**Stereochemistry**

**Isomerism**

Two or more compounds having same molecular formula and same or different structural formula but different physical or chemical properties are called isomers and this phenomenon is called isomerism.

The phenomenon of isomerism can be divided into two broad classes, constitutional isomerism and stereoisomerism.

**A) Constitutional Isomerism**

When the isomers have same molecular formula but different structural formula, then the isomers are called **Constitutional isomers** (structural isomers) and the phenomenon is called **Constitutional isomerism** (structural isomerism). In this case the two isomers differ in their connectivity. Structural isomerism is further divided into position isomerism, chain isomerism, functional group isomerism and metamerism.

**B) Stereo Isomerism**

Isomers that have same molecular and structural formula but different arrangement of atoms in three dimensional spaces are called stereo isomers and this phenomenon is called **stereoisomerism.** They differ in their physical or chemical properties.

Stereoisomerism can be further divided into two main branches.

**1) Configurational isomerism**

Stereoisomers that can be converted into each other only by making or breaking the bonds are called Configurational isomers. This type of isomerism is called Configurational isomerism.Changing the configuration of a molecule always mean that bonds are broken. A different configuration is a different molecule.

**2) Conformational isomerism**

Stereoisomers that can be converted into each other by just rotation about a single bond are called conformational isomers or conformers or rotamers. These can be converted without breaking or making bonds. This type of isomerism is called conformational isomerism.

In this chapter we will only discuss the **stereoisomerism**.

**1.1 Stereoisomerism**

***1.1.1 Configurational isomerism***

Configurational isomerism can be further divided into two types:

1-Optical Isomerism

2-Geomatrical Isomerism

**1-Optical Isomerism**

Before defining the optical isomerism, we will define some related terminologies.

**a) Enantiomers and Chiral molecules**

Two structures which are not identical but are mirror image of each other are called enantiomers and this phenomenon is called enantiomers.

Structures which are not super imposable on their mirror image and thus can exist as two enantiomers are called chiral and this phenomenon is called chairality.

Consider the following reaction between aldehyde and cyanide ion.



We will expect that only one product is formed. But actually two different products are formed.

**b) Chirality & Achirality**

Actually the carbonyl group has two faces. The cyanide ion could attack from either side, giving in each case, a different product.



These two structures are mirror images of each other both of which are not super imposable upon each other. It means that they are not identical. So these are chiral molecules which are called enantiomers of each other.



Now consider the following reaction between acetone and cyanide ion. Again the two products are formed by attacking the cyanide ion from front or from the back side.



However when one of the structure is rotated and matched, it comes to know that they are superimposable on to each other. So they are identical structures. Structures that are superimposable on their mirror images are called achiral and this phenomenon is called achirality.

**c) Plane of symmetry**

An imaginary plane that cuts a molecule into two identical halves, both of whcih is superimposable on to each other is called plane of symmetry. A molecule having this plane is called symmetrical molecules. All molecules having no plane of symmetry are called asymmetrical molecules.

A plane of symmetry is a major difference between chiral and achiral molecules.

Consider the following structures. Acetone cyanohydrin has a plane of symmetry running through the molecule.

  

This plane cuts the molecule into two identical halves. On the other hand aldehyde cyanohydrin has no plane of symmetry. So cutting the molecule into two halves will produce two different halves which will not be superimposable on to each other. So this compound is unsymmetrical and has two enantiomers.

It means that any structure that has no plane of symmetry ( asymmetrical ) is chiral and can exist as two mirror-image forms (enantiomers).

On the other hand, any structure with a plane of symmetry (symmetrical) is achiral and cannot exist as two enantiomers.

**d) Stereogenic or Chiral centre**

If a molecule contains one carbon atom carrying four different groups, it will not have a plane of symmetry and must therefore be chiral. A carbon atom carrying four different groups is a stereogenic or chiral centre.

If we consider the structure of aldehyde cyanohydrin, we come to know that it is unsymmetrical (Chiral) because it contains one tetrahedral carbon with four different groups. Such a carbon is called stereogenic or chiral centre.

**Fischer Projections**

Fischer developed a symbolic way of drawing asymmetric carbon atoms. Fischer projection looks like a cross with the asymmetric carbon at the point where two lines cross. Fischer projections are written with the main carbon chain extending from top to bottom. The horizontal lines are taken to be wedges that are bonds that project out toward the viewer. The vertical lines are taken to project away from the viewer, as dashed lines.

Fischer projections are so unlike real molecules that you should never use them. However, you may see them in older books, and you should have an idea about how to interpret them.



**e) *R* and *S* configuration of a chiral centre**

Before going on to talk about single enantiomers of chiral molecules in more detail, we need to

explain how chemists explain which enantiomer they’re talking about. For this purpose we can use the following set of rules to assign a letter, *R* or *S*, to describe the configuration of groups at a chiral centre in the molecule.

**Rules for assigning *R* and *S* configuration**

Here again is the enantiomer of alanine you get if you extract alanine from living things.

**1-** Assign a priority number to each substituent at the chiral centre. Atoms with higher atomic

numbers get higher priority.

Alanine’s chiral centre carries one N atom (atomic number 7), two C atoms (atomic number 6),

and one H atom (atomic number 1). So, we assign priority 1 to the NH2 group, because N has the highest atomic number. Priorities 2 and 3 will be assigned to the CO2H and the CH3 groups, and priority 4 to the hydrogen atom; but we need a way of deciding which of CO2H and CH3 takes priority over the other. If two (or more) of the atoms attached to the chiral centre are identical, then we assign priorities to these two by assessing the atoms attached to those atoms. In this case, one of the carbon atoms carries oxygen atoms (atomic number 8), and one carries only hydrogen atoms (atomic number 1). So CO2H is higher priority that CH3; in other words, CO2H gets priority 2 and CH3 priority 3.

**2-** Arrange the molecule so that the lowest priority substituent is pointing away from you.

In our example, naturally extracted alanine, H is priority 4, so we need to look at the molecule

with the H atom pointing into the paper, like this.

**3-**Mentally move from substituent priority 1 to 2 to 3. If you are moving in a clockwise manner,assign the label *R* to the chiral centre; if you are moving in an anticlockwise manner, assign thelabel *S* to the chiral centre.

A good way of visualizing this is to imagine turning a steering wheel in the direction of the

numbering. If you are turning your car to the right, you have *R*; if you are turning to the left you have *S*. For our molecule of natural alanine, if we move from NH2 (1) to CO2H (2) to CH3 (3) we’re going anticlockwise (turning to the left), so we call this enantiomer (*S*)-alanine.

**Is there a chemical difference between two enantiomers?**

These two enantiomers are chemically identical. Take (*S*)-alanine (in other words, alanine extracted from plants) and (*R*)-alanine (the enantiomer found in bacterial cell walls) as examples. They both have identical NMR spectra, identical IR spectra, and identical physical properties, with a single important exception. If you shine plane-polarized light through a solution of (*S*)-alanine, you will find that the light is rotated to the right. A solution of (*R*)-alanine rotates plane-polarized light to the left. Racemic alanine, on the other hand, will not rotate the plane polarized light to any direction.

**Optical isomerism**

Compounds that rotate the plane polarized light to the same extent but in opposite directions are called optical isomers and this phenomenon is called optical isomerism.

**Optical Activity**

The property of rotating a plane polarized light is called optical activity.

**Polimetry**

Observation of the rotation of plane-polarized light is known as polarimetry; it is a straightforward way of finding out if a sample is racemic or if it contains more of one enantiomer than the other. Polarimetric measurements are carried out in a polarimeter, which has a single-wavelength (monochromatic) light source with a plane-polarizing filter, a sample holder, where a cell containing a solution of the substance under examination can be placed, and a detector with a read-out that indicates by how much the light is rotated. Rotation to the right is given a positive value, rotation to the left a negative one.

**Specific rotation**

*Specific rotation is the rotation produced by one cm length of solution with a concentration of 1 g per cm3 for particular wave length at a given temperature.*

The angle through which a sample of a compound (usually a solution) rotates plane-polarized light depends on a number of factors, the most important ones being the path length (how far the light has to pass through the solution), concentration, temperature, solvent, and wavelength. Typically, optical rotations are measured at 20 °C in a solvent such as ethanol or chloroform, and the light used is from a sodium lamp, with a wavelength of 589 nm.

The observed angle through which the light is rotated is given the symbol a. By dividing this value by the path length *l* (in dm) and the concentration *c* (in g dm–3) we get a value, [α] which is specific to the compound in question.

Most [α] values are quoted as [α]D (where the D indicates the wavelength of 589 nm, the ‘D line’ of a sodium lamp) or [α]D20, the 20 indicating 20 °C. These define the remaining variables.

Here is an example. A simple acid, known as mandelic acid, can be obtained from almonds in an

enantiomerically pure state. 28 mg was dissolved in 1 cm3 of ethanol and the solution placed in a 10 cm long polarimeter cell. An optical rotation of – 4.35° was measured (that is, 4.35° to the left) at 20 °C with light of wavelength 589 nm.

**What is the specific rotation of the acid?**

First, we need to convert the concentration to grams per cubic centimeter: 28 mg in 1 cm3 is the same as 0.028 g cm–3. The path length of 10 cm is 1 dm, so

[α]D20 = = = 155.4 

**Enantiomers can be described as (+) or (–)**

On the basis of optical rotation, we can classify the enantiomers into two types; each of this type can rotate the plane-polarized light in opposite directions

The enantiomer that rotates the plane-polarized light to the right (gives a positive rotation) is called the **(+)-enantiomer** (or the *dextrorotatory* enantiomer) and the enantiomer that rotates plane-polarized light to the left (gives a negative rotation) the **(–)-enantiomer** (or the *laevorotatory* enantiomer). The direction in which light is rotated is not dependent on whether a stereogenic centre is *R* or *S*. An (*R*) compound is equally as likely to be (+) as (–) of course, if it is (+) then its (*S*) enantiomer must be (–). The enantiomer of mandelic acid we have just discussed, for example, is *R*-(–)-mandelic acid, because its specific rotation is negative, and (*S*)-alanine happens to be *S*-( +)-alanine. The labels (+) and (–) were more useful before the days of X-ray crystallography, when chemists did not know the actual configuration of the molecules they studied, and could distinguish two enantiomers only by the signs of their specific rotations.

**Racemization**

An equimolar mixture of pair of enantiomers is called racemate or racemic mixture. It is expressed by a symbol (dl).

Conversion of an optically active compound (enantiomer) into an equimolar mixture of its enantiomers is known as Racemization. A racemic mixture is does not show optical activity. It behaves like a single compound and has sharp M.P and constant B.P.

1) When a chiral compound is prepared from an achiral compound, the product is always a racemic mixture provided the reagent and reaction conditions are all symmetrical. For example the bromination of propanoic acid at the 2-position gives)-2-bromopropanoic acid, although a chiral carbon is created as a result of reaction.



2) The general method for the creation of asymmetric carbon or Racemization is that first breaks one of the bonds of the tetrahedral carbon and then makes it again tetrahedral carbon. The breaking of the bond will convert the sp3 hybridized tetrahedral carbon to sp2 hybridized planar carbon. During this process, asymmetric tetrahedral carbon will be converted into symmetric planar trigonal carbon. When the group becomes attached with this planar molecule, it can attack from both sides, as a result both of the enantiomers are produced in equal amounts and so a racemic mixture will be produced. When the group attacks from the same side, it is called retention of configuration. When the group attacked from the opposite side to form other enantiomers, it is called inversion of configuration. For example when a solution of one of the enantiomers of, say (S)-2-iodobutane is treated with a solution of NaI, an Iodide ion displaces the originally present iodide ion from back side, so that the opposite enantiomer (R)-2-iodobutane is produced. This again, then reacts in reverse manner with any other iodide ion to regenerate (S)-2-iodobutane. Eventually a point is reached when the equal amount of both enantiomers are in dynamic equilibrium in equal amounts to form racemic mixture.



Racemization occurs readily with compounds having some unsaturated function adjacent of a chiral carbon atom carrying a hydrogen atom that can undergo a tautomeric change. For example in lactic acid a carboxyl group is adjacent to symmetric carbon atom carrying hydrogen.



Racemization, in this case, takes place through the formation of an enol, which then converts into other enantiomer. The changes in this case are reversible, and the equilibrium thus obtained the racemic mixture of the acid that is (+) and (-) lactic acid.

**Relative and absolute configuration**

Before the development of X-ray crystallography and other sophisticated characterization techniques, chemists had to discover the detailed structure and stereochemistry of molecules by a complex series of degradations. A molecule was gradually broken down into its constituents, and from the products that were formed the overall structure of the starting molecule was deduced. This is called absolute configuration.

As far as stereochemistry was concerned, it was possible to measure the specific rotation of a compound, but not to determine its configuration.

However, by using series of degradations it was possible to tell whether certain compounds had the same or opposite configurations. This is called relative configuration.

 

Glyceraldehyde is one of the simplest chiral compounds in nature. Because of this, chemists

took it as a standard against which the configurations of other compounds could be compared.

The two enantiomers of glyceraldehyde were given the labels D (for dextro—because it was

the (+)-enantiomer) and L (for laevo—because it was the (–)-enantiomer). Any enantiomerically

pure compound that could be related, by a series of chemical degradations and transformations,

to D-(+)-glyceraldehyde was labelled D, and any compound that could be related

to L-(–)-glyceraldehyde was labelled L. The processes concerned were slow and laborious.

D and L are now used only for certain well known natural molecules, where their use is established by tradition, for example, the L-amino acids or the D-sugars. These labels, D and L, are in *small* *capital* letters.

**Diastereomers**

Stereoisomers that are not mirror images of one another are called **diastereoisomers**.

As we know that two enantiomers are chemically identical because they are mirror images of one another. However, other types of stereoisomers may be chemically (and physically) quite different. There are two types of compounds in which diastereoisomerism can be found, in geometrical isomers and in chiral compounds.

For example, these two alkenes, for example, are geometrical isomers (or *cis*–*trans* isomers). Their physical chemical properties are different, as you would expect, since they are quite different in shape.

A similar type of stereoisomerism can exist in cyclic compounds. In one of these 4-*t*-butylcyclohexanols the two similar substituents are on the same side of the ring; in the other, they are on opposite sides of the ring. Again, the two compounds have chemical and physical properties that are quite different. These two pairs of diastereoisomers are **achiral because** they each had a plane of symmetry through the molecule (they are symmetrical).

 

Stereoisomers that are not mirror images of one another are called **diastereoisomers**. Both of

these pairs of isomers fall into this category. Notice how the physical and chemical properties of a pair of diastereoisomers differ.

**Diastereomers can be chiral or achiral**

Second type of compounds in which diastereoisomerism may be found can be chiral or achiral.



This pair of epoxides was produced by chemists in Pennsylvania in the course of research on drugs intended to ease the symptoms of asthma. Clearly, they are not mirror images of each other, so they are diastereoisomerism, and have different properties. Although the reaction they were using to make these compounds gave some of each diastereoisomer, the chemists working on these compounds only wanted to use the first (*trans*) epoxide. They were able to separate it from its *cis* diastereoisomer by chromatography because the diastereoisomers differ in polarity.

These two diastereoisomers are a little more complex than the examples above. This pair of diastereoisomers is chiral. We know this because they do not have a plane of symmetry and we can check that by drawing the mirror image of each one: it is not superimposable on the first structure.

If a compound is chiral, it can exist as two enantiomers. We’ve just drawn the two enantiomers of each of the diastereoisomers of our epoxide.



This set of four structures contains two diastereoisomers (stereoisomers that are not mirror images). These are the two different chemical compounds, the *cis* and *trans* epoxides, that have different properties. Each can exist as two enantiomers (stereoisomers that are mirror images) indistinguishable except for rotation. We have two pairs of diastereoisomers and two pairs of enantiomers. When you are considering the stereochemistry of a compound, always distinguish the diastereoisomers first and then split these into enantiomers if they are chiral.

In fact, the chemists working on these compounds wanted only one enantiomer of the *trans*

epoxide—the top left stereoisomer. They were able to separate the *trans* epoxide from the *cis*

epoxide by chromatography, because they are diastereoisomers. However, because they

had made both diastereoisomers in the laboratory from achiral starting materials, both diastereoisomers were racemic mixtures of the two enantiomers. Separating two enantiomer of epoxide was much harder because enantiomers have identical physical and chemical properties.

**Diastereoisomers can arise when structures have more than one stereogenic centre**

When we analyze our set of four stereoisomers a little more closely, we come to know that these structures all contain stereogenic centers—two in each case, as given below:



It means that **any compound with more than one stereogenic centre can exist in more than one diastereoisomeric forms. To go from one *enantiomer* to another, *both* stereogenic centers are inverted. To go from one *diastereoisomer* to another, only *one* of the two is inverted.**

Now we take another example. Both ephedrine and pseudoephedrine are members of the amphetamine class of stimulants, which act by imitating the action of the hormone adrenaline. Ephedrine and pseudoephedrine are stereoisomersthat are clearly not mirror images of each other—only one of the two stereogenic centers in ephedrine is inverted in pseudoephedrine—so they must be diastereoisomers.



Now consider the case with more than two stereogenic centers. The family of sugars provides

lots of examples. Ribose is a 5-carbon sugar that contains three stereogenic centers. The enantiomer shown here is known as D-ribose. The three stereogenic centers of D-ribose have the *R* configuration.



In theory we can work out how many ‘stereoisomers’ there are of a compound with three stereogenic centre simply by noting that there are 8 (=23) ways of arranging *R*s and *S*s.

*RRR RRS RSR RSS*

*SSS SSR SRS SRR*



However, this method cannot distinguish between diastereoisomers and enantiomers. In each case, the combination in the top row and the combination directly below it are enantiomers (all three centers are inverted); the four columns are diastereoisomers. Three stereogenic centers therefore give four diastereoisomers, each a pair of two enantiomers. As we know that there’s a simple mathematical relationship between the number of stereogenic centers and the number of stereoisomers a structure can have. Usually, a structure with *n* stereogenic centers can exist as 2*n* stereoisomers. These stereoisomers consist of 2(*n* – 1) diastereoisomers, each of which has a pair of enantiomers. This is an oversimplification to be used cautiously because it works only if all diastereoisomers are chiral. We recommend that you find out how many diastereoisomers there are in every new molecule before considering enantiomers.

**Why only *usually*?—achiral compounds with more than one stereogenic centre**

Sometimes, symmetry in a molecule can cause some stereoisomers to be degenerate, or ‘cancel

out’—there aren’t as many stereoisomers as you’d expect. Take tartaric acid, for example.



Tartaric acid is found in grapes and has two stereogenic centre, so we expect 22 = 4 stereoisomers; two diastereoisomers, each a pair of enantiomers. While the pair of structures on the right is certainly enantiomers, if you look carefully at the pair of structures on the left, you’ll see that they are, in fact, not enantiomers but identical structures. To prove it, just rotate the top one through 180° in the plane of the paper.

*R,S*-Tartaric acid and *S,R*-tartaric acid are not enantiomers, but they are identical because, even

though they contain stereogenic centers, they are achiral. By Cutting *R,S*-tartaric acid, and *S,R*-tartaric acid in the middle, two parts are formed which are mirror image of each other. It means that these are symmetrical and so must be achiral.

The formula stating that a compound with *n* stereogenic centers has 2*n* – 1 diastereoisomers has worked but not the formula that states there are 2*n* ‘stereoisomers’. In general, it’s safer not to talk about ‘stereoisomers’ but to talk first about diastereoisomers and then to assess each one for enantiomers. So tartaric acid can exist as two diastereoisomers, one with two enantiomers and the other achiral (a *meso* compound). Since the molecule has symmetry, the RS and SR diastereoisomer cannot be chiral.

**Meso Compounds**

Compounds that contain stereogenic centers but are themselves achiral are called *meso* compounds. This means that there is a plane of symmetry with *same* stereochemistry on both sides.

**Separating enantiomers is called resolution**

Separation of the components of a racemic mixture into its two enantiomers is called **resolution**.

There are two general methods for the resolution of a racemic mixture.

**1) Mechanical separation**

This method is used for the solid enantiomers which can form well defined crystals which can be distinguished. Pasture used this method to separate the enantiomers of sodium ammonium tartarate. This method can be used for those racemic mixtures which on crystallization give two types of crystals, one for each enantiuomers. These two types of crystals are then picked by hand with the help of a pair of tweezer and a lens. In some cases only one form is obtained.

**2) Chemical methods**

Resolutions by chemical methods can be carried out only if we make use of a component that is already enantiomerically pure: it is very useful that Nature provides us with such compounds.

**i) Conversion into Diastereomers**

Imagine the reaction between a chiral, but racemic alcohol and a chiral, enantiomerically pure carboxylic acid, to give an ester in an ordinary acid-catalyzed Esterification.



The product contains two chiral centers and we will get two diastereoisomeric products, each one will be enantiomerically pure. If we now hydrolyse each diastereoisomer separately, we can separate the two enantiomers of the starting alcohol. Diastereoisomers have different physical properties, so they should be easy to separate, for example by chromatography. We could then reverse the esterification step, and hydrolyse either of these diastereoisomers, to regenerate enantiomerically pure alcohol and acid.

**Example from an acid**.

Chemists have synthesized following amino acid in racemic form. The racemic amino acid was reacted with acetic anhydride to make the mixed anhydride and then with the sodium salt of naturally derived, enantiomerically pure alcohol menthol to give two diastereoisomers of the ester. (see next page).

One of the diastereoisomers turned out to be more crystalline (that is, to have a higher melting point) than the other and by allowing the mixture to crystallize, the chemists were able to isolate a pure sample of this diastereoisomer. Evaporating the diastereoisomer left in solution (the ‘mother liquors’) gave them the less crystalline diastereoisomer.

Next the esters were hydrolysed by boiling them in aqueous KOH. The acids obtained were enantiomers, as shown by their (nearly) opposite optical rotations and similar melting points



**ii) Differential absorption**

When a racemic mixture is poured in a chromatographic column, if the column contains a chiral substance, then the two enantiomers should move at different rates through column. In this way these can be separated without converting them into disteromers. For example racemic mandelic acid can be resolved into enantiomers by column chromatography on starch.

**Chiral compounds with no stereogenic centers**

A few compounds are chiral, yet have no stereogenic centers.

1) First we take the example of **allene** which has no stereogenic center.

Allene or cumulated dienes are those in which the bonds appear at successive carbon atoms, and one carbon is a part of two double bonds. Allenes are the compounds with no chiral carbon, however some substituted allenes exhibit optical isomerism. The planes of the pi bonds of allenes are perpendicular to each other. Because of this, allenes with different substituents on the end carbons are chiral.



These mirror images (enantiomers) are not superimposable and so the allene is chiral.

2) Similarly, some substituted **biphenyl compounds** exist as two separate enantiomers if the two phenyl rings are permanently noncoplanar. When the substituents at the ortho positions of the phenyl rings in a biphenyl compound are large and prevent the rotation about the bond joining the two phenyl rings, these biphenyls then can show optical isomerism. For example 2,2’-disulphonic acid exists in two enantiomeric forms.



**3) Spiranes**

Compounds having a carbon atom common to two rings are called Spiranes. These have a similar structure as in allenes. These two rings are perpendicular to each other. So properly substituted Spiranes can show optical isomerism as given below.



**Stereoselective or stereospecific**

Stereoselective reactions give one predominant product because the reaction pathway has a choice. Either the pathway of lower activation energy is preferred (kinetic control) or the more stable product (thermodynamic control).

Reactions in which the stereochemistry of the product is determined by the stereochemistry of the starting material are called stereospecific.

**Asymmetric synthesis**

As it is clear from the title, synthesis in which one or more chiral or stereogenic centers are produces is called asymmetric synthesis.

When we create a new stereogenic centre in a previously achiral molecule using achiral reagents (addition of CN– to aldehydes was the example you met eaelier), we get a racemic mixture because the transition states leading to the two enantiomers are themselves enantiomeric and therefore equal in energy.

However in diastereoselective synthesis, transition states for both of the diastereoisomers have different energy and therefore favouring the formation of one diastereoisomer over another.

Here is a simple example: PhLi adds to this ketone to give one diastereoisomer of the tertiary alcohol and not the other. Attack on one or other face of the ketone leads to diastereomeric transition states. This is perhaps most obvious when you realize that one is axial and one equatorial attack. As the equatorial attack is favourable ( trans product with ee is more favourable than cis with ea) so one of the diastereoisomers is formed.



An energy diagram for this type of reduction is given below.

In resolution, we attach a pure enantiomer to the racemic substrate. In this way two diastereoisomers are produced instead of two enantiomers. As these diastereoisomers are chemically different, so these can be separated.

We can use this same idea to make two enantiomeric (and therefore equal in energy) *transition states* into diastereoisomeric ones (which will therefore be unequal in energy)? If we can, the lower-energy transition state will be favoured and we will get more of one enantiomer than the other.

For this method we just need an enantiomerically pure molecule or part of a molecule that will be present during the reaction and will interact with the transition state of the reaction in such a way that it controls the formation of the new stereogenic centre. This molecule might be a reagent or a catalyst, or it might be covalently attached to the starting material. We will consider all of these possibilities, the last first, and you will see that they really are the most powerful and versatile ways of making enantiomerically pure compounds.

**Chiral auxiliaries**

The product of a Diels–Alder reaction between cyclopentadiene and benzyl acrylate must necessarily be racemic as both reagents are achiral. Though only one *diastereoisomer*—the *endo* product—is formed, it must be formed as an exactly 50:50 mixture of *enantiomers*.



Now see what happens if we replace the achiral benzyl ester group with an amide derived from the natural amino acid valine (Chapter 49). The diastereoselectivity remains the same but the chiral environment created by the single enantiomer covalently bonded to the dienophile has a remarkable effect: only one enantiomer of the product is formed.



**2) Conformational isomerism**

The isomerism produced by the rotation about the same bond is called conformational isomers and these types of isomers are called conformational isomers or rotamers.

**Conformations of ethane**

As we know that the rate of a chemical process is associated with an energy barrier (this holds both for reactions and simple bond rotations): the lower the rate, the higher the barrier. Rotation about single bonds is much faster than others at room temperature, but there is still a barrier to rotation in ethane, for example, of about 12 kJ mol–1**.**

Why should there be an energy barrier in the rotation about a single bond? In order to answer this question, we should start with the simplest C–C bond possible—the one in ethane. Ethane has two extreme conformations called the **staggered** and **eclipsed conformations**. Three different views of these are shown below.

