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CHAPTER 7

The Nature of Molecules and Intermolecular Interactions

Read This Chapter to Learn About

- The Chemical Bond
- Molecular Shape
- Molecular Orbitals
- Noncovalent Bonds

THE CHEMICAL BOND

Without chemical bonds, molecules would not exist. Therefore, rationalizing chemical phenomena must begin with an understanding of bonding.

Types of Bonds

Nobel laureate Roald Hoffmann described molecules as "persistent groupings of atoms." Such assemblies are held together by chemical bonds, which conventionally fall into one of two categories: ionic and covalent. Both bonds involve electrostatic forces: **ionic bonds** are present between a positively-charged cation and a negatively charged anion (as in sodium chloride), whereas **covalent bonds** arise from the mutual attraction of two positively charged nuclei to negatively-charged electron

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density shared between them (as in diatomic nitrogen). However, covalent and ionic bonds are just two ends of a bonding continuum.

When the electronegativity difference between the atoms is quite small, the electron density is equitably distributed along the internuclear axis, and it reaches a maximum at the midpoint of the bond. Such a bond is said to be purely covalent. On the other hand, when the two nuclei have widely divergent electronegativities, the electron density is not "shared" at all: two ionic species are formed and the electron density approaches zero along the internuclear axis at the edge of the ionic radius.

However, organic chemistry rarely operates at the boundaries of purely covalent or purely ionic bonding. Instead, most examples lie along a continuum between these two extremes (see Figure 7-1). For example, **polar covalent bonds** result from an uneven sharing of electron density, a situation that sets up a permanent dipole along the bond axis. The O—H and C—F bonds are examples of polar covalent bonds. Such bonds are stronger than you would expect, because the covalent attraction is augmented by the coulombic forces set up by the dipole.

Conversely, there are many examples of essentially ionic compounds that exhibit covalent character. In other words, even though there are practically two ionic species bound together, electron density is still shared between them. Almost all carbon-metal bonds fall into this category. For example, methyllithium (H_3CLi) can be thought of as a methyl anion (H_3C^-) with a lithium counterion (Li^+). Even though this is not a strictly accurate representation (i.e, there is indeed shared electron density), it still allows you to make sound predictions about its chemical behavior.

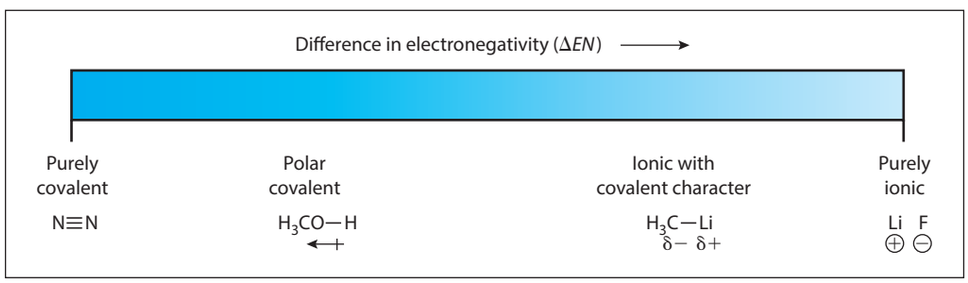

FIGURE 7-1 Types of bonding in organic molecules.

Lewis Structures and Resonance Forms

Examining electronegativity trends can allow you to make predictions about bond polarity, but you also need to understand the larger bonding picture: how many bonds are formed with each atom? The **Lewis dot diagram** represents a surprisingly simple device for representing global molecular bonding on a primary level. These diagrams are built up by considering the valence electrons brought to the table by each atom (conveniently remembered by counting from the left on the periodic table) and then forming bonds by intuitively combining unpaired electrons. For example, methane (CH_4) and formaldehyde (H_2CO) are constructed as shown in Figure 7-2.

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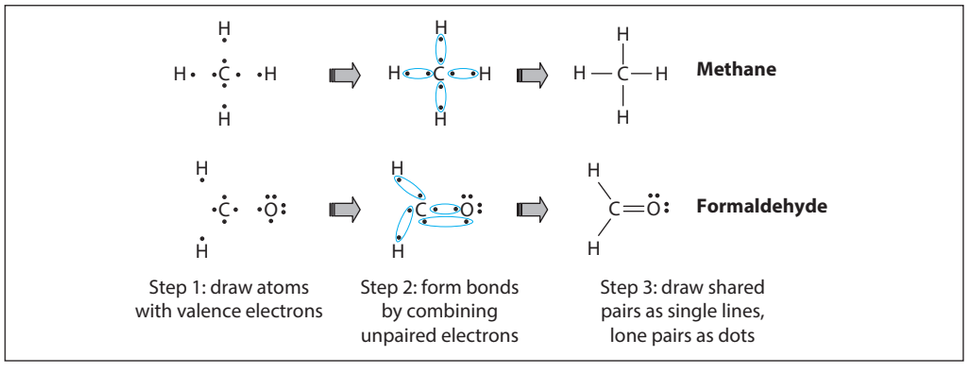


FIGURE 7-2 Lewis structures for methane and formaldehyde.

Notice that there are two types of electron pairs in the molecules in Figure 7-2: (1) **shared pairs (or bonds)**, which are represented by lines (each line representing two shared electrons), and (2) **lone pairs**, which are depicted using two dots. When calculating formal charges—which, incidentally, should always be done—assign to a given atom all of its lone pair electrons and half of each shared pair; then compare the sum to the number of valence electrons normally carried. For example, consider the amide species (see Figure 7-3). The nitrogen atom is surrounded by two lone pairs (nitrogen "owns" all four) and two shared pairs (nitrogen "owns" only one in each pair), giving a total of six electrons assigned to nitrogen. Compared to the five valence electrons normally carried by nitrogen, this represents an excess of one electron; therefore, a formal charge of −1 is given to the nitrogen atom.

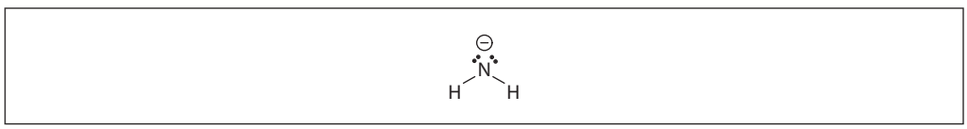
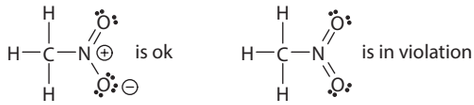


FIGURE 7-3 Lewis structure for the amide species.

Occasionally, the Lewis structures don't coalesce right away into such tidy packages. Therefore, you must often select the most reasonable Lewis representation from a collection of candidates. These are known as **resonance forms**, and while all reasonable candidates tell you something about the nature of the molecule they represent, some resonance structures are more significant contributors than others. In making such an assessment, the following guidelines are helpful:

A. Octet Rules

1. *Big octet rule*: no row 2 element can accommodate more than 8 electrons.



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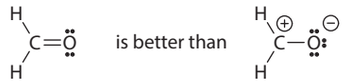
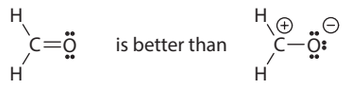
2. *Little octet rule*: all things being equal, each atom should have an octet.

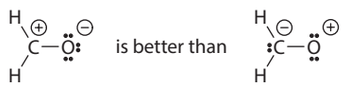


B. Rules of Charge Separation

1. All things being equal, structures should have minimal charge separation.



2. Any charge separation should be guided by electronegativity trends.



Of all these, only the big octet rule is inviolable. Structures that break the latter three rules are less desirable—those that break the first one are unreasonable and unsupportable. Keep in mind that Lewis structures are gross simplifications of a more complex reality, and sometimes no one representation is adequate to describe the total bonding within a molecule. Even when a structure satisfies all the rules—as with the first depiction of formaldehyde—other structures (resonance forms) may need to be considered to predict the properties of a molecule. The concept of resonance is considered later in this chapter.

The Condensed Formula and Line Notation

Another useful principle for constructing a structural representation from a molecular formula involves the idea of **valency**, or the number of bonds typically formed by a given element. For example, carbon normally has a valency of four; nitrogen, three; oxygen, two; hydrogen and the halogens, one. It is valency that underlies the hidden code of the so-called condensed formula, as illustrated in Figure 7-4 for the compound 3-hydroxypentanal. A **condensed formula** can appear to be ambiguous about structure, but in fact it is rich in structural information as long as you are aware of a few simple rules:

1. A condensed formula is read from left to right.
2. Each carbon atom in the formula is connected to the next carbon in the formula.
3. Everything to the right of a carbon (but before the next) is connected to that carbon.
4. Parentheses are used to indicate whole groups attached to a carbon.
5. Normal valencies must be satisfied (C = 4; N = 3; O = 2; H = 1; etc.).

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As the example in Figure 7-4 shows, the first step in converting a condensed formula into a **structural formula** is to lay out the **carbon backbone**—in this case a five-carbon chain. You then connect all the indicated substituents: three hydrogens to the first carbon, two hydrogens to the second, and so on, recognizing that the hydroxy (OH) moiety is treated as an entire group attached to the third carbon. The tricky part is the expansion of the CHO group. It is tempting to imagine a structure in which the carbon is attached to the hydrogen, which in turn is attached to the oxygen (lower left depiction). However, this would violate three valency guidelines: oxygen has only one bond, carbon only two, and hydrogen one too many. A proper reading of the condensed formula would be, "hydrogen belongs to the fifth carbon, and so does oxygen." With a bit of thought, the only reasonable arrangement would be the one shown in the lower right, which includes a carbon-oxygen double bond.

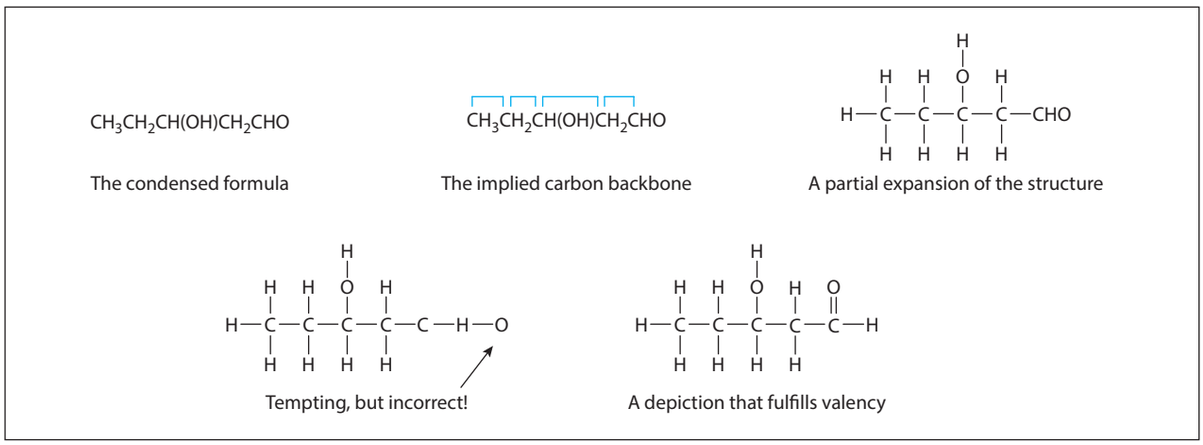

FIGURE 7-4 Converting a condensed formula to a full formula.

A condensed formula is one type of shortcut for depicting structure—its claim to fame is that it can be produced using a keyboard even when graphical software is unavailable. However, an even more important and widespread shortcut is **line notation**, which is universally used by organic chemists when they sketch compounds, its advantage being that the salient features of complex structures can be quickly and conveniently depicted. Figure 7-5 shows 3-hydroxypentanal in line notation. The assumptions underlying the simplification are these:

1. Every unlabeled vertex or terminus is a carbon atom.
2. Any unused valency of carbon is filled by hydrogen.

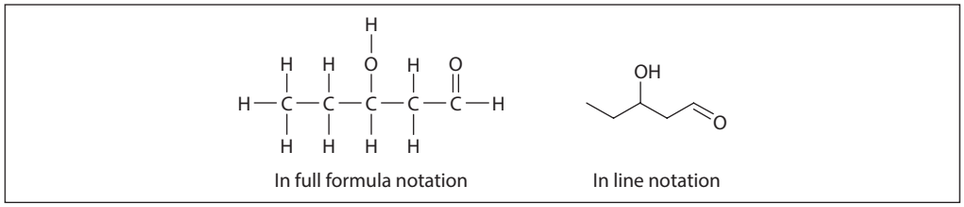

FIGURE 7-5 Two valid depictions of 3-hydroxypentanal.

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Keeping Track of Lone Pairs

You may have noticed that the preceding depictions do not include **lone pairs**—in fact, the depiction of lone pairs is an arbitrary matter, and they are often neglected in drawings. However, it is absolutely crucial to know where they are, as the presence or absence of lone pairs can define the chemistry of a species. For example, consider the two seemingly similar compounds, diethylborane and diethylamine (see Figure 7-6)—both have row 2 central atoms, which are trivalent, but their behaviors could not be more different. There is no lone pair on diethylborane—the central boron has only six electrons around it, thereby breaking the little octet rule. The molecule is starved for electron density, and it therefore reacts with electron-rich substrates. On the other hand, diethylamine does have a lone pair on the nitrogen, even though some depictions may not include this detail. Thus nitrogen fulfills the little octet rule, and the lone pair can even function as a source of electron density in many of its characteristic reactions.

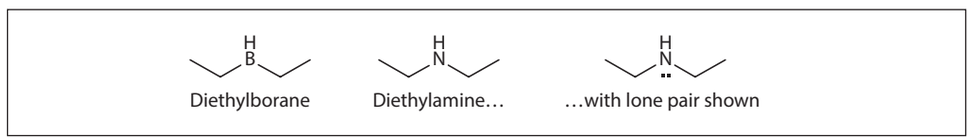

FIGURE 7-6 Two very different trivalent compounds.

The lone pair is a pivotal participant in an important intermolecular phenomenon known as the **hydrogen bond (H-bond)**. Two components are necessary for hydrogen bonding: an H-bond donor and an H-bond acceptor. An **H-bond donor** typically comes from a hydrogen bound to a **heteroatom**, which for organic chemists almost always means nitrogen, oxygen, or sulfur (and sometimes fluorine). These N—H, O—H, and S—H bonds are quite polar, with most of the electron density being hoarded by the heteroatom. As a result, the hydrogen starts to look rather like a proton (H^+) in need of extra electron density. Thus an **H-bond acceptor** is anything that can provide this electron density—and more often than not it comes in the form of a lone pair. This is nicely illustrated by the familiar H-bonding motif in DNA base pair recognition (see Figure 7-7). Three H-bonds are set up between cytosine and guanine, whereas

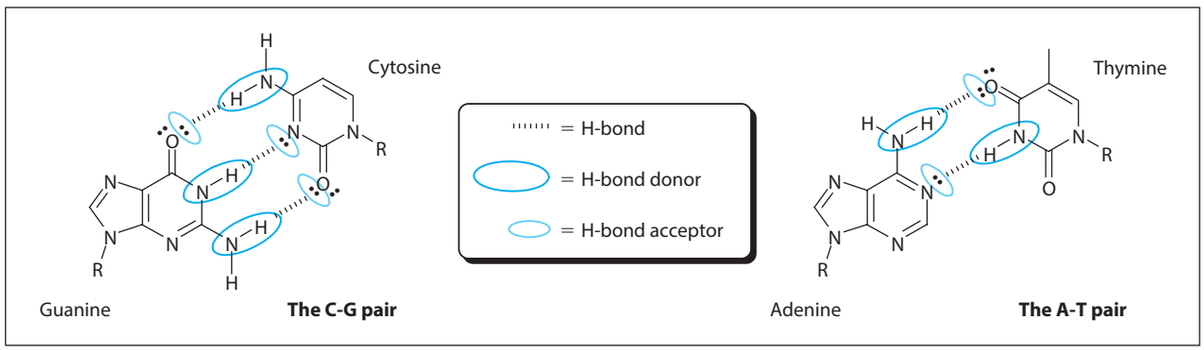

FIGURE 7-7 Hydrogen bonding in DNA base pair recognition.

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two are enjoyed by thymine and adenine. In each case, the H-bond donors are N—H bonds, while the H-bond acceptors are lone pairs on nitrogen or oxygen. Inspection reveals that the degree of H-bonding would be far less with a G-T pair or an A-C pair.

MOLECULAR SHAPE

With an understanding of connectivity among atoms within molecules, it is now appropriate to consider the three-dimensional arrangement of these atoms, since molecular shape is one of the chief factors determining the functionality and reactivity of a given molecule.

Geometry of Atoms Within Molecules

There are three frequently encountered geometries in organic chemistry: **digonal** (or linear), **trigonal**, and **tetrahedral** (see Figure 7-8). Each atom within a molecule is almost always characterized by one of these geometries, the chief hallmark of which is the associated bond angle: 180° for linear arrays, 120° for trigonal planar centers, and 109.5° for tetrahedral arrangements. Deviation from these ideal bond angles does occur, but significant deformation usually has a destabilizing effect known as **bond angle strain**.

Geometry	Arrangement	Bond angle	Hybridization of x
Digonal	a—x—b	180°	*sp*
Trigonal		120°	sp^2
Tetrahedral		109.5°	sp^3

FIGURE 7-8 Common central atom geometries in organic chemistry.

There are at least three ways to conceptualize molecular geometry. One classical approach is through the **hybridization of atomic orbitals**. If orbitals are derived from wave functions, then these functions can be combined mathematically to obtain hybrid descriptions. Thus if you combine an *s* orbital, which is spherically symmetrical, with a single *p* orbital, which has directionality along a single axis, it stands to reason that the outcome (two equivalent *sp* orbitals) should also have directionality along one dimension. Likewise, the combination of an *s* orbital with two *p* orbitals gives a result (three equivalent sp^2 orbitals) that defines a plane (see Figure 7-9).

Another framework is conceptually more straightforward. Known as **valence shell electron pair repulsion (VSEPR) theory**, this approach asks the question of how

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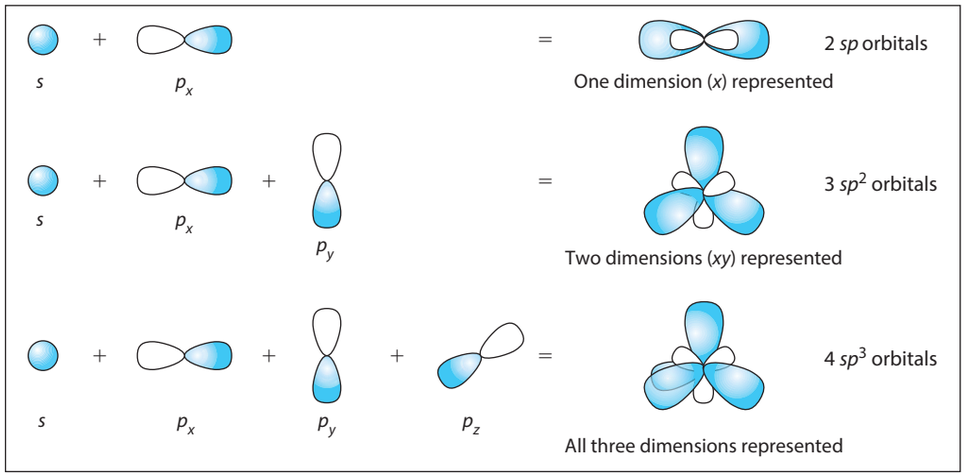

FIGURE 7-9 Central atom geometry as described by orbital hybridization.

negatively charged electron clouds can most effectively stay out of each other's way. If there are only two electron clouds, then the happiest arrangement is to be diametrically opposed to each other; for three clouds, a trigonal planar array; and for four clouds, a tetrahedral arrangement provides the maximum distance among them. Interestingly, these considerations predict exactly the same outcomes as hybrid orbital theory, although they are fundamentally different approaches. Strictly speaking, neither are theoretically accurate as compared to a strict **quantum mechanical analysis**—a third method not addressed here—however, they are useful predictive models nonetheless.

Thus to predict the geometry about a central atom, you must ask only how many things surround it—where "things" are understood to be either atoms or lone pairs. Figure 7-10 offers an illustration of this method, and experimental evidence backs up the predictions (e.g., the C—C—C bond angle is practically 120°). A generalization can also be derived from this example: since carbon is almost always tetravalent, then if only single bonds are attached to a carbon, it must have four other atoms surrounding it; if a double bond is attached to that carbon, then only three atoms can surround

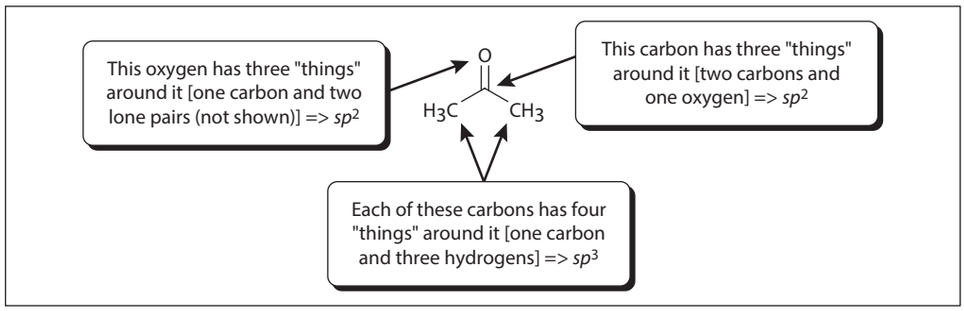

FIGURE 7-10 Prediction of geometry for acetone.

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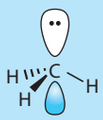
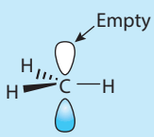
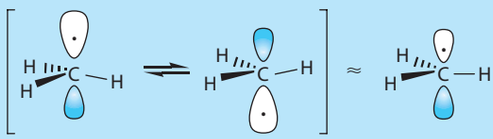
it; and so on. As a consequence, carbons with only single bonds tend to be tetrahedral (sp^3), carbons that are part of a double bond tend to be trigonal (sp^2), and triply bonded carbons are always digonal (sp).

There are three special cases for carbon that deserve mention: carbanions, carbocations, and radicals. Carbanions are carbons bearing a negative charge, as in the methyl anion (see the following table). **Carbanions** have lone pairs on carbon, even though they are rarely shown explicitly. Using the rules described previously, you would predict an sp^3 geometry about the carbon, and indeed most carbanions exhibit a pyramidal shape. **Carbocations** are carbon centers with only three bonds and a positive formal charge (e.g., methyl cation). Since the only things to accommodate are the three substituents (in this case, hydrogen atoms), the predicted geometry of carbon is sp^2—and experimental evidence supports the idea that carbocations are planar. **Radicals** lie somewhere between these two extremes. Since the p orbital is only half filled, it doesn't demand the same space that a doubly filled orbital would, but still requires more than an empty one. The most accurate way to think about such centers is as a shallow pyramid, which very rapidly inverts. A time-averaged representation would approximate a planar species; therefore, frequently radicals are depicted as being planar.

TABLE 7-1 Geometries of Some Special Carbon Centers

Species	Formula	Structure
methyl anion	$\ominus CH_3$	
methyl cation	$\oplus CH_3$	
methyl radical	$\ominus CH_3$	

Asymmetric Centers and Enantiomerism

Since they are inherently three-dimensional, tetrahedral carbons can impart a special characteristic to molecules, a property known as **asymmetry**. But before you can understand asymmetry, you first have to examine the idea of symmetry. The uninitiated think of symmetry as a binary state—that an object is either symmetrical or not symmetrical. However, there are degrees of symmetry, and many so-called elements of

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symmetry. This is a topic best treated in the domain of mathematics, but we shall very briefly scratch the surface here to gain some underpinnings for practical application. First, consider methane (CH_4)—a molecule that is unassuming, yet full of symmetry. Figure 7-11 shows three types of symmetry elements (there are others not shown here) belonging to methane. The sigma (σ) plane is an imaginary mirror that slices through the molecule—reflection through the plane results in an image identical to the starting depiction. Methane actually has six such planes: one with H_1 and H_2 in the plane; one with H_1 and H_3; one with H_1 and H_4; one with H_2 and H_3; one with H_2 and H_4; and one with H_3 and H_4. There are also two types of rotational axes. A C_2 axis has two "clicks" in a 360° rotation—180° each turn; methane has six of these, much like the sigma planes. A C_3 axis has three "clicks" in a full rotation—120° each turn; methane has four of these, one coinciding with each of the C—H bonds.

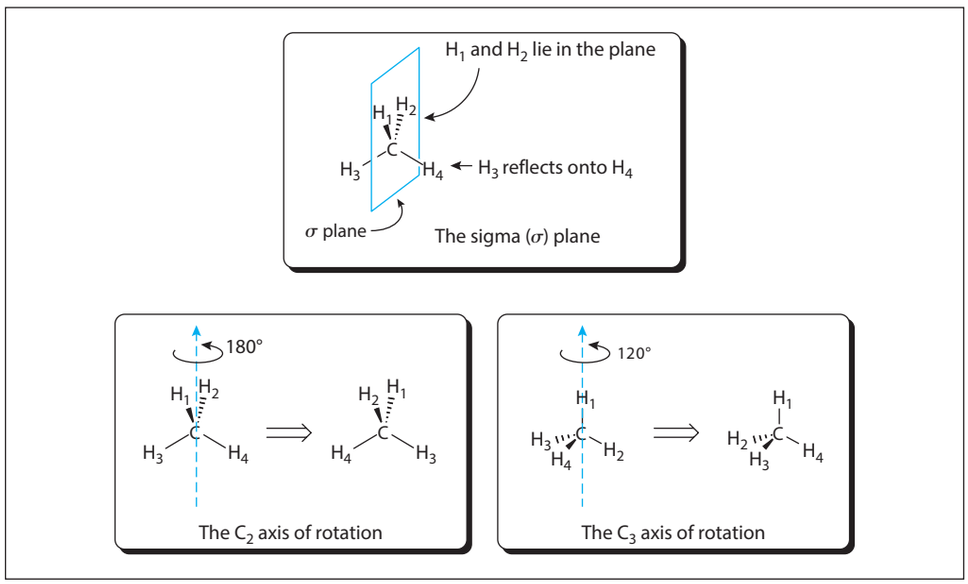

FIGURE 7-11 Symmetry elements of methane.

As you add substituents to methane, however, symmetry starts to drop off rapidly. For example, the addition of a single substituent, such as fluorine (see Table 7-2) reduces the number of sigma planes by half (each sigma plane must include the fluorine), slashes the number of C_3 axes to one (the axis which coincides with the C—F bond), and eliminates the C_2 axes altogether. A second substituent results in an even more impoverished symmetry environment, such that chlorofluoromethane has only a single sigma plane. After a third substituent is introduced (i.e., bromochlorofluoromethane), there are no symmetry elements left. Therefore, such a molecule is said to be **asymmetric**.

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TABLE 7-2 Symmetry Elements of Methane Derivatives

Compound	Structure	σ Planes	C_2 Axes	C_3 Axes
methane		6	6	4
fluoromethane		3	0	1
chlorofluoromethane		1	0	0
bromochlorofluoromethane		0	0	0

In other words, if a tetrahedral center is surrounded by four different groups, then the center is asymmetric. Furthermore, if a molecule contains an asymmetric center, it must exist as one of two enantiomers, or antipodes (literally, "opposite feet"). **Enantiomers** are nonsuperimposible mirror images, just like hands and feet (see Figure 7-12), and they represent two distinct compounds. Consequently, asymmetric centers are also called **stereogenic** centers and **chiral** (handed) centers.

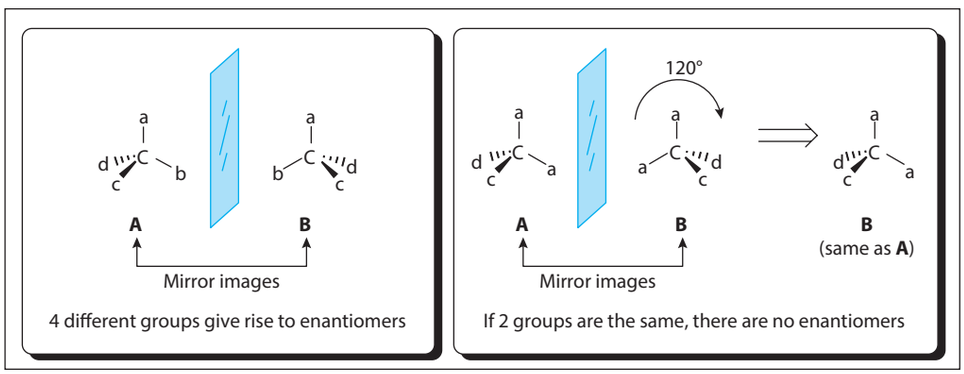

FIGURE 7-12 Tetrahedral centers and enantiomerism.

If any two or more groups are the same, then the center possesses a sigma plane, and the mirror image becomes a replica of the same molecule, so no enantiomerism exists. In other words, the mirror image is the compound itself, and there is only one chemical entity. Thus the presence of a sigma plane in a molecule destroys **chirality** (asymmetry). With more complex molecules, multiple chiral centers may be present; however, even in these cases a global sigma plane may be present.

Chiral compounds may be found in either of two enantiomeric forms. The enantiomers are identical in almost all physical properties: melting point, boiling point,

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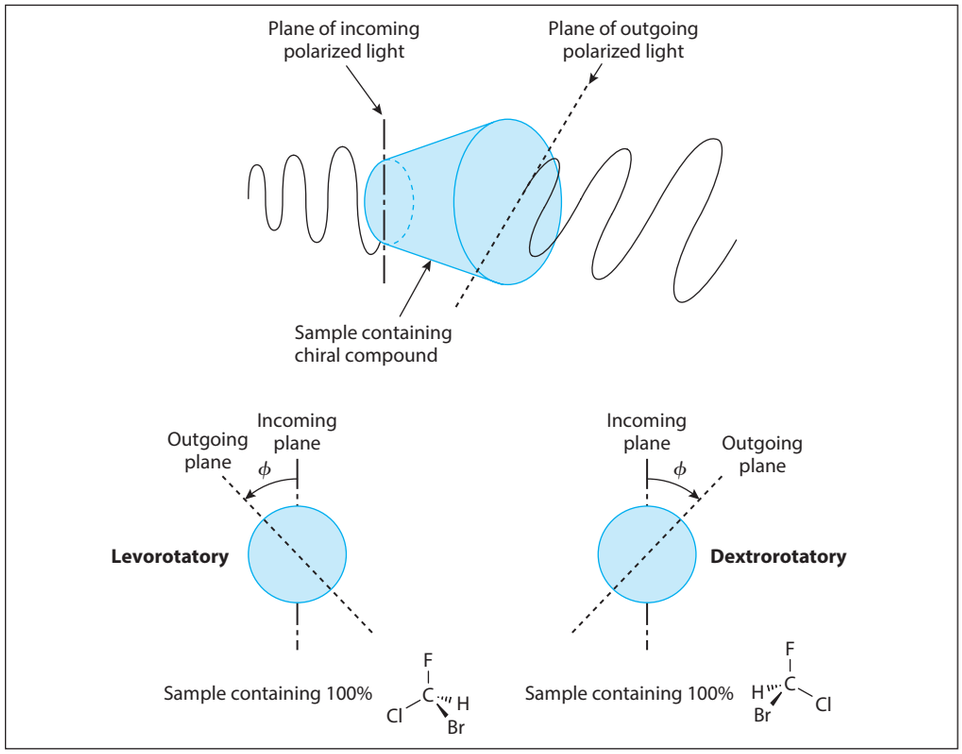

FIGURE 7-13 The phenomenon of optical rotation.

dielectric constant, and so on, with one notable exception. A solution of a chiral compound interacts with light in such a way that the plane of polarized light is rotated upon passing through a sample of the compound, a phenomenon known as **optical rotation** (see Figure 7-13, top). The other enantiomer rotates light to the same degree, but in the opposite direction (see Figure 7-13, bottom). Enantiomers that rotate light clockwise (i.e., to the right) are known as **dextrorotatory isomers**, and those that rotate light in a counterclockwise direction (i.e., to the left) are known as **levorotatory isomers**. It is important to understand that there is no straightforward way to correlate structure to behavior. In other words, you cannot tell just by looking at a molecule whether it would be dextrorotatory or levorotatory. By the same token, optical rotation tells you nothing about a molecule except that it is chiral.

A sample that rotates plane-polarized light is said to be optically active. The degree to which the sample rotates light is called the optical rotation (in degrees). If a sample is **optically inactive** (i.e., it does not rotate plane-polarized light), it could mean one of two things: either (1) the sample does not contain chiral molecules, or (2) the sample contains exactly equal quantities (50/50) of two enantiomers. The latter situation, known as a **racemic mixture**, produces no optical activity, because for each levorotatory molecule there is a dextrorotatory counterpart—equal numbers pulling in opposite directions maintain the status quo.

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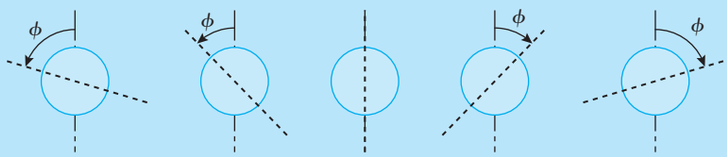
The term **racemic** refers to the composition of an enantiomeric mixture in which the components are exactly equal. Another term related to composition is **optically pure**, which means that only one enantiomer is present with no contamination from the other enantiomer. Of course, there are other compositions possible (e.g., a 60/40 mixture), which are neither racemic nor optically pure. Such lopsided mixtures are called **scalemic**; another term is **enantiomerically enriched**, since there is more of one enantiomer than another. Such scalemic mixtures can be defined by **enantiomeric excess** (or % ee), which is a quantitative term derived by subtracting the percentage of the lesser component from that of the greater. Therefore, a 55/45 mixture would have a 10% ee, a 95/5 mixture would have a 90% ee, and so forth.

All the vocabulary that surrounds this topic can easily get muddled. Always remember that chirality is a property of a **molecule** (it is a geometric reality derived from the molecular shape), whereas optical activity is a property of a **sample** (i.e., a macroscopic collection of molecules). In other words, molecules can be chiral or achiral, and samples can be optically active or inactive. Furthermore, the ideas of optical purity and optical activity are often confused. Here it is useful to keep in mind that optical purity is a **state** of a sample (i.e., a reflection of its composition), whereas optical activity is a **behavior** of a sample. Optically pure samples are always optically active, but not all optically active samples are optically pure, since scalemic mixtures are also optically active. The following table correlates these various properties and behaviors of enantiomeric mixtures.

TABLE 7-3 Properties and Behaviors of Enantiomeric Mixtures

State of Purity	Optically Pure	Scalemic	Racemic	Scalemic	Optically Pure
optical behavior					
% dextrorotatory enantiomer	0	25	50	75	100
% levorotatory enantiomer	100	75	50	25	0
enantiomeric excess (%)	100	50	0	50	100
optical rotation (°)	$-2x$	$-x$	0	x	$2x$
optically active?	yes	yes	no	yes	yes

Molecular Conformations

From this cursory inspection, it is clear that a fair amount of complexity surrounds the environment of a single carbon atom. But what about larger arrays of atoms? Since

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most molecules have considerable flexibility, it is important to understand what kinds of shapes are most stable and the energetics involved in their interconversion. Before doing this, however, it is necessary to come to terms with two additional methods of depiction for molecular structure: the **sawhorse (dash-wedge) projection**, and the **Newman projection**.

Consider a two-carbon array with three substituents on each carbon. Figure 7-14 shows such an array in two different depictions. The sawhorse projection views the molecule from the side. Substituents that come out of the plane toward us are depicted with wedges; those that go away from you are shown with dashes. If there is neither dash nor wedge, a plain line (and attached substituent) is assumed to lie in the plane of the paper. "Plain bonds lie in the plane," is a good mnemonic device in this regard.

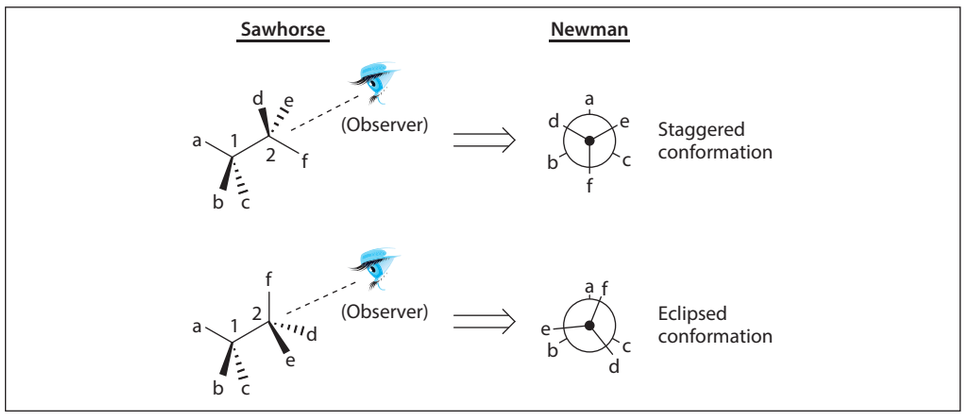

FIGURE 7-14 Sawhorse and Newman projections.

A Newman projection simply looks at the molecule from a different angle, namely down a carbon-carbon bond (indicated by the observer's eye). This is a much more straightforward way of showing the spatial relationship of substituents. Just remember that the small dot represents the front carbon, while the large circle represents the back carbon. Thus in the projections shown, the small dot is carbon-2 and the large circle is carbon-1; in other words, a C2→C1 Newman projection has been drawn. However, it could have just as easily been drawn as a C1→C2 variant, in which the small dot would be carbon-1.

Since there can be rotation about carbon-carbon bonds, this molecule can adopt a variety of conformations. In general, these conformations fall into one of two categories: staggered and eclipsed. Note that in the sawhorse depictions, the plain bonds (i.e., neither dash nor wedge) in the staggered conformation describe a "Z" or zigzag pattern, whereas in the eclipsed conformation they form a "U." This is a quick and easy way to distinguish one from another.

In staggered conformations, any two substituents are characterized by one of two relationships. Substituents are said to be **gauche** with respect to each other if they are

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side-by-side. In the illustration, there are six gauche relationships: a-e, e-c, c-f, f-b, b-d, and d-a. The other relationship is **antiperiplanar**, in which case the two substituents are as far away as possible from each other. In the same depiction, there are three antiperiplanar relationships: a-f, e-b, and d-c. In eclipsed conformations, there is only one type of relationship between substituents to care about, namely eclipsed. In the eclipsed Newman projection, there are three pairs of eclipsed substituents: a-f, c-d, and b-e. Don't be confused by the double duty of the term **eclipsed**—there are staggered and eclipsed **conformations**, which describe the global molecular attitude, and there are gauche, antiperiplanar, and eclipsed **relationships** between substituents. There are only gauche and antiperiplanar relationships in staggered conformations, and there are only eclipsed relationships in eclipsed conformations.

It should come as no surprise that eclipsed conformations are of higher energy than staggered conformations. This is due to the steric interactions that result from the very close proximity of substituents in the eclipsed relationships. By the same token, staggered conformations that place large groups in a gauche arrangement are of higher energy than those that have those groups antiperiplanar with respect to each other. Using these basic principles, you can construct a diagram showing the relative energies of a conformational ensemble, as illustrated in Figure 7-15 for butane ($CH_3CH_2CH_2CH_3$). This is a process known as **conformational analysis**.

To begin the conformational analysis, all the possible conformations for the molecule, both eclipsed and staggered, must be drawn. This might seem more difficult than it really is—first, just jot down any conformation and then methodically convert it to the remaining possibilities. For example, in Figure 7-15 the first conformation (A) is chosen arbitrarily. Conformation A is converted to C by rotating the front carbon (small dot) clockwise—notice that the back carbon does not change. This maneuver has the net effect of bringing the front methyl (CH_3) group from the 6 o'clock position to the 10 o'clock position. To get from A to C, the molecule must pass through the high-energy eclipsed conformer B. The remaining conformations are derived by continuing to rotate the front carbon in a clockwise fashion until you arrive back at A.

The next step is to assess all the group interactions in each conformer. For the sake of simplicity, neglect H—H interactions, since the hydrogen atom is so small. Thus in conformer A, observe four methyl-hydrogen gauche interactions (in other words, each methyl group has a hydrogen to either side—each flanking hydrogen counts as an interaction). In conformer C, there are only two methyl-hydrogen gauche interactions, but there is also a methyl-methyl gauche interaction. These interactions are used to estimate the relative placement of the conformers on the energy diagram.

The diagram can be constructed easily through a three-step approach. First, keep in mind that all eclipsed conformations will be higher than the staggered conformations, so there are two separate collections of conformers (i.e., staggered and eclipsed). Then estimate the relative placement of the conformers within each set. For example, in comparing the energetics of the staggered conformers A and C, you could say two methyl hydrogen gauche interactions (2 vs. 4) have been traded for one methyl-methyl

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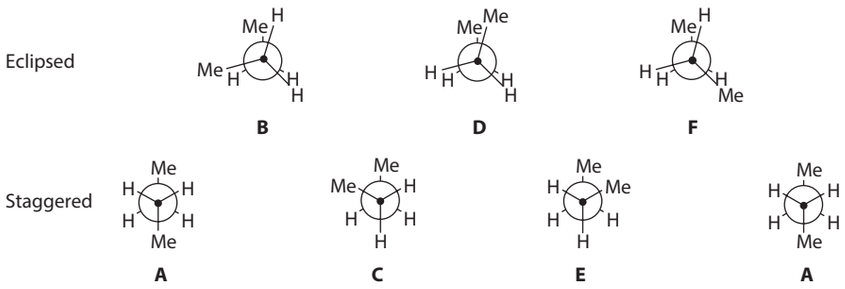
Newman projections of all conformations



Total number of gauche and eclipsing interactions

Conformer	A	B	C	D	E	F
Me-Me dihedral angle (ϕ)	180°	120°	60°	0°	60°	120°
Me-Me eclipsing interactions	n/a	0	n/a	1	n/a	0
Me-H eclipsing interactions	n/a	2	n/a	2	n/a	1
Me-Me gauche interactions	0	n/a	1	n/a	1	n/a
Me-H gauche interactions	4	n/a	2	n/a	2	n/a

Energy diagram for conformers

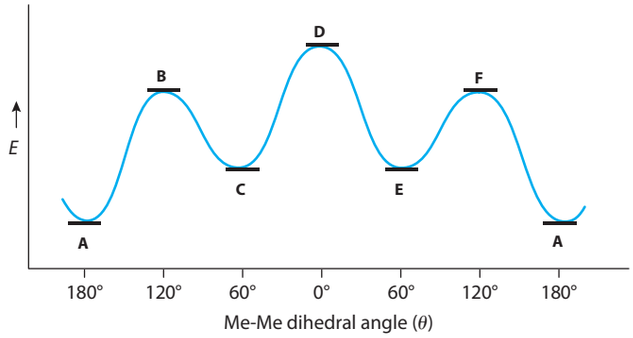


FIGURE 7-15 Conformational analysis of butane.

gauche interaction. Realizing that the methyl group is considerably larger than the hydrogen, it seems reasonable that the cost of having the two large groups next to each other outweighs the benefit of two less small-large interactions. This is the rationale for placing C higher on the diagram than A. Inspection of conformer E reveals that it exhibits the same type and number of gauche interactions as C; therefore, C and E are at the same energy level. Through similar analysis, the placement of the eclipsed conformations is estimated.

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Conformations of Cycloalkanes

There are special conformational issues for cyclic molecules. As a general rule, **cycloalkanes** are less flexible than open-chain analogs, and they can adopt far fewer conformations. However, both types have predictable low-energy conformations. For example, consider hexane (see Figure 7-16): inasmuch as there is free rotation about all the carbon-carbon bonds, you could envision the six conformational option described in butane for each of the internal C—C bonds (i.e., C2-C3, C3-C4, and C4-C5). The most stable conformation is the one that has all antiperiplanar relationships, as shown in Figure 7-16. Similarly, cyclohexane can and does adopt many conformations, but the most stable arrangement is the so-called **chair conformation**.

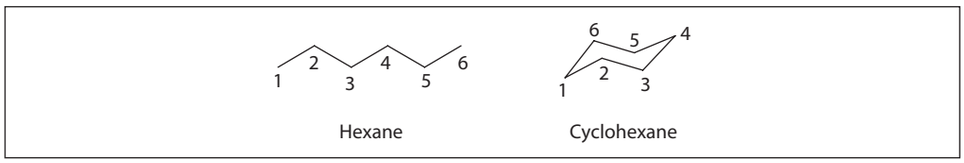

FIGURE 7-16 Stable conformations of hexane and cyclohexane.

Although it may not be evident, there are two alternate chair forms that are related by the **chair flip**. It is important to understand that the flip is not a rotation of the molecule, but a reconformation. As the top depiction in Figure 7-17 shows, carbon 1 flips from pointing downward to pointing upward, carbon 4 does the reverse, and the entire molecule reconforms in place. As a side note, always keep in mind that the chair projection is a side view of the ring, and the lower bond (i.e., C2-C3) is assumed to be in front.

When substituents are added to the cyclohexane, the chair flip takes on special significance. To understand this, first come to terms with some characteristics of the substituents on a cyclohexane ring. Examination of Figure 7-17 (lower depiction) reveals that substituents can adopt one of two attitudes: **axial** (shown as triangles in the left chair) or **equatorial** (shown as squares)—every chair conformation has six of each

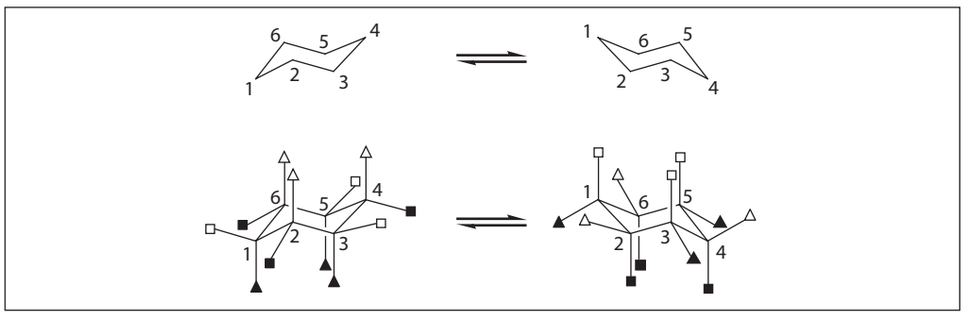

FIGURE 7-17 The chair flip of cyclohexane.

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type. Note that a chair flip interchanges axial and equatorial substituents, so that all of the triangles become equatorial on the right side. It is a good idea to construct a model and physically induce a ring flip to see how this works.

It is equally important to understand what does *not* change during a ring flip. Any ring has two faces—as these depictions are drawn, they can be called the top and bottom faces. Any substituent points toward either the top or the bottom face. Again, each chair cyclohexane has six of each type—the six white substituents are all pointing toward the top face, and the six black ones are pointing toward the bottom face. Note that there are three axial and three equatorial substituents pointing up, and three of each pointing down. Also note that a ring flip does not change whether a substituent points up or down. So in other words the triangle substituent on carbon 4 always points up, although it may convert from axial to equatorial. As a general rule, the bulkiest substituent prefers the equatorial position.

Other ring sizes have different lowest energy conformations, and a brief survey is worthwhile. For example, the most stable conformation of cyclopentane (see Figure 7-18) is the so-called **envelope**, which (like the chair) has two forms that equilibrate through the flipping of the envelope flap. Cyclobutane adopts a so-called **puckered conformation**, which again has two forms that equilibrate through a ring flip. Notice that the same rules for cyclohexanes hold true for these cycloalkanes—namely, that there are two types of substituent attitudes (here, called pseudoaxial and pseudoequatorial) that interconvert upon ring flips; also, the substituents point toward a certain face, and that face remains constant throughout conformational changes. Finally, cyclopropanes have practically no conformational flexibility—there is really only one possibility, and all substituents have equivalent attitudes. However, of course, there are still two faces to the molecule, so substituents can point toward the top face or the bottom face.

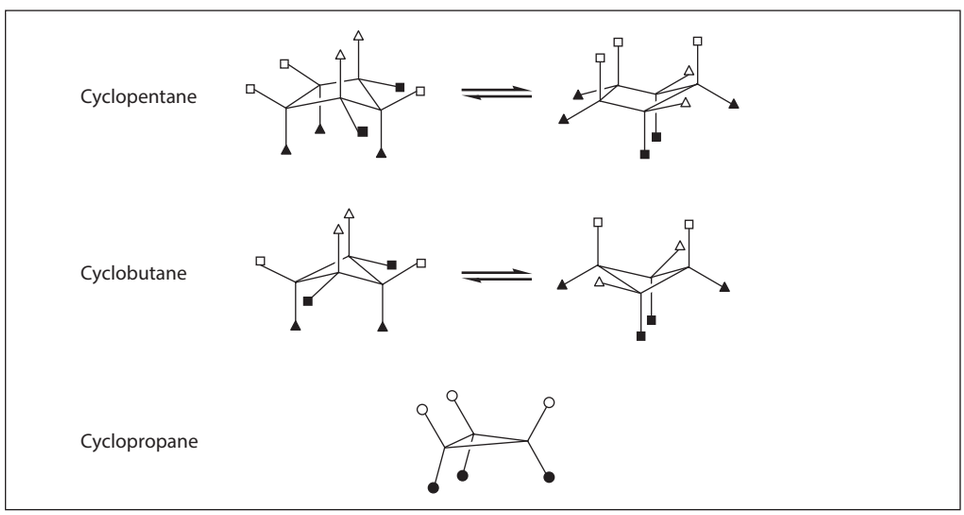

FIGURE 7-18 Stable conformations of other cycloalkanes.

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So what factors govern the adoption of a given stable conformation? The main determinant is the minimization of ring strain. In cyclic molecules, there are essentially two sources of strain: bond angle strain and torsional strain. **Bond angle strain** derives from a compression of the ideal sp^3 bond angle (109.5°) to accommodate a cyclic array. Not surprisingly, this is worst for the three-membered ring, and is almost nil for the five- and six-membered rings. The other source of strain is less obvious. **Torsional strain** derives from the torque on individual bonds from eclipsed substituents trying to get out of each other's way. Again, this is most pronounced in cyclopropane (compare Figure 7-18), and all the other cycloalkanes twist in ways to minimize or eliminate this strain. For example, inspection of a molecular model of chair cyclohexane will reveal that all carbon-carbon bonds have a perfectly staggered conformation. Interestingly, the five-membered ring is not so lucky. Even in the envelope conformation, substituents tend toward eclipsing each other. The following table summarizes the individual components, but a good overall take-home message is that ring strain decreases according to the trend: $3 > 4 \gg 5 > 6$. This has implications in reactivity of cyclic molecules.

TABLE 7-4 Ring Strain in Cycloalkanes

Cycloalkane	Torsional Strain	Bond Angle Strain
cyclopropane	a lot	a lot
cyclobutane	some	a lot
cyclopentane	a little	practically none
cyclohexane	none	none

Reconciling Visual Meaning

Coming to terms with the three-dimensionality of organic chemistry is often a challenge for students, yet this is possibly the most important transferable cognitive skill developed by the study of the subject. The novice is confronted with a jumble of alternative depictional devices that appear to be interchangeable. However, a structural drawing is a way of communicating, and specific information is carried in these depictions. For example, if you are presented with a simple line drawing (see the following table), you can quickly see the landscape of the molecule—what the **regiochemistry** is (that is, *where* the atoms are) and which functional groups are present—but you are told nothing about the **stereochemistry** (that is, the three-dimensional arrangement of the atoms). On the other hand, the **Fischer projection** was developed specifically for quickly conveying the absolute stereochemistry (configuration) of a molecule. You must carefully choose the right depiction for the information you wish to convey, and you must also be able to fully interpret the messages given by specific structures.

One particularly thorny depictional issue centers around relative and absolute stereochemistry. For example, you can draw a structure for *cis*-5-methylcyclohex-2-enol, which is unequivocal and easily distinguishable from the corresponding

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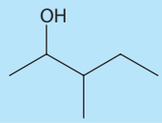
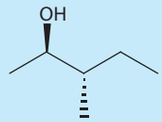
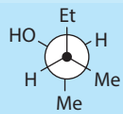
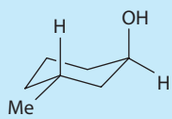
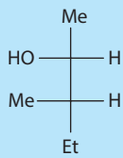
TABLE 7-5 Summary of Structural Depictions

Type of Depiction	Example	Best for Depicting
line structure		constitution and connectivity
sawhorse		relative and absolute stereochemistry
Newman		conformation
Chair		conformation
Fischer		configuration (absolute stereochemistry)

trans-isomer (see Figure 7-19). However, it has been arbitrarily chosen to draw the substituents with two wedges—a structure with two dashes would have been equally valid. In this example, the only intent was to show that the two substituents are on the same side of the molecule, that is, their relative stereochemistry. Whether carbon-1 is an *R* or *S* center is unknown.

Unfortunately, the same kind of depiction has been used to show absolute stereochemistry. For example, if you were to draw specifically the 1*S*, 5*S* enantiomer of *cis*-5-methylcyclohex-2-enol, both substituents would be attached with wedges (see the following table)—but here their *absolute* placement in space are depicted, not just their positions relative to each other. Conversely, the *R*, *R* enantiomer would be drawn with dashes. Note that when the configuration is included in the name, *cis*/*trans* designation

cis-5-methylcyclohex-2-enol *trans*-5-methylcyclohex-2-enol

FIGURE 7-19 Relative stereoisomers.

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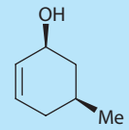
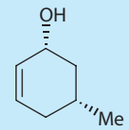
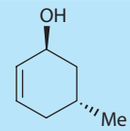
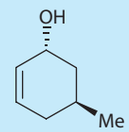
is unnecessary. Converting a name to a structure is relatively easy—if *R*/*S* information is given, simply represent it accurately in the structure; if only relative (*cis*/*trans*) stereochemical information is given, you have a couple of choices for the dashes and wedges; if no stereochemical information is provided, then you can draw only a simple line structure. However, the reverse operation is trickier: properly interpreting a sawhorse structure requires context. A good rule of thumb is that any sawhorse structure containing chiral centers is *assumed to be a racemic mixture* unless somehow identified as a single enantiomer. This context can be in the form of optical rotation data or explicit statements such as "single enantiomer" or "optically pure."

TABLE 7-6 Relative Versus Absolute Stereochemistry

Structural Depiction	Corresponding Name	*cis*/*trans*
 (Optically pure)	(1*S*, 5*S*)-5-methylcyclohex-2-enol	*cis*
 (Optically pure)	(1*R*, 5*R*)-5-methylcyclohex-2-enol	*cis*
 (Optically pure)	(1*S*, 5*R*)-5-methylcyclohex-2-enol	*trans*
 (Optically pure)	(1*R*, 5*S*)-5-methylcyclohex-2-enol	*trans*

Occasionally, you need to be deliberately ambiguous about the stereochemistry of a compound—for example, if the stereochemical arrangement has not been determined or if you know that there is a mixture of stereoisomers. For this there is a device known colloquially as the "squiggly line," which indicates the orientation of the substituent can be up, down, or both. In cyclic structures, the use of the squiggly line has the same effect as using plain line structure (see Figure 7-20, left). However, for alkenes there is really no other alternative to show a mixture of *cis* and *trans* isomers than to employ this handy depictional device (see Figure 7-20, right).

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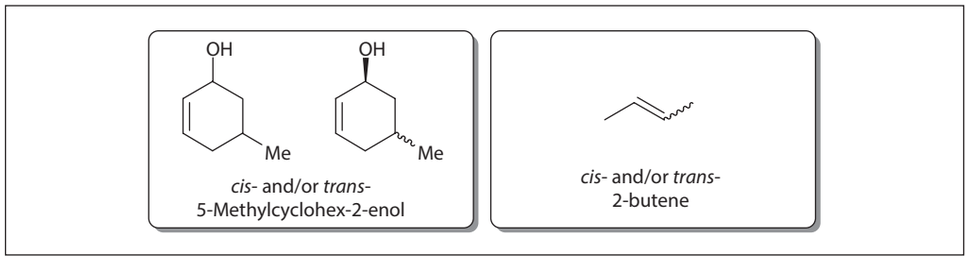

FIGURE 7-20 Deliberately ambiguous stereochemistry.

With this in mind, your choice of depiction must be carefully chosen to reflect what you know about a particular molecule or collection of molecules, and it must be suited to the task of representing this information. In addition, a given structural representation has specific meaning which you must properly interpret. As an organizing principle, it is very useful to think of structure (and representation) as layers of detail (see Figure 7-21), the lowest level of detail being constitutional (how the atoms are connected), then stereochemical, and ultimately conformational (the particular shape a molecule adopts)—not unlike the primary, secondary, and tertiary structure of proteins.

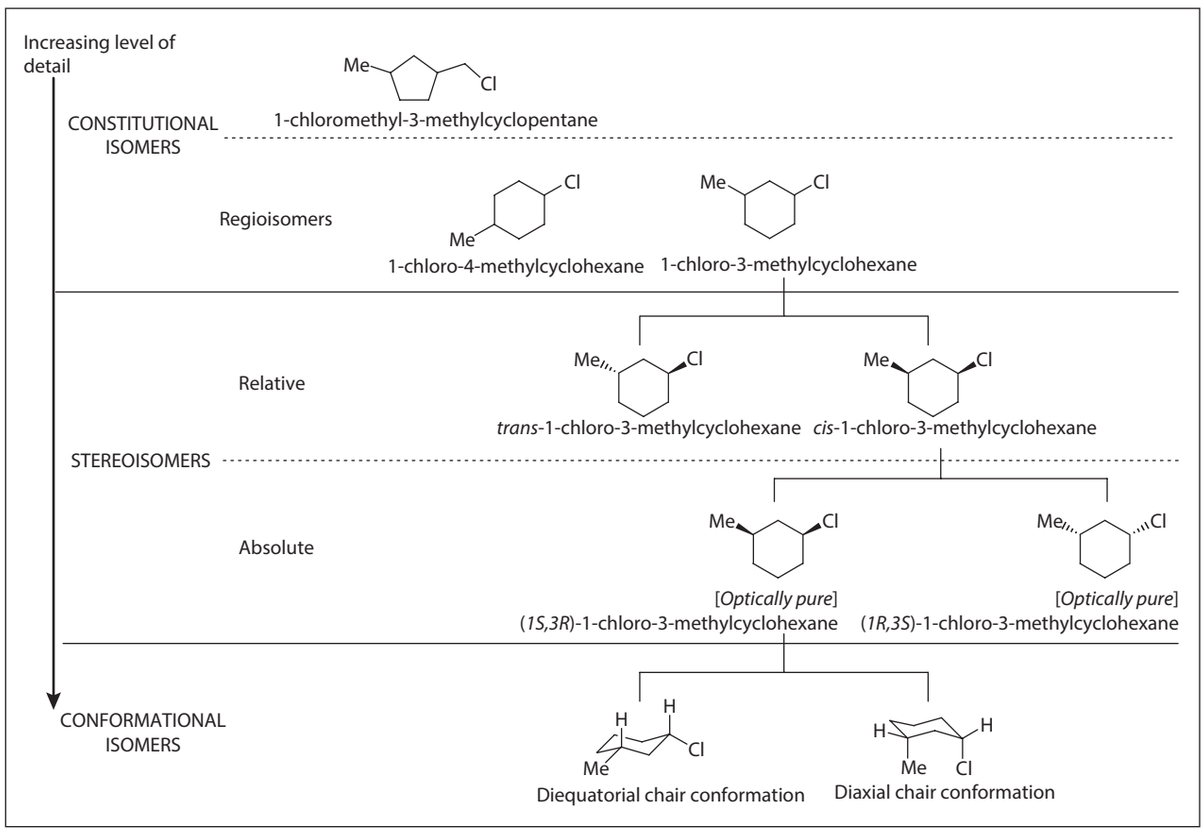

FIGURE 7-21 Levels of detail in structural representation.

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MANIPULATING STRUCTURES IN THREE-DIMENSIONAL SPACE

It is frequently necessary to compare two structures or convert one type of depiction into another. To do this one needs to have a clear understanding of the depictions themselves and the three-dimensional objects they represent. Ultimately, the challenge lies in being able to manipulate the two-dimensional drawings in ways that are three-dimensionally competent. For example, consider the chair form of *trans*-3-methylcyclohexanol shown in Figure 7-22. The six depictions shown are simply reorientations of the molecule by rotating in a plane perpendicular to the page, a process which can be thought of as "spinning the plate." Note that the molecule has not been reconfigured—these are not ring flips, but a static structure viewed from different angles, as if perusing it in the hands.

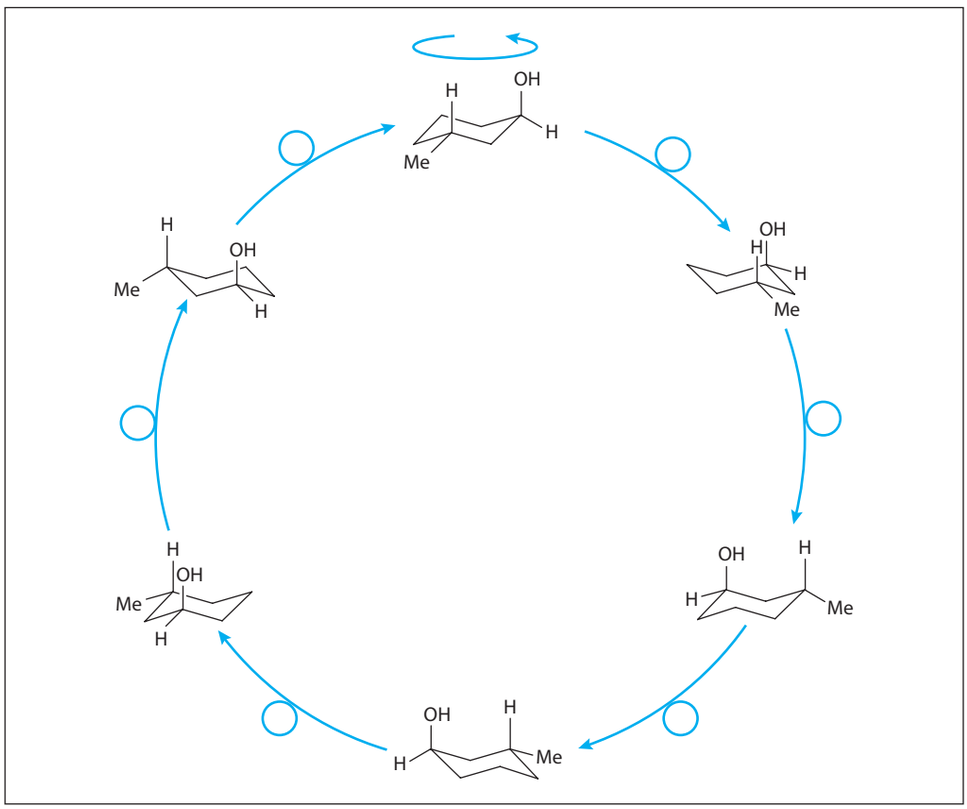

FIGURE 7-22 The spinning plate maneuver.

Similar things can be done with sawhorse structures, as shown in Figure 7-23. Here the molecule is first flipped horizontally, then vertically, and finally rotated 180° in plane, which here is called the **pinwheel turn**. Note that when a molecule is flipped, dashes become wedges (and vice versa), but they remain the same during an in-plane rotation. This is an obvious statement, but it is critical to be conscious of the fact as

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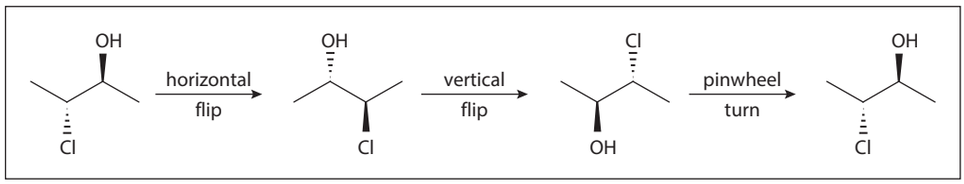

FIGURE 7-23 Some manipulations of sawhorse structures.

you manipulate structures later on. You can also perform these maneuvers on chair cyclohexanes as well.

When converting specialized depictions—like Newman or Fischer projections—to more conventional drawings (e.g., sawhorse structures), bear in mind that this is ultimately a change in point of view. So for a Newman projection, you sight the molecule down a carbon-carbon bond, but in a sawhorse you view the same bond side-on. An easy way to think about the conversion is to imagine that the Newman projection is hinged at the back carbon and you push the structure into the page much like you would shut an open door (see Figure 7-24); thus the bond that points directly toward you in structure A (the C2—C3 bond) lies in the plane in structure B. You can use the same technique with Fischer projections, as long as you remember that the stylized representation (C) really implies the dashes and wedges shown in structure D. Note that two-centered Fischer projections are always eclipsed.

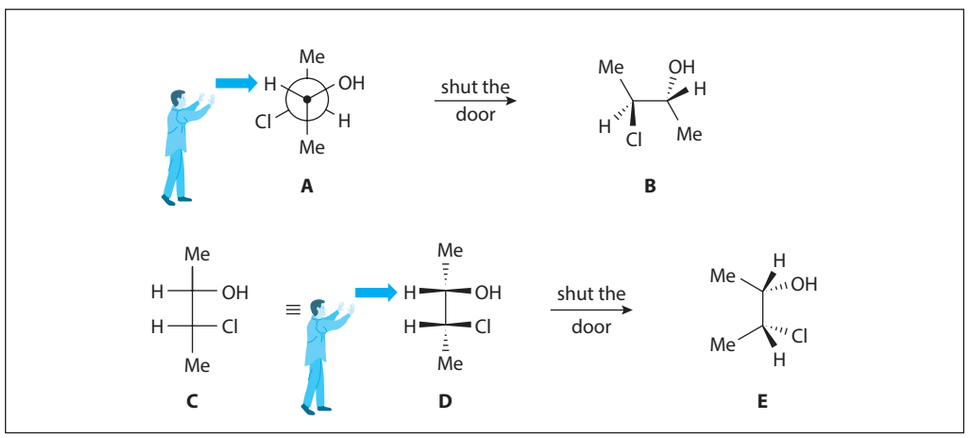

FIGURE 7-24 Shutting the door.

RAPID COMPARISON OF DEPICTIONS

Now imagine that you were asked to evaluate the two representations A and C, and decide whether they are enantiomers, diastereomers, or the same thing. First, review the difference between enantiomers and diastereomers. Both fall under the broader umbrella term of **stereoisomers**, which refers to different spatial orientation of

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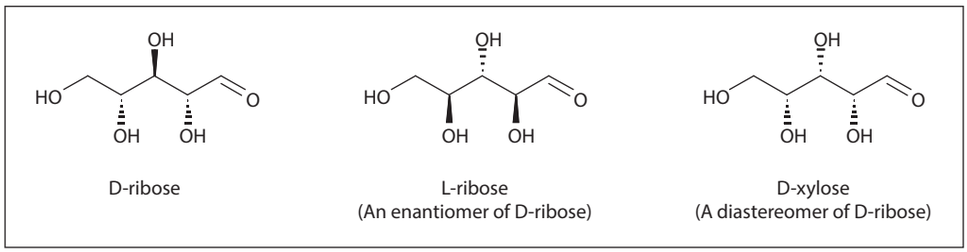

FIGURE 7-25 Enantiomers versus diastereomers.

substituents. As an illustration, consider the naturally occurring sugar D-ribose (see Figure 7-25), which has three chiral centers bearing hydroxy groups. Each group could be oriented in one of two ways—a dash or a wedge; so in essence it is a binary outcome. Since there are three centers, then the total number of unique permutations is $2^3 = 8$. D-ribose represents one such permutation, which here is called the "down-up-down" isomer (referring to the orientation of the hydroxy groups). The enantiomer of D-ribose is L-ribose (the D and L designations are peculiar to carbohydrate nomenclature), and you will notice that *each and every chiral center is inverted*—this is true for any set of enantiomers. So L-ribose accounts for one stereoisomer of D-ribose, but there are six others—all of them diastereomers of D-ribose. Figure 7-25 shows only one of the diastereomers, namely D-xylose, which has a down-down-down arrangement of hydroxy substituents. Therefore, you can define a **diastereomer** as a stereoisomer in which one or more, *but not all*, chiral centers have been inverted.

A common temptation for the novice is to assign R and S designations to each of the chiral centers and make the comparison in an algorithmic way. Indeed, you would find that the configuration for D-ribose is (2R, 3R, 4R) and for L-ribose is (2S, 3S, 4S), thus confirming the designation of enantiomer. However, this method is time consuming and error-prone. For each chiral center, you must assign the CIP priorities, orient the center correctly, and decide whether a→b→c is clockwise or counterclockwise. This means that to compare ribose with another structure, 36 discrete operations must be made, and if an error occurs in any one, the whole comparison breaks down. Instead, you should become skilled in analyzing these problems from a three-dimensional standpoint. In other words, manipulate the structures in your mind's eye so you can compare them visually.

With this backdrop, return to the question of comparing Newman projection A to Fischer projection C in Figure 7-24. The first order of business is to convert them to sawhorse representations (B and E, respectively). Then the question is how to compare the two very different sawhorses. To make a reliable comparison, you must first reorient the structures so they share elements of commonality. It is generally easier to simply take one as a reference and reorient the other—for example, to arbitrarily take structure B as a reference and manipulate E to adopt the elements of commonality (see Figure 7-26). So what are these elements? Examining structure B, you find that (1) it is

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a staggered conformation, (2) C1, C2, C3, and C4 are all in the plane, (3) the hydroxy group is on the right hand and pointed toward the top of the page, and (4) the chloro substituent is on the left hand and pointed toward the bottom of the page (never mind for the moment whether they are dashes or wedges).

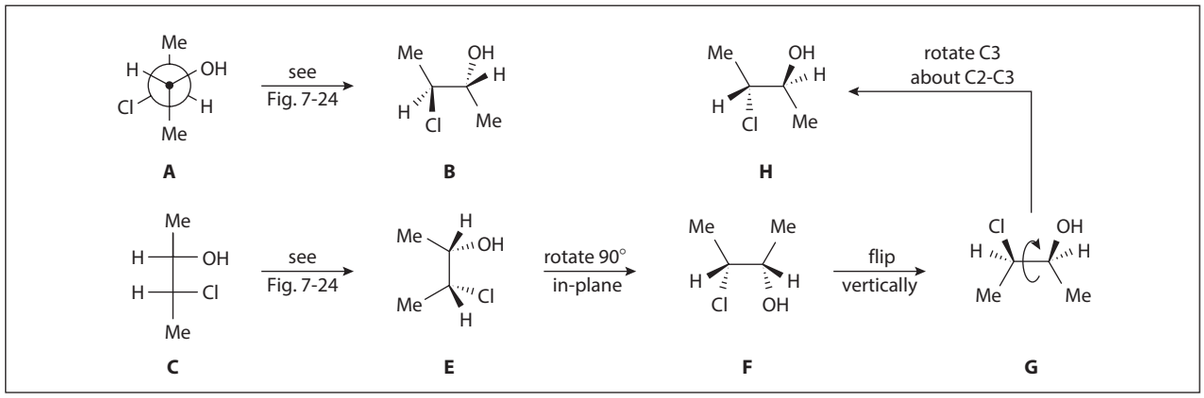

FIGURE 7-26 Comparing two representations.

Now set about the task of reorienting E to adopt these four elements, starting with an in-plane rotation to get structure F, followed by a vertical flip to obtain structure G. Notice that the dashes and wedges remain the same during the rotation, but change during the vertical flip. The motivation for this maneuver was to place the hydroxy group on the right side and pointing toward the top of the page. Notice, however, that the conformation is eclipsed (as indeed all Fischer projections must be). To make a comparison, you must then rotate about the C2—C3 bond 180° to arrive at structure H. Unlike the previous operations, this is a reconformation of the molecule—but the identity of the compound remains the same. Now you are in a position to evaluate the two structures (B and H). Notice that every chiral center in H is the opposite of that in B; therefore, the two must be enantiomers.

Similar operations can be carried out on cyclic molecules. Again, it is generally easier to convert all representations into dash-wedge drawings before making manipulations and comparisons. Figure 7-27 demonstrates two mnemonics for re-envisioning chair cyclohexane depictions. Imagine that the back carbon-carbon bond (highlighted in blue) is a hinge and that the cyclohexane ring is a flat surface, like a table or ironing board. You can push the molecule up on the hinge, much like a foldaway ironing board, in which case the hydroxy group becomes a dash at the 3 o'clock position and the methyl group is a wedge at the 10 o'clock position. Alternatively, you can let the surface fall suspended by the hinge, as if letting down a drop-leaf table. Here the hydroxy group would still be at 3 o'clock, but as a wedge, and the methyl group would be a dash at 8 o'clock.

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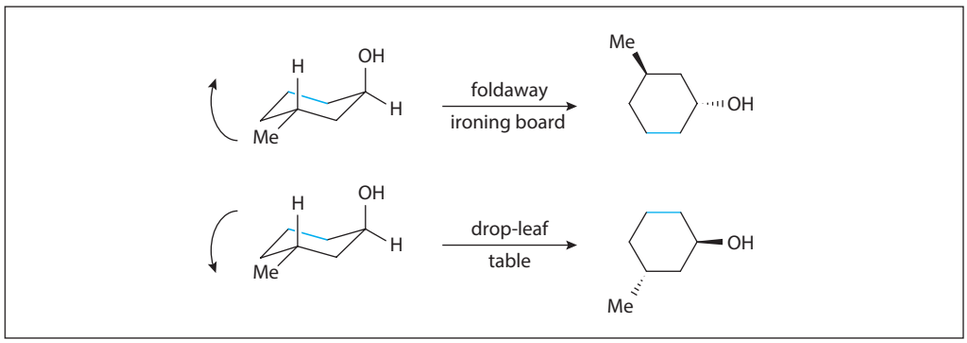

FIGURE 7-27 Converting chairs into dash-wedge representations.

You can apply these techniques to the comparison of a chair representation to a two-dimensional dash-wedge cyclohexane drawing, for example, structures A and B in Figure 7-28. You can use B as a reference structure and manipulate A to adopt the required orientation. Here the elements of commonality are quite straightforward: methyl is at 2 o'clock and chloro is at 4 o'clock. First use the drop-leaf table maneuver on A to obtain the dash-wedge structure C, which has methyl at 11 o'clock and chloro at 1 o'clock. Then recognize that a simple in-plane rotation of the molecule will put the substituents in the proper attitude for comparison. Inspection reveals that A and B are indeed the same thing.

Again, your goal should be the ability to carry out these manipulations in your mind's eye. As you practice this skill, sketching out intermediate steps with pencil and paper can be helpful, as shown in the previous figures. Also, molecular models are great support devices to help you see the three-dimensional reality of two-dimensional drawings. Once you develop this facility, comparing different representations becomes extremely rapid and reliable. Moreover, you hone the valuable (and increasingly rare) skill of three-dimensional visualization.

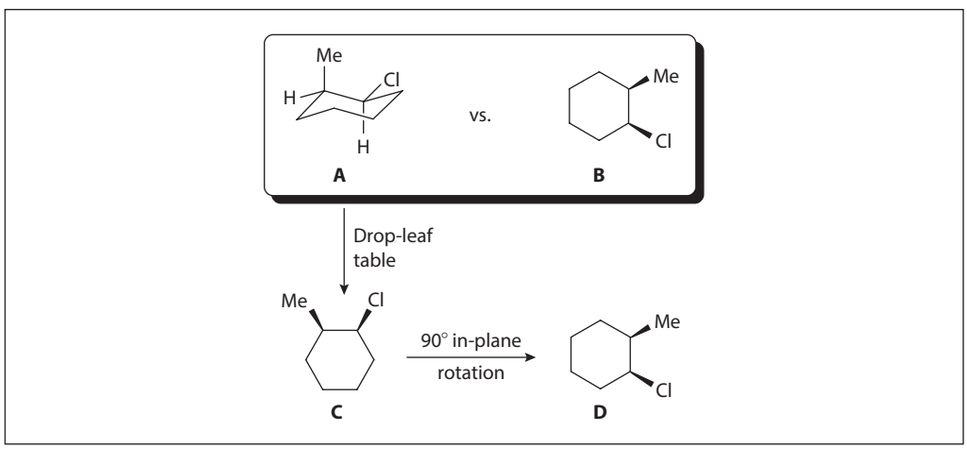

FIGURE 7-28 Comparing chair cyclohexane derivatives.

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MOLECULAR ORBITALS

The concept of hybridization was discussed earlier in this chapter and is a useful way to predict molecular shape. To understand the electronic behavior of molecules, however, it is necessary to introduce **molecular orbital (MO) theory**. While in fact there are many manifestations of molecular orbital theory, the basic premise is that when atoms are close enough to each other to form bonds, their orbitals combine in ways that produce a new molecular orbital outcome.

Alkenes

MO theory is very similar to the concept of **hybridization**, in which *s* and *p* orbitals combine to form new hybrid orbitals. For example, the unhybridized carbon atom has a 2*s* orbital and three identical 2 *p* orbitals in its valence shell. To accommodate three things (atoms or lone pairs) around carbon, two of the 2 *p* orbitals and the 2*s* orbital combine to form three identical sp^2 orbitals, leaving one 2 *p* orbital untouched (see Figure 7-29).

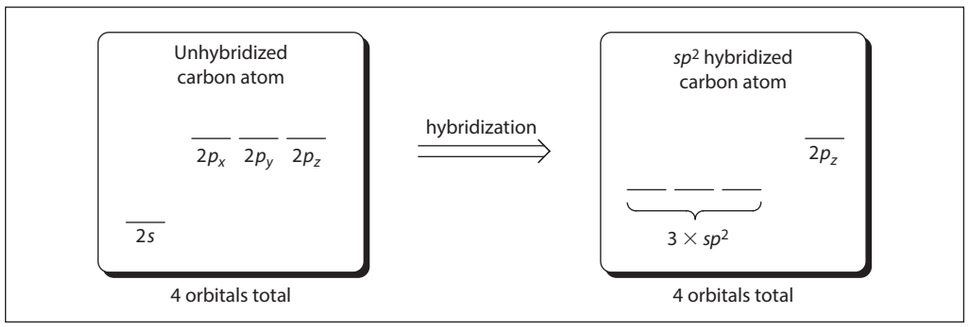

FIGURE 7-29 Atomic orbital hybridization.

While useful, the idea of hybridization is a simplification. It's tempting to imagine (and in fact some textbooks propose) that these hybrid orbitals interact in predictable ways to make new molecules. In reality, molecular orbitals are governed by complex quantum chemical considerations that can be predicted fully accurately only by sophisticated computer calculations. However, that is not to say that molecular orbitals are devoid of conceptual power. To explore some of these principles, examine the molecular orbital scenario for ethene (see Figure 7-30).

Ethene is constituted from two carbon atoms and four hydrogen atoms. Each carbon atom has four atomic orbitals (think of them as being sp^2 hybridized), and each of the four hydrogen atoms has a single 1s orbital, for a total of 12 atomic orbitals. These atomic orbitals combine to form 12 new and unique molecular orbitals, all of different energies. **Hund's rule** and the **Pauli exclusion principle** apply to molecules

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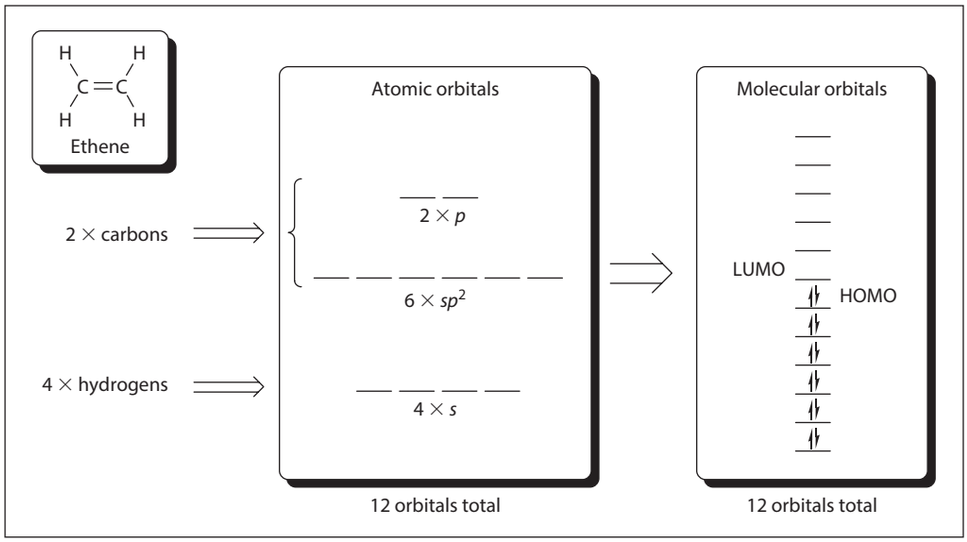

FIGURE 7-30 Molecular orbitals of ethene.

as well as atoms, so once these molecular orbitals are formed, they fill up from bottom to top. Since ethene has 12 electrons total (4 valence electrons from each carbon and 1 electron from each hydrogen), the bottommost 6 molecular orbitals are filled, and the topmost six are empty.

In general, the shapes of these orbitals (as calculated by computer algorithms) are complex and nonintuitive. However, there are special cases that can be very accurately predicted using **frontier molecular orbital (FMO) theory**. Here the frontier can be thought of as separating the filled from the unfilled orbitals—the frontier orbitals are thus the **highest occupied molecular orbital (HOMO)** and the **lowest unoccupied molecular orbital (LUMO)**. It turns out that these orbitals govern much of the reactivity of molecules, and moreover their shape can be predicted by manipulating the unhybridized p orbitals using a method called the **linear combination of atomic orbitals (LCAO)**.

The principle of LCAO is that adjacent p orbitals mix in predictable ways. If each orbital is a mathematical wave function, then they can be combined by addition and subtraction to result in new molecular orbitals. This principle is illustrated in the following table. If the wave function of the first p orbital (φ_1) is added to that of the second p orbital (φ_2), then a new molecular orbital is formed in which the two p orbitals are in-phase (lower row). A **constructive relationship** results, in which the electron density is shared between the two carbon atoms, providing a bonding interaction. This type of bond is designated a π bond. Conversely, if one p orbital is subtracted from the other, then a **destructive relationship** results, and the electron density drops to zero between the carbon atoms—this point of no electron density is called a **node** (designated by the dashed line in the schematic). In general, a node occurs every time the sign of the phase $(+/-)$ occurs.

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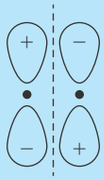
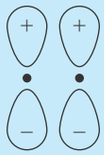
TABLE 7-7 Frontier Molecular Orbitals for Ethene

LCAO	Schematic	Model	Nodes	Symm	Population	Frontier
$+\varphi_1 - \varphi_2$			1	A	—	LUMO
$+\varphi_1 + \varphi_2$			0	S		HOMO

Extended π (pi) Systems

These π molecular orbitals arise anytime there are contiguous arrays of unhybridized p orbitals. **Extended π (pi) systems** develop when more than two adjacent p orbitals are present, as is the case with butadiene (see the following table), a molecule that has two adjacent double bonds. Historically, such double bonds have been called **conjugated**, a term that stems from their tendency to undergo chemistry together, rather than as isolated double bonds. This behavior is explained by FMO theory: each carbon bears an unhybridized p orbital, and this contiguous array interacts to give four new π molecular orbitals. Since they've been constructed using only the p orbitals, each of which housed a single electron, there are only four electrons to accommodate. Therefore, only the first two molecular orbitals are filled.

As it turns out, the two lowest energy molecular orbitals in butadiene have a net constructive effect, so they are called **bonding orbitals** and designated π. The two highest energy molecular orbitals, on the other hand, are overall destabilizing; therefore, they are called **antibonding orbitals** and designated π^*. Notice that increasing energy correlates with increasing number of nodes—this is a general trend. There is another guideline that derives from symmetry. An outcome of the mathematics behind LCAO dictates that all π molecular orbitals must be either symmetric (S) or antisymmetric (A). Symmetric, the more familiar term, means that the orbital reflects upon itself across a vertical center line, with phases matching exactly. **Antisymmetric** means that reflection across a center line results in the exact *opposite* phase for each and every point. When the π molecular orbitals are arranged properly, the progression usually alternates between symmetric and antisymmetric orbitals.

Generally speaking, the larger the extended π (pi) system, the lower the energy. Therefore, molecules with multiple double bonds are more stable if those bonds are arranged in alternating arrays. For example, 1,3-pentadiene is more stable than

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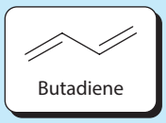
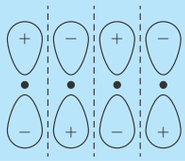
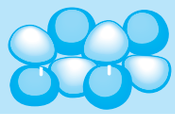
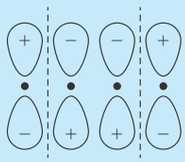
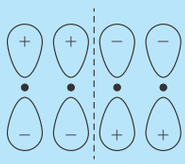
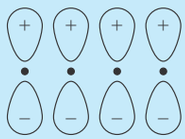
TABLE 7-8 **II** Molecular Orbitals for Butadiene



LCAO	Schematic	Model	Nodes	Symm	Population	Frontier
$+\varphi_1 - \varphi_2 + \varphi_3 - \varphi_4$			3	A	—	
$+\varphi_1 - \varphi_2 - \varphi_3 + \varphi_4$			2	S	—	LUMO
$+\varphi_1 + \varphi_2 - \varphi_3 - \varphi_4$			1	A		HOMO
$+\varphi_1 + \varphi_2 + \varphi_3 + \varphi_4$			0	S		

1,4-pentadiene, and 2-cyclohexanone is more stable than 3-cyclohexanone (see Figure 7-31). This is a phenomenon known as **conjugation**. Since you know that the origin of the effect can be described by MO theory, it comes as no surprise that conjugated double bonds often behave as a collective, whereas nonconjugated double bonds behave as two isolated species.

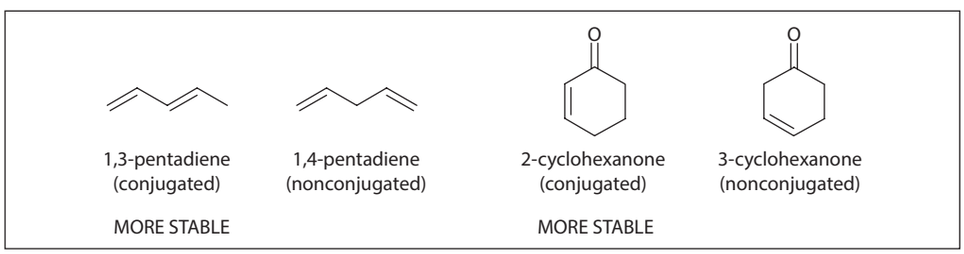


FIGURE 7-31 Conjugated vs. nonconjugated double bonds.

True conjugation arises from a mixing of adjacent p orbitals. A similar (but weaker) effect can arise from the interaction of p orbitals with adjacent bonds. For example, the methyl cation is not a very stable species, largely owing to the empty p orbital on

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carbon and the resulting violation of the octet rule. However, the ethyl cation is a bit more stable, because the C—H sigma bond on the methyl group can spill a bit of electron density into the empty *p* orbital, thereby stabilizing the cationic center (see Figure 7-32). This is an effect known as **hyperconjugation**, and while the sharing of electron density is not nearly as effective here as in true conjugation, it is still responsible for the following stability trend in carbocations and radicals: methyl < primary ≪ secondary < tertiary.

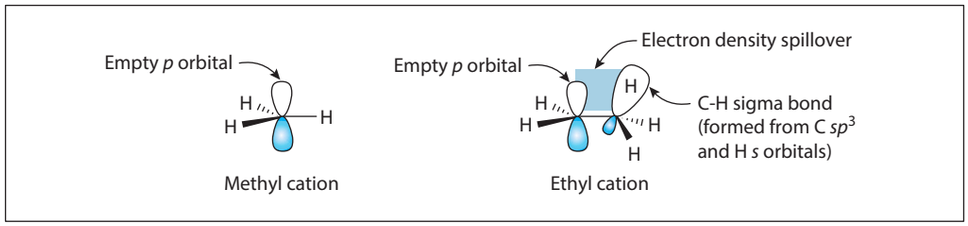

FIGURE 7-32 Hyperconjugation in the ethyl cation.

Aromatic Systems

In comparison with linear arrays, when *p* orbitals are arranged in a circle without interruption, as in benzene (see Figure 7-33), unexpected stabilization can emerge. As an outcome of the mathematics of LCAO (which is not discussed here), there are usually multiple sets of degenerate orbitals (i.e., orbitals of the same energy level). While it is not intuitively straightforward to construct molecular orbital diagrams themselves, there is a handy mnemonic device known as **Frost's circle**, which allows you to sketch out the relative energy levels of such molecules.

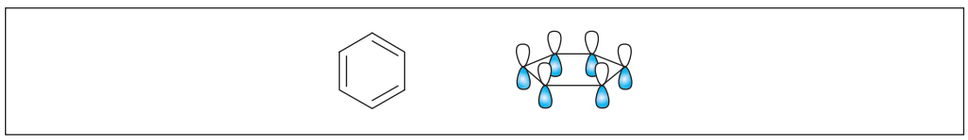

FIGURE 7-33 Contiguous *p* orbitals in benzene.

Frost's circle is really quite simple—it starts by drawing a regular polygon of the appropriate size with one point down. A circle is then drawn around the polygon, and each point of contact represents a molecular orbital energy level. For example, benzene is a six-membered ring, so its array of molecular orbitals starts with a single lowest-energy MO, followed by two sets of two MOs of the same energy, and then a single highest-energy MO (see Figure 7-34). Since benzene has 6π electrons, only the three lowest-energy orbitals are filled. This electronic arrangement accounts for the fact that benzene is particularly stable, a phenomenon known as aromaticity.

Aromaticity arises only from molecules possessing a cyclic, contiguous, and coplanar array of *p* orbitals. But this arrangement can also result in **antiaromaticity**,

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whereby molecules are less stable than expected. The difference between aromaticity and antiaromaticity lies in the number of π-electrons that must be accommodated. This can be predicted using **Hückel's rule**, which states that systems having $4n\pi$ electrons, (i.e., 4, 8, 12 electrons) tend to be antiaromatic, and those having $(4n+2)\pi$ electrons (i.e., 2, 6, 10 electrons) tend to be aromatic.

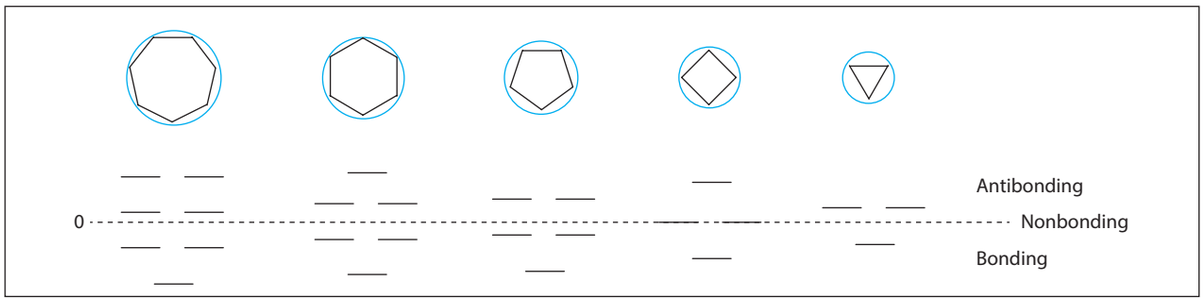

FIGURE 7-34 Frost's circle for determining aromatic MO energy levels.

Figure 7-35 demonstrates the molecular orbital basis of Hückel's rule using cyclopentadienyl ions. The molecular orbital energy levels are drawn using Frost's circle, and then populated with the appropriate number of p electrons. The cyclopentadienyl cation has only 4 electrons in the π (pi) system, whereas the corresponding anion has 6 (the negative charge represents a lone pair of electrons on carbon). Using Hückel's rule, you would predict the anion to be stable (aromatic) and the cation to be unstable (antiaromatic), which is indeed the experimentally observed result. However, the MO picture provides more insight into why the cation is so unstable—the molecule has 2 unpaired electrons. Finally, cyclopentadiene itself (far right), is considered nonaromatic. Since to be aromatic or antiaromatic, there must be a cyclic, contiguous, coplanar array of p orbitals, cyclopentadiene is out of the running because there is no p orbital at the methylene (CH_2) center, which interrupts the π (pi) system. Therefore,

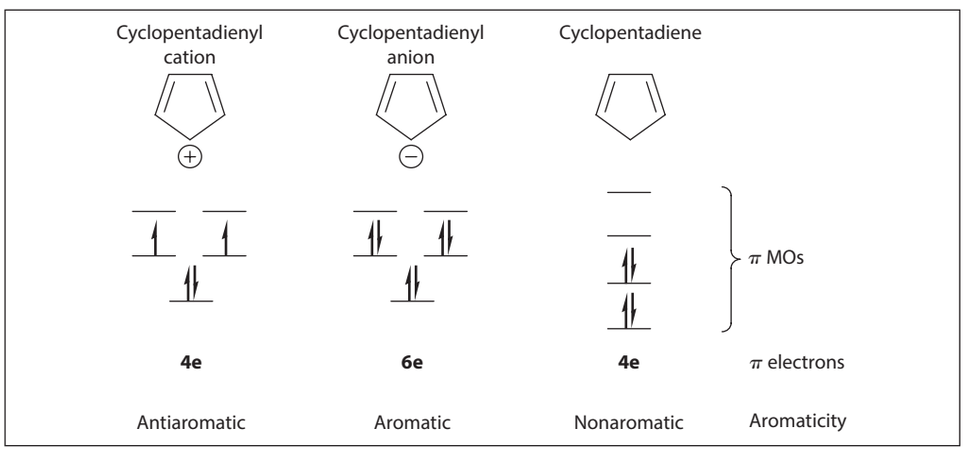

FIGURE 7-35 The molecular orbital origin of aromaticity.

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its MO diagram is analogous to that of butadiene (see the earlier table "Π Molecular Orbitals for Butadiene" on page 233).

MO Description of Resonance

MO theory also provides a more thorough understanding of resonance. For example, the acetaldehyde anion (see Figure 7-36) is stabilized by resonance delocalization, whereby the negative charge is distributed between the carbon and the oxygen. Resonance forms do not "equilibrate"—that is, the molecule does not oscillate between forms A and B—rather, the two resonance structures are an attempt to represent a more complete truth than any single Lewis structure can. However, if you apply simple geometrical rules to each form, you would predict an sp^3 hybridization for the anionic carbon in form A, but form B clearly indicates an sp^2 geometry. How do you accurately predict the geometry of the molecule?

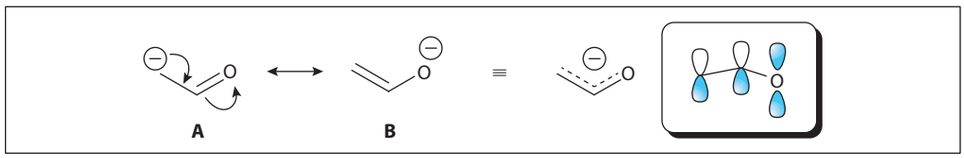

FIGURE 7-36 Resonance stabilization of the acetaldehyde anion.

Molecular orbital theory shows that an extended π system can be established by housing the negative charge in a p orbital. Thus the three-orbital array gives rise to a set of molecular orbitals in which the electron density is distributed throughout the molecule and the overall energy is minimized. For this reason, you expect both the anionic carbon and the oxygen to exhibit sp^2 hybridization, since this is the only way that all three atoms have unhybridized p orbitals. This is at variance with the predictions for the methyl anion (see earlier table "Geometries of Some Special Carbon Centers" on page 211), which was based on minimizing steric interactions; here the energy benefit of an extended π-system compensates for the steric cost. Therefore, the acetaldehyde anion is a completely planar molecule.

A similar anomaly can be seen with cations, as well. Thus the dimethylaminomethyl cation (see Figure 7-37) can be shown as two resonance forms (A and B), in which the nitrogen lone pair participates in stabilizing the adjacent positive charge on carbon. However, you are faced with a dilemma similar to the acetaldehyde anion: form A would predict an sp^3 hybridization for nitrogen, whereas form B appears to have sp^2 geometry. The only way for form B to have meaning is if a π bond is established between the 2 p orbitals on carbon and nitrogen (inset). Therefore, the species is planar.

Aside from the geometrical considerations, these two examples show the action of two specific types of functional groups. The carbonyl group (C=O) is an

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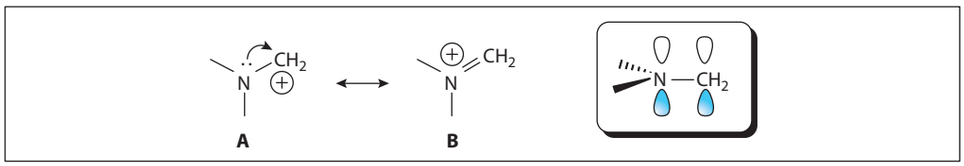

FIGURE 7-37 Resonance stabilization of the dimethylaminomethyl cation.

electron-withdrawing group (designated **EW**), while the amino group (NR_2) is an **electron-donating group (ED)**. This idea is important for a variety of chemical reactivities, but the easiest way to keep the categories straight is to examine whether the group would best stabilize a cation or an anion. Generally speaking, electron density can be pushed *into* EW groups, thus stabilizing a negative charge, whereas electrons can be pushed *from* ED groups, which stabilizes adjacent positive charges. For this reason, ED groups generally have lone pairs.

There are two components of electron-withdrawing and electron-donating behavior: resonance and induction. As the term suggests, the **resonance effect** can be represented by electron-pushing arrows to give different resonance forms. This effect may be weak or strong, but it can exert influence over very large distances through extended π-systems. The **inductive effect** stems primarily from electronegativity; it can be quite strong, but its influence is local—the magnitude drops off sharply as distance from the functional group increases. The following table summarizes these effects for some common functional groups. In most cases the inductive and resonance effects work in concert, while in some instances they are at odds. The amino and methoxy substituents are almost always classified as ED groups, even though the central atoms are electronegative—the activity of the lone pairs dominates their behavior. The halogens are more subtle (e.g., chlorine). Generally speaking, they are grouped with the EW substituents.

TABLE 7-9 Some Common ED and EW Groups

Functional	Group Formula	Resonance Effect	Inductive Effect
Electron-withdrawing (EW) groups			
acetyl	—$COCH_3$		
carbomethoxy	—CO_2CH_3		
chloro	—Cl		
cyano	—CN		
nitro	—NO_2		
phenylsulfonyl	—SO_2Ph		
Electron-donating (ED) groups			
amino	—NH_2		
methoxy	—OCH_3		
methyl	—CH_3		
		← more EW | more ED →	← more EW | more ED →

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NONCOVALENT BONDS

In addition to the fixed covalent bonds that hold molecules together, there are a host of so-called intermolecular forces that play a significant role in the properties of molecules.

Types of Intermolecular Forces

The magnitude of intermolecular forces spans a wide range, as depicted in Figure 7-38. Unlike covalent bonds, which are permanent and relatively easy to study thermodynamically, these noncovalent interactions are often fugitive, making unequivocal determination of their energies very difficult. Consequently, published values vary widely and are dependent upon the method of measurement (or calculation) and the types of systems studied. For the purposes of this overview, examples will be limited to organic molecules in solution.

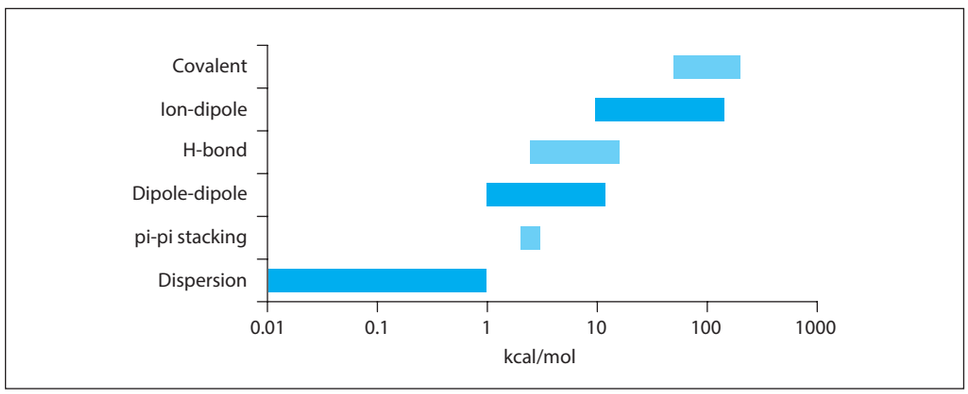

FIGURE 7-38 Comparison of intermolecular interaction energies.

ION-DIPOLE INTERACTIONS

Ion-dipole interactions are largely responsible for the dissolution of ionic compounds in water. For example, lithium chloride has a lattice enthalpy of 206 kcal/mol and a melting point of 605 °C, yet it dissolves rather easily in water. Remarkably, relatively weak ion-dipole forces (see Figure 7-39) overcome the strong ionic bonds holding the salt together. Obviously, this is an outcome of the sheer numbers of interactions in play: although small individually, these forces are quite significant in sum. Two effects are noteworthy in this interaction: the ions themselves are stabilized by the multiple interactions, and the water (or other solvent) is organized around the ions. This well-defined organization of solvent around a solute is often called the **solvent shell**.

Not surprisingly, the degree of organization around the ions is dependent upon the amount of charge. For example, the calcium ion (Ca^{2+}) exhibits a solvation enthalpy

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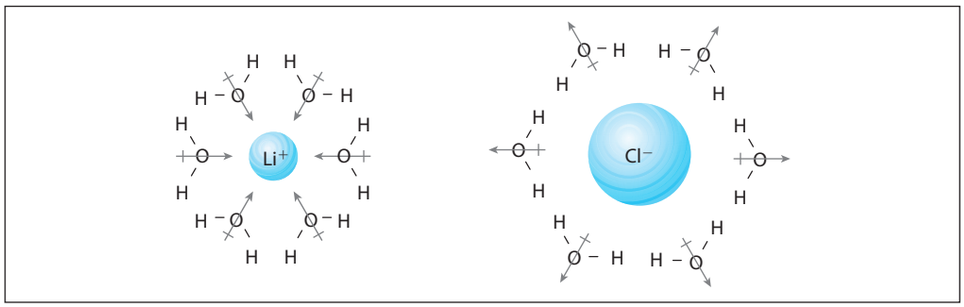

FIGURE 7-39 Ion-dipole forces around aqueous lithium chloride.

(ΔH_{solv}) in water of 416 kcal/mol, twice that of the similarly-sized sodium cation (Na^+). Conversely, with constant charge, the strength of solvation increases as ionic radius decreases. In other words, as the electrostatic charge is confined to a smaller space, its effect on the surrounding solvent is more pronounced. As one illustration of this effect, Figure 7-40 charts the dependence of solvation enthalpy on ionic radius among the alkali metal cations.

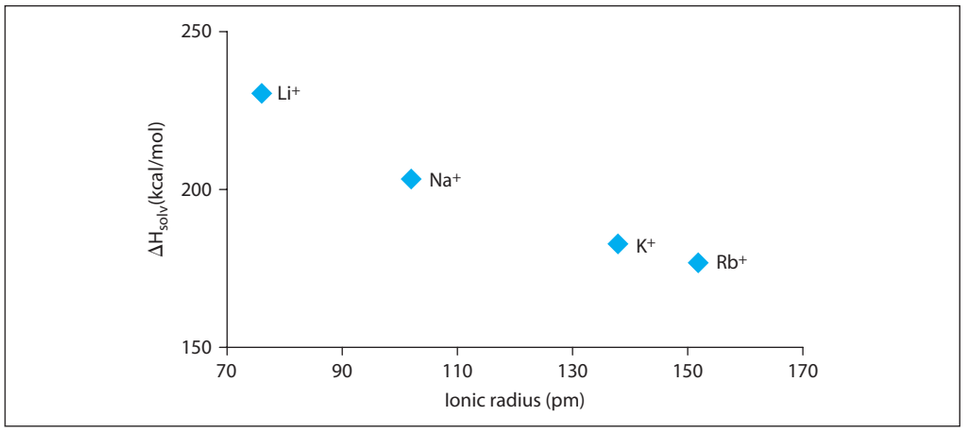

FIGURE 7-40 Solvation enthalpy as a function of ionic size.

HYDROGEN BONDING

The **hydrogen bond** is perhaps the most wide-ranging intermolecular force among biological molecules, and it remains a bit of an enigma. The classical view of the hydrogen bond (see Figure 7-41) is that of an interaction between an electron-rich lone pair (i.e., the hydrogen bond acceptor) and a highly polarized covalent bond involving hydrogen (i.e., the hydrogen bond donor).

Most textbooks relegate hydrogen bonds to compounds containing nitrogen, oxygen, and fluorine. However, there is considerable evidence that thiols (RSH) can serve as hydrogen bond donors, and one study suggests that more than 70 percent of

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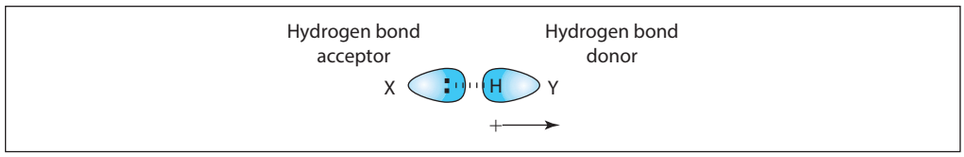

FIGURE 7-41 Model of hydrogen bonding.

cysteines in proteins have the thiol proton within hydrogen-bonding distance of a nitrogen or oxygen. The role of sulfur as a hydrogen bond acceptor is more controversial, however. In a very recent investigation using atomic force microscopy, 8-hydroxyquinoline was found to exhibit hydrogen bonds involving OH, NH, and CH bonds (see Figure 7-42).

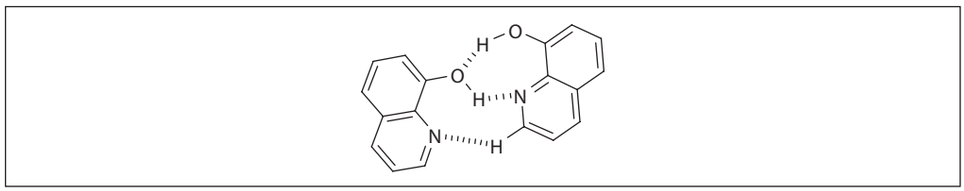

FIGURE 7-42 Hydrogen bonds observed in 8-hydroxyquinoline.

A particularly strong type of hydrogen bond occurs in proteins when two oppositely-charged amino acid residues are involved, a phenomenon known as a **salt bridge**. These interactions can be crucial in establishing the structure and function of proteins. For example, salt bridges in the active site of *Escherichia coli* aminopeptidase N (see Figure 7-43) have recently been shown to play a critical role in that enzyme's stability and activity.

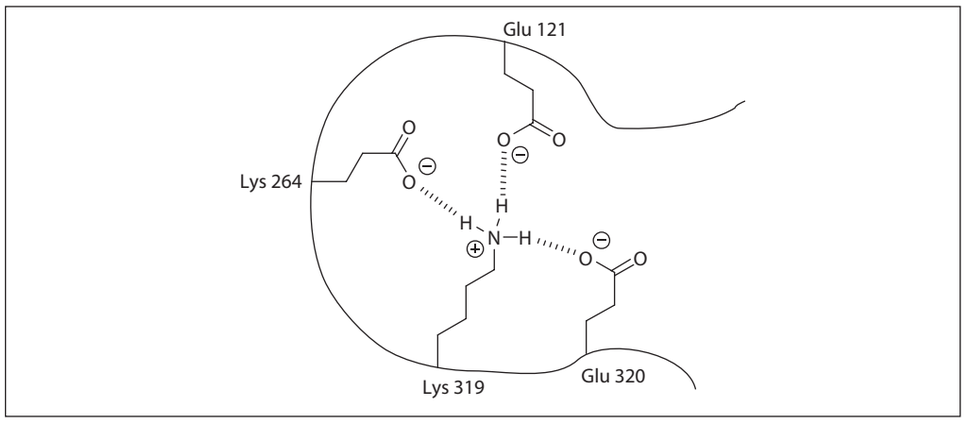

FIGURE 7-43 Salt bridges in the active site of *E. coli* aminopeptidase N.

DIPOLE-DIPOLE INTERACTIONS

Dipole-dipole forces arise when polar molecules are in proximity to each other. The force can be either attractive or repulsive, depending upon the relative directions of the

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two dipoles, with an antiparallel arrangement providing the greatest stabilizing effect. Thus, for example, when *p*-dichlorobenzene (a common ingredient in mothballs) is dissolved in acetone, much of the solvent power is provided by dipole-dipole forces (see Figure 7-44). One characteristic of the dipole-dipole interaction is its sensitivity to distance—the force drops off as a function of the distance cubed.

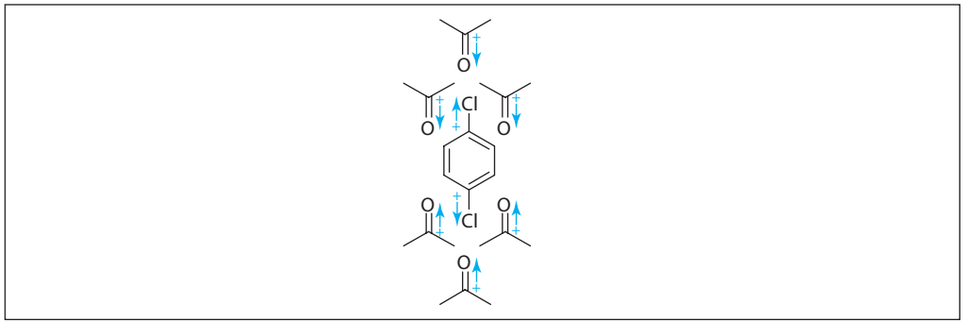

FIGURE 7-44 Dipole-dipole forces in acetone solution.

PI-PI STACKING

An often neglected contributor to intramolecular forces is the **pi-pi stacking** interaction. Aromatic compounds such as benzene have molecular orbitals that are in a circular array, and the particular arrangement leads to anisotropic electron densities. The areas above and below the ring (i.e., the faces) are slightly electron rich, while the perimeter (or edge) is slightly electron poor. This sets the stage for favorable electrostatic interactions between aromatic rings. Figure 7-45 shows two common motifs found in pi-pi interactions. One is an **off-center parallel arrangement**, in which electron-rich and electron-poor layers align so that there is a small amount of coulombic attraction at the edges. Another is an **edge-to-face alignment**, whereby the electron-poor edge of one aromatic ring aligns perpendicular to the electron-rich face of another. The strength of these interactions is on the order of weak dipole-dipole forces, but in large biopolymers such as DNA, the sum of these interactions can be substantial.

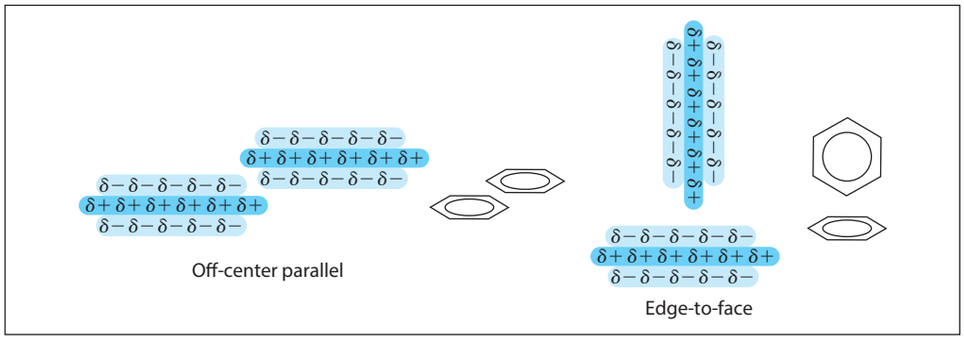

FIGURE 7-45 Two common pi-stacking motifs.

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DISPERSION FORCES

The weakest of the intermolecular forces, **London dispersion forces (LDF)**, are found in all molecules. In the case of nonpolar species, where stronger interactions are absent, LDFs are usually the sole cohesive principle between molecules. Were it not for the dispersion effect, noble gases would not exist in liquid form. Dispersion forces even account for about one-quarter of the attractive force between water molecules.

The basis of LDF lies in fairly complex quantum mechanical outcomes, but it is often described as the favorable coalignment of instantaneous dipoles that are randomly generated by momentary unequal distributions of electron density in a molecule. While these instantaneous dipoles average out to zero over time for a given molecule, the continual coordination of these microdipoles between molecules provides a net attractive force.

Effects of Intermolecular Forces

PHYSICAL PROPERTIES

One of the most obvious and pervasive impacts of intermolecular forces on molecules is seen in their boiling points. This is illustrated in the three molecules 2-methyl-1-butene, ethyl acetate, and propionic acid (see Figure 7-46), which have almost identical molecular weights. For the 2-methyl-1-butene, LDFs are the predominant intermolecular force. However, in the case of ethyl acetate, the introduction of the oxygen atoms results in polar bonds (between carbon and oxygen), leading to a net dipole. In the condensed phase, these dipoles align between molecules (left inset), providing a greater cohesive force, which is revealed in a higher boiling point (77 °C vs. 31 °C).

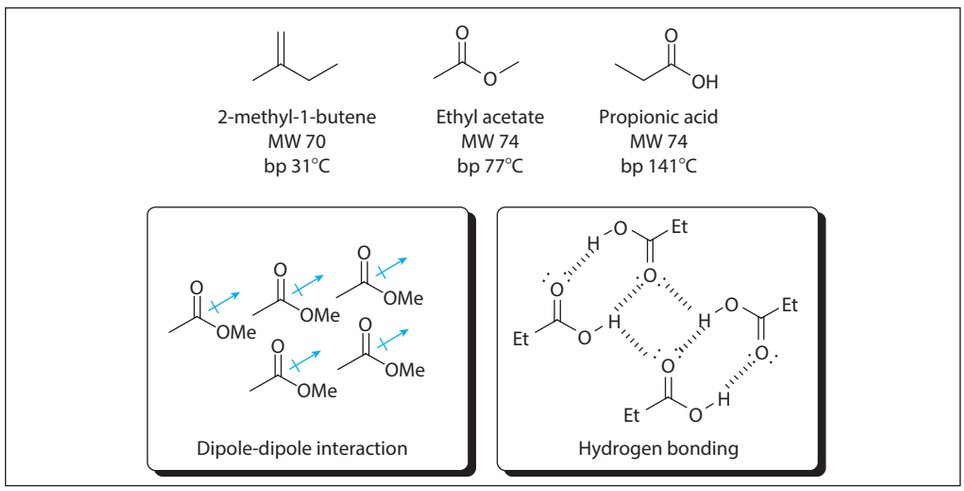

FIGURE 7-46 Impact of intermolecular forces on boiling points.

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With propionic acid, there are not only dipole-dipole interactions, but also opportunities for hydrogen bonding. In fact, most carboxylic acids in the condensed phase form strong dimeric structures with complementary hydrogen bonds (see Figure 7-46, right). Because of these additional intermolecular forces, propionic acid has a boiling point of 141 °C vs. 77 °C for ethyl acetate.

Molecular geometry can play an important role, as exemplified by the two geometric isomers of 1,2-dichloroethene (see Figure 7-47). In the *cis*-isomer, both of the polar C—Cl bonds are pointed in the same direction, so there is a net dipole for the whole molecule. In the *trans*-isomer, these bonds are antiparallel and the bond dipoles tend to cancel each other out, leading to a molecule with a very small net dipole. This is consequently reflected in the lower boiling point of the *trans*-isomer.

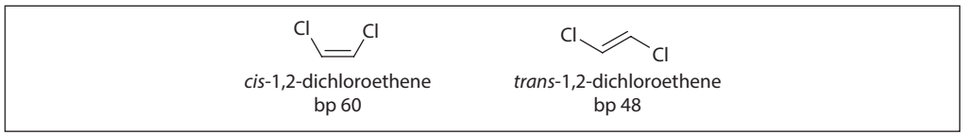

FIGURE 7-47 Impact of intermolecular forces on boiling points.

Intermolecular forces are additive, and since hydrogen bonds are relatively strong, polyols tend to have exceedingly high boiling points. Figure 7-48 provides a useful set of examples. In a series of nonpolar molecules, progressing from ethane to butane to 3-methylpentane results in a steady increase in boiling points, due to increased mass and a larger electronic cloud (i.e., greater LDFs). When one CH_2 group is replaced with an OH group (ethane to ethanol), the boiling point jumps from −88°C to 65°C, a 153°C difference. Additional OH groups magnify this effect, so the difference in boiling points between 3-methylpentane and glycerol is 226°C. Taking this to an extreme, the straight-chain hydrocarbon eicosane ($C_{20}H_{42}$, MW 283) has a boiling point of 343°C, as opposed to the much smaller, but much more polar, glucose molecule ($C_6H_{12}O_6$, MW 180), which has a calculated boiling point of 527° C (in practice, glucose burns before it boils).

CONFORMATIONAL IMPLICATIONS

Noncovalent forces can play a major role in many aspects of molecular shape and behavior. For example, in *trans*-1,2-dichlorohexane (see Figure 7-49, left), the chair conformer in which the two chloro substituents are diequatorial is preferred on steric grounds. However, the equilibrium is not as right-handed as you might expect, since the diaxial conformer allows the two polar bonds to be antiparallel, which avoids the unfavorable dipole-dipole interactions in the diequatorial conformer. Similarly, in *cis*-cyclohexanediol (see Figure 7-49, right), the equilibrium is less right-handed than steric considerations would predict, since the diaxial conformer can take advantage of an intramolecular hydrogen bond.

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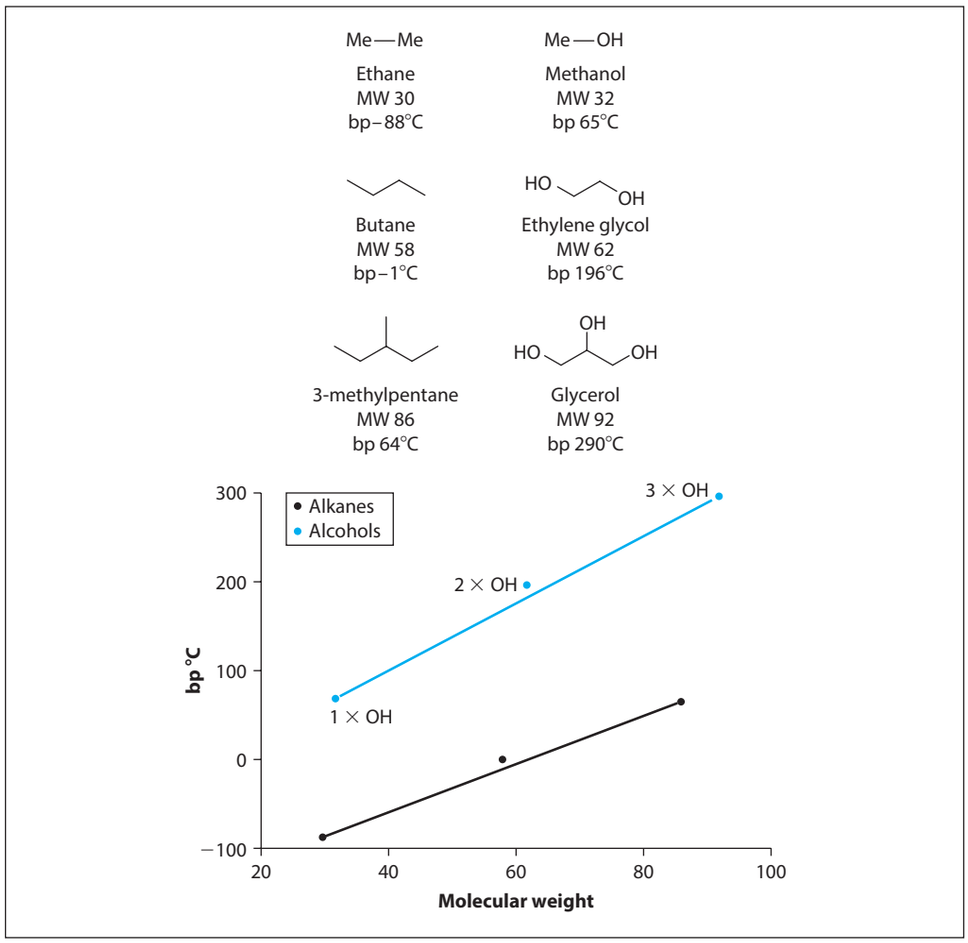

FIGURE 7-48 Impact of multiple functional groups on boiling points.

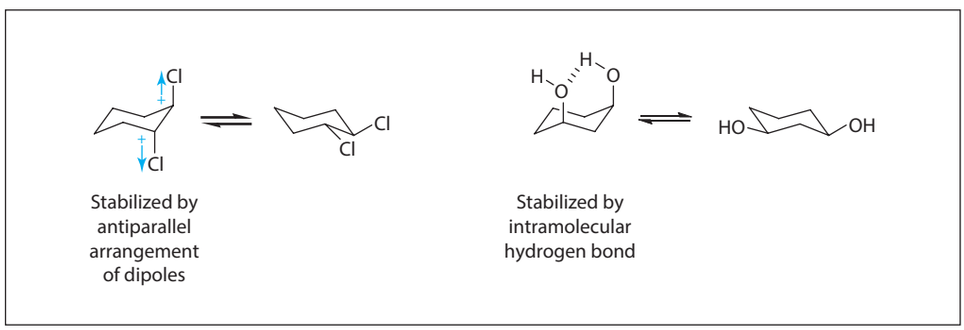

FIGURE 7-49 Conformational stabilization by noncovalent forces.

These factors even play out in chemical equilibria. For example, ketones are known to be in tautomeric equilibrium with their enol counterparts, but the keto form is generally the far more thermodynamically stable option. Thus 2-butanone exists almost exclusively in the keto form. However, pentane-2,4-dione exists as a mixture of keto

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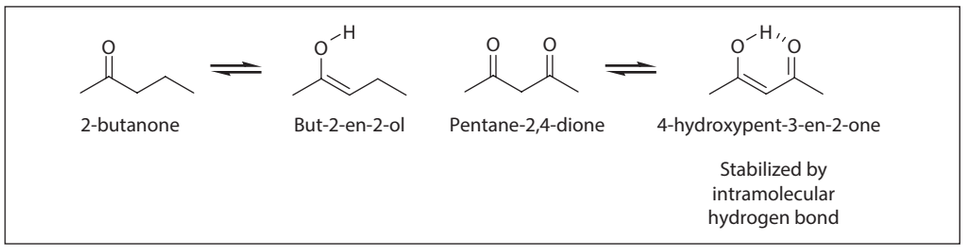

FIGURE 7-50 Stabilization of a β-ketoenol tautomer by hydrogen bonding.

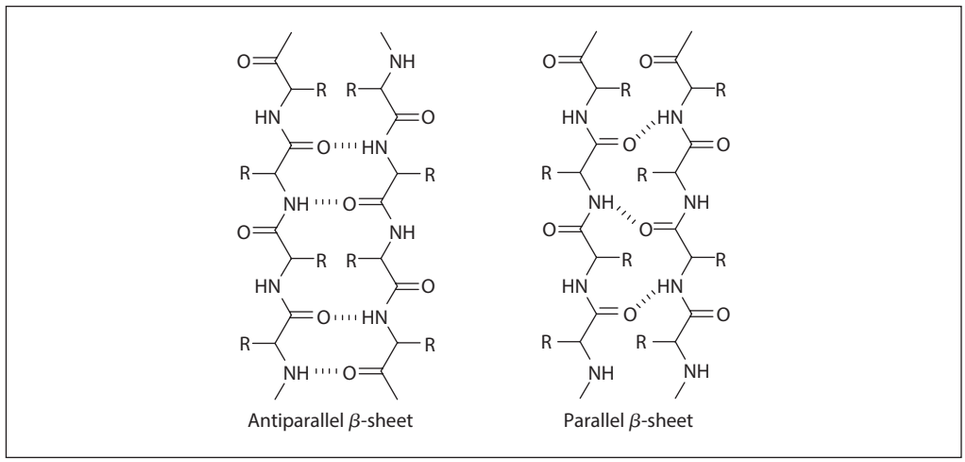

FIGURE 7-51 Two protein β-sheet geometries stabilized by hydrogen bonding.

and enol forms due to (among other things) the stabilization of the enol tautomer by an intramolecular hydrogen bond (see Figure 7-50).

Most significant for biomolecules, noncovalent forces are responsible for essential structural motifs found in macromolecular arrays. In addition to the familiar nucleotide base pairings through complementary hydrogen bonds (see Figure 7-7 on page 208), the α-helices and β-sheets found in proteins are the outcome of noncovalent forces (most significantly hydrogen bonding). Figure 7-51 illustrates two β-sheet patterns, both of which feature repeating hydrogen bonds between the amide carbonyl oxygen and the NH proton.

Material chemists can also take advantage of these interactions when designing molecules. For example, the polycyclic aromatic molecule shown in Figure 7-52 self-assembles into a repeating hexameric array, which forms an intriguing macromolecular honeycomb structure. The forces leading to this behavior have been traced to the dipole-dipole interactions between the trifluoromethylphenyl moieties on adjacent molecules, which are electron deficient on one end of the benzene ring due to the strong electron-withdrawing effects of the trifluoromethyl group.

Thus, while the chemical bond is the primary determinant in the structure of individual small molecules, intermolecular forces are of equal importance in dictating the structure of much larger biomolecules and macromolecular assemblies.

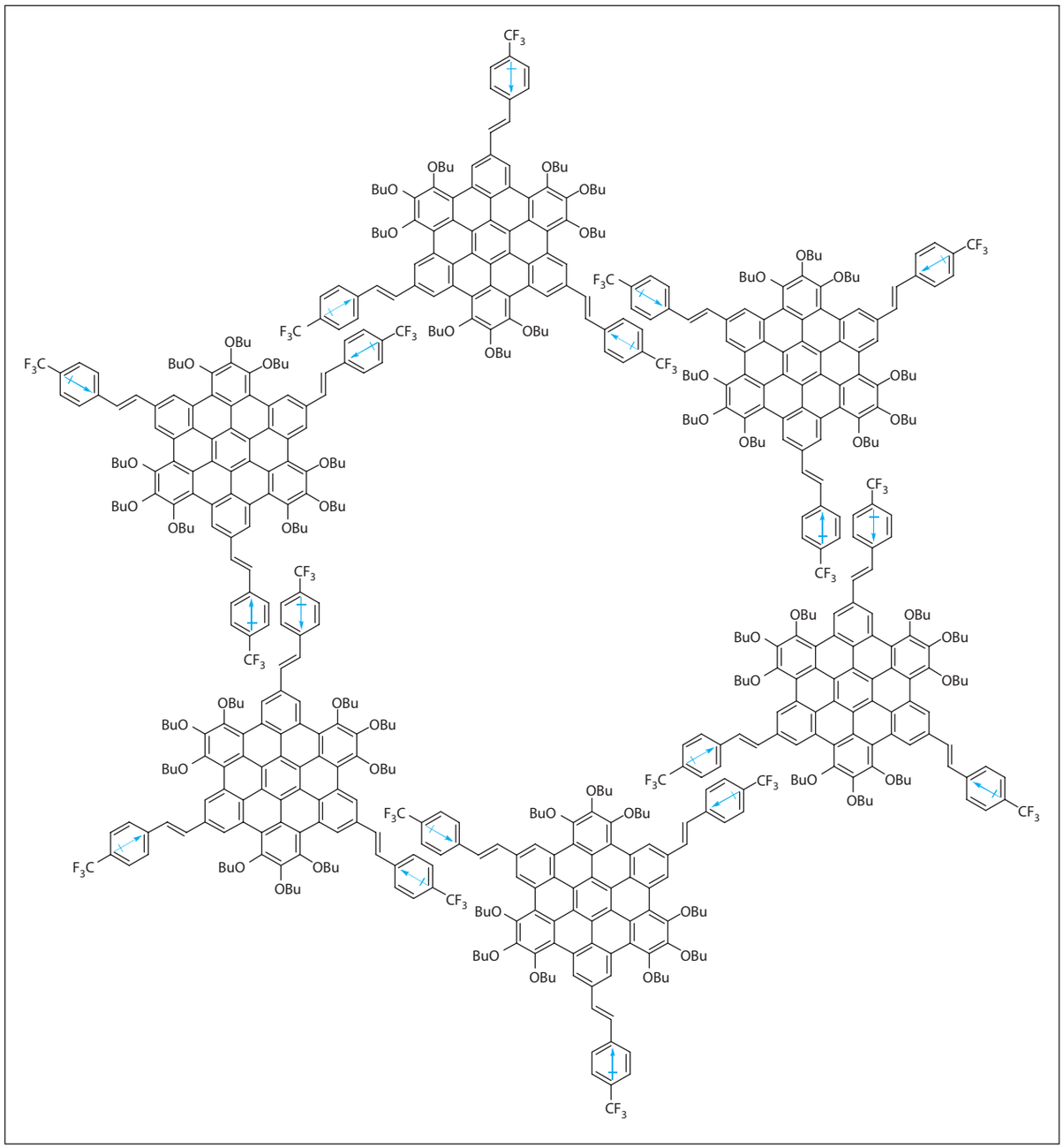

FIGURE 7-52 Molecular self-assembly driven by dipole-dipole interactions.