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A Commentary on the Topological Chirality and Achirality of Molecules*

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The concept of topological chirality is traced from its historic origins to its present-day connection to chemistry. In contrast to geometrical chirality, the topological chirality of molecules depends on models of bonding and is not directly tied to experimentally observable chirality phenomena. Nevertheless, studies dealing with the topological chirality and achirality of molecular graphs have played a significant role in an area where chemistry and topology intersect.

> »Insofern sich die Sätze der Mathematik auf die Wirklichkeit beziehen, sind sie nicht sicher, und insofern sie sicher sind, beziehen sie sich nicht auf die Wirklichkeit«.
>
> Albert Einstein (1921)[1]

Nearly four decades ago I spent a sabbatical year in Vlado Prelog's laboratory at the ETH. It was a memorable period for me, thanks in no small measure to the many hours of lively discussions with my host, whose thought-provoking disquisitions were invariably embellished by witty and pointedly apposite anecdotes. On the occasion of his 80th birthday, when I was honored as the first Prelog Medalist, I had the pleasure of dedicating a paper to my old friend and mentor. Now, ten years later, it is once again my privilege to dedicate a paper to a distinguished scientist and an inspiring teacher.

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* Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.

TOPOLOGICAL CHIRALITY AND ACHIRALITY

Herschel's finding, in 1822,[2] that there exists a causal relationship between the handedness of hemihedral quartz crystals and their sense of optical rotation, together with concurrent studies by Biot and Fresnel, had prepared the ground for Pasteur's momentous discovery, in 1848,[3] that crystalline hemihedry and optical rotation are similarly correlated in the tartrates. This discovery, which led to Pasteur's insight that the optical activity of tartaric acid is a manifestation of »dissymétrie moléculaire«,[4] marks the beginning of modern stereochemistry.

That same year, 1848, also saw the publication of a groundbreaking paper by Listing,[5] a contemporary of Gauss at Göttingen. In this paper, Listing laid the basis for a new branch of mathematics that he called »Topologie«:

> Unter der Topologie soll also die Lehre von den modalen Verhältnissen räumlicher Gebilde verstanden werden, oder von den Gesetzen des Zusammenhangs, der gegenseitigen Lage und der Aufeinanderfolge von Punkten, Linien, Flächen, Körpern und ihren Theilen oder ihren Aggregaten im Raume, abgesehen von den Mass- und Grössenverhältnissen.

The knottings and linkings of threads come under the heading of this new subject, and in that connection Listing pointed out that trefoil knots exist in two and only two distinct types, individual presentations of which (Figure 1) are related by a »Perversion«, the term that he used for reflection through a plane. Listing further noted that these two knot types cannot be transformed into one another by continuous deformations. It was not until 66 years later, after further developments in combinatorial topology, that this empirical observation could be backed by a rigorous mathematical proof.[6]

The property described above for the trefoil knot is now called topological chirality. A construction, such as a knot, link (catenane), or graph, is said to be topologically chiral if and only if it cannot be converted into its mirror image by a continuous deformation in 3-space; otherwise it is topologically achiral. Proof of an object's topological chirality is generally hard to come by. Thus, »there is no known [general] algorithm for deciding whether or not

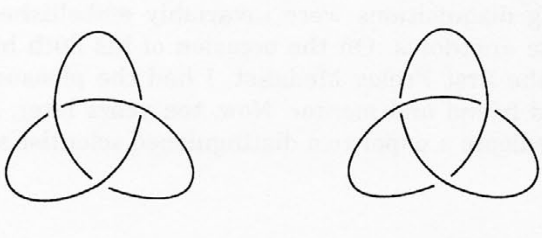


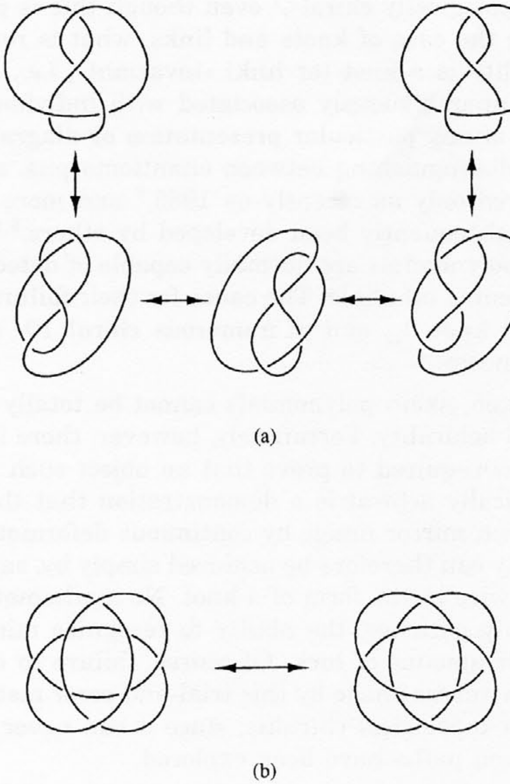
Figure 1.

a given graph is topologically chiral«,[7] even though this is possible in some particular cases. In the case of knots and links, what is required for proof of topological chirality is a knot (or link) »invariant«, *i.e.*, a mathematical object that can be unambiguously associated with individual knot or link types, independent of any particular presentation or diagram. The first invariant capable of distinguishing between enantiomorphs, a »skein polynomial«, was discovered only as recently as 1985,[8] and more powerful skein polynomials have subsequently been developed by others.[9,10] Nevertheless, even though these polynomials are normally capable of detecting topological chirality, none of them is infallible. The cause for their failure, as in the case of the classic chiral knot 9_{42} and of numerous chiral 10- and 12-crossing knots,[11] is still unknown.

By the same token, skein polynomials cannot be totally relied upon for proofs of topological achirality. Fortunately, however, there is a way out: by definition, all that is required to prove that an object such as a knot, link, or graph is topologically achiral is a demonstration that the object can be converted into its own mirror image by continuous deformation. An empirical proof of achirality can therefore be achieved simply by, say, manipulating a piece of string or wire in the form of a knot. No mathematical skill whatever is required, only patience, the ability to recognize mirror-image relationships, and a fair amount of luck. Of course, failure to convert a chiral presentation into its mirror image by this trial-and-error method is inadmissible as evidence for topological chirality, since it can never be proven that all possible conversion paths have been explored.

As an example of this method of proof, consider the figure-eight knot (Figure 2). A chiral presentation of this knot can be converted into its mirror image in two ways: either by reflection through the plane of projection, a physically impossible but mathematically realizable transformation that switches all over- and undercrossings in the enantiomorphous diagrams, or by the physically feasible transformation of continuous deformation, as illustrated in Figure 2a. It follows that the figure-eight knot must be topologically achiral.

The figure-eight knot belongs to a class of knots that can attain presentations with S_{2n} symmetry.[12] Presentations with achiral symmetries are called »rigidly achiral«.[13] Rigid achirality is synonymous with geometrical achirality, and suffices as proof of topological achirality in knots, links, and graphs. The S_4 presentation of the figure-eight knot can be converted into its mirror image in two ways: either by reflection through the plane of projection, which switches all over- and undercrossings in the diagram, or by a 90° rotation about the C_2 axis, as illustrated in Figure 2b. A rotation is merely a special type of continuous deformation, one that corresponds to an isometry. Isometries are transformations on rigid bodies in which the distances that separate any two points within the body remain invariant. They



(a)

(b)

Figure 2.

are of two kinds: translation and rotation (the first kind), and reflection, or reflection combined with translation or rotation (the second kind). Two objects are isometric if they can be rendered congruent by an isometry. We saw that congruence of the S_4 presentation and its mirror image can be achieved by either kind of isometry, but only the rotation in Figure 2b, which is an isometry of the first kind, qualifies as a continuous deformation.

There are also topologically achiral knots, links, and graphs that cannot attain rigidly achiral presentations. For objects in this class, interconversion of enantiomorphous presentations by continuous deformation, as exemplified for the knot 8_{17} in Figure 3, cannot proceed by way of a rigidly achiral state.[13] Consequently, failure to convert a chiral presentation of such an object into its mirror image by the manipulation of strings and the like means, given the fallibility of skein polynomials, that it may be impossible in certain cases to determine with complete certainty whether an object is topologically chiral or not.

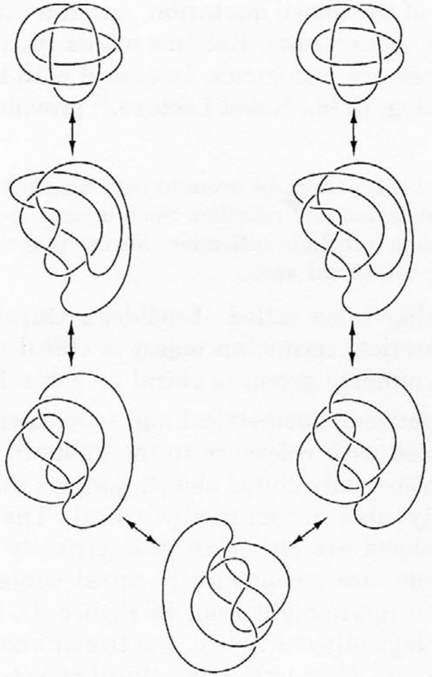


Figure 3.

GEOMETRICAL CHIRALITY AND ACHIRALITY

The definition of »chiral« made its first appearance in a footnote of a lecture entitled »The Molecular Tactics of a Crystal« that Sir William Thomson, who had become Lord Kelvin the year before, delivered to the Oxford University Junior Scientific Club on May 16, 1893.[14] Later reprinted verbatim as Appendix H of Kelvin's »Baltimore Lectures«,[15] the famous footnote reads:

> I call any geometrical figure, or group of points, *chiral*, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself. Two equal and similar right hands are homochirally similar. Equal and similar right and left hands are heterochirally similar or »allochirally« similar (but heterochirally is better). These are also called »enantiomorphs«, after a usage introduced, I believe, by German writers. Any chiral object and its image in a plane mirror are heterochirally similar.

The »Baltimore Lectures« were delivered at Johns Hopkins University in October of 1884, well before the lecture to the Oxford University Junior Scientific Club. A careful examination of the record shows, however, that the term »chiral« was not used in any of them at the time.[16]

From the context of the above quotation, »similar« may be taken to have the same meaning as »congruent«. Kelvin's words thus imply that the only allowed transformations are isometries. In accord with this definition of geometrical chirality, Prelog, in his Nobel Lecture,[17] provided the following definition:

> An object is chiral if it cannot be brought into congruence with its mirror image by translation and rotation. Such objects are devoid of symmetry elements which include reflection: mirror planes, inversion centers, or improper rotational axes.

Geometrical chirality (also called »Euclidean chirality«)[18] may thus be defined in group-theoretical terms: an object is chiral or achiral depending on whether its full symmetry group is chiral or achiral.[19]

The relationship between geometrical and topological chirality and achirality may be illustrated with reference to the knots in Figures 1–3. All the presentations of a topologically chiral object, such as the trefoil knot in Figure 1, are necessarily also geometrically chiral. The presentations of a topologically achiral object are either all geometrically chiral (*e.g.* the knot 8_{17} in Figure 3) or some are geometrically chiral while others are geometrically achiral (*e.g.* the figure-eight knot in Figure 2). Geometrically chiral objects are either topologically chiral (*e.g.* the trefoil knot) or achiral (*e.g.* the figure-eight and 8_{17} knots). Geometrically achiral objects are necessarily also topologically achiral. Similar relationships obtain for links and graphs.

In the course of studying some symmetry properties of topologically achiral knots,[12] we discovered that the definitions of geometrical and topological chirality (or of their conceptual equivalents) were, by a curious coincidence, enunciated at approximately the same time and place! The story is as follows.

On February 17, 1873, twenty years before his lecture to the Oxford University Junior Scientific Club in which he defined »chiral« and »chirality«, Thomson read a lecture to the Royal Society of Edinburgh entitled »Note on Homocheiral and Heterocheiral Similarity«.[20] Unfortunately, because the text of the lecture was never published, all that we are left with is the title. Evidently, after an interval of two decades, Thomson/Kelvin had decided to streamline these terms by dropping the »e« in »cheiral«, even though the original spelling was a more faithful transliteration of χειρ. As it happens, however, a related term, »amphicheiral«, is still current in the mathematical literature, its original spelling intact. This term, which is synonymous with »topologically achiral in 3-space«, was introduced and defined in 1877 by the Scottish physicist Peter Guthrie Tait.[21] Tait, the Professor of Natural Philosophy in the University of Edinburgh, was the foremost pioneer of what we might call empirical knot theory, to distinguish it from the mathematically rigorous discipline that it is today. Significantly, Thomson, who was the Professor of Natural Philosophy in the neighboring University of Glasgow, was a close colleague of Tait, whose work on knots was stimulated by Thomson's theory of vortex atoms.[22] »Homocheiral« and »heterocheiral«, which Kelvin later defined (after purging the »e«) with reference to geometrical chirality, and »amphicheiral«, which Tait defined with reference to topological chirality, are therefore contemporaneous coinages of Scottish provenance, all dating from the same period, around 1872–77.

In light of these findings, there is little doubt that »cheiral« and »cheirality« were the original spellings of these terms.

SYMMETRY OF STATIC AND DYNAMIC MOLECULAR MODELS

The abstract mathematical objects discussed above may be used as models of molecular structures. The former are intangible constructs that exist entirely within our imagination, whereas molecules or their ensembles are concrete entities that exist entirely within the realm of our experience. Nevertheless, a connection can be made. The classic example is the conjunction of axiomatic (mathematical) and practical (physical) geometry, which Einstein formulated as follows:[1]

> Feste Körper verhalten sich bezüglich ihrer Lagerungsmöglichkeiten wie Körper der euklidischen Geometrie von drei Dimensionen; dann erhalten die Sätze der euklidischen Geometrie Aussagen über das Verhalten praktisch starrer Körper.

The construction of a model requires a process of abstraction and idealization in which nonessential features are deliberately discarded; as a result, the model summarizes selected aspects of the system and suppresses, or even falsifies, others.[23] To exemplify this process of idealization, it may be useful to recall that although no two hands are strictly enantiomorphous or congruent (as any fingerprint expert will attest), one can still classify hands by their gross, inexact, but intuitively obvious symmetry-related properties: right hands are »alike« in the sense that they can shake each other, while left hands fail this test with right hands. A model of handshaking that attributes congruence, *i.e.*, homochirality,[14] to all right hands is thus a faithful one for this particular purpose, even though false to fact.

Because the concept of symmetry and chirality in chemistry has a well-defined meaning only in relation to experiment,[19] each structural model must be chosen appropriately to match a particular set of observations. In many types of observations, for example in the determination of X-ray structures, the molecule is approximated as a rigid body and is represented by a geometrical figure, the static model. Most commonly this takes flesh as an iconic model[24] of the familiar ball-and-stick or space-filling variety. Of course, even supposedly rigid molecules are far from that: their atoms vibrate about time-averaged positions. Nevertheless, the choice of a static model under the rigid-body approximation is reasonable because a rigid molecule occupies only a single minimum on the potential-energy hypersurface.

The symmetry of a static model (and, by implication, of the molecule that it represents) is given by its point group. Well before the advent of structural theory and the asymmetric carbon atom of van't Hoff, Pasteur[4] first discussed a static molecular model with reference to its chirality :

> Les atomes de l'acide [tartrique] droit sont-ils groupés suivant les spires d'une hélice dextrorsum, ou placés aux sommets d'un tétraèdre irrégulier, ou disposés suivant tel ou tel assemblage dissymétrique déterminé? Nous ne saurions répondre à ces questions. Mais ce qui ne peut être l'objet d'un doute, c'est qu'il y a groupement des atomes suivant un ordre dissymétrique à image non superposable. Ce qui n'est pas moins certain, c'est que les atomes de l'acide gauche réalisent précisément le groupement dissymétrique inverse de celui-ci.

More recent examples of static models in which chirality plays a central role are Prelog's stereomodel, on which the Cahn-Ingold-Prelog (CIP) system of stereochemical nomenclature is based,[25] and Ruch's model, developed in connection with his general theory of chirality products,[19,26] in which n ligands are partitioned among the n sites of an achiral permutation skeleton.

The rigid-body approximation becomes inappropriate in dealing with nonrigid, *i.e.*, flexible or fluxional, molecules because a nonrigid molecule occupies more than one minimum, with the various minima separated by low-energy barriers. Under these conditions a dynamic model is required.[23] As an example, consider the proton-decoupled ^{19}F-NMR spectrum of *cis*-1,2-difluorocyclohexane. At room temperature, only a single resonance line is observed, and the molecule behaves as if it had a plane of symmetry. It is therefore faithfully represented by a model with achiral (C_s) symmetry. One may, if one chooses, refer to a time-averaged structure at the fast inversion limit that results from the rapid interconversion of enantiomeric structures, but all one really needs to know is that the observation (in the absence of accidental isochrony) does not demand a model of lower symmetry. Because cyclohexane behaves at room temperature as if it had D_{6h} instead of D_{3d} symmetry,[27] what is actually observed is the physical manifestation of a symmetry higher than the »true« (*i.e.*, static) one. To the objection that knowledge of structural chemistry demands an asymmetric model for *cis*-1,2-difluorocyclohexane, in which one fluorine atom is axial while the other is equatorial, the response is that the failure to observe more than a single resonance line is merely the result of the particular conditions of observation: lower the temperature sufficiently, and the multiplet predicted by the static (*i.e.*, asymmetric) model at the slow exchange limit will be observed. We thus have two faithful representations for the same chemical system, one chiral and the other achiral, and which one applies depends on the particular conditions of measurement.

In the preceding example, one can at least conceive of a C_s-symmetric structure for *cis*-1,2-difluorocyclohexane and of a D_{6h}-symmetric structure for cyclohexane within the conformational spaces of these two molecules. Yet there are cases in which the symmetry of a nonrigid molecule on the fast-exchange time scale cannot be portrayed by the point-group formalism. The classic example is that of freely rotating ethane, whose dynamic symmetry is given by a permutation-inversion group[28] of order 36 that is isomorphic to the direct-product group $D_3 \times D_3$ but not isomorphic to the point group of any conceivable conformation of ethane, or indeed to any point group at all! In such a case, establishment of chirality or achirality of the model is far from straightforward. As an example, consider a compound of the type 4-[(*R*)-Cabc]-4'-[(*S*)-Cabc]-2,2',6,6'-tetra-R-biphenyl, such as (–)-menthyl (+)-menthyl 2,2',6,6'-tetranitro-4,4'-diphenate, in which conformational racemization cannot proceed *via* an achiral intermediate (Figure 4).[29] If the four blocking groups (R) in the 2,2',6,6'-positions are large enough, so that the two benzene rings cannot become coplanar, the molecule is asymmetric in all realizable conformations and the compound exists as a mixture of transient dl-pairs. However, these dl-pairs can interconvert by torsion around the bonds to -Cabc; for example, either one of the two enantiomorphous conformations in Figure 4 (related by the mirror line *m*) can convert into the other by a 90° twist of the biphenyl moiety (or, equivalently, of the two -Cabc end groups) in either direction. Like *cis*-1,2-difluorocyclohexane, this molecule is »chemically achiral«[30] because each momentary geometry of the molecule can be superposed on its mirror image by a combination of the rotations, translations, *and* intramolecular motions that can occur under the given

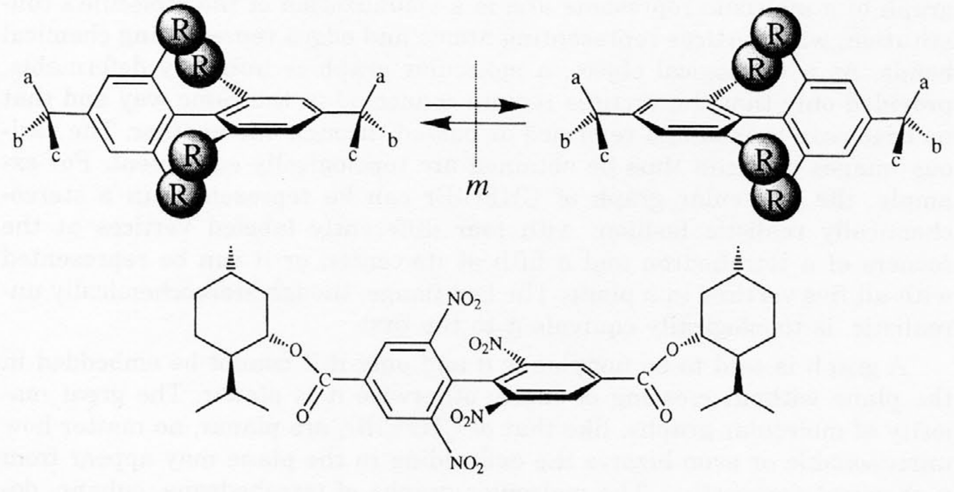


Figure 4.

conditions of observation. In contrast to *cis*-1,2-difluorocyclohexane, however, there is no realizable achiral structure within the conformational space of the biphenyl, whose dynamic symmetry cannot be expressed by any point group but only by supergroups patterned after the molecular symmetry group of Longuet Higgins,[28] such as Ugi's »chemical identity group«[30] or Günthard's »isometric group«.[31] Although the dynamic symmetry of the biphenyl is isomorphic to the point group S_4, which expresses the chemical achirality of the molecule, no conceivable conformation of the molecule belongs to this point group.

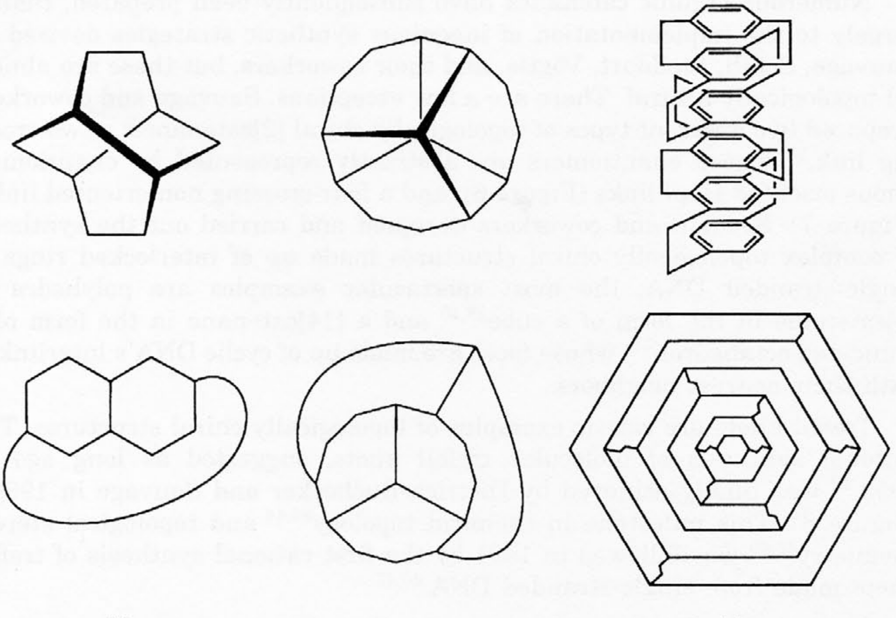
In short, regardless of whether the model is static or dynamic, chemical chirality or achirality is determined by geometrical transformations (isometries) combined with intramolecular motions (if any). The symmetry of the system is then given by a point group or by a supergroup.

TOPOLOGICAL MODELS OF MOLECULES

The models discussed in the preceding section all adhere to what might be called »essential shape conservation«. That is, bond distances and angles in such models remain within reasonable limits, while intramolecular deformations (mainly of torsion angles) are limited to those that are energetically feasible. Thus, a molecule is chemically achiral if its geometrical structure can be deformed to that of its mirror image by way of realizable molecular motions; otherwise it is chemically chiral.

None of these constraints on shape and energy apply to topological models of molecules. The most common of these is the molecular graph. The graph of a molecule represents and is a visualization of the molecule's constitution, with vertices representing atoms and edges representing chemical bonds. As a topological object, a molecular graph is infinitely deformable, provided only that the vertices remain connected in the same way and that no edges are broken and reformed or passed through one another. The various images that can thus be obtained are topologically equivalent. For example, the molecular graph of CHFClBr can be represented in a stereochemically realistic fashion, with four differently labeled vertices at the corners of a tetrahedron and a fifth at its center, or it can be represented with all five vertices in a plane. The last image, though stereochemically unrealistic, is topologically equivalent to the first.

A graph is said to be nonplanar if and only if it cannot be embedded in the plane without crossing of edges; otherwise it is planar. The great majority of molecular graphs, like that of CHFClBr, are planar, no matter how unreasonable or even bizarre the embedding in the plane may appear from a chemical perspective. The molecular graphs of tetrahedrane, cubane, dodecahedrane, and buckminsterfullerene, for example, are all planar. A pla-



(a) (b) (c)

Figure 5.

nar graph cannot be topologically chiral. It follows that, with few exceptions, the constitutions of geometrically chiral molecules, such as CHFClBr, are represented by topologically achiral graphs. We say that such molecules are topologically achiral. For example, the top row in Figure 5 depicts the structures of (a) twistane,[32] (b) tritwistane,[33] and (c) [6]chochin,[34] while the bottom row depicts the planar images of the corresponding molecular graphs. The three molecules, all of which are geometrically chiral and have been obtained in optically active form, are therefore topologically achiral.

One obvious way of achieving topological chirality is by knotting or catenating a molecular graph. Such a graph is topologically nonplanar, though not necessarily topologically chiral. When Wasserman reported the first synthesis of a molecule with two interlocked rings (a [2]-catenane) in 1960, he provided »the first demonstrated example of a compound in which the topology of the system must be considered in describing its structure«.[35] At about the same time, in a classic paper with Frisch,[36] Wasserman introduced the concept of topological isomerism, as between knotted and unknotted rings, and thus launched the subject of »chemical topology«. It is noteworthy that, according to Prelog, catenanes had already been mentioned by Willstätter in a seminar at Zürich, almost half a century earlier.[36]

Numerous organic catenanes have subsequently been prepared, thanks largely to the implementation of ingenious synthetic strategies devised by Sauvage, Schill, Stoddart, Vögtle, and their coworkers, but these are almost all topologically achiral. There are a few exceptions. Sauvage and coworkers prepared two different types of topologically chiral [2]catenanes: a two-crossing link,[37] whose enantiomers are abstractly represented by enantiomorphous oriented Hopf links (Figure 6), and a four-crossing non-oriented link[38] (Figure 7). Seeman and coworkers designed and carried out the synthesis of complex topologically chiral structures made up of interlocked rings of single-stranded DNA; the most spectacular examples are polyhedra (a [6]catenane in the form of a cube[39,40] and a [14]catenane in the form of a truncated octahedron[41]) whose faces are made up of cyclic DNA's interlinked with their nearest neighbors.

Trefoil knots are classic examples of topologically chiral structures. The rational synthesis of molecular trefoil knots, suggested as long ago as 1953,[42] was finally achieved by Dietrich-Buchecker and Sauvage in 1989[43] (Figure 8). This milestone in chemical topology[36,44] and topological stereochemistry[45,46] was followed in 1991 by the first rational synthesis of trefoil knots made from single-stranded DNA.[40,47]

Catenated molecules in Nature were first discovered in the mitochondrial DNA of human cells by Vinograd and coworkers in 1967,[48] while single- and double-stranded DNA knots were first observed in 1976.[49] A great variety of catenated and knotted circular DNA's have subsequently been observed in diverse biological systems,[50] and by now have become a common-

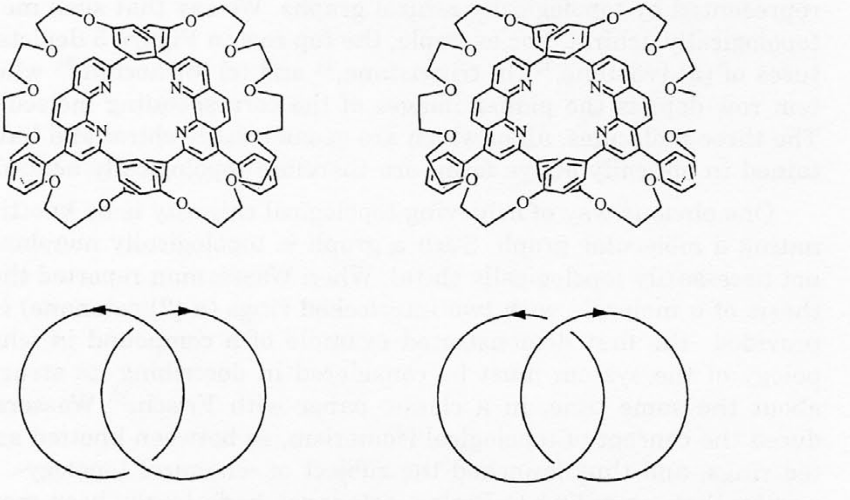


Figure 6.

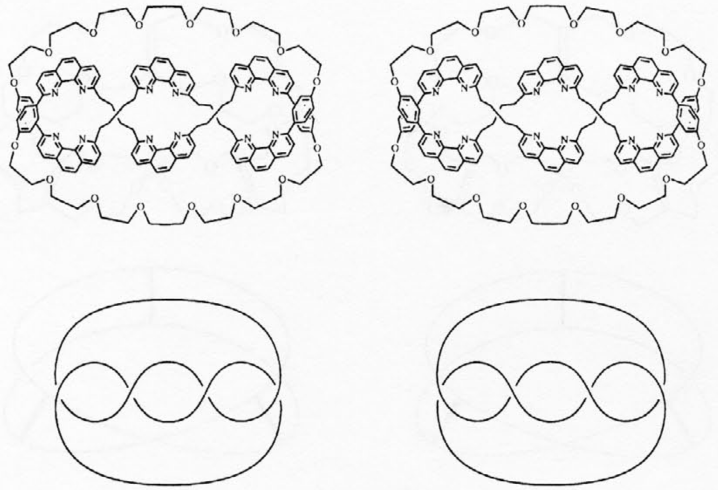


Figure 7.

place in »biochemical topology«.[51] A number of catenated and knotted structures have also been recently observed among proteins.[52] All of these natural products are topologically chiral.

The catalogue of topologically chiral molecular graphs is not restricted to knots and links.[53] Graphs of the latter, though nonplanar, all have at

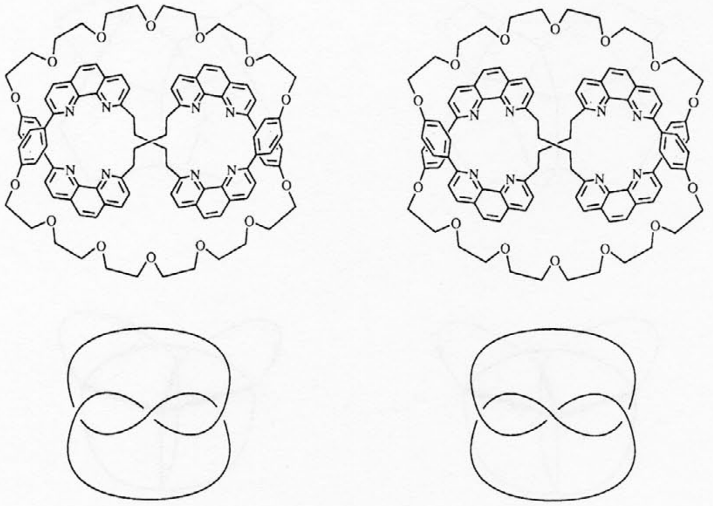


Figure 8.

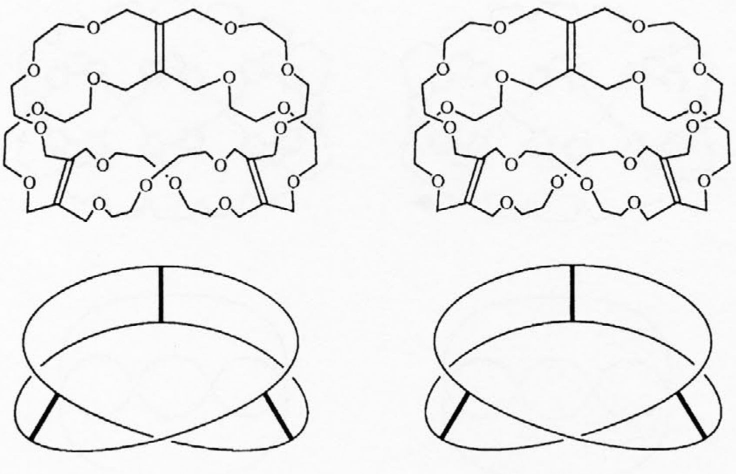


Figure 9.

least one planar, and hence achiral, embedding. For example, the trefoil knot can be embedded as a circle or a polygon (the »unknot«) and the oriented Hopf link as a pair of unlinked circles or polygons (the »unlink«). We say that all knots are homeomorphic to the unknot and all links to the unlink. There are, however, other nonplanar graphs that do not have any planar embeddings. Graphs in this class are said to be intrinsically nonplanar.

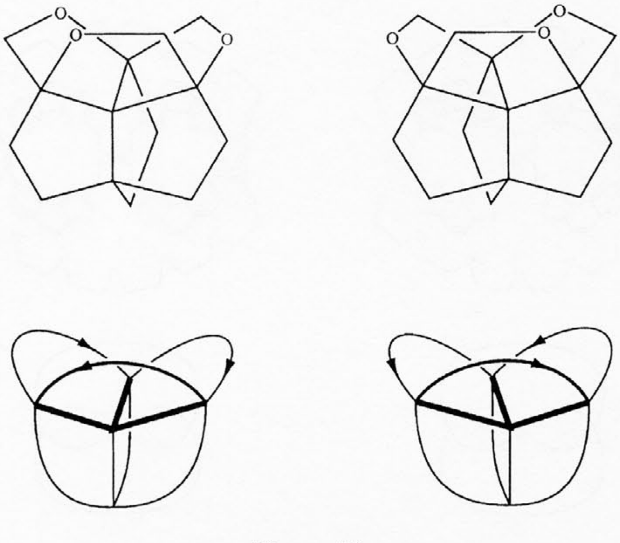


Figure 10.

The necessary and sufficient condition for intrinsic nonplanarity is the existence of a subgraph that is homeomorphic or contractible either to $K_{3,3}$, the complete bipartite graph on two sets of three vertices, or to K_5, the complete graph on five vertices.[54] What this means is that such a graph is reducible either to $K_{3,3}$ or to K_5 by suitable deletions of one or more edges or vertices, or by contractions of two adjacent vertices (by deletion of the edge(s) between them and then fusing the two vertices into a single one). The classic examples of topologically chiral molecular graphs in this class are Walba's 3-rung Möbius ladder molecule[55] and the Simmons-Paquette molecule.[56] As originally conjectured by Walba[46] and later proven by Simon,[7,57] both of these molecules are topologically chiral. Figure 9 depicts the enantiomers of Walba's molecule, along with the corresponing $K_{3,3}$ subgraphs, obtained by contraction, in which three edges corresponding to the three rungs (*i.e.* double bonds) in the Möbius ladder are colored, while Figure 10 depicts the enantiomers of the Simmons-Paquette molecule, along with the corresponding K_5 subgraphs, obtained by contraction, in which three edges are colored and three others are oriented.

Enantiomers of topologically chiral molecules are examples of topological stereoisomers.[36,46] Topological enantiomers are necessarily also geometrical enantiomers. The converse is rarely the case because most geometrically chiral molecules are topologically achiral. The distinction between geometrical and topological stereoisomers can be further illuminated with reference to geometrical and topological diastereomers. Although chemists write different planar projections for geometrical diastereomers, *e.g.* of *cis*- and *trans*-1,2-dichloroethene, or of glucose and mannose, the molecular graphs of these diastereomers are topologically equivalent. This is not the case for topological diastereomers. For example, a macrocyclic hydrocarbon such as $(CH_2)_{54}$ can, in principle, exist in knotted and in unknotted forms.[36] The constitutions of these two topological diastereomers are exactly the same, as are their adjacency matrices, but their molecular graphs are distinct: one is planar and topologically achiral, whereas the other is nonplanar and topologically chiral. Similarly, the constitutions and adjacency matrices of topologically diastereomeric links are exactly the same, but their molecular graphs are distinct. For example, the molecular graph of the topologically chiral four-crossing link in Figure 7 is distinct from that of the corresponding topologically achiral two-crossing link.

ON THE CHOICE OF TOPOLOGICALLY SIGNIFICANT BONDS

There is no problem in identifying the vertex set in a molecular graph that represents the constitutional formula of a molecule because each vertex bears a one-to-one correspondence to an appropriately labeled atom in the molecule. The relationship of edges in the graph to bonds in the molecule is, however, far less well defined. This point warrants an elaboration of some earlier remarks on this theme[52,53,58] because it has an important bearing on the subject of topological chirality in molecules.

The crucial question is: which bonds in the molecule are regarded as »topologically significant«?[46] Different authors differ in their answers to this question.[53] As Prelog and Helmchen pointed out, the concept of a chemical bond is »nicht scharf definierbar«;[25b] the root of the difficulty »lies in the historical sanction of localized valence bond formulas, which, for all their virtues of convenience, imply a sharpness of definition which is physically unsound: for the sake of simplicity, degrees of atomic interaction in a molecule are ignored, and pairs of atoms are regarded as either bonded or not«.[58] Inevitably, therefore, considerable arbitrariness is built into the definition of a molecular graph, specifically with regard to membership in the edge set. According to Walba, only covalent bonds are to be so regarded, while »H-bonds, ion-ion bonds, ion-dipole bonds, or dipole-dipole bonds are not considered edges of a molecular graph«.[46] While this definition has the advantage of being consistent with common usage in organic chemistry, where »molecular graph« carries the same meaning as »constitutional formula« or »localized valence bond diagram«, there is no good reason to limit the edge set to covalent bonds. Thus, Chambron *et al.*[18] included metal-ligand and metal-metal bonds in their edge set, along with »purely covalent« bonds, although, following Walba, they also excluded »H-bonds, ion-ion, ion-dipole and dipole-dipole bonds«. Nevertheless, as Walba remarked, »even the term covalent bond is arbitrary«,[46] since there is, in the general case, a continuum between covalent and ionic bonds. In the words of Cotton and Wilkinson:[59]

> As soon as one changes from elements, where the adjacent atoms are identical and the bonds are necessarily nonpolar, to compounds, there enters the vexatious question of when to describe a substance as ionic and when to describe it as covalent .... Suffice it to say that bonds between unlike atoms all have some degree of polarity and (1) when the polarity is relatively small it is practical to describe the bonds as polar covalent ones, and (2) when the polarity is very high it makes more sense to consider that the substance consists of an array of ions.

An element of uncertainty is thus introduced, and whether or not a given geometrically chiral molecular model is considered to be also topologically chiral depends on which subset of bonds in the molecule is considered to be topologically significant. As an extreme example of the sort of quandary that one may have to face, consider the hypothetical derivative of [1.1.1]propellane shown in Figure 11. The bridgehead atoms of this derivative are different isotopes of carbon, and the remaining carbons are bridged by three polymethylene chains of different lengths. There is no question whatsoever that this molecule is geometrically chiral, regardless of whether or not there is a bond between the isotopic bridgehead carbons. The topological chirality of this molecule, however, depends crucially on the existence of this bond.

If the bond exists, the molecule is topologically chiral because the molecular graph, shown at the top of Figure 11, is nonplanar (it is contractible to K_5) and all of its vertices are nonequivalent (the molecular constitution is asymmetric). If the bond does not exist, the molecule is topologically achiral because the molecular graph is planar, as shown in the structure at the bottom of Figure 11. The question of whether or not there is a central bond in [1.1.1]propellane has been studied at length,[60] but there is no universal consensus since »all of the arguments put forward for the existence of a central bond in [1.1.1]propellane can be matched with a counterargument except for the heat of formation«.[60c] On the one hand, the charge density distribution points to the existence of a bond between the bridgehead carbons.[60d] On the other hand, this electron density makes no contribution to holding the bridgehead carbons together.[60a] Hence, whether this molecule is considered to be topologically chiral or not depends entirely on what criteria are used to define the central bond.

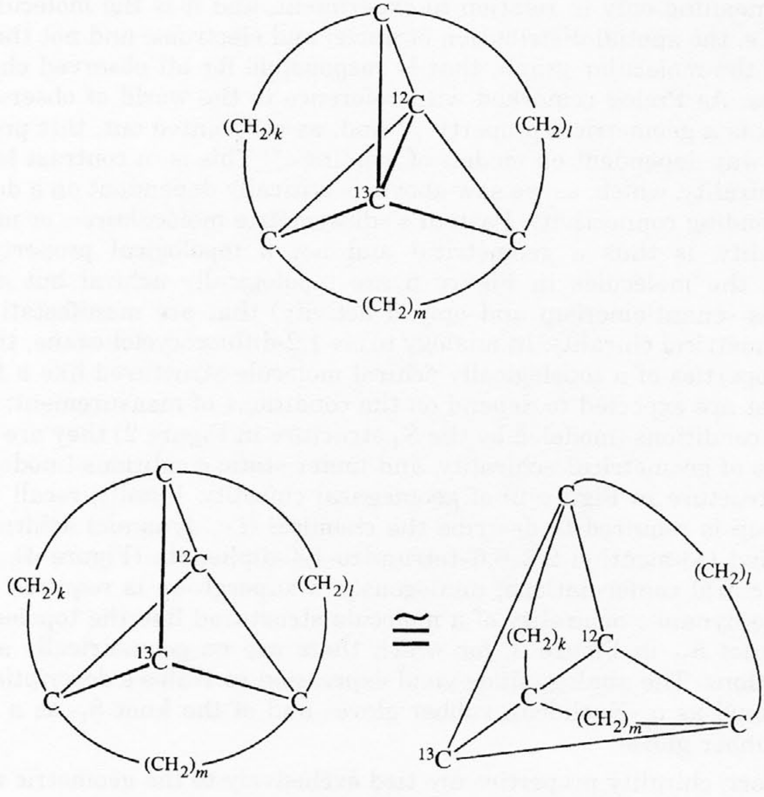


Figure 11.

TOPOLOGICAL CHIRALITY AND ACHIRALITY IN CHEMISTRY

As we saw, uncertainties in defining membership in the edge set are virtually unavoidable. Attribution of topological chirality to a molecule thus rests on shaky grounds because it is utterly dependent on an inherently arbitrary selection of »topologically significant« bonds. Nevertheless, for most organic compounds »chemists have no trouble at all constructing a molecular graph«, [46] and, once the members of the edge set are selected, all uncertainty vanishes. The molecular graph is then treated exactly as a topological object[7] in which consideration of metrics and internal energy play no role. For example, whereas it is physically impossible to flatten the molecules in Figure 5 so that all the atoms lie in a plane while all the bonds remain intact, planarization of the corresponding molecular graphs is a perfectly unexceptionable topological operation.

Thus, the topological chirality or achirality of a molecule refers exclusively to its molecular graph, and not necessarily to a physically realistic model. Yet, as noted above, the concept of chirality in chemistry has a well-defined meaning only in relation to experiment, and it is the molecular geometry, *i.e.* the spatial distribution of nuclei and electrons, and not the symmetry of the molecular graph, that is responsible for all observed chirality properties. As Prelog remarked with reference to the world of observables, »chirality is a geometrical property«,[17] and, as we pointed out, this property is »in no way dependent on models of bonding«.[61] This is in contrast to topological chirality, which, as we saw above, is critically dependent on a description of bonding connectivity. Pasteur's »dissymétrie moléculaire«, or molecular chirality, is thus a geometrical and not a topological property. For example, the molecules in Figure 5 are topologically achiral but exhibit properties (enantiomerism and optical activity) that are manifestations of their geometrical chirality. In analogy to *cis*-1,2-difluorocyclohexane, the chirality properties of a topologically achiral molecule structured like a figure-eight knot are expected to depend on the conditions of measurement: under dynamic conditions (modeled by the S_4 structure in Figure 2) they are manifestations of geometrical achirality, and under static conditions (modeled by the C_2 structure in Figure 2) of geometrical chirality. Finally, recall that a supergroup is required to describe the chemical (*i.e.* dynamic) achirality of (–)-menthyl (+)-menthyl 2,2',6,6'-tetranitro-4,4'-diphenate (Figure 4), which has no achiral conformations; analogously, a supergroup is required to describe the dynamic achirality of a molecule structured like the topologically achiral knot 8_{17} in Figure 3, for which there are no geometrically achiral presentations. The analogy finds vivid expression in Walba's description[46] of the biphenyl as a »Euclidean rubber glove« and of the knot 8_{17} as a »topological rubber glove«.

In short, chirality properties are tied exclusively to the geometric model. This being the case, what is the relevance of topological chirality or achirality to chemistry?

The answer, in brief, is that molecules with nonplanar graphs represent a novel, not to say exotic, structural type, that this topological perspective has sparked fruitful investigations in a previously unexplored area where chemistry and topology intersect, and that studies dealing with the topological chirality and achirality of such graphs have played a significant role in these investigations.

The last two decades witnessed a dramatic acceleration in the growth of topological chemistry and stereochemistry, due to a combination of factors. Continuing developments in biochemical topology played an important role, as did the pioneering groundwork laid by Wasserman,[36] Schill,[62] and Walba,[46] which suggested a variety of novel synthetic targets. The subsequent development of appropriate methodologies made possible the synthesis of molecular trefoil knots and of many different types of catenated molecules; a recent example is the topologically achiral [5]catenane »olympiadane«.[63] Aside from the challenge to devise novel synthetic strategies, motivation for this work derived no doubt also from the intellectual and aesthetic delight afforded to chemists, as much as to artists and mathematicians, by knotted or linked objects: their universal appeal lies in their apparently limitless capacity to adopt convoluted structures, and in the intricate beauty of some these structures. We are reminded of the intellectual and aesthetic allure of the regular (Platonic) solids, which served as the principal motivation for the synthesis of cubane and dodecahedrane and derivatives of tetrahedrane. Similar considerations undoubtedly played a part in the enormous effort invested in the study of buckminsterfullerene, a beautiful structure with the symmetry of a semiregular truncated icosahedron.

Another factor responsible for the recent spurt of studies in chemical topology was the synthesis of the Simmons-Paquette molecule and of Walba's 3-rung Möbius ladder molecule. Neither of these molecules qualifies as a knot or a link, yet both of their graphs are topologically chiral. Walba recently pointed out[55b] that the synthesis of the 3-rung Möbius ladder molecule »inspired the invention of new mathematics, which then suggested new targets for synthesis, and the cycle is continuing«, and went on to suggest several new targets for chemical synthesis that were inspired by topology. One of these, a molecular version of the topological rubber glove, has recently been realized in single-stranded DNA tied into a figure-eight knot.[64] Another target is a molecular version of the Borromean link, which is among the most fascinating of topological constructions: three mutually disjoint simple closed curves form a link, yet no two curves are linked (Figure 12). Thus, if any one curve is cut, the other two are free to separate. Given its unique construction, it comes as no surprise that realization of the Borromean link in molecular form is considered a synthetic goal well worth achieving.[65] As Martin Gardner put it,[66] »Who can guess what outlandish

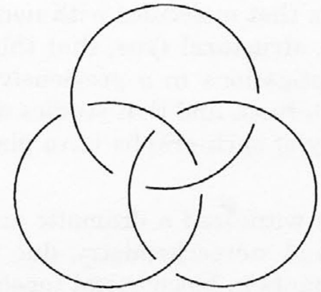


Figure 12.

properties a carbon compound might have...if its molecules were joined into triplets, each triplet interlocked like a set of Borromean rings?« Although more than 30 years have passed since Wasserman expressed the view that molecular Borromean links »require a minimum string of 30 carbons« in each of the three rings,[36] and since van Gulick discussed the 3-braid approach to the synthesis of such a link,[67] the synthetic goal remains elusive. Nevertheless, Walba has predicted that »certainly one day molecular Borromean rings will be created by a directed approach«.[55b]

As is evident from these examples, the process of mutual stimulation and crossfertilization between chemistry and topology may result in unforeseen conceptual (or at least methodological) advances in both fields. Some results from our own work on topological chirality, detailed below, further illustrate this interplay between chemistry and mathematics.

From Chemistry to Mathematics

The CIP system of stereochemical nomenclature allows the assignment of configurational descriptors (R and S) to a broad variety of organic molecules. Its successful use in chemistry prompted the thought that it might be possible to design a scheme to partition knots into mutually heterochiral classes. The challenge was to discover a way of assigning a knot to one of two homochirality classes, so that any two presentations of a given knot are homochirally similar. The homochirality concept is strictly applicable to knots because topological enantiomorphs cannot, by definition, be interconverted by continuous deformation; enantiomorphous knots are therefore not chirally connected. Topologically chiral knots vastly outnumber achiral ones: of the 12965 prime knots with a minimal crossing number of 13 or less, only 78 are topologically achiral.[12] We succeeded in developing a method that is applicable to all of these as well as to composite knots.[11] There are possible applications to biology: among DNA molecules, at least 13 different types of

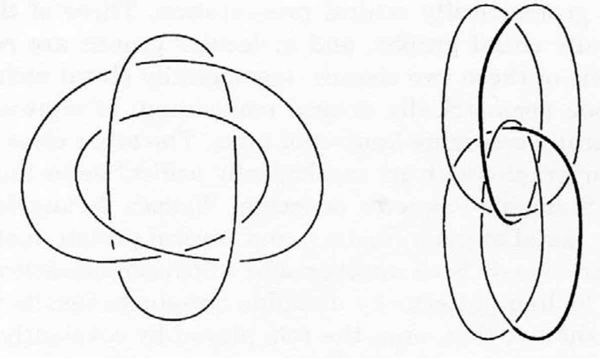


Figure 13.

topologically chiral prime knots (the trefoil knot, 3_1, and 12 others with up to nine crossings) have been identified, along with three topologically chiral composite knots (the granny knot, $3_1\#3_1$, and two others).[68]

The recent development of methods for detecting the topological chirality and achirality of links[65,69] furnished another instance in which concern with a chemical problem led to a novel development in mathematics. As noted above, numerous catenated molecules have been synthesized, and we were able to provide the first rigorous proof for the topological chirality of the four-crossing link (Figure 7), the abstract model of the only topologically chiral, non-oriented catenane synthesized so far.[38] In the course of this and related investigations we discovered the existence of a topologically achiral two-component link with an odd minimal crossing number.[69] No example had previously been known of a topologically achiral link, whether oriented or not, whose minimal crossing number is odd. Figure 13 shows a diagram of this unique link (left) and a geometrically achiral presentation of the same link with S_4 symmetry (right). Note that the S_4 presentation is equivalent to an array composed of the interlocked edges of two enantiomorphous Möbius strips! The serendipidous discovery of this link provided the opening for a more extensive investigation that led to the recognition of two unprecedented classes of topologically achiral links, one oriented and the other non-oriented, and both with odd crossing numbers.[69,70]

From Mathematics to Chemistry

We recently showed[53] that graphs are partitioned into six classes from the perspective of chirality, depending on whether they are topologically achiral, whether there is at least one topologically achiral embedding, whether there is at least one rigidly achiral embedding, and whether there is at least one geometrically achiral presentation. Three of the six classes cover topologically chiral graphs, and molecular graphs are represented in two of them. One of these two classes (topologically chiral molecular graphs with at least one geometrically achiral embedding) is represented by synthetic and naturally occurring knots and links. The other class (topologically chiral molecular graphs with no topologically achiral embeddings) is represented by the Simmons-Paquette molecule, Walba's 3-rung Möbius ladder molecule, a few metallorganic clusters, and several protein molecules. A few examples had previously been uncovered in which conformational restriction on polypeptide folding patterns by disulfide crosslinks results in topological chirality.[71] We showed that, once the role played by covalently bound cofactors (prosthetic groups) in conjugated proteins is taken into account, topological chirality in proteins is in fact more common than had previously realized; for example, in native iron-sulfur proteins, covalently bound Fe_4S_4 clusters induce topological chirality even in the absence of disulfide crosslinks.[52a] In the course of this work we discovered that quinoproteins with covalently bound cofactors contain catenated substructures, the first example of topological complexity found in a native protein. Motivated by this result we undertook a systematic survey of the Brookhaven Protein Data Bank. This search revealed the presence of catenated substructures in human chorionic gonadotropin, and of knotted and catenated substructures in ascorbate oxidase and human lactoferrin.[52b] All of these structures are topologically chiral. Though few in number, these are the first, and so far the only, examples of topologically non-trivial motifs in protein structures. Given the roughly exponential growth in new high-resolution protein structures that are solved every year,[72] it seems likely that additional examples will be uncovered in future years.

Of the six classes mentioned above, the three remaining ones cover topologically achiral graphs. Molecular graphs are represented in only one of these (topologically achiral graphs with at least one geometrically achiral presentation) because all known topologically achiral molecular graphs can assume geometrically achiral presentations. The vast majority of these graphs are planar, and hence are geometrically achiral when embedded in the plane. Far less common are topologically achiral molecular graphs with subgraphs that are either homeomorphic or contractible to $K_{3,3}$ or K_5. The presentations of such graphs are necessarily nonplanar.[54] A search for examples in this class revealed that, with rare exceptions, the graphs of these molecules are reducible both to $K_{3,3}$ and to K_5 by suitable deletions or contractions. The few exceptions are therefore of special interest. One of the earliest examples is basic beryllium acetate, Be_4OAc_6.[73] This molecule, whose graph is reducible only to K_5, is chiral in the crystal (T symmetry) but has attainable T_d symmetry. Kuck and Schuster reported the synthesis of the first geometrically achiral organic molecule whose graph is reducible only to K_5, the hydrocarbon centrohexaindane. The T_d conformation of this

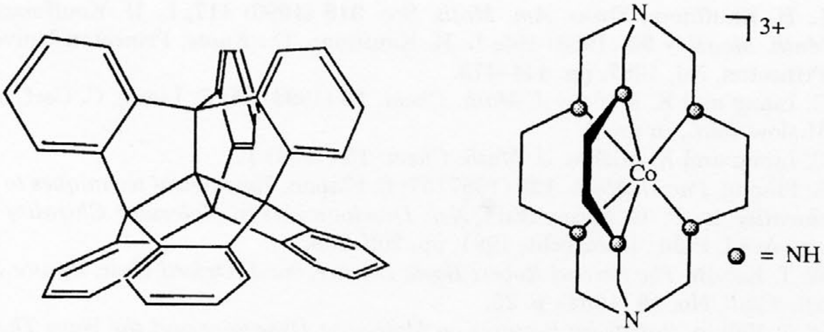


Figure 14.

molecule is depicted in Figure 14 (left).[74] Related molecules have been reported more recently.[75] Molecules with attainable geometrically achiral structures whose graphs are reducible only to $K_{3,3}$ are harder to find. Figure 14 (right) shows the D_{3h} conformation of a cobalt complex[76] that belongs to this class.

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SAŽETAK

Komentar topološke kiralnosti i akiralnosti molekula

Kurt Mislow

Skiciran je koncept topološke kiralnosti, od njegovih povijesnih početaka do njegove današnje veze s kemijom. Za razliku od geometrijske kiralnosti, topološka kiralnost molekula ovisi o modelima vezivanja i nije direktno povezana s eksperimentalno vidljivim fenomenima kiralnosti. Ipak, studije koje se bave topološkom kiralnosti i akiralnosti molekulskih grafova igraju značajnu ulogu u području gdje se kemija i topologija križaju.