (base)   (base)   (acid)

$$\text{H}_3\text{N:} + \text{H}_2\text{O} \rightleftharpoons \text{NH}_4^{(+)} + \text{HO}^{(-)}$$

(base)   (acid)   (acid)   (base)

The relative strength of a group of acids (or bases) may be evaluated by measuring the extent of reaction that each group member undergoes with a common base (or acid). Water serves nicely as the common base or acid for such determinations. Thus, for an acid H-A, its strength is proportional to the extent of its reaction with the base water, which is given by the **equilibrium constant** K_{eq}.

$$H\text{-}A + H_2O \rightleftharpoons H_3O^{(+)} + A{:}^{(-)} \qquad K_{eq} = \frac{[H_3\overset{\oplus}{O}][A{:}^{\ominus}]}{[HA][H_2O]}$$
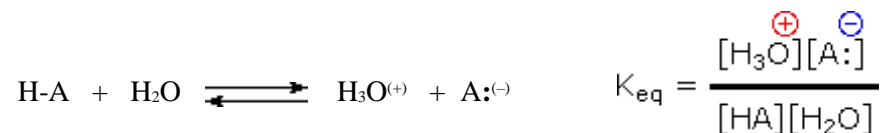
Since these studies are generally extrapolated to high dilution, the molar concentration of water (55.5) is constant and may be eliminated from the denominator. The resulting K value is called the **acidity constant**, K_a. Clearly, strong acids have larger K_a's than do weaker acids. Because of the very large range of acid strengths (greater than 10^{40}), a logarithmic scale of acidity (pK_a) is normally employed. **Stronger acids have smaller or more negative pK_a values than do weaker acids.**

$$K_a = \frac{[H_3\overset{\oplus}{O}][\overset{\ominus}{A:}]}{[HA]} \qquad pK_a = -logK_a = log\left(\frac{1}{K_a}\right)$$

Some useful principles of acid-base reactions are:
  • **Strong acids have weak conjugate bases, and weak acids have strong conjugate bases.**
  • **Acid-base equilibria always favor the weakest acid and the weakest base.**

Examples of Brønsted Acid-Base Equilibria

Acid-Base Reaction		Conjugate Acids	Conjugate Bases	K_a	pK_a
$HBr + H_2O$	$\rightleftharpoons$ $H_3O^{(+)} + Br^{(-)}$	HBr $H_3O^{(+)}$	$Br^{(-)}$ H_2O	10^5	-5
$CH_3CO_2H + H_2O$	$\rightleftharpoons$ $H_3O^{(+)} + CH_3CO_2^{(-)}$	CH_3CO_2H $H_3O^{(+)}$	$CH_3CO_2^{(-)}$ H_2O	$1.77*10^{-5}$	4.75
$C_2H_5OH + H_2O$	$\rightleftharpoons$ $H_3O^{(+)} + C_2H_5O^{(-)}$	C_2H_5OH $H_3O^{(+)}$	$C_2H_5O^{(-)}$ H_2O	10^{-16}	16
$NH_3 + H_2O$	$\rightleftharpoons$ $H_3O^{(+)} + NH_2^{(-)}$	NH_3 $H_3O^{(+)}$	$NH_2^{(-)}$ H_2O	10^{-34}	34

In all the above examples water acts as a common base. The last example (NH_3) cannot be measured directly in water, since the strongest base that can exist in this solvent is hydroxide ion. Consequently, the value reported here is extrapolated from measurements in much less acidic solvents, such as acetonitrile.

Since many organic reactions either take place in aqueous environments (living cells), or are quenched or worked-up in water, it is important to consider how a conjugate acid-base equilibrium mixture changes with pH. A simple relationship known as the **Henderson-Hasselbach equation** provides this information.

$$\text{Henderson-Hasselbach Equation:} \quad pK_a = pH + \log \frac{[HA]}{[A^-]}$$

When the pH of an aqueous solution or mixture is equal to the pK_a of an acidic component, the concentrations of the acid and base conjugate forms must be equal (the log of 1 is 0). If the pH is lowered by two or more units relative to the pK_a, the acid concentration will be greater than 99%. On the other hand, if the pH (relative to pK_a) is raised by two or more units the conjugate base concentration will be over 99%. Consequently, mixtures of acidic and non-acidic compounds are easily separated by adjusting the pH of the water component in a two

phase solvent extraction.

For example, if a solution of benzoic acid (pK_a = 4.2) in benzyl alcohol (pK_a = 15) is dissolved in ether and shaken with an excess of 0.1 N sodium hydroxide (pH = 13), the acid is completely converted to its water soluble (ether insoluble) sodium salt, while the alcohol is unaffected. The ether solution of the alcohol may then be separated from the water layer, and pure alcohol recovered by distillation of the volatile ether solvent. The pH of the water solution of sodium benzoate may then be lowered to 1.0 by addition of hydrochloric acid, at which point pure benzoic acid crystallizes, and may be isolated by filtration.

Lewis Theory

According to the Lewis theory, **an acid is an electron pair acceptor**, and **a base is an electron pair donor**. Lewis bases are also Brønsted bases; however, many Lewis acids, such as BF_3, $AlCl_3$ and Mg^{2+}, are not Brønsted acids. The product of a Lewis acid-base reaction, is a neutral, dipolar or charged complex, which may be a stable covalent molecule. Two examples of Lewis acid-base equilibria are shown in equations 1 & 2 below.
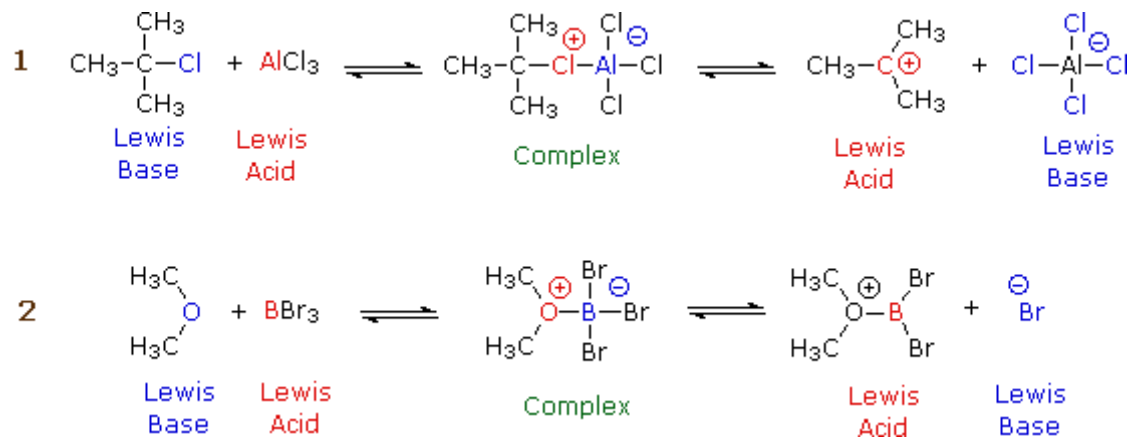
In the first example, an electron deficient aluminum atom bonds to a covalent chlorine atom be sharing one of its non-bonding valence electron pairs, and thus achieves an argon-like valence shell octet. Because this sharing is unilateral (chlorine contributes both electrons), both the aluminum and the chlorine have formal charges, as shown. If the carbon chlorine bond in this complex breaks with both the bonding electrons remaining with the more electronegative atom (chlorine), the carbon assumes a positive charge. We refer to such carbon species as **carbocations**. Carbocations are also Lewis acids, as the reverse reaction demonstrates.

Many carbocations (but not all) may also function as Brønsted acids. Equation 3 illustrates this dual behavior; the Lewis acidic site is colored red and three of the nine acidic hydrogen atoms are colored orange. In its Brønsted acid role the carbocation donates a proton to the base

(hydroxide anion), and is converted to a stable neutral molecule having a carbon-carbon double bond.
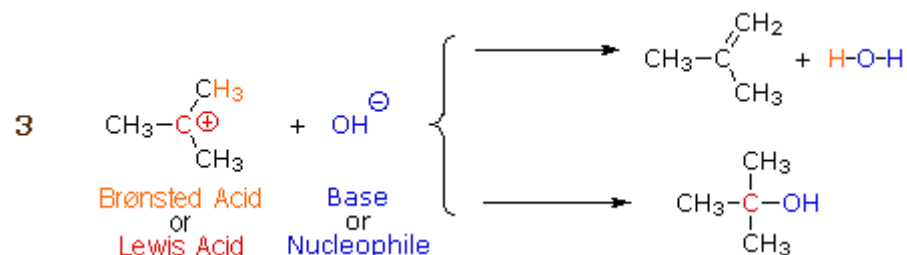
A terminology related to the Lewis acid-base nomenclature is often used by organic chemists. Here the term **electrophile** corresponds to a Lewis acid, and **nucleophile** corresponds to a Lewis base.

Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.

Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).
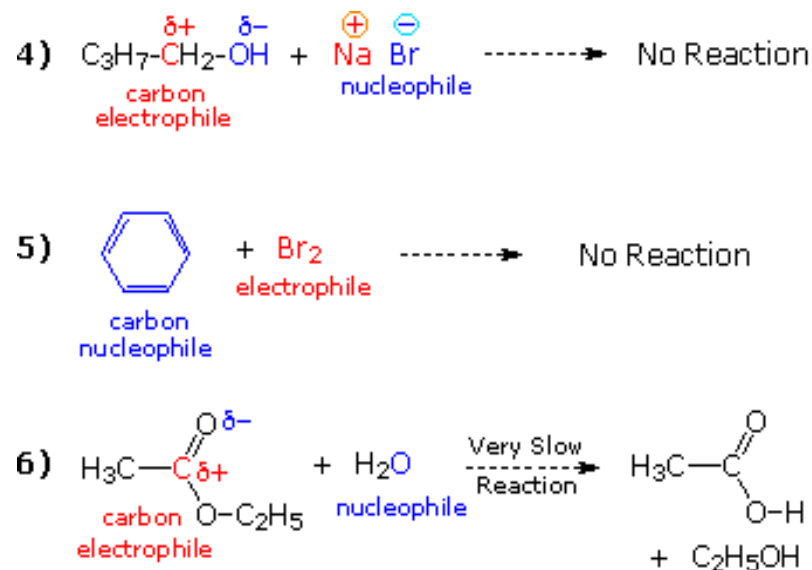
Acid-Base Catalysis

Acid-Base Catalysis

As we have noted, many common organic reactions proceed by bonding between nucleophilic and electrophilic sites in the reactant molecules. Three examples are shown in equations 1 through 3; electrophiles are colored red, and nucleophiles are colored blue.
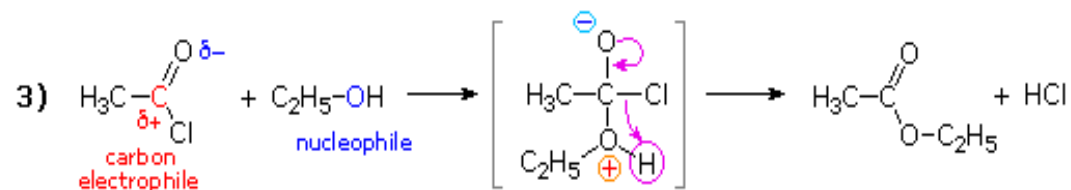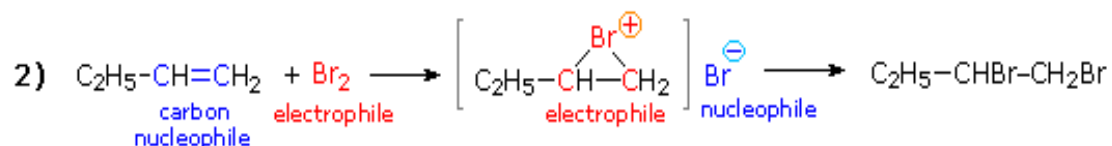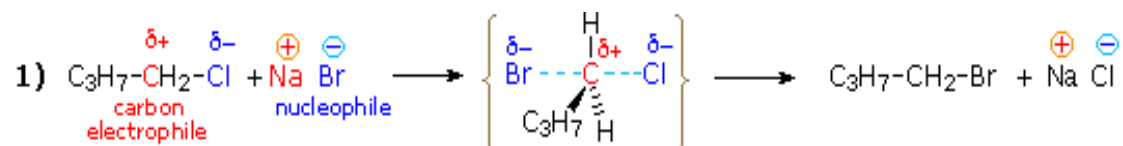
Reaction #1 is an example of a S_N2 substitution reaction. The electrophilic carbon of 1-chlorobutane is attacked by the nucleophilic bromide anion in a single-step displacement process. The curly brackets enclose a structure for the transition state in this reaction.

Reactions #2 and #3 are two-step sequences. In the former addition reaction, bromine (an electrophile) attacks the nucleophilic double bond of 1-butene to give an electrophilic cyclic-bromonium intermediate (enclosed in square brackets) accompanied by a nucleophilic bromide ion. This ion-pair is very short-lived, another nucleophile-electrophile bonding reaction leads to the product (1,2-dibromobutane). In reaction #3 (a substitution reaction) the electrophilic carbonyl carbon atom bonds to the nucleophilic oxygen atom of ethyl alcohol to give an intermediate (in square brackets) that eliminates HCl, yielding the ester ethyl acetate. In all of these examples the reactivity of the electrophiles and nucleophiles is sufficient to allow reaction to proceed spontaneously at room temperature.

It is not difficult, however, to find very similar combinations of compounds that either fail to react at all, or do so extremely slowly. Equations 4 through 6 illustrate this behavior for analogs of the first three reactions.

4) $C_3H_7\text{-}CH_2\text{-}OH$ (carbon electrophile, $\delta+$ $\delta-$) + Na Br (nucleophile, $\oplus$ $\ominus$) ----> No Reaction

5) (benzene ring, carbon nucleophile) + Br_2 (electrophile) ----> No Reaction

6) $H_3C\text{-}C$ (carbon electrophile, with O $\delta-$, $\delta+$, $O\text{-}C_2H_5$) + H_2O (nucleophile) --Very Slow Reaction--> $H_3C\text{-}C$ (with O, $O\text{-}H$) + C_2H_5OH

The factors that influence such differences in reactivity may be complex, but in the above cases are largely due to a poor anionic leaving group (eq. 4); aromatic stabilization and reduced nucleophilicity of a conjugated π-electron system (eq. 5); and reduced electrophilic character of a substituted carbonyl group (eq. 6).

First, compare reaction #4 with #1. Since oxygen is slightly more electronegative than chlorine (3.5 vs. 2.8 on the Pauling scale), we might expect a C-O bond to be more polar than a C-Cl bond. A better measure of the electrophilic character of a carbon atom in a compound comes from nmr chemical shifts (both [1]H & [13]C), and these indicate that oxygen and chlorine substituents exert

similar effects when bonded to sp^3 hybridized carbon atoms. In any event, the failure of reaction #4 cannot be due to differences in the electrophilicity and nucleophilicity of the reactants.

The key factor here is the stability of the leaving anion (chloride vs. hydroxide). We know that HCl is a much stronger acid than water (by more than 15 powers of ten), and this difference will be reflected in reactions that generate their conjugate bases. Thus, chloride anion is much more stable and less reactive than is hydroxide anion, so the former is a better and more common leaving group. Indeed, the failure of alcohols to undergo S$_N$2 substitution reactions makes them useful solvents for many such reactions, including #1.
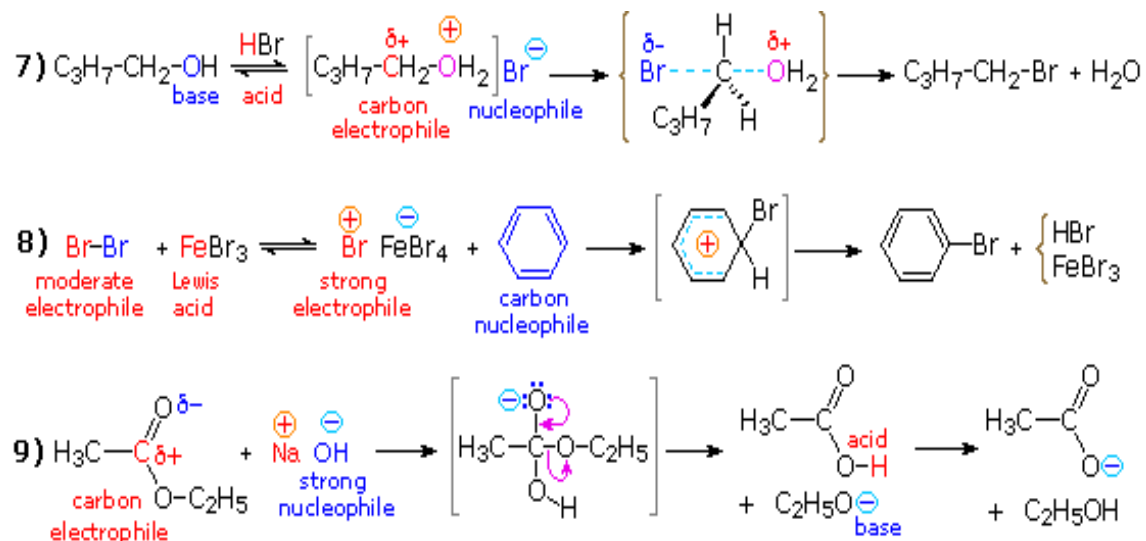
In the case of reaction #5, the aromatic stabilization of the benzene ring makes it less susceptible to attack by electrophiles than are simple alkenes. Thus, elemental bromine is not sufficiently electrophilic to induce a reaction with benzene, even though the latter is nucleophilic.

Lastly, reactions #3 and #6 illustrate differences in the reactivity of carbonyl compounds. We know that the carbon atom of a carbonyl group is electrophilic and undergoes reaction with a variety of nucleophiles. However, this electrophilic character may be enhanced or diminished by substituents. If we take saturated aldehydes (RCH=O) as a reference, the additional alkyl substituent present in

ketones slightly reduces this electrophilicity, but the general reactivity pattern of these classes is similar. On the other hand, a chlorine substituent is inductively electron withdrawing and increases the electrophilicity of the carbonyl carbon significantly. Thus, acid chlorides are very reactive with a wide range of nucleophiles, including water and alcohols (eq. 3).

The oxygen and nitrogen substituents present in esters and amides have a similar inductive effect, but also a pronounced electron donating character through a resonance interaction. Consequently, the carbonyl carbon atom becomes less electrophilic, and these functional groups are less reactive than other carbonyl compounds. Thus, the failure of ethyl acetate to react with water (eq. 6) reflects the reduced electrophilic character of its carbonyl group.

Fortunately, these retarding factors can often be overcome by acid or base catalysis, which in general enhances electrophilicity (acids) or nucleophilicity (bases). Equations 7 through 9 show how this tactic may be effectively applied to the unreactive examples given above.

7) $C_3H_7\text{-}CH_2\text{-}OH$ $\underset{\text{base}\quad\text{acid}}{\overset{HBr}{\rightleftharpoons}}$ $\left[C_3H_7\text{-}\overset{\delta+}{CH_2}\text{-}\overset{\oplus}{OH_2}\right]\overset{\ominus}{Br}$ $\longrightarrow$ $\left\{\overset{\delta-}{Br}\text{---}\overset{\overset{H}{|}}{\underset{\underset{C_3H_7}{|}}{C}}\text{---}\overset{\delta+}{OH_2}\right\}$ $\longrightarrow$ $C_3H_7\text{-}CH_2\text{-}Br + H_2O$

carbon electrophile   nucleophile

8) $Br\text{-}Br + FeBr_3 \rightleftharpoons \overset{\oplus}{Br}\,\overset{\ominus}{FeBr_4} + $ [benzene ring] $\longrightarrow$ [arenium ion, Br, H] $\longrightarrow$ [benzene]$\text{-}Br + \begin{cases} HBr \\ FeBr_3 \end{cases}$

moderate electrophile   Lewis acid   strong electrophile   carbon nucleophile

9) $H_3C\text{-}\underset{\underset{\text{carbon}}{\overset{|}{O\text{-}C_2H_5}}}{\overset{\overset{O}{\|}\,\delta-}{\underset{\delta+}{C}}} + \overset{\oplus}{Na}\,\overset{\ominus}{OH}$ $\longrightarrow$ $\left[H_3C\text{-}\underset{\underset{H}{\overset{|}{O}}}{\overset{\overset{\ominus:\ddot{O}:}{|}}{\underset{|}{C}}}\text{-}O\text{-}C_2H_5\right]$ $\longrightarrow$ $H_3C\text{-}\underset{\underset{\text{acid}}{O\text{-}H}}{\overset{\overset{O}{\|}}{C}} + C_2H_5\overset{\ominus}{O}$ $\longrightarrow$ $H_3C\text{-}\overset{\overset{O}{\|}}{C}\underset{O\ominus}{} + C_2H_5OH$

carbon electrophile   strong nucleophile   base

In strong acid, reaction #4 proceeds nicely, as shown in equation 7. This is because the leaving group has changed from hydroxide anion to water (the acidity of the conjugate acid $H_3O^{(+)}$ is nearly that of HCl). This type of catalysis is generally denoted as **Specific Acid catalysis (SAC).**

 In the second example, there are two obvious ways of circumventing the failure of benzene to react with bromine:

• The bromine can be made more electrophilic

• The benzene ring can be made more nucleophilic.

The first tactic can be implemented by mixing bromine with **ferric bromide**, a **Lewis acid catalyst**. This generates the **bromonium cation, Br$^{(+)}$, a powerful electrophile**. Equation #8 illustrates this

approach.

The second tactic requires that the benzene ring be activated (made more nucleophilic) by substitution with an electron donating group such as OH or NH_2. For example, we find that phenol (hydroxybenzene) reacts rapidly with bromine in the absence of any catalyst.

Finally, we can see that there are two ways of facilitating the ester hydrolysis reaction:

   •We can use a stronger nucleophile than water, such as hydroxide anion.

   •We can increase the electrophile reactivity by converting the ester to its conjugate acid, $CH_3C(OH)OC_2H_5^{(+)}$.

 Equation #9 shows the former approach, which is an example of base catalysis. It is also known as **<u>Specific Base Catalysis (SBC).</u>** Acid catalysis of the reaction also works well.
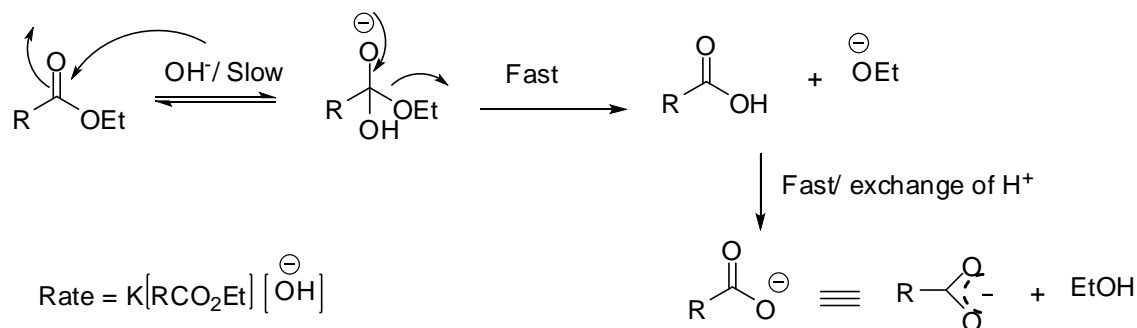
When the catalyst is not only H_3O^+ but also other acids are capable of being catalysts, they are called **General Acid Catalysis.(GAC).** GAC is effective at neutral pH.
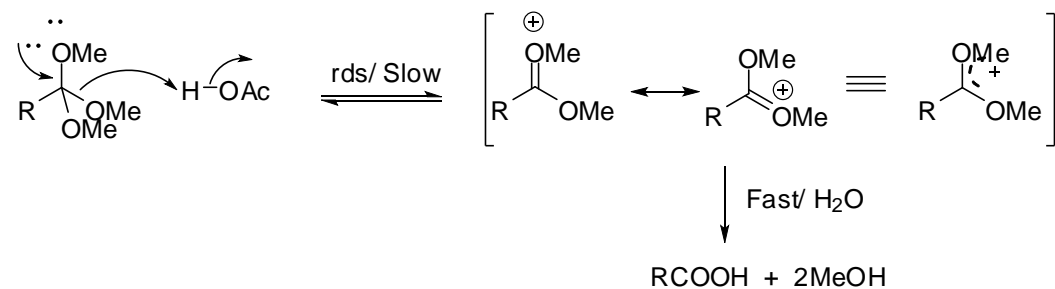
In **General Base catalysed (GBC)** reactions, bases apart from hydroxide ion are effective catalysts.

Base catalysed bromination of acetone

Enolate anion
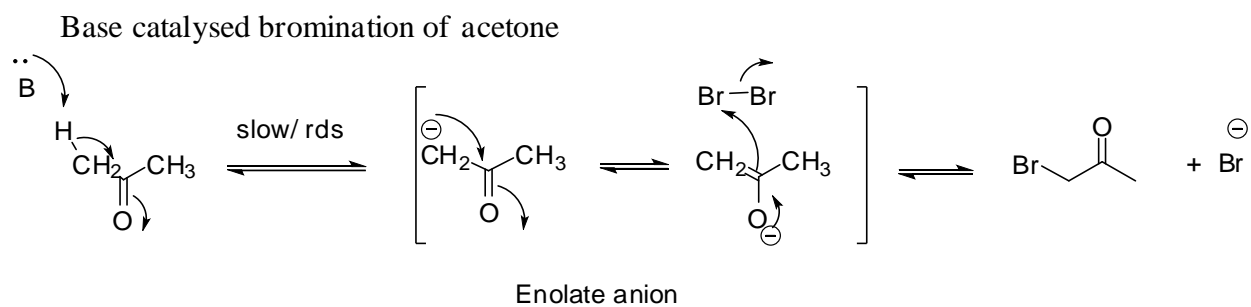
The Effect of Structure upon Acidity

Acid/base reactions are of tremendous importance in organic chemistry, as they are also in inorganic and biochemistry. Further, the acidity of hydrogen-containing compounds varies remarkably from one compound to another. In order to understand why acidities of Bronsted acids vary so widely, and to be able to systematically understand the trends in acidity, we will consider five main effects of structure upon acidity:

(1) **Periodicity within a column of the periodic table (equivalent to Bond Strength Effects)**;

(2)**Hybridization**

(3)**Resonance Effects**

(4)**Inductive Effects** and

(5)**Electronegativity effects**.

Consider the following acid dissociation:

$$H—A + H_2O \rightleftharpoons \overset{\ominus}{A} + H_3\overset{\oplus}{O}$$

Bond strength effect

Anion stability effect
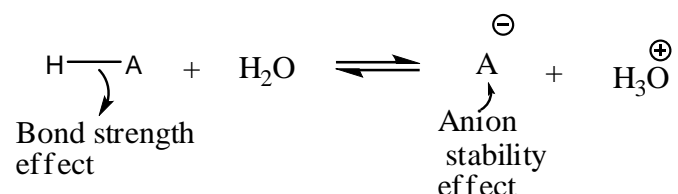
The factors which would favor dissociation, i.e., enhance acidity, are:

- **A weaker H-A bond**, because this destabilizes the left hand (reactant) side of the equation. This is the **bond strength effect**. A stronger H-A bond tends to decrease the acidity because the bond is harder to break. A weaker H-A bond increases acidity.

- **A more stable anion**, because this stabilizes the right hand side of the equation. This is the **Anion Stability Effect**.

It is an important general rule of thumb that Anion Stability usually exerts the strongest effect upon acidity, i.e., is dominant over bond strength effects.

Anion stability, in turn is affected by

(1) Resonance stabilization,

(2) Inductive effects,

(3) Hybridization effects,

(4) Electronegativity of the bonded atoms,

(5) Internal H-bonding effect,

(6) Steric effect,

(7) Solvation effect and

(8) Bond length

We discuss first the exceptional, but important case where bond strength effects predominate. However, even when they are not predominant, it should always be remembered that they always are operative and tend to increase or decrease acidity according to whether the bond is weaker or stronger. If there are opposing anion stability effects, the net effect will usually be qualitatively that predicted by considering the anion stability effect.

A Case Where Bond Strength Effects Predominate Over Anion Stability Effects

The Relative Acidities of H-X, i.e., of the hydrogen halides.*

- The pK_a's of H-F, H-Cl, H-Br, and H-I are respectively 3.5,-7,-8 and -9. That is, H-F is the weakest acid and H-I the strongest (recall that a negative pK_a corresponds to a strong acid.

- Based upon anion stability, the opposite trend should be observed, since fluoride ion should be the most stable of the halide anions (refer to the electronegativity of fluorine, which is the greatest of the halogens.)

- However, the H-F bond is extremely strong and hard to break, so the bond strength effect is acid weakening and is predominant here. The bond dissociation energies of the H-X bonds are, respectively, 136 (HF),103 (HCl),88 (HBr), and 71 (HI). So, the bond strength differences, being large, are greater than the differences in anion stability, causing the former effect to predominate. The effect is largest for fluorine, so that there is relatively little difference in the acidity of the other halogen acids. Thus the two effects are almost, but not quite in balance for these latter three H-X's.

- Similar considerations apply for comparisons in any case involving atoms in the same Group of the Periodic Table. But, rarely are bond strength effects dominant over anion stability effects in any other comparative situation.

RESONANCE EFFECTS

The more the number of contributing structures in a resonance hybrid of a neutral or negatively charged species, the more is the stability of the hybrid and the greater is the delocalization of the electrons. The greater the delocalization, the lower is the probability of donating electron-pair. Therefore, as the resonance stabilization increases, basicity decreases and hence relatively acidity increases.

WE ARE STILL FOCUSING UPON ANION STABILITY AS THE DOMINANT FACTOR IN DETERMINING THE RELATIVE ACIDITIES OF BRONSTED-LOWRY ACIDS. EVEN WHEN THE NEGATIVE CHARGE IS LOCATED ON THE SAME ATOM (SO THAT ELECTRONEGATIVITY IS NOT A FACTOR), AND WHEN THE HYBRIDIZATION STATE OF THE ATOM ISN'T DIFFERENT (SO THAT HYBRIDIZATION EFFECTS ARE NOT IMPORTANT), A SERIES OF ANIONS (CONJUGATE BASES OF THE BRONSTED-LOWRY ACIDS) CAN BE DIFFERENTIALLY STABILIZED BY RESONANCE. AS YOU SHOULD RECALL, DELOCALIZATION OF THE CHARGE OVER MORE THAN ONE ATOM RESULTS IN RESONANCE STABILIZATION. AN EXCELLENT EXMAPLE IS AVAILABLE IN THE COMPARISON OF THE ACIDITIES OF ALCOHOLS(RO-H) WITH CARBOXYLIC ACIDS (RCOOH):

- *The conjugate base of an alcohol is an alkoxide anion (RO⁻). In the case of ethanol, it is ethoxide anion. In such an alkoxide ion, **the negative charge is essentially localized upon oxygen**. This being an electronegative atom, the negative charge is fairly stable there, so that alcohols are modestly acidic, comparable to water. This is reasonable because in the conjugate base of water, the negative charge is also located upon an oxygen atom.*

- *The conjugate base of a carboxylic acid is a carboxylate anion. In the case of, say, acetic acid, it is acetate anion. **In such a carboxylate anion, the negative charge is also upon oxygen, but because of resonance effects it is delocalized over two oxygen atoms.** Therefore additional stabilization of the anion results, so that carboxylic acids are typically about 11 powers of ten more acidic than alcohols.*

$$R-OH \;+\; H_2O \;\rightleftharpoons\; RO^{\ominus} \;+\; H_3\overset{\oplus}{O} \qquad pka=16$$

$$R-\overset{\displaystyle |}{\underset{\displaystyle O}{C}}-OH \;+\; H_2O \rightleftharpoons \left[R-C{\overset{O^{\ominus}}{\underset{O}{}}} \;\longleftrightarrow\; R-C{=}O \right] \;+\; H_3\overset{\oplus}{O} \qquad pka=5$$
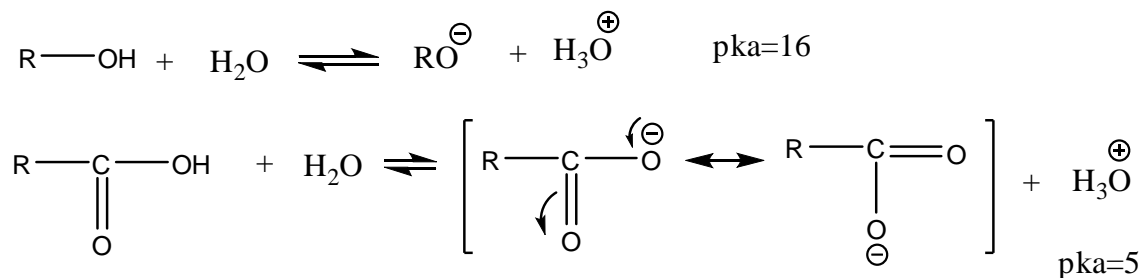
Strong –R group at the *ortho* or *para* position of an aromatic ring enhances acidity of phenolic compounds by stabilisation of conjugate bases (phenoxide ions) through

dispersion of negative charge.Such a group at the meta position does not participate in resonance.

1) PhO⁻ is a weaker base than EtO⁻ - explain.

2) Aniline is a stronger base than *p*-nitroaniline.

3) *p*-nitrophenol is a stronger acid than *m*-nitrophenol.

4) β-diketones or β-ketoesters are stronger acids than simple ketones or esters.

INDUCTIVE EFFECTS

We are again considering ways in which the anion produced by deprotonating a Bronsted-Lowry acid can be stabilized. The final way which we want to consider is by stabilizing the site of negative charge by interaction with other dipoles which may be present in the molecule. Typically, this kind of effect can be somewhat complex, but the overall result of this stabilization (or destabilization) is referred to as "the inductive effect". As an example, we consider the comparison of acetic acid and chloroacetic acid.

- **The pK$_a$ of acetic acid is 4.76, while that of chloroacetic acid is 2.86, i.e., the latter is almost 100 times more acidic than the former.**

- The conjugate base in each case is a carboxylate anion, so electronegativity effects and resonance effects should be equal in each case. What makes the chloroacetate anion relatively more stable than the acetate ion? This is the inductive effect.

- We recall that a C-Cl bond is substantially polar in the sense of carbon being partially positively charged and chlorine partially negatively charged, because of the electronegativity difference between these two atoms. The dipole in this bond is oriented with its positive end closer to the two sites of negative charge (the oxygens). There is therefore a stabilizing electrostatic attraction between the positive ends of the C-Cl dipole with the negative charge of the anion. This is larger than the destabilizing (repulsive) interaction of the negative charge with the chlorine end of the diple, because the distance between the latter and the negatively charged oxygens is greater. Thus, there is a net electrostatic attraction and stabilization in the anion because of the (1) existence of the dipole and (2) the orientation of the positive end toward the negatively charge oxygens.

- If the dipole were oriented with the negative end toward the anion site, there would be a destabilization, and a decrease in acidity.

$$CH_3\overset{O}{\underset{}{\overset{\parallel}{C}}}-O-H \ + \ H_2O \ \overset{pKa=4.76}{\rightleftharpoons} \ CH_3\overset{O}{\underset{}{\overset{\parallel}{C}}}-\overset{\ominus}{O} \ + \ H_3\overset{\oplus}{O}$$

$$Cl-CH_2\overset{O}{\underset{}{\overset{\parallel}{C}}}-O-H \ + \ H_2O \ \overset{pKa=2.86}{\rightleftharpoons} \ Cl-CH_2\overset{O}{\underset{}{\overset{\parallel}{C}}}-\overset{\ominus}{O} \ + \ H_3\overset{\oplus}{O}$$
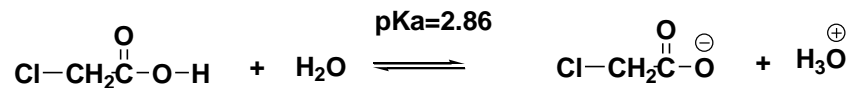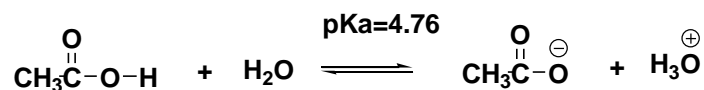
-I groups enhance the acidity of carboxylic acids by creating greater positivity on carboxylic carbon and stabilizing the conjugate base by reducing its charge density.

FCH_2COOH $ClCH_2OOH$ $BrCH_2COOH$ ICH_2COOH

pKa   2.56   2.86   2.90   3.16

$ClCH_2OOH$ $Cl_2CHCOOH$ Cl_3CCOOH

pKa   2.86   1.25   0.65

$CH_3CH_2CHClCOOH$ $CH_3CHClCH_2COOH$ $CH_2ClCH_2CH_2COOH$

pKa   2.84   4.06   4.52

$+$
O_2NCH_2COOH Me_3NCH_2COOH $OHCH_2COOH$

pKa   1.68   1.83   3.83

In dicarboxylic acids –I effect of one –COOH group enhances the acidity of the other –COOH group and this effect gradually decreases with the number of intervening carbon.

HOOCCOOH   HOOCCH$_2$COOH   HOOCCH$_2$CH$_2$COOH

pKa   1.23   2.83   3.82

pKa   2.98   3.46   3.52
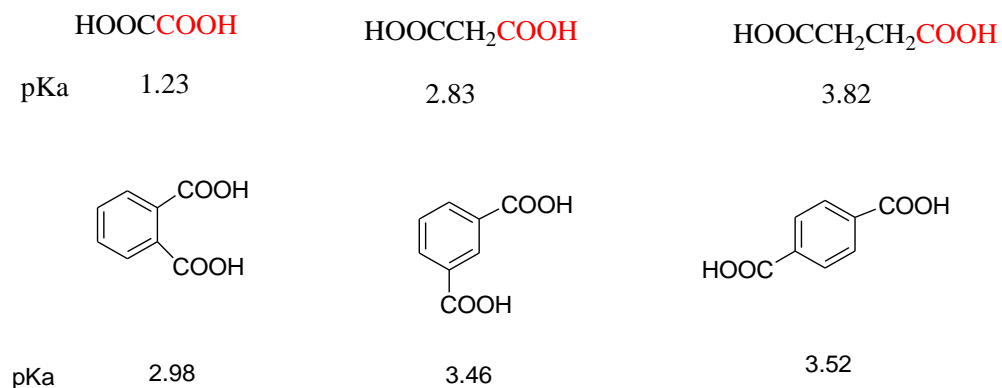
In their monocarboxylates +I effect of –COO⁻ group reduces the acidity of the remaining –COOH.

HOOCCOO⁻   HOOCCH$_2$COO⁻   HOOCCH$_2$CH$_2$COO⁻

Acidity increases

Acidity decreases
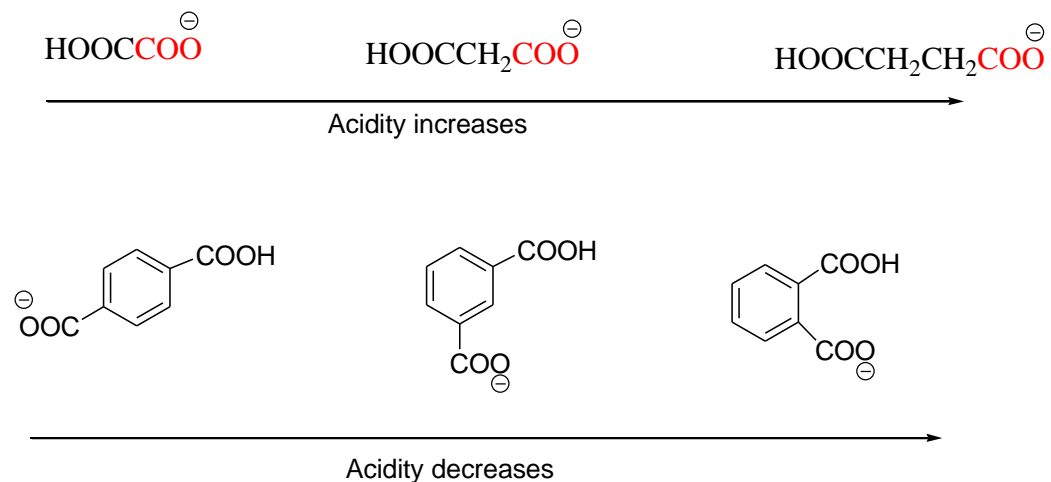
pK$_a$ Values for Some Aliphatic Carboxylic Acids (25 ºC in H$_2$O)

Compound	pK$_a$	Compound	pK$_a$	Compound	pK$_a$	Compound	pK$_a$
CH$_3$CO$_2$H	4.76	CH$_3$CH$_2$CO$_2$H	4.87	CH$_3$(CH$_2$)$_2$CO$_2$H	4.91	**(CH$_3$)$_3$CCO$_2$H**	5.05
FCH$_2$CO$_2$H	2.59	ClCH$_2$CO$_2$H	2.85	BrCH$_2$CO$_2$H	2.89	ICH$_2$CO$_2$H	3.13
NCCH$_2$CO$_2$H	2.50	HOCH$_2$CO$_2$H	3.82	Cl$_2$CHCO$_2$H	1.25	Cl$_3$CCO$_2$H	0.77
NCCH$_2$CH$_2$CO$_2$H	3.98	ClCH$_2$CH$_2$CO$_2$H	3.95	BrCH$_2$CH$_2$CO$_2$H	4.0	ICH$_2$CH$_2$CO$_2$H	4.06

Intramolecular Hydrogen bonding

Intramolecular H-bonding is a powerful tool for stabilization of conjugate bases and hence it is an important factor in determining acidity.

o-hydroxybenzoic acid   (pKa=2.98)

p-hydroxybenzoic acid   (pKa=4.6)

Stabilisation by H-bonding
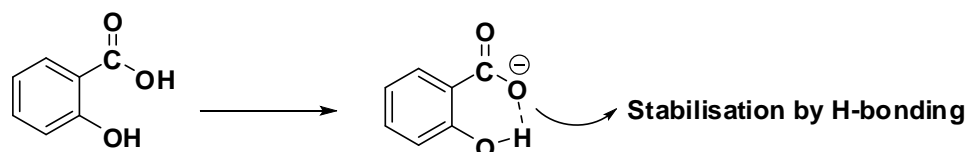
Lower dissociation and hence higher pKa value for the second –COOH group of maleic monocarboxylate (pKa=6.23) than that of fumaric monocarboxylate(pKa=4.38) is due to higher stability of former by intramolecular H-bonding for which it is difficult to remove proton from the remaining –COOH group. This however does not happen in fumaric monocarboxylate since –COOH group and –COO⁻ are farthest away.

Maleic monocarboxylate

Fumaric monocarboxylate
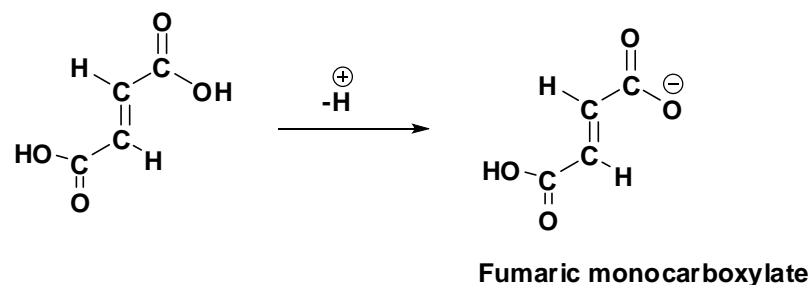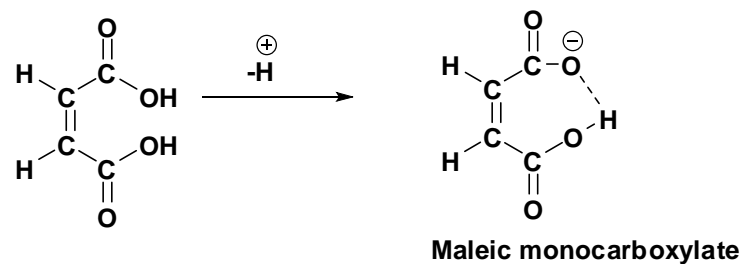
Steric Effects

The *ortho* substituted aromatic carboxylic acids are stronger acids than its *para isomer* irrespective of electronic nature of the substituent. Due to steric interaction between the groups, -COOH is displaced out of the plane of the ring which diminishes the resonance involving –COOH group and the aromatic ring. This almost prevents the flow of electron from the ring to the carboxylic carbon and –COOH remains quite active.

| pKa | 2.77 | 3.43 | 3.91 | 4.36 |
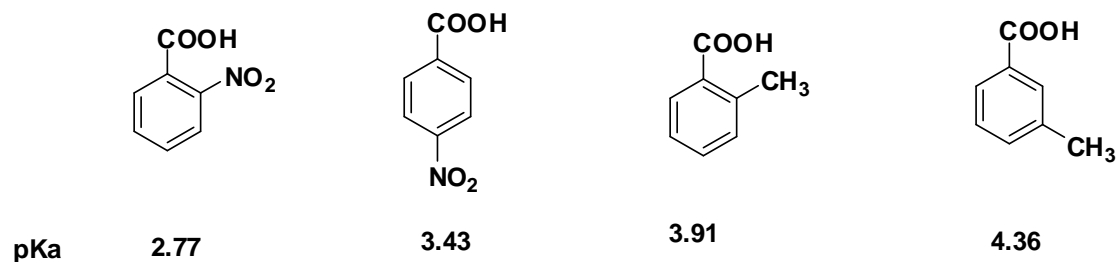
A branched aliphatic carboxylic acid is weaker acid than its unbranched isomer due to poorer solvation of its conjugation base. Spherical shape of branched carboxylate allows only few molecules of water for contact causing a weaker solvation while unbranched carboxylate due to elongated shape may be surrounded by larger number of molecules and hence solvated nicely.
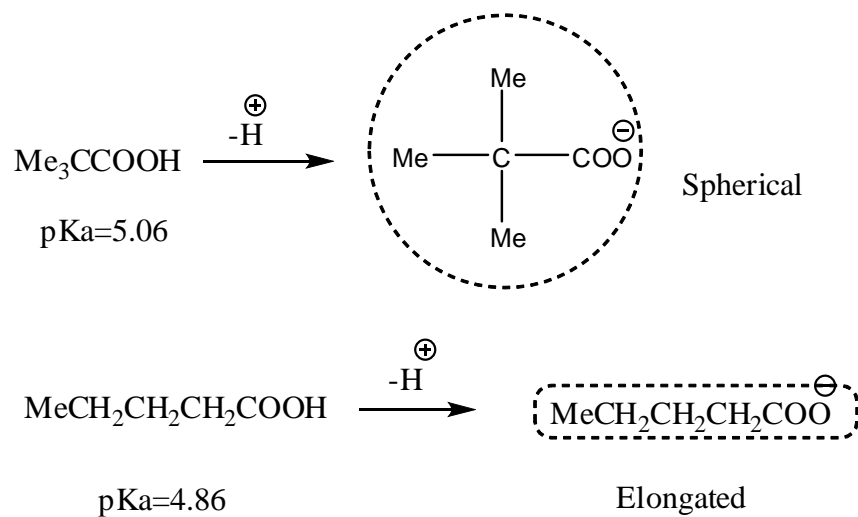
N,N-dimethylaniline is six times weaker in basicity than N,N,2,6-tetramethylaniline-explain.

2,4,6-trinitro-N,N-dimethylaniline is 40 000 times more basic than 2,4,6-trinitroaniline-explain.

ELECTRONEGATIVITY EFFECTS

Anion stability is strongly affected by the electronegativity of the atom upon which the negative charge rests, i.e., the ability of the atom to stabilize additional electrons.

- For example, negative charge is more stabilized by a fluorine nucleus than a nitrogen nucleus because fluorine has a nucleus which has a positive charge of +9 (nine protons), whereas that of nitrogen has only +7. So pure electrostatic effects (potential energy of attraction of the negatively charged electron to the positively charge nucleus) stabilize electrons on fluorine more than on other atoms. In general, electronegativity is a fairly good measure of the ability of an atom to stabilize negative charge.

- The electronegativity of fluorine is also greater than that of chlorine, bromine, or iodine, i.e., electronegativity decreases down a column of the Periodic Table. This is because the electron with chlorine, for example, must enter an orbital in the third main shell, which is much further from the nucleus than the second main shell, which would be involved for fluorine. The potential energy of attraction between the electron and the nucleus is inversely proportional to the distance. In the case of a comparison in the same row of the periodic table, the distance factor is the same, because the electrons are entering the same main shell, so it is the charge on the nucleus which is the determining factor of the electronegativity of the atom.

- The pK_a's of **methane, ammonia, water, and HF are respectively 51, 38, 15.7, and 4.0,** i.e., acidity sharply increases upon going from left to right in the periodic Table. This follows the order of anion stability, because the methyl anion is less stable than the amide anion, than the hydroxide anion, than fluoride anion. That is, negative charge is most stable on F, the most electronegative atom, and least stable on carbon, the least electronegative atom of this series. It is true that bond strength effects are in the opposite direction and would tend to make HF the weakest acid, but anion stabilization effects are larger. So it is good to remember that anion

stabilization effects are dominant in all cases except when comparisons are made within one group of the periodic table.

$CH_5-H + H_2O: \rightleftharpoons CH_3^\ominus + H_3O^\oplus$ pKa 51

methide anion

$NH_2-H + H_2O: \rightleftharpoons NH_2^\ominus + H_3O^\oplus$ pKa 38

amide anion

$HO-H + H_2O: \rightleftharpoons HO^\ominus + H_3O^\oplus$ pKa 15.7

hydroxide anion

$F-H + H_2O: \rightleftharpoons F^\ominus + H_3O^\oplus$ pKa 4.0

fluoride anion
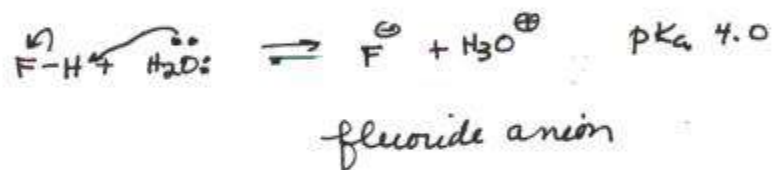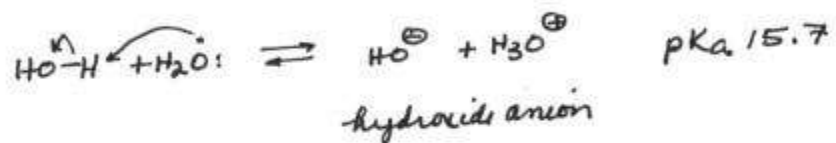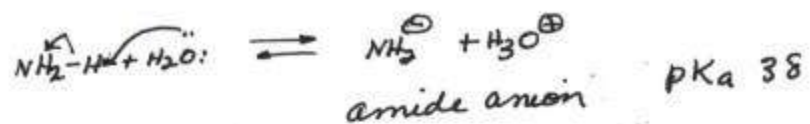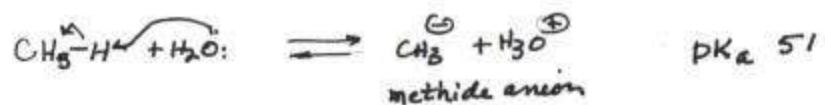
Acid Strength Increases →

Electronegativities:

Carbon 2.5 (applicable to $\overset{\ominus}{C}H_3$)

nitrogen 3.0 (see $NH_2^\ominus$)

oxygen 3.5 (see $OH^\ominus$)

fluorine 4.0 (see $F^\ominus$)

HYBRIDIZATION EFFECTS

An especially interesting case to consider is the comparison between anions in which the negative charge is on the same atom but the hybridization state of the atom is varied. The most important case here is that of carbon, which, as you know, has three distinct hybridization states.

Hybridization has a strong influence on acidity, as shown by the three carbon acids on the upper left below. The greater the s-character of the orbital holding the electron pair of the conjugate base, the greater will be the stability of the base. This corresponds to the lower energy of an s-orbital compared with p-orbitals in the same valence shell. It also corresponds to the increased electronegativity or inductive electron withdrawal that is found for different hybridization states of a given atom, as depicted in the graph on the right. The difference in acidity of 2-butynoic acid and butanoic acid, shown in the shaded

box at lower left, provides a further illustration of this inductive effect.

Carbocation stability is also influenced by hybidization, but in the **opposite direction** ($sp^3 > sp^2 > sp$).

Carbon Acids

Hybridization versus Electronegativity

Hybridization	sp	sp2	sp3
pKa (H_2O)	25	44-48	50-55

Inductive Effect

$CH_3-C\equiv C-C$ sp O-H $pK_a = 2.62$

$H_3C-CH_2-CH_2-C$ sp^3 O-H $pK_a = 4.82$
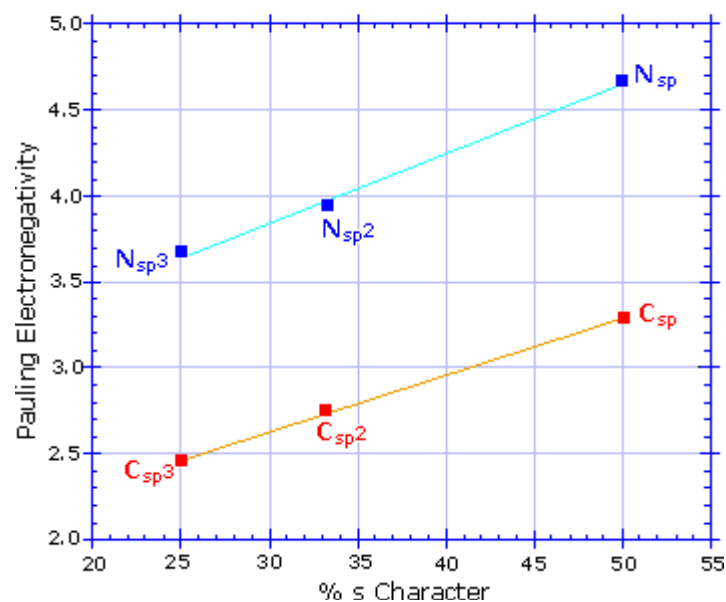
- The acidity of ethyne (acetylene) is much greater than that of ethene, which is much greater than that of ethane. The relevant pK_a's are 25, 44, and 51.

- The bond strengths would predict the opposite effect, since the C-H bond of ethyne is stronger than that of ethene than that of ethane. So, anion stabilization effects must be operative.

- The relevant anions, as shown in the figure, are the ethynide anion, in which carbon is sp hybridized, the vinyl anion (trigonally or sp^2 hybridized), and the ethyl anion (tetrahedrally or sp^3 hybridized).The former is the most stable and the last-named one least stable, so that the rule of controlling anion stability is obeyed.

- It is very important to understand the reason for the profound difference in acidity of C-H bonds as a function of their hybridization state. The key point here is that the lower the energy of the orbital in which the unshared pair resides in the anion, the more stable will be the anion. In the ethynide anion, the unshared pair is in a digonal

orbital which is 50% s and 50% p. In the vinyl anion, the unshared pair is in a trigonal orbital which is 33% s and 67% p, while in the ethyl anion the unshared pair is in a tetrahedral orbital which is 25% s and 75% p. Since the energy of an s orbital is much lower than that of the corresponding p orbital, the greater the "% s content" or "s character" of the orbital the lower its energy. Please note that ethyne is almost 20 powers of ten more acidic than ethene.

- It is also important to note that **ethyne is 13 powers of ten more acidic than ammonia,** even though in the latter case the negative charge in the amide anion is on a nitrogen atom, which has a much higher electronegativity than carbon. Thus hybridization effects are impressively large, and can cause carbon to appear as even more electronegative than nitrogen, when the former is in the diagonal hybridization state.

-

Effect of bond length

The longer the bond, the weaker is the bond and it breaks readily. Between R-S-H (thiols) and R-O-H (alcohols), the S-H bond is longer than the O-H bond. So S-H bond breaks readily than O-H bond. For this reason R-S-H is a stronger acid than R-O-H. Moreover, the corresponding conjugate bases are RS^- and RO^-, RS^- accommodates the negative charge better than RO^- because of the larger volume of S atom than that of O atom. So RS^- is a weaker base than RO^-; hence the conjugate acid RSH is stronger than the conjugate acid ROH.

2. Solvent Effects

Acidity

As noted earlier, a Brønsted acid base equilibrium involves a reversible proton transfer between a pair of acids and a pair of bases (referred to as conjugate pairs). The dissociation of a group of acids in a given solvent may be used as a measure of acid strength, and in such cases the solvent serves as a common reference base. The determination of K_a and pK_a values for any solvent system may be carried out in the same way as in water; however, the acidities obtained for a group of acids measured in different solvents will generally be different, both in the numerical value for each, and sometimes in relative order.

$$A–H \; + \; Sol: \; \rightleftharpoons \; A:^{(-)} \; + \; Sol–H^{(+)}$$

an acid   solvent   conjugate base   conjugate acid
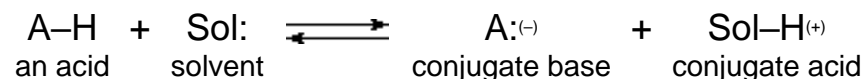
There are several factors which influence acidity measurements made in water and other solvents. These are:

1. Ionization of an acid produces ions. Solvents having large dielectric constants favor charge formation and separation.

2. The conjugate acid from the solvent is a cation that is stabilized by association with other

solvent molecules, a phenomenon called **solvation**.

3. The conjugate base of the acid is an anion, that in most cases is also stabilized by solvation.

As examples, consider the following data obtained for six strong acids in three common solvents.

Experimental pK$_a$ Values for Some Strong Acids in Different Solvents			
Compound	H$_2$O	DMSO	CH$_3$CN
HClO$_4$	−10*	−10*	1.6
CF$_3$SO$_3$H	−10*	−10*	2.6
HBr	−9	0.8	5.8
HCl	−7	1.8	10.4
H$_2$SO$_4$	−3	1.4	7.9
CF$_3$CO$_2$H	−0.25	3.5	12.7

* Perchloric acid and trifluoromethanesulfonic acid are both completely ionized in water and DMSO.
The pK$_a$ value of −10 is approximate, and is intended to reflect the high degree of dissociation.

All three solvents have fairly high dielectric constants, but water ($\varepsilon = 80$) is significantly greater than DMSO ($\varepsilon = 46.7$) or acetonitrile ($\varepsilon = 37.5$). The greater acidity (lower pK_a) of the last four compounds in water might be attributed to the dielectric difference; however, the superior anion solvation provided by water is considered to be the major factor. Both DMSO and acetonitrile are poor anion solvation solvents, consequently the ionization equilibrium shown above will be shifted to the left.

It is informative to focus first on the pK_a differences between water and DMSO. We do this because water and DMSO have similar basicities, so stabilization of the solvent conjugate acid species should not differ substantially. HBr and HCl display pK_as in DMSO that are roughly 9 to 10 powers of ten more positive than in water, and the weaker second period acid HF shows an even greater change ($pK_a = 3.17$ in water & 15 in DMSO). The conjugate bases of these acids are all single atom anions. Because the negative charge is localized, anion stabilization by solvation is probably the most important factor in establishing the position of these equilibria. In contrast, the conjugate bases from sulfuric acid and trifluoroacetic acid are internally stabilized by charge delocalization over two or three oxygen atoms. The importance of solvation is therefore less important, and the shift in acidity in DMSO is reduced to 4 powers of ten.

When acetonitrile is the solvent, the measured pK_as of these acids show a further increase, and even the strongest acids are not completely dissociated. This change may be attributed in large part to diminished solvation of the solvent conjugate acid, which is the chief cation species in dilute solutions. Since both the cationic and anionic species from acidic ionization are poorly stabilized by solvation, the dissociation equilibrium lies far to the left (no ionization).

Most organic compounds are much weaker acids than those listed above. It is therefore of interest to determine the changes in acidity that take place when such compounds are examined in the same three solvents. The first four compounds in the following table (shaded light green) are weak acids having conjugate bases in which the charge is localized on a single atom (O, C & S). Changing the solvent from water to DMSO decreases the acidity by 10 to 12 powers of ten for second period atoms (C & O), and by 6.5 for the third period sulfhydryl acid. Just as in the more acidic cases treated above, solvation of the conjugate base anions is an important stabilizing factor in water, although the lower charge density on sulfur reduces its significance. The further increase in pK_a that occurs in acetonitrile solutions, relative to DMSO, is fairly uniform (10 to12 units) and a bit larger than the shift found for the strong acids.

The last four compounds (shaded blue) have conjugate bases stabilized by charge delocalization.

Here, the decrease in acidity going from water to DMSO is lowered to 7 to 8 powers of ten for oxygen and is less than 4 for sulfur. As noted previously, charge delocalization within an anion reduces the importance of solvation stabilization. The increase in pK_a found for acetonitrile solutions remains roughly the same, and may be attributed to poor solvation of the nitrile conjugate acid, as noted above.

Experimental pK$_a$s for Some Weak Acids in Different Solvents			
Compound	H$_2$O	DMSO	CH$_3$CN
C$_2$H$_5$OH	17	29	42
CF$_3$CH$_2$OH	12.4	23.5	33.5
C$_6$H$_5$C≡CH	19	29	40.6
C$_4$H$_9$SH	10.5	17	28.6
CH$_3$CO$_2$H	4.8	12.8	22.3
C$_6$H$_5$CO$_2$H	4.2	11.1	20.7
C$_6$H$_5$OH	10	18	26.6
C$_6$H$_5$SH	6.6	10.3	20.6

With the exception of the acetylene derivative, the previous compounds are all heteroatom acids. Similar measurements for a group of activated carbon acids show agreement with the previous analysis, and illustrate the manner in which anionic charge delocalization reduces the pK_a difference between water and DMSO measurements. Note the near identity of the second and third examples in the following table. As expected, the pK_a increase in going to acetonitrile from DMSO remains roughly constant (ca. 11).

Experimental pK_as for Some Carbon Acids in Different Solvents			
Compound	H_2O	DMSO	CH_3CN
$(CH_3CO)_2CH_2$	9	13.3	24.4
$(N{\equiv}C)_2CH_2$	11.2	11.2	22.2
$(C_6H_5SO_2)_2CH_2$	11.6	12.2	23.2
$(C_2H_5OCO)_2CH_2$	13.5	16.4	27.8
$C_4H_4CH_2$ cyclopentadiene	15.0	18.0	31.2

Conjugation and Hybridization

The aliphatic acids discussed above do not provide any insight into p-π or π-π conjugation effects, since the sp^3-hybridized α-carbon insulates the carboxyl group from such interactions. Conjugation may be studied by using α,β-unsaturated and aromatic carboxylic acids. The two parent compounds of these classes, **acrylic acid (CH$_2$=CHCO$_2$H)** and **benzoic acid (C$_6$H$_5$CO$_2$H),** are both slightly stronger than acetic acid and have similar pK$_a$'s of 4.26 and 4.20 respectively. Since their influence is probably a combination of inductive and resonance effects, it would be helpful to evaluate one of these alone. The following four compounds represent acetic acid derivatives in which a methyl hydrogen has been replaced with a methyl group, a vinyl group, a phenyl group and a chlorine atom respectively. In each compound a methylene group insulates the substituent from the carboxyl group, prohibiting conjugative interactions. As noted above, the methyl substituent is weakly electron donating and the chlorine exerts a strong electron withdrawing influence. Comparatively, the vinyl and phenyl groups have an electron withdrawing inductive effect roughly 25% that of chlorine. From this we may conclude that resonance electron donation to the carboxyl function in acrylic acid and benzoic acid substantially dilutes the inductive effect of the sp^2 substituent groups.

CH$_3$CH$_2$CO$_2$H 4.87   CH$_2$=CHCH$_2$CO$_2$H 4.34   C$_6$H$_5$CH$_2$CO$_2$H 4.30   ClCH$_2$CO$_2$H 2.85

The increased electronegativity of sp^2 and sp hybridized carbon compared with sp^3 carbon was <u>noted earlier</u>. This increase is particularly dramatic for triply bonded substituents, as seen in the acidity of **2-propynoic acid, HC≡CCO$_2$H, and 3-butynoic acid, HC≡CCH$_2$CO$_2$H**, having respective pK$_a$'s of 1.90 and 3.30. Conjugative electron donation in 2-propynoic acid is very small, compared with acrylic acid, reflecting the poor electron donating character of the <u>triple bond</u>.

Another aspect of conjugation concerns the ability of a double bond, triple bond or aromatic ring to transmit the influence of a remote substituent to the carboxyl group. The compounds in the following table provide information bearing on this issue. The top row consists of β-substituted acrylic acid derivatives. Methyl and phenyl substituents exert a weakening effect; whereas chlorine strengthens the acid. Comparing these relationships with similar substituent effects in equivalent saturated acids (<u>previous table</u>) leads to some interesting differences.

- A β-chlorine substituent exerts the same acidity strengthening effect regardless of unsaturation in the connecting chain.

- A β-methyl group decreases the acidity of the unsaturated acid tenfold over that of the saturated analog.

- A β-phenyl group increases the acidity of the saturated acid, but decreases that of the

unsaturated acid by roughly the same degree.

These observations may be interpreted in several ways. First, the inductive electron withdrawal by chlorine through a C–C sigma-bond is about the same as through a pi-bond. Second, The inductive electron donation by a methyl group occurs to a significant degree by hyperconjugation or conjugated hyperconjugation. Finally, the curious inversion of the phenyl influence may be attributed to an exclusive inductive electron withdrawal down the saturated connecting group, overpowered by a conjugative donation through the unsaturated chain.

Substituent Effects in Some Unsaturated or Aromatic Carboxylic Acids (25 °C in H_2O)							
Compound	pK_a	Compound	pK_a	Compound	pK_a	Compound	pK_a
t-$CH_3CH=CHCO_2H$	4.74	$(CH_3)_2C=CHCO_2H$	5.12	$ClCH=CHCO_2H$	3.32	t-$C_6H_5CH=CHCO_2H$	4.50
p-$CH_3C_6H_4CO_2H$	4.36	p-$ClC_6H_4CO_2H$	3.98	p-$CH_3OC_6H_4CO_2H$	4.48	p-$O_2NC_6H_4CO_2H$	3.42
m-$CH_3C_6H_4CO_2H$	4.27	m-$ClC_6H_4CO_2H$	3.82	m-$CH_3OC_6H_4CO_2H$	4.10	m-$O_2NC_6H_4CO_2H$	3.47

The substituted benzoic acids in the above table exhibit many of the same effects noted for the acrylic acid derivatives. It must, however, be noted that the meta and para-substituent locations in these compounds are further removed from the carboxyl group, both in distance and number of

connecting bonds, than in the acrylic acid examples. This will reduce the magnitude of any inductive effects. The para-location permits conjugative interaction of the substituent with the carboxyl function; the meta location does not. For comparison purposes remember that benzoic acid itself has a $pK_a = 4.2$.

A para-methyl substituent appears to have double the electron donating effect of a meta-methyl group, again suggesting that conjugative hyperconjugation may be important. The meta-chlorobenzoic acid isomer is significantly more acidic than the para-isomer, largely because it is closer to the carboxyl function, and in part due to resonance electron donation by the para-chlorine. The two methoxybenzoic acids are particularly informative, in as much as the meta isomer has a slightly increased acidity, whereas the para-isomer is significantly weakened. Oxygen has a much larger electronegativity than carbon, but it is an excellent p-π electron donor to sp^2 carbon functions. For the meta isomer, the inductive effect is somewhat stronger than the resonance donation, but the para-isomer is able to donate an oxygen electron pair directly into the electrophilic carboxyl function. Both the meta and para-nitro substituent withdraw electrons from the benzene ring by a combination of inductive and resonance action, and the corresponding acids are greatly strengthened.

A quantitative treatment of meta and para-substituent effects on the properties and reactions of benzoyl derivatives has been developed by L.P. Hammett.

The Ortho Effect

In general, ortho-substituted benzoic acids are stronger acids than their meta and para isomers, regardless of the nature of the substituent. The ortho effect is large for the nitrobenzoic acids, which show nearly a 20 fold increase in acidity, roughly an 8 fold factor for the halobenzoic acids, and a 2.5 to 3 fold increase for methyl and cyano substituents. The methoxybenzoic acids are exceptional, in that the ortho and meta isomers have nearly identical pK_a's (ca. 4.1), presumably due to the exceptional p-π electron donation from oxygen noted above.

Many of the factors that influence the acidity of substituted benzoic acids are summarized in the following diagram. First, although the phenyl group is inductively electron withdrawing, it can donate electrons to a carboxyl group by π-π resonance, as shown in the green shaded box in the upper left. A substituent Y may perturb the balance of these two factors by its inductive influence or

by resonance. Two resonance cases, one showing electron withdrawal by a nitro substituent and the other electron donation by a methoxy substituent, are shown to the right of the green box.

| | electron donation from aromatic ring by π-π resonance | electron removal from aromatic ring by π-π resonance | electron donation from substituent by p-π resonance |

| Steric Hindrance | | |

Y	pKa	Y	pKa
CH₃	3.24	CH₃	4.33
Cl	1.60	Cl	3.50
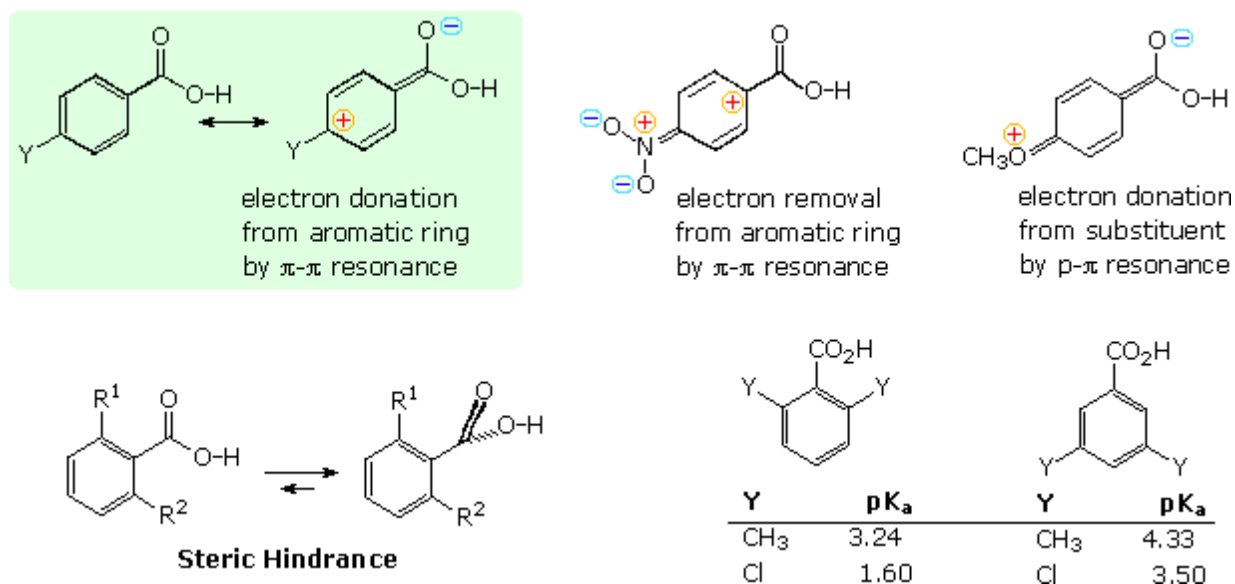
The increased acidity of ortho-substituted benzoic acids is attributed to steric hindrance that forces the carboxyl group to twist out of the plane of the benzene ring. The inductive character of the phenyl group does not change with such twisting, but resonance (conjugative electron donation) requires a coplanar relationship. For example, ortho-toluic acid ($R^1 = CH_3$ & $R^2 = H$) has a pKa of 3.9 compared with 4.2 for benzoic acid itself. If the methyl is changed to a larger *tert*-butyl group the pKa drops to 3. 53. By sandwiching the carboxyl group between two ortho substituents, it is forced

to lie perpendicular to the plane of the aromatic ring, and conjugation is prohibited completely. The dimethyl and dichlorobenzoic acid isomers shown at the lower right in the diagram provide dramatic evidence of this conformational effect, with the bis-ortho (2,6-) isomers representing the exclusive action of the inductive effect.

Steric interference with conjugation may also perturb the acidity of acyclic unsaturated acids. Thus, 2,3-dimethyl-2-butenoic acid has a pK_a of 4.41, compared with the 5.12 pK_a of 3-methyl-2-butenoic acid.

4. Stereoelectronic Control of Enolization

Many carbon acids have enhanced acidity because of a neighboring functional group. The acidity of alpha hydrogens in aldehydes, ketones and esters is well documented, and is the source of many important synthetic procedures. The following equation illustrates the general enolate anion transformation, with the acidic alpha-hydrogen colored red. The resulting ambident anion is stabilized by charge delocalization, and may react with electrophiles at both carbon and oxygen. . The bond from the alpha carbon to the acidic alpha-hydrogen must be oriented 90º to the plane of the carbonyl group, or parallel to the

pi-electron system (colored magenta here). The ideal overlap occurs with a 0° dihedral angle between this bond and the pi-orbital, as shown.

Enolate Anion Formation
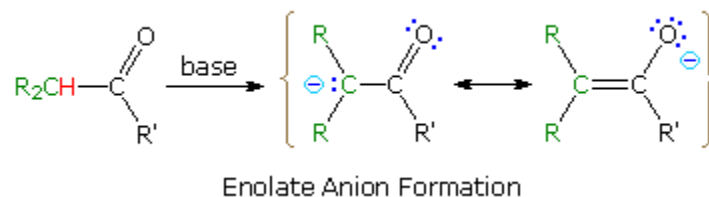
An increase in the acidity of carbon acids activated by two carbonyl groups is well known, and is illustrated by the two beta-dicarbonyl compounds on the left side of the diagram. In such cases the acidic C-H unit may be oriented perpendicular to both carbonyl groups, and the resulting planar anion is stabilized by additional charge delocalization (over both oxygens and the central carbon). In the case of the bicyclic diketone on the right, the C-H bond nearly eclipses the two carbonyl C-O bonds, resulting in a dihedral angle with the pi-electron systems of roughly 90°. Consequently, the acidity of this hydrogen is similar to that of the hydrogens of an alkane or cycloalkane. It should

also be apparent that if an enolate anion were to be formed to the bridgehead carbon, the double bond would be prohibited by Bredt's rule.

5. Kinetic Acidity

The most common acid-base terminology, pK_a , reflects an equilibrium acidity, extrapolated or normalized to water. In the following equation a base, $B:^{(-)} M^{(+)}$, abstracts a proton from an acid, H-A, to form a conjugate acid - base pair ($A:^{(-)} M^{(+)}$ & B-H). The rate of the forward proton abstraction is k_f , and the reverse rate of proton transfer is k_r. This kind of equilibrium is usually characterized by an equilibrium constant, K_{eq}, which is the ratio of the rate constants (k_f / k_r). If H-A is a weaker acid than H-B the equilibrium will lie to the left, and K_{eq} will be smaller than 1.

$$H\text{-}A \; + \; B:^{(-)} M^{(+)} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} A:^{(-)} M^{(+)} \; + \; B\text{-}H$$

(acid¹)   (base¹)   (base²)   (acid²)
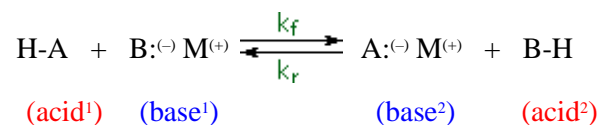
In cases where H-A is very much weaker than H-B, K_{eq} may be too small to measure, but it may be possible to determine the rate of the forward proton abstraction under certain circumstances. If an isotopically labled conjugate acid of the base is used as a solvent for the reaction (B-D in the following equations), then any proton abstraction that occurs will

be marked by conversion of H-A to D-A. The green shaded top equation shows the initial loss of the proton, and the second equation describes the rapid deuteration of the intermediate conjugate base, A:$^{(-)}$. As these reactions proceed, the H-A reactant will be increasingly labled as D-A, and the rate of isotope exchange will indicate the **kinetic acidity** of H-A. It is assumed that kinetic acidity is roughly proportional to equilibrium (thermodynamic) acidity, but this is not always true.

$$\text{solvent} = \text{B-D}$$

$$\text{H-A} \ + \ \text{B:}^{(-)} \text{M}^{(+)} \ \rightleftharpoons \ \text{A:}^{(-)} \text{M}^{(+)} \ + \ \text{B-H}$$

$$\text{D-A} \ + \ \text{B:}^{(-)} \text{M}^{(+)} \ \rightleftharpoons \ \text{A:}^{(-)} \text{M}^{(+)} \ + \ \text{B-D}$$
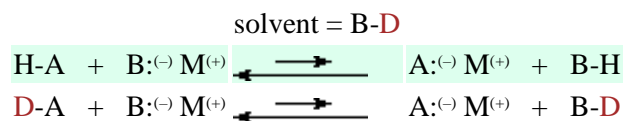
The following diagram provides an instructive example of these principles. The first equation, in the yellow shaded box, provides important information about heavy water (deuterium oxide), which will be used as a solvent for our experiment. Heavy water is similar to water in many respects, but is 10% more dense and a ten-fold weaker acid. A 1 molar concentration of sodium deuteroxide will serve as the base, and an equimolar quantity of 3,3-dimethyl-1-butyne will serve as the weak acid. The most acidic hydrogen in this hydrocarbon (colored red) is at C-1. In practice, we would need to use a co-solvent to completely dissolve the hydrocarbon in the heavy water, but this has been omitted in order to simplify the discussion.

The second equation describes the essential changes expected on combining these reactants in the heavy water solvent. Since the terminal alkyne is a much weaker acid than heavy water, acid-base equilibria do not favor its conjugate base. Nevertheless, if the

acetylide anion is formed, even in low concentration, it should react quickly by abstracting a deuterium from a neighboring deuterium oxide molecule. The result would be an observable exchange of deuterium for hydrogen, testifying that an acid-base reaction has occurred.

Solvent acidity $2 D_2O \rightleftharpoons D_3\overset{\oplus}{O} + \overset{\ominus}{D}O$ $K_a = 1.8 \times 10^{-17}$ $pK_a = 16.7$

$(CH_3)_3C-C\equiv C-H$ + $\overset{\ominus}{D}O$ $\overset{\oplus}{N}a$ $\xrightarrow{D_2O \text{ solvent}}$ $(CH_3)_3C-C\equiv \overset{\ominus}{C}:$ $\overset{\oplus}{N}a$ $\xrightarrow{D_2O \text{ solvent}}$ $(CH_3)_3C-C\equiv C-D$
$pK_a \approx 48$ $pK_a = 25$ + DOH + $\overset{\ominus}{D}O$ $\overset{\oplus}{N}a$

$R-C\equiv C-H$ + $\overset{\ominus}{D}O$ $\overset{\oplus}{N}a$ $\underset{k_r}{\overset{k_f}{\rightleftharpoons}}$ $R-C\equiv \overset{\ominus}{C}:$ $\overset{\oplus}{N}a$ + DOH $K_{eq} = \dfrac{[R-C\equiv C:Na][D_2O]}{[R-C\equiv C-H][DO Na]}$
[1 molar] [1 molar]

$K_{eq} \approx \dfrac{10^{-25}}{10^{-17}} = 10^{-8}$ At equilibrium the concentration of $R-C\equiv C:$ will be about 2×10^{-10} M.
$[D_2O] = 55.2$ M

The rate of proton abstraction, k_f, can be estimated from the equation $\left\{ \dfrac{k_f}{k_r} = K_{eq} \right.$ assuming that k_r is very fast (nearly diffusion controlled).

If $\dfrac{k_f}{10^{10}} = 10^{-8}$, k_f will be roughly 100 M s^{-1}.

Clearly, exchange of deuterium for hydrogen will be relatively fast - less than a minute at 25° C.

The green shaded box contains equations that help us to interpret the experimental results. In order to evaluate the equilibrium acidity of the substrate, we would need to

measure the equilibrium constant K_{eq} for the initial acid-base equilibrium, shown at the top of the shaded box. Since we know the K_a 's of 3,3-dimethyl-1-butyne and heavy water, we can estimate K_{eq} by dividing the former (10^{-25}) by the latter (10^{-17}). This calculation reveals a K_{eq} that would be difficult to measure directly because of its small magnitude (10^{-8}). Indeed, the equilibrium concentration of acetylide anion is estimated to be only $2*!0^{-10}$ M.

If we examine this experiment from the viewpoint of <u>kinetics</u>, easily observable evidence of terminal alkyne acidity is obtained. The last three rows of equations in the green shaded box make this clear. Since K_{eq} is the ratio of forward and reverse rate constants, it is possible to draw conclusions about the rate of terminal proton abstraction from the alkyne. This leads to the conclusion that reasonably rapid hydrogen-deuterium exchange will occur, even though the acetylide anion is never present in concentrations exceeding 10^{-9} M.

This example also demonstrates the limits of the isotope exchange approach. The 3,3-dimethyl-1-butyne substrate also has nine other hydrogen atoms (colored orange) that do not exchange with deuterium under these conditions. We know that these hydrogens are much less acidic (K_a ca. 10^{-48}), and it is interesting to consider their potential participation in acid-base reactions by the previous analysis. The estimated K_{eq} for such carbanion formation is ca. 10^{-30}, taking into account the nine-fold increase in concentration. This implies a concentration of one carbanion in every 10^9 liters of solution. The kinetic analysis is equally discouraging. The forward rate constant is

estimated to be 10^{-20} Ms^{-1}. The time required to exchange half these hydrogens for deuterium would therefore be about 10^{10} centuries!
In order to study the kinetic acidity of extremely weak acids (pK$_a$'s = 30 to 50) it is necessary to use much stronger bases, which of course have much weaker conjugate acids. Amide anions (pK$_a$'s = 26 to 36) have been used for this purpose.

By comparing the rates of hydrogen exchange for different compounds under identical conditions, tables of relative kinetic acidities may be assembled. An interesting example of such a study has been reported for a group of nitroalkanes having acidic α-hydrogens. Compared with the terminal alkyne discussed above, such nitroalkanes are relatively strong C-H acids. Removal of an α-hydrogen by a base generates a conjugate base called an **aci-anion**, as shown here.

$$R_2CH\text{-}NO_2 \ + \ B{:}^{(-)} \ M^{(+)} \ \rightleftharpoons \ R_2C{=}NO_2{}^{(-)} \ M^{(+)} \ + \ B\text{-}H$$

nitro compound   aci-conjugate base
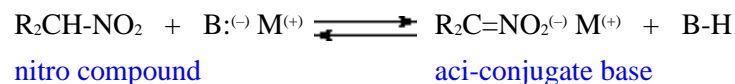
Since the nitroalkanes used in this study are stronger acids than water, the kinetic exchange experiments must be conducted under milder conditions than those used for the terminal alkyne. This is achieved by using smaller base concentrations and lowering the temperature of the exchange reaction. Accurate pK$_a$'s of 2-nitropropane, nitroethane and nitromethane may be measured directly in aqueous

Compound	pK$_a$	Relative Rate of Exchange
CH$_3$NO$_2$	10.2	120
CH$_3$CH$_2$NO$_2$	8.5	20
(CH$_3$)$_2$CHNO$_2$	7.7	1.0

solution. These kinetic and equilibrium acidities are listed in the table on the right. Note that for these three compounds, kinetic acidity changes in an opposite fashion to equilibrium acidity. The kinetic order seems to reflect steric hindrance and carbanion stability; whereas, the equilibria favor increased substitution of the aci-anion double bond.

Base-catalyzed isotope exchange studies of compounds incorporating more than one set of acidic hydrogens provides additional insight concerning the creation and use of nucleophilic conjugate bases. Ketones provide many examples of regioisomeric enolate base formation, and the following diagram shows two such cases. As noted in the nitroalkane study, hydrogens on an α-methyl group are exchanged more rapidly than those on more substituted α-carbon atoms. The equations in the diagram show only the initial product from a single exchange. These products have additional α-hydrogens which are also exchanged by subsequent reactions of this kind, so that complete replacement of all α-hydrogens by deuterium takes place in a short time.
The relative stability of the resulting enolates increases with substitution of the enolate double bond. Equations showing the equilibrium concentrations of these isomeric enolates will be displayed by clicking theToggle Equations button. In order to determine

enolate anion equilibria for these ketones, the bulky strong base sodium hexamethyldisilazide ($pK_a = 26$) was used.
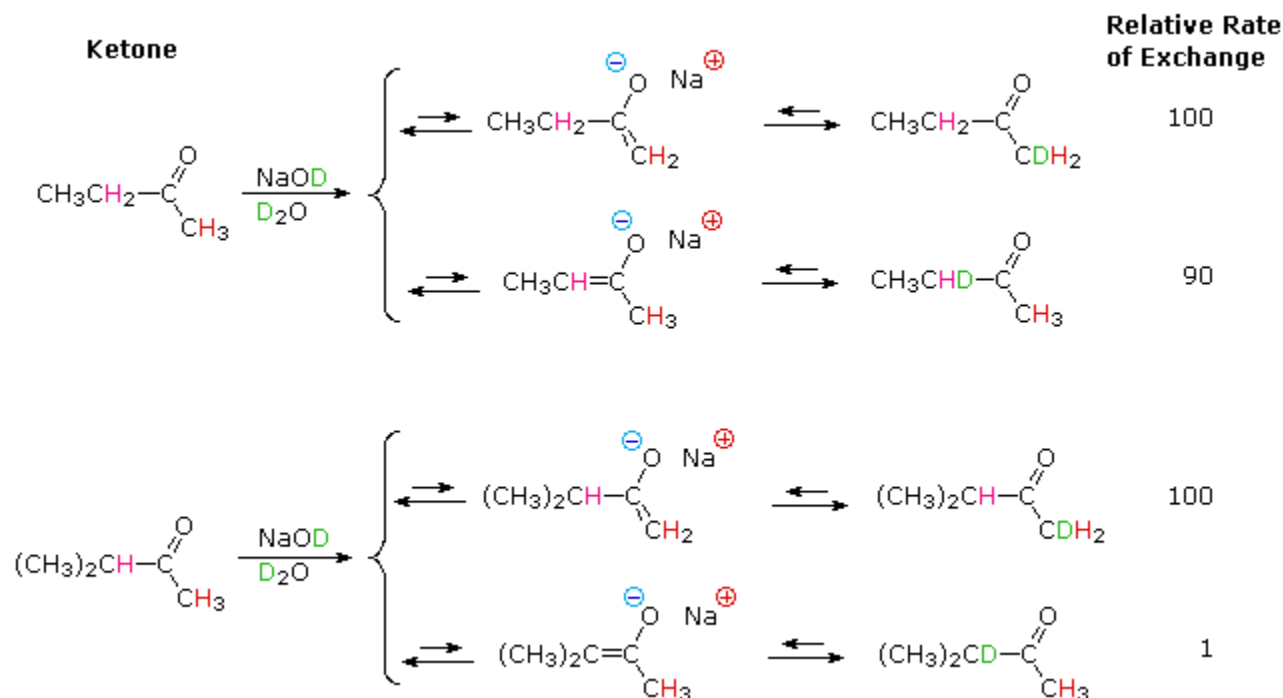
By clicking the <u>Toggle Equations</u> button a second time, the relative rates of α-hydrogen exchange for some susbstituted cyclohexanones will be displayed above. Once again, less substituted α-carbons exchange more rapidly, but more highly substituted enolates are found to predominate under equilibrium conditions. A third click of the <u>Toggle Equations</u> button will display an energy profile for the 2-methylcyclohexanone case,

which should clarify the distinction between kinetic and equilibrium acidity. Two other examples are also shown. These displays may be cycled repeatedly.

Most carbon acids yield conjugate bases that are stabilized by charge delocalization onto neighboring heteroatoms. This resonance stabilization requires significant structural reorganization of the initial compound, which in turn imposes an energy barrier that retards the rate of proton abstraction. For example, the alpha-carbon of a ketone or ester must undergo rehybridization as the enolate anion is formed. The stereoelectronic demands of this change were described above, and it is not surprising that enolate anion formation is much slower than equivalent proton transfers between alcohols and other hydroxylic compounds. Deprotonation rates of phenol and nitromethane, compounds with nearly identical pK$_a$'s (10.0), provide an instructive example of this structural reorganization factor. The acidic proton in phenol is bound to oxygen, so deprotonation requires little structure change and is very fast. Nitromethane is a carbon acid. Deprotonation to an aci-anion involves considerable structural change, and is a million times slower than phenolate formation. These structural changes are illustrated in the following diagram.

Phenol

minor structural reorganization

Nitromethane

major structural reorganization
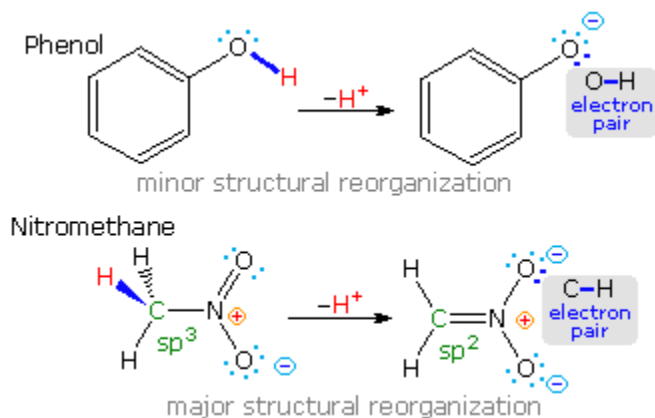
Note that the O-H electron pair in phenol remains largely on oxygen in the corresponding conjugate base, whereas the C-H electron pair in nitromethane is predominantly shifted to oxygen in its conjugate base (colored blue).

The trends outlined here are a bit oversimplified, since solvent and cation influences have been ignored. For a discussion of these factors, and practical applications of enolate anion intermediates in synthesisClick Here.

Hypohalous Acids

The most common hypohalous acids, HOCl and HOBr, are relatively weak acids ($pK_a = 7.5$ & 8.6 respectively) that are only stable in solution. These acids and their ester derivatives are formed reversibly when the corresponding halogens are dissolved in hydroxylic solvents.

$$X_2 + H_2O \rightleftharpoons HOX + HX$$

$$X_2 + ROH \rightleftharpoons ROX + HX$$
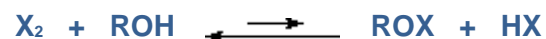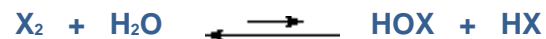
For a solution of chlorine in water the equilibrium constant is only about $5 * 10^{-4}$. The concentration of HOCl may be increased by adding silver oxide ($Ag^{(+)}$ reduces the chloride ion concentration and the oxide increases the pH), but this is not a common procedure. As a rule, these reagents are prepared by hydrolysis of N-chloro and N-bromo precursors immediately prior to their use.
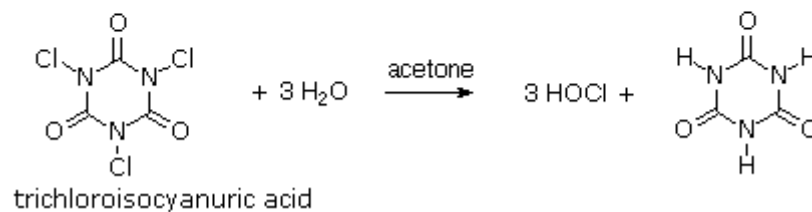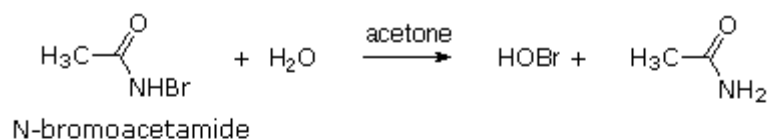
N-bromoacetamide

trichloroisocyanuric acid

This page has acidity tables for monoprotic acids and polyprotic acids.

Ionization Constants of Inorganic Monoprotic Acids

Common Name	Formula	Acidity Constant	pK$_a$
perchloric acid	$HClO_4$	*ca.* 10^{10}	*ca.* -10
hydrogen iodide	HI	*ca.* 10^9	*ca.* -9
hydrogen bromide	HBr	*ca.* 10^9	*ca.* -9
hydrogen chloride	HCl	*ca.* 10^7	*ca.* -7
nitric acid	HNO_3	*ca.* 200	*ca.* -2
thiocyanic acid	HSCN	70	-1.85
hydronium ion	H_3O^+	55	-1.74
chloric acid	$HClO_3$	10	-1.0
iodic acid	HIO_3	0.18	0.75
hypophosphorous acid	$H_2P(O)OH$	10^{-2}	2.0
hydrogen fluoride	HF	$6.6 * 10^{-4}$	3.2
nitrous acid	HNO_2	$5.0 * 10^{-4}$	3.3
cyanic acid	HOCN	$3.54 * 10^{-4}$	3.45
hydrazoic acid	HN_3	$2.37 * 10^{-5}$	4.63
hypochlorous acid	HOCl	$2.95 * 10^{-8}$	7.53
hypobromous acid	HOBr	$2.3 * 10^{-9}$	8.65
hydrocyanic acid	HCN	$5.8 * 10^{-10}$	9.25

ammonium	NH_4^+	$5.8 * 10^{-10}$	9.25
hypoiodous acid	HOI	10^{-10}	10
hydrogen peroxide	H_2O_2	$2.5 * 10^{-12}$	11.6
water	H_2O	$1.82 * 10^{-16}$	15.74
heavy water	D_2O	$3.5 * 10^{-17}$	16.55
ammonia	NH_3	*ca.* 10^{-34}	*ca.* 34

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Ionization Constants of Inorganic Polyprotic Acids

Common Name	Formula	Acidity Constant	pK$_a$
sulfuric acid	H_2SO_4 HSO_4^{-1}	$K_1 = 2.4 * 10^6$ $K_2 = 1.0 * 10^{-2}$	-6.62 1.99
chromic acid	H_2CrO_4 $HCrO_4^{-1}$	$K_1 = 3.55$ $K_2 = 3.36 * 10^{-7}$	-0.55 6.47
sulfurous acid	H_2SO_3 HSO_3^{-1}	$K_1 = 1.71 * 10^{-2}$ $K_2 = 5.98 * 10^{-8}$	1.77 7.22
phosphoric acid	H_3PO_4 $H_2PO_4^{-1}$ HPO_4^{-2}	$K_1 = 7.1 * 10^{-3}$ $K_2 = 6.2 * 10^{-8}$ $K_3 = 4.6 * 10^{-13}$	2.15 7.21 12.34
phosphorous acid	H_3PO_3 $H_2PO_3^{-1}$	$K_1 = 1.6 * 10^{-2}$ $K_2 = 6.3 * 10^{-7}$	1.8 6.2

pyrophosphoric acid	$H_4P_2O_7$ $H_3P_2O_7^{-1}$ $H_2P_2O_7^{-2}$ $HP_2O_7^{-3}$	$K_1 = 3 * 10^{-2}$ $K_2 = 4.4 * 10^{-3}$ $K_3 = 2.5 * 10^{-7}$ $K_4 = 5.6 * 10^{-10}$	1.52 2.36 6.60 9.25
carbonic acid	H_2CO_3 HCO_3^{-1}	$K_1 = 4.35 * 10^{-7}$ $K_2 = 4.69 * 10^{-11}$	6.36 10.33
hydrogen sulfide	H_2S HS^{-1}	$K_1 = 9 * 10^{-8}$ $K_2 = ca.10^{-15}$	6.97 *ca.*15
boric acid	H_3BO_3 $H_2BO_3^{-1}$ HBO_3^{-2}	$K_1 = 7.2 * 10^{-10}$ $K_2 = 1.8 * 10^{-13}$ $K_3 = 1.6 * 10^{-14}$	9.14 12.7 13.8

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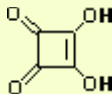
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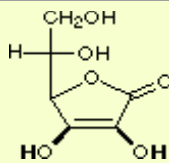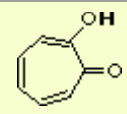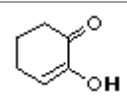
This page has acidity tables for heteroatom organic acids and carbon acids.
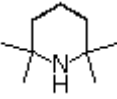
Because of the very large range of acid strengths (greater than 10^{40}), a logarithmic scale of acidity (pK_a) is normally employed. Stronger acids have smaller or more negative pK_a values than do weaker acids. A discussion of acid-base terminology is available **here. The pK_a values given here are extrapolated for water at 25 ºC.**

Other collections of pK_a values include those compiled by **Prof. D.A. Evans (Harvard)**; a large list compiled by **W.P Jencks & F.H. Westheimer**, presented by R. Williams (Penn. State); and a collection of pK_a measurements in **DMSO solution**, compiled by Prof. F.G.Bordwell and presented by Prof. H.J.Reich (Wisconsin).

Ionization Constants of Heteroatom Organic Acids

Common Name	Formula	Acidity Constant	pKa
trifluoromethanesulfonic acid	CF_3SO_3H	*ca.* 10^{13}	*ca.* -13
benzenesulfonic acid	$C_6H_5SO_3H$	*ca.* 10^3	*ca.* -2.5
methanesulfonic acid	CH_3SO_3H	*ca.* $3 * 10^2$	*ca.* -2.0
trifluoroacetic acid	CF_3CO_2H	1.0	0.0
picric acid	$(O_2N)_3C_6H_2OH$	0.5	0.3
squaric acid		$K_1 = 0.33$ $K_2 = 3.3 * 10^{-4}$	1.5 3.5
trichloroacetic acid	CCl_3CO_2H	0.23	0.77
oxalic acid	$(CO_2H)_2$	$K_1 = 6.5 * 10^{-2}$ $K_2 = 6.1 * 10^{-5}$	1.2 4.2
dichloroacetic acid	$CHCl_2CO_2H$	$5.5 * 10^{-2}$	1.25
fluoroacetic acid	FCH_2CO_2H	$2.5 * 10^{-3}$	2.6
chloroacetic acid	$ClCH_2CO_2H$	$1.36 * 10^{-3}$	2.87
citric acid	$C(OH)(CH_2CO_2H)_2CO_2H$	$K_1 = 7.4 * 10^{-4}$ $K_2 = 1.7 * 10^{-5}$ $K_3 = 4.0 * 10^{-7}$	3.13 4.76 6.40
formic acid	HCO_2H	$1.77 * 10^{-4}$	3.75
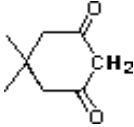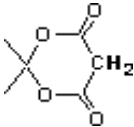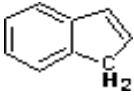
ascorbic acid		$K_1 = 6.7 * 10^{-5}$ $K_2 = 2.5 * 10^{-12}$	4.17 11.6
benzoic acid	$C_6H_5CO_2H$	$6.3 * 10^{-5}$	4.20
acetic acid	CH_3CO_2H	$1.77 * 10^{-5}$	4.75
Thiophenol	C_6H_5SH	$2.5 * 10^{-7}$	6.6
Tropolone		$2.0 * 10^{-7}$	6.7
p-nitrophenol	$O_2NC_6H_4OH$	$5.7 * 10^{-8}$	7.2
peracetic acid	CH_3COO_2H	$5.7 * 10^{-9}$	8.2
Succinimide	$(CH_2CO)_2NH$	$2.5 * 10^{-10}$	9.6
Phenol	C_6H_5OH	10^{-10}	10.0
chloral hydrate	$CCl_3CH(OH)_2$	10^{-10}	10.0
Benzenesulfonamide	$C_6H_5SO_2NH_2$	$8 * 10^{-11}$	10.1
2-hydroxy-2-cyclohexenone		$5.0 * 10^{-11}$	10.3
Ethanethiol	C_2H_5SH	$2.5 * 10^{-11}$	10.6
Acetoxime	$(CH_3)_2C=NOH$	$6 * 10^{-13}$	12.2

2,2,2-trifluoroethanol	CF_3CH_2OH	$4 * 10^{-13}$	12.4
Imidazole	$C_3H_3N_2H$	$3.3 * 10^{-15}$	14.5
Pyrrole	C_4H_4NH	10^{-15}	15
Ethanol	C_2H_5OH	10^{-16}	16
1°-amides	$RCONH_2$	10^{-17}	17
p-nitroaniline	$O_2NC_6H_4NH_2$	$3.3 * 10^{-19}$	18.5
t-butanol	$(CH_3)_3COH$	10^{-19}	19
Aniline	$C_6H_5NH_2$	10^{-27}	27
1,1,1,3,3,3,-hexamethyldisilazane	$[(CH_3)_3Si]_2NH$	10^{-30}	30
Pyrrolidine	C_4H_8NH	10^{-32}	32
Diisopropylamine	$[(CH_3)_2CH]_2NH$	$1.9 * 10^{-36}$	35.7
Tetramethylpiperidine		10^{-37}	37

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Ionization Constants of Carbon Acids

Common Name	Formula	Acidity Constant	pKa
tricyanomethane	$CH(CN)_3$	10^5	-5

Dinitromethane	$CH_2(NO_2)_2$	$2.5 * 10^{-4}$	3.6
5,5-dimethyl-1,3-cyclohexadione		$1.6 * 10^{-5}$	4.8
Malonaldehyde	$CH_2(CHO)_2$	10^{-5}	5.0
Meldrum's acid		$8 * 10^{-6}$	5.1
2,4-pentanedione	$CH_2(COCH_3)_2$	$1.26 * 10^{-9}$	8.9
hydrocyanic acid	HCN	$6.3 * 10^{-10}$	9.2
Nitromethane	CH_3NO_2	$6.3 * 10^{-11}$	10.2
Malononitrile	$CH_2(CN)_2$	10^{-11}	11.0
ethyl acetoacetate	$CH_3COCH_2CO_2C_2H_5$	10^{-11}	11.0
bis(methylsulfonyl)methane	$CH_2(SO_2CH_3)_2$	$2.0 * 10^{-13}$	12.7
diethyl malonate	$CH_2(CO_2C_2H_5)_2$	$3.2 * 10^{-14}$	13.5
Cyclopentadiene		10^{-16}	16.0
Phenylacetylene	$C_6H_5C \equiv CH$	10^{-19}	19.0
Indene		10^{-20}	20

tris(phenylthio)methane	$(C_6H_5S)_3CH$	10^{-23}	23
methyl ketones	$RCOCH_3$	10^{-25}	25
Methylsulfones	RSO_2CH_3	10^{-25}	25
alkyl esters	$RCH_2CO_2C_2H_5$	10^{-25}	25
Nitriles	RCH_2CN	10^{-25}	25
Acetylene	$HC{\equiv}CH$	10^{-25}	25
Methylsulfoxides	$RSOCH_3$	10^{-30}	30
1,3-dithiane	$(CH_2)_3S_2CH_2$	10^{-31}	31
Triphenylmethane	$(C_6H_5)_3CH$	$3.2 * 10^{-32}$	31.5
Diphenylmethane	$(C_6H_5)_2CH_2$	$3.2 * 10^{-34}$	33.5
Toluene	$C_6H_5CH_3$	10^{-40}	40
Benzene	C_6H_6	10^{-43}	43
Ethane	C_2H_4	10^{-44}	44
Cyclopropane	C_3H_6	10^{-46}	46
Ethane	C_2H_6	10^{-48}	48

Basicity

The most common notation for reporting relative base strengths is in terms of the pK_a's of the corresponding conjugate acids (these conjugate acids are often called "onium" cations). The following equation shows the equilibrium involved in this relationship. Note that strong bases will have weakly acidic conjugate acids, so the pK_a is proportional to the base strength of the base.

$$B–H^{(+)} \quad + \quad Sol: \quad \rightleftharpoons \quad B: \quad + \quad Sol–H^{(+)}$$

conjugate acid   solvent   a base   conjugate acid
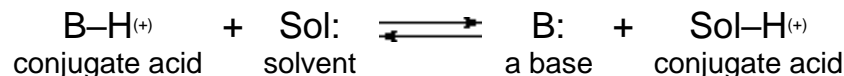
The previously defined factors that influenced acidity may now be reexamined for this new equilibrium.

> **1.** Ions are present on both sides of the equation. Consequently, differences in the solvent dielectric constant should be a relatively unimportant factor.
> **2.** The base and solvent conjugate acid cations are both stabilized by solvation. This will be a critical factor, and is related to solvent basicity.
> **3.** There are no anions in the above equation; however charge neutralization requires a counter anion. Since the same anion will be present on both sides of the equation, its influence on this equilibrium will be canceled.

The following table gives pK_a values for some commonly used nitrogen bases, some structures for which are shown to its right. In the triethylamine and DABCO examples at

the top of the table, the cationic charge is relatively localized on a single nitrogen atom. The charge in lutidine may be delocalized onto ring carbons at the cost of aromatic stabilization. The last three examples are compounds in which the charge is delocalized by resonance (protonation occurs at the light blue nitrogen) or internal hydrogen bonding (the proton sponge).

In contrast to the earlier examples of acid pK_as, the values for these ammonium cations are nearly identical in water and DMSO solvents. Indeed, the fact that most of the DMSO pK_as are a bit lower than their water counterparts suggests that DMSO is slightly more basic than water. In acetonitrile all the pK_a values are about 10 units higher than the DMSO values.

pKₐs for Some Ammonium Species in Different Solvents			
Ammonium Cation	**H₂O**	**DMSO**	**CH₃CN**
$(C_2H_5)_3N{-}H^{(+)}$	10.75	9.0	18.5
DABCO–H$^{(+)}$	8.8	8.9	18.3
Lutidine–H$^{(+)}$	6.75	4.45	14
DBU–H$^{(+)}$	12	12	24.3
$[(CH_3)_2N]_2C{=}NR{-}H^{(+)}$	13.8	13.6	23.3
Proton Sponge–H$^{(+)}$	12.3	7.5	ca. 18
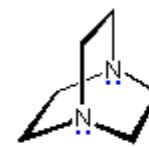
DABCO
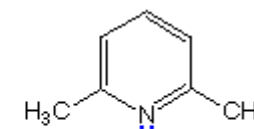
Lutidine
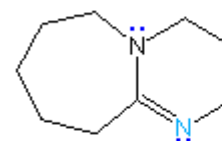
DBU
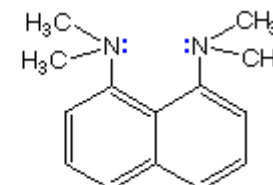
Proton Sponge

The influence of solvent on acidity and basicity noted above may cause unexpected changes in simple acid-base equilibria. If acetic acid and triethyl amine are mixed

together in water, a rapid proton transfer takes place to give nearly quantitative formation of triethyl ammonium acetate. The conjugate acids differ in strength by 10^6 and the weakest is favored at equilibrium. When the same two compounds are combined in DMSO solution there is negligible proton transfer, since acetic acid is now over 10^3 times weaker an acid than the triethyl ammonium cation.

Nonionic Superbases

The strongest bases available to organic chemists are alkali metal alkoxide salts, such as potassium tert.-butoxide, alkali metal alkyls, such as n-butyl lithium, and amide salts of alkali metals, such as LDA. These powerful bases are all potential nucleophiles (some more than others) and have partially ionic bonds to the metal. Recently, a new class of non-metallic, poorly nucleophilic, neutral bases have been prepared and studied. Some examples are shown in the following diagram.

The basic site in the Verkade base is the phosphorous atom, the conjugate acid being stabilized by transannular bonding to nitrogen. The strength of these bases may be modified by substituents on the flanking nitrogens. The Schwesinger phosphazene bases increase their strength as additional phosphazene units are added in conjugation with the

basic site (the light blue nitrogen atom). All the pK$_a$s for these bases are measured in acetonitrile.

A Verkade Base

pK$_a$ = 29.6

P$_1$ Base

pK$_a$ = 26.9

P$_2$ Base

pK$_a$ = 33.5

P$_4$ Base

pK$_a$ = 41.4

Schwesinger Phosphazene Bases
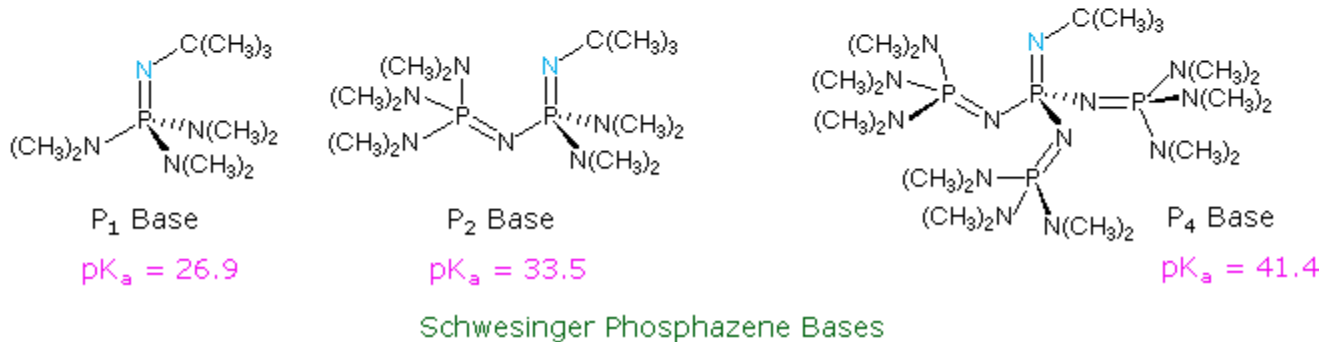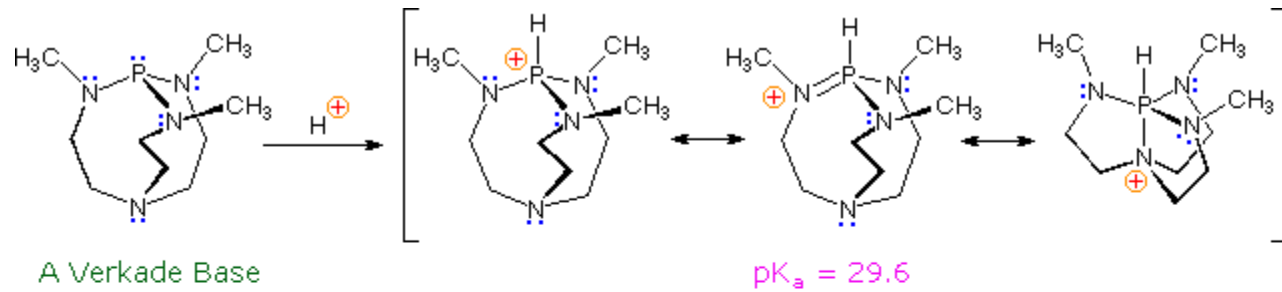
Nucleophilicity and Basicity Factors in Organic Reactions

General Principals

Recall the definitions of electrophile and nucleophile:

Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Definitions and examples of acids and bases were provided earlier in this text, and should be reviewed if the reader is not comfortable with this subject.

Many functional groups have weakly electrophilic carbon atoms (colored red in the following examples). These include *alkyl halides* and *sulfonate esters* {**C**-X and **C**-OSO$_2$R}, as well as carbonyl compounds such as *aldehydes* and *ketones* {**C**=O}. These electrophilic functions may react with nucleophiles (bases) in two distinct ways:

(i) Substitution or addition at carbon (this reflects nucleophilicity)
(ii) β-Elimination or enolate anion formation (this reflects basicity)

Because these electrophilic reactants are weak, such reactions normally require strong nucleophiles or bases to proceed. However, if a preliminary ionization to a strongly electrophilic carbocation occurs: [C-X——> C$^{(+)}$ + X$^{(-)}$]
or if the carbonyl group is converted to its more electrophilic conjugate acid: [C=O + A$^{(+)}$ ——> $^{(+)}$C-O-A]
then reactions with much weaker nucleophiles or bases may take place.
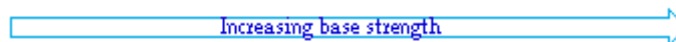
Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it.
Basicity refers to the ability of a base to accept a **proton**. Basicity may be related to the pK$_a$ of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and *vice versa*. The range of basicities included in the following table is remarkable, covering over fifty powers of ten!
In an acid-base equilibrium the weakest acid and the weakest base will predominate (they will necessarily be on the same side of the equilibrium). Learning the pK$_a$ values for common compounds provides a useful foundation on which to build an understanding of acid-base factors in reaction mechanisms.

Base	I $^{(-)}$	Cl $^{(-)}$	H$_2$O	CH$_3$CO$_2$$^{(-)}$	RS$^{(-)}$	CN$^{(-)}$	RO$^{(-)}$	NH$_2$$^{(-)}$	CH$_3$$^{(-)}$
Conj. Acid	HI	HCl	H$_3$O$^{(+)}$	CH$_3$CO$_2$H	RSH	HCN	ROH	NH$_3$	CH$_4$
pK$_a$	-9	-7	-1.7	4.8	8	9.1	16	33	48

$$\text{Increasing base strength} \longrightarrow$$

Nucleophilicity is a more complex property. It commonly refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH_3-Br. Thus the nucleophilicity of the Nu:$^{(-)}$ reactant in the following substitution reaction varies as shown in the chart below:

$$CH_3-Br + Nu:^{\ominus} \xrightarrow{CH_3OH \ soln} CH_3-Nu + Br:^{\ominus}$$

Nucleophilicity: $CH_3CO_2^{(-)} < Cl^{(-)} < Br^{(-)} < N_3^{(-)} < CH_3O^{(-)} < CN^{(-)} < I^{(-)} < CH_3S^{(-)}$

$$\text{Increasing nucleophile strength} \longrightarrow$$
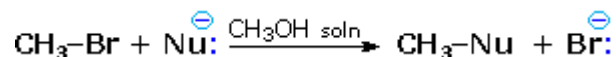
The reactivity range encompassed by these reagents is over 5,000 fold, thiolate being the most reactive. Clearly, there are significant differences between these nucleophilicities and the basicities discussed above.

Some useful trends have been documented:
   (i) For a given element, negatively charged species are more nucleophilic (and basic) than are equivalent neutral species.
   (ii) For a given period of the periodic table, nucleophilicity (and basicity) decreases on moving from left to right.

(iii) For a given group of the periodic table, nucleophilicity increases from top to bottom (*i.e.* with increasing size), although there is a solvent dependence due to hydrogen bonding. *Basicity varies in the opposite manner.*

For two or more molecules incorporating nucleophilic atoms of the same kind and charge, the stronger base is usually the stronger nucleophile. Thus, 2,2,2-trifluroethoxide (pK$_a$ 12) is a weaker base and nucleophile than ethoxide (pK$_a$ 16). A notable exception to this rule occurs when a vicinal (adjacent) atom carries a non-bonding electron pair. Two common examples of this exception, called **the alpha effect**, are hydroxide ion (pK$_a$ 15.7) compared with hydroperoxide ion (pK$_a$ 11.6), and ammonia (pK$_a$ 9.3) compared with hydrazine (pK$_a$ 8.0). In each of these pairs the weaker base is the stronger nucleophile.

Solvent Effects

Solvation of nucleophilic anions markedly influences their reactivity. The nucleophilicities cited above were obtained from reactions in methanol solution. Polar, protic solvents such as water and alcohols solvate anions by hydrogen bonding interactions, as shown in the diagram on the right. These solvated species are more stable and less reactive than the unsolvated "naked" anions. Polar, aprotic solvents such as DMSO (dimethyl sulfoxide), DMF (dimethylformamide) and acetonitrile do not solvate anions nearly as well as methanol, but provide good solvation of the accompanying cations. Consequently, most of the nucleophiles discussed here react more rapidly in solutions prepared from these solvents. These solvent effects are more pronounced for small basic anions than for large weakly basic anions. Thus, for reaction in DMSO solution we observe the following reactivity order:

Nucleophilicity: $I^{(-)} <\ Br^{(-)} <\ Cl^{(-)} \sim N_3^{(-)} <\ CH_3CO_2^{(-)} <\ CN^{(-)} \sim CH_3S^{(-)} <\ CH_3O^{(-)}$
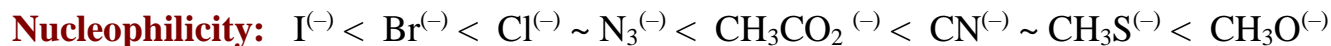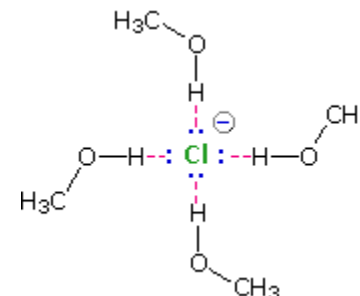
Increasing nucleophile strength →

Note that this order is roughly the order of increasing basicity (see above).

Basicity

The basicity of oxygen, nitrogen, sulfur and phosphorus compounds or ions may be treated in an analogous fashion. Thus, we may write base-acid equilibria, which define a K_b and a corresponding pK_b. However, a more common procedure is to report the acidities of the conjugate acids of the bases (these conjugate acids are often "onium" cations). The pK_a's reported for bases in this system are proportional to the base strength of the base. A useful rule here is: **$pK_a + pK_b = 14.$**
We see this relationship in the following two equilibria:
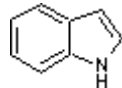
Acid-Base Reaction		Conjugate Acids	Conjugate Bases	K	pK
$NH_3 + H_2O$ ⇌ $NH_4^{(+)} + OH^{(-)}$		$NH_4^{(+)}$ H_2O	NH_3 $OH^{(-)}$	$K_b = 1.8*10^{-5}$	$pK_b = 4.74$
$NH_4^{(+)} + H_2O$ ⇌ $H_3O^{(+)} + NH_3$		$NH_4^{(+)}$ $H_3O^{(+)}$	NH_3 H_2O	$K_a = 5.5*10^{-10}$	$pK_a = 9.25$
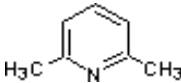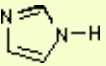
Tables of pK_a values for inorganic and organic acids (and bases) are available in many reference books, and may be examined here by clicking on the appropriate link:
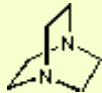
A common method for evaluating the strength of bases is to report the acidities of the conjugate acids of the bases (these conjugate acids are often "onium" cations). The resulting pK_a's are proportional to the base strength of the base.

A useful rule is: $pK_a + pK_b = 14$.

Ionization Constants of B-H$^\oplus$ Onium Acids			
Name of Base (B)	**Formula of B**	**K_a (BH$^+$)**	**pK_a**
aliphatic nitro cpd.	$R\text{-}NO_2$	*ca.* 10^{12}	*ca.* -12
aryl nitro cpd.	$C_6H_5NO_2$	*ca.* 10^{11}	*ca.* -11
nitriles	$R\text{-}C\equiv N$	*ca.* 10^{10}	*ca.* -10
aliphatic aldehydes	$R\text{-}CH=O$	*ca.* 10^8	*ca.* -8
aryl aldehydes	$C_6H_5CH=O$	*ca.* 10^7	*ca.* -7
aliphatic ketones	$R_2C=O$	*ca.* 10^7	*ca.* -7

esters	$R\text{-}CO_2R'$	*ca.* $3 * 10^6$	*ca.* -6.5
aryl alkyl ethers	$C_6H_5OCH_3$	*ca.* $3 * 10^6$	*ca.* -6.5
phenols	C_6H_5OH	*ca.* $3 * 10^6$	*ca.* -6.5
aryl ketones	$C_6H_5COCH_3$	*ca.* 10^6	*ca.* -6
carboxylic acids	$R\text{-}CO_2H$	*ca.* 10^6	*ca.* -6
sulfides	RSR	*ca.* 10^5	*ca.* -5
diethyl ether	$C_2H_5OC_2H_5$	*ca.* $3 * 10^3$	*ca.* -3.5
dioxane	$O(CH_2CH_2)_2O$	*ca.* 10^3	*ca.* -3
pyran	$(CH_2)_5O$	*ca.* $3 * 10^2$	*ca.* -2.5
tetrahydrofuran	$(CH_2)_4O$	*ca.* 10^2	*ca.* -2
alcohols	$R\text{-}CH_2\text{-}OH$	*ca.* 10^2	*ca.* -2
aryl amides	$C_6H_5C(NH_2)=O$	*ca.* 10^2	*ca.* -2
indole		*ca.* 10^2	*ca.* -2
water	H_2O	55	-1.74
aliphatic amides	$RC(NH_2)=O$	3.2	-0.5

dimethyl sulfoxide	$(CH_3)_2SO$	1	0
phosphine oxides	R_3PO	1	0
pyrrole	C_4H_4NH	1	0
urea	$(NH_2)_2C=O$	0.8	0.1
diphenylamine	$(C_6H_5)_2NH$	0.15	0.8
p-nitroaniline	$4-O_2NC_6H_4NH_2$	0.1	1.0
aniline	$C_6H_5NH_2$	$2.5 * 10^{-5}$	4.6
trimethylamine N-oxide	$(CH_3)_3NO$	$2.5 * 10^{-5}$	4.6
N,N-dimethylaniline	$C_6H_5N(CH_3)_2$	10^{-5}	5.1
pyridine	C_5H_5N	$6.3 * 10^{-6}$	5.2
hydroxyl amine	$HONH_2$	$1.3 * 10^{-6}$	5.9
2,6-dimethylpyridine		$2.0 * 10^{-7}$	6.7
imidazole		10^{-7}	7.0

hydrazine	H_2NNH_2	10^{-8}	8.0
alkyl phosphines	R_3P	10^{-8}	8.0
aziridine	▷N-H	10^{-8}	8.0
2,2,2-trifluoroethylamine	$CF_3CH_2NH_2$	$5.0*10^{-9}$	8.3
morpholine	$O(CH_2CH_2)_2NH$	$5.0*10^{-9}$	8.3
DABCO		$K_1 = 2.0 * 10^{-9}$ $K_2 = 6.3 * 10^{-5}$	8.7 4.2
ammonia	NH_3	$5.62 * 10^{-10}$	9.25
4-dimethylaminopyridine	$4-(CH_3)_2N-C_5H_4N$	$2.0 * 10^{-10}$	9.7
ethyl amine	$C_2H_5NH_2$	$2.0 * 10^{-11}$	10.7
triethyl amine	$(C_2H_5)_3N$	$1.8 * 10^{-11}$	10.8
diethyl amine	$(C_2H_5)_2NH$	10^{-11}	11.0

piperidine	$(CH_2)_5NH$	10^{-11}	11.0
pyrrolidine	$(CH_2)_4NH$	$6.3 * 10^{-12}$	11.2
Hünig's base		$3.4 * 10^{-12}$	11.4
DBU		10^{-12}	12
proton sponge		$4.4 * 10^{-13}$	12.3
guanidine	$(NH_2)_2C{=}NH$	$2.0 * 10^{-14}$	13.6
pentamethylguanidine	$[(CH_3)_2N]_2C{=}NCH_3$	$1.8 * 10^{-14}$	13.8

Although it is convenient and informative to express pK_a values for a common solvent system (usually water), there are serious limitations for very strong and very

weak acids. Thus acids that are stronger than the hydronium cation, $H_3O^{(+)}$, and weak acids having conjugate bases stronger than hydroxide anion, $OH^{(-)}$, cannot be measured directly in water solution. Solvents such as acetic acid, acetonitrile and nitromethane are often used for studying very strong acids. Relative acidity measurements in these solvents may be extrapolated to water. Likewise, very weakly acidic solvents such as DMSO, acetonitrile, toluene, amines and ammonia may be used to study the acidities of very weak acids. For both these groups, the reported pK_a values extrapolated to water are approximate, and many have large uncertainties.