

Classification of topologically chiral molecules

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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 rigidly achiral presentation. Three of these classes are well represented by a variety of chemical structures: topologically chiral molecular graphs with no topologically achiral embeddings, topologically chiral molecular graphs with at least one rigidly achiral embedding, and topologically achiral molecular graphs with at least one rigidly achiral presentation. Known representatives of these three classes are described. Various meanings associated with the concepts “molecular graph” and “intrinsic chirality” are critically discussed. Previous arrangements of molecular graphs and molecules in a hierarchical order, ranging from the most to the least chiral, are interpreted in terms of the graph’s and molecule’s “chiral persistence”.

1. Introduction

A *molecular graph* describes the molecular constitution or bond connectivity; in such a graph, differently labeled vertices represent different kinds of atoms and differently labeled edges represent different types of bonds, as will be discussed in further detail below. A graph is said to be *topologically chiral* if and only if it cannot be mapped onto its mirror image by continuous deformation. Because the vast majority of molecular graphs are *planar* – that is, embeddable in the plane without the intersection of any edges – and therefore necessarily achiral in euclidean 3-space, it follows that, with few exceptions, *geometrically* chiral molecules are *topologically* achiral (fig. 1). The inherent intellectual and aesthetic appeal of topologically *chiral* structures, such as knots, links, and Möbius strips or ladders, has long exerted a special fascination for chemists [1] and has motivated a spate of experiments aimed at the synthesis of molecules containing these exotic structural features [1–5]. Furthermore, the existence of this class of molecules has inspired a variety of schemes [6–8] designed to arrange molecular structures in a hierarchical order, ranging from the “most” to the “least” chiral [3,6,7]. In the present paper we present a systematic classification of chiral and achiral topological constructions and discuss the hierarchical ordering of chiral structures [3,6–8] in the light of this classification scheme.

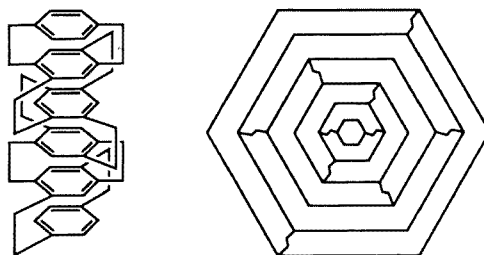


Fig. 1. An example of a geometrically chiral molecule paired with its topologically achiral planar graph: (-)-(R, R, R, R)-[6]Chochin, with hydrogen atoms suppressed for clarity (M. Nakazaki, K. Yamamoto, S. Tanaka and H. Kametani, *J. Org. Chem.* 42 (1977) 287).

2. Chirality as a criterion for the classification of graphs

We begin our discussion with a consideration of simple graphs. Abstractly defined [9], a simple graph is a pair $(V(G), E(G))$, where $V(G)$, the vertex set, is a non-empty finite set of points (vertices), and $E(G)$, the edge family of G , is a finite set of unordered pairs of vertices. The edges, though drawn as line segments, merely symbolize neighborhood relationships between pairs of vertices, so that the actual image (presentation) of a graph is infinitely deformable. This applies with equal force to knots and links, which, though normally drawn as smooth curves, may be viewed as simple closed polygonal curves in 3-space [10] and thus as circuit graphs, i.e. as connected graphs that are regular of degree two [9].

From the perspective of chirality, a simple graph may or may not (a) be topologically achiral, (b) have at least one topologically achiral embedding, (c) have at least one embedding that belongs to an achiral point group and that is therefore *geometrically* achiral (such an embedding is said to be *rigidly achiral*), and (d) have at least one rigidly achiral presentation. Ten of the $2^4 = 16$ possible combinations are logical contradictions because a topologically achiral graph must have at least one topologically achiral embedding, a graph with a rigidly achiral embedding must also have a topologically achiral embedding, and a graph with a rigidly achiral presentation must be topologically achiral and have a rigidly achiral embedding. Hence, only six classes are possible, as follows:

- A. Topologically chiral graphs with no topologically achiral embeddings.
- B. Topologically chiral graphs with at least one topologically but no rigidly achiral embedding.
- C. Topologically chiral graphs with at least one rigidly achiral embedding.
- D. Topologically achiral graphs with no rigidly achiral embeddings.
- E. Topologically achiral graphs with at least one rigidly achiral embedding but no rigidly achiral presentations.
- F. Topologically achiral graphs with at least one rigidly achiral presentation.

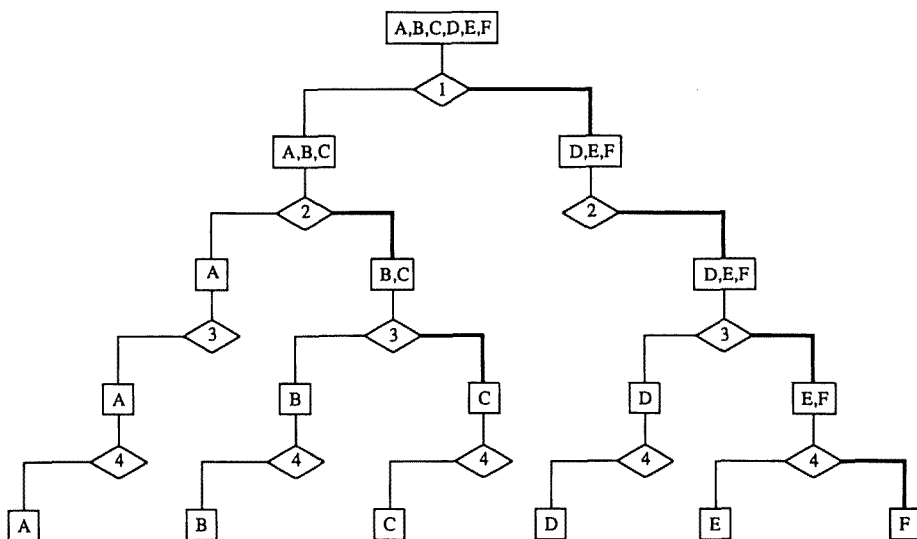


Fig. 2. Flowchart for the classification of simple graphs into six classes, denoted by capital letters. The decision in response to questions is given by heavy (yes) and light (no) lines. The questions are: (1) Is the graph topologically achiral? (2) Is there at least one topologically achiral embedding? (3) Is there at least one rigidly achiral embedding? (4) Is there at least one rigidly achiral presentation?

Figure 2 displays a flowchart that can be used to derive these six classes.

While classes A, C, and F are each well represented by a variety of chemical structures, as will be shown below, *no molecular graphs exist at present that belong to classes B, D, and E*. Flapan recently introduced the novel idea of topologically achiral graphs with no rigidly achiral embeddings (“intrinsically flexibly achiral graphs”) [8], and provided the first example (fig. 3(a)) of an abstract graph belonging to what we call class D. By linking two of the edges to form a trefoil knot, as shown in fig. 3(b), it is possible to generate a topologically chiral embedding of fig. 3(a) that belongs to class B. Class E is best represented by the seven non-invertible topologically achiral prime knots with up to 10 crossings (8_{17} , 10_{79} , 10_{81} , 10_{88} ,

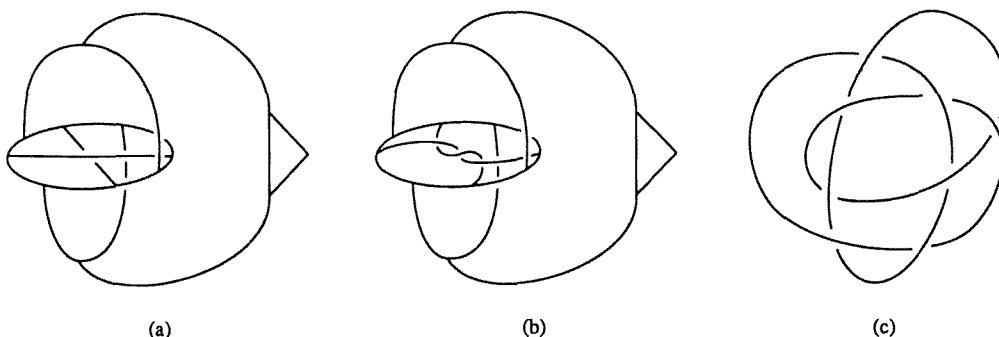


Fig. 3. (a) A topologically achiral graph with no rigidly achiral embeddings [8]. (b) A topologically chiral embedding of the graph in (a). (c) A topologically achiral knot with no rigidly achiral presentation (8_{17}).

10_{109} , 10_{115} , 10_{118}), which are asymmetric in all of their presentations [11]. One of these knots (8_{17}) is shown in fig. 3(c). In contrast to invertible amphicheiral prime knots, such as the figure-eight knot (4_1), non-invertible prime knots with up to 10 crossings cannot attain rigidly achiral presentations [12], and it follows that interconversion of enantiomorphous presentations of these knots by continuous deformation cannot proceed through a rigidly achiral state.

The realization of molecular graphs in these three classes remains an open challenge.

3. Molecular graphs

The notion of *molecular graph* lies at the heart of all discussions of topological chirality in chemistry. There is no problem in identifying the vertex set, since each vertex bears a one-to-one correspondence to an appropriately labeled atom in the molecule. The relationship of edges to bonds is, however, far less satisfactory. “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” [13]. Hence, because the concept of a chemical bond is “nicht scharf definierbar” [14a], “considerable arbitrariness is built into the definition of a molecular graph” [2], specifically with regard to membership in the edge set. In principle the problem is solvable by edge-weighting the complete graph, with each atom bonded to every other atom in the molecule and the set of edges mapped one-to-one onto a set of real numbers that “express in some manner the nature and extent” of bonding interactions between pairs of atoms [13]. The question remains, however, which of these bonds are to be regarded as *topologically significant* [2]. 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” [2]. While this definition has the advantage of being consistent with common usage in chemistry, where “molecular graph” carries the same meaning as “constitutional formula” or “localized valence bond diagram”, it suffers from two major disadvantages. First, “even the term covalent bond is arbitrary” [2], since there is, in the general case, a continuum between covalent and ionic bonds. Second, *the choice of bonds regarded as topologically significant depends on the molecular model under consideration*, and it may not always be appropriate to limit the edge set to covalent bonds. For example, Chambron et al. [4] included metal–ligand and metal–metal bonds in their edge set, along with “purely covalent” bonds. And, in a topological analysis of structural elements within a protein molecule, hydrogen bonds were included as edges in the molecular graph [15]; as the authors pointed out, “a description of molecular structural topology need not be limited only to covalent interactions, and can be generalized to include other weaker but specific interactions in protein molecules”. Thus, whether a molecule is

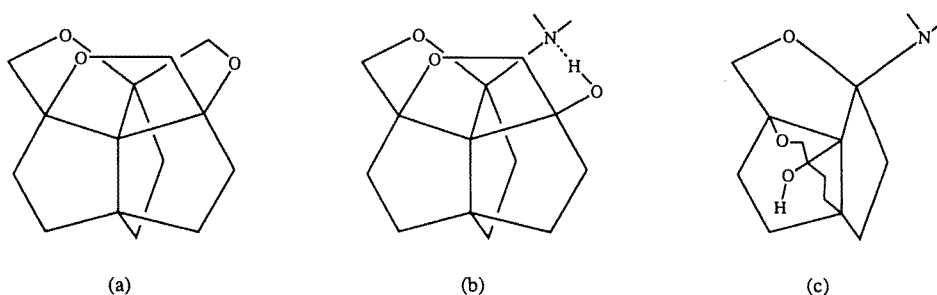


Fig. 4. (a) The Simmons–Paquette molecule [16]. Unlabeled vertices represent carbon atoms, and hydrogen atoms are suppressed for clarity. (b) A hypothetical derivative of (a) in which one of the $-\text{CH}_2\text{-O}-$ bonds is replaced by a $-(\text{CH}_3)_2\text{N}\dots\text{H-O}-$ hydrogen bond. (c) Planar embedding of the molecular graph of (b), with the hydrogen bond broken.

topologically chiral may depend on which bonds are considered topologically significant. For example, the Simmons–Paquette molecule [16] (fig. 4(a)) is topologically chiral [17], but the hypothetical derivative in fig. 4(b) is topologically chiral only if the $\text{N}\dots\text{H-O}$ hydrogen bond is considered topologically significant, otherwise the molecular graph can be embedded in the plane (fig. 4(c)) and the molecule is therefore topologically achiral.

Given these unavoidable uncertainties in defining membership in the edge set, the chemist has no alternative but to follow the advice of the mathematician Weyl [18] who had this to say with reference to valence bond diagrams (as translated in [14b]) “One cannot expect a rough sketch purporting to represent reality to contain all possible shades of that reality. Nonetheless the sketcher should have the courage of his convictions and draw the lines firmly”. Once the members of the edge set are selected, all uncertainty vanishes, and the molecular graph is treated exactly as a topological object [19], in which consideration of metrics and internal energy play no role. For example, whereas it is obviously physically impossible to flatten the *molecule* in fig. 1 so that all the atoms lie in a plane while all the bonds remain intact, planarization of the corresponding molecular *graph* is a perfectly unexceptionable topological operation. As this example illustrates, when we speak of the topological chirality or achirality of a molecule we actually refer to its graph, and not necessarily to a physically realistic model. It is well to keep this distinction in mind.

3.1. MOLECULAR GRAPHS IN CLASS A

Walba’s insightful conjecture [2,20] that the graphs of the Simmons–Paquette molecule [16] (fig. 4(a)), of the 3-rung Möbius ladder molecule [21] (fig. 5(a)), and of the ferrocenophenone in fig. 5(b) [22] are topologically chiral was subsequently proven by Simon and Wolcott [17,19,23]. Flapan proved that all the embeddings of the first two graphs are topologically chiral [24–26]. Hence, the graphs of the Simmons–Paquette molecule and of Walba’s 3-rung Möbius ladder molecule

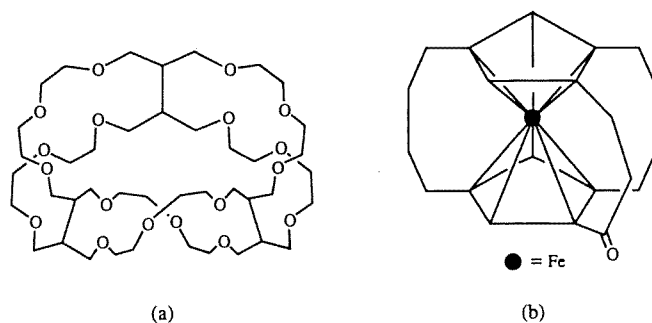


Fig. 5. (a) Walba's 3-rung Möbius ladder molecule [21]. (b) [4](1,1')[4](3,3')[3](4,4')-ferrocenophan-16-one [22]. Unlabeled vertices represent carbon atoms, and hydrogen atoms are suppressed for clarity.

belong to class A (table 1). With the exception of these two graphs and those of the two C_2 -symmetric triple-layered naphthalenophanes [27] (fig. 6(a) and (b)), all the graphs in table 1 are nonplanar and *constitutionally asymmetric*. That is, every vertex has a different connectivity and therefore carries a different label (or color). As shown by Wolcott [23], a nonplanar and constitutionally asymmetric graph G in 3-space containing a subgraph that is homeomorphic to M_3 , the six-vertex Möbius ladder with three colored rungs, must be topologically chiral. Since every embedding of G must also be nonplanar and constitutionally asymmetric, it follows that all these graphs belong to class A. More generally, any nonplanar graph with no automorphisms of order two is in class A [8]. Although the two naphthalenophanes are not constitutionally asymmetric, the three bridging edges in the central naphthalene can be regarded as three rungs (heavy lines in fig. 6(c)) of a graph that is contractible to M_3 ; hence these two graphs also belong to class A.

We conclude this section with some remarks concerning the other graphs listed in table 1. The ferrocenophenone in fig. 5(b) is one of a half dozen similar structures [22,28]. As has recently been noted [29], there are numerous proteins [30–40] that are topologically chiral; for the reasons given above, these all belong to class A. Representative examples are schematically depicted in fig. 7. Finally, the two clusters [41,42] in fig. 8 are remarkable chiefly because the coordination numbers of the central carbon atoms, 5 and 7, exceed the normal tetravalency of that element. In the formalism of the localized valence bond model, these carbon–metal bonds are merely “partial” bonds, and one might therefore question whether they should be included as edges in the molecular graph. In our decision to do so, we have followed Weyl's advice to “draw the lines firmly”.

3.2. MOLECULAR GRAPHS IN CLASS C

Molecular graphs that belong to this class are listed in table 2. Considered as abstract objects, knots are the traditional representatives of this class, which they populate in abundant numbers: of the 12,965 types of prime knots K with crossing numbers $c(K) \leq 13$, all but 78 are topologically chiral [43]. All nontrivial (nonpla-

Table 1
A survey of topologically chiral molecular graphs in class A.

Molecule	Reference	Figure
The Simmons–Paquette molecule	[16]	4(a)
Walba's 3-rung Möbius ladder molecule	[21]	5(a)
Triple-layered naphthalenophane	[27]	6(a)
Triple-layered tetrathia[3.3]naphthalenophane	[27]	6(b)
[4](1,1')[3](2,2')[3](4,4')-ferrocenophan-15-one	[22]	
[4](1,1')[3](2,2')[4](4,4')-ferrocenophan-15-one	[22]	
[4](1,1')[4](3,3')[3](4,4')-ferrocenophan-16-one	[22]	5(b)
[4](1,1')[4](3,3')[3](4,5')-ferrocenophan-16-one	[22]	
16-Methylene[4](1,1')[4](3,3')[3](4,4')-ferrocenophane	[22]	
[4][4][4]- α -oxo[3]ferrocenophane	[28]	
Quinoprotein TV-MADH	[30]	7(a)
Quinoprotein PD-MADH	[31]	
Quinoprotein AM1-MADH (tentative)	[32]	
<i>Chromatium</i> high potential iron protein (HiPIP)	[33]	7(b)
HiPIP from <i>Rhodocyclus tenuis</i>	[34]	
Iron–sulfur flavoprotein trimethylamine dehydrogenase	[35]	
Ferredoxin from <i>Azotobacter vinelandii</i>	[36]	
Ferredoxin from <i>Peptococcus aerogenes</i>	[37]	
Variant-3 protein scorpion Neurotoxin from <i>Centruroides sculpturatus</i> Ewing	[38]	
Toxin II from the scorpion <i>Androctonus australis</i> Hector	[39]	7(c)
γ 1-H and γ 1-P Thionins from barley and wheat (tentative)	[40]	
Cluster $\text{HOs}_5\text{C}(\text{CO})_{13}[\text{PO}(\text{OMe})\text{P}(\text{OMe})_2]$	[41]	8(a)
Cluster $\text{Rh}_8(\text{CO})_{19}\text{C}$	[42]	8(b)

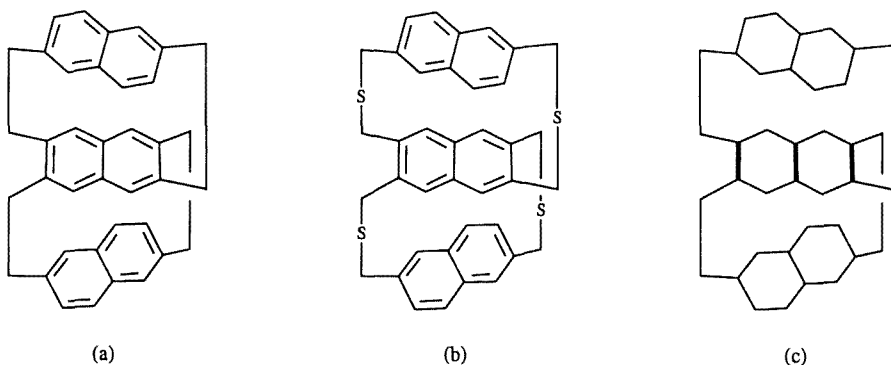


Fig. 6. (a) Triple-layered naphthalenophane [27]. (b) Triple-layered tetrathia[3.3]naphthalenophane [27]. Unlabeled vertices represent carbon atoms, and hydrogen atoms are suppressed for clarity. (c) Graph of (a), contractible to M_3 .

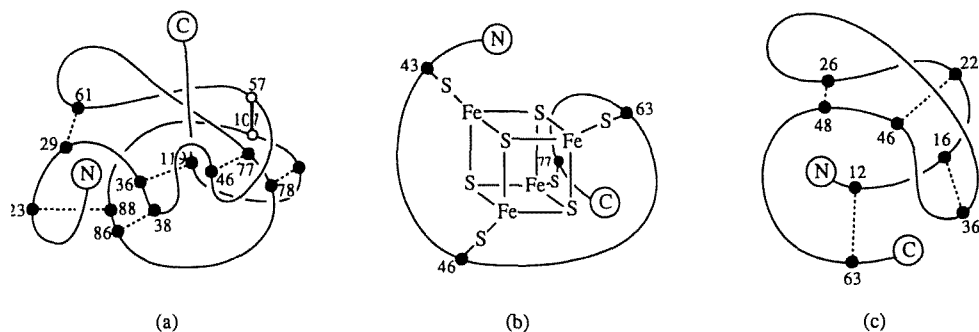


Fig. 7. Schematic diagrams of some representative topologically chiral proteins [29]. (a) Condensed schematic drawing of the L subunit of the quinoprotein TV-MADH [30]. The looped line represents the polypeptide backbone with N and C terminals. Cysteine (or half-cystine) residues are numbered and their α -carbons are indicated by solid circles. Intrachain disulfide bonds are shown as dashed lines joining a pair of solid circles. The heavy line symbolizes an intrachain cofactor link. (b) *Chromatium* high potential iron protein (HiPIP) [33], one of several Fe_4S_4 cluster-containing proteins. (c) Toxin II from the scorpion *Androctonus australis* Hector [39].

nar) knots are homeomorphic to the trivial knot, or unknot (a triangle, or a circle in the plane). As it happens, molecular knots are also dominant in this class: among DNA molecules, at least 13 different types of topologically chiral prime knots ($3_1, 5_1, 5_2, 6_1, 6_2, 7_1, 7_2, 7_3, 7_4, 7_5, 7_6, 7_7, 9_1$) have been identified, along with three topologically chiral product knots ($3_1\#3_1, 3_1\#4_1, 4_1\#5_1$) [44]. The rational synthesis of trefoil knots (fig. 9) by Sauvage and coworkers [45–47] provided the first – and so far the only – example of knotted molecules outside the realm of nucleic acids.

Links are multi-component knots, and as such are homeomorphic to sets of unlinked unknots. Hence, topologically chiral links also belong to class C. All

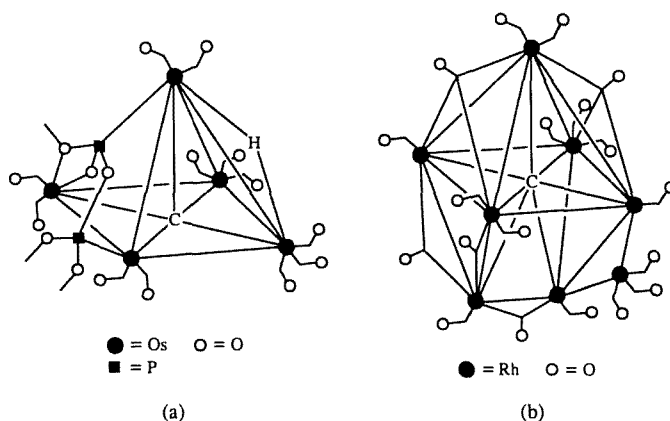


Fig. 8. (a) Cluster $\text{HO}_5\text{C}(\text{CO})_{13}[\text{PO}(\text{OMe})\text{P}(\text{OMe})_2]$ [41]. (b) Cluster $\text{Rh}_8(\text{CO})_{19}\text{C}$ [42]. All but the central (endohedral) carbon atoms are represented by unlabeled vertices. Except for the bridging hydride in (a), hydrogen atoms are suppressed for clarity.

Table 2
A survey of topologically chiral molecular graphs in class C.

Molecule	Reference	Figure
DNA knots	[44]	
Trefoil molecule K-86	[45]	9(a)
Dicopper(I) trefoil knot, $\text{Cu}_2\text{K-86}^{2+}$	[46]	9(b)
Dicopper(I) trefoil knots $\text{Cu}_2\text{K-80}^{2+}$, $\text{Cu}_2\text{K-82}^{2+}$, $\text{Cu}_2\text{K-84}^{2+}$, and $\text{Cu}_2\text{K-90}^{2+}$	[47]	
DNA links	[48]	
2-Crossing catenane	[49]	10(a)
4-Crossing catenane	[50]	10(b)
4-Rung Möbius ladder molecule	[51]	11(a)
$\text{Fe}_4\text{S}_4\{\text{cyclo}-(\text{XN}[\text{CH}_2]_8\text{NX-}p\text{-C}_6\text{H}_4\text{-}p\text{-CH}_2\text{C}_6\text{H}_4)_2\}^{2-}$ ($\text{X} = p\text{-SC}_6\text{H}_4\text{CO}$)	[52]	11(b)

known topologically chiral molecular links (catenanes) are made up of two topologically achiral components. The simplest of these is a 2-crossing link composed of two oriented unknots; orientation of *both* unknots is essential for chirality. Such a link is found among the nucleic acids [48], and a molecule with this property (fig. 10(a)) has also been synthesized in the laboratory of Sauvage [49]. Orientation of the component unknots is not required for topological chirality if there are more than two crossings in the link, as exemplified by the 4-crossing catenane in fig. 10(b) whose synthesis was achieved by Sauvage and coworkers [50]. Additional members of class C are a 5-crossing DNA link composed of two unknots, and a 6-crossing DNA link composed of one oriented unknot and one (topologically achiral) oriented figure-eight knot [48].

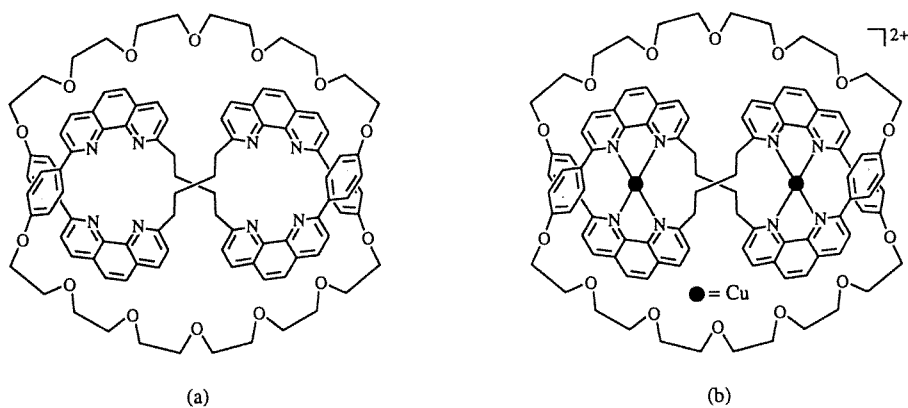


Fig. 9. (a) Trefoil molecule K-86 [45]. (b) Dicopper(I) trefoil knot $\text{Cu}_2\text{K-86}^{2+}$ [46]. Unmarked vertices represent carbon atoms, and hydrogen atoms are suppressed for clarity.

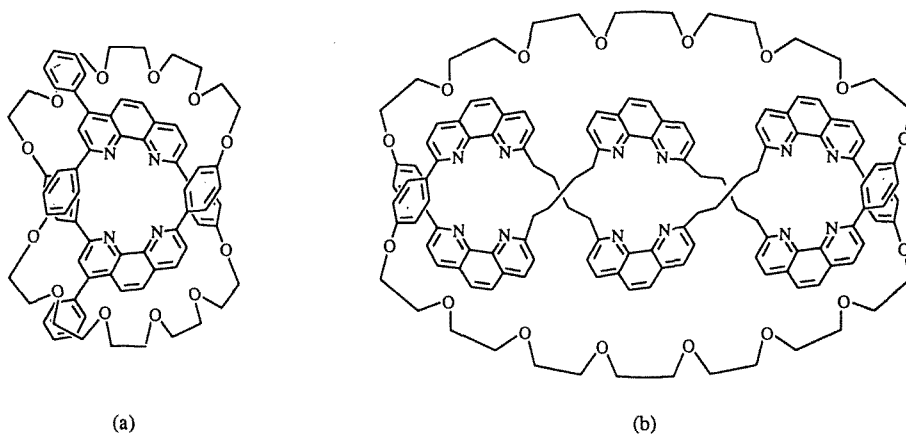


Fig. 10. (a) 2-Crossing catenane with oriented component rings [49]. (b) 4-Crossing catenane with nonoriented component rings [50]. Unmarked vertices represent carbon atoms, and hydrogen atoms are suppressed for clarity.

Two molecular graphs that belong to class C but that are neither knots nor links are shown in fig. 11. One is Walba's 4-rung Möbius ladder (fig. 11(a)) [51], which has an embedding with S_4 symmetry [24]. The other is a synthetic iron-sulfur protein analog (fig. 11(b)) [52] which is topologically chiral [29] but has a centrosymmetric embedding (fig. 11(c)).

3.3 MOLECULAR GRAPHS IN CLASS F

As of this writing, all known topologically achiral molecular graphs can assume rigidly achiral presentations. The great majority of these graphs are planar, and it is obvious that they are rigidly achiral when they are embedded in the plane. Rather more uncommon are topologically achiral molecular graphs which contain subgraphs that are either homeomorphic or contractible to the Kuratowski graphs $K_{3,3}$ or K_5 . The rigidly achiral presentations of such graphs are therefore nonplanar

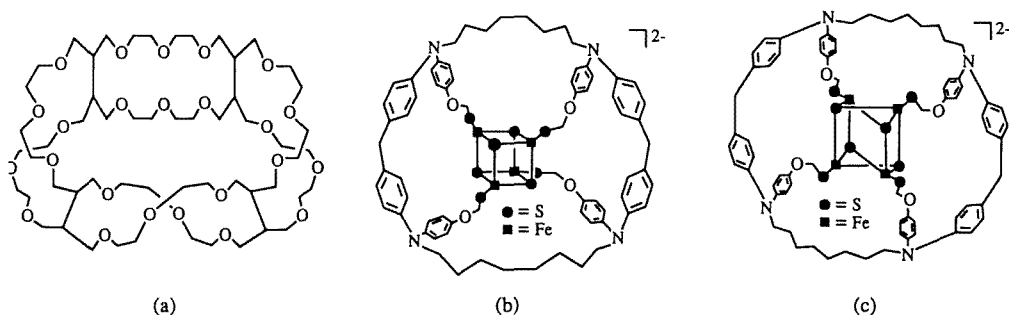


Fig. 11. (a) 4-Rung Möbius ladder molecule [51]. (b) $\text{Fe}_4\text{S}_4\{\text{cyclo}-(\text{XN}[\text{CH}_2]_8\text{NX}-p\text{-C}_6\text{H}_4-p\text{-CH}_2\text{C}_6\text{H}_4)_2\}^{2-}$ ($\text{X} = p\text{-SC}_6\text{H}_4\text{CO}$) [52]. Unmarked vertices represent carbon atoms, and hydrogen atoms are suppressed for clarity. (c) Rigidly achiral (C_i) embedding of (b).

[9]. Some examples [53–61] are shown in fig. 12. Except for the graphs of the molecules in fig. 12 (a) and (b), each of the molecular graphs in fig. 12 is reducible to either $K_{3,3}$ or to K_5 by suitable deletions or contractions. The molecular graphs in fig. 12 (a) and (b) are unique in this set because the former is reducible only to K_5 and the latter only to $K_{3,3}$. Note also the relationship between the molecular graphs in fig. 11(b) (class C) and 12 (c) (class F).

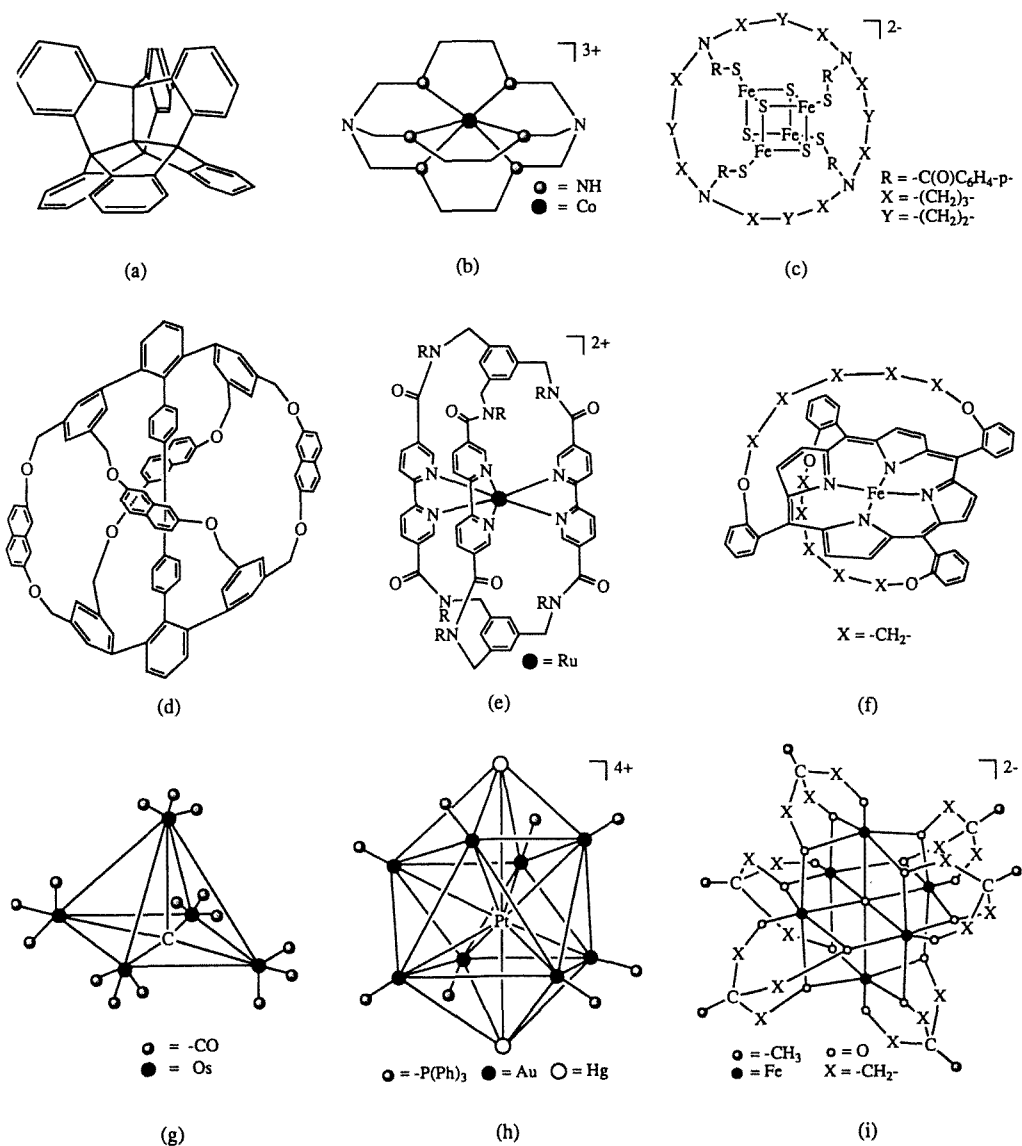


Fig. 12. Examples of molecules with nonplanar graphs that have rigidly achiral presentations, and their highest attainable symmetries. (a) [53] T_d . (b) [54] D_{3h} . (c) [52] D_{2d} . (d) [55] D_{2d} . (e) [56] D_{3h} . (f) [57] D_{2d} . (g) [58] C_s . (h) [59] D_{4d} . (i) [60] S_6 .

4. Hierarchical ordering of chiral structures

We saw (fig. 2) that the set of graphs can be partitioned into those that are topologically chiral (set ABC) and those that are not (set DEF), that the graphs in subset ABC can be further partitioned into those that have at least one topologically achiral embedding (set BC) and those that do not (set A), and so forth, until all six classes have become disjoint. Figure 2 thus displays a *hierarchical system*, that is, “a system that is composed of interrelated subsystems, each of the latter being in turn hierarchic in structure until we reach some lowest level of elementary subsystem” [61]. The following might serve as a chemical analogy: molecules with empirical formula CH_2 are partitioned into molecules with molecular formulas C_2H_4 , C_3H_6 , C_4H_8 , etc., molecules whose molecular formula is C_3H_6 are partitioned into those whose structural formula correspond to propene and cyclopropane, and so forth. The process of partitioning a set into equivalence classes thus generates hierarchical systems. Once a hierarchy is established, rank-ordering of the components according to their “level of complexity” becomes possible. In the preceding example, empirical formula CH_2 is situated at the apex of complexity, the structural formulas corresponding to CH_2 are the least complex “elementary subsystems”, while molecular formulas occupy an intermediate level of complexity. In fig. 2, the set ABCDEF qualifies as the most and the six disjoint classes as the least complex systems, while ABC, BC, and so forth represent intermediate levels of complexity.

There is, however, another way to develop a hierarchical ranking from fig. 2. If the flowchart is scanned horizontally from left to right, instead of vertically from top to bottom, the responses to the four questions concerning aspects of a graph's achirality are seen to range from four no's for class A to zero no's for class F, with classes B (three no's), C and D (two no's each), and E (one no) in between. This hierarchical order parallels, to some extent, the following three schemes that appear to have been developed independently of one another.

In Flapan's “hierarchy of intrinsic chirality” [8], graphs that are “intrinsically chiral” correspond to class A, those that are “intrinsically flexibly achiral” correspond to class D, as mentioned above, and “rigidly achirally embeddable graphs” correspond to classes C, E, and F.

Simon's “hierarchy of chirality” [6] is topped by “intrinsically chiral” graphs that correspond to class A as exemplified by the 5-rung Möbius ladder. Next come topologically chiral graphs that correspond to class C as exemplified by the trefoil knot, the oriented 2-crossing link, the 4-crossing link, and the 4-rung Möbius ladder. Finally, molecules that owe their chirality to geometric rigidity are shown whose molecular graphs are planar and which therefore belong to class F; knot 8_{17} , which belongs to class E, is shown separately in a “hierarchy of achirality”.

Walba's “topological hierarchy of molecular chirality” [7] is also headed by “intrinsically chiral graphs” that correspond to class A; as previously noted [62], the remaining five classes in his scheme may be reduced to three (C, E, F). Thus, despite substantial differences among them, all three schemes are in full agreement

that graphs in class A, famously realized in the Simmons-Paquette molecule and in Walba's 3-rung Möbius ladder molecule, are alone in being "intrinsically chiral". According to Flapan, "a property of an embedded graph is *extrinsic* if it depends on how the graph is embedded, and *intrinsic* if it is independent of the embedding", where "embedded graph" refers to "a graph with a fixed configuration in 3-dimensional space" [8]. In that sense, the graphs in class A are indeed "intrinsically" chiral.

In another sense, however, chirality is a property that is most decidedly *only extrinsic*. The reason is that whether or not an object is chiral "depends on the dimension of the space in which the object is embedded. Thus, objects that are enantiomorphs in E^n are superposable by proper rotations in E^{n+1} " [62]; that is, "reflections in any dimension of space can be considered as rotations in a space one dimension higher" [63]. A formal proof was recently provided of the theorem "Any object that is chiral in n -dimensions is achiral in $(n + 1)$ -dimensions and in any higher dimensions" [64]. All of this was recognized a long time ago by Martin Gardner, who noted that "If we could put a paper Möbius band into 4-space, it would be possible to deform it and drop it back into 3-space as a band with any odd number of half-twists of *either handedness* [emphasis added]. Similarly, a band with no twists . . . could be taken into 4-space, twisted and dropped back into our space with any even number of half-twists of *either handedness* [emphasis added]" [65].

Along the same lines, it is easy to imagine graphs that are chiral in 2-space, for example the graph of the carbon skeleton of 1,2,4-trimethylbenzene (the circuit graph C_6 with three univalent vertices adjacent to the vertices at positions 1, 2, and 4), but which are obviously achiral in 3-space. One would hesitate to call such graphs "intrinsically" chiral even if all of their embeddings in 2-space were chiral. Similarly, because *all* graphs embedded in 3-space are achiral in 4-space, it is hard to justify the characterization of any such graphs, *including* those in class A, as "intrinsically" chiral. In short, it could be argued that there is no such thing as an "intrinsically" chiral object! In order to avoid possible confusion resulting from the two different interpretations of "intrinsic" in connection with chirality, we have refrained from use of this terminology in this paper.

A final remark concerns the ranking of molecules or their graphs "by degree of chirality, from most chiral to least chiral" [7]. In connection with his "hierarchy of chirality", Simon noted that "Mathematically, at least, some molecules (or hypothetical structures) are more chiral than others" [6]. Along similar lines, Walba referred to his 3-rung Möbius ladder molecule as "the most chiral organic molecule known" [7] and to organic molecules in class A as "topologically most chiral" [3]. There are, of course, numerous measures by which chirality can be quantified; in all of these, however, the degree of chirality of an object is estimated by a numerical (real-valued) function, which may be continuous or non-continuous, and which is zero if and only if the object is achiral [62]. Because the hierarchical ordering schemes described above are not numerical functions, it follows that

the degree of chirality that is ascribed to molecules and their graphs [3,6,7] does not qualify as a *measure* of chirality. But if not as a measure, what basis is there for this rank ordering?

An answer to this question emerges upon consideration of molecular graphs whose chirality is independent of their embeddings in 3-space. To credit such a graph with being the “most chiral” – and then to transfer this attribution to the molecule itself – suggests translation into chemical terms: all topological stereoisomers [2] of molecules in class A are chiral, and this is true for none of the molecules in the other classes. Now consider the following analogy regarding molecules that owe their chirality to geometric rigidity: all stereoisomers of constitutionally and geometrically asymmetric molecules are chiral, and this is true for none of the molecules in the other chiral point groups (C_n , D_n , T, O, I) since those can also have achiral stereoisomers (diastereomers). Yet asymmetric molecules are no more chiral than those with rotational symmetry. This analogy tells us that what is at issue in these rankings [3,6,7] is not chirality (the absence of reflection symmetry) but what might be called *chiral persistence*! That is, chiral structures (or constructions) are judged to be “more” or “less” *chirally persistent* according to the degree or extent to which their chirality survives various geometric or topological distortions, embeddings, or even, in the case of molecules, thermal agitations [7]. This granted, if classes of molecular graphs, viewed as abstract topological objects embedded in 3-space, are ranked according to the chiral persistence of their membership, graphs in class A do indeed top the list as the most chirally persistent!

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References

- [1] H.L. Frisch and E. Wasserman, *J. Amer. Chem. Soc.* 83 (1961) 3789; E. Wasserman, *Sci. Amer.* 207/5 (1962) 94; N. van Gulick, *New J. Chem.* 17 (1993) 619 [manuscript originally submitted to *Tetrahedron*, August 1960]; G. Schill, *Catenanes, Rotaxanes, and Knots* (Academic Press, New York, 1971).
- [2] D.M. Walba, *Tetrahedron* 41 (1985) 3161, and references therein.
- [3] D.M. Walba, T.C. Homan, R.M. Richards and R.C. Haltiwanger, *New J. Chem.* 17 (1993) 661, and references therein.
- [4] J.-C. Chambron, C. Dietrich-Buchecker and J.-P. Sauvage, *Top. Curr. Chem.* 165 (1993) 131, and references therein.
- [5] N.C. Seeman, J. Chen, S.M. Du, J.E. Mueller, Y. Zhang, T.J. Fu, Y. Wang, H. Wang and S. Zhang, *New J. Chem.* 17 (1993) 739, and references therein.

- [6] J. Simon, A topological approach to the stereochemistry of nonrigid molecules, in: *Graph Theory and Topology in Chemistry*, eds. R.B. King and D.H. Rouvray (Elsevier, Amsterdam, 1987) pp. 43–75.
- [7] D.M. Walba, A topological hierarchy of molecular chirality and other tidbits in topological stereochemistry, in: *New Developments in Molecular Chirality*, ed. P.G. Mezey (Kluwer Acad. Publ., Dordrecht, 1991) pp. 119–129.
- [8] E. Flapan, *New J. Chem.* 17 (1993) 645.
- [9] R.J. Wilson, *Introduction to Graph Theory* (Oliver & Boyd, Edinburgh, 1972).
- [10] R.H. Crowell and R.H. Fox, *Introduction to Knot Theory* (Blaisdell, New York, 1963); C. Livingston, *Knot Theory* (Math. Assoc. of America, Washington DC, 1993).
- [11] G. Burde and H. Zieschang, *Knots* (Walter de Gruyter, Berlin, 1985) Appendix C: tables, pp. 311–343.
- [12] E. Flapan, Rigid and non-rigid achirality, *Pac. J. Math.* 129 (1987) 57;
E. Flapan, Topological techniques to detect chirality, in: *New Developments in Molecular Chirality*, ed. P.G. Mezey (Kluwer Acad. Publ., Dordrecht, 1991) pp. 209–239.
- [13] K. Mislow, *Bull. Soc. Chim. Belg.* 86 (1977) 595.
- [14] (a) V. Prelog and G. Helmchen, *Angew. Chem.* 94 (1982) 614;
(b) V. Prelog and G. Helmchen, *Angew. Chem. Int. Ed. Engl.* 21 (1982) 567.
- [15] B. Mao, K.-C. Chou and G.M. Maggiora, *Eur. J. Biochem.* 188 (1990) 361.
- [16] H.E. Simmons III and J.E. Maggio, *Tetrahedron Lett.* 22 (1981) 287;
L.A. Paquette and M. Vazeux, *Tetrahedron Lett.* 22 (1981) 291.
- [17] J. Simon, *Topology* 25 (1986) 229.
- [18] H. Weyl, *Philosophie der Mathematik und Naturwissenschaft*, 4th Ed. (Oldenbourg, München, 1976) p. 352.
- [19] J. Simon, *J. Comput. Chem.* 8 (1987) 718.
- [20] D.M. Walba, Stereochemical topology, in: *Chemical Applications of Topology and Graph Theory*, ed. R.B. King (Elsevier, Amsterdam, 1983) pp. 17–32.
- [21] D.M. Walba, R.M. Richards and R.C. Haltiwanger, *J. Amer. Chem. Soc.* 104 (1982) 3219.
- [22] M. Hisatome, N. Watanabe, T. Sakamoto and K. Yamakawa, *J. Organomet. Chem.* 125 (1977) 79.
- [23] K. Wolcott, Ph.D. Thesis, University of Iowa (1986).
- [24] E. Flapan, Chirality of non-standardly embedded Möbius ladders, in: *Graph Theory and Topology in Chemistry*, eds. R.B. King and D.H. Rouvray (Elsevier, Amsterdam, 1987) pp. 76–81.
- [25] E. Flapan, *Math. Ann.* 283 (1989) 271.
- [26] E. Flapan, unpublished results cited in ref. 37 of ref. [3].
- [27] T. Otsubo, F. Ogura and S. Misumi, *Tetrahedron Lett.* 24 (1983) 4851.
- [28] M. Hisatome, Y. Kawaziri and K. Yamakawa, *Tetrahedron Lett.* 20 (1979) 1777.
- [29] C. Liang and K. Mislow, *J. Amer. Chem. Soc.* 116 (1994) 3588.
- [30] F.M.D. Vellieux, F. Huitema, H. Groendijk, K.H. Kalk, J.F. Jzn., J.A. Jongejan, J.A. Duine, K. Petratos, J. Drenth and W.G.J. Hol, *The EMBO J.* 8 (1989) 2171.
- [31] L. Chen, F.S. Mathews, V.L. Davidson, E.G. Huizinga, F.M.D. Vellieux and W.G.J. Hol, *PROTEINS: Structure, Function, and Genetics* 14 (1992) 288.
- [32] Y. Ishii, T. Hase, Y. Fukumori, H. Matsubara and J. Tobar, *J. Biochem.* 93 (1983) 107.
- [33] C.W. Carter, Jr, J. Kraut, S.T. Freer, N.H. Xuong, R.A. Alden and R.G. Bartsch, *J. Biol. Chem.* 249 (1974) 4212.
- [34] I. Rayment, G. Wesenberg, T.E. Meyer, M.A. Cusanovich and H.M. Holden, *J. Mol. Biol.* 228 (1992) 672.
- [35] L.W. Lim, N. Shamala, F.S. Mathews, D.J. Steenkamp, R. Hamlin and N.H. Xuong, *J. Biol. Chem.* 261 (1986) 15140.

- [36] C.D. Stout, *J. Biol. Chem.* 263 (1988) 9256; *J. Mol. Biol.* 205 (1989) 205; M.K. Johnson, R.S. Czernuszewicz, T.G. Spiro, J.A. Fee and W.V. Sweeney, *J. Amer. Chem. Soc.* 105 (1983) 6671.
- [37] E.T. Adman, L.C. Sieker and L.H. Jensen, *J. Biol. Chem.* 248 (1973) 3987.
- [38] R.J. Almassy, J.C. Fontecilla-Camps, F.L. Suddath and C.E. Buggy, *J. Mol. Biol.* 170 (1983) 497.
- [39] J.C. Fontecilla-Camps, C. Habersetzer-Rochat and H. Rochat, *Proc. Natl. Acad. Sci. USA* 85 (1988) 7443.
- [40] M. Bruix, M.A. Jimenez, J. Santoro, C. Gonzalez, F.J. Colilla, E. Mendez and M. Rico, *Biochemistry* 32 (1993) 715.
- [41] J. Lewis and F.J. Johnson, *Pure Appl. Chem.* 54 (1982) 97.
- [42] V.G. Albano, P. Chini, S. Martinengo, M. Sansoni and D. Strumolo, *J. Chem. Soc. Chem. Commun.* (1974) 299.
- [43] C. Liang and K. Mislow, *J. Math. Chem.* 15 (1994) 1, and references therein.
- [44] F.B. Dean, A. Stasiak, T. Koller and N.R. Cozzarelli, *J. Biol. Chem.* 260 (1985) 4975.
- [45] C.O. Dietrich-Buchecker and J-P. Sauvage, *Angew. Chem. Int. Ed. Engl.* 28 (1989) 189.
- [46] C.O. Dietrich-Buchecker, J. Guilhem, C. Pascard and J-P. Sauvage, *Angew. Chem. Int. Ed. Engl.* 29 (1990) 1154.
- [47] C.O. Dietrich-Buchecker, J.-F. Nierengarten, J.-P. Sauvage, N. Armaroli, V. Balzani and L. De Cola, *J. Amer. Chem. Soc.* 115 (1993) 11237.
- [48] M.A. Krasnow, A. Stasiak, S.J. Spengler, F. Dean, T. Koller and N.R. Cozzarelli, *Nature* 304 (1983) 559; S.A. Wasserman, J.M. Dungan and N.R. Cozzarelli, *Science* 229 (1985) 171.
- [49] D.K. Mitchell and J-P. Sauvage, *Angew. Chem. Int. Ed. Engl.* 27 (1988) 930.
- [50] J.-F. Nierengarten, C.O. Dietrich-Buchecker and J.-P. Sauvage, *J. Amer. Chem. Soc.* 116 (1994) 375.
- [51] D.M. Walba, J.D. Armstrong III, A.E. Perry, R.M. Richards, T.C. Homan and R.C. Haltiwanger, *Tetrahedron* 42 (1986) 1883.
- [52] Y. Okuno, K. Uoto, Y. Sasaki, O. Yonemitsu and T. Tomohiro, *J. Chem. Soc. Chem. Commun.* (1987) 874.
- [53] D. Kuck and A. Schuster, *Angew. Chem. Int. Ed. Engl.* 27 (1988) 1192.
- [54] I.I. Creaser, R.J. Geue, J.M. Harrowfield, A.J. Herlt, A.M. Sargeson, M.R. Snow and J. Springborg, *J. Amer. Chem. Soc.* 104 (1982) 6016.
- [55] J. Siegel, private communication.
- [56] F. Barigelletti, L.D. Cola, V. Balzani, P. Belser, A.v. Zelewsky, F. Vögtle, F. Ebmeyer and S. Grammenudi, *J. Amer. Chem. Soc.* 111 (1989) 4662.
- [57] M. Momenteau, J. Mispelter, B. Looock and E. Bisagni, *J. Chem. Soc. Perkin Trans. I* (1983) 189.
- [58] P.F. Jackson, B.F.G. Johnson, J. Lewis and J.N. Nicholls, *J. Chem. Soc. Chem. Commun.* (1980) 564.
- [59] J.J. Bour, W.v.d. Berg, P.P.J. Schlebos, R.P.F. Kanters, M.F.J. Schoondergang, W.P. Bosman, J.M.M. Smits, P.T. Beurskens, J.J. Steggerda and P.v.d. Sluis, *Inorg. Chem.* 29 (1990) 2971.
- [60] K. Hegetschweiler, H. Schmale, H.M. Streit and W. Schneider, *Inorg. Chem.* 29 (1990) 3625.
- [61] H.A. Simon, *The Sciences of the Artificial*, 2nd Ed. (MIT Press, Cambridge, 1981) chapter VII ("The Architecture of Complexity").
- [62] A.B. Buda, T. Auf der Heyde and K. Mislow, *Angew. Chem. Int. Ed. Engl.* 31 (1992) 989, and references therein.
- [63] I. Stewart and M. Golubitsky, *Fearful Symmetry* (Blackwell, Oxford, 1992) p. 37.
- [64] P.G. Mezey, *J. Math. Chem.* 11 (1992) 27.
- [65] M. Gardner, *Sci. Amer.* 219/6 (1968) 112.