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ARTICLE

Metal-Organic Framework Tethering pH- and Thermo-Responsive Polymer for ON-OFF Controlled Release of the Guest Molecules

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The controlled release of small molecules from carrier materials by manipulating the environmental conditions has potential for use in drug delivery. In the present study, we demonstrate the controlled release of a guest molecule (procainamide) from a metal–organic framework (MOF). The MOF is covered with a copolymer of N-isopropyl acrylamide (NIPAM) and acrylic acid (AA) by post-synthetic modification. The polymer exhibits rapid and reversible coil–globule transition that is both pH- and thermoresponsive, thereby allowing the guest molecule to be released from the MOF in an "on-off" manner. At high pH (6.86) or low temperature (< 25 °C) — when the polymer adopts a coil conformation — the guest molecule is rapidly released from the MOF, whereas at low pH (4.01) or high temperature (> 40 °C) — when the polymer adopts a globule conformation — the release of the guest is suppressed. The release can be halted by the applying the external stimuli even after starting the release. The MOF-derived controllable container introduced here will facilitate targeted drug delivery and the controlled release of therapeutic agents.

Introduction

Carrier materials that are capable of controlled release of guest molecules in response to external stimuli have attracted much attention in the fields of chemistry, medicine, and pharmaceutical and materials sciences, because of their potential for use in smart materials such as drug delivery systems (DDSs) and cell imaging. Various porous materials have been explored for use as the host of such carrier materials, including mesoporous silica,[1-3] polymer gels,[4-6] and metal-organic frameworks (MOFs).[7-9] However, these materials have two primary drawbacks: low drug-loading capacity and lack of reversibility. To overcome these drawbacks, we recently reported the preparation of a polymer-coated MOF that is capable of releasing a guest molecule when triggered by temperature change.[10] The polymer coating comprised poly(N-isopropylacrylamide) (PNIPAM), which is a well-known thermoresponsive polymer that undergoes a phase transition from a dissolved to an aggregated state (the so-called coil-globule transition) in aqueous solution.[11,12] In our previous study, PNIPAM was attached to the surface of the MOF crystal in a post-synthetic modification,[13-17] and its rapid phase transition enabled to switch the releasing behaviour even after once stating the guest release. Therefore, the attachment of other stimuli-responsive polymers may yield MOFs with "on-off" releasing capability in response to other external stimuli, which will realize smart and designable carrier materials.

Carrier systems that are capable of the pH-triggered controlled release of guest molecules would be particularly promising candidates for drug delivery applications.18-28 In vivo environment often provides pH contrast. For examples, the surroundings of tumour cell often exhibit lower pH value than those of normal cell,[29-31] and each subcellular organelles also exhibit various pH values.[32,33] From this perspective, a copolymer comprising NIPAM and acrylic acid (AA) could be useful, because it would have dual pH and thermo responsivity.[34-36] At pH value higher than pK_a (4.95), poly(acrylic acid) (PAA) is soluble in the buffer, whereas it aggregates at pH values lower than its pK_a. Furthermore, PNIPAM is soluble in water at temperatures lower than 32 °C (the cloud point, T_c), whereas it forms aggregates at temperatures higher than its T_c. Using a copolymer of NIPAM-AA as examples, Hoffman et al. reported the copolymer hydrogel exhibiting a faster release of a model drug (indomethacin) in a higher pH (7.4) environment.[37-39] Jiang et al. prepared a copolymer hydrogel with hollow cages derived from an SiO_2 template via emulsion polymerization. The hydrogel was capable of releasing a model hydrophilic drug (isoniazid) in response to both temperature and pH.[40]

In this paper, we report the preparation of polymer-coated MOF that is capable of controllable "on–off" release of a guest molecule in response to pH and temperature changes using P(NIPAM-AA) as the modifying polymer. At higher pH values or lower temperatures, the polymer adopts a coil conformation corresponding to a "release-on" state, whereas at lower pH values or higher temperatures, the polymer has a globule conformation corresponding to a "release-off" state.

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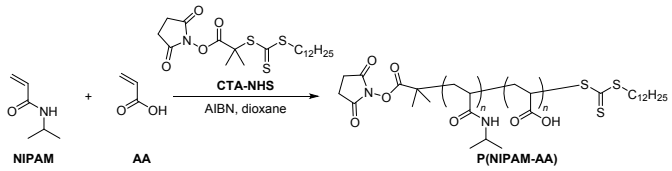
Experimental Section

Materials

The chain transfer agent with N-hydroxy succinimide (CTA-NHS) was synthesized according to the reported procedure.[41] All reagents were obtained from commercial sources and used without further purification. Phosphate pH standard solution (pH 6.86) and phthalate pH standard solution (pH 4.01) were purchased from Wako Chemical Ind. Co.

Measurements

^{1}H NMR measurements were recorded on a Bruker Biospin AVANCE DRX500 instrument (500 MHz), using 0.05% tetramethylsilane (TMS) as an internal standard. Size exclusion chromatography (SEC) at room temperature was carried out on a SHIMADZU LC-9A system (SHODEX KD-805 column) with a SPD-10AVP UV-Vis Detector using chloroform as an eluent, after calibration with the standard polystyrene samples. UV-vis spectra and turbidity were recorded on a JASCO V-570 spectrophotometer with a JASCO ETC-50ST temperature controller. Powder X-ray diffraction (XRD) patterns were obtained by Bruker AXS D8 ADVANCE. Transmitting electron microscope (TEM) images were acquired by using a JEOL JEM-2100F. Fourier transform infrared (FTIR) spectra were observed with a JASCO FTIR-4100 SK spectrometer with a ZnSe prism kit PKS-ZNSE for ATR technique. Dynamic light scattering (DLS) measurement was conducted by a Beckman-Coulter Delsa Nano HC in distilled water at 25 °C.



Scheme 1. Synthetic procedure for P(NIPAM-AA).

Synthesis of P(NIPAM-AA)

A solution of CTA-NHS (6.92 mg, 0.015 mmol), NIPAM (169 mg, 1.5 mmol), AA (27 mg, 0.375 mmol, 1/4eq./NIPAM) and AIBN (0.5 mg, 0.003 mmol) in dry dioxane (700 µL) was prepared. The solution was transferred to ampule, degassed, with three freeze-evacuate-thaw cycles, and sealed. The ampule was heated 60°C for 10 h. After the ampule was cooled, reaction mixture was reprecipitated with diethylether, filtered and dried to obtain P(NIPAM-AA) as a white powder. (167 mg). ^{1}H NMR (500 MHz, DMSO-d6, TMS standard, r.t.) δ(ppm) 0.82-1.48 (br), 1.48-1.86 (br), 2.82-2.92 (br, -CH_2-), 3.35-3.47 (br, -CH_2-), 3.82-4.27 (br, -CH-).

Synthesis of UiO-66-P(NIPAM-AA)

In a 5mL screw vial, UiO-66-NH_2 (60 mg) and 0.1 M P(NIPAM-AA) solution (500 µL) in chloroform were mixed, and the mixture was kept still at 60 °C for 24 h. After cooling to room temperature, the crystal was collected by filtration and repeatedly washed by chloroform and methanol. The modification ratio was determined by ^{1}H NMR after digestion of the crystal by HF aq.

Guest loading of UiO-66-P(NIPAM-AA)

In a 5 mL screw vial, UiO-66-P(NIPAM-AA) (10 mg) was immersed in 50 mM guest aqueous solution (pH 6.86, 1 mL), and it was kept standing at 60 °C for 24 h. The crystal was collected by centrifuge (10,000 rpm, 40 °C, 5 min) and washed by water (pH 4.01), and this cycle was repeated 10 times. The amount of whole guest was determined by ^{1}H NMR after digestion of the crystal by HF aq.

Results and discussion

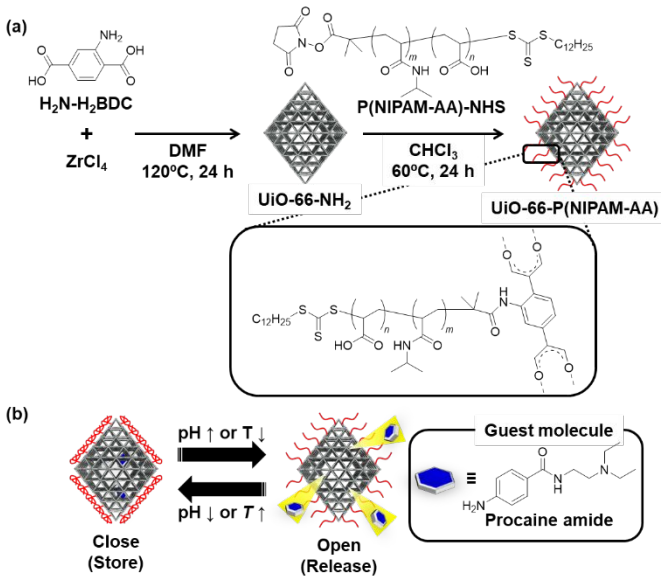


Fig.1 (a) Schematic image for preparing MOF tethered by P(NIPAM-AA) (UiO-66-P(NIPAM-AA)), and (b) controlled release using UiO-66-P(NIPAM-AA). H2N-H2BDC is 2-aminoterephthalic acid.

As a starting material, amino group functionalized UiO-66 (University of Oslo 66, UiO-66-NH_2) was selected owing to high stability of Zr-based MOF series,[42–44] and further modified by a pH-responsive polymer (P(NIPAM-AA)). UiO-66-NH_2 was synthesized according to the previous report,[10] providing an octahedral microcrystal. The modifying polymer, P(NIPAM-AA)-NHS (NHS; *N*-hydroxy succinimide), was synthesized by copolymerization of *N*-isopropylacrylamide (NIPAM) and acrylic acid (AA) via reversible addition-fragmentation transfer (RAFT) polymerization using chain transfer agent (CTA) with NHS moiety. The content of acrylic acid in the P(NIPAM-AA)-NHS was determined by FT-IR spectrum (Fig. S1), and the ratio of NIPAM/AA was determined as 5/1 by ^{1}H NMR. The number average molecular weight (M_n) of P(NIPAM-AA)-NHS was determined to be M_n = 4.1×10^3 through size-exclusion chromatography (SEC) with polystyrene standard in DMF. Regarding the pH sensitivity of P(NIPAM-AA)-NHS, the P(NIPAM-AA)-NHS aqueous solution became one phase at higher pH than pK_a, and the solution was conversely phase-separated at lower pH than pK_a (Fig. S2a). Also, at a lower

temperature than 31 °C (T_c), P(NIPAM-AA)-NHS was dissolved in pH 4.01, while it formed an aggregate at a higher temperature than T_c in pH 4.01 (Fig. S2b). These facts indicate the pH and lower critical solution temperature (LCST)-type thermosensitivity of P(NIPAM-AA)-NHS.

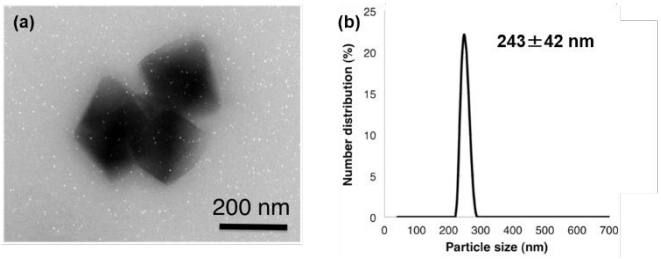


Fig. 2 (a) TEM image and (b) DLS histogram of UiO-66-P(NIPAM-AA).

By immersing it in 0.1 M P(NIPAM-AA)-NHS (NIPAM/AA= 5/1, determined by ^{1}H NMR) solution in chloroform, UiO-66-NH_2 crystal was subjected to the post-modification reaction subsequently, and then heated at 60 °C for 48 h to graft P(NIPAM-AA) onto the UiO-66-NH_2 to form amide bond between the polymer and MOF crystal (Fig. 1). TEM image (Fig. 2a) shows an octahedral crystal habit of MOF tethered by P(NIPAM-AA) (UiO-66-P(NIPAM-AA)) with around 200~300 nm diameter, and DLS measurement showed that the mean diameter of UiO-66-P(NIPAM-AA) was 243 ± 42 nm (Fig. 2b). Due to the larger size of MOF compared to P(NIPAM-AA) (~5 nm), the TEM observation and DLS measurement provided a similar result. The XRD of UiO-66-NH_2 and UiO-66-P(NIPAM-AA) exhibited identical patterns with that of reported UiO-66 pattern (Fig. S3).[45,46] These facts indicated that the surface-modification with P(NIPAM-AA) did not affect the crystal structure of UiO-66. From FT-IR spectra, UiO-66-P(NIPAM-AA) exhibited a stretching band at 1257 cm^{-1} assignable to amino group on the organic ligand, and another stretching band at 1627 cm^{-1} attributed to amide I band derived from P(NIPAM-AA) through the activated ester amidation (Fig. S1).

P(NIPAM-AA) modification ratio on H_2N-H_2BDC (2-aminoterephthalic acid) was estimated by ^{1}H NMR after digestion of the prepared UiO-66-P(NIPAM-AA) by HF aq. in DMSO-d_6 (1.4 mM), which was found to be 5.6% (Fig. S4). The slow diffusion of P(NIPAM-AA) to the micropore of UiO-66-P(NIPAM-AA) is probably responsible for the relatively low modification rate, therefore the surface-selective modification of P(NIPAM-AA) mainly underwent. From the fact that UiO-66-P(NIPAM-AA) is an octahedron of 243 nm mean diameter (from DLS), the outermost unit cell consists of 5.0% of whole organic ligands.[10] Therefore, we can provide a simple model that the surface of UiO-66-P(NIPAM-AA) is fully covered by P(NIPAM-AA).

Before use as a container, we confirmed the pH stability of UiO-66-P(NIPAM-AA) by immersing in pH buffer (pH 4.01 and pH 6.86) for 1 day. After UiO-66-P(NIPAM-AA) immersed in the two pH buffers was collected by centrifugation and washed with water, the pH stability of UiO-66-P(NIPAM-AA) was evaluated by XRD measurement. As a result, the XRD of both of UiO-66-P(NIPAM-AA) immersed in pH buffer represented identical patterns with that of reported UiO-66 patterns (Fig. S5). These facts suggested high stability of the crystal structure of UiO-66-P(NIPAM-AA) indicating potential application for a drug carrier.

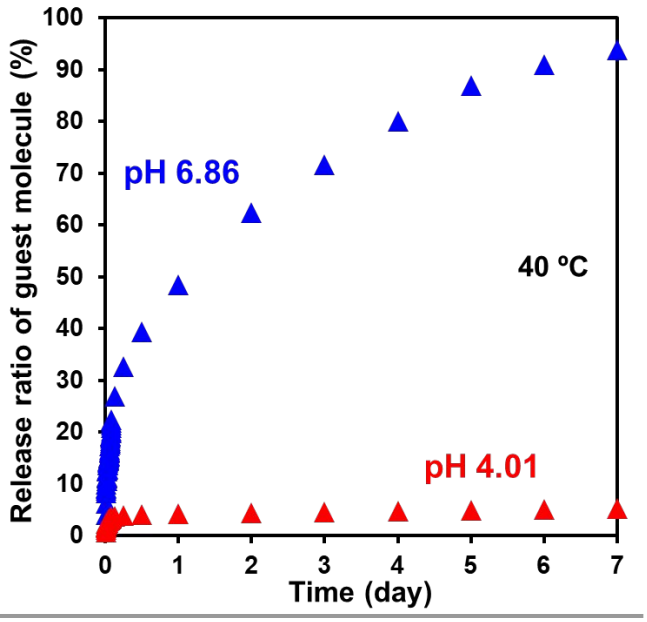


Fig. 3 Time-course observations of guest molecule (procainamide) released from UiO-66-P(NIPAM-AA) in pH buffers (6.86 and 4.01) at 40°C to seven days

pH-Dependent release behaviour of guest molecule from UiO-66-P(NIPAM-AA) was then investigated. An antiarrhythmic drug molecule, procainamide, was selected as the guest molecule (Fig. 1b), and loaded in UiO-66-P(NIPAM-AA) by immersion of the MOF in 50 mM aqueous solution of procainamide for 24 h at 40 °C. The fully loaded crystal was collected by centrifugation, and extensively washed with pH buffer (pH 4.01) to remove the surface-adsorbed guest molecule. Then, the crystal was immersed in water in a PMMA cell equipped with a magnetic stirrer, and the release behaviour of the guest molecule from UiO-66-P(NIPAM-AA) was detected by increase of UV-vis absorption at 311 nm derived from the released guest molecule. The loaded amount of procainamide was measured by UV-Vis absorption after digestion of the MOF by HF aq. Fig. 3 shows the time-course measurement of the guest release at different pH, using pH buffer (pH 6.86 or pH 4.01) at 40 °C. In pH 6.86 buffer where P(NIPAM-AA) adopts a coil conformation (Fig. S2a), the guest molecule was quickly released from UiO-66-P(NIPAM-AA), and the release was saturated after 7 days. On the contrary in pH 4.01 buffer at 40 °C where P(NIPAM-AA) adopts a globule conformation, release ratio was kept less 10% even after 7 days. Therefore, the release ratio of guest molecule can be drastically changed depending on pH of the solution. Without AA monomer, PNIPAM can only show thermoresponsivity, therefore previously reported UiO-66-PNIPAM at 40 °C always halted the release of the guest molecule.[10] The “release-off” state of UiO-66-P(NIPAM-AA)

(5.2% after 7 days) was improved compared to that of UiO-66-P(NIPAM) (20.4% after 7 days), probably due to the strong hydrogen bonding of -COOH groups.

As a reference experiment, release behaviour of the guest molecule from pristine UiO-66-NH_2 was examined in pH 6.86 and pH 4.01 buffers. As a result, almost the same release behaviour from UiO-66-NH_2 in pH 6.86 and pH 4.01 was observed, although release rate from UiO-66-P(NIPAM-AA) in pH 6.86 was decreased by covering polymer on the surface of UiO-66-P(NIPAM-AA) (Fig. S6). This fact indicates that the conformational change of P(NIPAM-AA) significantly contributed to the precise controlled release from UiO-66-P(NIPAM-AA). In the case of lower P(NIPAM-AA)-modification ratio (2.3 %), the guest was moderately released from UiO-66-P(NIPAM-AA) even in pH 4.01 buffer at 40°C as shown in Fig. S7, in which P(NIPAM-AA) shows globule conformation. This result shows that 2.3% P(NIPAM-AA)-modification ratio is not enough to cover all the surface of the MOF.

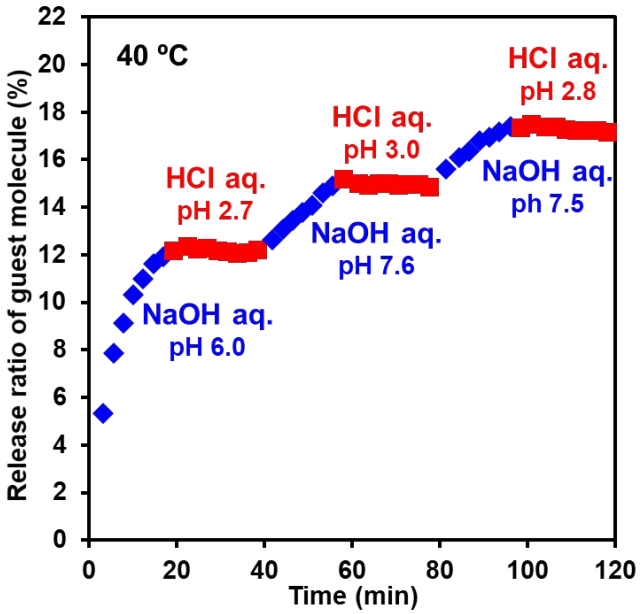


Fig. 4 Time-course of stepwise release-and-halt behaviour of the guest molecule (procaine amide) from UiO-66-P(NIPAM-AA) in water by pH variation.

In the presented system, the release rate is readily switched by pH change with keeping the mass balance. This property enables us to switch open and closed state, thus coil and globule state of P(NIPAM-AA), even after starting the guest release. Therefore, we carried out stepwise controlled release via pH change by alternately adding HCl aq. (0.05 M) and NaOH aq. (0.05 M) every ca. 20 minutes. As the result, the amount of released guest molecule was increased in incubation pH 6.0 by addition of NaOH aq., whereas guest release was mostly halted in incubation pH 3.0 by addition of HCl aq., shown in Fig. 4. It clearly displays that a fast coil-globule transition of polymer chain allows the stepwise and precise control of guest release driven by pH variation. Note that halting of started release was considered to be difficult to achieve by the already existing systems.

Since the thermosensitivity of P(NIPAM-AA) was confirmed in pH 4.01 (Fig. S2b), the temperature-controlled release behaviour of the guest molecule was investigated. The guest releasing behaviour was measured at 25 °C and 40 °C in pH 4.01. At 25 °C, where P(NIPAM-AA) adopts a coil conformation, guest molecule was rapidly released from UiO-66-P(NIPAM-AA) whilst at 40 °C, where P(NIPAM-AA) shows globule conformation, the amount of released guest was mostly suppressed contrariwise (Fig. S8). This observation indicates that the release of guest molecules is highly controlled not only by pH change but also by the temperature.

Conclusions

In the present study, we demonstrated a smart MOF exhibiting controlled release driven by pH and temperature variation, consisting of MOF tethered to a pH and thermosensitive polymer (P(NIPAM-AA)). To the best of our knowledge, this is the first example of controlled release in an MOF system triggered by dual external stimuli. As expected from the pH- and thermosensitivity of P(NIPAM-AA), we observed rapid release of the included guest molecules at pH values of 6.86 or higher, and at pH 4.01 when the temperature was 25 °C, whereas release was suppressed at pH values of 4.01 or lower when the temperature was 40°C. Furthermore, the facile switch between the two on and off states was accomplished by adjusting the pH and temperature. These features derived from the rapid conformational change (the coil-globule transition) of the pH and thermosensitive polymer on the surface of the MOF. This unique MOF tethered by a dual stimuli-sensitive polymer has potential for use in cell imaging applications, and it will open up new possibilities for targeted and controlled drug delivery.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Graphical Abstract for Table of Contents (TOC)

Metal-Organic Framework Tethering pH- and Thermo-Responsive Polymer for ON-OFF Controlled Release of the Guest Molecules

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