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Generation of thiyl radicals in a zinc(II) porous coordination polymer by light-induced post-synthetic deprotection

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Kinetic stabilisation of the unstable chemical species in nanospace is of potential importance in the field of material and synthetic chemistry, and porous coordination polymers (PCPs) represent a facile platform to provide such reaction fields. Thiyl radicals are important reactive substances that often play a leading role in organic and bioorganic chemistry. However, their generation in nanospace has been barely investigated due to synthetic difficulties. Here, we report a facile methodology for the fuctionalisation of active thiyl substituents on PCP pore surfaces using a post-synthetic protection and deprotection technique. The thiyl radicals were generated inside zinc(II)-based PCP upon the deprotection of asymmetric disulfide, which was used as protecting group, by ultraviolet light irradiation.

Porous coordination polymers (PCPs) or metal organic frameworks (MOFs) are new types of porous materials that are constructed using a self-assembling coordination process between metal ions and organic linkers.[1] Because of the tunability of the pore size, the shape and the environment of the framework, pores of PCPs are attracting significant attention as unprecedented reaction fields[2] since they exhibit unique reactivity such as the template effect or size/shape selectivity.[3] In particular, PCPs can kinetically stabilise reactive chemical species in their nanospace. Furthermore, the high crystallinity of PCPs renders them to be good platforms to investigate the reactivity of such chemical species using X-ray crystallography, which is substantially challenging in the phase of a homogeneous solution.[4] Thiyl radicals are renowned useful chemical species in material, organic and bioorganic chemistry.[5] One of the problems of these radical species is that they are prone to undergo dimerisation in solution phase, thereby limiting the development of various reactions used as independent molecules. In this regard, the confinement of thiyl radicals in nanospace could offer a strategy for their kinetic stabilisation by hampering the contact between them as well as the characteristic reactivity for processes such as metal accumulation,[6] oxygen trapping, thiol-ene click chemistry functionalisation and catalytic activation of olefins.[5] Nevertheless, the functionalisation of PCPs with thiyl substituents is extremely rare, even for a thiol as the more stable derivative,[6] which is probably due to their strong coordination ability with metal ions or dimerisation to disulfides during the process of construction of PCPs (Figure 1). In the current study, we demonstrate a post-synthetic protection and deprotection strategy to introduce thiyl substituents on the pore surfaces of a zinc(II)-based PCP. The protection and deprotection technique[7] is a post-synthetic method[8] in which PCP is constructed using ligands that contain protected functional groups, which is followed by their subsequent deprotection. Although this technique has been recognized as a powerful tool for the introduction of reactive

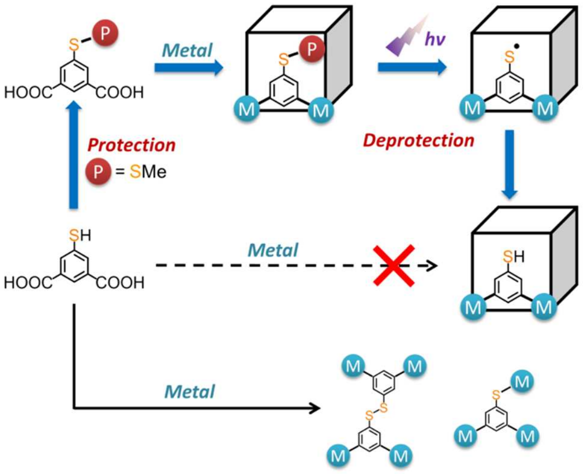

Figure 1 Protection and deprotection strategy for the generation of thiyl radicals inside nanospace of PCP.

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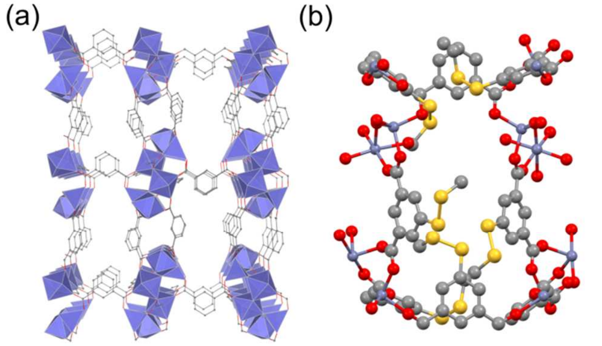

Figure 2 (a) Simplified crystal structure of **SEC-1** (Zn-O SBUs are represented as purple polyhedrons and substituents on ligands are omitted for clarity). (b) Zoom-up structure at around 1D channel pore (carbon: grey, sulfur: yellow, zinc: purple, oxygen: red, hydrogen atoms are omitted).

functional groups, such as free amino[7] or hydroxide[7a,c,d] groups into PCPs, to the best of our knowledge, it has not been applied for the introduction of sulfur analogue so far.

Thioethers or thioesters are frequently used protecting groups for thiols. However, their deprotection requires harsh conditions, such as hydrolysis or treatment with alkaline metal in liquid ammonia, that are incompatible with PCPs.[9] To circumvent this problem, we selected an asymmetric disulfide as a protecting group since it can be mildly eliminated by ultraviolet(UV)-light irradiation *via* the homoleptic cleavage of a S-S bond[10]. This light-induced post-synthetic modification has been reported to be successful in a few cases, including chemically labile zinc(II)-based PCPs.[7c,d] Furthermore, we anticipated that the disulfide unit would dissociate homoleptically, thereby acting as an effective precursor for the direct generation of thiyl radicals without derivatisation from thiols.

We selected 5-mercaptoisophthalic acid **1**[11] as the building block in which a methylthio group was introduced as the protecting group by the treatment of **1** with *S*-methylmethanethiosulfonate (see the supporting information). Disulfide functionalised PCP **SEC-1** (sulfur-embedded crystal) was synthesized from 5-(*S*-methylthio)mercaptoisophthalic acid **2** by heating a MeOH/H_2O solution at 80 °C using zinc(II) acetate as the metal source. A single crystal X-ray diffraction (SXRD) analysis (Figure 2) revealed that **SEC-1** was developed by isophthalates connected with Zn_6O_{26} clusters as a secondary building unit (SBU), which formed a 3D rectangular coordination network observed in some previously reported PCPs with other substituents.[12] **SEC-1** possessed 1D channel pores along the *c*-axis in which all the disulfide bonds were exposed, and no coordination of sulfur atoms to zinc(II) ions was observed. Notably, the sulfur atoms of the thiophenol units are apart from each other: The shortest atomic distance between sulfur atoms was calculated to be 3.58 Å (Figure S1, see the supporting information), which is much larger than that depicted by the typical sulfur-sulfur single bond (~2.0 Å). This would ensure the isolation of all sulfur atoms after deprotection. The powder X-ray diffraction (PXRD) patterns of **SEC-1** obtained after soaking with *N*,*N*-dimethylformamide (DMF) to exchange the crystal solvents were well matched with the simulated pattern from SXRD (Figure 3), although the patterns of the as-synthesized sample were different (Figure S2), which was probably caused due to the structural change induced by the mechanical stress and the loss of guest solvents. It is worth mentioning at this point that the direct synthesis of a thiol-containing PCP using ligand **1** was found to be unsuccessful. Treatment of thiol ligand **1** under the same synthetic condition as **SEC-1** produced an amorphous gel. Other reaction conditions were also attempted; however, no crystalline material was obtained in any case.

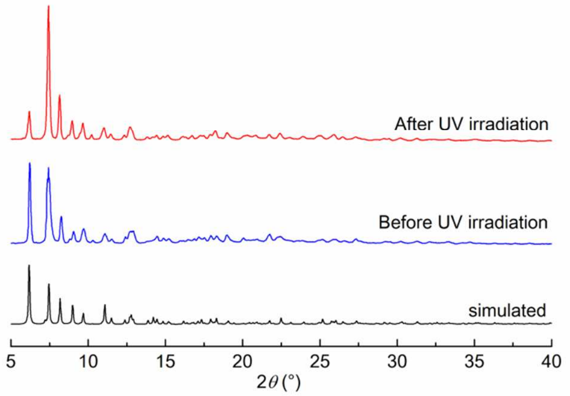

Figure 3 PXRD patterns of **SEC-1** simulated from SXRD (simulated), DMF exchanged **SEC-1** (before UV irradiation) and **SEC-2** (after UV irradiation).

We further investigated the photo-cleavage deprotection of disulfides. Crystals of **SEC-2** were obtained by UV-light (350 nm) irradiation of a dispersion of single crystals of **SEC-1** in DMF for 48 h. Crystals of **SEC-2** maintained their morphology and transparency, although the colour turned to pale yellow and the cracks somewhat increased (Figure S3). The reaction proceeded in a single-crystal-to-single-crystal[13] manner and SXRD analysis was succeeded to reveal that the crystal unit cell of **SEC-2** slightly shrunk from that was observed in **SEC-1** (Table S1), whereas the whole framework structure was unaltered. The PXRD pattern was also consistent with that of **SEC-1**, which indicated the formation of **SEC-2** in the bulk phase (Figure 3). The electron density corresponding to the –SMe protecting groups decreased considerably, and the total deprotection ratio of disulfides was crystallographically estimated to be 60% (see the supporting information). We additionally confirmed that the ^{1}H NMR spectrum of the digested **SEC-2** crystals in CD_3OD/DCl depicted signals corresponding to the isophthalic acid moiety of thiol **1** (29%) as the main deprotected product along with 3,3',5,5'-diphenyldisulfidetetracarboxylic acid **3** (22%), and other side products could be hardly observed (Figure S4, S5). The presence of ligand **1** further proves the success of the dissociation of the methylthio protecting groups. Since the sulfur atoms are sufficiently distant from each other in the crystal structure of **SEC-2**, the presence of disulfide **3** as minor product may be caused due to the oxidation of **1** during the treatment of **SEC-2** and/or partial degradation of the framework, allowing the close contact of two sulfur atoms on the mercaptophenyl groups. The deprotection ratio that was determined from ^{1}H NMR (51%) was observed to be approximately consistent with the result from SXRD. The peak assignable to the –SMe group was observed only for ligand **2** (Figure S6), supporting the absence of the dissociated protecting group in the crystal.

Interestingly, the deprotection ratio was strikingly different depending on the reaction centres (Figure S7) that ranged from 0% to 100%. The difference in the deprotection ratio can be explained in terms of the orientation of disulfide bonds around the pore. For example, S5 and S15 act as "high reactive sites" and are found to be highly deprotected (71% and 100%, respectively) in **SEC-2**, on the other hand, S3 and S13 are "low reactive sites" (0% and 37%, respectively) (Figure S8). Thus, when the –SMe protecting groups are sufficiently exposed to the pore, their diffusion elimination and the subsequent deprotection process can take place easily. However, when they are located in the opposite direction, the interruption of the solvent molecules between the two sulfur atoms is hindered. Furthermore, since the steric hindrance in the nanospace could prevent free bond rotation, the deprotection reaction could not proceed efficiently. The high deprotection ratio of some sulfur atoms indicates that UV-light transparency is sufficient to dissociate all the disulfide bonds in the crystal. The UV-light is likely to penetrate deep inside **SEC-1** (Figure S9) because the wavelength of 350 nm is near the absorption edge of ligand **2**. The process of the deprotection reaction was monitored by altering the irradiation time (Figure S10). The reaction was observed to proceed rapidly during the early stage (11% within first 1 h); however, the reaction speed gradually decreased. Finally, the reaction rate was almost saturated at 55% after 4 days of irradiation. Additionally, 2 days UV-light irradiation using the ground sample of **SEC-1** provided an almost identical result to that obtained from the as-synthesized **SEC-1** crystals, indicating that the crystal size has a minor influence on the final product (Figure S10). By considering these results and the SXRD analysis, it can be concluded that the insufficient UV-light activation of disulphides cannot be invoked to explain the incomplete deprotection reaction. Instead, the shrinkage of the framework is most likely to be responsible for the suppression of the elimination process of the protecting group. We confirmed the permanent porosity of both **SEC-1** and **SEC-2** by CO_2 adsorption study, although the adsorption amount **SEC-2** is lower than **SEC-1** due to collapse of the framework upon guest solvent removal (Figure S11). We also note that the deprotection reaction can proceed under other solvents and confirmed that the use of methanol has the similar deprotection product ratio to DMF.

We further conducted an electron spin resonance (ESR) study on **SEC-1** to observe the formation of thiyl radicals under vacuum. Irradiation of UV-light to the activated sample of **SEC-1** was performed at 95 K. The ESR signals at approximately 325 mT were immediately generated (Figure S12). The ESR peak are consistent with the "sulfur pattern"[14] derived from the strong spin-orbit coupling of the localized unpaired electron on the sulfur atom, indicating the formation of thiyl radicals. These ESR signals were almost saturated within 1 h. Thiyl radicals in the crystals were found to be thermally unstable at room temperature and no ESR signal was obtained at room temperature. Furthermore, the ^{1}H NMR spectrum of the irradiated sample displayed signals that could be attributable to ligands **2** and **3**, whereas no free thiol was observed, which indicates that all the dissociated disulfide bonds were recombined. In addition, this result suggests that the diffusion-elimination of the protecting group is the rate-determining step of the deprotection reaction.

Moreover, we found that the light-induced cleavage of disulfides proceeded in a much cleaner manner inside the PCP than that is observed in a solution. A pre-degassed solution of ligand **2** in DMF-d_7 was irradiated by 350 nm light for 24 h. The ^{1}H NMR spectrum of the resulting solution indicated that the main product was thiol **1**. However, many unidentified products were also observed (Figure S13) whose formation may be attributable to the reaction of the highly reactive thiyl radical with the aromatic rings or to the formation of polysulfides. In the case of the dissociation reaction in **SEC-1**, the mercaptophenyl groups generated during the reaction were spatially separated from each other, and the reactive –SMe protecting groups were eliminated by diffusion from the crystal to the solution, thereby preventing undesirable side reactions. This result demonstrates that the confinement of thiyl radicals in a nanospace causes unique reactivity compared to that in the solution state.

To summarize, we performed the UV-light-induced dissociation of disulfides inside a zinc(II) PCP with the concomitant generation of thiyl radicals on pore surfaces. The distinctive reactivity that was characterised by the confinement of the thiyl radicals in the nanospace was also demonstrated. We would also like to highlight that this study is the first example in which reactive sulfur species are introduced in a PCP using chemically labile metal as the node. We are confident that this work will help the development of new functionality of thiyl radicals as functional materials or catalysts to perform various reactions in nanospace.

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Conflict of interest

There are no conflicts of interest to declare.

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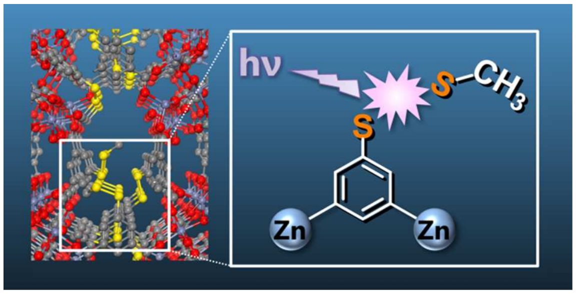
TOC Figure



Generation of highly reactive sulfur species in nanospace is demonstrated via the photo-dissociation of disulfides.