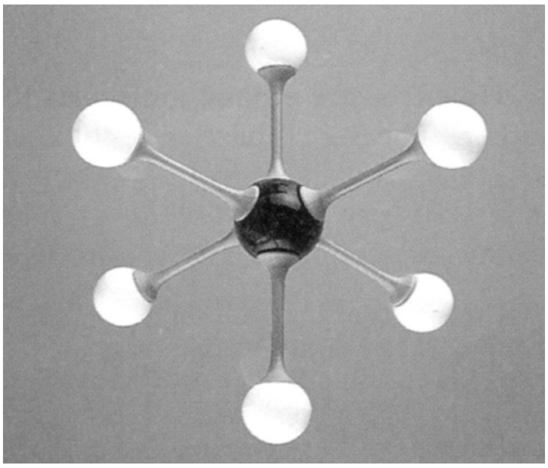
# 5

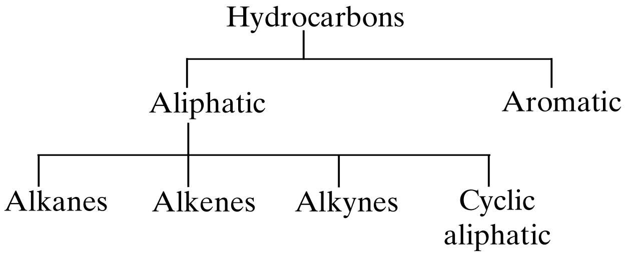


# Alkanes, Cycloalkanes and Aromatic Hydrocarbons

## 5AI. Introduction to Alkanes

### 5AI.1 Classification of hydrocarbons

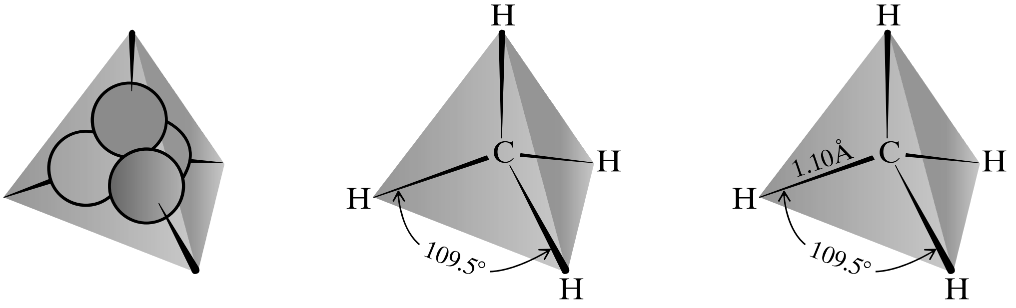
Certain organic compounds contain only two elements, hydrogen and carbon, and hence are known as **hydrocarbons**. On the basis of structure, hydrocarbons are divided into two main classes, **aliphatic** and **aromatic**. Aliphatic hydrocarbons are further divided into families: alkanes, alkenes, alkynes, and their cyclic analogs (cycloalkanes, etc.).



The simplest member of the alkane family and, indeed, one of the simplest of all organic compounds is **methane**, $CH_4$. We shall study this single compound at some length, since most of what we learn about it can be carried over with minor modifications to any alkane.

### 5AI.2 Alkanes: structure of methane

As we discussed in the previous chapter, each of the four hydrogen atoms is bonded to the carbon atom by a covalent bond, that is, by the sharing of a pair of electrons. When carbon is bonded to four other atoms, its bonding orbitals ($sp^3$ orbitals, formed by the mixing of one *s* and three *p* orbitals) are directed to the corners of a tetrahedron (Fig. 5AI.1*a*). This tetrahedral arrangement is the one that permits the orbitals to be as far apart as possible. For each of these orbitals to overlap most effectively the spherical *s* orbital of a hydrogen atom, and thus to form the strongest bond, each hydrogen nucleus must be located at a corner of this tetrahedron (Fig. 5AI.1*b*).

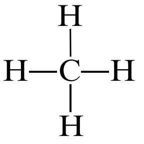


(*a*) (*b*) (*c*)

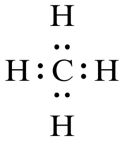
**Figure 5AI.1** Methane molecule. (*a*) Tetrahedral $sp^3$ orbitals. (*b*) Predicted shape: H nuclei located for maximum overlap. (*c*) Shape and size.

The tetrahedral structure of methane has been verified by electron diffraction (Fig. 5A.1*c*), which shows beyond question the arrangement of atoms in such simple molecules. Later on, we shall examine some of the evidence that led chemists to accept this tetrahedral structure long before quantum mechanics or electron diffraction was known.

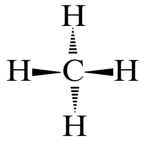
We shall ordinarily write methane with a dash to represent each pair of electrons shared by carbon and hydrogen (I). To focus our attention on individual electrons, we may sometimes indicate a pair of electrons by a pair of dots (II). Finally, when we wish to represent the actual shape of the molecule, we shall use a simple three-dimensional formula like III or IV.



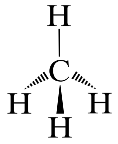
I



II



III



IV

In three-dimensional formulas of this kind, a solid wedge represents a bond coming toward us out of the plane of the paper; a broken wedge, a bond going away from us behind the plane of the paper; and an ordinary line, a bond lying in the plane of the paper. Thus, formulas III and IV represent methane as in Fig. 5A.1*a* and Fig. 5A.1*b*, respectively.

## 5AI.3 Classification by structure: the family

The basis of organic chemistry, we have said, is the structural theory. We separate all organic compounds into a number of families on the basis of structure. Having done this, we find that we have at the same time classified the compounds as to their physical and chemical properties. A particular set of properties is thus characteristic of a particular kind of structure.

Within a family there are variations in properties. All members of the family may, for example, react with a particular reagent, but some may react more readily than others. Within a single compound there may be variations in properties, one part of a molecule being more reactive than another part. These variations in properties correspond to variations in structure.

As we take up each family of organic compounds, we shall first see what structure and properties are characteristic of the family. Next we shall see how structure and properties vary within the family. We shall not simply memorize these facts, but, whenever possible, shall try to understand properties in terms of structure, and to understand variations in properties in terms of variations in structure.

Having studied methane in some detail, let us now look at the more complicated members of the alkane family. These hydrocarbons have been assigned to the same family as methane on the basis of their structure, and on the whole their properties follow the pattern laid down by methane. However, certain new points will arise simply because of the greater size and complexity of these compounds.

But, besides the chemistry of alkanes, we shall be learning something much more important: basic principles that we shall build on throughout our study. These comparatively simple compounds make an ideal starting point from which to expand our ideas of just what molecular structure is: to see the many ways in which a given set of atoms can be arranged; to find that molecules are not rigid and unchanging, but are flexible and can take on many shapes. Continuing with free-radical halogenation—a simple reaction, free of a complicating solvent—we shall use the concepts of energy of activation and transition state to see why one organic molecule reacts faster than another, and why one part of a molecule reacts faster than another part: a matter that lies at the heart of organic chemistry.

## 5AI.4 Structure of ethane

Next in size after methane is **ethane**, $C_2H_6$. If we connect the atoms of this molecule by covalent bonds, following the rule of one bond (one pair of electrons) for each hydrogen and four bonds (four pairs of electrons) for each carbon, we arrive at the structure

$$\begin{array}{ccccc} & H & & H & \\ & \cdot\cdot & & \cdot\cdot & \\ H & :C: & & C: & H \\ & \cdot\cdot & & \cdot\cdot & \\ & H & & H & \end{array} \qquad \begin{array}{ccccccc} & & H & & H & & \\ & & | & & | & & \\ H & — & C & — & C & — & H \\ & & | & & | & & \\ & & H & & H & & \end{array}$$

Ethane

Each carbon is bonded to three hydrogens and to the other carbon.

Since each carbon atom is bonded to four other atoms, its bonding orbitals ($sp^3$ orbitals) are directed toward the corners of a tetrahedron. As in the case of methane, the carbon–hydrogen bonds result from overlap of these $sp^3$ orbitals with the $s$ orbitals of the hydrogens. The carbon–carbon bond arises from overlap of two $sp^3$ orbitals.

The carbon–hydrogen and carbon–carbon bonds have the same general electron distribution, being cylindrically symmetrical about a line joining the atomic nuclei (see Fig. 5AI.2); because of this similarity in shape, the bonds are given the same name, $\sigma$ *bonds* (*sigma bonds*).

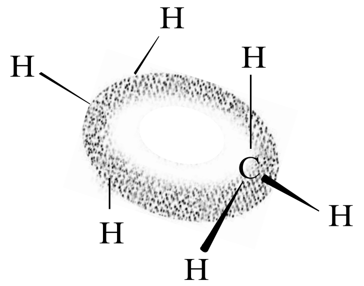


**Figure 5AI.2** Ethane molecule. Carbon–carbon single bond: $\sigma$ bond.

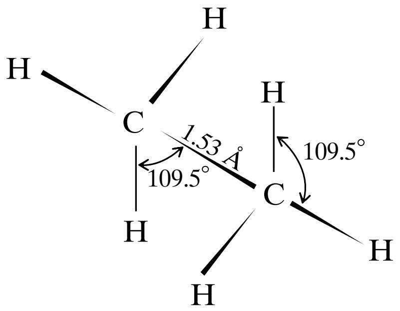
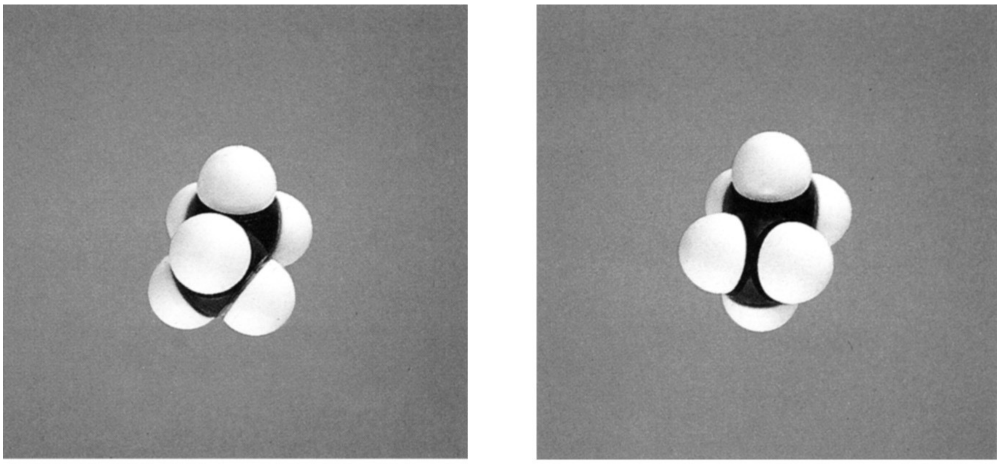


**Figure 5AI.3** Ethane molecule: shape and size.

In ethane, then, the bond angles and carbon–hydrogen bond lengths should be very much the same as in methane, that is, about 109.5° and about 1.10 Å, respectively. Electron diffraction and spectroscopic studies have verified this structure in all respects, giving (Fig. 5AI.3) the following measurements for the molecule: bond angles, 109.5°; C—H length, 1.10 Å; C—C length, 1.53 Å. Similar studies have shown that, with only slight variations, these values are quite characteristic of carbon–hydrogen and carbon–carbon bonds and of carbon bond angles in alkanes.

## 5AI.5 Free rotation about the carbon–carbon single bond. Conformations. Torsional strain

This particular set of bond angles and bond lengths still does not limit us to a single arrangement of atoms for the ethane molecule, since the relationship between the hydrogens of one carbon and the hydrogens of the other carbon is not specified. If we examine models of ethane (Fig. 5AI.4), we find that we could have an arrangement like I in which the hydrogens exactly oppose each other, an arrangement like II in



I
Eclipsed conformation

II
Staggered conformation

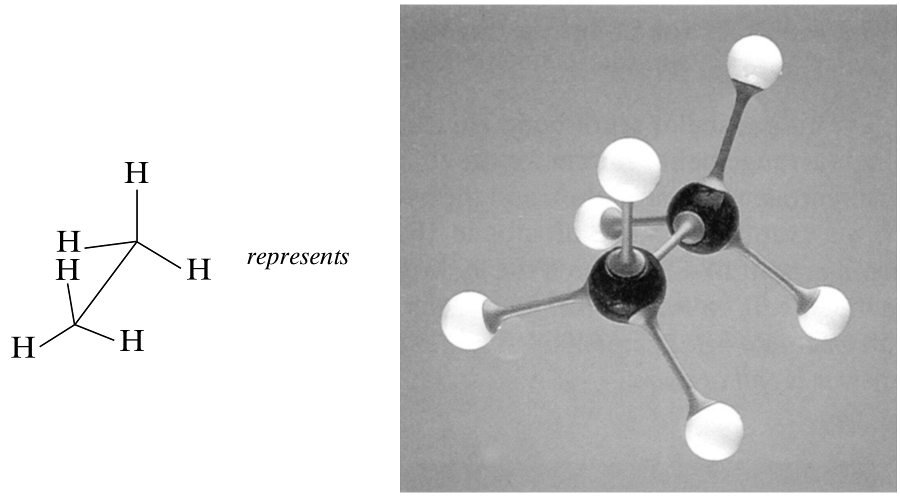
**Figure 5AI.4** Models of the ethane molecule in the eclipsed and staggered conformations.

which the hydrogens are perfectly staggered, or an infinity of intermediate arrangements. Which of these is the actual structure of ethane? The answer is: *all of them.*

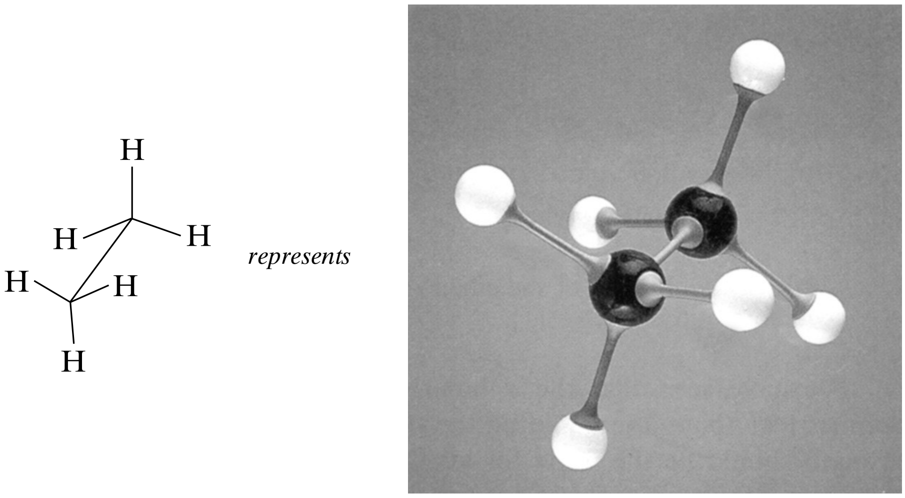
We have seen that the $\sigma$ bond joining the carbon atoms is cylindrically symmetrical about a line joining the two carbon nuclei; overlap and hence bond strength should be the same for all these possible arrangements. If the various arrangements do not differ in energy, then the molecule is not restricted to any one of them, but can change freely from one to another. Since the change from one to another involves rotation about the carbon–carbon bond, we describe this freedom to change by saying that *there is free rotation about the carbon–carbon single bond.*

*Different arrangements of atoms that can be converted into one another by rotation about single bonds are called* **conformations**. Arrangement I is called the *eclipsed conformation*; arrangement II is called the *staggered conformation.* (The infinity of intermediate conformations are called *skew conformations.*)

To represent such conformations, we shall often use two kinds of three-dimensional formulas: *andiron formulas* (Fig. 5AI.5);



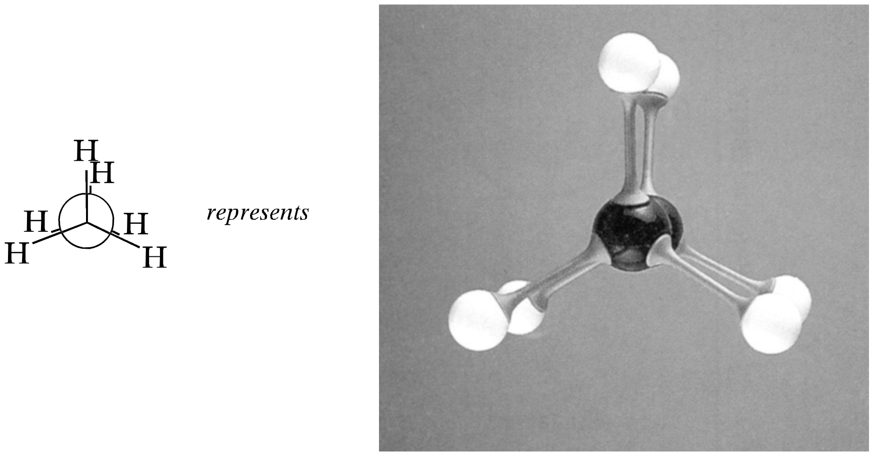
Eclipsed conformation



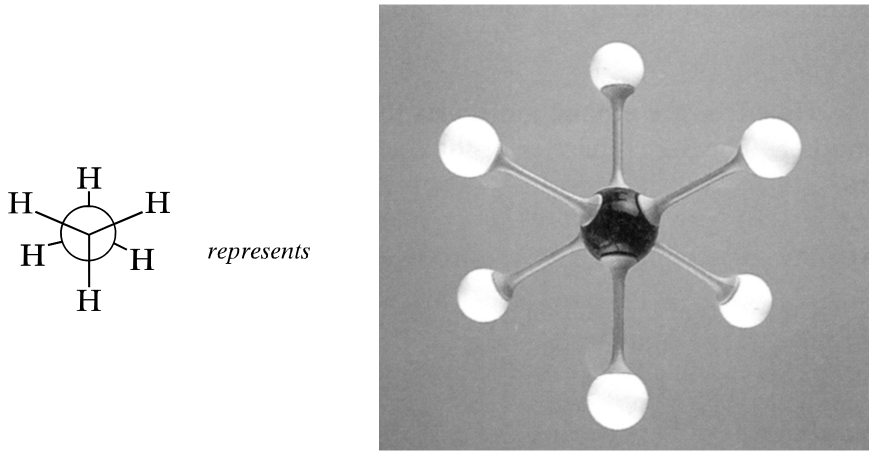
Staggered conformation

**Figure 5AI.5** Andiron formulas of ethane in the eclipsed and staggered conformations.

and *Newman projections* (Fig. 5AI.6), named for M. S. Newman, of the Ohio State University, who first proposed their use.



Eclipsed conformation



Staggerd conformation

**Figure 5AI.6** Newman projections of ethane in the eclipsed and staggered conformations.

The picture is not yet complete. Certain physical properties show that rotation is *not quite free*: there is an energy barrier of about 3 kcal/mol.The potential energy of the molecule is at a minimum for the staggered conformation, increases with rotation, and reaches a maximum at the eclipsed conformation (Fig. 5AI.7). Most ethane molecules, naturally, exist in the most stable, staggered conformation; or, put differently, any molecule spends most of its time in the most stable conformation.

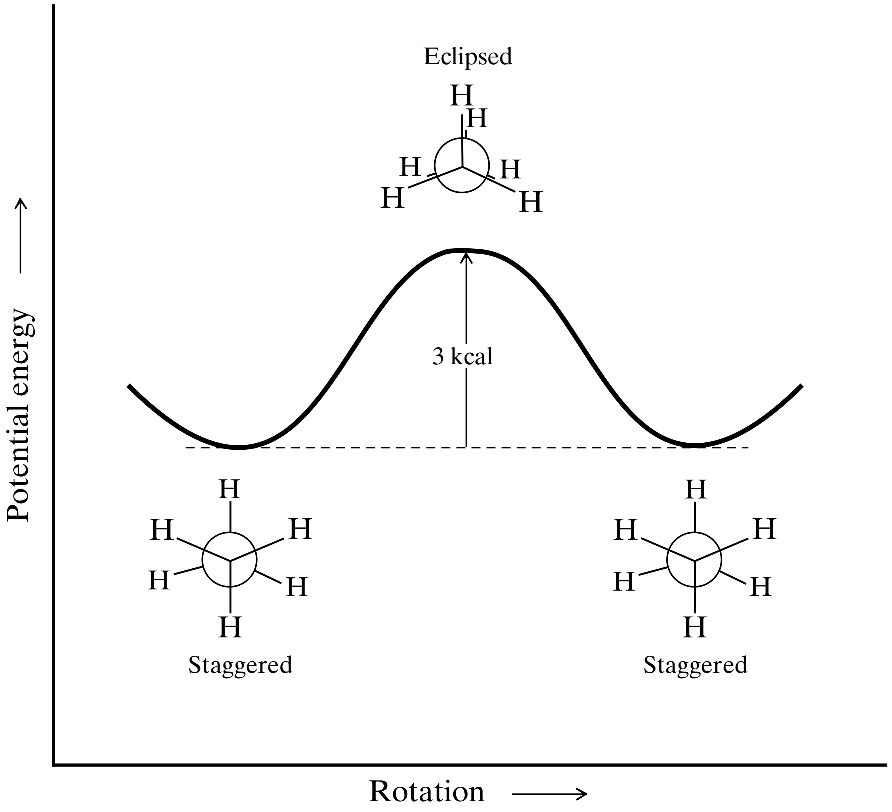


**Figure 5AI.7** Potential energy changes during rotation about the carbon–carbon single bond of ethane.

How free are ethane molecules to rotate from one staggered arrangement to another? The 3-kcal barrier is not a very high one; even at room temperature the fraction of collisions with sufficient energy is large enough that a rapid interconversion between staggered arrangements occurs. For most practical purposes, we may still consider that the carbon–carbon single bond permits free rotation.

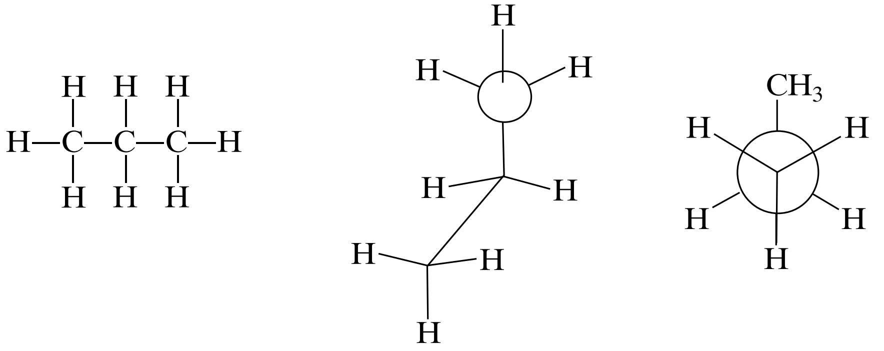
The nature of the rotational barrier in ethane is not understood or—what is not exactly the same thing—is not readily explained. It is too high to be due merely to van der Waals forces. Although thrown closer together in the eclipsed conformation than in the staggered conformation, the hydrogens on opposite carbons are not big enough for this to cause appreciable crowding. The barrier is considered to arise in some way from interaction among the electron clouds of the carbon–hydrogen bonds. Quantum mechanical calculations show that the barrier should exist, and so perhaps "lack of understanding" amounts to difficulty in paraphrasing the mathematics in physical terms. Like the bond orbitals in methane, the two sets of orbitals in ethane tend to be as far apart as possible—to be *staggered*.

The energy required to rotate the ethane molecule about the carbon–carbon bond is called *torsional energy*. We speak of the relative instability of the eclipsed conformation—or any of the intermediate skew conformations—as being due to *torsional strain*.

As the hydrogens of ethane are replaced by other atoms or groups of atoms, other factors affecting the relative stability of conformations appear: van der Waals forces, dipole–dipole interactions, hydrogen bonding. But the tendency for the bond orbitals on adjacent carbons remains to be staggered, and any rotation away from the staggered conformation is accompanied by torsional strain.

## 5AI.6 Propane and the butanes

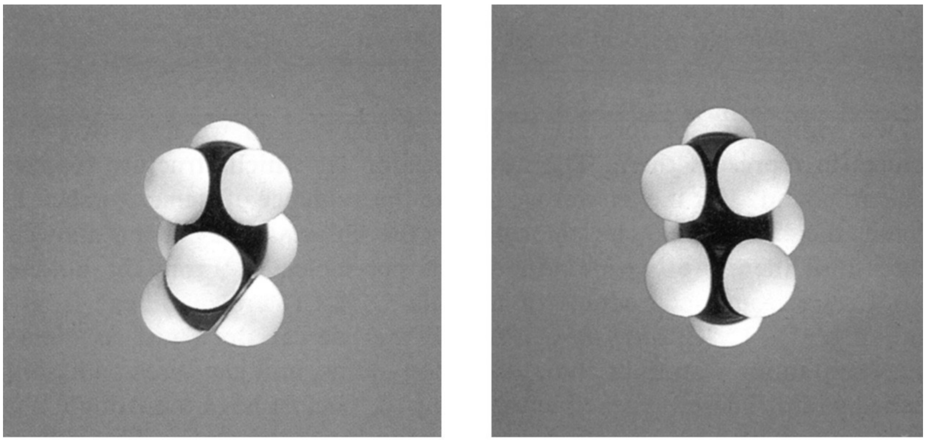
The next member of the alkane family is **propane**, $C_3H_8$. Again following the rule of one bond per hydrogen and four bonds per carbon, we arrive at structure I.



I

Propane

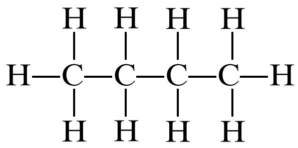
Here, rotation can occur about two carbon–carbon bonds, and again is essentially free. Although the methyl group is considerably larger than hydrogen, the rotational barrier (3.3 kcal/mol) is only a little higher than for ethane. Evidently there is still not very much crowding in the eclipsed conformation, and the rotational barrier is due chiefly to the same factor as the barrier in ethane: *torsional strain* (see Fig. 5AI.8).



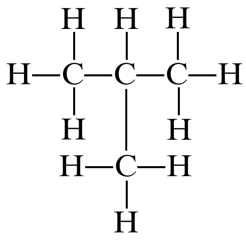
(*a*)

**Figure 5AI.8** Models of the propane molecule in (*a*) an eclipsed conformation and (*b*) a staggered conformation. There is little crowding in either conformation.

When we consider **butane**, $C_4H_{10}$, we find that there are two possible structures, II and III. Structure II has a four-carbon chain and III has a three-carbon chain with a one-carbon branch. There can be no doubt that these represent different



II
*n*-Butane



III
Isobutane

structures, since no amount of moving, twisting, or rotating about carbon–carbon bonds will cause these structures to coincide. We can see that in the *straight-chain* structure (II) each carbon possesses at least two hydrogens, whereas in the *branched-chain* structure (III) one carbon possesses only a single hydrogen; or we may notice that in the branched-chain structure (III) one carbon is bonded to three other carbons, whereas in the straight-chain structure (II) no carbon is bonded to more than two other carbons.

In agreement with this prediction, we find that two compounds of the same formula, $C_4H_{10}$, have been isolated. There can be no doubt that these two substances are different compounds, since they show definite differences in their physical and chemical properties (see Table 5AI.1); for example one boils at 0 °C and the other at –12 °C. By definition, they are *isomers*.

**Table 5AI.1** PHYSICAL CONSTANTS OF THE ISOMERIC BUTANES

| | *n*-Butane | Isobutane |
|---|---|---|
| B.p. | 0 °C | –12 °C |
| M.p. | –138 °C | –159 °C |
| Relative density at –20 °C | 0.622 | 0.604 |
| Solubility in 100 mL alcohol | 1813 mL | 1320 mL |

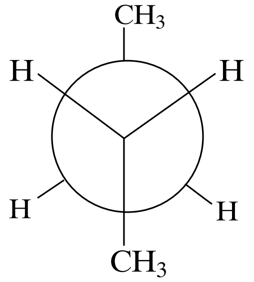
Two compounds of formula $C_4H_{10}$ are known and we have drawn two structures to represent them. The next question is: which structure represents which compound? For the answer we turn to the evidence of **isomer number**. Like methane, the butanes can be chlorinated; the chlorination can be allowed to proceed until there are two chlorine atoms per molecule. From the butane of b.p. 0 °C, *six* isomeric products of formula $C_4H_8Cl_2$ are obtained; from the butane of b.p. –12 °C, only *three*. We find that we can draw just six dichlorobutanes containing a straight chain of carbon atoms, and just three containing a branched chain. Therefore, the butane of b.p.0 °C must have the straight chain, and the butane of b.p. –12 °C must have the branched chain. To distinguish between these two isomers, the straight-chain structure is called ***n*-butane** (spoken "normal butane") and the branched-chain structure is called **isobutane**.

**Problem 5AI.1** Draw the structures of all possible dichloro derivatives of: (a) *n*-butane; (b) isobutane.

**Problem 5AI.2** Could we assign structures to the isomeric butanes on the basis of the number of isomeric *mono*chloro derivatives?

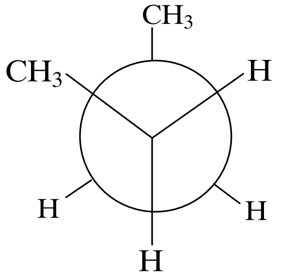
## 5AI.7 Conformations of *n*-butane. Van der Waals repulsion

Let us look more closely at the *n*-butane molecule and the conformations in which it exists. Focusing our attention on the middle C—C bond, we see a molecule similar to ethane, but with a methyl group replacing one hydrogen on each carbon. As with ethane, staggered conformations have lower torsional energies and hence are more stable than eclipsed conformations. But, due to the presence of the methyl groups: two new points are encountered here: first, there are several *different* staggered conformations, and second, a factor besides torsional strain comes into play to affect conformational stabilities.

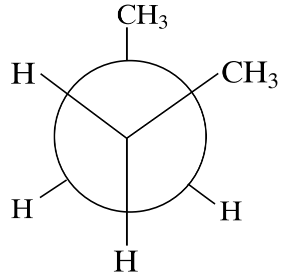


I

*Anti* conformation



II



III

*Gauche* conformations

*n*-Butane

There is the *anti* conformation, I, in which the methyl groups are as far apart as they can be (dihedral angle 180°). There are two *gauche* conformations, II and III, in which the methyl groups are only 60° apart. (Conformations II and III are mirror images of each other, and are of the same stability; nevertheless, they *are* different. Make models and convince yourself that this is so.)

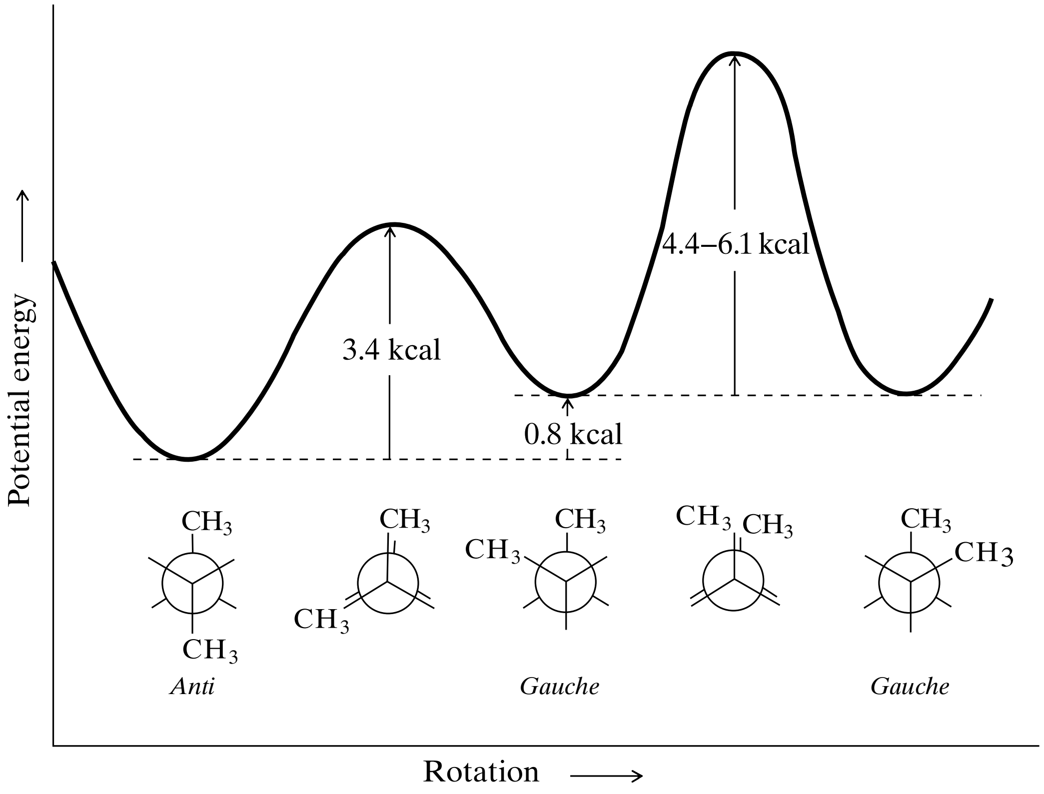


**Figure 5AI.9** Potential energy changes during rotation about the C(2)—C(3) bond of *n*-butane.

The *anti* conformation, it has been found, is more stable (by 0.8 kcal/mol) than the *gauche* (Fig. 5AI.9). Both are free of torsional strain. But in a *gauche* conformation, the methyl groups are crowded together, that is, are thrown together closer than the sum of their van der Waals radii; under these conditions, van der Waals forces are *repulsive* and raise the energy of the conformation. We say that there is *van der Waals repulsion* (or *steric repulsion*) between the methyl groups, and that the molecule is less stable because of *van der Waals strain* (or *steric strain*). We can see this crowding quite clearly in scale models (Fig. 5AI.10).

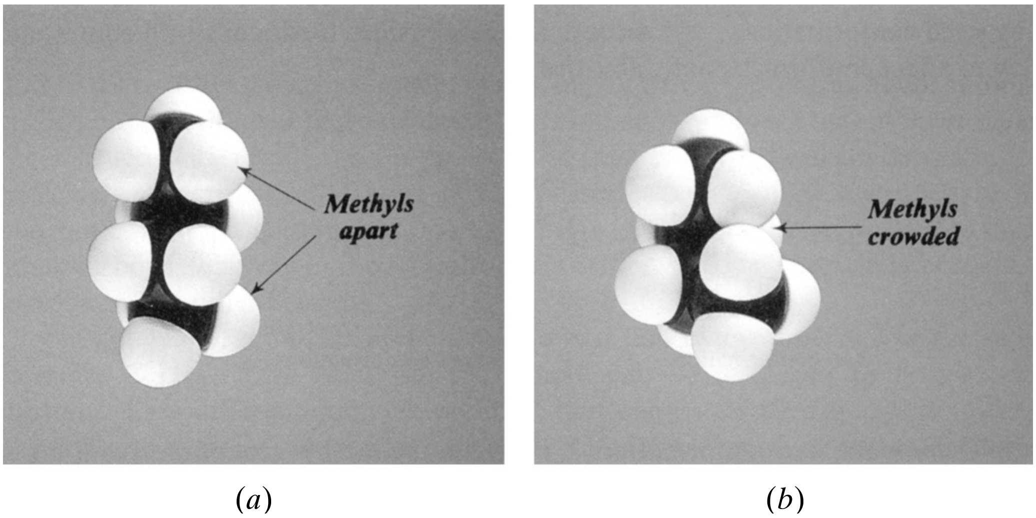


**Figure 5AI.10** Models of $n$-butane in (*a*) an *anti* conformation and (*b*) a *gauche* conformation. Note the crowding between the methyl groups in (*b*).

Van der Waals strain can affect not only the relative stabilities of various staggered conformations, but also the heights of the barriers between them. The energy maximum reached when two methyl groups swing past each other—rather than past hydrogens—is the highest rotational barrier of all, and has been estimated at 4.4–6.1 kcal/mol. Even so, it is low enough that—at ordinary temperatures, at least—the energy of molecular collisions causes rapid rotation; a given molecule exists now in a *gauche* conformation, and the next instant in the *anti* conformation.

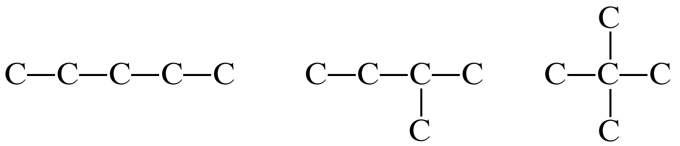
**Problem 5AI.3** Both calculations and experimental evidence indicate that the dihedral angle between the methyl groups in the *gauche* conformation of $n$-butane is actually somewhat *larger* than 60°. How would you account for this?

**Problem 5AI.4** Considering only rotation about the bond shown, draw a potential energy *vs.* rotation curve like Fig. 5AI.9 for:
(a) $(CH_3)_2CH—CH(CH_3)_2$; (b) $(CH_3)_2CH—CH_2CH_3$; (c) $(CH_3)_3C—C(CH_3)_3$.
(d) Compare the heights of the various energy barriers with each other and with those in Fig. 5AI.9.

## 5AI.8 Higher alkanes. The homologous series

If we examine the molecular formulas of the alkanes we have so far considered, we see that butane contains one carbon and two hydrogens more than propane, which in turn contains one carbon and two hydrogens more than ethane, and so on. *A series of compounds in which each member differs from the next member by a constant amount is called a* **homologous series***, and the members of the series are called* **homologs**. The family of alkanes forms such a homologous series, the constant difference between successive members being $CH_2$. We also notice that in each of these alkanes the number of hydrogen atoms equals two more than twice the number of carbon atoms, so that we may write as a *general formula* for members of this series, $C_nH_{2n+2}$. As we shall see later, other homologous series have their own characteristic general formulas.

In agreement with this general formula, we find that the next alkane, *pentane*, has the formula $C_5H_{12}$, followed by *hexane*, $C_6H_{14}$, *heptane*, $C_7H_{16}$, and so on. We would expect that, as the number of atoms increases, so does the number of possible arrangements of those atoms. As we go up the series of alkanes, we find that this is true: the number of isomers of successive homologs increases at a surprising rate. There are 3 isomeric pentanes, 5 hexanes, 9 heptanes, and 75 decanes ($C_{10}$); for the twenty-carbon icosane, there are 366 319 possible isomeric structures! The carbon skeletons of the isomeric pentanes and hexanes are shown below.

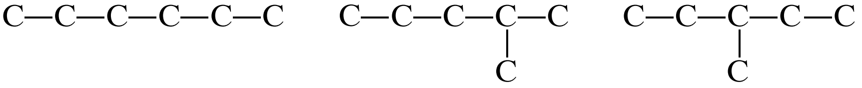


**Pentanes**

*n*-Pentane b.p. 36 °C

Isopentane b.p. 28 °C

Neopentane b.p. 9.5 °C

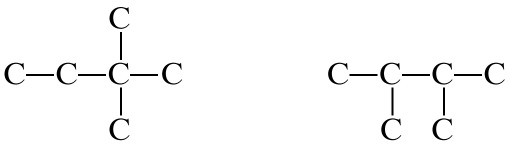


**Hexanes**

b.p. 69 °C

b.p. 60 °C

b.p. 63 °C



b.p. 50 °C

b.p. 58 °C

It is important to practice drawing the possible isomeric structures that correspond to a single molecular formula. In doing this, a set of molecular models is especially helpful since it will show that many structures which appear to be different when drawn on paper are actually identical.

**Problem 5AI.5** Draw the structures of: (a) the nine isomeric heptanes ($C_7H_{16}$); (b) the eight chloropentanes ($C_5H_{11}Cl$); (c) the nine dibromobutanes ($C_4H_8Br_2$).

## 5AI.9 Nomenclature

We have seen that the names *methane, ethane, propane, butane*, and *pentane* are used for alkanes containing respectively one, two, three, four, and five carbon atoms. Table 5AI.2 gives the names of many larger alkanes. Except for the first four members of the family, the name is simply derived from the Greek (or Latin) prefix for the particular number of carbons in the alkane; thus **pent**ane for five, **hex**ane for six, **hept**ane for seven, **oct**ane for eight, and so on.

**Table 5AI.2** NAMES OF ALKANES

| | | | |
|---|---|---|---|
| $CH_4$ | methane | $C_9H_{20}$ | nonane |
| $C_2H_6$ | ethane | $C_{10}H_{22}$ | decane |
| $C_3H_8$ | propane | $C_{11}H_{24}$ | undecane |
| $C_4H_{10}$ | butane | $C_{12}H_{26}$ | dodecane |
| $C_5H_{12}$ | pentane | $C_{14}H_{30}$ | tetradecane |
| $C_6H_{14}$ | hexane | $C_{16}H_{34}$ | hexadecane |
| $C_7H_{16}$ | heptane | $C_{18}H_{38}$ | octadecane |
| $C_8H_{18}$ | octane | $C_{20}H_{42}$ | icosane |

You should certainly memorize the names of at least the first ten alkanes. Having done this, you will have at the same time essentially learned the names of the first ten alkenes, alkynes, alcohols, etc., since the names of many families of compounds are closely related. Compare, for example, the names *propane, propene*, and *propyne* for the three-carbon alkane, alkene, and alkyne.

But nearly every alkane can have a number of isomeric structures, and there must be an unambiguous name for each of these isomers. The butanes and pentanes are distinguished by the use of prefixes: ***n***-butane and **iso**butane; ***n***-pentane, **iso**pentane, and **neo**pentane. But there are 5 hexanes, 9 heptanes, and 75 decanes; it would be difficult to devise, and even more difficult to remember, a different prefix for each of these isomers. It is obvious that some systematic method of naming is needed.

As organic chemistry has developed, several different methods have been devised to name the members of nearly every class of organic compounds; each method was devised when the previously used system had been found inadequate for the growing number of increasingly complex organic compounds. Unfortunately for us, perhaps, several systems have survived and are in current use. Even if we are content ourselves to use only one system, we still have to understand the names used by other chemists; hence it is necessary for us to learn more than one system of nomenclature. But before we can do this, we must first learn the names of certain organic groups.

## 5AI.10 Alkyl groups

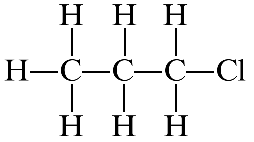
In our study of inorganic chemistry, we found it useful to have names for certain groups of atoms that compose only part of a molecule and yet appear many times as a unit. For example, $NH_4^+$ is called *ammonium*; $NO_3^-$, *nitrate*; $SO_3^{2-}$, *sulfite*; and so on.

In a similar way names are given to certain groups that constantly appear as structural units of organic molecules. We have seen that chloromethane, $CH_3Cl$, is also known as *methyl chloride*. The $CH_3$ group is called **methyl** wherever it appears,

$CH_3Br$ being *methyl* bromide; $CH_3I$, *methyl* iodide; and $CH_3OH$, *methyl* alcohol. In an analogous way, the $C_2H_5$ group is **ethyl**; $C_3H_7$, **propyl**; $C_4H_9$, **butyl**; and so on.

These groups are named simply by dropping *-ane* from the name of the corresponding alkane and replacing it by *-yl*. They are known collectively as **alkyl groups**. The general formula for an alkyl group is $C_nH_{2n+1}$, since it contains one less hydrogen than the parent alkane, $C_nH_{2n+2}$.

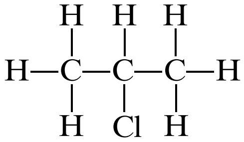
Among the alkyl groups we again encounter the problem of isomerism. There is only one methyl chloride or ethyl chloride, and correspondingly only one methyl group or ethyl group. We can see, however, that there are two propyl chlorides, I and II, and hence that there must be two propyl groups. These groups both contain the propane chain, but differ in the point of attachment of the chlorine; they are called ***n*-propyl** and **isopropyl**. We can distinguish the two chlorides by the names *n-propyl chloride* and *isopropyl chloride;* we distinguish the two propyl bromides, iodides, alcohols, and so on in the same way.



$$\begin{array}{ccccccccc} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \\ & & | & & | & & | & & \\ \mathrm{H} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{Cl} \\ & & | & & | & & | & & \\ & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \end{array}$$

I

*n*-Propyl chloride



$$\begin{array}{ccccccccc} & & \mathrm{H} & & \mathrm{H} & & \mathrm{H} & & \\ & & | & & | & & | & & \\ \mathrm{H} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{H} \\ & & | & & | & & | & & \\ & & \mathrm{H} & & \mathrm{Cl} & & \mathrm{H} & & \end{array}$$

II

Isopropyl chloride

$CH_3CH_2CH_2—$

*n*-Propyl

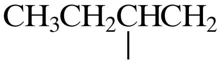
$$\mathrm{CH_3\underset{|}{C}HCH_3}$$

Isopropyl

We find that there are four butyl groups, two derived from the straight-chain *n*-butane, and two derived from the branched-chain isobutane. These are given the designations ***n-*** (*normal*), ***sec-*** (*secondary*), ***iso-***, and ***tert-*** (*tertiary*), as shown below. Again the difference between *n*-butyl and *sec*-butyl and between isobutyl and *tert*-butyl lies in the point of attachment of the alkyl group to the rest of the molecule.

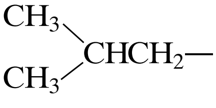
$CH_3CH_2CH_2CH_2—$

*n*-Butyl

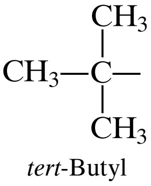


$$\mathrm{CH_3CH_2\underset{|}{C}HCH_2}$$

*sec*-Butyl



Isobutyl



$$\begin{array}{ccc} & & \mathrm{CH_3} \\ & & | \\ \mathrm{CH_3} & - & \mathrm{C}- \\ & & | \\ & & \mathrm{CH_3} \end{array}$$

*tert*-Butyl

Beyond butyl the number of isomeric groups derived from each alkane becomes so great that it is impracticable to designate them all by various prefixes. Even though limited, this system is so useful for the small groups just described that it is widely used; a student must therefore memorize these names and learn to recognize these groups at a glance in whatever way they happen to be represented.

However large the group concerned, one of its many possible arrangements can still be designated by this simple system. The prefix *n*- is used to designate any alkyl group in which all carbons form a single continuous chain and in which the point of attachment is the very end carbon. For example:

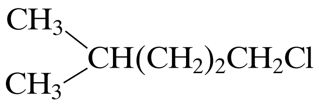
$CH_3CH_2CH_2CH_2CH_2Cl$ — *n*-Pentyl chloride

$CH_3(CH_2)_4CH_2Cl$ — *n*-Hexyl chloride

The prefix *iso*- is used to designate any alkyl group (of six carbons or fewer) that has a single one-carbon branch on the next-to-last carbon of a chain and has the point of attachment at the opposite end of the chain. For example:

$$\begin{array}{l} CH_3\diagdown \\ \qquad CHCH_2CH_2Cl \\ CH_3\diagup \end{array}$$

Isopentyl chloride



$$\begin{array}{l} CH_3\diagdown \\ \qquad CH(CH_2)_2CH_2Cl \\ CH_3\diagup \end{array}$$

Isohexyl chloride

If the branching occurs at any other position, or if the point of attachment is at any other position, this name does not apply.

Now that we have learned the names of certain alkyl groups, let us return to the original problem: the naming of alkanes.

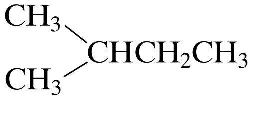
## 5AI.11 Common names of alkanes

As we have seen, the prefixes *n*-, *iso*-, and *neo*- are adequate to differentiate the various butanes and pentanes, but beyond this point an impracticable number of prefixes would be required. However, the prefix *n*- has been retained for any alkane, no matter how large, in which all carbons form a continuous chain with no branching:

$CH_3CH_2CH_2CH_2CH_3$ — *n*-Pentane

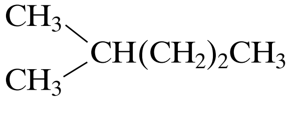
$CH_3(CH_2)_4CH_3$ — *n*-Hexane

An *isoalkane* is a compound of six carbons or fewer in which all carbons except one form a continuous chain and that one carbon is attached to the next-to-end carbon:



$$\begin{array}{l} CH_3\diagdown \\ \qquad CHCH_2CH_3 \\ CH_3\diagup \end{array}$$

Isopentane



$$\begin{array}{l} CH_3\diagdown \\ \qquad CH(CH_2)_2CH_3 \\ CH_3\diagup \end{array}$$

Isohexane

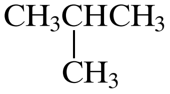
In naming any other of the higher alkanes, we make use of the IUPAC system, outlined in the following section.

## 5AI.12 IUPAC names of alkanes

To devise a system of nomenclature that could be used for even the most complicated compounds, various committees and commissions representing the chemists of the world have met periodically since 1892. In its present modification, the system so devised is known as the **IUPAC system** (International Union of Pure and Applied Chemistry). Since this system follows much the same pattern for all families of organic compounds, we shall consider it in some detail as applied to the alkanes.

Essentially the rules of the IUPAC system are:

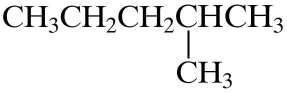
(i) Select as the parent structure the longest continuous chain, and then consider the compound to have been derived from this structure by the replacement of hydrogen by various alkyl groups. Isobutane (I) can be considered to arise from propane by the replacement of a hydrogen atom by a methyl group, and thus may be named *methylpropane.*



$$CH_3\underset{\substack{|\\CH_3}}{C}HCH_3$$

I

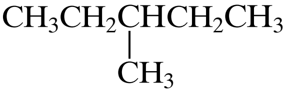
Methylpropane
(Isobutane)



$$CH_3CH_2CH_2\underset{\substack{|\\CH_3}}{C}HCH_3$$

II

2-Methylpentane



$$CH_3CH_2\underset{\substack{|\\CH_3}}{C}HCH_2CH_3$$

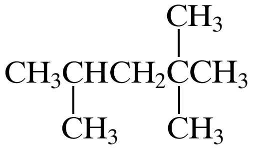
III

3-Methylpentane

(ii) Where necessary, as in the isomeric methylpentanes (II and III), indicate by a number the carbon to which the alkyl group is attached.

(iii) In numbering the parent carbon chain, start at whichever end results in the use of the lowest numbers; thus II is called *2-methylpentane* rather than 4-methylpentane.

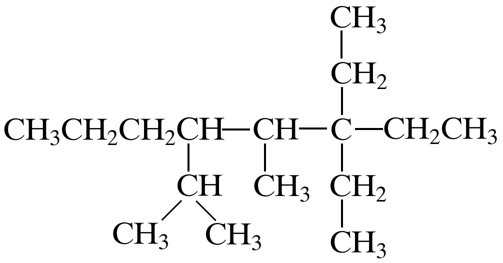
(iv) If the same alkyl group occurs more than once as a side chain, indicate this by the prefix *di-*, *tri-*, *tetra-*, etc., to show how many of these alkyl groups there are, and indicate by various numbers the positions of *each* group, as in *2,2,4-trimethyl-pentane* (IV).



$$CH_3\underset{\substack{|\\CH_3}}{C}HCH_2\overset{\substack{CH_3\\|}}{\underset{\substack{|\\CH_3}}{C}}CH_3$$

IV

2,2,4-Trimethylpentane



V

3,3-Diethyl-5-isopropyl-4-methyloctane

(v) If there are several different alkyl groups attached to the parent chain, name them in alphabetical order; as in *3,3-diethyl-5-isopropyl-4-methyloctane* (V). (Note that **i**sopropyl comes before **m**ethyl. A di**m**ethyl, however, would come after **e**thyl or di**e**thyl.)

There are additional rules and conventions used in naming very complicated alkanes, but the five fundamental rules given above will suffice for the compounds we are likely to encounter.

The alkyl halides which appear so often in alkane chemistry are named as *haloalkanes*; that is, halogen is simply treated as a side chain. We first name the alkane as though no halogen were present, and then add *fluoro, chloro, bromo*, or *iodo*, together with any needed numbers and prefixes.

$CH_3CH_2Cl$

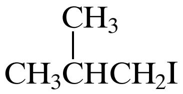
1-Chloroethane

$CH_3CH_2CH_2Br$

1-Bromopropane

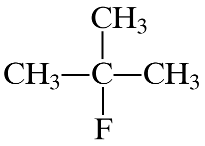
$CH_3CH_2\underset{\underset{Br}{|}}{C}HCH_3$

2-Bromobutane



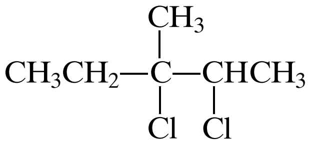
$CH_3\overset{\overset{CH_3}{|}}{C}HCH_2I$

1-Iodo-2-methylpropane



$CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{F}{|}}{C}}-CH_3$

2-Fluoro-2-methylpropane



$CH_3CH_2-\overset{\overset{CH_3}{|}}{\underset{\underset{Cl}{|}}{C}}-\underset{\underset{Cl}{|}}{C}HCH_3$

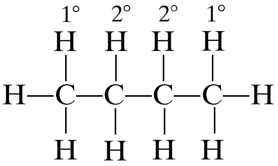
2,3-Dichloro-3-methylpentane

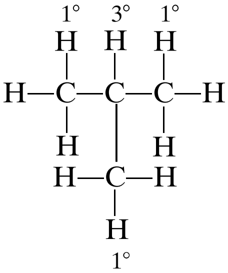
**Problem 5AI.6** Give the IUPAC names for: (a) the isomeric hexanes shown under Sec. (5AI.8); (b) the nine isomeric heptanes.

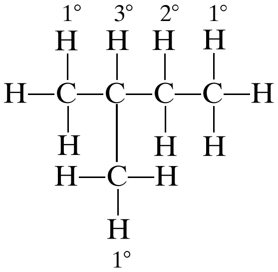
**Problem 5AI.7** Give the IUPAC names for: (a) the eight isomeric chloropentanes; (b) the nine isomeric dibromobutanes.

## 5AI.13 Classes of carbon atoms and hydrogen atoms

It has been found extremely useful to classify each carbon atom of an alkane with respect to the number of other carbon atoms to which it is attached. ***A* primary** (1°) *carbon atom is attached to only one other carbon atom; a* **secondary** (2°) *is attached to two others; and a* **tertiary** (3°) *to three others*. For example:







Each hydrogen atom is similarly classified, being given the same designation of *primary, secondary*, or *tertiary* as the carbon atom to which it is attached.

We shall make constant use of these designations in our consideration of the relative reactivities of various parts of an alkane molecule.

## 5AI.14 Physical properties

The physical properties of the alkanes follow the pattern laid down by methane, and are consistent with the alkane structure. An alkane molecule is held together entirely by covalent bonds. These bonds either join two atoms of the same kind and hence are non-polar, or join two atoms that differ very little in electronegativity and hence are only slightly polar. Furthermore, these bonds are directed in a very symmetrical way, so that the slight bond polarities tend to cancel out. As a result an alkane molecule is either non-polar or very weakly polar.

As we have seen, the forces holding non-polar molecules together (van der Waals forces) are weak and of very short range; they act only between the portions of different molecules that are in close contact, that is, between the surfaces of molecules. Within a family, therefore, we would expect that the larger the molecule—and hence the larger its surface area—the stronger the intermolecular forces.

Table 5AI.3 lists certain physical constants for a number of the *n*-alkanes. As we can see, the boiling points and melting points rise as the number of carbons increases. The processes of boiling and melting require overcoming the intermolecular forces of a liquid and a solid; the boiling points and melting points rise because these intermolecular forces increase as the molecules get larger.

**Table 5AI.3** ALKANES

| Name | Formula | M.P., °C | B.P., °C | Relative density (at 20 °C) |
|---|---|---|---|---|
| Methane | $CH_4$ | –183 | –162 | |
| Ethane | $CH_3CH_3$ | –172 | –88.5 | |
| Propane | $CH_3CH_2CH_3$ | –187 | –42 | |
| *n*-Butane | $CH_3(CH_2)_2CH_3$ | –138 | 0 | |
| *n*-Pentane | $CH_3(CH_2)_3CH_3$ | –130 | 36 | 0.626 |
| *n*-Hexane | $CH_3(CH_2)_4CH_3$ | –95 | 69 | 0.659 |
| *n*-Heptane | $CH_3(CH_2)_5CH_3$ | –90.5 | 98 | 0.684 |
| *n*-Octane | $CH_3(CH_2)_6CH_3$ | –57 | 126 | 0.703 |
| *n*-Nonane | $CH_3(CH_2)_7CH_3$ | –54 | 151 | 0.718 |
| *n*-Decane | $CH_3(CH_2)_8CH_3$ | –30 | 174 | 0.730 |
| *n*-Undecane | $CH_3(CH_2)_9CH_3$ | –26 | 196 | 0.740 |
| *n*-Dodecane | $CH_3(CH_2)_{10}CH_3$ | –10 | 216 | 0.749 |
| *n*-Tridecane | $CH_3(CH_2)_{11}CH^3$ | –6 | 234 | 0.757 |
| *n*-Tetradecane | $CH_3(CH_2)_{12}CH_3$ | 5.5 | 252 | 0.764 |
| *n*-Pentadecane | $CH_3(CH_2)_{13}CH_3$ | 10 | 266 | 0.769 |
| *n*-Hexadecane | $CH_3(CH_2)_{14}CH_3$ | 18 | 280 | 0.775 |
| *n*-Heptadecane | $CH_3(CH_2)_{15}CH_3$ | 22 | 292 | |
| *n*-Octadecane | $CH_3(CH_2)_{16}CH_3$ | 28 | 308 | |
| *n*-Nonadecane | $CH_3(CH_2)_{17}CH_3$ | 32 | 320 | |
| *n*-Icosane | $CH_3(CH_2)_{18}CH_3$ | 36 | | |
| Isobutane | $(CH_3)_2CHCH_3$ | –159 | –12 | |
| Isopentane | $(CH_3)_2CHCH_2CH_3$ | –160 | 28 | 0.620 |
| Neopentane | $(CH_3)_4C$ | –17 | 9.5 | |
| Isohexane | $(CH_3)_2CH(CH_2)_2CH_3$ | –154 | 60 | 0.654 |
| 3-Methylpentane | $CH_3CH_2CH(CH_3)CH_2CH_3$ | –118 | 63 | 0.676 |
| 2,2-Dimethylbutane | $(CH_3)_3CCH_2CH_3$ | –98 | 50 | 0.649 |
| 2,3-Dimethylbutane | $(CH_3)_2CHCH(CH_3)_2$ | –129 | 58 | 0.668 |

Except for the very small alkanes, *the boiling point rises 20 to 30 degrees for each carbon that is added to the chain*; we shall find that this increment of 20–30 degrees per carbon holds not only for the alkanes but also for each of the homologous series that we shall study.

The increase in melting point is not quite so regular, since the intermolecular forces in a crystal depend not only upon the size of the molecules but also upon how well they fit into a crystal lattice.

The first four *n*-alkanes are gases, but, as a result of the rise in boiling point and melting point with increasing chain length, the next thirteen ($C_5$–$C_{17}$) are liquids, and those containing 18 carbons or more are solids.

**Problem 5AI.8** Using the data of Table 5AI.3 make a graph of: (a) b.p. *vs*. carbon number for the *n*-alkanes; (b) m.p. *vs*. carbon number; (c) density *vs*. carbon number.

There are somewhat smaller differences among the boiling points of alkanes that have the same carbon number but different structures. On pages 84 and 87 the boiling points of the isomeric butanes, pentanes, and hexanes are given. We see that in every case a *branched-chain isomer has a lower boiling point than a straight-chain isomer*, and further, that the more numerous the branches, the lower the boiling point. Thus *n*-butane has a boiling point of 0 °C and isobutane –12 °C. *n*-Pentane has a boiling point of 36 °C, isopentane with a single branch 28 °C, and neopentane with two branches 9.5 °C. This effect of branching on boiling point is observed within all families of organic compounds. That branching should lower the boiling point is understandable: with branching the shape of the molecule tends to approach that of a sphere; and as this happens the surface area decreases, with the result that the intermolecular forces become weaker and are overcome at a lower temperature. Compare the shapes of the isomeric pentanes.

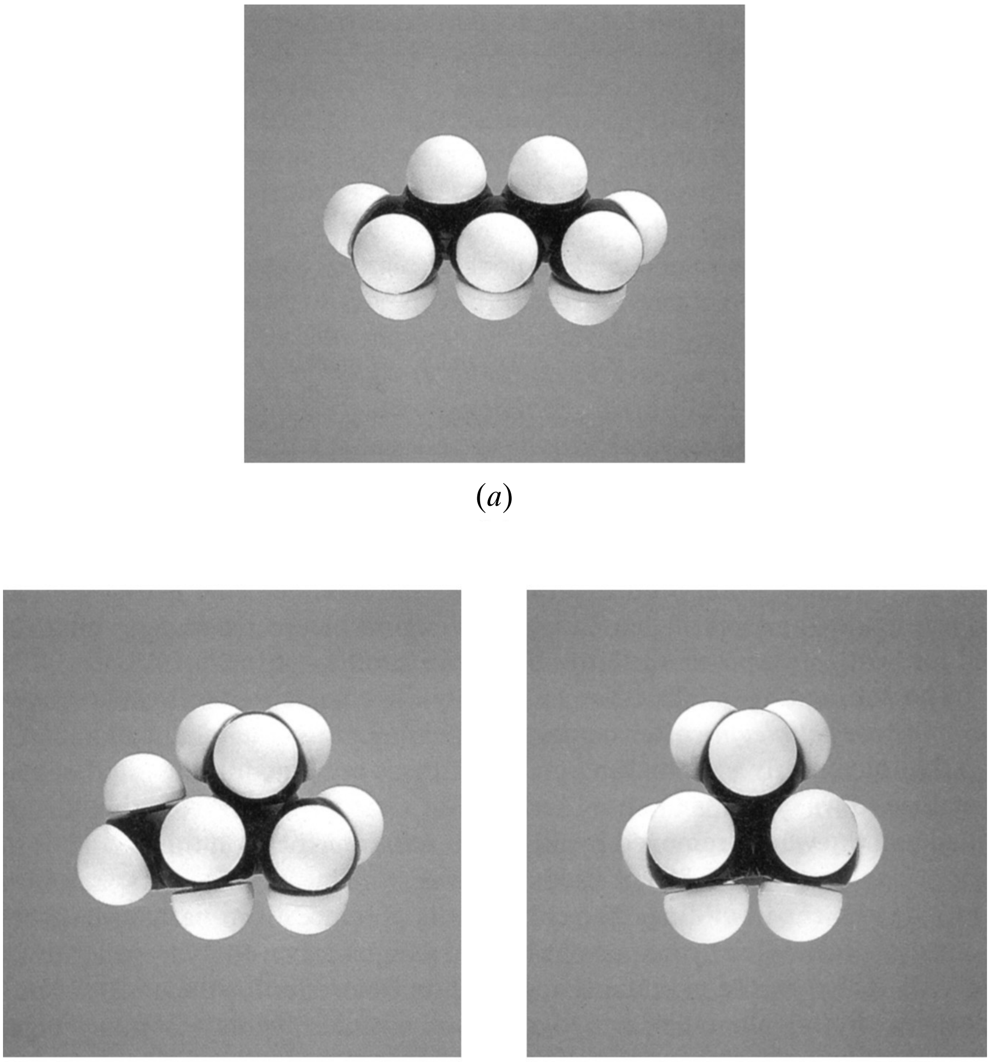
In agreement with the rule of thumb, "like dissolves like", the alkanes are soluble in non-polar solvents such as benzene, ether, and chloroform, and are insoluble in water and other highly polar solvents. Considered themselves as solvents, the liquid alkanes dissolve compounds of low polarity and do not dissolve compounds of high polarity.

The relative density increases with size of the alkanes, but tends to level off at about 0.8; thus all alkanes are less dense than water. It is not surprising that nearly all organic compounds are less dense than water since, like the alkanes, they consist chiefly of carbon and hydrogen. In general, to be denser than water a compound must contain a heavy atom like bromine or iodine, or several atoms like chlorine.

## 5AI.15 Industrial source

The principal source of alkanes is **petroleum**, together with the accompanying **natural gas**. Decay and millions of years of geological stresses have transformed the complicated organic compounds that once made up living plants or animals into a mixture of alkanes ranging in size from one carbon to 30 or 40 carbons. Formed along with the alkanes, and particularly abundant in California petroleum, are *cycloalkanes*, known to the petroleum industry as *naphthenes*.

The other fossil fuel, coal, is a potential second source of alkanes: processes are being developed to convert coal, through hydrogenation, into gasoline and fuel oil, and into synthetic gas to offset anticipated shortages of natural gas.



(*a*)

(*b*) (*c*)

**Figure 5AI.11** Molecular structure and physical properties: effect of branching. The isomeric pentanes: (*a*) *n*-pentane, b.p. 36 °C; (*b*) isopentane, b.p. 28 °C; (*c*) neopentane, b.p. 9.5 °C. Neopentane is the most highly branched and most nearly spherical, and has the smallest surface area; intermolecular forces are weakest, and it boils at the lowest temperature.

Natural gas contains, of course, only the more volatile alkanes, that is, those of low molecular weight; it consists chiefly of methane and progressively smaller amounts of ethane, propane, and higher alkanes. For example, a sample taken from a pipeline supplied by a large number of Pennsylvania wells contained methane, ethane, and propane in the ratio of 12 : 2 : 1, with higher alkanes making up only 3% of the total. The propane–butane fraction is separated from the more volatile components by liquefaction, compressed into cylinders, and sold as *bottled gas* in are as not served by a gas utility.

Petroleum is separated by distillation into the various fractions listed in Table 5AI.4; because of the relationship between boiling point and molecular weight, this amounts to a rough separation according to carbon number. Each fraction is still a very complicated mixture, however, since it contains alkanes of a range of carbon numbers, and since each carbon number is represented by numerous isomers. The use that each fraction is put to depends chiefly upon its volatility or viscosity, and it matters very little whether it is a complicated mixture or a single pure compound.

**Table 5AI.4** PETROLEUM CONSTITUENTS

| Fraction | Distillation temperature, °C | Carbon number |
|---|---|---|
| Gas | Below 20 °C | $C_1$–$C_4$ |
| Petroleum ether | 20–60 °C | $C_5$–$C_6$ |
| Ligroin (light naphtha) | 60–100 °C | $C_6$–$C_7$ |
| Natural gasoline | 40–205 °C | $C_5$–$C_{10}$, and cycloalkanes |
| Kerosine | 175–325 °C | $C_{12}$–$C_{18}$, and aromatics |
| Gas oil | Above 275 °C | $C_{12}$ and higher |
| Lubricating oil | Non-volatile liquids | Probably long chains attached to cyclic structures |
| Asphalt or petroleum coke | Non-volatile solids | Polycyclic structures |

The chief use of all but the non-volatile fractions is as fuel. The gas fraction, like natural gas, is used chiefly for heating. Gasoline is used in those internal combustion engines that require a fairly volatile fuel, kerosine is used in tractor and jet engines, and gas oil is used in diesel engines. Kerosine and gas oil are also used for heating purposes, the latter being the familiar “furnace oil”.

The lubricating oil fraction, especially that from Pennsylvania crude oil (*paraffin-base petroleum*), often contains large amounts of long-chain alkanes ($C_{20}$—$C_{34}$) that have fairly high melting points. If these remained in the oil, they might crystallize to waxy solids in an oil line in cold weather. To prevent this, the oil is chilled and the wax is removed by filtration. After purification this is sold as solid *paraffin wax* (m.p. 50–55 °C) or used in *petroleum jelly* (Vaseline). Asphalt is used in roofing and road building. The coke that is obtained from paraffin-base crude oil consists of complex hydrocarbons having a high carbon-to-hydrogen ratio; it is used as a fuel or in the manufacture of carbon electrodes for the electrochemical industries. Petroleum ether and ligroin are useful solvents for many organic materials of low polarity.

In addition to being used directly as just described, certain petroleum fractions are converted into other kinds of chemical compounds. Catalytic **isomerization** changes straight-chain alkanes into branched-chain ones. The **cracking** process converts higher alkanes into smaller alkanes and alkenes, and thus increases the gasoline yield; it can even be used for the production of “natural” gas. In addition, the alkenes thus formed are the most important raw materials for the large-scale synthesis of organic compounds. The process of **catalytic reforming** converts alkanes and cycloalkanes into aromatic hydrocarbons and thus provides the chief raw material for the large-scale synthesis of another broad class of compounds.

## 5AI.16 Industrial source *vs.* laboratory preparation

We shall generally divide the methods of obtaining a particular kind of organic compound into two categories: *industrial source* and *laboratory preparation*. We may contrast the two in the following way, although it must be realized that there are many exceptions to these generalizations.

An industrial source must provide large amounts of the desired material at the lowest possible cost. A laboratory preparation may be required to produce only a few hundred grams or even a few grams; cost is usually of less importance than the time of the investigator.

For many industrial purposes a mixture may be just as suitable as a pure compound; even when a single compound is required, it might be economically feasible to separate it from a mixture, particularly when the other components may also be marketed. In the laboratory a chemist nearly always wants a single pure compound. Separation of a single compound from a mixture of related substances is very time-consuming and frequently does not yield material of the required purity. Furthermore, the raw material for a particular preparation may well be the hard-won product of a previous preparation or even series of preparations, and hence one wishes to convert it as completely as possible into the desired compound. On an industrial scale, if a compound cannot be isolated from naturally occurring material, it may be synthesized along with a number of related compounds by some inexpensive reaction. In the laboratory, whenever possible, a reaction is selected that forms a single compound in high yield.

In industry it is frequently worthwhile to work out a procedure and design apparatus that may be used in the synthesis of only one member of a chemical family. In the laboratory a chemist is seldom interested in preparing the same compound over and over again, and hence makes use of methods that are applicable to many or all members of a particular family.

In our study of organic chemistry, we shall concentrate our attention on versatile laboratory preparations rather than on limited industrial methods. In learning these we may, for the sake of simplicity, use as examples the preparation of compounds that may actually never be made by the method shown. We may discuss the synthesis of ethane by the hydrogenation of ethylene, even though we can buy all the ethane we need from the petroleum industry. However, if we know how to convert ethylene into ethane, then, when the need arises, we also know how to convert 2-methyl-l-hexene into 2-methylhexane, or cholesterol into cholestanol, or, for that matter, cottonseed oil into oleomargarine.

## 5AI.17 Preparation

Each of the smaller alkanes, from methane through *n*-pentane and isopentane, can be obtained in pure form by fractional distillation of petroleum and natural gas; neopentane does not occur naturally. Above the pentanes the number of isomers of each homolog becomes so large and the boiling point differences become so small that it is no longer feasible to isolate individual, pure compounds; these alkanes must be synthesized by one of the methods outlined below.

In some of these equations, the symbol **R** is used to represent **any alkyl group**. This convenient device helps to summarize reactions that are typical of an entire family, and emphasizes the essential similarity of the various members.

In writing these generalized equations, however, we must not lose sight of one important point. An equation involving RCl, to take a specific example, has meaning only in terms of a reaction that we can carry out in the laboratory using a real compound, like methyl chloride or *tert*-butyl chloride. Although *typical* of alkyl halides, a reaction may differ widely in rate or yield depending upon the particular alkyl group actually concerned. We may use quite different experimental conditions for methyl chloride than for *tert*-butyl chloride; in an extreme case, a reaction that goes well for methyl chloride might go so slowly or give so many side products as to be completely useless for *tert*-butyl chloride.

## PREPARATION OF ALKANES

**1. Hydrogenation of alkenes**

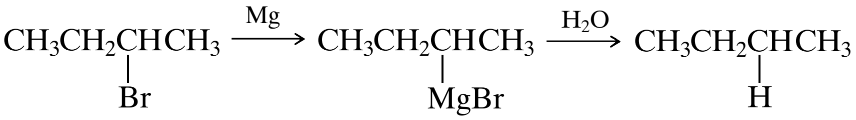
$$\underset{\text{Alkene}}{C_nH_{2n}} \xrightarrow{H_2 + \text{Pt, Pd, or Ni}} \underset{\text{Alkane}}{C_nH_{2n+2}}$$

**2. Reduction of alkyl halides**

**(a) Hydrolysis of Grignard reagent**

$$R{-}X + Mg \longrightarrow \underset{\text{Grignard reagent}}{R{-}MgX} \xrightarrow{H_2O} R{-}H$$

***Example:***



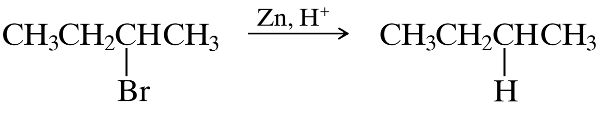
$$\underset{\displaystyle Br}{CH_3CH_2\underset{|}{C}HCH_3} \xrightarrow{Mg} \underset{\displaystyle MgBr}{CH_3CH_2\underset{|}{C}HCH_3} \xrightarrow{H_2O} \underset{\displaystyle H}{CH_3CH_2\underset{|}{C}HCH_3}$$

*sec*-Butyl bromide *sec*-Butylmagnesium bromide *n*-Butane

**(b) Reduction by metal and acid**

$$R{-}X + Zn + H^+ \longrightarrow R{-}H + Zn^{2+} + X^-$$

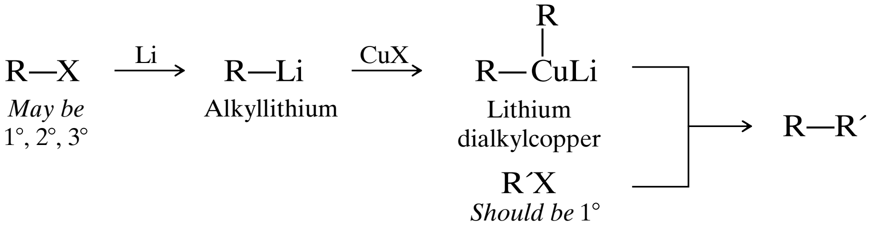
***Example:***



$$\underset{\displaystyle Br}{CH_3CH_2\underset{|}{C}HCH_3} \xrightarrow{Zn,\ H^+} \underset{\displaystyle H}{CH_3CH_2\underset{|}{C}HCH_3}$$

*sec*-Butyl bromide *n*-Butane

**3. Coupling of alkyl halides with organometallic compounds (Corey-House reaction)**



$$\underset{\substack{\textit{May be}\\ 1°,\,2°,\,3°}}{R{-}X} \xrightarrow{Li} \underset{\text{Alkyllithium}}{R{-}Li} \xrightarrow{CuX} \underset{\substack{\text{Lithium}\\ \text{dialkylcopper}}}{R{-}\overset{\displaystyle R}{\overset{|}{Cu}}Li} \quad + \quad \underset{\textit{Should be } 1°}{R'X} \longrightarrow R{-}R'$$

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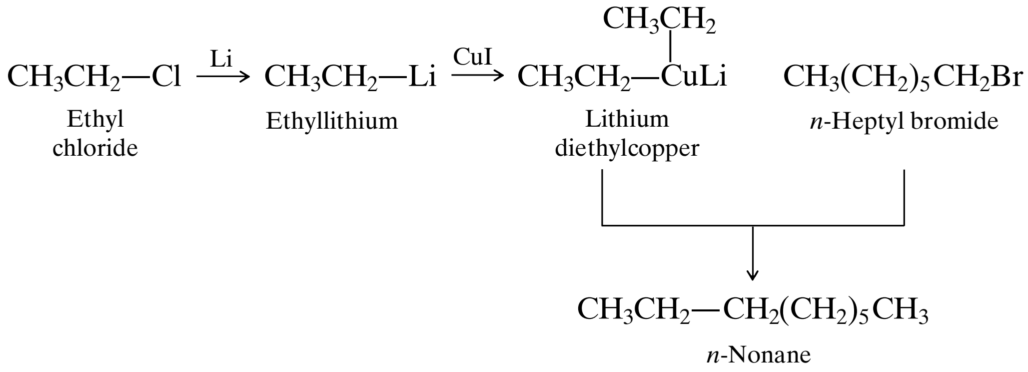
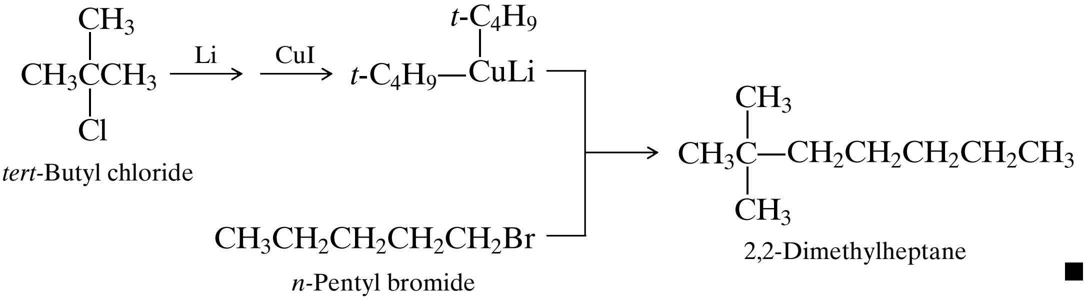
CONTINUED

***Examples:***



$$CH_3CH_2{-}Cl \xrightarrow{Li} CH_3CH_2{-}Li \xrightarrow{CuI} (CH_3CH_2)_2CuLi \qquad CH_3(CH_2)_5CH_2Br \longrightarrow CH_3CH_2{-}CH_2(CH_2)_5CH_3$$



$$(CH_3)_3CCl \xrightarrow{Li} \xrightarrow{CuI} (t\text{-}C_4H_9)_2CuLi \qquad CH_3CH_2CH_2CH_2CH_2Br \longrightarrow (CH_3)_3C{-}CH_2CH_2CH_2CH_2CH_3$$

By far the most important of these methods is the hydrogenation of alkenes. When shaken under a slight pressure of hydrogen gas in the presence of a small amount of catalyst, alkenes are converted smoothly and quantitatively into alkanes of the same carbon skeleton. The method is limited only by the availability of the proper alkene. This is not a very serious limitation; as we shall see, alkenes are readily prepared, chiefly from alcohols, which in turn can be readily synthesized in a wide variety of sizes and shapes.

Reduction of an alkyl halide, either via the Grignard reagent or directly with metal and acid, involves simply the replacement of a halogen atom by a hydrogen atom; the carbon skeleton remains intact. This method has about the same applicability as the previous method, since, like alkenes, alkyl halides are generally prepared from alcohols. Where either method could be used, the hydrogenation of alkenes would probably be preferred because of its simplicity and higher yield.

The coupling of alkyl halides with organometallic compounds is the only one of these methods in which in carbon–carbon bonds are formed and a new, bigger carbon skeleton is generated.

## 5AI.18 The Grignard reagent: an organometallic compound

When a solution of an alkyl halide in dry ethyl ether, $(C_2H_5)_2O$, is allowed to stand over turnings of metallic magnesium, a vigorous reaction takes place: the solution turns cloudy, begins to boil, and the magnesium metal gradually disappears. The resulting solution is known as a **Grignard reagent**, after Victor Grignard (of the University of Lyons) who received the Nobel Prize in 1912 for its discovery. It is one of the most useful and versatile reagents known to the organic chemist.

$$\underset{\text{Methyl iodide}}{CH_3I} + Mg \xrightarrow{\text{ether}} \underset{\text{Methylmagnesium iodide}}{CH_3MgI}$$

$$\underset{\text{Ethyl bromide}}{CH_3CH_2Br} + Mg \xrightarrow{\text{ether}} \underset{\text{Ethylmagnesium bromide}}{CH_3CH_2MgBr}$$

The Grignard reagent has the general formula RMgX, and the general name **alkylmagnesium halide**. The carbon–magnesium bond is covalent but highly polar, with carbon pulling electrons from electropositive magnesium; the magnesium– halogen bond is essentially ionic.

$$R:Mg^+ :\ddot{\underset{\cdot\cdot}{X}}:^-$$

Since magnesium becomes bonded to the same carbon that previously held halogen, the alkyl group remains intact during the preparation of the reagent. Thus *n*-propyl chloride yields *n*-propylmagnesium chloride, and isopropyl chloride yields isopropylmagnesium chloride.

$$\underset{n\text{-Propyl chloride}}{CH_3CH_2CH_2Cl} + Mg \xrightarrow{\text{ether}} \underset{n\text{-Propylmagnesium chloride}}{CH_3CH_2CH_2MgCl}$$

$$\underset{\text{Isopropyl chloride}}{CH_3CHClCH_3} + Mg \xrightarrow{\text{ether}} \underset{\text{Isopropylmagnesium chloride}}{CH_3CHMgClCH_3}$$

The Grignard reagent is the best-known member of a broad class of substances, called **organometallic** compounds, in which carbon is bonded to a metal: lithium, potassium, sodium, zinc, mercury, lead, thallium—almost any metal known. Each kind of organometallic compound has, of course, its own set of properties, and its particular uses depend on these. But, whatever the metal, it is less electronegative than carbon, and the carbon–metal bond—like the one in the Grignard reagent is highly polar. Although the organic group is not a full-fledged *carbanion*—an anion in which carbon carries negative charge—it nevertheless has considerable carbanion character. As we shall see, organometallic compounds owe their enormous usefulness chiefly to one common quality: they can serve as a source from which carbon is readily transferred *with its electrons.*

$$\overset{\delta_-}{R}—\overset{\delta_+}{M}$$

The Grignard reagent is highly reactive. It reacts with numerous inorganic compounds including water, carbon dioxide, and oxygen, and with most kinds of organic compounds; in many of these cases the reaction provides the best way to make a particular class of organic compound.

The reaction with water to form an alkane is typical of the behavior of the Grignard reagent—and many of the more reactive organometallic compounds—toward acids. In view of the marked carbanion character of the alkyl group, we may consider the Grignard reagent to be the magnesium salt, RMgX, of the extremely weak acid, R—H. The reaction

$$\mathrm{RMgX} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{HOH}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{R{-}H}} + \mathrm{Mg(OH)X}$$

is simply the displacement of the weaker acid, R—H, from its salt by the stronger acid, HOH.

An alkane is such a weak acid that it is displaced from the Grignard reagent by compounds that we might ordinarily consider to be very weak acids themselves, or possibly not acids at all. Any compound containing hydrogen attached to oxygen or nitrogen is tremendously more acidic than an alkane, and therefore can decompose the Grignard reagent: for example, ammonia or methyl alcohol.

$$\mathrm{RMgX} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{NH_3}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{R{-}H}} + \mathrm{Mg(NH_2)X}$$

$$\mathrm{RMgX} + \underset{\substack{\text{Stronger}\\ \text{acid}}}{\mathrm{CH_3OH}} \longrightarrow \underset{\substack{\text{Weaker}\\ \text{acid}}}{\mathrm{R{-}H}} + \mathrm{Mg(OCH_3)X}$$

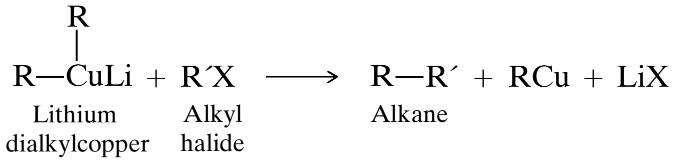
For the preparation of an alkane, one acid is as good as another, so we naturally choose water as the most available and convenient.

**Problem 5AI.9** (a) Which alkane would you expect to get by the action of water on *n*-propylmagnesium chloride? (b) On isopropylmagnesium chloride? (c) Answer (a) and (b) for the action of deuterium oxide (“heavy water”, $D_2O$).

**Problem 5AI.10** On conversion into the Grignard reagent followed by treatment with water, how many alkyl bromides would yield: (a) *n*-pentane; (b) 2-methylIbutane; (c) 2,3-dimethylbutane; (d) neopentane? Draw the structures in each case.

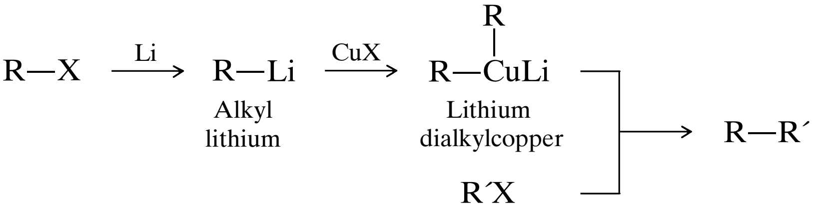
## 5AI.19 Coupling of alkyl halides with organometallic compounds

To make an alkane of higher carbon number than the starting material requires formation of carbon–carbon bonds, most directly by the coupling together of two alkyl groups. The most versatile method of doing this is through a synthesis developed during the late 1960s by E. J. Corey and Herbert House working independently. Coupling takes place in the reaction between a *lithium dialkylcopper*, $R_2CuLi$, and an alkyl halide, R′X. (R′ stands for an alkyl group that may be the same as, or different from, R.)

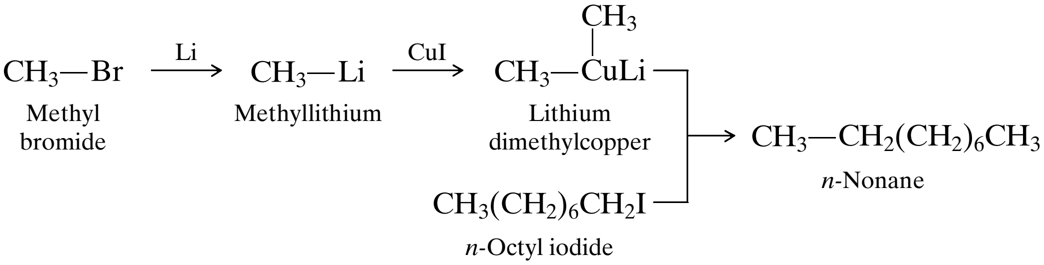


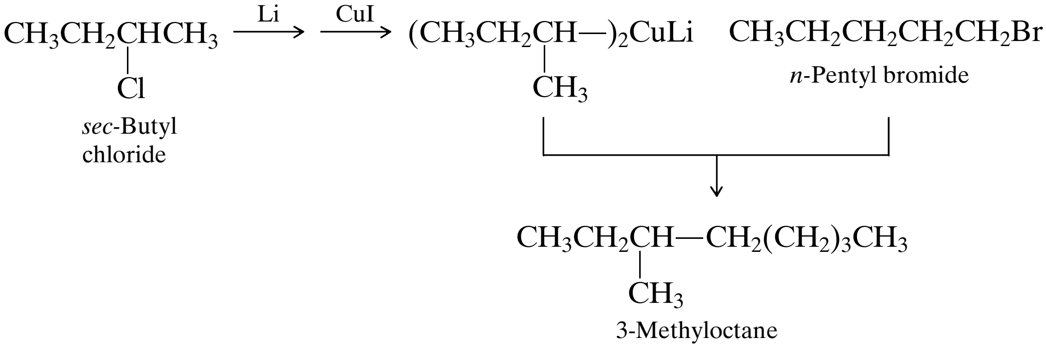
$$\underset{\substack{\text{Lithium}\\ \text{dialkylcopper}}}{\mathrm{R{-}\overset{\overset{\displaystyle R}{|}}{Cu}Li}} + \underset{\substack{\text{Alkyl}\\ \text{halide}}}{\mathrm{R'X}} \longrightarrow \underset{\text{Alkane}}{\mathrm{R{-}R'}} + \mathrm{RCu} + \mathrm{LiX}$$

An alkyllithium, RLi, is prepared from an alkyl halide, RX, in much the same way as a Grignard reagent. To it is added cuprous halide, CuX, and then, finally, the second alkyl halide, R′X. Ultimately, the alkane is synthesized from the two alkyl halides, RX and R′X.



For good yields, R′X should be a *primary* halide; the alkyl group R in the organometallic may be primary, secondary, or tertiary. For example:





The choice of organometallic reagent is crucial. Grignard reagents or organolithium compounds, for example, couple with only a few unusually reactive organic halides. Organosodium compounds couple, but are so reactive that they couple, as they are being formed, with their parent alkyl halide; the reaction of sodium with alkyl halides (*Wurtz reaction*) is thus limited to the synthesis of symmetrical alkanes, R—R.

Organocopper compounds were long known to be particularly good at the formation of carbon–carbon bonds, but are unstable. Here, they are generated *in situ* from the organolithium, and then combine with more of it to form these relatively stable organometallics. They exist as complex aggregates but are believed to correspond roughly to $R_2Cu^-Li^+$. The anion here is an example of an *ate* complex, the negative counterpart of an *onium* complex (amm*onium, oxonium*).

Although the mechanism is not understood, this much is clear: the alkyl group R is transferred from copper, taking a pair of electrons with it, and becomes attached to the alkyl group R′ in place of halide ion (*nucleophilic aliphatic substitution*).

**Problem 5AI.11** (a) Outline two conceivable syntheses of 2-methylpentane from three-carbon compounds, (b) Which of the two would you actually use? Why?

## 5AI.20 Reactions

The alkanes are sometimes referred to by the old-fashioned name of *paraffins*. This name (Latin: *parum affinis*, not enough affinity) was given to describe what appeared to be the low reactivity of these hydrocarbons.

But reactivity depends upon the choice of reagent. If alkanes are inert toward hydrochloric and sulfuric acids, they react readily with acids like HF–$SbF_5$ and $FSO_3H$–$SbF_5$ (“magic acid”) to yield a variety of products. If alkanes are inert toward oxidizing agents like potassium permanganate or sodium dichromate, most of this chapter is devoted to their oxidation by halogens. Certain yeasts feed happily on alkanes to produce proteins—certainly a chemical reaction. As Professor M. S. Kharasch used to put it, consider the “inertness” of a room containing natural gas, air, and a lighted match.

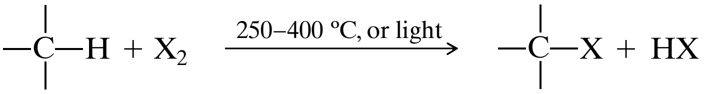
Still, on a comparative basis, reactivity is limited. “Magic acid”is, after all, one of the strongest acids known; halogenation requires heat or light; combustion needs a flame or spark to get it started.

Much of the chemistry of alkanes involves free-radical chain reactions, which take place under vigorous conditions and usually yield mixtures of products. A reactive particle—typically an atom or free radical—is needed to begin the attack on an alkane molecule. It is the generation of this reactive particle that requires the vigorous conditions: the dissociation of a halogen molecule into atoms, for example, or even (as in pyrolysis) dissociation of the alkane molecule itself.

In its attack, the reactive particle abstracts hydrogen from the alkane; the alkane itself is thus converted into a reactive particle which continues the reaction sequence, that is, carries on the chain. But an alkane molecule contains many hydrogen atoms and the particular product eventually obtained depends upon *which* of these hydrogen atoms is abstracted. Although an attacking particle may show a certain selectivity, it can abstract a hydrogen from any part of the molecule, and thus bring about the formation of many isomeric products.

### REACTIONS OF ALKANES

**1. Halogenation.**



$$-\overset{|}{\underset{|}{C}}-H + X_2 \xrightarrow{250\text{–}400\ ^\circ\text{C, or light}} -\overset{|}{\underset{|}{C}}-X + HX$$

*Usually a mixture*

**Reactivity** $X_2$: $Cl_2 > Br_2$

H: $3^\circ > 2^\circ > 1^\circ > CH_3{-}H$

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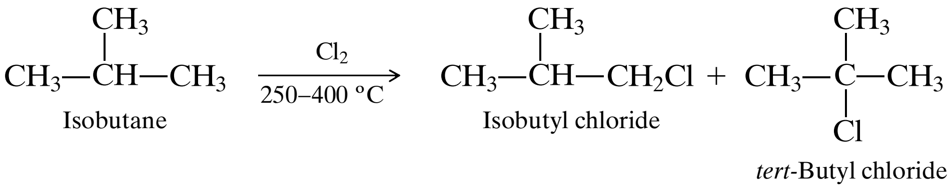
***Examples:***



$$\underset{\text{Isobutane}}{CH_3-\overset{\overset{CH_3}{|}}{C}H-CH_3} \xrightarrow[250\text{–}400\ ^\circ C]{Cl_2} \underset{\text{Isobutyl chloride}}{CH_3-\overset{\overset{CH_3}{|}}{C}H-CH_2Cl} + \underset{tert\text{-Butyl chloride}}{CH_3-\overset{\overset{CH_3}{|}}{\underset{\underset{Cl}{|}}{C}}-CH_3}$$

**2. Combustion**

$$C_nH_{2n+2} \ + \ \text{excess } O_2 \xrightarrow{\text{flame}} nCO_2 \ + \ (n+1)H_2O \quad \Delta H = \text{heat of combustion}$$

***Example:***

$$n\text{-}C_2H_{12} \ + \ 8O_2 \xrightarrow{\text{flame}} 5CO_2 \ + \ 6H_2O \quad \Delta H = -845 \text{ kcal}$$

**3. Pyrolysis (Cracking)**

$$\text{Alkane} \xrightarrow[\text{without catalyst}]{400\text{–}600\ ^\circ C\text{, with or}} H_2 \ + \ \text{smaller alkanes} \ + \ \text{Alkenes} \quad ■$$

## 5AI.21 Halogenation

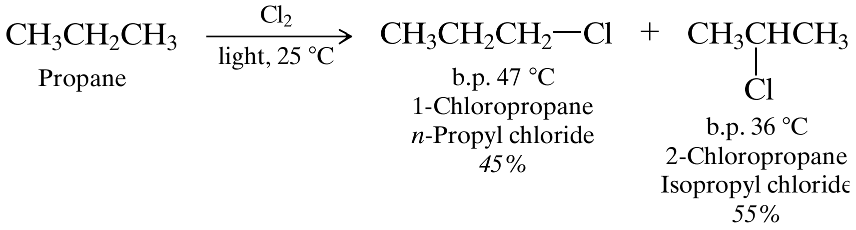
As we might expect, halogenation of the higher alkanes is essentially the same as the halogenation of methane. It can be complicated, however, by the formation of mixtures of isomers.

Under the influence of ultraviolet light, or at 250–400 °C, chlorine or bromine converts alkanes into chloroalkanes (alkyl chlorides) or bromoalkanes (alkyl bromides); an equivalent amount of hydrogen chloride or hydrogen bromide is formed at the same time. When diluted with an inert gas, and in an apparatus designed to carry away the heat produced, fluorine has recently been found to give analogous results. As with methane, iodination does not take place at all.

Depending upon which hydrogen atom is replaced, any of a number of isomeric products can be formed from a single alkane. Ethane can yield only one haloethane; propane, *n*-butane, and isobutane can yield two isomers each; *n*-pentane can yield three isomers, and isopentane, four isomers. Experiment has shown that on halogenation an alkane yields a mixture of all possible isomeric products, indicating that all hydrogen atoms are susceptible to replacement. For example, for chlorination:

$$\underset{\text{Ethane}}{CH_3CH_3} \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3CH_2-Cl$$

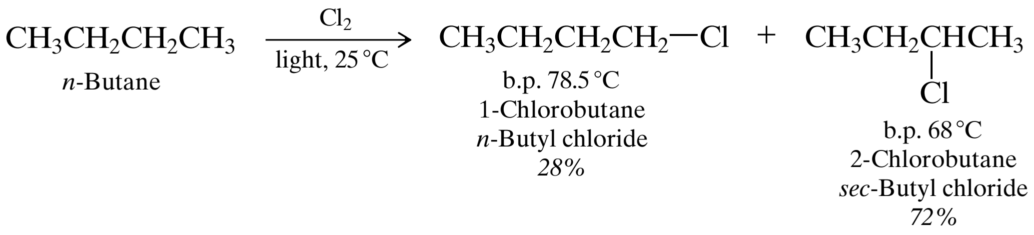
b.p. 13 °C
Chloroethane
Ethyl chloride



$$\underset{\text{Propane}}{CH_3CH_2CH_3} \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3CH_2CH_2-Cl \ + \ CH_3\underset{\underset{Cl}{|}}{C}HCH_3$$

b.p. 47 °C
1-Chloropropane
*n*-Propyl chloride
*45%*

b.p. 36 °C
2-Chloropropane
Isopropyl chloride
*55%*

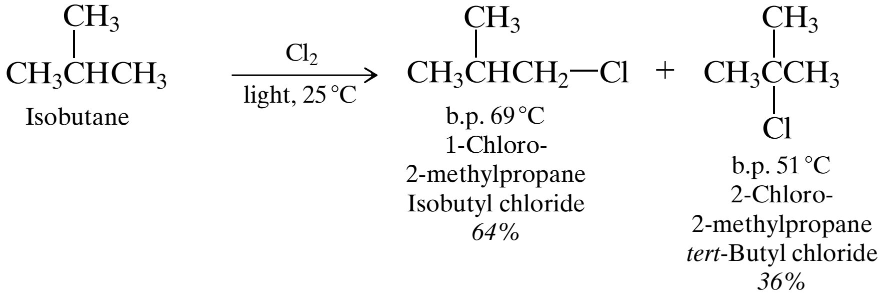


$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3CH_2CH_2CH_2{-}Cl + CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$$

*n*-Butane

b.p. 78.5 °C
1-Chlorobutane
*n*-Butyl chloride
*28%*

b.p. 68 °C
2-Chlorobutane
*sec*-Butyl chloride
*72%*



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_3 \xrightarrow[\text{light, 25 °C}]{Cl_2} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2{-}Cl + CH_3\underset{\displaystyle Cl}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CH_3$$

Isobutane

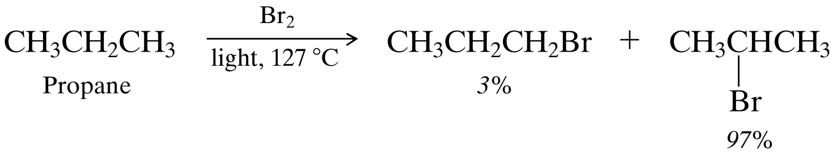
b.p. 69 °C
1-Chloro-
2-methylpropane
Isobutyl chloride
*64%*

b.p. 51 °C
2-Chloro-
2-methylpropane
*tert*-Butyl chloride
*36%*

Bromination gives the corresponding bromides but in different proportions:

$$CH_3CH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3CH_2Br$$

Ethane

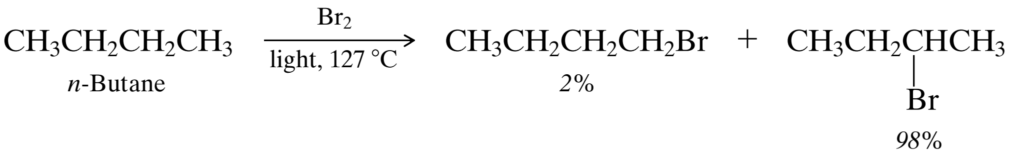


$$CH_3CH_2CH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3CH_2CH_2Br + CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

Propane

*3%*

*97%*

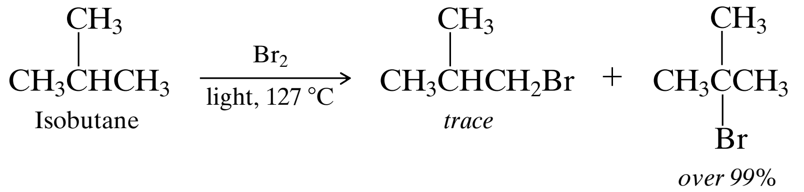


$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3CH_2CH_2CH_2Br + CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

*n*-Butane

*2%*

*98%*



$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_3 \xrightarrow[\text{light, 127 °C}]{Br_2} CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2Br + CH_3\underset{\displaystyle Br}{\underset{|}{\overset{\displaystyle CH_3}{\overset{|}{C}}}}CH_3$$

Isobutane

*trace*

*over 99%*

**Problem 5AI.12** Draw the structures of: (a) the three monochloro derivatives of *n*-pentane; (b) the four monochloro derivatives of isopentane.

Although both chlorination and bromination yield mixtures of isomers, the results given above show that the *relative amounts* of the various isomers differ markedly depending upon the halogen used. Chlorination gives mixtures in which no isomer greatly predominates; in bromination, by contrast, one isomer may predominate to such an extent as to be almost the only product, making up 97–99% of the total mixture. In bromination, there is a high degree of *selectivity* as to which hydrogen atoms are to be replaced.

With rare exceptions, *halogenation of alkanes is not suitable for the laboratory preparation of alkyl halides*. In chlorination, any one product is necessarily formed in low yield, and is difficult to separate from its isomers, whose boiling points are seldom far from its own. Even bromination of alkanes is seldom used. There are excellent alternative ways to make alkyl halides, conveniently and from readily available precursors.

We begin our study of organic reactions with halogenation of methane and other alkanes, not for its utility in laboratory synthesis; synthesis is only one aspect of organic chemistry. But this reaction offers an easily understood approach to principles underlying all reactions we shall study. Alkanes are simple compounds. The mechanism is well-understood, and based upon evidence that we can readily grasp. We can deal rigorously and quantitatively with the matter of relative rates and orientation, since values of $E_{act}$ and $\Delta H$ are accurately known. The nature of the transition state is unclouded by uncertainty as to the role played by a solvent. Finally, the study of free radicals is, in itself, an important part of organic chemistry.

On an industrial scale, chlorination of alkanes is important. For many purposes—for example, use as a solvent—a mixture of isomers is just as suitable as, and much cheaper than, a pure compound. It may be even worthwhile, when necessary, to separate a mixture of isomers if each isomer can then be marketed.

## 5AI.22 Mechanism of halogenation

Halogenation of alkanes proceeds by the same mechanism as halogenation of methane:

$$(1)\qquad X_2 \xrightarrow[\substack{\text{or}\\ \text{ultraviolet}\\ \text{light}}]{250\text{–}400\ ^\circ\text{C}} 2X\cdot \qquad \textbf{Chain-initiating step}$$

$$\left.\begin{array}{ll} (2) & X\cdot + RH \longrightarrow HX + R\cdot \\ (3) & R\cdot + X_2 \longrightarrow RX + X\cdot \end{array}\right\} \textbf{Chain-propagating steps}$$

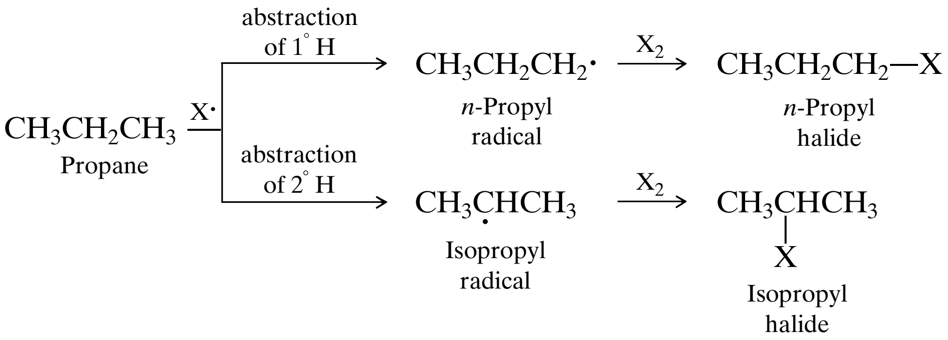
*then* (2), (3), (2), (3), *etc., until finally a chain is terminated*

A halogen atom abstracts hydrogen from the alkane (RH) to form an alkyl radical (R·). The radical in turn abstracts a halogen atom from a halogen molecule to yield the alkyl halide (RX).

Which alkyl halide is obtained depends upon which alkyl radical is formed.

$$\underset{\text{Methane}}{CH_4} \xrightarrow{X\cdot} \underset{\substack{\text{Methyl}\\ \text{radical}}}{CH_3\cdot} \xrightarrow{X_2} \underset{\substack{\text{Methyl}\\ \text{halide}}}{CH_3{-}X}$$

$$\underset{\text{Ethane}}{CH_3CH_3} \xrightarrow{X\cdot} \underset{\substack{\text{Ethyl}\\ \text{radical}}}{CH_3CH_2\cdot} \xrightarrow{X_2} \underset{\substack{\text{Ethyl}\\ \text{halide}}}{CH_3CH_2{-}X}$$



This in turn depends upon the alkane and which hydrogen atom is abstracted from it. For example, *n*-propyl halide is obtained from an *n*-propyl radical, formed from propane by abstraction of a primary hydrogen; isopropyl halide is obtained from an isopropyl radical, formed by abstraction of a secondary hydrogen.

How fast an alkyl halide is formed depends upon how fast the alkyl radical is formed. Here also, as was the case with methane, of the two chain-propagating steps, step (2) is more difficult than step (3), and hence controls the rate of overall reaction. Formation of the alkyl radical is difficult, but once formed the radical is readily converted into the alkyl halide (see Fig. 5AI.12).

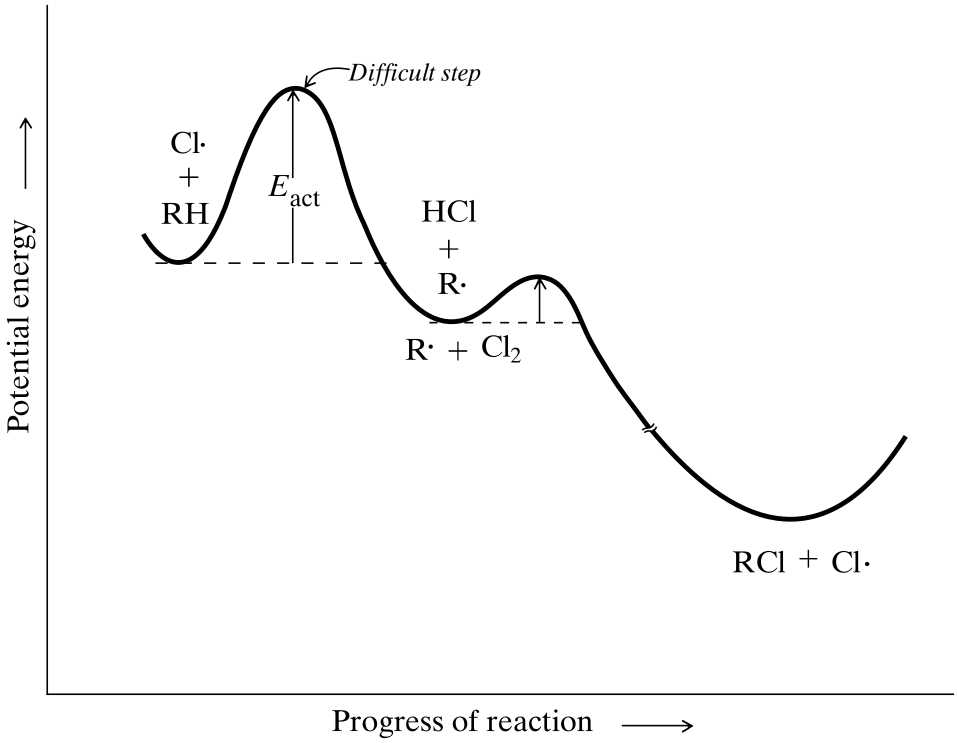
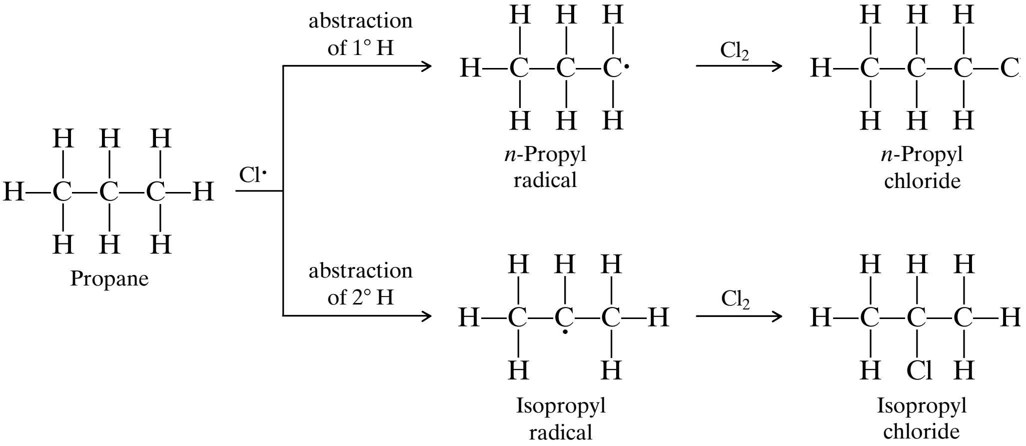


**Figure 5AI.12** Potential energy changes during the progress of reaction: chlorination of an alkane. Formation of the radical is the rate-controlling step.

## 5AI.23 Orientation of halogenation

With this background let us turn to the problem of **orientation**; that is, let us examine the factors that determine *where* in a molecule reaction is most likely to occur. It is a problem that we shall encounter again and again, whenever we study a compound that offers more than one reactive site to attack by a reagent. It is an important problem, because orientation determines what product we obtain.

As an example let us take chlorination of propane. The relative amounts of *n*-propyl chloride and isopropyl chloride obtained depend upon the relative rates at which *n*-propyl radicals and isopropyl radicals are formed. If, say, isopropyl radicals are formed faster, then isopropyl chloride will be formed faster, and will make up a larger fraction of the product. As we can see, *n*-propyl radicals are formed by abstraction of primary hydrogens, and isopropyl radicals by abstraction of secondary hydrogens.



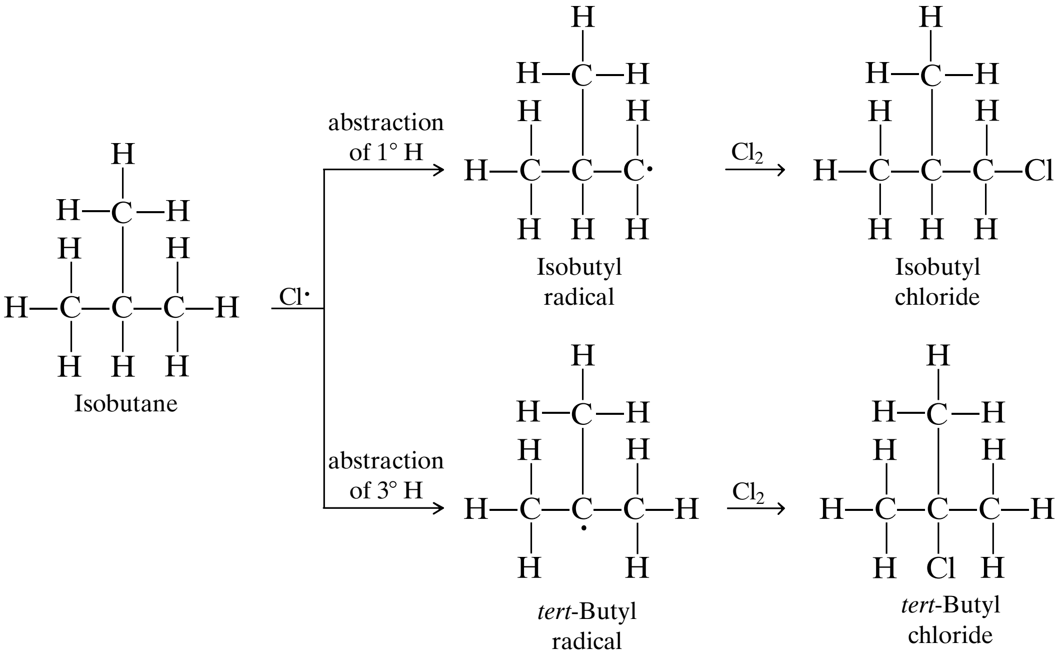
Thus *orientation is determined by the relative rates of competing reactions*. In this case we are comparing the rate of abstraction of primary hydrogens with the rate of abstraction of secondary hydrogens. What are the factors that determine the rates of these two reactions, and in which of these factors may the two reactions differ?

First of all, there is the collision frequency. This must be the same for the two reactions, since both involve collisions of the same particles: a propane molecule and a chlorine atom.

Next, there is the probability factor. If a primary hydrogen is to be abstracted, the propane molecule must be so oriented at the time of collision that the chlorine atom strikes a primary hydrogen; if a secondary hydrogen is to be abstracted, the propane must be so oriented that the chlorine collides with a secondary hydrogen. Since there are six primary hydrogens and only two secondary hydrogens in each molecule, we might estimate that the probability factor favors abstraction of primary hydrogens by the ratio of 6 : 2, or 3 : 1.

Considering only collision frequency and our guess about probability factors, we predict that chlorination of propane would yield *n*-propyl chloride and isopropyl chloride in the ratio of 3:1. As shown on page 104, however, the two chlorides are formed in roughly equal amounts, that is, in the ratio of about 1 : 1, or 3 : 3. The proportion of isopropyl chloride is about three times as great as predicted. Evidently, about three times as many collisions with secondary hydrogens are successful as collisions with primary hydrogens. If our assumption about the probability factor is correct, this means that $E_{act}$ is less for abstraction of a secondary hydrogen than for abstraction of a primary hydrogen.

Chlorination of isobutane presents a similar problem. In this case, abstraction of one of the nine primary hydrogens leads to the formation of isobutyl chloride, whereas abstraction of a single tertiary hydrogen leads to the formation of *tert*-butyl chloride. We would estimate, then, that the probability factor favors formation of



isobutyl chloride by the ratio of 9 : 1. The experimental results show that the ratio is roughly 2 : 1, or 9 : 4.5. Evidently, about 4.5 times as many collisions with the tertiary hydrogen are successful as collisions with the primary hydrogens. This, in turn, probably means that $E_{\text{act}}$, is less for abstraction of a tertiary hydrogen than for abstraction of a primary hydrogen, and, in fact, even less than for abstraction of a secondary hydrogen.

Study of the chlorination of a great many alkanes has shown that these are typical results. After allowance is made for differences in the probability factor, the rate of abstraction of hydrogen atoms is always found to follow the sequence 3° > 2° > 1°. At room temperature, for example, the relative rates *per hydrogen atom* are 5.0 : 3.8 : 1.0. Using these values we can predict quite well the ratio of isomeric chlorination products from a given alkane. For example:

$$\underset{n\text{-Butane}}{CH_3CH_2CH_2CH_3} \xrightarrow[\text{light, 25 °C}]{Cl_2} \underset{n\text{-Butyl chloride}}{CH_3CH_2CH_2CH_2Cl} + \underset{sec\text{-Butyl chloride}}{CH_3CH_2CHClCH_3}$$

$$\begin{aligned}\frac{n\text{-butyl chloride}}{sec\text{-butyl chloride}} &= \frac{\text{no. of 1° H}}{\text{no. of 2° H}} \times \frac{\text{reactivity of 1° H}}{\text{reactivity of 2° H}}\\ &= \frac{6}{4} \times \frac{1.0}{3.8}\\ &= \frac{6}{15.2}\ \textit{equivalent to}\ \frac{28\%}{72\%}\end{aligned}$$

In spite of these differences in reactivity, chlorination rarely yields a great preponderance of any single isomer. In nearly every alkane, as in the examples we have studied, the less reactive hydrogens are the more numerous; their lower reactivity is compensated for by a higher probability factor, with the result that appreciable amounts of every isomer are obtained.

**Problem 5AI.13** Predict the proportions of isomeric products from chlorination at room temperature of: (a) propane; (b) isobutane; (c) 2,3-dimethylbutane; (d) *n*-pentane (*Note:* There are *three* isomeric products); (e) isopentane; (f) 2,2,3-trimethylbutane; (g) 2,2,4-trimethylpentane. For (a) and (b) check your calculations against the experimental values.

The same sequence of reactivity, 3° > 2° > 1°, is found in bromination, but with enormously larger reactivity ratios. At 127 °C, for example, the relative rates per hydrogen atom are 1600 : 82 : 1. Here, differences in reactivity are so marked as vastly to outweigh probability factors.

**Problem 5AI.14** Answer Problem 5AI.13 for bromination at 127 °C.

## 5AI.24 Relative reactivities of alkanes toward halogenation

The best way to measure the relative reactivities of different compounds toward the same reagent is by the **method of competition**, since this permits an exact quantitative comparison under identical reaction conditions. Equimolar amounts of two compounds to be compared are mixed together and allowed to react with a limited amount of a particular reagent. Since there is not enough reagent for both compounds, the two compete with each other. Analysis of the reaction products shows which compound has consumed more of the reagent and hence is more reactive.

For example, if equimolar amounts of methane and ethane are allowed to react with a small amount of chlorine, about 400 times as much ethyl chloride as methyl chloride is obtained, showing that ethane is 400 times as reactive as methane. When allowance is made for the relative numbers of hydrogens in the two kinds of molecules, we see that each hydrogen of ethane is about 270 times as reactive as each hydrogen of methane.

$$\underset{1}{CH_3Cl} \xleftarrow{CH_4} \underset{\text{light, 25 °C}}{Cl_2} \xrightarrow{C_2H_6} \underset{400}{C_2H_5Cl}$$

**Problem 5AI.15** Because of the rather large difference in reactivity between ethane and methane, competition experiments have actually used mixtures containing more methane than ethane. If the molar ratio of methane to ethane were 10:1, what ratio of ethyl chloride to methyl chloride would you expect to obtain? What practical advantage would this experiment have over one involving a 1 : 1 ratio?

Data obtained from similar studies of other compounds are consistent with this simple generalization: *the reactivity of a hydrogen depends chiefly upon its class, and not upon the alkane to which it is attached*. Each primary hydrogen of propane, for example, is about as easily abstracted as each primary hydrogen in *n*-butane or isobutane; each secondary hydrogen of propane, about as easily as each secondary hydrogen of *n*-butane or *n*-pentane; and so on.

The hydrogen atoms of methane, which fall into a special class, are even less reactive than primary hydrogens, as shown by the above competition with ethane.

**Problem 5AI.16** On chlorination, an equimolar mixture of ethane and neopentane yields neopentyl chloride and ethyl chloride in the ratio of 2.3:1. How does the reactivity of a primary hydrogen in neopentane compare with that of a primary hydrogen in ethane?

## 5AI.25 Ease of abstraction of hydrogen atoms. Energy of activation

At this stage we can summarize the effect of structure on halogenation of alkanes in the following way. The controlling step in halogenation is abstraction of hydrogen by a halogen atom:

$$\mathrm{R{-}H} + \mathrm{X}\cdot \longrightarrow \mathrm{H-X} + \mathrm{R}^{\cdot}$$

The relative ease with which the different classes of hydrogen atoms are abstracted is:

**Ease of abstraction of hydrogen atoms**

$$3^\circ > 2^\circ > 1^\circ > \mathrm{CH_4}$$

This sequence applies (a) to the various hydrogens within a single alkane and hence governs **orientation** of reaction, and (b) to the hydrogens of different alkanes and hence governs **relative reactivities**.

Earlier, we concluded that these differences in ease of abstraction—like most differences in rate between closely related reactions—are probably due to differences in $E_{\mathrm{act}}$. By study of halogenation at a series of temperatures, the values of $E_{\mathrm{act}}$ listed in Table 5AI.5 were measured. In agreement with our tentative conclusions, the increasing rate of reaction along the series, methyl, 1°, 2°, 3°, is paralleled by a decreasing $E_{\mathrm{act}}$. In chlorination the differences in $E_{\mathrm{act}}$, like the differences in rate, are small; in bromination both differences are large.

We have seen that the larger the $E_{\mathrm{act}}$ of a reaction, the larger the increase in rate brought about by a given rise in temperature. We have just found that the differences in rate of abstraction among primary, secondary, and tertiary hydrogens are

**Table 5AI.5** ENERGIES OF ACTIVATION, KCAL/MOL

$R{-}H + X\cdot \longrightarrow R\cdot + H{-}X$

| R | X = Cl | X = Br |
|---|---|---|
| $CH_3$ | 4 | 18 |
| 1° | 1 | 13 |
| 2 ° | 0.5 | 10 |
| 3 ° | 0.1 | 7.5 |

due to differences in $E_{act}$. We predict, therefore, that a rise in temperature should speed up abstraction of primary hydrogens (with the largest $E_{act}$) most, and abstraction of tertiary hydrogens (with the smallest $E_{act}$) least; the three classes of hydrogen should then display more nearly the same reactivity.

This leveling-out effect has indeed been observed: as the temperature is raised, the relative rates per hydrogen atom change from 5.0 :3.8 :1.0 toward 1 :1 :1. At very high temperatures virtually every collision has enough energy for abstraction of even primary hydrogens. It is generally true that *as the temperature is raised a given reagent becomes less selective in the position of its attack*; conversely, as the temperature is lowered it becomes more selective.

How can we account for the effect of structure on ease of abstraction of hydrogen atoms? Since this is a matter of $E_{act}$, we must look for our answer, as always, in the transition state. To do this, however, we must first shift our focus from the hydrogen atom being abstracted to the radical being formed.

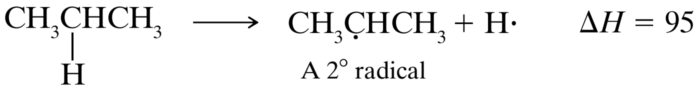
## 5AI.26 Stability of free radicals

We find the homolytic dissociation energies of the bonds that hold hydrogen atoms to a number of groups as follows:

$$CH_3{-}H \longrightarrow CH_3\cdot + H\cdot \qquad \Delta H = 104\,\text{kcal}$$

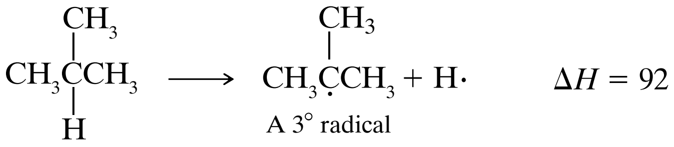
$$CH_3CH_2{-}H \longrightarrow \underset{\text{A 1° radical}}{CH_3CH_2\cdot} + H\cdot \qquad \Delta H = 98$$

$$CH_3CH_2CH_2{-}H \longrightarrow \underset{\text{A 1° radical}}{CH_3CH_2CH_2\cdot} + H\cdot \qquad \Delta H = 98$$



$$CH_3\underset{H}{\underset{|}{C}}HCH_3 \longrightarrow CH_3\dot{C}HCH_3 + H\cdot \qquad \Delta H = 95$$

A 2° radical



$$CH_3\underset{H}{\underset{|}{\overset{CH_3}{\overset{|}{C}}}}CH_3 \longrightarrow CH_3\overset{CH_3}{\overset{|}{\dot{C}}}CH_3 + H\cdot \qquad \Delta H = 92$$

A 3° radical

By definition, this bond dissociation energy is the amount of energy that must be supplied to convert a mole of alkane into radicals and hydrogen atoms. As we can see, the amount of energy needed to form the various classes of radicals decreases in the order: $CH_3\cdot > 1° > 2° > 3°$.

$$R{-}H \longrightarrow R\cdot + H\cdot \qquad \Delta H = \text{homolytic bond dissociation energy}$$

If less energy is needed to form one radical than another, it can only mean that, *relative to the alkane from which it is formed*, the one radical contains less energy than the other, this is to say, is *more stable* (see Fig. 5AI.13).

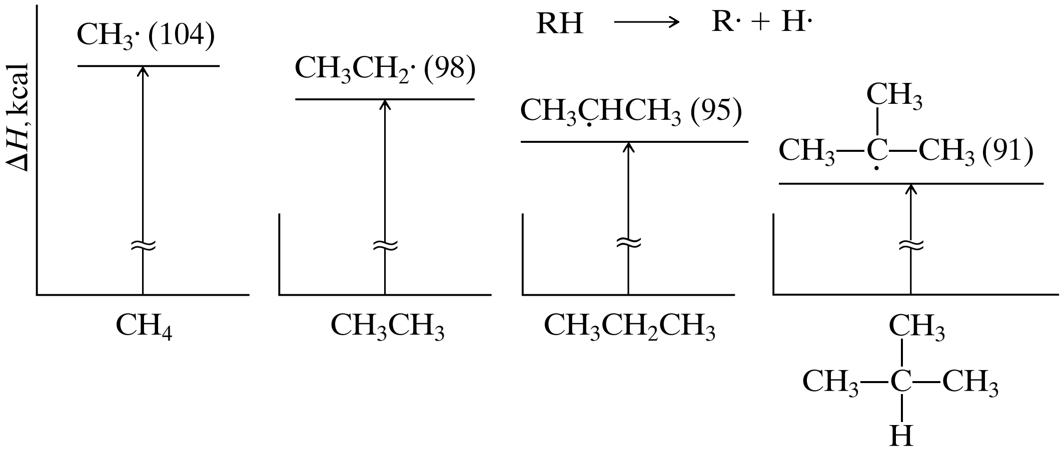


**Figure 5AI.13** Relative stabilities of free radicals. (The plots are aligned with each other for easy comparison.)

We are not attempting to compare the absolute energy contents of, say, methyl and ethyl radicals; we are simply saying that the difference in energy between methane and methyl radicals is greater than the difference between ethane and ethyl radicals. *When we compare stabilities of free radicals, it must be understood that our standard for each radical is the alkane from which it is formed.* As we shall see, this is precisely the kind of stability that we are interested in.

Relative to the alkane from which each is formed, then, the order of stability of free radicals is:

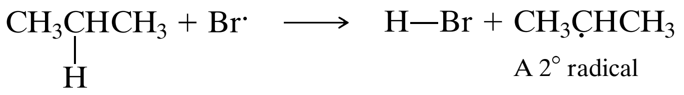
**Stability of free radicals** $3° > 2° > 1° > CH_3$

## 5AI.27 Ease of formation of free radicals

Let us return to the halogenation of alkanes. Orientation and reactivity are governed by the relative ease with which the different classes of hydrogen atoms are abstracted. But by definition, the hydrogen being abstracted and the radical being formed belong to the same class. Abstraction of a primary hydrogen yields a primary radical, abstraction of a secondary hydrogen yields a secondary radical, and so on. For example:

$$CH_3CH_2CH_2\text{—}H + Br\cdot \longrightarrow H\text{—}Br + CH_3CH_2CH_2\cdot$$

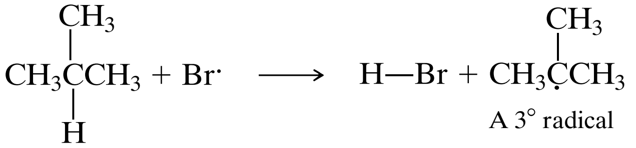
A 1° hydrogen A 1° radical



$$\underset{\underset{H}{|}}{CH_3CHCH_3} + Br\cdot \longrightarrow H\text{—}Br + CH_3\dot{C}HCH_3$$

A 2° radical

A 2° hydrogen



$$CH_3\overset{\overset{CH_3}{|}}{\underset{\underset{H}{|}}{C}}CH_3 + Br\cdot \longrightarrow H\text{—}Br + CH_3\overset{\overset{CH_3}{|}}{\dot{C}}CH_3$$

A 3° radical

A 3° hydrogen

If the ease of abstraction of hydrogen atoms follows the sequence 3° > 2° > 1° $CH_4$, then the ease of formation of free radicals must follow the same sequence:

**Ease of formation of free radicals**

$$3° > 2° > 1° > CH_3\cdot$$

In listing free radicals in order of their ease of formation, we find that we have at the same time listed them in order of their stability. **The more stable the free radical, the more easily it is formed**.

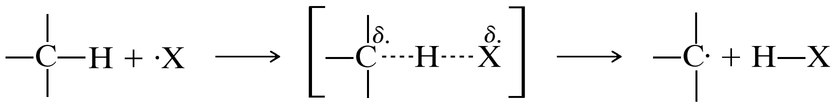
This is an extremely useful generalization. *Radical stability seems to govern orientation and reactivity in many reactions where radicals are formed.* The addition of bromine atoms to alkenes, for example, is a quite different sort of reaction from the one we have just studied; yet, there too, orientation and reactivity can be governed by radical stability. (Even in those cases where other factors—steric hindrance, polar effects—are significant or even dominant, it is convenient to use radical stability as a point of departure.)

## 5AI.28 Transition state for halogenation

Is it reasonable that the more stable radical should be formed more easily?

We have already seen that the differences in reactivity toward halogen atoms are due chiefly to differences in $E_{act}$: the more stable the radical, then, the lower the $E_{act}$ for its formation. This, in turn, means that the more stable the radical, the more stable the transition state leading to its formation—both stabilities being measured, as they must be, against the same standard, the reactants. (*Remember*: $E_{act}$ is the difference in energy content between reactants and transition state.)

Examination of the transition state shows that this is exactly what we would expect. As we saw before, the hydrogen–halogen bond is partly formed and the carbon–hydrogen bond is partly broken. To the extent that the bond is broken, the alkyl group possesses character of the free radical it will become. *Factors that tend to stabilize the free radical tend to stabilize the incipient free radical in the transition state.*



$$\text{—}\overset{|}{\underset{|}{C}}\text{—}H + \cdot X \longrightarrow \left[\text{—}\overset{|\delta\cdot}{\underset{|}{C}}\cdots H\cdots \overset{\delta\cdot}{X}\right] \longrightarrow \text{—}\overset{|}{\underset{|}{C}}\cdot + H\text{—}X$$

Reactants Transition state Products

*Halogen has odd electron* *Carbon acquiring free-radical character* *Carbon has odd electron*

We have seen that the stabilities of free radicals follow the sequence 3° > 2° > 1° > $CH_3\cdot$. A certain factor (*delocalization of the odd electron*,) causes the energy difference between isobutane and the *tert*-butyl radical, for example, to be smaller than between propane and the isopropyl radical. It is not unreasonable that this same factor should cause the energy difference between isobutane and the incipi*ent tert*-butyl radical in the transition state to be smaller than between propane and the incipient isopropyl radical in its transition state (Fig. 5AI. 14).

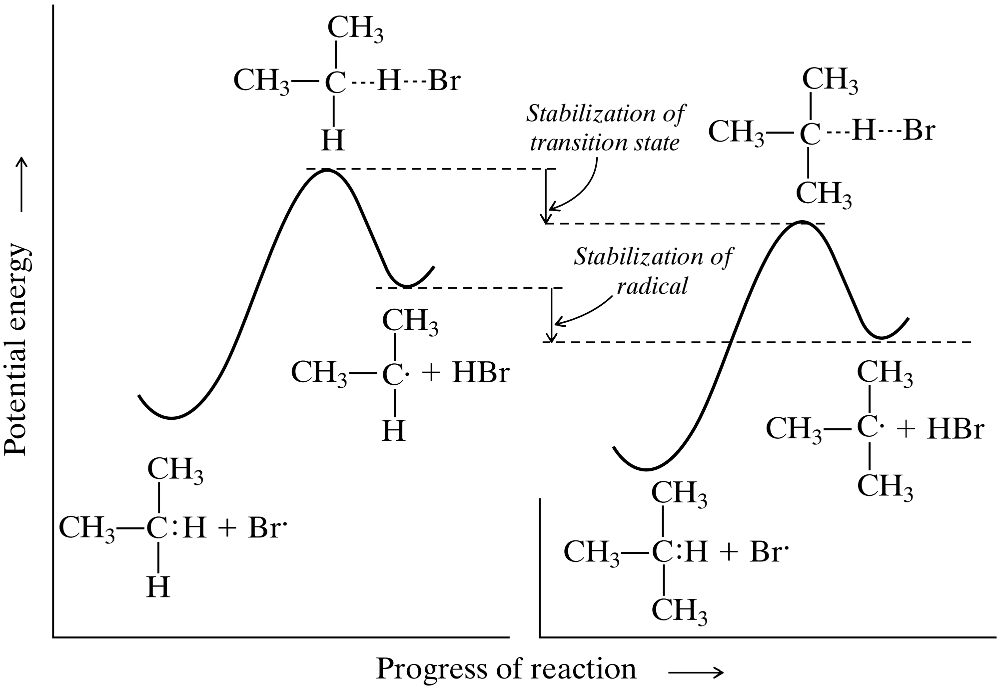


**Figure 5AI.14** Molecular structure and reactivity : free-radical substitution. The stability of the transition state parallels the stability of the radical: the more stable radical is formed faster. (The plots are aligned with each other for easy comparison.)

## 5AI.29 Orientation and reactivity

Throughout our study of organic chemistry, we shall approach the problems of orientation and reactivity in the following way.

Both problems involve comparing the rates of closely related reactions: in the case of orientation, reactions at different sites in the same compound; in the case of reactivity, reactions with different compounds. For such closely related reactions, variations in rate are due mostly to differences in $E_{act}$; by definition, $E_{act}$ is the difference in energy content between reactants and transition state.

We shall examine the most likely structure for the transition state, then, to see what structural features affect its stability without at the same time affecting by an equal amount the stability of the reactants; that is, we shall look for factors that tend to increase or decrease the energy difference between reactants and transition state. Having decided what structural features affect the $E_{act}$, we shall compare the transition states for the reactions whose rates we wish to compare: the more stable the transition state, the faster the reaction.

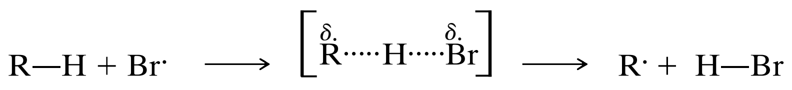
In many, if not most, reactions where a free radical is formed, as in the present case, the transition state differs from the reactants chiefly in being like the product. It is reasonable, then, that the factor most affecting the $E_{\mathrm{act}}$ should be the *radical character* of the transition state. Hence we find that the more stable the radical the more stable the transition state leading to its formation, and the faster the radical is formed.

## 5AI.30 Reactivity and selectivity

In its attack on alkanes, the bromine atom is much more selective than the chlorine atom (with relative rate factors of 1600 : 82 : 1 as compared with 5.0 : 3.8 : 1). It is also much less reactive than the chlorine atom (only 1/375 000 as reactive toward methane). This is just one example of a general relationship: in a set of similar reactions, the *less reactive* the reagent, the *more selective* it is in its attack.

In the attack by the comparatively unreactive bromine atom, the transition state is reached late in the reaction process, after the alkyl group has developed considerable radical character. In the attack by the highly reactive chlorine atom, the transition state is reached early, when the alkyl group has gained very little radical character.

**Bromination**



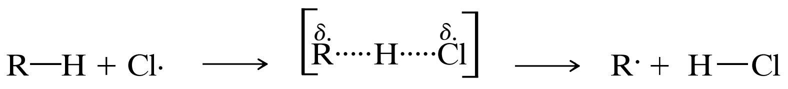
$$\mathrm{R{-}H} + \mathrm{Br}\cdot \longrightarrow \left[\overset{\delta\cdot}{\mathrm{R}}\cdots\cdots\mathrm{H}\cdots\cdots\overset{\delta\cdot}{\mathrm{Br}}\right] \longrightarrow \mathrm{R}\cdot + \mathrm{H{-}Br}$$

*Low reactivity; high selectivity*

Transition state

*Reached late: much radical character*

**Chlorination**



$$\mathrm{R{-}H} + \mathrm{Cl}\cdot \longrightarrow \left[\overset{\delta\cdot}{\mathrm{R}}\cdots\cdots\mathrm{H}\cdots\cdots\overset{\delta\cdot}{\mathrm{Cl}}\right] \longrightarrow \mathrm{R}\cdot + \mathrm{H{-}Cl}$$

*High reactivity; low selectivity*

Transition state

*Reached early: little radical character*

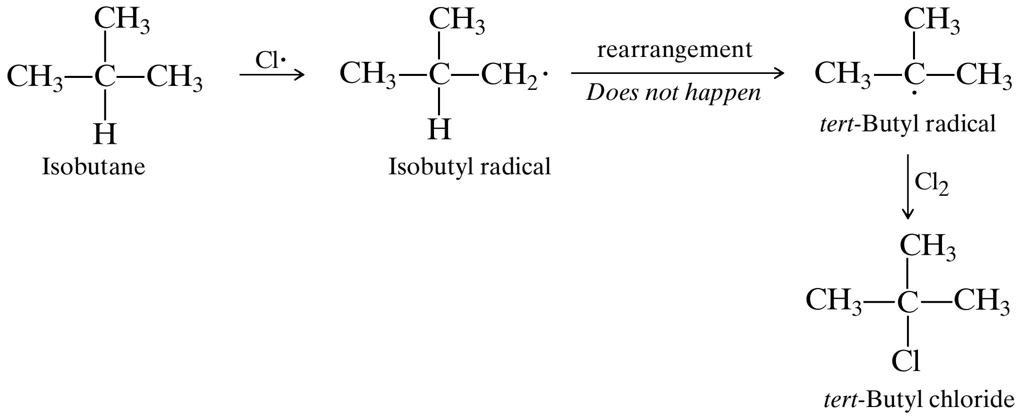
Now, by "selectivity" we mean here the differences in rate at which the various classes of free radicals are formed; a more stable free radical is formed faster, we said, because the factor that stabilizes it—delocalization of the odd electron—also stabilizes the incipient radical in the transition state. If this is so, then the more fully developed the radical character in the transition state, the more effective delocalization will be in stabilizing the transition state. The isopropyl radical, for example, is 3 kcal more stable than the *n*-propyl radical; if the radicals were *completely* formed in the transition state, the difference in $E_{act}$ would be 3 kcal. Actually, in bromination the difference in $E_{act}$ is 3 kcal: equal, within the limits of experimental error, to the maximum potential stabilization, indicating, as we expected, a great deal of radical character. In chlorination, by contrast, the difference in $E_{act}$ is only 0.5 kcal, indicating only very slight radical character.

A similar situation exists for reactions of other kinds. Whatever the factor responsible for differences in stability among a set of transition states—whether it is delocalization of an odd electron, or accommodation of a positive or negative charge, or perhaps a change in crowding of the atoms—the factor will operate more effectively when the transition state is more fully developed, that is, when the reagent is less reactive.

## 5AI.31 Non-rearrangement of free radicals. Isotopic tracers

Our interpretation of orientation was based on an assumption that we have not yet justified: that the relative amounts of isomeric halides we find in the product reflect the relative rates at which various free radicals were formed from the alkane. From isobutane, for example, we obtain twice as much isobutyl chloride as *tert*-butyl chloride, and we assume from this that, by abstraction of hydrogen, isobutyl radicals are formed twice as fast as *tert*-butyl radicals.

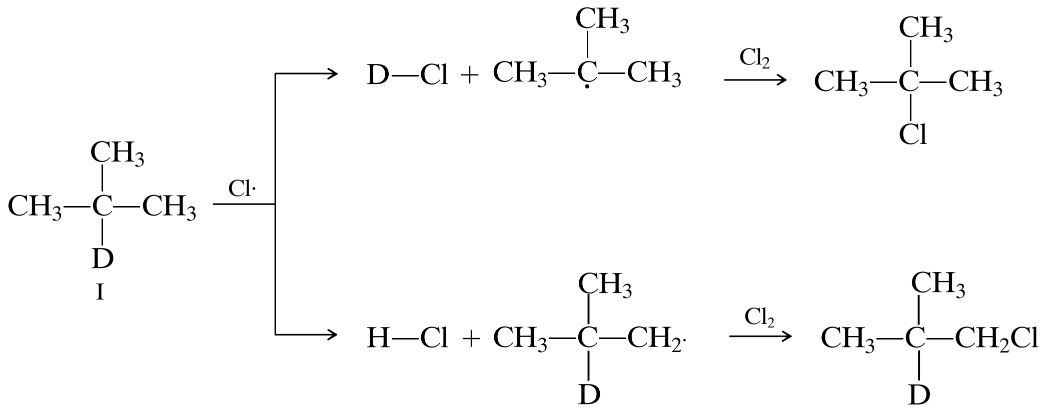
Yet how do we know, in this case, that every isobutyl radical that is formed ultimately yields a molecule of isobutyl chloride? Suppose some isobutyl radicals were to change—by *rearrangement* of atoms—into *tert*-butyl radicals, which then react with chlorine to yield *tert*-butyl chloride. This supposition is not so far-fetched as we, in our present innocence, might think; the doubt it raises is a very real one. We shall shortly see that another kind of reactive intermediate particle, the carbocation, is very prone to rearrange, with less stable ions readily changing into more stable ones.



H. C. Brown and Glen Russell decided to test the possibility that free radicals, like carbocations, might rearrange, and chose the chlorination of isobutane as a good test case, because of the large difference in stability between *tert*-butyl and isobutyl radicals. If rearrangement of alkyl radicals can indeed take place, it should certainly happen here.

What the problem comes down to is this: does every abstraction of primary hydrogen lead to isobutyl chloride, and every abstraction of tertiary hydrogen lead to *tert*-butyl chloride? This, we might say, we could never know, because all hydrogen atoms are exactly alike. But are they? Actually, three isotopes of hydrogen exist: $^1$H, *protium*, ordinary hydrogen; $^2$H or D, *deuterium*, heavy hydrogen; and $^3$H or T, *tritium*. Protium and deuterium are distributed in nature in the ratio of 5000 : 1. (Tritium, the unstable, radioactive isotope, is present in traces, but can be made by neutron bombardment of $^6$Li.) Modern methods of separation of isotopes have made very pure deuterium available, at moderate prices, in the form of deuterium oxide, $D_2O$, heavy water.

Brown and Russell prepared the deuterium-labeled isobutane I,

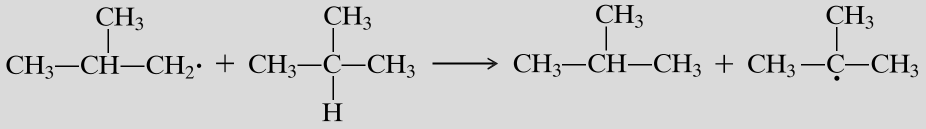


I

photochemically chlorinated it, and analysed the products. The DCl : HCl ratio (determined by the mass spectrometer) was found to be equal (within experimental error) to the *tert*-butyl chloride: isobutyl chloride ratio. Clearly, every abstraction of a tertiary hydrogen (*deuterium*) gave a molecule of *tert*-butyl chloride, and every abstraction of a primary hydrogen (*protium*) gave a molecule of isobutyl chloride. *Rearrangement of the intermediate free radicals did not occur.*

All the existing evidence indicates quite strongly that, although rearrangement of free radicals occasionally happens, it is not very common and does not involve simple alkyl radicals.

**Problem 5AI.17** (a) What results would have been obtained if some isobutyl radicals *had* rearranged to *tert*-butyl radicals? (b) Suppose that, instead of rearranging, isobutyl radicals were, in effect, converted into *tert*-butyl radicals by the reaction



$$\mathrm{CH_3{-}\overset{CH_3}{CH}{-}CH_2\cdot} + \mathrm{CH_3{-}\underset{H}{\overset{CH_3}{C}}{-}CH_3} \longrightarrow \mathrm{CH_3{-}\overset{CH_3}{CH}{-}CH_3} + \mathrm{CH_3{-}\underset{\bullet}{\overset{CH_3}{C}}{-}CH_3}$$

What results would Brown and Russell have obtained?

**Problem 5AI.18** Keeping in mind the availability of $D_2O$, suggest a way to make I from *tert*-butyl chloride.

The work of Brown and Russell is just one example of the way in which we can gain insight into a chemical reaction by using isotopically labeled compounds. We shall encounter many other examples in which isotopes, used either as *tracers*, as in this case, or for the detection of *isotope effects*, give us information about reaction mechanisms that we could not get in any other way.

Besides deuterium and tritium, isotopes commonly used in organic chemistry include: $^{14}C$, available as $^{14}CH_3OH$ and $Ba^{14}CO_3$; $^{18}O$, as $H_2{}^{18}O$; $^{15}N$, as $^{15}NH_3$, $^{15}NO_3-$, and $^{15}NO_2-$; $^{36}Cl$, as chlorine or chloride; $^{131}I$, as iodide.

**Problem 5AI.19** Bromination of methane is slowed down by the addition of HBr; this is attributed to the reaction

$$CH_3\cdot + HBr \longrightarrow CH_4 + Br\cdot$$

which, as the reverse of one of the chain-carrying steps, slows down bromination. How might you test whether or not this reaction actually occurs in the bromination mixture?

**Problem 5AI.20** The reaction

$$Cl\cdot + Cl_2 \longrightarrow Cl_2 + Cl\cdot$$

is considered to be listed as probable but unproductive. Given ordinary chlorine (made up of $^{35}Cl$ and $^{37}Cl$) and $^{36}Cl_2$, and a mass spectrometer, how would you go about finding out whether or not the reaction actually occurs?

## 5AI.32 Combustion

The reaction of alkanes with oxygen to form carbon dioxide, water, and—most important of all—*heat* is the chief reaction occurring in the internal combustion engine; its tremendous practical importance is obvious.

The mechanism of this reaction is extremely complicated and is not yet fully understood. There seems to be no doubt, however, that it is a free-radical chain reaction. The reaction is extremely exothermic and yet requires a very high temperature, that of a flame, for its initiation. As in the case of chlorination, a great deal of energy is required for the bond-breaking that generates the initial reactive particles; once this energy barrier is surmounted, the subsequent chain-carrying steps proceed readily and with the evolution of energy.

A higher compression ratio has made the modern gasoline engine more efficient than earlier ones, but has at the same time created a new problem. Under certain conditions the smooth explosion of the fuel–air mixture in the cylinder is replaced by **knocking**, which greatly reduces the power of the engine.

The problem of knocking has been successfully met in two general ways: (a) proper selection of the hydrocarbons to be used as fuel, and (b) addition of tetraethyllead.

Experiments with pure compounds have shown that hydrocarbons of differing structures differ widely in knocking tendency. The relative antiknock tendency of a fuel is generally indicated by its **octane number**. An arbitrary scale has been set up, with *n*-heptane, which knocks very badly, being given an octane number of zero, and 2,2,4-trimethylpentane ("isooctane") being given the octane number of 100. There are available today fuels with better antiknock qualities than "isooctane".

The gasoline fraction obtained by direct distillation of petroleum (*straight-run gasoline*) is improved by addition of compounds of higher octane number; it is sometimes entirely replaced by these better fuels. Branched-chain alkanes and alkenes, and aromatic hydrocarbons generally have excellent antiknock qualities; these are produced from petroleum hydrocarbons by *catalytic cracking* and *catalytic reforming.* Highly branched alkanes are synthesized from alkenes and alkanes by *alkylation*.

In 1922 T. C. Midgley, Jr., and T. A. Boyd found that the octane number of a fuel is greatly improved by addition of a small amount of tetraethyllead, $(C_2H_5)_4Pb$. Gasoline so treated is called *ethyl* gasoline or *leaded* gasoline. Nearly 50 years of research finally showed that tetraethyllead probably works by producing tiny particles of lead oxides, on whose surface certain reaction chains are broken.

In addition to carbon dioxide and water, however, the gasoline engine discharges other substances into the atmosphere, substances that are either smog-producing or downright poisonous: unburned hydrocarbons, carbon monoxide, nitrogen oxides, and, from leaded gasoline, various compounds of lead—in the United States, formerly, hundreds of tons of lead a day. The action of sunlight on smog further produces ozone, which is irritating and sometimes lethal. (This is *not* the ozone that, high in the atmosphere, forms the ozone shield.) Growing public concern about these pollutants has caused a minor revolution in the petroleum and auto industries. *Converters* have been developed to clean up exhaust emissions: by catalytic oxidation of hydrocarbons and carbon monoxide, and by the breaking down of nitrogen oxides into nitrogen and oxygen. But most of these oxidation catalysts contain platinum, which is poisoned by lead; there was a move to get the lead out of gasoline—not, initially, to cut down on lead pollution, but to permit converters to function. This has, in turn, brought back the problem of knocking, which is being met in two ways: (a) by lowering the compression ratio of the new automobiles being built; and (b) by increasing the octane number of gasoline through changes in hydrocarbon composition—through addition of aromatics and through increased use of isomerization.

But, as we shall see in the following section, the pollution we have just described—bad as it is—may not be the most serious problem created by combustion.

## 5AI.33 The greenhouse effect

During the 1980s the world became aware of the threat of global warming brought about by the *greenhouse effect.* And here the chief culprit is, not a noxious side product, but an unavoidable principal product of the burning of hydrocarbons: *carbon dioxide.*

The atmosphere contains a number of gases that act like the glass in a greenhouse. They are transparent to visible light from the sun, and allow it to pass through to the earth below; but they absorb and trap infrared light radiated outward from the earth and convert it into heat. The principal "greenhouse gases" are CFCs methane, and, most important of all, carbon dioxide.

The concentration of greenhouse gases is rising today because of two factors, both stemming from our technology: the manufacture of CFCs, never before present on our planet; and the burning of fossil fuels at a tremendous—and still increasing—rate. If this trend is not reversed, it is predicted, there will be a steady rise in the temperature of the earth. This global warming could cause drastic climatic changes with devastating results: shifting of seasonal winds, with the creation and spreading of deserts; alterations in crop patterns, with social upheaval and starvation; melting of the polar ice caps, with a rise in the level of the sea and the inundation of large areas of land and many of the biggest and most important cities.

The solution to the problem of CFCs—in principle, though not in practice—is simple: stop making them. (There is an even more pressing reason for doing that: the unrelated matter of depletion of the ozone shield.) But one cannot burn carbon compounds without producing carbon dioxide—and our way of life is centered on such burning. Clearly, other sources of energy must be developed.

## 5AI.34 Pyrolysis: cracking

Decomposition of a compound by the action of heat alone is known as **pyrolysis**. This word is taken from the Greek *pyr*, fire, and *lysis*, a loosing, and hence to chemists means "cleavage by heat"; compare *hydro-lysis*, "cleavage by water".

The pyrolysis of alkanes, particularly when petroleum is concerned, is known as **cracking**. In *thermal cracking* alkanes are simply passed through a chamber heated to a high temperature. Large alkanes are converted into smaller alkanes, alkenes, and some hydrogen. This process yields predominantly ethylene ($C_2H_4$) together with other small molecules. In a modification called *steam cracking*, the hydrocarbon is diluted with steam, heated for a fraction of a second to 700–900 °C, and rapidly cooled. Steam cracking is of great importance in the production of hydrocarbons as chemicals, including ethylene, propylene, butadiene, isoprene, and cyclopentadiene. Another source of smaller hydrocarbons is *hydrocracking*, carried out in the presence of a catalyst and hydrogen, at high pressure and at much lower temperatures (250–450 °C).

The low-molecular-weight alkenes obtained from these cracking processes can be separated and purified, and are the most important raw materials for the large-scale synthesis of aliphatic compounds.

Most cracking, however, is directed toward the production of fuels, not chemicals, and for this *catalytic cracking* is the major process. Higher boiling petroleum fractions (typically, gas oil) are brought into contact with a finely divided silica–alumina catalyst at 450–550 °C and under slight pressure. Catalytic cracking not only increases the yield of gasoline by breaking large molecules into smaller ones, but also improves the quality of the gasoline: this process involves carbocations and yields alkanes and alkenes with the highly branched structures desirable in gasoline.

Through the process of *alkylation*, some of the smaller alkanes and alkenes are converted into high-octane synthetic fuels.

Finally, by the process of *catalytic reforming*, enormous quantities of the aliphatic hydrocarbons of petroleum are converted into *aromatic* hydrocarbons which are used not only as superior fuels but as the starting materials in the synthesis of most aromatic compounds.

## 5AI.35 Determination of structure

One of the commonest and most important jobs in organic chemistry is to determine the structural formula of a compound just synthesized or isolated from a natural source.

The compound will fall into one of two groups, although at first we probably shall not know *which* group. It will be either (a) a previously reported compound, which we must identify, or (b) a new compound, whose structure we must prove.

If the compound has previously been encountered by some other chemist who determined its structure, then a description of its properties will be found somewhere in the chemical literature, together with the evidence on which its structure was assigned. In that case, we need only to show that our compound is identical with the one previously described.

If, on the other hand, our compound is a new one that has never before been reported, then we must carry out a much more elaborate proof of structure.

Let us see—in a general way now, and in more detail later—just how we would go about this job. We are confronted by a flask filled with gas, or a few milliliters of liquid, or a tiny heap of crystals. We must find the answer to the question: *what is it?*

First, we purify the compound and determine its physical properties: melting point, boiling point, density, refractive index, and solubility in various solvents. In the laboratory today, we would measure various spectra of the compound in particular the infrared spectrum and the NMR spectrum; indeed, because of the wealth of information to be gotten in this way, spectroscopic examination might well be the first order of business after purification. From the mass spectrum we would get a very accurate molecular weight. Increasingly, structure is being determined in the most direct way possible: by x-ray analysis, which can show the precise distribution of atoms in a molecule.

We would carry out a qualitative elemental analysis to see what elements are present. We might follow this with a quantitative analysis, and from this and the molecular weight we could calculate a molecular formula; we would certainly do this if the compound is suspected of being a new one.

Next, we study systematically the behavior of the compound toward certain reagents. This behavior, taken with the elemental analysis, solubility properties, and spectra, generally permits us to *characterize* the compound, that is, to decide what family the unknown belongs to. We might find, for example, that the compound is an alkane, or that it is an alkene, or an aldehyde, or an ester.

Now the question is: *which* alkane is it? Or which alkene, or which aldehyde, or which ester? To find the answer, we first go to the chemical literature and look up compounds of the particular family to which our unknown belongs.

If we find one described whose physical properties are identical with those of our unknown, then the chances are good that the two compounds are identical. For confirmation, we generally convert the unknown by a chemical reaction into a new compound called a **derivative**, and show that this derivative is identical with the product derived in the same way from the previously reported compound.

If, on the other hand, we do not find a compound described whose physical properties are identical with those of our unknown, then we have a difficult job on our hands: we have a new compound, and must prove its structure. We may carry out a *degradation*: break the molecule apart, identify the fragments, and deduce what the structure must have been. To clinch any proof of structure, we attempt to *synthesize* the unknown by a method that leaves no doubt about its structure.

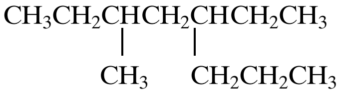
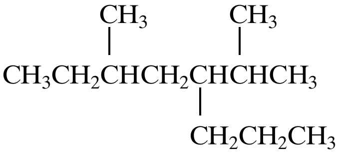
**Problem 5AI.21** The final step in the proof of structure of an unknown alkane was its synthesis by the coupling of lithium di-*tert*-butylcopper with *n*-butyl bromide. What was the alkane?

## EXERCISE

**1.** Give the structural formula of:

(a) 2,2,3,3-tetramethylpentane
(b) 2,3-dimethylbutane
(c) 3,4,4,5-tetramethylheptane
(d) 4-ethyl-3,4-dimethylheptane
(e) 4-ethyl-2,4-dimethylheptane
(f) 2,5-dimethylhexane
(g) 3-ethyl-2-methylpentane
(h) 2,2,4-trimethylpentane
(i) 3-chloro-2-methylpentane
(j) 1,2-dibromo-2-methylpropane

**2.** Draw out the structural formula and give the IUPAC name of:

(a) $(CH_3)_2CHCH_2CH_2CH_3$
(b) $CH_3CBr_2CH_3$
(c) $CH_3CH_2C(CH_3)_2CH_2CH_3$
(d) $(C_2H_5)_2C(CH_3)CH_2CH_3$
(e) $CH_3CH_2CH(CH_3)CH(CH_3)CH(CH_3)_2$
(f) 
$\mathrm{CH_3CH_2\underset{CH_3}{\underset{|}{CH}}CH_2\underset{CH_2CH_2CH_3}{\underset{|}{CH}}CH_2CH_3}$
(g) $(CH_3)_3CCH_2C(CH_3)_3$
(h) $(CH_3)_2CClCH(CH_3)_2$
(i) $(CH_3)_2CHCH_2CH_2CH(C_2H_5)_2$
(j) $(CH_3)_2CHCH(CH_3)CH_2C(C_2H_5)_2CH_3$
(k) $(CH_3)_2CHC(C_2H_5)_2CH_2CH_2CH_3$
(l) 
$\mathrm{CH_3CH_2\overset{CH_3}{\overset{|}{CH}}CH_2\underset{CH_2CH_2CH_3}{\underset{|}{CH}}\overset{CH_3}{\overset{|}{CH}}CH_3}$

**3.** Pick out an alkane in Problem 1 or 2 that has: (a) no tertiary hydrogen; (b) one tertiary hydrogen; (c) two tertiary hydrogens; (d) no secondary hydrogen; (e) two secondary hydrogens; (f) half the number of secondary hydrogens as primary hydrogens.

**4.** Pick out an alkane (if any) in Problem 1 or 2 that contains:

(a) one isopropyl group
(b) two isopropyl groups
(c) one isobutyl group
(d) two isobutyl groups
(e) one *sec*-butyl group
(f) two *sec*-butyl groups
(g) one *tert*-butyl group
(h) two *tert*-butyl groups
(i) an isopropyl group and a *sec*-butyl group
(j) a *tert*-butyl group and an isobutyl group
(k) a methyl, an ethyl, a *n*-propyl, and a *sec*-butyl group

**5.** What alkane or alkanes of molecular weight 86 have: (a) two monobromo derivatives? (b) three? (c) four? (d) five? (e) How many dibromo derivatives does the alkane in (a) have? (f) Name the dibromo derivatives in (e).

**6.** How many mono-, di-, and trichloro derivatives are possible for cyclopentane?

**7.** Without referring to tables, list the following hydrocarbons in order of decreasing boiling points (i.e., highest boiling at top, lowest at bottom):

(a) 3,3-dimethylpentane
(b) *n*-heptane
(c) 2-methylheptane
(d) *n*-pentane
(e) 2-methylhexane

**8.** Write balanced equations, naming all organic products, for the following reactions:

(a) isobutyl bromide + Mg/ether
(b) *tert*-butyl bromide + Mg/ether
(c) product of (a) + $H_2O$
(d) product of (b) + $H_2O$
(e) product of (a) + $D_2O$
(f) *sec*-butyl chloride + Li, then CuI
(g) product of (f) + ethyl bromide

**9.** Write equations for the preparation of n-butane from:

| | |
|---|---|
| (a) *n*-butyl bromide | (d) 1-butene, $CH_3CH_2CH{=}CH_2$ |
| (b) *sec*-butyl bromide | (e) 2-butene, $CH_3CH{=}CHCH_3$ |
| (c) ethyl chloride | |

**10.** Draw structures of all products expected from monochlorination at room temperature of:

| | |
|---|---|
| (a) *n*-hexane | (c) 2,2,4-trimethylpentane |
| (b) isohexane | (d) 2,2-dimethylbutane |

**11.** Predict the proportions of products in the preceding problem.

**12.** (a) Reaction of an aldehyde with a Grignard reagent is an important way of making alcohols. Why must one scrupulously dry the aldehyde before adding it to the Grignard reagent? (b) Why would one not prepare a Grignard reagent from $BrCH_2CH_2OH$?

**13.** Free-radical chlorination of *either* *n*-propyl or isopropyl bromide gives 1-bromo-2-chloropropane, and of *either* isobutyl or *tert*-butyl bromide gives 1-bromo-2-chloro-2-methylpropane. What appears to be happening? Is there any pattern to this behavior?

**14.** (a) If a rocket were fueled with kerosine and liquid oxygen, what weight of oxygen would be required for every liter of kerosine? (Assume kerosine to have the average composition of *n*-$C_{14}H_{30}$.) (b) How much heat would be evolved in the combustion of one liter of kerosine? (Assume 157 kcal/mol for each —$CH_2$— group and 186 kcal/mol for each —$CH_3$ group.) (c) If it were to become feasible to fuel a rocket with free hydrogen atoms, what weight of fuel would be required to provide the same heat as a liter of kerosine and the necessary oxygen? (Assume $H_2$ as the sole product.)

**15.** By what two quantitative methods could you show that a product isolated from the chlorination of propane was a monochloro or a dichloro derivative of propane? Tell exactly what results you would expect from each of the methods.

**16.** On the basis of certain evidence, including its infrared spectrum, an unknown compound of formula $C_{10}H_{22}$ is suspected of being 2,7-dimethyloctane. How could you confirm or disprove this tentatively assigned structure?

**17.** (a) A solution containing an unknown amount of methyl alcohol ($CH_3OH$) dissolved in *n*-octane is added to an excess of methylmagnesium iodide dissolved in the high-boiling solvent, *n*-butyl ether. A gas is evolved, and is collected and its volume measured; 1.04 mL (corrected to STP). What is the gas, and how is it formed? What weight of methyl alcohol was added to the Grignard reagent?

(b) A sample of 4.12 mg of an unknown alcohol, ROH, is added to methylmagnesium iodide as above; there is evolved 1.56 mL of gas (corrected to STP). What is the molecular weight of the alcohol? Suggest a possible structure or structures for the alcohol.

(c) A sample of 1.79 mg of a compound of mol. wt. about 90 gave 1.34 mL of the gas (corrected to STP). How many "active (that is, acidic) hydrogens" are there per molecule? Assuming all these to be in —OH groups, suggest a structure for the alcohol. (This is an example of the *Zerewitinoff active hydrogen determination*.)

**18.** (a) *tert*-Butyl peroxide is a stable, easy-to-handle liquid that serves as a convenient source of free radicals:

$$(CH_3)_3CO{-}OC(CH_3)_3 \xrightarrow[\text{or light}]{130\,^\circ\text{C}} 2(CH_3)_3CO\cdot$$

A mixture of isobutane and $CCl_4$ is quite stable at 130–140 °C. If a small amount of *tert*-butyl peroxide is added, a reaction occurs that yields (chiefly) *tert*-butyl chloride and chloroform. A small amount of *tert*-butyl alcohol $(CH_3)_3COH$, equivalent to the peroxide used) is also isolated. Give all steps in a likely mechanism for this reaction.

(b) When irradiated with ultraviolet light, or in the presence of a small amount of peroxides, *tert*-butyl hypochlorite, $(CH_3)_3C{-}O{-}Cl$, reacts with alkanes to form, in equimolar amounts, alkyl chlorides and, *tert*-butyl alcohol. Outline all steps in a likely mechanism for this reaction.

# 5AII. Stereoisomerism

## 5AII.1 Stereoisomerism

If molecules having same molecular formula are superimposable, then these are called *homomers*, and those that are not superimposable are called *isomers*. Isomers having different bond connectivities are called *constitutional isomers*, and isomers having same bond connectivities are called *stereoisomers*. This phenomenon is known as stereoisomerism. The part of chemistry that deals with the properties of stereoisomers is called stereochemistry.

Stereoisomers may be of different types. For example, stereoisomers that are readily interconvertible by rotation around a $\sigma$-bond are known as *conformational isomers*. Those stereoisomers that are not interconvertible by a simple rotation around a $\sigma$-bond are called *configurational isomers*. If the configurational isomers are related as nonsuperimposable mirror images, they are called *enantiomers* (or optical isomers), and if they are not related as such, they are called *diastereoisomers.*

## 5AII.2 Enantiomerism

A regular tetrahedral molecule of the type $Ca_4$ provides a 3D-framework of $T_d$ symmetry that changes to an asymmetric structure of $C_1$-symmetry in the molecules of the type $C_{abde}$. In such a C-atom, the four groups a, b, d, and e can be arranged at the four corners of the tetrahedron in two different orientations that are related to each other as nonsuperimposable mirror images. Since they are not superimposable and have the same bond connectivity, they represent two stereoisomers called enantiomers. This phenomenon is called enantiomerism (Fig. 5AII.1). It was the existence of enantiomers that convinced Van't Hoff and LeBel that the carbon atom is tetrahedral. But to understand what enantiomers are, we must first learn about the property called *optical activity*.

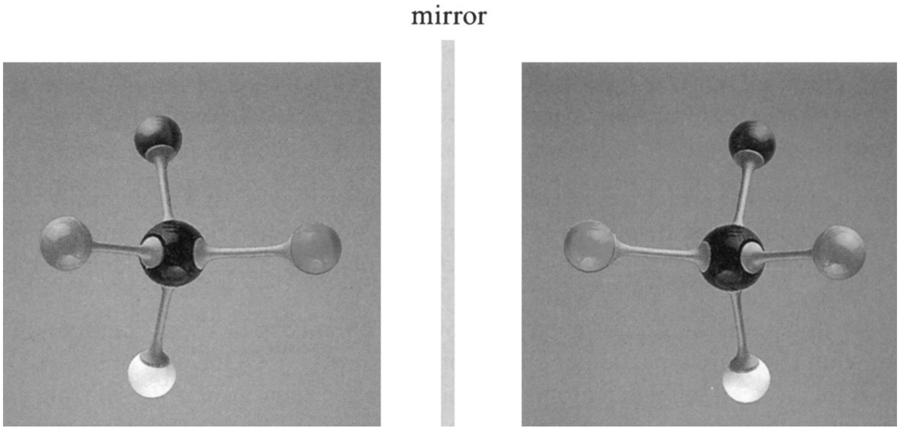


**Figure 5AII.1**

## 5AII.3 Plane-polarized light

Light possesses certain properties that are best understood by considering it to be a wave phenomenon in which the vibrations occur at right angles to the direction in which the light travels. There are an infinite number of planes passing through the line of propagation, and ordinary light is vibrating in all these planes. If we consider that we are looking directly into the beam of a flashlight, (Fig. 5AII.2) shows schematically the sort of vibrations that are taking place, all perpendicular to a line between our eye and the paper (flashlight). **Plane-polarized light** *is light whose vibrations take place in only one of these possible planes*. Ordinary light is turned into plane-polarized light by passing it through a lens made of the material known as Polaroid or more traditionally through pieces of *calcite* (a particular crystalline form of $CaCO_3$) so arranged as to constitute what is called a *Nicol prism*.

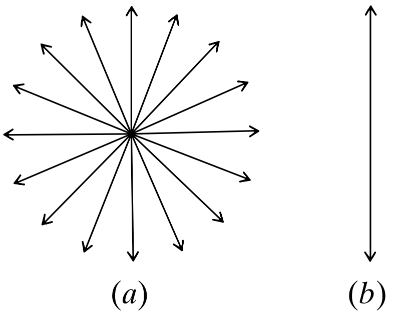


**Figure 5AII.2** Schematic representation of (*a*) ordinary light and (*b*) planepolarized light. The light is traveling perpendicular to the page; the vibrations are in the plane of the page.

*An* **optically active substance** *is one that rotates the plane of polarized light.* When polarized light, vibrating in a certain plane, is passed through an optically active substance, it emerges vibrating in a different plane.

## 5AII.4 Polarimeter

How can this rotation of the plane of polarized light—this optical activity—be detected? It is both detected and measured by an instrument called the **polarimeter**, which is represented schematically in Fig. 5AII.3. It consists of a light source, two lenses (Polaroid or Nicol), and between the lenses a tube to hold the substance that is being examined for optical activity. These are arranged so that the light passes through one of the lenses (*polarizer*), then the tube, then the second lens (*analyser*), and finally reaches our eye. When the tube is empty, we find that the maximum amount of light reaches our eye when the two lenses are so arranged that they pass light vibrating in the same plane. If we rotate the lens that is nearer our eye, say, we find that the light dims, and reaches a minimum when the lens is at right angles to its previous position.

Let us adjust the lenses so that a maximum amount of light is allowed to pass. (In practice, it is easier to detect a minimum than a maximum; the principle remains the same.) Now let us place the sample to be tested in the tube. If the substance does not affect the plane of polarization, light transmission is still at a maximum and the substance is said to be **optically inactive**. If, on the other hand, the substance rotates the plane of polarization, then the lens nearer our eye must be rotated to conform with this new plane if light transmission is again to be a maximum, and the substance is said to be **optically active**. If the rotation of the plane, and hence our rotation of

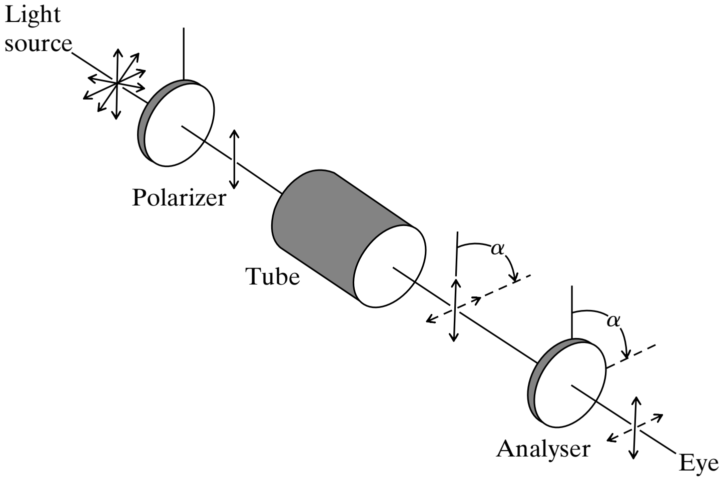


**Figure 5AII.3** Schematic representation of a polarimeter. Solid lines: before rotation. Broken lines: after rotation. $\alpha$ is the angle of rotation.

the lens, is to the right (clockwise), the substance is **dextrorotatory** (Latin: *dexter*, right); if the rotation is to the left (counterclockwise), the substance is **levorotatory** (Latin: *laevus*, left).

We can determine not only that the substance has rotated the plane, and in which direction, but also *by how much*. The amount of rotation is simply the number of degrees that we must rotate the lens to conform to the light. The symbols + and − are used to indicate rotations to the right and to the left, respectively.

The lactic acid that is extracted from muscle tissue rotates light to the right, and hence is known as *dextrorotatory* lactic acid, or (+)-lactic acid. The 2-methyl-1-butanol that is obtained from fusel oil (a by-product of the fermentation of starch to ethyl alcohol) rotates light to the left, and is known as *levorotatory* (−)2-methyl-1-butanol, or (−)-2-methyl-1-butanol.

## 5AII.5 Specific rotation

Since optical rotation of the kind we are interested in is caused by individual molecules of the active compound, *the amount of rotation depends upon how many molecules the light encounters in passing through the tube*.

The light will encounter twice as many molecules in a tube 20 cm long as in a tube 10 cm long, and the rotation will be twice as large. If the active compound is in solution, the number of molecules encountered by the light will depend upon the concentration. For a given tube length, light will encounter twice as many molecules in a solution of 2 g per 100 mL of solvent as in a solution containing 1 g per 100 mL of solvent, and the rotation will be twice as large. When allowances are made for the length of tube and the concentration, it is found that the amount of rotation, as well as its direction, is a characteristic of each individual optically active compound.

**Specific rotation** is the number of degrees of rotation observed if a 1-dm (10-cm) tube is used, and the compound being examined is present to the extent of 1 g/mL. This is usually calculated from observations with tubes of other lengths and at different concentrations by means of the equation

$$[\alpha] = \frac{\alpha}{l \times d}$$

$$\text{specific rotation} = \frac{\text{observed rotation (degrees)}}{\text{length (dm)} \times \text{g/mL}}$$

where $d$ represents density for a pure liquid or concentration for a solution.

The specific rotation is as much a property of a compound as its melting point, boiling point, density, or refractive index. Thus the specific rotation of the 2-methyl-l-butanol obtained from fusel oil is

$$[\alpha]_D^{20} = -5.90°$$

Here, 20 is the temperature and D is the wavelength of the light used in the measurement (D line of sodium, 5893 Å).

**Problem 5AII.1** The concentration of cholesterol dissolved in chloroform is 6.15 g per 100 mL of solution. (a) A portion of this solution in a 5-cm polarimeter tube causes an observed rotation of −1.2°. Calculate the specific rotation of cholesterol. (b) Predict the observed rotation if the same solution were placed in a 10-cm tube. (c) Predict the observed rotation if 10 mL of the solution were diluted to 20 mL and placed in a 5-cm tube.

**Problem 5AII.2** A sample of a pure liquid in a 10-cm tube is placed in a polarimeter and a reading of +45° is made. How could you establish that $[\alpha]$ is really +45° and not −315°? That it is +45° and not +405° or, for that matter, +765°?

## 5AII.6 Optical activity: how does it arise?

Most compounds do not rotate the plane of polarized light. How is it that *some* do? It is not the particular chemical family that they belong to, since optically active compounds are found in all families. To see what special structural feature gives rise to optical activity, let us look more closely at what happens when polarized light is passed through a sample of a single pure compound.

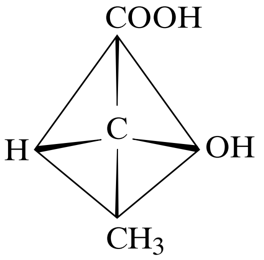
When a beam of polarized light passes through an individual molecule, in nearly every instance its plane is rotated a tiny amount by interaction with the charged particles of the molecule; the direction and extent of rotation varies with the orientation of the particular molecule in the beam. For most compounds, because of the random distribution of the large number of molecules that make up even the smallest sample of a single pure compound, for every molecule that the light encounters, there is another (identical) molecule oriented *as the mirror image of the first*, which exactly cancels its effect. The net result is no rotation, that is, optical inactivity. Thus optical inactivity is a property not of individual molecules, but rather of the *random distribution of molecules that can serve as mirror images of each other*.

Optical inactivity requires, then, that one molecule of a compound acts as the mirror image of another. But in the special case of CWXYZ, a molecule whose mirror image is not just another, identical molecule, but rather a molecule of a different, isomeric compound. In a pure sample of a single enantiomer, no molecule can serve as the mirror image of another; there is no exact canceling-out of rotations, and the net result is optical activity. Thus, the same non-superimposability of mirror images that gives rise to enantiomerism also is responsible for optical activity.

## 5AII.7 Projection structures of stereoisomers

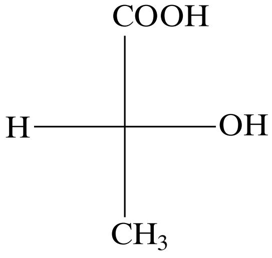
It is inconvenient to represent 3D-molecules in a paper or a board. So several 2D-formulas have been developed to represent the molecules having 3D-structures. For example,

1. *Fischer's projection of enantiomers.* This type of representation is done for chiral carbon. The chiral C-atom is assumed to be in the plane of the paper or the board. The four bonds are shown by two vertical and two horizontal straight lines. The point of intersection of the two straight lines is accepted as the chiral C-atom. The two vertical bonds actually project below the plane of the paper, and the two horizontal lines project above the plane. For example,



Tetrahedral formula

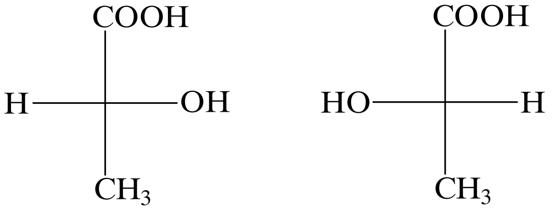
Chiral C-atom is in the plane of the paper, —COOH and $CH_3$ groups project below, and H and — OH project above the plane of the paper



Fischer's projection formula

in the tetrahedral model shown above, if the chiral C-atom is in the plane, the two groups —COOH and —$CH_3$ project below the plane, and the other two groups —OH and —H project above the plane. Therefore, in Fischer's projection formula, —COOH and —$CH_3$ groups are written in the vertical line and the groups —OH and —H in the horizontal line.

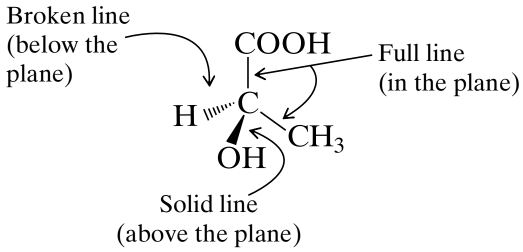
For the purpose of the comparison of the two Fischer's formulas, rotation or sliding of the structures in the plane of the paper is allowed, but no bond can be lifted from the plane of the paper. For example, the two Fischer's projection formulas written below are not superimposable if no bond is allowed to be lifted from the plane of the paper. So, these two are stereoisomers. Also, they are related as mirror images, therefore, these are enantiomers.



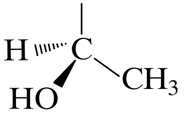
Enantiomers of lactic acid

As a rule, exchange of two groups in the Fischer's formula by *odd number of times* gives the structure of the enantiomer. But exchange of two groups by even number of times does not change the configuration.

2. *Flying-wedge representation.* This kind of representation is done for both chiral and achiral C-atoms. In this formula, two bonds of the chiral C-atom are shown in the plane of the paper by full lines, and of the other two bonds one is shown above the plane of the paper by a solid line, and another one is shown below the plane of the paper by a broken line.

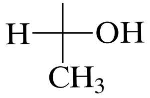


The two full lines of the flying-wedge formula are written as the vertical lines in the Fischer's formula. The other two groups are placed in the horizontal line. If the lower group with a full line in the flying-wedge formula is bent to the right, then the group held by the solid line is placed on the right in the horizontal line of the Fischer's formula. If it is bent to the left, the group held by the solid line is written on the left of the horizontal line of the Fischer's formula.



Flying-wedge formula

The lower group —$CH_3$ held by the full line is bent to the right



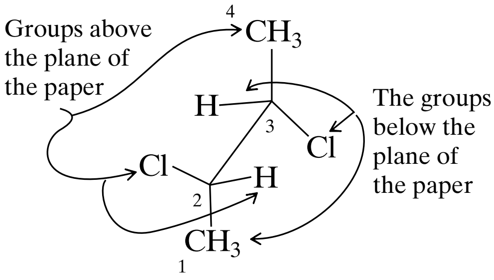
Fischer's formula

The group held by the solid line in flying-wedge formula is written on the right of the Fischer's formula

3. *Sawhorse projection.* When it is necessary to know the spatial relation between two adjacent C-atoms, both chiral or achiral, sawhorse representation is quite convenient. In this projection, the two key C-atoms are joined by a diagonal line in the plane of the paper. The remaining bonds are shown by smaller lines projected above and below the plane of the paper. There is a free rotation around the diagonal line either clockwise or anticlockwise.

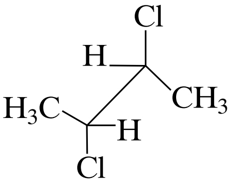
$$\overset{1}{C}H_3\overset{2}{C}HCl\overset{3}{C}HCl\overset{4}{C}H_3$$

Key atoms are C-2 and C-3

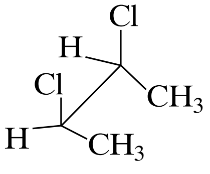


Sawhorse formula
of the above compound

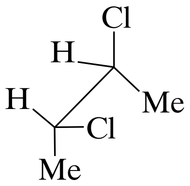
For example, in the molecule $\overset{1}{C}H_3\overset{2}{C}HCl\cdot\overset{3}{C}HCl\overset{4}{C}H_3$, the two key atoms are C-2 and C-3. Looking along $C_2$—$C_3$ $\sigma$-bond and drawing the diagonal in the plane of the paper, the sawhorse structure of the compound is written as shown above. The structure in which the bulky atoms or groups (Cl atoms in the case



Staggered sawhorse formula
($\theta = 180°$)



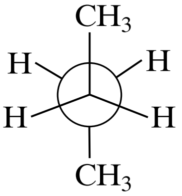
Eclipsed sawhorse formula
($\theta = 0°$)



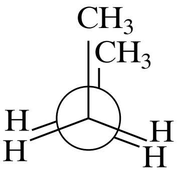
Partially eclipsed sawhorse formula
($\theta = 120°$)

shown below) make a dihedral angle $\theta = 180°$, the sawhorse conformation of the compound is called the staggered conformation. Since the free rotation along the diagonal $C_2$—$C_3$ bond is allowed, other conformations of the compound are also possible. For example, the conformation in which the dihedral angle $\theta$ between the two Cl atoms is equal to 0°, it is termed as the eclipsed sawhorse formula, and when $\theta$ is equal to 120°, the representation is known as the partially eclipsed sawhorse formula.

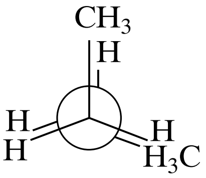
4. *Newman projection formula.* In this projection, the molecule is viewed along the bond that binds the two key C-atoms of the molecule, both chiral or achiral, and these atoms are represented as superimposed circles. Only one circle is drawn the center of which represents the front C-atom, and the circumference of the circle represents the rear C-atom. The three $\sigma$-bonds of the front C-atom are shown by three small lines drawn from the center of the circle, making an angle of 120° with one another. The three $\sigma$-bonds of the rear C-atom are drawn from the circumference of the circle. For example, the staggered, eclipsed, gauche, and partially eclipsed conformations of *n*-butane can be drawn as shown in the right.



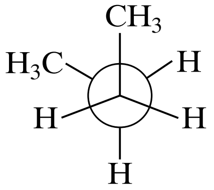
Staggered *n*-butane



Eclipsed *n*-butane



Partially eclipsed *n*-butane



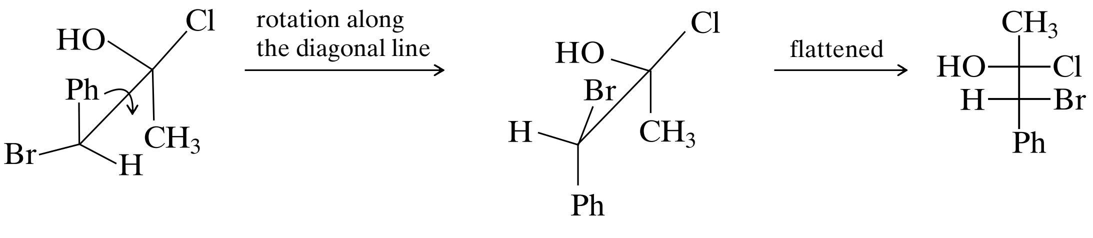
Gauche or skewed *n*-butane

*Interconversion of projection formulas.* Different projection formulas may be interconverted by following some simplified steps. For example, a sawhorse formula can be converted to a Fischer's formula following the steps mentioned below:

*Step 1.* The front C-atom of sawhorse formula is considered as the lowest chiral C-atom in Fischer's formula.

*Step 2.* The given sawhorse conformation is converted to an eclipsed sawhorse conformation by rotation along the diagonal line by the minimum number of degrees.

*Step 3.* The eclipsed sawhorse conformation so obtained after step 2 operation is now flattened to get the Fischer's projection formula. For example,



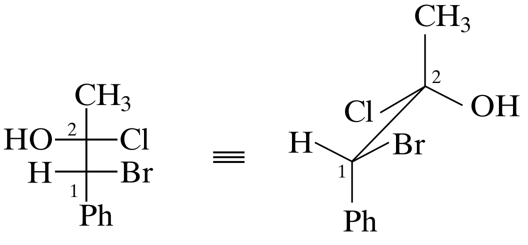
Eclipsed sawhorse formula

Fischer's formula

Similarly, a Fischer's formula can be converted to a sawhorse formula by the following simplified steps :

*Step 1.* The lowest chiral C-atom of the Fischer's formula becomes the front C-atom of the sawhorse formula.

*Step 2.* The groups in Fischer's formula that are drawn in *anti-* or *trans-*orientation with respect to each other are drawn on the same side of the diagonal line in the sawhorse formula. For example,



Fischer's formula Sawhorse formula

## 5AII.8 Properties of enantiomers

*Isomers that are mirror images of each other are called* **enantiomers**. The two different lactic acids are enantiomers (Greek: *enantio-*, opposite). So are the two 2-methyl-1-butanols, the two *sec*-butyl chlorides, etc. How do the properties of enantiomers compare?

**Enantiomers have identical physical properties, except for the direction of rotation of the plane of polarized light**. The two 2-methyl-1-butanols, for example,

| | (+)-2-Methyl-1-butanol | (−)-2-Methyl-1-butanol (fermentation product) |
|---|---|---|
| Specific rotation | +5.90° | −5.90° |
| Boiling point | 128.9 °C | 128.9 °C |
| Relative density | 0.8193 | 0.8193 |
| Refractive index | 1.4107 | 1.4107 |

have identical melting points, boiling points, densities, refractive indexes, and any other physical constant one might measure, except for this: one rotates plane-polarized light to the right, the other to the left. This fact is not surprising, since the interactions of both kinds of molecule with their fellows should be the same. Only the *direction* of rotation is different; the *amount* of rotation is the same, the specific rotation of one being +5.90°, the other −5.90°. It is reasonable that these molecules, being so similar, can rotate light by the same amount. The molecules are mirror images, and so are their properties: the mirror image of a clockwise rotation is a counterclockwise rotation—and of exactly the same *magnitude.*

**Enantiomers have identical chemical properties except toward optically active reagents**. The two lactic acids are not only acids, but acids of exactly the same strength; that is, dissolved in water at the same concentration, both ionize to exactly the same degree. The two 2-methyl-1-butanols not only form the same products—*alkenes* on treatment with hot sulfuric acid, *alkyl bromides* on treatment with HBr, *esters* on treatment with acetic acid—but also form them at exactly the same rate. We can see why this must be so: the atoms undergoing attack in each case are influenced in their reactivity by exactly the same combination of substituents. The reagent approaching either kind of molecule encounters the same environment, except, of course, that one environment is the mirror image of the other.

In the special case of a reagent that is itself optically active, on the other hand, the influences exerted on the reagent are *not* identical in the attack on the two enantiomers, and reaction rates will be different—so different, in some cases, that reaction with one isomer does not take place at all. In biological systems, for example, such stereochemical specificity is the rule rather than the exception, since the all-important catalysts, *enzymes*, and most of the compounds they work on, are optically active. The sugar (+)-glucose plays a unique role in animal metabolism and is the basis of a multimillion-dollar fermentation industry; yet (−)-glucose is neither metabolized by animals nor fermented by yeasts. When the mold *Penicillium glaucum* feeds on a mixture of enantiomeric tartaric acids, it consumes only the (+) enantiomer and leaves (−)-tartaric acid behind. The hormonal activity of (−)-adrenaline is many times that of its enantiomer; only one stereoisomer of chloromycetin is an antibiotic. (+)-Ephedrine not only has no activity as a drug, but actually interferes with the action of its enantiomer. Among amino acids, only one asparagine and one leucine are sweet, and only one glutamic acid enhances the flavor of food. It is (−)-carvone that gives oil of spearmint its characteristic odor; yet the enantiomeric (+)-carvone is the essence of caraway.

Consider, as a crude analogy, a right and left hand of equal strength (the enantiomers) hammering a nail (an optically inactive reagent) or, alternatively, inserting a right-handed screw (an optically active reagent). Hammering requires exactly corresponding sets of muscles in the two hands, and can be done at identical rates. Inserting the screw uses different sets of muscles: the right thumb pushes, for example, whereas the left thumb pulls.

Or, let us consider reactivity in the most precise way we know: by the transition state approach.

Take first the reactions of two enantiomers with an optically inactive reagent. The reactants in both cases are of exactly the same energy: one enantiomer plus the reagent, and the other enantiomer plus the same reagent. The two transition states for the reactions are mirror images (they are enantiomeric), and hence are of exactly the same energy, too. Therefore, the energy differences between reactants and transition states—the $E_{\text{act}}$ values—are identical, and so are the rates of reaction.

Now take the reactions of two enantiomers with an optically *active* reagent. Again the reactants are of the same energy. The two transition states, however, are *not* mirror images of each other (they are diastereomeric), and hence are of *different* energies; the $E_{\text{act}}$ values are different, and so are the rates of reaction.

The principle underlying all this is: enantiomers show different properties—physical or chemical—*only in a chiral medium*. Polarized light provides such a medium, and in it enantiomers differ in a physical property: direction of the rotation of the light. They may also differ in solubility in an optically active solvent, or in adsorption on an optically active surface. For enantiomers to react at different rates, the necessary chiral medium can be provided in a number of ways: by an optically active reagent, by a chiral solvent or the chiral surface of a catalyst; even—for some light-catalysed reactions—by irradiation with circularly polarized light. For simplicity, we shall often use the term "optically active reagent" or "chiral reagent" in speaking of reaction under any of these chiral conditions. We shall use the term "optically inactive reagent" or "achirai reagent" or even "ordinary conditions" in speaking of reaction in the absence of a chiral medium.

## 5AII.9 Racemic modification and resolution

*A mixture of equal parts of enantiomers is called a* **racemic modification**. *A racemic modification is optically inactive*: when enantiomers are mixed together, the rotation caused by a molecule of one isomer is exactly canceled by an equal and opposite rotation caused by a molecule of its enantiomer.

The prefix ± is used to specify the racemic nature of the particular sample, as, for example, (±)-lactic acid or (±)-2-methyl-l-butanol.

It is useful to compare a racemic modification with a compound whose molecules are superimposable on their mirror images, that is, with an achiral compound. They are both optically inactive, and for exactly the same reason. Because of the random distribution of the large number of molecules, for every molecule that the light encounters there is a second molecule, a mirror image of the first, aligned just right to cancel the effect of the first one. In a racemic modification this second molecule happens to be an isomer of the first; for an achiral compound it is not an isomer, but another, identical molecule.

(For an optically active substance uncontaminated by its enantiomer, we have seen, such cancellation of rotation cannot occur since no other molecule can serve as the mirror image of another, no matter how random the distribution.)

**Problem 5AII.3** To confirm the statements of the three preceding paragraphs, make models of: (a) a pair of enantiomers, for example, CHClBrI; (b) a pair of identical achiral molecules, for example, $CH_2ClBr$; (c) a pair of identical chiral molecules, for example, CHClBrI. (d) Which pairs are mirror images?

The identity of most physical properties of enantiomers has one consequence of great practical significance. They cannot be separated by ordinary methods: not by fractional distillation, because their boiling points are identical; not by fractional crystallization, because their solubilities in a given solvent are identical (unless the solvent is optically active); not by chromatography, because they are held equally strongly on a given adsorbent (unless it is optically active). The separation of a racemic modification into enantiomers—the *resolution* of a racemic modification—is therefore a special kind of job, and requires a special kind of approach.

The first resolution was, of course, the one Pasteur carried out with his hand lens and tweezers. But this method can almost never be used, since racemic modifications seldom form mixtures of crystals recognizable as mirror images. Indeed, even sodium ammonium tartrate does not, unless it crystallizes at a temperature below 28 °C. Thus, partial credit for *Pasteur's discovery* has been given to the cool Persian climate—and, of course, to the availability of tartaric acid from the wine makers of France.

The method of resolution nearly always used—the one also discovered by Pasteur—involves the use of optically active reagents.

Although, chiefly known for his great work in bacteriology and medicine, Pasteur was by training a chemist, and his work in chemistry alone would have earned him a position as an outstanding scientist.

So far in this chapter, we have discussed the reactions of chiral compounds only with optically inactive reagents. Now let us turn to reactions with optically *active* reagents, and examine one of their most useful applications: **resolution of a racemic modification**, that is, *the separation of a racemic modification into enantiomers*.

We know that, when optically inactive reactants form a chiral compound, the product is the racemic modification. We know that the enantiomers making up a racemic modification have identical physical properties (except for direction of rotation of polarized light), and hence cannot be separated by the usual methods of fractional distillation or fractional crystallization. Yet throughout this book are frequent references to experiments carried out using optically active compounds like (+)-*sec*-butyl alcohol, (−)-2-bromooctane, (−)-$\alpha$-phenylethyl chloride, (+)-$\alpha$-phenylpropionamide. How are such optically active compounds obtained?

Some optically active compounds are obtained from natural sources, since living organisms usually produce only one enantiomer of a pair. Thus only (−)-2-methyl-1-butanol is formed in the yeast fermentation of starches, and only (+)-lactic acid, $CH_3CHOHCOOH$, in the contraction of muscles; only (−)-malic acid, $HOOCCH_2CHOHCOOH$, is obtained from fruit juices, and only (−)-quinine from the bark of the cinchona tree. Indeed, we deal with optically active substances to an extent that we may not realize. We eat optically active bread and optically active meat, live in houses, wear clothes, and read books made of optically active cellulose. The proteins that make up our muscles and other tissues, the glycogen in our liver and glucose in our blood, the enzymes and hormones that enable us to grow and that regulate our bodily processes—all these are optically active. Naturally occurring compounds are optically active because the enzymes that bring about their formation—and often the raw materials from which they are made—are themselves optically active. As to the origin of the optically active enzymes, we can only speculate.

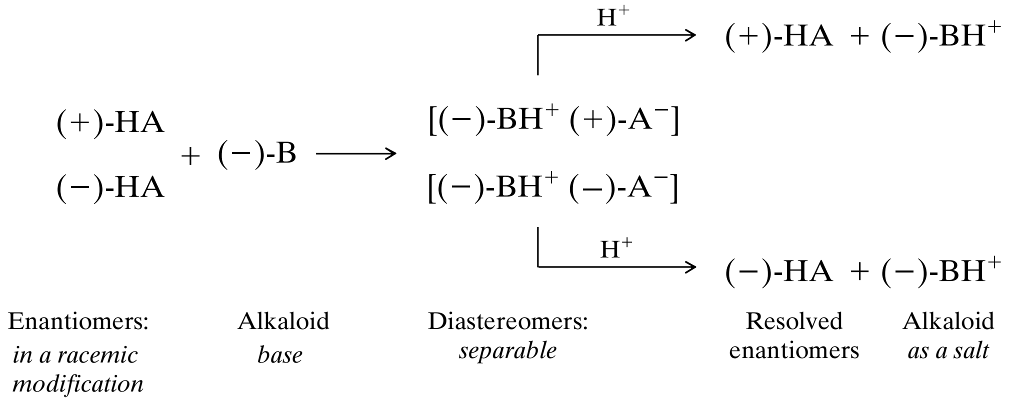
Amino acids, the units from which proteins are made, have been reported present in meteorites, but in such tiny amounts that the speculation has been made that "what appears to be the pitter-patter of heavenly feet is probably instead the print of an earthly thumb". Part of the evidence that the amino acids found in a meteorite by Cyril Ponnamperuma are really extraterrestrial in origin is that they are optically *inactive*—not optically active as earthly contaminants from biological sources would be.

From these naturally occurring compounds, other optically active compounds can be made. We have already seen, for example, how (−)-2-methyl-l-butanol can be converted without loss of configuration into the corresponding chloride or acid; these optically active compounds can, in turn, be converted into many others.

Most optically active compounds are obtained by the resolution of a racemic modification, that is, by a separation of a racemic modification into enantiomers. Most such resolutions are accomplished through the use of reagents that are themselves optically active; these reagents are generally obtained from natural sources.

The majority of resolutions that have been carried out depend upon the reaction of organic bases with organic acids to yield salts. Let us suppose, for example, that we have prepared the racemic acid, (±)-HA. Now, there are isolated from various plants very complicated bases called *alkaloids* (that is, *alkali-like*), among which are cocaine, morphine, strychnine, and quinine. Most alkaloids are produced by plants in only one of two possible enantiomeric forms, and hence they are optically active. Let us take one of these optically active bases, say a levorotatory one, (−)-B, and mix it with our racemic acid (±)-HA. The acid is present in two configurations, but the base is present in only one configuration; there will result, therefore, crystals of two different salts, $[(-)\text{-BH}^+ (+)\text{-A}^-]$ and $[(-)\text{-BH}^+ (-)\text{-A}^-]$.

What is the relationship between these two salts? They are not superimposable, since the acid portions are not superimposable. They are not mirror images, since the base portions are not mirror images. The salts are stereoisomers that are not enantiomers, and therefore are *diastereomers.*



These diastereomeric salts have, of course, different physical properties, including solubility in a given solvent. They can therefore be separated by fractional crystallization. Once the two salts are separated, optically active acid can be recovered from each salt by addition of strong mineral acid, which displaces the weaker organic acid. If the salt has been carefully purified by repeated crystallizations to remove all traces of its diastereomer, then the acid obtained from it is *optically pure*. Among the alkaloids commonly used for this purpose are (−)-brucine, (−)-quinine, (−)-strychnine, and (+)-cinchonine.

Resolution of organic bases is carried out by reversing the process just described: using naturally occurring optically active acids, (−)-malic acid, for example. Resolution of alcohols, which we shall find to be of special importance in synthesis, poses a special problem: since alcohols are neither appreciably basic nor acidic, they cannot be resolved by direct formation of salts. Yet they can be resolved by a rather ingenious adaptation of the method we have just described: one attaches to them an acidic "handle", which permits the formation of salts, and then when it is no longer needed can be removed.

Compounds other than organic bases, acids, or alcohols can also be resolved. Although the particular chemistry may differ from the salt formation just described, the principle remains the same: **a racemic modification is converted by an optically active reagent into a mixture of diastereomers which can then be separated**.

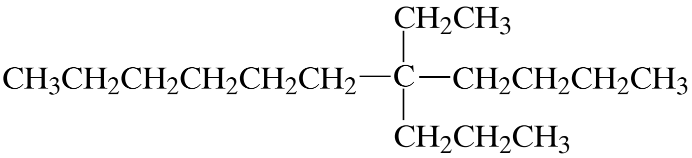
## 5AII.10 Optical activity: a closer look

We have seen that, like enantiomerism, optical activity results from—and *only* from—chirality: the non-superimposability of certain molecules on their mirror images. Whenever we observe (molecular) optical activity, we know we are dealing with chiral molecules.

Is the reverse true? Whenever we deal with chiral molecules—with compounds that exist as enantiomers—must we always observe optical activity? *No*. We have just seen that a 50:50 mixture of enantiomers is optically inactive. Clearly, if we are to *observe* optical activity, the material we are dealing with must contain an *excess* of one enantiomer: enough of an excess that the net optical rotation can be detected by the particular polarimeter at hand.

Furthermore, this excess of one enantiomer must persist long enough for the optical activity to be measured. If the enantiomers are rapidly interconverted, then before we could measure the optical activity due to one enantiomer, it would be converted into an equilibrium mixture, which—since enantiomers are of exactly the same stability—must be a 50:50 mixture and optically inactive.

Even if all these conditions are met, the magnitude—and hence the detectability—of the optical rotation depends on the structure of the particular molecule concerned. In compound I, for example, the four groups attached to the chiral center differ only in chain length.



$$CH_3CH_2CH_2CH_2CH_2CH_2-\overset{\displaystyle CH_2CH_3}{\underset{\displaystyle CH_2CH_2CH_3}{C}}-CH_2CH_2CH_2CH_3$$

I

Ethyl-*n*-propyl-*n*-butyl-*n*-hexylmethane

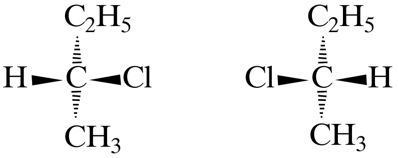
It has been calculated that this compound should have the tiny specific rotation of 0.000 01°—far below the limits of detection by any existing polarimeter. In 1965, enantiomerically pure samples of both enantiomers of I were prepared, and each was found to be optically inactive.

At our present level of study, the matter of speed of interconversion will give us no particular trouble. Nearly all the chiral molecules we encounter in this book lie at either of two extremes, which we shall easily recognize: (a) molecules, like those described in this chapter, which owe their chirality to chiral centers; here interconversion of enantiomers (*configurational* enantiomers) is so slow—because bonds have to be broken—that we need not concern ourselves at all about interconversion; (b) molecules whose enantiomeric forms (*conformational* enantiomers) are interconvertible simply by rotations about single bonds; here—for the compounds we shall encounter—interconversion is so fast that ordinarily we need not concern ourselves at all about the existence of the enantiomers.

## 5AII.11 Assignment of configuration

*The arrangement of atoms that characterizes a particular stereoisomer is called its* **configuration**.

Using the test of superimposability, we conclude, for example, that there are two stereoisomeric *sec*-butyl chlorides; their *configurations* are I and II. Let us say



I II

*sec*-Butyl chloride

that, by methods we shall take up later, we have obtained in the laboratory samples of two compounds of formula $C_2H_5CHClCH_3$. We find that one rotates the plane of polarized light to the right, and the other to the left; we put them into two bottles, one labeled "(+)-*sec*-butyl chloride" and the other "(−)-*sec*-butyl chloride".

We have made two models to represent the two configurations of this chloride. We have isolated two isomeric compounds of the proper formula. Now the question arises, which configuration does each isomer have? Does the (+) isomer, say, have configuration I or configuration II? How do we know which structural formula, I or II, to draw on the label of each bottle? That is to say, how do we *assign configuration*?

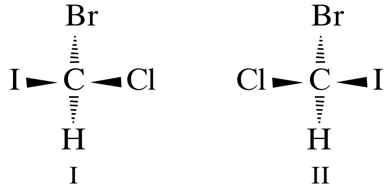
Until 1951 the question of configuration could not be answered in an absolute sense for any optically active compound. But in that year J. M. Bijvoet reported that, using a special kind of X-ray analysis (the method of anomalous scattering), he had determined the actual arrangement in space of the atoms of an optically active compound. The compound was a salt of (+)-tartaric acid, the same acid that—almost exactly 100 years before—had led Pasteur to his discovery of optical isomerism. Over the years prior to 1951, the relationships between the configuration of (+)-tartaric acid and the configurations of hundreds of optically active compounds had been worked out (by methods that we shall take up later); when the configuration of (+)-tartaric acid became known, these other configurations, too, immediately became known. (In the case of the *sec*-butyl chlorides, for example, the (−) isomer is known to have configuration I, and the (+) isomer configuration II.)

## 5AII.12 Specification of configuration: *R* and *S*

Now, a further problem arises. How can we specify a particular configuration in some simpler, more convenient way than by always having to draw its picture? The most generally useful way yet suggested is the use of the prefixes *R* and *S*. According to a procedure proposed by R. S. Cahn, Sir Christopher Ingold, and V. Prelog, two steps are involved.

*Step 1.* Following a set of *sequence rules*, we assign a sequence of priority to the four atoms or groups of atoms—that is, the four *ligands*—attached to the chiral center.

In the case of CHClBrI, for example, the four atoms attached to the chiral center are all different and priority depends simply on atomic number, the atom of higher number having higher priority. Thus I, Br, Cl, H.

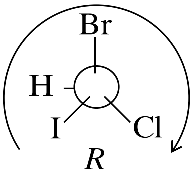


I II

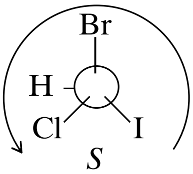
Bromochloroiodomethane

*Step 2.* We visualize the molecule oriented so that the ligand of *lowest* priority is directed *away* from us, and observe the arrangement of the remaining ligands. If, in proceeding from the ligand of highest priority to the ligand of second priority and thence to the third, our eye travels in a clockwise direction, the configuration is specified ***R*** (Latin: *rectus*, right); if counterclockwise, the configuration is specified ***S*** (Latin: *sinister*, left).

Thus, configurations I and II are viewed like this:



*R*



*S*

and are specified *R* and *S*, respectively.

A complete name for an optically active compound reveals—if they are known—both configuration and direction of rotation, as, for example, (*S*)-(+)-*sec*-butyl chloride. A racemic modification can be specified by the prefix *RS*, as, for example, (*RS*)-*sec*-butyl chloride.

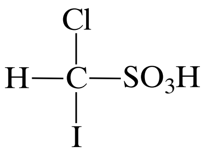
We must not, of course, confuse the direction of optical rotation of a compound—a physical property of a real substance, like melting point or boiling point—with the direction in which our eye happens to travel when we imagine a molecule held in an arbitrary manner. So far as we are concerned, unless we happen to know what has been established experimentally for a specific compound, we have no idea whether (+) or (−) rotation is associated with the *R* or the *S* configuration.

## 5AII.13 Sequence rules

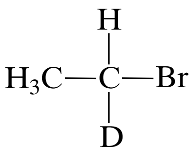
For ease of reference and for convenience in reviewing, we shall set down here those sequence rules we shall have need of. You should study Rules 1 and 2 now, and Rule 3 later when the need for it arises.

**Sequence Rule 1.** If the four atoms attached to the chiral center are all different, priority depends on atomic number, with the atom of higher atomic number getting higher priority. If two atoms are isotopes of the same element, the atom of higher mass number has the higher priority.

For example, in chloroiodomethanesulfonic acid the sequence is I, Cl, S, H; in $\alpha$-deuterioethyl bromide it is Br, C, D, H.


$$\mathrm{H{-}\overset{\displaystyle Cl}{\underset{\displaystyle I}{C}}{-}SO_3H}$$

Chloroiodomethanesulfonic acid

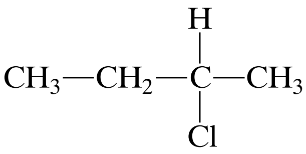

$$\mathrm{H_3C{-}\overset{\displaystyle H}{\underset{\displaystyle D}{C}}{-}Br}$$

$\alpha$-Deuterioethyl bromide

**Problem 5AII.4** Make models and then draw both wedge formulas and cross formulas for the enantiomers of: (a) chloroiodomethanesulfonic acid and (b) $\alpha$-deuterioethyl bromide. Label each as *R* or *S*.

**Sequence Rule 2.** If the relative priority of two groups cannot be decided by Rule 1, it shall be determined by a similar comparison of the next atoms in the groups (and so on, if necessary, working outward from the chiral center). That is to say, if two atoms attached to the chiral center are the same, we compare the atoms attached to each of these first atoms.

For example, take *sec*-butyl chloride, in which two of the atoms attached to the chiral center are themselves carbon. In $CH_3$ the second atoms are H, H, H; in $C_2H_5$

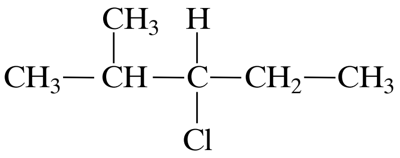


$$CH_3{-}CH_2{-}\underset{Cl}{\overset{H}{C}}{-}CH_3$$

*sec*-Butyl chloride

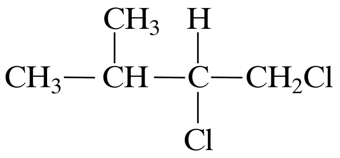
they are C, H, H. Since carbon has a higher atomic number than hydrogen, $C_2H_5$ has the higher priority. A complete sequence of priority for *sec*-butyl chloride is therefore Cl, $C_2H_5$, $CH_3$, H.

In 3-chloro-2-methylpentane the C, C, H of isopropyl takes priority over the C, H, H of ethyl, and the complete sequence of priority is Cl, isopropyl, ethyl, H.



$$CH_3{-}\overset{CH_3}{CH}{-}\underset{Cl}{\overset{H}{C}}{-}CH_2{-}CH_3$$

3-Chloro-2-methylpentane



$$CH_3{-}\overset{CH_3}{CH}{-}\underset{Cl}{\overset{H}{C}}{-}CH_2Cl$$

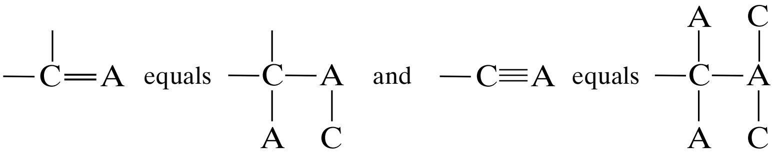
1,2-Dichloro-3-methylbutane

In 1,2-dichloro-3-methylbutane the Cl, H, H of $CH_2Cl$ takes priority over the C, C, H of isopropyl. Chlorine has a higher atomic number than carbon, and the fact that there are *two* C's and only *one* CI does not matter. (One higher number is worth more than two—or three—of a lower number.)

**Problem 5AII.5** Into what sequence of priority must these alkyl groups always fall: $CH_3$,1°, 2°, 3°?

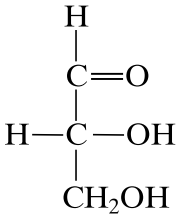
**Sequence Rule 3.** (*You should defer study of this rule until you need it.*)

Where there is a double or triple bond, both atoms are considered to be duplicated or triplicated. Thus



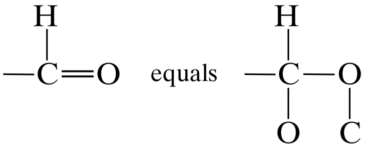
$$-\overset{|}{C}{=}A \text{ equals } -\underset{A}{\overset{|}{C}}{-}\underset{C}{A} \text{ and } -C{\equiv}A \text{ equals } -\underset{A}{\overset{A}{C}}{-}\underset{C}{\overset{C}{A}}$$

For example, in glyceraldehyde the OH group has the highest priority of all,



$$\begin{array}{c} H \\ | \\ C{=}O \\ | \\ H{-}C{-}OH \\ | \\ CH_2OH \end{array}$$

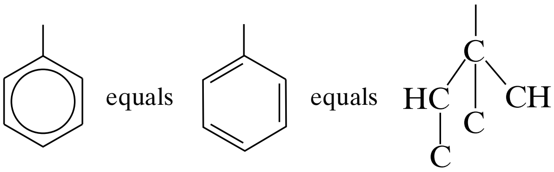
Glyceraldehyde



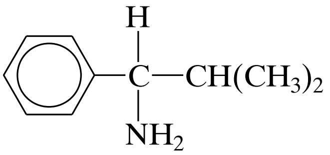
$$-\overset{H}{C}{=}O \text{ equals } -\underset{O}{\overset{H}{C}}{-}\underset{C}{O}$$

and the O, O, H of —CHO takes priority over the O, H, H of —$CH_2OH$. The complete sequence is then —OH, —CHO, —$CH_2OH$, —H.

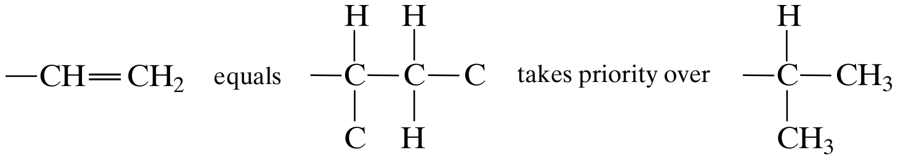
The phenyl group, $C_6H_5$—, is handled as though it had one of the Kekulé structures:



In 1-amino-2-methyl-1-phenylpropane, for example, the C, C, C of phenyl takes priority over the C, C, H of isopropyl, but not over N, which has a higher atomic number. The entire sequence is then $NH_2$, $C_6H_5$, $C_3H_7$, H.



The vinyl group, $CH_2{=}CH$—, takes priority over isopropyl.



$$-CH{=}CH_2 \quad \text{equals} \quad -\underset{C}{\overset{H}{C}}-\underset{H}{\overset{H}{C}}-C \quad \text{takes priority over} \quad -\underset{CH_3}{\overset{H}{C}}-CH_3$$

Following the "senior" branch, —$CH_2$—C, we arrive at C in vinyl as compared with H in the —$CH_2$—H of isopropyl.

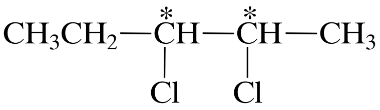
**Problem 5AII.6** Draw and specify as *R* or *S* the enantiomers (if any) of:

(a) 3-chloro-1-pentene
(b) 3-chloro-4-methyl-1-pentene
(c) $HOOCCH_2CHOHCOOH$, malic acid
(d) $C_6H_5CH(CH_3)NH_2$
(e) methylethyl-*n*-propylisopropylmethane
(f) $C_6H_5CHOHCOOH$, mandelic acid
(g) $CH_3CH(NH_2)COOH$, alanine

## 5AII.14 Diastereomers

Next, we must learn what stereoisomers are possible for compounds whose molecules contain, not just one, but *more than one* chiral center.

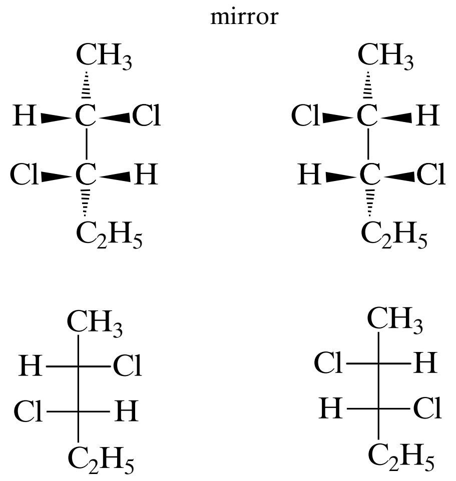
Let us start with 2,3-dichloropentane. This compound contains two chiral centers, C–2 and C–3. (What four groups are attached to each of these carbon atoms?) How many stereoisomers are possible?



$$CH_3CH_2-\underset{Cl}{\overset{*}{C}}H-\underset{Cl}{\overset{*}{C}}H-CH_3$$

2,3-Dichloropentane

Using models, let us first make structure I and its mirror image II, and see if these are superimposable. We find that I and II are not superimposable, and hence must be enantiomers. (As before, we may represent the structures by wedge formulas, and mentally try to superimpose these. Or, we may use the simple "cross" representations, being careful, as before, not to remove the drawings from the plane of the paper or blackboard.)

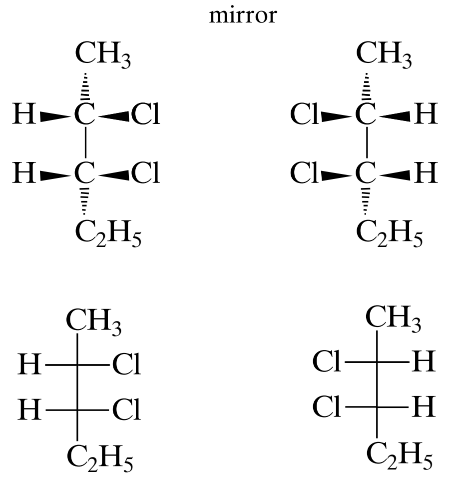


I II

*Not superimposable*
Enantiomers

Next, we try to interconvert I and II by rotations about carbon—carbon bonds. We find that they are not interconvertible in this way, and hence each of them is capable of retaining its identity and, if separated from its mirror image, of showing optical activity.

Are there any other stereoisomers of 2,3-dichloropentane? We can make structure III, which we find to be non-superimposable on either I or II; it is not, of course, the mirror image of either. What is the relationship between III and I? Between III and II? They are stereoisomers but not enantiomers. *Stereoisomers that are not*



III IV

*Not superimposable*
Enantiomers

*mirror images of each other are called* **diastereomers**. Compound III is a diastereomer of I, and similarly of II.

Now, is III chiral? Using models, we make its mirror image, structure IV, and find that this is not superimposable on (or interconvertible with) III. Structures III and IV represent a second pair of enantiomers. Like III, compound IV is a diastereomer of I and of II.

How do the properties of diastereomers compare?

**Diastereomers have similar chemical properties**, since they are members of the same family. Their chemical properties are *not identical*, however. In the reaction of two diastereomers with a given reagent, neither the two sets of reactants nor the two transition states are mirror images, and hence—except by sheer coincidence—will not be of equal energies. The $E_{\text{act}}$ values will be different and so will the rates of reaction.

**Diastereomers have different physical properties**: different melting points, boiling points, solubilities in a given solvent, densities, refractive indexes, and so on. Diastereomers differ in specific rotation; they may have the same or opposite signs of rotation, or some may be inactive.

As a result of their differences in boiling point and in solubility, they can, in principle at least, be separated from each other by fractional distillation or fractional crystallization; as a result of differences in molecular shape and polarity, they differ in adsorption, and can be separated by chromatography.

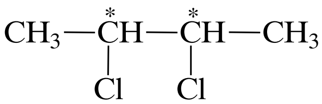
Given a mixture of all four stereoisomeric 2,3-dichloropentanes, we could separate it, by distillation, for example, into two fractions but no further. One fraction would be the racemic modification of I plus II; the other fraction would be the racemic modification of III plus IV. Further separation would require *resolution* of the racemic modifications by use of optically active reagents.

Thus the presence of two chiral centers can lead to the existence of as many as four stereoisomers. For compounds containing three chiral centers, there could be as many as eight stereoisomers; for compounds containing four chiral centers, there could be as many as sixteen stereoisomers, and so on. The maximum number of stereoisomers that can exist is equal to $2^n$, where $n$ is the number of chiral centers. (In any case where *meso* compounds exist, as discussed in the following section, there will be fewer than this maximum number.)

The sugar (+)-glucose is by far the most important and abundant of the carbohydrates. It is the compound oxidized in our cells to provide energy; it is the building block making up starch, from which our food ultimately comes, and cellulose, the framework of the plants that synthesize this starch. Glucose contains five chiral centers; this could— and does—give rise to $2^5$ or 32 stereoisomers. Of these only *one*, $\alpha$-D-glucose, is the unit of starch, and only one, $\beta$-D-glucose, is the unit of cellulose.

## 5AII.15 *Meso* structures

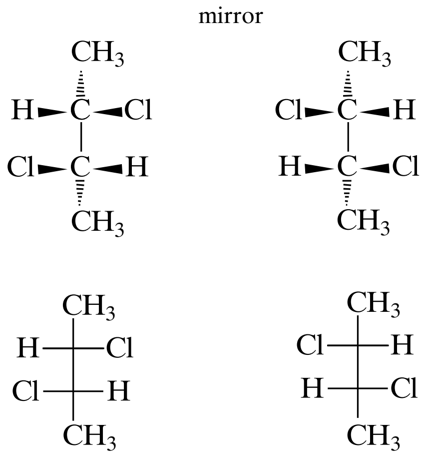
Now let us look at 2,3-dichlorobutane, which also has two chiral centers. Does this compound, too, exist in four stereoisomeric forms?



$$\mathrm{CH_3{-}\underset{\underset{\textstyle Cl}{|}}{\overset{*}{C}H}{-}\underset{\underset{\textstyle Cl}{|}}{\overset{*}{C}H}{-}CH_3}$$

2,3-Dichlorobutane

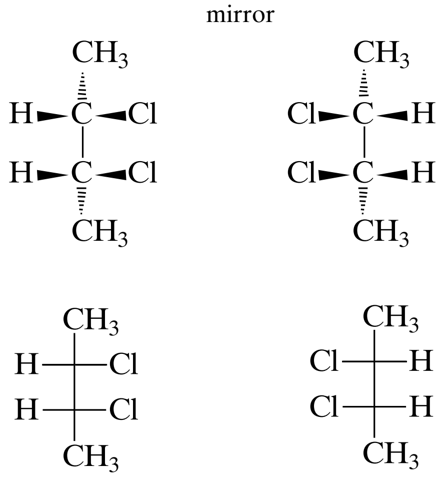
Using models as before, we arrive first at the two structures V and VI. These are mirror images that are not superimposable or interconvertible; they are therefore enantiomers, and each should be capable of optical activity.



V VI

*Not superimposable*
Enantiomers

Next, we make VII, which we find to be a diastereomer of V and of VI. We now have three stereoisomers; is there a fourth? *No*. If we make VIII, the mirror image of VII, we find the two to be superimposable; turned end-for-end, VII coincides in every respect with VIII. In spite of its chiral centers, VII is not chiral. It cannot exist in two enantiomeric forms, and it cannot be optically active. It is called a *meso* compound.

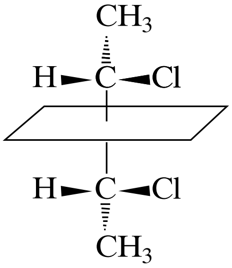


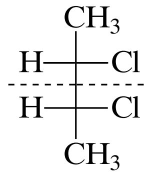
VII VIII

*Superimposable*
A *meso* compound

**A meso compound** *is one whose molecules are superimposable on their mirror images even though they contain chiral centers.* A *meso* compound is optically inactive for the same reason as any other compound whose molecules are achiral: the rotation caused by any one molecule is canceled by an equal and opposite rotation caused by another molecule that is the mirror image of the first.

We can often recognize a *meso* structure on sight by the fact that (in at least one of its conformations) one half of the molecule is the mirror image of the other half. This can be seen for *meso*-2,3-dichlorobutane by imagining the molecule to be





cut by a plane lying where the dotted line is drawn. The molecule has *a plane of symmetry*, and cannot be chiral. (*Caution*: If we do not see a plane of symmetry, however, this does not necessarily mean that the molecule is chiral.)

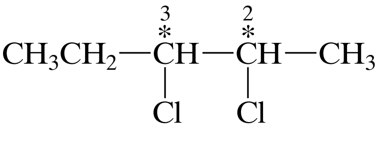
**Problem 5AII.7** Draw stereochemical formulas for all the possible stereoisomers of the following compounds. Label pairs of enantiomers, and *meso* compounds. Tell which isomers, if separated from all other stereoisomers, will be optically active. Pick out several examples of diastereomers.

(a) 1,2-dibromopropane
(b) 3,4-dibromo-3,4-dimethylhexane
(c) 2,4-dibromopentane
(d) 2,3,4-tribromohexane
(e) 1,2,3,4-tetrabromobutane
(f) 2-bromo-3-chlorobutane
(g) 1-chloro-2-methylbutane
(h) 1,3-dichloro-2-methylbutane

## 5AII.16 Specification of configuration: more than one chiral center

Now, how do we specify the configuration of compounds which, like these, contain more than one chiral center? They present no special problem; we simply specify the configuration about *each* of the chiral centers, and by use of numbers tell which specification refers to which carbon.

Consider, for example, the 2,3-dichloropentanes. We take each of the chiral centers, C–2 and C–3, in turn—ignoring for the moment the existence of the other—



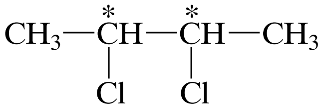
$$\mathrm{CH_3CH_2-\underset{\displaystyle Cl}{\underset{|}{\overset{\overset{3}{*}}{C}H}}-\underset{\displaystyle Cl}{\underset{|}{\overset{\overset{2}{*}}{C}H}}-CH_3}$$

2,3-Dichloropentane

and follow the steps, use the Sequence Rules. In order of priority, the four ligands attached to C–2 are Cl, $CH_3CH_2CHCl$—, $CH_3$, H. On C–3 they are Cl, $CH_3CHCl$—, $CH_3CH_2$—, H. (Why is $CH_3CHCl$—"senior" to $CH_3CH_2$—?)

Taking in our hands—or in our mind's eye—a model of the particular stereoisomer we are interested in, we focus our attention first on C–2 (ignoring C–3), and then on C–3 (ignoring C–2). Stereoisomer I, for example, we specify as (2*S*,3*S*)-2, 3-dichloropentane. Similarly, II is (2*R*,3*R*), III is (2*S*,3*R*), and IV is (2*R*,3*S*). These specifications help us to analyse the relationships among the stereoisomers. As enantiomers, I and II have opposite—that is, mirror-image—configurations about both chiral centers: 2*S*,3*S* and 2*R*,3*R*. As diastereomers, I and III have opposite configurations about one chiral center, and the same configuration about the other: 2*S*,3*S* and 2*S*,3*R*.

We would handle 2,3-dichlorobutane in exactly the same way. Here it happens that the two chiral centers occupy equivalent positions along the chain, and so it is



$$\mathrm{CH_3{-}\underset{\underset{Cl}{|}}{\overset{*}{C}}H{-}\underset{\underset{Cl}{|}}{\overset{*}{C}}H{-}CH_3}$$

2,3-Dichlorobutane

not necessary to use numbers in the specifications. Enantiomers V and VI are specified (*S*,*S*)- and (*R*,*R*)-2,3-dichlorobutane, respectively. The *meso* isomer, VII, can, of course, be specified as either (*R*,*S*)-or (*S*,*S*)-2,3-dichlorobutane—the absence of numbers emphasizing the equivalence of the two specifications. The mirror-image relationship between the two ends of this molecule is consistent with the *opposite* designations of *R* and *S* for the two chiral centers. (Not all *R*,*S* isomers, of course, are *meso* structures—only those whose two halves are chemically equivalent.)

**Problem 5AII.8** Give the *R/S* specification for each stereoisomer you drew in Problem 5AII.7.

## 5AII.17 Conformational isomers

We saw that there are several different staggered conformations of *n*-butane, each of which lies at the bottom of an energy valley—at an *energy minimum*—separated from the others by energy hills. *Different conformations corresponding to energy minima are called* **conformational isomers**, *or* **conformers**. Since conformational isomers differ from each other only in the way their atoms are oriented in space, they, too, are stereoisomers. Like stereoisomers of any kind, a pair of con-formers can either be mirror images of each other or not.

*n*-Butane exists as three conformational isomers, one *anti* and two *gauche*. The *gauche* conformers are mirror images of each other, and hence are (conformational) enantiomers. Conformers that are *not* mirror images of each other, and hence are (conformational) diastereomers.

Although the barrier to rotation in *n*-butane is a little higher than in ethane, it is still low enough that—at ordinary temperatures, at least—interconversion of conformers is easy and rapid. Equilibrium exists, and favors a higher population of the more stable *anti* conformer; the populations of the two *gauche* conformers—mirror images, and hence of exactly equal stability—are, of course, equal. Put differently, any given molecule spends the greater part of its time as the *anti* conformer, and divides the smaller part equally between the two *gauche* conformers. As a result of the rapid interconversion, these isomers cannot be separated.

Easy interconversion is characteristic of nearly every set of conformational isomers, and is the quality in which such isomers differ most from the kind of stereoisomers we have encountered so far in this chapter. This difference in interconvertibility is due to a difference in height of the energy barrier separating stereoisomers, which is, in turn, due to a difference in origin of the barrier. By definition, interconversion of conformational isomers involves rotation about single bonds; the rotational barrier is—in most cases—a very low one and interconversion is easy and fast. The other kind of stereoisomers, *configurational isomers*, or *inversional isomers*, differ from one another in configuration about a chiral center. Interconversion here involves the breaking of a covalent bond, for which there is a very high barrier: 50 kcal/mol or more. Interconversion is difficult, and—unless one deliberately provides conditions to bring it about—is negligibly slow.

Interconvertibility of stereoisomers is of great practical significance because it limits their *isolability*. Hard-to-interconvert stereoisomers can be separated (with special methods, of course, for resolution of enantiomers) and studied individually; among other things, their optical activity can be measured. Easy-to-interconvert isomers cannot be separated, and single isolated isomers cannot be studied; optical activity cannot be observed, since any chiral molecules are present only as non-resolvable racemic modifications.

Our general approach to stereoisomers involves, then, two stages: first, we test the *superimposability* of possible isomeric structures, and then we test their *interconvertibility*. Both tests are best carried out with models. We make models of the two molecules and, without allowing any rotations about single bonds, we try to superimpose them: if they cannot be superimposed, they represent isomers. Next, we allow the models all possible rotations about single bonds, and repeatedly try to superimpose them: if they still cannot be superimposed, they are non-interconvertible, and represent *configurational isomers*; but if they can be superimposed after rotation, they are interconvertible and represent *conformational isomers*.

In dealing with those aspects of stereochemistry that depend on isolation of stereoisomers—isomer number or optical activity, for example, or study of the reactions of a single stereoisomer—we can ignore the existence of easy-to-interconvert isomers, which means *most* conformational isomers. For convenience the following "ground rule" will hold for discussions and problems in this book: unless specifically indicated otherwise, *the terms "stereoisomers", "enantiomers", and "diastereomers" will refer only to configurational isomers, including geometric isomers*, and will exclude conformational isomers. The latter will be referred to as "conformational isomers", "conformers", "conformational enantiomers", and "conformational diastereomers".

There is no sharp boundary between easy-to-interconvert and hard-to-interconvert stereoisomers. Although we can be sure that interconversion of configurational isomers will be hard, we cannot be sure that interconversion of conformational isomers will be easy. Depending upon the size and nature of substituents, the barrier to rotation about single bonds can be of any height, from the low one in ethane to one comparable to that for breaking a covalent bond. Some conformational isomers exist that are readily isolated, kept, and studied; indeed, study of such isomers (*atropisomers*) makes up a large and extremely important part of stereochemistry, one which, unfortunately, we shall not be able to take up in this beginning book. Other conformational isomers exist that can be isolated, not at ordinary temperatures, but at lower temperatures, where the average collision energy is lower. The conformational isomers that we shall encounter in this book, however, have low rotational barriers, and we may assume—until we learn otherwise—that when we classify stereoisomers as configurational or conformational, we at the same time classify them as hard to interconvert or easy to interconvert.

**Problem 5AII.9** At low temperatures, where collision energies are small, two isomeric forms of the badly crowded $CHBr_2CHBr_2$ have been isolated by crystallization. (a) Give a formula or formulas (Newman projections) corresponding to each of the separable forms. (b) Which, if either, of the materials, as actually isolated at low temperatures, would be optically active? Explain.

## 5AII.18 Reactions involving stereoisomers

So far, our study of stereochemistry has been limited chiefly to finding out what the various kinds of stereoisomers are, how to predict their existence, and how to name and classify them. We have compared their properties, but only in a very general way.

Now let us go on from the *existence* of stereoisomers, and look at their *involvement* in chemical reactions: reactions in which stereoisomers are *formed*, and reactions in which stereoisomers are *consumed*; reactions in which the reagent is of the ordinary (that is, optically inactive) kind and those in which the reagent is optically active.

We shall take up:

(a) the conversion of an achiral molecule into a chiral molecule, with the generation of a chiral center;

(b) reactions of chiral molecules in which bonds to the chiral center are not broken, and see how such reactions can be used to relate the configuration of one compound to that of another;

(c) reactions of the kind in (b) in which a second chiral center is generated;

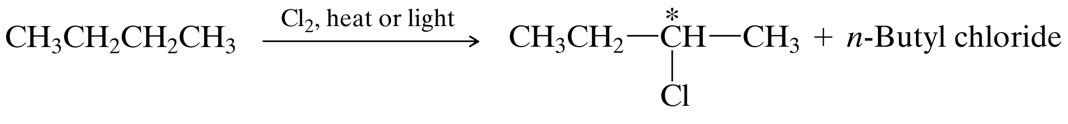
(d) reactions of chiral compounds with optically active reagents.

Then we shall examine the stereochemistry of a reaction we have already studied—free-radical halogenation of alkanes—and see how stereochemistry can be used to get information about reaction mechanism. In doing this, we shall take up:

(e) a reaction of a chiral compound in which a bond to a chiral center is broken.

## 5AII.19 Generation of a chiral center. Synthesis and optical activity

One of the products of chlorination of *n*-butane is the chiral compound, *sec*-butyl chloride.

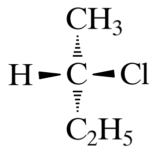


$$CH_3CH_2CH_2CH_3 \xrightarrow{Cl_2,\text{ heat or light}} CH_3CH_2{-}\underset{\underset{Cl}{|}}{\overset{*}{C}}H{-}CH_3 + n\text{-Butyl chloride}$$

*n*-Butane
*Achiral*

*sec*-Butyl chloride
*Chiral*

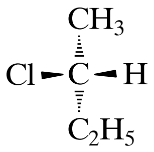
It can exist as two enantiomers, I and II, which are specified as *S* and *R*, respectively.



$\mathrm{H-\overset{CH_3}{\underset{C_2H_5}{C}}-Cl}$

I

(*S*)-(+)-*sec*-Butyl chloride



$\mathrm{Cl-\overset{CH_3}{\underset{C_2H_5}{C}}-H}$

II

(*R*)-(−)-*sec*-Butyl chloride

Each enantiomer should, of course, be optically active. Now, if we were to put the *sec*-butyl chloride actually prepared by the chlorination of *n*-butane into a polarimeter, would it rotate the plane of polarized light? The answer is *no*, because prepared as described it would consist of the racemic modification. The next question is: *why is the racemic modification formed*?

In the first step of the reaction, a chlorine atom abstracts hydrogen to yield hydrogen chloride and a *sec*-butyl free radical. The carbon that carries the odd electron in the free radical is $sp^2$-hybridized, and hence a part of the molecule is *flat*, the trigonal carbon and the three atoms attached to it lying in the same plane. In the second step, the free radical abstracts chlorine from a chlorine molecule to yield *sec*-butyl chloride. But chlorine may become attached to either face of the flat radical, and, depending upon which face, yield either of two products: *R* or *S* (see Fig. 5AII.4). Since the chance of attachment to one face is exactly the same as for attachment to the other face, the enantiomers are obtained in exactly equal amounts. The product is the racemic modification.

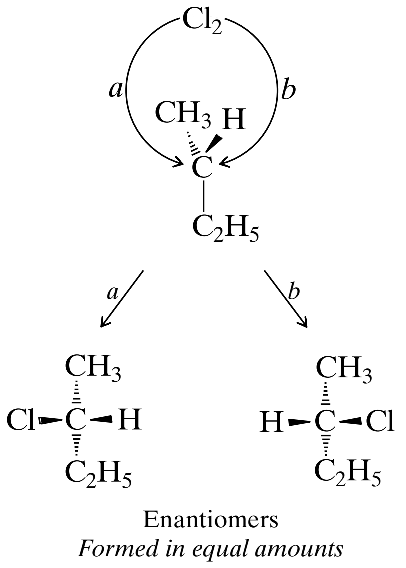


**Figure 5AII.4** Generation of a chiral center. Chlorine becomes attached to either face of the flat free radical, via (*a*) or (*b*), to give enantiomers, and in equal amounts.

If we were to apply the approach just illustrated to the synthesis of any compound whatsoever—and on the basis of any mechanism, correct or incorrect— we would arrive at the same conclusion: as long as neither the starting material nor the reagent (nor the environment) is optically active, we should obtain an optically inactive product. At some stage of the reaction sequence, there will be two alternative paths, one of which yields one enantiomer and the other the opposite enantiomer.

The two paths will always be equivalent, and selection between them *random*. The facts agree with these predictions. **Synthesis of chiral compounds from achiral reactants always yields the racemic modification**. This is simply one aspect of the more general rule: **optically inactive reactants yield optically inactive products**.

**Problem 5AII.10** Show in detail why racemic *sec*-butyl chloride would be obtained if: (a) the *sec*-butyl radical were not flat, but pyramidal; (b) chlorination did not involve a free *sec*-butyl radical at all, but proceeded by a mechanism in which a chlorine atom displaced a hydrogen atom, taking the position on the carbon atom formerly occupied by that hydrogen.

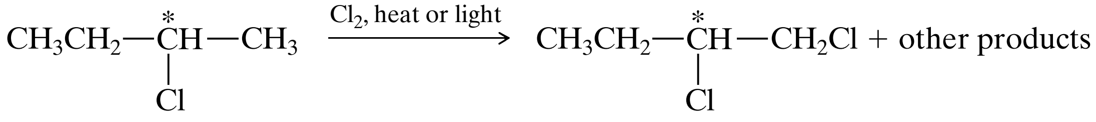
To purify the *sec*-butyl chloride obtained by chlorination of *n*-butane, we would carry out a fractional distillation. But since the enantiomeric *sec*-butyl chlorides have exactly the same boiling point, they cannot be separated, and are collected in the same distillation fraction. If recrystallization is attempted, there can again be no separation since their solubilities in every (optically inactive) solvent are identical. It is easy to see, then, that whenever a racemic modification is *formed* in a reaction, we will *isolate* (by ordinary methods) a racemic modification.

If an ordinary chemical synthesis yields a racemic modification, and if this cannot be separated by our usual methods of distillation, crystallization, etc., how do we know that the product obtained *is* a racemic modification? It is optically inactive; how do we know that it is actually made up of a mixture of two optically active substances? The separation of enantiomers (called *resolution*) can be accomplished by special methods; these involve the use of optically active reagents, and will be discussed later.

**Problem 5AII.11** Isopentane is allowed to undergo free-radical chlorination, and the reaction mixture is separated by careful fractional distillation. (a) How many fractions of formula $C_5H_{11}Cl$ would you expect to collect? (b) Draw structural formulas, stereochemical where pertinent, for the compounds making up each fraction. Specify each enantiomer as *R* or *S*. (c) Which, if any, of the fractions, as collected, would show optical activity? (d) Account in detail—just as was done above—for the optical activity or inactivity of each fraction.

## 5AII.20 Reactions of chiral molecules. Bond-breaking

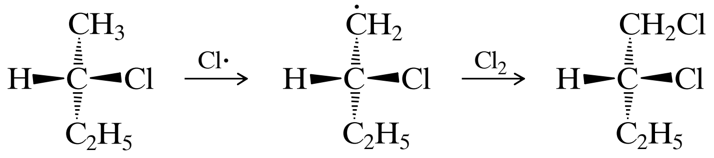
Having made a chiral compound, *sec*-butyl chloride, let us see what happens when it, in turn, undergoes free-radical chlorination. A number of isomeric dichlorobutanes are formed, corresponding to attack at various positions in the molecule. (*Problem*: What are these isomers?)



$$\mathrm{CH_3CH_2{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}}}H{-}CH_3} \xrightarrow{\mathrm{Cl_2,\ heat\ or\ light}} \mathrm{CH_3CH_2{-}\underset{\displaystyle Cl}{\underset{|}{\overset{*}{C}}}H{-}CH_2Cl} + \text{other products}$$

*sec*-Butyl chloride 1,2-Dichlorobutane

Let us take, say, (*S*)-*sec*-butyl chloride (happens to rotate light to the right), and consider only the part of the reaction that yields 1,2-dichlorobutane. Let us make a model (I) of the starting molecule, using a single ball for —$C_2H_5$ but a separate ball for each atom in —$CH_3$. Following the familiar steps of the mechanism, we remove an —H from —$CH_3$ and replace it with a —Cl. Since we break no bond to the chiral center in either step, the model we arrive at necessarily has configuration II, in which the spatial arrangement about the chiral center is unchanged—or, as we say, *configuration is retained*—with —$CH_2Cl$ now occupying the same relative position that was previously occupied by —$CH_3$. It is an axiom of stereochemistry that molecules, too, behave in just this way, and that *a reaction that does not involve the breaking of a bond to a chiral center proceeds with retention of configuration about that chiral center.*



I
(*S*)-*sec*-Butyl chloride

II
(*R*)-1,2-Dichlorobutane

(If a bond to a chiral center *is* broken in a reaction, we can make no general statement about stereochemistry, except that configuration *can* be—and more than likely *will* be—changed.

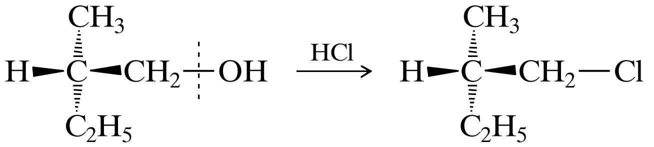
**Problem 5AII.12** We carry out free-radical chlorination of (*S*)-*sec*-butyl chloride, and by fractional distillation isolate the various isomeric products. (a) Draw stereochemical formulas of the 1,2-, 2,2-, and 1,3-dichlorobutanes obtained in this way. Give each enantiomer its proper *R* or *S* specification. (b) Which of these fractions, as isolated, will be optically active, and which will be optically inactive?

Now, let us see how the axiom about bond-breaking is applied in relating the configuration of one chiral compound to that of another.

## 5AII.21 Reactions of chiral molecules. Relating configurations

We learned that the configuration of a particular enantiomer can be determined directly by a special kind of X-ray diffraction, which was first applied in 1951 by Bijvoet to (+)-tartaric acid. But the procedure is difficult and time-consuming, and can be applied only to certain compounds. In spite of this limitation, however, the configurations of thousands of other compounds are now known, since they had already been related by chemical methods to (+)-tartaric acid. Most of these relationships were established by application of the axiom given above; that is, *the configurational relationship between two optically active compounds can be determined* *by converting one into the other by reactions that do not involve breaking of a bond to a chiral center.*

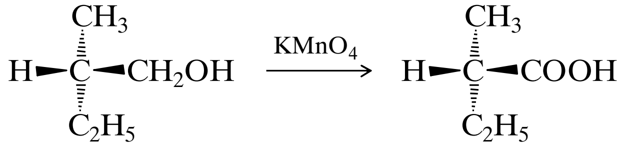
Let us take as an example (−)-2-methyl-1-butanol (the enantiomer found in fusel oil) and accept, for the moment, that it has configuration III, which we would specify *S*. We treat this alcohol with hydrogen chloride and obtain the alkyl chloride, 1-chloro-2-methylbutane. Without knowing the mechanism of this reaction, we can see that the carbon–oxygen bond is the one that is broken. *No bond to the chiral center is broken*, and therefore configuration is retained, with —$CH_2Cl$ occupying the same relative position in the product that was occupied by —$CH_2OH$ in the reactant. We put the chloride into a tube, place this tube in a polarimeter, and find that the plane of polarized light is rotated to the right; that is, the product is (+)-1-chloro-2-methylbutane. Since (−)-2-methyl-1-butanol has configuration III, (+)-1-chloro-2-methylbutane must have configuration IV.



III
(*S*)-(−)-2-Methyl-1-butanol

IV
(*S*)-(+)-1-Chloro-2-methylbutane

Or, we oxidize (−)-2-methyl-1-butanol with potassium permanganate, obtain the acid 2-methylbutanoic acid, and find that this rotates light to the right. Again, no bond to the chiral center is broken, and we assign configuration V to (+)-2-methylbutanoic acid.



III
(*S*)-(−)-2-Methyl-1-butanol

V
(*S*)-(+)-2-Methylbutanoic acid

We can nearly always tell whether or not a bond to a chiral center is broken by simple inspection of the formulas of the reactant and product, as we have done in these cases, and without a knowledge of the reaction mechanism. We must be aware of the possibility, however, that a bond may break and re-form during the course of a reaction without this being evident on the surface. This kind of thing does not happen at random, but in certain specific situations which an organic chemist learns to recognize. Indeed, stereochemistry plays a leading role in this learning process: one of the best ways to detect hidden bond-breaking is so to design the experiment that, if such breaking occurs, it must involve a chiral center.

But how do we know in the first place that (−)-2-methyl-1-butanol has configuration III? Its configuration was related in this same manner to that of another compound, and that one to the configuration of still another, and so on, going back ultimately to (+)-tartaric acid and Bijvoet's X-ray analysis.

We say that the (−)-2-methyl-1-butanol, the (+)-chloride, and the (+)-acid have *similar* (or the *same*) configurations. The enantiomers of these compounds, the (+)-alcohol, (−)-chloride, and (−)-acid, form another set of compounds with similar configurations. The (−)-alcohol and, for example, the (−)-chloride are said to have *opposite* configurations. As we shall find, we are usually more interested in knowing whether two compounds have similar or opposite configurations than in knowing what the actual configuration of either compound actually is. That is to say, we are more interested in *relative* configurations than in *absolute* configurations.

In this set of compounds with similar configurations, we notice that two are dextrorotatory and the third is levorotatory. The sign of rotation is important as a means of keeping track of a particular isomer—just as we might use boiling point or refractive index to tell us whether we have *n*-butane or isobutane, *now that their structures have been assigned*—but the fact that two compounds happen to have the same sign or opposite sign of rotation means little; they may or may not have similar configurations.

The three compounds all happen to be specified as *S*, but this is simply because —$CH_2Cl$ and —COOH happen to have the same relative priority as —$CH_2OH$. If we were to replace the chlorine with deuterium (*Problem*: How could this be done?), the product would be specified *R*, yet obviously it would have the same configuration as the alcohol, halide, and acid. Indeed, looking back to *sec*-butyl chloride and 1,2-dichlorobutane, we see that the similar configurations I and II *are* specified differently, one *S* and the other *R*; here, a group (—$CH_3$) that has a lower priority than —$C_2H_5$ is converted into a group (—$CH_2Cl$) that has a higher priority. We cannot tell whether two compounds have the same or opposite configurations by simply looking at the letters used to specify their configurations; we must work out and compare the absolute configurations indicated by those letters.

**Problem 5AII.13** Which of the following reactions could safely be used to relate configurations?

(a) (+)-$C_6H_5CH(OH)CH_3 + PBr_3 \longrightarrow C_6H_5CHBrCH_3$

(b) (+)-$CH_3CH_2CHClCH_3 + C_6H_6 + AlCl_3 \longrightarrow C_6H_5CH(CH_3)CH_2CH_3$

(c) (−)-$C_6H_5CH(OC_2H_5)CH_2OH + HBr \longrightarrow C_6H_5CH(OC_2H_5)CH_2Br$

(d) (+)-$CH_3CH(OH)CH_2Br + NaCN \longrightarrow CH_3CH(OH)CH_2CN$

(e) 
(+)-$CH_3CH_2\underset{\underset{O}{\|}}{C}—{}^{18}OCH(CH_3)C_2H_5 + OH^- \longrightarrow CH_3CH_2COO^- + CH_3CH_2CH^{18}OHCH_3$

(f) (−)-$CH_3CH_2CHBrCH_3 + C_2H_5O^- Na^+ \longrightarrow C_2H_5—O—CH(CH_3)CH_2CH_3$

(g) (+)-$CH_3CH_2CHOHCH_3 \xrightarrow{Na} CH_3CH_2CH(ONa)CH_3 \xrightarrow{C_2H_2Br} C_2H_5—O—CH(CH_3)CH_2CH_3$

**Problem 5AII.14** What general conclusion must you draw from each of the following observations? (a) After standing in an aqueous acidic solution, optically active $CH_3CH_2CHOHCH_3$ is found to have lost its optical activity. (b) After standing in solution with potassium iodide, optically active *n*-$C_6H_{13}CHICH_3$ is found to have lost its optical activity. (c) Can you suggest experiments to test your conclusions?

## 5AII.22 Optical purity

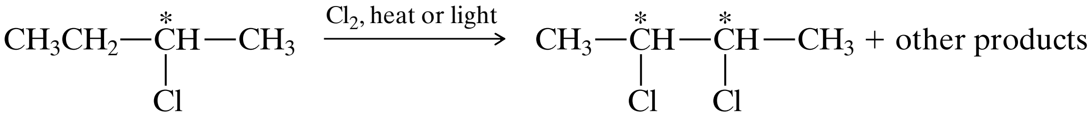
Reactions in which bonds to chiral centers are not broken can be used to get one more highly important kind of information: the specific rotations of optically pure compounds. For example, the 2-methyl-1-butanol obtained from fusel oil (which happens to have specific rotation –5.90°) is *optically pure*—like most chiral compounds from biological sources—that is, it consists entirely of the one enantiomer, and contains none of its mirror image. When this material is treated with hydrogen chloride, the 1-chloro-2-methylbutane obtained is found to have specific rotation of +1.67°. Since no bond to the chiral center is broken, every molecule of alcohol with configuration III is converted into a molecule of chloride with configuration IV; since the alcohol was optically pure, the chloride of specific rotation +1.67° is also optically pure. Once this *maximum rotation* has been established, anyone can determine the optical purity of a sample of 1-chloro-2-methylbutane in a few moments by simply measuring its specific rotation.

If a sample of the chloride has a rotation of +0.835°, that is, 50% of the maximum, we say that it is *50% optically pure*. We consider the components of the mixture to be (+) isomer and (+) isomer (not (+) isomer and (–) isomer). (*Problem*: What are the percentages of (+) isomer and (–) isomer in this sample?)

**Problem 5AII.15** Predict the specific rotation of the chloride obtained by treatment with hydrogen chloride of 2-methyl-1-butanol of specific rotation +3.54°.

## 5AII.23 Reactions of chiral molecules. Generation of a second chiral center

Let us return to the reaction we used, free-radical chlorination of *sec*-butyl chloride, but this time focus our attention on one of the other products, one in which a second chiral center is generated: 2,3-dichlorobutane.This compound, exists as three stereoisomers, *meso* and a pair of enantiomers.



$$CH_3CH_2-\underset{\displaystyle Cl}{\overset{*}{C}H}-CH_3 \xrightarrow{Cl_2,\ \text{heat or light}} CH_3-\underset{\displaystyle Cl}{\overset{*}{C}H}-\underset{\displaystyle Cl}{\overset{*}{C}H}-CH_3 + \text{other products}$$

*sec*-Butyl chloride 2,3-Dichlorobutane

Let us suppose that we take optically active *sec*-butyl chloride (the *S* isomer, say), carry out the chlorination, and by fractional distillation separate the 2,3-dichlorobutanes from all the other products (the 1,2 isomer, 2,2 isomer, etc.). Which stereoisomers can we expect to have?

Figure 5AII.5 shows the course of reaction. Three important points are illustrated:

(1) Since no bond to the original chiral center, C-2, is broken, its configuration is retained in all the products. This must apply in all cases where a second chiral center is generated.

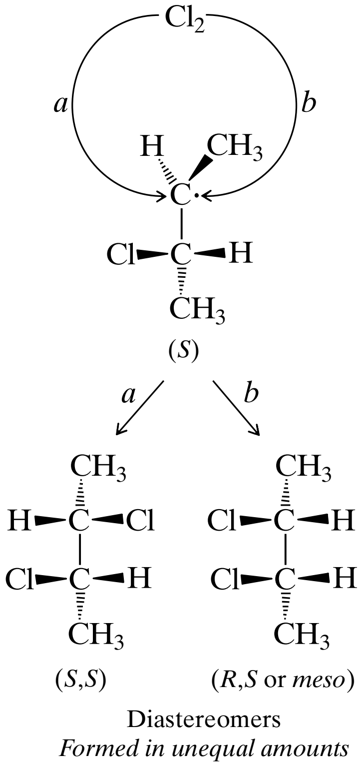


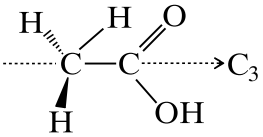
**Figure 5AII.5** Generation of a second chiral center. The configuration at the original chiral center is unchanged. Chlorine becomes attached via (*a*) or (*b*) to give diastereomers, and in unequal amounts.

(2) There are two possible configurations about the new chiral center, C-3, and both of these appear; in this particular case, they result from attacks (*a*) and (*b*) on opposite sides of the flat portion of the free radical, giving the diastereomeric *S*,*S* and *R*,*S* (or *meso*) products.

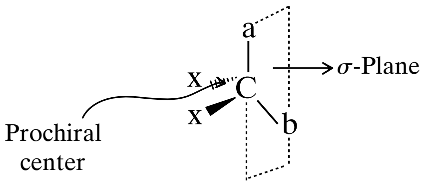
In some reactions, both configurations may not actually be generated, but we must always consider the *possibility* that they will be; this is our point of departure.

## 5AII.24 Topicity of ligands (prochirality)

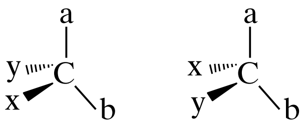
Groups or atoms that are symmetry equivalent by virtue of a $C_n$-axis where $n > 1$ are called *homotopic groups*. For example, in $CH_3COOH$ three H-atoms of the —$CH_3$ group are symmetry equivalent by virtue of a $C_3$-axis. So, these three hydrogen atoms are homotopic. Groups or atoms in a molecule that are symmetry equivalent by



virtue of a $\sigma$-plane, i, or $S_n$ (where $n$ = even) are called enantiotopic ligands. For example, in a molecule $C_{abx_2}$ the plane containing $C_{ab}$ bisects the angle x–ĉ–x without



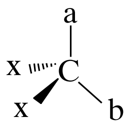
changing the identity of the molecule. So, these two *x*-groups are enantiotopic. Substitution of either x-group by another group y gives rise to enantiomers.



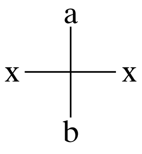
Enantiomers

Such a C-atom is called a prochiral center, and the phenomenon is called prochirality.

The configuration of the two enantiotopic groups are assigned by writing their Fischer's formulas. For example,

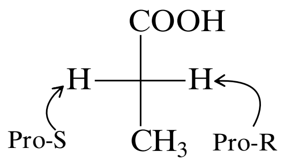


Flying-wedge
formula



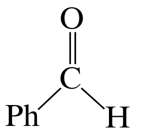
Fischer's
formula

If the priority of the group "a" (top) is higher than that of the group "b" (bottom), then the x-group on the right is the pro-R group. If the group "b" is of higher priority, then the x-group on the left is the pro-R group. (*mnemonics* top–right,bottom-left). Let us take the example of propanoic acid, $CH_3CH_2COOH$. The C-2-atom is the prochiral center. The two enantiotopic H-atoms are assigned configuration as follows:

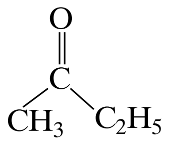


—COOH group has higher priority than the —$CH_3$ group, that is, the group at the top is of higher priority. So, H-atom on the right-hand side is the pro-R atom and the other H-atom is pro-S.

Like a C-atom in a tetrahedral molecule, the plane of a two-dimensionally asymmetric or chiral molecule possesses two enantiotopic faces. For example, aldehydes (except formaldehyde) and unsymmetrical ketones have prochiral faces.

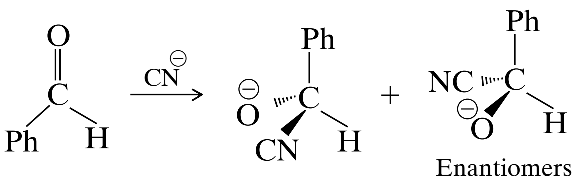


Aldehyde



Unsymmetrical ketone

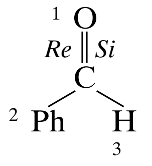
When a nucleophile $Nu^{\ominus}$ attacks the carbonyl group (C=O), it may attack the plane containing the C=O from either of its faces and enantiomers result.



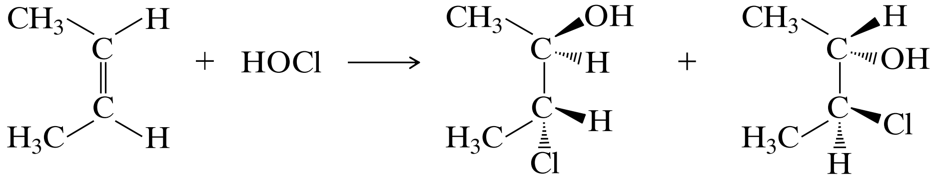
Enantiomers

Such a face of a molecule is called a prochiral face.

The assignment of configurations of the two faces are done by finding the priorities of the three groups as 1,2, and 3. Then in the case of the face in which in going from 1 ⟶ 2 ⟶ 3, the eye moves clockwise, the face is assigned the configuration, Re-. If in going from 1 ⟶ 2 ⟶ 3, the eye moves anticlockwise, the configuration of the face is Si-. For example, in benzadehyde molecule in case of the front face in going from 1 ⟶ 2 ⟶ 3, the eye moves counter clockwise. So, the front face is the Si-face and the rear face is the Re-face. (Re-stands for rectus meaning right handed, and Si-stands for sinister meaning left handed).

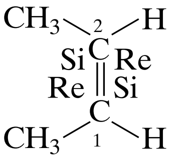


Like C=O, C=C containing plane also can give rise to prochirality, if the two C-atoms are suitably substituted. In such cases, an addition of an unsymmetric addendum to a $>$C=C$<$ gives rise to enantiomers. For example,

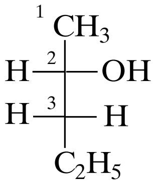


Enantiomers

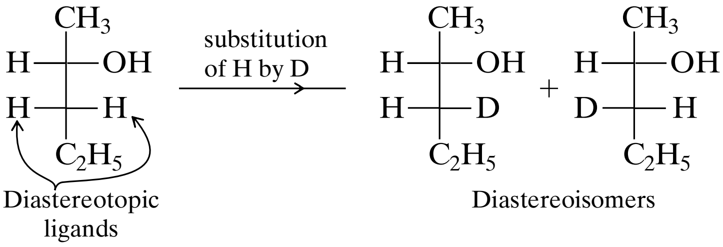
In such cases, the assignment of the configurations of the two prochiral faces is done by assigning the configurations of both the C-atoms. For example, in front face, the C1-atom has Si-, and C2-atom has Re-configuration. Therefore, the front face has Si-Re configuration, and the rear face has Re–Si configuration.



In case of molecules like RC(X)(Y) $CH_2R'$ that already have a chiral center in the molecule, the pro-stereogenic center in the —$CH_2$— group, is actually pro-diastereogenic because in such cases substitution of either of the two H-atoms by another atom or group gives rise to *diastereoisomers*. For example, in case of the molecule shown below,



the two H-atoms at C3-atom are diastereotopic.



## EXERCISE

**1.** What is meant by each of the following?

(a) optical activity
(b) dextrorotatory
(c) levorotatory
(d) specific rotation
(e) chirality
(f) chiral molecule
(g) chiral center
(h) superimposable
(i) enantiomers
(j) diastereomers
(k) *meso* compound
(l) racemic modification
(m) configuration
(n) conformations
(o) *R*
(p) *S*
(q) +
(r) −
(s) configurational isomers
(t) conformational isomers

**2.** (a) What is the necessary and sufficient condition for enantiomerism? (b) What is a necessary but not a sufficient condition for optical activity? (c) What conditions must be met for the observation of optical activity? (d) How can you tell from its formula whether or not a compound can exist as enantiomers? (e) What restrictions, if any, must be applied to the use of planar formulas in (d)? To the use of models in (d)? (f) Exactly how do you go about deciding whether a molecule should be specified as *R* or as *S*?

**3.** Compare the dextrorotatory and levorotatory forms of *sec*-butyl alcohol, $CH_3CH_2CHOHCH_3$, with respect to:

(a) boiling point
(b) melting point
(c) relative density
(d) specific rotation
(e) refractive index
(f) solubility in 100 g of water
(g) rate of reaction with HBr
(h) infrared spectrum
(i) NMR spectrum
(j) adsorption on alumina
(k) retention time in gas chromatography
(1) specification as *R* or *S*

**4.** Which of the following objects are chiral?

(a) nail, screw, pair of scissors, knife, spool of thread
(b) glove, shoe, sock, pullover sweater, coat sweater, scarf tied around your neck
(c) child's block, rubber ball. Pyramid of Cheops, helix, double helix
(d) basketball, football, tennis racket, golf club, baseball bat, shotgun barrel, rifle barrel
(e) your hand, your foot, your ear, your nose, yourself

**5.** Assuming both your hands to be of equal strength and skill, which of the following operations could you perform with equal speed and efficiency?

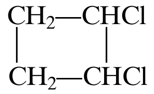
(a) driving a screw, sawing a board, drilling a hole
(b) opening a door, opening a soft-drink can, opening a coffee jar, turning on the hot water
(c) signing your name, sharpening a pencil, throwing a ball, shaking hands with someone's right hand.

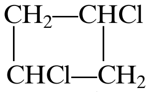
**6.** Draw and specify as *R* or *S* the enantiomers (if any) of:

(a) 3-bromohexane
(b) 3-chloro-3-methylpentane
(c) 1,2-dibromo-2-methylbutane
(d) 1,3-dichloropentane
(e) 3-chloro-2,2,5-trimethylhexane
(f) 1-deuterio-1-chlorobutane, $CH_3CH_2CH_2CHDCl$

**7.** (a) What is the lowest-molecular-weight alkane that is chiral? Draw stereochemical formulas of the enantiomers and specify each as *R* or *S*. (b) Is there another alkane of the same molecular weight that is also chiral? If there is, give its structure and name, and specify the enantiomers as *R* or *S*.

**8.** Draw stereochemical formulas for all the possible stereoisomers of the following compounds. Label pairs of enantiomers, and *meso* compounds. Tell which isomers, if separated from all other stereoisomers, will be optically active. Give one isomer of each set its *R/S* specification.

(a) $CH_3CHBrCHOHCH_3$
(b) $CH_3CHBrCHBrCH_2Br$
(c) $C_6H_5CH(CH_3)CH(CH_3)C_6H_5$
(d) $CH_3CH_2CH(CH_3)CH_2CH_2CH(CH_3)CH_2CH_3$
(e) $CH_3CH(C_6H_5)CHOHCH_3$
(f) $CH_3CHOHCHOHCHOHCH_2OH$
(g) $HOCH_2(CHOH)_3CH_2OH$
(h)


(*Make models.*)
(i)


(j) *n*-butylethylmethyl-*n*-propylammonium chloride, $(RR'R''R'''N)^+Cl^-$
(k) *sec*-butylethylmethyl-*n*-propylammonium chloride

**9.** (a) In a study of chlorination of propane, four products (A, B, C, and D) of formula $C_3H_6Cl_2$ were isolated. What are their structures?

(b) Each was chlorinated further, and the number of trichloro products ($C_3H_5Cl_3$) obtained from each was determined by gas chromatography. A gave one trichloro product; B gave two; and C and D each gave three. What is the structure of A? Of B? Of C and D?

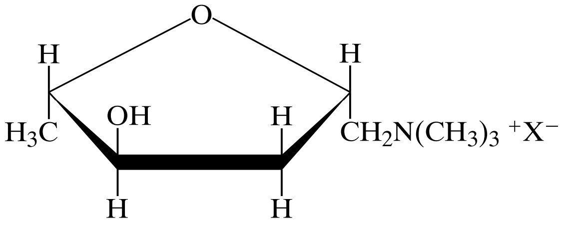
(c) By another synthetic method, compound C was obtained in optically active form. Now what is the structure of C? Of D?

(d) When optically active C was chlorinated, one of the trichloropropanes obtained was optically active, and the other two were optically inactive. What is the structure of the optically active one? Of the other two?

**10.** Draw configurational isomers (if any) of: (a) $CH_2BrCH_2Cl$; (b) $CH_3CHBrCH_2Cl$. (c) For each substance of (a) and (b), draw all conformers. Label pairs of conformational enantiomers.

**11.** The more stable conformer of *n*-propyl chloride, $CH_3CH_2—CH_2Cl$, is the *gauche*. What does this indicate about the interaction between —Cl and —$CH_3$? How do you account for this interaction?

**12.** It is October, 1929. In a lonely cottage in Devonshire, George Harrison, a middle-aged amateur mycologist, has died shortly after eating a mushroom stew he prepared from warty caps (*Amanita rubescens*) collected in nearby Five-Acre Wood. Cause of death: poisoning by *muscarine*, an alkaloid found in the fly agaric (*Amanita muscaria*).



Muscarine
An alkaloid found in
the mushroom *Amanita muscaria*

You are Sir James Lubbock, Home Office Analyst, and you have been asked to help solve a knotty problem crucial to the investigation: whether (a) a deadly *Amanita muscaria* found its way accidentally into the mess of closely similar, but harmless, *Amanita rubescens*; or (b) a lethal dose of synthetic muscarine (filched from a London laboratory) was deliberately added to the stew pot—perhaps by the lover of beautiful Mrs Harrison.

You have available a solution of muscarine that you isolated from left-over stew, a well-equipped (for 1929) laboratory, and ten minutes. Tell what you can do that might give a definite answer to the question: was there a fly agaric in Mr Harrison's soup—or did a second cook, wilfully and with malice aforethought, spoil the broth?

**13.** Each of the following reactions is carried out, and the products are separated by careful fractional distillation or recrystallization. For each reaction tell how many fractions will be collected. Draw stereochemical formulas of the compound or compounds making up each fraction, and give each its *R/S* specification. Tell whether each fraction, as collected, will show optical activity or optical inactivity.

(a) *n*-pentane + $Cl_2$ (300 °C) $\longrightarrow$ $C_5H_{11}Cl$
(b) 1-chloropentane + $Cl_2$ (300 °C) $\longrightarrow$ $C_5H_{10}Cl_2$
(c) (*S*)-2-chloropentane + $Cl_2$ (300 °C) $\longrightarrow$ $C_5H_{10}Cl_2$
(d) (*R*)-2-chloro-2,3-dimethylpentane + $Cl_2$ (300 °C) $\longrightarrow$ $C_7H_{14}Cl_2$
(e) *meso*-$HOCH_2CHOHCHOHCH_2OH$ + $HNO_3$ $\longrightarrow$ $HOCH_2CHOHCHOHCOOH$
(f) (*S*)-3-chloro-1-butene + HCl $\longrightarrow$ 2,3-dichloro-2-methylbutane
(g) racemic $C_6H_5COCHOHC_6H_5$ + $H_2$/Ni, catalyst $\longrightarrow$ $C_6H_5CHOHCHOHC_6H_5$

**14.** Give the absolute configuration and *R/S* specification of compounds E–K.

(a) (*R*)-$HOCH_2CHOHCH{=}CH_2$ + cold alkaline $KMnO_4$ $\longrightarrow$ E (optically active) + F (optically inactive); E and F are $HOCH_2CHOHCHOHCH_2OH$
(b) (*S*)-1-chloro-2-methylbutane + Li, then + CuI $\longrightarrow$ G
(c) G + (*S*)-1-chloro-2-methylbutane $\longrightarrow$ H
(d) (*R,R*)-$HOCH_2CHOHCHOHCH_2OH$ + HBr $\longrightarrow$ I ($HOCH_2CHOHCHOHCH_2Br$)
(e) (*R*)-2-ethyl-3-methyl-1-pentene ($CH_3CH_2CH(CH_3)C(C_2H_5){=}CH_2$) + $H_2$/Ni $\longrightarrow$
J (optically active) + K (optically inactive); both J and K are $C_8H_{18}$

**15.** An excess of the racemic acid $CH_3CHClCOOH$ is allowed to react with (*S*)-2-methyl-1-butanol to form the ester,

$$CH_3CHCl\underset{\underset{O}{\|}}{C}—OCH_2CH(CH_3)CH_2CH_3$$

and the reaction mixture is carefully distilled. Three fractions are obtained, each of which is optically active. Draw stereochemical formulas of the compound or compounds making up each fraction.

# 5BI. Cyclic Aliphatic Compounds (*Carbocyclic Compounds*)

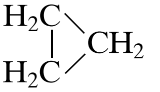
## 5BI.1 Open-chain and cyclic compounds

In this chapter, we shall take up *alicyclic* compounds (*aliphatic cyclic* compounds). Much of their chemistry we already know, since it is essentially the chemistry of their open-chain counterparts: a cycloalkane, for example, *is* an alkane, and in general acts like one. But the cyclic nature of some of these compounds confers very special properties on them. It was here that the study of conformational analysis had its real beginnings, and it is here that we, in turn, can begin to appreciate the practical importance of this branch of stereochemistry. Being a ring—or several rings—places restrictions on the shape a molecule can assume, or on just where solvent molecules can cluster; steric hindrance can be increased—or decreased; the attack by a reagent can be limited to just one direction. The very *size* of the ring can lead to unusual reactivity. Physical constants of a few common carbocyclic compounds are listed in Table 5BI.1

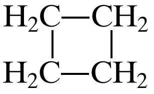
Most of the chapter will deal with *homocyclic* compounds, in which the rings are made up only of carbon atoms. Then we shall look briefly at some *heterocyclic* compounds, in which the rings contain more than one kind of atom. Throughout, it is on their special properties as cyclic compounds that we shall focus our attention.

## 5BI.2 Nomenclature

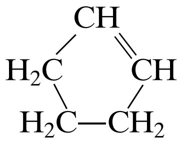
Cyclic aliphatic hydrocarbons are named by prefixing **cyclo-** to the name of the corresponding open-chain hydrocarbon having the same number of carbons as the ring. For example:



Cyclopropane

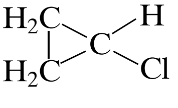


Cyclobutane

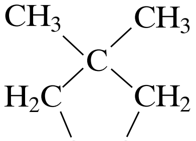


Cyclopentene

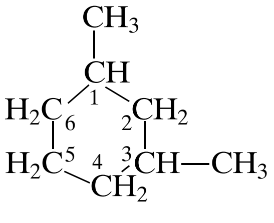
Substituents on the ring—alkyl groups, halogens—are named, and their positions are indicated by numbers. We assign position 1 to a particular carbon and then number either clockwise or counterclockwise around the ring; we do all this in such a way as to give the lowest combination of numbers. For example:



Chlorocyclopropane



1,1-Dimethylcyclopentane

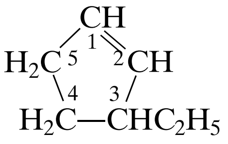


1,3-Dimethylcyclohexane

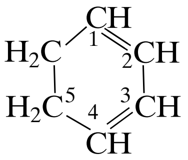
**Table 5BI.1** Carbocyclic compounds

| Name | M.p.,°C | B.p.,°C | Relative density (at 20 °C) |
|---|---|---|---|
| Cyclopropane | −127 | −33 | |
| Cyclobutane | −80 | 13 | |
| Cyclopentane | −94 | 49 | 0.746 |
| Cyclohexane | 6.5 | 81 | 0.778 |
| Cycloheptane | −12 | 118 | 0.810 |
| Cyclooctane | 14 | 149 | 0.830 |
| Methylcyclopentane | −142 | 72 | 0.749 |
| *cis*-1,2-Dimethylcyclopentane | −62 | 99 | 0.772 |
| *trans*-1,2-Dimethylcyclopentane | −120 | 92 | 0.750 |
| Methylcyclohexane | −126 | 100 | 0.769 |
| Cyclopentene | −93 | 46 | 0.774 |
| 1,3-Cyclopentadiene | −85 | 42 | 0.798 |
| Cyclohexene | −104 | 83 | 0.810 |
| 1,3-Cyclohexadiene | −98 | 80.5 | 0.840 |
| 1,4-Cyclohexadiene | −49 | 87 | 0.847 |

In simple cycloalkenes and cycloalkynes the doubly and triply bonded carbons are considered to occupy positions 1 and 2. For example:

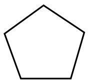


3-Ethylcyclopentene

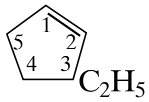


1,3-Cyclohexadiene

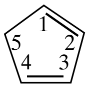
For convenience, aliphatic rings are often represented by simple geometric figures: a triangle for cyclopropane, a square for cyclobutane, a pentagon for cyclopentane, a hexagon for cyclohexane, and so on. It is understood that two hydrogens are located at each corner of the figure unless some other group is indicated. For example:



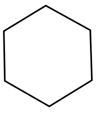
Cyclopentane



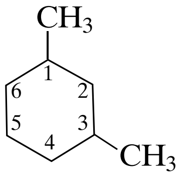
3-Ethylcyclopentene



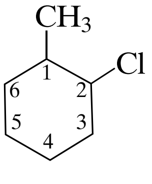
1,3-Cyclopentadiene



Cyclohexane

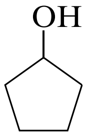


1,3-Dimethylcyclohexane

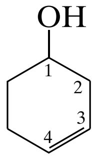


2-Chloro-1-methylcyclohexane

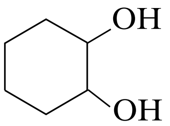
As usual, alcohols are given the ending *-ol*, which takes priority over *-ene* and appears last in the name. The OH group is considered to be attached to position 1.



Cyclopentanol

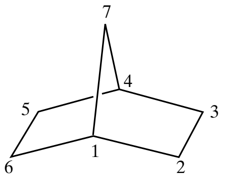


3-Cyclohexenol

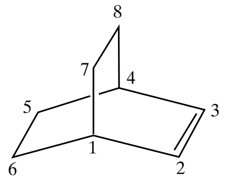


1,2-Cyclohexanediol

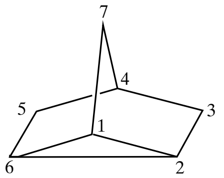
*Polycyclic* compounds contain two or more rings that share two or more carbon atoms. We can illustrate the naming system with *norbornane*, whose systematic name is bicyclo[2.2.1] heptane: (a) *heptane*, since it contains a total of *seven* carbon atoms; (b) *bicyclo*, since it contains *two* rings, that is, breaking two carbon–carbon bonds converts it into an open-chain compound; (c) [2.2.1], since the number of carbons between bridgeheads (shared carbons) is *two* (C–2 and C–3), *two* (C–5 and C–6), and *one* (C–7).



Bicyclo[2.2.1]heptane
Norbornane

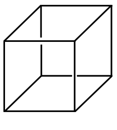


Bicyclo[2.2.2]octa-2-ene

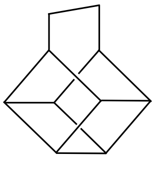


Tricyclo[2.2.1.$0^{2,6}$]heptane
Nortricyclene

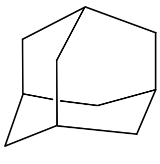
Polycyclic compounds in a variety of strange and wonderful shapes have been made, and their properties have revealed unexpected facets of organic chemistry. Underlying much of this research there has always been the challenge: *can such a compound be made*?



Cubane



Basketane

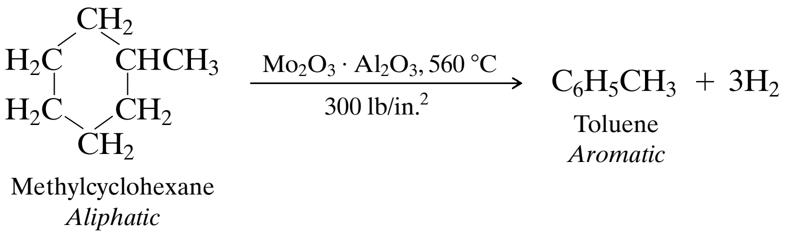


Adamantane

## 5BI.3 Industrial source

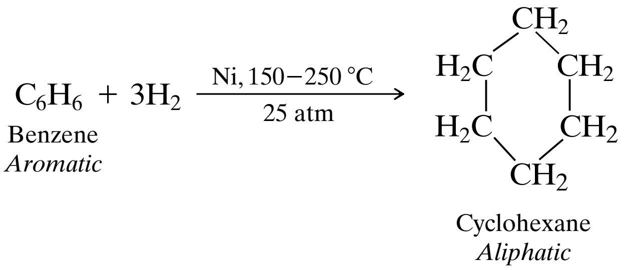
We have already mentioned that petroleum from certain areas is rich in cycloalkanes, known to the petroleum industry as *naphthenes*. Among these are cyclohexane, methylcyclohexane, methylcyclopentane, and 1,2-dimethylcyclopentane.

These cycloalkanes are converted by *catalytic reforming* into aromatic hydrocarbons, and thus provide one of the major sources of these important compounds. In this reaction there is *elimination* of hydrogen from the molecules. For example:



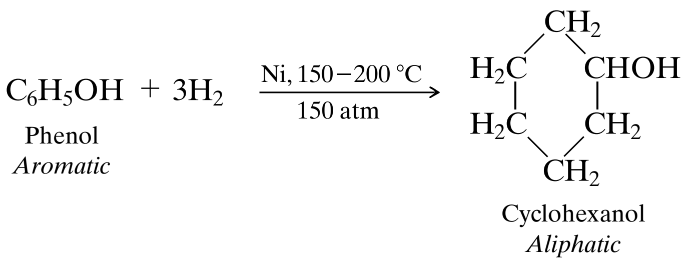
**Dehydrogenation**
*Elimination*

Just as elimination of hydrogen from cyclic aliphatic compounds yields aromatic compounds, so *addition* of hydrogen to aromatic compounds yields cyclic aliphatic compounds, specifically cyclohexane derivatives. An important example of this is the hydrogenation of benzene to yield pure cyclohexane.



**Hydrogenation**
*Addition*

As we might expect, hydrogenation of substituted benzenes yields substituted cyclohexanes. For example:

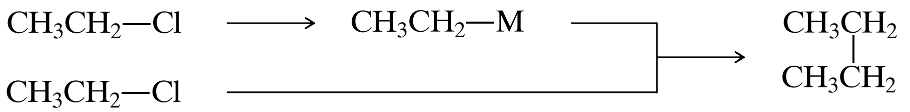


From cyclohexanol many other cyclic compounds containing a six-membered ring can be made.

## 5BI.4 Preparation

Preparation of alicyclic compounds from other aliphatic compounds generally involves two stages: (a) conversion of some open-chain compound or compounds into a compound that contains a ring, a process called *cyclization*; (b) conversion of the cyclic compound thus obtained into the kind of compound that we want: for example, conversion of a cyclic alcohol into a cyclic alkyl halide, or of a cyclic alkene into a cyclic alkane.

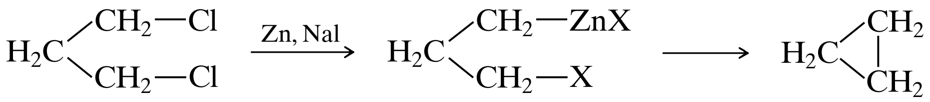
Very often, cyclic compounds are made by *adapting* a standard method of preparation to the job of closing a ring. For example, we have seen that the alkyl groups of two alkyl halides can be coupled together through conversion of one halide into an organometallic compound (a lithium dialkylcopper):



Ethyl chloride
*2 moles*

*n*-Butane

The same method applied to a *di*halide can bring about coupling between two alkyl groups *that are part of the same molecule*:



1,3-Dichloropropane

Cyclopropane

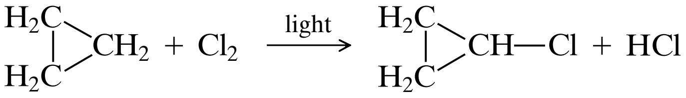
In this case zinc happens to do a good job. Although this particular method works well only for the preparation of cyclopropane, it illustrates an important technique: the carrying out of what is normally an *intermolecular* (between-molecules) reaction under such circumstances that it becomes an *intramolecular* (within-a-molecule) reaction. As we can see, it involves tying together the ends of a difunctional molecule.

Alicyclic hydrocarbons are prepared from other cyclic compounds (e.g., halides or alcohols) by exactly the same methods that are used for preparing open-chain hydrocarbons from other open-chain compounds. Because we are dealing with cyclic molecules, however, there can sometimes be special stereochemical features to these reactions; we shall look at one of these after we have learned something about the stereoisomerism of alicyclic compounds.

## 5BI.5 Reactions

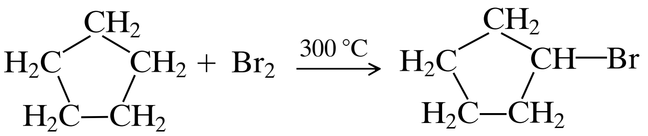
With certain very important and interesting exceptions, alicyclic hydrocarbons undergo the same reactions as their open-chain analogs.

Cycloalkanes undergo chiefly free-radical substitution. For example:



Cyclopropane

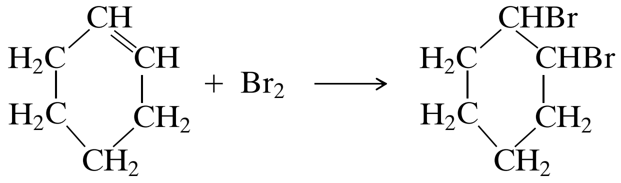
Chlorocyclopropane

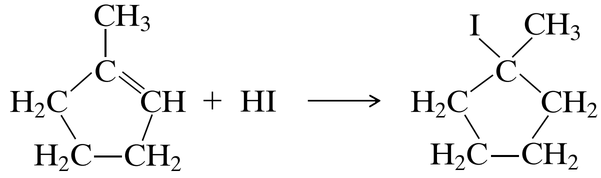


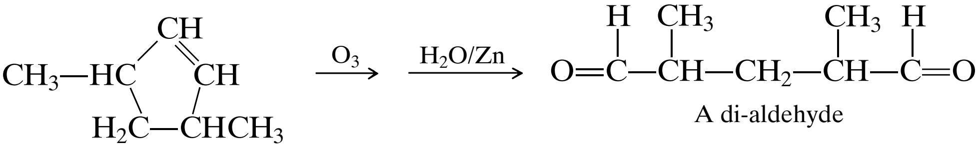
Cyclopentane

Bromocyclopentane

Cycloalkenes undergo chiefly addition reactions, both electrophilic and free-radical; like other alkenes, they can also undergo cleavage and allylic substitution. For example:


Cyclohexene 1,2-Dibromocyclohexane


1-Methylcyclopentene 1-Iodo-1-methylcyclopentane


3,5-Dimethylcyclopentene A di-aldehyde

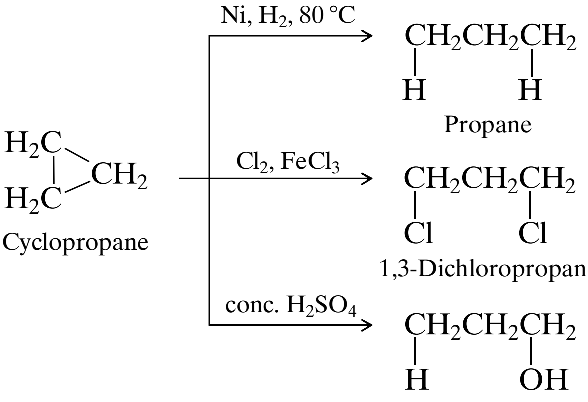
In the same way, alicyclic halides, alcohols, and ethers undergo the reactions we would expect of them: substitution and elimination, oxidation and cleavage.

The two smallest cycloalkanes, cyclopropane and cyclobutane, show certain chemical properties that are entirely different from those of the other members of their family. Some of these exceptional properties fit into a pattern and, as we shall see, can be understood in a general way.

The chemistry of bicyclic compounds is even more remarkable, and is one of the most intensively studied areas of organic chemistry.

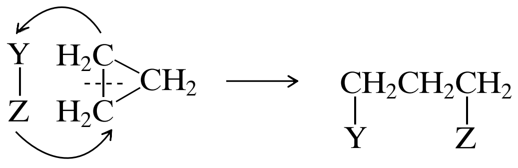
## 5BI.6 Reactions of small-ring compounds. Cyclopropane and cyclobutane

Besides the free-radical substitution reactions that are characteristic of cycloalkanes and of alkanes in general, cyclopropane and cyclobutane undergo certain addition reactions. These addition reactions destroy the cyclopropane and cyclobutane ring systems, and yield open-chain products. For example:



Cyclopropane Propane 1,3-Dichloropropane *n*-Propyl alcohol

In each of these reactions a carbon–carbon bond is broken, and the two atoms of the reagent appear at the ends of the propane chain:



In general, cyclopropane undergoes addition less readily than propylene: chlo-rination, for example, requires a Lewis acid catalyst to polarize the chlorine molecule. Yet the reaction with sulfuric acid and other aqueous protic acids takes place considerably faster for cyclopropane than for an alkene. (Odder still, treatment with bromine and $FeBr_3$ yields a grand mixture of bromopropanes.)

Cyclobutane does not undergo most of the ring-opening reactions of cyclopropane: it is hydrogenated, but only under more vigorous conditions than those required for cyclopropane. Thus cyclobutane undergoes addition less readily than cyclopropane and, with some exceptions, cyclopropane less readily than an alkene. The remarkable thing is that these cycloalkanes undergo addition at all.

## 5BI.7 Baeyer strain theory

In 1885 Adolf von Baeyer proposed a theory to account for certain aspects of the chemistry of cyclic compounds. The part of his theory dealing with the ring-opening tendencies of cyclopropane and cyclobutane is generally accepted today, although it is dressed in more modern language. Other parts of his theory have been shown to be based on false assumptions, and have been discarded.

Baeyer's argument was essentially the following. In general, when carbon is bonded to four other atoms, the angle between any pair of bonds is the tetrahedral angle 109.5°. But the ring of cyclopropane is a triangle with three angles of 60°, and the ring of cyclobutane is a square with four angles of 90°. In cyclopropane or cyclobutane, therefore, one pair of bonds to each carbon cannot assume the tetrahedral angle, but must be compressed to 60° or 90° to fit the geometry of the ring.

These deviations of bond angles from the "normal" tetrahedral value cause the molecules to be *strained*, and hence to be unstable compared with molecules in which the bond angles are tetrahedral. Cyclopropane and cyclobutane undergo ring-opening reactions since these relieve the strain and yield the more stable open-chain compounds. Because the deviation of the bond angles in cyclopropane ($109.5° - 60° = 49.5°$) is greater than in cyclobutane ($109.5° - 90° = 19.5°$), cyclopropane is more highly strained, more unstable, and more prone to undergo ring-opening reactions than is cyclobutane.

The angles of a regular pentagon (108°) are very close to the tetrahedral angle (109.5°), and hence cyclopentane should be virtually free of angle strain. The angles of a regular hexagon (120°) are somewhat larger than the tetrahedral angle, and hence, Baeyer proposed (incorrectly), there should be a certain amount of strain in cyclohexane. Further, he suggested (incorrectly) that as one proceeded to cycloheptane, cyclooctane, etc., the deviation of the bond angles from 109.5° would become progressively larger, and the molecules would become progressively more strained.

Thus Baeyer considered that rings smaller or larger than cyclopentane or cyclohexane were unstable; it was because of this instability that the three- and four-membered rings underwent ring-opening reactions; it was because of this instability that great difficulty had been encountered in the synthesis of the larger rings. How does Baeyer's strain theory agree with the facts?

## 5BI.8 Heats of combustion and relative stabilities of the cycloalkanes

We recall that the heat of combustion is the quantity of heat evolved when one mole of a compound is burned to carbon dioxide and water. Like heats of hydrogenation, heats of combustion can often furnish valuable information about the relative stabilities of organic compounds. Let us see if the heats of combustion of the various cycloalkanes support Baeyer's proposal that rings smaller or larger than cyclopentane and cyclohexane are unstable.

Examination of the data for a great many compounds has shown that the heat of combustion of an aliphatic hydrocarbon agrees rather closely with that calculated by assuming a certain characteristic contribution from each structural unit. For open-chain alkanes each methylene group, —$CH_2$—, contributes very close to 157.4 kcal/mol to the heat of combustion. Table 5BI.2 lists the heats of combustion that have been measured for some of the cycloalkanes.

**Table 5BI.2** HEATS OF COMBUSTION OF CYCLOALKANES

| Ring size | Heat of combustion per $CH_2$, kcal/mol | Ring size | Heat of combustion per $CH_2$, kcal/mol |
|---|---|---|---|
| 3 | 166.6 | 10 | 158.6 |
| 4 | 164.0 | 11 | 158.4 |
| 5 | 158.7 | 12 | 157.6 |
| 6 | 157.4 | 13 | 157.8 |
| 7 | 158.3 | 14 | 157.4 |
| 8 | 158.6 | 15 | 157.5 |
| 9 | 158.8 | 17 | 157.2 |
| | Open-chain 157.4 | | |

We notice that for cyclopropane the heat of combustion per —$CH_2$— group is 9 kcal higher than the open-chain value of 157.4 ; for cyclobutane it is 7 kcal higher than the open-chain value. Whatever the compound in which it occurs, a —$CH_2$— group yields the same products on combustion: carbon dioxide and water.

$$\text{—CH}_2\text{—} + \tfrac{3}{2}O_2 \longrightarrow CO_2 + H_2O + \text{heat}$$

If cyclopropane and cyclobutane evolve more energy per —$CH_2$— group than an open-chain compound, it can mean only that they *contain* more energy per —$CH_2$— group. In agreement with the Baeyer angle-strain theory, then, cyclopropane and cyclobutane are less stable than open-chain compounds; it is reasonable to suppose that their tendency to undergo ring-opening reactions is related to this instability.

According to Baeyer, rings larger than cyclopentane and cyclohexane also should be unstable, and hence also should have high heats of combustion; furthermore, relative instability—and, with it, heat of combustion—should increase steadily with ring size. However, we see from Table 5BI.2 that almost exactly the opposite is true. For none of the rings larger than four carbons does the heat of combustion per —$CH_2$— deviate much from the open-chain value of 157.4. Indeed, one of the biggest deviations is for Baeyer's "most stable" compound, cyclopentane: 1.3 kcal per —$CH_2$—, or 6.5 kcal for the molecule. Rings containing seven to eleven carbons have about the same value as cyclopentane, and when we reach rings of twelve carbons or more, heats of combustion are indistinguishable from the open-chain values. Contrary to Baeyer's theory, then, none of these rings is appreciably less stable than open-chain compounds, and the larger ones are completely free of strain. Furthermore, once they have been synthesized, these large-ring cycloalkanes show little tendency to undergo the ring-opening reactions characteristic of cyclopropane and cyclobutane.

What is wrong with Baeyer's theory that it does not apply to rings larger than four members? simply this: the angles that Baeyer used for each ring were based on the assumption that the rings were *flat*. For example, the angles of a regular (flat) hexagon are 120°, the angles for a regular decagon are 144°. But the cyclohexane ring is not a regular hexagon, and the cyclodecane ring is not a regular decagon. These rings are not flat, but are puckered (see Fig. 5BI.1) so that each bond angle of carbon can be 109.5°.

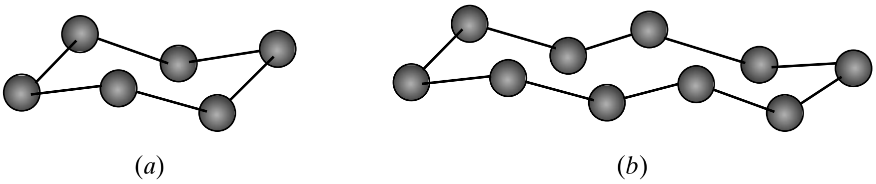

(*a*) (*b*)

**Figure 5BI.1** Puckered rings. (*a*) Cyclohexane. (*b*) Cyclodecane.

A three-membered ring must be planar, since three points (the three carbon nuclei) define a plane. A four-membered ring need not be planar, but puckering here would increase (angle) strain. A five-membered ring need not be planar, but in this case a planar arrangement would permit the bond angles to have nearly the tetrahedral value. All rings larger than this are puckered. (Actually, as we shall see, cyclobutane and cyclopentane are puckered, too, but this is *in spite of* increased angle strain.)

If large rings are stable, why are they difficult to synthesize? Here we encounter Baeyer's second false assumption. The fact that a compound is difficult to synthesize does not necessarily mean that it is unstable. The closing of a ring requires that two ends of a chain be brought close enough to each other for a bond to form. The larger the ring one wishes to synthesize, the longer must be the chain from which it is made, and the less is the likelihood of the two ends of the chain approaching each other. under these conditions the end of one chain is more likely to encounter the end of a *different* chain, and thus yield an entirely different product (see Fig. 5BI.2).

The methods that are used successfully to make large rings take this fact into consideration. Reactions are carried out in highly dilute solutions where collisions between two different chains are unlikely; under these conditions the ring-closing reaction, although slow, is the principal one. Five- and six-membered rings are the kind most commonly encountered in organic chemistry because they are large enough to be free of angle strain, and small enough that ring closure is likely.

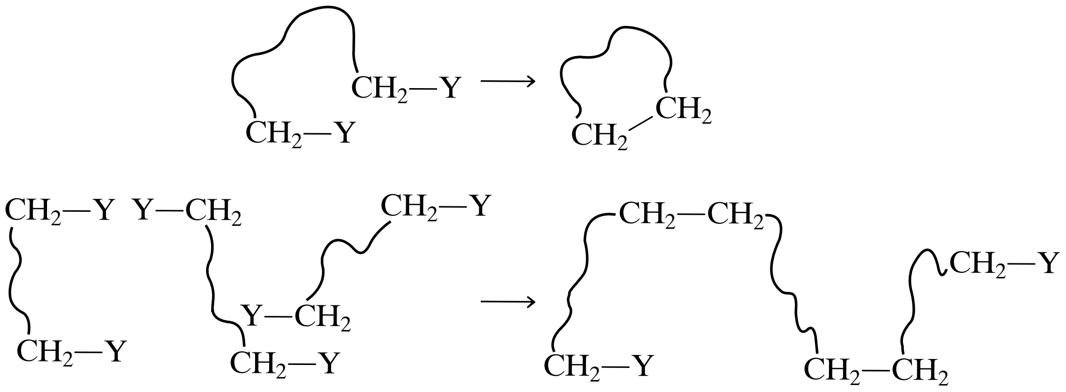


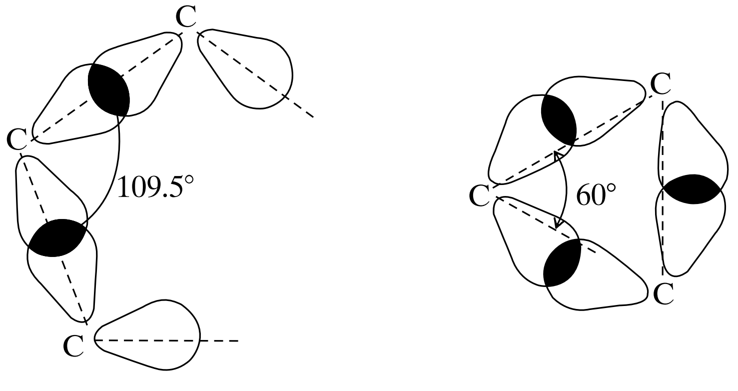
**Figure 5BI.2** Ring closure (upper) *vs.* chain lengthening (lower).

## 5BI.9 Orbital picture of angle strain

What is the meaning of Baeyer's angle strain in terms of the modern picture of the covalent bond?

We have seen that, for a bond to form, two atoms must be located so that an orbital of one overlaps an orbital of the other. For a given pair of atoms, the greater the overlap of atomic orbitals, the stronger the bond. When carbon is bonded to four other atoms, its bonding orbitals ($sp^3$ orbitals) are directed to the corners of a tetrahedron; the angle between any pair of orbitals is thus 109.5°. Formation of a bond with another carbon atom involves overlap of one of these $sp^3$ orbitals with a similar $sp^3$ orbital of the other carbon atom. This overlap is most effective, and hence the bond is strongest, when the two atoms are located so that an $sp^3$ orbital of each atom points toward the other atom. This means that when carbon is bonded to two other carbon atoms the C—C—C bond angle should be 109.5°.

In cyclopropane, however, the C—C—C bond angle cannot be 109.5°, but instead must be 60°. As a result, the carbon atoms cannot be located to permit their $sp^3$ orbitals to point toward each other (see Fig. 5BI.3). There is less overlap and the bond is weaker than the usual carbon–carbon bond.



(*a*) (*b*)

**Figure 5BI.3** Angle strain, (*a*) Maximum overlap permitted for open-chain or large-ring compounds, (*b*) Poor overlap for the cyclopropane ring. Bent bonds have much *p* character.

The decrease in stability of a cyclic compound attributed to *angle strain* is due to poor overlap of atomic orbitals in the formation of the carbon–carbon bonds.

On the basis of quantum mechanical calculations, C. A. Coulson and W. A. Moffitt proposed *bent bonds* between carbon atoms of cyclopropane rings; this idea is supported by electron density maps based on *x*-ray studies. Carbon uses $sp^2$ orbitals for carbon–hydrogen bonds (which are short and strong), and orbitals with much *p* character ($sp^4$ to $sp^5$) for the carbon–carbon bonds. The high *p* character of these carbon–carbon bonds, and their location—largely outside the ring—seems to underlie much of the unusual chemistry of these rings. The carbon–carbon bond orbitals can overlap orbitals on adjacent atoms; the resulting delocalization is responsible for the effects of cyclopropyl as a substituent. The carbon–carbon bond orbitals provide a site for the attack by acids that is the first step of ring-opening. (Indeed, "edge-protonated" cyclopropanes seem to be key intermediates in many reactions that do not, on the surface, seem to involve cyclopropane rings.)

Ring-opening is *due* to the weakness of the carbon–carbon bonds, but the *way in which it happens* reflects the unusual nature of the bonds; all this stems ultimately from the geometry of the rings and angle strain.

## 5BI.10 Factors affecting stability of conformations

To go more deeply into the chemistry of cyclic compounds, we must use conformational analysis. As preparation for that, let us review the factors that determine the stability of a conformation.

Any atom tends to have bond angles that match those of its bonding orbitals: tetrahedral (109.5°) for $sp^3$-hybridized carbon, for example. Any deviations from the "normal" bond angles are accompanied by **angle strain**.

Any pair of tetrahedral carbons attached to each other tend to have their bonds staggered. That is to say, any ethane-like portion of a molecule tends, like ethane, to take up a staggered conformation. Any deviations from the staggered arrangement are accompanied by **torsional strain**.

Any two atoms (or groups) that are not bonded to each other can interact in several ways, depending on their size and polarity, and how closely they are brought together. These non-bonded interactions can be either repulsive or attractive, and the result can be either destabilization or stabilization of the conformation.

Non-bonded atoms (or groups) that just touch each other—that is, that are about as far apart as the sum of their van der Waals radii—attract each other. If brought any closer together, they repel each other: such crowding together is accompanied by **van der Waals strain (steric strain)**.

Non-bonded atoms (or groups) tend to take positions that result in the most favorable **dipole–dipole interactions**: that is, positions that minimize dipole–dipole repulsions or maximize dipole–dipole attractions. (A particularly powerful attraction results from the special kind of dipole–dipole interaction called the **hydrogen bond**.)

All these factors, working together or opposing each other, determine the net stability of a conformation. To figure out what the most stable conformation of a particular molecule should be, one ideally should consider all possible combinations of bond angles, angles of rotation, and even bond lengths, and see which combination results in the lowest energy content. such calculations have become quite feasible through the use of computers.

Both calculations and experimental measurements show that the final result is a compromise, and that few molecules have the idealized conformations that we assign them and, for convenience, usually work with. For example, probably no tetravalent carbon compound—except one with four identical substituents—has *exactly* tetrahedral bond angles: a molecule accepts a certain amount of angle strain to relieve van der Waals strain or dipole–dipole interaction. In the *gauche* conformer of *n*-butane, the dihedral angle between the methyl groups is not 60°, but almost certainly larger: the molecule accepts some torsional strain to ease van der Waals strain between the methyl groups.

## 5BI.11 Conformations of cycloalkanes

Let us look more closely at the matter of puckered rings starting with cyclohexane, the most important of the cycloalkanes. Let us make a model of the molecule, and examine the conformations that are free of angle strain.

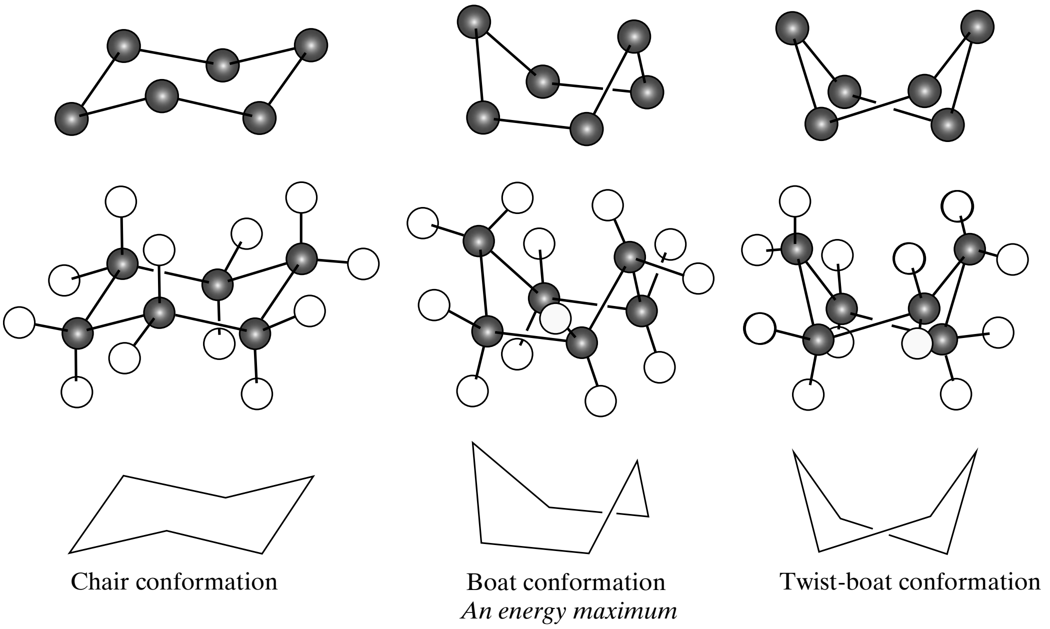
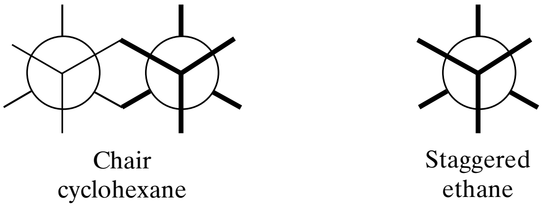


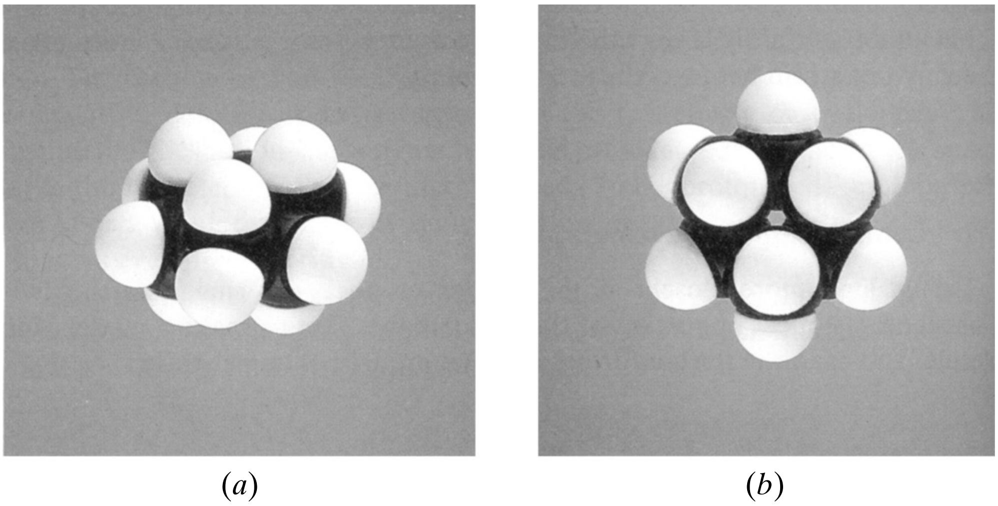
**Figure 5BI.4** Conformations of cyclohexane that are free of angle strain.

First, there is the **chair form** (Fig. 5BI.4). If we sight along each of the carbon–carbon bonds in turn, we see in every case perfectly staggered bonds:



The conformation is thus not only free of angle strain but free of torsional strain as well. It lies at an energy minimum, and is therefore a conformational isomer. *The chair form is the most stable conformation of cyclohexane, and, indeed, of nearly every derivative of cyclohexane* (see Fig. 5BI.5).

Now, let us take chair cyclohexane and flip the “left” end of the molecule up to make the *boat conformation*. (Like all the transformations we shall carry out in this



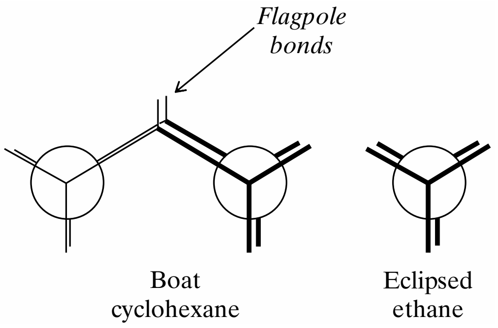
(*a*) (*b*)

**Figure 5BI.5** Electronic configuration and molecular shape. A model of cyclohexane in the chair conformation: two views.

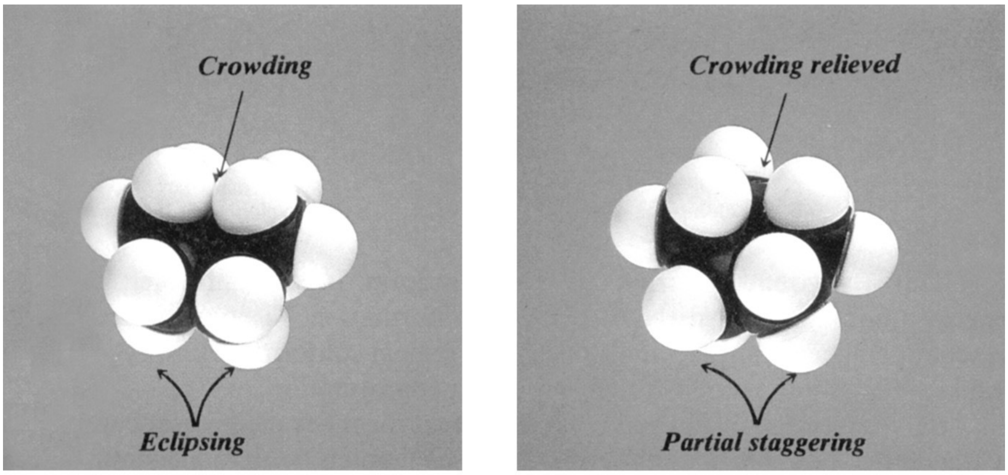
Only a scale model can show us what a marvelous creation chair cyclohexane is: symmetrical, compact, and completely free of strain—angle, torsional, van der Waals. Every angle is the tetrahedral angle. About every carbon–carbon bond there is precise staggering. There is no crowding of hydrogen atoms. Indeed, the hydrogens closest together may well feel mild van der Waals attraction for each other: hydrogens on adjacent carbons, and certain hydrogens on alternate carbons—the three facing us in (*b*) and the three corresponding ones on the opposite face of the molecule.

This architectural perfection results naturally—inevitably—from a happy coincidence: bond-angles, bond lengths, and atomic sizes happen to match exactly the geometrical demands of this six-membered ring. *Everything just fits*. Small wonder that we see cyclohexane chairs in the structure of diamond, the most stable form of carbon and the hardest substance known. Small wonder that—with an oxygen atom replacing one methylene group—similar chairs make up the most abundant building block of the organic world, D-glucose.

section, this involves only rotations about single bonds; what we are making are indeed conformations.) This is not a very happy arrangement. Sighting along either of two carbon–carbon bonds, we see sets of exactly eclipsed bonds,



and hence we expect considerable torsional strain: as much as in *two* ethane molecules. In addition, there is van der Waals strain due to crowding between the "flagpole" hydrogens, which lie only 1.83 Å apart, considerably closer than the sum of their van der Waals radii (2.5 Å). The boat conformation is a good deal less stable (7.1 kcal/mol, it has been calculated) than the chair conformation. It is



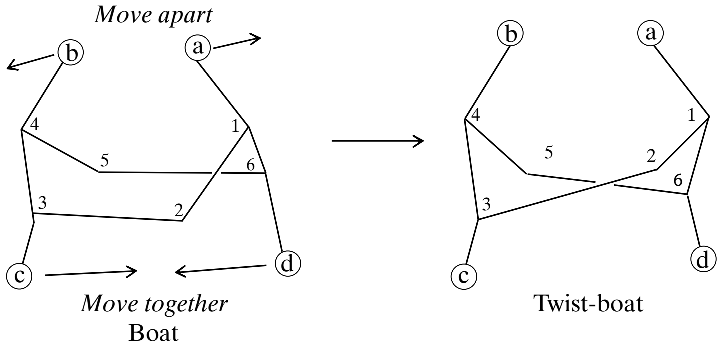
Boat
(*a*)

Twist-boat
(*b*)

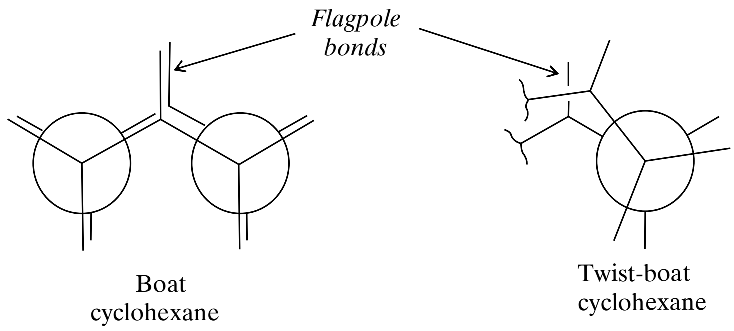
**Figure 5BI.6** Cyclohexane in the boat and twist-boat conformations. (*a*) In the boat conformation there is not only eclipsing of bonds, but crowding of flagpole hydrogens. (*b*) In the twist-boat conformation bonds are partially staggered, and the flagpole hydrogens have moved apart.

believed to lie, not at an energy minimum, but at an energy maximum; it is thus not a conformer, but a transition state between two conformers (Fig. 5BI.6*a*).

Now, what are these two conformers that lie—energetically speaking—on either side of the boat conformation? To see what they are, let us hold a model of the boat conformation with the flagpole hydrogens ($H_a$ and $H_b$) pointing up, and look down through the ring. We grasp C–2 and C–3 in the right hand and C–5 and C–6 in the left hand, and *twist* the molecule so that, say, C–3 and C–6 go *down*, and C–2 and C–5 come *up*. As we do this, $H_a$ and $H_b$ move diagonally apart, and we see (below the ring) a pair of hydrogens, $H_c$ and $H_d$ (on C–3 and C–6, respectively), begin to approach each other. (If this motion is continued, we make a new boat conformation with $H_c$ and $H_d$ becoming the flagpole hydrogens.) When the $H_a$–$H_b$ distance is equal to the $H_c$–$H_d$ distance, we stop and examine the molecule. We have minimized the flagpole–flagpole interactions, and at the same time have partly relieved the torsional strain at the C(2)–C(3) and C(5)–C(6) bonds (see Fig. 5BI.6*b*).



Cyclohexane



This new configuration is the **twist-boat form**. It is a conformer, lying at an energy minimum 5.5 kcal above the chair conformation. The twist-boat conformer is separated from another, enantiomeric twist-boat conformer by an energy barrier 1.6 kcal high, at the top of which is the boat conformation.

Between the chair form and the twist-boat form lies the highest barrier of all: a transition state conformation (the *half-chair*) which, with angle strain and torsional strain, lies about 11 kcal above the chair form.

The overall relationships are summarized in Fig. 5BI.7. Equilibrium exists between the chair and twist-boat forms, with the more stable chair form being favored—10 000 to 1 at room temperature.

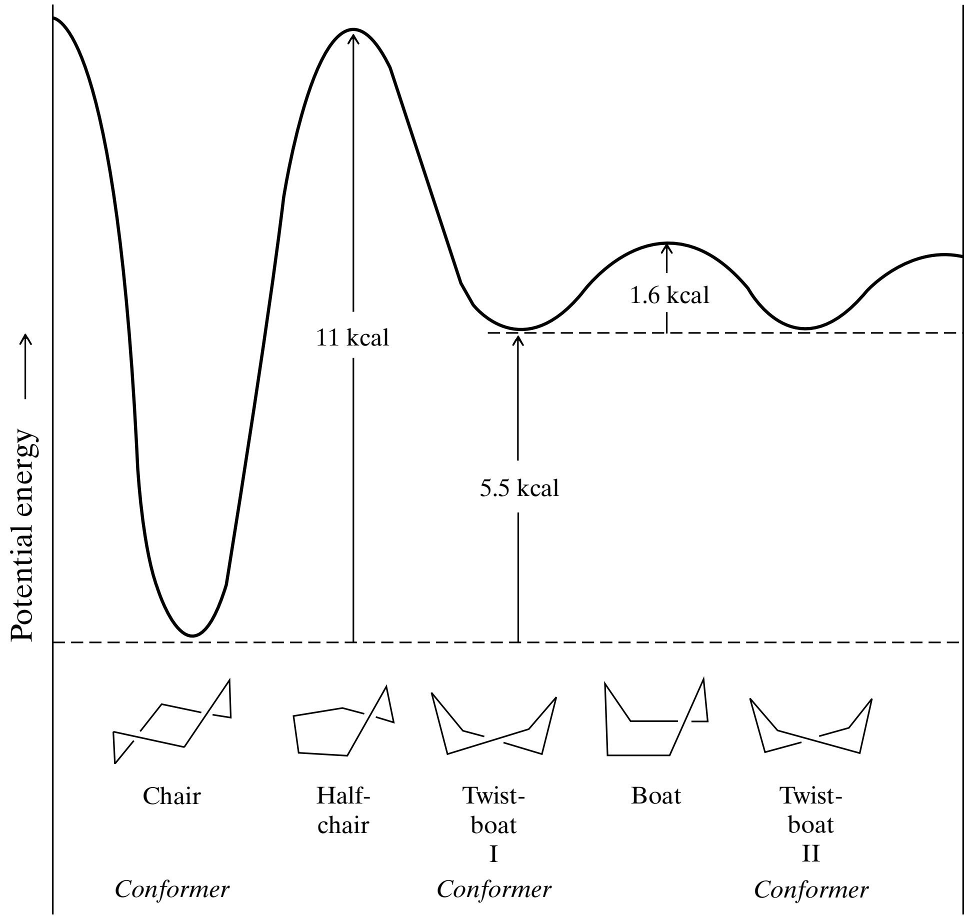


**Figure 5BI.7** Potential energy relationships among conformations of cyclohexane.

If chair cyclohexane is, conformationally speaking, the perfect specimen of a cycloalkane, planar cyclopentane (Fig. 5BI.8) must certainly be one of the poorest: there is exact bond eclipsing between every pair of carbons. To (partially) relieve this torsional strain, cyclopentane takes on a slightly puckered conformation, even at the cost of a little angle strain.

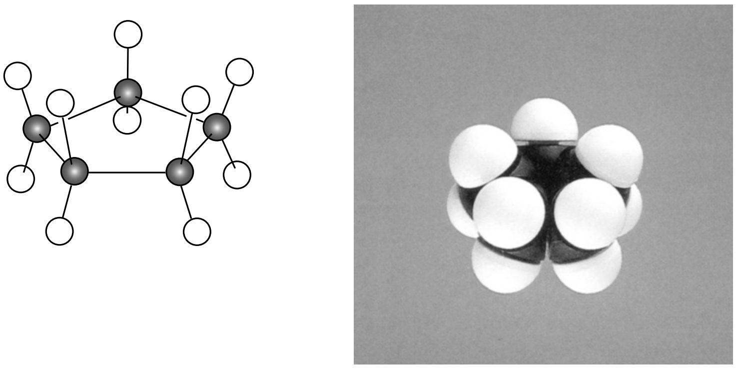


**Figure 5BI.8** Planar cyclopentane: much torsional strain. The molecule is actually puckered.

Evidence of many kinds strongly indicates that cyclobutane is not planar, but rapidly changes between equivalent, slightly folded conformations (Fig. 5BI.9). Here, too, torsional strain is partially relieved at the cost of a little angle strain.

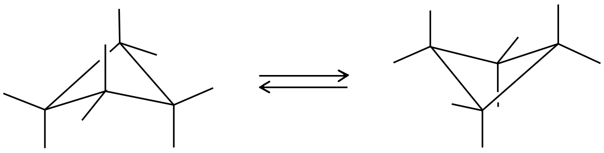


**Figure 5BI.9** Cyclobutane: rapid transformation between equivalent non-planar "folded" conformations.

Rings containing seven to twelve carbon atoms, too, are less stable than cyclohexane. They are subject to torsional strain and, as scale models reveal, to serious crowding of hydrogens inside the rings (see Fig. 5B.1.10). Only quite large ring systems are as stable as cyclohexane.

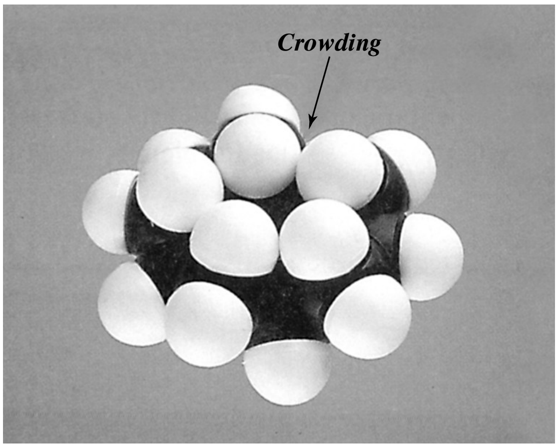


**Figure 5BI.10** Model of cyclodecane. Staggering about carbon–carbon bonds is achieved only at the expense of crowding of hydrogens inside the ring.

## 5BI.12 Equatorial and axial bonds in cyclohexane

Let us return to the model of the chair conformation of cyclohexane (see Fig. 5BI.11). Although the cyclohexane ring is not flat, we can consider that the carbon atoms lie roughly in a plane. If we look at the molecule in this way, we see that the hydrogen atoms occupy two kinds of position: six hydrogens lie in the plane, while six hydrogens lie above or below the plane. The bonds holding the hydrogens that are in the plane of the ring lie in a belt about the "equator" of the ring, and are called **equatorial bonds**. The bonds holding the hydrogen atoms that are above and below the plane are pointed along an axis perpendicular to the plane and are called **axial bonds**. In the chair conformation each carbon atom has one equatorial bond and one axial bond.

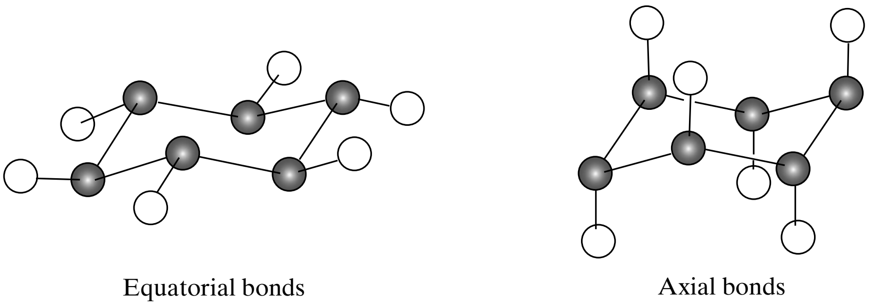


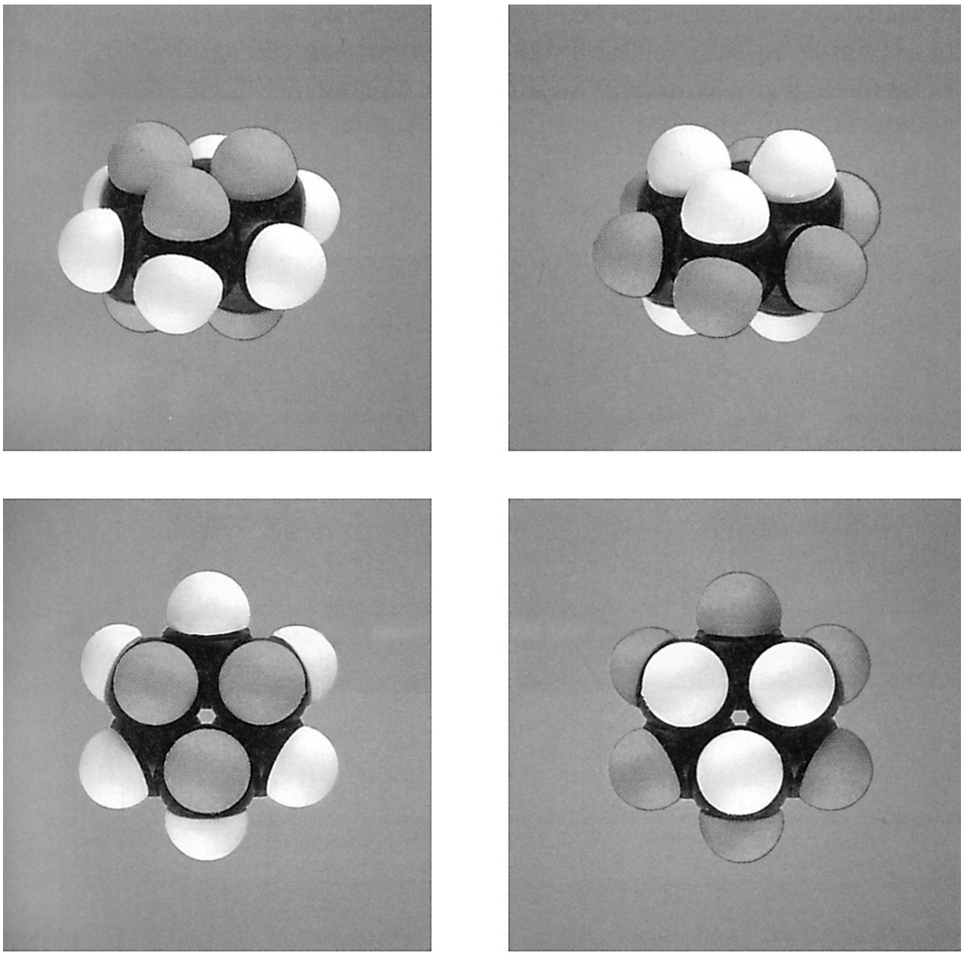
**Figure 5BI.11** Chair cyclohexane: equatorial and axial bonds.

Cyclohexane itself, in which only hydrogens are attached to the carbon atoms, is not only free of angle strain and torsional strain, but free of van der Waals strain as well (see Fig. 5BI.12). Hydrogens on adjacent carbons are the same distance apart (2.3 Å) as in (staggered) ethane and, if anything, feel mild van der Waals attraction for each other. We notice that the three axial hydrogens on the same side of the molecule are thrown rather closely together, despite the fact that they are attached to alternate carbon atoms; as it happens, however, they are the same favorable distance apart (2.3 Å) as the other hydrogens are.

If, now, a hydrogen is replaced by a larger atom or group, crowding occurs. The most severe crowding is among atoms held by the three axial bonds on the same side of the molecule; the resulting interaction is called **1, 3-diaxial interaction**. Except for hydrogen, *a given atom or group has more room in an equatorial position than in an axial position*.

As a simple example of the importance of 1, 3-diaxial interactions, let us consider methylcyclohexane. In estimating relative stabilities of various conformations of this compound, we must focus our attention on methyl, since it is the largest substituent on the ring and hence the one most subject to crowding. There are two possible chair conformations (see Fig. 5BI.13), one with —$CH_3$ in an equatorial position, the other with —$CH_3$ in an axial position. As shown in Fig. 5BI.14, the two axial hydrogens (on C–3 and C–5) approach the axial —$CH_3$ (on C–l) more closely than any hydrogens approach the equatorial —$CH_3$. We would expect the equatorial conformation to be the more stable, and it is, by about 1.8 kcal. Most molecules (about 95% at room temperature) exist in the conformation with methyl in the uncrowded equatorial position.

In an equatorial position, we see, —$CH_3$ points *away from* its nearest neighbors: the two hydrogens—one axial, and one equatorial—on the adjacent carbons. This is not true of —$CH_3$ in an axial position, since it is held by a bond that is *parallel* to the bonds holding its nearest neighbors, the two axial hydrogens.



Equatorial hydrogens
(*a*)

Axial hydrogens
(*b*)

**Figure 5BI.12** Models of chair cyclohexane. (*a*) Equatorial hydrogens are shown in white. (*b*) Axial hydrogens are shown in white.

Conformational analysis can account not only for the fact that one conformation is more stable than another, but often—with a fair degree of accuracy—for just *how much* more stable it is. We have attributed the 1.8-kcal energy difference between the two conformations of methylcyclohexane to 1, 3-diaxial interactions

Equatorial —$CH_3$

Axial —$CH_3$

**Figure 5BI.13** Chair conformations of methylcyclohexane.

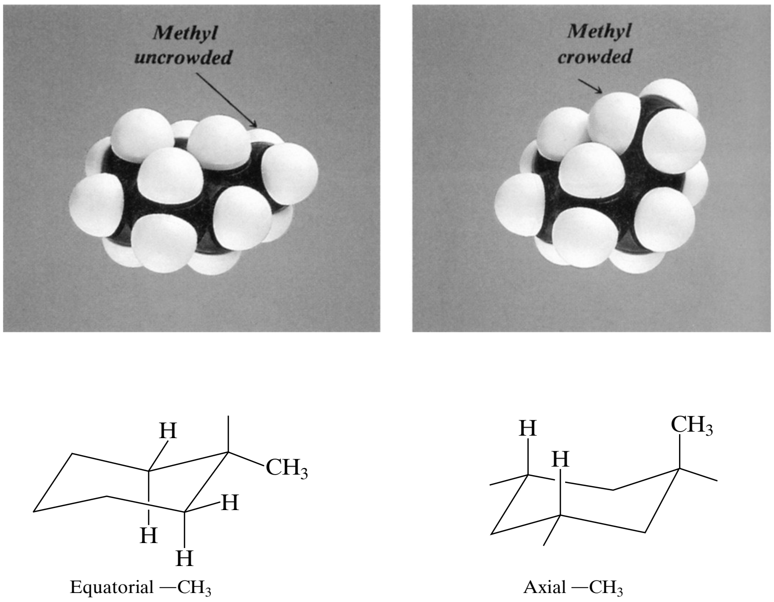
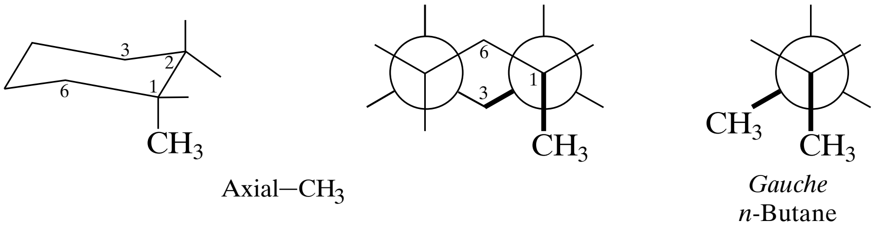


**Figure 5BI.14** 1, 3-Diaxial interaction in methylcyclohexane. An axial —$CH_3$ is more crowded than an equatorial —$CH_3$.

between a methyl group and *two* hydrogens. If, on that basis, we assign a value of 0.9 kcal/mol to each 1, 3-diaxial methyl–hydrogen interaction, we shall find that we can account amazingly well for the energy differences between conformations of a variety of cyclohexanes containing more than one methyl group.

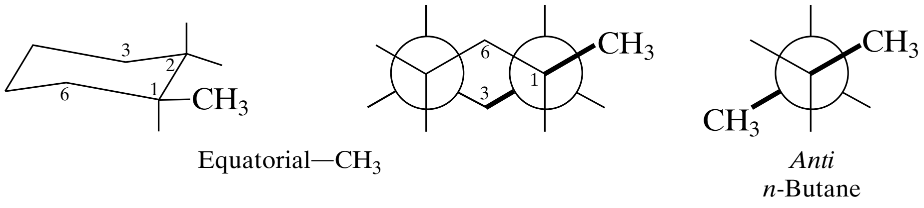
We notice that 0.9 kcal is nearly the same value that we earlier assigned to a *gauche* interaction in *n*-butane; examination of models shows that this is not just accidental.

Let us make a model of the conformation of methylcyclohexane with axial methyl. If we hold it so that we can sight along the C(1)–C(2) bond, we see something like this, represented by a Newman projection:



The methyl group and C–3 of the ring have the same relative locations as the two methyl groups in the *gauche* conformation of *n*-butane. If we now sight along the C(1)–C(6) bond, we see a similar arrangement but with C–5 taking the place of C–3.

Next, let us make a model of the conformation with equatorial methyl. This time, if we sight along the C(1)–C(2) bond, we see this:



Here, methyl and C–3 of the ring have the same relative locations as the two methyl groups in the *anti* conformation of *n*-butane. And if we sight along the C(l)–C(6) bond, we see methyl and C–5 in the *anti* relationship.

Thus, for each 1, 3-diaxial methyl–hydrogen interaction there is a "butane-*gauche*" interaction between the methyl group and a carbon atom of the ring. Of the two approaches, however, looking for 1, 3-diaxial interactions is much the easier and has the advantage, when we study substituents other than methyl, of focusing our attention on the sizes of the groups being crowded together.

In general, then, it has been found that (a) chair conformations are more stable than twist conformations, and (b) the most stable chair conformations are those in which the largest groups are in equatorial positions. There are exceptions to both these generalizations (which we shall encounter later in problems), but the exceptions are understandable ones.

## 5BI.13 Preparation of cyclopropane rings by $\pi$-insertion reaction of carbenes

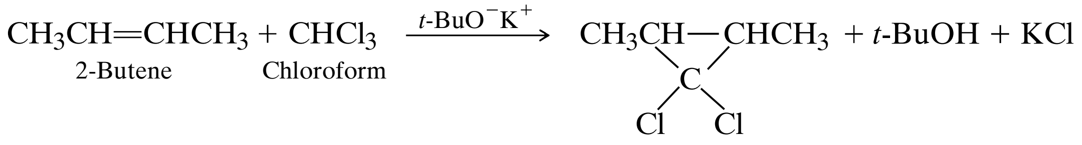
The most important route to cyclic compounds is via the class of reactions called *cycloaddition*. Let us look at one kind of cycloaddition and, at the same time, become acquainted with a highly unusual class of reagents.

The difference between successive members of a homologous series, we have seen, is the $CH_2$ unit, or *methylene*. But methylene is more than just a building block for the mental construction of compounds; it is an actual molecule, and its chemistry and the chemistry of its derivatives, the **carbenes**, has become one of the most exciting and productive fields of organic research.

### 5BI.13.1 Addition of substituted carbenes. 1, 1-Elimination

The addition of carbenes to alkenes is used principally to make cyclopropanes. For this purpose one seldom uses methylene itself, but rather various substituted carbenes. These are often generated in ways quite different from the photochemical reactions described in the preceding section.

A common method for making cyclopropanes is illustrated by the reaction of 2-butene with chloroform in the presence of potassium *tert*-butoxide:



$$\underset{\text{2-Butene}}{CH_3CH{=}CHCH_3} + \underset{\text{Chloroform}}{CHCl_3} \xrightarrow{t\text{-BuO}^-K^+} CH_3CH{-}CHCH_3\,(\text{bridged by } CCl_2) + t\text{-BuOH} + KCl$$

3, 3-Dichloro-1, 2-dimethylcyclopropane

The dichlorocyclopropanes obtained can be reduced to hydrocarbons or hydrolysed to *ketones*, the starting point for many syntheses.

Here, too, reaction involves a divalent carbon compound, a derivative of methylene: *dichlorocarbene*,: $CCl_2$. It is generated in two steps, initiated by attack on chloroform by the very strong base, *tert*-butoxide ion, and then adds to the alkene.

## EXERCISE

**1.** Draw structural formulas of:

(a) methylcyclopentane
(b) 1-methylcyclohexene
(c) 3-methylcyclopentene
(d) *trans*-l,3-dichlorocyclobutane
(e) *cis*-1-bromo-2-methylcyclopentane
(f) cyclohexylcyclohexane

(g) cyclopentylacetylene
(h) 4-chloro-1,1-dimethylcycloheptane
(i) bicyclo[2.2.1]hepta-2,5-diene
(j) 1-chlorobicyclo[2.2.2]octane

**2.** Give structures and names of the principal organic products expected from each of the following reactions:

(a) cyclopropane + $Cl_2$, $FeCl_3$
(b) cyclopropane + $Cl_2$(300 °C)
(c) cyclopropane + conc. $H_2SO_4$
(d) cyclopentane + $Cl_2$, $FeCl_3$
(e) cyclopentane + $Cl_2$(300 °C)
(f) cyclopentane + conc. $H_2SO_4$
(g) cyclopentene + $Br_2/CCl_4$
(h) cyclopentene + $Br_2$ (300 °C)
(i) 1-methylcyclohexene + HCl
(j) 1-methylcyclohexene + $Br_2$(aq)
(k) 1-methylcyclohexene + HBr (peroxides)
(l) 1,3-cyclohexadiene + HCl
(m) cyclopentanol + $H_2SO_4$ (heat)
(n) bromocyclohexane + KOH(alc)
(o) cyclopentene + cold $KMnO_4$
(p) cyclopentene + $HCO_2OH$
(q) cyclopentene + $C_6H_5CO_2OH$
(r) cyclopentene + hot $KMnO_4$
(s) cyclopentene + NBS
(t) 3-bromocyclopentene + KOH (hot)
(u) 1,4-cyclohexanediol + $H_2SO_4$ (hot)
(v) cyclohexene + $H_2SO_4 \longrightarrow C_{12}H_{20}$
(w) cyclopentene + $CHCl_3$ + *t*-BuOK
(x) cyclopentene + $CH_2I_2$ + Zn(Cu)
(y) chlorocyclopentane + $(C_2H_5)_2CuLi$
(z) 1-methylcyclopentene + cold conc. $H_2SO_4$
(aa) 3-methylcyclopentene + $O_3$, then $H_2O$/Zn
(bb) 1-methylcyclohexene + $(BH_3)_2$; $H_2O$, $OH^-$
(cc) 1-methylcyclohexene + $Hg(OAc)_2$, $H_2O$; $NaBH_4$

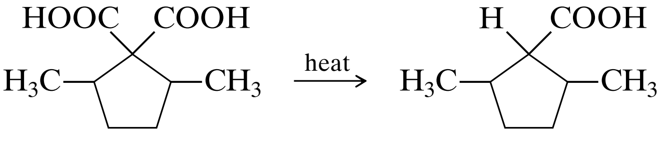
**3.** Outline all steps in the laboratory synthesis of each of the following from cyclohexanol.

(a) cyclohexene
(b) cyclohexane
(c) *trans*-1,2-dibromocyclohexane
(d) *cis*-l,2-cyclohexanediol
(e) *trans*-1,2-cyclohexanediol
(f) $OHC(CH_2)_4CHO$
(g) adipic acid, $HOOC(CH_2)_4COOH$
(h) bromocyclohexane
(i) 2-chlorocyclohexanol
(j) 3-bromocyclohexene
(k) 1,3-cyclohexadiene
(l) cyclohexylcyclohexane
(m) *norcarane*, bicyclo[4.1.0]heptane

**4.** Give structures for all isomers of the following. For cyclohexane derivatives, planar formulas will be sufficient here. Label pairs of enantiomers, and *meso* compounds.

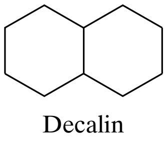
(a) dichlorocyclopropanes
(b) dichlorocyclobutanes
(c) dichlorocyclopentanes
(d) dichlorocyclohexanes
(e) chloro-1,1-dimethylcyclohexanes
(f) 1, 3, 5-trichlorocyclohexanes
(g) There are a number of stereoisomeric 1, 2, 3, 4, 5, 6-hexachlorocyclohexanes. Without attempting to draw all of them, give the structure of the most stable isomer, and show its preferred conformation.

**5.** (a) 2, 5-Dimethyl-1,1-cyclopentanedicarboxylic acid (I) can be prepared as two optically inactive substances (A and B) of different m.p. Draw their structures, (b) Upon heating, A yields two 2, 5-dimethylcyclopentanecarboxylic acids (II), and B yields only one. Assign structures to A and B.



I II

**6.** The compound *decalin*, $C_{10}H_{18}$, consists of two fused cyclohexane rings:

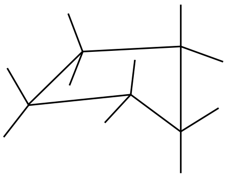


Decalin

(a) Using models, show how there can be two isomeric decalins, *cis* and *trans*, (b) How many dif-ferent conformations free of angle strain are possible for *cis*-decalin? For *trans*-decalin? (c) Which is the most stable conformation of *cis*-decalin? Of *trans*-decalin? (d) Account for the fact that *trans*-decalin is more stable than *cis*-decalin. (*Hint:* Consider each ring in turn. What are the largest sub-stituents on each ring?) (e) The difference in stability between *cis*- and *trans*-decalin is about 2 kcal/mol. Conversion of one into the other takes place only under very vigorous conditions. The chair and twist-boat forms of cyclohexane, on the other hand, differ in stability by about 6 kcal/mol, yet are readily interconverted at room temperature. How do you account for the contrast? Draw energy curves to illustrate your answer.

**7.** Allinger found the energy difference between *cis*- and *trans*-l,3-di-*tert*-butylcyclohexane to be 5.9 kcal/mol, and considers that this value represents the energy difference between the chair and twist-boat forms of cyclohexane. Defend Allinger's position.

**8.** It has been suggested that in certain substituted cyclopentanes the ring exists preferentially in the "envelope" form:



Using models, suggest a possible explanation for each of the following facts:

(a) The attachment of a methyl group to the badly strained cyclopentane ring raises the heat of combustion very little more than attachment of a methyl group to the unstrained cyclohexane ring. (*Hint:* Where is the methyl group located in the "envelope" form?)

(b) Of the 1, 2-dimethylcyclopentanes, the *trans* isomer is more stable than the *cis*. Of the 1, 3-dimethylcyclopentanes, on the other hand, the *cis* isomer is more stable than the *trans*.

**9.** Arrange the compounds of each set in order of reactivity toward the indicated reaction:

(a) bromocyclohexane, 1-bromo-1-methylcyclohexane, (bromomethyl) cyclohexane toward $S_N2$ displacement

(b) the compounds of part (a) toward $S_N1$ displacement

(c) 5-bromo-l,3-cyclohexadiene, bromocyclohexane, 3-bromocyclohexene, 1-bromocyclohexene toward dehydrohalogenation by strong base

(d) *cis*-and *trans*-2-bromo-1-methylcyclohexane toward dehydrohalogenation by strong base

**10.** When l,3,5,5-tetramethyl-l,3-cyclohexadiene is dissolved in cold concentrated $H_2SO_4$, the solution shows a freezing-point lowering that corresponds to two particles for each molecule of diene dissolved. On addition of water to the solution, the diene is completely regenerated. How do you account for these observations? Just what is happening and why?

**11.** Hydroboration–oxidation of 1, 2-dimethylcyclopentene gives only *cis*-l, 2-dimethyl-cyclopentanol. Assuming that this is typical (it is), what is the *stereochemistry of hydroboration– oxidation*?

**12.** Each of the following reactions is carried out, and the products are separated by careful distillation, recrystallization, or chromatography. For each reaction tell how many fractions will be collected. Draw a stereochemical formula of the compound or compounds making up each fraction. Tell whether each fraction, as collected, will be optically active or optically inactive.

(a) (*R*)-3-hydroxycyclohexene + $KMnO_4 \longrightarrow C_6H_{12}O_3$

(b) (*R*)-3-hydroxycyclohexene + $HCO_2OH \longrightarrow C_6H_{12}O_3$

(c) (*S*,*S*)-l,2-dichlorocyclopropane + $Cl_2$ (300 °C) $\longrightarrow C_3H_3Cl_3$

(d) *racemic* 4-methylcyclohexene + $Br_2/CCl_4$

(e) *trans*-4-methyl-1 -bromocyclohexane + $OH^-$ (second-order) $\longrightarrow C_7H_{14}O + C_7H_{12}$

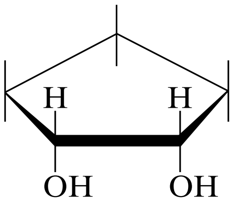
**13.** When *trans*-2-methylcyclopentanol is heated with acid, it gives chiefly 1-methylcyclopentene. When the same alcohal is treated with tosyl cholride,

$$R—O—H + Ts—Cl \longrightarrow R—O—Ts + HCl$$

## 5BII. Stereoisomerism

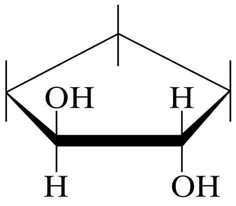
### 5BII.1 Stereoisomerism of cycloalkanes and their derivatives: configurational isomerism of cyclic compounds

We shall begin with the compound 1,2-cyclopentanediol. Using models, we find that we can arrange the atoms of this molecule as in I, in which both hydroxyls lie below (or above) the plane of the ring, and as in II, in which one hydroxyl lies above and the other lies below the plane of the ring.



I

*cis*-1,2-Cyclopentanediol



II

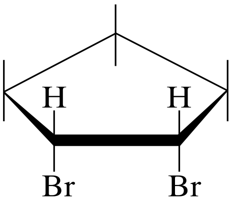
*trans*-1,2-Cyclopentanediol

I and II cannot be superimposed, and hence are isomers. They differ only in the way their atoms are oriented in space, and hence are stereoisomers. No amount of rotation about bonds can interconvert I and II, and hence they are not conformational isomers. They are configurational isomers; they are interconverted only by breaking of bonds, and hence are isolable. They are not mirror images, and hence are diastereomers; they should, therefore, have different physical properties, as the two diols actually have. Configuration I is designated the *cis* configuration, and II is designated the *trans* configuration.

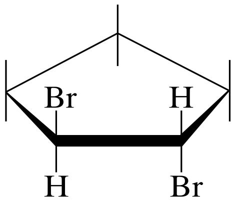
**Problem 5BII.1** You have two bottles labeled "1,2-Cyclopentanediol", one containing a compound of m.p. 30 °C, the other a compound of m.p. 55 °C; both compounds are optically inactive. How could you decide, beyond any doubt, which bottle should be labeled *"cis"* and which *"trans"*?

**Problem 5BII.2** (a) Starting from cyclopentanol, outline a synthesis of stereochemically pure *cis*-l,2-cyclopentanediol. (b) Of stereochemically pure *trans*-l,2-cyclopentanediol.

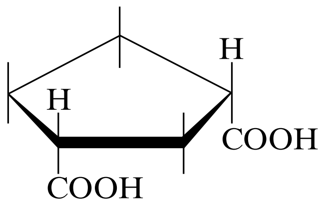
Stereoisomerism of this same sort should be possible for compounds other than diols, and for rings other than cyclopentane. Some examples of isomers that have been isolated are:



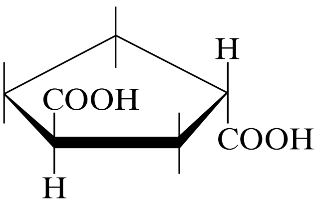
*cis*-1,2-Dibromocyclopentane



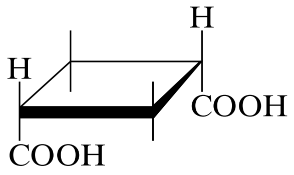
*trans*-1,2-Dibromocyclopentane



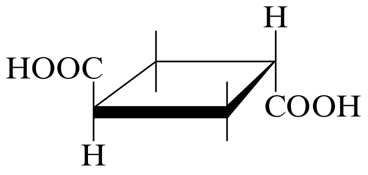
*cis*-1,3-Cyclopentanedicarboxylic acid



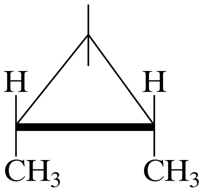
*trans*-1,3-Cyclopentanedicarboxylic acid



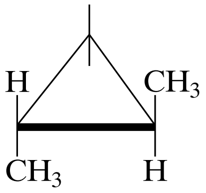
*cis*-1,3-Cyclobutanedicarboxylic acid



*trans*-1,3-Cyclobutanedicarboxylic acid

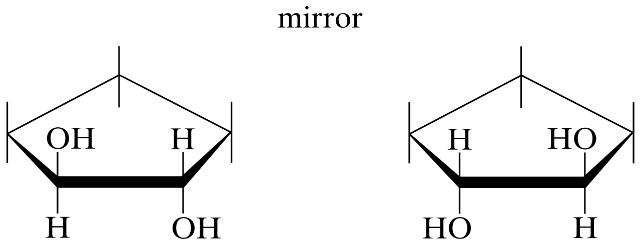


*cis*-1,2-Dimethylcyclopropane



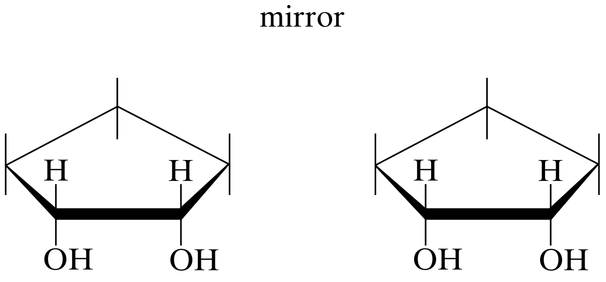
*trans*-1,2-Dimethylcyclopropane

If we examine models of *cis*- and *trans*-l,2-cyclopentanediol more closely, we find that each compound contains two chiral centers. We know that compounds containing more than one chiral center are often—but not always—chiral. Are these diols chiral? As always, to test for possible chirality, we construct a model of the molecule and a model of its mirror image, and see if the two are superimposable. When we do this for the *trans* diol, we find that the models are not superimposable. The *trans* diol is chiral, and the two models we have constructed therefore correspond to enantiomers. Next, we find that the models are not interconvertible by rotation about single bonds. They therefore represent, not conformational isomers, but configurational isomers; they should be capable of isolation—*resolution*—and, when isolated, each should be optically active.



*Not superimposable*
*Enantiomers : resolvable*
*trans*-1,2-Cyclopentanediol

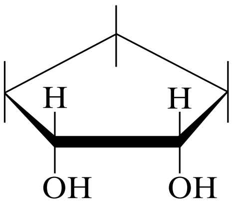
Next let us look at *cis*-l,2-cyclopentanediol. This, too, contains two chiral centers; is it also chiral? This time we find that a model of the molecule and a model of



*Superimposable*
*A meso compound*
*cis*-1,2-Cyclopentanediol

its mirror image *are* superimposable. In spite of its chiral centers, *cis*-1,2-cyclopentanediol is not chiral; it cannot exist in two enantiomeric forms, and cannot be optically active. It is a *meso* compound.

We might have recognized *cis*-l,2-cyclopentanediol as a *meso* structure on sight from the fact that one half of the molecule is the mirror image of the other half:



*A meso compound*
*cis*-1,2-Cyclopentanediol

Thus, of the two 1,2-cyclopentanediols obtainable by ordinary synthesis, only one is separable into enantiomers, that is, is *resolvable*; this must necessarily be the *trans* diol. The other diol is a single, inactive, non-resolvable compound, and it must have the *cis* configuration.

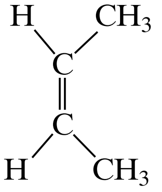
What is the relationship between the *meso cis* diol and either of the enantiomeric *trans* diols? They are *diastereomers*, since they are stereoisomers that are not enantiomers.

## 5BII.2 Geometric isomerism of alkenes

Since the isomeric 2-butenes differ from one another *only* in the way the atoms are oriented in space (but are like one another with respect to which atoms are attached to which other atoms), they belong to the general class we have called *stereoisomers*. They are not, however, mirror images of each other, and hence are not enantiomers. As we have already said, *stereoisomers that are not mirror images of each other are called* **diastereomers**.

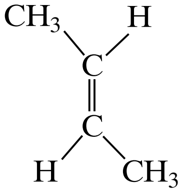
The particular kind of diastereomers that owe their existence to hindered rotation about double bonds are called **geometric isomers**. The isomeric 2-butenes, then, are diastereomers, and more specifically, geometric isomers.

We recall that the arrangement of atoms that characterizes a particular stereoisomer is called its *configuration*. The configurations of the isomeric 2-butenes are the structures I and II. These configurations are differentiated in their names by the prefixes ***cis-*** (Latin: on this side) and ***trans-*** (Latin: across), which indicate that the methyl groups are on the same side or on opposite sides of the molecule. In a way that we shall take up shortly, the isomer of b.p. +4 °C has been assigned the *cis* configuration, and the isomer of b.p. +1 °C has been assigned the *trans* configuration.



I

*cis*-2-Butene
b.p. +4 °C

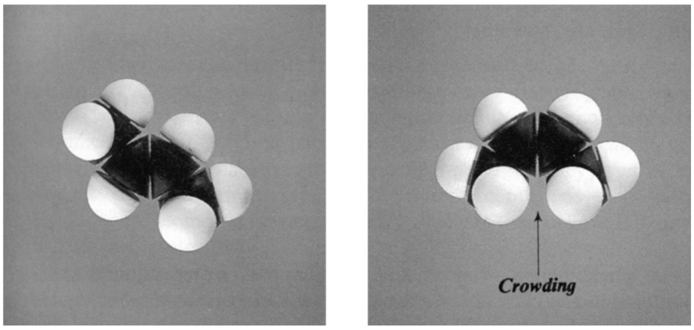


II

*trans*-2-Butene
b.p. +1 °C

**Geometric isomers**

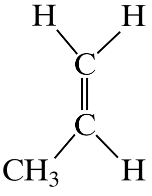
Figure 5BII.1 shows scale models of the isomeric 2-butenes. In the *trans* isomer, we see, the methyl groups are well separated; in the *cis* isomer, however, the methyls are thrown closely enough together to cause crowding. From this, we might expect the *cis* isomer to be less stable than the *trans*, and, as we shall see, it *is*.



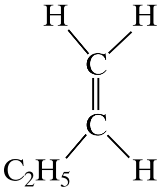
(*a*) (*b*)

**Figure 5BII.1** Models of the geometric isomers of 2-butene: (*a*) *trans*, (*b*) *cis*. Note the crowding between the methyl groups in the cis isomer.

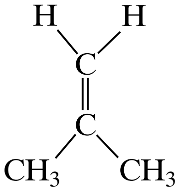
There is hindered rotation about *any* carbon–carbon double bond, but it gives rise to geometric isomerism only if there is a certain relationship among the groups attached to the doubly bonded carbons. We can look for this isomerism by drawing the possible structures (or better yet, by constructing them from molecular models), and then seeing if these are indeed isomeric, or actually identical. On this basis we find that propylene, 1-butene, and isobutylene should not show isomerism; this conclusion agrees with the facts. Many higher alkenes may, of course, show geometric isomerism.



Propylene



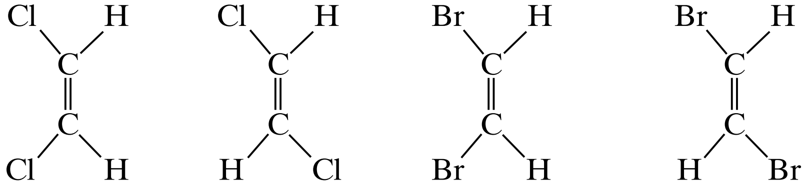
1-Butene



Isobutylene

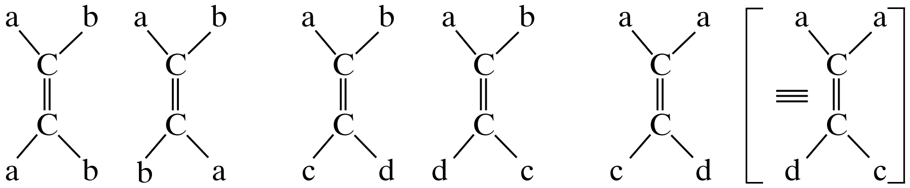
*No geometric isomerism*

If we consider compounds other than hydrocarbons, we find that 1,1 -dichloroethene and 1,1-dibromoethene should not show isomerism, whereas the 1,2-dichloroethenes and 1,2-dibromoethenes shoulC. In every case these predictions have been found correct. Isomers of the following physical properties have been isolated.



| *cis-* | *trans-* | *cis-* | *trans-* |
|---|---|---|---|
| 1,2-Dichloroethene | | 1,2-Dibromoethene | |
| b.p. 60 °C<br>m.p. −80 °C | b.p. 48 °C<br>m.p. −50 °C | b.p. 110 °C<br>m.p. −53 °C | b.p. 108 °C<br>m.p. −6 °C |

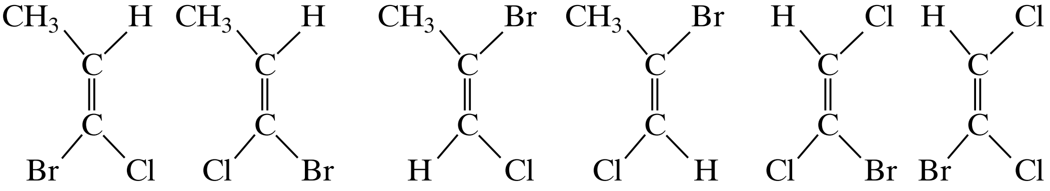
As we soon conclude from our examination of these structures, geometric iso-merism cannot exist if either carbon carries two identical groups. Some possible combinations are shown below.



*Isomerism* *Isomerism* *No isomerism*

The phenomenon of geometric isomerism is a general one and can be encoun-tered in any class of compounds that contain carbon–carbon double bonds (or even double bonds of other kinds).

The prefixes *cis*-and *trans-* work very well for disubstituted ethylenes and some trisubstituted ethylenes. But how are we to specify configurations like the following?



| *Z* *E* | *Z* *E* | *Z* *E* |
|---|---|---|
| 1-Bromo-1-chloropropene | 2-Bromo-1-chloropropene | 1-Bromo-1,2-dichloroethene |
| $CH_3 > H$<br>$Br > Cl$ | $Br > CH_3$<br>$Cl > H$ | $Cl > H$<br>$Br > Cl$ |

Which groups are our reference points? Looking at each doubly bonded carbon in turn, we arrange its two atoms or groups in their Cahn–lngold–Prelog sequence. We then take the group of higher priority on the one carbon and the group of higher priority on the other carbon, and tell whether they are on the same side of the molecule or on opposite sides. So that it will be clear that we are using this method of specification, we use the letter ***Z*** to mean *on the same side,* and the letter ***E*** to mean *on opposite sides.* (From the German: *zusammen*, together, and *entgegen*, opposite.) The appropriate letter then becomes part of the name of such an alkene: (*Z*)-1-bromo-1-chloropropene, for example.

A pair of geometric isomers are, then, diastereomers. Where do they fit into the other classification scheme, the one based on how stereoisomers are interconverted? There are, we saw:

(a) *configurational isomers*, interconverted by inversion (turning-inside-out) at a chiral center; and

(b) *conformational isomers*, interconverted by rotations about single bonds. Now, we add:

(c) *geometric isomers*, interconverted—in principle—by rotation about a double bond.

The operation required—rotation—is the same for interconversion of geometric and conformational isomers. But, from the very practical standpoint of *isolability*, geometric isomers are more akin to configurational isomers: interconversion requires bond-breaking— a $\pi$ bond in the case of geometric isomers—and hence is always a difficult process. Conformational isomers are interconverted by the (usually) easy process of rotation about single bonds.

For convenience, we laid down the following "ground rule" for discussions and problems in this book: unless specifically indicated otherwise, *the terms "stereoisomers", " enantiomers", and "diastereomers" will refer only to configurational isomers and geometric isomers,* and will exclude conformational isomers. The latter will be referred to as "conformational isomers", "conformers", "conformational enantiomers", and "conformational diastereomers".

In so far as chemical and physical properties are concerned, geometric isomers show the same relationship to each other as do the other diastereomers we have encountered. They contain the same functional groups and hence show similar chemical properties. Their chemical properties are *not identical,* however, since their structures are neither identical nor mirror images; they react with the same reagents, but at different rates. (Under certain conditions—especially in biological systems—geometric isomers can vary widely in their chemical behavior.)

As the examples above illustrate, geometric isomers have different physical properties: different melting points, boiling points, refractive indices, solubilities, densities, and so on. On the basis of these different physical properties, they can be distinguished from each other and, once the configuration of each has been determined, identified. On the basis of these differences in physical properties they can, in principle at least, be separated.

## 5BII.3 Conformational analysis

So far, we have described the relative positions of groups in *cis* and *trans* isomers in terms of fiat rings: both groups are below (or above) the plane of the ring, or one group is above and the other is below the plane of the ring. In view of what we have said about puckering, however, we realize that this is a highly simplified picture even for four- and five-membered rings, and for six-membered rings is quite inaccurate.

Let us apply the methods of conformational analysis to the stereochemistry of cyclohexane derivatives; and, since we are already somewhat familiar with interactions of the methyl group, let us use the dimethylcyclohexanes as our examples.

If we consider only the more stable, chair conformations, we find that a particular molecule of *trans*-l,2-dimethylcyclohexane, to take our first example, can exist in two conformations (see Fig. 5BII.2). In one, both —$CH_3$ groups are in equatorial positions, and in the other, both —$CH_3$ groups are in axial positions. Thus, we see, the two —$CH_3$ groups of the *trans* isomer are not necessarily on opposite sides of the ring; in fact, because of lesser crowding between —$CH_3$ groups and axial hydrogens of the ring (less 1,3-diaxial interaction), the more stable conformation is the diequatorial one.

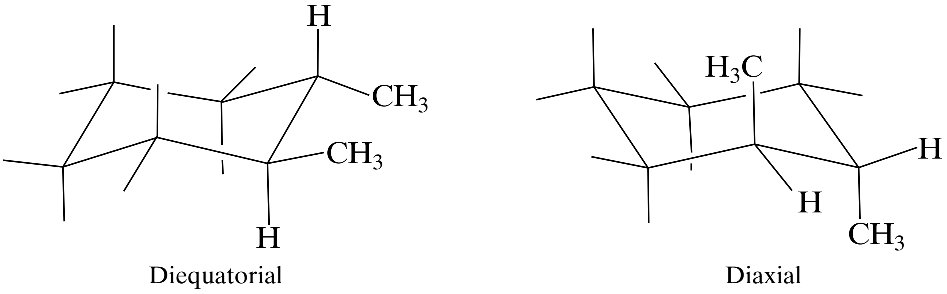


**Figure 5BII.2** Chair conformations of *trans*-1,2-dimethylcyclohexane.

A molecule of *cis*-l,2-dimethylcyclohexane can also exist in two conformations (see Fig. 5BII.3). In this case, the two are of equal stability (they are mirror images) since in each there is one equatorial and one axial —$CH_3$ group.

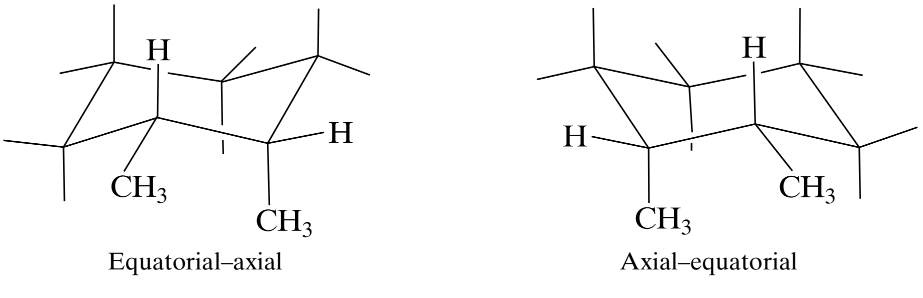


**Figure 5BII.3** Chair conformations of *cis*-1,2-dimethylcyclohexane.

In the most stable conformation of *trans*-1,2-dimethylcyclohexane,both —$CH_3$ groups occupy uncrowded equatorial positions. In either conformation of the *cis*-l,2-dimethylcyclohexane, only one —CH, group can occupy an equatorial position. It is not surprising to find that *trans*-1, 2-dimethylcyclohexane is more stable than *cis*-l,2-dimethylcyclohexane.

It is interesting to note that in the most stable conformation (diequatorial) of the *trans* isomer, the —$CH_3$ groups are exactly the same distance apart as they are in either conformation of the *cis* isomer. Clearly, it is not repulsion between the —$CH_3$ groups—as one might incorrectly infer from planar representations—that causes the difference in stability between the *trans* and *cis* isomers: the cause is 1,3-diaxial interactions.

Now, just *how much* more stable is the *trans* isomer? In the *cis*- 1,2-dimethyl cyclohexane there is one axial methyl group, which means *two* 1,3-diaxial methyl–hydrogen interactions: one with each of two hydrogen atoms. (Or, what is equivalent, there are two butane-*gauche* interactions between the methyl groups and carbon atoms of the ring.) In addition, there is one butane-*gauche* interaction between the two methyl groups. On the basis of 0.9 kcal for each 1,3-diaxial methyl–hydrogen interaction or butane-*gauche* interaction, we calculate a total of 2.7 kcal of van der Waals strain for the *cis*- 1,2-dimethylcyclohexane. In the (diequatorial) *trans* isomer there are no 1,3-diaxial methyl–hydrogen interactions, but there is one butane-*gauche* interaction between the methyl groups; this confers 0.9 kcal of van der Waals strain on the molecule. We subtract 0.9 kcal from 2.7 kcal and conclude that the *trans* isomer should be more stable than the *cis* isomer by 1.8 kcal/mol, in excellent agreement with the measured value of 1.87 kcal.

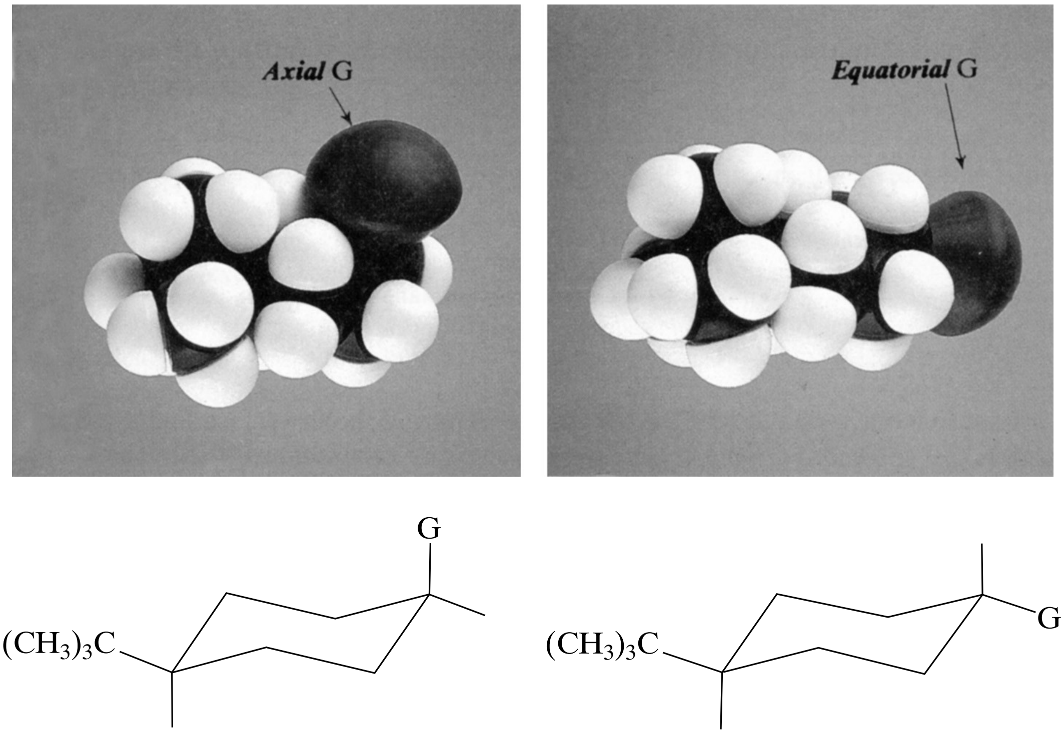
**Problem 5BII.3** Compare stabilities of the possible chair conformations of:

(a) *cis*- 1,2-dimethylcyclohexane
(b) *trans*-1,2-dimethylcyclohexane
(c) *cis*- 1,3-dimethylcyclohexane
(d) *trans*-1,3-dimethylcyclohexane
(e) *cis*-1,4-dimethylcyclohexane
(f) *trans*-1,4-dimethylcyclohexane
(g) On the basis of 0.9 kcal/mol per 1,3-diaxial methyl–hydrogen interaction, predict (where you can) the potential energy difference between the members of each pair of conformations.

**Problem 5BII.4** On theoretical grounds, K. S. Pitzer (then at the University of California) calculated that the energy difference between the conformations of *cis*-1,3-dimethylcyclohexane should be about 5.4 kcal, much larger than that between the chair conformations of *trans*-1,2-dimethylcyclohexane or of *trans*-1,4-dimethylcyclohexane. (a) What special factor must Pitzer have recognized in the *cis*-1,3 isomer? (b) Using the 0.9-kcal value where it applies, what value must you assign to the factor you invoked in (a), if you are to arrive at the energy difference of 5.4 kcal for the *cis*-1,3 conformations? (c) The potential energy difference between *cis*- and *trans*-1,1,3,5-tetramethylcyclohexane was then measured by Norman L. Allinger (University of Georgia) as 3.7 kcal/mol. This measurement was carried out because of its direct bearing on the matter of *cis*-1,3-dimethylcyclohexane. What is the connection between this measurement and parts (a) and (b)? Does Allinger's measurement support Pitzer's calculation?

**Problem 5BII.5** Predict the relative stabilities of the *cis* and *trans* isomers of: (a) 1,3-dimethylcyclohexane; (b) 1,4-dimethylcyclohexane. (c) On the basis of 0.9 kcal/mol per 1,3-diaxial methyl–hydrogen interaction or butane-*gauche* interaction, and assuming that each stereoisomer exists exclusively in its more stable conformation, predict the potential energy difference between members of each pair of stereoisomers.

Conformational analysis of cyclohexane derivatives containing several *different* substituents follows along the same lines as that of the dimethylcyclohexanes. We need to keep in mind that, of two groups, the larger one will tend to call the tune. Because of its very large 1,3-diaxial interactions, the bulky *tert*-butyl group is particularly prone to occupy an equatorial position. If—as is usually the case—other substituents are considerably smaller than *tert*-butyl, the molecule is virtually locked in a single conformation: the one with an equatorial *tert*-butyl group (see Fig. 5BII.4). Following a suggestion by Saul Winstein, *tert*-butyl has been widely used as a holding group, to permit the study of physical and chemical properties associated with a purely axial or purely equatorial substituent.



*cis* Isomer

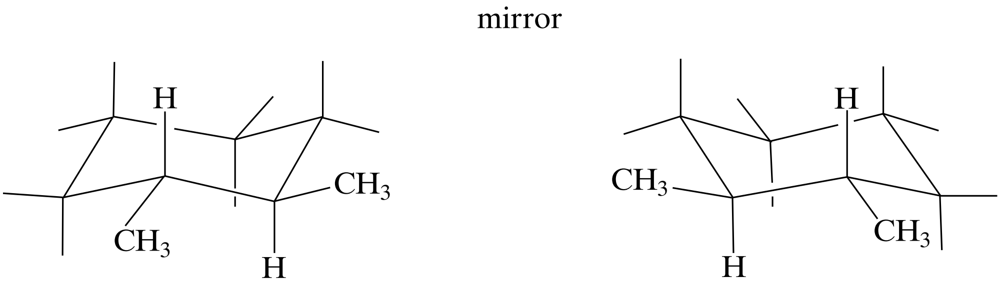
*trans* Isomer

**Figure 5BII.4** Diastereomeric cyclohexanes containing a 4-*tert*-butyl group *cis* or *trans* to another substituent, —G. In each diastereomer the very large *tert*-butyl group occupies an equatorial position. (Compare the size of *tert*-butyl with that of the brown bromine—itself a fairly large atom—in the CPK models.) The *tert*-butyl group holds —G exclusively in the axial or in the equatorial position, yet, becacuse of its distance, exerts little electronic effect on —G.

**Problem 5BII.6** Use the known energy differences to calculate values for the various alkyl-hydrogen 1,3-diaxial interactions, and from these calculate the difference in energy between the two conformations of:

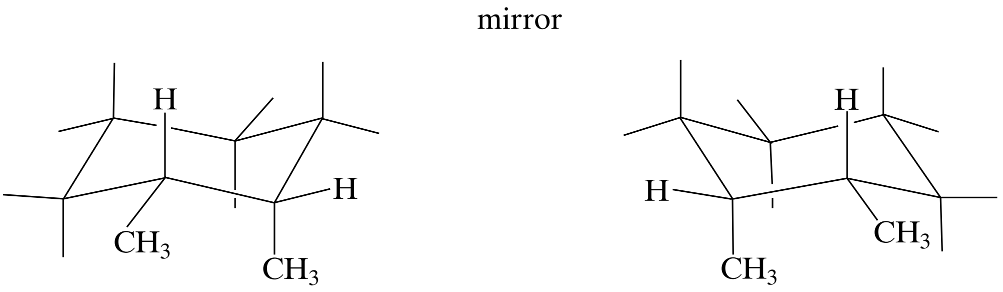
(a) *cis*-4-*tert*-butylmethylcyclohexane
(b) *trans*-4-*tert*-butylmethylcyclohexane
(c) *trans*-3-*cis*-4-dimethyl-tert-butylcyclohexane

Now, what can we say about the possible chirality of the 1,2-dimethylcyclohexanes? Let us make a model of *trans*-l,2-dimethylcyclohexane—in the more stable diequatorial conformation, say—and a model of its mirror image. We find they are not superimposable, and therefore are enantiomers. We find that they are not interconvertible, and hence are configurational isomers. (When we flip one of these into the opposite chair conformation, it is converted, not into its mirror image, but into a diaxial conformation.) Thus, *trans*-1,2-dimethylcyclohexane should, in principle, be resolvable into (configurational) enantiomers, each of which should be optically active.



*Not superimposable; not interconvertible*
*trans*-1,2-Dimethylcyclohexane
*A resolvable racemic modification*

Next, let us make a model of *cis*-1,2-dimethylcyclohexane and a model of its mirror image. We find they are not superimposable, and hence are enantiomers. In contrast to what we have said for the *trans* compound, however, we find that these models *are* interconvertible by flipping one chair conformation into the other. These are conformational enantiomers and hence, except possibly at low temperatures, should interconvert too rapidly for resolution and measurement of optical activity.

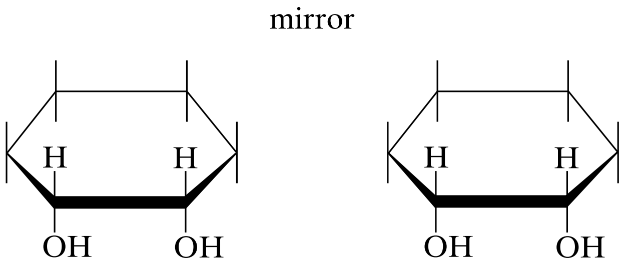


*Not superimposable, but interconvertible*
*cis*-1,2-Dimethylcyclohexane
*A non-resolvable racemic modification*

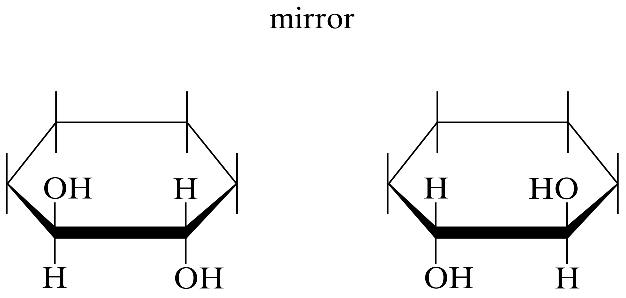
Thus, just as with the *cis*- and *trans*-1,2-cyclopentanediols, we could assign configurations to the *cis*- and *trans*-1,2-dimethylcyclohexanes by finding out which of the two is resolvable. The *cis*-1,2-dimethylcyclohexane is not literally a *meso* compound, but it is a non-resolvable racemic modification, which for most practical purposes amounts to the same thing.

To summarize, then, 1,2-dimethylcyclohexane exists as a pair of (configurational) diastereomers: the *cis* and *trans* isomers. The *cis* isomer exists as a pair of conformational enantiomers. The *trans* isomer exists as a pair of configurational enantiomers, each of which in turn exists as two conformational diastereomers (axial–axial and equatorial–equatorial).

Because of the ready interconvertibility of chair conformations, it is possible to use planar drawings to predict the configurational stereoisomerism of cyclo-hexane derivatives. To understand the true geometry of such molecules, however, and with it the matter of stability, one must use models and formulas like those in Figs. 5BII.2 and 5BII.3.



*Superimposable*
*cis*-1,2-Cyclohexanediol



*Not superimposable*
*trans*-1,2-Cyclohexanediol

**Problem 5BII.7** Which of the following compounds are resolvable, and which are non-resolvable? Which are truly *meso* compounds? Use models as well as drawings.:

(a) *cis*-l,2-cyclohexanediol
(b) *trans*-l,2-cyclohexanediol
(c) *cis*-l,3-cyclohexanediol
(d) *trans*-l,3-cyclohexanediol
(e) *cis*-l,4-cyclohexanediol
(f) *trans*-l,4-cyclohexanediol

**Problem 5BII.8** Tell which, if any, of the compounds of Problem 5BII.7 exist as:

(a) a single conformation;
(b) a pair of conformational enantiomers;
(c) a pair of conformational diastereomers;
(d) a pair of (configurational) enantiomers, each of which exists as a single conformation;
(e) a pair of (configurational) enantiomers, each of which exists as a pair of conformational diastereomers;
(f) none of the above answers. (Give the correct answer.)

**Problem 5BII.9** Draw structural formulas for all stereoisomers of the following. Label any *meso* compounds and indicate pairs of enantiomers. Do any (like *cis*-l,2-dimethylcyclohexane) exist as a non-resolvable racemic modification?

(a) *cis*-2-chlorocyclohexanol
(b) *trans*-2-chlorocyclohexanol
(c) *cis*-3-chlorocyclohexanol
(d) *trans*-3-chlorocyclohexanol
(e) *cis*-4-chlorocyclohexanol
(f) *trans*-4-chlorocyclohexanol

## EXERCISE

**1.** Draw structural formulas of:

(a) methylcyclopentane
(b) 1-methylcyclohexene
(c) 3-methylcyclopentene
(d) *trans*-l,3-dichlorocyclobutane
(e) *cis*-1-bromo-2-methylcyclopentane
(f) cyclohexylcyclohexane
(g) cyclopentylacetylene
(h) 4-chloro-1,1-dimethylcycloheptane
(i) bicyclo[2.2.1]hepta-2,5-diene
(j) 1-chlorobicyclo[2.2.2]octane

**2.** Give structures and names of the principal organic products expected from each of the following reactions:

(a) cyclopropane + $Cl_2$, $FeCl_3$
(b) cyclopropane + $Cl_2$(300 °C)
(c) cyclopropane + conc. $H_2SO_4$
(d) cyclopentane + $Cl_2$, $FeCl_3$
(e) cyclopentane + $Cl_2$(300 °C)
(f) cyclopentane + conc. $H_2SO_4$
(g) cyclopentene + $Br_2/CCl_4$
(h) cyclopentene + $Br_2$ (300 °C)
(i) 1-methylcyclohexene + HCl
(j) 1-methylcyclohexene + $Br_2$(aq)
(k) 1-methylcyclohexene + HBr (peroxides)
(l) 1,3-cyclohexadiene + HCl
(m) cyclopentanol + $H_2SO_4$ (heat)
(n) bromocyclohexane + KOH(alc)
(o) cyclopentene + cold $KMnO_4$
(p) cyclopentene + $HCO_2OH$
(q) cyclopentene + $C_6H_5CO_2OH$
(r) cyclopentene + hot $KMnO_4$
(s) cyclopentene + NBS
(t) 3-bromocyclopentene + KOH (hot)
(u) 1,4-cyclohexanediol + $H_2SO_4$ (hot)
(v) cyclohexene + $H_2SO_4 \longrightarrow C_{12}H_{20}$
(w) cyclopentene + $CHCl_3$ + *t*-BuOK
(x) cyclopentene + $CH_2I_2$ + Zn(Cu)
(y) chlorocyclopentane + $(C_2H_5)_2CuLi$
(z) 1-methylcyclopentene + cold conc. $H_2SO_4$
(aa) 3-methylcyclopentene + $O_3$, then $H_2O$/Zn
(bb) 1-methylcyclohexene + $(BH_3)_2$; $H_2O$, $OH^-$
(cc) 1-methylcyclohexene + $Hg(OAc)_2$, $H_2O$; $NaBH_4$

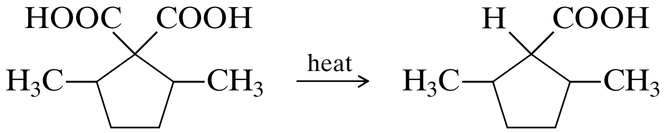
**3.** Outline all steps in the laboratory synthesis of each of the following from cyclohexanol.

(a) cyclohexene
(b) cyclohexane
(c) *trans*-1,2-dibromocyclohexane
(d) *cis*-l,2-cyclohexanediol
(e) *trans*-1,2-cyclohexanediol
(f) $OHC(CH_2)_4CHO$
(g) adipic acid, $HOOC(CH_2)_4COOH$
(h) bromocyclohexane
(i) 2-chlorocyclohexanol
(j) 3-bromocyclohexene
(k) 1,3-cyclohexadiene
(l) cyclohexylcyclohexane
(m) *norcarane*, bicyclo[4.1.0]heptane

**4.** Give structures for all isomers of the following. For cyclohexane derivatives, planar formulas will be sufficient here. Label pairs of enantiomers, and *meso* compounds.

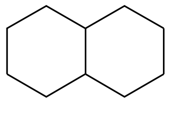
(a) dichlorocyclopropanes
(b) dichlorocyclobutanes
(c) dichlorocyclopentanes
(d) dichlorocyclohexanes
(e) chloro-1,1-dimethylcyclohexanes
(f) 1,3,5-trichlorocyclohexanes
(g) There are a number of stereoisomeric 1,2,3,4,5,6-hexachlorocyclohexanes. Without attempting to draw all of them, give the structure of the most stable isomer, and show its preferred conformation.

**5.** (a) 2,5-Dimethyl-1,1-cyclopentanedicarboxylic acid (I) can be prepared as two optically inactive substances (A and B) of different m.p. Draw their structures, (b) Upon heating, A yields two 2,5-dimethylcyclopentanecarboxylic acids (II), and B yields only one. Assign structures to A and B.



I II

**6.** The compound *decalin*, $C_{10}H_{18}$, consists of two fused cyclohexane rings:

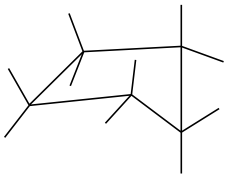


Decalin

(a) Using models, show how there can be two isomeric decalins, *cis* and *trans*, (b) How many different conformations free of angle strain are possible for *cis*-decalin? For *trans*-decalin? (c) Which is the most stable conformation of *cis*-decalin? Of *trans*-decalin? (d) Account for the fact that *trans*-decalin is more stable than *cis*-decalin. (*Hint:* Consider each ring in turn. What are the largest substituents on each ring?) (e) The difference in stability between *cis*- and *trans*-decalin is about 2 kcal/mol. Conversion of one into the other takes place under vigorous conditions. The chair- and twist-boat forms of cyclohexane, on the other hand, differ in stability by about 6 kcal/mol, yet are readily interconverted at room temperature. How do you account for the contrast? Draw energy curves to illustrate your answer.

**7.** Allinger found the energy difference between *cis*- and *trans*-l,3-di-*tert*-butylcyclohexane to be 5.9 kcal/mol, and considers that this value represents the energy difference between the chair and twist-boat forms of cyclohexane. Defend Allinger's position.

**8.** It has been suggested that in certain substituted cyclopentanes the ring exists preferentially in the "envelope" form:



Using models, suggest a possible explanation for each of the following facts:

(a) The attachment of a methyl group to the badly strained cyclopentane ring raises the heat of combustion very little more than attachment of a methyl group to the unstrained cyclohexane ring. (*Hint:* Where is the methyl group located in the "envelope" form?)
(b) Of the 1, 2-dimethylcyclopentanes, the *trans* isomer is more stable than the *cis*. Of the 1, 3-dimethylcyclopentanes, on the other hand, the *cis* isomer is more stable than the *trans*.

**9.** Arrange the compounds of each set in order of reactivity toward the indicated reaction:

(a) bromocyclohexane, 1-bromo-1-methylcyclohexane, (bromomethyl)cyclohexane toward $S_N2$ displacement
(b) the compounds of part (a) toward $S_N1$ displacement
(c) 5-bromo-l,3-cyclohexadiene, bromocyclohexane, 3-bromocyclohexene, 1-bromocyclohexene toward dehydrohalogenation by strong base
(d) *cis*-and *trans*-2-bromo-1-methylcyclohexane toward dehydrohalogenation by strong base

**10.** When l,3,5,5-tetramethyl-l,3-cyclohexadiene is dissolved in cold concentrated $H_2SO_4$, the solution shows a freezing-point lowering that corresponds to two particles for each molecule of diene dissolved. On addition of water to the solution, the diene is completely regenerated. How do you account for these observations? Just what is happening and why?

**11.** Hydroboration–oxidation of 1, 2-dimethylcyclopentene gives only *cis*-l, 2-dimethylcyclopentanol. Assuming that this is typical (it is), what is the *stereochemistry of hydroboration–oxidation*?

**12.** Each of the following reactions is carried out, and the products are separated by careful distillation, recrystallization, or chromatography. For each reaction tell how many fractions will be collected. Draw a stereochemical formula of the compound or compounds making up each fraction. Tell whether each fraction, as collected, will be optically active or optically inactive.

(a) (*R*)-3-hydroxycyclohexene + $KMnO_4 \longrightarrow C_6H_{12}O_3$
(b) (*R*)-3-hydroxycyclohexene + $HCO_2OH \longrightarrow C_6H_{12}O_3$
(c) (*S*,*S*)-l,2-dichlorocyclopropane + $Cl_2$ (300 °C) $\longrightarrow C_3H_3Cl_3$
(d) *racemic* 4-methylcyclohexene + $Br_2/CCl_4$
(e) *trans*-4-methyl-1 -bromocyclohexane + $OH^-$ (second-order) $\longrightarrow C_7H_{14}O + C_7H_{12}$

**13.** When trans-2-methylcyclopentanol is heated with acid it gives chiefly 1-methylcyclopentene. When the same alcohol is treated with tosyl chloride,

$$\text{R—O—H} \quad + \quad \text{Ts—Cl} \quad \longrightarrow \quad \text{R—O—Ts} \quad + \quad \text{HCl}$$

and the product is treated with K-*tert*-butoxide, the only alkene obtained is 3-methylcyclopentene. Account in detail for the contrast between the two synthetic routes.

**14.** When neomenthyl chloride undergoes E2 elimination, 2-menthene makes up one-fourth of the reaction product. Since menthyl chloride can yield *only* 2-menthene, we might expect it to react at one-fourth of the rate of neomenthyl chloride. Actually, however, it reacts only 1/200 as fast as neomenthyl chloride: that is, only 1/50 as fast as we would have expected. How do you account for this unusually slow elimination from menthyl chloride? (*Hint*: Use models.)

**15.** *cis*-4-*tert*-Butylcyclohexyl tosylate reacts rapidly with NaOEt in EtOH to yield 4-*tert*-butylcyclohexene: the rate of reaction is proportional to the concentration of both tosylate and ethoxide ion. Under the same conditions, *trans*-4-*tert*-butylcyclohexyl tosylate reacts slowly to yield the alkene (plus 4-*tert*-butylcyclohexyl ethyl ether); the rate of reaction depends only on the concentration of the tosylate.

How do you account for these observations?

**16.** Give the structures and names of the products you would expect from the reaction of ethylene oxide with:

(a) $H_2O, H^+$
(b) $H_2O, OH^-$
(c) $C_2H_5OH, H^+$
(d) product of(c), $H^+$
(e) $HOCH_2CH_2OH, H^+$
(f) product of (e), $H^+$
(g) anhydrous HBr
(h) HCN
(i) HCOOH
(j) $NH_3$
(k) diethylamine ($C_2H_5NHC_2H_5$)
(l) $HC{\equiv}C^-Na^+$

**17.** Propylene oxide can be converted into 1,2-propanediol by the action of either dilute acid or dilute base. When optically active propylene oxide is used, the 1,2-diol obtained from acidic hydrolysis has a rotation opposite to that obtained from alkaline hydrolysis. What is the most likely interpretation of these facts?

**18.** Give the structures (including configurations where pertinent) of compounds C–G:

(a) cyclohexane oxide + anhydrous HCl $\longrightarrow$ C ($C_6H_{11}OCl$)
(b) l-methylcyclohexene + $HCO_2OH \longrightarrow$ D ($C_7H_{14}O_2$)
(c) racemic 3,4-epoxy-l-butene + cold alkaline $KMnO_4$, then
    dilute acid $\longrightarrow$ E ($C_4H_{10}O_4$)
(d) *cis*-2-butene + $Cl_2/H_2O$, then $OH^-$, then dilute acid $\longrightarrow$ F ($C_4H_{10}O_2$)
(e) *trans*-2-butene treated as in (d) $\longrightarrow$ G ($C_4H_{10}O_2$)

**19.** Outline all steps in a possible laboratory synthesis of each of the following from acetylene, chloroform, diiodomethane, and alcohols of four carbons or fewer, using any needed inorganic reagents.

(a) *cis*-1,2-dimethylcyclopropane
(b) *trans*-1,2-dimethylcyclopropane
(c) *cis*-1,2-di(*n*-propyl)cyclopropane
(d) racemic *trans*-1,l-dichloro-2-ethyl-3-methylcyclopropane

**20.** Describe simple chemical tests that would distinguish between:

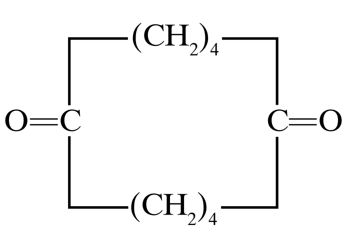
(a) cyclopropane and propane
(b) cyclopropane and propylene
(c) 1,2-dimethylcyclopropane and cyclopentane
(d) cyclobutane and 1-butene
(e) eyclopentane and 1-pentene
(f) eyclopentane and cyclopentene
(g) cyclohexanol and *n*-butylcyclohexane

(h) 1,2-dimethylcyclopentene and cyclopentanol
(i) cyclohexane, cyclohexene, cyclohexanol, and bromocyclohexane

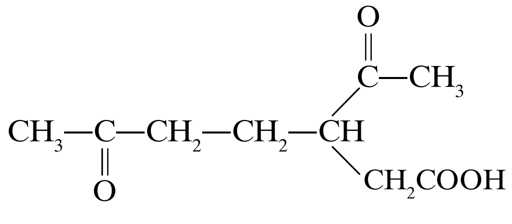
Tell exactly what you would be and *see*.

**21.** When l-bromocyclohexene (ordinary bromine) is allowed to react with radioactive $Br_2$, and the resulting tribromide is treated with iodide ion, there is obtained 1-bromocyclohexene that contains less than 0.3% of radioactive bromine. Explain in detail.

**22.** (a) A hydrocarbon of formula $C_{10}H_{16}$ absorbs only one mole of $H_2$ upon hydrogenation. How many rings does it contain? (b) Upon ozonolysis it yields 1,6-cyclodecanedione (III). What is the hydrocarbon?



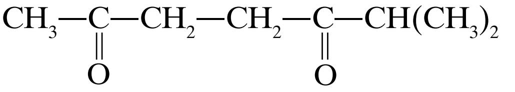
III



IV

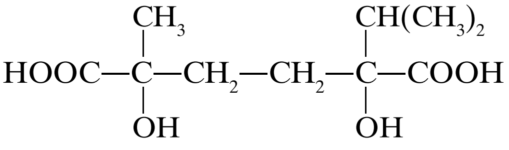
**23.** *Limonene,* $C_{10}H_{16}$, a terpene found in orange, lemon, and grapefruit peel, absorbs only two moles of hydrogen, forming *p-menthane,* $C_{10}H_{20}$. Oxidation by permanganate converts limonene into IV. (a) How many rings, if any, are there in limonene? (b) What structures are consistent with the oxidation product? (c) On the basis of the isoprene rule, which structure is most likely for limonene? For *p*-menthane? (d) Addition of one mole of $H_2O$ converts limonene into an alcohol. What are the most likely structures for this alcohol? (e) Addition of two moles of $H_2O$ to limonene yields *terpin hydrate*. What is the most likely structure for terpin hydrate?

**24.** α-*Terpinene,* $C_{10}H_{16}$, a terpene found in coriander oil, absorbs only two moles of hydrogen, forming *p-menthane*, $C_{10}H_{20}$. Ozonolysis of α-terpinene yields V; permanganate cleavage yields VI.



$$CH_3-\underset{\underset{O}{\|}}{C}-CH_2-CH_2-\underset{\underset{O}{\|}}{C}-CH(CH_3)_2$$

V

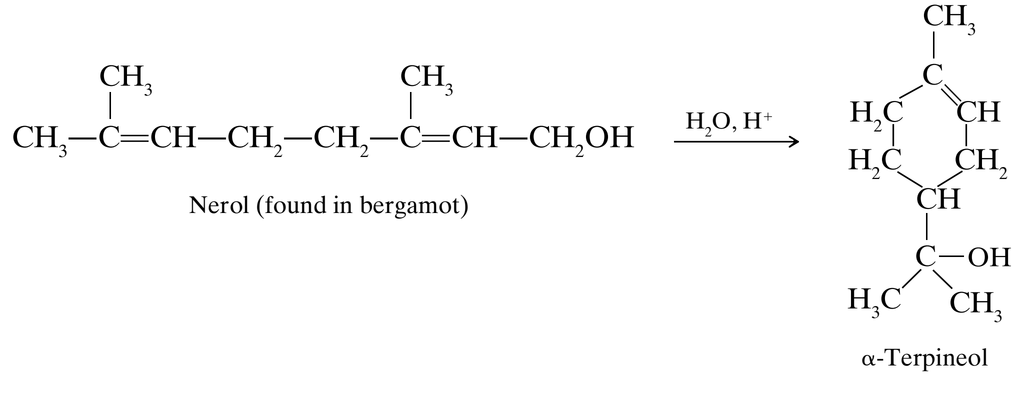


$$HOOC-\underset{OH}{\overset{CH_3}{C}}-CH_2-CH_2-\underset{OH}{\overset{CH(CH_3)_2}{C}}-COOH$$

VI

(a) How many rings, if any, are there in α-terpinene? (b) On the basis of the cleavage products, V and VI, and the isoprene rule, what is the most likely structure for α-terpinene? (c) How do you account for the presence of the —OH groups in VI?

**25.** Using only chemistry that you have already encountered, can you suggest a mechanism for the conversion of *nerol* ($C_{10}H_{18}O$) into α-terpineol ($C_{10}H_{18}O$) in the presence of dilute $H_2SO_4$?



Nerol (found in bergamot)

α-Terpineol

# 5C. Aromatic Hydrocarbons and Aromaticity

## 5C.1 Aliphatic and aromatic compounds

Chemists have found it useful to divide all organic compounds into two broad classes: **aliphatic** compounds and **aromatic** compounds. The original meanings of the words “aliphatic” (*fatty*) and “aromatic” (*fragrant*) no longer have any significance.

Aliphatic compounds are open-chain compounds and those cyclic compounds that resemble open-chain compounds. Except for the occasional appearance of a phenyl ($C_6H_5$) group, the hydrocarbon portions of the compounds that we have studied so far have been aliphatic.

**Aromatic compounds** *are benzene and compounds that resemble benzene in chemical behavior*. Aromatic properties are those properties of benzene that distinguish it from aliphatic hydrocarbons. The benzene molecule is a *ring*: a ring of a very special kind. There are certain compounds—other ring compounds—which seem to differ from benzene in structure, yet which behave very much like benzene. These other compounds, it turns out, actually do resemble benzene in structure—in basic electronic configuration—and they are aromatic, too.

Aliphatic hydrocarbons—alkanes, alkenes, alkynes, and their cyclic analogs—undergo chiefly addition and free-radical substitution: addition at multiple bonds, and free-radical substitution at other points along the aliphatic chain. These same reactions, as we have seen, take place in the hydrocarbon portions of other aliphatic compounds. The reactivity of these hydrocarbon portions is affected by the presence of other functional groups, and the reactivity of these other functional groups is affected by the presence of the hydrocarbon portions.

In contrast to aliphatic hydrocarbons, we shall find, *aromatic hydrocarbons are characterized by a tendency to undergo heterolytic substitution*. Furthermore, these same substitution reactions are characteristic of aromatic rings wherever they appear, regardless of other functional groups the molecule may contain. These other functional groups affect the reactivity of the aromatic rings, and the aromatic rings affect the reactivity of these other functional groups.

In this chapter, we shall examine the fundamental quality of *aromaticity*: just how aromatic compounds differ in behavior from aliphatic compounds, and what there is in their structure that makes them different. We shall see how these characteristic aromatic reactions take place, and how they are affected by substituents on the aromatic ring. We shall take the opposite viewpoint, and look at the remarkable effects that aromatic rings, acting themselves as substituents, exert on reactions taking place in other parts of the molecule.

In the remainder of the book, we shall do as organic chemists do, and deal with both aliphatic molecules and aromatic molecules as they happen to appear—or, as is commonly the case, with molecules that are *both* aliphatic *and* aromatic. It is important not to attach undue weight to the division between aliphatic and aromatic compounds. Although extremely useful, it is often less important than some other classification. The similarities between aliphatic and aromatic acids, for example, or between aliphatic and aromatic amines, are more important than the differences.

## 5C.2 Structure of benzene

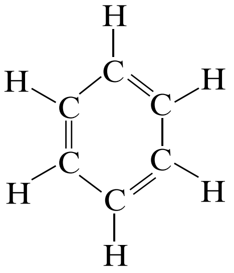
It is obvious from our definition of aromatic compounds that any study of their chemistry must begin with a study of benzene. Benzene has been known since 1825; its chemical and physical properties are perhaps better known than those of any other single organic compound. In spite of this, no satisfactory structure for benzene had been advanced until about 1931, and it was ten to fifteen years before this structure was generally used by organic chemists.

The difficulty was not the complexity of the benzene molecule, but rather the limitations of the structural theory as it had so far developed. Since an understanding of the structure of benzene is important both in our study of aromatic compounds and in extending our knowledge of the structural theory, we shall examine in some detail the facts upon which this structure of benzene is built.

## 5C.3 Molecular formula. Isomer number. Kekulé structure

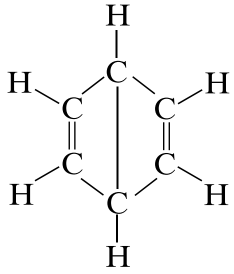
(a) *Benzene has the molecular formula* $C_6H_6$. From its elemental composition and molecular weight, benzene was known to contain six carbon atoms and six hydrogen atoms. The question was: how are these atoms arranged?

Possible structures of benzene are the following:



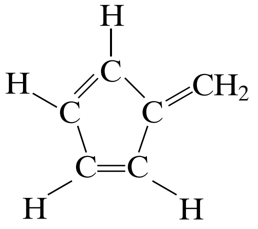
I

Kekulé formula



II

Dewar ” formula



III

$CH_3{-}C{\equiv}C{-}C{\equiv}C{-}CH_3$

IV

$CH_2{=}CH{-}C{\equiv}C{-}CH{=}CH_2$

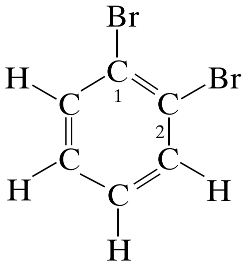
V

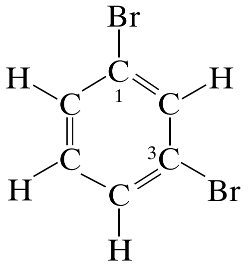
Structures I–V are consistent with the molecular formula $C_6H_6$. Kekulé's structure was accepted as the most nearly satisfactory; the evidence was of a kind with which we are already familiar: **isomer number**.

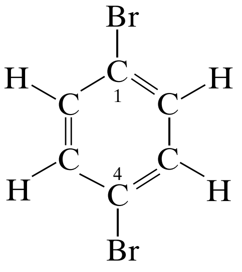
(b) *Benzene yields only one monosubstitution product,* $C_6H_5Y$. Only one bromobenzene, $C_6H_5Br$, is obtained when one hydrogen atom is replaced by bromine; similarly, only one chlorobenzene, $C_6H_5Cl$, or one nitrobenzene, $C_6H_5NO_2$, etc., has ever been made. This fact places a severe limitation on the structure of benzene: each hydrogen must be exactly equivalent to every other hydrogen, since the replacement of any one of them yields the same product.

(c) *Benzene yields three isomeric disubstitution products,* $C_6H_4Y_2$ or $C_6H_4YZ$. Three and only three isomeric dibromobenzenes, $C_6H_4Br_2$, three chloronitrobenzenes, $C_6H_4ClNO_2$, etc., have ever been made.

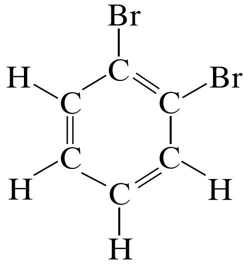
At first glance, structure I seems to be consistent with this new fact; that is, we can expect three isomeric dibromo derivatives, the 1,2-, the 1,3-, and the 1,4-dibromo compounds shown:

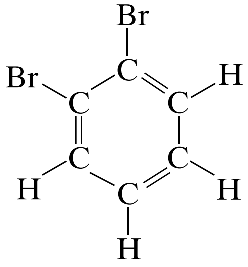

1,2-Dibromobenzene


1,3-Dibromobenzene

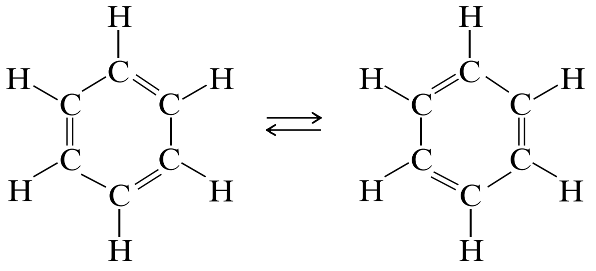

1,4-Dibromobenzene

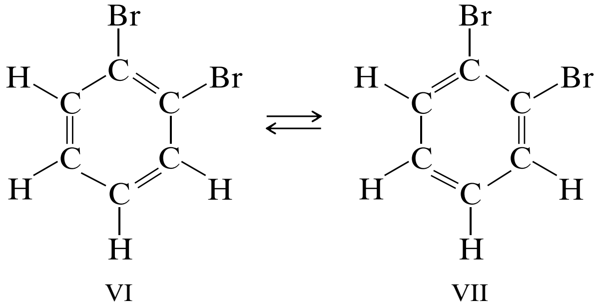
Closer examination of structure I shows, however, that *two* 1,2-dibromo isomers (VI and VII), differing in the positions of bromine relative to the double bonds, should be possible:


VI


VII

But Kekulé visualized the benzene molecule as a dynamic thing: ". . . the form whirled mockingly before my eyes . . .." He described it in terms of two structures, VIII and IX, between which the benzene molecule alternates. As a consequence, the two 1,2-dibromobenzenes (VI and VII) would be in rapid equilibrium and hence could not be separated.


VIII IX


VI VII

Later, when the idea of tautomerism became defined, it was assumed that Kekulé's "alternation" essentially amounted to tautomerism.

## 5C.4 Stability of the benzene ring. Reactions of benzene

Kekulé's structure, then, accounts satisfactorily for facts (a), (b), and (c) in Section 5C.3. But there are a number of facts that are still not accounted for by this structure; most of these unexplained facts seem related to unusual stability of the benzene ring. The most striking evidence of this stability is found in the chemical reactions of benzene.

(d) *Benzene undergoes substitution rather than addition.* Kekulé's structure of benzene is one that we would call "cyclohexatriene". We would expect this cyclohexatriene, like the very similar compounds, cyclohexadiene and cyclohexene, to undergo readily the addition reactions characteristic of the alkene structure. As the examples in Table 5C.1 show, this is not the case; under conditions that cause an alkene to undergo rapid addition, benzene reacts either not at all or very slowly.

**Table 5C.1** CYCLOHEXENE *vs.* BENZENE

| Reagent | Cyclohexene gives | Benzene gives |
|---|---|---|
| $KMnO_4$ (cold, dilute, oaqueous) | Rapid oxidation | No reaction |
| $Br_2/CCl_4$ (in the dark) | Rapid addition | No reaction |
| HI | Rapid addition | No reaction |
| $H_2 + Ni$ | Rapid hydrogenation at 25°C, 20 lb/in.$^2$ | Slow hydrogenation at 100–200°C, 1500 lb/in.$^2$ |

In place of addition reactions, benzene readily undergoes a new set of reactions, all involving **substitution**. The most important are shown below.

**REACTIONS OF BENZENE**

1. **Nitration.**

$$C_6H_6 + HONO_2 \xrightarrow{H_2SO_4} \underset{\text{Nitrobenzene}}{C_6H_5\text{—}NO_2} + H_2O$$

2. **Sulfonation.**

$$C_6H_6 + HOSO_3H \xrightarrow{SO_3} \underset{\text{Benzenesulfonic acid}}{C_6H_5\text{—}SO_3H} + H_2O$$

CONTINUED

CONTINUED

3. **Halogenation.**

$$C_6H_6 + Cl_2 \xrightarrow{Fe} \underset{\text{Chlorobenzene}}{C_6H_5\text{—}Cl} + HCl$$

$$C_6H_6 + Br_2 \xrightarrow{Fe} \underset{\text{Bromobenzene}}{C_6H_5\text{—}Br} + HBr$$

4. **Friedel–Crafts alkylation.**

$$C_6H_6 + RCl \xrightarrow{AlCl_3} \underset{\text{An alkylbenzene}}{C_6H_5\text{—}R} + HCl$$

5. **Friedel–Crafts acylation.**

$$C_6H_6 + \underset{\text{An acyl chloride}}{RCOCl} \xrightarrow{AlCl_3} \underset{\text{A ketone}}{C_6H_5\text{—}COR} + HCl$$

■

In each of these reactions an atom or group has been substituted for one of the hydrogen atoms of benzene. The product can itself undergo further substitution of the same kind; the fact that it has retained the characteristic properties of benzene indicates that it has retained the characteristic structure of benzene.

It would appear that benzene resists addition, in which the benzene ring system would be destroyed, whereas it readily undergoes substitution, in which the ring system is preserved.

## 5C.5 Stability of the benzene ring. Heats of hydrogenation and combustion

Besides the above qualitative indications that the benzene ring is more stable than we would expect cyclohexatriene to be, there exist quantitative data which show *how much* more stable.

(e) *Heats of hydrogenation and combustion of benzene are lower than expected.* We recall that heat of hydrogenation is the quantity of heat evolved when one mole of an unsaturated compound is hydrogenated. In most cases the value is about 28–30 kcal for each double bond the compound contains. It is not surprising, then, that cyclohexene has a heat of hydrogenation of 28.6 kcal and cyclohexadiene has one about twice that (55.4 kcal).

We might reasonably expect cyclohexatriene to have a heat of hydrogenation about three times as large as cyclohexene, that is, about 85.8 kcal. Actually, the value for benzene (49.8 kcal) is *36 kcal less* than this expected amount.

This can be more easily visualized, perhaps, by means of an energy diagram (Fig. 5C.1) in which the height of a horizontal line represents the potential energy content of a molecule. The broken lines represent the expected values, based upon three equal steps of 28.6 kcal. The final product, cyclohexane, is the same in all three cases.

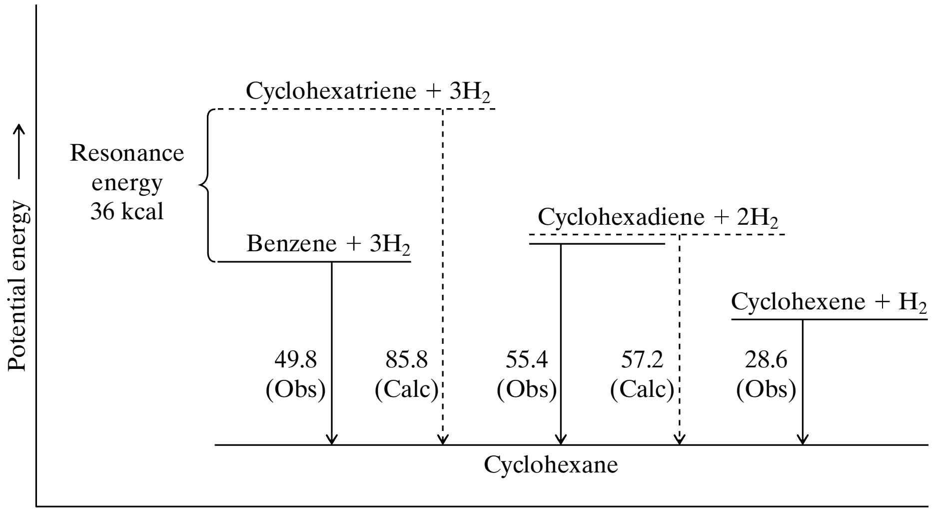


**Figure 5C.1** Heats of hydrogenation and stability: benzene, cyclohexadiene, and cyclohexene.

The fact that benzene *evolves* 36 kcal less energy than predicted can only mean that benzene *contains* 36 kcal less energy than predicted; in other words, benzene is more stable by 36 kcal than we would have expected cyclohexatriene to be. The heat of combustion of benzene is also lower than that expected, and by about the same amount.

**Problem 5C.1** From Fig. 5C. 1, determine the $\Delta H$ of the following reactions:

(a) benzene + $H_2 \longrightarrow$ 1,3-cyclohexadiene
(b) 1,3-cyclohexadiene + $H_2 \longrightarrow$ cyclohexene

**Problem 5C.2** For a large number of organic compounds, the heat of combustion actually measured agrees rather closely with that calculated by assuming a certain characteristic contribution from each kind of bond, e.g., 54.0 kcal for each C—H bond, 49.3 kcal for each C—C bond, and 117.4 kcal for each C=C bond (*cis*-1,2-disubstituted). (a) On this basis, what is the calculated heat of combustion for cyclohexatriene? (b) How does this compare with the measured value of 789.1 kcal for benzene?

## 5C.6 Carbon–carbon bond lengths in benzene

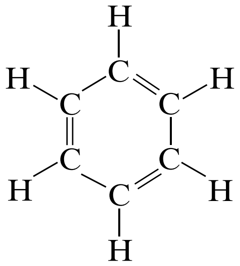
(f) *All carbon–carbon bonds in benzene are equal and are intermediate in length between single and double bonds.* Carbon–carbon double bonds in a wide variety of compounds are found to be about 1.34 Å long. Carbon–carbon single bonds, in which the nuclei are held together by only one pair of electrons, are considerably longer: 1.53 Å in ethane, for example, 1.50 Å in propylene, 1.48 Å in 1,3-butadiene.

If benzene actually possessed three single and three double bonds, as in a Kekulé structure, we would expect to find three short bonds (1.34 Å) and three long bonds (1.48 Å, probably, as in 1,3-butadiene). Actually, x-ray diffraction studies show that the six carbon–carbon bonds in benzene are equal and have a length of 1.39 Å, and are thus intermediate between single and double bonds.

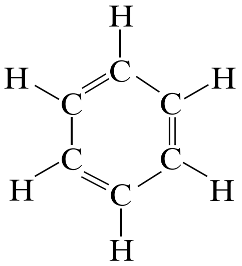
## 5C.7 Resonance structure of benzene

The Kekulé structure of benzene, while admittedly unsatisfactory, was generally used by chemists as late as 1945. The currently accepted structure did not arise from the discovery of new facts about benzene, but is the result of an extension or modification of the structural theory; this extension is the concept of *resonance.*

The Kekulé structures I and II, we now immediately recognize, meet the conditions for resonance: *structures that differ only in the arrangement of electrons.*

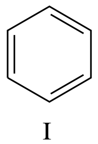


I

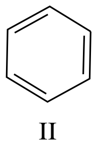


II

or



I

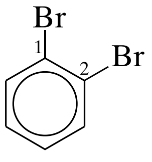


II

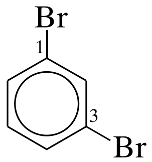
Benzene is a *hybrid* of I and II. Since I and II are exactly equivalent, and hence of exactly the same stability, they make equal contributions to the hybrid. And, also since I and II are exactly equivalent, stabilization due to resonance should be large.

The puzzling aspects of benzene's properties now fall into place. The six bond lengths are identical because the six bonds are identical: they are one-and-a-half bonds and their length, 1.39 Å, is intermediate between the lengths of single and double bonds.

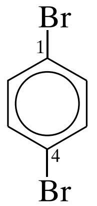
When it is realized that all carbon–carbon bonds in benzene are equivalent, there is no longer any difficulty in accounting for the number of isomeric disubstitution products. It is clear that there should be just three, in agreement with experiment:



1,2-Dibromobenzene



1,3-Dibromobenzene



1,4-Dibromobenzene

Finally, the "unusual" stability of benzene is not unusual at all: it is what one would expect of a hybrid of equivalent structures. The 36 kcal of energy that benzene does not contain—compared with cyclohexatriene—is resonance energy. It is the 36 kcal of resonance stabilization that is responsible for the new set of properties we call *aromatic properties.*

Addition reactions convert an alkene into a more stable saturated compound. Hydrogenation of cyclohexene, for example, is accompanied by the evolution of 28.6 kcal; the product lies 28.6 kcal lower than the reactants on the energy scale (Fig. 5C.1).

But addition would convert benzene into a *less* stable product by destroying the resonance-stabilized benzene ring system; for example, according to Fig. 5C.1

the first stage of hydrogenation of benzene requires 5.6 kcal to convert benzene into the less stable cyclohexadiene. As a consequence, it is easier for reactions of benzene to take an entirely different course, one in which the ring system is retained: *substitution.*

(This is not quite all of the story in so far as stability goes. As we shall see, an additional factor besides resonance is necessary to make benzene what it is.)

## 5C.8 Orbital picture of benzene

A more detailed picture of the benzene molecule is obtained from a consideration of the bond orbitals in this molecule.

Since each carbon is bonded to three other atoms, it uses $sp^2$ orbitals (as in ethylene). These lie in the same plane, that of the carbon nucleus, and are directed toward the corners of an equilateral triangle. If we arrange the six carbons and six hydrogens of benzene to permit maximum overlap of these orbitals, we obtain the structure shown in Fig. 5C.2*a*.

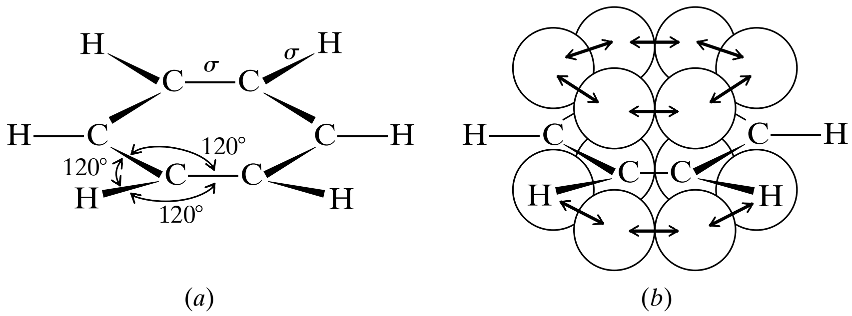


**Figure 5C.2** Benzene molecule. (*a*) Only the σ bonds are shown. (*b*) The *p* orbitals overlap to form π bonds.

Benzene is a *flat molecule*, with every carbon and every hydrogen lying in the same plane. It is a very *symmetrical molecule,* too, with each carbon atom lying at the angle of a regular hexagon; every bond angle is 120°. Each bond orbital is cylindrically symmetrical about the line joining the atomic nuclei, and hence, as before, these bonds are designated as σ bonds.

The molecule is not yet complete, however.There are still six electrons to be accounted for. In addition to the three orbitals already used, each carbon atom has a fourth orbital, a *p* orbital. As we know, this *p* orbital consists of two equal lobes, one lying above and the other lying below the plane of the other three orbitals, that is, above and below the plane of the ring; it is occupied by a single electron.

As in the case of ethylene, the *p* orbital of one carbon can overlap the *p* orbital of an adjacent carbon atom, permitting the electrons to pair and an additional π bond to be formed (see Fig. 5C.2*b*). But the overlap here is not limited to a pair of *p* orbitals as it was in ethylene; the *p* orbital of any one carbon atom overlaps equally well the *p* orbitals of *both* carbon atoms to which it is bonded. The result (see Fig. 5C.3) is two continuous doughnut-shaped electron clouds, one lying above and the other below the plane of the atoms.

As with the allyl radical, it is the overlap of the *p* orbitals in both directions, and the resulting participation of each electron in several bonds, that corresponds to our description of the molecule as a resonance hybrid of two structures. Again it is the *delocalization* of the $\pi$ electrons—their participation in several bonds—that makes the molecule more stable.

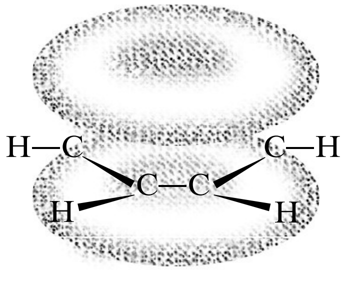


**Figure 5C.3** Benzene molecule: $\pi$ clouds above and below the plane of the ring.

To accommodate six $\pi$ electrons, there must be *three* orbitals. Their sum, however, is the symmetrical $\pi$ clouds we have described.

The orbital approach reveals the importance of the planarity of the benzene ring. The ring is flat because the trigonal ($sp^2$) bond angles of carbon just fit the 120° angles of a regular hexagon; it is this flatness that permits the overlap of the *p* orbitals in both directions, with the resulting delocalization and stabilization.

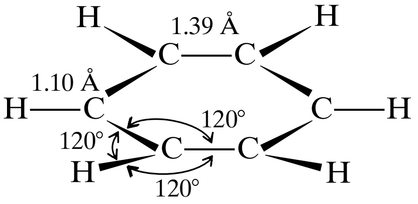


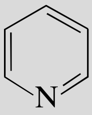
**Figure 5C.4** Benzene molecule: shape and size.

The facts are consistent with the orbital picture of the benzene molecule. X-ray and electron diffraction show benzene (Fig. 5C.4) to be a completely flat, symmetrical molecule with all carbon–carbon bonds equal, and all bond angles 120° (see Fig. 5C.5).

As we shall see, the chemical properties of benzene are just what we would expect of this structure. Despite delocalization, the $\pi$ electrons are nevertheless more loosely held than the $\sigma$ electrons. The $\pi$ electrons are thus particularly available to a reagent that is seeking electrons: *the typical reactions of the benzene ring are those in which it serves as a source of electrons for electrophilic* (*acidic*) *reagents.* Because of the resonance stabilization of the benzene ring, *these reactions lead to substitution,* in which the aromatic character of the benzene ring is preserved.

**Problem 5C.3** The carbon–hydrogen homolytic bond dissociation energy for benzene (110 kcal) is considerably larger than for cyclohexane. On the basis of the orbital picture of benzene, what is one factor that may be responsible for this? What piece of physical evidence tends to support your answer?

**Problem 5C.4** The molecules of *pyridine*, $C_5H_5N$, are flat, with all bond angles about 120°. All carbon–carbon bonds are 1.39 Å long and the two carbon–nitrogen bonds are 1.36 Å long. The measured heat of combustion is 23 kcal lower than that calculated theoretical energy. Pyridine undergoes such substitution reactions as nitration and sulfonation. (a) Is pyridine adequately represented by formula I? (b) Account for the properties of pyridine by both valence-bond and orbital structures.



I

**Problem 5C.5** The compound *borazole*, $B_3N_3H_6$, is shown by electron diffraction to have a flat cyclic structure with alternating boron and nitrogen atoms, and all boron–nitrogen bond lengths the same, (a) How would you represent borazole by valence-bond structures? (b) In terms of orbitals? (c) How many $\pi$ electrons are there, and which atoms have they "come from"?

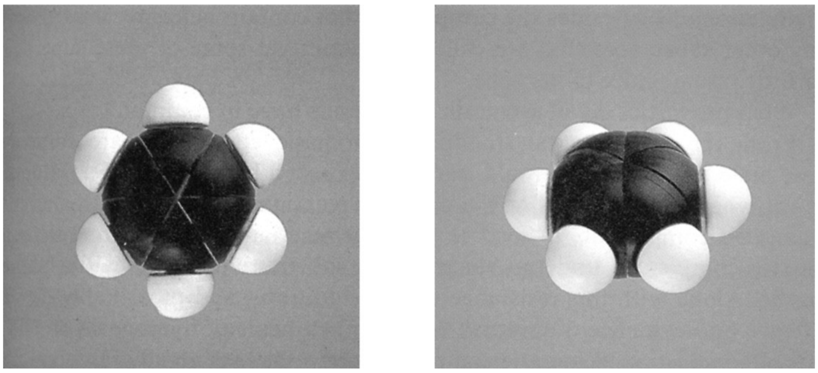
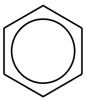


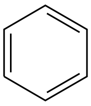
**Figure 5C.5** Electronic configuration and molecular shape. Model of benzene: two views. Like cyclohexane, benzene is a marvelous creation: flat, compact, symmetrical, and of a stability that makes it the model for an entire class of organic molecules. Here, too, the architectural perfection is the result of a happy coincidence. Six carbons make a hexagon, whose angles happen to match exactly the trigonal angle. Six carbons provide six $\pi$ electrons; and *six*, as we shall see, is a "magic" number of $\pi$ electrons.

## 5C.9 Representation of the benzene ring

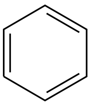
For convenience we shall represent the benzene ring by a regular hexagon containing a circle (I); it is understood that a hydrogen atom is attached to each angle of the hexagon unless another atom or group is indicated.



*means* a hybrid of



and



I II III

Formula I represents a resonance hybrid of the Kekulé structures II and III. The straight lines stand for the $\sigma$ bonds joining carbon atoms. The circle stands for the cloud of six delocalized $\pi$ electrons. (From another viewpoint, the straight lines stand for single bonds, and the circle stands for the extra *half-bonds*.)

Formula I is a particularly useful representation of the benzene ring, since it emphasizes the equivalence of the various carbon–carbon bonds. The presence of the circle distinguishes the benzene ring from the cyclohexane ring, which is generally represented today by a plain hexagon.

There is no complete agreement among chemists about how to represent the benzene ring. The student should expect to encounter it often as one of the Kekulé formulas. The representation adopted in this book has certain advantages, and its use is gaining ground. It is interesting that very much the same representation was advanced as long ago as 1899 by Johannes Thiele, who used a broken circle to stand for partial bonds ("partial valences").

## 5C.10 Aromatic character. The Hückel $4n + 2$ rule

We have defined aromatic compounds as those that resemble benzene. But just which properties of benzene must a compound possess before we speak of it as being aromatic? Besides the compounds that contain benzene rings, there are many other substances that are called aromatic; yet some of these superficially bear little resemblance to benzene.

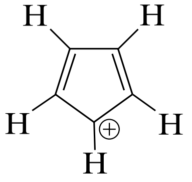
What properties do all aromatic compounds have in common?

From the experimental standpoint, aromatic compounds are compounds whose molecular formulas would lead us to expect a high degree of unsaturation, and yet which are resistant to the addition reactions generally characteristic of unsaturated compounds. Instead of addition reactions, we often find that these aromatic compounds undergo electrophilic substitution reactions like those of benzene. Along with this resistance toward addition—and presumably the cause of it—we find evidence of unusual stability: low heats of hydrogenation and low heats of combustion. Aromatic compounds are cyclic—generally containing five-, six-, or seven-membered rings—and when examined by physical methods, they are found to have flat (or nearly flat) molecules. Their protons show the same sort of *chemical shift* in NMR spectra as the protons of benzene and its derivatives.

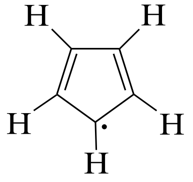
From a theoretical standpoint, to be aromatic a compound must have a molecule that contains *cyclic clouds of delocalized $\pi$ electrons above and below the plane of the molecule*; furthermore, *the $\pi$ clouds must contain a total of* **$(4n + 2)$ $\pi$ electrons**. That is to say, for the particular degree of stability that characterizes an aromatic compound, delocalization alone is not enough. There must be a particular number of $\pi$ electrons: 2, or 6, or 10, etc. This requirement, called the *$4n + 2$ rule* or *Hückel rule* (after Erich Hückel, of the Institut für theoretische Physik, Stuttgart), is based on quantum mechanics, and has to do with the filling up of the various orbitals that make up the $\pi$ cloud. The Hückel rule is strongly supported by the facts.

Let us look at some of the evidence supporting the Hückel rule. Benzene has six $\pi$ electrons, the *aromatic sextet*; six is, of course, a Hückel number, corresponding to $n = 1$. Besides benzene and its relatives (naphthalene, anthracene, phenanthrene), we shall encounter a number of heterocyclic compounds that are clearly aromatic; these aromatic heterocycles, we shall see, are just the ones that can provide an aromatic sextet.

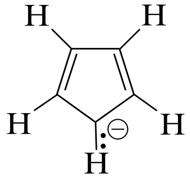
Or consider these six compounds, for each of which just one contributing structure is shown:



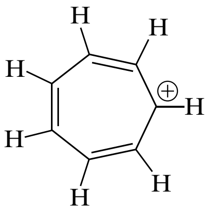
Cyclopentadienyl
cation
*Four π electrons*



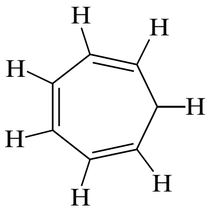
Cyclopentadienyl
radical
*Five π electrons*



Cyclopentadienyl
anion
*Six π electrons*
**Aromatic**

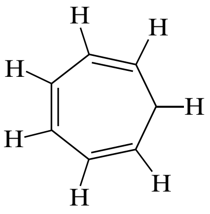


Cycloheptatrienyl
cation
(Tropylium ion)
*Six π electrons*
**Aromatic**



Cycloheptatrienyl
radical

*Seven π electrons*

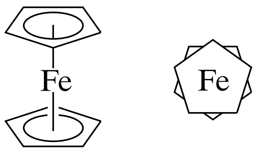


Cycloheptatrienyl
anion

*Eight π electrons*

Each molecule is a hybrid of either five or seven equivalent structures, with the charge or odd electron on each carbon. Yet, of the six compounds, only *two* give evidence of *unusually* high stability: the cyclopentadienyl anion and the cycloheptatrienyl cation (*tropylium ion*).

For a hydrocarbon, cyclopentadiene is an unusually strong acid ($K_a = 10^{-15}$), indicating that loss of a hydrogen ion gives a particularly stable anion. (It is, for example, a much stronger acid than cycloheptatriene, $K_a = 10^{-45}$, despite the fact that the latter gives an anion that is stabilized by seven contributing structures.) Dicyclopentadienyliron (*ferrocene*), $[(C_5H_5)^-]_2Fe^{2+}$, is a stable molecule that has been shown to be a "sandwich" of an iron atom between two flat five-membered rings. All carbon–carbon bonds are 1.4 Å long. The rings of ferrocene undergo two typically aromatic substitution reactions: sulfonation and the Friedel–Crafts reaction.



Ferrocene

Of the cycloheptatrienyl derivatives, on the other hand, it is the cation that is unusual. Tropylium bromide, $C_7H_7Br$, melts above 200°C, is soluble in water but insoluble in non-polar solvents, and gives an immediate precipitate of AgBr when treated with silver nitrate. This is strange behavior for an organic bromide, and strongly suggests that, even in the solid, we are dealing with an ionic compound, $R^+Br^-$, the cation of which is actually a *stable* carbocation.

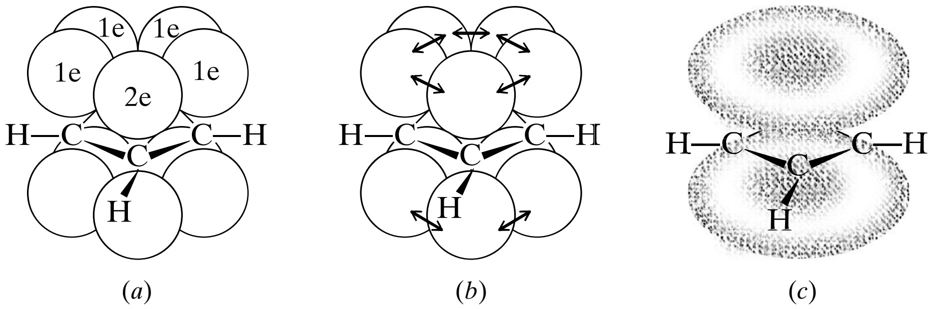


**Figure 5C.6** Cyclopentadienyl anion. (*a*) Two electrons in the *p* orbital of one carbon; one electron in the *p* orbital of each of the other carbons. (*b*) Overlap of the *p* orbitals to form $\pi$ bonds. (*c*) The $\pi$ clouds above and below the plane of the ring; a total of six $\pi$ electrons, the aromatic sextet.

Consider the electronic configuration of the cyclopentadienyl anion (Fig. 5C.6) Each carbon, trigonally hybridized, is held by a $\sigma$ bond to two other carbons and one hydrogen. The ring is a regular pentagon, whose angles (108°) are not a bad fit for the 120° trigonal angle; any instability due to imperfect overlap (angle strain) is more than made up for by the delocalization that is to follow. Four carbons have one electron each in *p* orbitals; the fifth carbon (the "one" that lost the proton, but actually, of course, indistinguishable from the others) has two electrons. Overlap of the *p* orbitals gives rise to $\pi$ clouds containing a total of six electrons, the aromatic sextet (see Fig. 5C.7).

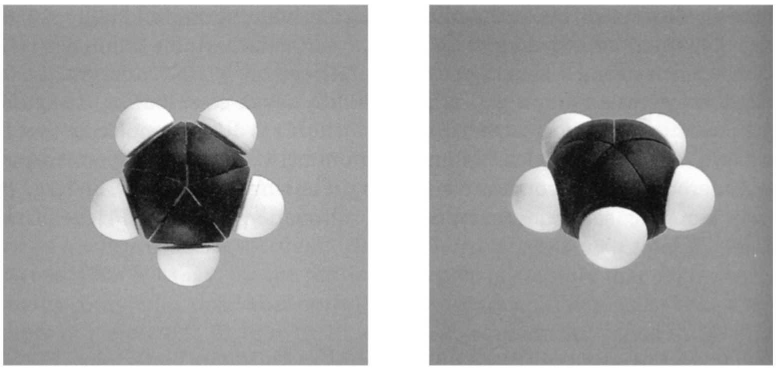


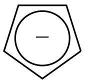
**Figure 5C.7** Electronic configuration and molecular shape. Model of the cyclopentadienyl anion: two views.

In ferrocene, each cyclopentadienyl anion is held to iron through overlap of the $\pi$ cloud with an empty orbital of the metal. This kind of bonding has been shown to exist between compounds with $\pi$ electrons—alkenes, aromatics—and acidic molecules of many kinds: silver ions, for example, or halogens. Such **$\pi$-complexes** have been detected spectroscopically and sometimes, as with ferrocene, isolated. Reversible formation of $\pi$-complexes has been postulated as a step preliminary to the reaction of many electrophiles with alkenes and aromatic compounds.

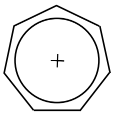
The isolation of ferrocene in 1951 aroused great interest, not just because it was an example of a non-benzenoid aromatic compound consistent with the Hückel rule. More important, the strength of this $\pi$ bonding sparked a revolution in the field of organic complexes of transition metals—a revolution that has given organic chemists catalysts of unprecedented selectivity and power.

In a similar way, we arrive at the configuration of the tropylium ion. It is a regular heptagon (angles 128.5°). Six carbons contribute one *p* electron each, and the seventh contributes only an empty *p* orbital. Result: the aromatic sextet.

The ions are conveniently represented as:



Cyclopentadienyl
anion



Cycloheptatrienyl
cation
(Tropylium ion)

*Six* is the Hückel number most often encountered, and for good reason. To provide *p* orbitals, the atoms of the aromatic ring must be trigonally ($sp^2$) hybridized, which means, ideally, bond angles of 120°. To permit the overlap of the *p* orbitals that gives rise to the $\pi$ cloud, the aromatic compound must be flat, or nearly so. The number of trigonally hybridized atoms that will fit a flat ring without undue angle strain (i.e., with reasonably good overlap for $\pi$ bond formation) is five, six, or seven. Six is the Hückel number of $\pi$ electrons that can be provided—as we have just seen—by these numbers of atoms. (Benzene, as we have seen, is the "perfect" specimen: six carbons to provide six $\pi$ electrons and to make a hexagon whose angles exactly match the trigonal angle.)

Now, what evidence is there that other Hückel numbers—2, 10, 14, etc.—are also "magic" numbers? We cannot expect aromatic character necessarily to appear here in the form of highly stable compounds comparable to benzene and its derivatives. The rings will be too small or too large to accommodate trigonally hybridized atoms very well, so that any stabilization due to aromaticity may be largely offset by angle strain or poor overlap of *p* orbitals, or both.

We must look for stability on a *comparative* basis-as was done above with the cyclopentadienyl and cycloheptatrienyl derivatives—and may find evidence of aromaticity only in the fact that one molecular species is *less unstable* than its relatives. The net effect of a great deal of elegant work is strongly to support the $4n + 2$ rule. The question now seems rather to be: over how unfavorable a combination of angle strain and multiple charge can aromaticity manifest itself?

**Problem 5C.6** Ronald Breslow (of Columbia University) found that treatment of 3-chlorocyclopropene with $SbCl_5$ yields a stable crystalline solid, I, of formula $C_3H_3SbCl_6$,

3-Chlorocyclopropene

insoluble in non-polar solvents but soluble in polar solvents like nitro-methane, acetonitrile, or sulfur dioxide. The NMR spectrum of I shows three exactly equivalent protons. 3-Chlorocyclopropene reacts with $AgBF_4$ to give AgCl and a solution with an NMR spectrum identical to that of I. Treatment of I with chloride ion regenerates 3-chlorocyclopropene.

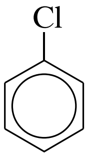
Conversion of I into $C_3H_3^+$ requires 153 kcal/mol, as compared with 173 kcal/mol for conversion of allyl chloride into $C_3H_5^+$.

(a) Give in detail the most likely structure of I, and show how this structure accounts for the various observations. (b) Of what theoretical significance are these findings?

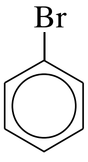
## 5C.11 Nomenclature of benzene derivatives

In later chapters we shall consider in detail the chemistry of many of the derivatives of benzene. Nevertheless, for our present discussion of the reactions of the benzene ring it will be helpful for us to learn to name some of the more important of these derivatives.

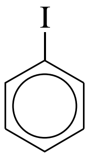
For many of these derivatives we simply prefix the name of the substituent group to the word *-benzene*, as, for example, in *chlorobenzene*, *bromobenzene*, *iodobenzene*, or *nitrobenzene*. Other derivatives have special names which may show no resemblance to the name of the attached substituent group. For example, methylbenzene is always known as *toluene*, aminobenzene as *aniline*, hydroxybenzene as *phenol*, and so on. The most important of these special compounds are:



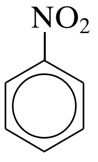
Chlorobenzene



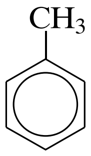
Bromobenzene



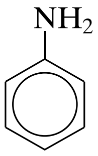
Iodobenzene



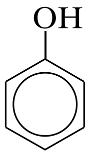
Nitrobenzene



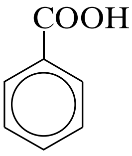
Toluene



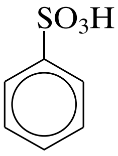
Aniline



Phenol

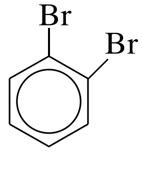


Benzoic acid

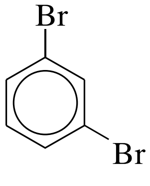


Benzenesulfonic acid

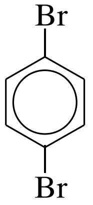
If several groups are attached to the benzene ring, we must not only tell what they are, but also indicate their relative positions. The three possible isomers of a disubstituted benzene are differentiated by the use of the names ***ortho***, ***meta***, and ***para***, abbreviated as ***o*-**, ***m*-**, and ***p*-**. For example:



*o*-Dibromobenzene
*ortho*



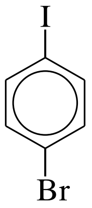
*m*-Dibromobenzene
*meta*



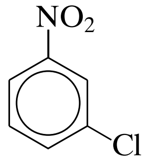
*p*-Dibromobenzene
*para*

If the two groups are different, and neither is a group that gives a special name to the molecule, we simply name the two groups successively and end the word with

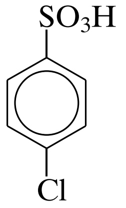
*-benzene*, as, for example, *chloronitrobenzene*, *bromoiodobenzene*, etc. If one of the two groups is the kind that gives a special name to the molecule, then the compound is named as a derivative of that special compound, as, for example, *nitrotoluene*, *bromophenol*, etc.



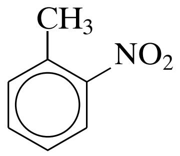
*p*-Bromoiodobenzene



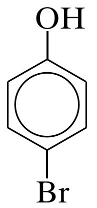
*m*-Chloronitrobenzene



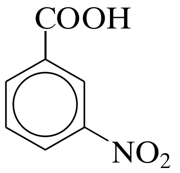
*p*-Chlorobenzenesulfonic acid



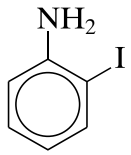
*o*-Nitrotoluene



*p*-Bromophenol

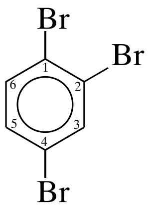


*m*-Nitrobenzoic acid

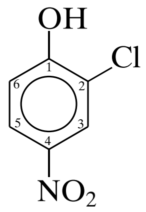


*o*-Iodoaniline

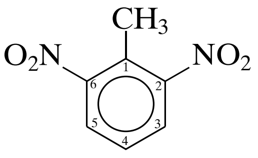
If more than two groups are attached to the benzene ring, numbers are used to indicate their relative positions. For example:



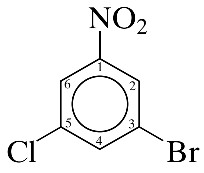
1,2,4-Tribromobenzene



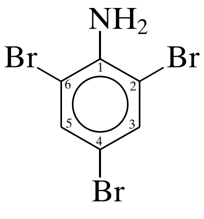
2-Chloro-4-nitrophenol



2,6-Dinitrotoluene



3-Bromo-5-chloronitrobenzene



2,4,6-Tribromoaniline

If all the groups are the same, each is given a number, the sequence being the one that gives the lowest combination of numbers; if the groups are different, then the last-named group is understood to be in position 1 and the other numbers conform to that, as, for example, in *3-bromo-5-chloronitrobenzene.* If one of the groups that gives a special name is present, then the compound is named as having the special group in position 1; thus in *2,6-dinitrotoluene* the methyl group is considered to be at the 1-position.

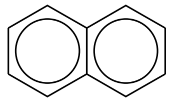
**Problem 5C.7** You have three bottles containing the three isomeric dibromobenzenes; they have the melting points +87°C, +6°C, and −7°C. By a great deal of work, you prepare six dibromonitrobenzenes ($C_6H_3Br_2NO_2$) and find that, of the six, *one* is related to (derived from or convertible into) the dibromobenzene of m.p. +87°C, *two* to the isomer of m.p. +6°C, and *three* to the isomer of m.p. −7°C.

Label each bottle with the correct name of *ortho*, *meta*, or *para*.

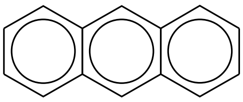
(This work was actually carried out by Wilhelm Körner, and was the first example of the Körner method of absolute orientation.)

## 5C.12 Polynuclear aromatic hydrocarbons. Naphthalene

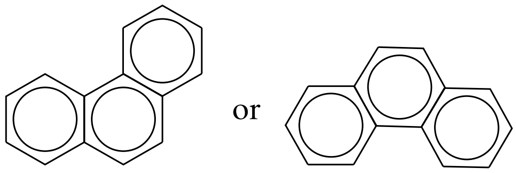
Two aromatic rings that share a pair of carbon atoms are said to *be fused*. In this chapter we shall look briefly at the simplest and most important of these fused-ring hydrocarbons, *naphthalene*.



Naphthalene



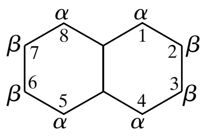
Anthracene



Phenanthrene

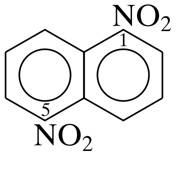
Like its relatives, *anthracene* and *phenanthrene*, naphthalene is obtained from coal tar, being the most abundant (5%) of all constituents of coal tar.

Positions in the naphthalene ring system are designated as in I. Two isomeric

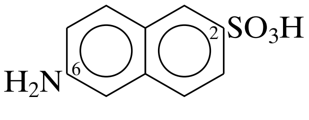


I

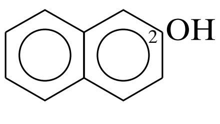
monosubstituted naphthalenes are differentiated by the prefixes 1- and 2-, or α- and β-. The arrangement of groups in more highly substituted naphthalenes is indicated by numbers. For example:



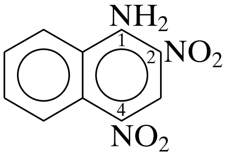
1,5-Dinitronaphthalene



6-Amino-2-naphthalenesulfonic acid



2-Naphthol
β-Naphthol



2,4-Dinitro-1-naphthylamine

**Problem 5C.8** How many different mononitronaphthalenes are possible? Dinitronaphthalenes? Nitronaphthylamines?

Naphthalene is classified as aromatic because its properties resemble those of benzene. Its molecular formula, $C_{10}H_8$, might lead one to expect a high degree of unsaturation; yet naphthalene is resistant (although less so than benzene) to the addition reactions characteristic of unsaturated compounds. Instead, the typical reactions of naphthalene are electrophilic substitution reactions, in which hydrogen is displaced as hydrogen ion and the naphthalene ring system is preserved. Like benzene, naphthalene is unusually stable: its heat of combustion is 61 kcal lower than that calculated on the assumption that it is aliphatic.

From the experimental standpoint, then, naphthalene is classified as aromatic on the basis of its properties. From a theoretical standpoint, naphthalene has the structure required of an aromatic compound: it contains flat six-membered rings, and consideration of atomic orbitals shows that the structure can provide $\pi$ clouds containing six electrons-the *aromatic sextet* (Fig. 5C.8). Ten carbons lie at the corners of two fused hexagons. Each carbon is attached to three other atoms by $\sigma$ bonds; since these $\sigma$ bonds result from the overlap of trigonal $sp^2$ orbitals, all carbon and hydrogen atoms lie in a single plane. Above and below this plane there is a cloud of $\pi$ electrons formed by the overlap of $p$ orbitals and shaped like a figure 8. We can consider this cloud as two partially overlapping sextets that have a pair of $\pi$ electrons in common (Fig. 5C.9).

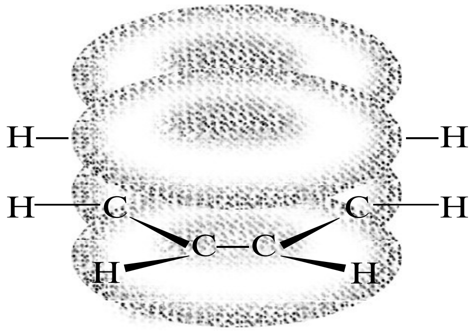


**Figure 5C.8** Naphthalene molecule. $\pi$ clouds above and below the plane of the rings.

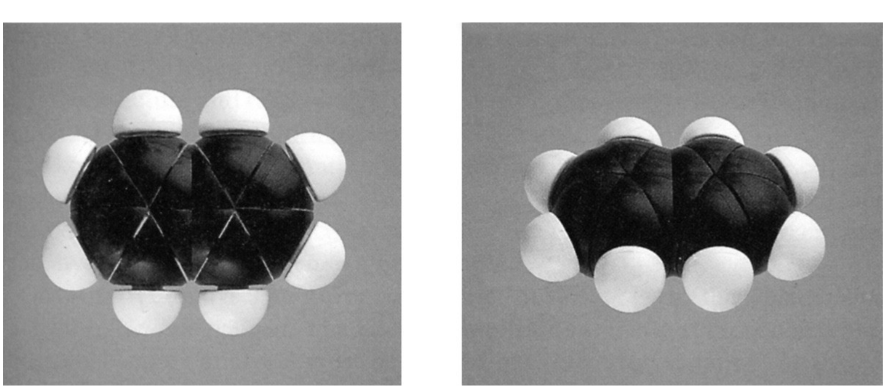
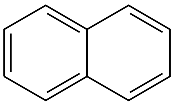
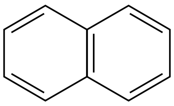


**Figure 5C.9** Electronic configuration and molecular shape. Model of the naphthalene molecule: two views.

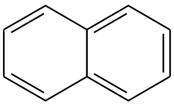
In terms of valence bonds, naphthalene is considered to be a resonance hybrid of the three structures I, II, and III. Its resonance energy, as shown by the heat of combustion, is 61 kcal/mol.



I

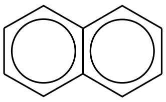


II



III

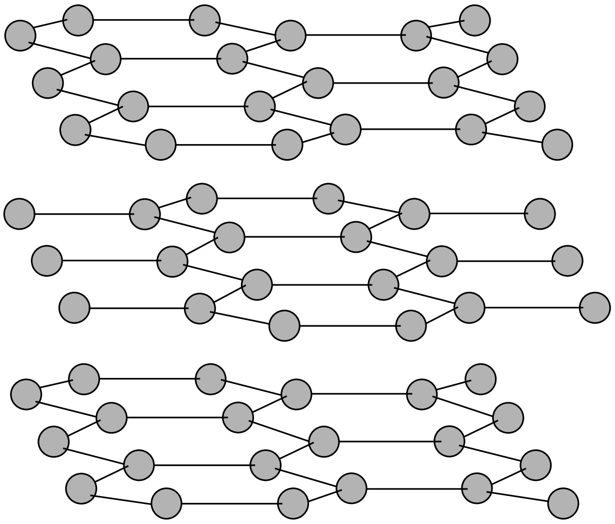
For convenience, we shall represent naphthalene as the single structure IV, in which the circles stand for partially overlapping aromatic sextets.



IV

**Problem 5C.9** In contrast to the six equivalent bonds in benzene, the carbon–carbon bonds in naphthalene come in two lengths: C(1)–C(2), for example, is 1.365 Å long, while C(2)–C(3) is 1.404 Å long. How do you account for this?

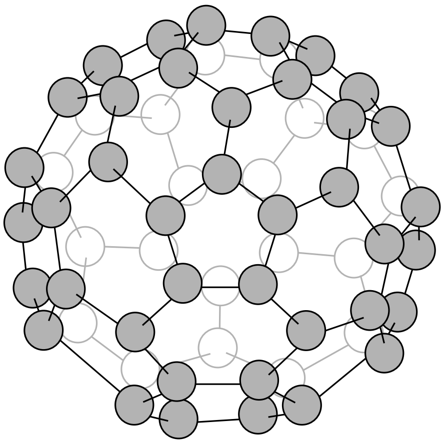
If diamond is the ultimate polycyclic aliphatic system, then another allotropic form of elemental carbon, *graphite*, might be considered the ultimate in fused-ring aromatic systems. X-ray analysis shows that the carbon atoms are arranged in layers. Each layer is a continuous network of planar, hexagonal rings; the carbon atoms within a layer are held together by strong, covalent bonds 1.42 Å long (only slightly longer than those in benzene, 1.39 Å). The different layers, 3.4 Å apart, are held to each other by comparatively weak forces. The lubricating properties of graphite (its "greasy" feel) may be due to slipping of layers (with adsorbed gas molecules between) over one another.



Graphite

A third, newly discovered (1985) allotrope of carbon is *buckminsterfullerene,* named for the designer of the geodesic dome. Unlike diamond and graphite, whose molecules go on and on, the fullerene has a definite formula: $C_{60}$. Here the fused-ring aromatic system bends around and closes to form a soccer ball-shaped molecule (a "buckyball") with 20 six-membered rings and 12 five-membered rings; it has been called the "most symmetrical possible molecule". Other fullerenes have been discovered, too: $C_{70}$ is elongated, like a rugby ball. Richard E. Smalley, who first reported $C_{60}$, predicts that a "Russian doll" molecule can be made: a $C_{60}$ molecule trapped inside a very large ($C_{240}$) fullerene.

Fullerenes have created great excitement in the organic chemistry world: there is room inside the hollow balls for metal ions; the outer surface can be modified by chemical reactions. No one knows quite what to expect of these strange new molecules. By 1991, only six years after the discovery, compounds of fullerenes had been reported to possess remarkable properties as superconductors; they are believed to offer the prospect of resistance-free conductivity of electricity, not at the very low temperatures so far required, but at room temperature.



$C_{60}$ buckminsterfullerene

It is fascinating to construct a model of $C_{60}$ using $sp^2$-hybridized carbons. As five-membered rings are introduced, the structure curves in one's hand; eventually the ball closes, seemingly by its own will. Some angle strain is introduced, but apparently this is compensated for, in part at least, by the formation of additional bonds and the delocalization of electrons over this marvelously symmetrical molecule.

## 5C.13 Electrophilic aromatic substitution

### 5C.13.1 Introduction

We have already seen that the characteristic reactions of benzene involve substitution, in which the resonance-stabilized ring system is preserved. What kind of reagents bring about this substitution? What is the mechanism by which these reactions take place?

Above and below the plane of the benzene ring there is a cloud of $\pi$ electrons (Fig. 5C.10). Through resonance, these $\pi$ electrons are more involved in holding together carbon nuclei than are the $\pi$ electrons of a carbon–carbon double bond. Still, in comparison with s electrons, these $\pi$ electrons are loosely held and are available to a reagent that is seeking electrons.

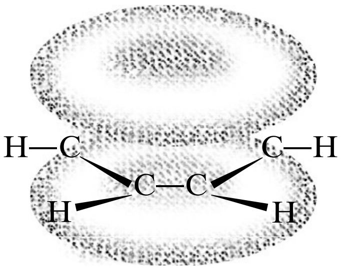


**Figure 5C.10** Benzene ring: the $\pi$ cloud is a source of electrons.

It is not surprising that *in its typical reactions the benzene ring serves as a* **source of electrons**, that is, as a **base**. The compounds with which it reacts are deficient in electrons, that is, are electrophilic reagents or acids. Just as the typical reactions of the alkenes are electrophilic addition reactions, so *the typical reactions of the benzene ring* are **electrophilic substitution reactions**.

These reactions are characteristic not only of benzene itself, but of the benzene ring wherever it is found—and, indeed, of many aromatic rings, benzenoid and nonbenzenoid.

Electrophilic aromatic substitution includes a wide variety of reactions: nitration, halogenation, sulfonation, and Friedel–Crafts reactions, undergone by nearly all aromatic rings; reactions like nitrosation and diazo coupling, undergone only by rings of high reactivity; and reactions like desulfonation, isotopic exchange, and many ring closures which, although apparently unrelated, are found on closer examination to be properly and profitably viewed as reactions of this kind. In synthetic importance electrophilic aromatic substitution is probably unequaled by any other class of organic reactions. It is the initial route of access to nearly all aromatic compounds: it permits the direct introduction of certain substituent groups which can then be converted, by replacement or by transformation, into other substituents, including even additional aromatic rings.

## ELECTROPHILIC AROMATIC SUBSTITUTION

Ar = *aryl,* any aromatic group with attachment directly to ring carbon

1. **Nitration.**

$$\mathrm{ArH + HONO_2 \xrightarrow{H_2SO_4} \underset{\text{A nitro compound}}{Ar{-}NO_2} + H_2O}$$

Electrophile: $NO_2^{\oplus}$
Formation of the electrophile: $HONO_2 + 2H_2SO_4 \rightleftharpoons H_3O^{\oplus} + 2HSO_4^{\ominus} + NO_2^{\oplus}$

2. **Sulfonation.**

$$\mathrm{ArH + HOSO_3H \xrightarrow{SO_3} \underset{\text{A sulfonic acid}}{Ar{-}SO_3H} + H_2O}$$

Electrophile: $SO_3$
Formation of the electrophile: $2H_2SO_4 \rightleftharpoons H_3O^{\oplus} + HSO_4^{\ominus} + SO_3$

3. **Halogenation.**

$$\mathrm{ArH + Cl_2 \xrightarrow{Fe} \underset{\text{An aryl chloride}}{Ar{-}Cl} + HCl}$$

$$\mathrm{ArH + Br_2 \xrightarrow{Fe} \underset{\text{An aryl bromide}}{Ar{-}Br} + HBr}$$

Electrophile: $Cl^{\oplus}$
Formation of the electrophile: $Cl_2 + FeCl_3 \rightleftharpoons FeCl_4^{\ominus} + Cl^{\oplus}$

CONTINUED

CONTINUED

### 4. Friedel–Crafts alkylation.

$$\mathrm{ArH} + \mathrm{RCl} \xrightarrow{\mathrm{AlCl_3}} \underset{\text{An alkylbenzene}}{\mathrm{Ar{-}R}} + \mathrm{HCl}$$

Electrophile: $\mathrm{R}^{\oplus}$

Formation of the electrophile: $\mathrm{RCl} + \mathrm{AlCl_3} \rightleftharpoons \mathrm{R}^{\oplus} + \mathrm{AlCl_4^{\ominus}}$

### 5. Friedel–Crafts acylation.

$$\mathrm{ArH} + \underset{\text{An acyl chloride}}{\mathrm{RCOCl}} \xrightarrow{\mathrm{AlCl_3}} \underset{\text{A ketone}}{\mathrm{Ar{-}COR}} + \mathrm{HCl}$$

Electrophile: $\mathrm{RCO}^{\oplus}$

Formation of the electrophile: $\mathrm{RCOCl} + \mathrm{AlCl_3} \rightleftharpoons \mathrm{AlCl_4^{\ominus}} + \mathrm{RCO}^{\oplus}$

### 6. Protonation.

$$\mathrm{ArSO_3H} + \mathrm{H^+} \xrightarrow{\mathrm{H_2O}} \mathrm{Ar{-}H} + \mathrm{H_2SO_4} \qquad \textit{Desulfonation}$$

$$\mathrm{ArH} + \mathrm{D^+} \xrightarrow{\mathrm{D_2O}} \mathrm{Ar{-}D} + \mathrm{H^+} \qquad \textit{Hydrogen exchange}$$

Electrophile: $\mathrm{H}^{\oplus}$

### 7. Nitrosation.

$$\mathrm{ArH} + \mathrm{HONO} \longrightarrow \underset{\text{A nitroso compound}}{\mathrm{Ar{-}N{=}O}} + \mathrm{H_2O}$$

*Only for highly reactive* ArH

Electrophile: $\mathrm{NO}^{\oplus}$

Formation of the electrophile: $\mathrm{HONO} + \mathrm{HCl} \rightleftharpoons \mathrm{H_2O} + \mathrm{NO}^{\oplus} + \mathrm{Cl}^{\ominus}$

### 8. Diazo coupling.

$$\mathrm{ArH} + \underset{\text{A diazonium salt}}{\mathrm{Ar'N_2{}^+X^-}} \longrightarrow \underset{\text{An azo compound}}{\mathrm{Ar{-}N{=}NAr'}} + \mathrm{HX}$$

*Only for highly reactive* ArH

Electrophile: $\mathrm{ArN_2^{\oplus}}$

### 9. Kolbe reaction.

*Only for phenols*

Electrophile: $\overset{\delta^-}{\mathrm{O}}{=}\overset{\delta^+}{\mathrm{C}}{=}\overset{\delta^-}{\mathrm{O}}$

### 10. Reimer–Tiemann reaction.

*Only for phenols*

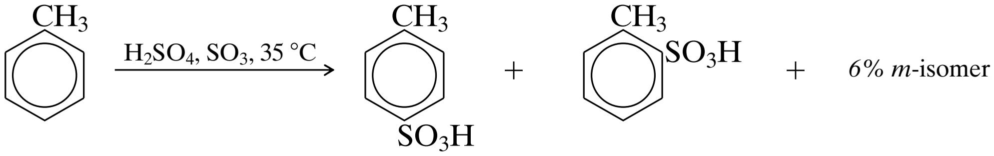
Electrophile: $\ddot{\mathrm{C}}\mathrm{Cl_2}$

Formation of the electrophile: $\mathrm{HCCl_3} + \mathrm{NaOH} \rightleftharpoons \ddot{\mathrm{C}}\mathrm{Cl_2} + \mathrm{H_2O} + \mathrm{NaCl}$

■

## 5C.14 Effect of substituent groups

Like benzene, toluene undergoes electrophilic aromatic substitution: sulfonation, for example. Although there are three possible monosulfonation products, this reaction actually yields appreciable amounts of only two of them: the *ortho* and *para* isomers.



Toluene

*p*-Toluene-
sulfonic
acid
*62%*

*o*-Toluene-
sulfonic
acid
*32%*

Benzene and toluene are insoluble in sulfuric acid, whereas the sulfonic acids are readily soluble; completion of reaction is indicated simply by disappearance of the hydrocarbon layer. When shaken with fuming sulfuric acid at room temperature, benzene reacts completely within 20 to 30 minutes, whereas toluene is found to react within only a minute or two.

Studies of nitration, halogenation, and Friedel–Crafts alkylation of toluene give analogous results. In some way the methyl group makes the ring more reactive than unsubstituted benzene, and *directs* the attacking reagent to the *ortho* and *para* positions of the ring.

On the other hand, nitrobenzene, to take a different example, has been found to undergo substitution more slowly than benzene, and to yield chiefly the *meta isomer.*

Like methyl or nitro, any group attached to a benzene ring affects the **reactivity** of the ring and determines the **orientation** of substitution. When an electrophilic reagent attacks an aromatic ring, it is the group already attached to the ring that determines *how readily* the attack occurs and *where* it occurs.

A group that makes the ring more reactive than benzene is called an **activating group**. A group that makes the ring less reactive than benzene is called a **deactivating group**.

A group that causes attack to occur chiefly at positions ***ortho*** and ***para*** to it is called an ***ortho, para*** **director**. A group that causes attack to occur chiefly at positions ***meta*** to it is called a ***meta*** **director**.

In this chapter we shall examine the methods that are used to measure these effects on reactivity and orientation, the results of these measurements, and a theory that accounts for these results. The theory is, of course, based on the most likely mechanism for electrophilic aromatic substitution; we shall see what this mechanism is, and some of the evidence supporting it. First let us look at the facts.

## 5C.15 Determination of orientation

To determine the effect of a group on orientation is, in principle, quite simple: the compound containing this group attached to benzene is allowed to undergo substitution and the product is analysed for the proportions of the three isomers. Identification of each isomer as *ortho*, *meta*, or *para* generally involves comparison with an authentic sample of that isomer prepared by some other method from a compound whose structure is known. In the last analysis, of course, all these identifications go back to absolute determinations of the Körner type.

In this way it has been found that every group can be put into one of two classes: *ortho, para* directors or *meta* directors. Table 5C.2 summarizes the orientation of nitration in a number of substituted benzenes. Of the five positions open to attack, three (60%) are *ortho* and *para* to the substituent group, and two (40%) are *meta* to the group; if there were no selectivity in the substitution reaction, we would expect the *ortho* and *para* isomers to make up 60% of the product, and the *meta* isomer to make up 40%.We see that seven of the groups direct 96–100% of nitration to the *ortho* and *para* positions; the other six direct 72–94% to the *meta* positions.

**Table 5C.2** ORIENTATION OF NITRATION OF $C_6H_5Y$

| Y | *Ortho* | *Para* | *Ortho* plus *para* | *Meta* |
|---|---|---|---|---|
| —OH | 50–55 | 45–50 | 100 | trace |
| —$NHCOCH_3$ | 19 | 79 | 98 | 2 |
| —$CH_3$ | 58 | 38 | 96 | 4 |
| —F | 12 | 88 | 100 | trace |
| —Cl | 30 | 70 | 100 | trace |
| —Br | 37 | 62 | 99 | 1 |
| —I | 38 | 60 | 98 | 2 |
| —$NO_2$ | 6.4 | 0.3 | 6.7 | 93.3 |
| —$N(CH_3)^+{}_3$ | 0 | 11 | 11 | 89 |
| —CN | — | — | 19 | 81 |
| —COOH | 19 | 1 | 20 | 80 |
| —$SO_3H$ | 21 | 7 | 28 | 72 |
| —CHO | — | — | 28 | 72 |

A given group causes the same general kind of orientation—predominantly *ortho*, *para* or predominantly *meta*—whatever the electrophilic reagent involved. The actual distribution of isomers may vary, however, from reaction to reaction. In Table 5C.3, for example, compare the distribution of isomers obtained from toluene by sulfonation or bromination with that obtained by nitration.

**Table 5C.3** ORIENTATION OF SUBSTITUTION IN TOLUENE

| | *Ortho* | *Meta* | *Para* |
|---|---|---|---|
| Nitration | 58 | 4 | 38 |
| Sulfonation | 32 | 6 | 62 |
| Bromination | 33 | — | 67 |

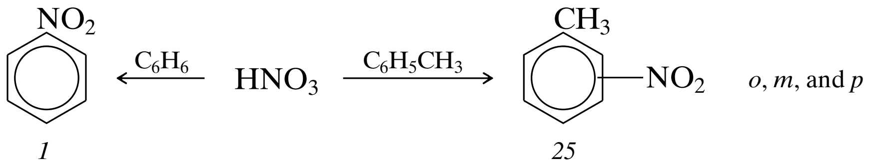
## 5C.16 Regioselectivity of electrophilic aromatic substitutions: relative reactivity of monosubstituted benzenes

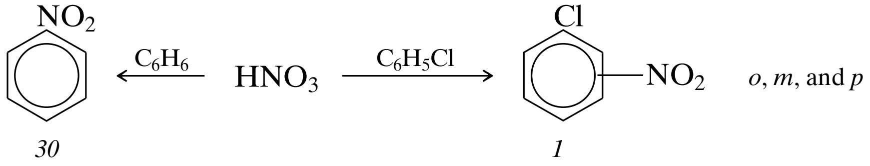
A group is classified as *activating* if the ring it is attached to is more reactive than benzene, and is classified as *deactivating* if the ring it is attached to is less reactive than benzene. The reactivities of benzene and a substituted benzene are compared in one of the following ways.

The **time required** for reactions to occur under identical conditions can be measured. Thus, as we just saw, toluene is found to react with fuming sulfuric acid in about one-tenth to one-twentieth the time required by benzene. Toluene is more reactive than benzene, and —$CH_3$ is therefore an activating group.

The **severity of conditions** required for comparable reaction to occur within the same period of time can be observed. For example, benzene is nitrated in less than an hour at 60°C by a mixture of concentrated sulfuric acid and concentrated nitric acid; comparable nitration of nitrobenzene requires treatment at 90°C with fuming nitric acid and concentrated sulfuric acid. Nitrobenzene is evidently less reactive than benzene, and the nitro group, —$NO_2$, is a deactivating group.

For an exact, quantitative comparison under identical reaction conditions, **competitive reactions** can be carried out, in which the compounds to be compared are allowed to compete for a limited amount of a reagent. For example, if equimolar





amounts of benzene and toluene are treated with a small amount of nitric acid (in a solvent like nitromethane or acetic acid, which will dissolve both organic and inorganic reactants), about 25 times as much nitrotoluene as nitrobenzene is obtained, showing that toluene is 25 times as reactive as benzene. On the other hand, a mixture of benzene and chlorobenzene yields a product in which nitrobenzene exceeds the nitrochlorobenzenes by 30 : 1, showing that chlorobenzene is only one-thirtieth as reactive as benzene. The chloro group is therefore classified as deactivating, the methyl group as activating. The activation or deactivation caused by some groups is extremely powerful: aniline, $C_6H_5NH_2$, is roughly one million times as reactive as benzene, and nitrobenzene, $C_6H_5NO_2$, is roughly one-millionth as reactive as benzene.

## 5C.17 Classification of substituent groups

The methods described in the last two sections have been used to determine the effects of a great number of groups on electrophilic substitution. As shown in Table 5C.4, nearly all groups fall into one of two classes: activating and *ortho*, *para*-directing, or deactivating and *meta*-directing. The halogens are in a class by themselves, being deactivating but *ortho*,*para*-directing.

**Table 5C.4** EFFECT OF GROUPS ON ELECTROPHILIC AROMATIC SUBSTITUTION

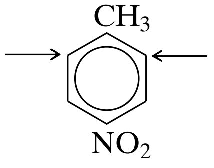
| **Activating: *Ortho, para* directors** | **Deactivating: *Meta* directors** |
|---|---|
| *Strongly activating* | $—NO_2$ |
| $—NH_2$ ($—NHR$, $—NR_2$) | $—N(CH_3)_3^+$ |
| $—OH$ | $—CN$ |
| | $—COOH$ ($—COOR$) |
| *Moderately activating* | $—SO_3H$ |
| $—OCH_3$ ($—OC_2H_5$, etc.) | $—CHO$, $—COR$ |
| $—NHCOCH_3$ | |
| | **Deactivating: *Ortho, para* directors** |
| *Weakly activating* | —F, —Cl, —Br, —I |
| $—C_6H_5$ | |
| $—CH_3$ ($—C_2H_5$, etc.) | |

Just by knowing the effects summarized in these short lists, we can now predict fairly accurately the course of hundreds of aromatic substitution reactions. We now know, for example, that bromination of nitrobenzene will yield chiefly the *meta* isomer and that the reaction will go more slowly than the bromination of benzene itself; indeed, it will probably require severe conditions to go at all. We now know that nitration of $C_6H_5NHCOCH_3$ (*acetanilide*) will yield chiefly the *ortho* and *para* isomers and will take place more rapidly than nitration of benzene.

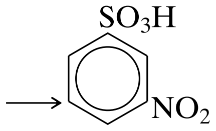
Although, as we shall see, it is possible to account for these effects, in a reasonable way, it is necessary for you to memorize the classifications in Table 5C.4 so that you may deal rapidly with synthetic problems involving aromatic compounds.

## 5C.18 Orientation in disubstituted benzenes

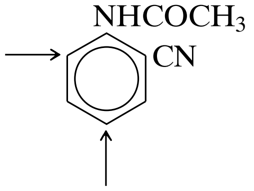
The presence of two substituents on a ring makes the problem of orientation more complicated, but even here we can frequently make very definite predictions. First of all, the two substituents may be located so that the directive influence of one *reinforces* that of the other; for example, in I, II, and III the orientation clearly must be that indicated by the arrows.



I



II



III

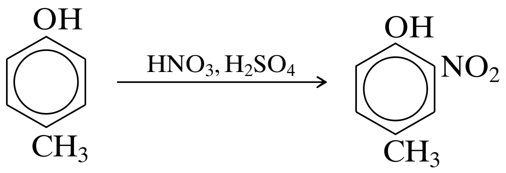
On the other hand, when the directive effect of one group *opposes* that of the other, it may be difficult to predict the major product; in such cases complicated mixtures of several products are often obtained.

Even where there are opposing effects, however, it is still possible in certain cases to make predictions in accordance with the following generalizations.

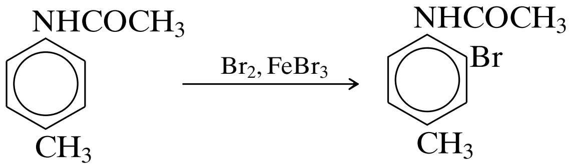
(a) *Strongly activating groups generally win out over deactivating or weakly activating groups.* The differences in directive power in the sequence

$$—NH_2, —OH > —OCH_3, —NHCOCH_3 > —C_6H_5, —CH_3 > \textit{meta}\text{ directors}$$

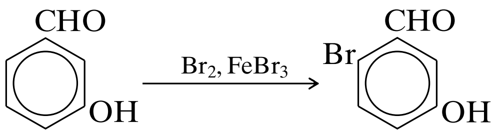
are great enough to be used in planning feasible syntheses. For example:



*Sole product*

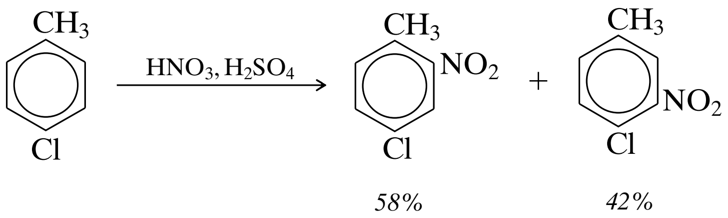


*Chief product*

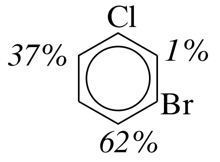


*Chief product*

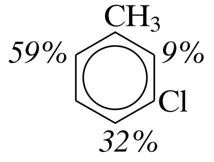
There must be, however, a fairly large difference in the effects of the two groups for clear-cut results; otherwise one gets results like these:



(b) *There is often little substitution between two groups that are meta to each other.* In many cases it seems as though there just is not enough room between two groups located *meta* to each other for appreciable substitution to occur there, as illustrated by IV and V:



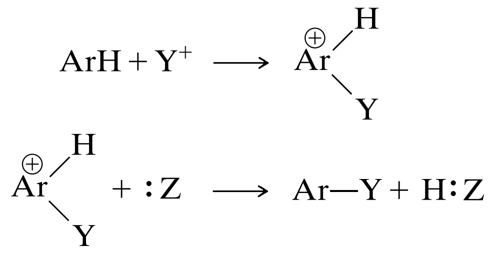
Nitration
IV



Nitration
V

## 5C.19 Mechanism of electrophilic aromatic substitution: the two steps

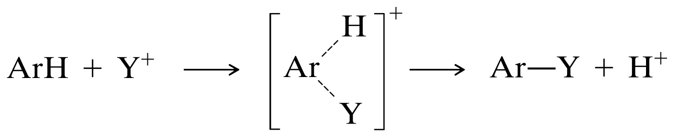
So far we have spoken only of evidence indicating that these reactions are electrophilic, and revealing what the actual electrophiles are likely to be. But this is only part of the mechanism. Granting that substitution is electrophilic, how do we know that electrophilic aromatic substitution involves *two* steps,



$$(1)\qquad \mathrm{ArH} + \mathrm{Y}^+ \longrightarrow \overset{\oplus}{\mathrm{Ar}}\genfrac{}{}{0pt}{}{\diagup \mathrm{H}}{\diagdown \mathrm{Y}} \qquad \textbf{Slow: } \textit{rate-determining}$$

$$(2)\qquad \overset{\oplus}{\mathrm{Ar}}\genfrac{}{}{0pt}{}{\diagup \mathrm{H}}{\diagdown \mathrm{Y}} + :\mathrm{Z} \longrightarrow \mathrm{Ar{-}Y} + \mathrm{H{:}Z} \qquad \textbf{Fast}$$

instead of just *one*,



$$(1a)\qquad \mathrm{ArH} + \mathrm{Y}^+ \longrightarrow \left[\mathrm{Ar}\genfrac{}{}{0pt}{}{\diagup \mathrm{H}}{\diagdown \mathrm{Y}}\right]^+ \longrightarrow \mathrm{Ar{-}Y} + \mathrm{H}^+$$

and how do we know that, of these two steps, the first is much slower than the second?

The answer is found in a series of studies begun by Lars Melander and extended by many other workers. A variety of aromatic compounds labeled with deuterium or tritium were subjected to nitration, bromination, and Friedel–Crafts alkylation. It was found that in these reactions deuterium or tritium is replaced at the *same* rate as protium; *there is no significant isotope effect.*

We have seen that a carbon–deuterium bond is broken more slowly than a carbon–protium bond, and a carbon–tritium bond more slowly yet. Such primary isotope effects are sizable: $k^{\mathrm{H}}/k^{\mathrm{D}}$ may be 5 to 8, and $k^{\mathrm{H}}/k^{\mathrm{T}}$ about twice that large. How, then, are we to interpret the fact that there is no isotope effect here? If the rates of replacement of the various hydrogen isotopes are the same, it can only mean that the reactions *whose rates we are comparing* do not involve the breaking of a carbon–hydrogen bond.

This interpretation is consistent with our mechanism. The rate of the overall substitution is determined by the slow attachment of the electrophilic reagent to the aromatic ring to form the carbocation. Once formed, the carbocation rapidly loses a hydrogen ion—a proton or deuteron—to form the products. Step (1) is thus the *rate-determining step.* Since it does not involve the breaking of a carbon–hydrogen bond, its rate—and hence the rate of the overall reaction—is independent of the particular hydrogen isotope that is present.

If substitution involved a *single* step, as in (1a), this step would necessarily be the rate-determining step and, since it involves breaking of the carbon–hydrogen bond, an isotope effect would be observed. Or, if step (2) of the two-step sequence were slow enough relative to step (1) to affect the overall rate, again we would expect an isotope effect. [Indeed, sulfonation *does* show a small isotope effect and, as we shall see, for just this reason. Even in sulfonation, however, the overall rate is controlled chiefly by step (1).]

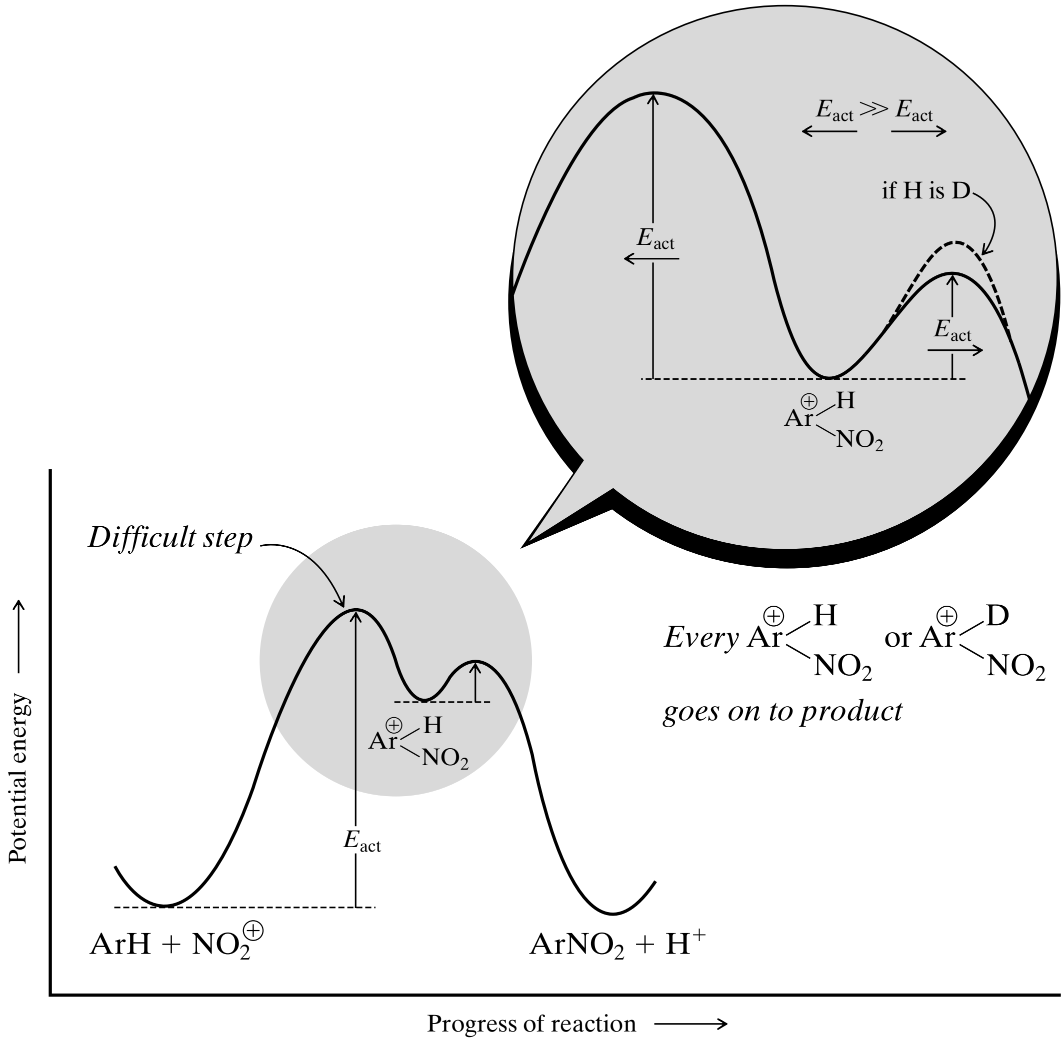
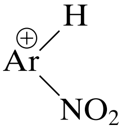
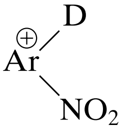


**Figure 5C.11** Nitration. Formation of the carbocation is the rate-controlling step; it occurs equally rapidly whether protium (H) or deuterium (D) is at the point of attack. All the carbocations go on to product. There is no isotope effect, and nitration is irreversible.

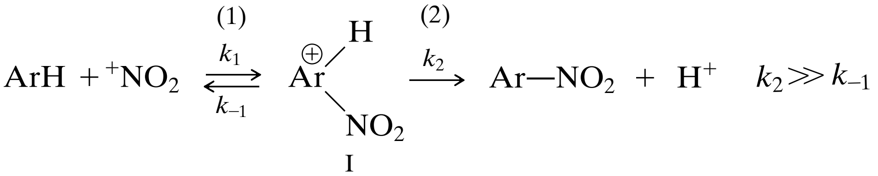
Thus the absence of isotope effects establishes not only the two-step nature of electrophilic aromatic substitution, but also the relative speeds of the steps. Attachment of the electrophile to a carbon atom of the ring is the difficult step (Fig. 5C.11); but it is equally difficult whether the carbon carries protium or deuterium. The next step, loss of hydrogen ion, is easy. Although it occurs more slowly for deuterium than for protium, this really makes no difference; slightly faster or slightly slower, its speed has no effect on the overall rate.

Let us look at this matter more closely (Fig. 5C.11, inset). Every carbocation formed, whether I(H) or I(D), goes on to product, since the energy barrier to the


I(H)


I(D)

right (ahead of the carbocation)—whether slightly higher for deuterium or slightly lower for protium—is still considerably lower than the barrier to the left (behind the carbocation). But the barrier behind the carbocation is the $E_{act}$ for the *reverse* of step (1). It is this reverse reaction that must be much slower than step (2) if step (1) is to be truly rate-determining. Summarized in terms of the *rate constants*, *k*, for the various steps, we have:

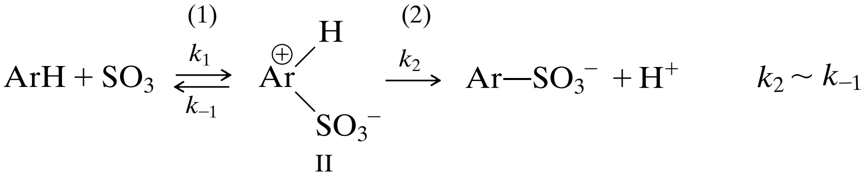


$$\mathrm{ArH} + {}^{+}\mathrm{NO_2} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overset{\oplus}{\mathrm{Ar}}\begin{matrix}\diagup \mathrm{H} \\ \diagdown \mathrm{NO_2}\end{matrix} \xrightarrow{k_2} \mathrm{Ar{-}NO_2} + \mathrm{H^+} \qquad k_2 \gg k_{-1}$$

I

We can see why nitration and reactions like it are not reversible. In the reverse of nitration, nitrobenzene is protonated (the reverse of reaction 2) to form carbocation I; but this is, of course, no different from the ion I formed in the nitration process, and it does the same thing: (re)forms nitrobenzene.

Unlike most other electrophilic substitution reactions, sulfonation shows a moderate isotope effect: ordinary hydrogen (protium) is displaced from an aromatic ring about twice as fast as deuterium. Does this mean that sulfonation takes place by a different mechanism than nitration, one involving a single step? Almost certainly not.



$$\mathrm{ArH} + \mathrm{SO_3} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \overset{\oplus}{\mathrm{Ar}}\begin{matrix}\diagup \mathrm{H} \\ \diagdown \mathrm{SO_3^-}\end{matrix} \xrightarrow{k_2} \mathrm{Ar{-}SO_3^-} + \mathrm{H^+} \qquad k_2 \sim k_{-1}$$

II

Unlike most other electrophilic substitution reactions, sulfonation is reversible, and this fact gives us our clue. Reversibility means that carbocation II can lose $SO_3$ to form the hydrocarbon. Evidently here reaction (2) is *not* much faster than the reverse of reaction (1). In sulfonation, the energy barriers on either side of the carbocation II must be roughly the same height; some ions go one way, some go the other (Fig. 5C.12). Now, whether the carbocation is II(D) or II(H), the barrier to the left (behind it) is the same height. But to climb the barrier to the right (ahead), a carbon-hydrogen bond must be broken, so this barrier is higher for carbocation II(D) than for carbocation II(H). More deuterated ions than ordinary ions revert to starting material, and so overall sulfonation is slower for the deuterated benzene. Thus, the particular shape of potential energy curve that makes sulfonation reversible also permits an isotope effect to be observed.

By use of especially selected aromatic substrates—highly hindered ones—isotope effects can be detected in other kinds of electrophilic aromatic substitution, even in nitration. In certain reactions the *size* of the isotope effect can be deliberately varied by changes in experimental conditions—and in a way that shows dependence on the relative rates of (2) and the reverse of (1). There can be little doubt that all these reactions follow the same two-step mechanism, but with differences in the shape of potential energy curves. In isotope effects the chemist has an exceedingly delicate probe for the examination of organic reaction mechanisms.

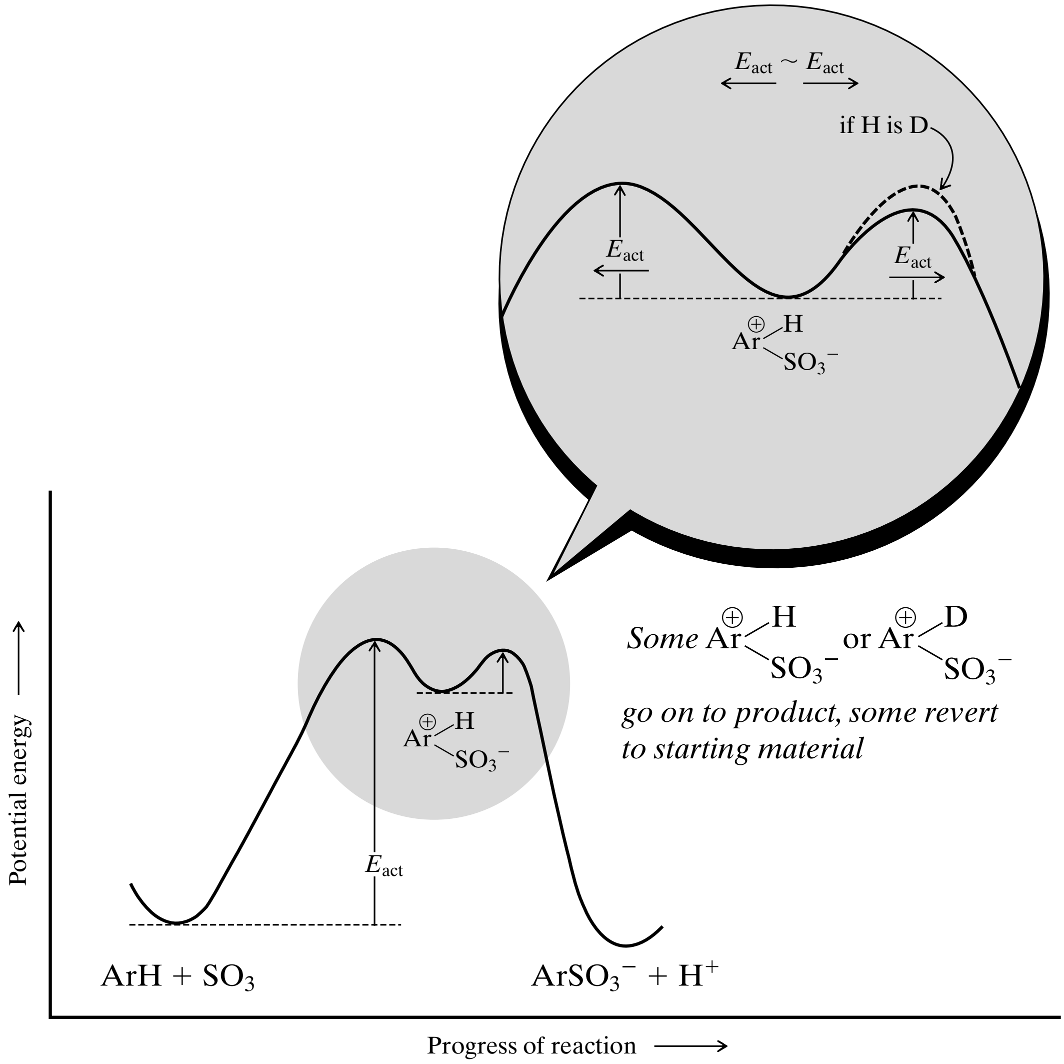


**Figure 5C.12** Sulfonation. Some carbocations go on to product, some revert to starting material. There is an isotope effect, and sulfonation is reversible.

**Problem 5C.10** From the reaction of mesitylene (1,3,5-trimethylbenzene) with HF and $BF_3$, Olah isolated at low temperatures a bright-yellow solid whose elemental composition corresponds to mesitylene :HF:$BF_3$ in the ratio 1 : 1 : 1. The compound was poorly soluble in organic solvents and, when molten, conducted an electric current; chemical analysis showed the presence of the $BF_4^-$ ion. When heated, the compound evolved $BF_3$ and regenerated mesitylene.

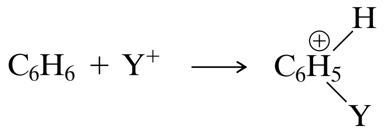
What is a likely structure for the yellow compound? The isolation of this and related compounds is considered to be strong support for the mechanism of electrophilic aromatic substitution. Why should this be so?

## 5C.20 Reactivity and orientation

Certain groups activate the benzene ring and direct substitution to *ortho* and *para* positions, and that other groups deactivate the ring and (except halogens) direct substitution to *meta* positions. Let us see if we can account for these effects on the basis of principles we have already learned.

First of all, we must remember that reactivity and orientation are both matters of relative rates of reaction. Methyl is said to activate the ring because it makes the ring react *faster* than benzene; it causes *ortho, para* orientation because it makes the *ortho* and *para* positions react *faster* than the *meta* positions.

Now, we know that, whatever the specific reagent involved, the rate of electrophilic aromatic substitution is determined by the same slow step—attack of the electrophile on the ring to form a carbocation:



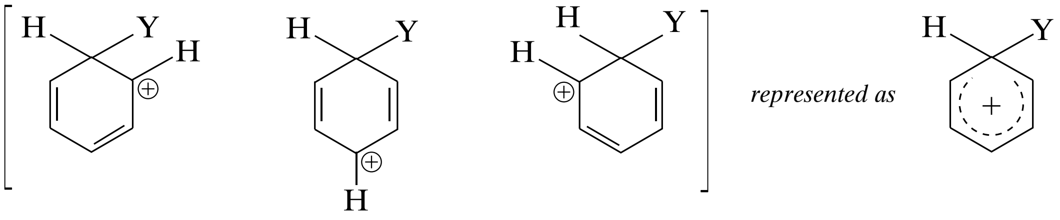
$$C_6H_6 + Y^+ \longrightarrow C_6H_5^{\oplus}(H)(Y)$$

**Slow:** *rate-determining*

Any differences in rate of substitution must therefore be due to differences in the rate of this step.

For closely related reactions, a difference in rate of formation of carbocations is largely determined by a difference in $E_{\text{act}}$, that is, by a difference in stability of transition states. As with other carbocation reactions we have studied, factors that stabilize the ion by dispersing the positive charge should for the same reason stabilize the incipient carbocation of the transition state. Here again we expect the more stable carbocation to be formed more rapidly. We shall therefore concentrate on the relative stabilities of the carbocations.

In electrophilic aromatic substitution the intermediate carbocation is a hybrid of structures I, II, and III, in which the positive charge is distributed about the ring, being strongest at the positions *ortho* and *para* to the carbon atom being attacked.

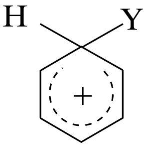


I II III IV

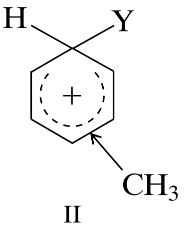
A group already attached to the benzene ring should affect the stability of the carbocation by dispersing or intensifying the positive charge, depending upon its electron-releasing or electron-withdrawing nature. It is evident from the structure of the ion (I–III) that this stabilizing or destabilizing effect should be especially important when the group is attached *ortho* or *para* to the carbon being attacked.

## 5C.21 Theory of reactivity

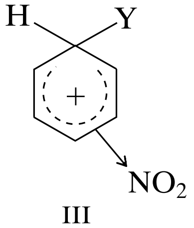
To compare rates of substitution in benzene, toluene, and nitrobenzene, we compare the structures of the carbocations formed from the three compounds:



I

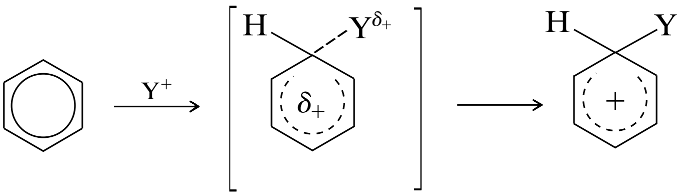


II



III

By releasing electrons, the methyl group (II) tends to neutralize the positive charge of the ring and so become more positive itself; this dispersal of the charge stabilizes the carbocation. In the same way the inductive effect stabilizes the developing positive charge in the transition state and thus leads to a faster reaction.



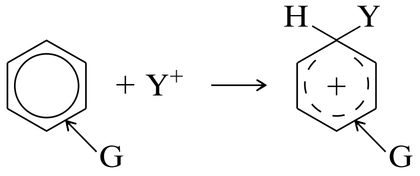
Transition state:
*developing positive charge*

Carbocation:
*full positive charge*

The $—NO_2$ group, on the other hand, has an electron-withdrawing inductive effect (III); this tends to intensify the positive charge, destabilizes the carbocation, and thus causes a slower reaction.

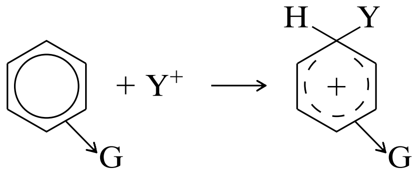
*Reactivity in electrophilic aromatic substitution depends, then, upon the tendency of a substituent group to release or withdraw electrons.* **A group that releases electrons activates the ring; a group that withdraws electrons deactivates the ring.**

### Electrophilic Aromatic Substitution



G *releases electrons: stabilizes carbocation, activates*

G = $—NH_2$
$—OH$
$—OCH_3$
$—NHCOCH_3$
$—C_6H_5$
$—CH_3$



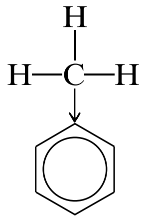
G *withdraws electrons: destabilizes carbocation, deactivates*

G = $—N(CH_3)_3^+$
$—NO_2$
$—CN$
$—SO_3H$
$—COOH$
$—CHO$
$—COR$
$—X$

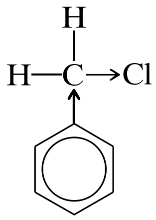
Like $—CH_3$, other alkyl groups release electrons, and like $—CH_3$ they activate the ring. For example, *tert*-butylbenzene is 16 times as reactive as benzene toward nitration. Electron release by $—NH_2$ and $—OH$, and by their derivatives $—OCH_3$ and $—NHCOCH_3$, is due not to their inductive effect but to resonance, and is discussed later.

We are already familiar with the electron-withdrawing effect of the halogens. The full-fledged positive charge of the $—N(CH_3)_3^+$ group has, of course, a powerful attraction for electrons. In the other deactivating groups (e.g., $—NO_2$, $—CN$, $—COOH$), the atom next to the ring is attached by a multiple bond to oxygen or nitrogen. These electronegative atoms attract the mobile $\pi$ electrons, making the atom next to the ring electron-deficient; to make up this deficiency, the atom next to the ring withdraws electrons from the ring.

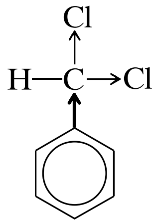
We might expect replacement of hydrogen in —$CH_3$ by halogen to decrease the electron-releasing tendency of the group, and perhaps to convert it into an electron-withdrawing group. This is found to be the case. Toward nitration, toluene is 25 times as reactive as benzene; benzyl chloride is only one-third as reactive as benzene. The —$CH_2Cl$ group is thus weakly deactivating. Further replacement of hydrogen by halogen to yield the —$CHCl_2$ and the —$CCl_3$ groups results in stronger deactivation.



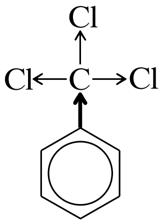
Activating



Weakly deactivating



Moderately deactivating



Strongly deactivating

## 5C.22 Theory of orientation

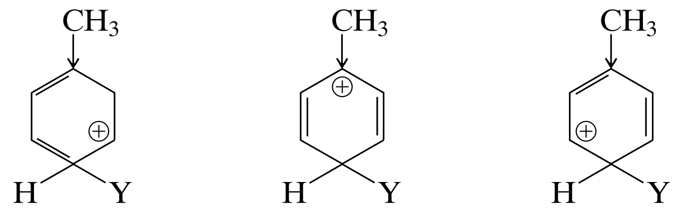
Before we try to account for orientation in electrophilic substitution, let us look more closely at the facts.

An activating group activates all positions of the benzene ring; even the positions *meta* to it are more reactive than any single position in benzene itself. It directs *ortho* and *para* simply because it activates the *ortho* and *para* positions much *more* than it does the *meta.*

A deactivating group deactivates all positions in the ring, even the positions *meta* to it. It directs *meta* simply because it deactivates the *ortho* and *para* positions even *more* than it does the *meta.*

Thus both *ortho, para* orientation and *meta* orientation arise in the same way: **the effect of any group—whether activating or deactivating—is strongest at the *ortho* and *para* positions**.

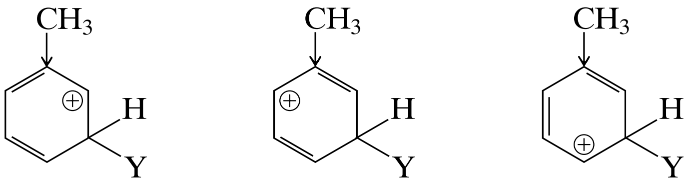
To see if this is what we would expect, let us compare, for example, the carbocations formed by attack at the *para* and *meta* positions of toluene, a compound that contains an activating group. Each of these is a hybrid of three structures, I–III for *para,* IV–VI for *meta.* In one of these six structures, II, the positive charge is located on the carbon atom to which —$CH_3$ is attached. Although —$CH_3$ releases electrons to all positions of the ring, it does so most strongly to the carbon atom nearest it; consequently, structure II is a particularly stable one. Because of contribution from structure II, the hybrid carbocation resulting from attack at the *para* position is more



I II III

*Especially stable: charge on carbon carrying substituent*

***Para* attack**

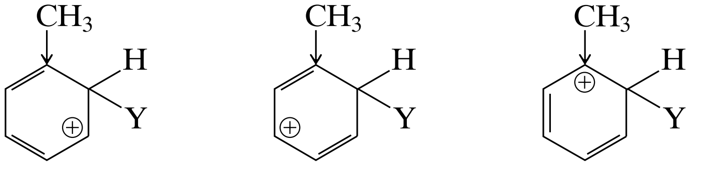


IV V IV

***Meta* attack**

stable than the carbocation resulting from attack at a *meta* position. *Para* substitution, therefore, occurs faster than *meta* substitution.

In the same way, it can be seen that attack at an *ortho* position (VII–IX) also yields a more stable carbocation, through contribution from IX, than attack at a *meta* position.



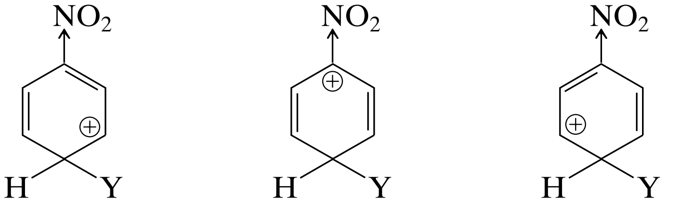
VII VIII IX

*Especially stable: charge on carbon carrying substituent*

***Ortho* attack**

In toluene, *ortho*, *para* substitution is thus faster than *meta* substitution because electron release by —CH$_3$ is more effective during attack at the positions *ortho* and *para* to it.

Next, let us compare the carbocations formed by attack at the *para* and *meta* positions of nitrobenzene, a compound that contains a deactivating group. Each of these is a hybrid of three structures, X–XII for *para* attack, XIII–XV for *meta* attack. In one of the six structures, XI, the positive charge is located on the carbon atom to which —NO$_2$ is attached. Although —NO$_2$ withdraws electrons from all positions, it does so most from the carbon atom nearest it, and hence this carbon atom, already positive, has little tendency to accommodate the positive charge of the carbocation.

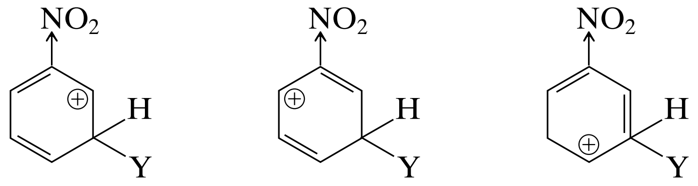


X XI XII

*Especially unstable: charge on carbon carrying substituent*

***Para* attack**

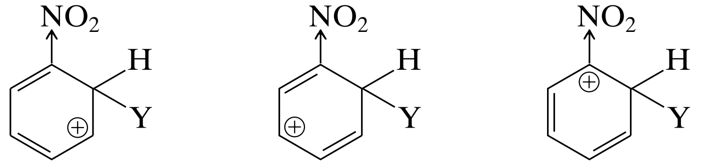
Structure XI is thus a particularly unstable one and does little to help stabilize the ion resulting from attack at the *para* position. The ion for *para* attack is virtually a hybrid of only two structures, X and XII; the positive charge is mainly restricted to only *two* carbon atoms. It is less stable than the ion resulting from attack at a *meta* position, which is a hybrid of three structures, and in which the positive charge is accommodated by *three* carbon atoms. *Para* substitution, therefore, occurs more slowly than *meta* substitution.



XIII XIV XV

***Meta* attack**

In the same way it can be seen that attack at an *ortho* position (XVI–XVIII) yields a less stable carbocation, because of the instability of XVIII, than attack at a *meta* position.



XVI XVII XVIII

*Especially stable: charge on carbon carrying substituent*

***Ortho* attack**

In nitrobenzene, *ortho, para* substitution is thus slower than *meta* substitution because electron withdrawal by $—NO_2$ is more effective during attack at the positions *ortho* and *para* to it.

Thus we see that both *ortho, para* orientation by activating groups and *meta* orientation by deactivating groups follow logically from the structure of the intermediate carbocation. The charge of the carbocation is strongest at the positions *ortho* and *para* to the point of attack, and hence a group attached to one of these positions can exert the strongest effect, whether activating or deactivating.

## 5C.23 Electron release via resonance

We have seen that a substituent group affects both reactivity and orientation in electrophilic aromatic substitution by its tendency to release or withdraw electrons. So far, we have considered electron release and electron withdrawal only as inductive effects, that is, as effects due to the electronegativity of the group concerned.

But certain groups ($—NH_2$ and —OH, and their derivatives) act as powerful activators toward electrophilic aromatic substitution, even though they contain electronegative atoms and can be shown in other ways to have electron-withdrawing inductive effects. If our approach to the problem is correct, these groups must release electrons in some other way than through their inductive effects; they are believed to do this by a resonance effect. But before we discuss this, let us review a little of what we know about nitrogen and oxygen.

Although electronegative, the nitrogen of the $—NH_2$ group is basic and tends to share its last pair of electrons and acquire a positive charge. Just as ammonia accepts a proton to form the ammonium ($NH_4^+$) ion, so organic compounds related to ammonia accept protons to form substituted ammonium ions.

$$\ddot{\mathrm{N}}\mathrm{H}_3 + \mathrm{H}^+ \longrightarrow \mathrm{NH}_4^+ \qquad \mathrm{R}\ddot{\mathrm{N}}\mathrm{H}_2 + \mathrm{H}^+ \longrightarrow \mathrm{RNH}_3^+$$

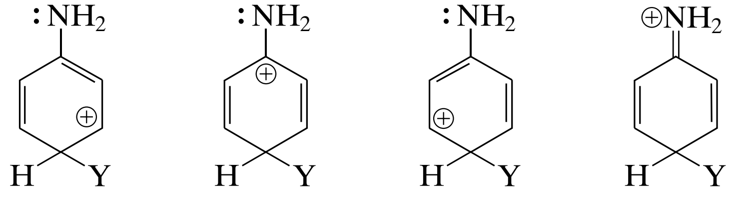
$$\mathrm{R}_2\ddot{\mathrm{N}}\mathrm{H} + \mathrm{H}^+ \longrightarrow \mathrm{R}_2\mathrm{NH}_2^+ \qquad \mathrm{R}_3\ddot{\mathrm{N}} + \mathrm{H}^+ \longrightarrow \mathrm{R}_3\mathrm{NH}^+$$

The —OH group shows similar but weaker basicity; we are already familiar with oxonium ions, $\mathrm{ROH}_2^+$.

$$\mathrm{H}_2\ddot{\mathrm{O}} + \mathrm{H}^+ \longrightarrow \mathrm{H}_3\mathrm{O}^+ \qquad \mathrm{R}\ddot{\mathrm{O}}\mathrm{H} + \mathrm{H}^+ \longrightarrow \mathrm{ROH}_2^+$$

The effects of —NH$_2$ and —OH on electrophilic aromatic substitution can be accounted for by assuming that nitrogen and oxygen can share more than a pair of electrons with the ring and can accommodate a positive charge.

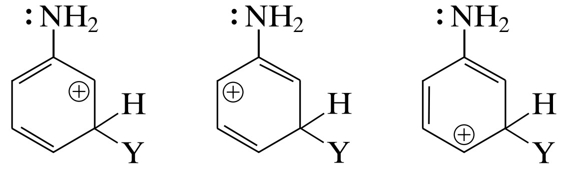
The carbocation formed by attack *para* to the —NH$_2$ group of aniline, for example, is considered to be a hybrid not only of structures I, II, and III, with positive charges located on carbons of the ring, but also of structure IV in which the positive charge is carried by nitrogen. Structure IV is especially stable, since in it *every atom* (except hydrogen, of course) *has a complete octet of electrons.* This carbocation is much more stable than the one obtained by attack on benzene itself, or the one obtained (V–VII) from attack *meta* to the —NH$_2$ group of aniline; in neither of these cases is a structure like IV possible. (Compare, for example, the stabilities of the ions NH$_4^+$ and CH$_3^+$. Here it is not a matter of which atom, nitrogen or carbon, can better accommodate a positive charge; it is a matter of which atom has a complete octet of electrons.)



I II III IV

*Especially stable: every atom has octet*

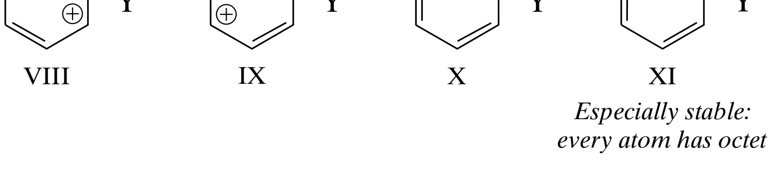
***Para* attack**



V VI VII

***Meta* attack**

Examination of the corresponding structures (VIII–XI) shows that *ortho* attack is much like *para* attack:



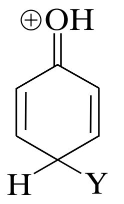
VIII IX X XI

*Especially stable: every atom has octet*

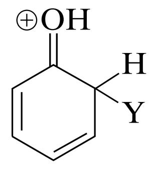
***Ortho* attack**

Thus substitution in aniline occurs faster than substitution in benzene, and occurs predominantly at the positions *ortho* and *para* to —$NH_2$.

In the same way activation and *ortho, para* orientation by the —OH group is accounted for by contribution of structures like XII and XIII, in which every atom has a complete octet of electrons:

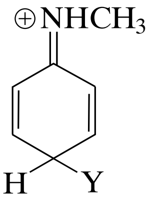


XII
*Para* attack

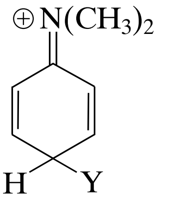


XIII
*Ortho* attack

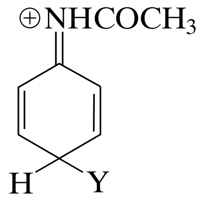
The similar effects of the derivatives of —$NH_2$ and —OH are accounted for by similar structures (shown only for *para* attack):



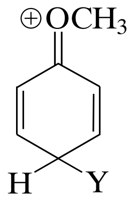
—$NHCH_3$



—$N(CH_3)_2$



—$NHCOCH_3$



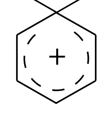
—$OCH_3$

## 5C.24 Effect of halogen on electrophilic aromatic substitution

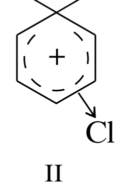
Halogens are unusual in their effect on electrophilic aromatic substitution: they are deactivating yet *ortho*, *para*-directing. Deactivation is characteristic of electron withdrawal, whereas *ortho*, *para* orientation is characteristic of electron release. Can halogen both withdraw and release electrons?

The answer is *yes*. Halogen withdraws electrons through its inductive effect, and releases electrons through its resonance effect. So, presumably, can the —$NH_2$ and —OH groups, but there the much stronger resonance effect greatly outweighs the other. For halogen, the two effects are more evenly balanced, and we observe the operation of both.

Let us first consider **reactivity**. Electrophilic attack on benzene yields carbocation I, attack on chlorobenzene yields carbocation II. The electron-withdrawing inductive effect of chlorine intensifies the positive charge in carbocation II, makes the ion less stable, and causes a slower reaction.



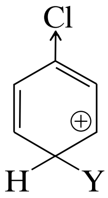
I

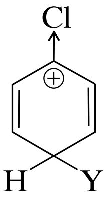


II

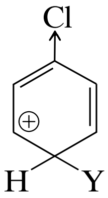
—Cl *withdraws electrons: destabilizes carbocation, deactivates ring*

Next, to understand **orientation**, let us compare the structures of the carbocations formed by attack at the *para* and *meta* positions of chlorobenzene. Each of these is a hybrid of three structures, III–V for *para*, VI–VIII for *meta*. In one of these six structures, IV, the positive charge is located on the carbon atom to which chlorine is attached. Through its inductive effect chlorine withdraws electrons most from the carbon to which it is joined, and thus makes structure IV especially unstable. As before, we expect IV to make little contribution to the hybrid, which should therefore be less stable than the hybrid ion resulting from attack at the *meta* positions. If only the inductive effect were involved, then, we would expect not only deactivation but also *meta* orientation.

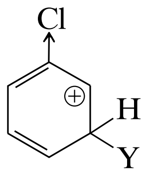

III

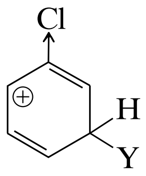

IV

*Especially unstable: charge on carbon bearing substituent*


V

***Para* attack**


VI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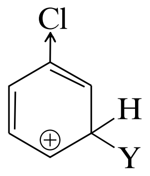
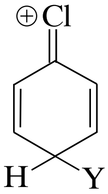

VIII

***Meta* attack**

But the existence of halonium ions has shown us that halogen can share more than a pair of electrons and can accommodate a positive charge. If we apply that idea to the present problem, what do we find? The ion resulting from *para* attack is a hybrid not only of structures III–V, but also of structure IX, in which chlorine bears a positive charge and is joined to the ring by a double bond. This structure should be comparatively stable, since in it every atom (except hydrogen, of course) has a *complete octet of electrons.* (Structure IX is exactly analogous to those proposed to account for activation and *ortho*, *para* direction by —$NH_2$ and —OH.) No such structure is possible for the ion resulting from *meta* attack. To the extent that structure IX contributes to the hybrid, it makes the ion resulting from *para*

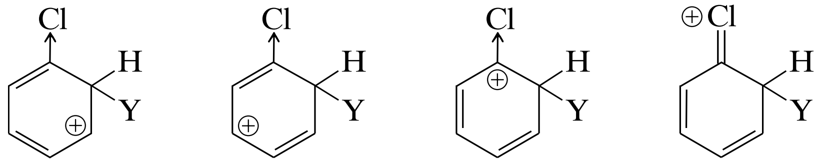

IX

*Comparatively stable: every atom has octet*

***Para* attack**

attack more stable than the ion resulting from *meta* attack. Although we could not have predicted the relative importance of the two factors—the instability of IV and the stabilization by IX—the result indicates that the contribution from IX is the more important.

In the same way it can be seen that attack at an *ortho* position also yields an ion (X–XIII) that can be stabilized by accommodation of the positive charge by chlorine.



**_Ortho_ attack**

X XI XII XIII

*Especially unstable: charge on carbon bearing substituent*

*Comparatively stable: every atom has octet*

Through its inductive effect halogen tends to withdraw electrons and thus to destabilize the intermediate carbocation. This effect is felt for attack at all positions, but particularly for attack at the positions *ortho* and *para* to the halogen.

Through its resonance effect halogen tends to release electrons and thus to stabilize the intermediate carbocation. This electron release is effective only for attack at the positions *ortho* and *para* to the halogen.

The inductive effect is stronger than the resonance effect and causes net electron withdrawal—and hence deactivation—for attack at all positions. The resonance effect tends to oppose the inductive effect for attack at the *ortho* and *para* positions, and hence makes the deactivation less for *ortho, para* attack than for *meta.*

Reactivity is thus controlled by the stronger inductive effect, and orientation is controlled by the resonance effect, which, although weaker, is more selective.

**Problem 5C.11** Hydrogen iodide adds to vinyl chloride more slowly than to ethylene, and yields 1-chloro-1-iodoethane. (a) Draw the formula of the carbocation formed in the initial step of the addition to vinyl chloride. (b) Of addition to ethylene. (c) Judging from the relative rates of reaction, which would appear to be the more stable carbocation? (d) Account for the difference in stability.

(e) Draw the formula for the carbocation that would be formed if vinyl chloride were to yield 1-chloro-2-iodoethane. (f) Judging from the actual orientation of addition, which carbocation from vinyl chloride is the more stable, (a) or (e)? (g) Account for the difference in stability.

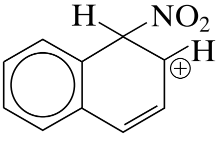
(h) Which effect, inductive or resonance, controls reactivity in electrophilic addition to vinyl halides? (i) Which effect controls orientation?

Thus we find that a single structural concept—partial double-bond formation between halogen and carbon—helps to account for unusual chemical properties of such seemingly different compounds as aryl halides and vinyl halides. The structures involving doubly bonded halogen, which probably make important contributions not only to benzenonium ions but to the parent aryl halides as well, certainly do not seem to meet our usual standard of reasonableness. The sheer weight of evidence forces us to accept the idea that certain carbon–halogen bonds possess double-bond character. If this idea at first appears strange to us, it simply shows how much, after all, we still have to learn about molecular structure.

## 5C.25 Electrophilic substitution in naphthalene

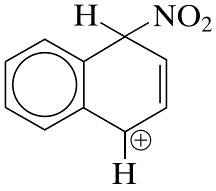
Like benzene, the polynuclear hydrocarbon naphthalene typically undergoes electrophilic substitution; this is one of the properties that entitle it to the designation of “aromatic”. Nitration and halogenation occur almost exclusively in the $\alpha$-position. Is this orientation what we might have expected? Let us apply the approach that we have used so far, and examine the carbocation formed in the initial attack.

Attack by nitronium ion at the $\alpha$-position of naphthalene yields an intermediate carbocation that is a hybrid of structures I and II in which the positive charge is accommodated by the ring under attack, and several structures like III in which the charge is accommodated by the other ring.



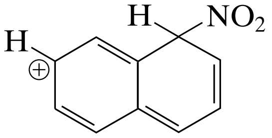
I

*More stable:*
*aromatic sextet*
*preserved*



II

*More stable:*
*aromatic sextet*
*preserved*

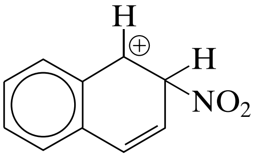


III

*Less stable:*
*aromatic sextet*
*disrupted*

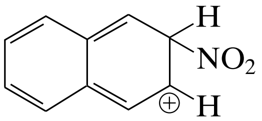
**Alpha attack**

Attack at the $\beta$-position yields an intermediate carbocation that is a hybrid of IV and V in which the positive charge is accommodated by the ring under attack, and several structures like VI in which the positive charge is accommodated by the other ring.



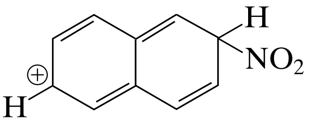
IV

*More stable:*
*aromatic sextet*
*preserved*



V

*Less stable:*
*aromatic sextet*
*disrupted*



VI

*Less stable:*
*aromatic sextet*
*disrupted*

**Beta attack**

In structures I, II, and IV, the aromatic sextet is preserved in the ring that is not under attack; these structures thus retain the full resonance stabilization of one benzene ring (36 kcal/mol). In structures like III, V, and VI, on the other hand, the aromatic sextet is disrupted in both rings, with a large sacrifice of resonance stabilization. Clearly, structures like I, II, and IV are much the more stable.

But there are two of these stable contributing structures (I and II) for attack at the $\alpha$-position and only one (IV) for attack at the $\beta$-position. On this basis we would expect the carbocation resulting from attack at the $\alpha$-position (and also the transition state leading to that ion) to be much more stable than the carbocation (and the corresponding transition state) resulting from attack at the $\beta$-position, and that nitration would therefore occur much more rapidly at the $\alpha$-position.

In the study of polynuclear hydrocarbons, substituted and unsubstituted, one finds that the matter of orientation is generally understandable on the basis of this principle: of the large number of structures contributing to the intermediate carbocation, the important ones are those that require the smallest sacrifice of resonance stabilization. Indeed, one finds that this principle accounts for orientation not only in electrophilic substitution but also in oxidation, reduction, and addition.

**Problem 5C.12** Sulfonation of naphthalene at 80°C yields chiefly 1-naphthalenesulfonic acid; sulfonation at 160°C or higher yields chiefly 2-naphthalenesulfonic acid. When 1-naphthalenesulfonic acid is heated in sulfuric acid at 160°C, it is largely converted into the 2-isomer. Account in detail for these facts.

**Problem 5C.13** Upon nitration, 1-naphthol (1-hydroxynaphthalene) yields 2,4-dinitronaphthol, and 1-nitronaphthalene yields 1,8-dinitronaphthalene and 1,5-dinitronaphthalene. How do you account for this contrast?

## EXERCISE

**1.** Draw structures of:

(a) *p*-dinitrobenzene
(b) *m*-bromonitrobenzene
(c) *o*-chlorobenzoic acid
(d) *m*-nitrotoluene
(e) *p*-bromoaniline
(f) *m*-iodophenol
(g) mesitylene (1,3,5-trimethylbenzene)
(h) 3,5-dinitrobenzenesulfonic acid
(i) 4-chloro-2,3-dinitrotoluene
(j) 2-amino-5-bromo-3-nitrobenzoic acid
(k) *p*-hydroxybenzoic acid
(l) 2,4,6-trinitrophenol

**2.** Give structures and names of all the possible isomeric:

(a) xylenes (dimethylbenzenes)
(b) aminobenzoic acids ($H_2NC_6H_4COOH$)
(c) trimethylbenzenes
(d) dibromonitrobenzenes
(e) bromochlorotoluenes
(f) trinitrotoluenes

**3.** (a) How many isomeric monosubstitution products are theoretically possible from each of the following structures of formula $C_6H_6$? (b) How many disubstitution products? (c) Which structures, if any, would be acceptable for benzene on the basis of isomer number?

$$HC\equiv C-CH_2-CH_2-C\equiv CH$$

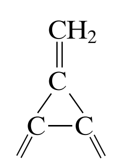
I

$$HC\equiv C-CH_2-C\equiv C-CH_3$$

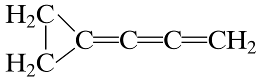
II

$$HC\equiv C-C\equiv C-CH_2-CH_3$$

III



IV

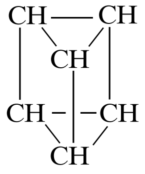


V

**4.** Give structures and names of all theoretically possible products of the ring mononitration of:

(a) *o*-dichlorobenzene
(b) *m*-dichlorobenzene
(c) *p*-dichlorobenzene
(d) *o*-bromochlorobenzene
(e) *m*-bromochlorobenzene
(f) *p*-bromochlorobenzene
(g) *o*-chloronitrobenzene
(h) *m*-chloronitrobenzene
(i) *p*-chloronitrobenzene
(j) 1,3,5-trimethylbenzene
(k) 4-bromo-1,2-dimethylbenzene
(l) *p*-ethyltoluene

**5.** For a time the prism formula VI, proposed in 1869 by Albert Ladenburg of Germany, was considered as a possible structure for benzene, on the grounds that it would yield one monosubstitution product and three isomeric disubstitution products.



VI

(a) Draw Ladenburg structures of three possible isomeric dibromobenzenes.
(b) On the basis of the Körner method of absolute orientation, label each Ladenburg structure in (a) as *ortho*, *meta*, or *para*.
(c) Can the Ladenburg formula actually pass the test of isomer number?
(Derivatives of Ladenburg "benzene", called *prismanes,* have actually been made.)

**6.** Give structures and names of all benzene derivatives that *theoretically* can have the indicated number of isomeric ring-substituted derivatives.

(a) $C_8H_{10}$: one monobromo derivative
(b) $C_8H_{10}$: two monobromo derivatives
(c) $C_8H_{10}$: three monobromo derivatives
(d) $C_9H_{12}$: one mononitro derivative
(e) $C_9H_{12}$: two mononitro derivatives
(f) $C_9H_{12}$: three mononitro derivatives
(g) $C_9H_{12}$: four mononitro derivatives

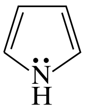
**7.** There are three known tribromobenzenes, of m.p. 44°C, 87°C, and 120°C. Could these isomers be assigned structures by use of the Körner method? Justify your answer.

**8.** In 1874 Griess reported that he had decarboxylated the six known diaminobenzoic acids, $C_6H_3(NH_2)_2$ COOH, to the diaminobenzenes. Three acids gave a diamine of m.p. 63°C, two acids gave a diamine of m.p. 104°C, and one acid gave a diamine of m.p. 142°C. Draw the structural formulas for the three isomeric diaminobenzenes and label each with its melting point.

**9.** For which of the following might you expect aromaticity (geometry permitting)?

(a) The annulenes containing up to 20 carbons. (*Annulenes* are monocyclic compounds of the general formula $[\text{—CH=CH—}]_n$.)
(b) The monocyclic polyenes $C_9H_{10}$, $C_9H_9^+$, $C_9H_9^-$.

**10.** The properties of *pyrrole*, commonly represented by VII,



VII

show that it is aromatic. Account for its aromaticity on the basis of orbital theory.

**11.** When benzene is treated with chlorine under the influence of ultraviolet light, a solid material of mol. wt. 291 is formed. Quantitative analysis gives an empirical formula of CHCl. (a) What is the molecular formula of the product? (b) What is a possible structural formula? (c)What kind of reaction has taken place? (d) Is the product aromatic? (e) Actually, the product can be separated into six isomeric compounds, one of which has been used as an insecticide

(Gammexane or Lindane). How do these isomers differ from each other? (f) Are more than six isomers possible?

**12.** Can you account for the following order of acidity.

acetylene > benzene > *n*-pentane

**13.** *1,3,5,7-Cyclooctatetraene,* $C_8H_8$, has a heat of combustion of 1095 kcal; it rapidly decolorizes cold aqueous $KMnO_4$ and reacts with $Br_2/CCl_4$ to yield $C_8H_8Br_8$. (a) How should its structure be represented? (b) Upon what theoretical grounds might one have predicted its structure and properties? (c) Treatment of cyclooctatetraene with potassium metal has been found to yield a stable compound $2K^+ C_8H_8^{2-}$. Of what significance is the formation of this salt? (d) Using models, suggest a possible shape(or shapes) for cyclooctatetraene.What shape would you predict for the $C_8H_8^{2-}$ anion?

**14.** Give structures and names of the principal products expected from the ring monobromination of each of the following compounds. In each case, tell whether bromination will occur faster or slower than with benzene itself.

(a) acetanilide ($C_6H_5NHCOCH_3$)
(b) iodobenzene
(c) *sec*-butylbenzene
(d) *N*-methylaniline($C_6H_5NHCH_3$)
(e) ethyl benzoate ($C_6H_5COOC_2H_5$)
(f) acetophenone ($C_6H_5COCH_3$)
(g) ethyl phenyl ether ($C_6H_5OC_2H_5$)
(h) diphenylmethane ($C_6H_5CH_2C_6H_5$)
(i) benzonitrile ($C_6H_5CN$)
(j) benzotrifluoride ($C_6H_5CF_3$)
(k) biphenyl ($C_6H_5$—$C_6H_5$)

**15.** Give structures and names of the principal organic products expected from mononitration of:

(a) *o*-nitrotoluene
(b) *m*-dibromobenzene
(c) *p*-nitroacetanilide
 (*p*-$O_2NC_6H_4NHCOCH_3$)
(d) *m*-dinitrobenzene
(e) *m*-cresol (*m*-$CH_3C_6H_4OH$)
(f) *o*-cresol
(g) *p*-cresol
(h) *m*-nitrotoluene
(i) *p*-xylene (*p*-$C_6H_4(CH_3)_2$)
(j) terephthalic acid (*p*-$C_6H_4(COOH)_2$)
(k) anilinium hydrogen sulfate
 ($C_6H_5NH_3^+ HSO_4^-$)

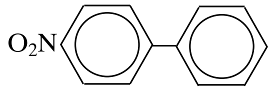
**16.** Give structures and names of the principal organic products expected from the monosulfonation of:

(a) cyclohexylbenzene
(b) nitrobenzene
(c) anisole ($C_6H_5OCH_3$)
(d) benzenesulfonic acid
(e) salicylaldehyde (*o*-$HOC_6H_4CHO$)
(f) *m*-nitrophenol
(g) *o*-fluoroanisole
(h) *o*-nitroacetanilide
 (*o*-$O_2NC_6H_4NHCOCH_3$)
(i) *o*-xylene
(j) *m*-xylene
(k) *p*-xylene

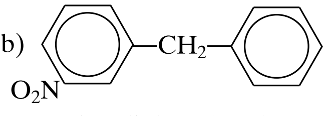
**17.** Arrange the following in order of reactivity toward ring nitration, listing by structure the most reactive at the top, the least reactive at the bottom.

(a) benzene, mesitylene (1,3,5-$C_6H_3(CH_3)_3$), toluene, *m*-xylene, *p*-xylene
(b) benzene, bromobenzene, nitrobenzene, toluene
(c) acetanilide ($C_6H_3NHCOCH_3$), acetophenone ($C_6H_5COCH_3$), aniline, benzene
(d) terephthalic acid, toluene, *p*-toluic acid (*p*-$CH_3C_6H_4COOH$), *p*-xylene
(e) chlorobenzene, *p*-chloronitrobenzene, 2,4-dinitrochlorobenzene
(f) 2,4-dinitrochlorobenzene, 2,4-dinitrophenol
(g) *m*-dinitrobenzene, 2,4-dinitrotoluene

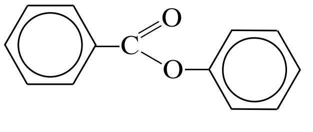
**18.** For each of the following compounds, indicate which ring you would expect to be attacked in nitration, and give structures of the principal products.

(a)


*p*-Nitrobiphenyl

(b)


*m*-Nitrodiphenylmethane

(c)


Phenyl benzoate

**19.** Arrange the compounds of each set in order of reactivity toward electrophilic substitution. Indicate in each set which would yield the highest percentage of *meta* isomer, and which would yield the lowest.

(a) $C_6H_5N(CH_3)_3^+$, $C_6H_5CH_2N(CH_3)_3^+$, $C_6H_5CH_2CH_2N(CH_3)_3^+$, $C_6H_5CH_2CH_2CH_2N(CH_3)_3^+$
(b) $C_6H_5NO_2$, $C_6H_5CH_2NO_2$, $C_6H_5CH_2H_2NO_2$
(c) $C_6H_5CH_3$, $C_6H_5CH_2COOC_2H_5$, $C_6H_5CH(COOC_2H_5)_2$, $C_6H_5C(COOC_2H_5)_3$

**20.** There is evidence that the phenyl group, $C_6H_5$—, has an electron-withdrawing inductive effect.Yet each ring of biphenyl, $C_6H_5$—$C_6H_5$, is more reactive than benzene toward electrophilic substitution, and the chief products are *ortho* and *para* isomers. Show how reactivity and orientation can be accounted for on the basis of resonance.

**21.** There is evidence that the reaction between $HNO_3$ and $H_2SO_4$ to generate $^+NO_2$ actually involves three steps, the second of which is the slowest one and the one that actually produces $^+NO_2$. Can you suggest a reasonable sequence of reactions?

**22.** Treatment of *sulfanilic acid* (*p*-$H_2NC_6H_4SO_3H$) with three moles of bromine yields 2,4,6-tribromoaniline.Treatment of 4-hydroxy-l,3-benzenedisulfonic acid with nitric acid yields picric acid, 2,4,5-trinitrophenol. (a) Outline the most probable mechanism for the replacement of —$SO_3H$ by —Br and by —$NO_2$. (b) To what general class of organic reactions do those reactions belong?

**23.** Using only individual steps with which you are already familiar, outline a likely mechanism for the following reaction.

$$C_6H_5C(CH_3)_3 + Br_2(AlBr_3) \longrightarrow C_6H_5Br + HBr + (CH_3)_2C{=}CH_2$$

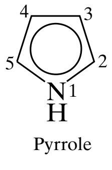
**24.** In light of what you have learned in this chapter, predict the major products of each of the following reactions.

(a) $(CH_3)_3\overset{+}{N}CH{=}CH_2 + HI$
(b) $CH_2{=}CHCF_3 + HBr(AlBr_3)$
(c) What is the function of $AlBr_3$ in (b)? Why is it needed here?

**25.** You are trying to find out whether or not there is an isotope effect in a particular kind of substitution in which the electrophile Y replaces a hydrogen of an aromatic ring. In each of the following cases, tell what you would *do,* and what you would *expect to observe* if there were an isotope effect. (You can quantitatively analyse mixtures of isomers. Your mass spectrometer will tell you what percentage of the hydrogen in a compound is deuterium, but not the location of deuterium in a molecule.)

(a) $C_6H_6$ and $C_6D_6$ are allowed to react separately but under identical conditions.
(b) A 50 : 50 mixture of $C_6H_6$ and $C_6D_6$ is allowed to react with a limited amount of the reagent.
(c) Anisole and [4-D]anisole are allowed to react separately. (Both your watch and your mass spectrometer are under repair when this particular experiment is carried out.)
(d) [1,3,5-$D_3$]benzene (1,3,5-trideuteriobenzene) is allowed to react.

**26.** You can account for the aromaticity of the heterocyclic compound *pyrrole.*



Pyrrole

Among its aromatic properties is the tendency to undergo eiectrophilic aromatic substitution, which it does extremely readily (like the most reactive of benzene derivatives) and predominantly at the 2-position. Drawing all pertinent resonance structures, account in detail for (a) its high reactivity and (b) the orientation of substitution.

**27.** Naphthalene undergoes oxidation or reduction more readily than benzene, but only to the stage where a substituted benzene is formed; further oxidation or reduction requires more vigorous conditions. Can you suggest an explanation for this?

**28.** Outline all steps in the laboratory synthesis of the following compounds from benzene and/or toluene, using any needed aliphatic or inorganic reagents. Assume that a pure *para* isomer can be separated from an *ortho*, *para* mixture.)

(a) *p*-nitrotoluene
(b) *p*-bromonitrobenzene
(c) *p*-dichlorobenzene
(d) *m*-bromobenzenesulfonic acid
(e) *p*-bromobenzenesulfonic acid
(f) *p*-bromobenzoic acid
(g) *m*-bromobenzoic acid
(h) 1,3,5-trinitrobenzene
(i) 2-bromo-4-nitrotoluene
(j) 2-bromo-4-nitrobenzoic acid
(k) 4-bromo-3-nitrobenzoic acid
(l) 3,5-dinitrobenzoic acid
(m) 4-nitro-1,2-dibromobenzene
(n) 2-nitro-1,4-dichlorobenzene

**29.** Outline all steps in the following laboratory syntheses, using any needed aliphatic or inorganic reagents.

(a) 4-nitro-2,6-dibromoanisole from anisole ($C_6H_5OCH_3$)
(b) 4-bromo-2-nitrobenzoic acid from *o*-nitrotoluene
(c) 2,4,6-tribromoaniline from aniline
(d) 2,4-dinitroacetanilide from acetanilide ($C_6H_5NHCOCH_3$)
(e) 5-nitroisophthalic acid from *m*-xylene
(f) 4-nitroisophthalic acid from *m*-xylene
(g) 2-nitroterephthalic acid from *p*-xylene (two ways)
(h) Which way in (g) is preferable? Why?