18th edition

Harper's Review of Biochemistry

Former title: *Review of Physiological Chemistry*

DAVID W. MARTIN, JR., MD
PETER A. MAYES, PhD, DSc
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Preface

Review of Physiological Chemistry was first published in 1939 and revised in 1944. In 1951, the third edition appeared with Harold A. Harper assuming the duties of authorship. From the outset, the *Review* was intended to serve as a concise survey of those aspects of chemistry most relevant to the study of biology and medicine. Forty-two years later, the 18th edition is impressive evidence of the success of Dr. Harper's effort. During this interval, the field has expanded at a truly remarkable rate, and its interaction with biology and medicine has become intimate.

The 18th edition of this *Review* has undergone major revision in order to achieve Professor Harper's original intentions and to keep abreast of advances in biochemistry and molecular and cellular biology. We have altered the title to include "biochemistry," a contemporary name for the subject matter. As is apparent in the table of contents, the chapters have been subjected to major reorganizations including their titles, contents, and order of presentation. We have tried again to balance our desire to include all we regard as significant against the student's need for a concise review of a comprehensive body of scientific information.

To the authors, the major change in the 18th edition is the retirement of Harold Harper from active authorship of the *Review*. We hope that the example of his guidance in previous editions will enable us, in this and future editions, to provide an educational service of comparable quality for the benefit of students at many levels in multiple disciplines.

The authors and their valued contributors are most gratified by the broad base of acceptance and support this book has received all over the world. Several editions of the English language version have been reprinted in Japan, Lebanon, Taiwan, Pakistan, the Philippines, and Korea. In addition, there are now translations in Italian, Spanish French, Portuguese, Japanese, Polish, German, Turkish, Czech, and Indonesian. Hindi, Greek, Serbo-Croatian, and Chinese translations are in preparation.

David W. Martin, Jr.
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San Francisco
July, 1981

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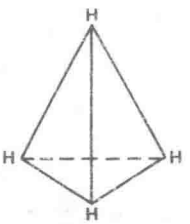
Introduction | 1

Victor W. Rodwell, PhD

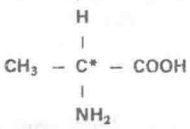
This chapter reviews certain aspects of organic chemistry relevant to biochemistry and provides guidelines to assist in learning and integrating the information. The early chapters of this book present basic data on the structures and chemical properties of important biochemical compounds. While some of these will be familiar, others are complex structures (eg, heterocyclic structures*) perhaps not previously encountered by the student. The biochemistry of unfamiliar molecules is largely predictable from that of structurally similar molecules (eg, molecules that possess the same functional groups†). **Each functional group in a molecule generally behaves in a predictable way with respect to its biochemical reactions.** This guideline simplifies the understanding of enzyme-catalyzed transformations in living cells. Although most biochemically important molecules contain multiple functional groups, as a rule, **only a single functional group undergoes change in a given enzyme-catalyzed reaction.** Learning is therefore enhanced by focusing attention **exclusively on that change** to the virtual exclusion of all other aspects of the molecule. The complexities of intermediary metabolism can generally be made manageable in this way.

STEREOISOMERS

Stereoisomers differ only in the way in which the constituent atoms are oriented in space. In methane (CH_4), the hydrogen atoms are at the vertices of an equilateral tetrahedron (4-sided pyramid) with the carbon atom at the center.



A carbon atom to which 4 different atoms or groups of atoms are attached is known as an asymmetric carbon atom. For example, in the formula for alanine, the asymmetric (alpha) carbon atom is starred (*).



Alanine

Since many biochemicals contain 2 or more asymmetric C atoms, a thorough understanding of the stereochemistry of systems with more than one asymmetric center is essential.

Representation of Spatial Relationships Between Atoms

Certain spatial relationships are readily visualized using ball-and-stick atomic models. A compound having asymmetric carbon atoms exhibits **optical isomerism.** Thus, lactic acid has 2 nonequivalent optical isomers, one being the mirror image or **enantiomer** of the other (Fig 1–1).

The reader may show that these structures are indeed different by changing the positions of either enantiomer by rotation about any axis and attempting to superimpose one structure on the other.

Although enantiomers of a given compound have the same chemical properties, certain of their physical and essentially all of their physiologic properties are different. Enantiomers rotate the plane of plane-polarized light to an equal extent but in opposite directions. Since enzymes act on only one of a pair of enantiomers, only half of a **racemic mixture** (a mix-

***Hetero atoms** (Greek *heteros* "other") such as O, N, and S also form covalent bonds with carbon, eg, in ethylamine, $C_2H_5NH_2$, ethyl alcohol, C_2H_5OH, and ethyl mercaptan, C_2H_5SH. Hetero atoms have one or more pairs of electrons not involved in covalent bonding. Since these unshared electrons have a negative field, **compounds with hetero atoms** attract protons, ie, they **act as bases** (see Chapter 2). Heterocyclic structures are cyclic structures that contain hetero atoms.

†**A functional group** (eg, $-NH_2$, $-COOH$, $-OH$) is a specific arrangement of linked chemical elements that has well-defined chemical and physical properties.

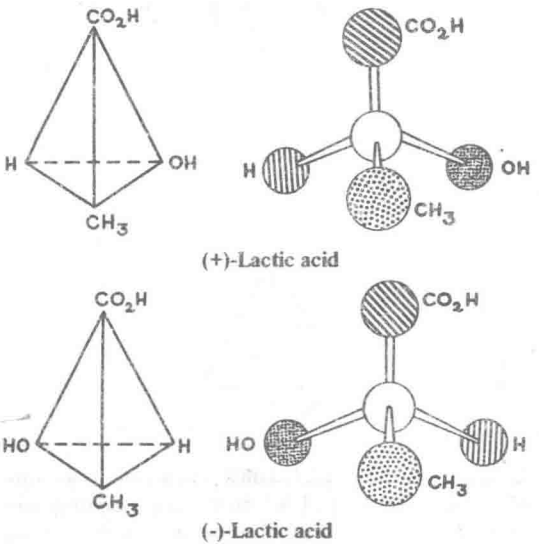


Figure 1–1. Tetrahedral and ball-and-stick model representation of lactic acid enantiomers.

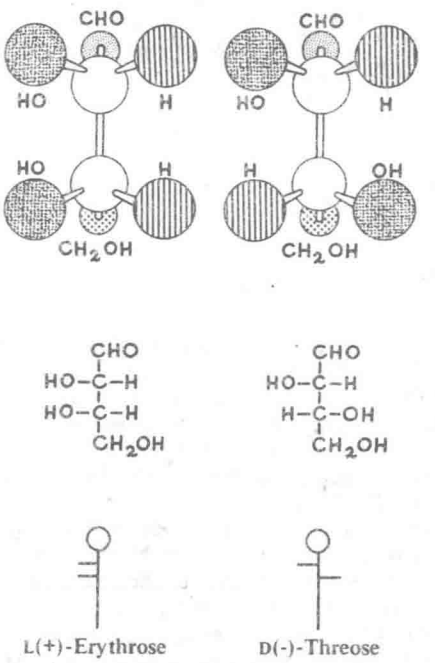


Figure 1–3. Two aldotetroses. *Top:* Ball-and-stick models. *Middle:* Fischer projection formulas. *Bottom:* Abbreviated projection formulas.

ture of equal quantities of both enantiomers) generally is physiologically active.

The number of possible different isomers is 2^n, where n = the number of different asymmetric carbon atoms. An aldotetrose, for example, contains 2 asymmetric carbon atoms; hence, there are $2^2 = 4$ optical isomers.

To represent 3-dimensional molecules in 2 dimensions, **projection formulas,** introduced by Emil Fischer, are used. The molecule is placed with the asymmetric carbon in the plane of the projection. The groups at the top and bottom project **behind** the plane of projection. Those to the right and left project equally **above** the plane of projection. The molecule is then projected in the form of a cross (Fig 1–2).

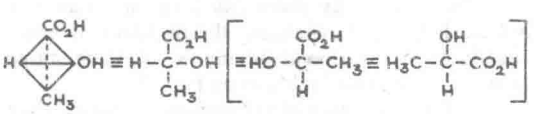
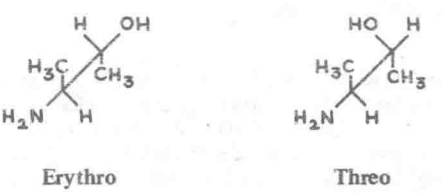


Figure 1–2. Fischer projection formula of (-)-lactic acid.

Unfortunately, the orientation of the tetrahedron differs from that of Fig 1–1. **Fischer projection formulas may never be mentally lifted from the plane of the paper and turned over.** Since the vertical bonds are really **below** the projection plane while the horizontal bonds are **above** it, **it also is not permissible to rotate the Fischer projection formula within the plane of the paper by either a 90-degree or a 270-degree angle, although it is permissible to rotate it 180 degrees.**

The nomenclature for molecules with 2 asymmetric carbon atoms derives from the names of the 4-carbon sugars erythrose and threose. If 2 like groups (eg, two OH groups) are on the same side, the isomer is called the **"erythro"** form; if on the opposite side, the **"threo"** isomer. Fischer projection formulas inadequately represent one feature of these molecules. Look at the models from which these formulas are



Erythro Threo

Figure 1–4. Sawhorse representations of the erythro and threo enantiomers of 3-amino-2-butanol. The **erythro** and **threo** refer to the relative positions of –OH and $–NH_2$ groups. Note that there are 3 ways to stagger C_2 with respect to C_3. That shown represents a structure with the bulky CH_3 groups oriented as far away from each other as possible.

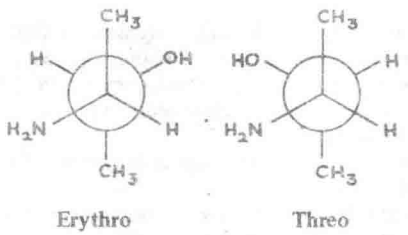


Figure 1–5. Staggered Newman projection formulas for the erythro and threo enantiomers of 3-amino-2-butanol.

derived. The upper part of Fig 1–3 represents molecules in the **"eclipsed"** form in which the groups attached to C_2 and C_3 approach each other as closely as possible. The real shape of the molecule more closely approximates an arrangement with C_2 and C_3 rotated with respect to each other by an angle of 60 degrees, so that their substituents are **staggered** with respect to each other and are as far apart as possible. One way to represent "staggered" formulas is to use **"sawhorse"** representations (Fig 1–4). **Newman projection formulas** (Fig 1–5) view the molecule front-to-back along the bond joining the asymmetric carbon atoms. These C atoms, which eclipse each other, are represented as 2 superimposed circles (only one is shown). The bonds and groups attached to the asymmetric C atoms are projected in a vertical plane and appear as "spokes" at angles of 120 degrees for each C atom. The spokes on the rear atom are offset 60 degrees with respect to those on the front C atom. Bonds to the front carbon are drawn to the center of the circle and those for the rear carbon only to its periphery (Fig 1–5).

It is desirable to be able to convert Fischer projection formulas to sawhorse or Newman projection formulas. These most accurately illustrate the true shape of the molecule and hence are most useful in understanding its chemical and biologic properties. One way is to build a model* corresponding to the Fischer projection formula, stagger the atoms, and draw the sawhorse or Newman formulas. Figure 1–6 shows how to interconvert these formulas without models. The Fischer projection formula is converted to an "eclipsed sawhorse" or Newman projection which then is rotated 180 degrees about the C_2–C_3 bond, producing a staggered sawhorse or Newman projection.

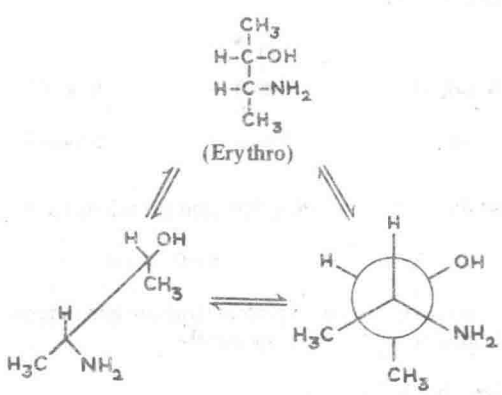


Figure 1–6. Transformation from Fischer to sawhorse or Newman formula.

Cis-Trans Isomerism

Cis-trans isomerism (Latin *cis* "this side," *trans* "across") occurs in compounds with double bonds. Since the double bond is rigid, the atoms attached to it are not free to rotate as are those attached to a single bond. Thus the structures

are not equivalent and have **different chemical and physiologic properties.** Fumaric acid, but not maleic acid, is physiologically active. The *cis* isomer has the 2 more "bulky" groups on the same side of the double

*The student is urged to purchase an inexpensive set of models. These will prove invaluable in studying the chemistry of sugars, amino acids, and steroids in particular.

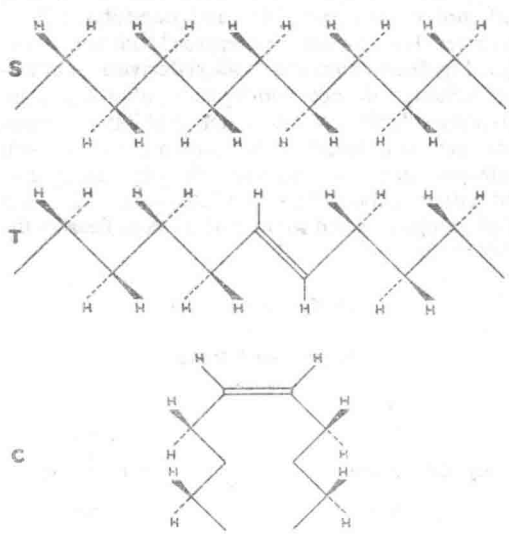


Figure 1–7. Representation of portions of the hydrocarbon backbones of a saturated fatty acid (S), an unsaturated fatty acid with a single *trans* double bond (T), and one with a single *cis* double bond (C). Bonds drawn as solid lines are in the plane of the paper. Bonds drawn as dotted lines project behind, and those drawn ▬ project in front of the plane of the paper.

bond. If they are on opposite sides of the double bond, the *trans* isomer is produced.

Introduction of *trans* double bonds in an otherwise saturated hydrocarbon chain deforms the shape of the molecule relatively little. A *cis* double bond, by contrast, entirely changes its shape. It can thus be appreciated why *cis* and *trans* isomers of a compound are not interchangeable in cells. Membranes composed of *trans* and *cis* isomers would have entirely different shapes. Enzymes acting on one isomer might be expected to be entirely inert with the other.

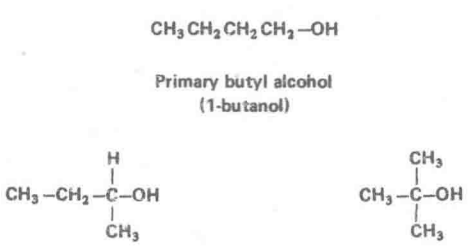
Again, the usual formulas fail to represent the actual shape of the molecules. Portions of the hydrocarbon backbone of a saturated fatty acid and of the *cis* and *trans* isomers of an 18-carbon unsaturated fatty acid are represented in Fig 1–7.

FUNCTIONAL GROUPS IMPORTANT IN BIOCHEMISTRY

A **functional group** is a specific arrangement of elements (generally C, H, O, N, P, or S) that has well-defined chemical and physical properties. The properties of biochemical molecules are best understood in terms of the chemical and physical properties of the functional groups these molecules contain.

Alcohols

Many biochemical compounds (eg, sugars, certain lipids, and amino acids) are **alcohols.** These have both **polar** (hydroxy, OH) and **nonpolar** (alkyl) character. They are thus best regarded both as **hydroxylated hydrocarbons** and as **alkyl derivatives of water.** Although alcohols with up to 3 carbon atoms are infinitely soluble in water, water solubility decreases with increasing length of the carbon chain, ie, with increasing nonpolar character. Primary, secondary, and tertiary alcohols have respectively one, 2, and 3 alkyl groups attached to the carbon atom bearing the –OH group.



Both monohydric (one –OH group) and polyhydric (more than one –OH group) alcohols are of physiologic significance. Sugars are derivatives of polyhydric alcohols, as are cyclic or ring-containing alcohols such as **inositol.** Their highly polar character makes polyhydric alcohols far more water-soluble than corresponding monohydric alcohols with equivalent numbers of carbon atoms. Thus, even polyhydric alcohols with 6 or more carbon atoms (eg, sugars) are highly water-soluble.

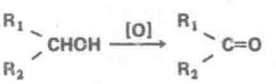
Chemical reactions of alcohols with biochemical analogies include:

A. Oxidation: Primary alcohols are oxidized by strong oxidizing agents to aldehydes and acids, whereas secondary alcohols are oxidized to ketones.

Primary:

$$R{-}CH_2OH \xrightarrow{[O]} RCHO + RCOOH$$

Secondary:



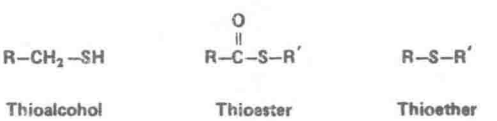
Tertiary alcohols cannot be oxidized (dehydrogenated) without rupture of a C–C bond.

B. Esterification: An ester is formed when water is split out between an alcohol and an acid.

The acid may be organic or inorganic. Esters of H_3PO_4 (see phosphorylated sugars and phospholipids) and H_2SO_4 are of great significance in biochemistry. Many lipids contain carboxylic ester linkages.

C. Ether Formation: Ethers are derivatives of alcohols in which the hydrogen of the –OH group is replaced by an alkyl group (R–O–R′). The ether linkage is comparatively uncommon in living tissues.

Sulfur, which is in the same group of the periodic table as oxygen, forms similar compounds. Thioalcohols (thiols, mercaptans), thioesters, and thioethers all occur in nature.



In addition, the disulfides (left) and peroxides (right)

play an important role in protein structure and in prostaglandin biosynthesis, respectively.

Aldehydes & Ketones

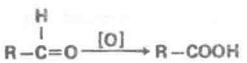
Aldehydes and ketones possess the strongly reducing carbonyl group > C=O. Aldehydes have one and ketones 2 alkyl groups attached to the carbon bearing the carbonyl group:

Aldehyde Ketone

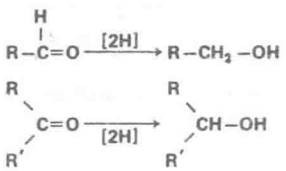
The sugars, in addition to being polyhydric alcohols, are also either aldehydes or ketones.

Reactions of aldehydes and ketones of biochemical interest include the following:

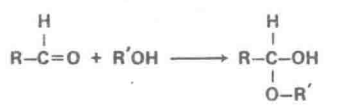
A. Oxidation: Oxidation of an aldehyde to the corresponding carboxylic acid. Ketones are not readily oxidized, since, like tertiary alcohols, they cannot lose hydrogen without rupture of a C–C bond.



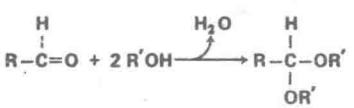
B. Reduction: Reduction of an aldehyde yields the corresponding primary alcohol, and reduction of a ketone yields the corresponding secondary alcohol.



C. Hemiacetal and Acetal Formation: Under acidic conditions, aldehydes can combine with one or 2 of the hydroxyl groups of an alcohol, forming, respectively, a hemiacetal or an acetal:



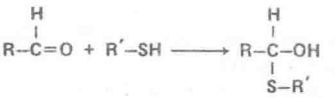
A hemiacetal



An acetal

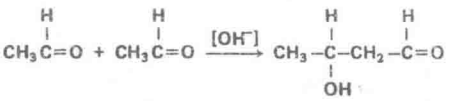
The carbonyl and alcohol functions may be part of the same molecule. For example, the aldose (aldehyde) sugars exist in solution primarily as internal hemiacetals. Analogous structures (hemiketals and ketals) are formed from alcohols and ketones.

Aldehydes may also form **thiohemiacetals** and **thioacetals** with thioalcohols. Thiohemiacetals function as enzyme-bound intermediates in the enzymic oxidation of aldehydes to acids.



A thiohemiacetal

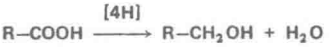
D. Aldol Condensation: In alkali, aldehydes and, to a lesser extent, ketones undergo condensation between their carbonyl and their α-carbon atoms to form aldols or β-hydroxy aldehydes or ketones. The β-hydroxy acids derived from these are important in fatty acid metabolism.



Carboxylic Acids

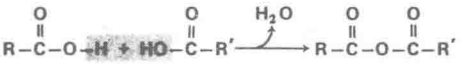
Carboxylic acids have both a carbonyl (> C=O) and a hydroxyl group on the same carbon atom. They are typical **weak acids** and only partially dissociate in water to form a hydrogen ion (H^+) and a **carboxylate anion** ($R–COO^-$) with the negative charge shared equally by the 2 oxygen atoms. Some reactions of carboxylic acids of biochemical interest include the following:

A. Reduction: Complete **reduction** yields the corresponding **primary alcohol.**

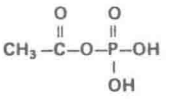


B. Ester and Thioester Formation: See alcohols.

C. Acid Anhydride Formation: A molecule of water is split out between the carboxyl groups of 2 acid molecules.



When both acid molecules are the same, a **symmetric anhydride** is produced. Molecules of different acids yield **mixed anhydrides.** Anhydrides found in nature include those of phosphoric acid (in ATP) and the **mixed anhydrides** formed from phosphoric acid and a carboxylic acid, eg:

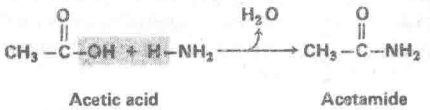


Acetyl phosphate

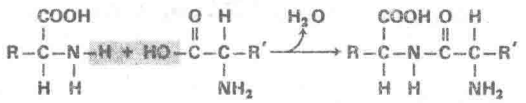
D. Salt Formation: Carboxylic acids react stoichiometrically (equivalent for equivalent) with

bases to form salts. Na^+ and K^+ salts are 100% dissociated in solution.

E. Amide Formation: Splitting out a molecule of water between a carboxylic acid and ammonia or an amine forms an amide. Particularly important amides are **peptides**, formed from the amino group of one amino acid and the carboxyl group of another.



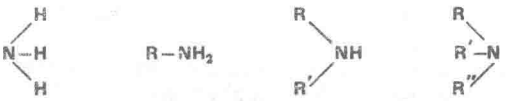
Acetic acid Acetamide



Peptide bond

Amines

Amines, alkyl derivatives of ammonia, are usually gases or volatile liquids with odors resembling ammonia but more "fishlike." Primary, secondary, and tertiary amines are formed by replacement of one, 2, or 3 of the hydrogens of ammonia, respectively.

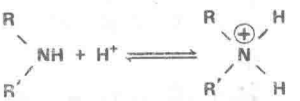


Ammonia Primary amine Secondary amine Tertiary amine

Ammonia in solution exists in both charged and uncharged forms:

Ammonia Ammonium ion

Amines behave in an entirely analogous way:



An amine An alkylammonium ion