

Isomers: The Same But Not The Same.

A most basic, and also most subtle, phenomenon of organic chemistry is that of *isomerism*, the existence of *different* molecules with the *same* composition.

In addition to the facts and concepts of isomerism I mention here some of the history of the development of the concepts.

I also give a few examples of the way the concepts of isomerism have been used to answer questions about the structures of molecules and about the mechanisms of reactions.

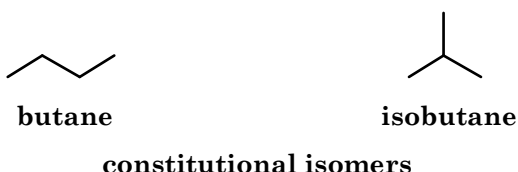
SOME OF THE FACTS, CONCEPTS, AND HISTORY OF ISOMERISM

TYPES OF ISOMERS

We usually distinguish three types of isomers. These are *constitutional* isomers, *stereoisomers* (also called *configurational isomers*), and *conformational* isomers.

Constitutional isomers

When the atoms of molecules with the same atomic composition are *differently connected* we speak of *constitutional isomers*. Butane and isobutane are examples.



Stereoisomers

When the atoms of molecules with the same composition are similarly connected but have *different permanent arrangements in space* we speak of *stereoisomers*, or *configurational isomers*.

Enantiomers

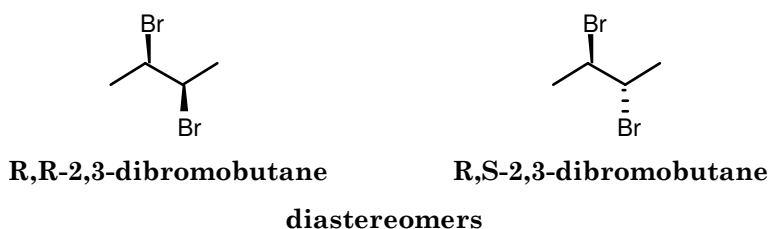
When the different arrangements in space *are* related as non-identical mirror images we call these stereoisomers *enantiomers*.



R-2-bromobutane **S-2-bromobutane**
enantiomers

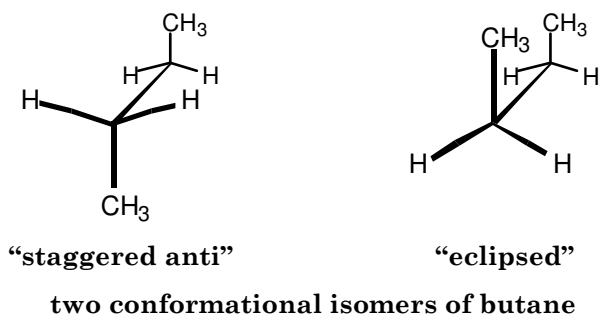
Diastereomers

When the different arrangements in space *are not* related as non-identical mirror images we call these stereoisomers *diastereomers*.



Conformational isomers

When the atoms of the molecules are identically connected, have the same permanent arrangement in space, or configuration, but have *different temporary arrangements in space* we speak of *conformational isomers*.



ENUMERATION OF ISOMERS

After recognizing the *existence* of isomers we then want to know the number of *possible* isomers. We can separate this question into two parts. The first part concerns the number of possible *constitutional* isomers for a particular composition, or molecular formula. The second part concerns the number of possible *stereoisomers* for a particular constitution.

Numbers of constitutional isomers

The question of the number of possible constitutional isomers was asked first of the alkanes, molecules of composition C_nH_{2n+2} . Cayle (reference 1), is given the credit for first addressing this question, in 1857, and Henze and Blair (reference 2) are generally given the credit for showing, in 1932, how to correctly answer the question. The question is still asked and answered at this time, as indicated by references 3 and 4.

References 2 and 5 present some of the history of this question and refer to many additional contributions to the answer.

The numbers of constitutional isomers of the alkanes

The numbers of possible constitutionally isomeric alkanes (C alkanes) of carbon number n from $n = 1$ to $n = 10$ are presented here. These numbers have been confirmed many times by drawing representations all of the possibilities and eliminating any duplicates; that is, these numbers have been confirmed by *enumeration*.

	Constitutionally Isomeric Alkanes									
carbon number, n	1	2	3	4	5	6	7	8	9	10
C alkanes	1	1	1	2	3	5	9	18	35	75

A natural question

A natural question is: Can you *calculate* (without enumeration) the number of possible alkane isomers with carbon number n ?

The unexpected answer

The answer to this question was provided by Henze and Blair (reference 2). They stated that “The problem was solved only by establishing a relationship between the number of isomeric hydrocarbons of a given carbon content and the previously calculated number of isomeric alcohols of lesser carbon contents.” The relationship involves a sum of terms and requires that “the total number of alkyl groups (i. e. the total number of isomeric alcohols) of $n/2$ and all lesser carbon contents must be known.”

The answer to the question is “Yes”, but the process is not as simple as merely substituting for n and solving.

Constitutional isomers of monosubstituted alkanes

As we just stated, Henze and Blair discovered that “the alcohol problem” had

to be solved prior to “the alkane problem.” Their method for calculating the number of possible constitutionally isomeric alcohols of molecular formula $C_nH_{2n+2}O$ is reported in reference 6. Their results, the numbers of possible constitutionally isomeric saturated alcohols (C alcohols) for carbon numbers from 1 to 10, are presented here (reference 6).

Constitutionally Isomeric Alcohols										
carbon number	1	2	3	4	5	6	7	8	9	10
C alcohols	1	1	2	4	8	17	39	89	211	507

These numbers also indicate the number of possible constitutional isomers of the monohaloalkanes, $C_nH_{2n+1}X$.

Comment

These numbers of “possible constitutional isomers” do *not include* possible stereoisomers, and do *not exclude* highly congested isomers.

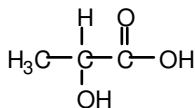
Numbers of stereoisomers

We turn now to the second part of the isomer question. The second part concerns the number of possible *stereoisomers* for a particular constitution.

The conception of stereoisomerism

The need for a concept beyond constitution was revealed by cases in which there were more isomers than constitutional possibilities. Wislicenus, referring in 1867 to the two isomers of lactic acid, described the situation in this way.

“This is the first definitely verified case in which the number of isomers can exceed the constitutional possibilities. Facts such as these will force us to explain differences between isomeric molecules with the same constitutional formula by different arrangements of these atoms in space, and to look for definite ideas on these arrangements.”



lactic acid; constitution only

Then, in 1874, van't Hoff and Le Bel both supplied the “definite ideas” that we use today: tetravalent carbon is tetrahedral, trivalent carbon is trigonal, and divalent carbon is linear.

Van't Hoff began his paper in this way:

“It appears more and more that the present constitutional formulas are incapable of explaining certain cases of isomerism; the reason for this is perhaps the fact that we need a more definite statement about the actual positions of the atoms.” (reference 7, p. 82)

Writing many years later about his conception of the tetrahedral carbon van't Hoff said:

“Students, let me give you a recipe for making discoveries. In connection with what has just been said about libraries, I might remark that they have always had a mind-deadening effect on me. When Wislicenus' paper on lactic acid appeared and I was studying it in the Utrecht library I ... broke off my study half-way through to go for a walk; and it was during this walk, under the influence of the fresh air, that the idea of the asymmetric carbon atom first struck me.” (reference 7, p. 82).

The ideas of van't Hoff and Le Bel were not greeted with enthusiasm. Kolbe, for example, reacted strongly against the new ideas as expressed by van't Hoff. One of Kolbe's more temperate sentences was:

“It is not possible, even cursorily, to criticize this paper, since its fanciful nonsense carefully avoids any basis of fact, and is quite unintelligible to the calm investigator...” (reference 7, p. 93)

Other chemists were more concerned with whether a concept was useful, rather than whether it was “really” true. Kekulé, for example, had written, in 1867:

“...The question whether atoms exist or not has but little significance in a chemical point of view, its discussion belongs rather to metaphysics. In chemistry we have only to decide whether the assumption of atoms is an hypothesis adapted to the explanation of chemical phenomena.” (reference 7, p. 93)

Richard Feynman makes the same point 100 years later:

“How do we *know* there are atoms? By one of the tricks mentioned earlier: we make the *hypothesis* that there are atoms, and one after another results come out the way we predict, as they ought to if things *are* made of atoms.” (reference 8, p. 19)

The possibilities for stereoisomerism

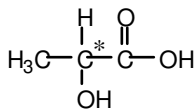
In order either to enumerate or to calculate the possibilities for stereoisomeric forms of a molecule with a given constitution we need to know about constitutional features that can lead to the existence of stereoisomers.

Stereogenic centers

Although configurational isomerism is a consequence of the total constitution of a molecule, there are features, *stereogenic centers*, that can indicate the possibility of configurational isomerism.

The “asymmetric carbon”

In the second of his quotations shown above van't Hoff speaks of the “asymmetric carbon”. He was referring to, in lactic acid for example, the presence of a carbon atom to which are bonded *four different atoms or groups of atoms*. In the case of lactic acid these four different atoms or groups of atoms are a hydrogen atom, a methyl group, an hydroxyl group, and a carboxyl group.



lactic acid; “asymmetric carbon” indicated by an asterisk

Van't Hoff saw that if carbon were tetrahedral lactic acid could then exist in either of two, non-superposable mirror image, *enantiomeric*, forms.



lactic acid; enantiomeric forms

We remember that Pasteur, in 1848, had proposed a connection between optically active isomers of equal but opposite optical rotatory power and the existence of these isomers as molecular enantiomers.

“Are the atoms of the right acid grouped on the spirals of a dextrogyrate helix, or placed at the summits of an irregular tetrahedron, or disposed according to some particular dissymmetric grouping or other? We cannot answer these questions. But it cannot be a subject of doubt that there exists an arrangement of the atoms in an dissymmetric order, having a non-superposable image. It is not less certain that the atoms of the left acid realize precisely the dissymmetric grouping which is the inverse of

this.” (reference 9)

Twenty six years later, as we have just seen, van't Hoff and Le Bel provided the atomic/molecular explanation for the existence of molecular enantiomers.

Chiral stereocenters on carbon

The term “asymmetric carbon” has now been replaced by the term “chiral stereocenter on carbon”. The presence of *exactly one chiral stereocenter on carbon* in the constitution of the molecules of a substance will guarantee that the substance can exist in exactly two stereoisomeric forms, in this case as *one pair of enantiomers*.

The converse is not true, however. A substance *can* exist in enantiomeric forms *without* the presence of a chiral stereocenter. The enantiomeric 2,3-pentadienes provide an example.



2,3-pentadiene; enantiomeric forms

Stereogenic double bonds

A suitably substituted carbon-carbon double bond can serve as an *achiral* stereocenter. There are, as indicated above, two stereoisomeric forms of 2-butene.



E-2-butene

Z-2-butene

diastereomers

In this case, however, the pair of isomers is not a pair of enantiomers but is a *pair of diastereomers*.

In order for a carbon-carbon double bond to be a stereogenic double bond each “end” of the double bond must bear two different substituents. If either end bears identical substituents (two hydrogen atoms, or two methyl groups, for example) the double bond will not be stereogenic.

The presence of *exactly one stereogenic carbon-carbon double bond* in the constitution of the molecules of a substance will guarantee that the molecules

can exist in exactly two stereoisomeric forms, in this case as *one pair of diastereomers*.

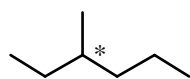
Stereoisomeric alkanes

We can now consider the possible existence of configurationally isomeric alkanes.

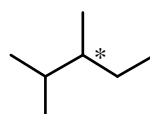
Since no alkane isomer of carbon number less than 7 contains a chiral stereocenter, all alkane isomers of carbon number 1 through 6 will be constitutional isomers.

For alkanes of carbon number 7 and greater, however, the existence of constitutional isomers that contain chiral stereocenters on carbon will cause the total of alkane isomers, constitutionally isomeric plus stereoisomeric alkanes, C+S alkanes, to be greater than the number of constitutionally isomeric alkanes, C alkanes.

For carbon number 7, for example, the constitutional isomers 3-methylhexane and 2,3-dimethylpentane each contain one chiral stereocenter on carbon. The number of constitutional isomers plus stereoisomers of carbon number 7 will therefore be 11, rather than 9.



3-methylhexane



2,3-dimethylpentane

The numbers of constitutionally isomeric and stereoisomeric alkanes, C+S alkanes, of carbon numbers 1 through 10 are presented here, along with, for comparison, the numbers of constitutionally isomeric alkanes, C alkanes.

Constitutionally and Stereoisomeric Alkanes

carbon number, n	1	2	3	4	5	6	7	8	9	10
C alkanes	1	1	1	2	3	5	9	18	35	75
C+S alkanes	1	1	1	2	3	5	11	24	55	136

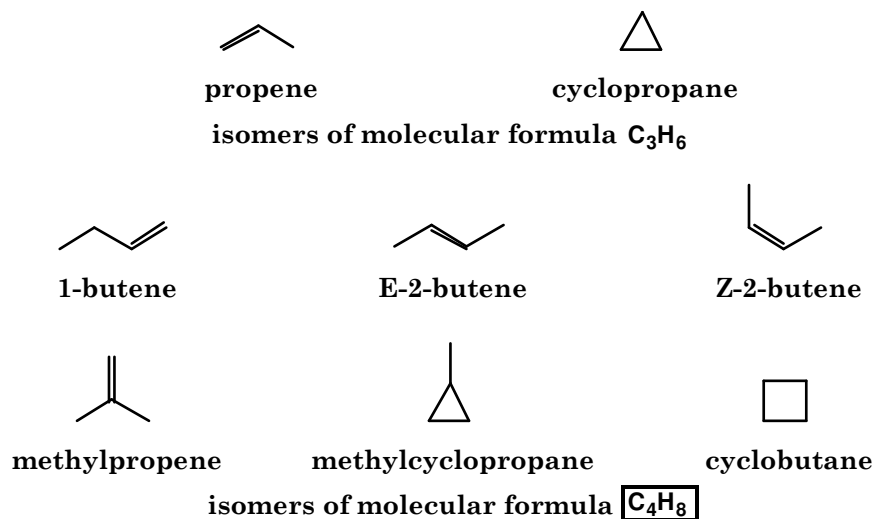
Isomers of molecular formula C_nH_{2n}

Before we continue with the possibilities for stereoisomerism we will briefly consider isomers of molecular formula C_nH_{2n} .

With two fewer hydrogen atoms than alkanes, molecules with molecular

formula C_nH_{2n} , or molecules with *one degree of unsaturation*, will have structures that contain one more carbon-carbon bond than the corresponding alkanes.

If we consider a carbon-carbon double bond to be a two-membered ring, we can say that molecules of molecular formula C_nH_{2n} will contain exactly one ring. Thus molecules of carbon number n can contain a ring with as few as 2 carbons (a double bond) or a ring with as many as n carbons. As examples there will be one isomer of molecular formula C_2H_4 , two of molecular formula C_3H_6 , and six of molecular formula C_4H_8 .



We can summarize and compare the total isomeric possibilities for alkanes and alkenes/cyclic alkanes in this way.

	Isomers of Molecular Formula C_nH_{2n+2} and C_nH_{2n}									
carbon number, n	1	2	3	4	5	6	7	8	9	10
C+S for C_nH_{2n+2}	1	1	1	2	3	5	11	24	55	136
C+S for C_nH_{2n}	0	1	2	6	13	38?	??			

NUMBERS OF STEREOISOMERS

We now continue with our consideration of the possibilities for the existence of stereoisomeric forms for molecules of a particular constitution.

Molecules with exactly one stereogenic feature

As we mentioned above, the presence of exactly one chiral stereocenter on

carbon will allow the molecule to exist in either of two enantiomeric forms, as R and S isomers. We also said that the presence of exactly one stereogenic carbon-carbon double bond will allow the molecule to exist in either of two diastereomeric forms, as Z and E isomers.

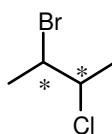
Molecules with two chiral stereocenters on carbon

There are two possibilities here that must be distinguished. For the first possibility the two chiral stereocenters are *differently* substituted. That is, if we make a list of the four different atoms or groups of atoms on the *two* chiral stereocenters, as was done for the one chiral stereocenter of lactic acid, the two lists will be *different*.

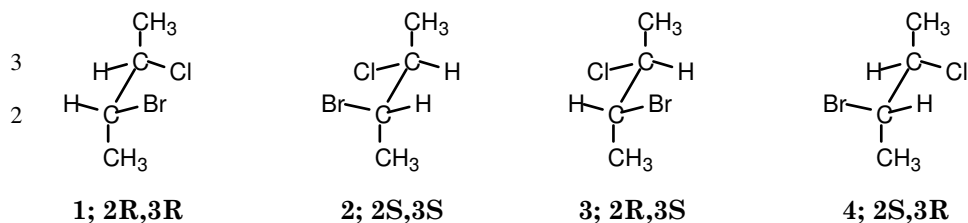
For the second possibility the two chiral stereocenters are *similarly* substituted. That is, if we make a list of the four different atoms or groups of atoms on the *two* chiral stereocenter, as was done for the one chiral stereocenter of lactic acid, the two lists will be *the same*.

Two chiral stereocenters differently substituted

If a molecule has two chiral stereocenters on carbon that are *differently* substituted the molecule can exist in *four* stereoisomeric forms; as two pairs of enantiomers. 2-Bromo-3-chlorobutane provides an example.



2-bromo-3-chlorobutane



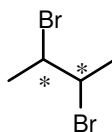
stereoisomeric forms of 2-bromo-3-chlorobutane

Isomers **1** and **2** are the first pair of enantiomers, and **3** and **4** are the second pair of enantiomers.

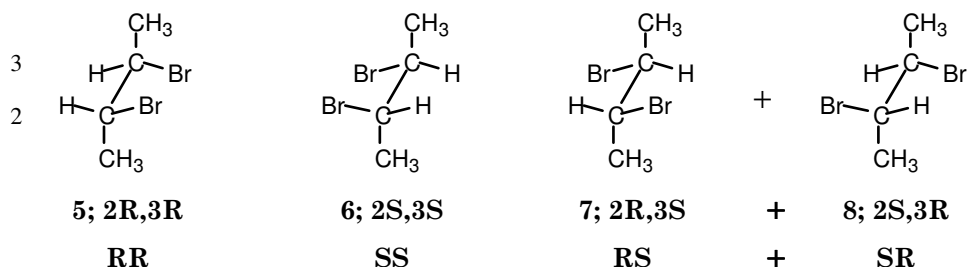
Two chiral stereocenters similarly substituted

If a molecule has two chiral stereocenters on carbon that are *similarly* substituted the molecule can exist in only *three* stereoisomeric forms; as *one*

pair of enantiomers and *one meso* form. 2,3-Dibromobutane provides the example.



2,3-dibromobutane



stereoisomeric forms of 2,3-dibromobutane

When the two chiral stereocenters on carbon are *similarly* substituted one of the potential pair of enantiomers turns out to be the same thing twice; there are actually only three stereoisomeric forms.

Molecules with more than two chiral stereocenters on carbon

Again, we must distinguish two possibilities. The first is that all the chiral stereocenters are differently substituted (typical), and the second is that this condition is not met (rare).

Chiral stereocenters are differently substituted

When this is true the number of stereoisomers doubles with the addition of another chiral stereocenter. The number of stereoisomers will be even, and the stereoisomers will occur as pairs of *enantiomers*. We can represent the pattern in this way:

Stereoisomers; chiral stereocenters are differently substituted

Chiral centers, n	0	1	2	3	4	5	6	7	8
Chiral forms	0	2	4	8	16	32	64	128	256
Meso forms	0	0	0	0	0	0	0	0	0
Total forms	1	2	4	8	16	32	64	128	256

The pattern can also be represented as:

$$\text{Total forms} = 2^n$$

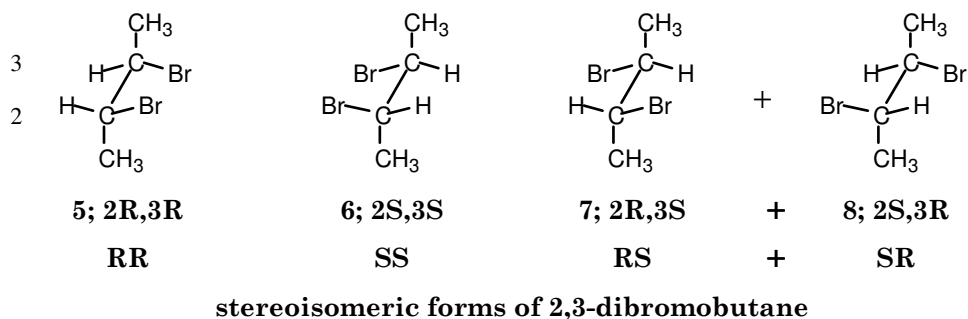
Chirality and symmetry

Most chiral objects are asymmetric; that is most chiral objects lack symmetry. Asymmetry, however, is *not a requirement* for chirality.

The requirement for chirality is the absence of any symmetry element whose associated operation involves reflection. Thus a chiral object *cannot* have a plane of symmetry, a center of symmetry, or a higher, even, improper axis of symmetry. A chiral object can, however, have an axis of symmetry.

Chiral stereocenters are similarly substituted

When the chiral stereocenters can be divided into two groups that are *similarly* substituted some stereoisomers will have a conformation that has either an axis of symmetry or a plane of symmetry. The stereoisomeric forms of 2,3-dibromobutane, shown above and again here, illustrates these possibilities.



Isomers **5** and **6** are chiral and are members of the pair of enantiomers. Each has a C_2 axis of symmetry in the conformation represented here. Isomer **7** is the meso form, and **8** is the identical mirror image of **7**, drawn as shown here to emphasize its mirror image relationship to **7**. Both **7** and **8**, in the conformation represented here, have a center of symmetry; the conformations in which the like atoms or groups are eclipsed would have a plane of symmetry.

The lesson we learn from this example is that when the chiral stereocenters of a molecule can be divided into two groups that are similarly substituted the number of possible stereoisomers will be less than the number that would be possible when the chiral stereocenters are differently substituted. Without showing more examples we can summarize the possibilities for 2 to 8 chiral stereocenters in this way:

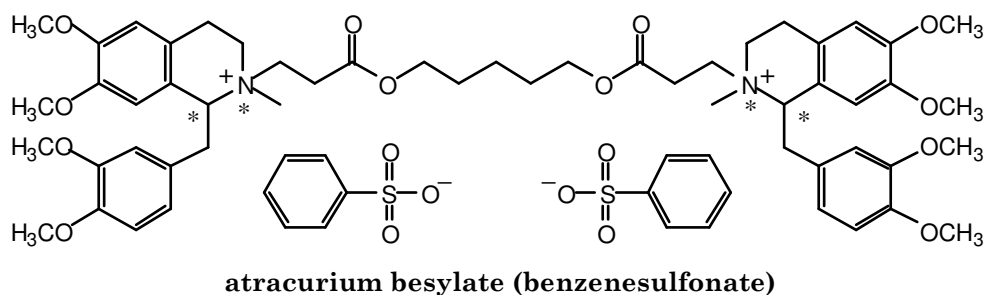
Stereoisomers; chiral stereocenters similarly substituted

Chiral centers, n	0	1	2	3*	4	5*	6	7*	8
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Chiral forms	-	-	2	2	8	12	32	56	128
Meso forms	-	-	1	2	2	4	4	8	8
Total forms	-	-	3	4	10	16	36	64	136

*The “middle center” is called a pseudoasymmetric center. It is split by the plane of symmetry of the meso forms.

Examples with 2 similarly substituted chiral stereocenters are quite common (“pair of enantiomers and a meso form”), but examples of the other possibilities are rather rare. An example of a substance with four chiral stereocenters, similarly substituted, is the muscle relaxant atracurium besylate, which can occur in ten stereoisomeric forms.



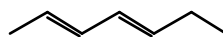
This substance is especially useful since its “metabolism” is independent of liver and kidney enzymes; it undergoes a “thermal” Hofmann elimination. The most active isomer is the R,R,R,R isomer, which is known as cisatracurium.

Molecules with two stereogenic double bonds

Again, we will distinguish two possibilities.

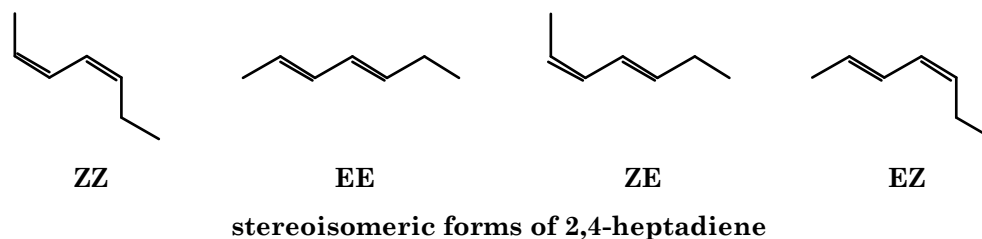
The two double bonds are differently substituted

2,4-Heptadiene provides a simple example:



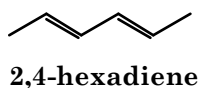
2,4-heptadiene

The double bonds are different; each can be either Z or E; there are 4 possible combinations: ZZ, EE, ZE, and EZ; there are four stereoisomeric forms. No molecule is chiral; all relationships are diastereomeric.

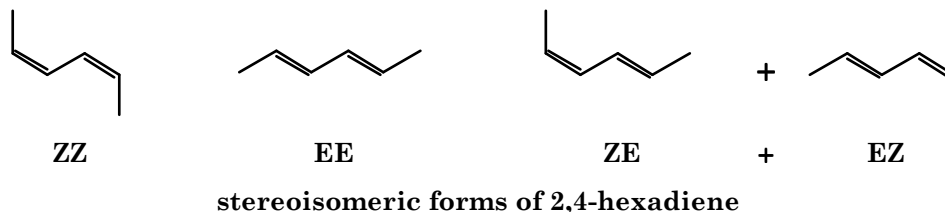


The two double bonds are similarly substituted

The double bonds will be similarly substituted when the ends are the same. 2,4-Hexadiene will then serve as an example:



This time there are only three combinations: ZZ, EE, and ZE, because ZE and EZ are the same; there are three stereoisomeric forms. Again, no molecule is chiral, and all relationships are diastereomeric.



Molecules with more than two stereogenic double bonds

An *unsymmetrical* triene can have 8 stereoisomeric forms, but a *symmetrical* triene can have only 6.

Molecules with both a chiral stereocenter on carbon and a stereogenic double bond

If the molecule is not constitutionally symmetric the number of possible stereoisomeric forms will be 2^n , where n is the number of chiral stereocenters on carbon plus the number of stereogenic double bonds. The stereoisomers will come as pairs of enantiomers. Thus if there is one chiral stereocenter on carbon and one stereogenic double bond there will be four possible stereoisomeric forms: a Z pair of enantiomers (the ZR and ZS isomers) and an E pair of enantiomers (the ER and ES isomers).

Cyclic alkenes

When the double bonds are in a small ring, the number of stereoisomeric

forms that actually can be made will be less than the number predicted for the open chain compounds.



cyclohexene



1,3-cyclohexadiene

only one stereoisomeric form is known

Molecular enantiomers and optical activity

As we have said, it was Pasteur who conceived of the connection between optical activity and molecular handedness, or chirality, and it was van't Hoff and Le Bel who saw that a tetrahedral geometry for the valences of carbon could account for the handedness of molecules that contained an "asymmetric carbon."

The fact of optical activity always indicates the presence of molecular handedness, but the absence of optical activity does not necessarily indicate the absence of molecular handedness, as we shall see now.

Molecular enantiomers and optical inactivity

Optical inactivity is associated with at least three types of sample: racemic mixtures, meso compounds, and members of sets of isomers none of which are chiral.

The optical inactivity of a racemic mixture

The optical inactivity of a racemic mixture is a consequence of the presence of equimolar amounts of the members of the pair of enantiomers. If either enantiomer is present in excess we can expect that the sample will be at least slightly optically active.

The optical inactivity of a meso form

The common assertion that "the meso form has a plane of symmetry and so it will be optically inactive" requires interpretation. If it is true that the molecules of the substance in the sample can achieve a conformation that has a plane or center of symmetry, it will then be true that the sample will contain equal numbers of the enantiomeric forms of all possible chiral conformations. It is for this reason that a sample of a meso compound will be optically inactive.

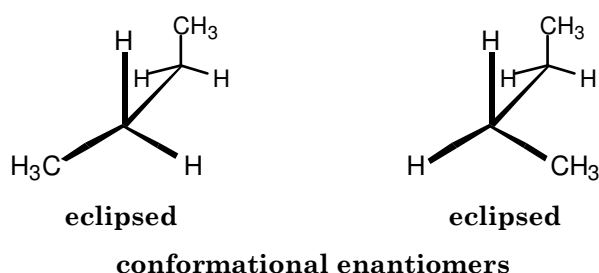
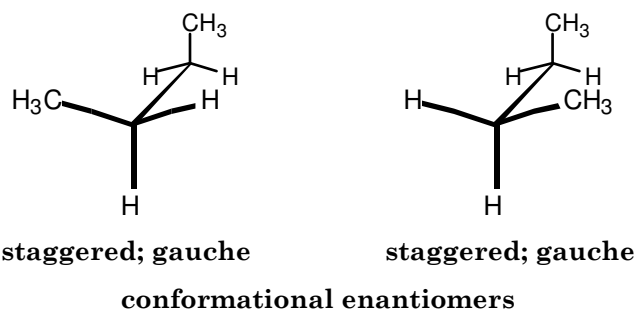
Thus we imagine that a picture of a million molecules taken at an instant

would reveal equal numbers of the various conformational enantiomers, and an occasional molecule either in a conformation that has a plane of symmetry or a conformation that has a center of symmetry. Alternatively we can imagine following one molecule around and making a video of its conformations over a microsecond. We would see that it spends equal amounts of time in the various enantiomeric conformations, and that it would occasionally assume a conformation that has a plane of symmetry or a conformation that has a center of symmetry.

The optical inactivity of an achiral substance

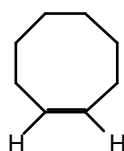
Most optically inactive, “achiral”, substances are actually racemic mixtures of chiral conformational enantiomers.

While butane molecules, for example, can exist in the two non-chiral conformations that were shown above, butane can also exist in many pairs of enantiomeric conformations such as the two pairs shown here. While butane is usually classified as achiral, it is more a racemic mixture of conformational enantiomers than it is a mixture of achiral molecules.



The three stereoisomeric cyclooctenes

There are three stereoisomeric cyclooctenes.



cyclooctene
three stereoisomeric forms

There is the *trans* pair of stable conformational enantiomers, and there is the *cis* isomer, which is classified as a meso form because it is an optically inactive member of a set of stereoisomers some of which are optically active.

A pair of stable conformational enantiomers

The *trans* form of cyclooctene can be resolved to give pure conformational enantiomers that are stable at room temperature.



cyclooctene; stable conformational enantiomers

Although these are conformational enantiomers their rates of interconversion at room temperature are low because it's hard for a vinyl hydrogen to rotate through the ring. Each isomer has a twofold axis of symmetry in the conformation shown above.

An optically inactive substance whose molecules are asymmetric

The *cis*, or *meso*, form of cyclooctene is not optically active. It undoubtedly consists of a racemic mixture of rapidly interconverting conformational enantiomers. This interconversion, however, is not likely to proceed by way of a transition state that has reflection symmetry. That is, every molecule, all the time, is chiral. The meso isomer does not have a plane of symmetry in any achievable conformation.

APPLICATIONS OF THE CONCEPT OF ISOMERISM

DETERMINATION OF CONSTITUTION AND CONFIGURATION

Contemporary problems in the determination of structure, both constitution and configuration, involve so many atoms that enumeration of the isomers and the elimination of all but one would be impossible.

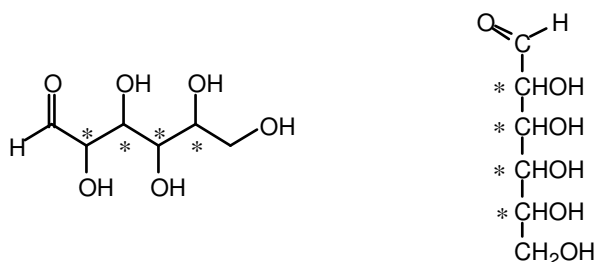
One of the most famous problems in the determination of "structure", however, was of this very nature, and this problem was the determination of the configuration of glucose. It is primarily for this accomplishment that we remember Emil Fischer (Reference 10).

The Fischer proof of the configuration of glucose

Fischer's "proof", published in 1891, opens with the following sentence (Reference 10).

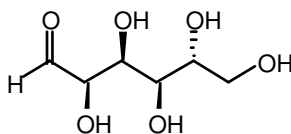
"All previous observations in the sugar group are in such complete agreement with the theory of the asymmetric carbon atom that the use of this theory as a basis for the classification of these substances seems justifiable."

Fischer knew that the composition of glucose was $C_6H_{12}O_6$ and that its constitution was 2,3,4,5,6-pentahydroxyhexanal. The remaining question, then, that Fischer set out to answer was: Which of the 16 possible stereoisomeric forms of 2,3,4,5,6-pentahydroxyhexanal represents glucose?



2,3,4,5,6-pentahydroxyhexanal; 16 possible stereoisomeric forms

Fischer was able to eliminate 14 possibilities and thus to narrow this field of 16 to 2, the members of one pair of enantiomers. Since it was impossible for him to determine which member of the pair of enantiomers should represent glucose he chose to represent glucose by what is known as the D member of the remaining pair of enantiomers. We know now that this arbitrary choice was correct.

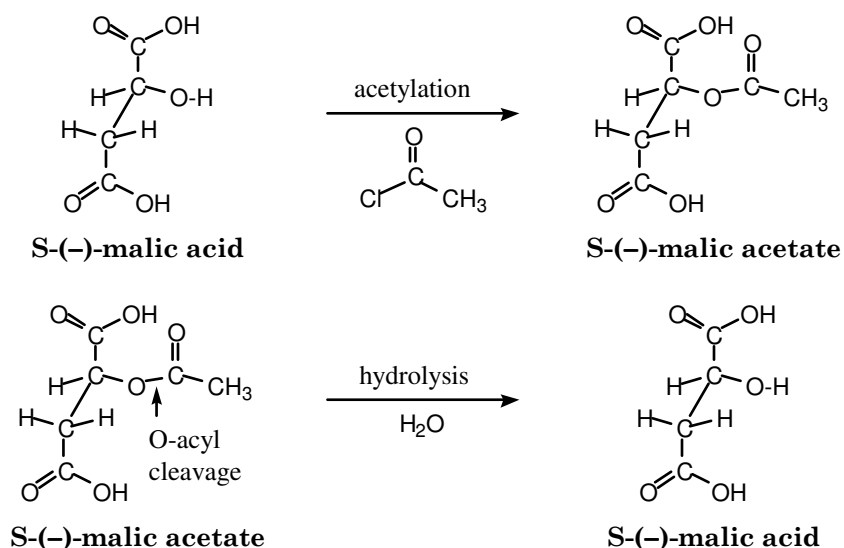


D-glucose; 2R,3S,4R,5R-2,3,4,5,6-pentahydroxyhexanal

As indicated in the quotation above, Fischer assumed that tetravalent carbon is tetrahedral, and his deductions were based on his understanding of the consequent relationships between stereoisomers that contained two, three, four, and more, chiral stereocenters on carbon, both differently and similarly substituted.

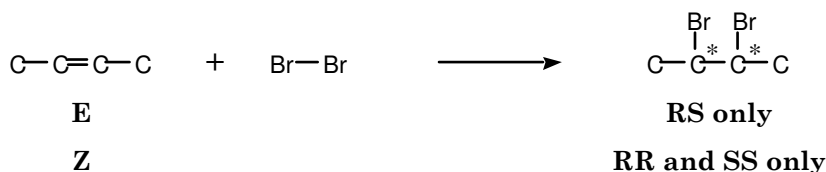
Fischer's brilliant analysis is presented in detail in Reference 10 and is summarized in several textbooks (References 11, 12, and 13). This achievement was ranked #3 in C&E News' list of "most beautiful"

acetylation of S(-)-malic acid with acetyl chloride, followed by hydrolysis. Since there are exactly two stereoisomers of malic acid and the same stereoisomer was recovered as was initially used, the number of inversions at the chiral stereocenter had to be either 0 or 2 or some other even number. Zero seemed most likely, indicating that the bond to oxygen at the chiral stereocenter had never been broken, and that, therefore, hydrolysis had taken place by O-acyl cleavage.



Overall *anti* addition of bromine to alkenes

The E isomer of 2-butene adds bromine to give only the RS isomer of 2,3-dibromobutane, and the Z isomer of 2-butene adds bromine to give only a racemic mixture of the R,R and S,S isomers of 2,3-dibromobutane (References 15, 16).



Each experiment indicates that the addition of bromine to 2-butene must take place by an overall *anti* mechanism. Since there are only two isomers of 2-butene, these experiments represent all possible outcomes. Any acceptable mechanism for this reaction must account for overall *anti* addition, and all mechanisms that would lead to overall *syn* addition can be ruled out. These results were the original reason for the conception of what is now known as the “cyclic bromonium ion” (Reference 15).

In other addition reactions of 2-butene, such as hydroxylation by

permanganate or osmium tetroxide, the *Z* isomer gives the meso form, and the *E* isomer gives the racemate. These experiments indicate that these two hydroxylation reactions must involve an overall *syn* mechanism.

The electrocyclic reactions

The electrocyclic reactions provide many more examples of reactions for which mechanistic insight is provided by the formation and fate of different isomers (Reference 17).

A comment on the Fischer Proof

Science advances most often by “ruling out” rather than by “ruling in.” This approach is sometimes called the “destructive testing of hypotheses”, “guess and test”, or, more eloquently, the method of “conjecture and refutation”. This method, however, can almost never reach a conclusion because there almost always remains the possibility that the results of the next experiment will be in conflict with the current hypothesis. That is, in general, hypotheses can never be proven to be true, only proven to be false. Thus it is only in a situation in which the number of possibilities is limited that one is able to reach a conclusion: all possibilities are known; all but one are ruled out. Fischer was able to *prove* that glucose was a member of a particular pair of enantiomers because there were exactly eight possibilities and he had ruled out seven.

COMPLETE SETS OF ISOMERS

Having considered the *possibilities* for isomerism, both constitutional and configurational, we might ask about the *actual existence* of complete sets of isomers.

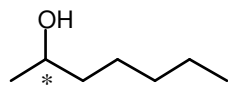
Complete sets of constitutional isomers

Complete sets of constitutional isomers are quite rare, and those that exist are most often sets of saturated alkanes and saturated alkyl halides. In 1966 G. W. Wheland (Reference 18) wrote that “The most complicated molecular formula for which all possible [constitutional] isomers have been prepared is probably C_9H_{20} , with altogether 35 nonequivalent [constitutions].” He also reported that “All 66 of the (constitutionally isomeric) octenes have been prepared...”.

Complete sets of stereoisomers

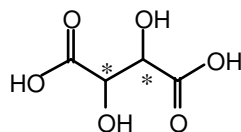
Isolation or preparation of complete sets of two, three, and four stereoisomers is quite common. The two 2-butenes, the two 2-octanols, the three tartaric

acids, and the four tetroses provide examples of complete sets of stereoisomers.



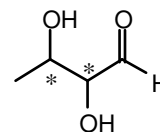
2-octanol

2 stereoisomeric forms



tartaric acid

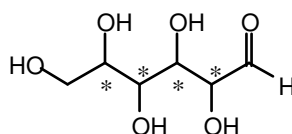
3 stereoisomeric forms



tetrose

4 stereoisomeric forms

More recently, in 1983, Masamuni and Sharpless directed the individual preparation of all eight of the L isomers of the aldohexoses.



aldohexose

8 D forms and 8 L forms

Use of the reagent with the opposite enantioselectivity in the first step would have led to the eight D isomers. Their approach is outlined on page 1011 of reference 13.

NUMBERS OF ISOMERS OF HIGH CARBON NUMBER

The On-Line Encyclopedia of Integer Sequences provides the numbers of isomers for alkanes and for alcohols with high carbon numbers, n (Reference 18). Some of that information is listed here.

n	Type	Isomers	Sequence Number
20	C alkanes	366 319	A000602 (18)
30	C alkanes	4 111 846 763	A000602 (18)
40	C alkanes	62 481 801 147 341	A000602 (19)
50	C alkanes	1 117 743 651 746 953 270	A000602 (19)
60	C alkanes	22 158 734 535 770 411 078 184	A000602 (19)
20	C alcohols	5 662 109	A000598 (18)
30	C alcohols	95 991 365 288	A000598 (18)
40	C alcohols	1 954 002 050 661 819	A000598 (19)
50	C alcohols	4 379 554 941 937 577 760	A000598 (19)
60	C alcohols	1 043 393 111 652 308 730 560 544	A000598 (19)

20	C&S alkanes	3 396 844	A000628 (18)
30	C&S alkanes	182 896 187 256	A000628 (18)

Summary

The need for concepts of isomerism

The need for concepts of isomerism arises from the fact that different substances can have the same composition; that is, different substances can be made up of the “same parts”.

Concepts of isomerism are applied in three steps

The concepts of isomerism are then applied in three steps. For a given *composition* there follows the question of the existence of *constitutional isomers*; for a given *constitution* there follows the question of *configurational isomers*; and for a given *configuration* there follows the question of *conformational isomers*.

The “Four Cs of Structure”

We could label this four-level hierarchy of atomic/molecular description the “Four Cs of Structure”: Composition, Constitution, Configuration, and Conformation. Here the word “structure” covers everything that could be said about the atomic/molecular nature of a substance; everything from composition through conformation.

Enantiomeric and diastereomeric relationships

For both configurational isomers and conformational isomers the only possible relationships between isomers are the enantiomeric relationship and the diastereomeric relationship. These are the only possibilities, and they are mutually exclusive. There is no need for the term “geometric isomers”.

The meso form

The meso form is an optically inactive member of a set of stereoisomers some of which (at least two of which) are optically active. This is an experimental definition, not a theoretical interpretation.

The absence of optical activity

The absence of optical activity does not preclude the presence of chiral molecules in the sample. Many optically inactive substances are racemic mixtures of conformational enantiomers.

Chirality and symmetry

Chirality is the consequence of the absence of a symmetry element whose associated operation involves reflection. Thus the absence of either a plane of symmetry, or a center of symmetry, or a higher order improper axis of rotation will permit the existence of enantiomers. Chiral molecules can contain an axis of symmetry.

Asymmetry, dissymmetry, and symmetry

Asymmetry implies the absence of both reflective and rotational symmetry. *Dissymmetry* implies the absence of reflective symmetry. Thus chiral objects can be either asymmetric or dissymmetric; chiral objects can have rotational symmetry. The word *symmetric* generally implies the presence of reflective symmetry.

Recommended reading

O. B. Ramsay's, *Stereochemistry* (Reference 7) and Kurt Mislow's *Introduction to Stereochemistry* (Reference 20) are especially useful and interesting.

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