Application of Heterometallic Supramolecular Cages in Treating Cancer

Zihan Cong *

Department of Chemistry, University of Manchester, Manchester, the United Kingdom

* Corresponding author: Zihan.Cong@postgrad.manchester.ac.uk

Abstract. Supramolecular complexes rely on non-covalent interactions, enabling a host-guest structure. When metal ions are introduced into the skeleton of 'host', the valance electron configuration of heteroatoms result in versatile stable structures of complexes. Heterometallic supramolecular cage is a kind of stable form which is able to act as a carrier. Instead of diffusing into circulatory system directly, carriers are used to hold the drug molecule and release it at an aim position. In this case, targeted therapy, which significantly reduce the side effect of drugs, can be achieved. There have been discussions on the potential of supramolecular structures as cytotoxic agents and drug delivery systems for anticancer drugs. Several anticancer, antibacterial, and other pharmacological analogue compounds were used to investigate the guest binding capabilities of the successfully synthesized heterometallic complexes. The stability of these cages in water and when coupled with specific guest molecules was examined. These cages' capacity for cytotoxicity as well as diverse host-guest combinations were investigated.

Keywords: heterometallic, supramolecular, cancer.

1. Introduction

The term "cancer" refers to a group of disorders brought on by the rapid and erratic proliferation of cells without the proper cellular apoptosis to ensure the death of harmful cells. Untreated malignant tumours can spread and take over healthy cells if harmful cell growth is left unchecked, making it impossible for organs to perform their essential duties. Death may eventually result from this. Chemotherapy, radiation, surgery, biotherapy, or a combination of several methods are being used to treat cancer [1, 2]. Chemotherapy, which is the administration of anticancer medications with the goal of either destroying malignant cells or reducing their rapid development, will be the treatment method covered in this article.

In order to self-assemble into specific discrete forms, metallosupramolecular architectures take advantage of the extremely brittle coordination bonds between some metals and donor atoms on ligands. The coordination angles of ligands and metal geometries is ignorable for self-assembly, resulting in thermodynamically advantageous end products. This leads to the creation of the smallest, lowest-energy, and least-sterically-strained product conceivable, which frequently produces cyclic molecules [1, 3]. There are several methods for creating metallosupramolecular assemblies, including ligand directed or directional bonding, weak link techniques, and symmetry interaction [4].

Metallosupramolecular cages' host-guest chemistry largely depends on the cavity's functioning and the cage's solubility. The ligands that are employed to construct the cage frequently control these features. As a result, the selectivity of host-guest interactions can be improved or enhanced by changing the ligand backbones [2]. As shown in Fig.1, these host structures have a variety of uses depending on the guest molecules they attach to, including reaction flasks, catalytic systems, drug delivery, molecular storage, and the capture of environmental pollutants.

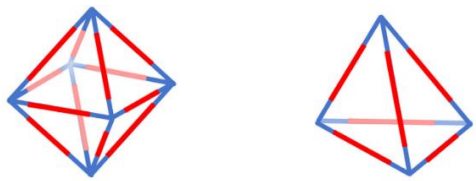


Figure 1. Octahedral chiral cage (left) and tetrahedral chiral cage (right) [2]

Metalloligands that comprise porphyrin or ferrocene are used to create heterometallic structures. Although heterometallic, these structures are well explored in the literature and have a very simple production process. By combining symmetry interaction with the chelation effect, the metal/ligand geometry and chelation guided technique is able to selectively coordinate a particular metal ion to a particular binding site in a ligand. As shown in Fig.2, subcomponent self-assembly is the reaction of one or more pre-formed metal complexes to construct the entire heterometallic architecture, as opposed to metal/ligand geometry and chelation driven approaches [3].

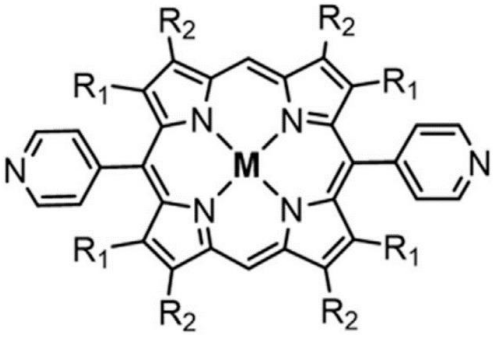


Figure 2. An Example of metalloligands (M=Zn, R_1=methyl, R_2=n-butyl) [2]

2. Synthesis of Heterometallic Supramolecular Cages

2.1. Post-assembly Modification

By exchanging a labile or sterically unfavourable metal for a sterically favourable one, transmetallation can create heterometallic structures. The synthesis of mixed metal MOFs frequently uses the transmetallation approach, and in some cases, complete transmetallation is also seen [3, 4].

The host-guest chemistry, however, that has been covered so far has only dealt with the encapsulation of a single type of guest molecule, often in a host/guest ratio of 1 to 1, bonded within monocavity structures. A portion of metallosupramolecular chemistry has been devoted to the creation of molecules that can bind numerous guests at once in an effort to improve the host-guest applications of supramolecular cages [3]. The harsh reaction conditions and challenges in ligand design and synthesis, however, limit this method's appeal. There are a few instances of monocavity cages designed to contain more than one guest, although these visitors are often smaller molecules or bind due to the hydrophobic effect [3].

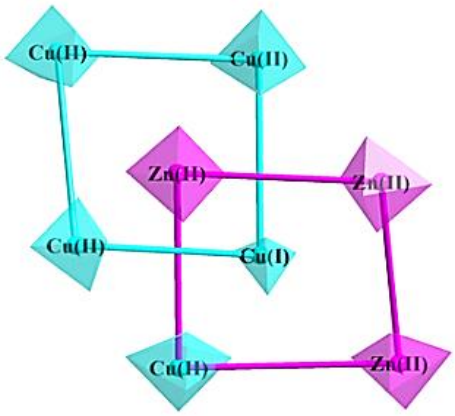
Due to its capacity to create systems with increased complexity, this method can be used to categorise the synthetic approach of heterometallic complexes. Also reviewed are the functional investigations into the heterometallic complexes, particularly for enzyme-inspired catalysis [5]. Strategies for creating molecules with numerous separate cavities have been devised to get around these problems. This covers the creation of multicavity cages that are linearly and laterally extended, as well as interpenetrated cages. While concurrently encasing numerous guest molecules at once, the usage of numerous distinct cavities preserves the supramolecular interactions seen in tiny cavity cages. Compared to a 1:1 host-guest complex, this makes guest binding more complex because guest binding can now be statistically determined or affected by the first binding event, either by changing the host's structural makeup or by changing the interactions that can be used for the second binding event. To overcome the difficulty of selective coordination to create heterometallic complexes, a variety of synthetic techniques were used.

Supramolecular structures are typically constructed using the metal acceptor and cyclopentadienyl or arene-metal moiety. The symmetrical twin cage and the unsymmetrical twin cage, however, were in balance because of the flexibility of the ligands, and the production of both cages was reliant on the solvent employed. An alternative strategy using linearly extended polytopic ligands has been developed to controllably and selectively synthesise multicavity systems [5, 6]. The core phenyl spacer cavity bound a triflate ion in the presence of cisplatin and triflate guest molecules, while the

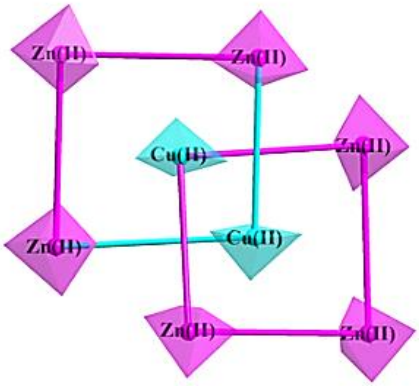
outside cavities created with pyridyl alkyne spacers bound two cisplatin molecules in each. This data is consistent with that previously demonstrated in related monocavity architectures, in which the pyridine spacers are required to provide suitable hydrogen bonding motifs to stabilise the binding of cisplatin, whereas the phenyl spacer's absence of the lone pair of electrons favoured the encapsulation of triflate in the middle cavity [5].

When the secondary building unit produces new supramolecular architectures in response to the metal acceptor, some positive charge is anticipated to be produced [6]. As a result, it is anticipated that such electron-deficient designs will be suitable hosts for electron-rich aromatic visitors. Therefore, this donor family offers enormous potential for the synthesis of novel structural heterometallic compounds by post-assembly.

The symmetry interaction method and weak donor atoms work together to create labile supramolecular frameworks that can be quickly converted into a more inert state by the addition of stronger donor ligands. A dinuclear macrocycle was created in the presence of Rh(I), an intermediate soft metal, with Rh(I) coordinating to two bidentate pockets in a square planar geometry. The inclusion of the ligand phenylenediisocyanide, which has soft cyanide donor sites, made it easier to separate the two oxygen donor sites from the Rh(I) metal centres. Instead, one cyanide from the phenylenediisocyanide and one acetonitrile molecule from the solvent were coordinated. It was demonstrated that carbon monoxide produces the same macrocycle opening. The cyclic nature of these metallosupramolecular structures often leave them with cavities that have potential to undertake host-guest chemistry. As shown in Fig.3, much like the active sites of enzymes, guest molecules can interact with the cavities of these structures using weak interactions such as hydrogen bonding, the hydrophobic effect, van der Waals forces and π interactions [5, 6].



110



111

Figure 3. Dinuclear macrocycle (110) and (111) [5]

2.2. Subcomponent self-assembly

It has already been mentioned that subcomponent self-assembly is a practical method for creating heterometallic architectures. It does away with the necessity of a metal ion being selective in order to coordinate to a single binding site on a ligand with several binding pockets. Sub-component self-assembly, on the other hand, frequently entails a reaction on a prefabricated complex to create the entire necessary architecture [3, 4].

In particular, metallarectangle demonstrated other metallarectangles which cannot support strong catalytic and the latter demonstrated reduced activity under the same conditions.[5] It is desirable to use metallic ligands with three attached groups for creating mixed-metal coordination cages. The hard and soft acids and bases idea has been the foundation for the majority of heteronuclear cage system syntheses to date. This idea, however, cannot be used in systems when the coordination locations are the same. The construction of subcomponent was controlled by the combination of 'inert and labile' components [5].

Different techniques developed from dynamic combinatorial chemistry and supramolecular synthesis have been used to create subcomponents [5]. On the other hand, the repetitive usage of numerous, identical building pieces is common [4, 5]. Self-assembled structures' high symmetry geometry has frequently been a restriction on their adaptability and diversity. The product is too big to fit inside the cavity once the intermediate has been protonated to produce it, thus it is expelled. The cavity can then bind a fresh substrate, enabling efficient catalytic turnover. By forming hydrogen bonds and stacking with the backbones of the ligands, the anthracene guest was kept stable inside the cavity. Because the reaction product's bent structure was too enormous to fit inside the cavity, the product was ejected from the prism. Over 60 hours at room temperature, the catalytic process demonstrated 84% conversion into the product with the cage present and only 12% conversion without it. The catalyst was recovered from the reaction mixture using chloroform, and the prism was collected using filtration [5].

There is still significant room for investigation into the host-guest chemistry, biological activity, and potentially novel switchable features of heterometallic cages, given their recent creation. This project's primary goal was to create procedures for the production of Pd(II)/Pt(II) heterometallic cages. In order to determine whether the relative lability of Pd(II) over Pt(II) may be used to develop structures that can open and close in the presence and then absence of competitive ligands, the switchable characteristics of these cages were investigated.[6] In addition, methods for synthesising linearly extended multicavity structures were modified after studies of the host-guest chemistry and anticancer activity of these designs. Exploring alternative synthetic pathways towards heterometallic structures employing octahedral metal centres was the second objective of this article.

Intermolecular interactions stabilise the encapsulation of molecules within the cavity of these cages, and solvophobic effects can improve it. As a result, favourable interactions make it possible to trap dangerous or reactive chemicals inside the cages' chamber. Despite being reactive outside of the cage, the initiators were shown to be stable against heat and light once bound inside the chamber [5, 6, 7]. Due to the hydrophobic environment present in the cavity in aqueous media, guest encapsulation happens. The huge anthracene panels of the four ligands, which are oriented to form a contained capsule around the visitor, produce shielding effects that stabilise the azo-radical initiators in the presence of heat and light [6]. The same team created a comparable capsule utilising acridinium linkers rather than anthracene linkers. The centre chamber of the cage nevertheless provided a hydrophobic environment, even if the positively charged ligands made the cage more soluble in water. Because of this, the cavity could attract organic anionic guest molecules even when they were dissolving in competitive aqueous media [5].

3. Cancer Treatment

3.1. Drug Delivery

With an expected 19.3 million new instances of cancer being diagnosed and 10 million deaths from its worldwide in 2020, cancer is one of the major killers [7]. The term "cancer" refers to a group of disorders that develop as a result of cells growing rapidly and irregularly without undergoing the requisite cellular apoptosis to ensure the death of harmful cells. Untreated malignant tumours can metastasize and take over healthy cells, preventing organs from performing their essential tasks, as a result of the unchecked proliferation of unhealthy cells. Death may eventually result from this. Chemotherapy, radiation, surgery, biotherapy, or a combination of several methods are being used to treat cancer. Unluckily, cisplatin does not just affect cancer cells; it can also bind to proteins in the plasma and become inactive before reaching carcinogenic cells. Due to the unfavourable side effects of this lack of selectivity, which include kidney and nerve damage, nausea, and bone marrow suppression, the maximum dosage of the medication that can be used must be reduced [8]. Additionally, certain cancer cells are cisplatin-resistant, or resistance develops with continued medication delivery [9].

Due to their great potential for structural modification to contain cellular targets and their ability to be appropriately size. In this case, metallosupramolecular architectures are of particular interest as potential anticancer therapeutics and drug delivery agents [3, 9, 10, 11]. The encapsulated anticancer medications can be protected from reaction or metabolization before reaching the targeted cells by adapting these structures to facilitate drug release once at the targeted areas. This should lessen the undesirable side effects now associated with chemotherapy and increase the selectivity and efficacy of the encapsulated anticancer medication [10].

3.2. Binding Method

The clinically authorised anticancer medications mentioned so far frequently function by irreversibly engaging with their target molecules to stop cell growth. Metallosupramolecular structures include significant structural variations, which can result in reversible weaker connections with specific molecules inside of cells and inhibit cell development via alternative modes of action. Numerous documented instances of metallosupramolecular structures that have been demonstrated to non-covalently bind to DNA or RNA and ultimately result in cytotoxic characteristics are available [9, 10].

Furthermore, the compounds' selectivity was superior to that seen with cisplatin and favoured malignant cells over healthy cells. The complexes were taken up by cells via macropinocytosis, caveolin- and clathrin-mediated endocytosis, which the authors found to be more evident in malignant cells. The hydrolysis of the imine bonds was made easier by the cancer tissue's lower pH as compared to healthy tissue. This made it possible for bound metals to be released, which is probably what caused the selectivity for malignant cells that was seen [8, 11].

3.3. Toxicity Study

The reversibility of imine and hydrazone linkages was taken advantage of in the synthesis of these cages. In the presence of water, this reversibility, however, also poses an increased risk of disintegration into their starting ingredients.[12] Even though synthetic receptors are becoming more sophisticated, designing receptors with adjustable guest affinities remains a difficult task in host-guest chemistry since it is a major technological obstacle to more exact replication of natural systems [10, 13].

Greater understanding of the operation of intricate natural signalling systems thanks to supramolecular crude synthetic copies of these systems' intricate operations. Understanding the variables that control the degree of biocompatibility and solubility is necessary for this design process. In biomolecular systems, anions are an example of a chemical signal, and several biological processes depend mainly on modification [12, 13].

4. Conclusion

The two primary methods for the self-assembly of metallosupramolecular architectures are covered in this article together with supramolecular chemistry. These include the weak link method, ligand directed, and symmetry interaction. It can cover the host-guest chemistry of cavity-containing supramolecular structures as well as their prospective uses as catalysts and reaction containers for the delivery of drugs, the storage of molecules, and the sequestration of environmental pollutants. The introduction to stimulus-responsive cages that can turn on and off host-guest interactions by adding or removing external stimuli comes next. The significance of heterometallic structures and the three primary synthetic methods—metal/ligand geometry, chelation-directed subcomponent self-assembly, and post-assembly modification—have then been described in details.

In-depth discussion of current developments in the synthesis of multicavity supramolecular structures is provided in this article. To create linearly expanded double and triple cavity heterometallic architectures, the techniques employed to create the initial heterometallic structures have been modified. This chapter has covered the synthesis of these structures, their host-guest chemistry, segregated guest binding, and stimuli sensitive switching. In order to synthesise more heterometallic multicavity structures, including a heptacavity laterally extended molecule, fresh directions are explored in the conclusion.

The potential of supramolecular structures as cytotoxic agents and drug delivery methods for anticancer medications has been discussed. The ability of the successfully synthesised heterometallic complexes to bind guests was investigated using a number of anticancer, antibacterial, and other pharmacological analogue chemicals. It was investigated how stable these cages were in water and when joined with particular guest molecules. We looked at the cytotoxic potential of these cages as well as other host-guest combinations. Characterised binding sites between cages and anticancer drugs can be further explored by trying different transition metal, and even f-block metals. Importantly, biocompatibility should always be the filter criteria. Cages with diverse heterometals perform different species adaptability, solubility, release rate and loss ratio, enabling multi-channels' synergistic effects in clinic treatments.

References

[1] Hao Li, Zi-Jian Yao, Dong Liu, et al. multi-component coordination-driven self-assembly toward heterometallic macrocycles and cages. Coordination Chemistry Reviews. 2015, 293 - 294: 139 - 157.

[2] Wen-Xi Gao, Hai-Ning Zhang, Guo-Xin Jin. Supramolecular catalysis based on discrete heterometallic coordination driven metallacycles and metallicizes. Coordination Chemistry Reviews. 2019, 386: 69 - 84.

[3] Qiang-Yu Zhu, Li-Peng Zhou, Li-Xuan Cai, et al. Stereo controlled Self-Assembly of Ln (III)-Pt (II) Heterometallic Cages with Temperature-Dependent Luminescence. Inorganic Chemistry. 2022, 61: 16814 - 16821.

[4] Laura Rodríguez, João C. Lima, Montserrat Ferrer, et al. 3D Au–Ag heterometallic supramolecular cage: Triplet capture by heavy atom effect. Inorganica Chimica Acta. 2012, 381: 195 - 202.

[5] Ying-Ying Zhang, Wen-Xi Gao, Lin Lin, et al. Recent advances in the construction and applications of heterometallic macrocycles and cages. Coordination Chemistry Reviews. 2017, 344: 323 - 344.

[6] Chao Shen, Aaron D.W. Kennedy, William A. Donald, et al. Self-assembled supramolecular cages containing dinuclear ruthenium (II) polypyridyl complexes. Inorganica Chimica Acta. 2017, 458: 122 - 128.

[7] William J. Ramsay, Tanya K. Ronson, Jack K. Clegg, et al. Bidirectional Regulation of Halide Binding in a Heterometallic Supramolecular Cube. Angew. Chem. Int. Ed. 2013, 52: 13439 - 13443.

[8] Hasti Iranmanesh, Kasun S. A. Arachchige, Mohan Bhadbhade, et al. Chiral Ruthenium (II) Complexes as Supramolecular Building Blocks for Heterometallic Self-Assembly. Inorganic Chemistry. 2016, 55: 12737 - 12751.

[9] Damien Simond, Sarah E. Clifford, Andreia F. Vieira, et al. An octahedral aluminium(III) complex as a threefold node for supramolecular heterometallic selfassemblies: solution and solid state chemistry. RSC Adv. 2014, 4: 16686 - 16693.

[10] Jin Tong, Li-Mei Jia, Ping Shang, et al. Controlled Synthesis of Supramolecular Architectures of Homo- and Heterometallic Complexes by Programmable Self-Assembly. Cryst. Growth Des. 2019, 19: 30 - 39.

[11] Guillem Aromi, Patrick Gamez, Jan Reedijk. Poly beta-diketones: Prime ligands to generate supramolecular metalloclusters. Coordination Chemistry Reviews. 2008, 252: 964 - 989.

[12] Maarten M. J. Smulders, Azucena Jimnez, Jonathan R. Nitschke. Integrative Self-Sorting Synthesis of a Fe8Pt6L24 Cubic Cage. Angew. Chem. Int. Ed. 2012, 51: 6681 - 6685.

[13] Manoranjan Maity, Prodip Howlader, Partha Sarathi Mukherjee. Coordination-Driven Self-assembly of Cyclopentadienyl-Capped Heterometallic Zr-Pd Cages. Cryst. Growth Des. 2018, 18: 6956 - 6964.