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A Topological Approach to Molecular Chirality

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Topology is the study of deformations of geometric figures. Chemistry is the study of molecular structures. At first glance these fields seem to have nothing in common. But let's take a closer look to see how these fields come together in the study of molecular symmetries.

Molecules are often modeled as graphs in space, where vertices represent atoms or groups of atoms, and edges represent bonds. For example, the molecule L–alanine can be illustrated by the graph in Figure 1. The dark triangular segment in the figure indicates an edge that comes out of the plane of the paper towards the reader, the dashed segment indicates an edge which goes back behind the plane of the paper, and the ordinary line segments indicate edges that lie in the plane of the paper. In 3–dimensional space, the four outer vertices of this graph lie at the four corners of a regular tetrahedron.

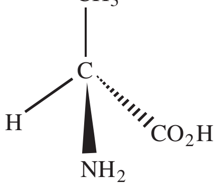

Figure 1: This molecule has the form of a tetrahedron

The 3-dimensional structure of a molecule determines many of its properties. For rigid molecules, like the one in Figure 1, this means its properties are determined by its geometry (i.e., by its bond angles and bond lengths). However, large molecules may be flexible, and even some small molecules can have pieces that rotate around specific bonds. For such molecules, topology can help us understand their structure.

For example, consider the molecular *Möbius ladder* illustrated in Figure 2. The graph is a 3-rung ladder where the ends have been joined with a half-twist. This molecule looks like a Möbius strip except it is made from a ladder rather than from a strip of paper. The sides of the ladder represent a polyether chain of 60 atoms which are all carbons and oxygens, and the rungs of the ladder represent carbon-carbon double bonds. The carbons are indicated by corners or vertices of the graph, and the oxygens are indicated by O's.

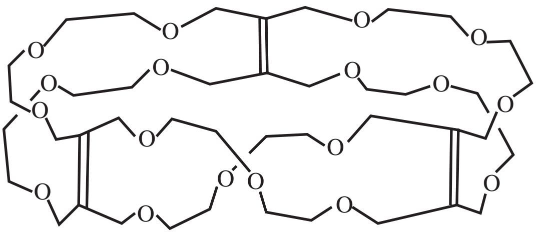

Figure 2: The molecular Möbius ladder

The molecular Möbius ladder was first synthesized in 1983 by David Walba [Wa]. In order to synthesize a molecular Möbius ladder, Walba created a molecular ladder and then made the ends of the ladder attach together. These ladders did not all join themselves in the same way. The ends of some of the ladders joined together without a twist, the ends of some joined as Möbius ladders with a left-handed half-twist, and the ends of others joined as Möbius ladders with a right-handed half-twist. Figure 3 illustrates a ladder whose ends are joined without a twist.

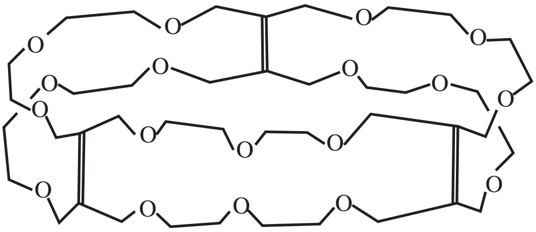

Figure 3: A molecular ladder in the form of a cylinder

Walba wanted to show that some of his ladders were Möbius ladders. The molecules were too small to see in a microscope, so Walba needed some other evidence to support his claim. He showed experimentally that some of his molecules were distinct from their mirror image. By the *mirror image* of an object we mean the object as seen in a mirror. Some objects are the same as their mirror image while others are different from their mirror image. For example, a ball is the same as its mirror image, but the mirror image of a left hand is a right hand.

The mirror image of a cylindrical ladder is exactly the same as the original cylindrical ladder. This is true no matter where we put the mirror. Since some of Walba's molecules were distinct from their mirror image, not all of his molecules could be cylindrical ladders. Walba wanted to say that a molecular Möbius ladder is distinct from its mirror image. Imagine a mirror that is perpendicular to the plane of this page and just to the right of Figure 2. The mirror image of Figure 2 in such a mirror would be Figure 4. Observe that the two figures are identical except for the crossing in the front.

While Figure 4 looks different from Figure 2, it is not obvious that one structure could not somehow change itself into the other. In particular, since the Möbius ladder is flexible, perhaps there

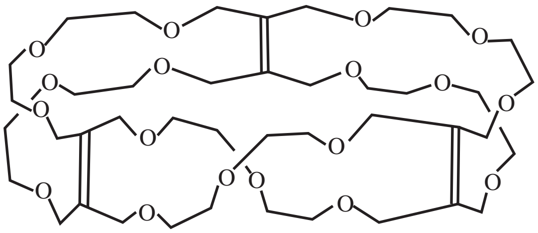

Figure 4: The mirror image of Figure 2

is some way it can be deformed to its mirror image. In fact, if we do not distinguish the different types of atoms and bonds then a Möbius ladder can be deformed to its mirror image. Figure 5 illustrates the Möbius ladder and its mirror image without specifying the atoms or distinguishing the different types of atoms or bonds. As an exercise, you should draw a deformation of one graph to the other.

Figure 5: A Möbius ladder and its mirror image without labeling the atoms or bonds

In 1983, the topologist, Jon Simon [Si], proved that if we distinguish between the different types of atoms, then the graph representing a molecular Möbius ladder cannot be deformed to its mirror image. It follows that a molecular Möbius ladder cannot change itself into its mirror form.

In general, knowing whether a molecular structure is the same or different from its mirror image is chemically significant. In order to refer to this property, we make the following definition.

Definition 1 *A molecule is said to be* chemically achiral *if it can change into its mirror image. Otherwise, it is said to be* chemically chiral.

Chemists say that a molecule is “chiral” or “achiral”, rather than saying that it is “chemically chiral” or “chemically achiral.” We insert the word “chemically” in our definition in order to distinguish this type of chirality from other types of chirality that we will introduce later.

At first this definition may seem confusing because a molecule is chiral if it is NOT the same as its mirror image and it is achiral if it IS the same as its mirror image. The definition makes more sense if you understand its etymology. The word *chiral* comes from the ancient Greek word *kheir*, which means hand. A left hand can never change into a right hand. Thus a hand is an example of a chiral object. So *chiral* means “like a hand”, and *achiral* means “not like a hand.” In fact, we think of the two forms of a chiral structure as the left-handed form and the right-handed form.

The left-handed and right-handed forms of a chiral molecule often exhibit different properties. For example, the molecule *carvone* is chiral, and one form of it smells like caraway while the mirror form smells like spearmint. Most biological organisms are chiral both in the large and in the small. We observe the large-scale chirality frequently in nature. For example, shells of a given species normally all spiral the same way, and climbing plants of a given species normally all wind around a pole in the same way. Because biological organisms are chiral on the molecular level they react differently to the two forms of another chiral molecule, just as my left foot reacts differently to a right shoe and to a left shoe. These different reactions are especially noteworthy for pharmaceutical products.

In particular, one form of a chiral medication is generally more effective, while the mirror form generally has more side effects. Most medications are synthesized in a 50:50 mix, and separating the two forms may be expensive. However, sometimes when the two forms of a medication are separated they each have a separate use. For example, *Darvon* is an effective painkiller, while its mirror form *Novrad* is an effective cough medicine.

All of this is to say that it is important to know whether or not a molecule is chiral, and if it is chiral it may be useful to separate the two mirror forms. Chemists can determine experimentally whether or not a particular molecule is chemically chiral (as Walba did). But suppose a chemist is designing a new molecule, and wants to know before it is synthesized whether the molecule will be chiral. To do this, chemists generally use a geometrical notion of chirality first introduced by Lord Kelvin in 1884. In fact, the word "chiral" was first introduced by Lord Kelvin in the following statement:

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

In other words, a structure is considered to be a rigid object and it is said to be chiral if it is different from its mirror image. Modern organic chemistry textbooks often paraphrase this definition as follows.

Definition 2 *A* chiral *molecule is one that is not superposable with its mirror image.*

This definition assumes that all molecules are rigid, and uses the word "superposable" instead of "superimposable." We shall use the following definition which restates the above definition more formally.

Definition 3 *A structure is said to be* geometrically achiral *if, as a rigid object, it can be superimposed on its mirror image. Otherwise, it is said to be* geometrically chiral.

Chemists use the word "chirality" for both geometric chirality and chemical chirality, because they consider these concepts to be interchangeable. However, these two concepts are not equivalent. For example, a right-handed glove is a geometrically chiral object, because as a rigid object it cannot be superimposed on a left-handed glove. Yet, if the glove is flexible (as a knitted or rubber glove is), then it can be turned inside out to get a left-handed glove. If the inside and outside of the glove are the same material and color, then in fact the glove is achiral even though it is not geometrically achiral.

On a molecular level, we see as follows that a molecule that is flexible or can rotate around certain bonds may be able to change into its mirror image without being able to be rigidly superimposed on its mirror image. In 1954, Mislow and Bolstadt [MB] synthesized the biphenyl derivative illustrated in Figure 6 to demonstrate that these two notions of chirality are not equivalent.

In this figure, the hexagon to the right of the central bond is horizontal, while the hexagon to the left of the central bond is vertical. The vertical hexagons on either end of the structure are behind the plane of the paper, as indicated by the dashed lines attaching them to the rest of the graph. Imagine a mirror that is perpendicular to this page. The image of the molecule in such a mirror will look the same except it will have a horizontal hexagon on the left of the central bond and a vertical hexagon to the right of the central bond. The mirror form is illustrated in Figure 7.

Figure 6 is rigid except that the two ends of the molecule rotate simultaneously as indicated by the arrows. We shall call these rotating pieces *propellers*. Observe that because the hexagons in the propellers are behind the plane containing the adjacent oxygens and carbon, the left propeller and

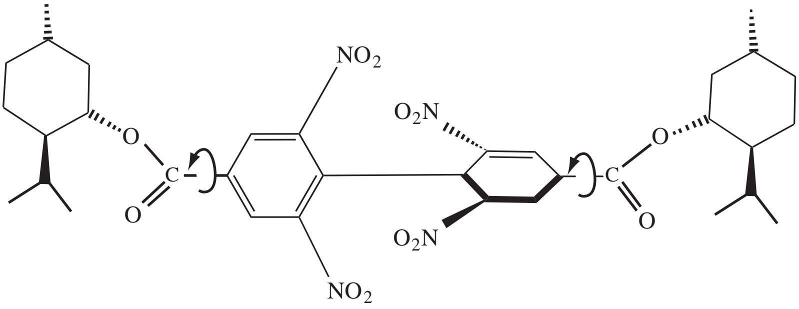

Figure 6: A molecule that is chemically achiral but geometrically chiral

the right propeller are distinct. That is, no matter how we turn the figure, there is no way for a left propeller to look like a right propeller.

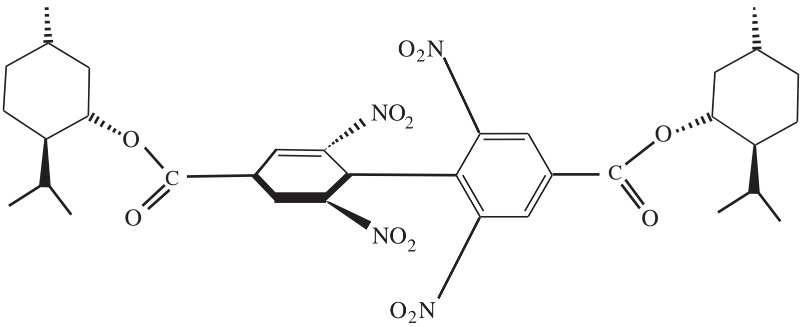

Figure 7: The mirror image of Figure 6

We see that the molecule in Figure 6 is chemically achiral as follows. Rotate the whole structure by 90° about a horizontal axis. After the rotation the hexagon on the left is horizontal and the hexagon on the right is vertical, and the hexagons in the two propellers are horizontal. Since the propellers rotate, we let them rotate back to their original vertical positions. In this way we obtain the structure in Figure 7. Since this motion can occur on a chemical level, we conclude that the structure is chemically achiral.

Now we prove that the molecule in Figure 6 is geometrically chiral. Observe that in Figure 6 the hexagon in the left propeller is parallel to the adjacent hexagon. In the mirror form the hexagon in the left propeller is perpendicular to the adjacent hexagon. Since, as a rigid object, there is no way for a left propeller to become a right propeller, there is no way to rigidly move this structure so as to superimpose it on its mirror image.

This phenomenon is occurring because the structure is rigid except that the propellers can rotate. If the molecule were completely rigid it would be chemically chiral. On the other hand, if it were completely flexible, it could lie in a plane and hence would become geometrically achiral. Below we define a term introduced by the chemist Van Gulick [VG] to describe examples of the above type.

Definition 4 *A molecular structure is said to be a* euclidean rubber glove *if it is chemically achiral, but it is chemically impossible for it to attain a position which can be rigidly superimposed on its mirror image.*

In order to understand this concept, we first consider a real rubber glove. As we observed above, a right-handed rubber glove becomes a left-handed rubber glove when it is turned inside out. However, due to the physical limitations of rubber, the glove cannot attain a position which can be rigidly superimposed on its mirror image. Just as with the above molecule, if the glove were completely flexible, it could be flattened into the plane so that it would be its own mirror image, and hence it would be geometrically achiral. We use the word "euclidean" in this definition to indicate that physical or geometric constraints are what prevent the structure from attaining a geometrically achiral position.

Walba asked if there could be a chemically achiral structure that could not be deformed to a geometrically achiral position, even ignoring physical or geometric constraints. In fact, Walba proposed the following definition.

Definition 5 *A molecular structure is said to be a* topological rubber glove *if it is chemically achiral, but even if it were completely flexible it could not be deformed to a position which could be rigidly superimposed on its mirror image.*

At first glance it seems impossible for a structure to be a topological rubber glove. If a structure can change into its mirror image and we ignore all physical and geometric constraints, shouldn't we be able to deform it to a symmetric position, which can be rigidly superimposed on its mirror image? But, in fact, this is not always the case.

Figure 8 illustrates the first molecule that was shown to be a topological rubber glove. This molecule was synthesized by Chambron, Sauvage, and Mislow [CSM] in 1997. A key feature of this molecule is that the pair of adjoining hexagons at the top of the molecule can rotate about the bonds that connect them to the rest of the molecule (as indicated by the arrows). We reflect Figure 8 in a mirror that is perpendicular to the plane of the paper to obtain Figure 9. Note that the H_3C in Figure 8 and the CH_3 in the mirror image are the same group of atoms. They are written as they are to indicate that the C is attached to the adjacent hexagon.

If we turn the lower ring over and rotate the pair of adjoining hexagons at the top, the molecule in Figure 8 becomes its mirror image. Since both of these motions can occur on a chemical level, the molecule is chemically achiral. However, we prove in [Fl] that even if this graph is completely flexible, because of its linked structure together with the asymmetric position of the H_3C, it cannot be deformed to a position which can be rigidly superimposed on its mirror image. Thus this molecule is a topological rubber glove.

We summarize the relationship between chemical chirality and geometric chirality as follows. A molecule that can be rigidly superimposed on its mirror image is chemically no different from its mirror image. Thus geometric achirality implies chemical achirality, and hence chemical chirality implies geometric chirality. On the other hand, the above examples show that geometric chirality does not imply chemical chirality. Thus geometry can help us prove chemical achirality, and can be used to prove chemical chirality for completely rigid molecules. But it will not help us prove chemical chirality for flexible molecules, or for those which can rotate around particular bonds. The assumption behind geometric chirality is that all molecules are rigid structures. Now we consider what happens if we treat molecules as flexible structures.

Definition 6 *A structure is said to be* topologically achiral *if (assuming complete flexibility) it can be deformed to its mirror image. Otherwise, it is said to be* topologically chiral.

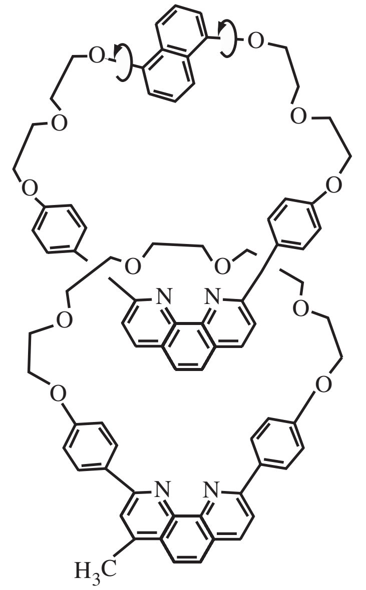

Figure 8: A topological rubber glove

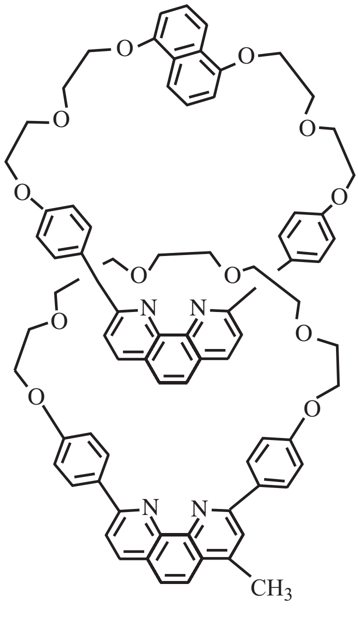

Figure 9: The mirror image of the molecule in Figure 8

Since any molecular motion is a deformation, chemical achirality implies topological achirality. Thus topological chirality implies chemical chirality. However, topological achirality does not imply chemical achirality, as Figure 10 illustrates. Since this molecule is rigid, it cannot be superimposed on its mirror image. On the other hand, if the graph were flexible, we could interchange the positions of CO_2H and NH_2. Thus the structure is topologically achiral.

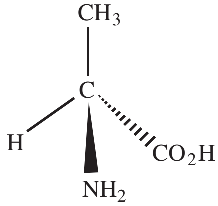

Figure 10: This molecule is topologically achiral but chemically chiral

So geometry enables us to prove chemical achirality, and topology enables us to prove chemical chirality. Furthermore, a molecule whose chirality comes from its rigidity can be forced to change into its mirror image by heating it. However, if a molecule is topologically chiral, then bonds would have to break for it to change into its mirror image. Thus it will not change into its mirror form even when heated. So topological chirality is a more enduring type of chirality than geometric chirality. All of this is to say that topological chirality is a useful concept for chemists.

Geometric chirality is not hard to determine by examining a rigid structure from all different angles to see whether it can be superimposed on its mirror form. Proving that a structure is topologically chiral is more difficult because we cannot consider all possible deformations of the structure. However, a number of useful techniques have been developed to prove topological chirality.

Technique 1: Use knot polynomials.

Knot polynomials were originally developed by Alexander in 1928 [Al] in order to distinguish different knots and links. The polynomials that are currently the easiest to use were developed in the 1980's by Vaughan Jones [Jo].

It is impossible to show that a knot or link cannot be deformed to another knot or link by considering every possible deformation. Instead, to every knot and link we assign a Jones polynomial which has the property that no matter how the knot or link is deformed, it will always have the same polynomial. Thus if a pair of knots or links have different polynomials then we know that one cannot be deformed to the other. In particular, if the knot or link can be deformed to its mirror image, then the mirror form will have the same polynomial as the original structure. So if we can show that a knot or link and its mirror image have different polynomials then we know that the knot or link cannot be deformed to its mirror image. These polynomials can also be used to show that certain knotted or linked molecules are topologically chiral.

For example, consider the knotted molecule illustrated in Figure 11. The Jones polynomial of this knot is $t + t^3 - t^4$. On the other hand, the Jones polynomial of the mirror image of this knot (shown in Figure 12) is $t^{-1} + t^{-3} - t^{-4}$. Since these polynomials are different, the molecule illustrated in Figure 11 is topologically chiral.

Strictly speaking knot polynomials are not really polynomials because they have negative integer exponents as well as positive integer exponents. Such functions are actually called *Laurent polynomials*. But it is common to abuse terminology and simply call them knot polynomials.

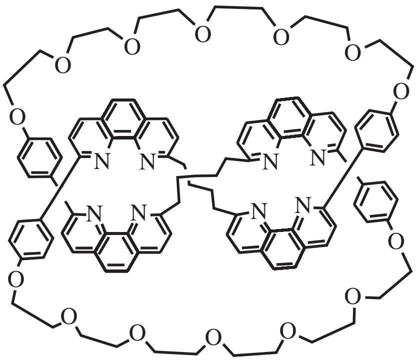

Figure 11: A molecular trefoil knot

The reader may have observed that in the above example, there was a relationship between the polynomial of the knot in Figure 11 and the polynomial of its mirror image. In fact, this relationship always holds. In particular, the Jones polynomial of the mirror image of a knot is always the same as the Jones polynomial of the knot except that the signs of the exponents have been reversed. So if we compute the polynomial of a knot and observe that it is not symmetric with respect to the signs of its exponents, then we immediately know that the knot is topologically chiral. So we could have known that Figure 11 was topologically chiral, by simply observing that the polynomial $t + t^3 - t^4$ has only positive exponents, and hence does not have exponents that are symmetric with respect to sign.

One note of caution, just because a knot has the same Jones polynomial as its mirror image does not mean that the knot is topologically achiral. Thus the Jones polynomial can be used to show topological chirality but not to show topological achirality.

Technique 2: Use a 2-fold branched cover

While 2-fold branched covers have been around for a long time, the idea of using them to prove that a molecule is topologically chiral was first introduced by Jon Simon [Si] in his analysis of the molecular Möbius ladder. Since the molecular Möbius ladder contains no knots or links, the Jones polynomial will not help us prove that it's topologically chiral. So Simon came up with the following new approach.

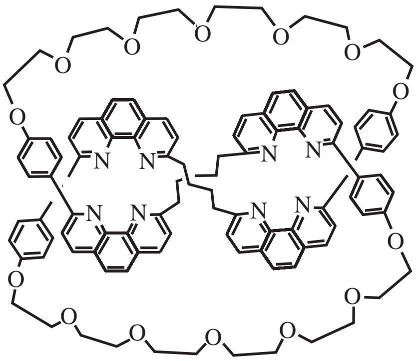

Figure 12: The mirror image of the molecule in Figure 11

Rather than drawing a molecular Möbius ladder with all the atoms labeled, we represent it symbolically as a colored graph where the rungs are one color and the sides are another color (see Figure 13). Since it would not make sense chemically to deform the graph so that an oxygen goes to a carbon, we make the rule that edges of a given color cannot be deformed to edges of a different color.

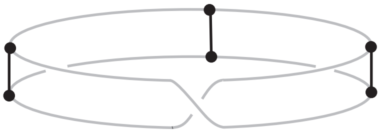

Figure 13: A colored Möbius ladder

We assume this graph is completely flexible, and deform the sides of the ladder to be a planar circle. After this deformation, the graph can be illustrated by Figure 14. (The reader should check that the graph can be deformed to look like this.) We have numbered the rungs so that rung 1 is at the bottom, rung 2 is in the middle, and rung 3 is at the top.

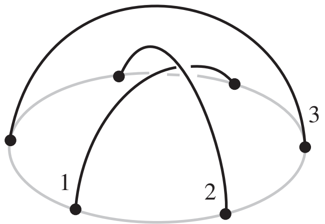

Figure 14: A colored Möbius ladder with planar sides and numbered rungs

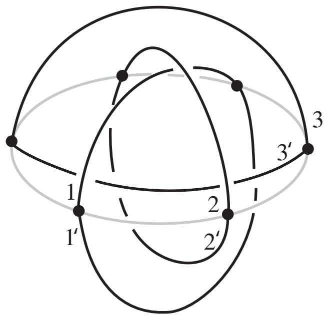

Figure 15: The 2-fold branched cover of the Möbius ladder

We now create the 2-fold branched cover of this figure, branched over the sides of the ladder. (We won't define branched covers because the definition is too technical, but we will give some intuition about how this method was used.) Creating the 2-fold branched cover has the effect of gluing two copies of Figure 14 together along the grey circle. In this way, we obtain the structure illustrated in Figure 15, which has only one grey circle, and three additional rungs, 1′, 2′ and 3′, directly under the original three, such that rungs 1′, 2′ and 3′ are in the same vertical order as rungs 1, 2, and 3. Thus rung 1′ has the same endpoints as rung 1 and is under all of the other rungs, rung 2′ has the same endpoints as rung 2 and is just above rung 1′, and rung 3′ has the same endpoints as rung 3 and is just above rung 2′.

If we erase the grey circle from Figure 15 we obtain a link with three components, which has the property that each component of the link is linked to each of the other components. (See Figure 16.) Simon proved that this link is topologically chiral, and that the topological chirality of this link implies that the colored Möbius ladder must be topologically chiral. Hence the molecular Möbius ladder is also topologically chiral.

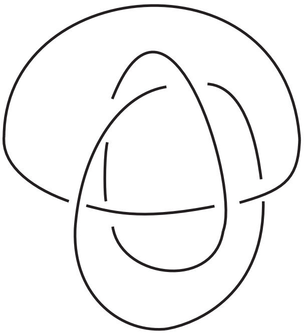

Figure 16: If we erase the grey circle in Figure 15 then we have this link

Technique 3: Find a unique Möbius ladder in the molecule.

This method was developed by the chemist Kurt Mislow to prove that the molecule *triple layered naphthalenophane* was topologically chiral. We illustrate triple layered naphthalenophane in Figure 17.

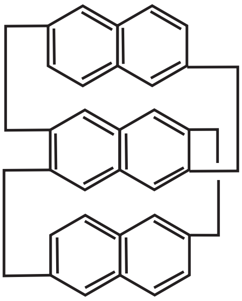

Figure 17: Triple layered naphthalenophane

A key observation is that the graph of triple layered naphthalenophane contains a unique circuit, which is longer than any other circuit in the graph. In Figure 18, we have illustrated the longest circuit in the graph by coloring it grey. The reader can check that this circuit is indeed longer than any other circuit in the graph.

The three vertical edges in the center of the graph are the only edges which have both endpoints on this unique circuit. We illustrate the unique circuit together with these three edges in Figure 19.

Suppose, for the sake of contradiction, that the graph of triple layered naphthalenophane can be deformed to its mirror image. Such a deformation would take the colored graph in Figure 19 to

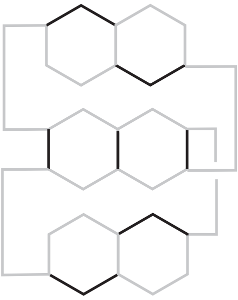

Figure 18: The unique longest circuit in triple layered naphthalenophane is colored grey

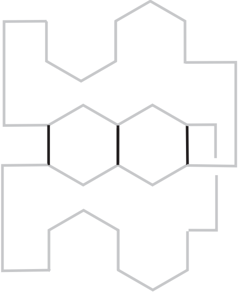

Figure 19: The longest circuit together with the three edges whose vertices are on the circuit

its mirror image. However, that figure can be deformed to the colored Möbius ladder illustrated in Figure 20, which we know is topologically chiral. Hence such a deformation is not possible. Therefore, triple layered naphthalenophane must be topologically chiral.

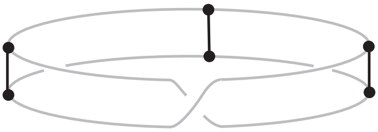

Figure 20: This colored Möbius ladder is topologically chiral

Technique 4: A combinatorial approach.

I developed the following method which analyzes the structure of the graph rather than the way the graph is embedded in 3-dimensional space. Before we explain the method we have to introduce several definitions.

Definition 7 *An* automorphism *of a graph is a permutation of the vertices that takes adjacent vertices to adjacent vertices. For molecular graphs an automorphism is also required to take atoms of a given type to atoms of the same type.*

For example, consider the Möbius ladder illustrated in Figure 21. We have numbered the vertices to make it easier to describe a particular permutation of the vertices. The permutation that interchanges vertices 2 and 6 and interchanges vertices 3 and 5 is an automorphism. On the other hand, the permutation that just interchanges vertices 2 and 5 is not an automorphism because vertex 2 is adjacent to vertex 3, while vertex 5 is not adjacent to vertex 3.

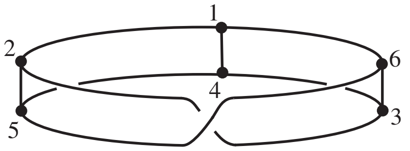

Figure 21: The permuation that interchanges vertices 2 and 6 and vertices 3 and 5 is an automorphism

The *valence* of a vertex is the number of edges that contain that vertex. For example, in a Möbius ladder all of the vertices have valence 3. The reader should prove that the following properties hold:

1) Any automorphism of a graph takes vertices of a given valence to vertices of the same valence.
2) Any automorphism of a graph takes a pair of vertices that are a given distance apart to a pair of vertices that are the same distance apart.

Definition 8 *The* order *of an automorphism is the smallest number n such that doing the automorphism n times takes each vertex back to its original position.*

For example the automorphism of the Möbius ladder which interchanges vertices 2 and 6 and vertices 3 and 5 has order two. The identity automorphism, which doesn't move any vertex, has order one.

The following theorem allows us to prove that many graphs are topologically chiral. This result has nothing to do with the way the graph is embedded in 3-dimensional space. So if it applies to one embedding of the graph then it applies to all embeddings of that graph.

Theorem. [Fl] *If a graph contains either the graph K_5 or $K_{3,3}$ (see Figure 22) and has no order two automorphism, then any embedding of the graph in* 3*-dimensional space is topologically chiral.*

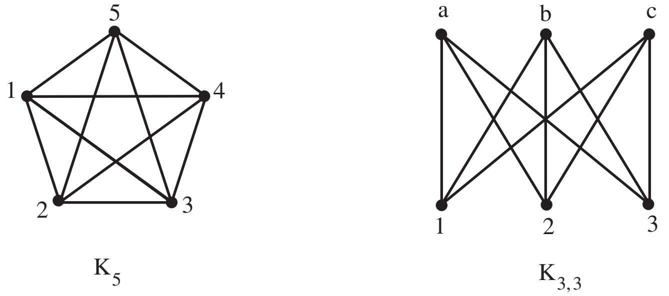

Figure 22: The complete graph K_5, and the complete bipartite graph $K_{3,3}$

The graphs K_5 and $K_{3,3}$ are special because any graph which contains one of these graphs cannot be embedded in a plane. If a graph is embedded in a plane then it is its own mirror image, hence it is topologically achiral.

To see how to apply this theorem we consider the molecule ferrocenophane, which is illustrated in Figure 23. All of the atoms of this molecule are carbons except for a single iron (indicated with an Fe) and a single oxygen (indicated with an O).

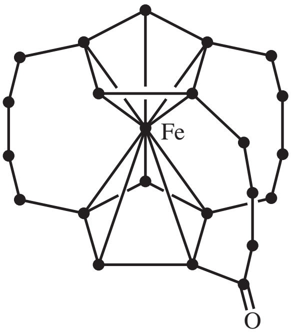

Figure 23: The molecule ferrocenophane is topologically chiral

While it may not be obvious at first glance, ferrocenophane contains the complete graph K_5. The graph K_5 consists of five vertices together with edges between every pair of vertices. We illustrate the K_5 contained in ferrocenophane in Figure 24.

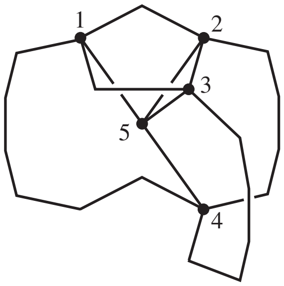

Figure 24: Ferrocenophane contains the graph K_5

In order to prove that ferrocenophane has no order two automorphisms we argue as follows. Suppose that Φ is an automorphism of ferrocenophane. Since Φ has to take atoms of a given type to atoms of the same type, it must take the single oxygen atom to itself. Now since Φ preserves adjacency, Φ takes the vertex which is adjacent to the oxygen atom to itself. There are two vertices adjacent to this vertex, however one has valence two and the other has valence four. Thus Φ must take each one to itself. We can continue going through the vertices, arguing in this way, to conclude that every vertex of ferrocenophane must be fixed by the automorphism Φ. But this means that Φ has order one. Hence ferrocenophane has no automorphism of order two. Now it follows from the above theorem that ferrocenophane is topologically chiral.

The final example we consider is the Simmons-Paquette molecule (illustrated in Figure 25). We only need to omit the vertices of valence two, to obtain the graph K_5. We number the remaining vertices in Figure 26 to illustrate the K_5 in the Simmons-Paquette molecule.

By contrast with ferrocenophane, the Simmons-Paquette molecule has an automorphism of order three. We show as follows that it has no automorphism of order two. First observe that the graph has a unique circuit which contains all three oxygen atoms. This circuit is colored grey in Figure 27.

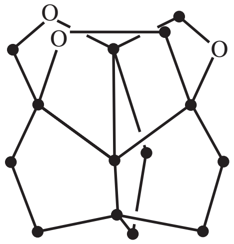

Figure 25: The Simmons-Paquette molecule is topologically chiral

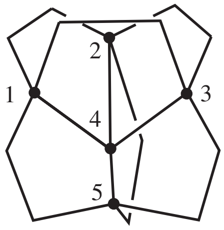

Figure 26: The Simmons-Paquette molecule contains a K_5

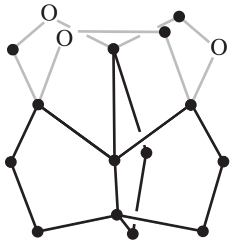

Figure 27: The unique circuit which contains all three oxygen atoms is colored grey

Suppose that Φ is an order two automorphism of the Simmons-Paquette molecule. Then Φ takes the grey circle in Figure 27 to itself. Since this circle has three oxygens, and the order of Φ is two, at least one of the oxygens must be fixed by Φ. Now the two vertices adjacent to the fixed oxygen have different valence, so they too must be fixed by Φ. We continue in this way to conclude that every vertex on the grey circle must be fixed by Φ. But once we know that all of these vertices are fixed, then using valence and adjacency we can argue vertex by vertex that every vertex in the graph must be fixed by Φ. Hence Φ could not have had order two. Thus the Simmons-Paquette molecule has no automorphism of order two. Now it follows from the above theorem that the Simmons-Paquette molecule is topologically chiral.

While all of the known topologically chiral molecules have been proved to be so using one of the above techniques, there may be molecules that are synthesized or discovered in the future whose topological chirality cannot be proved using one of these techniques. So topologists continue to search for new methods to recognize and prove topological chirality. To learn more about topology and chemistry, see [Fl].

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