Stereochemistry

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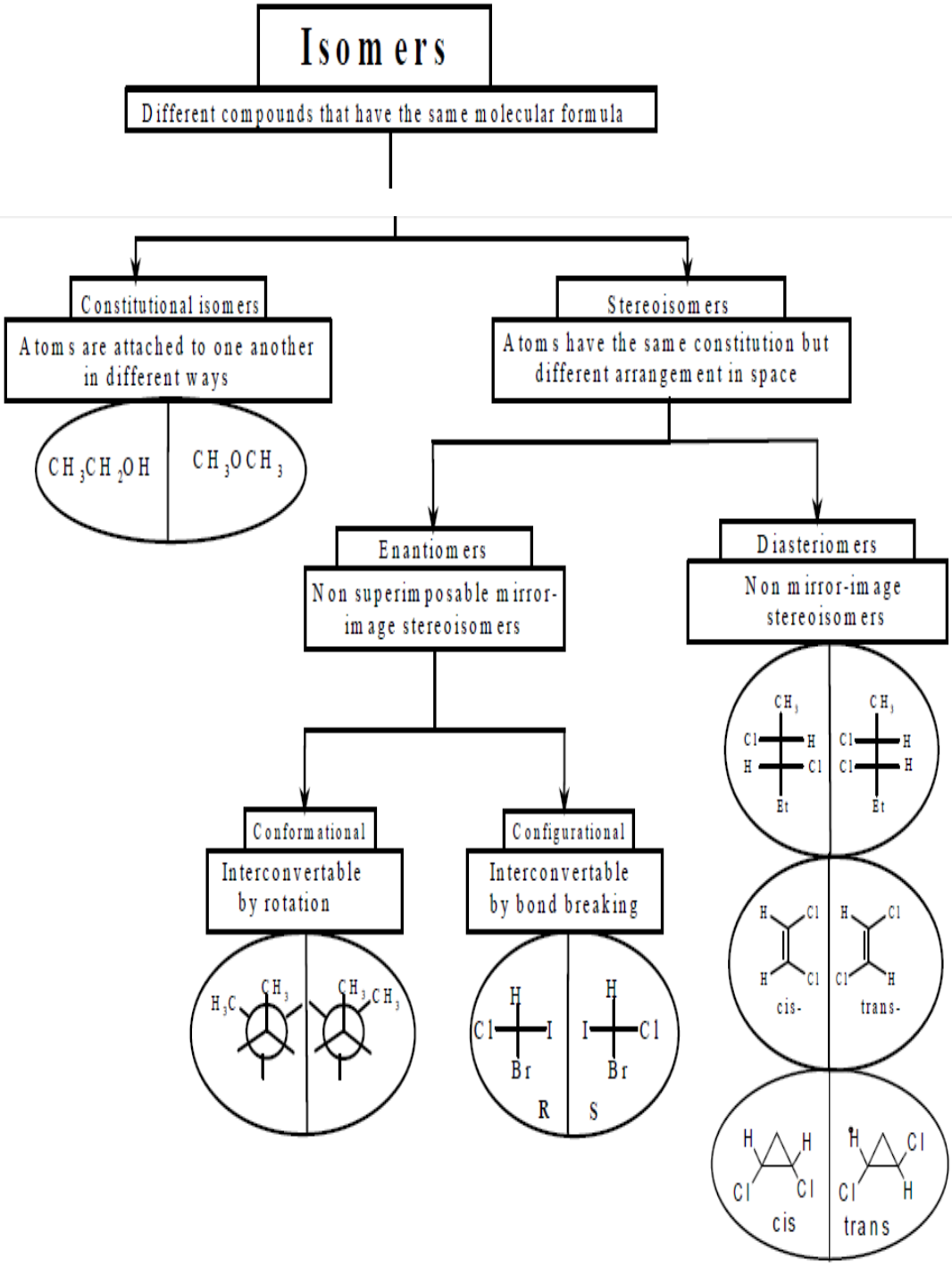
Isomers: different compounds having the same molecular formula



4.1 Stereochemistry and stereoisomerism

The science of organic chemistry, we said, is based on the relationship between molecular structure and properties. That part of the science which deals with structure *in three dimensions* is called **stereochemistry** (Gr.: *stereos*, solid).

One aspect of stereochemistry is *stereoisomerism*. Isomers, we recall, are different compounds that have the same molecular formula. The particular kind of isomers that are different from each other *only* in the way the atoms are oriented in space (but are like one another with respect to which atoms are joined to which other atoms) are called **stereoisomers**.

Pairs of stereoisomers exist that differ so little in structure—and hence in properties—that of all the physical measurements we can make, only one, involving a special instrument and an unusual kind of light, can distinguish between them. Yet, despite this close similarity, the existence of such stereoisomers provides us with one of our most sensitive probes into mechanisms of chemical reactions; very often, one of these isomers is selected for study, not because it is different from ordinary compounds in its three-dimensional chemistry, but because it can be made to reveal what ordinary compounds hide. And, again despite their close similarity, one isomer of such a pair may serve as a nourishing food, or as an antibiotic, or as a powerful heart stimulant, and the other isomer may be useless.

In this chapter, we shall learn how to predict the existence of the kinds of stereoisomers called *enantiomers* and *diastereomers*, how to represent and designate their structures, and, in a general way, how their properties will compare. Then, in following chapters, we shall begin to use what we learn in this one. In Secs. 5.5–5.6, we shall learn about the kind of stereoisomers called *geometric isomers*. In Chapter 7, the emphasis will shift from what these stereoisomers *are*, to how they are formed, what they do, and what they can tell us.

We have already (Secs. 3.3 and 3.5) begun our study of the branch of stereochemistry called *conformational analysis*; we shall return to it, especially in Chap. 9, and make use of it throughout the rest of the book.

4.2 Isomer number and tetrahedral carbon

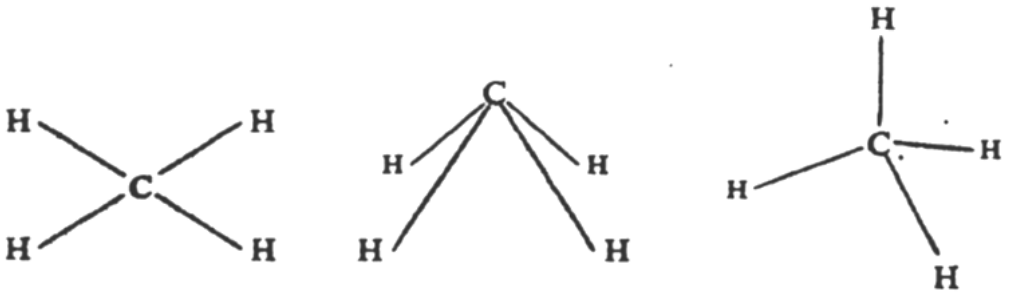
Let us begin our study of stereochemistry with methane and some of its simple substitution products. Any compound, however complicated, that contains carbon bonded to four other atoms can be considered to be a derivative of methane; and whatever we learn about the shape of the methane molecule can be applied to the shapes of vastly more complicated molecules.

The evidence of electron diffraction, X-ray diffraction, and spectroscopy shows that when carbon is bonded to four other atoms its bonds are directed toward the corners of a tetrahedron. But as early as 1874, years before the direct determination of molecular structure was possible, the tetrahedral carbon atom was proposed by J. H. van't Hoff, while he was still a student at the University of Utrecht. His proposal was based upon the evidence of **isomer number.**

For any atom Y, *only one substance of formula* CH_3Y *has ever been found.* Chlorination of methane yields only one compound of formula CH_3Cl; brominations yields only one compound of formula CH_3Br. Similarly, only one CH_3F is known, and only one CH_3I. Indeed, the same holds true if Y represents, not just an atom, but a group of atoms (unless the group is so complicated that in itself it brings about isomerism); there is only one CH_3OH, only one CH_3COOH, only one CH_3SO_3H.

What does this suggest about the arrangement of atoms in methane? It suggests that every hydrogen atom in methane is equivalent to every other hydrogen atom, so that replacement of any one of them gives rise to the same product. If the hydrogen atoms of methane were not equivalent, then replacement of one would yield a different compound than replacement of another, and isomeric substitution products would be obtained.

In what ways can the atoms of methane be arranged so that the four hydrogen atoms are equivalent? There are three such arrangements: (a) a *planar* arrangement (I) in which carbon is at the center of a rectangle (or square) and a hydrogen



I II III

atom is at each corner; (b) a *pyramidal* arrangement (II) in which carbon is at the apex of a pyramid and a hydrogen atom is at each corner of a square base; (c) a *tetrahedral* arrangement (III) in which carbon is at the center of a tetrahedron and a hydrogen atom is at each corner.

How do we know that each of these arrangements could give rise to only one substance of formula CH_3Y? As always for problems like this, the answer lies in the use of molecular models. (Gumdrops and toothpicks can be used to make structures like I and II, for which the bond angles of ordinary molecular models are not suited.) For example, we make two identical models of I. In one model we

replace, say, the upper right-hand H with a different atom Y, represented by a differently colored ball or gumdrop; in the other model we similarly replace, say, the lower right-hand H. We next see whether or not the two resulting models are *superimposable*; that is, we see whether or not, by any manipulations except bending or breaking bonds, we can make the models coincide in all their parts. If the two models are superimposable, they simply represent two molecules of the same compound; if the models are not superimposable, they represent molecules of different compounds which, since they have the same molecular formula, are by definition *isomers* (p. 37). Whichever hydrogen we replace in I (or in II or III), we get the same structure. From any arrangement other than these three, we would get more than one structure.

As far as compounds of the formula CH_3Y are concerned, the evidence of isomer number limits the structure of methane to one of these three possibilities.

Problem 4.1 How many isomers of formula CH_3Y would be possible if methane were a pyramid with a *rectangular* base? What are they? (*Hint:* If you have trouble with this question now, try it again after you have studied Sec. 4.7.)

For any atom Y *and for any atom* Z, *only one substance of formula* CH_2YZ *has ever been found.* Halogenation of methane, for example, yields only one compound of formula CH_2Cl_2, only one compound of formula CH_2Br_2, and only one compound of formula CH_2ClBr.

Of the three possible structures of methane, only the tetrahedral one is consistent with this evidence.

Problem 4.2 How many isomers of formula CH_2YZ would be expected from each of the following structures for methane? (a) Structure I with carbon at the center of a rectangle; (b) structure I with carbon at the center of a square; (c) structure II; (d) structure III.

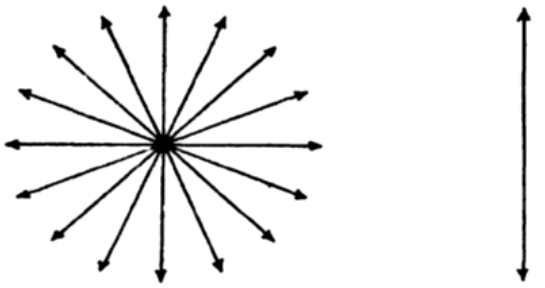
Thus, only the tetrahedral structure for methane agrees with the evidence of isomer number. It is true that this is negative evidence; one might argue that isomers exist which have never been isolated or detected simply because the experimental techniques are not good enough. But, as we said before, any compound that contains carbon bonded to four other atoms can be considered to be a derivative of methane; in the preparation of hundreds of thousands of compounds of this sort, the number of isomers obtained has always been consistent with the concept of the tetrahedral carbon atom.

There is additional, positive evidence for the tetrahedral carbon atom: the finding of just the kind of isomers—*enantiomers*—that are predicted for compounds of formula CWXYZ. It was the existence of enantiomers that convinced van't Hoff that the carbon atom is tetrahedral. But to understand what enantiomers are, we must first learn about the property called *optical activity.*

4.3 Optical activity. 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. 4.1



(*a*) (*b*)

Figure 4.1. Schematic representation of (*a*) ordinary light and (*b*) plane-polarized light. Light traveling perpendicular to page; vibrations in plane of page.

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.*

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.

4.4 The 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. 4.2. 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

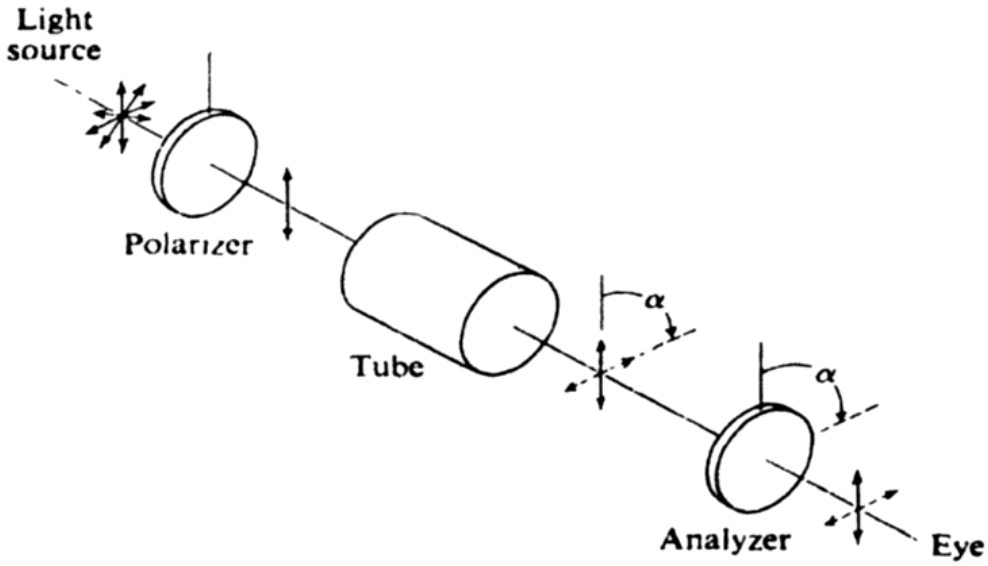


Figure 4.2. Schematic representation of a polarimeter. Solid lines: before rotation. Broken lines: after rotation. α is angle of rotation.

passes through one of the lenses (*polarizer*), then the tube, then the second lens (*analyzer*), 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 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 with the light. The symbols **+** and **−** are used to indicate rotations to the right and to the left, respectively.

The lactic acid (p. 121) 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.

4.5 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 cc of solvent as in a solution containing 1 g per 100 cc 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-decimeter tube is used, and the compound being examined is present to the extent of 1 g/cc. This is usually calculated from observations with tubes of other lengths and at different concentrations by means of the equation

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

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

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-1-butanol obtained from fusel oil is

$$[\alpha]_D^{20} = -5.756°$$

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

Problem 4.3 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 4.4 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, $+765°$?

4.6 Enantiomerism: the discovery

The optical activity we have just described was discovered in 1815 at the Collège de France by the physicist Jean-Baptiste Biot.

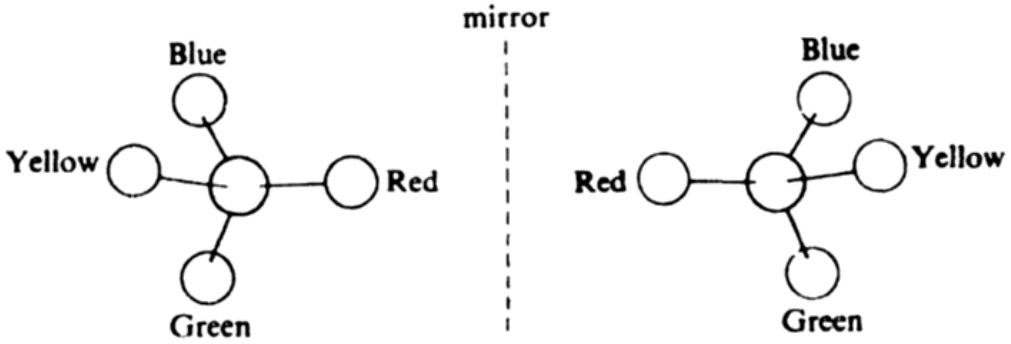
In 1848 at the École normale in Paris the chemist Louis Pasteur made a set of observations which led him a few years later to make a proposal that is the foundation of stereochemistry. Pasteur, then a young man, had come to the École normale from the Royal College of Besançon (where he had received his *baccalauréat ès sciences* with the rating of *médiocre* in chemistry), and had just won his *docteur ès sciences*. To gain some experience in crystallography, he was repeating another chemist's earlier work on salts of tartaric acid when he saw something that no one had noticed before: optically inactive sodium ammonium tartrate existed as a mixture of two different kinds of crystals, which were *mirror images* of each other. Using a hand lens and a pair of tweezers, he carefully and laboriously separated the mixture into two tiny piles—one of right-handed crystals and the other of left-handed crystals—much as one might separate right-handed and left-handed gloves lying jumbled together on a shop counter. Now, although the original mixture was optically inactive, each set of crystals dissolved in water was found to be *optically active*! Furthermore, the specific rotations of the two solutions were exactly *equal, but of opposite sign*: that is to say, one solution rotated plane-polarized light to the right, and the other solution an equal number of degrees to the left. In all other properties the two substances were identical.

Since the difference in optical rotation was observed *in solution*, Pasteur concluded that it was characteristic, not of the crystals, but of the *molecules*. He proposed that, like the two sets of crystals themselves, the molecules making up the crystals were *mirror images of each other*. He was proposing the existence of isomers whose structures differ only in being mirror images of each other, and whose properties differ only in the direction of rotation of polarized light.

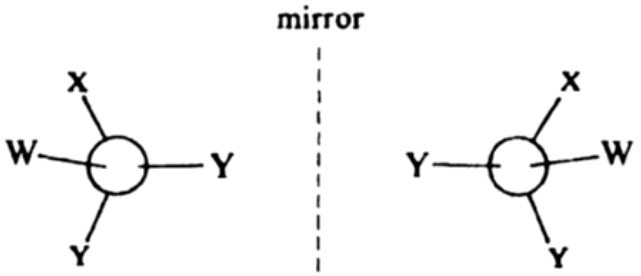
There remained only for van't Hoff to point out that a *tetrahedral* carbon atom would account not only for the absence of isomers of formula CH_3Y and CH_2YZ, but also for the existence of mirror-image isomers—*enantiomers*—like Pasteur's tartaric acids.

4.7 Enantiomerism and tetrahedral carbon

Let us convince ourselves that such mirror-image isomers should indeed exist. Starting with the actual, tetrahedral arrangement for methane, let us make a model of a compound CWXYZ, using a ball of a different color for each different atom or group represented as W, X, Y, and Z. Let us then imagine that we are holding this model before a mirror, and construct a second model of what its mirror image would look like. We now have two models which look something like this:



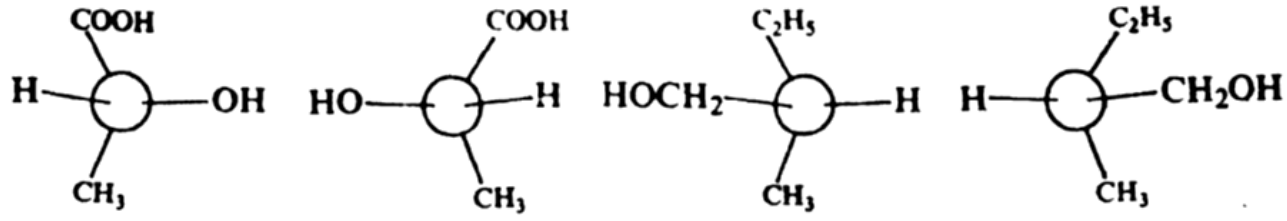
which are understood to stand for this:



Not superimposable: isomers

Are these two models superimposable? *No.* We may twist and turn them as much as we please (so long as no bonds are broken), but although two groups of each may coincide, the other two do not. The models are not superimposable, and therefore must represent two isomers of formula CWXYZ.

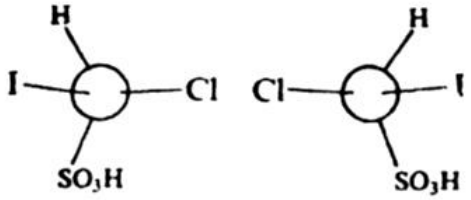
As predicted, mirror-image isomers do indeed exist, and thousands of instances besides the tartaric acids are known. There are, for example, two isomeric *lactic*



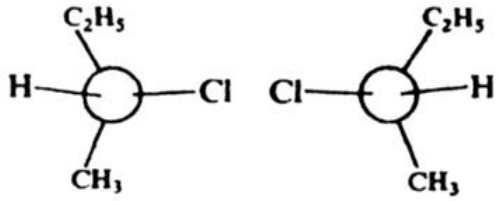
Lactic acid

2-Methyl-1-butanol

acids and two *2-methyl-1-butanols*, two *chloroiodomethanesulfonic acids* and two *sec-butyl chlorides*.



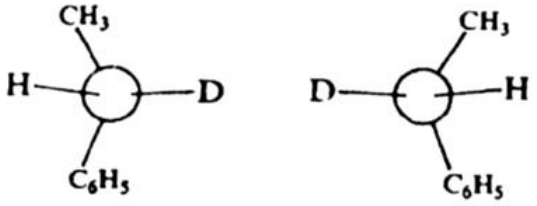
Chloroiodomethanesulfonic acid



sec-Butyl chloride

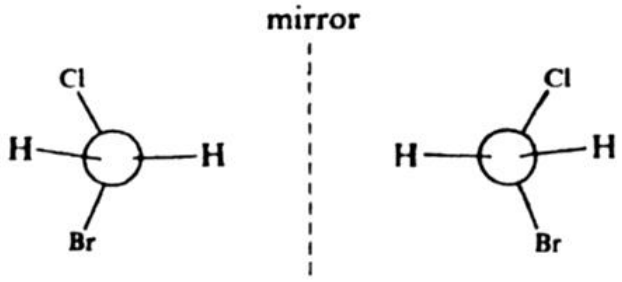
As we can see, the structures of each pair are mirror images; as we can easily verify by use of models, the structures of each pair are not superimposable and therefore represent isomers. (In fact, we have *already* verified this, since the models we made for CWXYZ can, of course, stand for any of these.)

At this point we do not need to know the chemistry of these compounds, or even what structure a particular collection of letters (—COOH, say, or —CH_2OH) stands for; we can tell when atoms or groups are the *same* or *different* from each other, and whether or not a model can be superimposed on its mirror image. Even two isotopes of the same element, like protium (ordinary hydrogen, H) and deuterium (heavy hydrogen, D) are different enough to permit detectable isomerism:



α-Deuterioethylbenzene

We must remember that *everything* (except, of course, a vampire) has a mirror image, including all molecules. Most molecules, however, are superimposable on their mirror images, as, for example, bromochloromethane, and do not show this mirror-image isomerism.



Bromochloromethane
Superimposable: no isomerism

Mirror-image isomers are called *enantiomers*. Since they differ from one another only in the way the atoms are oriented in space, enantiomers belong to the general class called *stereoisomers*. Later on we shall encounter stereoisomers that are *not* mirror images of each other; these are called *diastereomers*. *Any two stereoisomers are thus classified either as enantiomers or as diastereomers, depending upon whether or not they are mirror images of each other.*

The non-superimposability of mirror images that brings about the existence of enantiomers also, as we shall see, gives them their optical activity, and hence enantiomers are often referred to as (one kind of) *optical isomers*. We shall make no use of the term *optical isomer*, since it is hard to define- indeed, is often used undefined- and of doubtful usefulness.

4.8 Enantiomerism and optical activity

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 not a property 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 act as the mirror image of another. But in the special case of CWXYZ, we have found (Sec. 4.7) 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.

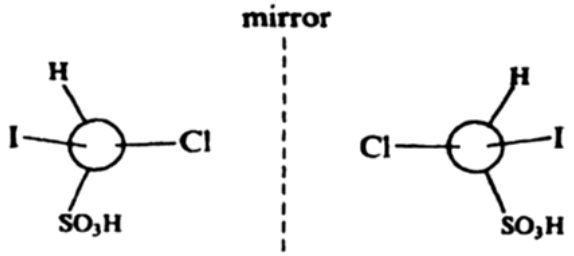
4.9 Prediction of enantiomerism. Chirality

Molecules that are not superimposable on their mirror images are **chiral.**

Chirality is the necessary and sufficient condition for the existence of enantiomers. That is to say: *a compound whose molecules are chiral can exist as enantiomers; a compound whose molecules are achiral* (without chirality) *cannot exist as enantiomers.*

When we say that a molecule and its mirror image are superimposable, we mean that if—in our mind's eye—we were to bring the image from behind the mirror where it seems to be, it could be made to coincide in all its parts with the molecule. To decide whether or not a molecule is chiral, therefore, we make a model of it and a model of its mirror image, and see if we can superimpose them. This is the safest way, since properly handled it must give us the right answer. It is the method that we should use until we have become quite familiar with the ideas involved; even then, it is the method we should use when we encounter a new type of compound.

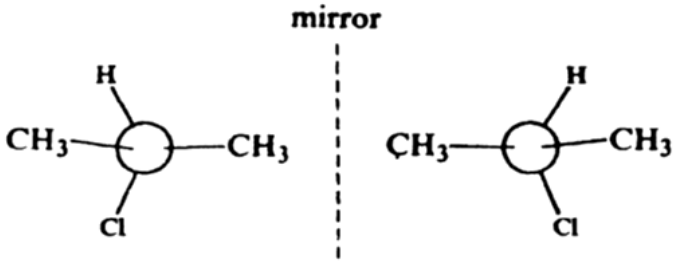
After we have become familiar with the models themselves, we can draw pictures of the models, and *mentally* try to superimpose them. Some, we find, are not superimposable, like these:



Chloroiodomethanesulfonic acid
Not superimposable: enantiomers

These molecules are chiral, and we know that chloroiodomethanesulfonic acid can exist as enantiomers, which have the structures we have just made or drawn.

Others, we find, are superimposable, like these:



Isopropyl chloride
Superimposable: no enantiomers

These molecules are achiral, and so we know that isopropyl chloride cannot exist as enantiomers.

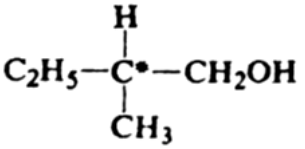
> "I call any geometrical figure, or any group of points, *chiral*, and say it has *chirality*, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself."—Lord Kelvin, 1893.

In 1964, Cahn, Ingold, and Prelog (see p. 130) proposed that chemists use the terms "chiral" and "chirality" as defined by Kelvin. Based on the Greek word for "hand" (*cheir*), chirality means "handedness," in reference to that pair of non-superimposable mirror images we constantly have before us: our two hands. There has been wide-spread acceptance of Kelvin's terms, and they have largely displaced the earlier "dissymmetric" and "dissymmetry" (and the still earlier—and less accurate—"asymmetric" and "asymmetry"), although one must expect to encounter the older terms in the older chemical literature.

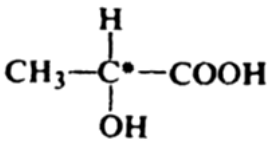
Whatever one calls it, it is non-superimposability-on-mirror-image that is the necessary and sufficient condition for enantiomerism; it is also a necessary—but *not* sufficient—condition for optical activity (see Sec. 4.13).

4.10 The chiral center

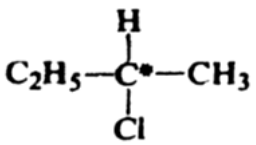
So far, all the chiral molecules we have talked about happen to be of the kind CWXYZ; that is, in each molecule there is a carbon (C*) that holds four different groups.



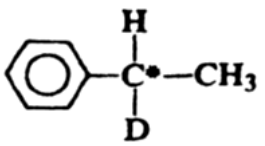
2-Methyl-1-butanol



Lactic acid



sec-Butyl chloride



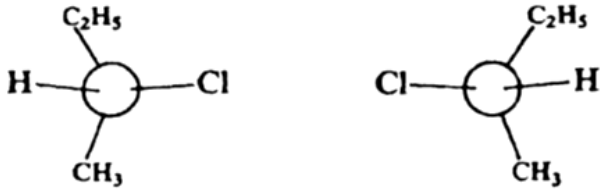
α-Deuterioethylbenzene

A carbon atom to which four different groups are attached is a **chiral center.** (Sometimes it is called *chiral carbon*, when it is necessary to distinguish it from *chiral nitrogen*, *chiral phosphorus*, etc.)

Many—*but not all*—molecules that contain a chiral center are chiral. Many—*but not all*—chiral molecules contain a chiral center. There are molecules that contain chiral centers and yet are achiral (Sec. 4.18). There are chiral molecules that contain no chiral centers (see, for example, Problem 6, p. 315).

The presence or absence of a chiral center is thus no criterion of chirality. However, most of the chiral molecules that we shall take up do contain chiral centers, and it will be useful for us to look for such centers; if we find a chiral center, then we should consider the *possibility* that the molecule is chiral, and hence can exist in enantiomeric forms. We shall later (Sec. 4.18) learn to recognize the kind of molecule that may be achiral in spite of the presence of chiral centers; such molecules contain more than one chiral center.

After becoming familiar with the use of models and of pictures of models, the student can make use of even simpler representations of molecules containing chiral centers, which can be drawn much faster. This is a more dangerous method, however, and must be used properly to give the right answers. We simply draw a cross and attach to the four ends the four groups that are attached to the chiral center. The chiral center is understood to be located where the lines cross. Chemists have agreed that such a diagram stands for a particular structure: *the horizontal lines represent bonds coming toward us out of the plane of the paper, whereas the vertical lines represent bonds going away from us behind the plane of the paper.* That is to say:



can be represented by

In testing the superimposability of two of these flat, two-dimensional representations of three-dimensional objects, we must follow a certain procedure and obey certain rules. First, we use these representations only for molecules that contain a chiral center. Second, we draw one of them, and then draw the other as its mirror image. (Drawing these formulas *at random* can lead to some interesting but quite *wrong* conclusions about isomer numbers.) Third, in our mind's eye we may slide these formulas or rotate them end for end, *but we may not remove them from the plane of the paper.* Used with caution, this method of representation is convenient; it is not foolproof, however, and in doubtful cases models or pictures of models should be used.

Problem 4.5 Using cross formulas, decide which of the following compounds are chiral. Check your answers by use of stick-and-ball formulas, and finally by use of models.

(a) 1-chloropentane
(b) 2-chloropentane
(c) 3-chloropentane
(d) 1-chloro-2-methylpentane
(e) 2-chloro-2-methylpentane
(f) 3-chloro-2-methylpentane
(g) 4-chloro-2-methylpentane
(h) 1-chloro-2-bromobutane

Problem 4.6 (a) Neglecting stereoisomers for the moment, draw all isomers of formula C_4H_6DCl. (b) Decide, as in Problem 4.5, which of these are chiral.

4.11 Enantiomers

Isomers that are mirror images of each other are called **enantiomers**. The two different lactic acids whose models we made in Sec. 4.7 are enantiomers (Gr.: *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	+5.756°	−5.756°
Boiling point	128.9°	128.9°
Density	0.8193	0.8193
Refractive index	1.4107	1.4107

have identical melting points, boiling points, densities, refractive indices, 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 +5.756°, the other −5.756°. 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. This is quite reasonable, since 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 (Sec. 34.3) and is the basis of a multimillion-dollar fermentation industry (Sec. 15.5); 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) and 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 (Sec. 2.22).

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_{act}'s—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_{act}'s are different, and so are the rates of reaction.

4.12 The racemic modification

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-1-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 (Sec. 4.8).

(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 4.7 To confirm the statements of the three preceding paragraphs, make models of: (a) a pair of enantiomers, e.g., CHClBrI; (b) a pair of identical achiral molecules, e.g., CH_2ClBr; (c) a pair of identical chiral molecules, e.g., 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 (Sec. 7.9).

The first resolution was, of course, the one Pasteur carried out with his hand lens and tweezers (Sec. 4.6). 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°. Thus partial credit for Pasteur's discovery has been given to the cool Parisian climate—and, of course, to the availability of tartaric acid from the winemakers of France.

The method of resolution nearly always used—one also discovered by Pasteur—involves the use of optically active reagents, and is described in Sec. 7.9.

Although popularly known chiefly 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.

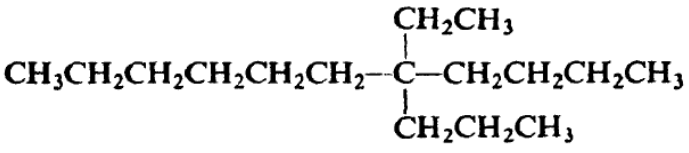
4.13 Optical activity: a closer look

We have seen (Sec. 4.8) 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.



I

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

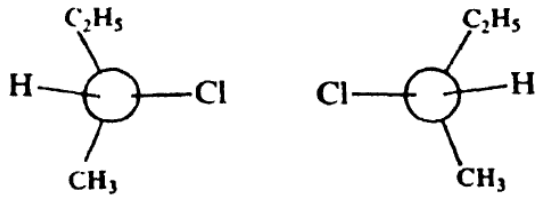
It has been calculated that this compound should have the tiny specific rotation of 0.00001° —far below the limits of detection by any existing polarimeter. In 1965, enantiomerically pure samples of both enantiomers of I were prepared (see Problem 19, p. 1026), and each was found to be optically inactive.

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.

4.14 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



I II

sec-Butyl chloride

say that, by methods we shall take up later (Sec. 7.9), 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*?

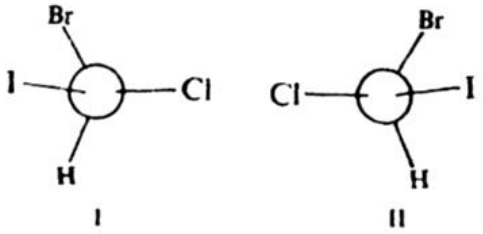
Until 1949 the question of configuration could not be answered in an absolute sense for any optically active compound. But in that year J. M. Bijvoet—most fittingly Director of the van't Hoff Laboratory at the University of Utrecht (Sec. 4.2)—reported that, using a special kind of x-ray analysis (the 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 1949, 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, Sec. 7.5); 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.)

4.15 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 (The Chemical Society, London), Sir Christopher Ingold (University College, London), and V. Prelog (Eidgenössiche Technische Hochschule, Zurich), two steps are involved.

Step 1. Following a set of *sequence rules* (Sec. 4.16), we assign a sequence of priority to the four atoms or groups of atoms 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.

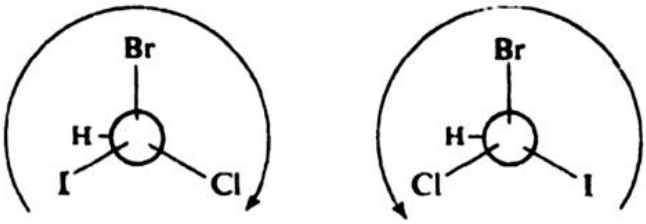


I II

Bromochloroiodomethane

Step 2. We visualize the molecule oriented so that the group of *lowest* priority is directed *away* from us, and observe the arrangement of the remaining groups. If, in proceeding from the group of highest priority to the group 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.

(Specification of compounds containing more than one chiral center is discussed in Sec. 4.19.)

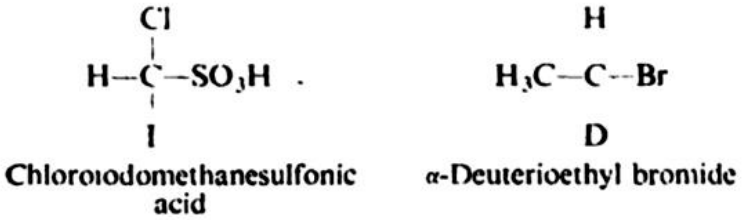
We must not, of course, confuse the direction of optical rotation of a compound—a physical property of a real substance, like melting point or boiling point—with the direction in which our eye happens to travel when we imagine a molecule held in an arbitrary manner. So far as we are concerned, unless 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.

4.16 Sequence rules

For ease of reference and for convenience in reviewing, we shall set down here those sequence rules we shall have need of. The student 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 α-deuterioethyl bromide it is Br, C, D, H.

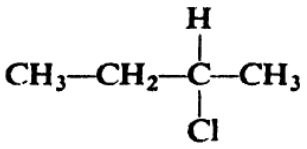


Chloroiodomethanesulfonic acid α-Deuterioethyl bromide

Problem 4.8 Make models and then draw both stick-and-ball pictures and cross formulas for the enantiomers of: (a) chloroiodomethanesulfonic acid and (b) α-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.

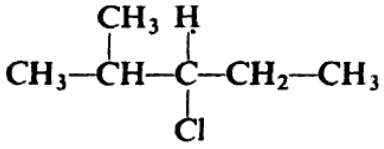
For example, take *sec*-butyl chloride, in which two of the atoms attached to the chiral center are themselves carbon. In CH_3 the second atoms are H, H, H;



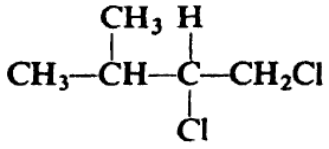
sec-Butyl chloride

in C_2H_5 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.



3-Chloro-2-methylpentane



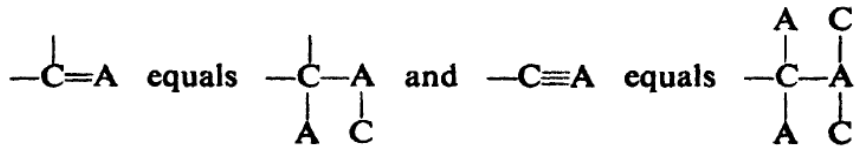
1,2-Dichloro-3-methylbutane

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* Cl does not matter. (One higher number is worth more than two—or three—of a lower number.)

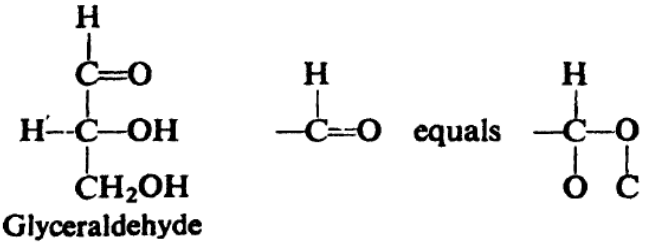
Problem 4.9 Into what sequence of priority must these alkyl groups always fall: CH_3, 1°, 2°, 3°?

Problem 4.10 Specify as R or S each of the enantiomers you drew: (a) in Problem 4.5 (p. 126); (b) in Problem 4.6 (p. 126).

Sequence Rule 3. (*The student should defer study of this rule until he needs it.*)
Where there is a double or triple bond, both atoms are considered to be duplicated or triplicated. Thus,



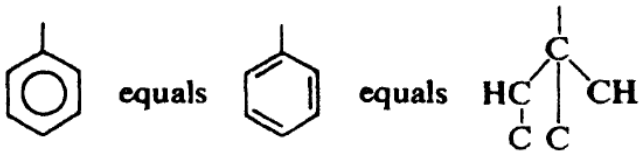
For example, in glyceraldehyde the OH group has the highest priority of all,



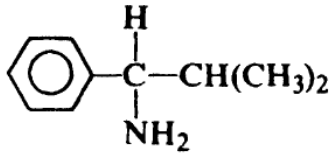
Glyceraldehyde

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:

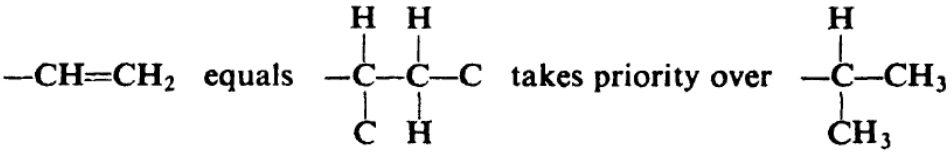


In 1-amino-2-methyl-1-phenylpropane, for example, the C, C, C, of phenyl takes



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.



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

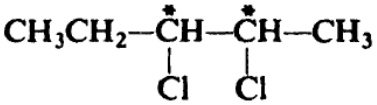
Problem 4.11 Draw and specify as R or S the enantiomers (if any) of:

(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

4.17 Diastereomers

Next, we must learn what stereoisomers are possible for compounds whose molecules contain, not just one, but *more than one* chiral center. (In Chapter 34, we shall be dealing regularly with molecules that contain *five* chiral centers.)

Let us start with 2,3-dichloropentane. This compound contains two chiral

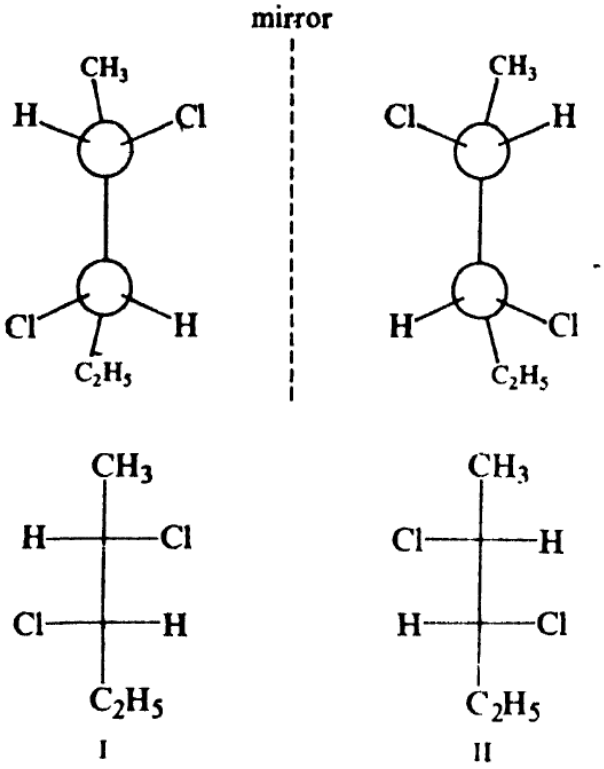


2,3-Dichloropentane

centers, C–2 and C–3. (What four groups are attached to each of these carbon atoms?) How many stereoisomers are possible?

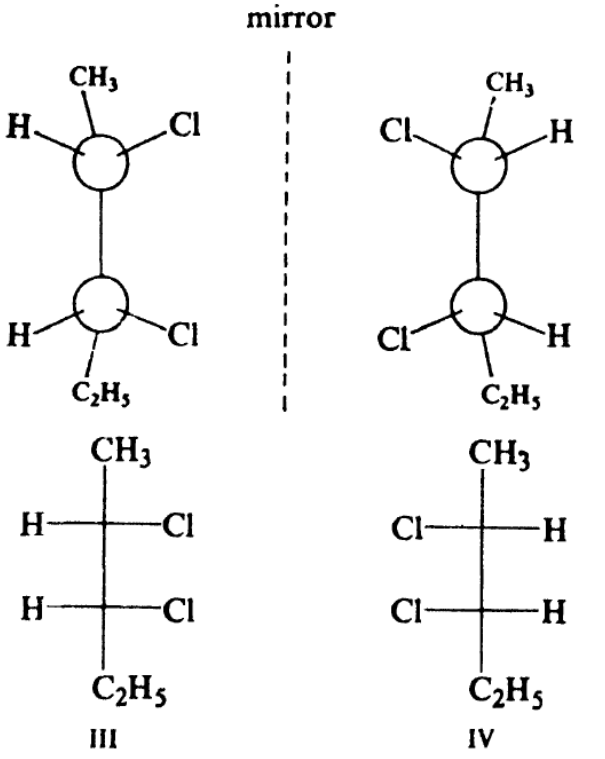
Using models, let us first make structure I and its mirror image II, and see if these are superimposable. We find that I and II are not superimposable, and hence must be enantiomers. (As before, we may represent the structures by pictures, and mentally try to superimpose these. Or, we may use the simple "cross" representations, being careful, as before (Sec. 4.10), not to remove the drawings from the plane of the paper or blackboard.)

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.



Not superimposable
Enantiomers

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



Not superimposable
Enantiomers

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 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. E_{act}'s 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.

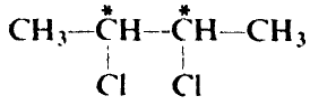
As a result of their differences in boiling point and in solubility, they can, in principle at least, be separated from each other by fractional distillation or fractional crystallization; as a result of differences in molecular shape and polarity, they differ in adsorption, and can be separated by chromatography.

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 (Sec. 7.9).

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.)

4.18 *Meso* structures

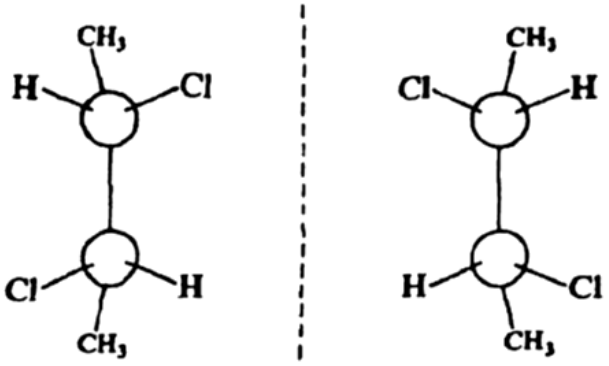
Now let us look at 2,3-dichlorobutane, which also has two chiral centers. Does this compound, too, exist in four stereoisomeric forms?

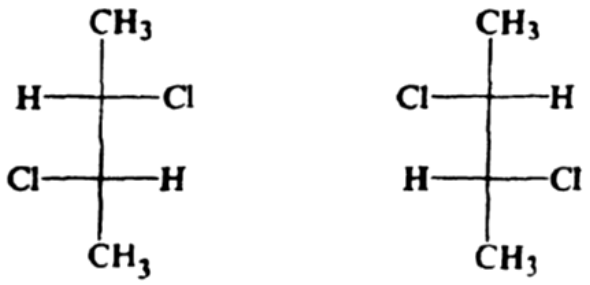


2,3-Dichlorobutane

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.

mirror



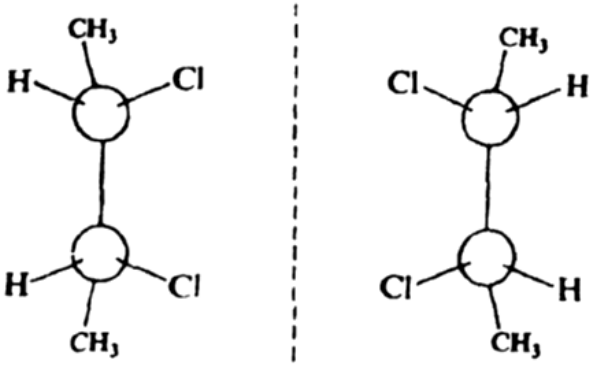


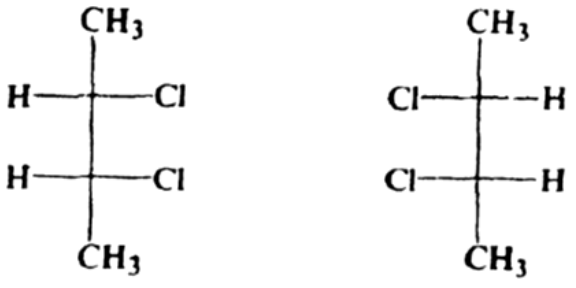
V VI

Not superimposable

Enantiomers

mirror





VII VIII

Superimposable

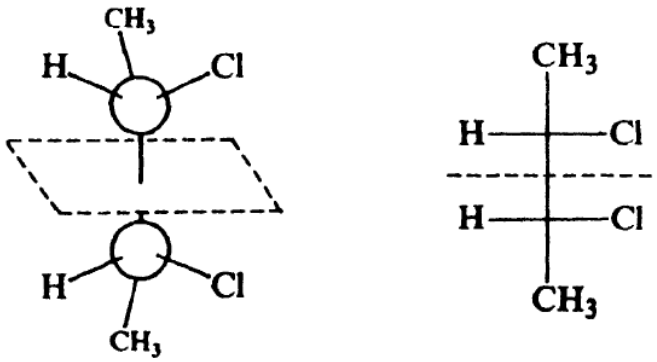
A *meso* compound

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.

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 cancelled by an equal and opposite rotation caused by another molecule that is the mirror image of the first (Sec. 4.8).

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.)



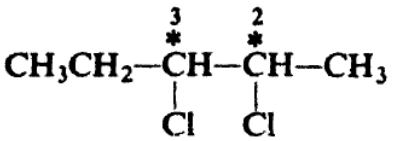
Problem 4.12 Draw stereochemical formulas for all the possible stereoisomers of the following compounds. Label pairs of enantiomers, and *meso* compounds. Tell which isomers, if separated from all other stereoisomers, will be optically active. Pick out several examples of diastereomers.

(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

4.19 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 (Sec. 4.17). We take each of the chiral centers, C–2 and C–3, in turn—ignoring for the moment the existence



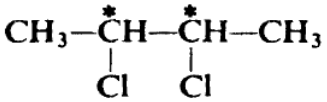
2,3-Dichloropentane

of the other—and follow the steps of Sec. 4.15 and use the Sequence Rules of

Sec. 4.16. In order of priority, the four groups 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 (p. 134), for example, we specify (2S,3S)-2,3-dichloropentane. Similarly, II is (2R,3R), III is (2S,3R), and IV is (2R,3S). These specifications help us to analyze the relationships among the stereoisomers. As enantiomers, I and II have opposite—that is, mirror-image—configurations about both chiral centers: 2S,3S and 2R,3R. As diastereomers, I and III have opposite configurations about one chiral center, and the same configuration about the other: 2S,3S and 2S,3R.

We would handle 2,3-dichlorobutane (Sec. 4.18) in exactly the same way. Here it happens that the two chiral centers occupy equivalent positions along the



2,3-Dichlorobutane

chain, and so it is not necessary to use numbers in the specifications. Enantiomers V and VI (p. 136) are specified (S,S)- and (R,R)-2,3-dichlorobutane, respectively. The *meso* isomer, VII, can, of course, be specified either as (R,S)- or (S,R)-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 4.13 Give the R/S specification for each stereoisomer you drew in Problem 4.12 (p. 137).

4.20 Conformational isomers

In Sec. 3.5, 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 (see Fig. 3.4, p. 79). *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 conformers can either be mirror images of each other or not.

n-Butane exists as three conformational isomers, one *anti* and two *gauche* (Sec. 3.5). The *gauche* conformers, II and III, are mirror images of each other, and hence are (conformational) enantiomers. Conformers I and II (or I and III) 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.

Problem 4.14 **Return to Problem 3.4 (p. 79) and, for each compound: (a) tell how many conformers there are, and label pairs of (conformational) enantiomers; (b) give the order of relative abundance of the various conformers.**

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/mole or more (Sec. 1.14). 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* (Sec. 5.6), 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 4.15 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.

PROBLEMS

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) specific gravity
(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
(l) 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 (p. 1157), double helix (p. 1179);

(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?

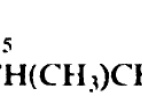
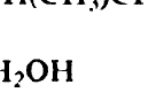
(a) driving a screw, sawing a board, drilling a hole;
(b) opening a door, opening a milk bottle, opening a coffee jar, turning on the hot water;
(c) signing your name, sharpening a pencil, throwing a ball, shaking hands with another right hand, turning to page 142.

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) methylethyl-*n*-propyl-*n*-butylammonium chloride, $(RR'R''R'''N)^+Cl^-$ (See Sec. 1.12.)
(k) methylethyl-*n*-propyl-*sec*-butylammonium 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 (E) obtained was optically active, and the other two were optically inactive. What is the structure of E? 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? (*Hint:* See Sec. 1.19.)

12. (a) What must be the dipole moment of the *anti* conformation of 1,2-dichloroethane, CH_2Cl—CH_2Cl? (b) At 32° in the gas phase, the measured dipole moment of

7.1 Stereoisomerism

Stereoisomers, we have learned, are isomers that differ only in the way their atoms are oriented in space. So far, our study has been limited to finding out what the various kinds of stereoisomers are, how to predict their existence, how to name them, and, in a general way, how their properties compare.

In Chap. 4, we learned that stereoisomers exist of the kind called *enantiomers* (mirror-image isomers), that they can be optically active, and that both their existence and their optical activity are the result of the *chirality* of certain molecules, that is, of the nonsuperimposability of such molecules on their mirror images. We learned how to predict, from a simple examination of molecular structure, whether or not a particular compound can display this kind of isomerism. We learned how to specify the configuration of a particular enantiomer by use of the letters R and S.

We learned about *diastereomers*: stereoisomers that are *not* mirror images. Some of these (Secs. 4.17 and 4.18) were of the kind that contained more than one chiral center. Others (Sec. 5.6) were the kind, *geometric isomers*, that owe their existence to hindered rotation about double bonds.

In Secs. 4.20 and 5.6, we learned that stereoisomers can be classified not only as to whether or not they are mirror images, but also—and quite independently of the other classification—as to how they are interconverted. Altogether, we have: (a) *configurational isomers*, interconverted by inversion (turning-inside-out) at a chiral center; (b) *geometric isomers*, interconverted—in principle—by rotation about a double bond; and (c) *conformational isomers*, interconverted by rotations about single bonds.

The operation required—rotation—is the same for interconversion of geometric and conformational isomers, and it has been suggested that they be called collectively *rotational* (or *torsional*) *isomers*. Geometric isomers are thus double-bond rotational isomers, and conformational isomers are single-bond rotational isomers.

On the other hand, from the very practical standpoint of *isolability*, geometric isomers are more akin to configurational isomers: interconversion requires bond breaking—a π 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 (Sec. 4.20) 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, including geometric isomers*, and will exclude conformational isomers. The latter will be referred to as "conformational isomers," "conformers," "conformational enantiomers," and "conformational diastereomers."

7.2 Reactions involving stereoisomers

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 (i.e., 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.

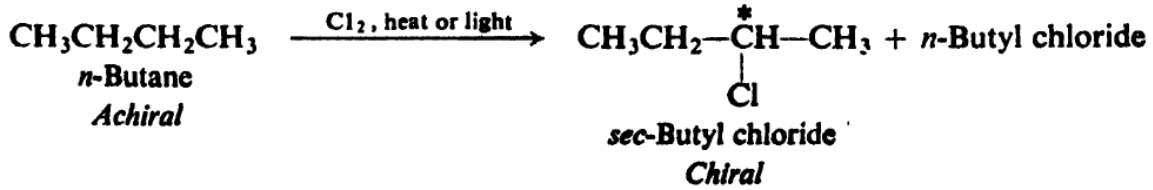
Then we shall examine the stereochemistry of several reactions we have already studied—free-radical halogenation of alkanes, and electrophilic addition of halogens to alkenes—and see how stereochemistry can be used to get information about reaction mechanisms. In doing this, we shall take up:

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

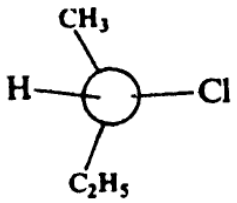
(f) a reaction of an achiral compound in which two chiral centers are generated at the same time.

7.3 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. It can exist as two enantiomers, I and II, which are specified

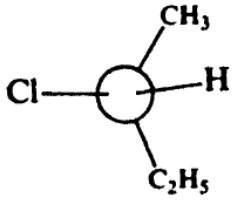


(Sec. 4.16) as S and R, respectively.



I

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



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 (*trigonal*, Sec. 2.21), 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. 7.1). 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.

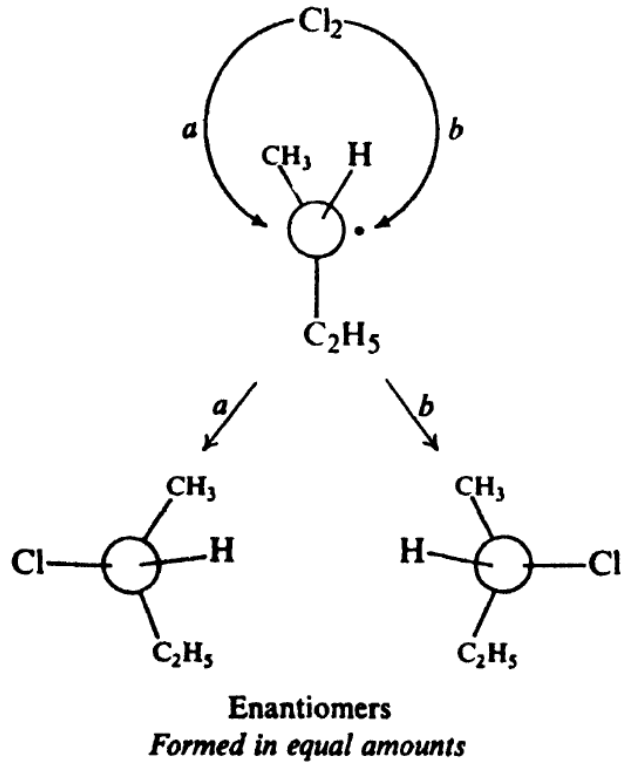


Figure 7.1. Generation of a chiral center. Chlorine becomes attached to either face of flat free radical, via (*a*) or (*b*), to give enantiomers, and in equal amounts.

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 7.1 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.

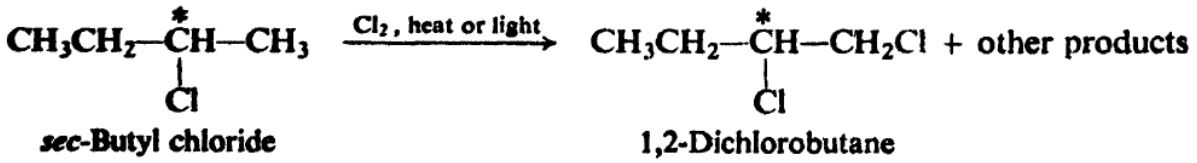
To purify the *sec*-butyl chloride obtained by chlorination of *n*-butane, we would carry out a fractional distillation. But since the enantiomeric *sec*-butyl chlorides have exactly the same boiling point, they cannot be separated, and are collected in the same distillation fraction. If recrystallization 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 (Sec. 7.9).

Problem 7.2 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 in the preceding section—for the optical activity or inactivity of each fraction.

7.4 Reactions of chiral molecules. Bond breaking

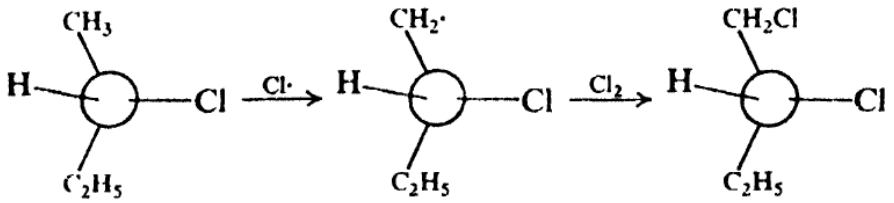
Having made a chiral compound, *sec*-butyl chloride, let us see what happens when it, in turn, undergoes free-radical chlorination. A number of isomeric dichlorobutanes are formed, corresponding to attack at various positions in the molecule. (*Problem:* What are these isomers?)



sec-Butyl chloride 1,2-Dichlorobutane

Let us take, say, (S)-*sec*-butyl chloride (which, we saw in Sec. 7.3, 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



I (S)-*sec*-Butyl chloride

II (R)-1,2-Dichlorobutane

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.*

(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. As discussed in Sec. 7.10, just what happens depends on the mechanism of the particular reaction.)

Problem 7.3 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?

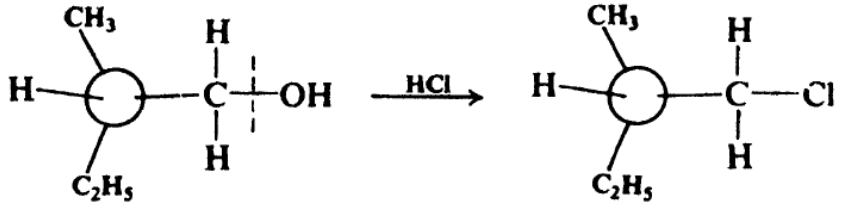
Now, let us see how the axiom about bond breaking is applied in relating the configuration of one chiral compound to that of another.

7.5 Reactions of chiral molecules. Relating configurations

We learned (Sec. 4.14) that the configuration of a particular enantiomer can be determined directly by a special kind of x-ray diffraction, which was first applied in 1949 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 hundreds 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;

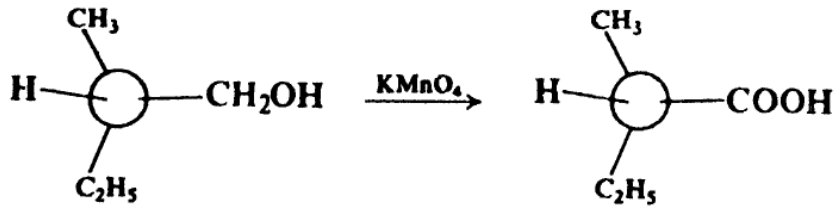


III S-(−)-2-Methyl-1-butanol

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

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.

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 *cis*- or *trans*-2-butene, *now that their configurations 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 configuration 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 7.4 Which of the following reactions could safely be used to relate configurations?

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

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

(c) $(-)\text{-}C_6H_5CH(OC_2H_5)CH_2OH + HBr \longrightarrow C_6H_5CH(OC_2H_5)CH_2Br$

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

(e) $(+)\text{-}CH_3CH_2C(=O)\text{-}{}^{18}OCH(CH_3)C_2H_5 + OH^- \longrightarrow CH_3CH_2COO^- + CH_3CH_2CH^{18}OHCH_3$

(f) $(-)\text{-}CH_3CH_2CHBrCH_3 + C_2H_5O^-Na^+ \longrightarrow C_2H_5\text{-}O\text{-}CH(CH_3)CH_2CH_3$

(g) $(+)\text{-}CH_3CH_2CHOHCH_3 \xrightarrow{Na} CH_3CH_2CH(ONa)CH_3 \xrightarrow{C_2H_5Br} C_2H_5\text{-}O\text{-}CH(CH_3)CH_2CH_3$

Problem 7.5 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 $n\text{-}C_6H_{13}CHICH_3$ is found to have lost its optical activity. (c) Can you suggest experiments to test your conclusions? (See Sec. 3.29.)

7.6 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 $-5.756°$) 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 $+1.64°$. Since no bond to the chiral center is broken, every

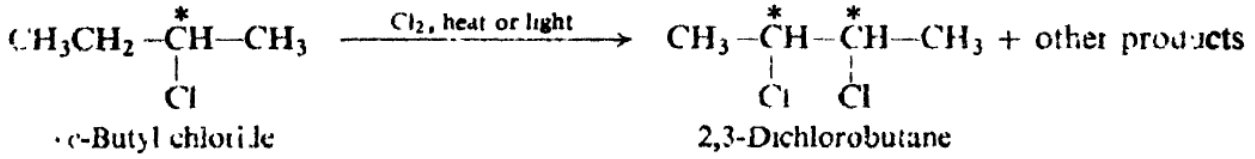
molecule of alcohol with configuration III is converted into a molecule of chloride with configuration IV; since the alcohol was optically pure, the chloride of specific rotation +1.64° is also optically pure. Once this *maximum rotation* has been established, anyone can determine the optical purity 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 +0.82°, 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 7.6 **Predict the specific rotation of the chloride obtained by treatment with hydrogen chloride of 2-methyl-1-butanol of specific rotation +3.12°.**

7.7 Reactions of chiral molecules. Generation of a second chiral center

Let us return to the reaction we used as our example in Sec. 7.4, 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, we have seen (Sec. 4.18), exists as three stereoisomers, *meso* and a pair of enantiomers.



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 7.2 shows the course of reaction. Three important points are illustrated which apply in all cases where a second chiral center is generated. First, since no bonds to the original chiral center, C–2, are broken, its configuration is retained in all the products. Second, 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. Third, the diastereomeric products will be formed in unequal amounts; in this case because attack (*a*) and attack (*b*) are not equally likely.

In Sec. 7.3 we saw that generation of the first chiral center in a compound yields equal amounts of enantiomers, that is, yields an optically inactive racemic modification. Now we see that generation of a new chiral center in a compound that is already optically active yields an optically active product containing unequal amounts of diastereomers.

Suppose (as is actually the case) that the products from (S)-*sec*-butyl chloride show an S,S:*meso* ratio of 29:71. What would we get from chlorination of (R)-*sec*-butyl chloride? We would get (R,R-) and *meso*-products, and the R,R:*meso* ratio would be exactly 29:71. Whatever factor favors *meso*-product over (S,S)-product will favor *meso*-product over (R,R)-product, and to exactly the same extent.

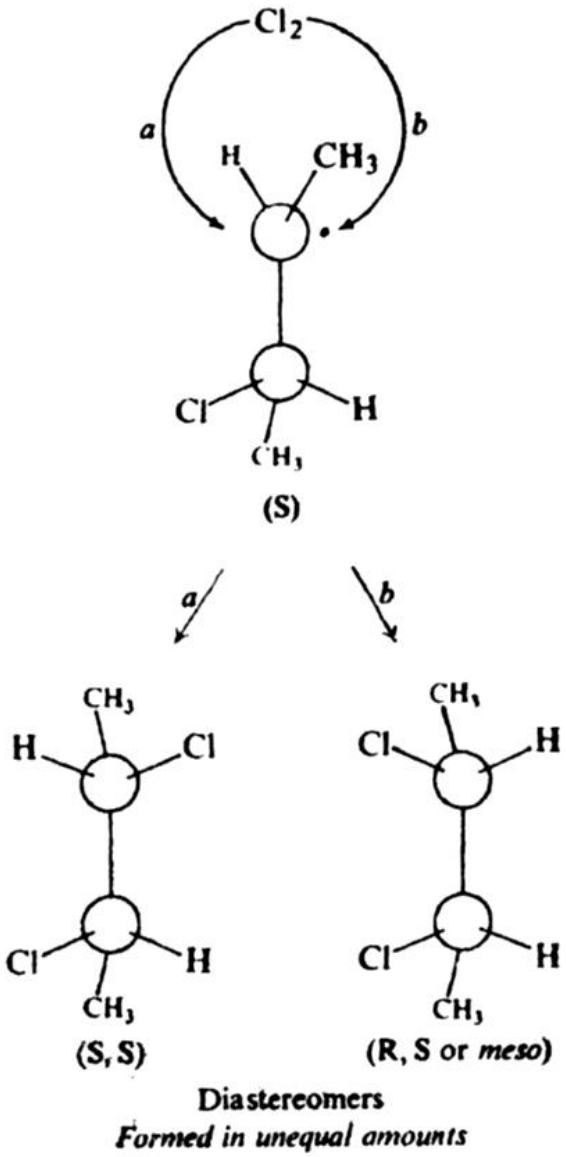


Figure 7.2. Generation of a second chiral center. Configuration at original chiral center unchanged. Chlorine becomes attached via (*a*) or (*b*) to give diastereomers, and in unequal amounts.

Finally, what can we expect to get from optically inactive, racemic *sec*-butyl chloride? The (S)-isomer that is present would yield (S,S)- and *meso*-products in the ratio of 29:71; the (R)-isomer would yield (R,R)- and *meso*-products, and in the ratio of 29:71. Since there are exactly equal quantities of (S)- and (R)-reactants, the two sets of products would exactly balance each other, and we would obtain racemic and *meso* products in the ratio of 29:71. Optically inactive reactants yield optically inactive products.

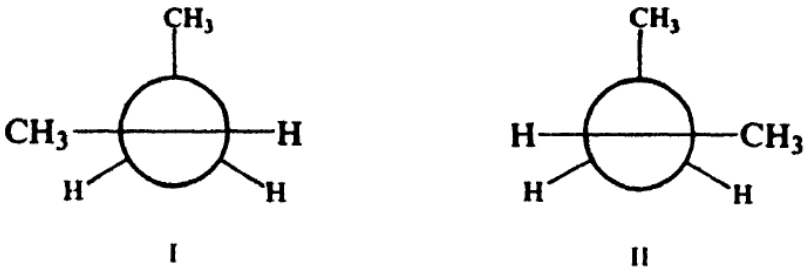
One point requires further discussion. Why are the diastereomeric products formed in unequal amounts? It is because the intermediate 3-chloro-2-butyl radical in Fig. 7.2 already contains a chiral center. The free radical is chiral, and lacks the symmetry that is necessary for attack at the two faces to be equally likely. (Make a model of the radical and assure yourself that this is so.)

In the following section, this point is discussed in more detail.

7.8 Formation of enantiomers and diastereomers: a closer look

To understand better how formation of diastereomers differs from formation of enantiomers, let us contrast the reaction of the chiral 3-chloro-2-butyl radical shown in Fig. 7.2 with the reaction of the achiral *sec*-butyl radical.

In Sec. 7.3, we said that attachment of chlorine to either face of the *sec*-butyl radical is equally likely. This is in effect true, but deserves closer examination. Consider any conformation of the free radical: I, for example. It is clear that attack by chlorine from the top of I and attack from the bottom are *not*



I II

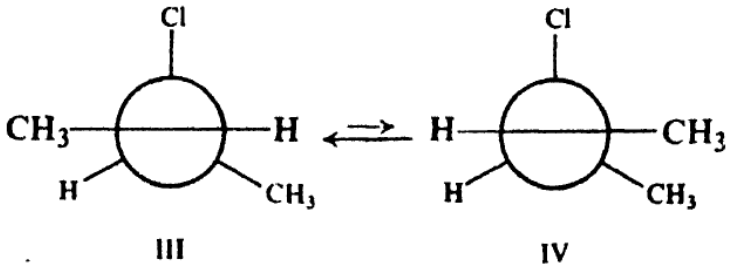
sec-Butyl radical
Achiral

equally likely. But a rotation of 180° about the single bond converts I into II; these are two conformations of the same free radical, and are, of course, in equilibrium with each other. They are mirror images, and hence of equal energy and equal abundance; any preferred attack from, say, the bottom of I to give the (R)-product will be exactly counterbalanced by attack from the bottom of II to give the (S)-product.

The "randomness of attack" that yields the racemic modification from achiral reactants is not necessarily due to the symmetry of any individual reactant molecule, but rather to the random distribution of such molecules between mirror-image conformations (or to random selection between mirror-image transition states).

Now, let us turn to reaction of the chiral 3-chloro-2-butyl radical (Fig. 7.2). Here, the free radical we are concerned with already contains a chiral center, about which it has the (S)-configuration; attack is *not* random on such a radical because mirror-image conformations are not present—they could only come from (R) free radicals, and there are none of those radicals present.

Preferred attack from, say, the bottom of conformation III—a likely preference since this would keep the two chlorine atoms as far apart as possible in the transition state—would yield *meso*-2,3-dichlorobutane. A rotation of 180° about the single bond would convert III into IV. Attack from the bottom of IV would



III IV

3-Chloro-2-butyl radical
Chiral

yield the (S,S)-isomer. But III and IV are not mirror images, are not of equal energy, and are not of equal abundance. In particular, because of lesser crowding between the methyl groups, we would expect III to be more stable and hence more abundant than IV, and the *meso* product to predominate over the (S,S)-isomer (as it actually does).

We might have made a different guess about the preferred direction of attack, and even a different estimate about relative stabilities of conformations, but we would still arrive at the same basic conclusion: except by sheer coincidence, the two diastereomers would not be formed in equal amounts.

In this discussion, we have assumed that the relative rates of competing reactions depend on relative populations of the conformations of the reactants. This assumption is correct here, if, as seems likely, reaction of the free radicals with chlorine is easier and faster than the rotation that interconverts conformations.

If, on the other hand, reaction with chlorine were a relatively difficult reaction and much slower than interconversion of conformations, then relative rates would be determined by relative stabilities of the transition states. We would still draw the same general conclusions. In the reaction of the achiral *sec*-butyl radical, the transition states are mirror images and therefore of the same stability, and the rates of formation of the two products would be exactly the same. In the reaction of the chiral 3-chloro-2-butyl radical, the transition states are not mirror-images and therefore not of the same stability, and rates of formation of the two products would be different. (In the latter case, we would even make the same prediction, that the *meso* product would predominate, since the same relationship between methyl groups that would make conformation III more stable would also make the transition state resembling conformation III more stable.)

Problem 7.7 Answer the following questions about the formation of 2,3-dichlorobutane from (R)-*sec*-butyl chloride. (a) Draw conformations (V and VI) of the intermediate radicals that correspond to III and IV above. (b) What is the relationship between V and VI? (c) How will the V:VI ratio compare with the III:IV ratio? (d) Assuming the same preferred direction of attack by chlorine as on III and IV, which stereoisomeric product would be formed from V? From VI? (e) Which product would you expect to predominate? (f) In view of the ratio of products actually obtained from (S)-*sec*-butyl chloride, what ratio of products must be obtained from (R)-*sec*-butyl chloride?

Problem 7.8 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) monochlorination of (R)-*sec*-butyl chloride at 300°;
(b) monochlorination of racemic *sec*-butyl chloride at 300°;
(c) monochlorination of racemic 1-chloro-2-methylbutane at 300°;
(d) addition of bromine to (S)-3-bromo-1-butene.

7.9 Reactions of chiral molecules with optically active reagents. Resolution

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 (Sec. 7.3) 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, (−)-α-phenylethyl chloride, (+)-α-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, 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 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.

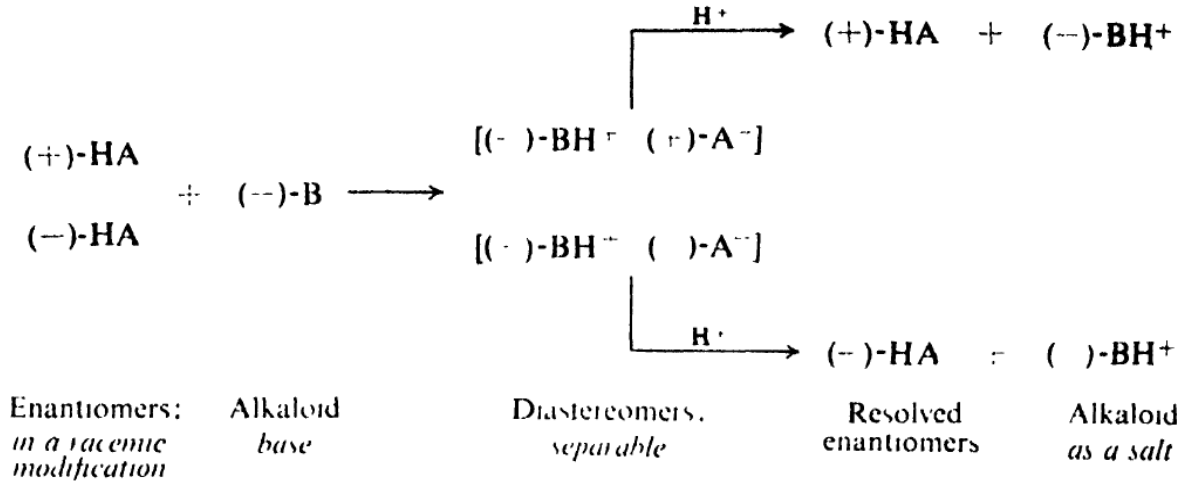
Amino acids, the units from which proteins are made, have been reported present in meteorites, but in such tiny amounts that the speculation has been made that "what appears to be the pitter-patter of heavenly feet is probably instead the print of an earthly thumb." Part of the evidence that the amino acids found in a meteorite by Cyril Ponnamperuma (of NASA) 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-1-butanol can be converted without loss of configuration into the corresponding chloride or acid (Sec. 7.5); 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 $[(-)\text{-}BH^+\text{-}(-)\text{-}A^-]$.

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.**

7.10 Reactions of chiral molecules. Mechanism of free-radical chlorination

So far, we have discussed only reactions of chiral molecules in which bonds to the chiral center are not broken. What is the stereochemistry of reactions in which the bonds to the chiral center *are* broken? The answer is: *it depends.* It depends on the *mechanism* of the reaction that is taking place; because of this, stereochemistry can often give us information about a reaction that we cannot get in any other way.

For example, stereochemistry played an important part in establishing the mechanism that was the basis of our entire discussion of the halogenation of alkanes (Chap. 3). The chain-propagating steps of this mechanism are:

(2a) $$X\cdot + RH \longrightarrow HX + R\cdot$$

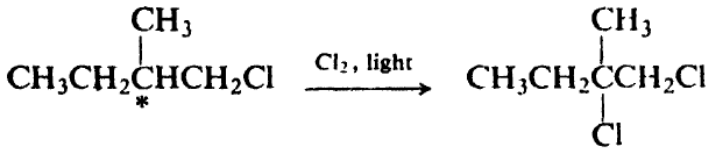
(3a) $$R\cdot + X_2 \longrightarrow RX + X\cdot$$

Until 1940 the existing evidence was just as consistent with the following alternative steps:

(2b) $$X\cdot + RH \longrightarrow RX + H\cdot$$

(3b) $$H\cdot + X_2 \longrightarrow HX + X\cdot$$

To differentiate between these alternative mechanisms, H. C. Brown, M. S. Kharasch, and T. H. Chao, working at the University of Chicago, carried out the photochemical halogenation of optically active S-(+)-1-chloro-2-methylbutane. A number of isomeric products were, of course, formed, corresponding to attack at various positions in the molecule. (*Problem:* What were these products?) They focused their attention on just *one* of these products: 1,2-dichloro-2-methylbutane, resulting from substitution at the chiral center (C–2).



(S)-(+)-1-Chloro-2-methylbutane — *Optically active*

(±)-1,2-Dichloro-2-methylbutane — *Optically inactive*

They had planned the experiment on the following basis. The two mechanisms differed as to whether or not a free alkyl radical is an intermediate. The most likely structure for such a radical, they thought, was *flat*—as, it turns out, it very probably is—and the radical would lose the original chirality. Attachment of chlorine to either face would be equally likely, so that an optically inactive, racemic product would be formed. That is to say, the reaction would take place *with racemization* (see Fig. 7.3).

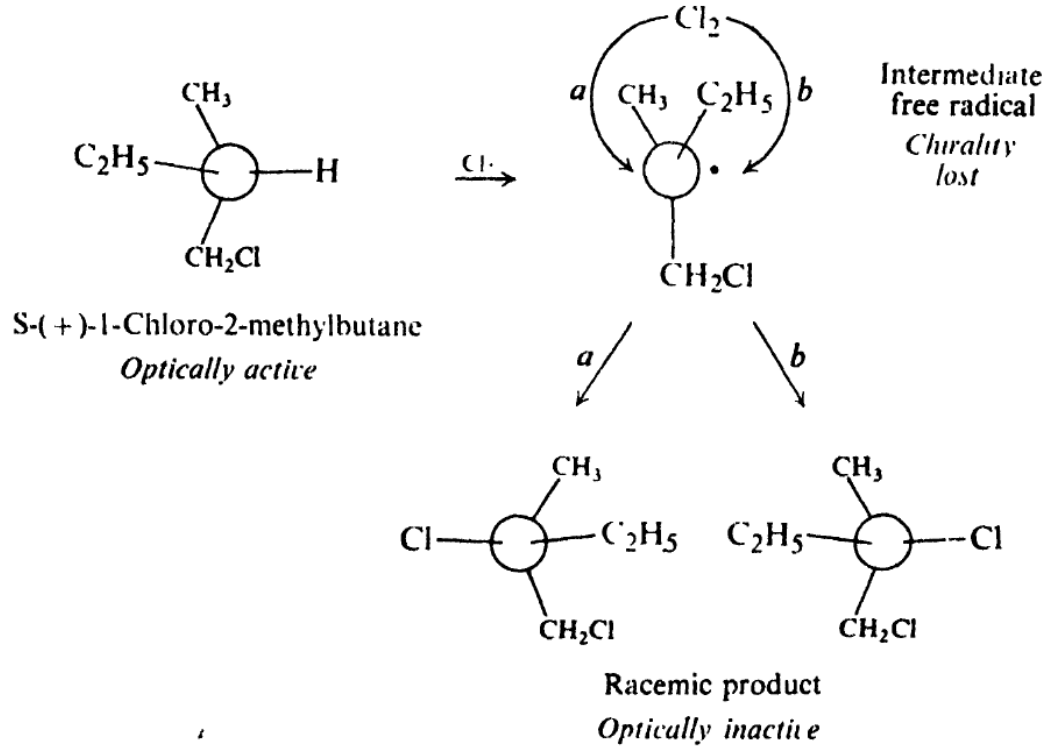


Figure 7.3. Racemization through free-radical formation. Chlorine becomes attached to either face of free radical, via (*a*) or (*b*), to give enantiomers, and in equal amounts.

For the alternative mechanism, in which chlorine would become attached to the molecule while the hydrogen was being displaced, they could make no prediction, except that formation of an optically inactive product would be highly unlikely: there was certainly no reason to expect that *back-side* attack (on the face opposite the hydrogen) would take place to exactly the same extent as *front-side* attack. (In ionic displacements, attack is generally back-side.)

By careful fractional distillation they separated the 1,2-dichloro-2-methylbutane from the reaction mixture, and found it to be *optically inactive*. From this they concluded that the mechanism involving free alkyl radicals, (2a), (3a), is the correct one. This mechanism is accepted without question today, and the work of Brown, Kharasch, and Chao is frequently referred to as evidence of the stereochemical behavior of free radicals, with the original significance of the work exactly reversed.

We can begin to see how stereochemistry provides the organic chemist with one of his most powerful tools for finding out what is going on in a chemical reaction.

Problem 7.9 This work does *not* prove that free radicals are flat. Racemization is consistent with what other structure for free radicals? Explain. (*Hint:* See Sec. 2.21.)

Problem 7.10 Altogether, the free-radical chlorination of (S)-(+)-1-chloro-2-methylbutane gave six fractions of formula $C_5H_{10}Cl_2$. Four fractions were found to be optically active, and two fractions optically inactive. Draw structural formulas for the compounds making up each fraction. Account in detail for optical activity or inactivity in each case.

7.11 Stereoselective and stereospecific reactions. *syn*- and *anti*-Addition

As our second example of the application of stereochemistry to the study of reaction mechanisms, let us take another familiar reaction: addition of halogens to alkenes. In this section we shall look at the stereochemical facts and, in the next, see how these facts can be interpreted.

Addition of bromine to 2-butene yields 2,3-dibromobutane. Two chiral centers are generated in the reaction, and the product, we know, can exist as a *meso* compound and a pair of enantiomers.

$$\underset{\text{2-Butene}}{CH_3CH{=}CHCH_3} + Br_2 \longrightarrow CH_3{-}\overset{*}{C}H{-}\overset{*}{C}H{-}CH_3 \quad (Br,\ Br)$$

2,3-Dibromobutane

The reactant, too, exists as diastereomers: a pair of geometric isomers. If we start with, say, *cis*-2-butene, which of the stereoisomeric products do we get? A mixture of all of them? No. *cis*-2-Butene yields *only* racemic 2,3-dibromobutane; none of the *meso* compound is obtained. *A reaction that yields predominantly one stereoisomer (or one pair of enantiomers) of several diastereomeric possibilities is called a* **stereoselective reaction.**

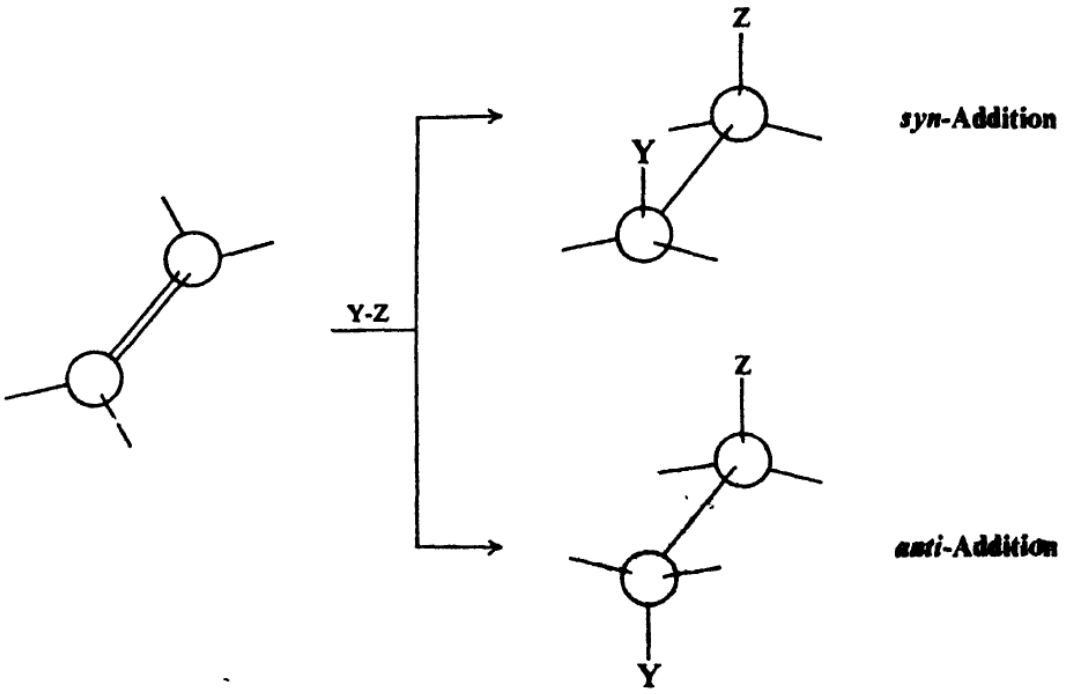
Now, suppose we start with *trans*-2-butene. Does this, too, yield the racemic dibromide? No. *trans*-2-Butene yields *only meso*-2,3-dibromobutane. *A reaction in which stereochemically different reactants give stereochemically different products is called a* **stereospecific reaction.**

Addition of bromine to alkenes is both stereoselective and stereospecific. We say it is *completely* stereoselective since, from a given alkene, we obtain *only* one diastereomer (or one pair of enantiomers). We say it is stereospecific, since just which stereoisomer we obtain depends upon which stereoisomeric alkene we start with.

In the above definition, *stereochemically different* means, in practice, *diastereomerically different*. The term *stereospecific* is not applied to reactions, like those in Secs. 7.4 and 7.5, in which enantiomerically different reactants give enantiomerically different products.

All stereospecific reactions are necessarily stereoselective, but the reverse is not true. There are reactions from which one particular stereoisomer is the predominant product *regardless* of the stereochemistry of the reactant; there are reactions in which the reactant cannot exist as stereoisomers, but from which one particular stereoisomer is the predominant product. Such reactions are stereoselective but not stereospecific.

To describe stereospecificity in addition reactions, the concepts of *syn*-addition and *anti*-addition are used. These terms are not the names of specific mechanisms. They simply indicate the stereochemical facts: that the product obtained is the one to be expected if the two portions of the reagent were to add to the same face of the alkene (*syn*) or to opposite faces (*anti*).



Addition of bromine to the 2-butenes involves *anti*-addition. If we start (Fig. 7.4) with *cis*-2-butene, we can attach the bromine atoms to opposite faces of the alkene either as in (*a*) or in (*b*) and thus obtain the enantiomers. Since, whatever the mechanism, (*a*) and (*b*) should be equally likely, we obtain the racemic modification.

Starting with *trans*-2-butene (Fig. 7.5), we can again attach the bromine atoms to opposite faces of the alkene in two ways but, whichever way we choose, we obtain the *meso*-dibromide.

anti-Addition is the general rule for the reaction of bromine or chlorine with simple alkenes. We shall encounter other examples of stereospecific additions, both *anti* and *syn*. We shall find that other reactions besides addition can be

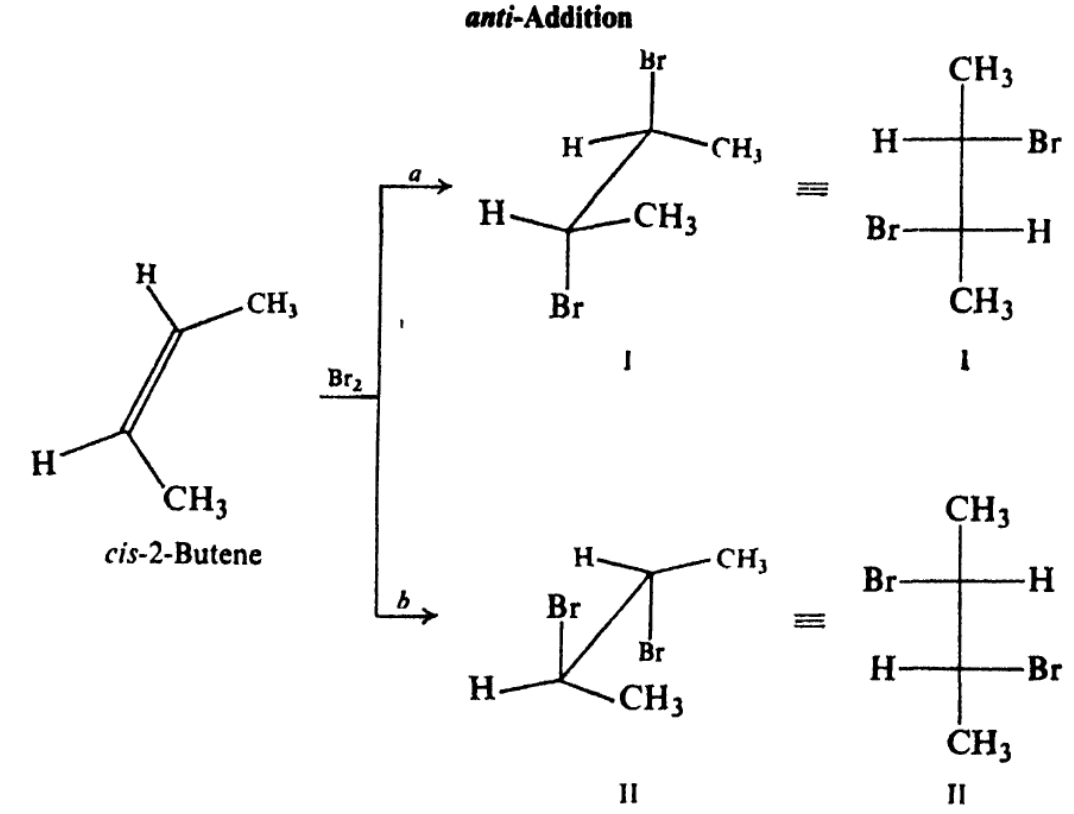


Figure 7.4. *anti*-Addition to *cis*-2-butene. Attachment as in (*a*) or (*b*) equally likely: gives racemic modification.

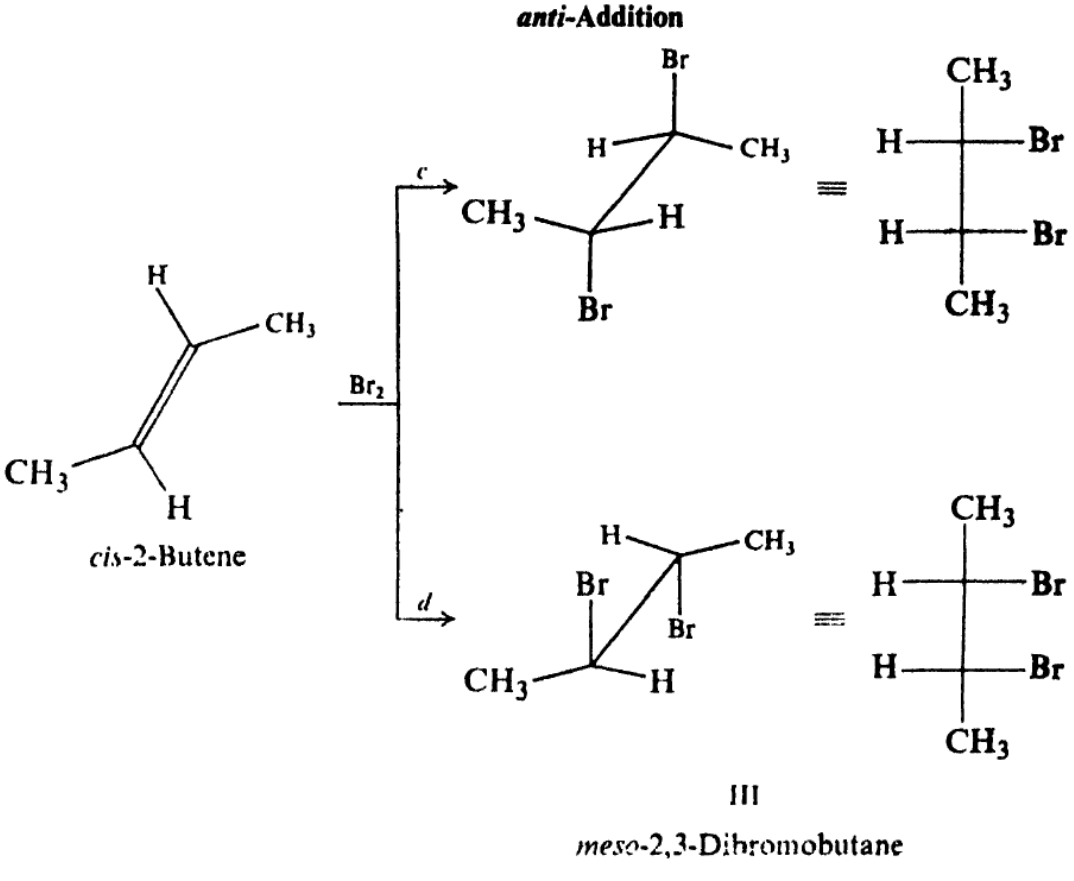


Figure 7.5. *anti*-Addition to *trans*-2-butene. Attachment as in (*c*) or (*d*) gives *meso* product.

stereospecific—and also that some can be non-stereospecific. Whatever the stereochemistry of a reaction, it must, of course, be accounted for by a satisfactory mechanism.

Problem 7.11 On treatment with permanganate, *cis*-2-butene yields a glycol of m.p. 34°, and *trans*-2-butene yields a glycol of m.p. 19°. Both glycols are optically inactive. Handling as described in Sec. 7.9 converts the glycol of m.p. 19° (but not the one of m.p. 32°) into two optically active fractions of equal but opposite rotation.

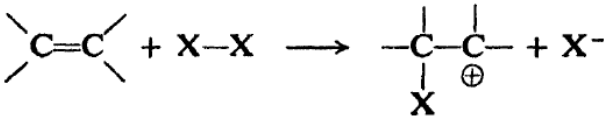
(a) What is the configuration of the glycol of m.p. 19°? Of m.p. 32°?

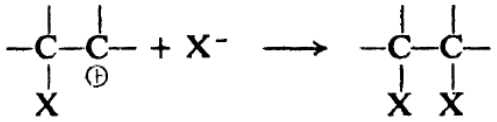
(b) Assuming these results are typical (they are), *what is the stereochemistry of hydroxylation with permanganate?*

(c) Treatment of the same alkenes with peroxy acids gives the opposite results: the glycol of m.p. 19° from *cis*-2-butene, and the glycol of m.p. 32° from *trans*-2-butene. *What is the stereochemistry of hydroxylation with peroxy acids?*

7.12 Mechanism of halogen addition

We saw earlier (Sec. 6.13) that addition of halogens to alkenes is believed to proceed by two steps: first, addition of a positive halogen ion to form an organic

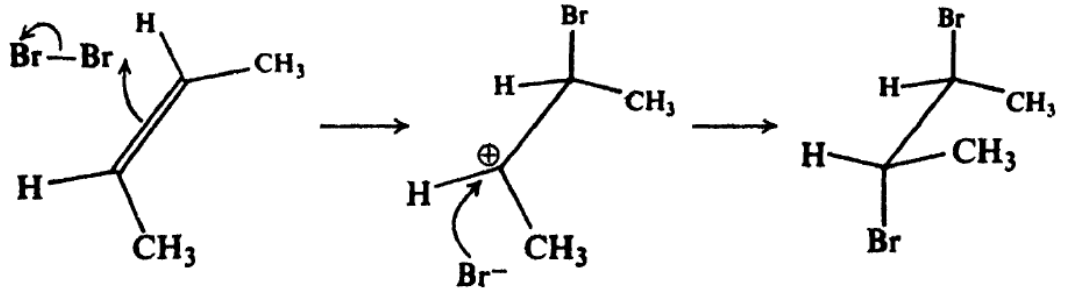
(1) 

(2) 

cation; then combination of this cation with a negative halide ion. We saw some of the facts that provide evidence for this mechanism.

In the last section, we learned another fact: halogens add to simple alkenes with *complete* stereospecificity, and in the *anti* sense. Let us reexamine the mechanism in the light of this stereochemistry, and focus our attention on the nature of the intermediate cation. This intermediate we represented simply as the carbonium ion. A part of a carbonium ion, we remember (Sec. 5.16), is *flat*: the carbon that carries the positive charge is sp^2-hybridized, and this trigonal carbon and the three atoms attached to it lie in the same plane.

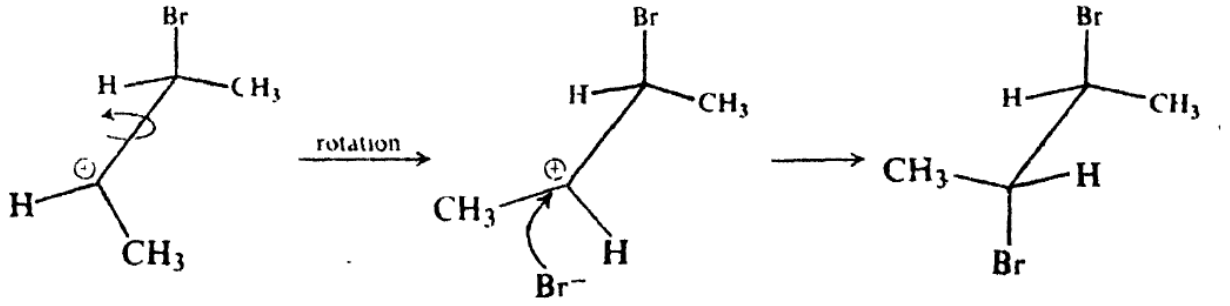
Now, is the observed stereochemistry consistent with a mechanism involving such an intermediate? Let us use addition of bromine to *cis*-2-butene as an example. A positive bromine ion is transferred to, say, the top face of the alkene to



cis-2-Butene Cation I (S,S)-2,3-Dibromobutane

form the carbonium ion I. Then, a bromide ion attacks the *bottom* face of the positively charged carbon to complete the *anti* addition; attack at this face is preferred, we might say, because it permits the two bromines to be as far apart as possible in the transition state. (We obtain the racemic product: the S,S-dibromide as shown, the R,R-dibromide through attachment of positive bromine to the near end of the alkene molecule.)

But this picture of the reaction is not satisfactory, and for two reasons. First, to account for the *complete* stereospecificity of addition, we must assume that attack at the bottom face of the cation is not just preferred, but is the *only* line of attack: conceivable, but—especially in view of other reactions of carbonium ions (Sec. 14.13)—not likely. Then, even if we accept this exclusively bottom-side attack, we are faced with a second problem. Rotation about the carbon–carbon bond would convert cation I into cation II; bottom-side attack on cation II would



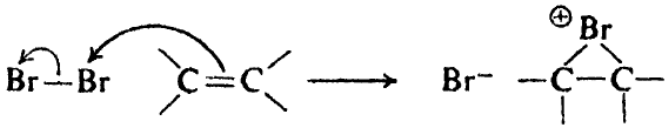
Cation I Cation II *meso*-2,3-Dibromobutane

yield not the racemic dibromide but the *meso* dibromide—in effect *syn*-addition, and contrary to fact.

To accommodate the stereochemical facts, then, we would have to make two assumptions about halogen addition: after the carbonium ion is formed, it is attacked by bromide ion (a) before rotation about the single bond can occur, and (b) exclusively from the side away from the halogen already in the cation. Neither of these assumptions is very likely; together, they make the idea of a simple carbonium ion intermediate hard to accept.

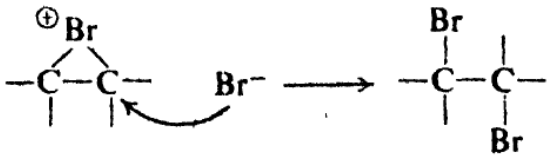
In 1937, to account better for the observed stereochemistry, I. Roberts and G. E. Kimball at Columbia University proposed the following mechanism. In step (1) of the addition of bromine, for example, positive bromine attaches itself

(1)



A bromonium ion

(2)



not to just one of the doubly-bonded carbon atoms, but to both, forming a cyclic **bromonium ion.** In step (2), bromide ion attacks this bromonium ion to yield the dibromide.

Now, how does the bromonium ion mechanism account for *anti*-addition? Using models, let us first consider addition of bromine to *cis*-2-butene (Fig. 7.6).

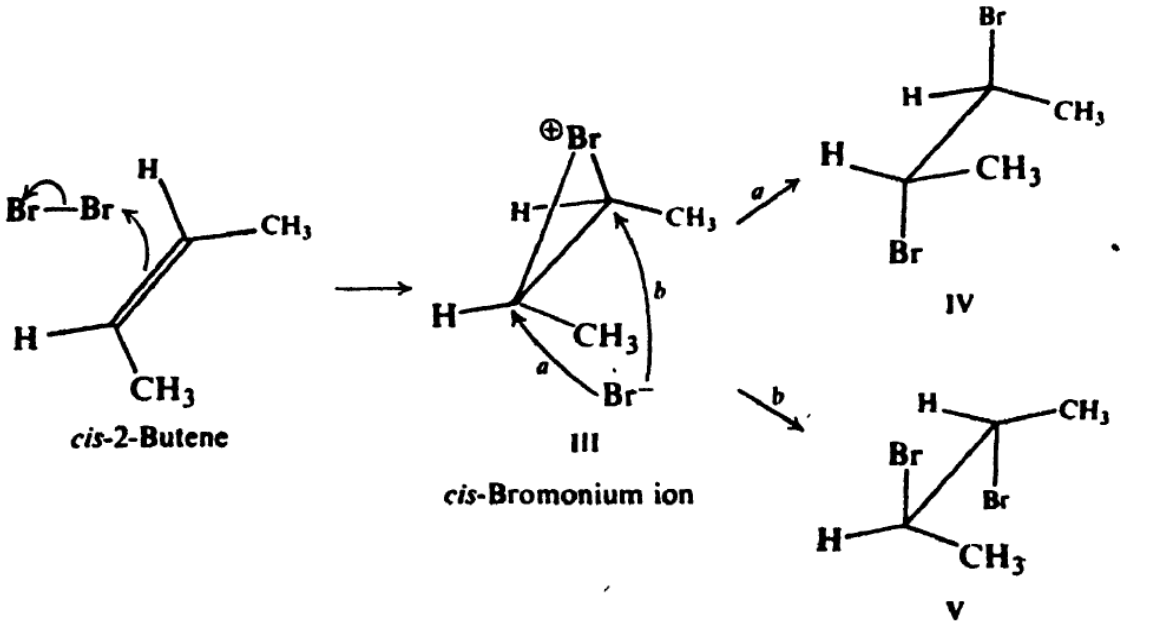


Figure 7.6. Addition of bromine to *cis*-2-butene via cyclic bromonium ion. Opposite-side attacks (*a*) and (*b*) equally likely, give enantiomers in equal amounts.

In the first step, positive bromine becomes attached to either the top or bottom face of the alkene. Let us see what we would get if bromine becomes attached to the top face. When this happens, the carbon atoms of the double bond tend to become tetrahedral, and the hydrogens and methyls are displaced downward. The methyl groups are, however, still located across from each other, as they were in the alkene. In this way, bromonium ion III is formed.

Now bromonium ion III is attacked by bromide ion. A new carbon–bromine bond is formed, and an old carbon–bromine bond is broken. This attack occurs on the bottom face of III, so that the bond being formed is on the opposite of carbon from the bond being broken. Attack can occur by path (*a*) to yield structure IV or by path (*b*) to yield structure V. We recognize IV and V as enantiomers. Since attack by either (*a*) or (*b*) is equally likely, the enantiomers are formed in equal amounts, and thus we obtain the racemic modification. The same results are obtained if positive bromine initially becomes attached to the bottom face of *cis*-2-butene. (Show with models that this is so.)

Next, let us carry through the same operation on *trans*-2-butene (Fig. 7.7). This time, bromonium ion VI is formed. Attack on it by path (*c*) yields VII, attack by (*d*) yields VIII. If we simply rotate either VII or VIII about the carbon–carbon bond, we readily recognize the symmetry of the compound. It is *meso*-2,3-dibromo-butane; VII and VIII are identical. The same results are obtained if

positive bromine is initially attached to the bottom face of *trans*-2-butene. (Show with models that this is so.)

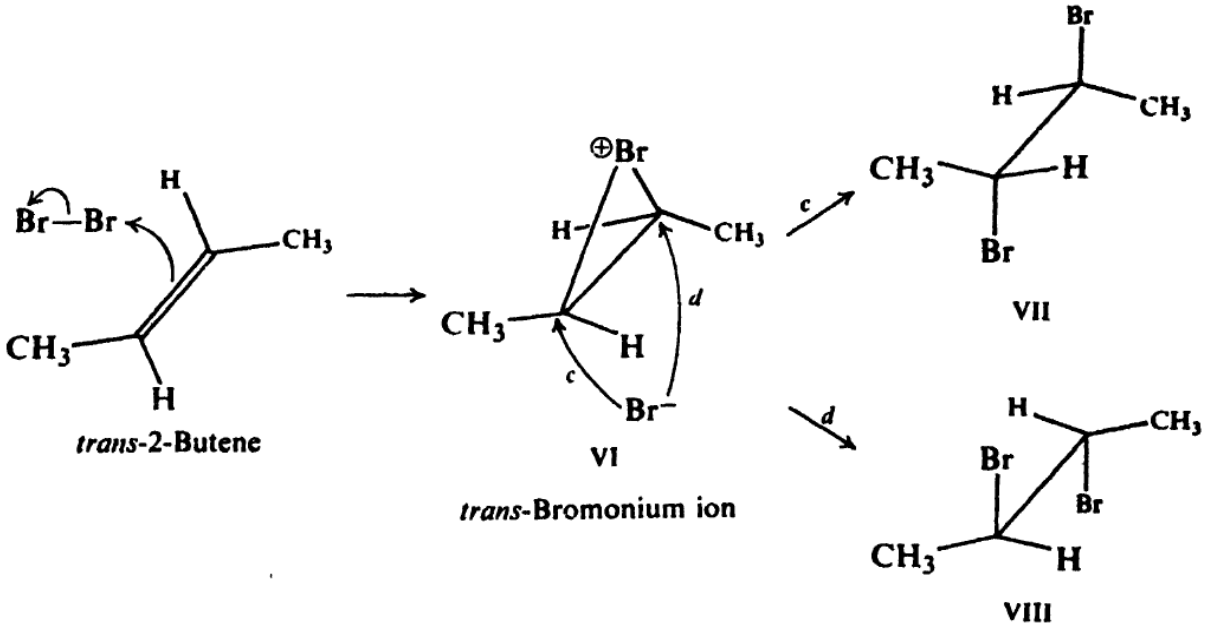


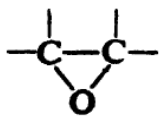
Figure 7.7. Addition of bromine to *trans*-2-butene via cyclic bromonium ion. Opposite-side attacks (*c*) and (*d*) give same product.

Problem 7.12 (a) What is the relationship between the bromonium ions formed by attachment of positive bromine to the top and bottom faces of *trans*-2-butene? In what proportions are they formed? (b) Answer the same questions for *cis*-2-butene. (c) For *trans*-2-pentene. (d) For *cis*-2-pentene.

Problem 7.13 (a) Predict the products of addition of bromine to *trans*-2-pentene. Is attack by bromide ion by the two paths equally likely? Account for the fact that inactive material is actually obtained. (b) Do the same for *cis*-2-pentene.

The concept of a halonium ion solves both of the problems associated with an open carbonium ion: a halogen bridge prevents rotation about the carbon–carbon bond, and at the same time restricts bromide ion attack exclusively to the opposite face of the cation. This opposite-side approach, we shall find (Sec. 14.10), is *typical* of attack by bases (nucleophiles) on tetrahedral carbon.

That such cyclic intermediates *can* give rise to *anti*-addition is demonstrated by hydroxylation with peroxy acids (Problem 7.11, p. 242): there, analogous intermediates—perfectly respectable compounds called *epoxides* (Chap. 17)—can actually be isolated and studied.



An epoxide

Cyclic halonium ions were first proposed, then, simply as the most reasonable explanation for the observed stereochemistry. Since that time, however,

more positive evidence has been discovered. In 1967, Olah (p. 160) prepared cations whose nmr spectra indicate that they are indeed cyclic halonium ions. For example:

$$(CH_3)_2C(F)-CH(Br)CH_3 + SbF_5 \xrightarrow{\text{liquid } SO_2} (CH_3)_2C(\overset{\oplus}{Br})-CHCH_3 \quad SbF_6^-$$

The idea of a bromonium or chloronium ion may appear strange to us, in contrast to the already familiar oxonium and ammonium ions. The tendency for halogen to share two pairs of electrons and acquire a positive charge, we might say, should be weak because of the high electronegativity of halogens. But the evidence—here, and in other connections (Sec. 11.21 and Sec. 25.6)—shows that this tendency is *appreciable*. In halogen addition we are concerned with this question: which is more stable, an open carbonium ion in which carbon has only a sextet of electrons, or a halonium ion in which each atom (except hydrogen, of course) has a complete octet? It is not a matter of which atom, halogen or carbon, can better accommodate a positive charge; it is a matter of completeness or incompleteness of octets.

In halonium ion formation we see one more example of what underlies all carbonium ion behavior: *the need to get a pair of electrons to complete the octet of the positively charged carbon.*

There are exceptions to the rule of *anti*-addition of halogens, but exceptions that are quite understandable. If the alkene contains substituents that can strongly stabilize the open carbonium ion—as, for example, in a *benzyl* cation (Sec. 12.19)—then addition proceeds with little or no stereospecificity. Carbon is getting the electrons it needs, but in a different way.

Problem 7.14 Olah treated compounds of the formula $(CH_3)_2CXCF(CH_3)_2$ with SbF_5. He observed the formation of halonium ions when X = Cl, Br, or I, but an open carbonium ion when X = F. How do you account for the difference in behavior of the difluoro compound? (*Hint:* See Sec. 1.15.)

PROBLEMS

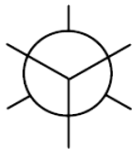
1. Each of the following reactions is carried out, and the products are separated by careful fractional distillation or recrystallization. For each reaction tell how many fractions will be collected. Draw stereochemical formulas of the compound or compounds making up each fraction, and give each its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

(a) *n*-pentane + Cl_2 (300°) $\longrightarrow$ $C_5H_{11}Cl$;
(b) 1-chloropentane + Cl_2 (300°) $\longrightarrow$ $C_5H_{10}Cl_2$;
(c) (S)-2-chloropentane + Cl_2 (300°) $\longrightarrow$ $C_5H_{10}Cl_2$;
(d) (R)-2-chloro-2,3-dimethylpentane + Cl_2 (300°) $\longrightarrow$ $C_7H_{14}Cl_2$;
(e) *meso*-$HOCH_2CHOHCHOHCH_2OH$ + HNO_3 $\longrightarrow$ $HOCH_2CHOHCHOHCOOH$;
(f) (R)-*sec*-butyl chloride + KOH (alc);
(g) (S)-3-chloro-1-butene + HCl;
(h) racemic $C_6H_5COCHOHC_6H_5$ + H_2, catalyst $\longrightarrow$ $C_6H_5CHOHCHOHC_6H_5$.

2. In Problem 7.11 we saw that *hydroxylation with permanganate is syn*, and *hydroxylation with peroxy acids is anti*. Keeping in mind that reaction of epoxides (Sec. 17.12) is acid-catalyzed, give a detailed mechanism for hydroxylation with peroxy acids. (Check your answer in Sec. 17.12.)

Newman Projections

The circle in the Newman projection represents the carbon-carbon bond, viewed one carbon in front of the other. Bonds attached to the front carbon are shown by lines going to the center of the circle. Bonds attached to the rear carbon are shown by lines going to the edge of the circle.



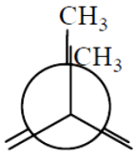
Staggered

Eclipsed

Rotation around the carbon-carbon bond alternates between staggered and eclipsed.
Newman Projections show the relationships (angles) between the substituents.

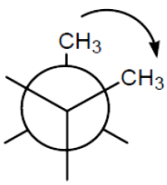
Eclipsed

Conformation of butane (2 methyl groups are eclipsed. Circle represents the C2-C3 bond of butane)

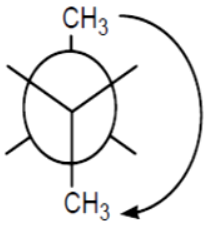


Staggered (Gauche)

60 degree dihedral angle



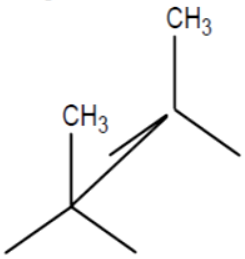
Staggered (Anti)



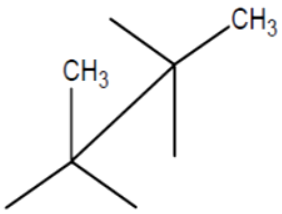
180 degree dihedral angle

Sawhorses

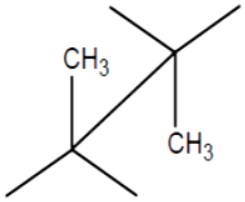
Eclipsed



Gauche



Anti



Strain and Stability

Torsional Strain	Strain on a molecule caused by bond opposition, electron repulsion between eclipsing bonds.
Steric Strain	Repulsion between atoms and groups

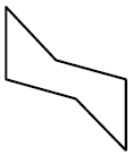
The higher the strain, the less stable the conformation

Eclipsed conformations are less stable than staggered conformations. Why? The main reason is that torsional strain is high in eclipsed confirmations. The bonds on the front and back carbons are close to each other and repel each other destabilizing the molecule.

Conformations of Cyclohexane

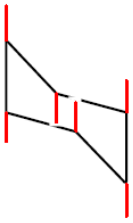
Cyclohexane moves into a 3-D conformation, called a chair conformation, that relieves both torsional and ring strain.

Cyclohexane Chair

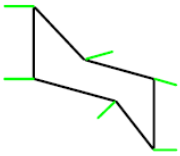


Axial and Equitorial bonds in Cyclohexane

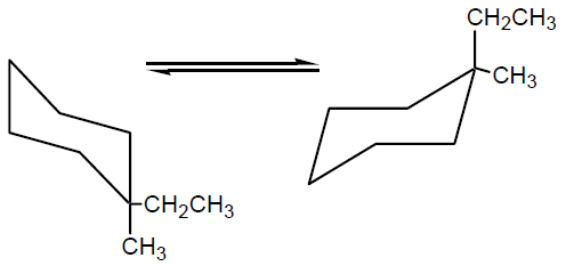
Axial Positions



Equitorial Positions



Notice that axial positions and equatorial positions alternate their up or down orientation. Rings can flip so that substituents in the axial position move to the equatorial position and vice versa. However, during this flip, the general up or down direction is retained. This means that axial up flips to be come equatorial up. Equitorial down flips to become axial down.

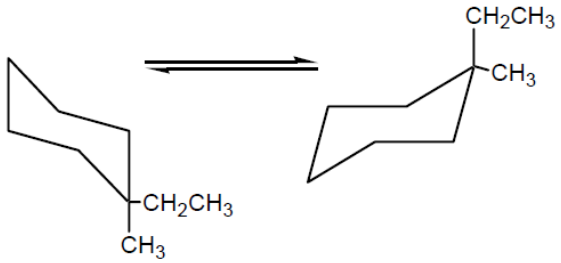


Substituents in the equatorial position contribute less steric strain to the molecule. Substituents in the axial position contribute more steric strain to the molecule. Therefore, the conformation with the bigger groups in the equatorial position is more stable.

Practice Problems

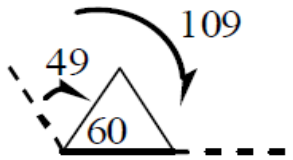
2. Which is the most stable conformation?

A B

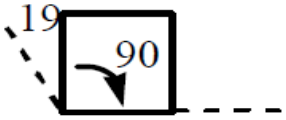


Conformation and Stability of Cycloalkanes: The Baeyer Strain theory

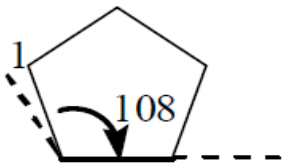
Baeyer suggested that, since carbon prefers tetrahedral geometry (~109°), ring sizes other than 5 and 6 may be too ***strained*** to exist.



Cyclopropane



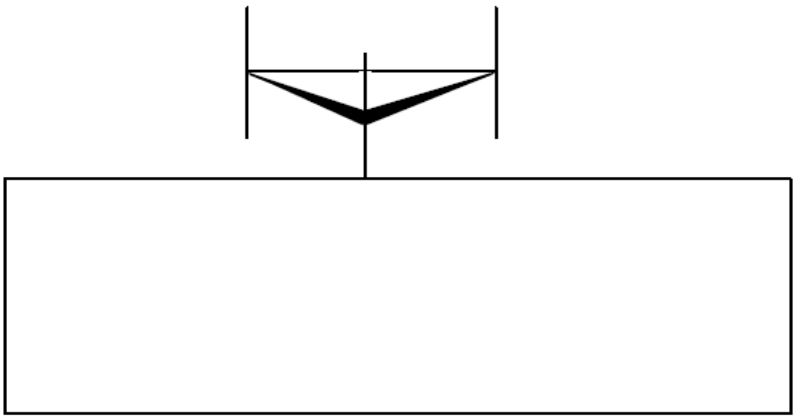
Cyclobutane



Cyclopentane

Cyclopropane

- Poor overlap of atomic orbitals in the formation of C-C bonds.

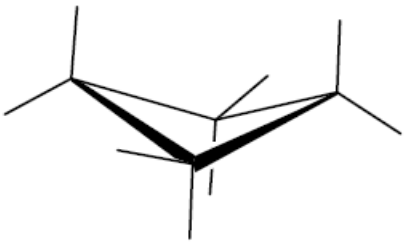


typical C-C bond bent cyclopropane bond

C-C-C bond angle can not be 109.5°, but instead 60°(angle strain = 49.5°). There is less overlap therefore, the bond is weaker than the usual C-C bond. Cyclopropane has "bent bonds".

- Total strain energy for cyclopropane = 114.9 kJ/mol

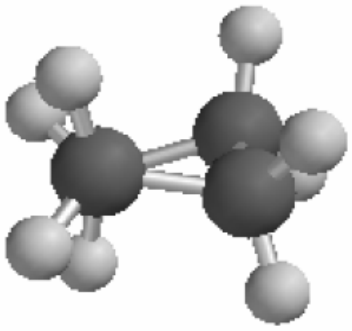
Cyclobutane



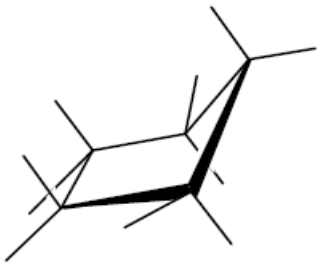
Less angle strain than cyclopropane, but more torsional strain.

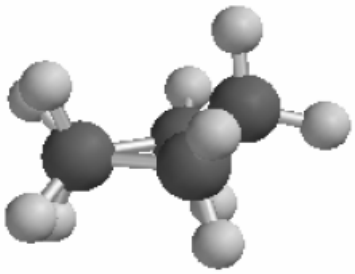
- Total strain energy 110.4 kJ/mol
- Is not flat, see figure 4.12

Almost eclipsed



Cyclopentane

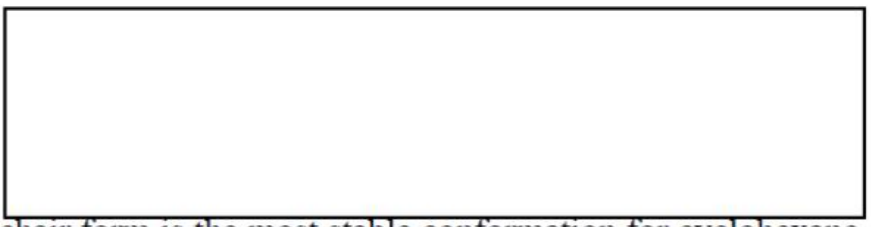




- Internal angles = 108° (1° angle strain)
- Adopts a puckered out-of-plane conformation
- Total strain energy = 26.0 kJ/mol (from torsional strain), fig 4.13

Cyclohexane

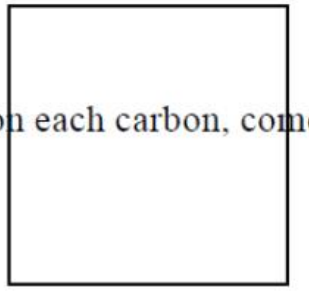
- All angles = 109.5°
- There are different conformations:



The chair form is the most stable conformation for cyclohexane.

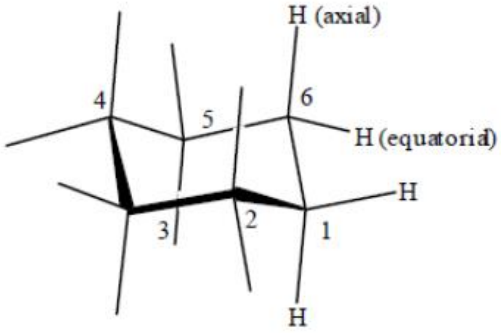
How to draw a chair conformation?

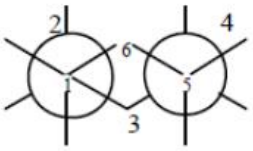
Six axial bonds, one on each carbon, are parallel and alternate up and down



Six equatorial bonds, one on each carbon, come in three sets of two Parallel lines.

Chair cyclohexane has no torsional strain

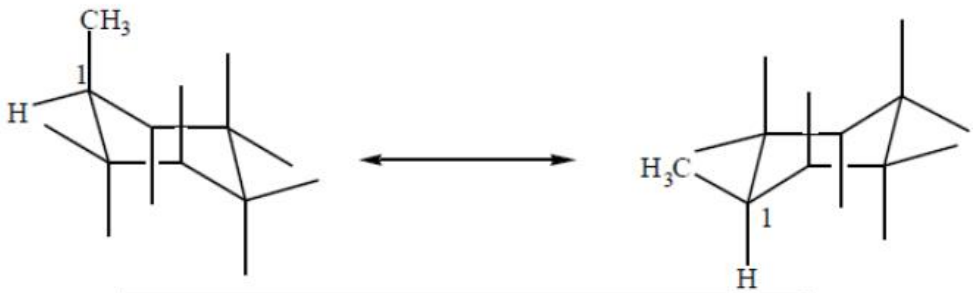




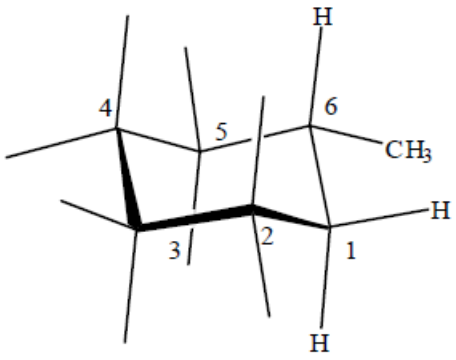
newman projection

staggered ethane

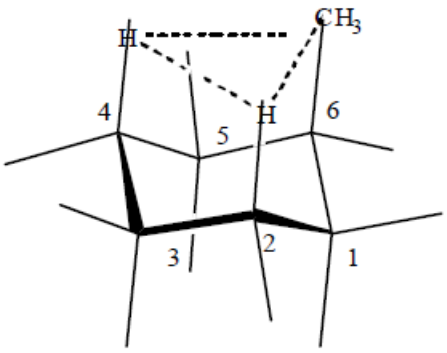
Chair cyclohexanes can rapidly interconvert (ring flip)



A substituent is always more stable in an equatorial position than in an axial position



equatorial CH_3



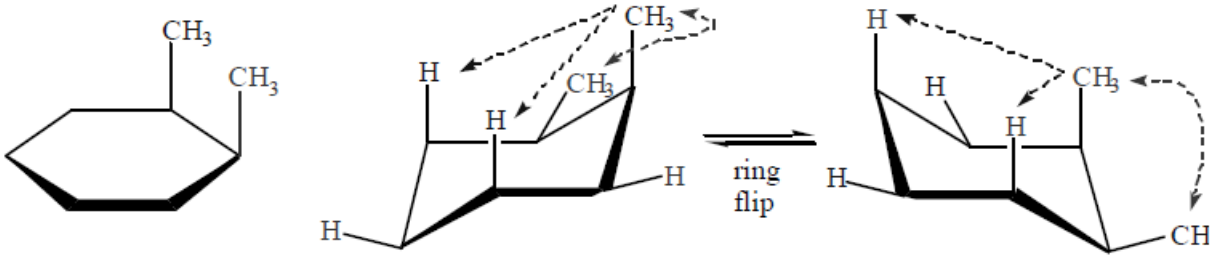
axial CH_3

Disubstituted Cyclohexanes

Monosubstituted cyclohexanes usually have the substituent in equatorial position.

Disubstituted cyclohexanes $\Longrightarrow$ more complex situation: Steric effect

Example: Cis-1,2-Dimethylcyclohexane

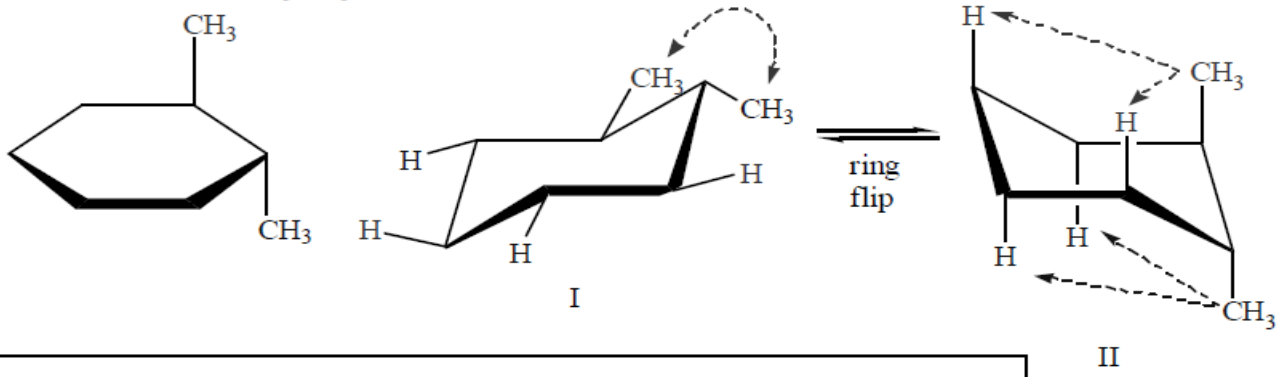


Two CH_3-H diaxial interactions =

One gauche interaction =

Total strain =

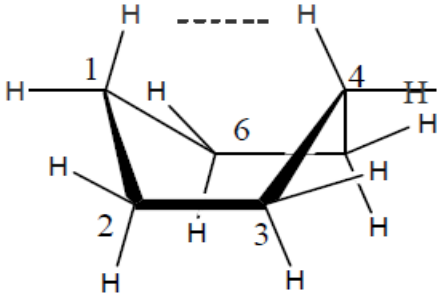
Trans-1,2-Dimethylcyclohexane



I II

Boat cyclohexane:

- Free of angle strain
- Less stable than chair conformation (steric and torsional strain)



Note eclipsing and Steric strain from 1,4 interaction

Total strain = 29 kJ/mol

Twist-boat conformation = 23 kJ/mol