TEXTBOOK

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FUNDAMENTALS OF BIOORGANIC CHEMISTRY

3rd edition

Министерство науки и высшего образования РФ
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Chapter 5
ACIDITY AND BASICITY OF ORGANIC COMPOUNDS

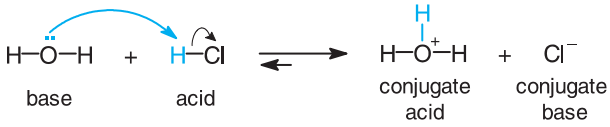
Acidity and basicity are the main notions determining many fundamental physico-chemical and biochemical properties of organic compounds. First of all, acid and basic catalyses are the most widespread enzymatic reactions. Besides, the acid-base behaviour of organic compounds helps explain much of their chemistry.

5.1. GENERAL CONCEPTS OF ACIDS AND BASES

At present, there are two main concepts of acids and bases in organic chemistry. In the first one, independently proposed by the Danish physico-chemist J.N. Brønstedt and the English chemist T.M. Lowry (in the 1920's), it is stated that:

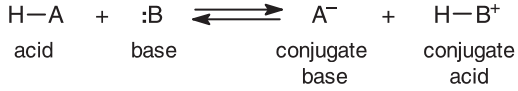
An acid is a neutral molecule or an ion that can donate a proton, and a base is a neutral molecule or an ion that can accept a proton.

For example, when gaseous hydrogen chloride dissolves in water, the latter accepts a proton from hydrogen chloride:

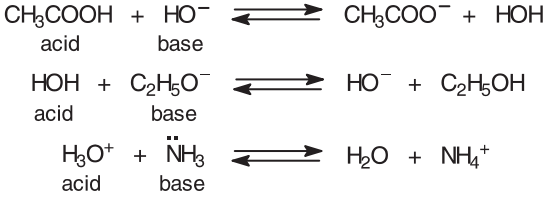


Here hydrogen chloride acts as a proton donor (an acid), and water acts as a proton acceptor (a base). The products of this reaction are the hydronium ion, H_3O^+ (the *conjugate acid* of water), and the chloride ion, Cl^- (the *conjugate base* of hydrogen chloride). Note that the term *conjugate* is used in another sense different from that in Chapter 3.

In a general sense, acid–base reaction can be expressed in the following way:



Other examples of acid–base interaction are presented below:

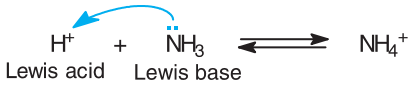


In the above examples, water acts either as an acid or as a base, as well as it represents either a conjugate acid or conjugate base.

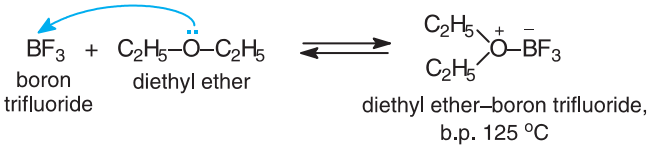
Another definition of acids and bases was proposed by G.N. Lewis (in 1926).

A Lewis acid is any substance that can accept an electron pair, and a Lewis base is any substance that can donate an electron pair in forming a covalent bond.

According to this definition, a Lewis acid must have a vacant orbital for bonding. The simplest Lewis acid is a proton because it can accept an electron pair from a Lewis base to fill its 1*s* shell, for example:



Not only proton donors belong to Lewis acids but also many other species with an atom whose valence shell is unfilled, such as various metal cations or compounds of Group 3A elements (BF_3, $AlCl_3$). Thus, boron trifluoride (a gaseous Lewis acid) reacts with diethyl ether (a liquid Lewis base, boiling point 36 °C) to form a stable addition product:



The Lewis definition of acids is much broader than the Brønstedt definition, whereas bases are defined very similarly in both theories. The Lewis conception finds a use for a big variety of organic reactions. The only, but substantial, disadvantage of the Lewis theory consists in the absence of quantitative acidity and basicity scales. The Brønstedt concept is, therefore, more widely used in organic chemistry.

5.2. ACIDS

Acids differ greatly in their proton-donating properties. Stronger acids, such as sulfuric, nitric, hydrochloric and similar acids, react almost completely with water, whereas weaker acids, such as acetic acid (and most of organic acids), react only slightly. The exact strength of an acid can be measured quantitatively by its *acidity constant*.

Acid-base interaction in aqueous solution can be expressed by means of the equilibrium constant for its dissociation (K_{eq}), where HA represents any acid[1]:

$$HA + H_2O \rightleftharpoons A^- + H_3O^+ \qquad K_{eq} = \frac{[A^-]\,[H_3O^+]}{[HA]\,[H_2O]}$$

Since the concentration of water, $[H_2O]$, is nearly constant (~55.5 M), it is combined with K_{eq} to give the acidity constant, K_a:

$$K_a = K_{eq}\,[H_2O] = \frac{[A^-]\,[H_3O^+]}{[HA]}$$

[1] Remember that square brackets denote molar concentration (M) of the enclosed species.

Strong inorganic acids have their equilibrium shifted to the right, thus increasing the concentration of H_3O^+ and the value of K_a. They have K_a's in the range from 10^2 to 10^{10}. Organic acids belong to weaker acids and have their equilibrium shifted to the left that results in smaller acidity constants (less than 10^{-4} for carboxylic acids).

In order to avoid using numbers with negative exponents, acid strengths are often expressed as pK_a, which is equal to the negative logarithm of the acidity constant: $pK_a = -\log K_a$.

The relationship between K_a and pK_a values signifies that:

A stronger acid has a lower pK_a, and a weaker acid has a higher pK_a.

The Brønstedt definition of acidity is extremely useful in organic and bioorganic chemistry because almost all organic compounds contain hydrogen and are, therefore, potential acids. Usually, organic acids are classified into:

- OH acids (carboxylic acids, alcohols, and phenols);
- SH acids (thiols);
- NH acids (amines, amides, some heterocycles, and ammonium salts);
- CH acids (hydrocarbons and their derivatives).

A part of a molecule that involves hydrogen together with an atom attached to it is called an *acidic site*.

We can compare the strength of different acids if we know their pK_a values. These values were determined for most important organic compounds. Table 5.1 lists pK_a values for selected representatives of different organic classes; some inorganic compounds are given for reference.

Problem 5.1. The K_a of nitric acid is about 44. Find the pK_a's of acetic acid and phenol from Table 5.1 and rank all the three compounds on their acidity strength.

If pK_a values are not available, we nevertheless are able to compare the strength of Brønstedt acids in terms of stability of their conjugate bases (anions) according to the objective regularity:

The more stable is an anion, the stronger is an acid.

The following factors influence the stability of conjugate bases:

- electronegativity and polarizability of the atom in the acidic site;
- delocalization of a negative charge due to the effect of substituents in a molecule;
- solvation effects.

These factors will be discussed below.

5.2.1. Electronegativity and Polarizability of an Atom

The greater electronegativity of an atom in the acidic site, the more stable conjugate base is observed within one row of the periodic table of the elements. This is accounted for the higher ability of oxygen (in comparison with nitrogen and carbon, elements of the second row) to hold a negative charge. For this reason, alcohols are stronger as acids than amines, and alkanes show extremely low acidity, as shown in Table 5.2.

Table 5.1. The values of pK_a for selected Brønstedt acids

Name	*Formula*	*Conjugate base*	pK_a*
Organic acids			
OH acids			
Ethanol	C_2H_5OH	$C_2H_5O^-$	16.0
Phenol	C_6H_5OH	$C_6H_5O^-$	10.0
Acetic acid	CH_3COOH	CH_3COO^-	4.8
Benzoic acid	C_6H_5COOH	$C_6H_5COO^-$	4.2
Lactic acid	$CH_3CH(OH)COOH$	$CH_3CH(OH)COO^-$	3.9
Citric acid	$HOOCCH_2\underset{\displaystyle COOH}{\overset{\displaystyle |}{C}}H(OH)CH_2COOH$	$HOOCCH_2\underset{\displaystyle COO^-}{\overset{\displaystyle |}{C}}H(OH)CH_2COOH$	3.1
SH acids			
Ethanethiol	C_2H_5SH	$C_2H_5S^-$	12
Thiophenol	C_6H_5SH	$C_6H_5S^-$	8
Thioacetic acid	$CH_3C(O)SH$	$CH_3C(O)S^-$	3.3
NH acids			
Acetamide	$CH_3C(O)NH_2$	$CH_3C(O)NH^-$	25
CH acids			
Methane	CH_4	CH_3^-	40
Acetylene	$CH{\equiv}CH$	$CH{\equiv}C^-$	25
Acetone	$CH_3C(O)CH_3$	$CH_3C(O)CH_2^-$	20
Chloroform	Cl_3CH	Cl_3C^-	15.7
Inorganic acids			
Strong acids			
Hydroiodic acid	HI	I^-	–11
Hydrobromic acid	HBr	Br^-	–9
Hydrochloric acid	HCl	Cl^-	–7
Sulfuric acid	H_2SO_4	HSO_4^-	–3
Nitric acid	HNO_3	NO_3^-	–1.6
Weak acids			
Phosphoric acid	H_3PO_4	$H_2PO_4^-$	2.1
Hydrofluoric acid	HF	F^-	3.4
Carbonic acid	H_2CO_3	HCO_3^-	6.4
Hydrogen sulfide	H_2S	HS^-	7.0
Ammonium ion	NH_4^+	NH_3	9.2
Water	H_2O	HO^-	15.7
Ammonia**	NH_3	NH_2^-	36

* Approximate values for very strong acids (pK_a <–2) and very weak acids (pK_a >16).

** Do not be surprised to see ammonia in the list. The NH_3 molecule contains hydrogen atoms and is, therefore, a potential acid.

Table 5.2. Acid strength of compounds of different classes

Class of compounds	*Formula*	*Element's electronegativity in the acidic site*	pK_a
Alkanes	RCH_3	2.5	~44
Amines	RNH_2	3.0	~30
Alcohols	ROH	3.5	16–18
Thiols	RSH	2.6	11–12
Phenols	ArOH	3.5	~10
Carboxylic acids	RCOOH	3.5	~5

Another stabilizing factor is the *polarizability* (opposed to polarity) of an element in the acidic site. This term means the ability of the electrons to respond to a changing electric field, as a result of its interaction with solvent or with other polar reagents. Relative polarizability increases *within one group* of the Periodic Table from top to bottom because a larger atom holds electrons more loosely than a smaller atom with tightly held electrons. For example, iodine whose electrons are far from the nucleus is much more polarizable than fluorine whose electrons are close to the nucleus. Thus, the polarizability of halogens increases in the following order: F < Cl < Br < I. Stability of the corresponding halide ions increases in the same order.

Problem 5.2. Fluorine is much more electronegative than iodine, yet hydroiodic acid is much stronger than hydrofluoric acid (by a factor of approximately 10^{14}). Explain this difference.

Similarly, the size of the sulfur atom is larger than that of oxygen. Therefore, the negative charge in a thiolate ion, RS^-, is delocalized more effectively in comparison with an alkoxide ion, RO^-. Indeed, thiols show evidently higher acidity than alcohols (Tables 6.1 and 6.2).

The difference in the acidity of thiols and alcohols is displayed in the reactions with aqueous alkali. Thiols do react to give salts, whereas alcohols practically do not react:

$$\underset{\text{thiol}}{RSH} + NaOH \longrightarrow \underset{\text{sodium thiolate}}{RS^-Na^+} + H_2O$$

$$ROH + NaOH \rightleftharpoons RO^-Na^+ + H_2O$$

Alkoxides (alcohol salts) can be obtained only in the reaction of alcohols with active metals or with extremely strong bases, such as sodium hydride, NaH, or sodium amide, $NaNH_2$. For example:

$$\underset{\text{alcohol}}{ROH} + NaH\ (\text{or } Na) \longrightarrow \underset{\text{sodium alkoxide}}{RO^-Na^+} + H_2\uparrow$$

Metal salts of alcohols are themselves strong bases used frequently as reagents in organic chemistry.

Problem 5.3. Show the order of acidity increase for the following compounds: (a) butan-1-ol, (b) ethanethiol, (c) ethanol; (d) ethylamine. Explain the reasons for your choice. Write an equation for the salt formation for the most acidic compound.

5.2.2. Delocalization of a Charge in an Anion

As we have seen, there are three types of OH acids, namely carboxylic acids, alcohols, and phenols. As follows from their general name, carboxylic acids are acidic compounds. They, therefore, react with bases such as metal hydroxides to give metal carboxylate salts:

$$\underset{\text{carboxylic acid}}{RCOOH} + NaOH \longrightarrow \underset{\text{sodium carboxylate}}{RCOO^- Na^+} + H_2O$$

Unsubstituted carboxylic acids are much weaker than mineral acids; nevertheless they are much stronger than alcohols and phenols (compare the pK_a values in Tables 5.1 and 5.2). The question arises, why carboxylic acids are the most acidic organic compounds even though all the three types of the OH acids contain the same acidic site?

To answer this question let us consider, first of all, at the relative stability of an alkoxide ion, RO^-, a phenoxide ion, ArO^-, and a carboxylate ion, $RCOO^-$. The former is an oxygen anion in which the negative charge is localized on a single electronegative atom.

$$\underset{\text{ethanol}}{C_2H_5OH} + H_2O \rightleftharpoons \underset{\substack{\text{ethoxide ion}\\ \textit{unstabilized}}}{C_2H_5O^-} + H_3O^+$$

Phenols are stronger acids than alcohols by a factor of at least 10^5. The difference is to be accounted for by higher stability of the phenoxide ion that, in turn, is a result of a p,π conjugation (Fig. 5.1, *a*). Stability of the phenoxide ion is also manifested by resonance theory. We can write several resonance structures for the anion, showing delocalization of the negative charge over the benzene ring (Fig. 5.1, *b*). At the same time, no analogous resonance ions are possible for an alkoxide ion.

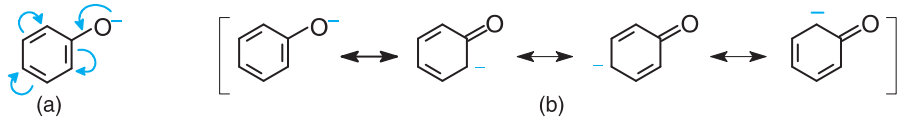


Figure 5.1. Representation of charge delocalization in the phenoxide ion: p,π conjugation (a), and resonance hybrid (b)

Unlike alcohols, phenols react with alkalis to give water-soluble salts, phenoxides:

$$\underset{\substack{\text{phenol}\\ \textit{slightly soluble}}}{C_6H_5OH} + NaOH \longrightarrow \underset{\substack{\text{sodium phenoxide}\\ \textit{soluble}}}{C_6H_5O^- Na^+} + H_2O$$

The carboxylate ion is also an oxygen anion, but the negative charge is delocalized over both oxygen atoms through p,π conjugation (Fig. 5.2, *a*). This results in stabilization of the anion. In resonance terms, the carboxylate ion is a stabilized resonance hybrid of two *equivalent* structures (Fig. 5.2, *b*) neither of which contains a localized charge (Fig. 5.2, *c*).

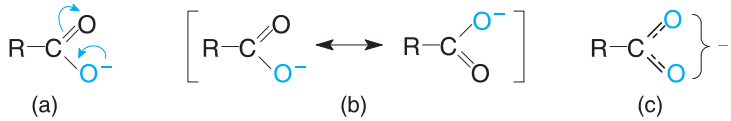


Figure 5.2. Representation of charge delocalization in the carboxylate ion: p,π conjugation (a), resonance hybrid (b), and equal charges on both oxygens (c)

Equivalence of both carbon–oxygen bonds becomes clear from an orbital picture of the carboxylate ion shown in Fig. 5.3. Four *p* electrons of a conjugated system are delocalized throughout three *p* orbitals. Consequently, the *p* orbital on the carboxylate carbon overlaps equally well with *p* orbitals of both oxygen atoms, thus making both carbon–oxygen bonds intermediate between single and double bonds (see also Fig. 5.2, *c*).

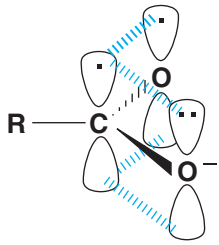
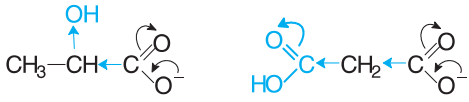


Figure 5.3. Orbital overlap in a carboxylate ion

Effects of substituents on acidity. Other factors that stabilize a conjugate base (alkoxide, phenoxide, or carboxylate ion) result in increased acidity. It might be an electron-withdrawing group disposed near an acidic site. Such groups in aliphatic series are, for example, halogens, the hydroxy group, and an additional carboxy group. Let us consider acidity of substituted carboxylic acids.

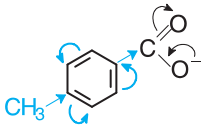
Electron-withdrawing substituents shift inductively electron density from the anionic site, delocalizing the negative charge on the carboxylate ion, stabilizing it, and increasing acidity. Lactic acid (pK_a 3.9) and malonic acid (pK_a 2.9) exemplify this consideration (compare these values with the value of 4.8 for unsubstituted propionic acid):



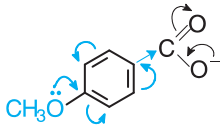
lactate ion malonate ion

In contrast to the substituents mentioned just before, electron-donating groups should have the opposite effect by localizing the negative charge, destabilizing the carboxylate ion, and decreasing acidity. It is interesting that there are no carboxylic acids having electron-donating groups attached to an aliphatic chain.

Electron-donating substituents, however, can be present in aromatic carboxylic acids (recall positive inductive or mesomeric effect of alkyl, amino, hydroxy, and alkoxy groups attached to the benzene ring). But these substituents influence the negative charge of a carboxylate ion only inductively. Thus, a slight decrease of acidity is observed for 4-methylbenzoic and 4-methoxybenzoic acids (compare the values given below with the value of 4.2 for benzoic acid itself).



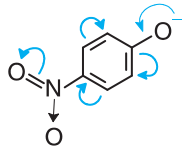
4-methylbenzoate ion, pK_a 4.4 for conjugate acid



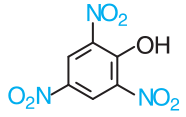
4-methoxybenzoate ion, pK_a 4.5 for conjugate acid

For an obvious reason, electron-withdrawing groups introduced in the benzene ring increase the acidity of substituted benzoic acids. Here we also notice a moderate acidity increase even though a substituent is a very strong electron-withdrawing nitro group. This is supported by the acidity data for 4-nitrobenzoic acid (pK_a 3.4) and 4-chlorobenzoic acid (pK_a 4.0).

Inductive and mesomeric effects of substituents are also important in determining acidity of substituted phenols. Very similar regularities are to be observed in this case. As a rule, phenols bearing an electron-withdrawing substituent are more acidic than phenol itself, and phenols with electron-donating substituents are less acidic by the reasons that have just been discussed for substituted carboxylic acids. For example, 4-nitrophenol (pK_a 7.1) is a markedly stronger acid than phenol (pK_a 10.0). The nitro group acts in two ways: it stabilizes the anion not only through the inductive effect, but also through a long chain of conjugation as shown below. Additional electron-withdrawing substituents further increase acidity. Thus, 2,4,6-trinitrophenol, commonly called *picric acid*, is much stronger than most carboxylic acids.



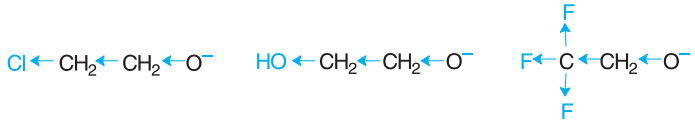
4-nitrophenoxide ion



2,4,6-trinitrophenol (picric acid), pK_a 0.8

Problem 5.4. Compare the acidic sites in the salicylic (2-hydroxybenzoic) acid molecule. Write an equation for its reaction with: (a) equimolar amount of sodium hydroxide; (b) excess sodium hydroxide.

In the alcohol series, electron-withdrawing substituents make a compound more acidic owing to the fact that the negative charge in a substituted alkoxide ion is spread out over a larger area. Usually, electron-withdrawing substituents increase acidity of alcohols slightly, by a factor within 1–2. Only several strongly electronegative fluorine atoms (as in a CF_3 group) increase acidity obviously. The pK_a values for 2-chloroethanol, ethylene glycol, and 2,2,2-trifluoroethanol (presented below) support this reasoning:



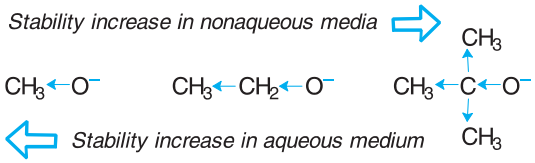
pK_a's of conjugate acids:	14.3	14.8	12.4

In general, alcohols are the weakest OH acids.

5.2.3. Solvation Effects

Solvation of an anion is a further factor that influences stability of the conjugate base. Water is a solvent in biological systems; therefore, an effect of hydration (interaction of a substance with water) must be taken into consideration.

Lower alcohols, such as methanol and ethanol, are similar to water in acidity (Table 5.1), while *tert*-butyl alcohol, $(CH_3)_3COH$, is slightly less acidic (pK_a ~18). It is surprising, because the *tert*-butoxide ion is more stable than the ethoxide and methoxide ions, when we *only* compare the inductive effect of alkyl groups:



In fact, this is true for solutions in nonpolar solvents. In an aqueous solution, water surrounds the oxygen atom, thus helping to stabilize the anion. Small anions of unhindered lower alcohols (Fig. 5.4, *a*) are better hydrated than bulky alkoxide ions of tertiary alcohols (Fig. 5.4, *b*).

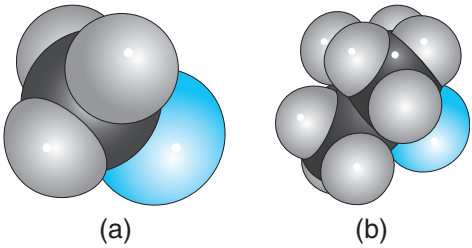


Figure 5.4. Space-filling models:
a methoxide ion (a) and *tert*-butoxide ion (b)

5.3. BASES

According to the Brønstedt–Lowry definition given earlier, any anion or neutral compound, containing a heteroatom with a lone-pair of electrons, can act as a base. This is the main group of bases called *n-bases* (having **non**shared electrons). They are further classified into the following types, depending on the nature of heteroatom, which represents the *basic site* (only neutral compounds are listed here and in the following Tables 5.3 and 5.4):

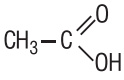
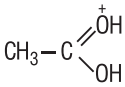
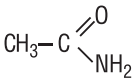
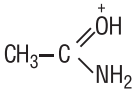
- N-bases (amines and many heterocycles);
- O-bases (alcohols, phenols, ethers, and compounds with the >C=O group);
- S-bases (thiols and sulfides).

A less significant group of bases constitutes π-*bases*, in which electrons of the localized π bond or π electrons of the conjugated system can accept a proton to form noncovalent complexes. Table 5.4 lists some representatives of *n*-bases and their strength, which will be discussed below.

Table 5.3. Base strength of compounds of different classes

Class of compounds	*Formula*	*Name of onium salts produced*	$pK_{BH}+$
Aliphatic amines	RNH_2	Ammonium	10–11
Aromatic amines	$ArNH_2$	Ammonium	4–5
Alcohols	ROH	Oxonium	from –2 to –5
Phenols	ArOH	Oxonium	–6
Ethers	ROR	Oxonium	from –3 to –6
Thiols	RSH	Sulfonium	–7

Table 5.4. The values of $pK_{BH}+$ for selected bases

Name	*Formula*	*Conjugate acid*	$pK_{BH}+$
N-Bases			
Ammonia	NH_3	NH_4^+	9.2
Ethylamine	$C_2H_5NH_2$	$C_2H_5NH_3^+$	10.7
Diethylamine	$(C_2H_5)_2NH$	$(C_2H_5)_2NH_2^+$	10.9
Triethylamine	$(C_2H_5)_3N$	$(C_2H_5)_3NH^+$	10.9
Aniline	$C_6H_5NH_2$	$C_6H_5NH_3^+$	4.6
Diphenylamine	$(C_6H_5)_2NH$	$(C_6H_5)_2NH_2^+$	0.8
O-Bases			
Water	H_2O	H_3O^+	–1.7
Ethanol	C_2H_5OH	$C_2H_5OH_2^+$	–2.5
Diethyl ether	$(C_2H_5)_2O$	$(C_2H_5)_2OH^+$	–3.6
Phenol	C_6H_5OH	$C_6H_5OH_2^+$	–6.7
Acetic acid			–6
Acetamide			–0.5
Acetone	$(CH_3)_2C{=}O$	$(CH_3)_2C{=}OH^+$	–7
Urea	$(NH_2)_2C{=}O$	$(NH_2)_2C{=}OH^+$	0.1
S-Bases			
Methanethiol	CH_3SH	$CH_3SH_2^+$	–6.7
Dimethyl sulfide	$(CH_3)_2S$	$(CH_3)_2SH^+$	–5.3

Organic N-bases react with acids to yield stable ammonium salts, which, usually, are soluble in water. Many drugs are used as salts because of their better solubility.

$$\underset{\text{alkylamine}}{RNH_2} + HCl \longrightarrow \underset{\text{alkylammonium chloride}}{RNH_3^+\,Cl^-}$$

Bases differ too much in their proton-accepting ability. The strength of bases depends on the electronegativity and polarizability of the atom, which represents the basic site. Within one row of the periodic table, an atom with higher electronegativity is less capable of proton acceptance; therefore, amines are more basic than alcohols (just as ammonia is a stronger base than water).

When we compare basicity of alcohols (as O-bases) and thiols (as S-bases), the difference in polarizability of oxygen and sulfur should be taken into consideration. The size of the sulfur atom is larger than that of the oxygen atom; therefore, electron density is less on sulfur. For this reason, thiols, as well as organic sulfides, are not able to form a strong bond with a proton, i.e., they are weaker bases than alcohols. Thus we can say that the strength of bases with the same or similar R substituents increases in the following way[1]:

$$\textit{Basicity increase} \Rightarrow$$

$$RSH < ROH << RNH_2$$

Acid-base interaction in an aqueous medium can be used for quantitative determination of the base strength, where K_b is the basicity constant:

$$\underset{\text{base}}{\ddot{B}} + \underset{\text{acid}}{H_2O} \rightleftharpoons \underset{\text{conjugate acid}}{BH^+} + \underset{\text{conjugate base}}{HO^-}; \qquad K_b = \frac{[BH^+]\,[HO^-]}{[B]}$$

A more convenient way for basicity evaluation is to consider the acidity of the corresponding conjugate acid. For example, a primary amine RNH_2 and its ammonium ion RNH_3^+ are related to each other as a base and its conjugate acid, according to the following equilibrium:

$$\underset{\text{conjugate acid}}{RNH_3^+} + H_2O \rightleftharpoons \underset{\text{base}}{RNH_2} + H_3O^+$$

The acidity constant of the conjugate acid designated in this case by K_{BH^+} is expressed as follows:

$$K_{BH^+} = \frac{[B]\,[H_3O^+]}{[BH^+]} \quad \text{and} \quad pK_{BH^+} = -\log K_{BH^+}$$

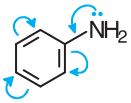
This constant is designated more often by pK_a. It should be differentiated whether it is really related to the acidity of a compound or to the acidity of its conjugate base.

Table 5.3 and previous general consideration clearly show superior basicity of N-bases (with few exceptions) to O- and S-bases. Aliphatic amines are the strongest of the N-bases, somewhat stronger than ammonia. They have K_{BH^+} values in the narrow range (10–11), regardless of their structure.

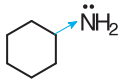
Aromatic amines, or arylamines, are less basic than aliphatic, because the nitrogen lone pair of electrons is delocalized by orbital overlap with the aromatic

[1] This is in accordance with a mnemonics *SON* (sulfur, oxygen, nitrogen).

π-electron system through *p*,π conjugation. They are, therefore, less available for proton acceptance. Cyclohexylamine, for example, is 10^6 times stronger as a base than aniline.

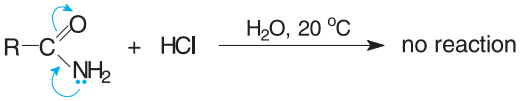


aniline, pK_{BH^+} 4.6



cyclohexylamine, pK_{BH^+} 10.6

Amides, $RC(O)NH_2$, are much weaker bases on a similar reason. Here, the nitrogen lone pair of electrons is *p*,π conjugated with the C=O double bond. Extremely low basicity of amides is confirmed by the fact that water insoluble amides do not dissolve in aqueous solutions of strong mineral acids.



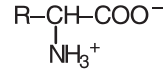
Substituents in the alkyl or aryl part of an amine molecule affect basicity. Electron-withdrawing groups increase it; in other words, they decrease the acidity of the conjugate acid. Conversely, electron-donating groups increase basicity.

Problem 5.5. Show the order of basicity increase for the following compounds: (a) ammonia; (b) ethanethiol; (c) propan-1-ol; (d) ethylmethylamine. Explain the reasons for your choice. Write an equation for the salt formation for the most basic compound.

Basic properties of heterocycles will be considered in Chapter 16.

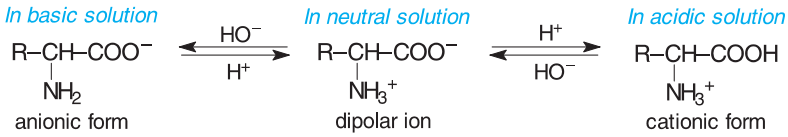
5.4. ACIDIC AND BASIC SITES IN A MOLECULE

Many organic compounds are *amphoteric*. That is, they are capable of functioning either as an acid or as a base, depending on the circumstances. Typical examples of these compounds are natural (or protein) amino acids. Their structure is usually written as $RCH(NH_2)COOH$ with two independent functional groups. The presence of an acidic (COOH) and a basic (NH_2) sites in the same molecule result in an acid–base interaction to produce a salt-like compound. Therefore, the real structure of amino acids in neutral solution and in the crystalline state is a *dipolar ion* structure, sometimes called *zwitterion* (from the German *Zwitter* – hybrid).



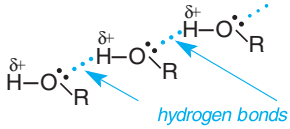
dipolar structure
of an amino acid

The amino acids can be protonated in acidic medium, thus converting into a cationic (ammonium) form. In alkaline medium, they exist as carboxylate ions with a free amino group:



Molecules containing a weak acidic and weak basic site in their structure can form an intramolecular or intermolecular *hydrogen bond*. Water is the simplest and most known amphoteric compound that forms intermolecular hydrogen bonds (shown usually by a dotted line).

Intermolecular Hydrogen Bonding In Alcohols



Additional Problems

5.6. Show the order of acidity increase for the following compounds: (a) ethane-1,2-diol; (b) ethanol; (c) 4-nitrophenol; (d) phenol.
Explain the reasons for your choice. Write an equation for the salt formation using the most acidic compound.

5.7. Show the order of basicity increase for the following compounds: (a) ammonia; (b) aniline; (c) cyclohexylamine; (d) phenol.
Explain the reasons for your choice. Write an equation for the salt formation using the most basic compound.

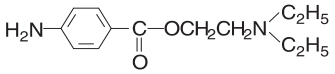
5.8. Propose a chemical method for isolating phenol and aniline from their mixture in benzene solution.

5.9. Propose a chemical procedure for isolating butan-1-ol and butane-1-thiol from the mixture of the two compounds. Notice that both compounds are liquids insoluble in water.

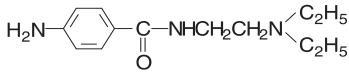
5.10. Explain the reason of the greater pK_a value for *p*-hydroxybenzoic acid (4.5) compared with that for benzoic acid (4.2).
Try to explain why *o*-hydroxybenzoic (salicylic) acid is a stronger acid (pK_a 3.0) than benzoic acid. (*Hint*: Consider all factors that stabilize a conjugate base.)

5.11. The pK_a values for phenol and 4-nitrophenol are 7.1 and 10.0, whereas the pK_a values for benzoic and 4-nitrobenzoic acids differ to a lesser extent (3.4 and 4.2).
Explain these differences, but first refer the pK_a values to each compound in the absence of reference data.

5.12. Discuss all the basicity sites in the Procaine molecule (see the structure). Draw the structure of Procaine hydrochloride (also called Novocain).



5.13. Procainamide, or Novocainamide (see the structure), is used in medicine in the form of hydrochloric acid salt. Discuss all the basicity sites in the Procainamide molecule and draw the structure of its hydrochloride salt.



5.14. The antibacterial drug (see the structure below) is used as the sodium salt, Sulfacyl soluble. Discuss all the acidity sites in the molecule and draw the structure of its sodium salt.