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Macrocyclic catalysis mediated by water: opportunities and challenges

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Nanospaces within enzymes play a crucial role in chemical reactions in biological systems, garnering significant attention from supramolecular chemists. Inspired by the highly efficient catalysis of enzymes, artificial supramolecular hosts have been developed and widely employed in various reactions, paving the way for innovative and selective catalytic processes and offering new insights into enzymatic catalytic mechanisms. In supramolecular macrocycle systems, weak non-covalent interactions are exploited to enhance substrate solubility, increase local concentration, and stabilize the transition state, ultimately accelerating reaction rates and improving product selectivity. In this review, we will focus on the opportunities and challenges associated with the catalysis of chemical reactions by supramolecular macrocycles in the aqueous phase. Key issues to be discussed include limitations in molecular interaction efficiency in aqueous media, product inhibition, and the incompatibility of catalysts or conditions in "one-pot" reactions.

1. Introduction

In the complex chemical reactions of biological systems, enzymes play a crucial role due to their superior catalytic activity and precise substrate selectivity.[1] Enzymes possess highly active sites and multiple compartmentalized cavities, enabling them to efficiently capture substrates or reaction intermediates from bulk solution, while providing unique internal nanoenvironments for these components. These discrete and confined spaces enhance the effective local concentration of specific reaction species, facilitate their preorganization, stabilize transition states, and promote efficient mass transfer of substrates, intermediates, and products, ensuring reactions proceed with high selectivity and continuity.[2] To explore the highly efficient catalytic mechanisms of enzymes, an effective strategy involves initially constructing structurally simple systems with well-defined structure–activity relationships that mimic a single catalytic site of enzymes, and then gradually increase system complexity to understand the catalytic coupling mechanisms. For this purpose, various supramolecular macrocyclic host molecules have been developed as nanoreactors, including crown ethers,[3] cyclodextrins,[4] cucurbiturils,[5] calixarenes[6] and pillararenes.[7] Subsequently, strategies for the precise control of non-covalent interactions between multiple components—such as hydrogen bonds, van der Waals forces, the hydrophobic effect, electrostatic interactions, π–π interactions, cation–π interactions, and anion–π interactions—are used to construct highly ordered, self-assembled aggregates with desired structures and functions, making the development of such approaches a significant research area in supramolecular chemistry.[8,9] These aggregates are not only widely applied in fields such as chemical sensors, drug delivery, and separation but are also utilized in biomimetic studies of enzymatic catalytic coupling mechanisms.[10] The core strategy of supramolecular catalysis lies in leveraging the interactions between supramolecular hosts (such as cucurbiturils, cages, and capsules) and guests (*i.e.*, reactants or catalysts) to achieve precise control over chemical reactions. On the one hand, by designing and synthesizing supramolecular hosts with specific structures and functions, efficient recognition and capture of substrates, preorganization of reactants, and enhancement of local concentrations can be accomplished. On the other hand, supramolecular catalysis can accurately catalyze specific reaction pathways within complex reaction systems and stabilize particular transition states, thereby effectively lowering the activation energy and minimizing the generation of by-products, ultimately enhancing catalytic efficiency.[11,12]

Currently, artificial supramolecular hosts have been widely employed in a variety of reactions, with numerous examples reported of using well-defined nanospaces to catalyze new reactions and generate molecules that are challenging to obtain through traditional catalytic methods. To date, several reviews have explored the diversity of supramolecular assembly,[13,14] the size effects of nanospaces[15,16] and variations in specific system

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regulation strategies from multiple perspectives.[17,18] This review highlights representative studies from the past five years, elucidating how supramolecular chemists have addressed three key challenges in aqueous-phase macrocyclic catalysis: (1) limitations in molecular interaction efficiency in aqueous environments; (2) product inhibition; and (3) incompatibility of catalysts or conditions in "one-pot" reactions. For readers seeking a more comprehensive overview of the field and those interested in related topics, the aforementioned reviews are recommended.

2. Challenge 1: limitations in molecular interaction efficiency in aqueous medium

Aqueous catalytic reactions offer significant advantages, including environmental friendliness, mild reaction conditions, and ease of product separation, making them an important area of research.[19,20] However, the limited interaction efficiency of molecules in aqueous environments has constrained the development of this field. This limitation arises from three primary factors, each of which is addressed by various supramolecular strategies. First, substrates dispersed in solution must diffuse towards each other or to the catalyst surface before interaction can occur. The low concentration of reaction species due to their low solubility can significantly limit reaction efficiency. In some cases, the diffusion rate can be much slower than the reaction rate, making the overall process limited by diffusion rather than the chemical reaction itself, resulting in a diffusion-controlled process with low reaction efficiency.[21] Supramolecular hosts can act as phase transfer catalysts, effectively enhancing the local concentration of substrates and catalysts, facilitating a close association between these reaction species.[22] Second, the formation of solvation shells—due to hydrogen bonding and other weak interactions between reaction species and polar water—hinders molecular proximity and effective collisions between these reaction species, and also destabilizes intermediates. These issues can be solved by encapsulating the reaction species within the hydrophobic cavity of supramolecular hosts. Third, the relatively high degree of freedom of molecules in solution reduces the probability of effective collisions at the reaction site.[23–25] Encapsulating them within the confined cavity of supramolecular hosts restricts their free motion and facilitates their preorganization.

2.1 Size matching of hosts and guests

Addressing the challenge of limited water solubility of reaction species, macrocyclic hosts in aqueous solution selectively recognize substrates and encapsulate them within their internal cavities, essentially functioning as phase transfer catalysts, effectively enhancing substrate solubility[26] and increasing local concentrations.[27] The core principle is precise size matching between hosts and guests,[28] as quantified by the packing coefficient (PC), which is the ratio of guest(s) volume to macrocycle cavity volume. Rebek summarized that optimal binding between hosts and guests occurs when the PC is approximately 0.55.[29] Guests that are too small must occupy the cavity along with several "high-energy" water molecules, which cannot form optimized hydrogen bonds as effectively as those in bulk solution. On the other hand, guests that are too large cause deformation in both the guest and host due to strain, with both scenarios leading to an unstable encapsulation process. Reinhoudt *et al.* observed that substrates around a PC of 0.55 achieve optimal template reactions, with a PC of 0.58 resulting in 50% yield, whereas the yield for substrates with a PC of 0.74 is less than 5%.[30] Nau *et al.* conducted an in-depth investigation into the use of cucurbit[*n*]urils (CB[*n*]) with varying cavity sizes for catalyzing the Diels–Alder reaction (Fig. 1).[31] Cucurbit[5]uril (CB[5]) resulted in 3.5% conversion due to its inability to effectively encapsulate substrates. Cucurbit[6]uril (CB[6]) could just accommodate a single cyclopentadiene (CPD), thereby hindering its dimerization. Cucurbit[7]uril (CB[7]) tightly bound two substrates, forming a ternary complex with a PC of 0.63. As the Diels–Alder reaction progressed, the PC of the transition state decreased to 0.6, effectively alleviating the tight packing state and internal pressure, which increased the reaction rate by approximately five orders of magnitude. However, cucurbit[8]uril (CB[8]) did not provide sufficient confinement for the substrate (PC $\approx$ 0.41), causing the reaction to proceed in a loosely packed state. Additionally, the packing of the product, endo-dicyclopentadiene (DCPD), was not efficient (PC $\approx$ 0.38), leading to a lack of catalytic effect.

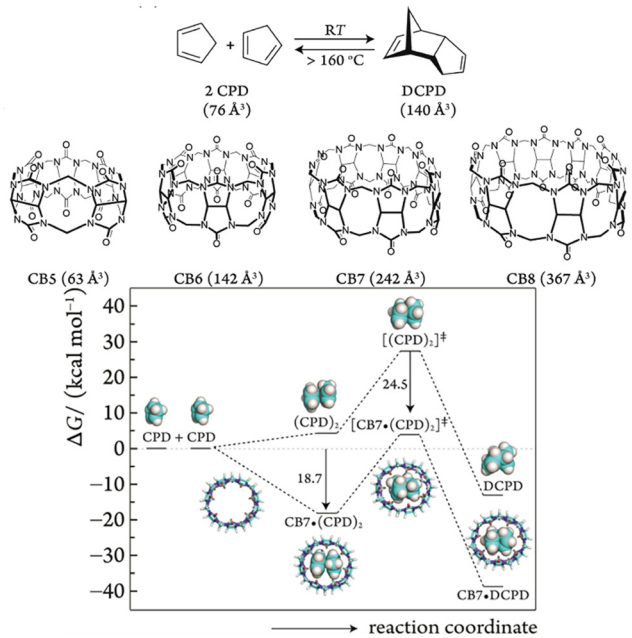

Fig. 1 Cucurbit[*n*]urils with varying cavity sizes used for catalyzing the Diels–Alder reaction. Adapted from ref. 31 with permission from ACS Publishing Group.

2.2 Activation of reaction components

In addition to the packing coefficient between the host and the guest, their geometric shapes and electronegativity, the structure and position of substituents, as well as the coexistence of ions and co-solvent all influence the host's ability to

encapsulate and desolvate guests, which in turn enhances substrate reactivity, activates catalysts, and stabilizes transition states as well as final products.[32–34]

2.2.1 Modulation of substrates' reactivity. By providing a hydrophobic cavity that protects substrates from the external solvent environment,[35] these hosts can fine-tune the thermal stability,[36,37] electrophilicity,[38] acidity/basicity,[39] and biological activity[40] of the substrates. Additionally, they modulate charge transfer[41] and electron transfer processes of substrates, thereby significantly influencing their reactivity.[42] Tiefenbacher *et al.* assembled a unique capsule I by utilizing six resorcin[4]arene units and eight water molecules through a hydrogen bond network, which catalyzed the formation of novel terpenoid skeletons (Fig. 2(a)).[43,44] In the absence of water molecules within the hydrogen bond network of the capsule, the terpene cyclization cannot be catalyzed (Fig. 2(b)). Scarso *et al.* found that the hydrogen bond network in the capsule was capable of activating water molecules within the cavity.[45] Yu *et al.* demonstrated that water molecules integrated into the hydrogen bond network acted as proton wires, precisely orienting and efficiently activating substrates through proton transfer.[46] Additionally, Tiefenbacher *et al.* discovered that the introduction of HCl as a cocatalyst promoted the protonation of substrates.[47] Furthermore, they noted that when a substrate entered and displaced a bulkier solvent previously occupying the capsule cavity, it experienced conformational restrictions near the portal of the capsule, thereby affecting the substrate reactivity.[48]

The binding mode[49] between the macrocycle and substrates as well as the arrangement of binding sites[50] can significantly influence substrate reactivity.[51] Sashuk *et al.* reported that the aldehyde groups of azo pyridinium aldehyde were encapsulated within the cavity of CB[7], while the azo moiety remained exposed to the solution and was subsequently attacked by hydrazine, leading to the formation of hydrazone.[52] Aliaga *et al.* found that the formation of a 1 : 1 host–guest complex between CB[7] and aromatic Schiff bases promoted hydrolysis, whereas the formation of a 2 : 1 host–guest complex resulted in an inhibitory effect.[53]

2.2.2 Catalyst activation. Supramolecular hosts can increase the local concentration of catalysts,[54] and protect catalysts from external contaminants to enhance their stability.[55] Moreover, the macrocyclic cavity can modulate the spatial arrangement of catalysts, reducing their random motion and ineffective collisions within the reaction system, thereby regulating catalyst activity.[56–58] Lercher *et al.* constructed a catalytically active capsule with hydronium ions as the catalyst, resulting in a two-order-of-magnitude increase in the reaction rate for the dehydration of cyclohexanol (Fig. 3).[59] In the absence and presence of the capsule, cyclohexanol underwent dehydration to form cyclohexene through E2 and E1 mechanisms, respectively, indicating that the capsule facilitated the shift from an E2 to an E1 mechanism. In the latter case, the capsule stabilized cyclohexanol, forming a metastable cyclohexyl carbocation intermediate. Furthermore, by introducing supramolecular recognition motifs around the active site of catalysts,[60–62] precise modulation of catalytic activity is achieved through interactions such as cation–macrocycle interactions, which further influence regio- and stereoselectivity in the reactions.[63–67]

The supramolecular host can fine-tune the protonation degree and electrophilicity of catalysts upon encapsulation into its hydrophobic cavity.[68–71] Eelkema *et al.* discovered that the encapsulation of organic catalysts such as aniline, 1,4-diazabicyclo[2.2.2]octane, and prolinol within CB[7] significantly reduced their catalytic activity, while enhancing the catalytic activity of nornicotine.[72] This difference was attributed to the fact that the former catalysts were completely isolated within the CB[7] cavity, whereas the aliphatic amine of

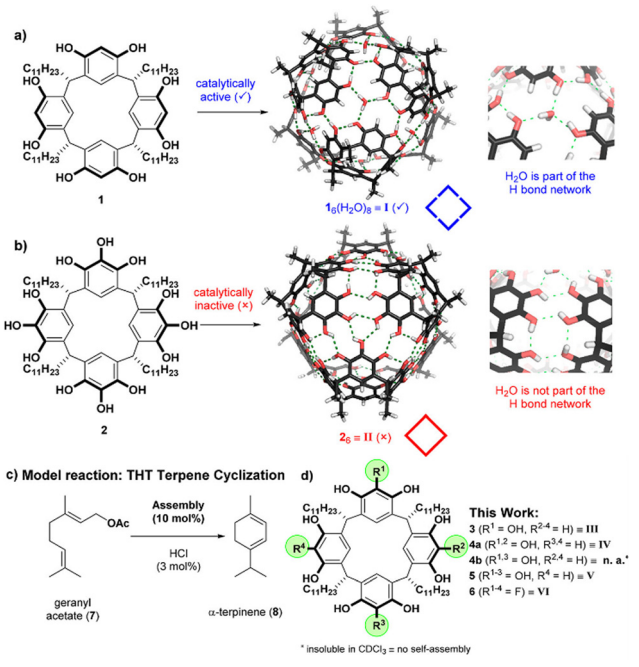

Fig. 2 Two examples of capsules featuring hydrogen-bond networks with (a) and without (b) water embedded, as well as the catalysis of the tail-to-head terpene cyclization (c) by a series of capsules (d). Adapted from ref. 47 with permission from ACS Publishing Group.

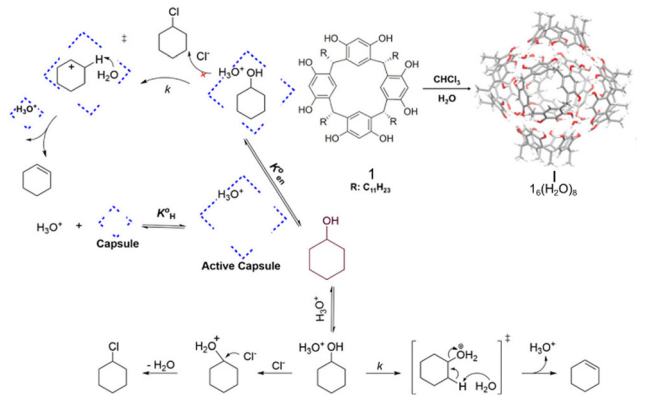

Fig. 3 Catalysis of the dehydration of cyclohexanol to produce cyclohexene using the capsule I. Adapted from ref. 59 with permission, copyright 2020, American Chemical Society.

nornicotine extended beyond the carbonyl portal of CB[7], altering its protonation equilibrium.

Additionally, various factors, including the host/catalyst ratio, the solvent polarity,[73] and the presence of cofactors such as acid/base, metal ions, and guests,[74] can collectively regulate the catalytic activity. These guests may function as synergists, such as radical stabilizing agents like C_{60},[75] or as competitive agents. Eelkema *et al.* demonstrated that the dynamic assembly/disassembly process between hosts and catalysts could be modulated by the addition of hosts or a competitive guest, allowing for a switch from "off" to "on".[76] Reek *et al.* discovered that the addition of a small cofactor allowed the previously independent zinc porphyrin and pyridine ligand to form an effective catalyst, resulting in an eightfold enhancement of rhodium catalyst activity.[77]

2.2.3 Transition-state stabilization. The regulation of the reactivity of intermediates in chemical reactions is crucial, as they often play pivotal roles in the key step of these processes.[78] Zhang *et al.* employed a host–guest strategy based on CB[7] to enhance the quantum yield of benzyl acetate photolysis reactions by 40-fold (Fig. 4).[79] Mechanistic studies showed that this reaction follows a heterolytic bond cleavage mechanism, forming a contact ion pair as an intermediate, which was stabilized by binding with CB[7]. Later, the research group discovered that CB[7] can stabilize two key intermediates—ketyl and benzoyl radicals—through host–guest interactions during the photoinduced oxidation of benzyl alcohol.[80] The steric hindrance effect of CB[7] inhibited side reactions of ketyl radicals, such as homocoupling, ensuring the transformation of the benzyl alcohol into aldehyde. Meanwhile, the electrostatic effect of CB[7] significantly suppressed overoxidation of benzoyl radicals, ensuring the transformation of benzyl aldehyde into carboxylic acid, thereby enhancing the selectivity of photoinduced oxidation from benzyl alcohol to aldehyde. Wang *et al.* designed and synthesized a class of prism-like cages featuring three separate cationic aromatic walls.[81] This molecular cage effectively stabilized a contracted anionic transition state through both anion–π interactions between the intermediate and the aromatic walls, and hydrophobic effects within the cavity, efficiently catalyzing decarboxylative aldol reactions involving aldehydes and malonic acid half thioesters in aqueous solutions.

Supramolecular hosts effectively modulate the reactivity of various intermediates, including cationic,[82–84] radical, and anionic[85–87] intermediates, through their surface charge characteristics,[88] host–guest interactions (such as electrostatic, cation–π, and anion–π interactions), solvent polarity,[89] and external stimuli like exogenous salts. This mechanism alters the geometry and electronic properties of the reaction transition state, resulting in a significant reduction in the activation energy and influencing the mode of attack of reagents on the intermediates.[90] Consequently, the reaction process becomes smoother, while significantly suppressing the premature quenching of intermediates,[91,92] thereby ensuring that the reaction proceeds continuously and stably.[93] Gibb *et al.* reported that the positively charged capsule stabilizes a negatively charged transition state through the coulombic force generated by its electrostatic potential (EP) field, thereby accelerating the rate of cyclization of α,ω-thioalkane halides.[94] Moreover, exogenous salts, featuring counterions that complement the surface charge of the capsule, can bind to the outer wall of the capsule, weakening the EP field and influencing transition state reactivity.[95]

2.2.4 Product stability. Supramolecular hosts not only stabilize transition states through noncovalent interactions but also demonstrate high efficiency in stabilizing the final products, facilitating their subsequent isolation. Yoshizawa *et al.* reported a polyaromatic capsule that can selectively and efficiently bind menthone (MTO) (Fig. 5).[96] The encapsulated MTO undergoes an unusual isomerization reaction upon heating, transforming from a typical chair conformer to the typically unstable diaxial chair (ACI) and twist-boat conformers (TBI-a and -b). This capsule effectively stabilized these unstable conformers through multiple CH–π and hydrogen-bonding interactions. Moreover, the shape of the substrate and the characteristic of substituents also influence the ability of the capsule to stabilize the final product. Research on the role of macrocycles in the stabilization of products is relatively limited. They primarily stabilize products through host–guest interactions or by providing a protective environment within the macrocyclic cavity, shielding the product from the attack of reagents in solution.

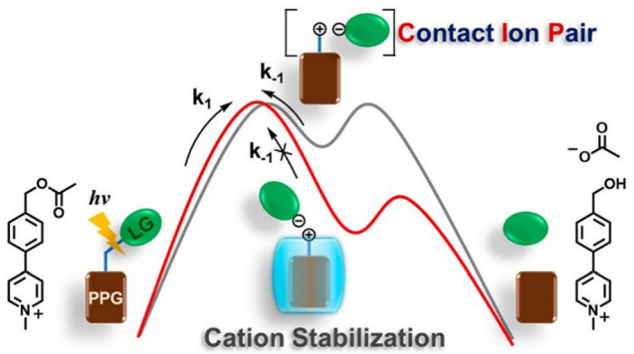

Fig. 4 Catalysis of photolysis reactions of benzyl acetate using CB[7]. Reproduced with permission from ref. 79, copyright 2023, American Chemical Society.

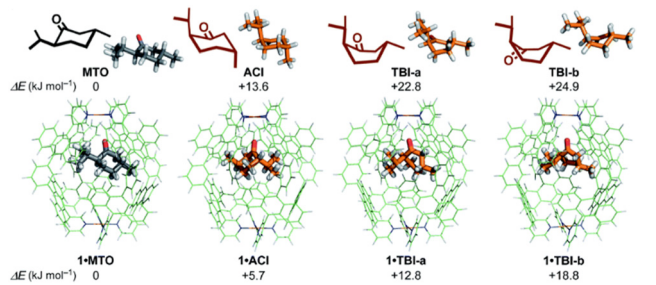

Fig. 5 Stabilization of conformers of MTO using a polyaromatic capsule. Adapted from ref. 96 with permission from the Royal Society of Chemistry.

2.3 Regulation of molecular freedom

Supramolecular hosts selectively recognize guests (*i.e.*, reaction species), encapsulating them within a confined cavity. This process may involve conformational changes or structural adaptations in both the host and guest molecules to achieve optimal complementarity or an optimized arrangement of binding sites. The specific cavity shape, arrangement of binding sites, and electronegativity of the host help maintain the guests in a defined position and orientation, restricting their free motion and facilitating their preorganization. This preorganization optimizes the spatial relationship between substrates or between substrates and catalysts of the catalytic systems, lowers activation energy, promotes the desired reaction pathways, and allows for precise control over the reaction rate, selectivity, and efficiency under mild, tunable conditions.

2.3.1 Regulation of substrate conformation. Preorganization of substrates includes conformational adjustment of substrates induced by macrocycles during their interaction, promoting optimal accommodation within the internal environment of the macrocycles.[97] Taking advantage of this process, the spatial arrangement of substrates—such as bending and folding—through host–guest interactions may bring two reactive groups, either within a single substrate or across two substrates, closer together, allowing them to align optimally for reaction progress.[98] Moreover, factors such as substrate solubility and concentration, solvent polarity, temperature, shape and size of both the cavity and the substrates, and their supramolecular interactions can influence the host's ability to encapsulate and preorganize substrates, thereby significantly affecting reaction performance.[99] Rebek *et al.* employed cavitands to facilitate the selective intramolecular aldol/dehydration reaction of long-chain α,ω-dialdehydes in aqueous solution (Fig. 6).[100] Long-chain dialdehydes encapsulated within the cavitand cavity adopt folded conformations driven by hydrophobic effects, bringing their terminal reactive groups close together. These terminal groups were positioned near the cavity opening, exposed to water and reagents in the solution, enabling the formation of 11- to 17-membered ring structures with high yield and good selectivity. In contrast, shorter dialdehydes are sequestered entirely within the cavity, effectively shielding them from external reagents and preventing any reactions from occurring. Moreover, hosts must exhibit high affinities for guests ($K_a > 10^3$ M^{-1}) to ensure that reactions occur effectively within the confined environment of the host cavity.[101] Ballester *et al.* employed CB[7] to preorganize and stabilize the encapsulated unactivated substrate of tertiary *N*-methyl-*N*-allyl-2-furfurylamine and *N*-methyl-*N*-(homo)allyl-2-furfurylamine, facilitating the proximity of two reactive functional groups within these molecules.[102] This arrangement positions them in the geometry of the highly ordered transition state required for the IMDA reaction. In contrast, substrates encapsulated in the larger cavity of CB[8] exhibit a conformationally less organized arrangement, leading to decreased reaction acceleration factors. Yoshizawa *et al.* synthesized an anisotropically contracted spherical polyaromatic capsule, which effectively encapsulates a bowl-shaped sumanene through hydrophobic effects and π–π/CH–π interactions thereby accelerating the bowl-to-bowl transformation of sumanene.[103]

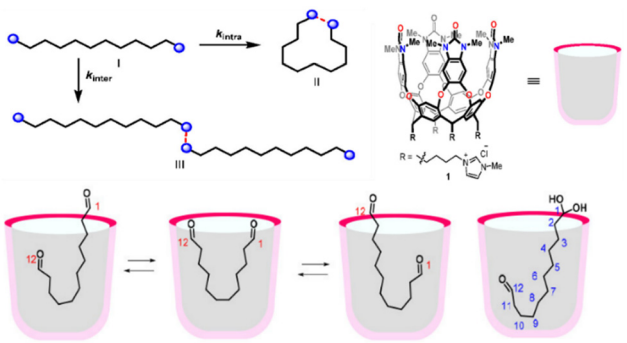

Fig. 6 Enhancement of the conformational arrangement of the substrate by cavitand preorganization. Adapted from ref. 100 with permission, copyright 2021, American Chemical Society.

2.3.2 Regulation of host conformation. The scaffold structure of hosts,[104] along with the arrangement of the host–guest binding sites,[105,106] and various other structural factors work synergistically to organize multiple catalytic active sites onto an ordered framework, inducing cooperative interactions among the catalytic groups. Thus, developing strategies to adjust the host's conformation is crucial for catalysis.

Controlling the conformation of individual macrocycles may be achieved through structural design. Cacciapaglia *et al.* grafted the guanidine/guanidinium dyad onto a calixarene scaffold *via* carbonyl bridging, which moderately increased the conformational flexibility of the host, enabling it to transform into a highly catalytically active protonated form.[107] Tiefenbacher *et al.* discovered that chirality transfer in the nerol cyclization was only observed when the involved capsule was attached at the edge to a linear alkyl chain containing an odd number of carbon atoms (enantiomeric excess >5%).[108] This finding indicates an odd–even effect, wherein the structure and properties of the material exhibit alternating changes based on whether the number of structural units in the molecule is odd or even.[109,110] Yang *et al.* successfully prevented the interconversion of conformers by grafting bulky β-cyclodextrin (β-CD) substituents at both ends of pillar[5]-arene (P5), thereby obtaining a pair of enantiomers.[111] The absolute configuration of the central P5 and the conjugating position on β-CD jointly determined regio- and stereoselectivity in the chiral catalytic reaction.

The conformation of macrocycles can also be regulated by forming aggregates. Salvio *et al.* systematically investigated multifunctional guanidinium-decorated calix[4]arenes derived from four guanidine or arginine units at the upper rim, which can self-assemble into aggregates in aqueous solution through hydrophobic effects.[112] These aggregates can rearrange, mold, and flex to meet the geometric and electronic requirements of the substrates, significantly enhancing the efficiency of phosphodiester bond cleavage in the aqueous phase. We synthesized a series of monoester copillar[5]arenes, where the position of the ester group modulates their self-inclusion behavior, resulting in varying guest selectivity.[113] Monoester

copillar[5]arenes derived from acetate chains can form stable self-inclusion complexes in both low- and high-concentration solutions, exhibiting high guest selectivity. However, the butyrate chain-functionalized monoester copillar[5]arene could not form a self-inclusion complex and showed lower guest selectivity. Furthermore, the position of the ester group is critical for the generation of stable self-inclusion complexes.

During host/guest binding, in addition to inducing conformational changes in the guest, the host also undergoes conformational changes. Guan *et al.* observed that a metallocage ($K_{12}[Ga_4L_6]$, L = *N*,*N*′-bis(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene, KGaL) exhibits a unique ''breathing'' mechanism for substrate encapsulation.[114] The naphthalene rings of KGaL rotated toward the closing direction of the guest-entry face to adapt to the shape of the substrate, resulting in a reduction of the cavity volume. As the guest gradually entered, a shape change was induced in one side of the ''concave cup'' structure for KGaL, leading to an increase in the cavity volume.

The solvent environment and coexisting species can also influence the conformation of macrocycles. Inoue discovered that by finely tuning the hydrophobicity and ionic strength of an aqueous solution, the penetration depth and orientation of the hydrophobic sensitizing moiety grafted onto the CD portal could be precisely controlled.[115] This flexibility allows for the adjustment of the size and shape of the nanospace provided by the CD cavity to accommodate the requirements of different guests. Reek *et al.* found that introducing an additional cofactor such as water at the edge of the hydrogen bond network leads to the breaking of hydrogen bonds between adjacent capsule faces, consequently altering the connectivity of the entire supramolecular system and ultimately affecting the acidity and structure of the host.[116] Lusby *et al.* employed a simple Pd_2L_4 capsule that utilizes endotopic and exotopic binding sites to separately bind substrates and effectors.[117] When an effector binds to the outer surface of the capsule, it partially neutralizes charges on that surface, leading to subtle electronic effects. The effector can modulate the binding affinity of the capsule for substrates and their transition states through an allosteric regulation mechanism, wherein enzymes adjust the properties of their active sites by binding a control molecule on the protein exterior.[118] We synthesized two novel copillar[5]arenes functionalized with ω-hydroxyalkoxy groups.[119] Among them, the copillar[5]arene functionalized with a 6-hydroxyhexyloxy group exhibits reversible self-assembly behavior, leading to the formation of self-inclusion monomers and hugging dimers. By adjusting factors such as solvent, temperature, guest, and hydrogen-bond interactions, the reversible self-assembly behavior can be controlled. In contrast, the copillar[5]arene functionalized with a shorter 4-hydroxybutyloxy group does not display any self-assembly behavior.

In response to external stimuli such as light,[120] acid and base,[121] and the binding of effectors such as solvents,[122] substrates,[123,124] sensitizers,[125] and exotopic ligands, the host may undergo deformation and experience dynamic reversible assembly and disassembly processes.[126,127] Beves *et al.* designed and synthesized a heteroleptic coordination cage $\left[Pd_2L_2L_2'\right]^{4+}$ featuring a photoswitchable azobenzene-derived ligand, which effectively

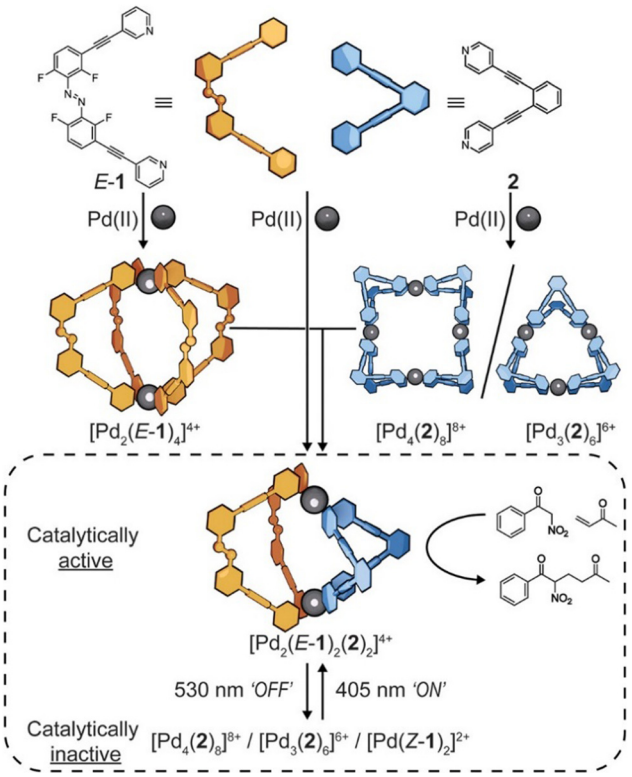

Fig. 7 Reversible dynamic processes of cage assembly and disassembly enabled by light stimuli. Reproduced with permission from ref. 128, copyright 2024, American Chemical Society.

catalyzed the Michael addition reaction between methyl vinyl ketone and benzoyl nitromethane (Fig. 7).[128] After irradiation with a 530 nm LED light source for 10 minutes, the cage successfully disassembled, resulting in a tenfold reduction in the product formation rate. Conversely, when exposed to a 405 nm LED light source for 5 minutes, the cage was able to reassemble and restore its original catalytic activity, thereby enabling the on-and-off control of the catalytic reaction in the cage. Notably, the corresponding homoleptic cages exhibited no catalytic activity. Yoshizawa *et al.* designed and synthesized a heterocyclic capsule constructed from bent amphiphilic compounds containing two phenothiazine redox switches, which demonstrated reversible behavior in response to redox stimuli, facilitating the assembly and disassembly of the capsule.[129]

2.3.3 Regulation of spatial orientation of reactants and/or catalysts. When encapsulated within macrocycles, substrates may align with specific spatial orientation driven by the confinement effect within the specific environment of the cavities. Moreover, the distance and orientation of reaction species encapsulated within the macrocyclic cavity may be influenced by factors such as the size and shape of the macrocyclic cavity, the substituents on substrates,[130] the solvent environment, and the presence of ions.[131]

Supramolecular strategies were used to increase the frequency of effective collisions between the substrates and accelerate the reaction process.[132,133] Li *et al.* designed and synthesized a calix[4]squaramide organocatalyst functionalized

with bis-squaramide and cyclohexanediamine scaffolds.[134] The cooperative effect between the cavity and the chiral squaramide catalytic center effectively reduced the distance between two substrates, facilitating the asymmetric Michael addition between 1,3-dicarbonyl and α,β-unsaturated carbonyl compounds (Fig. 8). Liu *et al.* discovered that cucurbit[10]uril could bind two substrates to form ternary complexes with a 1 : 2 stoichiometry.[135] This complex altered the distance and orientation between two substrates, placing them in a "reaction-ready" state, which enhances the selectivity and yield of the photodimerization of substrates. In contrast, the anthracene moieties of substrates incorporated within CB[8] adopt a head-to-tail orientation, which was unfavorable for photodimerization and stabilized the carbocation intermediate, unexpectedly yielding the photosolvolysis product of 9-anthracenemethanol. Furthermore, the supramolecular regulation strategy can be used to suppress unwanted reactions. Rescifina *et al.* found that CB[7] can bind nitrone and styrene separately to form a singular complex.[136] This binding model effectively prevents close contact between two substrates, thereby reducing their reaction yield.

Anchoring of catalysts by the cavity effectively desolvates them, thereby lowering the reaction energy barrier,[137] and regulates the spatial orientation between the catalysts and substrates, thus modulating chemoselectivity and regioselectivity.[138,139] Anchoring can be achieved through weak interactions between the catalyst and the host. For example, by grafting coordinating groups onto a macrocyclic skeleton, metal catalysts can be bound either at the macrocycle portals[140] or encapsulated within the cavities.[141,142] Jiang *et al.* successfully constructed a highly active $Fe(OTf)_3$/CD complex by binding $Fe(OTf)_3$ to the primary hydroxyl groups located on the narrower rim of the cyclodextrin (CD) scaffold.[143] The CD cavity effectively modulated the interaction between $Fe(OTf)_3$ and encapsulated substrates, such as carbazoles, within the cavity. Podewitz *et al.* designed and synthesized a calix[8]arene modified with a phenanthroyl group capable of coordinating Cu(I) within its cavity.[144] Substrates were enriched within the calixarene cavity, facilitating effective interactions with the Cu(I) center.[145] Moreover, hosts can simultaneously encapsulate complementary substrates

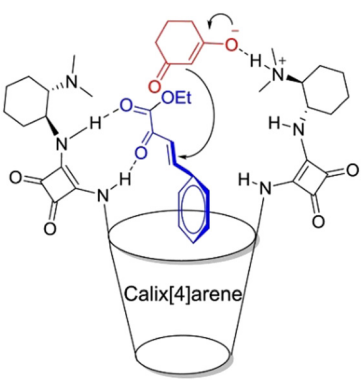

Fig. 8 Control of the distance between two substrates by calix[4]squaramide. Reproduced with permission from ref. 134, copyright 2020 Elsevier Publishing Group.

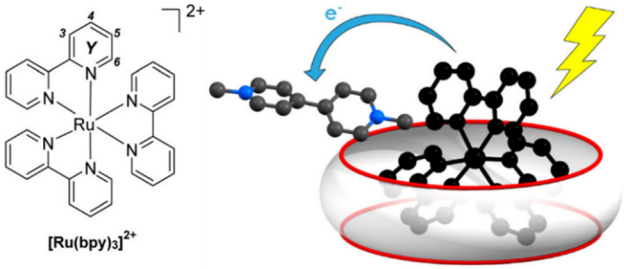

Fig. 9 Simultaneous encapsulation of both the catalyst and the substrate by CB[10]. Adapted from ref. 147 with permission, copyright 2020, American Chemical Society.

and catalysts, forming synergistic ternary complexes.[146] Beves *et al.* utilized CB[10] to encapsulate $[Ru(bpy)_3]^{2+}$, the photocatalyst, along with substrates simultaneously, forming ternary complexes (Fig. 9).[147] The arrangement facilitated intermolecular charge transfer to methyl viologen when the photocatalyst is in an excited state, thereby enhancing oxidative quenching efficiency.

Anchoring of catalysts can be achieved by incorporating the catalytic active sites into the macrocyclic skeleton.[148] Wang *et al.* adopted a strategy of incorporating catalytic active sites into a macrocyclic skeleton, successfully synthesizing a series of chiral bis-phosphate macrocycles.[149] Through the synergistic effect of complementary ion-pair binding and cavity-directed non-covalent interactions, they adjusted the distance between the catalyst and the substrate, thereby enhancing the catalytic activity of the reaction. Duan *et al.* embedded NADH active sites within a metal–organic capsule, which was assembled using preorganization ligands and functionalized metallocorners (Fig. 10).[150] In the external environment of the capsule, the presence of a reductant or photosensitizer facilitated a typical $1e^-$ hydrogenation, enabling the highly selective reduction of nitro groups over carbonyl groups. Inside the capsule, the substrate was encapsulated within the cavity, allowing for preorganization that forced the active sites to closely contact the substrate. Consequently, the ADH active site achieved highly selective reduction of carbonyl groups through a typical $2e^-$ hydride transfer hydrogenation, thereby enabling selective

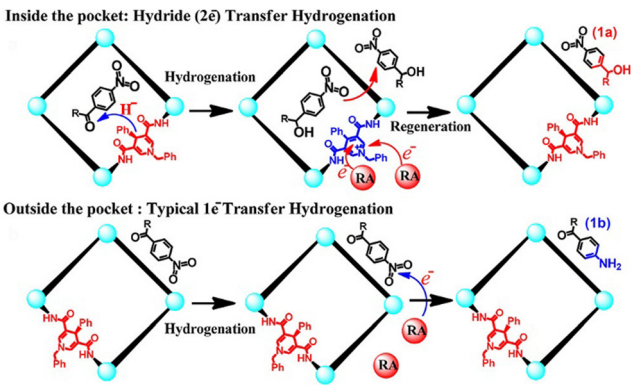

Fig. 10 The regulation of selective reduction of carbonyl and nitro groups by the capsule. Reproduced with permission from ref. 150, copyright 2019, American Chemical Society.

reduction between carbonyl and nitro groups in switchable bifunctional compounds.

3. Challenge 2: product inhibition

Supramolecular catalysis enables efficient regulation of chemical reaction processes; however, it faces a significant challenge—product inhibition due to the difficulty of product release.[151,152] Product inhibition typically arises from strong non-covalent interactions between the product and macrocycles, leading to the occupation of active sites. As a result, it prevents new substrates from entering, hindering subsequent reactions and potentially bringing the entire catalytic process to a halt. Several strategies have been employed to effectively address this issue and significantly enhance the turnover number (TON) of the catalyst: altering the binding affinity for substrates and products; selectively binding the catalyst rather than the substrate and the product; phase separation of the products or catalyst; and implementing self-catalysis.

3.1 Altering the binding affinity for substrates and products

The design of ideal catalytic hosts should ensure that their binding affinity for substrates is significantly stronger than that for products, allowing substrates to readily displace products in the cavity, thereby facilitating subsequent reactions. The selective binding can inherently occur for certain reactions. For example, when hydrophilic reactants transform into hydrophobic products, the enhanced hydrophilicity drives the product to escape this unfavourable environment.[59] Selective binding can be achieved by tuning host–guest interactions through the design of hosts tailored for specific reactions. For example, when positively charged substrates react to yield neutral products, negatively charged macrocycles are an effective choice due to their higher binding affinity for substrates compared to products.[147] Similarly, when neutral substrates convert into negatively charged products, a hydrophobic cavity is ideal, as the negatively charged products are preferentially solvated by bulk water rather than remaining in the cavity.[153] Moreover, appropriate size matching between the cavity and the substrates rather than the products may play a crucial role in preventing product inhibition.[83,102]

Another strategy to tune the host–guest binding affinity is to adjust solvent polarity by adding a less polar solvent. With the decrease of solvent polarity, the binding affinity of the product to the host can be substantially reduced. Nau *et al.* demonstrated that introducing a less polar cosolvent, such as 10% methanol, effectively decreased the binding constant of highly hydrophobic products with the host, enabling the catalytic reaction to proceed with turnover numbers (TON) of 10 or higher, thereby addressing the issue of product inhibition.[31]

3.2 Selectively binding the catalyst

To prevent product inhibition, macrocycles can be used to selectively bind and activate catalysts instead of directly interacting with substrates or products. Wang *et al.* designed bis-diarylthiourea macrocycles that contain two cooperative diarylthiourea binding sites and two BINOL moieties (Fig. 11).[154] The macrocycles selectively bind disulfonate especially ethanedisulfonate anions by the diarylthiourea groups, establishing a well-confined chiral microenvironment for protonated electrophilic substrates. Utilizing only 1 mol% macrocycles and acid, cooperative interactions in the Friedel–Crafts reaction of indoles with imines can achieve yields of up to 99% and an enantiomeric excess of 99%. Yang *et al.* successfully synthesized β-cyclodextrin derivatives modified with triazole functional groups, which exhibited a strong coordination capability with metals. These derivatives effectively bound Cu(I) catalysts, facilitating the reaction of Cu(I)-catalyzed azide–alkyne cycloaddition to yield 1,4-disubstituted 1,2,3-triazoles in aqueous environments.[155] The reaction exhibited a TON of up to 45 000, and the catalyst retained high catalytic activity even after multiple cycles.

3.3 Phase separation of the products or catalyst

Phase separation methods such as distillation or extraction can also be applied in supramolecular catalytic systems to prevent product inhibition by separating products from the reaction system. This approach allows for the recovery and reuse of the host in a new solvent, maintaining the efficiency of the catalytic cycle.[156] Dreimann *et al.* utilized methylated β-cyclodextrin in combination with a Rh-based catalyst for the continuous hydroformylation of 1-decene.[157] The process employed vacuum distillation (at temperatures below 150 °C) to separate the products, enabling efficient turnover cycles with a high TON. This setup allowed the entire continuous process to operate stably for over 200 hours, achieving a chemical selectivity of more than 97% for the desired linear aldehyde product throughout this period. Bisht *et al.* developed spatially directional multivalent resorcin[4]arene cavitand glycoconjugates as phase transfer catalysts for organic reactions, including thiazole formation, thiocyanation, and Mannich reactions in aqueous media.[158] After the reactions, the products were extracted with dichloromethane or ethyl acetate, allowing the aqueous solution containing the macrocyclic catalyst to be directly reused for up to five reaction cycles while maintaining high catalytic activity.

Separation of the macrocyclic catalyst from the product can be also achieved through catalyst precipitation. By reducing the

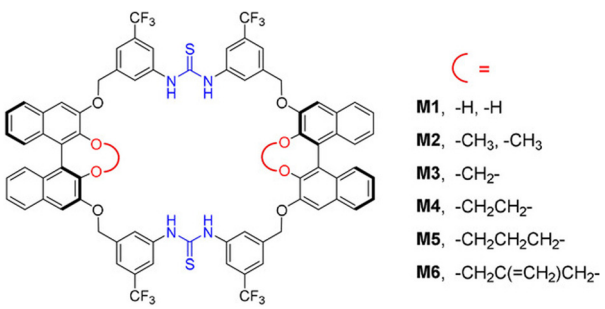

Fig. 11 Structure of bis-diarylthiourea macrocycles. Reproduced with permission from ref. 154, copyright 2020, Wiley Publishing group.

solubility of the catalyst to promote its precipitation, this method facilitated the separation of the product from the catalyst, thereby addressing the issue of product inhibition. Young *et al.* induced the precipitation of capsules in the reaction mixture by adding acetonitrile, followed by centrifugation, which effectively separated the majority of capsules with a recovery rate of up to 90%.[159] The recovered capsule exhibited the same catalytic activity as the pristine sample.

3.4 Autocatalysis

Autocatalytic reactions use their products as catalysts for subsequent reactions, forming a self-sustaining catalytic system. This strategy not only avoids product inhibition but also significantly enhances reaction rates. Matile *et al.* reported the catalysis of epoxide-opening ether cyclizations within a series of capsules with π-basic but Brønsted acidic inner surfaces.[160] Their study highlighted that autocatalysis was driven by the formation of hydrogen bonds between the transition state and the product on π-acidic surfaces, which activated both the nucleophile and the leaving group. This interaction enhances the reaction rate and promotes chemo- and diastereoselectivity, though enantioselectivity remains unattained. The unique structural properties of π-acidic surfaces of capsules facilitate these interactions, making them distinct from other catalytic environments. Matile *et al.* employed supramolecular capsules to catalyze House–Meinwald rearrangements to obtain new cyclic hemiacetals, discovering that the autocatalysis on anion–π catalysts was independent of substrate stereochemistry.[161]

4. Challenge 3: incompatibility of catalysts or conditions in "one-pot" reactions

In the field of complex chemical synthesis, "one-pot" reactions in the aqueous phase have garnered significant attention due to their environmental friendliness, high efficiency, and ease of operation. However, a notable challenge arises from the incompatibility of catalysts or conditions in "one-pot" reactions. Specifically, the catalysts or reaction conditions required for two reactants or two consecutive steps often cannot coexist in the same aqueous environment. This issue severely restricts the development and application range of "one-pot" reactions in aqueous medium. Moreover, enzymes provide distinct catalytic microenvironments through cavity pockets to facilitate cascade reactions. Therefore, studying the catalysis of "one-pot" reactions also aids in understanding the relationship between the structure and function of enzymes. Supramolecular macrocycles inherently possess two distinct microenvironments—inside and outside the cavity—making it possible for two mutually exclusive catalytic conditions to coexist within a single system. Moreover, arranging different catalytic active sites on the macrocycle allows for the creation of a diverse and compatible catalytic environment where multiple catalytic conditions can coexist. Su *et al.* reported a $[(Pd/Pt)_6(RuL_3)_8]^{28+}$ nanocage for

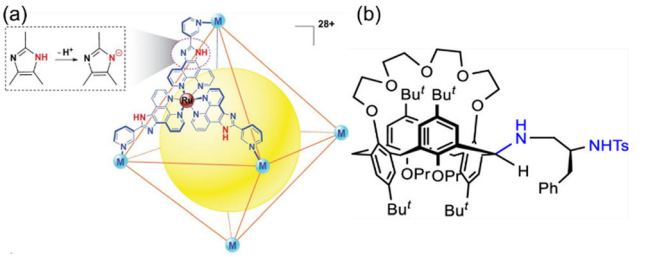

Fig. 12 Structure of (a) $[(Pd/Pt)_6(RuL_3)_8]^{28+}$ nanocage highlighting the protonation of the imidazole groups on the framework; (b) a bridging calix[4]crown-5 with two well-designed binding sites. Adapted from ref. 162 with permission, copyright 2021, National Science Review and ref. 163 with permission, copyright 2021, American Chemical Society.

cascade reaction. They discovered that the highly positive charge (+28) on the surface of the nanocage induces protonation of the 24 imidazole groups on its framework (Fig. 12(a)), shifting ionization equilibrium and pK_a, thus creating positively charged confined nanospaces in aqueous solution. This nanocage acted as a bifunctional acid–base catalyst, with extrinsic Brønsted acidity facilitating acid-catalyzed acetal hydrolysis in the bulk solution and intrinsic basicity promoting Knoevenagel condensation in cage-confined nanospaces.[162] Li *et al.* synthesized chiral *p-tert*-butylcalix[4]crown-5 with a mononitro bridge substituent in a 1,3-alternate conformation, serving as a bifunctional organocatalyst for the asymmetric Henry reaction of aromatic aldehydes and nitromethane (Fig. 12(b)).[163] The catalyst demonstrated good catalytic activity, achieving yields of up to 95% and enantioselectivity up to 22.3% ee. The secondary amino group functioned as a base to activate nitromethane, while the sulfonamido group acted as an acid to activate the aromatic aldehyde.

5. Conclusions and outlook

This minireview focuses on the challenges encountered for macrocyclic catalysis in the aqueous phase and their corresponding solutions. The specific issues addressed include (1) limited molecular interaction efficiency in aqueous environments, (2) product inhibition, and (3) incompatibility of catalysts or conditions in "one-pot" reactions. To tackle the first issue, the matching of hosts and substrates can be optimized, enabling the hosts to specifically recognize and effectively encapsulate substrates within their cavities. During the reaction process, the charge distribution and the characteristic of the binding site of macrocycles can influence the interaction efficiency of reaction species involved, including substrates, catalysts, transition states, and products. These effects on the reaction species may include, but are not limited to, facilitating desolvation, increasing local concentration, modifying photophysical properties, and adjusting their acidity and basicity. The macrocyclic cavity can preorganize two reactive groups or intramolecular fragments of the substrate, facilitating their adaptation to the internal environment of the host. Additionally, the host can undergo conformational changes or dynamic

reversible assembly/disassembly processes to better accommodate the shape of the substrates. Furthermore, the host can facilitate interactions between two substrates or the catalytic active center and the substrate. For the second issue, one of the key factors is to ensure that the binding affinity of hosts for substrates is greater than for products, allowing substrates to displace products in the host cavity. Moreover, the host can be designed to preferentially bind to catalysts rather than to substrates or products, facilitating the smooth release of products from the macrocycle upon formation. Techniques such as distillation or extraction can be employed to separate products, or the addition of organic solvents and guest molecules can induce catalyst precipitation for effective separation. Additionally, employing an autocatalytic system may be a promising strategy to mitigate product inhibition. To address the third issue, developing macrocyclic catalysts with dual catalytic active sites or hosts featuring distinct internal and external environments can enable ''one-pot'' reactions that are otherwise hindered by incompatible catalysts or reaction conditions needed for two reactants or sequential steps.

Despite significant progress in addressing the three issues of aqueous catalysis within macrocycle chemistry, further exploration of strategies to solve these issues remains a critical and important area of research. Additionally, a key challenge lies in monitoring and regulating the mass transfer of intermediates within catalytic systems, critical for preventing the intermediate deactivation and the inhibition of active sites. Supramolecular macrocycle catalysis has potential advantages in monitoring and regulating the mass transfer of intermediates: macrocycles have simple structures, well-defined cavity microenvironments, stable functionality resistant to deactivation, ease of design and synthesis, and clear structure–activity relationships. These features make them ideal simplified models for complex systems like enzymes, where substrate mass transfer channels are also crucial in catalysis research, thereby facilitating fundamental studies on chemical kinetics at the elementary reaction level. Moreover, kinetic studies of macrocycle systems have also advanced. For example, in-depth studies have been conducted on the regulation mechanisms of conformational changes in macrocyclic aromatics by small guest molecules or coexisting ions.[164–166] Additionally, kinetic methodologies have been developed for elucidating the host–guest binding mechanisms in ternary and more complex systems.[167–170] However, despite these research advancements, no related research has been reported in the field of macrocyclic catalysis regarding intermediate mass transfer. This may be due to two reasons: (1) in single-macrocycle catalysis systems, the specific stepwise reactions are carried out in aqueous media, making it difficult to precisely control the relative positions of the two catalytic sites; intermediates diffuse through the aqueous phase, which is relatively inefficient. (2) In complicated systems such as the supramolecular and biocatalytic coupled systems, the diversity and complexity of components, binding sites, interaction forces, binding extent and speed, as well as structural changes during the binding process are often too complex and varied, making it challenging to study the mass transfer of intermediates at the elementary reaction level. Future research should focus on developing advanced macrocyclic systems capable of controlling intermediate mass transfer more efficiently, emulating the complexity and specificity of enzyme systems. Furthermore, integrating supramolecular catalysts with dynamic, adaptable features could unlock new catalytic pathways, expanding the scope and applicability of macrocyclic catalysis in sustainable and green chemistry. We hope that this review will inspire new research directions to better facilitate macrocyclic catalysis in aqueous environments.

Author contributions

D. C. and H. T. designed the scope of the manuscript. D. Z. and H. T. wrote the original draft of the manuscript. L. W. and W. W. discussed and helped revise the manuscript.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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