Chemical Synthesis
Molecular Engineering Toward Large Pore-Sized Covalent Organic Frameworks

--Manuscript Draft--

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<th>CS-2023-63</th>
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</tr>
<tr>
<td>Manuscript Type:</td>
<td>Mini Review</td>
</tr>
<tr>
<td>Special Issue:</td>
<td>Innovations in Functional Porous Frameworks</td>
</tr>
<tr>
<td>Keywords:</td>
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<tr>
<td>Funding Agency and Grant Number:</td>
<td>National Natural Science Foundation of China, 22288101, 22201092, B17020</td>
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Molecular Engineering Toward Large Pore-Sized Covalent Organic Frameworks

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Abstract
In recent years, covalent organic frameworks (COFs) as designable crystalline porous polymers have attracted widespread attention because of their tunable structures and functionalities. In particular, the unique characteristics of COFs, such as readily controllable pore size, high surface area, editable pore surface environment, and exceptional chemical stability, provide a structural basis for loading large-sized organic, inorganic, and biological molecules for hetero-catalysis, energy storage, and other applications. In this review, we discuss state-of-the-art strategies for the structural design and synthesis, properties, and functionalities of large pore size two-dimensional (2D) and three-dimensional (3D) COFs, spotlighting recent breakthrough achievements and remarkable progress to guide further efforts in this field.

Keywords: Large pore size, Covalent Organic Frameworks, Mesopore, Macromolecule Absorption
INTRODUCTION
Exploring crystalline porous materials has recently become a focal research topic due to their great potential in solving energy and environmental issues and promoting sustainable social development. Since the first synthesis of boronic ester-linked COF by Yaghi et al. in 2005\cite{1}, hundreds of COFs with versatile chemical and topological structures have been developed\cite{2–8}. Essentially, COFs integrate organic building blocks into an ordered lattice through covalent bonds. In the past few decades, they have aroused growing interest and have been widely applied in numerous fields\cite{9} such as gas separation and sorption, catalysis, energy conversion, etc. One representative advantage of COFs over other porous analogues lies in the ease of obtaining robust ordered polymeric lattices with large mesopores.

To date, most reported COFs are micro- or small mesoporous COFs with pore sizes ranging from 0.5 nm to 4.0 nm. In sharp contrast, COFs with pore sizes larger than 4.0 nm have rarely been reported\cite{10–15}, which limits their application in loading sizeable guest molecules\cite{16–18}. In this sense, the development of COFs with regular networks that can accommodate macromolecules such as proteins or peptides holds great promise for drug delivery and heterogeneous catalysis by providing sufficient diffusion of substrates and products\cite{19}. To this end, recent efforts have been made to explore synthetic routes for large pore-sized COFs, which are expected to significantly expand the scope of practical applications and improve overall performance.

OVERVIEW OF 2D COFS WITH LARGE PORES
For the skeleton of 2D COFs, organic motifs undergo topological polymerization via condensation to form layered structures, which are further vertically stacked to form periodic columns through interlayer $\pi-\pi$ interactions. The pore size and shape of the formed ordered open nano-channels are closely related to the stacking modules of the 2D layers. Conventional strategies to explore large linkers with intense stacking interactions and suitable solubility have enabled the construction of 2D COFs with
well-defined porous structures and pore sizes up to 4.0 nm. However, preparing 2D COFs with even larger pore sizes remains challenging. A key fact hindering the development of COFs with larger pores is that the 2D layers tend to stabilize the networks by lateral sliding, a common way of reducing free energy in COFs. Consequently, the pore size and surface area of COFs are diminished because of the structural collapse and pore occlusion, which limits the successful construction of large pore-sized structures.

To date, several promising approaches have been developed to address this crucial issue. They can generally be classified as follows: (a) rational design of 2D COFs with honeycomb (hcb) and kagome (kgm) topologies, which make it easier to form larger pore size compared to other topologies; (b) employing specific linkages such as imides to generate large mesopores in the skeleton of 2D COFs; (c) using large molecule-sized building blocks with charged parts or branched side-chains to prevent the pore shrinkage and interlayer slippage, resulting in the formation of 2D COFs with large pores.

**Topology-Oriented Synthetic Strategy**

In 2016, McGrier et al. reported three novel COFs containing homogeneous and heterogeneous distributions of π-conjugated dehydrobenzoannulene (DBA), DBA-12 and DBA-18 units with varied triangular molecular sizes[20]. Polycondensation between the \( C_3 \)-symmetric monomeric catechol DBA-12 or DBA-18 and \( C_2 \)-symmetric pyrene-2,7-dibronic acid (PDBA) yielded three kagome topological COFs, termed Py-DBA-COF 1, Py-DBA-COF 2 and Py-MV-DBA-COF, with pore sizes of 3.8, 4.3 and 4.1 nm [Figure 1], respectively. The unique kagome lattice composed of large triangular planar molecules enables the formation of large hexagonal pores in the 2D COFs. It is worth noting that the as-synthesized Py-DBA-COF 2 shows excellent luminescent properties and has the largest pore size among solid-state luminescent 2D COFs, which has great potential in the field of optoelectronic applications.
Figure 1. Schematics for the synthesis of Py-MV-DBA-COF and Py-DBA-COF 2. (i) 3-Pentanone/Mesitylene = 2/1 (v/v), 105 °C and 3 days; (ii) 3-Pentanone/Mesitylene = 2/1 (v/v), 105 °C and 3 days.

Linkage-Oriented Synthetic Strategy
In 2014, Yan et al. successfully synthesized imide-linked COFs for the first time via
the condensation reaction between extended aromatic dianhydrides and triamine building blocks\[^{[12]}\]. Accordingly, a series of highly crystalline PI-COFs were yielded with a large pore size of 5.3 nm and a considerable surface area of 2346 m\(^2\)/g [Figure 2]. These PI-COFs are thermally robust up to 530 °C. Afterward, a large dye molecule was incorporated into the pore of PI-COF-3 to make temperature-sensing devices.

Figure 2. Skeleton design of PI-COF-3 with imide linkage. (i) Mesitylene/N-methyl-2-pyrrolidone/ Isoquinoline = 1/1/1 (v/v/v), 250 °C and 7 days.

Fragment-Oriented Synthetic Strategies

In 2016, Li et al. reported an imine-linked polycationic (PC) 2D COF through the condensation of 1,3,5-tris(4-aminophenyl) benzene (TAPB) and 1,1-bis(4-formylphenyl)-4,4'-bipyridinium dichloride (BFBP\(^{2+}\cdot2\text{Cl}^-\))\[^{[13]}\]. The resultant polycationic COF exhibits a hexagonal structure with a pore diameter of 5.8 nm [Figure 3]. The bipyridine (BIPY)-doped COF exhibits outstanding stability in water due to its polycationic nature and can almost quantitatively absorb anionic organic dyes in water at low concentrations. This makes the new polycationic COF a promising adsorbent for the removal of dye residues from water. The unique cationic BIPY-derived fragment with a large molecule size is believed to provide the structural
basis for stabilizing the large pore-sized 2D crystalline skeleton.

Figure 3. Synthesis route of PC-COF. (i) o-Dichlorobenzene (o-DCB):Ethanol = 9/1 (v/v), HAc (6 M), 120 °C and 7 days.

Expect that the pore sizes of most reported MOFs are smaller than 3.0 nm[21], in 2015, Deng et al. reported a 4.9 nm-sized MOF with a strategy of incorporating pore-directing “anchors” (i.e., side chains) into building blocks to modulate the interlayer π–π interactions[22]. Along with this scenario, Lotsch et al. successfully obtained dpp-TAB COF and dpp-TAPB COF with pore sizes of 4.8 nm and 5.8 nm, and surface areas of 1467 m²/g and 1670 m²/g, respectively [Figure 4][19]. The success lies in the use of methoxy groups as pore orientated “anchors” to prevent pore occlusion and collapse, and ultimately produce highly crystalline and porous COFs.
**Figure 4.** Synthesis routes of dPP-TAB COF and dPP-TAPB COF. (i) Mesitylene/1,4-Dioxane = 7/3 (v/v), HAc (12 M), 120 °C and 3 days; (ii) Mesitylene/1,4-Dioxane = 3/1 (v/v), HAc (6 M), 120 °C and 3 days.

In 2022, based on the same strategy as above, Feng et al. realized the synthesis of a
2D COF with a record pore size of 10 nm, termed TDCOF-3 [Figure 5][23]. This milestone is achieved by creatively integrating methoxy side chains and alkyne units into a single monomeric structure. Such combination not only enlarges the length of building blocks but also overcomes the intrinsic flexibility of growing polymeric chains. The resultant large pore-sized 2D COF is capable of separating 7.0 nm pepsin and protecting tyrosinase from heat-induced inactivation. Furthermore, this work also provides conclusive evidence that large mesoporous COFs can efficiently load enzymes of large molecular size and act as a protective layer to avoid enzyme inactivation under stringent conditions.

Figure 5. Schematic of TDCOF-3. (i) Mesitylene/1,4-Dioxane = 1/1 (v/v), HAc (6
M), 120 °C and 5 days.

Table 1. Summary of the porosity of the 2D COFs mentioned above

<table>
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OVERVIEW OF 3D COFS WITH LARGE PORES

Compared to 2D COFs, the construction of 3D COFs with regular, periodic structures is proven to be a more complicated process. In particular, 3D COFs are generally less stable than 2D layered architectures due to more cavities and the lack of π–π stackings. 3D COFs tend to form cage-like structures when extended in three dimensions, and monomers can continue to react and grow outward in the cavity, which makes it easy for 3D COFs to generate multiple interspersed structures. Notably, the interpenetration between pores that occurs in diamondoid (dia) or pts topologies unfortunately leads to a high degree of channel constriction. Taking these facts into account, current strategies for constructing 3D macroporous COFs
mainly include: (a) synthesizing monomers with side chains to prevent collapse of large pores; (b) synthesize novel topologies as well as fragments to construct macroporous structures.

In sharp contrast to 2D COFs, the development history of large-pore 3D COFs is relatively short. In 2020, Fang et al. reported the work of expanding the pore size of 3D COFs up to 2.7 nm and achieving a high surface area of 3023 m²/g through steric hindrance engineering[25]. It is worth noting that all JUC-550, 551, and 552 have non-interpenetrating dia topology by introducing methyl and methoxy groups into the building blocks [Figure 6]. For 3D COFs, it appears easier to shrink the pores or collapse the layers. As shown in Figure 7, either the (a) unmodified or (b) partially modified monomers result in shrinkage or interpenetration of the cavities[25]. Only the pores of the 3D COF built with (c) all modified units can be well maintained after the guest removal. Given that 3D cage-cavity organic structures are more prone to collapse, steric hindrance and expanding monomeric fragments are not feasible in producing large-pore 3D COFs, although they work well for creating large-pore 2D COFs.
**Figure 6.** Synthesis routes of (A) JUC-550, (B) JUC-551, (C) JUC-552. (i) 1,4-Dioxane, 120 °C and 3 days; (ii) Mesitylene, 120 °C and 3 days; (iii) Mesitylene, 120 °C and 3 days. Reproduced with permission from reference 25. Copyright © 2020, American Chemical Society.
Figure 7. Synthesis for 3D mesoporous COFs for three possible: (a) unmodified, (b) partially modified units and (c) all modified units. Reproduced with permission from reference 25. Copyright © 2020, American Chemical Society.

Topology-Oriented Synthetic Strategy
In 2007, the first two 3D boronate ester-linked COFs (COF-105 and COF-108) were reported by Yaghi et al., which exhibited ctn and boracite (bor) topologies with pore sizes of 1.8 and 3.0 nm, respectively.[26] Since then, the synthesis of 3D bor topotactic COFs has been rare until the development of the first imine-linked COFs with bor topology in 2022.[27] All the three developed 3D-bor-COFs possess large pore sizes, i.e., 3.1 nm for 3D-bor-COF-1, 3.6 nm for 3D-bor-COF-2, and 3.8 nm for 3D-bor-COF-3 [Figure 8]. The resultant 3D-bor-COFs serve as excellent capture materials for benzene vapor, with an adsorption capacity of 983.3 mg/g for 3D-bor-COF-1, 953.5 mg/g for 3D-bor-COF-2, and 1203.9 mg/g for 3D-bor-COF-3, which are among the highest for porous materials.
**Figure 8.** Synthesis routes of (A) 3D-bor-COF 1, (B) 3D-bor-COF 2, (C) 3D-bor-COF 3; (i) o-DCB, HAc (6 M), 120 °C and 4 days; (ii) o-DCB, HAc (6 M), 120 °C and 4 days; (iii) o-DCB, HAc (6 M), 120 °C and 4 days. Reproduced with permission from reference 27. © 2022 The Authors. SusMat published by Sichuan University and John Wiley & Sons Australia, Ltd.

**Fragment-Oriented Synthetic Strategy**

Recently, the exploration of specific fragments has also been considered a promising strategy for creating large-pore 3D COFs. For example, in 2020, Fang *et al.* reported the synthesis of JUC-564 with an unprecedented stp topology, a pore size of 4.3 nm, and a large BET surface area of 3383 m$^2$/g [Figure 9][28]. The JUC-564 was synthesized through the condensation of specific 2,3,6,7,14,15-hexa(4'-formylphenyl)triptycene (HFPTP) with steric configuration and planar 1,3,6,8-
tetrakis(4-aminophenyl) pyrene (TAPPy) units. In light of the large 3D porous
channels, JUC-564 was utilized to load the biomolecule myoglobin with a molecular
size of 3.5 nm.

Figure 9. Synthesis route of JUC-564. (i) Mesitylene/1,4-Dioxane = 3/2 (v/v), HAc (6
M), 120 °C and 3 days. Reproduced with permission from reference 28. Copyright ©
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On this basis, Fang et al. further reported another series of JUC-COFs using HFPTP
as one of the monomers\(^{[29]}\). Notably, JUC-640-H achieved a record large pore size of
4.6 nm in 3D COFs with a surface area of 2204 m\(^2\)/g, which abundantly exposed
porphyrin moieties (0.845 mmol/g) [Figure 10]. The JUC-640-Co containing the Co
metalized porphyrin units was used for the photoreduction of CO\(_2\) to CO, with a high
CO generation rate of 15.1 mmol g/h and a selectivity of 94.4%. It is worth noting
that the catalytic efficiency of JUC-640-Co exceeds all reported COF-based materials
so far.
Figure 10. Synthesis scheme of JUC-640-M. (i) o-DCB/n-BuOH = 1/1, HAc (6 M), 120 °C and 7 days. Reproduced with permission from reference 29. Copyright © 2023, American Chemical Society.

Table 2. Summary of the porosity of the 3D COFs mentioned above

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CONCLUSION AND OUTLOOK

Similar to other porous analog materials, the structural characteristics and applicational performances of COFs are highly dependent on their porosity, especially pore size. In particular, COFs with large mesopores enable the entry of unique large-sized guest molecules, which undoubtedly expands their functionalities. Therefore, it is crucial to develop efficient approaches to rationally design and synthesize large pore-sized COFs. In this work, we review several state-of-the-art strategies for
producing large-pore COFs, including: (a) designing COFs with specific topologies, such as hcb, kgm, stp, bor, etc.; (b) using imide linkage to prepare target COFs; (c) employing sizeable molecular building blocks with charged part or side chains to prevent shrinkage of macropores and interlayer slippage; (d) developing organic unit with unique steric configurations to maintain large pores in 3D COFs. We call upon the fact that despite significant progress in this appealing research area, the synthetic mechanisms remain elusive. Further efforts combining molecular-level simulations and in situ structural characterization may provide a microscopic view of the large-pore formation.

As discussed above, most reported preparations of large pore-sized COFs still rely on simply increasing the length of the building blocks, but this results in low overall reaction yields and a tendency for structural collapse or interlayer interpenetration. Although several fragments with specific steric configurations can yield large pore-sized 3D COFs, the intrinsic relationship between structure and pore size is still unclear. In addition, all COFs with large pores reported to date are prepared using organic units with imine or boronic ester linkages, which also limits stability and subsequent functional exploration. Developing macroporous COFs with other linkages remains a challenge and requires further efforts.

We emphasize that an ideal and effective strategy of designing large pore-sized COFs should not only produce regular porous structure with good structural stability, but also have simple synthetic processes, high total reaction yields, and great generality. Such efficient synthetic approach needs to be proposed and developed in the future. It is hoped that the continuous development of large mesoporous COFs will extend and promote their applications in more specific fields, including but not limited to the absorption and separation of macromolecules, bio-catalysis, etc.

DECLARATIONS

Authors’ contributions
Prepared and revised the manuscript: Li X
Revised the manuscript: Geng KY, Fu S
Designed and revised the manuscript: Jin EQ
All authors contributed to the discussion and preparation of the manuscript.

Availability of data and materials
Not applicable.

Financial support and sponsorship
This work was financially supported by the National Natural Science Foundation of China (22288101, 22201092) and the 111 Project (B17020). Jin, E. acknowledges the support from the start-up grant of Jilin University.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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REFERENCE


Su YC, Yuan GQ, Hu JL, et al. Recent Progress in Strategies for Preparation of


