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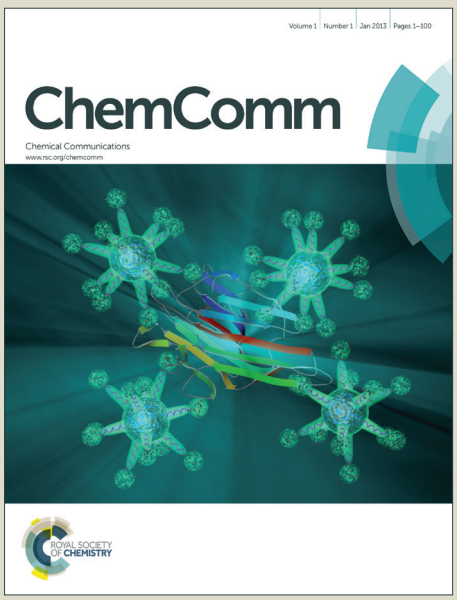

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Metal-Organic Framework Tethering PNIPAM for ON-OFF Controlled Release in Solution

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A smart metal-organic framework (MOF) exhibiting controlled release was achieved by modification with thermoresponsive polymer (PNIPAM) via a surface-selective post-synthetic modification. Simple temperature variation readily switch "open" (lower temperature) and "closed" (higher temperature) states of the polymer-modified MOF through conformational change of PNIPAM grafted on the MOF, resulting in controlled release of the included guest molecules such as resorufin, caffeine, and procainamide.

Metal-organic frameworks (MOFs) or porous coordination polymers (PCPs) have been a new class of porous materials possessing finely designable nanopores.[1] In the past decade, they have offered various functions related to storage,[2] catalysis,[3] separation,[4] and so on, derived from their nano-porosity. Despite the high expectations of MOFs for nano-containers or carriers for gaseous and other guest molecules,[5] a controlled release of them from nanopores of MOF by external stimuli is still challenging. For gaseous guest molecules, Kitagawa et al. have pioneered MOFs exhibiting gate-opening behaviour upon the guest molecule adsorption,[6] while such example in solution or liquid phase is exceptionally limited.[7] For an example, Rosi et al. presented bio-MOFs containing procaine amide, exhibiting stimuli-responsive release of procaine amide triggered by cation exchange.[7a] Another example was reported by Lin et al, in which MIL-101 tethering a prodrug are coated by silica shell, and degradation of the shell in PBS buffer or intracellular environment promoted drug release by hydrolysis of the prodrug.[7b] Although these examples are sophisticated and elaborated for guest release by the external triggers, these MOFs are not equipped with any device halting the guest release. When once the release of guest molecules starts, it becomes uncontrollable. Toward smart or intelligent MOF, imparting a stimuli-responsive releasing and ON-OFF switching ability in solution to MOFs is highly desired.

Herein, we demonstrate construction of a precisely controllable "ON-OFF" releasing MOFs, by polymer modification on the surface of MOFs via post synthetic modification technique.[8] Our strategy relies on phase transition of thermo-sensitive polymer solution between dissolved and aggregated state, so-called coil-globule transition, which is vigorously reported on water solution of amphiphilic polymer such as poly(N-isopropylacrylamide) (PNIPAM).[9] At lower temperature than 32 ºC (cloud point, T_c), PNIPAM are dissolved in water, while it forms aggregate at higher temperature than T_c. Because of this advantageous property, many researches have focused on the application of PNIPAM as thermosensitive smart materials including drug delivery,[10] gene therapy,[11] thermosensitive chromatography,[12] surface modifiers,[13] and cell cultivation sheets.[14] On the basis of these findings, we conceived that PNIPAM modification on the surface of MOFs allows us to construct MOFs with thermosensitive releasing ability with temperature as a variable and external stimulus, thus the release function on the MOFs can be reversibly switched between the "open (ON)" state at lower temperature due to the coil conformation of PNIPAM and "closed (OFF)" state at higher temperature due to the collapsed globule (Fig.1a).

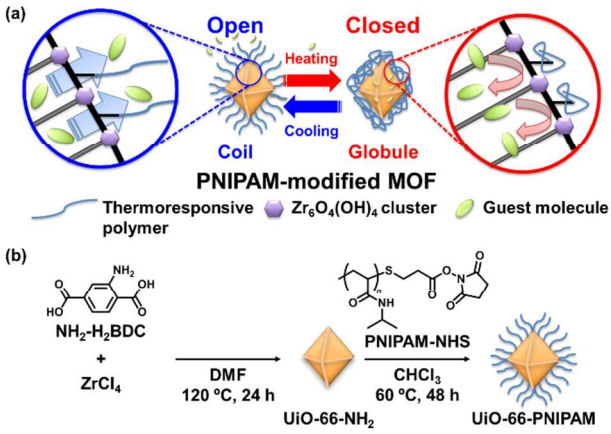

Fig. 1 (a) Schematic image of controlled release using MOF tethering PNIPAM. (b) Preparation method for MOF tethering PNIPAM (**UiO-66-PNIPAM**).

As the platform MOF, we selected UiO-66, basically consisting of Zr(IV) and terephthalate, expecting its stability against hydrolytic and heat treatment.[15] To undergo further surface

modification of the MOF, we used an organic ligand having amino group. Amino-functionalized UiO-66 (**UiO-66-NH$_2$**) was synthesized via solvothermal synthesis between 2-amino-benzenedicarboxylic acid (H_2N-H_2BDC) and $ZrCl_4$ in DMF. The solution was heated at 120 °C for 24 hours, and then collected by centrifugation. The obtained **UiO-66-NH$_2$** crystal was washed with methanol to remove excess 2-amino-benzenedicarboxylic acid and DMF. The crystal was subsequently subjected to post-modification reaction by immersing it in 0.1 M PNIPAM-NHS (M_n ~ 2,000, M_w/M_n = 1.05 T_c = 31 °C, Fig. S1) solution in chloroform, and then heated at 60 °C for 48 hours to graft PNIPAM onto the **UiO-66-NH$_2$** (Fig. 1b).

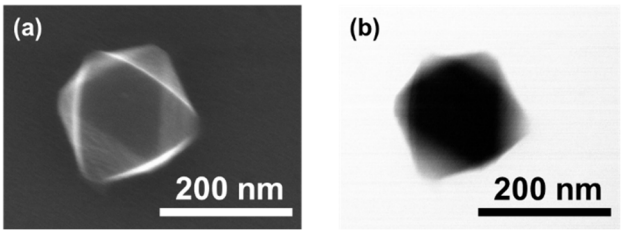

Fig. 2 (a) SEM and (b) TEM images of **UiO-66-PNIPAM**.

SEM and TEM images (Fig. 2a and 2b) shows octahedral crystal shape of MOF tethering PNIPAM (**UiO-66-PNIPAM** with around 100~200 nm diameter, and DLS measurement revealed that the size of **UiO-66-PNIPAM** was 218 ± 88 nm (Fig. S2). The XRD of **UiO-66-NH$_2$** and **UiO-66-PNIPAM** represented identical patterns with that of reported UiO-66 patterns (Fig. S3).[15] These facts meant that the crystal structure of UiO-66 was not affected by PNIPAM-surface-modification. In FT-IR spectra, **UiO-66-PNIPAM** has a stretching band at 1257 cm^{-1} attributable to amino group on organic ligand, and another stretching band at 1627 cm^{-1} assigned to amide I band derived from PNIPAM-modification through amidation of activated ester (Fig. S4).

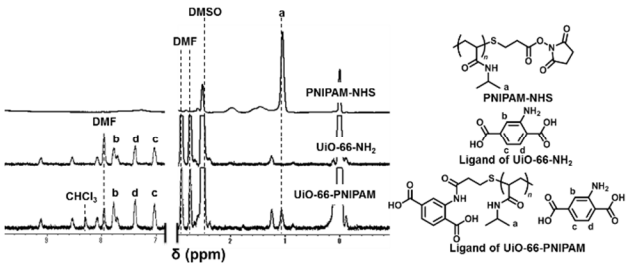

Fig. 3 ^{1}H NMR spectra of digesting solution of PNIPAM-NHS, **UiO-66-NH$_2$**, and **UiO-66-PNIPAM**.

PNIPAM modification rate on the organic ligand was estimated by 1H NMR after digestion of the obtained **UiO-66-PNIPAM** by HF aq. in DMSO-d_6 (1.4 mM for HF) As shown Fig. 3, it was found to be 11.2% according to the ratio of integration of PNPAM and the organic ligand. The relatively low modification rate probably derived from the slow diffusion of PNIPAM-NHS to the nanopore of **UiO-66-NH$_2$**, thus surface-selective modification of PNIPAM-NHS predominantly occurred. Given **UiO-66-PNIPAM** as an octahedron 218 nm on a side (from DLS), 10.9% of whole organic ligands are included in the unit cells of the outermost surface (5.6%), and in the second outermost (5.3%). From this postulation, we can propose that the surface of **UiO-66-PNIPAM** is fully covered by PNIPAM. To elucidate the size effect on polymer modification, we carried out post-modification with different molecular size from PNIPAM-NHS. Acetic anhydride was chosen as the substrate, which is small enough to introduce in the nanopore of **UiO-66-NH$_2$** or **UiO-66-PNIPAM**. As a result, both **UiO-66-PNIPAM** and **UiO-66-NH$_2$** showed high modification rate of acetyl group (**UiO-66-NH$_2$**: 100%, **UiO-66-PNIPAM**: 89%, Fig. S5). This observation revealed that small molecules such as acetic anhydride can reach all parts of the MOF even after PNIPAM modification, resulting in such a high modification rate. On another front, additional PNIPAM-NHS modification on acetyl-functionalized MOF was unsuccessful, thus no signals derived from PNIPAM was observed after digestion. Apparently, full conversion of reacting amino group by acetic anhydride is responsible for this result. These findings disclose that PNIPAM-NHS conducts surface-selective modification due to the large molecular size compared to the pore size of MOF. Indeed, the size of substituent usually shows a negative correlation with the modification rate in the nanopore of MOF.[8f]

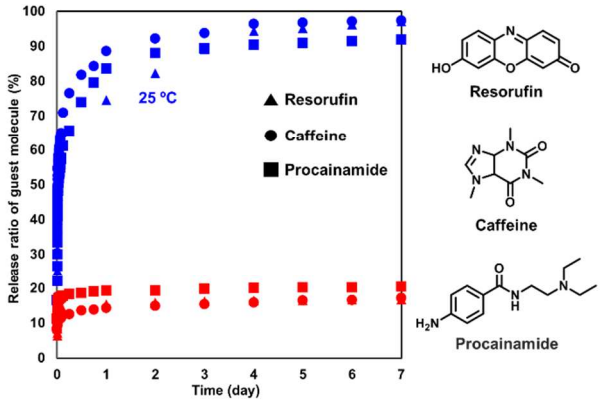

Fig. 4 Release behaviour of guest molecules (resorufin, caffeine, procainamide) from **UiO-66-PNIPAM** in water at 25 °C and 40 °C for seven days. The release ratio was determined from the absorbance at 572 nm (resorufin), 273 nm (caffeine), 311 nm (procainamide).

Since PNIPAM-modification was confirmed by the spectroscopic studies (vide supra), we next investigated temperature-dependent release behaviour of guest molecule included in **UiO-66-PNIPAM**. Resorufin, caffeine, and procainamide were selected as the guest molecule (Fig. 4), and loaded in **UiO-66-PNIPAM** by soaking the MOF in 50 mM guest solutions in water for 24 hours at 25 °C. The fully loaded crystal was collected by centrifugation at 40 °C, and extensively washed with 60 °C water to remove guest molecules absorbed on the surface, and dried at 60 °C. Release behaviour of the guest molecule from **UiO-66-PNIPAM** was monitored by incremental UV-Vis absorption derived from the released guest molecule, therein the crystal was immersed in water in a PMMA cell equipped with a magnetic stirrer. Full release was determined by UV-Vis absorption spectroscopy after digestion of the MOF by HF aq. Time-course measurement of the guest releasing at different temperatures is shown in Fig. 4, which were recorded at 25 °C or 40 °C. At 25 °C where PNIPAM shows coil conformation, all the guests were rapidly released from **UiO-66-PNIPAM**, and the release ratio was saturated within 4 days (see also Fig. S6). On the contrary at 40°C where PNIPAM shows globule conformation, release ratio for all the guests were held less 20% even after 7 days. Thus, the release ratio of guest molecules drastically turned upon the temperature variation. Pristine **UiO-66-NH$_2$** showed almost identical release behaviour to that of **UiO-66-PNIPAM** at 25 ºC

(Fig. S7), implying that the released guest molecules derived from the pore of the MOF, not from the grafted polymer layer.

Considering T_c of the employed PNIPAM (31 °C), this behaviour apparently resulted from the phase transition of polymer conformation in water. Contraction of PNIPAM chain above T_c effectively acts as a diffusion barrier, in sharp contrast to the solvated state of PNIPAM chain below T_c. In other words, above T_c, PNIPAM forms collapsed globule conformation as a closed state that prevents release of guest molecules, while below T_c, the random coil conformation of PNIPAM permits the diffusion out of the pores as an open state. Actually, loading of guest molecule (resorufin) at high temperature resulted in no guest molecule inclusion, revealed by 1H NMR measurement after digestion (Fig. S8). To further confirm our idea, we underwent another experiment of the release behaviour by using **UiO-66-PNIPAM** with less modification rate (4.2%) of PNIPAM-NHS (**UiO-66-PNIPAM(4.2)**), which was prepared by short reaction time as 3 hours. In a resorufin release test for **UiO-66-PNIPAM(4.2)** (Fig. S9), release rate was elevated both at 25 °C and 40 °C compared to those of **UiO-66-PNIPAM**. This fact means that 4.2% modification is noticeably not sufficient to block the diffusion of guest molecules, resulting in uncontrollable release behaviour.

In the above experiment, **UiO-66-PNIPAM** showed similar release behaviour for all the used guest molecules regardless of their distinctive molecular structure, because this system requires no specific intermolecular inter-action between host and guest molecules. On the contrary, **UiO-66-PNIPAM** could not contain larger molecules than the pore size in the least, such as protoporphyrin IX (**PPIX**), revealed by ^{1}H NMR measurement after digestion (Fig. S10). These observations indicated that the size of guest molecules is essential for inclusion on them in the nanopore of MOF, rather than specific affinity or intermolecular interaction between guest and the MOF. After the release of a guest molecule, **UiO-66-PNIPAM** could include another guest molecule via the same procedure with the first loading, i.e., immersing in 50 mM guest solutions in water for 24 hours. We confirmed that the reloaded **UiO-66-PNIPAM** exhibited almost identical release behaviour to that of the first cycle until third cycles, thus we could switch the releasing rate of guest molecule by temperature variation (Fig. S11).

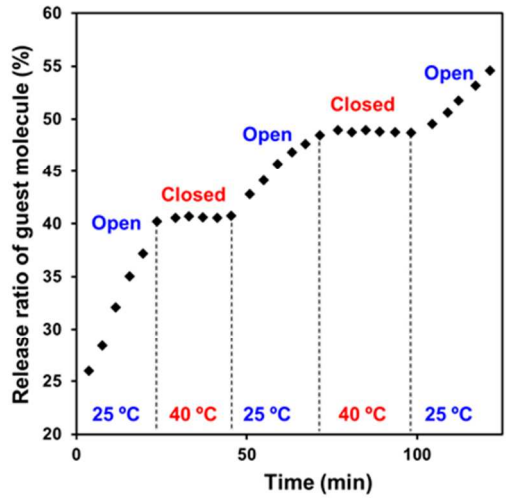

Fig. 5 Stepwise release-and-halt behaviour of resorufin from **UiO-66-PNIPAM** in water by temperature variation. The release ratio was determined from the absorbance at 572 nm.

In the present system, the releasing ability are readily controlled only by temperature with keeping the chemical mass balance. This characteristic enables us to switch open and closed state, i.e., coil and globule state of PNIPAM, even after the beginning of the guest release. Thus, we carried out stepwise controlled release by change of temperature every about 20 minutes. As shown in Fig. 5, the amount of released guest (resorufin) was increased during the period at 25 °C, whereas guest release was mostly halted during another period at 40 °C. Although the increment of released guest molecules became smaller after each releasing period, the switching capability was unchanged. This observation clearly displays that a swift coil-globule transition of polymer chain was capable of stepwise and precise control of guest release driven by temperature variation.

In conclusion, we have demonstrated a smart MOF exhibiting controlled release driven by temperature variation, consisting of MOF tethering thermoresponsive polymer (PNIPAM). In our best knowledge, this is the first example of MOF tethering thermoresponsive polymer, exhibiting thermally ON-OFF controllable behaviour. As expected, the obtained polymer-modified MOF (**UiO-66-PNIPAM**) exhibited rapid release of including guest molecules at lower temperature (25 °C), while it was suppressed at higher temperature (40 °C), across its T_c (31 °C), regardless of the guest molecular structure. Furthermore, facile switch between these two states was accomplished by just varying temperature. These features derived from swift conformational change (coil-globule transition) of the attached thermoresponsive polymer on the surface of MOF. Our idea to provide a switching capability of guest release included in MOFs will open a new frontier for practical usage of MOFs Variation of the modifying polymer on MOF other than PNIPAM[16] can expand the design possibility of the commanding stimuli manner or direction, which is valuable for intelligent transportation system such as drug delivery realized in polymer gels.[17] A MOF with smart releasing system controlled by another external stimuli is currently under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: FT IR spectra, XRD patterns, NMR analysis for polymer-modification, releasing behaviour chased by ^{1}H NMR and UV-vis absorption, and acknowledgement. See DOI: 10.1039/c000000x/

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