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Review

Frontiers in design and applications of biomacromolecule@COFs composites

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ABSTRACT

Biomacromolecules with complex structures, are important components of living things. Due to the sensitivity of biomacromolecules to various influencing factors like temperature, acid/alkali, or organic solvent, they would be easily deactivated under various related conditions during the applications. It is necessary to exploit immobilization materials for biomacromolecules to achieve low deactivation rate, high stability and advanced functions. Covalent organic frameworks (COFs) exhibit high porosity, tunable function and biocompatibility, making them to be excellent host materials for immobilizing biomacromolecules. Up to date, the related works about the immobilization of biomacromolecules by COFs have been reported continuously and some reviews have also separately summarized the loading of biomacromolecules like enzyme or nucleic acid into COFs. However, the systematic reviews about the fixation of various biomacromolecules (e.g., enzymes, proteins, peptides, and nucleic acids) in COFs to discuss their differences are still rare. A comprehensive review would be demanded to summarize their varied properties like sizes, types, or functions of biomacromolecules in interaction with COFs, as well as their synergistically integrated effects on various applications. In this review, we will systematically summarize the recent research progress about different biomacromolecule@COFs and their related applications. We will also discuss the challenges or bottlenecks faced by biomacromolecule@COFs and give perspectives of COFs in this field. We hope this review could provide new insights for scientists in this field.

1. Introduction

Biomacromolecules, including enzymes, proteins, nucleic acids and peptides, are important components of living things, possessing biological function, complex structures, and large molecular weight [1–6]. The unique structures and components of biomacromolecules determine their special properties, in which their movement and change can reflect important life information [7–9]. Nevertheless, the complex structures of biomacromolecules and their susceptibility to temperature, acid/alkali, or organic solvent result in much difficulty in stabilizing biomacromolecules in addition to developing their advanced functions [10–14]. Up to date, there are many works focused on the development of effective immobilization strategies to overcome the disadvantages of biomacromolecules [15–17]. However, several issues need to be addressed: 1) the development of appropriate host materials to be matched with biomacromolecules is still unmet; 2) the exploration of application fields is still limited; 3) the unclear structure-to-property relationships based on the complex structures are difficult for the mechanistic study. Therefore, the development of novel materials that can effectively immobilize biomacromolecules are highly desired to extend their application fields.

In the past decades, porous materials have witnessed fast development as the host materials of biomacromolecules [18–24]. Porous inorganic materials (e.g., graphene, graphitic oxide, MXene or SiO_2) are competitive candidates in the immobilization of biomacromolecules [25–28]. However, their low porosity and irregular channels would result in the uncertain loading position and low loading efficiency, meanwhile the possibly existed swelling or instability problems might lead to the leakage or denaturation of biomacromolecules, which set obstacles for the application of inorganic materials in this field. As comparison, porous and crystalline organic materials, including metal–organic frameworks (MOFs) [29], hydrogen-bonded organic

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frameworks (HOFs) [30] and COFs [31], with the inherent advantages of high crystallinity, accessible pores, well-defined structure and tunable functions are more favorable to be applied in the immobilization of biomacromolecules. Among them, MOFs and HOFs are traditional host materials for the immobilization of biomacromolecules, yet they still face some inevitable issues like the toxic metal ions of MOFs [32,33] or relatively poorer stability of HOFs [34–36], thus limiting their applications in this field. In 2005, Yaghi's group reported the first case of COFs [37]. Afterwards, much attention has been attracted around the world owing to their advantages of low density, high porosity and superior stability to traditional porous materials [38–43]. Compared to other porous crystalline materials, COFs are more potential host materials for biomacromolecules owing to: 1) low density and uniform pores could facilitate the high loading and dispersion of biomacromolecules; 2) tunable and desibable functions might provide specific interactions with biomacromolecules and controllable release; 3) hypotoxicity would make them to be more compatible with biomacromolecules and suitable for in vivo or vitro operation and 4) well-defined crystalline structures are beneficial for the study of structure-to-property relationships [44–49]. Thanks to the protection and dispersion of COFs, biomacromolecule@COFs shows superior activity, stability, reusability, and biocompatibility that have been applied in a broad range of applications (Fig. 1) [50–53]. Up to date, the related works about the immobilization of biomacromolecules by COFs have been reported continuously and some reviews have also separately summarized the loading of biomacromolecules like enzyme [18,54,55] or nucleic acid [56,57] into COFs (Fig. 2). However, the systematic reviews about the fixation of various biomacromolecules (e.g., enzymes, proteins, peptides, and nucleic acids) in COFs and distinction of the immobilization requirements, immobilization advantages and immobilization applications of COFs for various biomacromolecules are still rare. Therefore, a comprehensive review would be demanded to systematically summarize the varied properties like types, sizes, or functions of biomacromolecules in interaction with COFs, as well as their integrated effects on various applications.

Thus, in this review, we will provide a systematic summary about biomacromolecule@COFs including their design, immobilization strategies and applications (Fig. 3). Initially, we discuss the immobilization of various biomacromolecules (e.g., enzymes, nucleic acids, proteins and peptides) and their different immobilization positions (e.g., surface, pore and cavity) in COFs. After that, we present the immobilization strategies of biomacromolecules including post-modification and *in-situ* encapsulation. Additionally, we focus on the application (e.g., biosensing, biocatalysis, drug delivery and separation/enrichment) of biomacromolecule@COFs. Finally, we will present a perspective and provide future insights for biomacromolecule@COFs.

At present, there are many kinds of biomacromolecule@COFs that have been reported and we thus have summarized the majority of them in a table (Table 1). In this table, we list the types of COFs and biomacromolecules, the immobilization strategies as well as the applications of biomacromolecule@COFs. Referring to the summary table, we will discuss related contents based on the types of biomacromolecules, the fixation positions in COFs, the immobilization strategies and application fields in detail (Fig. 3).

2. The type of biomacromolecules

COFs as ideal host materials with good biocompatibility could be used to fix various types of biomacromolecules such as enzymes, proteins, peptides or nucleic acids (Fig. 4) [90,91]. In 2018, Sun et al. fixed lipase into COF-OMe for the first time, confirming the application feasibility of COFs in enzyme fixation [58]. Since then, different types of enzymes (e.g., trypsin, glucose oxidase and horseradish peroxidase) immobilized by COFs have been reported [68,89]. Based on the high catalytic activity of enzymes and the efficient protection of COFs, enzyme@COFs composites have started to be applied as sensitive biosensors or stable biocatalysts. Except for enzymes, proteins (e.g., bovine serum albumin (BSA) and Myoglobin (Mb)), the carriers of life activities, have also been immobilized into COFs and showed potential applications in protein separation or drug delivery. Meanwhile, peptides (e.g., C-peptide and C_{10}FFVK), serving as important components of proteins, have proven to be applicable in biocatalysis and enrichment applications after the immobilization by COFs [92–94]. In addition, after immobilizing into COFs, nucleic acids (e.g., DNA and RNA) as important carriers of genetic information can be well-protected and utilized [95,96]. Interestingly, due to the specificity of nucleic acids and appropriate protection of COFs, nucleic acid@COFs were widely explored to prepare targeted drugs, or used as biosensors to detect specific RNA [57,97,98].

3. The immobilization position and strategy of biomacromolecule@COFs

3.1. The immobilization positions

3.1.1. Loading on the surface

The pore sizes of microporous COFs (<2 nm) and even some mesoporous COFs are smaller than the sizes of biomacromolecules, thus biomacromolecules would hardly enter into the pores of COFs. In this regard, biomacromolecules would be more easily fixed onto the surface

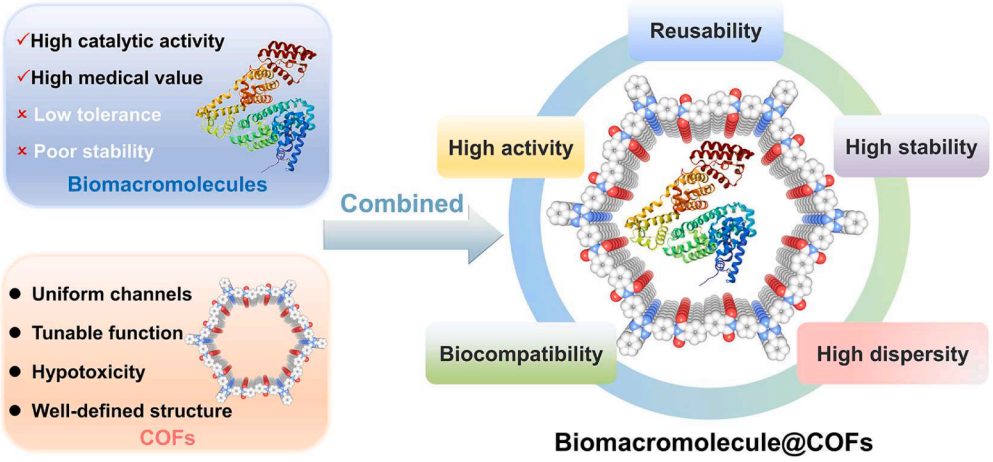


Fig. 1. Advantages of biomacromolecule@COFs compared with free biomacromolecules.

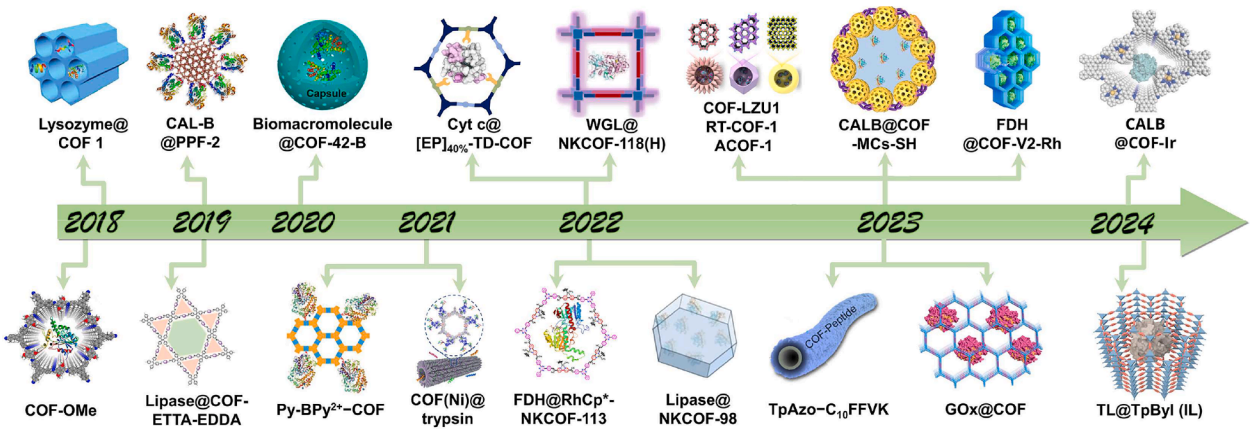


Fig. 2. Evolution timeline of COFs in encapsulated biomacromolecules. Image for COF-OMe: Reproduced with permission [58]. Copyright 2018, American Chemical Society. Image for lysozyme@COF 1: Reproduced with permission [59]. Copyright 2018, Wiley-VCH. Image for CAL-B@PPF-2: Reproduced with permission [60]. Copyright 2019. Wiley-VCH. Image for lipase@COF-ETTA-EDDA: Reproduced with permission [61]. Copyright 2019, Wiley-VCH. Image for biomacromolecule@COF-42-B: Reproduced with permission [62]. Copyright 2020, American Chemical Society. Image for Py-BPy^{2+}-COF: Reproduced with permission [63]. Copyright 2021, Royal Society of Chemistry. Image for FDH@RhCp*-NKCOF-113: Reproduced with permission [64]. Copyright 2022, Wiley-VCH. Image for lipase@NKCOF-98: Reproduced with permission [65]. Copyright 2022, Wiley-VCH. Cyt c@$[EP]_{40\%}$-TD-COF: Reproduced with permission [66]. Copyright 2022, Wiley-VCH. Image for WGL@NKCOF-118(H): Reproduced with permission [67]. Copyright 2022, American Chemical Society. Image for COF-LZU1, RT-COF-1 and ACOF-1: Reproduced with permission [68]. Copyright 2023, Wiley-VCH. Image for CAL-B@COF-MCs-SH: Reproduced with permission [69]. Copyright 2023, Wiley-VCH. Image for GOx@COF: Reproduced with permission [70]. Copyright 2023, American Chemical Society. Image for TpAzo-C_{10}FFVK: Reproduced with permission [71]. Copyright 2023, American Chemical Society. Image for FDH@COF-V2-Rh: Reproduced with permission [72]. Copyright 2023, American Chemical Society. Image for TL@TpByl (IL): Reproduced with permission [73]. Copyright 2024, Wiley-VCH. Image for CALB@COF-Ir: Reproduced with permission [74]. Copyright 2024 Wiley-VCH.

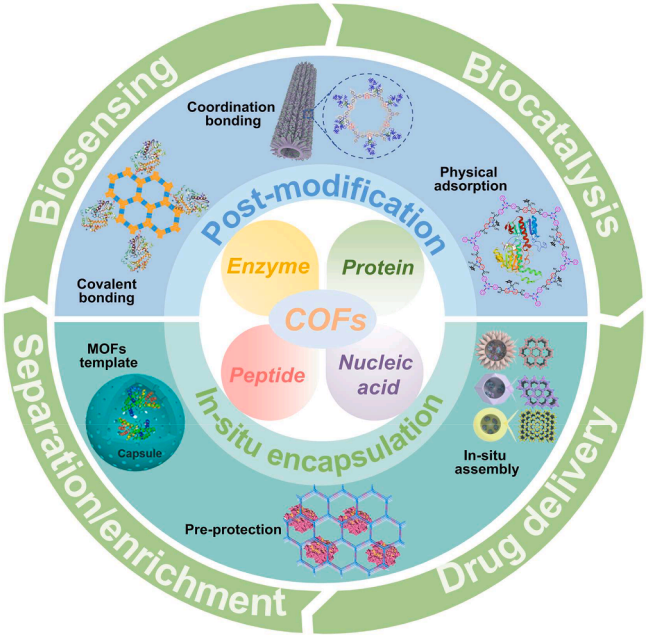


Fig. 3. The schematic representation of biomacromolecule@COFs.

of COFs through physical adsorption or chemical bonding interactions (Fig. 5). For example, the size of organophosphorus hydrolase (OPH) is 9.2 × 5.6 × 4.0 nm^3, which is larger than the pore size of Tz-Da (3.05 nm) and it can only be immobilized on the surface. Zhao et al. immobilized OPH on the surface of Pd@Tz-Da by covalent bonding connection [85]. The results of SDS-PAGE analysis of Pd@Tz-Da@OPH washed with a 10 % SDS solution prove that the OPH indeed immobilized onto the surface of Pd@Tz-Da.

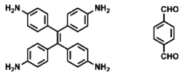
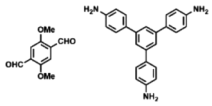
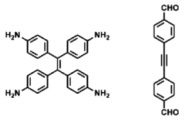
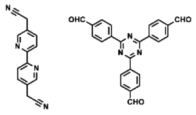
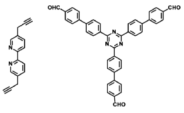
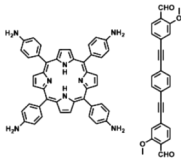
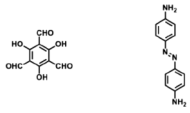
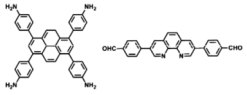
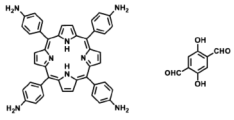
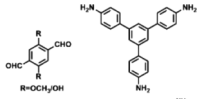
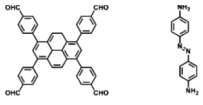
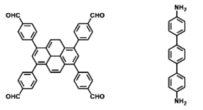
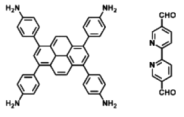
3.1.2. Loading in the pore

The pores of COFs can provide a protective effect on biomacromolecules, which can avoid agglomeration to effectively improve their heat or solvent resistances. When the pore sizes of COFs are close to or larger than the sizes of biomacromolecules, biomacromolecules can be fixed in the pore channels of COFs (Fig. 5). Some small sized biomacromolecules, such as wheat germ lipase (WGL 3.2 × 3.7 × 5.6 nm^3), trypsin (3.8 × 3.8 × 3.8 nm^3), and glucose oxidase (GOx 2.3 × 3.2 × 5.6 nm^3), could enter into size-matched COFs pores by physical adsorption or chemical bonding interactions (Table 1). For instance, mesoporous NKCOF-118(H) (3.5 nm) was selected as the host material for the immobilization of WGL. Due to the size matching between WGL and NKCOF-118(H), Jin et al. believed that the WGL was fixed in the pore of NKCOF-118(H) [67]. To prove the immobilization of WGL in the pore channels, a series of characterizations were implemented. After the loading of WGL, the Brunauer-Emmett-Teller surface area (S_{BET}) was significantly diminished from 1436 to 712 m^2/g (Fig. 6a). Meanwhile, the pore volume of NKCOF-118(H) diminished from 1.08 to 0.45 $cm^3\ g^{-1}$ (Fig. 6b). In addition, the confocal laser scanning microscopy (CLSM) images displayed uniform luminescence inside the FITC-tagged WGL@NKCOF-118(H) (Fig. 6c). Based on the above results, the WGL was evenly fixed in the pore of NKCOF-118(H). In addition, Sun et al. prepared a kind of hierarchically porous COF (i.e. COF-ETTA-EDDA) to fix lipase (3.0 × 3.2 × 6.0 nm^3).[61]. There are two types of pores in COF-ETTA-EDDA (i.e. hexagonal and triangular pores), in which lipase can be readily loaded in hexagonal pores (3.85 nm). The results of FT-IR, STEM, and CLSM tests prove that lipase occupies the pores of COF-ETTA-EDDA rather than the surface.

3.1.3. Loading in the cavity

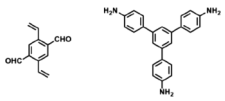
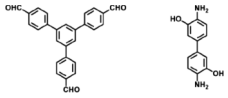
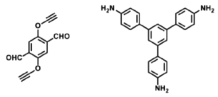
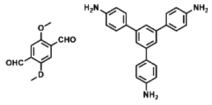
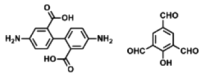
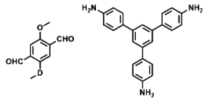
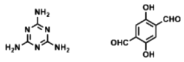
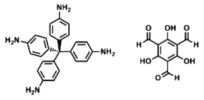
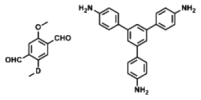
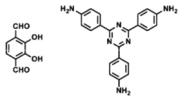
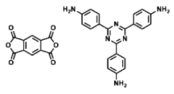
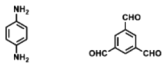
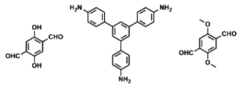
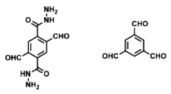
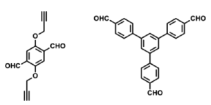
In order to overcome the influence of size on biomacromolecule immobilization, COF-based nanomaterials with cavities that are much larger than the sizes of biomacromolecules have attracted much attention of scientists. For example, Chao et al. synthesized COF-LZU1 with large cavities during the Ostwald ripening process and fixed trypsin (3.8 × 3.8 × 3.8 nm^3) *in-situ* into the cavity [89]. The COF-LZU1 with a cavity of about 200 nm in size is an ideal fixation location for trypsin. To prove it, the CLSM images were used and the results showed that the FITC-trypsin was only observed inside the trypsin@COFs-LZU1. In addition,

Table 1
A summary of COFs as host materials for biomacromolecules.

	COFs	Ligand	Pore size	Biomacromolecule (size)	Immobilization strategy	Application	Ref.
1	$COF_{ETTA-TPAL}$		3.06 nm 0.87 nm	GOx (2.3 × 3.2 × 5.6 nm^3), MP-11 (1.3 × 0.8 × 2.6 nm^3)	Physical adsorption	Biosensing	[75]
2	COF-OMe		3.30 nm	Lipase PS (3.0 × 3.2 × 6.0 nm^3)	Physical adsorption	Biocatalysis	[58]
3	COF-ETTA-EDDA		1.39 nm 3.85 nm	Lipase PS (3.0 × 3.2 × 6.0 nm^3)	Physical adsorption	Biocatalysis	[61]
4	NKCOF-113		3.90 nm	FDH (5.5 × 4.0 × 9.0 nm^3)	Physical adsorption	Biocatalysis	[64]
5	COF-V2		5.20 nm	FDH (5.5 × 4.0 × 9.0 nm^3)	Physical adsorption	Biocatalysis	[72]
6	NKCOF-118(H)		3.50 nm	WGL (3.2 × 3.7 × 5.6 nm^3)	Physical adsorption	Biocatalysis	[67]
7	TpAzo COF		2.70 nm	C_{10}FFVK (24.3 ± 0.1 nm)	Physical adsorption	Physical adsorption	[71]
8	PPCOF		3.40 nm	CALB (2.9 × 4.9 × 6.2 nm^3)	Physical adsorption	Physical adsorption	[74]
9	TpDh		2.00 nm	Single-stranded DNA[a]	Physical adsorption	Drug delivery	[76]
10	TPB-DMTP-COF		3.30 nm	Lysozyme (3.0 × 3.0 × 4.5 nm^3)	Physical adsorption	Protein separation	[77]
11	Tp-COF		2.99 nm	Cyt c (2.6 × 3.0 × 3.2 nm^3), Mb (4.5 × 3.5 × 2.5 nm^3)	Physical adsorption	Protein separation	[78]
12	Azo-COF		2.78 nm	Cyt c (2.6 × 3.0 × 3.2 nm^3)	Physical adsorption	Protein separation	[78]
13	Py-BPy^{2+}-COF		2.20 nm	Cyt c (2.6 × 3.0 × 3.2 nm^3), Lysozyme (3.0 × 3.0 × 4.5 nm^3), BSA (4.0 × 4.0 × 14 nm^3)	Physical adsorption	Protein separation	[79]

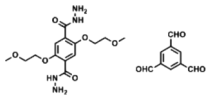
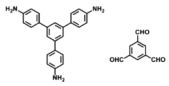
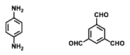
(*continued on next page*)

Table 1 (*continued*)

	COFs	Ligand	Pore size	Biomacromolecule (size)	Immobilization strategy	Application	Ref.
14	COFs		2.73 nm	C-Peptide[a]	Physical adsorption	Peptide enrichment	[80]
15	COFs		3.30 nm	Phosphopeptide[a]	Physical adsorption	Peptide enrichment	[81]
16	Alkynyl-COF		2.80 nm	Oligonucleotide[a]	Covalent bonding	Biosensing	[82]
17	COF		3.36 nm	Duplex DNA (H1/H2)[a]	Covalent bonding	Biosensing	[83]
18	COF_{HD}		1.95 nm	GOx ($2.3 \times 3.2 \times 5.6$ nm^3)	Covalent bonding	Biosensing	[63]
19	COF		3.36 nm	HRP ($4.0 \times 4.4 \times 6.8$ nm^3)	Covalent bonding	Biosensing	[84]
20	Tz-Da		3.05 nm	OPH ($9.2 \times 5.6 \times 4.0$ nm^3)	Covalent bonding	Biocatalysis	[85]
21	PPF-2-NH_2		1.10 nm	CAL-B ($3.0 \times 4.0 \times 5.0$ nm^3)	Covalent bonding	Biocatalysis	[60]
22	H-COF-OMe		3.36 nm	Laccase ($6.5 \times 5.5 \times 4.5$ nm^3)	Covalent bonding	Biocatalysis	[86]
23	TatDha-COF		3.20 nm	Trypsin ($3.8 \times 3.8 \times 3.8$ nm^3)	Coordination bonding	Biocatalysis	[87]
24	COF 1		3.60 nm	Lysozyme ($3.0 \times 3.0 \times 4.5$ nm^3)	Covalent bonding	Biocatalysis	[59]
25	COF-1		1.50 nm	Insulin (2.5–3 nm), GOx ($2.3 \times 3.2 \times 5.6$ nm^3)	Covalent bonding	Drug delivery	[88]
26	COF-LZU1		4.02 nm	Trypsin ($5.5 \times 5.5 \times 10.9$ nm^3)	*In-situ* assembly	Biosensing	[89]
27	$[EP]_{40\%}$-TD-COF		3.30 nm	Cyt c ($2.6 \times 3.0 \times 3.2$ nm^3)	Covalent bonding	Biocatalysis	[66]
28	COF-42-B		1.90 nm	CAT ($11.0 \times 18.0 \times 4.1$ nm^3)	MOFs template	Biocatalysis	[62]
29	TAPB-BPTA-COF		2.80 nm	CAL-B ($3.0 \times 4.0 \times 5.0$ nm^3)	*In-situ* assembly	Biocatalysis	[69]

(*continued on next page*)

Table 1 (*continued*)

	COFs	Ligand	Pore size	Biomacromolecule (size)	Immobilization strategy	Application	Ref.
30	NKCOF-98		2.10 nm	Lipase ($3.0 \times 3.2 \times 6.0$ nm^3)	*In-situ* assembly	Biocatalysis	[65]
31	COF-LZU1 RT-COF-1 ACOF-1		1.89 nm 1.98 nm 1.54 nm	HRP ($4.0 \times 4.4 \times 6.8$ nm^3)	*In-situ* assembly	Biocatalysis	[68]
32	TpBpy		2.7 nm	Thermophila lanuginosus[a]	*In-situ* assembly	Biocatalysis	[73]
33	COFs		3.30 nm	GOx ($2.3 \times 3.2 \times 5.6$ nm^3), HRP ($4.0 \times 4.4 \times 6.8$ nm^3)	Pre-protection	Biocatalysis	[70]

[a] The size of these biomacromolecules is not mentioned.

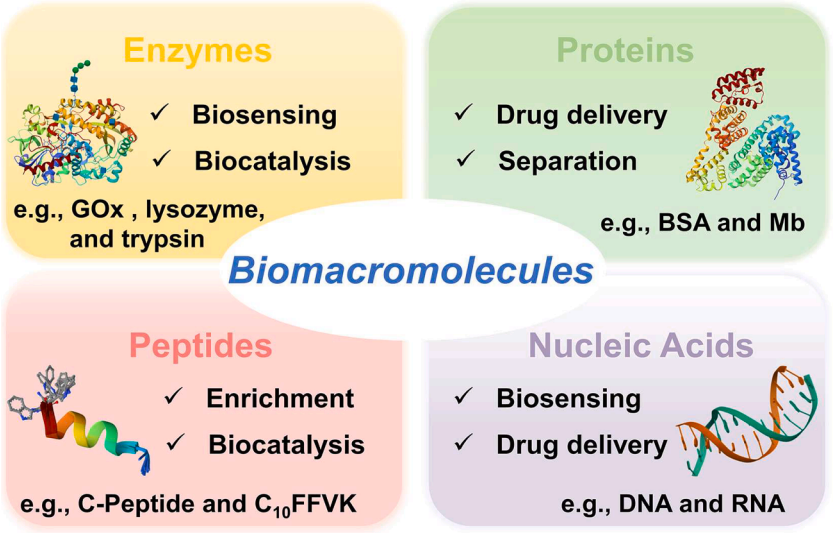


Fig. 4. Different types of biomacromolecules and their applications in combination with COFs.

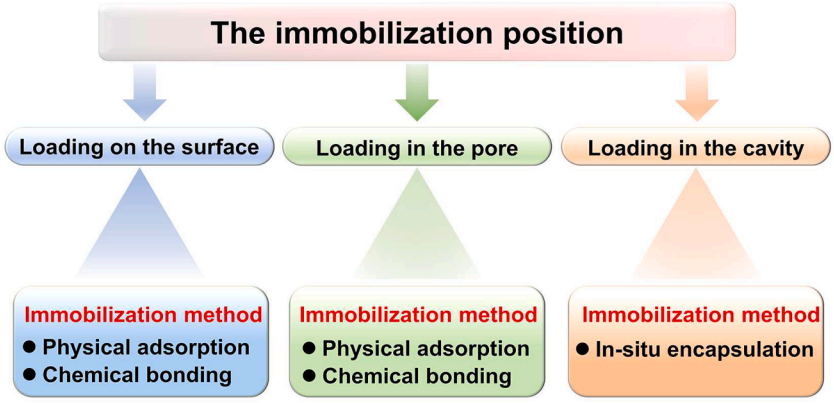


Fig. 5. The immobilization position of biomacromolecule@COFs.

FITC-trypsin presented the strongest fluorescence intensity at the center of COFs-LZU1 in layer-by-layer CLSM images. These results provide strong evidence for the fixation of trypsin in the cavities of COFs-LZU1.

3.2. *The immobilization strategy*

In the reported literatures on biomacromolecule@COFs, there are two kinds of immobilization strategies, including post-modification and encapsulation (Fig. 7) [52]. The above two immobilization strategies will be introduced separately in the following sections.

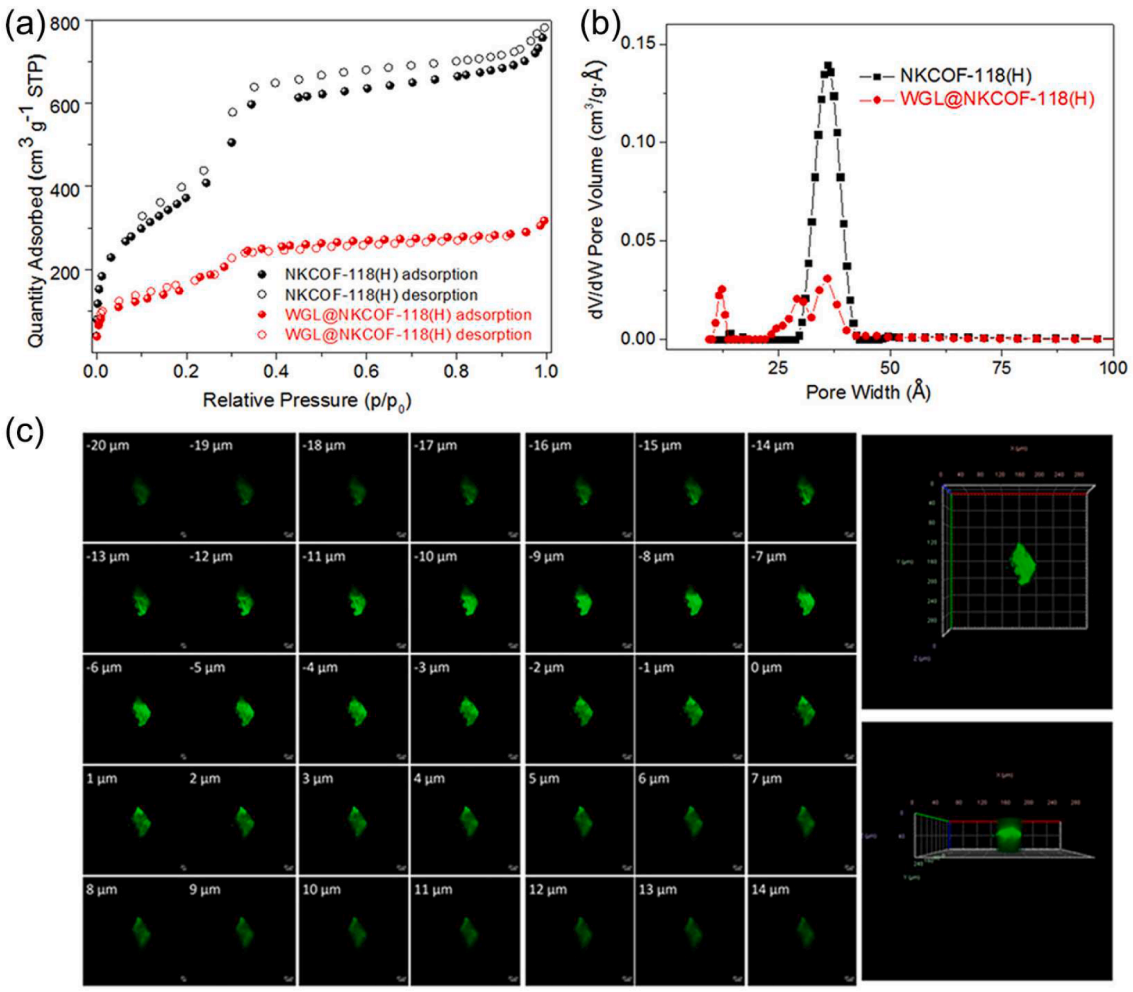


Fig. 6. Characterization of WGL@NKCOFs-118(H). (a) N_2 sorption curves. (b) Pore size distribution. (c) CLSM images. Reproduced with permission [67]. Copyright 2022, American Chemical Society.

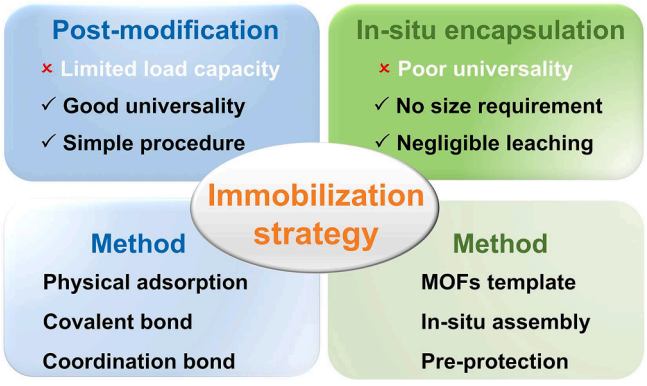


Fig. 7. The immobilization strategy of biomacromolecule@COFs.

3.2.1. *Post-modification strategy*

The post-modification method is a common strategy for the loading of biomacromolecules, which has the advantages of good universality and simple procedures (Fig. 7) [99,100]. It generally needs to mix the pre-synthesized COFs in the agents containing biomacromolecules, during which biomacromolecules could be readily fixed into COFs through physical adsorption or chemical bonding interactions [54].

Physical adsorption is the earliest method utilized to fix biomacromolecules, during which hydrophilic-hydrophobic, hydrogen bonding or electrostatic interactions would be utilized. Due to the biomacromolecules are generally dispersed in aqueous solutions, the hydrophilic-hydrophobic interaction is important in the fixation of biomacromolecules [101,102]. The key issue to fix biomacromolecules through hydrophilic-hydrophobic interaction is the successful construction of functional COFs, in which their hydrophilic/hydrophobic channels could pose strong interaction with hydrophilic/hydrophobic biomacromolecules. For instance, Sun et al. designed hydrophobic COFs (COF-OMe and COF-V) and hydrophilic COFs (COF-OH and COF-ONa) to fix lipase (Fig. 8a) [58]. The lipase loadings of COF-V and COF-OMe were 0.78 and 0.89 mg mg^{-1}, respectively, which were higher than those of COF-OH (0.75 mg mg^{-1}), COF-ONa (0.59 mg mg^{-1}) and other porous materials (Fig. 8b). Additionally, hydrophobic lipase@COF-OMe exhibited the highest activity in the kinetic resolution of 1-phenylethan when compared with other reported materials (Fig. 8c) and no significant activity reduction after 6 cycles in the recycling test (Fig. 8d). These results support that hydrophilic-hydrophobic interaction is an important interaction for physical adsorption method.

Except for hydrophilic-hydrophobic interaction, hydrogen bonding is another important interaction that could facilitate the combination of COFs with biomacromolecules. For example, Wang et al. dropped MP-11 and GOx mixture on the surface of $COF_{ETTA\text{-}TPAL}$/GCE to prepare the GOD-MP-11/$COF_{ETTA\text{-}TPAL}$/GC [75]. The hydrogen bonds existed between N atoms of $COF_{ETTA\text{-}TPAL}$ and carboxyl groups of enzymes in GOD-MP-11/$COF_{ETTA\text{-}TPAL}$/GC were beneficial for the loading of MP-11 and GOx. In addition to hydrogen bonding, electrostatic interaction is also a

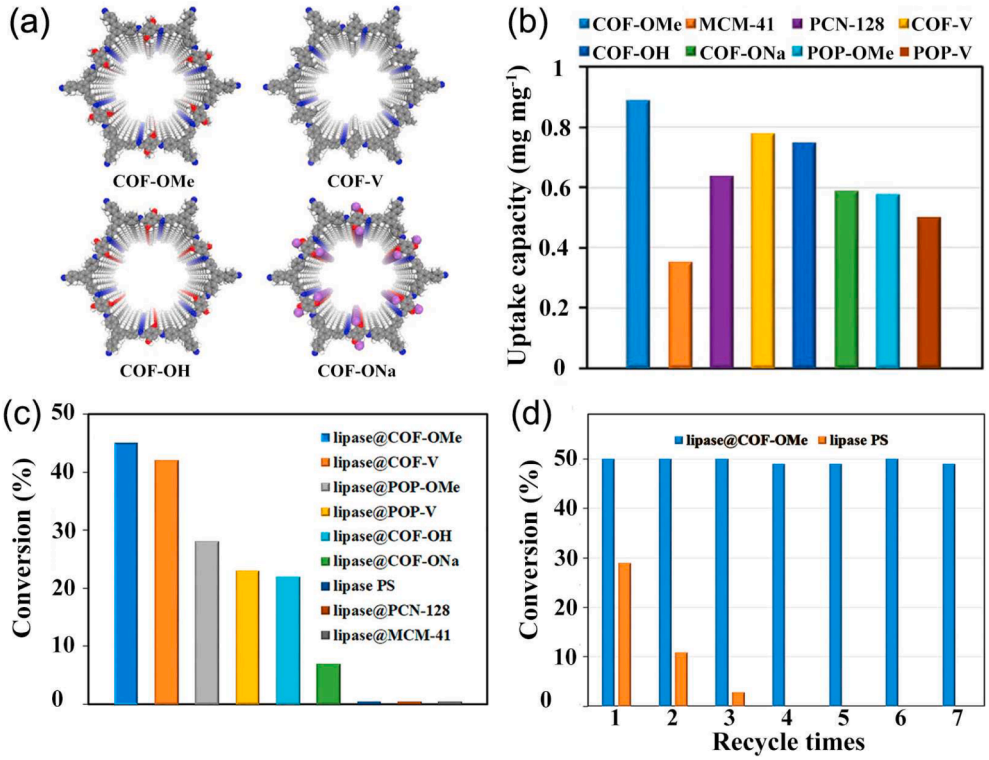


Fig. 8. The enzyme uptake capacity and conversion of lipase@COF-OMe compare with other porous materials. (a) Graphic of hydrophobic/ hydrophilic COFs. (b) Enzyme loading capacity. (c) The enzymatic activities in the kinetic resolution of 1-phenylethanol. (d) Recycling tests. Reproduced with permission [58]. Copyright 2017, American Chemical Society.

vital interaction of the physical adsorption method. When the Zeta potentials (ζ) of COFs and biomacromolecules are different, strong electrostatic interaction would be generated between them. For example, Zhao et al. transformed the ζ values of NKCOF-113 from positive to negative by modifying the electronic mediator RhCp* (Fig. 9a-b) [64]. Thus, RhCp*-NKCOF-113 might generate stronger electrostatic interaction with negatively charged formate dehydrogenase (FDH) when compared with NKCOF-113. Specifically, RhCp*-NKCOF-113 showed higher FDH loading (~275 mg mg^{-1}) than that of NKCOF-113 (~200 mg mg^{-1}). Additionally, FDH@RhCp*-NKCOF-113 retained most of the activity of FDH when treated with high temperature, organic solvents, or proteinase, showing excellent FDH protection effect (Fig. 9c).

Although physical adsorption methods have been widely applied in biomacromolecules fixation, their weak forces will still inevitably result in leakage to some extent. Therefore, chemical bonding interaction was developed by scientists as another post-modification strategy that could effectively diminish leakage by forming a strong chemical bond between biomacromolecules and COFs. The generation of covalent bonds through the Williamson ether reaction is a common chemical bonding interaction for the immobilization of biomacromolecules into COFs. For example, Xing et al. achieved the Cytochrome *c* (Cyt c) modification through the interaction between epibromohydrin and phenol groups in $[OH]_{x\%}$-TD-COF (Fig. 10a) [66]. Due to the covalent interactions could regulate more favorable enzyme conformations, Cyt c@$[EP]_{40\%}$-TD-COF exhibited higher stability after both heating (92 % activity maintained) and tetrahydrofuran soaking (89 % activity maintained) treatments than those of free Cyt c (73 % and 40 %) and physical adsorption Cyt c (77 % and 70 %).

Except for the Williamson ether reaction, the amidation reaction is another important chemical bonding interaction for the immobilization of biomacromolecules into COFs (Fig. 10b). For example, Zhang et al. loaded lysozyme into COF 1 through the amidation reaction [59]. Compared with physical adsorption interaction, the lysozyme loading by chemical bonding interaction (22 μmol g^{-1}) was almost twice higher than that by physical adsorption interaction (12 μmol g^{-1}). In addition, the leakage of lysozyme by covalent bonding interaction was negligible

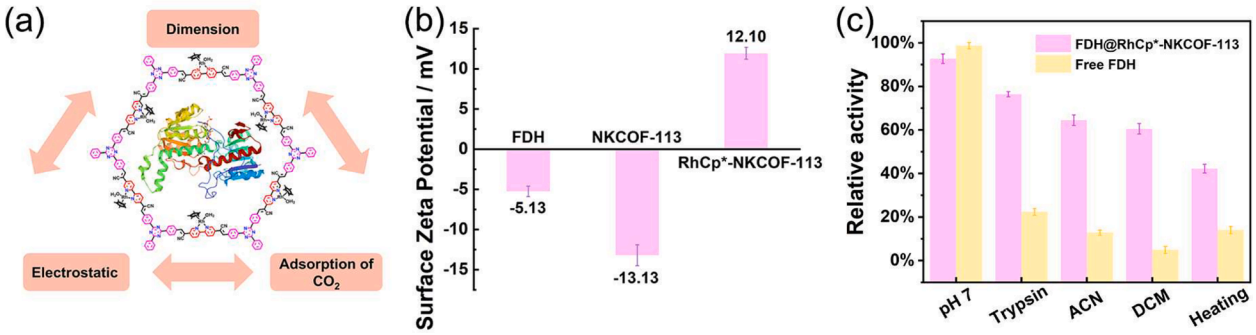


Fig. 9. The schematic illustration and characterization of FDH@RhCp*-NKCOF-113. (a) Interaction between COFs and FDH. (b) ζ potentials. (c) Stability test. Reproduced with permission [64]. Copyright 2022, Wiley-VCH.

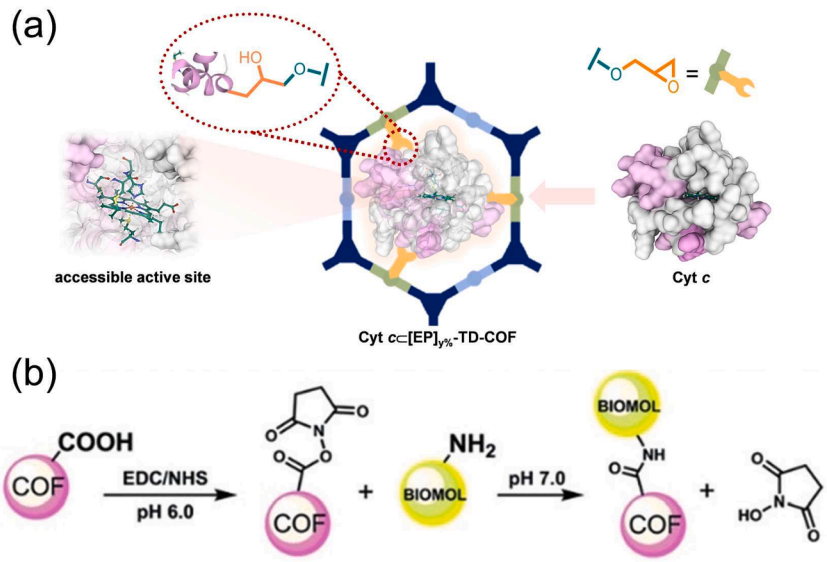


Fig. 10. Illustration of covalent immobilization by Williamson ether reaction and amidation reaction. (a) Covalent immobilization of Cyt c into $[EP]_{y\%}$-TD-COF by Williamson ether reaction. Reproduced with permission [66]. Copyright 2022, Wiley-VCH. (b) Covalent immobilization of lysozyme into COF 1 by amidation reaction. Reproduced with permission [59]. Copyright 2018, Wiley-VCH.

when compared to physical adsorption (90 %).

In addition to Williamson ether and amidation reactions, coordination bonding interaction is also an important type of chemical bonding interaction that has been reported. For example, Zhong et al. synthesized a kind of hollow microtubule TatDha-COFs and loaded trypsin by coordination bond [87]. Ni^{2+}, chelated with triazine bonds and hydroxyl groups on TatDha-COFs, could serve as coordination sites for biomacromolecules binding (Fig. 11). After loading with trypsin, its loading was 453 mg g^{-1} as detected by the UV–vis spectra.

3.2.2. *The in-situ encapsulation strategy*

In addition to post-modification strategy, *in-situ* encapsulation strategy is a new fixation strategy that enables the COFs synthesis and biomacromolecules encapsulation to occur simultaneously. Compared with post-modification, *in-situ* encapsulation is not affected by the size effect and could achieve high biomacromolecules loading and negligible leakage (Fig. 7). Up to date, the reported *in-situ* encapsulation strategies can be basically concluded as metal organic frameworks (MOFs) template, *in-situ* assembly and pre-protection. The following sections will discuss them in detail.

Sacrificing the MOFs template to construct COFs capsules for the immobilization of biomacromolecules is an ingenious encapsulation method. This method has the following advantages: 1) MOFs template could protect biomacromolecules from synthetic processes of COFs and 2) the high porosity of COFs shell could tolerate subsequent digestion of MOFs and promote mass transfer. Based on this, Li et al. exploited ZIF-90 template to *in-situ* encapsulate Catalase (CAT) (Fig. 12a) [62]. COF-42-B was selected to construct the capsule. At last, the ZIF-90 was decomposed by protic acid. Thus, the obtained COF-42-B capsule exhibited high CAT loading (1.66 g g^{-1}), high CAT activity retention after treating with various conditions (acid 85 %; acetone 95 %; protease trypsin, 100 % and heating, 88 %) (Fig. 12b), and excellent recyclable performance (Fig. 12c). Nevertheless, this method had complex operation procedure and required multiple steps to complete the immobilization, and would lead to the inactivation of biomacromolecules during the decomposed of MOFs template.

Compared with MOFs template method, *in-situ* assembly method without the utilization of template not only can simplify the operation procedure, but also prevent the denaturation of biomacromolecules in the immobilization process. For instance, Zheng et al. created a

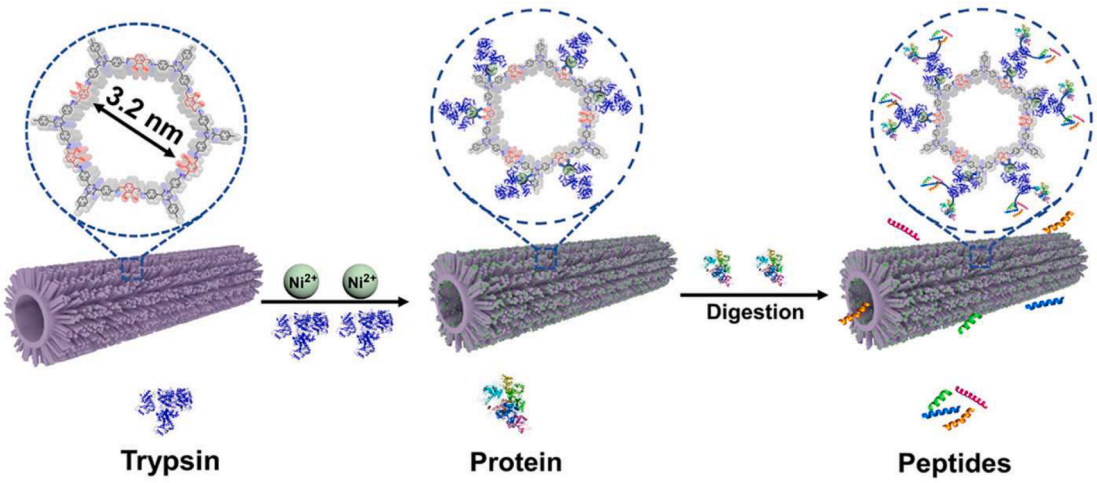


Fig. 11. Schematic representation of the synthesis of COF(Ni)@trypsin. Reproduced with permission [87]. Copyright 2021, American Chemical Society.

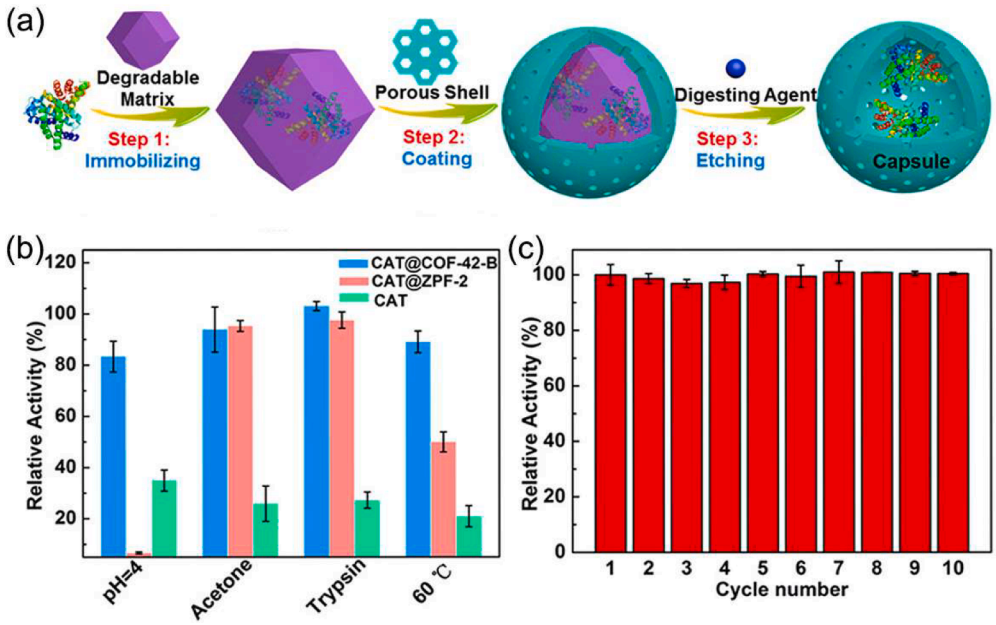


Fig. 12. (a) The synthesis route CAT@COF-42-B. (b) Activity percentage of CAT, CAT@ZPF-2, and CAT@COF-42-B. (c) Recycling experiments. Reproduced with permission [62]. Copyright 2020, American Chemical Society.

biomacromolecules immobilization platform to achieve *in-situ* assembly of lipase and NKCOF-98 (Fig. 13a) [65]. During the synthesis process, the mild synthesis conditions of COFs allowed for the *in-situ* encapsulation of lipase and the lipase loading was 0.74 g g^{-1}. Similarly, Liang et al. constructed ACOF-1, COF-LZU1 and RT-COF-1 to *in-situ* encapsulate horseradish peroxidase (HRP) via a one-pot strategy under mild conditions, and their HRP loadings were 4.0, 28.5, and 17.0 wt%, respectively (Fig. 13b) [68]. However, *in-situ* assembly method only suitable for a few COFs with mild synthesis conditions, because it could only be implemented in mild aqueous environment.

Compared with MOFs template and *in-situ* assembly methods, pre-protection is a novel encapsulation method that uses the self-repair process of COFs to encapsulate biomacromolecules. It generally includes two steps: the formation of low-crystalline polymer precursors for enzyme loading, and then the precursors transform into crystalline COFs to complete the encapsulation. For example, Zhang et al. applied low-crystalline aCOFs to load GOx and HRP by physical adsorption, and then completed the encapsulation with the transformation of aCOFs into crystalline COFs (Fig. 14) [70]. The enzyme@COFs showed high loadings of GOx (8.5 %) and HRP (4.8 %). Specifically, high GOx activity retention after treating with harsh conditions (heating, 61 %; organic solvent, 67 % and acid solution, 120 %) could be still achieved.

4. Applications of biomacromolecule@COFs

Combined the advantages of both biomacromolecule and COFs, biomacromolecule@COFs are widely applied in a series of applications like biosensing, biocatalysis, drug delivery and separation/enrichment and so on (Fig. 15). Their related applications will be discussed in the following contents.

4.1. Biosensing

Biomacromolecules can be broadly applied as biosensors with excellent selectivity and sensitivity [103–105]. With the protection of COFs, they can further enhance the stability and cyclicity of biosensors when compared with individual biomacromolecules. In general, the biosensing applications of biomacromolecule@COFs can be basically classified as colorimetric sensing and electrochemical sensing, which will be subsequently discussed in following section.

4.1.1. Colorimetric sensing

Colorimetric sensors can be used to detect target objects based on visible color changes, possessing the advantages of simple operation, low cost and fast response [106]. Due to the excellent sensitivity of GOx to glucose, the colorimetric sensors based on GOx could be widely used to effectively detect blood glucose concentration and control diabetes [107]. What is more, the protection of COFs on GOx can improve the stability and reusability of colorimetric sensors. For example, Yue et al. applied COF_{HD}-GOx as colorimetric biosensor to trace glucose [63]. COF_{HD}-GOx based biosensor showed low detection limit (0.54 mM) and a good linear range (0.005 mM to 2 mM) (Fig. 16a-b). In addition, COF_{HD}-GOx biosensor also exhibited superior stability, selectivity and reusability (Fig. 16c-d). Similarly, Wang et al. combined the Fe-COF with glucose oxidase (GOx) to assemble colorimetric biosensor and trace glucose [108]. The colorimetric biosensor achieved good detection range (5 to 350 μM) and detection limit (1.0 μM).

4.1.2. Electrochemical sensing

In addition to colorimetric sensing, biomacromolecule@COFs can also be used for electrochemical biosensing, in which it combines biosensing with electrochemical analysis [109–111]. For example, Sun et al. encapsulated HRP into Fe_3O_4@COF and the obtained Fe_3O_4@COF@HRP could serve as electrochemical biosensor for the accurate hydroquinone determination [84]. Compared with other electrochemical sensors, Fe_3O_4@COF@HRP showed advantages of lower detection limit (0.12 mmol/L) and wider linear range (0.5–300 μmol/L). Besides, Luo et al. constructed a ratiometric electrochemical biosensor by loading AChE into $COF_{Thi\text{-}TFP}$, in which the positively charged surface was beneficial for retaining the bioactivity and catalytic effect of AChE [112]. The constructed AChE@$COF_{Thi\text{-}TFP}$ based electrochemical biosensor was applied to the detection of carbaryl, and displayed a linear range of 2.2–60 μM with a detection limit of 0.22 μM. In addition, Lu et al. enabled DNA modification of COFs through cycloaddition reaction catalyzed by Cu(I)-azide/alkyne (Fig. 17) [82]. Furthermore, an electrochemical sensor was constructed by the DNA-COFs to detect exosomes. It shows good sensitivity (detection limit, 9661 particle μL^{-1}), specificity and repeatability (relative standard deviation for six

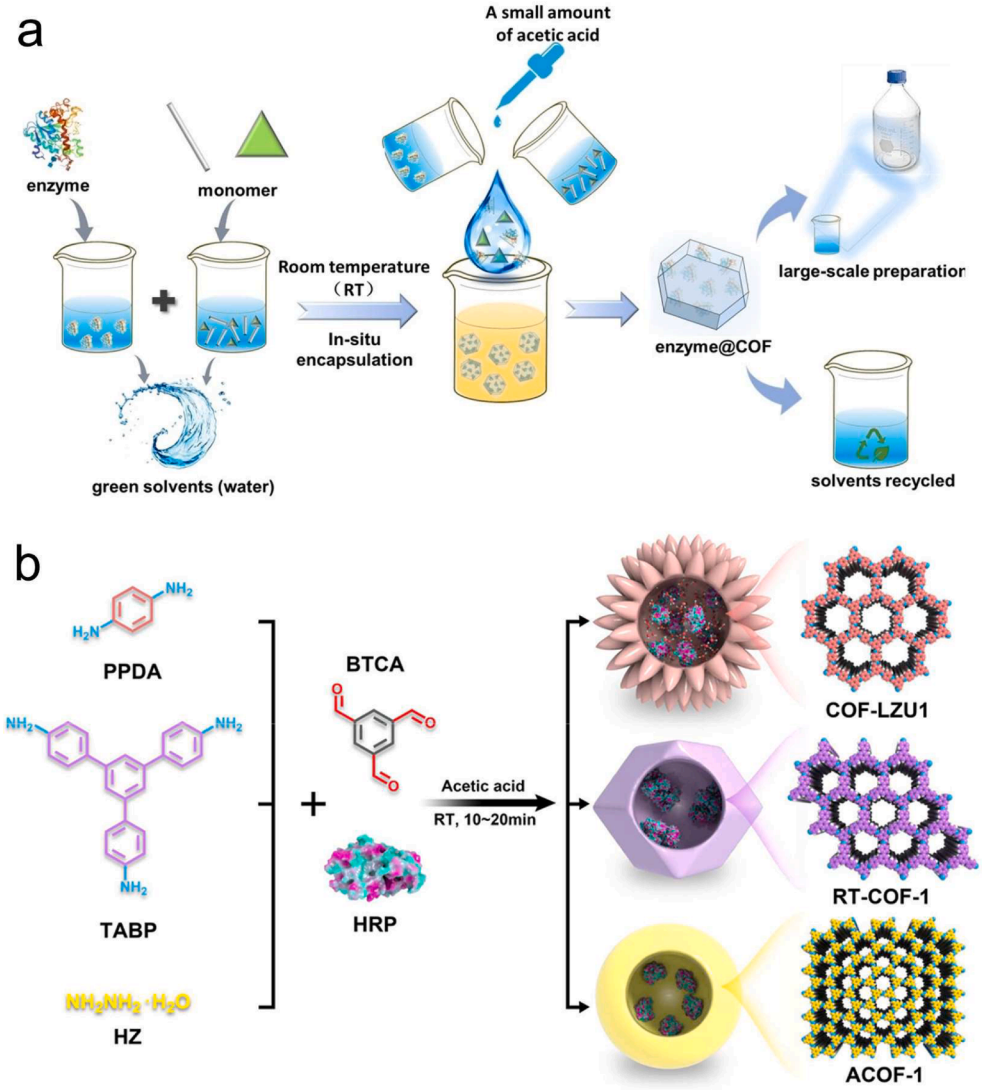


Fig. 13. Schematic diagram of the in-situ assembly method. (a) The synthesis process of lipase@NKCOF-98. Reproduced with permission [65]. Copyright 2022, Wiley-VCH. (b) The formation of HRP-COFs. Reproduced with permission [68].

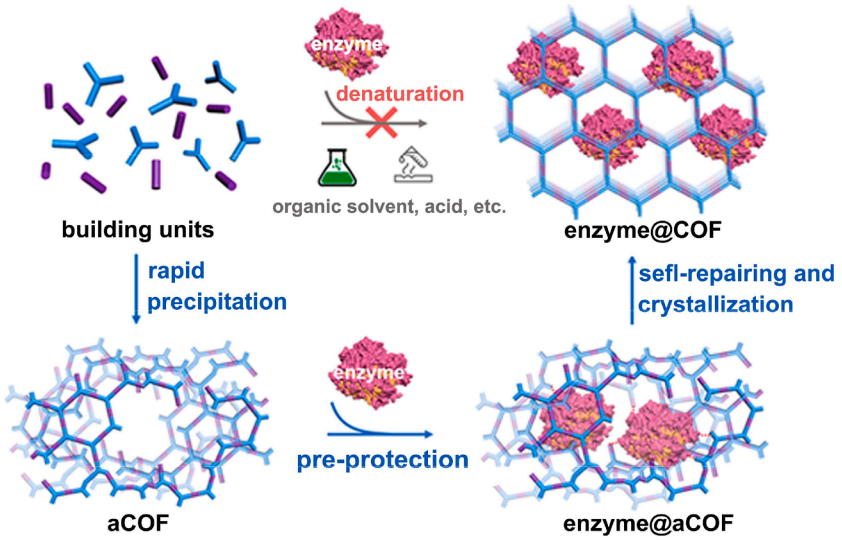


Fig. 14. Schematic diagram of pre-protection method. Reproduced with permission [70]. Copyright 2023, American Chemical Society.

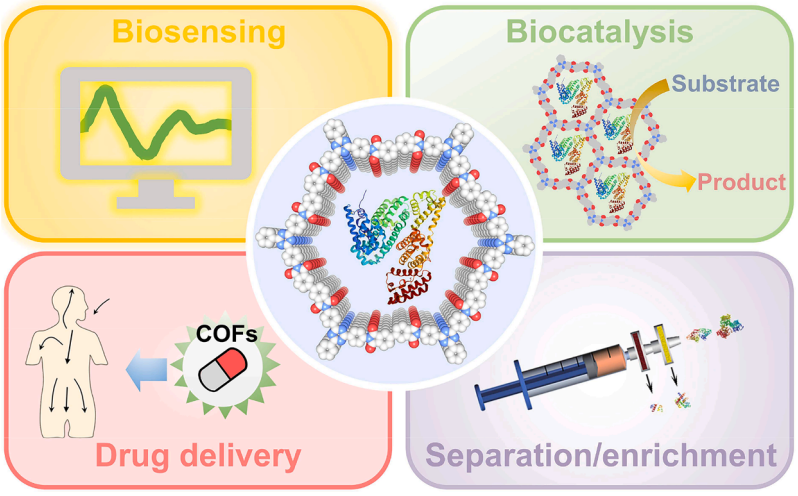


Fig. 15. The applications of biomacromolecule@COFs.

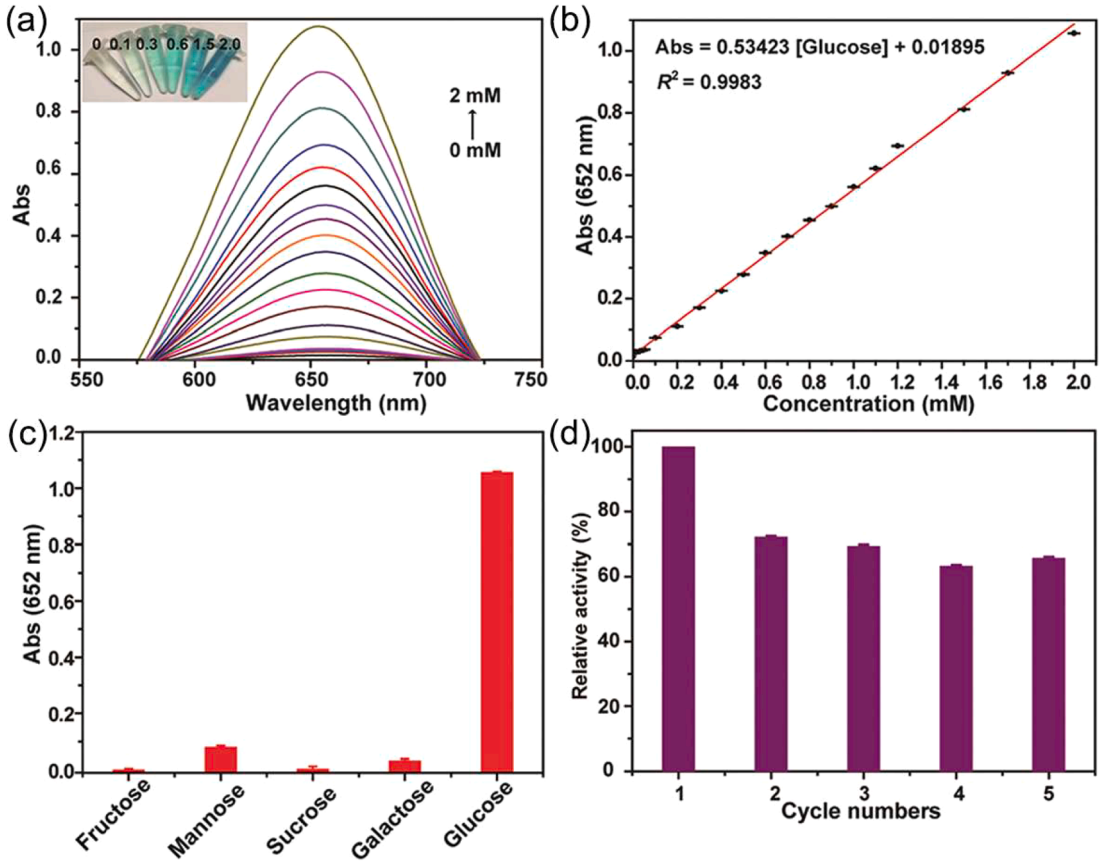


Fig. 16. The performance of COF_{HD}-GO_X sensors. (a) The UV spectrum. (b) The responsive curve; (c) The selectivity of COF_{HD}-GOx; (d) Recyclability of COF_{HD}-GOx sensors. Reproduced with permission [63]. Copyright 2021, Royal Society of Chemistry.

biosensors is 2.0 %) to exosomes, which could be operated in complex environments.

4.2. Biocatalysis

Enzymes and peptides can be used as biocatalysts because of their high activity and selectivity [87]. The protection of COFs can significantly boost the stability and repeatability of biocatalyst, meanwhile maintaining catalytic activity. For example, Chen et al. fabricated an artificial photoenzymatic system through the immobilization of FDH into the pore of COFs (i.e. COF-V1, COF-V2, COF-I1 and COF-I2) (Fig. 18a) [72]. The cofactors NADH could be regenerated by COF-V2-Rh to attain high apparent quantum efficiency (AQE 13.95 %) and photocatalytic turnover frequency (TOF, 5.3 mmol g^{-1} h^{-1}). Based on the above results, FDH@COF-V2-Rh photoenzymatic systems were constructed to catalyze the formation of HCOOH from CO_2 with high specific activity (1.46 mmol g^{-1} h^{-1}) and stability (81.8 % retaining activity after three cycles) (Fig. 18b).

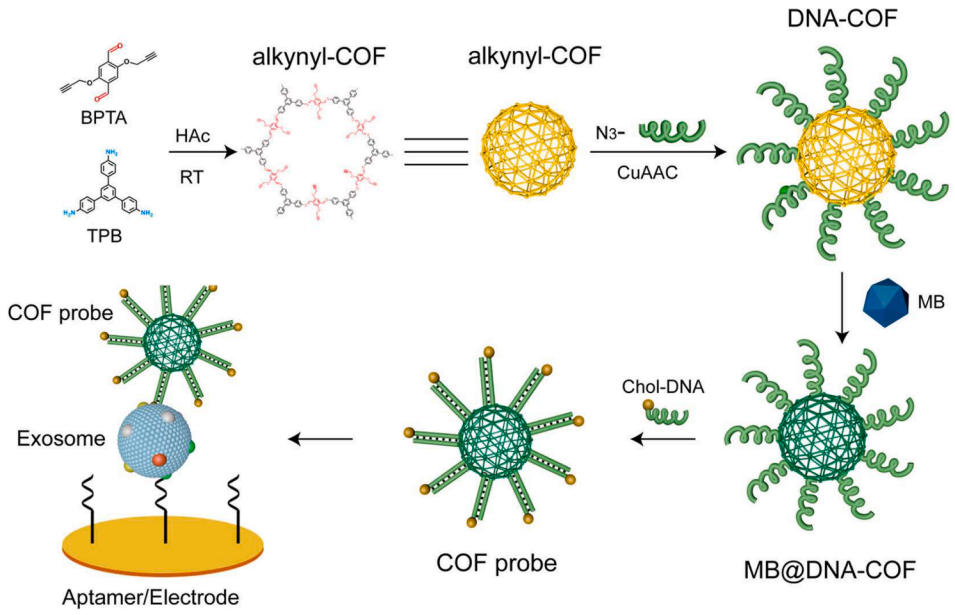


Fig. 17. The schematic diagram of the construction of DNA-COFs based electrochemical biosensor. Reproduced with permission [82]. Copyright 2022, American Chemical Society.

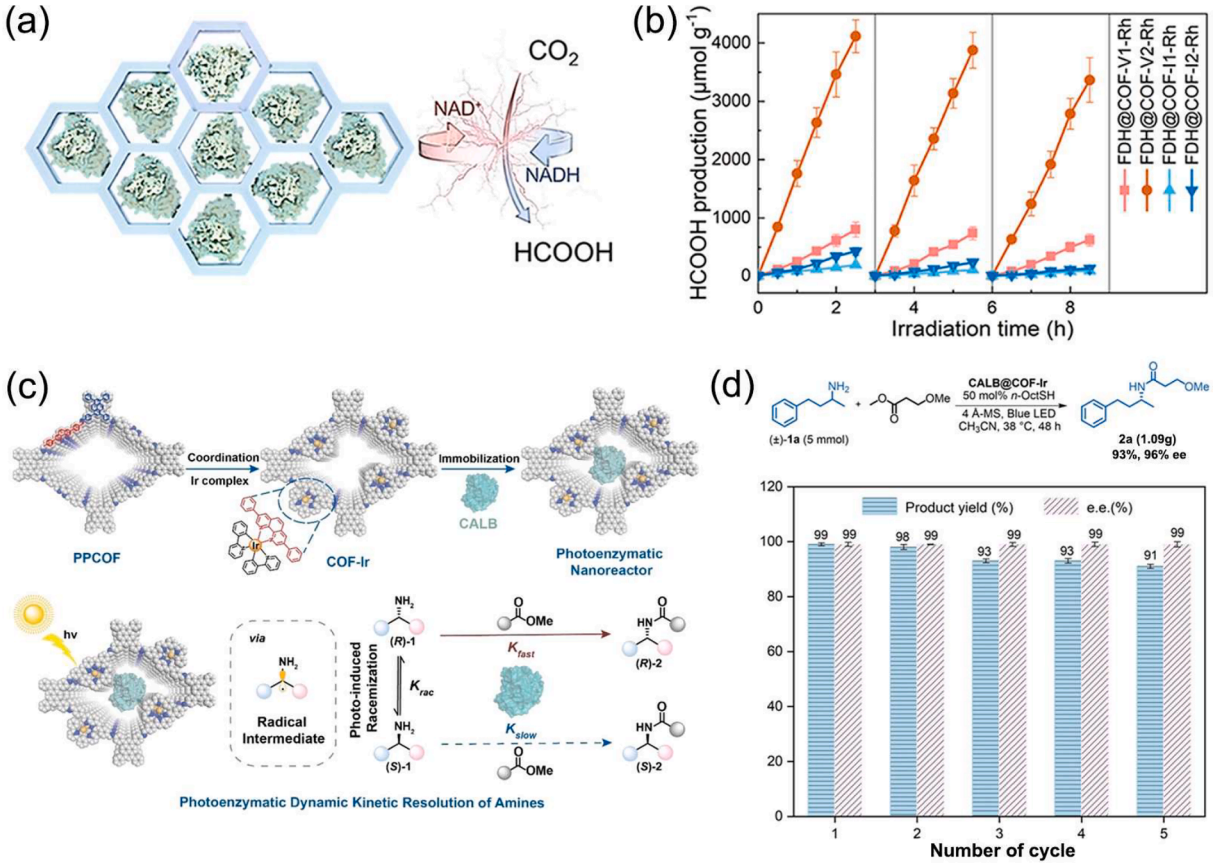


Fig. 18. Catalytic performance of FDH@COF-Rh based photoenzyme system. (a) Schematic Illustration. of catalytic process. (d) Reusability of FDH@COF-Rh. Reproduced with permission [72]. Copyright 2023, American Chemical Society. (c) The schematic diagram of CALB@COF-Ir based photoenzymatic nanoreactor. (d) Gram-Scale reaction. Reproduced with permission [74]. Copyright 2024 Wiley-VCH.

Except for enzyme@COFs, peptide@COFs can also be used as biocatalysts. For example, Mahato et al. designed TpAzo-C_{10}FFVK biocatalyst with core–shell nano-tubular structure to catalyze the C-C bond cleavage [71]. The catalytic rate and yield of TpAzo-C_{10}FFVK were 0.035 μM min^{-1} and 7 %. After 10 cycles of catalysis, there was no obvious diminution in yield (6.5 to 6.2 %), confirming the good stability of TpAzo-C_{10}FFVK. Furthermore, chiral catalysis is an important catalytic reaction, which requires the loading of chiral biomacromolecules

(e.g., lysozyme and Candida antarctica lipase B (CAL-B)) into COFs. For instance, Oliveira et al. investigated the chiral catalysis of CAL-B@COFs [60]. The optimal CAL-B@PPF-2-NH_2 displayed an outstanding enantiomeric excess (99 %) with moderate conversion rate (32 %) for *rac*-1-phenylethanol, suggesting that it has much potential for the applications in chiral catalysis. In addition, Ran et al. designed a multifunctional photoenzymatic nanoreactor for asymmetric kinetic resolution of secondary amines by immobilizing CALB in COF-Ir (Fig. 18c) [74]. In gram-scale reaction, raceme-4-phenyl-2-butanamine (±) was used as substrate, and the yield and ee of the product was 93 % and 96 %, respectively. After reusing for 5 times of the photoenzyme bioreactor, the yield only decreased from 99 % to 91 %, and the ee remained the initialed high level (99 %) (Fig. 18d), indicating the excellent chiral catalysis and recyclability performance of CALB@COF-Ir based photoenzyme bioreactor.

4.3. Drug delivery

The drug delivery is also an important application of biomacromolecule@COFs. Ideal drug delivery systems consisting of nanocarriers and drugs need to satisfy the following characteristics: 1) the non-toxic nature and possibility of surface engineering of the nanocarriers; 2) appropriate interactions between the drug and nanocarriers to ensure the effective delivery and release; 3) excellent loading capacity of nanocarriers and sustained release of drugs and 4) local control of drug release at specific sites [113–117]. To approach the ideal requirements, some important works have been reported. For example, Zhang et al. exploited the insulin delivery system with glucose and pH dual-responsive based on the breakdown of COFs carriers in vitro and in vivo [88]. Insulin and glucose oxidase were successfully immobilized in the FITC-PEG-COF, and FITC-PEG-COF-1 and FITC-PEG-COF-5 were obtained, respectively. The hydrophilic tail thiol (−SH) of the polymer (FITC-PEG) could facilitate the fixation of insulin and GOx in the COFs, as well as the insulin delivery applications in vitro and in vivo. In hyperglycemic conditions, the glucose could be catalyzed by GOx to generate gluconic acid, which then degraded COF-1 or COF-5 to release insulin (Fig. 19a). Thus, FITC-PEG-COFs with high response speed enabled the normalization of the glucose levels of type I diabetes in a mouse model and exhibited high performance. Furthermore, Gao et al. reported a TpDh-DT-based nanosystem, which could achieve the simultaneous cancer specific imaging and DNA drug release [76]. In detail, when the nanosystem enters the cancer cells, the fluorescently labeled drug DNA would bind specifically to the TK1 mRNA in the cancer cells, and the fluorescently quenched doxorubicin will be released, resulting in fluorescence recovery (Fig. 19b). In simulated cancer cells, 37.5 % drug release could be achieved after 24 h. The construction of the above nanosystems provides a new idea for efficient cancer treatment.

4.4. Separation/enrichment

In recent years, the protein separation and peptides enrichment through biomacromolecule@COFs, have been widely developed [79]. The separation of proteins (e.g., Mb and BSA) and enrichment of peptides (e.g., phosphopeptide and glycopeptide) by different biomacromolecule@COFs have been summarized. which will be separately introduced in the following sections.

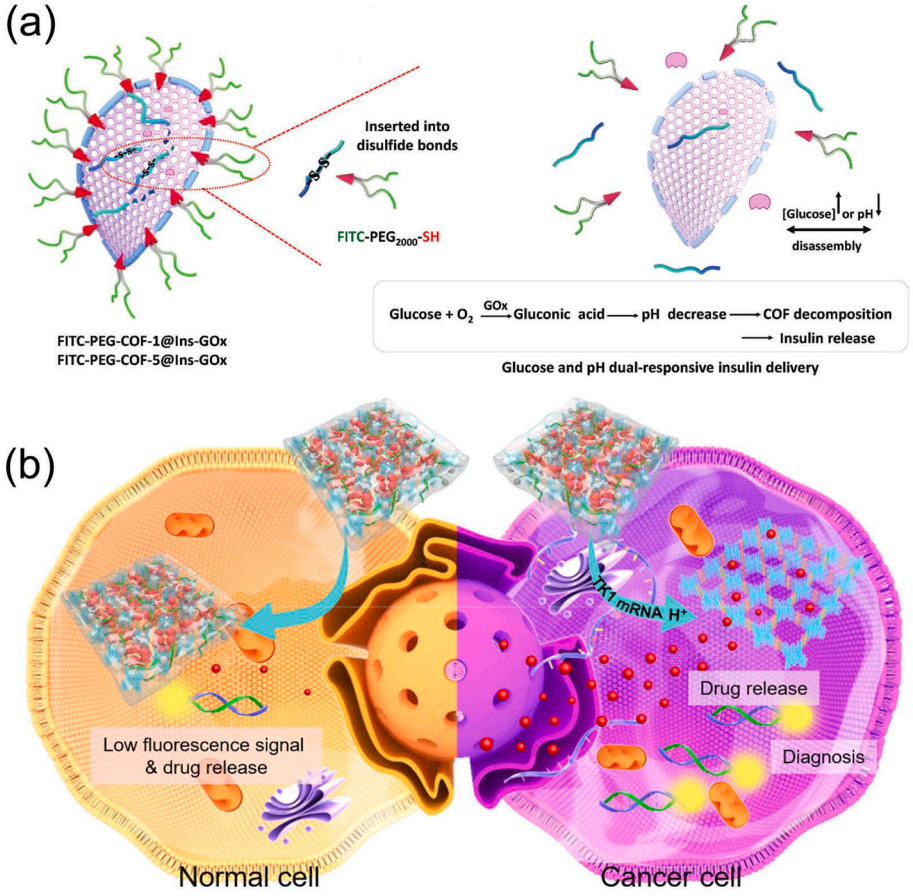


Fig. 19. The schematic diagram of FITC-PEG-COF and TpDh-DT based drug release systems. (a) FITC-PEG-COF based glucose and pH dual-responsive insulin delivery release system. Reproduced with permission [88]. Copyright 2021, Wiley-VCH. (b) TpDh-DT based drug release system. Reproduced with permission [76]. Copyright 2021, American Chemical Society.

4.4.1. Protein separation

Proteins are often found in complex mixtures in tissues or cells with thousands of types [118]. Obtaining target proteins from mixtures is challenging because proteins vary in size, charge, and water solubility [119–122]. Because of the unique pores of COFs, they are widely used in protein separation. For instance, Wang et al. synthesized two COFs (i.e., Tp-COF and Azo-COF) with different pore sizes [78]. The slight pore size difference between Tp-COF and Azo-COF could be favorable for the protein separation. Specifically, Tp-COF could adsorb Cyt-c and Mb, while Azo-COF could only adsorb Cyt-c (Fig. 20a). By preparing a simple separation device (Fig. 20b), Azo-COF as the first filter and Tp-COF as the second filter can adsorb Cyt-c and Mb in the protein mixture, respectively. (Fig. 20c-d). With this device in hand, the particle size screening of low MW proteins with similar molecular weight can be conveniently realized. In addition, Mosleh et al. designed a positively charged Py-BPy^{2+}-COF for separating the amino acids (e.g., tryptophan, leucine, alanine, histidine, aspartic acid, and glutamic acid) and three proteins (i.e. Cyt c, lysozyme, and BSA) [79]. Due to the different charging conditions of various proteins, the adsorption capacity of Py-BPy^{2+}-COF was varied for these proteins (Cyt c, 5800 μg mg^{-1}; lysozyme, 1400 μg mg^{-1} and BSA 16 μg mg^{-1}), indicating its selective adsorption and separation ability for proteins.

4.4.2. Peptide enrichment

The development of an effective and low abundance endogenous peptide enrichment method may help in the diagnosis of cancer or other diseases [123,124]. COFs with tunable pores and functions could be used for peptide enrichment [124–133]. For example, Ma et al. synthesized spherical COFs to selectively enrich hydrophobic peptides (C-Peptide) from complex samples [80]. Owing to the high porosity, excellent stability, and strong hydrophobicity of spherical COFs, the loading capacity of FGFGF (a model peptide) was as high as 150 mg g^{-1}. In addition, spherical COFs realized the enrichment of spherical COFs in human serum and urine. For instance, Gao et al. synthesized core–shell nano-structured COFs (MCNC@COF@Zr^{4+}) to selectively enrich phosphopeptides [81]. The capacity of MCNC@COF@Zr^{4+} for the adsorption of adenosine triphosphate and phosphopeptide (TRG[pY]GTSTRK) were 58.50 and 46.48 mg g^{-1}, respectively, higher than those of adenosine (4.5 mg g^{-1}) and non-phosphopeptide (5.1 mg g^{-1}). The results prove that the selective enrichment of phosphopeptide can be achieved by MCNC@COF@Zr^{4+}.

5. Perspective and conclusions

Although biomacromolecule@COFs reported in previously works have exhibited much potential in various applications, there are still some unresolved issues: 1) most of the reported methods for the immobilization of biomacromolecules into COFs are still time-consuming, high cost and short in generality; 2) the limited biocompatibility of COFs especially for that synthesized or post-treated in organic solvents set bottlenecks for the in vivo or vitro experiments and 3) directionally designed stability that can meet the specific requirements of different applications are still challenging. Therefore, there is long way to go to achieve the lab-to-industry production for biomacromolecule@COFs. Based on the above unresolved issues, we propose some perspectives for the future development of biomacromolecule@COFs: 1) for the synthesis of biomacromolecule@COFs, advanced synthesis methods (e.g., ultrasonic, ball milling, microwave or laser-induced methods) would be more desired to achieve the facile or even scale up production; 2) for the biocompatibility of COFs, greener synthesis methods (e.g., hydrothermal or solvent-free methods) might meet the stringent need of biocompatibility and 3) for the directionally designed stability of COFs, the broad range of bonding interactions needs to be taken into considerations to design COFs with suitable stability for specific application scenarios. Besides, in terms of the practical applications like in vivo conditions, it is also necessary to study the absorption, distribution, metabolism, and excretion of COFs in the whole body. It will need to consider all of the related issues from material design to applications. In addition, the advantages of biomacromolecules and auxiliary COFs need to be maximized to develop more intriguing and important application fields to expand the potentials of biomacromolecule@COFs.

In summary, we systematically review the design and applications of biomacromolecule@COFs composites. Initially, the immobilization of different biomacromolecules including enzymes, proteins, nucleic acids and peptides in COFs was discussed as a whole, and then the

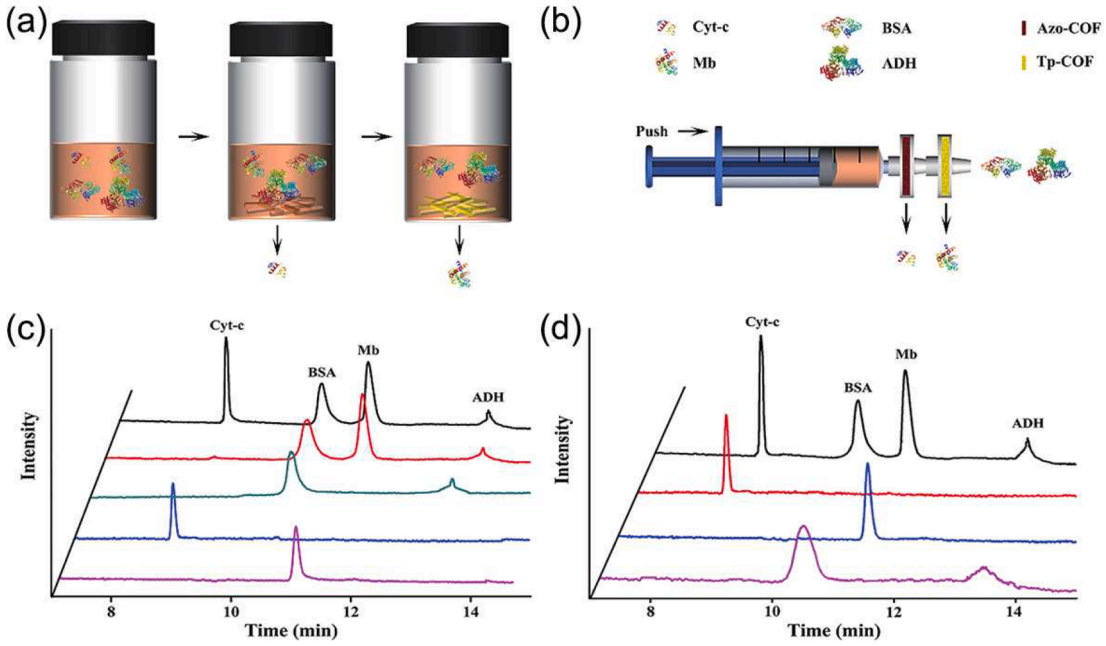


Fig. 20. Proteins separation by Tp-COF and Azo-COF. Schematic illustration of proteins separation (a) in vials and (b) COF-based device. CE-UV analyzed of proteins separation of (c) tandem utilization Tp-COF and Azo-COF, and (d) COF-based separation device. Reproduced with permission [78]. Copyright 2022, Springer Nature.

immobilization position was present. After that, we focus on the immobilization strategies (post-modification and encapsulation) and the application of biomacromolecule@COFs (biosensing, biocatalysis, drug delivery and separation/enrichment). Finally, new perspectives on the future development and challenges of biomacromolecule@COFs are presented. We hope this review wound provide insights for the combination of COFs and biomacromolecules and motivate scientists to develop more applications of biomacromolecule@COFs in diverse field.

CRediT authorship contribution statement

Wenhai Feng: Writing – original draft. **Can Guo:** Writing – original draft. **Rui Xu:** Writing – review & editing. **Zhi Yang:** Writing – review & editing. **Haifu Zhang:** Writing – review & editing. **Luanhua Zhou:** Writing – review & editing. **Hai-Ning Wang:** Supervision. **Yifa Chen:** Supervision. **Ya-Qian Lan:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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