Photochemical & Photobiological Sciences

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Photochem. Photobiol. Sci.*, 2019, **18**, 2849

Received 24th September 2019,
Accepted 14th October 2019

DOI: 10.1039/c9pp00392d

rsc.li/pps

On-demand guest release from MOF-5 sealed with nitrophenylacetic acid photocapping groups†

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Recently, we demonstrated that triphenylacetic acid could be used to seal dye molecules within MOF-5, but guest release required the digestion of the framework by treatment with acid. We prepared the sterically bulky photocapping group [bis-(3-nitro-benzyl)-amino]-(3-nitro-phenyl)-acetic acid (PC1) that can prevent crystal violet dye diffusion from inside MOF-5 until removed by photolysis.

Storage and transport of sensitive, volatile and reactive materials poses a significant challenge in a broad range of chemical research fields.[1,2] The blending of large void spaces and high surface areas impart metal organic frameworks (MOFs) with attractive properties for engineering storage systems for gases such as H_2[2,3] and CO_2.[4,5] Trapping these gases, however, requires the MOFs to be contained within pressure vessels,[6] so the primary benefits derive from van der Waals forces that increase the density of gas within the storage volume. Alternatively, intermolecular forces such as electrostatic interactions,[7,8] hydrogen bonding,[9,10] and π–π stacking[11,12] can impart additional stabilization between MOFs and larger guests such as dye molecules; however, guests can leach out when the concentration gradient changes.[13–15]

MOFs can also be conscripted for drug delivery, but storing and releasing therapeutic payloads in a constructive manner is limited by the same host–guest interactions. With weaker interactions, drug molecules leach from MOF pores passively, which might be exploited for gradual delivery, but could also squander valuable pharmaceuticals with premature release.[15–17] With strong interactions, drug molecules might be released more slowly than the rate of MOF excretion from the body.[18–20]

The desired equilibrium between encapsulation and liberation might be achievable by manipulating the intermolecular forces between MOFs and guests, but a triggered release mechanism would impart the necessary control for MOFs to be used more universally as delivery vehicles. Additive chelators have been used to control MOF crystal size,[21–23] but fewer examples of MOFs with rationally modified surfaces exist. Post-synthetic MOF surface modifications have been used to introduce fluorescent monolayers[24] and induce the aggregation of crystals,[25] but the potential to trap guests in pores had not been explored until recently.

In recent investigations with MOF-5 ($Zn_4O(BDC)_3$, BDC: 1,4-benzodicarboxylate), we demonstrated that introducing triphenylacetic acid (TPAA) capping groups effectively traps organic dyes such as crystal violet (CV) within the MOF crystals.[26] The observations were consistent with surface-bound TPAA groups blocking the MOF pores, which prevents the encapsulated dye from diffusing back into solution. Liberating the TPAA from the surface by protonation can reverse guest trapping, but acidic conditions can also degrade the MOF by extruding the carboxylate struts,[27,28] so the pH must be controlled carefully to prevent unwanted decomposition. In parallel efforts, we have been exploring photodecarboxylation as a strategy to control the temporal and spatial release of metal ions in biology.[29] We hypothesized that an analogous strategy could be used to engineer a MOF photocapping group that could be used to release guest molecules with light.

MOF-5 contains spherical cavities formed by the Zn_4O nodes and BDC struts with diameters of 18.5 Å as calculated by Cerius.[30,31] The 7.6 Å spherical radius of CV,[32] a dye utilized in our previous studies, lies near the upper size limit of guests that MOF-5 can accommodate. Early results from molecular dynamics simulations suggest that TPAA capping groups bound to surface Zn_4O nodes can associate with adjacent capping groups. A critical result of these interactions is a decrease in the accessible area between these capping groups that may limit the exit of any guest with a radius larger than 2.7 Å. Smaller carboxylate capping groups also prevent CV leakage to varying degrees, which suggests either differing modes of capping group coordination to the MOF surface, or

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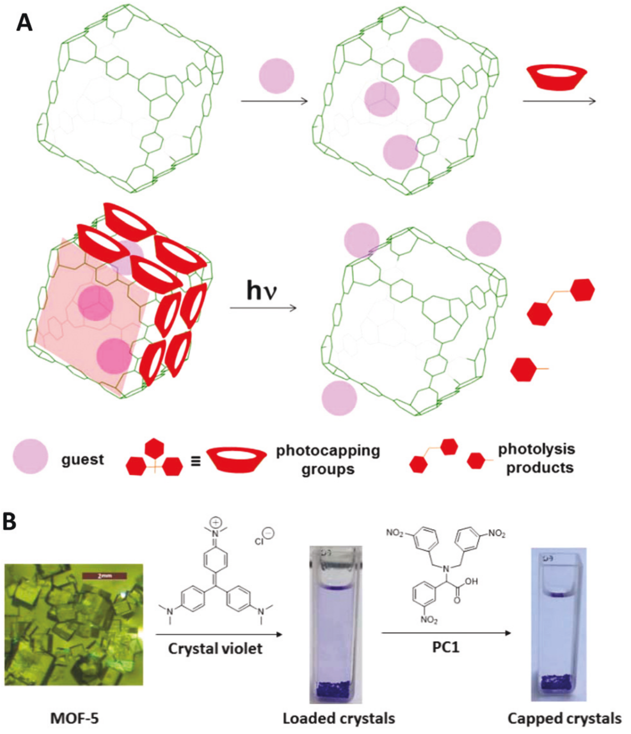
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9pp00392d

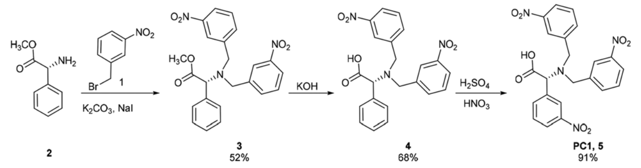
that trapping a guest as large as CV does not require a bulky capping group. Additional simulations and experiments with implications for pore capping, guest trapping, and interfacial MOF chemistry are the subject of ongoing investigations.

Since TPAA most effectively prevented CV release, we rationalized that a TPAA derivative capable of undergoing photodecarboxylation would be the ideal candidate to test our light-driven guest release hypothesis (Scheme 1A). Attempts to nitrate TPAA directly provided an inseparable mixture of products due to non-specific nitration at *ortho*-, *meta*- and *para*-positions on all three phenyl rings, so a new target was designed. Our Zn^{2+} photocage is based on a phenylglycine framework, and the compounds undergo stereoselective nitration at the *meta*-position.[29] The α-amine can also be alkylated using a variety of electrophiles. We reasoned that alkylating the amine with deactivated benzylic groups would not only provide a capping group with the necessary steric bulk, but also yield a compound where a single phenyl group could be nitrated cleanly. By treating phenylglycine methyl ester with 3-nitrobenzyl bromide, we obtained **3** in reasonable yield (Scheme 2). After saponification, the carboxylic acid **4** was nitrated to yield pure **PC1** (**PhotoCap-1**) in 32% overall yield for the three-step reaction sequence.

The photoactivity of **PC1** was assessed by LCMS and GCMS analysis after photolysis with 365 nm light. Upon irradiation, two new peaks appeared in the LC trace corresponding to bis(*m*-nitrobenzyl)amine and *m*-nitrobenzaldehyde (Fig. 1). A 28% photolysis quantum yield ($\Phi_{\text{photolysis}}$) was calculated by monitoring the disappearance of **PC1**. Earlier investigations demonstrated that although a large capping group such as TPAA efficiently traps CV in MOF-5, smaller carboxylate ligands could also prevent CV release to varying degrees. As the smallest possible *m*-nitrophenylacetic acid derivative, analysis of the trapping efficiency and guest release with 3-nitrophenyl acetic acid (**PhotoCap-2**, **PC2**) would help establish thresholds necessary to trap CV in MOF-5. Although **PC2** is less sterically demanding than **PC1**, we still anticipated efficient blocking of the MOF-5 pores with CV. The photoactivity of **PC2** was analyzed analogously to **PC1** (see the ESI†), and the primary photoproduct detected was 3-nitrotoluene with a $\Phi_{\text{photolysis}}$ value of 9.5%.



Scheme 1 (A) Guest molecule loading into MOF-5 channels, encapsulating by the surface coordination of capping reagents, and light induced guest release. (B) Photos taken of MOF-5 crystals before and after CV loading, and soaking in EtOH before light induced release.



Scheme 2 The synthetic route of photocapping group **PC1**.

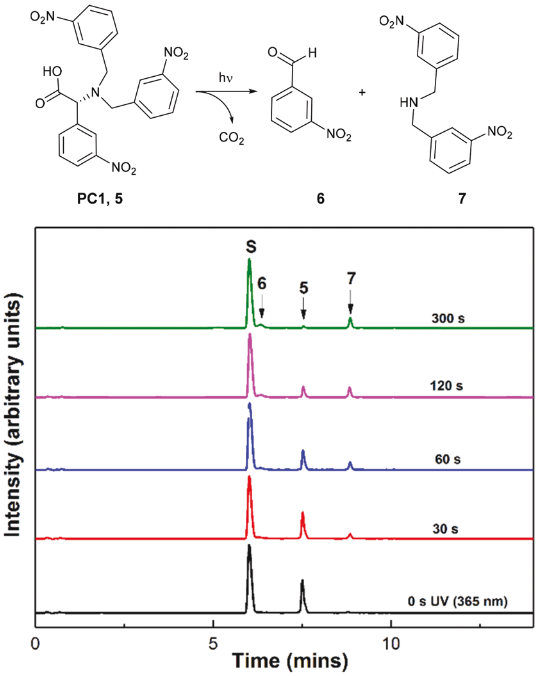


Fig. 1 Photodecarboxylation reaction of **PC1**, and monitoring in MeOH (2.5% water) with 365 nm light as measured by HPLC. Ketoprofen was used as an internal standard (**S**). A decrease in the intensity of the **PC1** peak (**5**) was accompanied by an increase in the intensity of the photoproduct peaks, *m*-nitrobenzaldehyde (**6**) and bis(*m*-nitrobenzyl)amine (**7**).

MOF-5 encapsulates 10 wt% CV (**CVMOF**), which is comparable to CV loading in CuBTC MOF, which contains either 11.9 wt% or 27.5 wt% CV depending on the preparation method.[33] MOF-5 can absorb up to 59.2 wt% capsaicin, 31.5 wt% 5-fluorouracil,[34] or 20 wt% benzene.[35] The loading capacity can be rationalized on the relative size of each guest, and although capsaicin is large in one dimension, CV has a larger diameter and is more spherical than cylindrical compared to capsaicin. In the absence of a capping group, rapid CV release from **CVMOF** is evident upon visual inspection, which suggests that CV slowly leaks from inside the MOF into the EtOH solution. Equilibrium is reached after 2 h with approximately 45% of the internalized CV having been released (Fig. 2, green curve). After three cycles that involve decanting the supernatant and replacement with fresh EtOH, almost 60% of the total CV can be recovered. Some residual CV remains permanently associated with the MOF barring treatment with acid or other harsh conditions that compromise the macromolecular structure. These results are similar to the amount of CV released from mechano-synthesized CuBTC MOF (52%),[33] which can be attributed to the similarity in pore sizes and internal surface chemistry.[36] The persistence of some CV in both MOF-5 and CuBTC MOF suggests that strong π–π stacking interactions prevent complete guest release. The plateauing of CV release may also indicate that there are steric barriers to releasing large guests if they penetrate deeply into the MOF that are not present with smaller guests such as capsaicin and 5-fluorouracil that are released more efficiently (>70%).[34]

Although uncapped **CVMOF** rapidly releases CV until an apparent equilibrium is reached, introducing TPAA can effectively trap CV within the MOF crystals. After subjecting **CVMOF** to a capping procedure, **CVMOF@TPAA** shows negligible loss of CV over extended periods of time (Fig. 2, red curve). This suggests that the dye remains internalized due to surface-bound TPAA groups blocking the MOF pores. Although CV can be released after treatment with strong acid, this approach is susceptible to degrading the MOF structure in addition to releasing the CV guest and lacks the desired degree of finesse for applications in controlled release.

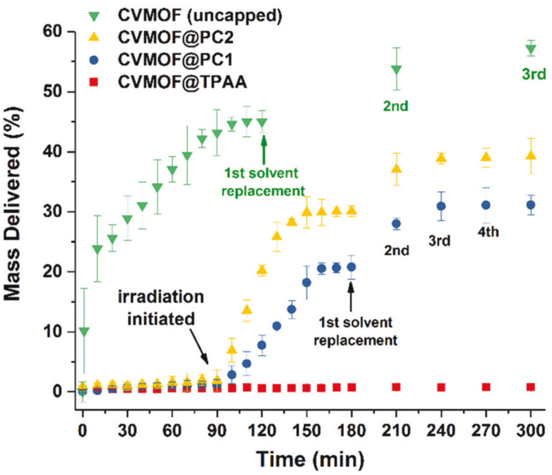


Fig. 2 Trapping and CV photo-release profile of **CVMOF@PC1** (blue), **CVMOF@PC2** (yellow) and **CVMOF@TPAA** (red). A sample of capped crystals was dispersed in EtOH, and changes in the absorbance at 580 nm were monitored over time. The samples were shielded from light for 90 min, and then irradiated for 90 min with 365 nm light. Subsequently, EtOH was decanted and replaced prior to an additional 30 min of irradiation. Four replenishments and irradiation cycles were conducted until no further evidence of CV release was observed. For comparison, uncapped CVMOF (green) immediately begins leaching CV until equilibrium is reached. Additional CV can be liberated by exchanging the EtOH solution. Error bars represent the standard deviation for three trials for each MOF.

The TPAA capping groups originally were introduced to MOF-5 using additional Zn^{2+} and temperatures analogous to solvothermal conditions used to prepare MOF-5. Owing to the thermal instability of **PC1**, a modified room temperature synthesis of **CVMOF@PC1** was devised. In contrast to solvothermal conditions where DMF or DEF decomposition releases amines to serve as the base,[37] the room temperature synthesis requires the addition of a base to buffer the protons from the ligand. DIPEA (*N*,*N*-diisopropylethylamine) is sufficiently basic to deprotonate the carboxylate ligands but cannot interact strongly with the MOF surface owing to the steric congestion triggered by the alkyl substituents. **CVMOF@PC2** can be prepared by analogous solvothermal conditions used to prepare capped **CVMOF@TPAA.** Both the capping protocols were successful as indicated by the transformation of the MOF-5 from clear to purple crystals where the coloration persists when the MOF crystals are immersed in EtOH for 24 h (Scheme 1B).

PC1 was designed to mimic the steric requirements of TPAA, and **CVMOF@PC1** exhibits a lack of CV release similar to **CVMOF@TPAA** under light-free conditions (Fig. 2, red curve). When light is introduced, however, a dramatic increase in CV absorbance is measured in the solution containing the **CVMOF@PC1** crystals (Fig. 2, blue curve). Equilibrium is reached after 1 h of irradiation after approximately 20% of the CV has been released. Following four cycles that involve decanting the supernatant, replacing the CV-containing solvent with fresh EtOH, and irradiating for additional time periods, over 30% of the originally internalized dye can be recovered. Our previous investigations demonstrated that amines can also seal CV inside MOF channels, so we hypothesize that the bis(*m*-nitrobenzyl)amine photoproduct (7) from **PC1** photolysis blocks MOF pores after photolysis. The control compound DBA, a structural analogue of **7**, was used to prepare **CVMOF@DBA**, and capping experiments suggests that MOF pores are partially blocked in the presence of diamines of this size (see the ESI†).

To test the size-dependence of the pore blocking, **PC2** was used to prepare **CVMOF@PC2**. **PC2** is the smallest possible nitrophenylacetic acid derivative that will undergo photodecaboxylation. Similar to both TPAA and **PC1**, **PC2** traps CV in MOF-5 (Fig. 2, yellow curve) with only slightly higher leaking of the dye into solution after capping. This suggests that large guests such as CV may not require bulky capping groups to achieve guest trapping, whereas this might not be sufficient to contain smaller guests. Consistent with our hypothesis and model studies with diamine trapping, 30% of the initial CV is released from **CVMOF@PC2** after only 1 h of irradiation since the 3-nitrotoluene photoproduct cannot bind to the MOF surface (Fig. 2). Following four cycles of solvent replacement, almost 40% of the CV can be recovered. The reduced leaching of CV compared to **CVMOF** may indicate that the smaller **PC2** photocapping group can enter the MOF channels where the photodecarboxylation reaction is inhibited.

Photocapping reagents have been introduced to the surface of MOF-5 to trap CV, which can be liberated only upon irradiation. This approach provides a novel process for introducing trapped MOF guests with light that can be developed for a variety of applications that require encapsulation and controlled release of small molecules. Despite the size discrepancy, both **PC1** and **PC2** exhibit similar trapping and releasing properties when used in conjunction with a large guest such as CV. Correlating trapping and releasing abilities with the sizes of caps and guest will require a systematic investigation that will also include probing the nature of the capping group–MOF surface interaction. Our current efforts are focused on both understanding the relationship between different capping groups and various guests and exploring whether analytical techniques such as X-ray photoelectron spectroscopy can provide insight into how these carboxylic acid groups interact with the MOF surface. Moisture sensitivity is a significant limitation of MOF-5, which limits the ability to reuse the MOF crystals as well as to explore biological applications. Although there are several prominent MOFs with higher aqueous stability and other exploitable properties, each system will require new sealing protocols to be devised; however, as we explore MOF-5 as well as these other three-dimensional coordination polymers, we anticipate that this approach will lead to a more general approach to exploiting MOFs for the storage and delivery of guest molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the American Chemical Society Petroleum Research Fund (grant 53977-ND3), the National Science Foundation (grant CHE-1659529) and the Worcester Polytechnic Institute.

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