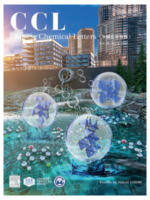
Chinese Chemical Letters 36 (2025) 110806

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet



Editorial

Functional macrocyclic arenes with active binding sites inside cavity for biomimetic molecular recognition

Molecular recognition of bioreceptors and enzymes relies on orthogonal interactions with small molecules within their cavity. To date, Chinese scientists have developed three types of strategies for introducing active sites inside the cavity of macrocyclic arenes to better mimic molecular recognition of bioreceptors and enzymes. The editorial aims to enlighten scientists in this field when they develop novel macrocycles for molecular recognition, supramolecular assembly, and applications.

In life sciences, non-covalent interactions serve as essential driving forces which are not only pivotal in forming spatial structure of biomacromolecules but also play a significant role in attaining highly specific and selective molecular recognition among molecules, such as in enzyme-substrate, receptor-ligand, antibody-antigen, and nucleic acid-protein interactions. Mimicking the important biological processes of receptors and enzymes by artificially synthesized macrocycles derived from crown ethers led to the awarding of the Nobel Prize in Chemistry to Donald J. Cram, Jean-Marie Lehn and Charles J. Pedersen in 1987, thereby sparking the burgeoning of supramolecular and host-guest chemistry. The accomplishments in employing macrocycles to construct molecular machines crucially contributed to the second time awarding of the Nobel Prize in the related field of supramolecular and host-guest chemistry in 2016. Over the past decades, several types of classic macrocycles including crown ethers, cyclodextrins, calixarenes, cucurbiturils and pillararenes have been developed, and their molecular recognition behaviors have been comprehensively studied, which has substantially advanced supramolecular and host-guest chemistry. The interdisciplinary fusion of supramolecular and host-guest chemistry with materials science, nanotechnology and biomedical sciences has remarkably promoted the diverse applications of macrocycles in various fields. Scientists from China have made remarkable contributions in this regard. For example, Yu Liu group developed construction strategies for macrocycle-based multidimensional smart supramolecular assemblies, and Xi Zhang group developed controllable supramolecular polymerization strategies with the help of macrocycles.

Despite these exciting successes, mimicking molecular recognition behaviors of receptors and enzymes with the help of current classic macrocycles is still far from satisfactory, due to these macrocycles only have a hydrophobic deep cavity fringed with active sites, lacking similar inside cavity characteristic orthogonal interactions to receptors and enzymes when they bind small molecules. Macrocycles containing aromatic structure elements are particularly appealing because they can recognize small molecules through orthogonal interactions of π interactions together with hydrophobic interactions inside cavity as well as noncovalent interactions around portal. These macrocycles referred to macrocyclic arenes have experienced rapid expansion over the past few decades, which was systematically summarized by Chuan-Feng Chen group recently [1]. In regard to introduce more active binding sites inside the cavity of macrocyclic arenes to strengthen orthogonal interactions when they bind guest molecules for realizing biomimetic molecular recognition, the late pioneer Wei Jiang group developed a family of macrocycles called naphthotubes. In addition, Chunju Li group and Huan Cong group also reported the endo-functionalized biphenarenes. Very recently, Shengke Li and Leyong Wang group reported a novel family of macrocyclic arenes called cyclicurilarene, of which the glycoluril units adopted an inward orientation inside cavity for providing additional active binding sites. These three different types of macrocyclic arenes represent three different strategies for positioning active binding sites inside deep cavity of macrocyclic arenes to obtain bioinspired macrocycles with a biomimetic cavity feature. Summarizing and identifying these strategies are essential to enlighten the development of novel macrocycles for biomimetic molecular recognition and the expansion of their diverse applications. Therefore, the three different macrocycles were introduced, and their construction strategies were elaborated.

Naphthotubes. The construction strategy of this type of macrocyclic arenes mainly depends on using functional groups as linkers to offer active binding sites inside the deep cavity. In 2015, Wei Jiang group proposed for the first time to position functional groups inside the deep cavity of naphthotubes to obtain macrocycles with a biomimetic cavity feature (Fig. 1) [2]. They first synthesized naphthotubes consisted of two bis(naphthalene) clefts bridged by two methylene group-linked urea groups. Methylene groups were intelligently introduced into the linkers to force the NH protons of the urea groups to adopt an inward orientation in order to provide active binding sites within the cavity for hydrogen bonding formation. The orthogonal interactions derived from the urea groups and the deep cavity led to an enhanced molecular recognition with guest molecules. By varying the linkers with thiourea, amine, amide, ester and ether groups, a series of naphthotubes were obtained with different active binding sites inside the cavity for regulating their molecular recognition behaviors. Naphthotubes were discovered to exhibit promising applications in sensing due to their unique recognition properties [3].

Endo-functionalized biphenarenes. The strategy for developing endo-functionalized biphenarenes mainly depends on the nonplanar conformation of biphenyl monomer. In 2021, Huan Cong group synthesized a monomer by coupling octahydrobinaphthol with two *para*-dimethoxy benzyl groups and developed

https://doi.org/10.1016/j.cclet.2024.110806

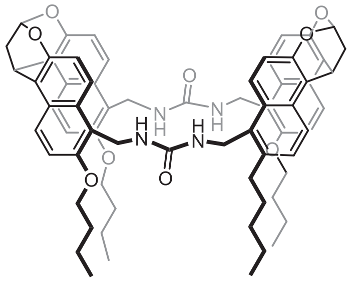


Fig. 1. Chemical structure of naphthotubes with methylene group-linked urea group as linker.

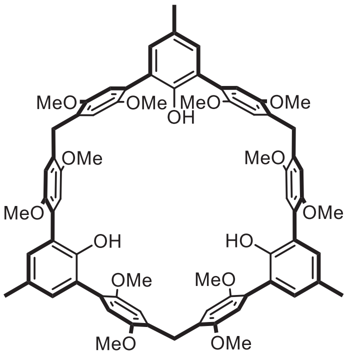


Fig. 2. Chemical structure of biphenarenes with hydroxyl groups pointing inside the cavity.

macrocyclic RhombicArene *via* Friede-Crafts condensation of the monomer with *para*-formaldehyde [4]. The *para*-dimethoxy benzyl groups, as macrocycle sidewalls, stood axially, while octahydrobinaphthol adopted a non-planar conformation, resulting in the inward-orientation of its hydroxyl groups. The crystal structure suggested that RhombicArene can form host-guest complex with cyclohexanone through C–H···π interactions and hydrogen bonds inside the cavity. In 2022, Chunju Li group developed a modular strategy for introducing active binding sites into the cavity of their biphenarenes macrocycles (Fig. 2) [5]. They designed a V-shaped monomer bearing active binding sites in the middle aromatic structure unit, and both sides were connected with *para*-dimethoxy benzyl groups by Suzuki–Miyaura coupling. Macrocyclization of the V-shaped monomer produced a macrocycle with middle aromatic structure unit adopting a non-planner conformation to the sidewall to provide active binding sites inside the cavity. With this modular strategy, biphenarenes with different types of active binding sites inside the cavity can be provided by varying the middle aromatic structure unit. They also demonstrated that biphenarenes bearing hydroxyl groups within cavity exhibited improved molecular recognition towards neutral azacycles through forming hydrogen bonds.

Cyclicurilarenes. Very recently, Shengke Li and Leyong Wang group developed a novel type of macrocycles named cyclicurilarene by embedding glycoluril units in the sidewall of macrocyclic arenes, providing another strategy for introducing active binding sites into the cavity (Fig. 3) [6]. Different from the above two strategies, this strategy directly utilized bent non-aromatic heterocycles with functional groups in the waist as the sidewall of macrocyclic arenes. They first synthesized the precursor with two *para*-dimethoxy benzyl groups respectively connected to the 2- and 6-positions of glycoluril *via* methylene group. The bent glycoluril was found to adopt an inward orientation after forming a pillar-shaped macrocycle of pillarurilarenes, resulting in the methine protons of glycoluril pointing inside the cavity to provide active binding sites. Crystal structures demonstrated that ethyl acetate situated inside the cavity was stabilized through forming multiple interactions, including hydrogen bonds and C–H···π interactions. The methine protons of glycoluril can be functionalized with different groups to vary their molecular recognition capability. By embedding different bent non-aromatic heterocycles in the sidewall, this family of macrocyclic arenes can also be expanded.

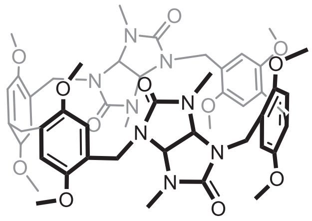


Fig. 3. Chemical structure of pillar-shaped cyclicurilarenes, named pillarurilarenes, with bent glycoluril adopting an inward orientation.

In conclusion, the development of functional macrocyclic arenes with active binding sites inside the cavity will facilitate our understanding of the biological processes of bioreceptors and enzymes and will promote the construction of advanced supramolecular assemblies for diverse applications across various fields. More bioinspired macrocycles with a biomimetic cavity feature are expected to be reported based on these three pioneering strategies and future novel ones.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in the paper.

CRediT authorship contribution statement

Xixian Sun: Writing – original draft. **Shengke Li:** Writing – review & editing. **Ruibing Wang:** Writing – review & editing. **Leyong Wang:** Writing – review & editing.

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Received 18 December 2024
Revised 22 December 2024
Accepted 26 December 2024
Available online 26 December 2024

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