CHEMISTRY
FOR PHARMACY STUDENTS

General, Organic and Natural Product Chemistry

SATYAJIT D SARKER LUTFUN NAHAR

WILEY

Chemistry for Pharmacy Students

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Other Wiley Editorial Offices

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Jossey-Bass, 989 Market Street, San Francisco, CA 94103-1741, USA

Wiley-VCH Verlag GmbH, Boschstrasse 12, D-69469 Weinheim, Germany

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Anniversary Logo Design: Richard J. Pacifico

Library of Congress Cataloging-in-Publication Data

Sarker, Satyajit D.
Chemistry for pharmacy students: general, organic, and natural product chemistry / Satyajit D. Sarker, Lutfun Nahar.
p.; cm.
Includes bibliographical references.
ISBN 978-0-470-01780-7 (cloth : alk. paper)
1. Chemistry–Textbooks. I. Nahar, Lutfun, Ph. D. II. Title.
[DNLM: 1. Chemistry, Pharmaceutical. 2. Chemistry. QV 744 S517c 2007]
QD31.3.S377 2007
540–dc22 2007017895

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 978-0-470-01780-7 (HB) 978-0-470-01781-4 (PB)

Typeset in 11/14pt Times by Thomson Digital
Printed and bound in Great Britain by Antony Rowe Ltd., Chippenham, Wilts
This book is printed on acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production.

This book is dedicated to
pharmacy students
from all over the world

Contents

Preface

The pharmacy profession and the role of pharmacists in the modern healthcare systems have evolved quite rapidly over the last couple of decades. The services that pharmacists provide are expanding with the introduction of supplementary prescribing, provision of health checks, patient counselling and many others. The main ethos of pharmacy profession is now as much about keeping people healthy as treating them when they are not well. The modern pharmacy profession is shifting away from a product focus and towards a patient focus. To cope with these changes, and to meet the demand of the modern pharmacy profession, the pharmacy curriculum, especially in the developed world, has evolved significantly. In the western countries, almost all registered pharmacists are employed by the community and hospital pharmacies. As a consequence, the practice, law, management, care, prescribing science and clinical aspects of pharmacy have become the main components of pharmacy curriculum. In order to incorporate all these changes, naturally, the fundamental science components, e.g. chemistry, statistics, pharmaceutical biology, microbiology, pharmacognosy and a few other topics, have been reduced remarkably. The impact of these recent changes is more innocuous in the area of pharmaceutical chemistry.

As all drugs are chemicals, and pharmacy is mainly about the study of various aspects of drugs, including manufacture, storage, actions and toxicities, metabolisms and managements, chemistry still plays a vital role in pharmacy education. However, the extent at which chemistry used to be taught a couple of decades ago has certainly changed significantly. It has been recognized that while pharmacy students need a solid foundation in chemistry knowledge the extent cannot be the same as chemistry students may need.

There are several books on general, organic and natural product chemistry available today, but all of them are written in such a manner that the level is only suitable for undergraduate Chemistry students, not for Pharmacy undergraduates. Moreover, in most modern pharmacy curricula, general, organic and natural product chemistry is taught at the first and second year undergraduate levels only. There are also a limited number of Pharmaceutical Chemistry books available to the students, but none of them can meet the demand of the recent changes in pharmacy courses in the developed

countries. Therefore, there has been a pressing need for a chemistry text covering the fundamentals of general, organic and natural product chemistry written at a correct level for the Pharmacy undergraduates. Physical (Preformulation) and Analytical Chemistry (Pharmaceutical Analysis) are generally taught separately at year 2 and year 3 levels of any modern MPharm course, and there are a number of excellent and up-to-date texts available in these areas.

During our teaching careers, we have always struggled to find an appropriate book that can offer general, organic and natural product chemistry at the right level for Pharmacy undergraduate students, and address the current changes in pharmacy curricula all over the world, at least in the UK. We have always ended up recommending several books, and also writing notes for the students. Therefore, we have decided to address this issue by compiling a chemistry book for Pharmacy students, which will cover general, organic and natural product chemistry in relation to drug molecules. Thus, the aims of our book are to provide the fundamental knowledge and overview of all core topics related to general, organic and natural product chemistry currently taught in Pharmacy undergraduate courses in the UK, USA and various other developed countries, relate these topics to the better understanding of drug molecules and their development and meet the demand of the recent changes in pharmacy curricula. This book attempts to condense the essentials of general, organic and natural product chemistry into a manageable, affordable and student-friendly text, by concentrating purely on the basics of various topics without going into exhaustive detail or repetitive examples.

In Pharmacy undergraduate courses, especially in the UK, we get students of heterogeneous educational backgrounds; while some of them have very good chemistry background, the others have bare minimum or not at all. From our experience in teaching Pharmacy undergraduate students, we have been able to identify the appropriate level that is required for all these students to learn properly. While we recognise that learning styles and levels vary from student to student, we can still try to strike the balance in terms of the level and standard at a point, which is not too difficult or not too easy for any students, but will certainly be student friendly. Bearing this in mind, the contents of this book are organized and dealt with in a way that they are suitable for year 1 and year 2 levels of the pharmacy curriculum. While the theoretical aspects of various topics are covered adequately, much focus has been given to the applications of these theories in relation to drug molecules and their discovery and developments. Chapter 1 provides an overview of some general aspects of chemistry and their importance in modern life, with particular emphasis on medicinal applications, and brief discussions of various physical characteristics of drug molecules, e.g. pH, polarity and solubility. While Chapter 2 deals with the fundamentals of atomic structure

and bonding, chapter 3 covers various aspects of stereochemistry. Chapter 4 incorporates organic functional groups, and various aspects of aliphatic, aromatic and heterocyclic chemistry, amino acids and nucleic acids and their pharmaceutical importance. Major organic reactions are covered adequately in Chapter 5, and various types of pharmaceutically important natural products are discussed in Chapter 6.

While the primary readership of this book is the Pharmacy undergraduate students (BPharm/MPharm), especially in their first and second years of study, the readership could also extend to the students of various other subject areas within Food Sciences, Life Sciences and Health Sciences who are not becoming chemists yet need to know the fundamentals of chemistry for their courses.

Dr Satyajit D Sarker
Dr Lutfun Nahar

1
Introduction

Learning objectives

After completing this chapter the student should be able to

- describe the role of chemistry in modern life;
- define some of the physical properties of drugs, e.g. polarity, solubility, melting point, boiling point 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 matter, especially of atomic and molecular systems.

Life itself is full of chemistry; i.e., 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 constructed physically 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, heredities and continuation of generations are all governed by chemistry.

In our everyday life, whatever we see, use or consume is the gift of research in chemistry for thousands of years. In fact, chemistry is applied

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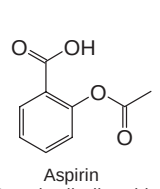
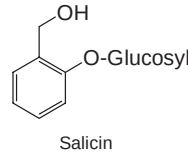
everywhere in modern life. From the colouring of our clothes to the shapes of our PCs, all are possible due to chemistry. It has played a major role in pharmaceutical advances, forensic science and modern agriculture. Diseases and their remedies have also been a part of human lives. Chemistry plays an important role in understanding diseases and their remedies, i.e. drugs. The focus of this section is given to the role of chemistry in modern medicine.

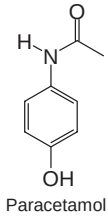
Medicines or drugs that we take for the treatment of various ailments are chemicals, either organic or inorganic. However, most drugs are organic molecules. Let us take aspirin as an example. It is probably the most popular and widely used analgesic drug because of its structural simplicity and low cost. Aspirin is chemically known as acetyl salicylic acid, an organic molecule. The precursor of aspirin is salicin, which is found in willow tree bark. However, aspirin can easily be synthesized from phenol using the *Kolbe reaction* (see Section 4.6.10). As we progress through various chapters of this book, we will come across a series of examples of drugs and their properties.



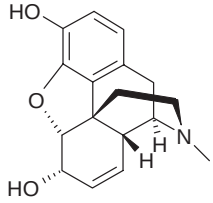
Aspirin
Acetyl salicylic acid



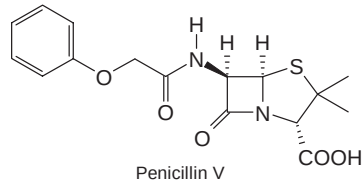
Salicin
The precursor of aspirin



Paracetamol



Morphine



Penicillin V

In order to have a proper understanding and knowledge of 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 involved directly.

In the drug discovery stage, suitable sources are explored. Sources of drug molecules can be natural, e.g. narcotic analgesic, morphine, from *Papaver somniferum* (Poppy plant), synthetic, e.g. a popular analgesic and antipyretic, paracetamol, or semi-synthetic, e.g. semi-synthetic penicillins.

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, e.g. a plant, processes such as extraction, isolation and identification are used, and all these processes involve chemistry.

Similarly, in the drug development steps, especially in the 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, e.g. 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. 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.

1.2 Physical properties of drug molecules

1.2.1 Physical state

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

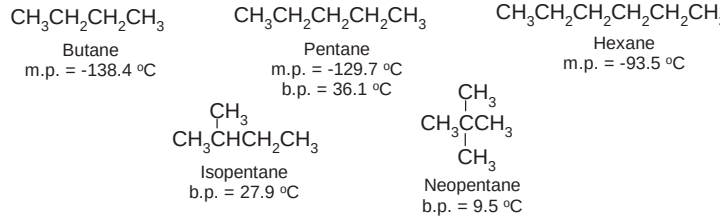
1.2.2 Melting point and boiling point

The *melting point (m.p.)* is the temperature at which a solid becomes a liquid, and the *boiling point (b.p.)* is the temperature at which the vapour pressure of the liquid is equal to the atmospheric pressure. The 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 atmosphere of pressure is 0 °C (32 °F, 273.15 K; this is also known as the *ice point*) and the boiling point of water 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. 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. In contrast, between two alkanes having same molecular weights, the more highly branched alkane has a lower boiling point.



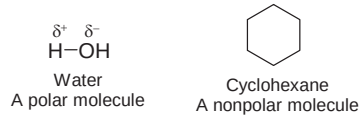
1.2.3 Polarity and solubility

Polarity is a physical property of a compound, which relates other physical properties, e.g. 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 or nonpolar covalent bond that are present. In a few cases, a molecule having polar bonds, but in a symmetrical arrangement, may give rise to a nonpolar molecule, e.g. carbon dioxide (CO_2).

The term *bond polarity* is used to describe the sharing of electrons between atoms. 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. When this relative attraction is strong, the bond is an ionic bond.

The polarity in a bond arises from the different electronegativities of the two atoms that take part in the bond formation. The greater the difference in electronegativity between the bonded atoms, the greater is the polarity of the bond. For example, water is a polar molecule, whereas cyclohexane is nonpolar. The bond polarity and electronegativity are discussed in Chapter 2.



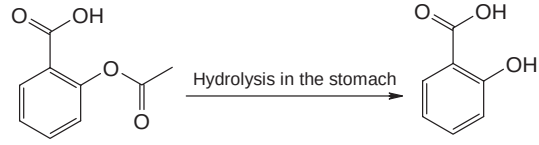
Solubility is the amount of a solute that can be dissolved in a specific solvent under given conditions. The dissolved substance is called the *solute* and the dissolving fluid is called the *solvent*, which together form a *solution*. The process of dissolving is called *solvation*, or *hydration* when the solvent is water. In fact, the interaction between a dissolved species and the molecules of a solvent is *solvation*.

The solubility of molecules can be explained on the basis of the polarity of molecules. Polar, e.g. water, and nonpolar, e.g. benzene, solvents do not mix. In general, like dissolves like; i.e., materials with similar polarity are soluble in each other. A polar solvent, e.g. water, has partial charges that can interact with the partial charges on a polar compound, e.g. sodium chloride (NaCl). As nonpolar compounds have no net charge, polar solvents are not attracted to them. Alkanes are nonpolar molecules, and are insoluble in polar solvent, e.g. water, and soluble in nonpolar solvent, e.g. petroleum ether. The hydrogen bonding and other nonbonding interactions between molecules are described in Chapter 2.

A solution at *equilibrium* that cannot hold any more solute is called a *saturated solution*. The equilibrium of a solution depends mainly on temperature. The maximum equilibrium amount of solute that can usually dissolve per amount of solvent is the *solubility* of that solute in that solvent. It is generally expressed as the maximum concentration of a saturated solution. The solubility of one substance dissolving in another is determined by the *intermolecular forces* between the solvent and solute, temperature, the entropy change that accompanies the solvation, the presence and amount of other substances and sometimes pressure or partial pressure of a solute gas. The *rate of solution* is a measure of how fast a solute dissolves in a solvent, and it depends on size of the particle, stirring, temperature and the amount of solid already dissolved.

1.2.4 Acid–base properties and pH

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. The carboxylic acid group (−COOH) and a phenolic hydroxyl group (−OH) present in salicylic acid make this molecule acidic. Thus, intake of aspirin increases the acidity of the stomach significantly, and if this increased acidic condition remains in the stomach for a long period, it may cause stomach bleeding. Like aspirin, there are a number of 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.



Aspirin Salicylic acid

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

Arrhenius acids and bases

According to Arrhenius's definition, an *acid* is a substance that produces hydronium ion (H_3O^+), and a base produces hydroxide ion (OH^-) in aqueous solution. An acid reacts with a base to produce salt and water.

$$\text{HCl (Acid)} + \text{NaOH (Base)} \rightleftharpoons \text{NaCl (Salt)} + \text{H}_2\text{O (Water)}$$

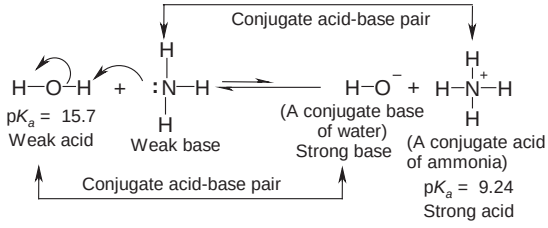
Brønsted–Lowry acids and bases

The Danish chemist Johannes Brønsted and the English chemist Thomas Lowry defined an *acid* as a proton (H^+) donor, and a *base* as a proton (H^+) acceptor.

$$\text{HNO}_2\text{ (Acid)} + \text{H}_2\text{O (Base)} \rightleftharpoons \text{NO}_2^-\text{ (Conjugate base)} + \text{H}_3\text{O}^+\text{ (Conjugate acid)}$$

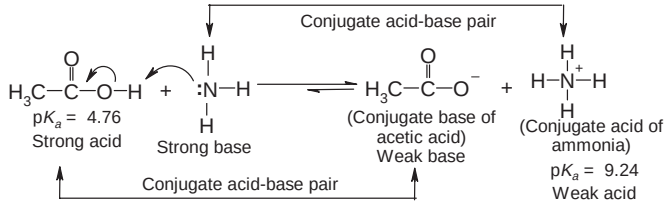
Each acid has a *conjugate base*, and each base has a *conjugate acid*. These conjugate pairs only differ by a proton. In the above example, HNO_2 is the acid, H_2O is the base, NO_2^- is the conjugate base, and H_3O^+ is the conjugate acid. Thus, a conjugate acid can lose an H^+ ion to form a base, and a conjugate base can gain an 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_3O^+), 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_2O 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.



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 (CH_3CO_2H) and NH_3, a proton is transferred from CH_3CO_2H, an acid, to NH_3, a base.



In the above acid–base reaction, NH_3 is a base because it accepts a proton, and CH_3CO_2H is an acid because it donates a proton. In the reverse reaction,

ammonium ion ($^{+}NH_4$) is an acid because it donates a proton, and acetate ion ($CH_3CO_2^{-}$) is a base because it accepts a proton. The curved arrows show the flow of electrons in an acid–base reaction.

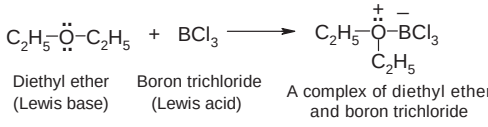
Two half-headed arrows are used for the equilibrium reactions. A longer arrow indicates that the equilibrium favours the formation of acetate ion ($CH_3CO_2^{-}$) and ammonium ion ($^{+}NH_4$). Because acetic acid (CH_3CO_2H) is a stronger acid than ammonium ion ($^{+}NH_4$), the equilibrium lies towards the formation of weak acid and weak base.

Lewis theory of acids and bases

The Lewis theory of acids and bases defines an acid as an electron-pair acceptor, and a base as an electron-pair donor. Thus, a proton is only one of a large number of species that may function as a *Lewis acid*. Any molecule or ion may be an acid if it has an empty orbital to accept a pair of electrons (see Chapter 2 for orbital and Lewis theory). Any molecule or ion with a pair of electrons to donate can be a base.

Using this theory, a number of organic reactions can be considered as acid–base reactions, because they do not have to occur in solution. Lewis acids are known as *aprotic acids*, compounds that react with bases by accepting pairs of electrons, not by donating protons.

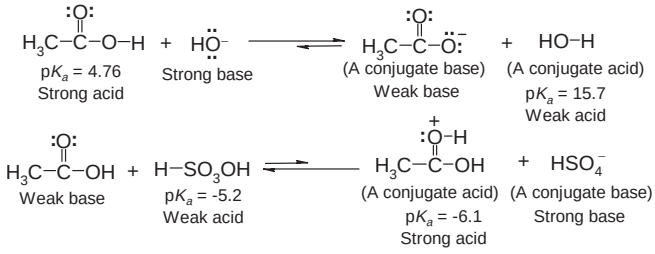
Borane (BH_3), boron trichloride (BCl_3) and boron trifluoride (BF_3) are known as *Lewis acids*, because boron has a vacant *d* orbital that accepts a pair of electrons from a donor species. For example, diethyl ether acts as a *Lewis base* towards BCl_3 and forms a complex of boron trichloride.



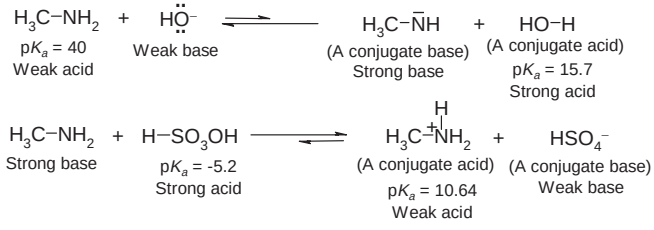
Acid–base properties of organic functional groups

Let us see the acid–base properties of some molecules having different functional groups. The most common examples are carboxylic acids, amines, alcohols, amides, ethers and ketones. Drug molecules also contain various types of functional group, 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* or *Brønsted bases*. They react with Lewis acids or Brønsted acids. Lewis acids may be either protic or aprotic acids. Brønsted acids are also called *protic acids*.

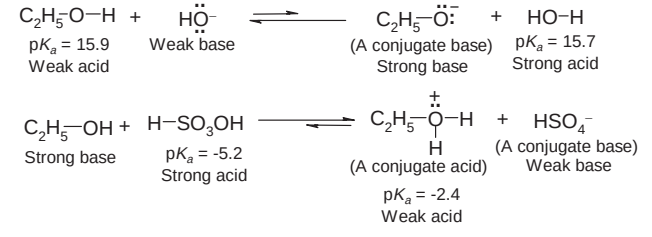
The most common organic acids are carboxylic acids. They are moderately strong acids having pK_a values ranging from about 3 to 5. Acetic acid (p$K_a = 4.76$) can behave as an acid and donate a proton, or as a base and accept a proton. A protonated acetic acid (p$K_a = -6.1$) is a strong acid. Equilibrium favours reaction of the stronger acid and stronger base to give the weaker acid and weaker base.



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.

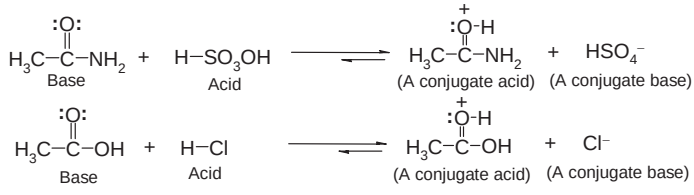


An alcohol can behave like an acid and donate a proton. However, alcohols are much weaker organic acids, with pK_a values close to 16. Alcohol may also behave as a base; e.g., ethanol is protonated by sulphuric acid and gives ethyloxonium ion ($C_2H_5OH_2^+$). A protonated alcohol (p$K_a = -2.4$) is a strong acid.

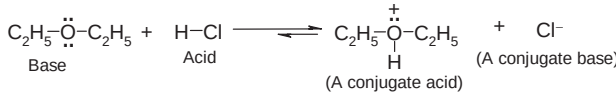


Some organic compounds have more than one atom with nonbonding electrons, thus more than one site in such a molecule can react with acids. For example, acetamide has nonbonding electrons on both nitrogen and oxygen atoms, and either may be protonated. However, generally the reaction stops when one proton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

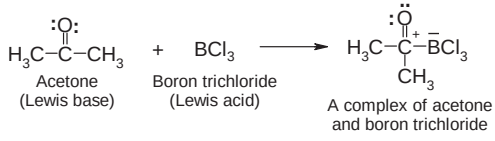
Both acetamide and acetic acid are more readily protonated at the carbonyl oxygen than the basic site. The protonation of the nonbonding electrons on the oxygen atom of a carbonyl or hydroxyl group is an important first step in the reactions under acidic conditions of compounds such as acetamide, acetic acid and alcohols. The conjugate acids of these compounds are more reactive towards Lewis bases than the unprotonated forms are. Therefore, acids are used as catalysts to enhance reactions of organic compounds.



The reaction of diethyl ether with concentrated hydrogen chloride (HCl) is typical of that of an oxygen base with a protic acid. Just like water, organic oxygenated compounds are protonated to give oxonium ions, e.g. protonated ether.



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



The reaction of an organic compound as an acid depends on how easily it can lose a proton to a base. 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, in which the hydrogen atoms are bonded to carbon atoms, is a very weak acid. 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. Weak acids produce strong conjugate bases. Thus, ethane gives a stronger conjugate base than methylamine and methanol. The conjugate bases of ethane, methylamine and methanol are shown below.

CH_3CH_3 (Ethane) $\rightarrow$ CH_3NH_2 (Methylamine) $\rightarrow$ CH_3OH (Methanol)
(Increasing acidity of hydrogen bonded to carbon, nitrogen and oxygen)
CH_3O^- (Methoxide anion) $\rightarrow$ CH_3NH^- (Methylamide anion) $\rightarrow$
$CH_3CH_2^-$ (Ethyl anion)
(Increasing basicity of the conjugate base)

pH and pK_a values

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.

$$pH = -\log_{10}[H_3O^+]$$

The acidity of an aqueous solution is determined by the concentration of H_3O^+ ions. Thus, the pH of a solution indicates the concentration of hydrogen ions in the solution. The concentration of hydrogen ions can be indicated as $[H^+]$ or its solvated form in water as $[H_3O^+]$. 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 solution. The pH of a solution can be changed simply by adding acid or base to the 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.

The pH of the salt depends on the strengths of the original acids and bases as shown below.

Acid	Base	Salt pH
Strong	Strong	7
Weak	Strong	>7
Strong	Weak	<7
Weak	Weak	Depends on which one is stronger

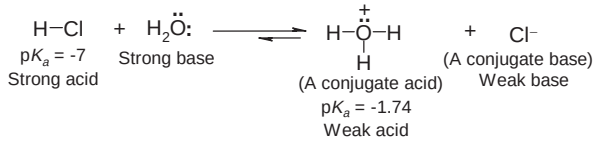
At equilibrium the concentration of H^+ is 10^{-7}, so we can calculate the pH of water at equilibrium as

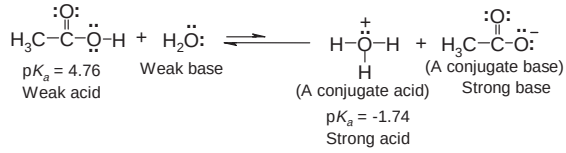
$pH = -\log_{10}[H^+] = -\log[10^{-7}] = 7$. Solutions with a pH of 7 are said to be *neutral*, while those with pH values below 7 are defined as acidic, and those above pH of 7 as being basic. The pH of blood plasma is around 7.4, whereas that of the stomach is around 1.

Strong acids, e.g. HCl, HBr, HI, H_2SO_4, HNO_3, $HClO_3$ and $HClO_4$, completely ionize in solution, and are always represented in chemical equations in their ionized form. Similarly, *strong bases*, e.g. 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 H^+ ions while the base releases OH^- 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 is its conjugate base.

When a strong acid, e.g. 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, e.g. acetic acid (an organic acid), is dissolved in water, it dissociates only to a small extent, so the reactants are favoured at equilibrium.





Whether a reversible reaction favours reactants or products at equilibrium is indicated by the equilibrium constant of the reaction (K_{eq}). Remember that square brackets are used to indicate concentration in moles/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.

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

The larger the acid dissociation constant, the stronger is the acid. Hydrochloric acid has an acid dissociation constant of 10^7, whereas acetic acid has an acid dissociation constant of only 1.74×10^{-5}. For convenience, the strength of an acid is generally indicated by its pK_a value rather than its K_a value. The pK_a of hydrochloric acid, strong acid, is -7, and the pK_a of acetic acid, much weaker acid, is 4.76.

$$pK_a = -\log K_a$$

Very strong acids	$pK_a < 1$	Moderately strong acids	$pK_a = 1-5$
Weak acids	$pK_a = 5-15$	Extremely weak acids	$pK_a > 15$

Buffer

A *buffer* is a solution containing a weak acid and its conjugate base (e.g. CH_3COOH and CH_3COO^-) or a weak base and its conjugate acid (e.g. NH_3 and NH_4^+).

The most important application of acid–base solutions containing a common ion is buffering. Thus, a buffer solution will maintain a relatively constant pH even when acidic or basic solutions are added to it. The most important practical example of a buffered solution is human blood, which can absorb the acids and bases produced by biological reactions without changing its pH. The normal pH of human blood is 7.4. A constant pH for blood is vital, because cells can only survive this narrow pH range around 7.4.

A buffered solution may contain a weak acid and its salt, e.g. acetic acid and acetate ion, or a weak base and its salt, e.g. NH_3 and NH_4Cl. By choosing the appropriate components, a solution can be buffered at virtually 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 unity. The pK_a of the weak acid selected for the buffer should be as close as possible to the desired pH, because it follows the following equation:

$$pH = pK_a$$

The role of a buffer system in the body is important, because it tends to resist any pH changes as a result of metabolic processes. Large fluctuation in

pH would denature most enzymes and hence interfere with the body metabolism. Carbon dioxide from metabolism combines with water in blood plasma to produce carbonic acid (H_2CO_3). The amount of H_2CO_3 depends on the amount of CO_2 present. The following system acts as a buffer, since carbonic acid can neutralize any base:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$
$$H_2CO_3 + H_2O \rightleftharpoons H_3O^+ + HCO_3^-$$

Acid–base titration: neutralization

The process of obtaining quantitative information on a sample using a fast chemical reaction by reacting with a certain volume of reactant whose concentration is known is called *titration*. 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. 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*.

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*, 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.

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

where pH is the log of the molar concentration of the hydrogen, pK_a is the equilibrium dissociation constant for the acid, [base] is the molar concentration of the basic solution and [acid] is the molar concentration of the acidic solution.

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 that the $pH = pK_a$ of the weak acid. 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. The following table contains the names and the pH range of some commonly used acid–base indicators.

Indicator	pH range	Quantity to be used per 10 mL	Colour in acid	Colour in base
Bromophenol blue	3.0–4.6	1 drop of 0.1% aq. solution	Yellow	Blue–violet
Methyl orange	3.1–4.4	1 drop of 0.1% aq. solution	Red	Orange
Phenolphthalein	8.0–10.0	1–5 drops of 0.1% solution in 70% alcohol	Colourless	Red
Thymol blue	1.2–2.8	1–2 drops of 0.1% aq. solution	Red	Yellow

Recommended further reading

Ebbing, D. D. and Gammon, S. D. *General Chemistry*, 7th edn, Houghton Mifflin, New York, 2002.