Covalent surface modification of a metal-organic framework: Selective surface engineering via Cu^I-catalyzed Huisgen cycloaddition

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Materials. All chemicals were used as received from commercial sources unless otherwise noted. Dichlorobis(triphenylphosphine)palladium and copper iodide were purchased from Strem Chemicals. Tetrahydrofuran and *N,N'*-dimethylformamide were purchased from Fisher Scientific. 3-Bromo-4-pyridine-carboxaldehyde, potassium *tert*-butoxide, trimethylsilylacetylene, triethylamine, zinc nitrate hexahydrate, 2,6-naphthalenedicarboxylic acid (NDC), tetrabutylammonium fluoride (TBAF), ethidium bromide monoazide ($\mathbf{E_{azide}}$), *O*-(2-aminoethyl)-*O'*-(2-azidoethyl)nonaethylene glycol ($\mathbf{PEG_{azide}}$), tris[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl]amine (TBTA), sodium ascorbate, copper(II) sulfate pentahydrate, dichloromethane, ethyl acetate, hexanes, and ethanol were purchased from Aldrich Chemicals. Triethylamine was distilled under nitrogen over potassium hydroxide and kept under nitrogen in a Straus flask.

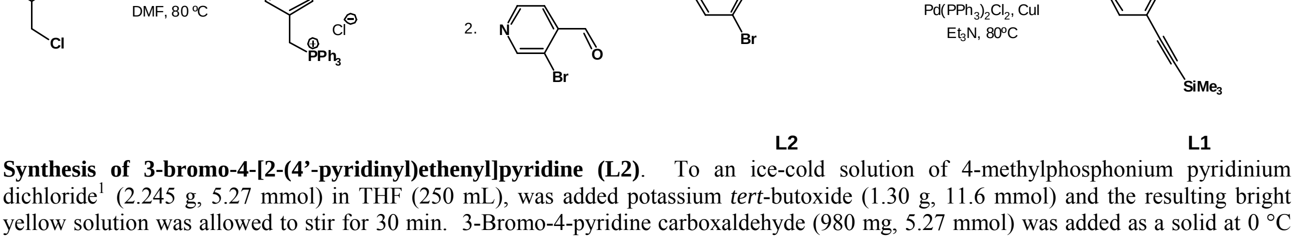
Characterization. Contact-angle and confocal microscopy experiments were carried out in the Geiger and O'Halloran laboratories at NU. Other characterization was performed in the IMSERC facilities at NU.

^1H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA 500 NMR spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C). NMR chemical shifts were reported in ppm against residual solvent resonance as the internal standard ($\delta(CHCl_3)$ = 7.27 ppm (^1H), 77.2 ppm (^{13}C). ^1H NMR data were reported as follows: chemical shift (multiplicity (s = singlet, d = doublet), integration, assignment).

Gas Chromatography-Mass Spectrometry (GC-MS) analyses were performed on a Hewlett-Packard 6890 GC interfaced to a HP 5972 Mass Selective Detector Quadrupole Mass Spectrometer. Matrix-assisted laser desorption mass spectrometry was performed on a PE Voyager DE-Pro MALDI-TOF mass spectrometer in positive, reflector ionization mode, using 2-hydroxy-1-naphthoic acid as a matrix. For PEG-containing samples, where the signal intensity is generally low, the MALDI-TOF experiments were carried out in linear mode, with α-cyano-4-hydroxycinammic acid matrix. Inductively coupled plasma (ICP) spectroscopy was conducted on a Varian model ICP spectrometer equipped to cover the spectral range from 175 to 785 nm. Samples (3-5 mg) were digested in concentrated H_2SO_4: 30%H_2O_2 (3:1 v/v) by being heated at 120°C until the solution became clear, diluted to 5% in deionized (DI) H_2O, and analyzed for Si (λ = 185.005 nm) and Zn (λ = 206.200nm) content. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA) after drying samples under vacuum at 100ºC overnight.

Contact-angle measurements are performed using an FTA 125 Contact Angle Analyzer (First Ten Ångstroms, Portsmouth, VA). The sessile volume of the water droplet was 4 - 7 μL, and the contact angle was calculated using the FTA software (value reported is the average of four measurements). All fluorescence microscopy images were obtained using a Zeiss AxioPhot epifluorescence microscope (Carl Zeiss Inc., GmbH, Jena, Germany) equipped with fluorescein isothiocyanate (FITC) and tetramethyl rhodamine isocyanate filter sets and a Zeiss AxioCam camera for image acquisition. Confocal microscopy imaging was performed using two-photon excitation (TPE) laser scanning microscopy on a Zeiss 510 LSM (upright configuration) equipped with a 63x oil-immersion objective (Carl Zeiss, Inc.). The sample was excited using an argon laser source at 488 nm and emission was collected with a KP 685 filter that passes wavelengths less than 685 nm to the detector. Sectioning images were obtained at 3-μm intervals.

Synthetic Procedures



L2 **L1**

Synthesis of 3-bromo-4-[2-(4'-pyridinyl)ethenyl]pyridine (L2). To an ice-cold solution of 4-methylphosphonium pyridinium dichloride[1] (2.245 g, 5.27 mmol) in THF (250 mL), was added potassium *tert*-butoxide (1.30 g, 11.6 mmol) and the resulting bright yellow solution was allowed to stir for 30 min. 3-Bromo-4-pyridine carboxaldehyde (980 mg, 5.27 mmol) was added as a solid at 0 °C and the resulting solution was stirred overnight at room temperature. After removing the solvent under reduced pressure, the solid was dissolved in CH_2Cl_2 (200 mL). The solution was washed with aqueous $NaHCO_3$ (2 x 100 mL) and H_2O (2 x 100 mL), dried over $MgSO_4$, and evaporated to dryness using a rotary evaporator. The collected solid was purified by flash column chromatography on silica gel, using a 56-mm inner diameter column containing 250 cm^3 of silica gel under a positive pressure of lab air, with dichloromethane:acetone (7:3 v/v) as eluent. The collected fractions were analyzed using TLC; the fractions that showed a single spot with R_f = 0.42 were combined and evaporated to dryness to give a white solid (1.180 g, 86%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H, Ar*H*), 8.45 (d, 2H, *J* = 5 Hz, Ar*H*), 8.29 (d, 1H, *J* = 5 Hz, Ar*H*), 6.98 (d, 2H, *J* = 5 Hz, Ar*H*), 6.96 (d, 1H, *J* = 5 Hz, Ar*H*), 6.76 (d, 2H, *J* = 12 Hz, C*H*), 6.29 (d, 1H, *J* = 12 Hz, C*H*). ^{13}CNMR (500 MHz, $CDCl_3$): δ 152.7, 150.3, 149.3, 144.8, 143.5, 131.8, 130.8, 124.9, 123.5, 122.1. GC-MS(EI): m/z (%) 260 (100, $[M]^+$), 262 (100).

Synthesis of 3-[(trimethylsilyl)ethynyl]-4-[2-(4'-pyridinyl)ethenyl]pyridine (L1). Inside a nitrogen-filled drybox, a 30-mL glass vial equipped with a Teflon-coated magnetic stir bar was charged with $PdCl_2(PPh_3)_2$ (56 mg, 2 mol%), CuI (40 mg, 5 mol%), and **L2** (1.044 g, 4 mmol). Triethylamine (10 mL) and trimethylsilylacetylene (570 µL, 4.02 mmol) were then added to start the reaction, and the vial was capped with a gas-tight screw cap. Next, the vial was taken out of the drybox, and the reaction vial was then covered up with aluminum foil and allowed to stir at 80 °C in a heated aluminum block for 2 h, over which time the reaction became darker in color. Upon completion, triethylamine was removed under reduced pressure, and the remaining solid was completely dissolved in a minimal amount of CH_2Cl_2. The collected solid was purified by flash column chromatography on neutral alumina gel, using a 56-mm inner diameter column containing 250 cm^3 of alumina under a positive pressure of lab air, with hexanes:ethyl acetate (7:3 v/v) as eluent. The collected fractions were analyzed using neutral alumina TLC; the fractions that showed a single spot with $R_f = 0.25$ were combined and evaporated to dryness to give a pale yellow solid (745 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H, Ar*H*), 8.68 (d, 2H, *J* = 5 Hz, Ar*H*), 8.55 (d, 1H, *J* = 5 Hz, Ar*H*), 7.07 (d, 2H, *J* = 5 Hz, Ar*H*), 6.98 (d, 1H, *J* = 5 Hz, Ar*H*), 6.90 (d, 2H, *J* = 12.5 Hz, C*H*), 6.76 (d, 1H, *J* = 12.5 Hz, C*H*), 0.34 (s, 9H, C*H*$_3$). ^{13}CNMR (500 MHz, $CDCl_3$): δ 154.0, 150.0, 148.5, 146.0, 144.2, 132.4, 132.3, 132.2, 131.7, 130.3, 104.2, 103.7, 0.1. MALDI-TOF: m/z 278.9 $[M+H^+]$, 279.9, 280.9.

Synthesis of MOF 1. $Zn(NO_3)_2{\cdot}6H_2O$ (0.05 mL of a 100 mM solution in DMF, 5 µmol), **L1** (0.1 mL of a 50-mM solution in DMF, 5 µmol), and NDC (0.1 mL of a 50 mM solution in DMF, 5 µmol) were combined in a 4-mL glass vial. The vial was capped and placed in a sonicating bath until all solid was uniformly dispersed (~ 1 min). The reaction vial then was placed in an oven and heated at 80 ˚C for 1 day. Pale yellow crystals (1.2 mg, 57%) of the product were collected by filtration and washed with DMF (~ 4 x 1 mL). EA: Calculated for evacuated **1** ($C_{26}H_{16}O_4N_2Zn$): (%) C, 58.51; H, 4.07; N, 3.33. Found: C, 58.46; H, 3.81; N, 3.27. To obtain large quantities of MOF **1**, several vials were set up in parallel and combined prior to work up.

General procedure for the surface modification of 1. MOF **1** (25 mg) was weighed into a 1.5-mL polypropylene centrifuge tube, to which TBAF (1 mL of a 0.02 M solution in THF/water (95:5 v/v)) was added. The reaction mixture was agitated via continuous inversion of the reaction tube overnight. The tube was then centrifuged, the supernatant removed, and the MOF resolvated with DMF (1 mL). After six cycles of agitation (1 h each) in fresh DMF (1 mL), followed by centrifugation and decantation of supernatant, the "click" components were added to the remaining MOF solid in the tube as solutions in DMF: organic azide (50 µL of a 50 mM solution, 2.5 µmol), TBTA (50 µL of a 50 mM solution, 2.5 µmol), $CuSO_4$ (50 µL of a 50 mM solution, 2.5 µmol) and sodium ascorbate (50 µL of a 50 mM solution, 2.5 µmol). The tube was capped and the reaction mixture was agitated overnight via continuous inversion of the reaction tube. In the morning, the MOF was collected via centrifugation and subjected through 12 cycles of shaking (1 h each) with fresh DMF (1 mL), followed by centrifugation and decantation of the supernatant. The collected modified MOF was air-dried for a few hours.

In the synthesis of $\mathbf{1_{PEG}}$, the PEGylated MOF was further purified via dialysis to remove any physisorbed $\mathbf{PEG_{azide}}$. The isolated MOF was suspended in a small amount of DI water and transferred into a-500 µL Spectra/Por RC dialysis bag (10,000 MWCO, Spectrum Laboratories), and dialyzed over 4 days in a 500-mL Erlenmeyer flask of DI water containing Amberlyst-15 resins (~15 g, Rohm & Haas, used as received). Dialysis was followed by centrifugation, decantation of the supernatant, and collection of the modified MOF, which was then air-dried overnight before subsequent analysis.

Determination of the extent of surface modification of with ethidium bromide monoazide. In the $\mathbf{E_{azide}}$ modification, solid $\mathbf{E_{azide}}$ (2.5 mg) and DMF (100 µL) was combined to make a DMF solution that is approximately 50 mM in concentration. To determine the absolute concentration of this solution (57 mM), a 20-µL aliquot of it was then diluted to 100 mL with DMF in a volumetric flask and analyzed by UV-Vis spectroscopy. A 50-µL aliquot of this 57-mM solution (2.8 µmol of $\mathbf{E_{azide}}$) was then used for the reaction with MOF **1** (28 mg, 33 µmol) in the same manner as described above. After reaction, the supernatant solution, and subsequent rinses, were combined and diluted up to 500 mL with DMF in a volumetric flask. The concentration of this post- reaction solution was determined by UV-Vis spectroscopy to be 5.15 µM, giving a total of 2.57 µmol of remaining dye. The difference between starting and remaining dye was calculated to be 0.27 µmol, or ~0.8 mol% of the starting BPE ligands (Table S1 and Figure S1).

Table S1. Calculations to determine extent of reaction between $\mathbf{E_{azide}}$ and MOF **1**.

Before		**After**	
V (mL)	100	**V (mL)**	500
$\mathbf{A_{462nm}}$	0.06145	$\mathbf{A_{462nm}}$	0.02779
L (cm)	1	**L (cm)**	1
ε ($\mathbf{M^{-1}cm^{-1}}$)	5400	**ε ($\mathbf{M^{-1}cm^{-1}}$)**	5400
C of 100 mL (M)	1.138×10^{-5}	**C of 500 mL (M)**	5.146×10^{-6}
C of 20 µL (M)	0.0569		
Mol in 50 µL	2.845×10^{-6}	**Mol in 500 mL**	2.573×10^{-6}

Mol difference of $\mathbf{E_{azide}}$	2.721×10^{-7}
Mass of MOF (mg)	25
FW of MOF	842.62
Mol of MOF	3.323×10^{-5}
Mol % MOF reacted	0.82

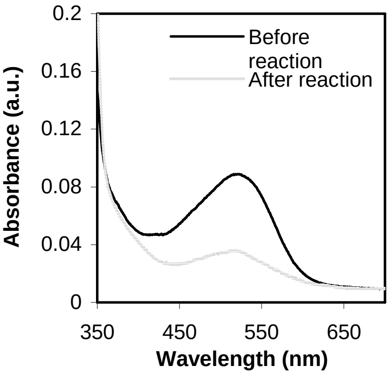


Fig S1. The UV spectra of $\mathbf{E_{azide}}$ solutions before and after reaction with MOF **1**.

MALDI-TOF sample preparation. A small sample of the MOF (~1 mg) was transferred into a 0.5-mL polypropylene Eppendorf Safe-Lock microtube. Approximately 0.1 mL of pyridine was added to the tube, which was capped and sonicated for 15 minutes. The supernatant solution was then spotted onto a MALDI plate, which was left in a fume hood until all the pyridine had evaporated. A saturated solution of the MALDI matrix in acetone was then spotted on top of the dissolved MOF spot and also allowed to dry in the fume hood prior to analysis.

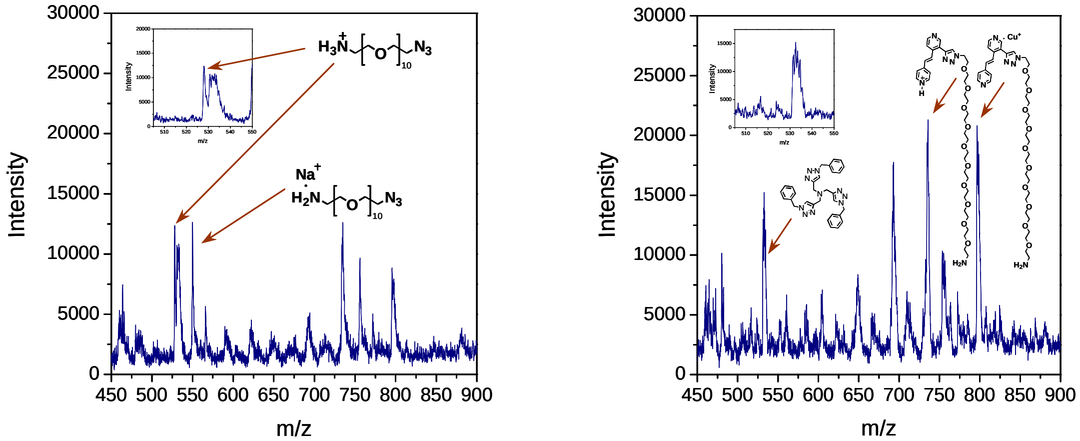


Fig. S2. The linear-mode MALDI-TOF spectra of dissolved 1_{PEG}, before (left) and after (right) extensive dialysis, showing the PEGylated products of the click reaction. The insets are expansions of the region m/z =505 to 550. The free $[PEG_{azide} + H]^+$ (m/z = 528) is conspicuously absent in the spectrum of the dialyzed 1_{PEG}, suggesting that the dialysis protocol have removed all physisorbed PEG_{azide}. The ligand for "click" chemistry, TBTA, is present in both spectra at m/z = 531.

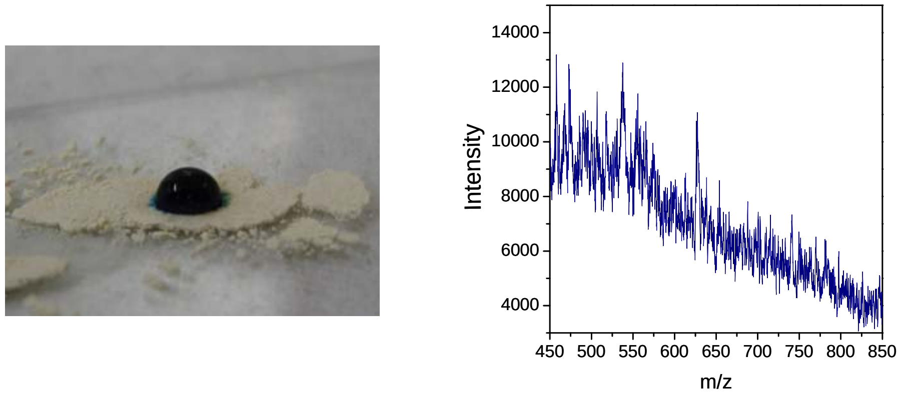


Fig. S3. Wettability test of a sample of **1** that has been exposed to $\mathbf{PEG_{azide}}$ for 24 h. After extensive dialysis to remove physisorbed $\mathbf{PEG_{azide}}$ and drying, this sample still repels a drop of blue-colored water (left panel), albeit to a lesser extent than **1** (Fig. 3). The contact angle of the water droplet is 97(4)°, slightly less that that observed for a powder sample of **1**. This slight decrease in hydrophobicity may partially be attributed to the highly imprecise nature of the contact-angle measurements of powder samples—no attempt was made to ensure that the samples were packed in the same manner, density, surface smoothness. Because contact-angle experiments for powder samples are largely qualitative due to the macroscopic roughness of samples and the penetration of water into the spaces between particles,[2] these measurements only determine whether or not our materials are wettable. While there was no evidence of physisorbed $\mathbf{PEG_{azide}}$ in the MALDI-TOF mass spectrum of a dissolved sample of this material (right panel), we still can't completely rule this out due to the generally low sensitivity of PEGylated compounds in MALDI-TOF analysis.

Water stability of 1 and $\mathbf{1_{PEG}}$. Samples of MOF (10 mg) were transferred to NMR tubes and D_2O (1 mL) was added to each tube. The tubes were axially shaken continuously for 3 weeks, after which NMR spectra were collected. To the extent that NMR spectroscopy can detect organic carboxylates in D_2O, no trace of the NDC ligand was observed. The NMR solutions were filtered, and diluted up to 5 mL with deionized water in a volumetric flask. These solutions were then subjected to ICP analysis, showing very little lost of the Zn corners (Table S2). Together, these data suggest that our MOFs are quite stable to water.

Table S2. ICP-MS data of the aqueous filtrates collected from long exposures of MOFs **1** and $\mathbf{1_{PEG}}$ to D_2O.

	ppm Zn	**Net Zn in 5 mL (mg)**	**Zn in sample (mg)**	**% Zn lost**
$\mathbf{D_2O}$	0.024			
1	1.204	0.0059	1.55	0.30
$\mathbf{1_{PEG}}$	0.831	0.0040	1.55	0.26

Crystal Characterization

Single-crystal X-ray structure determination. Single crystals were mounted on a Bruker SMART APEX II CCD diffractometer equipped with a graphite-monochromated MoKα (λ = 0.71073 Å) radiation source in a cold nitrogen stream at 100(2) K. See the CIF file for **1**, available as a separate file of this ESI, for details of the structure solution.

Powder X-ray diffraction (PXRD). Powder X-ray diffraction patterns (Figure S4) were recorded on a Rigaku XDS 2000 diffractometer using nickel-filtered Cu Kα radiation (λ = 1.5418 Å) over a range of $5° < 2\theta < 40°$ in 0.1° steps with a 1-s counting time per step. Simulations were made based on the single-crystal data using the Mercury software.

"As-synthesized" and "resolvated" samples were collected from the bottom of the reaction vial (or tube) as a thick suspension in DMF and spread on a fritted glass slide immediately before PXRD measurements. Given the high boiling point of DMF, the crystals never dry out during the PXRD measurement.

The evacuated samples were prepared by drying the as-synthesized samples in a vacuum oven at 100 °C (~ 25 inches of Hg) overnight. The resulting powder samples were then mounted on clear cellophane tape and PXRD data were collected immediately after mounting.

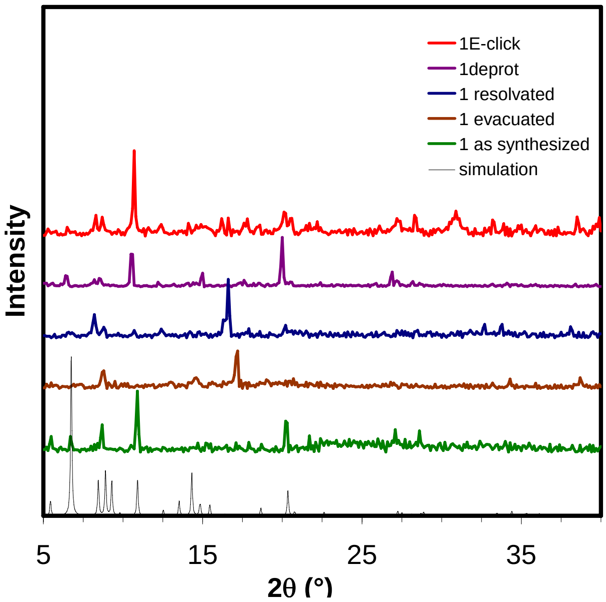


Fig. S4. Powder X-ray diffraction patterns for MOF **1**, $\mathbf{1}_{\mathbf{deprot}}$, and $\mathbf{1}_{\mathbf{E\text{-}click}}$.

Thermogravimetric analysis. Thermal gravimetric analysis (Figure S5) was performed on a Mettler Toledo TGA/SDTA851 interfaced with a PC using Star software. Samples were heated at a rate of 10 °C/min under a nitrogen atmosphere.

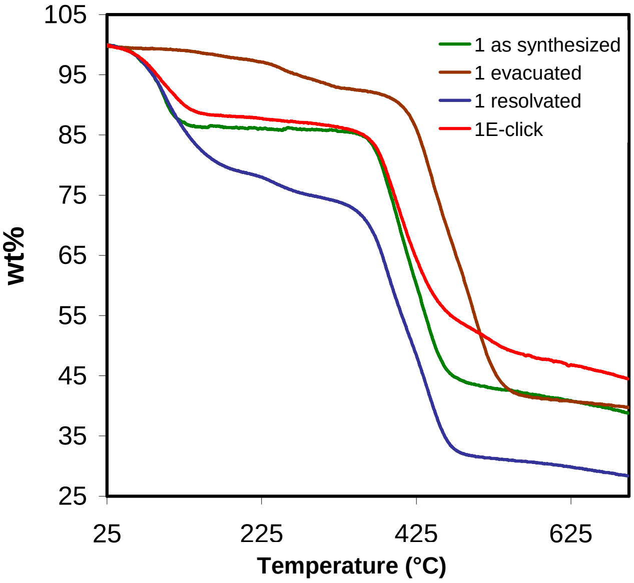


Fig. S5. TGA curves for MOF **1** and $\mathbf{1}_{\mathbf{E\text{-}click}}$.

N_2 uptake and desorption. Nitrogen adsorption/desorption isotherms were measured volumetrically at 77 K in the range $8.0 \times 10^{-6} \leq P/P_o \leq 1.0$ using an Autosorb 1 instrument (Quantachrome Instruments) equipped with the ASWin software package. Ultra-high purity N_2 (99.999%) was purchased from Airgas Inc. and used as received. Prior to measurement, all samples were outgassed at 100 °C at the outgas port of the Autosorb 1. Surface areas were calculated by applying Brunauer-Emmet-Teller (BET) theory over the linear region of the isotherm ($0.007 \leq P/P_o \leq 0.11$). Pore size distributions were calculated by applying the Horvath-Kawazoe (HK) method over the full range of the isotherms shown below.

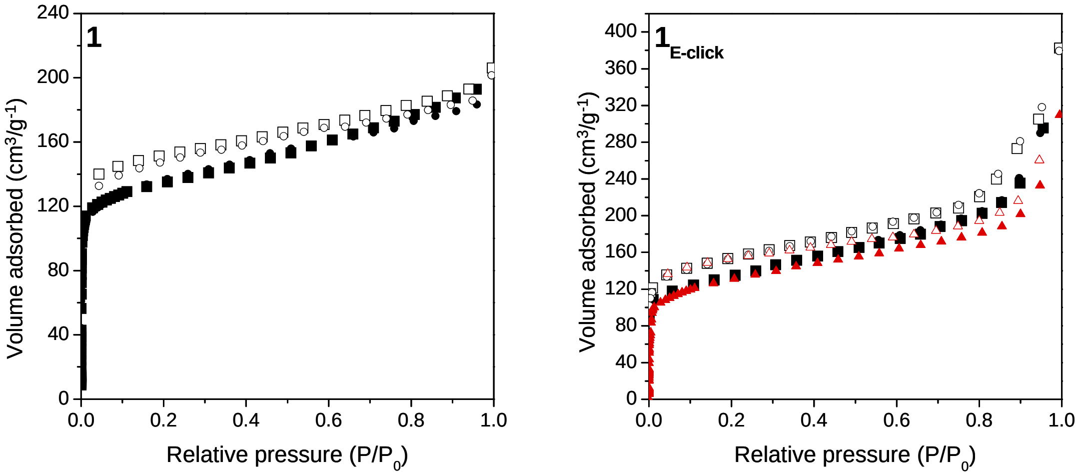


Fig. S6. N_2 adsorption (closed), and desorption (open) isotherms for **1** and $\mathbf{1_{E\text{-}click}}$. For **1**, two different runs were carried out on the same sample. For $\mathbf{1_{E\text{-}click}}$ two separate samples were analyzed, only one of them in duplicate (circles and squares). These data suggest that our BET instruments have good reproducibility, and differences are most likely due to variations in samples.

References

1. B. R. Baker and M. H. Doll, *J. Med. Chem.*, 1971, **14**, 793-799.
2. M. Lazghab, K. Saleh, I. Pezron, P. Guigon and L. Komunjer, *Powder. Tech.*, 2005, **157**, 79-91.