Functional Groups, Isomers and Principles of Stereochemistry
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Preface

This textbook is comprised of two parts. The first part focuses on organic functional groups, paying attention to the IUPAC nomenclature for naming organic compounds, and physical and chemical properties of organic functional groups, with emphasis on those found in biological compounds. In this part, the reader starts understanding how carbon and a very small number of other elements on the periodic table can combine in predictable ways to produce a virtually limitless chemical repertoire necessary for all forms of life on Earth—the hydrogen H, nitrogen N, oxygen O, sulfur S, phosphorus P, plus the halogens fluorine F, chlorine Cl, bromine Br, and iodine I. The identification of functional groups and the ability to predict reactivity based on functional group properties is one of the cornerstones of modern organic chemistry. Part 2, on this book, consists of four chapters on isomers and principles of stereochemistry; introduction to and classification of isomers, structural isomers, and stereoisomers. It includes IUPAC nomenclature for isomers, correlation between their physical and chemical properties with the spatial arrangement of their constituent atoms, E/Z isomerism, chirality, and conformational analysis. Stereochemistry is of critical importance to drug action because the shape of a drug molecule is an important factor in determining how it interacts with the various biological molecules (enzymes, receptors, etc.) that it encounters in the body, affecting both its desired biological activity and its potential for exhibiting undesired effects. Many drugs used in medicine nowadays exhibit stereoisomerism, so knowledge of isomerism has helped pharmacists and pharmaceutical scientists in introducing safer and more effective drug alternatives of the newer as well as existing drugs. The significance of enantiomers—also called chiral or handed molecules, is that the vast majority of organic molecules in the biological universe show this type of isomerism. Furthermore, more than half of the existing medical drugs used today have gone chiral i.e., switching from racemic mixture to one of its isomers.

The authors attempted to survey the current IUPAC nomenclature recommendations in organic chemistry with the hope that this volume will cover the nomenclature requirements of students at undergraduate levels. It is hoped that the material enables the students and teachers altogether to learn the basic principles of the systematic nomenclature methods so that they can apply them accurately and with confidence. When the systematic nomenclature was provided for particular organic compounds, the authors also tried to mention the common (trivial) nomenclature, or laboratory shorthand names, used mainly by chemists. One of authors’ major objective in this book was to develop a feeling for molecules as three-dimensional objects with the hope that the use of molecular models (especially, ball-and-stick and space filling models) will help the reader develop the ability to visualize three-dimensional structures and will make the two-dimensional pictures on each illustration “come to life”.

The structured presentation, highly graphical nature on the text and practice problems will provide an instrumental framework and aid to revision for students preparing for examinations. The intention was to provide a comprehensive and accessible overview of functional groups and isomerism in organic chemistry before going into a more detailed study. The authors designed and formatted this textbook with educational principles in mind. Numerous tables, figures, and example problems and survey questions have been included in the chapters for further clarification of the instructional material. Either inside or at the end of each important chapter, the authors included sample problems or question sets around important topics based on material covered in the chapter.

The authors intended to carry out a comprehensive, up-to-date, and easy to understand project for students at all levels and also for both instructors and practitioners. This book was meant from the beginning to be a constantly evolving work on progress. Each chapter and sub-chapter of this book capitalizes on the strengths, comments, feedback and criticism that the authors expect to have from students, faculty and working professionals. As such, all readers sending any comments, suggestions, or notification of errors to the authors at support@shutterwaves.com will be greatly appreciated.

The authors,
In the beginning of organic chemistry classes students typically start exploring hydrocarbon molecules and saturated hydrocarbons, and then familiarize with unsaturated hydrocarbons and aromatic hydrocarbons. While in unsaturated hydrocarbons, professors usually refer to the carbon-carbon double (or triple) bond as a functional group. The “functional group” dictates the chemical properties of such unsaturated hydrocarbons based on how the carbon-carbon double (or triple) bond reacts with reagents. Students learn that hydrocarbons that contain only single bonds are fairly unreactive except under high temperature and pressure conditions such as those found in our cars’ engines. If a hydrocarbon contains carbon-carbon double ($> C = C <$) or triple ($-C \equiv C -$) bonds, reactions tend to occur at or near those bonds. We may also notice that reactions tend to occur at or near heteroatoms (any other atoms than carbon and hydrogen atoms) in organic molecules. Basically, as a broad definition, the structures in organic molecules that contain heteroatoms or $\pi$ bonds, or both, that impart a characteristic chemical reactivity to the molecule are called functional groups.

The main objective of this first part of the book is to review the general topics of IUPAC nomenclature, physical properties (with specific emphasis placed on water solubility, as well as on boiling and melting points), and chemical properties (the stability or lack of stability) of organic functional groups found in biological compounds. There will be no attempt to cover synthesis, nor will great emphasis be placed on chemical reactions specific to particular functional groups. This review is meant to provide background material for the formal courses in pharmacy and medicinal chemistry, clinical biology or biochemistry. As you progress through the text, you will be able to develop such important skills as drawing chemical structures and predicting the solubilities, instabilities, and physical properties of each important organic functional group. The example problems or questions around important topics in each chapter are followed by a detailed discussion explaining the process leading to the correct answer. If you do not understand an answer or the process leading to the answer, return to the appropriate section of the chapter and review that section again.
1. INTRODUCTION to FUNCTIONAL GROUPS

A functional group is a specific group of atoms that are attached to an organic molecule that gives its functionality, determines the chemical characteristics of the molecule and participates in predictable reactions regardless of the other atoms present in the molecule. The basic backbone of those two organic molecules illustrated in Figure 1-1 is the hydrocarbon chain, upon which functional groups are attached to it.

![Figure 1-1. Alanine and mercaptoethanol molecules feature specific functional groups attached to their hydrocarbon backbones. Carboxyl (in red), amino (in dark yellow), and methyl (in light blue) functional groups in the alanine and hydroxyl (in red) and sulfhydryl (in orange) functional groups in mercaptoethanol provide the physical and chemical characteristics, structure and function of each of these individual molecules.](image)

The “functional group approach” is useful because the chemistry of an organic compound can be understood by looking at the chemistry of its functional groups. The non-hydrogen atoms of functional groups are always bonded to each other and to the rest of the molecule by covalent bonds. When the functional group bears a net electric charge, thus being associated with the rest of the molecule primarily by ionic forces, the group is referred to more properly as a polyatomic or complex ion. Any subgroup of atoms of a compound is called radical (represented as R in many drawings), and if a covalent bond is broken homolytically, the resulting fragment radicals are referred as free radicals. In the formulas, the symbols R and/or R’ usually denote an attached hydrogen atom, or a hydrocarbon side chain of any length called hydrocarbon radical, or any group of atoms, or stands for the rest of the molecule. The first carbon atom after the carbon atom that attaches to the functional group is called the α (alpha) carbon; the second, β (beta) carbon, the third, γ (gamma) carbon, etc. In the present section we will familiarize with the most common functional groups in
organic chemistry, among them the seven functional groups that are most likely to be found in many biological molecules. A selection of common functional groups is listed in Table 1-1.

**TABLE 1-1. Common functional groups in organic chemistry**

<table>
<thead>
<tr>
<th>Functional Group</th>
<th>Structural Formula</th>
<th>Family of molecules</th>
<th>Prefix or Suffix</th>
<th>Specific Properties</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydroxyl</strong></td>
<td>R–OH</td>
<td>Alcohols</td>
<td>-ol</td>
<td>Highly polar, forms hydrogen bonds. Present in sugars, proteins, nucleic acids, carbohydrates, lipids, some amino acids and nucleotides.</td>
<td>Ethanol</td>
</tr>
<tr>
<td><strong>Carbonyl aldehyde</strong></td>
<td>R–C=H</td>
<td>Aldehydes</td>
<td>-al</td>
<td>Aldehyde, when carbonyl group is located at the end of the carbon skeleton. Ketone, when carbonyl group is located within carbon skeleton. Polar compounds, aldehydes and ketones are present in carbohydrates, nucleic acids, fats, proteins, and sugars.</td>
<td>Propanal</td>
</tr>
<tr>
<td><strong>Carbonyl ketone</strong></td>
<td>R–C=R'</td>
<td>Ketones</td>
<td>-one</td>
<td></td>
<td>Propan-2-one</td>
</tr>
<tr>
<td><strong>Carboxyl</strong></td>
<td>R–C=O</td>
<td>Carboxylic acids</td>
<td>-oic acid</td>
<td>Highly polar, forms hydrogen bonded dimmer. As weak acid, it occurs widely in living organisms. Present in fatty acids, amino acids, proteins and lipids.</td>
<td>Ethanoic acid</td>
</tr>
<tr>
<td><strong>Amino</strong></td>
<td>R–N</td>
<td>Amines</td>
<td>-amine</td>
<td>Act as proton acceptors (weak bases), reacting with acids to form salts. Found in proteins, amino acids, and the nitrogenous bases of DNA and RNA.</td>
<td>Methylamine</td>
</tr>
<tr>
<td><strong>Sulphydryl</strong></td>
<td>R–SH</td>
<td>Thiols</td>
<td>-thiol</td>
<td>Sulphur-organic compounds similar to alcohols and phenols. Found in proteins and some amino acids.</td>
<td>Methanethiol</td>
</tr>
<tr>
<td><strong>Phosphate</strong></td>
<td>R–OPO_3^-</td>
<td>Organic phosphates</td>
<td>Phosphonoxo-</td>
<td>Highly acidic and reactive: a transfer of a phosphate group from one molecule to another delivers large amounts of energy. Found in the form of adenosine phosphates, in nucleic acids and in certain phospholipids.</td>
<td>3-phosphoglyceric phosphate</td>
</tr>
</tbody>
</table>
1. INTRODUCTION to FUNCTIONAL GROUPS

<table>
<thead>
<tr>
<th>Functional Group</th>
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<th>Specific Properties</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl</td>
<td>R – C – H</td>
<td>Alkyl</td>
<td>methylated</td>
<td>Nonpolar, hydrophobic. Found in proteins, fatty acids, oils, waxes. Addition of a methyl group to DNA, or to molecules bound to DNA, affects the expression of genes.</td>
<td>Alanine (2-amino propanoic acid)</td>
</tr>
</tbody>
</table>

B. OTHER IMPORTANT FUNCTIONAL GROUPS in ORGANIC CHEMISTRY

| Alkane          | R – H              | Alkyl               | -ane             | Nonpolar, hydrophobic, found in petroleum products. Consist of only C – H and C – C single bonds. General formula: CₙH₂n₊₂. | Ethane |
| Alkene          | R=C=C=R           | Alkenes             | -ene             | General formula: CₙH₂n. Consist of a (C = C) function. Alkenes are electron reach reactive centers and are susceptible to electrophilic addition. | Ethene |
| Alkyne          | R’-C≡C-C-R        | Alkynes             | -yne             | Gen. formula: CₙH₂n₋₂. Carbon-carbon triple bond (C ≡ C). | Ethyne |
| Arene           | -R                 | Benzene derivatives | -yl benzene      | Hydrocarbon with at least one benzene functional group. | Methylbenzene |
| Haloalkane      | R – X              | Halohydrocarbons    | halo-            | Compounds in which one or more hydrogen atoms have been replaced by halogen atoms. Halogen atom bonded to a saturated carbon atom. | Chloromethane |
| Ether           | R-O-R’             | Ethers              | -oxy-           | Have a pair of alkyl or aromatic groups attached to a linking oxygen atom. They are common linkages in carbohydrates. | Methoxymethane |
| Nitrile         | R-C≡N              | Nitriles            | Cyanonitrile-    | Nitriles (or organo cyanides) have an alkyl (or aromatic) group attached to a carbon-triple-bond-nitrogen function (−C ≡ N). | Ethanenitrile |
| Peroxy          | R-O-O-R            | Peroxides           | Peroxy-         | Organic peroxides contain a relatively weak −O − O − bond within the molecular structure. | Hydrogen peroxide |

Example Problem #1: Functional Groups

**Question:** What is a functional group?

**Answer:** It is a specific structural arrangement of atoms and bonds that imparts a wide range of important properties and chemical reactivity to an organic compound.
2. FUNCTIONAL GROUPS COMMONLY FOUND IN BIOLOGICAL COMPOUNDS

In this section the major functional groups commonly found in biological compounds are described in a broader detail. After familiarization with the concepts we expect that we will be able to have the following skills:

- be able to recognize what distinguishes each functional group from the others.
- be able to recognize the functional group within the context of a larger molecule.
- be able to name simple molecules containing a specific functional group.
- be able to name more complex molecules containing multiple functional groups.

Each major topic is followed by sample problems and related practice problems.

2.1 Alcohols

In a hydroxyl group (represented as $-OH$ or $-HO$), a hydrogen atom is bonded to an oxygen atom, which in turn is bonded to the carbon skeleton of the organic molecule. A hydroxyl group is highly polar as a result of the electrons spending more time near the more electronegative oxygen atom. Compounds with hydroxyl groups can form hydrogen bonds with water molecules, thus helping dissolve organic compounds such as sugars. Organic compounds that contain the hydroxyl group are called alcohols. If one of the hydrogen atoms of an alkane is replaced by a hydroxyl group, then the compound becomes an alcohol, $R - OH$. Their general formula is $C_nH_{2n+1}OH$. There are also many alcohols that have more than one hydroxyl functional group. We name alcohols by adding the suffix $-ol$ to the end of the name of the parent alkane, using a numerical prefix if the position of the hydroxyl group on the chain is ambiguous (see later IUPAC Nomenclature for Alcohols).

Alcohols are one of the most widely found functional groups in nature, including in living organisms. Hydroxyl group is found in alcohols and carbohydrates (they include sugar alcohols). Nucleic acids such as ribonucleic acids (RNA) and deoxyribonucleic acids (DNA) contains hydroxyl groups that ultimately derive from sugars (ribose or deoxyribose) as well. Some proteins, lipids, amino acids, and nucleotides contain hydroxyl groups as well. Methanol, ethanol and propanol are the most common alcohols (see their molecular structures illustrated in Figure 1-2), but others are also commercially important. The simplest possible example of an alcohol, methanol, $CH_3OH$, also known as methyl alcohol or wood alcohol, is primarily used to make methanal (a formaldehyde), $HCHO$, and acetic acid (ethanoic acid – a carboxylic acid), $CH_3COOH$, both important chemicals used in a wide variety of applications. Methanol is also used as a solvent, as an antifreeze, and fuel additive in gasoline, and as a denaturant for ethanol. Methanol was often called wood alcohol because it was originally produced by heating wood in the absence of air. It is found in low concentrations in new wine, where it contributes to the odor, or wine’s “bouquet”.

A colorless, light, volatile, flammable and highly polar liquid at room temperature, methanol is highly toxic when ingested in large quantities. Like ethanol, methanol causes intoxication, but methanol is more poisonous than ethanol because the human body converts it to formaldehyde ($HCHO$) and then to formic acid ($HCOOH$) or to other specific salts. These compounds attack the cells of the retina in the eye, leading to blindness, or even worse, may cause coma and death. Methanol burns in oxygen atmosphere, forming carbon dioxide and water, as follows:

$$2 CH_3OH + 3 O_2 \rightarrow 2 CO_2 + 4 H_2O$$

Methanol is produced also naturally by many varieties of bacteria through the anaerobic metabolism. It is commonly present in small amounts in environment in vapor phase. Over the course of several days,
2. FUNCTIONAL GROUPS COMMONLY FOUND IN BIOLOGICAL COMPOUNDS

Figure 1-10. Butanol isomers illustrated in different representations: structural formula, ball-and-stick and space filling. Butan-1-ol and 2-methylpropan-1-ol (isobutanol) are primary alcohols, whereas butan-2-ol is a secondary alcohol and 2-methylpropan-2-ol is a tertiary alcohol, respectively. The carbon atom drawn in blue in all structural formulas represents the carbon atom bearing the hydroxyl group.

Example Problem #4: Alcohols

**Question:** Why 1-propanol is more soluble in water than 1-heptanol?

**Answer:** 1-Propanol has one hydroxyl group, \(-\text{OH}\), and three carbon atoms in the hydrocarbon chain whereas 1-heptanol has one hydroxyl group, \(-\text{OH}\), and seven carbon atoms in the hydrocarbon chain. Thus the hydrocarbon portion in the 1-heptanol is longer than that in 1-propanol and the alcohol molecule becomes more like a hydrocarbon.
2.1.3 Classification of Alcohols
Many of the reactions that alcohols undergo depend on the number of carbon atoms that are bound to the carbon bearing the hydroxyl (–OH) group. For this reason chemists classify alcohols as primary (1°), secondary (2°), or tertiary (3°) alcohols, depending on whether the carbon atom bearing the hydroxyl (–OH) group is bound to one, two, or three carbon atoms. Figure 1-10 illustrates four structural isomers of butanol, in which each isomer has the carbon atom bearing the hydroxyl group attached to a different carbon atom in the hydrocarbon chain. Butanol, C₄H₁₀OH, is commonly represented by the molecule butan-1-ol, which is a primary alcohol. In butan-1-ol the carbon atom bearing the hydroxyl group is bonded to only one carbon atom (at the end of carbon chain), thus the alcohol is called a primary alcohol. The second isomer of butanol shown in Figure 1-10 is butan-2-ol, which is a secondary alcohol because the carbon atom bearing the hydroxyl group is bonded to two other carbon atoms in the hydrocarbon chain. The third isomer of butanol shown in Figure 1-10 is a primary alcohol called 2-methylpropan-1-ol. The fourth isomer of butanol illustrated in Figure 1-10 is a tertiary alcohol called 2-methylpropan-2-ol. It is a tertiary alcohol because the carbon atom bearing the hydroxyl group is bonded in a tetrahedral geometry to other three carbon atoms.

2.1.4 Reactions of Alcohols
The hydroxyl group, –OH, attached to a relatively nonreactive hydrocarbon chain accounts for the reactive properties of alcohols. In general alcohols undergo reactions analogous to those of water. For example, if a small piece of metallic sodium (alkali metal) is dropped in ethanol, it reacts to give off bubbles of hydrogen gas and leaves a colorless solution of sodium ethoxide (an alkoxide), as follows:

\[ 2 \text{CH}_3\text{CH}_2\text{OH} + 2 \text{Na} \rightarrow 2 \text{CH}_3\text{CH}_2\text{ONa} + \text{H}_2 \]

Comparing this reaction to the reaction between sodium and water

\[ 2 \text{H} - \text{OH} + 2 \text{Na} \rightarrow 2 \text{H} - \text{ONa} + \text{H}_2 \]

… you may notice that in fact it is exactly the same type of reaction. Alkoxides are strong Lewis bases, which are electron-pair donors. Hydroxyl group, –OH, in an alcohol can be replaced (substituted) by a halogen such as chlorine or bromide to form a haloalkane (called also an alkyl halide). The general reaction is

\[ \text{ROH} + \text{HX} \rightarrow \text{RX} + \text{H}_2\text{O} \]

Tertiary alcohols react reasonably rapidly with concentrated hydrochloric acid, but for primary or secondary alcohols the reaction rates are too slow. For example, 2-methylpropan-2-ol (a tertiary alcohol) reacts with concentrated hydrochloric acid if it is shaken at room temperature and tert-butyl chloride is formed, as follows

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 - \text{C} - \text{OH} + \text{HCl} & \rightarrow \quad \text{CH}_3 - \text{C} - \text{Cl} + \text{H}_2\text{O} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

Alcohols can be converted to alkenes using aluminum oxide as catalyst or by acid-catalyzed dehydration. For example, if ethanol vapor is passed over heated aluminum oxide powder, the ethanol is cracked to give gaseous ethane and water vapor as follows:

\[ \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{Al}_2\text{O}_3} \text{CH}_2 = \text{CH}_2 + \text{H}_2\text{O} \]

When converting alcohols to alkenes by dehydration the acid catalysts used are either concentrated sulphuric acid, \(\text{H}_2\text{SO}_4\), or concentrated phosphoric acid, \(\text{H}_3\text{PO}_4\) as follows:

\[ \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{concentrated } \text{H}_2\text{SO}_4, \text{T}=170 ^\circ \text{C}} \text{CH}_2 = \text{CH}_2 + \text{H}_2\text{O} \]
2.3 Carboxylic Acids

A carboxylic acid (RCOOH) contains the functional group, $-\text{COOH}$, called the carboxyl group. When an oxygen atom is double-bonded to a carbon atom that is also bonded to an $-\text{OH}$ group, the entire assembly of atoms forms what is called a carboxyl group ($-\text{COOH}$). General formula of carboxylic acids is $C_nH_{2n+1}\text{COOH}$. Carboxylic group gives vinegar (acetic acid) its sour taste. Carboxylic group has acidic properties because they are highly polar molecules and readily engage in hydrogen bonding, so they have relatively high boiling points. There are many familiar carboxylic acids. The $R$ group may be a hydrogen atom (as in formic acid, $\text{HCOOH}$), and alkyl group (as in acetic acid, $\text{CH}_3\text{COOH}$), or an aryl group (as in benzoic acid, $C_6\text{H}_5\text{COOH}$). As shown in Figure 1-24 the carboxylic acids have alkyl or aromatic groups attached to hydroxy-carbonyl functional group.

Figure 1-24. Molecular structure and shape of some carboxylic acids. Carboxylic acids feature a carbon atom double-bonded to an oxygen atom and also joined to a hydroxyl group OH.

The simplest carboxylic acid, formic acid $\text{HCOOH}$, known by its IUPAC systematic name methanoic acid, is a colorless liquid having a pungent and penetrating odor. It was firstly obtained by the distillation of ants (its name comes from Latin formica, meaning “ant”). Formic acid is used as a preservative and antibacterial agent in livestock feed; it is also used in the production of leather, textiles, and rubber. The second simplest carboxylic acid is acetic acid, $\text{CH}_3\text{COOH}$, which is probably the most familiar weak acid used in educational and industrial chemistry laboratories. Acetic acid can be produced by fermenting cider and honey in the presence of oxygen. The fermentation produces vinegar, which is a solution containing about 3 to 10% acetic acid. Known by its IUPAC name as ethanoic acid (see Figure 1-25), acetic acid is used in the production of cellulose acetate for photographic films and polyvinyl acetate for wood glue, as well as synthetic fibers and fabric. In household, diluted acetic acid is used in descaling agents and food additive. Pure acetic acid solidifies at 16.6 °C, just slightly below the room temperature. In the past two centuries in Northern America and Europe the pure acetic acid has been known as the glacial acetic acid because it was often found “frozen” on the storage shelf in poorly heated laboratories. The acid with the carboxyl group attached directly to a benzene (aromatic) ring is called benzoic acid ($C_6\text{H}_5\text{COOH}$). A colorless crystalline solid with a faint and
2. FUNCTIONAL GROUPS COMMONLY FOUND IN BIOLOGICAL COMPOUNDS

Pleasant odor, benzoic acid is used in the production of phenol, benzoate plasticizers, preservatives, and topical antiseptics.

Noted earlier, the oxidation of aldehydes or primary alcohols forms carboxylic acids as follows,

$$\text{RCH}_2\text{OH} \xrightarrow{\text{oxidation}} \text{RCHO} \xrightarrow{\text{oxidation}} \text{RCOOH}$$

Carboxylic acids are weak acids; they tend to ionize to release $H^+$ ions (protons) into solution. They react with bases to form salts and with carbonates and bicarbonates to form carbon dioxide gas and the salt of the acid. They are found in organic acids such as fatty acids and amino acids, proteins, and lipids. In living cells they are called carboxylate ions because they are in the ionized form with a ‘−1’ charge. Carboxylic acids occur widely in living organisms. The fatty acids are components of glycerides, which in turn are components of fat. Proteins are made up of amino acids, which also contain carboxyl groups. Hydroxyl acids, such as citric acid and lactic acid, and many keto acids are important metabolic products that exist in living cells. Since the carboxylic acids contain both hydroxyl and carbonyl functional groups, they participate in hydrogen bonding as both hydrogen acceptors and hydrogen donors, as we will see it later.

2.3.1 IUPAC Nomenclature of Carboxylic Acids

Stem names of carboxylic acids are derived from those of the parent alkanes, using a characteristic suffix to carboxylic acids −oic.

The basic IUPAC rules for naming carboxylic acids are as follows:

1. The stem names of carboxylic acids are derived from those of the parent alkanes, defined by the longest continuous chain of carbon atoms that contains the functional group. The chain is numbered such that the – C=O carbon atom (carboxyl group carbon atom) is in the “1” position, unless other functional groups of higher precedence are present.

2. Carboxylic acids take their name from their parent alkane chains. The –e ending of the parent alkane is replaced by the suffix –oic and the word acid. All substituents are named and numbered as in alkanes. When the carbonyl group – COOH is attached to a ring the suffix –carboxylic acid is added, and the carbon attached to that group is in the “1” position.

Many carboxylic acids are called by the common names that include prefixes form, acet, propion, butyr. Carboxylic acids were among the first organic compounds to be isolated and purified by chemists, thus there is a large number of carboxylic acids with common names. In many chemistry books and articles the systematic names must be used on most carboxylic acids, but the common names formic acid and acetic acid are already established names and widely used. In common names of carboxylic acids, carbon atoms near the carbonyl...
3. OTHER IMPORTANT FUNCTIONAL GROUPS IN ORGANIC CHEMISTRY

3.2.1.3 Polysubstituted Benzenes

When more than two substituents are attached to a benzene ring, the numerical position system is used. Firstly, a parent name is chosen on one of the substituents, which determines position 1 (numbering must start at the principal functional group if it determines the base name). Then other substituents are located using the numbers 2 through 6 and keeping the numbers as small as possible. All substituents are mentioned in the name in alphabetical order.

For example, 2-methyl-1,3,5-trinitrobenzene (an explosive material called trinitrotoluene, or TNT, firstly prepared by the German chemist Julius Willbrand in 1863), illustrated in Figure 1-51, is the correct name following the IUPAC rule, whereas “1,3,5-trinitro-2-methylbenzene” is not. If the substitution is symmetrical the numbering order must correspond to the alphabetical order. Prefixes “di”, “tri”, etc. are not considered for alphabetical priority.

3.2.1.4 The Phenyl and Benzyl Groups

When a benzene ring is used as a substituent (prefix) we call it the phenyl group. In some instances, the naming may appear confusing because this name bears no connection to the root hydrocarbon called benzene.

A methylbenzene (toluene) substituent is frequently called a benzyl group. Illustrated in Figure 1-52, the phenyl group is simply based on benzene, with one hydrogen atom removed from the ring, whereas the benzyl
group is based on methylbenzene (toluene), with one hydrogen atom removed from the methyl group. In the IUPAC nomenclature the prefix phenyl refers to a $C_6H_5$ substituent, whereas the prefix benzyl, which refers to a $C_6H_5CH_2$ substituent, is mostly used in the common names of chemical compounds. The compounds, in which the benzene ring is attached to a branched alkyl chain or unsaturated alkyl groups, are named phenylalkanes, phenylalkenes, or phenylalkynes. A few examples are illustrated in Figure 1-52.

### 3.3 Haloalkanes

Haloalkanes, called also alkyl halides, are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). For simplicity of this introduction to haloalkanes, let us look at several haloalkanes compounds containing one halogen atom. Figure 1-53 illustrates fluoromethane, chloromethane, fluoroethane, and chloroethane in different representations. Fluoromethane, known by its common name as methyl fluoride or Freon 41, is a colorless gas with an agreeable ether-like odor. The compound is the lowest mass member of the hydrofluorocarbon (HFC) family, compounds containing only hydrogen, carbon and fluorine, which are not destructive to the ozone layer. It is though related to the chlorofluorocarbon (CFC) family of compounds, a family containing chlorine, fluorine and carbon and no hydrogen, which is destructive to the ozone layer.

Fluoromethane is highly flammable gas, burning with evolution of highly toxic hydrogen fluoride in a colorless flame, similar to alcohols. Its main use is in the production of semiconductor and electronic products. Chloromethane, also known by its common name methyl chloride, is a colorless and extremely flammable gas with a sweet odor, which was once used as a refrigerant (R-40). More than half of the chloroethane produced in U.S. today is used in the manufacture of silicone fluids, elastomers and resins. The rest is used into the
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Figure 1-62. Ethanenitrile molecular structure and geometry.

The molecule has five \( \sigma \) bonds and two \( \pi \) bonds; the first carbon atom is \( sp^3 \) hybridized (tetrahedral) while the second carbon atom attached to the nitrogen atom is \( sp \) hybridized (linear). With a dipole moment of 3.92 D, ethanenitrile dissolves a wide range of ionic and non-polar compounds, but its mainly application is as a solvent in the purification of 1,3-butadiene, \( \mathcal{R} \mathcal{C} = CH - CH = CH_2 \) - an important industrial chemical used as a monomer in the production of synthetic rubber. Among other applications, it is used as solvent in lithium batteries because of its high dielectric constant and ability to dissolve electrolytes, used intensively in high-performance liquid chromatography (HPLC) because of high transparency in ultraviolet, as well as for the manufacture of pharmaceuticals and photographic films.

Figure 1-63. Cyanamide molecular structure and shape.

The cyanamide molecule, known by its IUPAC name as \textit{aminomethanenitrile}, which is illustrated in Figure 1-63, is an organic compound that features a nitrile group \( (-CN) \) attached to an amino group \( (-NH_2) \). It is a white solid compound, widely used in agriculture as a dehydration agent, and also in the production of pharmaceuticals.

3.6.1 IUPAC Nomenclature for Nitriles

The basic IUPAC rules for naming nitriles are as follows:

1. Simple open chain nitriles are named by adding \textit{–nitrile} as a suffix to the alkane name, with the nitrile carbon located in the position “1” (or numbered C1). Cycloalkanes are followed by the word \textit{carbonitrile}. When the nitrile functional group has lower priority the prefix name is \textit{cyano-}. Figure 1-64 illustrates some examples of simple nitriles with their IUPAC names.
3. OTHER IMPORTANT FUNCTIONAL GROUPS IN ORGANIC CHEMISTRY

Figure 1-64. Examples of the application of IUPAC rules for simple nitriles. Cyclohexanecarbonitrile is known by its common name cyanocyclohexane

2. More complex nitriles are named as derivatives of carboxylic acids by replacing the –ic acid or –oic acid ending with –onitrile, or by replacing –carboxylic acid ending with –carbonitrile. In all these cases, the nitrile carbon atom is attached to the first carbon atom C1 but it is not itself numbered. Figure 1-65 illustrates some examples of complex nitriles with their IUPAC names.

In 2-acetyl-4-methylbenzonitrile the nitrile group has higher priority over the ketone group. In organic chemistry a methyl group single-bonded to a carbonyl group is called the acetyl functional group. In a compound of 3-(3-cyanophenyl)propanoic acid the carboxylic acid group has higher priority over nitrile and arene groups.

3.6.2 Properties of Nitriles

The boiling points of nitriles are very high for the size of the molecules, being comparable to those for compounds with constituents that hydrogen bond themselves. However, nitriles do not hydrogen bond because they do not have a hydrogen atom bonded to the electronegative atom nitrogen. Such high boiling points result from the fact that nitriles are highly polar molecules. In the triple bond the electrons are easily pulled towards the more electronegative nitrogen atom. Therefore, strong dipole-dipole intermolecular forces as well as London dispersion forces are responsible for that strong attraction between neighboring molecules in nitriles.

<table>
<thead>
<tr>
<th>Condensed structural formula</th>
<th>IUPAC name</th>
<th>Common name</th>
<th>Molar mass (g/mol)</th>
<th>Melting point, °C</th>
<th>Boiling point, °C</th>
<th>Water solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CN</td>
<td>Ethanenitrile</td>
<td>Acetonitrile</td>
<td>41.05</td>
<td>-44</td>
<td>81.6</td>
<td>miscible</td>
</tr>
<tr>
<td>CH₃CH₂CN</td>
<td>Propanenitrile</td>
<td>Propionitrile</td>
<td>55.08</td>
<td>-91.8</td>
<td>97.2</td>
<td>103 g/L at 20 °C</td>
</tr>
<tr>
<td>CH₃CH₂CH₂CN</td>
<td>Butanenitrile</td>
<td>Butyronitrile</td>
<td>69.11</td>
<td>-111.9</td>
<td>117.5</td>
<td>33 g/L at 25 °C</td>
</tr>
</tbody>
</table>

Solubility of nitriles in water decreases as the chain length increase. For example, ethanenitrile is completely soluble in water, but solubilities of propanenitrile and butanenitrile in water decrease sharply, as presented in Table 1-8. Such high solubility of nitriles in water is explained by the fact that the molecules of nitriles can hydrogen bond with water molecules. The energy released in such process is sufficient to separate.
Glossary of Terms

**Acid halide**, or acyl halide, has an alkyl (or aromatic) group attached to a carbonyl group plus an easily displaced halogen.

**Alcohols** are organic compounds that contain a hydroxyl group; when one of the hydrogen atoms of an alkane is replaced by a hydroxyl group, then the compound becomes an alcohol. Chemists classify alcohols as primary (1°), secondary (2°), or tertiary (3°) alcohols, depending on whether the carbon atom bearing the hydroxyl group is bound to one, two, or three carbon atoms.

**Aldehyde** is a compound made up of molecules in which a carbon atom is double-bonded to an oxygen atom and single-bonded to a hydrogen atom, leaving only one bond available for a hydrocarbon chain.

**Aldose** is a carbohydrate containing an aldehyde functional group.

**Alkane** is an organic compound in which the number of hydrogen atoms is always two more than twice the number of carbon atoms. It is the most basic unit in organic chemistry, containing only single bonds.

**Alkenes** are hydrocarbon chains that have at least one double carbon-carbon bond (C = C).

**Alkyl group** is an “incomplete” molecule consisting of an alkane with one hydrogen atom removed.

**Alkynes** are hydrocarbon molecules that have at least one triple carbon-carbon bond (C≡C).

**Amide functional group** has a carbonyl group joined to a nitrogen atom from ammonia or an amine. Primary amides have an alkyl or aromatic group attached to an amino-carbonyl group. Secondary amides have an alkyl or aryl group attached to the nitrogen atom, whereas tertiary amides have two alkyl or aryl groups attached to the nitrogen atom. An amide is the product of the reaction between an amine and a carboxylic acid.

**Amines** are organic compounds with a functional group that contains a nitrogen atom with a lone pair of electrons and with one, two, or three alkyl or aryl groups attached. An amine is a compound derived from ammonia (NH₃); it has one, two, or all three hydrogen atoms of NH₃ replaced by an alkyl or aryl group.
Correct answers: choose from 1-ethoxybutane, methoxybenzene, 4-ethoxy-2-methyl-1-hexene

64) Provide the IUPAC names for the following peroxides

Correct answers: choose from methyl-propyl-peroxide, 2-(isopropylperoxy)propane, di-tert-butyl-peroxide

65) Provide the IUPAC names for the following nitriles

Correct answers: choose from 2-bromo-3-ethyl-butanenitrile, 2-cyclohexenecarbonitrile, 2-hydroxy-2-methylpropanenitrile, 2-hydroxy-propanenitrile

66) Provide the IUPAC names for the following compounds

Correct answers: choose from 2-ethoxy-2-methyl-1-propene, 3,4,5-trihydroxybenzoic acid, but-2-en-1-thiol (2-butanethiol), thiophenol, N-methylpentanamide, 2-ethylpentanenitrile, 2-propen-1-ol, 2-methyl-1-hepten-6-yne.
Part 2

ISOMERS and PRINCIPLES OF STEREOCHEMISTRY

Isomers by definition are two or more different molecules of identical atomic compositions that have the same atomic connectivity, but with different bonding arrangements of atoms or orientations of their atoms in space. Stereochemistry or spatial chemistry – a topic positioned at the confluence of the three classical subdivisions of chemistry into organic, inorganic and physical chemistry - is the study of the relationship between the three dimensional shape of a molecule and its chemistry. Stereochemistry is of critical importance to drug action because the shape of a drug molecule is an important factor in determining how it interacts with the various biological molecules (enzymes, receptors, etc.) that it encounters in the body, affecting both its desired biological activity and its potential for exhibiting undesired effects. Many drugs used in medicine nowadays exhibit stereoisomerism, so knowledge of isomerism has helped pharmacists and pharmaceutical scientists in introducing safer and more effective drug alternatives of the newer as well as existing drugs.

In this second part of the book, we will discuss how to recognize different categories and subcategories of isomers, how to properly identify their names, and correlate their physical and chemical properties with the spatial arrangement of their constituent atoms. In doing so, we will address four topics that are crucial to an understanding of the structure of molecules; structural isomerism, E/Z isomerism, chirality, and conformational analysis. We will study the relationship between objects and their mirror images, which - as we will see it in this part - will define the two types of configurational stereoisomers called enantiomers and diastereomers. The significance of enantiomers – also called chiral or handed molecules is that, except for inorganic molecules and a few simple organic molecules, the vast majority of organic molecules in the biological universe show this type of isomerism. Furthermore, more than half of the existing medical drugs used today have gone chiral i.e., switching from racemic mixture to one of its isomers.

Our major objectives in this part of the book are to develop a feeling for molecules as three-dimensional objects and to become familiar with stereochemical principles, terms, and notations. The use of molecular models (especially, ball-and-stick and space filling models) will help the reader develop the ability to visualize three-dimensional structures and will make the two-dimensional pictures on each illustration “come to life”. A full understanding of organic and biological chemistry principles requires awareness of the spatial requirements for interactions between molecules; this book provides just the basis for that understanding. For your information, the Swedish chemist Jacob Berzelius, one of the fathers of modern chemistry, introduced the term isomerism in 1830 (isos, Greek for equal, and meros, Greek for part).
1. Introduction to ISOMERISM

Figure 2-1. Examples of two isomers: ethanol and methoxymethane are compounds with the same molecular formula, $C_2H_6O$, but with different structural formulas. Methoxymethane is a constitutional isomer of ethanol, but with an ether functional group rather than an alcohol functional group as in ethanol. Density of ethanol is 0.789 g/cm$^3$ (at 20 °C) and density of dimethyl ether is 2.115 mg/cm$^3$ (at 0 °C). The net dipole moment for ethanol is 1.69 D (Debye) and for dimethyl ether is 1.3 D.

The fundamental difference between these two compounds is the presence of the hydroxyl group in the alcohol that is missing in the ether. The polar hydroxyl group in ethanol molecule makes possible hydrogen bonding between ethanol molecules, as illustrated schematically in Figure 2-2. (a). Dimethyl ether is a polar molecule with a partial negative charge on the oxygen atom (“lone electron pair”) with no hydrogen atom attached to the oxygen atom, so there is no hydrogen bonding between ether molecules. The major intermolecular attraction in dimethyl ether involves regular dipole moments. Hydrogen bonding attraction is typically stronger than dipole interactions. Thus, a group of ethanol molecules is much harder to separate from each other than a group of dimethyl ether molecules and, therefore, ethanol will have a higher boiling point. Mentioned earlier, water has an unusually high boiling point because of the maximum four hydrogen bonds between the $H_2O$ molecules. Alcohols can form similar hydrogen bonds. As a result, alcohols have boiling points that are much higher than alkanes with similar molecular weights. For example, the boiling point of ethanol is 78.37 °C (173.97 °F), whereas propane, with about the same molecular weight, boils at -42.1 °C (-231 K or -43.4 °F). The oxygen atoms in ethers can act as a hydrogen-bond acceptor, but ether cannot act as a hydrogen-bond donor.
molecular formula: ethyl alcohol and dimethyl ether (see Figure 2-1). Although the molecular formulas of the two compounds are identical, \( \text{C}_2\text{H}_6\text{O} \), their functional groups are different. The atomic connectivity \( \text{C} - \text{C} - \text{O} \) in the isomer forms an alcohol; the hydrocarbon chain \( \text{C} - \text{OH} \) functionality is called hydroxyl group, which is associated to alcohols. In contrast, the \( \text{C} - \text{O} - \text{C} \) connectivity in the isomer forms ether; the hydrocarbon chain-\( \text{O} \)-hydrocarbon chain functionality is called ether. Looking at illustrations shown in Figure 2-9, we find out that \text{propan-1-ol} and \text{2-propanol} are positional isomers because the hydroxyl functional group is the same in both, but are positioned at different locations, whereas \text{methoxyethane} is a functional isomer, a very different compound than the two alcohols.

![Cyclopropane, \( \text{C}_3\text{H}_6 \)](image1)

![Propene, \( \text{C}_3\text{H}_6 \)](image2)

**Figure 2-11.** Cyclopropane and propene are isomers of the compound with the molecular formula \( \text{C}_3\text{H}_6 \).

Alkenes and alkynes are unsaturated hydrocarbons, which respectively have double bond \( \text{C} = \text{C} \) and triple bond \( \text{C} \equiv \text{C} \) functional groups. Alkenes are isomeric with cycloalkanes and bicycloalkanes. Shown in Figure 2-11, cyclopropane and propene are structural functional isomers of the compound with the molecular formula \( \text{C}_3\text{H}_6 \). Functional isomers of the compound with the molecular formula \( \text{C}_4\text{H}_8 \) are illustrated in Figure 2-12. The compound \( \text{C}_4\text{H}_8 \) has an isomer called \text{but-2-ene}, which is not illustrated in Figure 2-12, that is categorized as an \( E/Z \) - isomer because it adopts two possible configurations of stereoisomerism.

![Cyclobutane, \( \text{C}_4\text{H}_8 \)](image3)

![2-Methylpropene, \( \text{C}_4\text{H}_8 \)](image4)

![Methylcyclopropane, \( \text{C}_4\text{H}_8 \)](image5)

![But-1-ene, \( \text{C}_4\text{H}_8 \)](image6)

**Figure 2-12.** Functional isomers of the compound with the molecular formula \( \text{C}_4\text{H}_8 \).
3. STRUCTURAL ISOMERS

All functional isomers are unique compounds because of their structural differences and they have different physical and chemical properties. A term frequently used by chemists is the so called “ring-chain isomerism”, exemplified in Figure 2-11 and Figure 2-12. In this “type of isomerism” one isomer possesses an open chain structure while the other possesses a cyclic structure. For example, propene and cyclopropane are ring-chain isomers of each other, also but-1-ene, cyclobutane and methylcyclopropane are ring-chain isomers of each other. All “ring-chain isomers” are always functional isomers.

Example Problem #19: Positional and Functional Isomers

PROBLEM: Isomers having the molecular formula C₆H₁₂O₆ are alcohols and ethers. Draw below the structural formula of three possible functional and/or positional isomers of the compound C₃H₇O and name them in accord to the IUPAC nomenclature.

SOLUTION: Positional isomerism arises due to different positions of side chains, substituents, functional groups, double bonds or triple bonds on the parent chain, whereas the functional isomerism arises due to the presence of different functional groups.

1) Firstly, let us draw a chain of three carbon atoms as shown in the picture below.

2) Next, let us attach the oxygen atom to the terminal carbon atom in the chain. When an oxygen atom bonds to the surface of the carbon skeleton, by inserting itself between a carbon atom and a hydrogen atom (oxygen atoms forms two bonds), a hydroxyl functional group is formed (OH).

3) Lastly, we populate the structure with necessary hydrogen atoms and identify the IUPAC name of the structure. Therefore this isomer is called propan-1-ol or propanol (common name n-propyl alcohol) because the alkane bearing the functional hydroxyl group is propane.

Since the hydroxyl functional group “OH”, as a substituent attached to a three member carbon skeleton, only forms one bond, the number of possible isomers is no different than that of butane (try to imagine butane isomers as a methyl group attached to two carbon atoms belonging to the propane carbon skeleton). So using the same three carbon skeleton as above, there would be another possible isomeric alcohol as shown below. Therefore, the second alcohol isomer is propan-2-ol (common name isopropyl alcohol).

Oxygen not only bonds to the surface of the carbon skeleton, but also can insert itself in between two carbon atoms (it forms again two bonds). When oxygen is surrounded on both sides by a carbon atom, the functional group is ether (ROH). The necessary steps to build the isomer of the compound with the molecular formula C₃H₆O containing the ether functional group are shown below. The corresponding IUPAC name is methoxyethane (common name methyl ethyl ether).
interconversion is a very slow process. If an alkene has two different groups or substituents at each end of the $C = C$ bond, then the alkene can exhibit stereoisomerism.

Known in the past as the geometrical isomerism, which was referring to the relative position of substituents around a planar carbon-carbon double bond ($C = C$), the new IUPAC nomenclature strongly encourages to use the more precise $E/Z$ designation, based on the sequence rules. As illustrated in Figure 2-17, the methyl groups or hydrogen atoms are locked into a configuration where they are attached either on the same side or on the opposite sides of the double bond. The newer method of specifying the configuration of alkenes, which is recommended by IUPAC, uses the designations $E$ (entgegen, German for opposite) or $Z$ (zusammen, German for together). An advantage of this system is that it is reliable and suitable for specification of the configuration of tri- and tetra-substituted alkenes and it is also applicable for substituents other than alkyl groups. The older more common method of naming and specifying the configuration of alkenes by using the prefixes cis- and trans- is based on the longest chain rule, whereas the $E/Z$ method is based on a set of priority rules, which will be specified a bit later. To assign $E$ or $Z$, one needs to prioritize the groups attached to each carbon atom of the double bond. The cis/trans notation rule becomes ambiguous when there are three or four substituents on the double bond. The limited cis-trans convention in assigning the names to a particular stereoisomer may still be used when referring to some published work. Looking at the two isomers illustrated in Figure 2-17, we notice each isomer contains four carbon atoms and eight hydrogen atoms.
Prioritization Rule 3

Double or triple bonds that are part of the groups attached to the double bond are treated as they are constructed from two or three single bonds, respectively. Thus, atoms bonded to a double or triple bond are treated as if they were singly bonded to the same number of atoms.

For example,

\[
\begin{array}{c}
\text{HC} &=& \text{CH}_2 \\
\text{is treated as} &=& \text{C} &=& \text{C} \\
\text{H} &=& \text{H} \\
\text{H} &=& \text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{O} &=& \text{C} \\
\text{is treated as} &=& \text{C} &=& \text{O} \\
\text{C} &=& \text{N} \\
\text{N} &=& \text{H}
\end{array}
\]

Note that the newly added atoms do not have their valences completed. Notice that the second and the third bonds of a triple bond are replaced with single bonds to the same kind of atom, as shown for the cyano group. The following example will help illustrate the use of prioritization Rule 3 (see Figure 2-22). For 1-chloro-1,3-hexadiene, the upper substituent (Cl) on the left side of the first double bond has higher priority. On the right side of the first double bond, the upper substituent has higher priority, so the notation of isomer includes (1Z) because the locant of the first carbon atom in the first double bond is #1. When looking at the second double bond we notice that on the right side of it the upper substituent has higher priority, so the notation of isomer would include (3E) because the locant of the first carbon in the second bond is #3. Therefore the name of the isomer is (1Z, 3E)-1-chloro-1,3-hexadiene. Following similar analysis approach for the second compounds leads us to its name as (2Z, 4E)-3,4-dimethyl-2,4-hexadiene.

\[
\begin{array}{c}
\text{(1Z, 3E)-1-chloro-1,3-hexadiene} \\
\text{(2Z, 4E)-3,4-dimethyl-2,4-hexadiene}
\end{array}
\]

Figure 2-22. Configurational isomers of some dienes.

A diene such as 1-bromo-2,4-heptadiene has four configurational isomers because each of the double bonds can have either the E or the Z configuration. Thus there are E-E, Z-Z, E-Z, and Z-E isomers, as illustrated in Figure 2-23.

\[
\begin{array}{c}
\text{(2E, 4E)-1-bromo-2,4-heptadiene} \\
\text{(2Z, 4E)-1-bromo-2,4-heptadiene}
\end{array}
\]

\[
\begin{array}{c}
\text{(2E, 4Z)-1-bromo-2,4-heptadiene} \\
\text{(2Z, 4Z)-1-bromo-2,4-heptadiene}
\end{array}
\]

Figure 2-23. Configurational isomers of 1-bromo-2,4-heptadiene.
have $2^n$ possible combinations of drawing the compound with the groups around these centers. Depending on whether the compound has an overall symmetry, we would expect to find up to $2^n$ stereoisomers (evidently, fewer in case of a symmetrical compound). Part of these stereoisomers will have enantiometric relationships, and the other part will have diastereomeric relationships. Enantiomers will always come in pairs.

In the above example, either of the 2,3-dihydroxybutanoic acid enantiomers has a diastereomeric relationship with either of the 2,3-dihydroxybutanoic acid enantiomers.

**Example Problem #22: Enantiomers**

**PROBLEM:** Assign absolute configurations as $R$ or $S$ to each of the following compounds and name each of them according to the IUPAC rules.

**SOLUTION:** In practice the first step in assigning absolute configurations as $R$ or $S$ for enantiomers is to prioritize the four atoms, or groups of atoms, attached to the chiral center based on the first point of difference. Firstly, consider the atomic number of the atom that is bonded to the chiral center; the highest the atomic number, the higher the priority. If two or more atoms that are bonded directly to the chiral center are the same, then prioritize these groups based on the next/adjacent set of atoms to the directly–bonded atoms, until priority is assigned. The second step will consist in repositioning the molecule in space so that the lowest priority atom or group (#4) is directed away from the observer looking along the bond connecting the lowest priority atom or group to the chiral center. The remaining three atoms or groups bonded to the chiral center will be directed towards you. Finally, in the last step you will assign the absolute configuration based on the order of priority: if the order of priority from highest to lowest is counterclockwise then the configuration you assign is $S$; otherwise the absolute configuration is $R$.

a) We identify the compound as 2-hydroxypropanoic acid (see the numbering of carbon atoms in the alkane chain containing the hydroxyl and carboxylic functional groups attached to the chiral center at C2).
The \((R)\) or \((S)\) absolute configuration of a chiral molecule does not tell us the direction the compound rotates the plane-polarized light, because some compounds with the \((S)\) configuration rotate the plane to the right (+) and some compounds with the \((S)\) configuration rotate the light to the left (-). Up to this point we learned how to identify if a chiral compound has the \((R)\) or \((S)\) configuration, but the only way we can tell whether the compound rotates a plane-polarized light dextrorotatory (+) or levorotatory (-) is to put the compound in a polarimeter. Then we can incorporate the sign (+) or (-) into the name of the enantiomer after we identify the direction the optically active compound rotates the plane of polarization. A solution containing an excess of pure enantiomer over racemate rotates the angle of polarization through an angle \(\alpha\); conventionally the clockwise rotations are regarded as positive and counterclockwise rotations are regarded as negative. A racemic mixture or racemate has equal amounts of left- and right-handed enantiomers of a chiral molecule (equimolar mixture) of both enantiomers and it is therefore optically inactive. A racemate does not rotate plane-polarized light because one enantiomer cancels out the rotation of plane-polarized light caused by the other enantiomer. Optical purity is quoted in terms of enantiometric excess, \textit{i.e.} the excess of pure enantiomer over racemate. The symbols (+) and (-) are used to show which direction an enantiomer rotates plane-polarized light. The direction of rotation can only be determined by experimentation.

\textbf{Figure 2-35. Schematic diagram of a modern polarimeter.}

A polarimeter is an analytical instrument used for measuring the angle of rotation of plane-polarized light caused by a solution containing an optically active inorganic or organic compound. A schematic diagram of a polarimeter is shown in \textit{Figure 2-35}, indicating the light path from the light source to the photodetector. The polychromatic light produced by a light source passes through an interference filter of a definitive wavelength and then reaches a collimating lens to form a beam of parallel rays. When the beam of unpolarized light passes through the first polarizing filter, only one plane emerges and subsequently enters into a Faraday
Let us look at the examples below exhibiting a meso compound (i.e. the tartaric acid, known by its IUPAC name as 2,3-dihydroxybutanedioic acid), which has two stereogenic centers.

If the Fischer projection can be divided into two halves that are mirror images of each other then the structure may be identified as a meso compound. The above meso compound has two chiral centers, yet it is achiral because it exhibits an internal plane of symmetry. We will see it in the next section that a family of stereoisomers with \( n \) stereogenic centers containing a meso compound will have fewer than \( 2^n \) stereoisomers.

Fischer projections are not used as extensively as they once were. However, using Fischer projections maybe convenient because simply switching any two groups on the horizontal line or the vertical line around the stereogenic center generates the enantiomer. As noticed earlier, switching both the vertical and horizontal lines does not generate the enantiomer. Interchanging groups on the horizontal line or vertical line gives its mirror image, which is the enantiomer. The later may be a convenient method to generate and evaluate two structures for superposability.

### 4.6 DIASTEREOMERS

Diastereomers are stereoisomers that are not mirror images of each other. Diastereomers are the result of either \( R/S \) differences in compounds with two or more stereogenic centers that are not mirror images of each other, \( E/Z \) differences in alkenes or points producing \( cis/trans \) differences in cyclic (ring) structures. Diastereomers differ in most chemical and physical properties, in contrast to enantiomers, whose nearly all properties are the same (i.e. boiling and melting points, solubility, etc.) except in only two areas: their interaction with plane-polarized light and their interaction with other chiral molecules. In fact, stereoisomers that are not enantiomers are classified as diastereomers. Earlier in previous sections we introduced the \( E/Z \) and \( cis/trans \) isomers of both the alkene and the cycloalkane types. Next we will familiarize with diastereomeric forms of the compounds containing more than one asymmetric center. We will learn that molecules having two or more asymmetric centers can have several stereoisomers (configurational isomers).

There are \( 2^n \) possible stereoisomers for a molecule containing \( n \) asymmetric centers. Because every stereoisomer has a mirror image, therefore there are only \( 2^{n-1} \) sets of enantiomers. We will also introduce meso compounds, which are defined as those compounds that contain two or more chiral centers, yet they are achiral and optically inactive and also are identical with their mirror images. A meso compound is achiral because it usually has a plane of symmetry, which divides the molecule in two identical halves and, therefore, optical isomers are not possible.

![Figure 2-36. Two examples of diastereomeric relationship between (left) two chair forms of cis-1,3-dimethylcyclohexane which are a pair of nonsuperposable non-mirror images and (right) cis- and trans-1,2-dibromocyclohexane (right)](image-url)
Figure 2-42. Two conformations of methylcyclohexane. At equilibrium (T= 25 °C) methylcyclohexane exists as a 95:5 ratio of conformers, favoring the equatorial chair form. The steric repulsions between the hydrogen atoms shown in pink are responsible for the higher energy of the axial conformation compared to the equatorial isomer. The overlapping arcs between the methyl group and the hydrogen atoms represent repulsive interactions between the non-bonded atoms in close proximity.

Each of these interactions has about the same energy (3.68 kJ/mol or 0.88 kcal/mol) as a gauche butane conformation. The term diaxial interaction refers to the steric strain between an axial substituent and axial hydrogen (or another group) on the same side of a cyclohexane molecule. The axial positions on the same side of the ring are extremely close to each other, and any atom or group larger than the hydrogen atom will introduce steric strain between the larger atom or group and the other two axial hydrogen atoms. In case of methylcyclohexane one of the hydrogen atoms of the methyl group is within 190 – 200 pm of the axial hydrogen atoms at carbon atoms C3 and C5. This interatomic distance is less than the sum of the van der Waals radii of the two hydrogen atoms (240 pm) and causes van der Waals strain in the axial conformation.

The van der Waals repulsive forces arise when the electron clouds surrounding the atoms get close enough to repeal each other. Because this type of steric strain originates between groups on carbon atoms 1 and 3 of a cyclohexane ring, the steric strain is often called a 1,3-diaxial interaction. When the methyl group is in
We cannot label yet *trans*-1,2-dimethylcyclohexane as having no symmetry until all its chair conformations are analyzed. From *Figure 2-46*, we notice there is no plane of symmetry (or any other element of symmetry) because one chair conformation does not superpose on the other. Since there is no symmetry after comparing all four chair conformations, we conclude that *trans*-1,2-dimethylcyclohexane has no symmetry, and any mirror image must be an enantiomer.

Looking closely at chair conformations of *trans*-1,2-dimethylcyclohexane in *Figure 2-46* we deduce the following:

- all conformations of each stereoisomer (A, B, C, D) are chiral and therefore, each stereoisomer is chiral.
- the ring flip between chair conformations converts each enantiomer into a conformational diastereomer, therefore, *trans*-1,2-dimethylcyclohexane consists of two pairs of enantiomeric conformers or alternately, four sets of diastereomeric conformers.
- two pairs of diastereomeric conformers cannot be separated into two isomers since they are interconverted by rapid ring flipping.
- each enantiomer is capable of independent existence and can be isolable and resolvable in an optically active form since each pair of enantiomers are not interconverted by ring flipping.

Therefore, we conclude that the enantiomers of *trans*-1,2-dimethylcyclohexane cannot be interconverted into one another by ring flip; therefore, they are configurational enantiomers with different physical properties which makes them isolable and resolvable.

### Glossary of Terms

**Isomers** are compounds with same molecular formula but have different structural or spatial arrangements of atoms.

**Isomerism** occurs when two or more compounds have the same molecular formula but exist in at least two different tridimensional shapes due to some structural or spatial arrangement difference. Their physical and chemical properties may be quite similar or significantly different.

**Structural (or constitutional) isomers** are those molecular structures whose atoms are linked together in a different skeletal framework and represent compounds with completely different chemical and physical properties.

**Positional isomers** are structural (constitutional) isomers that have the same molecular formula, the same carbon skeleton, and the same functional groups but differ from each other in the location of the functional or substituted groups attached to the carbon skeleton.

**Functional isomers** are structural (constitutional) isomers that have the same molecular formula, but their atoms are connected in different ways so that they bear different functional groups.

**Tautomers** are structural isomers of organic compounds with same molecular formula but different connectivity that rapidly interconvert with each other.

**Tautomerization** is called the chemical reaction that leads to the change in connectivity of the atoms to yield two different constitutional isomers.

**Tautomerism** is defined as the spontaneous interconversion of two isomeric forms with different functional groups.

**Metamers** are isomers that contain the same number and type of atoms but with a different distribution of radicals attached to the same functional group.