

Three-Dimensional sp^2 Carbon-Linked Covalent Organic Frameworks for Bioresponsive Fluorescence Imaging

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Supporting Information Placeholder

ABSTRACT: Three-dimensional (3D) covalent organic frameworks (COFs) are crystalline porous polymers with potential in numerous high-tech applications, but the linkages involved in their synthesis are still rather limited. Herein we report the first case of 3D sp^2 carbon-linked COFs fabricated by the formation reaction of C=C bonds and their application in bioresponsive fluorescence imaging. These new COFs, namely JUC-580 and JUC-581, showed high stability and excellent light-emitting properties in solid state and dispersed in various solvents. Furthermore, we investigated the potential application of JUC-581 for a drug carrier combined with bioresponsive fluorescence imaging. The results indicated that 3D sp^2 carbon-linked COFs are not only potential drug-loaded and sustained release materials but also promising cell fluorescent stains. This study expands the structural categories of 3D COFs based on different linkages, and promotes their prospective applications for biomedicine and fluorescent materials.

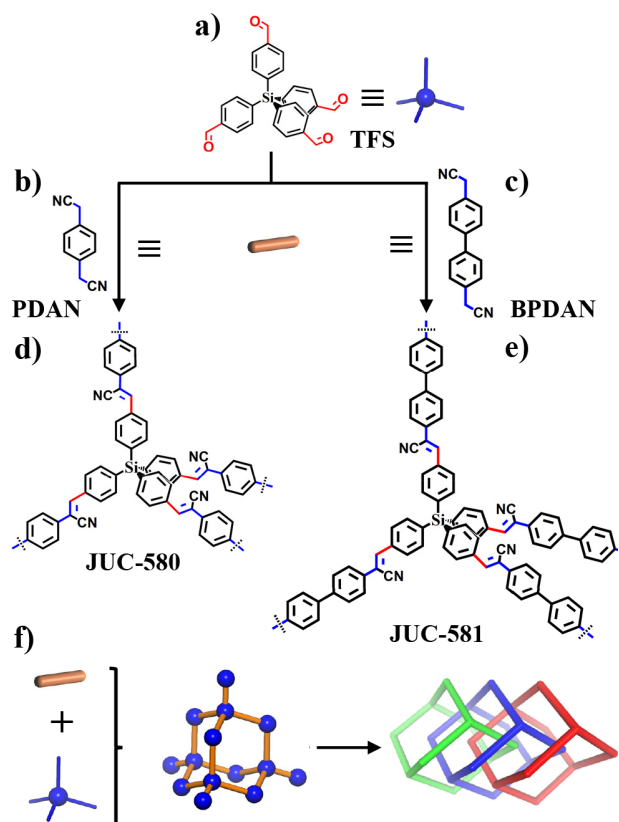
Covalent organic frameworks (COFs),¹⁻⁶ a new class of crystalline porous polymers with large surface areas and high stabilities, have attracted interest in different fields involving gas storage and separation,⁷⁻¹⁰ catalysis,¹¹⁻¹⁶ organic optoelectronics,¹⁷⁻²¹ and many others.²²⁻²⁶ To date, most studies are focused on two-dimensional (2D) architectures with eclipsed AA or staggered AB stacking modes. Three-dimensional (3D) COFs have recently been considered as promising platforms for a wide range of applications due to unique pore structures, high surface areas and modulable active sites.²⁷⁻³⁶ However, only limited linkages in 3D COF materials were reported so far, and especially most of them were based on the C=N or B-O linkage, which have seriously

hindered the structural diversities and potential uses of 3D COFs.⁴

Lately, a new type of 2D COF materials connected by C=C bonds, sp^2 carbon-linked COFs (also known as olefin- or vinylene-linked COFs), have gained considerable attention.³⁷⁻⁴⁴ For example, Feng and co-workers have developed the first example of 2D sp^2 carbon-linked COF, 2DPPV, via a Knoevenagel polycondensation reaction of 1,4-phenylene diacetonitrile and three-armed aromatic aldehyde.³⁷ Subsequently, Jiang et al. designed a fully π -conjugated 2D sp^2 -carbon framework, sp^2c -COF, by the C=C condensation reaction of tetrakis(4-formylphenyl)pyrene and 1,4-phenylenediacetonitrile.³⁸ Recently, Yaghi and co-workers have also reported the first unsubstituted 2D sp^2 carbon-linked COF, COF-701, constructed from 2,4,6-trimethyl-1,3,5-triazine and 4,4'-biphenyldicarbaldehyde by the Aldol condensation.³⁹ Notably, the inherent sp^2 C=C linkages simultaneously improve both in-plane π -electron delocalization and chemical stability of material, and thus sp^2 carbon-linked COFs are endowed with unique performance, such as ferromagnetic and especially optical applications. In principle, the combination of C=C bonds and 3D frameworks will be beneficial for structural diversity and turning the properties of COF materials. However, this avenue has not been explored yet.

Taking these considerations in mind, we report herein two 3D sp^2 carbon-linked COFs, termed as JUC-580 and JUC-581 (JUC = Jilin University China). Our results demonstrated that the obtained COFs had large channels, permanent porosity, high chemical stability, and excellent luminescence in solid state and suspended in various solvents. The potential application of JUC-581 with a larger pore (19.8 Å) for a cancer drug (cisplatin, CIS) carrier was explored. The related drug-loaded material (CIS@JUC-581) showed an exceptional

Scheme 1. Designed synthesis of 3D sp^2 carbon-linked COFs^a



^aMolecular structures of TFS (a) as a tetrahedral building unit, and PDAN (b) as well as BPDAN (c) as linear building units. 3D sp^2 carbon-linked COFs, denoted as JUC-580 (d) and JUC-581 (e), were constructed by the condensation reaction of TFS and PDAN or BPDAN, and showed 3-fold interpenetrated diamondoid (**dia**) topology (f).

bioresponsive fluorescence imaging, which is highly consistent with that from commercial dye. In addition, we also studied the cytotoxicity by flow cytometry experiments and successfully illustrated good biocompatibility for JUC-581 and high cytotoxicity for CIS@JUC-581. To the best of our knowledge, this study is the first example of 3D sp^2 carbon-linked COFs and their application as candidate materials for bioresponsive fluorescence imaging.

Our strategy for the preparation of 3D sp^2 carbon-linked COFs is based on the formation reaction of C=C bonds from aldehyde and acetonitrile groups. As shown in Scheme 1, tetrakis(4-formylphenyl)silane (TFS, Scheme 1a) was designed as a tetrahedral building unit, and 2,2'-(1,4-phenylene)diacetonitrile (PDAN, Scheme 1b) or 2,2'-(biphenyl-4,4'-diyl)diacetonitrile (BPDAN, Scheme 1c) was chosen as a linear linker. The condensation of TFS and PDAN or BPDAN produced two extended 3D COF frameworks, JUC-580 (Scheme 1d) and JUC-581 (Scheme 1e), respectively. Owing to the tetrahedral centers separated by long linear linkers, PDAN (~ 6.1 Å) and BPDAN (~ 10.7 Å), the resulting structures tend to be 3-fold interpenetrated diamondoid (**dia**) networks (Scheme 1f).⁴⁵

The synthesis of 3D sp^2 carbon-linked COFs was carried out through the traditional solvothermal approach by suspending

TFS and PDAN or BPDAN in a mixed solution of mesitylene and dioxane containing 5 M 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by heating at 120 °C for 5 days. Complementary methods were employed to determine the physicochemical properties of crystalline material. Scanning electron microscopy (SEM, Figures S1 and S2) images revealed isometric microcrystals with a size of about 0.1 μm for both COFs. The Fourier transform infrared (FT-IR) spectra demonstrated the formation of COFs by a newly appeared C \equiv N vibration band at 2220 cm^{-1} and a greatly decreased band at 2740 cm^{-1} for the C-H stretching vibration of aldehyde units (Figure S3). Solid-state ^{13}C cross-polarization magic-angle-spinning (CP/MAS) NMR spectroscopy further verified the presence of C=C bonds by the peak at 142 ppm for JUC-580 or 143 ppm for JUC-581 (Figures S4 and S5). Both 3D sp^2 carbon-linked COFs had high thermal stability (up to 550 °C) as manifested by the thermogravimetric analysis (TGA, Figures S6 and S7), and excellent chemical stability, i.e., no changes in the

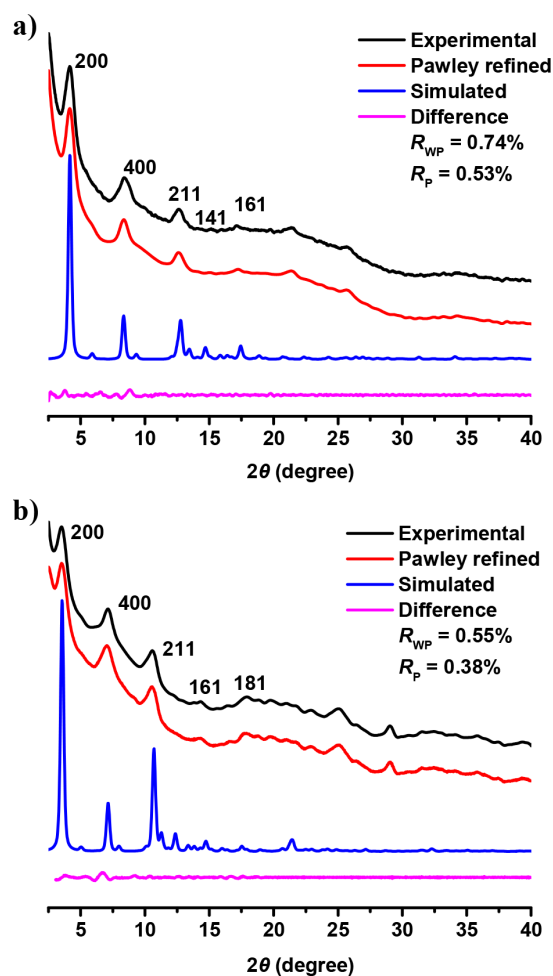


Figure 1. PXRD patterns of JUC-580 (a) and JUC-581 (b).

PXRD patterns of COFs exposed to different organic solvents and aqueous solutions of 3 M HCl or 3 M NaOH were observed (Figures S8 and S9).

The crystal structures of 3D sp^2 carbon-linked COFs were confirmed by PXRD measurements in conjunction with structural simulations (Figure 1). After a geometrical energy minimization by using the Materials Studio software package⁴⁶

based on 3-fold interpenetrated **dia** topology, their unit cell parameters were acquired ($a = b = 42.386$ Å, $c = 7.441$ Å and $\alpha = \beta = \gamma = 90^\circ$ for JUC-580; $a = b = 49.550$ Å, $c = 8.914$ Å and $\alpha = \beta = \gamma = 90^\circ$ for JUC-581). The simulated PXRD patterns were in good agreement with the experimental ones. Furthermore, the full profile pattern matching (Pawley) refinement was applied for the experimental PXRD patterns. Peaks at 4.16 , 8.34 , 12.80 , 14.68 , and 17.21° for JUC-580 belong to the (200), (400), (211), (141), and (280) Bragg peaks of space group $I4_1/a$ (No. 88). Similarly, peaks at 3.59 , 7.12 , 10.70 , 14.31 , and 17.72° for JUC-581 correspond to the (200), (400), (211), (161), and (181) Bragg peaks of the same space group. The refinement results match well with the observed ones with a negligible difference and good agreement factors ($R_p = 0.53\%$ and $\omega R_p = 0.74\%$ for JUC-580; $R_p = 0.38\%$ and $\omega R_p = 0.55\%$ for JUC-581). In addition, we also tried alternative structures, such as non- and 2-fold interpenetrated **dia** nets for both 3D COFs. However, these simulated PXRDs did not match the experimental ones (Figures S10–15). Based on the above results, the obtained COFs are proposed to be the expected architectures with 3-fold interpenetrated **dia** nets (Tables S1–6) and microporous cavities of about 17.9 Å for JUC-580 and 19.8 Å for JUC-581 (Figure 2).

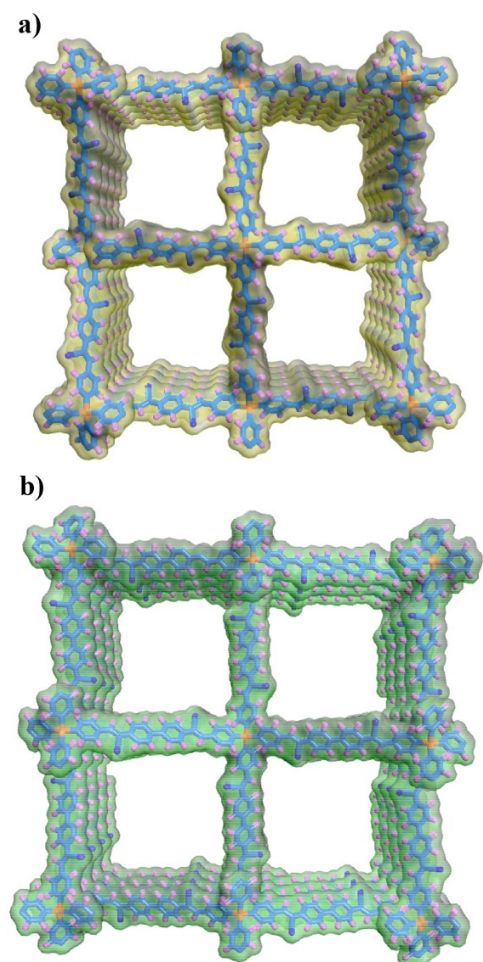


Figure 2. Extended structures of JUC-580 (a) and JUC-581 (b) viewed along the c axis. C, cyan; H, pink; N, blue; Si, yellow.

The porosity and specific surface areas of 3D sp^2 carbon-linked COFs were determined by N_2 adsorption analysis at 77 K. As shown in Figure S16, a sharp increase in gas uptake is observed at low pressure (below $0.1 P/P_0$) for both COFs, which reveals their microporous nature, followed by a gradual increase of the uptake, ranging from $P/P_0 = 0.1$ to 0.8 . Considering that the pore diameter from each crystal structure is in the micropore region, a unique profile of the isotherm accompanying a hysteresis loop can be attributable to textural mesopores from the agglomeration of crystals.²⁹ The Brunauer–Emmett–Teller (BET) specific surface areas were 713 m^2/g for JUC-580 and 741 m^2/g for JUC-581 (Figure S17). Their pore-size distributions were calculated by nonlocal density functional theory (NLDFT), and both materials showed a microporous pore width of 16.0 Å for JUC-580 and 18.0 Å for JUC-581 (Figure S18), which are in good agreement with those of the proposed models (17.9 Å for JUC-580 and 19.8 Å for JUC-581).

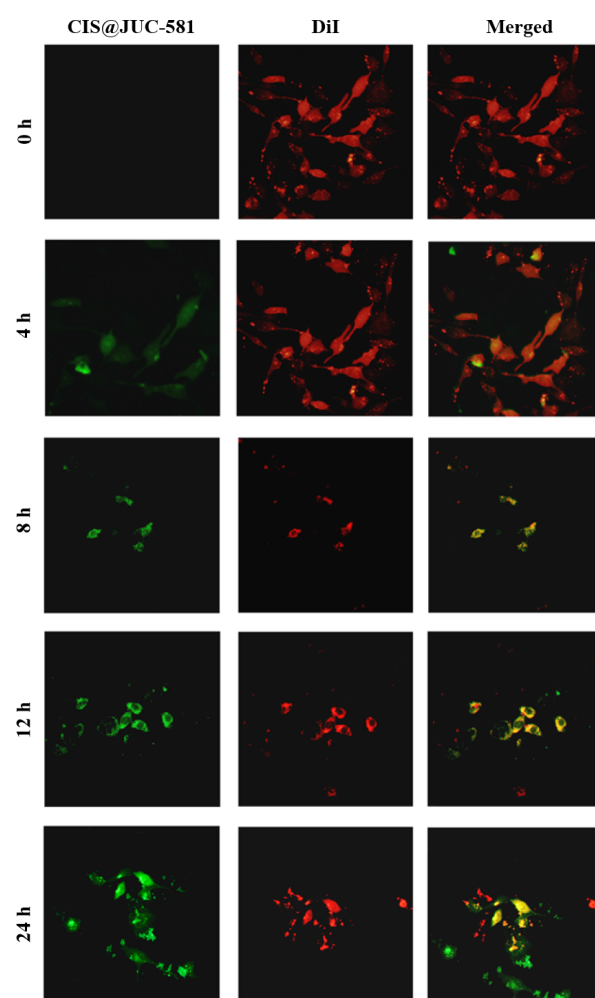


Figure 3. Cell fluorescence imaging of CIS@JUC-581 (left), DiI (middle), and merged (right) at different times.

We further investigated the fluorescent emission of 3D sp^2 carbon-linked COFs. As shown in Figures S19 and S20, the solid samples were excited at 363 nm for JUC-580 and 365 nm for JUC-581, and showed emission bands centered at 505 nm for JUC-580 and 503 nm for JUC-581, respectively. Their absolute

fluorescence quantum yields were as high as 6% for JUC-580 and 8% for JUC-581. Fluorescence microscopy confirmed that these COFs were highly emissive across the entire bands (Figure S21). The fluorescence lifetimes of the solid samples were estimated to be 28.81 ns for JUC-580 and 28.07 ns for JUC-581, respectively (Figure S22). As a comparison, 3D imine-linked COFs with similar structures, COF-300⁴⁷ and COF-320⁴⁸, have been prepared. However, they almost did not emit the luminescence in solid state (Figures S19 and S20), indicating that these

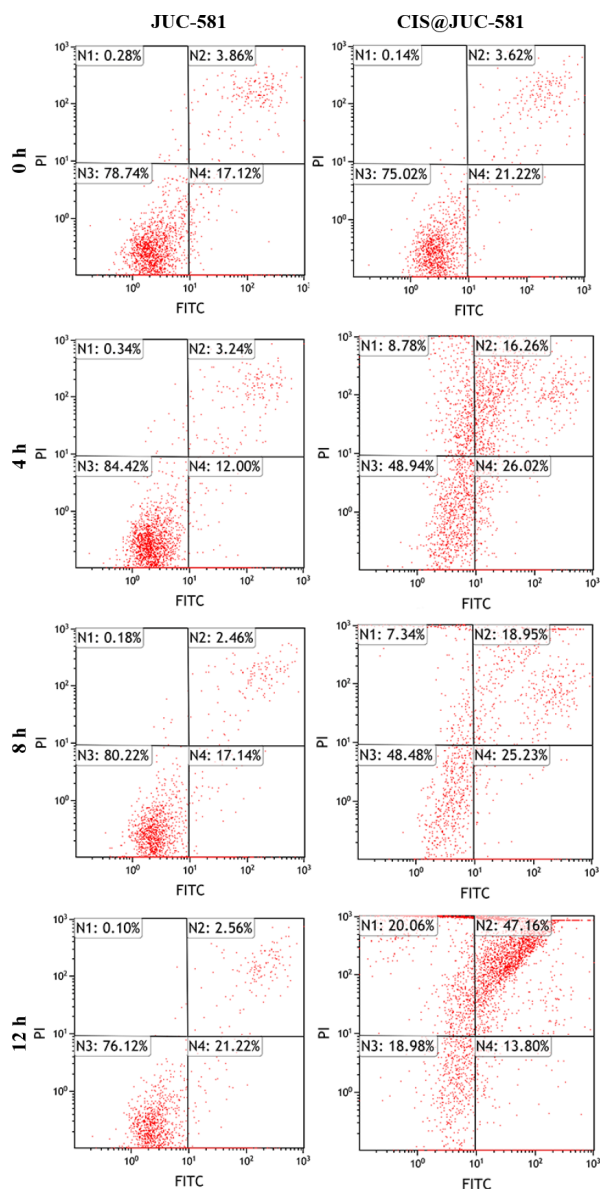


Figure 4. Flow cytometry experiments of JUC-581 (left) and CIS@JUC-581 (right) at different times.

sp² carbon-linked COFs had more excellent light-emitting characteristics. Furthermore, we dispersed both COFs in different solvents, such as acetonitrile, dichloromethane and hexane, and measured their fluorescence spectra (Figures S23 and S24). Compared to the solid samples, their fluorescence emissions exhibited only minor variations due to the change of the solvents. Moreover, these 3D sp² carbon-linked COFs dispersed in

different solvents had similar fluorescence lifetimes of 26.94–29.63 ns (Figures S25 and S26). Therefore, these novel COF materials are highly luminescent and robust in both solid state and various solvents.

Given the excellent luminescence, favorable porosity, and highly chemical stability of 3D sp² carbon-linked COFs, we investigated the potential application of JUC-581 with a pore of 19.8 Å as a drug carrier and its bioresponsive fluorescence imaging. Herein, CIS (~4.3 Å) was chosen as a model drug because JUC-581 contained abundant electron-withdrawing groups, cyano groups, preferring to attract the amino groups of CIS.⁴⁹ It is well-known that CIS as an anticancer drug is widely used to treat many kinds of cancers, such as ovarian cancer, prostatic cancer, lymphoma, etc.^{50,51} However, CIS is easily hydrolyzed in the aqueous solution, making it lose the curative effect. Therefore, we used JUC-581 with high stability and strong luminescence as a drug carrier material to prevent the hydrolysis of CIS and improve its treatment ability.

Typically, to obtain the drug-loaded material (CIS@JUC-581), JUC-581 was immersed in a dimethyl sulfoxide solution of CIS, and stirred for 24 h. The resultant PXRD pattern of CIS@JUC-581 was consistent with that of the starting material, demonstrating the structural integrity of JUC-581 after loading the drug (Figure S27). The successful saturation with CIS was also confirmed by the transmission electron microscopy (TEM) elemental mapping (Figure S28). Inductively coupled plasma optical emission spectrometry (ICP-OES) further indicated that JUC-581 had a load of CIS as high as 20 wt%. Based on these results, we explored the imaging capability of CIS@JUC-581 in PC-3 cancer cells. Remarkably, CIS@JUC-581 could easily enter into cancer cells and displayed bright green fluorescence. The cyano groups in JUC-581 is most probably the origin of high permeability through the cell membrane that helps the COF to pass through and move into the cytoplasm. Thanks to stable luminescence characteristics of JUC-581, the drug delivery process of CIS@JUC-581 could be clearly monitored through the fluorescence imaging. As shown in Figure 3, the fluorescence intensity of CIS@JUC-581 in the cells was measured at different times. Obviously, the presence of CIS@JUC-581 in the cytoplasm was observed between 0 to 24 h, and the lysis and death of cells were found to be accompanied by the release of drug in CIS@JUC-581 (Figure S29). The fluorescence intensity increases with time. The dyeing range of JUC-581 is highly consistent with that of commercial DiI dyes (Figure 3), indicating that JUC-581 is not only a potential drug-loaded and sustained release material but also a promising cell fluorescent stain. Furthermore, we studied the cytotoxicity on annexin V-fluorescein isothiocyanate (Annexin V-FITC) and propidium iodide (PI) staining assay by flow cytometry experiments.⁵² As shown in Figure 4, JUC-581 presented no cytotoxicity to PC-3 cancer cells, confirming that JUC-581 was biocompatible. In contrast, CIS@JUC-581 possessed obvious cytotoxicity. The quantity of late apoptotic cells and dead cells increased significantly over time because the long-term and sustained drug release from CIS@JUC-581 could effectively kill cancer cells.

In summary, we have designed and synthesized two new 3D sp² carbon-linked COFs, JUC-580 and JUC-581, by the C=C condensation reactions. These novel crystalline frameworks showed large pores, high chemical stability, and outstanding luminescence feature in solid state and dispersed in various solvents. Moreover, the application of JUC-581 as a cancer drug (CIS) carrier conjoined with bioresponsive fluorescence imaging was investigated. The results pointed out that 3D sp² carbon-linked COFs are not only good drug-loaded and sustained release materials but also potential cell fluorescent dyestuff. In

addition, the cytotoxicity by flow cytometry experiments demonstrated good biocompatibility of JUC-581 and high cytotoxicity of CIS@JUC-581. This work enriches the structural diversities of 3D COFs based on new linkages, and unlocks their potential applications in biomedicine and fluorescent probes.

Supporting Information

Methods and synthetic procedures, SEM, FTIR, solid state ^{13}C NMR, TGA, BET plot, and unit cell parameters. This material is available free of charge via the internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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TOC Graphic:

