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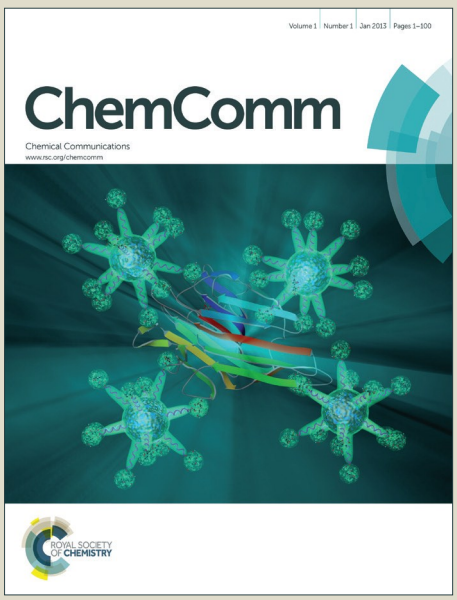

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Moisture-triggered Controlled Release of a Natural Food Preservative by a Microporous Metal-Organic Framework

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In this work we demonstrate that Allyl isothiocyanate (AITC), a common food flavoring agent and food preservative, can be effectively captured by and released in a controlled manner from a microporous metal-organic framework (MOF). The extent of AITC-MOF interactions is quantitatively measured by orbital overlap population calculations. Controlled release experiments show that loaded AITC can be released by applying higher relative humidity. Further analysis reveals that the underlying mechanism of the controlled release is associated with a transformation of the MOF from a porous to a nonporous structure at high humidity. This study represents the first example of making use of MOF porosity in food preservation.

Food quality and safety are global issues attracting tremendous attention worldwide. Recently, there has been an increasing interest in making use of natural antimicrobial agents and preservatives to improve food quality and safety, due to their potential health benefits.[1] Allyl isothiocyanate (AITC), a major essential oil component found in plants from the *Cruciferae* family, such as mustard, broccoli, horseradish and cabbage, is widely used as a natural food-flavoring agent (Fig. S1).[2] AITC can inhibit growth of a wide range of foodborne pathogens and spoilage-inducing microorganisms (including yeasts and molds) when used at low concentrations; stronger antibacterial activity has been observed when it is in the vapor phase compared to the liquid phase.[3] Despite its antimicrobial properties, incorporation of AITC in food systems is currently limited due to two reasons. First, it is highly volatile and produces a pungent flavor at high concentrations. Secondly, as it binds to and reacts with some food ingredients (e.g. water, lipids, and proteins), often a large amount of AITC is required to provide sufficient antimicrobial activity, which can negatively impact the sensory attributes of the food product.[4]

To address these issues, one strategy is to incorporate volatile preservatives such as AITC into a food carrier material. Following well developed methods,[5] AITC loaded carrier material can be packed within sachets. Upon external stimuli, AITC will be released onto the food surface. This method guarantees no direct contact between the food product and the carrier material or its components. In addition, this strategy has the advantage of requiring less amount of AITC since it targets only the food surface where microbial contamination usually occurs instead of the entire food product. Therefore, developing new types of packaging materials that are capable of encapsulating AITC with fully controlled release is much needed. In this context, an ideal AITC carrier material should satisfy the following criteria: (a) It can take up a large quantity of AITC and the loading process is facile; (b) It is able to physically entrap and retain AITC molecules such that they will not desorb under normal conditions; and, most importantly, (c) The release of AITC from carrier material can be triggered by a select external stimulus such as increased relative humidity (RH).

There have been only a few studies using porous materials to control the release of AITC. For example, Park and coworkers[6] reported the use of mesoporous silica SBA-15 for the adsorption and release of AITC. They showed that SBA-15 can take up a large amount of AITC at room temperature. Siahaan and coworkers[7] tested *Laminaria Japonica* powder and mesoporous silica MCM-41 as AITC delivery vectors against bacteria. Both materials were found to be capable of adsorbing and releasing AITC molecules, effectively delaying the growth of bacterial cells. However, due to the relatively large pore size of these carrier materials (several nanometers) and weak adsorbate-adsorbent interaction, none of them can entrap AITC molecules in their pore space upon adsorption resulting in a rapid loss of AITC without any external stimuli. Thus, release of AITC in a fully controlled manner can not be achieved by these carrier materials.

Over the past two decades, metal-organic frameworks (MOFs) have emerged as a new class of adsorbent materials that are built on metal ions (or clusters) and organic linkers to form

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porous three-dimensional (3D) frameworks.[8] While early studies of MOFs emphasized their applications in gas storage and separation,[9] catalysis[10] and chemical sensing,[11] more recently, MOFs have also been studied in health and personal care areas such as drug delivery[12] and fragrance release.[13]

One well-recognized challenge of MOFs is their poor water stability,[14] as most tend to rupture when immersed in liquid water or simply when exposed to air for a given time period. In this work, we take advantage of this "drawback" and use high humidity as an external stimulus to induce the breakdown of a MOF structure thereby triggering the release of AITC in a fully controlled manner.

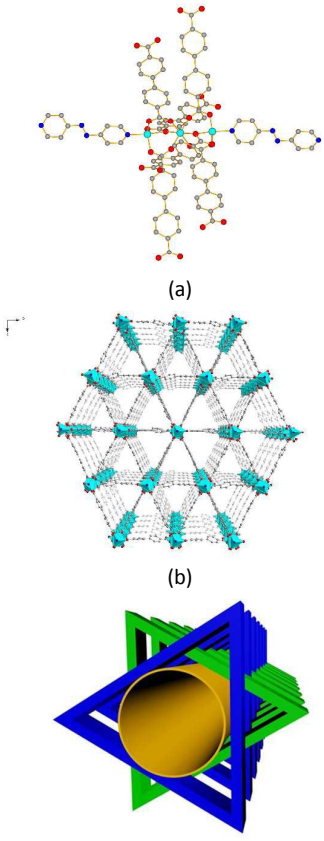

Fig. 1. (a) $Zn_3(\mu_2\text{-}OCO)_2(COO)_4N_2$ building unit (Zn: teal , O: red, C: grey, N: blue). (b) Perspective view of a single 3D net along the *a*-axis. (c) The 1D channel along the *a*-axis. The two-fold interpenetrated nets are simplified by the two triangles (green and blue).

One group of MOFs that possess the desirable properties as carriers for AITC are RPMs (Rutgers Recyclable Porous Materials).[15] These 3D microporous materials feature similar crystal structures, tunable chemical composition and porosity. More interestingly, they all undergo a common and reversible structural transformation in water, which can be considered as an ideal external stimulus for controlled release of adsorbed molecules. In this work, we introduce a new member, $[Zn_3(bpdc)_3(apy)]\cdot 3.08DMF$ (**1**, bpdc = biphenyl-4,4'-dicarboxylate, apy = 4,4'-azobispyridine), to the RPM family. Compound **1** was solvothermally synthesized by reacting $Zn(NO_3)\cdot 6H_2O$, H_2bpdc and apy in DMF (dimethylformamide, see Supporting Information S1 for details). Single crystal X-ray structure analysis revealed that **1** crystallizes in monoclinic space group $P2_1/c$ (Table S1). Two crystallographically independent zinc centers existing in the structure are five- and six-coordinated, respectively. Three zinc centers and six carboxylate groups form the trinuclear secondary building unit (SBU) $Zn_3(\mu_2\text{-}OCO)_2(COO)_4$ (Fig. 1a), similar to that of a recently reported structure.[16] Each SBU is connected to six adjacent SBUs, resulting in a two-dimensional (2D) layer parallel to the *bc* plane. The 2D layers are further linked through an apy pillar to generate a 3D network (Fig. 1b). Two of these 3D networks, which are identical in structure, interpenetrate to yield an overall 3D porous framework of compound **1**, containing one-dimensional (1D) open channels with a hexagon-shaped cross section (Fig. 1c).

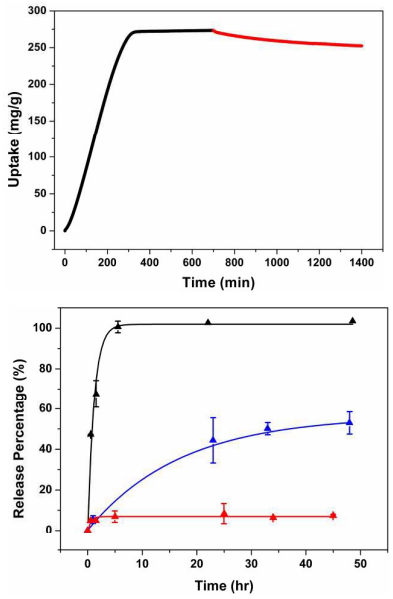

Fig. 2. Top: AITC adsorption curve (black) under $P/P_0 = 0.5$ and desorption curve (red) under pure nitrogen at room temperature on **1'**; Bottom: Release profiles of pure AITC under room humidity (black), AITC loaded **1'** under room humidity (red) and AITC loaded **1'** under 100% relative humidity (blue).

$Zn_3(bpdc)_3(apy)$ (**1'**), the guest-free form of compound **1**, remains highly crystalline and maintains the same structure as **1**. Permanent porosity of **1'** was confirmed by gas sorption experiments. Argon adsorption and desorption isotherms at 87K show that **1'** takes up 290 cc/g argon at 1 bar, yielding a BET (Brunauer-Emmett-Teller) surface area and pore volume of 609 m^2/g and 0.29 cc/g, respectively (Fig. S4). The matching pore size of **1'** and the molecular diameter of AITC prompted us to investigate the suitability of this MOF as a new type of carrier materials for AITC. He simulation (see Supporting Information, S5) shows the 1D open channel is made of

segments of cylinder shape, with dimension of 7 Å × 20 Å, with two segments per unit cell.

Orbital overlap population calculations indicate exteremely strong AITC-MOF interactions for AITC loaded **1'** (See Supporting Information S5 for detail). To experimentally verify this and evaluate **1'** as a carrier and release agent for AITC, we first loaded AITC onto **1'** via vapor adsorption. Nitrogen was used as a carrier gas to flow through an AITC bubbler, while the sample weight was monitored using a thermogravimetric (TG) analyzer. For the desorption sequence, pure nitrogen was flowed through the sample. As shown in Fig. 2, compound **1'** can take up as much as 27.3% w/w AITC at room temperature. Notably, more than 90% of the adsorbed AITC was retained in the pores of **1'** even after 10 hours of flushing by pure nitrogen. The negligible desorption may come from surface-adsorbed AITC. This suggests that **1'** can effectively entrap AITC molecules at room temperature.

Based on this finding, and the fact that the framework of compound **1'** breaks down upon exposure to water, we further evaluated controlled release of AITC from **1'** in an environment with high moisture as an external stimulus. A readily achievable external stimulus such as moisture is particularly desirable for controlled release of food packaging materials as the process is simple, natural, and nontoxic. The controlled release of AITC was monitered by measuring the AITC concentration in gaseous headspace of a sealed glass jar containing AITC@**1'** samples via gas chromatography (GC) system (See Supporting Information S4 for detail). Fig. 2 shows the release profiles of AITC from **1'**. Under room relative humidity (30% < RH% < 35%), the AITC concentration in the headspace remained constant throughout the experimental period (~2 days) after an initial increase in the first few hours corresponding to ~10% of loaded AITC (Fig. 2, red curve). Again, this confirms **1'** can entrap and retain AITC molecules in its pore space under room temperature and room humidity. This is significant, as encapsulation of AITC has so far not been achieved by any other porous carrier materials.

To test the effectiveness of using moisture to trigger the release of AITC from AITC@**1'**, in a parallel experiment, relative humidity of 95-100% RH was generated in the glass jar to mimic the highly humid atmosphere within a package of fresh produce. The obtained release profile (Fig. 2, blue curve) shows that AITC was gradually released to the headspace and reached a release level of ~55% of the total adsorbed AITC after ~2 days of the experimental period in two consecutive phases. The early moderately high release of gaseous AITC molecules within the first 10-20 hours generates a rapidly lethal dose or concentration of AITC that inhibits the growth of selected food-borne pathogens, while the extended slow release of AITC during the second phase can distinctly reduce the remaining viable counts of these harmful microorganisms.[17] Thus the release performance in this work makes **1'** an excellent carrier material of AITC for food safety applications. Evaporation of pure AITC sample (without MOF) was also carried out as a control experiment. A total release of AITC was completed in less than 2 hours (Fig. 2, black curve). All release measurements were carried out multiple times and the results were consistent (as indicated by error bars). These results confirm that compound **1'** represents an excellent encapsulant and releasing agent that is not only capable of effectively entrapping and retaining AITC within its pores but can also be triggered to start a controlled and slow release of AITC when exposed to an atmosphere of high moisture content. Humidity dependent PXRD analysis (See Supporting Information S6 for detail) shows the structure of **1'** ruptures at different rate under different humidity, indicating the release of AITC can be triggered in a fully controlled manner.

The prolonged (up to several days) and controlled release of AITC in this study suggests a practical approach to addressing

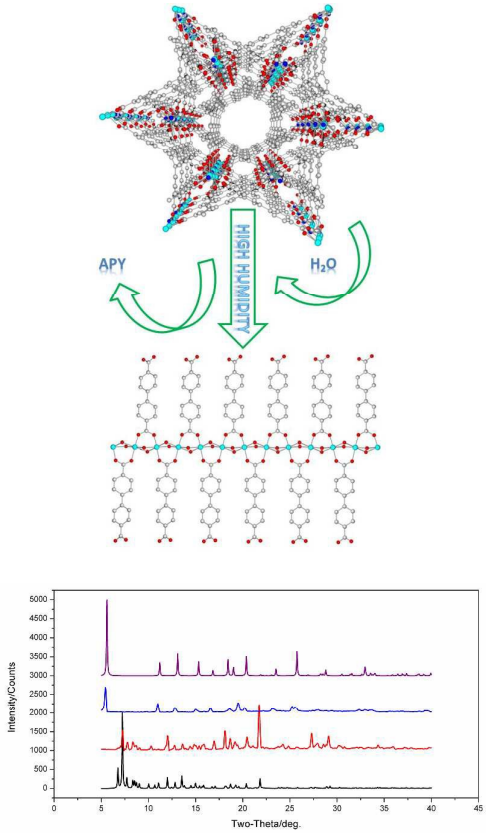

Fig. 3. Top: Proposed mechanism of controlled release of AITC from **1'** under high humidity (teal: Zn, red: O, blue: N, grey: C, white: H). Bottom: PXRD patterns of compound **1**: simulated (black) and as-made (red) sample, and of compound **2**: simulated (blue) and sample after release study (purple).

the main concerns that limit the use of AITC as a natural food preservative under current technology. Controlled release of AITC also improves the stability of the molecule by reducing the interaction time between AITC and food components, avoiding possible degradation or unavailability of AITC to act as an effective natural food antimicrobial agent. The amount of AITC@**1'** can be adjusted to reach the minimum inhibitory concentration (MIC) for different organisms.[18]

The underlying mechanism of controlled release of AITC triggered by moisture is related to the structural

transformation of **1'** upon exposure to a high concentration of water vapour, as schematically shown in Fig. 3 (top). Due to poor water stability of the Zn-N bond, when humidity is sufficiently high, water molecules gradually replace apy pillars by forming Zn-O bonds. This results in a structural transformation turning **1'** into a nonporous 1D $Zn(bpdc)(H_2O)_2$ compound (**2**, Fig. 3, top)[19]. In order to confirm this hypothesis, we performed powder X-ray diffraction (PXRD) analysis on the sample after controlled release experiments. The results are presented in Fig. 3 (bottom). The PXRD pattern of the sample after release study matches very well with that of Compound **2** and the release of apy is confirmed by UV spectroscopic study (See Supporting Information S7 for detail). To confirm that compound **2** does not adsorb AITC, we performed the same experiment to load AITC in **2** as described earlier for **1'**. The result shows that there was essentially no AITC uptake over a time period of 10 hours (see Fig. S5).

In summary, we have synthesized and structurally characterized a microporous metal-organic framework, $Zn_3(bpdc)_3(apy)$ (**1'**). Its permanent porosity was confirmed by high BET surface area. Compound **1** undergoes a structural transformation to a nonporous 1D chain compound, $Zn(bpdc)(H_2O)_2$ (**2**), upon exposure to moisture. Results from theoretical calculations and simulations show that the interactions between AITC molecules and the MOF internal pore surface are extremely strong, and are therefore capable of entrapping the molecules within the pores. Based on these properties and findings, **1'** was tested as a carrier material for the encapsulation of AITC, an antibacterial and food flavoring agent, and for its controlled release under high humidity conditions. An uptake of 27.3% w/w AITC was achieved, and entrapped AITC molecules remained in the MOF pores at room temperature and under room humidity conditions over the entire experimental period (~ 2 days). A controlled release study showed that the release of adsorbed AITC could be triggered by increasing relative humidity. The release time lasted several days. Further study revealed that the controlled release was a result of structural transformation from **1'** to **2** at high relative humidity. To the best of our knowledge, this work represents the first example of making use of water-sensitive MOFs for the controlled release of food preservatives and antimicrobial agents by using moisture as the release trigger. We believe that our finding not only serves as a proof-of-concept case but also opens new directions for possible applications of MOFs in food safety management.

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