Small Molecules, Energy, and Biosynthesis

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"I must tell you that I can prepare urea without requiring a kidney or an animal, either man or dog." This sentence, written 150 years ago by the young German chemist Wöhler, signaled an end to the belief in a special *vital force* that exists in living organisms and gives rise to their distinctive properties and products. But what was a revelation in Wöhler's time is common knowledge today—living creatures are made of chemicals. There is no room in the contemporary view of life for vitalism—or for anything else outside the laws of chemistry and physics. This is not to say that no mysteries remain in biology: there are many areas of ignorance, as will become apparent in later chapters. But we should begin by emphasizing the enormous amount that is known.

We now have detailed information about the essential molecules of the cell—not just a small number of molecules, but thousands of them. In many cases we know their precise chemical structures and exactly how they are made and broken down. We know in general terms how chemical energy drives the biosynthetic reactions of the cell, how thermodynamic principles operate in cells to create molecular order, and how the myriad intracellular chemical changes occurring continuously within them are controlled and coordinated.

In this and the next chapter we briefly survey the chemistry of the living cell. Here we deal with the processes involving small molecules: those mechanisms by which the cell synthesizes its fundamental chemical ingredients and by which it obtains its energy. Chapter 3 describes the giant molecules of the cell, which are polymers of small molecules and whose properties are responsible for the specificity of biological processes and the transfer of biological information.

The Chemical Components of a Cell

Cell Chemistry Is Based on Carbon Compounds[1]

A living cell is composed of a restricted set of elements, four of which (C, H, N, and O) make up nearly 99% of its weight. This composition differs markedly from that of the earth's crust and is evidence of a distinctive type of chemistry (Figure 2–1). What is this special chemistry, and how did it evolve?

The most abundant substance of the living cell is water. It accounts for about 70% of a cell's weight, and most intracellular reactions occur in an aqueous environment. Life on this planet began in the ocean, and the conditions in that

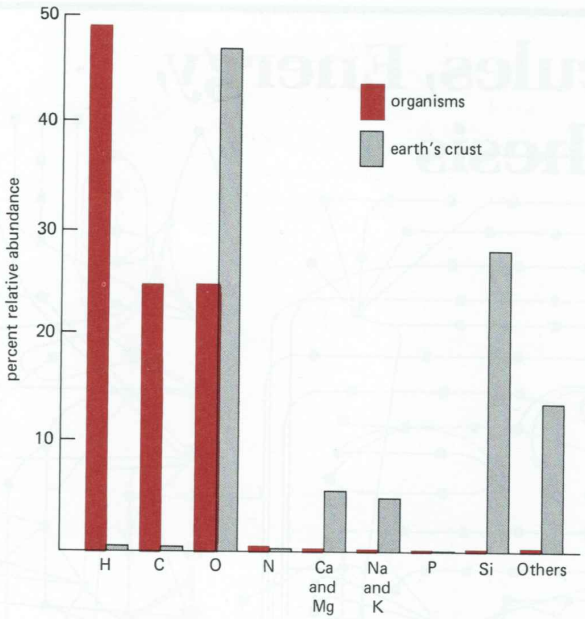


Figure 2–1 The relative abundance of chemical elements found in the earth's crust (the nonliving world) compared to that in the soft tissues of living organisms. The relative abundance is expressed as a percentage of the total *number* of atoms present. Thus, for example, nearly 50% of the atoms in living organisms are hydrogen atoms.

primeval environment put a permanent stamp on the chemistry of living things. All organisms have been designed around the special properties of water, such as its polar character, its ability to form hydrogen bonds, and its high surface tension. Some important properties of water are summarized in Panel 2–1 (pp. 46–47).

If we disregard water, nearly all of the molecules in a cell are carbon compounds, which are the subject matter of **organic chemistry.** Carbon is outstanding among all the elements on earth for its ability to form large molecules; silicon is a poor second. The carbon atom, because of its small size and four outer-shell electrons, can form four strong covalent bonds with other atoms. Most important, it can join to other carbon atoms to form chains and rings and thereby generate large and complex molecules with no obvious upper limit to their size. The other abundant atoms in the cell (H, N, and O) are also small and able to make very strong covalent bonds (Panel 2–2, pp. 48–49).

In principle, the simple rules of covalent bonding between carbon and other elements permit an infinitely large number of compounds. Although the number of different carbon compounds in a cell is very large, it is only a tiny subset of what is theoretically possible. In some cases we can point to good reasons why this compound or that performs a given biological function; more often it seems that the actual "choice" was one among many reasonable alternatives, and therefore something of an accident (Figure 2–2). Once established, certain chemical themes and patterns of reaction were preserved, with variations, during the course of evolution. Apparently the development of new classes of compounds was only rarely necessary or useful.

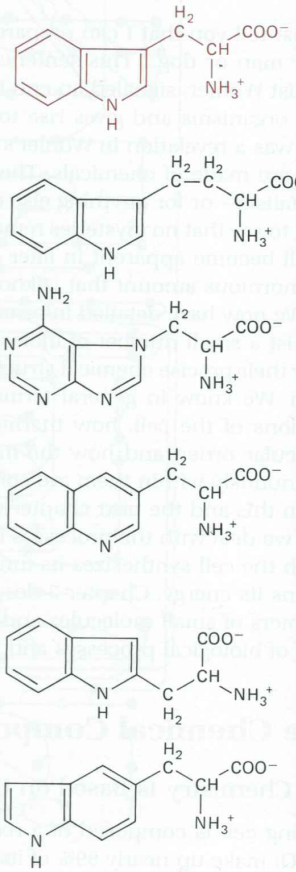


Figure 2–2 Living organisms synthesize only a small number of the organic molecules that they could in principle make. Of the six amino acids shown, only the top one (tryptophan) is made by cells.

Cells Use Four Basic Types of Small Molecules[2]

Certain simple combinations of atoms—such as the methyl (—CH_3), hydroxyl (—OH), carboxyl (—COOH), and amino (—NH_2) groups—recur repeatedly in biological molecules. Each such group has distinct chemical and physical properties that influence the behavior of whatever molecule the group occurs in. The main types of chemical groups and some of their salient properties are summarized in Panel 2–2 (pp. 48–49).

The **small organic molecules** of the cell are carbon compounds with molecular weights in the range 100 to 1000 and containing up to 30 or so carbon atoms. They are usually found free in solution in the cytoplasm, where some of them form a pool of intermediates from which large polymers, called **macro-**

Table 2–1 The Approximate Chemical Composition of a Bacterial Cell

	Percent of Total Cell Weight	Number of Types of Each Molecule
Water	70	1
Inorganic ions	1	20
Sugars and precursors	1	250
Amino acids and precursors	0.4	100
Nucleotides and precursors	0.4	100
Fatty acids and precursors	1	50
Other small molecules	0.2	~300
Macromolecules (proteins, nucleic acids, and polysaccharides)	26	~3000

molecules, are made. They are also essential intermediates in the chemical reactions that transform energy derived from food into usable forms (see below).

The small molecules amount to about one-tenth of the total organic matter in a cell, and (at a rough estimate) only on the order of a thousand different kinds are present (Table 2–1). All biological molecules are synthesized from and broken down to the same simple compounds, synthesis and breakdown occurring through sequences of chemical changes that are limited in scope and follow definite rules. As a consequence, the compounds in a cell are chemically related and can be classified into a small number of distinct families. Since the macromolecules in a cell, which form the subject of Chapter 3, are assembled from the same small molecules, they belong to the same families.

Broadly speaking, cells contain just four major families of small organic molecules: the simple **sugars,** the **fatty acids,** the **amino acids,** and the **nucleotides.** Each of these families contains many different members with common chemical features. Although some cellular compounds do not fit into these categories, the four families, together with the macromolecules made from them, account for a surprisingly large fraction of the cell mass (Table 2–1).

Sugars Are Food Molecules of the Cell[3]

The simplest sugars—the **monosaccharides**—are compounds with the general formula $(CH_2O)_n$, where n is an integer from 3 through 7. *Glucose,* for example, has the formula $C_6H_{12}O_6$ (Figure 2–3). As shown in Figure 2–3, sugars can exist in either a ring or an open-chain form. In their open-chain form, sugars contain a number of hydroxyl groups and either one aldehyde ($_H>C{=}O$) or one ketone ($>C{=}O$) group. The aldehyde or ketone group plays a special role. First, it can react with a hydroxyl group in the same molecule to convert the molecule into a ring; in the ring form, the carbon of the original aldehyde or ketone group can be recognized as the only one that is bonded to two oxygens. Second, once the ring is formed, this carbon can become further linked to one of the carbons bearing a hydroxyl group on *another* sugar molecule, creating a *disaccharide* (Panel 2–3, pp. 50–51). The addition of more monosaccharides in the same way results in **oligosaccharides** of increasing length (trisaccharides, tetrasaccharides, and so on) up to very large **polysaccharide** molecules with thousands of monosaccharide units (residues). Because each monosaccharide has several free hydroxyl groups that can form a link to another monosaccharide (or to some other compound), the number of possible polysaccharide structures is extremely large. Even a simple disaccharide consisting of two glucose residues can exist in 11 different varieties (Figure 2–4), while three different hexoses ($C_6H_{12}O_6$) can join together to make several thousand different trisaccharides. For this reason it is very difficult to determine the structure of any particular polysaccharide; with present methods it takes longer to determine the arrangement of half a dozen linked sugars (for example, those in a glycoprotein) than to determine the nucleotide sequence of a DNA molecule containing many thousands of nucleotides.

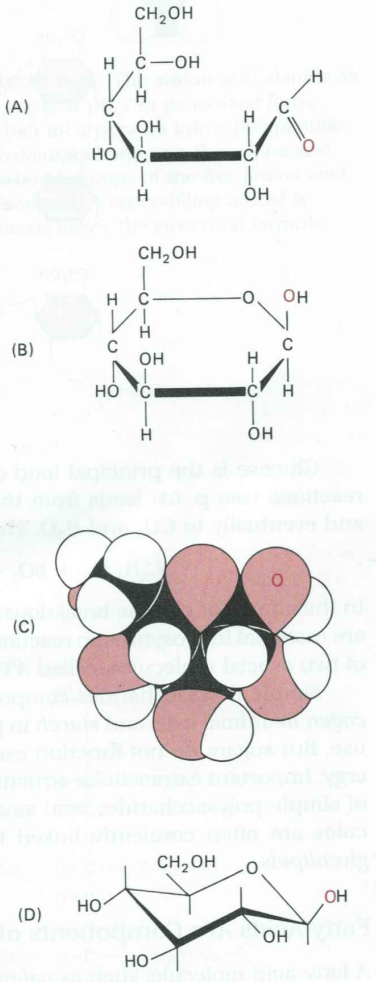


Figure 2–3 The structure of the monosaccharide glucose, a common hexose sugar. (A) The open-chain form of this sugar, which is in equilibrium with the more stable cyclic or ring form shown below it (B). (C) A space-filling model of this cyclic form (β-D-glucose). The chair form (D) is an alternative representation of the cyclic form that is frequently used instead of the cyclic form (B) because it more accurately reflects the structure. In all four representations, the colored O denotes the oxygen atom of the aldehyde group. For an outline of sugar structures and chemistry, see Panel 2–3 (pp. 50–51).

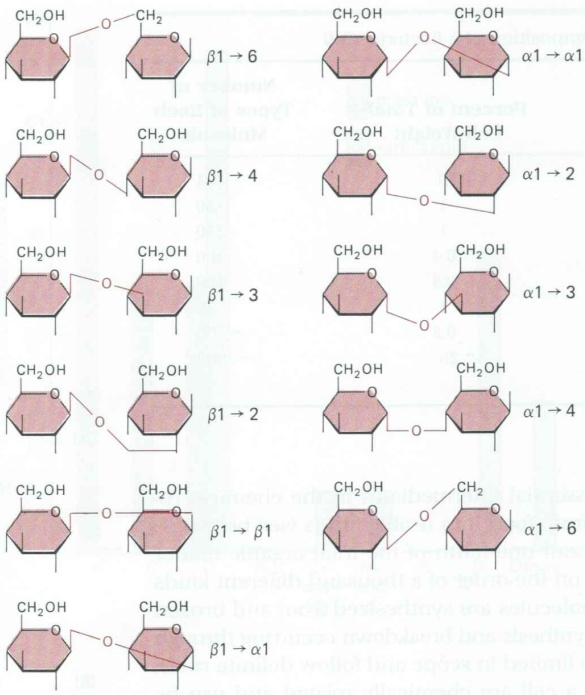


Figure 2–4 Eleven disaccharides consisting of two D-glucose units. Although these differ only in the type of linkage between the two glucose units, they are chemically distinct. Since the oligosaccharides associated with proteins and lipids may have six or more different kinds of sugar joined in both linear and branched arrangements through linkages such as those illustrated here, the number of possible distinct types of oligosaccharides is extremely large.

Glucose is the principal food compound of many cells. A series of oxidative reactions (see p. 61) leads from this hexose to various smaller sugar derivatives and eventually to CO_2 and H_2O. The net result can be written

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \text{energy}$$

In the course of glucose breakdown, energy and "reducing power," both of which are essential in biosynthetic reactions, are salvaged and stored, mainly in the form of two crucial molecules, called **ATP** and **NADH,** respectively (see p. 66).

Simple polysaccharides composed only of glucose residues—principally *glycogen* in animal cells and *starch* in plant cells—are used to store energy for future use. But sugars do not function exclusively in the production and storage of energy. Important extracellular structural materials (such as cellulose) are composed of simple polysaccharides, and smaller but more complex chains of sugar molecules are often covalently linked to proteins in *glycoproteins* and to lipids in *glycolipids*.

Fatty Acids Are Components of Cell Membranes[4]

A fatty acid molecule, such as *palmitic acid* (Figure 2–5), has two distinct regions: a long hydrocarbon chain, which is hydrophobic (water insoluble) and not very reactive chemically, and a carboxylic acid group, which is ionized in solution (COO^-), extremely hydrophilic (water soluble), and readily forms esters and amides. In fact, almost all of the fatty acid molecules in a cell are covalently linked to other molecules by their carboxylic acid group. The many different fatty acids found in cells differ in such chemical features as the length of their hydrocarbon chains and the number and position of the carbon-carbon double bonds they contain (Panel 2–4, pp. 52–53).

Fatty acids are a valuable source of food since they can be broken down to produce more than twice as much usable energy, weight for weight, as glucose. They are stored in the cytoplasm of many cells in the form of droplets of *triglyceride* molecules, which consist of three fatty acid chains, each joined to a glycerol molecule (Panel 2–4, pp. 52–53); these molecules are the animal fats familiar from

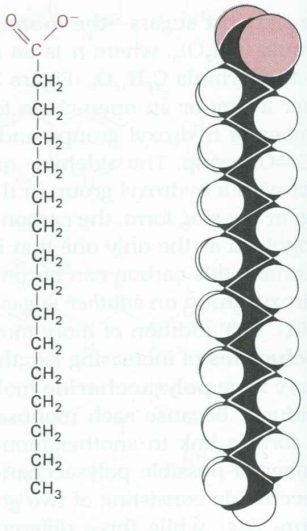


Figure 2–5 Palmitic acid. The carboxylic acid group *(color)* is shown in its ionized form. A space-filling model is presented on the right.

everyday experience. When required, the fatty acid chains can be released from triglycerides and broken down into two-carbon units. These two-carbon units, present as the acetyl group in a water-soluble molecule called *acetyl CoA*, are then further degraded in various energy-yielding reactions, which will be described below.

But the most important function of fatty acids is in the construction of cell membranes. These thin, impermeable sheets that enclose all cells and surround their internal organelles are composed largely of **phospholipids,** which are small molecules that resemble triglycerides in that they are constructed mostly from fatty acids and glycerol. However, in phospholipids the glycerol is joined to two rather than three fatty acid chains. The remaining site on the glycerol is coupled to a phosphate group, which is in turn attached to another small hydrophilic compound such as *ethanolamine*, *choline*, or *serine*.

Each phospholipid molecule, therefore, has a hydrophobic tail—composed of the two fatty acid chains—and a hydrophilic polar head group, where the phosphate is located. Thus phospholipid molecules are, in effect, detergents, and this is evident in their properties. A small amount of phospholipid will spread over the surface of water to form a *monolayer* of phospholipid molecules; in this thin film, the tail regions pack together very closely facing the air and the head groups are in contact with the water (Panel 2–4, pp. 52–53). Two such films can combine tail to tail to make a phospholipid sandwich, or **lipid bilayer,** which is the structural basis of all cell membranes.

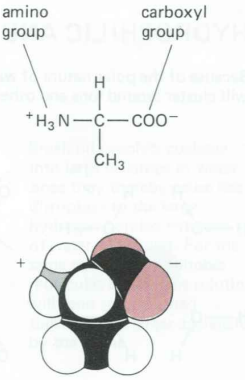


Figure 2–6 The amino acid alanine as it exists at pH 7 in its ionized form. When incorporated into a polypeptide chain, the charges on the amino and carboxyl groups of the free amino acid disappear. A space-filling model is shown below the structural formula.

Amino Acids Are the Subunits of Proteins

The common amino acids are chemically varied, but they all contain a carboxylic acid group and an amino group, both linked to a single carbon atom (Figure 2–6). They serve as subunits in the synthesis of **proteins,** which are long linear polymers of amino acids joined head to tail by a *peptide bond* between the carboxylic acid group of one amino acid and the amino group of the next (Figure 2–7). There are 20 common amino acids in proteins, each with a different *side chain* attached to the α-carbon atom (Panel 2–5, pp. 54–55). The same 20 amino acids occur over and over again in all proteins, including those made by bacteria, plants, and animals. Although the choice of precisely these 20 amino acids is probably an example of an evolutionary accident, the chemical versatility they provide is vitally important. For example, 5 of the 20 amino acids have side chains that can carry a charge (Figure 2–8), whereas the others are uncharged but reactive in specific ways (Panel 2–5, pp. 54–55). As we shall see, the properties of the amino acid side chains, in aggregate, determine the properties of the proteins they constitute and underlie all of the diverse and sophisticated functions of proteins.

Nucleotides Are the Subunits of DNA and RNA[5]

In nucleotides, one of several different nitrogen-containing ring compounds (often referred to as *bases* because they can combine with H^+ in acidic solutions) is linked to a five-carbon sugar (either *ribose* or *deoxyribose*) that carries a phosphate group. There is a strong family resemblance between the nitrogen-containing rings found in nucleotides. *Cytosine* (C), *thymine* (T), and *uracil* (U) are called **pyrimidine** compounds because they are all simple derivatives of a six-membered pyrimidine ring; *guanine* (G) and *adenine* (A) are **purine** compounds, with a second five-membered ring fused to the six-membered ring. Each nucleotide is named by reference to the unique base that it contains (Panel 2–6, pp. 56–57).

Nucleotides can act as carriers of chemical energy. The triphosphate ester of adenine, **ATP** (Figure 2–9), above all others, participates in the transfer of energy in hundreds of individual cellular reactions. Its terminal phosphate is added using energy from the oxidation of foodstuffs, and this phosphate can be readily split off by hydrolysis to release energy that drives energetically unfavorable biosynthetic reactions elsewhere in the cell. Other nucleotide derivatives serve as carriers for the transfer of particular chemical groups, such as hydrogen atoms or sugar residues, from one molecule to another. And a cyclic phosphate-containing ad-

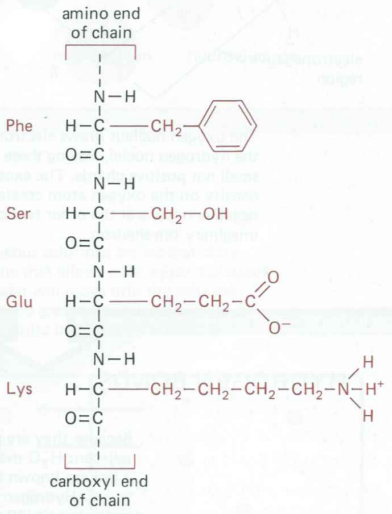
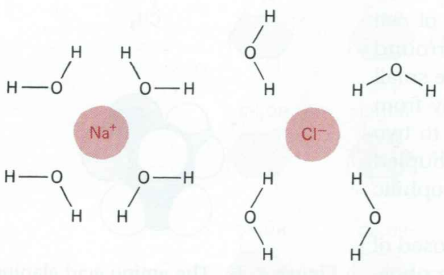
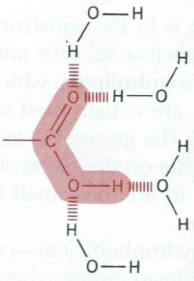


Figure 2–7 A small part of a protein molecule. The four amino acids shown are linked together by a type of covalent bond called a peptide bond. A protein is therefore also sometimes referred to as a polypeptide. The amino acid *side chains* are shown here in color.

HYDROPHILIC AND HYDROPHOBIC MOLECULES

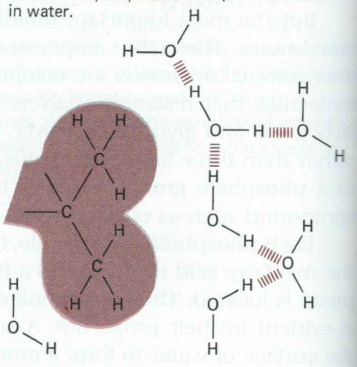
Because of the polar nature of water molecules, they will cluster around ions and other polar molecules.





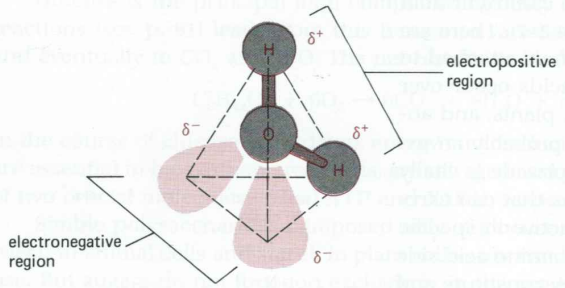
Molecules that can thereby be accommodated in water's hydrogen-bonded structures are hydrophilic and relatively water-soluble.

Nonpolar molecules interrupt the H-bonded structure of water without forming favorable interactions with water molecules. They are therefore hydrophobic and quite insoluble in water.



WATER

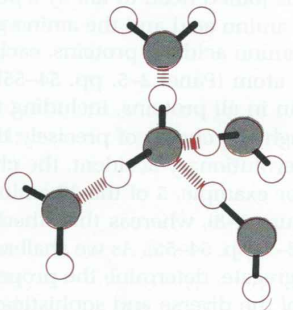
Although a water molecule has an overall neutral charge (having the same number of electrons and protons), the electrons are asymmetrically distributed, which makes the molecule polar.



The oxygen nucleus draws electrons away from the hydrogen nuclei, leaving these nuclei with a small net positive charge. The excess of electron density on the oxygen atom creates weakly negative regions at the other two corners of an imaginary tetrahedron.

WATER STRUCTURE

Molecules of water join together transiently in a hydrogen-bonded lattice. Even at 37°C, 15% of the water molecules are joined to four others in a short-lived assembly known as a "flickering cluster."

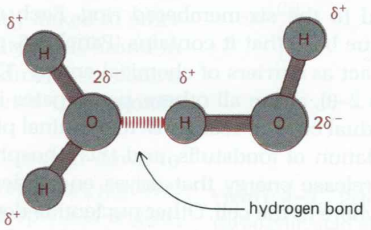


The cohesive nature of water is responsible for many of its unusual properties, such as high surface tension, specific heat, and heat of vaporization.

HYDROGEN BONDS

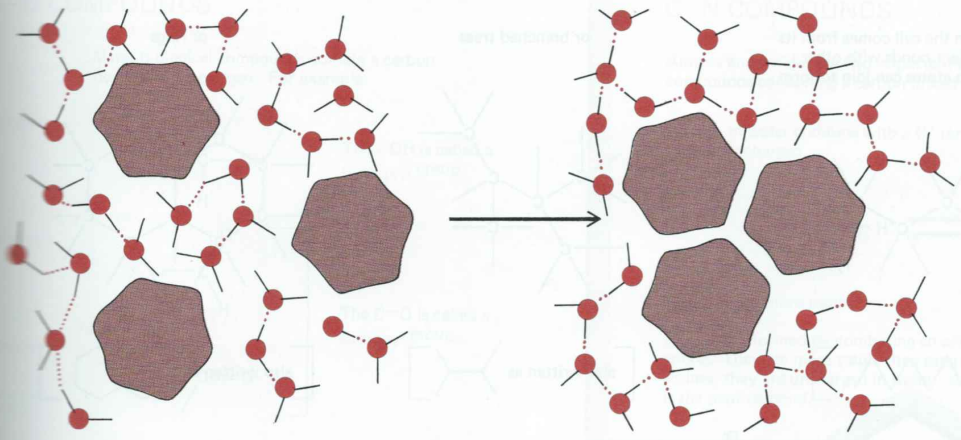
Because they are polarized, two adjacent H_2O molecules can form a linkage known as a hydrogen bond. Hydrogen bonds have only about 1/20 the strength of a covalent bond.

Hydrogen bonds are strongest when the three atoms lie in a straight line.



 Panel 2–1 The chemical properties of water and their influence on the behavior of biological molecules.

HYDROPHOBIC REPULSION CAN HOLD MOLECULES TOGETHER

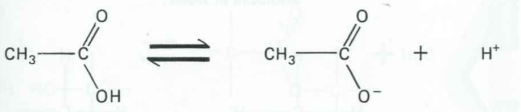


Small oil droplets coalesce into large oil drops in water since they thereby cause less disruption to the large hydrogen-bonded network of water molecules. For the same reason, hydrophobic molecules in aqueous solution will tend to be pushed together into larger aggregates by the water.

ACIDS AND BASES

An acid is a molecule that releases an H^+ ion (proton) in solution.

e.g.



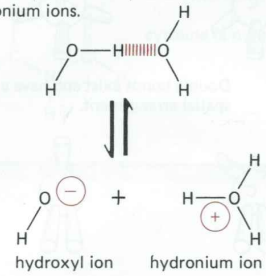
acid base proton

A base is a molecule that accepts an H^+ ion (proton) in solution.

e.g.

base proton acid

Water itself has a slight tendency to ionize and therefore can act as both a weak acid and as a weak base. When it acts as an acid, it releases a proton to form a hydroxyl ion. When it acts as a base, it accepts a proton to form a hydronium ion. Most protons in aqueous solutions exist as hydronium ions.



hydroxyl ion hydronium ion

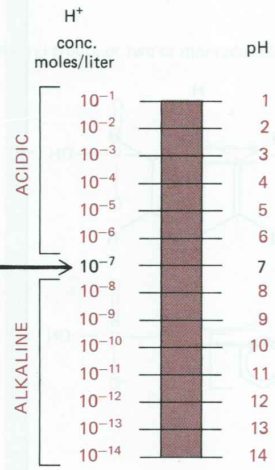
pH

The acidity of a solution is defined by the concentration of H^+ ions it possesses. For convenience we use the pH scale where

$pH = -\log_{10}[H^+]$

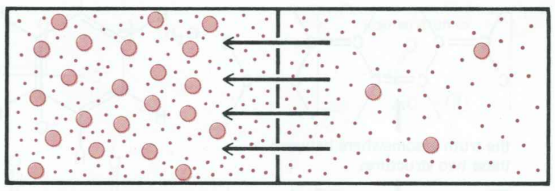
For pure water

$[H^+] = 10^{-7}$ moles/liter



OSMOSIS

If two aqueous solutions are separated by a membrane that allows only water molecules to pass, water will move into the solution containing the greatest concentration of solute molecules by a process known as osmosis.



This movement of water from a hypotonic to a hypertonic solution can cause an increase in hydrostatic pressure in the hypertonic compartment. Two solutions that have identical solute concentrations and are therefore osmotically balanced are said to be isotonic.