Chapter 1
Introduction

Learning Objectives
After completing this chapter, students should be able to:

• describe the role of chemistry in modern life;
• define some of the physical properties of drugs, for example, melting point, boiling point, polarity, solubility and acid-base properties;
• explain the terms pH, \( pK_a \), buffer and neutralization.

1.1 ROLE OF CHEMISTRY IN MODERN LIFE

Chemistry is the science of the composition, structure, properties and reactions of matters, especially of atomic and molecular systems.

Life itself is full of chemistry, that is, life is the reflection of a series of continuous biochemical processes. Right from the composition of the cell to the whole organism, the presence of chemistry is conspicuous. Human beings are physically constructed of chemicals, live in a plethora of chemicals and are dependent on chemicals for their quality of modern life. All living organisms are composed of numerous organic substances. Evolution of life begins from one single organic compound called a nucleotide. Nucleotides join together to form the building blocks of life. Our identities, hereditries and continuation of generations, all are governed by chemistry.

In our everyday life, whatever we see, use or consume have been the gifts of research in chemistry for thousands of years. In fact, chemistry is applied everywhere in modern life. From the colour of our clothes to the shapes of our PCs,
Chemistry for Pharmacy Students

All are possible due to chemistry. It has played a major role in pharmaceutical advances, forensic science and modern agriculture. Diseases and their remedies have also been a part of human lives. Chemistry plays an important role in understanding diseases and their remedies; that is, drugs.

Medicines or drugs that we take for the treatment of various ailments are chemicals, either organic or inorganic molecules. However, most drugs are organic molecules. These molecules are either obtained from natural sources or synthesized in chemistry laboratories. Some important drug molecules are discussed here.

Aspirin, an organic molecule, is chemically known as acetyl salicylic acid and is an analgesic (relieves pain), antipyretic (reduces fever) and anti-inflammatory (reduces swelling) drug. Studies suggest that aspirin can also reduce the risk of heart attack. It is probably the most popular and widely used analgesic drug because of its structural simplicity and low cost. Salicin is the precursor of aspirin. It is found in the willow tree bark, whose medicinal properties have been known since 1763. Aspirin was developed and synthesized in order to avoid the irritation in the stomach caused by salicylic acid, which is also a powerful analgesic, derived from salicin. In fact, salicin is hydrolysed in the gastrointestinal tract to produce D-glucose and salicyl alcohol (see Section 8.4). Salicyl alcohol, on absorption, is oxidized to salicylic acid and other salicylates. However, aspirin can easily be synthesized from phenol using the *Kolbe reaction* (see Section 4.7.10.6).

Paracetamol (acetaminophen), an \(N\)-acylated aromatic amine having an acyl group (\(R\-\text{CO}-\)) substituted on nitrogen, is an important over-the-counter headache remedy. It is a mild analgesic and antipyretic medicine. The synthesis of paracetamol involves the reaction of \(p\)-aminophenol and acetic anhydride (see Section 4.7.10.6).

L-Dopa (L-3,4-dihydroxyphenylalanine), an amino acid, is a precursor of the neurotransmitters dopamine, norepinephrine (noradrenaline) and epinephrine.
(adrenaline), collectively known as catecholamines, and found in humans as well as in some animals and plants. It has long been used as a treatment for Parkinson’s disease and other neurological disorders. L-Dopa was first isolated from the seedlings of *Vicia faba* (broad bean) by Marcus Guggenheim in 1913, and later it was synthesized in the lab for pharmaceutical uses.

![Chemical structure of L-Dopa and Morphine]

Morphine is a naturally occurring opiate analgesic found in opium and is a strong pain reliever, classified as a narcotic analgesic (habit-forming) (see Section 8.2.2.5). Opium is the dried latex obtained from the immature poppy (*Papaver somniferum*) seeds. Morphine is widely used in clinical pain management, especially for pain associated with terminal cancers and post-surgery pain.

Penicillin V (phenoxymethylpenicillin), an analogue of the naturally occurring penicillin G (see Section 7.3.2), is a semisynthetic narrow-spectrum antibiotic useful for the treatment of bacterial infections. Penicillin V is quite stable even in high humidity and strong acidic medium (e.g. gastric juice). However, it is not active against beta-lactamase-producing bacteria. As we progress through various chapters of this book, we will come across a series of other examples of drug molecules and their properties.

![Chemical structure of Penicillin G and Penicillin V]

In order to have proper understanding and knowledge about these drugs and their behaviour, there is no other alternative but to learn chemistry. Everywhere, from discovery to development, from production and storage to administration, and from desired actions to adverse effects of drugs, chemistry is directly involved.

In the drug discovery stage, suitable sources of potential drug molecules are explored. Sources of drug molecules can be natural, such as a narcotic analgesic, morphine, from *P. somniferum* (poppy plant), synthetic, such as a popular
analgesic and antipyretic, paracetamol, and semisynthetic, such as penicillin V. Whatever the source is, chemistry is involved in all processes in the discovery phase. For example, if a drug molecule has to be purified from a natural source, for example, plant, the processes like extraction, isolation and identification are used, and all these processes involve chemistry (see Section 8.1.3.1).

Similarly, in the drug development steps, especially in pre-formulation and formulation studies, the structures and the physical properties (e.g. solubility and pH), of the drug molecules are exploited. Chemistry, particularly physical properties of drugs, is also important to determine storage conditions. Drugs having an ester functionality, for example, aspirin, could be quite unstable in the presence of moisture and should be kept in a dry and cool place. The chemistry of drug molecules dictates the choice of the appropriate route of administration. Efficient delivery of drug molecules to the target sites requires manipulation of various chemical properties and processes; for example, microencapsulation, nanoparticle-aided delivery and so on. When administered, the action of a drug inside our body depends on its binding to the appropriate receptor and its subsequent metabolic processes, all of which involve complex enzyme-driven biochemical reactions.

All drugs are chemicals, and pharmacy is a subject that deals with the study of various aspects of drugs. Therefore, it is needless to say that to become a good pharmacist the knowledge of the chemistry of drugs is essential. Before moving on to the other chapters, let us try to understand some of the fundamental chemical concepts in relation to the physical properties of drug molecules (see Section 1.6).

1.2 SOLUTIONS AND CONCENTRATIONS

A solution is a mixture where a solute is uniformly distributed within a solvent. A solute is the substance that is present in smaller quantities and a solvent usually the component that is present in greater quantity. Simply, a solution is a special type of homogenous mixture composed of two or more substances. For example, sugar (solute) is added to water (solvent) to prepare sugar solution. Similarly, saline (solution) is a mixture of sodium chloride (NaCl) (solute) and water (solvent). Solutions are extremely important in life as most chemical reactions, either in laboratories or in living organisms, take place in solutions.

Ideally, solutions are transparent and light can pass through the solutions. If the solute absorbs visible light, the solution will have a colour. We are familiar with liquid solutions, but a solution can also be in any state, such as solid, liquid or gas. For example, air is a solution of oxygen, nitrogen and a variety of other gases all in the gas state; steel is also a solid-state solution of carbon and iron. Solute may be crystalline solids, such as sugars and salts that dissolve readily into solutions, or colloids, such as large protein molecules, which do not readily dissolve into solutions (see Section 1.3).
In Chemistry, especially in relation to drug molecules, their dosing, therapeutic efficacy, adverse reactions and toxicity, we often come across with the term concentration, which can simply be defined as the amount of solute per unit of solvent. Concentration is always the ratio of solute to solvent and it can be expressed in many ways. The most common method of expressing the concentration is based on the amount of solute in a fixed amount of solution where the quantities can be expressed in weight (w/w), in volume (v/v) or both (w/v). For example, a solution containing 10 g of NaCl and 90 g of water is a 10% (w/w) aqueous solution of NaCl.

Weight measure (w/w) is often used to express concentration and is commonly known as percent concentration (parts per 100), as shown in the previous example of 10% NaCl aqueous solution. It is the ratio of one part of solute to one hundred parts of solution. To calculate percent concentration, simply divide the mass of the solute by the total mass of the solution, and then multiply by 100. Percent concentration also can be displayed, albeit not so common, as parts per thousand (ppt) for expressing concentrations in grams of solute per kilogram of solution. For more diluted solutions, parts per million (ppm), which is the ratio of parts of solute to one million parts of solution, is often used. To calculate ppm, divide the mass of the solute by the total mass of the solution, and then multiply by 10^6. Grams per litre is the mass of solute divided by the volume of solution in litres. The ppt and ppm can be either w/w or w/v.

Molality of a solution is the number of moles of a solute per kilogram of solvent, while molarity of a solution is the number of moles of solute per litre of solution. Molarity (M) is the most widely used unit for concentration. The unit of molarity is mol/l or M. One mole is equal to the molecular weight (MW) of the solute in grams. For example, the MW of glucose is 180. To prepare a 1 M solution of glucose, one should add 180 g of glucose in a 1.0 l volumetric flask and then fill the flask with distilled water to a total volume of 1.0 l. Note that molarity is defined in terms of the volume of the solution, not the volume of the solvent. Sometimes, the term normality (N), which can be defined as the number of mole equivalents per litre of solution, is also used, especially for various acids and bases, to express the concentration of a solution. Like molarity, normality relates the amount of solute to the total volume of solution. The mole equivalents of an acid or base are calculated by determining the number of H+ or HO− ions per molecule: N = n × M (where n is an integer). For an acid solution, n is the number of H+ ions provided by a formula unit of acid. For example, a 3 M H₂SO₄ solution is the same as a 6 N H₂SO₄ solution. For a basic solution, n is the number of HO− ions provided by a formula unit of base. For example, a 1 M Ca(OH)₂ solution is the same as a 2 N Ca(OH)₂ solution. Note that the normality (N) of a solution is never less than its molarity.

A concentrated solution has a lot of solute per solvent, a diluted solution has a lot of solvent, a saturated solution has maximum amount of solute, and a supersaturated solution has more solute than it can hold. Supersaturated solutions are relatively unstable, and solute tends to precipitate out of the mixture to form...
crystals, resulting in a saturated solution. The equilibrium of a solution depends on the temperature.

A stock solution is prepared with a known concentration, from which a diluted solution can be made. The process of adding more solvent to a solution or removing some of the solute is called dilution. In other words, dilution is the process of reducing the concentration of a solute in solution, usually simply by mixing with more solvent. Any unit can be used for both volume and concentration as long as they are the same on both sides of the equation. The concentration of the diluted solution can easily be calculated from the following equation:

$$C_1V_1 = C_2V_2$$

Where, $C_1$ and $C_2$ are the initial and final concentrations and $V_1$ and $V_2$ are the initial and final volumes of the solution.

A serial dilution, often used in various in vitro assays, is simply a series of simple dilutions. Serial dilutions are made in increments of 1000 (10^3), 100 (10^2), 10 (10-fold) or 2 (twofold), but 10-fold and twofold serial dilutions are commonly used. Serial dilutions are an accurate method of making solutions of low molar concentrations. The first step in making a 10-fold serial dilution is to take stock solution (1 ml) in a tube and then to add distilled water (9 ml) or other suitable solvents. For making a twofold serial dilution one should take stock solution (1 ml) in a tube and then add distilled water (1 ml) or other suitable solvents.

### 1.3 Suspension, Colloid and Emulsion

A suspension is a heterogeneous mixture between two substances one of which is finely dispersed into the other. Note that in a suspension, the solute particles do not dissolve, but are suspended throughout the bulk of the solvent. Most common suspensions include sand in water, dust in air and droplets of oil in air. The size of the particles is large enough (more than 1 μm) to be visible to the naked eye. In suspension, particles are so large that they settle out of the solvent if not constantly stirred. Therefore, it is possible to separate particles in any suspension through filtration. A suspension of liquid droplets or fine solid particles in a gas is called an aerosol. In relation to the atmosphere, the suspended particles, for example, fine dust and soot particles, sea salt, biogenic and volcanogenic sulphates, nitrates and cloud droplets, are called particulates.

A colloid is a mixture, where microscopically dispersed insoluble particles (10–1000 nm) of one substance are evenly suspended throughout another substance indefinitely. Note that to qualify as a colloid, the mixture must not settle. Like a suspension, a colloid consists of two separate phases, a dispersed phase (solute) and a dispersing medium (continuous phase or solvent). Colloidal particles consist of small particles of one substance dispersed in a continuous phase of a different composition, known as colloidal dispersions. The properties of colloids
and solutions are different due to their particle size. A colloidal dispersion, for example, milk, is not a true solution but it is not a suspension either, because it does not settle out on standing over time like a suspension.

Colloidal particles can be studied by various methods, for example, diffusion, electrophoresis and scattering of visible light and X-rays. There are several types of colloids, and the most popular one is called colloidal solution, where the solid forms the dispersed phase and the liquid forms the dispersion medium. The particles of the dispersed phase in a colloidal solution are known as colloidal particles or micelles. A gas may be dispersed in a liquid to form a foam (e.g. shaving lather) or in a solid to form a solid foam (e.g. marshmallow); a liquid may be dispersed in a gas to form an aerosol (e.g. aerosol spray), in another liquid to form an emulsion (e.g. mayonnaise) or in a solid to form a gel (e.g. cheese); a solid may be dispersed in a gas to form a solid aerosol (e.g. smoke in air), in a liquid to form a sol (e.g. ink) or in a solid to form a solid sol (e.g. certain alloys). Colloids are often purified by dialysis, which is a slow process.

Colloids are important in drug delivery, as colloidal carriers (e.g. nanoparticles) are used in controlled or sustained release and site-specific delivery of drugs. Nanoparticles are solid, colloidal particles consisting of macromolecular substances that vary in size from 10–1000 nm; they are natural or synthetic polymers. Depending on the interactions between the dispersed phase and the dispersing medium, colloidal solutions are classified as lyophilic (solvent loving) and lyophobic (solvent hating). The colloidal particles are strongly solvated in the dispersing medium of a lyophilic colloidal solution, for example, emulsion. When water is the dispersing medium, it is known as hydrophilic. The colloidal particles are not solvated in the dispersing medium of a lyophobic colloidal solution, such as a suspension. When water is the dispersing medium, it is called hydrophobic.

An emulsion is an integrated mixture of two immiscible liquids such as oil and water, stabilized by an emulsifying agent (emulsifier or surfactant). Simply, an emulsion is a fine dispersion of minute droplets of one liquid in another in which it is not soluble or miscible. For example, a type of paint used for walls, consisting of pigment bound in a synthetic resin, which forms an emulsion with water. An emulsifying agent (emulsifier) is a substance that keeps the parts of an emulsion mixed together. Water soluble emulsifiers form oil in water (o/w) emulsion, while oil soluble emulsifiers usually give water in oil (w/o) emulsion. Emulsions are usually prepared by vigorously shaking the two components together, often with the addition of an emulsifying agent, in order to stabilize the product formed.

1.4 ELECTROLYTES, NONELECTROLYTES AND ZWITTERIONS

Electrolytes are species that form ions, when dissolved in water and commonly exist as solutions of acids, bases or salts. They are essential minerals in the body,
they control osmosis of water between body compartments, and help maintain
the acid-base balance required for normal cellular activities. Many salts dissociate
in water and break up into electrically charged ions. The salt NaCl breaks up into
one ion of sodium (\( \text{Na}^+ \)) and one ion of chloride (\( \text{Cl}^- \)). These charged particles can
conduct electricity. The number of ions that carry a positive charge (cations) and
ions that carry a negative charge (anions) should be equal.

\[
\text{NaCl} \xrightarrow{\text{H}_2\text{O}} \text{Na}^{+}(\text{aq}) + \text{Cl}^{-}(\text{aq})
\]

The sweat that evaporates from the skin contains a variety of electrolytes, for
example, cations such as sodium (\( \text{Na}^+ \)), potassium (\( \text{K}^+ \)) calcium (\( \text{Ca}^{2+} \)) and magnesium
(\( \text{Mg}^{2+} \)), and anions such as chloride (\( \text{Cl}^- \)), bicarbonate (\( \text{HCO}_3^- \)), phosphate (\( \text{HPO}_4^{2-} \))
and sulphate (\( \text{SO}_4^{2-} \)).

Nonelectrolytes are species that do not form ions when dissolved in water. Thus, aqueous solutions of nonelectrolyte do not conduct electricity, for example, aqueous glucose (\( \text{C}_6\text{H}_{12}\text{O}_6 \)). Glucose does not dissociate when dissolved in water.
Most organic molecules are nonelectrolytes as they have covalent bonds and they
do not form ions when dissolved in water.

\[
\text{C}_6\text{H}_{12}\text{O}_6 + \text{H}_2\text{O} \rightarrow \text{C}_6\text{H}_{12}\text{O}_6(\text{aq})
\]

Zwitterions (ion pair) can bear both a positive and a negative charge, for example,
amino acids. Amino acids are the building blocks of proteins (see Section 7.2). They
contain functional groups, amino groups (\( \text{NH}_2 \)) that can accept protons, and car-
boxyl groups (\( \text{COOH} \)) that can lose protons. Under certain conditions, both of
these events can occur, and the resulting molecule becomes a zwitterion. The sim-
plest of the 20 amino acids that occur in proteins is glycine, \( \text{H}_2\text{NCH}_2\text{COOH} \), whose
solutions are distributed between the acidic–, zwitterion– and basic–species as
shown next.

\[
\text{NH}_3\text{CH}_2\text{COOH} \leftrightarrow \text{NH}_3\text{CH}_2\text{COO}^- \leftrightarrow \text{NH}_2\text{CH}_2\text{COO}^-
\]

1.5 OSMOSIS AND TONICITY

Living cells have the potential of gaining or losing water through semipermeable
membranes by osmosis. Osmosis is the process by which molecules of a solvent tend
to pass through a semipermeable membrane from a less concentrated solution
into a more concentrated one. Generally, osmosis occurs when the concentration
of solutes on one side of the cell membrane is higher than the other. Molecules can
move across the cell membranes from a low concentrated solution (dilute solution/
pure solvent) to a high concentrated one (concentrated solution) by diffusion as shown next. Eventually, the concentrations of the two solutions become equal.

In the body, water is the solvent, and the solutes include electrolytes, \( \text{O}_2 \), \( \text{CO}_2 \), glucose, urea, amino acids and proteins. Osmole is the measure of the total number of particles in a solution. Number of particles can be either molecules (e.g. sugar) or ions (e.g. NaCl). For example, 1 g mole of non-ionizable sugar is 1 Osm, whereas 0.5 g mol of NaCl ionizes into two ions (Na\(^+\) and Cl\(^-\)) is also 1 Osm.

The concentration of solutes in body fluids is usually expressed as the osmolality, which is a measure of the osmoles (Osm) of solute per kilogram of solvent (Osm/kg). The ability of a semipermeable membrane solution to make water move into or out of a cell by osmosis is known as its tonicity. In general, a solution’s tonicity can be defined by its osmolarity, which is defined as the number of osmoles of solute per litre of solution (Osm/l). A solution with low osmolarity has fewer solute particles per litre of solution, while a solution with high osmolarity has more solute particles per litre of solution.

A hypertonic solution has a higher concentration of solutes than the surrounding semipermeable membrane (lower concentration) and water will move out of the cells. This can cause cell to shrink. So, a hypertonic solution has higher osmolarity than blood plasma and red blood cells. A hypotonic solution has a lower concentration of solutes than the surrounding semipermeable membrane (higher concentration) and the net flow of water will be into the cells. This can result in cell to swell and eventually burst. So, a hypotonic solution has lower osmolarity than blood plasma and red blood cells. An isotonic solution has same concentration of solutes as the surrounding semipermeable membrane and there will be no net movement of water into or out of the cell. Therefore, an isotonic solution has same osmolarity as blood plasma and red blood cells.
1.6 PHYSICAL PROPERTIES OF DRUG MOLECULES

1.6.1 Physical State

Drug molecules exist in various physical states, for example, amorphous solid, crystalline solid, hygroscopic solid, liquid or gas. Physical state of drug molecules is an important factor in the formulation and delivery of drugs.

1.6.2 Melting Point and Boiling Point

Melting point (mp) is the temperature at which a solid becomes a liquid, and boiling point (bp) is the temperature at which the vapour pressure of the liquid is equal to the atmospheric pressure. Boiling point of a substance can also be defined as the temperature at which it can change its state from a liquid to a gas throughout the bulk of the liquid at a given pressure. For example, the melting point of water at 1 atm of pressure is 0 °C (32 °F, 273.15 K); this is also known as the ice point, and the boiling point of H₂O is 100 °C.

Melting point is used to characterize organic compounds and to confirm the purity. The melting point of a pure compound is always higher than the melting point of that compound mixed with a small amount of an impurity. The more impurity is present, the lower the melting point is. Finally, a minimum melting point is reached. The mixing ratio that results in the lowest possible melting point is known as the eutectic point.

The melting point increases as the molecular weight increases, and the boiling point increases as the molecular size increases. The increase in melting point is less regular than the increase in boiling point, because packing influences the melting point of a compound.

Packing of the solid is a property that determines how well the individual molecules in a solid fit together in a crystal lattice. The tighter the crystal lattice, the more energy is required to break it and eventually melt the compound. Alkanes with an odd number of carbon atoms pack less tightly, which decreases their melting points. Thus, alkanes with an even number of carbon atoms have higher melting points than the alkanes with an odd number of carbon atoms.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molecular Formula</th>
<th>Mp</th>
<th>Bp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butane</td>
<td>CH₃CH₂CH₂CH₃</td>
<td>-138.4°C</td>
<td></td>
</tr>
<tr>
<td>Pentane</td>
<td>CH₃CH₂CH₂CH₂CH₃</td>
<td>-129.7°C</td>
<td>36.1°C</td>
</tr>
<tr>
<td>Hexane</td>
<td>CH₃CH₂CH₂CH₂CH₂CH₃</td>
<td>-93.5°C</td>
<td></td>
</tr>
</tbody>
</table>

On the contrary, between two alkanes having same molecular weights, the more highly branched alkane has a lower boiling point.
Ionic compounds are held together by extremely strong interactions of positive and negative charges, and they tend to have high boiling and melting points. For example, the ionic solid NaCl (salt) melts at >800 °C.

1.6.3 Polarity and Solubility

Polarity is a physical property of a compound, which relates to other physical properties, for example, melting and boiling points, solubility and intermolecular interactions between molecules. Generally, there is a direct correlation between the polarity of a molecule and the number and types of polar and nonpolar covalent bonds (see Section 2.3.4.2). In a few cases, a molecule having polar bonds, but in a symmetrical arrangement, may give rise to a nonpolar molecule, for example, carbon dioxide (CO$_2$).

The term bond polarity is used to describe the sharing of electrons between atoms (see Section 2.4). In a nonpolar covalent bond, the electrons are shared equally between two atoms. A polar covalent bond is one in which one atom has a greater attraction for the electrons than the other atom (see Section 2.3.4.2). When this relative attraction is strong, the bond is an ionic bond (see Section 2.3.4.1).

The polarity in a bond arises from the different electronegativities of the two atoms that take part in bond formation (see Section 2.3.3). The greater the difference in electronegativity between the bonded atoms, the greater the bond polarity. Thus, electronegativity of an atom is related to bond polarity (see Section 2.4). For example, water is a polar molecule, whereas cyclohexane is nonpolar.
More examples of polar and nonpolar molecules are shown in the following Table. The bond polarity and electronegativity are discussed in Chapter 2.

<table>
<thead>
<tr>
<th>Polar</th>
<th>Nonpolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (H₂O)</td>
<td>Toluene (Ph—Me)</td>
</tr>
<tr>
<td>Methanol (MeOH)</td>
<td>n-Hexane (C₆H₁₂)</td>
</tr>
<tr>
<td>Ethanol (EtOH)</td>
<td>Benzene (Ph—H)</td>
</tr>
<tr>
<td>Acetic acid (AcOH)</td>
<td>Toluene (Ph—Me)</td>
</tr>
</tbody>
</table>

Life occurs exclusively in water. Solutions in which water is the dissolving medium are called *aqueous solutions*. In aqueous solutions, the polar parts are hydrated and the nonpolar parts are excluded. Hydrogen bonding is a consequence of the basic molecular structure of water. Water has very high boiling point compared with small organic molecules due to the hydrogen bonding. The hydrogen bonding and other nonbonding interactions between molecules are described in Chapter 2. Examples of some common solvents and their boiling points are compared with the boiling point of water in the following Table.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Formula</th>
<th>Molecular weight</th>
<th>bp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>C₃H₆O</td>
<td>58.08</td>
<td>56.05</td>
</tr>
<tr>
<td>Benzene</td>
<td>C₆H₆</td>
<td>78.11</td>
<td>80.10</td>
</tr>
<tr>
<td>Chloroform</td>
<td>CHCl₃</td>
<td>119.38</td>
<td>61.2</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>C₆H₁₂</td>
<td>84.16</td>
<td>80.70</td>
</tr>
<tr>
<td>Ethanol</td>
<td>C₂H₆O</td>
<td>46.07</td>
<td>78.50</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>C₄H₈O₂</td>
<td>88.11</td>
<td>77.00</td>
</tr>
<tr>
<td>Methanol</td>
<td>CH₃O</td>
<td>32.04</td>
<td>64.60</td>
</tr>
<tr>
<td>Water</td>
<td>H₂O</td>
<td>18.02</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The concept of solution has already been outlined earlier (see Section 1.2). Let’s now delve into the concept of solubility. *Solubility* is the amount of a solute that can be dissolved in a specific solvent under given conditions. Therefore, solubility is a measure of how much of the solute can be dissolved into the solvent at a specific temperature. The process of dissolving solute in solvent is called *solvation*, or *hydration* when the solvent is water. In fact, the interaction between a dissolved species and the molecules of a solvent is solvation. The process of mixing solute (s) and solvent to form a solution is called *dissolution*. The stronger the intermolecular attractions (interactions) between solute and solvent, the more likely the solute will dissolve in a solvent.

The *rate of solution* is a measure of how fast a solute is dissolved in water or a particular solvent. It also depends on size of the particle, stirring, temperature and
the amount of solid already dissolved. For example, glucose (which has hydrogen bonding) is highly soluble in water, but cyclohexane (which only has dispersion forces) is insoluble in water. Solubility largely depends on temperature, polarity, molecular size and stirring. Temperature always affects solubility and an increasing temperature usually increases the solubility of most solids in a liquid solvent. The solubility of gases decreases with increase in temperature. The polarity of the solute and solvent also affects the solubility. The stronger the attractions between solute and solvent molecules, the greater the solubility. Thus the solubility of molecules can also be explained on the basis of the polarity of molecules. In general, like dissolves like; that is, materials with similar polarity are soluble in each other. Thus, polar solvent, for example, water (H₂O), and nonpolar solvent, for example, benzene (C₆H₆), do not mix.

The term miscible is used to describe two substances (usually liquids) that are soluble in each other. If they do not mix, as oil and water, they are said to be immiscible. For example, ethyl alcohol and water are miscible liquids as both are polar molecules, n-hexane and dodecane are also miscible in one another as both are nonpolar molecules, whereas chloroform (nonpolar) and water (polar) are immiscible. A polar solvent, such as H₂O, has partial charges that can interact with the partial charges on a polar compound, such as sodium chloride (NaCl). As nonpolar compounds have no net charge, polar solvents are not attracted to them. For example, alkanes are nonpolar molecules and are insoluble in polar solvents such as H₂O, but are soluble in nonpolar solvents such as chloroform.

<table>
<thead>
<tr>
<th>CH₃CH₂OH</th>
<th>H₂O</th>
<th>CHCl₃</th>
<th>C₆H₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>Water (polar)</td>
<td>Chloroform (nonpolar)</td>
<td>Dodecane (nonpolar)</td>
</tr>
</tbody>
</table>

Remember, size matters. Organic molecules with a branching carbon increases the solubility than a long-chain carbon, because branching reduces the size of the molecule and makes it easier to solvate. For example, isobutanol is more soluble in water than butanol.

1.7 ACID–BASE PROPERTIES AND pH

Drug molecules contain various types of functional groups, and these functional groups contribute to the overall acidity or basicity of drug molecules. One of the adverse effects of aspirin is stomach bleeding, which is partly due to its acidic nature. In the stomach, aspirin is hydrolysed to salicylic acid and acetic acid (see Section 4.9). The carboxylic acid group (─COOH) and a phenolic hydroxyl group (─OH) present
in salicylic acid, make this molecule acidic. Moreover, acetic acid is formed and that is also moderately acidic. Thus, intake of aspirin increases the acidity of stomach significantly, and if this increased acidic condition stays in the stomach for a long period, it may cause stomach bleeding. Like aspirin, there are a number of other drug molecules that are acidic in nature. Similarly, there are basic and neutral drugs as well. Now, let us see what these terms *acid*, *base* and *neutral* compounds really mean, and how these parameters are measured. Most drugs are organic molecules and can be acidic, basic or neutral in nature.

\[
\text{Aspirin} \xrightarrow{\text{Hydrolysis in the stomach}} \text{Salicylic acid} + \text{Acetic acid}
\]

Simply, an electron-deficient species that accepts an electron pair is called an *acid*, for example, hydrochloric acid (HCl), and a species with electrons to donate is a *base*, for example, sodium hydroxide (NaOH). A neutral species does not do either of these. Most of the organic reactions are either *acid–base* reactions or involve catalysis by an acid or base at some point.

### 1.7.1 Acid–Base Definitions

Acids turn blue litmus red and have a sour taste, whereas bases turn red litmus to blue and have a bitter taste. Litmus is the oldest known pH indicator. Acid reacts with certain metals to produce hydrogen gas.

\[
\text{Na} + \text{HCl} \rightarrow \text{NaCl} + \text{H}_2 \\
\text{Zn} + \text{H}_2\text{SO}_4 \rightarrow \text{ZnSO}_4 + \text{H}_2
\]

Acids and bases are important classes of chemicals that control carbon dioxide (CO\(_2\)) transport in the blood. Carbon dioxide (CO\(_2\)) dissolves in the body fluid (H\(_2\)O) to form carbonic acid (H\(_2\)CO\(_3\)), and is excreted as a gas by the lungs.

\[
\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3
\]

Stomach acid is hydrochloric acid (HCl), which is a strong acid. Acetic acid (CH\(_3\)COOH) is a weak organic acid that can be found in vinegar. Citrus fruits such as lemons, grapefruit, oranges and limes have citric acid (C\(_6\)H\(_8\)O\(_7\)) as well as ascorbic acid (vitamin C). Both these acids increase the acidity of foods and make it harder for bacteria to grow. Also, because of the antioxidant property, ascorbic acid prevents food items from oxidative spoilage. Sour milk, sour cream, yoghurt and cottage cheese have lactic acid from the fermentation of the sugar lactose. Certain bacteria break down the sugars in milk and make lactic acid, which reacts with milk proteins. This causes the milk to thicken and
develop a creamy or curdy texture and sour flavour. Yoghurt is an example of a fermented dairy product whose texture and flavour both depend on the presence of lactic acid. Both citric acid and lactic acid are weak organic acids. They are used largely as food preservatives, curing agents and flavouring agents.

Several definitions have been used to describe the acid-base properties of aqueous solvents as well as other solvents. The Arrhenius definitions or the Brønsted–Lowry definitions adequately describe aqueous acids and bases.

1.7.1.1 Arrhenius Acids and Bases
According to Arrhenius’ definition, an *acid* produces hydrogen ion (H\(^+\)), and a base produces hydroxide or hydroxyl ion (HO\(^-\)) in water. Salts are formed in the acid–base reactions, usually in neutralization reactions. Thus, a salt is an ionic compound that is made with the anion of an acid and the cation of a base. Arrhenius’ definition only works for strong acids and strong bases and it is limited to aqueous solutions.

\[
\text{HCl (Acid) + NaOH (Base)} \rightarrow \text{NaCl (Salt) + H}_2\text{O (Water)}
\]

1.7.1.2 Brønsted–Lowry Acids and Bases
Danish chemist Johannes Brønsted and the English chemist Thomas Lowry expanded the Arrhenius definition. They defined an *acid* as a proton (H\(^+\)) donor, and a *base* as a proton (H\(^+\)) acceptor. Brønsted–Lowry definitions work better for weak acids and weak bases.

\[
\text{HNO}_2 (\text{Acid}) + \text{H}_2\text{O (Base)} \rightarrow \text{NO}_2^- (\text{A conjugate base}) + \text{H}_3\text{O}^+ (\text{A conjugate acid})
\]

Each acid has a *conjugate base*, and each base has a *conjugate acid*. An acid reacts with a base to produce conjugate base and conjugate acid. These conjugate pairs only differ by a proton. In the example, HNO\(_2\) is the acid, H\(_2\)O is the base, NO\(_2^-\) is the conjugated base, and H\(_3\)O\(^+\) is the conjugated acid. Thus, a conjugate acid can lose a H\(^+\) ion to form a base, and a conjugate base can gain a H\(^+\) ion to form an acid. Water can be an acid or a base. It can gain a proton to become a hydronium ion (H\(_3\)O\(^+\)), its conjugate acid, or lose a proton to become the hydroxide ion (HO\(^-\)), its conjugate base.

When an acid transfers a proton to a base, it is converted to its conjugate base. By accepting a proton, the base is converted to its conjugate acid. In the following acid-base reaction, H\(_2\)O is converted to its conjugate base, hydroxide ion (HO\(^-\)), and NH\(_3\) is converted to its conjugate acid, ammonium ion (‘NH\(_4^+\)’). Therefore, the conjugate acid of any base always has an additional hydrogen atom and an increase in positive charge or a decrease in negative charge. On the other hand, the conjugate base of an acid has one hydrogen atom less and an increase in negative charge or lone pair of
electrons, and also a decrease in positive charge. The stronger the acid, the weaker the conjugate base and vice versa.

According to the Brønsted–Lowry definitions, any species that contains hydrogen can potentially act as an acid, and any compound that contains a lone pair of electrons can act as a base. Therefore, neutral molecules can also act as bases if they contain an oxygen, nitrogen or sulphur atom. Both an acid and a base must be present in a proton transfer reaction, because an acid cannot donate a proton unless a base is present to accept it. Thus, proton-transfer reactions are often called acid–base reactions. For example, in the following reaction between acetic acid (CH₃COOH) and ammonia (NH₃), a proton is transferred from CH₃COOH, an acid, to NH₃, a base.

Acid strength is related to base strength of its conjugate base. For an acid to be weak, its conjugate base must be strong. In general, in the reaction between an acid and base, the equilibrium favours the weaker acid or base. In the acid–base reaction that follows, NH₃ is a base because it accepts a proton, and CH₃COOH is an acid because it donates a proton. In the reverse reaction, ammonium ion (‘NH₄⁺) is an acid because it donates a proton, and acetate ion (CH₃COO⁻) is a base because it accepts a proton. The curly arrows show the flow of electrons in an acid-base reaction. Two half-headed arrows are used for the equilibrium reactions. A longer arrow indicates that the equilibrium favours the formation of acetate ion (CH₃COO⁻) and ammonium ion (‘NH₄⁺). Because acetic acid (CH₃COOH) is a stronger acid than ammonium ion (‘NH₄⁺), the equilibrium lies towards the formation of weak acid and weak base.
1.7.1.3 Lewis Theory of Acids and Bases

The Lewis definitions describe acids and bases for both organic and inorganic solvents. The advantage of Lewis definitions is that many more organic reactions can be considered as acid–base reactions because they do not have to occur in solutions.

The Lewis theory of acids and bases defines an acid as an electron-pair acceptor, and a base as an electron-pair donor to form a covalent bond. A Lewis acid is a species that accepts electrons and it is termed as an electrophile. A Lewis base is a species that donates electrons to a nucleus with an empty orbital, and is termed as a nucleophile. Thus, Lewis acids are electron-deficient species, whereas Lewis bases are electron-rich species. For example, the methyl cation (CH$_3^+$) may be regarded as a Lewis acid or an electrophile, because it accepts electrons from reagent such as chloride ion (Cl$^-$). In turn, because chloride ion (Cl$^-$) donates electrons to the methyl cation (CH$_3^+$), it is classified as a Lewis base or a nucleophile.

Lewis acids are known as aprotic acids and they react with Lewis bases by accepting pairs of electrons, not by donating protons. Since aprotic acids do not have any acidic hydrogens. Borane (BH$_3$), boron trichloride (BCl$_3$) and boron trifluoride (BF$_3$) are known as Lewis acids, because boron has a vacant d orbital that accepts a pair of electrons from a donor species. For example, diethyl ether (C$_2$H$_5$OC$_2$H$_5$) acts as a Lewis base towards BCl$_3$ and forms a complex of diethyl ether and boron trichloride (a salt).

Boron trifluoride (BF$_3$) reacts with a Lewis bases, such as tertiary methyl amine and generates a complex of complex of trimethyl amine and boron trifluoride (a salt).
1.7.2 Electronegativity and Acidity

Electronegativity is a measure of the tendency of an atom to attract a bonding pair of electrons (see Section 2.3.3). The relative acidity of HA within a period is determined by the stability of A−. The greater the electronegativity, the greater is the stability of A−. We know that carbon is less electronegative than nitrogen, which in turn is less electronegative than oxygen, and that oxygen is less electronegative than fluorine. Therefore, the strength of acidity increases from methane to hydrogen fluoride as shown next.

<table>
<thead>
<tr>
<th></th>
<th>H₃C-H</th>
<th>H₂N-H</th>
<th>HO-H</th>
<th>F-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKₐ <em>A</em></td>
<td>51</td>
<td>38</td>
<td>15.7</td>
<td>3.5</td>
</tr>
<tr>
<td>Electronegativity of A in A-H</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

A molecule is said to have resonance when its structure cannot be adequately described by a single Lewis structure. Resonance may delocalize the electron pair that A− needs to form the new bond with a proton. Delocalization increases the stability of A− that also decreases the reactivity. A base that has resonance delocalization of the electron pair that is shared with the proton will therefore be less basic than a base without this feature. Since a weaker base has a stronger conjugate acid, a compound whose conjugate base has resonance stabilization will be more acidic.

Both carboxylic acids and alcohols contain an —OH group, but a carboxylic acid is a stronger acid than an alcohol. As we can see, that deprotonation of ethanol (CH₃CH₂OH) affords the ethoxide ion (CH₃CH₂O⁻), which has no resonance (only one Lewis structure can be drawn), but deprotonation of acetic acid (CH₃CH₂CO₂H) affords an acetate ion (CH₃CH₂CO₂⁻) that has resonance (two contributing Lewis structures can be drawn).

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{O} & \rightleftharpoons \text{CH}_3\text{CH}_2\text{O}^- + \text{H}_3\text{O}^+ \\
pK_a = 15.9 & \quad \text{(A weak base)}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} - \text{C} - \text{O}^- - \text{H} + \text{H}_2\text{O} & \rightleftharpoons \text{H}_3\text{C} = \text{C} \equiv \text{O}^- + \text{H}_3\text{O}^+ \\
pK_a = 4.76 & \quad \text{(A weak acid)}
\end{align*}
\]

The carboxylate anion is stabilized by delocalization of the negative charge.

\[
\begin{align*}
\text{H}_3\text{C} - \text{C} \equiv \text{O}^- & \quad \text{(Carboxylate)}
\end{align*}
\]

A conjugate acid  A conjugate base

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{O}^- + \text{H}_3\text{O}^+ & \rightleftharpoons \text{CH}_3\text{CH}_2\text{OH} + \text{H}_2\text{O} \\
pK_a = 1.74 & \quad \text{(A strong acid)}
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} = \text{C} \equiv \text{O}^- + \text{H}_3\text{O}^+ & \rightleftharpoons \text{H}_3\text{C} - \text{C} - \text{O}^- - \text{H} + \text{H}_2\text{O} \\
pK_a = -1.74 & \quad \text{(A strong acid)}
\end{align*}
\]
This is because the acetate ($\text{CH}_3\text{COO}^-$) ion has resonance that delocalizes the electron pair to be shared with a proton, and the ethoxide ($\text{CH}_3\text{O}^-$) ion does not. Therefore, the acetate ($\text{CH}_3\text{COO}^-$) ion is a weaker base than the ethoxide ($\text{CH}_3\text{O}^-$) ion, which makes acetic acid ($\text{CH}_3\text{COOH}$) a stronger acid than ethanol ($\text{CH}_3\text{OH}$). Recalling that weaker bases have stronger conjugate acids, acetic acid has a $pK_a = 4.76$ (the lower the $pK_a$, the stronger the acid), whereas ethanol has a $pK_a = 15.9$ (the higher the $pK_a$, the weaker the acid).

1.7.3 Acid–Base Properties of Organic Functional Groups

Let us see the acid–base properties of some molecules with different functional groups. Organic functional groups have been discussed in Chapter 4. Most organic acids and bases are weak acids and weak bases. The most common examples are carboxylic acids, amines, alcohols, amides, ethers and ketones. Drug molecules also contain various types of functional groups, and these functional groups contribute to the overall acidity or basicity of drug molecules. Organic compounds with nonbonding electrons on nitrogen, oxygen, sulphur or phosphorus can act as Lewis bases.

The most common organic acids are carboxylic acids. They are moderately strong acids having $pK_a$ values ranging from about 3 to 5. Acetic acid ($pK_a = 4.76$) can behave as an acid and donate a proton, or as a base and accept a proton. A protonated acetic acid ($pK_a = −6.1$) is a stronger acid than $\text{H}_2\text{SO}_4$ ($pK_a = −5.2$). Equilibrium always favours a reaction of the stronger acid and stronger base to give the weaker acid and weaker base.

\[
\begin{align*}
\text{H}_3\text{C}^-\text{C}^-\text{O}^-\text{H}^+ + \text{HO}^- \rightleftharpoons \text{H}_3\text{C}^-\text{C}^-\text{O}^-\text{H} + \text{HO}^-
\end{align*}
\]

$pK_a = 4.76$

(A strong acid)

\[
\begin{align*}
\text{H}_3\text{C}^-\text{C}^-\text{O}^-\text{H} + \text{H}^+-\text{SO}_3\text{OH} \rightleftharpoons \text{H}_3\text{C}^-\text{C}^-\text{O}^-\text{H} + \text{HSO}_4^-
\end{align*}
\]

$pK_a = −5.2$

(A weak acid)

Amines are the most important organic bases as well as weak acids. Thus, an amine can behave as an acid and donate a proton, or as a base and accept a proton. The most common organic bases are alkyl amines. They are moderately strong bases having $pK_a$ values ranging from about 30 to 40. Methylamine ($pK_a = 38.0$) can behave as an acid and donate a proton, or as a base and accept a proton. A protonated methylamine ($pK_a = 10.64$) is a much weaker acid than $\text{H}_2\text{SO}_4$ ($pK_a = −5.2$), but
a much weaker base than methylamide ion. Equilibrium always favours a reaction of the stronger acid and stronger base to give the weaker acid and weaker base.

\[
\begin{align*}
\text{H}_3\text{C} - \text{NH}_2 + \text{H} - \text{SO}_3\text{OH} & \rightleftharpoons \text{H}_3\text{C} - \text{NH}_3 + \text{HSO}_4^- \\
pK_a &= 5.2 & (\text{A strong acid})
\end{align*}
\]

\[
\begin{align*}
\text{H}_3\text{C} - \text{NH}_2 + \text{H}_2\text{O} & \rightleftharpoons \text{H}_3\text{C} - \text{NH} + \text{H}_2\text{O} \\
pK_a &= 38.0 & (\text{A weak acid})
\end{align*}
\]

An alcohol can behave like an acid and donate a proton. However, alcohols are much weaker organic acids with \(pK_a\) values close to 16. Alcohol may also behave as a base, for example, ethanol is protonated by \(\text{H}_2\text{SO}_4\) and gives ethyloxonium ion \((\text{CH}_3\text{CH}_2\text{O}^+\text{H}_2)\). A protonated ethanol \((pK_a = -2.4)\) is a stronger acid than ethanol \((pK_a = 15.9)\).

\[
\begin{align*}
\text{H}_5\text{C}_2\text{─OH} + \text{H} - \text{SO}_3\text{OH} & \rightleftharpoons \text{H}_5\text{C}_2\text{─OH} + \text{HSO}_4^- \\
pK_a &= 5.2 & (\text{A strong acid})
\end{align*}
\]

Some organic compounds have more than one atom with nonbonding electrons, thus more than one site in such a molecule can react with acids. For example, acetamide \((\text{CH}_3\text{CONH}_2)\) has nonbonding electrons on both nitrogen and oxygen atom, and either may be protonated. However, generally the reaction stops when one proton is added to the molecule.

Both acetamide \((\text{CH}_3\text{CONH}_2)\) and acetic acid \((\text{CH}_3\text{COOH})\) are more readily protonated at the carbonyl oxygen rather than the basic site. The protonation of the nonbonding electrons on the oxygen atom of a carbonyl \((\text{─C}=\text{O})\) or hydroxyl \((\text{─OH})\) group is an important first step in the reactions under acidic conditions of compounds like acetamide, acetic acid, diethyl ether and alcohol. The conjugate acids of these compounds are more reactive towards Lewis bases than the unprotonated
forms. Therefore, acids are used as catalysts to enhance reactions of organic compounds.

![Chemical reactions](image)

The reaction of diethyl ether with concentrated hydrogen chloride (HCl) is typical of that of an oxygen base with a protic acid. Protic acids have hydrogens that can form hydrogen bonds with water, alcohols and ammonia. Therefore, just like water, organic oxygenated compounds are protonated to give oxonium ions, for example, protonated ether.

![Chemical reactions](image)

Ketones can behave as a base. Acetone donates electrons to boron trichloride, a Lewis acid and forms a complex of acetone and boron trichloride.

![Chemical reactions](image)

Most organic reactions are either acid–base reactions or catalysed by an acid or a base. The reaction of an organic compound as an acid depends on how easily it can lose a proton to a base. Electronegativity is the ability of an atom, which is bonded to another atom or atoms, to attract electrons strongly towards it. The acidity of the hydrogen atom depends on the electronegativity of the bonded central atom. The more electronegative the bonded central atom, the more acidic are the protons. Carbon is less electronegative than nitrogen and oxygen. Thus,
carbon attracts and holds electrons less strongly than nitrogen and oxygen do. For example, ethane is a very weak acid in which the hydrogen atoms are bonded to carbon atoms.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \text{-} \text{C} \text{-} \text{C} \text{-} \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Ethane

Nitrogen is less electronegative than oxygen. Thus, nitrogen attracts and holds the electrons less strongly than oxygen does. For example, in methylamine, the hydrogen atoms on nitrogen are acidic, but the hydrogen atom bonded to the oxygen atom in methanol is even more acidic.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \text{-} \text{C} \text{-} \text{OH} \\
\text{H} & \quad \text{H}
\end{align*}
\]

Methanol

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \text{-} \text{C} \text{-} \text{NH}_2 \\
\text{H} & \quad \text{H}
\end{align*}
\]

Methyl amine

Weak acids produce strong conjugate bases. Thus, ethane gives stronger conjugate base than methylamine and methanol. The conjugate bases of ethane, methylamine and methanol are shown next.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{(Ethane)} & \rightarrow \text{CH}_3\text{NH}_2\text{(Methylamine)} \rightarrow \text{CH}_3\text{OH}\text{(Methanol)} \\
(\text{Increasing acidity of hydrogen bonded to carbon,nitrogen,and oxygen}) \\
\text{CH}_3\text{O}^-\text{(Methoxide anion)} & \rightarrow \text{CH}_3\text{NH}^-\text{(Methylamide anion)} \rightarrow \text{CH}_3\text{CH}_2^-\text{(Ethyl anion)} \\
(\text{Increasing basicity of the conjugate base})
\end{align*}
\]

1.7.4 pH, pOH and pKₐ Values

The pH and pOH logarithmic scales are used to keep track of a large concentration of acids and bases. When an acid is added to a solution, the pH gets lower (acidic), but when base is added, the pH gets higher (basic). The pH value is defined as the negative of the logarithm to base 10 of the concentration of the hydrogen ion. The acidity or basicity of a substance is defined most typically by the pH value. We write log as \( \log_{10} \) for convenience.

\[
pH = -\log_{10}\left[\text{H}_2\text{O}^+\right] = -\log\left[\text{H}_3\text{O}^+\right]
\]

The acidity of an aqueous solution is determined by the concentration of \( \text{H}_3\text{O}^+ \) ions. Thus, the pH of a solution indicates the concentration of hydrogen ions in the solution. The pH is a measure of the concentration of hydrogen ions in a
solution. The pH equation also can be written as the logarithm of the reciprocal of the hydrogen ion concentration.

$$pH = -\log[H^+] = \log \frac{1}{[H^+]}$$

A substance that can act as an acid or a base is known as **amphiprotic** or **amphoteric**. Water is amphiprotic, as it acts both as an acid or a base. Pure water ionizes partially or undergoes auto-ionization (autoprotolysis). Two molecules of water react with each other to form hydronium and hydroxide ions.

$$H_2O \text{ (Acid)} + H_2O \text{ (Base)} \rightarrow H_3O^+ \text{ (A conjugate acid)} + HO^- \text{ (A conjugate base)}$$

The acidity of an aqueous solution is determined by the concentration of hydrogen ($H_3O^+$, hydronium) ions. The pH of a solution indicates the concentration of hydronium ($H_3O^+$) ions in the solution. The acidity or basicity of a substance is defined most typically by the pH value. Because the $[H_3O^+]$ in an aqueous solution is typically quite small, chemists have found an equivalent way to express $[H_3O^+]$ as a positive number, whose value normally lies between 0 and 14. The lower the pH, the more acidic is the substance or the solution. The pH of a solution can be changed simply by adding either acid or base to the solution.

When water molecules react with one another they form hydronium ($H_3O^+$) and hydroxide ($HO^-$) ions. The ratio of the molar concentrations of reactants and products is a constant at certain temperature and is known as equilibrium constant, $K$.

$$H_2O + H_2O \rightarrow H_3O^+ + HO^-$$

$$pK_a = 7.0 \quad \text{(A weak acid and a weak base)}$$

$$pK_b = -1.74 \quad \text{(A strong base)}$$

Equilibrium constant, $K$ can be written as:

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

Where, $[H_3O^+]$, $[HO^-]$ and $[H_2O]$ are molar concentrations of hydronium ion, hydroxide ion and water, respectively. Remember, molar concentration (mol dm$^{-3}$ or mol l$^{-1}$) is also called molarity (M). Only a very few water molecules are ionized, so $[H_2O]$ can be regarded as constant. Therefore, for pure water the reaction equilibrium can be expressed as:

$$K [H_2O] = [H^+][HO^-] = K_w$$

Here, $K_w$ is the ionic product of water. We write $[H^+]$ instead of $[H_3O^+]$ for convenience.
The hydrogen \([H^+]\) and hydroxide \([HO^-]\) ions are always present in aqueous solutions. In acid or basic solutions, the concentrations of \(H^+\) and \(HO^-\) ions are not equal. For a neutral solution \(H^+\) and \(HO^-\) ions are at the same concentration and the pH of the neutral solution is exactly 7.

In an acidic solution, there is an excess of hydrogen ions over hydroxide ions, therefore the pH of the acidic solution is below 7. In a basic solution, there is an excess of hydroxide ions over hydrogen ions, so the pH of the basic solution is above 7.

The \(pK_w\) is the negative logarithm (to base 10) of the \(K_w\). The relationship between \(K_w\) and \(pK_w\) is exactly the same as that between \([H^+]\) and pH.

\[
pK_w = -\log K_w
\]

The pOH is the negative logarithm (to base 10) of the hydroxide \((HO^-)\) ion concentration.

\[
pOH = -\log[HO^-]
\]

The pOH gives us another way to measure the acidity of a solution. It is just the opposite of pH. The higher pOH means the solution is acidic and the lower pOH means the solution is basic. Whereas, the higher pH indicates basic solution and lower pH means acidic solution. Do not confuse pH with \(pK_a\). The pH scale is used to describe the acidity of a solution. The \(pK_a\) is characteristic of a particular compound, and it tells how readily the compound gives up a proton. At equilibrium, the concentration of \(H^+\) is \(10^{-7}\), so we can calculate the pH of water at equilibrium as: \(pH = -\log [H^+] = -\log [10^{-7}] = 7\). Solutions with a pH of 7 are said to be neutral, while those with pH values below 7 are defined as acidic, and those are above pH of 7 as being basic.

The pH of blood plasma is around 7.4 (slightly basic), whereas the gastric juice is around 1.6 (highly acidic). The pH scales of acids and bases are shown next.
Acids and bases that are *strong electrolytes* are called strong acids and strong bases. Those that are weak electrolytes are called weak acids and weak bases. *Strong acids*, for example, HCl, HBr, HI, \( \text{H}_2\text{SO}_4 \), HNO₃, HCIO₃, and HCIO₄, completely ionize in solution, and are always represented in chemical equations in their ionized form. Similarly, *strong bases*, for example, LiOH, NaOH, KOH, RbOH, Ca(OH)₂, Sr(OH)₂, and Ba(OH)₂, completely ionize in solution and are always represented in their ionized form in chemical equations. A *salt* is formed when an acid and a base are mixed and the acid releases \( \text{H}^+ \) ions, while the base releases \( \text{HO}^- \) ions. This process is called *hydrolysis*. The conjugate base of a strong acid is very weak and cannot undergo hydrolysis. Similarly, the conjugate acid of a strong base is very weak and likewise does not undergo hydrolysis.

*Acidity* and *basicity* are described in terms of equilibria. Acidity is the measure of how easily a compound gives up a proton, and basicity is a measure of how well a compound shares its electrons with a proton. A strong acid is one that gives up its proton easily. This means that its conjugate base must be weak, because it has little affinity for a proton. A weak acid gives up its proton with difficulty, indicating that its conjugate base is strong because it has a high affinity for a proton. Thus, the stronger the acid, the weaker its conjugate base.

When acids or bases are ionized, the amount of ionization will depend on the strength of acids and bases. Strong acids and bases are almost completely ionized in water. A stronger acid produces a weaker conjugate base, likewise a stronger base produces a weaker conjugate acid. For strong acids and bases, we can directly calculate the pH, if we know the molar concentration (M) of the solution.

An acid–base reaction is favoured in the direction from the stronger member to the weaker member of each conjugate acid–base pair. Thus, in an acid–base reaction, the equilibrium will always favour the reaction that moves the proton to the stronger base. For example, when a strong acid, such as hydrochloric acid (an inorganic or mineral acid), is dissolved in water, it dissociates almost completely, which means that the products are favoured at equilibrium. When a much weaker acid, such as acetic acid (an organic acid), is dissolved in water, it dissociates only to a small extent, so the reactants are favoured at equilibrium.

\[
\text{H}^+ + \text{Cl}^- \rightleftharpoons \text{HCl} \quad \text{pK}_a = -7.0 \\
\quad \text{A conjugate acid}
\]

\[
\text{H}^+ \quad \text{pK}_a = -1.74 \\
\quad \text{A conjugate base}
\]

The \( \text{H}_3\text{O}^+ \) (\( \text{pK}_a = -1.74 \)) is the conjugate acid of water. The \( \text{pK}_a \) of \( \text{H}_3\text{O}^+ \) is higher than HCl (\( \text{pK}_a = -7.0 \)). This means that HCl will give up its protons to water completely to
form the H$_3$O$^+$ ion. The lower the value of p$K_a$ stronger is the acid and the higher the value of p$K_a$ stronger is the base.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{C} \quad \text{H} \quad \text{H} \\
\text{H} \quad \text{O} & \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{H} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{H} \quad \text{O} \quad \text{H} \quad \text{H} \quad \text{H} \\
\text{H}_2\text{C} & \quad \text{C} \quad \text{O} \quad \text{H}
\end{align*}
\]

\[pK_a = 4.76\] 
(A weak acid)

\[pK_a = -1.74\] 
(A strong acid)

The p$K_a$ is the negative logarithm (to base 10) of the $K_a$. The relationship between $K_a$ and p$K_a$ is exactly the same as that between $K_w$ and p$K_w$.

\[pK_a = -\log K_a\]

We know that the p$K_a$ is characteristic of a particular compound, and it tells how readily the compound gives up a proton. $K_a$ values are very small and hard to remember. Therefore, the strength of an acid is generally indicated by its p$K_a$ values rather than its $K_a$ value. The lower the value of p$K_a$, the stronger is the acid. For example, hydrochloric acid is a strong acid and has p$K_a = -7.0$, and acetic acid is a weak acid and has p$K_a = 4.76$.

<table>
<thead>
<tr>
<th>Very strong acids</th>
<th>p$K_a &lt; 1$</th>
<th>Moderately strong acids</th>
<th>p$K_a = 1–5$</th>
<th>Weak acids</th>
<th>p$K_a = 5–15$</th>
<th>Extremely weak acids</th>
<th>p$K_a &gt; 15$</th>
</tr>
</thead>
</table>

The strength of an acid and a base is described in terms of the acid–base reaction equilibrium. Acid and base dissociation constants ($K_a$ and $K_b$) are the measure of the strength of acids and bases. Usually, $K_a$ and $K_b$ values are used to compare, respectively, the strength of weak acids and weak bases. Acid dissociation constant ($K_a$) is a measure of the strength of an acid. For example, ethanol is a very weak acid ($pK_a = 15.9$), acetic acid ($pK_a = 4.76$) is somewhat stronger than ethanol, but trichloroacetic acid ($pK_a = 0.66$) is much stronger acid than acetic acid.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{CH}_3 & \quad \text{OH} \\
\text{CH}_3 & \quad \text{C} \quad \text{O} \quad \text{H} \\
\text{Cl}_3 & \quad \text{O} \quad \text{H}
\end{align*}
\]

Ethanol 
$pK_a = 15.9$

Acetic acid 
$pK_a = 4.76$

Trichloroacetic acid 
$pK_a = 0.66$

The strength of an acid depends on its degree of dissociation in water. The acid dissociation constant, $K_a$, is the equilibrium constant for a dissociation
reaction. Let us consider first a simple reaction and its equilibrium features as shown next.

\[
\begin{align*}
\text{HA} + H_2O & \rightleftharpoons H_3O^+ + A^- \\
\text{Weak acid} & \quad \text{Weak base} & \quad \text{Strong acid} \quad \text{(A conjugate acid)}
\end{align*}
\]

\(pK_a = -1.74\)

Weak acid is only partially ionized in water and the reaction equilibrium lies on the left. Whether a reversible reaction favours reactants or products at equilibrium is indicated by the equilibrium constant of the reaction \((K_{eq})\). Remember that brackets are used to indicate concentration in moles per litre = molarity (M). The degree to which an acid (HA) dissociates is described by its acid dissociation constant \((K_a)\). The acid dissociation constant is obtained by multiplying the equilibrium constant \((K_{eq})\) by the concentration of the solvent in which the reaction takes place. Thus at equilibrium, the strength of an acid dissociation constant, \(K_a\) can be expressed as:

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

Here, \([H_2O]\) is constant and is included in the acid dissociation constant, \(K_a\). The \(K_a\) values can be used to describe the relative strength of acids. It is a constant at constant temperature. Strong acids have \(K_a\) larger than 1 and weak acids have \(K_a\) smaller than 1. Therefore, the larger the acid dissociation constant, the stronger is the acid. Hydrochloric acid (strong acid) has an acid dissociation constant of \(10^1\), whereas acetic acid (weak acid) has an acid dissociation constant of \(1.74 \times 10^{-5}\).

A weak base is only partially ionized and the reaction equilibrium lies on the left.

\[
\begin{align*}
\text{B}^- + H_2O & \rightleftharpoons BH^+ + HO^- \\
\text{Weak base} & \quad \text{Weak acid} & \quad \text{Strong acid} \quad \text{(A conjugate base)} & \quad \text{Strong base} \quad \text{(A conjugate acid)}
\end{align*}
\]

At equilibrium, the strength of a base dissociation constant, \(K_b\), can be expressed as:

\[
K_b = K \left[ H_2O \right] = \frac{[BH^+][OH^-]}{[B]}
\]
Here, $[\text{H}_2\text{O}]$ is a constant and is included in the base dissociation constant, $K_b$. The $K_b$ is the negative logarithm (to base 10) of the $K_b$. The relationship between $K_b$ and $pK_b$ is exactly the same as that between $K_a$ and $pK_a$.

$$pK_b = -\log K_b$$

The $pK_b$ is also characteristic of a particular compound, and it tells how readily the compound gives up a hydroxide (hydroxyl) ion. The $K_b$ values are very small and hard to remember. The lower the value for $pK_b$ or higher the value of $K_b$, the stronger the base. The higher the value for $pK_b$ or lower the value of $K_b$, the weaker the base.

Weak acids and bases are only partially ionized. The dissociation constant can be used to calculate the amount ionized and the pH of the acids or bases. For weak acids and bases $K_a$ and $K_b$ always have values that are smaller than one. Acids with a larger $K_a$ are stronger acids, and bases with smaller $K_b$ are stronger bases. Bases with a larger $K_b$ are stronger bases, and acids with smaller $K_b$ are stronger acids.

Weak acids, for example, HF, HCN, H$_2$S, H$_2$O, NH$_3$, HNO$_2$ (nitrous acid), HCO$_2$H (formic acid), CH$_3$CO$_2$H (acetic acid), C$_6$H$_5$CO$_2$H (benzoic acid) and weak bases, for example, H$_2$O, NH$_3$, NH$_4$OH (ammonium hydroxide), N$_2$H$_4$ (hydrazine), CH$_3$NH$_2$ (methylamine), CH$_3$CH$_2$NH$_2$ (ethylamine), are only partially ionized in solution and are always represented in their ionized form in chemical equations. When acids or bases are ionized, the amount of ionization will depend on the strength of acids and bases. An acid–base reaction is favoured in the direction from the stronger member to the weaker member of each conjugate acid–base pair. When a weak acid, such as acetic acid (ethanoic acid or acetyl hydroxide), is dissolved in water, it dissociates only a small amount so the reactants are favoured at equilibrium.

$$\begin{align*}
\text{H}_3\text{C} &- \text{C} - \tilde{\text{O}} - \text{H} \\
\text{pK}_a &= 4.76 \\
\text{Weak acid}
\end{align*}$$

$$\begin{align*}
\text{H}_2\tilde{\text{O}} \\
\text{Weak base}
\end{align*}$$

$$\begin{align*}
\text{H}_3\text{C} &- \text{C} - \tilde{\text{O}}^- \\
\text{pK}_a &= -1.74 \\
\text{Strong base} \\
\text{(A conjugate acid)}
\end{align*}$$

$$\begin{align*}
\text{H}_3\tilde{\text{O}}^+ \\
\text{Strong acid} \\
\text{(A conjugate base)}
\end{align*}$$

The H$_3$O$^+$ ($pK_a = -1.74$) is the conjugate acid of water. The $pK_a$ of H$_3$O$^+$ is lower than CH$_3$CO$_2$H ($pK_a = 4.76$). This means that H$_3$O$^+$ (strong acid) will give up its protons to CH$_3$CO$_2$ (strong base) completely to form the CH$_3$CO$_2$H.

A salt is an ionic compound formed by the reaction of an acid and a base. This is called a neutralization reaction. The reverse of the neutralization reaction is called hydrolysis. In a hydrolysis reaction, a salt reacts with water to reform the acid and base. The conjugate base of a strong acid is very weak and cannot undergo
hydrolysis. Similarly, the conjugate acid of a strong base is very weak and likewise does not undergo hydrolysis.

\[
\text{H}_2\text{SO}_4 \text{ (Strong acid)} + \text{Zn(OH)}_2 \text{ (Strong base)} \rightarrow \text{ZnSO}_4 \text{(Salt)} + 2\text{H}_2\text{O (water)}
\]

There are four combinations of strong and weak acids and bases. Salt hydrolysis usually affects the pH of a solution. The pH of the salt depends on the strengths of the original acids and bases as shown here.

<table>
<thead>
<tr>
<th>Acid</th>
<th>Base</th>
<th>Salt pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Strong</td>
<td>7.0</td>
</tr>
<tr>
<td>Weak</td>
<td>Strong</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>Strong</td>
<td>Weak</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>Weak</td>
<td>Weak</td>
<td>Depends on which one is stronger</td>
</tr>
</tbody>
</table>

Strong acids and strong bases react with each other almost completely, and salt and water are produced. The strong acid and strong base neutralizes each other and forms a neutral salt.

\[
\text{HCl (Strong acid)} + \text{NaOH (Strong base)} \rightarrow \text{NaCl (Salt)} + \text{H}_2\text{O (water)}
\]

Hydrolysis of NaCl produces Na\(^+\) and Cl\(^-\) ions and they do not react with water. This is called a neutralization reaction.

\[
\text{NaCl (Salt)} + \text{H}_2\text{O} \rightarrow \text{Na}^+ + \text{Cl}^-
\]

Salts of strong acids and weak bases form acidic solutions. The reaction between a strong acid and a weak base only yields a salt, and water is not formed since a weak base tends not to be a hydroxide.

\[
\text{HCl (Strong acid)} + \text{NH}_3 \text{ (Weak base)} \rightarrow \text{NH}_4\text{Cl (Salt)}
\]

Hydrolysis of ammonium chloride produces NH\(_4^+\) and Cl\(^-\) ions when water is added.

\[
\text{NH}_4\text{Cl (Salt)} + \text{H}_2\text{O} \rightarrow \text{NH}_4^+ + \text{Cl}^-
\]

The Cl\(^-\) ion does not react with water but the NH\(_4^+\) ion reacts with water and produces H\(_3\)O\(^+\) and NH\(_3\). Since the H\(_3\)O\(^+\) (pK\(_a\) = −1.74) ion is present in the solution, it is acidic.

\[
\text{NH}_4^+ + \text{H}_2\text{O} \rightarrow \text{H}_3\text{O}^+ + \text{NH}_3
\]
Salts of weak acids and strong bases form basic solutions. A weak acid reacts with a strong base and produces a basic salt.

$$\text{CH}_3\text{CO}_2\text{H} \text{ (Weak acid)} + \text{NaOH} \text{ (Strong base)} \rightarrow \text{CH}_3\text{CO}_2\text{Na} \text{ (Salt)} + \text{H}_2\text{O}$$

Hydrolysis of $\text{CH}_3\text{CO}_2\text{Na}$ forms $\text{CH}_3\text{CO}_2^-\text{ and Na}^+$ ions. The $\text{Na}^+$ ion does not react with water but $\text{CH}_3\text{CO}_2^-$ ion reacts with water and produces $\text{CH}_3\text{CO}_2\text{H}$ and $\text{HO}^-$. Since the $\text{HO}^-$ ($pK_a = 15.7$) ion is present in the solution, it is basic. The higher the value of $pK_a$, the stronger the base.

$$\text{CH}_3\text{CO}_2\text{Na} \xrightarrow{\text{H}_2\text{O}} \text{CH}_3\text{CO}_2^- + \text{Na}^+$$

$$\text{CH}_3\text{CO}_2^- + \text{H}_2\text{O} \xrightarrow{} \text{CH}_3\text{CO}_2\text{H} + \text{HO}^-$$

When a weak acid reacts with a weak base, a salt is formed and the resulting pH of the solution depends on the relative strength of the acid and base. The solution formed in the reaction may be slightly acidic, basic or neutral depending on the relative concentrations of $\text{H}^+$ and $\text{HO}^-$ ions. If $K_a$ for the cation is greater than $K_b$ for the anion, the solution is acidic. If $K_b$ for the anion is greater than $K_a$ for the cation, the solution is basic. If $K_a$ and $K_b$ are similar, the solution is close to neutral. For example, if the acid HClO has a $K_a = 3.4 \times 10^{-8}$ and the base NH$_3$ has a $K_b = 1.6 \times 10^{-5}$, then the aqueous solution of HClO and NH$_3$ will be basic, because the $K_b$ of NH$_3$ is higher than the $K_a$ of HClO. Acid with higher $K_a$ (acid dissociation constant) is a strong acid, and base with higher $K_b$ (base dissociation constant) is a strong base.

$$\text{HClO} \text{ (Weak acid)} + \text{NH}_3 \text{ (Weak base)} \xleftrightarrow{} \text{NH}_4\text{ClO} \text{ (Basic salt)}$$

Most organic acids and bases are weak acids and weak bases. The $pK_a$ and $pK_b$ values of weak acids and bases at 25°C are shown here.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$pK_a$</th>
<th>$pK_b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>4.76</td>
<td>9.24</td>
</tr>
<tr>
<td>Ammonium ion</td>
<td>9.25</td>
<td>4.75</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>4.19</td>
<td>9.81</td>
</tr>
<tr>
<td>Formic acid</td>
<td>3.74</td>
<td>10.26</td>
</tr>
<tr>
<td>Lactic acid</td>
<td>3.86</td>
<td>10.14</td>
</tr>
<tr>
<td>Phenol</td>
<td>9.89</td>
<td>4.11</td>
</tr>
</tbody>
</table>

### 1.7.5 Acid–Base Titration: Neutralization

The process of obtaining quantitative information of a sample using a fast chemical reaction by reacting with a certain volume of reactant whose
concentration is known is called titration. The goal is to determine the pH during the course of titration. In a titration, a solution of accurately known concentration is added gradually to another solution of unknown concentration until the chemical reaction between the two solutions is complete. Titration is also called volumetric analysis, which is a type of quantitative chemical analysis. Generally, the titrant (the known solution) is added from a burette to a known quantity of the analyte (the unknown solution) until the reaction is complete.

The titration curve is the pH change against the amount of titrant added. From the added volume of the titrant, it is possible to determine the concentration of the unknown. Often, an indicator is used to detect the end of the reaction, known as the endpoint at which the indicator changes colour. The endpoint is determined by the sudden change of pH.

An acid–base titration is a method that allows quantitative analysis of the concentration of an unknown acid or base solution. In an acid–base titration (neutralization), the base will react with the weak acid and form a solution that contains the weak acid and its conjugate base until the acid is completely neutralized. The following equation is used frequently, when trying to find the pH of buffer solutions.

\[ pH = pK_a + \log \frac{[\text{Base}]}{[\text{Acid}]} \]

where, pH is the log of the molar concentration of the hydrogen, 
\(pK_a\) is the equilibrium dissociation constant for an acid, \([\text{Base}]\) is the molar concentration of a basic solution and \([\text{Acid}]\) is the molar concentration of an acidic solution.

The point at which the acid and base are present in equal stoichiometric amounts is called the equivalence point. In other words, an equivalence point is reached, when the reaction is completed. Generally, for the titration of a strong base with a weak acid, the equivalence point is reached when the pH is greater than 7. The half equivalence point is when half of the total amount of base needed to neutralize the acid has been added. It is at this point, where the pH = \(pK_a\) of the weak acid.

An indicator is a substance that changes colour at the equivalence point over a specific pH range. An indicator can exist in either its acid or base form and it changes colour when proton gain or loss occurs. In acid–base titrations, a suitable acid–base indicator is used to detect the endpoint from the change of colour of the indicator used. An acid–base indicator is a weak acid or a weak base. For example, when a weak acid is titrated with a strong base containing phenolphthalein indicator, it produces a conjugate base of weak acid at the equivalence point.
pH > 7. The names and the pH range of some common acid-base indicators are shown in the following Table.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>pH range</th>
<th>Colour in acid</th>
<th>Colour in base</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thymol blue</td>
<td>1.2–2.8</td>
<td>Red</td>
<td>Yellow</td>
</tr>
<tr>
<td>Bromophenol blue</td>
<td>3.0–4.6</td>
<td>Yellow</td>
<td>Blue-violet</td>
</tr>
<tr>
<td>Methyl orange</td>
<td>3.1–4.4</td>
<td>Orange</td>
<td>Yellow</td>
</tr>
<tr>
<td>Methyl red</td>
<td>4.2–6.3</td>
<td>Red</td>
<td>Yellow</td>
</tr>
<tr>
<td>Chlorophenol blue</td>
<td>4.8–6.4</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Bromothymol blue</td>
<td>6.0–7.6</td>
<td>Yellow</td>
<td>Blue</td>
</tr>
<tr>
<td>Cresol red</td>
<td>7.2–8.8</td>
<td>Yellow</td>
<td>Red</td>
</tr>
<tr>
<td>Phenolphthalein</td>
<td>8.0–10.0</td>
<td>Colourless</td>
<td>Red</td>
</tr>
</tbody>
</table>

### 1.8 BUFFER AND ITS USE

A buffer is a solution containing a weak acid and its conjugate base (i.e. CH₃COOH and CH₃COO⁻) or a weak base and its conjugate acid (i.e. NH₃ and NH₄⁺). Buffers are commonly used, when pH must be maintained at a relatively constant value in many biological systems as well as useful for monitoring pH for reaction at an optimum value. A buffer solution has the ability to resist changes in pH on addition of small amounts of acid or base. For example, when a strong acid is added, the base present in the buffer solution neutralizes the hydronium (H₃O⁺) ions. Similarly, when a strong base is added, the acid present in the buffer solution neutralizes the hydroxide (HO⁻) ions.

By choosing the appropriate components, a solution can be buffered virtually at any pH. The pH of a buffered solution depends on the ratio of the concentrations of buffering components. When the ratio is least affected by adding acids or bases, the solution is most resistant to a change in pH. It is more effective when the acid-base ratio is equal to 1. Therefore, the pKₐ of the weak acid selected for the buffer should be as close as possible to the desired pH, because it follows the following equation.

\[ \text{pH} = \text{pK}_a \]

An acidic buffer solution is simply the one, which has a pH less than 7. Therefore, acidic buffer solutions are commonly made from a weak acid and one of its salts, often a sodium salt. A basic buffer solution has a pH greater than 7. Thus, basic buffer solutions are commonly made from a weak base and one of its salts. An acidic buffer solution consists of a mixture of a weak acid and its salt at predetermined concentration. For a weak acid HA that ionizes to H⁺ and its salt A⁻.

\[ \text{HA} \rightleftharpoons [\text{H}^+] + [\text{A}^-] \]
The acid equilibrium can be written as:

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

The hydrogen ion concentration can be written as:

$$[H^+] = K_a \frac{[HA]}{A^-}$$

Taking the −log on both sides of the equation gives:

$$-\log[H^+] = -\log K_a - \log \frac{[HA]}{A^-}$$

$$\text{pH} = pK_a - \log \frac{[HA]}{A^-}$$

On converting the last log term, it becomes positive.

$$\text{pH} = pK_a + \log \frac{A^-}{HA}$$

$$\text{pH} = pK_a + \log \frac{\text{Salt}}{\text{Acid}}$$

Therefore, $\text{pH} = pK_a + \log [\text{Salt}] - \log [\text{Acid}]$. This equation is known as the **Henderson–Hasselbalch equation**, or simply **buffer equation**. It is useful for calculating the pH of a weak acid solution containing its salt.

Buffers play an important role in cellular processes, because they maintain the pH at an optimal level for biological processes. Strong acids, such as HCl, are poor buffers, while weaker acids, such as acetic acid, are good buffers in the pH ranges found in biological environments. Thus, the role of a buffer system in the body is important as it tends to resist any pH changes as a result of metabolic processes. The most important practical example of a buffered solution is blood, which can absorb the acids and bases produced by biological reactions without changing its pH. The normal pH of blood is 7.4. Blood can absorb the acids and bases produced in biological reactions without changing its pH. Thus, blood is a buffer solution. A constant pH for blood is vital, because cells can survive only this narrow pH range around 7.4.

One common buffer system in the body is the carbonic acid buffer system. It helps keep the blood at a fairly constant pH at around 7.4. If it goes below 7.35, someone may experience a condition known as **acidosis** and triggers **hyperventilation**, which
causes to breathe at an abnormally rapid rate. If it goes above 7.45, someone may experience a condition known as alkalosis and trigger hyperventilation, which causes to breathe at an abnormally slow rate. Therefore, if blood pH goes below 6.8 or above 7.8, cells of the body can stop functioning and the person eventually can die.

Water is the medium for metabolic reactions within cells. Carbon dioxide from metabolism combines with water in blood plasma to produce carbonic acid ($H_2CO_3$), which is weakly ionic and can dissociate to form hydronium ($H_3O^+$) ions and the bicarbonate ($HCO_3^-$) ions as shown next. The amount of $H_2CO_3$ depends on the amount of $CO_2$ present.

$$CO_2 + H_2O \rightarrow H_2CO_3$$

$$H_2CO_3 + H_2O \rightarrow H_3O^+ + HCO_3^-$$

The pH of blood is maintained at about 7.4 by the carbonic acid-bicarbonate ion buffering system. When any acidic substance enters the bloodstream, the bicarbonate ($HCO_3^-$) ions neutralize the hydronium ($H_3O^+$) ions forming carbonic acid and water. Carbonic acid ($H_2CO_3$) is already a component of the buffering system of blood. Thus hydronium ($H_3O^+$) ions are removed, preventing the pH of blood from becoming acidic.

$$HCO_3^- + H_3O^+ \rightarrow H_2CO_3 + H_2O$$

On the other hand, when a basic substance enters the bloodstream, carbonic acid ($H_2CO_3$) reacts with the hydroxide ($HO^-$) ions producing bicarbonate ($HCO_3^-$) ions and water. Bicarbonate ions ($HCO_3^-$) are already a component of the buffer. In this manner, the hydroxide ($HO^-$) ions are removed from blood, preventing the pH of blood from becoming basic.

$$H_2CO_3 + HO^- \rightarrow HCO_3^- + H_2O$$

Therefore, by far the most important buffer for maintaining acid-base balance in the blood is the carbonic acid–bicarbonate buffer.

### 1.8.1 Common Ion Effects and Buffer Capacity

The most important application of acid–base solutions containing a common (same) ion is buffering. The pH of a buffer does not depend on the absolute amount of the conjugate acid–base pair. It is based on the ratio of the two. In other words, it depends on the common ion effect. The solution containing both the weak acid and its conjugate base has a pH much higher than the solution containing only the weak base. The conjugate base is referred to as a common ion, because it is found in both the weak acid and the anion. The common ion effect can also be applied to a solution containing a weak base and its conjugate acid. The common ion effect

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is the suppression of the ionization of a weak acid or a weak base by the presence of a common ion from a strong electrolyte.

The buffer capacity is a measure of the effectiveness of a buffer. The amount of acid and base that can be added without causing a large change in pH is governed by the buffering capacity of the solution. This is determined by the concentrations of acid and its conjugate base. The higher the concentrations of the acid and its conjugate base, the addition of more acid or base can tolerate the solution. In other words, the more concentrated the acid and its conjugate base in a solution, the more added acid or base the solution can neutralize. The buffering capacity is governed by the ratio of acid and its conjugate base. Therefore, buffer capacity is a measure of how well a solution resists changes in pH when strong acid or base is added. A buffer is most effective if the concentrations of the buffer acid and its salt are equal.

\[
pH = pK_a + \log(1) = pK_a + 0
\]

Thus, \( pH = pK_a \)