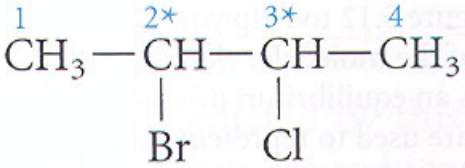
5.8 Compounds with More Than One Stereogenic Center; Diastereomers

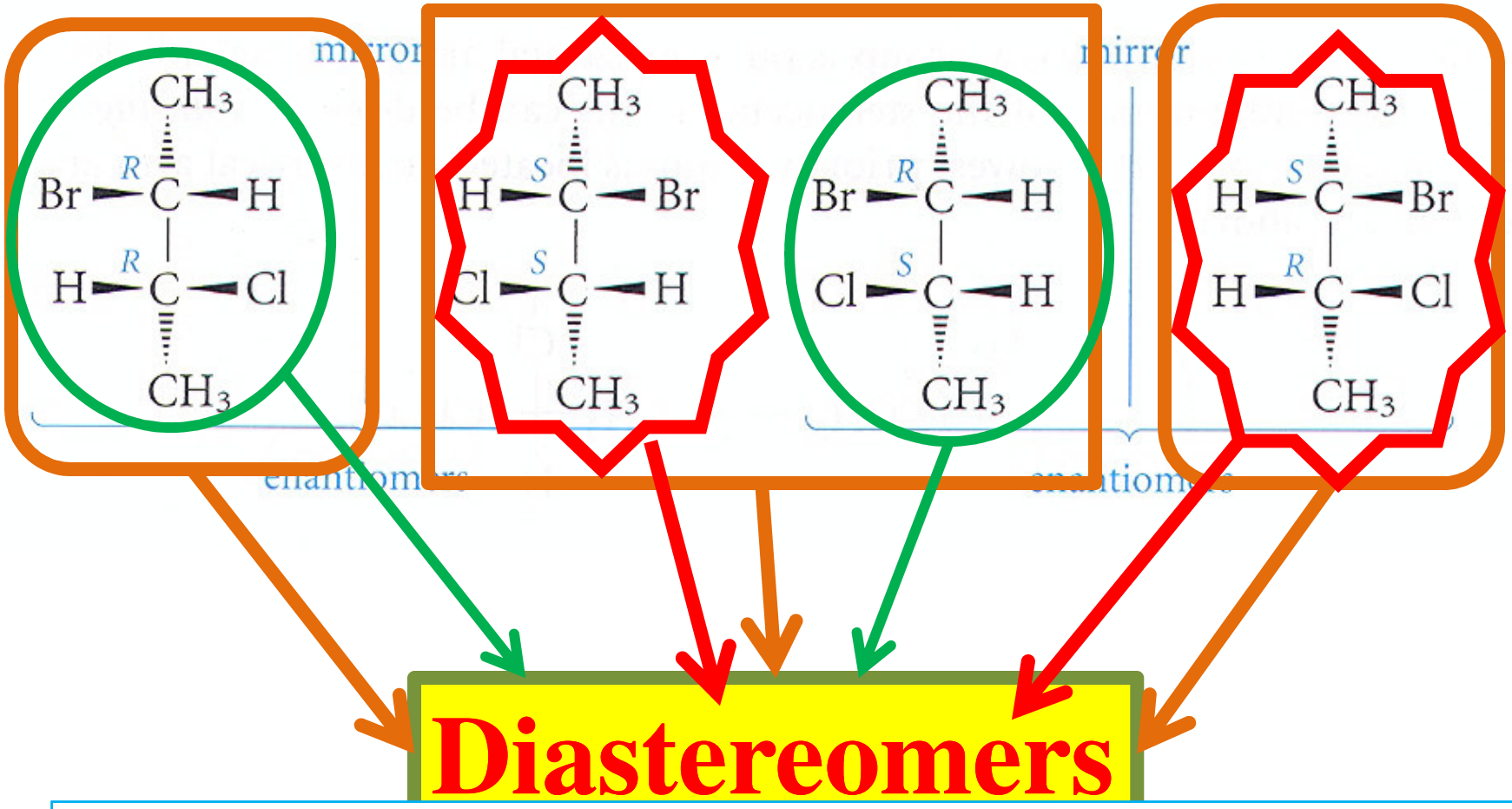
Compounds may have more than one stereogenic center, so it is important to be able to determine how many isomers exist in such cases and how they are related to one another. Consider the molecule 2-bromo-3-chlorobutane.



2-bromo-3-chlorobutane

As indicated by the asterisks, the molecule has two stereogenic centers. Each of these could have the configuration *R* or *S*. Thus, four isomers in all are possible: (2*R*,3*R*), (2*S*,3*S*), (2*R*,3*S*), and (2*S*,3*R*). We can draw these four isomers as shown in Figure 5.12. Note that there are two pairs of enantiomers. The (2*R*,3*R*) and (2*S*,3*S*) forms are nonsuperimposable mirror images, and the (2*R*,3*S*) and (2*S*,3*R*) forms are another such pair.

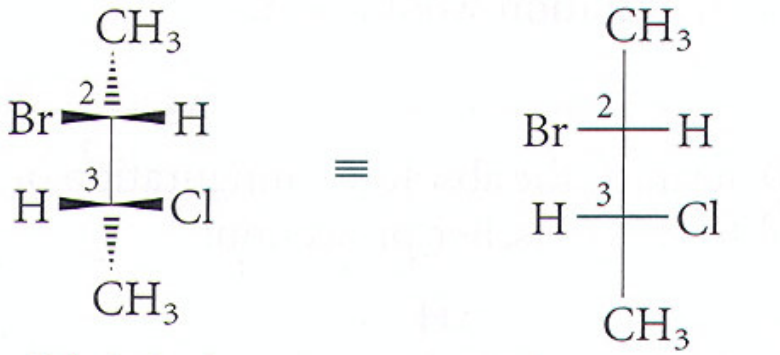
Let us see how to use Fischer projection formulas for these molecules. Consider the (2*R*,3*R*) isomer, the one at the left in Figure 5.12. The solid-dashed wedge drawing has horizontal groups projecting out of the plane of the paper toward us and vertical



Diastereomers

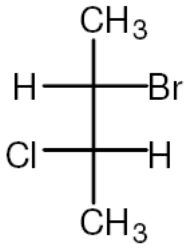
Diastereomers are stereoisomers that are not mirror images of each other.

Fischer projection formula as shown.*



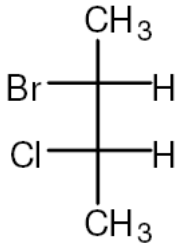
solid-dashed wedge formula

Fischer projection formula

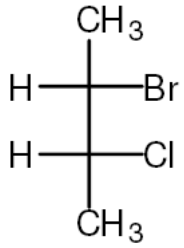


(2*S*,3*S*)-2-bromo-3-chlorobutane

This is the enantiomer of (2*R*,3*R*)-2-bromo-3-chlorobutane (Fig. 5.12)



(2*R*,3*S*)-2-bromo-3-chlorobutane



(2*S*,3*R*)-2-bromo-3-chlorobutane

These compounds are enantiomers.

Diastereomers are stereoisomers that are not mirror images of one another. They may differ in all types of properties, and may be chiral or achiral.

PROBLEM 5.18 How do you expect the specific rotations of the (2*R*,3*R*) and (2*S*,3*S*) forms of 2-bromo-3-chlorobutane to be related? Answer the same question for the (2*R*,3*R*) and (2*S*,3*R*) forms.

5.18 The (2*R*,3*R*) and (2*S*,3*S*) isomers are a pair of enantiomers. Their specific rotations will be equal in magnitude and opposite in sign.

The (2*R*,3*R*) and (2*S*,3*R*) isomers are a pair of diastereomers. Their specific rotations will be unequal in magnitude and may or may not differ in sign.

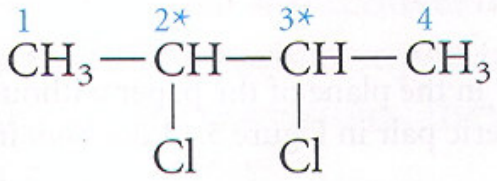
Can we generalize about the number of stereoisomers possible when a larger number of stereogenic centers is present? Suppose, for example, that we add a third stereogenic center to the compounds shown in Figure 5.12 (say, 2-bromo-3-chloro-4-iodopentane). The new stereogenic center added to each of the four structures can once again have either an *R* or an *S* configuration, so that with three different stereogenic centers, eight stereoisomers are possible. The situation is summed up in a single rule: If a molecule has *n* different stereogenic centers, it may exist in a maximum of 2^n stereoisomeric forms. There will be a maximum of $2^n/2$ pairs of enantiomers.

Compounds with *n* different stereogenic centers may exist in a maximum of 2^n forms.

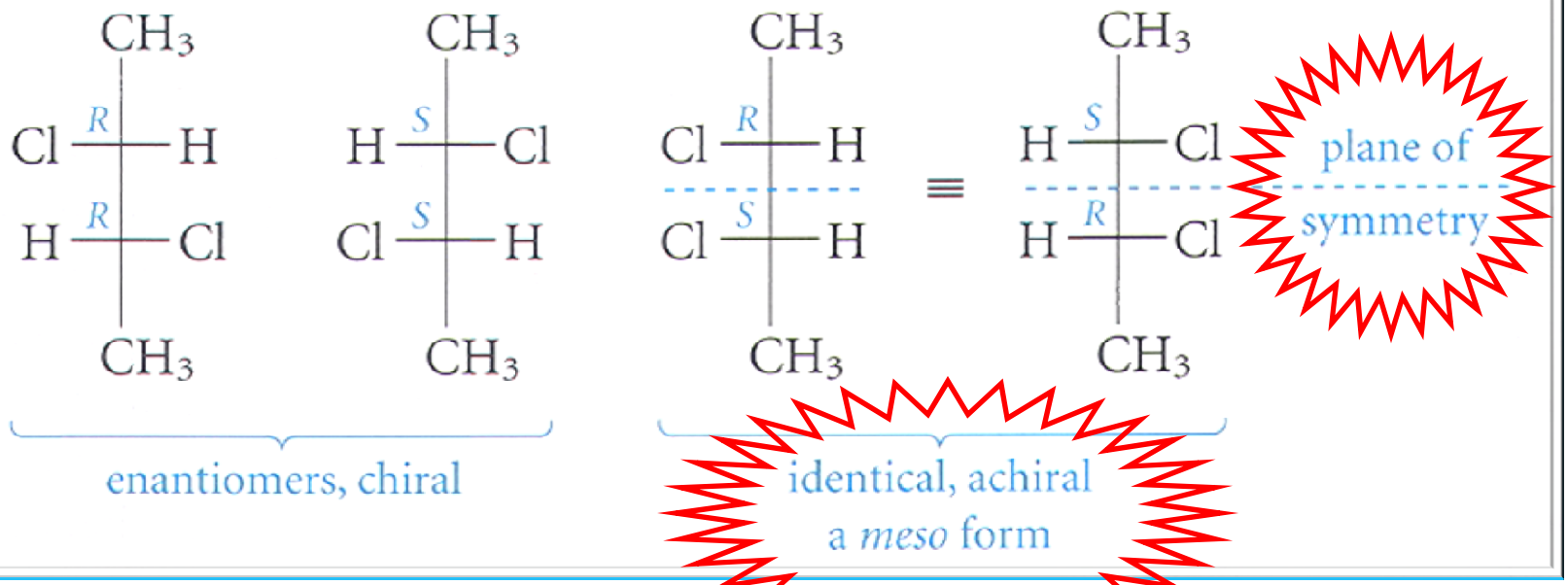
Actually, the number of isomers predicted by this rule is the *maximum* number possible. Sometimes certain structural features reduce the actual number of isomers. In the next section, we examine a case of this type.

5.9 *Meso* Compounds; the Stereoisomers of Tartaric Acid

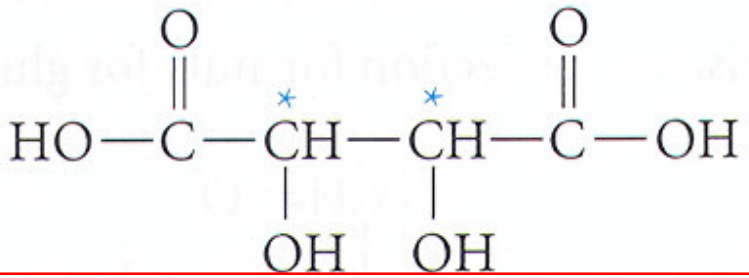
Consider the stereoisomers of 2,3-dichlorobutane. There are two stereogenic centers.

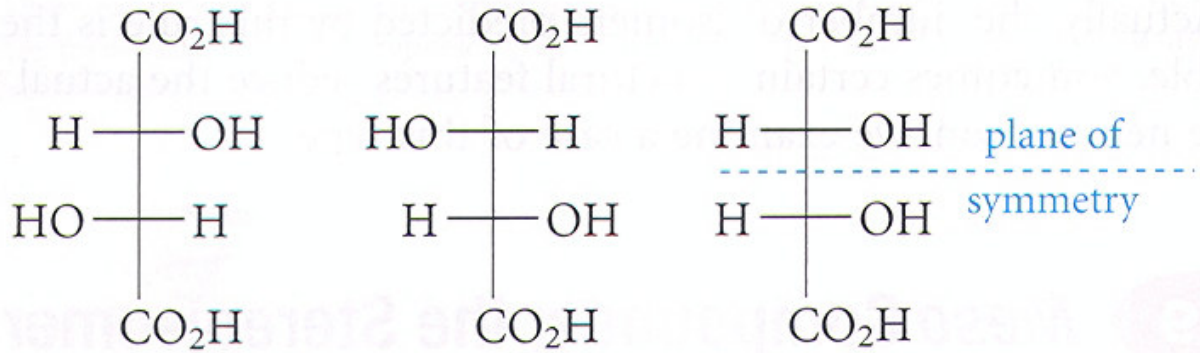


2,3-dichlorobutane



Compounds with *n* different stereogenic centers may exist in a maximum of 2^n forms. Of these, there will be $2^n/2$ pairs of enantiomers. Compounds from different enantiomeric pairs are diastereomers. If two (or more) of the stereogenic centers are identical, certain isomers will be achiral. A **meso form** is an optically inactive, achiral form of a compound with stereogenic centers. **Tartaric acid**, which has two identical stereogenic centers, exists in three forms: the *R,R* and *S,S* forms (a pair of enantiomers) and the achiral *meso* form.





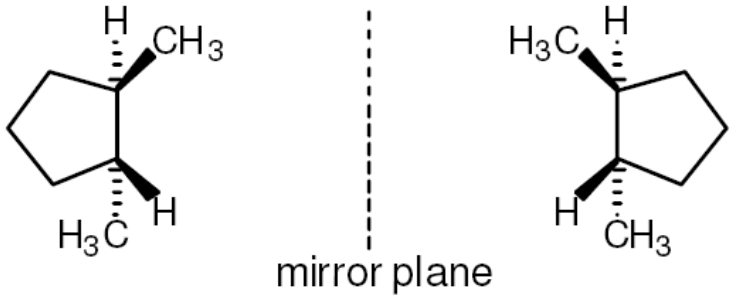
Configuration	(*R,R*)	(*S,S*)
$[\alpha]_D^{20°}$ (H_2O)	+12	−12
Melting point, °C	170	170

A ***meso* compound** is an achiral diastereomer of a compound with stereogenic centers.

The correctly assigned (*R* or *S*) configuration of a stereocenter in a molecule is called the **absolute configuration** of the stereocenter.

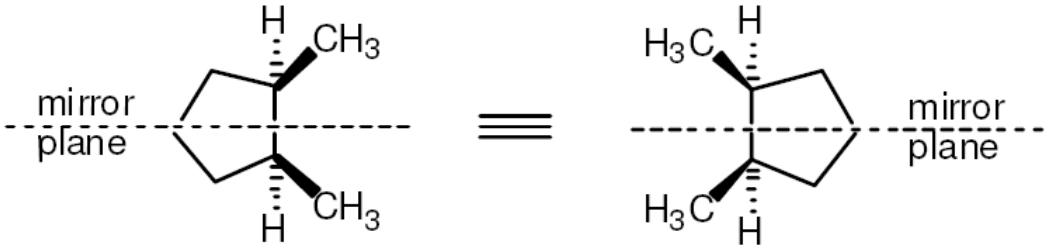
PROBLEM 5.20 Show that *trans*-1,2-dimethylcyclopentane can exist in chiral, enantiomeric forms.

5.20 When the three CH_2 groups are superimposed, the methyl groups of one mirror image are superimposed on the hydrogens of the other mirror image. The mirror images are nonsuperimposable and are therefore enantiomers.



PROBLEM 5.21 Is *cis*-1,2-dimethylcyclopentane chiral or achiral? What stereochemical term can we give to it?

5.21 *cis*-1,2-Dimethylcyclopropane is achiral. It has a mirror plane of symmetry and is a *meso* compound.



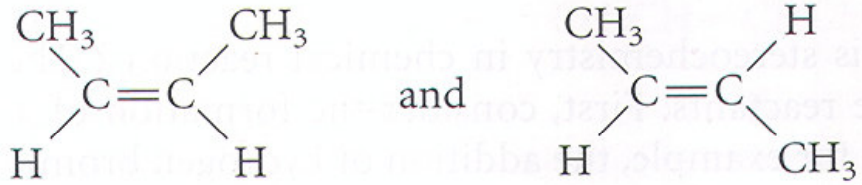
5.10 Stereochemistry: A Recap of Definitions

We have seen here and in Section 2.11 that *stereoisomers* can be classified in three different ways. They may be either *conformers* or *configurational isomers;* they may be *chiral* or *achiral;* and they may be *enantiomers* or *diastereomers.*

A	*Conformers:*	interconvertible by rotation about single bonds
	Configurational Isomers:	not interconvertible by rotation, only by breaking and making bonds
B	*Chiral:*	mirror image not superimposable on itself
	Achiral:	molecule and mirror image are identical
C	*Enantiomers:*	mirror images; have opposite configurations at all stereogenic centers
	Diastereomers:	stereoisomers but not mirror images; have same configuration at one or more centers, but differ at the remaining stereogenic centers

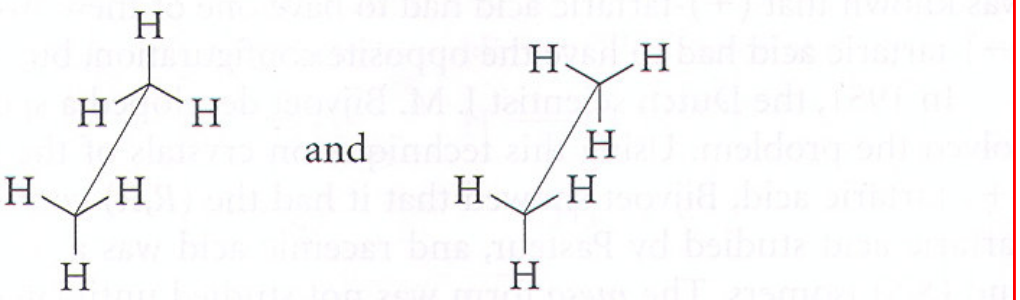
Various combinations of these three sets of terms can be applied to any pair of stereoisomers. Here are a few examples:

1. *Cis*- and *trans*-2-butene (*Z*- and *E*-2-butene).



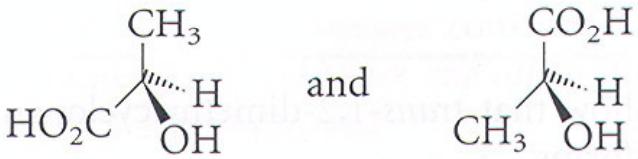
These isomers are *configurational* (not interconverted by rotation about single bonds), *achiral* (the mirror image of each is superimposable on the original), and *diastereomers* (although they are stereoisomers, they are *not* mirror images of one another; hence they must be diastereomers).

2. Staggered and eclipsed ethane.



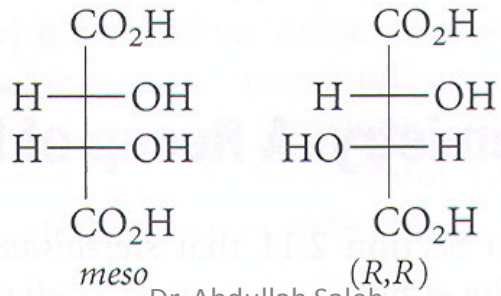
These are *achiral conformers.* They are *diastereomeric conformers* (but without stereogenic centers) because they are not mirror images.

3. (*R*)- and (*S*)-lactic acid.



These isomers are *configurational,* each is *chiral,* and they constitute a pair of *enantiomers.*

4. *Meso*- and (*R*,*R*)-tartaric acids.

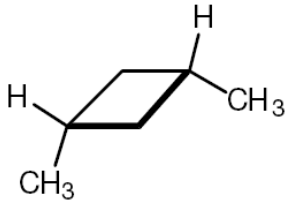


These isomers are *configurational* and *diastereomers*. One is *achiral*, and the other is *chiral*.

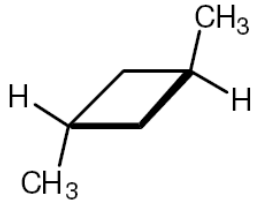
Enantiomers, such as (*R*)- and (*S*)-lactic acid, differ only in chiral properties and therefore cannot be separated by ordinary achiral methods such as distillation or recrystallization. Diastereomers differ in all properties, chiral or achiral. *If* they are also configurational isomers (such as *cis*- and *trans*-2-butene, or *meso*- and (*R*,*R*)-tartaric acid), they can be separated by ordinary achiral methods, such as distillation or recrystallization. *If*, on the other hand, they are conformers (such as staggered and eclipsed ethane), they may interconvert so readily by bond rotation as to not be separable.

PROBLEM 5.22 Draw the two stereoisomers of 1,3-dimethylcyclobutane, and classify the pair according to the categories listed in A, B, and C above.

5.22



cis-1,3-dimethylcyclobutane



trans-1,3-dimethylcyclobutane

There are *no* stereogenic centers. Both molecules have planes of symmetry. The *cis* isomer has two such planes, through opposite corners of the ring. The *trans* isomer has one such plane, through the opposite methyl-bearing corners. Both compounds are optically inactive and achiral. They are not *meso* compounds because there are no chiral centers. To summarize, the two isomers are configurational, achiral and diastereomers.

5.11 Stereochemistry and Chemical Reactions

How important is stereochemistry in chemical reactions? The answer depends on the nature of the reactants. First, consider the formation of a chiral product from achiral reactants; for example, the addition of hydrogen bromide to 1-butene to give 2-bromobutane in accord with Markovnikov's rule.

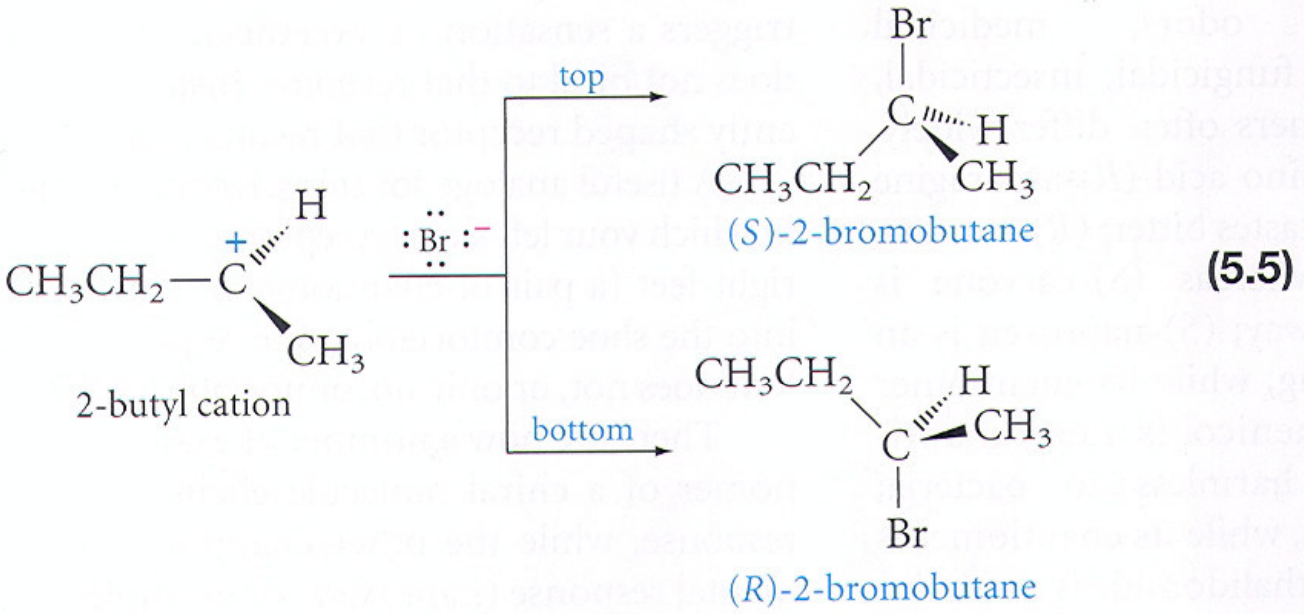
$$CH_3CH_2CH{=}CH_2 + HBr \longrightarrow CH_3CH_2\overset{*}{C}HCH_3 \quad (5.3)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Br$$

1-butene — 2-bromobutane

The product has one stereogenic center, marked with an asterisk, but both enantiomers are formed in exactly equal amounts. The product is a **racemic mixture**. Why? Although this result will be obtained *regardless* of the reaction mechanism, let us consider the generally accepted mechanism.

$$CH_3CH_2CH{=}CH_2 + H^+ \longrightarrow \underset{\text{2-butyl cation}}{CH_3CH_2\overset{+}{C}HCH_3} \xrightarrow{Br^-} CH_3CH_2CHCH_3 \quad (5.4)$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad Br$$

The intermediate 2-butyl cation obtained by adding a proton to the end carbon is planar, and bromide ion can combine with it from the "top" or "bottom" side with exactly equal probability.

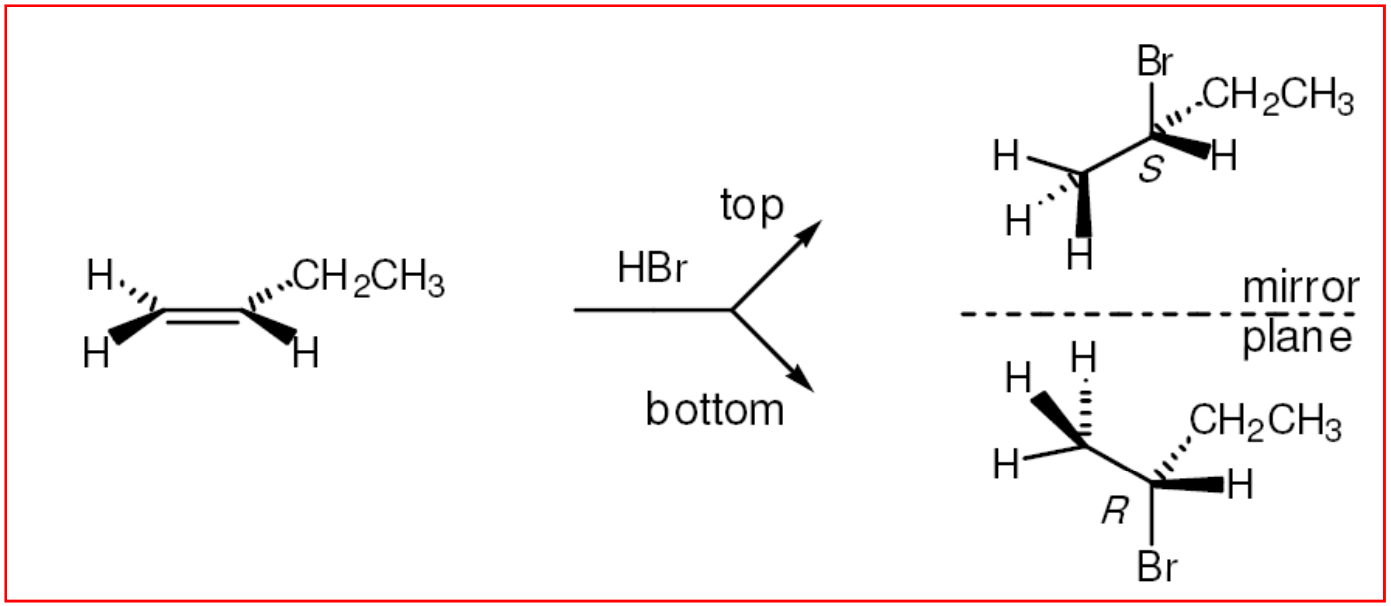


(5.5)

The product is therefore a racemic mixture, an optically inactive 50:50 mixture of the two enantiomers.

We can generalize this result. *When chiral products are obtained from achiral reactants, both enantiomers are formed at the same rates, in equal amounts.*

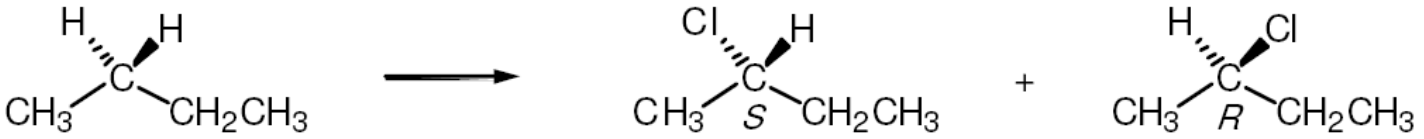
Assuming one-step mechanism



One-step addition of H–Br to the top face of the double bond gives (*S*)-2-bromobutane. Addition of H–Br to the bottom face gives (*R*)-2-bromobutane. Since 1-butene is achiral, the probability of addition to either face of the double bond is equal, and the product will be racemic (an equal mixture of enantiomers).

PROBLEM 5.24 Show that the chlorination of butane at carbon-2 will give a 50:50 mixture of enantiomers.

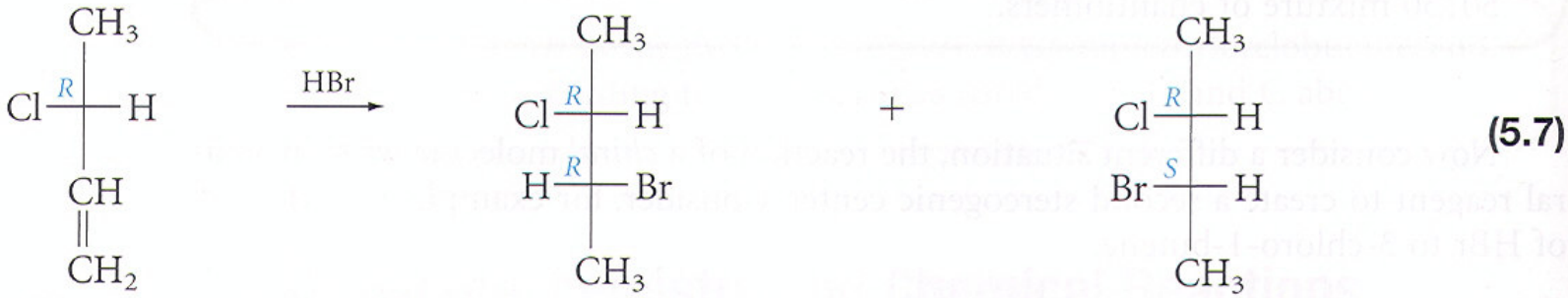
5.24 If we draw the structure in three dimensions, we see that either hydrogen at C-2 can be replaced with equal probability:



Thus a 50:50 mixture of the two enantiomers is obtained.

Now consider a different situation, the reaction of a *chiral* molecule with an achiral reagent to create a second stereogenic center. Consider, for example, the addition of HBr to 3-chloro-1-butene.

Suppose we start with one pure enantiomer of 3-chloro-1-butene, say, the *R* isomer. What can we say about the stereochemistry of the products? One way to see the answer quickly is to draw Fischer projections.



(5.7)

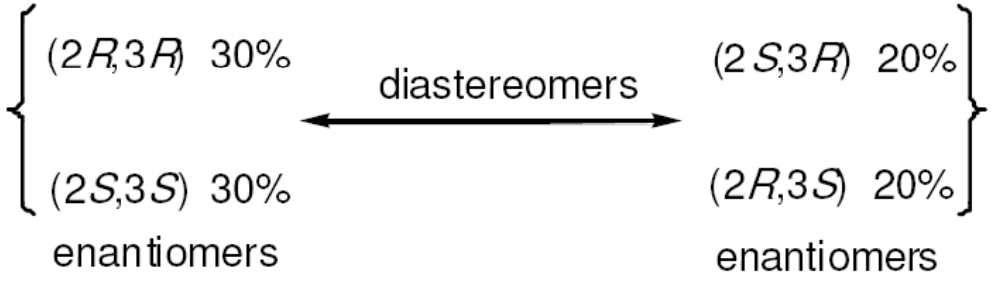
(*R*)-3-chloro-1-butene (2*R*,3*R*)-2-bromo-3-chlorobutane (2*S*,3*R*)-2-bromo-3-chlorobutane

The configuration where the chloro substituent is located remains unchanged and *R*, but the new stereogenic center can be either *R* or *S*. Therefore, the products are *diastereomers*. Are they formed in equal amounts? No. Looking at the starting material in eq. 5.7, we can see that it has no plane of symmetry. Approach of the bromine to the double bond from the H side or from the Cl side of the stereogenic center should not occur with equal ease.

We can generalize this result. *Reaction of a chiral reagent with an achiral reagent, when it creates a new stereogenic center, leads to diastereomeric products at different rates and in unequal amounts.*

PROBLEM 5.25 Let us say that the (2*R*,3*R*) and (2*S*,3*R*) products in eq. 5.7 are formed in a 60 : 40 ratio. What products would be formed and in what ratio by adding HBr to pure (*S*)-3-chloro-1-butene? by adding HBr to a racemic mixture of (*R*)- and (*S*)-3-chloro-1-butene?

5.25 (*S*)-3-chloro-1-butene is the enantiomer of (*R*)-3-chloro-1-butene, and it will react with HBr to give the enantiomers of the products shown in eq. 5.7 [(2*S*, 3*S*)- and (2*R*, 3*S*)-2-bromo-3-chlorobutane], in the same 60:40 ratio. Therefore a racemic mixture of 3-chloro-1-butene will react with HBr to give the following mixture of 2-bromo-3-chlorobutanes:



In other words, a 60:40 mixture of the two diastereomeric products will be obtained, each as a racemic mixture.

5.12 Resolution of a Racemic Mixture

We have just seen (eq. 5.5) that, when reaction between two achiral reagents leads to a chiral product, it always gives a racemic (50:50) mixture of enantiomers. Suppose we want to obtain each enantiomer pure and free of the other. The process of separating a racemic mixture into its enantiomers is called **resolution**. Since enantiomers have identical achiral properties, how can we resolve a racemic mixture into its components? The answer is to convert them to diastereomers, separate the *diastereomers*, and then reconvert the now-separated diastereomers back to enantiomers.

To separate two enantiomers, we first let them react with a chiral reagent. The product will be a pair of *diastereomers.* These, as we have seen earlier, differ in all types of

properties and can be separated by ordinary methods. This principle is illustrated in the following equation:

$$\begin{Bmatrix} R \\ S \end{Bmatrix} + R \longrightarrow \begin{Bmatrix} R\text{—}R \\ S\text{—}R \end{Bmatrix} \qquad \textbf{(5.8)}$$

pair of enantiomers (not separable)	chiral reagent	diastereomeric products (separable)

After the diastereomers are separated, we then carry out reactions that regenerate the chiral reagent and the separated enantiomers.

$$R\text{—}R \longrightarrow R + R \qquad \textbf{(5.9)}$$

and

$$S\text{—}R \longrightarrow S + R$$

Louis Pasteur was the first to resolve a racemic mixture when he separated the sodium ammonium salts of (+)- and (−)-tartaric acid. In a sense, he was the chiral reagent, since he could distinguish between the right- and left-handed crystals. In Chapter 11, we will see a specific example of how this is done chemically.

The principle behind the resolution of racemic mixtures is the same as the principle involved in the specificity of many biological reactions. That is, a chiral reagent (in a cell, usually an enzyme) can discriminate between enantiomers.

End of Chapter 5

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