A Journal of the Gesellschaft Deutscher Chemiker

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201912579
Angew. Chem. 10.1002/ange.201912579

Link to VoR: http://dx.doi.org/10.1002/anie.201912579
http://dx.doi.org/10.1002/ange.201912579

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Angewandte Chemie International Edition 10.1002/anie.201912579

Amidation, Esterification, and Thioesterification of a Carboxyl-Functionalized Covalent Organic Framework

Lei Guo, Shang Jia, Christian S. Diercks, Xuejing Yang, Sultan A. Alshmimri, and Omar M. Yaghi*

Abstract: Three new post-synthetic modification reactions, namely amidation, esterification, and thioesterification, were demonstrated on a novel highly crystalline two-dimensional covalent organic framework (COF), COF-616, bearing pre-installed carboxyl groups. The strategy can be used to introduce a large variety of functional groups into COFs and the modifications can be carried out under mild reaction conditions, with high yields, and an easy work-up protocol. As a proof of concept, various chelating functionalities were successfully incorporated into COF-616 to yield a family of adsorbents for efficient removal of several contaminants in the water.

Covalent organic frameworks (COFs) are made by stitching together molecular building units into crystalline porous extended structures.[1,2] To take full advantage of the high porosity and surface areas of these frameworks, specific chemical functionality needs to be introduced into their pores to tailor interactions with guest species for a targeted application.[3–5] This introduction can be affected both pre-synthetically by modifying the molecular building units,[6,7] or post-synthetically by modifying the organic backbone of the framework.[8–16] Pre-synthetic modification of COFs is generally limited because it demands tedious synthetic efforts and may interfere with the COF forming reaction. Post-synthetic modification provides higher versatility, with click chemistry currently being the most widely-used protocol.[17,18] However, conducting such copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions on COFs generally requires anaerobic handling, involves heterogeneous Cu(I) catalysts that need to be removed from the pores of the framework, and is incompatible with molecules featuring chelating functionalities — all of which greatly limit the generality of this approach. As such, a more general and facile strategy for post-synthetic modification of COFs is highly sought after.

We developed a new COF, termed COF-616, whose backbone is functionalized with carboxyl groups, which serve as orthogonal handles for facile post-synthetic functionalization reactions (Figure 1a). The carboxyl groups of COF-616 were found to be amenable to post-synthetic amidation, esterification, and thioesterification reactions. Such transformations have been well-developed in terms of reactivity, yield, compatibility, and separation to offer fast and clean products, especially in solid-state peptide synthesis. As such, it holds promise as a mild and effective toolbox for introduction of complex payloads onto COFs. To demonstrate the versatility of this approach, a series of chelating functionalities were successfully introduced into the framework. Such modification is incompatible with copper-assisted click reactions due to the strong chelating ability of these payloads. The resulting frameworks can serve as efficient adsorbents of various contaminants for water treatment.

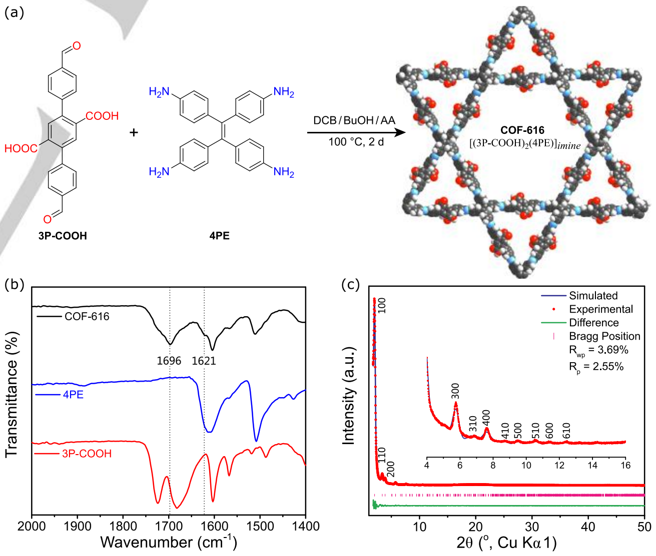

Figure 1. (a) Synthetic scheme of COF-616. Color code: H, white; C, gray; N, blue; O, red. (b) FT-IR spectra of COF-616 and comparison to the starting materials 4PE and 3P-COOH, respectively. (c) PXRD pattern and Pawley refinement of COF-616.

COF-616 was synthesized from *p*-terphenyl-2',5'-dicarboxylic acid-4,4''-dicarboxaldehyde (3P-COOH) and 1,1,2,2-tetraphenylethene (4PE) under solvothermal reaction conditions in a mixture of 1,2-dichlorobenzene (DCB) and butanol (BuOH) using glacial acetic acid as a catalyst (Figure 1a). The reaction mixture was sealed in a Pyrex tube and heated at 100 °C for 2 days. COF-616 was obtained by filtration as a yellow microcrystalline powder, which was found to be insoluble

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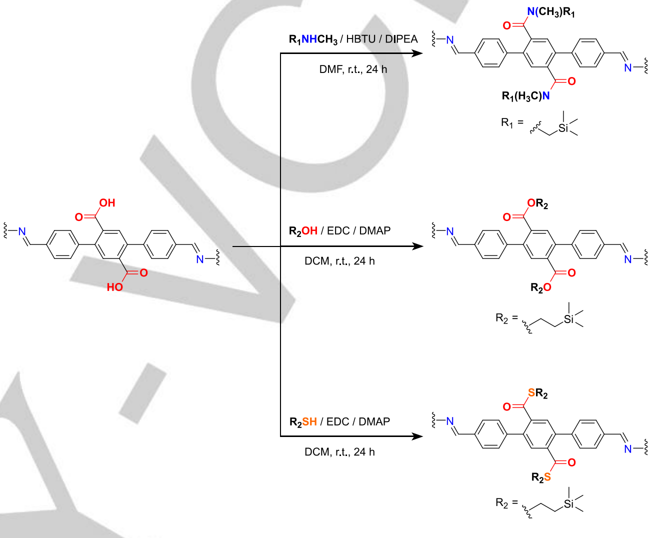
10.1002/anie.201912579

in common organic solvents such as alcohols, acetone, dichloromethane, tetrahydrofuran, N,N-dimethylformamide (DMF), and N-methyl-2-pyrrolidione. The completeness of the reaction was confirmed by Fourier-transform infrared (FT-IR) spectroscopy, with appearance of a characteristic absorbance of imine stretch at 1621 cm^{-1} and disappearance of both the characteristic absorbance of aldehyde stretch at 1682 cm^{-1} and amine stretch at 3500-3150 cm^{-1} (Figure 1b and S1). The carbonyl stretching band of the carboxylic acid functional groups is red-shifted from 1723 cm^{-1} in the starting material 3P-COOH to 1696 cm^{-1} in COF-616, which is consistent with what is observed for the molecular analogue (Figure S2). The thermal stability of COF-616 was evaluated by thermogravimetric analysis, where no significant weight loss was observed until 310 °C under N_2 atmosphere (Figure S28). The chemical formula of activated COF-616 was determined by elemental analysis and was found to be consistent with the expected elemental composition (Calcd. for $C_{35}H_{24}N_2O_4.H_2O$: C, 75.80%; H, 4.73%; N, 5.06%; O, 14.42%. Found: C, 74.18%; H, 5.11%; N, 5.25%; O, 15.46%).

Scanning electron microscopy (SEM) images of COF-616 showed that all particles displayed a homogeneous morphology, consisting of aggregated flake-shaped crystals (Figure S29). The crystallinity of COF-616 was confirmed by powder X-ray diffraction (PXRD) and the framework was found to crystallize in the hexagonal space group *P*6 (Figure 1c). Pawley refinement yielded unit cell parameters of a = b = 55.038(56) Å, and c = 3.930(21) Å with good agreement factors (R_p = 2.55 % and R_{wp} = 3.69 %).

With the highly crystalline carboxyl-functionalized COF-616 in hand, we sought to demonstrate the first example of converting carboxyl groups on COF backbones into amides through activation followed by nucleophilic substitution reactions. Amide coupling on COF-616 was performed using uronium salts as coupling reagents.[19–21] While primary amines are not compatible for this post-synthetic modification due to off-pathway transimination reactions with the linkages of the framework,[22] secondary amines are great candidates to append organic moieties onto COFs and therefore *N*-methyl-1-(trimethylsilyl)methanamine was selected as a model compound (Scheme 1). To carry out the post-synthetic amidation, COF-616 was added to a solution of *N*-methyl-1-(trimethylsilyl)methanamine, hexafluorophosphate benzotriazole tetramethyl uronium (HBTU), and *N,N*-diisopropylethylamine (DIPEA) in DMF and the mixture was allowed to react at room temperature for 24 h. The amidated product, COF-616-CON(CH_3)R_1 [R_1 = (trimethylsilyl)methyl], was obtained by filtration, washed with an excess of DMF, followed by hot anhydrous methanol in a Soxhlet extractor, and eventually evacuated under dynamic vacuum. Near-quantitative conversion (95%) of carboxyl groups to amides was confirmed by the appearance of characteristic peaks (δ = -0.09 ppm for trimethylsilyl group) in the ^{1}H NMR spectrum of the digested sample (Figure 2a and S10). High-performance liquid chromatography (HPLC) analysis of the digested sample of COF-616-CON(CH_3)R_1 confirmed that building block 3P-COOH was converted to 3P-CON(CH_3)R_1 (Figure S18). This was further supported by FT-IR spectra, where the modified product exhibited the emergence of a characteristic absorbance of C=O amide stretch (1648 cm^{-1}) and the disappearance of absorbance of C=O carboxyl stretch (1696 cm^{-1}) of the carboxylic acid precursor (Figure 2b). On top of this, the PXRD pattern and SEM micrographs demonstrated that COF-616-CON(CH_3)R_1 retained its crystallinity throughout the post-synthetic modification process (Figure 2c and S29).



Scheme 1. Post-synthetic amidation, esterification, and thioesterification of COF-616.

The protocol for post-synthetic amide coupling was further adapted to Steglich esterification and thioesterification reactions by changing to a stronger coupling reagent, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC). Post-synthetic modifications to yield COF-616-COOR_2 and COF-616-COSR_2 [R_2 = 2-(trimethylsilyl)ethyl] were investigated as model reactions: these functionalities were incorporated from the respective alcohol or thiol in the presence of EDC·HCl as the coupling reagent and 4-dimethylaminopyridine (DMAP) as an activator (Scheme 1). The modification can be carried out in various solvents, among which dichloromethane provided the highest yields (74% and 63%, respectively) as confirmed by ^{1}H NMR spectroscopy and HPLC analysis of the digested sample (Figure 2a, S11, S12, and S18). Similarly, conversion of the carboxylic acid was corroborated by FT-IR spectroscopy (Figure 2b), and the crystallinity and morphology of resulted modified products was well-preserved during the modification (Figure 2c and S29).

Encouraged by the synthetic ease of these post-synthetic modifications, we aimed at demonstrating that COF-616 can serve as a versatile functionalizable platform that can be readily modified by any functionalities that would be highly challenging, if not impossible, to be introduced using existing protocols. Various chelating functional groups were selected to be incorporated into COF-616. Specifically, post-synthetic amidation using *N,N*-bis(2-((2-(ethylthio)ethyl)thio)ethyl)amine

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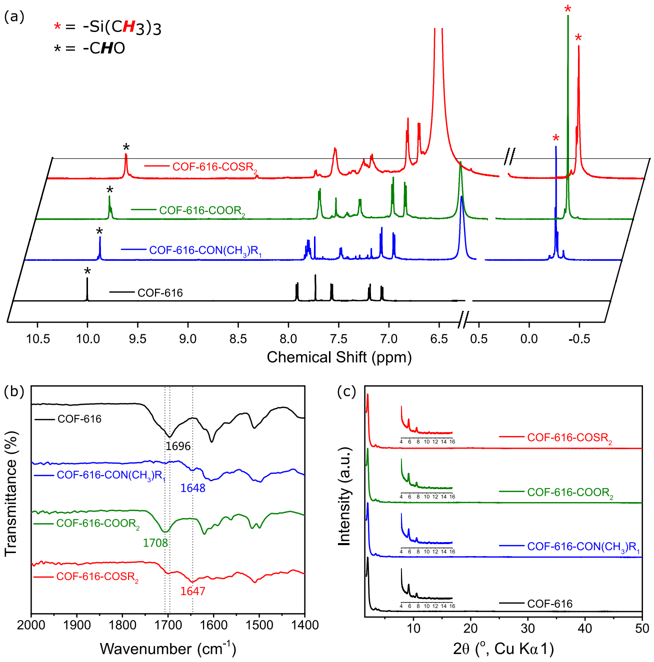

Figure 2. (a) ^{1}H NMR spectra of the digested samples, (b) FT-IR spectra, and (c) PXRD patterns of COF-616-CON(CH_3)R_1, COF-616-COOR$_2$, and COF-616-COSR$_2$, respectively.

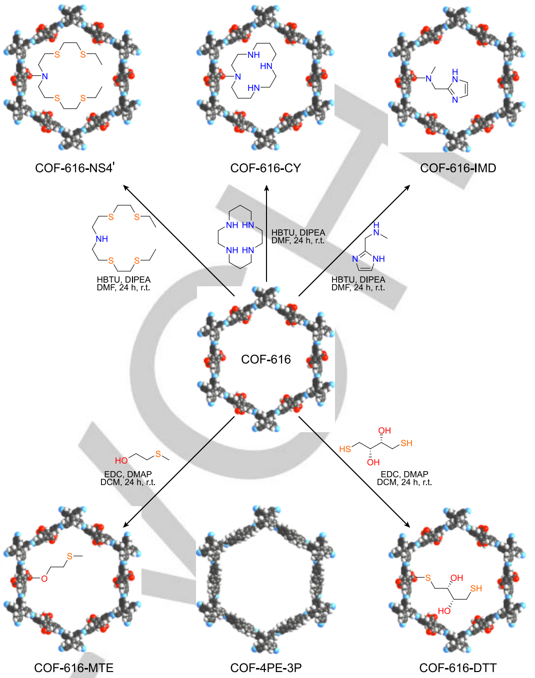

Figure 3. Synthesis of COF-616-NS4', COF-616-CY, COF-616-IMD, COF-616-MTE, and COF-616-DTT by post-synthetic modification of carboxyl-functionalized COF-616, along with illustration of the unfunctionalized COF-4PE-3P.

(NS4'), cyclam (CY), and 1-(1H-imidazol-2-yl)-*N*-methylmethanamine (IMD), post-synthetic esterification using 2-(methythio)ethanol (MTE), and post-synthetic thioesterification to introduce dithiothreitol (DTT) yielded the functionalized frameworks COF-616-NS4', COF-616-CY, COF-IMD, COF-616-MTE, and COF-616-DTT, respectively (Figure 3). The successful incorporation of the functionalities was confirmed by FT-IR spectroscopy, ^{1}H NMR spectra of the digested samples (Figure S4-8 and S13-17), and elemental analysis. The crystallinity of the materials remained intact throughout the modification as confirmed by PXRD and SEM micrographs (Figure S22 and S29).

With the high density of chelating groups anchored onto the backbone of the framework, modified COF-616 family can be directly utilized to remove heavy metal ions in water. The performance of this series of functionalized COFs (COF-616, COF-616-NS4', COF-616-CY, COF-616-IMD, COF-616-MTE, and COF-616-DTT) as well as the unfunctionalized COF-4PE-3P[23,24] were assayed for the uptake of metal ions (K^+, Ca^{2+}, Pb^{2+}, Hg^{2+}, Cu^{2+}, Zn^{2+}, and Ni^{2+}) from water (Figure 4a). While the thiol groups of COF-616-DTT outperformed other chelators due to their superior soft Lewis basicity,[18,25,26] nitrogen-rich chelators also showed appreciable adsorption of heavy metal ions (*i.e.*, COF-616-CY for removal of Pb^{2+}, Cu^{2+}, Zn^{2+}, and Ni^{2+}, and COF-616-IMD for removal of Hg^{2+}), thus providing a viable alternative for designing heavy metal ions adsorbents. The varying uptake capacities and selectivities towards heavy metal ions with different chelating groups (Figure S32) illustrate the importance of screening and optimizing the performance of a given framework by appending a library of functional groups through facile post-synthetic modification.

COF-616 adsorbents family can also be employed for water treatment in terms of removal of residual oxidants from water cleanup and disinfection, soil remediation, or food processing.[27–29] However, residual oxidants from these processes are harmful to aquatic life and can generate disinfection byproducts that can be bio-accumulated in food chains.[30] Current practice to remove such strong oxidants requires large amounts of soluble reductants, the dose of which is hard to administer.[31] This inevitably introduces unnecessary secondary inorganic pollutants into the effluent.[32] In this regard, heterogeneous oxidant adsorbents can provide a more environmentally-friendly alternative. Towards this end, aqueous solutions of most commonly used oxidants with a concentration of 100 ppm were treated with COF-616-series adsorbents, and the residual oxidant species concentration was detected colorimetrically (Figure 4b).[33] Sulfur-functionalized COFs (*i.e.* COF-616-NS4', COF-616-MTE, and COF-616-DTT) showed higher redox reactivity with the oxidants owing to the propensity of thiols and thioethers towards oxidation. In particular, functionalization with DTT yielded the highest removal efficiency among all functionalized COFs and COF-616-DTT was able to effectively remove sodium hypochlorite in as little as 5 min at room temperature with [COF] of 200 mg L^{-1}. This result collectively suggests that COF-616 platform can be tailored for targeted water treatment applications. To close, this work provides a starting point for modular, high-throughput, and application-directed development of functionalized COFs in an efficient manner.

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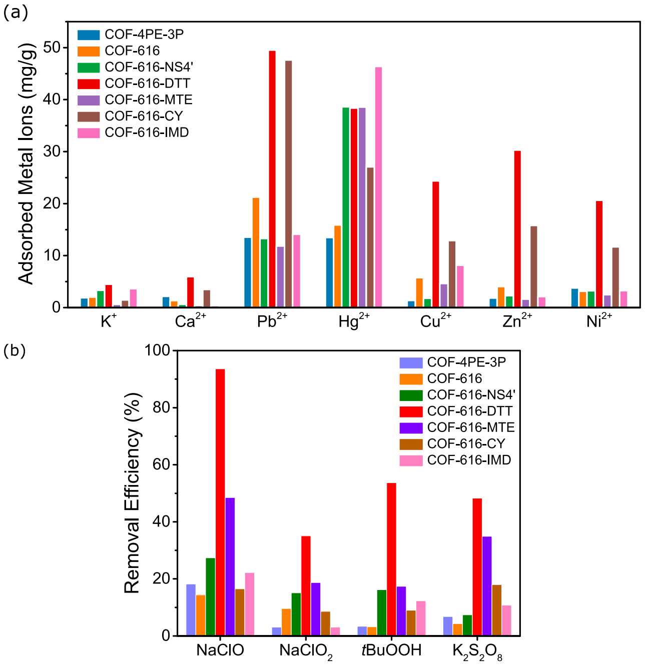

Figure 4. Metal ions adsorption measurement (a) and removal efficiency of residual oxidant (b) with COF-4PE-3P, COF-616 and its post-synthetically modified products.

Acknowledgements

Synthesis in this work was supported by King Abdulaziz City for Science and Technology (Center of Excellence for Nanomaterials and Clean Energy Applications). We acknowledge Dr. C. Zhu for the help with wide-angle X-ray scattering measurement, the Catalysis Facility of Lawrence Berkeley National Laboratory, supported by the Office of Science of the US Department of Energy under contract No. DE-AC02-05CH11231, for the help with gas adsorption experiments, and College of Chemistry's NMR facility for resources provided and the staff for their assistance, where instruments are supported in part by NIH S10OD024998.

Keywords: carboxylic acids • conjugation • covalent organic frameworks • post-synthetic modification • water treatment

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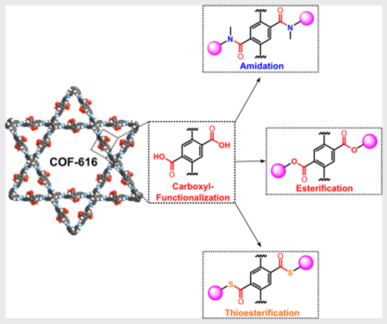
A novel highly crystalline two-dimensional covalent organic framework (COF) bearing pre-installed carboxyl groups is reported. The carboxylic acids enable facile post-synthetic modification by amidation, esterification, and thioesterification for introduction of virtually any functionality to the framework.



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