



# 2

## Intermolecular Interactions

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### Goal

To understand the role of electrostatics in intermolecular interactions.

### Objectives

After this chapter, you should be able to

- distinguish between polar and nonpolar bonds.
- describe and draw diagrams of hydrogen bonds.
- distinguish between functional groups and molecules.
- describe how the functional groups within molecules facilitate intermolecular interactions.

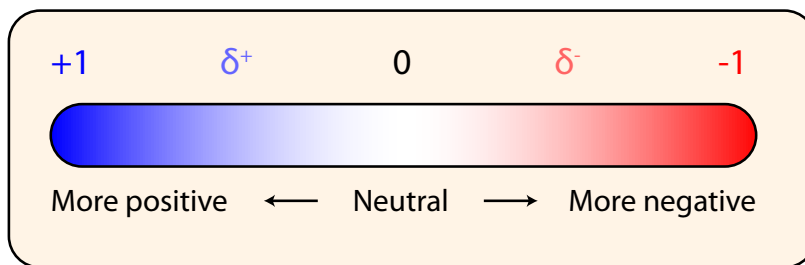
Molecules in the cell do not exist in isolation; instead, they are densely packed in an aqueous solution in which they interact both with water and with other molecules. These *intermolecular* interactions are generally weak compared to the covalent bonds that hold atoms together in molecules. Nonetheless, weak, and hence readily reversible, interactions mediate many of the fundamental processes of living things, such as the binding of an enzyme to its substrate, the formation of a multiprotein complex, or the interaction between DNA and the p53 protein that helps prevent cancer, which we introduced in the previous chapter. As we shall see in later chapters, weak interactions also dictate many *intramolecular* interactions, such as the folding of a polypeptide or a polynucleotide chain. Large numbers of small energy interactions can add up to significant energies and consequences.

### Intermolecular interactions are electrostatic

Intermolecular interactions are electrostatic, meaning that they result from the attraction between positive and negative charges. The strength of these attractions is dependent on the magnitude of the charges and the distance between the charged species. This dependency is described by Coulomb's law [ $F = k_e (q_1 q_2 / r^2)$ ], in which  $F$  is the electrostatic force between two charged species,  $q_1$  and  $q_2$  are the magnitudes of the charges,  $r$  is their distance from one another, and  $k_e$  is a constant. When applied to molecules in a cell, Coulomb's law reveals that the attractive force between molecules increases as the charge of either molecule increases and that it decreases

### Figure 1 Partial charges have a smaller magnitude than full charges

Full charges have a charge that is equal to the charge of a proton or an electron (depicted as +1 and -1, respectively). Partial charges are smaller than a full charge. Blue is a common convention for representing positive charges and red for representing negative charges.



as the distance between the two molecules increases. Thus, interactions involving large amounts of charge are stronger than those involving smaller amounts of charge. As we shall see, intermolecular interactions occur between fully charged, partially charged, and transiently charged atoms.

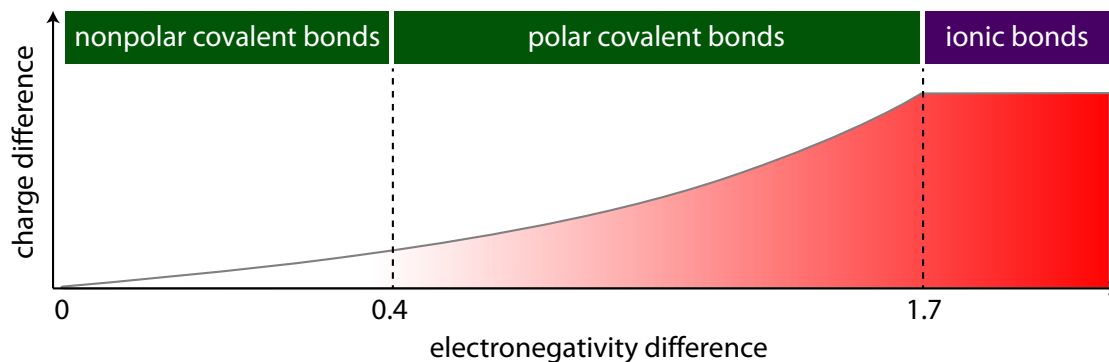
### The strongest interactions are between ions

**Ionic interactions** are attractive interactions that occur between oppositely charged ions, that is, atoms that carry a charge that is at least equal to the full charge of a proton or electron. Because ionic interactions involve the most charge, they are the strongest intermolecular interactions that occur in living systems. As an example, which we will reexamine in Chapter 8, the ability of proteins to bind to DNA is often enabled by favorable ionic interactions that form between the negatively charged phosphate groups in DNA and positively charged amino acid side chains in proteins. The strength of ionic interactions in the aqueous environment of the cell is mitigated by water, due to its high concentration and the polarity of water molecules, as we explain below.

### Covalent bonds in which atoms share electrons unequally are polar

Covalent bonds involve the sharing of electrons between two atoms, but those electrons are not always shared equally. As the electronegativity difference between atoms in a covalent bond increases, electron sharing becomes less even. When electrons are shared unequally, they are more likely to be found near one atom than the other. As a result, the more-electronegative atom to which electrons are more attracted will be slightly more negative than the other atom. Consequently, the less-electronegative atom will be somewhat positive. This arrangement, in which one atom in a covalent bond is slightly more negative and the other slightly more positive, creates a **dipole**. A bond in which electrons are shared unevenly is known as a **polar bond**. Much like the poles on a mini magnet, the atoms connected by a polar bond become positive and negative poles. The charge carried by an atom in a polar bond is smaller in magnitude than the full charge of a proton or electron, and it is therefore termed a **partial charge**. Partial charges are represented using the lowercase Greek letter delta,  $\delta$ , and partial-positive and partial-negative charges are expressed using the symbols  $\delta^+$  and  $\delta^-$ , respectively (Figure 1).

The electronegativity difference between atoms that are bonded to each other varies along a continuum. As we saw in Chapter 1, covalent bonds

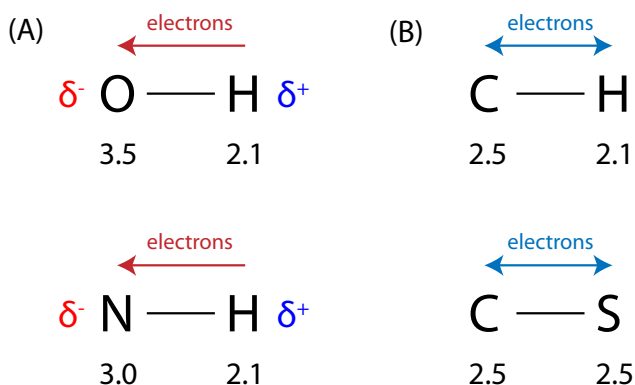


**Figure 2** The electronegativity differences between covalently bonded atoms fall along a continuum in which bonds with larger differences are more polar

As the electronegativity difference between bonded atoms increases (from left to right in the figure), the charge separation between the atoms increases, meaning that the bonds become more polar and the atoms carry greater charges. When the electronegativity difference is above 1.7, an electron has been transferred from one atom to the other, and the resulting ions form an ionic bond.

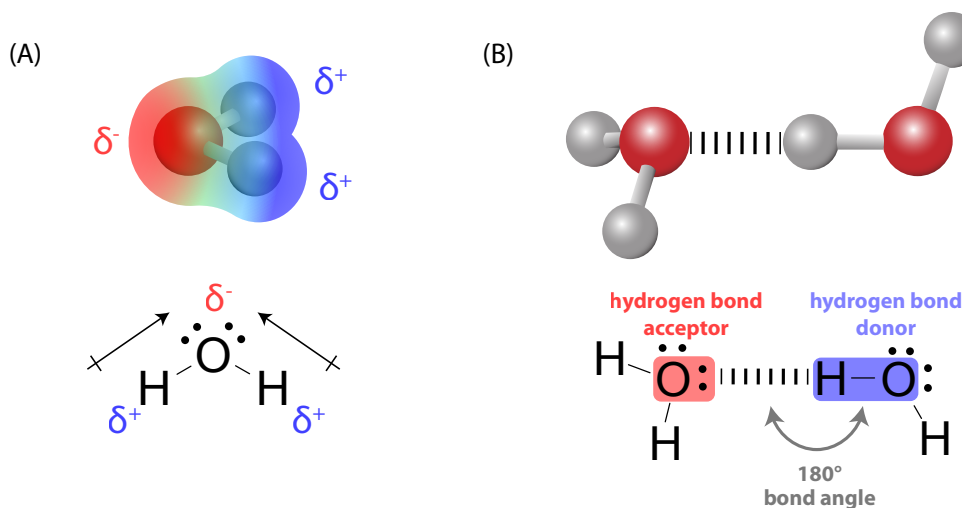
can form between atoms that have an electronegativity difference that is less than 1.7. In fact, if the difference is less than or equal to 0.4, then the bond is considered to be **nonpolar**, as the electrons are shared roughly equally. In a nonpolar bond, the atoms have little charge separation. If the difference is between 0.4 and 1.7, then the bond is polar, the electrons are shared unequally, and both atoms carry partial charges (Figures 2 and 3).

Now let's return to the issue of the effect of water on intermolecular interactions in the cell. Atoms that have charges can interact electrostatically with oppositely charged atoms in other molecules. For example, DNA is a polymeric macromolecule whose backbone is negatively charged due to the presence of phosphate groups. These negatively charged phosphates can form favorable electrostatic interactions with positively charged groups on proteins. The strength of these “ionic” (charge-charge) interactions would be huge if these molecules existed in isolation, but in the aqueous environment of the cell these ionic interactions are diminished by competition from water molecules. Water contains polar O-H bonds in which oxygen is partially negative and hydrogen is partially positive, and the charges carried by these atoms can form favorable interactions with charged molecules. Thus, in an aqueous environment, water molecules, which are at a very high



**Figure 3** Covalent bonds are polar when the electronegativity difference is  $> 0.4$  and nonpolar when it is  $\leq 0.4$

(A) The bonds between oxygen and hydrogen (O-H) and between nitrogen and hydrogen (N-H) are examples of polar bonds. Electronegativity values are listed under each atom. Because of the large electronegativity difference, electrons are attracted to the more-electronegative atom (*red arrows*), resulting in a partial-negative charge on the more-electronegative atom and a partial-positive charge on the less-electronegative atom. (B) The bonds between carbon and hydrogen (C-H) and between carbon and sulfur (C-S) are examples of nonpolar bonds. Because the electronegativity difference is so small, electrons are not attracted to one atom over the other (*blue arrows*), and as a result, no separation of charge occurs (i.e., the atoms do not carry partial charges).



**Figure 4** Water is a polar molecule that can both accept and donate hydrogen bonds

(A) Water contains two polar O-H bonds in which oxygen is partially negative (*red*) and hydrogen is partially positive (*blue*). The arrows in the line drawing indicate the orientation of the O-H dipole by pointing toward the more-electronegative atom. (B) Since it can both accept and donate hydrogen bonds, water can form hydrogen bonds to other water molecules. The hydrogen bond is shown as a black dashed line. This interaction occurs between the positive portion of one water molecule and the negative portion of a second water molecule. The oxygen atom that takes part in the hydrogen bond is the hydrogen bond acceptor (*boxed in red*). The hydrogen atom that takes part in the hydrogen bond and the oxygen to which it is covalently bound is the hydrogen bond donor (*boxed in blue*). Notice that the “O-H-O” bond angle is 180°.

concentration, compete with the formation of electrostatic interactions between proteins and DNA, in effect weakening the attraction between the macromolecules. Indeed, electrostatic interactions are much stronger in nonpolar solvents, where the charge-charge interaction is not attenuated by polar water molecules.

### Dipoles interact with other dipoles

Molecules that contain dipoles can also interact with one another, even if neither molecule is an ion. Such **dipole-dipole interactions** occur because of electrostatic attraction between the partially positive atom of one polar bond and the partially negative atom of another polar bond. **Hydrogen bonds (H-bonds)** are a specific type of dipole-dipole interaction that is particularly strong and especially common in living systems (Figure 4). We will have much more to say about hydrogen bonds in later chapters, where we will see that they lie at the heart of many kinds of interactions between the molecules of life, such as pairing between the bases in DNA and the binding of proteins to each other.

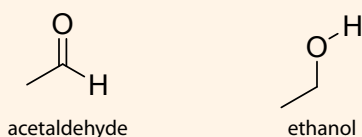
A hydrogen bond is an electrostatic attraction between a partially negative N or O atom and a partially positive hydrogen atom that is covalently bound to a different N or O atom. The partially negative N or O atom is known as the **hydrogen bond acceptor**, and it must have a free lone pair of electrons in order to participate in a hydrogen bond. The hydrogen atom and the more-electronegative atom to which it is covalently bound are collectively known as the **hydrogen bond donor**. Hydrogen atoms must be sufficiently positive in order to be hydrogen bond donors; this only occurs when hydrogen is bound to a highly electronegative atom like N or O.

Hydrogen bond strength does not depend exclusively on the magnitude of the charges involved and the distance between them, as Coulomb's law would predict; instead, there is a dependence on the bond angle between the hydrogen bond and the covalent bond linking the donor hydrogen to the electronegative atom of the donor. Hydrogen bonds are strongest when this bond angle is  $180^\circ$ , and their strength diminishes rapidly as the bond angle deviates from this ideal. The directional dependence of hydrogen

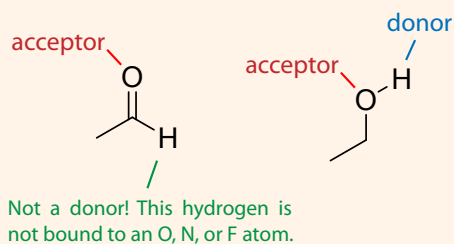
## Box 1 Drawing hydrogen bonds

Use a dashed line to draw a hydrogen bond between ethanol ( $\text{CH}_3\text{CH}_2\text{OH}$ ) and acetaldehyde ( $\text{CH}_3\text{CHO}$ ). Draw a box around the hydrogen bond donor and a circle around the hydrogen bond acceptor. The hydrogen bond should be drawn with an optimal hydrogen bond angle.

① Start by drawing the structures of the molecules.

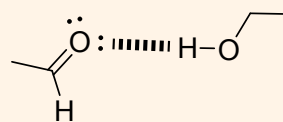


② Next, identify the hydrogen bond donors and acceptors in each molecule. Hydrogen bond donors contain a hydrogen atom covalently bound to an electronegative atom (O, N, or F). Hydrogen bond acceptors are partially negative electronegative atoms (O, N, or F) that have a free lone pair.

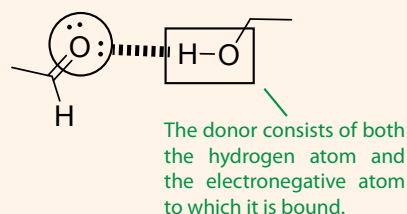


③ Next we need to determine the donor and acceptor for the hydrogen bond we will draw. Since acetaldehyde *only* contains an H-bond acceptor, it must be the hydrogen bond acceptor. Consequently, ethanol must be the H-bond donor since it is the only molecule here that contains an H-bond donor.

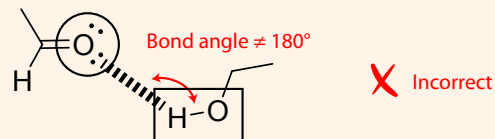
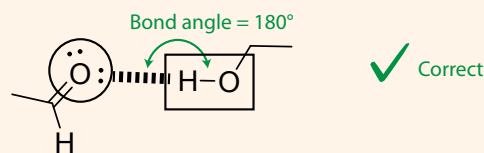
④ Now draw the hydrogen bond.



⑤ Draw a box around the hydrogen bond donor and a circle around the hydrogen bond acceptor.

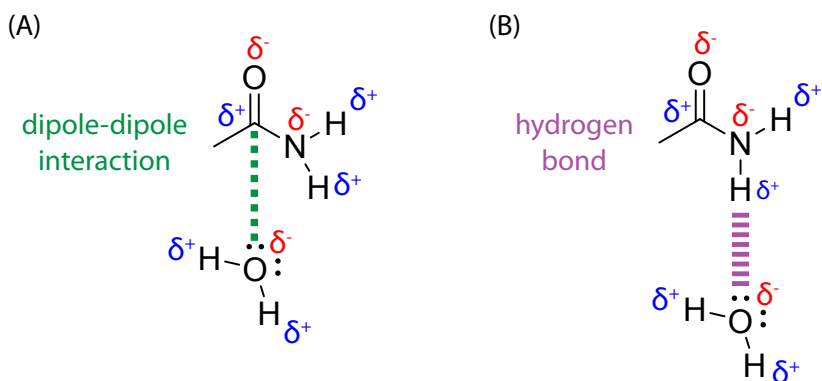


⑥ Check for mistakes. The most common mistake is to draw the hydrogen bond without an optimal bond angle.



### Figure 5 Hydrogen bonds are stronger than other dipole-dipole interactions

Acetamide ( $\text{CH}_3\text{CONH}_2$ ), shown here as an example, can form several different interactions with water, including the dipole-dipole interaction shown in (A) and the hydrogen bond shown in (B). The hydrogen bond (0.2-10 kcal/mol) is approximately 10 times stronger the dipole-dipole interaction (0.02-1 kcal/mol).



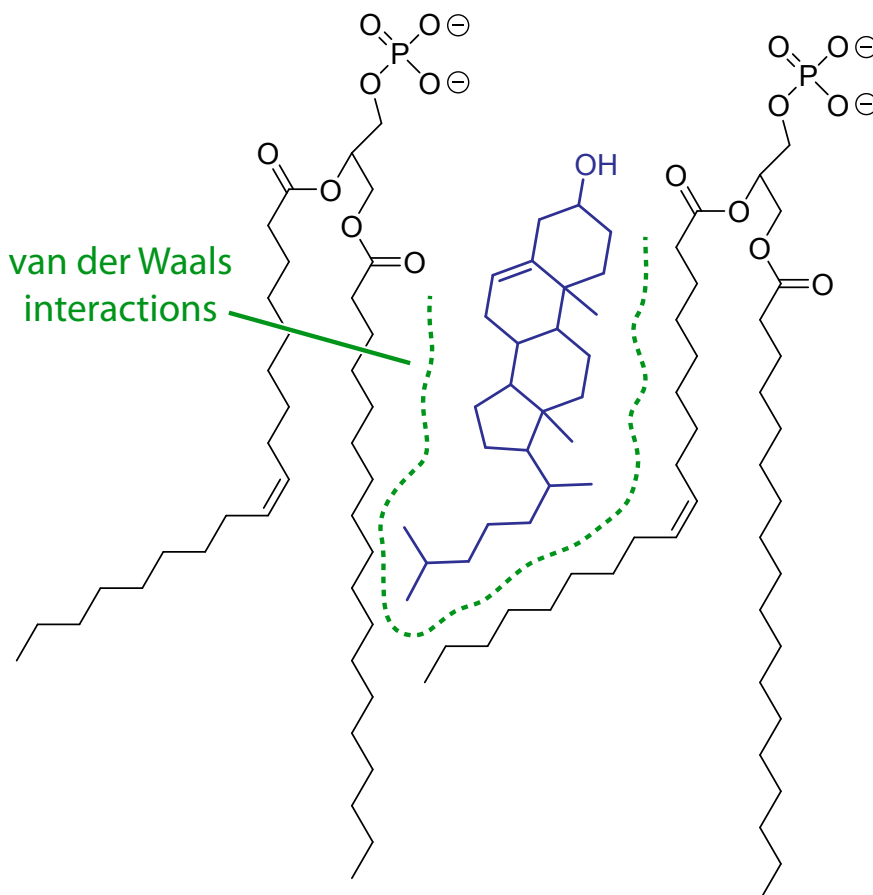
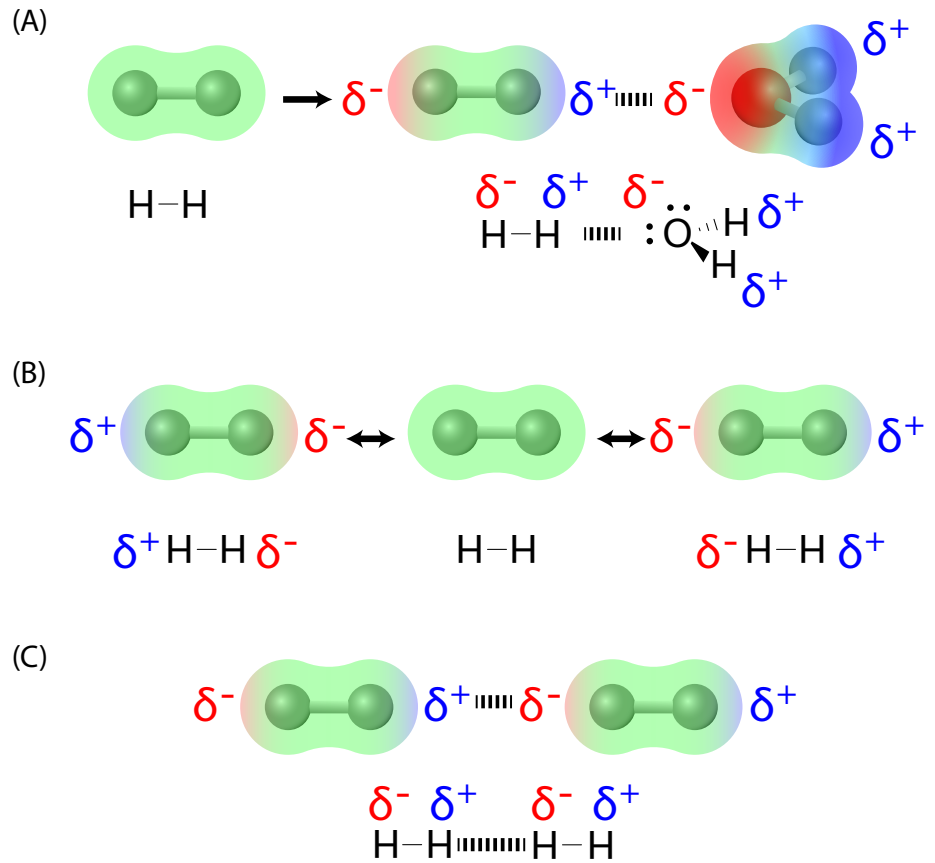
bonds exists because these interactions are partially covalent in character, meaning that they involve some slight sharing of electrons between the electronegative acceptor atom and the donor hydrogen. This type of electron sharing is only possible when the orbitals of the two interacting atoms overlap, which only occurs within certain directional constraints. The partially covalent character of hydrogen bonds is the reason why these interactions are stronger than other dipole-dipole interactions. The strength of hydrogen bonds typically ranges from 0.2 to 10 kcal/mol, whereas other dipole-dipole interactions are roughly a tenth as strong, ranging from 0.02 to 1 kcal/mol (Figure 5). While hydrogen bonds are an order of magnitude weaker than covalent bonds, they nevertheless play a central role in the molecules of life. Indeed, the solvent of living systems, water, has many properties that arise from its ability to form extensive networks of hydrogen bonds with other water molecules.

### Instantaneous dipoles facilitate interactions between nonpolar molecules

Even molecules that are uncharged and contain only nonpolar bonds can interact electrostatically. Although the covalent bonds in a molecule may be nonpolar, dipoles can develop transiently when electrons in a nonpolar bond become unevenly distributed due to the random motion of electrons. These transient dipoles, which exist only for an instant, are referred to as **instantaneous dipoles**. Instantaneous dipoles can be induced when a nonpolar bond comes into close contact with a polar bond or charged atom (Figure 6); such dipoles are called induced dipoles. Dipoles can also be induced when a nonpolar bond comes into close contact with another nonpolar bond that has instantaneously formed a dipole. The electrostatic attractions between instantaneous dipoles are known as **van der Waals forces**. Due to the transient nature of instantaneous dipoles, van der Waals forces are much weaker than dipole-dipole interactions. Even though these interactions are weak when considered individually, the cumulative effect of many such interactions and the fact that van der Waals forces are not directional, make it possible for large, nonpolar surfaces to adhere to each other effectively (Figure 7).

### Figure 6 Instantaneous dipoles enable interactions involving atoms in nonpolar bonds

(A) Polar bonds and ions can induce the formation of instantaneous dipoles in nonpolar bonds. Shown is a water molecule interacting with a hydrogen gas ( $H_2$ ) molecule. The partial-negative charge carried by the oxygen repels the electrons in the H-H bond, inducing a dipole in the  $H_2$  molecule. The induced dipole of  $H_2$  and the dipole of water are subsequently attracted to each other. (B) Instantaneous dipoles can form spontaneously in nonpolar molecules like  $H_2$ .  $H_2$  contains a nonpolar H-H bond in which electrons are shared equally on average; however, at any given time, this bond can be transiently polarized due to the random motion of electrons.  $H_2$  molecules can interconvert between nonpolar (*center*) and instantaneously polarized states (*left and right*) in which the hydrogen atoms carry small amounts of charge. (C) Instantaneous dipoles can induce the formation of instantaneous dipoles in other nonpolar bonds, which subsequently attract one another. Colors indicate charge: negative, red; positive, blue; neutral, green.

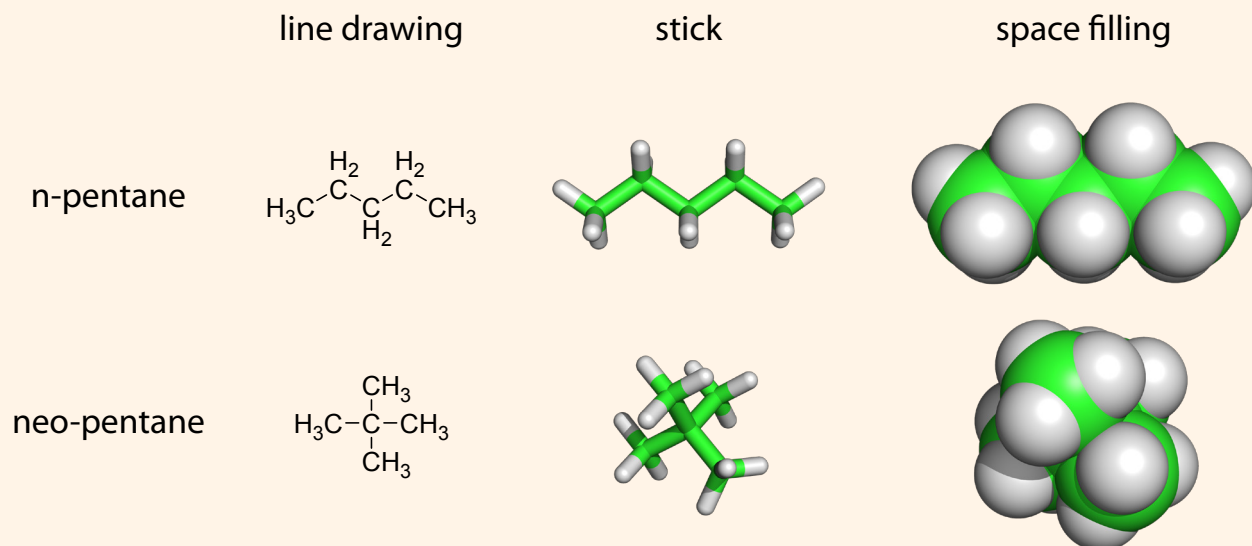


### Figure 7 Van der Waals forces are individually weak but collectively strong

Molecules containing only nonpolar bonds can interact with each other via van der Waals interactions. These interactions are individually weak, but they are collectively significant when they occur over large surfaces. Shown is a molecule of cholesterol (*dark blue*) forming extensive van der Waals interactions (*green*) with lipids in a membrane. The interactions shown here result from attractions between instantaneous dipoles that occur within the nonpolar carbon-hydrogen bonds of each molecule. As we will see in later chapters, van der Waals interactions help to stabilize biological membranes.

**Breakout**

Shown below are the structures of two molecules, both of which contain the same number of carbon and hydrogen atoms.



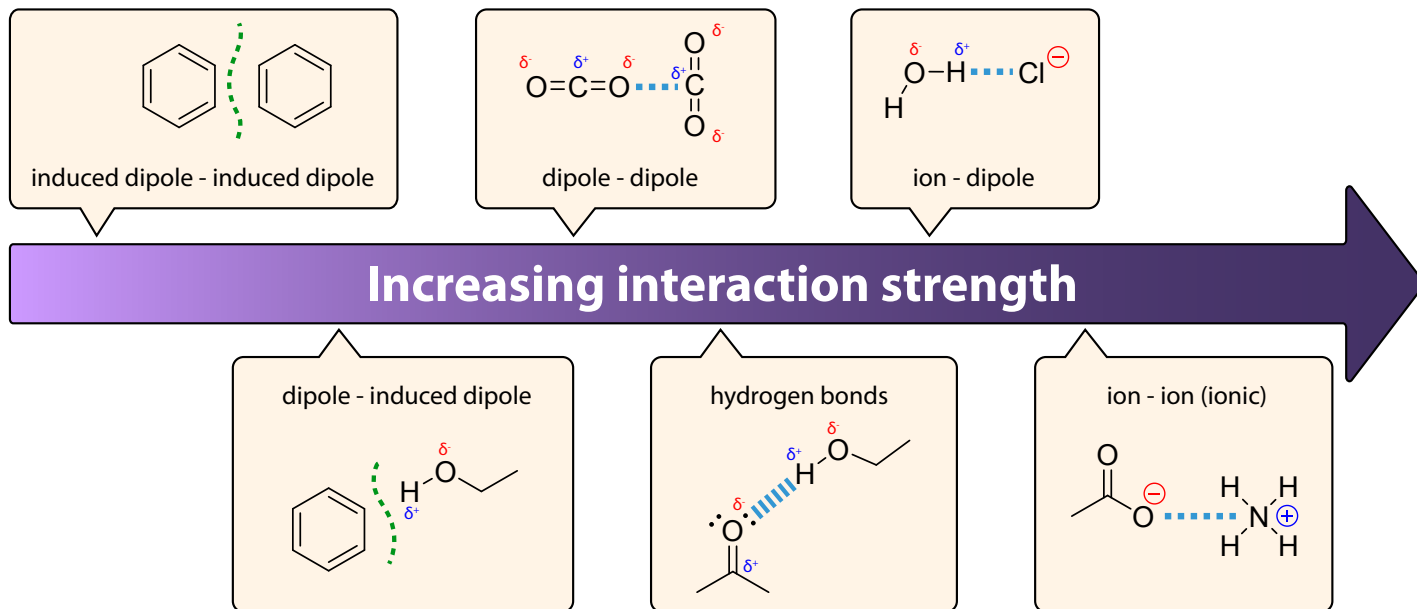
Based on the structures of these molecules, which of the following statements is true?

- (A) The boiling point of n-pentane is lower than the boiling point of neo-pentane.
- (B) The boiling point of n-pentane is higher than the boiling point of neo-pentane.
- (C) N-pentane and neo-pentane have almost the same boiling point.

### The strongest intermolecular interactions involve the most charge

Intermolecular interactions can form between ions, between atoms in polar bonds, and between atoms in nonpolar bonds. All of these atoms contain charges that can facilitate interaction with any other category of atom. Ions contain full charges due to the loss or gain of a proton or electron, and since they contain more charge than any other atom, they form the strongest intermolecular interactions. Atoms involved in polar bonds carry partial charges. Because partial charges have smaller magnitudes than full charges, intermolecular interactions involving atoms in polar bonds are generally weaker than interactions made by atoms with full charges. Nonpolar molecules do not contain polar bonds; therefore, they do not contain permanent dipoles. Instead, the bonds within nonpolar molecules can transiently polarize, and the resulting instantaneous dipoles can interact, forming van der Waals interactions with other molecules. Because instantaneous dipoles are transient, interactions involving them are much weaker than interactions involving permanent dipoles or ions. Taken together, intermolecular interactions generally form a continuum from strongest to weakest as follows: ionic interactions, ion-dipole interactions, hydrogen bonds, dipole-dipole interactions, dipole-induced dipole interactions, and induced dipole-induced dipole interactions (van





**Figure 8** The strength of an intermolecular interaction depends on the amount of charge that is involved

The strength of an intermolecular interaction is principally dependent upon the amount of charge that is involved. Consequently, ionic interactions, which involve the most charge, are the strongest. In contrast, induced dipole interactions involve very small partial charges, making them weakest among intermolecular interactions. Other intermolecular interactions exist along a continuum between these two extremes.

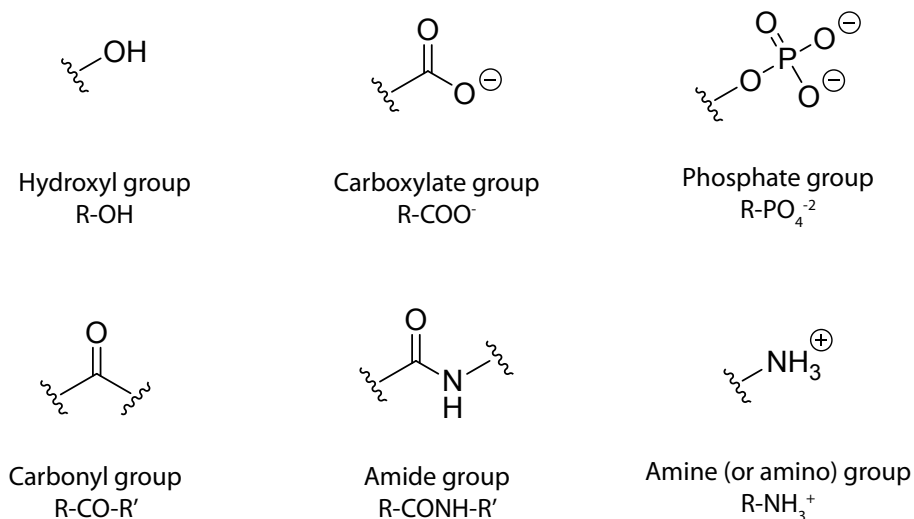
der Waals interactions) (Figure 8). Ion-induced dipole interactions cannot be unambiguously placed along this continuum, as their strengths vary, but they are generally stronger than dipole-induced dipole interactions and weaker than dipole-dipole interactions.

### Functional groups are groups of atoms that are associated with particular chemical properties

Molecules vary greatly in size and in the numbers and kinds of interactions that they make with other molecules. Individual interactions are mediated by groups of atoms known as **functional groups**. A functional group is a group of atoms and/or bonds within a larger molecule that exhibits a particular chemical property and/or reactivity. Proteins, which are composed of thousands of atoms, display hundreds of functional groups.

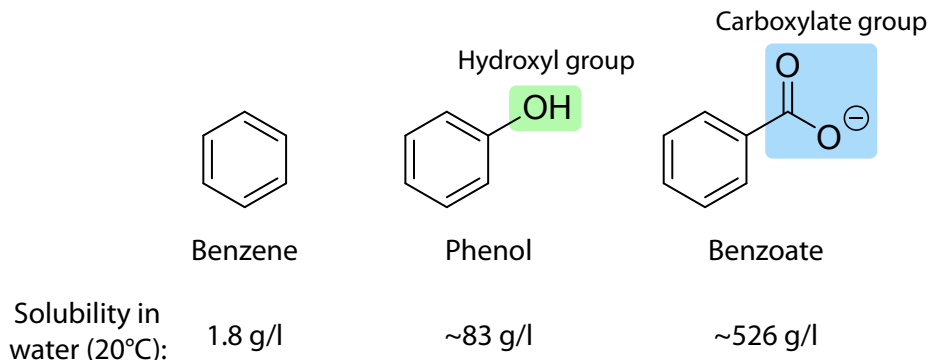
**Figure 9** Functional groups commonly found in biological molecules

Shown are examples of functional groups that are frequently found in biological molecules. The squiggly line (also known as “spinach”) in each structure indicates where that functional group attaches to the remainder of the larger molecule. The letter “R” in the molecular formula is a generic placeholder for the remainder of the larger molecule. Structures are drawn as they predominantly exist at physiological pH, a topic we come to in the next chapter.



**Figure 10 Functional groups affect the properties of molecules and the intermolecular interactions they form**

The molecules benzene, phenol, and benzoate are related structures that contain different functional groups. Benzene dissolves poorly in water, meaning that it forms very weak intermolecular interactions with water. Solubility in water is greatly enhanced when a hydroxyl group or a carboxylate group is added to benzene, as in phenol and benzoate, respectively. The hydroxyl and carboxylate groups enhance solubility by enabling stronger, more numerous interactions with water.



Functional groups are often classified by their properties; for example, they can be polar, nonpolar, positively charged, negatively charged, or neutral. Figure 9 lists a few of the functional groups that are important in biological systems.

The functional groups present in a molecule govern the intermolecular interactions it can form. For example, benzene ( $C_6H_6$ ) contains only nonpolar bonds that interact weakly with water (via dipole-induced dipole interactions). As one might expect, benzene does not dissolve in water as readily as benzoate ( $C_6H_5COO^-$ ), which is identical to benzene except that it carries a negatively charged carboxylate group (Figure 10). The higher solubility of benzoate owes to the favorable ion-dipole interactions that the carboxylate group makes with water molecules.

### Summary

All intermolecular interactions are electrostatic, meaning that they result from the attraction of opposite charges. The strength of such interactions increases with charge. Ions have the most charge, and as a result, the interactions that form between oppositely charged ions are the strongest intermolecular interactions. Next strongest are interactions between molecules that contain polar bonds. Polar bonds are covalent bonds in which electrons are shared unequally, such that the more-electronegative atom carries a partial-negative charge and the less-electronegative atom carries a partial-positive charge. This arrangement, in which positive and negative charges are separated between the atoms, is known as a dipole. Atoms in polar bonds can interact with atoms in other polar bonds via the partial charges they carry.

Hydrogen bonds are a particularly strong type of dipole-dipole interaction. They can form between a partially negative N or O atom with a lone pair and a partially positive hydrogen atom that is covalently attached to an electronegative N or O atom. Hydrogen bonds are approximately 10 times stronger than ordinary dipole-dipole interactions because they involve some sharing of electrons (i.e., they have a partially covalent character).

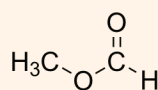
Electron sharing can only occur, however, when the atoms that form the hydrogen bond are precisely oriented. The optimal bond angle about the hydrogen atom is  $180^\circ$ , and the strength of the hydrogen bond diminishes as the bond angle deviates from this ideal. The hydrogen involved in the hydrogen bond and the electronegative atom to which it is covalently bound are together known as the hydrogen bond donor. The electronegative atom that bears the lone pair is known as the hydrogen bond acceptor.

Molecules can also interact with each other through atoms in nonpolar bonds. These interactions are mediated by instantaneous dipoles that are formed by the random motion of electrons. Such dipoles can also be induced by the presence of an ion or dipole. In such cases, the charge of the ion/dipole repels or attracts electrons in the nonpolar bond, causing the bond to temporarily polarize. Because they involve very small amounts of charge, interactions between transient dipoles, known as van der Waals interactions, are weak; however, these interactions can collectively be significant over large surface areas.

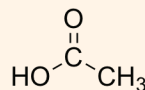
Finally, functional groups are groups of atoms and bonds (within a larger molecule) that can mediate interactions with other molecules. The functional groups carried by a small molecule or a macromolecule determine the kind of interactions that the molecule will have with other molecules.

## Practice problems

1. Draw a hydrogen bond between hydrogen cyanide (HCN) and water. Draw a box around the hydrogen bond donor and a circle around the hydrogen bond acceptor. The hydrogen bond should be drawn with an optimal hydrogen bond angle.
2. Draw the maximal number of water molecules to which a single molecule of water can simultaneously form hydrogen bonds. Indicate these hydrogen bonds using dashed lines. All hydrogen bonds should be drawn with optimal bond angles.
3. Living things must separate compartments containing molecules. When salad oil and vinegar are stirred together, they phase separate into two layers. Vinegar is primarily water, while salad oil is primarily hydrocarbon. What leads to this phase separation?
4. Methyl formate has a boiling point of  $32^\circ\text{C}$ , while the isomeric acetic acid has a boiling point of  $118^\circ\text{C}$ . Why do these molecules of identical molecular weight have such different boiling points? (Note that if you remove the  $\text{CH}_3$  group (methyl) from one end of the molecule and stick it on the other end, that will convert methyl formate to acetic acid.)



Methyl formate



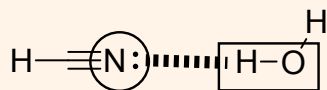
Acetic acid

5. Sodium chloride has a strong ionic interaction between the  $\text{Na}^+$  and  $\text{Cl}^-$  ions: its boiling point is  $1413^\circ\text{C}$ . It does not measurably dissolve in non-polar solvents like hexane or olive oil. However, on exposure to water, sodium chloride rapidly dissolves at room temperature, and the ions separate from one another within the solution. Why?
6. Hydrogen bonds form through interactions between a hydrogen bond donor and a hydrogen bond acceptor. Describe which atoms are found in each.

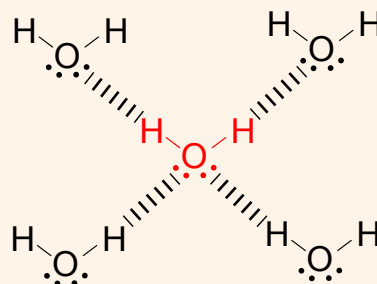
(Solutions are located on the next page)

## Solutions to practice problems

Question 1:



Question 2:



Question 3:

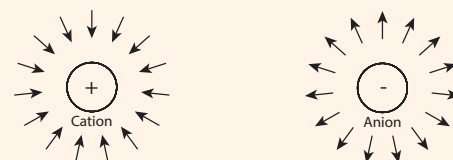
The water molecules (vinegar) have dipoles that can strongly attract other dipoles including the transient ones present in hydrocarbons (salad oil). However, the water-water interactions, which involve hydrogen bonds, are stronger than the water-hydrocarbon interactions, which involve dipole-induced dipole interactions between the water and hydrocarbon molecules. Therefore water molecules stick together tightly and squeeze out the non-polar hydrocarbon groups. The molecules in the hydrocarbon layer primarily associate by van der Waals interactions.

Question 4:

During boiling, intermolecular interactions must be broken to release molecules into the gas phase. The strongest intermolecular interactions methyl formate can form are dipole-dipole interactions while acetic acid can form even stronger hydrogen bonds. As a result, more energy must be added to acetic acid to break these hydrogen bonds and cause boiling, giving acetic acid a higher boiling temperature. The reason hydrogen bonds are the strongest kind of dipole-dipole interaction is because the hydrogen atom is small, allowing the negative end of a neighboring dipole to approach closely.

Question 5:

This solvation of ions is an extraordinary feature of water that is due to the large molecular dipole, small size, and accessibility of both the positive and the negative ends of the dipoles. The coulombic energy of small ions can be reduced by letting the charge repel itself and become more diffuse. That is essentially what water does. Imagine each arrow represents a water dipole, with a partial negative charge at the head and a partial positive charge at the tail. The partial negative charges near the cation effectively cancel part of that charge, moving it out to the tails and allowing the cation to lower its energy by repelling itself. The oppositely oriented water molecules surrounding the anion similarly lower its energy. The small size of the water molecules allows more of these to pack around each ion than other solvents. This effect dramatically reduces the propensity of these particles to stick tightly together, more easily allowing them to be separated from the crystal of salt. In addition, there is another important effect required to explain why salts dissolve called entropy, as we will come to in chapter 6.



Question 6:

H-bond donors are the positive end of the dipole and can be recognized by the H atom bonded to an electronegative atom like O or N. H-bond acceptors are the negative end of the dipole and are electronegative atoms that have a lone pair of electrons in their Lewis structures.