17th Edition

# Review of Physiological Chemistry



H.A. Harper
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# Preface

The purpose of this *Review* has not changed since its first appearance in 1939: to provide a comprehensive, reasonably concise survey of those aspects of physiological chemistry most relevant to the study of biology and medicine. We began with a ''whole organ'' concept of biologic phenomena and have introduced subcellular and molecular concepts as they have come to dominate the research efforts of new generations of investigators. We believe this approach directly serves the interests of students and practitioners in the health sciences related to medicine without neglecting fundamental principles of molecular chemistry and biology.

In this 17th edition, the reorganization of the textual material which had commenced with the prior edition has been continued. The authorship of the chapters, as listed in the table of contents, is as before. Once again we are fortunate to have the skillful assistance of Laurel V. Schaubert in the presentation of visual material.

With some apology we acknowledge that the book has again become slightly larger. This is necessitated by the rapid growth of all segments of biochemistry both as a clinical and as a research specialty. Nonetheless, we have tried to balance our desire to include all that we regard as of significant interest against the student's need for a concise presentation of a comprehensive body of scientific information.

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, the Philippines, and Korea. In addition, there are now translations in Spanish, Japanese, Pakistani, Turkish, French, Italian, Portuguese, Czech, German, and Polish. Greek, Serbo-Croatian, Hindi, Chinese, and Indonesian translations are in preparation.

Harold A. Harper
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June, 1979

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The purpose of this chapter is (1) to review certain aspects of organic chemistry relevant to the understanding of physiologic chemistry and (2) to provide certain guidelines designed to assist the student in learning and integrating the information presented in this book.

The early chapters of this book deal with the structures and properties of chemical compounds important in physiologic chemistry. Some of these structures will be familiar from the study of organic chemistry, but many are highly complex structures (eg, heterocyclic structures*) perhaps not previously encountered. The chemistry and the physiologic chemistry of unfamiliar molecules are largely predictable from those of structurally similar molecules as well as from the structure of molecules that possess identical functional groups.† In general, each functional group in a molecule will behave in a predictable way with respect to the reactions it will undergo. This will be a valuable guide also to the kinds of enzyme-catalyzed transformations that the group undergoes in living cells. The chemical elements that comprise functional groups will first be considered.

## THE ELEMENTS OF THE SECOND & THIRD PERIODS OF THE PERIODIC TABLE

With the exception of certain metal ions, physiologic chemistry is, for the most part, related to the chemistry of the elements of the second and third periods of the periodic table.

In 1976, instruments designed to detect either new or the known forms of life were landed on the planet Mars. The experiments that were conducted assumed the existence of certain probable similarities between terrestrial life and hypothetical life elsewhere in the universe. One central assumption was that extraterrestrial life would use some or all of the same elements used by terrestrial life.

On earth, all cells, regardless of their origin (animal, plant, or microbial), contain the same elements in approximately the same proportions (Table 1–1). Thus, of the more than 100 known elements, only 19 are essential for terrestrial life. Perhaps there is some logical chemical explanation for their selection.

Six nonmetals (O, C, H, N, P, and S), which contribute almost 98% of the total mass of cells, provide the structural elements of protoplasm. From them, the functional components of cells (walls, membranes, genes, enzymes, etc) are formed. These 6

**Table 1–1.** The elemental composition of living cells.

| Element | Composition by Weight (%) | Element | Composition by Weight (%) |
|---|---|---|---|
| O | 65 | | |
| C | 18 | Cu, Zn | 0.70 |
| H | 10 | Se, Mo | |
| N | 3 | F, Cl, I | |
| Ca | 1.5 | Mn, Co, Fe | |
| P | 1.0 | | |
| K | 0.35 | Li, Sr | Traces† |
| S | 0.25 | Al, Si, Pb | |
| Na | 0.15 | V, As | |
| Mg | 0.05 | Br | |
| Total | 99.30 | | |

†Variable occurrence in cells. No known function in most cases.

**Table 1–2.** The structural elements of protoplasm.

| Period | Group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI | VII | VIII |
| 1 | H | | | | | | | He |
| 2 | Li | Be | B | C | N | O | F | Ne |
| 3 | Na | Mg | Al | Si | P | S | Cl | Ar |

***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.

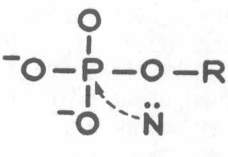
†**A functional group** (eg, $-NH_2$, $-COOH$, $-OH$) is a specific arrangement of linked chemical elements that has well-defined chemical and physical properties.

elements all occur in the first 3 periods of the periodic table (Table 1–2).

The relative abundance of these 6 elements in the seas, crust, and atmosphere of earth does not by itself explain their utilization for life. Aluminum is more abundant than carbon, but it performs no known function essential to life. By contrast, the intrinsic chemical properties of these 6 elements suggest their unique suitability as building blocks for life. Desirable features for structural elements apparently are as follows: (1) Small atomic radius. (2) The versatility conferred by the ability to form 1-, 2-, 3-, and 4-electron bonds. (3) The ability to form multiple bonds.

Small atoms form the tightest, most stable bonds—a distinct advantage for structural elements. **H, O, N, and C are the smallest atoms capable of forming 1-, 2-, 3-, and 4-electron bonds, respectively.** Utilization of all possible types of electron bonds permits maximum versatility in molecular design. So also does the ability to form multiple bonds, a property confined almost entirely to P, S, and the elements of period 2. Advantages of C- versus Si-based life include the following: (1) Greater chemical stability of C–C versus Si–Si bonds. (2) The ability of C, but not of Si, to form multiple bonds (eg, the oxides of C are diffusible, monomeric gases, whereas the oxide of Si is a viscous polymer). (3) The stability of C–C bonds, but not of Si–Si bonds, to rupture by nucleophilic reagents* such as $O_2$, $H_2O$, or $NH_3$.

Similar factors uniquely qualify P and S for utilization in energy transfer reactions. **Energy transfer is facilitated by bonds susceptible to nucleophilic attack**† (eg, nucleophilic attack of the 6-OH of glucose on the terminal P–O–P bond of ATP, forming ADP plus glucose 6-phosphate). P and S resemble Si in that P–O–P or S–O–S bonds, like Si–Si bonds, are susceptible to nucleophilic rupture by virtue of their unoccupied third orbitals. However, unlike Si, P and S form multiple bonds (more versatile), a consequence of their smaller atomic diameters. Most energy transfer reactions in biochemistry may be visualized as resulting from attack of a nucleophil (N) on the unoccupied third orbital of a phosphorus atom:




The characteristic chemical and physical properties of the chemical elements of life are the same throughout the known universe. It thus seems probable that if life exists elsewhere, the same elements are employed for the same or similar reasons. Taking this one step further, it seems likely that the kinds of biologic molecules formed from these elements and the kinds of reactions they might undergo would bear strong similarities to those on earth. For this reason, a biochemist is probably the scientist most likely to recognize and understand extraterrestrial life in whatever size or physical shape it might occur.

*Electron-rich elements or compounds.

†Attack of an electron-rich center upon an electron-deficient center.

## REVIEW OF ORGANIC CHEMISTRY

A sound understanding of organic chemistry is an essential prerequisite to the study of physiologic chemistry. Satisfactory knowledge of organic chemistry will enhance an understanding of the reactions of chemical compounds that are catalyzed in cells by the class of proteins known as enzymes.

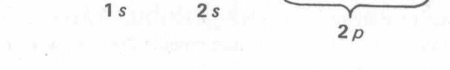
This section is not intended as a complete review of organic chemistry but rather as a summary of the main points. The material should be quite familiar to those who have only recently completed the study of this branch of chemistry.

### The Covalent Bond

The region in space where an electron is most likely to be found is termed an **orbital.** The sizes and shapes of different orbitals may be thought of as determining the spatial arrangements of atoms in molecules. The most fundamental of the "rules" that describe the electronic configurations of **atoms** is the **Pauli exclusion principle: Only 2 electrons can occupy any given orbital, and these must have opposite spins.** Electrons of like spin tend to get as far away from each other as possible. Electrons in **molecules** occupy orbitals in accordance with similar rules.

To form a covalent bond, 2 atoms must be positioned so that an orbital of one overlaps an orbital of the other. Each orbital must contain a single electron, and these must have opposite spins. The 2 atomic orbitals merge, forming a single **bond orbital** containing both electrons. Since this new arrangement contains less energy (ie, is more stable) than that of the isolated atoms, **energy is evolved when bonds are formed.** The amount of energy (per mole) given off when a bond is formed is called the **bond dissociation energy.** For a given pair of atoms, the greater the overlapping of atomic orbitals, the stronger the bond.

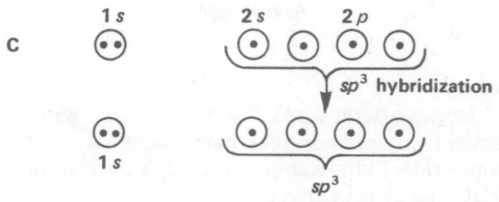
The carbon atom (atomic number = nuclear charge = 6) has 6 electrons, 2 of which are unpaired and occupy separate $2p$ orbitals:



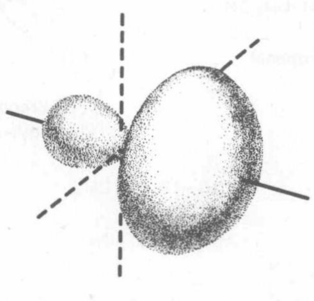
Although this suggests that C should form 2 bond orbitals with H, four bonds are formed, giving $CH_4$. Since bond formation is an exergonic (stabilizing) process, as many bonds as possible tend to be formed. This occurs even if the resulting bond orbitals bear little resemblance to the original atomic orbitals.

To produce a tetravalent C atom, mentally "promote" one of the 2*s* electrons to the empty *p* orbital:

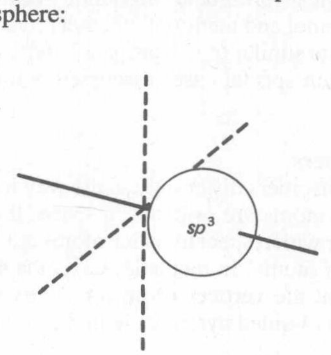

While this representation suggests C should form 3 bonds of one type (using the *p* orbitals) and a fourth of another type (using the *s* orbital), the 4 bonds of methane are known to be equivalent. The **molecular** orbitals have a mixed or **hybridized** character and are termed $sp^3$ orbitals since they are considered to arise from mixing of one *s* and 3 *p* orbitals:




$sp^3$ orbitals have the following shape:



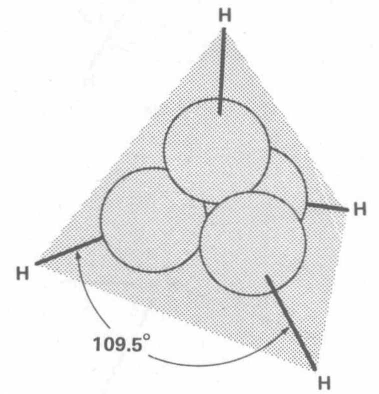
We shall neglect the back lobe and represent the front lobe as a sphere:




Concentrating atomic orbitals in the direction of a bond permits greater overlapping and strengthens the bond. The most favored hybrid orbital is therefore much more strongly directed than either *s* or *p* orbitals, and the 4 orbitals are exactly equivalent. Most important, these hybrid orbitals are directed toward the corners of a regular **tetrahedron.** This permits them to be as far away from each other as possible (recall Pauli exclusion principle).

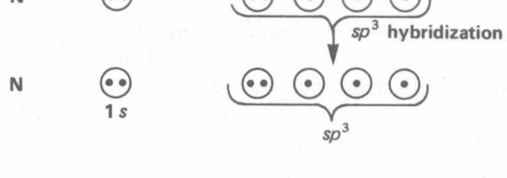
## Bond Angle

For maximum overlapping of the $sp^3$ orbitals of C with the *s* orbitals of hydrogen, the four H nuclei must be along the axes of the $sp^3$ orbitals and at the corners of a tetrahedron. The angle between any two C–H bonds must therefore be the **tetrahedral angle 109.5 degrees:**

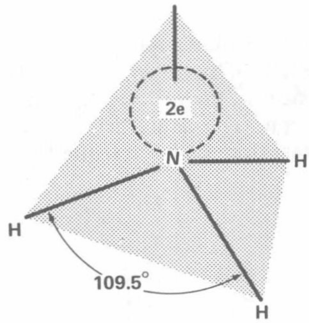



Methane has been shown experimentally to conform to this model. Each C–H bond has exactly the same length (0.109 nm) and dissociation energy (102 kcal/mol), and the angle between any pair of bonds is 109.5 degrees. **Characteristic bond lengths, bond energies, and bond angles thus are associated with covalent bonds.** Unlike the ionic bond, which is equally strong in all directions, **the covalent bond has directional character.** Thus, the chemistry of the covalent bond is much concerned with molecular size and shape. Three kinds of C atom are encountered: **tetrahedral** ($sp^3$ hybridized), **trigonal** ($sp^2$ hybridized), and **digonal** (*sp* hybridized).

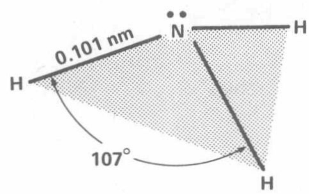
In ammonia ($NH_3$), nitrogen (atomic number = 7) has a valence state similar to that described for carbon: 4 $sp^3$ orbitals directed to the corners of a tetrahedron.



Each of the unpaired electrons of N occupying one of the $sp^3$ orbitals can pair with that of an H atom, giving $NH_3$. The fourth $sp^3$ orbital contains an unshared electron pair. The unshared electron pair appears to occupy more space and to compress the bond angles slightly to 107 degrees. It is a region of high electron density and confers on $NH_3$ its basic properties (attracts protons).

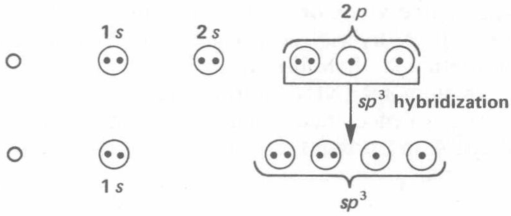



Predicted shape

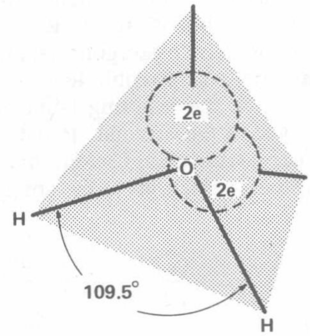



Actual shape

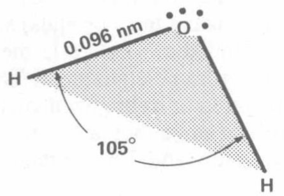
In $H_2O$, the O (atomic number = 8) has only 2 unpaired electrons and hence bonds to only 2 hydrogens.




**The water molecule also is tetrahedral.** The 2 hydrogens occupy 2 corners of the tetrahedron and the 2 unshared electron pairs the remaining corners. The H–O–H bond angle (105 degrees) is even smaller than that in $NH_3$.




Predicted shape



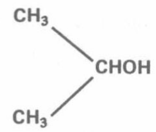

Actual shape

### Isomers

Isomers (Greek *isos* ''same''; *meros* ''part'') are chemical compounds that have identical elemental compositions. For example, for the empirical formula $C_3H_8O$, three isomers are possible.

$CH_3CH_2CH_2OH$

1-Propanol




2-Propanol (1-methylethanol)

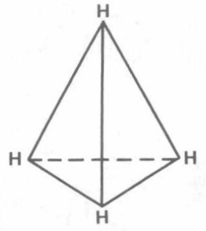
$CH_3{-}O{-}CH_2CH_3$

Methylethyl ether

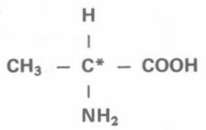
The chemical properties of compounds having the same empirical formula are frequently quite different (eg, 1-propanol and methylethyl ether). Occasionally, they are quite similar (eg, 1-propanol and 2-propanol), and in certain special cases discussed below they are identical.

### Stereoisomers

Stereoisomers differ only in the way in which the constituent atoms are oriented in space; they are like one another with respect to which atoms are attached to which other atoms. In methane, $CH_4$, the 4 hydrogen atoms are at the vertices of an imaginary 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 asymmetrical carbon atom.** For example, in the formula for alanine, the asymmetrical (alpha) carbon atom is starred (*).




Alanine

Many carbohydrates, peptides, steroids, nucleic acids, etc contain 2 or more asymmetrical C atoms. A thorough understanding of the stereochemistry of systems with more than one asymmetrical center is therefore essential.

### Representation of Spatial Relationships Between Atoms

Certain spatial relationships are readily visualized using ball-and-stick atomic models. A compound having asymmetrical 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).

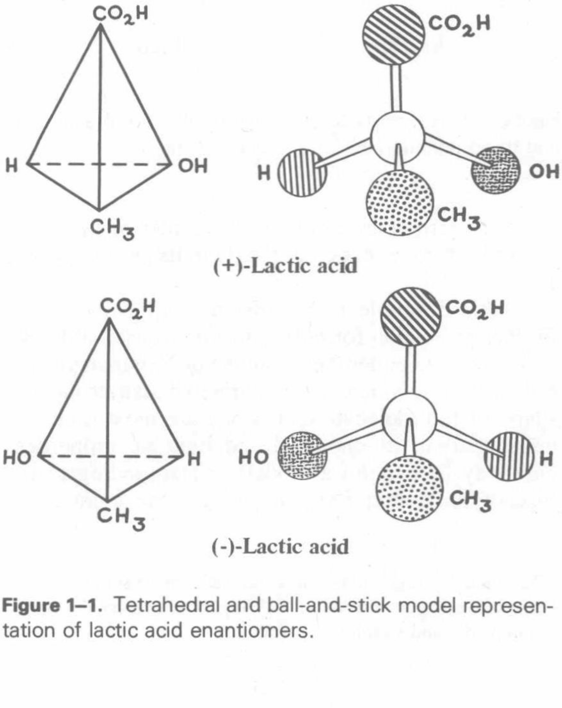



**Figure 1–1.** Tetrahedral and ball-and-stick model representation of lactic acid enantiomers.

The reader may convince himself 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 mixture 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 asymmetrical carbon atoms. An aldotetrose, for example, contains 2 asymmetrical 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 asymmetrical 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).

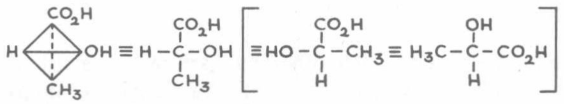


**Figure 1–2.** Fischer projection formula of (-)-lactic acid.

Unfortunately, the orientation of the tetrahedron differs from that of Fig 1–1. **Fischer projection formulas may never be 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.**

A special representation and nomenclature for molecules with 2 asymmetrical carbon atoms derives from the names of the 4-carbon sugars erythrose and threose. If 2 like groups (eg, 2 –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 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**

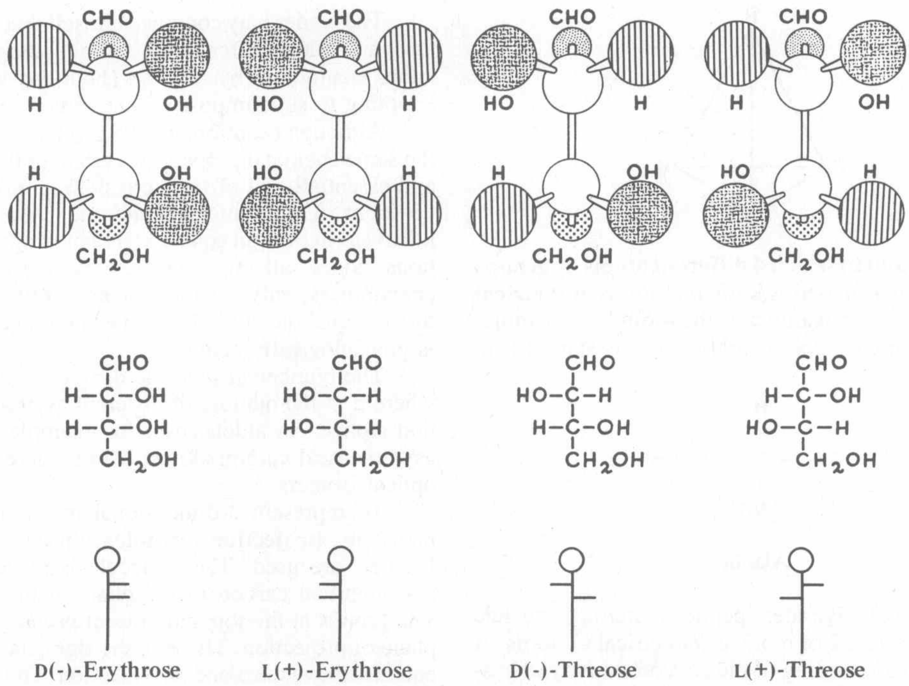



**Figure 1–3.** The aldotetroses. *Top:* Ball-and-stick models. *Middle:* Fischer projection formulas. *Bottom:* Abbreviated projection formulas.

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).

A second representation is the **Newman projection formula** (Fig 1–5). The molecule is viewed front-to-back along the bond joining the asymmetrical carbon atoms. These 2 atoms, which thus exactly eclipse each other, are represented as 2 superimposed circles (only one is shown). The bonds and groups attached to the asymmetrical 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. To distinguish the 2 sets of bonds, those for

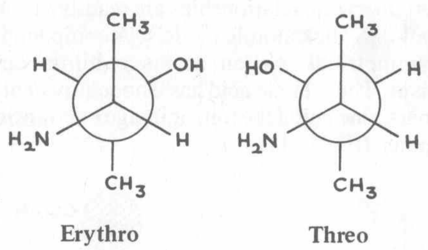



**Figure 1–5.** Newman projection formulas for the erythro and threo enantiomers of 3-amino-2-butanol.

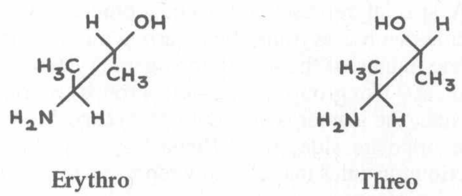



**Figure 1–4.** Sawhorse representations of the erythro and threo enantiomers of 3-amino-2-butanol. The **erythro** and **threo** refer to the relative positions of –OH and $-NH_2$ groups. Note that there are 3 ways to stagger $C_2$ with respect to $C_3$. That shown represents a structure with the bulky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

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 shift between the Fischer projection formulas most often used in books and articles to either the sawhorse or Newman projection formulas, which 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

*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.