Residual Topological Isomerism

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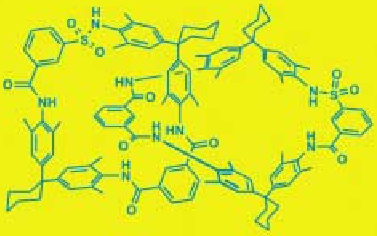
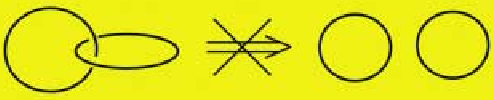
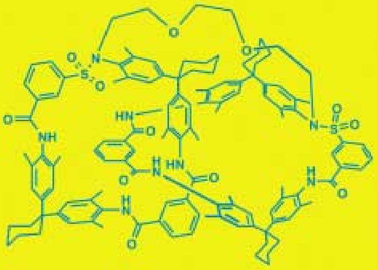
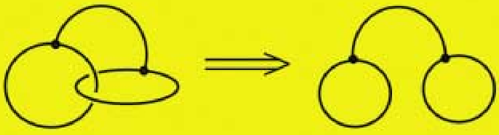




(A stone sculpture at the entrance of the Volksbank building, Bonn)

Residual Topology:





# of Intertwined Molecules

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Residual Topological Isomerism of Intertwined Molecules[+]

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Abstract: The growing number of molecular assemblies with unusual geometry and topology requires from time to time a revision of certain aspects of stereochemistry. The present paper analyzes several representatives of intertwined molecules that have bridges connecting their loops. In spite of the experimentally proven chirality, these species lack elements of both classical and topological chirality. Due to the relationship of these types of molecules to the well-recognized topologically nontrivial compounds, such as catenanes and knots, we propose the term "residual topology" illustrated by a simple scheme of excessive or missing bridges that could be excluded or included, respectively, in molecular graphs of these species to render them topologically nontrivial. This concept paper represents, therefore, an update on the currently applied nomenclature.

Keywords: catenanes · chemical topology · chirality · isomers · knots · rotaxanes

Introduction

Significant achievements in the synthesis of a variety of topologically nontrivial species, such as catenanes and knots,[1,2] stimulated the increase in communication between topologists and chemists.[3–5] In his book[1] Schill noticed "as the chemistry of molecules with mechanical bonds is extended and with it isomeric possibilities increase, further differentiations will have to be introduced into the nomenclature." Indeed, the topological techniques, such as knot theory,[3] and theories of molecular graphs[4] and molecular cell complexes[5] have evolved resulting in numerous interpretations of topological isomerism and topological chirality reviewed both by experimentalists and theoreticians.[4–9]

Topology studies those properties of an object that are invariant under conditions of arbitrary deformations.[3,5] In chemical topology[4,6] the object is a molecule or a molecular assembly that is schematically represented on paper as a graph. If the graph contains cross lines, then the graph and the molecule are called nonplanar and topologically nontrivial, respectively. Figure 1 shows examples of both nonplanar (**I** and **II**) and planar (**III**) graphs, which are simplified projections of trefoil knot (trefoilane) enantiomers and a cyclic molecule, respectively. The three structures **I**–**III** are topological isomers.

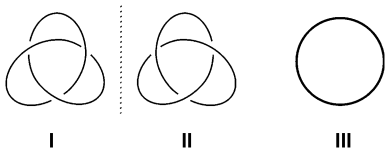

Figure 1. Nonplanar (**I** and **II**) and planar (**III**) graphs that are simplified projections of trefoil knot (trefoilane) enantiomers and a cyclic molecule, respectively.

Despite the simple topological rule to apply arbitrary deformation[3] on the molecular graph to find out whether two molecules are topologically isomeric or not, the differences between a real molecule and its mathematical representation initiated the revision of topological models.[5,8] For example, endohedral fullerene complexes and rotaxanes are topologically trivial from the viewpoint of graph theory. However, taking into account the chemical reality of stable endohedral fullerene complexes and rotaxanes, these compounds have been recently suggested to be considered as topologically nontrivial structures despite their planar molecular graphs.[8] The authors[8] go beyond the limitations of two-dimensional graphs and view a fullerene as an impenetrable polyhedron surface prohibiting the decomposition of endohedral complexes, and the stoppers of a rotaxane as infinite planes to reflect the actual impossibility of the wheel de-threading under common laboratory conditions.

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An additional, aggravating aspect is the chirality. If a nonplanar graph, such as **I** or **II** in Figure 1, cannot be deformed into its mirror image without cutting then such a graph is topologically chiral. Thus, chemical topology classifies the pair **I/II** in Figure 1 as topological enantiomers. In their fruitful discussion on the classification of topologically chiral molecules Liang and Mislow[7] used the molecular-graph approach to discern between classical and topological chirality. According to this classification the former category includes molecules that contain the classical stereogenic units,[10,11] such as, point, axis, helix, and plane, while the latter refers to the chirality of the nonplanar molecular graph.[4–9] However, as Mislow pointed out,[12] theoretical analysis of molecular graphs is extremely complex, because a general algorithm is lacking for deciding whether or not a given graph is topologically chiral.

Interesting examples are the molecular Möbius ladders (möbiusanes) with a variable number of rungs *n* (Figure 2). If $n=2$, the graph can be rendered planar making the molecule a topologically trivial, achiral object (Figure 2). If $n=3$, then the species is topologically nontrivial as can be deduced from the fact that the 3-rung Möbius ladder fits to the $K_{3,3}$ graph of Kuratowski.[5,13] Nevertheless, as illustrated in Figure 2, there exists a possibility to deform the three-rung Möbius ladder, such that it has a symmetry plane and is therefore lacking chirality.[14] Nonetheless, experimentally it has been proven[15–18] that the compounds **1**–**3** corresponding to Möbius ladders with $n=2$ or 3 depicted in Figure 2 are chiral though they do not have any classical stereogenic unit.[10,11] Agreement between theory and experiment can be obtained if one distinguishes sides and rungs of the three-rung Möbius ladder by assigning them different “colors”.[5] The discrepancy can also be overcome if the Möbius ladders are treated as Möbius strips,[8] which are classical topological objects.

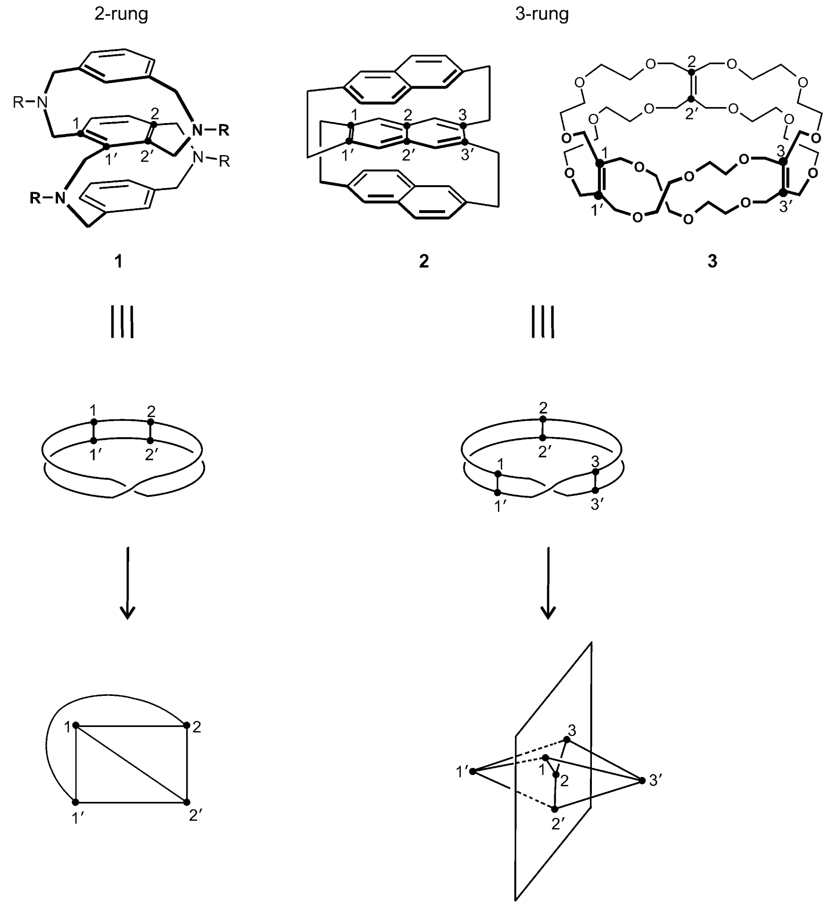
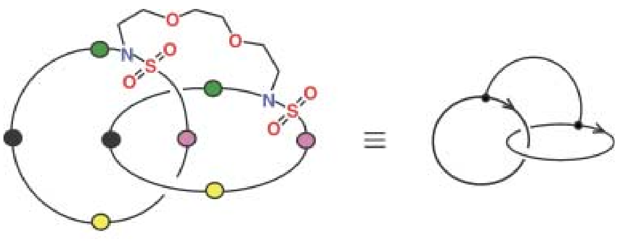


Figure 2. Molecular Möbius ladders with a variable number of rungs *n* ($n=2$ or 3).

As becomes evident from the short discussion on endohedral fullerenes, rotaxanes, and möbiusanes, there are different approaches for the translation of a real molecule into its graph and, as a consequence, the theoretical detection of both topology and chirality of a molecule depends on the method that is applied.[3,5] Nonetheless, chemists may not discard the mathematical analysis of molecular systems, since it provides useful insights into the origin of molecular symmetry, topology, and chirality. In this context a method based on building of a “molecular-cell complex”,[5] for example, in which impenetrable rings (e.g., benzene ring) are cells in the molecular graph, is an attractive theoretical tool that takes into account information regarding physically admissible deformations of a molecule and can therefore be recommended to chemists. This approach was shown to be very helpful in analyzing the origin of the chirality of [*m*][*n*]paracyclophanes and multilayered cyclophanes.[19] According to their molecular-cell complexes, the chirality of these cyclophanes is due to their topology rather than their geometry.[5] This conclusion contradicts, on the one hand, the accepted practical nomenclature on helical[10] or planar[11] chirality in cyclophanes and related systems. On the other hand, such contradictions indicate the necessity of an update on the established nomenclature pertaining to the molecular isomerism and elements of chirality in the light of the growing number of molecular assemblies with unusual geometrical and topological isomerism.[4–9,20] For instance, Diederich et al.[21] have recently introduced new chirality descriptors based on the clockwise and anticlockwise atom numbering in chiral fullerenes. The need for the new descriptors in this case was due to the fact that none of the standard stereogenic units could be assigned to the intrinsically chiral fullerene spheroids. Nicolaou, Boddy, and Siegel,[22] in turn, have discussed the limits of the Cahn–Ingold–Prelog (CIP) nomenclature concerning its applicability to some systems that involve different stereogenic units.



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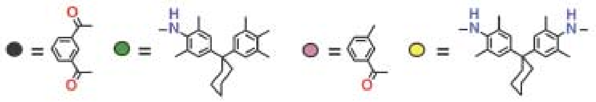

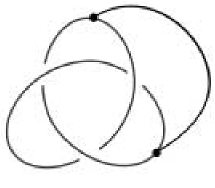

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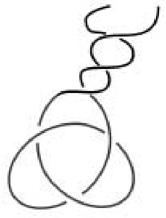

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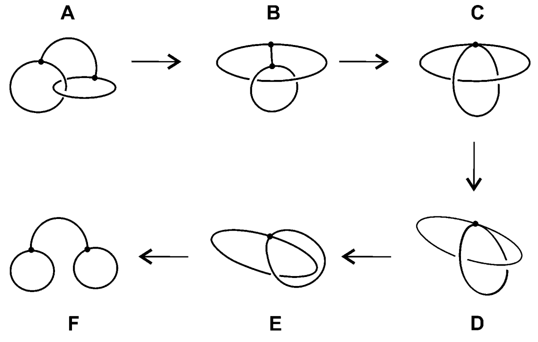


Figure 3. How a pretzel-shaped body can be converted into a topologically trivial species composed of two bridged rings.

In this contribution we want to draw attention to some problems regarding to the isomerism classification and their solution on the borderline between the rules of the standard topology and the physicochemical properties of the real molecules. Our interest was initiated by a figure showing how the pretzel-shaped body (a representation of the pretzel-shaped molecule **4**,[23] which can be viewed as a bridged [2]catenane) is converted into a topologically trivial species composed of two bridged rings (Figure 3).[24] The connection ("bridge" in the IUPAC language[25]) between the two rings may collapse to a point, which is common to the two rings. Then the two rings of the pretzel-shaped figure can dethread. The same procedure unties the bridged knot **5**.[26] This is especially remarkable, since the parent links and knots, representing molecular catenanes and knots, respectively, are well established to be topologically nontrivial. However, for real molecular examples of **4** and **5** de-threading without bond breaking appears impossible. If de-threading and threading were possible for compound **4**, an optically inactive mixture of pretzel-shaped molecule should result. On the contrary, the observed chirality of pretzelane **4**[23] is even more pronounced than that of its parent topologically chiral catenane (which is equivalent to an oriented Hopf link in topology[3,5]). A related issue has recently been pointed out by Taylor and co-workers,[27] who analyzed a number of knotted proteins. Despite the fact that some proteins have been shown to contain knots with loose termini (i.e., they may not be called "knots" in the strict mathematical sense), in reality it is impossible to disentangle these proteins due to numerous intramolecular hydrogen bonds. A knot **6** with coiled loose ends is the cartoon representation of one of the possible structures that such protein may assume. The authors call such proteins "pseudoknots"[27] to distinguish them from the true topological knots that are closed loops due to covalent bonds. Thus, as the authors point out, the definition becomes a matter of energy.

The evident problem for chemists in research and teaching at this point is to deal with the real isomerism of such topologically trivial compounds. In other words, the question arises how to describe the experimentally found chirality of these systems in the context of existing classifications if the chirality cannot be rationalized by means of classical stereogenic units and is not recognized in topology.[7] The abovementioned approach[8] going beyond graph theory to extend topological isomerism to rotaxanes and endohedral fullerene complexes fails at interpreting the topology of pretzelanes, pseudoknots, and related species.

Fortunately, there are intertwined molecules, including catenanes[1,2] (in topology they are called "links"[3,5]) and trefoil knots,[28–31] which belong to the well-established topological objects. We suggest using these structures as reference points in the analysis of the isomerism. Topologically trivial molecules such as the pretzelane **4** and the bridged knot **5** are then viewed as derived from topologically nontrivial species, such as [2]catenane and knot, respectively, through addition of bridges, and topologically trivial molecules, such as rotaxanes and the "pseudoknot" **6**, are similarly viewed as derived from [2]catenane and knot, respectively, through removal of bridges. In Figure 4 some examples with "missing" or "excessive" bridges are shown. Taking this relationship and the isomerism of the real molecules into account, we propose "residual topological isomerism" as the term to name this kind of isomerism.[32] In this way, the pretzel-shaped compound **4** represented in Figure 3 as graph **A** would be the "residual topological isomer" (or simply RT isomer) of two bridged rings corresponding to the graph **F** in Figure 3. Similarly, the enantiomers of **4** could be called "residual topological enantiomers". Interestingly, this approach allows for the rational treatment of isomerism and chirality in rotaxanes and their derivatives, such as the "molecular-8" structure[33] and the [1]rotaxane[34] (Figure 5) prepared by bridging the wheel and axle of the corresponding

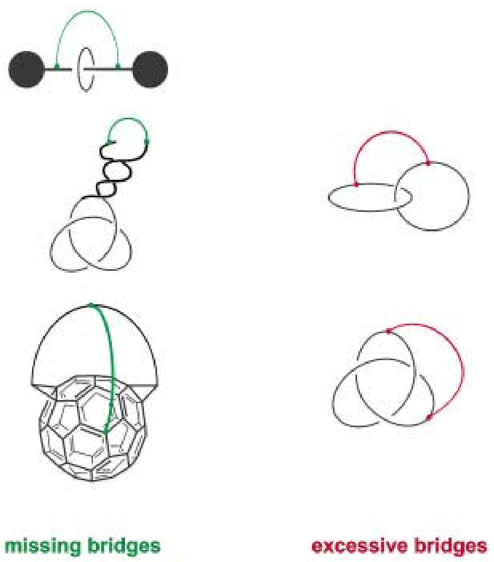


Figure 4. Examples of molecules with “missing” or “excessive” bridges.

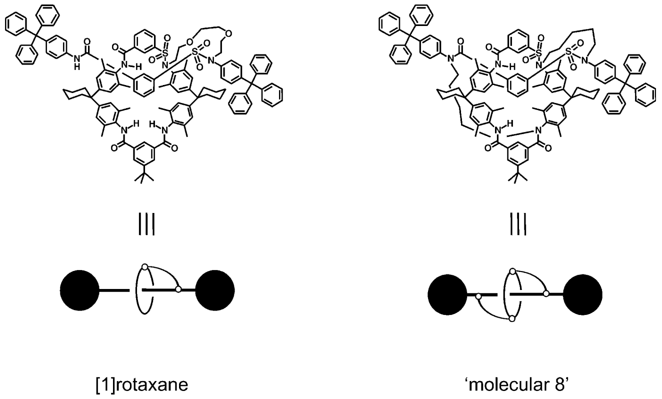
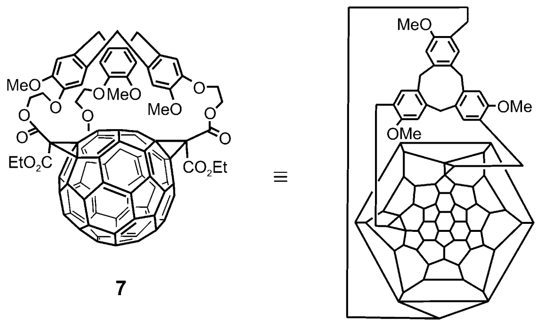


Figure 5. [1]Rotaxane and “molecular-8” structures.

[2]rotaxanes. Both compounds are examples of species with missing bridges. A doubly bridged catenane that has recently been obtained from tetraurea-calix[4]arene dimer is in turn a new representative of the pretzelane family bearing excessive bridges.[35] Moreover, the term “residual topological isomerism” can be applied to chiral fullerenes that contain bridges. Figure 4 shows how an additional bridge on a bridged fullerene transforms it into a topologically chiral object. Triply bridged C_{60} derivatives, such as **7**, have been established to be topologically chiral.[36] One could also think of an extension of the suggested approach toward interlocked compounds in which, similarly to the pseudoknots,[27] mechanically bonded constituent parts have bridges of noncovalent nature. This last class of compounds could be exemplified by catenanes and rotaxanes built up of metal-coordinated counterparts.[2,37,38]



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Conclusions and outlook

From the theoretical standpoint pretzelanes, pseudoknots, and related species are topologically trivial and achiral, but chemically they are certainly intertwined and chiral. What type of chirality is that? It is not a topological and not a classical one, so there is an apparent practical need for a name for this phenomenon. We propose “residual topological isomerism” (RT isomerism) as a descriptive term that views such compounds as derived from parent, topologically nontrivial species by addition or removal of bridges and thus accounts for the origin of experimentally found isomerism. Isomers of such molecular structures can be called RT isomers, while in case of chiral systems of this type the term “residual topological chirality” (RT chirality) can be applied.

Even though the present concept might not eliminate all the uncertainties that have to be clarified in the field of molecular entities with unusual geometry and topology, it helps to systematize a considerable number of mechanically intertwined species. The updates on the established nomenclature applicable to the molecular isomerism and elements of chirality will further be necessary due to the developments of relevant theoretical tools and the growing number of molecular assemblies with unusual geometrical and topological isomerism. Future theoretical efforts stimulated by corresponding experimental results should lead to the more accurate partition in the description of geometrical and topological means of isomerism and chirality phenomena.

Acknowledgement

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