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Controlled release of drug molecules by pillararene-modified nanosystems

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Stimuli-responsive nanosystems have attracted the interest of researchers due to their intelligent function of controlled release regulated by a variety of external stimuli and have been applied in biomedical fields. Pillar[*n*]arenes with the advantages of a rigid structure, electron holes and easy functionalization are considered as excellent candidates for the construction of host–guest nanosystems. In recent years, many pillararene modified nanosystems have been reported in response to different stimuli. In this feature article, we summarize the advance of stimuli-responsive pillararene modified nanosystems for controlled release of drugs from the perspectives of decomposition release and gated release, focusing on the control principles of these nanosystems. We expect that this review can enlighten and guide investigators in the field of stimuli-responsive controlled release.

1. Introduction

Stimuli-responsive nanosystems constitute an increasingly popular interdisciplinary research field because of their potential to perform intelligent functions through appropriate stimuli,[1–3] such as light,[4] temperature,[5] magnetic field,[6,7] redox,[8] and pH.[9] One kind of stimuli-responsive nanosystem is fabricated on the basis of host–guest systems.[10] The intermolecular interaction and spatial structure of these host–guest systems change dynamically and reversibly according to specific stimulus. Various stimuli-responsive host–guest systems have been applied in different fields, such as fluorescent sensors,[11] drug delivery systems,[12] and smart functional materials.[13,14]

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Controlled release of drugs is one of the most significant applications of stimuli-responsive nanosystems, which contributes to targeted therapy.[15,16] Drugs are loaded into a nanosystem formed by the self-assembled host–guest system. Under specific stimuli (light, temperature, pH, glutathione, ions, *etc.*), the chemical structure or property of host or guest molecules changes and results in the disassembly of the host–guest system, and thus drugs are released from the nanosystem.[17,18] Therefore, the essence of controlled release is to regulate the assembly and disassembly of host–guest nanosystems (Scheme 1).

Macrocyclic compounds, including cyclodextrin,[19] calixarene,[20] cucurbituril,[21] and most recently pillar[*n*]arenes, are considered as excellent hosts to construct host–guest nanosystems.[22–24] Due to their various properties and ability to self-assemble into supramolecular structures through non-covalent interactions,[25] these host–guest nanosystems play a vital role in the fields of controlled release,[26] nanotechnology,[27,28] materials chemistry,[29] artificial molecular machines and artificial ion channels.[30,31] Pillar[*n*]arenes are a type of macrocyclic host which were synthesized for the first time in 2008.[32] Pillar[*n*]arenes are composed of hydroquinone or hydroquinone ether units, connected by a methylene bridge at the *para* position of the benzene ring.[33] Pillar[*n*]arenes have received great attention in the field of supramolecular chemistry and have broad application prospects due to the advantages including a rigid and symmetrical columnar structure, electron-rich holes and good biocompatibility as well as highly adjustable host–guest properties. The above characteristics of pillar[*n*]arenes are conducive to their application in artificial transmembrane channels,[34] controlled release systems,[33] gas adsorption,[35] sensing and detection,[36]

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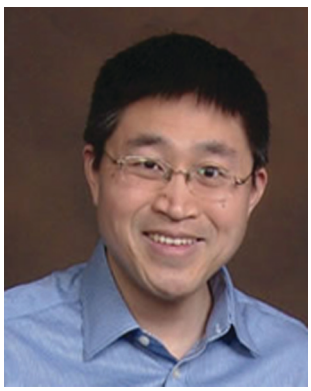

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stabilization of nanoparticles,[37] and other typical biological applications.[38]

As reported by researchers in recent years, pillar[*n*]arene-based host–guest nanosystems that respond to specific external stimuli such as pH, enzymes, gas, light, *etc.*[39–42] have been constructed. In this review, the advance of stimuli-responsive controlled release of drug molecules by pillar[*n*]arene modified nanosystems is summarized, including the types of photo-responsive, temperature-responsive, and pH-responsive controlled release (Scheme 2). In addition, we divide controlled release into two categories: (1) decomposition release, where host–guest nanosystems respond to a specific external stimulus, leading to guest molecules being released from the host macrocyclic molecules; generally the morphology and structure of nanosystems change greatly, with some decomposing into small molecules and some undergoing extensive structural changes. (2) Gated release, where the pillar[*n*]arenes are covalently fixed or self-assembled on the surface of nanocarriers to act as a gate for selective controlled release in response to stimuli. Unlike decomposition release, gate release is largely reversible. Finally, we look forward to the research prospects of pillar[*n*]arene-based controlled release systems. We hope that this review not only helps researchers in the relevant fields but also opens researchers' ideas and achieves new progress in extensive research areas.

2. Photo-responsive controlled release

2.1 Photo-responsive decomposition release

Light is an ideal external stimulus for *in situ* chemical operation,[43] because it is clean, remote and non-invasive.[44]

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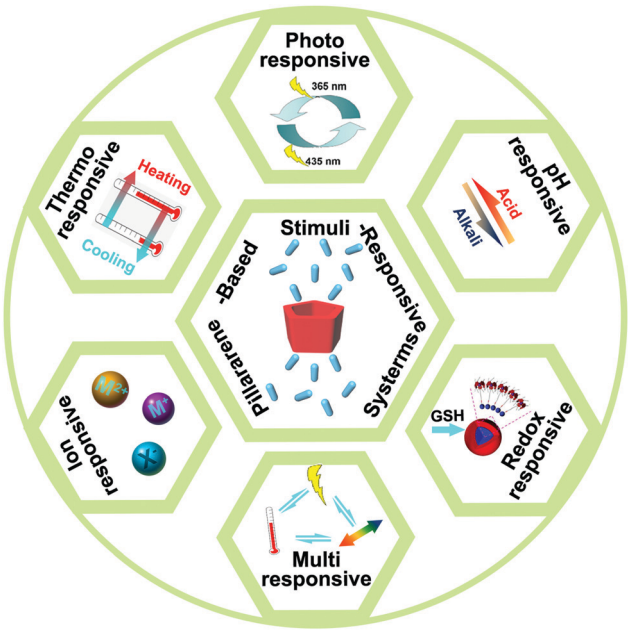
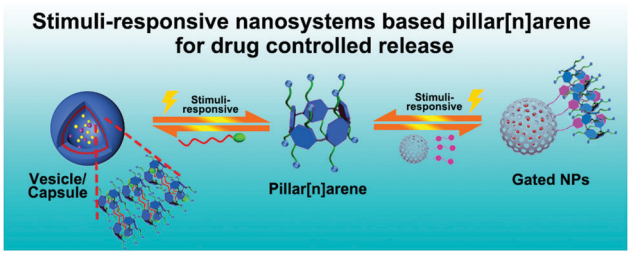
Haibing Li received PhD from the Department of Chemistry and Molecular Science at Wuhan University. After one year post-doctoral fellowship at CNRS, France, in 2003, he returned back to China to work at Huazhong University of Science and Technology. In 2006, he moved to Central China Normal University in Wuhan as a professor. In 2015, he visited the University of Utah for half a year. His research interest focuses on supramolecular chemistry on surfaces. To date, his research records 130 scientific publications and 10 domestic and international patents.



Scheme 1 Illustration of pillar[*n*]arene-based different stimuli-responsive drug delivery systems.



Scheme 2 The construction of stimuli-responsive nanosystems: decomposition release (left) and gated release (right).

Therefore, the researchers have intensively used light as an external stimulus to achieve controlled release. In photo-responsive nanosystems, the host–guest assembled vesicles decompose and release drugs as the host–guest system disassembles under light stimuli. This section focuses on the study of photoreactive decomposition systems based on pillararenes. The photo-responsive system is mainly designed by integrating the luminescent response structure into the guest or pillar[*n*]arene. The structural components of photoreactive decomposition systems are mainly comprised of azobenzene and anthracene.[45,46]

In 2011, Stoddart *et al.* synthesized a mono-modified pillar[5]arene (MAP5) and the azobenzene unit imparted light responsiveness.[47] This is the first reported example of photo-responsive decomposition release. As the photo-responsive self-assembly nanosystems have been found to have the advantages of simple operation, high sensitivity and good controllability, most of the subsequent research focused on the biomedical field. For example, Yang and co-workers established photo-responsive host–guest recognition motifs based on water-soluble pillar[6]arene and azobenzene derivatives in water. The intelligent inclusion complex was further applied to construct supra-amphiphile vesicles, which could be self-assembled reversibly. Drugs can be loaded or released "on demand" under UV or vis irradiation.[48] With the in-depth study of azobenzene as a photosensitive structure, Huang's group constructed another pillar[*n*]arene-based decomposition release system by using WP6 and azobenzene guest molecules through the host–guest interaction.[49] In recent years, stilbene has attracted the attention of researchers due to its rigid structure and stability. Xia *et al.* reported a bola-type amphiphile constructed from a water-soluble pillar[6]arene (P1) host and a naphthyl modified azobenzene (*trans* G1) guest.[50] The amphiphile and the *trans* G1 self-assembled as nanosheets when stimulated by UV light at different wavelengths, respectively. Reversible transformations can be achieved between supramolecular vesicles and nanosheets (Fig. 1a). In addition, when the vesicles were loaded with the anticancer drug (doxorubicin) DOX, they decomposed into nanosheets in response to UV stimulation at 365 nm, thus achieving controlled release of the drug (Fig. 1b). 80% of DOX was released within 40 min. This vesicle structure has a good

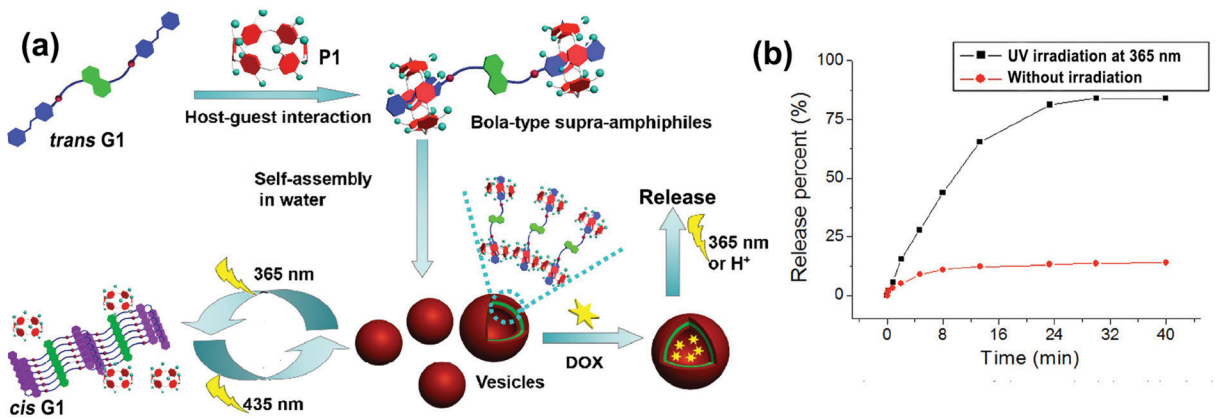


Fig. 1 (a) Cartoon representation of the photo-responsive self-assembly between P1 and G1 in water. (b) Release percentage of the DOX-loaded vesicles upon irradiation with UV light at 365 nm from 0 to 40 min by UV-vis absorption spectroscopy. Reproduced from ref. 50 with permission from the Royal Society of Chemistry.

response to the change of UV light, which is conducive to its application in drug delivery as a photo-responsive decomposition release system.

Recently, Tong *et al.* reported the photo-responsive polymer vesicles P1@*trans G2* used for the controlled release of the drug DOX·HCl, which were self-assembled from water-soluble pillar[6]arene (P1) and azo-benzene ended functionalized poly(ε-caprolactone) (*trans G2*) through host–guest interactions. Reversible transformation of vesicles and aggregates can be achieved under light stimulation (Fig. 2a).[51] In this work, in order to explore the response to light stimulus, the morphological changes of vesicle molecules were observed in the absence of light stimulus and upon UV light and visible light irradiation for 30 min respectively (Fig. 2b). In addition, the drug release behavior of the DOX·HCl loaded vesicles was investigated under 365 nm UV light (Fig. 2c). In the absence of stimulation, the release of DOX·HCl was stable and less than 20% in 30 min. UV exposure for the same amount of time resulted in 60% of the drug release. These pillararene-based drug delivery systems had good biocompatibility and low toxicity.

We found that most of the studies on photo-responsive systems are based on pillar[5,6]arene host molecules, and there are less studies on other pillar[*n*]arene molecules. In addition, the photosensitive guest molecule is azobenzene, which is widely used. Due to the difference of the *cis*/*trans* structure of azobenzene, the structure of nanosystems changes, so as to achieve controlled release of loaded drugs. However, there are a lot of photosensitive guest molecules, which are seldom used by researchers. Hence, the future research should focus on host–guest interaction nanosystems based on more complex host molecules of pillararenes and other photosensitive guest molecules, which will be conducive to the development of more pillararene modified drug delivery systems.

2.2 Photo-responsive gated release

Light controls the mass transport in mesoporous systems, which are functionalized photo-responsive host–guest systems.[52] The host works as a valve to switch the states of load (assembly) or release (disassembly), which is called gated release. Compared with the decomposition release based on host–guest assembled vesicles, the gated release based on host–guest functionalized solid porous nanoparticles has the advantages of reversibility and recyclability. The external light sources usually used are ultraviolet light and visible light. This part will focus on the alignment release example based on pillararenes and explain its application prospects.

Ma's group constructed a fluorescent optical switch based on pseudo[3]rotaxane between the AIE-active pillar[5]arene host and the bithienylethene guest, which can be applied in the field of reversible information and state storage media, soft rewritable systems, and optical control molecules.[53] In 2017, Huang *et al.* synthesized a near-infrared NIR-responsive nano-valve by embedding monodisperse silica nanospheres embedded in gold nanorods at the sealing end of phosphonated pillar[5]arene (P2).[54] After loading the anticancer drug DOX, the host–guest interaction was weakened under NIR irradiation, thus achieving controlled release of the cargos (Fig. 3a). Fig. 3b shows that the nanocarriers depend on the photothermal effect of laser power density. The NIR responsiveness of the supramolecular nano-valve was verified. The nano-valve possesses low toxicity and a good anti-tumor effect. This research provides another idea for cancer treatment, which has potential biomedical applications. In previous studies, most of the controlled release systems were constructed from water-soluble carboxylated pillar[*n*]arenes. The above photo-responsive gated release nanosystem was the first to be constructed from phosphonated pillar[5]arene. This work explored the diversity of pillararene-based molecular machines and provided a new idea for the construction of pillararene-based controlled drug release systems. It greatly promoted the work of later researchers.

3. pH-Responsive controlled release

3.1 Acid–base regulated decomposition release

The change in acidity is a typical stimulation regulating the supramolecular structure of host–guest nanosystems. Thus, drug release can be controlled by the pH difference between

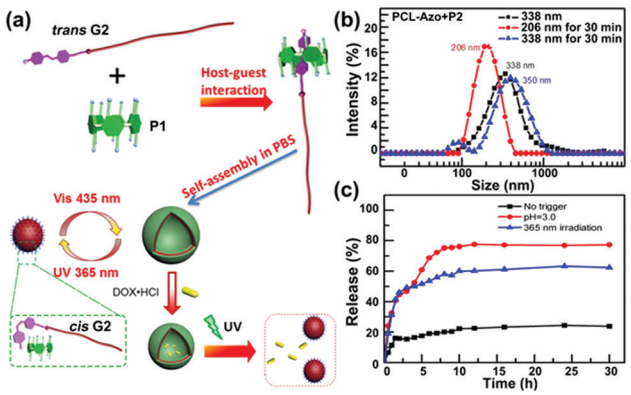


Fig. 2 (a) Chemical structures of *trans* G2 and P1 and the illustration of formation of the polymeric vesicle, reversible morphological transitions and the process of photo-responsive release of DOX·HCl. (b) DLS results of *trans* G2 + P1 after UV irradiation for 30 min and further vis irradiation for 30 min. (c) Photo-responsive release behavior of DOX·HCl-loaded vesicles with or without external stimulus. Copyright 2017, Wiley-VCH Verlag GmbH & Co. KGaA.

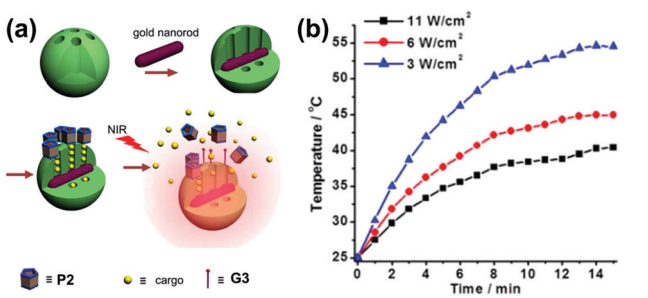


Fig. 3 (a) Illustration of P2-valved MSN and GNR@MSN drug delivery systems for NIR-responsive controlled release. (b) Photothermal effects of GNR@MSNs (0.3 mg mL^{-1}) upon irradiation of 808 nm NIR light at different power densities for 15 min. Copyright 2017, American Chemical Society.

normal and pathophysiological cells.[55] Therefore, the construction of pillar[*n*]arene-based pH-responsive systems has been generalized, in which typical water-soluble carboxylated pillar[*n*]arenes (*n* = 5, 6, 7, 9, 10) are typically used as host molecules or building blocks.[56] Various functional groups, such as phosphoric acid and rhodamine B10, are grafted on pillar[*n*]arenes to construct pH-responsive hosts. This part will review the examples of pH-responsive decomposition and release.

Wang *et al.* reported that water-soluble pillar[6]arene (WP6) and hydrophobic ferrocene derivatives were self-assembled into supramolecular vesicles and loaded with mitoxantrone (MTZ). The rapid release of MTZ was achieved under acidic pH.[57] This strategy laid the foundation for a pH-responsive controlled release system based on pillar[*n*]arene, which attracted more people to study in this field. Furthermore, Yao and co-workers doped water-soluble pillar[5]arene (P1) into hollow mesoporous silica nanoparticles (HMNPs) and loaded DOX through host–guest complexation, thus designing and synthesizing a novel nano-carrier (DOX-loaded P1@HMNPs) for the treatment of cancer (Fig. 4).[58] The load efficiency of DOX in HMNPs increased with increasing pH and DOX concentration. The maximum load efficiency of DOX reached 1000 mg g^{-1} at pH 7.4, while the release reached maximum at the lowest pH. The advantage of P1@HMNPs is that they are easier to break down under acidic conditions, and the nanofragments have good biocompatibility with the body, suggesting their good application prospect in the biomedical field.

Hu *et al.* successfully constructed a pH-responsive hollow supramolecular vesicles based on water-soluble phosphate pillar[6]arene (P2) and pyridinium bromide guest (G6).[59] The vesicle loaded with the hydrophilic anti-cancer drug MTZ (load efficiency is 76%) can effectively release MTZ at a lower pH (Fig. 5a). The drug release behavior of the drug-loaded supramolecular nanocarrier was further studied at two pH values respectively. The cumulative MTZ release was about 70% at pH 5.0 within 12 h, but almost no MTZ was released at physiological pH (Fig. 5d). Most importantly, the cytotoxicity tests showed that the phosphate-based water-soluble pillar[6]arene had good biocompatibility and the cytotoxicity of the drug-loaded vesicles was low. Therefore, the construction strategy of pH-responsive supramolecular nanocarriers opens a new path in the field of controlled drug delivery.

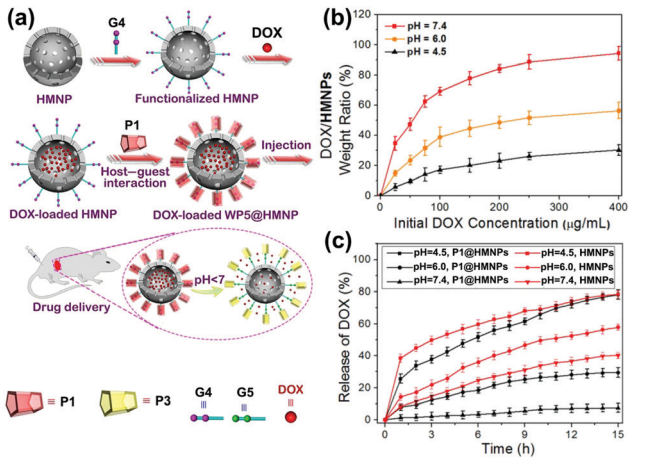


Fig. 4 (a) Functionalized hollow mesoporous silica nanoparticles (HMNPs) with amines and anionic pillar[5]arene P1 for controlled delivery of DOX. (b) Functionalized HMNPs were mixed with DOX of different concentrations (0 to 400 μg mL^{-1}) at various pH values ranging from 4.5 to 7.4. (c) DOX-release profiles for DOX-loaded HMNPs and DOX-loaded P1@HMNPs measured at different pH values. Reproduced from ref. 58 with permission from the Royal Society of Chemistry.

In 2018, Yang and co-workers reported a new pH-sensitive supramolecular hybrid material ZIF-8@DOX@P1@G7 for targeted administration.[60] In this study, DOX loaded ZIF-8 was first prepared, followed by host–guest complexation between carboxylated pillar[6]arene (P1) and a galactose derivative (G7) to form P1@G7, and finally, supramolecular nanomaterials were synthesized by an environmentally friendly one-pot method (Fig. 5b). In order to study the pH-responsive release behavior of ZIF-8@DOX@P1@G7, the *in vitro* DOX release was performed in phosphate buffer solution (PBS) under three pH conditions, respectively. As shown in Fig. 5e, ZIF-8@DOX@P1@G7 exhibits significant sustained release behavior of DOX in acidic PBS compared with neutral pH, since ZIF-8 is dissolved in an acidic environment. Noticeably, the lower the pH, the higher the release efficiency. Finally, flow cytometry demonstrated that the material has good targeting ability. This study provides a new approach for the application of pillar[*n*]arenes in the biomedical field.

Subsequently, Wang and co-workers reported a new pH-responsive drug delivery system based on phosphoryl-functionalized pillar[5]arene (P4) modified with b-$NaYF_4$:Yb/Er upconversion nanoparticles (UCNPs) for controlled cargo release and cell imaging (Fig. 5c).[61] Rhodamine B (RhB) was loaded to simulate different pH conditions in the gastrointestinal tract to study the release process of the RhB cargo. At pH = 7.4, RhB delivered 72% of the drug within 90 min, while at pH = 5.0 and 1.9, it delivered less than 17% and 2% of the drug within the same time (Fig. 5f). The results showed that the release of RhB increased with the increase in the pH value. Finally, the biocompatibility of the nanosystem was demonstrated by the MTT method. Notably, the nanosystem allows imaging of cells.

For most pH-responsive pillararene-based nanosystems reported in this part, water-soluble carboxylated pillar[5,6]arenes and phosphonated pillar[5,6]arenes are the host molecules. The special acidic environment of tumor cells is used as exogenous or endogenous stimulation to decompose nanosystems, thus achieving controlled release of loaded drugs. They are all biocompatible, water-dispersible and low-toxicity small molecules that are friendly to organisms. However, few nanosystems achieve clinical application. Therefore, future research should focus on exploring new avenues for drug delivery systems and cell imaging.

3.2 Acid–base regulated gated release

With pH being the most commonly used stimulus for development of gating materials, pH-driven gates are a very promising tool for developing a biomedical controlled release system. In

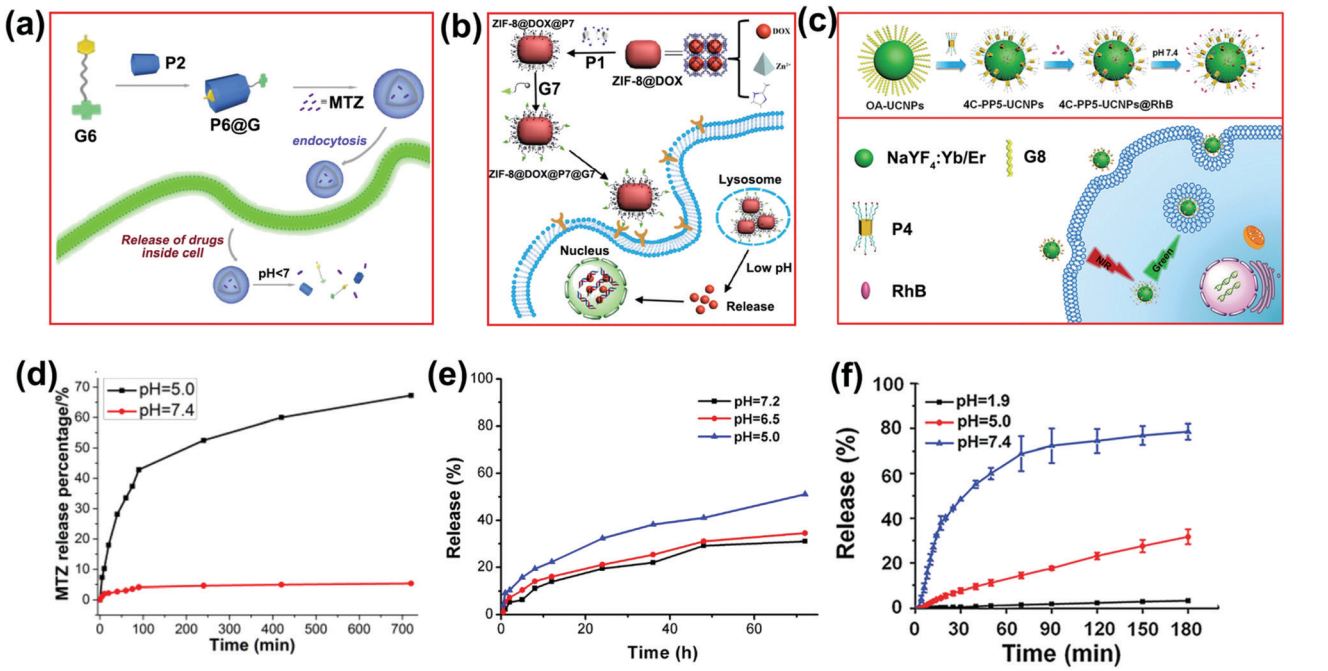


Fig. 5 (a) Schematic illustration of the controllable construction of supramolecular vesicles (P2@G6) in selective drug delivery. (b) Schematic of the construction of ZIF-8@DOX based on host–guest complexation. (c) Schematic representation of the construction of the nanosystem and its application for targeted drug delivery and UCL cell imaging. (d) pH-responsive MTZ release profiles of the MTZ-loaded vesicles at different pH values. (e) DOX release profiles from ZIF-8@DOX@P1@G7 in PBS at different pH values. (f) Release profiles of RhB in PBS. (a and d) Copyright 2016, American Chemical Society, (b and e) reproduced from ref. 60 with permission from the Royal Society of Chemistry, (c and f) reproduced from ref. 61 with permission from the Royal Society of Chemistry.

the reported examples, the system on/off switching typically depends on the size/shape change caused by proton addition or extraction, or changes in the attraction/repellency of other charged species. At the cell level, the drug can be selectively released due to a particular acid pH environment. For tumor cells, it can be used to target delivery payloads. The pH triggering system has the advantage of being completely independent, without any additional devices, and in most cases, the close and open mechanisms are reversible. Therefore, pillar[*n*]arene-based pH-responsive gated systems can be used for drug delivery multiple times, which is conducive to cost savings.

Ronconi *et al.* designed and successfully assembled non-functionalized (MCM-41) and carboxylic acid functionalized (MCM-41-COOH) containers, and loaded DOX in the two containers, and finally used water soluble pillar[5]arene (P5) nanogate sealing.[62] Two new types of pH-responsive nano-carriers DOX-P5@MCM-41 (Fig. 6b) and DOX-P5@MCM-41-COOH (Fig. 6a) were constructed based on the electrostatic interaction between the host and the guest. At acidic pH, MCM-41 was protonated and DOX-P5@MCM-41 released P5 and DOX (Fig. 6d). The reversibility of the nanogate was studied by continuously adding HCl and NaOH to adjust the pH between 2.0 and 5.5 (Fig. 6c). The results showed that the nanogate was reversible and could be reused at least 8 times. These nano-carriers could release drugs in the nucleus and have good cell viability. Therefore, this system is expected to be another candidate for use as a cancer treatment system.

Wang and co-workers reported MSN-OH NPs functionalized with the nanogate of carboxylatopillar[5]arene (P6) and quaternary ammonium salt (G11).[63] This supramolecular nano-platform (P6@MSN-G11) was loaded with fungicide berberine hydrochloride (BH) (Fig. 7a). The controlled release of BH by the nano-platform was tested at different pH values (Fig. 7b). The cumulative release of BH under acidic conditions was higher compared to that under neutral pH. This nanoplatform can effectively control *Staphylococcus cinerea*.

Compared with pH-responsive decomposition release nanosystems, pH-responsive gated nanosystems are usually constructed by attaching guests on mesoporous silica nanoparticles and assembling with pillararene hosts. These pillararene hosts reversibly open and close the entrance of mesoporous silica nanoparticles based on the external stimuli, allowing the release and loading of the drug. Therefore, the future research should focus on the design of efficient pillar[*n*]arene hosts, and explore the host–guest nanogates in detail to greatly promote the development of this aspect.

4. Thermo-responsive controlled release

4.1 Thermo-responsive decomposition release

Thermal stimulation technology has the advantages of fast, cheap, clean and easy access. In addition, temperature variations or different temperatures are specific to certain diseases,

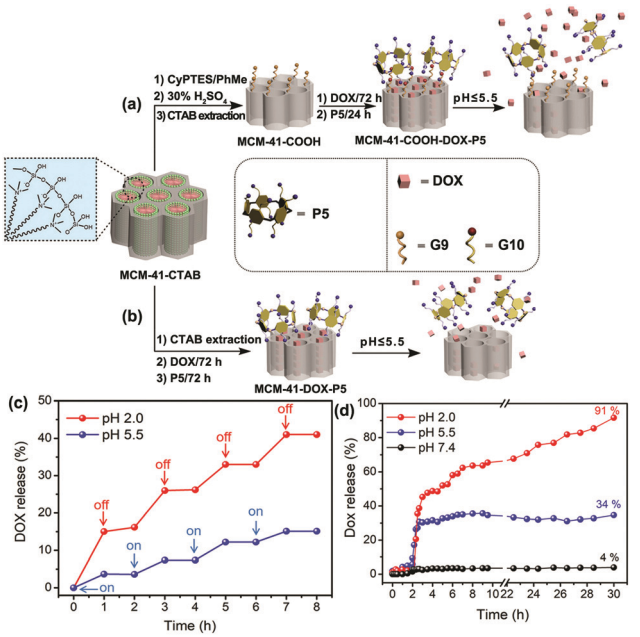


Fig. 6 Schematic representation of the assembly of (a) DOX-P5@MCM-41-COOH *via* interactions between COO^- groups and cationic P5 and (b) DOX-P5@MCM-41 by interactions of $-OSO_3^-$ and cationic P5. (c) DOX release profiles as a function of time from MCM-41-COO-DOX-P5 after consecutive additions of acid and base to a suspension of the nanocarrier in PBS at 37 °C. (d) DOX release profiles of DOX-P5@MCM-41. Reproduced from ref. 62 with permission from the Royal Society of Chemistry.

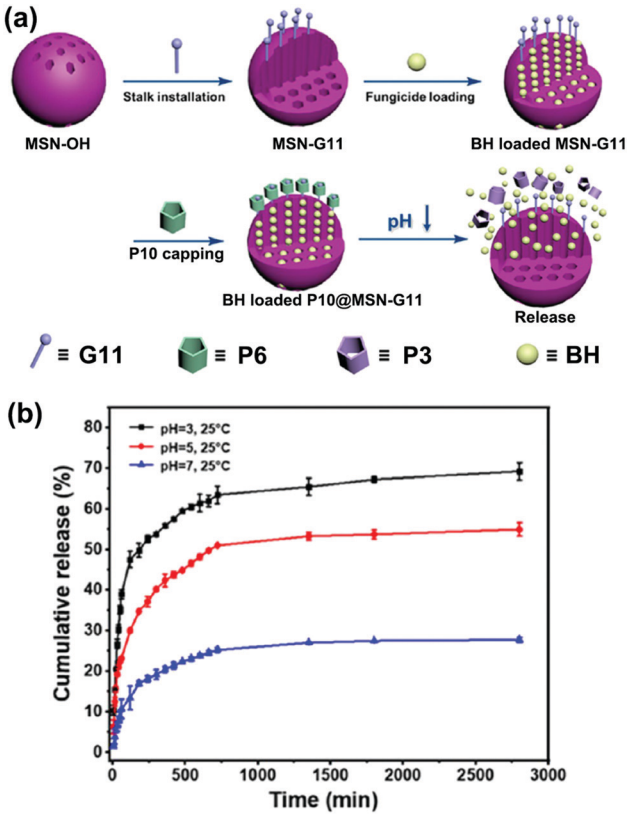


Fig. 7 (a) Schematic diagram of the fabrication of the fungicide nanoplatform. (b) Cumulative release profiles of BH from BH-loaded P6@MSNs-G11 NPs in PBS at different pH values. Copyright 2021, American Chemical Society.

such as cancer. This part introduces several decomposition release systems that utilize temperature dependent responses from host–guest systems. Most of these systems use thermal polymers, which can transport the cargo after the temperature dependent phase transition. Thermo-responsive decomposition release has a wide range of specific applications in controlled drug delivery, intelligent surfaces, biomaterials, and mass separation.

Based on the host–guest system of pillar[6]arene (P7)-terminal-modified poly(*N*-isopropyl-acrylamide) (PNIPAM-P7) and ferrocene-terminal-modified methoxy-poly(ethylene glycol) (G12), Wang *et al.* reported a novel thermo-responsive supramolecular polymer vesicle (PNIPAM-P7@G12) (Fig. 8a).[64] When the aqueous solution of host and guest was heated from room temperature to 37 °C, the host and guest self-assembled into vesicles, while the vesicles decomposed into amphiphilic fragments at 25 °C. The supramolecular vesicles have good reversible thermal response. Subsequently, the release behavior of the vesicles for the anticancer drug DOX·HCl was studied under different temperatures (Fig. 8b). At 25 °C, DOX·HCl was released rapidly within the first 3 h and reached 90% after 12 h. In contrast, the structure of vesicles remained stable at 37 °C, and only 18% of DOX·HCl was released over 12 h. It is further demonstrated that the polymer vesicles are thermo-responsive and have potential applications in intelligent drug delivery systems.

Furthermore, Chi and co-workers reported a new amphiphilic supramolecular diblock copolymer micelle, composed of water-soluble pillar[10]arenes (P8) and paraquat-containing poly(*N*-isopropylacryl-amide) (PNIPAM) (G13) (Fig. 9a).[65] The loading and release of DOX in this polymer micelle was monitored by DLS. The results showed that the micelle loaded DOX with a mean diameter of 70 nm at 37 °C, while it released DOX at 25 °C, the diameter of which sharply increased to 3580 nm (Fig. 9b). At normal human temperature, less than 20% of DOX was released within 24 h. When the system was heated up to 60 °C, DOX release reached 30% within a day. Both thermo-responsive decomposition release nanosystems reported above form vesicles in water. The difference is that the thermo-sensitive polymer poly(*N*-isopropylacrylamide) (PNIPAM) was respectively grafted on host (P7) and guest (G13). These examples provide significant guidance for later researchers to construct thermo-responsive decomposition release nanosystems.

4.2 Thermo-responsive gated release

Various sealing materials constructed from thermo-sensitive pillararene-based nanogates can control drug release based on the temperature dependent phase change. Wang *et al.* developed a pillar[5]arene (P5A)-gated nanochannel, where P5A reversibly assembled with the ionic liquid (IL) guest according to the thermal stimuli.[66] Li *et al.* reported the host–guest system of anthracene pillar[5]arene (MAP5) and imidazolyl ionic liquid (IL).[67] The thermo-responsive host–guest

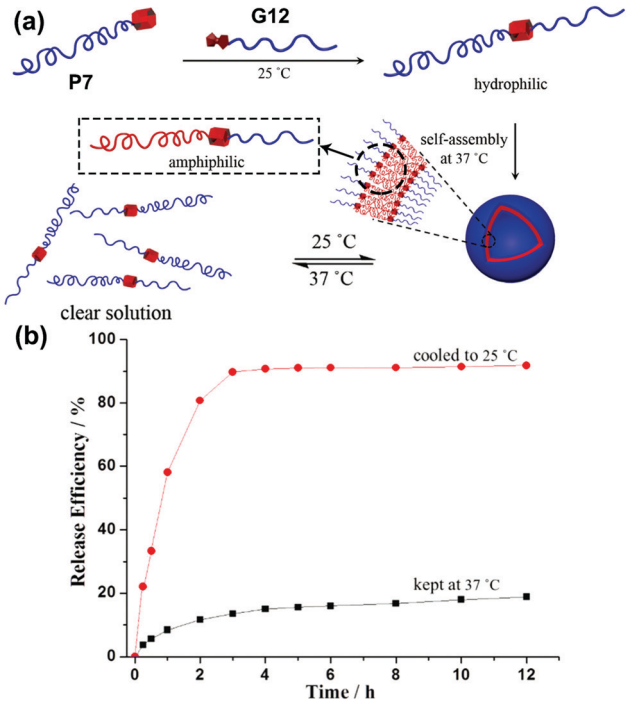


Fig. 8 (a) Illustration of the assembly and disassembly of thermo-responsive supramolecular polymeric vesicles from PNIPAM-P7@G12. (b) The *in vitro* cumulative release profiles of thermo-responsive DOX·HCl-loaded vesicles in aqueous solution under different temperatures. Reproduced from ref. 64 with permission from the Royal Society of Chemistry.

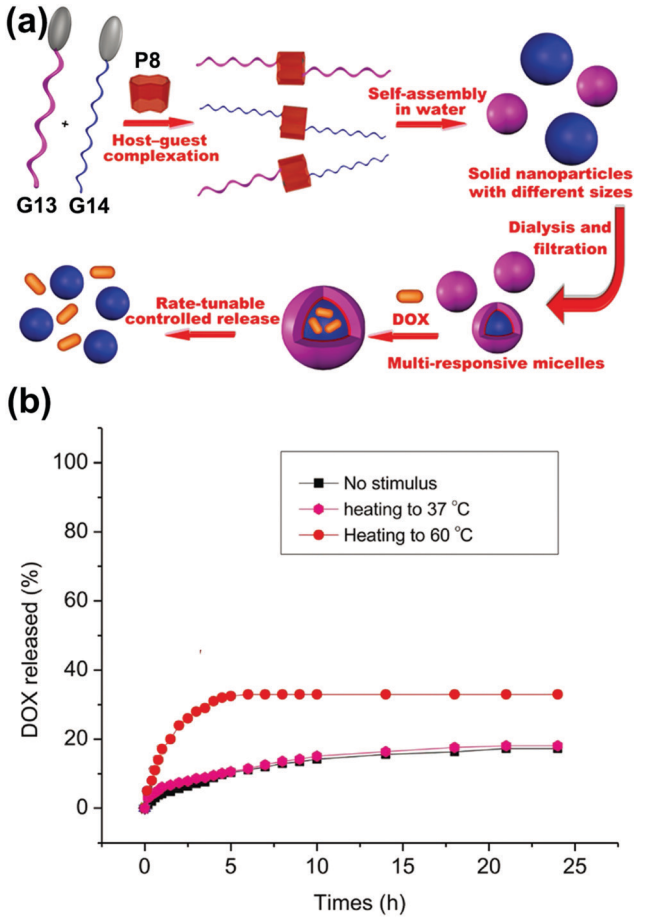


Fig. 9 (a) Schematic illustration of preparation of a temperature-responsive amphiphilic supramolecular diblock copolymer in water based on pillar[10]-arene/paraquat complexation for rate-tunable controlled release. (b) Controlled release of DOX from polymeric micelles upon exposure to different temperatures. Copyright 2017, Wiley-VCH Verlag GmbH & Co. KGaA.

nanosystems can can be applied in memory storage, drug delivery systems, and sensors.

Furthermore, nanosystems based on mesoporous silica (MSNs) have been reported. Wang *et al.* synthesized a new thermo-responsive drug delivery system based on carboxylatopillar[5]arene (P6) modified rhodamine (RhB)-loaded quaternary ammonium salt functionalized mesoporous silica nanoparticles (MSN-G11) (Fig. 10a).[68] The controlled release behavior of the nanosystem for RhB was studied at four different temperatures (Fig. 10b). As the temperature rises, the amount of drug released increases at the same time. However, drug loading can be achieved when the temperature drops up to room temperature or normal body temperature. These results indicate that the drug-loaded nanosystem can be reused many times, which makes it a promising candidate for drug delivery systems. Currently, few thermo-responsive gated release nanosystems have been reported. Improving the sensitivity of thermo-response should be the research focal point in the future.

5. Chemical-responsive controlled release

5.1 Redox-responsive controlled release

The redox reaction easily improves the lipid bilayer activity, changing the membrane potential.[69] The study on redox-responsive pillararene-based nanosystems is of interest for researchers in the field of controlled release. A large number of examples have been described in this field, which can be summarized as two categories: one class based on redox driven supramolecular interactions and the other based on disulfide bond fracture.[70]

Chi *et al.* reported a redox-responsive vesicular system constructed by the self-assembly of water-soluble pillar[5]arene (P9) and a paraquat-containing homopolymer (G14) (Fig. 11). The paraquat-containing homopolymer and P9 self-assembled into a vesicle and loaded DOX·HCl. This vesicle slowly released cargo (less than 30%) without trigger. As the amount of the reducing agent ($Na_2S_2O_4$) added increased, the nanocarrier released more drugs at the same time. This indicates that the redox-responsive nanocarrier system is a good candidate for drug delivery.

In 2018, Wu *et al.* reported a glutathione (GSH)-responsive pillar[5]arene-based supramolecular vesicle, where the specific feature was that the amphiphilic guest (G15) contained the structure of chemotherapeutic prodrug camptothecin (CPT) (Fig. 12a).[71] Thus, the drugs internalized vesicle, not be loaded in vesicle. The vesicle decomposed in the presence of GSH, while CPT was released. 50% and 95% of CPT was released at 1.0 and 10.0 mM GSH, respectively. In contrast, only 8% of CPT

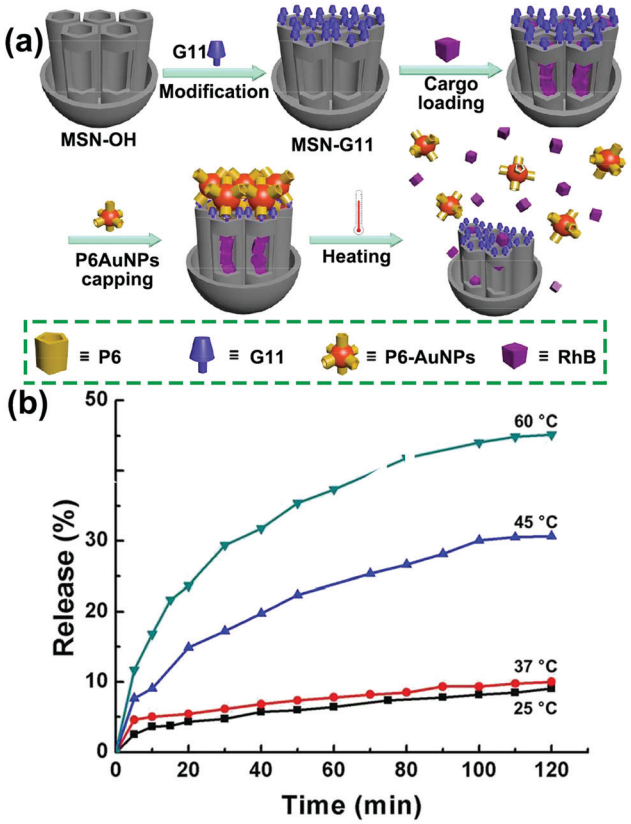


Fig. 10 (a) Schematic illustration of the rhodamine (RhB)-loaded, AuNP-capped MSN nanosystem, and its controlled release mechanism in response to temperature variations. (b) Controlled release profile of the RhB-loaded, AuNP-capped MSN-G11 hybrid system triggered by temperature changes (25, 37, 45 and 60 °C). Reproduced from ref. 68 with permission from the Royal Society of Chemistry.

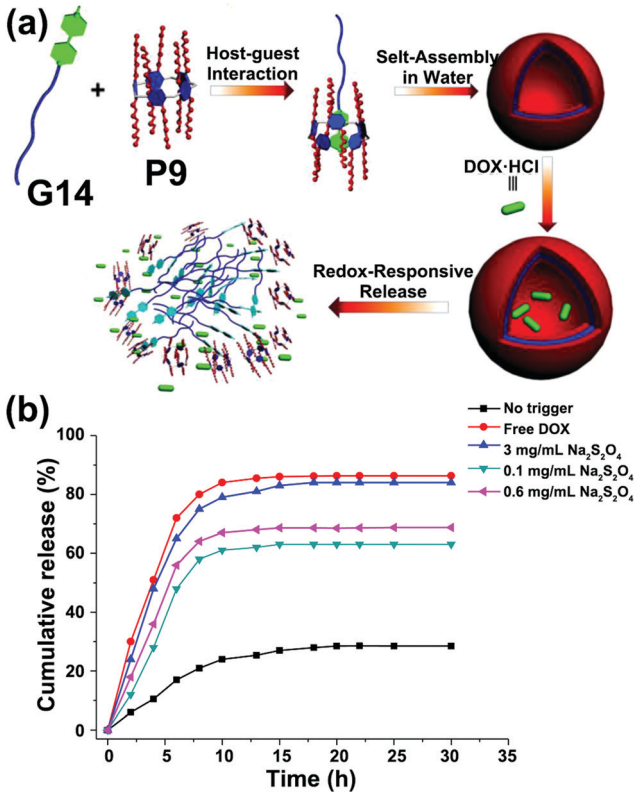


Fig. 11 (a) Cartoon representation of the preparation of polymeric vesicles and the process of redox-controlled release. (b) Drug release profiles of DOX-loaded assemblies with or without different concentrations of the reducing agent. Copyright 2015, American Chemical Society.

was released within 24 h in the absence of GSH, indicating the good stability and sensitivity of this supramolecular nanoparticle under physiological conditions. MTT assay proved its good anticancer effect on different types of cancer cells. This new strategy will be a new road to the application of amphiphile-based molecular machinery in cancer treatment.

Subsequently, Sun and co-workers constructed a redox-responsive supramolecular prodrug vesicle P1@G16 based on the host–guest complexation between water-soluble pillar[5]-arene (P1) and G16.[72] At high GSH concentrations, G16 effectively releases the drug 7-ethyl-10-hydroxy-camptothecin (SN-38) for cancer diagnosis and treatment (Fig. 12b). With the increase of GSH concentration from low to high, the cumulative release of SN-38 within 7 h increased from 30% to 90%, indicating that the nanovesicle system was particularly sensitive to GSH. Cytotoxicity tests demonstrated that the vesicles were effective in killing cancer cells and had minor side effects on normal cells. This work provides a new idea for the construction of redox-responsive nanocarrier drug delivery systems, which is expected to realize the diagnosis and treatment of tumors in medicine. In future research, more redox agents and the amphiphilic guests that can contain various prodrugs should be developed for controlled release nanosystems.

5.2 Ion-responsive controlled release

In the human body, ions play an important role in various physiological processes, such as gene expression, immunoreaction and protein transport. The supramolecular structure of pillararene-based nano-carriers can be regulated by the complexation of ions with the functional groups on pillararene. Various ions, such as metal cations (Zn^{2+}, Cu^{2+}, Hg^{2+}, K^{+}, Na^{+}, Ag^{+}) or halogen negative ions (F^{-}, Cl^{-}, I^{-}),[73,74] are used as the trigger to release cargo from the nano-carriers. This provides the possibility of designing precise systems for special biomedical applications. In this part, we will list the examples and explain their applications.

Li *et al.* reported the tunable mass transport by the stimulus of mercury ions, as a mercaptoacetic acid-pillar[5]arene (MAP5) functionalized nanochannel.[75] This study paved new paths to better understand the physiological phenomena of mercury toxicity, and showed huge prospects in biomedical research. In 2015, Tan *et al.* firstly constructed a Zn^{2+}-triggered targeted drug release system, based on the nanoporous zirconium metal–organic framework (UiO-66-NH_2). The release of 5-fluorouracil (Fu) was controlled by the Zn^{2+}-responsive gating of carboxylatopillar[5]arene (P6) and quaternary ammonium salt (G11) (Fig. 13).[76] When the concentration of Zn^{2+} was the normal intracellular concentration, only 5% of Fu was released in 80 min. With the increase of Zn^{2+} concentration, the amount of drug release increased significantly, suggesting that different stages of

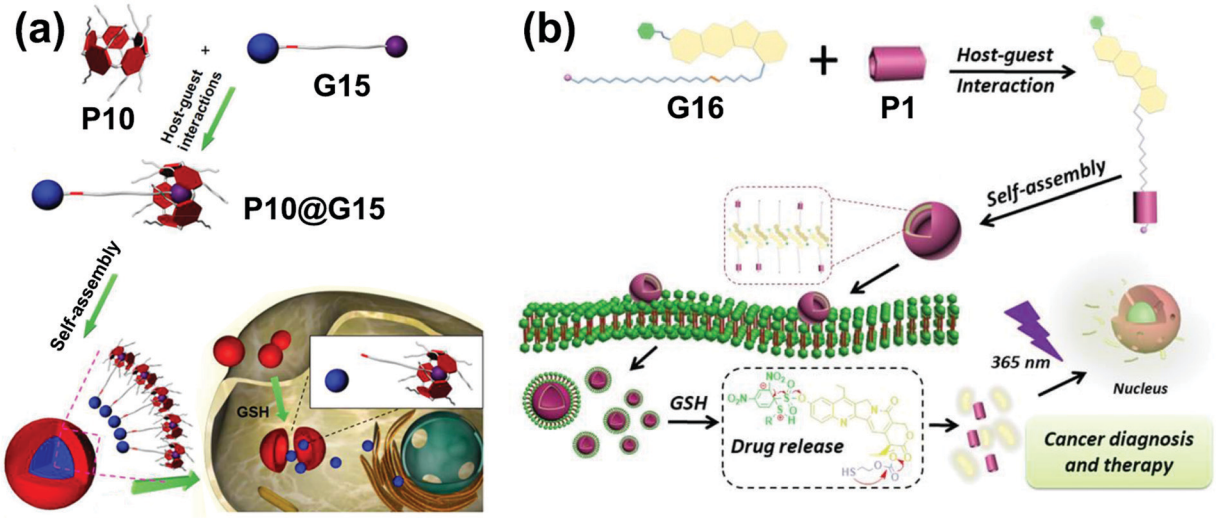


Fig. 12 (a) Schematic diagram of the formation of therapeutic supramolecular amphiphile P10@G15. (b) Schematic illustration of constructing redox-responsive supramolecular prodrug vesicles and their application in cancer diagnosis and therapy. (a) Reproduced from ref. 71 with permission from the Royal Society of Chemistry. (b) Reproduced from ref. 72 with permission from the Royal Society of Chemistry.

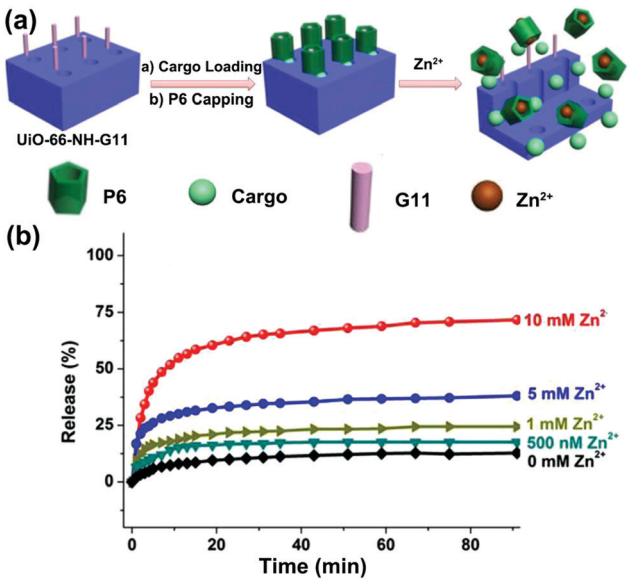


Fig. 13 (a) Schematic representation of stimuli-responsive mechanized UiO-66-NH_2 MOFs equipped with positively charged quaternary ammonium salt (G11) encircled by pillar[5]arene [2]pseudorotaxanes. (b) Release profiles of the Fu-loaded, CP5-capped UiO-66-NH-Q operated by competitive binding with Zn^{2+}. Copyright 2015, Wiley-VCH Verlag GmbH & Co. KGaA.

disease could be periodically treated by regulating intracellular Zn^{2+} concentration. The negligible toxicity suggests a broad application prospect of this ion-responsive controlled release nanosystem for drug delivery for central nervous system diseases.

6. Multi-responsive controlled release

6.1 Multi-responsive decomposition release

In order to develop a more intelligent drug delivery system, multi-responsive controlled release nanosystems were designed, wherein more stimuli-responsive functional groups were introduced into pillararene hosts.[17] The multi-responsive controlled release nanosystems developed in recent years and their application in drug delivery are described below.

In 2017, Jiang *et al.* reported a novel supramolecular vesicle based on carboxylate substituted pillar[6]arene (P6) and disulfide bonded benzimidazole amphiphiles. This supramolecular vesicle controlled the drug release in response to five stimuli: glutathione (GSH), pH, CO_2, Zn^{2+} ions, and hexanediamine (HAD) (Fig. 14a).[77] GSH severed the disulfide bond of benzimidazole amphiphiles, thereby destroying supramolecular vesicles and achieving controlled release (Fig. 14b). When the vesicle was delivered to the tumor cells, P6 was protonated in the acidic environment, resulting in the decomposition of the vesicle and the release of the drug. A high concentration of CO_2 created acidic intracellular environment, and regulated the release of drugs from supramolecular vesicles like the stimulation of pH. However, the drug release caused by CO_2 was less than that caused by pH 5.0 at the same time (Fig. 14c), which suggested that it was easier for an acidic drug to be released. The zinc ion, at a high level in tumor cells, was one of the stimuli in this work. When the carboxylic acid group of P6 was chelated with Zn^{2+}, the host–guest electrostatic interaction weakened, and supramolecular vesicles decomposed and released drug, where the release efficiency increased with the increasing concentration of Zn^{2+} (Fig. 14d). HDA, a biogenic amine related to cell growth and tumor, was another stimulus that could decompose the supramolecular vesicles and trigger drug release (Fig. 14e). This is the first report of intelligent supramolecular vesicles based on pillararenes in response to five stimuli, which have broad application prospects in controlled drug release and the treatment of cancer diseases.

In 2020, Lin and co-workers reported on a novel intelligent glucose- and pH-sensitive insulin delivery nanoplatform. The polymer vesicles were constructed by host–guest interactions

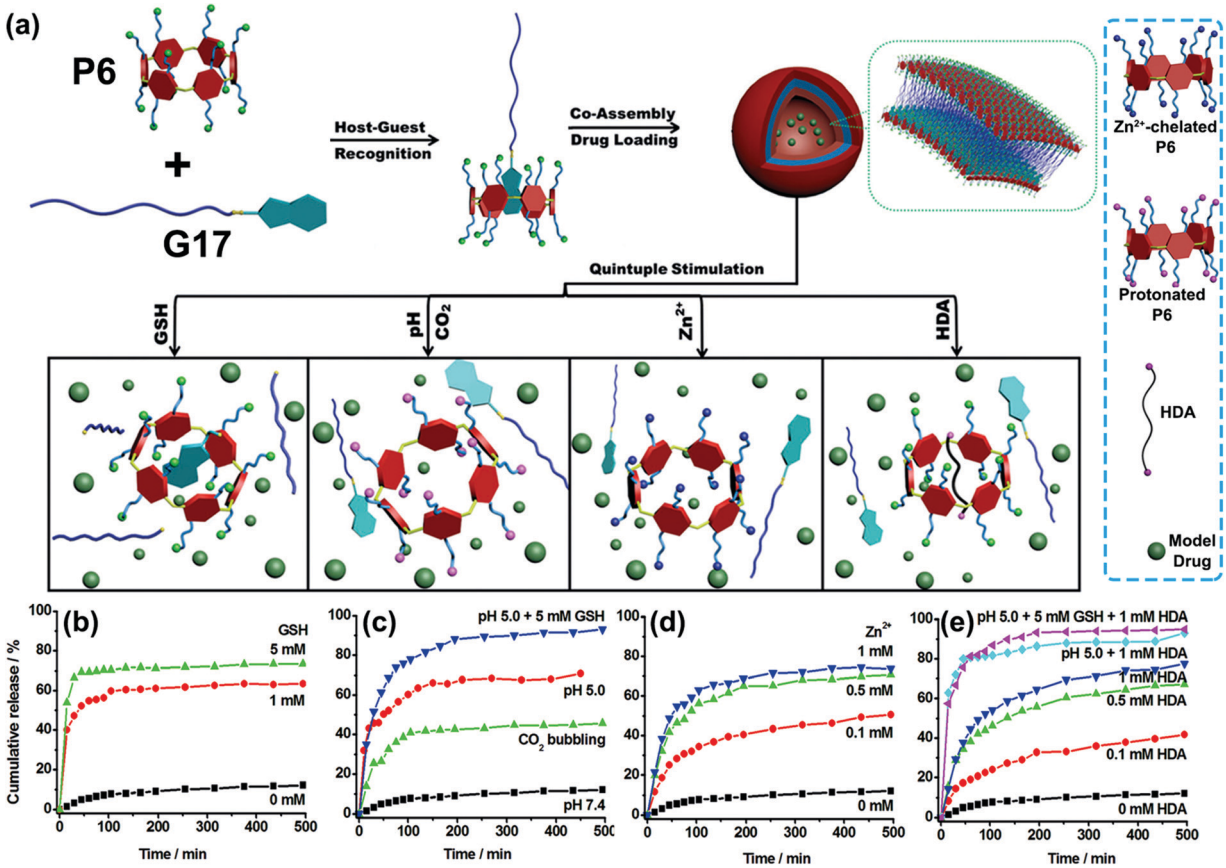


Fig. 14 (a) Chemical structures of P6, disulfide-linked benzimidazolium amphiphiles, and the benzimidazolium guest, as well as illustrations of their inclusion complexes, supramolecular vesicles, and the controlled drug release in response to the five stimuli. Controlled release of $Ru(bipy)_3Cl_2$ from the supramolecular vesicles of P6 and disulfide-linked benzimidazolium amphiphiles when triggered by various stimuli: (b) GSH; (c) pH, CO_2 bubbling, and pH/GSH; (d) Zn^{2+}; (e) HDA, pH/HDA, and pH/GSH/HDA. Copyright 2017, Wiley-VCH Verlag GmbH & Co. KGaA.

between water-soluble pillar[5]arene (P1) and paraquat-ended poly(phenylboronic acid) (G20).[78] The controlled release behavior of insulin under glucose and pH stimulation was studied by loading the system with insulin and glucose oxidase (GOx). At high blood glucose concentrations, insulin release exceeded 80% within 25 h, while control and normal blood glucose concentrations showed approximately 20% insulin release. Under different pH conditions, insulin release increased significantly with the decrease of pH. These results indicated that the polymer vesicles are responsive to both glucose and pH stimuli. More interestingly, the GOx loaded reacted with glucose, effectively boosting the rate of insulin release. Rapid insulin release was demonstrated in both *in vitro* and *in vivo* experiments, indicating that the nanoplatform has the advantages of rapid response and minimal side effects. The insulin delivery platform prepared by this work has potential application value in the treatment of diabetes.

In the latest study, Chen and co-workers reported on supramolecular vesicles (P6@G21) based on water-soluble pillar[5]arene (P6) and an aniline tetramer (G21). The controlled release of DOX was achieved in acidic environments and under different NIR stimuli (Fig. 15).[79] The release amount of DOX increased as the pH value decreased and the wavelength of NIR irradiation

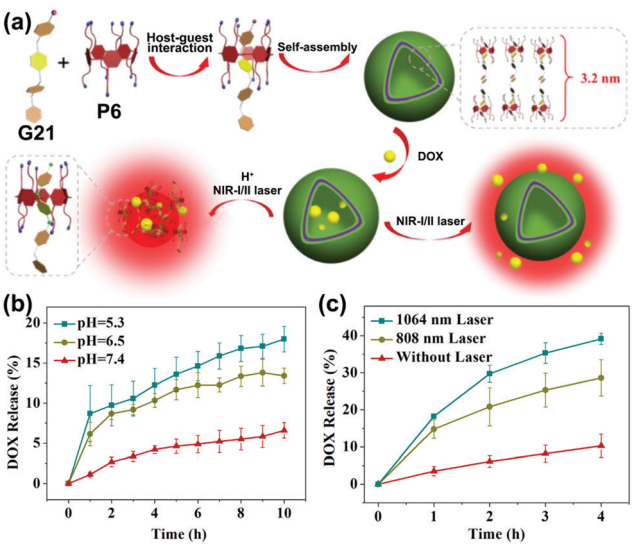


Fig. 15 (a) Chemical structures of P6 and G21 and schematic illustration of the formation of P6@G21 supramolecular vesicles and their pH and NIR-triggered drug release. (b) DOX release curves of WP5@TANI vesicles at different pH. (c) DOX release curves of P6@G21 vesicles at pH 5.3 with NIR-I and NIR-II laser irradiation. Copyright 2021, with permission from Elsevier.

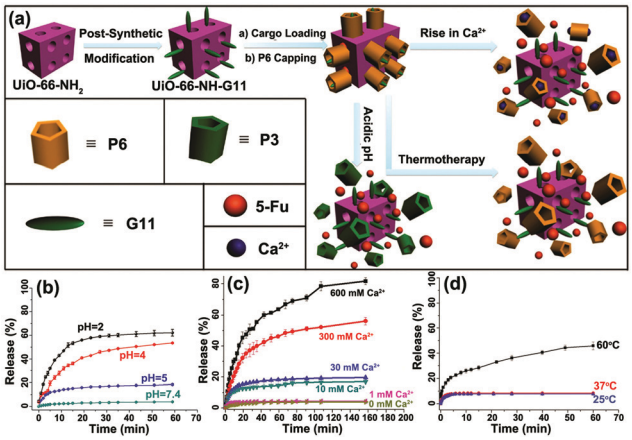


Fig. 16 (a) Schematic representation of stimuli-responsive mechanized Zr-MOFs (UiO-66-NH_2) with positively charged A stalks encircled by carboxylatopillar[5]arene (P6) rings on the surfaces. Controlled release profiles of 5-Fu-loaded, P6-capped UiO-66-NH-G11 operated by (b) pH changes, (c) Ca^{2+} concentration and (d) thermal activation. Reproduced from ref. 81 with permission from the Royal Society of Chemistry.

increased. The drug loading capacity and the encapsulation efficiency of P6@G21 vesicles were 13.1% and 91.7%, respectively, indicating the structural stability and high drug loading capacity of P6@G21. The results of chemo-photothermal synergistic therapy indicated that supramolecular vesicles prepared by this study have potential applications in actual tumor therapy.

In recent years, many multi-stimuli responsive drug delivery nanosystems based on pillar[*n*]arenes have been constructed. Researchers generally consider the stimulation of the microenvironment of human tumor cells (such as acidity, Zn^{2+} overexpression, biogenic amines, *etc.*) as well as the external stimulation (such as light and heat). Because of the complex environment of the tumor cell, not all nanosystems accurately control the drug release. Therefore, the research on multi-stimuli responsive drug delivery systems based on pillar[*n*]arenes should be intensified, and it is hoped that it can be applied in clinical trials in the near future.

6.2 Multi-responsive gated release

Most stimuli-responsive delivery nanosystems use mesoporous silica (MSNs) or MOFs as a carrier, where the host–guest self-assembly works as a nano-valve to control the drug release.[80] This part introduces the pillar[*n*]arene-gated multi-responsive release nanosystems in recent years.

In 2016, Yang *et al.* reported a mechanized Zr-MOF nanocarrier with stimulus response characteristics to pH, Ca^{2+} and temperature (Fig. 16).[81] In this work, UiO-66-NH_2 was first modified with G11, and then loaded with 5-fluorouracil (5-Fu) and terminated with carboxylatopillar[5]arene (P6). Under normal physiological conditions, almost no drug was released. The drug release increased as the acidity, the concentration of Ca^{2+} or the temperature increased. This study opens up the possibility of developing smart biomaterials for bone regeneration and cancer treatment.

Compared with multi-stimuli responsive decomposition release nanosystems, few multi-stimuli responsive gated release nanosystems have been reported. This is mainly due to the fact that there are few substances that meet the requirements of targeted controlled release, good biological activity and distant premature leakage. Therefore, in this aspect of research, we should find more substances that meet these conditions, so as to build more pillararene-gated drug delivery systems.

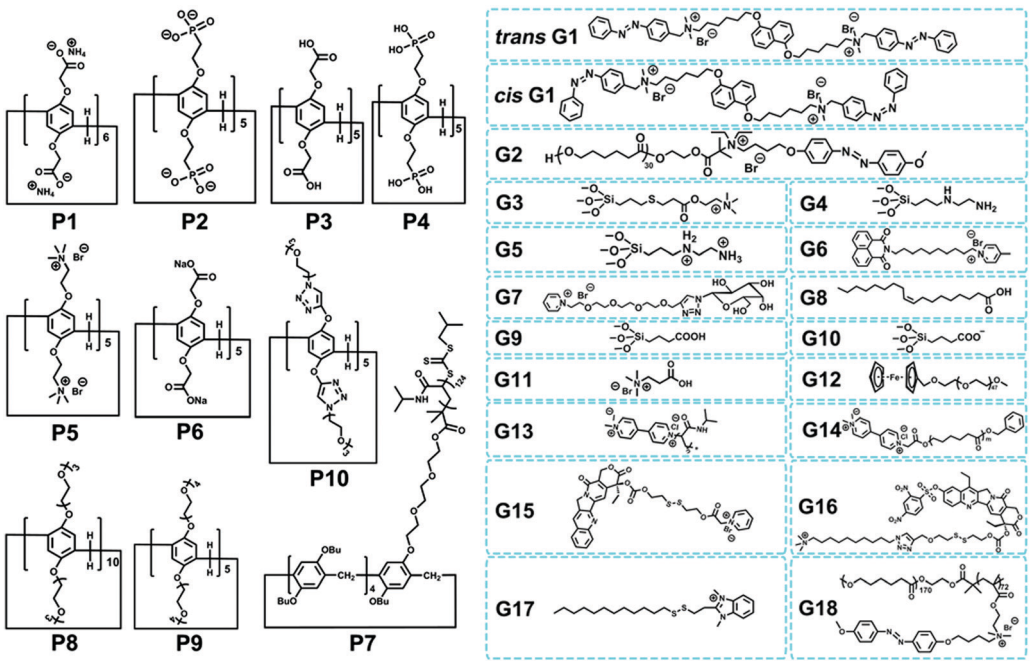


Fig. 17 The index of pillar[*n*]arene hosts (P1 to P10) and guests (G1 to G18).

7. Conclusion

In conclusion, all controlled release systems link functional groups responding to specific stimuli to macrocyclic pillar[*n*]-arene hosts through host–guest interactions without complex organic synthesis.[82–84] These specific functional groups give these nanosystems rich stimulation responsiveness to light, pH, temperature, redox and ions. In order to improve the readability of the paper, we have summarized pillar[*n*]arene hosts (P) and guests (G) in the paper as shown in Fig. 17. From the summary in the figure, it can be seen that most pillar[*n*]arenes hosts are water-soluble, such as those with carboxyl and phosphoric groups. These pillar[*n*]arenes with good biocompatibility can be widely used in biomedical delivery. These guest molecules can then be freely designed as needed, such as photo-responsive azo guests, hydrophobic alkyl chain guests, pH-responsive ammonium salt guests, and thermo-responsive oxygen containing long chains. It is worth mentioning that the above constructed controlled release systems respond to most of the external stimuli by considering the microenvironment of tumor cells without providing external stimuli, which greatly reduces energy consumption and has broad application prospects in the treatment of cancer.

Although many of the pillar[*n*]arene-based controlled release systems have been reported in recent years,[85] the research in this field is still in its infancy and they are difficult to test in clinical trials.[86] We need to work hard to address the unresolved issues and greet new challenges. Firstly, the design and assembly of the pillar[*n*]arene and guest molecules are still semi-experience.[87,88] Theoretical tools that can calculate energy optimization models and provide evidence have not been appropriately developed. Only through extensive mechanism studies and the construction of more new systems will we be able to develop a general approach and bring the technology to maturity. Secondly, most of the reported stimuli-responsive nanosystems are based on carboxylated pillar[5–6]arenes.[89] However, compared with the diversity of pillar[*n*]arenes, the exploited pillararenes are only the tip of the iceberg, which severely limits the development of stimuli-responsive systems. Most importantly, the construction of pillararene-based host–guest nanosystems is greatly limited due to the small cavities of pillar[5-6]arenes used by most predecessors, which can only contain small molecules. Therefore, it is urgent to establish new pillar[*n*]arene ($n > 6$)-based stimuli-responsive controlled release systems due to their larger cavities. Finally, known controlled release systems are generally limited to the anti-cancer drug DOX,[90–92] small molecules or ions,[93] and there is almost no report on larger biomolecules because of the complexity and vulnerability of biomolecules. Due to the advantages of application of biomolecules in disease treatment, it is urgent to develop biomolecular-loaded pillar[*n*]arene-based nanosystems. This work could potentially pave the way for exploiting previously unexplored controlled release drug molecules with pillar[*n*]arenes. More meaningful, for the deficiencies mentioned, we expect that these aspects will be improved and overcome in the future research, which will lay a foundation for the stimuli-responsive drug delivery systems. And they will be more widely used in clinical drug delivery, improving the accuracy and efficiency of drugs, and avoiding the risk of drug abuse.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 A. L. Fameau, A. Arnould, M. Lehmann and R. von Klitzing, *Chem. Commun.*, 2015, **51**, 2907–2910.
2 C. W. Jung, J. S. Lee, G. Jalani, E. Y. Hwang and D. W. Lim, *Front. Chem.*, 2019, **7**, 73.
3 W. Lee, D. Kim, S. Lee, J. Park, S. Oh, G. Kim, J. Lim and J. Kim, *Nano Today*, 2018, **23**, 97–123.
4 Y. Zhou and K. Jie, *Tetrahedron Lett.*, 2017, **58**, 2217–2222.
5 Z. Y. Li, Y. Zhang, C. W. Zhang, L. J. Chen, C. Wang, H. Tan, Y. Yu, X. Li and H. B. Yang, *J. Am. Chem. Soc.*, 2014, **136**, 8577–8589.
6 F.-C. Lin and J. I. Zink, *J. Am. Chem. Soc.*, 2020, **142**, 5212–5220.
7 X. Liu, Y. Zhang, Y. Wang, W. Zhu, G. Li, X. Ma, Y. Zhang, S. Chen, S. Tiwari and K. Shi, *Theranostics*, 2020, **10**, 3793.
8 W. Xia, M. Ni, C. Yao, X. Wang, D. Chen, C. Lin, X.-Y. Hu and L. Wang, *Macromolecules*, 2015, **48**, 5456–5458.
9 X. Yan, P. Wei, Z. Li, B. Zheng, S. Dong, F. Huang and Q. Zhou, *Chem. Commun.*, 2013, **49**, 2512–2514.
10 L. E. Khalil-Cruz, P. Liu, F. Huang and N. M. Khashab, *ACS Appl. Mater. Interfaces*, 2021, **18**, 31337–31354.
11 M. Cheng, G. Li, W. Xu, H. Qu, X. Mao and H. Li, *Dyes Pigm.*, 2021, **194**, 109646.
12 M. Jin, K. Yang, Y. Pei and Z. Pei, *Chem. Commun.*, 2018, **54**, 13626–13640.
13 Y. Yao, Y. Wang and F. Huang, *Chem. Sci.*, 2014, **5**, 4312–4316.
14 S. Zhang, M. Cheng, M. K. Dhinakaran, Y. Sun and H. Li, *ACS Nano*, 2021, **15**, 13148–13154.
15 H. T. Z. Zhu, Q. Li, L. E. Khalil-Cruz, N. M. Khashab, G. C. Yu and F. H. Huang, *Sci. China: Chem.*, 2021, **64**, 688–700.
16 G. Cafeo, G. Carbotti, A. Cuzzola, M. Fabbi, S. Ferrini, F. H. Kohnke, G. Papanikolaou, M. R. Plutino, C. Rosano and A. J. White, *J. Am. Chem. Soc.*, 2013, **135**, 2544–2551.
17 X. Wu, L. Gao, X. Y. Hu and L. Wang, *Chem. Rec.*, 2016, **16**, 1216–1227.
18 W. Xu, M. Cheng, S. Zhang, Q. Wu, Z. Liu, M. K. Dhinakaran, F. Liang, E. G. Kovaleva and H. Li, *Chem. Commun.*, 2021, **57**, 7480–7492.
19 G. Gonzalez-Gaitano, J. Ramon Isasi, I. Velaz and A. Zornoza, *Curr. Pharm. Des.*, 2017, **23**, 411–432.
20 J. S. Kim and D. T. Quang, *Chem. Rev.*, 2007, **107**, 3780–3799.
21 Z. Xu, S. Jia, W. Wang, Z. Yuan, B. J. Ravoo and D.-S. Guo, *Nat. Chem.*, 2019, **11**, 86–93.
22 K. Jie, Y. Zhou, E. Li and F. Huang, *Acc. Chem. Res.*, 2018, **51**, 2064–2072.
23 T. Ogoshi, S. Kanai, S. Fujinami, T. A. Yamagishi and Y. Nakamoto, *J. Am. Chem. Soc.*, 2008, **130**, 5022–5023.
24 H. Zhang and Y. Zhao, *Chemistry*, 2013, **19**, 16862–16879.
25 D.-Y. Kim, T. Christoff-Tempesta, G. Lamour, X. Zuo, K.-H. Ryu and J. H. Ortony, *Nano Lett.*, 2021, **21**, 2912–2918.

26 S. Dong, B. Zheng, F. Wang and F. Huang, *Acc. Chem. Res.*, 2014, **47**, 1982–1994.
27 V. Montes-Garcia, J. Perez-Juste, I. Pastoriza-Santos and L. M. Liz-Marzan, *Chemistry*, 2014, **20**, 10874–10883.
28 P. Taladriz-Blanco, P. Hervés and J. Pérez-Juste, *Top. Catal.*, 2013, **56**, 1154–1170.
29 E. Busseron, Y. Ruff, E. Moulin and N. Giuseppone, *Nanoscale*, 2013, **5**, 7098–7140.
30 Y. Sun, S.-Q. Cheng, J. Ma, F. Zhu, W. Hong and H. Li, *Sens. Actuators, B*, 2020, **323**, 128705.
31 S. p. Zheng, L. b. Huang, Z. Sun and M. Barboiu, *Angew. Chem., Int. Ed.*, 2021, **60**, 566–597.
32 M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294–1308.
33 T. Ogoshi, T.-a. Yamagishi and Y. Nakamoto, *Chem. Rev.*, 2016, **116**, 7937–8002.
34 T. S. Fernandes, E. C. S. Santos, V. G. C. Madriaga, I. A. A. Bessa, V. Nascimento, F. Garcia and C. M. Ronconi, *J. Braz. Chem. Soc.*, 2019, **30**, 2452–2463.
35 F. Guo, Y. Sun, B. Xi and G. Diao, *Supramol. Chem.*, 2018, **30**, 81–92.
36 N. Song, X.-Y. Lou, L. Ma, H. Gao and Y.-W. Yang, *Theranostics*, 2019, **9**, 3075.
37 S. Guo, T. Liang, Y. Song, M. Cheng, X.-Y. Hu, J.-J. Zhu and L. Wang, *Polym. Chem.*, 2017, **8**, 5718–5725.
38 A. R. Hughes, M. Liu, S. Paul, A. I. Cooper and F. Blanc, *J. Phys. Chem. C*, 2021, **12**, 13370–13381.
39 J. Chang, Q. Zhao, L. Kang, H. Li, M. Xie and X. Liao, *Macromolecules*, 2016, **49**, 2814–2820.
40 H. Chen, X. Jia and C. Li, *Chin. J. Chem.*, 2015, **33**, 343–345.
41 A. Blanco-Gomez, P. Corton, L. Barravecchia, I. Neira, E. Pazos, C. Peinador and M. D. Garcia, *Chem. Soc. Rev.*, 2020, **49**, 3834–3862.
42 L. Gao, T. Wang, K. Jia, X. Wu, C. Yao, W. Shao, D. Zhang, X.-Y. Hu and L. Wang, *Chem. – Eur. J.*, 2017, **23**, 6605–6614.
43 D.-H. Qu, Q.-C. Wang, Q.-W. Zhang, X. Ma and H. Tian, *Chem. Rev.*, 2015, **115**, 7543–7588.
44 H. Zhu, L. Shangguan, D. Xia, J. H. Mondal and B. Shi, *Nanoscale*, 2017, **9**, 8913–8917.
45 L. Shao, B. Hua, J. F. Sun, Q. Li, J. Yang and G. C. Yu, *Tetrahedron Lett.*, 2017, **58**, 1863–1867.
46 L. Shao, B. Hua, J. Yang and G. Yu, *Chem. Commun.*, 2016, **52**, 6573–6576.
47 N. L. Strutt, H. Zhang, S. T. Schneebeli and J. F. Stoddart, *Acc. Chem. Res.*, 2014, **47**, 2631–2642.
48 J. Yang, L. Shao and G. Yu, *Chem. Commun.*, 2016, **52**, 3211–3214.
49 D. Xia, G. Yu, J. Li and F. Huang, *Chem. Commun.*, 2014, **50**, 3606–3608.
50 D. Xia, L. Shangguan, M. Xue and B. Shi, *New J. Chem.*, 2016, **40**, 9890–9894.
51 Z. Tong, J. Zhou, R. Huang, J. Zhou, R. Zhang, W. Zhuo and G. Jiang, *J. Polym. Sci. Part A: Polym. Chem.*, 2017, **55**, 2477–2482.
52 E. Aznar, M. Oroval, L. Pascual, J. R. Murguia, R. Martinez-Manez and F. Sancenon, *Chem. Rev.*, 2016, **116**, 561–718.
53 L. Ma, S. Wang, C. Li, D. Cao, T. Li and X. Ma, *Chem. Commun.*, 2018, **54**, 2405–2408.
54 X. Huang, S. Wu, X. Ke, X. Li and X. Du, *ACS Appl. Mater. Interfaces*, 2017, **9**, 19638–19645.
55 Z. Li, J. Yang and F. Huang, *Chin. J. Chem.*, 2018, **36**, 59–62.
56 Y. Wang, Z. Pei, W. Feng and Y. Pei, *J. Mater. Chem. B*, 2019, **7**, 7656–7675.
57 Q. Duan, Y. Cao, Y. Li, X. Hu, T. Xiao, C. Lin, Y. Pan and L. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 10542–10549.
58 Y. Yao, Y. Wang, R. Zhao, L. Shao, R. Tang and F. Huang, *J. Mater. Chem. B*, 2016, **4**, 2691–2696.
59 X.-Y. Hu, X. Liu, W. Zhang, S. Qin, C. Yao, Y. Li, D. Cao, L. Peng and L. Wang, *Chem. Mater.*, 2016, **28**, 3778–3788.
60 K. Yang, K. Yang, S. Chao, J. Wen, Y. Pei and Z. Pei, *Chem. Commun.*, 2018, **54**, 9817–9820.
61 X. Wang, J. Yang, X. Sun, H. Yu, F. Yan, K. Meguellati, Z. Cheng, H. Zhang and Y. W. Yang, *Chem. Commun.*, 2018, **54**, 12990–12993.
62 E. C. S. Santos, T. C. Dos Santos, T. S. Fernandes, F. L. Jorge, V. Nascimento, V. G. C. Madriaga, P. S. Cordeiro, N. R. Checca, N. M. Da Costa, L. F. R. Pinto and C. M. Ronconi, *J. Mater. Chem. B*, 2020, **8**, 703–714.
63 C. Y. Wang, X. Y. Lou, Z. Cai, M. Z. Zhang, C. Jia, J. C. Qin and Y. W. Yang, *ACS Appl. Mater. Interfaces*, 2021, **13**, 32295–32306.
64 S. Wang, C. Yao, M. Ni, Z. Xu, M. Cheng, X.-Y. Hu, Y.-Z. Shen, C. Lin, L. Wang and D. Jia, *Polym. Chem.*, 2017, **8**, 682–688.
65 X. Chi, X. Ji, L. Shao and F. Huang, *Macromol. Rapid Commun.*, 2017, **38**, 1600626.
66 R. Wang, Y. Sun, F. Zhang, M. Song, D. Tian and H. Li, *Angew. Chem., Int. Ed.*, 2017, **56**, 5294–5298.
67 J. Bi, X. Zeng, D. Tian and H. Li, *Org. Lett.*, 2016, **18**, 1092–1095.
68 X. Wang, L. L. Tan, X. Li, N. Song, Z. Li, J. N. Hu, Y. M. Cheng, Y. Wang and Y. W. Yang, *Chem. Commun.*, 2016, **52**, 13775–13778.
69 X. Chi, G. Yu, X. Ji, Y. Li, G. Tang and F. Huang, *ACS Macro Lett.*, 2015, **4**, 996–999.
70 H. Gu, S. Mu, G. Qiu, X. Liu, L. Zhang, Y. Yuan and D. Astruc, *Coord. Chem. Rev.*, 2018, **364**, 51–85.
71 D. Wu, Y. Li, J. Shen, Z. Tong, Q. Hu, L. Li and G. Yu, *Chem. Commun.*, 2018, **54**, 8198–8201.
72 G. Sun, Z. He, M. Hao, Z. Xu, X. Y. Hu, J. J. Zhu and L. Wang, *Chem. Commun.*, 2019, **55**, 10892–10895.
73 X.-M. Jiang, X.-J. Huang, S.-S. Song, X.-Q. Ma, Y.-M. Zhang, H. Yao, T.-B. Wei and Q. Lin, *Polym. Chem.*, 2018, **9**, 4625–4630.
74 P. Wang, J. Ma and D. Xia, *Org. Chem. Front.*, 2018, **5**, 1297–1302.
75 F. Zhang, J. Ma, Y. Sun, I. Boussouar, D. Tian, H. Li and L. Jiang, *Chem. Sci.*, 2016, **7**, 3227–3233.
76 L. L. Tan, H. Li, Y. Zhou, Y. Zhang, X. Feng, B. Wang and Y. W. Yang, *Small*, 2015, **11**, 3807–3813.
77 L. Jiang, X. Huang, D. Chen, H. Yan, X. Li and X. Du, *Angew. Chem., Int. Ed.*, 2017, **56**, 2655–2659.
78 Y. Lin, W. Hu, X. Bai, Y. Ju, C. Cao, S. Zou, Z. Tong, C. Cen, G. Jiang and X. Kong, *ACS Appl. Bio Mater.*, 2020, **3**, 6376–6383.
79 X. Chen, Z. Wang, X. Sun, Y. Han, Y. Huang, J. Xi, X. Bian, J. Han and R. Guo, *Chem. Eng. J.*, 2021, **403**, 126423.
80 T. Faust, *Nat. Chem.*, 2015, **7**, 270–271.
81 L. L. Tan, N. Song, S. X. Zhang, H. Li, B. Wang and Y. W. Yang, *J. Mater. Chem. B*, 2016, **4**, 135–140.
82 X. B. Hu, Z. Chen, L. Chen, L. Zhang, J. L. Hou and Z. T. Li, *Chem. Commun.*, 2012, **48**, 10999–11001.
83 Q. Li, X. Li, L. Ning, C. H. Tan, Y. Mu and R. Wang, *Small*, 2019, **15**, 1804678.
84 T. Ogoshi, N. Ueshima, F. Sakakibara, T. A. Yamagishi and T. Haino, *Org. Lett.*, 2014, **16**, 2896–2899.
85 K. Yang, Y. Pei, J. Wen and Z. Pei, *Chem. Commun.*, 2016, **52**, 9316–9326.
86 R. Zhang, J. Huang, K. Chen, I. Boussouar, X. Chen, Y. Fan, Y. Sun and H. Li, *Anal. Chem.*, 2021, **93**, 3280–3286.
87 X. P. Tan, J. H. Xu, T. Huang, S. Wang, M. J. Yuan and G. F. Zhao, *RSC Adv.*, 2019, **9**, 38372–38380.
88 P. Xin, H. Kong, Y. Sun, L. Zhao, H. Fang, H. Zhu, T. Jiang, J. Guo, Q. Zhang, W. Dong and C. P. Chen, *Angew. Chem., Int. Ed.*, 2019, **58**, 2779–2784.
89 F. Guo, Y. Sun, B. Xi and G. Diao, *Supramol. Chem.*, 2018, **30**, 81–92.
90 Y. Sun, F. Guo, T. Zuo, J. Hua and G. Diao, *Nat. Commun.*, 2016, **7**, 12042.
91 G. Yu and X. Chen, *Theranostics*, 2019, **9**, 3041–3074.
92 Q. Zou, M. Abbas, L. Zhao, S. Li, G. Shen and X. Yan, *J. Am. Chem. Soc.*, 2017, **139**, 1921–1927.
93 B. Hua, L. Shao, Z. H. Zhang, J. F. Sun and J. Yang, *Sens. Actuators, B*, 2018, **255**, 1430–1435.