Three-Dimensional Covalent Organic Framework with scu-c Topology for Drug Delivery

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ABSTRACT: Three-dimensional (3D) covalent organic frameworks (COFs) exemplify a new generation of crystalline extended solids with intriguing structures and unprecedented porosity. Notwithstanding substantial scope, the reticular synthesis of 3D COFs from pre-designed building units leading to new network topologies yet remains a demanding task owing to the shortage of 3D building units and inadequate reversibility of the linkages between the building units. In this work, by linking a tetragonal prism (8-connected) node with a square planar (4-connected) node, we report the first 3D COF with scu-c topology. The new COF, namely, TUS-84, features a two-fold interpenetrated structure with well-defined porosity and a Brunauer–Emmett–Teller surface area of 679 m$^2$ g$^{-1}$. In drug delivery applications, TUS-84 shows efficient drug loading and sustained release profile.

KEYWORDS: covalent organic framework, three-dimensional, topology, two-fold interpenetrated, drug delivery

INTRODUCTION

An emerging class of porous organic materials developed from linking molecular building blocks with strong covalent bonds into crystalline, extended two-dimensional (2D) and three-dimensional (3D) structures called covalent organic frameworks (COFs).\textsuperscript{1-14} COFs have recently aroused great interest in catalysis,\textsuperscript{15,16} sensing,\textsuperscript{17,18} separation,\textsuperscript{19} semiconduction,\textsuperscript{20} proton conduction,\textsuperscript{21} biomedicine,\textsuperscript{22,23} among others. COFs emerged in 2005\textsuperscript{24} as the second series of reticular materials, the first one being metal–organic frameworks (MOFs).\textsuperscript{25,26} “Reticular” means “anything that has the structure of a net”. By reticular synthesis, we refer to the extended structure regime that combines (i) molecular-level control over matter and (ii) robustness.\textsuperscript{27-29} A top-down reticular synthesis scheme starts with a desired net topology, followed by disassembling it into vertices and edges, finding secondary building units with the right connectivities and aligning them with the vertices, obtaining an augmented net by replacing the vertices of an $n$-connected net by a group of $n$-vertices, and finally linking the molecular building blocks by robust bonds into crystalline extended structures.\textsuperscript{1,30-34} Alternatively, the bottom-up scheme of reticular synthesis proceeds from pre-designed building units, leading to unprecedented network topologies.\textsuperscript{35} COFs feature one of the highest open-pore scaffolds. The COF scaffold is built out of organic units, and it imparts tunable chemical environments for encapsulating a wide array of guest molecules.

Based on the extension of their covalent connectivity, COFs can be categorized into 2D and 3D COFs.\textsuperscript{36} With covalent connectivity extending only in 2D, 2D COFs crystallize as layered structures in which the layers are stacked through non-covalent interactions ($\pi-\pi$ stack, van der Waals interactions, hydrogen bonds), giving rise to one-dimensional (1D) straight channels.\textsuperscript{14,37} On the other hand, with covalent connectivity extending along the entire 3D scaffold, 3D COFs often have the upper hand over 2D COFs, attributed to their interconnected channels and readily accessible active sites.\textsuperscript{38,39} Topological consideration is crucial to 3D extended structures, considering that it largely dictates their pore architecture, active site formation, and mass transport behavior.\textsuperscript{38} Albeit highly sought after, discovery of new 3D COF topologies yet remains a herculean task because the highly connected 3D organic building blocks are hard to come by and it is very difficult to solve the crystal structures. Thus far, the type of 3D topologies of COFs is limited to about 20.\textsuperscript{40} The tetratopic ($T_4$)-based 3D COF nets are bor,\textsuperscript{39} ctn,\textsuperscript{39} dis,\textsuperscript{40} pts,\textsuperscript{41} rra,\textsuperscript{42} lon,\textsuperscript{43} and ljh.\textsuperscript{44} Fang et al. and He and et al. prepared several hexatopic ($D_6$)-based 3D COFs, for example,
Different from triangular prismatic ($D_{3h}$) nodes, triangular antiprismatic ($D_{3d}$) nodes were utilized by Mateo-Alonso and co-workers to construct pcu topology 3D COFs. Other unprecedented 3D COF topologies reported are ffc, srs, fjh, tbo, and nbo. Recently, octatopic nodes have been used to prepare pcb and bcu topology 3D COFs.

Herein, we report the first 3D COF with scu topology, namely, TUS-84, formed through the combination of a tetragonal prism (8-connected) node with a square planar (4-connected) node. After this article was available online in open access preprint archive, a 3D COF with non-interpenetrated scu topology, NKCOF-25-H, constructed from the same strategy has been published. Differing from NKCOF-25-H with non-interpenetrated scu topology, TUS-84 exhibits a two-fold interpenetrated scu net, denoted as scu-c (c for catenated), and different unit cell parameters from NKCOF-25-H. Of note, the simulated non-interpenetrated scu net X-ray diffraction (XRD) pattern did not accord with our experimental powder XRD (PXRD) pattern. This case is similar to the non-interpenetrated stp COF (JUC-564) reported by Fang and co-workers and the 2-fold interpenetrated stp COF (Trip-COF 2) reported by Zhao and co-workers, both of which were synthesized using the same building blocks. Structural elucidation of TUS-84 was carried out thoroughly through different characterization techniques. Interestingly, TUS-84 shows efficient drug loading and extended release profile in simulated physiological media. Scheme 1 depicts the strategic approach to construct 3D COFs with a scu-c net via the [8 + 4] imine condensation reaction of a $D_{2h}$-symmetric linker, 4',5'-bis(3,5-diformylphenyl)-3',6'-dimethyl-[1,1':2',1''-terphenyl]-3,3, "5,5"-tetracarbaldehyde (DPTB-Me), and a $C_4$-symmetric linker, 5,10,15,20-tetrakis(4-aminophenyl)porphyrin (TAPP).

**RESULTS AND DISCUSSION**

TUS-84 was synthesized by the solvothermal reaction of DPTB-Me (19.0 mg, 0.03 mmol) and TAPP (40.48 mg, 0.06 mmol) in a 5:5:2 (v/v/v) mixture of mesitylene, 1,4-dioxane, and 6 M aqueous acetic acid under 120 °C for 3 days. The acid-catalyzed Schiff-base condensation reaction yielded the COF as a dark purple crystalline solid at a yield of 76%. The solid-state $^{13}$C cross-polarization magic angle spinning (CP/MAS) NMR and Fourier-transform infrared (FT-IR) spectrosopies provided definitive evidence for atomic-level connectivity of the imine linkage in TUS-84. In the FT-IR spectrum of TUS-84, the C=$\equiv$N vibration peak at 1625 cm$^{-1}$ was observed. Significant attenuation of the N–H (3433, 3465 cm$^{-1}$ for TAPP) and C=$\equiv$O (1703 cm$^{-1}$ for DPTB-Me) stretching vibration bands in the FT-IR spectrum of TUS-84
implies a high degree of polymerization for the imine COF (Figure S2). Isometric microcrystals of TUS-84 were observed from scanning electron micrographs (Figure S3). High-resolution transmission electron microscopy (HRTEM) imaging (Figures 1b,c and S4,5) showed the ordered structure of TUS-84, comprising rhombus pores viewed along the z-direction in the simulated structure (Figure 2a). Thermogravimetric analysis (TGA) curve indicates high thermal stability for TUS-84 retaining 95% of its weight up to 500 °C (Figure S6). Chemical stability of the COF was substantiated from its preservation of crystallinity and imine linkage after treatment with organic solvents, water, and aqueous HCl and NaOH solutions, as can be seen from the PXRD profiles (Figure S7) and FT-IR spectra (Figure S8).

The crystal structure of TUS-84 was unraveled by PXRD analysis combined with structural modeling and simulation (Figure 1a). Geometry optimization (energy minimization) was performed in the Materials Studio 7.0 Forcite program that afforded the unit cell parameters of TUS-84 with a scu-c net and Pm space group as \( a = 39.9205 \text{ Å}, b = 18.7162 \text{ Å}, c = 23.6564 \text{ Å}, \alpha = \beta = \gamma = 90^\circ \). The simulated PXRD pattern (Figure 1a, green curve) showed great alignment with the observed diffraction pattern (Figure 1a, red dots). Sharp Bragg peaks observed at 4.38 and 6.44° correspond to the (200) and (111) facets, respectively, and relatively weak peaks at 9.10, 10.23, 11.15, 12.83, 14.38, and 16.19° correspond to the (112), (020), (221), (222) (130), and (132) facets, respectively.

Figure 1. (a) PXRD patterns of TUS-84: experimental pattern (red dots), Pawley refined (black curve), simulated (green curve) pattern from the scu-c modeled structure, and the difference plot (blue curve) between the experimental and refined patterns. The Bragg positions are denoted by magenta ticks. (b, c) HRTEM images of TUS-84. The inset in (b) shows the fast Fourier transform (FFT) pattern acquired from the area enclosed by the white box.

Figure 2. (a, b) Extended structures of TUS-84.
reinforce its prospects in carbon capture and clean energy applications. As illustrated in Figure S10, the H\textsubscript{2} uptake capacities at 77 and 87 K under 1 bar are 131 and 88 cm\textsuperscript{3} g\textsuperscript{−1}, respectively. The isosteric enthalpy of adsorption (Q\textsubscript{st}) of H\textsubscript{2} was calculated to be 6.8 kJ mol\textsuperscript{−1} (Figure S11). TUS-84 shows a CO\textsubscript{2} uptake capacity of 55 and 31 cm\textsuperscript{3} g\textsuperscript{−1} at 273 and 298 K, respectively, under 1 bar (Figure S12). The Q\textsubscript{st} of CO\textsubscript{2} adsorption was evaluated as 24.9 kJ mol\textsuperscript{−1} (Figure S13). The CH\textsubscript{4} sorption isotherms shown in Figure S14 reveal an uptake capacity of 14 and 10 cm\textsuperscript{3} g\textsuperscript{−1} at 273 and 298 K under 1 bar, respectively, and the value of Q\textsubscript{st} was obtained as 6.5 kJ mol\textsuperscript{−1} (Figure S15).

Intrigued by the 3D functional scaffold with permanent porosity and high chemical stability, we utilized TUS-84 in in vitro drug delivery studies. Ibuprofen is one of the most common nonsteroidal anti-inflammatory drugs (NSAIDs) used for the treatment of rheumatoid arthritis, osteoarthritis, mild–moderate pain, and primary dysmenorrhea.\textsuperscript{62–64} The selection of ibuprofen as the drug in this study is based on the following: (a) ibuprofen has a short half-life (1.8–2.0 h) that calls for extended release formulations\textsuperscript{62} and (b) pore dimensions of TUS-84 (1.05 nm) is benefitting for encapsulation of ibuprofen with molecular size of 0.5 × 1 nm\textsuperscript{2}.\textsuperscript{65,66}

For drug loading, 50 mg of TUS-84 was suspended in 30 mL of 0.1 M hexane solution of ibuprofen under magnetic stirring for 4 h. The drug-loaded COF sample was isolated from suspension via vacuum filtration, washed with hexane, and subsequently dried at room temperature. 1.0 mL of the filtrate was collected and 50 times diluted to evaluate the loading amount of ibuprofen using a UV–vis spectrophotometer by measuring the absorbance at 261 nm of ibuprofen in hexane and supernatant (see Supporting Information for details). UV–vis absorption data showed 11.05 wt % loading of ibuprofen in TUS-84 (Figure S24). As can be seen from Figure S22, the value of drug loading amount is in good agreement with that obtained from TGA (11 wt %). PXRD analysis (Figure S18) of ibuprofen-loaded TUS-84 revealed that the COF crystalline structure was retained after drug loading. As evident from the scanning electron micrograph (Figure S19) of ibuprofen-loaded TUS-84, no significant morphological change
in COF was observed. N₂ sorption measurements of ibuprofen-loaded TUS-84 were carried out to ascertain the successful loading of ibuprofen inside the COF pores. The reduction in BET surface area from 679 to 462.7 m² g⁻¹ after ibuprofen loading was owing to the occupancy of COF pores by ibuprofen molecules. The drug release study was performed by placing 40 mg of the drug-loaded TUS-84 sample inside a semipermeable bag, followed by immersing in 10 mL of phosphate buffer solution (simulated body fluid, pH 7.4) at a constant temperature of 37 °C. The dissolution solvent was taken out at specified time intervals for evaluation of the ibuprofen concentration and replenished with 10 mL of fresh buffer solution. The ibuprofen concentration was determined UV–vis spectrophotometrically using a calibration curve (Figure 4a,b). TUS-84 showed an extended drug release performance of about 35% after 5 days (Figure 4c). In comparison with the ibuprofen release rates of 78% for Cage-COF-TT and 49% for PI-COF-5, respectively, after 12 h, a considerably slower release rate of 24% was observed for TUS-84 after 12 h. This long-acting ibuprofen formulation could deliver sustained concentrations of drug over a prolonged period of time, thereby reducing dosing frequency and ensuring more consistent control of long-lasting pains.  

For more detailed studies of TUS-84 on drug delivery, we also performed the loading and release of captopril. TGA trace of captopril-loaded TUS-84 revealed 16 wt % loading of captopril in TUS-84 (Figure S28). The majority of the captopril was released from TUS-84 after about 5 days, with total delivery reaching about 98% of the total captopril loading (Figure S29c).

## CONCLUSIONS

To conclude, a 3D COF with a novel scu-c topology was designed and synthesized, utilizing a D₃₅-symmetric linker, DPTB-Me, and a C₃-symmetric linker, TAPP. The resultant TUS-84 COF displays an ordered microporous structure with high crystallinity and excellent stability. Furthermore, TUS-84 shows great promise as drug delivery vehicle owing to its efficient drug loading and controlled release behavior. This study may not only expand the library of 3D COF topologies but also facilitate the design of new 3D COF structures for biomedical applications.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmi.2c15152.

Materials and characterization; synthetic procedures; solid-state ¹³C CP/MAS NMR spectroscopy; FT-IR spectroscopy; SEM and TEM images; TGA; chemical stability test; N₂ adsorption; structure simulations and XRD analyses; drug delivery; and crystallographic information (PDF)

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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