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TUTORIAL REVIEW

Calixarene-based supramolecular polymerization in solution[†]

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Calixarenes are one kind of phenol–formaldehyde cyclic oligomers, discovered from the Bakelite process. Their intrinsic characteristics, including the unique structural scaffold, facile modification and adjustable inclusion property, show pronounced potential for supramolecular polymerization. In this *tutorial review*, we summarize the current stage of fabrication of calixarene-based supramolecular polymers. Three types of calixarene-based supramolecular polymers are, respectively, illustrated according to the different activities of calixarenes: (1) calixarene-based supramolecular polycaps, (2) supramolecular polymers with polymeric calixarene scaffolds where the cavities remain unexploited; (3) supramolecular polymers formed by the host–guest interactions offered by calixarene cavities. Furthermore, the stimuli-responsiveness and functions of calixarene-based supramolecular polymers are illustrated, which endow them with a broad range of potential applications as smart, self-healing materials and delivery carriers.

1. Introduction

Supramolecular polymers, emerged from the combination of supramolecular chemistry and polymer science, are polymers based on monomeric units held together by directional and reversible non-covalent interactions.^{1,2} As well known, most covalent chemistry is irreversible and so occurs under kinetic control while most supramolecular non-covalent chemistry is reversible and so occurs under thermodynamic control.³

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This results in the intrinsic difference between supramolecular and conventional polymers. There are three major advantages of supramolecular polymers: (1) the reversibility of noncovalent interactions facilitates their processing and recycling, and also endows them with responsiveness to external stimuli; (2) supramolecular polymers have the capability of self-healing and adaptation; (3) they can act as shape-memory materials if combined with covalent cross-linking.⁴ Lehn *et al.* designed and synthesized the first example of a linear supramolecular polymer based on hydrogen bonding among small molecules in 1990.⁵ In the last two decades, supramolecular polymers have gained more and more interests from scientists after Lehn's seminal work, assuming a fascinating class of smart soft materials.

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Kong Scholars Programme of China'. He won the second prize of National Natural Science Award in 2010. His research interests are mainly focused on molecular recognition and assembly of macrocyclic receptors. Among the non-covalent interactions, coordination, $\pi \cdots \pi$ stacking and hydrogen bonding have been widely used so far to drive the self-assembly of supramolecular polymers.^{6,7} One representative system that has been demonstrated by the Meijer group uses quadruple hydrogen bonds to form supramolecular polymers.8,9 The host-guest interactions have also attracted considerable attention in recent years, and occupy a special position in supramolecular polymerization with crown ethers, cryptands, cyclodextrins, cucurbiturils, calixarenes, and resorcinarenes as host monomer units.^{10–13} More recently, pillararenes, a new class of cyclophanes consisting of 1,4-disubstituted hydroquinones linked by methylene bridges in the 2,5-positions, were also engaged in this field. Huang et al. reported that the supramolecular AB-type polymers from copillararene monomers are driven by quadruple $C-H\cdots\pi$ interactions.¹⁴ In this tutorial review, we focus solely on supramolecular polymers based on calixarene and resorcinarene macrocycles.

Calixarenes and resorcinarenes are phenol-derived cyclic oligomers based on a hydroxyalkylation product of a phenol and an aldehyde (Fig. 1). They represent a particularly significant family of macrocyclic hosts in host-guest and supramolecular chemistry.¹⁵ In fact, there has been a close relationship between calixarene and polymer chemistry since the pioneering discovery of calixarenes from the Bakelite process. In the following decades, calixarenes and resorcinarenes have been widely used in polymer chemistry, as catalysts for the polymerization, backbones or cores of polymers, and polymer-based graft substitutes.^{16–18} In an alternative way, the project of building supramolecular polymers in solution based on calixarenes and resorcinarenes has also been described to a certain extent. Calixarene-based supramolecular polymers can be classified into three types according to the activities of calixarenes: (1) calixarene-based supramolecular polymeric capsules, "polycaps", relying on multiple-hydrogen bonds as well as guest encapsulation; (2) supramolecular polymers with calixarene scaffolds where the cavities remain unexploited; (3) supramolecular polymers formed by host-guest interactions offered by calixarene cavities, which act as the exclusive driving forces to hold monomer units together. This review provides an overview of these three types of calixarene-based supramolecular polymers reported by recent studies in this field. It should be mentioned that purely solid-state supramolecular polymers based on calixarenes and resorcinarenes are excluded here.

2. Calixarene-based supramolecular polycaps

The first calixarene-based supramolecular polymer was achieved by Rebek's group early in 1997.¹⁹ They established a series of conceptually innovative polycaps based on calixarenes. Unlike other main-chain, hydrogen-bonded polymers, the polycaps, reminiscent of beads-on-a-string, are with functional host units



Fig. 1 Structural illustration of calixarene and resorcinarene macrocyclic hosts.

and their formation depends on guests of proper size, shape, and chemical surface to a certain extent. These supramolecular polycaps are responsive to chemical, thermal, and external stimuli, and show desirable and intriguing properties such as informational encodement, viscoelasticity, mesogeneity, mechanical integrity, and gelation.

As shown in Fig. 2, in calix[4]arene derivative 1, the cup-like shape of the calix[4]arene provides half of each capsule, while the ureas on its upper rim provide the hydrogen bonds that permit the molecules to dimerize with association constants of up to 10^6 – 10^8 M⁻¹.^{20,21} Two calix[4]arene units were covalently bound at the carboxyl functions on their lower rims, giving the homoditopic subunits (2 and 3) for the polycaps (Fig. 2). Although the present polycaps are dominantly driven by selfcomplementary hydrogen bonds, polycap formation can be dramatically induced by guest species, and polycap destruction occurs via the formation of dumbbell-shaped heterodimers. At the melting point (equal amounts of monomer and assembly are present in solution), addition of a suitable guest nucleates the formation of more polycaps and does so at the expense of the monomeric species. Then, an excess of a simple dimeric capsule 1 could depolymerize the linear array as the formation of heterodimers takes place, leading ultimately to the dumbbelllike 2 : 1 complex shown in Fig. 3a.

Castellano and Rebek further synthesized a series of homoditopic (4), heteroditopic (5), homotritopic (6) subunits for supramolecular polycaps (Fig. 2).²² They found that the heterodimers form exclusively with respect to the homodimers when different ureas (such as aryl and sulfonyl) are present.²³ The heterodimerization encodes information at the molecular level, and can be used to construct programmed, or "smart" polymers. As shown in Fig. 3b, the heterodimerization tendency predicts that a combination of 3 and 4 should lead to polycaps with alternating subunits. Likewise, the self-complementary heteroditopic 5 is expected to polymerize "head to tail" with alternating aryl urea and sulfonyl urea rims. The preference for heterodimerization represents information in the form of a binary code, leading to a new type of informational polymer. Interestingly, addition of CDCl₃ to the homotritopic 6 produces an uncharacterized insoluble gel, presumably through the formation of cross-linked polycaps. Nonetheless, sonication of another calixarene monomer with the 6-directed gel in CDCl₃ yields a homogeneous solution, and the capped derivative emerges as the only species.

Increasing order of certain polycaps would lead to spontaneous formation of polymeric liquid crystals and then micrometer-scale fibrous assemblies.²⁴ The polycap based on **7** exhibits typically Schlieren textures that are characteristic of lyotropic, nematic, liquid crystalline phases. As a control experiment, no liquid crystalline behavior was observed for subunit **2**. This demonstrates that the shorter alkyl chains do not impart a sufficiently liquid-like environment to the polymer. Moreover, the covalent linker between the two calixarenes also contributes to the intermediate behavior. The polycap material no longer displays liquid crystallinity if the phenyl spacer is replaced by a flexible alkyl chain. Viscosity measurements show that the viscosity increases slowly with concentration of **7** until a critical concentration of 0.6% by weight is attained, at which point the viscosity begins to rise much more significantly.²⁵



Fig. 2 Chemical structures of monotopic ditopic, tritopic and tetratopic calix[4]arene tetraureas (1–8) employed to form supramolecular polycaps. Two calixarene tetraureas (1) assemble to provide a host capsule for small molecule guests.



Fig. 3 Schematic depiction of (a) polycap formation of 2 induced by guest encapsulation and the following "dumbbell-shaped" biscapsules formed *via* disproportionation of the polycap with simple calixarene capsule 1; (b) homopolycaps of homoditopic 3 and 4, a heteropolycap of 3.4, a head-to-tail polycap of heteroditopic 5.

This phenomenon indicates a transition from the dilute to semidilute concentration regime, where individual polymer chains overlap and entanglements influence the observed viscoelasticity. The mechanical integrity of the polycaps was then estimated by measuring normal stresses in solution. Despite the reversible nature of the polycaps, the authors observed normal stresses in excess of 100 g (\approx 1000 Pa) from a solution of 7 (3.7% by weight) in *o*-dichlorobenzene; namely, the reversible polymerization is strong enough to withstand these disruptive conditions.

The tetratopic subunit $\mathbf{8}$ was synthesized by Rebek *et al.* to create 3D networks, which is promising for the formation of supramolecular gels. Different to the conventionally physical gels, in which covalent polymers are cross-linked through

weakly associative interactions, the noncovalent chains have interspersed covalent cross-links, leading to a greater number of relaxation and rearrangement pathways in the network formed by **8**. As a result, supramolecular gels formed from 0.5% **8**, and 4.5% **7** in *o*-dichlorobenzene. The gelation concentration of **7** is 9 times higher than that of **8**, which is reasonable in that the structural component of tetravalent **8** favors more the construction of a cross-linking network.

With regard to controlling the assembly and dissipation of polycaps, two pathways can be proposed: one operates with the capsule units; the other operates with the spacers that link two calixarenes at their lower rims. Rudkevich et al. reported a series of supramolecular polycaps based on calixarenes, which are switchable by adjusting the linking spacers. As one of their motivations, they revealed how to turn "on-off" properties of supramolecular polymers without breaking their unique polymeric structure. A switchable, supramolecular polycap was then introduced which reversibly precipitates and redissolves upon subtle pH control (Fig. 4).²⁶ Bis-calix[4]arene 9, in which two calixarene tetraureas are stitched together with a dipeptide chain, shows the expected assembling behavior in apolar solutions with the formation of polycaps $(9 \cdot \text{Solvent})_n$. The polycap based on 9 changes aggregation properties upon pH changes with polymeric chains remaining intact. Upon addition of small quantities (5-7 equiv.) of trifluoroacetic acid (TFA) to the benzene solution of $(9 \cdot \text{Benzene})_n$, the insoluble



Fig. 4 Chemical structure of 9 and cartoon illustration of switchable formation of polycaps, (9-Solvent), and (9-Solvent), nTFA.

(9.Benzene)_n nTFA salt formed as the α -NH₂ groups in 9 become protonated. Reversibly, addition of Et₃N to the suspension of (9.Benzene)_n nTFA in benzene regenerates (9.Benzene)_n, which dissolves without breaking the self-assembled polymeric chain. This fascinating, switchable property of (9.Solvent)_n endows itself with feasible application of encapsulation.

The dynamic, reversible chemistry of CO_2 has been involved in building supramolecular polymeric materials.²⁷ CO₂ combines smoothly with amines at ordinary temperatures and pressures to yield carbamates, and reversibly, carbamates are thermally unstable and release CO₂ upon heating. As a result, Rudkevich *et al.* outlined a new strategy to construct two-parameter switchable supramolecular polycaps and organogels by virtue of hydrogen bonding and dynamic carbamate chemistry (between CO₂ and primary amines), showing robust applications in entrapment, storage, and controlled release. They designed monotopic calix[4]arene tetraurea **10** (Fig. 5), possessing a primary amino group at its lower-rim periphery. **10** forms a dimeric capsule in apolar solutions as desired, and hierarchically, bubbling CO₂ through a solution of the capsule in benzene causes a rapid precipitation of supramolecular polycaps (Fig. 6).²⁸ The capsular dimers are joined together to generate desired polymers through carbamate $CH_2N^+H_3\cdots O^-C(O)NHCH_2$ salt bridges. This is an elegant example in which two binding sites independently, in an orthogonal way, lead to stepwise polymerization. The polycap from **10** and CO₂ can therefore assemble and dissipate in a twoparameter fashion, upon changing either the solvent polarity or temperature. Noticeably, carbamate–ammonium electrostatics is nondirectional and may show disadvantages in fabrication of supramolecular polymers. The authors then performed the viscosity measurements, and proposed that oligomeric rings rather than linear polymeric chains form upon reaction of **10** with CO₂.²⁹

The same authors further achieved the conversion from linear supramolecular polycaps based on bis-calix[4]arene 11 to supramolecular, three dimensional polymeric networks, employing CO₂ as a cross-linking agent (Fig. 7).²⁹ 11 was designed for hierarchical, CO₂-based cross-linking, where two calix[4]arene tetraurea units were covalently attached with



Fig. 5 Chemical structures of monotopic and ditopic calix[4]arene tetraureas (10–12) employed to form supramolecular polycaps and crosslinking by virtue of dynamic carbamate chemistry.



Fig. 6 Schematic illustration of two-parameter switchable formation of polycaps from calix[4]arene tetraurea **10** *via* hydrogen bonding and dynamic carbamate chemistry.



Fig. 7 Schematic illustration of switchable formation of polycaps from bis-calix[4]arenes **11** *via* hydrogen bonding and a hierarchical cross-linking network *via* dynamic carbamate chemistry.

the divergent orientation for linear, hydrogen-bonded polymerization, and the " CO_2 -philic" amino groups were grafted perpendicular to the main chain (Fig. 5). The viscosity measurements proved the self-assembled polymeric structure of **11**, but not ring species, which is a prerequisite for the subsequent cross-linking by CO_2 . Bubbling the CO_2 gas through a solution of **11** in CHCl₃ or benzene yielded cross-linked organogels as expected. The gel from **11** and CO_2 is also switchable in a twoparameter fashion, solvent polarity or temperature.

At a molecular level, multiple voids are generated in the organogel from **11** and CO₂ with 15–20 Å dimensions, which allows the gel to be employed in the entrapment and controlled release of model guest molecules. For this project, Rudkevich *et al.* applied the gel to trap commercial dyes such as coumarin 314 and tetraphenylporphyrin, where controlled dye release can be readily achieved upon increasing solvent polarity or temperature.³⁰ A fluorescent gel was further obtained from bis-calix[4]arene **12** appended with a pyrene fluorophore upon reaction with CO₂, which may act as a vehicle for energy migration.³¹ Two xerogels were obtained from different solutions, one is benzene, and the other is 95 : 5 benzene–nitrobenzene. Dramatically, they exhibit distinct photophysical behaviors,



Fig. 8 Chemical structure of 13 and cartoon illustration of formation of unimolecular capsules and bis-heterodimers upon addition of 1.

the xerogel from benzene is strongly fluorescent, whereas the xerogel from 95 : 5 benzene–nitrobenzene shows no emission of pyrene fluorescence. This is owing to the photo-induced electron transfer from pyrene to nitrobenzene. These observations show pronounced potential in the design of switchable light harvesting materials.

Assuming a different linking manner, two tetra-urea calix[4]arene units were covalently connected at their upper rims, which can also lead to intermolecular polymerization. This depends absolutely on the flexibility of the linking spacers. Rebek's group synthesized a bis-(calix[4]arene tetraurea) 13 in which two calix[4]arene units are connected by a flexible spacer at their upper rims. 13 forms a discrete assembly, called "unimolecular capsule", by intramolecular dimerization.³² The exclusive formation of bis-heterodimers was further found for 13 upon addition of a double amount of tetra-urea calix[4]arene 1 (Fig. 8). This observation reveals that the upper-rim bridged species can possibly form not only an intramolecular but also an intermolecular assembly. Toward this goal, the group of Böhmer prepared a series of bis-(calix[4]arene tetraureas) 14 in which two calix[4]arene units are connected by rigid spacers between their urea groups at their upper rims.³³ The rigid spacer groups entirely prevent the intramolecular dimerization of 14, and therefore, their self-assembly can merely result in supramolecular polymers (Fig. 9). Compared to the aforementioned polycaps in which calix[4]arene units are linked at their lower rims, the polycaps from upper-rim bridged bis-calix[4]arenes 14 are more restricted in conformational freedom.

3. Supramolecular polymers with calixarene scaffolds

As compared to other macrocyclic hosts such as crown ethers, cyclodextrins, and cucurbiturils, showing desired inclusion properties with their native unsubstituted cavities, calixarenes often require an additional chemical modification of their cavities to give similar results. More frequently, calixarenes serve as fundamental scaffolds in the construction of podandlike receptors where their cavities always remain unexploited, benefiting from the facile modification of their lower-, upper-rims,



Fig. 9 (a) Chemical structures of the upper-rim linked bis-(calix[4]arene tetraureas)s 14; (b) schematic illustration of intermolecular polymerization of 14 *via* hydrogen bonding.

as well as bridges. There are also some examples of supramolecular polymers containing calixarene frameworks, where subunits are held together by other non-covalent interactions, but the driving forces are not offered by calixarene cavities.

In 1999, the group of Reinhoudt reported the intermolecular polymerization via cyclodextrin-based host-guest interactions, where the calix[4]arene acts as a scaffold that covalently links β-cyclodextrin and guest substituents together.³⁴ They grafted both a β -cyclodextrin and a fluorophore on the upper rim of the calix[4]arene (distal location), giving two β-cyclodextrincalix[4]arene conjugates bearing the dansyl (15) and naphthyl (16) chromophores, respectively (Fig. 10).³⁵ The calix[4]arene serves as a scaffold to not only orient cyclodextrin and fluorophore for intra- or intermolecular inclusion but also enlarge the hydrophobic surface for binding analytes in aqueous surroundings. Both 15 and 16 are of amphiphilic nature, cyclodextrin being the hydrophilic part and calixarene being the hydrophobic part, but their assembly behaviors are definitely distinguishable. 15 forms vesicles both in the absence and in the presence of the adamantane guest, while 16 forms fibers, which change into vesicles upon guest addition. 15 was proven to be an independent amphiphile with the dansyl group intramolecularly included in the cyclodextrin's cavity, and therefore, the vesicular aggregate is composed of an assembly of individual subunits, where the driving force is the intrinsic amphiphilic nature of 15. Since the self-inclusion of the dansyl group into the cyclodextrin cavity is very strong that it cannot



Fig. 10 Structural illustration of β -cyclodextrin-calix[4]arene conjugates 15 and 16, resorcinarene derivative 22 and calix[4]arene derivative 23.

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be competed by the adamantane guest, **15** appears to be insensitive to the guest addition. **16** amphiphiles are interconnected by inclusion of a naphthyl group of a molecule into the cyclodextrin cavity of an adjacent one. The fiber-like structure results therefore from the molecular threading of non-covalently polymerized molecules of **16**, besides the effort of amphiphilic aggregation. The addition of the adamantane guest displaces the naphthyl group from the cyclodextrin cavity, and then, the complex of **16** with guest acts as an independent amphiphile too, giving vesicular structure similar to **15**. The assembly of **16** is intriguing in that two complementary forces, amphiphilicity and intermolecular host–guest complexation, are concurrently involved.

Liu's group synthesized two lower-rim naphthalene-grafted calixarene derivatives 17 and 18, which act as tailored scaffolds to form supramolecular polymers with organo-selenium bridged bis(β -cyclodextrins) via iterative host-guest inclusion complexation (Fig. 11).^{36,37} The naphthalene substituent is promising as an ideal guest to be included into the cavity of β -cyclodextrin, which was validated by the 2D NOESY spectrum that the naphthalene ring is longitudinally included into the cavity from the secondary side of β-cyclodextrin. Herein, calix[4]arene derivatives with naphthyls 17 and 18 are ditopic guests, and bridged bis(β -cyclodextrins) are ditopic hosts, and thereby two binding modes can be assumed: (1) simple 1 : 1 complexation in which two naphthyls in one 17 (or 18) subunit insert simultaneously into two cavities in one bridged bis(β -cyclodextrins) subunit; (2) alternating *n*:*n* polymerization in which two naphthyls in one 17 (or 18) subunit insert respectively into cavities in different bridged bis(β-cyclodextrins) subunits. The former is reasonably excluded by examination of the CPK models, making the operation of the stoichiometric 1:1 inclusion complex difficult. The assembled morphology was proved as a linear polymer by STM (scanning tunneling microscopy) and TEM (transmission electron microscopy) images. More interestingly, the authors examined whether the molecular recognition can control the linear aggregation compactness. There are α -naphthyl and β -naphthyl substituents in 17 and 18, respectively. Fluorescence titrations show that $bis(\beta$ -cyclodextrins) offer stronger binding affinity to 18 than 17. Examinations with CPK models also validate that β -substituted naphthalene is embedded deeply into the cavity of β -cyclodextrin in the longitudinal direction, while α -substituted naphthalene only shallowly penetrates into the cavity. As a result, the different binding behaviors of $bis(\beta$ -cyclodextrins)



Fig. 11 (a) Chemical structures of naphthyl-modified calix[4]arenes 17 and 18; (b) schematic illustration of formation of a supramolecular polymer from 17 (or 18) and organo-selenium bridged bis(β -cyclodextrins).



Fig. 12 Supramolecular linear polymer formed by azo-modified calix[4]arene 19 and metallo-bridged bis(β -cyclodextrins), showing selective binding for Ca²⁺.

with two calix[4]arene derivatives lead to two different density linear aggregations.

The assembly of polymeric supramolecules is a powerful alternative to prepare the functional materials that display the unexpected properties, such as the specific molecules/ions selectivity. Based on the same building strategy above, Liu et al. further fabricated a water-soluble metallocapped polyrotaxane by the inclusion complexation of azo-modified calix[4]arene (19) with metallo-bridged bis(β-cyclodextrins) (Fig. 12).³⁸ It is noted that the metallo-capped polyrotaxane possesses multiple chelating units like the salen derivatives, and hence it could further selectively bind guest ions, showing a high affinity ($\lg K_S = 4.00$) for Ca^{2+} and an exciting Ca^{2+}/K^+ selectivity up to 218. In the complexation with the metal ions, β-cyclodextrins fix the geometrical disposition of azo-calixarene 19 in the polyrotaxane, making 19 more preorganized to coordinate metal ions. Consequently, the dimensions of the metal ions, rather than their charge density, become the main factor in determining the binding ability of the polyrotaxane to a series of metal ions.

Besides the examples mentioned above where calixarenes serve as scaffolds offering interaction sites for cyclodextrin cavities, there are also some occasional reports in which calixarenes act as fundamental scaffolds, and other noncovalent interactions, hydrogen bonding and electrostatic, are engaged in supramolecular polymerization. The Reinhoudt group prepared the calix[4]arene dimelamine **20** and calix[4]arene dicyanurate **21**, where melamine and cyanurate are complementary hydrogen-bonding pairs that can form rosette-like nanostructures. The "nonmatching" assembly of **20** with **21** leads to the formation of infinite rodlike polymeric nanostructures $[20_3 \cdot 21_3]_n$ (Fig. 13), which were characterized by tapping-mode scanning force microscopy and ¹H NMR spectroscopy. The solubility of the assembly $[20_3 \cdot 21_3]_n$ is obviously distinguishable from that of disk-like $20_3 \cdot (5,5\text{-diethylbarbituric acid})_6$, which virtually excludes the formation of "closed" assembly $20_3 \cdot 21_3$, and only the isomeric "open" form, with the top complementary to the bottom, is possible.



Fig. 13 Schematic representation of chemical structures of 20 and 21 and the hydrogen-bond directed polymerization to rod-like nano-structures $[20_3 \cdot 21_3]_{n}$.

Assembly $[20_3 \cdot 21_3]_n$ has a hydrophobic outer shell and a polar core. The hydrogen-bonding interactions between melamines and cyanurates compose the polar core, and therefore, the nature of the microscopy substrate (graphite or mica) does not prevent the hydrogen-bonded polymerization. Ziganshina *et al.* designed a resorcinarene derivative 22 with sodium sulfonato-ethylene groups on the lower rim and aminoalkylated moieties on the upper rim (Fig. 10), and studied its ability to self-assemble in aqueous media *via* the head-to-tail electrostatic interaction.³⁹ The assembly of 22 is not only pH-dependent but also guest-controllable. Another example is that reported by Casnati *et al.* in which a self-assembled polymer formed upon reaction of the upper rim of 1,3-diaminocalix[4]arene 23 (Fig. 10) with CO₂ is held together by ammonium–carbamate salt bridges.⁴⁰

4. Supramolecular polymers directed by calixarene-based host-guest interactions

Supramolecular polymerization triggered directly by molecular recognition of calixarene cavities with model guests was reported by Parisi and co-workers in 2003.⁴¹ They prepared a series of calixarene-based supramolecular polymers, utilizing the tight host–guest binding affinity between *p-tert*-butylcalix[5]arene derivatives and unbranched primary alkylammonium ions (involving a concerted set of weak interactions, such as N–H···O, C–H···π, cation···π), discovered by Pappalardo and co-workers.^{42,43} Two kinds of supramolecular polymers were respectively achieved in their works: one is the AB type *via* iterative intermolecular inclusion of self-complementary heteroditopic monomers; the other is the AA/BB type *via* iterative intermolecular inclusion between complementary homoditopic host and guest monomers.

In the quest for supramolecular AA/BB-type polymers,^{41,44} they synthesized homoditopic bis-calix[5]arenes *p*-, *m*-, and *o*-24 connected at their lower rims by a rigid α, α' -dixylyl spacer in a centrosymmetric divergent arrangement (Fig. 14a). The two tail-to-tail cavities in 24 are desired binding receptors to primary ammonium cations, and thereby, homoditopic α, ω -alkanediyldiammonium dipicrate salts C_n.2Pic (*n* = 8–12) were employed as connecting guests. The complementary host–guest pairs show a remarkable tendency to spontaneously and reversibly form supramolecular assemblies, whose composition and dynamics strongly depend on the length of the connector,

the geometry of the spacer, as well as the concentration and/or molar ratios of the host and the guest. A total of 4 types of assemblies were monitored when mixing 24 with C_n 2Pic. The formation of cyclic $[24 \supset C_n \subset 24 \supset C_n \subset]$ species was reasonably ruled out by molecular modeling and inspection of CPK models. Self-assembly of cyclic species would require a spacer longer than a xylyl moiety, and/or a guest much longer than a dodecanedivldiammonium dication. They found that assemblies of types III and IV cannot be obtained from C₈ and C₉ guests. The dication guests of C₈ and C₉ are not long enough to span the cavities of two host molecules. For C_{10-12} guests, the host-guest complexation with 24 generates a variety of assembled species as a result of single to multiple intermolecular inclusion events, which can be reversibly manipulated by basic external inputs benefiting from the dynamic feature of selfassembly. The cyclic and reversible process is shown in Fig. 14b. Addition of a defect (≤ 0.5 equiv.) of $C_n \cdot 2Pic$ ($n \geq 10$) to a solution of 24 (10-50 mM) affords almost exclusively monocapsular assemblies (type III). Upon further addition of guest (1:1 host-guest ratio), the monocapsular assemblies transfer to the oligomeric or polymeric species (type IV). Dilution of solutions leads to the formation of 1 : 1 endo-cavity complexes (type I). Addition of excess amounts of the guest to type I solutions yields bis-endo-cavity assemblies (type II). In turn, addition of excess amounts of the host to type II solutions regenerates type III assemblies.

In 2006, Takeoka et al. found the supramolecular oligomerization of 25-(4-pyridiniumbutoxy)-26.27.28-trihydroxycalix[4]arene bromide. This compound combines both a host unit and a guest unit in one molecule. The calix[4]arene cavity acts as a receptor for the grafted pyridinium moiety of the neighboring compound *via* weak cation $\cdot \cdot \pi$ interaction, and then, an oligomer was observed in concentrated solutions.⁴⁵ In their work, the authors proposed an initial host-guest strategy for supramolecular AB-type polymers based on molecular recognition of calixarenes, however, the cation $\cdot \cdot \cdot \pi$ interaction between calix[4]arene and pyridinium is not strong enough to achieve polymerization. Following this work, Cohen and co-workers synthesized a calix[5]arene derivative 25 bearing a long-chain alkylamino pendant group on the lower rim.⁴⁶ It is known that the calix[5]arene binds tightly the alkylammonium cation but not the neutral alkylamino group. Consequently, 25, upon protonation, would undergo AB-type oligomerization/polymerization



Fig. 14 (a) Chemical structures of the bis-calix[5]arenes hosts 24 and alkanediyldiammonium cation guests C_n . (b) Schematic illustration of the cyclic and reversible processes featuring the self-assembly dynamics of modular homoditopic 24 and C_n ($n \ge 10$).



Fig. 15 Chemical structures of the self-complementary heteroditopic bis-calix[5]arene hosts 26 (a) and 27 (b), and their acid/base-controlled self-assembly processes *via* iterative intermolecular head-to-tail inclusion.

via iterative intermolecular head-to-tail inclusion processes (Fig. 15a). The self-assembly of 25 can not only be reversibly switched on/off by means of simple acid-base treatment but also controlled in size by monomer's concentration and counterion species. By treating with different acids, including HCl, HBr, and picric acid, the authors found that the degree of polymerization increases obviously in the order of HCl, HBr, and picric acid. This phenomenon is owing to the dependence of stability constants between neutral hosts and ionic guests on the extent of ion-pairing in low polarity media. The looser the ion-pairing interactions between the ammonium monomer and its counterion, the higher the degree of polymerization observed. Importantly, the alternative process of endo-cavity intramolecular inclusion of the dodecylammonium moiety, either via the upper or the lower rim, has been definitely ruled out by not only inspection of CPK models but also chemical shift and diffusion measurements.

As a natural evolution of their ongoing work in this field, Gattuso and co-workers further fabricated a supramolecular AB-type polymer from a highly lipophilic aminododecyloxy-calix[5]arene monomer precursor 26.⁴⁷ Interestingly, chainlength regulation was feasibly achieved by employing orthogonal chain stoppers capable of selectively interacting with a given moiety of the AB-type monomer/polymer. Addition of either a competitive receptor, a polymerization-inert calix[5]arene 'cap', or a competitive guest, a polymerization-inert *n*-butylammonium ion 'plug', resulted in a progressive decrease in the number-average degree of polymerization. In fact, chain-length control is a crucial factor in supramolecular polymerization, and their work opens an alternative way for greater control over the macroscopic properties of the supramolecular polymeric materials.

In the aforementioned examples, the growth of such ionizable polymers is anion-dependent. With regard to the drawback represented by ion-pairing effects, Gattuso and co-workers demonstrated an elegant strategy to enhance the degree of polymerization by synthesizing heteroditopic AB-type monomers that will also incorporate an auxiliary counterion binding site in their structure.⁴⁸ Such an additional structural feature would facilitate salt dissociation (by overriding ion-pair interactions) and ultimately make polymer formation more efficient. The desired calix[5]arene derivative **27** was prepared, in which an ancillary anion-binding site (namely a ureido moiety) was

additionally grafted on the upper rim of the calix[5]arene (Fig. 15b). NMR data as well as DLS (dynamic light scattering) measurements adequately indicate that the degree of polymerization of **27** is markedly enhanced over that of **25**. Moreover, the supramolecular polymer from **27** is thermally stable over a wide temperature range (-60 to 100 °C). The lower the temperature, the higher the degree of supramolecular polymerization. More significantly, addition of a chiral carboxylic acid to the monomer precursor **27** is envisaged as a smart way to generate chiral supramolecular polymers with a significant "chiral memory" effect. However, as a control experiment, simple inclusion species between ureido-calix[5]arene and alkylammonium does not show such intriguing "chiral memory" capability.

Coincidentally, Dalcanale's group reported the AB-type and AA/BB-type supramolecular polymerization directed by the molecular recognition of tetraphosphonate cavitands with methylpyridinium guests in recent works.^{49,50} The heteroditopic AB (28) and homoditopic AA (29) tetraphosphonate cavitands were prepared from the resorcin[4]arene macrocycle. The inwardfacing P=O groups offer not only a multiple ion-dipole interaction to a positively charged guest but also hydrogen bonding. They further introduced four methyl groups in the apical positions to deepen the cavity and to strengthen C-H \cdots π interactions. Consequently, this kind of tetraphosphonate cavitand is expected to show high binding affinity to organic cations.⁵¹ The iterative self-association mode of self-complementary 28 leads to the polymer formation. In comparison with 28, the structurally related tetrathiophosphonate cavitand is complexation-inefficient because the P=O/P=S exchange diminishes completely the main driving force of cation-dipole interaction, and then, the degree of polymerization of 28 can be subtly tuned by addition of the tetrathiophosphonate analogue as a chain stopper. Adding 5,10,15,20-tetrakis(1-methyl-4-pyridinio)porphyrin tetra(p-toluene sulfonate) would not only enhance the weight-average molecular weight of the 28-based polymer, but also transform its morphology from linear to star-branched form with tetracationic porphyrin as a template and nucleation unit (Fig. 16). More importantly, the reversible control of assembly-disassembly of 28 can be achieved by introducing a competitive guest, N-butylmethylammonium iodide. The tetraphosphonate cavitand binds *N*-butylmethylammonium much stronger than methylpyridinium,



Fig. 16 Chemical structures of 28 and 29 and schematic illustration of AB-type linear and star-branched polymers formed by 28, and an AA/BB-type linear polymer formed by 29.

and the polymer is entirely dissipated when adding competitive *N*-butylmethylammonium at close to the stoichiometric ratio. Inversely, the original polymer regenerates upon addition of 1,8-diazobicyclo[5.4.0]undec-7-ene, where 1,8-diazobicyclo-[5.4.0]undec-7-ene breaks the complexation of the cavitand with *N*-butylmethylammonium by deprotonating the guest.

In an alternative way, the same authors fabricated one kind of supramolecular AA/BB-type polymer by homoditopic hosts (AA) with two tetraphosphonate cavitands covalently attached at their lower rim interacting with homoditopic guests (BB), in which flexible ethylene oxide chains of different length are functionalized with two N-methylpyridinium end groups. Three ditopic hosts 29a-c and three ditopic methylpyridinium guests G1-3 with different spacers were synthesized to evaluate the influence of spacer lengths and flexibilities on the polymerization process (Fig. 16). Isothermal titration calorimetry (ITC) measurements were performed for the accurate thermodynamic description of the binding events leading to polymerization. The solvent-dependent binding affinity was clarified from the viewpoint of the thermodynamic origin. The complexation stability of 29b with G3 achieves a gain of two orders of magnitude on going from methanol to dichloromethane, and the gain is totally enthalpic in origin. Two factors contribute to the more favorable enthalpy gain in dichloromethane: (1) the limited solvation exerted by dichloromethane on the methylpyridinium moieties results in a preference for its inclusion into the cavitand; (2) the cavitand shows considerable affinity to methanol, which competes with the guest complexation. Although the longer and flexible spacer is thermodynamically favorable for supramolecular assembly, the conformational mobility of the spacer allows for the formation of a cyclic oligomer, but not the desired linear polymer. At low concentrations, $G3 \subset 29b$ forms cyclic oligomers with constant size $((H+G)_1 \text{ and } (H+G)_2)$. In the intermediate regime, the cyclic adducts transform into open oligomers gradually. At high concentrations, $G3 \subset 29b$ forms linear polymers definitely. The conversion of cyclic oligomeric species to linear polymeric chains is not only concentration-dependent but also temperature-dependent,

which is reasonably accepted when taking the thermodynamics into account.

Based on the strong host-guest interaction between covalently linked double-calix[5]arenes and C₆₀,⁵² Haino et al. reported the supramolecular polymeric network and cross-linking by the molecular-recognition-directed self-assembly (Fig. 17).53,54 Toward this goal, homoditopic calix[5]arene host 30 was synthesized. When a dumbbell-shaped C₆₀ guest was employed, the desired host-guest interaction between 30 and dumbbellshaped C₆₀ leads to formation of a supramolecular polymer. When a C_{60} -tagged polyphenylacetylene (poly- C_{60}) was employed as a guest, the host-guest recognition leads to remarkably stable supramolecular cross-linking. Using the nonlinear regression analysis of fluorescence titration, they obtained the association constants (K_1 and K_2) of **30** with C₆₀ in toluene according to a 2:1 model. Both association constants are in the magnitude of $10^4 \,\mathrm{M}^{-1}$, which is strong enough to joint the host and guest monomers together effectively. Diffusion NMR, size-exclusion chromatography, SEM and AFM (atomic force microscopy) were further performed to identify the size distribution and morphology of these polymeric materials. Free poly-C₆₀ was observed as nanoparticle-like agglomerates, while the complexation of poly-C₆₀ with 30 shows formation of the well-oriented fibrils, indicating that supramolecular cross-linking leads to highly ordered nanostructures. It should be mentioned that the complexation stability between calix[5]arene and C₆₀ is solvent-dependent, and therefore, both the supramolecular polymerization and cross-linkage are solvent-dependent. As a result, these polymeric materials can be regulated by the solvent system.

p-Sulfonatocalixarenes, one robust family of water-soluble calixarene derivatives, show strong binding affinity and high molecular selectivity towards organic cations, driven by the synergistic effect of additional anchoring points donated by sulfonate groups together with the intrinsic cavities.⁵⁵ Inspired by the desired inclusion property of *p*-sulfonatocalixarenes, Liu and co-workers designed a series of water-soluble calixarene-based supramolecular polymers using the "cleanest"





Fig. 17 Chemical structure of homoditopic calix[5]arene 30 and cartoon illustration of a supramolecular linear polymer formed by 30 and crosslinking upon complexation with dumbbell-shaped C_{60} and poly- C_{60} guests.

solvent (that is, water). A minimum of two interacting sites is needed to form supramolecular polymers from two complementary monomers (host and guest), and therefore, the homoditopic bis(p-sulfonatocalix[5]arene) **31** and bis(p-sulfonatocalix[4]arene) 32 bridged at their lower rims were prepared, where the divergent tail-to-tail arrangement of two cavities favors iterative intermolecular inclusion that leads to formation of supramolecular polymers. Two highly complex supramolecular polymers with 2D netlike and 1D linear topological structures were constructed by employing tetracationic and dicationic porphyrins as model guests, respectively, upon complexation with 31 (Fig. 18).⁵⁶ Corresponding to the molecular design, the assembly morphologies are well manipulated by the inherent binding sites of the molecular building blocks through strong host-guest interactions. Upon determining the binding stoichiometries between calixarene host and porphyrin guest by the Job method, they found that the complexation exceeds the conventional 1: 1 (one cavity to one binding site) molar ratio, and dramatically, 31 forms 2:5 and 1:5 complexes with tetracationic and dicationic porphyrins. It is noticed that the host-guest stoichiometries are significantly satisfied to charge matching. The number of negative sulfonate groups on the calixarenes is equal to the number of the positive charges on the porphyrins. Besides the precursory host-guest interactions between calixarene and pyridinium moiety, charge interactions also play a pivotal role in self-assembly. Porphyrins are fascinating antenna molecules possessing solar light-harvesting capability, whereas calixarenes are efficient electron donors

on account of their electron-rich cavities. In these supramolecular systems, calixarene and porphyrin act not only as the interacting tectons but also as the effective electron donor-acceptor pairs,



Fig. 18 Schematic representation of the construction of a supramolecular 2D network and 1D linear polymers based on the complexation of the ditopic bis(*p*-sulfonatocalix[5]arenes) host 31 with tetracationic and dicationic porphyrin guests.

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and an unambiguous photo-induced electron transfer is observed, which was validated by (time-resolved) fluorescence and transient absorption spectroscopy, as well as the electrochemical cyclic voltammetry (CV) method. Subsequent to Liu's work, Micali and co-workers reported an alternative method in which the complexation of a water-soluble octacationic bis(calix[4]arene) with a tetraanionic porphyrin generates 2D or 3D supramolecular multiporphyrin assemblies.⁵⁷ The assembled structures are hierarchically controlled by the host–guest molar ratio in a stepwise fashion, where the pivotal 4 : 5 (host–guest) complex with a cruciform structure is the key fork-point for the subsequent higher-order assembly.

Liu et al. further reported the construction of supramolecular polymers based on bis(p-sulfonatocalix[4]arene) 32 and homoditopic bis(viologens) guests.^{58,59} The iterative complexation of 32 with ethylene-bridged bis(viologens) (EBV⁴⁺) generates a linear polymer, whereas the iterative complexation of 32 with hexamethylene-bridged bis(viologens) (HBV^{4+}) generates merely a cyclic oligomer (Fig. 19). The topological difference between EBV^{4+} and HBV^{4+} is ascribed to the longer flexible spacer that favors the formation of a cyclic oligomer, rather than a linear polymer. Interestingly, a ternary linear polymer was obtained when cucurbit[n]uril (CB[n]) (n = 7, 8) was further involved in the calixarene-viologen binary system. As can be seen from Fig. 19, HBV⁴⁺ possesses a flexible aliphatic spacer that can be strongly captured by CB[n]. With CB[n] threading on the spacer of HBV⁴⁺, the rigidity of the HBV⁴⁺ \subset CB[*n*] complex increases much more than that of free HBV⁴⁺. It has been wellestablished that building blocks with more rigid spacer groups favor the formation of a linear polymer, not a cyclic oligomer.60 Consequently, in this design, one can control the assembly morphology by not only adjusting the length of the spacer, but also introducing a third component for additional complexation.

The most exciting feature of the supramolecular species formed from **32** and bis(viologens) is its responsiveness to the electrochemical stimulus. Viologens are one class of important redox couples, and exist in dicationic, radical cationic, or neutral form *via* a reversible redox process. The complexation stability of the *p*-sulfonatocalixarene is dramatically sensitive to the redox process of viologen, decreasing in magnitude from dicationic to radical cationic, to neutral form, which means that assembly–disassembly of the polymer can be manipulated by

electrochemical switching and redox control.⁶¹ CV experiments show that the assembly of 32 with EBV^{4+} is dissipated upon consecutive two-step reduction processes of EBV⁴⁺ to its neutral form, but not upon one-step reduction to its radical cationic form. This means that viologen cannot be released from the cavity of calixarenes until it is reduced to the waterinsoluble neutral form, and therefore, reversible control of the assembly-disassembly processes seems to be difficult for practical operation. As a subtle evolution, the ternary polymer from 32, HBV⁴⁺ and CB[8] disassembles into free 32 and molecular loop $HBV^{2+} \subset CB[8]$ once HBV^{4+} is reduced to its radical cationic form HBV^{2+} ([2]pseudorotaxane $HBV^{4+} \subset CB[8]$ transforms into molecular loop $HBV^{2+} \subset CB[8]$ upon one-step reduction).⁶² The reversible assembly-disassembly processes were conveniently examined by UV-Vis and DLS measurements. In the ternary system, CB[8] can not only modulate the topology of supramolecular assemblies, but also make their switching between assembly and disassembly more practically operational.

Based on the same homoditopic host 32, Tian et al. reported an electrochemical and pH dual stimuli-responsive supramolecular polymer by employing a viologen and dimethylamino unit containing a connector decorated with a fluorophore as a guest.⁶³ There are two diverse binding sites on the guest, the dimethylamino portion with pH-sensitivity and the viologen portion with redoxsensitivity, and thereby, the corresponding system can be reversibly controlled via two pathways. The polymer is formed when two complexation processes occur simultaneously, that is, the viologen moiety is included into one cavity of 32, and, the protonated dimethylamino moiety is in the other cavity (Fig. 20). For the pH route, deprotonation would result in release of the dimethylamino moiety from the calixarene cavity, and the polymer disassembles into a viologen ⊂ calixarene complex. For the redox route, reduction would result in release of the neutral form of viologen from the calixarene cavity, and the polymer disassembles into a dimethylamino calixarene complex.

In the aforementioned examples, it is the host–guest interaction offered by calixarenes that contributes directly to the regular extension of polymeric assemblies, either in the AB-type or in the AA/BB type. Liu and co-workers outlined an alternative novel way to obtain supramolecular polymers *via* calixareneinduced aggregation of perylene bisimides (Fig. 21).⁶⁴ Benefiting from that, *p*-sulfonatocalixarenes can induce the aggregation of



Fig. 19 Chemical structures of ditopic bis(*p*-sulfonatocalix[5]arenes) **32**, **CB**[**8**], **EBV**⁴⁺ and **HBV**⁴⁺, and cartoon illustration of a supramolecular binary polymer, a cyclic oligomer and a ternary polymer formed by **32** upon complexation with **EBV**⁴⁺, **HBV**⁴⁺ and **HBV**⁴⁺ \subset **CB**[**8**] [2]pseudorotaxane.



Fig. 20 Structural illustration of the reversible assembly–disassembly processes of a supramolecular polymer based on **32** and heteroditopic guest induced by the respective stimuli of protonation/deprotonation and electrochemical redox.



Fig. 21 Schematic illustration of the complex-induced aggregation of **BPTA-PBI** by *p*-sulfonatocalix[5]arene.

certain organic dye molecules effectively, exceeding the conventional 1 : 1 host-guest binding stoichiometry.⁵⁶ Free discotic **BPTA-PBI** molecules form merely oligomers *via* $\pi \cdots \pi$ stacking interactions between perylene backbones. Upon addition of *p*-sulfonatocalix[*n*]arenes (n = 4, 5), both host-guest and electrostatic interactions take place, boosting the $\pi \cdots \pi$ stacking interactions markedly. The synergetic contribution of these driving forces endow perylene backbones with better aggregation stability, shorter aggregation distance, as well as higher-order degree of aggregation, and leads ultimately to the hierarchically well-defined polymerization. The degree of order of the stacking molecules plays a vital role



Fig. 22 Schematic illustration of the complex-induced aggregation of asymmetric viologen by *p*-sulfonatocalix[4]arene to generate the supramolecular binary vesicle with multistimuli-responsiveness, upon heating, addition of cyclodextrin, and reduction.



Fig. 23 Histogram showing the number of papers on the three types of calixarene-based supramolecular polymers in recent 15 years, 'polycap' represents calixarene-based supramolecular polymeric capsules by virtue of multiple-hydrogen bonds as well as guest encapsulation, 'scaffold' represents supramolecular polymers composed of calixarene scaffolds with the cavities unexploited, 'cavity' represents supramolecular polymerization directed by the host–guest interactions offered by calixarene cavities.

in the charge-carrier mobility, and hence the performance of optoelectronic devices.

Recently, "supramolecular amphiphiles", which are generated by non-covalent synthesis, have emerged as a smart strategy to construct supramolecular nanoarchitectures. Liu and co-workers constructed a new kind of supramolecular binary vesicles based on the unique complexation-induced aggregation capability of *p*-sulfonatocalix[*n*]arenes.^{65,66} Benefiting from the intrinsic advantages of supramolecules, the obtained vesicles show reversibility to external surroundings: the vesicle from *p*-sulfonatocalix[5]arene and 1-pyrenemethylaminium is thermo-responsive, and more interestingly, the vesicle from *p*-sulfonatocalix[4]arene and asymmetric viologen is multistimuliresponsive (Fig. 22). Reduction of asymmetric viologen to the radical cationic state can adjust the vesicle to smaller species



Fig. 24 Cartoon illustration of crown ether, cyclodextrin and calixarene macrocycles, as well as the supramolecular AB-type and AA/BB-type polymers based on molecular recognition of these three macrocycles.

and *vice versa*. Reduction to the neutral form, increasing temperature, and inclusion of cyclodextrin can all lead to the vesicle disruption completely. All these external stimuli can act as an effective switch that triggers the efficient release of the entrapped substrates. Cell experiments were further performed to explore its drug delivery application, showing that the loading of doxorubicin by a vesicle does not affect the therapeutic effect of doxorubicin in normal cells is reduced. Such smart self-assembled modeling materials promise substantial applications in the fields of controlled release and drug delivery.

5. Conclusion and outlook

Among the three kinds of calixarene-based supramolecular polymers, the supramolecular polymer based on molecular recognition of calixarene cavity has received considerable attention in merely recent 5 years (Fig. 23). However, it remains an immature project to build supramolecular polymers based on calixarenes, compared to the other macrocycles, such as crown ethers and cyclodextrins. This is because of the limited binding capability of intrinsic cavity of mother calixarene. In this regard, one can design the desired calixarene derivatives suitable for supramolecular polymerization via simple covalent syntheses. Calixarenes are facilely modified on their upper rim, lower rim, as well as bridging linkage, so they are described as 'macrocycles with (almost) unlimited possibilities'.67 Importantly, the structural characteristics of calixarene cavity endow calixarene with some intriguing advantages in construction of supramolecular polymers (Fig. 24). For crown ether and cyclodextrin macrocycles, there are two pathways by which the guest enters into their cavities. Consequently, there is a competitive balance between intramolecular self-encapsulation and iterative intermolecular polymerization in the case of a self-complementary heteroditopic AB-type monomer, and so it is between intramolecular 1:1 complexation and iterative intermolecular polymerization in the case of a homoditopic AA-type host binding BB-type guest. Whereas in the case of calixarenes, there is no such competition since the model guest enters regioselectively into its cavity from the upper rim. More excitingly, such calixarene-based supramolecular assemblies are mildly responsive to external stimuli, such as temperature, concentration, polarity, acid-base, competitive components, electrochemistry, and thus show feasible functions including self-healing, entrapment, storage, controlled release, sensing, photoelectricity, informational encodement, and chiral memory. Some alternative stimuli-responsive (enzyme- and photo-) supramolecular polymers based on calixarenes are currently under our investigation. We therefore believe that the calixarene-based supramolecular polymerization is entering its adolescence, and will be much more prosperous and valuable in the near future.

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