Lutfun Nahar
Satyajit Sarker

Chemistry for Pharmacy Students

SECOND EDITION

General, Organic and Natural Product Chemistry

WILEY

CHEMISTRY
FOR PHARMACY STUDENTS

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Second Edition

LUTFUN NAHAR
Liverpool John Moores University
UK

SATYAJIT SARKER
Liverpool John Moores University
UK

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Dedicated to pharmacy students, from home and abroad

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Preface to the second edition

The first edition of *Chemistry for Pharmacy Students: General, Organic and Natural Product Chemistry* was written to address the need for the right level and appropriate coverage of chemistry in any modern Pharmacy curricula. The first edition reflected on the changing face of Pharmacy profession and the evolving role of pharmacists in the modern healthcare systems, and was aimed at placing chemistry more in the context of medicines and patients. Since the publication in 2007, in subsequent years, the first edition has been translated into the Greek, Japanese and Portuguese languages, and has acclaimed huge acceptance and popularity among Pharmacy students, as well as among academics who teach chemistry in Pharmacy curricula all over the world.

It has been over a decade since the publication of the first edition. We feel that it has now become necessary to compile a second edition, which should be a thoroughly revised and enhanced version of the first. The second edition will also cater for the chemistry requirements in any 'Integrated Pharmacy Curricula', where science in general is meant to be taught 'not in isolation', but together with, and as a part of, other practice and clinical elements of Pharmacy curricula. Whatever may be the structure and content of any Pharmacy curriculum, there will always be two fundamental aspects in it – medicines (drugs) and patients.

Pharmacy began its journey as a medicine (drug)-focused science subject but, over the years, it has evolved as a more patient-focused subject. Irrespective of the focus, the need for chemistry knowledge and understanding in any Pharmacy curricula cannot be over-emphasized. We know that all drugs are chemicals. The ways any drug exerts its pharmacological actions and also toxicity in a patient are governed by a series of biochemical reactions. Therefore, chemistry knowledge and understanding are fundamental to any Pharmacy programme, which is essentially the study of various aspects of drugs, their applications in patients, patient care and overall treatment outcome.

Like the first edition, this revised, reorganized and significantly enhanced second edition covers all core topics related to general, organic and natural product chemistry currently taught in Pharmacy undergraduate curricula in the UK, USA and various other developed countries, and relates these topics to drug molecules, their development and their fate once given to patients. While the second edition still provides a concise coverage of 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, the first chapter, which deals with various properties of drug molecules, has been significantly 'beefed up' in this second edition. Generally, the contents of the second edition are organized and dealt with in a similar way, to the first to ensure that the contents are suitable for year 1 (level 4) and year 2 (level 5) levels of most of the Pharmacy curricula. Theoretical aspects have been covered in the context of applications of these theories in relation to drug molecules, their discovery and developments.

Chapter 1 presents an account of general aspects of chemistry and their contributions to modern life, with particular emphasis on modern medicine and discussions on various important properties of drug molecules, for example, pH, polarity and solubility; it also covers some related fundamental concepts like electrolytes, zwitterion, osmosis, tonicity and so on. Chapter 2 incorporates the fundamentals of atomic structure and bonding and discusses the relevance of chemical bonding in drug molecules and drug–receptor interactions, while Chapter 3 covers key aspects of stereochemistry with particular focus given on the significance of stereoisomerism in determining drug action and toxicity. Chapter 4 deals with organic functional groups, their preparations, reactions and applications. All major types of organic reactions and their importance in drug discovery, development, delivery and metabolism in patient's body are outlined in Chapter 5. Chapter 6 is about heterocyclic compounds; their preparations, reactions and applications. While nucleic acids are covered in Chapter 7, various aspects of natural products including the origins, chemistry, biosynthesis and pharmaceutical importance of alkaloids, carbohydrates, glycosides, iridoids and secoiridoids, phenolics, steroids and terpenoids are presented in Chapter 8.

Although the primary readership of the second edition still remains to be the Pharmacy undergraduate students (BPharm/MPharm), especially in their first and second years of study, further readership can come from the students of various other subject areas within Biomedical Science and the Food Sciences, Life Sciences and Health Sciences, where the basic chemistry knowledge is essential for their programmes.

Dr Lutfun Nahar

Professor Satyajit Sarker

Preface to the first edition

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. 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, 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 remarkably. It has been recognised that, while pharmacy students need a solid foundation in chemistry knowledge, the extent cannot be the same as the chemistry students may need.

There are several books on general, organic and natural product chemistry available today, but all of them are written in 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 products 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 products 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 products 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 the 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 organised and dealt with in a way that they are suitable for year 1 and year 2 levels of 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, 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 on 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, 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 year 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 they need to know the fundamentals of chemistry for their courses.

Dr Satyajit Sarker

Dr Lutfun Nahar

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, heredities 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,

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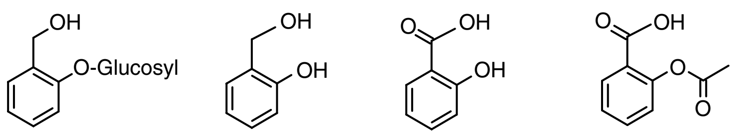
all are possible due to chemistry. It has played a major role in pharmaceutical advances, forensic science and modern agriculture. Diseases and their remedies have also been a part of human lives. Chemistry plays an important role in understanding diseases and their remedies; that is, drugs.

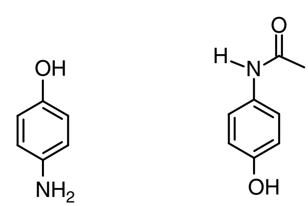
Medicines or drugs that we take for the treatment of various ailments are chemicals, either organic or inorganic molecules. However, most drugs are organic molecules. These molecules are either obtained from natural sources or synthesized in chemistry laboratories. Some important drug molecules are discussed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



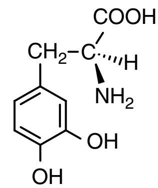
Salicin (A precursor of aspirin) | Salicyl alcohol | Salicylic acid | Aspirin *Acetyl salicylic acid*

Paracetamol (acetaminophen), an *N*-acylated aromatic amine having an acyl group (R—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).

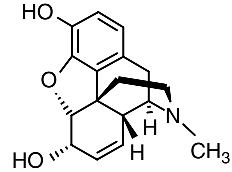


4-Aminophenol | Paracetamol *Acetaminophen*

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.



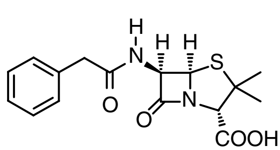
(L)-Dopa
(The precursor of dopamine)



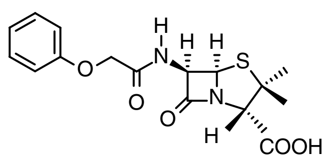
Morphine

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.



Penicillin G
(The first penicillin of the penicillin group of antibiotics)



Penicillin V
Phenoxymethylpenicillin

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. Solutes 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 c*oncentration*, 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: $N = n \times M$ (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 H_2SO_4 solution is the same as a 6 N H_2SO_4 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