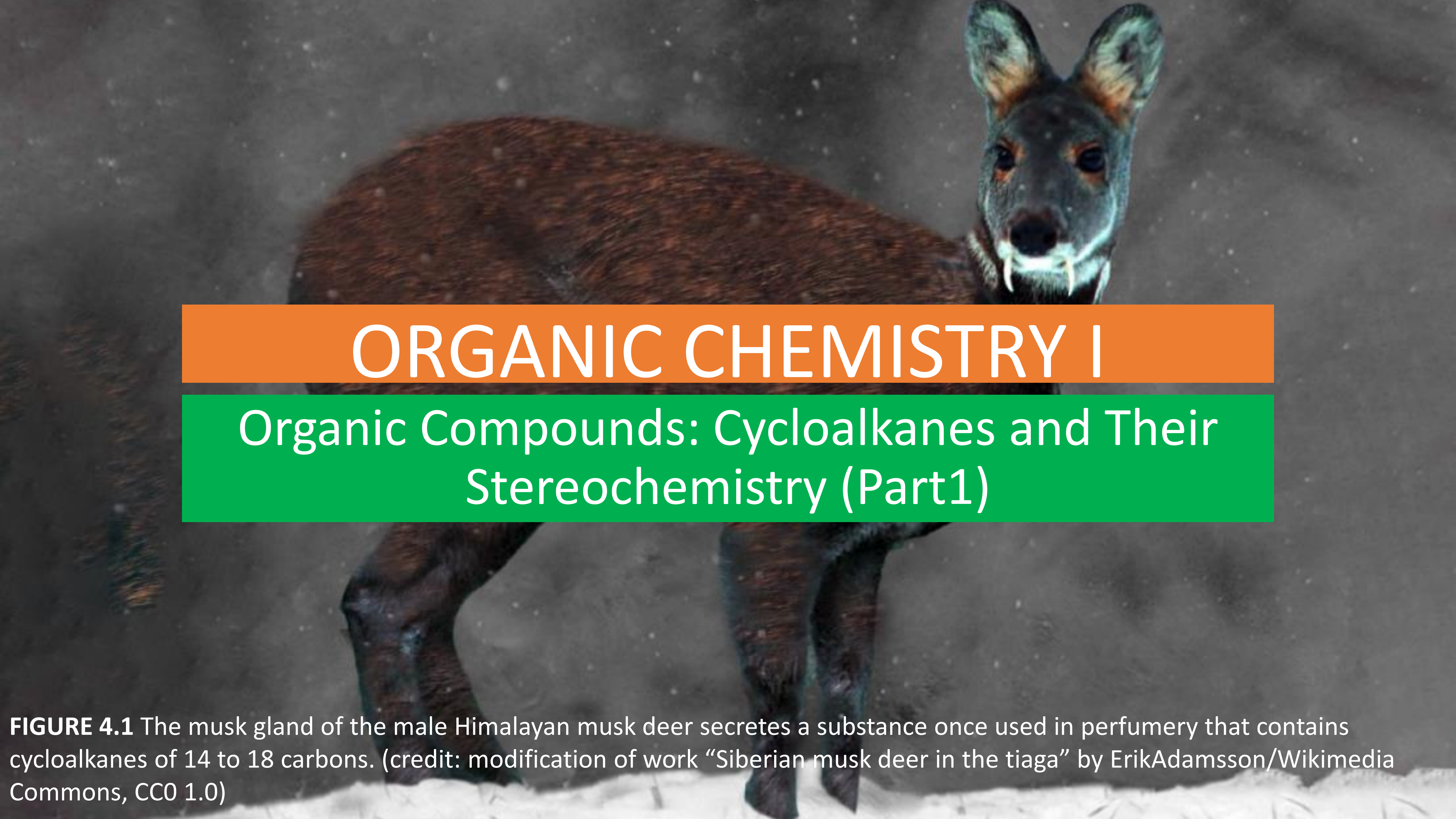


ORGANIC CHEMISTRY I

Organic Compounds: Cycloalkanes and Their Stereochemistry (Part1)

FIGURE 4.1 The musk gland of the male Himalayan musk deer secretes a substance once used in perfumery that contains cycloalkanes of 14 to 18 carbons. (credit: modification of work “Siberian musk deer in the tiaga” by ErikAdamsson/Wikimedia Commons, CC0 1.0)

Topic Discussion

Why This Chapter?
4.1 Naming Cycloalkanes
4.2 Cis–Trans Isomerism in Cycloalkanes
4.3 Stability of Cycloalkanes: Ring Strain
4.4 Conformations of Cycloalkanes
4.5 Conformations of Cyclohexane
4.6 Axial and Equatorial Bonds in Cyclohexane
4.7 Conformations of Monosubstituted Cyclohexanes
4.8 Conformations of Disubstituted Cyclohexanes
4.9 Conformations of Polycyclic Molecules
Chemistry Matters—Molecular Mechanics

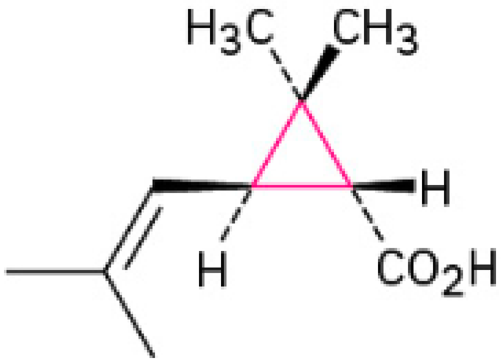
WHY THIS CHAPTER?

We’ll see numerous instances in future chapters where the chemistry of a given functional group is affected by being in a ring rather than an open chain.

Because cyclic molecules are encountered in most pharmaceuticals and in all classes of biomolecules, including proteins, lipids, carbohydrates, and nucleic acids, it’s important to understand the behavior of cyclic structures.

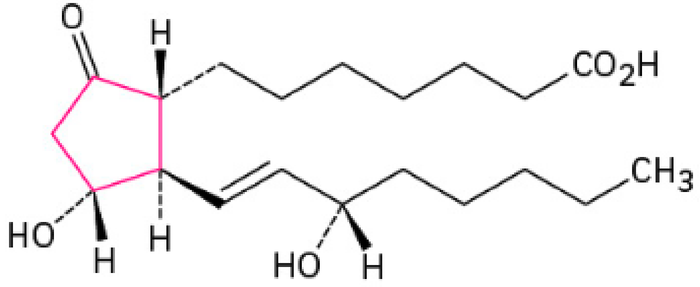
Although we've only discussed open-chain compounds up to now, most organic compounds contain rings of carbon atoms.

Chrysanthemic acid, for instance, whose esters occur naturally as the active insecticidal constituents of chrysanthemum flowers, contains a three-membered (cyclopropane) ring.



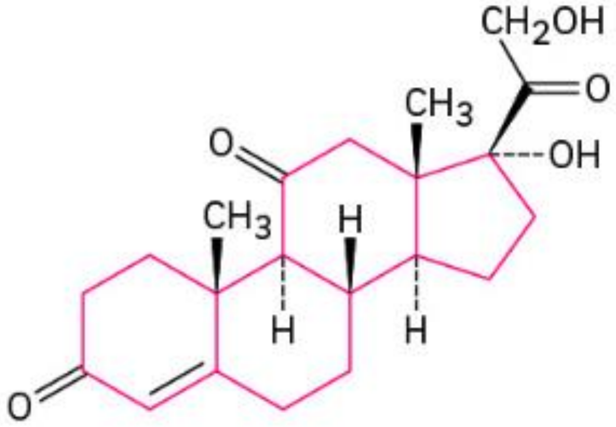
Chrysanthemic acid

Prostaglandins, potent hormones that control an extraordinary variety of physiological functions in humans, contain a five-membered (cyclopentane) ring.



Prostaglandin E_1

Steroids, such as cortisone, contain four rings joined together—three six-membered (cyclohexane) and one five- membered. We’ll discuss steroids and their properties in more detail in **Sections 27.6** and **27.7**.

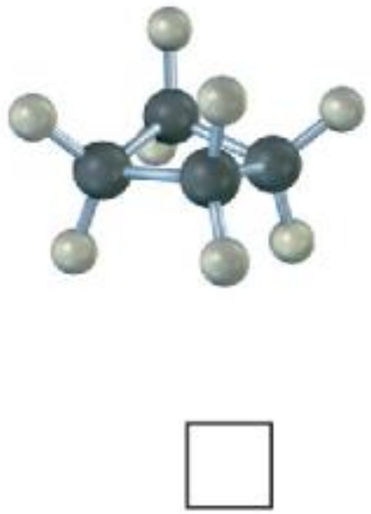


Cortisone

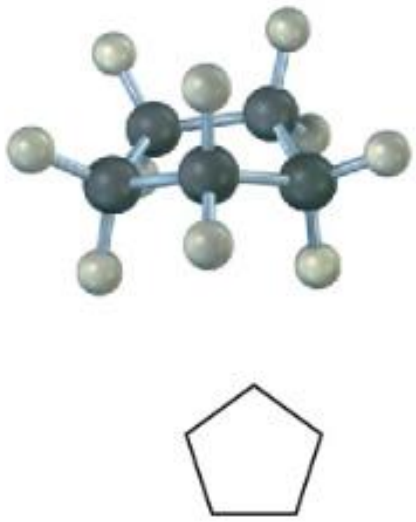
4.1 Naming Cycloalkanes

Saturated cyclic hydrocarbons are called **cycloalkanes**, or **alicyclic** compounds (**ali**phatic **cyclic**). Because cycloalkanes consist of rings of $-CH_2-$units, they have the general formula $(CH_2)_n$, or C_nH_{2n}, and can be represented by polygons in skeletal drawings.

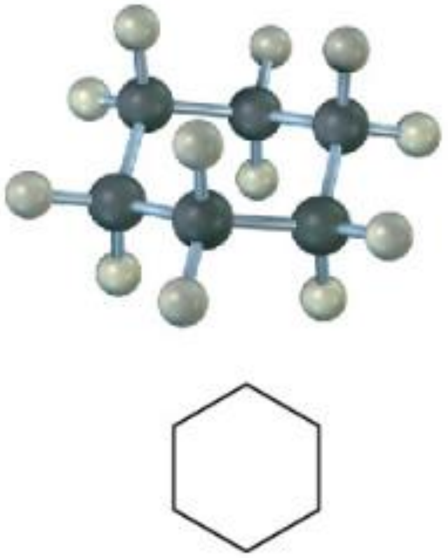
Cyclopropane



Cyclobutane



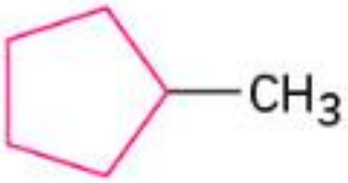
Cyclopentane



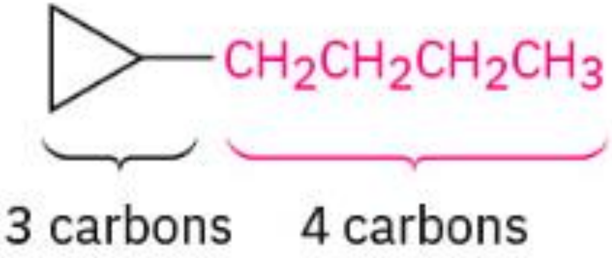
Cyclohexane

STEP 1 Find the parent.

Count the number of carbon atoms in the ring and the number in the largest substituent. If the number of carbon atoms in the ring is equal to or greater than the number in the substituent, the compound is named as an alkyl-substituted cycloalkane. If the number of carbon atoms in the largest substituent is greater than the number in the ring, the compound is named as a cycloalkyl-substituted alkane. For example:



Methylcyclopentane

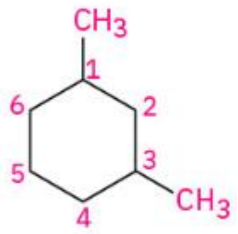


1-Cyclopropylbutane

STEP 2

Number the substituents, and write the name.

For an alkyl- or halo-substituted cycloalkane, choose a point of attachment as carbon 1 and number the substituents on the ring so that the second substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found.

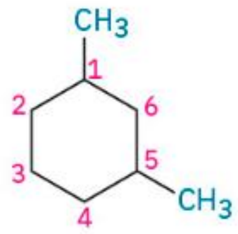


1,3-Dimethylcyclohexane

↑

Lower

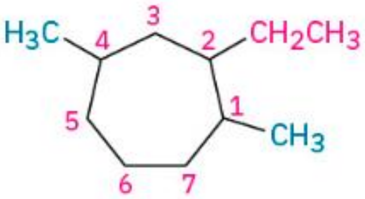
NOT



1,5-Dimethylcyclohexane

↑

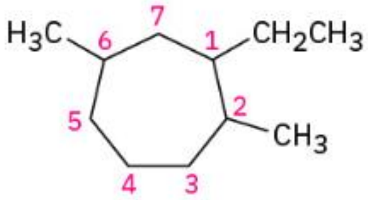
Higher



2-Ethyl-1,4-dimethylcycloheptane

↑ Lower ↑ Lower

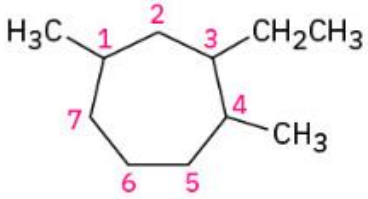
NOT



1-Ethyl-2,6-dimethylcycloheptane

↑

Higher

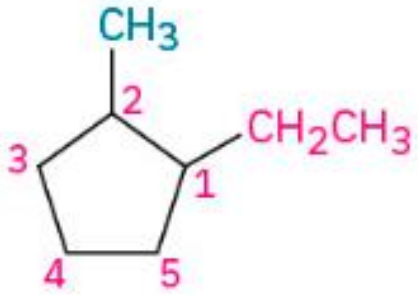


3-Ethyl-1,4-dimethylcycloheptane

↑

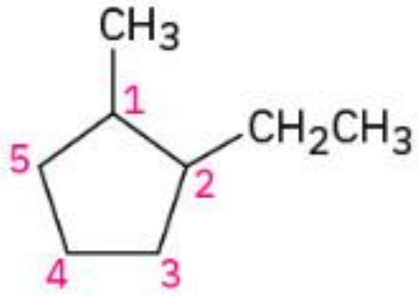
Higher

(a) When two or more different alkyl groups are present that could potentially take the same numbers, number them by alphabetical priority, ignoring numerical prefixes such as di- and tri-.



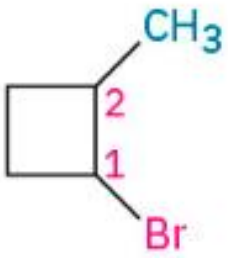
1-Ethyl-2-methylcyclopentane

NOT



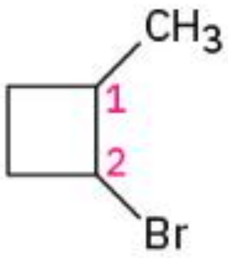
2-Ethyl-1-methylcyclopentane

(b) If halogens are present, treat them just like alkyl groups.



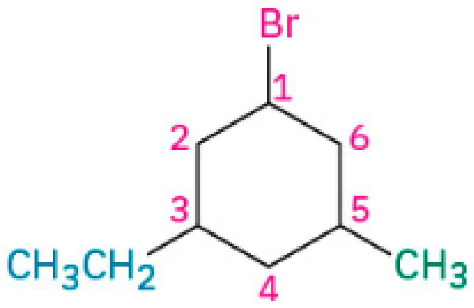
1-Bromo-2-methylcyclobutane

NOT

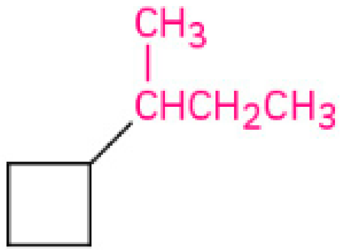


2-Bromo-1-methylcyclobutane

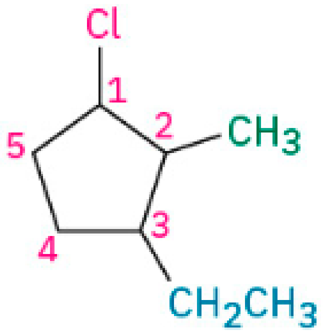
Some additional examples follow:



1-Bromo-3-ethyl-5-methyl-cyclohexane



(1-Methylpropyl)cyclobutane or *sec*-butylcyclobutane



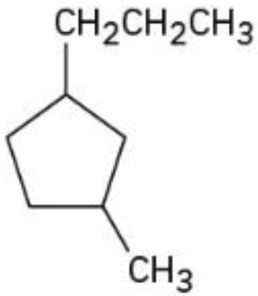
1-Chloro-3-ethyl-2-methyl-cyclopentane

PROBLEM 4-1

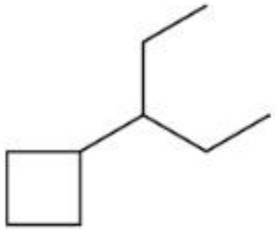
Give IUPAC names for the following cycloalkanes

(a)

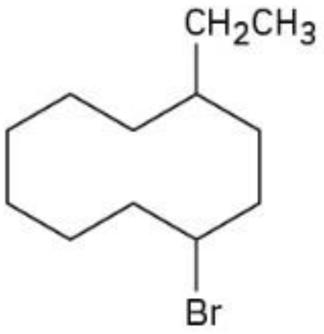
(b)



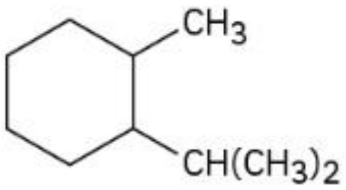
(c)



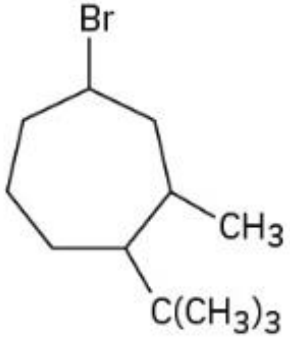
(d)



(e)



(f)



PROBLEM 4-2

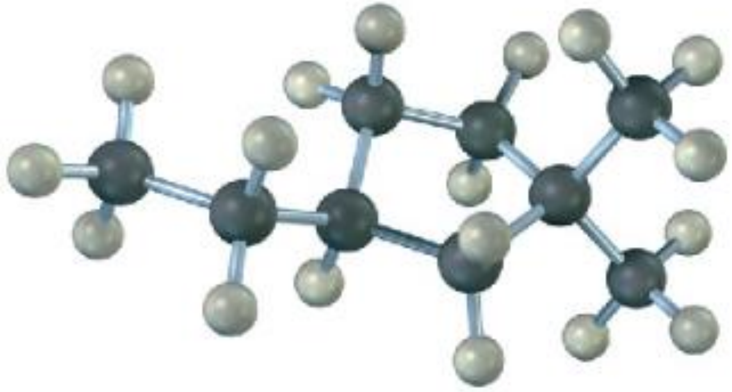
Draw structures corresponding to the following IUPAC names:

(a) 1,1-Dimethylcyclooctane (b) 3-Cyclobutylhexane

(c) 1,2-Dichlorocyclopentane (d) 1,3-Dibromo-5-methylcyclohexane

PROBLEM 4-3

Name the following cycloalkane:



4.2 Cis–Trans Isomerism in Cycloalkanes

In many respects, the chemistry of cycloalkanes is like that of open-chain alkanes: both are nonpolar and fairly inert. There are, however, some important differences. One difference is that cycloalkanes are less flexible than open-chain alkanes. In contrast with the relatively free rotation around single bonds in open-chain alkanes (**Section 3.6** and **Section 3.7**), there is much less freedom in cycloalkanes. Cyclopropane, for example, must be a rigid, planar molecule because three points (the carbon atoms) define a plane. No bond rotation can take place around a cyclopropane carbon–carbon bond without breaking open the ring (**FIGURE 4.2**).

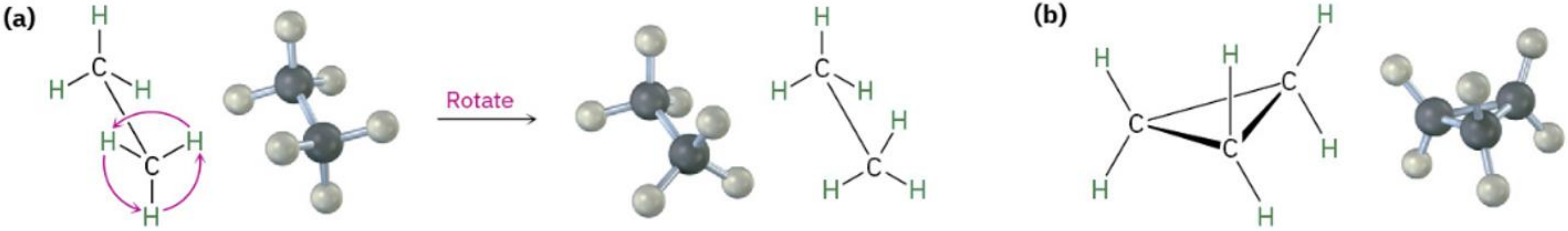
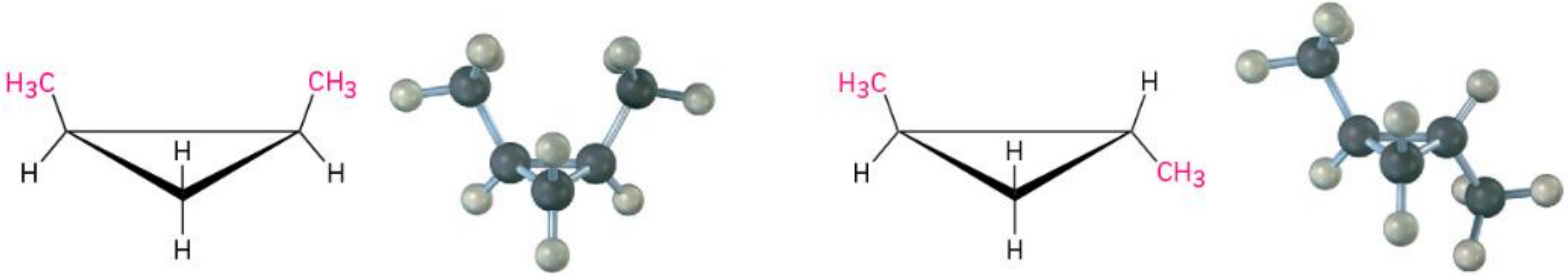


FIGURE 4.2 Bond rotation in ethane and cyclopropane. (a) Rotation occurs around the carbon–carbon bond in ethane, but (b) no rotation is possible around the carbon–carbon bonds in cyclopropane without breaking open the ring.

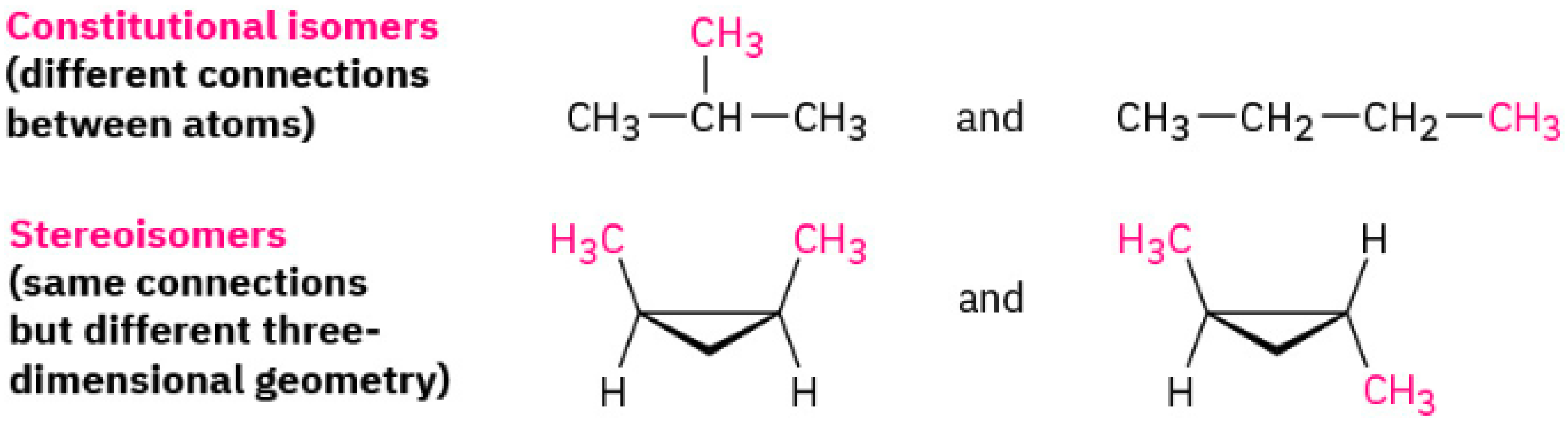


cis-1,2-Dimethylcyclopropane

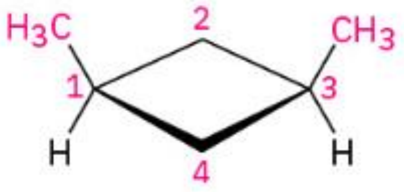
trans-1,2-Dimethylcyclopropane

FIGURE 4.3 There are two different 1,2-dimethylcyclopropane isomers, one with the methyl groups on the same face of the ring (cis) and the other with the methyl groups on opposite faces of the ring (trans). The two isomers do not interconvert.

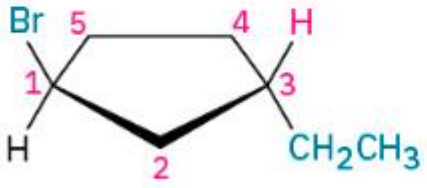
Unlike the constitutional isomers butane and isobutane, which have their atoms connected in a different order (**Section 3.2**), the two 1,2-dimethylcyclopropanes have the same order of connections but differ in the spatial orientation of the atoms. Such compounds, with atoms connected in the same order but differing in three- dimensional orientation, are called stereochemical isomers, or **stereoisomers**. As we saw in **Section 3.6**, the term stereochemistry is used generally to refer to the three-dimensional aspects of structure and reactivity.



The 1,2-dimethylcyclopropanes are members of a subclass of stereoisomers called **cis–trans isomers**. The prefixes *cis*- (Latin “on the same side”) and *trans*- (Latin “across”) are used to distinguish between them. *Cis–trans* isomerism is a common occurrence in substituted cycloalkanes and in many cyclic biological molecules



***cis*-1,3-Dimethylcyclobutane**



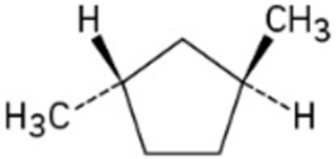
***trans*-1-Bromo-3-ethylcyclopentane**

WORKED EXAMPLE 4.1

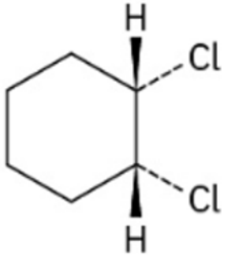
Naming Cycloalkanes

Name the following substances, including the *cis-* or *trans-* prefix:

(a)



(b)



Strategy

In these views, the ring is roughly in the plane of the page, a wedged bond protrudes out of the page, and a dashed bond recedes into the page. Two substituents are cis if they are both out of or both into the page, and they are trans if one is out of and one is into the page.

Solution

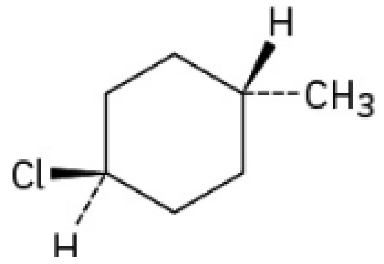
(a) *trans*-1,3-Dimethylcyclopentane

(b) *cis*-1,2-Dichlorocyclohexane

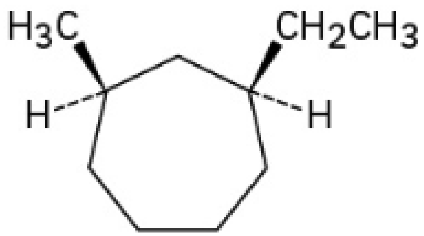
PROBLEM 4-4

Name the following substances, including the cis- or trans- prefix:

(a)



(b)



PROBLEM 4-5

Draw the structures of the following molecules:

(a) trans-1-Bromo-3-methylcyclohexane

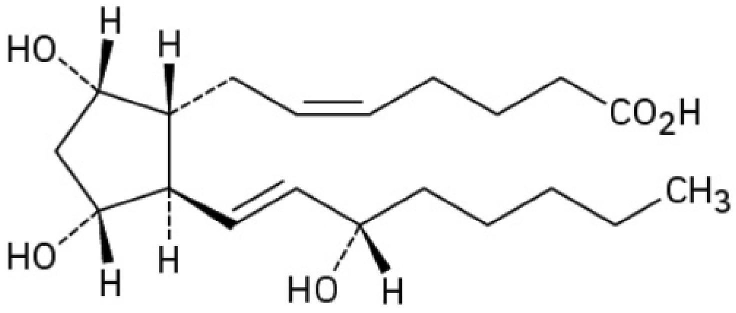
(b) cis-1,2-Dimethylcyclobutane

(c) trans-1-tert-Butyl-2-ethylcyclohexane

PROBLEM 4-6

Prostaglandin $F_{2\alpha}$ a hormone that causes uterine contraction during child birth, has the following structure.

- Are the two hydroxyl groups(–OH) on the cyclopentane ring *cis* or *trans* to each other?
- What about the two carbon chains attached to the ring?

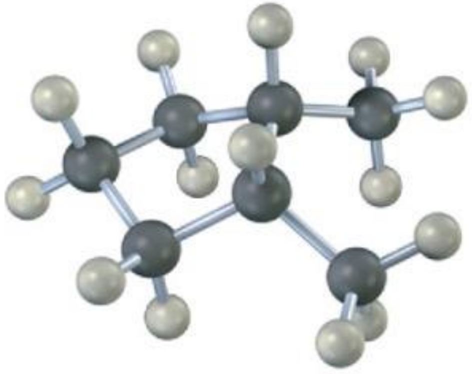


Prostaglandin $F_{2\alpha}$

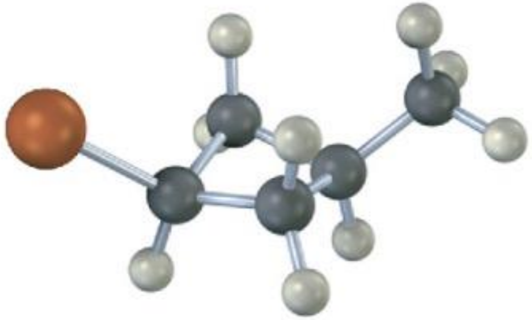
PROBLEM 4-7

Name the following substances, including the cis- or trans- prefix (red-brown = Br):

(a)

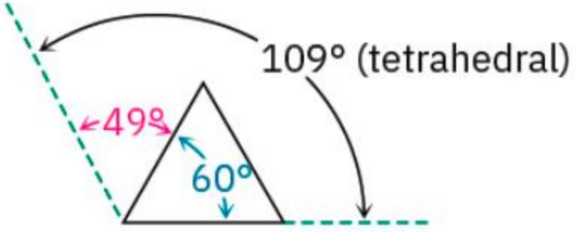


(b)

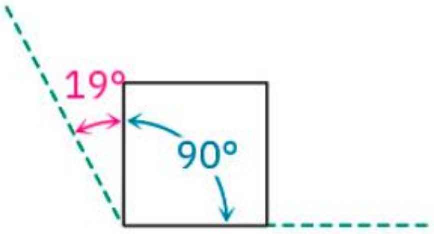


4.3 Stability of Cycloalkanes: Ring Strain

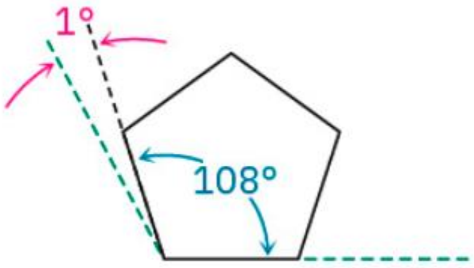
A theoretical interpretation of this observation was proposed in 1885 by Adolf von Baeyer, who suggested that small and large rings might be unstable due to **angle strain**—the strain induced in a molecule when bond angles are forced to deviate from the ideal 109° tetrahedral value. Baeyer based his suggestion on the simple geometric notion that a three-membered ring (cyclopropane) should be an equilateral triangle with bond angles of 60° rather than 109°, a four-membered ring (cyclobutane) should be a square with bond angles of 90°, a five- membered ring should be a regular pentagon with bond angles of 108°, and so on. Continuing this argument, large rings should be strained by having bond angles that are much greater than 109°.



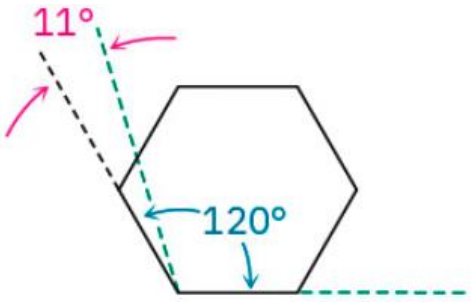
Cyclopropane



Cyclobutane



Cyclopentane



Cyclohexane

What are the facts? To measure the amount of strain in a compound, we have to measure the total energy of the compound and then subtract the energy of a strain-free reference compound. The difference between the two values should represent the amount of extra energy in the molecule due to strain. The simplest experimental way to do this for a cycloalkane is to measure its heat of combustion, the amount of heat released when the compound burns completely with oxygen. The more energy (strain) the compound contains, the more energy (heat) is released by combustion.

$$(CH_2)_n + 3n/2\,O_2 \longrightarrow n\,CO_2 + n\,H_2O + \text{Heat (add)}$$

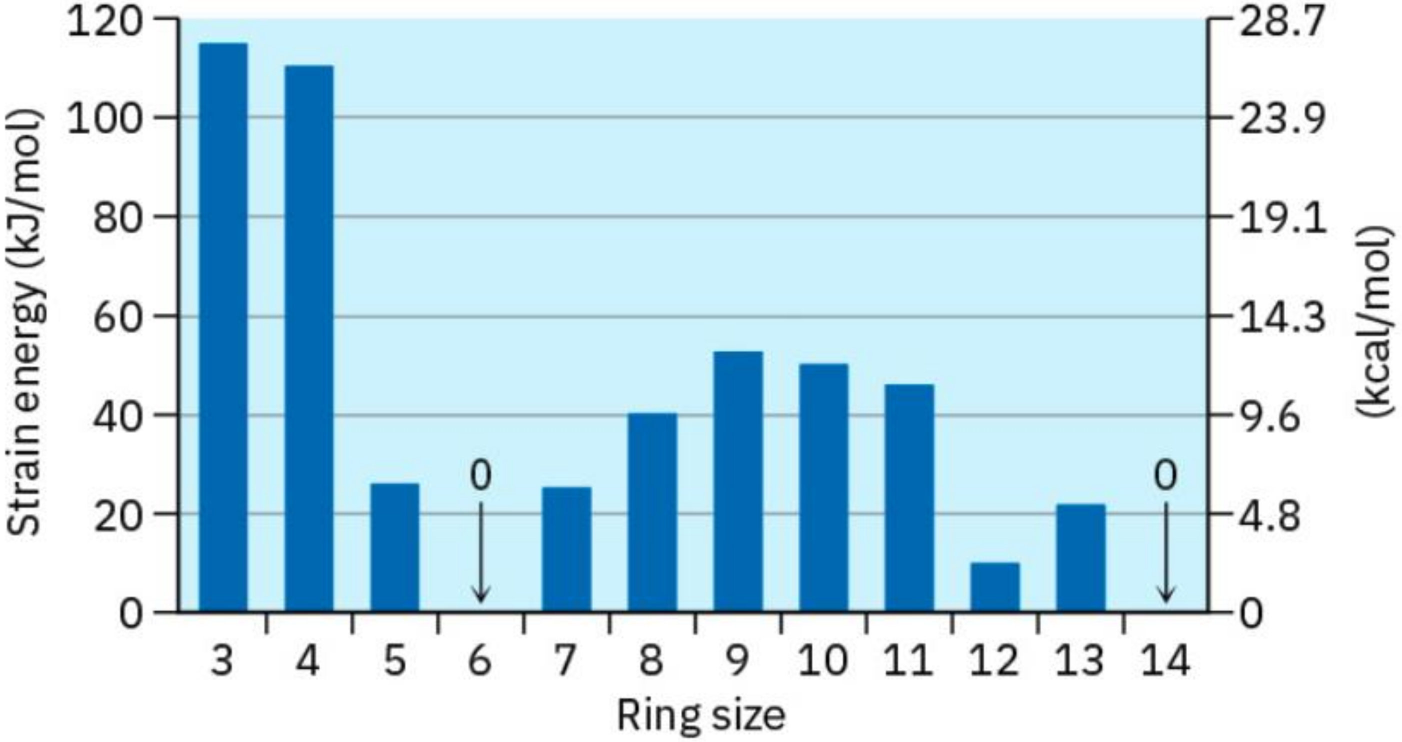


FIGURE 4.4 Cycloalkane strain energies, as calculated by taking the difference between cycloalkane heat of combustion per CH_2 and acyclic alkane heat of combustion per CH_2, and multiplying by the number of CH_2 units in a ring. Small and medium rings are strained, but cyclohexane rings and very large rings are strain-free.

The data in **FIGURE 4.4** show that Baeyer’s theory is only partially correct. Cyclopropane and cyclobutane are indeed strained, just as predicted, but cyclopentane is more strained than predicted, and cyclohexane is strain- free. Cycloalkanes of intermediate size have only modest strain, and rings of 14 carbons or more are strain-free. Why is Baeyer’s theory wrong?

In fact, as we’ll see in the next section, most cycloalkanes are not flat; instead, they adopt puckered three-dimensional conformations that allow bond angles to be nearly tetrahedral. As a result, angle strain occurs only in three- and four- membered rings, which have little flexibility. For most ring sizes, particularly the medium-ring (C7–C11) cycloalkanes, torsional strain caused by H ⟷ H eclipsing interactions at adjacent carbons (**Section 3.6**) and steric strain caused by the repulsion between nonbonded atoms that approach too closely (**Section 3.7**) are the most important factors. Thus, three kinds of strain contribute to the overall energy of a cycloalkane.

- **Angle strain**—the strain due to expansion or compression of bond angles
- **Torsional strain**—the strain due to eclipsing of bonds between neighboring atoms
- **Steric strain**—the strain due to repulsive interactions when atoms approach each other too closely

PROBLEM 4-8

Each H⟷H eclipsing interaction in ethane costs about 4.0kJ/mol. How many such interactions are present in cyclopropane? What fraction of the overall 115kJ/mol(27.5kcal/mol) strainenergy of cyclopropane is due to torsional strain?

PROBLEM 4-9

cis-1,2-Dimethylcyclopropane has more strain than trans-1,2-dimethyl cyclopropane. How can you account for this difference? Which of the two compounds is more stable?

4.4 Conformations of Cycloalkanes

Cyclopropane

Cyclopropane is the most strained of all rings, primarily due to the angle strain caused by its 60° C−C−C bond angles. In addition, cyclopropane has considerable torsional strain because the C−H bonds on neighboring carbon atoms are eclipsed (**FIGURE 4.5**).

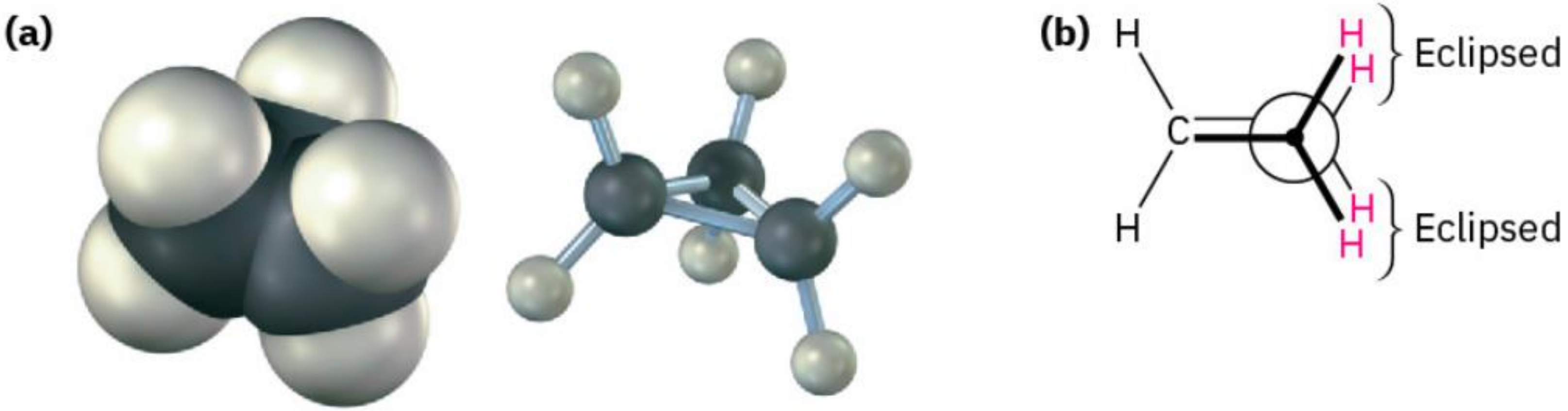
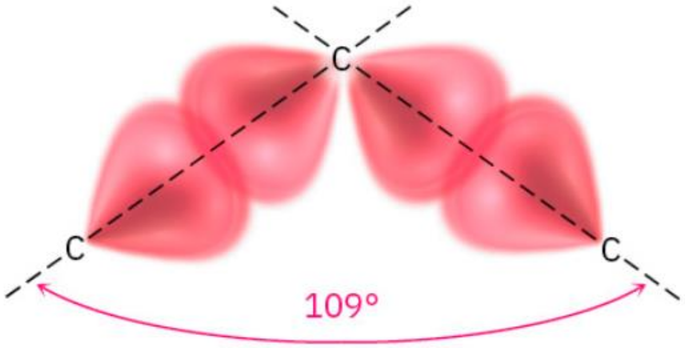


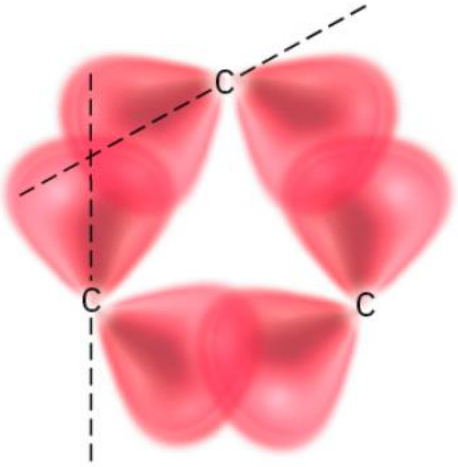
FIGURE 4.5 The structure of cyclopropane, showing the eclipsing of neighboring C−H bonds that gives rise to torsional strain. Part (b) is a Newman projection along a C−C bond.

How can the hybrid-orbital model of bonding account for the large distortion of bond angles from the normal 109° tetrahedral value to 60° in cyclopropane?

The answer is **that cyclopropane has bent bonds.**



Typical alkane C–C bonds



Typical bent cyclopropane C–C bonds

Cyclobutane

Cyclobutane has less angle strain than cyclopropane but has more torsional strain because of its larger number of ring hydrogens. As a result, the total strain for the two compounds is nearly the same—110 kJ/mol (26.4 kcal/ mol) for cyclobutane versus 115 kJ/mol (27.5 kcal/mol) for cyclopropane. Cyclobutane is not quite flat but is slightly bent so that one carbon atom lies about 25° above the plane of the other three (**FIGURE 4.6**). The effect of this slight bend is to increase angle strain but to decrease torsional strain, until a minimum-energy balance between the two opposing effects is achieved.

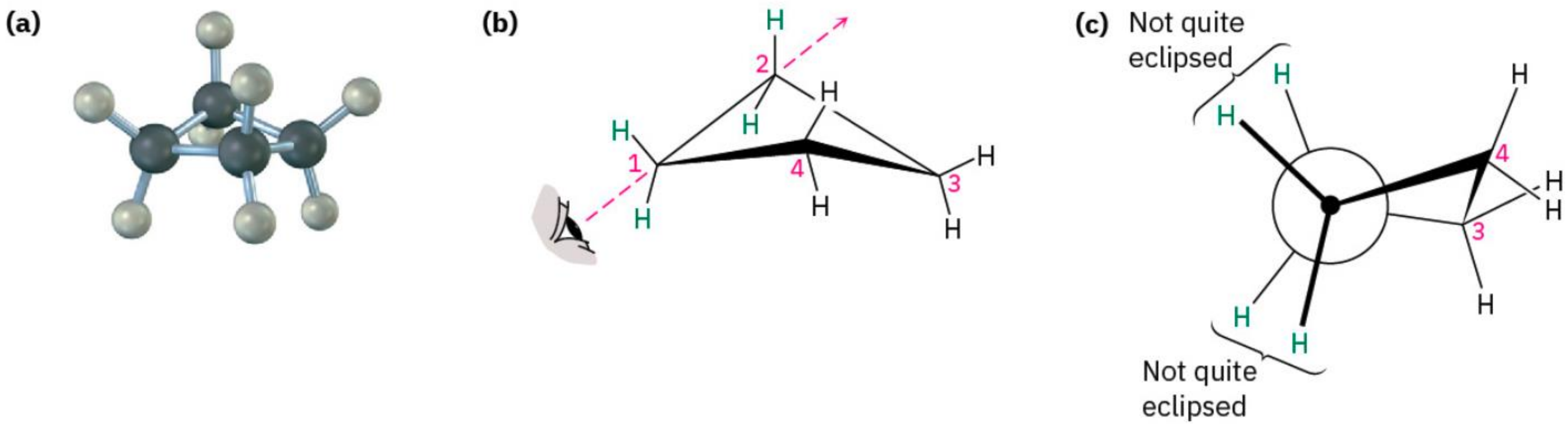


FIGURE 4.6 The conformation of cyclobutane. Part (c) is a Newman projection along a C−C bond, showing that neighboring C−H bonds are not quite eclipsed.

Cyclopentane

Cyclopentane was predicted by Baeyer to be nearly strain-free, but it actually has a total strain energy of 26 kJ/mol (6.2 kcal/mol). Although planar cyclopentane has practically no angle strain, it has a large torsional strain. Cyclopentane therefore twists to adopt a puckered, nonplanar conformation that strikes a balance between increased angle strain and decreased torsional strain. Four of the cyclopentane carbon atoms are in approximately the same plane, with the fifth carbon atom bent out of the plane. Most of the hydrogens are nearly staggered with respect to their neighbors (**FIGURE 4.7**).

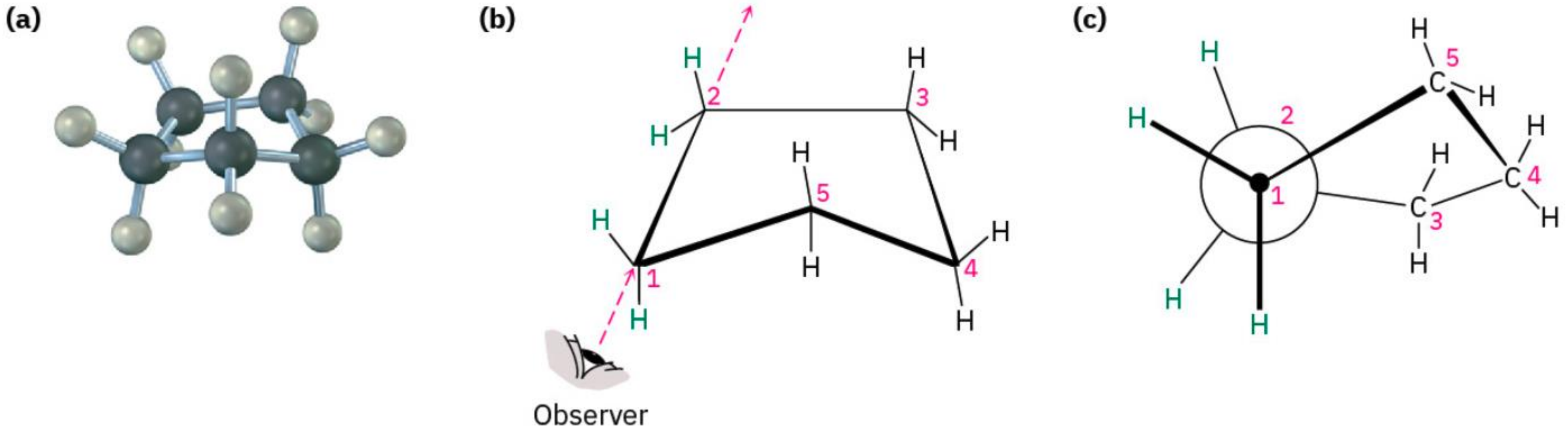


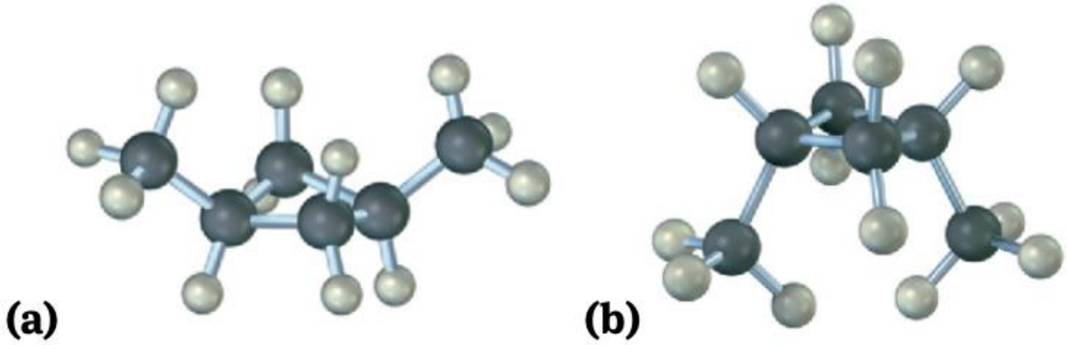
FIGURE 4.7 The conformation of cyclopentane. Carbons 1, 2, 3, and 4 are nearly coplanar, but carbon 5 is out of the plane. Part (c) is a Newman projection along the C1–C2 bond, showing that neighboring C−H bonds are nearly staggered.

PROBLEM 4-10

How many H⟷H eclipsing interactions would be present if cyclopentane were planar? Assuming an energy cost of4.0 kJ/mol for each eclipsing interaction, how much torsional strain would planar cyclopentane have? Since the measured total strain of cyclopentane is 26 kJ/mol, how much of the torsional strain is relieved by puckering?

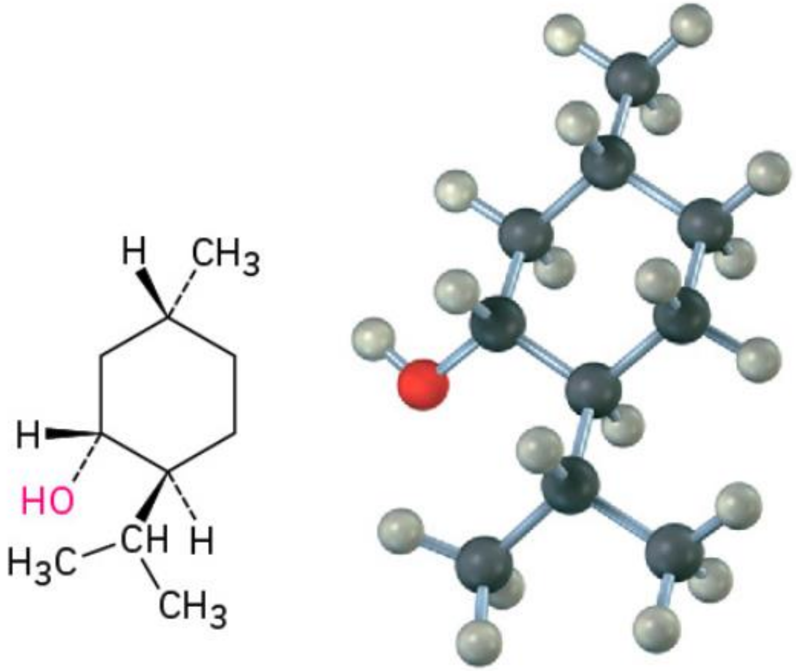
PROBLEM 4-11

Two conformations of cis-1,3-dimethylcyclobutane are shown. What is the difference between them, and which do you think is likely to be more stable?



4.5 Conformations of Cyclohexane

Substituted cyclohexanes are the most common cycloalkanes and occur widely in nature. A large number of compounds, including steroids and many pharmaceutical agents, have cyclohexane rings. The flavoring agent menthol, for instance, has three substituents on a six-membered ring.



Menthol

Cyclohexane adopts a strain-free, three-dimensional shape that is called a **chair conformation** because of its similarity to a lounge chair, with a back, seat, and footrest (**FIGURE 4.8**). Chair cyclohexane has neither angle strain nor torsional strain—all C−C−C bond angles are near the 109° tetrahedral value, and all neighboring C−H bonds are staggered.

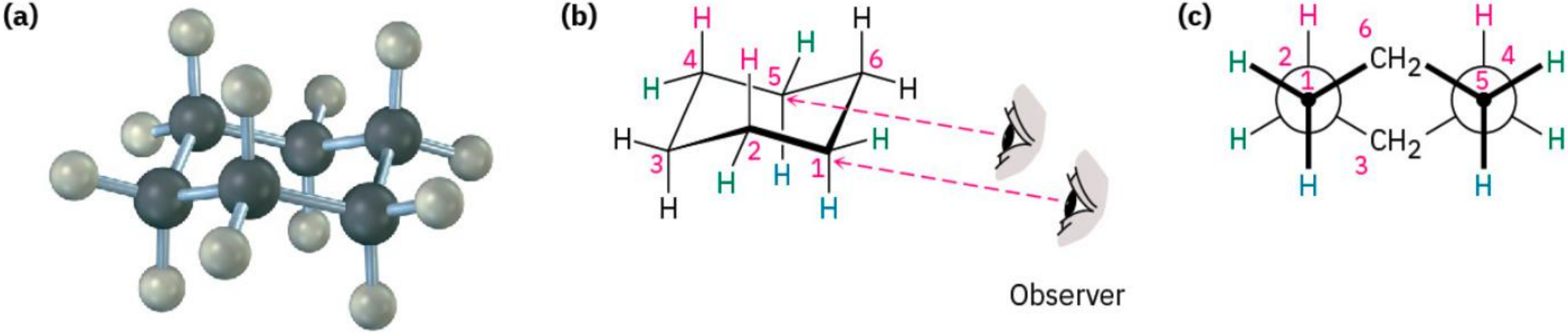
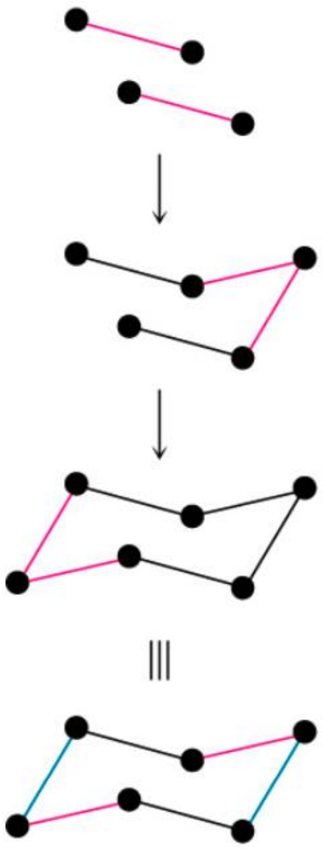


FIGURE 4.8 The strain-free chair conformation of cyclohexane. All C−C−C bond angles are 111.5°, close to the ideal 109° tetrahedral angle, and all neighboring C−H bonds are staggered.

The easiest way to visualize chair cyclohexane is to build a molecular model if you have access to a model kit, or alternatively to explore with one of the many computer-based modeling programs you may have access to.

The chair conformation of cyclohexane can be drawn in three steps.

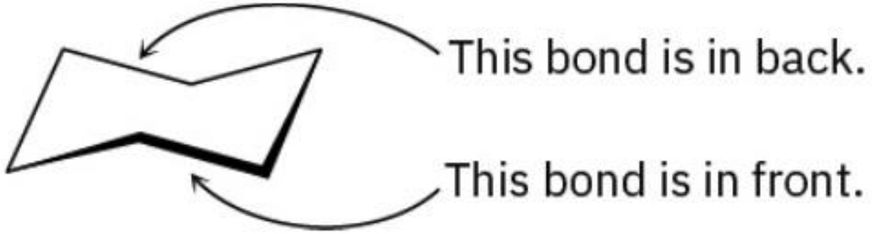


STEP 1 Draw two parallel lines, slanted downward and slightly offset from each other. This means that four of the cyclohexane carbons lie in a plane.

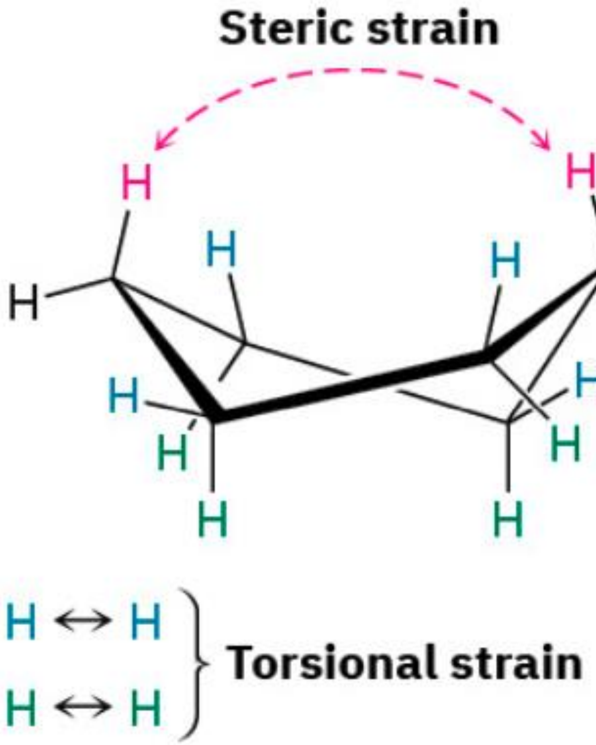
STEP 2 Place the topmost carbon atom above and to the right of the plane of the other four, and connect the bonds.

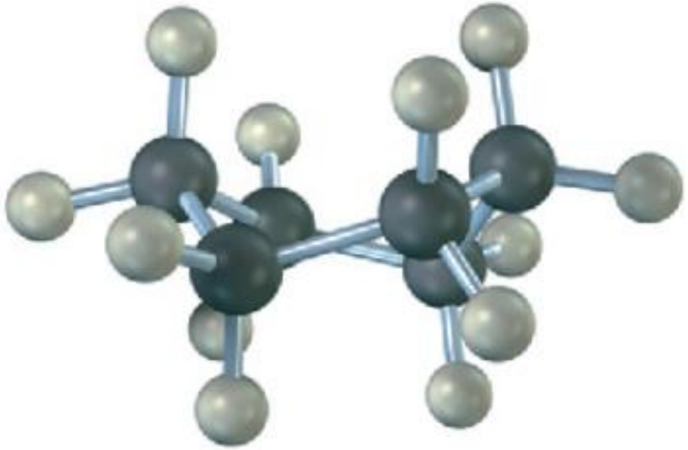
STEP 3 Place the bottommost carbon atom below and to the left of the p lane of the middle four, and connect the bonds. Note that the bonds to the bottommost carbon atom are parallel to the bonds to the topmost carbon.

When viewing cyclohexane, it's helpful to remember that the lower bond is in front and the upper bond is in back. If this convention isn't defined, it can appear that the reverse is true. For clarity, all cyclohexane rings drawn in this book will have the front (lower) bond heavily shaded to indicate nearness to the viewer.



In addition to the chair conformation of cyclohexane, there is an alternative conformation of cyclohexane that bears a slight resemblance to a twisted boat. Called the **twist-boat conformation**, it is nearly free of angle strain. It does, however, have both steric strain and torsional strain and is about 23 kJ/mol (5.5 kcal/mol) higher in energy than the chair conformation. As a result, molecules adopt the twist-boat geometry only rarely.

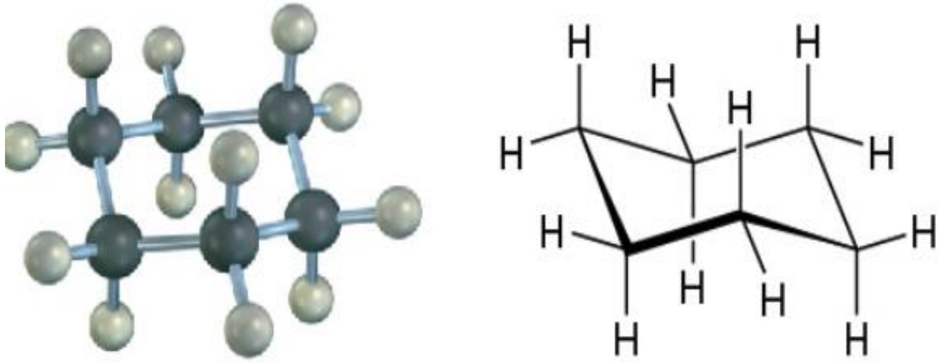




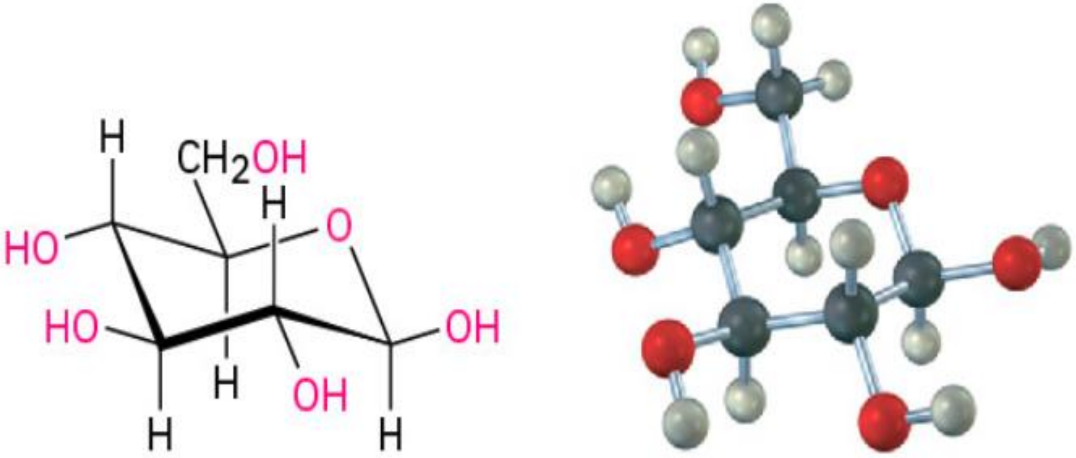
Twist-boat cyclohexane
(23 kJ/mol strain)

4.6 Axial and Equatorial Bonds in Cyclohexane

The chair conformation of cyclohexane has many consequences. We’ll see in **Section 11.9**, for instance, that the chemical behavior of many substituted cyclohexanes is influenced by their conformation. In addition, we’ll see in **Section 25.5** that simple carbohydrates, such as glucose, adopt a conformation based on the cyclohexane chair and that their chemistry is directly affected as a result.



Cyclohexane
(chair conformation)



Glucose
(chair conformation)

Another trait of the chair conformation is that there are two kinds of positions for substituents on the cyclohexane ring: axial positions and equatorial positions (as shown in **FIGURE 4.9**). The six **axial** positions are parallel to the ring **axis**, while the six **equatorial** positions are in the rough plane of the ring, around the ring **equator**.

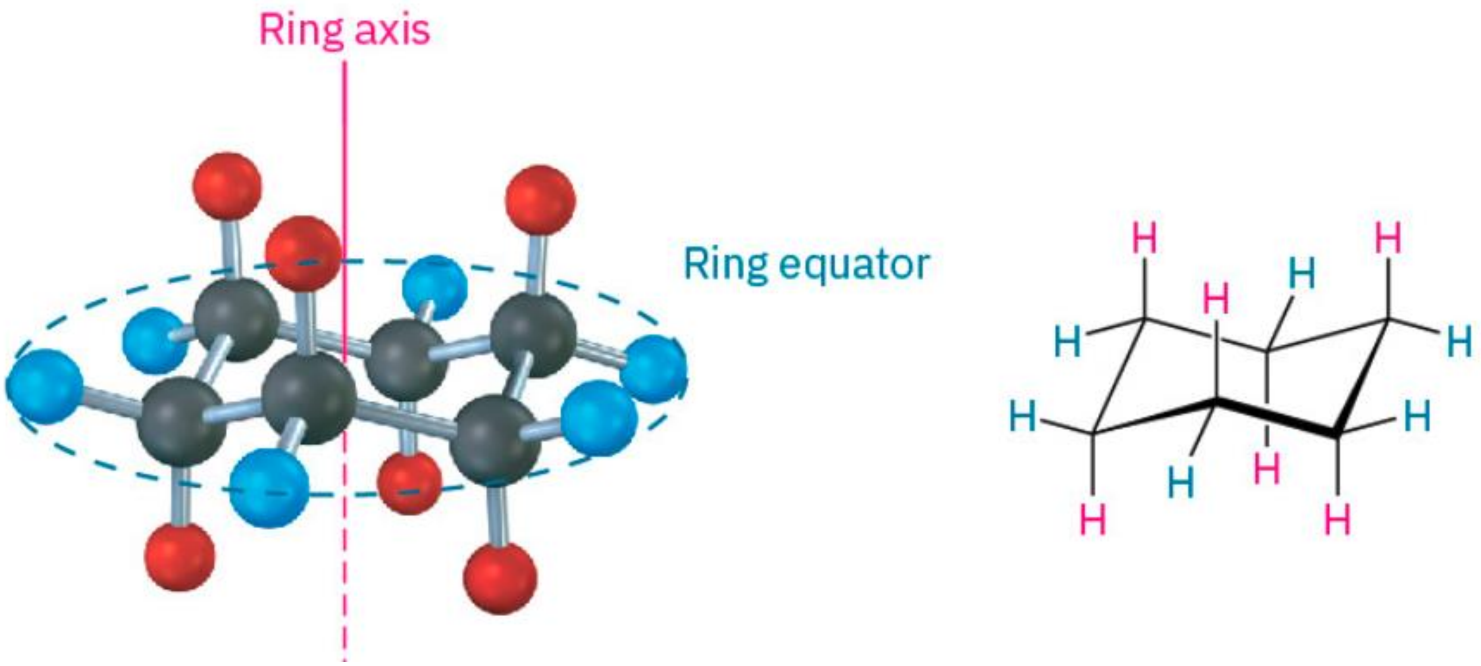


FIGURE 4.9 Axial and equatorial positions in chair cyclohexane. The six axial hydrogens are parallel to the ring axis, and the six equatorial hydrogens are in a band around the ring equator.

As shown in **FIGURE 4.9**, each carbon atom in chair cyclohexane has one axial and one equatorial hydrogen. Furthermore, each side of the ring has three axial and three equatorial hydrogens in an alternating arrangement. For example, if the top side of the ring has axial hydrogens on carbons 1, 3, and 5, then it has equatorial hydrogens on carbons 2, 4, and 6. The reverse is true for the bottom side: carbons 1, 3, and 5 have equatorial hydrogens, but carbons 2, 4, and 6 have axial hydrogens (**FIGURE 4.10**).

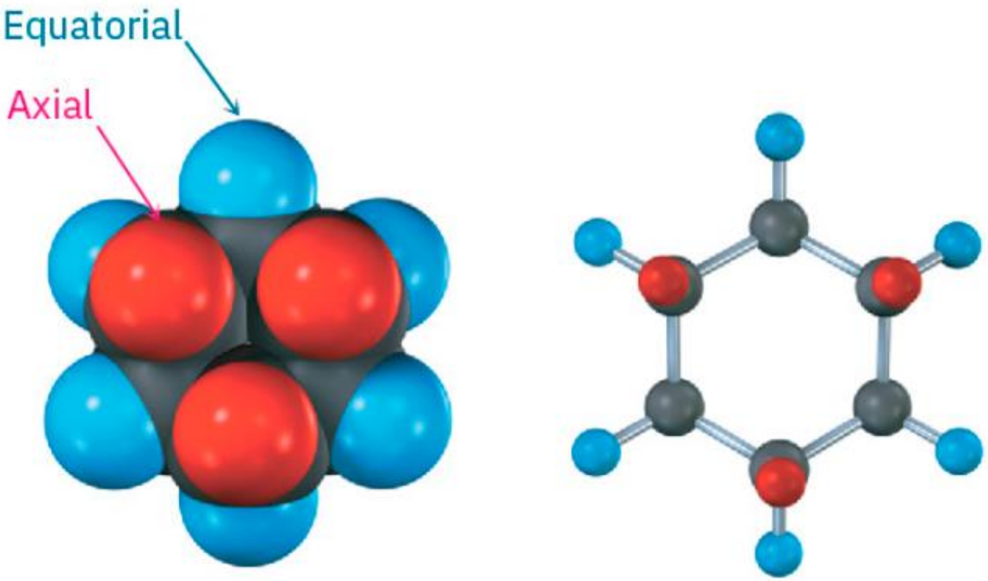
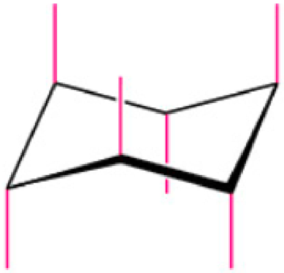


FIGURE 4.10 Alternating axial and equatorial positions in chair cyclohexane, looking directly down the ring axis. Each carbon atom has one axial and one equatorial position, and each face has alternating axial and equatorial positions.

Axial and equatorial bonds can be drawn following the procedure shown in **FIGURE 4.11**. If possible, look at a molecular model as you practice.

Axial bonds: The six axial bonds, one on each carbon, are parallel and alternate up–down.



Equatorial bonds: The six equatorial bonds, one on each carbon, come in three sets of two parallel lines. Each set is also parallel to two ring bonds. Equatorial bonds alternate between sides around the ring.

Completed cyclohexane

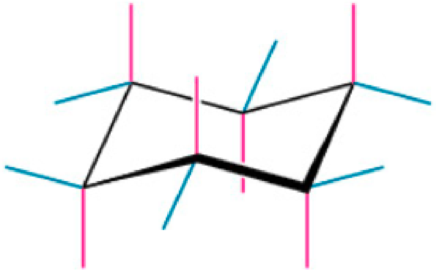


FIGURE 4.11 A procedure for drawing axial and equatorial bonds in chair cyclohexane.

Because chair cyclohexane has two kinds of positions—axial and equatorial—we might expect to find two isomeric forms of a monosubstituted cyclohexane. In fact, we don't. There is only one methylcyclohexane, one bromocyclohexane, one cyclohexanol (hydroxycyclohexane), and so on, because cyclohexane rings are conformationally mobile at room temperature. Different chair conformations readily interconvert, exchanging axial and equatorial positions. This interconversion, called a **ring-flip**, is shown in **FIGURE 4.12**.

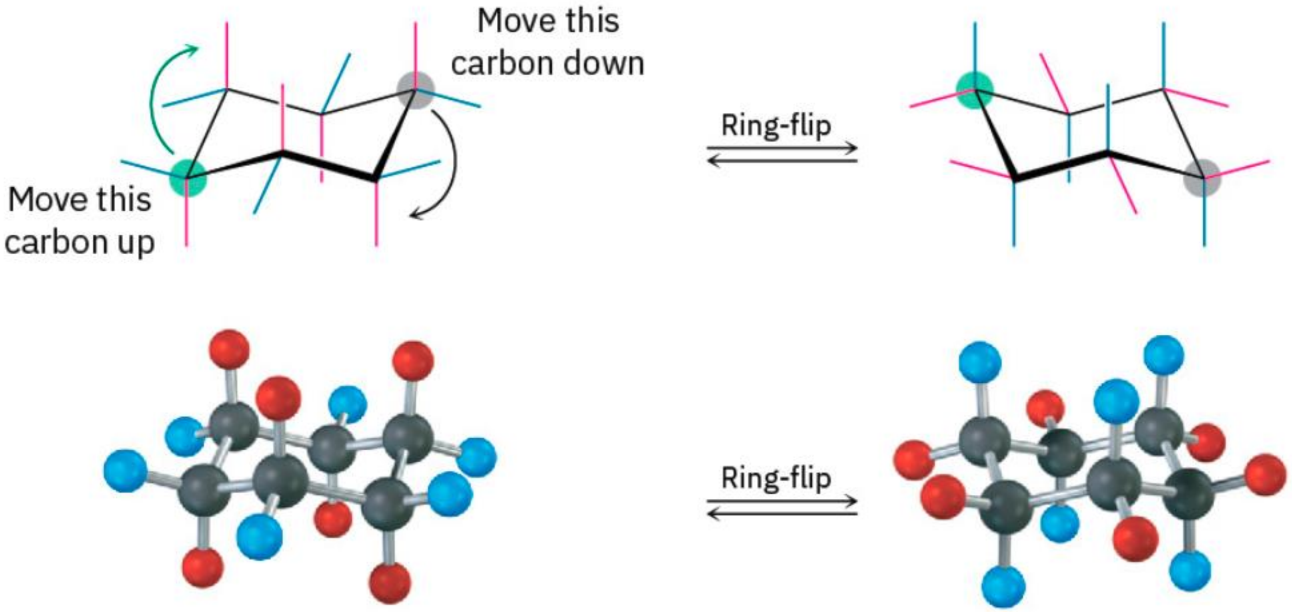
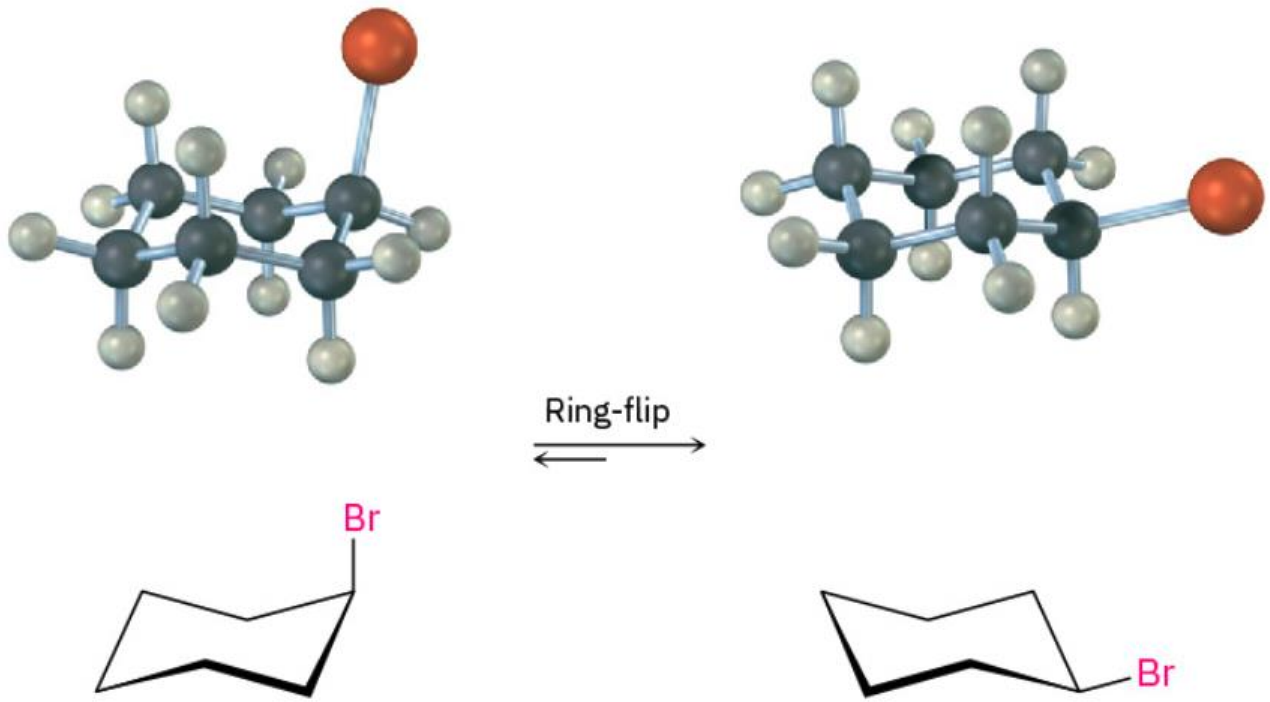


FIGURE 4.12 A ring-flip in chair cyclohexane interconverts axial and equatorial positions. What is axial in the starting structure becomes equatorial in the ring-flipped structure, and what is equatorial in the starting structure is axial after ring-flip.

As shown in **FIGURE 4.12**, a chair cyclohexane can be ring-flipped by keeping the middle four carbon atoms in place while folding the two end carbons in opposite directions. In so doing, an axial substituent in one chair form becomes an equatorial substituent in the ring-flipped chair form and vice versa. For example, axial bromocyclohexane becomes equatorial bromocyclohexane after a ring-flip. Since the energy barrier to chair–chair interconversion is only about 45 kJ/mol (10.8 kcal/mol), the process is rapid at room temperature and we see what appears to be a single structure rather than distinct axial and equatorial isomers.



Axial bromocyclohexane **Equatorial bromocyclohexane**

WORKED EXAMPLE 4.2

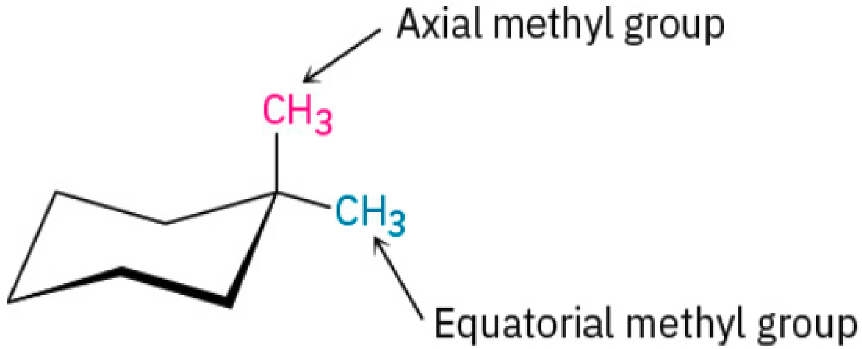
Drawing the Chair Conformation of a Substituted Cyclohexane

Draw 1,1-dimethylcyclohexane in a chair conformation, indicating which methyl group in your drawing is axial and which is equatorial.

Strategy

Draw a chair cyclohexane ring using the procedure in **FIGURE 4.11**, and then put two methyl groups on the same carbon. The methyl group in the rough plane of the ring is equatorial, and the one directly above or below the ring is axial.

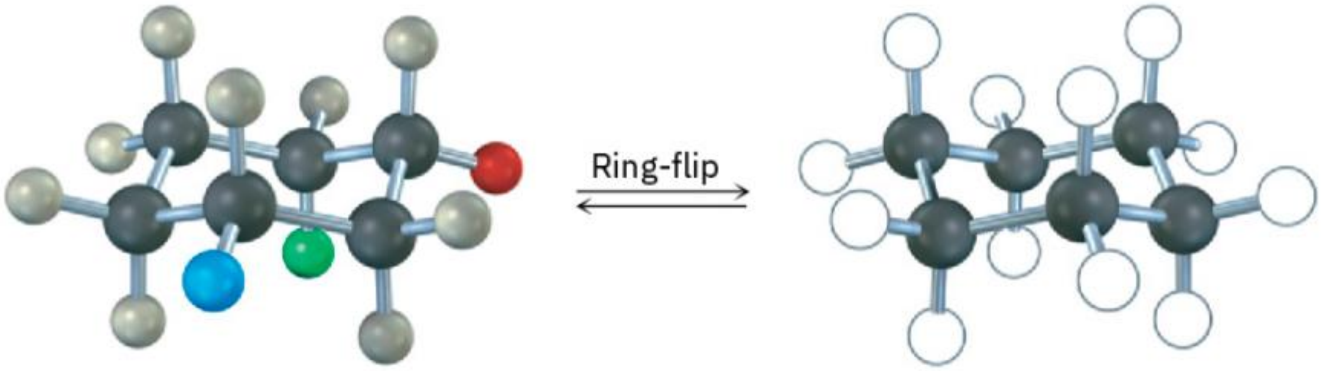
Solution



PROBLEM 4-12 Draw two different chair conformations of cyclohexanol (hydroxycyclohexane), showing all hydrogen atoms. Identify each position as axial or equatorial.

PROBLEM 4-13 Draw two different chair conformations of trans-1,4-dimethylcyclohexane, and label all positions as axial or equatorial.

PROBLEM 4-14 Identifyeachofthecoloredpositions—red,blue,andgreen—asaxialorequatorial.Thencarryouta ring-flip, and show the new positions occupied by each color.



4.7 Conformations of Monosubstituted Cyclohexanes

Even though cyclohexane rings flip rapidly between chair conformations at room temperature, the two conformations of a monosubstituted cyclohexane aren’t equally stable. In methylcyclohexane, for instance, the equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol (1.8 kcal/mol). The same is true of other monosubstituted cyclohexanes: a substituent is almost always more stable in an equatorial position than in an axial position.

You might recall from your general chemistry course that it’s possible to calculate the percentages of two isomers at equilibrium using the equation $\Delta E = -RT \ln K$, where ΔE is the energy difference between isomers, R is the gas constant [8.315 J/(K·mol)], T is the Kelvin temperature, and K is the equilibrium constant between isomers. For example, an energy difference of 7.6 kJ/mol means that about 95% of methylcyclohexane molecules have an equatorial methyl group at any given instant while only 5% have an axial methyl group. **FIGURE 4.13** plots the relationship between energy and isomer percentages.

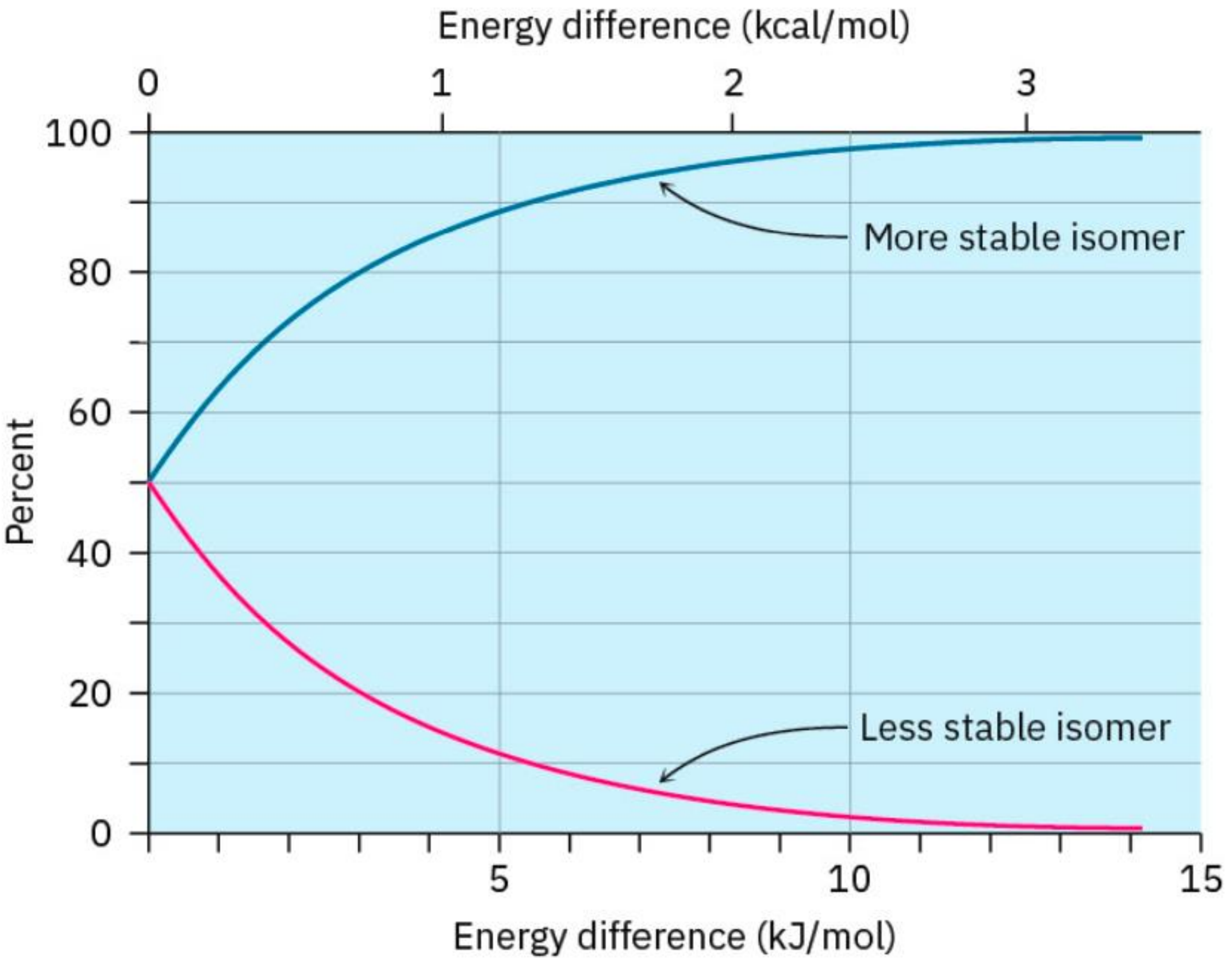


FIGURE 4.13 A plot of the percentages of two isomers at equilibrium versus the energy difference between them. The curves are calculated using the equation $\Delta E = -RT \ln K$.

The energy difference between axial and equatorial conformations is due to steric strain caused by **1,3-diaxial interactions**. The axial methyl group on C1 is too close to the axial hydrogens three carbons away on C3 and C5, resulting in 7.6 kJ/mol of steric strain (**FIGURE 4.14**).

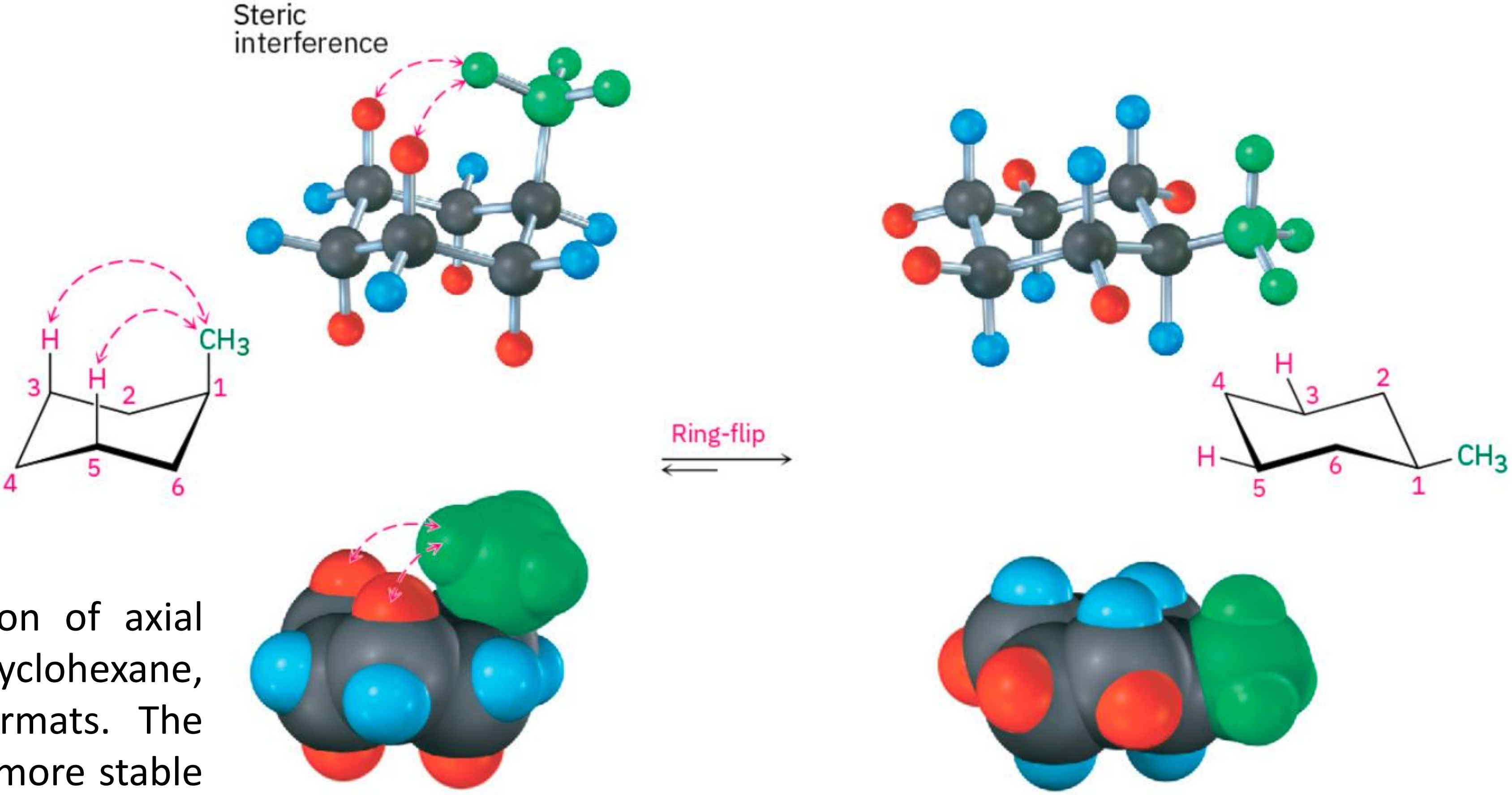


FIGURE 4.14 Interconversion of axial and equatorial methylcyclohexane, represented in several formats. The equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol.

Comparing a four-carbon fragment of axial methylcyclohexane with gauche butane shows that the steric interaction is the same in both (**FIGURE 4.15**). Because axial methylc yclohexane has two such interactions,it has 2×3.8 = 7.6kJ/mol of steric strain. Equatorial methylcyclohexane has no such interactions and is therefore more stable.

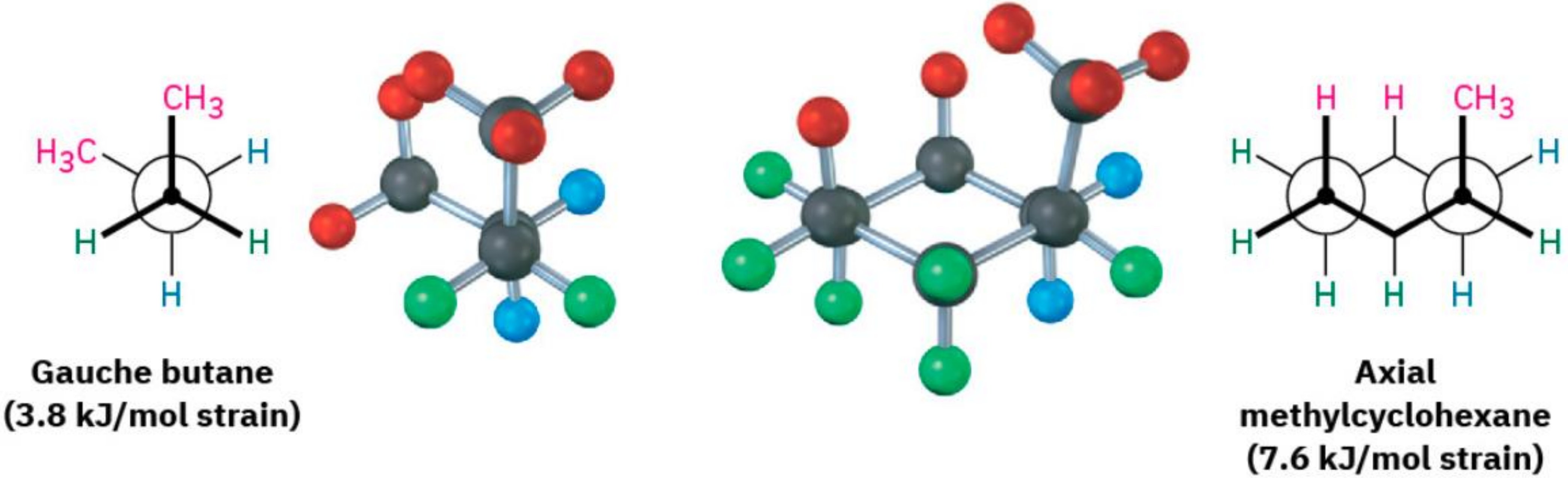


FIGURE 4.15 The origin of 1,3-diaxial interactions in methylcyclohexane. The steric strain between an axial methyl group and an axial hydrogen atom three carbons away is identical to the steric strain in gauche butane. (To display clearly the diaxial interactions in methylcyclohexane, two of the equatorial hydrogens are not shown.)

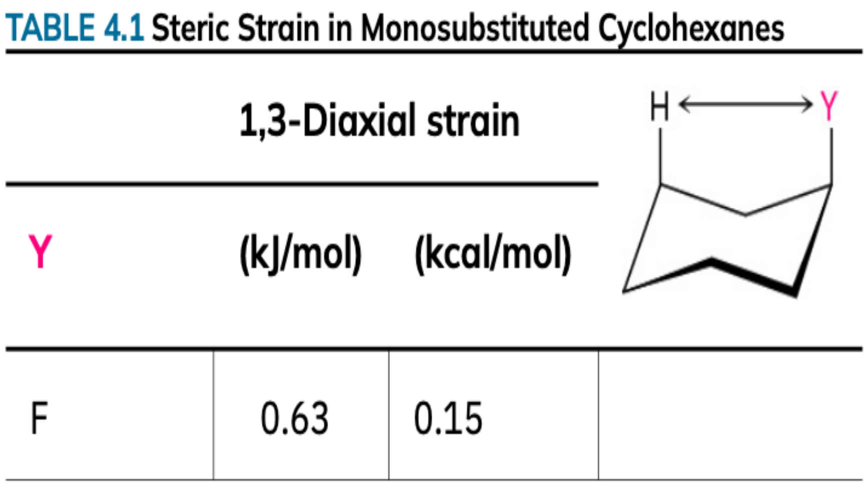
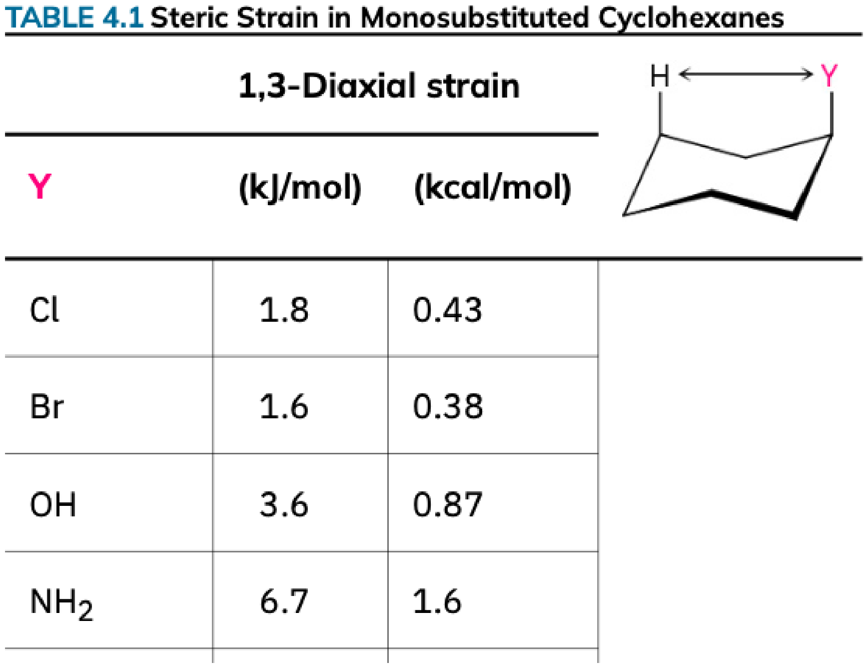


TABLE 4.1 Steric Strain in Monosubstituted Cyclohexanes

	1,3-Diaxial strain	
Y	(kJ/mol)	(kcal/mol)
F	0.63	0.15



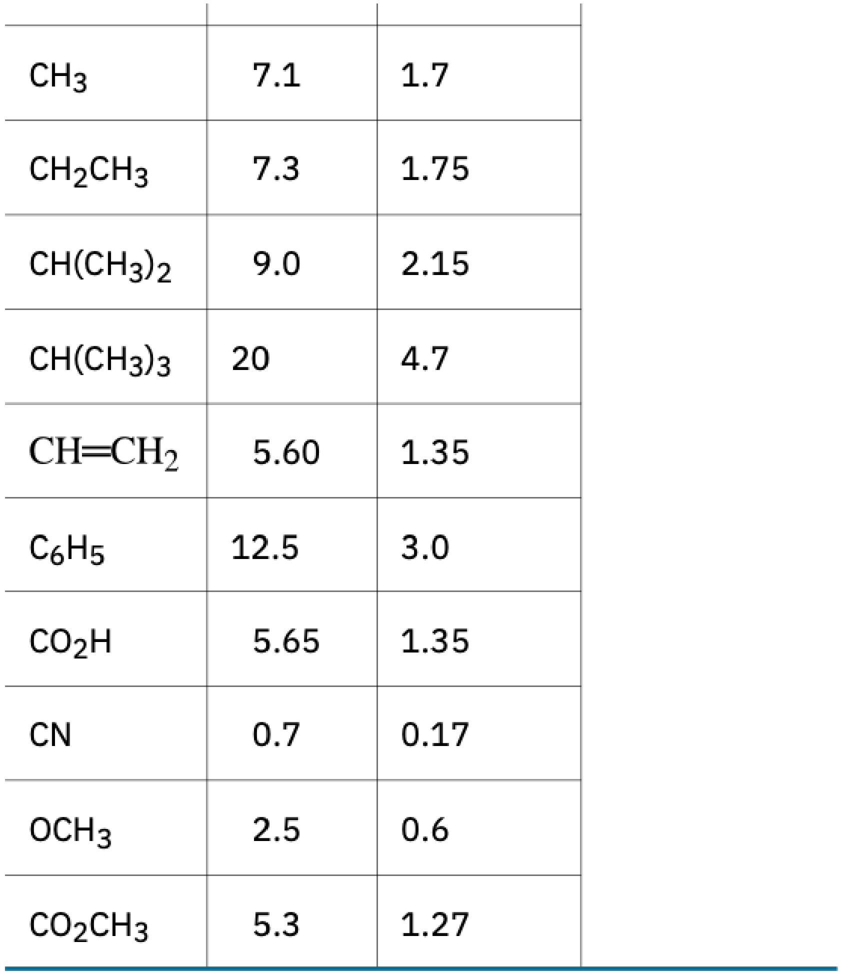


TABLE 4.1 Steric Strain in Monosubstituted Cyclohexanes

	1,3-Diaxial strain	
Y	(kJ/mol)	(kcal/mol)
Cl	1.8	0.43
Br	1.6	0.38
OH	3.6	0.87
NH_2	6.7	1.6
CH_3	7.1	1.7
CH_2CH_3	7.3	1.75
$CH(CH_3)_2$	9.0	2.15
$CH(CH_3)_3$	20	4.7
$CH{=}CH_2$	5.60	1.35
C_6H_5	12.5	3.0
CO_2H	5.65	1.35
CN	0.7	0.17
OCH_3	2.5	0.6
CO_2CH_3	5.3	1.27

PROBLEM 4-15

What is the energy difference between the axial and equatorial conformations of cyclohexanol (hydroxycyclohexane)?

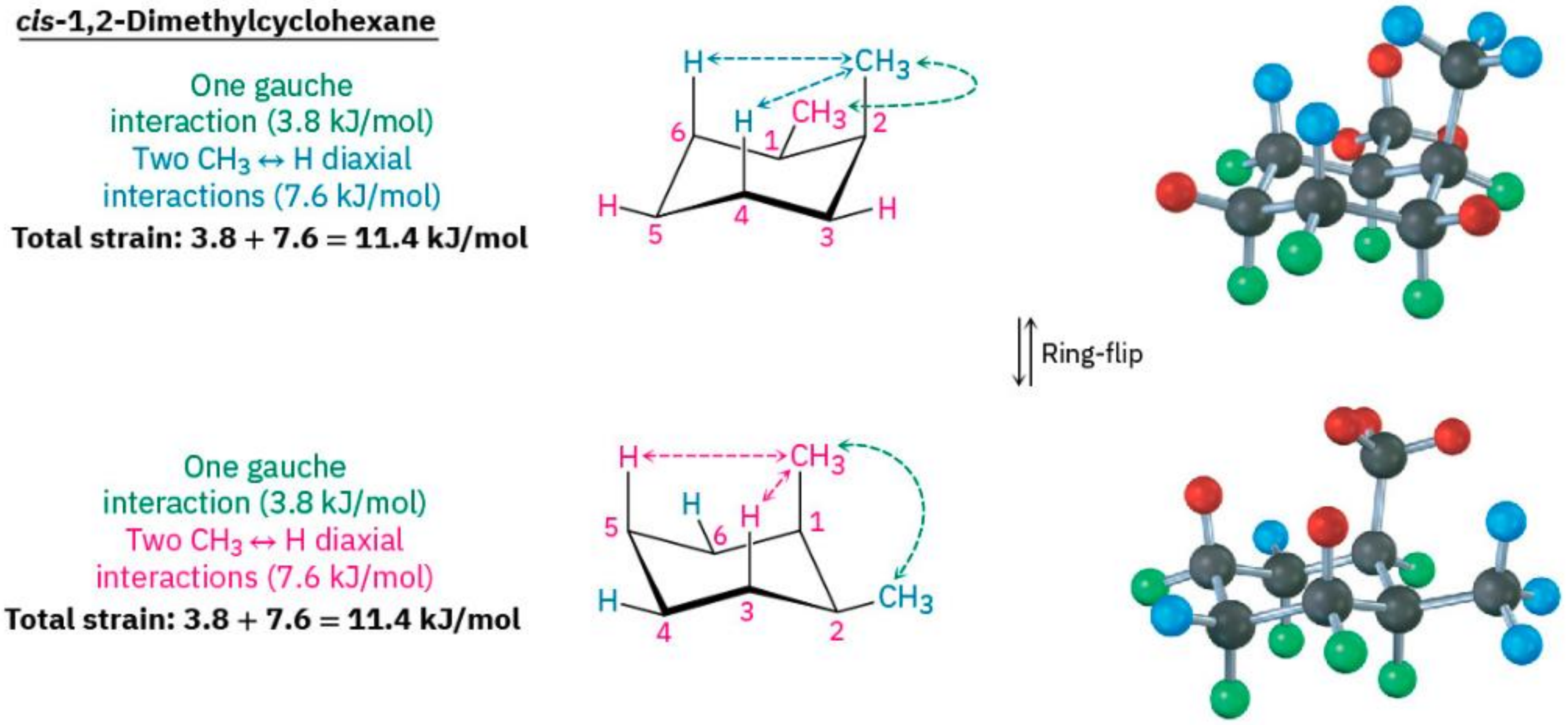
PROBLEM 4-16

Why do you suppose an axial cyano(–CN)substituent causes practically no1,3-diaxial steric strain (0.4 kJ/mol)?

PROBLEM 4-17

Look back at Figure 4.13 and estimate the percentages of axial and equatorial conformations present at equilibrium in bromo cyclohexane.

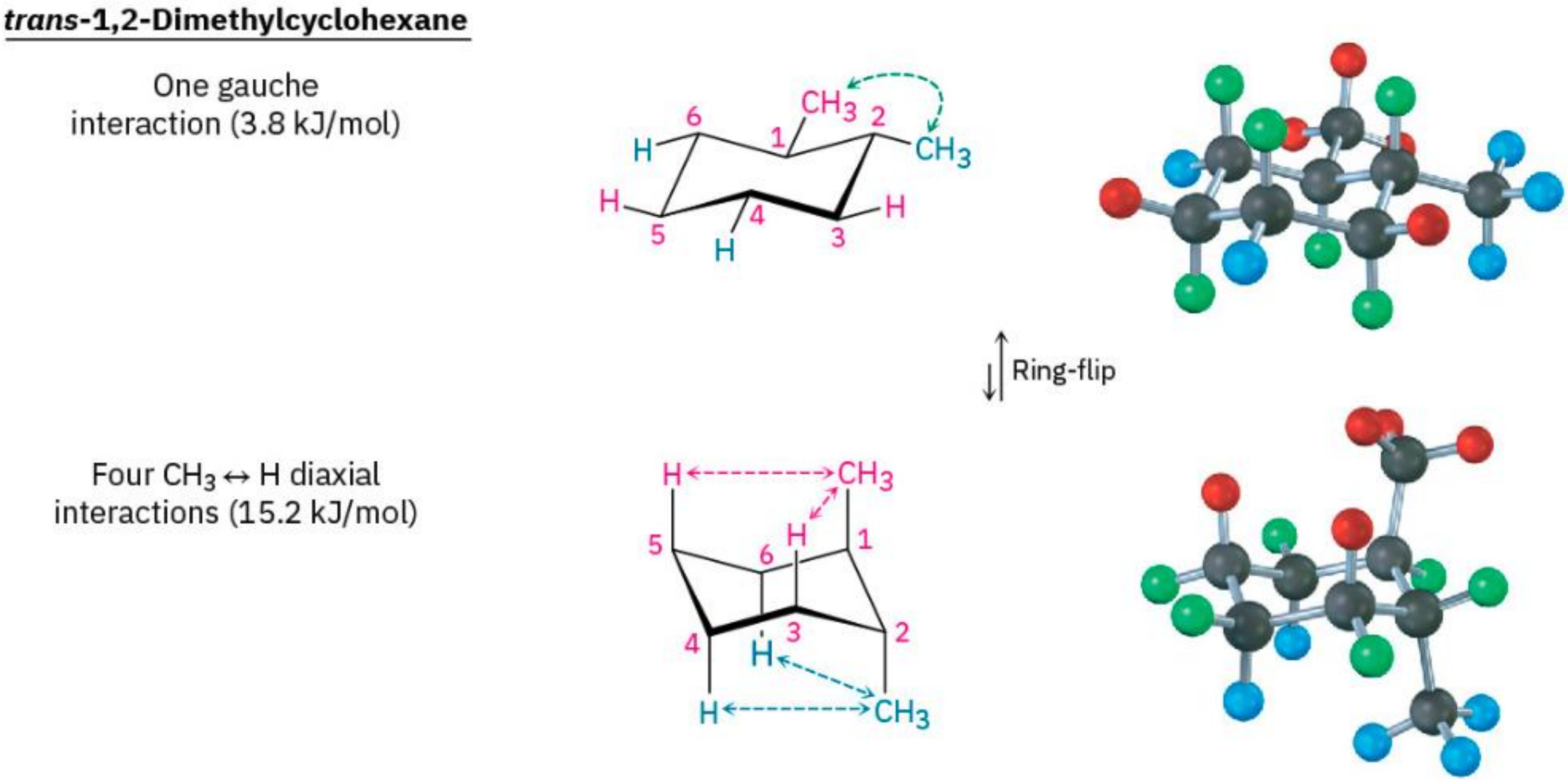
4.8 Conformations of Disubstituted Cyclohexanes


cis-1,2-Dimethylcyclohexane

One gauche interaction (3.8 kJ/mol)
Two $CH_3 \leftrightarrow H$ diaxial interactions (7.6 kJ/mol)
Total strain: 3.8 + 7.6 = 11.4 kJ/mol

One gauche interaction (3.8 kJ/mol)
Two $CH_3 \leftrightarrow H$ diaxial interactions (7.6 kJ/mol)
Total strain: 3.8 + 7.6 = 11.4 kJ/mol

FIGURE 4.16 Conformations of cis-1,2-dimethylcyclohexane. The two chair conformations are equal in energy because each has one axial methyl group and one equatorial methyl group.



***trans*-1,2-Dimethylcyclohexane**

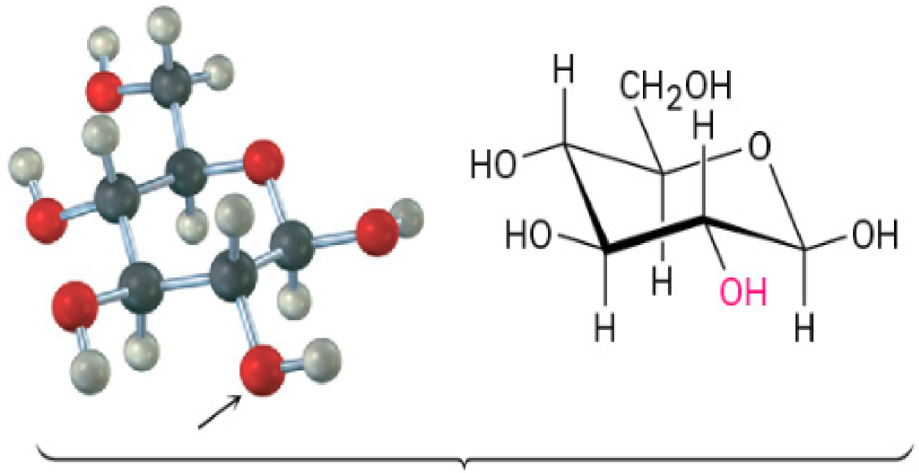
One gauche interaction (3.8 kJ/mol)

Four $CH_3 \leftrightarrow H$ diaxial interactions (15.2 kJ/mol)

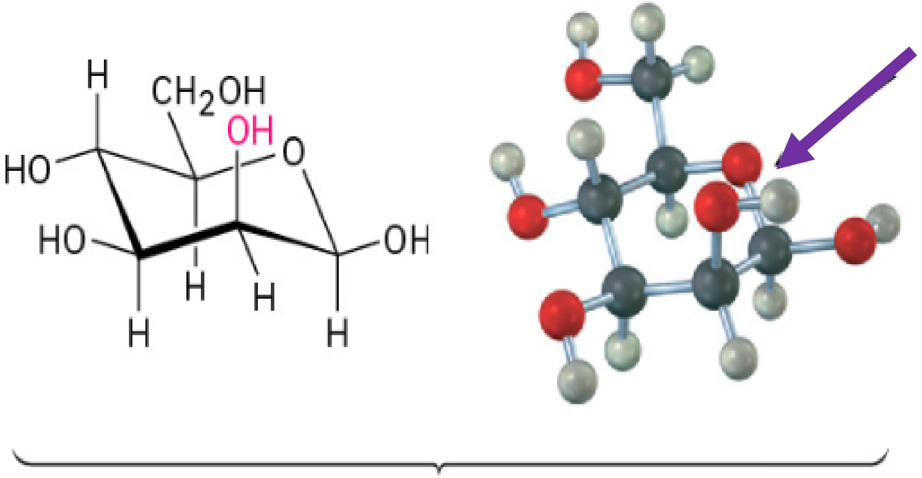
FIGURE 4.17 Conformations of trans-1,2-dimethylcyclohexane. The conformation with both methyl groups equatorial (top) is favored by 11.4 kJ/mol (2.7 kcal/mol) over the conformation with both methyl groups axial (bottom).

The same kind of **conformational analysis** just carried out for cis- and trans-1,2-dimethylcyclohexane can be done for any substituted cyclohexane, such as cis-1-tert-butyl-4-chlorocyclohexane (see **Worked Example 4.3**).

As you might imagine, though, the situation becomes more complex as the number of substituents increases. For instance, compare glucose with mannose, a carbohydrate present in seaweed. Which do you think is more strained? In glucose, all substituents on the six-membered ring are equatorial, while in mannose, one of the −OH groups is axial, making it more strained.



Glucose



Mannose

A summary of the various axial and equatorial relationships among substituent groups in the different possible cis and trans substitution patterns for disubstituted cyclohexanes is given in **TABLE 4.2**.

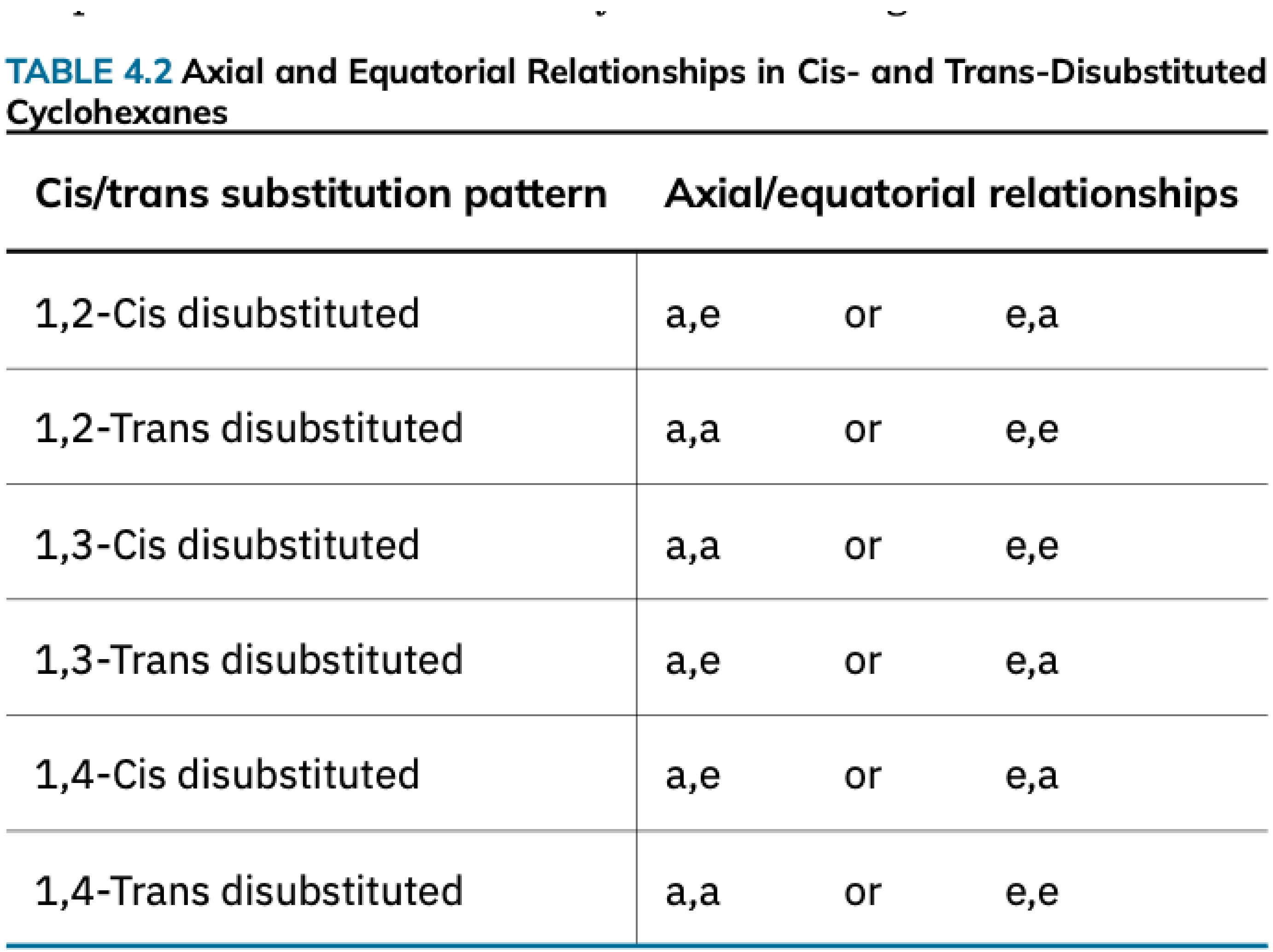


TABLE 4.2 Axial and Equatorial Relationships in Cis- and Trans-Disubstituted Cyclohexanes

Cis/trans substitution pattern	Axial/equatorial relationships
1,2-Cis disubstituted	a,e or e,a
1,2-Trans disubstituted	a,a or e,e
1,3-Cis disubstituted	a,a or e,e
1,3-Trans disubstituted	a,e or e,a
1,4-Cis disubstituted	a,e or e,a
1,4-Trans disubstituted	a,a or e,e

WORKED EXAMPLE 4.3

Drawing the Most Stable Conformation of a Substituted Cyclohexane

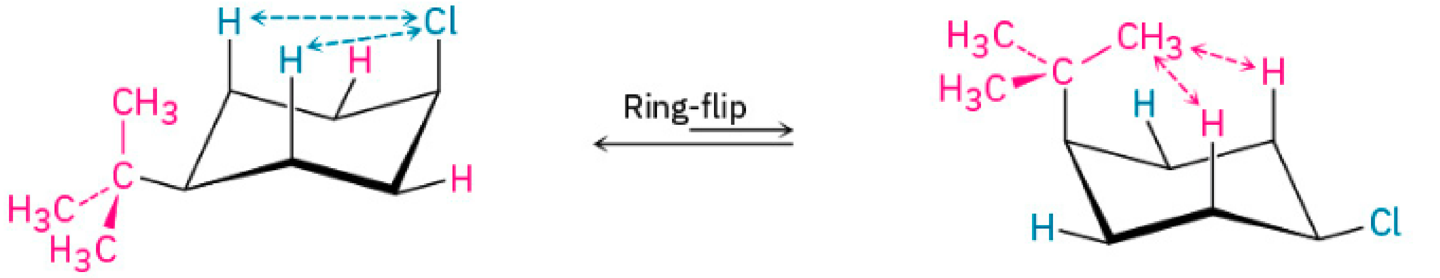
Draw the more stable chair conformation of *cis*-1-*tert*-butyl-4-chlorocyclohexane. By how much is it favored?

Strategy

Draw the two possible chair conformations, and calculate the strain energy in each. Remember that equatorial substituents cause less strain than axial substituents.

Solution

First draw the two chair conformations of the molecule:



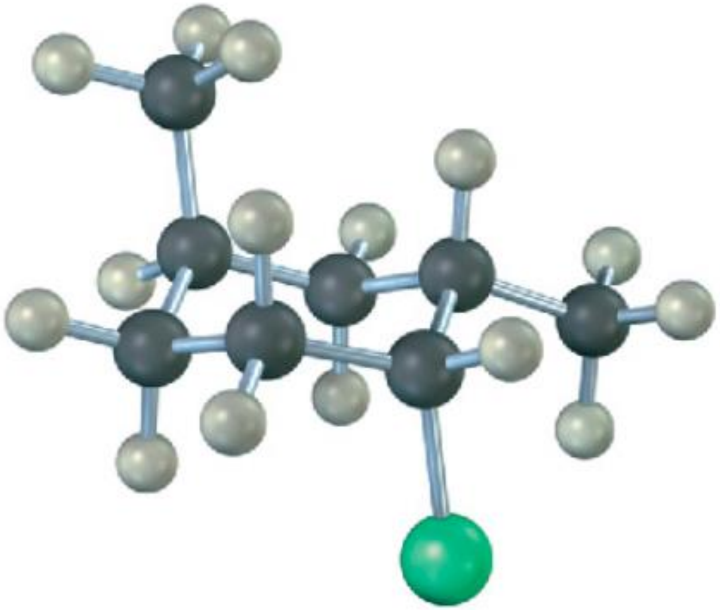
2 × 1.0 = 2.0 kJ/mol steric strain

2 × 11.4 = 22.8 kJ/mol steric strain

In the conformation on the left, the tert-butyl group is equatorial and the chlorine is axial. In the conformation on the right, the tert-butyl group is axial and the chlorine is equatorial. These conformations aren’t of equal energy because an axial tert-butyl substituent and an axial chloro substituent produce different amounts of steric strain. **TABLE 4.1** shows that the 1,3-diaxial interaction between a hydrogen and a tert-butyl group costs 11.4 kJ/mol (2.7 kcal/mol), whereas the interaction between a hydrogen and a chlorine costs only 1.0 kJ/ mol (0.25 kcal/mol). An axial tert-butyl group therefore produces (2 × 11.4 kJ/mol) − (2 × 1.0 kJ/mol) = 20.8 kJ/mol (4.9 kcal/mol) more steric strain than an axial chlorine, and the compound preferentially adopts the conformation with the chlorine axial and the tert-butyl equatorial.

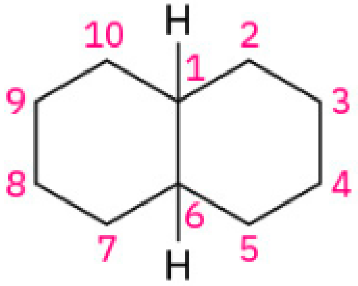
PROBLEM 4-18 Draw the more stable chair conformation of the following molecules, and estimate the amount of strain in each:
(a) trans-1-Chloro-3-methylcyclohexane (b) cis-1-Ethyl-2-methylcyclohexane (c) cis-1-Bromo-4-ethylcyclohexane (d) cis-1-tert-Butyl-4-ethylcyclohexane

PROBLEM 4-19 Identify each substituent in the following compound as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):



4.9 Conformations of Polycyclic Molecules

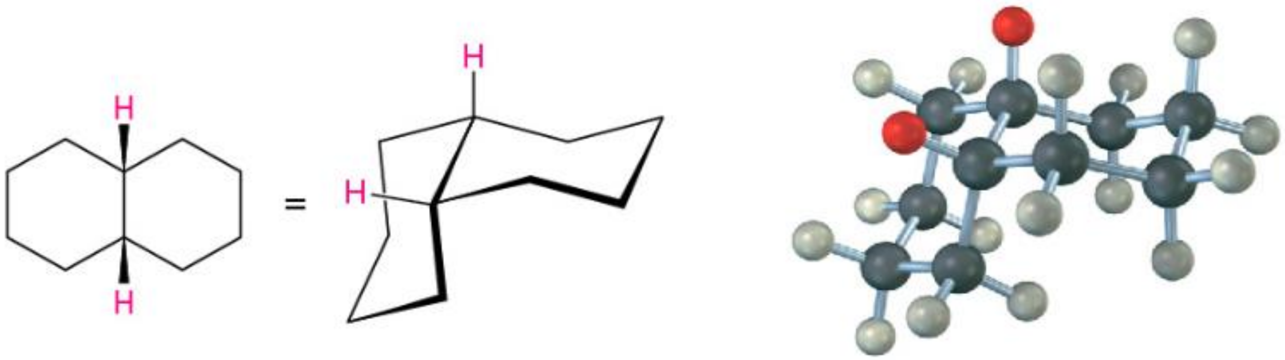
The final point we'll consider about cycloalkane stereochemistry is to see what happens when two or more cycloalkane rings are fused together along a common bond to construct a **polycyclic molecule**—for example, decalin.



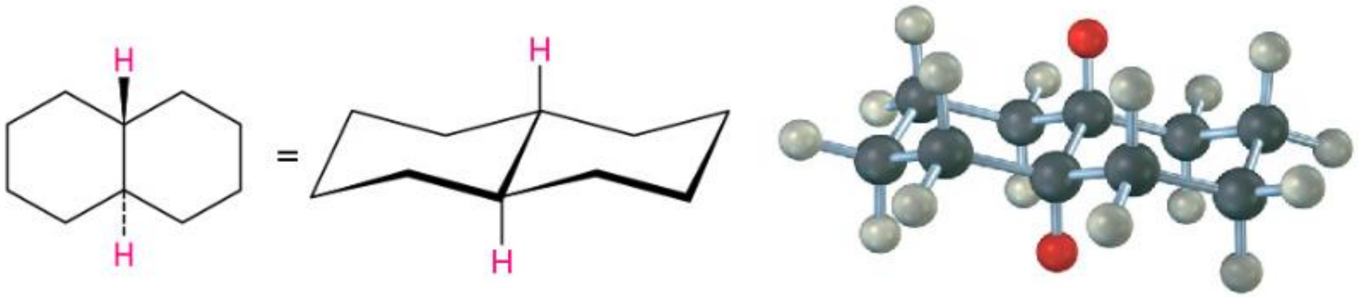
Decalin—two fused cyclohexane rings

Decalin consists of two cyclohexane rings joined to share two carbon atoms (the bridgehead carbons, C1 and C6) and a common bond. Decalin can exist in either of two isomeric forms, depending on whether the rings are trans fused or cis fused. In cis-decalin, the hydrogen atoms at the bridgehead carbons are on the same side of the rings; in trans-decalin, the bridgehead hydrogens are on opposite sides. **FIGURE 4.18** shows how both compounds can be represented using chair cyclohexane conformations.

Note that the two decalin isomers are not interconvertible by ring-flips or other rotations. They are cis–trans stereoisomers and have the same relationship to each other that cis- and trans-1,2-dimethylcyclohexane have.



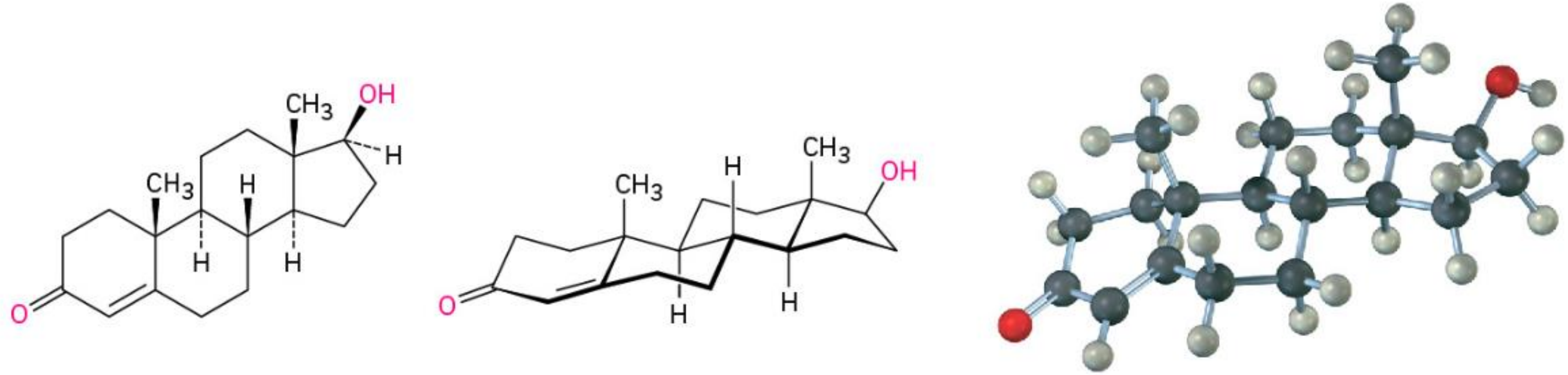
***cis*-Decalin**



***trans*-Decalin**

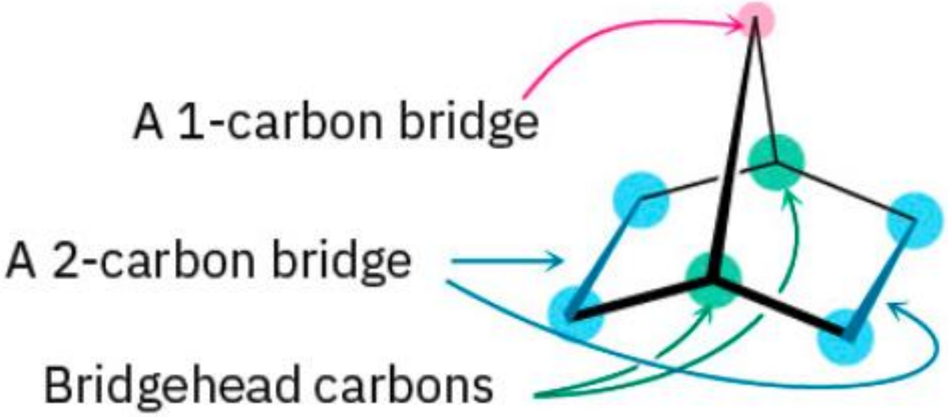
FIGURE 4.18 Representations of cis- and trans-decalin. Hydrogen atoms at the bridgehead carbons are on the same face of the rings in the cis isomer but on opposite faces in the trans isomer.

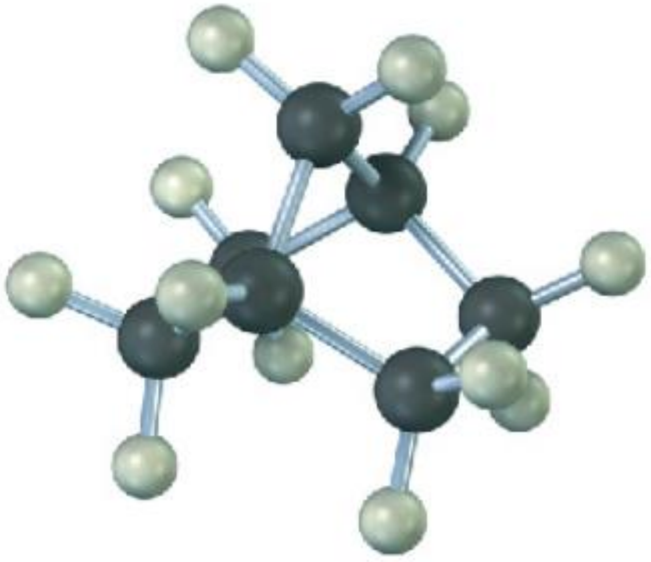
Polycyclic compounds are common in nature, and many valuable substances have fused-ring structures. For example, steroids, such as testosterone, the primary sex hormone in males, have three six-membered rings and one five-membered ring fused together. Although steroids look complicated compared with cyclohexane or decalin, the same principles that apply to the conformational analysis of simple cyclohexane rings apply equally well (and often better) to steroids.



Testosterone (a steroid)

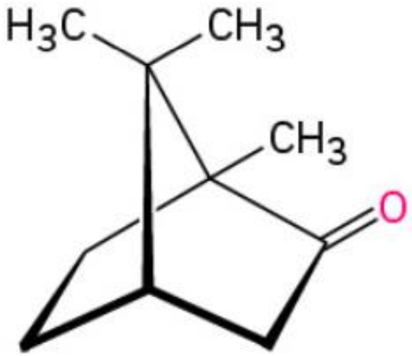
Another common ring system is the norbornane, or bicyclo[2.2.1]heptane, structure. Like decalin, norbornane is a bicycloalkane, so called because two rings would have to be broken open to generate an acyclic structure. Its systematic name, bicyclo[2.2.1]heptane, reflects the fact that the molecule has seven carbons, is bicyclic, and has three “bridges” of 2, 2, and 1 carbon atoms connecting the two bridgehead carbons.



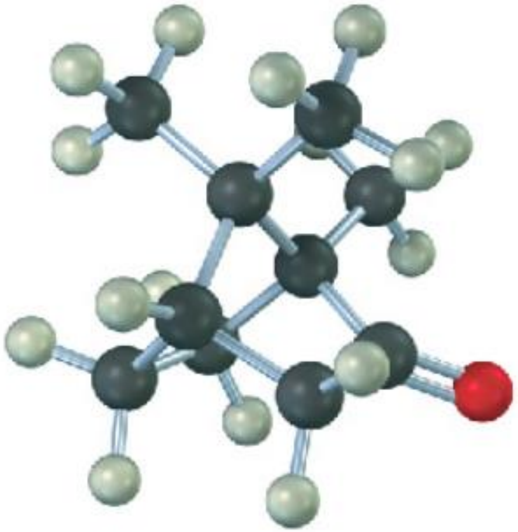


Norbornane has a conformationally locked boat cyclohexane ring (**Section 4.5**) in which carbons 1 and 4 are joined by an additional CH2 group. In drawing this structure, a break in the rear bond indicates that the vertical bond crosses in front of it. Making a molecular model is particularly helpful when trying to see the three-dimensionality of norbornane.

Substituted norbornanes, such as camphor, are found widely in nature, and many have been important historically in developing organic structural theories.



Camphor

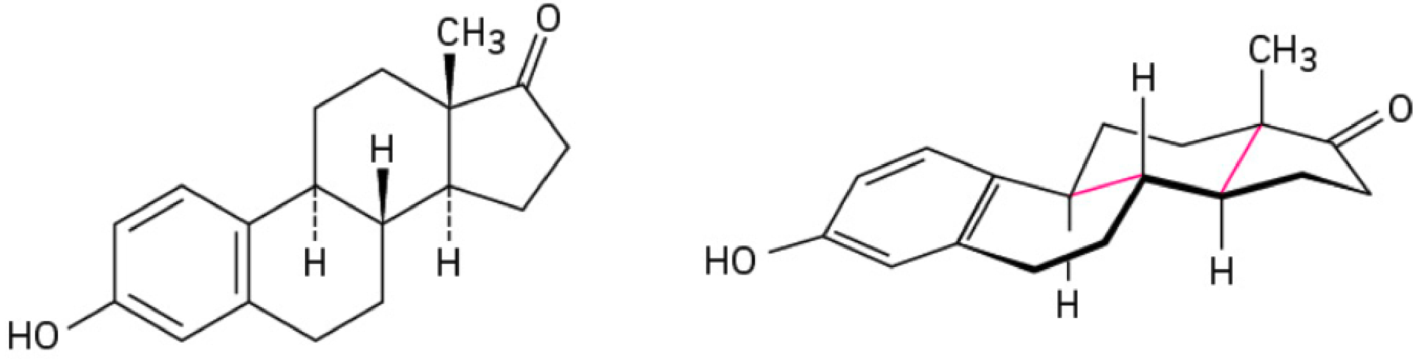


PROBLEM 4-20

Which isomer is more stable, cis-decalin or trans-decalin (Figure 4.18)? Explain.

PROBLEM 4-21

Look at the following structure of estrone, the primary sex hormone in females, and tell whether each of the two indicated (red) ring-fusions is cis or trans.



Estrone

CHEMISTRY MATTERS

Molecular Mechanics

All the structural models in this book are computer-drawn. To make sure they accurately represent bond angles, bond lengths, torsional interactions, and steric interactions, the most stable geometry of each molecule has been calculated on a desktop computer using a commercially available molecular mechanics program based on work by Norman Allinger at the University of Georgia.

The idea behind molecular mechanics is to begin with a rough geometry for a molecule and then calculate a total strain energy for that starting geometry, using mathematical equations that assign values to specific kinds of molecular interactions. Bond angles that are too large or too small cause angle strain; bond lengths that are too short or too long cause stretching or compressing strain; unfavorable eclipsing interactions around single bonds cause torsional strain; and nonbonded atoms that approach each other too closely cause steric, or van der Waals, strain.

$$E_{\text{total}} = E_{\text{bond stretching}} + E_{\text{angle strain}} + E_{\text{torsional strain}} + E_{\text{van der Waals}}$$

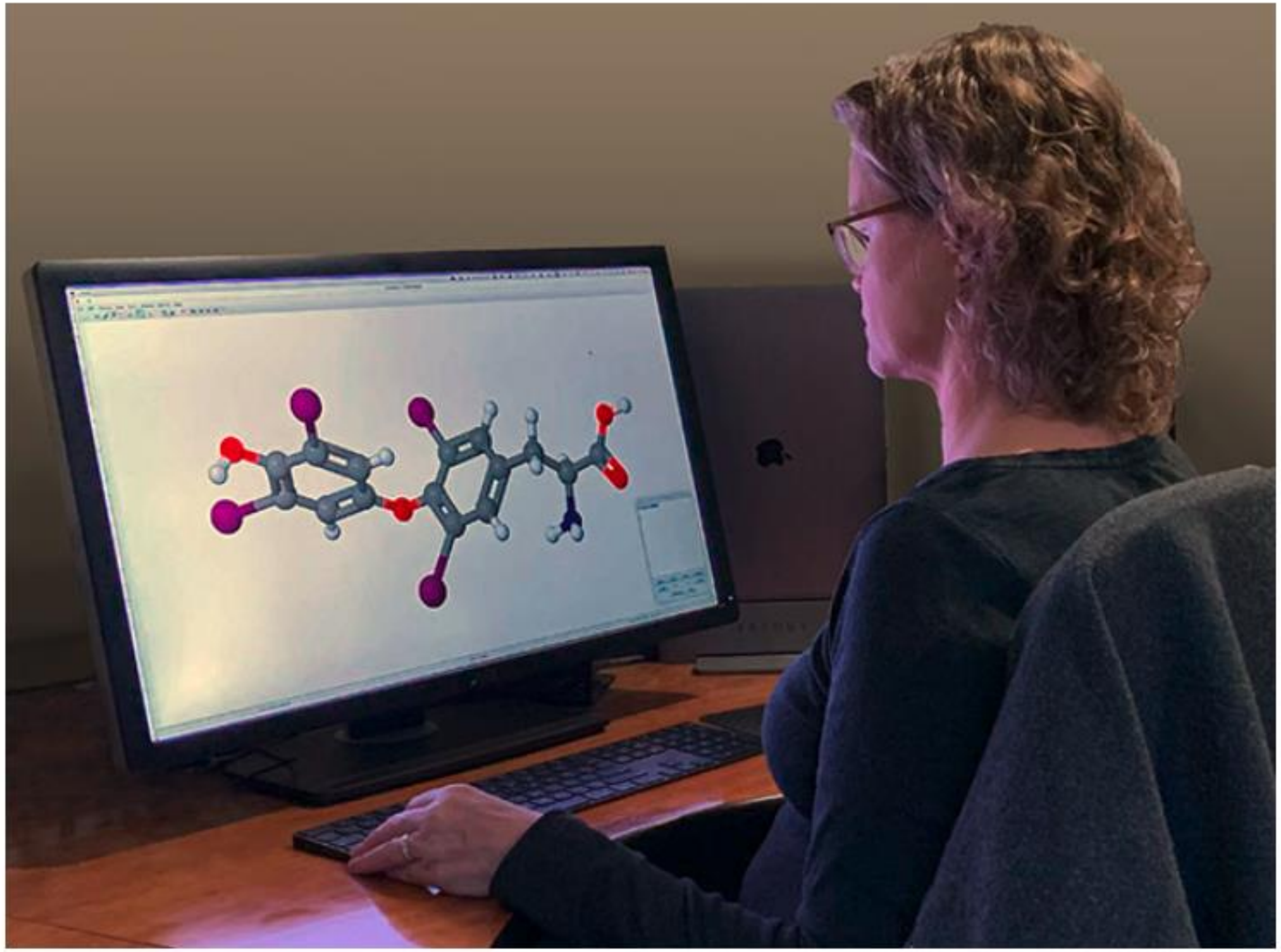
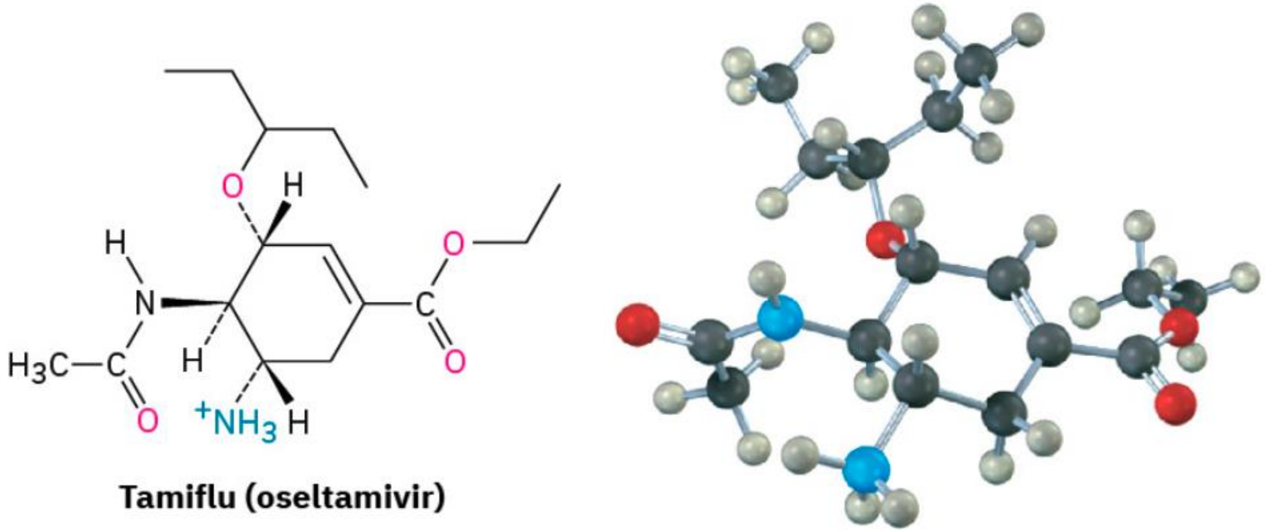


FIGURE 4.19 Computer programs make it possible to accurately represent molecular geometry. (credit: “Molecular geometry” by Jane Whitney/Flickr, CC BY 4.0)

After calculating a total strain energy for the starting geometry, the program automatically changes the geometry slightly in an attempt to lower strain—perhaps by lengthening a bond that is too short or decreasing an angle that is too large. Strain is recalculated for the new geometry, more changes are made, and more calculations are done. After dozens or hundreds of iterations, the calculation ultimately converges on a minimum energy that corresponds to the most favorable, least strained conformation of the molecule.

Similar calculations have proven to be particularly useful in pharmaceutical research, where a complementary fit between a drug molecule and a receptor molecule in the body is often the key to designing new pharmaceutical agents (**FIGURE 4.20**).



Tamiflu (oseltamivir)

FIGURE 4.20 The structure of Tamiflu (oseltamivir), an antiviral agent active against type A influenza, along with a molecular model of its minimum-energy conformation as calculated by molecular mechanics.

See you next week……….