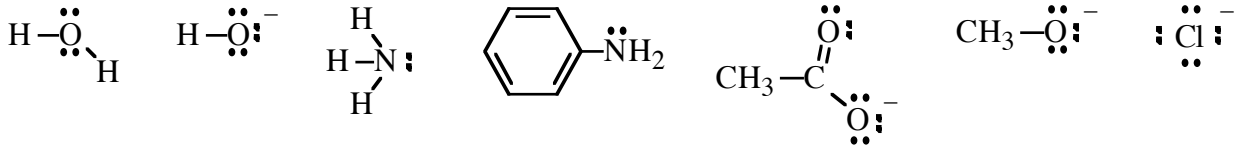
Acids and Bases

Reference: P. Bruice, Organic Chemistry, 6th Edition, Chapters 1.16-1.26, 7.9, 16.5.

Definitions

Bases (general definition) - All substances that contain unshared electron pairs are bases.

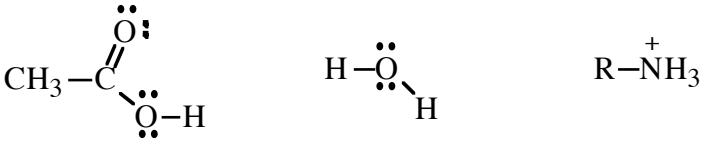
Examples:



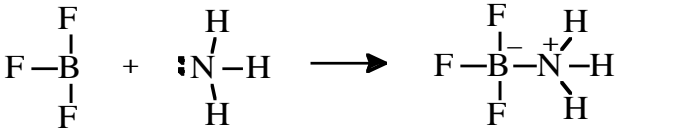
Acids

1. Proton or protonic acids - Proton acids (Brønsted acids) are substances that can transfer a proton to a base. They are proton donors. They are usually substances that have a hydrogen atom bonded to an electronegative atom.

Examples:

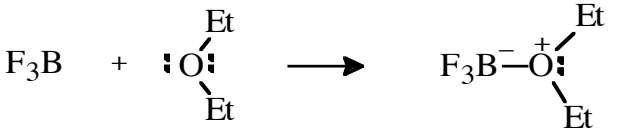
HCl 

2. Lewis Acids - According to the concept of G. N. Lewis, acids are not limited to proton donors, but an acid is any substance that contains an element having a vacant orbital that can accept a pair of electrons in forming a bond. According to the Lewis concept it is the bare proton with its vacant s orbital that is the acidic entity in protonic acids. But bare unsolvated protons do not exist in solution and it is now customary to differentiate between proton acids and Lewis acids. The term 'Lewis acid' is used to designate substances having a vacant orbital, usually substances containing an element that is two electrons short of having a complete valence shell.



Lewis Acid Base Addition Compound

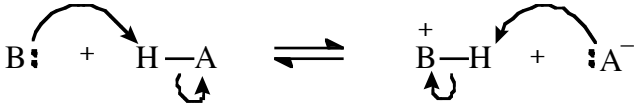
Note that the resulting addition compounds formed from electrically neutral molecules have a formal negative charge on the boron (the electron acceptor) and a formal plus charge on the electron donor.



Lewis Acid Base Addition Compound

Proton Acids and Bases (Conjugate Acid-Base Pairs) - The ionization of a proton acid involves the transfer of a proton from the acid to a base, or more correctly, the removal of a proton from the acid by a base. Strong acids are able to transfer their proton to weak bases, but weak acids may require a very strong base to bring about the proton transfer of ionization. When an acid ionizes in water, the water molecules, with their unshared pairs of electrons, serve as the base. It is important to realize that bare unsolvated protons do not exist in solution. Ionization of a proton acid always requires a base to remove or accept the proton. Often the solvent molecules serve as the base.

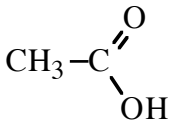
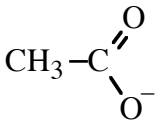
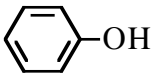
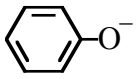
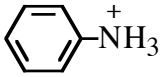
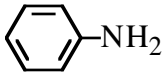
The process can be shown by following general equation, where B represents a base and H–A represents a proton acid.



Note that the anion ($:A^-$) that results from the removal of the proton from the acid H–A, is itself a base. It is called the conjugate base of acid H–A. The protonated species B^+–H is now an acid, and it is called the conjugate acid of base B:. The acid-base reaction is therefore a competition reaction between two bases for a single proton. The reaction is an equilibrium process. The position of the equilibrium is affected by the relative basicities of the competing bases B: and $:A^-$.

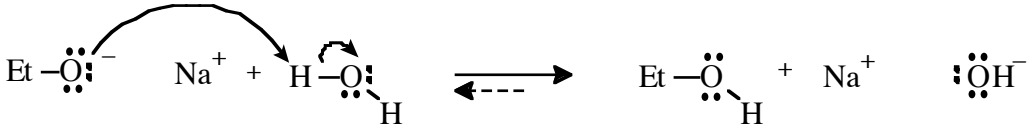
Conjugate Acid-Base Pairs - An acid and the base resulting from removal of the proton from the acid form a conjugate acid - conjugate base pair. A base and the acid that results from protonation of the base give a conjugate base - conjugate acid pair. Removal of the proton from an acid gives its conjugate base and protonation of a base gives the conjugate acid of the base.

Examples of conjugate pairs:

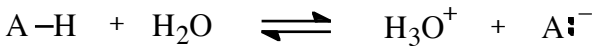
Conjugate Acid	Conjugate Base	Conjugate Acid	Conjugate Base
H_2O	OH^-		
H_3O^+	H_2O	NH_4^+	NH_3
HCl	Cl^-		
H_2SO_4	HSO_4^-		
HSO_4^-	SO_4^{-2}	Et–OH	$Et–O^-$

It should be obvious that conjugate bases of strong acids are very weak bases (the chloride anion for example) and that conjugate bases of weak acids are very strong bases (the ethoxide anion for example). Also, the conjugate acids of strong bases are very weak acids (water, the conjugate acid of OH^-, for example) and those of weak bases are strong acids: HCl, the conjugate acid of Cl^-, is of course, a strong acid. Anhydrous HCl (gaseous) is a covalent compound. It ionizes completely in water, so the water molecule is a stronger base than the chloride anion.

The strongest base that can exist in a protic solvent (solvents that can donate protons) is the conjugate base of the solvent. The hydroxide anion is the strongest base that can exist in water. Sodium ethoxide cannot exist in water because the ethoxide anion is a stronger base than OH^-.



Scale of Acidity and Basicity - The acidity of an acid refers to the proton donating power of the acid, to the degree to which the proton is transferred from the acid to a given base. In order to make a meaningful comparison of the acidity of different acids a common reference base must be used. The reference base adopted is water.



The protonation of water by an acid is an equilibrium reaction and for most acids the reaction is extremely fast and the equilibrium is reached almost instantaneously.

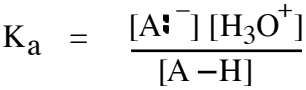
The law of mass action allows the concentrations at equilibrium to be related to an equilibrium constant (K), as shown below, for the ionization of acetic acid.

$$K'_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][H_2O]} \qquad K_a = K'_a\ [H_2O] = \frac{[CH_3COO^-]\,[H_3O^+]}{[CH_3COOH]}$$

Since the measurements are made at relatively low concentrations of the acid, the concentration of the water remains essentially constant and it is usually incorporated in the equilibrium constant to give the expression:

$$K_a = \frac{[CH_3COO^-]\,[H_3O^+]}{[CH_3COOH]} = K'_a\ [H_2O] = 1.75 \times 10^{-5}$$

Where Ka is called the acidity constant, the ionization or dissociation constant. The terms in brackets refer to concentrations in moles per liter after equilibrium is reached. Using A–H to represent any acid gives the general equilibrium equation:



The acidity constant Ka is an equilibrium constant. It allows the calculation of the ratio of the free acid and its conjugate base, at equilibrium, for a solution of known concentration of the acid in water.

The pK_a - a single scale for reporting and comparing the ionization capacity of acids and bases. Since every base has its conjugate acid, it is possible to compare all acids and bases on a single scale. The scale commonly used is the acidity constant of the conjugate acid of any conjugate pair, expressed in logarithmic units. This is called the pK_a. By definition, the pK_a is the negative logarithm of K_a value.

$$pK_a = -\log K_a$$

For acetic acid, $K_a = 1.75 \times 10^{-5}$ and $pK_a = -\log (1.75 \times 10^{-5}) = 5 - \log 1.75 = 4.76$.

It is very important to recognize that the pK_a of bases, such as ammonia or the organic amines, is a measure of the acidity of the conjugate acid of the base, a measure of the acidity of the salts of ammonia or amines.

The pK_a of methylamine $[CH_3\overset{+}{N}H_3]$ is given as 10.6. This means that a salt of methylamine, such as $CH_3NH_3Cl^-$, has an acidity constant $K_a = 10^{-10.6}$, or 2.51×10^{-11}.

$$CH_3\overset{+}{N}H_3\ Cl^- + H_2O \rightleftharpoons CH_3NH_2 + H_3O^+ + Cl^-$$

$$K_a = \frac{[CH_3NH_2]\ [H_3O^+]}{[CH_3\overset{+}{N}H_3]} = 2.51 \times 10^{-11}$$

$$pK_a = -\log (2.51 \times 10^{-11}) = 10.6$$

The ionization of water is K_w.

$$2\ H_2O \rightleftharpoons H_3O^+ + OH^-$$

$$K_w = [H_3O^+]\ [OH^-] = 10^{-14}$$

$$pK_w = -\log K_w = 14$$

$$K_a = \frac{[H_3O^+]\ [OH^-]}{[H_2O]} = \frac{K_w}{55.5} = 10^{-15.7}$$

$$pK_a = 15.7$$

Here again, the constant concentration term of the water is incorporated in the constant K_w. In pure water the concentration of hydronium and hydroxide ions must of course be equal. At 25° C, the concentration of each is 10^{-7} mole/liter.

pH - By definition, the pH of a water solution is the negative log of the hydronium ion concentration in moles/liter.

$pH = -\log [H_3O^+]$

For pure water, the pH is 7. The water is said to be 'neutral', neither acidic nor basic. If the concentration of hydronium ion is increased above $[10^{-7}]$, by the addition of some acid that is more acidic than water the solution is said to be acidic. The addition of a base increases the concentration of hydroxide ions and correspondingly decreases the concentration of the hydronium ion and the solution is said to be basic. The product of the concentration of H_3O^+ and OH^- is the K_w and retains the constant value 10^{-14}. Water solutions with pH values less than 7 are acidic and those having pH values larger than 7 are basic.

More on pKa scale - The experimental measurement of pKa values in water are, of course limited to acids that are stronger acids than water, acids that will ionize to some degree in water (where the conjugate base of the acid is a weaker base than the hydroxyl anion), but at the same time are not acidic enough to be completely ionized in water, acids with pKa values between 0 and 14.

The relationship

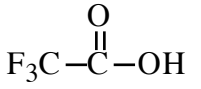
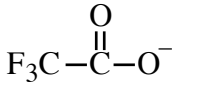
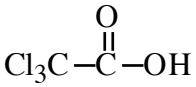
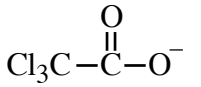
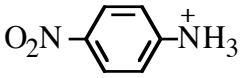
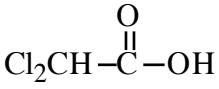
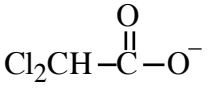
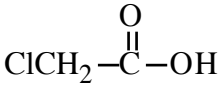
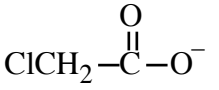
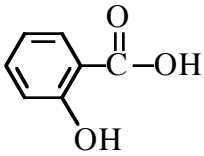
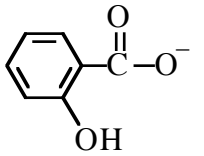
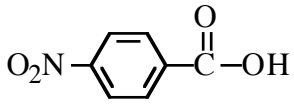
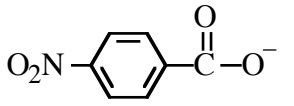
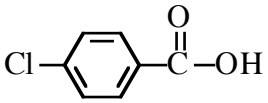
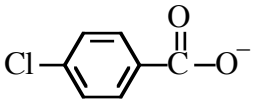
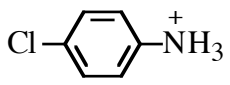
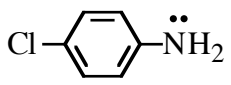
$$K_a = \frac{[A:^-]\,[H_3O^+]}{[A-H]}$$

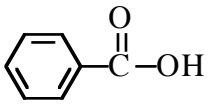
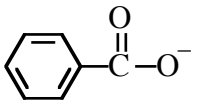
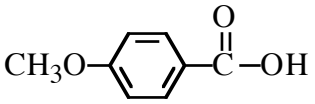
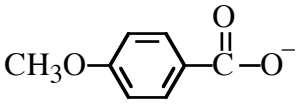
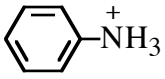
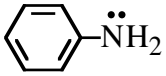
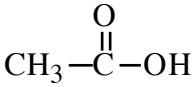
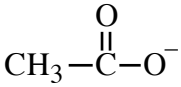
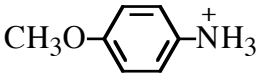
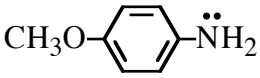
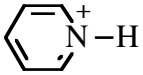
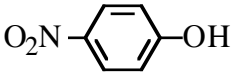
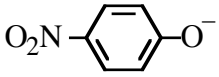
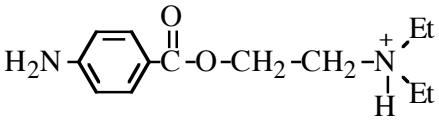
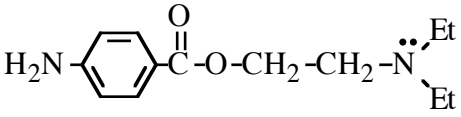
requires that there be measurable concentrations of both the conjugate acid and conjugate base at equilibrium in order to determine Ka. For very strong acids (pKa < 0) and very weak acids (pKa > 14), indirect nonaqueous competition experiments using acids and bases of known pKa's must be used in order to compare them on the same scale as those measurable in water. The pKa values at the two extremes of the scale (beyond 0 and 14 each way) are less accurate than those between 0 and 14.

Examples of Acids and Acidity Scale

	Conjugate Acid	pK_a	Conjugate Base
	Strong Acids		
1.	H–I	~ –10	$:\ddot{I}:^-$
2.	H–Cl	~ –7	$:\ddot{Cl}:^-$
3.	H_2SO_4	~ –3	HSO_4^-

The above acids cannot exist as such in aqueous solution. In each case the conjugate base is a weaker base than the water molecule. The proton would be completely transferred to the water molecules. The standard "strong" acids are completely ionized in water. These are $HClO_4$, HI, HCl and H_2SO_4 (first proton).

4.		~ 0	
5.		~ 0.8	
6.		1.0	
7.		1.3	
8.		2.8	
9.		3.0	
10.		3.4	
11.		4.0	
12.		4.0	

	Conjugate Acid	pK_a	Conjugate Base
13.		4.2	
14.		4.5	
15.		4.6	
16.		4.76	
17.		5.3	
18.		5.3	
19.		7.2	
20.	 Procaine	8.9	
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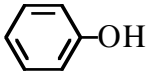
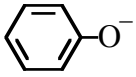
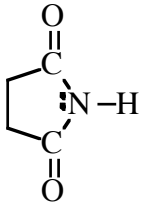
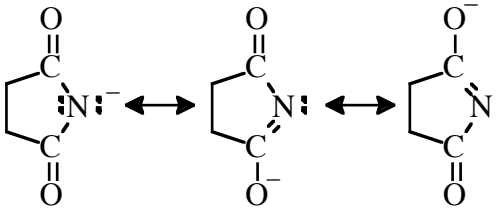
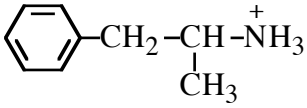
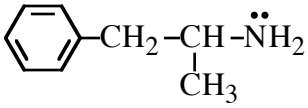
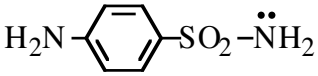
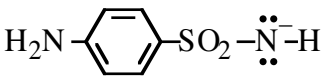
22.		9.6	
23.	 An imide	9.6	
24.	 Amphetamine	~ 10	
25.	 Sulfanilamide	10.6	

	Conjugate Acid	pK_a	Conjugate Base
26.	$CH_3-\overset{+}{N}H_3$	10.6	$CH_3-\ddot{N}H_2$
27.	$H_2N-C(=\overset{+}{N}H_2)-H_2N$	~ 14	$H_2N-C(=NH)-H_2N$ Guanidine
28.	CH_3-CH_2OH	~ 16	$CH_3-CH_2O^-$
29.	$CH_3-C(=O)-CH_3$	~ 20	$CH_3-C(-O^-)=CH_2 \longleftrightarrow CH_3-C(=O)-\bar{C}H_2$

The very strong acids ($pK_a < -2$) will completely transfer their protons to water in dilute solutions. The pH of dilute solutions of these strong acids can therefore be calculated directly from the concentration of the acid. In a 0.1 N solution of HCl, the H_3O^+ concentration is 10^{-1} mole/liter and the pH is 1. The conjugate bases of these strong acids are weaker bases than the water molecules and salts of the acids, such as Na^+Cl^-, $Na^+ClO_4^-$, Na^+I^-, do not change the pH of the water; these anions are not basic enough to remove a proton from a neutral water molecule.

The very weak acids, $pK_a > 14$, are weaker acids than water and cannot transfer their protons to a water molecule. Ethanol and acetone, which are soluble in water, do not change the pH of water. The conjugate bases of these weak acids are all stronger bases than the OH^- ion and they cannot be formed or exist in the presence of water.

For acids of intermediate strengths (pKa between 0 and 14) which are soluble in water, the degree of water protonation will depend on the pKa of the acid. For a 0.1 N solution of acetic acid most of the acid is in the nonionized form. Taking the pKa as 5 would give:

$$\underset{\text{0.1 molar}}{AcOH} + H_2O \rightleftharpoons \underset{x}{AcO^-} + \underset{x}{H_3O^+}$$

$$K_a = \frac{[AcO^-]\,[H_3O^+]}{[AcOH]} \qquad 10^{-5} = \frac{x^2}{0.1 - x}$$

Since x is small (compared to 0.1M), it can be neglected in the denominator and $x^2 = 10^{-6}$, $x = 10^{-3}$.

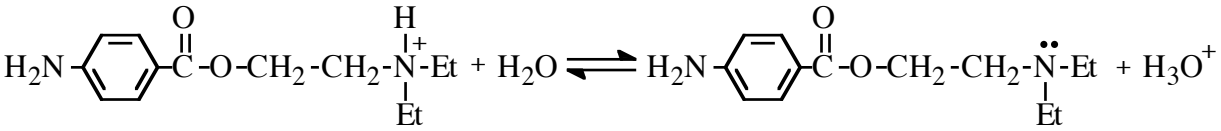
$$K_a = \frac{x^2}{[AcOH]} \; ; \quad x^2 = K_a[AcOH] \; ; \; x = \sqrt{K_a[AcOH]}$$

The pH of the solution is about 3 and the ratio of ionized to nonionized acetic acid is about 1/100.

For dilute aqueous solutions of weak acids the approximate pH can be calculated as the negative log of the square root of the product of the K_a and the molar concentration.

$$pH \cong -\log \sqrt{K_a[\text{molar concentration of acid}]}$$

Drugs which are amines (weak bases) are sometimes used as their hydrochloride salts, procaine hydrochloride for example. Salts of amines are the conjugate acids of amines and are of course acidic. The pH of a 0.1 N solution of procaine hydrochloride will be about 5.

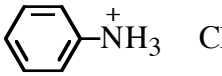


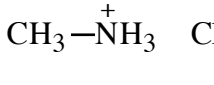
[0.1 molar]

$pK_a = 8.9 \sim 9$

$$K_a = \frac{[B:]\,[H_3O^+]}{[BH^+]}\ ,\ K_a\,[BH^+] = x^2 = (10^{-9})\,(10^{-1}) = 10^{-10},\ x = 10^{-5},\ pH = 5.$$

It is important to remember that pKa values are logarithmic values. A difference of one pKa unit means that the ionization constant varies by a factor of ten. Compare the acidity of the salts of aromatic and aliphatic amines.


Cl^-, $pK_a = 4.6$


Cl^-, $pK_a = 10.6$

pH of a 0.1 Molar solution,

$K_a\,[BH^+] = x^2 = (10^{-4.6})\,(10^{-1}) = 10^{-5.6}$,
$x = 10^{-2.8}$, $pH = 2.8$.

pH of a 0.1 Molar solution,

$K_a\,[BH^+] = x^2 = (10^{-10.6})\,(10^{-1}) = 10^{-11.6}$,
$x = 10^{-5.8}$, $pH = 5.8$.

The aniline hydrochloride is 10^6 (one million times) more acidic than methylamine hydrochloride. The aliphatic methylamine is one million times more basic than the aromatic amine, aniline.

Degree of Ionization of Acids and Bases at Controlled pH in Buffered Solutions. The Henderson-Hasselbalch equation.

It is obvious that when an acid (more acidic than water) is added to water it will ionize by transferring its protons to water and thus increase the hydronium ion concentration and lower the pH of the water solution.

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

The pH of the resulting solution will depend on the concentration and the pK_a of the acid.

In the pharmaceutical sciences, a very important question regarding acids and bases is the degree of ionization of acids and bases of known pKa values at a given, constant pH, in buffered systems such as the blood and plasma. Many important drugs are weak acids or weak bases. A knowledge of the degree of ionization of such drugs at physiological pH is very important to problems of absorption, distribution in body tissues, and excretion. Such a knowledge is also basic to problems of solubilization of drugs in the preparation of suitable dosage forms.

The Henderson-Hasselbalch equation allows the calculation of the ratio of conjugate acid and conjugate base for a conjugate acid-conjugate base pair of known pKa at any given pH.

$$pH = pK_a + \log \frac{[\text{Conjugate base}]}{[\text{Conjugate acid}]}$$

The equation is readily derived: memory not required for its application.

$$\text{Conjugate acid} + H_2O \rightleftharpoons H_3O^+ + \text{Conjugate base}$$

$$K_a = \frac{[H_3O^+]\,[\text{Conjugate base}]}{[\text{Conjugate acid}]}$$

Taking the log of each side of the equation gives:

$$\log K_a = \log [H_3O^+] + \log \frac{[\text{Conjugate base}]}{[\text{Conjugate acid}]}$$

Rearranging,

$$-\log [H_3O^+] = -\log K_a + \log \frac{[\text{Conjugate base}]}{[\text{Conjugate acid}]}$$

By definition, $-\log [H_3O^+]$ is pH and $-\log K_a$ is pK_a, therefore

$$pH = pK_a + \log \frac{[\text{Conjugate base}]}{[\text{Conjugate acid}]}$$

Thus, if the conjugate acid is a non-ionized compound such as a carboxylic acid, then the conjugate base is the ionized form, the anion; and when dealing with amines, it is the conjugate acid that is the ionized form (the protonated amine, the cation).

In buffered solutions (solution at constant pH) a conjugate acid - conjugate base pair will adjust itself to a particular ratio of ionized to non-ionized species that is dependent only on the pKa of the acid-base pair and the pH of the solution. The same ratio is obtained regardless of whether the conjugate acid or the conjugate base was used to prepare the solution. If a solution of acetic acid (pKa 4.8) were injected in the blood stream (pH 7.4), the acetic acid would ionize to the extent of more than 99%, difference greater than 2 log units. The same result would be obtained by injecting a solution of sodium acetate.

It is obvious from the Henderson-Hasselbalch equation that the pH and the pKa are numerically equal when the ratio of conjugate acid and conjugate base is equal to one, when the substance is 50% ionized. An acid or base is 50% ionized at the pH that equals its pKa.

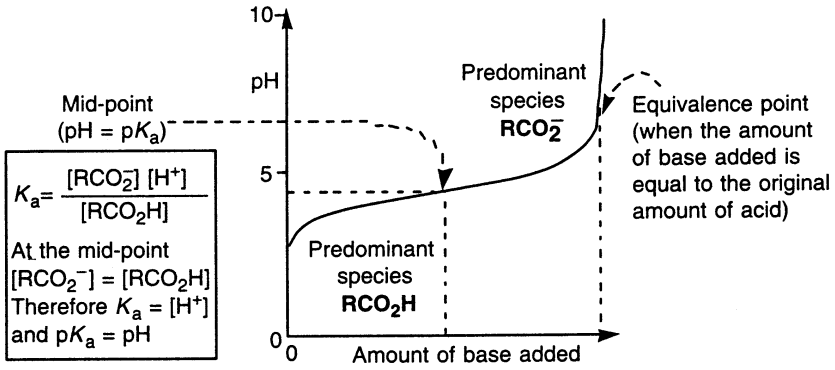


Fig. 2.3 Titration curve for a typical carboxylic acid.

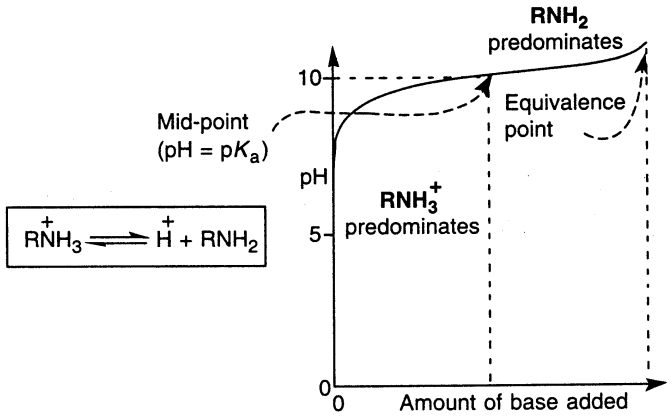


Fig. 2.4 Titration curve for a typical amine.

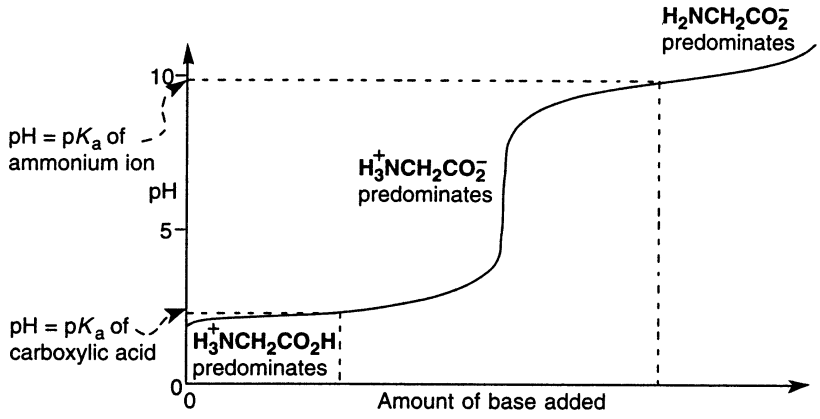


Fig. 2.5 Titration curve for glycine.

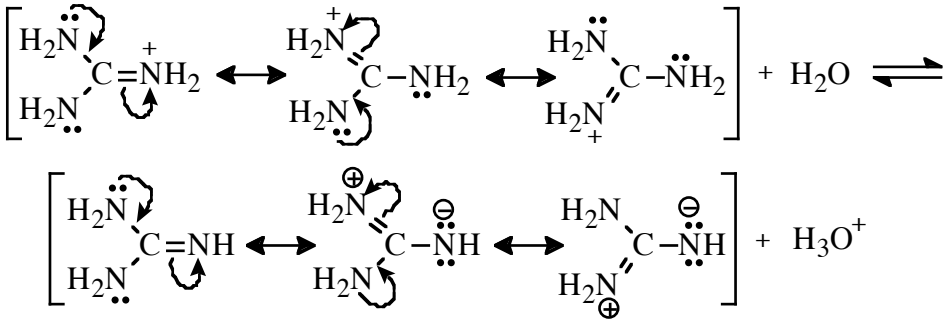
Drugs as Acids and Bases

A. Guanidines and Amidines

Basicity of Guanidine

Guanidine, pKa ~ 14, is almost completely ionized in water. Some substituted guanidines are useful drugs.

$$BH^+ + H_2O \rightleftharpoons B: + H_3O^+$$



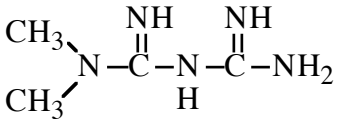
pKa ~ 14

Ka = 10^{-14}

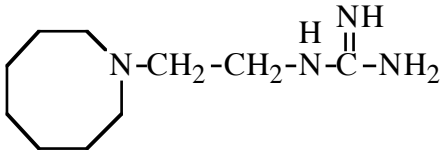
Three identical resonance structures and no separation of charges in the guanidinium cation. Resonance stabilizes the protonated species. The plus charge is equally distributed on the three nitrogen atoms.

The reason for the very strong basicity of guanidine is the great stabilization of the cation resulting from the dispersal of the positive charge, which is equally distributed between the three nitrogen atoms, and the gain in resonance upon protonation.

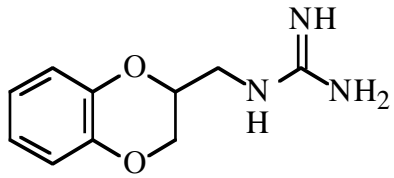
Several substituted amidines and guanidines are useful drugs. These agents have effects in the periphery, and appear not to be transported in significant amounts to the central nervous system, probably due to their polarity. Some are also not absorbed well for the same reason.



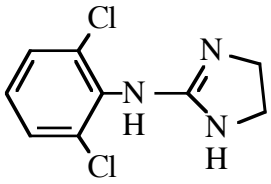
Metformin $pK_a = 12.4$



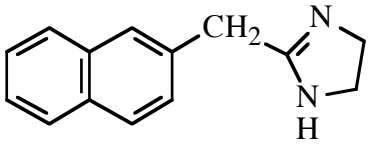
Guanethidine pK_as = 11.9, 8.3



Guanoxan $pK_a = 12.3$

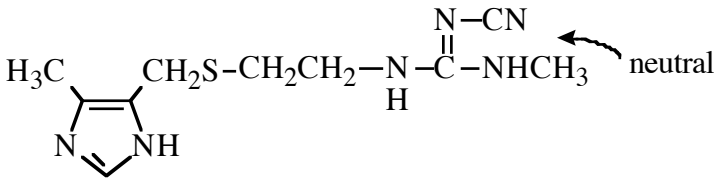


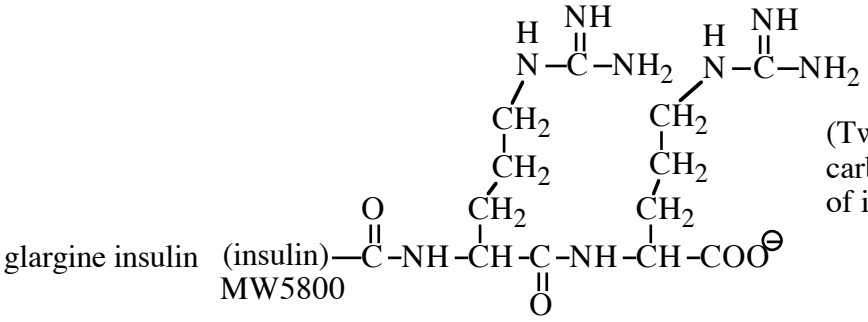
Clonidine $pK_a = 8.4$



Naphazoline $pK_a = 10.9$

Guanidines substituted with electron withdrawing groups have greatly reduced basicity, e.g. cimetidine.





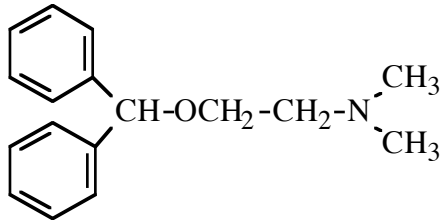
(Two arginines added to the carboxyl end of the B-chain of insulin.)

Soluble HCl salt administered subcutaneously. It precipitates and the slow rate of subsequent dissolution and then absorption into the blood stream provides a long duration of effect.

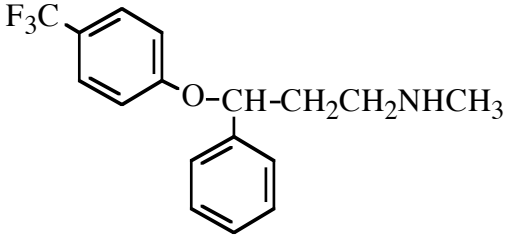
B. Amines - Tertiary, Secondary, and Primary

Many drugs are tertiary or secondary aliphatic amines, a few are primary amines. Tertiary amines usually are metabolized by fewer independent pathways than those with fewer alkyl groups on nitrogen, i.e. secondary and primary aliphatic amines may be metabolized by different processes. Most amine drugs are basic (pKa ~ 9). Even though they are highly ionized at physiological pH, most are readily absorbed after oral administration (rapid equilibrium between ionized and non-ionized forms to penetrate membranes), and many lipophilic ones reach the CNS.

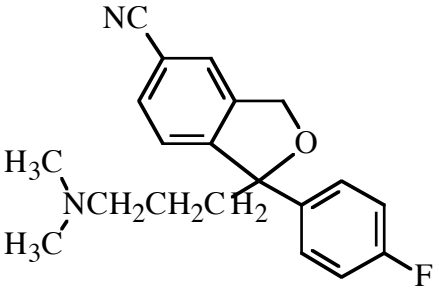
Examples



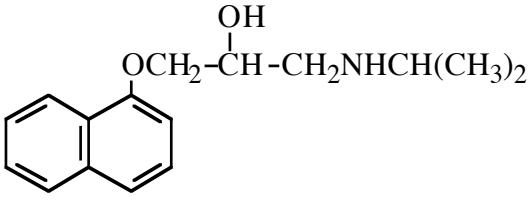
Diphenhydramine $pK_a = 9.1$



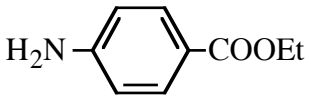
Fluoxetine $pK_a = 8.7$



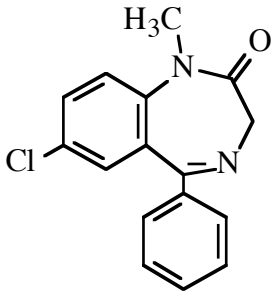
Citalopram $pK_a = 9.5$



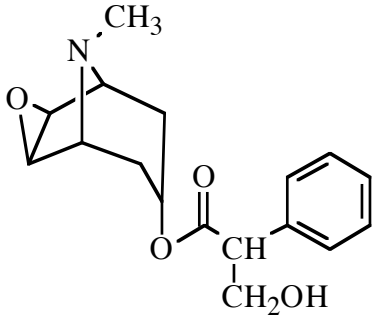
Propranolol $pK_a = 9.5$



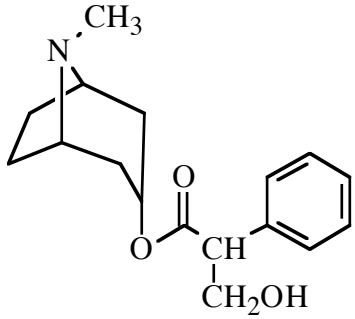
Benzocaine $pK_a = 2.8$



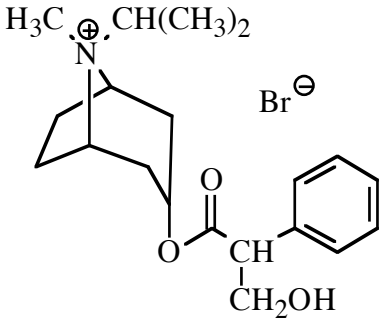
Diazepam $pK_a = 3.4$



Scopolamine $pK_a = 7.6$



Atropine $pK_a = 9.8$



Ipratropium

Note: Quaternary ammonium ions are not basic amines. They are salts (always charged, regardless of pH).

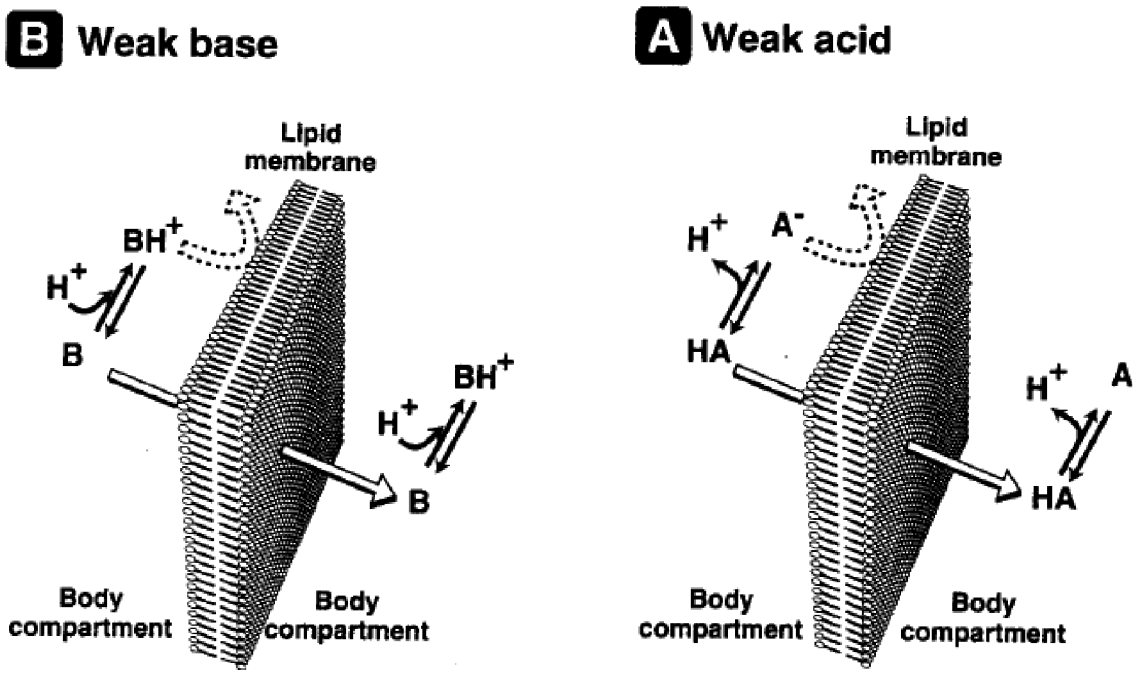
gut lumen		blood		organ
$BH^+ + H_2O \rightleftharpoons H_3O^+ + B$	membrane	$BH^+ + H_2O \rightleftharpoons H_3O^+ + B$	membrane	$BH^+ + H_2O \rightleftharpoons H_3O^+ + B$

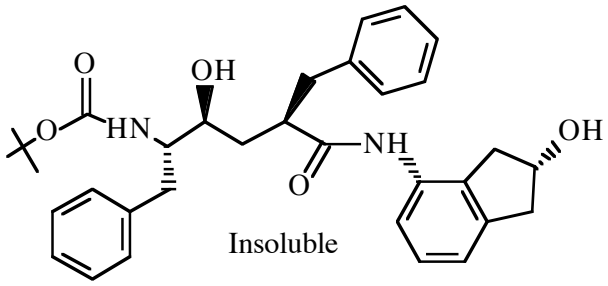
Very strong bases are generally poorly absorbed.

$pH = pKa + \log B/A$ $\quad BH^+ + H_2O \rightleftharpoons B\!: + H_3O^+$

(physiological pH) 7.4 = 13.4 + log B/A
(duodenum 5) -6 = log B/A
10^{-6} = B/A

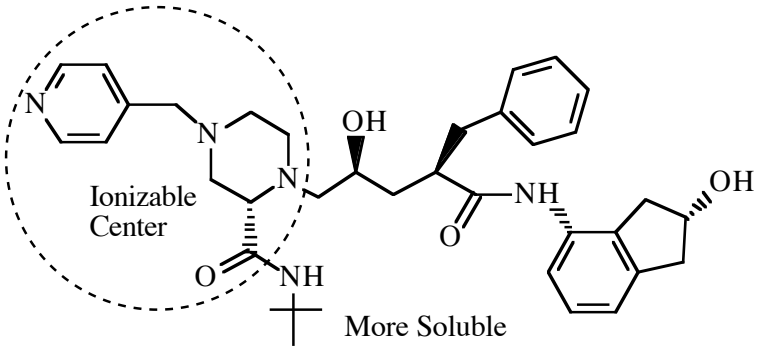
amidines – pKa ~ 13-14
aliphatic amines pKa ~ 9-10
(generally well absorbed)





L-685,434
IC_{50} - 0.3 nM

No Oral Bioavailability



indinavir
IC_{50} - 0.41 nM

Oral Bioavailability = 60% Human

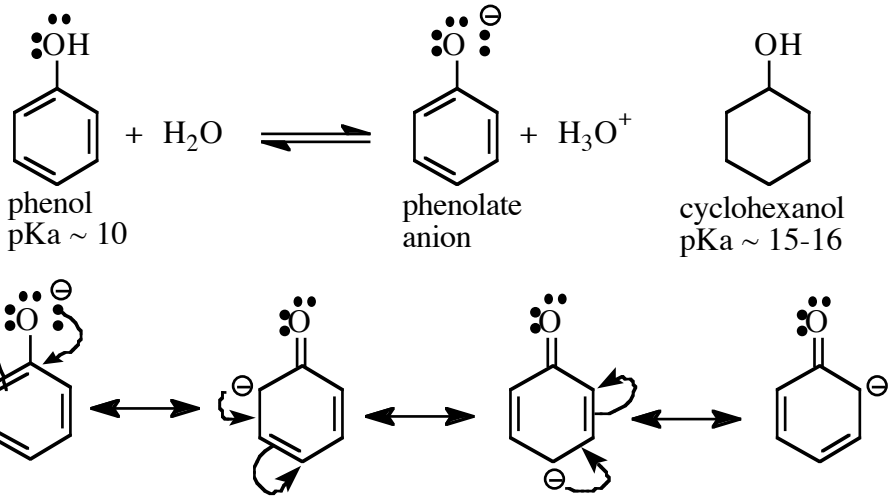
Effect of aqueous solubility on oral bioavailability.

C. Phenols, Enols, Imides, Sulfonamides and Related Compounds

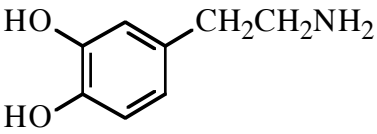
Increased acidity (dissociation of acid) is associated with stabilization of resulting structures by resonance (anions especially), to a greater extent than in the non-dissociated acid.

Resonance rules:

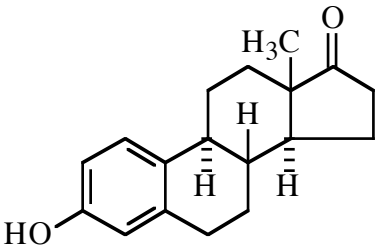
1. Only electrons move. The nuclei of the atoms never move.
2. Only π electrons or non-bonding electrons contribute.
3. Electrons move toward a positive charge or toward a π bond.
4. Total number of electrons does not change. The number of paired and unpaired electrons does not change.



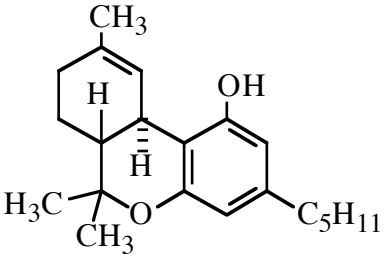
Examples



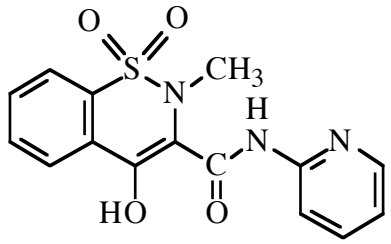
Dopamine $pK_a = 10.6$ (phenol)
8.9 ($R\overset{+}{N}H_3$)



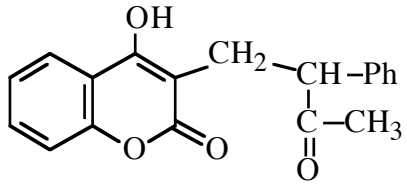
Estrone $pK_a = 10.8$



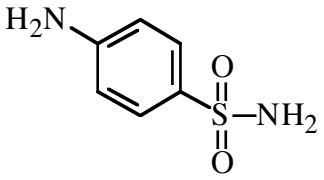
Δ^9-THC $pK_a = 10.6$



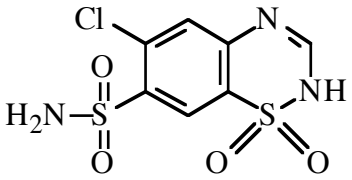
Piroxicam $pK_a = 4.6$



Warfarin $pK_a = 5.1$



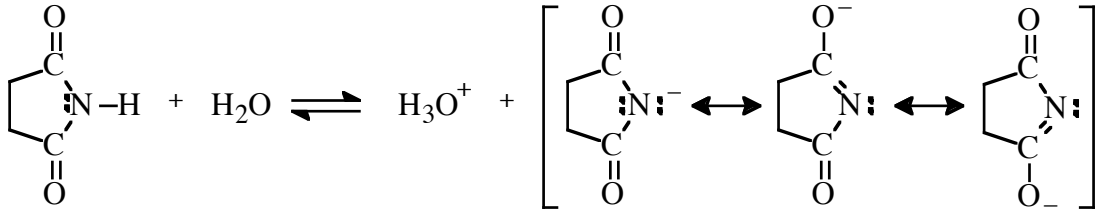
Sulfanilamide $pK_a = 10.6$



Chlorthiazide $pK_a = 6.7, 9.5$

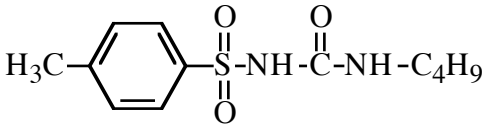
Imides and Related Compounds

The imides, where the nitrogen is flanked by two carbonyl groups, are much stronger acids (pKa ~ 9) than amides, which have no detectable basicity or acidity in water. Salts of imides can be formed in water. The acidity of imides results from a greater resonance stabilization of the conjugate base than the conjugate acid and stabilization of the conjugate base by a dispersal of the negative change between the two oxygens and the nitrogen. The oxygen, being more electronegative than nitrogen, is a better accommodator of a negative charge than nitrogen. The structure of the anion is better written with the negative charge on the oxygen.

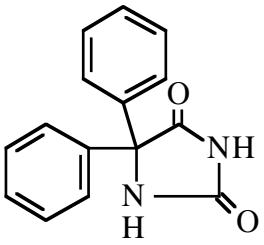


Succinimide
pKa = 9.6
(Resonance structures require separation of charges)

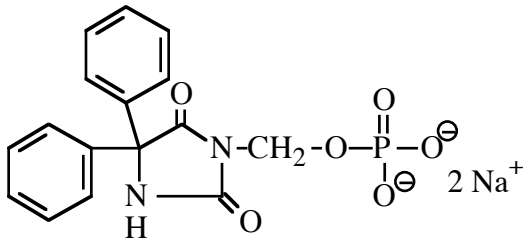
Resonance in succinimide anion. No separation of charges. Good delocalization of the negative charge.



Tolbutamide $pK_a = 5.4$

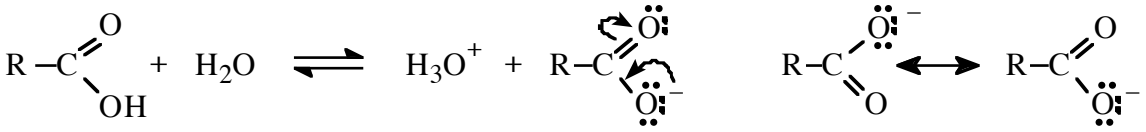


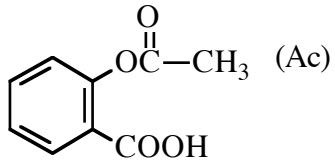
Diphenylhydantoin $pK_a = 8.3$



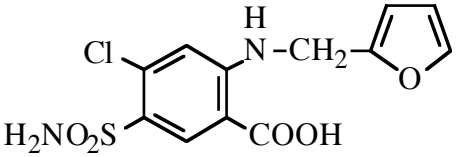
D. Carboxylic Acids and Tetrazoles

Many carboxylic acids as well as sulfonamides, warfarin, etc., when absorbed systematically are highly bound to plasma proteins.

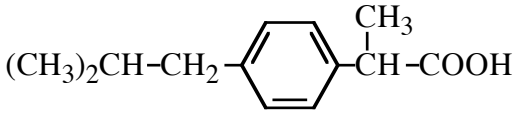




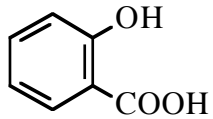
Aspirin $pK_a = 3.5$



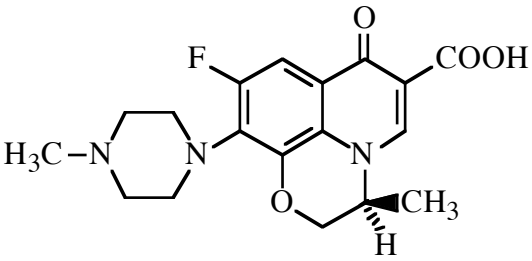
Furosemide $pK_a = 3.9$



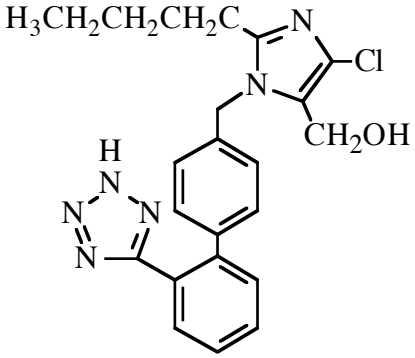
Ibuprofen $pK_a = 5.2$



Salicylic acid pKa = 3.0, 13 (used topically as a corn or callus remover)



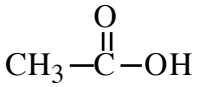
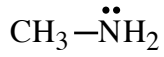
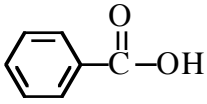
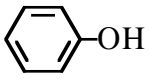
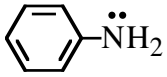
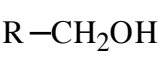
Levofloxacin $pK_a = 5.4$ (COOH)



Losartan $pK_a = 3.2$

Relative Acidity and Basicity - Effects of Structural Changes

Carboxylic acid and phenols are among the most important organic acids, and amines (aliphatic and aromatic) are among the most important organic bases. Actual acidity constants must be determined experimentally, but it is important to be able to predict effects of structural changes on the acidity or basicity of given acids or bases. For purpose of comparison, it is useful to commit to memory the pKa values of certain important acids and bases as points of reference. The following serve as important references.

Acids	pK_a	Bases	pK_a
	4.6		9.2
	4.2		10.6
	9.9		4.6
	~16		

Carboxylic acids in general (R-COOH) have pKa ~ 4.5 ± 0.5. Those of phenols are close to 10 and alcohols are weaker acids than the water molecule. It is interesting to note the large differences in the acidity of these three classes of acids, even though all have the acidic proton bonded to an oxygen atom.

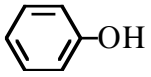
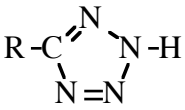
In the amine series, a huge difference of one million fold is seen between the basicity of aliphatic and aromatic amines.

From the general equation for ionization of acids,

Conjugate acid + H_2O $\rightleftharpoons$ H_3O^+ + Conjugate base

It is obvious that any structural change that stabilizes the conjugate base more than the conjugate acid will shift the equilibrium to the right and will therefore have an acid strengthening effect (lower the pKa). Conversely, any factor that stabilizes the conjugate acid more than the conjugate base will shift the equilibrium to the left and such factors have an acid weakening effect (a base strengthening effect of the conjugate base).

Acidity of Organic Acids

Most organic acids (R–COOH,  ,  , some enols, R–OH, etc.) are neutral molecules, the conjugate bases of which are anions.

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

Structural changes that stabilize the anion A:– to a greater extent than the conjugate acid A–H will have an acid strengthening effect.

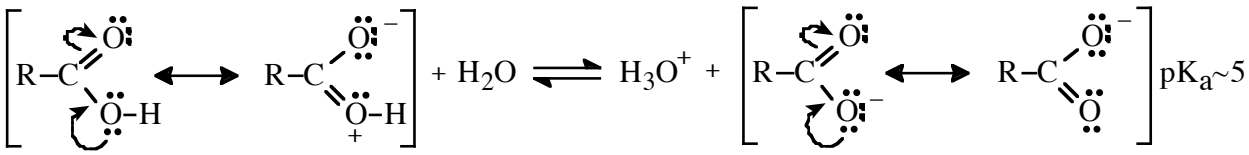
Factors that Affect the Stability of Ions

Factors that can bring about a delocalization of the charge on an ion have a stabilizing effect. For any given ion the greater the localization of the charge on a single atom, the greater the energy level of the ion. Factors that contribute to a delocalization of the charge, to a greater dispersal of the charge over several atoms of the molecule, have a stabilizing effect on the ion. Stabilization of anions is brought about by factors that cause a delocalization of electrons (solvation of the ions also plays an important role, but contribution from solvation is more difficult to assess.)

Important factors:

1) Resonance
2) Inductive effects
3) Intramolecular hydrogen bonding
4) Steric factors

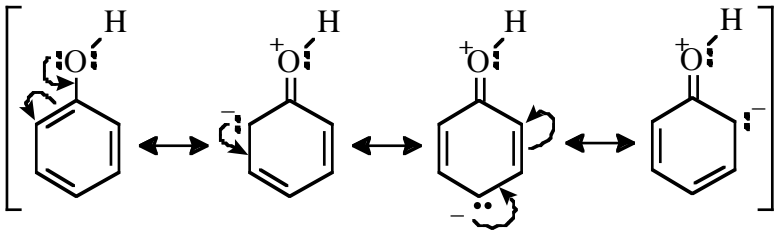
Comparison of acidity of carboxylic acids, phenols, and alcohols (all with acidic proton on an oxygen):

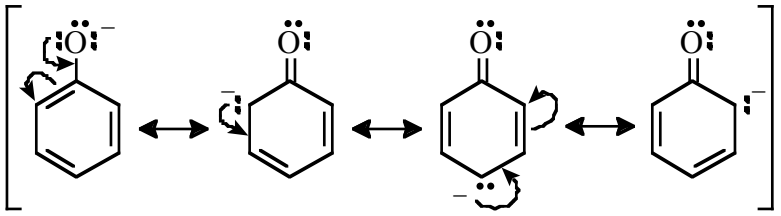


Less resonance in free acid than in the anion because of separation of + and – charges.

The negative charge is equally distributed on the two oxygens.

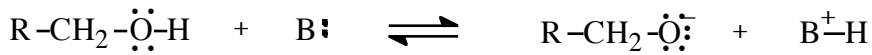
In the carboxylate anion (the conjugate base of carboxylic acids) the negative charge is distributed equally between the two oxygens. Resonance allows a great delocalization of nonbonded electrons which results in the dispersal of the negative charge and stabilization of the anion. Resonance also contributes in another way to the acidity of carboxylic acids, because there is greater resonance in the carboxylate anion than in the undissociated acid. Resonance in the free acid requires a separation of plus and negative charges, which is not the case in the anion where the resonance forms are identical. Increases in resonance are always a stabilizing factor because resonance involves a delocalization of electrons. The gain in resonance in the anion contributes to lowering the energy of the anion in relationship to the free acid and, therefore, contributes to the shifting of the equilibrium to the right.





pK_a~10

There is a greater contribution of resonance in the phenolate anion than in the free phenol, since the resonance structure in the nonionized form requires separation of plus and negative charges and there is no separation of charge in the anion. Resonance also contributes to the stabilization of the anion by contributing to a dispersal of the negative charge through a delocalization of nonbonded electrons. Through resonance, the negative charge is partially localized in the aromatic ring but since the oxygen atom is much more electronegative than the carbon atom, the overall localization of the negative charge is much greater on the oxygen than on the aromatic ring. There is less stabilization of the anion through dispersal of the negative charge in the phenolate than in the carboxylate anion.



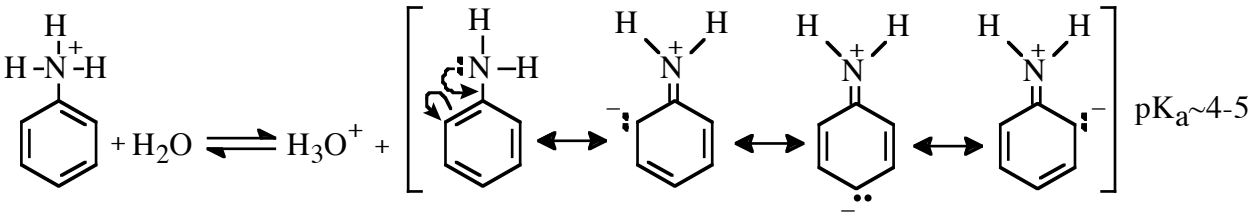
pKa~16-17

There is no measurable ionization of alcohols in water. A stronger base is needed.

The negative charge is localized on the oxygen.

Difference in the Acidity of Aliphatic and Aromatic Ammonium Ions

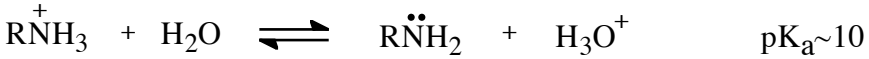
Aniline is a weaker base than is an aliphatic amine, by a factor of about 10^6. This dramatic difference is due mostly to the resonance stabilization of the free base of aniline, which is lost about protonation of the amino group.



The electrons of the nitrogen are all involved in single bond formation. The nitrogen can no longer participate in resonance with the ring.

Resonance stabilization of the free base by participation of the nonbonded electron pair of the nitrogen in resonance with the π electron system of the aromatic ring.

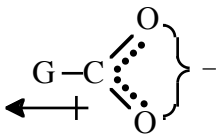
Since there is much more resonance stabilization in the conjugate base than in the conjugate acid, resonance contributes to shifting the equilibrium in the direction of the conjugate base. In ammonia of the aliphatic amines, there is no resonance effect, since the unshared pair of electrons is localized on the nitrogen.



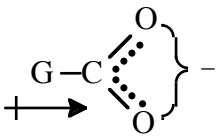
Effects of Substituents

Any substituent that causes some degree of electronic perturbation on the functional group of an acid or a base will usually affect the acidity or basicity of the compound. This is so because the effect of electronic perturbation on the thermodynamic stability of the conjugate acid and conjugate base of a conjugate pair will almost never be identical.

Substituents may have either electron withdrawing or electron releasing properties. These effects can operate either by inductive effect or by resonance, or by a combination of the two. Acids, such as carboxylic acids and phenols, that have an anionic conjugate base will experience an acid strengthening effect from electron withdrawing substituents because the net effect from such groups is a stabilization of the anion (conjugate base) through an increase in the dispersal of the negative charge. Electron releasing (donating) groups will have the opposite effect.

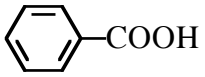
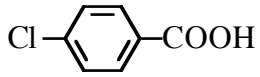
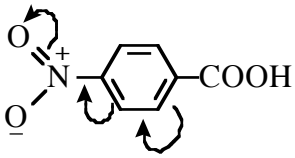
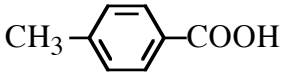


An electron withdrawing group contributes to a greater dispersal of the negative charge and stabilizes the conjugate base more than the conjugate acid.

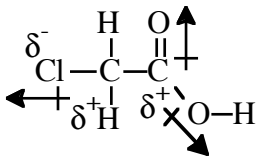


An electron releasing group tends to cause a greater localization of electrons on the anion. Its net effect is to destabilize the anion relative to the conjugate acid.

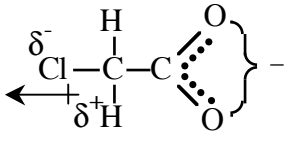
Examples of Electron Perturbing Effects in Carboxylic Acids

By Inductive Effect	pK_a	By Resonance and Inductive Effect	pK_a
CH_3COOH	4.76		4.21
HCOOH ←+	3.74	 ←+ inductive effect	3.99
$Cl–CH_2COOH$ ←+	2.81		4.47
$Cl_2CHCOOH$ ←+	1.37		3.44
Cl_3CCOOH ←+	0.65	 +→	4.34
$Cl–CH_2CH_2COOH$ ←+	4.00		
$Cl–CH_2CH_2CH_2COOH$ ←+	4.51		

Halogens on the α–carbon of carboxylic acids have a significant acid strengthening effect. The halogens are more electronegative than the carbon and there is a permanent dipole moment in the Cl–C bond. This gives a positive character to the α–carbon.



Any dipole effect on the free acid will be a destabilizing effect because of repulsing dipoles.

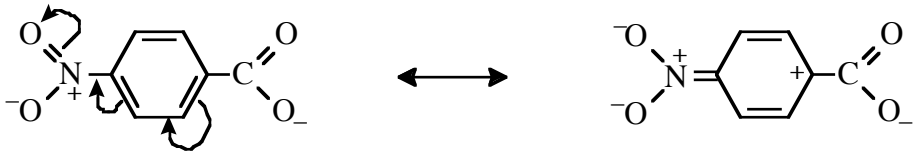


The partial positive charge on the α–carbon attracts electrons from the anion and stabilizes the conjugate base.

The influence of the inductive effect falls off rapidly through a saturated aliphatic chain, but is still measurable in 3-chloropropionic acid and 4-chlorobutanoic acid; compare the acidity of these compounds with chloroacetic acid and acetic acid.

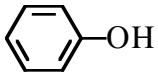
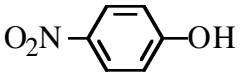
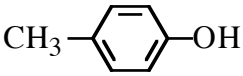
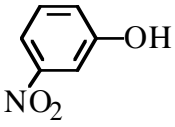
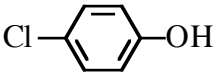
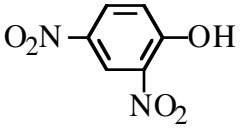
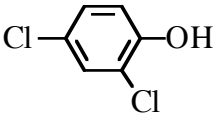
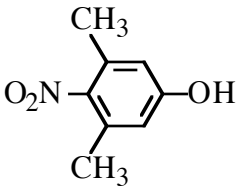
In general, substituents that cause a decrease in electron density in the vicinity of the carboxyl groups have an acid strengthening effect and those that increase the electron density have an acid weakening effect, as expected.

In the aromatic acids, the inductive effect can be transmitted across the ring. Resonance effects are more pronounced when the substituent is either ortho or para to the acidic functional group.

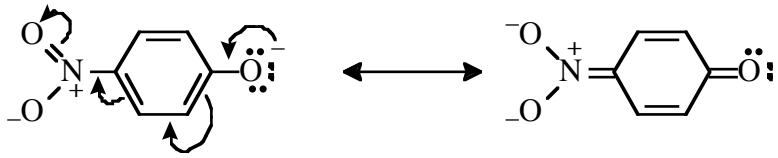


This resonance hybrid contributes to the stabilization of the anion.

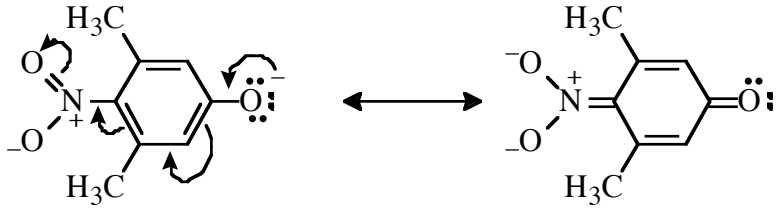
Substituent Effects on the Acidity of Phenols

	pK_a		pK_a
	9.95		7.14
	10.19		8.35
	9.38		4.04
	8.05		8.20

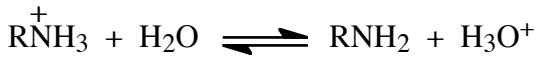
The effects of ring substituents on the acidity of phenols are analogous to those seen for aromatic carboxylic acids but the effects are more pronounced for phenols, especially with electron withdrawing groups which participate in resonance with the ring, when these groups are para or ortho to the OH group. Such groups increase the resonance in the anion and increase the delocalization of the negative charge on the anionic conjugate base.

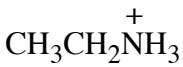
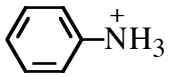
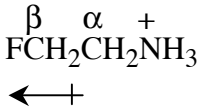
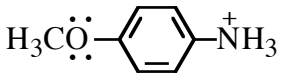
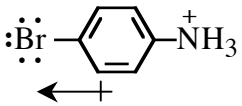
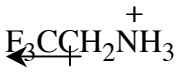
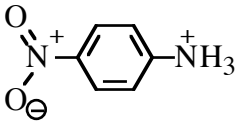
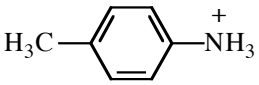


A resonance structure can be written where the nitro group and the phenol oxygen participate in the same molecular orbital and where the negative charge is acquired by the nitro group. This delocalization of electrons and negative charge contributes to a resonance stabilization of the anion. Note that the transfer of the negative charge to the nitro group is only possible when the groups are ortho or para to each other but not when they are meta. Note also that for maximum resonance pariticpation of the nitro group with the ring, it must become coplanar with the ring. Steric factors that prevent this coplanarity will reduce the acid strengthening effect of the nitro group in aromatic system. The lower acidity of 3,5-dimethyl-4-nitrophenol compared to 4–nitrophenol is attributed in part to steric repulsion of the methyl groups which prevents coplanarity of the nitro group and the aromatic ring.



Examples of Electron Perturbing Effects on the Ionization of Conjugate Acids of Amines



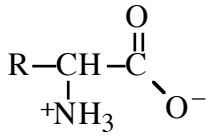
By Inductive Effect	pK_a	By Resonance and Inductive Effect	pK_a
	10.63		4.62
	8.02		5.29
	7.09		3.91
	5.47		0.98
			2.57
			5.23

Fluorines on the β-carbon of aliphatic amines have an acid strengthening effect. Other halogens do as well, but the conjugate bases undergo intramolecular displacement of the halide, and are thus unstable. In the conjugate acids of aromatic amines, the inductive effect is transmitted across the ring. Resonance effects are more pronounced when the substituent is para to the acidic functional group (protonated amine). Resonance effects are greater than inductive effects for the p-OMe group. The p-OMe group makes the anilinium ion less acidic. The p-Br substituent increases the acidity of the anilinium ion because inductive effects are greater than resonance effects. The p-CF_3 is electron withdrawing via inductive effects only.

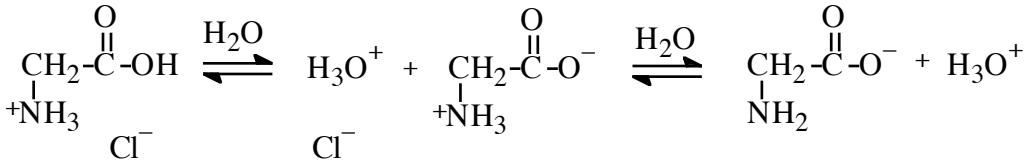
Amino Acids

The α–amino acids are amphoteric compounds which contain at least one carboxyl group and one amino group in the same molecule. The amino acids are the "building blocks" of proteins and they are extremely important organic compounds.

Since the amino group is more basic than the carboxylate anion the proton is on the amino group instead of on the carboxyl group. The amino acids exist as inner salts with a dipolar structure, often referred to as a Zwitterion structure, although sometimes the non-ionized form of the amino and carboxyl groups are written.



The amino acids exist predominantly as dipolar structures. It is conventional to express the basicity of bases and acidity of acids on a common scale, the pKa of acids or bases. The acidity of the conjugate acid of an amino acid is the acidity of the protonated amino acid, such as glycine hydrochloride. The amino acids, therefore, have two pKa values, the pKa of the conjugate acid and that of the inner salt or dipolar structure.



glycine hydrochloride $pK_{a_1} = 2.35$

glycine $pK_{a_2} = 9.78$

The pKa1 measures the acidity of the carboxyl group of the conjugate acid of glycine as affected by the electronegative protonated amine which has an acid strengthening effect. This explains the higher acidity of glycine hydrochloride compared to that of acetic acid (4.76). The pKa2 measures the acidity of the protonated amine of glycine as affected by the presence of the adjacent carboxylate anion.

At most pH's the dipolar structure exists:

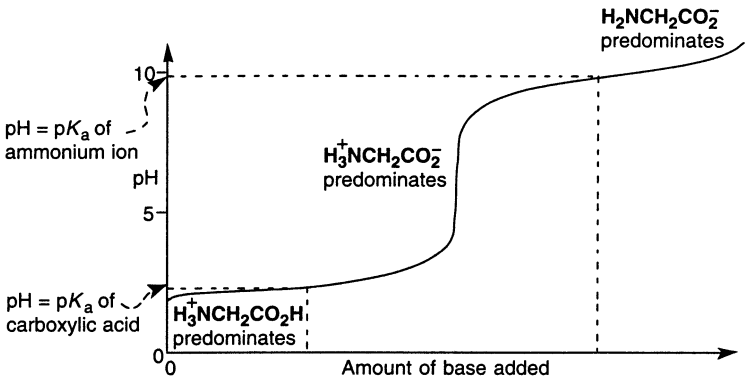
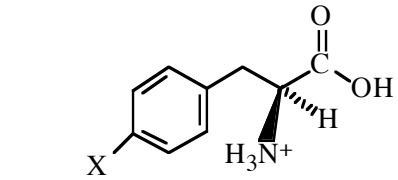
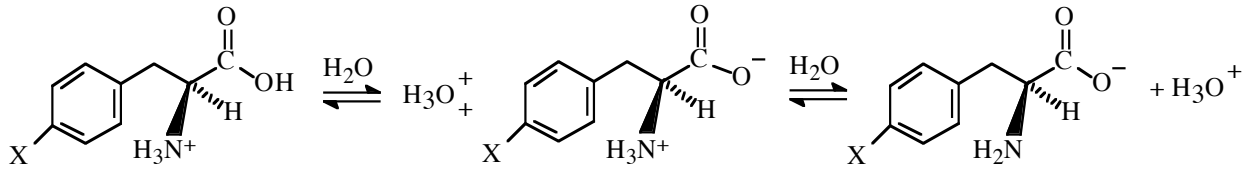


Fig. 2.5 Titration curve for glycine.

Substituent Effects on pK_a of Amino Group



	pK_{a1}	pK_{a2}
X = H phenylalanine	2.20	9.31
X = OH tyrosine	2.20	9.21
X = Cl p-Cl-phenylalanine	2.18	9.11



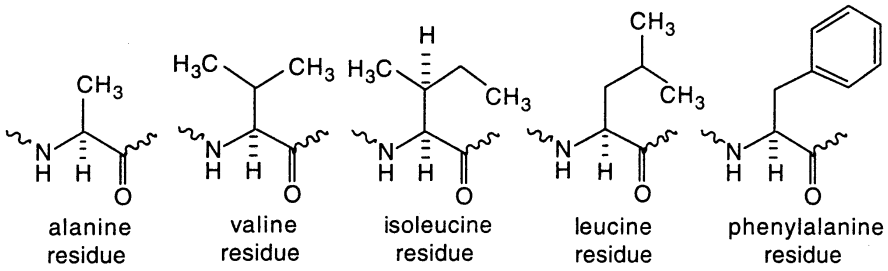
Inductive effect of substituent in aromatic ring influences pK_a of the α-NH_3^+ group.

Acidic and Basic Groups in Enzyme Catalysis

Enzymes are proteins or have a protein component. Proteins are macromolecules made up of amino acids linked by amide or peptide linkages. The amide linkages involve the α–amino and carboxyl groups of the amino acids making up the macromolecules. With the exception of glycine, all amino acids have groups on the α–carbon which result in side chains on the protein molecule. Certain functional groups on these side chains play a role in the catalytic action of enzymes. Certain amino acids have acidic and some have basic groups in the side chain. These groups can play a role in enzyme catalysis, acting as acids and/or bases.

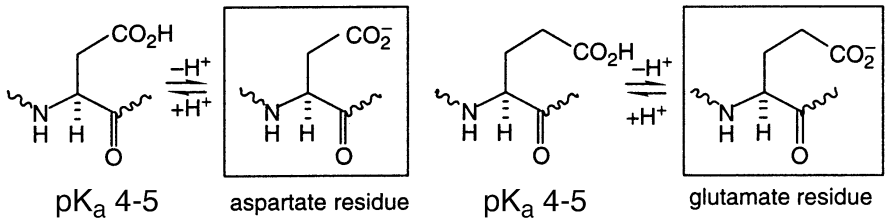
Amino Acid Residues with Hydrocarbon Side Chains

The side chains of several of the amino acids in proteins are simple hydrocarbons. Thus, when they are incorporated into a protein chain, no additional functional groups are introduced into the molecule. The non-polar nature of these residues, which precludes hydrogen bonding, plays a critical role in the structure of proteins: these residues are hydrophobic.



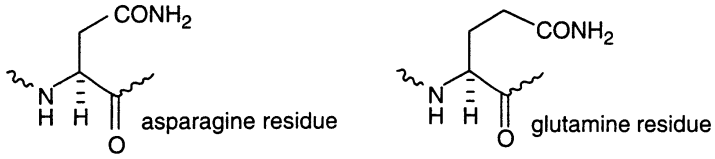
Amino Acid Residues With Carboxylic Acid Side Chains

The side chains of two of the amino acids, aspartic and glutamic acids, contain carboxylic acid functional groups linked by a hydrocarbon spacer, of one or two methylene groups respectively, to the α–carbon. At neutral pH, these groups will be present in the anionic conjugate base form (aspartate and glutamate).



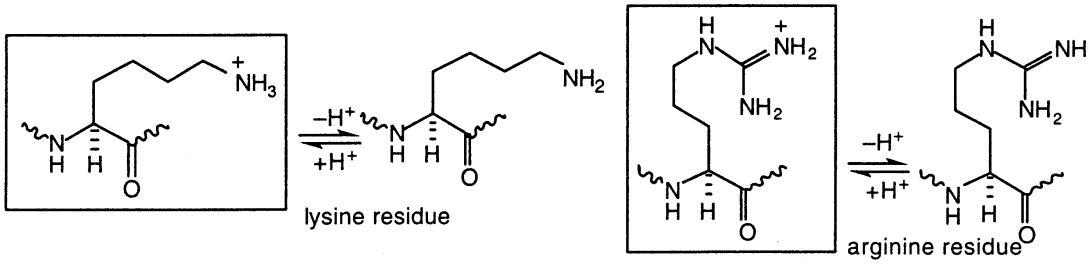
Amino Acid Residues with Amide Side Chains

A further two amino acids, asparagine and glutamine, are closely related to aspartic and glutamic acids. In these, instead of carboxylic acid, the side chain contains an amide group. Amides can participate in hydrogen bonding, but they are neither strong acids nor bases, and do not affect the acid–base chemistry of proteins.



Acyclic Amino Acid Residues with Basic Nitrogen-Containing Side Chains

Two of the protein amino acids have side chains consisting of a linear carbon chain terminating in a basic nitrogen functional group. The side chain of lysine is a four–carbon chain ending in an amino group. This primary amine bears a non–bonding electron pair and is of similar basicity to the amines considered previously. The pKa of the corresponding ammonium ion is 10.5 and, at neutral pH, this group is present in solution as a cation.

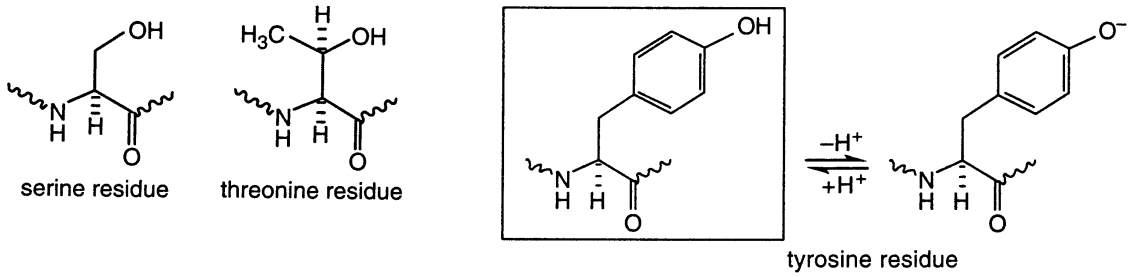


In the case of arginine, protonation of the basic nitrogen leads to a cation in which the positive charge is dispersed over three nitrogen atoms. This factor ensures and enhanced stability to the protonated form of arginine which has a pKa of 12.5 and is present as a cation under physiological conditions.

Amino Acid Residues with Hydroxyl Functional Groups

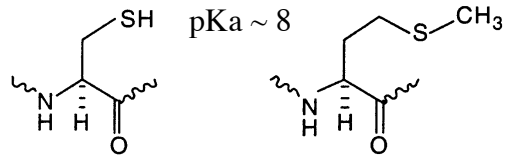
The side chains of three amino acids contain hydroxyl groups. Serine and threonine are simple alcohols. For each of these residues, the hydroxyl group is attached to a carbon adjacent to the α–carbon. Threonine is distinguished from serine by an extra methyl group that makes it a secondary alcohol. An isolated hydroxyl group can act as an acid or a base, but neither process is especially favorable (the pKa of the hydroxyl or serine is approximately 16).

In tyrosine, the hydroxyl function is attached to an aromatic ring. Here the functional group is a phenol. The aromatic ring stabilizes the charge on the deprotonated form. This enhances the stability of the conjugate base and lowers the pKa (to ca. 10) facilitating acid–base chemistry. Tyrosine is usually found in the hydroxyl form, but it is occasionally found to act as an acid under physiological conditions.



Sulphur–Containing Amino Acid Residues

The side chains of two protein amino acids have sulphur–based functional groups. Cysteine is the sulphur analogue of serine, containing a thiol functional group rather than a hydroxyl function. In aqueous solution such groups are moderately acidic (pKa ca• 8). However, the properties of sulphur differ from those of oxygen and thiols do not form strong hydrogen bonds. In general, sulphur–containing side chains behave as relatively non–polar groups. In addition, the thiol group has unique chemical properties: it is the most reaily oxidized of all the functional groups under consideration. When two thiols are oxidized, a disulfide bond results. Disulfide bonds are important features of some protein structures.



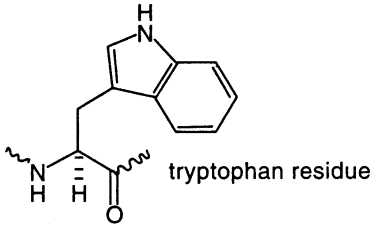
cysteine residue methionine residue

The amino acid methionine contains a thioether group rather than a thiol. For the present discussion, the most significant feature of the methionine side chain is its generally non–polar character.

Amino Acids Containing Nitrogen Heterocycles

The final three common amino acids are rather different from one another, but they each contain cyclic structures involving nitrogen which are responsible for their distinctive chemistry.

Tryptophan has a nitrogen embedded in a large aromatic framework (an indole) which behaves as a non–basic nitrogen, although it can form hydrogen bonds. Tryptophan is more like the side chain of phenylalanine than most of the remaining nitrogen–containing side chains. Its is a hydrophobic residue.

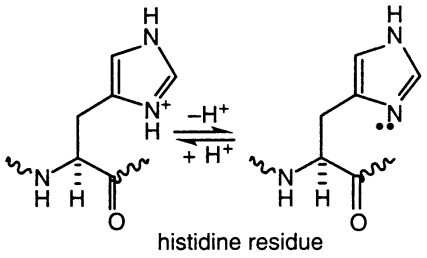


tryptophan residue

A heterocyclic compound contains a ring in which one of the ring atoms is not carbon.

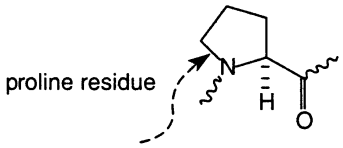
Histidine also has a side chain with an aromatic ring. In this case the ring (an imidazole) has two nitrogen atoms, and can be protonated. The charge on the cation of the protonated form is dispersed over the two nitrogen atoms. Histidine is moderately basic with the pKa of the conjugate acid being ca 7. Such a pKa allows both conjugate acid and base forms to be readily accessible at neutral pH. Histidine is ideally placed to act as an acid–base catalyst in proteins operating at around pH 7.

If both protonated and non-protonated forms are present, then the side chain can act as both an acid and a base. This is the situation for histidine. For this reason, histidine residues are often important in catalysing biochemical acid–base processes. The special chemistry of histidine is important in the functioning of many proteins.



Protonated and neutral forms of histidine are both physiologically important. This evenly balanced equilibrium underpins a key role of histidine in biological acid–base chemistry.

Finally, proline is fundamentally different from the other protein amino acids. The side chain comprises a three–carbon and, as with other hydrocarbon side chains, contributes no unusual chemical features to the amino acid or derivatives. In this case, however, a ring structure is formed by the side chain linking back to the α–amino nitrogen. This cyclic structure constrains the shapes which this amino acid can adopt. As a result, the presence of proline in a protein has significant effects on its three–dimensional structure.



The side chain links back and connects to the α–nitrogen, forming a ring.