

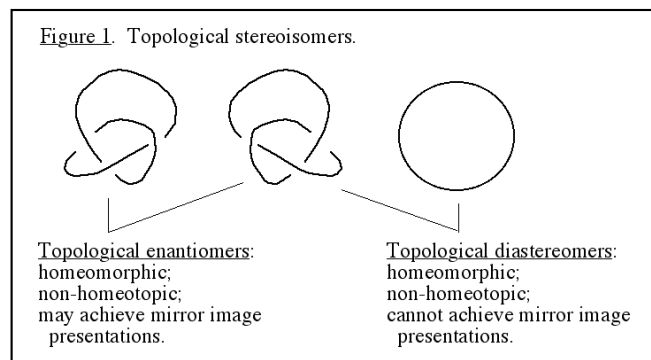
A Topological Hierarchy of Molecular Chirality and other Tidbits in Topological Stereochemistry

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Chemists have long been intrigued by the molecular basis of isomerism. Indeed, much of the powerful paradigm of structure based upon the molecular graph was first invented to explain isomerism, including the classifications used in modern stereochemistry. Thus, constitutional isomers describe pairs of isomeric molecular structures possessing non-homeomorphic molecular graphs, while the classical stereoisomers (enantiomers and diastereomers) possess molecular graphs which are homeomorphic and also homeotopic (interconvertible by continuous deformation in 3-space). This means that classical stereoisomerism is derived from the Euclidean properties of molecular graphs, being a manifestation of some kind of molecular rigidity.

Wasserman in his classic papers entitled "Chemical Topology" first focused the attention of chemists on the relevance of low dimensional topology in chemistry by proposing a possible approach to the synthesis of a molecular trefoil knot in addition to providing the foundation for the Biochemistry sub-discipline dealing with isomerism in circular DNAs.¹ The trefoil, recently realized in a small molecule structure for the first time by Dietrich-Buchecker and Sauvage,² serves as an example of a third type of isomerism which we first defined as topological stereoisomerism,³ as shown in Figure 1.



Topological stereoisomers possess molecular graphs which are homeomorphic but non-homeotopic. The trefoil has long been known to be topologically chiral, thus the two trefoils serve as the prototypical topological enantiomers (non-homeotopic mirror images). In addition, either trefoil and the unknot are homeomorphic, non-homeotopic, and unable to achieve mirror image presentations, and thus serve as prototypical topological diastereomers.

It was not until our synthesis of the first molecular Möbius strip,⁴ and the mathematical interest that followed, however, that the concepts of low dimensional topology

were applied to molecular graphs more complex than simple circuits (linked and knotted rings). In this paper, a brief discussion of some chemical implications of this fascinating interface between mathematics and chemistry are presented.

The Uncolored Möbius Ladders: An Application of Low Dimensional Topology in Chemistry

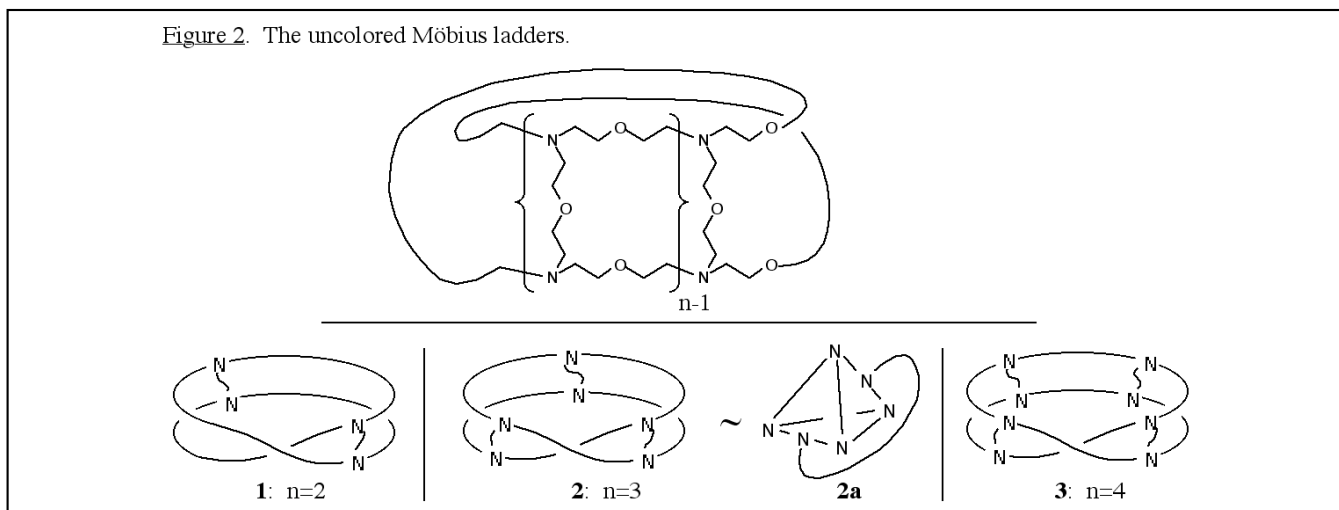
A fundamental question one may ask about the relationship between two molecular structures is whether the structures represent compounds which are, in principle, isolable under some stated conditions; in the following discussion room temperature and the "human time scale". This is equivalent to asking whether the molecular graphs are interconvertible, and when applied to knotted molecular graphs with the same molecular formula and constitution (homeomorphic) and a large number of atoms in the ring (flexible), is similar to the isotopy problem in knot theory. Of course, in small molecule chemistry, where only the simplest knot and simple links have been prepared to date, no new mathematics is required. It is well known, for instance, that even given infinite flexibility, the enantiomeric trefoils are indeed isolable (resolvable) under any conditions preserving constitution.

The novelty of modern topological stereochemistry is illustrated by the fact that a molecular graph may be topologically chiral even when possessing no knotted or linked subgraph. Thus, to our knowledge, the first graphs shown to be capable of supporting topological chirality independent of knots and links were the Möbius ladders.⁵ In the context of topological stereochemistry, Jonathan Simon and Erica Flapan proved several theorems on the low dimensional topological properties of the Möbius ladders.^{6,7} Here we describe some chemical implications of these theorems, illustrating an important application of low dimensional topology in chemistry.

First, consider the structures shown in Figure 2. While the arguments presented here hold for any compounds possessing the appropriate molecular graph, we chose to discuss the problem in terms of the homologous series of polycyclic amines shown in the Figure. We have discussed these particular compounds in the literature in terms of their intrinsic topology,⁸ and here extend the discussion to include extrinsic properties of the embedding in 3-space.

Note first that these graphs are uncolored in the sense that each edge ($-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$) and each vertex (N) is identical when taken independently of the graph. A chemi-

Figure 2. The uncolored Möbius ladders.



cally relevant question would be: which of these compounds is resolvable?

The lowest member of the series (**1**) has been prepared and characterized by Lehn and Graf.⁹ The "two-rung Möbius ladder" is, in fact, not a Möbius ladder, but a tetrahedral graph. Since the graph is planar (may be embedded in a plane with no crossings),¹⁰ it must be topologically achiral. Also, as may be seen in the rigidly achiral drawing of the structure indicated in the Figure (**2a**), the compound represented by the structure is clearly not resolvable at room temperature since chemistry tells us that even if the achiral conformation indicated is not an accessible minimum, at room temperature enantiomeric conformers would be rapidly interconverting. This illustrates the typical approach to determining whether a molecular structure is resolvable: attempting to find an achiral conformation.

Now consider the 3-rung uncolored Möbius ladder **2** (to our knowledge no such structure has yet been synthesized). While the presentation **2** is certainly rigidly chiral, it would be possible to prove using physical models that, in fact, the graph is topologically achiral, since it is possible to deform **2** into its mirror image! Indeed, the uncolored 3-rung ladder possesses rigidly achiral presentations (one is indicated in structure **2a**). Finally, chemical knowledge suggests that the compound is not resolvable at room temperature, since under these conditions the deformation taking **2** to its mirror image should be allowed.

So, using only the typical tools of the chemist (models and some chemical knowledge) we have managed to answer the question of resolvability for structures **1** and **2**. This, of course, assumes that the model manipulator is able to find the pathway for racemization of the 3-rung ladder or an achiral presentation. However, now consider graph **3**. One could make a model of this graph and try to find a pathway for racemization or an achiral presentation, but here no such pathway or presentation would be found. Nevertheless, this does not prove that the compound is resolvable, since a negative result with physical models is not rigorous.

One might argue that with enough work, a model manipulator would eventually find any racemization pathway existing in a graph as simple as **3**, but somehow this seems unsatisfying, since it is often surprisingly difficult to find specific continuous deformations (i.e. from **3** to its mirror im-

age) in this type of system. Clearly, it would be useful to know whether **3** is resolvable. This is the role of low dimensional topology. By application of the mathematical machinery of knot theory to graphs, one may prove unequivocally whether a graph is topologically chiral. If the graph is topologically achiral, then application of chemical knowledge is necessary to determine whether the interconversion between mirror images is possible in the chemical system. If, however, the graph is topologically chiral, then any molecular realization of that graph must be chemically chiral under conditions preserving constitution.

Thus, Simon provides an elegant answer to the resolvability question in regard to compound **3** with his proof that the uncolored 4-rung Möbius ladder is, indeed, topologically chiral.⁶ Therefore, compound **3** must, in principle, be resolvable based upon rigorous geometrical proof rather than a negative result using model manipulation. It is also interesting to note, as we have pointed out,⁸ that conventional graph theory shows that all nine edges of the 3-rung ladder are in fact homotopic (the deformation of graph **2** into its mirror image takes a "rung" to an "edge"), while the rungs of the 4-rung ladder are heterotopic with the edges, i.e. the rungs essentially color themselves in the 4-rung case. Thus, as shown by Lehn experimentally, the 2-rung ladder has only 2 peaks in the carbon NMR spectrum, and the 3-rung ladder would also show only 2 peaks. However, the 4-rung ladder (racemic or enantiomerically pure) would exhibit in principle (and probably in practice with available spectrometers) 4 peaks in the carbon spectrum, two each for the edges and the rungs.

A Topological Hierarchy of Molecular Chirality

Consideration of the low dimensional topological properties of graphs more complex than simple circuits has led to the discovery of new ways to classify chiral and achiral molecular graphs. This classification is completely rigorous, being based upon Euclidean and topological properties of the graphs. But, it is also possible to rank the classes of molecular graphs by "degree of chirality", from most chiral to least chiral. While this ranking is to some extent ad hoc (a compound is either resolvable or not, and one cannot really say that one molecule is "more chiral" than another),

Table 1. Topological Hierarchy of Molecular Chirality.

Most Chiral	↑	<u>Intrinsically chiral graph</u> : No topologically achiral embeddings
Resolvable	↓	<u>Topologically chiral embedding of an intrinsically achiral graph</u>
	↓	<u>Nominal Euclidean chirality</u> : Rigidly chiral presentation (or set of presentations) of a topologically achiral graph with no pathway for racemization

Non-resolvable	↓	<u>Topological rubber glove</u> : Topologically and chemically achiral but rigidly chiral in every presentation
	↓	<u>Euclidean rubber glove</u> : Topologically and chemically achiral but rigidly chiral in every accessible presentation (conformation)
Least Chiral		<u>Nominally achiral</u> : Rigidly achiral presentation accessible

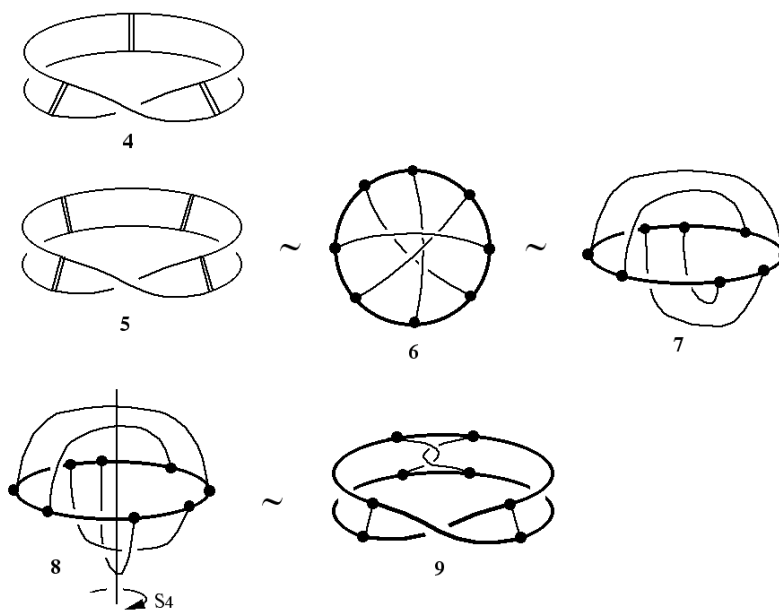
it is reasonable, and affords an interesting framework for discussion of the classification scheme, as described here.

Classes of Resolvable Graphs

As shown in Table 1, our hierarchy of chirality has six classes: three resolvable and three non-resolvable. At the top of the list, representing the most chiral molecules, are those possessing intrinsically chiral molecular graphs. An intrinsically chiral graph is defined as a graph possessing no achiral embeddings in 3-space.¹¹ That is, any embedding of an intrinsically chiral graph is homeomorphic only to topologically chiral graphs. Note that prior to the exploration of topological stereochemistry, no such object had every been described, since knot theory dealt with knots and links, and all knots and links are homeomorphic to achiral embeddings (unknotted or unlinked rings).

Stimulated by topological stereochemistry, and in particular the low dimensional topology of the Möbius ladders, Erica Flapan first proved the existence of intrinsically chiral graphs in 1987.⁷ Thus, Simon proved that the 3-rung Möbius ladder with colored rungs, realized chemically in the 3-rung molecular Möbius strip **4** shown in Figure 3, (a tetrahydroxymethylethylene-fused (THYME) poly crown ether), is topologically chiral.⁶ Flapan then showed that indeed this graph, and any Möbius ladder with an odd number of colored rungs, possesses no

Figure 3. Intrinsically chiral 3-rung Möbius ladder with colored rungs, and chiral and achiral embeddings of the 4-rung ladder.



achiral embedding. This makes compound **4** the most chiral organic molecule known, at the top of the hierarchy shown in Table 1.

Interestingly, Flapan showed that the 4-rung Möbius ladder **5**, also realized chemically in the THYME polyethers, and also proven by Simon to be topologically chiral, is in fact intrinsically achiral. This rather surprising result is easily proved using physical models. Thus, two alternative presentations of the 4-rung ladder embedded as in **5** are indicated by **6** and **7**. In the latter, the coloring of the rungs is indicated not by a double bond, but rather by different line weights.

It is easily seen that drawing **8** is in fact an alternative embedding of the 4-rung ladder. However, note that **8** is rigidly achiral, possessing an S_4 axis normal to the plane of the ring as indicated. Thus, we have a proof that the 4-rung ladder **5** is homeomorphic to an achiral embedding, and is therefore not intrinsically chiral. An alternative presentation of graph **8** is shown in **9**. It is interesting to note that cursory examination suggests that **9** is perhaps even more chiral than **5**, although a chemical realization of **9** with enough flexibility (probably necessary for the synthesis anyway), would not be resolvable.

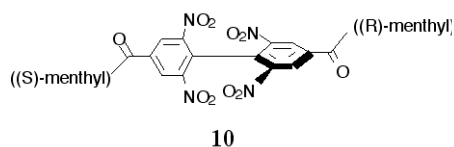
Thus, compound **5** joins the molecular trefoil knot, the topologically chiral link of Sauvage,¹² and the 4-rung THYME Möbius ladder synthesized in our laboratories¹³ as examples of the second most chiral molecules: topologically chiral embeddings of intrinsically achiral graphs. Of course to date an achiral colored Möbius ladder such as **8/9** has not yet been realized chemically.

Lowest on the list of resolvable molecular graphs are those topologically achiral graphs which are resolvable due to Euclidean properties, the typical scenario in chemistry for resolvable compounds.

Classes of Non-Resolvable Graphs

At the bottom of the hierarchy of chirality are, of course, nominally achiral molecules with accessible rigidly achiral conformations. In some accessible minimum on the conformational hypersurface, the molecular graph of such molecules possesses an improper axis of symmetry, and is congruent with its mirror image. It has been known within the chemical community for quite some time, however, that non-resolvable (as opposed to achiral) molecules need not possess accessible rigidly achiral conformations. Mislow first pointed this out in 1954,¹⁴ and actually synthesized the very elegant example shown in Figure 4.¹⁵

Figure 4. The Mislow Euclidean rubber glove.



Thus, the biphenyl derivative **10** possesses four nitro substituents meta to the Ph-Ph bond, and chiral carbonyloxy groupings at the p-p' positions. The chiral alcohol units are enantiomeric. If the biphenyl unit could become coplanar, then the molecule would represent a typical meso compound, with a mirror plane of symmetry bisecting the Ph-Ph bond. However, with the nitro substituents in place, the structure with coplanar phenyls is not accessible at room temperature, and in fact the molecular graph can not become rigidly achiral. Concurrent rotation about the p-p' bonds by 90° , however, interconverts mirror image conformations, thus providing an obligatory chiral pathway for racemization.

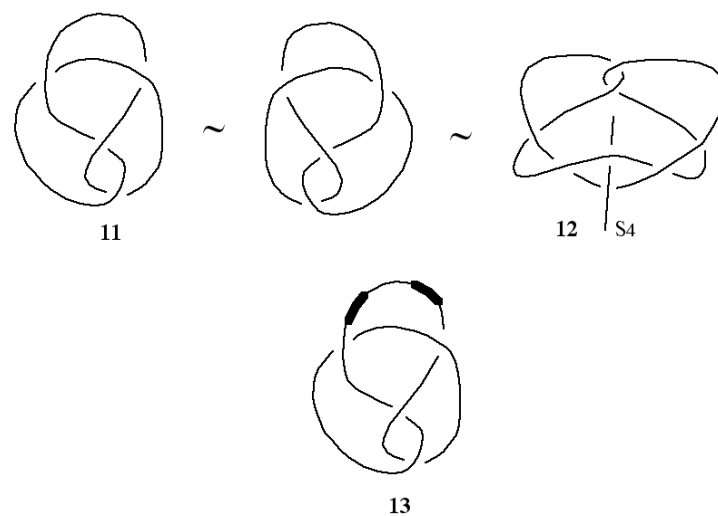
Given specified conditions, the lack of an accessible achiral conformation or intermediate in non-resolvable

molecules is a well defined Euclidean property of the molecular graph. Such molecules share this property with Euclidean rubber gloves, which also "racemize" via a chiral pathway (by turning "inside-out") and are referred to as molecular Euclidean rubber gloves in the hierarchy. Note that Euclidean obligatory chiral pathways for racemization of non-resolvable molecules is not restricted to exotic structures such as **10**. Indeed, cis-1,2-dimethylcyclohexane also racemizes by a chiral pathway at room temperature.

The biphenyl **10**, cis-1,2-dimethylcyclohexane, and a rubber glove all racemize by chiral pathways due to the Euclidean properties of the objects. Topologically, the molecules, and even the rubber glove, have rigidly achiral presentations. For the glove, one such presentation is simply a flat disk. In the context of topological stereochemistry it is natural to ask whether any object exists which is topologically achiral but rigidly chiral in every possible presentation. We have dubbed such objects topological rubber gloves by analogy with their Euclidean counterparts.

It may be argued that a molecular topological rubber glove represents the most chiral non-resolvable class of compounds, and thus we put this class at the top of the non-resolvable classes in the hierarchy. But, do such objects exist? Indeed, the answer to this question was unknown when first posed by us in 1983. At that time, using a negative result with physical models, we had pro-

Figure 5. The figure-of-eight knot and a topological rubber glove.



posed a candidate topological rubber glove: the figure-of-eight knot **11** (Figure 5).^{3a}

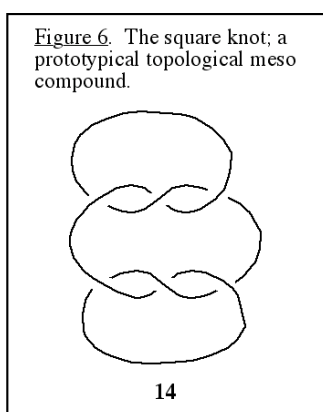
However, in this case the negative result was in fact false. The figure-of-eight does possess the rigidly achiral presentation **12** with an S_4 axis of symmetry. It was not until later that Erica Flapan proved that indeed topological rubber gloves do exist, and showed that one of the knots with a minimum of 10 crossings represents such an object.¹⁶ Later still, Simon and Flapan showed that a figure-of-eight knot with a single colored point (or line segment), two colored points (**13**) or three colored points is

also a topological rubber glove. To our knowledge this is structurally the simplest example known.^{3c} It is interesting to point out that the topological rubber glove is the only class in the hierarchy which has not yet been realized in a molecular structure. Work aimed at remedying this situation is in progress in our group.

Cubane Diyl and a Topological Meso Compound

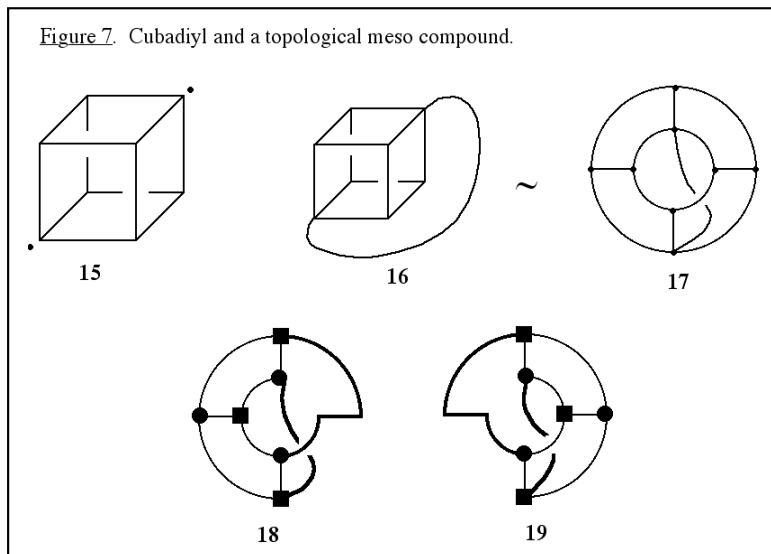
There are now several examples known of topological enantiomerism and topological diastereoisomerism. But, to date there is still no example of a topological meso compound. Indeed, there is no definition of such an object, though certain structures certainly fit the intuitive meaning of the phrase. Thus, the sum of two enantiomeric trefoils (the square knot **14** illustrated in Figure 6) possesses rigidly achiral presentations, and is obviously topologically achiral, although it possesses two topologically chiral parts. One possible definition of a topological meso compound would be as follows: A topologically achiral object which can be converted to a topologically chiral object by simplifying moves, i.e. removing crossings of a knot, or removing vertices and/or edges of a graph.

We have recently discovered a surprisingly simple graph representing a topological meso compound, and describe it as a fascinating illustration of how seemingly



simple graphs can possess topologically interesting properties. To introduce the topological meso compound, we will first consider the 1,4-dehydrocubane species recently discussed in the literature by the groups of Eaton, Michl and Borden.¹⁷ This structure is composed of an array of carbon atoms at the vertices of a cube, with valences filled by hydrogen at each carbon except at two diagonal corners. If a bond forms between these two atoms, an interesting nonplanar graph results. 1,4-dehydrocubane itself almost surely exists as a biradical as shown in Figure 7 (**15**; cubadiyl). However, a molecule with the same topology as the hypothetical 1,4-bonded dehydrocubane can be easily envisioned by linking the 1,4 positions of the cube by a long chain of atoms as indicated by structure **16**.

Consider the topological properties of this relatively simple molecule. A more illuminating homeotopic presentation of the graph is shown in **17**. From this presentation it seems clear that the graph is non-planar, and the proof of this assertion is given in **18**, showing a $K_{3,3}$ subgraph.



In fact, the $K_{3,3}$ graph in **18** is a 3-rung Möbius ladder with two colored rungs. By Simon's proof of the topological chirality of the colored 3-rung ladder, the graph **18** is topologically chiral. Thus, the 1,4-linked cubane possesses a topologically chiral subgraph. However, the graph itself is obviously achiral, possessing rigidly achiral presentations! How can this be? Of course the homeotopic graphs **16** and **17** possess two 3-rung Möbius ladder subgraphs which are topologically enantiomeric (**18** and **19**), and graph **16** is a topological meso compound.

It may be stated with a high degree of confidence that structure **16** will be much more easily prepared than a molecular square knot. In addition, while none of the achiral Möbius ladders discussed above (the uncolored 3-rung ladder or the achiral embedding of the colored 4-rung ladder (**9**)) has yet been prepared, a synthesis of **16** would in fact represent realization in covalent bonds and atoms of an achiral Möbius ladder (actually two enantiomeric Möbius ladders in the same structure). To our knowledge, no such synthesis has yet been accomplished.

Conclusion

While we consider the topological results described above highly interesting, the real chemical implications seem restricted to the important task of determining the limits on resolvability (and all this implies) of compounds with topologically non-trivial molecular graphs. We have yet to discover a purely chemical means of differentiating intrinsically chiral molecules from Euclideanly chiral molecules, for instance. Topology does, however, serve as a rich source of new targets for total synthesis, and the field of synthetic topological stereochemistry is quite active. Sauvage's beautiful synthesis of the first molecular knotted ring serves as the most recent landmark result in this area. However, examples such as the topological rubber glove and achiral Möbius ladders, in addition to more classic problems such as the Borromean rings, provide additional challenges in topologically stereocontrolled synthesis.

Acknowledgements

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