Coordination Chemistry Reviews 384 (2019) 90–106

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Incorporation of biomolecules in Metal-Organic Frameworks for advanced applications

Hongde An [a,b,1], Mingmin Li [a,b,1], Jia Gao [c], Zhenjie Zhang [a,c], Shengqian Ma [d], Yao Chen [a,b,*]

[a] State Key Laboratory of Medicinal Chemical Biology, Nankai University, Tianjin 300071, China
[b] College of Pharmacy, Nankai University, Tianjin 300071, China
[c] College of Chemistry, Nankai University, Tianjin 300071, China
[d] Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620, USA

ARTICLE INFO

Article history:
Received 30 November 2018
Received in revised form 28 December 2018
Accepted 1 January 2019
Available online xxxx

Keywords:
Metal-Organic Frameworks
Biomolecules
Immobilization
Applications

ABSTRACT

Incorporation of biomolecules in metal-organic frameworks (MOFs) to form Biomolecules-MOFs composites has attracted great attention as an emerging class of hybrid materials. A wide range of Biomolecules-MOFs composites have been designed and synthesized, which combine the excellent physical and chemical properties of MOFs (e.g. high porosity, tunable pore size) with the versatile functionalities of biomolecules, and applied in various fields including biocatalysis, sensing, separation, imaging and drug delivery. This review thoroughly summarized the state of the art of strategies used to incorporate biomolecules with metal-organic frameworks (MOFs), and emphasized on the remarkable advances of the applications of Biomolecules-MOFs composites, including the current challenges and potential directions in the future.

Contents

* Corresponding author at: College of Pharmacy, Nankai University, Tianjin 300071, China.
E-mail address: chenyao@nankai.edu.cn (Y. Chen).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.ccr.2019.01.001
0010-8545/

1. Introduction

Biomolecules are a kind of active substance in organisms, including large macromolecules like proteins, nucleic acids, carbohydrates and lipids, as well as small molecules such as amino acids, nucleotides, fatty acids, glycolipids. They are ubiquitous in nature and essential for maintaining basic life activities. Apart from the fundamental biological functions, biomolecules are also of great values in industrial applications, especially in food and pharmaceutical production. For examples, they can serve as natural catalysts, sensors or oxidation-reductants [1]. As for industrial applications, unnatural environments such as organic solvents, variable temperatures, low or high pH values or mechanical processing are often needed. However, most biomolecules can only be operated under very mild conditions. The fragile nature of biomolecules including low operational stability, poor robustness, difficulties in recovery and reuse may greatly thwart their further applications. Therefore, stabilizing biomolecules while retaining their functions in unnatural or complex environments are essential for their successful applications [2,3].

Incorporation of biomolecules within protective exteriors has been proved to be an effective method to promote their stabilities and applications [2–8]. Compared to biomolecules' free states, the resulting composites would possess significantly enhanced thermal, chemical and even mechanical stability, and thus dramatically broaden their operational conditions and extend their potential applications in vitro and in vivo. Moreover, the introduction of contamination can be vastly reduced due to the heterogeneous nature of the incorporated biomolecules. As for the immobilization of biomolecules, it could date back to as early as 1916, when Nelson and Griffin discovered that after being physically adsorbed on charcoal, invertase could retain its catalytic activity [9]. This research laid the foundation of immobilizing kinds of biomolecules for various applications. Since then, a series of solid supports (e.g. sol gels hydrogels, organic microparticles, nonporous and porous inorganic supports) have been used to immobilize biomolecules to realize stability enhancement, ease of separation and reuse while protecting them from harsh environments [3–6]. Among these supports, mesoporous silicate (MPS) is one of the most widely used materials for enzyme immobilization [10,11]. However, some drawbacks such as leaching of guest molecules, low loading efficiency and modification difficulties remain challenges for MPS's applications. The exploration of advanced porous materials to incorporate biomolecules is of great significance and urgently demanded.

Metal-Organic Frameworks (MOFs), also known as porous coordination polymers (PCPs) [12–17], are a kind of porous crystalline material constructed from the coordination of organic ligands and inorganic metal ions (or metal clusters). Their inherent properties such as ordered and tunable porosity, good crystallinity and high surface areas make them excellent host matrix for biomolecules' immobilization: 1) Their high surface area and porosity facilitate the high loading of biomolecules, especially for the fact that many MOFs with large cavities were reported in recent years [10,12,13]. 2) MOFs exhibit open architectures. Substrates and products can transport from the pores, so the guest biomolecules could interact with external environment. 3) The metal nodes, ligands as well as topological structures of MOFs are with high variety. The geometry and properties could be well designed and tailored to match their applications. 4) Various active groups can be uniformly distributed both in the pore and on the surface of MOFs, which could interact with biomolecules to eliminate or reduce their leaching. 5) The high crystallinity of MOFs provides defined networks and clear structural information, which is critical when investigating their interaction/mechanisms with guest molecules. These excellent and unique properties of MOFs entitle them to serve as outstanding supports for the incorporation of biomolecules for advanced applications. The formed Biomolecules-MOFs composites can combine the properties of both constitutes, where MOFs and biomolecules are indeed mutually beneficial. MOFs can not only create stabilizing microenvironments for biomolecules to improve their performance against perturbation conditions, but also promote the separation and recovery of biomolecules from products. Moreover, the heterogeneous property provided by MOFs facilitates the applications of biomolecules in various fields (e.g. catalysis, sensors and separation, Fig. 1). On the other hand, the immobilized biomolecules functionalize the Biomolecules-MOFs composites, and impart new properties to MOFs, thus vastly expand the possible applications of MOFs in different technologies, especially in fields of biocatalysis and biomedicine [18–21]. Overall, MOFs and biomolecules in the hybrid materials are complementary and indispensable, and the incorporation of biomolecules in MOFs enlarges the advanced applications of both fields.

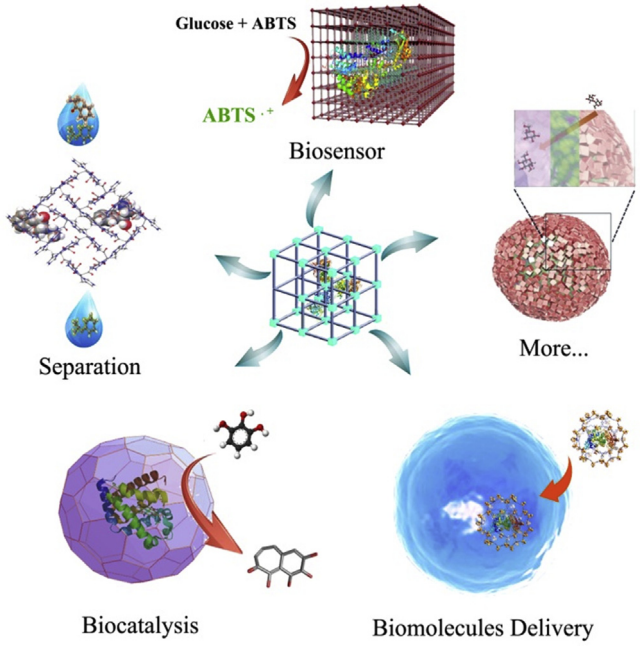

Fig. 1. Schematic illustration of different applications of Biomolecules-MOFs composites.

From nucleic acids to enzymes, many kinds of biomolecules with different dimensions, have been successfully incorporated in MOFs using different approaches, including pore encapsulation, surface attachment, covalent linkage and in-situ encapsulation [10,22–24]. In this review, we first summarized the state of the art of immobilization strategies. More importantly, the applications and future prospective of Biomolecules-MOFs composites have been discussed in detail. We hope this review will make a clear picture and provide helpful guidance for researchers to prepare new Biomolecules-MOFs composites and explore their advanced applications in various fields.

2. Strategies to incorporate biomolecules with MOFs

The special chemical and structural features (e.g. high crystallinity, high surface area, large pore volume and great structural variety) of MOFs endow them great potentials in adsorbing or entrapping biomolecules within their pores as well as on their external surfaces [10,19,21–28]. In the past decade, immobilization of biomolecules using MOFs has been extensively investigated. Many kinds of biomolecules such as enzymes [29–35], antibodies

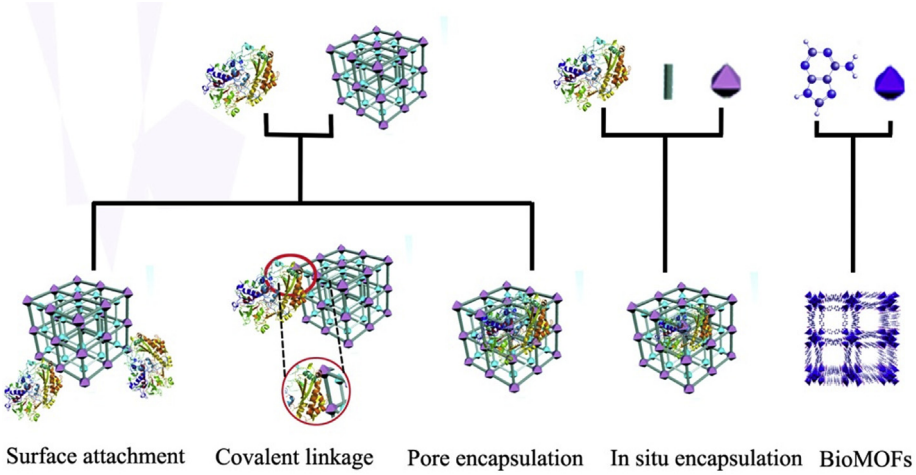

Fig. 2. Schematic representation of different immobilization methods.

[36–38], peptides [39–41], and nucleic acids [42–45] have been successfully incorporated with MOFs. Biomolecules-MOFs composites offer a novel platform for various emerging applications including biocatalysis, biosensors, biofuel cells and bioelectronic devices. In general, biomolecules are often incorporated with MOFs through four different patterns: 1) Biomolecules can be absorbed into the pores of MOFs. 2) Biomolecules can be attached on the external surface of MOF crystals. 3) Biomolecules can be in-situ encapsulated into MOF crystals as 'crystal defect'. 4) Biomolecules can be directly used as ligands to synthesize MOFs. The incorporation process can be realized via five major routes as illustrated in Fig. 2, including pore encapsulation, surface attachment, covalent linkage, in situ encapsulation and bio-MOFs. Van der Waals interaction, π-π interaction or hydrogen bonding are dominant forces for the first two methods. As for covalent linkage, it is based on chemical bonds between biomolecules and MOFs. A summary of the reported preparation of Biomolecules-MOFs composites was shown in Table 1. In this part, we mainly aim to describe the state of the art of strategies for the design and synthesis of Biomolecules-MOFs composites in detail. A comparison of the merits and drawbacks among these methods is also highlighted.

2.1. Pore encapsulation

The pore size of MOFs can be tuned from ultra-microporous to mesoporous (>2 nm). Hence, the pores of MOFs can accommodate many types of biomolecules. Up to now, pore encapsulation is the most straightforward and widely used method to incorporate biomolecules with MOFs [33–35,46–56]. It is an efficient post-modification strategy to achieve high loading of biomolecules. Since the synthesis of MOFs is usually under harsh conditions (e.g. high temperature, organic solvents), this post-synthetic modification strategy can incorporate biomolecules under mild conditions and mostly avoid the influence on biomolecules' structures and activities. Moreover, the pores of MOFs provide a protective environment that can prevent the aggregation of biomolecules and further limits the influence of denaturation factors. In current years, the preparation processes of MOFs have achieved progressive development. Apart from the microporous MOFs, many mesoporous MOFs have been reported in succession, giving rise to new possibilities for immobilization of large molecules. Some MOFs exhibit interesting hierarchical pores, so they can selectively trap different kinds of substrates, enzymes or cofactors into different pores for advanced applications [24,30,35,57]. In this pore encapsulation method, MOFs with good water stability as well as appropriate window sizes are essential. Three-dimensional (3D) MOFs with polyhedral cages have been extensively studied for biomolecules entrapment. This type of structure is preferable sometime, because their relatively small windows (compared to the diameters of the cages) can facilitated to trap the guest molecules and provide confined spaces that is critical for some applications [58].

Many studies have proved pore encapsulation can be a versatile and efficient way to incorporate biomolecules with MOFs. During the process, biomolecules (e.g. enzyme) can enter the pores of MOFs accompanied with a conformation change, which are distinct from either their native or denatured conformations [59]. In 2011, We first successfully immobilized microperoxidase-11(MP-11) into mesoporous Tb-mesoMOF, which possess hierarchical cavities with diameters of 3.9 and 4.7 nm [33]. Notably, the encapsulated enzyme can retain its activity and exhibit superior activity than that encapsulated in mesoporous silica. We then further proceeded to unveil the mechanism during the encapsulation process. Cytochrome *c* (Cyt *c*), which has a molecular dimension of ~2.6 nm × 3.2 nm × 3.3 nm, could be entrapped by Tb-mesoMOF, whose pore window sizes (1.3 nm and 1.7 nm) was smaller than the entrapped protein. We attributed this phenomenon to the flexibility of protein. Cyt *c* molecules could undergo a significant conformational change during translocating into the MOF interior through the relatively small pore window (Fig. 3). This assumption was verified by fluorescent analysis [59]. This work laid a theoretical foundation for researchers to unveil the complicated process of biomolecules translocation. Moreover, based on previous studies, we studied the interaction of MP-11 with Tb-mesoMOF by confocal Raman spectroscopy and explained why enzyme can be retained in the interior of MOFs [58]. All these results provide important guidance to motivate the expansion of the pore encapsulation strategy and explore many other combinations of MOFs and biomolecules.

Along the same line, the Zhou group further expanded this strategy. They prepared a series of mesoporous MOFs including PCN-333 and PCN-332, which possessed high water stability and polyhedral cages. These MOFs can be used as single-molecular traps (SMT) for enzymes, thus protecting these biomolecules from aggregation and leaching. After immobilization, the catalytic activities of enzymes were well sustained and the property of recyclability was greatly improved [34]. The same group also developed a hierarchical mesoporous MOF, PCN-888, which contains three types of cages with different sizes (2 nm × 5 nm × 6.2 nm). It can couple two enzymes in a tandem manner with a precise control of the distribution of each enzyme. The largest cavity (6.2 nm) can be used as SMT of glucose oxidase (GOx), the intermediate

Table 1
Summary of the strategies to incorporate biomolecules with MOFs reported.

Incorporation method	MOFs	Biomolecules	Ref.
Cage encapsulation	Tb-mesoMOF	MP-11	[33]
	Tb-mesoMOF	Cyt *c*	[59]
	PCN-333	HRP, MP-11, Cyt *c*	[34]
	PCN-128y	OPAA	[49]
	PCN-888	GOx and HRP	[30]
	PCN-333	tyrosinase	[31]
	PCN-333	SOD and CAT	[35]
	Cu-MOF	MP-11	[51]
	Mn-MOF	Cyt *c*	[52]
	PCN-333	HRP	[53]
	IR-MOF-74-Y	VB_{12}, MOP-18	[54]
	Tb-mesoMOF	myoglobin	[55]
	POST-66(Y)	VB_{12}, Cyt *c*, myoglobin, HRP	[56]
Surface attachment	Cu-MOF	MP-11	[51]
	ZIF-70	glucose dehydrogenase	[63]
	ZIF-8	Cyt *c*	[64]
	MIL-101(Cr), MIL-100(Cr), UiO-66(Zr) and to our own CYCU-4(Al)	trypsin	[61]
	Cu-BTC	*Bacillus subtilis* lipase	[67]
	ZIF-8	lysozyme	[68]
	ZIF-8	carbonic anhydrase	[65]
	UiO-66, UiO-66-NH_2(Zr), and MIL-53(Al) and carbonized MIL-53(Al)	porcine pancreatic lipase	[62]
Covalent linkage	MIL-100(Fe)	laccase	[79]
	UiO-66-NH_2	soybean epoxide hydrolase	[80]
	NH_2-MIL-53(Al)	β-glucosidase enzyme	[81]
	MIL-100(Fe)	GOx	[32]
	IRMOF-3	GFP, lipase	[72]
	NH_2-MOFs	GOx	[73]
	MIL53(Al) and NH_2-MIL101(Cr)		
	MIL-88B(Cr)-NH_2	trypsin	[74]
	MOF-5	anti-BSA	[100]
	UiO-66-N_3	DNA	[42]
In situ encapsulation	ZIF-8	hemin, GOx	[84]
	ZIF-8	CAT	[85]
	ZIF-8	GOx, HRP	[86]
	ZIF-8	GOx	[87]
	ZIF-8	Cyt *c*	[90]
	ZIF-90	urease, CAT	[91]
	ZIF-90	CAT	[88]
Bio-MOFs	bMOFs	adenine	[99]
	PCN-530	adenine, thymine	[104]
	[Zn(Gly-Ala)$_2$]·(solvent)	peptide	[106]
	ZnCar	peptide	[107]

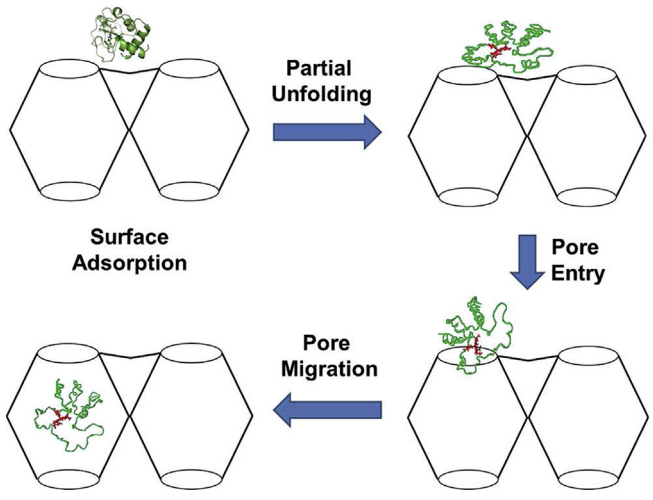

Fig. 3. The tentative mechanism of Cyt *c* diffusing into the pores of Tb-meso MOF. The process was started from surface adsorption and followed by a conformation change to migrate into interior cavities. Reproduced from Ref. [59] with permission of American Chemical Society.

cavity (5.0 nm) was used as SMT of horseradish peroxidase (HRP) and the small cavity (2.0 nm) could make sure the diffusion of substrates. The obtained nanoreactor showed high catalytic efficiency, good cycling performance and outstanding stability against the digestion of trypsin because of the protection effect of PCN-888 (Fig. 4a) [30]. Based on the similar theory, they later proposed a nanofactory by coupling superoxide dismutase (SOD) and catalase (CAT) into PCN-333 (Fig. 4b) [35]. Since PCN-333 was stable in complex medium and showed good biocompatibility, they investigated the cellular activity of SC@FNPCN-333, the results showed that this hybrid material could protect human cells from toxic reactive oxygen species for up to one week. These results demonstrated the potential biotechnological applications of Biomolecules-MOFs complex.

Besides polyhedral-cage-based MOFs, MOFs with mesoporous channel structures can also be used to encapsulate biomolecules [49,51,54]. Both the size and hydrophilicity of the pores affected the adsorption process. In 2012, the Yaghi group prepared a series of MOF-74 analogues with pore apertures ranging from 1.4 to 9.8 nm via varying the ligand length. Large molecules like vitamin B12, metal-organic-polyhedron-18, myoglobin and green fluorescent protein (GFP) were immobilized into the pores of MOFs

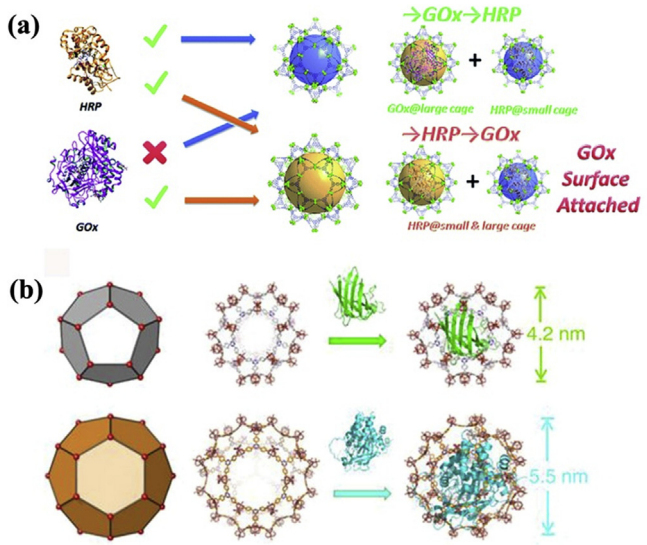

Fig. 4. (a) Schematic illustration of the stepwise encapsulation of GOx and HRP with different orders by PCN-888. Reproduced from Ref. [30] with permission of Royal Society of Chemistry. (b) The schematic diagram of the relative size present in FNPCN-333 and the immobilization of SOD and CAT. Reproduced from Ref. [35] with permission of Nature.

[54]. The Ouyang group prepared a mesoporous Cu-MOF with pore diameter of 15.2–20.7 nm (using CTAB as template agent) that can immobilize laccase [50]. The research of the Farha group also promoted the field of using MOFs to incorporate enzymes. They successfully encapsulated organophosphorus acid anhydrolase (OPAA) into PCN-128y with a matching pore size of 4.4 nm, and demonstrated that after immobilization, the stability of enzyme enhanced vastly (Fig. 5) [49]. NU-1000, a mesoporous MOF with hierarchical pores could also be applied as a solid support to encapsulate, protect and deliver enzyme [57]. Along the same line, using similar method, isoreticular NU-100x series were prepared with hierarchical mesoporous channels ranging from 3.3 to 6.7 nm. This hierarchical structure can be used to immobilize larger size enzyme as well as relatively small size coenzyme, in the meantime, the channels also ensured the diffusion of substrates, and thus enhanced the reaction activity [46].

2.2. Surface attachment

Apart from pore encapsulation, surface attachment is also a common method to prepare Biomolecules-MOFs composites. This strategy has no strict requirement on MOFs' pore size and the immobilization process is usually quicker and easier compared with other incorporation methods. However, the leaching of biomolecules is a challenge to be overcome for this strategy, and the protection effect of MOFs is usually weak due to the exposure of biomolecules.

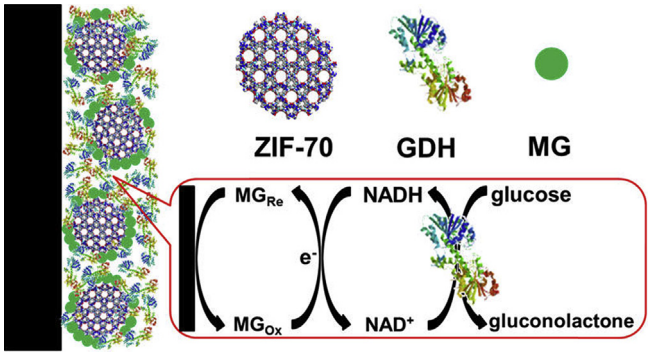

Fig. 6. Schematic diagram illustrating that ZIF-70 was able to serve as a matrix for coimmobilizing electrocatalysts (i.e., methylene green, MG) and dehydrogenases (i.e., glucose dehydrogenase, GDH) by surface immobilization onto the electrode surface, forming an integrated electrochemical biosensor for glucose. Reproduced from Ref. [63] with permission of American Chemical Society.

Several groups contributed to the development of this method [51,60–69]. The first example can track back to 2006 reported by Balkus group [51]. They explored the immobilization of MP-11 in a Cu-based MOF as well as five mesoporous organosilicas through weak physical interaction. The results demonstrated that peroxidase retained activity after immobilization. This attempt held great promise for the preparation of Biomolecules-MOFs hybrid materials.

Similarly, Huang and Lin groups developed a series of crystalline microporous MOFs for enzyme immobilization without any chemical modification on the MOFs' surface or enzymes. Hydrogen bonding and π-π interaction mainly contribute to the host-guest attraction between the enzymes and the organic linkers in the MOFs [60,61]. The bioreactor exhibited great potential in many fields, especially in catalysis and proteomics [62]. Mao and Yang groups fabricated an integrated electrochemical biosensor using zeolitic imidazolate frameworks (ZIFs) as the matrix for co-immobilizing methylene green (MG) and glucose dehydrogenase (GDH) (Fig. 6) [63]. The Ge group also attached Cyt *c* on the surface of ZIF-8, which showed a 128% activity and improved apparent substrate affinity compared to native Cyt *c* [64].

Nucleotide can also be immobilized on MOFs through surface attachment. The π-electron of ligands and metal ions can facilitate the binding of nucleotides with MOFs. Chen and Tang groups successfully synthesized and characterized a moisture and water-stable three-dimensional (3D) MOF based on a zwitterionic carboxylate ligand (N-carboxymethyl-(3,5-dicarboxyl)-pyridinium bromide (H_3CmdcpBr)), which could form electrostatic, p-stacking and/or hydrogen bonding interactions with ss-DNA [44].

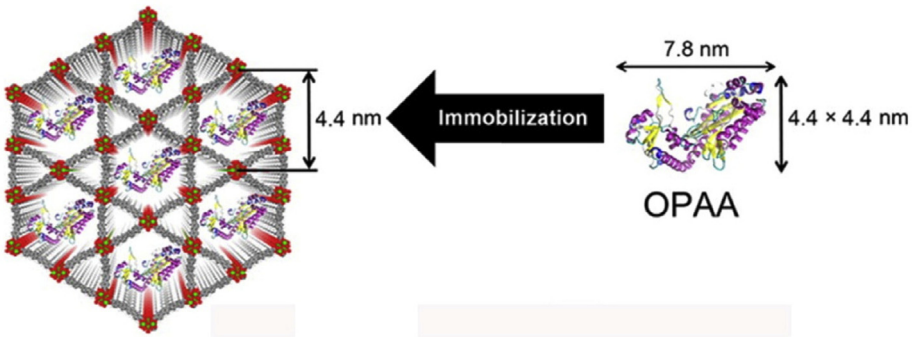

Fig. 5. Immobilization of OPAA in the mesoporous channels of PCN-128y. Reproduced from Ref. [49] with permission of American Chemical Society.

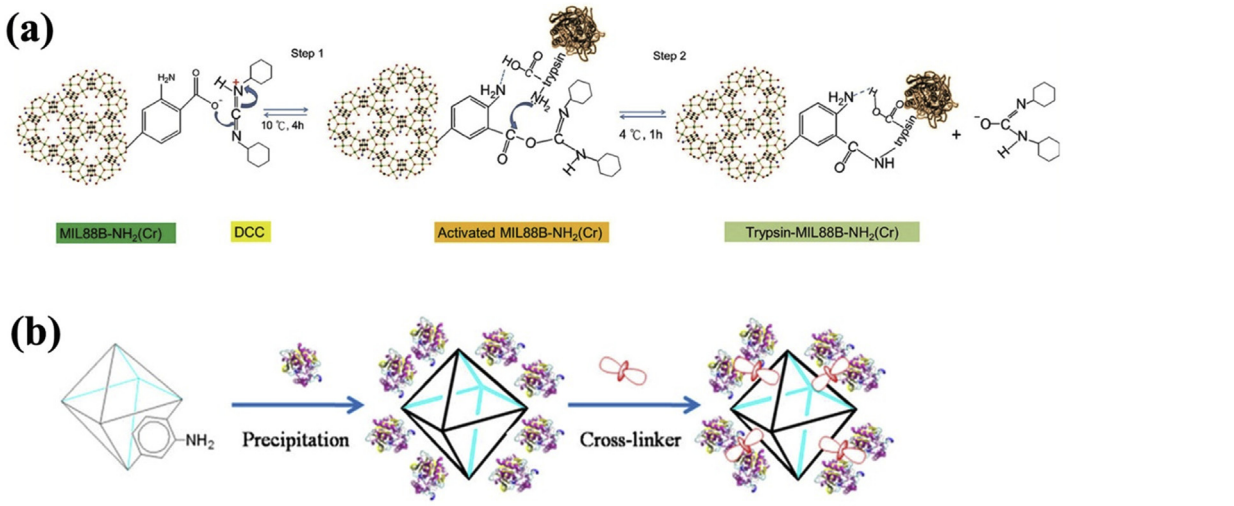

Fig. 7. (a) Trypsin immobilization onto DCC-activated MOFs. Reproduced from Ref. [75] with permission of Wiley. (b) Schematic illustration of the immobilization of SEH onto UiO-66-NH_2. Glutaraldehyde (GA) was used to cross-link the amino groups of protein and MOFs. Reproduced from Ref. [80] with permission of American Chemical Society.

2.3. Covalent linkage

Although various biomolecules have been successfully immobilized into MOFs by physical adsorption, the relatively weak interactions between biomolecules and matrix may lead to slow leaching of biomolecules in certain conditions. To avoid leaching, a feasible method is to immobilize biomolecules through covalent linkage [40,42,70–78]. There are many nucleophiles such as amino group, carboxylic group, phenolic group, thiol group, imidazole group, indole group and hydroxyl group in biomolecules, which can form covalent interactions with the organic linkers in MOFs. The surface of MOF crystals also presents a wide variety of functional groups (e.g. free carboxyl, amino, hydroxyl groups) that can couple with reactive groups of biomolecules. Up to now, biomolecules have been covalently linked to MOFs in three modes: 1) Biomolecules can be cross-linked by linker molecules such as glutaraldehyde to form a self-assembled monolayer (SAM) on the surface of MOFs. 2) Biomolecules can directly bind with the active groups of MOFs via covalent bonds. 3) Biomolecules can also be pre-covalently conjugated to organic ligands and then form MOFs via self-assembly process.

2.3.1. Cross-linking biomolecules with MOFs

Several groups reported this strategy in succession by coupling biomolecules with cross-linking agents such as glutaraldehyde [32,79–81]. Based on this method, Falcaro and Doherty groups patterned MOF films on SU-8 and firstly realized the bio-grafting of β-Glucosidase on MOF films [81]. Similarly, Legrand and Steunou groups also fabricated a GOx–MIL-100(Fe)–PtNP bioelectrode for the detection of glucose by immobilization Glucose oxidase (GOx) on MOFs (i.e. MIL-100 (M), M = Fe, Al, Cr) and iron(III) azobenzenetetracarboxylate MIL-127 (Fe). They compared the parameters of different MOF-based biosensors and demonstrated that Fe-based MOFs exhibited superior properties compared to other inorganic host matrices for enzyme immobilization [32]. They also successfully co-immobilized 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and laccase to MIL-100(Fe) via exposing bioelectrodes to saturated glutaraldehyde vapor [79]. Lin and Huang groups developed a novel biocatalyst based on the immobilization of trypsin on DCC-activated MOFs (Fig. 7a) [75]. The Lou group also used glutaraldehyde (GA) to cross-link soybean epoxide hydrolase with UiO-66-NH_2 and prepared a novel nano-/micro-biocatalyst system (Fig. 7b) [80].

2.3.2. Covalent linkage of biomolecules with MOFs

Covalent Linkage approach has also been extensively studied in literatures. Up to now, most of the related studies were conducted on the surface of MOFs. The activation of MOFs' surface is essential before interacting with biomolecules. Active groups such as amino group and carboxylate group were generally adopted to realize the immobilization process via Schiff base reaction, click reaction or chemisorption. In terms of post-synthetic modification (PSM) of MOFs, the Cohen group did some pioneering works [76]. Adopting the PSM strategy, many studies have been reported to incorporate biomolecules with MOFs via covalent bonds. Park and Huh groups developed this method using MOFs' linking group [72]. After the formation of MOFs, the exposed carboxylate groups in organic linkers were activated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) or dicyclohexyl carbodiimide (DCC). Then, the activated carboxylates can be conjugated with many biomolecules. MOFs were successfully conjugated with EGFP using EDC to activate the dangling carboxylate groups of MOFs. IR spectrum, fluorescence microscope, Solid-state luminescence as well as confocal laser scanning microscope (CLSM) confirmed the surface modification of MOFs. Rassaei and Tudisco groups successfully immobilized glucose oxidase on two amino-MOFs via a post-synthetic method (Fig. 8) [73]. Other groups later used this method to immobilize many kinds of biomolecules for different applications [75,77].

Click reaction can also be used for biomolecules immobilization. Mirkin group first synthesized nucleic acid-MOF nanoparticle conjugates based on the reaction between N_3 and dibenzylcyclooctyne (DBCO). UiO-66-N_3 nanoparticle was pre-synthesized and used to react with DBCO functionalized DNA (Fig. 9) [42]. After this PSM reaction, the structure of MOFs was retained. DNA was only immobilized on the surface of MOFs because of the pore size of UiO-66 is too small to accommodate DNA. In addition, they explored the colloidal stability and cellular transfection capabilities of this DNA-MOF composite. The results showed that this composite exhibited increased stability and enhanced cellular uptake compared with undecorated MOF particles.

2.3.3. Pre-crosslink biomolecules on MOF ligands

Besides the cross-linking or post-modification approaches, biomolecules can also covalently pre-crosslink on ligands. However, due to the synthetic challenge, this method is rarely studied. The Fujita group firstly constructed a cage material around a covalently

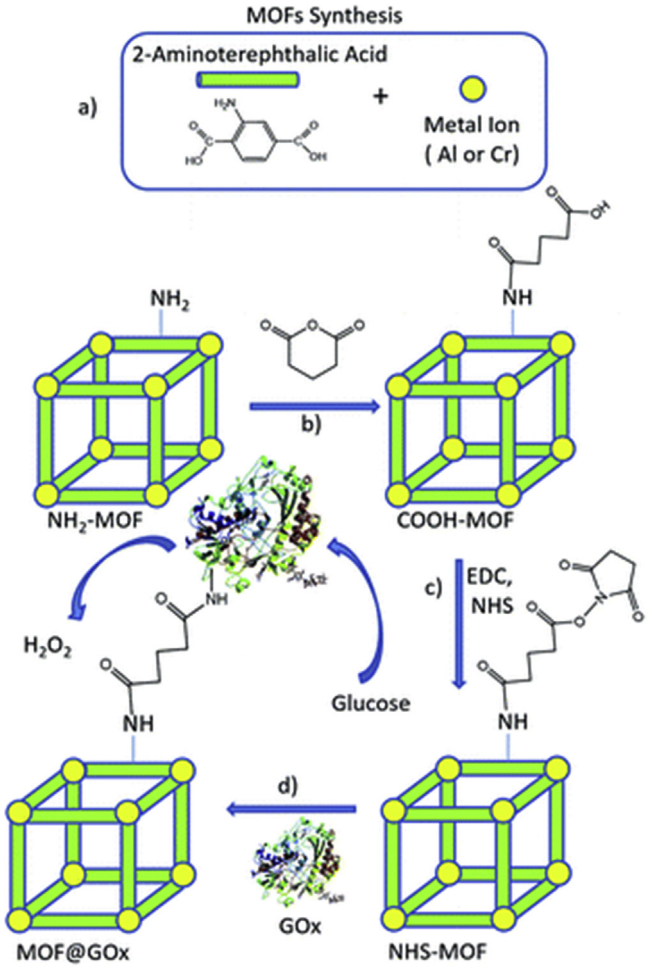

Fig. 8. Schematic diagram of the reaction steps for the preparation of GOx functionalized MOFs through covalent linkage. Reproduced from Ref. [73] with permission of The Royal Society of Chemistry.

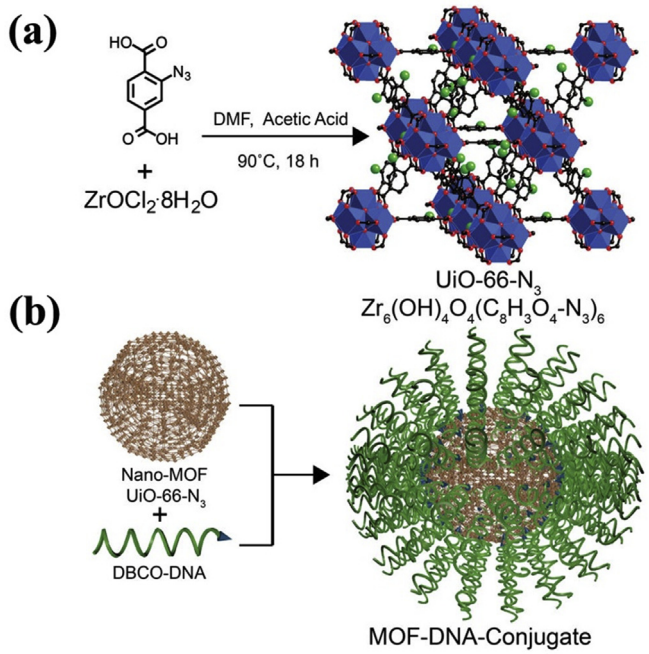

Fig. 9. Schematic illustration of (a) Synthesis of UiO-66-N_3 ($Zr_6O_4OH_4(C_8H_3O_4\text{-}N_3)_6$) nanoparticles. (b) Utilizing dibenzylcyclooctyne (DBCO) functionalized DNA and UiO-66-N_3 nanoparticles to construct MOF-DNA-Conjugate. Reproduced from Ref. [42] with permission of American Chemical Society.

tethered protein via using self-assembly process [78]. They attached a small protein, ubiquitin, to one bidentate ligand. After the addition of Pd(II) ions (M) and ligands (L), $M_{12}L_{24}$ coordination nanocages self-assembled around the protein. This report made an important milestone to the conformational and functional control of encapsulated proteins.

2.4. In-situ encapsulation

Although surface adsorption, cage encapsulation and covalent linkage have been proved to be efficient approaches to incorporate biomolecules, these strategies still have limitations, especially for incorporating biomolecules of large size. In the past few years, in-situ encapsulation has emerged as a powerful tool to incorporate biomolecules. In this strategy, MOFs grow around biomolecules which lead to high loading efficiency and almost no leaching of biomolecules. The nucleation and immobilization occur simultaneously in one pot synthesis. This in-situ encapsulation of biomolecules in MOFs has many advantages over conventional post-adsorption. One obvious advantage of this strategy is that there is nearly no size limitation for biomolecules. Therefore, broad spectrum of biomolecules can be encapsulated, and thus greatly broaden the application of this strategy. In addition, this facile'one-pot' strategy can encapsulate various types of biomolecules in high loading efficiency during the formation process of MOFs, and thus the biomolecules can uniformly distributed within MOFs without leaching. This rapid and low cost approach will vastly facilitate the application of biomolecules in many fields. However, it must be noted that the in-situ strategy can only be conducted under mild conditions in aqueous solutions, because most biomolecules cannot survive in violent synthetic conditions such as high temperature and organic solvents, which greatly restricted the number of MOFs that can be used in this strategy [82–91].

Liu and Ge groups did the pioneering work in this field. They firstly embedded Cyt *c* into ZIF-8 by a one-pot co-precipitation strategy [90]. It's worth to mention that a certain amount of PVP was mixed with enzyme before the addition of zinc nitrate hexahydrate. PVP was used to maintain the dispersion and stabilize the protein. This work surely opened a new avenue to simply and quickly prepare Biomolecules-MOFs hybrid materials. Based on the similar strategy, the same group then embedded multi enzymes (glucose oxidase (GOx) and horseradish peroxidase (HRP)) into ZIF-8 by one-step facile synthesis [86]. This hybrid material exhibited high sensitivity, selectivity as well as long-term storage stability. As multi-components system is promising for a range of applications like industrial biocatalysis, pharmaceuticals and biomedical devices, this simple strategy gives rise to new possibilities to prepare and apply these hybrid materials in advanced fields. Referring to the preliminary studies, the Chu group immobilized protein into ZIF-8 nanoparticles to obtain a novel system used as an efficient platform for the delivery and endo-lysosomal release of active proteins in living cells [92]. Cheng *et al.* subsequently encapsulated glucose oxidase in ZIF-8 via a co-precipitation method for the detecting of glucose in vivo (Fig. 10a) [84]. Other groups also made important contribution to this filed based on the similar method [93–95]. Inspired by natural biomineralization processes, the Falcaro group proposed that MOFs can act as protective coatings for biomacromolecules by de novo encapsulation [89]. In their work, not only various biomacromolecules (e. g. proteins, DNA and enzymes) but also various MOFs (ZIF-8, HKUST-1, Eu/Tb-BDC and MIL-88A) were studied. The results demonstrated that enzymes were able to maintain their activity even in inhospitable environments after encapsulation. Moreover, they proposed that there existed some interactions between the MOF precursors and biomacromolecules, which

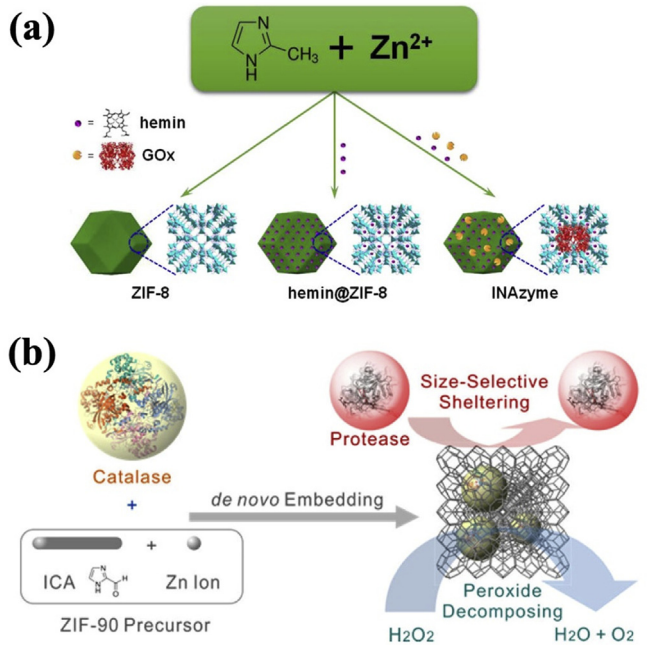

Fig. 10. (a) Schematic representation of biocompatible one-step synthetic approaches to synthesize nanoscaled ZIF-8 and ZIF-8-based nanozymes in aqueous solution at room temperature. Reproduced from Ref. [84] with permission of American Chemical Society. (b) Schematic representation of synthesis of Water-Based ZIF-90 with encapsulated catalase enzyme and its functional activity. Reproduced from Ref. [88] with permission of American Chemical Society.

facilitated the formation of MOFs around biomacromolecules. The Gassensmith group successfully encapsulated whole tobacco mosaic virus (TMV) inside ZIF-8 and prepared TMV@ZIF-8 rod-shaped core–shell bionanoparticle (CSBN) with tunable shell thickness [19]. This work demonstrated that this de novo method can be applied for the capture of extremely large biomolecules. Subsequently, they conducted a comprehensive study and elucidated the mechanistic underpinnings of core-shell biomimetic mineralization process with ZIF-8 on TMV. They found that ZIF-8 crystallization parameters greatly affected the final morphology of TMV@ZIF-8, and that TMV-Zn interaction rather than charge plays a pivotal role in this mineralization process. They also discovered that ZIF-8 can grow on the surface of a PEG coated protein [96]. Their work further broadened the application of this de novo encapsulation strategy, and their related mechanism studies provide guidance for the design of biomimetic mineralization of MOFs on proteinaceous materials.

ZIF-90 is also a good choice to immobilize biomolecules using this strategy. Tsung and Wu groups did in-depth exploration in this area. They embedded catalase molecules into ZIF-90 through de novo approach and then demonstrated the universality of this method (Fig. 10b) [88].

Up to now, only a few MOFs such as ZIF-8 and ZIF-90 have been used for in-situ encapsulation of biomolecules [82–91]. It is mostly because that the appropriate MOFs must be prepared under mild biocompatible conditions. The limited pore sizes of the used MOFs (e.g. ZIF-8, ZIF-90 and MIL-88A) may hinder the wide application of this strategy in some fields (e.g. biocatalysis and sensing), because the substrates may not be able to diffuse into such small pores to contact with the encapsulated enzymes. More MOFs structures that can adapted with mild synthetic conditions are urgently needed to further promote the in-situ encapsulation strategy.

2.5. Bio-MOFs

Biomolecules usually contain amino acids, peptides, nucleobases and saccharides that possess reactive chemical groups in their structures. These groups can coordinate with a variety of metals and act as organic linkers for MOF synthesis [20,97]. Direct use of biomolecules as ligands to coordinate with metals can form a new type of MOFs, bio-MOFs. Bio-MOFs are prone to have better biocompatibilily and tend to provide special functionality [98,99]. Because of the symmetry deficiency as well as the high flexibility of biomolecules, it is usually very difficult to obtain high-quality crystals for bio-MOFs. In order to design bio-MOFs, it is usually required to choose highly-symmetric biomolecules or introducing a symmetric co-ligand. Nucleobases, amino acid, polypeptides and even proteins have been reported to build Bio-MOFs.

Nucleobase is the most widely studied compounds to construct bio-MOFs for several reasons: 1) It is natural abundant, with low cost and can be easily prepared. 2) It has several accessible nitrogen and oxygen lone pairs which are prone to coordinate with metal ions. Typically, nucleobases with highly symmetric structure are preferable in this method [100,101]. Adenine contains five nitrogen atoms, a purine ring with four nitrogen and an exocyclic amino group (Fig. 11) [99,100,102], and thus can serve as a great candidate to coordinate with metals or metal clusters and afford bio-MOFs. Adopting a mixed ligand strategy via introduction of biphenyldicarboxylic acid into reactions between adenine and zinc acetate dihydrate in dimethylformamide (DMF), Rosi group reported a single crystalline material formulated as $Zn_8(ad)_4$

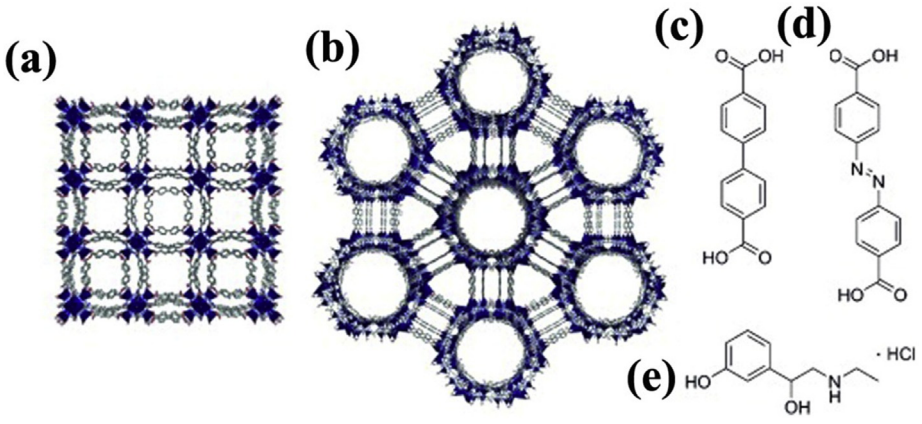

Fig. 11. The Structure of A) bMOF-1 and B) bMOF-100, C) BPDC, D) Azo-BPDC, and E) etilefrinehydrochloride (Zn^{2+}, dark blue; C, dark gray; N, blue; O, red; H omitted for clarity). Reproduced from Ref. [98] with permission of Wiley.

$(BPDC)_6O{\cdot}2Me_2NH_2{\cdot}8DMF{\cdot}11H_2O$, Bio-MOF-1, which is the earliest adenine-incorporated MOFs with a significant porosity [102]. The same group used zinc-adeninate clusters as vertices to coordinate with dicarboxylate linker molecules and obtained a new kind of porous material named Bio-MOF-100 [103]. The Zhou group then smartly introduced a highly symmetric linker to construct Bio-MOF, which overcame the disadvantages of low symmetry of nucleobases [104].

Amino acids have been used as organic ligands to construct MOFs ascribed to their abundant coordination groups including carboxylate and amino. McDonald group developed a complex named $[Hg_{12}(ala)_8(NO_3)_8]{\cdot}2H_2O$ by simply mixing mercurous nitrate and L- or D-alanine together [105]. Dipeptide was also used as organic linkers to construct MOFs [106,107]. Rosseinsky group reported a porous 3D ZnCar-framework based on dipeptide carnosine (b-alanyl-l-histidine) and Zn^{2+}. This kind of framework showed permanent microporosity and strong adsorption affinity for CO_2 and CH_4 [107]. They experimentally demonstrated that if peptide showed low-energy torsions and displacements, the available pore volume could increase [106].

3. The applications of Biomolecules-MOFs composites

The Biomolecules-MOFs composites combined the properties and features from both components (biomolecules and MOFs materials), which endow them diverse functionalities and great performances in many fields. In the past few decades, MOFs with pore sizes from microporous to mesoporous have been reported. Biomolecules, from nucleic acids to enzymes, have been successfully immobilized in MOFs through various strategies (Fig. 12) [2,3]. In this part, we highlight the remarkable advances in the extensive applications of Biomolecules-MOFs composites including biocatalysis, biosensors, drug delivery, cell imaging and separation. A summary of the reported applications of Biomolecules-MOFs composites was shown in Table 2.

3.1. Biocatalysis

Enzymes have been well known as highly efficient and selective natural catalysts. However, the fragile nature of enzymes such as narrow pH tolerance ranges, low thermal stability and low resistance to organic solvents hindered their practical applications. Attributed to the fascinating structural and chemical properties of MOFs, they are perfectly suited to serve as the host matrixes for enzyme immobilization [21,108]. Enzyme-MOFs composites have been exploited as new platforms for heterogenous biocatalysis that possess many advantages, including high stability and reusability, easy separation of products and better catalytic selectivities.

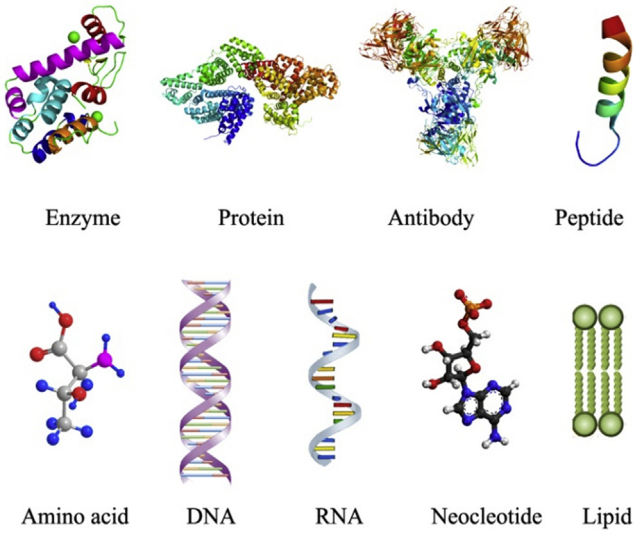

Fig. 12. Schematic of different biomolecules that can be immobilized into MOFs for further applications.

Heme proteins (e.g. horseradish peroxidase, cytochrome *c*, microperoxidase and myoglobin) that contain porphyrin prosthetic groups are one family of enzymes that were most widely used to construct enzymes-MOFs composites for catalysis, probably due to their high activities, suitable dimensions and dark color for easy tracking. In 2011, we reported the earliest enzyme encapsulation (MP-11@Tb-mesoMOF) in MOFs cavities. The MP-11@Tb-mesoMOF was used to catalyze the oxidation of 3,5-di-tert-butylcatechol in the presence of H_2O_2. After being immobilized, the enzymatic catalysis performances were superior compared to its mesoporous silica counterpart (Fig. 13) [33]. We further successfully immobilized myoglobin (Mb) into the Tb-mesoMOF. The Mb@MOF composite demonstrated interesting size-selective biocatalysis as well as better catalytic activities toward small substrate oxidation than free Mb [55]. Based on the same method, The Zhou group developed a series of mesoporous MOFs (e.g. PCN-333(Al)) to encapsulate enzymes (horseradish peroxidase, cytochrome *c* and MP-11). Enzymes immobilized in PCN-333(Al) were used to catalyze the oxidation of o-Phenylenediamine or 2-2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) in the presence of H_2O_2 [34].

MOFs with mesoporous cavities can not only accommodate enzymes to improve their stability, but also provide size selectivity, which can be hardly realized in other systems. Because of the high crystallinity of MOFs, the porosity can be highly organized or uniform, which is essential for enzyme-MOFs composites' size selective catalysis. And the improved selectivity of catalysts is critical for industrial applications. Beside of mesoporous MOFs, microporous ZIFs including ZIF-8 and ZIF-90 are also widely used to incorporate enzymes in an in-situ immobilization manner. For in-situ synthesis method, guest molecules whose size is larger than the pores of MOFs can also be encapsulated into MOFs, where MOFs act as a protective shell. Lyu *et al.* firstly embedded Cyt *c* into ZIF-8 using one-pot co-precipitation strategy. The resulting composite showed a 10-fold increase in peroxidase activity compared to free Cyt *c*. It provided a convenient, fast, and highly sensitive detection method for trace amounts of organic peroxides [90]. The Falcaro group further demonstrated that de novo synthesis method can be widely used to immobilize various kinds of biomolecules into ZIF-8. The authors used a wide range of biomolecules such as ribonuclease A, human serum albumin, pyrroloquinoline quinone-dependent glucose dehydrogenase, lipase, hemoglobin, lysozyme, HRP, trypsin, urease and oligonucleotide. The results demonstrated that enzymes@ZIF-8 can retain enzymatic activity under harsh conditions (Fig. 14) [89]. The Ge group subsequently encapsulated horseradish peroxidase (HRP) into ZIF-8 through this in-situ synthesis method. The formed HRP-MOF composite with an average size around 30 nm showed an enhanced catalytic activity compared to the native enzyme [109]. Shieh *et al.* embedded catalase into ZIF-90 through the in-situ synthesis method for the first time. The formed composites showed high activity towards hydrogen peroxide degradation even in the presence of protease proteinase K [88].

MOFs can also be combined with other materials and biomolecules to form more complicated complex. Therefore, different materials in this complex can play their own roles to realize the purpose of the application. Naik and Singamaneni groups used ZIF-8 as protecting shell to encapsulate gold nanorods-HRP

Table 2
Summary of the applications of Biomolecules-MOFs composites.

Metal organic frameworks	Biomolecules	Applications	Ref.
Tb-mesoMOF	MP-11	catalyze the oxidation of 3,5-di-tert-butyl-catechol	[33]
PCN-333(Al)	HRP, Cyt *c* and MP-11	catalyze the oxidation of o-Phenylenediamine and 2-2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid)	[34]
PCN-128y	OPAA	detoxify diisopropyl fluorophosphate (DFP) and Soman	[49]
CYCU-4	trypsin	BSA digestion	[60]
UiO-66-NH_2	soybean epoxide hydrolase	hydrolyse 1,2-epoxyoctane	[80]
ZIF-90	CAT	catalyze the degradation of hydrogen peroxide(H_2O_2)	[88]
ZIF-8	lipase	catalyze the oxidation of p-nitrophenylbutyrate	[115]
ZIF-8	GOx	detection of glucose	[87]
ZIF-8	Cyt *c*	sensing of hydrogen peroxide and explosive organic peroxides	[90]
ZIF-8	bovine hemoglobin	sensing of H_2O_2 and phenol	[119]
HP-DUT-5	GOx and uricase with HRP	detection of glucose and uric acid	[120]
Cu-MOF	tyrosinase	sensing of bisphenol A (BPA)	[121]
Fe-MIL-88	GOx	sensing of thrombin	[122]
Cu-MOF	nuclear acids	lipopolysaccharide (LPS) detection	[123]
HKUST-1	hairpin DNA	DNA sensing	[128]
Uio-66	miRNA	miRNA sensing	[130]
bioMOF-1	adeninate	Fe^{3+} sensing	[132]
(Fe-P)n-MOF	DNA	Pb^{2+} sensing	[134]
UiO-66-N_3	DNA	drug delivery	[42]
UiO-Cis	siRNA	drug delivery	[137]
Zr based MOF	DNA	cell imaging	[142]
ZIF-8	histidine	separation of racemic alanine and glutamic acid	[144]
Cu-MOF	tripeptide Gly-L-His-Gly (GHG)	enantioselective separation of metamphetamine and ephedrine	[146]
MIL-101	laccase	micropollutants removal	[147]
CuJAST-1	peptide	chemical motor	[41]
ZIF-8	*β*-galactosidase	exoskeleton	[152]
ZIF-8, ZIF-90	antibody	protective shell	[153]

conjugates. This composite showed an increased biocatalytic activity of enzyme compared to its native counterpart due to the photothermal effect of plasmonic nanostructures [110]. Xu *et al.* developed a compartmentalized system via the encapsulation of MOF nanoparticles into MOF capsules (MOF-Cs). This composite can protect the immobilized enzymes (catalase, glucose oxidase, horseradish peroxidase, and protease) from denaturation and maintain their activity [111]. On the other hand, different enzymes can also be incorporated in one system for cascaded usage. Falcaro and Kim groups recently developed a novel enzyme immobilization method using a continuous-flow droplet microfluidic system of MIL-88A(Fe). The formed hollow spheres of MIL-88A (Fe) could encapsulate three different enzymes (glycerol dehydroxygenase, HRP and acetylcholinesterase) at the same time. The immobilized enzymes showed better activity and recyclability than free enzymes [112].

Another class of enzyme, hydrolases, have also been widely used to construct enzymes-MOFs composites. The Farha group used PCN-128y to immobilize organophosphorus acid anhydrolase (OPAA). OPAA@PCN-128y was used to detoxify diisopropyl fluorophosphate (DFP) and Soman, an extremely toxic nerve agent. This novel hybrid material exhibited high conversion of DFP and Soman within a few minutes [49]. In channel-type MOFs such as PCN-128y, enzymes can enter MOFs without the change of their conformation, thus can maintain their activity well. On the other hand, the channels in MOFs can also act as substrate channel to facilitate the interactions between enzymes and their substrate. For channel-type MOFs, the incorporation strategy must be carefully chosen to avoid possible leaching of biomolecules. However,

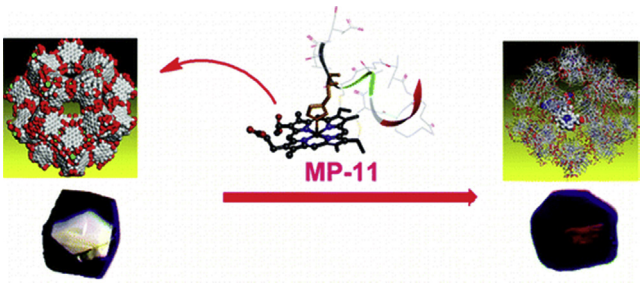

Fig. 13. Schematic illustration of the immobilization of Microperoxidase-11 in Tb-mesoMOF by cage inclusion. Reproduced from Ref. [33] with permission of American Chemical Society.

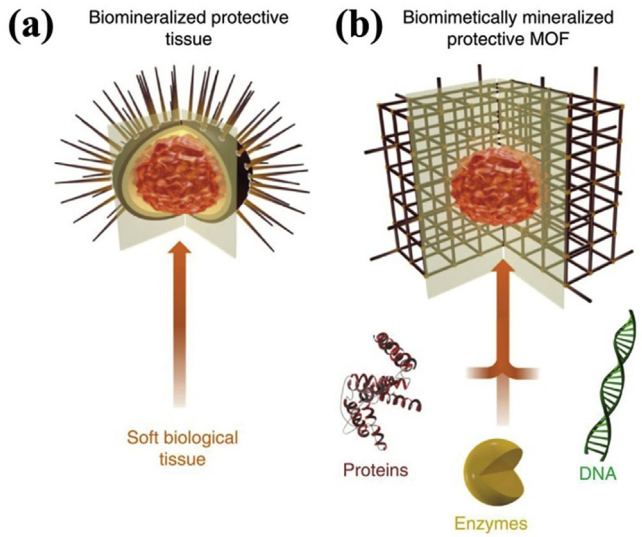

Fig. 14. Schematic illustration of biomimetically mineralized MOF. (a) Schematic of a sea urchin; a hard porous protective shell that is biomineralized by soft biological tissue (b) Schematic of a MOF biocomposite showing a biomacromolecule (for example, protein, enzyme or DNA), encapsulated within the porous, crystalline shell. Reproduced from Ref. [89] with permission of Nature.

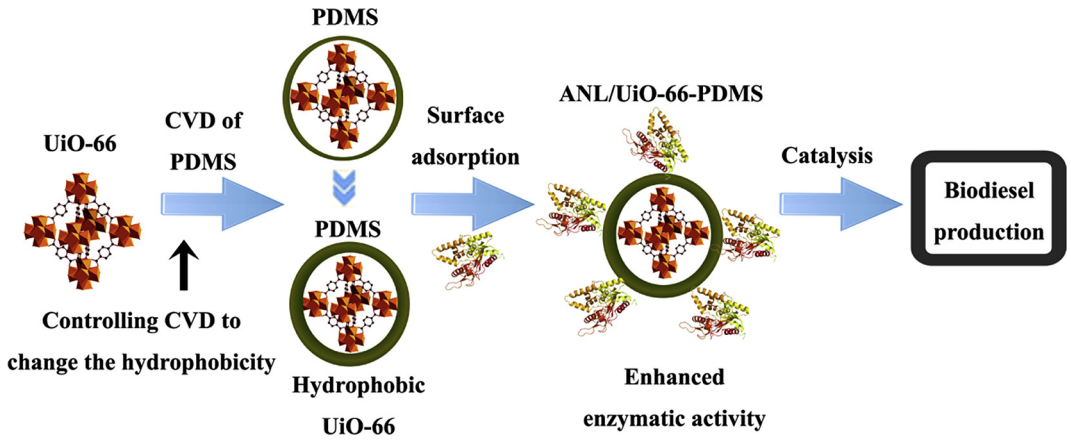

Fig. 15. Schematic illustration of the immobilization of Aspergillus niger lipase (ANL) on UiO-66 by surface immobilization. Reproduced from Ref. [114] with permission of The Royal Society of Chemistry.

the organic ligands in the wall of the MOFs channel may provide relative strong interactions to facilitate the retain of biomolecules. Another hydrolase, soybean epoxide hydrolase (SEH), was immobilized on UiO-66-NH_2 through covalent linking by Lou *et al.* This composite was used to catalyze the hydrolysis of 1,2-epoxyoctane and its activity was comparable with that of free enzyme [80]. Lin and co-workers designed a novel trypsin–FITC@CYCU-4 composite. This trypsin bioreactor exhibited high digestion efficiency for BSA [60]. Rafiei *et al.* constructed a new biocatalyst by encapsulating lipase into the microporous zeolite imidazolate framework (ZIF-67). The resulting lipase@ZIF-67 composite was successfully applied to catalyze the transesterification of soybean oil to biodiesel [113]. The Du group used hydrophobic UiO-66 as the host matrix for the immobilization of *Aspergillus niger* lipase through hydrophobic interactions and the hydrophobic modification of UiO-66 significantly enhanced the catalytic activity of lipase for biodiesel preparation (Fig. 15) [114]. Pitzalis *et al.* immobilized lipase into ZIF-8 via a 'one pot' synthesis method. The lipase@MOF composite was used to catalyze the oxidation of p-nitrophenylbutyrate (PNPB) [115].

Oxidases have also been immobilized into MOFs to catalyze the specific oxidation reactions. Zhao and Lan groups prepared a MOF-based porous carbon of ZIF-67 to encapsulate glucose oxidase (GOx). The embedded GOx showed high loading amount and fast electron transfer activity [116]. In addition, Liu *et al.* established a multienzyme system by encapsulate natural enzymes (glucose oxidase and uricase) into hierarchically porous MOFs (HP-PCN-224 (Fe)). In this study, HP-PCN-224 (Fe) was also an effective enzyme mimic, which could cooperate with the immobilized enzyme for tandem catalysis [117].

The topic of Enzyme- or protein-mediated biocatalysis has received significant attention in various areas over the past several decades, especially in food and pharmaceutical industrial applications. MOFs have successfully coupled with enzymes to improve their activity, stability and specificity. Furthermore, additional studies should be undertaken to enlarge the types of reactions that can be catalyzed by enzyme@MOFs biocatalysts, and broaden their practical applications. Moreover, those novel biocatalysts need to be evaluated and operated under a wider range of reaction conditions, especially in real industrial or biological conditions.

3.2. Biosensors

Biosensors are considered as a promising tool to rapidly, selectively and sensitively analyze target molecules. Biomolecules-MOFs composites have been designed and synthesized as an innovative sensing platform for the extensive detection of environmental and biologically significant target molecules such as glucose, L-cysteine, H_2O_2, dopamine, and ascorbic acid [118–120]. In this section, various types of sensing applications are thoroughly discussed based on recent developments of Biomolecules-MOFs composites.

Enzymes, a major kind of biomolecules, have been widely used for the optical sensing of various biological molecules. Lyu *et al.* firstly constructed a Cyt *c*@ZIF-8 composite using in situ encapsulation method. This composite was used for fluorometric sensing of hydrogen peroxide and explosive organic peroxides, including methyl ethyl ketone peroxide (MEKP) and tertiary butyl hydroperoxide (TBHP). This hybrid material had rapid and sensitive respond to H_2O_2, MEKP, and TBHP [90]. Along the same line, the Lin group synthesized a bovine hemoglobin (BHb)-MOF composite (BHb@ZIF-8) which displayed signals rapidly for sensing of H_2O_2 and phenol [119]. Furthermore, Hou *et al.* developed a multi-enzyme mimic system, which was composed of GOx and magnetic ZIF-8 (mZIF-8). The GOx@mZIF-8 composite was used for the detection of glucose. Due to the magnetic property of mZIF-8, this system can be easily recycled. The recycled materials exhibited almost the same activity after several cycles [87]. Ma *et al.* developed a sensor for in-vivo monitoring of glucose via constructing a dehydrogenase (GDH)-ZIF based electrochemical system. The results demonstrated that these ZIF-based biosensors can selectively monitor dialysate glucose collected from the brain of guinea pigs in a near real-time pattern [63]. Besides ZIF-based biosensors, MOFs with hierarchical pores have been also used to construct multi-enzyme system for cascade reactions. Partial connections between these hierarchical pores can facilitate the mass transfer of substrates and products in catalysis and sensing. Liu et al. developed a facile method for enzyme immobilization using hierarchically porous metal–organic frameworks (HP-MOFs). They constructed two multi-enzyme biosensors for glucose and uric acid by immobilizing GOx and uricase with horseradish peroxidase (HRP) on HP-DUT-5, respectively. These sensors showed good sensitivity, selectivity, and recyclability for the detection of glucose and UA [120]. Wang *et al.* reported a MOF-tyrosinase (try) chitosan composite for electrochemically sensing of bisphenol A (BPA). In addition, the composite was also investigated as an electrochemical sensor for other BPs, e.g., bisphenol B (BPB), bisphenol F (BPF), bisphenol E (BPE) and bisphenol Z (BPZ) [121]. Legrand *et al.* developed another Pt-NPs/MOF/GOD nanocomposite material for electrochemically sensing of glucose. This composite exhibited exceptional selectivity towards glucose even in the presence of other sugars (fructose, galactose, and mannose), ascorbic acid (AA), and uric acid (UA). The sensor exhibited good performance for the accurate determination of glucose in serum of diabetes

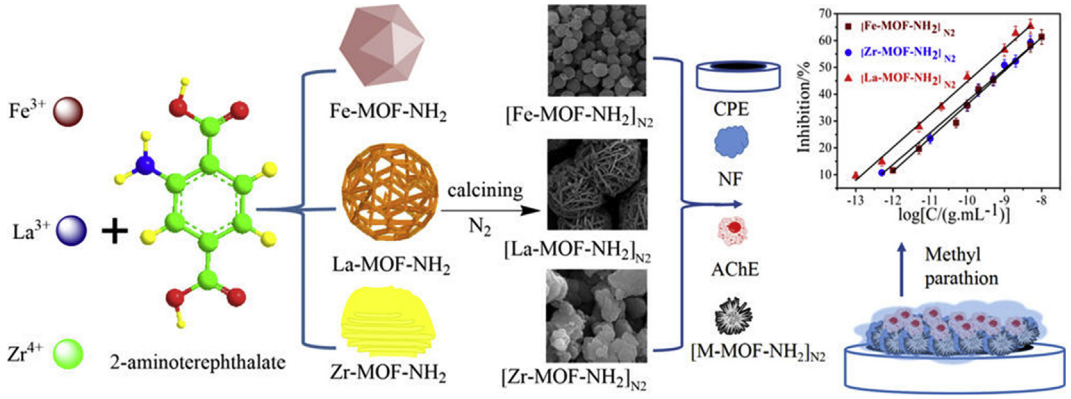

Fig. 16. Schematic of an efficient and facile metal–organic framework (MOF)-template strategy for preparing enzyme embedded carbon nanocomposites. Reproduced from Ref. [125] with permission of American Chemical Society.

mellitus patients [32]. Yuan and Chai groups reported a multifunctional bioconjugate material (Au/hemin@MOF–TBA II (thrombin binding aptamer)–GOx (glucose oxidase)) for electrochemically sensing of thrombin (TB) [122]. They further reported another AuNPs/MOF composite to immobilize HP_3 (a labeled hairpin probe) for lipopolysaccharide detection. The sensor exhibited specificity towards lipopolysaccharide in the presence of human serum albumin, procalcitonin, and C-reactive protein [123]. Similarly, Dong *et al.* used Ag/MOF (Zn-TSA) composite as highly efficient immobilization matrixes of myoglobin (Mb)/glucose oxidase (GOx) for electrochemical detection of hydrogen peroxide, nitrite, and glucose [124]. The same group subsequently synthesized a series of MOFs containing Fe^{3+}, Zr^{4+}, La^{3+}, and 2-aminoterephthalate (H_2ATA). These MOFs were successfully used as immobilization matrixes of acetylcholinesterase (AChE) to construct biosensors for the detection of methyl parathion (Fig. 16) [125]. Zhang *et al.* used GOx-MOF composite (GOx@ZIF-8) as signal transduction unit via biomimetic mineralization process for the construction of fluorescence immunosensor for galectin-4. The developed composite was applied for monitoring galectin-4 in real cancerous samples. This sensing system was also able to detect target proteins in cell lysates [126]. Wang *et al.* encapsulated MP-11 in PCN-333 (Al) and used this composite as a biosensor for hydrogen peroxide [127].

In the past few years, MOF based biosensors have demonstrated excellent performance in DNA and RNA detection. The Lei group developed a DNA sensor based on mimetic catalysis of MOF and allosteric switch of hairpin DNA. The specific recognition between aptamer structure and streptavidin (SA) resulted in bringing the probe close to the electrode. The MOF-based DNA sensor can detect target DNA with a detection range of 10 fM to 10 nM. [128]. The He group reported an electrochemical DNA sensor constructed through the combination of biotin-modified capture probe (Bio-CP) with hemin-MOFs/PtNPs composite. This novel biosensor exhibited sensitive detection of $FGFR_3$ from 0.1 fM to 1 nM with a low detection limit of 0.033 fM [129]. Kang and Xu groups presented a novel sensing strategy based on peptide nucleic acid (PNA) probes labeled with fluorophores and conjugated with a nano-MOF (NMOF) vehicle. The composite was used to monitor multiplexed miRNAs in living cancer cells. In the presence of target miRNA, PNA was hybridized and released from the NMOF, leading to the recovery of fluorescence signal (Fig. 17) [130].

Heavy metal ions in waste water threat the environment and health of animals all over the world. There have been a series of reported Biomolecules-MOFs composites that can efficiently detect metal ions in waste water. Yan group reported a series of adeninate embedded MOFs (bioMOF-1) by encapsulating different lanthanide ions (e.g., Eu^{3+} or Tb^{3+}) through post-synthetic cation-exchange method. These bio-MOFs have then been exploited for sensing of Fe^{3+} in waste water. In the same way, Eu^{3+}-β-diketonate loaded bioMOF-1 exhibited color variations in the presence of organic amines (e.g. methyl amine). This anionic bio-MOF could act as a platform of interest because the cationic guest molecules can take part in facile exchange with other cationic species [131,132]. Subsequently, they developed a composite by fabricating FAM (FAM = carboxyfluorescein) labeled ssDNA with Eu^{3+}@bioMOF-1. This hybrid material can be used for the detection of Cu^{2+}, with detection limit of 0.14 mM [133]. They further developed a AuNPs based electrochemical biosensor on paper working electrode (PWE) for the detection of Pb^{2+} using DNA modified iron-porphyrinic MOF ((Fe-P)n-MOF-Au-GR) hybrids as signal probes. The biosensor was selective for Pb^{2+} in the presence of many other competing metal ions [134]. Along the same line, the Chen group prepared a composite by combining MOF with a single stranded probe DNA (ss-DNA, denoted as P-DNA) labeled with fluorophore FAM. This biosensor is highly selective and sensitive for Hg^{2+} with a detection limit of 3.2 nM [135].

In recent years, many efforts have been devoted to the rapid and accurate detection of biological molecules, nucleic acids and metal ions *etc*. Biosensors have shown great potentials in this field due to their advantages of high sensitivity and selectivity. The combination of biomolecules with MOFs can not only improve the stability, reusability and bio-recognition ability of the formed biosensors,

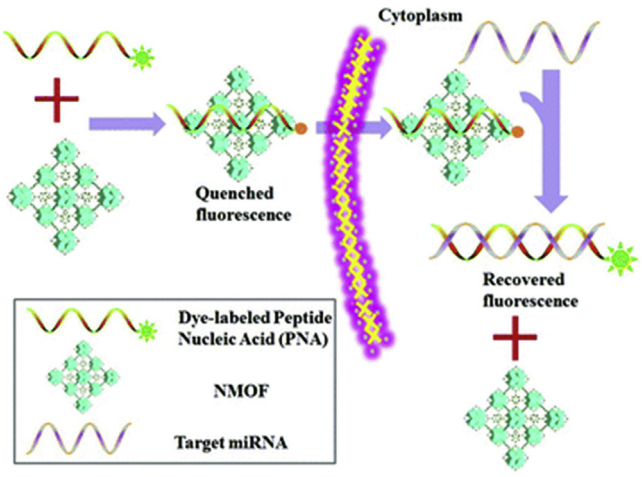

Fig. 17. The PANMOF-based miRNA sensing mechanism. Reproduced from Ref. [130] with permission of The Royal Society of Chemistry.

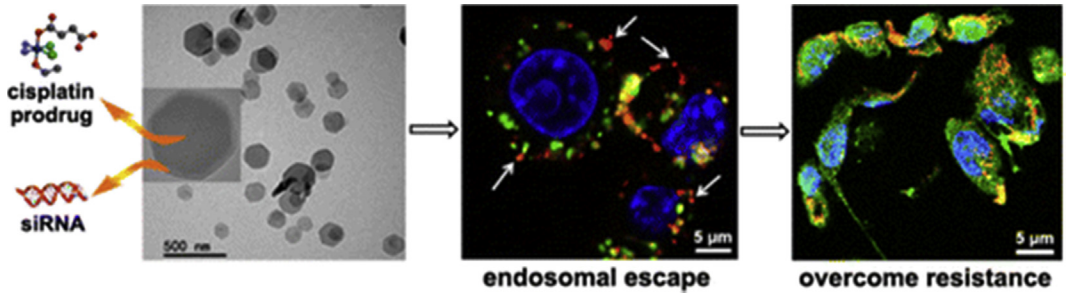

Fig. 18. Nanoscale metal-organic frameworks for the co-delivery of cisplatin and pooled siRNAs to enhance therapeutic efficacy in drug-resistant ovarian cancer cells. Reproduced from Ref. [137] with permission of American Chemical Society.

but also enhance their selectivity due to specific biomolecules-analytes interactions. Despite the recent developments achieved by Biomolecules-MOFs composites in biosensing, extensive efforts should be devoted to optimize these hybrid materials for single molecule detection and point-of-care testing (POTC).

3.3. Drug delivery and molecular imaging

Since an early report by Ferey in 2006 [136], MOFs have been proved to be a promising platform for drug delivery due to their high drug loadings, biodegradability and functionality. When the particle size of MOFs was scaled down to nanoscale, the nano MOFs (NMOFs) can serve as efficient nanocarriers for the delivery of imaging contrast agents, chemotherapeutics and other types of medicine. In this section, we mainly focus on the delivery of bimolecular drugs (e.g. nucleic acid and protein) using MOFs.

Mirkin *et al.* synthesized the first nucleic acid-MOF composite based on dibenzylcyclooctyne (DBCO)-functionalized DNA and an azide-functionalized UiO-66-N_3 via a strain-promoted click reaction. The results revealed a higher cellular uptake efficiency for DNA-MOF nanoparticles (14 and 19 nm) than that of unfunctionalized MOF nanoparticles [42]. The Lin group subsequently reported the co-delivery of cisplatin and siRNAs using UiO MOF as nanocarriers. This composite can not only stabilize UiO MOF, but also protected the siRNA from degradation by nucleases, and thus facilitated the cellular uptake of siRNA (Fig. 18) [137].

Besides nucleic acids, other bioactive molecules can also be delivered into cells by forming complex with MOFs. A core@shell nanocomposite was synthesized by Zheng *et al.* using bovine serum albumin (BSA) as the core and a pH-sensitive MOF as the shell. Doxorubicin (DOX) was encapsulated in BSA core before the formation of MOF shell. The composite showed a much higher efficacy against the breast cancer cell line MCF-7 than free DOX (Fig. 19) [95]. The Serre group synthesized a new bioMOF (bioMIL-1), built up from non-toxic iron and the bioactive linker nicotinic acid. Nicotinic acid can be released through the degradation of bioMIL-1 under simulated physiological conditions, allowing for the delivery of the bioactive molecule into cells [138]. Fan *et al.* functionalized of MOF nanoparticles with oligonucleotides based on a coordination chemistry strategy. This work provided us a new group of nucleic acid–MOF conjugates for measuring and manipulating intracellular processes [43]. Zhou group reported a tyrosinase-MOF nanoreactor which can activate the prodrug paracetamol in cancer cells. By regulating the concentration of reactive oxygen species (ROS) and glutathione (GSH), the product of paracetamol can kill the drug-resistant cancer cells [31]. Wuttke *et al.* synthesized a MOF@lipid nanoparticle. Dye molecules can be effectively immobilized into the pore of the MOF while the lipid bilayer prevents their release. Efficient uptake of the MOF@lipid nanoparticles by cancer cells makes these composites promising for drug delivery and cellular imaging [139].

Recently, MOF-based multifunctional probes for dual-modality MR/optical imaging have also been studied. Liu *et al.* developed Zr-based MOF nanoparticles conjugated with DNA aptamers for target-induced bioimaging and photodynamic therapy. Results demonstrated that target-induced imaging is achieved due to the structural change of the aptamer upon binding with the target molecules. Moreover, DNA-MOF composite also significantly enhanced the photodynamic therapy effect [140]. The Lei group synthesized a core–shell nanocomposite by combining a pH-sensitive MOFs shell with a peptide-functionalized gold nanoparticle. The nanostructure can be used as a dual-recognition switch under acidic environment, and thus leading to a novel strategy for imaging lysosomal cathepsin B [141]. Wang *et al.* prepared a DNA–MOF composite by intrinsically coordinating cytosine–phos phate–guanosine (CpG) oligonucleotides on biocompatible zirconium MOF nanoparticles. The results revealed that this DNA-MOF composite exhibited high cellular uptake, organelle specificity, and spatiotemporal control of Toll-like receptors (TLR)-triggered immune responses [142]. Cheng *et al.* encapsulated guest proteins in MOFs through a biocompatible strategy. This composite had high efficiency (up to ~94%) and high loading amount. They found that the formed nanoparticles can protect guest proteins against protease digestion. Moreover, they can improve tumor cell uptake and autonomous release of the guest molecules [143].

3.4. Separation

MOFs are also ideally suited to be applied in separation based on their well-defined open channels, molecular-sized cavities,

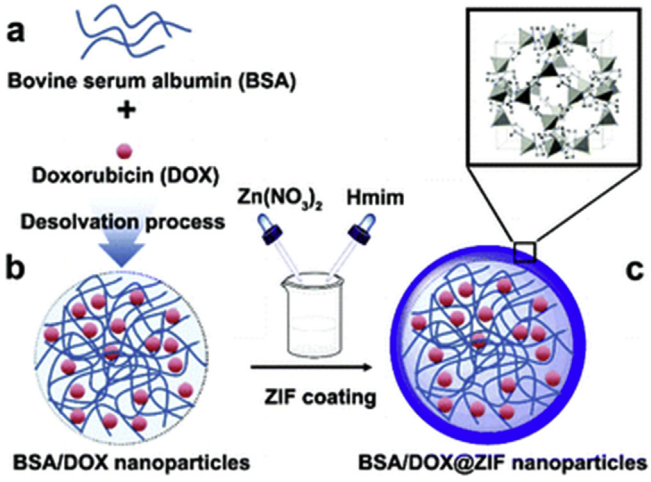

Fig. 19. Fabrication of BSA/DOX@ZIF nanoparticles for drug delivery. Reproduced from Ref. [95] with permission of The Royal Society of Chemistry.

impressive internal surface area, and ease of modification [144]. Biomolecules-MOFs composites have shown great potential for enantioselective separation of biomolecules and removal of heavy metals, pesticides and dyes. Wang and Feng groups reported a microporous MOF structure with a chiral environment. The composite was synthesized through a simple ligand in situ substitution (LIS) of 2-methyl imidazolate (mIm) with D-histidine. This chiral MOF composite showed exceptional selective separation capability for racemic alanine and glutamic acid [145]. The Marti-Gastaldo group reported the use of a chiral Cu(II) 3D MOF based on the tripeptide Gly-L-His-Gly (GHG) for the enantioselective separation of metamphetamine and ephedrine (Fig. 20) [146]. Wan and Luo groups reported a biocatalytic membrane with immobilized laccase for micropollutants removal. Polyethyleneimine (PEI), MOFs, laccase and polydopamine (PDA) were sequentially modified on the separation and support layers of polyacrylonitrile (PAN) ultrafiltration membrane. The LacPAN-MIL-101-L biocatalytic membrane showed high permeability with desirable micropollutants removal performance [147]. Mon *et al.* reported a robust and water-stable MOF decorated with methionine residues. It can selectively capture toxic species such as CH_3Hg^+ and Hg^{2+} from water, which exhibited the largest Hg^{2+} uptake capacity among all reported MOFs [148].

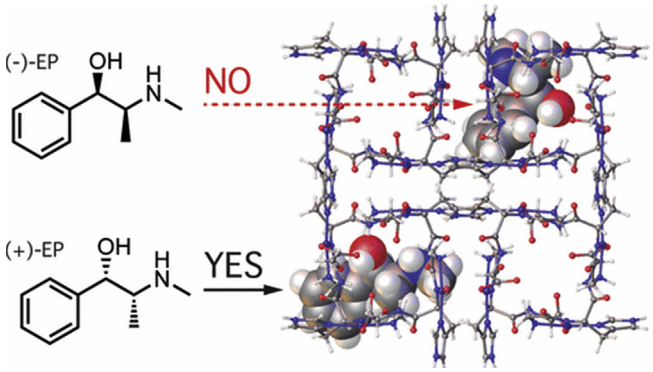

Fig. 20. Schematic illustration of a chiral Cu (II) 3D MOF based on the tripeptide Gly-L-His-Gly (GHG) for the enantioselective separation of ephedrine. Reproduced from Ref. [146] with permission of American Chemical Society.

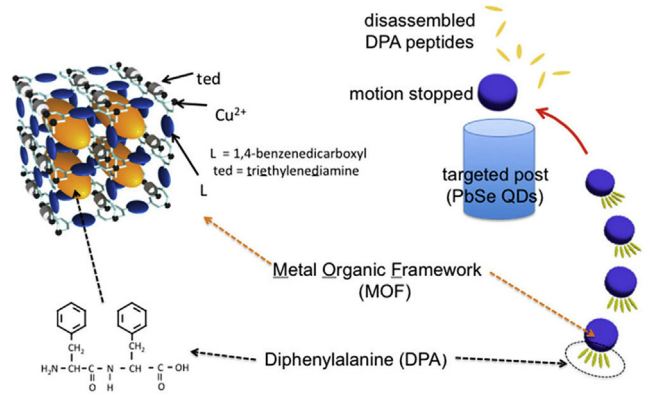

Fig. 21. Design of the peptide-MOF motor to swim toward high pH. (left) The robust reassembly of released hydrophobic DPA peptides at the edge of MOF creates the asymmetric surface tension distribution that can power the motion toward high surface tension side. (right) The change of pH gradient in environment triggers the completion of motion because higher pH condition disassembles DPA peptides on the MOF. Reproduced from Ref. [41] with permission of American Chemical Society.

3.5. Other advanced applications

In addition to the applications mentioned above, some other interesting applications have also been developed using Biomolecules-MOFs composites. For example, The Matsui group integrated peptide with MOF and created an intelligent biochemical swimmer. This peptide-MOF composite could sense toxic heavy metals in solution and swim towards the targets (Fig. 21) [41]. They further developed a new diphenylalanine (DPA) peptides–MOF swimmer based on HKUST-1. This microbot can release the DPA peptides without the destruction of HKUST-1 via water exchange in pores [39]. Kahn *et al.* have recently demonstrated the design of stimuli-responsive DNA-modified MOFs. They synthesized a pH and K^+ responsive DNA-functionalized MOFs, which is promising for the improvement of sensors, new catalysts, and drug delivery carriers [149]. Guo *et al.* introduced single-strand DNA molecules into ZIF-8 membranes through a solid-confined conversion process. The DNA-conjugated ZIF-8 membrane exhibited high proton conductivity and high selective permeability. This study facilitates the research on exploration of functionalized MOF-based membranes for the fuel cell usage [150].

Liang *et al.* demonstrated that MOFs can be used for the production of exoskeletons for microorganisms. This homogenous ZIF-8 coating can protect living cells from anti-fungal agents and large cytotoxic proteins [151]. Their group further reported an enzyme-coated MOF shell which was contracted to enable cells to survive in perturbation environments. Yeast cells were firstly coated with a β-galactosidase (β-gal). A MOF film was subsequently formed on the enzyme coating. This protective shell enabled cells survive in simulated extreme oligotrophic environments for more than 7 days [152]. Our group recently developed a new platform based on ZIF-8 and ZIF-90 systems to efficiently protect antibodies and greatly enhance their thermal, chemical

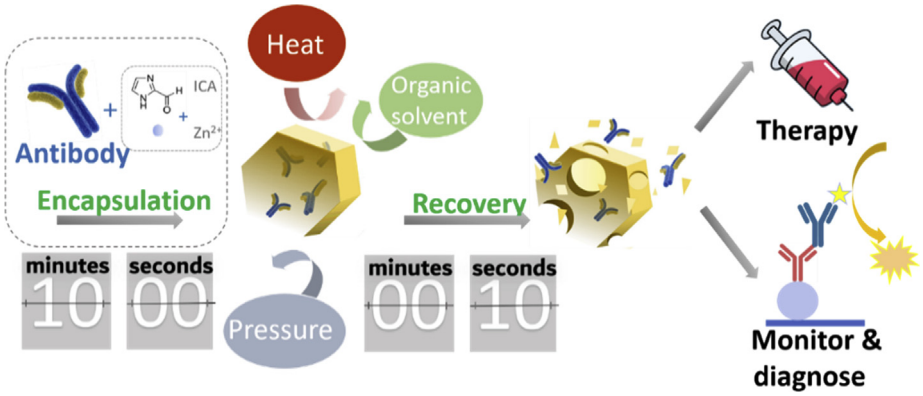

Fig. 22. Schematic illustration of antibody storage and transportation strategy by MOFs that can be separated in vitro. Reproduced from Ref. [153] with permission of Wiley.

and mechanical stabilities. The results demonstrated that MOFs can completely encapsulate and release human IgG, goat anti BSA IgG and Adalimumab in a very short timeframe with high efficiency. Moreover, the protected antibodies can retain structural integrity and bioactivity under harsh conditions including high temperature, mechanical force, organic solvent and freeze-thawing cycles treatment. The protected antibodies can also survive from long term storage under temperature variation environment. This research will facilitate the applications of MOFs in biomedical fields and provide a new strategy for biopharmaceuticals' stabilization, preparation and storage (Fig. 22) [153].

4. Conclusions and perspectives

In the past few years, the incorporation of biomolecules in MOFs for various applications have been flourishing and attracted great attention from researchers in diverse fields including materials, biochemistry, inorganic chemistry and medicine. Indeed, MOFs offer great advantages as platforms for the immobilization of biomolecules. However, the development of this field is still in its infancy. In this review, we summarized the state of the art of preparation strategies for biomolecules' incorporation in MOFs, and then thoroughly discussed the applications of Biomolecules-MOFs composites in biocatalysis, biosensors, separation and other areas.

Although remarkable advances have been achieved in the fabrication and applications of various Biomolecules-MOFs composites, several challenges still remain. In terms of immobilization strategies, although several methods have been developed, they all have their own merits and drawbacks. For instance, adsorption methods can usually maintain high activities of biomolecules, but this method greatly restricted by the dimensions of biomolecules and pore size of MOFs. Moreover, guest molecules only have weak interactions with MOFs and are prone to leak from matrix. Covalent linkage can often overcome this shortcoming due to the strong covalent bonding, but this method can be complicated and costly, and sometimes may influence biomolecules' activities. In-situ encapsulation has no special requirements on the size of guest molecules. But this strategy can only be conducted under mild conditions in aqueous solutions, which ruled out many MOFs that cannot be synthesized in these conditions. Therefore, synergetic of those incorporation approaches, or exploration of new strategies may further carry forward this field and broaden the applications. Besides, operating of Biomolecules-MOFs composites in industrial or biological conditions has been rarely reported. It is essential to study the behavior of such composites in the desired environments, and in-depth studies are urgently needed for more practical and specific functions. In addition, large scale preparation process to afford low-cost Biomolecules-MOFs composites also needs to be developed for practical applications.

Biomolecules-MOFs composites have been demonstrated to be an efficient platform in various fields, such as biocatalysis, biosensor, separation, drug delivery, microreactors and microbots. It is desirable to develop advanced incorporation strategies or broaden the spectrum of MOFs or MOFs-hybrid materials, which is necessary to cope with large biomolecules of industrial significance. Overall, although only proof-of-concept studies are accomplished on this novel composite, the development of MOF–biomolecules composites have shown vast potential, providing a springboard for further development. We believe along with the dramatic development of biochemistry, materials and engineering, this research area will witness a rapid growth in the near future.

Acknowledgements

The authors acknowledge the financial support from the National Natural Science Foundation of China (31800793, 21871153) and Tianjin Natural Science Foundation of China (18JCZDJC37300).

References

[1] S. Prasad, I. Roy, Recent Pat. Biotechnol. 12 (2018) 33–56.
[2] Z. Lei, C. Gao, L. Chen, Y. He, W. Ma, Z. Lin, J. Mater. Chem. B 6 (2018) 1581–1594.
[3] H.H. Nguyen, M. Kim, Appl. Sci. Converg. Technol. 26 (2017) 157–163.
[4] M. Hartmann, X. Kostrov, Chem. Soc. Rev. 42 (2013) 6277–6289.
[5] E. Magner, Chem. Soc. Rev. 42 (2013) 6213–6222.
[6] S. Hudson, J. Cooney, E. Magner, Angew. Chem. Int. Edit. 47 (2008) 8582–8594.
[7] S. Kumar, D. Kumar, R. Ahirwar, P. Nahar, Anal. Bioanal. Chem. 408 (2016) 6945–6956.
[8] H. Jiang, F.J. Xu, Chem. Soc. Rev. 42 (2013) 3394–3426.
[9] J. Nelson, E.G. Griffin, J. Am. Chem. Soc. 38 (1916) 1109–1115.
[10] X. Lian, Y. Fang, E. Joseph, Q. Wang, J. Li, S. Banerjee, C. Lollar, X. Wang, H.C. Zhou, Chem. Soc. Rev. 46 (2017) 3386–3401.
[11] P. Torres-Salas, A. del Monte-Martinez, B. Cutino-Avila, B. Rodriguez-Colinas, M. Alcalde, A.O. Ballesteros, F.J. Plou, Adv. Mater. 23 (2011) 5275–5282.
[12] B. Li, H.M. Wen, Y. Cui, W. Zhou, G. Qian, B. Chen, Adv. Mater. 28 (2016) 8819–8860.
[13] M.I. Nandasiri, S.R. Jambovane, B.P. McGrail, H.T. Schaef, S.K. Nune, Coord. Chem. Rev. 311 (2016) 38–52.
[14] Y. Cui, B. Li, H. He, W. Zhou, B. Chen, G. Qian, Acc. Chem. Res. 49 (2016) 483–493.
[15] Q.L. Zhu, Q. Xu, Chem. Soc. Rev. 43 (2014) 5468–5512.
[16] S.T. Meek, J.A. Greathouse, M.D. Allendorf, Adv. Mater. 23 (2011) 249–267.
[17] H.C. Zhou, J.R. Long, O.M. Yaghi, Chem. Rev. 112 (2012) 673–674.
[18] M. Xu, S.S. Yang, Z.Y. Gu, Chem. Eur. J. 24 (2018) 15131–15142.
[19] S. Li, M. Dharmarwardana, R.P. Welch, Y. Ren, C.M. Thompson, R.A. Smaldone, J.J. Gassensmith, Angew. Chem. Int. Edit. 55 (2016) 10691–10696.
[20] S.L. Anderson, K.C. Stylianou, Coord. Chem. Rev. 349 (2017) 102–128.
[21] E. Gkaniatsou, C. Sicard, R. Ricoux, J.P. Mahy, N. Steunou, C. Serre, Mater. Horiz. 4 (2017) 55–63.
[22] J. Zhuang, A.P. Young, C.K. Tsung, Small 13 (2017) 1700880–1700893.
[23] J. Mehta, N. Bhardwaj, S.K. Bhardwaj, K.H. Kim, A. Deep, Coord. Chem. Rev. 322 (2016) 30–40.
[24] J. Cui, S. Ren, B. Sun, S. Jia, Coord. Chem. Rev. 370 (2018) 22–41.
[25] X. Zhu, H. Zheng, X. Wei, Z. Lin, L. Guo, B. Qiu, G. Chen, Chem. Commun. 49 (2013) 1276–1278.
[26] Q. Wang, X. Lian, Y. Fang, H.C. Zhou, Catalysts 8 (2018) 166–175.
[27] X. Wu, M. Hou, J. Ge, Catal. Sci. Technol. 5 (2015) 5077–5085.
[28] L. Chen, R. Luque, Y. Li, Chem. Soc. Rev. 46 (2017) 4614–4630.
[29] S. Pang, Y. Wu, X. Zhang, B. Li, J. Ouyang, M. Ding, Process Biochem. 51 (2016) 229–239.
[30] X. Lian, Y.P. Chen, T.F. Liu, H.C. Zhou, Chem. Sci. 7 (2016) 6969–6973.
[31] X. Lian, Y. Huang, Y. Zhu, Y. Fang, R. Zhao, E. Joseph, J. Li, J.P. Pellois, H.C. Zhou, Angew. Chem. Int. Edit. 57 (2018) 5725–5730.
[32] S. Patra, T.H. Crespo, A. Permyakova, C. Sicard, C. Serre, A. Chausse, N. Steunou, L. Legrand, J. Mater. Chem. B 3 (2015) 8983–8992.
[33] V. Lykourinou, Y. Chen, X.S. Wang, L. Meng, T. Hoang, L.J. Ming, R.L. Musselman, S.Q. Ma, J. Am. Chem. Soc. 133 (2011) 10382–10385.
[34] D.W. Feng, T.F. Liu, J. Su, M. Bosch, Z.W. Wei, W. Wan, D.Q. Yuan, Y.P. Chen, X. Wang, K.C. Wang, X.Z. Lian, Z.Y. Gu, J. Park, X.D. Zou, H.C. Zhou, Nat. Commun. 6 (2015) 5979–5986.
[35] X.Z. Lian, A. Erazo-Oliveras, J.P. Pellois, H.C. Zhou, Nat. Commun. 8 (2017) 2075–2084.
[36] C.H. Wang, J. Gao, H.L. Tan, ACS Appl. Mater. Interfaces 10 (2018) 25113–25120.
[37] S.K. Bhardwaj, N. Bhardwaj, G.C. Mohanta, P. Kumar, A.L. Sharma, K.H. Kim, A. Deep, ACS Appl. Mater. Interfaces 7 (2015) 26124–26130.
[38] S. Kempahanumakkagari, V. Kumar, P. Samaddar, P. Kumar, T. Ramakrishnappa, K.H. Kim, Biotechnol. Adv. 36 (2018) 467–481.
[39] Y. Ikezoe, J. Fang, T.L. Wasik, T. Uemura, Y.T. Zheng, S. Kitagawa, H. Matsui, Adv. Mater. 27 (2015) 288–291.
[40] H. Hintz, S. Wuttke, Chem. Commun. 50 (2014) 11472–11475.
[41] Y. Ikezoe, J. Fang, T.L. Wasik, M.L. Shi, T. Uemura, S. Kitagawa, H. Matsui, Nano Lett. 15 (2015) 4019–4023.
[42] W. Morris, W.E. Briley, E. Auyeung, M.D. Cabezas, C.A. Mirkin, J. Am. Chem. Soc. 136 (2014) 7261–7264.
[43] S.Z. Wang, C.M. McGuirk, M.B. Ross, S.Y. Wang, P.C. Chen, H. Xing, Y. Liu, C.A. Mirkin, J. Am. Chem. Soc. 139 (2017) 9827–9830.
[44] G.H. Qiu, Z.H. Weng, P.P. Hu, W.J. Duan, B.P. Xie, B. Sun, X.Y. Tang, J.X. Chen, Talanta 180 (2018) 396–402.
[45] H.T. Zhang, J.W. Zhang, G. Huang, Z.Y. Du, H.L. Jiang, Chem. Commun. 50 (2014) 12069–12072.
[46] P. Li, Q. Chen, T.C. Wang, N.A. Vermeulen, B.L. Mehdi, A. Dohnalkoya, N.D. Browning, D. Shen, R. Anderson, D.A. Gomez-Gualdron, F.M. Cetin, J. Jagiello, A.M. Asiri, J.F. Stoddart, O.K. Farhal, Chemistry 4 (2018) 1022–1034.
[47] Y.J. Chen, P. Li, J.A. Modica, R.J. Drout, O.K. Farha, J. Am. Chem. Soc. 140 (2018) 5678–5681.

[48] E. Gkaniatsou, C. Sicard, R. Ricoux, L. Benahmed, F. Bourdreux, Q. Zhang, C. Serre, J.-P. Mahy, N. Steunou, Angew. Chem. Int. Edit. 57 (2018) 16141–16146.
[49] P. Li, S.Y. Moon, M.A. Guelta, S.P. Harvey, J.T. Hupp, O.K. Farha, J. Am. Chem. Soc. 138 (2016) 8052–8055.
[50] Z.W. Zhong, S.L. Pang, Y.W. Wu, S. Jiang, J. Ouyang, J. Chem. Technol. Biotechnol. 92 (2017) 1841–1847.
[51] T.J. Pisklak, M. Macias, D.H. Coutinho, R.S. Huang, K.J. Balkus Jr., Top Catal. 38 (2006) 269–278.
[52] D. Rambabu, C.P. Pooja, A. Pradeep, J. Dhir, Mater. Chem. A 2 (2014) 8628–8631.
[53] W. Chen, W. Yang, Y. Lu, W. Zhu, X. Chen, Anal. Methods 9 (2017) 3213–3220.
[54] H.X. Deng, S. Grunder, K.E. Cordova, C. Valente, H. Furukawa, M. Hmadeh, F. Gandara, A.C. Whalley, Z. Liu, S. Asahina, H. Kazumori, M. O'Keeffe, O. Terasaki, J.F. Stoddart, O.M. Yaghi, Science 336 (2012) 1018–1023.
[55] Y. Chen, V. Lykourinou, T. Hoang, L.J. Ming, S.Q. Ma, Inorg. Chem. 51 (2012) 9156–9158.
[56] Y. Kim, T. Yang, G. Yun, M.B. Ghasemian, J. Koo, E. Lee, S.J. Cho, K. Kim, Angew. Chem. Int. Edit. 54 (2015) 13273–13278.
[57] P. Li, J.A. Modica, A.J. Howarth, E.L. Vargas, P.Z. Moghadam, R.Q. Snurr, M. Mrksich, J.T. Hupp, O.K. Farha, Chemistry 1 (2016) 154–169.
[58] Y. Chen, S.Y. Han, X. Li, Z.J. Zhang, S.Q. Ma, Inorg. Chem. 53 (2014) 10006–10008.
[59] Y. Chen, V. Lykourinou, C. Vetromile, T. Hoang, L.J. Ming, R.W. Larsen, S.Q. Ma, J. Am. Chem. Soc. 134 (2012) 13188–13191.
[60] W.L. Liu, S.H. Lo, B. Singco, C.C. Yang, H.Y. Huang, C.H. Lin, J. Mater. Chem. B 1 (2013) 928–932.
[61] W.L. Liu, C.Y. Wu, C.Y. Chen, B. Singco, C.H. Lin, H.Y. Huang, Chem. Eur. J. 20 (2014) 8923–8928.
[62] W.L. Liu, N.S. Yang, Y.T. Chen, S. Lirio, C.Y. Wu, C.H. Lin, H.Y. Huang, Chem. Eur. J. 21 (2015) 115–119.
[63] W. Ma, Q. Jiang, P. Yu, L. Yang, L. Mao, Anal. Chem. 85 (2013) 7550–7557.
[64] C. Zhang, X. Wang, M. Hou, X. Li, X. Wu, J. Ge, ACS Appl. Mater. Interfaces 9 (2017) 13831–13836.
[65] Y.M. Zhang, H.X. Wang, J.D. Liu, J.W. Hou, Y.T. Zhang, J. Mater. Chem. A 5 (2017) 19954–19962.
[66] F.X. Qin, S.Y. Jia, F.F. Wang, S.H. Wu, J. Song, Y. Liu, Catal. Sci. Technol. 3 (2013) 2761–2768.
[67] Y. Cao, Z. Wu, T. Wang, Y. Xiao, Q. Huo, Y. Liu, Dalton Trans. 45 (2016) 6998–7003.
[68] G. Liu, Y. Xu, Y. Han, J. Wu, J. Xu, H. Meng, X. Zhang, Dalton Trans. 46 (2017) 2114–2121.
[69] X. Lu, X. Wang, L. Wu, L. Wu, Dhanjai, L. Fu, Y. Gao, J. Chen, ACS Appl. Mater. Interfaces 8 (2016) 16533–16539.
[70] P. Kumar, K.H. Kim, V. Bansal, A.K. Paul, A. Deep, Microchem. J. 128 (2016) 102–107.
[71] A. Zare, A.K. Bordbar, F. Jafarian, S. Tangestaninejad, J. Mol. Liq. 254 (2018) 137–144.
[72] S. Jung, Y. Kim, S.J. Kim, T.H. Kwon, S. Huh, S. Park, Chem. Commun. 47 (2011) 2904–2906.
[73] C. Tudisco, G. Zolubas, B. Seoane, H.R. Zafarani, M. Kazemzad, J. Gascon, P.L. Hagedoorn, L. Rassaei, Rsc Adv. 6 (2016) 108051–108055.
[74] X. Wang, T.A. Makal, H.C. Zhou, Aust. J. Chem. 67 (2014) 1629–1631.
[75] Y.H. Shih, S.H. Lo, N.S. Yang, B. Singco, Y.J. Cheng, C.Y. Wu, I.H. Chang, H.Y. Huang, C.H. Lin, Chempluschem 77 (2012) 982–986.
[76] Z. Wang, S.M. Cohen, J. Am. Chem. Soc. 129 (2007) 12368–12369.
[77] P. Kumar, A. Deep, A.K. Paul, L.M. Bharadwaj, J. Porous Mater. 21 (2014) 99–104.
[78] D. Fujita, K. Suzuki, S. Sato, M. Yagi-Utsumi, Y. Yamaguchi, N. Mizuno, T. Kumasaka, M. Takata, M. Noda, S. Uchiyama, K. Kato, M. Fujita, Nat. Commun. 3 (2012) 1093–1099.
[79] S. Patra, S. Sene, C. Mousty, C. Serre, A. Chausse, L. Legrand, N. Steunou, ACS Appl. Mater. Interfaces 8 (2016) 20012–20022.
[80] S.L. Cao, D.M. Yue, X.H. Li, T.J. Smith, N. Li, M.H. Zong, H. Wu, Y.Z. Ma, W.Y. Lou, ACS Sustainable Chem. Eng. 4 (2016) 3586–3595.
[81] C.M. Doherty, G. Grenci, R. Ricco, J.I. Mardel, J. Reboul, S. Furukawa, S. Kitagawa, A.J. Hill, P. Falcaro, Adv. Mater. 25 (2013) 4701–4705.
[82] F.K. Shieh, S.C. Wang, S.Y. Leo, K.C.W. Wu, Chem. Eur. J. 19 (2013) 11139–11142.
[83] Z.Q. Jia, G.R. Wu, D.Z. Wu, Z. Tong, W.S.W. Ho, J. Porous Mater. 24 (2017) 1655–1660.
[84] H.J. Cheng, L. Zhang, J. He, W.J. Guo, Z.Y. Zhou, X.J. Zhang, S.M. Nie, H. Wei, Anal. Chem. 88 (2016) 5489–5497.
[85] J.D. Cui, Y.X. Feng, T. Lin, Z.L. Tan, C. Zhong, S.R. Jia, ACS Appl. Mater. Interfaces 9 (2017) 10587–10594.
[86] X.L. Wu, J. Ge, C. Yang, M. Hou, Z. Liu, Chem. Commun. 51 (2015) 13408–13411.
[87] C. Hou, Y. Wang, Q.H. Ding, L. Jiang, M. Li, W.W. Zhu, D. Pan, H. Zhu, M.Z. Liu, Nanoscale 7 (2015) 18770–18779.
[88] F.K. Shieh, S.C. Wang, C.I. Yen, C.C. Wu, S. Dutta, L.Y. Chou, J.V. Morabito, P. Hu, M.H. Hsu, K.C.W. Wu, C.K. Tsung, J. Am. Chem. Soc. 137 (2015) 4276–4279.
[89] K. Liang, R. Ricco, C.M. Doherty, M.J. Styles, S. Bell, N. Kirby, S. Mudie, D. Haylock, A.J. Hill, C.J. Doonan, P. Falcaro, Nat. Commun. 6 (2015) 7240–7247.
[90] F.J. Lyu, Y.F. Zhang, R.N. Zare, J. Ge, Z. Liu, Nano Lett. 14 (2014) 5761–5765.
[91] F.S. Liao, W.S. Lo, Y.S. Hsu, C.C. Wu, S.C. Wang, F.K. Shieh, J.V. Morabito, L.Y. Chou, K.C.W. Wu, C.K. Tsung, J. Am. Chem. Soc. 139 (2017) 6530–6533.
[92] T.T. Chen, J.T. Yi, Y.Y. Zhao, X. Chu, J. Am. Chem. Soc. 140 (2018) 9912–9920.
[93] W.B. Liang, R. Ricco, N.K. Maddigan, R.P. Dickinson, H.S. Xu, Q.W. Li, C.J. Sumby, S.G. Bell, P. Falcaro, C.J. Doonan, Chem. Mater. 30 (2018) 1069–1077.
[94] C.Z. Wang, H.C. Sun, J.Y. Luan, Q.S. Jiang, S. Tadepalli, J.J. Morrissey, E.D. Kharasch, S. Singamaneni, Chem. Mater. 30 (2018) 1291–1300.
[95] Z.Z. Liang, Z.Y. Yang, H.T. Yuan, C. Wang, J. Qi, K.Q. Liu, R. Cao, H.Q. Zheng, Dalton Trans. 47 (2018) 10223–10228.
[96] S. Li, M. Dharmarwardana, R.P. Welch, C.E. Benjamin, A.M. Shamir, S.O. Nielsen, J.J. Gassensmith, ACS Appl. Mater. Interfaces 10 (2018) 18161–18169.
[97] M. Zhang, Z.Y. Gu, M. Bosch, Z. Perry, H.C. Zhou, Coord. Chem. Rev. 293 (2015) 327–356.
[98] S. Rojas, T. Devic, P. Horcajada, J. Mater. Chem. B 5 (2017) 2560–2573.
[99] H. Oh, T. Li, J. An, Chem. Eur. J. 21 (2015) 17010–17015.
[100] J. An, O.K. Farha, J.T. Hupp, E. Pohl, J.I. Yeh, N.L. Rosi, Nat. Commun. 3 (2012) 604–609.
[101] P. Amo-Ochoa, F. Zamora, Coord. Chem. Rev. 276 (2014) 34–58.
[102] J. An, S.J. Geib, N.L. Rosi, J. Am. Chem. Soc. 131 (2009) 8376–8377.
[103] T. Li, M.T. Kozlowski, E.A. Doud, M.N. Blakely, N.L. Rosi, J. Am. Chem. Soc. 135 (2013) 11688–11691.
[104] M. Zhang, W. Lu, J.R. Li, M. Bosch, Y.P. Chen, T.F. Liu, Y. Liu, H.C. Zhou, Inorg. Chem. Front. 1 (2014) 159–162.
[105] C.D.L. Saunders, N. Burford, U. Werner-Zwanziger, R. McDonald, Inorg. Chem. 47 (2008) 3693–3699.
[106] J. Rabone, Y.F. Yue, S.Y. Chong, K.C. Stylianou, J. Bacsa, D. Bradshaw, G.R. Darling, N.G. Berry, Y.Z. Khimyak, A.Y. Ganin, P. Wiper, J.B. Claridge, M.J. Rosseinsky, Science 329 (2010) 1053–1057.
[107] A.P. Katsoulidis, K.S. Park, D. Antypov, C. Marti-Gastaldo, G.J. Miller, J.E. Warren, C.M. Robertson, F. Blanc, G.R. Darling, N.G. Berry, J.A. Purton, D.J. Adams, M.J. Rosseinsky, Angew. Chem. Int. Edit. 53 (2014) 193–198.
[108] M.B. Majewski, A.J. Howarth, P. Li, M.R. Wasielewski, J.T. Hupp, O.K. Farha, CrystEngComm. 19 (2017) 4082–4091.
[109] P. Chulkaivalsucharit, X.L. Wu, J. Ge, Rsc Adv. 5 (2015) 101293–101296.
[110] S. Tadepalli, J. Yim, S. Cao, Z. Wang, R.R. Naik, S. Singamaneni, Small 14 (2018) 1702382–1702389.
[111] Z.L. Xu, G.W. Xiao, H.F. Li, Y. Shen, J. Zhang, T. Pan, X.Y. Chen, B. Zheng, J.S. Wu, S. Li, W.N. Zhang, W. Huang, F.W. Huo, Adv. Funct. Mater. 28 (2018) 1802479–1802487.
[112] G.Y. Jeong, R. Ricco, K. Liang, J. Ludwig, J.O. Kim, P. Falcaro, D.P. Kim, Chem. Mater. 27 (2015) 7903–7909.
[113] S. Rafiei, S. Tangestaninejad, P. Horcajada, M. Moghadam, V. Mirkhani, I. Mohammadpoor-Baltork, R. Kardanpour, F. Zadehahmadi, Chem. Eng. J. 334 (2018) 1233–1241.
[114] Y. Hu, L. Dai, D. Liu, W. Du, Green Chem. 20 (2018) 4500–4506.
[115] F. Pitzalis, C. Carucci, M. Naseri, L. Fotouhi, E. Magner, A. Salis, Chemcatchem 10 (2018) 1578–1585.
[116] L. Shi, X. Cai, H. Li, H. He, H. Zhao, M. Lan, Electroanalysis 30 (2018) 466–473.
[117] X. Liu, W. Qi, Y. Wang, D. Lin, X. Yang, R. Su, Z. He, ACS Appl. Mater. Interfaces (2018) 33407–33415.
[118] V. Chakrapani, K.B.A. Ahmed, V.V. Kumar, V. Ganapathy, S.P. Anthony, V. Anbazhagan, Rsc Adv. 4 (2014) 33215–33221.
[119] Y.Q. Yin, C.L. Gao, Q. Xiao, G. Lin, Z. Lin, Z.W. Cai, H.H. Yang, ACS Appl. Mater. Interfaces 8 (2016) 29052–29061.
[120] X. Liu, W. Qi, Y.F. Wang, R.X. Su, Z.M. He, Nanoscale 9 (2017) 17561–17570.
[121] X. Wang, X.B. Lu, L.D. Wu, J.P. Chen, Biosens. Bioelectron. 65 (2015) 295–301.
[122] S.B. Xie, J.W. Ye, Y.L. Yuan, Y.Q. Chai, R. Yuan, Nanoscale 7 (2015) 18232–18238.
[123] W.J. Shen, Y. Zhuo, Y.Q. Chai, R. Yuan, Anal. Chem. 87 (2015) 11345–11352.
[124] S.Y. Dong, D.D. Zhang, G.C. Suo, W.B. Wei, T.L. Huang, Anal. Chim. Acta 934 (2016) 203–211.
[125] S. Dong, L. Peng, W. Wei, T. Huang, ACS Appl. Mater. Interfaces 10 (2018) 14665–14672.
[126] X.L. Zhang, Y.Y. Zeng, A.X. Zheng, Z.X. Cai, A.M. Huang, J.H. Zeng, X.L. Liu, J.F. Liu, Microchim Acta 184 (2017) 1933–1940.
[127] C.C. Gong, Y. Shen, J.Y. Chen, Y.G. Song, S.L. Chen, Y.H. Song, L. Wang, Sens. Actuators B 239 (2017) 890–897.
[128] P.H. Ling, J.P. Lei, L. Zhang, H.X. Ju, Anal. Chem. 87 (2015) 3957–3963.
[129] J. Chen, C. Yu, Y.L. Zhao, Y.Z. Niu, L. Zhang, Y.J. Yu, J. Wu, J.L. He, Biosens. Bioelectron. 91 (2017) 892–899.
[130] Y.F. Wu, J.Y. Han, P. Xue, R. Xu, Y.J. Kang, Nanoscale 7 (2015) 1753–1759.
[131] X. Shen, B. Yan, J. Mater. Chem. C 3 (2015) 7038–7044.
[132] X. Shen, B. Yan, J. Colloid. Interf. Sci. 451 (2015) 63–68.
[133] H. Weng, B. Yan, Anal. Chim. Acta 988 (2017) 89–95.
[134] X. Wang, C.L. Yang, S.J. Zhu, M. Yan, S.G. Ge, J.H. Yu, Biosens. Bioelectron. 87 (2017) 108–115.
[135] P.P. Hu, N. Liu, K.Y. Wu, L.Y. Zhai, B.P. Xie, B. Sun, W.J. Duan, W.H. Zhang, J.X. Chen, Inorg. Chem. 57 (2018) 8382–8389.
[136] P. Horcajada, C. Serre, M. Vallet-Regi, M. Sebban, F. Taulelle, G. Ferey, Angew. Chem. Int. Edit. 45 (2006) 5974–5978.
[137] C.B. He, K.D. Lu, D.M. Liu, W.B. Lin, J. Am. Chem. Soc. 136 (2014) 5181–5184.
[138] R.M. Stuart, H. Daniela, B. Tarek, H. Patricia, M.G. Jean, S. Christian, Chem. Commun. 46 (2010) 4526–4528.
[139] S. Wuttke, S. Braig, T. Prei, A. Zimpel, J. Sicklinger, C. Bellomo, J.O. Rädler, A.M. Vollmar, T. Bein, Chem. Commun. 51 (2015) 15752–15755.
[140] Y. Liu, W.J. Hou, L. Xia, C. Cui, S. Wan, Y. Jiang, Y. Yang, Q. Wu, L.P. Qiu, W.H. Tan, Chem. Sci. 9 (2018) 7505–7509.

[141] H. Shen, J.T. Liu, J.P. Lei, H.X. Ju, Chem. Commun. 54 (2018) 9155–9158.
[142] Z.J. Wang, Y. Fu, Z.Z. Kang, X.G. Liu, N. Chen, Q. Wang, Y.Q. Tu, L.H. Wang, S.P. Song, D.H. Ling, H.Y. Song, X.Q. Kong, C.H. Fan, J. Am. Chem. Soc. 139 (2017) 15784–15791.
[143] G. Cheng, W.Q. Li, L. Ha, X.H. Han, S.J. Hao, Y. Wan, Z.G. Wang, F.P. Dong, X. Zou, Y.W. Mao, S.Y. Zheng, J. Am. Chem. Soc. 140 (2018) 7282–7291.
[144] T. Uemura, N. Yanai, S. Kitagawa, Chem. Soc. Rev. 38 (2009) 1228–1236.
[145] J.S. Zhao, H.W. Li, Y.Z. Han, R. Li, X.S. Ding, X. Feng, B. Wang, J. Mater. Chem. A 3 (2015) 12145–12148.
[146] J. Navarro-Sanchez, A.I. Argente-Garcia, Y. Moliner-Martinez, D. Roca-Sanjuan, D. Antypov, P. Campins-Falco, M.J. Rosseinsky, C. Marti-Gastaldo, J. Am. Chem. Soc. 139 (2017) 4294–4297.
[147] Z.Y. Ren, J.Q. Luo, Y.H. Wan, Chem. Eng. J. 348 (2018) 389–398.
[148] M. Mon, F. Lloret, J. Ferrando-Soria, C. Marti-Gastaldo, D. Armentano, E. Pardo, Angew. Chem. Int. Edit. 55 (2016) 11167–11172.
[149] J.S. Kahn, L. Freage, N. Enkin, M.A.A. Garcia, I. Willner, Adv. Mater. 29 (2017) 1602782–1602787.
[150] Y. Guo, Z.Q. Jiang, W. Ying, L.P. Chen, Y.Z. Liu, X.B. Wang, Z.J. Jiang, B.L. Chen, X.H. Peng, Adv. Mater. 30 (2018) 1705155–1705162.
[151] K. Liang, J.J. Richardson, J.W. Cui, F. Caruso, C.J. Doonan, P. Falcaro, Adv. Mater. 28 (2016) 7910–7914.
[152] K. Liang, J.J. Richardson, C.J. Doonan, X. Mulet, Y. Ju, J.W. Cui, F. Caruso, P. Falcaro, Angew. Chem. Int. Edit. 56 (2017) 8510–8515.
[153] Y. Feng, H. Wang, S. Zhang, Y. Zhao, J. Gao, Y. Zheng, P. Zhao, Z. Zhang, M.J. Zaworotko, S. Ma, Y. Chen, Adv. Mater. (2018), https://doi.org/10.1002/adama.201805148.