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Editorial

Macrocyclic host molecules: Rising as a promising supramolecular material



The ring has been a romantic fascination throughout the ages, embodying not only beauty and order but also harboring numerous undisclosed properties awaiting discovery. In the realm of supramolecular chemistry, macrocycles, with a cyclic structure and a central cavity like a doughnut, captivate the attention of scientists [1]. In 1967, Pedersen's groundbreaking revelation that alkali metal ions could "fall into" the cavities of a cyclic ether named crown ether, even in organic solvents, unveiled a novel universe of macrocycle chemistry. Since then, numerous macrocyclic structures in nature have been discovered, isolated, and scrutinized. Drawing inspiration from nature, chemists endeavor to explore the vast potential of macrocyclic compounds by designing and synthesizing artificial macrocycles with diverse structural features and recognition properties.

Compared to non-cyclic host molecules, the cyclization process of macrocycles compensates for the energy required to pre-organize and match the size and shape of guest molecules (Fig. 1). Hence, macrocyclic molecules typically exhibit a high recognition ability for guests. Their relatively fixed skeleton, cavity shape and size enable macrocycles to exhibit selectivity towards specific guests. Furthermore, unique characteristics, the synthetic challenge, and the aesthetic appeal of symmetry are pivotal drivers motivating supramolecular chemists to create an ever-increasing array of artificial macrocycles. Over three decades of development, people are increasingly recognizing the important value of macrocyclic host molecules in solving concern problems in different fields. Therefore, the domain of macrocyclic chemistry has expanded sufficiently to intertwine with various fields, including molecular machines, smart materials, biomedicine and so on. Herein, we give some examples of pillar[*n*]arenes as a new material to solve practical problems in different fields, to visualize the potential and value of macrocyclic host molecule as a new material.

1. Anti-bacterial materials

The antibiotic crisis is intensifying as bacteria become increasingly resistant to current treatments, outpacing the creation of new antibiotics. Decreased investment in research and development means that minor injuries and common infections could become deadly in the future. This post-antibiotic era poses major health challenges, raising medical costs and increasing hospital stays and mortality from resistant infections. Developing new antibiotics is crucial. They can bolster traditional treatments, advance

modern medicine, and tackle antibiotic resistance. In macrocyclic chemistry, innovative antibacterial materials with unique properties could transform clinical practice and offer fresh approaches to combat global antimicrobial resistance [2,3].

In general, macrocyclic compounds are capable of interacting with the lipid membranes of bacteria, forming transmembrane channels. Due to their specific shape and size, positively charged framework, and precise charge localization, these macrocyclic compounds can insert into bacterial membranes, resulting in the leakage of cellular contents and ultimately cell death. For example, as shown in Fig. 2, fully guanidinium-functionalized pillar[5]arene is capable of penetrating the biofilm formed by *Escherichia coli* and forming host-guest complexes with the antibiotic cefazolin sodium, synergistically eliminating the biofilm [4].

2. Macrocycles-based drug delivery systems

Drug delivery systems represent a range of technologies that enhance drug efficacy, reduce side effects, minimize dosage, improve patient compliance, and protect drugs from degradation in the body, thereby optimizing pharmacokinetics and bioavailability. They achieve this by controlling the rate, site, and duration of drug release within the body. These systems enable timed and targeted drug release, simplify dosing protocols, and hold particular significance for the treatment of chronic and complex diseases such as cancer and diabetes. With technological advancements, modern drug delivery systems not only deliver medications but also integrate diagnostic, therapeutic, and monitoring capabilities, offering new possibilities for personalized medicine and enhancing patients' quality of life. Macrocyclic compounds play a pivotal role in drug delivery systems (Fig. 3) [5,6]. They can enhance the water solubility and bioavailability of poorly soluble drugs through solubilization, achieve targeted drug delivery through molecular recognition techniques to minimize damage to normal tissues, and be designed to be sensitive to specific stimuli such as pH changes or light exposure, enabling controlled drug release in specific environments and reducing systemic toxicity. Additionally, macrocyclic compounds protect drug molecules from adverse environmental effects, ensuring their stability until they reach the site of action. Furthermore, they can serve as components of multifunctional nano-drug delivery systems, integrating diagnostic and therapeutic functions, demonstrating broad application potential within nanotechnology. Due to their unique functionalities compared to traditional drug delivery systems, the development of drug delivery

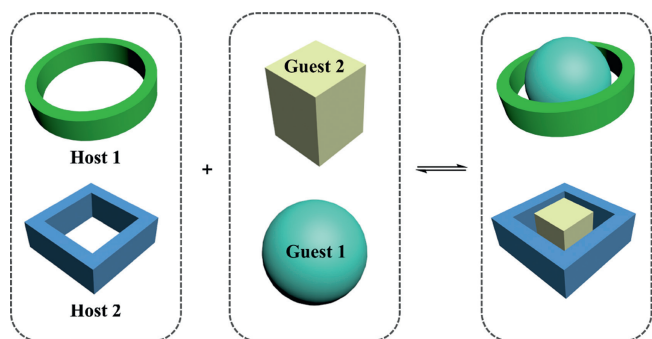


Fig. 1. The shape and size match of the guests to corresponding macrocycles.

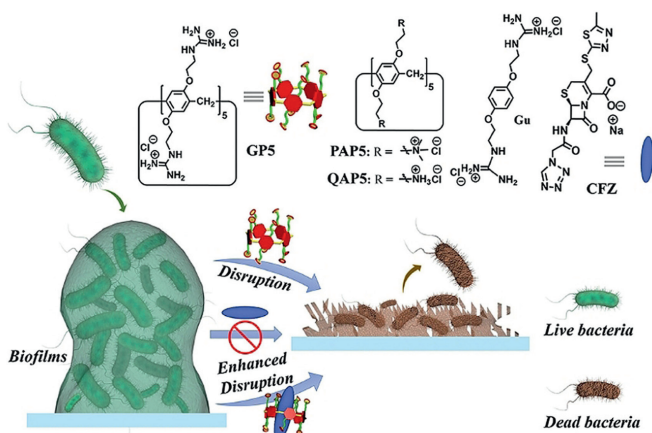


Fig. 2. Fully guanidinium-functionalized pillar[5]arene as the fungicides. Reproduced with permission [4]. Copyright 2021, Wiley Publishing Group.

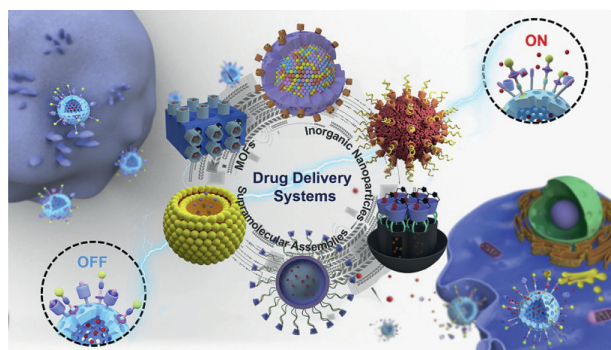


Fig. 3. The schematic diagram of drug delivery systems based on the macrocycles. Reproduced with permission [5]. Copyright 2019, Cell Press.

systems based on macrocyclic host molecules is garnering increasing attention in recent years.

3. Adsorption and separation of materials

In industrial production, the synthesis and preparation of critical chemical intermediates, such as gaseous hydrocarbon compounds and liquid aromatic hydrocarbon compounds, poses significant challenges for purification and separation due to the presence of numerous chemically and physically similar homologues, isomers, and other compounds with similar polarity. Low-purity chemical raw materials drastically reduce their application value and may lead to various hazardous accidents. To enhance the purity of these industrial intermediates, various complex techniques

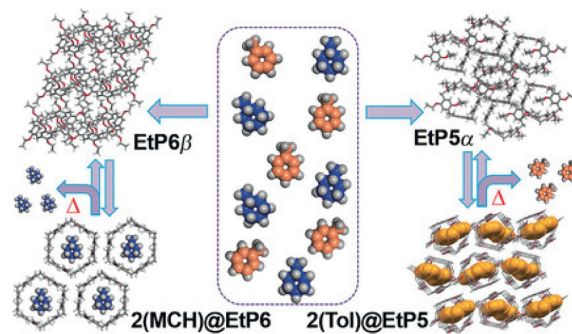


Fig. 4. The separation of toluene and methylcyclohexane through pillararenes. Reproduced with permission [8]. Copyright 2018, Wiley Publishing Group.

and devices are often employed, significantly increasing the difficulty of manual operations and substantially elevating the cost of using high-purity chemical raw materials. Macrocyclic compounds, featuring cavities of specific shapes and sizes capable of accommodating guest molecules of corresponding shapes, can form effective host-guest interactions with target molecules through their unique cavity structures. This enables them to achieve highly selective adsorption of specific components from mixtures containing numerous isomers and substances with similar physicochemical properties, thereby demonstrating significant advantages in this application area [7]. For example, the crystalline pillar[5]arene and pillar[6]arene showed fantastic ability to separate toluene and methylcyclohexane, respectively, which are two non-polar molecules with similar shape and physicochemical property (Fig. 4) [8]. Additionally, the incorporation of macrocyclic compounds offers an effective means to adjust the porosity and pore surface properties of materials. This flexibility allows the materials to cater to diverse separation needs. In addition to crystalline adsorbent materials, macrocyclic host molecules can also be used as MOF and COF, which are star materials that have just emerged in materials chemistry in recent years, materials for gas selective adsorption and separation applications.

Furthermore, macrocycles have found widespread application in other diverse areas, including the creation of full-color-tunable thermally activated delayed fluorescence materials [9] and the fabrication of porous polymers [10]. As supramolecular chemistry continues to evolve, the functional-oriented structural design and synthesis of specific macrocycles will increasingly emerge as a pivotal research approach. This shift will facilitate the discovery and exploration of novel macrocyclic host compounds possessing unique properties, thereby accelerating advancements in macrocyclic chemistry. Moreover, the functionality and synthetic feasibility are often two sides of a single macrocyclic compound, unquestionably, redundant synthesis steps often limit the synthesis efficiency of macrocyclic compounds, thus diminishing their practical value. Conversely, essential synthesis steps introduce new prospects for the structure and function of macrocyclic compounds. Balancing these two aspects necessitates the collaborative efforts of scientists dedicated to advancing macrocyclic supramolecular chemistry into practical applications. Regardless, macrocyclic host molecules are emerging as a novel class of basic materials distinguished by their unique structures and functionalities, poised to drive material diversification and intelligence.

Declaration of competing interest

On the behalf of all co-authors and myself here, I declare that we have no any known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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