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CRITICAL REVIEW**Artificial enzymes based on supramolecular scaffolds†****Zeyuan Dong, Quan Luo and Junqiu Liu****Received 28th March 2012*

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Enzymes are nanometer-sized molecules with three-dimensional structures created by the folding and self-assembly of polymeric chain-like components through supramolecular interactions. They are capable of performing catalytic functions usually accompanied by a variety of conformational states. The conformational diversities and complexities of natural enzymes exerted in catalysis seriously restrict the detailed understanding of enzymatic mechanisms in molecular terms. A supramolecular viewpoint is undoubtedly helpful in understanding the principle of enzyme catalysis. The emergence of supramolecular artificial enzymes therefore provides an alternative way to approach the structural complexity and thus to unravel the mystery of enzyme catalysis. This *critical review* covers the recent development of artificial enzymes designed based on supramolecular scaffolds ranging from the synthetic macrocycles to self-assembled nanometer-sized objects. Such findings are anticipated to facilitate the design of supramolecular artificial enzymes as well as their potential uses in important fields, such as manufacturing and food industries, environmental biosensors, pharmaceuticals and so on.

1. Introduction

Enzymes are sophisticated proteins with supramolecular structures formed by folding and self-assembly of one or more polymeric peptide sequence components through non-covalent interactions. Due to a diverse array of functional groups in the active sites of enzymes, they are capable of carrying out

abundant chemical biotransformations under physiological circumstances with astonishing catalytic efficiency and substrate specificity. An unprecedented catalytic landscape is provided by enzymes in living systems.^{1–3}

Over the past several decades, enzymes have been widely investigated, not only for understanding their catalytic mechanisms but also for their potential applications.^{4–8} So far, biologists have been able to scrutinize the biological functions of most natural enzymes by means of various modern techniques. However, it is still challenging for both biologists and biochemists to unravel the detailed catalytic mechanism of

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natural enzymes.⁹ Although considerable progress in enzyme catalysis has been realized by directly monitoring the catalytic processes of natural enzymes *via* steady-state and transient kinetics,^{5,10–12} single-molecule kinetics,^{13,14} nuclear magnetic resonance (NMR),^{15–19} and molecular dynamics simulations,²⁰ the relationships between the supramolecular dynamic structures and the particular features of enzyme are still specious.⁹ Therefore, a complete and profound comprehension, for example, of how enzymes display incredible catalytic efficiency and selectivity due to supramolecular structure, is strongly required. While a direct investigation into the molecular level relationships between supramolecular structures and catalytic features of enzymes is not easy to perform at present, the emergence of man-made materials with supramolecular structures provides an alternative approach for exploring the molecular coordination of enzyme actions.

Development of artificial enzyme models mimicking natural enzymes is a promising and active field that has been pursued by researchers for several decades.^{21–23} Although many attempts have been made to reproduce the structures and functions of enzymes, the complexity of enzymes *via* natural selection and evolution severely constrained the ability of researchers to replicate the enzymatic features. Therefore, it is a long-term goal for chemists to develop synthetic chemical equivalents to natural enzymes in terms of structure, catalytic efficiency, specificity, selectivity, *etc.* Beyond understanding the behavior of molecules composed of constituent atoms, the advent of supramolecular chemistry allows one to capture the collective behavior of organized ensembles of molecules.²⁴ The features of enzymes, both substrate recognition and catalysis, were intrinsically managed by their supramolecular structures.^{9,25,26} Essentially, the combined complexity and cooperativity of enzymes can be adequately achieved by the dynamic assembly of supramolecular blocks with catalytic moieties and binding sites. Recently, based on their structurally dynamic nature, supramolecular enzyme models with complex and hierarchical architectures have attracted considerable attention in the

research area of mimicking the particular features of natural enzymes.^{27–30} By taking the advantages of supramolecular chemistry and the design principles of artificial enzymes into account, a number of supramolecular artificial enzymes were prepared based on various supramolecular materials including macrocycles and container molecules (such as cyclodextrins, calixarenes, cyclophanes, crown ethers, cavitands, capsules, molecular cages and others), and self-assembled nanometer-sized objects (for example, ligand-anchoring supramolecular complexes, micelles, vesicles, nanoparticles, nanotubes and nanogels) and so on (Chart 1).^{22,23,29–32}

In this critical review, enzyme mimics based on supramolecular scaffolds will be highlighted, especially those that have interesting structures and functions. After an introduction (Section 1), we give a short overview of understanding enzyme catalysis through supramolecular viewpoints in Section 2. According to the structural characteristics, the supramolecular enzyme mimics included in this review are categorized into four classes: (i) cavity-containing artificial enzymes (Section 3), mimicking the binding site of natural enzymes; (ii) artificial enzymes designed with non-covalent anchoring strategies (Section 4); (iii) nanometer-sized artificial enzymes (Section 5); (iv) smart artificial enzymes (Section 6), mimicking the dynamic features and catalysis regulation of natural enzymes. Sections 7 and 8 describe briefly the potential application and future development of supramolecular artificial enzymes, respectively.

2. Principles of enzyme catalysis through supramolecular viewpoints

The hypothesis of “lock and key” theory proposed by Emil Fischer in 1894 was established at the early stage of enzyme catalysis understanding.³³ Later, Haldane³⁴ and Pauling³⁵ refined this hypothesis, and the transition state theory was generally accepted.³⁶ In addition, the induced fit model suggested by Koshland allows one to further understand the enzymatic catalysis.³⁷ In the past several decades, these hypotheses evoked impressive advances and achievements in the research area of design and construction of artificial enzymes, prior to the known detailed rules of the enzymatic reaction mechanism.^{38,39} One example is the design of catalytic antibody with great success by using the transition state theory.⁴⁰ These hypotheses, however, cannot fully explain enzyme catalysis; the detailed mechanism of enzyme action is still a mystery.

It is believed that the first step of enzyme catalysis is substrate recognition dominated by supramolecular interactions. The great progress in supramolecular chemistry allows one to completely understand and reasonably manipulate the supramolecular interactions, which provides an opportunity to discover the process of substrate recognition during enzyme catalysis.^{22,41} The supramolecular structures of enzymes strongly suggest that they often have multiple conformations, that is, enzymes exist in ensembles of coupled conformational states.²⁶ This suggestion has been undoubtedly underpinned by fundamental research in supramolecular chemistry. For instance, the mimics of the secondary structures of biopolymers exist in at least two conformations as demonstrated by NMR and X-ray crystallographic structures.^{42,43} In accordance with the above observation, the current investigations indicate that



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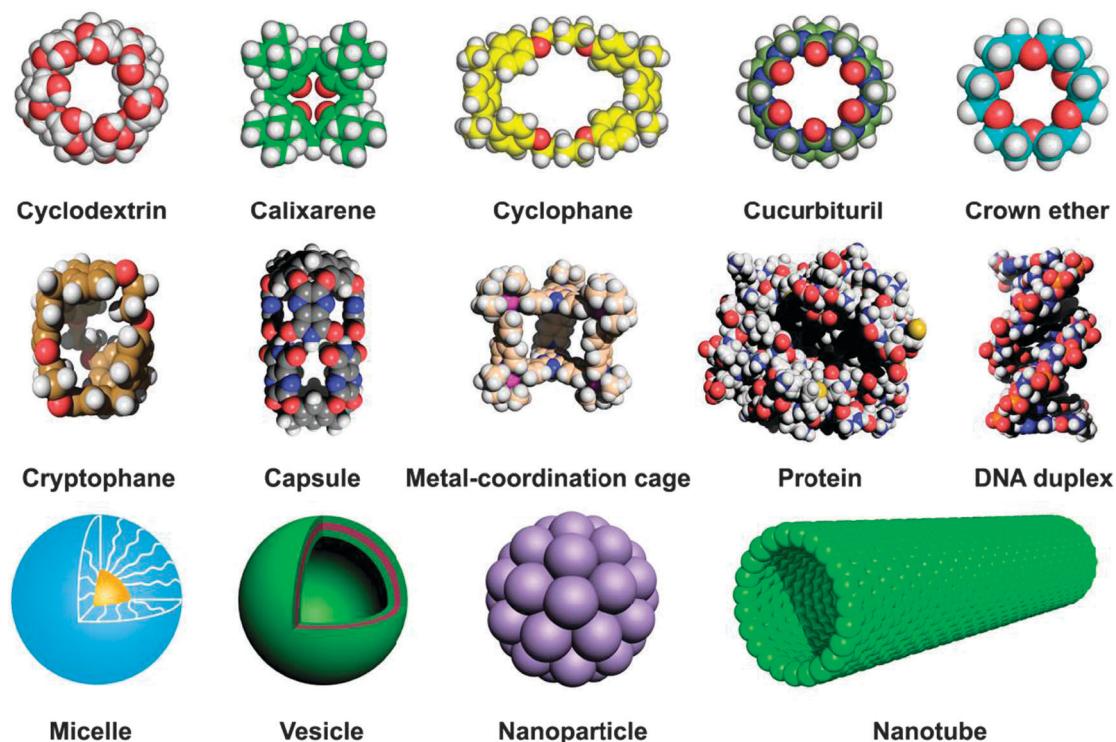


Chart 1 Diverse scaffolds for the design of supramolecular enzyme models.

the catalytic process of enzymes involves multiple conformations and numerous parallel paths. The conformational changes of enzymes during catalysis have been observed in both experiments and simulations.^{3,44,45} Moreover, the compositions of the ensembles of coupled conformational states are changed as the substrates bind to the enzymes. The motions of enzyme structure provide the catalytic power by increasing transition state stabilization during the enzymatic reaction in comparison with the nonenzymatic reaction. Therefore, the complex of enzyme and the reactive transition state has a lower free energy than that of the enzyme–substrate complex so as to stabilize the transition state of the reaction before the release of products.⁷ To enhance the catalytic turnover, the product inhibition was evolutionally avoided by natural enzymes, suggesting that the product binds to the enzyme with much lower affinity than the substrate binds to the enzyme. Recently, a complex and multidimensional free energy diagram for enzyme catalysis has been proposed,^{3,44} although further investigation is necessary to define this complicated landscape. These observations present a deep understanding of the catalytic mechanism, but it is not facile to present a molecular description about what happens during catalysis.⁴⁶ The slight alteration of enzyme structure by chemical modification or site-directed mutagenesis can dramatically alter the catalytic capacity. Furthermore, the entire macromolecule is substantially involved in catalysis to perform the cooperative motions so as to have high catalytic efficiency. A machine-like motion of macromolecules impossibly provides energy to cross the catalytic barrier. The combination of both, the precise array of catalytic elements in the active site of enzyme and the contributing motions of preorganized macromolecular structures, promotes catalytic

cycles. Therefore, the synergy of the flexibility, diversity, and cooperative motion of enzyme structure is essential for catalysis.³

The supramolecular interactions, including hydrogen bonding, electrostatics, van der Waals interaction, π – π interaction, steric effect, shape complementarity and so on, inevitably exist in catalysis and continuously control the motions of macromolecular structure, substrate recognition, transition state stabilization, and product release. Undoubtedly, the change of activation free-energy of the reaction drives the equilibrium of the catalyzed reaction. The extremely strong binding of the enzyme to the transition state significantly lowers the activation free-energy of the enzymatic reaction, thus contributing to the remarkable catalytic capacity.⁷ It is demonstrated that, on the basis of experimental evidence and simulations, most enzymes are able to strongly bind to the transition state with a binding constant far beyond 10^{11} M⁻¹,⁴⁷ suggesting that the covalent bond formation is a possible mechanism of action of enzymes in catalysis besides the concatenation of non-covalent effects.⁴⁸ To address the hitherto unknown details of the enzymatic mechanism, the relationships between the enzyme structure and catalytic action need to be further investigated. A few questions exist, for example, whether the motions of preorganized biomacromolecular structure are predictable or random in molecular terms, and how to quantify the percentage of contributing motions of enzyme structure for catalysis if the enzymes exist in ensembles of multiple conformational states. Therefore, it is strongly anticipated that the design and development of artificial enzymes with supramolecular structures can give rise to a new viewpoint to reveal the mysteries of enzyme catalysis.

3. Cavity-containing artificial enzymes

Enzymes exhibit high catalytic capacity and substrate specificity, thanks to their unique catalytic microenvironments. In the enzyme's active site, a pocket is available for substrate recognition and catalysis. This innate structure has inspired a number of supramolecular artificial enzymes containing cavities to be designed and synthesized.^{29–32,38,49} The cavity-containing molecules can effectively accelerate the chemical transformations by increasing the effective molarity or by the substrate preorganization, even without a catalytic group, thus mimicking the pocket features of enzymes. When a catalytic moiety is chemically incorporated into the cavity-containing molecules, the resultant models are able to copy both features, substrate recognition and catalysis, of enzymes. Analysis of cavity-containing artificial enzymes provides useful insight into the understanding of substrate-binding roles of enzymes in catalysis.

3.1 Macroyclic compounds as artificial enzymes

In an attempt to simulate the cavity functions of enzymes, numerous macrocyclic compounds including cyclodextrins, cyclophanes, cavitands, calixarenes and other synthetic macrocycles have been studied.^{50–55} The macrocyclic compounds are capable of isolating the chemical reactions from the surrounding medium, similar to the enzymes. Furthermore, the cavities in the structures allow the chemical reactions to follow a specific path, thus presenting the enzyme-like specificity and selectivity.

3.1.1 Cyclodextrins. Cyclodextrins, a family of cyclic oligomers, can accommodate small guest molecules in their hydrophobic cavities to form inclusion complexes. By using the specific microenvironment, cyclodextrins are able to efficiently catalyze a number of chemical reactions with or even without catalytic moieties.^{56,57} Research into cyclodextrins mediating the reactions has been investigated and reviewed recently.^{57–64} More interestingly, following the pioneering work contributed by Breslow,⁶⁵ Tabushi,⁶⁶ Saenger,⁶⁷ and D'Souza and Bender,⁶⁸ a large number of cyclodextrin-based artificial enzymes have been designed and studied in recent years (Chart 2).^{65–72}

Bols and co-workers prepared a series of enzyme mimics by simple chemical modification of cyclodextrins. In particular, model **1** is an artificial glycosidase with a $k_{\text{cat}}/k_{\text{uncat}}$ of 35 for the hydrolysis of 4-nitrophenyl- β -D-glucoside.⁷³ However, substitution of functional groups gave rise to a rate acceleration of 10^3 -fold for model **2** as a glycosidase mimic for the identical reaction.⁷⁴ Via NMR and UV spectroscopy, enzyme mimic **2** was found to catalyze the conversion of 4-nitrophenyl- β -D-glucoside into glucose and *p*-nitrophenol. Under the conditions used in the study, the catalytic reaction gives a $K_m = 5.4 \text{ mM}$, a $k_{\text{cat}} = 3.0 \times 10^{-5} \text{ s}^{-1}$, and a $k_{\text{cat}}/k_{\text{uncat}} = 1047$. Importantly, the catalysis can be inhibited by the addition of cyclopropanol, indicating that the cyclodextrin cavity is involved in the process. Neither the cavity of cyclodextrin nor catalytic group, mandelonitrile, displays catalytic activity, suggesting that the assembly of the binding cavity and the cyanohydrin group is essential for catalysis. Notably, this promising model **2** simulated part of the mechanism of natural glycosidase with an entirely different catalytic group cyanohydrin. Later, they reported an excellent artificial enzyme **3** for supramolecular oxidation of amine in

the presence of hydrogen peroxide.⁷⁵ The amine oxidation follows Michaelis–Menten kinetics where the rate of the catalyzed reaction significantly depends on the nature of the substrate. They also found that the artificial enzyme **3** can efficiently catalyze the transformation of benzylic alcohols into aldehydes or ketones in the presence of hydrogen peroxide under mild conditions ($k_{\text{cat}}/k_{\text{uncat}} = 60\,000$).⁷⁶ Very recently, the aldehyde-functionalized cyclodextrin **4** exhibited excellent oxidase-like catalytic capacity ($k_{\text{cat}}/k_{\text{uncat}} = 4600$) towards oxidation of 4-methoxy benzyl alcohol with hydrogen peroxide as a stoichiometric oxidant. These studies^{73–78} indicate that, by a minor modification of pendant functionalities of cyclodextrins, the catalytic properties of resulting enzyme mimics, such as selectivity and catalytic capacity, are significantly improved, or even changed.

In order to understand the catalytic mechanism of selenium-containing antioxidant glutathione peroxidase (GPx), numerous cyclodextrin-based GPx models have recently been designed and elucidated.⁷⁹ Enzyme mimics **5–13** show excellent GPx-like functions towards the consumption reaction of hydroperoxides in the presence of substrate thiols.^{80–87} Among them, model **13** shows very interesting properties with high catalytic efficiency and strong substrate specificity when a cyclodextrin-favorable aromatic substrate is used instead of natural substrate glutathione (GSH).⁸⁷ Mimic **13** catalyzes the reduction of cumene peroxide 200 000-fold more efficiently than a GPx mimic diphenyl diselenide. The kinetics study shows that the second rate constant is as high as $1.05 \times 10^7 \text{ M}^{-1} \text{ min}^{-1}$, similar to that of natural GPx.

French *et al.* synthesized a cyclodextrin-based carotene dioxygenase mimic **14** which enables selective cleavage of carotenoids.⁸⁸ The enzyme model **14** contains a reactive metal center which is capable of cleaving *E*-configured, conjugated double bonds to aldehydes in the presence of co-oxidant *tert*-butyl hydroperoxide (TBHP). The binding constant (K_a) of **14** for substrate carotenoid is a magnitude of about three orders greater than for the retinal product, thus avoiding product inhibition. The experiments demonstrate that the selectivity for the formation of the retinal product is almost exclusive while other products are found only in trace amounts. The combination of substrate binding and the proper position of the reactive metal center conferred the enzyme mimic **14** with regioselective catalytic capacity.

Mao and coworkers reported two cyclodextrin-based metallo-hydrolase models **15** and **16** for the ester hydrolysis.^{89,90} Cyclodextrin dimer model **15** shows very high catalytic activity towards the hydrolysis of bis(4-nitrophenyl) carbonate with a $k_{\text{cat}}/k_{\text{uncat}}$ of 38 900. However, a relatively low rate acceleration ($k_{\text{cat}}/k_{\text{uncat}} = 42$) is observed for the hydrolysis of 4-nitrophenyl acetate.⁸⁹ Additionally, model **15** can also catalyze the hydrolysis of bis(4-nitrophenyl)phosphate with a catalytic efficiency of $9.9 \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$. At the same time, the enzyme model **16** containing a β -cyclodextrin dimer and dinuclear Zn(II) can strongly accelerate the hydrolysis of bis(4-nitrophenyl)phosphate (as a DNA substitute).⁹⁰ However, for the hydrolysis of 2-hydroxypropyl-4-nitrophenyl phosphate (HPNP) (as a RNA substitute), model **16** follows a different catalytic mechanism. Kinetics analysis of model **16** indicates that the $k_{\text{cat}}/k_{\text{uncat}}$ for bis(4-nitrophenyl)phosphate is as high as 2 000 000, whereas

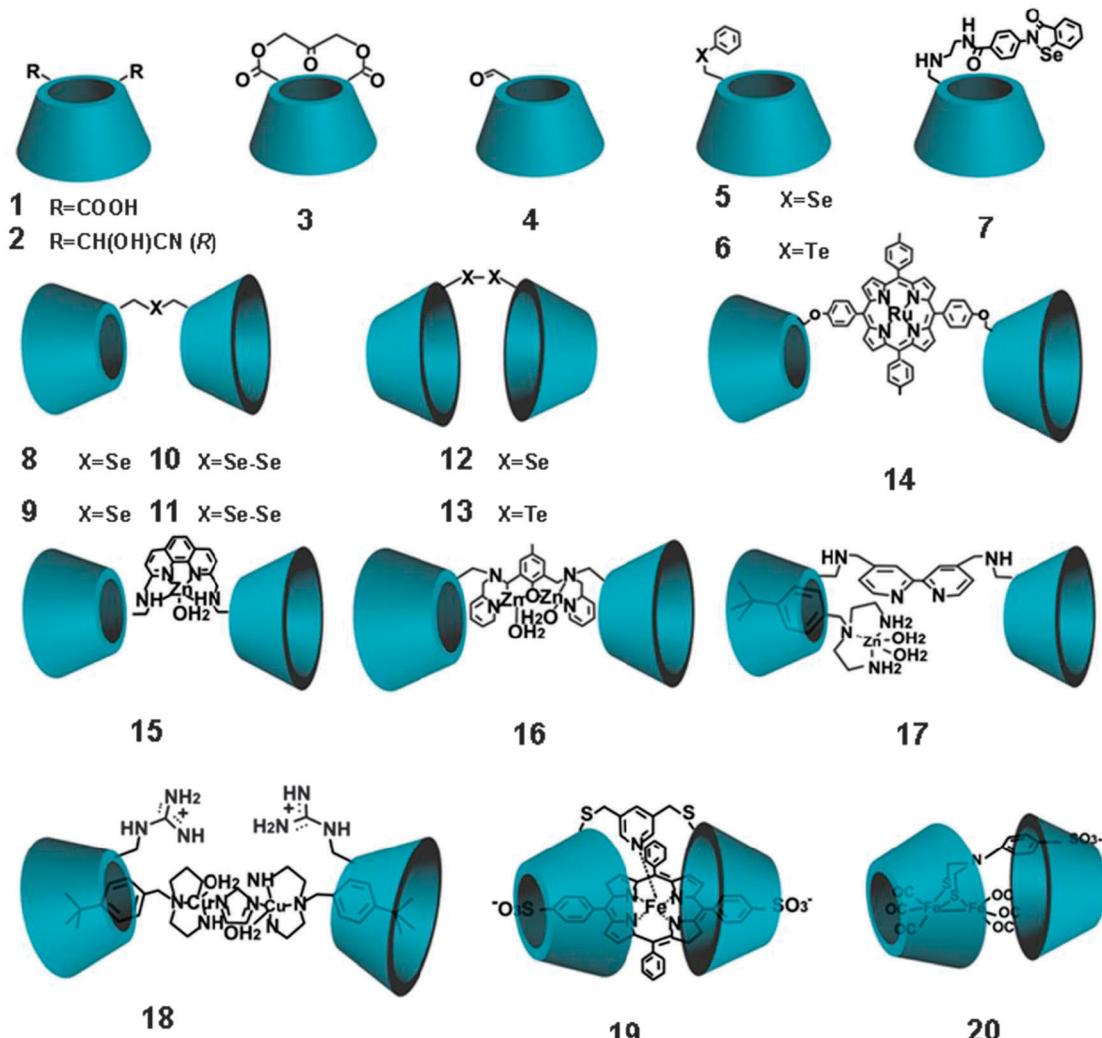


Chart 2 Recent representative examples of β -cyclodextrin-based enzyme models.

160 000 is obtained for HPNP. These studies suggest that the selective substrate binding *via* hydrophobic interactions might be vital for the highly efficient catalysis of metallohydrolase models **15** and **16**.

At the same time, cyclodextrins have been studied as one of the most important receptors in supramolecular chemistry.²² Through host–guest chemistry they can self-assemble into complicated supramolecular complexes possessing enzyme-like properties and functions.^{91,92} A supramolecular metallohydrolase model **17** containing Zn(II)-coordinated complexes loaded into a β -cyclodextrin dimer has been designed.⁹³ Model **17** can be stabilized by supramolecular interactions, and therefore acts as a hydrolase mimic for catalyzing the hydrolysis of *p*-nitrophenyl acetate. Similarly, depending on coordination chemistry and host–guest chemistry, a cyclodextrin-based supramolecular superoxide dismutase (SOD) model **18** has been reported.⁹⁴ Model **18** shows a high SOD activity ($IC_{50} = 0.16 \mu\text{M}$ in contrast to natural SOD with an IC_{50} of $0.04 \mu\text{M}$). Interestingly, the positive guanidinium attached on cyclodextrin plays a significant role in increasing the SOD activity by guiding the superoxide to enter and the peroxide to leave from the catalytic sites. In accord with the design above, a myoglobin

model **19** has been developed *via* the supramolecular complexes of β -cyclodextrin dimer and porphyrin. Interestingly, model **19** reproduces the functions of myoglobin in water.⁹⁵ Very recently, Singleton *et al.* built a supramolecular hydrogenase model **20** by positioning the active site into the cavity of β -cyclodextrin by means of host–guest chemistry.⁹⁶ The inclusion not only distorted the structure of the diiron moiety as demonstrated by the X-ray crystallographic structure, but also caused the change in the redox and electrocatalytic features of small active sites. The hydrogenase model formed by supramolecular interactions possibly facilitates H⁺ reduction or H₂ oxidation.

3.1.2 Calixarenes. Calixarenes are macrocyclic molecules made up of phenol and methylene units, and they usually have many conformational isomers due to the two possible rotational modes of the phenol unit.⁵⁰ Inspired by their unique geometry, calixarenes are attractive for applications in the design of artificial enzymes.⁵³ The functional groups can readily be positioned on the structure of calixarenes by chemical modifications. Interestingly, calixarenes are capable of adopting different

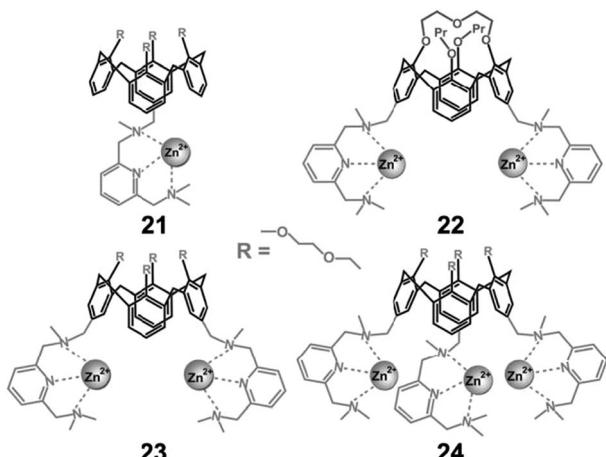


Fig. 1 Mono-, di- and trinuclear Zn(II) phosphatase mimics.¹⁰⁰

conformations to accommodate substrate molecules, virtually mimicking the dynamic feature of enzymes (induced fit).

Recently, great advances have been made in the field of calixarene-based artificial enzymes.^{53,97,98} For example, Reinhoudt and coworkers reported a class of phosphatase models attached with one, two, or three catalytic sites (such as Zn²⁺) on the calix[4]arene scaffolds (Fig. 1).^{99,100} The catalytic activities of calix[4]arenes **21–24** are investigated toward the transesterification of the RNA model substrate HPNP in an acetonitrile and aqueous buffer mixture. The experiment shows that the catalytic moiety itself has a lower catalytic activity than its mononuclear calixarene-based mimic **21**, indicating that the calixarene cavity is involved in the catalysis. The dinuclear **23** and trinuclear **24** exhibit rate accelerations of 23 000-fold and 32 000-fold in the transesterification of HPNP over the non-catalyzed reaction, respectively, whereas the mononuclear **21** is about 50-fold less active. This suggests that the catalytic sites have function cooperativity in catalysis (Fig. 2). Interestingly, a more rigid model compound **22** exhibits a lower binding constant for the substrate and a lower catalytic activity than the conformationally less restricted **23**, which implies that the flexibility within the calixarene structure is necessary to achieve the cooperative effects between the catalytic sites. The observations above suggest that the preorganization of catalytic sites on the rigid synthetic platform in three-dimensional space is essential for the efficient catalysis by cooperative action (Fig. 2). A later study proposed a similar mechanism as depicted in Fig. 2, wherein the artificial acylases containing two Ba²⁺-ions bound by crown ether moieties on the upper rim of calix[4]arenes are investigated for the ethanolysis

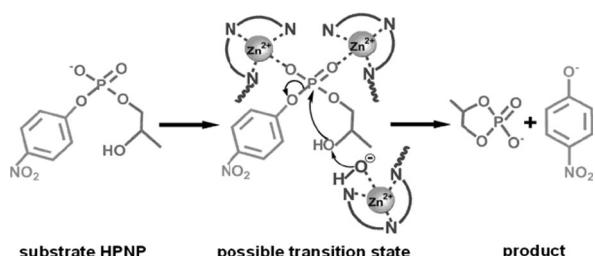


Fig. 2 Proposed mechanism for HPNP cleavage by trinuclear phosphatase model **24**.¹⁰⁰

studies of various phenol esters.¹⁰¹ In addition, based on the similar design mode as shown in Fig. 1, a series of metallo-hydrolase models with various Zn(II)-chelated azacrown ethers attached to the upper rim of calix[4]arenes were prepared.^{102–104} Unexpectedly, these models show relatively low catalytic activities towards the cleavage of HPNP. However, they can efficiently catalyze the solvolysis of various phenol esters by methanol. Model reactions with HPNP demonstrate that the arranged distance between catalytic moieties is sensitive to synergistic effects in catalysis.

Calixarenes are very useful in the design of supramolecular artificial enzymes and the supramolecular complexes exhibit significant properties that neither of the individual components has. For instance, a supramolecular heme mimetic is generated by the formation of a complex between *p*-sulfonato calixarene and porphyrins through strong charge–charge interactions with association constants of 10⁵ M⁻¹ in water.¹⁰⁵ The supramolecular model is capable of facilitating O₂-transport through membranes by reversible binding of oxygen to the complex. At the same time, Bakirci *et al.* reported the fabrication of supramolecular enzyme mimics by self-assembly of *p*-sulfonato calixarene with a rationally selected guest molecule and a transition-metal ion.¹⁰⁶ The resulting complexes were formed by the host-assisted metal–ligand coordination. Moreover, the self-assembled system shows very high selectivity resulting from the cooperative nature of various supramolecular interactions.

3.1.3 Cyclophanes and other macrocycles. Besides cyclodextrins and calixarenes, other macrocycles such as cyclophanes, crown ethers, cucurbiturils and so on have been used as scaffolds for constructing supramolecular enzyme mimics.²² These enzyme models generally possess a binding site and one or more functional groups. The creation of a specific microenvironment at the active center is believed to play an important role in the enzyme-like reactions even though it is synthetically difficult to achieve such environments with relatively small molecule scaffolds.

The macrocycles of cyclophane type have been emphasized in artificial host–guest systems.^{107–111} A detailed study of the complexation between cyclophane and the substrate has been undertaken by Marakumi *et al.*¹⁰⁷ The study showed that the substrate is undoubtedly bound to the cyclophane cavity which causes the conformational changes in the host. The dynamic behavior of induced-fit substrate recognition is invaluable in the understanding of enzyme catalysis. Therefore, the cyclophane skeletons are attractive with respect to the design of artificial enzymes. For instance, Diederich and co-workers prepared a variety of thiazolocyclophanes with binding sites for aromatic substrates to mimic the mode of action of thiaminediphosphate-dependent enzymes (Fig. 3).^{112–115} As a mimic of pyruvate oxidase, thiazolio-cyclophane **25** can efficiently catalyze the oxidation of aromatic aldehydes to their corresponding carboxylic esters in the presence of an oxidizing agent.¹¹⁵ On the basis of this work, a type of pyruvate oxidase mimics was prepared by positioning a catalytic cyclophane moiety at the core of a dendrimer.¹¹⁶ The dendronised cyclophane model with the catalytic group thiazolium on the rim of the macrocycle is capable of catalyzing the model reaction of oxidation of naphthalene-2-carbaldehyde. The substrate can

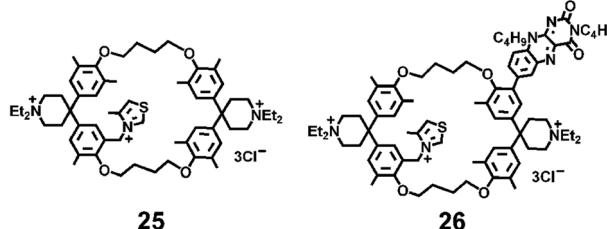


Fig. 3 Typical cyclophane-based enzyme models developed by Mattei and Diederich.¹¹³

dynamically enter into the macrocyclic cavity through $\pi-\pi$ and/or hydrophobic interactions. Interestingly, the dendritic branches have no detrimental effect on substrate binding. Evidently, the dendronised cyclophane model has a similar binding affinity for substrate naphthalene-2-carbaldehyde compared to the simple cyclophane **25** ($K_a = 300 \text{ M}^{-1}$). This study suggests that the interior of densely packed dendrimers might not be a favorable environment for the multistep catalysis as it was observed that the dendronised cyclophane model shows a lower catalytic activity than **25**. By the combination of a well-established binding site with both the flavin and thiazolium groups, a pyruvate oxidase mimic **26** was synthesized.¹¹³ The complexation of substrate 2-naphthaldehyde with flavo-thiazolio-cyclophane **26** was investigated in proton NMR binding titrations, and a high affinity ($K_a = 2900 \text{ M}^{-1}$) was obtained. The model reaction study of the oxidation of 2-naphthaldehyde in methanol to methyl 2-naphthoate indicates that the turnover number of **26** is as high as 0.24 s^{-1} which is one of the highest values reported for pyruvate oxidase mimics. The spatial proximity of the functional groups to the binding site as well as the intramolecularity of the oxidation step are therefore essential for enhancing catalysis. This biomimetic system copies the situation in the enzyme where the cofactors are located in the enzyme active site thus increasing the effective molarity of the substrates.

In addition, crown ethers and polyammonium macrocycles as important molecular acceptors have been used to develop enzyme-like functions. In an early study, Hosseini *et al.* reported a type of polyammonium macrocycles which catalyze the hydrolysis of adenosine triphosphate.¹¹⁷ Substitution of the macrocycles causes an obvious difference in the reaction rate, implying the important role of structural effects in the complexes formed with adenosine triphosphate. These enzyme mimics exhibit the remarkable selectivity for substrate binding during the supramolecular catalysis and obey the Michaelis–Menten behavior. Recently, Jiang *et al.* synthesized a series ofaza crown ether derivatives with carboxyl groups which act as artificial aspartic proteinases.¹¹⁸ In particular, model **27** shows good catalytic activity in the deacylation reaction of amino acid *p*-nitrophenyl ester. The study of the structure–activity relationship suggests a nucleophilic catalytic mechanism (Fig. 4). A detailed analysis of catalytic activity on the effects of length and rigidity of functional side arms as well as the ring size of crown ether was completed, giving the way to the origin of substrate selectivity of model **27**. The results obtained from the biomimetic system are very helpful in understanding the detailed catalytic process of aspartic proteinases.

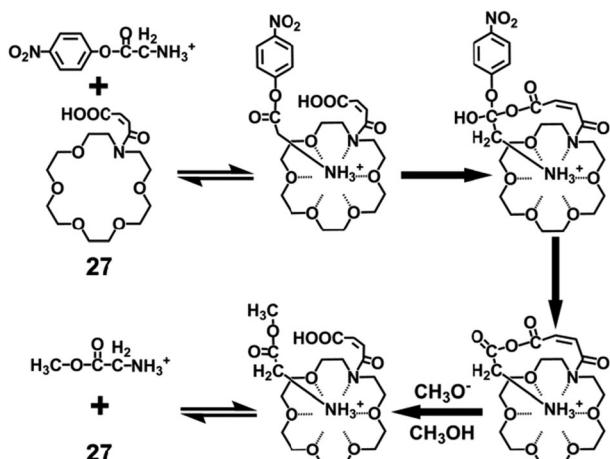


Fig. 4 Nucleophilic mechanism of artificial aspartic proteinase **27**.¹¹⁸

Besides the macrocycle-based enzyme models mentioned above, other simple macrocyclic enzyme mimics can be designed by conventional chemical synthesis or self-assembly (Fig. 5). Model **28** is designed and prepared to be a functional model of SOD.¹¹⁹ It catalyzes the dismutation of the superoxide radical with a second-order rate constant of above $2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ approaching that of the native Mn-SOD enzyme. Moreover, model **28** is chemically and biologically stable *in vivo*, suggesting that it might be applicable in clinical therapies for diseases mediated by superoxide radicals. Model **29**, reported by Sanders, is a cyclic zinc porphyrin acceptor which possesses convergent binding sites that can bind two substrates in close proximity.¹²⁰ It catalyzes the model reaction of Diels–Alder between pyridine-modified maleimide and furan-based diene with a rate acceleration of 200-fold as compared to the uncatalyzed reaction. Additionally, Sanders and coworkers constructed receptor **30** through a dynamic combinatorial chemistry system in which a guest molecule is used as a template.¹²¹ In a model system, the template molecule can be the product of Diels–Alder reaction between acridizinium bromide and cyclopentadiene, which leads to the generation of macrocycle **30** via disulfide bond formation from the slow oxidation of various dithiol building blocks. Macrocycle **30** is therefore used as a catalyst toward the Diels–Alder reaction

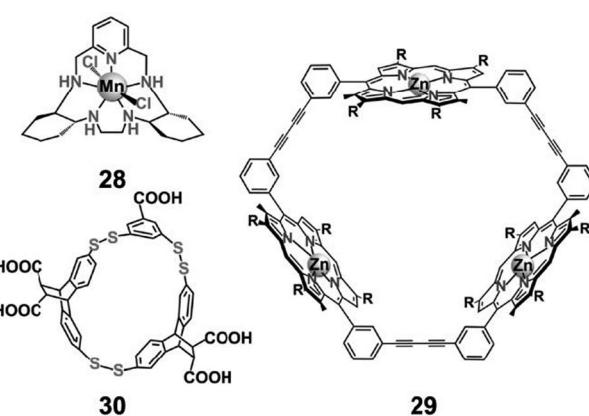


Fig. 5 Several typical macrocycle-based enzyme models obtained with synthetic (**28**)¹¹⁹ and (**29**)¹²⁰) or self-assembly (**30**)¹²¹) approaches.

between acridizinium bromide and cyclopentadiene. Although macrocycle **30** is inactive for catalysis, this study provides an excellent strategy to exploit the role of substrate binding during catalytic processes.

3.2 Container molecules as artificial enzymes

Enzymes catalyze chemical transformations in a confined microenvironment thus presenting specificity and stereo-selectivity. The synthetic molecules, which can be designed with a confined microenvironment, can efficiently reproduce the specific features of enzymes. A lot of examples demonstrate that the synthetic container molecules are able to catalyze numerous chemical reactions, like enzymes.^{122–126} Currently, the container molecules can be prepared either by chemical synthesis⁵² or by a self-organized approach.²⁹

3.2.1 Synthetic container molecules. It seems reasonable to chemically synthesize a container molecule as an enzyme model with both the substrate binding site and the catalytic group in a proper position. Based on this idea, Thordarson *et al.* introduced an excellent processive enzyme mimic **31** with a confined space for the substrate polybutadiene polymer (Fig. 6).¹²⁷ The enzyme mimic **31** catalyzes the conversion of the double bonds into the corresponding epoxides by inclusively moving along a polybutadiene polymer. The direction of substrate binding is controlled by the size of chelate ligands and the reaction rates inside and outside the cavity are significantly different. The catalysis taking place in the cavity gives high catalytic activity and virtually simulates the actions of processive enzymes. The cavity-inhibitor experiment gives rise to a remarkable decrease (*ca.* 40%) in the reaction rate. The subsequent study of kinetics and thermodynamics demonstrated that the processive enzyme mimic **31** most likely operates by randomly sliding along its macromolecular substrate.^{128,129}

In addition, cavitands as molecular acceptors have been designed and synthesized. They are bowl-shaped container molecules that possess concave surfaces. A recent study of functional cavitands points to the interesting features of catalysis that have been observed from the understanding of enzymes.⁵¹ By positioning the catalytic groups on the ridge of concave surfaces, some ideal cavitand-based enzyme mimics can be generated.^{130–134} For example, by positioning hydrogen-bonding groups such as a dienophilic maleimide on the rim of

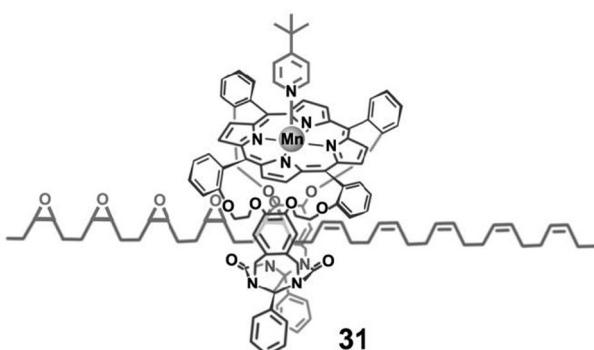


Fig. 6 A container molecule as processive enzyme mimic **31** for the epoxidation of a polybutadiene polymer.¹²⁷

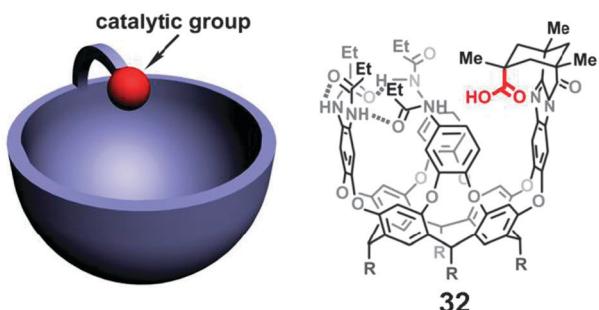


Fig. 7 Schematic representation of the cavitand-based enzyme models and a typical enzyme model **32** designed by Rebek.¹³⁶

cavitand, a rate acceleration of 60-fold was observed for the cycloaddition reaction between the maleimide and 9-anthracene-methanol.¹³⁵ Rebek and coworkers recently built a synthetic enzyme mimic **32** in which a deep and open-ended cavity was designed (Fig. 7).¹³⁶ The cavitand **32** can accommodate suitable guest molecules, and the conformation complex between cavitand and substrate is dynamically stabilized by hydrogen bond interactions around the rim of the receptor. Compared to flexible receptors for selective molecular recognition,¹³⁷ the cavitand **32** is capable of catalyzing the regiocontrolled transformation of epoxyalcohols into cyclic ethers with a rate acceleration of 50- to 300-fold. This biomimetic system incorporates the features of both the reasonable position of catalytic functionality and the specific microenvironment akin to the structural interiors of natural enzymes.

3.2.2 Self-assembled container molecules. Substantial progress has been made in fabricating container molecules that emulate the enzymatic pockets.^{22–24,122} By hydrogen bonding interactions and metal coordination, the self-organization of synthetic building blocks can result in container molecules with various degrees of complexity. It is rather difficult to incorporate a catalytic group onto the skeleton of the container molecule. However, the three-dimensionally enclosed cavity endows these kinds of molecules with remarkable catalytic capacity.^{22–24,29–32,51,122–126,138–141}

The Rebek group has developed a series of capsular molecules formed by self-assembly of complementary concave receptors *via* hydrogen bonding interactions (Fig. 8).^{51,138–142} These capsules are not only good acceptors for recognizing different guests but also active catalysts possessing enzyme-like functions.^{130,143–145} The studies from this group demonstrate that the behavior of molecules in solution is quite different from their behavior in capsules. The novel phenomena observed inside capsules provide new insights into biological rules and allow one to differentiate the conventional molecular behavior in solution.¹⁴⁶ The observation of different behaviors of molecular motions will certainly be useful in the understanding of the motions of substrates in catalysis.

Recent development in the design and construction of coordination container molecules has made great contributions. A number of coordination ensembles, such as nanocapsules **33** and **34**, metallocryptand **35**, and metallocage **36** (Chart 3), can be successfully prepared by means of self-assembly and metal coordination. The group of Fujita developed a large family of cage-like hosts through self-assembly and metal

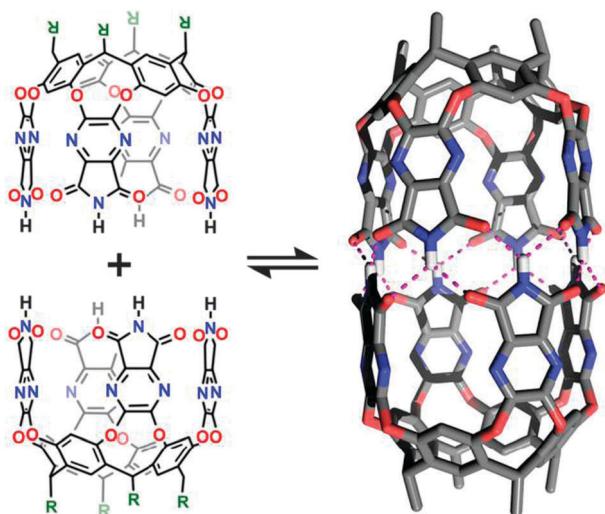


Fig. 8 Classic self-assembled container molecule from Rebek's group.¹⁴³

coordination approaches.^{147,148} These self-assembled hosts employ enclosed cavities to encapsulate various guests. Due to the hydrophobic cavities of hosts, these models are able to selectively control the chemical reactions and even stabilize the reactive transition states during the reactions. Moreover, some interesting chemical phenomena have been discovered within the container molecules. For example, the minimal nucleotide duplex is stable when it is located in the enclosed cavity of the molecular cage.^{149,150} This self-assembled system provides an excellent framework to explore and reproduce the molecular realities during the enzyme catalysis.^{151–157} For instance, a classic Diels–Alder coupling reaction of anthracenes and maleimides was tested in the self-assembled biomimetic system (Fig. 9).¹⁵⁸ The Diels–Alder reaction of 9-hydroxymethylanthracene **38** and *N*-phenylmaleimide **41** in solution generally produces an adduct **42** bridging the center ring

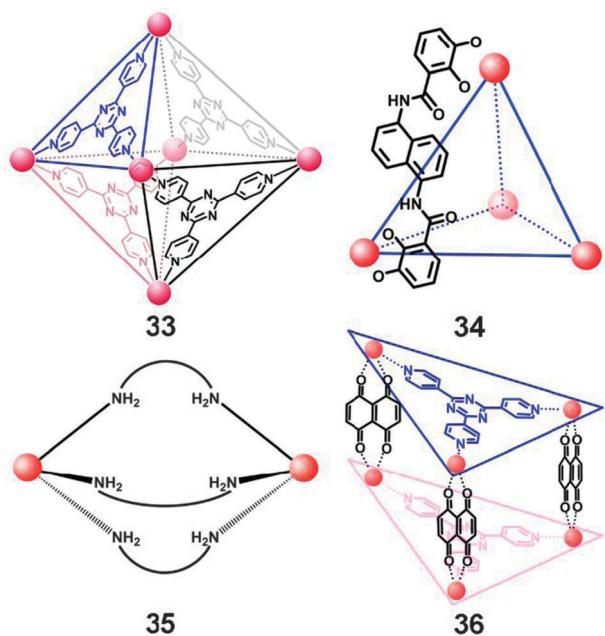


Chart 3 Examples of coordination container molecules 33–36.

(9,10-position) due to the high localization of π -electron density at that site (Fig. 9C). In the presence of cage **33**, the well-established selectivity can significantly change, thus leading to the adduct **40** formation at a terminal ring (1,4-position). The study indicates that the unusual regioselectivity originates from topochemical control induced by the proximity of the 1,4-position of **38** to the dienophile in the cage **33**. In detail, the inclusion complex **33** \supset (**38**–**39**) can selectively form within 5 min in an aqueous solution as observed by proton NMR analysis. On heating the solution of complex at 80 °C for 5 hours, the signals derived from **38** and **39** disappear and are replaced by resonances consistent with a Diels–Alder adduct **40**. The unusual structure of the 1,4-Diels–Alder adduct **40** is unambiguously characterized by X-ray crystallographic analysis of inclusion complex **33** \supset **40**. The 1,4-regioselective Diels–Alder reaction is further applied to different substrates. The reactions of carboxyl-, cyano-, and vinyl-substituted anthracenes with *N*-cyclohexylmaleimide **39** in the presence of cage **33** result in the corresponding 1,4-adduct in 92%, 88%, and 80% yields, respectively. Bowl **37** is able to efficiently catalyze the Diels–Alder reaction of **38** and **41**. However, NMR analysis demonstrates that the catalyzed reaction takes place at the conventional 9,10-position of anthracene to give adduct **42**. The difference between cage **33** and bowl **37** in the Diels–Alder reaction is mainly caused by the geometry-fixed encapsulation. Bowl **37** has an open concave space that facilitates the rapid binding and release of the substrate. Importantly, the product inhibition can be excluded in the biomimetic system. The encapsulated product is significantly destabilized due to the loss of host–guest aromatic stacking interactions, and can be smoothly replaced by incoming substrates.

It is a primary goal to design and synthesize molecular hosts with the typical reactivity of natural enzymes. Raymond, Bergman and co-workers have made substantial progress in

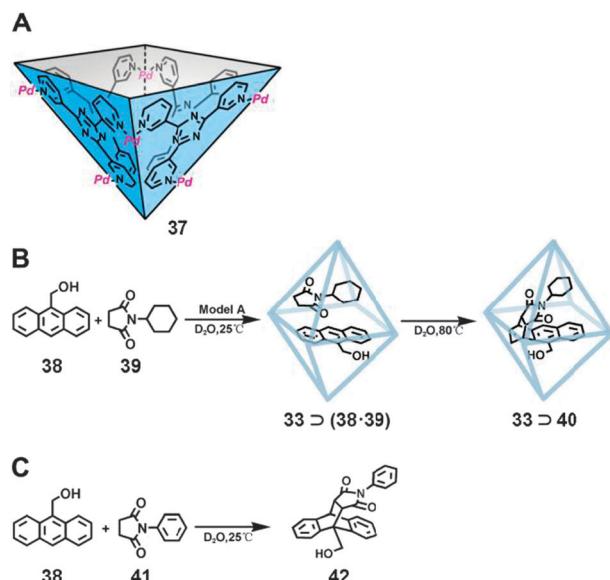


Fig. 9 (A) The structure of self-assembled bowl molecule **37**. (B) Syn-1,4-regioselective Diels–Alder reaction of 9-hydroxymethylanthracene **38** and *N*-cyclohexylmaleimide **39** within cage **33**. (C) Diels–Alder reaction of **38** and **41** catalyzed by bowl **37** in the aqueous solution.¹⁵⁸

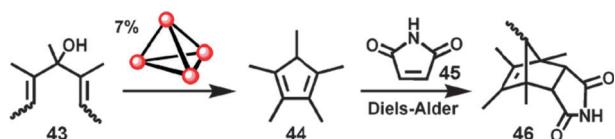


Fig. 10 (A) Schematic view of the Nazarov reaction catalyzed by host **34** and the conversion of the product.¹⁶¹

supramolecular catalysis by self-assembled container molecules with unprecedented catalytic capacity.^{159,160} For example, a self-assembled host **34** is used to catalyze the Nazarov cyclization that permits stereospecific construction of a new carbon–carbon bond (Fig. 10).¹⁶¹ The three stereoisomers of **43** can be selectively catalyzed by host **34** to form product cyclopentadiene **44**. The inhibitor experiment indicates that the special interior of **34** plays a vital role in catalysis. Moreover, the product inhibition causes a decrease in the reaction rate in the self-assembled biomimetic system. To overcome this issue, the product is successfully converted into a poor guest for the cavity of host **34**. By the Diels–Alder reaction using maleimide **45** as a trapping agent, **44** is chemically transferred into a cavity-unfavorable guest **46**. Interestingly, the rate acceleration of the catalyzed reaction over the uncatalyzed reaction is on the order of 10^6 , representing the first example of host-mediated supramolecular catalysis that reaches rate enhancements comparable to those found in enzymatic systems. The study indicates that the extremely high catalytic activity of host **34** is due to the combination of preorganization of the encapsulated substrate and the stabilization of the transition state of the catalytic reaction by constrictive binding, besides an increase in the basicity of alcohol functionality caused by encapsulation. The container molecule **34** follows the Michaelis–Menten behavior during the enzyme-like catalysis. In addition, a catalyst encapsulated in a supramolecular host exhibits a remarkable enhancement in catalytic capacity.¹⁶² The gold(i)–phosphine complexes are readily encapsulated by host **34**. The resulting complexes are capable of catalyzing the intramolecular hydroalkoxylation of allenes with a rate acceleration of 8-fold compared to the unencapsulated gold(i)–phosphine complexes. The kinetics analysis demonstrates that the gold(i)–phosphine complexes encapsulated in host **34** have 67 catalytic turnovers.

4. Artificial enzymes designed with non-covalent anchoring strategies

Recent progress in host–guest chemistry allows chemists to use non-covalent anchoring strategies to build supramolecular complexes that behave as enzyme mimics. Besides the synthetic host–guest systems, proteins and nucleic acids provide excellent frameworks to construct the supramolecular artificial enzymes. A typical example is use of the biotin–avidin system to design supramolecular artificial enzymes.¹⁶³

4.1 Synthetic acceptor–ligand complexes

By employing a synthetic donor–acceptor system, some supramolecular enzyme mimics have been designed and synthesized (Fig. 11). Successful examples, such as enzyme models **17–20**, that have hydrophobic interactions in their supramolecular structures have been established. In fact, to design supramolecular

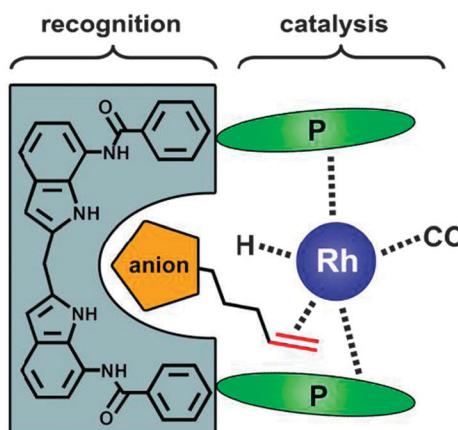


Fig. 11 An example of supramolecular catalysis based on the synthetic donor–acceptor system. In this case, the anionic substrate preorganization was achieved by an Rh catalyst that bears a ligand furnished with an anion-binding pocket.

enzyme mimics, a supramolecular substrate preorganization strategy with hydrophobic interactions has been proposed by Breslow *et al.*¹⁶⁴ Recently, a similar supramolecular substrate preorganization strategy by hydrogen bonding interactions has been elegantly developed.^{165–171} For example, Dydio *et al.* reported a supramolecular catalyst with an integral anion-recognition site (Fig. 11).¹⁷¹ The resultant rhodium-based complexes can regioselectively catalyze the hydroformylation reactions for substrates that have anionic groups. Interestingly, the linear product is almost exclusively produced (*ca.* 97% in contrast to 3% of the branched product) for the substrate. To address the source of the significantly high regioselectivities, experiments and DFT calculations have been carried out. The study demonstrates that the undesired product is blocked by host–guest interactions, whereas the desired product is lowered in energy because of the suitable length of the substrate.

4.2 Protein–ligand complexes

It is well recognized that many protein enzymes possess the binding pockets for molecular recognition. By employing a non-covalent anchoring strategy, various functional ligands can be incorporated into the binding pockets of proteins, resulting in the formation of stable supramolecular complexes. On the basis of this design principle, the supramolecular enzyme mimics based on protein–ligand complexes have been extensively developed (Fig. 12).^{172–179}

In particular, the biotin–(strept)avidin technology has been widely used to create protein-based supramolecular enzyme mimics.^{163,173,180–182} These mimics can be further optimized by chemical modification of the biotin moiety and genetic mutagenesis of protein avidin or streptavidin.¹⁸³ Ward and co-workers developed a series of artificial transfer hydrogenases based on biotin–(strept)avidin technology. A designed evolution protocol has been implemented to identify both *R*- and *S*-selective variants for reduction of acetophenone derivatives (up to 96% ee) and dialkyl ketone substrates (up to 90% ee).^{184,185} In addition, other anchoring strategies for generating protein–ligand complexes have been exploited to synthesize supramolecular artificial enzymes for ester hydrolysis,¹⁸⁶

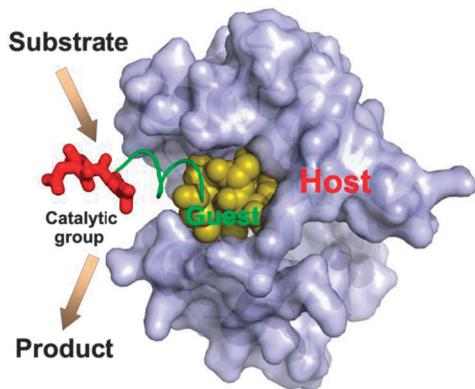


Fig. 12 Schematic representation of supramolecular enzyme models in which a catalytic group is non-covalently incorporated onto the protein matrix.

dihydroxylation,¹⁸⁷ sulfoxidation,^{188,189} hydrogenation,¹⁹⁰ epoxidation,^{191,192} and Diels–Alder reactions.¹⁹³

Recently, Creus *et al.* reported a (*S*)-selective transfer hydrogenase model through the biotin–streptavidin technology.¹⁹⁴ The structurally full characterization of the supramolecular enzyme mimic provides insights into a designed evolution protocol for the optimization of artificial transfer hydrogenases. The study indicates that the enantioselectivity displayed by the supramolecular mimic depends on the specific interaction between the host protein and the ligand. Considering that the biotin-binding cavity of streptavidin can accommodate small coordination compounds, Pordea *et al.* successfully synthesized an artificial metalloenzyme for enantioselective sulfoxidation based on vanadyl-loaded streptavidin (Fig. 13).¹⁹⁵ Incorporation of a vanadyl ion into the biotin-binding pocket of streptavidin gives rise to a type of artificial enzyme for the enantioselective oxidation of prochiral sulfides. The supramolecular enzyme mimics display enhanced activity and selectivity (up to 93% ee for the sulfoxidation of methyl-2-naphthylsulfide **47**) in the presence of TBHP compared to the protein-free salt. Inhibitor experiments indicate that the metal moiety occupies the biotin-binding site of streptavidin. The analysis experiments including EPR spectroscopy, docking simulation, and chemical or genetic

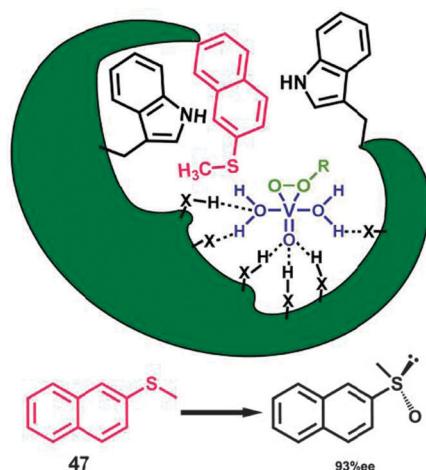


Fig. 13 Vanadium-dependent artificial peroxidase for enantioselective sulfoxidation reactions.¹⁹⁵

modification of the protein scaffold demonstrate that the catalytic group functions only *via* a second coordination sphere within the biotin-binding pocket of streptavidin.

More recently, Oliveri *et al.* synthesized a SOD enzyme mimic by the non-covalent conjugation of the manganese(III) complex of *N,N'*-bis(salicylidene)-3,4-diaminobenzoic acid onto the scaffold of bovine serum albumin.¹⁹⁶ The study shows that the albumin environment affords a positive effect on the SOD activity of the inorganic complex. The analysis of catalysis indicates that the supramolecular enzyme model has a high SOD activity (IC_{50} : 0.19 μ M, catalytic efficiency: $7.7 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$).

4.3 Nucleic acid–ligand complexes

Many enzymes carry out the catalytic functions in the presence of cofactors or prosthetic groups. The chemical compositions of DNA and RNA apparently lack the functional groups and instead depend upon the coenzymes to supply the functionalities for catalysis. By using a non-covalent anchoring strategy, the various functional ligands can be rationally incorporated into the matrices of nucleic acids. The fantastic nucleic acid structures, such as the DNA duplex, aptamers, and G-quadruplexes, provide excellent scaffolds for designing the supramolecular artificial enzymes.^{176,197–200} Recently, immense progress has been made in the field of catalysis of supramolecular enzyme mimics based on nucleic acid–ligand complexes.^{197,201–211} Due to their stable and well-defined supramolecular structures, the analysis of catalysis of these enzyme mimics affords useful information on the understanding of structure–function relationships and provides them with the potential applications in industrial biocatalysts and biomedicines as well.

Inspired by the absolute handedness of helical structures of the DNA duplex, Roelfes and Feringa reported a promising example of DNA-based asymmetric catalysis by placing the catalytically achiral ligands into DNA scaffolds through non-covalent interactions (Fig. 14).¹⁹⁸ In this supramolecular system, the chirality of the DNA duplex can be directly transferred into the catalytic reaction to control the formation of products. This indicates that the chiral scaffold of DNA plays an essential role in the DNA-based catalytic reactions. Furthermore, a complete study on the enantioselective addition of water to olefins in aqueous media by using this supramolecular system proved to be a successful example of a non-enzymatic enantioselective and diastereospecific syn hydration of α,β -unsaturated ketones.²¹² The enantioselectivity originates

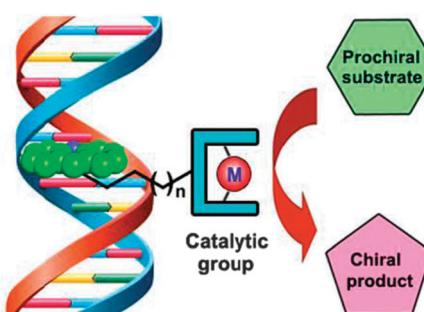


Fig. 14 Schematic representation of duplex DNA-based asymmetric catalysis applied in catalytic enantioselective reaction.



Ligand:

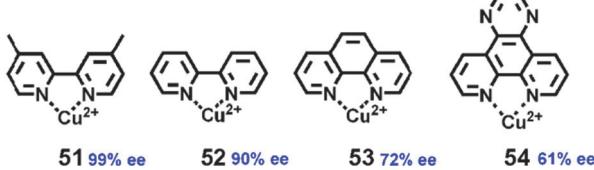


Fig. 15 DNA-ligand catalyzed Diels–Alder cycloaddition between **48** and **49**.²⁰⁷

from the DNA, and the enantiomeric excess of the chiral β -hydroxy ketone product is up to 82%. This study clearly underpins the versatility of the DNA-based catalysis concept and its ability to mimic nature's use of water as a reagent in asymmetric conjugate-addition reactions in water.

The chiral scaffolds of nucleic acids play an essential role in the enantioselective catalysis of supramolecular artificial enzymes based on nucleic acid–ligand complexes. Boersma *et al.* reported a detailed study of DNA-based asymmetric catalysis.²⁰⁷ The supramolecular models exhibit ligand- and sequence-dependent rate acceleration and enantioselectivity. As seen in Fig. 15, for the Diels–Alder reaction of azachalcone **48** with cyclopentadiene **49** resulting in the formation of product **50**, ligands **51–54** inserting DNA scaffolds show different enantioselectivity, and among them ligand **51** is the best ligand which gives rise to high enantioselectivity of up to 99% ee. Furthermore, DNA in combination with **51** results in a rate acceleration of 2 orders of magnitude compared to ligand **51** alone. More interestingly, the enantioselectivity and the absolute configuration of the Diels–Alder adduct prove to be strongly dependent upon the sequence of the DNA scaffold. The study demonstrates that the presence of G-tracts in the sequence (*e.g.*, *d*(TCAGGGCCCTGA)₂) is effective to achieve the highest enantioselectivities (>99% ee), suggesting the importance of the microenvironment structure provided by the nucleic acid scaffold. This is a clear demonstration of the power of the supramolecular catalysis in a simple organized system.

5. Nanometer-sized artificial enzymes

Enzymes are nanometer-sized macromolecules formed by the folding and self-assembly of polypeptides by supramolecular interactions. In the synthetic system, self-assembly of functional building blocks gives rise to the formation of diverse and complex aggregate morphologies such as spherical micelles, vesicles, nanoparticles, nanotubes, and nanogels.²² These nanomaterials are attractive candidates for constructing supramolecular artificial enzymes because of their chemically tailorable physical properties directly related to composition and size as well as their unusual target binding properties. Depending on rational design of building blocks, the self-assembled nanomaterials can act as artificial enzymes with particular capacity

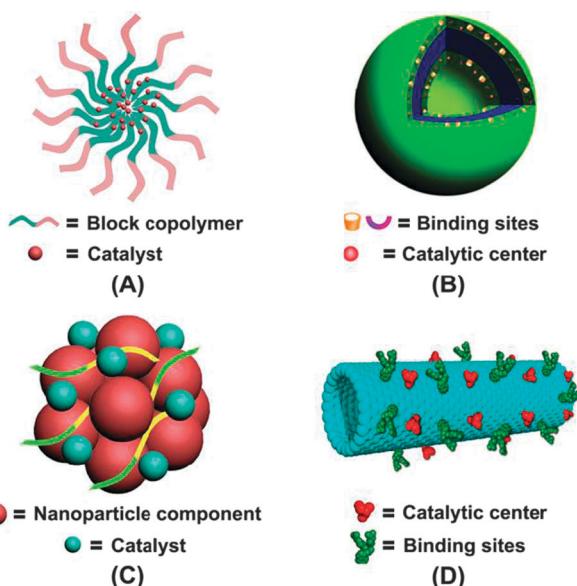


Fig. 16 Schematic representation of enzyme mimics based on micelles (A), vesicles (B), nanoparticles (C), and nanotubes (D).

to bind to the substrate and catalyse (Fig. 16).^{30,79,213–222} Micelles represent a well-studied area in biomimetic chemistry due to their special properties.²²³ They have two typologically different regions and can be used as scaffolds to make supramolecular artificial enzymes. Wang *et al.* reported a micelle-based GPx model (structural diagram shown in Fig. 16A) in which the catalytic ligand dibenzyl diselenide was incorporated into a block copolymer micelle based on polystyrene-*b*-poly(acrylic acid).²²⁴ This supramolecular enzyme model composed of dibenzyl diselenide and block copolymers by self-assembly is relatively stable and affords effective GPx-like activity. Interestingly, the catalytic activity can be affected by the ionic strength of the solution. An increase in the ionic strength of the solution simply upon addition of NaCl leads to an enhanced GPx activity. Moreover, dibenzyl diselenide incorporated into the micelles is quite stable and maintains its GPx activity even after exposure to the atmosphere. Additionally, Huang *et al.* designed a smart artificial GPx micelle with a temperature-sensitive block copolymer carrying a catalytic element.²²⁵ The enzyme mimic displays good GPx-like activity and classical saturation kinetics. In this biomimetic system, as expected, the catalytic activity can be altered with the temperature due to the temperature-responsive poly(*N*-isopropylacrylamide) moiety of the copolymer.

The dispersion of certain bilayer-forming amphiphilic molecules in aqueous solution gives rise to the formation of vesicles. The stable vesicles are spherical in shape and contain curved and self-closed molecular bilayers that are composed of the amphiphiles. The interior of the vesicles is generally an aqueous core. Because of their special structural properties, vesicle-based supramolecular artificial enzymes have been considered. Yin *et al.* recently prepared a vesicle-based enzyme mimic (structural diagram shown in Fig. 16B) composed of the temperature-sensitive poly(*N*-isopropylacrylamide)-*b*-polyacrylamides by a bending process.²²⁶ To optimize the function of artificial enzymes, the molar ratio of the functional copolymers is measured to

obtain a relatively stable vesicle with good GPx-like activity. Furthermore, the catalytic activity can be well adjusted by a change of temperature.

Currently, nanoparticle research is of great scientific interest due to a wide variety of potential applications in catalysis, biomedical, optical and electronic fields. The specific properties of nanoparticles originate from the surface coating. In particular, the surface coating can manage stability, solubility and target binding. Enzyme mimics based on functionalized nanoparticles can efficiently catalyze many chemical reactions (Fig. 16C).^{227–231} Recently, Scrimin and coworkers reported a series of gold-nanoparticle-based supramolecular enzyme mimics for catalyzing the transphosphorylation reaction.^{232,233} The enzyme models are obtained by self-assembling multiple copies of thiolated ligands on the surface of monolayer-protected gold nanoparticles. The cooperative and multivalent nature of the nanoparticle-based enzyme mimics leads to the impressive catalysis with a rate acceleration of up to 300 000-fold. Slocik *et al.* reported an enzyme mimic designed with the biotemplated nanoparticles.²³⁴ The nanoparticles are made up of biotemplated cadmium sulfide and cadmium sulfide–platinum, and display the nitrate reductase activity in the reduction of nitrate to nitrite. Remarkably, the cadmium sulfide–platinum exhibits an extremely high catalytic activity which is 23-fold higher at room temperature than that of natural nitrate reductase. Furthermore, the activity of cadmium sulfide–platinum improves with increasing temperature due to the enhanced electron diffusion increasing along the energy scale. These features of activity and temperature dependence indicate the potential of hybrid nanoparticles as supramolecular enzyme mimics.

Recently, supramolecular nanotubes formed by self-assembly of amphiphilic molecules have attracted much attention.²³⁵ These self-assembled tubular structures have been used as scaffolds to yield supramolecular artificial enzymes (Fig. 16D).^{236–238} For instance, by a molecular imprinting strategy *via* the functionalities assembled on the surface of giant nanotubes, a class of artificial GPx enzymes were designed and synthesized by Liu and coworkers.²³⁶ Research shows that the selenium- and guanidine-functionalized cyclodextrins behave as both the catalytic groups and binding sites. The preorganized, highly-ordered structures are dynamically stable and the resulting functionalized nanotubes show high GPx-like activity of 140 U, which is only one order of magnitude lower than that of natural GPx.

Since gels formed by three-dimensional elastic networks possess interstitial space filled with liquid, they have great potential in various applications such as biocatalyst preparation and drug delivery. Recently, numerous artificial enzymes based on nanogels have been investigated and highlighted.^{239–242} Rodríguez-Llansola *et al.* prepared an L-proline based supramolecular organogel to catalyze the Henry nitroaldol reaction.²⁴² The catalyst functions only upon the formation of fibrillar networks by self-assembly. Different solvents result in the formation of different structures and differing activities of catalytic gels are also observed experimentally. As predicted, the catalytic capacity of supramolecular gels can be significantly varied when the temperature changes. At the same time, Wang *et al.* reported a series of hydrogel-based horseradish peroxidase enzyme models formed by self-assembly of functional group hemin and amino

acid derivatives.²⁴³ The catalytic activity of the supramolecular artificial enzyme is at least two orders of magnitude higher than that of free hemin. Furthermore, the enzyme mimic exhibits the highest activity (up to 60% of the activity of horseradish peroxidase) for an oxidation reaction in organic solvent, toluene, implying that the formation of the highly-ordered structure driven by different solvents has a significantly positive effect on the catalytic actions. The scaffold of supramolecular hydrogels prevents the hemin monomer from dimerization and degradation and thus facilitates the catalytic reaction by providing a nanoporous catalytic microenvironment. In addition, by using the molecular imprinting strategy, the soluble single-molecule nanogels with controlled structures have been designed as a matrix for artificial enzymes.²⁴⁴ The enzyme mimic has only one active site per particle and meets the Michaelis–Menten kinetics, akin to natural enzymes. These gel-based supramolecular enzyme models provide a new opportunity to perform catalysis with high operational stability and reusability.

The study above suggests that the hierarchically highly-ordered structures formed by self-assembly of building blocks are essentially connected with the enzyme-like catalysis. The modulation of catalytic activity endows these supramolecular enzyme mimics with promising potential in many applications, such as biosensors and biomedicines. Moreover, the nanometer-sized biomimetic systems provide a supramolecular viewpoint on the understanding of structure–function relationships of enzymes.

6. Smart enzyme models

It is well recognized that the biological systems can be smartly regulated in response to additional chemical or physical signals. For example, protein kinase C has multiple regulatory sites and affords a special structure for catalysis *via* step-by-step binding of three effectors including diacylglycerol, Ca^{2+} , and a phospholipid.²⁴⁵ Rapid progress is being made in contriving such artificial allosteric systems.^{246–249} This fantastic biomimetic system inspires chemists to design smart enzyme models with regulatory catalytic functions caused by the structural, conformational, and configurational changes *via* the internal or external stimulus.^{29,250} Thus far, several kinds of smart enzyme mimics have been reported (Fig. 17A–D). The study of smart enzyme models is of great significance to decipher the structure–function relationships during catalysis.^{251–257}

In order to observe allosteric regulation of catalysts, Yoon *et al.* delicately designed and synthesized a triple-layer complex composed of two transition metal nodes, two chemically inert blocking exterior layers, and a single catalytically active interior Al(III)–salen complex (Fig. 17B).^{258–260} This complex functions as a ring opening polymerization catalyst with ϵ -caprolactone as the substrate. Interestingly, the catalytic activity of this complex can be reversibly regulated through the interconversion of the triple-layer structure caused by the abstraction and subsequent addition of Cl^- . This allosteric process can efficiently control the molecular weights of the polymer products.

Recently, Schmittel and coworkers reported a coordination-driven nanoswitch and its reversible locking and unlocking corresponding to the ON and OFF triggering of the catalytic cycle, respectively (see the diagram in Fig. 17C).²⁵⁵ In the

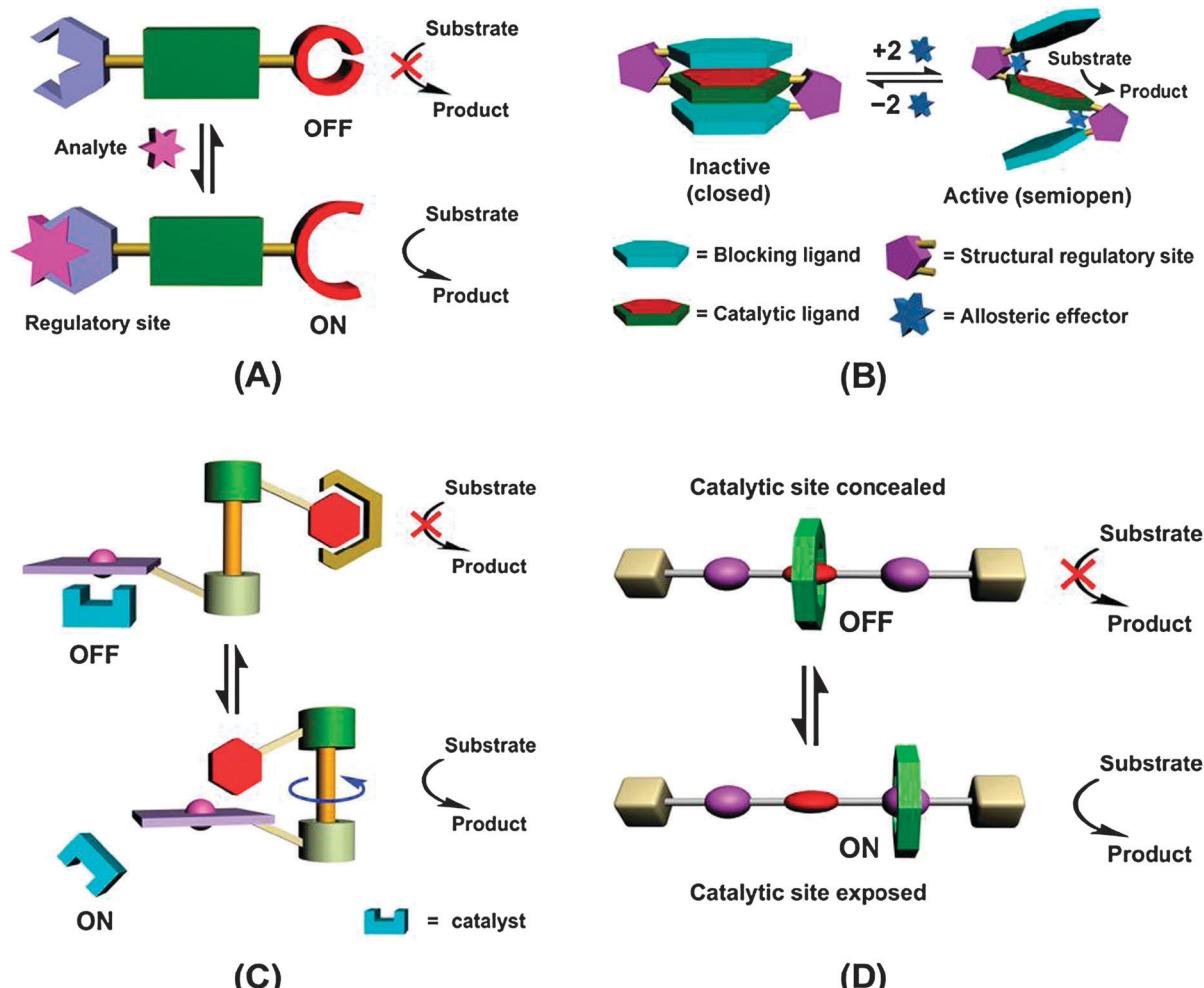


Fig. 17 Schematic representation of smart supramolecular enzyme models for the regulation of the catalytic action *via* the internal or external stimulus.

locked state, piperidine is not captured at the porphyrin docking station of the nanoswitch. Consequently, free piperidine is catalytically active in the Knoevenagel reaction (ON). However, the addition of copper(I) ions and phenanthroline as external agents causes the nanoswitch to exist in the unlocked state, thus permitting strong coordination of piperidine to the zinc porphyrin docking station. In this unlocked state, piperidine is trapped and inactive for catalysis. This smart biomimetic system is reminiscent of that in kinase II activation and deactivation and has no detectable loss of the catalytic activity over three cycles.

The mechanically interlocked molecules have been well-established, and the molecular-level motions can be exactly controlled in those molecular machines.²⁶¹ Therefore, the supramolecular enzyme models based on molecular machines behave as smart catalysts and present great potential towards mimicking structures and functions of natural enzymes. Very recently, Leigh and coworkers reported a rotaxane-based switchable organocatalyst consisting of a dibenzo[24]crown-8 macrocycle and an axle containing both triazolium rings and a dibenzylamine/ammonium moiety (Fig. 17D).²⁶² As known, a secondary amine/ammonium can perform iminium catalysis. When the organocatalyst is protonated, the ammonium group

is a more favorable binding site for the macrocycle than the triazolium rings. Therefore, the macrocycle encapsulates the ammonium group region of the axle, blocking the approach of substrates to the catalytic site. However, when the secondary amine of the rotaxane is deprotonated, the triazolium groups are the preferential binding sites for the macrocycle, thus the amine group on the axle is exposed and available to carry out catalysis. This biomimetic system can effectively manage the reaction rate of Michael addition of an aliphatic thiol to *trans*-cinnamaldehyde by switching ON or OFF upon addition of acid or base.

7. Applications

To date, the explanation of the enzyme catalytic mechanism is plausible. The characterizations of enzyme catalysis strongly depend upon the development of measurable tools. Except for the conventional techniques such as bulk biochemistry, X-ray crystallography and NMR, a few new tools, *e.g.*, electron paramagnetic resonance spectroscopy²⁶³ and single-molecule force spectroscopy,²⁶⁴ have also been used to study the catalytic properties of enzymes. In addition to the importance of biological relevance, the new functions of natural enzymes

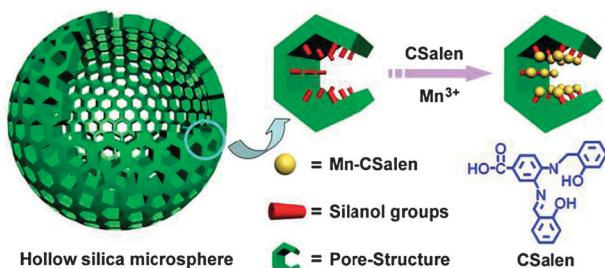


Fig. 18 Procedure of the Mn-CSalen complex modified hollow silica microsphere.²⁷⁶

are further explored. For example, enzymes can manipulate the controlled assembly and morphological transformation of nanomaterials^{265,266} and the controlled release of drugs in nanovalves.²⁶⁷ Also, enzymes can be used in the logic systems for information processing.²⁶⁸ Unfortunately, the issues with the stability, selectivity and specificity block the use of natural biocatalysts in some industrial applications. To overcome these issues, artificial biocatalysts have been used to replace the natural ones. Similar to the way that regulatory subunits of natural biocatalysts can be activated by the binding of small molecules,²⁶⁹ the catalysis of artificial enzymes can also be controlled and driven by small molecules or light.²⁷⁰ This feature allows them to be used in biosensors.^{259,271}

The use of biocatalysts becomes more and more popular in industrial biotransformations²⁷² and numerous artificial biocatalysts have been rationally designed to facilitate the industrial chemical synthesis.²⁷³ Furthermore, the biocatalytic processes can take place in organic solvents or aqueous medium.²⁷⁴ The immobilization of biocatalysts can not only solve the issue of enzymatic instability and facilitate their applicability, but can also enable the employment of enzymes in different solvents at extreme pH and temperature levels and exceptionally high substrate concentrations.²⁷⁵ For example, a SOD model immobilized on the hollow silica microspheres has been reported (Fig. 18).²⁷⁶ This rigid mimic possesses the functions of SOD. It can be used in biosensors and easily recovered for repeated utilization. Alternatively, a recent study demonstrated that the coupled biocatalysts can be encapsulated in multicompartment microparticles.²⁷⁷ In addition, the asymmetric catalysis of chiral enzyme mimics, such as models based on DNA-ligand complexes, will be rather valuable in the production of chiral compounds. Although progress in the use of novel biocatalysts significantly depends upon the timely development of enabling biotechnology and on experience gained in the past, the observations described above allow natural or artificial biocatalysts to be applied in different fields of industry.

8. Conclusions and perspectives

Enzymes are nanometer-sized objects with supramolecular structures created by the folding and self-assembly of polymeric chain-like components through supramolecular interactions. They carry out catalytic functions usually accompanied by a variety of conformational states. It is clearly demonstrated that the entire motions of enzyme structures confer the catalytic power during catalysis. The conformational diversities and

complexities of natural enzymes exerted in catalysis seriously restrict the detailed understanding of the enzymatic mechanism in molecular terms. The emergence of artificial enzymes based on supramolecular scaffolds likely provides an alternative method to investigate the structural complexities of enzymes and thus to unravel the mystery of enzyme catalysis.

The supramolecular complexes, especially complexes formed by the aggregation of various functionalities, possess complex and hierarchical architectures as well as the dynamic features which are desirable frameworks for the development of novel enzyme models. By the method of rationally tailored design relying on chemical and biological techniques, a great number of artificial enzymes using supramolecular scaffolds have been constructed and studied. Specifically, ranging from the synthetic macrocyclic compounds to self-assembled nanometer-sized objects, all complexes have been exploited as scaffolds to design the supramolecular artificial enzymes. Based on these observations, several key requirements to fabricate highly efficient supramolecular artificial enzymes should be systematically considered and rationally assembled as follows: (i) the rational design of binding sites for recognizing the substrates, especially the transition states of reactions; (ii) the precise position of catalytic groups for high synergy between recognition and catalysis; and (iii) generating suitable flexibility in a designed active center. Encouragingly, some supramolecular artificial enzymes possessing very interesting structural properties and quite strong enzyme-like catalytic capacities have been discovered thus far. These biomimetic systems not only provide fresh insight into elucidating the catalytic mechanism of natural enzymes, but also demonstrate the underlying principles in structure-based catalysis. Although the complexity of artificial enzymes designed based on supramolecular approaches is still far away from that of natural enzymes at present, further improvement of enzyme models, which mainly depends on the development of fundamental comprehension of supramolecular chemistry and biochemistry, will possibly replicate the features of natural enzymes, particularly in regard to the constitutional complexity as well as cooperative motions. With the functional enhancements of enzyme models as well as the advantages of stability and production cost, supramolecular artificial enzymes are eagerly anticipated to replace the natural enzymes for future use in various fields such as manufacturing and food industries, environmental biosensors, pharmaceuticals, and more.

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