The synthesis and application of the catenane

Suzhou Li*

High School Affiliated to Jiaotong University, Shanghai, China

*Corresponding author: Laura.guan@cn.ey.com

Abstract. Over the past six decades, research on catenanes and application of catenanes have become more and more mature. Catenane is a mechanically interlocking molecule containing two or more interlocking macrocyclic molecules. The interlocking rings cannot be separated unless the covalent bonds within the ring molecules are broken. This review will introduce the definition of the catenane and a brief history of its research, the two common synthetic mechanisms: self-assembly and template synthesis. The supramolecular principles underlying the different templates are introduced like π-π stacking, Hydrophobic interaction, hydrogen bond, coordination bond and the results of the experiments are presented. The differences between the two mechanisms as well as the different templates are analyzed through data, and finally the main applications of catenanes related to molecular machines are presented .Therefore, through this review, I hope that readers will learn about an interesting and fascinating molecule, and its promising future research and development space.

Keywords: Catenanes; Supramolecule; Molecular machine.

1. Introduction

Catenane is a mechanically interlocking molecule including two or more interlocking macrocyclic molecules. The interlocking rings cannot be separated unless the covalent bonds within the ring molecules are broken. Richard Wilstedt, winner of the 1915 Nobel Prize in Chemistry, first mentioned the possibility of mechanically linked cyclic molecules at a symposium in Zurich between 1906 and 1912. It was only about half a century later that chemists began to study catenanes and their synthesis. The development of the synthesis of catenanes is an example of the beauty of chemistry and the creation of chemical topology [1].

There are currently two main methods for synthesizing catenanes. The first method is a simple ring-closing reaction, in which it is hoped that the molecules are located in just the right place when we close the ring to synthesize a catenane. This method, also known as the “statistical method”, was used in the synthesis of the first catenanes, utilizing the keto-alcohol condensation reaction of dibasic acid esters. The greatest disadvantage of the method is that the yield of it is so low that it is rarely used. The second approach relies on supramolecular preassembly of precursor macrocyclic molecules, e.g., using hydrogen bonding, metal coordination, hydrophobic interactions, or Coulombic interactions. These noncovalent interactions counteract some of the binding entropy and put the reacting molecules in the proper conformation. This is also known as the “template-guided method”, and if high pressure is applied, yields in excess of 90% can be obtained, which has led to the widespread use of catenanes and it is the second method with higher yields that we will focus on today.

The chemists who devised the earlier synthetic routes to catenanes did not know that the mechanically interlocking macrocyclic rings arose naturally. Electron microscope showed catenanes consisted of rounded DNA separated from the mitochondria of hela cells and human leukaemic leucocytes in 1967. Hence, scientists have found and synthesized a lot of diverse interlocking DNA topologies. It is worth mentioning that the 2016 Nobel Prize in Chemistry winner's main research result, Molecular Machines, is also based on this [1,2].

2. Mechanisms

There are two main kinds of syntheses of catenanes: self-assembly and template synthesis. Self-assembly refers to the formation of interlocked catenanes by the completion of ring-closing reactions of molecules in the presence of cyclic molecules. Template synthesis, on the other hand, refers to the control of molecular synthesis through some supramolecular forces, thus generating solanine molecules in relatively higher yields.

2.1. Self-assembly Synthesis

The first [2] catenane was synthesized by Wasserman in 1960, and the evidence supports its structure. In 1961 Schill and Lüttringhaus experimentally realized the covalently bonded oriented synthesis of catenane as shown below (figure 1). In their stepwise route, a 28-membered ring was constructed first, based on the benzene ring, which, due to its larger size, helped to overcome the distorted ring tension introduced by the benzene ring. Then the reaction of the keto group with the diol is carried out followed by nitration of the ring and then reduction to the amino group, allowing the position of the amino group in the intermediate 8 just inside the macrocyclic cavity. Finally, as the two electrophilic chlorine atoms in intermediate 8 are positioned just above and below the macrocyclic plane, the intramolecular cyclization is guided, finally giving rise to the threaded structure 9 . The intermediate 9 is then oxidized by trivalent iron ions and undergoes cleavage of the aryl-nitrogen bond to give the final catenane product 10 from the readily available phosphonium salt. This example has been the most effective ways in catenane synthesis for nearly 20 years, superseded by Sauvage's template method. The synthesis routine discovered by Schill and Lüttringhaus was a precursor to imagination and skill scientists would apply to the synthesis of interlocking molecules for the future [1]

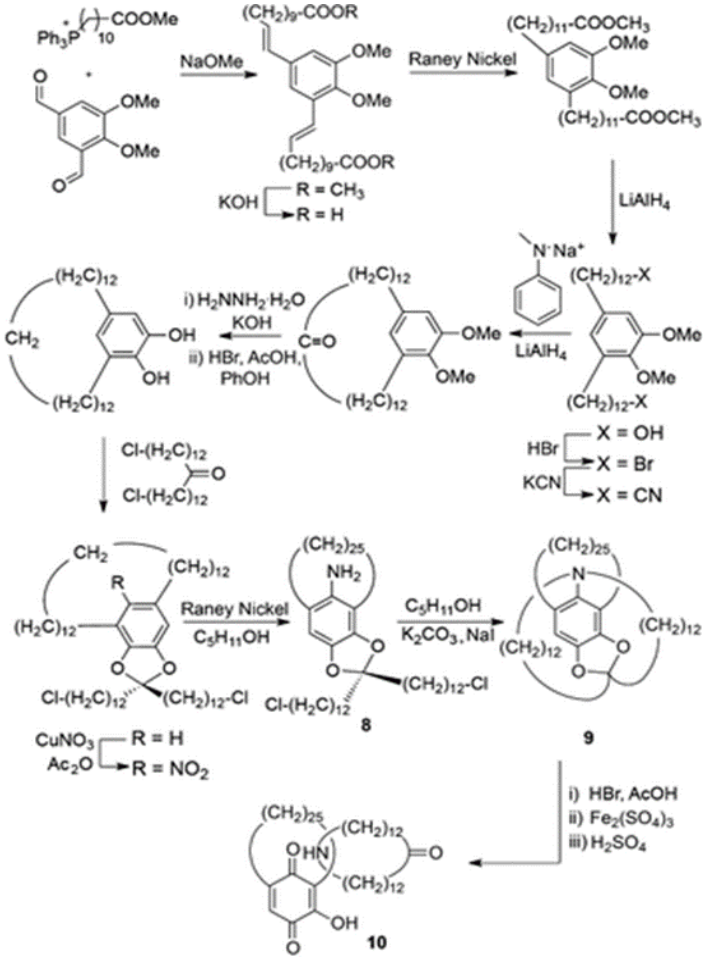

Fig. 1 The covalently bonded oriented synthesis of catenane [1]

Scientists have since tried a number of different methods to synthesize catenanes via self-assembly, but experimental results have shown that the yields are not ideal, which makes sense when you think about it on a microscopic level. This is because self-assembly synthesis essentially requires that the ends of the molecules be exactly on the top and bottom of the cyclic molecule at the completion of the ring-closing reaction, which is probabilistically very low, and results in a lower yield in the end.

Although early orientations and statistical approaches to catenanes suggested that the synthesis of interlocking molecules was feasible just in the experiment. But the low yields and long multi-step routes meant that a completely new synthetic approach was needed to make catenanes more than just an academic curiosity. In 1983 scientists began to study a new approach to synthesize the catenane. Jean-Pierre Sauvage found that the orthogonal array of bidentate ligands in tetrahedral Cu me complexes could be used to produce the crossovers needed for the synthesis of catenanes. Since then, we have used template synthesis to synthesize most catenanes [1].

2.2. Supramolecular Chemistry

Before introducing template synthesis we introduce supramolecular chemistry, which is at the heart of template synthesis. Supramolecular chemistry, firstly proposed by French scientist J.M Lehn, is a fringe science consisting of the intersection of chemistry and many other disciplines such as biology, physics, material science, information science and environmental science. Its research is divided into two directions, supramolecular chemistry (subject-object chemistry) and supramolecular ordered assembly chemistry [3].

Chemistry as it is known is primarily the study of the synthesis, structure, properties, and laws of transformation of molecules bound by covalent bonds. Supramolecular chemistry advocated by scholars represented by J. M. Lehn has become another brand new field for future chemical development. Supramolecular usually refers to the combination of two or more molecules relying on intermolecular interactions to form complex, organized aggregates, and maintain a certain degree of integrity so that it has a clear microstructure and macroscopic properties. Some of the supramolecular macrocyclic subjects that have been reported are DNA, crown ethers, cyclodextrins, cuproaromatics, cuprules, cuprocarbazoles, gua-cyclic cucurbiturons, and columnar aromatics [4].

Common supramolecular forces include ligand bonding of metal ions, hydrogen bonding, π-π interactions (formation of off-domain Π-bond stacking), electrostatic interactions, and hydrophobic interactions. The synthesis of catenanes via supramolecular templates is controlled by the different types of forces mentioned above, respectively, for the targeted and efficient synthesis.

3. Template Synthesis

3.1. π-π Interaction Assembly

π-π stacking action originates from the attraction between different signed electron clouds between aromatic systems.π-π stacking refers to the interaction between the π electrons of two aromatic rings. The two rings are often one with rich π electrons and another with deficient π electrons so that π-π stacking action occurs. And through this force we are able to synthesize catenanes.

As can be seen in the example shown below (figure 2), this is a series of catenanes synthesized by Stoddart and colleagues using π-π interactions, where compound 22 acts as a crown ether-like structure in that the aromatic ring it contains is electron rich. The aromatic rings in compounds 23, 24, 25, and 26 are electron-deficient due to the electron-withdrawing effect of the nitrogen and bromine atoms. Thus, during the synthesis, the aromatic rings will control their relative positions to each other through π-π interactions, thus finally completing the ring-closing reaction on both sides of 22 to form the final catenane product. The second reaction below it forms a polycyclic catenane due to the fact that the macrocyclic molecules synthesized by, 25, 26 are larger and can accommodate two naphthalene molecules [5-8].

As can be seen from the yields, it is relatively more efficient to assemble and synthesize catenane molecules via π-π interactions.

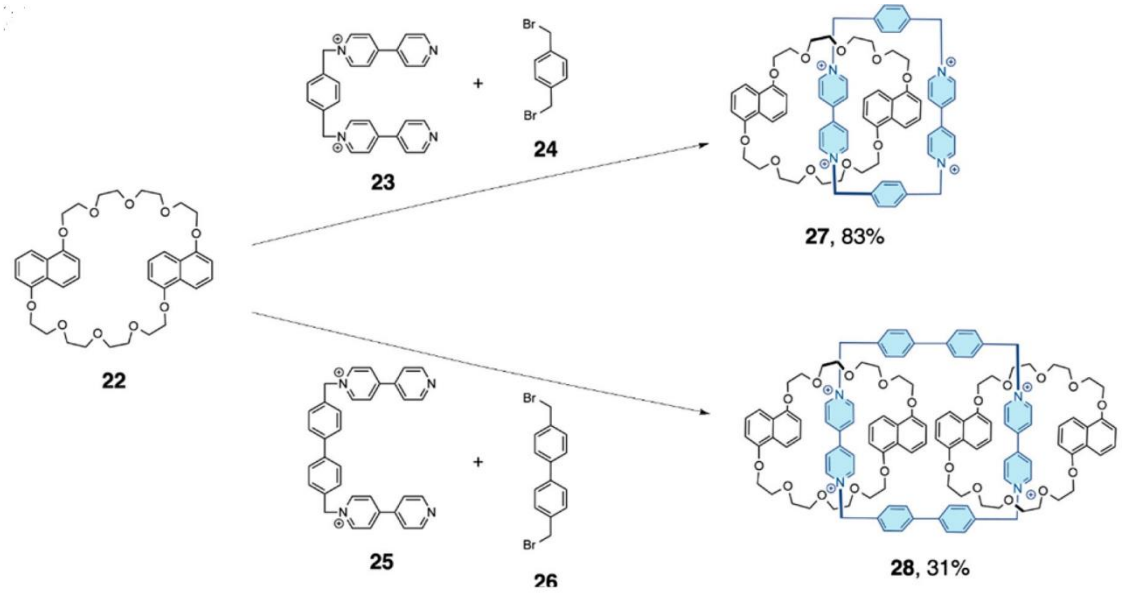

Fig. 2 Catenanes synthesized by Stoddart and colleagues using π-π interactions [5]

3.2. Hydrophobic Effect Driven Templates

Hydrophobic interaction is the phenomenon that the folding of spherical proteins in an aqueous medium is always inclined to bury hydrophobic residues inside themselves. Hydrophobic interaction and the balance between hydrophobicity and hydrophilicity play a crucial role in all aspects of protein structure and function. And through this role scientists have also developed methods to synthesize catenanes.

We can use the hydrophobic solvent effect to promote threading of components to create catenanes (or their precursors) by forming inclusion complexes to reduce the surface area of hydrophobic substrates exposed to polar solvents. The following example is an example that Stoddart and colleagues use this template to synthesize the catenane 65. The yield is 3% as showed below (figure 3) [1].

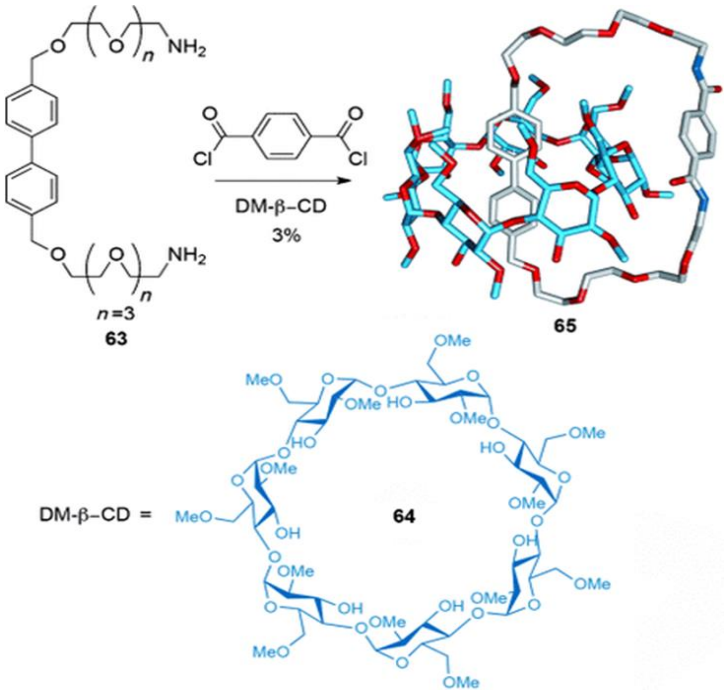

Fig. 3 [2] Catenane synthesized by Stoddart and colleagues [1]

It is also easy to see by the yields that the hydrophobic effect alone does not seem to be ideal for the synthesis of catenanes due to the relative weakness of the hydrophobic effect in the supramolecular forces.

So as shown in the example below (figure 4), Sanders and colleagues combined hydrophobic interactions, π-π interactions, and electrostatic interactions to synthesize [3]catenane 54 from the aqueous dynamic library of disulfides. It is not difficult to see that 54 has a great advantage in thermodynamic generation [5].

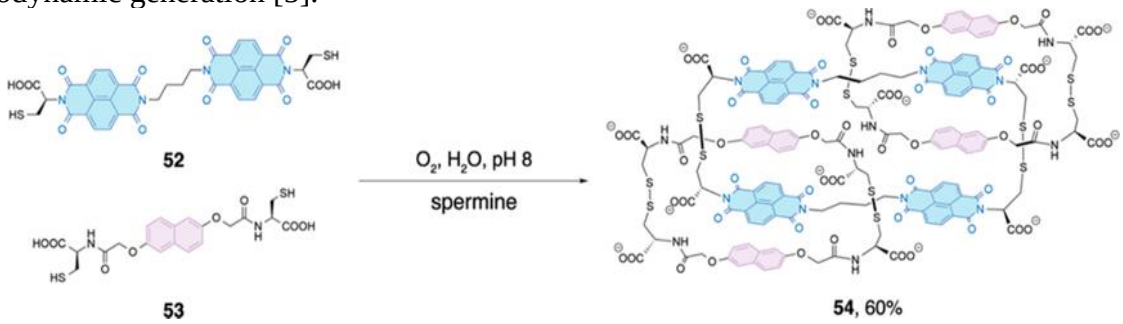

Fig. 4 [3] Catenane 54 synthesized by Sanders and colleagues [5]

3.3. Hydrogen Bonding Template

Hydrogen bonding can usually be represented by X-H...Y. Where X is covalently (or ionically) bonded to hydrogen and has a high electronegativity that stabilizes the negative charge, so that hydrogen dissociates easily and is acidic (proton donor). Y, on the other hand, has a high electron density and is generally an atom containing a lone pair of electrons, which tends to attract hydrogen protons, thus forming a three-center four-electron bond with X and H atoms.

As shown in the figure below, in a direct octamer condensation reaction, catenane 57 was synthesized in one step which uses dibenzylamine and resorcinol dichloride with a 20% yield of catenane. This is much higher than expected due to the hydrogen bonding present. As shown in 57 (figure 5), there are as many as six hydrogen bonds in the molecule, and it is evident that the configuration of the resulting catenane is the one that makes the two rings most stable.

Currently, the synthesis mentioned above from chemicals that are more available and common remains one of the easiest methods for obtaining catenanes. The X-ray structure is the first of the amidocatenanes, confirming the amide-amide hydrogen bonding array. A structure of π-π stacking interactions that stabilizes the whole structure is also shown. The macrocyclic components of catenane 57 can rotate with each other in solution. Benzylamidocatenanes are generally easy to prepare with a high degree of structural versatility as well as variable and controllable ring dynamics [1].

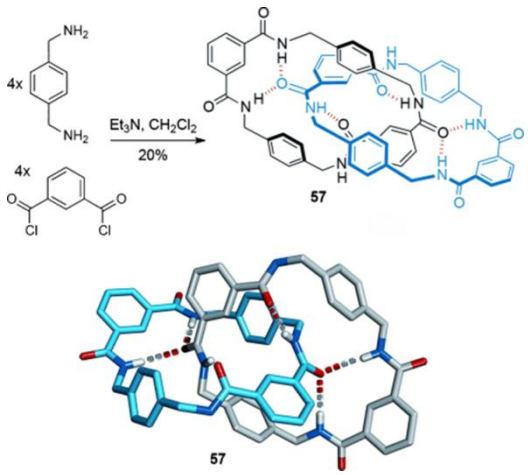

Fig. 5 The synthesis of catenane 57 [1]

3.4. Metal Coordination Bonding Templates

A coordination bond, also known as a coordination covalent bond, or simply a coordination bond, is a special type of covalent bond. A coordination bond is formed when the electron pairs shared in a covalent bond are supplied by one of the atoms alone, with the other atom providing the empty orbital. Once a coordination bond is formed, it is no different from a normal covalent bond. The two electrons shared between the two atoms that form the bond are not supplied by one of each atom, but come from one atom.

As shown in the example below (figure 6), by combining well-defined geometries and organic building blocks with linear anti-Platinum(II) centers, Stang and colleagues have completed the assembly of radial [4] catenanes 20 and [7] catenanes 21, which consist of a central molecular triangle and a hexagon, respectively. The two catenanes in structural units 18 and 19 are located at 60° and 120°, respectively, which directly directs the assemblies to full [3 + 3] and [6 + 6] macrocyclization. Subsequent addition of the diammonium unit to dibenzo-24-crown-8 (DB24C8) yields quantitative yields of the [4]- and [7]-catenane [5].

In this case, the coordination of platinum atoms plays a larger role in building the overall catenane structure, and the final yields illustrate the efficient characteristics of the metal coordination templates.

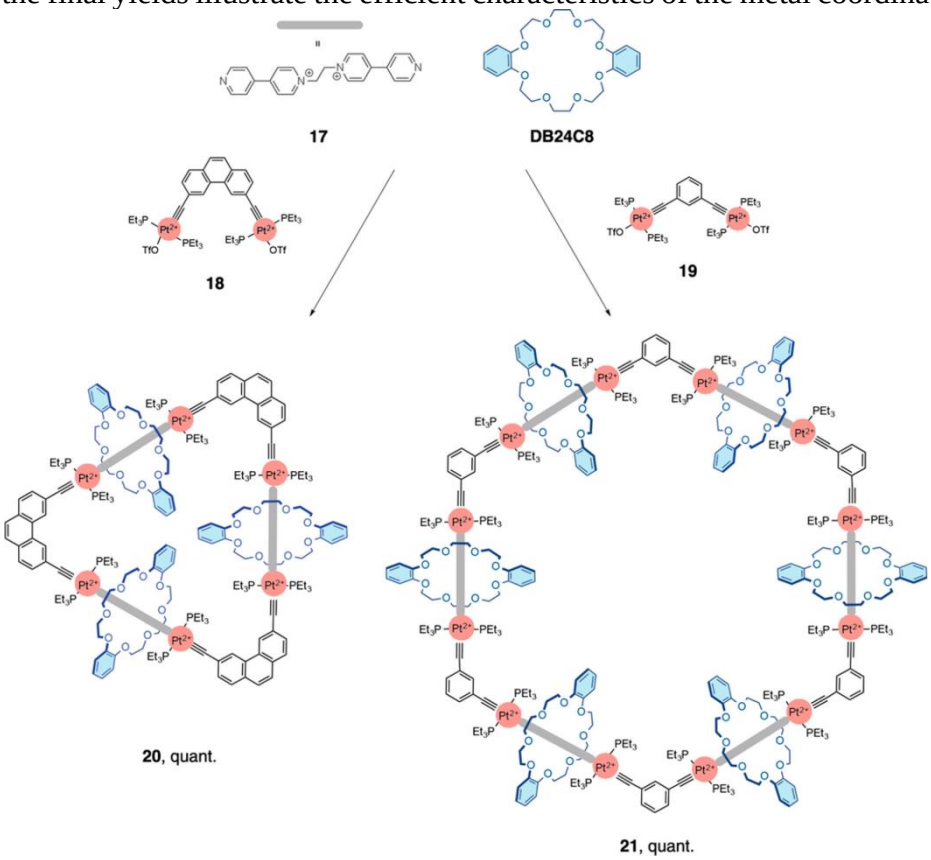

Fig. 6 The synthesis of catenane20 and catenane21 [5]

4. Molecular Machine

Molecular machine, refers to a machine composed of molecular-scale substances that can exercise certain processing functions, and its building blocks are mainly biological molecules such as proteins. Because its size is mostly nanoscale, also known as biological nano-machine, it has small size, diversity, self-direction, organic composition, self-assembly, accurate and efficient, molecular flexibility, self-adaptation, relying only on chemical or thermal energy to drive, molecular modulation, and other man-made machines are difficult to compare, so the study of biological nano-machine is of great significance. It can promote biological discovery, deepen the understanding of protein

molecular machine mechanism, develop biomolecular machines and promote the development of bionics [9].

And the main character of our today-mentioned catenane molecule is an indispensable part of molecular machine research. As shown in the example below (figure 7) when [c2] daisy chains are doped into polymers, their synchronized and collective molecular level motions can be amplified to be driven at the macroscopic level. Harada and coworkers recently showed how this strategy can be used to design molecular muscles. Their system relies on the fact that α-cyclodextrin (α-CD) binds more strongly to trans-stilbene than to cis-stilbene, thus allowing the α-CD ring to photo-inducedly slip from the stilbene station to the poly(ethylene glycol) collection region upon trans to cis isomerization. This movement in the daisy-chain monomer propagates throughout the polymer, resulting in the contraction/swelling of the cross-linked hydrogel. This phenomenon is then used to actuate the polymer membrane and even perform mechanical work by resisting gravity pulling a heavy object [10].

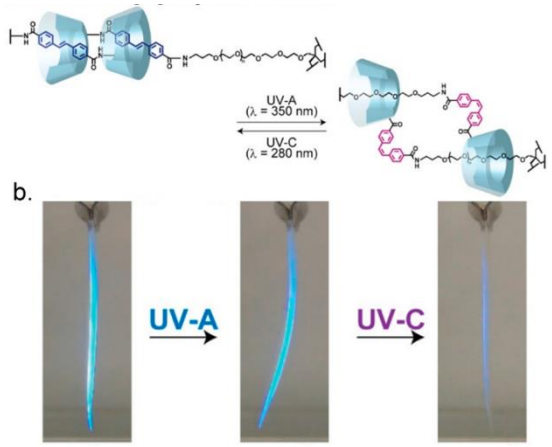

Fig. 7 The mechanism of molecular machine [10]

5. Conclusion

This paper introduces the history of the discovery and research of catenanes, the two main different synthesis mechanisms self-assembly synthesis as well as template synthesis, and demonstrates through theoretical and experimental data that template synthesis is a more efficient synthesis method. Then this paper introduces the template synthesis through different types of supramolecular forces: π-π interaction assembly, hydrophobic effect-driven, hydrogen-bonding templates, and metal-coordination-bonding templates, and compares them with the data, which shows that the metal templates and the π-π interaction templates are comparatively more efficient, which is also in line with the strength of supramolecular forces. Finally, the main application of catenanes, molecular machines, is introduced at present, and examples are given to explain the importance of catenanes in the field of molecular machines. However, applications of catenanes in molecular machines as those mentioned above are still in the initial stage of research, which shows the great potential of catenanes in the future.

References

[1] Gil-Ramírez, Guzmán, Leigh, David A. Stephens, Alexander J. Catenanes: Fifty Years of Molecular LinksAngewandte Chemie International Edition Angew. Chem. Int. 2015 54(21): 6110-6150.

[2] Qu, Zhiyu Fang, Jing Wang, Yu-Xiang Sun, Yibin Liu, Yajie Wu, Wen-Hao Zhang, Wen-Bin A single-domain green fluorescent protein catenane Nature Communications 2023 14(1): 3480-3480.

[3] Shu Zhang, Liyan Zhang, Aocheng Chen, Yi An, Xu-Man Chen, Hong Yang, Quan Li, Cucurbit[8]uril-Mediated Supramolecular Heterodimerisation and Photoinduced [2+2] Heterocycloaddition to Generate Unexpected [2]Rotaxanes, Angewandte Chemie International Edition, 2024,63(39): e202410130.

[4] Datta, Sougata Kato, Yasuki Higashiharaguchi, Seiya Aratsu, Keisuke Isobe, Atsushi Saito, Takuho Prabhu, Deepak D. Kitamoto, Yuichi Hollamby, Martin J. Smith, Andrew J. Dalgliesh, Robert Mahmoudi, Najet Pesce, Luca Perego, Claudio Pavan, Giovanni M Yagai, Shiki Self-assembled poly-catenanes from supramolecular toroidal building blocks Nature 2020 583(7816): 400-405.

[5] Au-Yeung, Ho Yu, Yee, Chi-Chung, Hung Ng, Antony Wing, Hu, Keling, Strategies To Assemble Catenanes with Multiple Interlocked Macrocycles, ACS Central Science, American Chemical Society2018 57(7): 3475-3485.

[6] Leigh, David A Pritchard, Robin G. Stephens, Alexander J. A Star of David catenane Nature Chemistry 2014 6(11): 978-982.

[7] Fan, Yang-Yang Chen, Dandan Huang, Ze-Ao Zhu, Jun Tung, Chen-Ho Wu, Li-Zhu Cong, Huan An isolable catenane consisting of two Möbius conjugated nanohoops Nature Communications 2018 9(1): 3037-3037.

[8] Baluna, Andrei S. Galan, Albano Leigh, David A. Smith, Gareth D. Spence, Justin T. J. Tetlow, Daniel J. Vitorica-Yrezabal, Iñigo J. Zhang, Min In Search of Wasserman's Catenane J. Am. Chem. Soc. 2023 145(17): 9825-9833.

[9] Richards, Victoria, Molecular machines, Nature Chemistry, 2016, 8(12): 1090-1090.

[10] Aprahamian, Ivan, The Future of Molecular MachinesACS Central Science, American Chemical Society 2020 6(3): 347-358.