Objectives

After completing this section, you should be able to

1. use molecular models to show that only a tetrahedral carbon atom satisfactorily accounts for the lack of isomerism in molecules of the type CH₂XY, and for the existence of optical isomerism in molecules of the type CHXYZ.

2. determine whether two differently oriented wedge-and-broken-line structures are identical or represent a pair of enantiomers.

Key Terms

Make certain that you can define, and use in context, the key term below.

• enantiomer

Study Notes

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of their most interesting type of isomer is the mirror-image stereoisomers, a non-superimposable set of two molecules that are mirror image of one another. The existence of these molecules are determined by concept known as chirality. The word “chiral” was derived from the Greek word for hand, because our hands display a good example of chirality since they are non-superimposable mirror images of each other.

Introduction

The opposite of chiral is achiral. Achiral objects are superimposable with their mirror images. For example, two pieces of paper are achiral. In contrast, chiral molecules, like our hands, are non superimposable mirror images of each other. Try to line up your left hand perfectly with your right hand, so that the palms are both facing in the same directions. Spend about a minute doing this. Do you see that they cannot line up exactly? The same thing applies to some molecules
A Chiral molecule has a mirror image that cannot line up with it perfectly- the mirror images are non superimposable. The mirror images are called enantiomers. But why are chiral molecules so interesting? A chiral molecule and its enantiomer have the same chemical and physical properties (boiling point, melting point, polarity, density etc...). It turns out that many of our biological molecules such as our DNA, amino acids and sugars, are chiral molecules.

It is pretty interesting that our hands seem to serve the same purpose but most people are only able to use one of their hands to write. Similarly this is true with chiral biological molecules and interactions. Just like your left hand will not fit properly in your right glove, one of the enantiomers of a molecule may not work the same way in your body.

This must mean that enantiomers have properties that make them unique to their mirror images. One of these properties is that they cannot have a plane of symmetry or an internal mirror plane. So, a chiral molecule cannot be divided in two mirror image halves. Another property of chiral molecules is optical activity.

Organic compounds, molecules created around a chain of carbon atom (more commonly known as carbon backbone), play an essential role in the chemistry of life. These molecules derive their importance from the energy they carry, mainly in a form of potential energy between atomic molecules. Since such potential force can be widely affected due to changes in atomic placement, it is important to understand the concept of an isomer, a molecule sharing same atomic makeup as another but differing in structural arrangements. This article will be devoted to a specific isomers called stereoisomers and its property of chirality (Figure 5.1.1).

Figure 5.1.1. Two enantiomers of a tetrahedral complex. Image used with permission from Wikipedia

The concepts of stereoisomerism and chirality command great deal of importance in modern organic chemistry, as these ideas helps to understand the physical and theoretical reasons behind the formation and structures of numerous organic molecules, the main reason behind the energy embedded in these essential chemicals. In contrast to more well-known constitutional isomerism, which develops isotopic compounds simply by different atomic connectivity, stereoisomerism...
generally maintains equal atomic connections and orders of building blocks as well as having same numbers of atoms and types of elements.

What, then, makes stereoisomers so unique? To answer this question, the learner must be able to think and imagine in not just two-dimensional images, but also three-dimensional space. This is due to the fact that stereoisomers are isomers because their atoms are different from others in terms of spatial arrangement.

**Spatial Arrangement**

First and foremost, one must understand the concept of spatial arrangement in order to understand stereoisomerism and chirality. Spatial arrangement of atoms concern how different atomic particles and molecules are situated about in the space around the organic compound, namely its carbon chain. In this sense, spatial arrangement of an organic molecule are different another if an atom is shifted in any three-dimensional direction by even one degree. This opens up a very broad possibility of different molecules, each with their unique placement of atoms in three-dimensional space.

**Stereoisomers**

Stereoisomers are, as mentioned above, contain different types of isomers within itself, each with distinct characteristics that further separate each other as different chemical entities having different properties. Type called entaniomer are the previously-mentioned mirror-image stereoisomers, and will be explained in detail in this article. Another type, diastereomer, has different properties and will be introduced afterwards.

**Enantiomers**

This type of stereoisomer is the essential mirror-image, non-superimposable type of stereoisomer introduced in the beginning of the article. Figure 3 provides a perfect example; note that the gray plane in the middle demotes the mirror plane.

![Figure 5.1.2.](image)
Note that even if one were to flip over the left molecule over to the right, the atomic spatial arrangement will not be equal. This is equivalent to the left hand - right hand relationship, and is aptly referred to as 'handedness' in molecules. This can be somewhat counter-intuitive, so this article recommends the reader try the 'hand' example. Place both palm facing up, and hands next to each other. Now flip either side over to the other. One hand should be showing the back of the hand, while the other one is showing the palm. They are not same and non-superimposable. This is where the concept of chirality comes in as one of the most essential and defining idea of stereoisomerism.

**Chirality**

*Chirality* essentially means 'mirror-image, non-superimposable molecules', and to say that a molecule is chiral is to say that its mirror image (it must have one) is not the same as it self. Whether a molecule is chiral or achiral depends upon a certain set of overlapping conditions. Figure 5.1.1 shows an example of two molecules, chiral and achiral, respectively. Notice the distinct characteristic of the achiral molecule: it possesses two atoms of same element. In theory and reality, if one were to create a plane that runs through the other two atoms, they will be able to create what is known as bisecting plane: The images on either side of the plan is the same as the other (Figure 5.1.3).

![Figure 5.1.3.](image)

In this case, the molecule is considered 'achiral'. In other words, to distinguish chiral molecule from an achiral molecule, one must search for the existence of the bisecting plane in a molecule. All chiral molecules are deprive of bisecting plane, whether simple or complex. As a universal rule, no molecule with different surrounding atoms are achiral. Chirality is a simple but essential idea to support the concept of stereoisomerism, being used to explain one type of its kind. The chemical properties of the chiral molecule differs from its mirror image, and in this lies the significance of chirality in relation to modern organic chemistry.

**Contributors**

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Objectives

After completing this section, you should be able to

1. determine whether or not a compound is chiral, given its Kelviné, condensed or shorthand structure, with or without the aid of molecular models.
2. label the chiral centres (carbon atoms) in a given Kelviné, condensed or shorthand structure.

Key Terms

Make certain that you can define, and use in context, the key terms below.

- achiral
- chiral
- chiral (stereogenic) centre
- plane of symmetry

A consideration of the chirality of molecular configurations explains the curious stereoisomerism observed for lactic acid, carvone and a multitude of other organic compounds. Tetravalent carbons have a tetrahedral configuration. If all four substituent groups are the same, as in methane or tetrachloromethane, the configuration is that of a highly symmetric "regular tetrahedron". A regular tetrahedron several planes of symmetry and is achiral.

A carbon atom that is bonded to four different atoms or groups loses all symmetry, and is often referred to as an asymmetric carbon. The configuration of such a molecular unit is chiral, and the structure may exist in either a right-handed configuration or a left-handed configuration (one the mirror image of the other). This type of configurational stereoisomerism is termed enantiomorphism, and the non-identical, mirror-image pair of stereoisomers that result are called enantiomers. In the general figure below, A and B are nonsuperposable mirror images of one another, and thus are a pair of enantiomers.

The structural formulas of lactic acid and carvone are drawn on the right with the asymmetric carbon colored red. Consequently, we find that these compounds exist as pairs of enantiomers. The presence of a single asymmetrically
substituted carbon atom in a molecule is sufficient to render the whole configuration chiral, and modern terminology refers to such groupings as chiral centers. Most of the chiral centers we shall discuss are asymmetric carbon atoms, but it should be recognized that other tetrahedral or pyramidal atoms may become chiral centers if appropriately substituted. When more than one chiral center is present in a molecular structure, care must be taken to analyze their relationship before concluding that a specific molecular configuration is chiral or achiral. This aspect of stereoisomerism will be treated later.

A useful first step in examining structural formulas to determine whether stereoisomers may exist is to identify all stereogenic elements. A stereogenic element is a center, axis or plane that is a focus of stereoisomerism, such that an interchange of two groups attached to this feature leads to a stereoisomer. Stereogenic elements may be chiral or achiral. An asymmetric carbon is often a chiral stereogenic center, since interchanging any two substituent groups converts one enantiomer to the other. Alkenes having two different groups on each double bond carbon constitute an achiral stereogenic element, since interchanging substituents at one of the carbons changes the cis/trans configuration of the double bond.

Some of the structures in the figure above are chiral and some are achiral. First, try to identify all chiral stereogenic centers. Formulas having no chiral centers are necessarily achiral. Formulas having one chiral center are always chiral; and if two or more chiral centers are present in a given structure it is likely to be chiral, but in special cases, to be discussed later, may be achiral.

Structures F and G are achiral. The former has a plane of symmetry passing through the chlorine atom and bisecting the opposite carbon-carbon bond. The similar structure of compound E does not have such a symmetry plane, and the carbon bonded to the chlorine is a chiral center (the two ring segments connecting this carbon are not identical). Structure G is essentially flat. All the carbons except that of the methyl group are sp^2 hybridized, and therefore trigonal-planar in configuration. Compounds C, D & H have more than one chiral center, and are also chiral. Remember, all chiral structures may exist as a pair of enantiomers. Other configurational stereoisomers are possible if more than one stereogenic center is present in a structure.
In the 1960’s, a drug called thalidomide was widely prescribed in the Western Europe to alleviate morning sickness in pregnant women.

![Thalidomide molecule]

Thalidomide had previously been used in other countries as an antidepressant, and was believed to be safe and effective for both purposes. The drug was not approved for use in the U.S.A. It was not long, however, before doctors realized that something had gone horribly wrong: many babies born to women who had taken thalidomide during pregnancy suffered from severe birth defects.

Researchers later realized the that problem lay in the fact that thalidomide was being provided as a mixture of two different isomeric forms.

![Effective and mutagenic isomers of thalidomide]

One of the isomers is an effective medication, the other caused the side effects. Both isomeric forms have the same molecular formula and the same atom-to-atom connectivity, so they are not constitutional isomers. Where they differ is in the arrangement in three-dimensional space about one tetrahedral, sp³-hybridized carbon. These two forms of thalidomide are **stereoisomers**.

Note that the carbon in question has **four different substituents** (two of these just happen to be connected by a ring structure). Tetrahedral carbons with four different substituent groups are called **stereocenters**.

**Example 5.2.1**

Locate all of the carbon stereocenters in the molecules below.
Looking at the structures of what we are referring to as the two isomers of thalidomide, you may not be entirely convinced that they are actually two different molecules. In order to convince ourselves that they are indeed different, let's create a generalized picture of a tetrahedral carbon stereocenter, with the four substituents designated R₁-R₄. The two stereoisomers of our simplified model look like this:

If you look carefully at the figure above, you will notice that molecule A and molecule B are mirror images of each other (the line labeled 's' represents a mirror plane). Furthermore, they are not superimposable: if we pick up molecule A, flip it around, and place it next to molecule B, we see that the two structures cannot be superimposed on each other. They are different molecules!
If you make models of the two stereoisomers of thalidomide and do the same thing, you will see that they too are mirror images, and cannot be superimposed (it well help to look at a color version of the figure below).

Thalidomide is a chiral molecule. Something is considered to be chiral if it cannot be superimposed on its own mirror image – in other words, if it is asymmetric (lacking in symmetry). The term ‘chiral’ is derived from the Greek word for ‘handedness’ – ie. right-handedness or left-handedness. Your hands are chiral: your right hand is a mirror image of your left hand, but if you place one hand on top of the other, both palms down, you see that they are not superimposable.

A pair of stereoisomers that are non-superimposable mirror images of one another are considered to have a specific type of stereoisomeric relationship – they are a pair of enantiomers. Thalidomide exists as a pair of enantiomers. On the macro level, your left and right hands are also a pair of enantiomers.

Here are some more examples of chiral molecules that exist as pairs of enantiomers. In each of these examples, there is a single stereocenter, indicated with an arrow. (Many molecules have more than one stereocenter, but we will get to that a little later!)

Here are some examples of molecules that are achiral (not chiral). Notice that none of these molecules has a stereocenter.
It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. Chirality is tied conceptually to the idea of asymmetry, and **any molecule that has a plane of symmetry cannot be chiral**. When looking for a plane of symmetry, however, we must consider all possible conformations that a molecule could adopt. Even a very simple molecule like ethane, for example, is asymmetric in many of its countless potential conformations – but it has obvious symmetry in both the eclipsed and staggered conformations, and for this reason it is achiral.

Looking for planes of symmetry in a molecule is useful, but often difficult in practice. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions (see section 3.7B), the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral. Carbon stereocenters are also referred to quite frequently as **chiral carbons**.

When evaluating a molecule for chirality, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). Conversely, wedges may be used on carbons that are not stereocenters – look, for example, at the drawings of glycine and citrate in the figure above. Just because you see dashed and solid wedges in a structure, do not automatically assume that you are looking at a stereocenter.

Other elements in addition to carbon can be stereocenters. The phosphorus center of phosphate ion and organic phosphate esters, for example, is tetrahedral, and thus is potentially a stereocenter.

We will see in chapter 10 how researchers, in order to investigate the stereochemistry of reactions at the phosphate center, incorporated sulfur and/or $^{17}$O and $^{18}$O isotopes of oxygen (the 'normal' isotope is $^{16}$O) to create chiral phosphate groups. Phosphate triesters are chiral if the three substituent groups are different.

Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.
Example 5.2.2

Label the molecules below as chiral or achiral, and locate all stereocenters.

**Answer:**

- **a)** [Structure](image) fumarate (achiral)
- **b)** [Structure](image) malate (achiral)
- **c)** [Structure](image) ibuprofen (chiral)
- **d)** [Structure](image) acetylsalicylic acid (aspirin) (achiral)
- **e)** [Structure](image) acetaminophen (active ingredient in Tylenol) (achiral)

**Exercises**

**Questions**

**Q5.2.1**

Identify the chiral centers in each of the following:
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