Molecular Topology

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Molecular topology applies valuable tools from topology and graph theory to understand the molecular structure and synthesis of complex, functional organic molecules. At its core, molecular chemistry shares many concepts and ideas with topology; molecules and surfaces are best described with graphs—comprised of vertices, edges, and faces—which are further explained with several matrices. Building upon that foundation, molecular topology bonds topological surfaces with molecular counterparts. Simple surfaces such as the Mobius Band, as well as complex topological rings and knots, have analogous molecular partners. These recently discovered synthetic molecules have great functionality in 21st century technology, but it isn’t until we understand the roots of molecular topology that we can begin to explore the synthesis and application of topological molecules.

To start understanding topology, we know that topological surfaces can be represented as graphs; identifying faces, edges, and vertices arranged geometrically, usually in $\mathbb{R}^2$, present a unique surface up to isomorphism. Similarly, chemical compounds can be represented as molecular graphs. Molecules are broken down such that bonds and atoms are identified as edges and vertices respectively (though atoms are often represented by letters or atomic symbols. Commonly, molecular graphs are presented in their “hydrogen depleted” form, as cause congestion throughout the graph.
Tools that have been developed for cutting, pasting, and otherwise altering topological surfaces have equivalence in the molecular field, commonly called reactions. Molecular transformations are visualized as reaction graphs. Reaction graphs can be drawn simply, with the starting compounds separated from the products with an arrow, or they can be drawn intricately, showing all intermediate steps along with pointers to show on which parts of the molecule the reaction occurs. The latter approach is often called a mechanism, and in these reaction graphs and mechanisms, vertices are represented by individual chemical species, and edges correspond to reaction pathways. For example, a simple hydrogenated non-alkane can be converted into a cycloalkane. Intuitively, we cannot connect the opposite ends of the alkane, as it introduces too many bonds, or topologically, violates the degree of the vertices. Thus closing the cycle requires removal of two hydrogen atoms, topologically called cutting, and formation of a new bond, topologically pasting. Figure 1 above describes this cyclization process which is used greatly in the formation of topologically relevant molecules. [1]

As in topology, chemical graphs are described by a variety of matrices. The Adjacency Matrix, as in topology, characterized a chemical graph up to isomorphism. The entries of the matrix represent the number of walks of length e, for Adjacency Matrix $A^e$. For chemical graphs with multiple bonds, an analogous matrix called the Connectivity Matrix is constructed to describe the molecular bonds in the graph. A second parallel matrix in molecular topology is the Laplacian (or Kirchoff) Matrix. The Kirchoff Matrix is defined as the difference between the diagonal matrix of vertex degrees and the adjacency matrix, and describes the relationship between individual atoms in the overall molecule; how many carbon atoms each individual carbon atom is touching, as well as which atoms are bonded to which (see Figure 2). A third comparable matrix is the Distance Matrix. In topology and graph theory, the distance matrix describes the topological distance between vertices i and j. In molecular topology and chemistry, it has a similar meaning; describing the
distance between all pairs of distinct atoms in the overall molecule. These matrices, among many other more complex matrices including Detour, Combinatorial, Weiner, and Szeged matrices, are the first and most basic bridge of molecular topology.[2]

As previously discussed, molecular graphs are often presented in R². However, most molecules naturally exist in R³, and there are three models that show this: Ball-and-Stick, VanderWaal, and Space-Filling. Each model employs a different method to convey the same message; molecules in R³ can vary in three dimensional space, and thus may appear identical but have different orientation. This property is called chirality, and it a concept critical to understanding molecular topology. Chemically, a molecule is chiral if reflection about its central carbon atom results in a non-superimposable mirror image. Human hands are a concrete example of chirality; the right hand is a non-superimposable mirror image of the left hand. In R², it is difficult to see chirality. Chemical graphs drawn in R³, which denote atoms in the x, y, and z directions, allow us to understand this property. Accordingly, we define two additional terms. Two molecules with the same molecular formula and sequence of bonded atoms are called stereoisomers; stereoisomers differ only in the orientation of the atoms in three dimensions. A pair of chiral stereoisomers, two molecules which differ only in their orientation of atoms in R³ with non-superimposable mirror images, is called an enantiomer; enantiomers allow us to implant molecules into simple topological spaces.

The Mobius band is the topological equivalent of enantiomers; the non-superimposable mirror image isomers are represented by the conjugate pair of Mobius bands with clockwise and counter-clockwise twists. This relationship can be seen by the following: drawing a molecular graph on a Mobius band and passing the graph around the strip reverses the stereochemistry of the molecule.[3] A Mobius band with a clockwise twist

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\begin{bmatrix}
3 & -1 & -1 & 0 & 0 & 0 \\
2 & -1 & 2 & 0 & 0 & 0 \\
3 & -1 & 2 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots & \\
9 & -1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -1 & 1 & 0 \\
0 & 0 & 0 & -1 & 0 & 1 \\
\end{bmatrix}
\]

Figure 2: Kirchoff Matrix for T-Butyl Cyclopropane
would reverse stereochemistry of the graph in one direction, while the Mobius band with counter-clockwise twist would reverse stereochemistry oppositely. Just as a topological graph is non-orientable if it contains a Mobius band, a molecule is chiral if it is non-orientable. These simple, but important relationships establish the basis for all of molecular topology.

The use of the Mobius band to describe enantiomers pushed chemists to synthesize Mobius molecules. Chemical bonds generally allow atoms to move and rotate freely, so long as the bonds between atoms remain intact. Thus chemically, a Mobius molecule requires a two-sided band or a pi-electron system (a series of atoms all bonded with double bonds) to restrict movement. The two-sided band approach is much simpler and much easier to synthesize, thus a more popular approach. The pi-electron system requires a much deeper knowledge of orbital chemistry (which would certainly push this paper over the page limit).

In the early 1960s, Wasserman and van Gulick independently proposed syntheses of Mobius molecules, called Mobius ladders though only as intermediates in the synthesis of larger compounds. But in 1982, David Walba studied the experiments of Wasserman and van Gulick and noticed that each experiment yielded a shared intermediate product, a THYME diol-ditosylate. Walba was able to take this ladder and synthesize a biomacrocycle, a larger ring structure composed of rings of diol-ditosylate. Dilution at high concentration was used to cut the ladder, and three isomers were formed in the cyclization; the ring with zero twists, and two Mobius strips each with a single half-twist in opposite directions. The half-twisted Mobius molecules are clearly under higher stress than the untwisted ring, and thus form in smaller percentages of final yield. However, the stereoisomeric Mobius molecules were nevertheless synthesized, isolated, and studied for their physical properties. Walba noted that “improvements in
small molecule topological stereocontrol” would happen with time, and that one day, more complicated Borromean Rings would be created using a directed synthesis. He predicted the Mobius molecules and Borromean Rings would likely enable important technological advances, a forecast that took over twenty years to come to fruition. [4]

Walba’s design of simpler Mobius molecules paved the way for more complex topological molecules to be synthesized. Knotanes, Catenanes, and Borromean Rings are three molecular “surfaces” that, when synthesized, have great potential for functionality (as noted by Walba) particularly in nanotechnology. Catenanes are the simplest surface of the three. Catenanes are interlocked macrocycles consisting of two or more macrocycles, which cannot be separated without breaking the covalent bonds of the macrocycles. Catenanes were first of the three to be synthesized in 1983 and have since been manufactured in higher percentage yields and purities [4]. They can now be constructed using a variety of chemical interactions, including hydrogen bonding, metal-ligand centers, and pi-electron clouds, which has led to synthesis of [n]catenanes (catenanes with n linked components) with increasingly large n.

Before describing the other surfaces, it is important to understand the synthesis of the catenane. Catenanes were the first of the three surfaces to be synthesized, and there has been great success in synthesizing catenanes with a variety of mechanisms involving several organic adjuncts and function groups. Molecules are obviously free flowing bodies and too small to be manually threaded into one another to create linked components. Thus chemists have induced other techniques, specifically hydrogen bonding, to create linked molecules. Similar to Walba’s synthesis, catenanes and Borromean rings are made from Mobius ladders, something that Wasserman and van Gulick first observed. The ladders are transformed into rings using simple cutting and pasting techniques as described above, with the only difference being the functional groups on the ladders. Instead of Walba’s
poly-ether and poly-ester rings, catenane and ring synthesis involves reacting acid chlorides and amines to form amides – functional groups with carbon double bonded to an oxygen, and bonded to an NH2 group – a group which contains superfluous hydrogen atoms, oxygen atoms, and electron pairs, keys to hydrogen bonding. Hydrogen bonding, which occurs naturally in substances like water, can occur as long as the pairs of rings are pushed close together. Polarized oxygen atoms with extra electron lone pairs will chase polarized positive hydrogen atoms, and create ionic bonds between the rings, holding them together and synthesizing a larger ring – a catenane, Borromean ring, or knotane – depending upon the foundational ladders and functional groups used. [5]

Other popular syntheses include metal-ligand reactions, commonly used in pharmaceutics. Long ligand chains are attached to metal elemental centers like cobalt, gallium, and copper with multiple stable states. Metal centers can often form up to 6 bonds, and thus create a very stable molecular nucleus on which the ligands are built. The long ligand chains extend from the metal-alkylate in pairs. The ends of the ligand chains, equipped with double bonds for extra hydrogen pairs, cut and paste to themselves to complete two respective rings/cycles. Because the rings are attached at the central metal-alkylate, it is simply a matter of crossing the ligands across the metal-alkylate at the start of the reaction to create interlocked rings.
Knotanes, commonly called molecular knots, are exactly what they sound like; molecules equipped with a knot amid its chemical architecture. Knotanes are naturally found in DNA molecules and certain proteins. Knotanes were first synthesized in 1989 and have potential for greater functionality including non-biological use. Naturally occurring knotanes have such great functionality – DNA being the building block of all life—that scientists are hopeful to build even stronger, more stable knots. Chirality is a key concept for knots, as knots can vary between chiral and achiral, and their enantiomers can possess greatly differing characteristics that make a pair of knots exceedingly more valuable.

The third molecular surface, an analogue of the catenane, is the Molecular Borromean ring. The molecular Borromean ring, whose topological counterpart is the Borromean ring, is unlike the catenane because it has at least three macrocycles. Additionally the macrocycles are all intertwined together, not a series of chain links, such that no two links are connected and cutting one ring frees all three rings. Molecular Borromean rings were not synthesized until 2004 using the metal-ligand mechanism described previously. Diamine compounds were bonded to the zinc center and reacted
with 2,6-diformylpyridine, yielding the three-ring structure. The product is only possible because it requires a high volume of smaller molecular groups such as pyridine, which each contribute double-bonded cyclohexenes which are integral in the complex pi-electron system that covers the macrocycle and allows stability of the borromeate product.[7] Borromean ring products are the least common of the three larger topological molecular surfaces as it is the most recently synthesized, and though the reaction is relatively simple to execute, the mechanism is fairly complex and difficult to duplicate with other organic molecules or inorganic metal-ligand groups. Thus there has been the least success with synthesis of various Borromean rings, and therefore the least amount of data and research on these structures.

Of course there is a reason why chemists and topologists have been synthesizing topological molecules since the 1960s. Large interlocked rings, knots, and chains have increased functionality because they can be more easily manipulated. Interlocked molecules have controlled rotational and translational motions. The rings and chains are interconnected, thus as long as they are not broken and separated, their motion can be restricted by the amount of torque and strain the molecular bonds can take. Similarly, the motion of the individual chain-links will have limited elasticity and flexibility. Just as the rings cannot be twisted at too great an angle, they also cannot be pulled too far “apart” (of course, they are never really apart). By controlling the movement of the molecular structures, it is therefore easier to manipulate the inter- and intra-molecular interactions.

The ability to direct the inter and intra-molecular interactions means that more complex syntheses can be used to place particular organic and inorganic functional groups near one another to increase stability of the knots and rings, and direct more precise functionality of the entire molecule in nanotechnology. Controlling these submolecular motions is an active area of research. Submolecular motion of components in interlocked molecules is leading to the creation of novel functional molecules which change their
properties in response to some external stimulus (e.g. light, electricity or a chemical reagent). Such molecules will form the basis of molecular machines and devices which are predicted to be the key protagonists in the development of a “bottom-up” nanotechnology.[5] Mechanically interlocked molecules are particularly intriguing synthetic targets because of their promise in the pursuit of electronic paper, nanovalves, molecular switches, and other nanoelectronic components.[6]

The ability to create catenanes, knots, and rings composed of virtually any chemical units is an extremely attractive prospect. The main motivation for research on interlocked molecules today, however, is not the synthetic challenge but the properties and applications of the molecules themselves. Interlocked molecules often exhibit markedly different properties to their non-interlocked analogues. This can include differences in spectroscopic responses, chemical reactivity or mechanical properties. Theoretically, the only difference between a single ring and an [n]-catenane is linkage, and the chemical differences are likely a direct result of the interlocked architecture. However, the most innovative consequence of the linkage is the unique way in which different parts of the molecule can move with respect to the rest of the system.

Synthetic challenges still remain however. Controlling the movement of the molecular ring is drawn back only by the limitations of the syntheses. Successful creation of knotanes, catenanes, and borromean rings is infrequent and has been limited to formation of bulky, cluttered molecules; extraneous functional groups are only included because of their value in creating efficient syntheses. The necessity for interactions between components naturally places restrictions on the structural and functional make-up of the final product. Intermediate reactions necessary for synthesis of the final product introduces larger chemical compounds onto the edges of
the ring. Depending on the orientation of the functional group and its neighboring groups, it may be possible that the neighboring groups introduce unwanted chemical interactions; change of polarity, induced hydrogen bonding, or fluctuation of pH among potential problems. Just as submolecular motions are a valuable aspect to synthesis of interlocked molecules, submolecular motions also presents serious challenges in creating fully stables molecules.

Fortunately, the benefits of interlocked molecules greatly outweigh the drawbacks, and with time, the submolecular motions will surely be optimized to maximize functionality and decrease interference. As stated above, the development of nanotechnology is largely dependent on the bottom-up construction of assemblies of molecules with device-like properties. The efficient preparation of molecules exhibiting desired and designed functions is therefore important. The syntheses of interlocked molecules will hopefully soon be established to the point of being able to make virtually any molecule, though overall yield and the time required are often prohibitive for practical applications.

There is still great work to be done to perfect the established syntheses of interlocked molecules, as well as designing faster, more efficient mechanisms to create a larger variety of molecules. Researchers have already begun work on more complex topological molecules, such as the Figure-8 Knot, and ideally, more complex yet stable surfaces will yield more functional molecules. From their roots, topology and chemistry are organically intertwined; basic mathematical ideas such as graphs, to simple Mobius Band surfaces, and more intricate shapes are shared in both fields. Undoubtedly, as one field grows, it will allow the other to grow, and the relatively new topic will continue to thrive and intensify in relevancy in the 21st century.
References