1.1 · Distinctive Properties of Living Systems

[Please consider this question from a more specific, molecular point of view, and as it would apply to the earliest organisms rather than contemporary life.]

The most obvious quality of living organisms is that they are complicated and highly organized.

Biological structures serve functional purposes. That is, biological structures have a role in terms of the organism’s existence. From parts of organisms, such as limbs and organs, down to the chemical agents of metabolism, such as enzymes and metabolic intermediates, a biological purpose can be given for each component. Indeed, it is this functional characteristic of biological structures that separates the science of biology from studies of the inanimate world such as chemistry, physics, and geology. In biology, it is always meaningful to seek the purpose of observed structures, organizations, or patterns, that is, to ask what functional role they serve within the organism.

Living systems are actively engaged in energy transformations. The maintenance of the highly organized structure and activity of living systems depends upon their ability to extract energy from the environment. The ultimate source of energy is the sun. Solar energy flows from photosynthetic organisms (those organisms able to capture light energy by the process of photosynthesis) through food chains to herbivores and ultimately to carnivorous predators at the apex of the food pyramid.

The biosphere is thus a system through which energy flows. Organisms capture some of this energy, be it from photosynthesis or the metabolism of food, by forming special energized biomolecules, of which ATP and NADPH are the two most prominent examples.

(Commonly used abbreviations such as ATP and NADPH are defined on the inside back cover of this book.) ATP and NADPH are energized biomolecules because they represent chemically useful forms of stored energy. We explore the chemical basis of this stored energy in subsequent chapters. For now, suffice it to say that when these molecules react with other molecules in the cell, the energy released can be used to drive unfavorable processes. That is, ATP, NADPH, and related compounds are the power sources that drive the energy-requiring activities of the cell, including biosynthesis, movement, osmotic work against concentration gradients, and, in special instances, light emission (bioluminescence). Only upon death does an organism reach equilibrium with its
inanimate environment. The living state is characterized by the flow of energy through the organism. At the expense of this energy flow, the organism can maintain its intricate order and activity far removed from equilibrium with its surroundings, yet exist in a state of apparent constancy over time. This state of apparent constancy, or so-called steady-state, is actually a very dynamic condition: energy and material are consumed by the organism and used to maintain its stability and order. In contrast, inanimate matter, as exemplified by the universe in totality, is moving to a condition of increasing disorder or, in thermodynamic terms, maximum entropy. Living systems have a remarkable capacity for self-replication. Generation after generation, organisms reproduce virtually identical copies of themselves. This self-replication can proceed by a variety of mechanisms, ranging from simple division in bacteria to sexual reproduction in plants and animals, but in every case, it is characterized by an astounding degree of fidelity.

Indeed, if the accuracy of self-replication were significantly greater, the evolution of organisms would be hampered. This is so because evolution depends upon natural selection operating on individual organisms that vary slightly in their fitness for the environment. The fidelity of self-replication resides ultimately in the chemical nature of the genetic material. This substance consists of polymeric chains of deoxyribonucleic acid, or DNA, which are structurally complementary to one another.

These molecules can generate new copies of themselves in a rigorously executed polymerization process that ensures a faithful reproduction of the original DNA strands. In contrast, the molecules of the inanimate world lack this capacity to replicate. A crude mechanism of replication, or specification of unique chemical structure according to some blueprint, must have existed at life’s origin. This primordial system no doubt shared the property of structural complementarity (see later section) with the highly evolved patterns of replication prevailing today.
1.2 · Biomolecules: The Molecules of Life

The elemental composition of living matter differs markedly from the relative abundance of elements in the earth’s crust (Table 1.1).

<table>
<thead>
<tr>
<th></th>
<th>Earth’s Crust</th>
<th>Seawater</th>
<th>Human Body†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Element</td>
<td>%</td>
<td>Compound</td>
<td>%</td>
</tr>
<tr>
<td>O</td>
<td>47</td>
<td>CH</td>
<td>54</td>
</tr>
<tr>
<td>Si</td>
<td>28</td>
<td>Na⁺</td>
<td>470</td>
</tr>
<tr>
<td>Al</td>
<td>7.9</td>
<td>Mg²⁺</td>
<td>54</td>
</tr>
<tr>
<td>Fe</td>
<td>4.5</td>
<td>SO₄²⁻</td>
<td>25</td>
</tr>
<tr>
<td>Ca</td>
<td>3.5</td>
<td>Ca²⁺</td>
<td>10</td>
</tr>
<tr>
<td>Na</td>
<td>2.5</td>
<td>K⁺</td>
<td>10</td>
</tr>
<tr>
<td>K</td>
<td>2.5</td>
<td>HCO₃⁻</td>
<td>1.5</td>
</tr>
<tr>
<td>Mg</td>
<td>2.2</td>
<td>NO₃⁻</td>
<td>0.11</td>
</tr>
<tr>
<td>Ti</td>
<td>0.46</td>
<td>HPO₄²⁻</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>H</td>
<td>0.02</td>
<td>Na⁺</td>
<td>0.18</td>
</tr>
<tr>
<td>C</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Figures for the earth’s crust and the human body are presented as percentages of the total number of atoms, seawater data are in millimoles per liter. Figures for the earth’s crust do not include water whereas figures for the human body do.† Trace elements found in the human body serving essential biological functions include Mn, Fe, Cu, Zn, Zr, Mn, C, N, and Na.

Hydrogen, oxygen, carbon, and nitrogen constitute more than 99% of the atoms in the human body, with most of the H and O occurring as H₂O. Oxygen, silicon, aluminum, and iron are the most abundant atoms in the earth’s crust, with hydrogen, carbon, and nitrogen being relatively rare (less than 0.2% each). Nitrogen as dinitrogen (N₂) is the predominant gas in the atmosphere, and carbon dioxide (CO₂) is present at a level of 0.05%, a small but critical amount. Oxygen is also abundant in the atmosphere and in the oceans. What property unites H, O, C, and N and renders these atoms so suitable to the chemistry of life? It is their ability to form covalent bonds by electron-pair sharing. Furthermore, H, C, N, and O are among the lightest elements of the periodic table capable of forming such bonds (Figure 1.6).
Because the strength of covalent bonds is inversely proportional to the atomic weights of the atoms involved, H, C, N, and O form the strongest covalent bonds. Two other covalent bond-forming elements, phosphorus (as phosphate -OPO$_3^{2-}$ derivatives) and sulfur, also play important roles in biomolecules.

**Biomolecules Are Carbon Compounds**

All biomolecules contain carbon. The prevalence of C is due to its unparalleled versatility in forming stable covalent bonds by electron-pair sharing. Carbon can form as many as four such bonds by sharing each of the four electrons in its outer shell with electrons contributed by other atoms. Atoms commonly found in covalent linkage to C are C itself, H, O, and N. Hydrogen can form one such bond by contributing its single electron to formation of an electron pair. Oxygen, with two unpaired electrons in its outer shell, can participate in two covalent bonds, and nitrogen, which has three unshared electrons, can form three such covalent bonds. Furthermore, C, N, and O can share two electron pairs to form double bonds with one another within biomolecules, a property that enhances their chemical versatility. Carbon and nitrogen can even share three electron pairs to form
triple bonds.

Two properties of carbon covalent bonds merit particular attention. One is the ability of carbon to form covalent bonds with itself. The other is the tetrahedral nature of the four covalent bonds when carbon atoms form only single bonds. Together these properties hold the potential for an incredible variety of linear, branched, and cyclic compounds of C. This diversity is multiplied further by the possibilities for including N, O, and H atoms in these compounds (Figure 1.7, next page). We can therefore envision the ability of C to generate complex structures in three dimensions. These structures, by virtue of appropriately included N, O, and H atoms, can display unique chemistries suitable to the living state. Thus, we may ask, is there any pattern or underlying organization that brings order to this astounding potentiality?
Figure 1.7 • Examples of the versatility of C—C bonds in building complex structures: linear aliphatic, cyclic, branched, and planar.
1.3 · A Biomolecular Hierarchy: Simple Molecules Are the Units for Building Complex Structures

Examination of the chemical composition of cells reveals a dazzling variety of organic compounds covering a wide range of molecular dimensions (Table 1.2). As this complexity is sorted out and biomolecules are classified according to the similarities in size and chemical properties, an organizational pattern emerges. The molecular constituents of living matter do not reflect randomly the infinite possibilities for combining C, H, O, and N atoms. Instead, only a limited set of the many possibilities is found, and these collections share certain properties essential to the establishment and maintenance of the living state. The most prominent aspect of biomolecular organization is that macromolecular structures are constructed from simple molecules according to a hierarchy of increasing structural complexity. What properties do these biomolecules possess that make them so appropriate for the condition of life?

Metabolites and Macromolecules

The major precursors for the formation of biomolecules are water, carbon dioxide, and three inorganic nitrogen compounds—ammonium (NH$_4^+$), nitrate (NO$_3^-$), and dinitrogen (N$_2$). Metabolic processes assimilate and transform these inorganic precursors through ever more complex levels of biomolecular order (Figure 1.8).

![Figure 1.8](image-url) Molecular organization in the cell is a hierarchy.

In the first step, precursors are converted to metabolites, simple organic compounds that are intermediates in cellular energy transformation and in the biosynthesis of various sets of building blocks: amino acids, sugars, nucleotides, fatty acids, and glycerol. By covalent linkage of these building blocks, the macromolecules are constructed: proteins, polysaccharides, polynucleotides (DNA and RNA), and lipids. (Strictly speaking, lipids contain relatively few building blocks and are therefore not really polymeric like other macromolecules; however, lipids are important contributors to higher levels of complexity.) Interactions among macromolecules lead to the next level of structural organization, supramolecular complexes. Here, various members of one or more of the classes of macromolecules come together to form
specific assemblies serving important subcellular functions. Examples of these supramolecular assemblies are multifunctional enzyme complexes, ribosomes, chromosomes, and cytoskeletal elements. For example, a eukaryotic ribosome contains four different RNA molecules and at least 70 unique proteins. These supramolecular assemblies are an interesting contrast to their components because their structural integrity is maintained by noncovalent forces, not by covalent bonds. These noncovalent forces include hydrogen bonds, ionic attractions, van der Waals forces, and hydrophobic interactions between macromolecules. Such forces maintain these supramolecular assemblies in a highly ordered functional state. Although noncovalent forces are weak (less than 40 kJ/mol), they are numerous in these assemblies and thus can collectively maintain the essential architecture of the supramolecular complex under conditions of temperature, pH, and ionic strength that are consistent with cell life.

Organelles

The next higher rung in the hierarchical ladder is occupied by the organelles, entities of considerable dimensions compared to the cell itself. Organelles are found only in eukaryotic cells, that is, the cells of “higher” organisms. Several kinds, such as mitochondria and chloroplasts, evolved from bacteria that gained entry to the cytoplasm of early eukaryotic cells. Organelles share two attributes: they are cellular inclusions, usually membrane bounded, and are dedicated to important cellular tasks. Organelles include the nucleus, mitochondria, chloroplasts, endoplasmic reticulum, Golgi apparatus, and vacuoles as well as other relatively small cellular inclusions, such as peroxisomes, lysosomes, and chromoplasts. The nucleus is the repository of genetic information as contained within the linear sequences of nucleotides in the DNA of chromosomes. Mitochondria are the “power plants” of cells by virtue of their ability to carry out the energy-releasing aerobic metabolism of carbohydrates and fatty acids, capturing the energy in metabolically useful forms such as ATP. Chloroplasts endow cells with the ability to carry out photosynthesis. They are the biological agents for harvesting light energy and transforming it into metabolically useful chemical forms.

Membranes

Membranes define the boundaries of cells and organelles. As such, they are not easily classified as supramolecular assemblies or organelles, although they share the properties of both. Membranes resemble supramolecular complexes in their construction because they are complexes of proteins and lipids maintained by noncovalent forces. Hydrophobic interactions are particularly important in maintaining membrane structure. Hydrophobic interactions arise because water molecules prefer to interact with each other rather than with nonpolar substances. The presence of nonpolar molecules lessens the range of opportunities for water-water interaction by forcing the water molecules into ordered arrays around the nonpolar groups. Such ordering can be minimized if the individual nonpolar molecules redistribute from a dispersed state in the water into an aggregated organic phase surrounded by water. The spontaneous assembly of membranes in the aqueous environment where life arose and exists is the natural result of the
hydrophobic ("water-fearing") character of their lipids and proteins. Hydrophobic interactions are the creative means of membrane formation and the driving force that presumably established the boundary of the first cell. The membranes of organelles, such as nuclei, mitochondria, and chloroplasts, differ from one another, with each having a characteristic protein and lipid composition suited to the organelle’s function. Furthermore, the creation of discrete volumes or compartments within cells is not only an inevitable consequence of the presence of membranes but usually an essential condition for proper organelar function.

**The Unit of Life Is the Cell**

The **cell** is characterized as the unit of life, the smallest entity capable of displaying the attributes associated uniquely with the living state: growth, metabolism, stimulus response, and replication. In the previous discussions, we explicitly narrowed the infinity of chemical complexity potentially available to organic life, and we previewed an organizational arrangement, moving from simple to complex, that provides interesting insights into the functional and structural plan of the cell. Nevertheless, we find no obvious explanation within these features for the living characteristics of cells. Can we find other themes represented within biomolecules that are explicitly chemical yet anticipate or illuminate the living condition?
1.4 · Properties of Biomolecules Reflect Their Fitness to the Living Condition

If we consider what attributes of biomolecules render them so fit as components of growing, replicating systems, several biologically relevant themes of structure and organization emerge. Furthermore, as we study biochemistry, we will see that these themes serve as principles of biochemistry. Prominent among them is the necessity for information and energy in the maintenance of the living state. Some biomolecules must have the capacity to contain the information or “recipe” of life. Other biomolecules must have the capacity to translate this information so that the blueprint is transformed into the functional, organized structures essential to life. Interactions between these structures are the processes of life. An orderly mechanism for abstracting energy from the environment must also exist in order to obtain the energy needed to drive these processes. What properties of biomolecules endow them with the potential for such remarkable qualities?

Biological Macromolecules and Their Building Blocks Have a “Sense” or Directionality

The macromolecules of cells are built of units—amino acids in proteins, nucleotides in nucleic acids, and carbohydrates in polysaccharides—that have structural polarity. That is, these molecules are not symmetrical, and so they can be thought of as having a “head” and a “tail.” Polymerization of these units to form macromolecules occurs by head-to-tail linear connections. Because of this, the polymer also has a head and a tail, and hence, the macromolecule has a “sense” or direction to its structure (Figure 1.9).
Figure 1.9 • (a) Amino acids build proteins by connecting the α-carboxyl C atom of one amino acid to the α-amino N atom of the next amino acid in line. (b) Polysaccharides are built by combining the C-1 of one sugar to the C-4 O of the next sugar in the polymer. (c) Nucleic acids are polymers of nucleotides linked by bonds between the 3¢-OH of the ribose ring of one nucleotide to the 5¢-PO₄ of its neighboring nucleotide. All three of these polymerization processes involve bond formations accompanied by the elimination of water (dehydration synthesis reactions).

[See movie versions of each part of 1.9 at http://www.web.virginia.edu/Heidi/chapter1/chp1frameset.htm]

Biological Macromolecules Are Informational

Because biological macromolecules have a sense to their structure, the sequential order of their component building blocks, when read along the length of the molecule, has the capacity to specify information in the same manner that the letters of the alphabet can form words when arranged in a linear sequence (Figure 1.10).
The sequence of monomeric units in a biological polymer has the potential to contain information if the diversity and order of the units are not overly simple or repetitive. Nucleic acids and proteins are information-rich molecules; polysaccharides are not.

Not all biological macromolecules are rich in information. Polysaccharides are often composed of the same sugar unit repeated over and over, as in cellulose or starch, which are homopolymers of many glucose units. On the other hand, proteins and polynucleotides are typically composed of building blocks arranged in no obvious repetitive way; that is, their sequences are unique, akin to the letters and punctuation that form this descriptive sentence. In these unique sequences lies meaning. To discern the meaning, however, requires some mechanism for recognition.

**Biomolecules Have Characteristic Three-Dimensional Architecture** The structure of any molecule is a unique and specific aspect of its identity. Molecular structure reaches its pinnacle in the intricate complexity of biological macromolecules, particularly the proteins. Although proteins are linear sequences of covalently linked amino acids, the course of the protein chain can turn, fold, and coil in the three dimensions of space to establish a specific, highly ordered architecture that is an identifying characteristic of the given protein molecule (Figure 1.11).

**Figure 1.10** The sequence of monomeric units in a biological polymer has the potential to contain information if the diversity and order of the units are not overly simple or repetitive. Nucleic acids and proteins are information-rich molecules; polysaccharides are not.

**Figure 1.11** Three-dimensional space-filling representation of part of a protein molecule, the antigen-binding domain of immunoglobulin G (IgG). Immunoglobulin G is a major type of circulating antibody. Each of the spheres represents an atom in the structure.
Following material is on noncovalent weak interactions between biological molecules.
Weak Forces Maintain Biological Structure and Determine Biomolecular Interactions

Covalent bonds hold atoms together so that molecules are formed. In contrast, weak chemical forces or noncovalent bonds, (hydrogen bonds, van der Waals forces, ionic interactions, and hydrophobic interactions) are intramolecular or intermolecular attractions between atoms. None of these forces, which typically range from 4 to 30 kJ/mol, are strong enough to bind free atoms together (Table 1.3). The average kinetic energy of molecules at 25°C is 2.5 kJ/mol, so the energy of weak forces is only several times greater than the dissociating tendency due to thermal motion of molecules. Thus, these weak forces create interactions that are constantly forming and breaking at physiological temperature, unless by cumulative number they impart stability to the structures generated by their collective action. These weak forces merit further discussion because their attributes profoundly influence the nature of the biological structures they build.

**Table 1.3**

<table>
<thead>
<tr>
<th>Force</th>
<th>Strength (kJ/mol)</th>
<th>Distance (nm)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Waals forces</td>
<td>0.4–4.0</td>
<td>0.2</td>
<td>Strength depends on the relative size of the atoms or molecules and the distance between them. The size factor determines the area of contact between two molecules. The greater the area, the stronger the interaction.</td>
</tr>
<tr>
<td>Hydrogen bonds</td>
<td>12–30</td>
<td>0.3</td>
<td>Relative strength is proportional to the polarity of the H bond donor and H bond acceptor. More polar atoms form stronger H bonds.</td>
</tr>
<tr>
<td>Ionic interactions</td>
<td>20</td>
<td>0.25</td>
<td>Strength also depends on the relative polarity of the interacting charged species. Some ionic interactions are also H forces. For example, O–H...O–H.</td>
</tr>
<tr>
<td>Hydrophobic forces</td>
<td>&lt; 40</td>
<td>—</td>
<td>Force is a complex phenomenon determined by the degree to which the structure of water is disrupted or hydrophobic molecules or molecular regions dissolve.</td>
</tr>
</tbody>
</table>

**Van der Waals Attractive Forces**

Van der Waals forces are the result of induced electrical interactions between closely approaching atoms or molecules as their negatively-charged electron clouds fluctuate instantaneously in time. These fluctuations allow attractions to occur between the positively charged nuclei and the electrons of nearby atoms. Van der Waals interactions include dipole-dipole interactions, whose interaction energies decrease as $1/r^3$; dipole-induced dipole interactions, which fall off as $1/r^5$ and induced dipole-induced dipole interactions, often called dispersion or London dispersion forces, which diminish as $1/r^6$. Dispersion forces contribute to the attractive intermolecular forces between all
molecules, even those without permanent dipoles, and are thus generally more important than dipole-dipole attractions. Van der Waals attractions operate only over a limited interatomic distance and are an effective bonding interaction at physiological temperatures only when a number of atoms in a molecule can interact with several atoms in a neighboring molecule. For this to occur, the atoms on interacting molecules must pack together neatly. That is, their molecular surfaces must possess a degree of structural complementarity (Figure 1.12).

**Figure 1.12**  Van der Waals packing is enhanced in molecules that are structurally complementary. Gln\(^121\) represents a surface protuberance on the protein lysozyme. This protuberance fits nicely within a pocket (formed by Tyr\(^{101}\), Tyr\(^{32}\), Phe\(^{91}\), and Trp\(^{92}\)) in the antigen-binding domain of an antibody raised against lysozyme. (See also Figure 1.16.) (a) A space-filling representation. (b) A ball-and-stick model. *(From Science 233:751 (1986), figure 5.)*

At best, van der Waals interactions are weak and individually contribute 0.4 to 4.0 kJ/mol of stabilization energy. However, the sum of many such interactions within a macromolecule or between macromolecules can be substantial. For example, model studies of heats of sublimation show that each methylene group in a crystalline hydrocarbon accounts for 8 kJ, and each C-H group in a benzene crystal contributes 7 kJ of van der Waals energy per mole. Calculations indicate that the attractive van der Waals
energy between the enzyme lysozyme and a sugar substrate that it binds is about 60 kJ/mol.

When two atoms approach each other so closely that their electron clouds interpenetrate, strong repulsion occurs. Such repulsive van der Waals forces follow an inverse 12th-power dependence on $r \ (1/ r^{12})$, as shown in Figure 1.13.

Figure 1.13 • The van der Waals interaction energy profile as a function of the distance, $r$, between the centers of two atoms. The energy was calculated using the empirical equation $U = B/r^{12} - A/r^6$. (Values for the parameters $B = 11.5 \times 10^{-6}$ kJnm$^{12}$/mol and $A = 5.96 \times 10^{-3}$ kJnm$^6$/mol for the interaction between two carbon atoms are from Levitt, M., 1974, Journal of Molecular Biology 82:393-420.)

Between the repulsive and attractive domains lies a low point in the potential curve. This low point defines the distance known as the **van der Waals contact distance**, which is the interatomic distance that results if only van der Waals forces hold two atoms together. The limit of approach of two atoms is determined by the sum of their van der Waals radii (Table 1.4).
### Table 1.4

<table>
<thead>
<tr>
<th>Atom</th>
<th>Van der Waals</th>
<th>Covalent</th>
<th>Representation</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.1</td>
<td>0.037</td>
<td>○</td>
</tr>
<tr>
<td>C</td>
<td>0.17</td>
<td>0.071</td>
<td>○</td>
</tr>
<tr>
<td>N</td>
<td>0.15</td>
<td>0.078</td>
<td>○</td>
</tr>
<tr>
<td>O</td>
<td>0.14</td>
<td>0.056</td>
<td>○</td>
</tr>
<tr>
<td>P</td>
<td>0.10</td>
<td>0.050</td>
<td>○</td>
</tr>
<tr>
<td>S</td>
<td>0.106</td>
<td>0.124</td>
<td>○</td>
</tr>
</tbody>
</table>

Note: The representation shows the relative size and shape of the atoms.
Hydrogen bonds form between a hydrogen atom covalently bonded to an electronegative atom (such as oxygen or nitrogen) and a second electronegative atom that serves as the hydrogen bond acceptor. Several important biological examples are given in Figure 1.14.

**Figure 1.14**  *Some of the biologically important H bonds and functional groups that serve as H bond donors and acceptors.*

Hydrogen bonds, at a strength of 12 to 30 kJ/mol, are stronger than van der Waals forces and have an additional property: H bonds tend to be highly directional, forming straight bonds between donor, hydrogen, and acceptor atoms. Hydrogen bonds are also more specific than van der Waals interactions because they require the presence of complementary hydrogen donor and acceptor groups.
**Ionic Interactions**

**Ionic interactions** are the result of attractive forces between oppositely charged polar functions, such as negative carboxyl groups and positive amino groups (Figure 1.15).

These electrostatic forces average about 20 kJ/mol in aqueous solutions. Typically, the electrical charge is radially distributed, and so these interactions may lack the directionality of hydrogen bonds or the precise fit of van der Waals interactions. Nevertheless, because the opposite charges are restricted to sterically defined positions, ionic interactions can impart a high degree of structural specificity.

The strength of electrostatic interactions is highly dependent on the nature of the interacting species and the distance, r, between them. Electrostatic interactions may involve **ions** (species possessing discrete charges), **permanent dipoles** (having a
permanent separation of positive and negative charge), and **induced dipoles** (having a temporary separation of positive and negative charge induced by the environment). Between two ions, the energy falls off as $1/r$. The interaction energy between permanent dipoles falls off as $1/r^3$, whereas the energy between an ion and an induced dipole falls off as $1/r^4$.

**Hydrophobic Interactions**

**Hydrophobic interactions** are due to the strong tendency of water to exclude nonpolar groups or molecules. Hydrophobic interactions arise not so much because of any intrinsic affinity of nonpolar substances for one another (although van der Waals forces do promote the weak bonding of nonpolar substances), but because water molecules prefer the stronger interactions that they share with one another, compared to their interaction with nonpolar molecules. Hydrogen-bonding interactions between polar water molecules can be more varied and numerous if nonpolar molecules coalesce to form a distinct organic phase. This phase separation raises the entropy of water because fewer water molecules are arranged in orderly arrays around individual nonpolar molecules. It is these preferential interactions between water molecules that “exclude” hydrophobic substances from aqueous solution and drive the tendency of nonpolar molecules to cluster together. Thus, nonpolar regions of biological macromolecules are often buried in the molecule’s interior to exclude them from the aqueous milieu. The formation of oil droplets as hydrophobic nonpolar lipid molecules coalesce in the presence of water is an approximation of this phenomenon. These tendencies have important consequences in the creation and maintenance of the macromolecular structures and supramolecular assemblies of living cells.
6.1 • Forces Influencing Protein Structure

Several different kinds of noncovalent interactions are of vital importance in protein structure. Hydrogen bonds, hydrophobic interactions, electrostatic bonds, and van der Waals forces are all noncovalent in nature, yet are extremely important influences on protein conformations. The stabilization free energies afforded by each of these interactions may be highly dependent on the local environment within the protein, but certain generalizations can still be made.

Hydrogen Bonds

Hydrogen bonds are generally made wherever possible within a given protein structure. In most protein structures that have been examined to date, component atoms of the peptide backbone tend to form hydrogen bonds with one another. Furthermore, side chains capable of forming H bonds are usually located on the protein surface and form such bonds primarily with the water solvent. Although each hydrogen bond may contribute an average of only about 12 kJ/mol in stabilization energy for the protein structure, the number of H– bonds formed in the typical protein is very large. For example, in a-helices, the C=O and N–H groups of every residue participate in H bonds. The importance of H bonds in protein structure cannot be overstated.

Hydrophobic Interactions

Hydrophobic “bonds,” or, more accurately, interactions, form because nonpolar side chains of amino acids and other nonpolar solutes prefer to cluster in a nonpolar environment rather than to intercalate in a polar solvent such as water. The forming of hydrophobic bonds minimizes the interaction of nonpolar residues with water and is therefore highly favorable. Such clustering is entropically driven. The side chains of the amino acids in the interior or core of the protein structure are almost exclusively hydrophobic. Polar amino acids are almost never found in the interior of a protein, but the protein surface may consist of both polar and nonpolar residues.
**Electrostatic Interactions**

Ionic interactions arise either as electrostatic attractions between opposite charges or repulsions between like charges. Chapter 4 discusses the ionization behavior of amino acids. Amino acid side chains can carry positive charges, as in the case of lysine, arginine, and histidine, or negative charges, as in aspartate and glutamate. In addition, the NH$_2$-terminal and COOH-terminal residues of a protein or peptide chain usually exist in ionized states and carry positive or negative charges, respectively. All of these may experience electrostatic interactions in a protein structure. Charged residues are normally located on the protein surface, where they may interact optimally with the water solvent. It is energetically unfavorable for an ionized residue to be located in the hydrophobic core of the protein. Electrostatic interactions between charged groups on a protein surface are often complicated by the presence of salts in the solution. For example, the ability of a positively charged lysine to attract a nearby negative glutamate may be weakened by dissolved NaCl (Figure 6.1). The Na$^+$ and Cl$^-$ ions are highly mobile, compact units of charge, compared to the amino acid side chains, and thus compete effectively for charged sites on the protein. In this manner, electrostatic interactions among amino acid residues on protein surfaces may be damped out by high concentrations of salts. Nevertheless, these interactions are important for protein stability.

![Figure 6.1](image)

**Figure 6.1**  
An electrostatic interaction between the e–amino group of a lysine and the g–carboxyl group of a glutamate residue.
2.2. Noncovalent Bonds

Several types of noncovalent bonds are critical in maintaining the three-dimensional structures of large molecules such as proteins and nucleic acids (see Figure 2-1b). Noncovalent bonds also enable one large molecule to bind specifically but transiently to another, making them the basis of many dynamic biological processes.

The energy released in the formation of noncovalent bonds is only 1 – 5 kcal/mol, much less than the bond energies of single covalent bonds (see Table 2-1). Because the average kinetic energy of molecules at room temperature (25 °C) is about 0.6 kcal/mol, many molecules will have enough energy to break noncovalent bonds. Indeed, these weak bonds sometimes are referred to as interactions rather than bonds. Although noncovalent bonds are weak and have a transient existence at physiological temperatures (25 – 37 °C), multiple noncovalent bonds often act together to produce highly stable and specific associations between different parts of a large molecule or between different macromolecules (Figure 2-11). In this section we consider the four main types of noncovalent bonds and discuss their role in stabilizing the structure of biomembranes.

Figure 2-11. Multiple weak bonds stabilize specific associations between large molecules. (Left) In this hypothetical complex, seven noncovalent bonds bind the two protein molecules A and B together, forming a stable complex. (Right) Because only four noncovalent bonds can form between proteins A and C, this interaction may be too weak for the A-C complex to exist in cells.

The Hydrogen Bond Underlies Water’s Chemical and Biological Properties

Hydrogen bonding between water molecules is of crucial importance because all life
requires an aqueous environment and water constitutes about 70–80 percent of the weight of most cells. The mutual attraction of its molecules causes water to have melting and boiling points at least 100 °C higher than they would be if water were nonpolar; in the absence of these intermolecular attractions, water on earth would exist primarily as a gas. The exact structure of liquid water is still unknown. It is believed to contain many transient, maximally hydrogen-bonded networks. Most likely, water molecules are in rapid motion, constantly making and breaking hydrogen bonds with adjacent molecules. As the temperature of water increases toward 100 °C, the kinetic energy of its molecules becomes greater than the energy of the hydrogen bonds connecting them, and the gaseous form of water appears.

Properties of Hydrogen Bonds
Normally, a hydrogen atom forms a covalent bond with only one other atom. However, a hydrogen atom covalently bonded to a donor atom, D, may form an additional weak association, the hydrogen bond, with an acceptor atom, A:

\[
\text{D}^{\delta^-} - \text{H}^{\delta^+} + : \text{A}^{\delta^-} \leftrightarrow \text{D}^{\delta^-} - \text{H}^{\delta^+} \cdots \cdots : \text{A}^{\delta^-}
\]

Hydrogen bond

In order for a hydrogen bond to form, the donor atom must be electronegative, so that the covalent D—H bond is polar. The acceptor atom also must be electronegative, and its outer shell must have at least one nonbonding pair of electrons that attracts the δ+ charge of the hydrogen atom. In biological systems, both donors and acceptors are usually nitrogen or oxygen atoms, especially those atoms in amino (—NH₂) and hydroxyl (—OH) groups. Because all covalent N—H and O—H bonds are polar, their H atoms can participate in hydrogen bonds. By contrast, C—H bonds are nonpolar, so these H atoms are almost never involved in a hydrogen bond.

Water molecules provide a classic example of hydrogen bonding. The hydrogen atom in one water molecule is attracted to a pair of electrons in the outer shell of an oxygen atom in an adjacent molecule. Not only do water molecules hydrogen-bond with one another, they also form hydrogen bonds with other kinds of molecules, as shown in Figure 2-12.
Figure 2-12. Water readily forms hydrogen bonds. In liquid water, each water molecule apparently forms transient hydrogen bonds with several others, creating a fluid network of hydrogen-bonded molecules (a). The precise structure of liquid water is still not known with certainty. Water also can form hydrogen bonds with methanol (b) and methylamine (c). Each of the two pairs of nonbonding electrons in the outer shell of an oxygen atom can accept a hydrogen atom in a hydrogen bond. Similarly, the single pair of unshared electrons in the outer shell of a nitrogen atom is capable of becoming an acceptor in a hydrogen bond. The hydroxyl oxygen and the amino nitrogen can also be the donor in hydrogen bonds to oxygen atoms in water.

The presence of hydroxyl (—OH) or amino (—NH₂) groups makes many molecules soluble in water. For instance, the hydroxyl group in methanol (CH₃OH) and the amino group in methylamine (CH₃NH₂) can form several hydrogen bonds with water, enabling the molecules to dissolve in water to high concentrations. In general, molecules with polar bonds that easily form hydrogen bonds with water can dissolve in water and are said to be hydrophilic (Greek, “water-loving”). Besides the hydroxyl and amino groups, peptide and ester bonds are important chemical groups that interact well with water:

Most hydrogen bonds are 0.26 – 0.31 nm long, about twice the length of covalent bonds between the same atoms. In particular, the distance between the nuclei of the hydrogen and oxygen atoms of adjacent hydrogen-bonded molecules in water is approximately 0.27 nm,
about twice the length of the covalent O—H bonds in water. The hydrogen atom is closer to
the donor atom, D, to which it remains covalently bonded, than it is to the acceptor. The
length of the covalent D—H bond is a bit longer than it would be if there were no hydrogen
bond, because the acceptor “pulls” the hydrogen away from the donor. The strength of a
hydrogen bond in water (≈5 kcal/mol) is much weaker than a covalent O—H bond (≈110
kcal/mol).

**Hydrogen Bonds as a Stabilizing Force in Macromolecules**
An important feature of all hydrogen bonds is directionality. In the strongest hydrogen
bonds, the donor atom, the hydrogen atom, and the acceptor atom all lie in a straight line.
Nonlinear hydrogen bonds are weaker than linear ones; still, multiple nonlinear hydrogen
bonds help to stabilize the three-dimensional structures of many proteins. It is only because
of the aggregate strength of multiple hydrogen bonds that they play a central role in the
architecture of large biological molecules in aqueous solutions (see Figure 2-11).

The strengths of the hydrogen bonds in proteins and nucleic acids are only 1 to 2 kcal/mol,
considerably weaker than the hydrogen bonds between water molecules. The reason for this
difference can be seen from Figure 2-13, which depicts the formation of a hydrogen bond
between two amino acids in a protein. Initially, both the —OH and —NH₂ groups in the
protein are hydrogen-bonded to water, and the formation of a hydrogen bond between these
groups involves disruption of their hydrogen bonds with water. Thus the net change in
energy in forming this —OH···N hydrogen bond will be less than the 5 kcal/mol
characteristic of hydrogen bonds between water molecules.

![Figure 2-13. In order for a hydrogen bond (red dots) to form between a —OH and
an —NH₂ group in a protein (right), the hydrogen bonds between these groups and
water must be disrupted (left).](image)

**Ionic Interactions Are Attractions between Oppositely Charged Ions**
In some compounds, the bonded atoms are so different in electronegativity that the bonding
electrons are never shared: these electrons are always found around the more electronegative
atom. In sodium chloride (NaCl), for example, the bonding electron contributed by the
sodium atom is completely transferred to the chlorine atom. Even in solid crystals of NaCl,
the sodium and chlorine atoms are ionized, so it is more accurate to write the formula for the
compound as Na⁺Cl⁻.
Because the electrons are not shared, the bonds in such compounds cannot be considered covalent. They are, rather, ionic bonds (or interactions) that result from the attraction of a positively charged ion — a cation — for a negatively charged ion — an anion. Unlike covalent or hydrogen bonds, ionic bonds do not have fixed or specific geometric orientations because the electrostatic field around an ion — its attraction for an opposite charge — is uniform in all directions. However, crystals of salts such as Na$^+$Cl$^-$ do have very regular structures because that is the energetically most favorable way of packing together positive and negative ions. The force that stabilizes ionic crystals is called the lattice energy.

In aqueous solutions, simple ions of biological significance, such as Na$^+$, K$^+$, Ca$^{2+}$, Mg$^{2+}$, and Cl$^-$, do not exist as free, isolated entities. Instead, each is surrounded by a stable, tightly held shell of water molecules (Figure 2-14).

![Figure 2-14](image)

**Figure 2-14.** In aqueous solutions, a shell of water molecules surrounds ions. In the case of a magnesium ion (Mg$^{2+}$), six water molecules are held tightly in place by electrostatic interactions between the two positive charges on the ion and the partial negative charge on the oxygen of each water molecule.

An ionic interaction occurs between the ion and the oppositely charged end of the water dipole, as shown below for the K$^+$ ion:

![Ionic Interaction](image)

Ions play an important biological role when they pass through narrow, protein-lined pores, or channels, in membranes. For example, ionic movements through membranes are essential for the conduction of nerve impulses and for the stimulation of muscle contraction. As we will see in Chapter 21, ions must lose their shell of water molecules in order to pass through ion channel proteins; channel proteins can then selectively admit only Na$^+$, or K$^+$, or Ca$^{2+}$ ions, a selectivity essential for nerve function.
Most ionic compounds are quite soluble in water because a large amount of energy is released when ions tightly bind water molecules. This is known as the energy of hydration. Oppositely charged ions are shielded from one another by the water and tend not to recombine. Salts like Na\(^{+}\)Cl\(^{-}\) dissolve in water because the energy of hydration is greater than the lattice energy that stabilizes the crystal structure. In contrast, certain salts, such as Ca\(_3\)\((PO_4)_2\), are virtually insoluble in water; the large charges on the Ca\(^{2+}\) and PO\(_4^{3-}\) ions generate a formidable lattice energy that is greater than the energy of hydration.

Van der Waals Interactions Are Caused by Transient Dipoles

When any two atoms approach each other closely, they create a weak, nonspecific attractive force that produces a van der Waals interaction, named for Dutch physicist Johannes Diderik van der Waals (1837 – 1923), who first described it. These nonspecific interactions result from the momentary random fluctuations in the distribution of the electrons of any atom, which give rise to a transient unequal distribution of electrons, that is, a transient electric dipole. If two noncovalently bonded atoms are close enough together, the transient dipole in one atom will perturb the electron cloud of the other. This perturbation generates a transient dipole in the second atom, and the two dipoles will attract each other weakly. Similarly, a polar covalent bond in one molecule will attract an oppositely oriented dipole in another. [NOTE: These are usually called London forces, since van der Waals did not investigate them as far as I know.]

Van der Waals interactions, involving either transient induced or permanent electric dipoles, occur in all types of molecules, both polar and nonpolar. In particular, van der Waals interactions are responsible for the cohesion between molecules of nonpolar liquids and solids, such as heptane, \(CH_3-(CH_2)_5-CH_3\), that cannot form hydrogen bonds or ionic interactions with other molecules. When these stronger interactions are present, they override most of the influence of van der Waals interactions. Heptane, however, would be a gas if van der Waals interactions could not form.

The strength of van der Waals interactions decreases rapidly with increasing distance; thus these noncovalent bonds can form only when atoms are quite close to one another. However, if atoms get too close together, they become repelled by the negative charges in their outer electron shells. When the van der Waals attraction between two atoms exactly balances the repulsion between their two electron clouds, the atoms are said to be in van der Waals contact (Figure 2-15).
Figure 2-15. Two oxygen molecules in van der Waals contact. Transient dipoles in the electron clouds of all atoms give rise to weak attractive forces, called van der Waals interactions. Each type of atom has a characteristic van der Waals radius at which van der Waals interactions with other atoms are optimal. Because atoms repel one another if they are close enough together for their outer electron shells to overlap, the van der Waals radius is a measure of the size of the electron cloud surrounding an atom. The covalent radius indicated here is for the double bond of O=O; the single-bond covalent radius of oxygen is slightly longer.

Each type of atom has a van der Waals radius at which it is in van der Waals contact with other atoms. The van der Waals radius of an H atom is 0.1 nm, and the radii of O, N, C, and S atoms are between 0.14 and 0.18 nm. Two covalently bonded atoms are closer together than two atoms that are merely in van der Waals contact. For a van der Waals interaction, the internuclear distance is approximately the sum of the corresponding radii for the two participating atoms. Thus the distance between a C atom and an H atom in van der Waals contact is 0.27 nm, and between two C atoms is 0.34 nm. In general, the van der Waals radius of an atom is about twice as long as its covalent radius. For example, a C—H covalent bond is about 0.107 nm long and a C—C covalent bond is about 0.154 nm long.

The energy of the van der Waals interaction is about 1 kcal/mol, only slightly higher than the average thermal energy of molecules at 25 °C. Thus the van der Waals interaction is even weaker than the hydrogen bond, which typically has an energy of 1 – 2 kcal/mol in aqueous solutions. The attraction between two large molecules can be appreciable, however, if they have precisely complementary shapes, so that they make many van der Waals contacts when they come into proximity. Van der Waals interactions, as well as other noncovalent bonds, mediate the binding of many enzymes with their specific substrates (the substances on which an enzyme acts) and of each type of antibody with its specific antigen (Chapter 3).

**Hydrophobic Bonds Cause Nonpolar Molecules to Adhere to One Another**

Nonpolar molecules do not contain ions, possess a dipole moment, or become hydrated. Because such molecules are insoluble or almost insoluble in water, they are said to be hydrophobic (Greek, “water-fearing”). The covalent bonds between two carbon atoms and between carbon and hydrogen atoms are the most common nonpolar bonds in biological...
systems. Hydrocarbons — molecules made up only of carbon and hydrogen — are virtually insoluble in water. A large triacylglycerol (or triglyceride) such as tristearin, a component of animal fat, is also insoluble in water, even though its six oxygen atoms participate in some slightly polar bonds with adjacent carbon atoms (Figure 2-16). When shaken in water, tristearin forms a separate phase similar to the separation of oil from the water-based vinegar in an oil-and-vinegar salad dressing.

Figure 2-16. The chemical structure of tristearin, or tristearoyl glycerol, a component of natural fats. It contains three molecules of the fatty acid stearic acid, \( \text{CH}_3(\text{CH}_2)_{16}\text{COOH} \), esterified to one molecule of glycerol, \( \text{HOCH}_2\text{CH(OH)}\text{CH}_2\text{OH} \). One end of the molecule (green) is hydrophilic; the rest of the molecule is highly hydrophobic.

The force that causes hydrophobic molecules or nonpolar portions of molecules to aggregate together rather than to dissolve in water is called the hydrophobic bond. This is not a separate bonding force; rather, it is the result of the energy required to insert a nonpolar molecule into water. A nonpolar molecule cannot form hydrogen bonds with water molecules, so it distorts the usual water structure, forcing the water into a rigid cage of hydrogen-bonded molecules around it. Water molecules are normally in constant motion, and the formation of such cages restricts the motion of a number of water molecules; the effect is to increase the structural organization of water. This situation is energetically unfavorable because it decreases the randomness (entropy) of the population of water molecules. The role of entropy in chemical systems is discussed further in a later section.

The opposition of water molecules to having their motion restricted by forming cages around hydrophobic molecules or portions thereof is the major reason molecules such as tristearin and heptane are essentially insoluble in water and interact mainly with other hydrophobic molecules. Nonpolar molecules can also bond together, albeit weakly, through van der Waals interactions. The net result of the hydrophobic and van der Waals interactions is a very powerful tendency for hydrophobic molecules to interact with one another, and not with water.

Small hydrocarbons like butane \( (\text{CH}_3—\text{CH}_2—\text{CH}_2—\text{CH}_3) \) are somewhat soluble in water, because they can dissolve without disrupting the water lattice appreciably. However, 1-
butanol (CH$_3$—CH$_2$—CH$_2$—CH$_2$OH) mixes completely with water in all proportions. The replacement of just one hydrogen atom with the polar —OH group allows the molecule to form hydrogen bonds with water and greatly increases its solubility.

Simply put, *like dissolves like.* Polar molecules dissolve in polar solvents such as water, while nonpolar molecules dissolve in nonpolar solvents such as hexane.

**Multiple Noncovalent Bonds Can Confer Binding Specificity**

Besides contributing to the stability of large biological molecules, multiple noncovalent bonds can also confer *specificity* by determining how large molecules will fold or which regions of different molecules will bind together. All types of these weak interactions are effective only over a short range and require close contact between the reacting groups. For noncovalent bonds to form properly, there must be a complementarity between the sites on the two interacting surfaces. Figure 2-17 illustrates how several different weak bonds can bind two protein chains together. Almost any other arrangement of the same groups on the two surfaces would not allow the molecules to bind so tightly. Such multiple, specific interactions allow protein molecules to fold into a unique three-dimensional shape (Chapter 3) and the two chains of DNA to bind together (Chapter 4).

![Figure 2-17](image-url)

*Figure 2-17. The binding of a hypothetical pair of proteins by two ionic bonds, one hydrogen bond, and one large combination of hydrophobic and van der Waals interactions. The structural complementarity of the surfaces of the two molecules gives rise to this particular combination of weak bonds and hence to the specificity of binding between the molecules.*

**Phospholipids Are Amphipathic Molecules**

Multiple noncovalent bonds also are critical in stabilizing the structure of biomembranes, whose primary components are phospholipids. Because the essential properties of biomembranes derive from phospholipids, we first examine the chemistry of these
compounds and then see how they associate into the sheetlike structures that are the foundation of biomembranes.

All phospholipids contain one or more acyl chains derived from fatty acids, which consist of a hydrocarbon chain attached to a carboxyl group (—COOH). Fatty acids are insoluble in water and salt solutions; they differ in length and in the extent and position of their double bonds. Table 2-2 lists the principal fatty acids found in cells. Most fatty acids have an even number of carbon atoms, usually 16, 18, or 20.

Fatty acids with no double bonds are said to be saturated; those with at least one double bond are unsaturated. Unsaturated fatty acid chains normally have one double bond, but some have two, three, or four. Two stereoisomeric configurations, cis and trans, are possible around each double bond:

A cis double bond introduces a rigid kink in the otherwise flexible straight chain of a fatty acid (Figure 2-18). In general, the fatty acids in biological systems contain only cis double bonds.

Phospholipids consist of two long-chain fatty acyl groups linked (usually by an ester bond) to small, highly hydrophilic groups. Consequently, unlike tristearin, phospholipids do not clump together in droplets but orient themselves in sheets, exposing their hydrophilic ends

Figure 2-18. The effect of a double bond. Shown are space-filling models and chemical structures of the ionized form of palmitic acid, a saturated fatty acid, and oleic acid, an unsaturated one. In saturated fatty acids, the hydrocarbon chain is linear; the cis double bond in oleate creates a kink in the hydrocarbon chain.
to the aqueous environment. Molecules in which one end (the “head”) interacts with water and the other end (the “tail”) is hydrophobic are said to be amphipathic (Greek, “tolerant of both”). The tendency of amphipathic molecules to form organized structures spontaneously in water is the key to the structure of cell membranes.

In phosphoglycerides, a principal class of phospholipids, fatty acyl side chains are esterified to two of the three hydroxyl groups in glycerol

![Glycerol](image)

but the third hydroxyl group is esterified to phosphate. The simplest phospholipid, phosphatidic acid, contains only these components:

![Phosphatidic Acid](image)

where \(R_1\) and \(R_2\) are fatty acyl groups.

In most phospholipids, however, the phosphate group is also esterified to a hydroxyl group on another hydrophilic compound. In phosphatidylcholine, for example, choline is attached to the phosphate (Figure 2-19).
Figure 2-19. Phosphatidylcholine, a typical phosphoglyceride, has a hydrophobic tail and a hydrophilic head in which choline is linked to glycerol by phosphate. Either or both of the fatty acyl side chains in a phosphoglyceride may be saturated or unsaturated.

In other phosphoglycerides, the phosphate group is linked to other molecules, such as ethanolamine, the amino acid serine, or the sugar inositol. The negative charge on the phosphate as well as the charged groups or hydroxyl groups on the alcohol esterified to it interact strongly with water.
The Phospholipid Bilayer Forms the Basic Structure of All Biomembranes

When a suspension of phospholipids is mechanically dispersed in aqueous solution, they can assume three different forms: micelles, bilayer sheets, and liposomes (Figure 2-20).

Figure 2-19. Phosphatidylcholine, a typical phosphoglyceride, has a hydrophobic tail and a hydrophilic head in which choline is linked to glycerol by phosphate. Either or both of the fatty acyl side chains in a phosphoglyceride may be saturated or unsaturated.

The type of structure formed by a pure phospholipid or a mixture of phospholipids depends on the length of the fatty acyl chains and their degree of saturation, on the temperature, on the ionic composition of the aqueous medium, and on the mode of dispersal of the phospholipids in the solution. In all three forms, hydrophobic interactions cause the fatty acyl chains to aggregate and exclude water molecules from the “core.” Micelles are rarely formed from natural phosphoglycerides, whose fatty acyl chains generally are too bulky to fit into the interior of a micelle.

Under suitable conditions, phospholipids of the composition present in cells spontaneously form symmetric sheetlike structures, called phospholipid bilayers, that are two molecules thick. Each phospholipid layer in this lamellar structure is called a leaflet. The hydrocarbon side chains in each leaflet minimize contact with water by aligning themselves tightly together in the center of the bilayer, forming a hydrophobic core that is about 3 nm thick. The close packing of these hydrocarbon side chains is stabilized by van der Waals
interactions between them. Ionic and hydrogen bonds stabilize the interaction of the phospholipid polar head groups with each other and with water. At neutral pH, the polar head groups in some phospholipids (e.g., phosphatidylcholine) have no net electric charge, whereas the head groups in others have a net negative charge. Nonetheless, all phospholipids can pack together into the characteristic bilayer structure.

A phospholipid bilayer can be of almost unlimited size — from micrometers (µ) to millimeters (mm) in length or width — and can contain tens of millions of phospholipid molecules. Because of their hydrophobic core, bilayers are impermeable to salts, sugars, and most other small hydrophilic molecules. Like a phospholipid bilayer, all biological membranes have a hydrophobic core, and they all separate two aqueous solutions. The plasma membrane, for example, separates the interior of the cell from its surroundings. Similarly, the membranes that surround the organelles of eukaryotic cells separate one aqueous phase — the cell cytosol — from another — the interior of the organelle. Several types of evidence indicate that the phospholipid bilayer is the basic structural unit of nearly all biomembranes (Chapter 5). Associated with membrane phospholipids are various proteins that help confer unique properties on each type of membrane. We describe the general structure of membrane proteins and their association with the phospholipid bilayer in Chapter 3.

**SUMMARY**

- Noncovalent bonds determine the shape of many large biological molecules and stabilize complexes composed of two or more different molecules.
- There are four main types of noncovalent bonds in biological systems: hydrogen bonds, ionic bonds, van der Waals interactions, and hydrophobic bonds. The bond energies for these interactions range from about 1 to 5 kcal/mol.
- In a hydrogen bond, a hydrogen atom covalently bonded to an electronegative donor atom associates with an acceptor atom whose nonbonding electrons attract the hydrogen (see Figure 2-12). Hydrogen bonds among water molecules are largely responsible for the properties of both liquid water and the crystalline solid form (ice).
- Ionic bonds result from the electrostatic attraction between the positive and negative charges of ions. In aqueous solutions, all cations and anions are surrounded by a tightly bound shell of water molecules.
- The weak and relatively nonspecific van der Waals interactions are created whenever any two atoms approach each other closely (see Figure 2-15). They result from the attraction between transient dipoles associated with all molecules.
- Hydrophobic bonds occur between nonpolar molecules, such as hydrocarbons, in an aqueous environment. Hydrophobic bonds result mainly because aggregation of the hydrophobic molecules necessitates less organization of water into “cages” (and, hence, less reduction in entropy) than if many cages of water molecules had to surround individual hydrophobic molecules.
- Although any single noncovalent bond is quite weak, several such bonds between molecules or between the parts of one molecule can stabilize the threedimensional structures of proteins and nucleic acids and mediate specific binding interactions.
- Phospholipids, the main components of biomembranes, are amphipathic molecules (see Figure 2-19). Noncovalent bonds are responsible for organizing and stabilizing phospholipids into one of three structures in aqueous solution (see Figure 2-20).
Structural Complementarity Determines Biomolecular Interactions

Structural complementarity is the means of recognition in biomolecular interactions. The complicated and highly organized patterns of life depend upon the ability of biomolecules to recognize and interact with one another in very specific ways. Such interactions are fundamental to metabolism, growth, replication, and other vital processes. The interaction of one molecule with another, a protein with a metabolite, for example, can be most precise if the structure of one is complementary to the structure of the other, as in two connecting pieces of a puzzle or, in the more popular analogy for macromolecules and their ligands, a lock and its key (Figure 1.16).

This principle of structural complementarity is the very essence of biomolecular recognition. Structural complementarity is the significant clue to understanding the functional properties of biological systems. Biological systems from the macromolecular level to the cellular level operate via specific molecular recognition mechanisms based on structural complementarity: a protein recognizes its specific metabolite, a strand of DNA recognizes its complementary strand, sperm recognize an egg. All these interactions involve structural complementarity between molecules.

Notice that structural complementarity implies that the macromolecules have already evolved significantly (since the chance for such “fits” at random is ~ zero). Thus structural complementarity could not have been available to the earliest organisms.
Biomolecular Recognition Is Mediated by Weak Chemical Forces

The biomolecular recognition events that occur through structural complementarity are mediated by the weak chemical forces previously discussed. It is important to realize that, because these interactions are sufficiently weak, they are readily reversible. Consequently, biomolecular interactions tend to be transient; rigid, static lattices of biomolecules that might paralyze cellular activities are not formed. Instead, a dynamic interplay occurs between metabolites and macromolecules, hormones and receptors, and all the other participants instrumental to life processes. This interplay is initiated upon specific recognition between complementary molecules and ultimately culminates in unique physiological activities. Biological function is achieved through mechanisms based on structural complementarity and weak chemical interactions.

This principle of structural complementarity extends to higher interactions essential to the establishment of the living condition. For example, the formation of supramolecular complexes occurs because of recognition and interaction between their various macromolecular components, as governed by the weak forces formed between them. If a sufficient number of weak bonds can be formed, as in macromolecules complementary in structure to one another, larger structures assemble spontaneously. The tendency for nonpolar molecules and parts of molecules to come together through hydrophobic interactions also promotes the formation of supramolecular assemblies. Very complex subcellular structures are actually spontaneously formed in an assembly process that is driven by weak forces accumulated through structural complementarity.
Weak Forces Restrict Organisms to a Narrow Range of Environmental Conditions

The central role of weak forces in biomolecular interactions restricts living systems to a narrow range of physical conditions. Biological macromolecules are functionally active only within a narrow range of environmental conditions, such as temperature, ionic strength, and relative acidity. Extremes of these conditions disrupt the weak forces essential to maintaining the intricate structure of macromolecules. The loss of structural order in these complex macromolecules, so-called denaturation, is accompanied by loss of function (Figure 1.17).

![Denaturation and renaturation of the intricate structure of a protein.](image)

Figure 1.17 • Denaturation and renaturation of the intricate structure of a protein.

As a consequence, cells cannot tolerate reactions in which large amounts of energy are released. Nor can they generate a large energy burst to drive energy-requiring processes. Instead, such transformations take place via sequential series of chemical reactions whose overall effect achieves dramatic energy changes, even though any given reaction in the series proceeds with only modest input or release of energy (Figure 1.18).
Metabolism is the organized release or capture of small amounts of energy in processes whose overall change in energy is large. (a) For example, the combustion of glucose by cells is a major pathway of energy production, with the energy captured appearing as 30 to 38 equivalents of ATP, the principal energy-rich chemical of cells. The ten reactions of glycolysis, the nine reactions of the citric acid cycle, and the successive linked reactions of oxidative phosphorylation release the energy of glucose in a stepwise fashion and the small “packets” of energy appear in ATP. (b) Combustion of glucose in a bomb calorimeter results in an uncontrolled, explosive release of energy in its least useful form, heat.

These sequences of reactions are organized to provide for the release of useful energy to the cell from the breakdown of food or to take such energy and use it to drive the synthesis of biomolecules essential to the living state. Collectively, these reaction sequences constitute cellular metabolism—the ordered reaction pathways by which cellular chemistry proceeds and biological energy transformations are accomplished.

Enzymes The sensitivity of cellular constituents to environmental extremes places another constraint on the reactions of metabolism. The rate at which cellular reactions proceed is a very important factor in maintenance of the living state. However, the common ways chemists accelerate reactions are not available to cells; the temperature cannot be raised, acid or base cannot be added, the pressure cannot be elevated, and concentrations cannot be dramatically increased. Instead, biomolecular catalysts mediate cellular reactions. These catalysts, called enzymes, accelerate the reaction rates many orders of magnitude and, by selecting the substances undergoing reaction, determine the specific reaction taking place. Virtually every metabolic reaction is served by an enzyme whose sole biological purpose is to catalyze its specific reaction.
Carbonic anhydrase, a representative enzyme, and the reaction that it catalyzes. Dissolved carbon dioxide is slowly hydrated by water to form bicarbonate ion and H⁺: At 20°C, the rate constant for this uncatalyzed reaction, \( k_{uncat} \), is 0.03/sec. In the presence of the enzyme carbonic anhydrase, the rate constant for this reaction, \( k_{cat} \), is \( 10^6 \)/sec. Thus carbonic anhydrase accelerates the rate of this reaction \( 3.3 \times 10^7 \) times. Carbonic anhydrase is a 29-kD protein.

Metabolic Regulation Is Achieved by Controlling the Activity of Enzymes Thousands of reactions mediated by an equal number of enzymes are occurring at any given instant within the cell. Metabolism has many branch points, cycles, and interconnections, as a glance at a metabolic pathway map reveals (Figure 1.20).
All of these reactions, many of which are at apparent cross-purposes in the cell, must be fine-tuned and integrated so that metabolism and life proceed harmoniously. The need for metabolic regulation is obvious. This metabolic regulation is achieved through controls on enzyme activity so that the rates of cellular reactions are appropriate to cellular requirements.

Despite the organized pattern of metabolism and the thousands of enzymes required, cellular reactions nevertheless conform to the same thermodynamic principles that govern any chemical reaction. Enzymes have no influence over energy changes (the thermodynamic component) in their reactions. Enzymes only influence reaction rates. Thus, cells are systems that take in food, release waste, and carry out complex degradative and biosynthetic reactions essential to their survival while operating under conditions of essentially constant temperature and pressure and maintaining a constant internal environment (homeostasis) with no outwardly apparent changes. Cells are open thermodynamic systems exchanging matter and energy with their environment and functioning as highly regulated isothermal chemical engines.