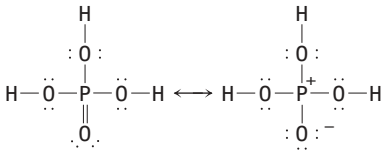
Electrons Are Shared Unequally in Polar Covalent Bonds

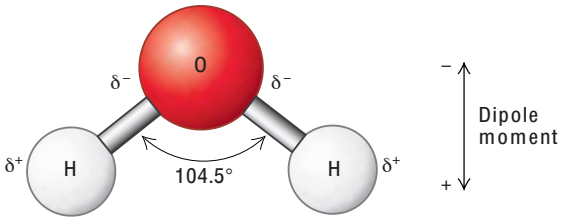
In many molecules, the bonded atoms exert different attractions for the electrons of the covalent bond, resulting in unequal sharing of the electrons. The extent of an atom's ability to attract an electron is called its **electronegativity**. A bond between atoms with identical or similar electronegativities is said to be **nonpolar**. In a nonpolar bond, the bonding electrons are essentially shared equally between the two atoms, as is the case for most C—C and C—H bonds. However, if two atoms differ in their electronegativities, the bond between them is said to be **polar**.

One end of a polar bond has a partial negative charge (δ^-), and the other end has a partial positive charge (δ^+). In an O—H bond, for example, the greater electronegativity of the oxygen atom relative to hydrogen results in the electrons spending more time around the oxygen atom than the hydrogen. Thus the O—H bond possesses an **electric dipole**, a positive charge separated from an equal but opposite negative charge. We can think of the oxygen atom of the O—H bond as having, on average, a charge of 25 percent of an electron, with the H atom having an equivalent positive charge. Because of its two O—H bonds, water molecules (H_2O) are dipoles that form electrostatic, noncovalent interactions with one another and with other molecules (Figure 2-3). These interactions play a critical role in almost every biochemical interaction and are thus fundamental to cell biology.

The polarity of the O═P double bond in H_3PO_4 results in a "resonance hybrid," a structure between the two forms shown below in which nonbonding electrons are shown as pairs of dots:



In the resonance hybrid on the right, one of the electrons from the P═O double bond has accumulated around the O atom, giving it a negative charge and leaving the P atom with a positive charge. These charges are important in noncovalent interactions.



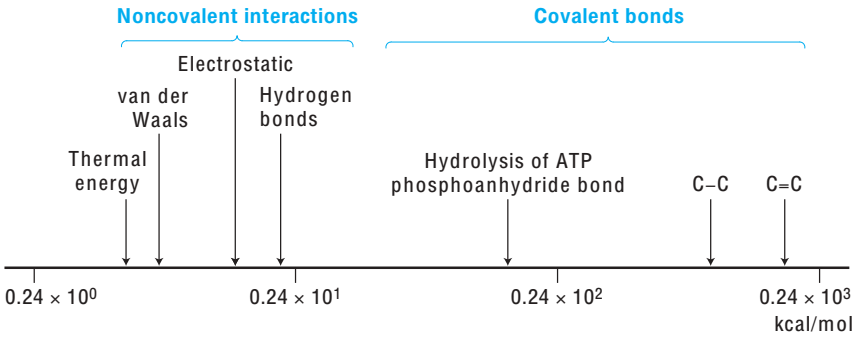
▲ **FIGURE 2-3 The dipole nature of a water molecule.** The symbol δ represents a partial charge (a weaker charge than the one on an electron or a proton). Because of the difference in the electronegativities of H and O, each of the polar H—O bonds in water has a dipole moment. The sizes and directions of the dipole moments of each of the bonds determine the net dipole moment of the molecule.

Covalent Bonds Are Much Stronger and More Stable Than Noncovalent Interactions

Covalent bonds are very stable because the energies required to break them are much greater than the thermal energy available at room temperature (25 °C) or body temperature (37 °C). For example, the thermal energy at 25 °C is approximately 0.6 kilocalorie per mole (kcal/mol), whereas the energy required to break the carbon-carbon single bond (C—C) in ethane is about 140 times larger (Figure 2-4). Consequently at room temperature (25 °C), fewer than 1 in 10^{12} ethane molecules is broken into a pair of $\cdot CH_3$ radicals, each containing an unpaired, nonbonding electron.

Covalent single bonds in biological molecules have energies similar to that of the C—C bond in ethane. Because more electrons are shared between atoms in double bonds, they require more energy to break than single bonds. For instance, it takes 84 kcal/mol to break a single C—O bond, but 170 kcal/mol to break a C═O double bond. The most common double bonds in biological molecules are C═O, C═N, C═C, and P═O.

The energy required to break noncovalent interactions is only 1–5 kcal/mol, much less than the bond energies of covalent bonds (see Figure 2-4). Indeed, noncovalent interactions are weak enough that they are constantly being



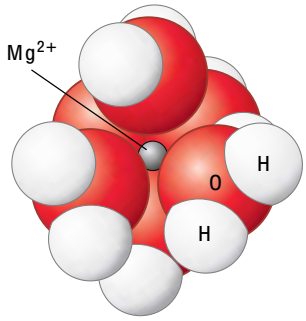
► **FIGURE 2-4 Relative energies of covalent bonds and noncovalent interactions.** Bond energies are determined as the energy required to break a particular type of linkage. Covalent bonds are one to two powers of 10 stronger than noncovalent interactions. The latter are somewhat greater than the thermal energy of the environment at normal room temperature (25 °C). Many biological processes are coupled to the energy released during hydrolysis of a phosphoanhydride bond in ATP.

formed and broken at room temperature. Although these interactions are weak and have a transient existence at physiological temperatures (25–37 °C), multiple noncovalent interactions can act together to produce highly stable and specific associations between different parts of a large molecule or between different macromolecules. We first review the four main types of noncovalent interactions and then consider their role in the binding of biomolecules to one another and to other molecules.

Ionic Interactions Are Attractions Between Oppositely Charged Ions

Ionic interactions result from the attraction of a positively charged ion—a **cation**—for a negatively charged ion—an **anion**. In sodium chloride (NaCl), for example, the bonding electron contributed by the sodium atom is completely transferred to the chlorine atom. Unlike covalent bonds, ionic interactions 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.

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 hydrated, surrounded by a stable shell of water molecules, which are held in place by ionic interactions between the central ion and the oppositely charged end of the water dipole (Figure 2-5). Most ionic compounds dissolve readily in water because the energy of hydration, the energy released when ions tightly bind water molecules, is greater than the lattice energy that stabilizes the crystal structure. Parts or all of the aqueous hydration shell must be removed from ions when they directly interact with proteins. For example, water of hydration is lost when ions pass through protein pores in the cell membrane during nerve conduction (Chapter 7).



▲ FIGURE 2-5 Electrostatic interaction between water and a magnesium ion (Mg^{2+}). Water molecules are held 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. In aqueous solutions, all ions are surrounded by a similar hydration shell.

The relative strength of the interaction between two ions, A^- and C^+, depends on the concentration of other ions in a solution. The higher the concentration of other ions (e.g., Na^+ and Cl^-), the more opportunities A^- and C^+ have to interact ionically with these other ions, and thus the lower the energy required to break the interaction between A^- and C^+. As a result, increasing the concentrations of salts such as NaCl in a solution of biological molecules can weaken and even disrupt the ionic interactions holding the biomolecules together.

Hydrogen Bonds Determine Water Solubility of Uncharged Molecules

A **hydrogen bond** is the interaction of a partially positively charged hydrogen atom in a molecular dipole (e.g., water) with unpaired electrons from another atom, either in the same (intramolecular) or in a different (intermolecular) molecule. Normally, a hydrogen atom forms a covalent bond with only one other atom. However, a hydrogen atom covalently bonded to an electronegative donor atom D may form an additional weak association, the hydrogen bond, with an acceptor atom A, which must have a nonbonding pair of electrons available for the interaction:

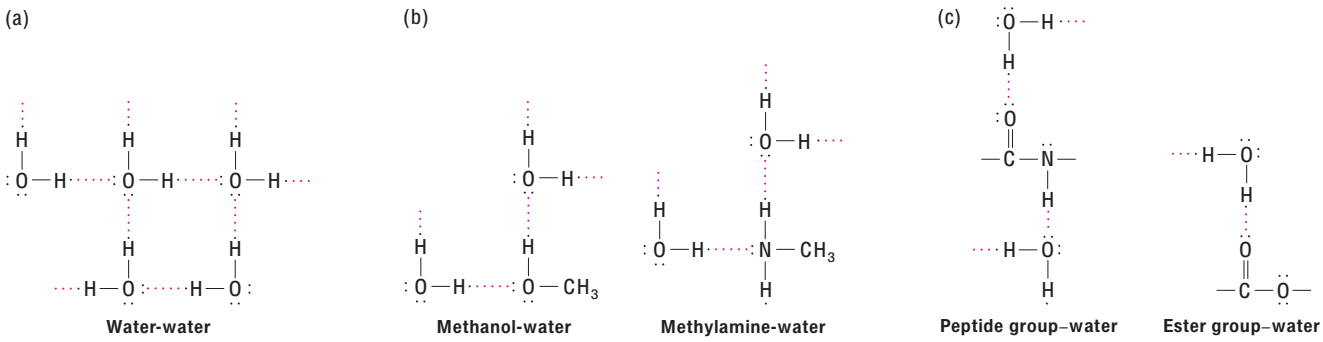
$$D^{\delta-}—H^{\delta+} + :A^{\delta-} \rightleftharpoons D^{\delta-}—H^{\delta+}\cdots\cdots:A^{\delta-}$$

Hydrogen bond

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. 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.

Hydrogen bonds are both longer and weaker than covalent bonds between the same atoms. In water, for example, the distance between the nuclei of the hydrogen and oxygen atoms of adjacent, hydrogen-bonded molecules is about 0.27 nm, about twice the length of the covalent O—H bonds within a single water molecule (Figure 2-6a). The strength of a hydrogen bond between water molecules (approximately 5 kcal/mol) is much weaker than a covalent O—H bond (roughly 110 kcal/mol), although it is greater than that for many other hydrogen bonds in biological molecules (1–2 kcal/mol). The extensive hydrogen bonding between water molecules accounts for many of the key properties of this compound, including its unusually high melting and boiling points and its ability to interact with many other molecules.

The solubility of uncharged substances in an aqueous environment depends largely on their ability to form hydrogen bonds with water. For instance, the hydroxyl group (—OH) in methanol (CH_3OH) and the amino group (—NH_2) in methylamine (CH_3NH_2) can form several hydrogen bonds with water, enabling these molecules to dissolve in water to



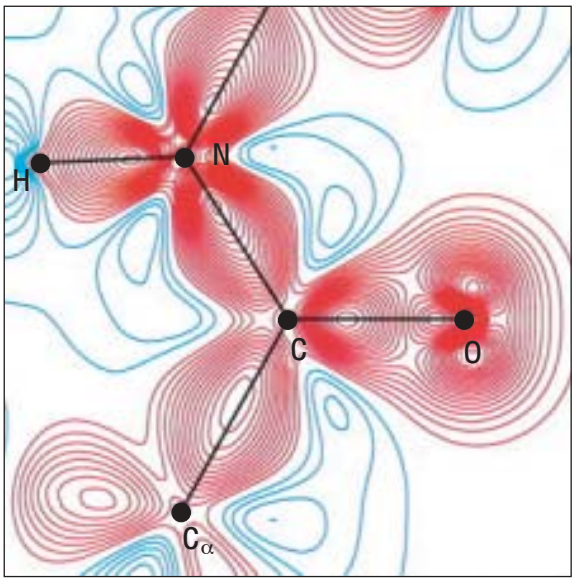
▲ FIGURE 2-6 Hydrogen bonding of water with itself and with other compounds. Each pair of nonbonding outer electrons in an oxygen or nitrogen atom can accept a hydrogen atom in a hydrogen bond. The hydroxyl and the amino groups can also form hydrogen bonds with water. (a) In liquid water, each water molecule apparently forms transient hydrogen bonds with several others, creating a dynamic network of hydrogen-bonded molecules. (b) Water also can form hydrogen bonds with methanol and methylamine, accounting for the high solubility of these compounds. (c) The peptide group and ester group, which are present in many biomolecules, commonly participate in hydrogen bonds with water or polar groups in other molecules.

high concentrations (Figure 2-6b). In general, molecules with polar bonds that easily form hydrogen bonds with water can readily dissolve in water; that is, they are hydrophilic. Many biological molecules contain, in addition to hydroxyl and amino groups, peptide and ester groups, which form hydrogen bonds with water (Figure 2-6c). X-ray crystallography combined with computational analysis permits an accurate depiction of the distribution of electrons in covalent bonds and the outermost unbonded electrons of atoms, as illustrated in Figure 2-7. These unbonded electrons can form hydrogen bonds with donor hydrogens.

Van der Waals Interactions Are Caused by Transient Dipoles

When any two atoms approach each other closely, they create a weak, nonspecific attractive force called a van der Waals interaction. 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. If two noncovalently bonded atoms are close enough together, electrons of one atom will perturb the electrons of the other. This perturbation generates a transient dipole in the second atom, and the two dipoles will attract each other weakly (Figure 2-8). Similarly, a polar covalent bond in one molecule will attract an oppositely oriented dipole in another.

Van der Waals interactions, involving either transiently 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. The strength of van der Waals interactions decreases rapidly with increasing distance; thus these noncovalent bonds can form only when



▲ FIGURE 2-7 Distribution of bonding and outer nonbonding electrons in the peptide group. Shown here is one amino acid within a protein called crambin. The black lines diagrammatically represent the covalent bonds between atoms. The red (negative) and blue (positive) lines represent contours of charge. The greater the number of contour lines, the higher the charge. The high density of red contour lines between atoms represents the covalent bonds (shared electron pairs). The two sets of red contour lines emanating from the oxygen (O) and not falling on a covalent bond (black line) represent the two pairs of nonbonded electrons on the oxygen that are available to participate in hydrogen bonding. The high density of blue contour lines near the hydrogen (H) bonded to nitrogen (N) represents a partial positive charge, indicating that this H can act as a donor in hydrogen bonding. [From C. Jelsch et al., 2000, *Proc. Nat'l. Acad. Sci.* USA **97:**3171. Courtesy of M. M. Teeter.]