

Biomimetic Synthesis of Sub-20 nm Covalent Organic Frameworks in Water

Original

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Biomimetic synthesis of sub-20 nanometer Covalent Organic Frameworks in water

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4 375
6 38 **Abstract**

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8 39 Covalent organic frameworks (COFs) are commonly synthesized under harsh conditions yielding
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10 40 unprocessable powders. Control in their crystallization process and growth has been limited to
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12 41 studies conducted in hazardous organic solvents. Herein, we report a one-pot synthetic method that
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14 42 yields stable aqueous colloidal solutions of sub-20 nm crystalline imine-based COF particles at
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16 43 room temperature and ambient pressure. Additionally, through the combination of experimental
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18 44 and computational studies, we investigated the mechanisms and forces underlying the formation of
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20 45 such imine-based COF colloids in water. Further, we show that our method can be used to process
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22 46 the colloidal solution into 2D and 3D COF shapes, as well as to generate a COF ink that can be
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24 47 directly printed onto surfaces. These findings should open new vistas in COF chemistry enabling
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26 48 new application areas.
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33 50 **Introduction**

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35 51 Covalent organic frameworks (COFs) are porous crystalline materials generated from organic
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37 52 molecules linked via reversible covalent bonds.¹ Since its discovery, COF chemistry has facilitated
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39 53 a modular construction of periodic crystalline matter by connecting molecular subunits in a
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41 54 predictable and modular fashion.² This strategy has proved efficient in generating extended
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43 55 crystalline and porous networks possessing permanent porosity, high specific surface areas and
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45 56 excellent thermal/chemical stability; features that have found potential applications in a vast
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47 57 number of fields.³ However, conventional routes for COF synthesis involve high temperatures,
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49 58 which when combined with the low solubility of the initial building blocks in common reaction
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51 59 media, yield poor control over the size of the crystalline domains and the morphology of COF
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53 60 crystals.⁴ Unsurprisingly, such drawbacks have hampered the extraction of reliable information
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4 61 regarding the effects of crystallite size and morphology on COF properties. Accordingly, much
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6 62 effort is now focused on both understanding and controlling the growth of COF crystals at length
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8 63 scales spanning the nanometer to micron scales.

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11 64 Recently, Dichtel and co-workers reported on the preparation of stable particles of boronate ester-
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14 65 linked COFs, whose size can be modulated between 40 and hundreds of nanometers by using
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16 66 mixtures of organic solvents at high temperature.⁵ Later, such COFs colloidal solutions in organic
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18 67 media have been used by the same authors for preparing micron-sized single crystals of boronate
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21 68 ester-linked COFs via a seeded growth procedure.⁶ Therefore, having access to nanometer-sized
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23 69 particles of COFs allowed the authors to overcome a long-standing challenge in the field, i.e. the
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25 70 formation of large single crystals of COFs. Besides this specific example, COF crystal-downsizing
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28 71 will be key to transforming COFs from unprocessable crystalline powders into processable
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30 72 materials, integrating COFs into nanoscale devices,⁷ as well as establishing relationships between
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32 73 COF crystal size and properties. In addition, COF crystal downsizing will expand the range of
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34 74 applications of these materials, such as in the biomedical, device and printing arenas,⁸ and enhance
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36 75 their bioavailability.⁹ However, only nanoparticles of boronate ester-linked COFs in organic
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39 76 solvents have been reported so far.⁵ Unfortunately, boron-based COFs have poor chemical
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41 77 stabilities, which limits their practical implementation. In addition, the fact that hazardous organic
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43 78 solvents are still required as a medium to stabilize their colloidal dispersion precludes their use in
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45 79 biological environments. In contrast, imine-based COFs are significantly more stable and robust
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48 80 for practical use.¹⁰ Nevertheless, despite the high number of reports on imine-based COFs, it has
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50 81 not been possible yet to downsize them to the nanoscale.¹¹ Put simply, routes for producing aqueous
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52 82 colloidal solutions of imine-linked COF nanoparticles are still missing.

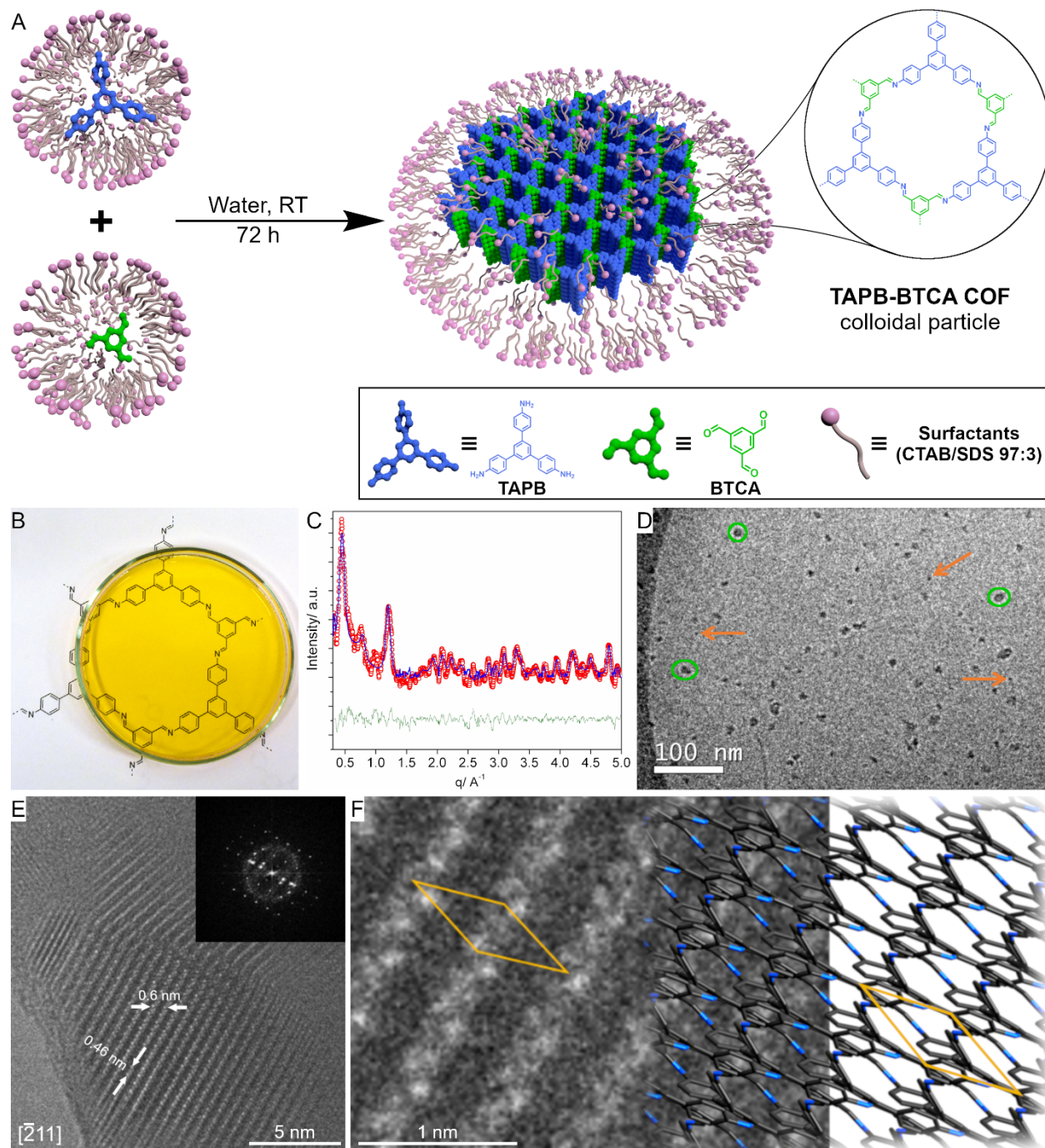
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4 83 To overcome this limitation, we report here an efficient one-pot method to generate stable and
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6 84 homogeneous colloidal solutions of sub-20 nanometer imine-linked COF particles in water. The
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8 85 synthesis of crystalline COF colloids was performed for the first time at room temperature using
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10 86 micelles as reaction nanocompartments. This approach was inspired by living systems that make
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12 87 use of confined volumes (such as intracellular compartments) to control crystallization processes
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14 88 in aqueous media.^{12–16} This method allowed us to use a combination of experimental scattering
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16 89 techniques in solution, that together with computational calculations, gave unprecedented insights
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18 90 into the mechanism and forces underlying the formation of imine-linked COFs. Additionally, we
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20 91 show that the produced colloids enable the processing of COFs into 2D and 3D shapes such as
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22 92 crystalline freestanding films and monoliths. Further, we prove that such colloids can also be used
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24 93 as inks to directly print COFs onto surfaces. Finally, we demonstrated the generality of our method
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26 94 by applying it to the synthesis of metal-organic frameworks (MOFs) colloids. In particular, we
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28 95 show the synthesis of 20 nanometer MIL-100(Fe) particles at room temperature and ambient
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30 96 pressure. MIL-100(Fe) is a prototypical MOF that requires harsh conditions for its synthesis¹⁷ and
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32 97 only forms larger crystals.¹⁸ We expect that the presented methodology will vastly increase
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34 98 knowledge on structure-property correlations in COFs and MOFs, allowing access to a large
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36 99 number of new applications and functions, whilst significantly enhancing the bioavailability and
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38 100 processability of these materials.
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46 101 **Results**

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48 102 **TAPB-BTCA COF** is typically obtained via imine condensation between 1,3,5-tris(4-
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50 103 aminophenyl)benzene (**TAPB**) and 1,3,5-triformylbenzene (**BTCA**) in *meta*-cresol or DMSO.
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52 104 Additionally, acetic acid is used as a catalyst to yield **TAPB-BTCA COF** as an insoluble and
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54 105 unprocessable crystalline powder.¹⁹ Herein, we employed the *catanionic* micellar system^{20,21}
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4 106 formed from a mixture of cationic hexadecyltrimethylammonium bromide (CTAB) and anionic
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6 107 sodium dodecyl sulfate (SDS) surfactants (CTAB/SDS 97:3) to generate stable colloidal solutions
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8 108 of crystalline **TAPB-BTCA COF** nanoparticles in water (**Fig. 1A**). Note that this surfactant ratio
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10 109 guarantees the formation of small mixed micelles in the *catanionic* mixture, instead of bigger
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12 110 vesicles as previously reported,²⁰ and here it was optimized to achieve the smallest size of
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14 111 **colloidally stable TAPB-BTCA COF** nanoparticles (**Fig. S1**). The micellar medium allows the
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16 112 solubilization in water of the otherwise insoluble molecular building blocks **BTCA** and **TAPB** at
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18 113 room temperature, yielding two homogeneous solutions of the reactants loaded into CTAB/SDS
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20 114 mixed micelles.²² After mixing the solutions and adding acetic acid, the reaction mixture turned
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22 115 orange, indicating the formation of imine bonds characteristic of **TAPB-BTCA COF** growth.
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24 116 However, and in contrast to observations in standard synthetic protocols, the reaction mixture
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26 117 remained clear and homogeneous with no apparent precipitation (**Fig. 1B**), even after storage at
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28 118 room temperature for **six** months. Indeed, when irradiated with a laser ($\lambda = 630$ nm), the reaction
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30 119 mixture clearly exhibited Willis–Tyndall scattering behavior,²³ confirming the presence of
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32 120 colloidal particles (**Fig. S2**). To validate the existence of crystalline **TAPB-BTCA COF**
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34 121 nanoparticles in the reaction mixture, synchrotron X-ray diffraction measurements were performed
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36 122 directly on the colloidal solution generated after mixing. The experimental differential diffraction
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38 123 data were fitted using the Le Bail method^{24,25} against the reported structural model for **TAPB-**
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40 124 **BTCA COF** (*P3*, $a \sim 15.91$ Å and $c \sim 3.54$ Å as refined cell parameters) (**Fig. 1C**), demonstrating
41
42 125 the presence of the crystalline COF phase with a main low-angle peak centered **at $q = 0.46$ Å⁻¹**
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44 126 associated with the (100) Bragg reflection.¹⁹ Accordingly, this result unambiguously confirmed the
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46 127 formation of crystalline **TAPB-BTCA COF** nanoparticles via the mixed micelle method. The sizes
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48 128 and morphology of the obtained **TAPB-BTCA COF** nanoparticles were subsequently studied by
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50 129 dynamic light scattering (DLS) and cryogenic transmission electron microscopy (cryo-TEM). DLS
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4 130 measurements conducted on the reaction mixture after 24 hours (**Fig. S3A**) reported a
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6 131 monodisperse distribution of scatterers centred at 16 nm. Remarkably, the colloidal behaviour of
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8 132 the reaction mixture remains stable and homogeneous (with no appreciable turbidity or size
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10 133 increase) for periods in excess of six months (**Fig. S3B**). Additionally, cryo-TEM images of the
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12 134 reaction mixture after 24 hours (**Fig. 1D**) showed two different populations of objects; one centred
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14 135 at 5 ± 1 nm and the other at 16 ± 1 nm in diameter. The former value correlated well with the size of
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16 136 surfactant micelles determined by small-angle X-ray scattering (SAXS) in the pure CTAB/SDS
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18 137 (97:3) mixture (see below and **Fig. S4**), with the latter comparing well with the size distribution
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20 138 measured by DLS, and thus being ascribed to **TAPB-BTCA COF** nanoparticles. The high-
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22 139 resolution transmission electron microscopy (HR-TEM) study of drop cast reaction mixtures
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24 140 further confirmed the crystallinity of **TAPB-BTCA COF** nanoparticles. **Fig. 1E** shows a
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26 141 characteristic HRTEM image and its corresponding Fast Fourier Transform (FFT). The measured
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28 142 periodicities (white arrows in **Fig. 1E**) match well with the unit cell geometry of **TAPB-BTCA**
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30 143 **COF** as viewed along the $[-211]$ zone axis. **Fig. 1F** presents a magnified detail of the above HR-
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32 144 TEM image overlapped with the simulated crystal structure of **TAPB-BTCA COF** viewed along
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34 145 the $[-211]$ zone axis, suggesting a good match between the light and dark fringes of the micrograph
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36 146 and the higher and lower atomic density regions of the COF structure. Additionally, scanning
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38 147 electron microscopy (SEM) images of drop cast reaction mixtures revealed the presence of well-
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40 148 defined and uniform nanoparticles (and nanoparticle clusters), with a size that correlates well with
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42 149 both DLS and cryo-TEM measurements (**Fig. S1A**).



150
151 **Fig. 1. TAPB-BTCA COF nanoparticles.** (A) Schematic representation of the synthesis of colloidal TAPB-BTCA
152 COF nanoparticles in water. (B) Photograph of the transparent reaction mixture. (C) Synchrotron X-ray differential
153 diffraction data of the reaction mixture containing TAPB-BTCA COF nanoparticles. Experimental differential data
154 obtained after subtracting the data corresponding to the solvent mixture to that collected on reaction mixture containing
155 TAPB-BTCA COF nanoparticles are shown in red, with the calculated fit using $P3$, $a \sim 15.91 \text{ \AA}$ and $c \sim 3.54 \text{ \AA}$ as
156 refined cell parameters in blue and associated residuals in green with R_p and R_{wp} values of 16.3 % and 13.7 %.

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4 157 **respectively.** (D) Cryo-TEM image of **TAPB-BTCA COF** colloid. For clarity, some **TAPB-BTCA COF**
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6 158 nanoparticles are outlined in green and some micelles are indicated by orange arrows. (E) HR-TEM image of a **TAPB-**
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8 159 **BTCA COF** nanoparticle along the [-211] zone axis, with the inset showing the FFT. (F) Magnified HR-TEM image
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10 160 of a defined area in (E) overlaid with the schematic structural model of **TAPB-BTCA COF** along the [-211] projection.
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14 162 After confirming that sub-20 nanometer **TAPB-BTCA COF** particles can be generated, we
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16 163 investigated the possibility of isolating the COF material as a bulk solid. To this purpose, we added
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18 164 ethanol to the reaction mixture to destabilize the surfactant aggregates,²⁶ which triggered the
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20 165 flocculation of **TAPB-BTCA COF** nanoparticles as an insoluble yellow powder, hereafter termed
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22 166 **TAPB-BTCA COF(s)**. After flocculation, **TAPB-BTCA COF(s)** could be simply isolated from
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24 167 the reaction mixture by centrifugation. **TAPB-BTCA COF(s)** was characterized by Fourier-
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26 168 transform infrared (FT-IR) spectroscopy and solid-state Cross Polarization/Magic Angle Spinning
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28 169 Nuclear Magnetic Resonance (¹³C CP-MAS NMR). FT-IR spectra confirmed the presence of imine
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30 170 bonds through the appearance of the characteristic imine C=N stretching band at 1623 cm⁻¹ (**Fig.**
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32 171 **S5**), while solid state ¹³C CP-MAS NMR spectra exhibited the representative signal of the imine
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34 172 carbon atom at 157.1 ppm (**Fig. S6**). Additionally, powder X-ray diffraction (PXRD) patterns of
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36 173 **TAPB-BTCA COF(s)** (**Fig. S7**) were in excellent accordance with those previously reported for
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38 174 this material.¹⁹ It should be noted that the measured PXRD peaks were broader than those usually
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40 175 observed for **TAPB-BTCA COF(s)** prepared by conventional bulk synthetic methods,¹¹
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42 176 suggesting the presence of smaller crystalline domains in **TAPB-BTCA COF(s)**.²⁷ The permanent
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44 177 porosity of **TAPB-BTCA COF(s)** was also confirmed by nitrogen adsorption isotherm
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46 178 measurements on previously activated samples, showing a characteristic isotherm with a Brunauer–
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48 179 Emmet–Teller (BET) area (A_{BET}) of 687 m² g⁻¹ at 77 K (**Fig. S8**). Finally, the CO₂ and water
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50 180 sorption properties of **TAPB-BTCA COF(s)** were also measured (**Fig. S9** and **S10**). It was found
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4 181 to be porous to CO₂ with a total uptake of 9 mmol g⁻¹ at 203 K and 760 torr (1 mmol g⁻¹ at 298 K
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6 182 and 760 torr). Moreover, water-vapour sorption isotherms showed a step between 40-50% relative
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8 183 humidity, after which the water uptake increases monotonically until a maximum of 15% in mass
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10 184 (0.15 g_{water} g_{COF}⁻¹), which is the typical behaviour for this class of materials bearing hydrophobic
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13 185 walls.¹¹
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16 186 To clarify the processes underlying the formation of **TAPB-BTCA COF** nanoparticles in the
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18 187 *catanionic* micellar medium, time-resolved *in-situ* DLS and SAXS experiments were performed.
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21 188 DLS indicated that the average hydrodynamic diameter of colloidal particles increased during the
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23 189 first few hours (after the addition of acetic acid), leveling off to yield a final average hydrodynamic
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25 190 diameter of 16 nm (**Fig. S11**). In contrast, when the synthesis was performed in pure CTAB
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27 191 micelles (*i.e.* without SDS), the size of **TAPB-BTCA COF** continued to increase until precipitation
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29 192 occurred. Accordingly, the role of the anionic surfactant was clearly evidenced, with SDS reducing
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32 193 the electrostatic repulsion of CTAB heads in the micellar aggregates (*i.e.* decreasing the surface
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34 194 energy), and favoring the formation of assemblies with lower curvatures.^{21,28} This is demonstrated
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37 195 by the increase in size of the nanoparticles when increasing the amount of SDS in the CTAB/SDS
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39 196 mixture (**Table S1**). In addition, the decrease in curvature caused by SDS facilitates the colloidal
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41 197 stabilization of COF oligomers and of the final **TAPB-BTCA COF** nanoparticles even over
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43 198 extended periods of time. Time-resolved SAXS experiments provided further insights into the
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46 199 growth mechanism of **TAPB-BTCA COF** nanoparticles. SAXS spectra of the two micellar
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48 200 solutions containing the **TAPB** and **BTCA** precursors (in the presence of acetic acid) indicated the
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50 201 existence of 4.8 ± 2 nm diameter ellipsoidal micelles; comparable to what it was observed in pure
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53 202 CTAB/SDS (97:3) solutions (**Fig. S4**). These data indicate that solubilization of COF precursors
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55 203 has a negligible effect on the size and shape of the CTAB/SDS micellar aggregates. However, after
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4 204 mixing the two micellar solutions loaded with COF precursors, clear changes in the SAXS profiles
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6 205 were observed as a function of time. Scattering profiles at selected reaction times (5, 13, and 21
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8 206 hours) are shown in **Fig. 2**, along with their best fits obtained from the used scattering model
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10 207 (further details are provided in Supplementary Materials). These three SAXS spectra describe three
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12 208 different regimes during the progress of the reaction (**Fig. 2A-C** and **Fig. S12**). At short reaction
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14 209 times (5 hours in **Fig. 2A**), SAXS profiles fit well to a disk-particle model with a radius of 6.4 nm
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16 210 and a thickness of 0.354 nm, which corresponds to a single layer of bare **TAPB-BTCA COF** (**Fig.**
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18 211 **S13A** and **Table S2**). As the reaction proceeded (13 hours in **Fig. 2B**), SAXS data showed a
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20 212 significant increase in intensity at low values of the scattering vector ($q < 1 \text{ nm}^{-1}$), together with
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22 213 the appearance of a broad feature around 2 nm^{-1} , suggesting changes of electron density contrast
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24 214 (further discussion on the particle models used for the analysis of the SAXS data, including details
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26 215 of the fitting procedure are provided in the Supplementary Materials).²⁹ This spectrum could then
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28 216 be better fitted to a COF-core@double-shell disk model, with a core thickness of 0.91 nm
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30 217 corresponding to a three-layered **TAPB-BTCA COF** stack surrounded by surfactant molecules
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32 218 (**Fig. S13B** and **Table S2**). At longer reaction times (21 hours in **Fig. 2C**), the SAXS profile showed
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34 219 a marked change at $q < 1 \text{ nm}^{-1}$, with a clear slope variation at 0.5 nm^{-1} . This spectrum could also
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36 220 be described using a COF-core@double-shell disk model, but with a core radius of 8.9 nm and a
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38 221 thickness of 3.74 nm (**Fig. S13B** and **Table S2**). This thickness corresponds to ten-layered **TAPB-**
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40 222 **BTCA COF** stacks fully covered by surfactant. Importantly, these extracted values were in good
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42 223 agreement with the overall size of the colloidal particles as measured by DLS and cryo-TEM. It
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44 224 should be noted that the formation of a compact surfactant layer around the COF nanoparticles is
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46 225 crucial for their stabilization in the reaction mixture, preventing further growth and flocculation.
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48 226 Accordingly, SAXS data suggest that after an initial phase of lateral growth by covalent
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50 227 polymerization, the increase in size of **TAPB-BTCA COF** nanoparticles is essentially driven by
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the π - π stacking of COF layers (**Table S2**). Coarse grained molecular dynamics (CG-MD) simulations of single-, three- and ten-layered **TAPB-BTCA COF** particles were performed to gain further insight into the forces driving the self-assembly process. The simulations were run in water as well as hexadecane to simulate the hydrophobic environment of the micellar interior (see **Supplementary Materials** for further details about the CG model and simulations).

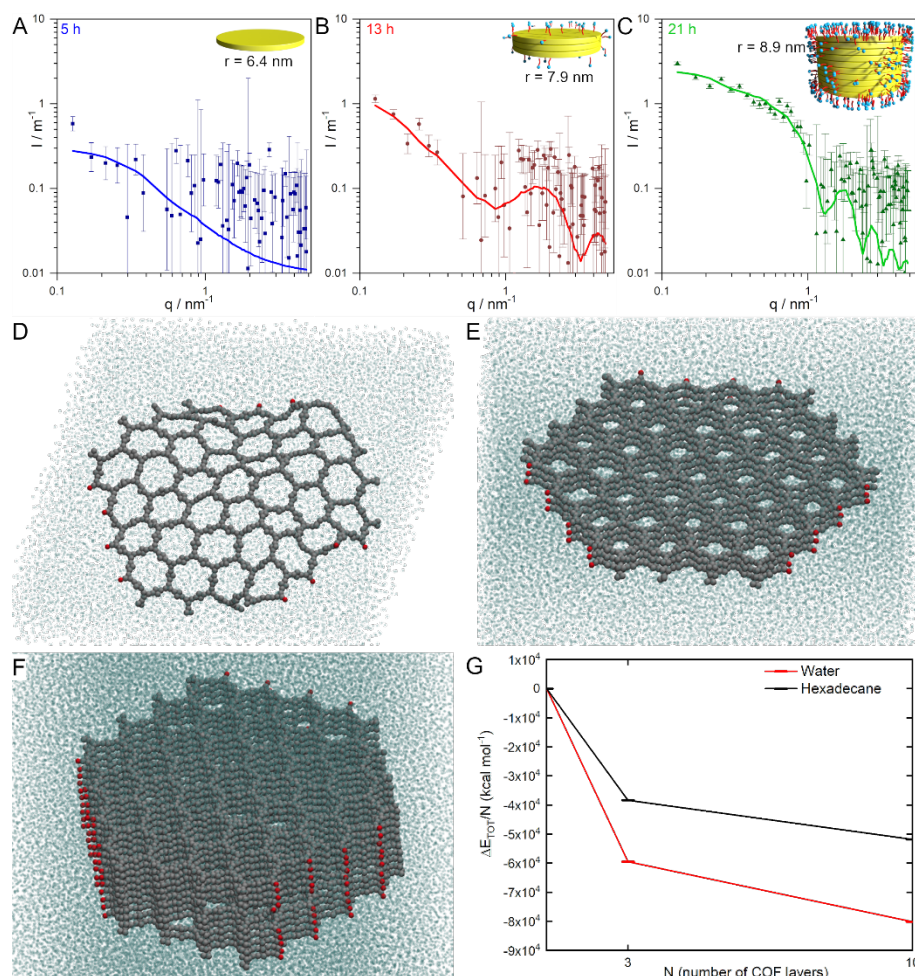


Fig. 2. Growth of TAPB-BTCA COF nanoparticles. (A), (B) and (C) SAXS spectra of the reaction mixture at 5, 13 and 21 hours, respectively. Experimental data (symbols) and best fits to the used scattering model (line). The insets illustrate the species measured at the three different regimes, with yellow disks representing the **TAPB-BTCA COF** core, red cylinders the hydrophobic tails of the surfactants, and blue spheres their polar heads. (D), (E) and (F) Snapshots of **TAPB-BTCA COF** assemblies comprising 1, 3 and 10 layers respectively, after CG-MD simulation in water. **(G) Total interaction energy (sum of solute-solute + solute-solvent + solvent-solvent interaction terms) between**

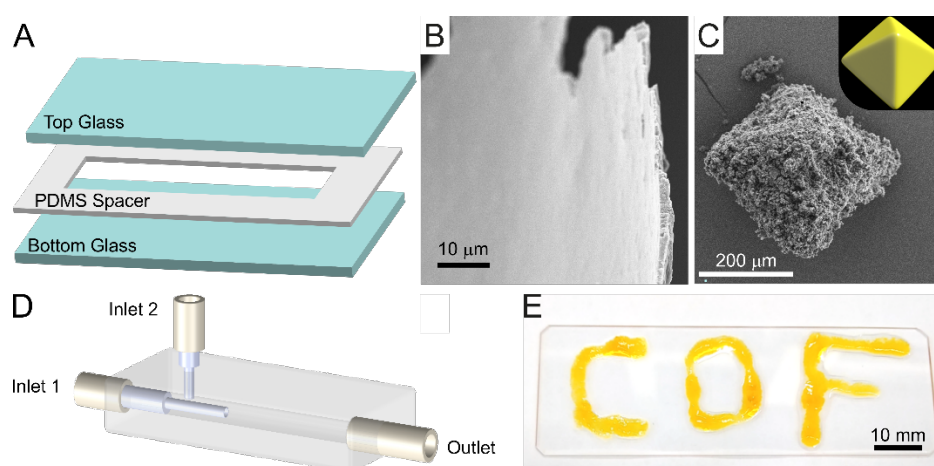
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4 240 the COF layers normalized per-COF layer, $\Delta E_{\text{COF}/N}$, calculated from the MD simulations of TAPB-BTCA COF
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6 241 assemblies in water (red) and hexadecane (black). Energy of a single layer set to 0 as reference in the plot. The $\Delta E_{\text{COF}/N}$
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8 242 becomes more and more favorable while the number of layers in the COF stacking increases, that is an evidence of
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10 243 cooperativity.

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14 245 **Fig. 2 D-F** present snapshots of the equilibrated assemblies in water (see **Fig. S14** for the associated
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16 246 simulations in hexadecane). Simulations confirmed the strong cooperativity in the interaction
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18 247 between COF layers in both solvents, where the total interaction energy per-COF layer ($\Delta E_{\text{COF}/N}$:
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20 248 accounting for solute-solute + solute-solvent + solvent-solvent interactions) becomes more and
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22 249 more favorable for the three and ten-layered **TAPB-BTCA COF** particles. Comparing the two
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24 250 cases, the aggregation is found stronger and more cooperative in water than in hexadecane (**Fig.**
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26 251 **2G**, total energetic gain per-COF layer), suggesting that the self-assembly and stacking of the COF
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28 252 layers is globally more stabilized in water (higher cooperativity) compared to hexadecane (lower
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30 253 cooperativity). However, when considering only the solute-solute contribution in this analysis, the
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32 254 data extracted from the simulations show that the cooperativity, although always present, is rather
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34 255 similar in the two cases (**Fig. S15**). Altogether, these results indicate that the additional driving
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36 256 force that makes the aggregation more cooperative in water than in hexadecane can be imputed to
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38 257 solvent effects. The more the COF layers interact between them, the less these interact with solvent
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40 258 molecules, which interact more between them. The fact that this leads to a greater advantage in
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42 259 water is consistent with the hydrophobic nature of the COF layers. In other words, the driving force
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44 260 for aggregation predominantly arises due to an increase in the water-water interactions upon COF
45
46 261 aggregation, that is a signature of the hydrophobic effect. In addition, MD simulations reveal a
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48 262 higher flexibility of the COF single-layer, which deformed significantly during the simulations
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50 263 (e.g. **Fig. 2D** and **Fig. S14**) compared to the stacked systems (**Fig. 2E-F**). These data also explain

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4 264 the greater tendency of surfactant molecules to interact with thicker assemblies (as measured by
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6 265 SAXS), since rigid COF stacks have more extended hydrophobic patches (e.g. pore walls) than
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8 266 rippled single-layers.
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11
12 267 In addition to the importance of obtaining colloidal solutions of sub-20 nanometer COF particles
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14 268 in water, the described methodology also offers new opportunities for particle processing. Indeed,
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16 269 until now, a major limitation for the further implementation of COFs outside of laboratory
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18 270 environments has been their unprocessable nature.³⁰ Here, we show that by controlling the
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20
21 271 flocculation and aggregation of **TAPB-BTCA COF** nanoparticles in the reaction mixture (through
22
23 272 the addition of ethanol), 2D and 3D **TAPB-BTCA COF** shapes could be easily achieved. For
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25 273 example, films of **TAPB-BTCA COF(s)** on the millimeter scale were prepared by confining a
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28 274 concentrated reaction mixture into a home-made microengineered clamp (**Fig. 3A**), followed by
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30 275 evaporation of the solvent. The concentrated reaction mixture was prepared by exchanging water
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32 276 for ethanol (further details are provided in the Supplementary Materials). **We observed that highly**
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34
35 277 **uniform freestanding films with controlled thickness in the range of 0.5 to 50 μm were efficiently**
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37 278 **obtained via this approach (**Fig. 3B** and **Fig. S16-17**).** Alternatively, reducing the size of the home-
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39 279 made microengineered clamp to squares of 500 μm lateral size or even changing its 2D shape to
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41
42 280 3D morphologies led to the generation of smaller **TAPB-BTCA COF(s)** films (**Fig. S18**) or 3D
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44 281 octahedrons (**Fig. 3C** and Supplementary Materials). SEM analysis of these structures showed a
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46 282 nanoparticulated texture similar to the one observed for **TAPB-BTCA COF(s)** (**Fig. S19**). These
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48 283 data indicate that the processing steps allowed **TAPB-BTCA COF(s)** to be shaped into 2D and 3D
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51 284 morphologies, with negligible reductions in the integrity of the COF material. Additionally, PXRD
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53 285 patterns of these structures were identical to those previously reported in the literature for this COF
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55 286 (**Fig. S20A**). Interestingly, the controlled diffusion of ethanol to the reaction mixture through a 3D
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4 287 flow-focusing microfluidic device allowed us to generate a processable COF ink from the initial
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6 288 colloidal solution. Indeed, the laminar flow conditions operating within such a device provided
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8 289 control over the flocculation and aggregation of **TAPB-BTCA COF** nanoparticles (**Fig. 3D**).
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10 290 Accordingly, a direct printing of **TAPB-BTCA COF(s)** onto surfaces was possible through the
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12 291 tubing connected to the outlet of the microfluidic device (**Fig. 3E** and **Video S1**). PXRD analysis
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14 292 of the printed structures confirmed that **TAPB-BTCA COF(s)** was deposited (**Fig. S20B**).



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34 294 **Fig. 3. Processability of the reaction mixture.** (A) Schematic illustration of the home-made microengineered clamp
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36 295 used to generate **TAPB-BTCA COF(s)** films. (B) SEM image of the cross-section of a freestanding mm-sized film
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38 296 obtained using the setup shown in (A). (C) SEM image of a **TAPB-BTCA COF(s)** octahedron (500 μm edge). (D)
39
40 297 Schematic illustration of the continuous 3D flow-focusing microfluidic device used to print **TAPB-BTCA COF(s)**.
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42 298 The reaction mixture was directly injected through inlet 1, while ethanol was introduced via inlet 2. (E) Photograph of
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44 299 "COF" printed with **TAPB-BTCA COF** on a planar surface using the device shown in (D).

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46 300
47
48 301 To demonstrate the generality of our method, we prepared another imine-based COF, namely **Tz-**
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50 302 **COF**³¹ via the reaction of 2,4,6-tris(4-aminophenyl)-1,3,5-triazine and **BTCA** in a CTAB/SDS
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52 303 (97:3) mixture. SEM, DLS, and PXRD analysis clearly confirmed the formation of **Tz-COF**
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54 304 particles with a size distribution centered around 20 nm (**Fig. S21-S24**).³² Permanent porosity was
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56 305 measured using BET analysis, with results agreeing with previously reported values for the same
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4 306 COF material (**Fig. S25**).³³ Finally, it is significant to note that our method can be extended to
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6 307 MOFs. To demonstrate such generality, we synthesized a prototypical MOF that requires harsh
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8 308 conditions to crystalize, *i.e.* **MIL-100(Fe)**¹⁷. *In-situ* synchrotron X-ray diffraction measurements
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10 309 of the homogenous reaction mixture clearly confirmed the formation of **MIL-100(Fe)** (**Fig. S26**).
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12 310 Furthermore, DLS measurements of drop-cast reaction mixtures indicated a particle size
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14 311 distribution centered around 20 nm (**Fig. S27**). To the best of our knowledge, this is the smallest
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16 312 size reported for this biodegradable and non-toxic MOF.³⁴ After flocculation of the colloid with
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18 313 ethanol, PXRD and BET analysis of the resulting powder additionally confirmed the formation of
19
20 314 **MIL-100(Fe)**, (**Fig. S28** and **Fig. S29**, respectively). Surprisingly, and in spite of the nanometer
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22 315 size of the generated **MIL-100(Fe)** particles, the measured BET surface area was high (1068 m²g⁻
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24 316 ¹).

30 317 **Conclusion**

31
32 318 In summary, we have demonstrated a mild procedure for the preparation of stable aqueous colloidal
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34 319 solutions of crystalline imine-linked COF nanoparticles assisted by micelles of a *catanionic*
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36 320 surfactant mixture. The micellar medium provides control over the growth of the COF crystallites,
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38 321 which allowed us to reach the smallest size for COF particles among those reported so far.
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40 322 Additionally, by a combination of experimental and computational studies, we were able to shed
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42 323 light into the mechanism and forces underlying the growth of such COF colloids. Note that this
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44 324 mechanistic study is unprecedented for imine-based COFs. Remarkably, the colloidal nature of the
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46 325 formed imine-based COF nanoparticles enabled their processing into 2D and 3D shapes, as well as
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48 326 the generation of an ink for their direct printing onto surfaces. Finally, to demonstrate the generality
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50 327 of our method we extended it to the preparation of colloidal nanoparticles of other porous
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52 328 crystalline materials, such as MOFs. We foresee that the preparation of chemically stable and easily
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4 329 processable imine-based COF colloids will open the door to new applications of these materials,
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6 330 for example in the field of functional devices, due to improved integration possibilities, or
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8 331 biomedicine, thanks to improved bioavailability.
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10
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13
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17
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29
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31
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37 343 **Competing interests:** A patent related to the work presented in this document has been filed.
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39 344 **Data and materials availability:** All data needed to evaluate the conclusions in the article is
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41 345 present in the main text and supplementary materials.
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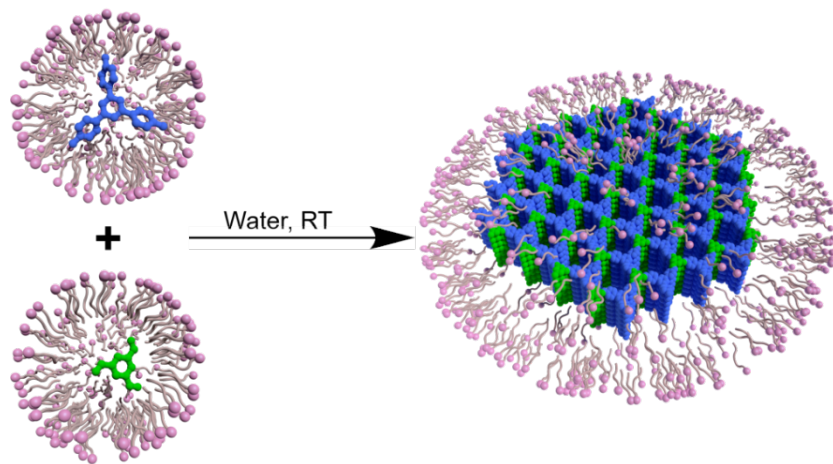
45 346 **Supplementary Materials:** Materials and Methods; Supplementary Text; Figures S1-S33;
46
47 347 Tables S1, S2; Movie S1.
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