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Design of artificial enzymes by supramolecular strategies

Tingting Wang[1], Xiaotong Fan[1], Chunxi Hou and Junqiu Liu

Enzymes are biomacromolecules with three-dimensional structures composed of peptide polymers via supramolecular interactions. Owing to the incredible catalytic efficiency and unique substrate selectivity, enzymes arouse considerable attention. To rival natural enzymes, various artificial enzymes have been developed over the last decades. Since supramolecular interactions play important roles in both substrate recognition and the process of enzymatic catalysis, designing artificial enzymes using supramolecular strategies is undoubtedly significant. Here we discuss the recent advances in constructing artificial enzymes using supramolecular platforms.

Address
State Key Laboratory of Supramolecular Structure and Materials, College of Chemistry, Jilin University, Changchun 130012, China

Corresponding author: Liu, Junqiu (junqiuliu@jlu.edu.cn)
[1] These authors contributed equally.

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Introduction

Enzymes are biomacromolecules which act as biological catalysts. Enzymes participate in almost all metabolic processes in cells with substrate specificity and unbelievable catalytic efficiency. The wisdom of nature prompts researchers to explore the underlying rules of the nature and develop artificial analogues. Great attention has been paid to investigate the structure and the catalytic mechanism of natural enzymes. In order to explore the catalytic process and observe the intermediates occurring during the enzymatic reactions, various methods such as nuclear magnetic resonance (NMR) [1–3], single-molecule kinetics [4], steady-state kinetics [5] and molecular dynamic simulation [6] are developed. However, to date we still cannot give an accurate answer how enzymes have substrate selectivity and high catalytic efficiency.

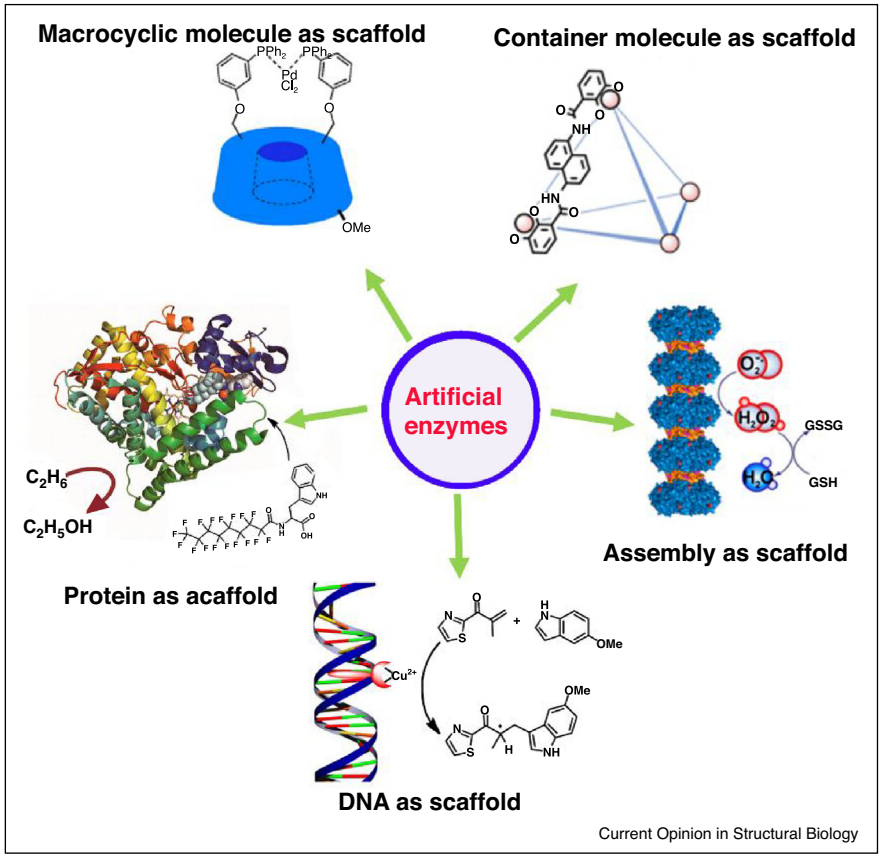
Despite a plenty of studies on natural enzymes, artificial enzymes provide an alternative choice for researchers to understand the behaviors of enzymes and considerable progress has been made in the field of mimicking natural enzymes [7–11]. As far as we know, supramolecular interactions, including hydrophobic interaction, electrostatic attraction, hydrogen bonding, van der Waals interaction and metal–ligand coordination, play important roles in both substrate recognition and the process of enzyme catalysis. So constructing artificial enzymes based on supramolecular strategies attracts much attention and excellent work has been done. In this critical review, we mainly focus on the examples published in the past three years. Different approaches for designing artificial enzymes from supramolecular strategies are presented in Figure 1.

Macrocyclic molecules for the design of artificial enzymes

It is believed that a suitable microenvironment is indispensable when an enzymatic reaction is carried out. An eligible pocket could not only segregate substrates and active sites of enzymes from the surroundings, but also provide the microenvironment for accomplishing the substrates recognition and enzymatic reaction. Cavity-containing molecules, such as cyclodextrins, cucurbiturils, calixarenes, container molecules, with the advantage that is similar to the pocket of enzyme, attract researchers' attention and have been extensively studied [12–16].

These macrocyclic molecules can protect the enzymatic reaction from the surroundings similar to enzymes. The related researches have confirmed that modifications on cavity or portals of these macrocyclic molecules will influence the catalytical ability and substrate selectivity. Many artificial enzymes have been developed based on this unique characteristic of macrocyclic molecules with examples provided by Bender [17], Bleslow [18], our group [19–22], Bols [23–24] and so on. Recently, Matt and co-workers published a review summarizing the coordination chemistry based on cyclodextrins and phosphorus (III), and discussed the catalytic properties of these cavity-shaped ligands [25]. Bols' group also reported an artificial metalloenzyme using cyclodextrin diacids in an unprecedented simple method [26••]. They synthesized cyclodextrin diacids and studied the binding to various metal ions, such as iron, zinc and copper. When the catalyst was used that was generated from $Fe(ClO_4)_2$ and cyclodextrin diacids, 100–1000 times of oxidation rate of substituted benzyl alcohol was observed, but no

Figure 1



Different approaches for designing artificial enzymes using supramolecular strategies.
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acceleration was observed for catalysts from $Zn(ClO_4)_2$ and cyclodextrin diacids or $Cu(ClO_4)_2$ and cyclodextrin diacids. When they substitute succinic acids for cyclodextrin diacids to form iron complex, the catalytic rate rarely increases, which suggests the cyclodextrin cavity is essential for catalysis.

As for cucurbiturils, an oligomer of glycolurils. Werner and co-workers recently provided a delicate review about the synthesis and high-affinity binding of cucurbiturils, describing the catalytic application of cucurbiturils in detail [27]. It is well known that cucurbituril (CB6) can form stable 1:1 complexes via host–guest interaction with diprotonated diaminopentane or diaminobutane. However, the host–guest interaction decreases significantly when the diprotonated state is destroyed. Considering for this, our group successfully constructed a pH-responsive artificial glutathione peroxidase (GPx) which was a well-known selenoenzyme via using a cucurbit [6]uril-pseudorotaxane-based molecular switch and an organoselenium compound [28]. When pH was below 6 because of two nitrogen atoms of compound 1 diprotonated, the GPx mimic formed a 1:1 host–guest pseudorotaxane complex. Therefore, compound 1 did not show apparently GPx activity due to encapsulation of the active site of compound 1 into CB [6]. At pH above 7, the two nitrogen atoms of compound 1 were deprotonated and the binding ability of CB [6] with compound 1 was significantly reduced, so it caused a gradually increased GPx activity. As shown in Figure 2, the activity of selenoenzyme can be turned on/off between pH = 7 and pH = 6. Calixarenes are also used to construct artificial enzymes. For example, Schatz's recent study indicated that sulfocalixarenes could boost the catalytic activity of Grubbs-type catalysts in the olefin metathesis reaction [29].

Container molecules for the design of artificial enzymes

Despite the classic host molecules, researchers have aimed at constructing container molecules which mimick the enzymatic pockets by providing the microenvironment for enzymatic reactions [30]. In the last two years, Fujita [31••], Nitschke [32•], Nolte [33,34], and Raymond [35–38] have made great progress in constructing